Peroxide Chemistry in Organic Syntheses

Historical Mementos

- In the 18th century, the chemistry of organic peroxides was initiated in the age of Phlogiston Theory on interpreting how the air interacted with organic substance.
- In 1774, the Phlogiston Theory collapsed since the discovery of oxygen (both oxidation and peroxide chemistry began).
- In 1900, Bayer and Villiger discovered perbenzoic acid (same time, Gomberg discovered radical).
- In 1940s, H. Hock, R. Criegee and E. H. Farmer corrected the structures of peroxides formed from oxygen.
- From 1940s to 1960s, the development of analytical methods especially NMR accelerated peroxide chem.
- Singlet oxygen was discovered in 1930s by Kautsky which was widely accepted after 30 years!
- From 1900s to 1960s, the ozone chemistry was well developed by Stauring, Schroder, Engler, Criegee, Rieche and others.
- Since the discovery of hydrogen peroxide by L. J. Thenard in 1818, Schroder and Schwarz corrected its structure in 1930s.
- Landmarks of modern peroxide chemistry is to successfully elucidate prostaglandin synthesis in vivo and in vitro; the studies on the biochemical oxidation of polyunsaturated carboxylic acids and their esters; the chemistry of the cytochrome P450.

![Prostaglandin H2 from prostaglandin family](image)

The enzyme shown here on the left is a fungal cytochrome p450 that performs a step in sterol synthesis (PDB entry 1eat). The enzyme complex on the right provides electrons for the reaction (PDB entry 1e6e).

Notable name reactions involving peroxides:

- Baeyer-Villiger oxidation
- Kharasch oxidation
- Criegee rearrangement (ozonolysis)
- Henry-Drysdale Dakin Dakin oxidation
- Mukaiyama hydration
- Sharpless epoxidation
- Jacobsen Katsuki epoxidation
- Shi epoxidation
- Minicici reaction
- Fleming-Tamao oxidation
- Wohl-Ziegler Bromonation (allylic/benzyl bromination)
- Hock rearrangement (cumene process)
- Kornblum-DeLaMare rearrangement
- Payne oxidation
- Rubottom oxidation
- Prilezhav reaction (mCPBA epoxidation)
- Wharton transposition

Peroxides can be treacherous

- Peroxidized reagent explosions almost always follow distillation or some other step that results in concentration of the peroxide. The hydroperoxides initially formed are probably only moderately higher boiling than the parent compound but are known to undergo spontaneous condensation reactions to form less volatile dimers and/or higher polymers (5, 7). These secondary products accumulate in still bottoms and can reach very high concentrations if distillation is carried toward dryness. Accident reports indicate that explosion usually occurs at or near the end point of the distillation, likely triggered by temperature rise. The descriptions suggest high-rate explosions of very small weights of material, on the order of tens of grams. There seems to be no evidence of explosion in the bulk of an accidentally autoxidized reagent.
- Polymeric or cyclic peroxides may also become insoluble and settle out as crystalline solids or separate liquid phases. The second phase may be very high in active oxygen and highly explosive. Appearance of a second phase in any peroxidizable compound should be taken to indicate a possibly serious explosion hazard.
## Peroxide Chemistry in Organic Syntheses

### Commercial available peroxides*

#### Inorganic peroxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Formula or name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium peroxide</td>
<td>Na$_2$O$_2$</td>
<td></td>
</tr>
<tr>
<td>Calcium peroxide</td>
<td>CaO$_2$</td>
<td></td>
</tr>
<tr>
<td>Lithium peroxide</td>
<td>Li$_2$O$_2$</td>
<td></td>
</tr>
<tr>
<td>Barium peroxide</td>
<td>BaO$_2$</td>
<td></td>
</tr>
<tr>
<td>Nickel peroxide</td>
<td>Ni$_2$O$_3$</td>
<td></td>
</tr>
<tr>
<td>Nickel(II) peroxide hydrate</td>
<td>NiO$_2$$\cdot$H$_2$O</td>
<td>$40/1$g</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>H$_2$O$_2$</td>
<td>$350/4$L</td>
</tr>
<tr>
<td>Zinc peroxide</td>
<td>ZnO$_2$</td>
<td>$75/1$kg</td>
</tr>
<tr>
<td>Magnesium peroxide</td>
<td>MgO$_2$</td>
<td>$40/250$g</td>
</tr>
<tr>
<td>Strontium peroxide</td>
<td>SrO$_2$</td>
<td>$39/1$00g</td>
</tr>
<tr>
<td>Sodium percarbonate</td>
<td>Na$_2$CO$_3$$\cdot$1.5H$_2$O</td>
<td>$91/2.5$kg</td>
</tr>
</tbody>
</table>

#### Organic peroxides-1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Physical form</th>
</tr>
</thead>
<tbody>
<tr>
<td>tert-Butyl hydroperoxide solution (5-6 M)</td>
<td>tBuOOH</td>
<td>47/25mL</td>
</tr>
<tr>
<td>Urea hydrogen peroxide</td>
<td>urea$\cdot$H$_2$O</td>
<td>88/250g</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>BzOOBz</td>
<td>$92/500$g</td>
</tr>
<tr>
<td>Cyclobutane maloyl peroxide</td>
<td>mCPBA</td>
<td>$81/100$g</td>
</tr>
<tr>
<td>tert-Butyl peroxybenzoate</td>
<td>tert-Butyl peroxybenzoate</td>
<td>$86/500mL</td>
</tr>
<tr>
<td>tert-Butyl peroxide acetate solution, 50% in mineral spirits</td>
<td>tert-Butyl peroxybenzoate</td>
<td>77/500mL</td>
</tr>
<tr>
<td>Dicumyl peroxide</td>
<td>Dicumyl peroxide</td>
<td>$123/500$g</td>
</tr>
<tr>
<td>tert-Butyl peroxide</td>
<td>tert-Butyl peroxide</td>
<td>$134$/1L</td>
</tr>
<tr>
<td>tert-Butyl peroxybenzoate</td>
<td>tert-Butyl peroxybenzoate</td>
<td>$86$/500mL</td>
</tr>
<tr>
<td>tert-Butyl peroxide</td>
<td>tert-Butyl peroxybenzoate</td>
<td>$86$/500mL</td>
</tr>
</tbody>
</table>

### Other peroxides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Physical form</th>
</tr>
</thead>
<tbody>
<tr>
<td>tert-Butyl monoperoxymaleate</td>
<td>tert-Butyl monoperoxymaleate</td>
<td>$75/5g</td>
</tr>
<tr>
<td>tert-Butyl peroxyacetate</td>
<td>tert-Butyl peroxyacetate</td>
<td>$150/250$g</td>
</tr>
<tr>
<td>tert-Butyl peroxybenzoate</td>
<td>tert-Butyl peroxybenzoate</td>
<td>$78/500$g</td>
</tr>
<tr>
<td>tert-Butyl peroxyacetic acid</td>
<td>tert-Butyl peroxyacetic acid</td>
<td>$45/500$mL</td>
</tr>
<tr>
<td>tert-Butyl peroxybenzoate</td>
<td>tert-Butyl peroxybenzoate</td>
<td>$74/500$g</td>
</tr>
</tbody>
</table>

* Prices are based on Aldrich Inventory (price from other suppliers will not be noted); any resource less than 10 mg will not be included.
Peroxide Chemistry in Organic Syntheses

Commercial available peroxides*

Organic peroxides-

1. Endoperoxide-cholesterol derivatives $101/25mg
2. Endoperoxide-cholesterol derivatives $100/25mg
3. Chemiluminescent substrate, 0.25 M/H₂O $369/100mL
4. Qinghaosu Artemisinin $107/5g
5. Artemiunate $113/25g
6. 2,5-Bis(tert-butylperoxy)-2,5-dimethyl/hexane $50/100mL

Common peroxide reagents in synthesis:

Hydrogen peroxide based oxidants:

- 0.147 Å, 37±1 kcal/mol
- Hydrogen peroxide
- NBS, 0 °C, 60%
- Ph, Ph
- H₂O₂
- OH
- O
- OH
- Fe³⁺/H₂O₂
- Iron (II) sulfate
- Fenton reagent
- H₂O₂
- Fe²⁺
- Hydrogen peroxide
- Tellurium dioxide
- Application: epoxidation of electron deficient alkenes
- Weak electrophile whose reactivity was enhanced by LA or TM
- Strong nonpolluting oxidant
- H₂O₂
- Fe(acac)₃
- Iron (III) Acetylacetonate
- Hydrogen Peroxide
- Application: epoxidation of cholesterol derivatives and transepoxidation of alkenes (limited cases: epoxidation of stilbene)

* Prices are based on Aldrich Invetory (price from other suppliers will not be noted); any resource less than 10 mg will not be included
Peroxide Chemistry in Organic Syntheses

Hydrogen peroxide based oxidants:

Prep: H₂O₂ and Mo reagent mixing for the reaction; stable powder

Application: 1) (Mo) Among the best catalyst for the epoxidations since it is cheap and easy handling; 2) Mono and di-substituted alkenes react very slowly

selectively on more hindered alcohol

without the base, epoxidation can occur


TBHP:

Prep: 70-90% aqueous solution or anhydrous solution in hydrocarbon solvents (Sharpless’ Aldrich procedure to prepare anhydrous TBHP)

Application: 1) Oxidation of alkenes to diols; 2) Oxidation of allylic or benzylic or propargylic positions with SeO₂ and TBHP; 3) Epoxidation widely applied; 4) Vicinal diol can be cleaved by TBHP with MoO₂; 5) Alcohol can be oxidized by TBHP with Se or Cr compound; 6) Sulfide can be oxidized to sulfone or sulfoxide; 7) Phosphines can be oxidized to phosphine oxide; 8) Amine can be oxidized to N-oxide or imine; 9) Peroxoy acetal can be made from aldehyde or ketone with TBHP; 10) Alkyl halide can be converted to alkyl alcohol from Grignard reagent with TBHP.

Some noticeable examples

mCPBA and its families:

Prep: stable in 85% purity, 100% purity is possible, stored in polyethylene container in fridge

Application: 1) Epoxidation of alkenes (electron-riched); 2) B-V reaction; 3) Rubottom oxidation; 4) Oxidation of sulfide to sulfoxide (tandem with Mislow-Evans rearrangement); 5) Oxidation of selenides and phosphines and phosphites;
**Peroxide Chemistry in Organic Syntheses**

**Changxia Yuan**

**Baran Group Meeting 4/5/2014**

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**meta-chloroperbenzoic acid-2,2,6,6-tetramethylpiperidine hydrochloride**

Application: 1) oxidation of alcohol at room temp for high yield; 2) epoxy ketone can be prepared in one step from allylic alcohol; 3) forced conditions lead to lactone or ester from alcohol

Characterization: Stable at ambient temperature as white crystal; Application: epoxidation of alkenes; B-V reaction

---

**p-Nitrobenzoic peroxide**

Application: 1) oxidation of alcohol at room temp for high yield; 2) epoxy ketone can be prepared in one step from allylic alcohol; 3) forced conditions lead to lactone or ester from alcohol

Characterization: Stable at ambient temperature as white crystal; Application: epoxidation of alkenes; B-V reaction

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**Perbenzoic acid**

Prep: from corresponding benzoic acid with t-Butyl hydroperoxide. Application: low-temperature initiation (360 nm, compared to reflux of AIBN) of radical reaction;

Utilization: very similar as mCPBA

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**p-Methoxy carbonylperbenzoic acid**

Prep: from ester aldehyde which was irradiated with 2 kW high pressure Mercury light with O₂, as stable as mCPBA; Utilization: very similar as mCPBA

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**Persulfate based peroxide reagents:**

**K₂S₂O₈/(NH₄)₂S₂O₈**

Application: 1) oxidizing primary and secondary alcohols to aldehyde w/o cat. (kinetically slow to acid; 2) oxidizing ether to aldehyde; 3) oxidizing aldehyde or ketones to benzoic acid with metal catalysts; 4) oxidizing aliphatic amines to amidines or nitriles with Cu(II)/Ni(II) as catalyst; 5) oxidizing carboxylic acid to peracid under phase transfer condition;

Elbs oxidation:

Boyland-Sims oxidation:

C-H oxidation:

Oxidation of alkenes:

---

**Elbs oxidation:**

**Boyland-Sims oxidation:**

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**Oxidation of alkenes:**

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**Elbs oxidation:**

**Boyland-Sims oxidation:**

**C-H oxidation:**

**Oxidation of alkenes:**
Peroxide Chemistry in Organic Syntheses

Changxia Yuan

Oxidation of alcohols:

\[
	ext{OH} \quad \text{(NH}_4\text{)}_2\text{S}_2\text{O}_8, \text{ Cu(II)} \quad \text{AcOH, 100 °C} \quad 96\% \\
\]

C-H oxidation:

\[
\text{CO}_2\text{H} \quad \text{Ag(I), Cu(II), MeCN, 80 °C} \quad 56\% \\
\text{Tetrahedron. Lett. 1985, 2525.}
\]

\[
\text{CONHMe} \quad \text{K}_2\text{S}_2\text{O}_8 \quad \text{H}_2\text{O, 100 °C} \quad \text{R = H, 86%} \\
\text{Na}_2\text{S}_2\text{O}_8, \text{ K}_2\text{CO}_3 \quad \text{R = OMe, 76%} \\
\text{J. Am. Chem. Soc. 1979, 5687.}
\]

Application: Pseudohalogen reagent whose reactivity is comparable to that of chlorine; 
α-hydroxy ketone can be made from enol derivatives (OTMS, OA, NR₂)

\[
\text{CO}_2\text{H} \quad \text{SO}_3\text{H} \\
\text{p-Sulfoperbenzoic acid}
\]

Preparation: in situ with KO₂ and sulfonyl chloride
Application: epoxidation of alkenes (basic condition epoxidation); 
oxidation of benzylic position (few cases); oxidative desulfurization of thiocarbonyl compounds (sulfuryl urea to urea)

\[
\text{NO}_2 \quad \text{S}_2\text{O}_8^2- \\
\text{p-Nitrobenzenesulfonyl peroxide}
\]

Preparation: potassium carbonate, sulfonyl chloride and hydrogen peroxide; 
Application: moderate aromatic substitution to give aryl sulfonates, which can be hydrolyzed to phenols

Application: one electron oxidant of electron-rich aromatic compounds. 
can be also in catalytic version with K₂S₂O₈

\[
\text{O}_2 \quad \text{MeOH} \\
\text{Symmetric peroxide reagents:}
\]

Alternate name: DBP; relative unstable; 
Application: 1) widely used as radical initiator; classic anti-Markovnikov reaction; Minisci reaction of radical from alkyl halides, dioxane, DMF and even cyclohexane to protonated heteroaromatic compounds; used as benzoyloxylation of aromatics; used in hydroxylation of enolate

Alternate name: dibenzoyl peroxide

\[
\text{O}_2 \quad \text{Ph} \\
\text{Ph}
\]
Peroxide Chemistry in Organic Syntheses

**BuSn-O-SnBu**

Bis(tributyltin) Peroxide

*Application:* hard to prepare (BuSnH + anhydrous H₂O₂), only recommend on microscale

*Preparation:* mild nonalkaline source of dinucleophilic peroxide react with alkyl triflate to give dialkyl peroxide, higher yield than H₂O₂ + base

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**TMS-O-O-TMS**

Bis(trimethylsilyl) Peroxide

*Preparation:* from TMSI with urea + CO₂ stable (bp 41 °C at 30 mm Hg)

*Application:* 1) Li/Mg enolate to α-hydroxy-ketone; 2) E/Z vinyllithiums to E/Z vinylic enol ether

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**Me₅SiO-(OSiMe₅)₂VO(acac)₂**

Bis(trimethylsilyl) Peridoxy (Vanadyl bis(acetylacetonate)

*Preparation:* mixing TMSOCDTMS with vanadyl complex

*Application:* superfacial vanadium-assisted allylic rearrangement, allenic isomerization was also feasible

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**Caution:** extreme sensitive to shock when dry; use after prepared from oxalyl chloride with tBuOOH and pyridine;

**Utilization:** radical initiator; autooxidation DTBP + TBHP to functionalize hydrocarbons; extensively applied to low-temperature initiator for radical polymerization and radical trapping experiment, can be substituted by Di-tributyl hypoitrite.

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**1,1-di-t-butyl peroxoylate**

*Application:* fluorosulfating reagents of alkyl halides and hydrogen abstraction to give esters of fluorosulfuric acid; very strong oxidant (CO₂ to CO₂⁻) most of the ress from Soviet Union areas!

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**Di-t-butyl peroxyolate**

*Application:* fluorosulfating reagents of alkyl halides and hydrogen abstraction to give esters of fluorosulfuric acid; very strong oxidant (CO₂ to CO₂⁻) most of the ress from Soviet Union areas!
**Peroxide Chemistry in Organic Syntheses**

**DMDO and TFDO:** (it is worthy to give another group meeting on these two reagents!)

**Dimethyldioxirane (DMDO):**

- **Preparation:** recent easy Organic Synthesis procedure.
- **Application:** Epoxidation of kinds of alkenes! C-H activation of alkanes with the retention of the stereochemistry; readily oxidize amines and sulfide.

  \[
  \text{HO} - \text{OH} \quad 1.2 \text{ eq DMDO} \\
  \text{acetone, 0 °C} \\
  \text{98%} \\
  \text{Tetrahedron. Lett. 1993, 4559.}
  \]

  \[
  \text{HO} - \text{OH} \quad 1.2 \text{ eq DMDO} \\
  \text{acetone, 0 °C} \\
  \text{96%} \\
  \text{J. Org. Chem. 1993, 3600.}
  \]

**Methyl(trifluoromethyl)dioxirane (TFDO):**

- **Preparation:** Guillaume's procedure, stable in fridge for a week.
- **Utilization:** Epoxidation of extreme inert alkenes such as CF₃ substituted alkenes; oxidation of hindered phenols such as 2,6-di-t-butyl phenol; some magic C-H oxidation.

  \[
  \text{HO} - \text{OH} \quad 1 \text{ eq TFDO} \\
  \text{CH₂Cl₂, 0 °C, 3 h} \\
  \text{85%} \\
  \text{J. Org. Chem. 1992, 5052.}
  \]

**Metal-based peroxides:**

- **NaBO₂•4H₂O (sodium perborate):** oxidizing agent for a variety of functional groups; cheap/safe/convenient alternative to oxidants such as H₂O₂, MeCO₂H or MCPBA; In general, not good for dihydroxylation, B-V reaction though which was reported before; industry level viable alternative to hydrogen peroxide for the oxidative decomposition of organophosphorus ester wastes.

  \[
  \text{NaBO₂•4H₂O} \\
  \text{Ac₂O, H₂SO₄, reflux} \\
  \text{59%} \\
  \text{Synth. Comm. 1988, 937.}
  \]

- **H₂O₂—BF₃•Et₂O (hydrogen peroxide-Boron trifluoride):**

  - Utilization: B-V reaction using 90% H₂O₂ and BF₃•Et₂O, much stronger condition; moderate hydroxylation of arenes with HF as additive.

  \[
  \text{H₂O₂—BF₃•Et₂O} \\
  \text{J. Am. Chem. Soc. 1992, 1375.}
  \]

- **Mg₃(VO)₆H₂O (monoperoxyphthalic acid):**

  - Preparation: phthalic anhydride and H₂O₂ in the presence of NaOH or MgO
  - Utilization: epoxidation of alkenes, B-V rxns; and oxidation of amine, sulfide and selenium

**Ce(OH)₃O₂H (cerium(IV) tribhydroxide hydroperoxide):**

- **Prepared in situ with LiOH and H₂O₂:**
- **Utilization:** cleavage of different kinds of amide ligands, such as Evan's oxazolidones, Davis' sultam auxiliary, and Myer's pseudoephedrine auxiliary; ester can be also cleaved.

**LIOOH (lithium hydroperoxide):**

- **Prepared in situ with LiOH and H₂O₂:**
- **Utilization:** oxidation of vincinal diols.

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**Changxia Yuan Baran Group Meeting 4/5/2014**

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**1BuMe₂SiOOOH—Hg(OTf)₂ (hydroperoxide - mercury triflate):**

- **Preparation:** used in peroxy-mercuration to epoxidation (by Corey)

  \[
  \text{1BuMe₂SiOOOH—Hg(OTf)₂} \\
  \]

---
**Benzeneperoxyseleninic acid**

- **Application**: Major for B-V reaction; and oxidizing agent for multiple functional groups such as hydrazyl imine to cyano groups.
- **m.p.**: 52 °C w/ detonation.
- **Preparation**: Diphenyl diselenide with 30% H₂O₂.

**Nickel(II) Peroxide**

- **Black hydrous powder**
- **Utilization**: Oxidation of primary alcohols to carboxylic acid in aqueous media, or oxidize allylic, benzylic alcohol to aldehyde in organic solvent; oxidize phenols to polymeric mixtures and quinones; oxidize alcohol or aldehyde to amide in ammoniasolution; oxidize amine to cyano or diazo compounds; dehydrogenation of unsaturated heterocycles.

**Oxoperoxobis(N-phenylbenzohydroxamato)molybdenum(VI)**

- **Preparation**: MoO₃, 30% hydrogen peroxide with HMPA, free-flowing yellow crystal.
- **Application**: Common reagent for hydroxylation of enolates; oxidation N, S, P.

**Peracid series**

- **Electrophilic reagent capable of reacting with many functional groups**; prepared in situ in industry for epoxidation of vegetable oil and fatty acid esters; broad range of epoxides formation when carrying no acid sensitive groups; (terminal alkenes are sluggish); in some cases, different regioselectivities can be observed comparing to mCPBA; oxidation of amines to phenols in low yield; B-V reaction; amine to nitroso, sulfide to sulfone.

**Palladium t-Butyl Peroxide Trifluoroacetate**

- **Preparation**: Yellow crystal from Palladium(II) acetate and trifluoroacetic acid and TBHP.
- **Utilization**: Alkenes to methyl ketone.

**Peracid**

- Electrophilic reagent capable of reacting with many functional groups; prepared in situ in industry for epoxidation of vegetable oil and fatty acid esters; broad range of epoxides formation when carrying no acid sensitive groups; (terminal alkenes are sluggish); in some cases, different regioselectivities can be observed comparing to mCPBA; oxidation of amines to phenols in low yield; B-V reaction; amine to nitroso, sulfide to sulfone.

**J. Organo. Met. 1975, 115.**

**Chem. Lett. 1983, 1771.**

**J. Org. Chem. 1993, 2929.**
Peroxyacetic acid

Preparation: in situ with Tf₂O and 90% H₂O₂ or Urea⋅H₂O₂
Application: the strongest organic peroxy acid; very powerful epoxidation reagents, more than mCPBA; diols are the subsequently hydrolysis by TFA; B-V reaction is facile; various of heteroatoms can be oxidized

Miscellaneous peroxides:

- O-ethylperoxycarbonic acid
  - Preparation: not stable to store; ethyl chloroformate with hydrogen peroxide in situ
  - Utilization: epoxidation of alkenes on biphasic condition, cheap and environmentally benign

- 2-Hydroperoxymethyl-2-propanol
  - Preparation: hexafluoropropionate with 30% or 90% H₂O₂
  - Utilization: epoxidation of alkene and oxidize sulfide to sulfoxide and sulfones

- Peroxyacetyl nitrate
  - Oxidant useful for enantioselective metal-catalyzed epoxidation of allylic alcohols and enantioselective oxidation of sulfides to sulfoxides (moderate to poor result)

- Peroxyacetic acid
  - Better leaving group than HO-OH
  - Peroxyacetic acid (Payne oxidation)

- Peroxytrichloroacetamidic acid
  - Prepared with trichloroacetonitrile and 30% H₂O₂; most of the time which can be substituted by common reagents for epoxidation

- Peroxymaleic acid
  - Prepared from 90% hydrogen peroxide and maleic anhydride
  - Utilization: for epoxidation; B-V reaction (most common) no buffer needed; oxidize amine to nitro group

- Peroxytrichloroacetamidic acid
  - Prepared from the tetralin and C
  - Utilization: for epoxidation, usu mCPBA or TBHP/Mo is superior; oxidation of aromatics to give ph low yield

- α-Tetralyl hydroperoxide
  - Prepared from diphenylpyrazole, 90% hydrogen peroxide (caution!)

- Triethylsilyl Hydrotrioxide
  - Prepared from SO₃ and TMSOOTTMS using as crude at -30 °C decompose (explode) at rt! Use immediately

- Bis(trimethylsilyl) monoperoxysulfate
  - Preparation: from SO₃ and TMSOOTTMS using as crude at -30 °C
Peroxide Chemistry in Organic Syntheses

Synthetic methods to access peroxides:

\[ \text{Me} - \text{OMe} \xrightarrow{\text{KOO}, 18-C-6, DMSO} \text{Me} - \text{O} - \text{Ph} \]

35%

\[ \text{Me} - \text{OMe} \xrightarrow{\text{N-isopropyl perester, ALD00008}} \text{Me} - \text{O} - \text{Ph} \]


\[ \text{MeO} - \text{NR}_2 \xrightarrow{\text{Ti(OiPr)}_4, allylTMS}} \text{N-succinimidyl perester} \]

63%

60%


\[ \text{R} = \text{Me or (CH}_2\text{)}_3 \]

86%

\[ R = \text{alkyl or aryl} \]

\[ R^2 = \text{EWG or EDG} \]


\[ \text{N} \xrightarrow{\text{CuCl, decumyl peroxide}} \text{N} \]

60-80%

proposed radical mechanism


\[ \text{Me} - \text{O} - \text{Me} \xrightarrow{\text{O}_2, \text{Ph}_2\text{Se}, \text{IBN, MeCN, } 0^\circ \text{C}} \text{Me} - \text{O} - \text{CO}_2\text{Me} \]

88%

cis >95%

Peroxide Chemistry in Organic Syntheses

**Cyclic Peroxide in synthesis:**

**J. Am. Chem. Soc. 2010, 140(9).**

\[
\text{Cl} \quad \text{C} \quad \text{Cl} \rightarrow \text{Cl} \quad \text{C} \quad \text{Cl} \quad \text{HOH} \quad \text{HOH} \\
\text{NaOCl} \cdot \text{H}_2 \text{O}_2 \text{ CHCl}_2(0.2 \text{ eq} \text{HO}), 23^\circ \text{C} \quad \text{60}\% \\
1) \text{R}^1 \quad \text{R}^2 \quad \text{CHCl}_240^\circ \text{C} \\
2) \text{K}_2 \text{CO}_3, \text{MeOH,} \text{H}_2 \text{O}, 23^\circ \text{C} \rightarrow \text{HO} \quad \text{R}^1 \quad \text{HO} \quad \text{R}^2 \\
\]

**Examples:**

- \( \text{R} = \text{H} \): 72%, 20:1
- \( \text{R} = \text{OMe} \): 56%
- \( \text{R} = \text{tBu} \): 66%

71%, 4:1, 45%, 25:1, 30%, 25:1, 44%, 25:1

**General reactions:**

- 1. HFIP, 23–50 °C
- 2. MeOH/sat. NaHCO\(_3\), 40 °C

**Proposed mechanism:**

**Nature 2013, 499, 192.**

- PPO
- reverse rebound diradical activation

- hydrolysis
- phenols

**Noticeable examples:**

- 42% (sm 37%) on 0.85 gram scale

**J. Org. Chem. 2011, 921.**

**Example:**

- BocHN

- 30%
Some peroxides contained natural products:

**Ascaridole**
First studied naturally occurring organic peroxide

**Yingzhaosu A and C**
Yingzhaosu A and C both contain a 1,2-dioxane core structure. These compounds have been extensively studied for their potential antimalarial activity

**Qinghaosu or Artemisinin**
1,2,4-trioxane core, artemisinin and its derivatives are a group of drugs that possess the most rapid action of all current drugs against falciparum malaria

**Plakinic acid A**
The first isolated five-membered ring peroxide which has a big family on the side chain; remarkable cytotoxicity against fungal and cancer cell lines

**Prostaglandin G2**
Key intermediates in prostaglandin's biosynthesis from arachidonic acid within a big family of prostaglandin

**Termenic peroxide**
Moderate antimalarial activity

**Verruculogen**
Produces severe tremors and acute toxicity

**Gracilioether A**
Show considerable antimalarial activity

**Plakortide E**
Selectively inhibits the beetle's fungal antagonist

**Plakortide G**

**Plakortide**

**Mycangimycin**
Selectively inhibits the beetle's fungal antagonist

**Chondrillin**
First cyclic peroxide to be isolated from marine sources

**Talaperoxides A**
Colllected on the coastal saltmarsh of the South China Sea

**Chondrillin Plakorin**

**Plakortide**

**Trunculin B**

**Dioxetanone**
Semi-synthesis of Artemisinin-Qinghaosu in industry:
Malaria is a disease that affects millions of people; Discovery by Keasling of a biosynthetic pathway for artemisinic acid;
An industrial process was fully implanted to produce 60t in 2014.

**Diastereoselective hydrogenation**

**Artemisinic acid**

\[
\begin{align*}
\text{RuCl}_2[(R)-\text{DTBM-Segphos}](\text{DMF})_2 & \quad \text{S/C >8000/1} \\
\text{S/C is 2000/1} & \quad \text{S/C is 8000/1, with more time, 16000/1} \\
\text{NiBH}_4 & \quad \text{but the d.r. is not perfect with extensive screen}
\end{align*}
\]

**Photooxidation of artemisinin**

**Mechanism**: Schenck ene reaction/Hock cleavage/subsequent oxygenation/cyclization

- 41% yield from the lead by Amyris with significant impurities
- Aubry reaction is to avoid photochemical equipment
- The first generation of peroxide is dangerous

**Diastereoselective hydrogenation**

- RuCl₂[(R)-DTBM-Segphos](DMF)_2 catalyst that is favor of inherent diastereoselectivity of artemisinic acid (AA) with an appropriately matched chiral ligand, Ru is much more affordable
- S/C is 8000/1, with more time, 16000/1

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**Mixed anhydride linear peroxide**

- 95% in all total steps including crystallization of the final product
- Reaction performed at 15 °C showed accumulation of the hydroperoxide, one-pot procedure was needed, therefore the ester was orchestrated to more activated anhydride ester