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New Methods for Synthesis of Organic Peroxides and Application of Peroxide Electrophiles to Synthesis of Functionalized Ethers

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NEW METHODS FOR SYNTHESIS OF ORGANIC PEROXIDES AND APPLICATION OF PEROXIDE ELECTROPHILES TO SYNTHESIS OF FUNCTIONALIZED ETHERS

by

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NEW METHODS FOR SYNTHESIS OF ORGANIC PEROXIDES AND APPLICATION OF PEROXIDE ELECTROPHILES TO SYNTHESIS OF FUNCTIONALIZED ETHERS

Shiva Kumar Kyasa, Ph.D.
University of Nebraska, 2015
Adviser: Patrick H. Dussault

New Method for Synthesis of Alkyl Hydroperoxides: There are a number of methods reported for synthesis of alkyl hydroperoxides, but most of them suffer either from poor yields or the formation of unwanted side products. I will be discussing new methodology for efficient synthesis of pure samples of 1° and 2° alkyl hydroperoxides via alkylation of readily available cyclododecanone 1,1-dihydroperoxide followed by hydrolysis of the resulting bis peroxyacetals.

Peroxide Electrophiles for Synthesis of Functionalized Ethers: Peroxides are underexplored functional groups as precursors for C-O bond formation and ether synthesis. The reactivity of dialkyl peroxides towards organometallics such as alkyl lithium and magnesium reagents is known. However, there has been little application of this reaction to C-O bond formation due to limitations in the reactivity of available reagents for alkoxide transfer**.** We have studied the reactivity of a variety of dialkyl peroxides, alkyl/silyl peroxides, and monoperoxyacetals towards simple organolithium and organomagnesium reagents and found that thermally stable 2-tetrahydropyranyl peroxides enable efficient and highly selective transfer of 1°, 2° and 3° alkoxide (RO) groups to carbanions to form the corresponding ethers. The method was applied to synthesis of a variety of functionalized ethers, including *S,S,O*-orthoesters, difluoroethers, mixed *O,O*-acetals, and cyclopropyl ethers. The observed results are discussed in terms of possible mechanisms for C-O bond formation.

To,

My Parents Balaiah & Laxmi and wife Jyothi

Acknowledgements

I am extremely grateful to Prof. Patrick H. Dussault for his guidance for my doctoral research and teaching of organic chemistry in the classroom. I couldn't go into the depths of organic synthesis and peroxide chemistry without his help.

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Chapter-1. Reductive amination of hydroperoxy acetals; application of reductive amination in tandem with ozonolysis.

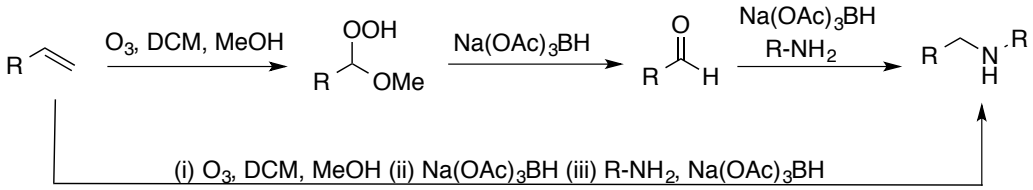
Chapter-2: A New Synthesis of Alkyl hydroperoxides.

Chapter-1. Reductive amination of hydroperoxy acetals; application of reductive amination in tandem with ozonolysis.

Portions of this chapter were reproduced from *Synthesis*, 2011, 3475 with the permission of the publisher.[1]

In this chapter, I will discuss the development of new methodology for one-pot conversion of alkenes to amines. The discussion will begin with the formation of hydroperoxy acetals from alkene ozonolysis and then discuss our development of a mild reduction of hydroperoxy acetals to carbonyl compounds using $Na(OAc)_3BH$. The chapter will conclude with the application of this methodology to reductive amination, including a one-pot synthesis of amines from alkenes (Scheme-1).

Scheme-1:

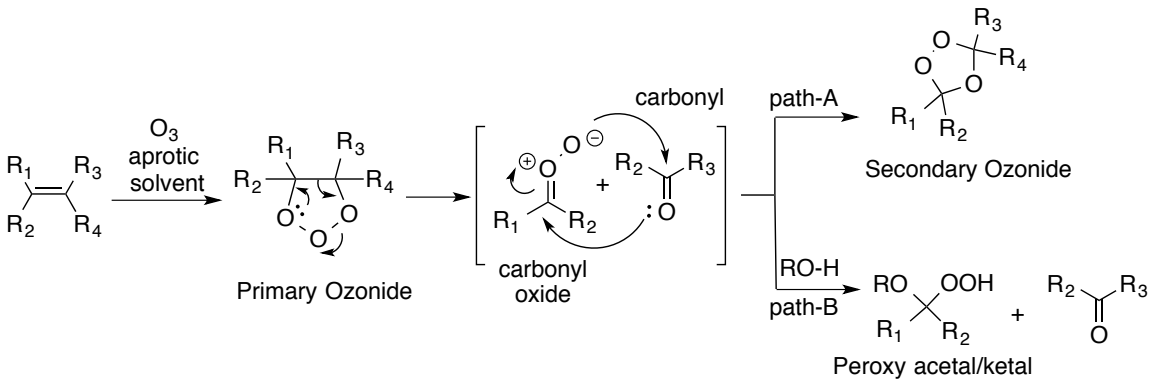


Section-1: Introduction

Alkene ozonolysis is a classic strategy for cleaving C-C double bonds.[2] A search using the term ‘‘ Ozonolysis’’ in SciFinder generated more than 14,000 references for the exact term and more than 53,000 references containing the concept of ozonolysis. When the search was narrowed with the term ‘‘alkene’’ there were still more than 2100 references related to alkene ozonolysis.

The mechanism of alkene ozonolysis is summarized in Scheme 2. Cycloaddition of ozone and an alkene forms a primary ozonide that can easily fragment into a carbonyl oxide/carbonyl pair.[3]

Scheme-2: Criegee mechanism for alkene ozonolysis



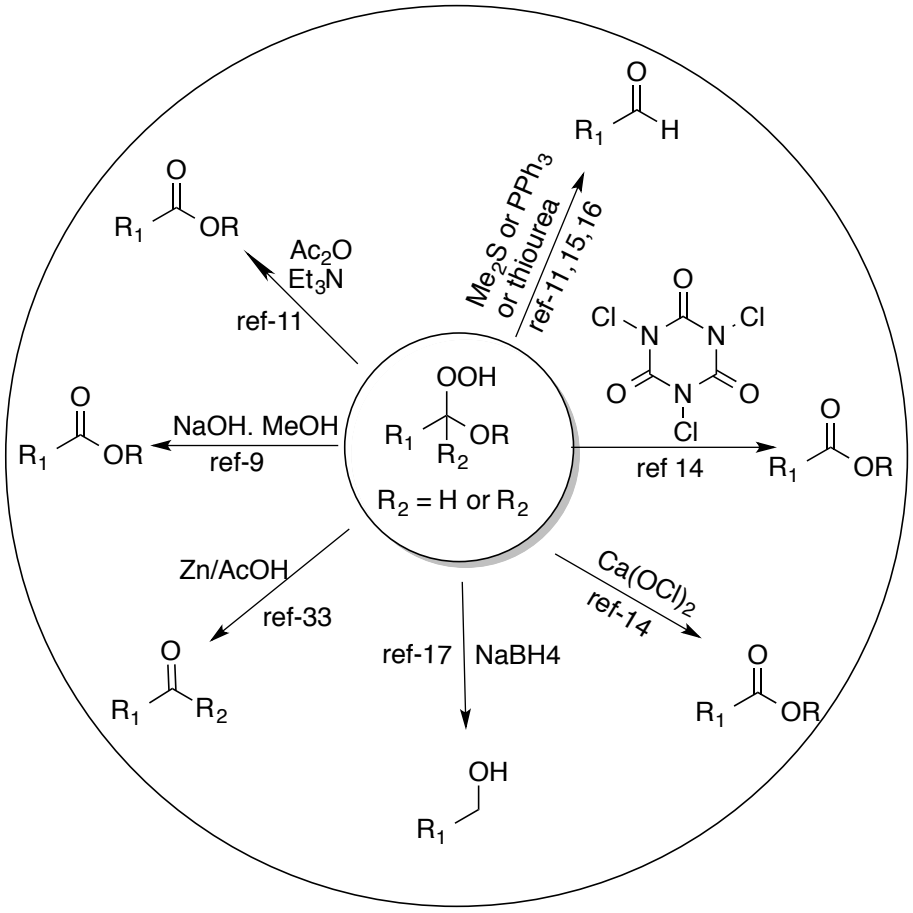
The carbonyl oxide is highly reactive.[4] In the absence of a protic nucleophile such as an unhindered alcohol, 1,3-cycloaddition of the carbonyl oxide and the co-generated carbonyl will frequently take place, leading to formation of a secondary ozonide (Path-A). Ozonolysis in presence of methanol or a similar nucleophile results in addition to the carbonyl oxide to furnish a hydroperoxyacetal, accompanied by the carbonyl group generated during the fragmentation of the primary ozonide. (Path-B).

The secondary ozonides or hydroperoxyacetals generated by alkene ozonolysis potentially hazardous to isolate, particularly on a large scale. [5] A large number of procedures have been described for reduction of secondary ozonides to carbonyl compounds.[6] A smaller group of methods target the generation of carbonyls through direct capture and decomposition of the carbonyl oxides.[7, 8,9] This section will focus on the chemistry of hydroperoxyacetals and their application in tandem functionalization.

Section-2: Background on Hydroperoxyacetals functionalization

Hydroperoxyacetals generated during ozonolysis can either be isolated or converted to other functionality. Examples of common transformations are illustrated in Scheme 3. (detailed discussion and references below). The methods shown in Scheme 3 all preserve the original skeleton of the hydroperoxyacetal.

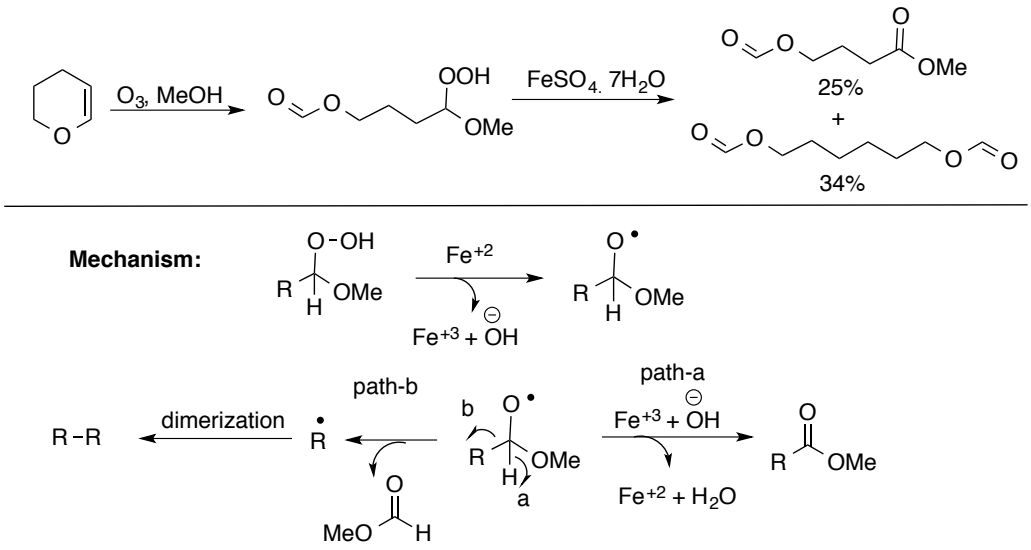
Scheme-3: Hydroperoxy acetal functionalization.



Hydroperoxyacetals also undergo fragmentation in presence of metal salts such as Fe^{+2} by single electron transfer (SET) to give radical scission products derived from intermediate alkoxide radicals. The intermediate alkoxy radical can undergo homolytic cleavages in two ways (path A and B, Scheme-4 mechanism). [10] Path-A generates esters by homolytic C-H bond cleavage. Path-B, involves a homolytic C-R bond cleavage

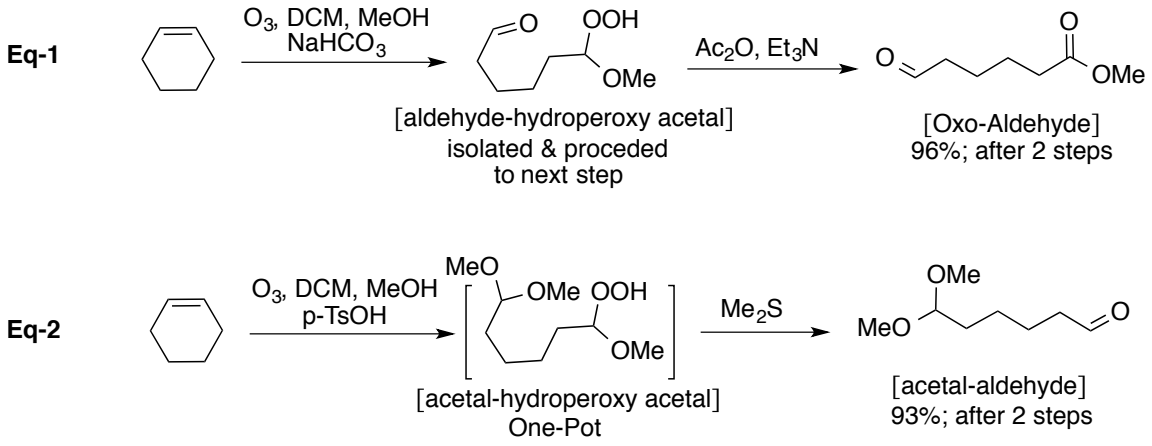
leading to an alkyl radical that can undergo dimerization, oxidation[10] (in the presence of Fe^{+2}).

Scheme-4: ref-10



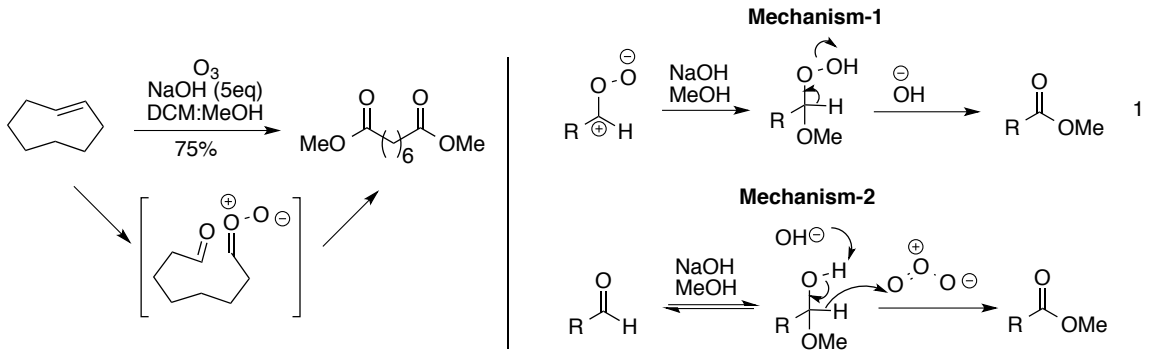
These reactions can be applied within cycloalkenes as a means of preparing end-differentiated products (Scheme-5). [11] Ozonolysis of cyclohexene, followed by base-promoted dehydration of hydroperoxy acetals after activation by conversion to the corresponding peresters, furnishes an oxoalkanoate (Scheme-5, Eq-1). Alternatively, conducting ozonolysis in the presence of protic solvent and a Brønsted acid results in formation of a hydroperoxyacetal/acetal; (Scheme-5, Eq-2) the aldehyde group that would be generated under neutral conditions is converted under these conditions to a dimethyl acetal. [11] Treatment of the crude reaction mixture with dimethyl sulfide achieves reduction of the hydroperoxyacetal to give mono protected di-aldehyde product (acetal-aldehyde). This method is valuable as selective protection of dialdehydes taking place.

Scheme-5:



Scheme-6 shows some related chemistry for formation for conversion of a cycloalkene to a diester through ozonolysis in presence of base and alcohol as solvent.[9] The method, which has been more frequently applied to cleavage of terminal alkenes to form monoesters, illustrates the formation of esters through two different mechanisms. One ester is presumably formed from the hydroperoxyacetal via base promoted dehydration without any activation such as acetylation as above (mechanism-1). The other ester must be formed from oxidation of the aldehyde that is co-generated during cyclo-reversion of the primary ozonide.

Scheme-6:

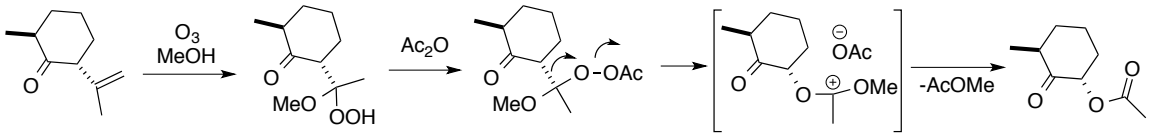


Although oxidation of aldehydes by ozone is usually quite slow, the reaction conditions (methanolic base) favor rapid equilibration with an intermediate hemiacetal that can more

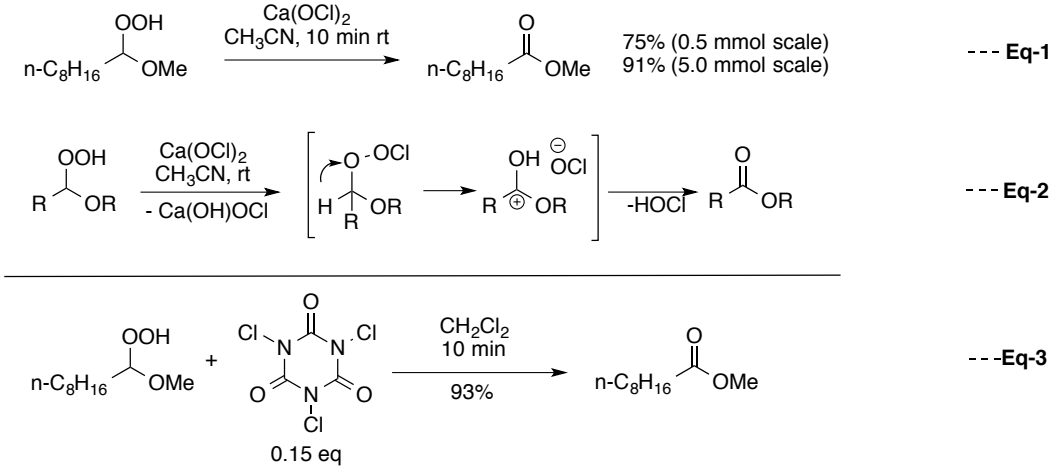
readily undergo oxidation via fragmentation in the presence of base and ozone (mechanism-2).

Hydroperoxyketal-derived peresters, which are unable to undergo elimination, were shown to undergo Criegee rearrangement to produce esters through a C-to-O-migration; the net process involves loss of both alkene carbons and stereospecific replacement of the C-alkene bond with a C-O bond (Scheme-7). [13]

Scheme-7: Criegee rearrangement of ozonolysis-derived peresters



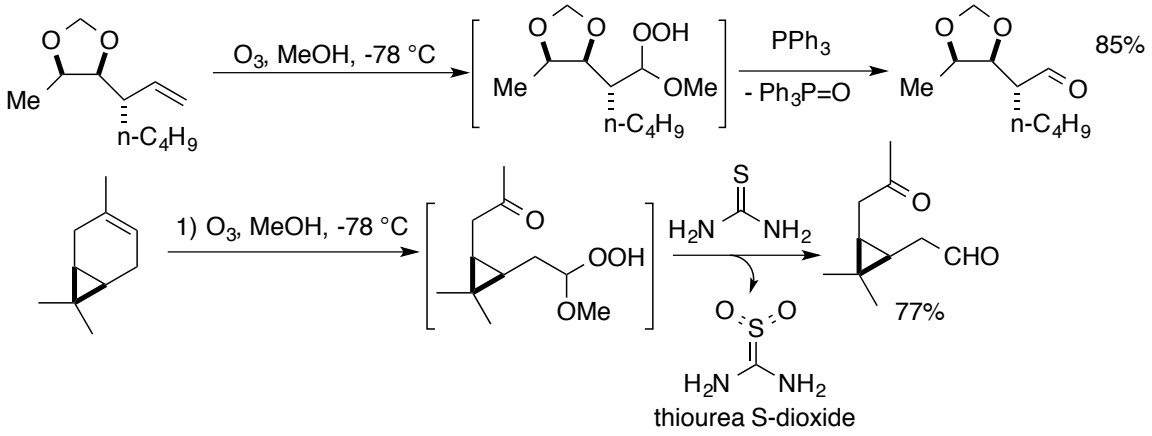
Scheme-8:



Dehydration of hydroperoxy acetals to esters has also been efficiently achieved in the presence of hypochlorite or trichlorocyanuric acid. (Scheme-8). [14] A radical mechanism was ruled out based upon the lack of ring opening of a substrate incorporating a radical clock (not shown here). The reaction is believed to involve a heterolytic fragmentation of an intermediate chloroperoxide.

In addition to dimethyl sulfide (discussed above), triphenyl phosphine[15] and thiourea [16] have also been used for reduction of hydroperoxy acetals to aldehydes; triphenyl phosphine oxide and thiourea S-dioxide are the byproducts of these reductions (Scheme-9).

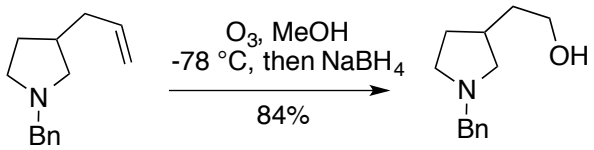
Scheme-9: Hydroperoxy acetal reduction by PPh_3 and thiourea.



Reduction with hydride sources:

Although we found no reports describing reaction of isolated hydroperoxy acetals with hydride reducing agents, this chemistry has certainly taken place in the course of reductive work-ups of ozonolysis reactions. Equation-1 shows a typical example involving reduction of ozonolyzed products with $NaBH_4$ to generate an alcohol.[17]

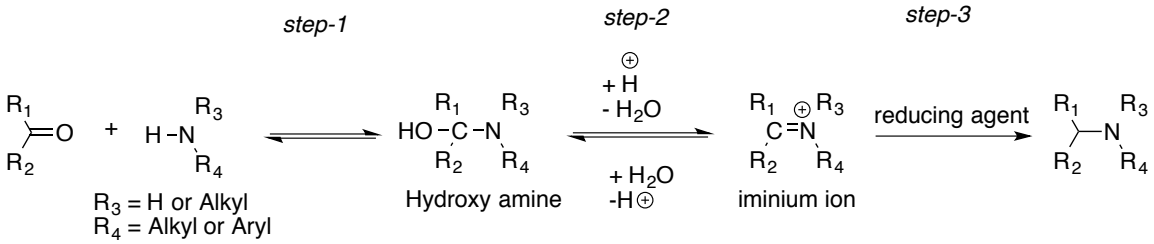
Equation-1:



Section-3: Brief introduction about reductive amination

Carbonyl compounds react with amines to form hemiaminals, which can undergo elimination to form iminium ions. These ions can be reduced with hydride sources to form amines. The overall process is an important synthetic strategy called reductive amination. Equation-2 shows a general Scheme of this process.[18]

Equation-2: ref-18



A large variety of reductants[19, 20] have been applied to reductive amination, including hydrogen (catalytic hydrogenation) and formate salts (Leuckart reduction). However, the most common approach to reductive aminations, and the one relevant to the research described here, involves the use of hydride reducing agents.

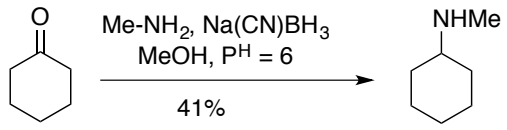
Hydride sources:

There are a variety of reducing agents that have been employed for reduction of iminium ions intermediates during the reaction of carbonyl compound and amine.[20] Here I am discussing selected examples of relevance to the research reported here.

Sodium borohydride has been applied for reductive amination. However, because this reagent rapidly reduces aldehydes, the reductive amination can only be conducted after the aldehyde has been converted to the imine/iminium ion or in presence of protic acids.[20] $Na(CN)BH_3$ is an early successful example of hydride source which is effective at pH 3-4 for aldehyde and ketone reductive aminations.[21] The ability to conduct reduction at low pH helps promote iminium ion formation (step-2 in equation-2), minimizing the

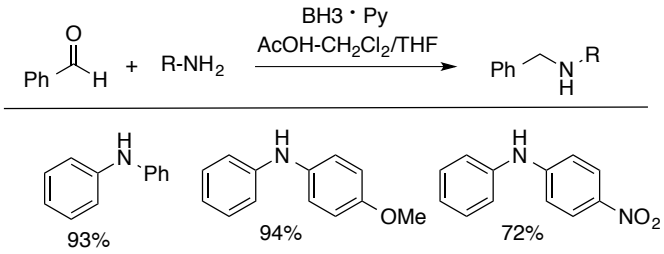
formation of alcohol byproduct resulting from reduction of carbonyl starting material. Some limitations of this reagent include the typical requirement of excess amine to suppress the possible side reaction of carbonyl reduction, and the generation of cyanide as a byproduct. A representative example with $Na(CN)BH_3$ is shown in equation-3.

Equation-3:



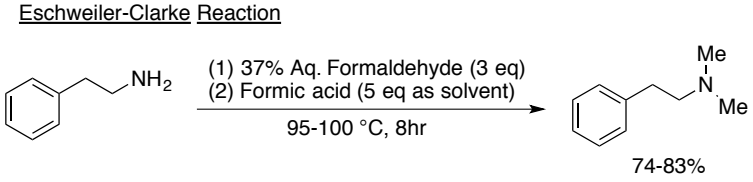
Borane-pyridine complex (BH_3•Py) has also been utilized as a selective reagent for reductive amination; this deactivated borane is superior to BH_3•Et_3N or BH_3•Me_2NH in terms of selective reduction of iminium intermediates over carbonyl starting materials at neutral conditions (Scheme-10). [22]

Scheme-10



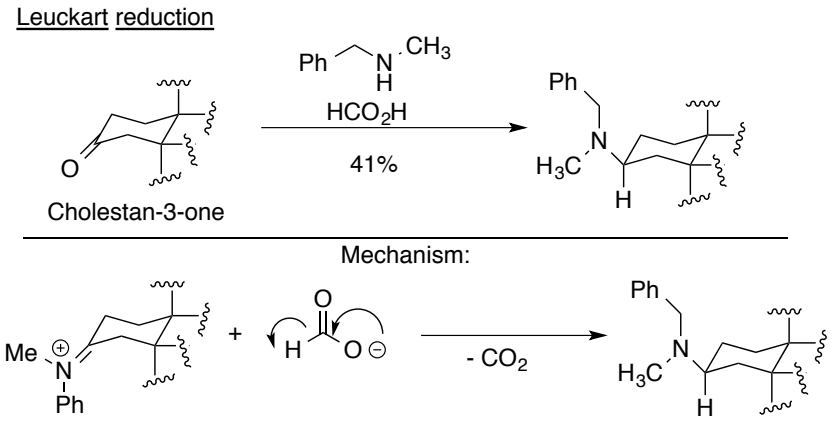
Formate as hydride source: Formic acid or formate salts such as ammonium formate was shown to reduce iminium ions. The Eschweiler-Clarke reaction employs a mixture of formaldehyde and formic acid for *N*-methylation of amines (Scheme-11). [23]

Scheme-11:



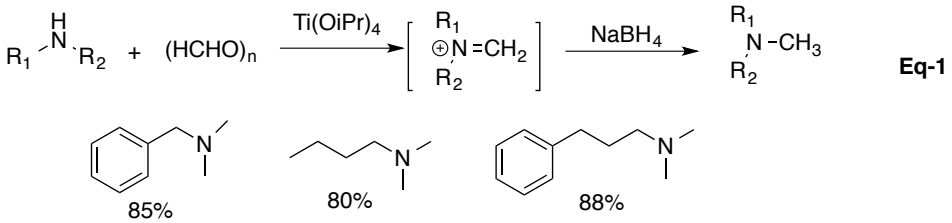
The related Leuckart reduction [24, 25] involves reductive aminations of ketones and aldehydes with primary and secondary amines, using formic acid, ammonium formate or formamide as reducing agents (Scheme-12).

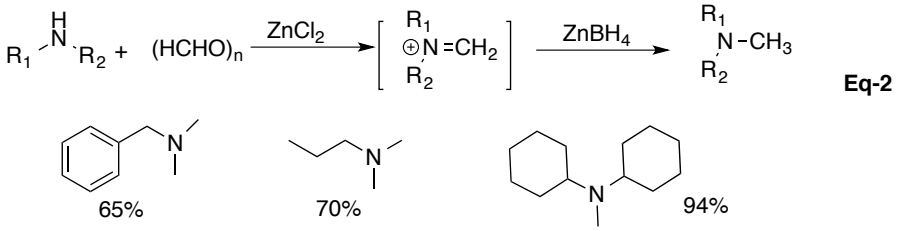
Scheme-12:



The combination of Lewis acids and reducing agents, e.g. $Ti(OiPr)_4/NaBH_4$ or $ZnCl_2$-$ZnBH_4$, have been applied to *N*-methylation of amines with paraformaldehyde.[26, 27] (Scheme-13, Eq 1 and 2 showing examples). The Lewis acid presumably catalyzes conversion of paraformaldehyde to formaldehyde and assists in the initial formation of iminium ion.

Scheme-13: N-methylation using formaldehyde reductive amination

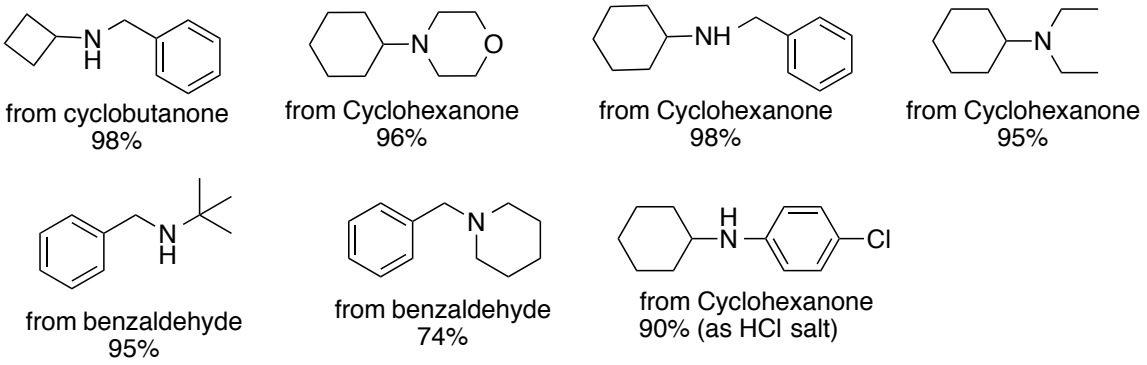




Eq-2

Sodium (triacetoxy)borohydride has been utilized as a hydride source for room temperature reductive amination with a wide range carbonyl compounds reductive amination[18] (aliphatic and aromatic aldehydes, aliphatic cyclic and acyclic ketones) and amines (primary and secondary) without use of acid catalyst or the need for excess amine. This reagent has the advantage of very high selectivity for iminium ions compared with the precursor aldehydes. As a result, sodium triacetoxyborohydride, much like sodium cyanoborohydride, can be reacted with a mixture of the aldehyde and amine without fear of extensive reduction of the aldehyde. Methylene chloride or 1,2-dichloroethane are most commonly used as solvents. Representative examples are shown below (Scheme-14).

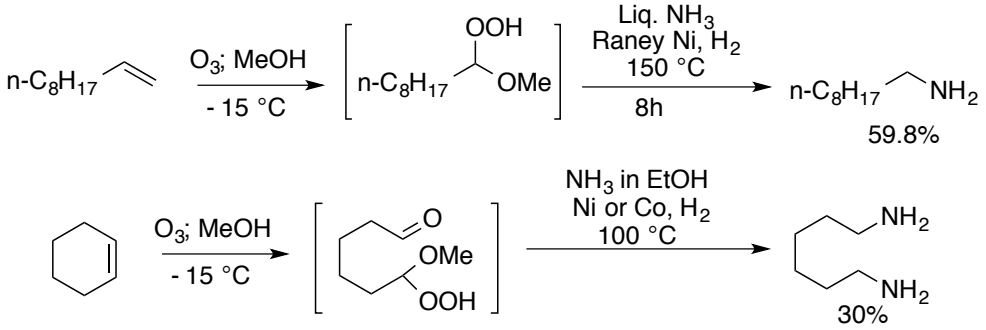
Scheme-14: Reductive amination products using $Na(OAc)_3BH$ [ref-18]



Section-4: Previous reductive amination of peroxyacetals in tandem with alkene cleavage

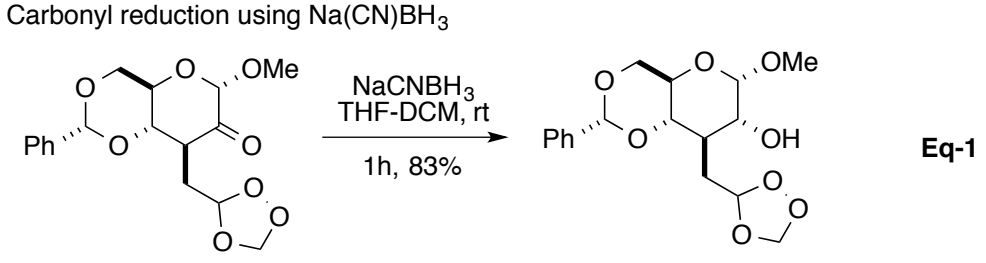
Two previous reports have described ozonolysis of alkene applied in tandem with reductive amination of hydroperoxy acetals. One involved hydrogenation using either a Ni or Co catalyst; the other involves hydrogenation with Raney nickel. (Scheme-15). [28, 29]

Scheme-15:



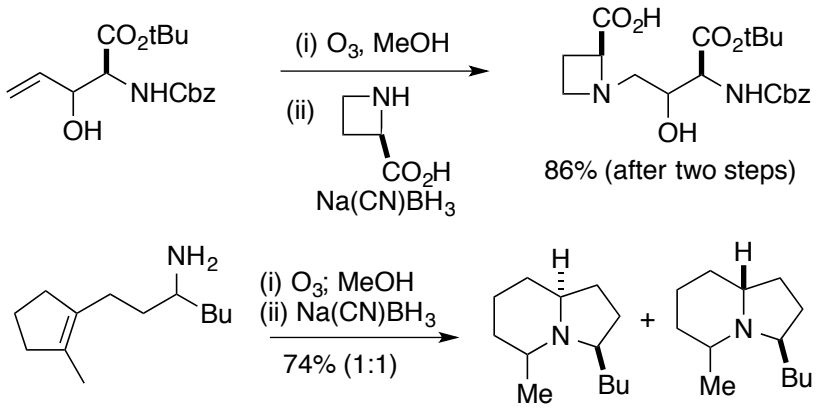
$Na(CN)BH_3$, which is unreactive towards secondary ozonides (Scheme-16, Eq-1),[30] has been explored for reductive amination of ozonolysis-derived hydroperoxy acetals (Scheme-16, Eq-2 and 3). However, as will be discussed later, we observed that use of this reagent generated alcohol by-product from over-reduction of initially generated carbonyl compounds.[31, 32] For this reason**,** we became interested in the use of the mild reducing agent $Na(OAc)_3BH$ for reduction of hydroperoxy acetals to form carbonyl compounds.

Scheme-16:



Eq-1

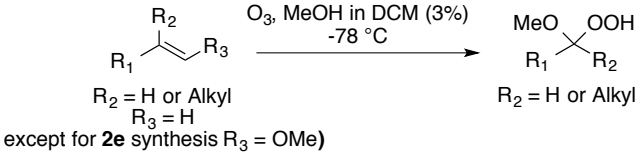
One pot ozonolysis and reductive amination using $Na(CN)BH_3$

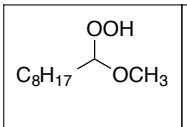
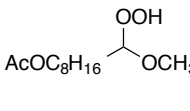
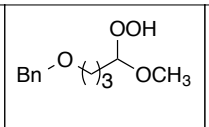
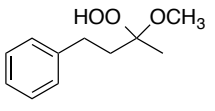
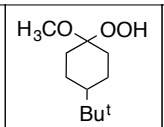
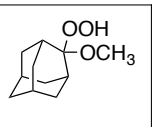


Section-5: Synthesis of hydroperoxyacetals/ketals and reduction with $Na(OAc)_3BH$

Initially, hydroperoxyacetals were synthesized from alkenes by ozonolysis in dichloromethane containing a small amount of methanol. Peroxyketal **2e** was synthesized from corresponding enol ether (Scheme-17).

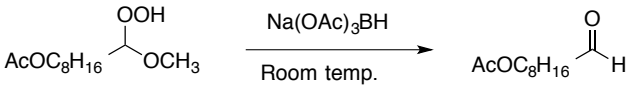
Scheme-17: Hydroperoxyacetal synthesis from alkene.



					
2a (70%)	**2b** (67%)	**2c** (69%)	**2d** (38%)	**2e** (74%)	**2f** (63%)

In an initial screening, the reduction of **2a** with $NaHB(OAc)_3$ was investigated at room temperature in dichloromethane, dichloroethane, THF and MeOH solvent (Scheme-18). Regardless of solvent, we obtained good yields of the aldehyde. Reaction in the presence of a slight excess of $NaHB(OAc)_3$ (last entry) gave no evidence of over-reduction to alcohol.

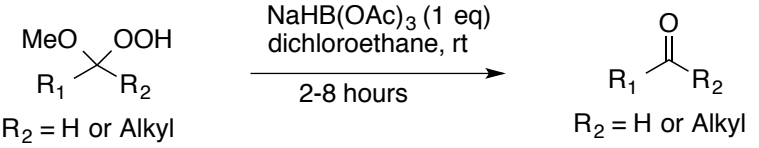
Scheme-18:

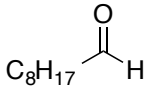
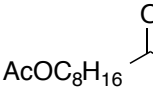
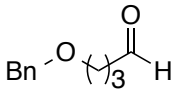
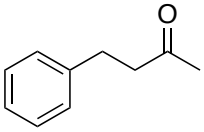
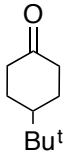
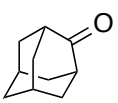


Solvent	$Na(OAc)_3BH$ (eq)	mmol	Time	Yield (%)
MeOH	1	0.5	10-30 min	78
CH_2Cl_2	1	0.5	3-4h	80
Cl-CH_2CH_2-Cl	1	0.5	3-4h	85
THF	1.2	0.5	1-2h	85

We next investigated a broader range of reductions in dichloroethane, a solvent already established to be a good choice for the planned reductive aminations (Scheme-19).[18]

Scheme-19:



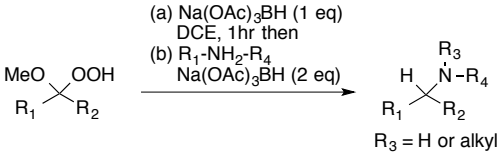
					
3a (63%) 2h	**3b** (85%) 2h	**3c** (91%) 2h	**3d** (70%) 5h	**3e** (68%) 5h	**3f** (68%)[a] 8h

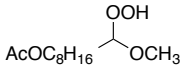
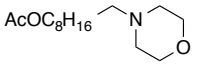
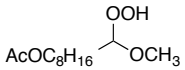
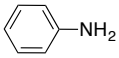
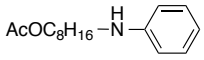
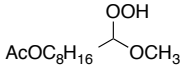
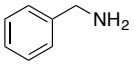
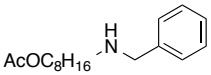
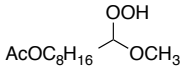
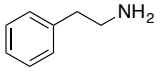
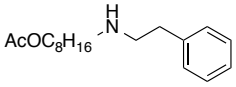
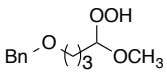
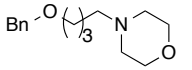
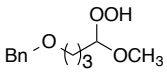
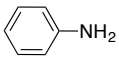
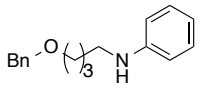
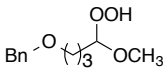
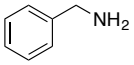
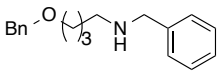
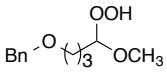
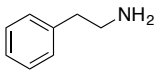
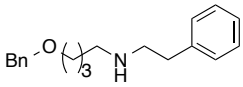
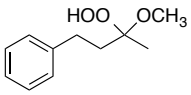
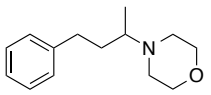
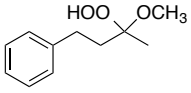
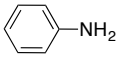
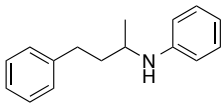
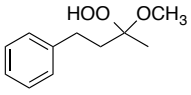
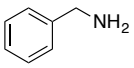
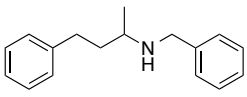
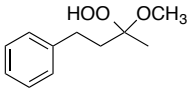
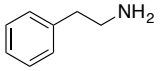
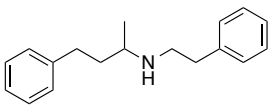
a = based on 15% starting material recovery

Reduction of hydroperoxy acetals occurs more rapidly (with in two hours) compared to hydroperoxy ketals (**3d, 3e, 3f**; 5-8 hours). Adamantyl hydroperoxy ketal was not converted completely in to products even with extended reaction times.

Section-6: One pot synthesis of amines from hydroperoxy acetals.

Table-1: One pot reduction and reductive amination of hydroperoxy acetals



Entry	Hydroperoxyacetal	R_3-NH-R_4	Amine	Yield (%)
1				85
2				75
3				67[a]
4				63
5				89
6				69
7				63
8				65
9				45
10				60
11				75
12				52

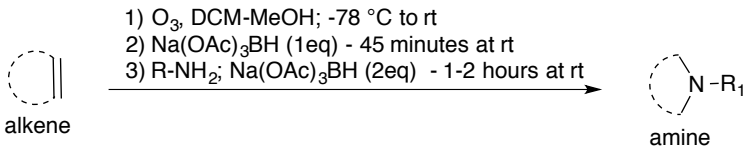
a = 8% dialkylated product formed

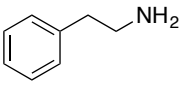
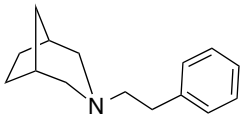
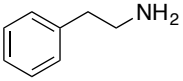
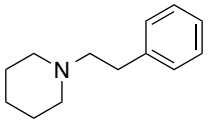
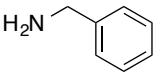
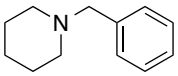
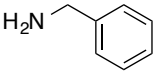
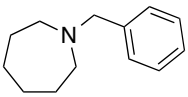
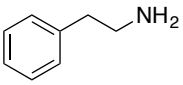
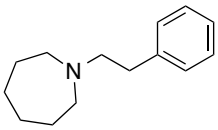
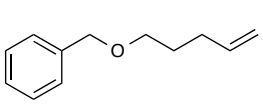
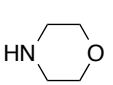
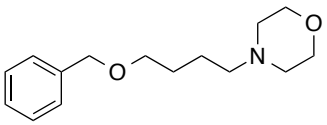
Based upon the successful conversion of hydroperoxyacetals to carbonyl compounds with sodium (triacetoxy)borohydride, a reagent proven effective for reductive amination,[18] we turned our attention to the one-pot conversion of hydroperoxy acetals in to amines. Table-1 illustrates the results obtained for converting hydroperoxyacetals to amines in two steps conducted in the same pot. Reduction of the hydroperoxyacetal with one equivalent $NaHB(OAc)_3$ is followed by addition of amine and additional $NaHB(OAc)_3$ to achieve reductive amination. The process results in good yields with primary, secondary, and aromatic amines.

Section-7: One pot synthesis of amines from alkenes

The successful preparation of amines from hydroperoxyacetals led us to investigate the possibility of a direct synthesis of amines from alkenes through a one-pot ozonolysis/reductive amination procedure with no purification of intermediates. Our investigations are summarized in Table 2

Table-2: Conversion of alkene to amines-Stepwise addition of $NaHB(OAc)_3$ after ozonolysis



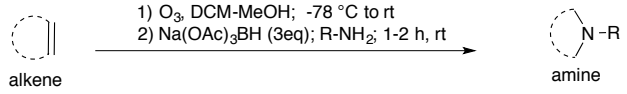
Entry	Alkene	R-NH-R	Amine	Yield (%)
1				66
2				70
3				65
4				57
5				63
6				64

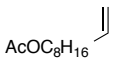
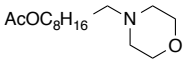
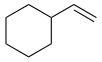
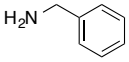
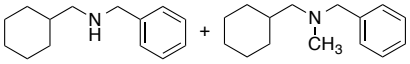
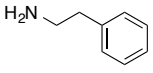
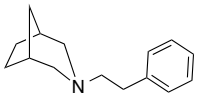
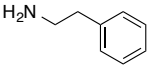
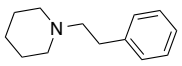
This conversion requires at least two equivalents $Na(OAc)_3BH$, one for reduction of the hydroperoxyacetal and a second equivalent for reductive amination. Initially we were

concerned about over reduction of carbonyl compounds in presence of excess $Na(OAc)_3BH$. Therefore, we began our investigations through addition of $Na(OAc)_3BH$ in two separate increments. The reaction solution derived from alkene ozonolysis, consisting mainly of hydroperoxyacetal, was treated with one equivalent $Na(OAc)_3BH$ to achieve reduction to a carbonyl. After the mixture had stirred for one hour, we added an amine and additional triacetoxyborohydride. This procedure gave good yield of amines derived from a variety of cyclic alkenes (requiring two-fold reductive amination) and one acyclic alkene (table-2).

We next investigated the one-pot synthesis of amines involving one-time addition of excess acetoxyborohydride, followed by addition of amine. The revised procedure is as efficient as the stepwise addition described above (table-3).

Table-3: Conversion of alkene to amines-One time addition of $Na(OAc)_3BH$ after ozonolysis

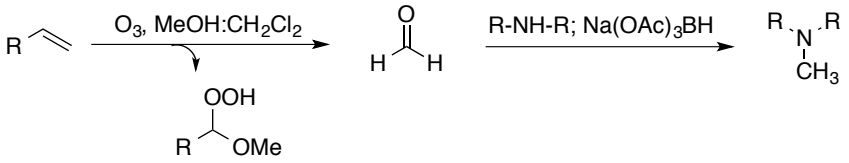


Entry	Alkene	R-NH_2	Amine	Yield
1				66%
2				50 % 10% (N-Methyl amine)
3				65%
4				62%

Although the tandem ozonolysis/reductive amination of a terminal alkene and a 2° amine produced high yields of a single tertiary amine (entry-1; table-3), the corresponding reaction with a 1° amine resulted in isolation of a mixture of the desired secondary amine

and a tertiary amine containing an additional *N*-methyl substituent. The methylated product is assumed to result from reductive amination of the desired secondary amine by residual formaldehyde that is cogenerated during the ozonolysis of terminal alkenes. The results suggest the formaldehyde is not lost by evaporation during the ozonoysis reaction or is it removed by reduction with acetoxyborohydride. (Scheme-20).

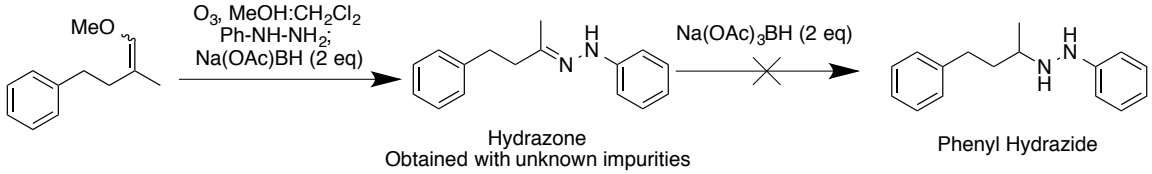
Scheme-20:



Section-8: Reductive formation of hydrazides

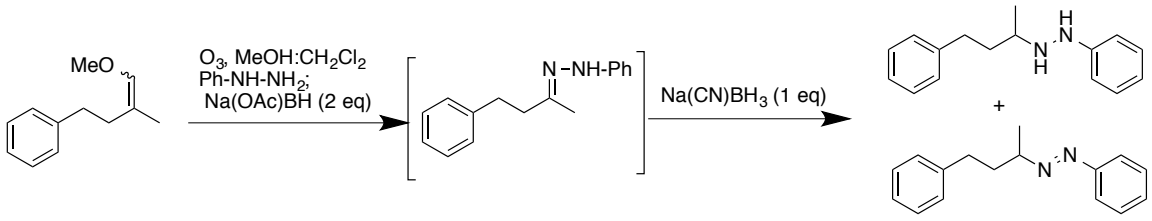
We were interested in whether the direct conversion of alkenes to amines could be extended to the formation of hydrazides. We initially screened this process using an enol ether, a class of substrate known to undergo ozonolysis with high selectivity for formation of hydroperoxyacetals and an unreactive ester byproduct. Ozonolysis of the enol ether, followed by reduction of the hydroperoxyacetal and subsequent addition of phenyl hydrazine and additional triacetoxyborohydride, furnished the phenyl hydrazone, not the hydrazide. Although the reaction TLC suggested a relatively clean conversion, the hydrazone was not isolated in pure form. Attempted in situ reduction with excess $NaHB(OAc)_3$ failed to give phenyl hydrazide product (Scheme-21).

Scheme-21:



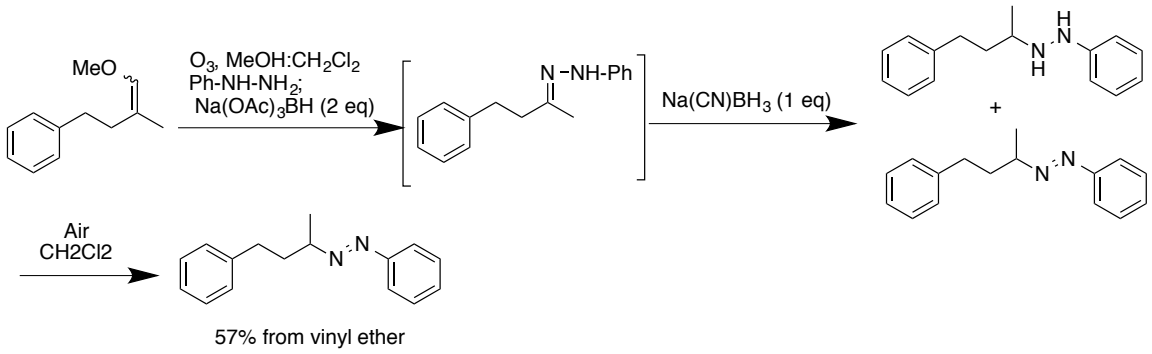
Therefore we treated the hydrazone with the stronger reducing agent $Na(CN)BH_3$ and obtained phenyl hydrazide. However, during purification, the hydrazide slowly underwent oxidation to produce azo byproducts (Scheme-22).

Scheme-22:



Passing a stream of air through a methylene chloride solution of the hydrazide/azo mixture resulted in complete oxidation to the azo compound as shown in Scheme-23.

Scheme-23:



Section-9: Conclusions:

- In this project we have successfully converted alkenes in to amines, without isolation of intermediates, through sequential ozonolysis, hydroperoxyacetal reduction, and reductive amination, all in one pot.
- We have shown that the tandem ozonolysis/reductive amination can be achieved through stepwise or one-time addition of $NaHB(OAc)_3$. However, in the case of terminal alkenes, we have shown that stepwise addition of borohydrides produces amine products free of *N*-methylated side products derived from the formaldehyde byproduct generated during ozonolysis.
- This method is particularly attractive in converting cyclic alkenes to cyclic amines with one atom increment in the ring size.
- We demonstrated efficient ozonolysis and reductive amination using $NaHB(OAc)_3$, a convenient and easily handled reagent that avoids the need for H_2 gas, high pressures, or long reaction times (Scheme-15).

Section-10: Experimental Section.

Detailed procedures and associated data for synthesis, purification and spectral data for compounds described in Schemes 9, 11, and 13 as well as tables 1, 2 and 3 have been published. [1] All products were characterized by ^{1}H and ^{13}C NMR. New compounds were also characterized by IR and HRMS

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Chapter-2: A New Synthesis of Alkyl hydroperoxides

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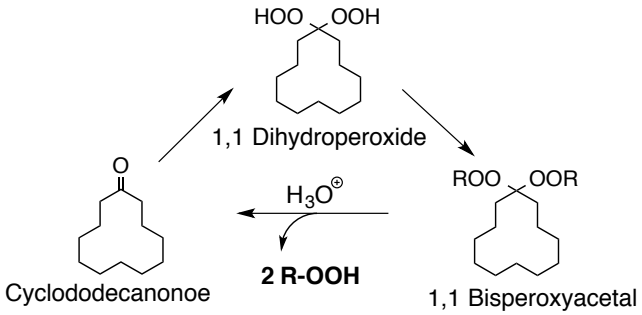
In this chapter, I will discuss a novel method for the synthesis of alkyl hydroperoxides from alkyl triflates via intermediate 1,1 bisperoxy acetals (Scheme-1).

Scheme-1:



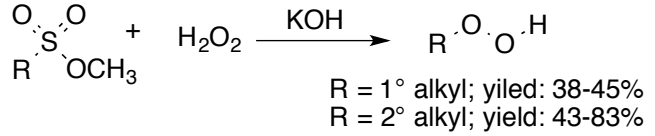
Section-1: Background on alkyl hydroperoxide synthetic methods

A number of methods have been reported for synthesis of alkyl hydroperoides.[1] Most of the methodologies suffer at least one shortcoming such as limited substrate scope, poor yields, or side product formation. The following section briefly overviews existing synthetic approaches to alkyl hydroperoxides.

Nucleophilic substitution reactions: Peroxide synthesis via nucleophilic substitution reactions with hydrogen peroxide and carbon electrophiles such as alkyl mesylates has been known for some time. This method has been used to synthesize 1° and 2° hydroperoxides, often in poor yields (scheme-2, Eq-1). As aqueous hydrogen peroxide is used in this method, alcohols and dialkylated products (dialkyl peroxides) are generated as side products in these reactions .[2-6] Although phase transfer catalysts (PTCs) were used to synthesize dialkyl peroxides,[27-30] no examples were found for alkyl hydroperoxide synthesis using PTCs via nucleophilic substitution reactions. (Note: PTCs were used

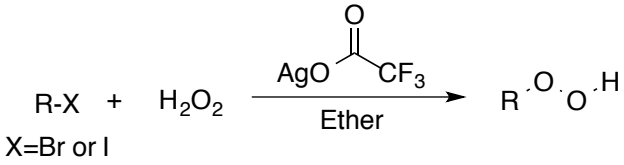
during the photo-oxygenations in order to solubilize the sensitizer, examples not shown. [6])

Scheme-2:



Silver-mediated nucleophilic substitution of alkyl bromides or iodides with hydrogen peroxide produces moderate yields of alkyl hydroperoxides (scheme-2, Eq-2). [7]

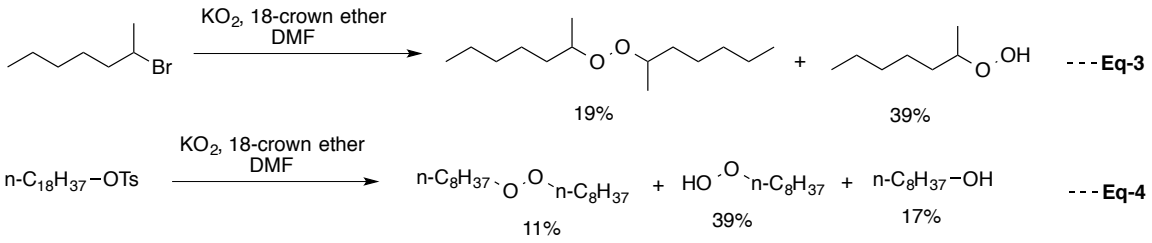
Scheme-2, Equation-2:



38%	42%	30%	40%	45%	60%

Reactions of alkyl halides and alkyl sulfonates with superoxide (radical anion) in aprotic solvents of low or moderate polarity (benzene, toluene, and THF) produce a small amount of hydroperoxide; the major product is often the dialkyl peroxide. However reaction in DMF furnishes alkyl hydroperoxides as major products, although alcohols and dialkyl peroxide byproducts are also typically formed. (Scheme-3; Eq-3, 4). [8]

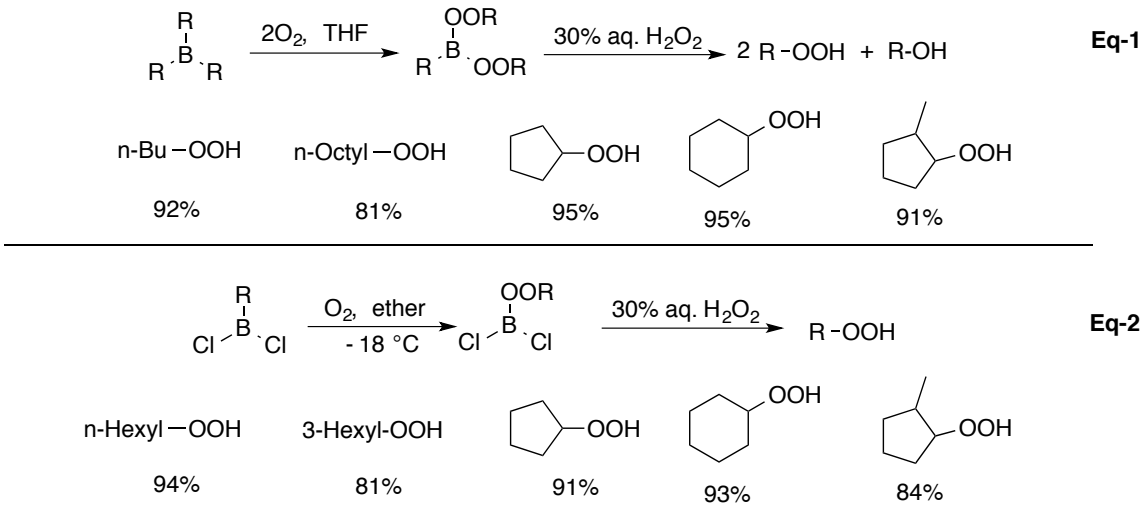
Scheme-3:



Alkyl hydroperoxide synthesis using molecular oxygen:

(A) *Using Trialkylboranes*: Trialkylboranes were shown to undergo oxidation with molecular oxygen to generate dialkylperoxyalkylboranes. These undergo cleavage with hydrogen peroxide to give two equivalents of alkyl hydroperoxide, and one equivalent of alcohol.[9] Interestingly, the aerobic decomposition of triethyl borane is now a popular method for initiation of radical reactions.[38] Although the method provides good yields of alkyl hydroperoxide according to iodometry, the reported separation method (basic extraction of the hydroperoxide) gave poor yields with long chain substrates due to the difficulty in removal of alcohol byproducts. (Scheme-4, Eq-1 showing general outline and representative examples). However, a modification of the method using alkyl dichloroboranes as substrates gave only alkyl hydroperoxides (Eq-2; Scheme-4) with no alcohol byproducts. [9]

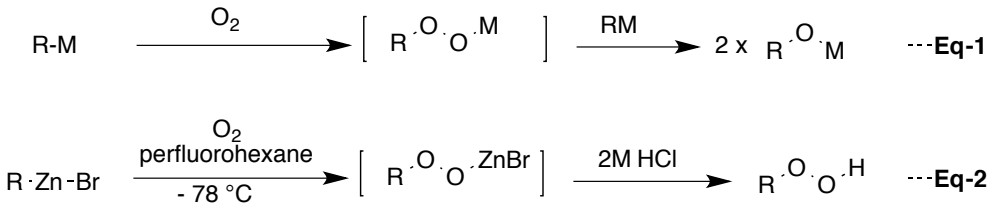
Scheme-4:



(B) *Reaction involving organometallic reagents:* A number of organometallic reagents react with molecular oxygen to form metalated alkyl hydroperoxides. If oxygen availability is limited in the reaction flask, then the initial metalated peroxides further

undergo alkylation with organometallic reagent to form two equivalents of alcohol (scheme-5; Eq-1). This reaction is known for organomagnesium and organolithium reagents, [39] but is most efficient for organozinc reagents. [40]

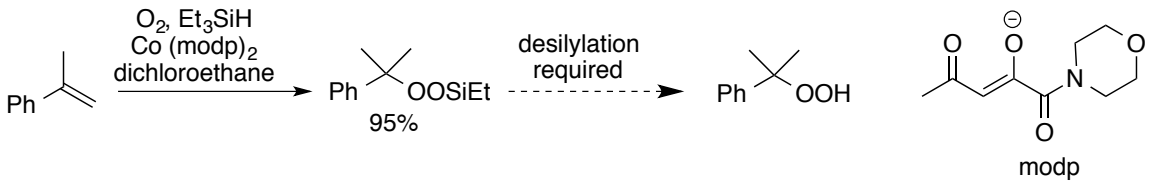
Scheme-5:



Organozinc reagents react efficiently with molecular oxygen to form alkyl hydroperoxides. The use of perfluoroalkane solvents, which enhances the solubility of oxygen, provides good yields and minimizes formation of alcohol byproduct. (Scheme-5; Eq-2) with the obvious drawback that this method requires expensive perfluorinated alkanes as solvents.[10]

(C) *Reactions involving Co (II) catalysts*: Alkenes undergo oxidation with molecular oxygen in presence of Co(II) catalysts and Et_3SiH to give silylated hydroperoxide through a net addition of H/OOSiEt_3; regioselection can be described as "Markovnikov" in the sense that the oxygen typically ends up attached to the more electron-rich carbon.[11-12] The proposed mechanism involves addition of H/Co across an alkene followed by oxygen trapping of an intermediate carbon radical.[13-14]

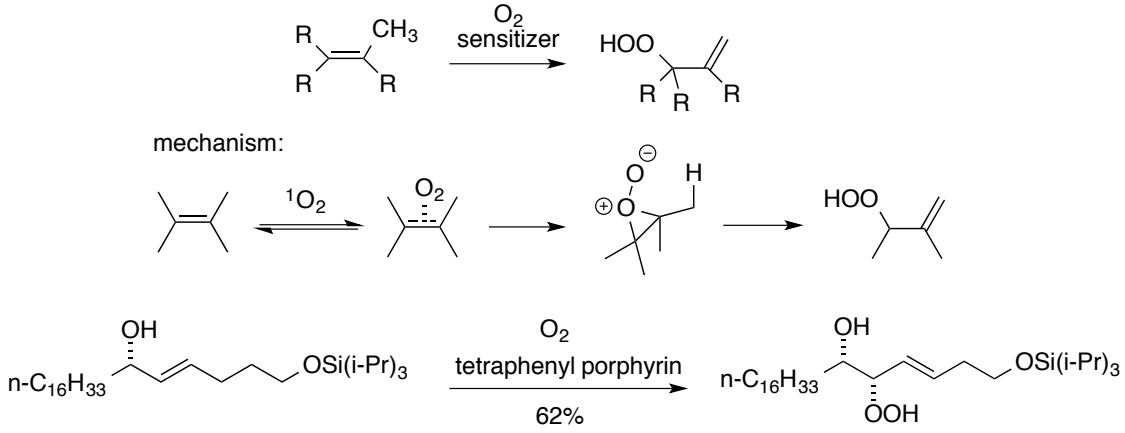
Scheme-6:



This method does not generate alkyl hydroperoxides directly; they can be obtained after desilylation, which is two-step process (Scheme-6 showing representative example). Use of alcohol, as co-solvent in this reaction will provide alkyl hydroperoxides directly.[45]

(D) *Photo-oxygenation*: Hydroperoxides can be synthesized from reaction of alkenes with singlet oxygen through a stepwise reaction that for historical reasons is describe as a '*singlet oxygen ene reaction*'; the actual mechanism is now thought to involve an intermediate peroxide. The hydroperoxide is generated on one of the original alkene carbons while the position of the alkene is shifted. Singlet oxygen is typically generated in situ by photosensitized excitation in the presence of light and a triplet sensitizer. Here a general reaction, and representative example shown in Scheme-7.[15, 16]

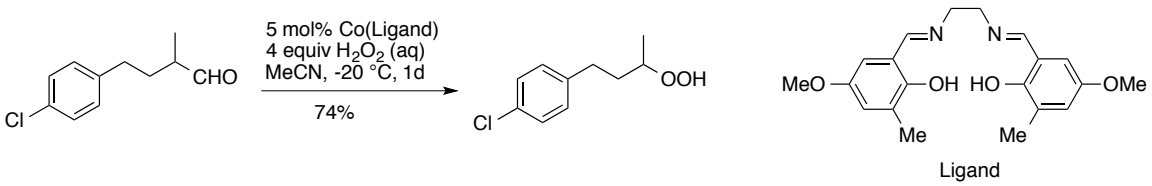
Scheme-7: Peroxide synthesis by photo-oxygenations



From carbonyl compounds:

Decarbonylation: Recently, alkyl hydroperoxides have been synthesized by oxidative decarbonylation of aldehydes in a Co-promoted reaction found to involve alkyl radicals derived from fragmentation of a peroxy hemiacetal. (Scheme-8).[17]

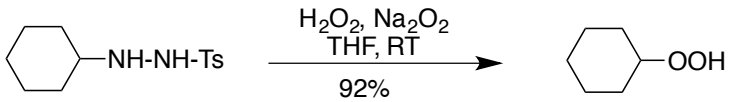
Scheme-8:



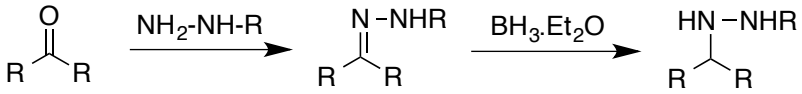
via Hydrazine oxidation: Hydrazines and tosyl hydrazines were oxidized in presence of Na_2O_2/H_2O_2 to give alkyl hydroperoxides (Scheme-9, Eq-1). Alkyl hydrazines are not commercially available, and are prepared from carbonyl precursor in two-step procedure (Scheme-9, Eq-2). [18,19]

Scheme-9:

Equation-1:

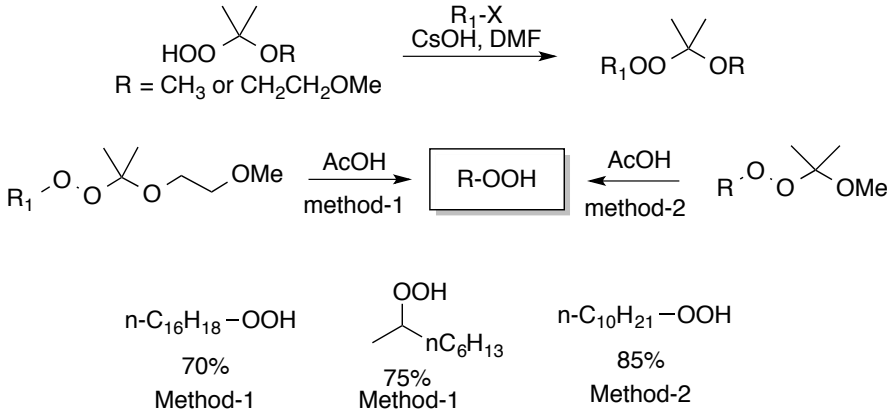


Equation-2:



Hydrolysis: Monoperoxyacetals were hydrolyzed in presence of acetic acid, to give alkyl hydroperoxides. Monoperoxyacetals were obtained by alkylation of α-alkoxy hydroperoxides, which are obtained through alkene ozonolysis (Scheme-10). [20, 21] This method, which employs an acetal-protected hydroperoxide as a synthon for hydrogen peroxide, is the method most similar to our research. This method, which was developed by earlier investigators in our group,[20, 21] can be highly useful but is limited by a potentially dangerous concentration/transfer of the low-molecular weight hydroperoxyacetal reagent.

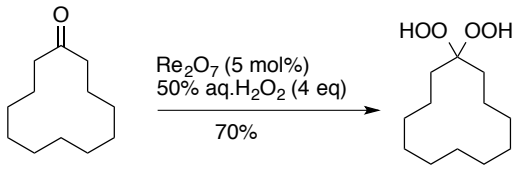
Scheme-10:



Section-2: 1,1-Dihydroperoxides synthesis and use as nucleophiles

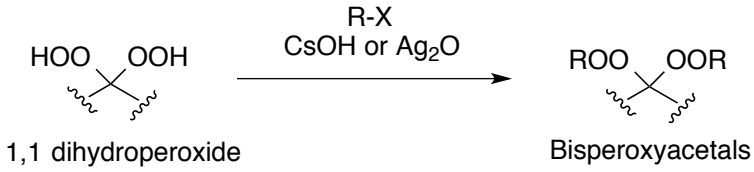
Preparation: 1,1-Dihydroperoxides (DHP) have been primarily synthesized through two methods: (i) ozonolysis of enol ethers in presence of hydrogen peroxide;[41] (ii) peroxyacetalization of carbonyl compounds with hydrogen peroxides. The second approach, which is generally better suited for preparative work, has been conducted in the presence of a variety of promoters: Bronsted acids, Lewis acids, iodine, ceric ammonium nitrate, and methyl rhenium trioxide. A number of these methodologies can be successfully applied to simple substrates. The challenge in these reactions is to generate the DHP without using a large excess of hydrogen peroxide and without generating significant amounts of cyclic or oligomeric peroxide byproducts. Our lab recently reported a method for peroxyacetalization of carbonyls in the presence of catalytic Re_2O_7. (Equation-1). [22] This method, which has good substrate scope and requires only a two-fold excess of hydrogen peroxide, was used to prepare the substrates for this research.

Equation-1:



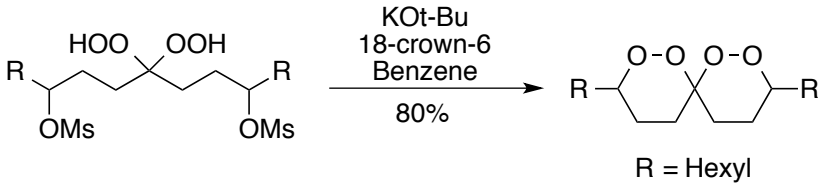
Use as nucleophiles: Unlike alkylation of alkyl hydroperoxides, there are fewer methods reported for alkylation of 1,1 dihydroperoxides. Mono and dialkylations of 1,1 dihydroperoxides have been carried out with alkyl iodides in the presence of $CsOH•H_2O$ or with alkyl iodides presence of Ag_2O. These methods gave moderate yields of bis-peroxyacetals with allyl bromides, but no reaction with alkyl bromides (general scheme shown in equation-2, detailed description vide infra-Scheme-11). [23-24.]

Equation-2:



Intra-molecular alkylation of 1,1-dihydroperoxides with alkyl methane sulfonates using KOtBu and 18-crown-6 additives in benzene solvent has been utilized to prepare spiro-bisperoxyketals. (Equation-3). [25]

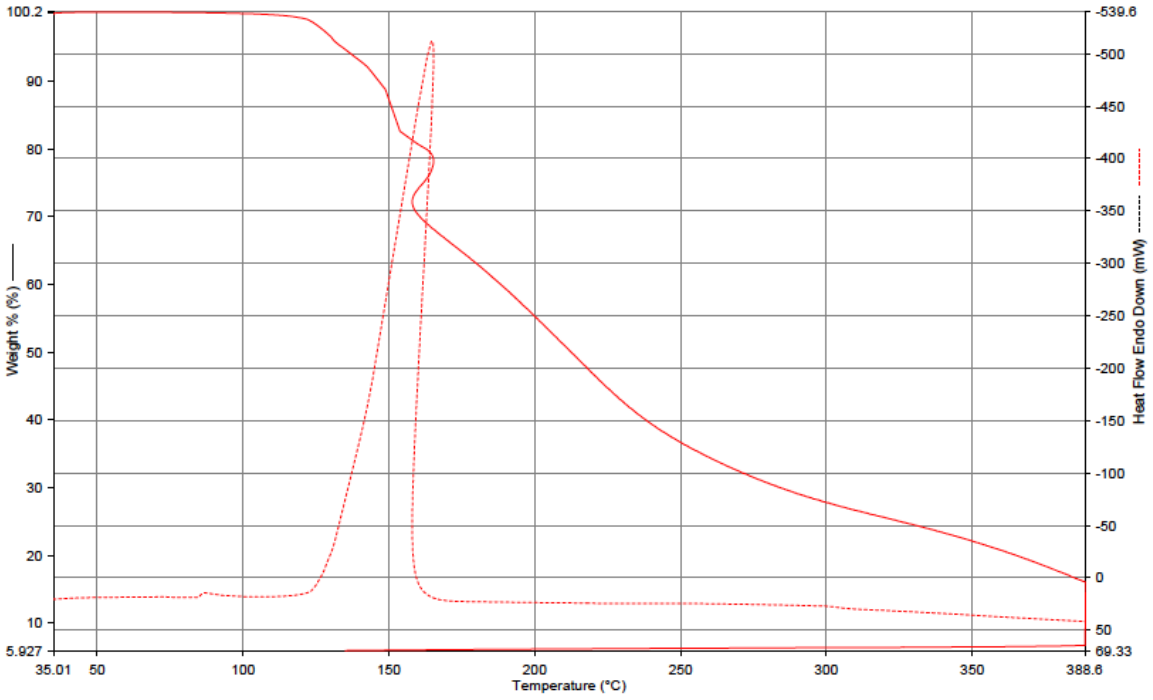
Equation-3:



Properties of 1,1-DHPs: As 1,1-DHPs have two peroxy functional groups the active oxygen content[26] in the molecule will be high compared to a simple alkyl hydroperoxide with similar molecular weight. As active oxygen content increases, the amount of

potential energy release from a molecule will also increase. We therefore investigated the thermal stability of cyclododecyl 1,1-dihydroperoxide (active oxygen content close to 14%) using differential scanning calorimetry/thermal gravimetric analysis (DSC-TGA. As illustrated in figure 2, this DHP was stable beyond 100 °C but decomposed with significant release of heat and loss of mass at temperatures above 120 °C. (figure-2).

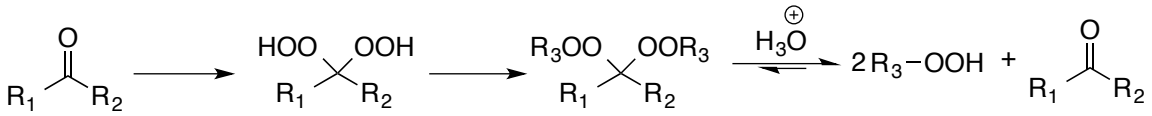
Figure-2: DSC-TGA graph for cyclododecyl 1,1 hydroperoxide.



Section-3: Bisperoxyacetals

We are interested in the preparation of bisperoxyacetals and in their subsequent hydrolysis as a new method for synthesis of alkyl hydroperoxide. Our overall approach, illustrated in Scheme-11, pursues a three-step synthesis of alkyl hydroperoxides using ketones as an auxiliary that can be recovered.

Scheme-11: Overall goal of the project



Bisperoxyacetals have been explored for antimalarial activity.[23, 24] Bisperoxyacetal are also subunits of spiro-bisperoxyketals, and tetraoxanes.[25, 26] In addition to the alkylation of 1,1-dihydroperoxides described above,[23, 24] bisperoxyacetals have also been prepared through Brønsted acid or iodine-promoted reaction of alkyl hydroperoxides and carbonyls.[42] For our proposed synthesis of alkyl hydroperoxides, the key steps are alkylation of the 1,1 dihydroperoxides to form the bisperoxyacetals and the deprotection (hydrolysis) of the bisperoxyacetals under mild conditions. The following section focuses on synthesis of bis-peroxyacetals from 1,1 dihydroperoxides.

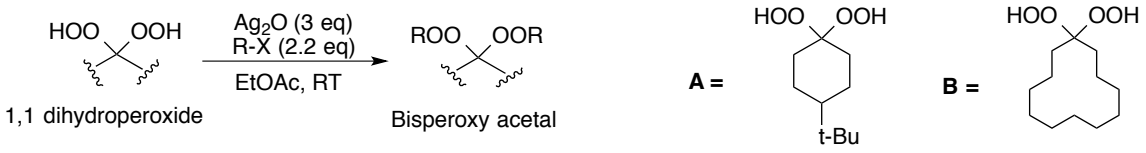
Section-3.1: Synthesis of Bisperoxyacetals from 1,1 dihydroperoxides

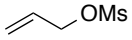
We initially screened method for alkylation of 1,1-dihydroperoxides (DHPs) on 1,1-dihydroperoxy-4-t-butylcyclohexane and 1,1-dihydroperoxycyclododecane. As will be discussed in more detail below, the cyclododecyl DHP was ultimately chosen as the platform for the hydroperoxide synthesis methodology due to relative ease of hydrolysis of the intermediate bisperoxyacetal.

Using Ag_2O: Our investigations into alkylation of 1,1 dihydroperoxide (containing 6- and 12-membered rings) with alkyl iodides and freshly prepared Ag_2O are summarized in Table 1. Reaction of long chain 1° alkyl iodides provided bisperoxy acetals in good yields (entries 1-3, 9) but no product was obtained from a 2° iodide (entry-7). Benzyl bromide gave moderate yield of product, but n-decyl bromide failed to give product (entry 4, 6). Reaction with t-BuBr provides only a low yield of monoalkylated product

(entry-8). As expected based upon a mechanism involving Ag(I)-activation of a halide, a methanesulfonate failed to react (entry 5).

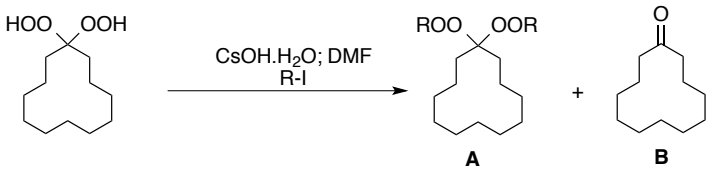
Table-1:



S.No	1,1 dihydroperoxide	R-X	Time (hour)	Yield (%)
1	A	n-$C_{10}H_{21}$-I	16	93
2	A	n-C_6H_{13}-I	8	79
3	A		10	79
4	A	Bn-Br	5	56
5	A		24	-
6	A	n-$C_{10}H_{21}$-Br	48	-
7	A	2-Iodo octane	48	-
8	A	t-BuBr	24	35% monoalkylated
9	B	n-C_6H_{13}-I	30	89

Base mediated alkylations: As discussed above, the base-mediated alkylation of 1,1 dihydroperoxide has been described, [23, 24] predominantly for reactions of alkyl iodides using CsOH base and DMF solvent. However, in our hands this method suffered from poor yields and the formation of carbonyl byproducts, presumably due to the Kornblum fragmentation of resulted mono/dialkylated bisperoxy acetal (see table-3 for control experiments). Scheme-12 shows few examples of alkylation of cyclododecanone 1,1 dihydroperoxide. Ketone byproduct formation is high when longer chain iodides were used.[24]

Scheme-12

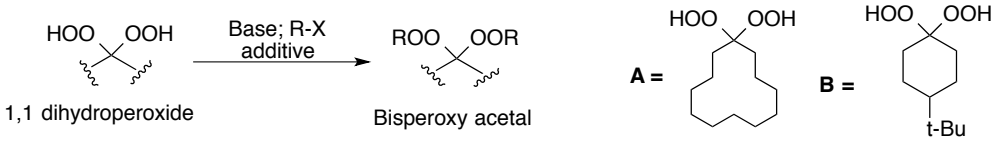


R	A (%)	B (%)
Me	57	12
Et	46	30
Pr	25	54
Bu	33	48
$CH_2CH=CH_2$	24	51
$CH_2C(CH_3)=CH_2$	35	45

When we tested the reaction with *n*-decyl iodide using CsOH, we obtained only 19% of the desired bisperoxyacetal and the ketone byproduct (entry-1, table-2). Interested in developing an efficient base mediated dialkylation protocol that can be used for longer alkyl chain alkyl iodides, we subjected cyclododecanone 1,1-dihydroperoxide and cyclohexanone 1,1-dihydroperoxide to various base mediated alkylation conditions. Although some of these methods have been successfully applied for alkyl hydroperoxide alkylations, they failed for the 1,1-dihydroperoxide substrates.

(i) Reaction with 1° alkyl iodide with $CsOH•H_2O$ base provided only 19% product (entry-1). Application of similar conditions to a 2° alkyl iodide (entry-6) resulted in isolation of 65% of the ketone byproduct. No product was observed when non-polar solvent such as toluene used (entry-17). (ii) Reaction using $CsCO_3$ in DMF for 1° and 2° alkyl idodides failed to give any products (entry 2, 9). (iii) Although hydroperoxides have been alkylated successfully using PTC catalyst under aqueous condition,[27 -30] similar conditions[30] failed for a 1,1-dihydroperoxide (entry 4).

Table-2:

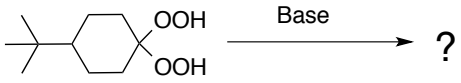


Entry	1,1 Dihydro-peroxide	R-X	Base (Eq.)	Solvent	Temp (°C)	Additive	Yield (%)	Ketone byproduct
1	A	*n*-$C_{10}H_{21}$-I	CsOH.H_2O(2.0)	DMF	rt	-	19	-
2	A	*n*-$C_{10}H_{21}$-I	$CsCO_3$ (2.0)	DMF		-	7	-
3	A	*n*-$C_{10}H_{21}$-I	KOtBu (2.1)	THF		-	-	by TLC
4	A	*n*-$C_{10}H_{21}$-Br	50% aq.KOH		50	n-Bu_4Br (10%)	-	-
5	A	2- Iodooctane	KOtBu (2.1)	THF	rt	18-crown-6	-	-
6	A	2- Iodooctane	CsOH.H_2O (2)	DMF	0 to rt	-	-	65%
7	A	2- Iodooctane	KOtBu (2.1)	DMSO	rt	-	-	by TLC
8	A	2- Iodooctane	KOtBu (2.1)	Toluene	rt	18-crown-6	-	by TLC
9	A	2- Iodooctane	$CsCO_3$ (2.0)	DMF	80	-		crude NMR
10	A	2- Iodooctane	NaH (2.0)	THF	rt	n-Bu_4Br (10%)	-	crude NMR
11	A	t-BuBr	K_2CO_3	Acetone	rt		-	-
12	A	t-BuBr	K_2CO_3	DMF	70	n-Bu_4Cl	-	-
13	B	*n*-$C_{10}H_{21}$-I	KOtBu (2.0)	DMSO	RT	-	-	by TLC
14	B	*n*-$C_{10}H_{21}$-I	KOtBu (2.1)	Toluene	rt	18-crown-6		by TLC
15	B	*n*-$C_{10}H_{21}$-I	NaH (2.0)	THF	rt	-		by TLC
16	B	*n*-$C_{10}H_{21}$-I	NaH (2.0)	THF	rt	Bu_4N-I		by TLC
17	B	*n*-$C_{10}H_{21}$-I	CsOH.H_2O (2)	Toluene	rt	n-Bu_4I	-	by TLC

(iv) KO*t*-Bu in the presence of 18-Crown-6 in a nonpolar solvent was used successfully for 1,1 dihydroperoxide dialkylation by alkyl sulfonates.[25] However, similar conditions failed for the DHPs (entry 3, 5, 7, 8, 13, and 14); disappearance of 1,1-DHP (TLC) was accompanied by formation of significant amount of carbonyl byproducts. (v) Alkylations using NaH as base were unsuccessful with or without phase transfer catalyst (entry 10, 15 and 16). (vi) Attempted alkylation with t-BuBr in the presence of the milder base K_2CO_3 failed in room temperature acetone and or DMF at 70 °C (entry 11, 12). (vii) In a number

of cases shown in table 2, the ketone was a significant byproduct. As discussed above this could be due to Kornblum decomposition of the product or the intermediate mono-alkylated product. For this we ran few control experiments, where 1,1-dihydroperoxide treated with only base. Cyclohecanone derived 1,1-DHP was not affected when treated with potassium carbonate or cesium hydroxide in DMF. In contrast, treatment of DHP with potassium tert-butoxide in DMSO resulted in rapid decomposition and formation of carbonyls byproducts.

Table-3: TLC analysis for 1,1-DHP decomposition.



Base	Solvent	Result
K_2CO_3	DMF	1,1-DHP survived, No ketone formation
$CsOH{\cdot}H_2O$	DMF	1,1-DHP survived, No ketone formation
KOt-Bu	DMSO	1,1-DHP completely decomposed, only ketone shown

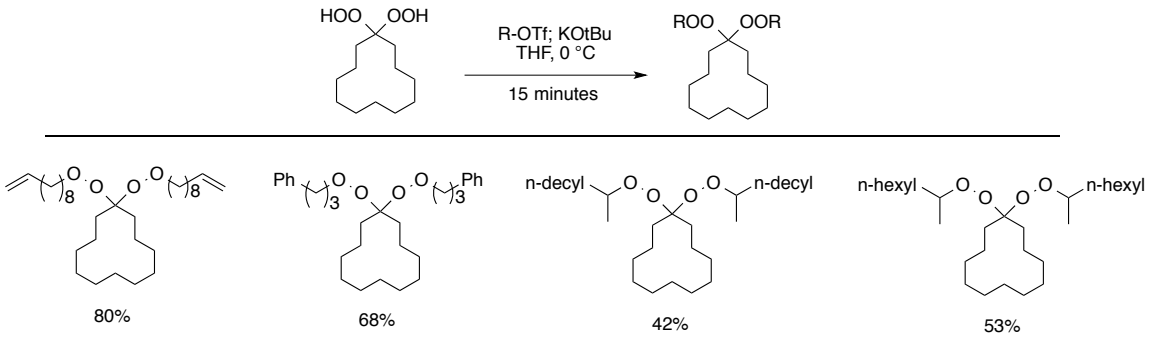
Similarly, when bisperoxyacetal subjected to the base KOt-Bu in THF solvent similar decomposition observed on TLC, but there is also unreacted starting material along with ketone (result not shown).

Section-3.2: DHP alkylation using alkyl triflates

After the series of failures described above, we realized that 1,1-dihydroperoxide alkylation requires shorter reaction times and milder conditions such as room temperature or below, in order to avoid decomposition of the 1,1-dihydroperoxide or the intermediates. We therefore focused our attention towards alkyl triflates, powerful electrophiles previously used for alkylation of alkyl hydroperoxides. [31] In our hands, alkylation of 1,1-dihydroperoxides with primary and secondary alkyl triflates using KO*t*-Bu in tetrahydrofuran at 0 °C provided desired products in moderate to good yields

(Scheme-13). Notably, the alkylations were efficient for both primary and secondary electrophiles.

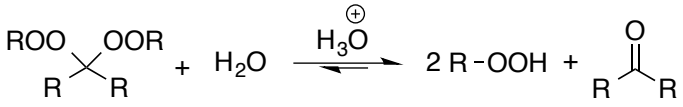
Scheme-13:



Section-4: Synthesis of alkyl hydroperoxides from bisperoxy acetals hydrolysis.

We next investigated the deprotection of the bisperoxyacetals to liberate the desired alkyl hydroperoxides. Protection of carbonyl functional group by acetalization and deprotection back to carbonyl at suitable stage of multistep synthesis is a common strategy in organic synthesis. However, earlier work from our group [43] demonstrating the stability of bisperoxyacetals to the presence of strong Lewis acids suggested that the deprotection would not be trivial. The following section will discuss hydrolysis conditions for synthesis of alkyl hydroperoxides.

Equation-5:



Although monoperoxyacetal hydrolysis is known (vide supra) to provide alkyl-hydroperoxides, the corresponding hydrolysis of bisperoxyacetals is relatively unexplored. As shown in equation-5 it is a reversible reaction and requires a Brønsted acid catalyst as similar to any other acetal hydrolysis.[33, 20, 21]

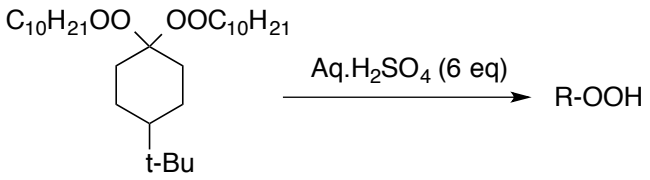
Table-4:

Entry	Solvent	Acid (equiv)	T (°C)	time (hours)	Yield (%)
1	EtOH	1 M aq H_2SO_4 (6)	rt	8	NR
2	MeOH	H_2SO_4 (6)	reflux	1	8
3	MeOH	50% aq H_2SO_4 (6)	reflux	0.16	84
4	MeOH	50% aq H_2SO_4 (6)	rt	48	19
5	MeOH	30% aq H_2SO_4 (6)	rt	1.5	NR
6	THF	camphorsulfonic (2)	rt	3	NR
7	THF	**50% aq H_2SO_4 (6)**	**55**	**3**	**78**
8	THF	50% aq H_2SO_4 (6)	rt	24	20

We initially screened hydrolysis conditions on the bisdecyl peroxyacetal of cyclododecanone (Table-4). Hydrolysis in EtOH in the presence of a six equivalents of 1M aq. H_2SO_4 resulted in traces of hydroperoxide product (TLC). Reaction in MeOH containing six equivalents of anhydrous H_2SO_4 provided only 8% of product (entry 1,2). Reaction in MeOH using aqueous H_2SO_4 of various concentrations was tested at room temperature and reflux conditions (entry 3-5). Complete conversions of bisperoxyacetal was observed at reflux conditions using 50% aq. H_2SO_4 to generate an 84% isolated yield of alkyl hydroperoxide (entry-3). Reaction using 50% aq. H_2SO_4 in tetrahydrofuran (THF) as solvent provided comparable yields at 55 °C (entry-7). Attempted room temperature hydrolysis under the same conditions in THF provided a poor yield of alkyl hydroperoxides (entry-8). No hydrolysis was observed in the presence of camphorsulfonic acid (entry-6).

Hydrolysis of the corresponding cyclohexanone bisperoxyacetal under the optimal conditions described above failed to achieve complete conversion to decyl hydroperoxide (Table-5).

Table-5:



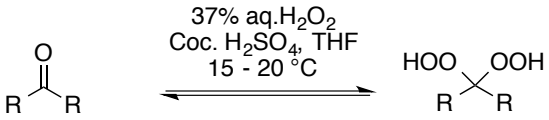
Entry	Solvent	temp (°C)	time	yield (%)
1	MeOH	reflux	0.25	21
2	tetrahydrofuran	50-55	6	34[a]

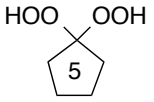
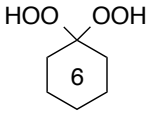
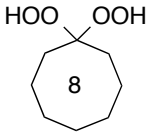
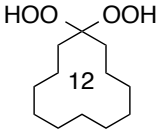
a = yield determined by NMR

Effect of bisperoxyacetal ring size on perhydrolysis/peracetalization

Although hydrolysis of 6- and 12-membered cyclic bisperoxyacetals both provided alkyl hydroperoxides, there is a significant difference in yields (table-4 entry-3, 7 vs table-5). These observations are consistent with literature reports on hydrolysis of 1,1-dihydroperoxides. For example, investigations of the synthesis of 1,1-dihydroperoxides through H_2O_2 peracetalization using protic acids observed that acetal formation varies with ketone ring size (table-6).[32] As the ketone ring size increases, reactions slowed, required increased equivalents of acid and H_2O_2 and yet furnished lower yields of products.

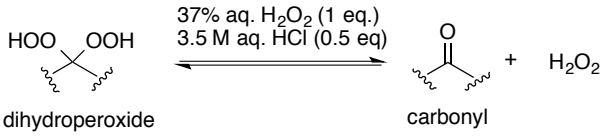
Table-6: Effect of ring size on peracetal formation [ref 32]



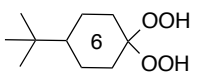
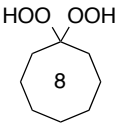
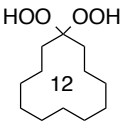
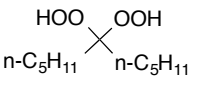
1,1 dihydroperoxide	Time (h)	H_2O_2 equiv.	H_2SO_4 equiv.	Yield (%)
	2	8	0.3	80
	2	8	0.3	81
	4	14	0.8	39
	6	14	0.8	12

The opposite effect was observed in hydrolysis of cyclic 1,1 dihydroperoxides to corresponding ketones (Table-7), with the relative ease of hydrolysis increasing with the ring size of the 1,1 dihydroperoxide.[33]

Table-7: Effect of ring size on hydrolysis of 1,1 dihydroperoxides [ref 33]



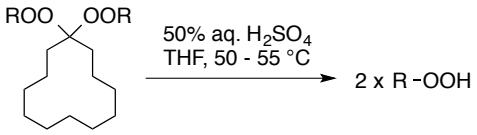
1,1 dihydroperoxide carbonyl

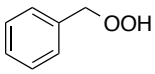
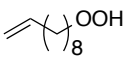
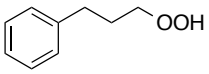
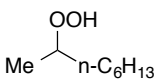
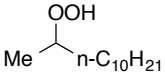
Entry	1	2	3	4
1,1 dihydroperoxide				
time (hours)	24	22	20	25
Ratio 1,1DHP : ketone	> 95:5	20:80	10:90	27:73

The results in Table-6 and Table-7 clearly reveal the decreased stability of the cyclooctyl, cyclododecyl, and tridecyl DHPs compared with the cyclohexyl DHP. Our results demonstrate these same trends extend to the relative stability of the cyclododecyl and cyclohexyl bisperoxyacetals. The lower stability of the cyclododecyl presumably reflects a combination of torsional and transannular strain present in the bisperoxyacetal that is reduced upon hydrolysis.

We next investigated more examples of the hydrolysis of cyclododecanone-derived bisperoxyacetals under the aq. H_2SO_4/THF conditions described above. Alkyl hydroperoxides were obtained in good yields (Table-8).

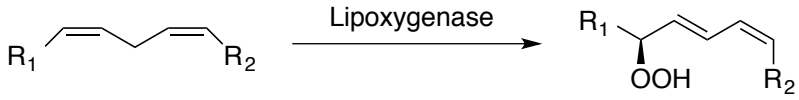
Table-8: Synthesis of alkyl hydroperoxides



Entry	alkylhydroperoxide (R-OOH)	Yield (%)
1	n-$C_{10}H_{21}$–OOH	78
2	n-C_6H_{13}–OOH	49
3		60
4		62
5		79
6		48
7		63

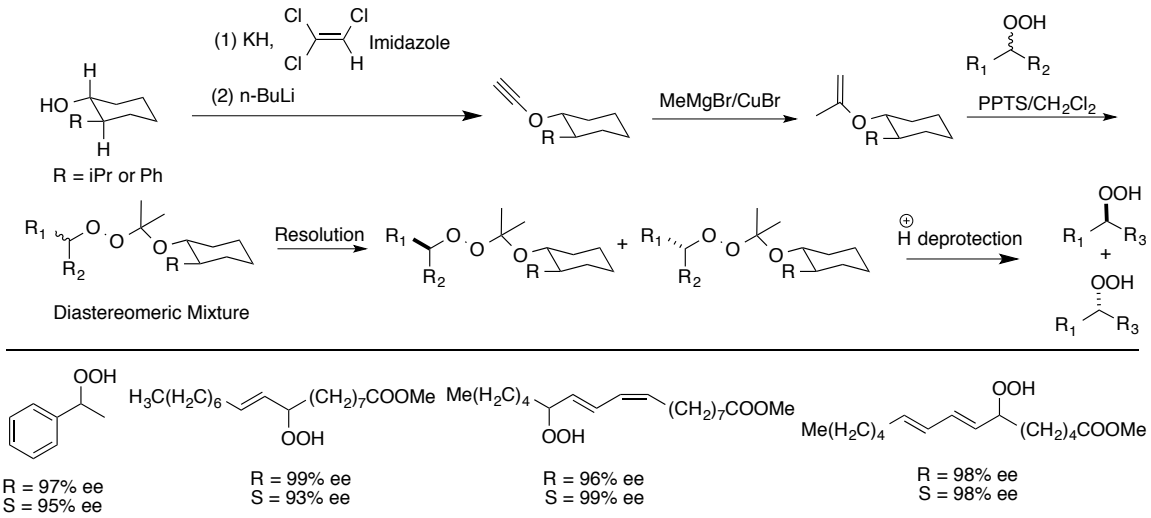
Section-4.1: Studies toward chiral alkyl hydroperoxides

In natural biological systems polyunsaturated fatty acids can be converted to chiral fatty acid hydroperoxides in presence of enzymes such as lipoxygenases (equation-6).[34]



There have been several chemical approaches to obtaining enantiomerically enriched chiral alkylhydroperoxides. Initially efforts made based on chiral resolution of racemic alkyl hydroperoxides. Alkyl hydroperoxides were reacted with chiral enol ethers to form diastereomeric mixtures, which could be separated by chromatography. Deprotection of the individual diasteromers gave individual enantiomers with high ee (scheme-14). [34]

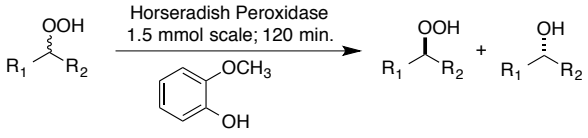
Scheme-14: Resolution by forming diastereomers

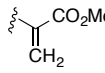
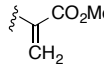


Kinetic enzymatic resolutions of racemic alkyl hydroperoxides has also been accomplished, but with a limited scope of substrates and at a cost of destroying one hydroperoxide enantiomers. Scheme-15 shows a highly successful resolution of a 2° benzylic hydroperoxide using horseradish peroxidase.[35] The reaction utilizes guaiacol (2-

methoxy phenol) as a reducing agent that provides electrons to the peroxidase and is converted into guaiacol dimer.[47]

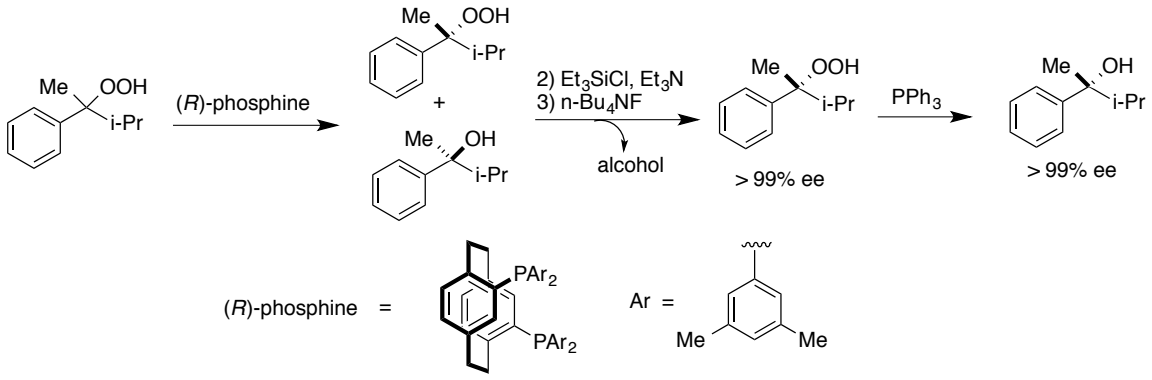
Scheme-15: Enzymatic kinetic resolution



Entry	R_1	R_2	peroxide(ee%)	Alcohol (ee%)
1	Ph	Me	> 99	> 99
2		Me	95	98
3		Et	91	95

Chiral phosphines have also been investigated for kinetic resolution of alkyl hydroperoxides. Scheme-15 showing a representative example of enantioselective reduction of one enantiomer of a racemic benzylic hydroperoxide. The resolved peroxide was protected selectively with TMS-Cl as following previous method[36] to facilitate separation of alcohol from peroxide. The hydroperoxides and the alcohols were each isolated in high enantiomeric excess. (Scheme-16). [37] Sharpless epoxidation using a chiral catalyst and a prochiral allylic alcohol has been used as tool for the kinetic resolution of alkyl hydroperoxides; however, results were relatively poor.[46]

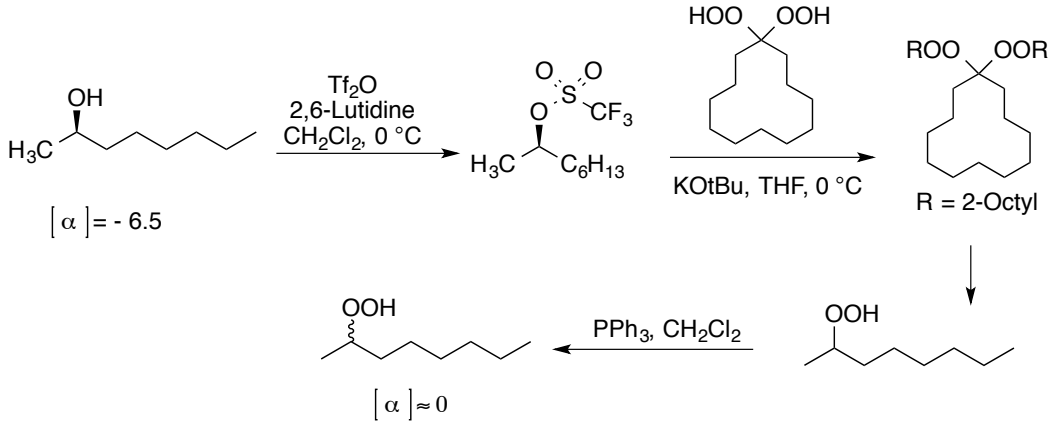
Scheme-16: Kinetic resolution using chiral phosphines.



We thought it would be possible to use our approach to synthesize chiral alkyl hydroperoxides if we started with chiral triflates derived from enantiomerically pure

alcohols. As shown in Scheme 17, chiral triflates were treated with 1,1-dihydroperoxides to form bisperoxyacetals. Then resultant bisperoxyacetal was hydrolyzed to alkyl hydroperoxide, which was reduced to the alcohol with PPh_3 to enable correlation with the starting material. The final alcohol product had no net optical rotation suggesting that the substitution proceeded without stereospecficity. (Scheme-17). This could be due a greater fraction of carbocationic nature in the transition state for displacement of alkyl triflates resulting in formation of the new peroxide linkage as a mixture of stereoisomers.

Scheme-17: Attempts towards chiral hydroperoxide synthesis.

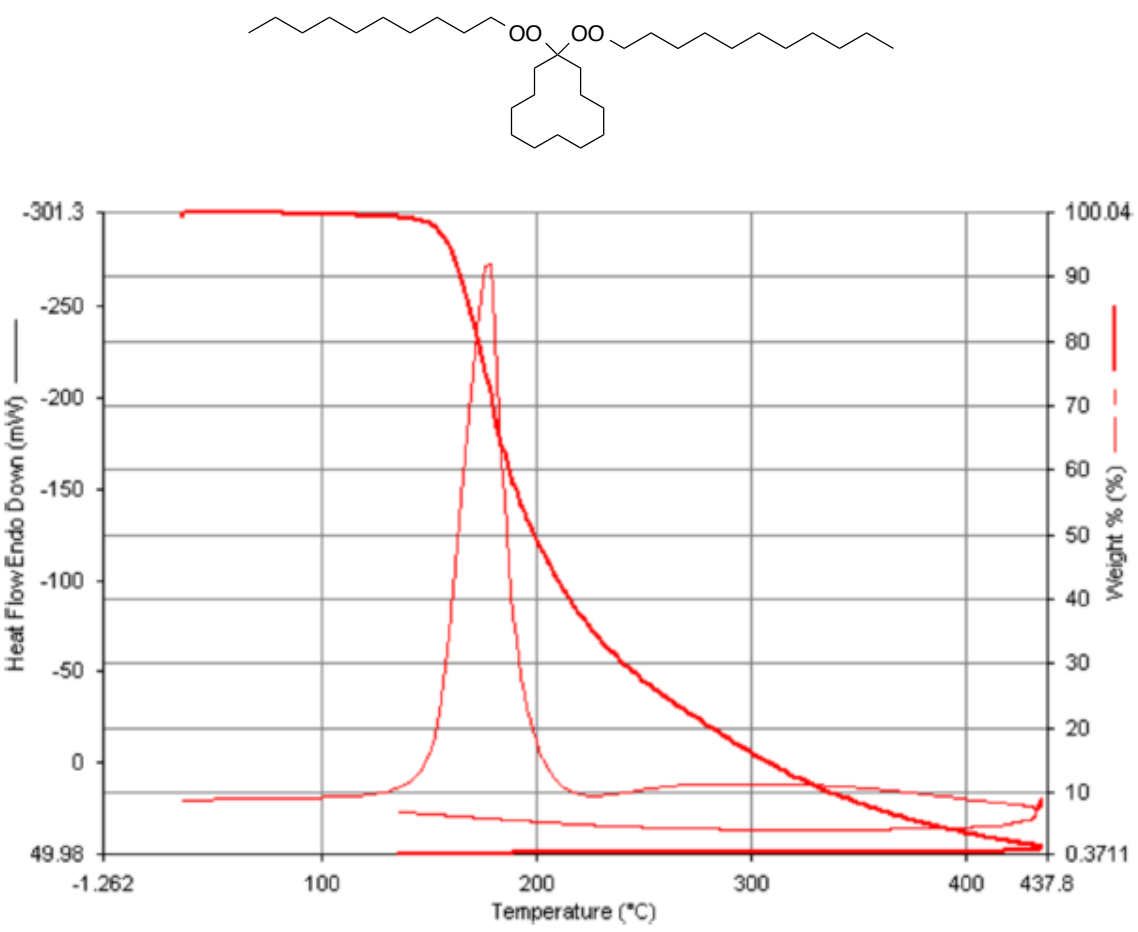


Section-4.2: Stability studies of bisperoxyacetals.

In this methodology we have found conditions allowing hydrolysis of the cyclododecanone-derived bisperoxyacetals at temperatures as low as 50-55 °C. We were interested to determine the thermal stability of bisperoxyacetals to see the window of safety between the temperatures required for deprotection and temperatures which would result in exothermic decomposition of the peroxides. Analysis of the bis decyl peroxyacetal of cyclododecane (Figure-1) by differential scanning calorimetry/thermo-gravimetric analysis data demonstrated that the bisperoxyacetal is stable until

temperatures of approximately 125 °C, at which point a highly exothermic decomposition is observed.

Figure-1: TGA-DSC for bis (n-decyl) peroxyacetal.



Note: The thick line represents thermo gravimetric curve indicating weight loss. The thin line represents differential scanning calorimetric curve showing heat of formation.

Section-5: Experimental Procedures

(i) General experimental procedures, as well as detailed procedures for synthesis, purification and spectral data for all compounds described in Schemes 12 and 16 and Tables 1-4 and 7 are available in reference 44. New compounds were characterized by ^{1}H

and ^{13}C NMR, as well as IR and mass spectroscopy. ^{1}H and ^{13}C NMR spectra for all new compounds are included in the supporting information for the paper.

(ii) 1,1-Dihydroperoxides were synthesized using known procedure from reference-22

(iii) A procedure for synthesis of alkyl triflates is discussed in chapter-4.

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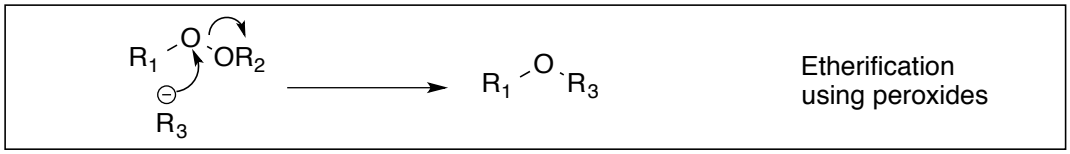
Chapter-3: Investigations of factors controlling reactivity of dialkyl peroxides with organometallic species.

In this chapter, I will discuss the reaction of peroxides with unstabilized organometallic compounds such as organolithium and organomagnesium (Grignard) reagents as a means of achieving etherification (C-O bond formation). The discussion will begin with an overview of the application of peroxide electrophiles for reaction with nucleophiles. The section will continue with a discussion of previous investigations into reactions of organometallics and peroxides, the influence of peroxide structural class on reactivity with nucleophiles, and possible reaction mechanism involved in the etherification. I will then discuss our investigations of reactions of tetrahydropyranyl alkyl peroxides (tetrahydropyranyl monoperoxyacetals of hydroperoxides) with an emphasis on reactivity and regioselectivity in reactions with alkyl lithium and magnesium reagents.

Section-1: Background on peroxides as electrophiles

Ethers are significant functional groups in natural products and synthetic materials. They are most commonly synthesized by Williamson etherification (Nucleophilic displacement of halides or sulfonates), Mitsunobu displacements of alcohols via intermediate oxyphosphonium species, C-O bond formation by reductive elimination, Ullman couplings between alcohols and sp^2 centers, and carbene insertions into O-H groups.[1] The majority of these methods are based upon reaction of an oxygen nucleophile with a carbon electrophile. In contrast, there are fewer examples of reactions reversing this polarity through reaction of carbon nucleophiles with oxygen electrophiles.[2] This chapter will discuss our investigations into methods for activation of organic peroxides towards reaction with carbanions (scheme-1).

Scheme-1:



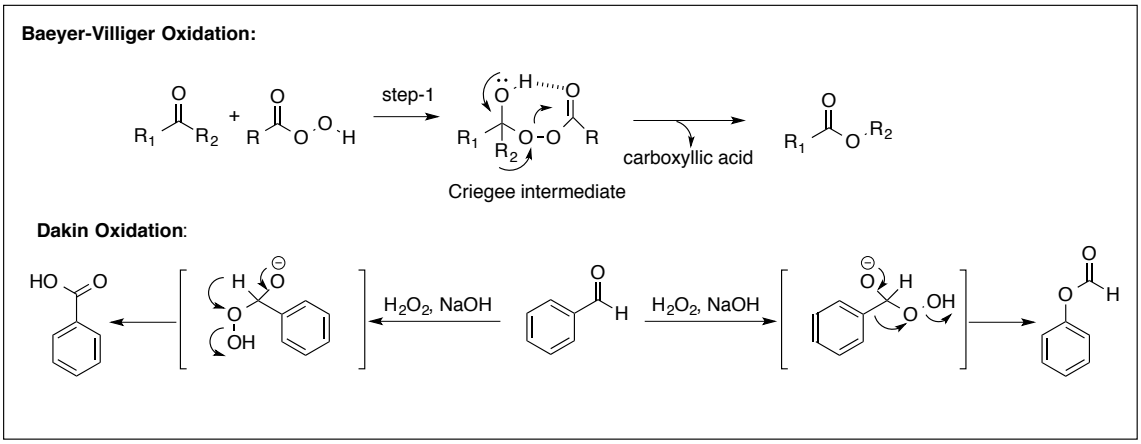
As an introduction to this topic, it is useful to overview the reactions of peroxide electrophiles with carbon nucleophiles (carbanions, alkenes, carbon-carbon sigma bonds) as well as sulfur, nitrogen, and phosphorous nucleophiles.

Section-1.1: Reaction of peroxides with C-C single bonds

Several important reactions involve attack of the electron density in a C-C sigma bond on an activated peroxide. The Baeyer-Villiger (hereafter, BV) oxidation is a classic example of 1,2 migration of a carbon to form a new C-O bond through cleavage of a peroxide. In the first step of BV oxidation, a ketone undergoes reversible addition of a hydroperoxide or similar reagent to form a tetrahedral intermediate, a peroxyhemiacetal often called a Criegee adduct.[3] This tetrahedral intermediate can be generated from a variety of reagents, including percarboxylic acids (peracids), hydrogen peroxide (in the presence of acid or Lewis acid catalysts), and the flavin hydroperoxide cofactors for monooxygenase enzymes. The combination of aldehydes and molecular oxygen can be used to generate a reactive peracid in situ.[3c, d]

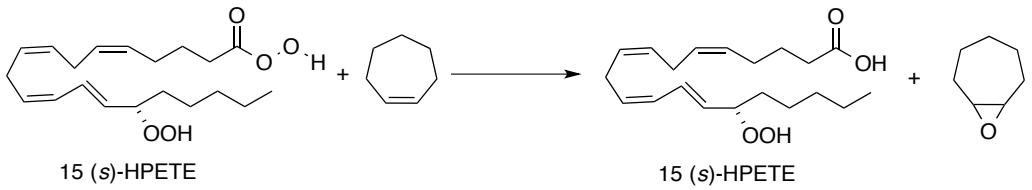
In a second step of the BV oxidation, intramolecular migration of a neighboring C-C bond results in formation of a new C-O bond with cleavage of the peroxide; the developing hydroxyl-substituted cation is the equivalent of a protonated carbonyl group. A similar mode of reaction in hydroxyl substituted aromatic carbonyl compounds, either involving 1,2-migration of a C-H or C-aryl bond, can be seen in Dakin oxidation [4] (scheme-2).

Scheme-2:



There are several ways to activate the substrate, intermediate, and peroxide for BV oxidation.[3b] As discussed above, several oxidants can be used for BV oxidation. However, peracids are most commonly used, as the addition and alkyl migration can takes place without any further activation due to the electrophilic activation provided by the acyl group; heterolytic cleavage of the peracid forms a carboxylate. In the case of hydrogen peroxide, the intermediate peroxyacetal must be activated by a Brønsted or Lewis acid. The greater electrophilicity of peracids compared with hydroperoxides is well known for epoxidation reactions, as can be seen in equation 1. In the case of Caro's reagent (peroxymonosulfate), alkyl migration results in loss of the highly stabilized sulfate-leaving group.

Equation-1:

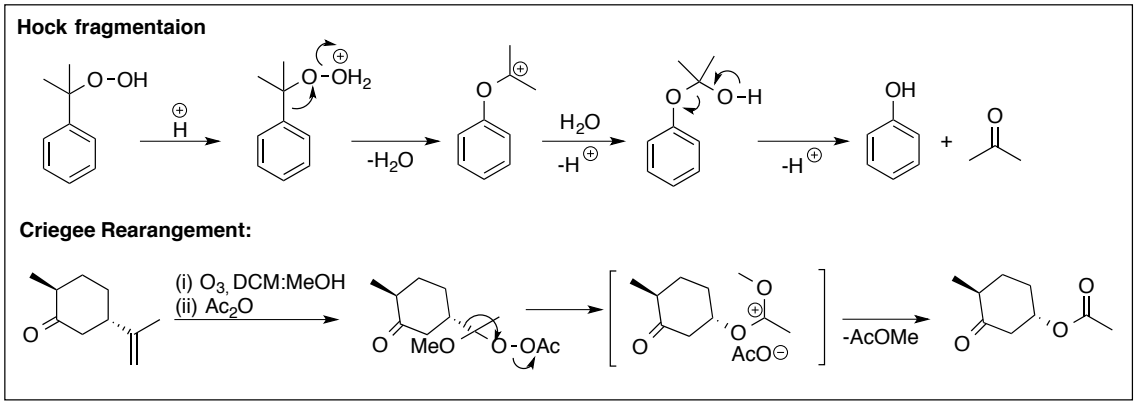


The Hock rearrangement also involves intramolecular attack of a C-C sigma bond on a neighboring peroxide which has been activated by protonation or Lewis acid

complexation (Scheme-3).[5] This reaction is best known for migration of aryl groups in benzylic peroxides but can also occur through migration of sp^3 C atoms. Migratory aptitude follows as: cyclobutyl/cyclopropyl > phenyl > vinyl > hydrogen > alkyl (3° >2°>1°). [5b, 6]

The Criegee rearrangement involves formation of new C-O bonds through 1,2-migration of C-C sigma bonds with cleavage of a neighboring perester or persulfonate. The best known version of the Criegee rearrangement was reported by Schreiber as a workup for ozonolysis reactions.[7] Acylation of ozonolysis-derived α-alkoxy hydroperoxides results in rearrangement with oxidative loss of carbon; the reaction achieves stereospecific introduction of a C-O bond in place of a C-C bond. Migratory aptitudes are similar as in Hock rearrangements.[7] (scheme-3).

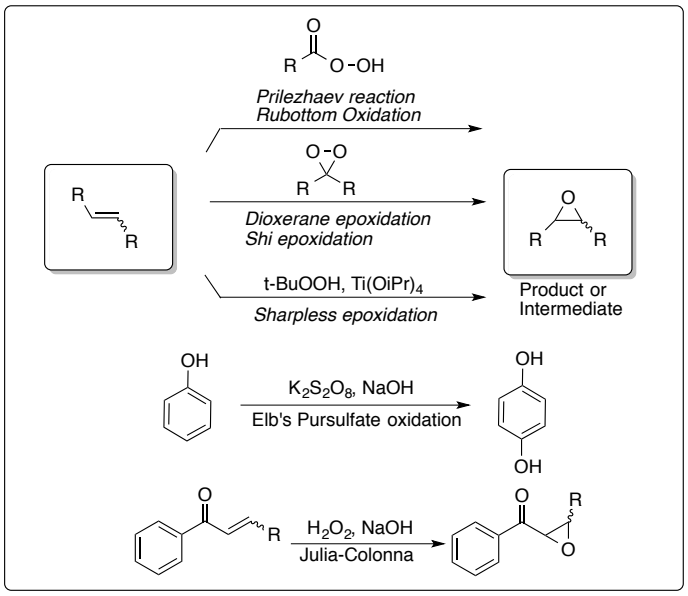
Scheme-3:



π -bond as nucleophile: The pi system of alkenes react with various peroxides to form epoxides (Scheme 4). Percarboxylic acids (Prilezhaev reaction) and dioxiranes can directly transfer the oxygen without any further activation, [8d, 9] Peracids are activated electronically[8], while dioxiranes are activated by the strain of the three-membered ring. [9] Persulfate, a highly electrophilic inorganic peroxide, can directly oxygenate activated

arenes. [10] Alkyl hydroperoxides[11] and hydrogen peroxide[12] can also epoxidize un-activated alkenes, but generally only in the presence of transition metal catalysts. The exception is the Julia-Colonna oxidation of electrophilically activated alkenes by hydroperoxides or hydrogen peroxide under basic conditions; however, this reaction actually involves intramolecular reaction of an electron-rich alkene (enolate) / peroxide pair derived from a conjugate addition.[13]

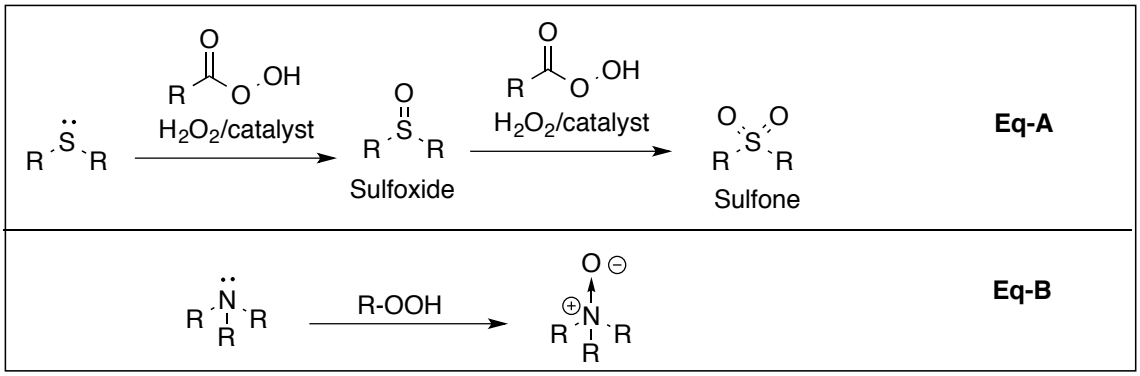
Scheme-4:



Section-1.2: Heteroatom Nucleophiles

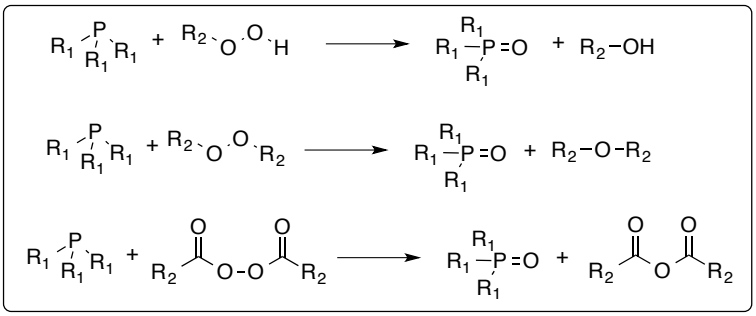
Heteroatoms such as N, S and P are known for their reactivity toward peroxides. Dialkyl sulfides react with alkyl hydroperoxides and hydrogen peroxide (with & without metal catalysts) to give sulfones and sulfoxides (scheme-5-A). [14] Similarly most amines are readily oxidized to *N*-oxides and nitoso compounds by peracids (scheme-5-B). [15] Molecules containing trivalent P, chiefly phosphines and phosphites, are also oxidized by peroxides to corresponding phosphine oxides and phosphates (scheme-6).[16] In this section, the greatest emphasis will be placed on the phosphorous nucleophiles.

Scheme-5:



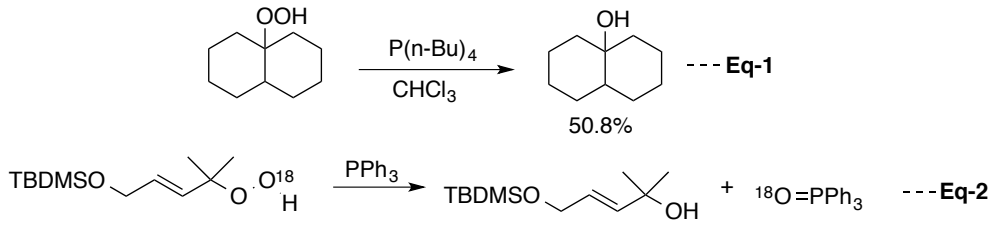
Reaction with phosphines: As illustrated in Scheme 6, phosphines react with a variety of peroxides with cleavage of the O-O bond and net formation of the phosphine oxide. The proposed mechanism for all these substrates follows heterolytic bond cleavage of peroxides.[16]

Scheme-6:



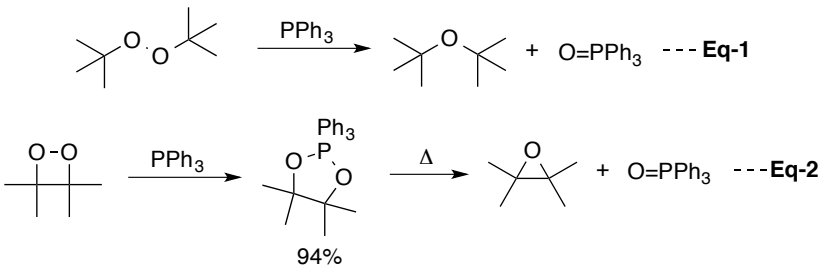
Alkyl hydroperoxides: Alkyl hydroperoxides react with phosphines to form alcohols (scheme-7; equation-1). [17, 18] Porter and coworkers, during the synthesis of unsymmetrically ^{18}O-labeled peroxides, demonstrated selective transfer of the terminal OH from alkyl hydroperoxides to triphenylphosphine (scheme-7; equation-2). [19]

Scheme-7:



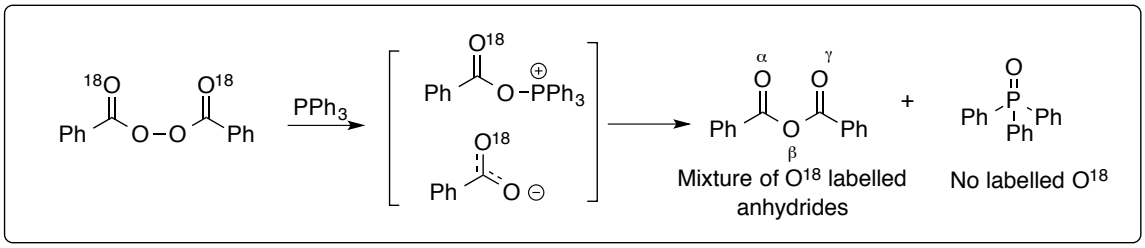
Dialkylperoxides: Di tert-butyl peroxide was shown to react with PPh_3 to form di-tert-butyl ether (scheme-8; eq-1). [17] An investigation of the triphenylphosphine reduction of the highly reactive dioxetane provided a clear evidence that reaction proceeds through an intermediate phosphorane (scheme-8; eq-2). [20] Phosphines were also explored for deoxygenation of endoperoxides (not shown). [21]

Scheme-8:

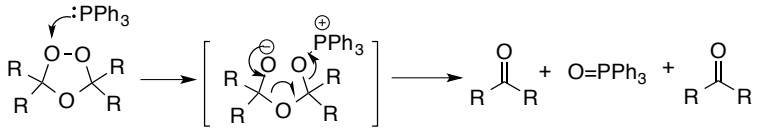


Diacyl peroxides: Diacyl peroxides have been shown to react with phosphines to form anhydrides and the phosphine oxide. The reaction of phosphines with dibenzoyl peroxides containing ^{18}O-labeled carbonyl oxygens produced triphenyl phosphine oxide with no incorporation of ^{18}O, revealing preferential attack of PPh_3 on the peroxide and not the carbonyl oxygen of the acyl peroxide (Scheme-9).[22] Ozonoides appear to also be reduced heterolytically by phosphines to form carbonyl compounds (Scheme-10).[16]

Scheme-9:

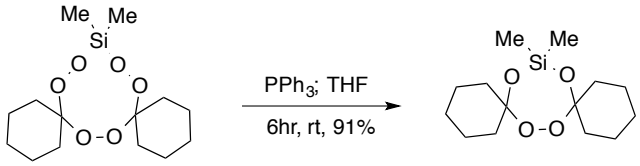


Scheme-10:



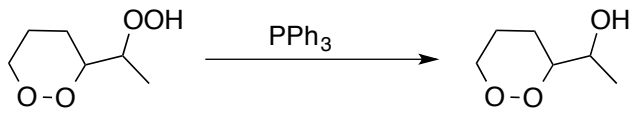
Bis-silyl peroxides are reduced with triphenylphosphine to form the corresponding bis-silyl ethers (Scheme-11).

Scheme-11



Relative rates, and solvent effects have been studied for the triphenyl phosphine reduction of 1°, 2° and 3° butyl hydroperoxides. The rate of reduction was n-butyl > s-butyl > t-butyl. For a given hydroperoxide, the rate of reduction is faster in non-polar solvents such as n-hexane compared to CH_2Cl_2 and EtOH. An example from Porter and coworkers illustrates the preferential reduction of hydroperoxides over dialkyl peroxides by PPh_3 (Scheme 14). [26]

Scheme-14:

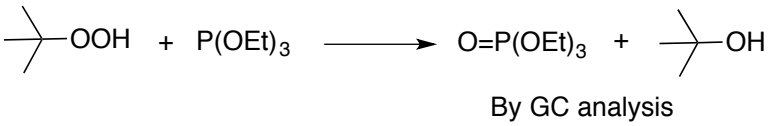


Reaction with phosphites:

Trialkyl phosphites react with alkyl hydroperoxides and dialkyl peroxides to form trialkyl phosphates.

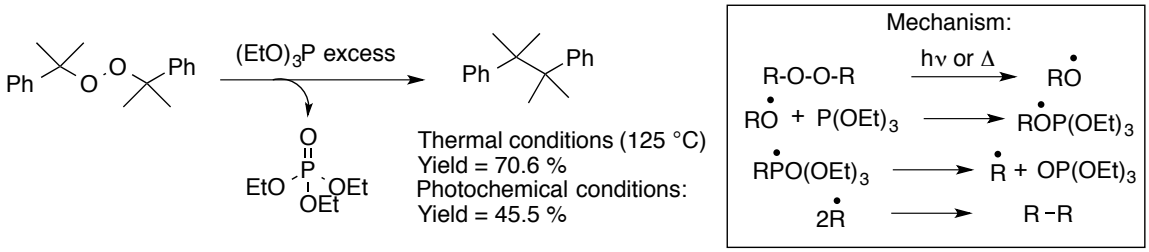
Alkyl hydroperoxides: The reaction of t-butyl hydroperoxides with triethyl phosphites generates t-butanol (equation-2). [23]

Equation-2

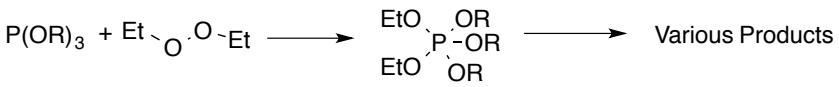


Dialkyl peroxides: Phosphite reduction of sterically hindered dialkyl peroxides such as dicumyl peroxide requires harsher conditions. At elevated temperatures or under photochemical irradiation, these reactions produce dimerized alkyl backbones, apparently via a radical pathway (Scheme-12). [16, 23] Reactions at room temperature in the dark require prolonged reaction times. Phosphites reactions have been shown (GC, also ^{31}P NMR) to involve intermediacy of pentavalent oxa-phosphoranes (shown in general scheme-13). [24]

Scheme-12:



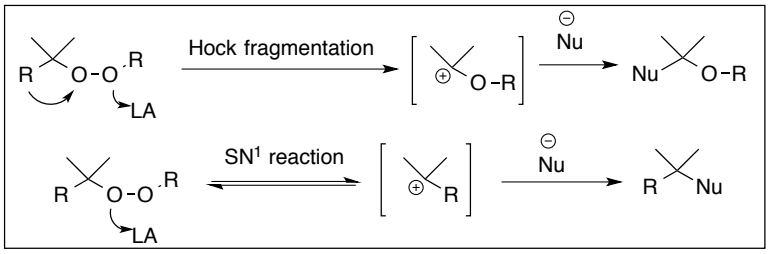
Scheme-13:



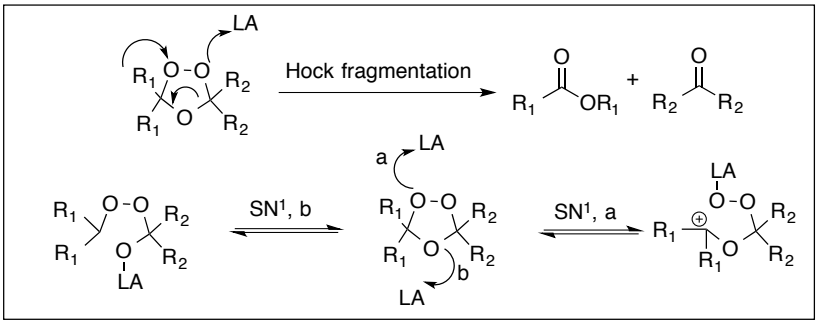
Section-1.3: Lewis acid activated reactions of peroxides and hydroperoxides

Peroxide heterolytic O-O cleavage has been observed in the presence of Lewis acids such $TiCl_4$, BF_3•Et_2O, $SnCl_4$, $EtAlCl_2$, $SbCl_5$, and TMSOTf.[6] Depending on the peroxide structure, Lewis acids can coordinate to either peroxide oxygen, resulting in Baeyer-Villiger and Hock rearrangements via migration of a neighboring C-C bond (or occasionally a pi system, as observed by Dai et. al -*vide-infra*). Lewis acid mediated activation of peroxides has been studied for ozonides, alkyl hydroperoxides and dialkyl peroxides.[27] Either Hock-type fragmentation or S_N1 ionization can takes place depending upon Lewis acid and conditions, suggesting different modes of activation based upon the peroxide coordination site (scheme-15 and 16).

Scheme-15: Hock vs. $S_N{}^1$

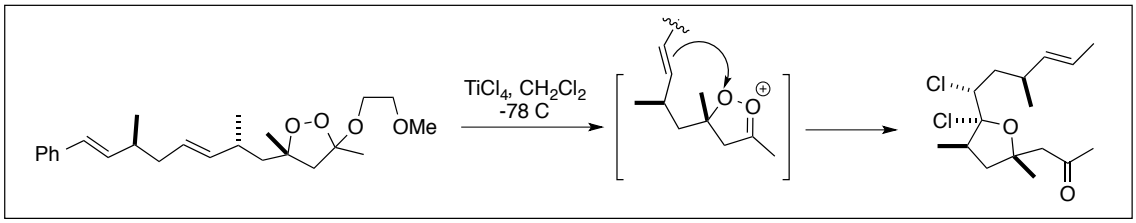


Scheme-16:



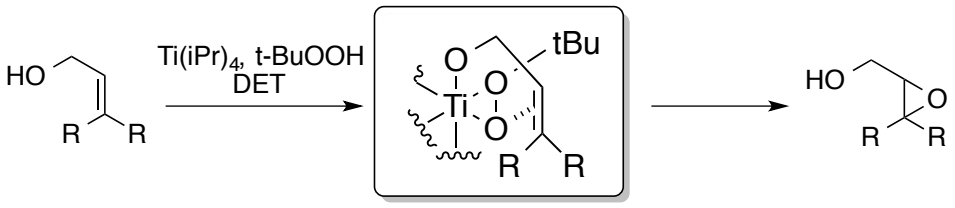
During the synthesis of Plakinic acid-A, Dai and coworkers observed $TiCl_4$-mediated 5-*exo* cyclization by a π-bond onto an activated 1,2-dioxolane to give a substituted tetrahydrofuran.[28] (scheme-17).

Scheme-17:



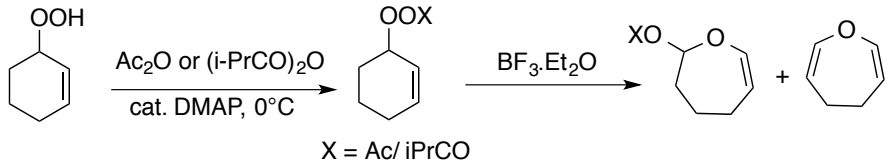
The heterolytic transfer of peroxide oxygen to a nearby alkene is also a key component in the Ti(IV)-catalyzed epoxidation of allylic alcohols by t-BuOOH as part of the Sharpless asymmetric epoxidation (scheme-18).[11a] A related mode of activation is also seen in epoxidations mediated by vanadium, and molybdenum.[11c]

Scheme-18:



Kishi and Goodman employed Lewis acid activation to extend the Criegee rearrangement to allow selective synthesis of cyclic and acyclic enol ethers from peroxide precursors otherwise capable of elimination to enones. In the presence of BF_3•Et_2O, the intermediate peresters underwent Criegee rearrangement in good yield and without the formation of the enone.[29] (Scheme-19).

Scheme-19:



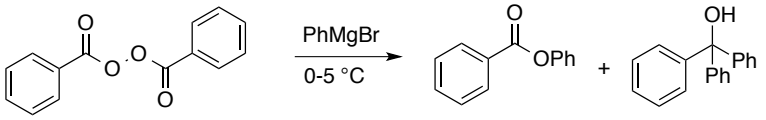
Section-2: Background on reaction of peroxides with organometallic reagent.

Peroxides are also known to undergo reaction with organolithium, organomagnesium, and organozinc reagents. As will be seen in the examples below, the nature of the peroxide can have a significant impact on substrate reactivity and, in the case of unsymmetrical peroxides, on the oxygen atom attacked.

Section-2.1: Reaction with Grignard reagents.

Gillman and Adams[30] investigated reactions of dibenzoyl peroxide, triacetone peroxide, and diethyl peroxide towards organomagnesium halides and obtained mixture of products with varying yields depends on molar ratio of peroxide and nucleophile. Scheme 20 illustrates reactions of diacyl peroxides.

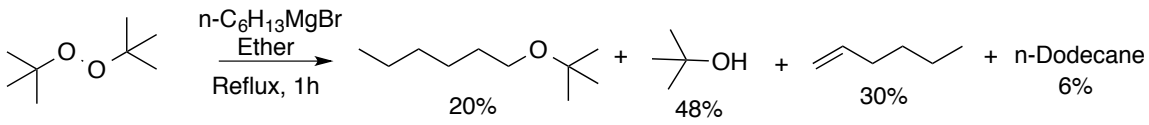
Scheme-20:



Eq (PhMgBr)	Ester	Alcohol
1 eq	28%	--
2 eq	3%	23%

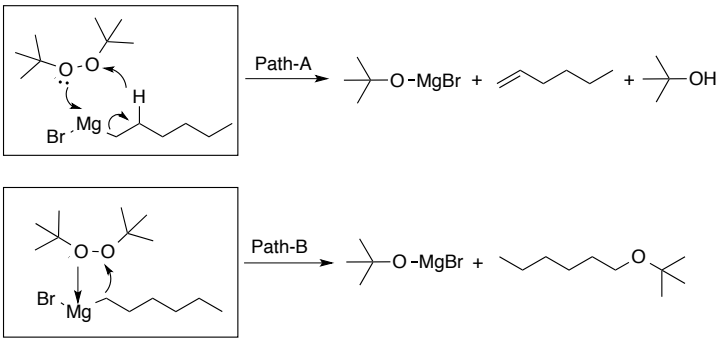
Campbell et.al next studied di t-butyl peroxide as an electrophile towards alkyl magnesium halides containing β hydrogen atoms. Reaction of hexyl magnesium bromide with di *tert*-butylperoxide gave a low yield of t-butyl ether along with three different byproducts (scheme-21, showing isolated yields). [31]

Scheme-21:



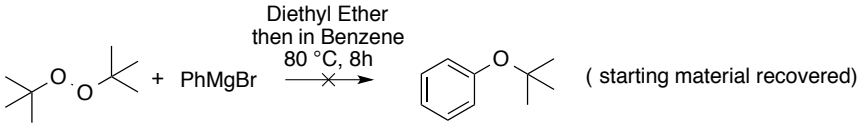
Byproduct formation was attributed to reduction of the peroxide by transfer of beta hydride through a cyclic transition state (scheme-22; path-A). However, this mechanism does not explain the oxidation of the organometallic to an alcohol or the dimerization of the carbon framework, pathways that would seem to better fit a single electron transfer mechanism involving an intermediate carbon radical.

Scheme-22:



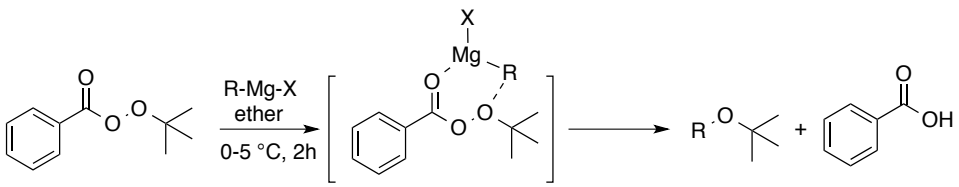
Although alkyl magnesium reagents are reactive to some extent towards di t-butyl peroxide (Scheme-22), PhMgBr is completely unreactive (equation-3).

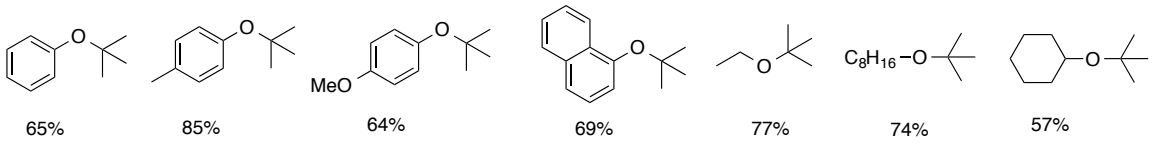
Equation-3:



Lawesson studied[32] the reactions of t-butyl perbenzoate with alkyl and aryl Grignard reagent and demonstrated that this methodology could be use to synthesize a series of tert-butyl ethers in good to moderate yields (scheme-23).

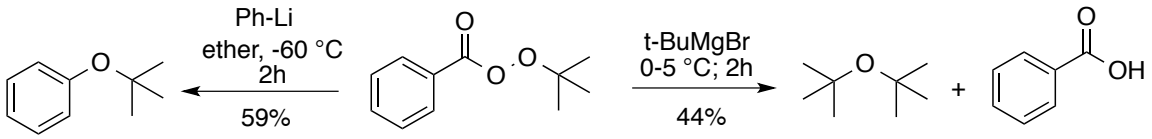
Scheme-23:





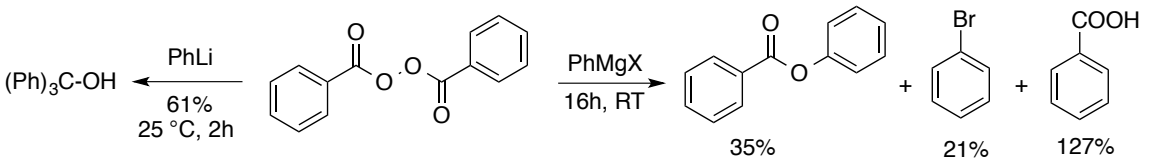
The same report also described reaction of t-butyl perbenzoate with phenyl lithium at -60 °C to furnish 59% of anisole. More interestingly, the authors applied the method to di-tert-butyl ether synthesis using t-butyl magnesium chloride, demonstrating the methodology could be applied to a substrate impossible to prepare via Williamson etherification due to competition with E2 elimination. The results can be explained by better co-ordination of Mg with carbonyl oxygen, which is not possible in the case of di-tert butyl peroxide, and the inherent superiority of benzoate as leaving group compared with an alkoxide (equation-4).

Equation-4:



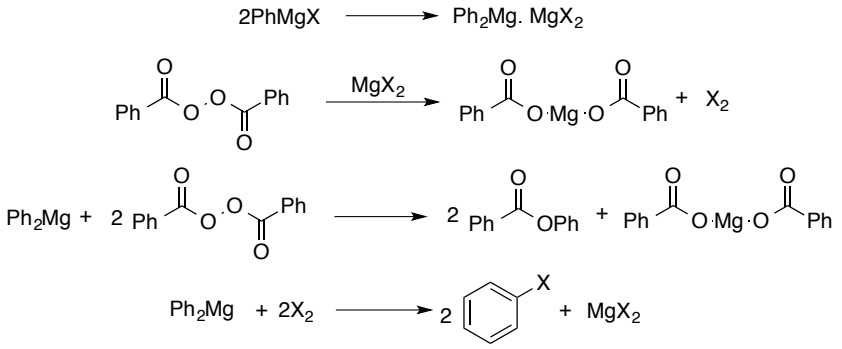
R-Li vs RMgX show different modes of reactivity in their reactions of dibenzoyl peroxide (equation-5). Reaction with phenyl magnesium bromide provided 35% phenyl benzoate along with bromobenzene and excess of benzoic acid. In contrast, PhLi gave triphenyl methanol as major product, suggesting that magnesium is important counter ion.

Equation-5:



The authors proposed a mechanism for formation of bromobenzene based upon the presence of bromine derived from oxidation of bromide by the acyl peroxide.[33] The mechanism also explained the greater than expected yield of benzoic acid by invoking peroxide cleavage in presence of the organomagnesium (scheme-24).

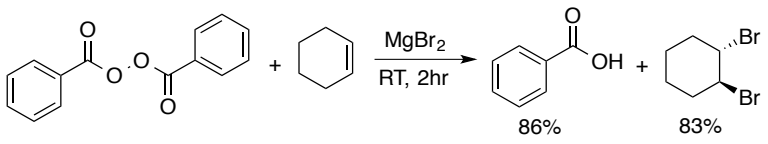
Scheme-24:



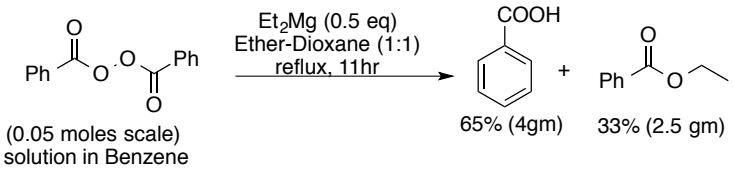
Proposed mechanism (scheme-24), was supported in two separate experiments: (1) trapping the halogen, i.e. when benzoyl peroxide treated with MgX_2 in the presence of cyclohexene, *trans*- 1,2 dibromocyclohexane obtained in very good yield (equation-6); (2) isolating 33% of ethyl benzoate upon reaction of benzoyl peroxide with diethyl magnesium (equation-7).

Another possibility could be alternative pathway involving singlet electron transfer (SET) from RMgX to the peroxide would give a benzoyloxy radical, benzoate and $[RMgX]^{\bullet+}$ which could lead to same product combination.

Equation-6:



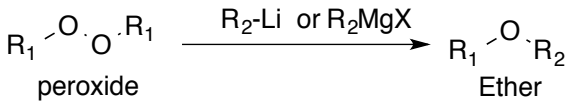
Equation-7:



Section-2.2 Reaction with organo lithium reagents:

Baramki and coworkers investigated[34] reactivity of various dialkylperoxides towards aryl lithium and aryl magnesium reagents. Two distinct features can seen in their results, which are summarized in Table-1: (i) Yields with Ph-Li were superior to those obtained with the analogous Grignard reagent (ii) Methyl t-butyl peroxide preferentially underwent nucleophilic attack at least hindered side to give methyl ether as solely product. This is the first example of regioselective reaction of a dialkyl peroxide electrophile.

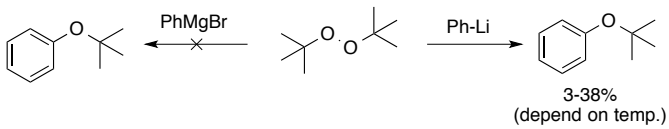
Table-1:



Peroxide	Ether	T (°C)	Yield from PhLi (%)	Yield from Ph-Mg-Br (%)
Me-O-O-Me	Ph-O-Me	15-20	80	77
Et-O-O-Et	Ph-O-Et	15-20	38	30
Me-O-O-tBu	Ph-O-Me	15-20	63	20
Me-O-O-tBu	Ph-O-Me	35	72	38

Table 2 illustrates results with di-tert-butyl peroxide. This more hindered substrate is completely inert to PhMgBr, while it reacts with PhLi to some extent to give t-butyl ether in moderate yields. This could result from better coordination of the small lithium atom with peroxide oxygen, greater reactivity of the organolithium, or reaction through a different mechanism.

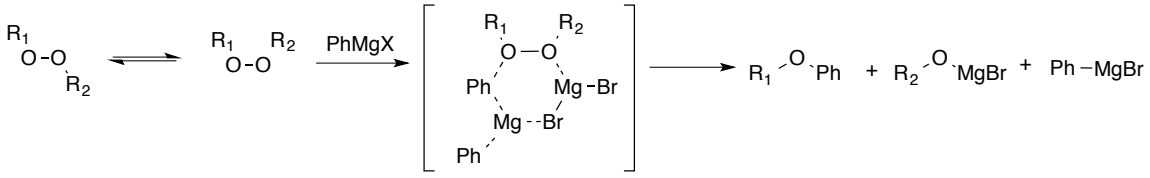
Table-2: Ph-Li and Ph-Mg-Br reaction at various temperatures



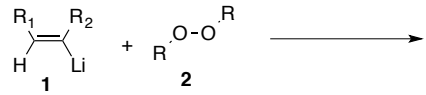
Peroxide	Ether	T (°C)	Yield from PhLi (%)	Yield from PhMgBr (%)
tBu-O-O-tBu	Ph-O-tBu	0-5	3.3	0
tBu-O-O-tBu	Ph-O-tBu	15-20	19	0
tBu-O-O-tBu	Ph-O-tBu	35	39	0
tBu-O-O-tBu	Ph-O-tBu	80	38	0

Based on the studies from Dessy, et al[33] (*vide supra*), Baramki proposed a four-center mechanism for formation of ethers (scheme-25).

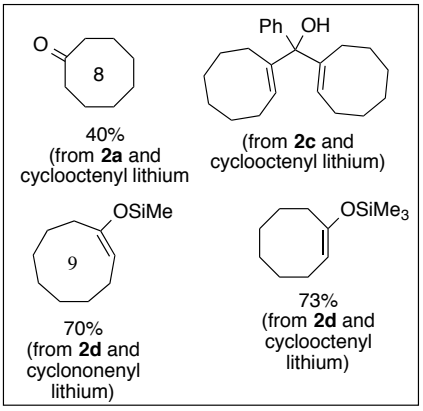
Scheme-25:



Scheme-26:



Peroxide (R/R)	tBu/Li	tBu	C_8H_5CO	$Si(Me)_3$	$Si(Me)_3(tBu)$	$ArSO_2$
2	2a	2b	2c	2d	2e	2f

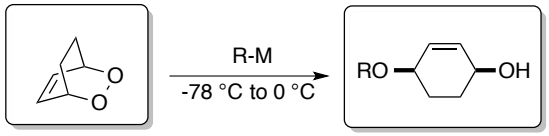


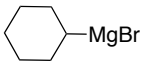
Seebach and Neumann investigated reactions of vinyl lithium with various peroxides (2a-2f in Scheme-26). [35] Reaction of cyclooctenyl lithium with the lithium salt of t-BuOOH provided only 40% ketone. In the case of dibenzoyl peroxide, only 1,2 addition product

was obtained. Where as cyclooctenyl and cyclononenyl lithiums successfully gave vinyl ether when reacted with Bis(trimethyl silyl) peroxide.

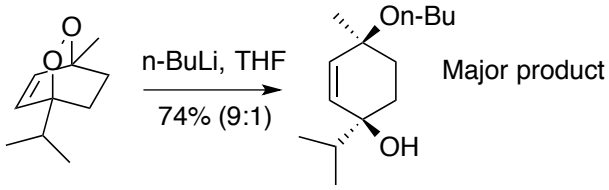
Little and Schwaebe explored endoperoxides as electrophiles towards alkyl, vinyl lithium, magnesium and zinc reagents (Table-3).[37] Vinyl and alkyl zinc reagents produced moderate yields of ethers, but organo lithium and magnesium reagents produced excellent yields. Reaction of the asymmetric cyclic peroxide ascaridole with n-BuLi produced 9:1 mixture of ether products, with the major product resulting from attack on the less sterically hinderd peroxide (Equation-8).

Table-3:



Entry	1	2	3	4	5	6	7
Organometallic (R-M)	$H_2C=CHMgBr$	$H_2C=CHLi$	$(H_2C=CH)_3Zn$	n-BuLi	$(n\text{-}BuLi)_3Zn$	PhMgBr	
Yield (%)	93	94	45	96	50	98	69

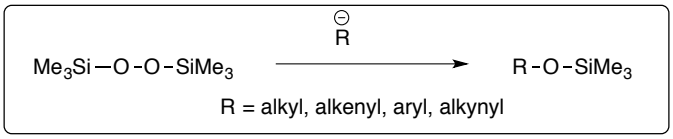
Equation-8:

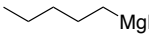
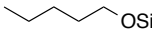
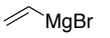
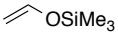
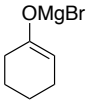
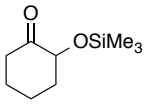
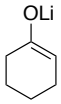
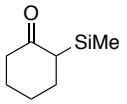
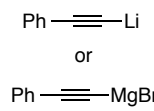
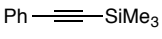


Ricci and Taddei explored bis-(trimethylsilyl) peroxide as an electrophile towards alkyl and aryl lithiums and magnesium. [38] Table-4 shows selected examples of the formation of silyl ethers vs C-silylated product formation from various RLi and RMgX with reaction of trimethyl silyl peroxides. Reactions with Grignard reagents were found to result in exclusive formation of ethers except for alkynyl magnesium reagents, which underwent

C-silylation (entry-6). In contrast, vinyl lithium reacted mainly through C-silylation. Lithium enolates reacted to form only C-silylated products whereas the magnesium enolate furnished only silyloxyether (entry-3, 5).

Table-4

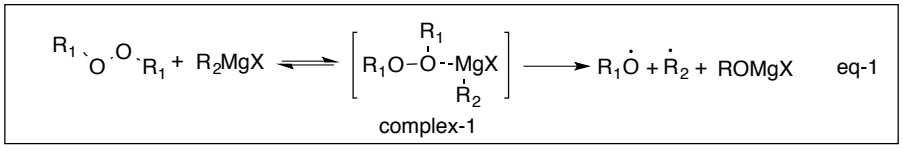


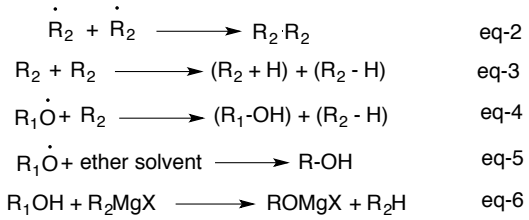
Entry	Organo Metallic Reagent	R-SiMe$_3$: R-OSiMe$_3$ (GC ratio)	Major Product	Major product Yield (%)
1		0 : 100		89
2		0 : 100		40-60
3		80 : 20		45
4		0 : 100		61
5		100 : 0		--
6		100 : 0		--

Section-2.3- Studies towards radical pathways

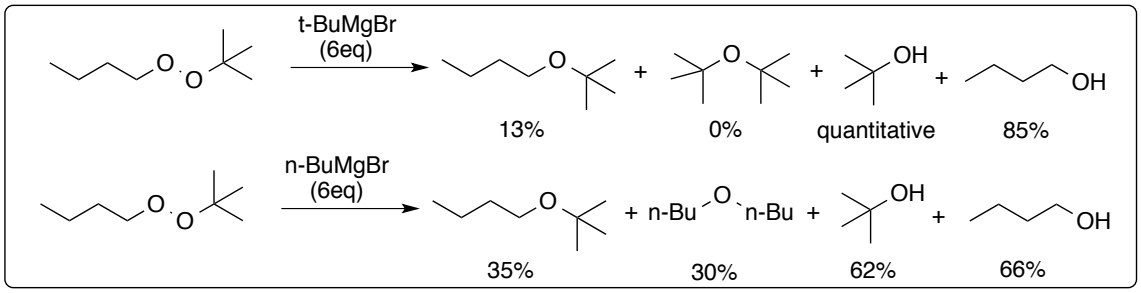
Jarvie and Skelton investigated the reaction of dialkyl peroxides with Grignard reagents and proposed the formation of radicals via complex-1 (scheme-28, eq-1), observing products consistent with radical recombination (Eqs 2 to 6).[39] In their study, the reactivity of RMgX in terms of formation of ethers (eq-1) was: allyl MgBr > RMgCl > RMgBr > RMgI. The results were explained based on the lifetime of halide radicals in the protective cage.

Scheme-28:



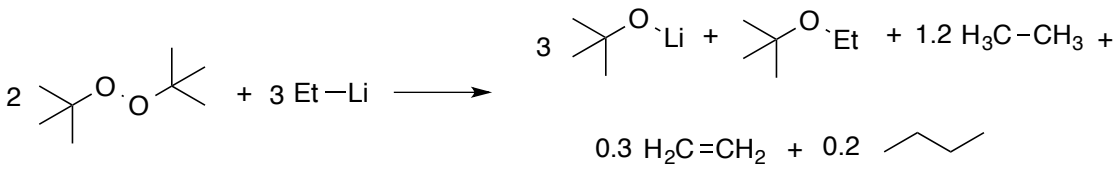


Examples for Scheme-28:



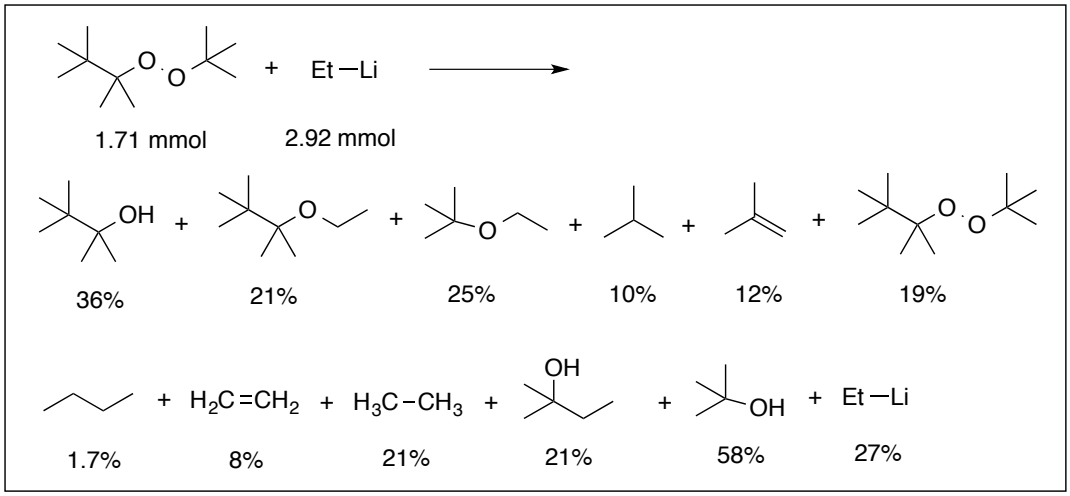
Kochi and coworkers studied[40] extensively the possibility of radical pathway for reaction of dialkyl peroxides and alkyl lithiums. An investigation of the reaction of ethyl lithium and di tert-butyl peroxide (DTBP) at five different concentrations of starting materials was found to result in the product distribution shown in equation 9, in which the expected ether and alcohol products are accompanied by ethane, butane and ethylene as side products.

Equation-9:

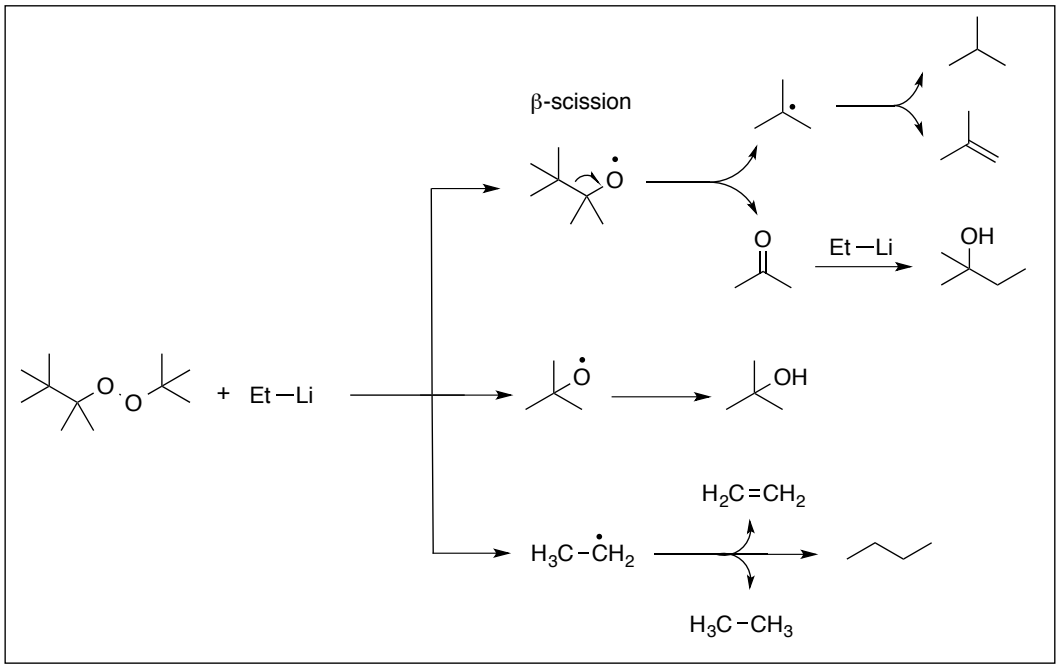


Kochi's results were explained through beta scission reactions of tert-alkyl radicals. The unstable 2,3,3-trimethyl-2-butoxy radical generated during the reaction of triptyl t-butyl peroxide with ethyl lithium was observed to generate a variety of products via β-scission (scheme-29) Recombination of intermediate radicals accounted for the observed products (scheme-30).

Scheme-29:



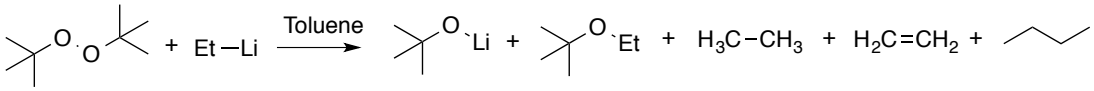
Scheme-30: Mechanism:



Reaction with radical trapping additives:

The presence of intermediate alkyl radicals was further explored by conducting reactions in the presence of additives such as styrene, which is capable of scavenging intermediate carbon radicals (scheme-31).

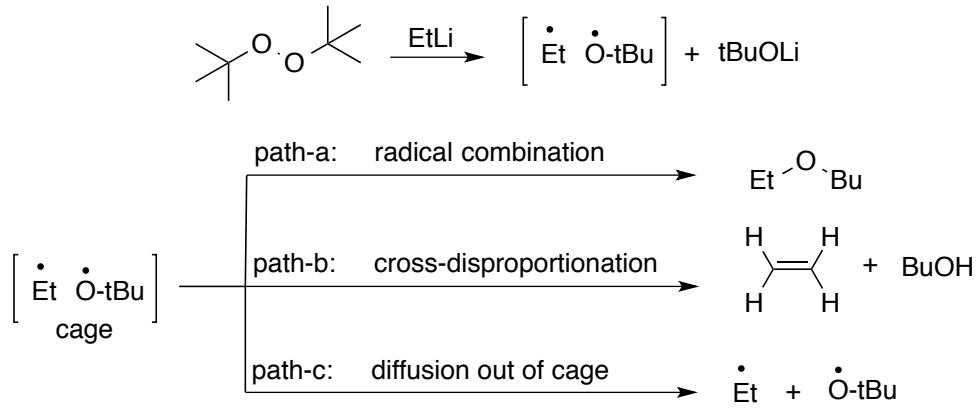
Scheme-31:



No additive	75%	25%	30%	9%	4.7%
with styrene additive	80%	9.5%	15%	2%	0.6%

When DTBP was reacted with ethyl lithium in the presence of added styrene, yields of ethyl t-butyl ether, ethane, ethylene and butanes were reduced significantly, pointing to the intermediacy of carbon radicals in the formation of these products. Although the yield of the ethyl ether was also greatly reduced, the yield of tert-butoxy lithium was not affected, suggesting that DTBP reduction not effected by the presence of a radical trap. Based upon these observations, Kochi proposed a mechanism involving three different reactions of caged radicals derived from scission of DTBP (scheme 32): (i) formation of tert-butyl ethyl ether by cross combination of radical (ii) cross-disproportionation via transfer of hydrogen atom from ethyl radical to tert-butoxyl (iii) and diffusion of radicals from the cage.

Scheme-32:

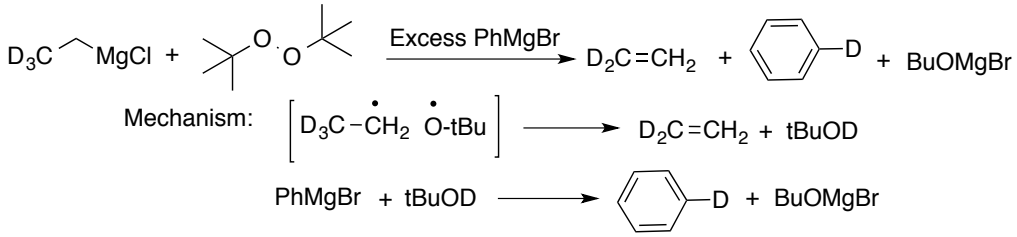


Radicals which have escaped from the solvent cage can undergo variety of cross combinations to generate the other products described in schemes 29 and 30.

The proposed mechanism was supported by 4 different pieces of evidence.

(i) Ethyl tert-butyl ether formation was lowered in the reaction run in the presence of added styrene. (ii) Kochi cited work by Morrison and Epstein as an evidence for his cross-disproportionation reaction. [36] When 2,2,2-trideutero-ethyl magnesium was treated with DTBP in presence of excess phenyl magnesium bromide, these authors obtained deuterobenzene as byproduct. Based on the fact that phenyl magnesium bromide is inert towards DTBP, it is considered that deutero-benzene formation was due to cross-disproportionation (scheme-33).

Scheme-33:



(iii) Increasing the solvent viscosity increases the yield of the tert-butyl ether product.

(iv) The products derived from reaction of triptyl t-butyl peroxide are difficult to explain other than by a process involving β -scission to form tert-butyl radical and acetone. Isobutene and isobutane formation takes place via disproportionation (scheme-30).

Section-2.4: Brief Summary- two-electron vs. radical mechanisms in organometallic reactions with dialkyl peroxides.

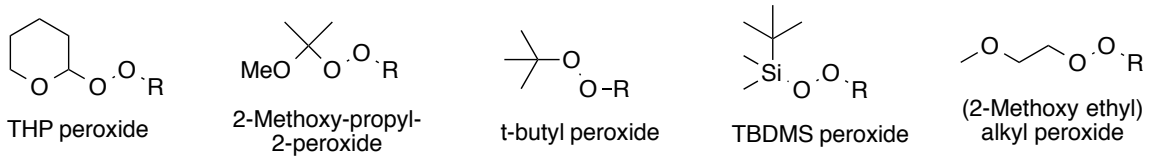
The above discussion makes it clear that there is evidence for at least two mechanistic pathways, radical and two-electron, in the formation of ethers from organometallic reagents and dialkyl peroxides. When one also considers structural features of the peroxides, the following conclusions can be made. Heterolytic cleavage predominates when the substrate is activated by (i) by peroxide-Lewis acid coordination or (ii) electronic stabilization of charge on the leaving group. Homolytic cleavage predominates when: (i) there is no such above factor absent; or, (ii) the peroxide is sterically hindered, and the slow transfer of alkoxide to carbanion can lead to radical cage formation in presence of organometal.

Section-3: Results and Discussion

In this section I will discuss (i) Synthesis of peroxide electrophiles employed in these studies; (ii) Reactivity of the various peroxides toward various organolithium and organomagnesium reagents for C-O bond formation.

We are investigating new classes of peroxides that address the issues of selectivity and reactivity in etherification reactions. Our studies have involved five different types of peroxides (figure-1).

Figure-1:



Section-3.1: Synthesis of dialkyl peroxide electrophiles

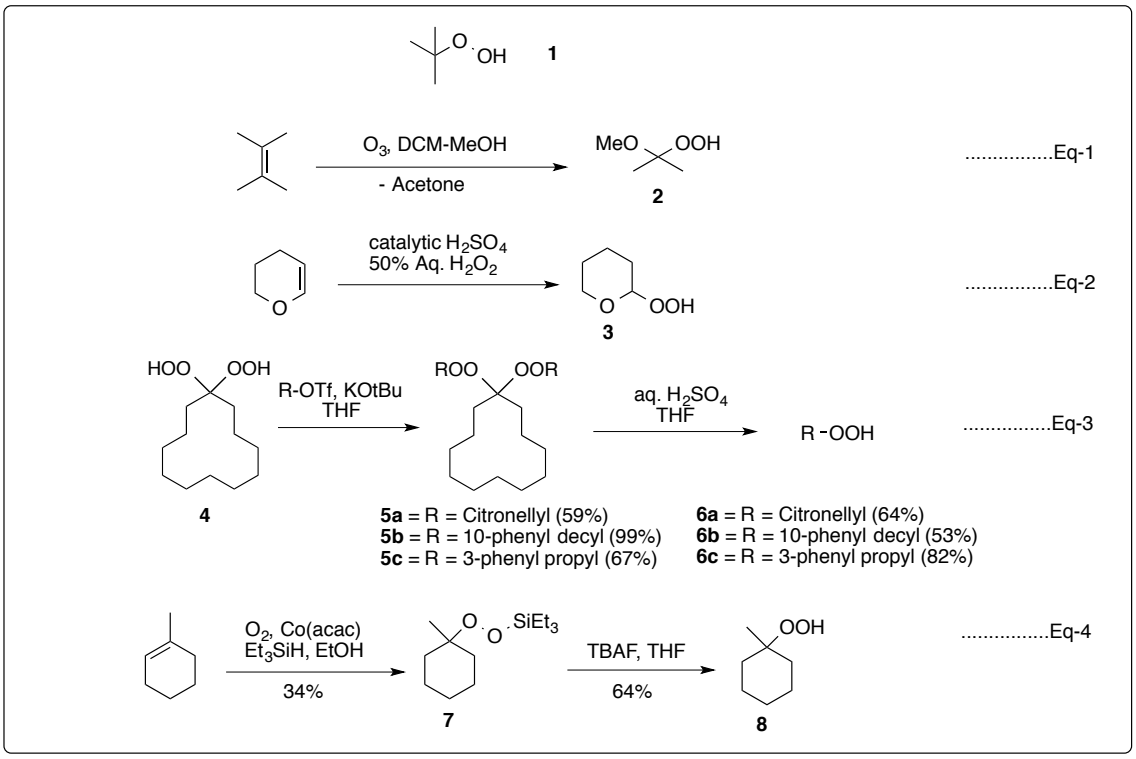
This section discusses the synthesis of peroxide substrates via reactions of alkyl hydroperoxides which were in turn derived from sulfonates, halides, or enol ethers.

Synthesisis of hydroperoxide precursors:

t-Butyl hydroperoxide is commercially available. 2-Methoxyprop-2-yl hydroperoxide (**2**), tetrahydropyranyl (THP) hydroperoxide (**3**), and primary alkyl hydroperoxides **6a-c** were synthesized using known procedures (scheme-34). 2-Methoxyprop-2-yl hydroperoxide was synthesized from ozonolysis of 2,3-dimethyl butene in presence of MeOH (eq-1).[41] THP hydroperoxide could also be synthesized from acid-catalyzed per-hydrolysis of 2,3 dihydropyran[42] (eq-2). Primary alkyl hydroperoxides were synthesized from acid hydrolysis of 1,1 bis-peroxyacetals[43] (eq-3; see chapter-2 for description), which were in turn available from alkylation of 2-methoxy-2-propyl hydroperoxides. A single 3°- alkyl

hydroperoxide (**8**) was synthesized from the corresponding silylated peroxide, which was obtained from cobalt-catalyzed alkene peroxidation[44] in the presence of O_2 (eq-4).

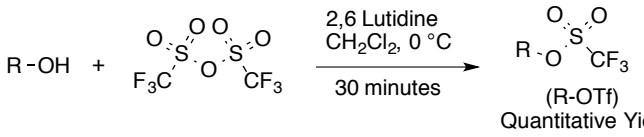
Scheme-34: Synthesis of alkylhydroperoxides

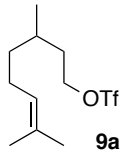
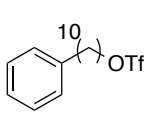
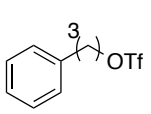
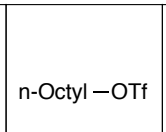
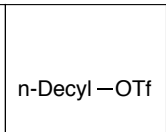
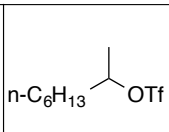
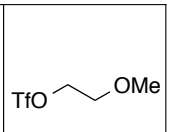


Synthesis of alkyl triflates and alkyl halides:

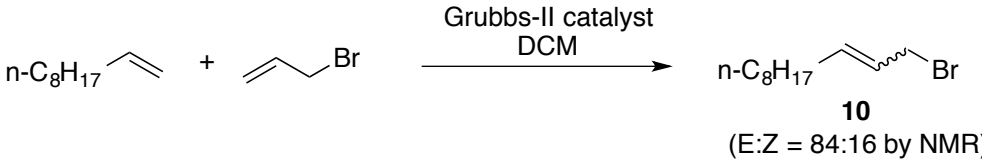
The synthesis of trifluoromethane sulfonates and halide electrophiles as synthetic precursors for peroxide substrates is shown in scheme-35, and scheme-36. Triflates were prepared using established procedures.[46] An allylic bromide was prepared as an approximately (84:16) E/Z mixture through alkene cross-metathesis in the presence of allyl bromide.

Scheme-35: Alkyl triflate synthesis from commercial alcohols



						
9a	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**

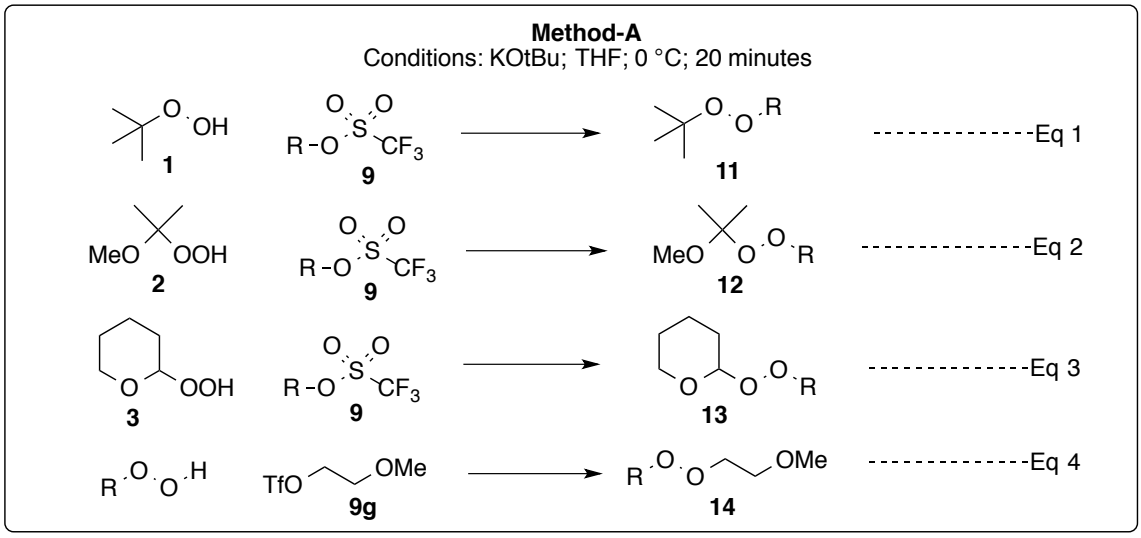
Scheme-36: Synthesis of allyl bromide (procedure ref-45)



Synthesis of peroxide substrates:

A number of the dialkyl peroxides and monoperoxyacetals were prepared by alkylation of the corresponding hydroperoxide with an alkyl triflate in the presence of KOt-Bu (Scheme 37).

Scheme-37: Nucleophilic substitution of alkyl triflates by hydroperoxides (Method-A)



THP monoperoxyacetals were also synthesized by acid-catalyzed acetalization of 2,3-dihydropyran (scheme-38; method-B). Alkyl/allyl peroxides were synthesized using Ag_2O-promoted reaction of the alkyl hydroperoxide and allyl bromide **10** (scheme-38; method-C). *tert*-Butyl dimethyl silyl ethers of peroxides (here onwards TBDMS) were synthesized by protection of alkyl hydroperoxides with TBDMSCl (method-D).

Scheme-38: Methods B-C for peroxide synthesis

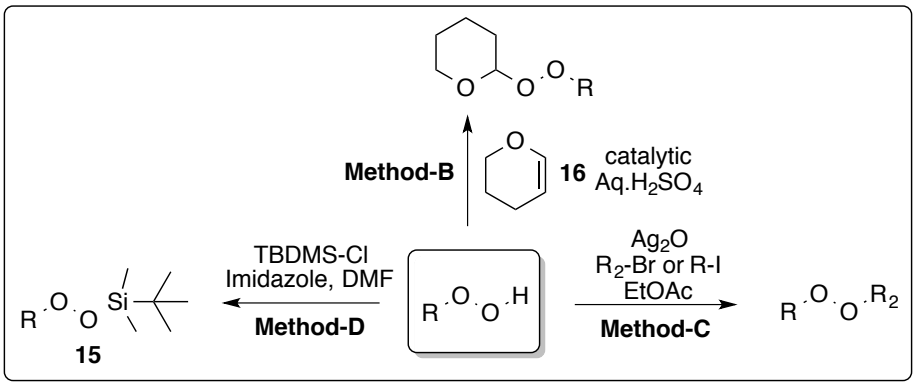


Chart-1: Peroxide electrophiles.

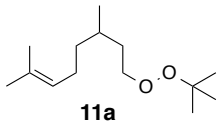
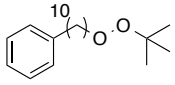
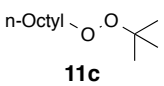
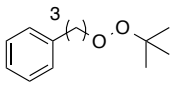
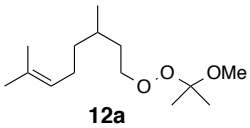
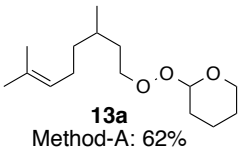
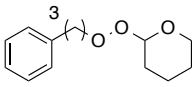
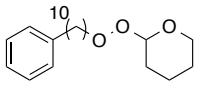
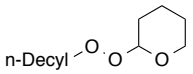
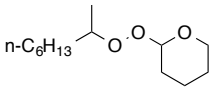
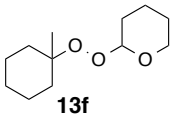
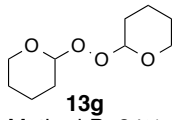
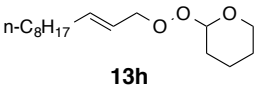
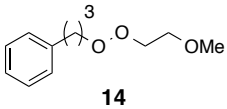
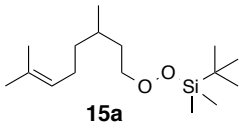
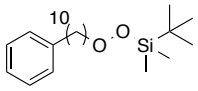
 **11a** Method-A: 69% (from **9a, 1**)	 **11b** Method-A: 92% (from **9b, 1**)	 **11c** Method-A: 88% (from **9d, 1**)	 **11d** Method-A: 73% (from **9c, 1**)
 **12a** Method-A: 61% (from **9a, 2**)	 **13a** Method-A: 62% (from **9a, 3**)	 **13b** Method-A: 82% (from **9c, 3**)	 **13c** Method-A: 75% (from **9b, 3**)
 **13d** Method-A: 79% (from **9e, 3**)	 **13e** Method-A: 70% (from **9f, 3**)	 **13f** Method-B: 74% (from **8**, dihydropyran)	 **13g** Method-B: 84% (from **1**, dihydropyran)
 **13h** Method-C: 73% (from **10, 3**)	 **14** Method-A: 74% (from **9g, 6c**)	 **15a** Method-D: 58% (from **6a**)	 **15b** Method-D: 75% (from **6b**)

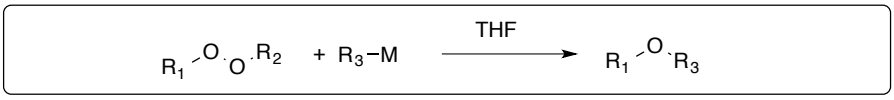
Chart-1 displays peroxide electrophiles employed in these studies and the method (A-D) employed for their formation.

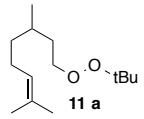
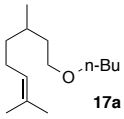
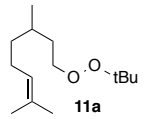
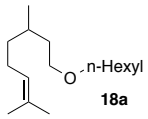
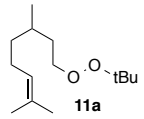
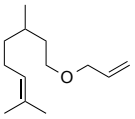
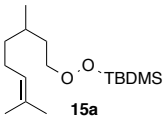
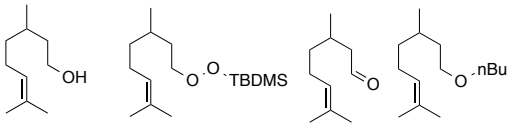
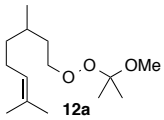
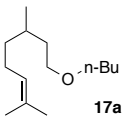
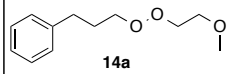
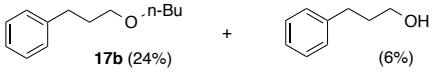
Section-3.2: C-O bond formation using peroxide electrophiles

Initially we screened dialkyl peroxides (R_1-O-O-R_2) for reaction with sp^3 RLi and RMgX. t-Butyl alkyl peroxide **11a** underwent reaction with n-BuLi in 4 hours to give a good yield of the corresponding n-butyl ether, but complete consumption of starting material requires 2 equivalent of RLi, whether the reaction was conducted at -78 °C or room temperature. Reaction of the same peroxide with n-hexyl magnesium bromide (-78 C to room temperature, 8 hours) gave only moderate yield of the hexyl ether (table-5; entry-2). Reaction with allyl magnesium provided only 27% of corresponding ether (entry-3). The reaction of the monosilylated peroxide (**15a**) with n-BuLi provided multiple products along with unreacted starting material (entry-4), byproducts include n-

butylether, citronellyl aldehyde, citronellyl alcohol, and unreacted starting material. Formation of citronellyl alcohol is indication of nucleophilic substitution at more hindered oxygen.

Table-5: Reactivity of several classes of peroxide electrophiles towards organometallic reagents



Entry	Peroxide	Nucleophile (Eq)	Temperature (°C) and Time	Ethers	Yield (%)
1[a]	 **11 a**	n-BuLi (2 eq)	-78 4 hour	 **17a**	75
2[a]	 **11a**	n-Hexyl-MgBr (1.1eq)	0 8 hours	 **18a**	42
3	 **11a**		-78 to rt		27
4	 **15a**	n-BuLi (1.1eq)	-78 to rt 2h		--
5[a]	 **12a**	n-BuLi (1.1eq)	-78	 **17a**	87
6	 **14a**	n-BuLi (1.1eq)	-78	 **17b** (24%) + (6%)	24 + 6

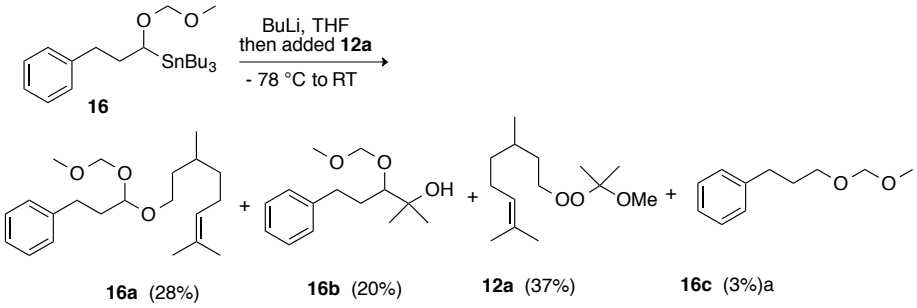
a = Reaction performed by Ben Puffer

The reaction of n-BuLi with 2-methoxyprop-2-yl citronellyl peroxide (table-5; entry-5) gave an excellent yield of the corresponding n-butyl ether (entry-5). In contrast to the results with the t-butyl peroxide, the monoperoxyacetal reacted in 10 minutes. In the hope of determining whether the enhanced reactivity of the monoperoxyacetal was due to the

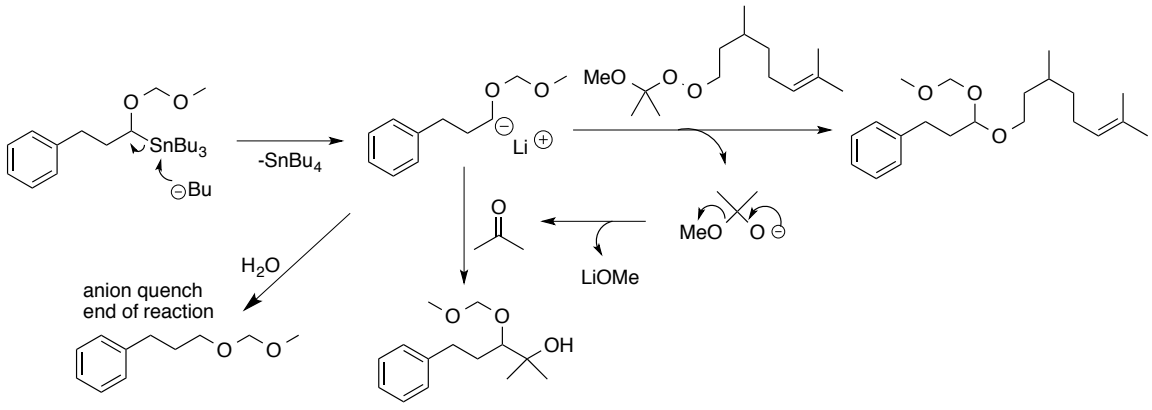
ability to chelate the lithium ion, we investigated the reaction of 2-methoxy ethyl peroxide (**14a**) reaction with n-BuLi. However, reaction of this substrate required 2 hours and gave only 24% of butylated ether; we note that it is possible that some of the transferred organometallic was captured by transfer of the methoxyethoxy group to form butyl 2-methoxyethyl ether as we isolated 6% 3-phenyl propanol (entry-6).

Although we were pleased by the enhanced reactivity of the 2-methoxypropyl peroxy-acetals, the anticipated formation of acetone as a co-product suggested the possibility of undesired consumption of additional organometallic reagent.

Equation-10:



Scheme-39:



This side reaction is not particularly important for test reactions with commercially available organometallics but assumes more significance with more complex nucleophiles, such as α-alkoxy carbanions generated in-situ from α-alkoxy stannanes

(Equation 10). In this case, a significant amount of the starting organometallic is now captured by acetone.

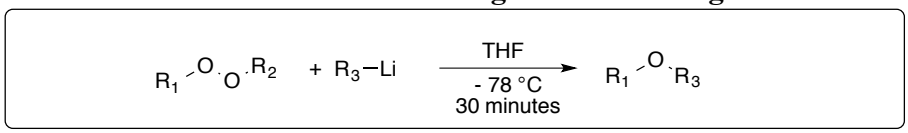
Note: The synthesis and reaction of α-alkoxy lithium molecules is described in more detail in Chapter 4.

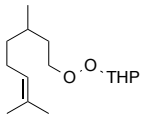
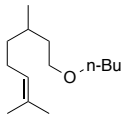
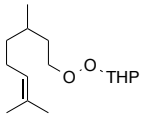
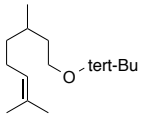
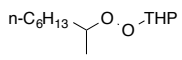
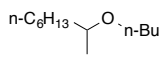
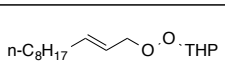
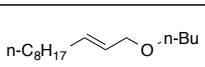
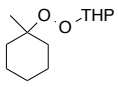
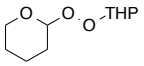
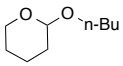
Scheme 39 illustrates the proposed mechanism of formation of the products described in equation 7. Along with the desired mixed acetal (**16a**, 28%), I observed two other byproducts along with unreacted starting material. The methoxymethyl ether is presumably derived from protonation of unreacted anion. However, byproduct **16b**, a tertiary alcohol, appears to arise via trapping of the intermediate organolithium with the acetone byproduct of the desired reaction.

Section-3.3: Reactivity of THP peroxides towards sp^3 RLi and RMgX

Hoping to find an acetal-type leaving group that would not generate a reactive carbonyl byproduct, we turned to tetrahydropyranyl (THP) alkyl peroxides. These monoperoxyacetals were anticipated to have similar reactivity to the methoxypropyl alkyl peroxides but it was hoped that the released tetrahydropyranyloxy anion would have greater stability than the 2-methoxypropyl-2-oxy anion. The results, which are illustrated in Table 6, were exciting.

Table-6: Reaction with Organolithium reagents

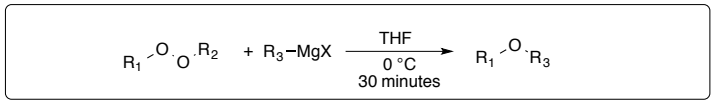


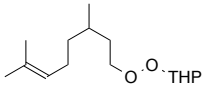
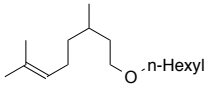
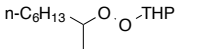
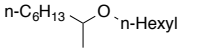
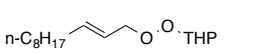
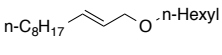
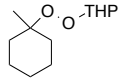
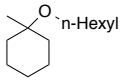
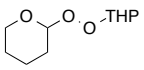
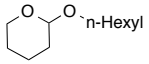
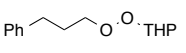
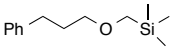
Entry	Peroxide	Nucleophile (1.1 Eq)	Ethers	Yield (%)
1	 **13a**	n-BuLi	 **17a**	81
2	 **13a**	**t-BuLi**	 **17b**	51
3	 **13e**	n-BuLi	 **17c**	78
4	 **13h**	n-BuLi	 **17d**	73
5	 **13f**	n-BuLi	 **17e**	71
6	 **13g**	n-BuLi	 **17f**	15

Initially, we screened a number of THP peroxides for reaction with simple organolithium reagents (Table 6). In general, good yields (71-81%) were obtained for reactions of nBuLi with a variety of mixed THP peroxides: primary (**13a**, entry 1), secondary (**13e**, entry 3), tertiary (**13f**, entry 5) and allylic (**13h**, entry 4). Reactions were complete in less than 30 min at -78 °C. The selective transfer of secondary alkoxide (from **13e**) and a

tertiary alkoxide (**13f**) are noteworthy, particularly given that the latter reaction requires attack on an oxygen which is essentially neopentyl. We also note that the allylic THP peroxide reacted without any evidence for allylic displacement. The only poor yield observed with nBuLi as a nucleophile was for reaction of a bis THP peroxide (**13g**); this reaction (entry 6) generated only 15% of the butyl THP ether as well as several other species visible by TLC but not characterized. Reaction of **13a** with t-BuLi in place of nBuLi proceeded in somewhat lower yield.

Table-7: Reaction with Grignard Reagents.



Entry	Peroxide		Nucleophile (1.1 eq)	Ethers		Yield (%)
1		**13a**	Hexyl-MgBr		**18a**	88
2		**13e**	Hexyl-MgBr		**18b**	88
3		**13h**	Hexyl-MgBr		**18c**	81
4		**13f**	Hexyl-MgBr		**18d**	65
5		**13g**	Hexyl-MgBr		**18e**	61
6		**13b**			**18f**	75

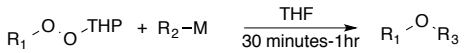
Enhanced reactivity was also observed in reaction of THP peroxides with n-hexyl magnesium bromide (table-7). Whereas the corresponding reactions of the t-butyl alkyl peroxides took place at 0 °C over 2 hours, the THP peroxides underwent reaction at either -78 °C or 0 °C in minutes. As with n-BuLi, successful ether formation was observed for primary, secondary, tertiary, and allylic peroxyacetals. Yields were similar, and sometimes slightly superior to, those obtained with nBuLi; the exception was for reaction

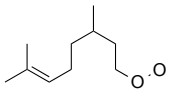
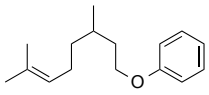
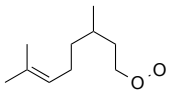
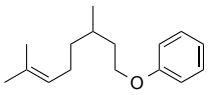
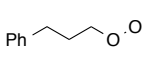
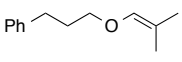
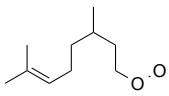
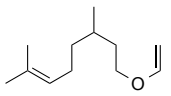
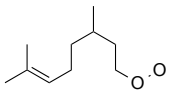
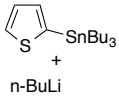
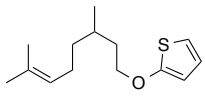
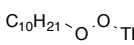
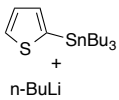
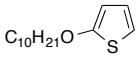
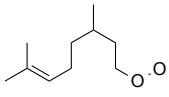
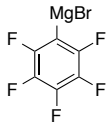
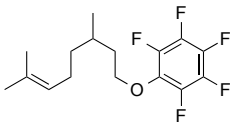
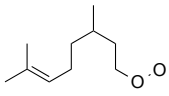
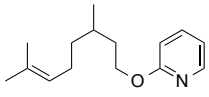
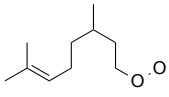
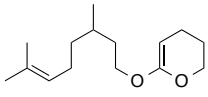
of the bis THP peroxide, where reaction with the Grignard reagent took place in much better yield (entry-5). Reaction of the primary THP peroxide with trimethylsilyl methyl magnesium bromide furnished the a-trimethylsilyl ether in good yield (entry-6).

Section-3.4: Application to couplings with sp^2 RLi and RMgX

After the successful reaction of sp^3 carbanions with THP peroxides described above, we focused our attention towards sp^2 carbanions. The results are shown in Table 8.

Table-8:



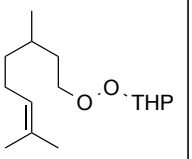
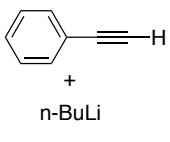
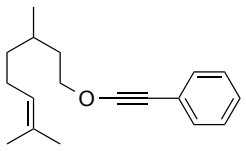
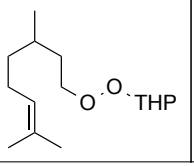
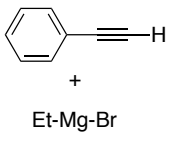
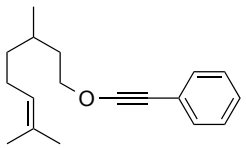
Entry	THP peroxide	RM	Temp (°C)	Ether	Yield (%)
1			-78	 **19a**	87
2			0	 **19a**	75
3			0	 **19b**	41
4			-78	 **19c**	40
5			-78	 **19d**	38
6			-78	 **19e**	36
7			0		--
8			-78 to rt		--
9			-78 to rt		--

THP primary alkyl peroxides showed good reactivity towards PhLi and PhMgBr. (entries-1 and 2). Although reaction of vinyl magnesium bromide proceeded cleanly according to TLC, we could only isolated product in moderate yields (entry 3-6). Although this could be due to decomposition of the acid-sensitive vinyl ether during the work-up and purification, reaction of vinyl lithium generated in-situ from Li/Sn exchange with vinyl tributylstannane, provided much better yields; the same was true with 2-methyl-2-propenyl MgBr (entry 3, 4). Reaction of primary THP peroxides with 2-lithio thiophene, generated in situ from the corresponding tributylstannane, provided clean conversions (TLC) but produced moderate yields of the thiophene ethers[47] (entries 5 and 6), a little known class of molecules. 2-Lithiodihydropyran,[48] 2-lithiopyridine,[49] and pentafluorophenyl magnesium bromide all failed to react with THP peroxide.

Section-3.5: Reaction with alkynyl lithium and magnesium.

I next investigated reactions of a primary THP peroxide (**13a**) with alkynyl lithium and magnesium reagents, generated by deprotonation of phenylacetylene with n-BuLi and EtMgBr. No reaction was observed at room temperature and even after 5 hours, the reaction mixture showed only unreacted starting materials by TLC (table-9).

Table-9:

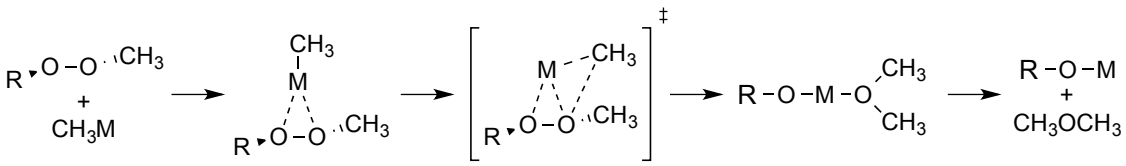
Entry	THP Peroxide	RM	Expeted ether	Result
1		 + n-BuLi		Only SM by TLC
2		 + Et-Mg-Br		Only SM by TLC

Section-4: Computational Studies

This section summarizes preliminary computational mechanistic studies performed by our collaborator, Prof. Keith Kuwata (Macalaster College). I am reproducing figures and calculations from his study by permission. We recently began a collaboration with Prof. Kuwata with a goal of better understanding the dependence of ether formation on a number of variables: (1) the alkali metal counterion (2) the nature of the alkoxide leaving group, (3) the solvent, (4) the extent of delocalization in the carbanion. Preliminary computational results related to the transfer of alkoxide from t-butyl vs. THP peroxides are discussed below.

Proposed pathways and relative energies of transition states for reaction through a mechanism involving simultaneous formation of the new C-O bond and cleavage of the O-O bond (scheme-40, table-10) were modeled using B3LYP/6-31G(d) calculations.

Scheme-40: Calculated energies for ether formation through a concerted mechanism.



I **II** **TS III** **IV** **V**

Table-10: B3LYP/6-31G(d) relative energies (at 0 K, kcal/mol) for the structures in Scheme-30

M	R	**I**	**II**	**TS III**	**IV**	**V**
Li	t-butyl	0.0	-22.0	-9.9	-107.5	-86.6
Li	THP	0.0	-29.4	-25.3	-123.4	-103.9
Na	t-butyl	0.0	-13.2	1.1	-92.0	-74.9
Na	THP	0.0	-19.3	-13.4	-110.8	-94.8

The computational studies suggest four steps that are important to the reaction pathway: (i) initial formation of metal-peroxide complex **II** (ii) formation of a four-centered

transition state (**TS-III**) for peroxide-cleavage and transfer of alkyl from the metal to an oxygen; (iii) formation of an alkoxide/ether complex (**IV**) (iv) finally cleavage of **IV** in to product **V**.

The results of the DFT calculations suggest the following:

(i) Reaction of an organolithium is more favorable and proceeds with lower barriers compared with reaction of a hypothetic organosodium reagent.

(ii) The effect of the tetrahydropyranyl peroxide is to lower the energy of intermediate II and the transition state for O-O cleavage, and to stabilize the alkoxide (tetrahydropyranyloxide) product of the reaction. These finding are consistent with experimental results.

The nature of the oxygen/lithium interaction in the predicted transition state was examined. Results showed that approximate distance between pyranyl O-Li bond is 2.316 A°.

Figure-2:

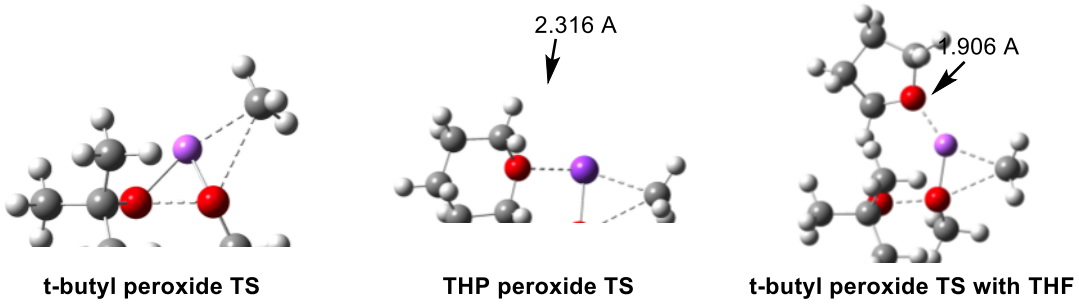


Figure X. B3LYP/6-31G(d) transition state geometries for the concerted transfer of CH_3 from Li to O

(Graphics reproduced with permission of Prof. Keith Kuwata).

Preliminary B3LYP/6-31G(d) calculations were also performed (not shown) for the influence of a single THF solvent molecule in the transition state. The results found that

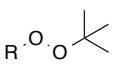
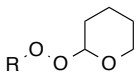
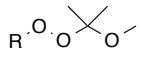
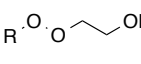
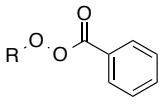
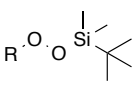
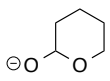
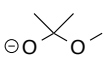
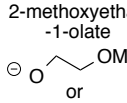
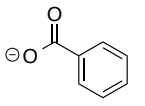
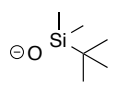
the presence of the THF molecule stabilized structures by -10 to -16 kcal/mol due to Li and furan oxygen atom interactions.

Section-5: Leaving Group Effects

Our investigations significantly expand the range of leaving groups that have been investigated for peroxide/organometallic reactions, and enable a much more detailed discussion regarding the influence of peroxide substituents on reactivity towards organometallics as well as selectivity for attack on a particular oxygen.

Peroxides can be first divided into two classes: symmetrical and unsymmetrical. Symmetric peroxides can form a desired either through attack on either peroxide oxygen. However, the use of a symmetric peroxide is inherently wasteful for complicated substrates, may make experiments impractical or dangerous (for example, Baramki's experiments with dimethyl peroxide),[34] and may limit the ability to activate the peroxide for reaction. Unsymmetric peroxides (for example, mixed t-butyl/primary peroxides) avoid some of these issues but may not solve the issue of peroxide activation and can limit regioselectivity in the alkoxide transfer reaction. Scheme-41 illustrates different classes of leaving groups that have been used for reactions of organometallics and peroxides.

Scheme-41:

Entry	1	2	3	4	5	6
Peroxide						
Leaving Group	 t-Butoxide	 tetrahydro-2*H*-pyran-2-olate	 2-methoxypropan-2-olate	2-methoxyethan-1-olate  or R-O⊖ alkoxide	 Benzoate	 Siloxide

The use of several classes of leaving groups has been previously reported: alkoxides (from dialkyl peroxides);[34] carboxylates (from peresters),[32] and silyloxide (from peroxysilanes).[38] Our work has investigated three previously unreported leaving groups: 2-methoxy-2-propyloxide (from methoxypropyl peroxyketals); 2-tetrahydropyranyloxide (from THP monoperoxyacetals), and 2-methoxyethoxide (from 2-methoxyethyl peroxides). Some interesting features of peroxide electrophiles/leaving groups are summarized below:

(i) Among all leaving groups, t-butoxide is generated as a strong base and unstabilized conjugate leaving group. The precursor electrophiles (t-butyl peroxides) are easily prepared and stable. Reactivity towards organolithium reagents is much greater than towards organomagnesium halides. [14]

(ii) Perbenzoates are highly active peroxide electrophiles, as benzoate is resonance stabilized good leaving group. Starting material may be sensitive to decomposition if electron-rich or if possesses a C-H bond adjacent to the peroxide.

(iiii) Bistrimethylsilyl peroxide, which reacts to liberate Trimethyl silyloxy leaving group, is a good electrophile towards organolithium and organomagnesium reagents. However, a side reaction involving transfer of the trialkyl silyl to the nucleophile is sometimes observed (see discussion in page-68, Table-4). In our work mixed alkyl trialkyl silyl peroxides demonstrated poor reactivity towards simple organolithium reagents.

(v) 2-Methoxypropyl monoperoxyacetals are more reactive than t-butyl peroxides towards organometallics to form ethers and 2-methoxy propane 2-oxide (entry-3). The

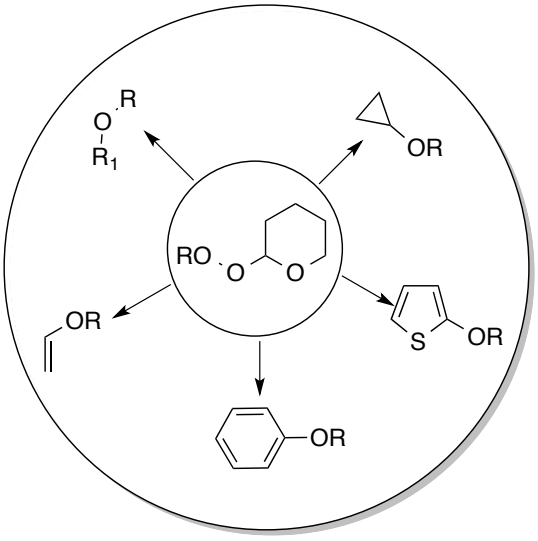
latter can undergo loss of methanol to give acetone, a potent electrophile which can capture organometallic reagents as shown in Equation-7.

(vi) Tetrahydropyranyl monoperoxyacetals (THP peroxides) are also much more reactive towards organometallic reagents than simple dialkyl peroxides and react with complete reagioselectiivty for transfer of the nonacetal alkoxide. In contrast to the methoxypropyl peroxyacetals, the THP peroxides have never generated products derived from trapping of the acyclic aldehyde derived from the tetrahydropyranyl-2-oxide leaving group.

Section-6: Conclusions

We have designed and synthesized tetrahydropyranyl monoperoxyacetals as a new class of peroxide electrophiles for reaction with organometallic nucleophiles. Compared with dialkyl peroxides or silyl ethers of alkyl hydroperoixdes, the THP peroxides display-enhanced reactivity towards organolithium and organomagnesium reagents. Moreover, whereas the regioselectivity for attack on dialkyl peroxides is determined by the size of the attached alkyl groups, the THP peroxides react through highly regioselective transfer of the attached alkoxide, regardless of the steric size of that alkoxide.

Figure-3:



Section-7: Experimental Section

Table of contents:

5.2. General procedure for etherification using sp^3 Grignard reagent.

5.3. General procedure for etherification by using sp^2 C-O bond formation

Section-1: General notes

(i) Abbreviations: Hexane = Hex; EA = Ethyl acetate; THF = tetrahydrofuran

TBDMS(or TBS) = tert.Butyl dimethyl silyl

(ii) All ^{1}H and ^{13}C NMR data was recorded at 400/100 MHz in $CDCl_3$ unless noted.

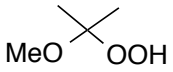
Section-2. General Procedure for Synthesis of Alkyl hydroperoxides

2.1. Synthesis of alkyl hydroperoxides.

(1) t-Butyl hydroperoxide: A 5.0-6.0 M solution of t-BuOOH in decane was used as purchased from commercial source (Aldrich).

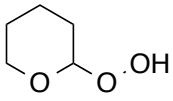
(2) 2-Methoxyprop-2-yl hydroperoxide (CAS # 10027-74-4; ksk07-61).

A solution of 2,3-dimethyl-2-butene (10 mmol, 841 mg) in 1 mL methanol and 25 mL dry methylene chloride was cooled to -78 °C and a gaseous mixture of ozone/oxygen was passed through the solution (approximately 1 mmol/minute). The crude reaction mixture was warmed under nitrogen blanket, and solution concentrated on rotary evaporator followed by high vacuum (approximately 1 minute at 0.2 mm Hg) to generate the hydroperoxide as a colorless oil: Yield: 82% (878 mg); R_f = 0.3 (15% EA:Hex).



^{1}H NMR (300 MHz): 7.92-7.83 (m, 1H), 3.32 (s, 3H), 1.42 (s, 6H); ^{13}C NMR (75 MHz): 105.4, 49.2, 22.1;

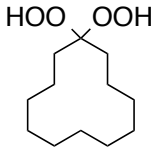
(3) 2-Tetrahydropyranyl hydroperoxide (THP hydroperoxide):



10% aq. H_2SO_4 (0.1 mL) was added to a 0 °C solution of 50 wt% aq. H_2O_2 (6.66 mL, ~118 mmol based upon calculated molarity). The mixture was stirred for 10 minutes at 0 °C after which 3,4 dihydro-2H-pyran (4.94 g, 58.8 mmol) was added over a period of 3 minutes. The reaction was stirred for 1 h at 0 °C and then diluted with sat. aq. NH_4Cl (15 mL). The solution was extracted with ether (150 mL) and the organic layer washed with aq. sat. ammonium sulfate (5 x 10 mL). The resulting solution was dried over Na_2SO_4 and concentrated on a rotary evaporator. The residue obtained was purified by silica gel (2 inch x 3 inch) column chromatography using 4-25% EA/ Hex to afford the hydroperoxide as a thick and colorless oil (4.60 g, 66%). CAS # 4676-84-0; R_f (40% EA/Hex) 0.45; ^{1}H NMR (300 MHz): 9.24-9.08 (m, 1H), 5.11-5.09 (m, 1H), 4.04-3.96 (m, 1H), 3.70-3.63 (m, 1H), 1.79-1.68 (m, 2H), 1.66-1.55 (m, 4H). ^{13}C NMR (75 MHz): 102.5, 62.8, 27.3, 25.0, 19.5. Product spectral data matched with literature report. [51]

Section-2.2: Synthesis of alkylhydroperoxides via cyclododecanonoe 1,1 bis-peroxy-acetals.

4. Cyclododecanone 1,1 dihydroperoxide was synthesized as described in a literature report. [46]



2.2.1. General procedure for synthesis of cyclododecanone 1,1-bisperoxiacetals

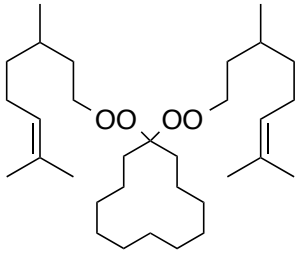
(Synthesized by following known procedure[43])

To a 0 °C solution of cyclododecanone 1,1 dihydroperoxide (**4,** 10 mmol) in dry THF (50 mL) was added potassium *tert*-butoxide (21 mmol), followed by alkyl triflate (22 mmol). The reaction mixture was stirred until the starting material was no longer visible by TLC

(20 minute). The reaction mixture was then quenched with water (25 mL) and extracted with EA (50 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified by silica chromatography using 1% EA/hex.

5a) 1,1-Bis (3,7 dimethyl 6-octenyl) peroxy cyclododecane: (ksk08-37)

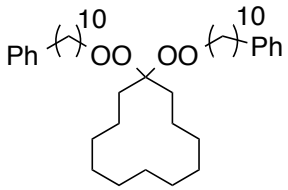
By the general procedure described above, dihydroperoxide **4** (2.196 g, 9.469 mmol) was reacted with triflate **9a** (6 g, 20.8 mmol) to furnish bisperoxyacetal **5a** as colorless oil (2.841 g. Yield: 59%); R_f = 0.75 (10% EA:Hex).



^{1}H NMR: 5.10 (m, 2H), 4.17-3.99 (m, 4H), 2.07-1.91 (m, 4H), 1.72-1.64 (m, 9H), 1.69 (s, 3H), 1.61 (s, 3H), 1.58-1.53 (m, 7H), 1.48-1.28 (m, 20H), 1.24-1.15 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR: 131.2, 124.6, 113.1, 73.4, 37.1, 34.6, 29.7, 27.0, 26.1, 25.7, 25.4, 22.3, 21.9, 19.6, 19.4, 17.6; HRMS (TOF-MS-ES+): Calcd for $C_{32}H_{60}O_4Na$ $(M+Na)^+$ 531.4389 found: 531.4373 IR (neat): 2926, 2850, 1445, 1052.

5b) 1,1 Bis (10-phenyldecyldioxy)cyclodecanone: (ksk08-70):

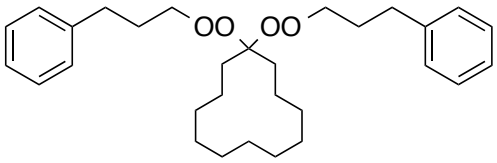
By the general procedure described above, dihydroperoxide **4** (0.293 g, 1.26 mmol) was reacted with triflate **9b** (1.02 g, 2.787 mmol) to furnish bisperoxyacetal **5b** as a colorless oil (0.834 g, 99%); R_f = 0.74 (15% EA/Hex).



^{1}H NMR (300 MHz): 7.32-7.29 (m, 4H), 7.21-7.19 (m, 6H), 4.09 (t, J = 6.6 Hz, 4H), 2.62 (t, J = 7.7 Hz, 4H), 1.72-1.59 (m, 12H), 1.37-1.30 (m, 42H); ^{13}C NMR: 142.9, 128.4, 128.2, 125.5, 113.1, 75.0, 36.0, 31.5, 29.57, 29.53, 29.48, 29.36, 27.8, 27.0, 26.2, 26.1, 22.3, 21.9, 19.4. HRMS (TOF-MS-ES+): Calcd for $C_{44}H_{72}O_4Na$ $(M+Na)^+$ 687.5328 found 687.5300; IR (neat): 2914, 2845, 1462, 1053.

5c) 1,1-Bis((3-phenylpropyl) peroxy)cyclododecane (ksk10-57):

By the general procedure described above, dihydroperoxide **4** (1.05 g, 4.545 mmol) was reacted with triflate **9c** (2.6 g, 10 mmol) to furnish bisperoxyacetal **5c** as a colorless oil (1.4381 g, 67%); R_f = 0.6 (15% EA/Hex).



^{1}H NMR: 7.32-7.29 (m, 4H), 7.23-7.21 (m, 6H), 4.11 (t, *J* = 6.4 Hz, 4H), 2.73 (t, *J* = 7.5 Hz, 4H), 2.02-1.95 (m, 4H), 1.74-1.70 (m, 4H), 1.56-1.46 (m, 4H), 1.45-1.31 (m, 14H). ^{13}C NMR: 141.7, 128.4, 128.3, 125.8, 113.3, 74.2, 32.3, 29.5, 27.1, 26.1, 22.3, 22.0, 19.4.

Section-2.2.2: Synthesis of alkyl hydroperoxides.

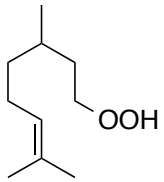
2.2.2. General procedure for synthesis of alkyl hydroperoxides from 1,1 bis-alkyperoxides.

(This procedure is reproduced from *J. Org. Chem.* 2013, 78, 3452 with permission of publisher)

To a room temperature solution of bisperoxyacetal (2 mmol) in tetrahydrofuran (20 mL). was added a solution of 50% aq. H_2SO_4 (1.8 mmol, 6 equiv) and the reaction mixture stirred at 55 °C until starting material was nearly consumed (TLC, 1-3 hours). The reaction was then quenched with saturated aq. Na_2CO_3 (25 mL) and the resulting mixture extracted with ethyl acetate (30mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated on rotary evaporator. The crude product was purified by silica chromatography using 1-3% ethyl acetate / hexane.

6a) Citronellyl hydroperoxide (**CAS # 123369-58-4, ksk08-38**).

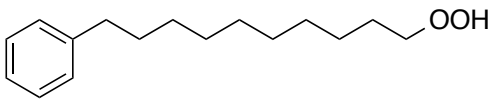
By the general procedure described above, hydrolysis of bisperoxyacetal **5a** (1.01 g, 2 mmol) furnished hydroperoxide **6a** as a colorless oil (0.364 mg, 53%). R_f = 0.4 (10% EA/Hex).



^{1}H NMR (300 MHz): 8.53 (s, 1H), 5.09 (m, 1H), 4.10-4.00 (m, 2H), 2.06-1.93 (m, 2H), 1.73-1.63 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.54-1.35 (m, 2H), 1.33-1.14 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz): 131.3, 124.6, 75.5, 37.1, 34.3, 29.5, 25.7, 25.4, 19.5, 17.6.

6b) 10-Phenyldecyl hydroperoxide: (**ksk08-71**):

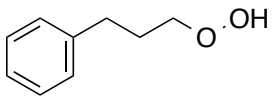
By the general procedure described above, hydrolysis of bisperoxyacetal **5b** (0.755 g, 1.14 mmol) furnished alkyl hydroperoxide **6b** as colorless oil (0.243 g, 64%). R_f = 0.55 (15% EA/Hex).



^{1}H NMR (300 MHz): 8.04 (t, J = 6.5, 1H), 7.33-7.28 (m, 2H), 7.22-7.20 (m, 3H), 4.04 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 1.68-1.61 (m, 4H), 1.32 (m, 12H); ^{13}C NMR: 142.9, 128.4, 128.2, 125.5, 76.6, 36.0, 31.5, 29.5, 29.4, 29.3, 27.5, 25.9; HRMS (TOF-MS-EI+): Note: The $(M\text{-}OH)^{+}$ derived from peroxide bond cleavage was observed rather than a molecular ion. Calcd for $C_{16}H_{25}O$ $(M\text{-}OH)^{+}$ 233.1905; found: 233.1920; IR (neat): 3390, 2922, 2852, 1453, 696.

(6c) 10-Phenylpropyl hydroperoxide: (**CAS # 60956-33-4, ksk10-58**):

By the general procedure described above, hydrolysis of bisperoxyacetal **5c** (1.35 gm., 2.88 mmol) furnished alkyl hydroperoxide **6c** as a colorless oil (0.725 g, 82%). R_f = 0.57 (20% EA/Hex).



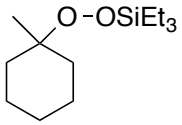
^{1}H NMR: 8.19-8.12 (m, 1H), 7.34-7.30 (m, 2H), 7.24-7.22 (m, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.04-1.97 (m, 2H); ^{13}C NMR: 141.5, 128.4, 125.9, 76.2, 32.0, 29.1.

2.3. Synthesis of alkyl hydroperoxides from alkenes

7) Triethyl((1-methylcyclohexyl)peroxy)silane (CAS # 634600-89-8, ksk09-10)

1-Methyl cyclohexene (0.96 g, 10 mmol) and Et_2SiH (2.32 gm., 20 mmol) were sequentially added to a solution of $Co(acac)_2$ (0.257 g, 1 mmol) in ethanol (35 mL). The reaction mixture was stirred under an O_2 balloon at room temperature until no starting material was observed by TLC (14 hours). The residue obtained upon concentration in vacuo was purified by silica gel chromatography (1.5 inch diameter x 7.5 inch tall) using

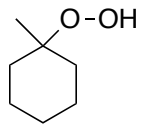
1-8% EA:Hexane to obtain required product as colorless oil (0.844 g, 34%); $R_f = 0.7$ (10% EA/Hex):



^{1}H NMR: 1.81-1.75 (m, 2H), 1.63-1.54 (m, 2H), 1.49-1.43 (m, 1H), 1.42-1.26 (m, 5H), 1.20 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.69 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR: 81.1, 34.9, 25.8, 24.2, 22.4, 6.8, 3.9.

8) 1-Hydroperoxy-1-methylcyclohexane (CAS # 4952-03-8; ksk09-11)

Tetra (n-butyl) ammonium fluoride (3.83 mL, 1M solution in THF, 3.83 mmol) was added to the solution of silyl peroxide **7** (0.78 gm., 3.19 mmol) in dry THF (10 mL) and the reaction stirred at room temperature until TLC showed no starting material (5 min). The residue obtained upon concentration in vacuo was diluted with water (10 mL) and extracted with hexane (30 mL, 10 mL). The combined organic layers were dried on Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (3 inch tall x 1 inch diameter; 2 iterations) chromatography using 5% EA:Hexane to obtain the hydroperoxide as a colorless oil (0.266 g, 64%). (Note: product purified twice by column chromatography in order to remove $Et_3SiOH/Et_3SiOSiEt_3$ byproduct completely).



^{1}H NMR: 7.34 (s, 1H), 1.80-1.74 (m, 2H), 1.63-1.53 (m, 2H), 1.51-1.38 (m, 5H), 1.34-1.29 (m, 1H), 1.25 (s, 3H); ^{13}C NMR: 81.7, 34.4, 25.6, 23.8, 22.2, 6.55, 5.76.

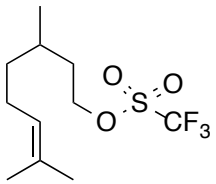
Sectrion-3. General procedures and compound characterization for alkyl triflates and alkyl halides.

3.1. General procedure for synthesis of alkyl triflates from alcohols:

A solution of the alcohol (10 mmol in dry CH_2Cl_2 (30 mL) was cooled to 0 °C and triflic anhydride (14 mmol) and 2,6-lutidine (14.5 mmol) were sequentially added via syringe. The reaction was stirred for 15 minutes at 0 °C and then diluted with ice-cold hexane (60 mL). The resulting solution was washed with ice cold 0.1 M aq. $KHSO_4$ (40 mL) and the separated aqueous layer was extracted with another portion of cold Hex (40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated on a rotary evaporator (bath temperature 10 °C). The residue was placed under high vacuum (≤ 0.5 mm Hg) approximately 5 minutes to generate nearly pure triflate which was immediately placed in a -20 °C freezer and used within the next hour for preparation of alkyl peroxides (**11-15**) as described below.

(9a) 3,7-Dimethyloct-6-en-1-yl trifluoromethanesulfonate (CAS # 207509-09-9, ksk08-75)

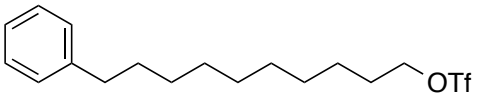
Light brown oil; yield: 98% (1.693 g); R_f (10% EA/Hex): 0.59;



^{1}H NMR (300 MHz): 5.11-5.07 (m, 1H), 4.61-4.57 (m, 2H), 2.06-1.96 (m, 2H), 1.93-1.85 (m, 1H), 1.72-1.68 (m, 1H), 1.70 (s, 3H), 1.66-1.64 (m, 1H), 1.62 (s, 3H), 1.42-1.32 (m, 1H), 1.29-1.20 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz): 131.8, 123.9, 118.5 (q, J = 323 Hz), 76.2, 36.6, 36.0, 28.6, 25.6, 25.1, 19.0, 17.6.

(9b) 10-Phenyldecyl trifluoromethanesulfonate:

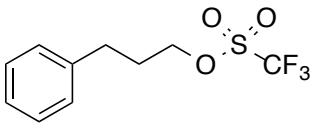
Light brown oil; Yield: Quantitative (1.098 gm.); R_f (10% EA/Hex): 0.65;



^{1}H NMR (300 MHz): 7.33-7.28 (m, 2H), 7.22-7.18 (m, 3H), 4.56 (t, *J* = 6.5 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 1.85 (m, 2H), 1.69-1.59 (m, 2H), 1.46-1.33 (m, 12H). ^{13}C NMR (75 MHz): 142, 128.4, 128.2, 125.5, 118.6 (q, J = 320 Hz), 77.7, 35.9, 31.5, 29.4, 29.37, 29.30, 29.27, 29.22, 28.8, 25.0. HRMS (ESI): Calcd for $C_{17}H_{25}F_3NaO_3S$ (M+Na) 389.1374, found 389.1369;

(9c) 3-Phenylpropyl trifluoromethanesulfonate (ksk-08-85):

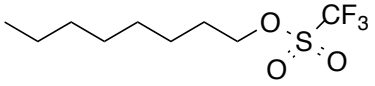
Light brown oil; Yield: Quantitative (1.34 gm.). R_f (10% EA/Hex): 0.5;



^{1}H NMR: 7.38-7.33 (m, 2H), 7.29-7.21 (m, 3H), 4.57 (t, J = 6.2 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 7.19 (m, 2H); ^{13}C NMR: 139.5, 128.7, 128.4, 126.5, 116.5, 76.6, 31.1, 30.8.

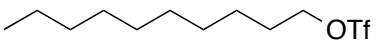
(9d) 1-Octyl trifluoromethane sulfonate (CAS # 71091-89-9; ksk-08-05)

Light brown oil; Yield: 98% (3.08 gm.). R_f (10% EA/Hex): 0.52;



^{1}H NMR: 4.55 (t, *J* = 6.54 Hz, 2H), 1.87-1.80 (m, 2H), 1.46-1.40 (m, 2H), 1.36-1.29 (m, 8H), 0.90 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR: 118.2 (q, *J* = 320.1 Hz), 76.7, 31.6, 29.2, 28.9, 28.8, 25.0, 22.5, 13.99.

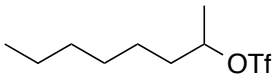
(9e) n-Decyl trifluoromethanesulfonate: Light brown oil; Yield: Quantitative (2.9 gm.);



^{1}H NMR: 4.55 (t, J = 6.5 Hz, 2H), 1.84 (m, 2H), 1.43 (m, 2H), 1.36-1.28 (m, 12H), 0.9 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: 118.6 (q, *J* = 320 Hz), 77.7, 31.8, 29.4, 29.3, 29.2, 28.8, 25.0, 22.6, 14.0.

(9f) 2-Octyl trifluoromethanesulfonate:

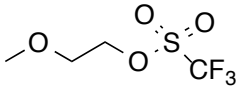
Light brown oil; Yield: 73% (1.472 gm.);



^{1}H NMR: 5.10 (m, 1H), 1.90-1.80 (m, 2H), 1.53 (d, *J* = 6.3 Hz, 3H), 1.45-1.31 (m, 8H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: 90.1, 36.6, 31.5, 28.8, 24.7, 22.5, 21.0, 14.0.

(9g) 2-Methoxyethyl trifluoromethanesulfonate (CAS # 112981-50-7; ksk10-59)

Light brown oil; Yield: quatitative (2.08 gm.); Rf = 0.5 (30% EA: Hex)



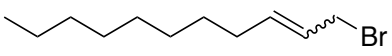
^{1}H NMR: 4.63 (t, *J* = 4.3 Hz, 2H), 3.71 (t, *J* = 3.71 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR: 118.6 (q, 320 Hz); 75.3, 69.6, 59.1.

3.2. Synthesis of allyl bromide:

(10) 1-Bromo-2-undecene (CAS # 67952-61-8; ksk09-26).

This product synthesized as a (84:16) *E/Z* mixture via cross-metathesis of 1-octene, allyl bromide and Grubbs-II catalyst, using known procedure.[45]

Colorless Oil; Yield: 80% (1.109 gm.); R_f = 0.8 (hexane)



^{1}H NMR: 5.82-5.58 (m, 2H), 4.01 (d, *J* = 8.3 Hz, 0.32 H), 3.96 (d, *J* = 8.2 Hz, 1.68 H), 2.14 (m, 0.32H), 2.07 (m, 1.68), 1.40-1.35 (m, 2H), 1.34-1.28 (m, 10H), 0.89 (t, *J* = 6.8

Hz, 3H); ^{13}C NMR (*major isomer*): 136.7, 126.2, 33,6, 32.0, 31.9, 29.4, 29.2, 29.1, 28.8, 22.7, 14.1.

Section-4: General procedures and compound characterizations for dialkyl peroxides

Method A: General procedure for synthesis from alkyl triflates

The alkyl hydroperoxide (**1, 2, or 3**, 10 mmol) was added under nitrogen to a 0 °C solution of KOtBu (10 mmol) in dry THF (50 mL). The reaction mixture was stirred for 3 minutes after which was added alkyl triflate preformed by the procedure described above (10 mmol as neat, then traces of remaining triflate rinsed into the reaction using 1 mL THF) The reaction was stirred for 15 minutes at same temperature and then quenched with water (20 mL). The mixture was extracted with 10% EA:Hexanes (50 mL x 2) and the organic layer was dried over Na_2SO_4. The residue obtained upon concentration was purified by Silica gel chromatography using 1% EA:Hexanes.

Method B: General procedure for preparation of THP monoperoxyacetals

Alkyl hydroperoxide (1.0 mmol) and 2,3-dihydropyran (1.0 mmol) were dissolved in 5 mL tetrahydrofuran. The solution was cooled to 0 °C, after which was added 0.05 mL of 10% aq. H_2SO_4. The reaction mixture was stirred for 45 minutes while coming to room temperature. The reaction was diluted with 10% Ether:Hexanes (15 mL) and then washed with 1 mL of water. The separated organic layer was dried over sodium sulfate and concentrated on rotary evaporator. The residue was purified by silica gel chromatography using 4% EA:Hex.

Method C: General procedure for using silver oxide.

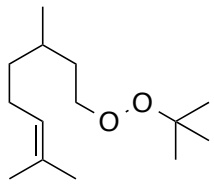
Alkyl hydroperoxide (1.0 mmol) was added to an EtOAc (10 ml) suspension of freshly prepared silver oxide (1.2 mmol). Alkyl halide (1.0 mmol) was added and the reaction was stirred at room temperature under nitrogen until no starting material could e observed (TLC, (\approximately 4-10 hours). The reaction mixture was filtered through a small pad of Celite and the filtered residue washed with EtOAc (5-10 mL). The combined filtrates were concentrated and the residue purified by silica gel chromatography using 1-3% EA:Hex.

Method-D: Silyl protection of alkyl hydroperoxides.

To a solution of alkyl hydroperoxide (1.0 mmol) in *N,N*-dimethylformamide (2 mL) at room temperature was added *tert*-butyl dimethyl silyl chloride (1.2 mmol) followed by imidazole (1.4 mmol). The reaction was stirred for 1 hour and then diluted with water (10 mL). The hexane extracts (50 mL then 10 mL) were dried over sodium sulfate and concentrated on a rotary evaporator. The obtained residue was purified by silica gel chromatography (4.0 inch tall x 0.5 inch column) using 1% ether:hexane.

(11a) (2,6 Dimethyl octenyl) t-butyl peroxide (CAS # 1592933-34-0; ksk08-46)

Using method-A, t-butylhydroperoxide (5.0-6.0 M nominal solution in decane 0.588 mL, 3.235 mmol) was reacted with alkyl triflate **9a** (1.025 g, 3.559 mmol) to furnish peroxide **11a** as a colorless oil (0.511 g, 69%); R_f = 0.6 (10% EA/Hex);

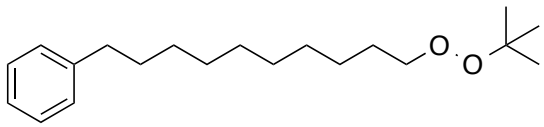


^{1}H NMR: 5.1 (broad triplet, *J* = 7.1 Hz, 1H), 3.98 (m, 2H), 1.98 (m, 2H), 1.69 (s, 3H), 1.66-1.53 (m, 2H), 1.61 (s, 3H), 1.44-1.32 (m, 2H), 1.25 (s, 9H), 1.18-1.13 (m, 1H), 0.91

(d, J =6.31 Hz, 3H), ^{13}C NMR: ($CDCl_3$, 400MHz) δ: 131.2, 124.7, 79.8, 73.4, 37.1, 34.6, 29.7, 26.3, 25.7, 25.4, 19.6, 17.6.

(11b) *t*-Butyl 10-phenyldecyl peroxide (ksk08-32)

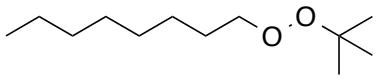
Using method A, t-butylhydroperoxide (1.41 mL, 5.0-6.0 M nominal solution in decane 7.76 mmol) was reacted with alkyl triflate **9b** (3.125 g, 8.54 mmol) to furnish peroxide **11b** as acolorless oil (2.42 g, 92%). R_f = 0.73 (10% EA/Hex);



^{1}H NMR (300 MHz): 7.33-7.20 (m, 2H), 7.22-7.17 (m, 3H), 3.96 (t, J = 6.7 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H), 1.69-1.56 (m, 4H), 1.32-1.28 (m, 12H), 1.27 (s, 9H); ^{13}C NMR: δ (75 MHz): 142.9, 128.4, 128.2, 125.5, 80.0, 75.1, 36.0, 31.5, 29.5, 29.3, 27.8, 26.3, 26.2. HRMS (ESI$^+$ TOF): Calcd for $C_{20}H_{34}NaO_2$ (M+Na) 329.2451, found 329.2470; IR (neat): 2924.8, 2853.72, 1361.5, 697.

(11c) *t*-Butyl octyl peroxide (CAS # 38375-34-7; ksk-08-06)

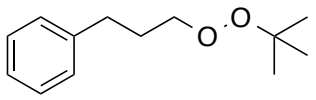
Using method-A, t-butylhydroperoxide (1.81 mL, 5.0-6.0 M nominal solution in decane, 10 mmol) was reacted with alkyl triflate **9d** (2.88 g, 11 mmol) to furnish peroxide **11c** as a colorless oil (1.78 g, 88%) Colorless Liquid; R_f (10% EA/Hex): 0.79.



^{1}H NMR (300 MHz): 3.93 (t, J = 6.7 Hz, 2H), 1.63-1.55 (m, 2H), 1.34-1.26 (m, 10H), 1.25 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR: 79.9, 75.1, 31.8, 29.4, 29.2, 27.8, 26.3, 26.2, 22.6, 14.0; HRMS (ESI-TOF-MS): $C_{12}H_{26}NaO_2$ (M+Na) Calcd for 225.1825, found 225.1840; IR (neat): 2924, 2856, 1361, 1197.

(11d) (3-(tert-Butylperoxy)propyl)benzene (CAS # 419568-76-6; ksk09-53)

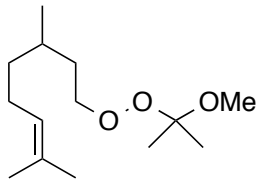
Using method-A, t-butylhydroperoxide (1,8 mL, 5.0-6.0 M nominal solution in decane, 10 mmol) was reacted with triflate **9c** (2.68 g, 10 mmol) to furnish peroxide **11d** as a colorless liquid (1.5151 g. 73%); R_f (10% EA/Hex): 0.65.



^{1}H NMR: 7.32-7.29 (m, 2H), 7.23-7.20 (m, 3H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.00-1.93 (m, 2H), 1.28 (s, 9H); ^{13}C NMR: 141.8, 128.42, 128.36, 125.8, 80.1, 74.2, 32.4, 29.6, 26.4.

(12a) 2,6 Dimethyl octenyl (1-methoxy 1-methylethyl) peroxide (KSK07-90):

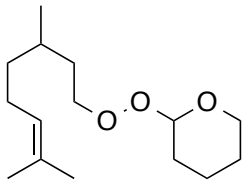
Using method-A, hydroperoxide **2** (0.674 g, 6.35 mmol, 1.5 eq.) was reacted with alkyl triflate **9a** (1.21 g, 4.2 mmol) to furnish peroxide **12a** as a colorless oil (0.627 g, yield: 61%); R_f = 0.4 (10% EA/Hex).



^{1}H NMR: 5.1 (m, 1H), 4.11-4.01 (m, 2H), 3.33 (s, 3H), 2.06-1.91 (m, 2H), 1.71-1.64 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.62-1.54 (m, 1H), 1.47-1.31 (m, 2H), 1.40 (s, 6H), 1.24-1.10 (m, 1H), 0.91 (d, J =6.5 Hz, 3H); ^{13}C NMR:131.2, 124.7, 104.5, 73.4, 49.2, 37.1, 34.6, 29.6, 25.7, 25.4, 22.76, 22.74, 19.5, 17.6; HRMS (TOF-MS-ES+): Calcd for $C_{14}H_{28}NaO_3$ (M+Na) 267.1931 found 267.1926; IR (neat): 2954, 2874, 1457, 836.

(13a) Citronellyl (2-tetrahydropyranyl) hydroperoxide (ksk08-76)**:**

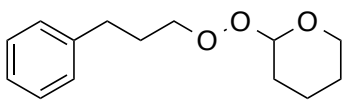
Using method-A, 2-tetrahydropyranyl hydroperoxide **3** (0.63 g, 5.34 mmol) was reacted with alkyl triflate **9a** (1.69 g, 5.87 mmol) to furnish peroxide **13a** as colorless oil (0.854 g, yield: 62%) R_f (10% EA/Hex): 0.42.



^{1}H NMR: 5.15 (t, *J* = 3.5 Hz, 1H), 5.10 (m, 1H), 4.19-4.00 (m, 2H), 4.02 (m, 1H), 3.66-3.61 (m, 1H), 1.98 (m, 2H), 1.78-1.71 (m, 2H), 1.70-1.65 (m, 1H), 1.68 (s, 3H), 1.64-1.53 (m, 5H), 1.60 (s, 3H), 1.49-1.42 (m, 1H), 1.41-1.32 (m, 1H), 1.23-1.1 (m, 1H), 0.92 (d, *J* =6.6 Hz, 3H). ^{13}C NMR δ: 131.2, 124.7, 100.8, 73.7, 62.5, 37.1, 34.6, 29.6, 27.96, 25.7, 25.4, 25.1, 19.7, 19.5, 17.6. HRMS (ESI$^+$ TOF): Calcd for $C_{15}H_{28}NaO_3$ (M+Na) 279.1931, found 279.1934. IR (neat): 2923, 2861, 1440, 1040

(13b) 3-Phenylpropyl tetrahydropyran-2-yl peroxide (CAS # 1630792-49-2, ksk-09-48):

Using method-A, 2-tetrahydropyranyl hydroperoxide **3** (1.18 g, 10 mmol) was reacted with alkyl triflate **9c** (2.68 g, 10 mmol) to furnish peroxide **13** as a colorless oil (1.937 g, 82%).); R_f = 0.66 (15% EA/Hex).

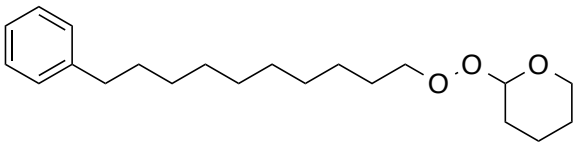


^{1}H NMR (300 MHz): 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 5.1 (t, J = 3.6 Hz, 1H), 4.13 (t, J = 6.4 Hz, 2H), 4.06-4.00 (m, 1H), 3.68-3.62 (m, 1H), 2.74 (t, J = 7.8 Hz, 2H), 2.03-1.96 (m, 2H), 1.79-1.71 (m, 2H), 1.67-1.54 (m, 4H); ^{13}C NMR δ: 141.6, 128.4, 128.3,

125.8, 100.8, 74.4, 62.6, 32.1, 29.5, 27.9, 25.1, 19.7; HRMS (ESI/TOF): Calcd for $C_{14}H_{20}NaO_3$ $(M+Na)^+$: 259.1305; found: 259.1321; IR (neat): 2935, 2868, 1448, 1098

(13c) 10-Phenyldecyl tetrahydropyran-2-yl peroxide (ksk08-65):

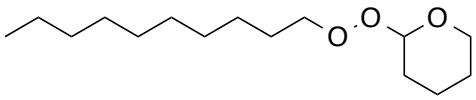
Using method-A, 2-tetrhydropyranyl hydroperoxide **3** (0.20 g, 1.77 mmol) was reacted with alkyltriflate **9b** (0.65 g, 1.775 mmol) to furnish peroxide **13c** as a colorless oil (0.448 g, 75%); R_f = 0.42 (10% EA/Hex);



^{1}H NMR: (300 MHz): 7.33-7.29 (m, 2H), 7.22-7.17 (m, 3H), 5.1 (t, J = 3.5 Hz, 1H), 4.12 (t, J = 6.7 Hz, 2H), 4.09-4.01 (m, 1H), 3.69-3.62 (m, 1H), 2.63 (t, J = 7.8 Hz, 2H), 1.84-1.57 (m, 10H), 1.43-1.32 (m, 12H). ^{13}C NMR δ: 142.9, 128.4, 128.2, 125.5, 100.7, 75.3, 62.5, 36.0, 31.5, 29.5, 29.4, 29.3, 27.9, 27.8, 26.0, 25.2, 19.7; HRMS (ESI/TOF): Calcd for $C_{21}H_{34}NaO_3$ $(M+Na)^+$ 357.2400, found 357.2405; IR (neat): 2923, 2852, 1451, 697.

(13d) Decyl tetrahydropyran-2-yl peroxide (CAS # 1630792-51-6, ksk10-43):

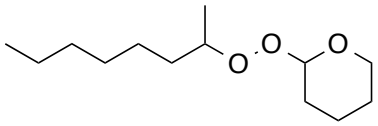
Using method-A, 2-tetrahydropyranyl hydroperoxide **3** (1.18 g, 10 mmol) was reacted with alkyl triflate **9e** (2.98 g, 10 mmol) to furnish peroxide **13d** as a colorless oil (2.05 g, 79%); R_f = 0.56 (15% EA/Hex).



^{1}H NMR: 5.15 (t, J = 3.6 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 4.05-3.99 (m, 1H), 3.66-3.61 (m, 1H), 1.77-1.79 (m, 2H), 1.67-1.53 (m, 6H), 1.38-1.27 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR: 100.7, 75.4, 62.5, 31.9, 29.5, 29.4, 29.3, 27.9, 27.8, 26.0, 25.1, 22.6, 19.7, 14.1; IR (neat): 2936, 2857, 1097.

(13e) 2-Octyl tetrahydropyran-2-yl peroxide (CAS # 1630792-50-5; ksk08-95):

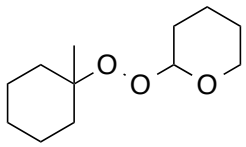
Using method-A, 2-tetrhydropyranyl hydroperoxide **3** (0.595 g, 5.01 mmol) was reacted with alkyl triflate **9f** (1.47 g, 5.61 mmol) to furnish peroxide **13e** as a colorless oil (0.808 g, 70%) R_f = 0.61 (20% EA/Hex);



^{1}H NMR: 5.11 (m, 1H), 4.03-3.98 (m, J = 6.1Hz, 1H), 4.03-3.98 (m, 1H), 3.64-3.59 (m, 1H), 1.76-1.70 (m, 2H), 1.66-1.51 (m, 5H), 1.44-1.27 (m, 9H), 1.24-1.21 (m, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR: 101.1, 100.6, 80.4, 80.2, 62.58, 62.55, 34.3, 31.7, 29.35, 29.31, 27.97, 27.92, 25.42, 25.40, 25.18, 22.6, 19.84, 19.82, 18.7, 18.5, 14.0; HRMS (ESI/TOF): Calcd for $C_{13}H_{26}NaO_3$ $(M+Na)^+$ 253.1774, found 253.1773.6. IR (neat): 2928, 2856, 1451, 1363, 698.

(13f) 1-Methylcyclohexyl 2-tetrahydropyranyl peroxide (KSK09-13):

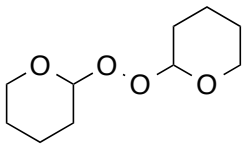
Using method-B, reaction of 2-tetrahydropyranyl hydroperoxide **3** (0.266 g, 2.04 mmol) and dihydropyran (0.171 g, 2.04 mmol) furnished peroxide **13f** as a colorless oil (0.326 g, 74%) R_f = 0.50 (10% EA/Hex); R_f (10% EA/Hex): 0.50.



^{1}H NMR (300 MHz): 5.04 (broad triplet, 1H), 4.02 (m, 1H), 3.60 (m, 1H), 1.75 (m, 5H), 1.68-1.53 (m, 6H), 1.47-1.35 (m, 6H), 1.26 (s, 3H). ^{13}C NMR (75 MHz): 101.0, 81.5, 62.7, 35.0, 27.8, 25.7, 25.1, 24.3, 22.5, 22.3, 20.0; HRMS (ESI$^+$ TOF): Calcd for $C_{12}H_{22}NaO_3$ (M+Na) 237.1461, found 237.1469. IR (neat): 2931, 2852, 1443, 962.

(13g) Bis (Tetrahydro-2H-pyranyl) peroxide (CAS # 685877-38-7; ksk09-19)

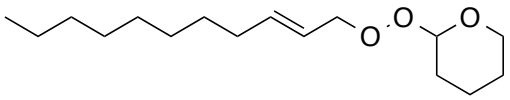
Using method-B, reaction of 2-tetrahydropyranyl hydroperoxide **3** (0.35 g, 2.966 mmol) and dihydropyran (0.249 g, 2.966 mmol) furnished peroxide **13g** as a colorless oil (0.493 g, 84%); R_f = 0.50 (10% EA/Hex);



^{1}H NMR: 5.22 (m, 2H), 4.09 (m, 1H), 4.00 (m, 1H), 3.63-3.60 (m, 2H), 1.76-1.74 (m, 4H), 1.66-1.53 (m, 8H); ^{13}C NMR: 101.8, 100.2, 62.5, 62,1, 27.9, 27.7, 25.1, 25.0, 19.6, 19.4.

(13h) (E/Z)-2-(Undec-2-en-1-ylperoxy) tetrahydro-2H-pyran (ksk09-27):

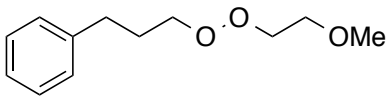
Using method-C, 2-tetrahydropyranyl hydroperoxide **3** (0.118 mg, 1 mmol) was reacted with allyl bromide **10** (0.232 g, 1 mmol) to furnish peroxide **13h** as a colorless oil (0.197 mg, 73%) consisting of an (84:16) E/Z mixture: R_f = 0.42 (10% EA:Hex)



^{1}H NMR: 5.82-5.74 (m, 1H), 5.69-5.55 (m, 1H), 5.16 (m, 1H), 5.64 (d, *J* = 6.8 Hz, 0.24 H), 4.51 (d, *J* = 6.8 Hz, 1.76 H), 4.01 (m, 1H), 3.64-3.60 (m, 1H), 2.13-2.02 (m, 2H), 1.73-1.68 (m, 2H), 1.65-1.53 (m, 4H), 1.38-1.35 (m, 2H), 1.31-1.26 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: 137.8, 123.7, 100.8, 76.2, 62.4, 32.3, 31.8, 29.4, 29.2, 29.1, 28.8, 27.8, 25.1, 22.6, 19.6, 14.0. HRMS (TOF-MS-ES+) Calcd for $C_{16}H_{30}NaO_3$ (M+Na) 293.2087, found 293.2087 IR (neat): 2923, 2851, 1202, 962.

(14) (2-Methoxyethyl 3-phenylpropyl peroxide (ksk10-60)

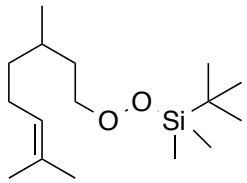
Using method-A, alkyl hydroperoxide **6c** (0.70 g, 4.6 mmol) was reacted with triflate **9g** (0.956 g, 4.6 mmol) to furnish peroxide **14** as a colorless oil (0.723 g, 74%); R_f = 0.62 (20% EA:Hex).



^{1}H NMR: 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.16-4.14 (m, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.63-3.61 (m, 2H), 3.40 (s, 3H), 2.71 (t, *J* = 7.8 Hz, 2H), 2.01-1.93 (m, 2H); ^{13}C NMR: 141.6, 128.46, 128.39, 125.9, 73.59, 73.54, 69.8, 59.1, 32.2, 29.4; HRMS (TOF-MS-CI+); Caliculated for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1433; IR (neat): 2924, 1496, 1453, 745.

(15a) Citronellyl t-butyl dimethylsilyl peroxide (ksk-08-78):

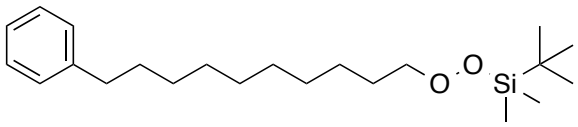
Using method-D, alkyl hydroperoxide **6a** (0.22 g, 1.279 mmol) was converted to silyl ether **15a**, which was obtained as a colorless oil; Yield: 58% (0.212 g); R_f = 0.75 (10% EA/Hex).



^{1}H NMR: 5.12 (m, 1H), 4.06-3.97 (m, 2H), 2.06-1.91 (m, 2H), 1.69 (s, 3H), 1.67-1.59 (m, 1H), 1.61 (s, 3H), 1.59-1.51 (m, 1H), 1.46-1.30 (m, 2H), 1.22-1.15 (m, 1H), 0.95 (s, 9H), 0.91 (d, J = 6.6 Hz), 0.17 (s, 6H); ^{13}C NMR: 131.2, 124.6, 75.3, 37.1, 34.5, 29.6, 26.1, 25.7, 25.4, 19.6, 18.1, 17.6, -5.9; HRMS (TOF-MS-EI+): $C_{16}H_{34}NaO_2Si$ (M+Na) 309.2220, found 309.2218; IR (neat): 2928, 2857, 1461, 834.

(15b) 10-Phenyldecyl t-butyldimethylsilyl peroxide (ksk08-72):

Using method-D, alkylhydroperoxide **6b** (0.22 g, 0.89 mmol) was converted into the corresponding silyl ether **15b**, which was obtained as colorless oil; Yield: 82% (0.267 g); R_f (10% EA/Hex): 0.80.



^{1}H NMR: (300 MHz): 7.32-7.28 (m, 2H), 7.22-7.19 (m, 3H), 3.99 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 1.66-1.56 (m, 4H), 1.32 (m, 12H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz): 142.9, 128.4, 128.2, 125.5, 76.6, 36.0, 31.5, 29.5, 29.3, 27.7, 26.2, 26.1, 18.1, -5.8; HRMS (ESI$^+$ TOF): Calcd for $C_{22}H_{40}NaO_2Si$ (M+Na) 387.2690, found 387.2677. IR (neat): 2925, 2854, 1462, 1248.

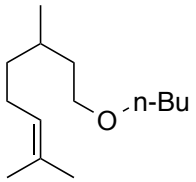
Section-5: General synthetic procedures and characterization for ethers

5.1. General procedure for etherification using sp^3 alkyl lithium

Alkyllithium (0.55 mmol, 1.1 equivalent) was added to the solution of THP peroxide (0.5 mmol) in dry THF (3 mL) at -78 °C and the reaction stirred for 15 minutes. The reaction was brought to room temperature for 15 minutes and then quenched with water (2 mL). The mixture was extracted with 20% ether in hexanes (25m, 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography(0.5 x 4 inch column) using 1% ether in hexanes. Note: For volatile ethers (e.g. **17c**) column fractions were concentrated on rotary evaporator at 20 °C bath temperature. Pure samples were dried on high vacuum approximately 1 minute while keeping the sample vial in ice bath.

17a) 8-Butoxy-2,6-dimethyl-2-octene (CAS # 71077-30-0; ksk08-80).

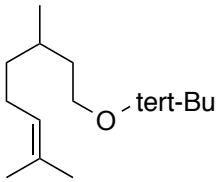
Using the general procedure for etherification described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with n-BuLi (0.34 mL 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **17a** as a colorless oil (86 mg, 81%); R_f = 0.6 (5% EA:Hex);



^{1}H NMR: 5.11 (m, 1H), 3.46-3.39 (m, 4H), 1.98 (m, 2H), 1,69 (s, 3H), 1.65-1.52 (m, 4H), 1.61 (s, 3H), 1.43-1.30 (m, 4H), 1.21-1.12 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: 131.0, 124.8, 70.6, 69.1, 37.2, 36.7, 31.9, 29.6, 25.7, 25.4, 19.5, 19.3, 17.6, 13.9.

17b) 8-*tert*-Butoxy-2,6-dimethyl-2-octene: (CAS # 436141-44-5; ksk10-38)

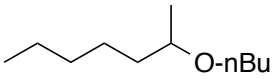
Using the general procedure for etherification described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with t-BuLi (0.32 mL 1.7 M nominal solution in pentane, 0.55 mmol) to furnish ether **17b** as a colorless oil. (55 mg, 51%); R_f = 0.6 (5% EA:Hex).



^{1}H NMR: 5.11 (m, 1H), 3.42-3.31 (m, 2H), 2.06-1.91 (m, 2H), 1.69 (s, 3H), 1.61 (m, 3H), 1.59-1.51 (m, 2H), 1.39-1.27 (m, 2H), 1.19 (s, 9H), 1.17-1.10 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR: 131.0, 124.9, 72.3, 59.7, 37.7, 37.2, 29.6, 27.5, 25.7, 25.4, 19.6, 17.6.

17c) 2-Butoxy octane (CAS # 110458-41-8; ksk08-96)

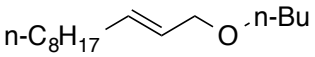
Using the general procedure for etherification described above, peroxide **13e** (115 mg, 0.5 mmol) was reacted with n-BuLi (0.34 mL 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **12c** as a colorless oil (73 mg, 78%); R_f = 0.6 (5% EA/Hex).



^{1}H NMR (300 MHz): 3.51 (m, 1H), 3.37-3.31 (m, 2H), 1.58-1.49 (m, 3H), 1.43-1.29 (m, 9H), 1.12 (d, J = 6.1 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz): 75.3, 68.1, 36.7, 32.3, 31.8, 29.4, 25.6, 22.6, 19.7, 19.4, 14.0, 13.9.

17d) 1-Butoxyundec-2-ene (ksk09-28).

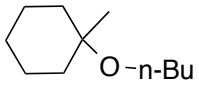
Using the general procedure for etherification described above, peroxide **13h** (135 mg, 0.5 mmol) was reacted with n-BuLi (0.34 mL 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **17d** as a colorless oil (86 mg, 76%); R_f = 0.63 (10 % EA/Hex).



^{1}H NMR: 5.73-5.66 (m, 1H), 5.59-5.52 (m, 1H), 4.01 (m, 0.23 H), 3.91 (dd, J = 0.6, 6.15, 1.76 H), 3.41 (t, J = 6.6 Hz, 2H), 2.05 (m, 2H), 1.61-1.54 (m, 2H), 1.43-1.35 (m, 4H), 1.33-1.27 (m, 10H), 0.93 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR: 134.5, 126.4, 71.6, 69.8, 32.3, 31.88, 31.87, 29.4, 29.27, 29.21, 29.0, 22.7, 19.3, 14.0, 13.9; HRMS (TOF-MS-EI$^+$): Calcd for $C_{15}H_{30}O$: 226.2297; found: 226.2297; IR (neat): 2954, 2923, 2852, 1465, 1105.

17e) 1-Butoxy 1-methyl cyclohexane (ksk09-15)

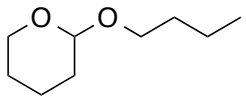
Using the general procedure for etherification described above, peroxide **13f** (107 mg, 0.5 mmol) was reacted with n-BuLi (0.34 mL 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **17e** as a colorless oil (61 mg, 71%); R_f = 0.70 (10% EA/Hex).



^{1}H NMR (300 MHz): 3.32 (t, J = 6.4 Hz, 2H), 1.71-1.64 (m, 2H), 1.61-1.45 (m, 5H), 1.43-1.19 (m, 7H), 1.10 (s, 3H), 0.93 (t, J = 7.20 Hz, 3H); ^{13}C NMR (75 MHz): 72.8, 59.9, 36.5, 32.8, 25.86, 24.6, 22.2, 19.6, 13.99. HRMS (TOF-MS-EI$^+$): Calcd for $C_{15}H_{30}O$: 170.1671; found: 170.1671; IR (neat): 2962, 2925, 2862, 1447, 1081.

17f) 2-Butoxy-tetrahydro-2H-pyran (CAS # 1927-68-0; ksk09-20):

Using the general procedure for etherification described above, peroxide **13g** (101 mg, 0.5 mmol) was reacted with n-BuLi (0.31 mL 1.6 M nominal solution in hexane, 0.5 mmol) to furnish ether **17f** as colorless oil; Yield: 15% (12 mg) R_f = 0.5 (15% EA:Hex); Recovered starting material: 16% (16 mg);



^{1}H NMR: 4.59 (m, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.65-1.49 (m, 6H), 1.45-1.35 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: 98.8, 67.3, 62.3, 31.8, 30.8, 25.5, 19.7, 1.4, 13.9.

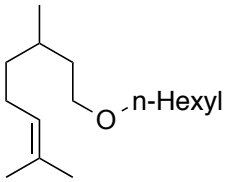
5.2. General procedure for etherification using sp^3 Grignard reagent

A solution of the alkyl magnesium bromide (0.55 mmol, 1.1 equivalent, in diethyl ether) was added to a solution of the THP peroxide (0.5 mmol) in dry THF (3 mL) at 0 °C. The reaction was stirred for 15 minutes and then brought to room temperature. After 15 min, the reaction was quenched with water (2 mL) and extracted with 20% ether in hexanes (25m, 5 mL). The combined organic layers were dried over Na_2SO_4 and the concentrated residue purified by silica gel chromatography (0.5 x 4 inch column) using 1% ether in hexanes. Note: For volatile ethers (**18b**) column fractions were concentrated on a rotary

evaporator at 20 °C bath temperature. Pure samples were dried on high vacuum approximately 1 minute while keeping the sample vial in ice bath.

18a) 8-Hexyloxy-2,6-dimethyl-2-octene (ksk09-08)

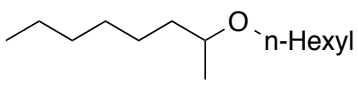
Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with n-hexyl magnesium bromide (0.27 mL, 2 M nominal solution in diethyl ether, 0.55 mmol) to furnish hexyl ether **18a** as a colorless oil (106 mg, 88%); R_f = 0.70 (10% EA:Hex).



^{1}H NMR (300 MHz): 5.11 (m, 1H), 3.47-3.38 (m, 4H), 2.08-1.94 (m, 2H), 1.69 (s, 3H), 1.65-1.53 (m, 4H), 1.61 (s, 3H), 1.45-1.31 (m, 8H), 1.23-1.11 (m, 1H), 0.91-0.88 (m, 6H); ^{13}C NMR (75 MHz): 131.1, 124.8, 71.0, 69.1, 37.2, 36.7, 31.7, 29.7, 29.6, 25.9, 25.7, 25.4, 22.6, 19.6, 17.6, and 14.0. HRMS (TOF-MS-EI$^+$): Calcd for $C_{16}H_{32}O$: 240.2453; found: 240.2453. IR (neat): 2954, 2927, 2858, 1455, 1376, 1112,

18b) 2-Hexyloxy octane (CAS # 51182-98-0; ksk09-17):

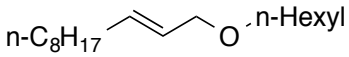
Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13e** (115 mg, 0.5 mmol) was reacted with n-hexyl magnesium bromide (0.27 mL, 2 M nominal solution in diethyl ether, 0.55 mmol) to furnish hexyl ether **18b** as a colorless oil (95 mg, 88%); R_f = 0.6 (5% EA/Hex):



^{1}H NMR (300 MHz): 3.51-3.29 (m, 1H), 3.40-3.29 (m, 2H), 1.57-1.53 (m, 3H), 1.41-1.29 (m, 15H), 1.12 (d, J = 6.1 Hz, 3H), 0.9 (m, 6H); ^{13}C NMR (75 MHz): 75.3, 68.4, 36.7, 31.8, 31.7, 30.1, 29.4, 25.9, 25.6, 22.63, 22.62, 19.7, 14.05, 14.02.

18c) Hexyl 2-undecenyl ether (ksk09-30):

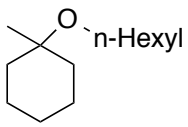
Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13h** (115 mg, 0.5 mmol) was reacted with n-hexyl magnesium bromide (0.27 mL, 2 M nominal solution in diethylether, 0.55 mmol) to furnish hexyl ether **18c** as a colorless oil (104 mg, 81%); R_f = 0.67 (10 % EA/Hex).



^{1}H NMR: 5.73-5.66 (m, 1H), 5.59-5.52 (m, 1H), 4.01 (m, 0.24 H), 3.91 (dd, J = 0.6, 6.15, 1.76 H), 3.40 (t, J = 6.7 Hz, 2H), 2.05 (m, 2H), 1.58 (m, 2H), 1.43-1.27 (m, 18H), 0.90-0.87 (m, 6H). ^{13}C NMR: 134.5, 126.4, 71.6, 70.2, 32.3, 31.88, 31.74, 29.76, 29.46, 29.28, 29.22, 29.1, 25.9, 22.67, 22.62, 14.08, 14.03. HRMS (TOF-MS-EI^{+}): Calcd for $C_{17}H_{34}O$: 254.2610; found: 254.2610; IR (neat): 2954, 2923, 2852, 1465, 1105.

18d) 1-Hexyloxy 1-methyl cyclohexane (ksk09-18):

Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13f** (107 mg, 0.5 mmol) was reacted with n-hexyl magnesium bromide (0.27 mL, 2 M nominal solution in diethylether, 0.55 mmol) to furnish hexyl ether **18d** as a colorless oil (64 mg, 65%); R_f = 0.65 (5% EA/Hex).

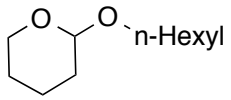


^{1}H NMR: 3.29 (t, *J* = 6.7 Hz, 2H), 1.71-1.66 (m, 2H), 1.64-1.47 (m, 5H), 1.44-1.27 (m, 11H), 1.11 (s, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: 72.9, 60.2, 36.5, 31.8, 30.7, 26.1,

25.8, 24.6, 22.6, 22.2, 14.0; HRMS (TOF-MS-EI$^+$): Calcd for $C_{13}H_{26}O$: 198.1984; found: 198.1992; IR (neat): 2962, 2925, 2862, 1447, 1081.

18e) 2-Hexyloxy-tetrahydro-*2H*-pyran (CAS # 1927-63-5; ksk09-21):

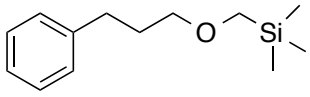
Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13f** (107 mg, 0.5 mmol) was reacted with n-hexyl magnesium bromide (0.25 mL, 2 M nominal solution in diethyl ether, 0.5 mmol) to furnish hexyl ether **18e** as a colorless oil (57 mg, 61%); R_f = 0.5 (15 % EA/Hex).



^{1}H NMR: 4.57 (m, 1H), 3.90-3.84 (m, 1H), 3.76-3.70 (m, 1H), 3.52-3.47 (m, 1H), 3.41-3.35 (m, 1H), 1.87-1.79 (m, 1H), 1.74-1.68 (m, 1H), 1.62-1.50 (m, 6H), 1.42-1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR: 98.8, 67.6, 62.3, 31.7, 30.8, 29.7, 25.9, 25.5, 22.6, 19.6, 14.0.

18f) 3-Phenylpropyl trimethylsilylmethyl ether (ksk12-08)

Using the general procedure for etherification with alkyl magnesium bromide described above, peroxide **13b** (118 mg, 0.5 mmol) was reacted with 2-trimethylsilyl methyl magnesium chloride (0.65 mL, 1 M nominal solution in diethyl ether, 0.65 mmol) to furnish hexyl ether **18f** as a colorless oil (84 mg, 75%); R_f = 0.8 (10 % EA/Hex).



^{1}H NMR (700 MHz): 7.31-7.29 (m, 2H), 7.22-7.19 (m, 3H), 3.42 (t, *J* = 6.3 Hz, 2H), 3.12 (s, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 1.91-1.87 (m, 2H), 0.09 (s, 9H). ^{13}C NMR (176 MHz): 142.3, 128.5, 128.2, 125.6, 74.2, 64.7, 32.3, 31.2, -2.98; Mass (TOF-MS-EI+): Calcd for $C_{13}H_{22}OSi$ $(M)^+$: 222.1440; found: 222.1442; IR (neat): 2955, 2845, 1246, 839.

5.3. General procedure for etherification using sp^2 C-O bond formation:

Reactions involving commercially available alkyl lithium and alkyl magnesium reagents were conducted as described for sp^3 C-O bond formations. Reactions involving vinyl or heteroaryllithium reagents generated from tri-butyl stannanes were conducted as described below.

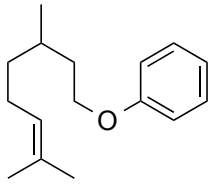
n-BuLi (0.55 mmol, 1.6 M nominal solution in hexanes) was added to the cold solution of vinyl or aryl tributyl tin (0.55 mmol) in dry tetrahydrofuran (3 mL) at -78 °C. The reaction mixture was stirred for 40 minutes afterwhich was added a solution of the THP peroxide (0.5 mmol) in 1 mL tetrahydropyran. The reaction mixture was stirred until no starting material could be detected on TLC (approximately 30 minutes) and then diluted with hexane (10 mL). The resulting solution was passed though a column of neutral alumina (1 x 2 inch) and then concentrated. The residue was purified by silica gel (0.5 inch diameter, 4 inch tall) chromatography using 1% ether:hexane containing 0.2% triethyl amine.

19a) 3,7-Dimethyl-6-octen-1-yl phenyl ether (CAS # 51113-53-2; ksk11-96; ksk11-94)

Using the general procedure for etherification with alkyl lithium described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with phenyl lithium (0.3 mL, 1.8 M nominal solution in dibutyl ether, 0.55 mmol) to furnish phenyl ether **19a** as colorless oil (102 mg, 87%); R_f = 0.66 (10 % EA/Hex).

Using the general procedure for etherification with alkyl magnesium halide described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with phenyl magnesium bromide

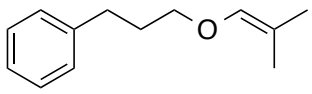
(0.18 mL, 3.0 M nominal solution in diethyl ether, 0.55 mmol) to furnish phenyl ether **19a** as colorless oil (78 mg, 67%); R_f = 0.66 (10 % EA/Hex).



^{1}H NMR (700 MHz): 7.32-7.30 (m, 2H), 6.97-6.93 (m, 3H), 5.15 (m, 1H), 4.03 (m, 2H), 2.08 (m, 1H), 2.02 (m, 1H), 1.88 (m, 1H), 1.75-1.71 (m, 1H), 1.73 (s, 3H), 1.65 (s, 3H), 1.64-1.61 (m, 1H), 1.46-1.41 (m, 1H), 1.30-1.24 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz): 151.1, 131.3, 129.4, 124.7, 120.5, 114.5, 66.1, 37.2, 36.1, 29.6, 25.8, 25.5, 19.6, 17.7;

19b) 2-Methylprop-1-en-1-yl propyl phenyl ether (ksk12-14)

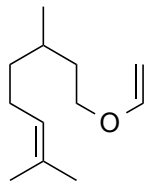
Using the general procedure for etherification with Grignard reagents described above, peroxide **13b** (118 mg, 0.5 mmol) was reacted with 2-methyl-1-propenyl magnesium bromide (1.3 mL, 0.5 M nominal solution in THF, 0.65 mmol) to furnish ether **19b** as colorless oil (36 mg, 38 %).



^{1}H NMR: 7.34-7.30 (m, 2H), 7.26-7.21 (m, 3H), 5.83-5.82 (m, 1H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 7.8 Hz, 2H), 2.00-1.93 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H); ^{13}C NMR: 141.8, 140.0, 128.5, 128.4, 125.8, 110.5, 70.7, 32.0, 31.4, 19.5, 15.0. HRMS (TOF-MS-EI$^+$): Calcd for $C_{13}H_{18}O$ $(M)^+$: 190.1358; found: 190.1363; IR (neat): 2918, 2865, 1689, 1496, 1159.

19c) 3,7-Dimethyl-6-octen-1-yl vinyl ether (ksk12-03):

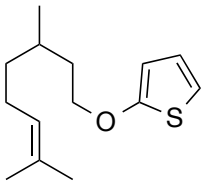
Using the procedure described above for etherification with a stannane-derived organolithium, peroxide **13a** (128 mg, 0.5 mmol) was reacted with mixture of tributyl (vinyl) stannane (174 mg, 0.55 mmol) and n-BuLi (0.34 mL, 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **19c** as colorless oil (37 mg, 40 %).



^{1}H NMR: 6.48 (dd, *J* = 6.8, 14.1 Hz, 1H), 5.12 (t, *J* = 7.0 Hz, 1H), 4.19 (d, *J* = 14.1 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 1H), 3.78-3.68 (m, 2H), 2.08-1.93 (m, 2H), 1.77-1.69 (m, 1H), 1.70 (s, 3H), 1.65-1.58 (m, 1H), 1.62 (s, 3H), 1.54-1.44 (m, 1H), 1.42-1.33 (m, 1H), 1.25-1.16 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: 152.0, 131.3, 124.7, 86.2, 66.3, 37.1, 35.9, 29.5, 25.7, 25.4, 19.5, 17.6. HRMS (TOF-MS-EI^{+}): Calcd for $C_{12}H_{22}O$ $(M-H)^{+}$: 181.1598; found: 181.1602; IR (neat): 2961, 2913, 2871, 1647, 1609, 1200.

19d) 3,7-Dimethyloct-6-en-1-yl) thiophene-2-yl ether (ksk12-04)

Using the general procedure-3 for etherification with tributyl aryl tin described above, peroxide **13a** (128 mg, 0.5 mmol) was reacted with mixture of 2-(tributylstannyl) thiophene (205 mg, 0.55 mmol) and n-BuLi (0.34 mL, 1.6 M nominal solution in hexane, 0.55 mmol) to furnish ether **19b** as colorless oil (45 mg, 38 %).

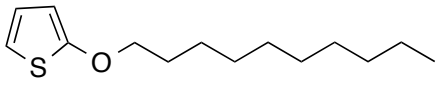


^{1}H NMR (700 MHz): 6.73 (dd, *J* = 3.7, 6.0 Hz, 1H), 6.56 (dd, *J* = 1.2, 6.0 Hz, 1H), 6.22 (dd, *J* = 1.2, 3.7 Hz, 1H), 5.13 (t, *J* = 7.1 Hz, 1H), 4.10-4.06 (m, 2H), 2.08-1.98 (m, 2H),

1.89-1.84 (m, 1H), 1.74-1.67 (m, 1H), 1.72 (s, 3H), 1.64 (s, 3H), 1.62-1.59 (m, 1H), 1.43-1.38 (m, 1H), 1.27-1.22 (m, 1H), 0.97 (d, J = 6.6Hz, 3H); ^{13}C NMR: 165.8, 131.4, 124.7, 124.6, 111.7, 104.6, 72.3, 37.0, 36.0, 29.4, 25.7, 25.4, 19.5,17.7; HRMS (TOF-MS-EI$^+$): Calcd for $C_{14}H_{22}OS$ $(M)^+$: 238.1391; found: 238.1390; IR (neat): 2963, 2925, 2913, 2871, 1536, 1193.

19e) 2-Decyloxy thiophene (ksk12-13):

Using the general procedure-3 for etherification with tributyl aryl tin described above, peroxide **13d** (129 mg, 0.5 mmol) was reacted with mixture of 2-(tributylstannyl) thiophene (242 mg, 0.65 mmol) and n-BuLi (0.4 mL, 1.6 M nominal solution in hexane, 0.65 mmol) to furnish ether **19e** as colorless oil (43 mg, 36 %).



^{1}H NMR: 6.74-6.72 (m, 1H), 6.56-6.54 (m, 1H), 6.23-6.21 (m, 1H), 4.04 (t, J =6.4 Hz, 2H), 1.83-1.76 (m, 2H), 1.48-1.44 (m, 2H), 1.38-1.30 (m, 12H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR: 165.9, 124.6, 111.6, 104.5, 74.0, 31.9, 29.5, 29.3, 29.2, 25.8, 22.7, 14.1. HRMS (TOF-MS-EI$^+$): Calcd for $C_{14}H_{24}OS$ $(M)^+$: 240.1548; found: 240.1548; IR (neat): 2920, 2853, 1536, 1456, 1193.

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Chapter-4: Applications of peroxides to synthesis of functionalized ethers.

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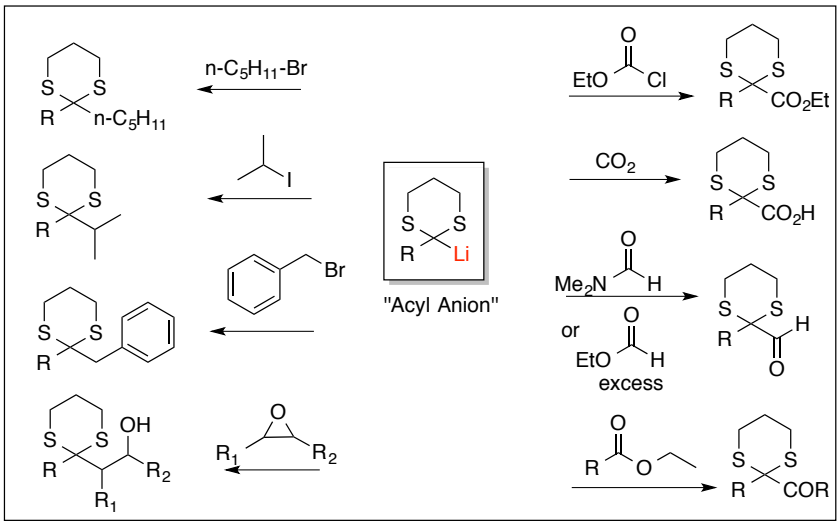
In Chapter-3, we discussed the intermolecular reaction of peroxides with unstabilized organometallics such as Grignard and organolithium reagents. In this chapter, we describe investigations into the intermolecular reactions of peroxides with three classes of stabilized carbanions: lithiated 1,3-dithianes; lithiated cyanohydrins; and, α-alkoxylithium reagents generated from alkyl tin compounds. This chapter will also discuss application of peroxides to synthesis of cyclopropyl ethers. Discussion begins with the reaction of peroxides with lithiated dithianes.

Section-1: Dithiane nucleophiles.

Dithiane derivatives of carbonyls are widely used in organic synthesis. Dithiane derivatives can either be deprotected to regenerate the original carbonyl functional group or can be reductively removed to achieve an overall deoxygenation. Dithianes are also notable for their use as acyl anion equivalents allowing polarity reversal or "umpolung" relative to the parent carbonyl. [1-5] Dithianes can be prepared from carbonyl compounds through the protection with dithiols, most commonly 1,3-propanedithiol, in presence of Lewis acid such as BF_3•Et_2O. 1,3-Dithianes of formaldehyde or aldehydes can undergo deprotonation with alkyl lithium reagents. The resulting lithiated dithianes are able to undergo C-C bond forming reaction with a variety of carbon electrophiles including such as carbonyls (ketones and aldehydes), carboxyl derivatives (acid chlorides, carbon dioxide, formamides, esters), alkyl halides (primary, secondary and benzyl, allyl), epoxides, and oxetanes (Scheme 1).[1-3] When combined with deprotection of the modified

dithiane (below), the result is the equivalent of C-C bond formations involving an acyl anion, RC(O)-.

Scheme-1: Dithiane reactivity towards various electrophiles

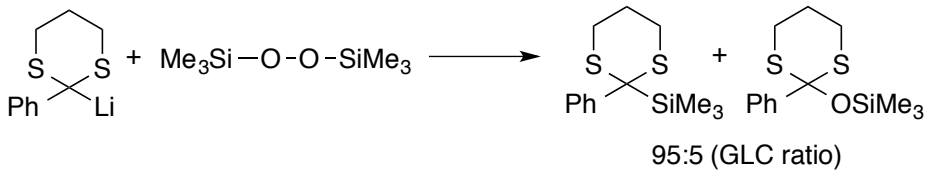


We are interested in investigating the reactivity of lithiated dithianes towards peroxide oxygen as a means of achieving a net transfer of alkoxide and formation of *S,S,O-orthoesters* (Equation-1).

Equation-1

There is little precedent for this reaction. The Taddei group, building upon the successful reaction of bis(trimethylsilyl)peroxide with aryl lithiums, [6-8] attempted electrophilic oxysilylation of lithiated phenyl dithiane with bis(trimethylsilyl)peroxide. However, the intended product, a silylated *S, S, O* orthoesters, was obtained as a minor product; the major product was a silylated 1,3-dithiane. (Equation-2). [8]

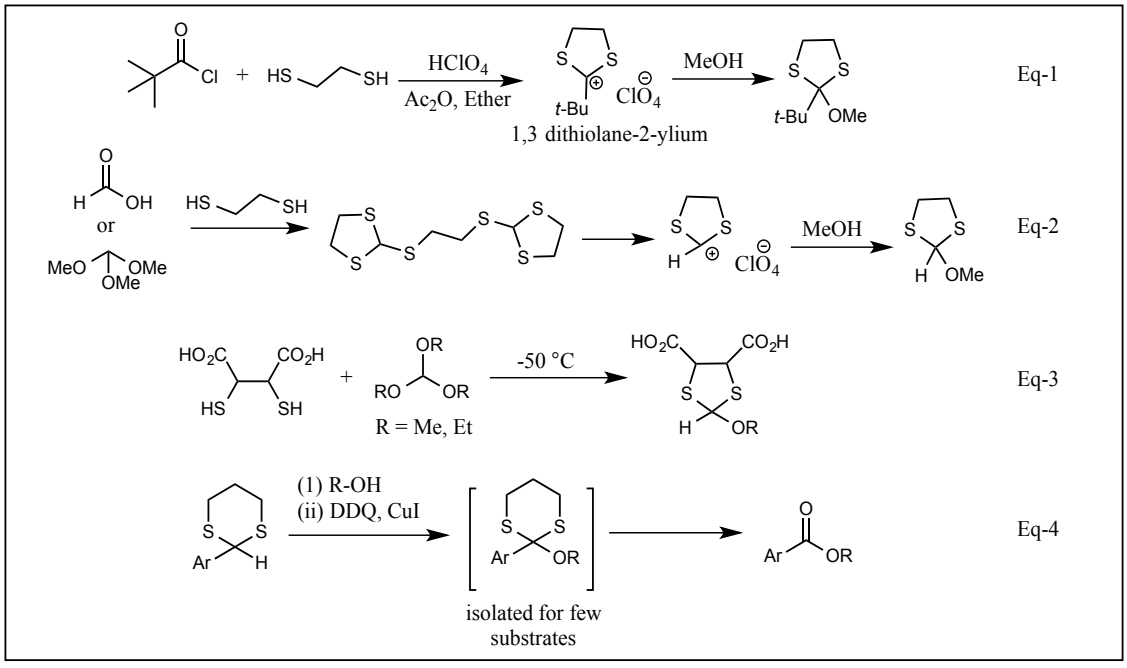
Equation-2:



Section 1.1: Previous approaches to *S,S,O*-Orthoesters

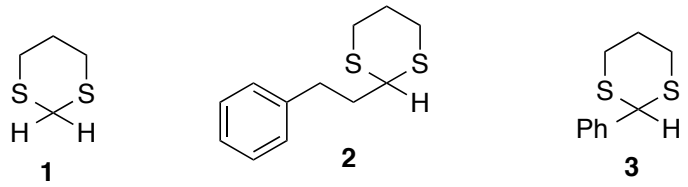
There are only a few reports describing synthesis of *S,S,O*-orthoesters; these are summarized in Scheme-2. *S,S,O*-orthoesters have been prepared by trapping 1,3-dithiolane-2-ylium percholorate with an alcohol.[9, 10] (Scheme 2, Equations 1, 2) and by thioacetalization of orthoformates at low temperatures (Scheme-2; Eq-3).[11] *S,S,O-orthoesters* have also been seen as intermediates during the cross-dehydrogenative coupling of dithianes and alcohols (Scheme-2; Eq-4).[12]

Scheme-2:



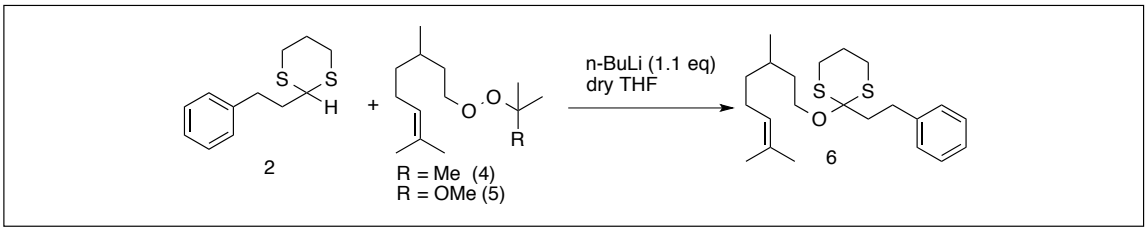
Section-1.2: Reaction of lithiated dithianes with peroxide electrophiles

The following dithianes shown below were used as starting materials. 1,3-dithiane (**1**) and 2-phenyl-1,3-dithianes (**3**) were commercially available. 2-Phenethyl-1,3-dithiane (**2**) was synthesized by known procedure.[13]



In preliminary experiments, the anion of 2-phenyl-1,3-dithiane, prepared through deprotonation of the neutral dithiane with *n*-BuLi , was reacted with peroxides **4** and **5** at room temperature to furnish an incompletely resolved mixture of *S,S,O* orthoester **6**, recovered starting material, and unknown impurities. (Scheme-3).

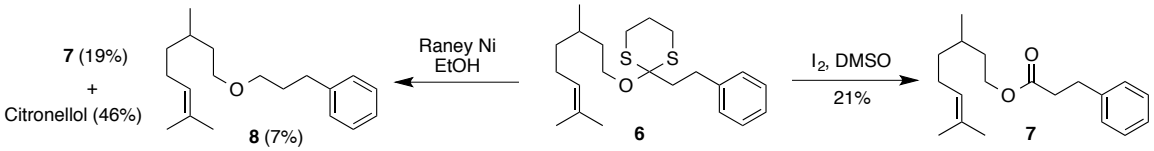
Scheme-3: Initial reaction of lithiated dithiane with a peroxide.



We initially explored the reactivity of **6** in an effort to generate derivatives, which could be easily purified (Scheme 4). An attempt to reduce **6** to an ether, using Raney-Ni, proceeded in only 7% yield; the major products were citronellol and the citronellyl ester of 3-phenylpropanoic acid (**7**). The ester byproduct **7** could have resulted from hydrolysis of **6** with traces of water carried in from Raney- Ni. *S,S,O* orthoester **6** was also treated with iodine in DMSO solvent, a procedure previously used to convert dithianes to

carbonyl compounds.[14] Although the yields of derived products (**7**, **8**) are poor, we had clear evidence of the conversion of peroxide to an orthoester (Scheme 4).

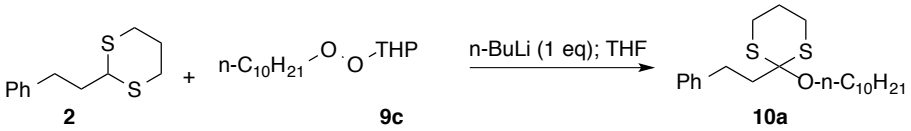
Scheme-4



Our initial investigations on the reaction of dithiane **2** with peroxide **5** (2-methoxypropyl peroxyacetal) suggested (TLC analysis) a greater fraction of orthoesters product and less recovery of starting material compared to reactions employing **4 (***t* -butyl peroxide). However, we also knew that the 2-methoxypropyl peroxyacetals had the potential to generate not only the desired product, but also products generated from trapping of the acetone released upon cleavage of this ketal (see section-19). For this reason, we repeated this series of experiments with 2-tetrahydropyranyl (THP) monoperoxyacetal (**9c**), prepared as described in Chapter 3. We had previously observed THP monoperoxyacetals to have enhanced reactivity towards organolithium reagents compared with simple dialkyl peroxides. Moreover, the released tetrahydropyranyl oxyanion appears to be unreactive towards common organometallics.

Lithiation of dithiane **2** using 1.0 eq. n-BuLi followed by reaction with **9c** generated *S,S,O* orthoester **10a** in good yield at room temperature (Table 1, entry 2). Conducting the reaction at -78 °C or in refluxing solvent did not improve the yield (Table-1, entry-1 and 3).

Table-1: Screening reactions with THP peroxides.

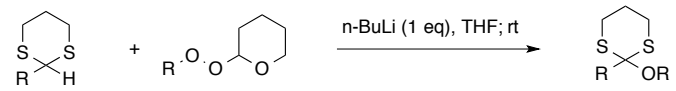


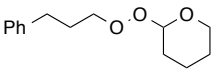
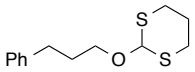
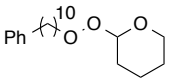
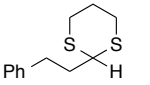
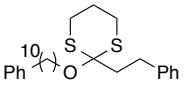
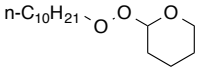
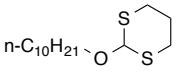
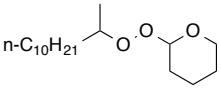
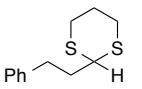
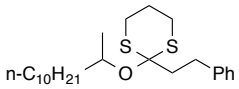
2 **9c** **10a**

Entry	Temperature (°C)	Yield (%)
1	-78	65
2	rt	70
3	70	66

Therefore, room temperature conditions were applied to most of the reactions discussed below. Reaction of peroxides **9a-9d** with dithianes **1** and **2** produced *S,S,O*-orthoesters **10b-10e** in good to moderate yields. (Table-2). Orthoesters **10b** and **10d** were obtained as pure products after flash column chromatography, where as **10c** and **10e** required additional purification (HPLC).

Table-2: Examples of S,S,O orthoestes using 1.0 equivalent n-BuLi



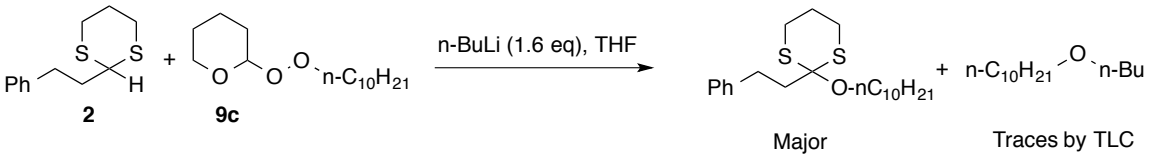
Entry	Peroxide		Dithiane		Orthoester		Yield
1		**9a**		**1**		**10b**	63
2		**9b**		**2**		**10c**	57a
3		**9c**		**1**		**10d**	33(54)[a]
4		**9d**		**2**		**10e**	25

a = Yield determined by NMR using trichloroethylene as standard

The *S,S,O*-orthoesters are stable at room temperature and can be isolated in pure form. However, these compounds can decompose in presence of acids and light.[15,16] The separation of orthoesters product from recovered dithiane was typically the most

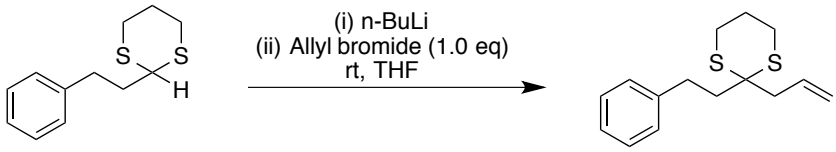
challenging part of the purification. In an effort to minimize the recovered dithiane, we explored deprotonation of the dithiane with varying amounts of n-BuLi ranging from 1.2 to 2.0 equivalents. Increased yields of orthoesters were observed until we reached 1.6 equivalents of n-BuLi (equation 3), at which point we began to detect formation of the n-butyl ether derived from reaction of unreacted n-BuLi with THP peroxide (**9c**).

Equation-3:



The use of 1.5 equivalent n-BuLi resulted in maximal yields of *S,S,O*-orthoester and no detectable butyl ether. This could be possible that dithiane deprotonation on this scale requires more than 1.0 equivalent of n-BuLi, [17] to understand this we have conducted control experiments with highly reactive allyl bromide. Increased yield was observed when 1.5 eq. n-BuLi was used in the reaction (table-3).

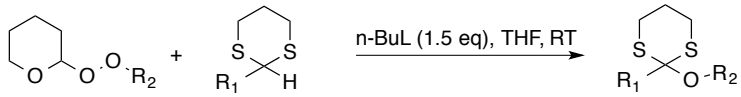
Table-3:

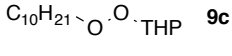
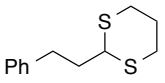
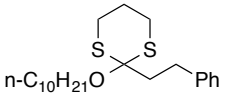
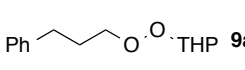
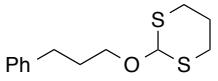
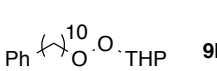
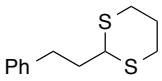
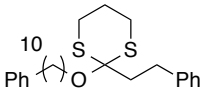
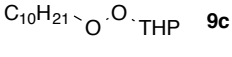
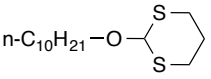
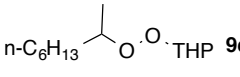
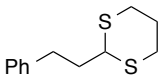
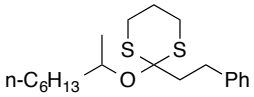
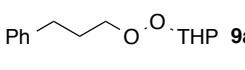
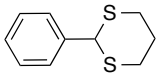
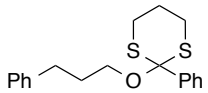
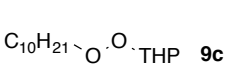
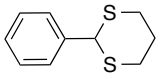
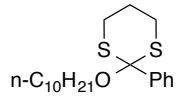
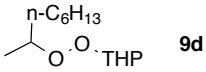
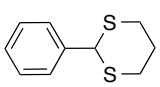
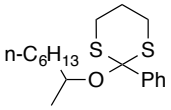


Entry	n-BuLi (eq)	Result
1	1.0	41% (based on NMR, as product and unreacted starting material inseperable mixture)
2	1.5	71% (isolated yield)

The amended conditions were applied to the examples illustrated in Table-4, which includes examples of reactions on both 0.5 and 5 mmol scale.

Table-4: *S,S,O*-Orthoesters synthesis using 1.5 equivalent n-BuLi



Entry	Peroxide	Dithiane	S,S,O-Orthoester	0.5 mmol scale	5 mmol scale
1	 **9c**		 **10e**	71	55
2	 **9a**		 **10b**	67	58
3	 **9b**		 **10c**	72	73
4	 **9c**		 **10d**	64	60
5	 **9d**		 **10e**	--	45
6	 **9a**		 **10f**	77	--
7	 **9c**		 **10g**	71	--
8	 **9d**		 **10h**	65	--

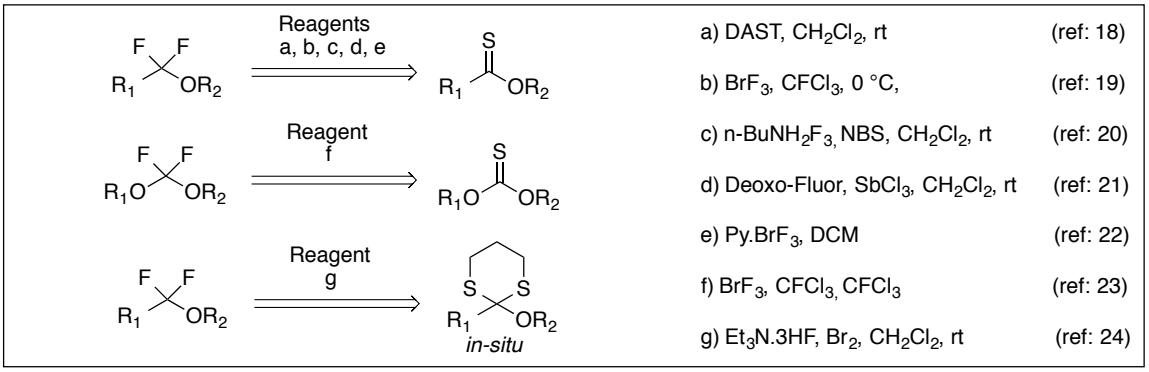
Section-2: Synthesis of Difluoroethers

In this section I will discuss functionalization of *S,S,O*-orthoesters to generate difluoroethers.

Section-2.1: Background on fluorodesulfurization

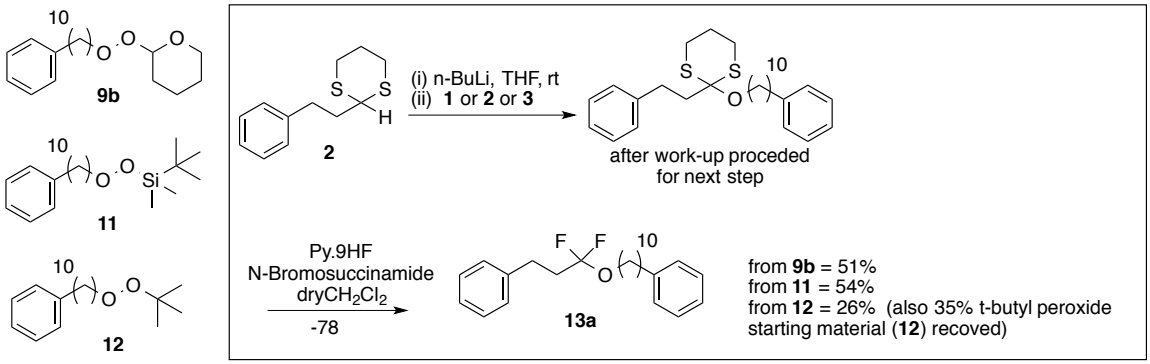
Some of our interest in the preparation of *S,S,O*-orthoester was the opportunity to investigate their conversion to difluoroethers. Fluoro-desulfurization has been previously applied to the synthesis of difluoroethers (Scheme 5).[18-24] We were interested in a method that have been applied for the conversion of carbonyl derived 1,3-dithianes to difluoro alkanes and wondered if these could be applied. [25]

Scheme-5: Previous approaches.



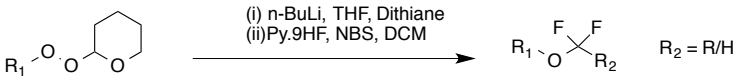
Initially peroxides **9b, 11** and **12** were reacted with lithiated dithianes (**2**) and the resulting *S,S,O-orthoesters* were subjected, without purification, to fluorodesulfurization using Py.9HF and N-bromosuccinimide at -78 C (Scheme 6). All three peroxides, which differ in the nature of the peroxide-leaving group, provided difluoroether (**13a**). The THP (**9b**) and silyl peroxide (**11**) provided the difluoroether in similar yield. The *t*-butyl peroxide (**12**) provided a much lower yield of difluoroether, along with a significant amount of recovered starting material.

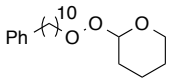
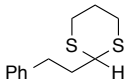
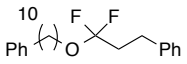
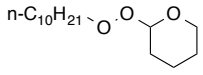
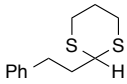
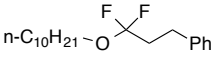
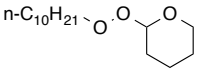
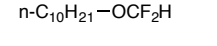
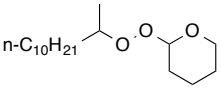
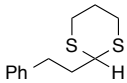
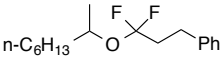
Scheme-6: Screening fluorodesulfurization



Due to the ease of synthesis of the THP monoperoxyacetals, we applied the dithiane/desulfurization methodology to additional examples of difluoroether synthesis. The two-step protocol, which did not involve purification of the intermediate orthoesters, furnished moderate yields (Table-5).

Table-5: Two-step synthesis of difluoroethers from THP peroxides



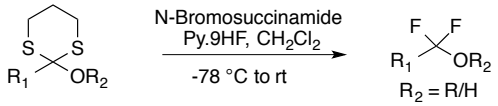
S.No	Peroxide		Dithiane		Difluoroether		Yield[a]
1		**9b**		**2**		**13a**	51
2		**9c**		**2**		**13b**	43
3		**9c**		**1**		**13c**	26
4		**9d**		**2**		**13d**	39

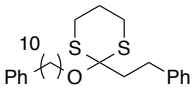
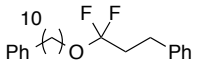
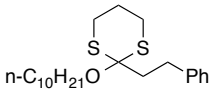
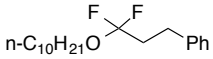
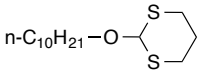
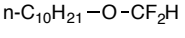
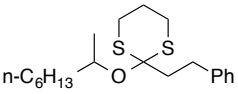
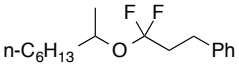
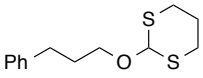
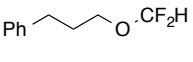
a = Yield after two steps

Section-2.2: Synthesis of difluoroethers from pure S,S,O-orthoesters

We also subjected pure samples of isolated *S,S,O*-orthoesters **10a-10b** to fluorodesulfurization using *N*-bromosuccinimide and Py-9HF at -78 C. This method furnished difluoroethers in good yields (Table-6). Fluorodesulfurization using dibromohydantoin as electrophilic bromine source did not improve the yields of difluoroethers (not shown).

Table-6: **Synthesis of Difluoroethers from S,S,O-orthoesters**



Entry	S,S,O Orthoester		Difluoroether		Yield(%)
1		**10c**		**13a**	70
2		**10e**		**13b**	69
3		**10d**		**13c**	73
4		**10d**		**13d**	40
5		**10b**		**13e**	62

Section-3: Studies towards synthesis of trifluoroethers

This section describes known approaches towards synthesis of trifluoromethyl ethers synthesis, as well as our investigations into the reaction of peroxide electrophiles with nucleophilic sources of trifluoromethyl anion or a synthetic equivalent.

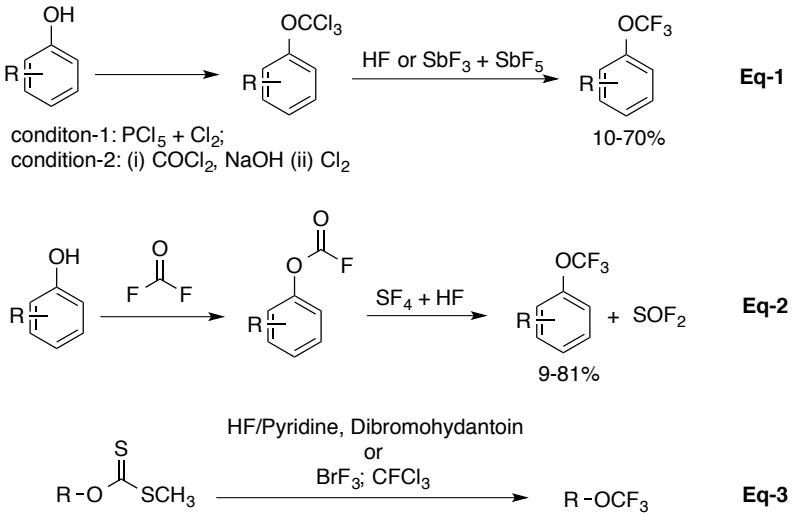
Section-3.1: Previous approaches for synthesis of trifluoromethyl ethers

There are only a handful of methods reported for synthesis of trifluoromethylethers. These can be classified into three types (i) Trifluorination of a functionalized carbon; (ii) O-CF_3 bond formation; (iii) C-OCF_3 bond formation.[26-29]

(i) Tri-fluorination of carbon:

Initially, trifluoromethyl aryl ethers were synthesized by fluorination of trichloromethyl aryl ethers using hydrogen fluoride or toxic antimony fluoride salts (Scheme 7, Eq-1).[26,30] Fluoro-deoxygenation of fluoroformates by mixture of SbF_3 and SbF_5 (scheme-7, eq-1), and fluorodesulfurization of xanthates have also been applied to synthesis of trifluoromethyl ethers (scheme-7, eq-2, 3).[31]

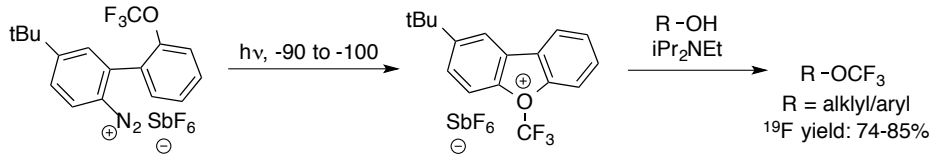
Scheme-7: Trifluorination methods



ii. O-CF_3 bond formation

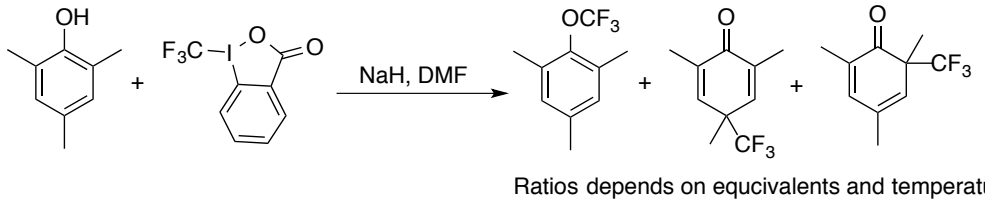
O-(Trifluoromethyl)dibenzofuranium salts were generated from corresponding diazonium salts and applied in-situ as electrophiles for the preparation of trifluomethyl ethers from alcohol precusors.[32] This method shows good yields of trifluoromethyl ethers only by ^{19}F NMR, no isolated yield were reported (Scheme 8).

Scheme-8: Electrophilic trifluoromethyl sources



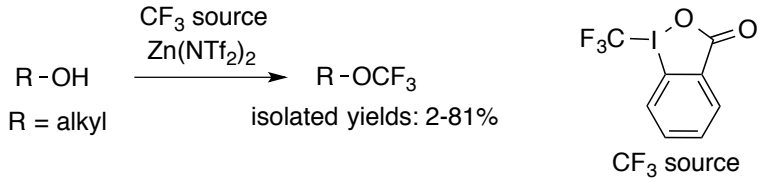
Iodonium salts such as the Togni-II reagent have been utilized to convert phenoxide salts in trifluoromethyl ethers. However, this method was not applicable for aliphatic trifluoroethers. Due to aromatic electrophilic substitution side reactions, low yields were obtained for Ar-OCF_3 (Scheme 9). [33]

Scheme-9:



However, in the presence of Zn salt such as $Zn(NTf_2)_2$, trifluoromethyl ethers were obtained with improved yields. This method is applicable for aliphatic trifluoromethyl ethers synthesis and requires either excess alcohol as solvent or reaction for 2-3 days (Scheme 10). [34]

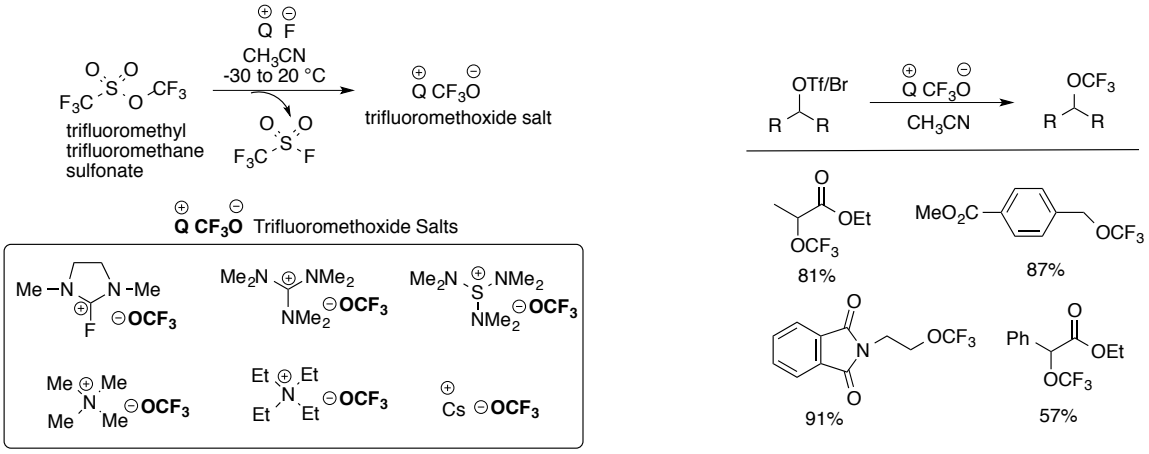
Scheme-10:



(iii) C-OCF_3 bond formation:

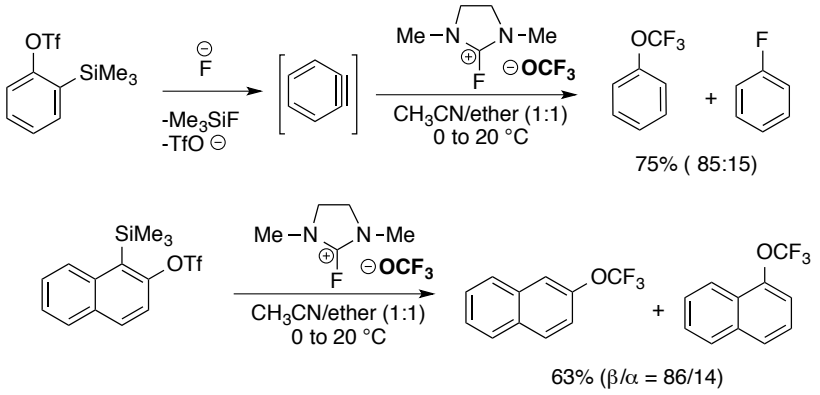
Trifluoromethoxide salts (OCF_3 salts) [35] were also investigated as nucleophiles for synthesis of trifluoromethyl ethers. OCF_3 salts were synthesized from trifluoromethyl trifluoromethane sulfonate ($CF_3SO_2OCF_3$) and used for trifluoromethylation of alkyl triflates and bromides (Scheme 11).

Scheme-11: Use of trifluoromethoxide salt and its preparation



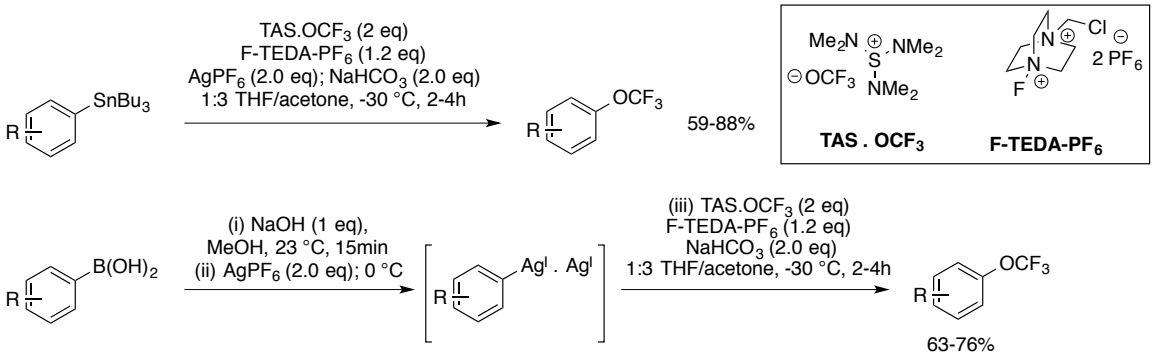
OCF_3 salts can react with benzyne intermediates. [35] Regioselectivity is an issue for unsymmetrical benzyne intermediates such as naphthalene (Scheme 12). Moreover, addition of fluoride formed n in-situ by α- elimination of OCF_3 can generate aryl fluoride side products.

Scheme-12: Aryl trifluoromethyl ethers synthesis



Trifluoromethoxide salt was successfully used for the synthesis of aryl trifluoromethyl ether by silver mediated cross coupling with aryl stannanes and aryl boronates (Scheme-13). This method is tolerant to various functional groups on aromatic ring, but only applicable for aryl stannane and boronic acids.[36]

Scheme-13: Silver mediated cross-coupling reactions

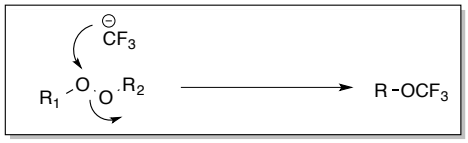


Section-3.2: Investigation of peroxide electrophiles for trifluoromethylation

In this section we are describing two approaches to synthesize trifluoromethyl ethers (i) direct nucleophilic CF_3 substitution on peroxide electrophiles, (ii) synthesis of *S,S,S,O* orthocarbonates from peroxides followed by fluorodesulfurization.

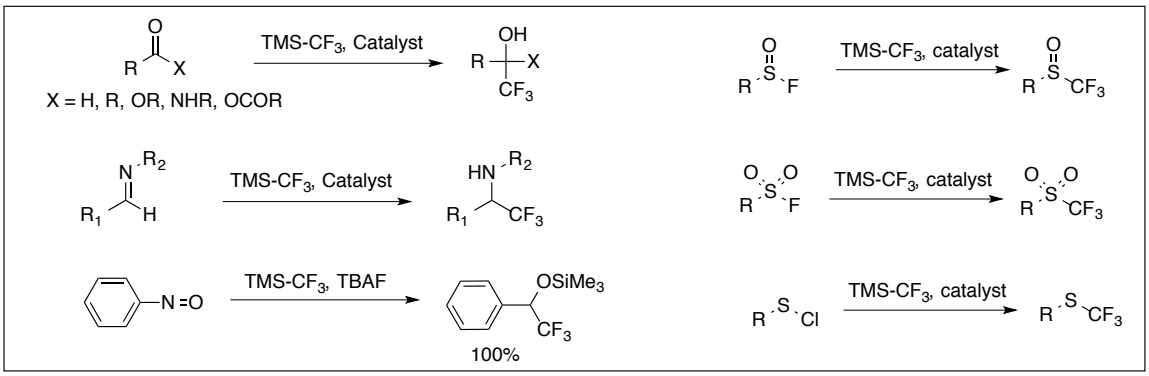
Our initial approach investigated the direct reaction of trifluoromethyl anion or a synthetic equivalent with dialkyl peroxides (Figure 1).

Figure-1:



Several nucleophilic CF_3 sources have been applied for trifluoromethylation of various functional groups and reaction sites in different molecules. [37-38.] We initially investigated trifluoromethyl trimethyl silane (TMS-CF_3), a widely used reagent (Prakash reagent) which reacts with a Lewis base to generate an intermediate pentavalent silicon intermediate capable of delivering CF_3 anion.[38]

Scheme-14: Examples of nucleophilic trifluoromethylation using the Prakash reagent

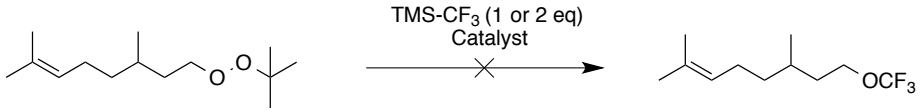


As shown in Scheme 14, TMS-CF_3 has been widely used for trifluoromethylation of a wide variety of electrophiles. [40]

Section-3.3: Attempted nucleophilic trifluoromethylatiion of peroxides

In initial experiments, DMF and THF solutions of citronellyl t-butyl peroxide (**4**) were treated with a mixture of TMS-CF_3 and tetra n-butyl ammonium fluoride (TBAF). Although we had hoped the *in-situ* generated trifluoromethylated pentavalent silicon would react with the peroxide, we did not observe any trifluoromethyl ether (Table-7, entry-1 and 2). A control experiment with similar condition as entry-1 with benzyl acetone (using TMS-CF_3 2 equivalents and catalytic TBAF) provided 91% trifluoromethyl silyated alcohol (reaction not shown).

Table-7: Trifluoromethylation screening

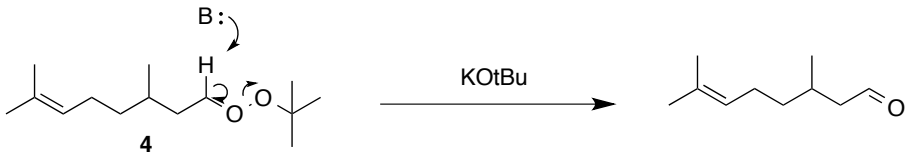


Entry	Catalyst (eq)	Solvent	Additives	Temperature	Result
1	TBAF (0.1)	THF	-	0 °C to RT	Only unreacted starting material by TLC
2	TBAF (0.1)	DMF	-	0 °C to RT	--
3	KOtBu (0.1)	DMF	-	0 °C to RT	Only unreacted starting material by TLC
4	KOtBu (1))	DMF	-	0 °C to RT	Citronellal formation by TLC
5	KOtBu (2)	DMF	-	-40 °C to RT	38% Citronellal isolated
6	CH_3OLi	THF	-	-10 °C to RT	Only unreacted starting material by TLC
7	TBAF and TMS-CF_3 (1:1)	DMF	CuI	-60 °C to RT	--
8	KOtBu and TMS-CF_3 (1:1)	DMF	CuI	RT	--
9	KF	THF	-	-78 °C	Only unreacted starting material by TLC

We also investigated KOtBu, which is also known to activate TMS-CF_3 towards generation of a CF_3 anion.[41] We hypothesized that catalytic KOtBu should enough to activate TMS-CF_3, assuming t-butoxide would be generated during the cleavage of the t-butyl peroxide substrate (Table-7, entries 3). When we used KOtBu base as activator in

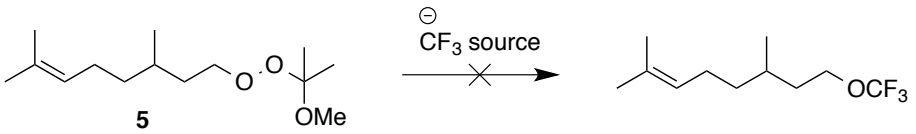
stoichiometric amounts (1 or 2 equivalents), we were able to isolate citronellal, a product resulting from Kornblum fragmentation of the peroxide (entry-4, 5; equation-4). [42]

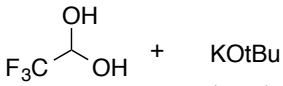
Equation-4: Kornblum fragmentation.



However, no trifluoromethyl ether was observed in a similar experiment employing KF as an activator (entry-9). Entries 6-8 illustrate the lack of effect of lithium alkoxide or Cu(I) counter ions.

Table-8:

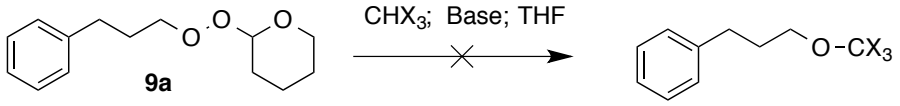


Entry	⊖CF_3 source	Solvent	T (°C)
1	TMS-CF_3 (2eq) + TBAF (catalytic)	THF	-40 to RT
2	TMS-CF_3 (2eq) + KOtBu (2eq)	DMF	-40 to RT
3	 (1.5 eq) + KOtBu (6 eq)	DMF	-50 to RT

We also investigated the reaction between the more reactive peroxide **5** and the Rupport-Prakash reagent, but again failed to observe formation of product (Table 8; entry-1,2). A control experiment (not shown) demonstrated that alkoxide-mediated reaction of trifluoroacetaldehyde hydrate with adamantanone resulted in an 82% yield of the trifluoromethyl carbinol. [43] However, applying the same conditions to peroxide **5** failed to provide trifluoromethyl ether (Table 8, entry-3).

We next investigated reactivity of peroxides towards a trifluoromethyl anion generated by direct deprotonation. The deprotonation of flouroform with KHMDS/KOtBu has been shown to generate KCF_3, which has been successfully applied at low temperatures to synthesis of trifluoromethyl silanes , trifluoromethyl borates, and aromatic non-enolizable carbonyl compounds.[44]

Table-9: THP peroxide reaction with haloform



Entry	CHX_3	Base	Temperature (°C)
1	CHF_3	n-BuLi	-78
2	CHF_3	LHMDS	-78
3	CHF_3	KHMDS	-50 to rt
4	$CHCl_3$	n-BuLi	-110
5	$CHBr_3$	n-BuLi	-110
6	$CHBr_3$	n-BuLi	-110 to -50

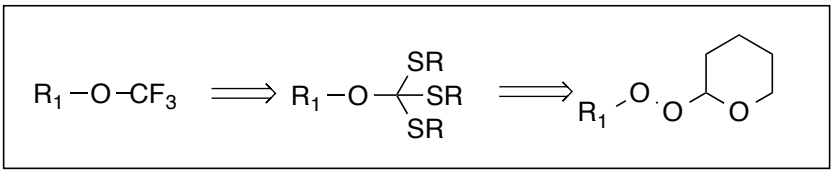
Attempt to react trifluoromethyl anion with THP peroxide (**9a**) by CHF_3 using KHMDS, LHMDS or n-BuLi failed to give trifluoromethyl ether (table-9, entry-1-3). We observed a similar failure with the carbanions generated from $CHCl_3$ and $CHBr_3$. These had to be generated and reacted at much lower temperature to slow down decomposition [81] (Table 9, entry 4-6).

Section-3.4: Synthesis of *S,S,S,O*-orthocarbonates trifluoromethyl ethers

After the successful conversion of *S,S,O-orthoesters* to difluoroethers as described earlier in this chapter, we became interested in an approach to trifluoromethyl ethers based upon fluorodesulfurization of *S,S,S,O*-orthocarbonates. There are few synthetic methods reported for preparation of these orthocarbonates and we suspected they could be

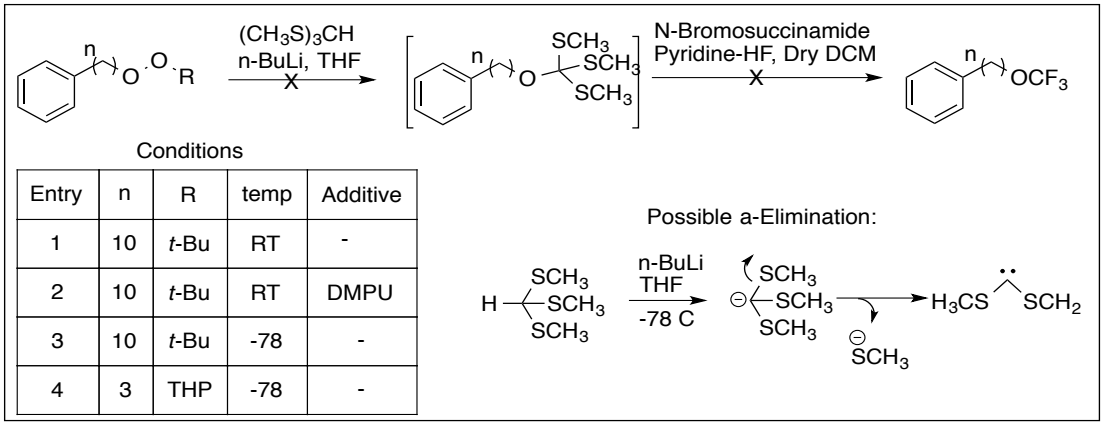
prepared via alkoxide transfer from dialkyl peroxides to lithiated trithianes.[45, 46] (Figure-2).

Figure-2: Approach to trifluoromethyl ethers



Room temperature reaction of lithiated tris(methylthio)methane with a dialkyl peroxide (Scheme-15, entry-1) gave no sign of formation of the *S,S,S,O*-orthocarbonate (TLC) and fluorodesulfurization of crude reaction mixture analysis gave no evidence for the presence of the trifluoroether (^{19}F-NMR). Repeating this reaction in the presence of N,N´ Dimethylpropyleneurea (DMPU), anticipated to activate the intermediate carbanion by solvating lithium ion, also failed to result in product formation (entry-2).

Scheme-15:



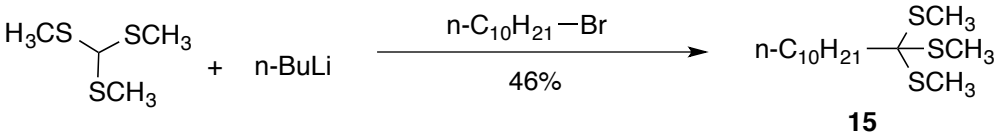
Entry	n	R	temp	Additive
1	10	*t*-Bu	RT	-
2	10	*t*-Bu	RT	DMPU
3	10	*t*-Bu	-78	-
4	3	THP	-78	-

Concerned that the lithiated trithiane nucleophile was decomposing too rapidly (see below), we also investigated mixing reactants at -78 °C and slowly warming the reaction to room temperature. However, following fluorodesulfurization, we still could not detect

a ^{19}F signal corresponding to OCF_3. We also failed to see any improvement upon the use of more reactive THP peroxide (**8a**, entry-4, Scheme 15).

However, the presence of a reactive tris (thiomethyl)methyl anion was confirmed with a model substrate n-decylbromide, which alkylated the carbanion to furnish trithiane (**15**) in moderate yield (Equation-5).

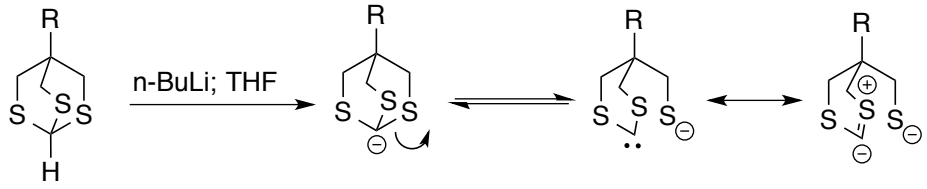
Equation-5:



15

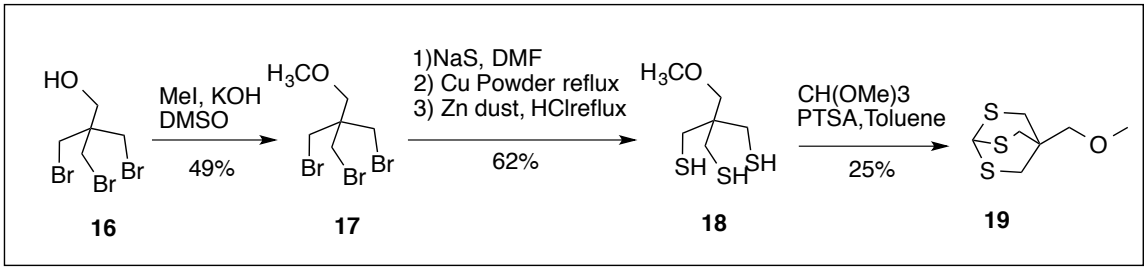
At this point, we realized that we were clearly generating the desired tris(thiomethyl) methyl anion, but the decomposition, presumably α-elimination of a thiomethyl anion to a carbene, was occurring more rapidly than the reaction with peroxides.[47] Therefore, we re-designed our synthesis to use a bicyclic trithiane in which the carbanions and the carbene would presumably remain in equilibrium (Scheme 16).

Scheme-16: Postulated equilibrium of the bicyclic carbanion



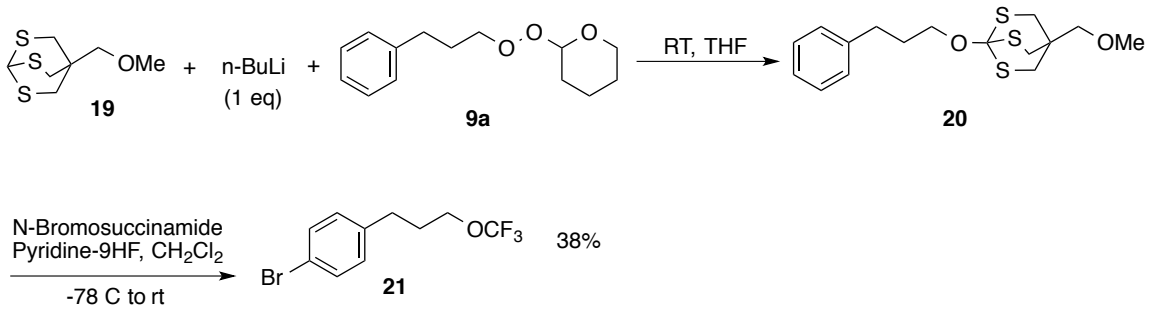
To test this hypothesis, we synthesized a tris-thio (2,2,2) bicyclo octane (**19**) from pentaerythrytol tribromide (**16**) by a known procedure (Scheme 17). [48]

Scheme-17:



The bicyclic trithiane was treated with n-BuLi and resulting carbanion reacted with peroxide **9a** to furnish a moderate yield of the *S,S,S,O*-orthocarbonate (**20**) along with unreacted starting material. Heating the reactions to reflux did not improve the yield of orthocarbonate. Fluorodesulfurization of the orthocarbonate using Py•9HF and *N*-bromosuccinamide generated the corresponding *p*-brominated trifluoromethylether, **21** in moderate overall yield (Scheme 18).

Scheme-18:

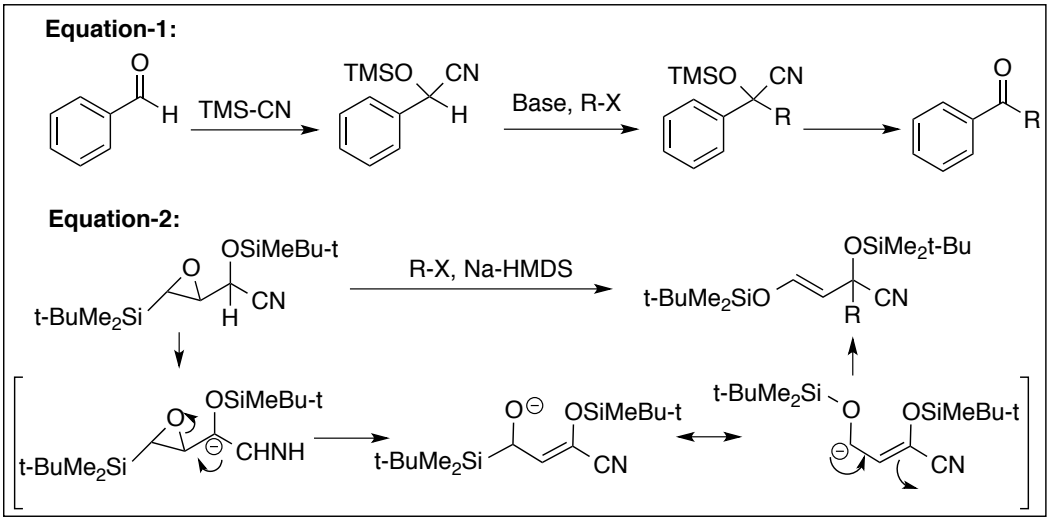


Section-4: Silylated cyanohydrins as nucleophiles

Background

Although not as versatile as dithianes, silyl protected cyanohydrins (SPC) are related as aldehyde derivatives that can be applied as acyl anion equivalents. Lithiated cyanohydrins can undergo reaction with electrophiles to furnish cyanohydrins of ketones; the net transformation, following deprotection, is alkylation of an aldehyde acyl anion to generate a ketone. Several methodologies are available for the synthesis of protected cyanohydrins.[49] Lithiated O-silylalated cyanohydrins have been explored as nucleophiles toward sp^3 electrophiles, including alkyl halides (scheme-19; equation-1), allyl halides, and alkyl tosylates.[50-54] A novel example of cyanohydrin reactivity is an E_1CB-type elimination of an adjacent epoxide. (Scheme-19, Equation-2). [55]

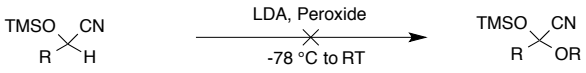
Scheme-19:

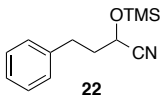
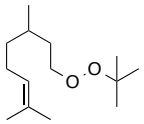
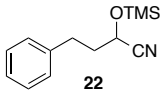
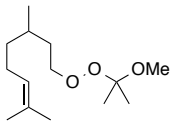
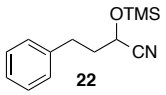
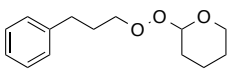
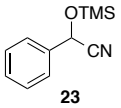
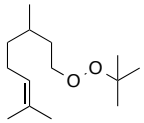


Aryl or alkenyl-substituted *O*-silyl cyanohydrin have been shown to react with electrophiles, but there are no examples of similar reactions for aliphatic cyanohydrins, We attempted reaction of lithiated aliphatic cyanohydrin (**22**), with citronellyl peroxide (**4** and **5;** entry 1,2) but did not see any alkoxide transfer either at 0 °C or -78 °C. As shown

in entry-4; scheme-20, we also failed to see any alkoxide transfer from reaction of a lithiated aryl-substituted cyanohydrin (**23**) with t-butyl peroxide (**4**). Preparation of the silylated cyanohydrins is described in the experimental section that follows this chapter.

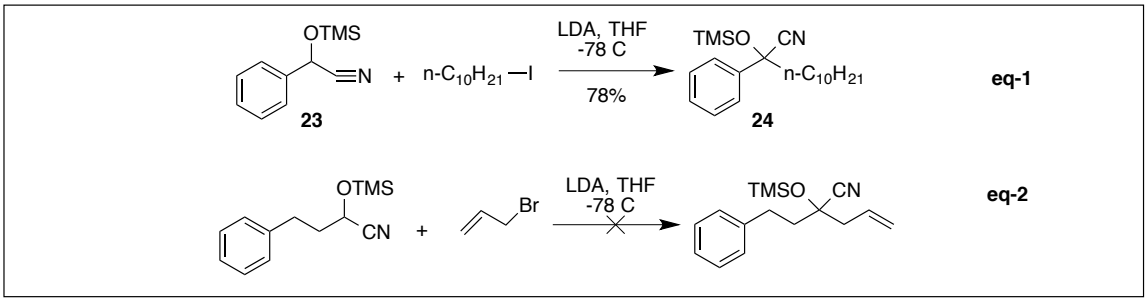
Scheme-20:



Entry	Silyl cyanohydrin	Peroxide
1	 **22**	 **4**
2	 **22**	 **5**
3	 **22**	 **9a**
4	 **23**	 **4**

A control experiment investigating the reactivity of a lithiated aryl cyanohydrin (**23**) with iododecane gave a good yield of alkylation even at – 78 °C. In contrast, an alkyl-substituted cyanohydrin failed to react with allyl bromide, a much more reactive substrate. (Scheme-21).

Scheme-21:



The results confirm the greater reactivity of aryl-substituted cyanohydrins. The fact that this lithiated cyanohydrin was able to achieve C-C and not C-O bond formation gives evidence of the lower kinetic reactivity of the peroxides (BDE approximately 35-40 kcal/mol)[75] compared with iodoalkanes (BDE > 50 kcal/mol).[76]

Section-5: Synthesis of cyclopropyl ethers

Few methods, none of them particularly efficient, are available for the synthesis of cyclopropyl ethers. Previously, cyclopropyl alkyl ethers were synthesized by Simmons-Smith cyclopropanation of vinyl ethers, [56] reaction of alkenes with sulfonium ylide. [57] A two step synthesis of cyclopropyl aryl ethers has been achieved using SN1-type reaction of 1-halo-1-thiophenyl cyclopppropanes with phenols, followed by desulfurization of the thioacetal intermediate.[58]

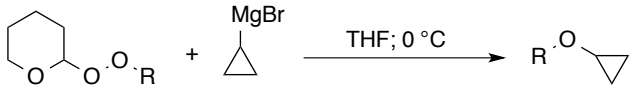
Substituted cyclopropyl alcohols can be synthesized by the Kulinkovich reaction[60] from ester substrates, but simple cyclopropanol is an expensive commercial material. However, no reports have been found for Williamson etherification involving cyclopropoxide nucleophiles. This could be explained by the tendency of cyclopropanol to undergo strain-induced ring-opening (Scheme 22).[59]

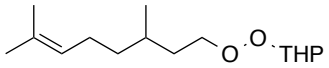
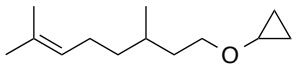
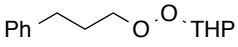
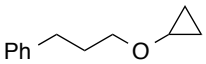
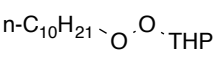
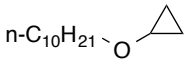
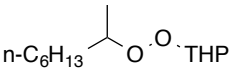
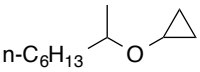
Scheme-22: Cyclopropyl ring opening

In a literature example particularly relevant to my research, cyclopropyl magnesium bromide was reacted with tert-alkyl peresters as an approach to the synthesis of cyclopropyl t-alkyl ethers. [61] Due to the typical limitations of peresters (facile elimination

for peroxides bearing a OOCH linkage), this methodology was limited to tertiary peroxides and therefore synthesis of t-alkyl esters. As shown in Table 10, the use of THP peroxides as electrophiles towards cyclopropyl magnesium bromide provides a very general methodology for the synthesis of cyclopropyl ethers.

Table-10: Cyclopropyl ethers synthesis.



Entry	Peroxide	Ethers	Yield (%)
1	 **9e**	 **25**	81
2	 **9a**	 **26**	72
3	 **9c**	 **27**	80
4	 **9d**	 **28**	70

Section-6: Reaction of peroxides with α-alkoxylithiums - synthesis of mixed acetals.

In this section, we describe our investigations of the reaction of dialkyl peroxides and monopeorxyacetals with α-alkoxy lithium reagents to generate mixed acetals.

Section-6.1: Background on α-alkoxy stannanes.

Organolithium reagents can be generated from the corresponding organostannanes by reacting with an alkyl lithium via tin-lithium exchange.[62, 63] Applying this reaction to α-alkoxy stannanes provides a means of generating lithiated α-alkoxy carbanions.[62] The α-alkoxy stannanes can be synthesized by addition of Bu_3SnLi to aldehydes, followed by protection of the intermediate tributylstannyl alcohol. The overall process is summarized in Scheme 23.

Scheme-23:

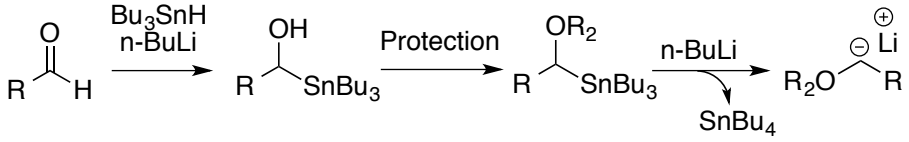
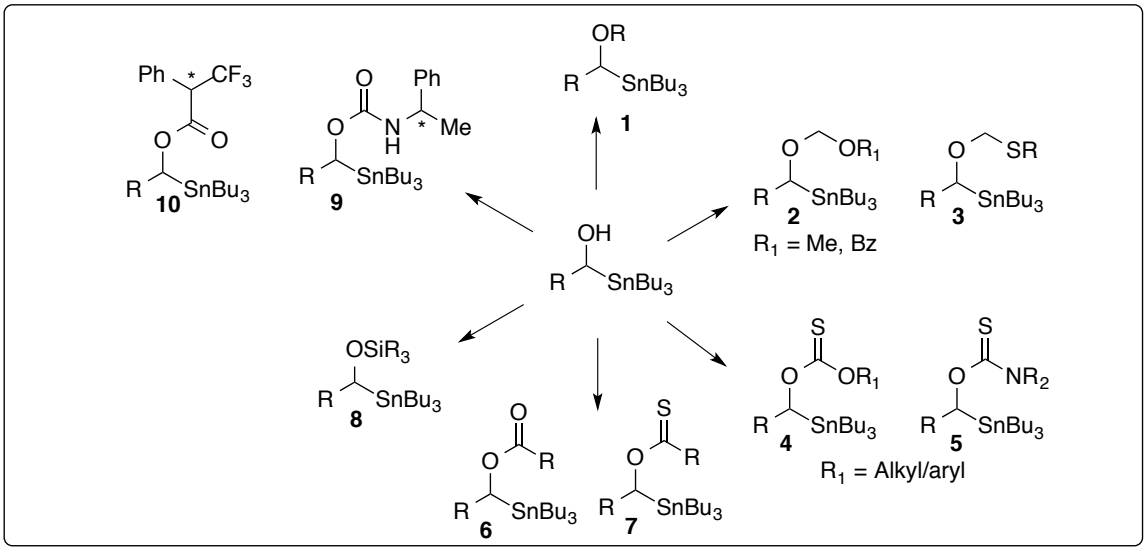


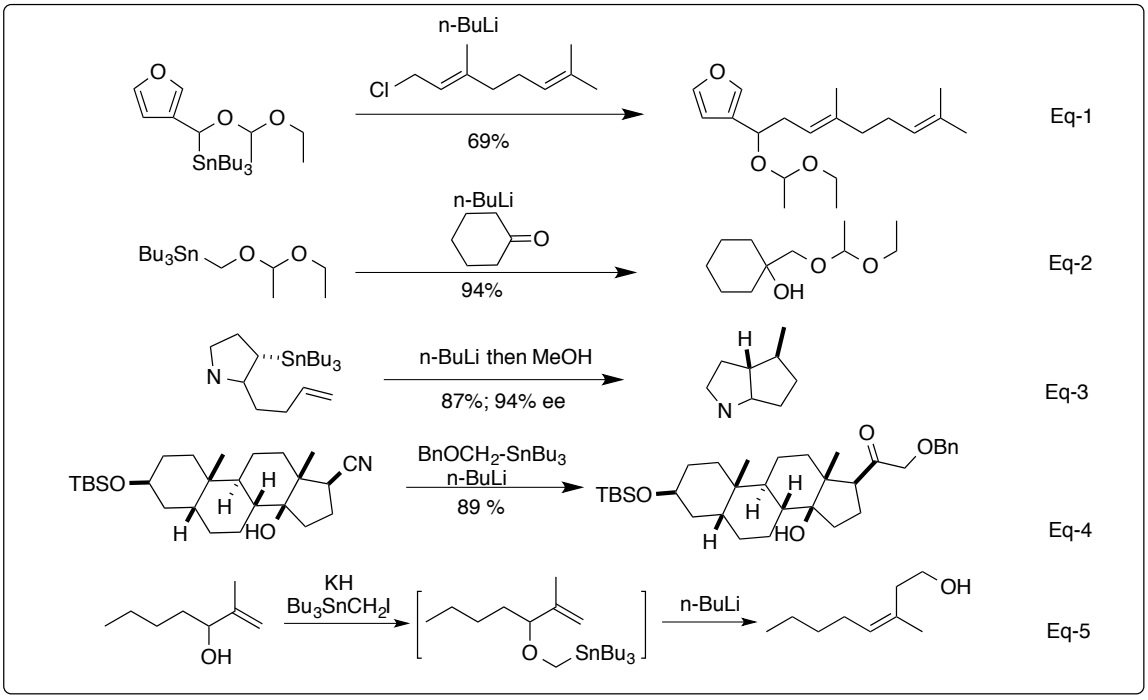
Figure-3 shows the range of protecting strategies that have been applied to stannyl alcohols. Alpha hydroxyl stannane is most commonly protected as methoxymethyl (MOM) or benzyloxymethyl (BOM) ethers (**2**, in Figure-3) by reaction with the chloromethyl alkyl ether.[62, 64] Other derivatives are known, including alkyl (**1**, in figure-3), [62, 65] methylthiomethyl (**3**), [66] thiocarbonates and thiocarbamates (**4** and **5**) [66], esters and thioesters (**6** and **7**) [66], trimethyl silyl (**8**). [67] There are also derivatives to form diastereomers such as mosher esters and carbamates (**9** and **10**). [68, 69] Racemic tributylstannyl alcohols have been resolved by enzymatic esterification[70] (hydrolysis), or conversion to chiral esters or carbamates (9 and 10 in Figure-3) [68, 69]

Among all these protected derivatives, (**1**, **2** and **3**), silyl ethers (8) and carbamate[79] can be used for tin-lithium exchange reactions such as alkoxy/alkyl methyl ethers. The rest of the protected functional groups potentially undergo reaction with alkyl lithium.

Figure-3:



Scheme-24:

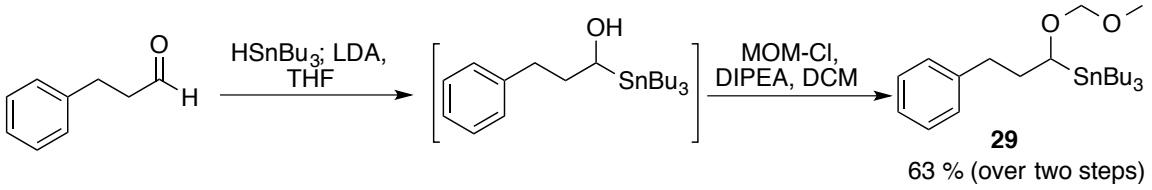


The stannane-derived α-alkoxy lithium carbanions have been applied for addition to carbonyls or nitriles, displacement of alkyl halides, or as starting materials for anion cyclizations and 2,3-wittig rearrangement of allyl ethers (Scheme 24, Eq-1-5). [63, 71, 72, 80]

Section-6.2: Reaction of α-alkoxylithium reagents with organic peroxides

We are interested in testing in situ generated α-alkoxy lithium nucleophiles towards peroxide electrophiles. For this, we have prepared the 1-methoxymethyl-1-tributylstannane **29** by reaction of hydrocinnamaldehyde with Bu_3SnH and LDA followed by MOM protection of the intermediate alcohol (Equation 6).

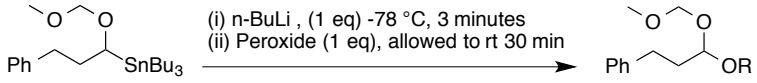
Equation-6:

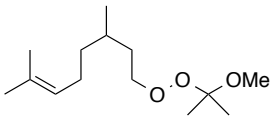
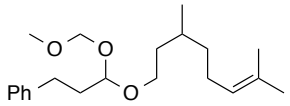
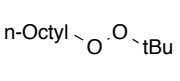
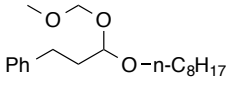
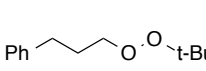
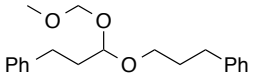
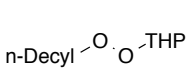
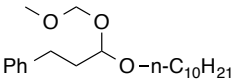


29

63 % (over two steps)

Table-11: Synthesis of mixed acetals



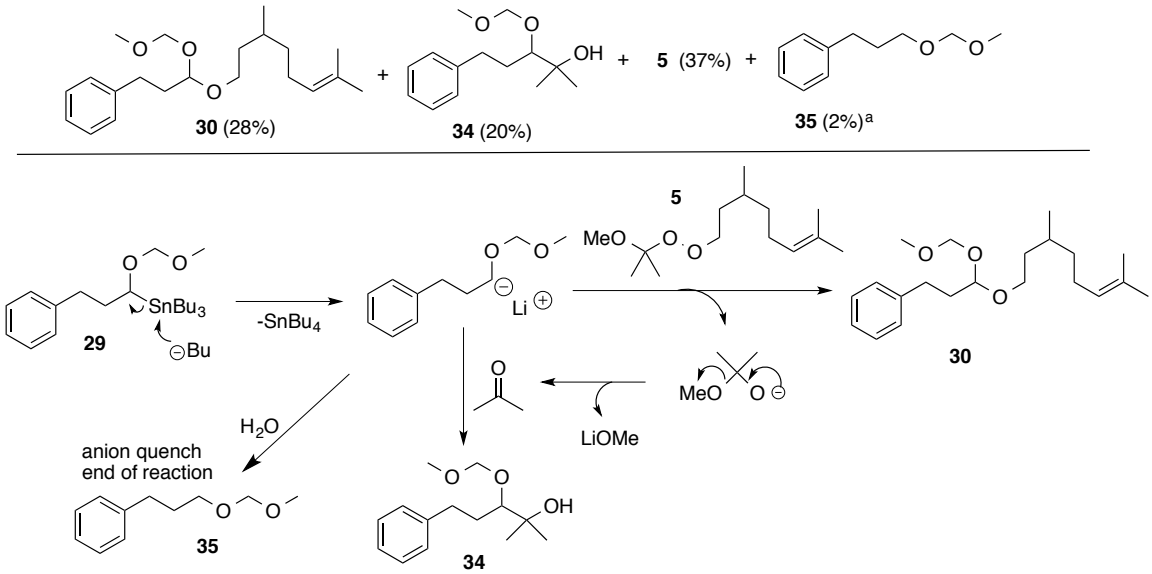
Entry	peroxide		mixed acetal		Yield (%)
1		**5**		**30**	28 + Byproducts[a]
2		**42**		**31**	57[b]
3		**43**		**32**	55[c]
4		**9c**		**33**	55

(a) = See equation-**7** for byproducts; and scheme-19 for mechanism; (b) 10% unreacted starting material isolated
(c) 1.2 eq. of stannane and n-BuLi mixture used (which is equal to 0.2 eq. extra lithiated nucleophile)

The lithiated ether derived from stannane **29**, derived by treatment with stoichometric n-BuLi at -78 °C, was used as a nucleophile for reactions with several peroxides (Table-11). Good yields were obtained with the t-butyl and THP peroxides (entry 2-4). However a much lower yield was obtained for the methoxypropyl peroxyacetal (entry-1).

Reaction of stannane **29** with peroxide **5** (entry-1 in table-11), successfully produced a mixed acetal (**30**). However the reaction did not go to completion and also generated several byproducts, which are illustrated Scheme-25. As shown in the mechanism (Scheme 25), byproduct **35** was obtained from protonation of unreacted nucleophile. Byproduct-**34** resulted from the trapping of acetone, which is generated as a byproduct of the attack of the organometallic on the 2-methoxy-2-propyl peroxide (**5**).

Scheme-25: Byproduct formed in entry-1; Table-7 and mechanism:

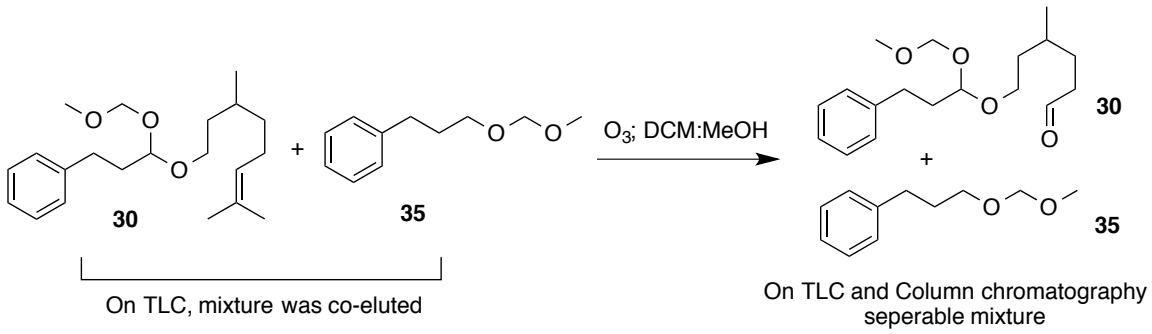


a = **35** co-eluted with **30** as inseperable mixure. In seperated experiment (same reaction scale) this mixture ozonolyzed to get pure 35.

Byproduct **35** coeluted with the desired product **30** (entry-1; table-7). Therefore, in a separate experiment (same scale), the crude reaction mixture was subjected to ozonolysis,

converting the mixed acetal to a more polar aldehyde, which was easily separated from **35** on TLC and column chromatography (scheme-26).

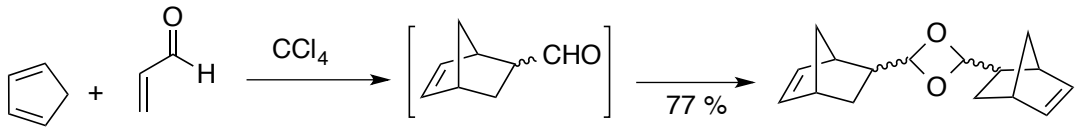
Scheme-26:



Section-6.3: Studies towards 1,3-Dioxetanes

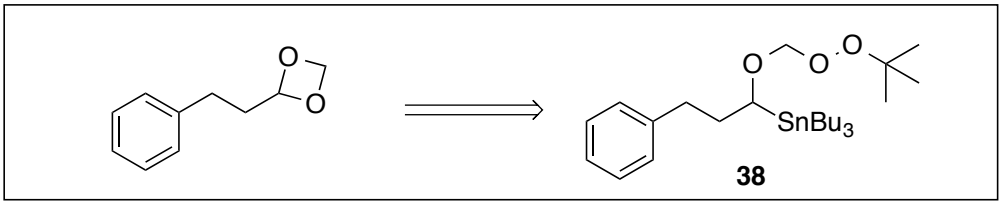
1, 3-Dioxetanes are 4-membered cyclic diethers. Although SciFinder search shows numerous hits for the 1,3-dioxetane skeleton, that does not have any synthetic procedures. During the Diels-Alder reaction of cyclopentadiene with acrolene in CCl_4, 1,3-dioxetane was formed unexpectedly from resulted Diels-Alder adduct[83] (Scheme-27).

Scheme-27:



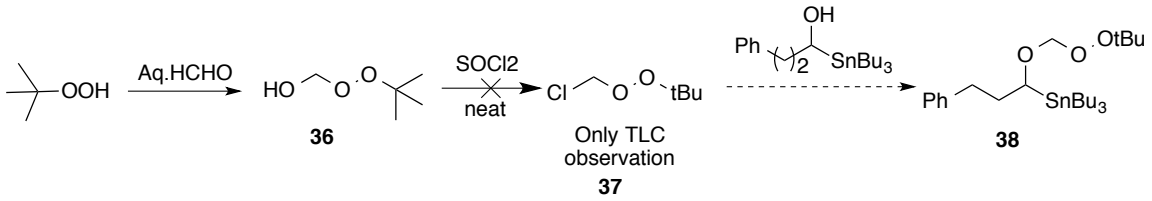
We were interested in whether we could synthesize these new classes of molecules from t-butoxy peroxy methyl ether **36**, via a 4-exo-tet closure[82] of an intermediate α-alkoxy-lithium (Figure 4).

Figure-4: Retro synthesis.



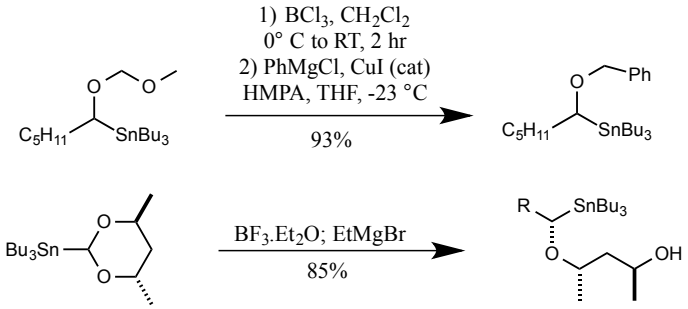
Initially, we planned to synthesize peroxide **38** by preparing t-butoxy methylene chloride (**37**). Although corresponding alcohol (**36**) was synthesized by a known procedure[73], the chlorination with $SOCl_2$ failed to provide isolable material (Section-28).

Scheme-28:



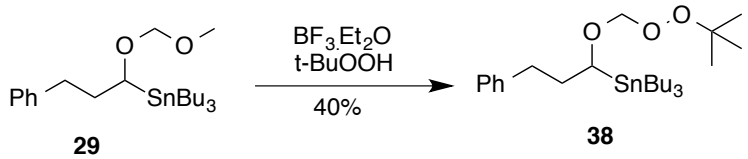
The alkoxy moieties in alkoxy methyl ethers (e.g. MOM ether) and in α-stannane acetals have been substituted with nucleophiles in presence of Lewis acids (Scheme 29). [64, 74]

Scheme-29: Lewis acid catalyzed acetal alkylation.



We found that α-methoxymethyl stannane **29** reacted with t-BuOOH in presence of BF_3. Et_2O to provide peroxide **38** (Equation-7).

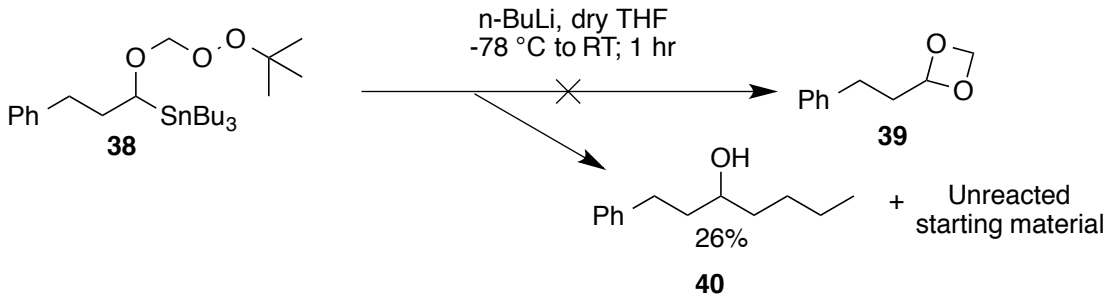
Equation-7: *trans*-acetalization with t-BuOOH



We then investigated the products of lithiation of **38** with n-BuLi, with a hope of obtaining the 1,3-dioxetane. Unfortunately, the reaction failed to give intended product (**39**), but produced the butyl alcohol (**40**). Although the mechanism is not fully

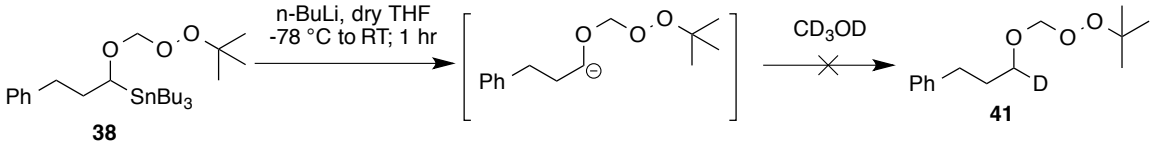
understood, it is expected that hydrocinnamaldehyde could be a possible intermediate for the following reaction (Scheme 30).

Scheme-30:



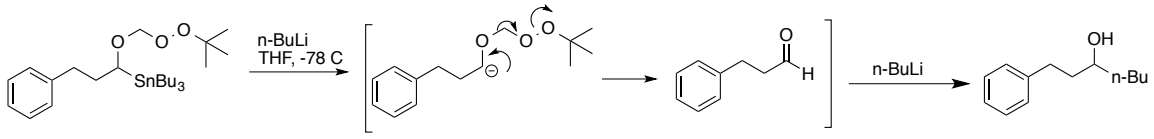
Trapping Experiment: We quenched the lithiation reaction with deuterated solvent at different intervals to determine whether the anticipated alkoxylithium was stable at low temperature. We could not found any signature of the protonated byproduct (**41**) by ^{1}H NMR (Scheme-31).

Scheme-31:



Formation of byproduct could be from anion-promoted fragmentation that can form cinnamaldehyde, formaldehyde and t-butoxide as shown in Scheme-32. Cinnamaldehyde further reacts with n-BuLi to give product **40**.

Scheme-32:

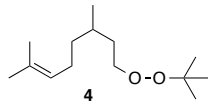
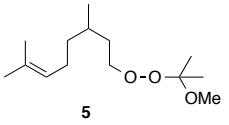
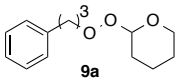
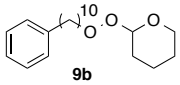
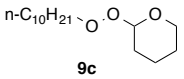
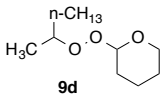
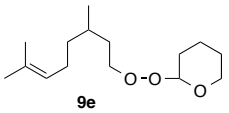
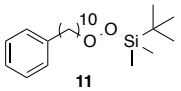
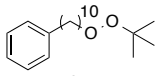
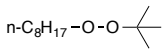
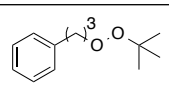


Section-7: Experimental Section

Synthetic procedures and spectral data are grouped below within sections corresponding to the order in the results and discussion.

Peroxides used in this chapter are illustrated in Chart-1; synthetic procedures and spectral characterization of these molecules is described in Chapter 3.

Chart-1: Peroxide electrophiles used in this chapter

 **4**	 **5**	 **9a**	 **9b**	 **9c**
 **9d**	 **9e**	 **11**	 **12**	 **42**
 **43**				

<u>Section-1: Peroxides, and 1,3-dithianes, S,S,O-orthoesters and their derivatives</u>

(i) Synthetic procedures and spectral data for peroxides **4**, **5,** and **9a-9d** were described in chapter-3.

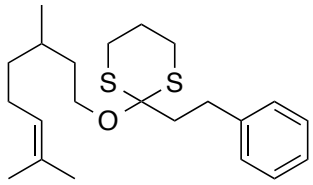
(ii) Synthetic procedures and spectral data for *S,S,O*-orthoesters **10a** through **10h** have been published.[77]

(iii) Dithianes **1** and **3** were used as purchased from commercial sources without further purification.

2-Phenethyl 1,3-dithiane (**2**) (ksk07-54) was synthesized from hydrocinnamaldehyde using a known procedure. [13] Yield: 82% (2.79 g). Spectral data matched those reported in the literature.

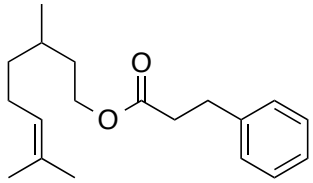
(6) Synthesis of 2-((3,7-dimethyloct-6-en-1-yl)oxy)-2-phenethyl-1,3-dithiane (ksk07-58).

Synthesized by following procedure described in reference 77, lithiated dithiane (**2**, 173 mg, 0.77 mmol) was reacted with peroxide **4**, (266 mg, 1.17 mmol) to furnish orthoester **6**, which was characterized following conversion to ester **7** or ether **8** as described below.



(7) Synthesis of 3,7-dimethyloct-6-en-1-yl 3-phenylpropanoate (CAS # 1636892-14-2; ksk07-71):

Using a reported procedure, [14] a solution of orthoester **6** (290 mg, 0.59 mmol) in DMSO (1 ml) was treated with iodine (300 mg, 1.18 mmol) to furnish ester **7** as a clear liquid (36 mg, 21%); R_f = 0.4 (10% EA:Hex).



^{1}H NMR: 7.32-7.29 (m, 2H), 7.23-7.20 (m, 3H), 5.12-5.09 (m, 1H), 4.18-4.08 (m, 2H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.64 (t, *J* = 6.9 Hz, 2H), 2.11-1.96 (m, 2H), 1.70 (s, 3H), 1.69-1.60 (m, 1H), 1.62 (s, 3H), 1.55-1.49 (m, 1H), 1.47-1.31 (m, 2H), 1.24-1.4 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H). C^{13} NMR: 172.99, 140.6, 131.3, 128.4, 128.3, 126.2, 124.6, 63.0, 36.9, 35.9, 35.4, 31.0, 29.5, 25.7, 25.4, 19.3, 17.6.

Reduction of S,S,O orthoester with Raney nickel:

Procedure: Raney nickel (approximately 1 g as a slurry in water) was placed in a 50 mL single neck round bottom flask. Methyl alcohol (5 mL) was added to the slurry and the

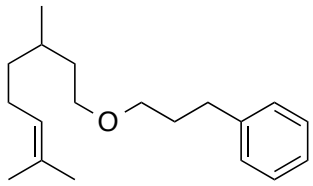
mixture of water:methanol was removed by pipette; this process was repeated another two times to leave only Raney Ni. Then solution of trithioorthoester **6** (260 mg in 5 mL methanol) was added and the reaction stirred for 2 hours at room temperature. At this point reaction TLC shown unreacted starting material, therefore another 4 gm. of Raney nickel (prewashed with methanol to remove water as described above) was added to the reaction mixture, which was stirred until the reaction appeared complete (approximately an hour). The reaction mixture was filtered though Celite and the filter pad was washed with ethanol. The concentrated filtrate was purified by silica gel chromatography using ether:hexane (1-2%) followed by ethyl acetate:hexane (2-20%) to furnish a mixture of ester **7**, ether **8**, and citronellol.

(7) Synthesis of 3,7-dimethyloct-6-en-1-yl 3-phenylpropanoate (CAS 1636892-14-2; ksk07-74-f2);

Obtained as colorless liquid (38 mg, 19%) in the above reaction; Spectral data as shown above.

(8) (3-((3,7-Dimethyloct-6-en-1-yl)oxy)propyl)benzene (ksk07-74-f1)

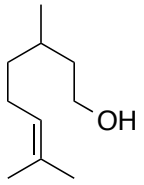
Obtained as colorless liquid (14 mg, 7%) in the above reaction; R_f = 0.5 (10% EA:Hex)



H^1 NMR: 7.32-7.28 (m, 2H), 7.22-7.20 (m, 3H), 5.15-5.11 (m, 1H), 3.48-3.41 (m, 4H), 2.71 (m, 7.7 Hz, 2H), 2.05-1.99 (m, 2H), 1.97-1.88 (m, 2H), 1.70 (s, 3H), 1.69-1.57 (m, 2H), 1.62 (s, 3H). 1.46-1.32 (m, 3H), 1.25-1.15 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H); C^{13}

NMR: 142.1, 131.1, 128.4, 128.3, 125.7, 124.8, 69.9, 69.2, 37.2, 36.7, 32.4, 31.4, 29.6, 25.7, 25.5, 19.6, 17.6.

3,7-Dimethyloct-6-en-1-ol (ksk07-74-f3): Colorless oil; 46% (50 mg); R_f = 0.2 (10% EA: Hex)



H^1 NMR (300 MHz): 5.12-5.07 (m, 1H), 3.72-3.61 (m, 2H), 2.06-1.89 (m, 2H), 1.68 (s, 3H), 1.67-1.49 (m, 2H), 1.60 (s, 3H), 1.44-1.11 (m, 4H), 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz): 131.2, 124.7, 61.1, 39.8, 37.2, 29.1, 25.7, 25.4, 19.5, 17.6.

Section-2: Difluoroethers

(i) Synthetic procedures and spectral data for peroxides **11** and **12** were described in chapter-3.

(ii) Synthetic procedures and spectral data for difluoroethers **13a** to **13d** have been published. [77]

Section-3.3: S,S,S,O orthocarbonates, triflouoromethyl ethers.

(i) Compound **19** synthesized using known procedure.[48] Synthetic procedure and spectral data of S,S,S,O orthocarbonate (**20**) and trifluoromethyl ether (**21**) were reported.

Section-4.1: Silylated cyanohydrins

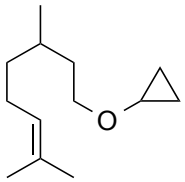
Silyl cyanohydrins **22** and **23** were synthesized from carbonyl compounds and trimethyl silyl cyanide following a known procedure.[78]

Section-5: Synthesis of cyclopropyl ethers

General Procedure: The THP peroxide (0.5 mmol) was dissolved in dry THF (5 ml) and the solution cooled to 0 °C. Cyclopropyl magnesium bromide (1.3 ml 0.5M nominal solution in THF, 0.65 mmol) was then added. The cooling bath was removed and the reaction was stirred for 45 min prior to quenching by dilution with 1M aq. hydrochloric acid (~ 2mL) followed by 10 mL water. Note: the aq. HCl treatment clarified a previously hazy solution. The hexane extracts (20 mL x 2) were dried over Na_2SO_4 and concentrated on rotary evaporator. The residue was purified by silica gel chromatography (5 inch tall; 0.5 inch width silica) using 1-2% ethyl acetate in hexane. Fractions were concentrated on the rotary evaporator at (80-120 torr) and then subjected briefly (1 min, 0 °C) to high vacuum (< 0.5 mm).

25) ((3,7-dimethyloct-6-en-1-yl)oxy)cyclopropane: ksk12-10

By the general procedure described above, THP peroxide **9e** (128 mg, 0.5 mmol) reacted with cyclopropyl magnesium bromide (1.3 ml 0.5 M nominal solution in THF, 0.65 mmol) to furnish cyclopropyl ether **25** as a colorless oil (79 mg, 80%). R_f = 0.52 (10% EA: Hex).

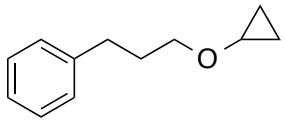


^{1}H NMR: 5.13-5.09 (m, 1H), 3.58-3.48 (m, 2H), 3.28-3.24 (m, 1H), 2.05-1.91 (m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.58-1.49 (m, 2H), 1.42-1.31 (m, 2H), 1.23-1.09 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.58-0.54 (m, 2H), 0.48-0.43 (m, 2H); ^{13}C NMR: 131.1, 124.8, 68.9,

52.9, 37.2, 36.6, 29.5, 25.7, 25.4, 19.5, 17.6, 5.45, 5.41; HRMS: (TOF-MS CI^+): calcd for $C_{13}H_{25}O$ $(M+H)^+$ 196.1827 found 197.1913; IR (neat): 2960, 2916, 1452, 1342.

26) 3-(Cyclopropoxy)propyl benzene: ksk12-09

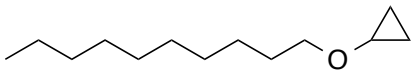
By the general procedure described above, THP peroxide **9a** (118 mg, 0.5 mmol) reacted with cyclopropyl magnesium bromide (1.3 ml 0.5 M nominal solution in THF, 0.65 mmol) to furnish cyclopropyl ether **26** as colorless oil (64 mg, 72%). R_f = 0.46 (10% EA: Hex);



^{1}H NMR: 7.32-7.29 (m, 2H), 7.22-7.19 (m, 3H), 3.52 (t, *J* = 6.4 Hz, 2H), 3.28 (app septet, likely tt, *J* = 3.0, 6.0 Hz, 1H), 2.70 (t, *J* = 7.7 Hz, 2H), 1.94-1.87 (m, 2H), 0.61-0.57 (m, 2H), 0.49-0.45 (m, 2H). ^{13}C NMR: 141.9, 128.4, 128.3, 125.8, 69.7, 53.0, 32.4, 31.2, 5.5; HRMS: (TOF-MS EI^+), calcd for $C_{12}H_{16}O$ (M^+) 176.1201 found 176.1199; IR (neat): 3031, 2938, 2850, 1452, 1342.

27) Decyloxycyclopropane: ksk12-11

By the general procedure described above, THP peroxide **9c** (129 mg, 0.5 mmol) was reacted with cyclopropyl magnesium bromide (1.3 ml 0.5 M nominal solution in THF, 0.65 mmol) to furnish cyclopropyl ether **27** as a colorless oil (79 mg, 80%). R_f = 0.56 (10% EA: Hex);

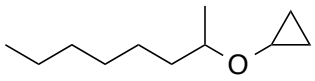


^{1}H NMR (700 MHz): 3.49 (t, *J* = 6.7 Hz, 2H), 3.26 (app septet, likely tt, *J* = 3.0, 6.0 Hz, 1H), 1.58-1.54 (m, 2H), 1.34-1.27 (m, 14H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.57-0.55 (m, 2H), 0.47-1.95 (m, 2H); ^{13}C NMR (176 MHz): 70.7, 52.9, 31.9, 29.68, 29.60, 29.57, 29.5,

29.3, 26.2, 22.7, 14.1, 5.4; HRMS: (TOF-MS CI$^+$), calcd for $C_{13}H_{27}O$ $(M+H)^+$ 199.2062 found 199.2057; IR (neat): 2922, 2853, 1453, 1343.

28) (Octane-2-yloxycyclopropane: (ksk12-12)

By the general procedure described above, THP peroxide **9d** (115 mg, 0.5 mmol) reacted with cyclopropyl magnesium bromide (1.3 ml 0.5 M nominal solution in THF, 0.65 mmol) to furnish cyclopropyl ether **28** as a colorless oil (60 mg, 70%). R_f = 0.6 (10% EA:Hex);

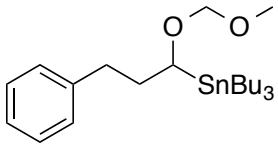


^{1}H NMR: 3.57-3.49 (m, 1H), 3.33-3.29 (m, 1H), 1.41-1.23 (m, 10H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.61-0.56 (m, 1H), 0.54-0.51 (m, 1H), 0.49-0.47 (m, 1H), 0.46-0.40 (m, 1H). ^{13}C NMR: 75.7, 50.7, 36.6, 31.8, 29.4, 25.4, 22.6, 19.9, 14.0, 5.96, 5.42; HRMS (TOF-MS EI$^+$): calcd for $C_{11}H_{22}O$ $(M)^+$ 170.1671 found 170.1678; IR (neat): 2927, 2857, 1452, 1373.

Section 6*: *mixed acetals (table-7)

29) Synthesis of Tributyl(1-(methoxymethoxy)-3-phenylpropyl)stannane: (CAS # 123294-00-8; ksk08-12 and 13)

Colorless Oil; Yield: 63% (598 mg) note: yield after 2 steps, from hydrocinnamaldehyde.



(Procedure modified from: JCS Perkin Trans-1; 1989, 1521).

Step-I: A solution of diisopropyl amine (1.1 eq.) in 5 mL dry THF was cooled to 0 °C and n-BuLi (2.2 mmol, 1.1 eq.) was added. The reaction was stirred for 10 minutes after

which was added Bu_3SnH (2 mmol, 1 eq.). The reaction was stirred for 15 minutes at 0 °C and then cooled to -78 °C, whereupon was added hydrocinnamaldehyde (268 mg, 2mmol) in 10 mL dry THF. After stirring at -78 °C for 5 minutes, the reaction was quenched with 10 mL saturated ammonium chloride at -78 °C, then warmed to room temperature. The separated organic layer was dried over $MgSO_4$ and concentrated (rotary evaporator followed by high vacuum).

Step-II: The residue from step-I was dissolved in 12 mL dry DCM and the solution cooled to -10 °C. Diisopropyl ethylamine (1.2 eq.) was added, followed by MOM chloride (1 eq.). The reaction was stirred for 7 hour at room temperature and then washed with water (10 ml). The separated organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was chromatographed on silica gel using 1% EA:Hex to afford a colorless liquid (63%, 598 mg).

1H NMR: 7.33-7.27 (m, 2H), 7.23-7.19 (m, 3H), 4.65 (d, J = 6.5 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 4.15-4.11 (m, 1H), 3.41 (s, 3H), 2.82-2.66 (m, 2H), 2.22-2.05 (m, 2H), 1.60-1.49 (m, 6H), 1.39-1.29 (m, 6H), 0.96-0.88 (m, 12H), 0.92 (t, J = 7.3 Hz, 3H); 13C NMR: 142.4, 128.4, 128.3, 125.7, 96.6, 73.7, 55.5, 37.4, 34.5, 29.2, 27.5, 13.7, 9.2.

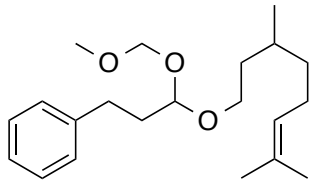
General Procedure for mixed acetals:

Stannane **29** (0.5 mmol) was dissolved in dry THF (3 mL) and the solution cooled to -78 C. A solution of n-BuLi (0.5 mmol) in hexane (1.6 M nominal) was added. After the reaction had stirred for 3 minutes, peroxide (0.5 mmol) was added and reaction stirred for additional 30 minutes at same temperature. The cold bath was removed and the reaction was allowed to warm to room temperature (about 30 minutes). The reaction was quenched with 1 mL of water and diluted with hexane (40 ml). The mixture was washed

with 10 ml water and the separated aqueous layer back extracted with 10 ml hexane. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography using ether:hexane (1-5%).

30) (3-((3,7-Dimethyloct-6-en-1-yl)oxy)-3-(methoxymethoxy)propyl)benzene (ksk08-15-fraction-3).

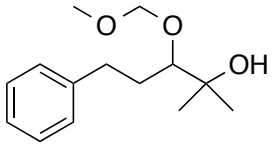
By the general procedure described above, peroxide **5** (244 mg, 0.5 mmol) was reacted with a solution generated from reaction of tributyl stannane **29** (235 mg, 0.5 mmol) and n-BuLi (0.31 ml, 1.6 M nominal solution in hexaene, 0.5 mmol) to furnish mixed acetal **30** as colorless oil (48 mg, 28%). R_f = 0.5 (5% EA: Hex), accompanied by tertiary alcohol **34** (23 mg, 43%) and acetal **35** (3 mg, 3%). Note: Approximately 10% (by NMR) acetal **35** accompanied with this mixed acetal.



^{1}H NMR: 7.32-7.27 (m, 2H), 7.23-7.19 (m, 3H), 5.12 (m, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.68-4.66 (m, 1H), 3.73-3.64 (m, 1H), 3.52-3.44 (m, 1H), 3.43 (s, 3H), 2.74 (m, 2H), 2.08-1.91 (m, 4H), 1.70 (s, 3H), 1.68-1.56 (m, 2H), 1.62 (s, 3H), 1.49-1.31 (m, 2H), 1.28-1.14 (m, 1H), 0.93-0.91 (m, 3H); ^{13}C NMR: 141.7, 131.2, 128.4, 128.4, 128.39, 125.8, 124.7, 101.5, 101.4, 93.3, 64.9, 64.8, 55.7, 37.2, 37.1, 36.8, 36.78, 36.39, 30.83, 29.5, 25.7, 25.5, 19.6, 19.5, 17.6; HRMS (TOF-ESI$^+$): Calcd for $C_{21}H_{34}O_3Na$ $(M+Na)^+$ 357.4898. Found 357.2401; IR (neat) cm^{-1}: 2927, 1454, 1369, 1002.

34) 3-(Methoxymethoxy)-2-methyl-5-phenylpentan-2-ol (ksk08-15, fraction-2):

R_f = 0.3 (15% EA:Hex)

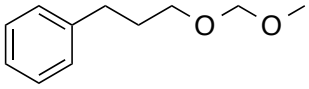


^{1}H NMR: 7.33-7.27 (m, 2H), 7.22-7.20 (m, 3H), 4.84 (d, *J* = 6.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 3.58 (s, 1H), 3.49 (s, 3H), 3.29 (m, 1H), 2.94-2.87 (m, 1H), 2.66-2.58 (m, 1H), 1.88-1.81 (m, 1H), 1.78-1.70 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H); ^{13}C NMR: 141.9, 128.5, 128.4, 125.9, 99.2, 89.9, 72.0, 56.0, 33.5, 32.7, 26.3, 23.7. HRMS (TOF-ESI$^+$): calcd for $C_{14}H_{22}O_3Na$ $(M+Na)^+$ 261.3162. Found 261.1483. IR (neat) cm^{-1}: 3461, 2930, 2889, 1028.

35) (3-(Methoxymethoxy)propyl)benzene (CAS # 91898-11-2, ksk08-22)

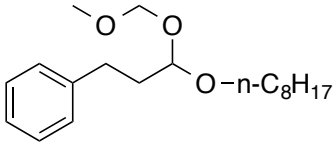
The reaction of peroxide **5** with the organolithium reagent derived from **29** also appeared to generate a small amount of byproduct that could not be separated from the desired ether. The reaction was therefore repeated except the reaction byproducts were subjected to treatment with ozone.

The mixture of **30** and **35** (44 mg) was dissolved in dry CH_2Cl_2 (2 ml) and a gas solution of O_3/O_2 (~2%, ~ 1 mmol O3/minute) was passed through the solution at room temperature until a pale blue color persisted. Ozonolysis was stopped and the reaction was purged with N_2. The reaction mixture was concentrated and purified by silica gel column using hexane and ethyl acetate (2%) to furnish MOM ether **35** as colorless liquid (3 mg, ~3%); R_f = 0.5 (20% EA: Hex).



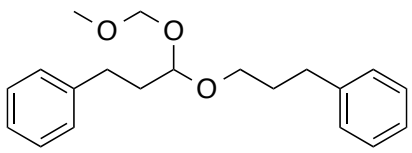
^{1}H NMR: 7.33-7.28 (m, 2H), 7.23-7.18 (m, 3H), 4.66 (s, 3H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.39 (s, 3H), 2.73 (t, *J* = 7.8 Hz, 2H), 1.99-1.89 (m, 2H); ^{13}C NMR: 141.9, 128.4, 128.3, 125.8, 96.5, 67.1, 55.2, 32.4, 31.4.

31) (3-(methoxymethoxy)-3-(octyloxy)propyl)benzene (ksk-08-28) was synthesized from stannane **29**, peroxide **42** using the general procedure described above as a colorless Oil; Yield: 57% (88 mg); R_f = 0.36 (10% EtOAc: Hexane). In this reaction, 10% unreacted peroxide **42** was recovered.



^{1}H NMR: 7.32-7.27 (m, 2H), 7.24-7.19 (m, 3H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.70-4.66 (m, 1H), 3.68-3.63 (m, 1H), 3.47-3.40 (m, 1H), 3.43 (s, 3H), 2.71-2.72 (m, 2H), 2.04-1.98 (m, 2H), 1.64-1.57 (m, 2H), 1.40-1.30 (m, 10H), 0.91 (t, *J* = 6.7Hz, 3H); ^{13}C NMR: 141.7, 128.4, 125.8, 101.4, 93.3, 66.7, 55.7, 36.4, 31.8, 30.8, 29.8, 29.4, 29.2, 26.2, 22.6, 14.1; HRMS (ESI+ TOF): Calcd for $C_{19}H_{32}O_3$ $(M+Na)^+$ 331.4512. found 331.2265; IR (neat): 2925, 2855, 1149, 1002.

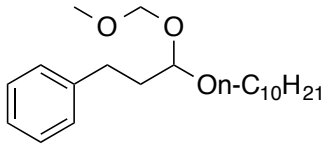
32) (3-(methoxymethoxy)-3-(3-phenylpropoxy)propyl)benzene (ksk11-19) was synthesized from **43** using the general procedure described above except that 0.2 equiv excess of tributylstannane **29** and n-BuLi were used. Colorless Oil; Yield: 55% (86 mg); R_f = 0.43 (10% EtOAc:Hexane).



^{1}H NMR: 7.35-7.31 (m, 4H), 7.28-7.21 (m, 6H), 4.85 (d, , J = 6.6 Hz, 1H), 4.73 (d, , J = 6.6 Hz, 1H), 4.72-4.70 (m, 1H), 3.74-3.69 (m, 1H), 3.51-3.47 (m, 1H), 3.44 (s, 3H), 2.81-2.74 (m, 4H), 2.08-2.02 (m, 2H), 2.00-1.93 (m, 2H); ^{13}C NMR: 141.88, 141.7, 128.5, 128.49, 128.45, 128.42, 128.39, 125.9, 125.8, 101.6, 93.5, 65.8, 55.8, 36.4, 32.4, 31.4, 30.8; HRMS (TOF MS ES+): Calcd for $C_{20}H_{26}NaO_3$ $(M+Na)^+$ 337.1780, Found 337.1775. IR (neat): 2927, 1453, 1122, 1000, 697.

33) (3-(Decyloxy)-3-(methoxymethoxy)propyl)benzene (ksk12-26):

was synthesized from stannane **29**, peroxide **9c** using the general procedure described above. Colorless Oil; Yield: 53% (89 mg); R_f = 0.40 (10% EtOAc:Hexane).



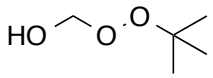
^{1}H NMR: 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 4.82-4.80 (m, 1H), 4.69-4.63 (m, 2H), 3.66-3.60 (m, 1H), 3.40 (s, 3H), 2.74-2.70 (m, 2H), 2.05-1.95 (m, 2H), 1.60-1.54 (m, 2H), 1.38-1.27 (m, 15H), 0.88 (t, J = 6.80 Hz, 3H); ^{13}C NMR: 141.9, 128.4, 125.9, 101.5, 93.4, 66.9, 55.8, 36.4, 32.0, 30.9, 29.9, 29.7, 29.6, 29.5, 29.4, 26.3, 22.7, 14.2. HRMS (TOF MS ES+): Calcd for $C_{21}H_{36}NaO_3$ $(M+Na)^+$ 359.2562, found 359.2578. IR (neat): 2925, 2856, 1149, 1000

Section-5.2: 1,3-dioxetanes

36) (tert-Butylperoxy)methanol (CAS # 17742-78-8, ksk09-32)

In a 25 mL single neck round bottom flask, 37% aq. formaldehyde (10 mmol, 0.81 ml) and 70% aq. t-BuOOH (10 mmol, 1.1 ml) were dissolved in 4 mL ether. The reaction was stirred at room temperature for 40 hours, then diluted with ether (50 mL) and washed

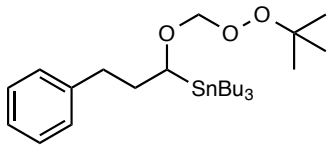
with water (10 ml x 2). The separated organic layer was dried over Na_2SO_4 and concentrated on rotary evaporator. The residue was purified by silica gel chromatography (CH_2Cl_2 eluent) to furnish a colorless oil; Yield; 54% (709 mg); R_f = 0.5 (25% EA: Hex).



^{1}H NMR: 5.08 (s, 2H), 3.25 (bs, 1H) 1.27 (s, 9H); ^{13}C NMR: 92.2, 80.8, 26.4.

38) Tributyl(1-((tert-butylperoxy)methoxy)-3-phenylpropyl)stannane (ksk11-08, 09 and **12):**

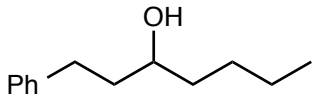
To a 0 °C solution of MOM acetal **29** (1 mmol) in dry CH_2Cl_2 (10 mL) was added BF_3•Et_2O (1 mmol) followed by t-BuOOH. The ice bath was removed and the reaction was allowed to stir for 2 hours. The reaction was then diluted with 30 mL CH_2Cl_2, and the mixture washed with 20 ml water. The separated organic layer was dried over sodium sulfate and concentrated on rotary evaporator. The residue was purified by silica gel column using 2% CH_2Cl_2: Hexane solution containing 0.1% MeOH to afford the peroxide **38** as a colorless oil in 40% yield (211 mg); R_f = 0.35 (5% EA: Hex).



^{1}H NMR: 7.32-7.29 (m, 2H), 7.25-7.18 (m, 3H), 5.05 (d, *J* = 9.7 Hz, 1H), 4.97 (d, *J* = 9.70 Hz, 1H), 4.17-4.14 (m, 1H), 2.86-2.70 (m, 2H), 2.25-2.16 (m, 1H), 2.14-2.02 (m, 1H), 1.57-1.47 (m, 6H), 1.38-1.30 (m, 6H), 1.28 (s, 9H), 0.99-0.88 (m, 15H). ^{13}C NMR: 142.60, 128.5, 128.2, 125.6, 98.8, 80.4, 74.5, 37.5, 34.2, 29.2, 27.5, 26.4, 13.7, 9.2.

HRMS (TOF-MS-EI+): Calcd for $C_{26}H_{48}NaO_3$ $(M+Na)^+$ 551.2523, found 551.2504. IR (neat): 2955, 2922, 1454, 1095.

40) 1-Phenylheptan-3-ol (CAS # 19969-03-0, ksk11-10) was isolated from the reaction of **38** (264 mg, 0.5 mmol), with n-BuLi (0.31 ml, 1.6 M nominal solution in hexane, 0.5 mmol) as a colorless oil (25 mg, 26%); $R_f = 0.3$ (15% EA: Hex). Similar procedure as mixed acetal synthesis (**31-34**). Note: This byproduct was generated during efforts to synthesize a 1,3-dioxetane.



^{1}H NMR: 7.33-7.29 (m, 2H), 7.24-7.19 (m, 3H), 3.65 (bs, 1H), 2.86-2.79 (m, 1H), 2.73-2.66 (m, 1H), 1.87-1.71 (m, 2H), 1.56-1.41 (m, 4H), 1.38-1.28 (m, 3H), 0.93 (t, J = 7.1Hz, 3H). ^{13}C NMR: 142.2, 128.42, 128.40, 125.8, 71.4, 39.1, 37.3, 32.1, 27.8, 22.7, 14.0.

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