pharmaceuticals

Review

Lewis Acids and Heteropoly Acids in the Synthesis of Organic Peroxides

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Abstract: Organic peroxides are an important class of compounds for organic synthesis, pharmacological chemistry, materials science, and the polymer industry. Here, for the first time, we summarize the main achievements in the synthesis of organic peroxides by the action of Lewis acids and heteropoly acids. This review consists of three parts: (1) metal-based Lewis acids in the synthesis of organic peroxides; (2) the synthesis of organic peroxides promoted by non-metal-based Lewis acids; and (3) the application of heteropoly acids in the synthesis of organic peroxides. The information covered in this review will be useful for specialists in the field of organic synthesis, reactions and processes of oxygen-containing compounds, catalysis, pharmaceuticals, and materials engineering.

Keywords: Lewis acid; heteropoly acid; hydrogen peroxide; organic peroxides; catalysis

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1. Introduction

Organic peroxides, due to their unique ability to form O-centered radicals via cleavage of the O-O bond, are widely used in polymer chemistry. In particular, dicumyl peroxide, dibenzoyl peroxide, 1,1-di-*tert*-butyl hydroperoxy cyclohexane, *tert*-butyl hydroperoxide, which are convenient in handling, have found application as initiators for low-temperature polymerization of styrene, butadiene, vinyl chloride, acrylates, ethylene [1,2], and as reagents for vulcanization of rubbers [3,4]. According to the latest research, the global organic peroxide market size was around US $2 billion in 2020 [5]. Despite the successful application of peroxides in the polymer industry, it was believed for a long time that the application of organic peroxides as drugs was not possible due to their low stability and the generation of hazardous reactive oxygen species, which can quickly and nonspecifically interact with biomolecules. Discovery of the natural peroxide Artemisinin (Qinghaosu) and its outstanding antimalarial activity [6,7] in 1972, showed that cyclic peroxides can be used in medicine as drugs. In 2015, Youyou Tu was awarded the Nobel Prize "for her discoveries regarding a new therapy for malaria" [8,9].

Drugs based on Artemisinin and its semisynthetic analogues are recommended by WHO as one of the most effective agents for the treatment of malaria (Figure 1) [10–12]. To overcome the emerging problem of drug resistance and to further improve the efficacy of Artemisinin, numerous derivatives of this unique natural product have recently been designed, synthesized and evaluated for biological activities [13,14].

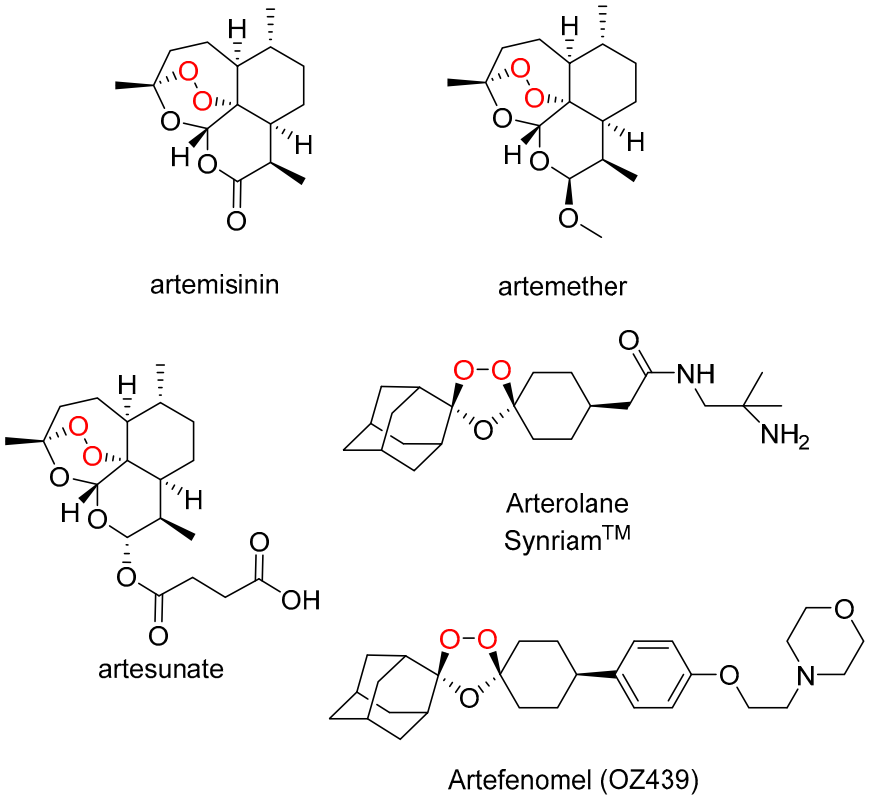


Figure 1. Artemisinin, its semi-synthetic derivatives, and synthetic Arterolane.

The growing demand for Artemisinin has pushed scientists to develop its total synthesis. The disadvantage of the available methods for synthesis of Artemisinin is the low overall yield, which prompted the search for synthetic peroxides with antimalarial properties. Currently, the most promising classes of synthetic peroxides are 1,2-dioxolanes, 1,2,4-trioxolanes (ozonides), 1,2-dioxanes, 1,2,4-trioxanes, and 1,2,4,5-tetraoxanes. Representatives of these families have demonstrated antimalarial [10,11,15], anthelmintic [16–28], antitumor [29,30], anti-tuberculosis [31–33], growth regulatory [34–36] and fungicidal activity [37–40]. In 2012, arterolane (ozonide OZ277) was the first synthetic peroxide to be approved for treatment of malaria in medical practice (Figure 1) [41–45]. Ozonide artefenomel (OZ 439) is a second generation clinical candidate against malaria [46]. Very recently, it has been shown that arterolane exhibits in vitro activity against α-coronavirus NL63 and β-coronaviruses OC43, and SARS-CoV-2 [47,48]. Artemisinin and its derivatives were also found to be active against SARS-CoV-2 in vitro as well [49].

Modern approaches to the synthesis of organic peroxides are based upon the use of oxygen, ozone, and hydrogen peroxide as sources of the O-O group. The most common methods for the construction of the O-O group are the ene reaction of singlet oxygen with alkenes [50–52], [4 + 2], the cycloaddition of singlet oxygen to dienes [53,54], the peroxysilylation of alkenes by the Isayama-Mukayama reaction [55–62], the cyclization of unsaturated hydroperoxides by the Kobayashi reaction [63–65], processes with the participation of destabilized peroxycarbenium ions [66–68], the ozonolysis of alkenes [69–74], the nucleophilic addition of hydrogen peroxide to carbonyl compounds and their analogs catalyzed by acids [75–91], and the ring opening reaction of Donor–Acceptor cyclopropanes with alkyl hydroperoxides [92]. The most affordable starting materials for the synthesis of organic peroxides are carbonyl compounds and hydrogen peroxide.

This review, which covers the major achievements in the synthesis of organic peroxides (Figure 2) using Lewis acids and heteropoly acids, consists of three parts: (1) metal-based Lewis acids in the synthesis of organic peroxides; (2) synthesis of organic peroxides promoted by non-metal-based Lewis acids; (3) application of heteropoly acids in the synthesis

of organic peroxides. This review provides information that will be useful to specialists in the field of organic synthesis, catalysis, pharmaceuticals, and the polymer industry.

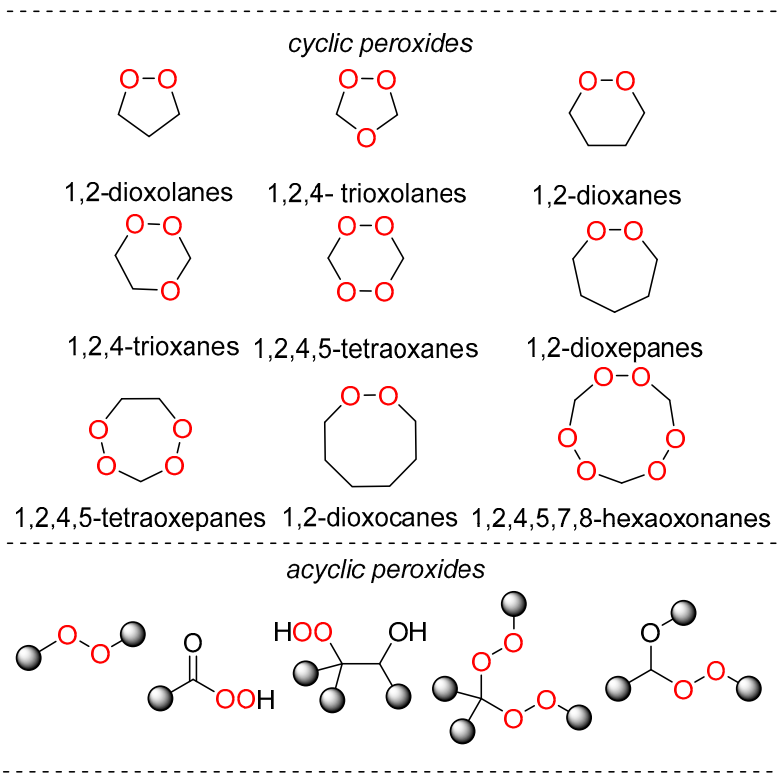


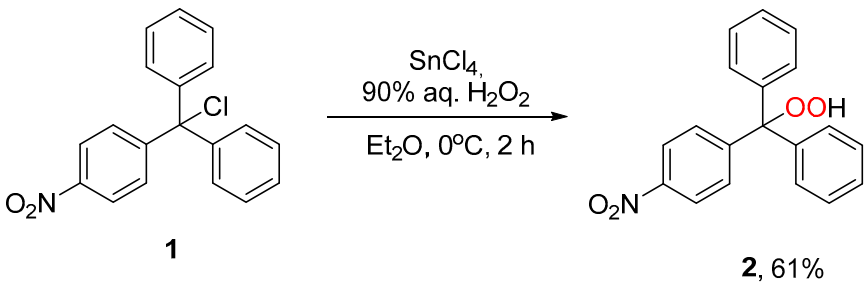
Figure 2. Reviewed cyclic and acyclic peroxides.

2. Metal-Based Lewis Acids as Catalysts in the Synthesis of Organic Peroxides

Traditionally, strong Bronsted acids play the role of a catalyst in the synthesis of organic peroxides. The use of metal-based Lewis acids for the synthesis of peroxides is a surprising phenomenon. Generally, peroxides decompose or rearrange under the action of transition metal salts [93,94]. However, some metal-based Lewis acids, on the contrary, promote the assembly of peroxides. In this section, we summarized the approaches on the synthesis of 1,2-dioxolanes, 1,2-dioxanes, 1,2-dioxepanes, 1,2-dioxocanes, 1,2,4,5-tetraoxanes, 1,2,4,5,7,8-hexaoxonanes, and acyclic peroxides under the action of metal-based Lewis acids.

2.1. Synthesis of Organic Peroxides Catalyzed by $SnCl_4$, Me_2SnCl_2, $SnCl_2$, and $TiCl_4$

The first example of selective synthesis of organic peroxide using a metal-based Lewis acid $SnCl_4$ as a catalyst goes back to 1950 [95]. Bartlett P. D. et al. carried out the nucleophilic substitution of the halogen atom in **1** with hydrogen peroxide in the presence of tin (IV) (Scheme 1). The hydroperoxide **2** formed granular crystals of a monohydrate melting at 99–101 °C with loss of water.

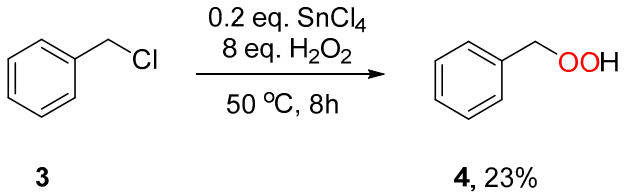


1

2, 61%

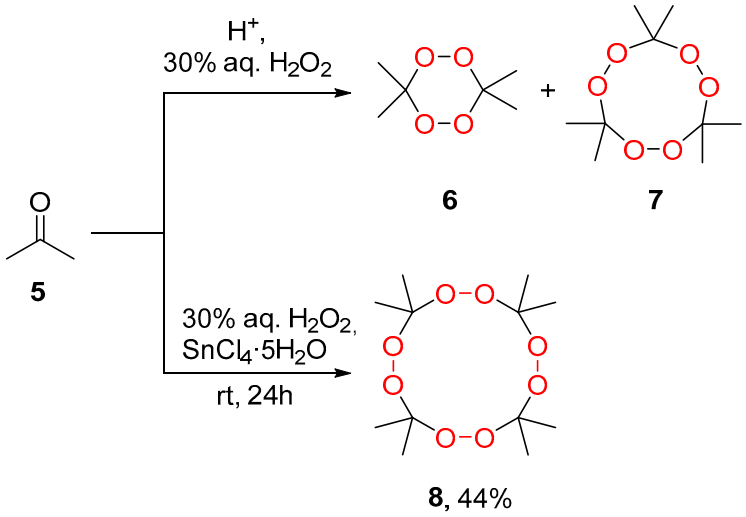
Scheme 1. Synthesis of hydroperoxide **2**.

In 1959, R. Huttel et al. found that benzyl hydroperoxide **4** is formed by treating benzyl chloride **3** with an excess of hydrogen peroxide (90% aq. solution) in the presence of tin (IV) chloride as a catalyst [96]. The yield of benzyl hydroperoxide **4** was 23% (Scheme 2).



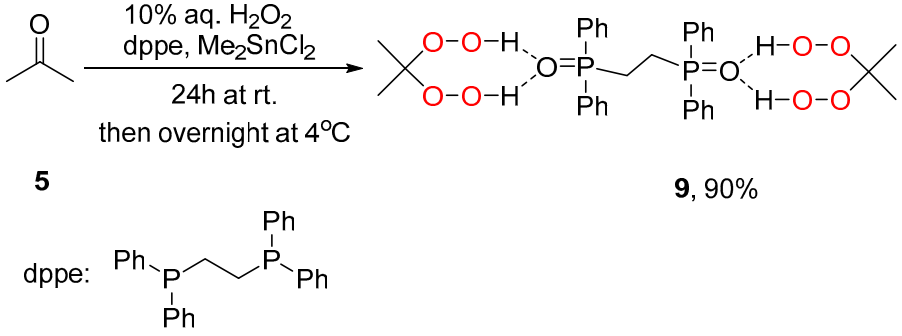
Scheme 2. Synthesis of benzyl hydroperoxide **4**.

The reaction of acetone **5** with hydrogen peroxide in the presence of protic acid leads to the formation of tetraoxane **6** and hexaoxonane **7**. However, the peroxidation of acetone under the action of $SnCl_4$ allows the obtaining of tetramer **8** in 44% yield (Scheme 3) [97]. Peroxide **8** was identified by molecular weight determination, elemental analysis, FTIR, NMR, and MS.



Scheme 3. Synthesis of cyclic peroxides from acetone.

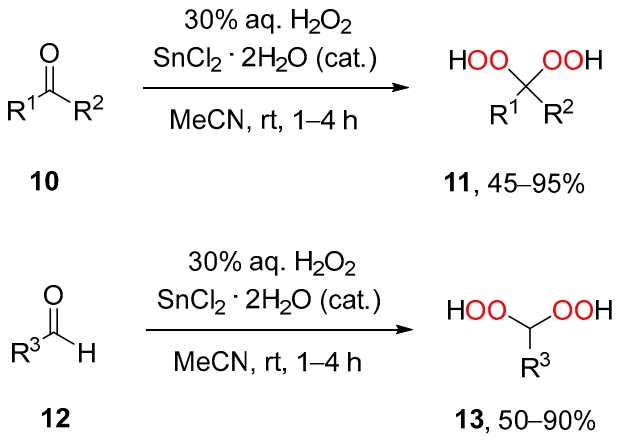
The reaction of H_2O_2 with 1,2-bis(diphenylphosphino)ethane (dppe) in acetone in the presence of Me_2SnCl_2 leads to (bis(diphenylphosphinoyl)ethane)·2(2,2-dihydroperoxypropane) 1:2 adduct **9**, stabilized by hydrogen bonds between hydroperoxide groups and oxygen atoms of phosphorus groups (Scheme 4) [98].



Scheme 4. Synthesis of (bis(diphenylphosphinoyl)ethane)·2(2,2-dihydroperoxypropane) 1:2 adduct **9**.

The synthesis of *gem*-bishydroperoxides **11** from ketones **10** was successfully carried out under the action of 30% aq. H_2O_2 using tin (II) chloride in catalytic amounts under

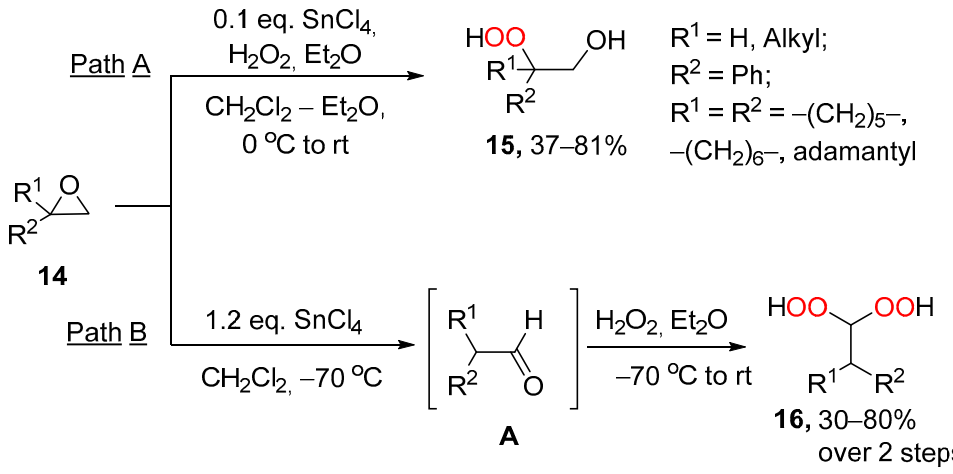
mild conditions [91]. As starting substrates, cyclic or acyclic ketones, as well as substituted acetophenones and aldehydes, can be used. The yield of the peroxides **11** and **13** was 45–95% (Scheme 5).



R^1 = Alkyl, Ph, 4-MePh, 4-MeOPh, 4-ClPh;
R^2 = Alkyl; R^1– R^2 = –$(CH_2)_4$–, –$(CH_2)_5$–;
R^3 = Alkyl, Ph, 4-MePh, 4-MeOPh;

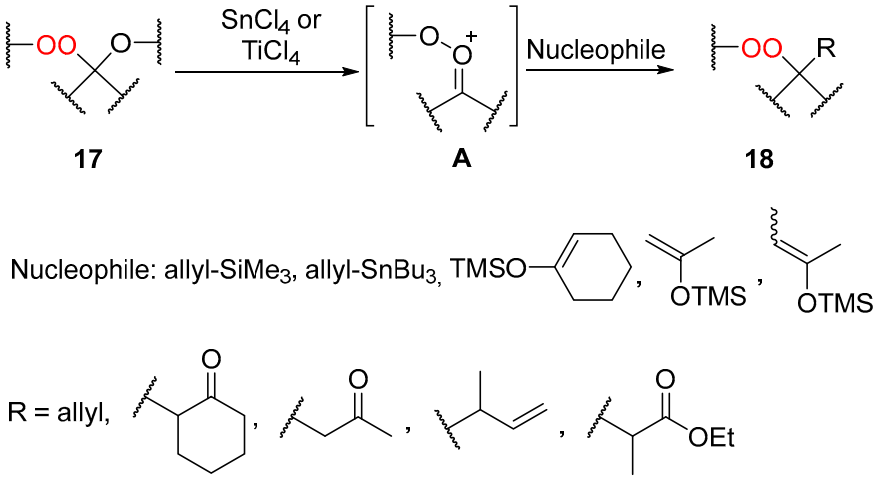
Scheme 5. Synthesis of *gem*-bishydroperoxides **11**, **13** from ketones **10** and aldehydes **12**.

Substituted oxiranes **14** are easily transformed into the corresponding α-hydroxo-hydroperoxides **15** in good yield in the presence of a $SnCl_4$-H_2O_2 system at 0 °C (Scheme 6, Path A) [99]. However, the opening of the oxirane ring at −78 °C, using $SnCl_4$ in the amount of 1.2 eq., with the subsequent addition of an ethereal solution of H_2O_2 into the reaction, leads to the formation of geminal 1,1-dihydroperoxides **16**. This new pathway results from $SnCl_4$-catalyzed rearrangement of oxiranes to aldehydes **A**, which then interact with hydrogen peroxide to form bishydroperoxides **16** (Scheme 6, Path B).



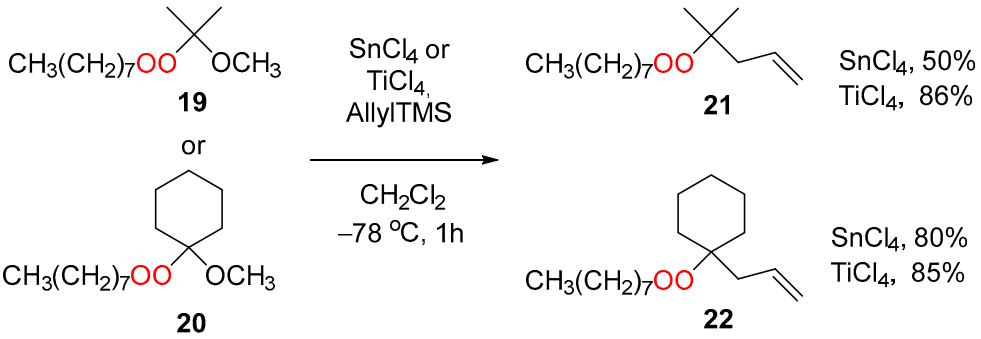
Scheme 6. Transformation of substituted oxiranes **14** into the corresponding α-hydroxo-hydroperoxides **15** and geminal 1,1-dihydroperoxides **16**.

Dussault P. et al. developed an approach to the synthesis of allylated peroxides, peroxyketones, and peroxyesters **18** by $SnCl_4$ or $TiCl_4$-mediated reaction of peroxyacetals **17** with electron-rich alkenes, proceeding via peroxycarbenium ion **A**. (Scheme 7) [100–102].



Scheme 7. Synthesis of alkyl peroxides **18**.

Allylation of monoperoxyacetals **19**, **20** makes it possible to obtain peroxides **21**, **22** in good yield at −78 °C in methylene chloride. The reaction is catalyzed by $TiCl_4$ and $SnCl_4$ (Scheme 8) [100].

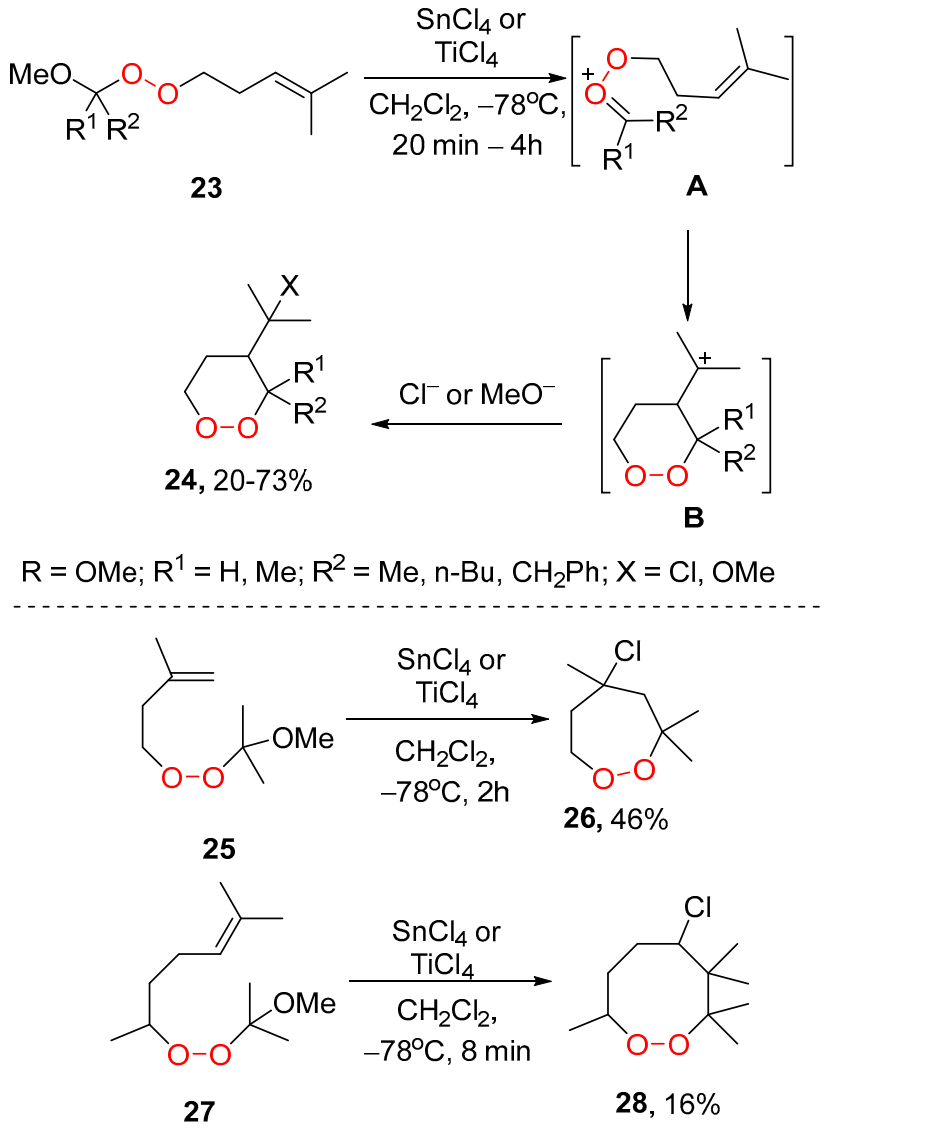


Scheme 8. Allylation of peroxyacetals **19** and **20**.

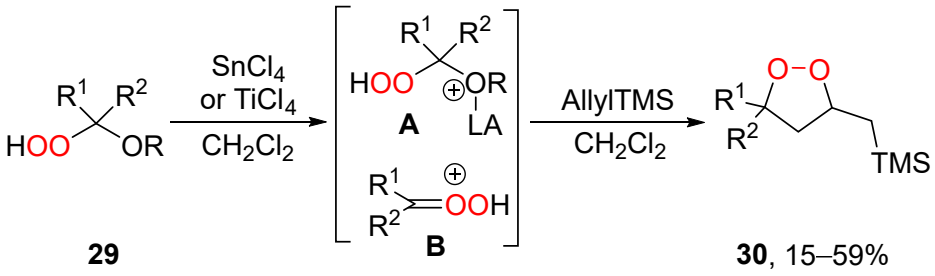
The transformation of alkyl peroxides under the action of Lewis acids has been described, where 1,2-dioxanes, 1,2-dioxepanes, and 1,2-dioxocanes are formed as target products [87]. Thus, intramolecular cyclization of peroxyacetals **23**, **25**, and **27**, containing an electron-rich double bond, occurs with the formation of cyclic peroxides **24**, **26**, and **28**, respectively, under action of 1 equiv. of $TiCl_4$ or $SnCl_4$ at −78 °C in CH_2Cl_2 at the N_2 atmosphere (Scheme 9). The size of the peroxide ring depends on the position of the double bond in the starting alkyl peroxide.

The interaction of allyltrimethylsilane with α-alkoxyhydroperoxides **29**, promoted by $SnCl_4$ and $TiCl_4$, afforded with the formation of substituted 1,2-dioxolanes **30** (Scheme 10) [101].

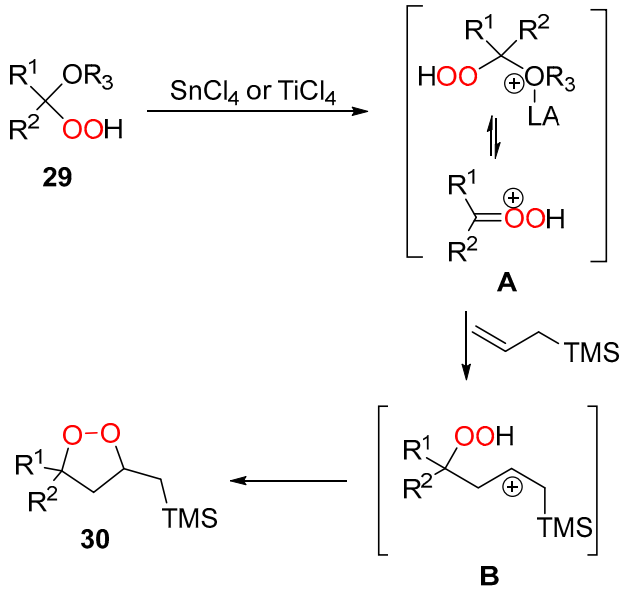
The reaction mechanism of the formation of 1,2-dioxolane **30** includes the formation of hydroperoxycarbenium ion **A** peroxyacetal **29** under the action of $SnCl_4$ or $TiCl_4$ at the first step. Then hydroperoxycarbenium ion **A** undergoes nucleophilic attack by allyltrimethylsilane to form cation **B**, the cyclization of which leads to the 1,2-dioxolane **30** (Scheme 11) [101].



Scheme 9. Intramolecular cyclization of peroxyacetals **23**, **25**, and **27**.

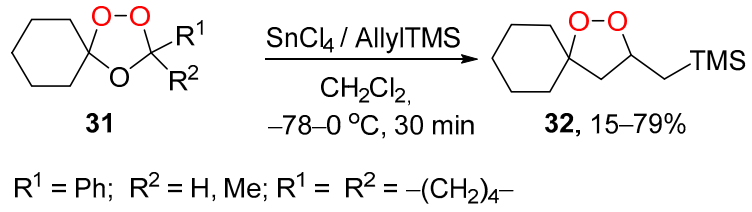


Scheme 10. Synthesis of substituted 1,2-dioxolanes **30**.



Scheme 11. Probable mechanism of 1,2-dioxolane **30** formation.

The above-mentioned approach was used to transform ozonides **31** into 1,2-dioxolanes **32**. This reaction proceeds under the action of $SnCl_4$/AllylTMS system in a nitrogen atmosphere at the temperature range from −78 °C to 0 °C (Scheme 12) [103].



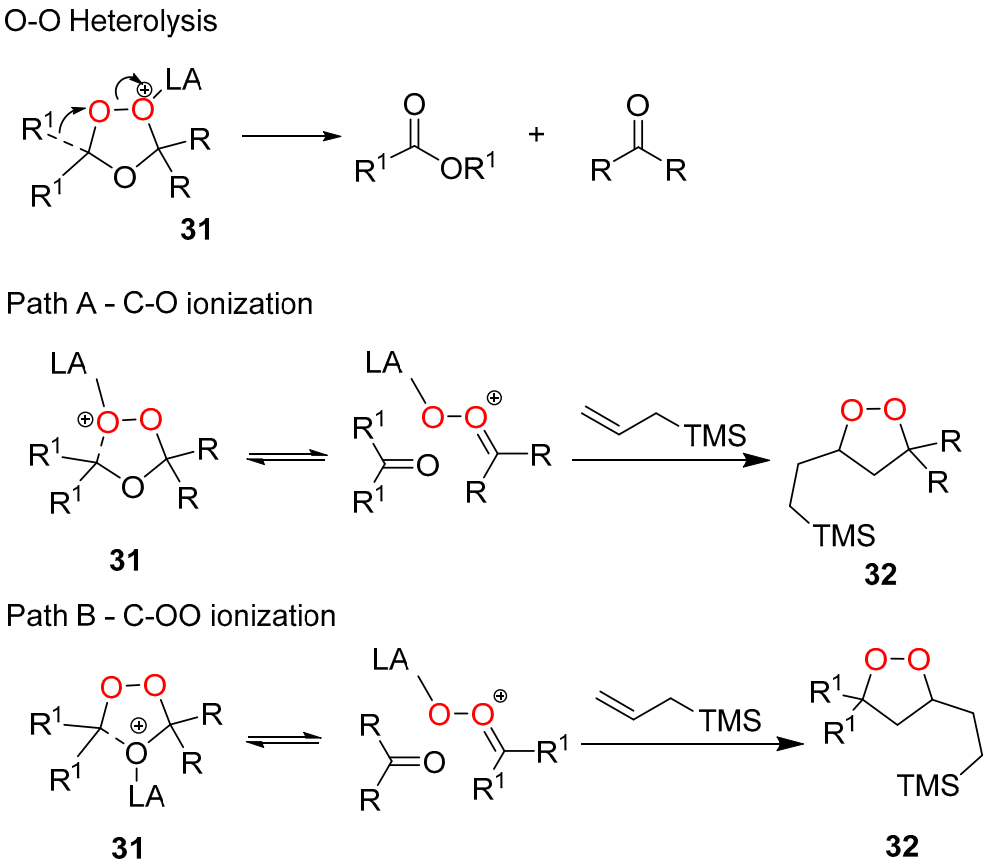
Scheme 12. Synthesis of 1,2-dioxolanes **32** from ozonides **31**.

In the absence of allyltrimethylsilane, $TiCl_4$ or $SnCl_4$ can catalyze the heterolysis of the O-O-bond in ozonides. This reaction proceeds with the formation of the corresponding lactones and ketones (Scheme 13). The transformation of ozonides **31** into 1,2-dioxolanes **32** under the action of $SnCl_4$ in the presence of allyltrimethylsilane proceeds through Path A and Path B, including the ionization of both C-O and C-OO bonds [104].

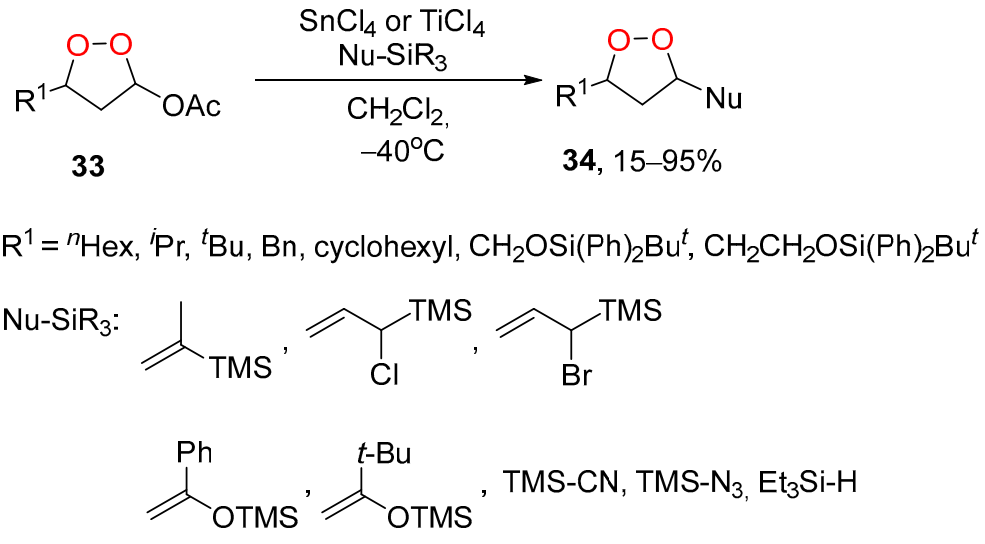
The $SnCl_4$ or $TiCl_4$-mediated reaction between peroxyacetals **33** and electron-rich alkenes results in the formation of functionalized 3,5-disubstituted 1,2-dioxolanes **34** through the formation of a peroxycarbenium ion, which is attacked by the nucleophile. (Scheme 14) [105].

The interaction of silylperoxyacetals **35** with alkenes **36** promoted by $SnCl_4$ leads to in the formation of substituted 1,2-dioxolanes **37**. This process proceeds through the formation of the trimethylsilyl peroxycarbenium ion (Scheme 15) [82,106,107]. It was found that 1,2-dioxolanes **37a** and **37b** have a high antimalarial activity against *P. falciparum* [108].

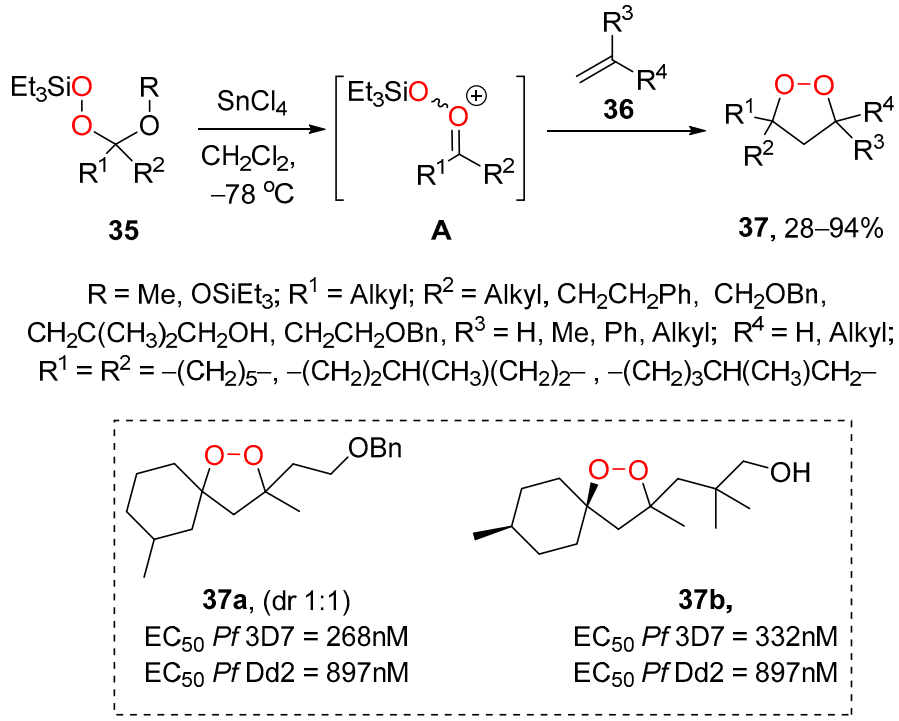
This approach was used for the synthesis of 1,2-dioxalane (OZ78) **40**, which exhibits high activity against *Fasciola hepatica* (Scheme 16) [109].



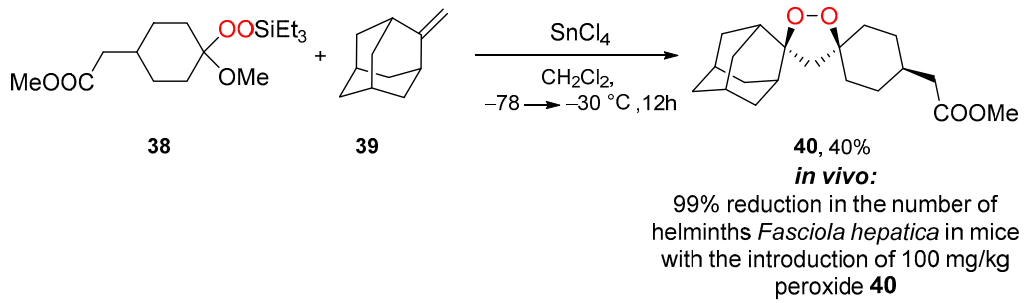
Scheme 13. Mechanism of 1,2-dioxolanes formation **32** from ozonides **31**.



Scheme 14. Synthesis of substituted 1,2-dioxolanes **34**.

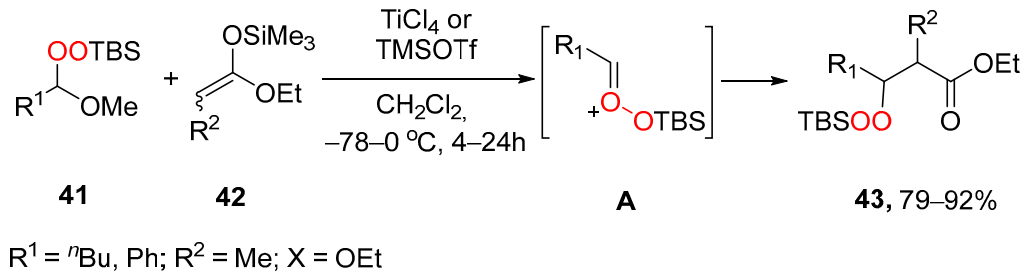


Scheme 15. Synthesis and activity of 1,2-dioxolanes **37**.



Scheme 16. Synthesis and activity of 1,2-dioxolane (OZ78) **40**.

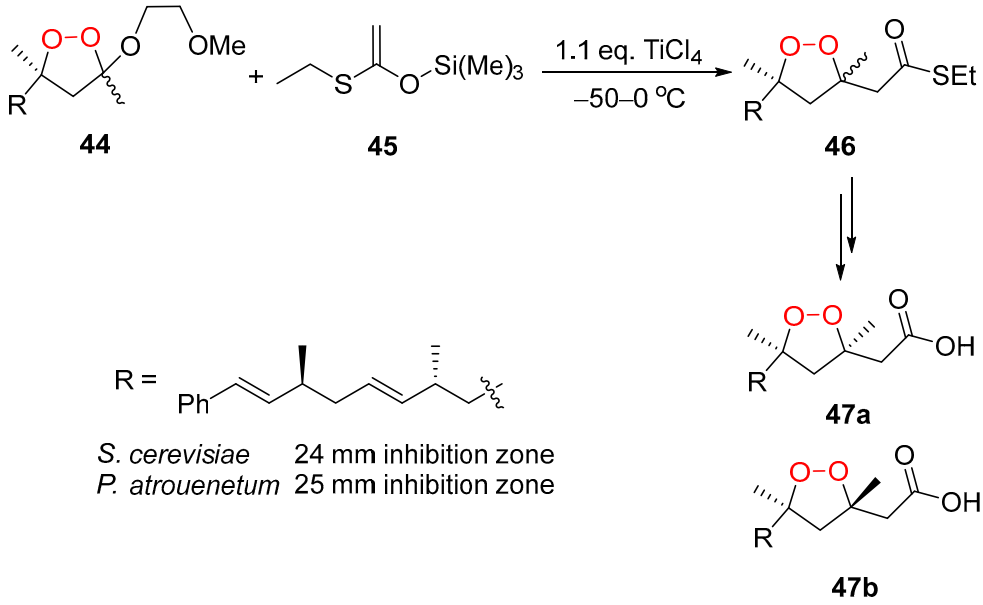
The reaction of peroxyacetal **41** with SKA (trimethylsilylketene acetal) **42** leads to the formation of peroxide **43**, containing ester functional group (Scheme 17) [102]. The best yield of peroxide **43** was achieved in the case of peroxyacetal **41** where R^1 = Ph [110].



Scheme 17. Synthesis of 3-peroxy-2-methylalkanoates **43**.

Natural compounds with antitumor activity, such as stereoisomers of plakinic acids **47a,b**, were synthesized from peroxide **44** in three steps (Scheme 18). The key 1,2-dioxolane **46** in this sequence was synthesized from α-alkoxydioxolane **44** and O,S-ketene acetal **45** promoted by $TiCl_4$ in 82% yield (Scheme 18). Both isomers of acid **47a,b** were isolated in

individual form [111]. Also it was found that plakinic acids **47** inhibit the growth of the fungi *Saccharomyces cerevisiae* and *Penicillium atrounenetum* [39].



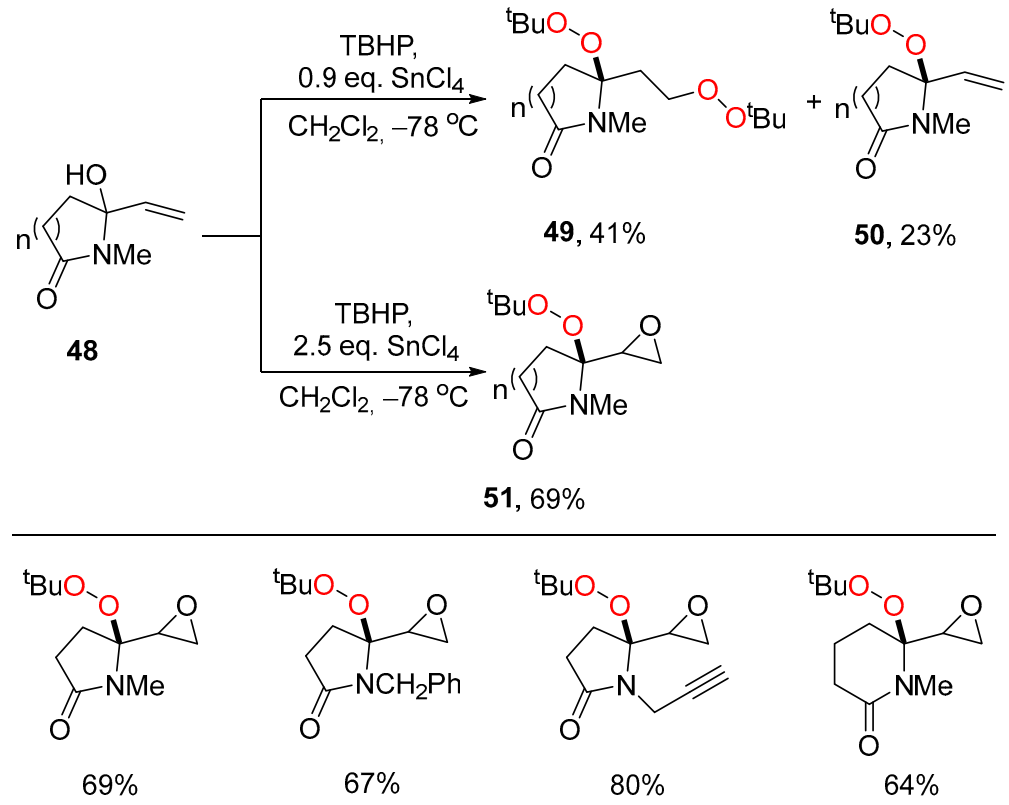
Scheme 18. Synthesis of plakinic acid A **47a**,**b**.

It was found that the type of peroxidation product of allylic alcohols containing a lactam ring **48** depends on the amount of Lewis acid. Thus, peroxidation of alcohol **48** with the use of 0.9 eq. of $SnCl_4$ leads to the formation of both mono- and diperoxides **49** and **50**. Increasing the amount of acid to 2.5 eq. with respect to **48** leads to the formation of epoxyalkyl peroxide **51** (Scheme 19) [112]. Anchimeric assistance of the hydroxyl group facilitates the addition of *tert*-butyl hydroperoxide to the double bond. Under the action of $SnCl_4$, through the formation of a carbocation, the nucleophilic substitution of the hydroxyl group for *tert*-butyl peroxide occurs.

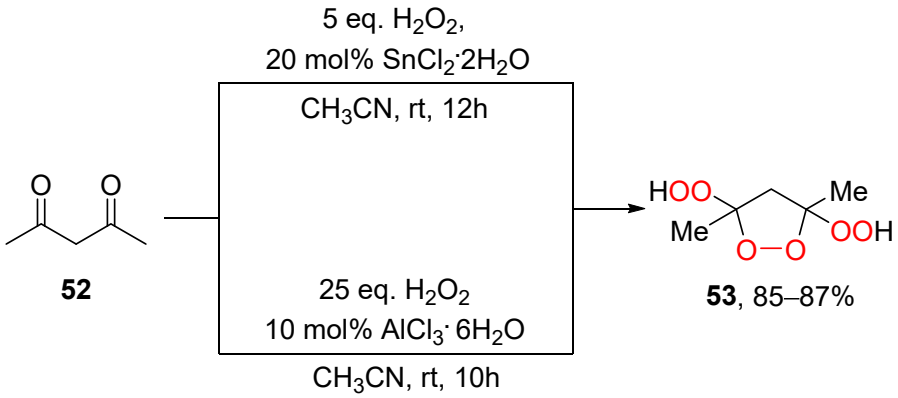
Catalysis of the peroxidation reaction of acetylacetone **52** by strong protic acids (H_2SO_4, $HClO_4$, HCl) leads to a complex mixture of cyclic and acyclic peroxides. However, with the use of $SnCl_2{\cdot}2H_2O$ and $AlCl_3{\cdot}6H_2O$ as a catalyst, the peroxidation of acetylacetone **52** proceeds selectively with the formation of dihydroperoxo-1,2-dioxolane **53** (Scheme 20) [113,114]. The reaction was carried out at a room temperature with 5–25 molar excess of 30% aq. solution of H_2O_2 and 10–20 mol% LA with respect to **52**.

The $SnCl_2{\cdot}2H_2O/H_2O_2$ system was used in the peroxidation of 2,5-heptadione **54**. In this case, the reaction proceeds with the formation of hydroxyhydroperoxy 1,2-dioxane **55**, but in a low yield of target compound of 15% (Scheme 21) [115]. The reaction was carried out at a room temperature with 5-fold molar excess of 50% aq. solution of H_2O_2 and 20 mol. % $SnCl_2{\cdot}2H_2O$ with respect to **54**.

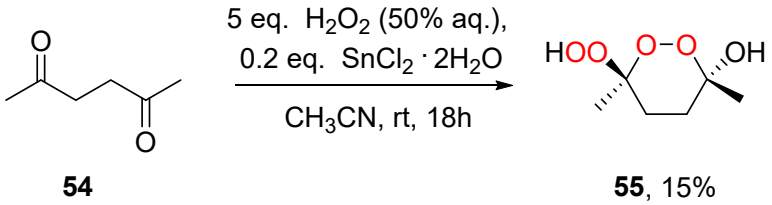
The reaction of acetals **56** with 1,1′-dihydroperoxydi (cycloalkyl) peroxides **57** catalyzed by $SnCl_4$ afforded with the formation of 1,2,4,5,7,8-hexaoxananes **58**. This approach makes it possible to solve the problem of the synthesis of hexaoxonanes from cycloalkanones with ring sizes C6–C8 and C12 (Scheme 22) [88].



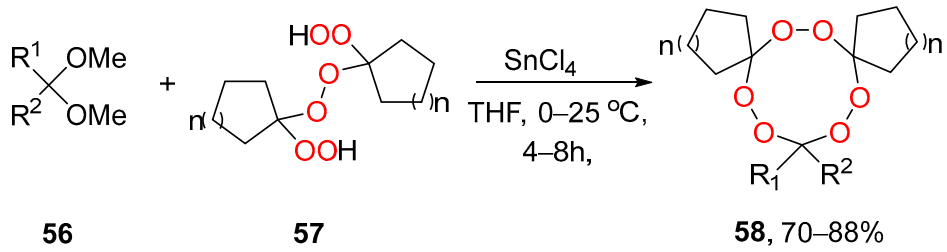
Scheme 19. Synthesis of peroxides **49–51**.



Scheme 20. Synthesis of dihydroperoxy-1,2-dioxolane **53** from acetylacetone **52**.



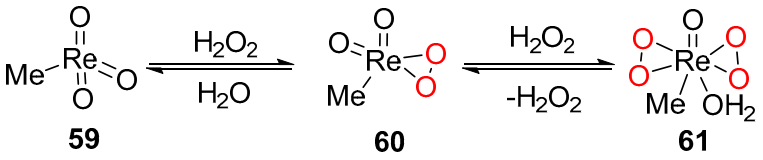
Scheme 21. Synthesis of hydroxyhydroperoxy 1,2-dioxane **55** from 2,5-heptadione **54**.



Scheme 22. Synthesis of 1,2,4,5,7,8-hexaoxananes **58**.

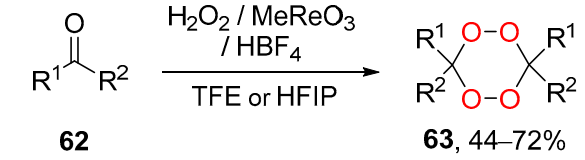
2.2. Peroxidation of Ketones and Aldehydes in the Presence of $MeReO_3$

The proposed mechanism of ketone peroxidation by the H_2O_2/$MeReO_3$ system is based on the coordination of hydrogen peroxide with rhenium, which acts as a Lewis acid with the formation of peroxocomplex **61** (Scheme 23) [116–118]. The resulting peroxocomplex **61** interacts with a carbonyl compound with the transfer of a peroxo group. Furthermore, $MeReO_3$ can react with a carbonyl group, as a Lewis acid to activate the carbonyl carbon atom.



Scheme 23. Formation of the peroxo complexes $MeReO_3$.

The addition of HBF_4 to the 30% aq. H_2O_2/$MeReO_3$ system leads to the formation of symmetric 1,2,4,5-tetraoxanes **63** from cyclic ketones **62**, as well as 3,3,6,6-tetraalkyl-1,2,4,5-tetraoxanes **63** from unsymmetrical ketones **62**, respectively (Scheme 24) [119]. 1,2,4,5-Tetraoxanes **63a–e** exhibit antimalarial activity against the chloroquine-resistant strain of *P. falciparum*.

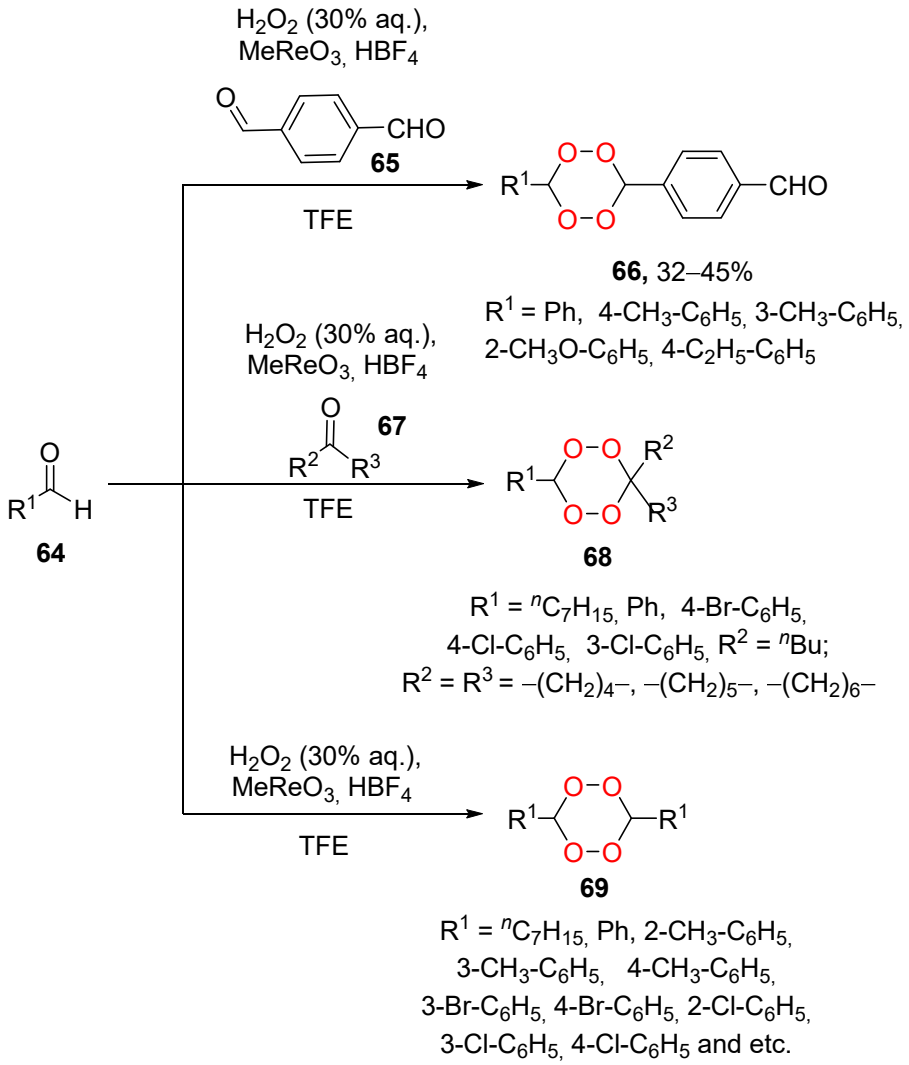


			P. falciparum
	R_1	R_2	IC_{50} (nM)
63a	–$(CH_2)_6$–		82.9
63b	^{n}Pr	^{n}Pr	183.4
63c	Et	^{n}Pr	179.4
63d	Et	^{n}Bu	151.4
63e	Et	$CH_2CH(CH_3)_2$	135.8
Artemeter			3.5

Scheme 24. Synthesis and antimalarial activity of 1,2,4,5-tetraoxanes **63**.

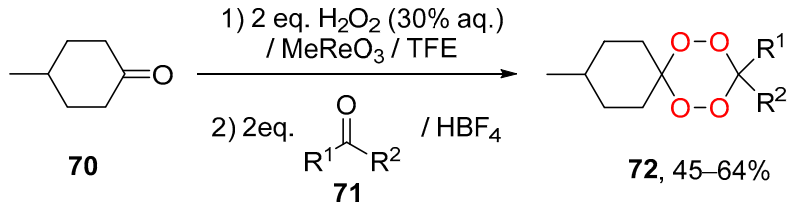
The combination 30% aq. H_2O_2/$MeReO_3$/HBF_4 in TFE is an effective system for the synthesis of both symmetric **69** and non-symmetric tetraoxanes **66** or **68** from aldehy-

des **64** in good yields (Scheme 25) [120–122]. It was found that such tetraoxanes exhibit antimalarial activity in vitro.



Scheme 25. Synthesis of tetraoxanes **66, 68** and **69** from aldehydes **64**.

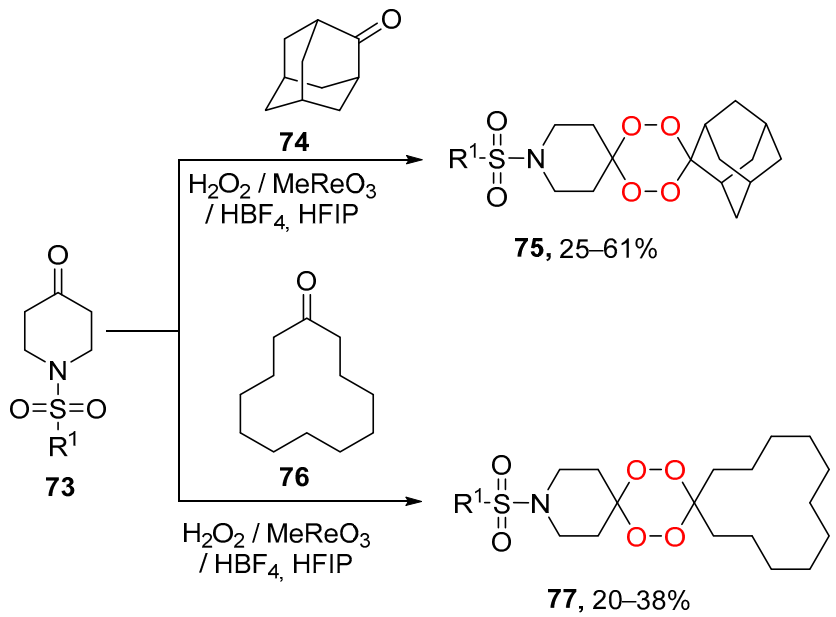
Non-symmetric tetraoxanes **72** were synthesized from 4-methyl cyclohexanone **70** and ketone or aldehyde **71** under the action of H_2O_2 in the presence of 1 eq. of HBF_4 and 0.1 mol% of $MeReO_3$ with respect to the starting ketone in TFE medium. (Scheme 26) [122].



R^1 = ^{n}Bu, Ph, ^{n}C$_7$H$_{15}$; R^2 = H, ^{n}Bu; $R^1 = R^2$ = –(CH$_2$)$_2$CH(^{t}Bu)(CH$_2$)$_2$–

Scheme 26. Synthesis of unsymmetrical 1,2,4,5-tetraoxanes **72**.

The interaction of sulfonylpiperide-4ones **73** with ketones **74**, **76** promoted by H_2O_2/$MeReO_3$/HBF_4 in HFIP leads to the formation of non-symmetric 1,2,4,5-tetraoxanes **75** and **77**, which exhibit high antimalarial activity (Scheme 27) [123].



	EC_{50} *Pf* 3D7, nM
Artemisinin	9,20
75,a-c	
Et	5,55
^{i}Pr	5,87
Cp	3,52
77,a-b	
Et	29,13
^{i}Pr	86,37

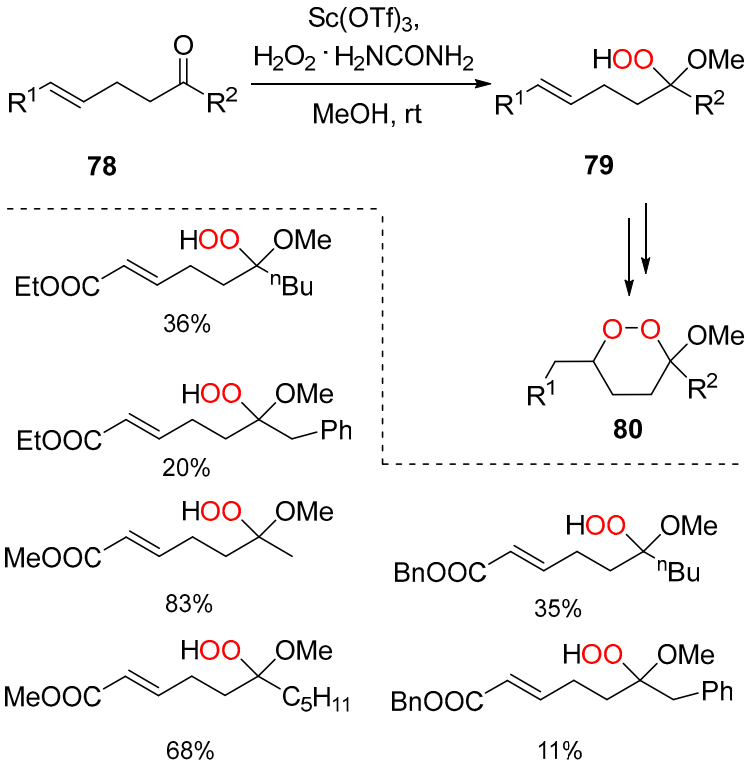
Scheme 27. Synthesis of non-symmetric 1,2,4,5-tetraoxanes **75** and **77**.

2.3. Sc(OTf)$_3$, Yb(OTf)$_3$, InCl$_3$ and In(OTf)$_3$ in the Synthesis of Organic Peroxides

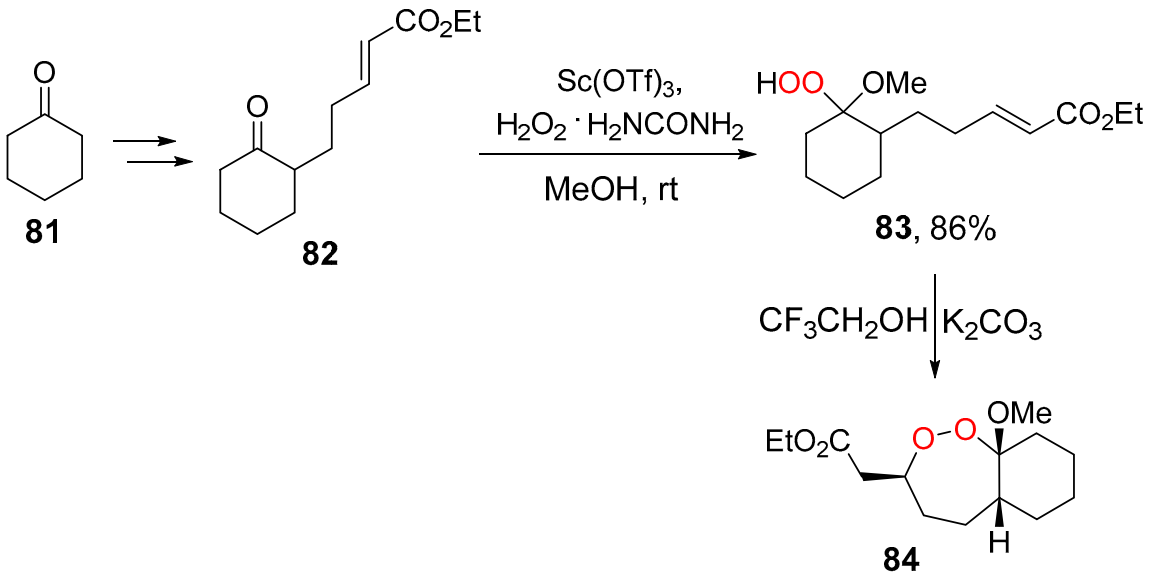
In 2001, Kobayashi and colleagues developed a new method for the synthesis of alkoxyhydroperoxides **79** based on the reaction of the carbonyl group of unsaturated ketones **78** with $H_2O_2 \cdot H_2NCONH_2$, catalyzed by Sc(OTf)$_3$. Cyclization of alkyl hydroperoxides **79** leads to 1,2-dioxanes **80** according to the Michael reaction. This method allows for the obtaining of substituted cyclic peroxides containing various functional groups in their structure (Scheme 28) [63–65,124].

The system $H_2O_2 \cdot H_2NCONH_2$/Sc(OTf)$_3$ was used in the synthesis of peroxyacetal **83**, which under basic conditions undergoes intramolecular cyclization with the formation of cyclic peroxide **84** (Scheme 29) [125].

Recently, Saha et al. found that the ring opening of Donor–Acceptor (D–A) cyclopropanes **85** in the presence of ^{t}BuOOH or hydroperoxides **86** under the action of Sc(OTf)$_3$ leads to the formation of various peroxides **87** in 51–91% yield (Scheme 30) [92]. The reaction can be carried out on a gram scale in 74% yield of the target peroxide.



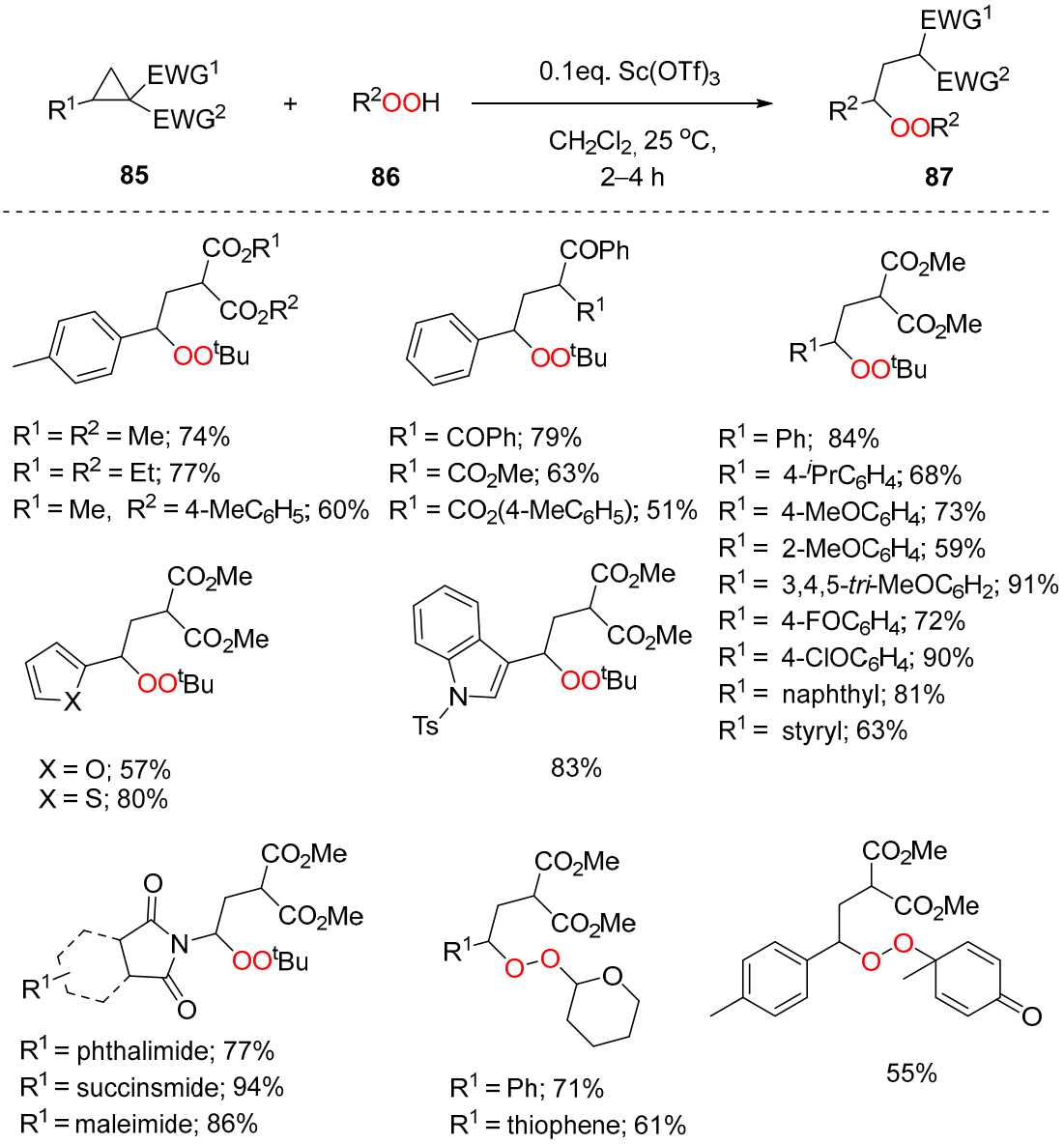
Scheme 28. Synthesis of alkoxyhydroperoxides **79**.



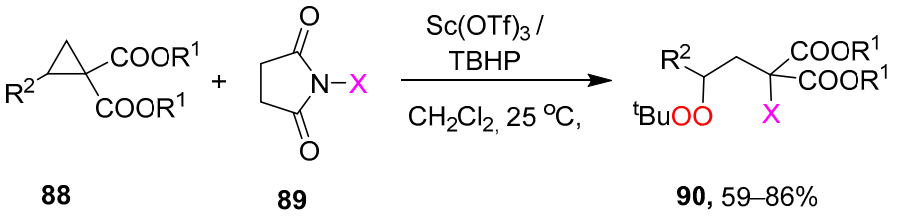
Scheme 29. Synthesis of cyclic peroxide **84**.

The interaction of Donor–Acceptor cyclopropane **88** with ^{t}BuOOH and *N*-halosuccinimides **89**, which acts as a source of halogen, provides haloperoxides **90** in moderate to good yields (Scheme 31) [92].

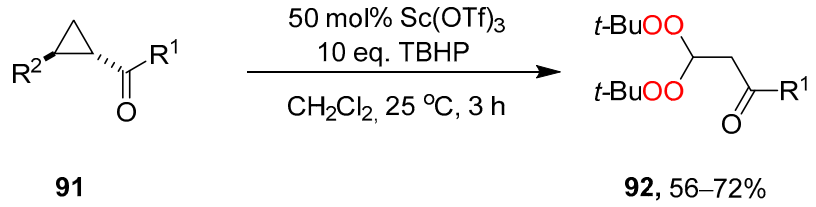
It is noteworthy that the interaction of cyclopropanes **91** containing one acceptor substituent with *tert*-butyl hydroperoxide under the action of 0.5 eq. $Sc(OTf)_3$ leads to bis-*tert*-butyl peroxides **92** in 56–72% yields (Scheme 32) [92].



Scheme 30. Synthesis of peroxides **87**.



Scheme 31. Synthesis of haloperoxides **90**.

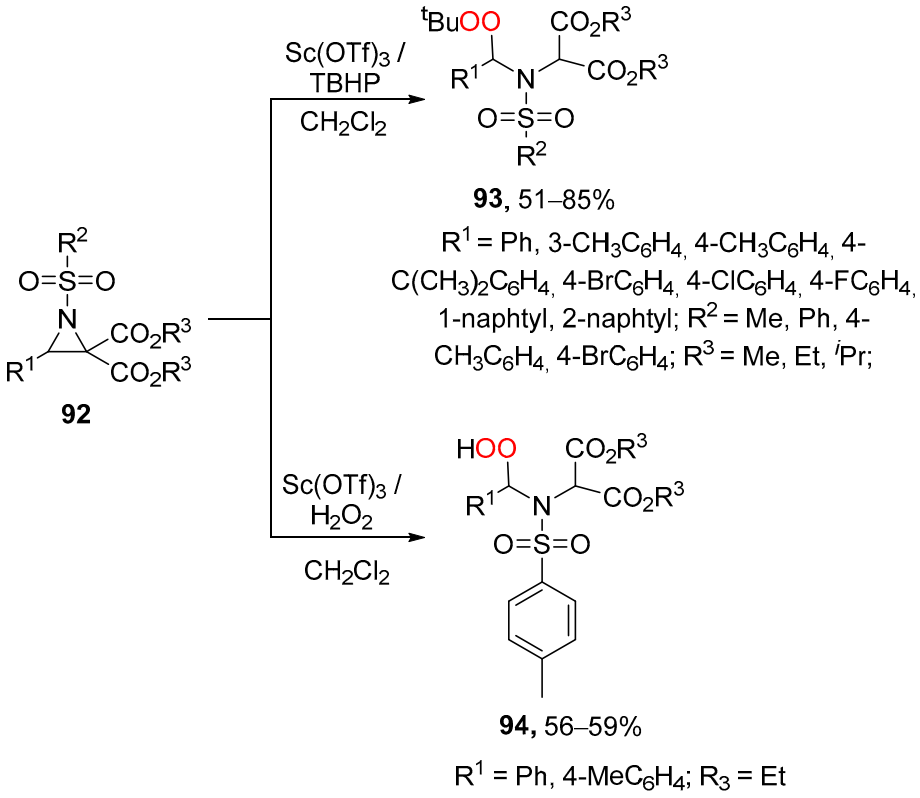


91 **92,** 56–72%

R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, thiophene;
R^2 = 4-$MeOC_6H_4$; 3,4,5-$(MeO)_3C_6H_2$;

Scheme 32. Synthesis of bis-*tert*-butyl peroxides **92**.

The use of the H_2O_2 or TBHP/$Sc(OTf)_3$ system for ring opening of donor-acceptor aziridines **92** leads to α-sulfanilamido peroxides **93** and **94** in good yield (Scheme 33) [126]. The reaction can be scaled up to the grams in 70% yield.

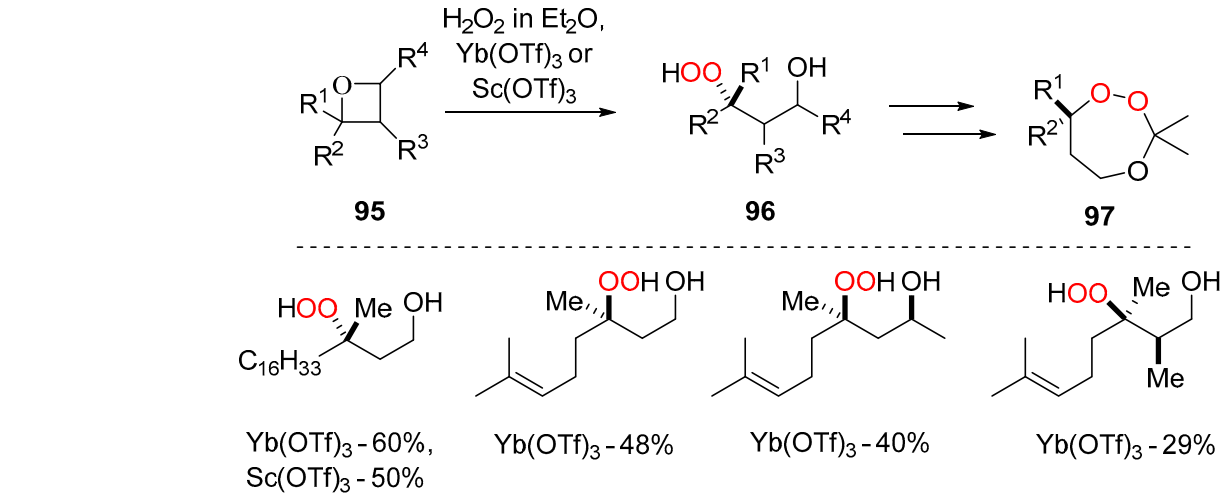


Scheme 33. Synthesis of peroxides **93** and **94** from donor-acceptor aziridines **92**.

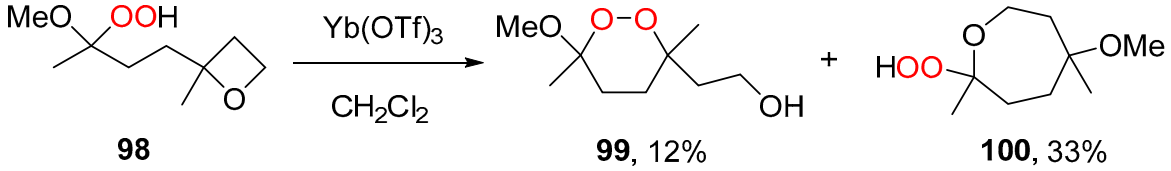
In 2002, Dussault et al. [127] demonstrated the ring opening of oxetanes **95** with an ethereal solution of H_2O_2, catalyzed by $Yb(OTf)_3$ and $Sc(OTf)_3$ with the formation of peroxides **96**, which act as intermediates in the synthesis 1,2,4-trioxepanes **97** (Scheme 34).

Hydroperoxyoxetane **98** rearranged into endoperoxide **99** in 12% yield and exoperoxide **100** in 33% yield under the action of $Yb(OTf)_3$ in methylene chloride (Scheme 35) [74].

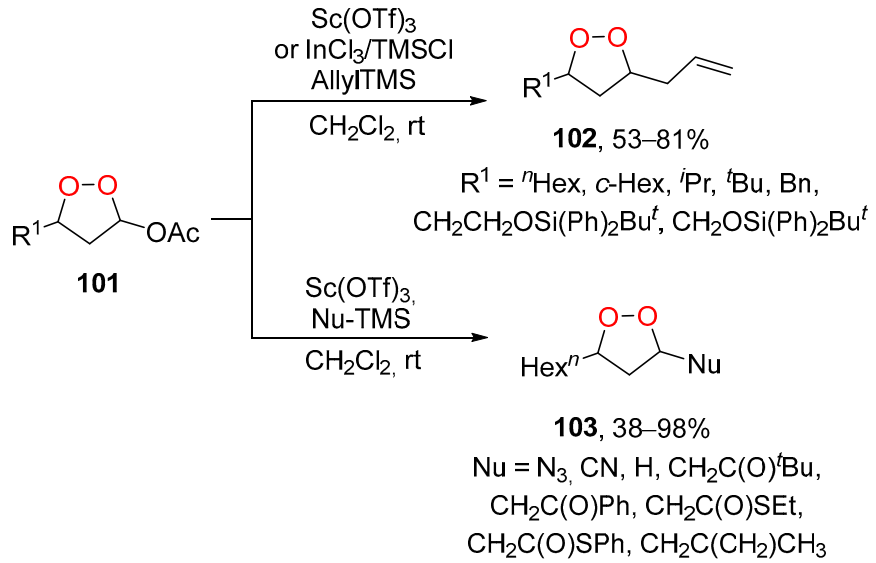
The use of catalytic amounts of $Sc(OTf)_3$ or $InCl_3$ in the reaction of endoperoxyacetals **101** with allyltrimethylsilane (AllylTMS) and its derivatives (Nu-TMS) makes it possible to obtain 3,5-disubstituted-1,2-dioxolanes **102** and **103** by the Sakurai reaction. $Sc(OTf)_3$ or $InCl_3$ allow the reaction to be carried out under milder conditions than when using $SnCl_4$ and $TiCl_4$ (Scheme 36) [128,129].



Scheme 34. Synthesis of hydroperoxides **96** from oxetanes **95**.



Scheme 35. Synthesis of peroxides **99** and **100** from hydroperoxyoxetane **98**.

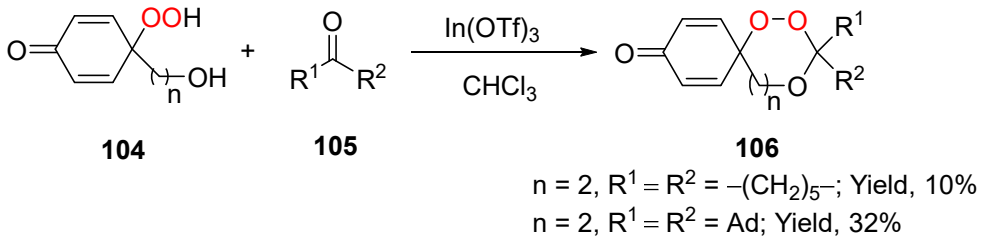


Scheme 36. Synthesis of 1,2-dioxolanes **102** and **103** from peroxyacetals **101**.

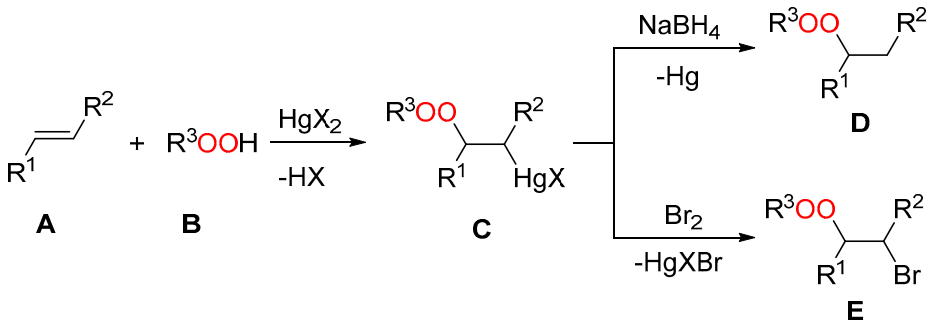
Cyclic peroxides such as spiro 1,2,4-trioxepanes **106** were obtained from hydroperoxides **104** and ketones **105** by using Indium (III) triflate as a catalyst (Scheme 37) [130].

2.4. Mercury Salts in the Synthesis of Peroxides

In a process known as peroxymercuration, alkyl peroxides **D**, **E** can be prepared from alkenes **A** and alkyl hydroperoxide **B** in the presence of a suitable mercury (II) salt (Scheme 38). In this case, mercury salts act as a mild electrophilic reagent. The interaction of mercury (II) salt with an alkene leads to cationic species, which reacts with alkyl hydroperoxide to form mercurylalkyl peroxides **C**. The obtained mercurylalkyl peroxides **C** can be demercurated using sodium borohydride or by bromonolysis. Both peroxymercuration and demercuration occur rapidly under mild conditions.

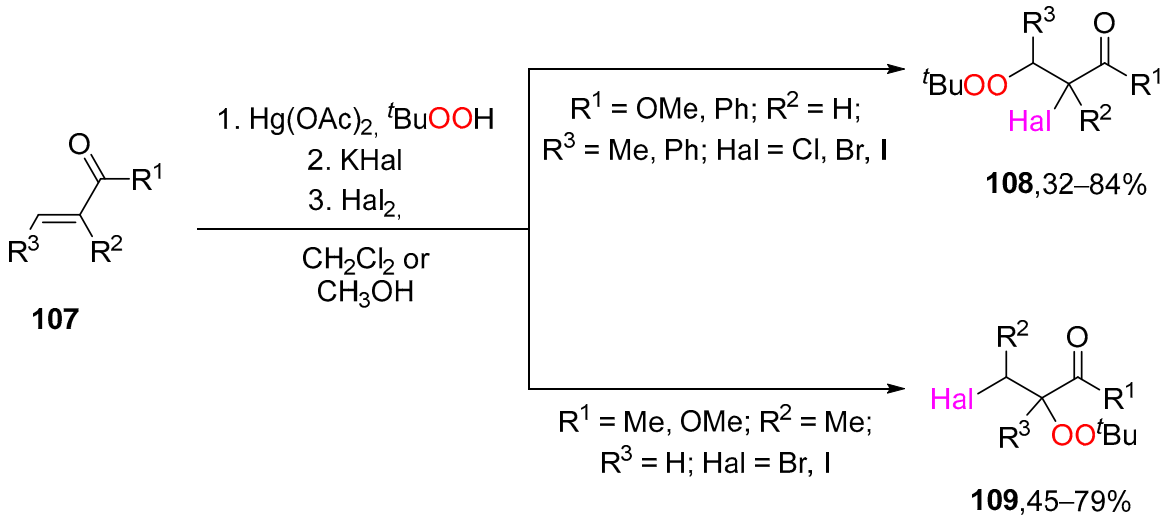


Scheme 37. Synthesis of 1,2,4-trioxepanes **106**.



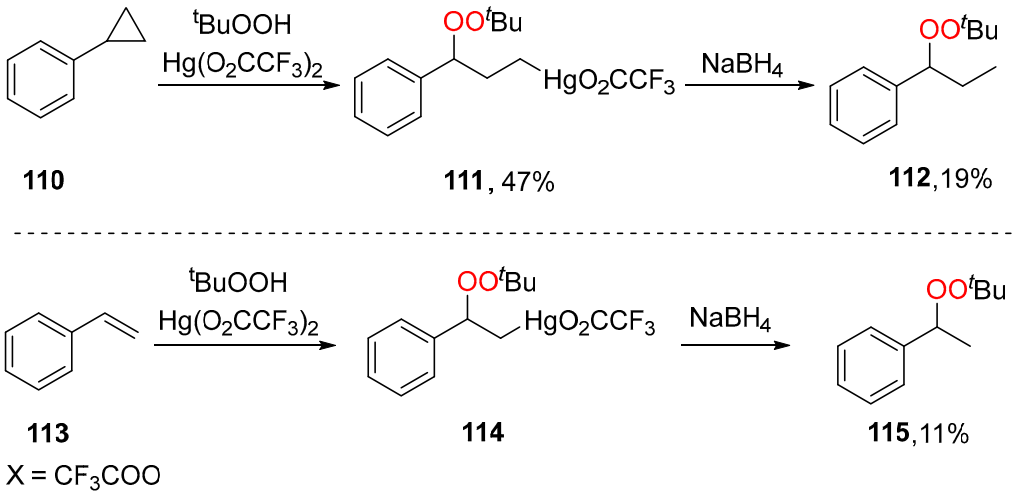
Scheme 38. Synthesis of acyclic peroxides **D** and **E**.

Bloodworth A.J. demonstrated a two-stage approach to halogeno-alkyl peroxides **108**, **109** (Scheme 39) [131]. At the first stage, peroxymercuration of such unsaturated ketones **107** was carried out with the use of ^{t}BuOOH/Hg(OAc)$_2$ system then demercuration of peroxymercurated product afforded with the formation of target peroxides **108**, **109** in 32–84% and 45–79% yields, respectively.



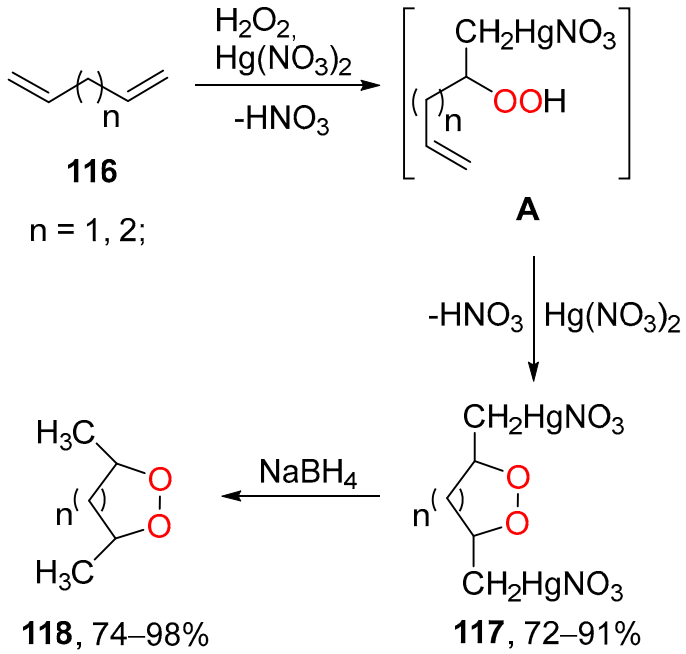
Scheme 39. Synthesis of peroxides **108**, **109**.

Phenyl cyclopropane **110** undergoes ring opening under the action of the ^{t}BuOOH/Hg(CF$_3$COO)$_2$ system with the formation of mercurylalkyl peroxide **111** in a 47% yield. Further reduction **111** leads to alkyl peroxide **112** in a 19% yield [132]. The same system was applied for the synthesis of peroxide **115** from styrene **113** (Scheme 40).



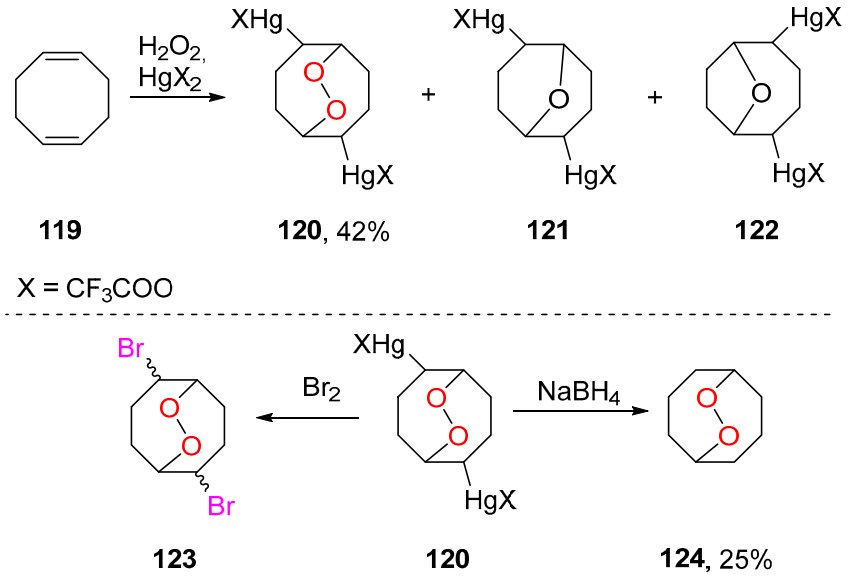
Scheme 40. Synthesis of alkyl peroxides **112** and **115**.

In 1976, Bloodworth A. J. and colleagues described a method for the synthesis of cyclic peroxides **117** by the peroxymercuration of non-conjugated acyclic dienes **116**. The demercuration of **117** under the action of $NaBH_4$ led to peroxides **118** (Scheme 41) [133].



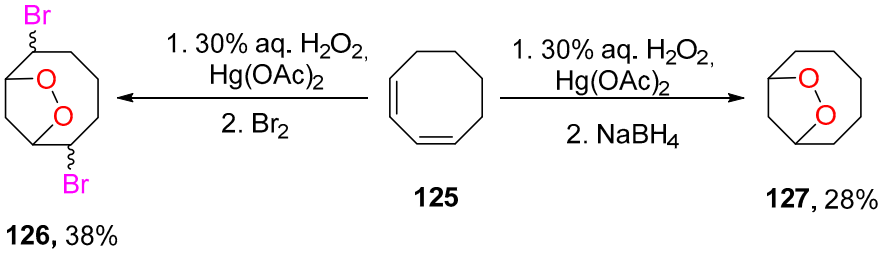
Scheme 41. Synthesis of cyclic peroxides **117** and **118**.

Adam W. et al. presented a method for the regioselective synthesis of bicyclic peroxide **120** by the peroxymercuration of non-conjugated cyclic dienes **119** (Scheme 42) [134]. Organo-mercury trifluoroacetates were separated by dissolving their mixture in benzene. The peroxide **120** did not dissolve in benzene and precipitated as white crystals. Reductive demercuration of **120** proceeded under mild conditions with the formation of bridged 1,2-dioxepane **124**. Bromination of peroxide **120** followed by demercuration led to dibromocycloperoxide **123**.



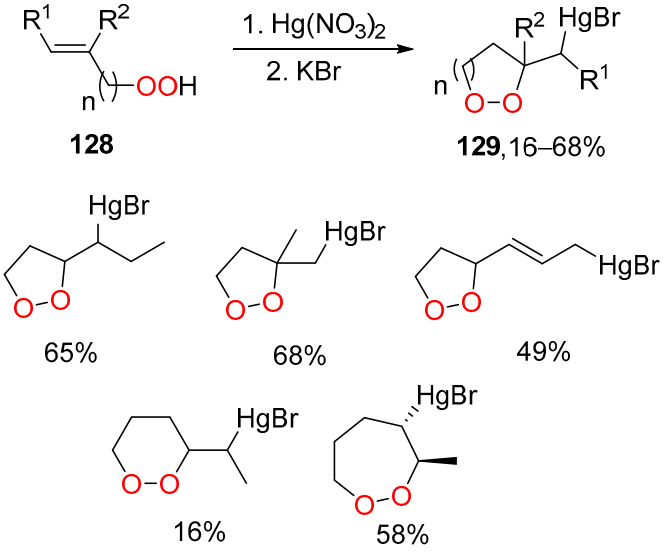
Scheme 42. Synthesis of bicyclic peroxides **120**, **123** and **124**.

The peroxymercuration and demercuration of 1,4-cyclooctadiene **125** proceeded in a similar way with the formation of peroxides **126** and **127** (Scheme 43). Peroxides **126** and **127** were obtained in 38% and 28% yield respectively [135].



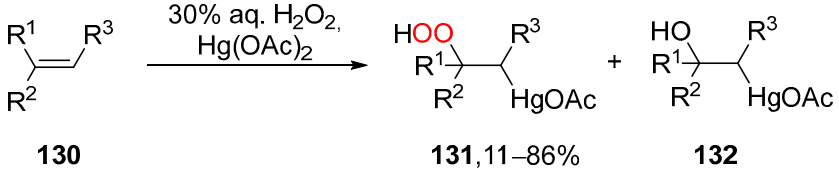
Scheme 43. Synthesis of bicyclic peroxides **126** and **127**.

Hydroperoxides **128** in the presence of mercury (II) nitrate undergo intramolecular cyclization with the formation of cyclic peroxides **129** in a yield of 16 to 68%. (Scheme 44) [136].



Scheme 44. Synthesis of cyclic peroxides **129**.

Hydroperoxymercuration of alkenes **130** with the use of aq. H_2O_2 proceeds with the formation of hydroperoxide **131** and alcohol **132**. The resulting peroxides **131** were obtained in yield up to 86% (Scheme 45) [137,138].

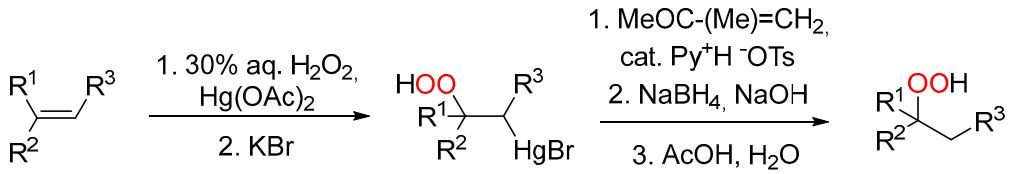


130 **131**,11–86% **132**

R^1 = H, Me, Et; R^2 = H, Me, ^{n}Pr, Et;
R^3 = H, ^{n}Bu, Ph, 4-MeC_6H_5, Et;
$R^1 = R^3$ = –$(CH_2)_3$–, –$(CH_2)_4$–;

Scheme 45. Synthesis of hydroperoxide **131**.

Direct demercuration of peroxides **134** is not possible because the hydroperoxide group is reduced under the action of sodium borohydride. However, the subsequent protection of hydroperoxy group by 2-methoxypropene, borohydride reduction, and deprotection of peroxy group led to peroxides **135** in 30–54% yield (Scheme 46) [138].

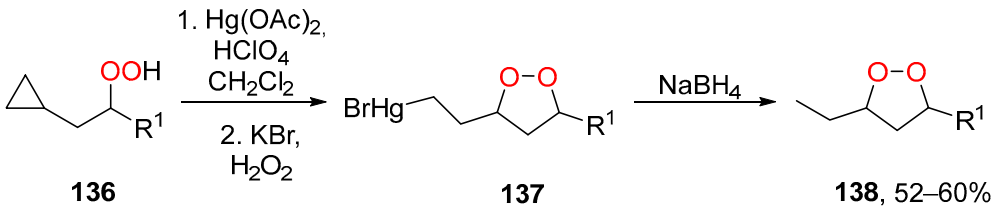


133 **134** **135**, 30–54%

R^1 = H, ^{n}Bu, 2-MeC_6H_5, 4-$MeOC_6H_5$, 4-MeC_6H_5; R^2 = H, Me; R^3 = H;
$R^2 = R^3$ = –$(CH_2)_4$–, –$(CH_2)_3CHCH_3$–

Scheme 46. Synthesis of hydroperoxides **134** and **135**.

Hydroperoxycyclopropanes **136** under the action of $Hg(OAc)_2$ in the presence of perchloric acid were transformed into 1,2-dioxolanes **137**, the bromodemercuration of which led to 1,2-dioxolanes **138** (Scheme 47) [139]. Cyclic peroxides were isolated by column chromatography on SiO_2 at 0 °C. The target peroxides **138** were obtained in 52–60% yield.

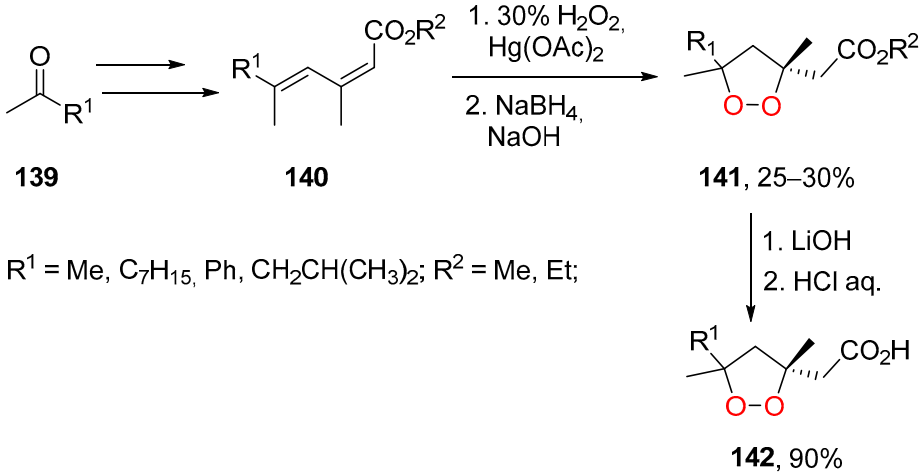


136 **137** **138**, 52–60%

R = Me, Et, ^{i}Pr, *c*-Hex

Scheme 47. Synthesis of 1,2-dioxolane **138**.

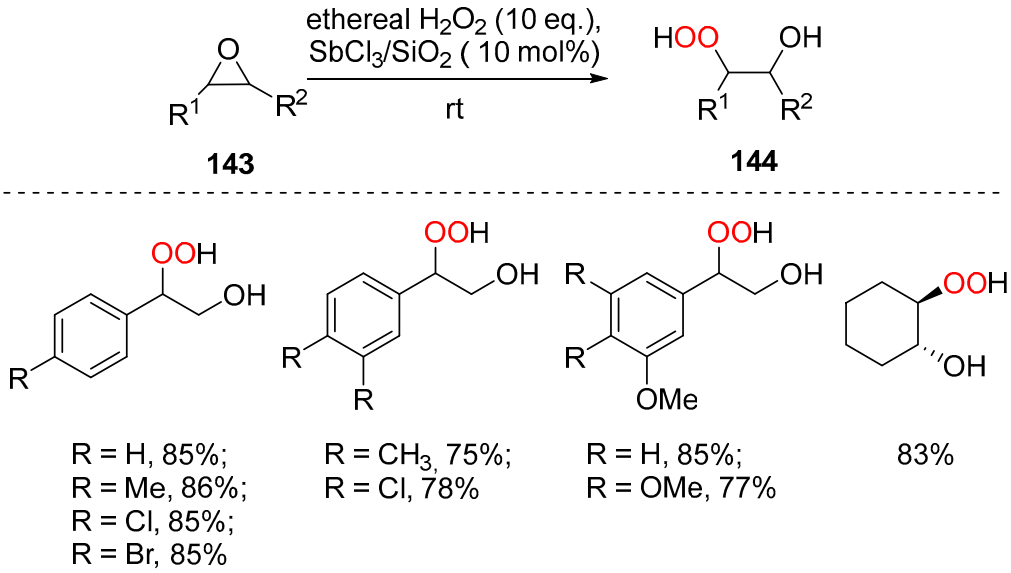
The first example of the synthesis of diastereomeric saturated analogs of plakinic acids A, C and D **142** was described in 1996 by Bloodworth A. J. and colleagues [140]. Peroxides **142** were obtained in four stages from ketones **139**. At one stage of this synthetic route, the peroxymercuration of esters **140** was used with the formation of 1,2-dioxolanes **141**. Saponification of which led to 1,2-dioxolanes **142** with a free carboxyl group (Scheme 48).



Scheme 48. Synthesis of plakinic acids **142**.

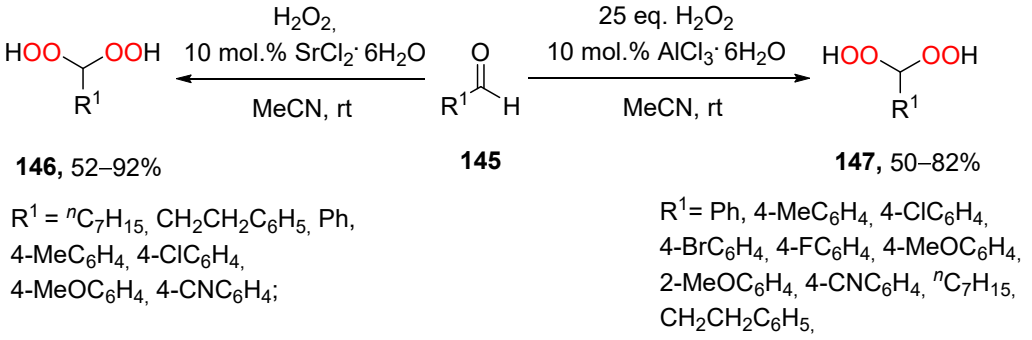
2.5. Other Metal-Based Lewis Acids

Zhang and Li reported the synthesis of β-hydroperoxy alcohols **144** by the reaction of epoxides **143** with H_2O_2, catalyzed by silica-supported antimony trichloride ($SbCl_3/SiO_2$) (Scheme 49) [141]. Interestingly, the authors demonstrated that $SbCl_3/SiO_2$ is more active than unsupported-$SbCl_3$. Under the best conditions, a range of β-hydroxy hydroperoxides **144** was obtained in 72–86% isolated yields.



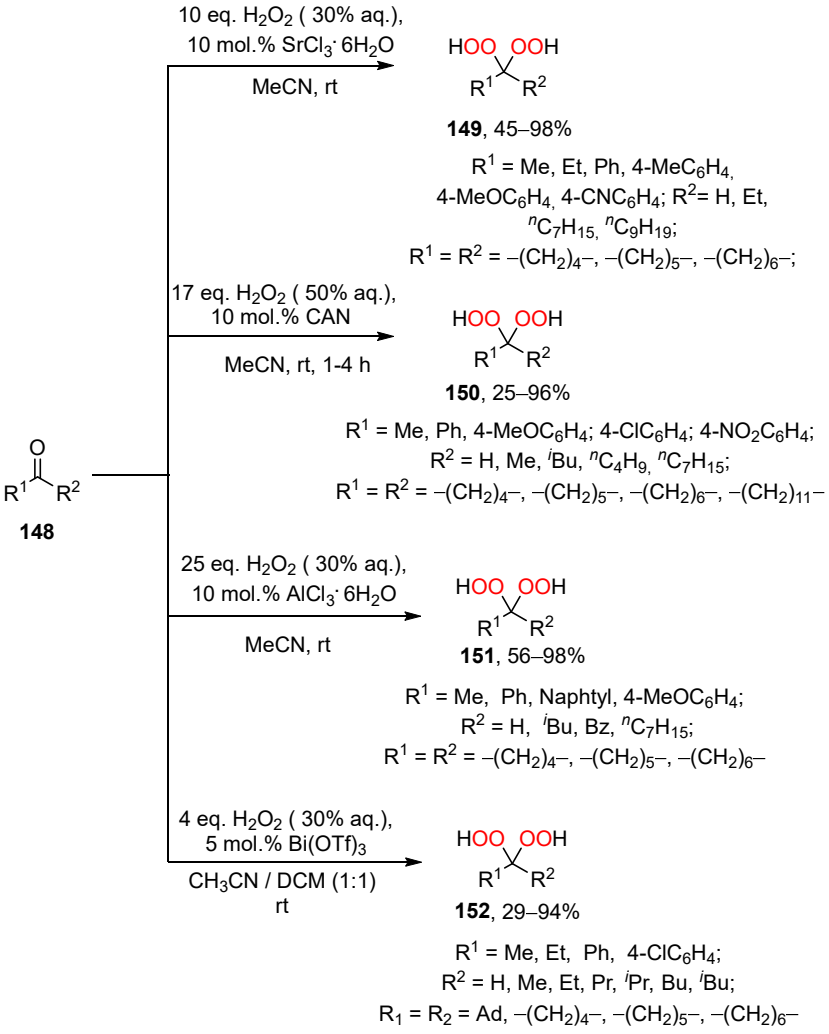
Scheme 49. Synthesis of β-hydroperoxy alcohols **144**.

Azarifar D. et.al. developed a method for the synthesis of geminal bishydroperoxides **146** from aldehydes **145** and hydrogen peroxide under the action of $AlCl_3 \cdot 6H_2O$ (Scheme 50) [114]. $SrCl_2 \cdot 6H_2O$ can also be used as a catalyst for the transformation of aldehydes **145** to the corresponding geminal bishydroperoxides **147**. Both catalysts allow the synthesis of target peroxides **146** and **147** under mild conditions at room temperature in good yields (Scheme 50) [142].



Scheme 50. Synthesis of geminal bishydroperoxides **146** and **147** from aldehydes **145**.

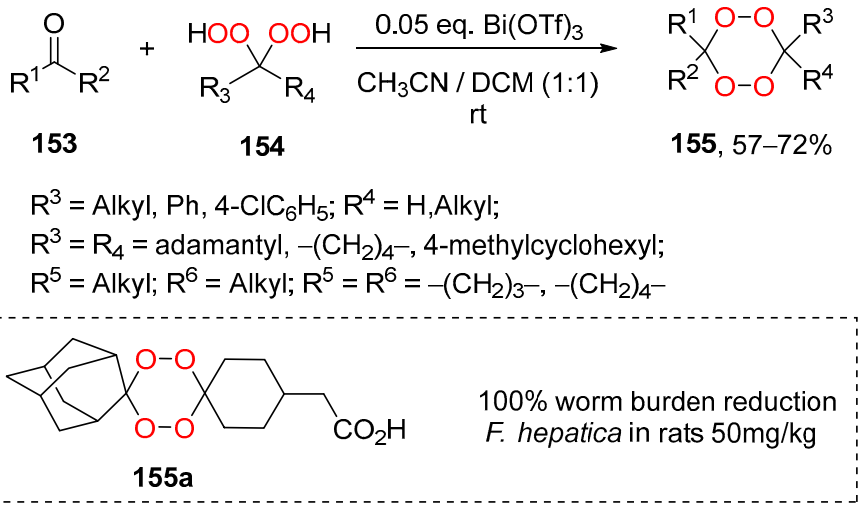
Lewis acids such as $SrCl_3 \cdot 6H_2O$ [142], cerium ammonium nitrate (CAN) [143], $Bi(OTf)_3$ [144], and $AlCl_3 \cdot 6H_2O$ [114] are effective catalysts for the synthesis of bishydroperoxides **149**–**152** from cyclic and acyclic ketones and aldehydes **148**. Peroxidation proceeds under mild conditions at room temperature with the formation of target peroxides in a good yield. All Lewis acids demonstrated approximately equal efficiency in the peroxidation reaction. The main advantage of these methods is the use of Lewis acids in catalytic amounts and an inexpensive 30% aqueous H_2O_2 (Scheme 51).



Scheme 51. Synthesis of geminal bishydroperoxides **149**–**152**.

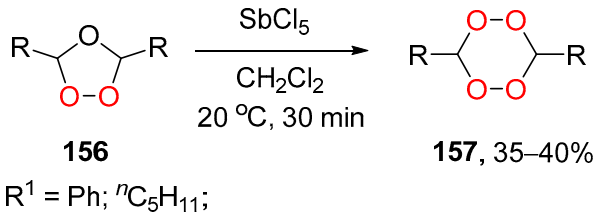
Also, bismuth (III) triflate is a good catalyst for the synthesis of 1,2,4,5-tetraoxanes **155**. In this case, the target peroxides **152** were obtained in a yield up to 94%. Synthetic

1,2,4,5-tetraoxane **155a** exhibits high activity against helminths *Fasciola hepatica* and in rats in vivo (Scheme 52) [144,145].



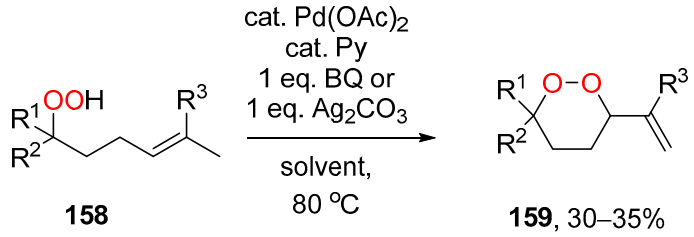
Scheme 52. Synthesis of 1,2,4,5-tetraoxanes **155**.

The interaction of 1,2,4-trioxolanes (ozonides) **156** with Lewis acid $SbCl_5$ in methylene chloride led to 1,2,4,5-tetraoxanes **157** (Scheme 53) [146].



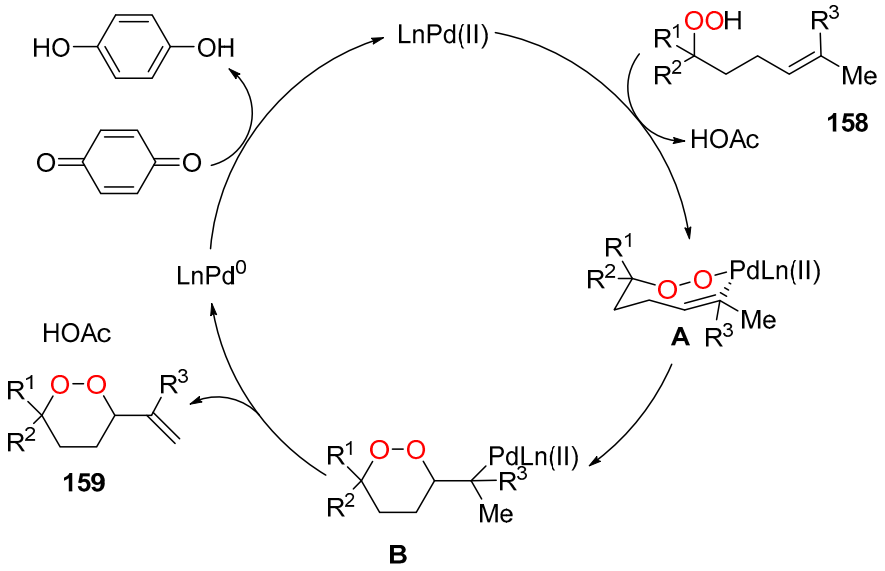
Scheme 53. Synthesis of 1,2,4,5-tetraoxanes **157** from 1,2,4-trioxolanes **156**.

The palladium-catalyzed cyclization of unsaturated hydroperoxides **158** afforded with the formation of 1,2-dioxanes **159** (Scheme 54) [147]. The reaction was carried out in toluene, 1,4-dioxane, or 1,2-dichloroethane at 80 °C for 3h. To oxidize Pd(0), which is formed in the catalytic cycle, *p*-benzoquinone (BQ) or silver carbonate were used.



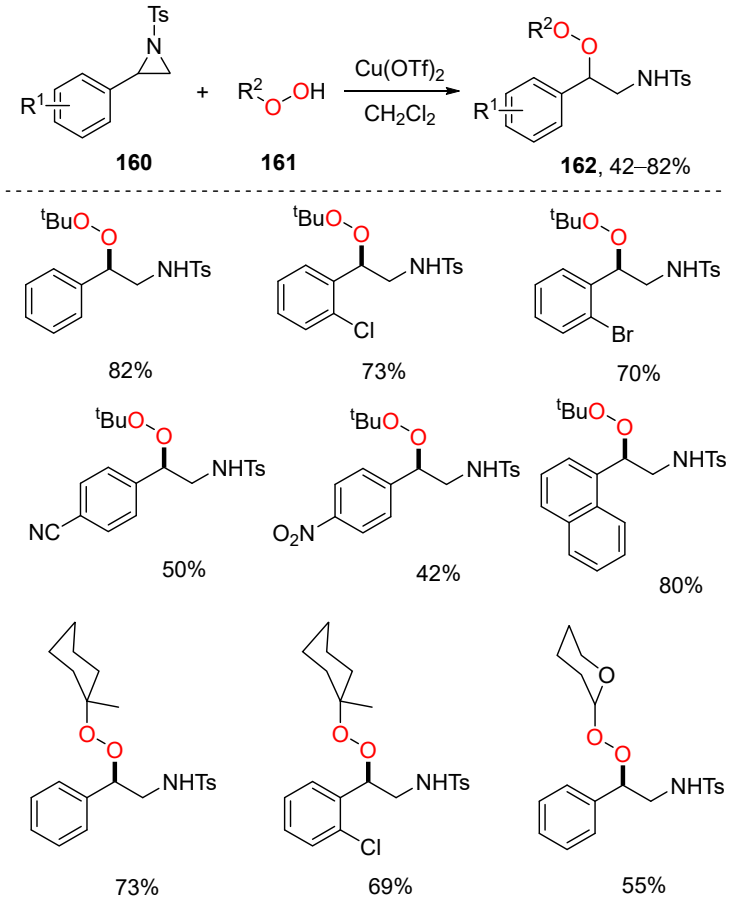
Scheme 54. Synthesis of 1,2-dioxanes **159**.

Presumably, the reaction proceeds according to the characteristic Pd-catalyzed cycle, which is demonstrated in Scheme 55. Pd (II) is coordinated both with the double bond and the peroxide group to form cyclic intermediate **A**, which is further rearranged into endoperoxide **B**. Then endoperoxide **B** is converted to the target product **159**.



Scheme 55. Synthesis of 1,2-Dioxanes **159** from hydroperoxides **158**.

Such a Lewis acid as $Cu(OTf)_2$ turned out to be the most effective catalyst for the synthesis of peroxides **162** by the ring opening reaction of activated aziridines **160** under the action of various hydroperoxides **161**. It was found that electron-neutral or halogenated substrates **160** provide better results in comparison with substrates containing electron-withdrawing substituents in an aromatic ring (Scheme 56) [126].



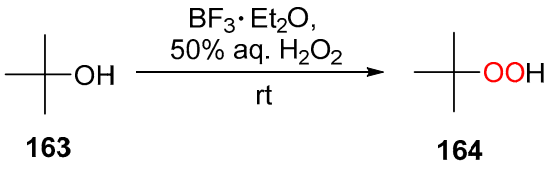
Scheme 56. Synthesis of peroxides **162** from substituted aziridines **160**.

3. Non-Metal-Based Lewis Acids in the Synthesis of Organic Peroxides

There is great interest in Lewis acids based on non-metals. Their use as a catalyst or reagent made it possible to discover new classes of peroxides of various structures. This section contains data on the synthesis of 1-hydroperoxy-1′-alkoxyperoxides, β-hydroperoxy-β-peroxylactones, 1,2-dioxanes, 1,2,4-trioxepanes, 1,2,4-trioxocanes, 1,2,4-trioxonanes and 1,2,4,5,7,8-hexaoxananes.

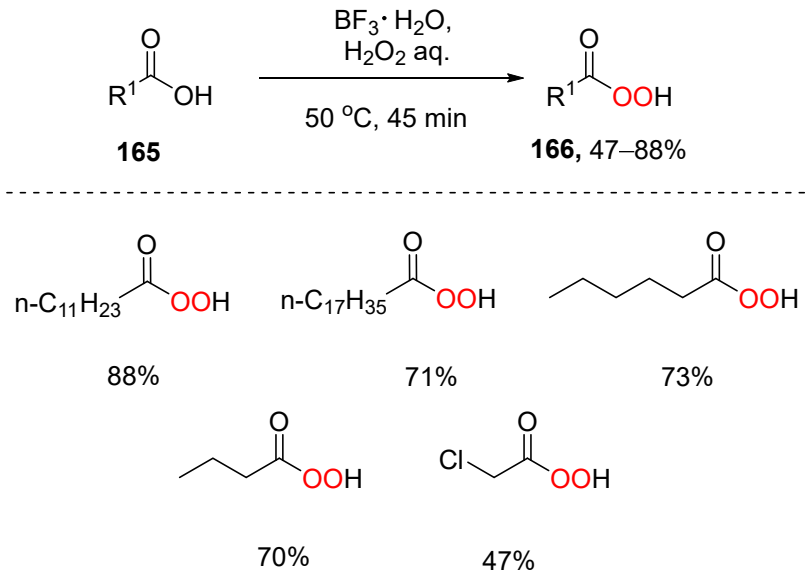
3.1. Application of BF_3·Et_2O in the Synthesis of Organic Peroxides

The first mentions of the formation of peroxides under the action of boron trifluoride goes back to the 1950s. A US patent 2,630,456 [148] from 1953 describes a selective method for producing *tert*-butyl hydroperoxide **164** from the corresponding alcohol **163** [149]. The reaction was carried out at room temperature using an equimolar amount of a 50% aqueous solution of hydrogen peroxide with 0.3 eq. of boron trifluoride etherate (Scheme 57). Since BF_3 can form BF_3·H_2O complex [150–155], this makes it possible to use BF_3·Et_2O in the presence of water.



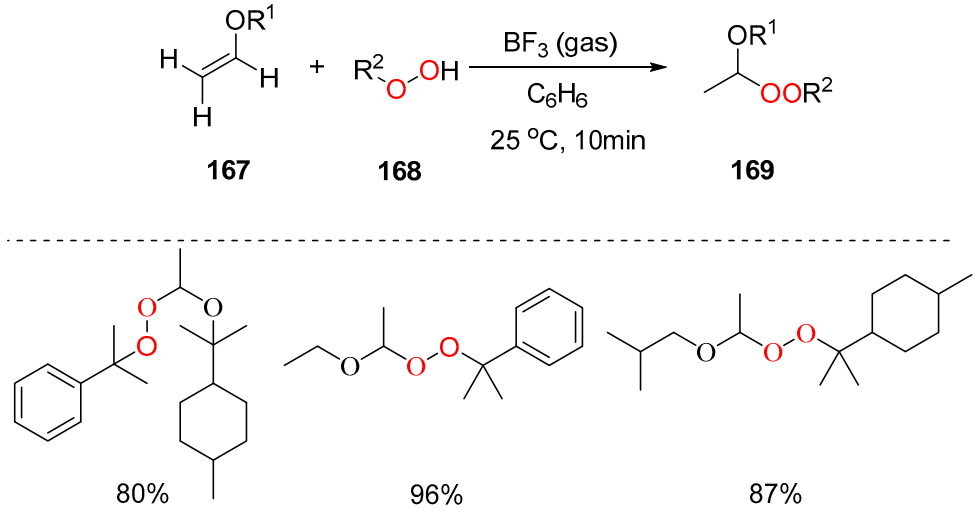
Scheme 57. Synthesis of *tert*-butyl hydroperoxide **164**.

In 1956, a method was developed for the synthesis of peroxy acids **166** with the use of boron trifluoride [156]. The synthesis was based on the interaction of a 90% aq. solution of hydrogen peroxide with carboxylic acids **166** in the presence of boron trifluoride monohydrate. The reaction was carried out for 45 min at 50 °C (Scheme 58). This approach was used for the synthesis of butyric, nylon and α-chloroacetic peroxy acids.



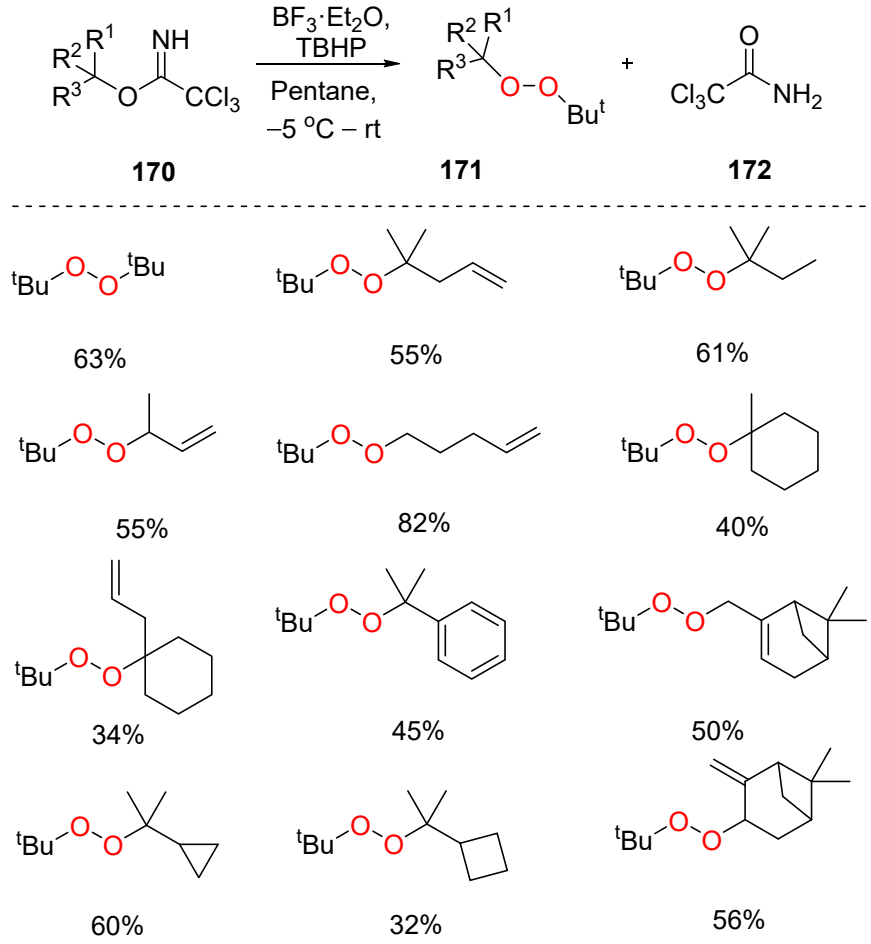
Scheme 58. Synthesis of peroxy acids **166**.

The reaction of vinyl esters **167** and hydroperoxides **168** in the presence of gaseous boron trifluoride leads to the formation of monoperoxyketals **169**. The reaction was carried out in benzene or hexane at temperatures from 0 to 30 °C (Scheme 59) [157]. The reaction proceeds within 5–10 min with a yield of 80–96%. This method is the first way to obtain monoperoxyacetals in high yields.



Scheme 59. Synthesis of peroxyacetals **169** from vinyl esters **167**.

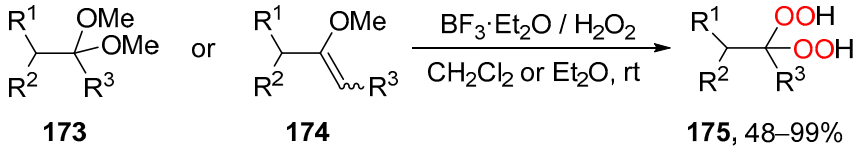
The synthesis of alkyl peroxides **171** was carried out by the reaction of tertiary alkyltrichloroacetimides **170** with *tert*-butyl hydroperoxide in the presence of boron trifluoride etherate (Scheme 60) [158].



Scheme 60. Synthesis of alkyl peroxides **171**.

A wide range of bishydroperoxides **175** was obtained from acetals **173**, enol ethers **174** and hydrogen peroxide in the presence of boron trifluoride etherate (Scheme 61) [159,160]. The developed method allows one to obtain peroxides of various structures. The advantages

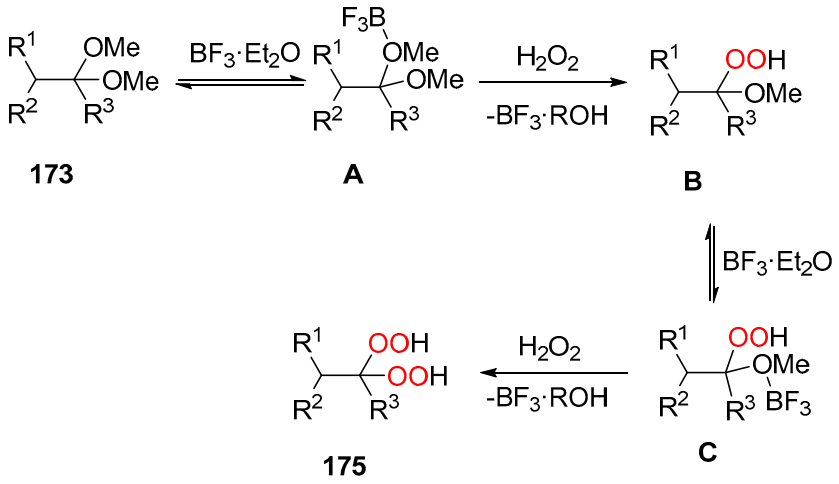
of these reactions are the rapidity and ease of its implementation, and among the disadvantages can be noted the formation of by-products, as well as the impossibility of synthesizing bishydroperoxides from acetals or enol ethers obtained from aryl-substituted ketones.



R^1 = H, Alky, R^2 = Alkyl; $R^2 = R^3$ = Ad, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_{10}-$

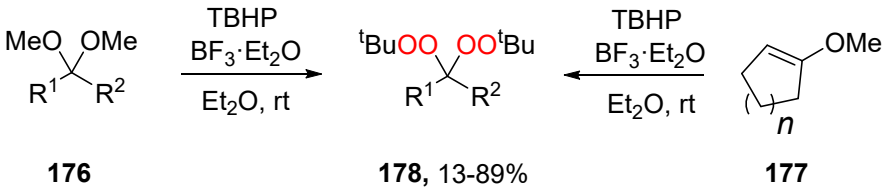
Scheme 61. Synthesis of bishydroperoxides **175**.

Presumably, the reaction proceeds according to the following mechanism: $BF_3 \cdot Et_2O$ and $BF_3 \cdot MeOH$ equally catalyze the reaction, forming intermediate complexes **A** and **B**, which then interact with hydrogen peroxide with the formation of bishydroperoxide **175** (Scheme 62).



Scheme 62. Mechanism of acetal peroxidation **173**.

The possibility to obtain geminal bis(*tert*-butyl)peroxides **178** of both cyclic and acyclic structures with a yield of 13% to 89%, respectively, was described from acetals **176** and enol ethers **177** (Scheme 63) [161]. The reaction of the enol esters **177** with *tert*-butyl hydroperoxide, catalyzed by boron trifluoride etherate, is a general approach for the preparation of geminal bishydroperoxides.

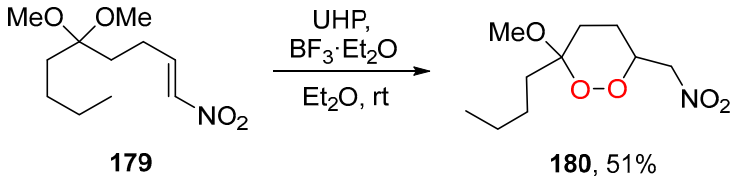


n = 2, 3; R^1 = Alkyl; R^2 = H, Alkyl;

Scheme 63. Synthesis of germinal bis(*tert*-butyl) peroxides **178**.

1,2-Dioxane **180** was obtained by the reaction of the corresponding acetal **179** with urea hydrogen peroxide, catalyzed by boron trifluoride etherate (Scheme 64) [162]. Under these conditions, only one of the two methoxyl groups is exchanged for the hydroperoxide one, and the intermediate hydroperoxyketal undergoes intramolecular cyclization (according to

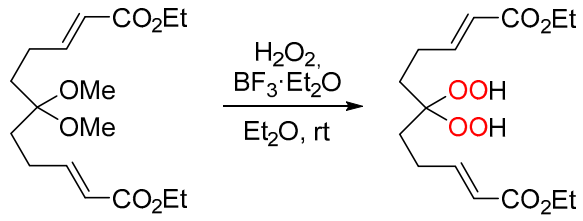
Michael) due to the attack of the hydroperoxide group on the double bond activated by the nitro group with the formation of 1,2-dioxane in 51% yield.



179 **180**, 51%

Scheme 64. Synthesis of 1,2-dioxane **180**.

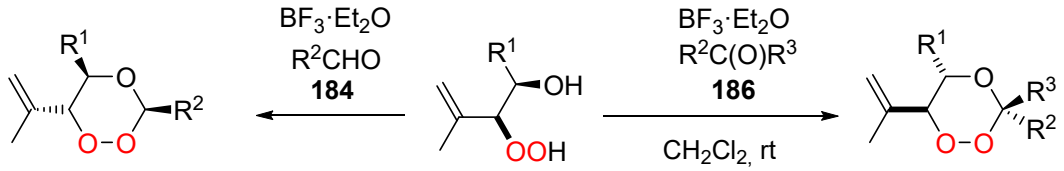
However, when NO_2 was replaced by C(O)OEt, the reaction proceeded with the formation of bisperoxide **182** (Scheme 65) [163]. This is probably due to the fact that the ester group has lower electron-withdrawing properties.



181 **182**, 45%

Scheme 65. Synthesis of bishydroperoxide **182**.

An efficient and stereoselective method for the synthesis of 1,2,4-trioxanes **185** and **187** has been reported by J.L. Vennerstrom (Scheme 66). Such peroxides were obtained by the interaction of α-hydroxyperoxides **183** with aldehydes **184** and ketones **186** [52,164–167]. The resulting cyclic peroxides were tested in vitro for antimalarial activity against *P. falciparum*. 1,2,4-Trioxanes **187** containing an adamantane substituent in their composition exhibit high antimalarial activity.



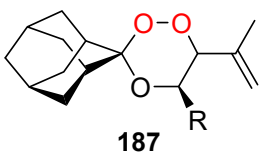
185, 24–78%

R^1 = Me, Et, ^{n}Pr, Cyclopropyl,
R^2 = Napthyl

183

187, 12–70%

R_1 = Alkyl, Cyclopropyl;
R_2 = H; R_3 = Alkyl, Ph, 2-ClC_6H_4;
R_2 = R_3 = Adamantyl, $–(CH_2)_4–$, $–(CH_2)_5–$



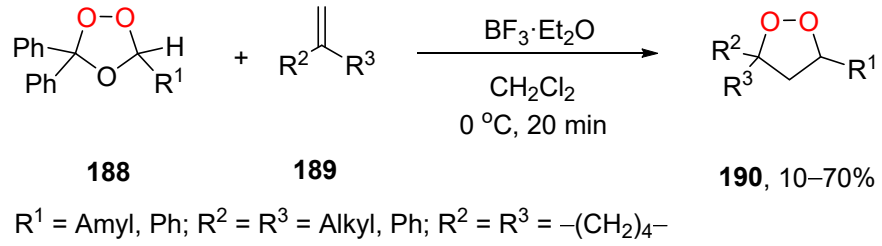
187

R = Me, ^{i}Pr, ^{n}Pr, cyclopropyl;

	EC_{50} *Pf* K1, nM
Artemisinin	2,8
Me	4,9
^{n}Pr	1,8
cyclopropyl	1,9
^{i}Pr	4,8

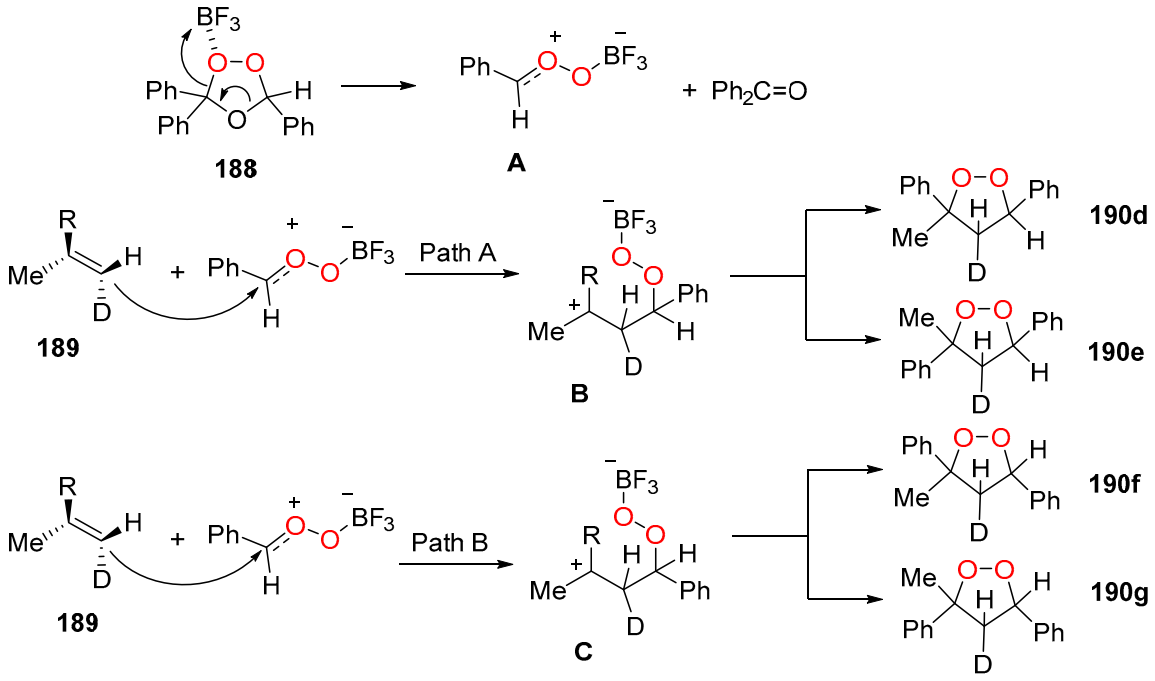
Scheme 66. Synthesis of 1,2,4-trioxanes **185** and **187**.

An unusual method for the synthesis of 1,2-dioxolanes **190** was developed, which is based on the reaction of ozonides **188** with olefins **189** in the presence of boron trifluoride etherate with a yield of 10% to 70% (Scheme 67) [168].



Scheme 67. Synthesis of 1,2-dioxolanes **190**.

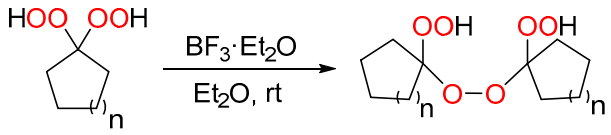
Presumably, the reaction proceeds along the following route: the first stage of the reaction involves the opening of the ozonide cycle in **188** under the action of $BF_3 \cdot Et_2O$ with the formation of a BF_3-coordinated intermediate **A**, containing a peroxide fragment. The attack of intermediate **A** at the alkene **189** is accompanied by the formation of two intermediates, **B** and **C**, which, in turn, leads to ring closure and gives 1,2-dioxolane. However, the rate of ring closure is much slower than the rotation of the C-C bond, so the formation of four isomeric products occurs. The mechanism in Scheme 68 illustrates that the ratio of (**190d** + **190e**) to (**190f** + **190g**) corresponds to the ratio of the two approaches of BF_3-coordinated intermediate **A** to alkene.



Scheme 68. The proposed mechanism of 1,2-dioxolanes **190** formation.

$BF_3 \cdot Et_2O$ is an efficient catalyst for the synthesis of 1,1′-bishydroperoxy-(cycloalkyl) peroxides **192** from geminal bisperoxides **191** in yields of up to 86% (Scheme 69) [89].

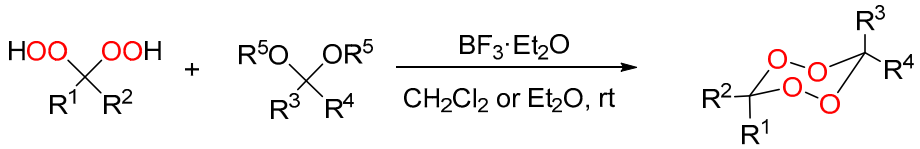
Terent'ev et al. developed a method for the synthesis of 1,2,4,5-tetraoxanes **195** from bishydroperoxides **193** and acetals **194** (Scheme 70) [169]. The reaction was carried out under mild conditions at room temperature using 0.3–0.4 eq. $BF_3 \cdot Et_2O$. This method is general to the synthesis of unsymmetrical tetraoxanes from readily available carbonyl compounds.



191 **192**, 36 – 86%

n = 2, 6, 7, 8, 9

Scheme 69. Synthesis of 1,1′-bishydroperoxy(cycloalkyl)peroxide **192**.

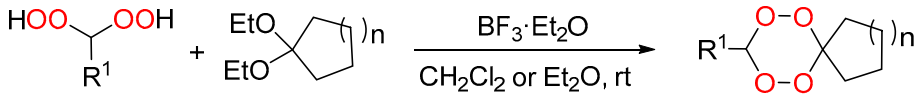


193 **194** **195**, 13–90%

$R^1 = R^2$ = Ad, $–(CH_2)_4–$, $–(CH_2)_5–$, $–(CH_2)_6–$, $–(CH_2)_{11}–$; R^3 = Alkyl, Ph;
R^4 = H, Alkyl; $R^3 = R^4$ = Ad, $–(CH_2)_4–$, $–(CH_2)_5–$, $–(CH_2)_6–$, $–(CH_2)_{11}–$;
R^5 = Me, Et;

Scheme 70. Synthesis of 1,2,4,5-tetraoxanes **195**.

Unsymmetrical tetaraoxanes **198** can be obtained from geminal bisperoxides **196** and cyclic acetals **197** in the presence of boron trifluoride etherate (Scheme 71) [170]. This method for the synthesis of 1,2,4,5-tetraoxanes is a convenient and simple approach to the synthesis of both symmetric and asymmetrical 1,2,4,5-tetraoxanes.

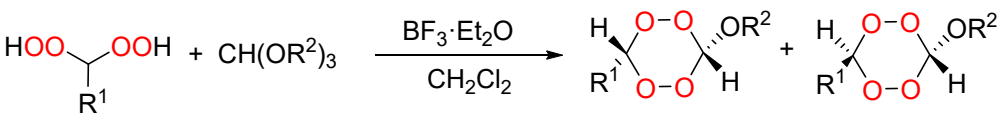


196 **197** **198**, 33–50%

n = 1, 2; R = Et, ^{n}Pr, ^{i}Pr;

Scheme 71. Synthesis of asymmetrical 1,2,4,5-tetraoxanes **198**.

Also, boron trifluoride etherate is efficient for the synthesis of 1,2,4,5-tetraoxanes **201** from gem-bisperoxides **199** and orthoformates **200** (Scheme 72) [170]. The *trans*-isomer **201** was the major product in all cases as determined by NMR, while the *cis*-isomer was found only in trace amounts. The reaction was carried out in dichloromethane at room temperature. This approach was the first method for the preparation of tetraoxanes ***cis*-201** and ***trans*-201** with an alkoxy substituent.



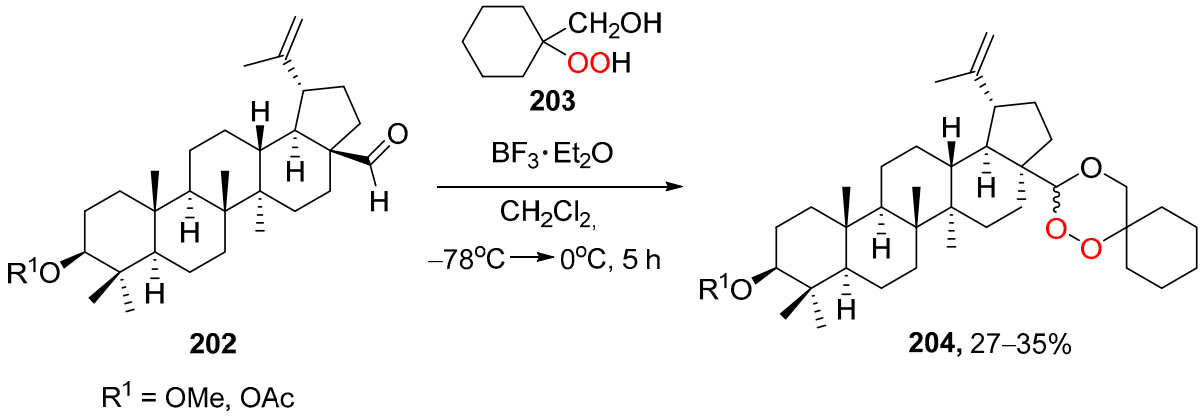
199 **200** ***cis*-201** ***trans*-201**

R^1 = Et, ^{n}Pr, ^{i}Pr, ^{t}Bu, Ph, 2-naphthyl; R^2 = Me, Et;

Scheme 72. Synthesis of 1,2,4,5-tetraoxanes ***cis*-201** and ***trans*-201**.

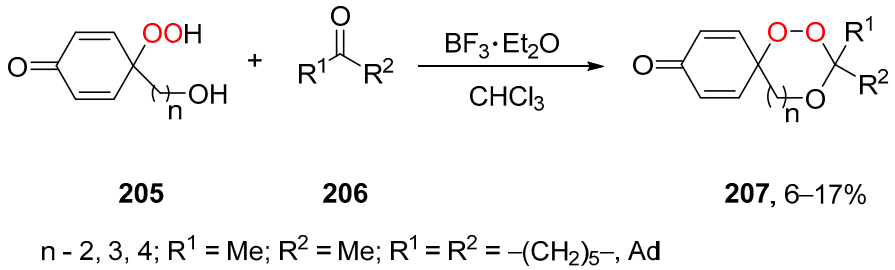
In the study on the synthesis of pharmacologically important endoperoxides, peroxide **204** was synthesized from substituted aldehydes **202**; boron trifluoride etherate was used as a catalyst in this reaction. Condensation of peroxide **203** with betulin aldehydes **202**

in the presence of $BF_3 \cdot Et_2O$ led to the assembly of peroxides **204**. The yield of the target peroxide was low, and the resulting diastereoisomers could not be separated. Unfortunately, mixtures of isomers did not show significant anticancer activity (Scheme 73) [171].



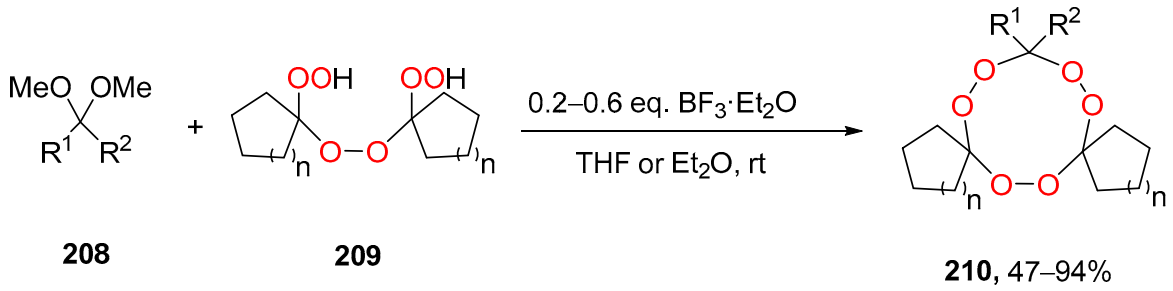
Scheme 73. Synthesis of 1,2,4-trioxanes **204** from aldehydes **202**.

Cyclic peroxides **207** can be obtained from hydroperoxides **205** and ketones **206** in the presence of boron trifluoride etherate in up to 17% yield (Scheme 74) [130]. The yield of the target peroxides **207** was in the same range as when using $In(OTf)_3$ as a catalyst (see Scheme 33). However, $BF_3 \cdot Et_2O$ is less expensive than $In(OTf)_3$.



Scheme 74. Synthesis of macrocyclic peroxides **207**.

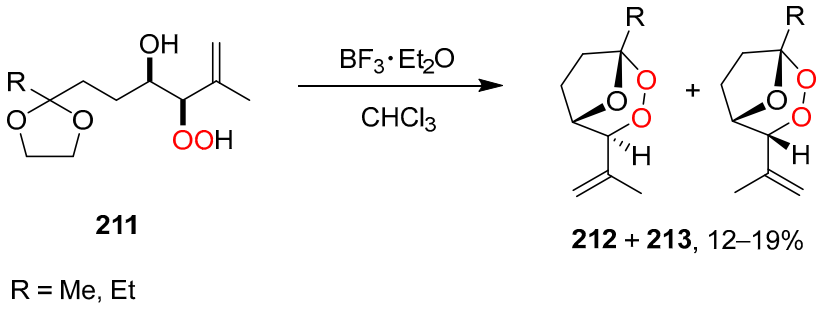
The reaction of 1,1′-bishydroperoxy(cycloalkyl)peroxides **209** with ketals **208** in the presence of $BF_3 \cdot Et_2O$ afforded 1,2,4,5,7,8-hexaoxonanes **210** in up to 94% yields (Scheme 75) [172]. This approach is convenient and simple for the synthesis of 1,2,4,5,7,8-hexaoxonanes, which significantly expands the structural diversity of these compounds and, in most cases, allows them to be synthesized in high yield.



Scheme 75. Synthesis of 1,2,4,5,7,8-hexaoxonanes **210**.

The assembly of bridged 1,2,4-trioxanes **212** and **213** can be accomplished by intramolecular cyclization of peroxyacetals **211** with simultaneous removal of the acetal

protecting group. Cyclic peroxides were obtained in a yield of 12% to 19% (Scheme 76) [173].



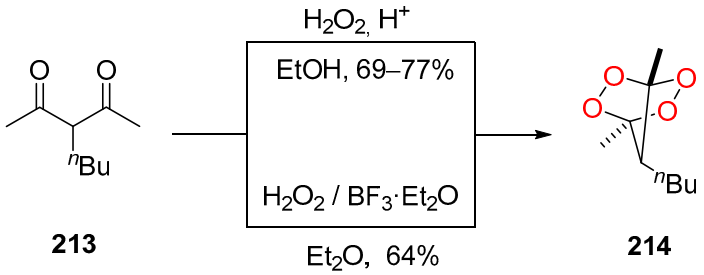
211

212 + **213**, 12–19%

R = Me, Et

Scheme 76. Synthesis of bridged 1,2,4-trioxanes **212** and **213**.

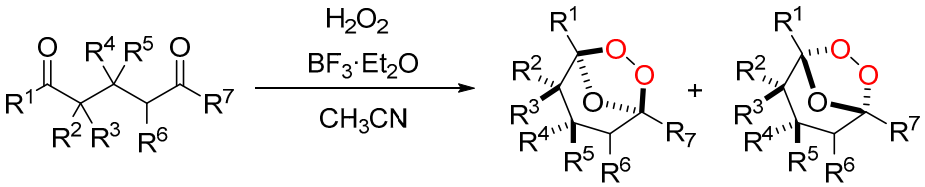
A convenient, experimentally simple and selective method was developed for the synthesis of bridged 1,2,4,5-tetraoxanes based on the reaction of hydrogen peroxide with β-diketone **213** catalyzed by strong acids (H_2SO_4, $HClO_4$, HBF_4) with a yield of 49–77% (Scheme 77) [37,76]. This process can also proceed with the use of Lewis acid ($BF_3 \cdot Et_2O$). For example, tetraoxane **214** was obtained in 64% yield [76].



213 **214**

Scheme 77. Synthesis of bridged 1,2,4,5-tetraoxane **214**.

The method for the synthesis of ozonides **216** and **217** from 1,5-diketones **215** and hydrogen peroxide, which does not require the use of toxic ozone, was reported (Scheme 78) [84,174]. It was found that the interaction of 1,5-diketones **215** with H_2O_2, in the presence of $BF_3 \cdot Et_2O$ leads to the selective assembly of stereoisomeric ozonides **216** and **217**. Peroxides **216** and **217** exhibit antimalarial [175] and anticancer [175,176] activity.



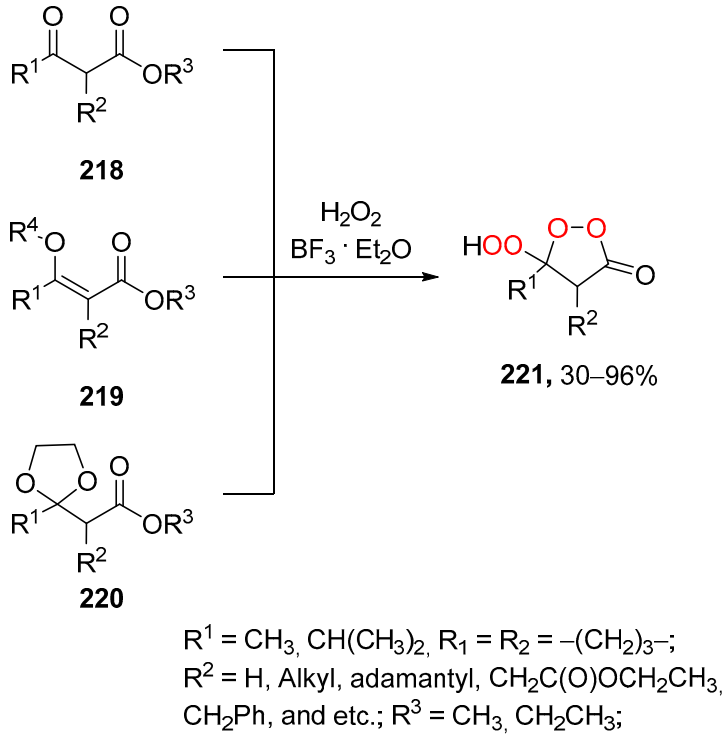
215

216+217, 23–91%

$R^1 = R^7 = CH_3$; R^1 - $R^2 = R^6$ - $R^7 = -(CH_2)_4-$; R^2 = C(O)OEt, C(O)OBu^t;
R^3 = H, Alkyl, Allyl, 4-$BrC_2H_4CH_2$, 4-$CH_3C_2H_4CH_2$, and etc.; R^4 = H;
R^5 = H; R^6 = H;

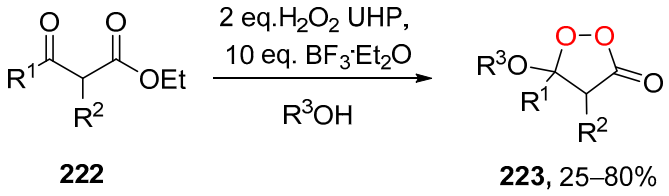
Scheme 78. Synthesis of diastereomeric ozonides **216** and **217** from 1,5-diketones **215**.

Recently a new class of peroxides, namely β-hydroperoxy-β-peroxylactones **221,** was discovered. They were obtained by the peroxidation of β-ketoesters **218** and their derivatives **219** and **220** (silylenol ethers, alkylene ethers, enol acetates, cyclic acetals) with the $H_2O_2/BF_3 \cdot Et_2O$ system. The reaction proceeded with the formation of β-hydroperoxy-β-peroxylactones in a yield of 30–96% (Scheme 79) [85,177]. These β-peroxylactones are stable and can be useful for further synthetic transformations.



Scheme 79. Synthesis of β-hydroperoxy-β-peroxylactones **221**.

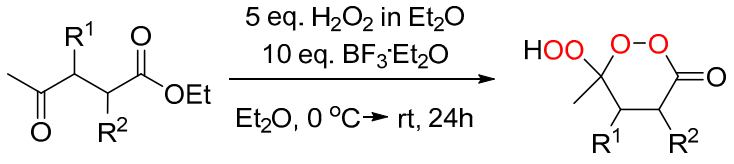
The three-component cyclization/condensation of β-ketoesters **222**, H_2O_2 UHP, and alcohols proceeded with the formation of β-alkoxy-β-peroxylactoctones **223** in 25–80% yield (Scheme 80) [178].



Scheme 80. Synthesis of β-alkoxy-β-peroxylactones **223**.

In continuation of studies in this direction, the $BF_3 \cdot Et_2O/H_2O_2$ system was applied to the γ-ketoesters **224**. Peroxidation proceeded with the formation of cyclic γ-hydroperoxy-γ-peroxylactones **225** in 44–83% yields (Scheme 81) [179].

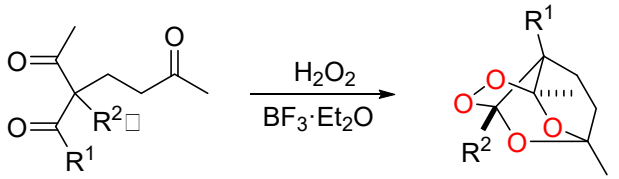
Tricyclic monoperoxides **227** were obtained by the peroxidation of β,δ′-triketones **226** with the $H_2O_2/BF_3 \cdot Et_2O$ system (Scheme 82) [81,86]. Peroxidation was carried out under mild conditions at room temperature for 1 h. Despite the presence of three carbonyl groups, peroxidation proceeded selectively with the formation of cyclic product **227**. The yield of target peroxides **227** was 48–93%. It was found that the tricyclic monoperoxide exhibits a high in vitro and in vivo anthelmintic activity against *S. mansoni*.



224 **225**, 44–83%

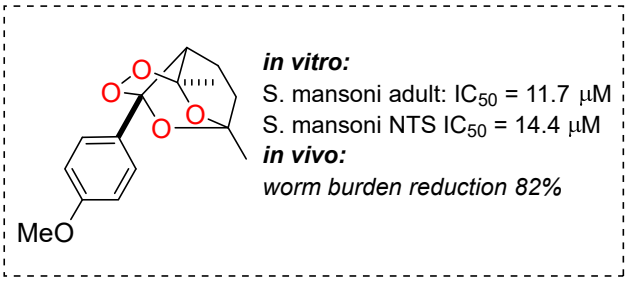
R^1 = H, alkyl, Bn, 2-$ClC_6H_4CH_2$, 3-$CH_3C_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 4-$NO_2C_6H_4CH_2$, 4-$CH_3C_6H_4CH_2$; R^2 = H, alkyl

Scheme 81. Synthesis of γ-alkoxy-γ-peroxylactones **225**.



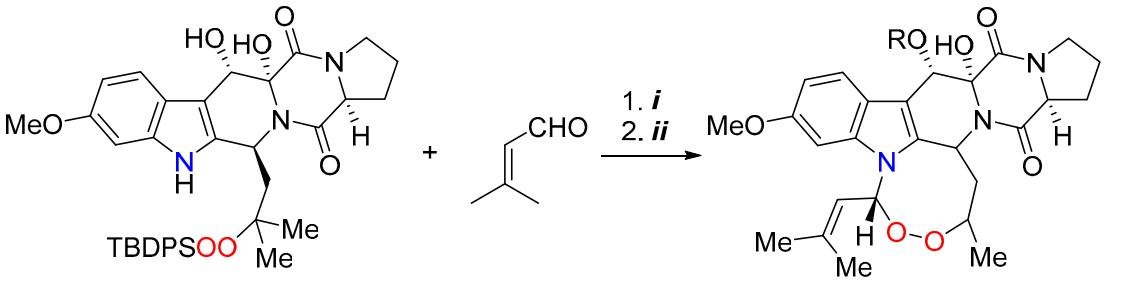
226 **227,** 48–93%

R^1 = H, Bu, CH_2CH_2CN, CH_2CH_2COOEt, CH_2Ph, 4-$MeC_6H_4CH_2$, 4-MeC_6H_4 and etc. R^2 = Me, Ph



Scheme 82. Synthesis and anthelmintic activity of tricyclic monoperoxides **227**.

The first total synthesis of natural bioactive azaperoxides Verruculogen **230a** and Fumitremorgin A **230b** was developed in 2015 by the Baran group [180]. The final step included the catalyzed by $BF_3{\cdot}Et_2O$ condensation of aldehyde **229** with peroxide **228** (Scheme 83).



228 **229** **230**, 30% over 2 steps

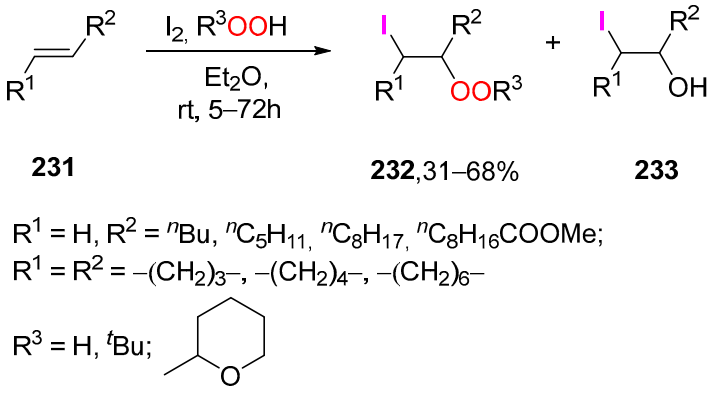
i: TBAF, THF, AcOH, 0 °C
ii: $BF_3 \cdot Et_2O$, DCE, –20°C
iii: prenyl bromide

230a Verruculogen; R = H
230b Fumitremorgin A; R = prenyl ***iii***

Scheme 83. Synthesis of natural Verruculogen **230a** and Fumitremorgin A **230b**.

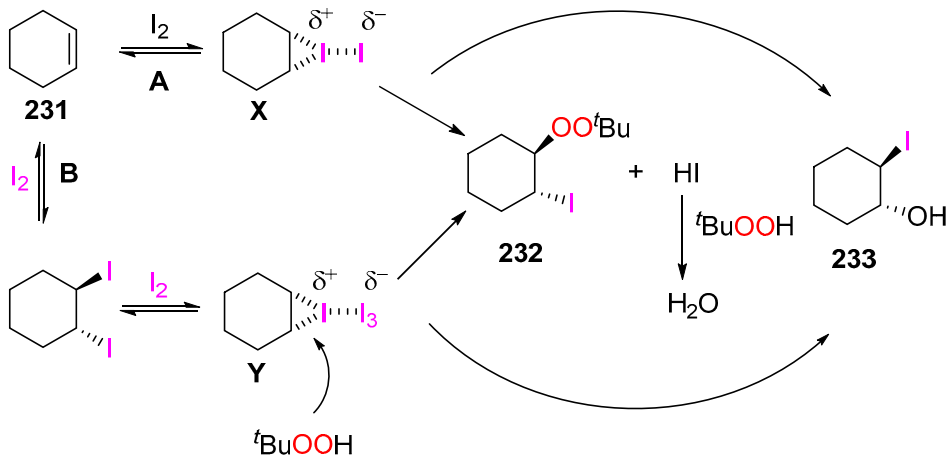
3.2. Iodine in the Synthesis of Organic Peroxides

Iodine in the synthesis of organic peroxides can act as both a catalyst and a reagent. The presence of iodine can activate substrates via halogen bonding (acts as Lewis acid), iodonium(I) species or formation of "hidden" HI Broensted acid [181–187]. The interaction of alkenes **231** with hydroperoxide in the presence of molecular iodine makes it possible to obtain vicinal iodoperoxyalkanes **232** (Scheme 84) [188]. This reaction was carried out with 0.7 eq. iodine and 4 eq. hydroperoxide in diethyl ether or dichloromethane at room temperature. Depending on the reactivity of the hydroperoxide, the reaction time was from 5 to 72 h.



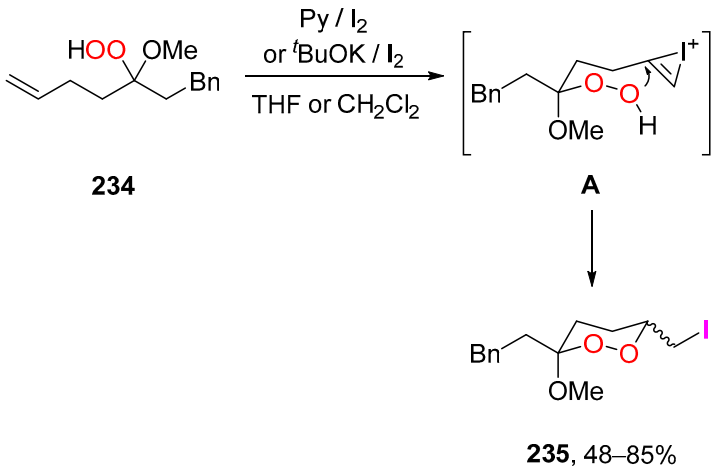
Scheme 84. Synthesis of vicinal iodoperoxyalkanes **232**.

The mechanism of the formation of iodoperoxyalkanes and iodoalkanols is shown in Scheme 85. Presumably, the formation of iodoperoxyalkane can proceed along path **A** or **B**. Path **A** corresponds to the classical scheme of sequential addition of electrophilic iodine and nucleophilic hydroperoxide to the double bond. Path **B** is based on experimental data according to which an increase in the amount of iodine (a nucleophile competing with *tert*-butyl hydroperoxide) leads to an increase in the yield of 1-(*tert*-butylperoxy)-2-iodocyclohexane, while the expected 1,2-diiodocyclohexane is formed in trace amounts. Iodoperoxide appears to be formed by pathway **B** through a previously unknown process. Initially, the reaction forms 1,2-diiodocyclohexane, which is converted by iodine to intermediate **Y**, which contains a partially positive charge on the carbon atoms. The latter reacts with hydroperoxide.



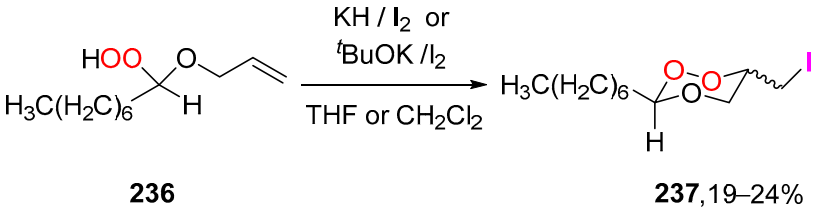
Scheme 85. The mechanism of formation of iodoperoxyalkanes **232** and iodohydroxyalkanes **233**.

The cyclization of unsaturated hydroperoxyacetal **234** was performed using systems such as pyridine/I_2 or *t*-BuOK/I_2. The use of the latter made it possible to obtain 1,2-dioxanes **235** in a yield up to 85% (Scheme 86) [189].



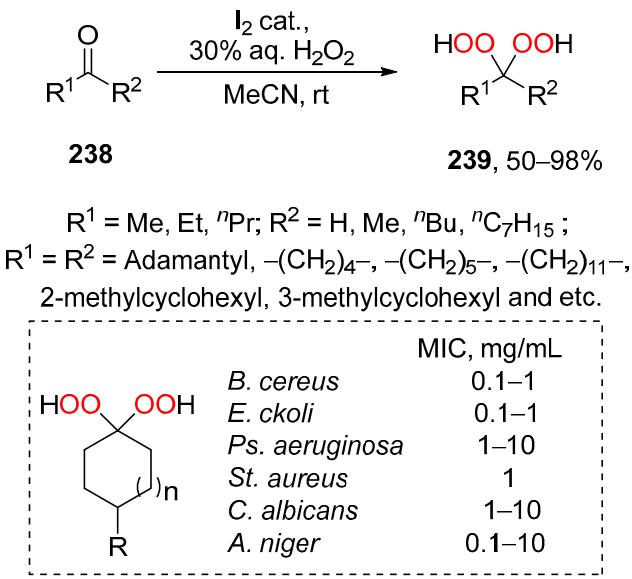
Scheme 86. Cyclization of unsaturated alkoxy hydroperoxide **234**.

However, the use of the pyridine/I_2 system for unsaturated hydroperoxyacetal **236** did not provide the assembly of 1,2,4-trioxane **237**. The *t*-BuOK/I_2 system, which performed well in the assembly of 1,2-dioxalane **235** (Scheme 87), led to peroxide **237**, but in low yield. Cyclization **236** under the action of the KH/I_2 system also proceeded in a low yield (Scheme 87) [189].



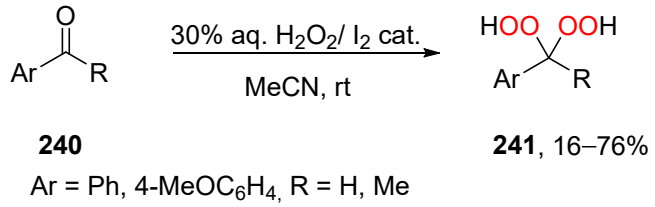
Scheme 87. Synthesis of 1,2,4-trioxane **237**.

Using 30% aq. H_2O_2 and iodine as a catalyst, geminal bishydroperoxides **239** were obtained from cyclic and acyclic ketones **238** in a yield of 50 to 98% (Scheme 88). All geminal bishydroperoxides **239** exhibit pronounced in vitro antimicrobial and antifungal activity against *B. cereus*, *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans*, and *A. niger* [190].



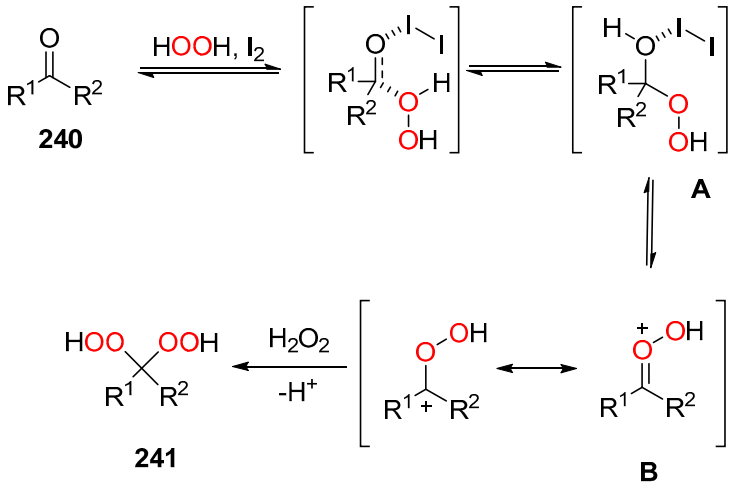
Scheme 88. Synthesis of geminal bishydroperoxides **239** and their activity.

This approach was also used in the synthesis of bishydroxyperoxides **241** from acetophenone and benzaldehydes **240**. Unfortunately, peroxidation of compounds containing an electron-withdrawing substituent in the ring did not lead to the target geminal bishydroxyperoxides (Scheme 89) [190].



Scheme 89. Synthesis of geminal dihydroperoxides **241**.

The action of iodine as a Lewis acid is based on its interaction with the oxygen atom of the carbonyl group of **240**, which facilitates the nucleophilic attack of hydrogen peroxide on the neighboring carbon atom. Iodine then eliminates the hydroxy group from the sp^3-carbon atom of intermediate **A** and the peroxycarbenium ion **B** is formed, which is attacked by the second hydrogen peroxide molecule to form the final product **241**. The last stage of this mechanism is irreversible (Scheme 90).



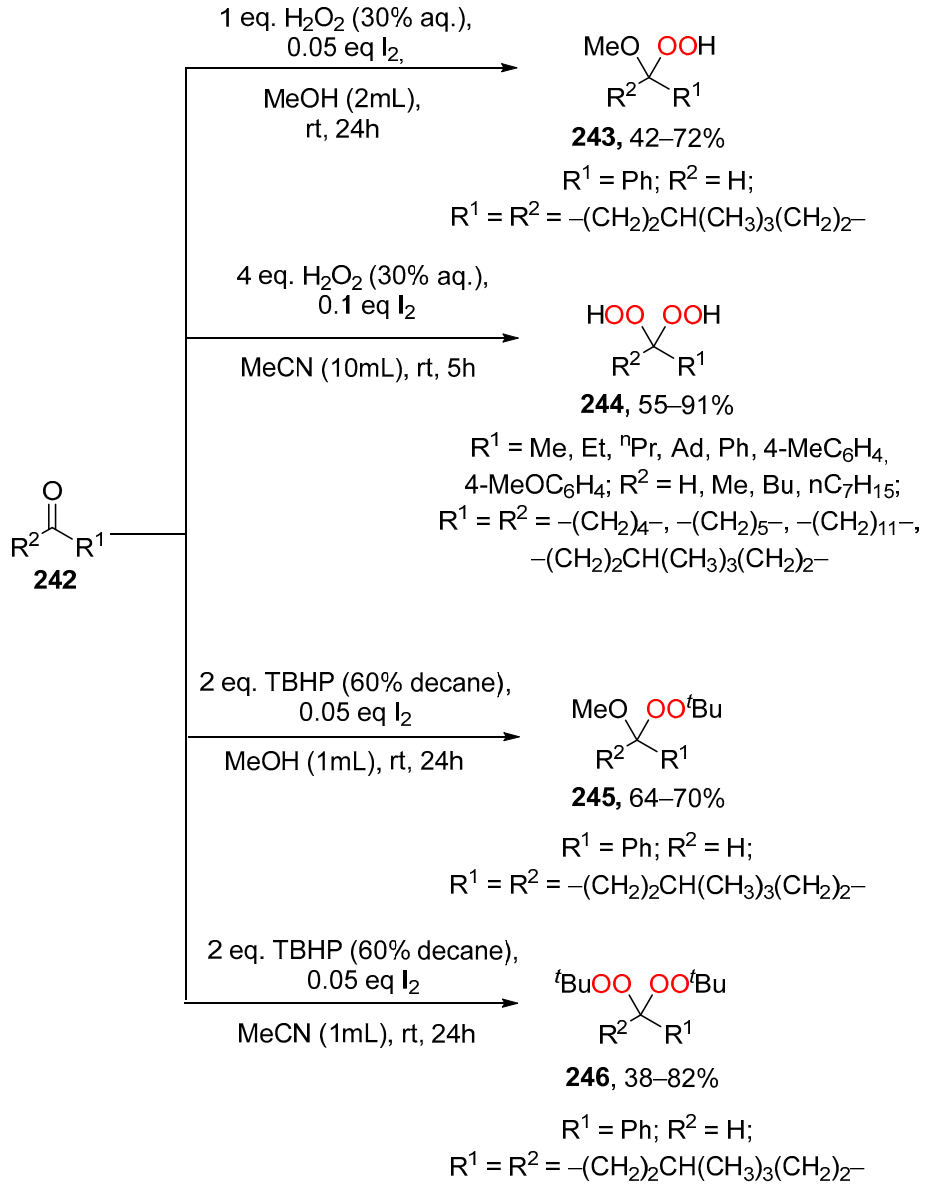
Scheme 90. The proposed mechanism for the assembly of geminal bisperoxide **241**.

The iodine-catalyzed peroxidation of carbonyl compounds **242** (acyclic and cyclic ketones and aromatic aldehydes), is a simple and effective approach to obtain geminal hydroperoxides **244** and geminal *tert*-butyl peroxides **246**. A similar reaction in methanol led to hydroperoxyacetals **243** and *tert*-butylperoxyacetals **245** (Scheme 91) [90].

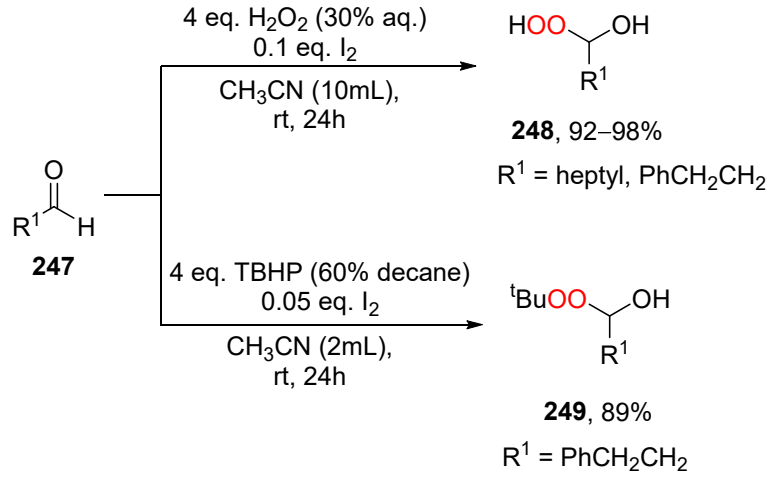
The application of I_2/H_2O_2 and I_2/TBHP systems to non-aromatic aldehydes allows one to obtain hydroxy-hydroperoxides **248** and *tert*-butylhydroxyperoxides **249** (Scheme 92) [190].

Iodine-catalyzed peroxidation of enol ethers **250** and **253** in Et_2O led to formation of 2-iodo-1-methoxy hydroperoxides **251** and **254**, respectively, with a yield of 32–41% (Scheme 93) [191]. α-Iodo ketones **252** and **255** were formed as byproducts.

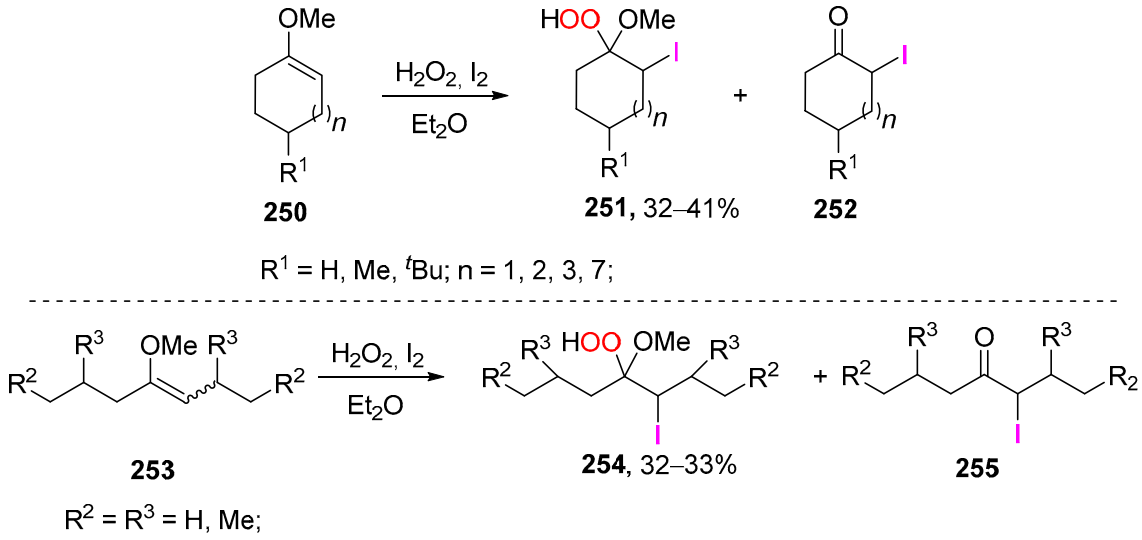
Peroxidation of monocyclic enol ethers **256** under the action of the I_2/H_2O_2 system proceeded with the formation of iodo-hydroperoxides **257** and α-iodo hemiacetals **258**, while the reaction with I_2/ROOH led only to iodoperoxides **259** (Scheme 94) [192].



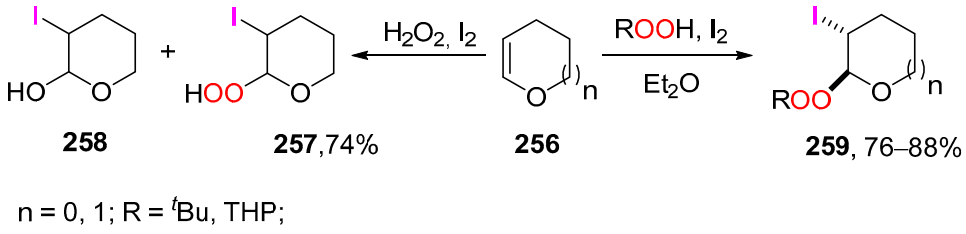
Scheme 91. Iodine-catalyzed peroxidation of carbonyl compounds **242**.



Scheme 92. Iodine-catalyzed peroxidation of aldehydes **247**.

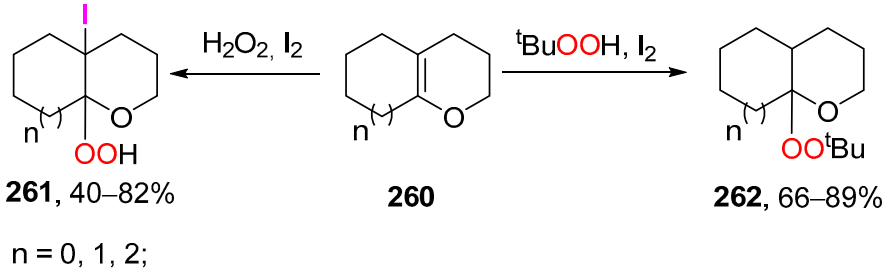


Scheme 93. Synthesis of 2-iodo-1-methoxy hydroperoxides **251** and **254**.



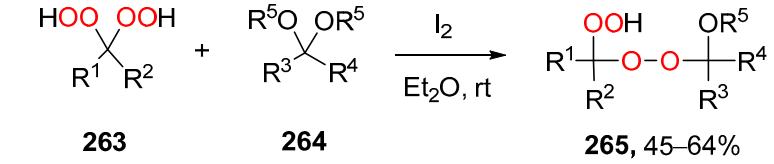
Scheme 94. Synthesis of iodoperoxides **257** and **259**.

Bicyclic enol esters were converted to vicinal iodoperoxides **261** under the action of I_2/H_2O_2 system in 40–82% yield. However, the use of *t*-BuOOH instead of H_2O_2 led to the formation of peroxides **262** without iodine in their composition with a yield of 66–89% yield (Scheme 95) [192].



Scheme 95. Synthesis of vicinal iodoperoxides **261** and peroxides **262**.

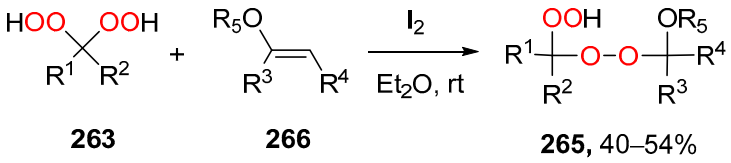
The previously unknown 1-hydroperoxy-1′-alkoxyperoxides **265** were synthesized in 45–64% yield by iodine-catalyzed reaction of geminal bishydroperoxides **263** with acetals **264** (Scheme 96) [193]. The nature of the solvent has a decisive influence on the yield of the target peroxides. Good results were obtained in such solvents as Et_2O and THF. The formation of cyclic peroxides was not observed. 1-Hydroperoxy-1′-alkoxyperoxides **265** were readily isolated from the reaction mixture by column chromatography.



$R^1 = R^2 = –(CH_2)_5–$, $–(CH_2)_6–$, $–(CH_2)_{11}–$, $–(CH_2)_2CH(CH_3)(CH_2)_2–$;
R^3 = Me; R^4 = Me, $^nC_7H_{15}$;
$R^3 = R^4 = –(CH_2)_4–$, $–(CH_2)_5–$, $–(CH_2)_6–$; R^5 = Me, Et;

Scheme 96. Synthesis of 1-hydroperoxy-1′-alkoxyperoxides **265**.

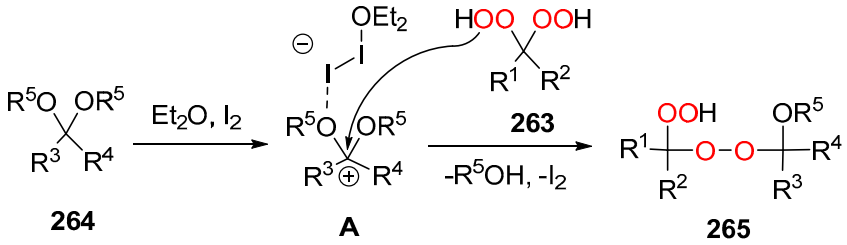
Also, 1-hydroperoxy-1′-alkoxyperoxides **265** are formed by the interaction of bishydroperoxides **263** with enol ethers **266** in the presence of molecular iodine (Scheme 97) [193].



$R^1 = R^2 = –(CH_2)_5–$, $–(CH_2)_{11}–$, $–(CH_2)_2CH(CH_3)(CH_2)_2–$;
$R^2 = R^3 = –(CH_2)_4–$, $–(CH_2)_5–$

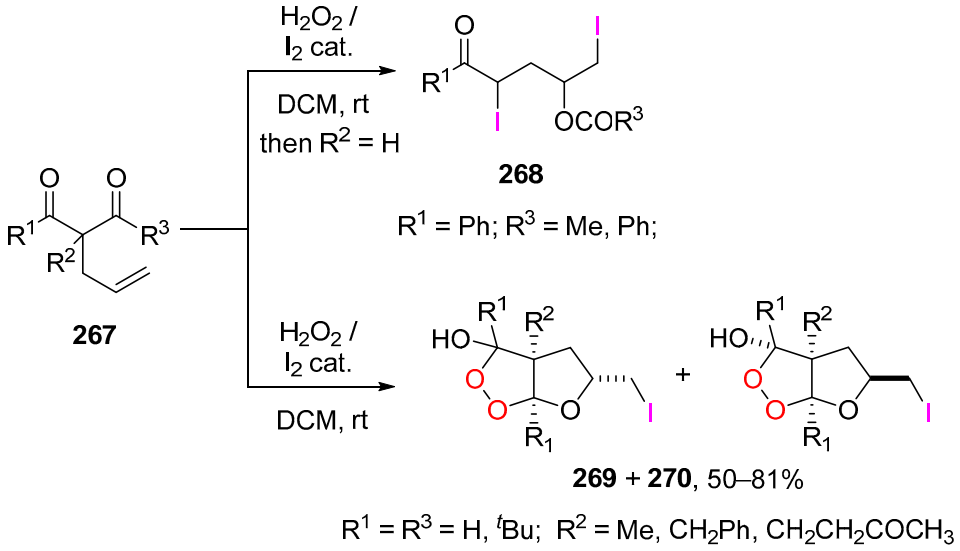
Scheme 97. Synthesis of 1-hydroperoxy-1′-alkoxyperoxides **265**.

Initially, iodine, which is probably in the form of a complex with diethyl ether (or tetrahydrofuran), interacts with the oxygen atom of the methoxy group of acetal **264**. Then the geminal bishydroperoxide **263** attacks the electrophilic center that is formed at the quaternary carbon atom **A**. Finally, the elimination of methanol proceeds with the formation of target peroxide **265** (Scheme 98).



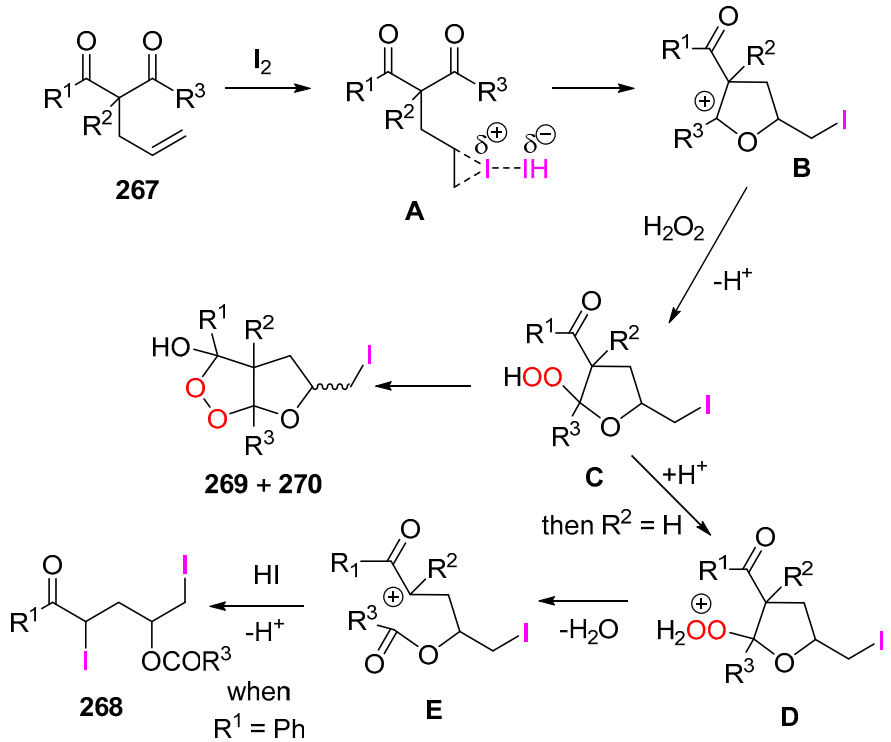
Scheme 98. The proposed mechanism for the assembly of 1-hydroperoxy-1′-alkoxyperoxides **265**.

Peroxidation of 2-allyl-1,3-diketones **267** under the action of the I_2/H_2O_2 led to the formation of diastreoisomeric bicyclic peroxides **269** and **270** (Scheme 99) [194]. The reaction was carried out under mild conditions in dichloromethane at 20–25 °C with the use of a five-fold molar excess of H_2O_2 and a two-fold excess of I_2 with respect to the starting diketone. It should be noted that the expected bridged tetraoxanes were not found during the peroxidation of 1,3-diketones **267**. Diastereomeric iodine peroxides **269** and **270** were obtained as a mixture of diastereoisomers with a yield of 50 to 81%. The interaction of ketones **267** containing an aromatic ring adjacent to the carbonyl group with the I_2/H_2O_2 system led to the formation of iodides **268** with a yield of 11–24%, but not to the bicyclic peroxides **269** and **270**.



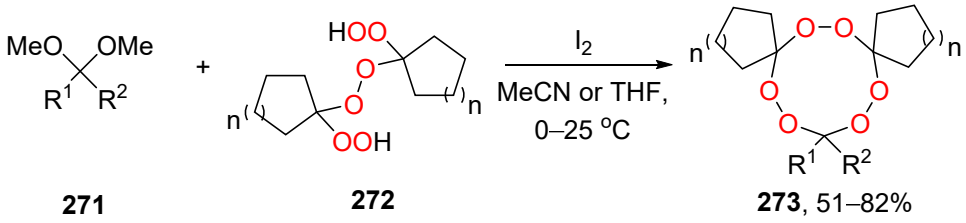
Scheme 99. Synthesis of diastereomeric bicyclic peroxides **269** and **270**.

The first stage involves the interaction of iodine with a double bond to form the iodonium cation **A**, which undergoes cyclization to the intermediate tetrahydrofuran **B,** stabilized by the anomeric effect [66–68] (Scheme 100). Then H_2O_2 attacks **B** with the formation of iodoperoxide **C**, which undergoes cyclization with the formation of **269** + **270**. In the case of compounds containing an aryl substituent at the carbonyl group, peroxide **C** is protonated with the formation of **D**, which undergoes Baeyer-Villiger rearrangement to form cation **E**, which is iodinated by HI to form **268**.



Scheme 100. The proposed mechanism for the assembly of bicyclic peroxides **269** and **270**.

A method was proposed for the synthesis of 1,2,4,5,7,8-hexaoxananes **273**, based on the I_2-catalyzed reaction of acetals **271** with 1,1′-dihydroperoxydi(cycloalkyl) peroxides **272** (Scheme 101) [195]. This method allows for the obtaining of cyclic triperoxides in good yields from 51 to 82%.



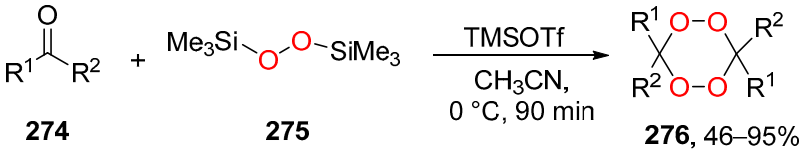
271 **272** **273**, 51–82%

n = 2, 3, 8; R^1 = Me, ^{i}Bu, ^{n}Bu; R^2 = ^{i}Bu, ^{n}Bu, $(CH_2)_7CH_3$;
$R^1 = R^2$ = –$(CH_2)_2CH(CH_3)(CH_2)_2$–, –$(CH_2)_2CH(^t$Bu$)(CH_2)_2$–;

Scheme 101. Synthesis of 1,2,4,5,7,8-hexaoxananes **273**.

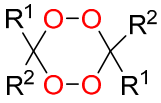
3.3. Synthesis of Peroxides Promoted by TMSOTf and TBDMSOTf

A convenient method has been developed for the synthesis of symmetric 1,2,4,5-tetraoxanes **276** from carbonyl compounds **274** and peroxidizing agent bis(trimethylsilyl) peroxide **275** in the presence of 1 equiv. of TMSOTf. The reaction was carried out at 0 °C in acetonitrile or at −70 °C in CH_2Cl_2 (Scheme 102) [196]. The in vitro and in vivo studies demonstrated that these types of cyclic peroxides are active against *P. falciparum* [197].



274 **275** **276**, 46–95%

R^1 = H, Me, $^n C_5H_{11}$, $^n C_9H_{19}$, cyclohexyl, Ph, ; R^2 = H, Me;
$R^1 = R^2$ = –$(CH_2)_5$–, –$(CH_2)_2O(CH_2)_2$–, –$CH_2C(CH_3)_2CH_2C(CH_3)_2CH_2$–



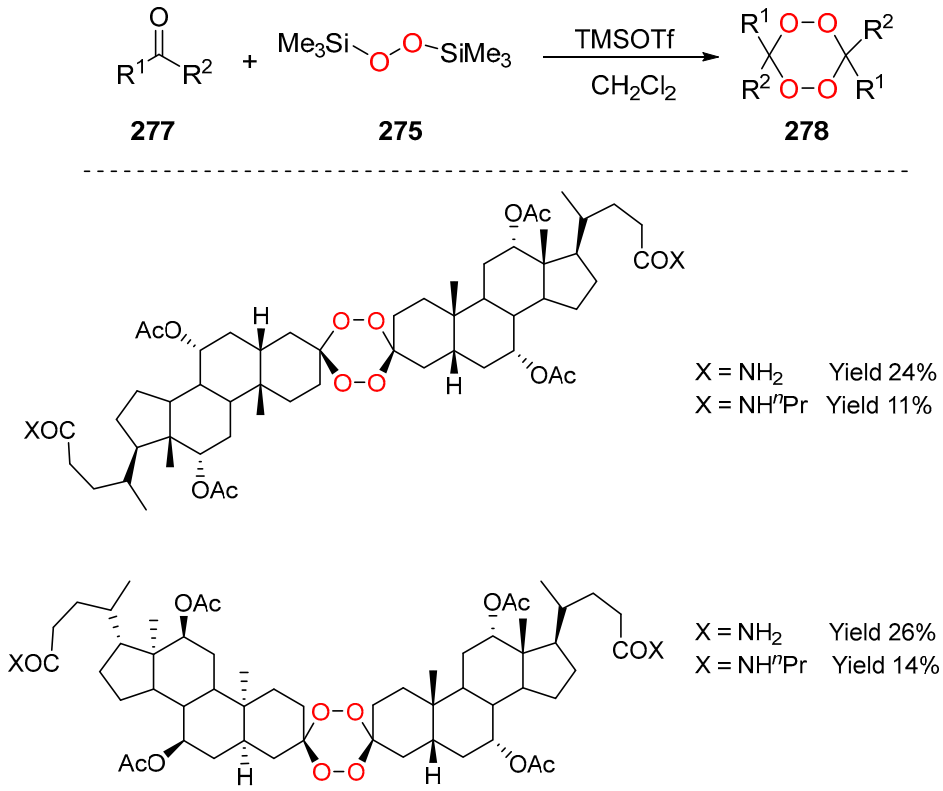
	EC_{50} (M) *P. falciparum*	Growth inhibition (%) of *P. berghei* in mice 50 mg/kg/day
276a, R^1 = cyclohexyl, R^2 = H	$2.0\ 10^{-7}$	96
276b, R^1 = Ph, R_2 = H	$1.1\ 10^{-6}$	50
Artemisinin	$7.8\ 10^{-9}$	100

Scheme 102. Synthesis and activity of 1,2,4,5-tetraoxanes **276**.

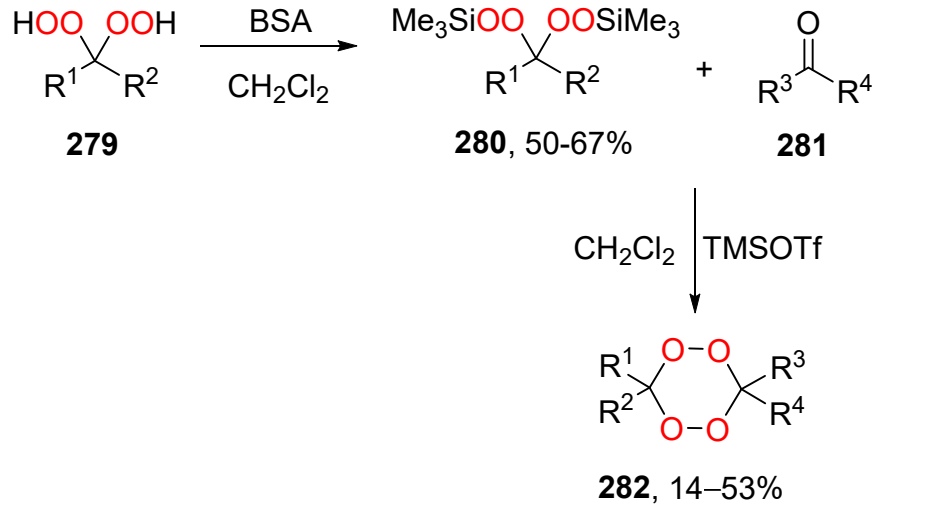
Peroxidation of carbonyl compounds with the use of $Me_3SiOOSiMe_3$/TMSOTf system allows one to obtain steroidal tetraoxanes **278** (Scheme 103) [198]. The reaction was carried out at 0 °C in acetonitrile using a 1.5-fold molar excess of $Me_3SiOOSiMe_3$ and TMSOTf with respect to ketone **277**.

The synthesis of unsymmetrical 1,2,4,5-tetraoxanes **282** proceeds through the interaction of geminal bis(trimethylsilyl)peroxides **280** with carbonyl compounds **281** in the presence of TMSOTf. 1,2,4,5-Tetraoxanes **282** are formed in yields up to 53% (Scheme 104) [197]. Corresponding bis(trimethylsilyl) peroxides **280** were obtained by the interaction of geminal bishydroperoxides **279** with BSA (N, O-bis (trimethylsilyl) acetamide) in 50–67% yield.

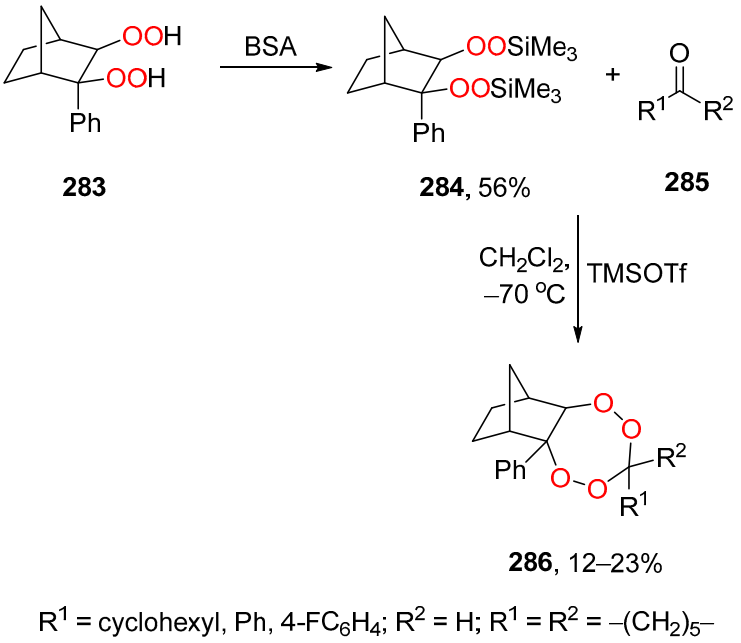
In addition, TMSOTf is used as a catalyst in the synthesis of 1,2,4,5-tetraoxepanes **286** by the reaction of 1,2-bis (trimethylsilyl) peroxide **284** with carbonyl compounds **285** (Scheme 105) [197,199]. Silyl peroxide **284** was synthesized by reaction of BSA (N, O-bis (trimethylsilyl) acetamide) on 1,2-dihydroperoxide **283** in 56% yield.



Scheme 103. Synthesis of tetraoxanes **278**.

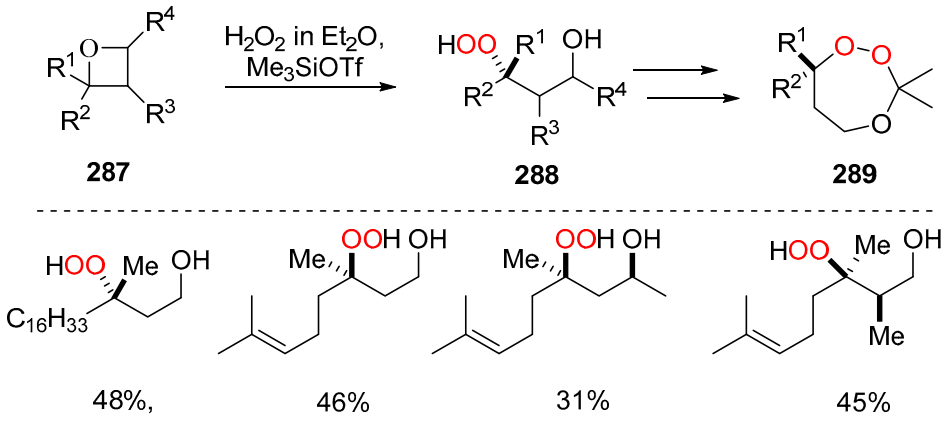


Scheme 104. Synthesis of unsymmetrical 1,2,4,5-tetraoxanes **282**.



Scheme 105. Synthesis of 1,2,4,5-tetraoxepanes **286**.

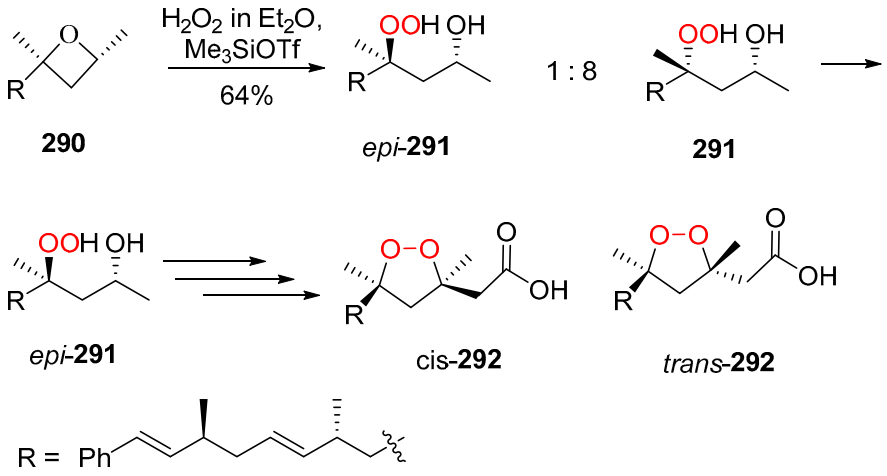
In 2002, Dussault et al. [111,127] demonstrated the oxetane ring opening in **287** with an ether solution of H_2O_2, catalyzed by $Yb(OTf)_3$, with the formation of 3-hydroxyhydroperoxide **288**, which act as an intermediate in the synthesis of 1,2,4-trioxepanes **289**. However, the use of TMSOTf in some cases led to a better result (Scheme 106).



Scheme 106. Synthesis of 1,2,4-trioxepanes **289**.

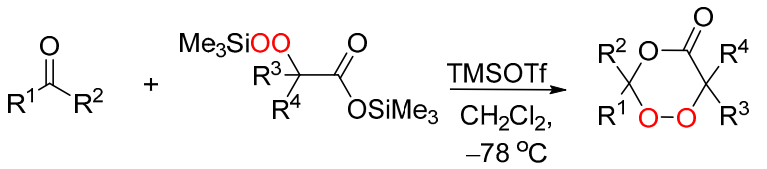
The developed system TMSOTf/H_2O_2 for oxetane ring opening in **290** was successfully used at one of the stages in the total synthesis of plakinic acid A ***cis*-292** and ***trans*-292**, a natural compound with antitumor activity (Scheme 107) [111]. Opening of the oxetane ring in **290** by TMSOTf resulted in the formation of readily separable 3-hydroxyhydroperoxides **291** and ***epi*-291**. Then, in several steps, cyclic peroxides ***cis*-292** and ***trans*-292** were obtained from ***epi*-291**.

Cyclic peroxolactones (1,2,4-trioxan-5-ones) **295** were obtained by the reaction of carbonyl compounds **293** with silyl peroxides **294** under the action of $TfOSiMe_3$. This reaction does not proceed in the absence of $TfOSiMe_3$. The synthesis was carried out in methylene chloride at a temperature of −78 °C (Scheme 108) [200,201].



290 *epi*-**291** **291** *epi*-**291** cis-**292** *trans*-**292**

Scheme 107. Synthesis 3-hydroxy hydroperoxides **291** and ***epi*-291**.

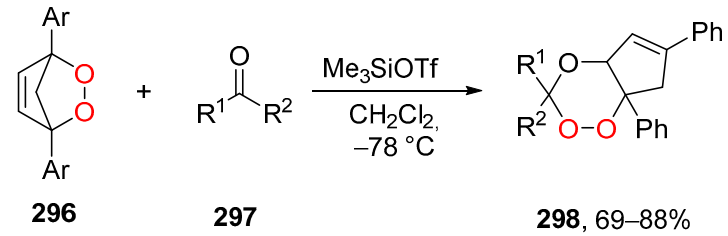


293 **294** **295**, 45–93%

$R^1 = R^2$ = H, Me, ^{t}Bu, COOEt, Ph, 4-ClC$_6$H$_4$; $R^1 = R^2$ = –(CH$_2$)$_5$–;
R^3 = H; R^4 = Adamantyl, Me, ^{t}Bu; $R^3 = R^4$ = Adamantyl, –(CH$_2$)$_5$–

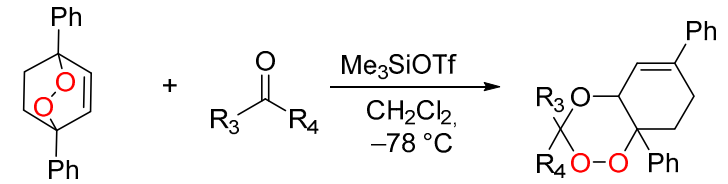
Scheme 108. Synthesis of 1,2,4-trioxan-5-ones **292**.

The TMSOTf-catalyzed interaction of endoperoxides **296** and **299** with ketones **297** and **300** proceeds with the formation of above-mentioned substituted 1,2,4-trioxanes **298** and **301** with moderate to good yields (Scheme 109) [202–204].



296 **297** **298**, 69–88%

Ar = Ph, 4-FC$_6$H$_4$; R^1 = H, Me; R^2 = H, Me; $R^1 = R^2$ = –(CH$_2$)$_4$–;

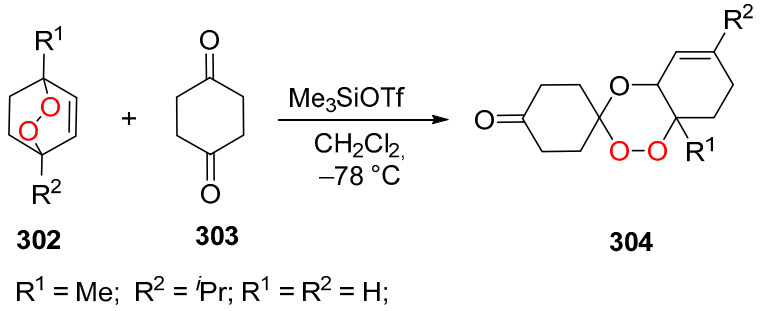


299 **300** **301**, 77–86%

R^3 = H, Me; R^4 = H, Me; $R^3 = R^4$ = –(CH$_2$)$_4$–

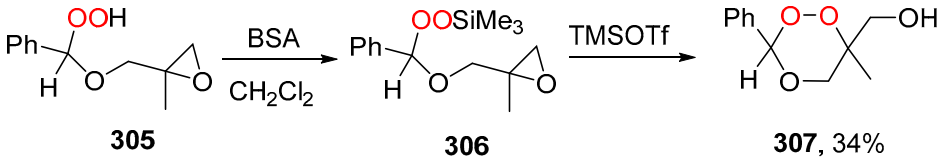
Scheme 109. Synthesis of substituted 1,2,4-trioxanes **298** and **301**.

1,2,4-Trioxanes **304** were obtained by the reaction of diketone **303** with containing alkyl substituents endoperoxides **302** (Scheme 110) [205]. Unfortunately, the yield of target peroxides did not exceed 10%.



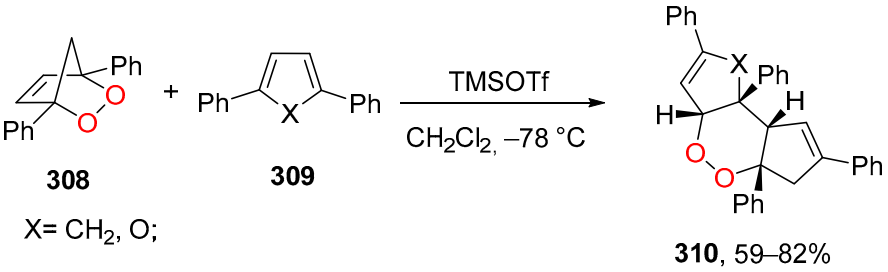
Scheme 110. Synthesis of substituted 1,2,4-trioxanes **304**.

Trimethylsilyl peroxide **306**, which was obtained by the reaction of BSA (*N*,*O*-bis (trimethylsilyl) acetamide) with hydroperoxide **305**, intramolecularly reacts with the oxirane ring under the action of TMSOTf to form 1,2,4-trioxane **307** in 34% yield (Scheme 111) [206].



Scheme 111. Synthesis of substituted 1,2,4-trioxane **307**.

The use of TMSOTf in the reaction of endoperoxide **308** with cyclic diene **309** opened access to tetrasubstituted 1,2-dioxanes **310** (Scheme 112) [207].

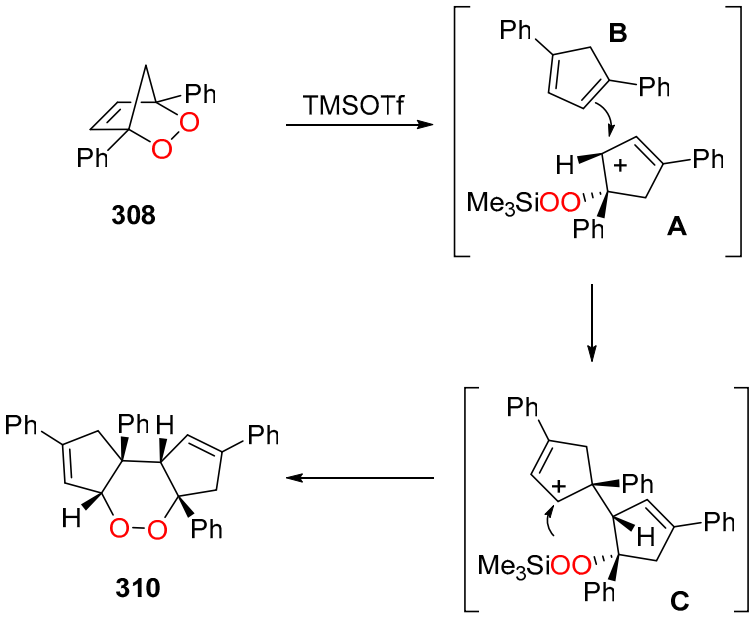


Scheme 112. Synthesis of tetrasubstituted 1,2-dioxanes **310**.

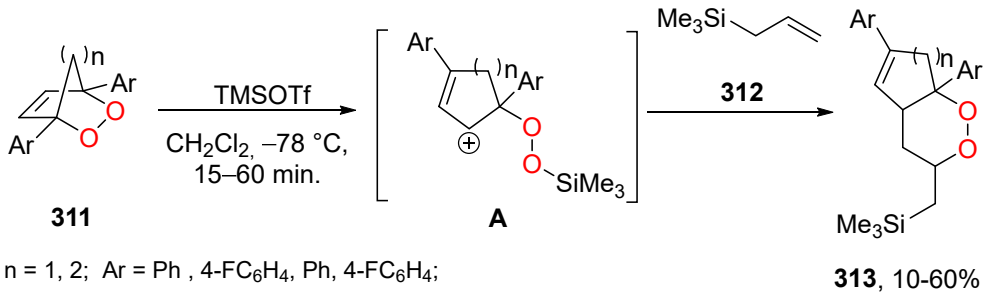
At the first step, the interaction of endoperoxide **308** with TMSOTf leads to the formation of carbocation **A**. The subsequent attack of 1,4-diphenyl-1,3-cyclodiene **B** on carbocation **A** occurs in a regio- and diastereospecific manner. The intramolecular attack of the peroxysilyl function on the carbocation in **C** leads to product **310** (Scheme 113).

The reaction of allyltrimethylsilane **312** with endoperoxides **311** in the presence of catalytic amounts of TMSOTf resulted in bicyclic 1,2-dioxanes **313** with a yield of 10% to 60% (Scheme 114) [208].

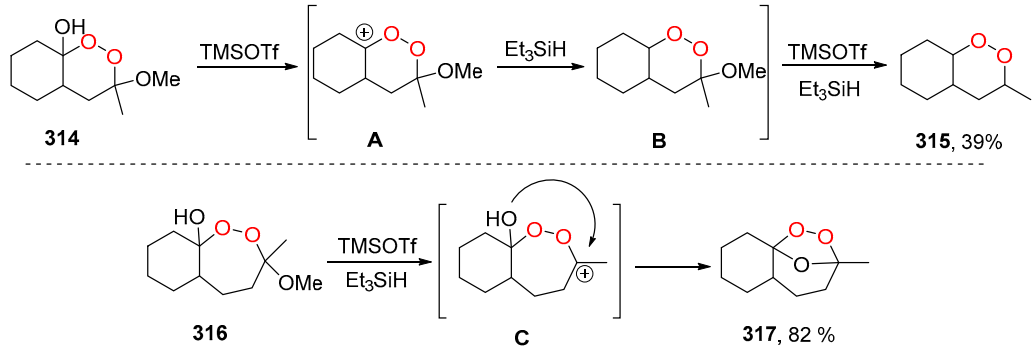
The use of TMSOTf/Et_3SiH system in the reaction with bicyclic peroxides **314** and **316** led to unusual results. Substituted 1,2-dioxane **314** was transformed into 1,2-dioxane **315**. But in the case of a 7-membered cyclic peroxide **316**, the main product was bicyclic peroxide containing ozonide cycle **317** (Scheme 115) [209].



Scheme 113. The proposed mechanism for the assembly of tetrasubstituted 1,2-dioxanes **310**.

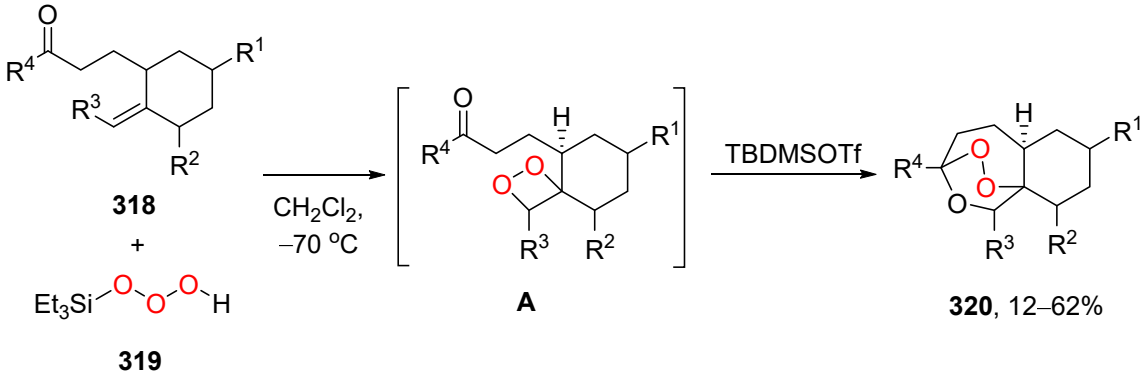


Scheme 114. Synthesis of bicyclic 1,2-dioxanes **313**.



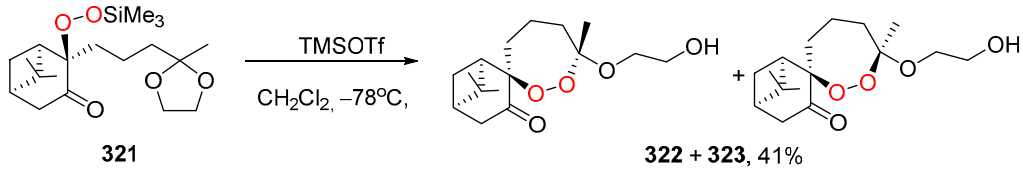
Scheme 115. Synthesis of substituted 1,2-dioxane **315** and 1,2,3-trioxolane (ozonide) **317**.

It has been shown that triethylsilyl hydrotrioxide **319** ($Et_3SiOOOH$), obtained in situ from ozone and triethylsilane, is a mild and effective dioxetane-forming reagent from vinyl ethers and vinyl thioethers on a relatively small (50–100 mg) scale. A number of studies have demonstrated that the interaction of TBDMSOTf with dioxetane **A** leads to its rearrangement into 1,2,4-trioxanes **320**. Such peroxides exhibit in vitro antimalarial activity, which is not inferior to peroxides like Artemisinin (Scheme 116) [210–212].



Scheme 116. Synthesis of 1,2,4-trioxanes **320**.

In a study [213] on the synthesis of cyclic peroxides **322** and **323** with high antimalarial activity, TMSOTf was used as a catalyst at the stage of peroxide cycle assembly (Scheme 117). Peroxoacetals **322** and **323** were obtained from substrate **321** in 41% yield. The antimalarial activity of peroxides **322** and **323** is comparable to the antimalarial activity of Artemisinin.

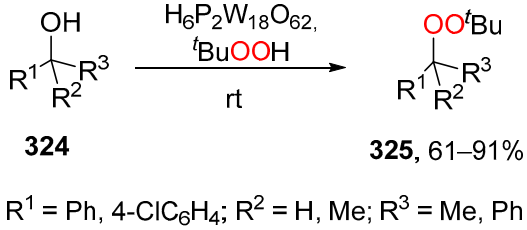


Scheme 117. Synthesis of cyclic peroxides **322** and **323**.

4. Heteropoly Acids in the Synthesis of Organic Peroxides

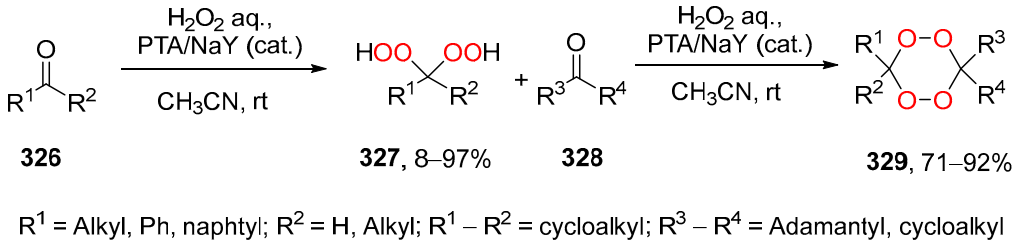
In recent years, great interest has been paid to heteropoly acids as catalysts in the synthesis of organic peroxides. Heteropoly acids such as phosphomolybdic (PMA) and phosphotungstic (PTA) acids have a unique ability to form peroxo complexes with hydrogen peroxide and transfer the peroxide function to the substrate [37,214–216]. The deposition of heteropoly acids on a support allows them to be reused after regeneration [37,216]. This section covers approaches on the synthesis of bisperoxides, 1,2,4-trioxolanes, 1,2,4,5-tetraoxanes, and tricyclic monoperoxides with the use of heteropoly acids.

The use of the ^{t}BuOOH/$H_6P_2W_{18}O_{62}$ system allows one to obtain dialkyl peroxides **325** from alcohols **324** in good yield (Scheme 118) [217]. In the case of secondary alcohols, the formation of an ether was observed in the reaction, which led to a decrease in the yield of the target peroxide. No by-product formation was observed in the case of tertiary alcohols.



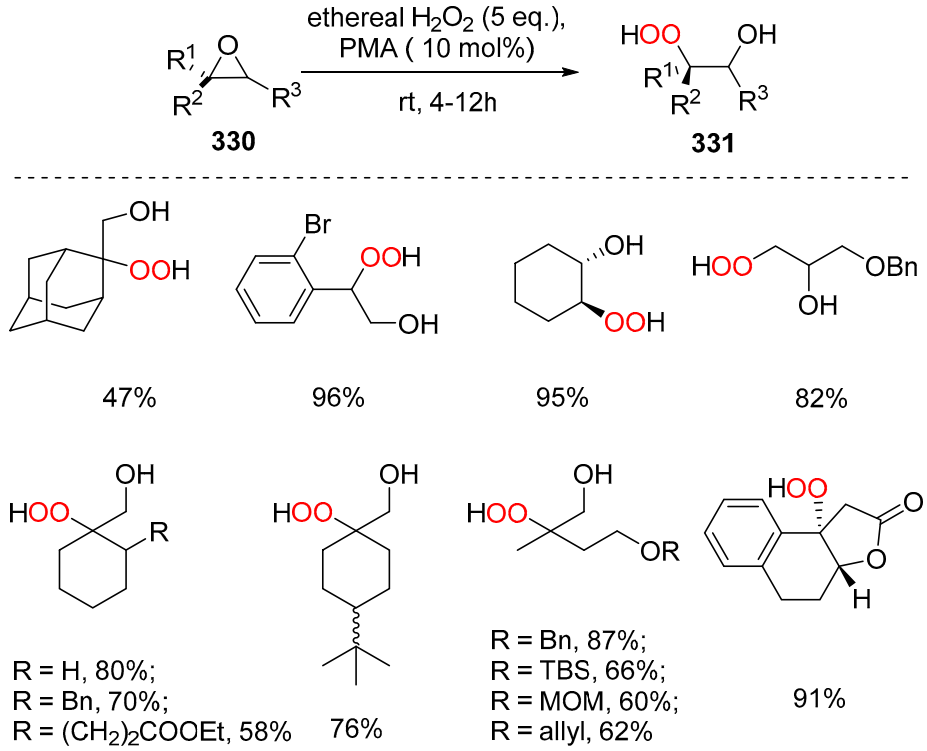
Scheme 118. Synthesis of peroxides **325**.

Supported phosphotungstic acid (PTA) on zeolite (NaY) allows the synthesis of a wide range of geminal bisperoxides **327** under heterogeneous conditions with a yield of 8 to 97% (Scheme 119) [216]. Such a system (H_2O_2, PTA/NaY) is effective for the synthesis of 1,2,4,5-tetraoxanes **329**. Target products **329** were obtained in 71% to 92% yield.



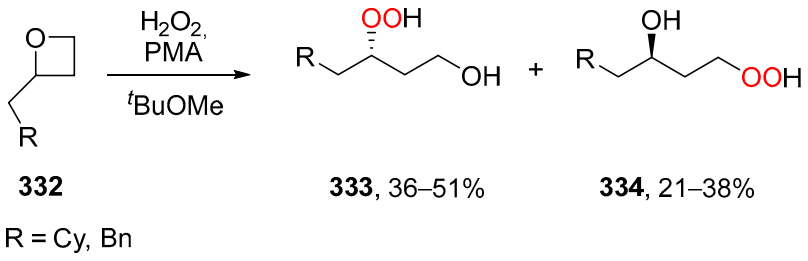
Scheme 119. Synthesis of geminal bisperoxides **327** and 1,2,4,5-tetraoxanes **329** on their basis.

In 2009, the group of Wu et. al. reported the application phosphomolybdic acid (PMA) as a catalyst for the ring-opening of epoxides with H_2O_2. This method gives the opportunity to obtain β-hydroperoxy alcohols **331** at ambient temperature (Scheme 120) [218]. For all tested substrates the ring-opening of epoxides **330** is highly regioselective to give the hydroperoxyl group at the quaternary carbon.



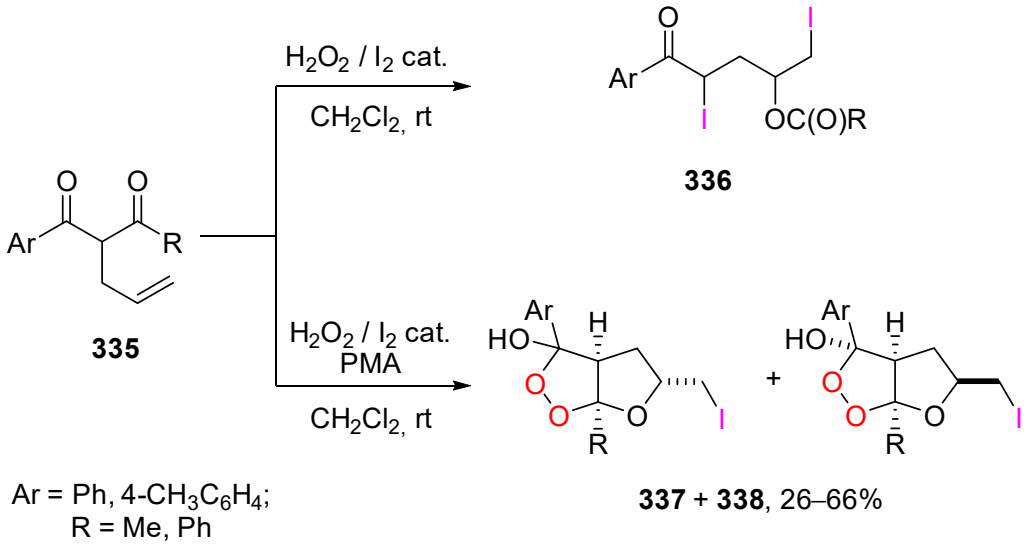
Scheme 120. Synthesis of β-hydroperoxy alcohols **331** from epoxides **330**.

In 2014, Han et. al. performed the ring opening of oxetane **332** with hydrogen peroxide in the presence of phosphomolybdic acid (PMA). This interaction resulted in a mixture of two peroxides **333** and **334** (Scheme 121) [219].



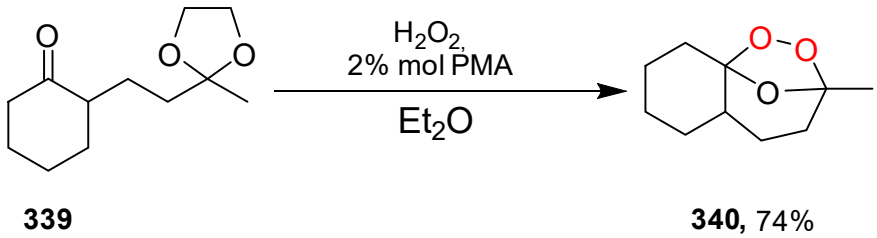
Scheme 121. Synthesis of peroxide **333** and **334**.

The ability of heteropoly acids to form peroxo complexes and coordinate with the carbonyl group allows the peroxidation of ketones and their derivatives under milder conditions. For example, peroxidation of 1-aryl-2-allylalkane-1,3-diones **335** with I_2/H_2O_2 system proceeds with the formation of iodinated ketoesters **336**. The addition of catalytic amounts of PMA to the I_2/H_2O_2 system facilitates the assembly of bicyclic peroxides **337** and **338** (Scheme 122) [220].



Scheme 122. Synthesis of bicyclic peroxides **337** and **338**.

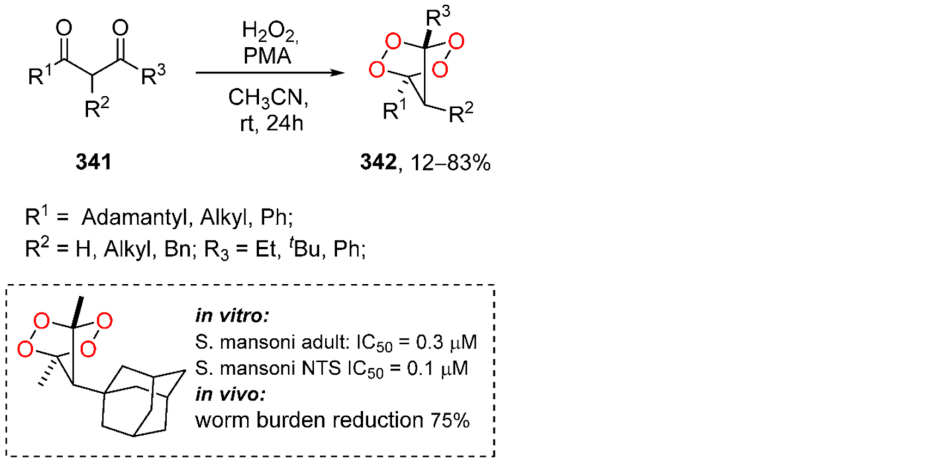
Ozonide **340** was obtained in one step by peroxidation of ketoacetal **339** with a yield of 74%. Phosphoromolybdic acid (PMA) was used as a catalyst in the amount of 0.02 equiv. with respect to **339**. (Scheme 123) [218].



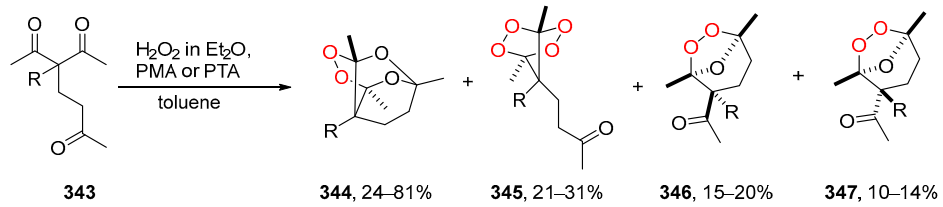
Scheme 123. Synthesis of ozonide **340**.

Phosphomolybdic (PMA) and phosphotungstic (PTA) acids efficiently catalyze the peroxidation reaction of β-diketones **341**, including easily oxidized diketones, with the formation of bridged 1,2,4,5-tetraoxanes **342** (Scheme 124) [214]. Peroxides can be obtained in grams. The bridged 1,2,4,5-tetraoxane **342** containing an adamantane substituent in its composition exhibit a high activity (IC_{50}: 0.3 μM) in vitro and in vivo (worm burden reduction was 75%) against *S. mansoni* [16].

The reaction of β,δ′-triketones **343**, containing a benzyl substituent in the α-position, with an ethereal solution of H_2O_2, catalyzed by heteropoly acids (PMA, PTA) in a polar aprotic solvent, proceeds along three paths with the formation of three classes of peroxides: tricyclic monoperoxides **344**, bridged tetraoxanes **345** and a pair of stereoisomeric ozonides **346** and **347** (Scheme 125) [215,221]. The reaction is unusual in that bridged tetraoxanes and ozonides with a free carbonyl group were formed. The synthesis of ozonides from ketones and H_2O_2 is a unique process in which ozonide is formed with the participation of two carbonyl groups. Bridged ozonides exhibit high in vitro cytotoxicity against androgen dependent prostate cancer cell lines DU145 and PC3. In some cases the anticancer activity of ozonides is higher than that of doxorubicin, cisplatin, and etoposide [222].



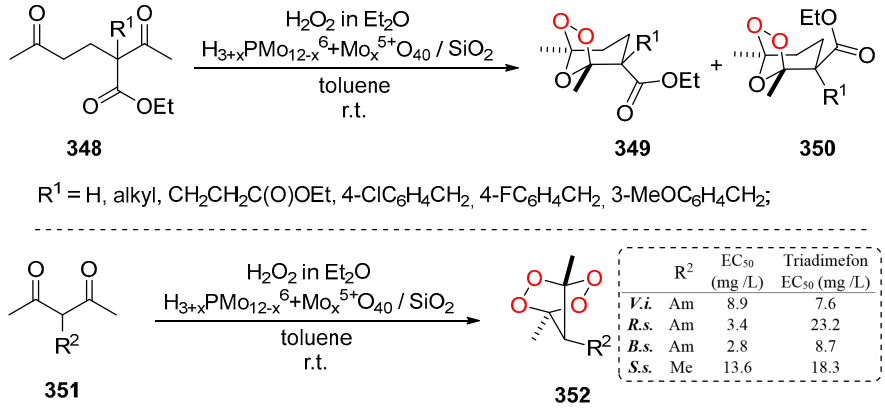
Scheme 124. Synthesis of bridged 1,2,4,5-tetraoxanes **342**.



	PC3, IC_{50} μM	PZ-HPV-7, IC_{50} μM
346, R= 4-$CH_3C_6H_4CH_2$	5.2	15.5
347, R= 4-$BrC_6H_4CH_2$	3.0	4.9
Doxorubicin	2.4	1.2
Cisplatin	21.0	17.3
Etoposite	17.0	6.1

Scheme 125. Synthesis and activity of cyclic peroxides **344**–**347**.

More recently, an efficient catalyst $H_{3+x}PMo_{12-x}^{6+}Mo_x^{5+}O_{40}/SiO_2$ was developed for the synthesis of bridged ozonides **349**, **350** and 1,2,4,5-tetraoxanes **352** under heterogeneous conditions (Scheme 126) [37] The synthesis of peroxides under heterogeneous conditions is a rare process and presents a challenge in this area of chemistry, as peroxides tend to decompose on the catalyst surface. The yield of diastereoisomeric bridged ozonides **349**, **350** was up to 90%, and of bridged 1,2,4,5-tetraoxanes **352** wasup to 86%.



	R^2	EC_{50} (mg /L)	Triadimefon EC_{50} (mg /L)
V.i.	Am	8.9	7.6
R.s.	Am	3.4	23.2
B.s.	Am	2.8	8.7
S.s.	Me	13.6	18.3

Scheme 126. Synthesis of bridging ozonides **349**, **350** and 1,2,4,5-tetraoxanes **352**.

5. Summary and Outlook

This review summarizes approaches to the synthesis of organic peroxides under the action of Lewis acids and heteropoly acids. The possibility of Lewis acids to coordinate with the oxygen atom of the carbonyl group, as well as to generate a peroxycarbenium ion in the starting compounds, allows for the expansion of the potential of the peroxidation reaction of carbonyl compounds.

The possibility of metal-containing compounds such as PMA, PTA, and $MeReO_3$ to form peroxo complexes with hydrogen peroxide makes it possible to transfer the peroxide function to the substrate. This transfer of peroxide groups, mediated by metal complexes, makes it possible to obtain organic peroxides under heterogeneous conditions.

Analysis of the literature allows us to conclude that in the next decade the vector in peroxide chemistry will shift towards the use of the Lewis acid/peroxidizing agent system. This system is promising and its use will open up new horizons in peroxide chemistry for the chemical and medical industries.

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