Article

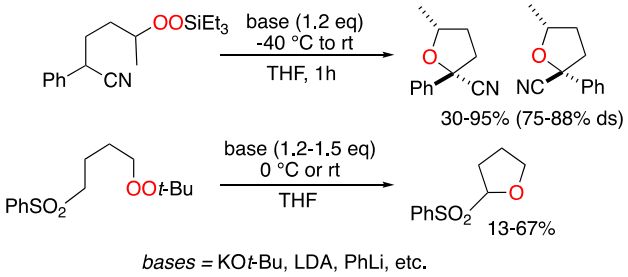
Synthesis of #-cyano and #-sulfonyl cyclic ethers via intramolecular reactions of peroxides with sulfone- and nitrile-stabilized carbanions

Alissa Horn, and Patrick H. Dussault

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02112 • Publication Date (Web): 08 Oct 2019

Synthesis of α-cyano and α-sulfonyl cyclic ethers via intramolecular reactions of peroxides with sulfone- and nitrile-stabilized carbanions

Alissa Horn and Patrick H. Dussault
Department of Chemistry
University of Nebraska-Lincoln
Lincoln, NE 68588-0304
pdussault1@unl.edu



ABSTRACT: The intramolecular reaction of carbon nucleophiles with oxygen-centered electrophiles has been little explored outside of nucleophilic epoxidation. We now report the synthesis of sulfonyl- and cyano-substituted oxacycles via intramolecular reaction of sulfone- and nitrile-stabilized carbanions with dialkyl peroxides, triethylsilyl/alkyl peroxides, and monoperoxyacetals. The cyclizations are successfully applied to synthesis of oxetanes, tetrahydrofurans, and tetrahydropyrans but fail for oxepanes. Cyclizations involving the relatively stabilized anion derived from a benzylic nitrile proceed in high yield for a variety of peroxides, including those in which the electrophilic oxygen is formally isobutyl or neopentyl. Corresponding cyclizations of an alkanenitrile are successful with both dialkyl and alkyl silyl peroxides but demonstrate much greater variability in yield. Reactions of sulfone-containing substrates are successful only with dialkyl peroxides. The success of reactions appears to be strongly influenced by the rate of peroxide decomposition, which appears to be highest for reactions involving poorly stabilized anions. The significant variation in diastereoselectivity observed for different classes of peroxide on a common framework suggests the possibility of substrate-dependent reaction mechanisms.

Introduction: Cyclic ethers are important structural elements in organic chemistry, and can be found at the core of molecules ranging from common solvents to complex natural products.[1] The majority of synthetic approaches to cyclic ethers are based upon reactions of nucleophilic oxygen with electrophilic carbon (Figure 1a-d). [2,3,4,5]

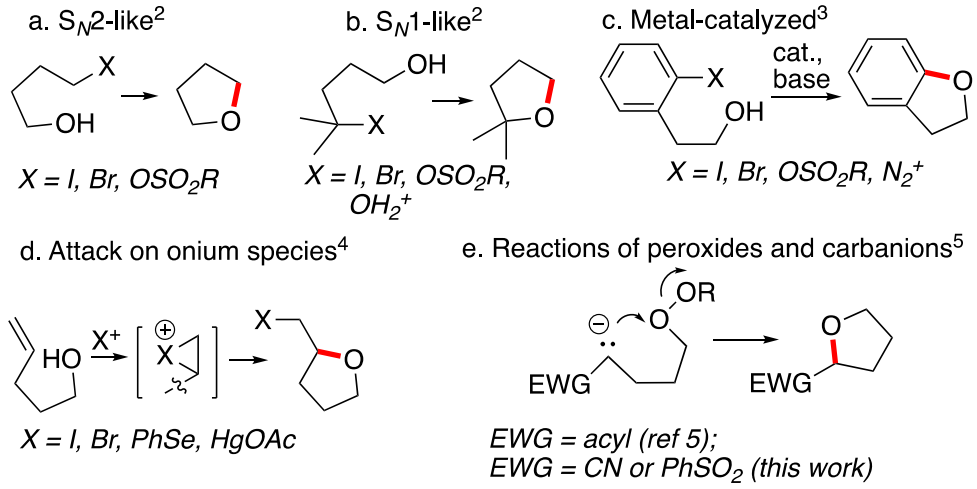
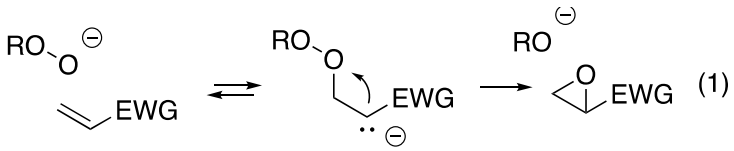


Figure 1: Selected approaches to intramolecular C-O bond formation

We recently described a synthesis of cyclic and spirocyclic ethers based upon intramolecular reaction of ketone enolates and dialkyl peroxides.[5] Extension of this chemistry to stabilized anions derived from nitriles and sulfones would provide a means of accessing the rich chemistry associated with these functional groups (Figure 1e).[6,7] However, while *inter*molecular reactions of nitrile- or sulfone-stabilized carbanions with simple oxygen electrophiles have been demonstrated,[8,9] the corresponding *intra*molecular reactions have not been reported outside of 3-*exo* closures during nucleophilic epoxidations (eq 1).[10,11,12] We now report a new approach to functionalized oxetanes, tetrahydrofurans, and tetrahydropyrans based upon intramolecular reactions of peroxides with metalated nitriles and sulfones.

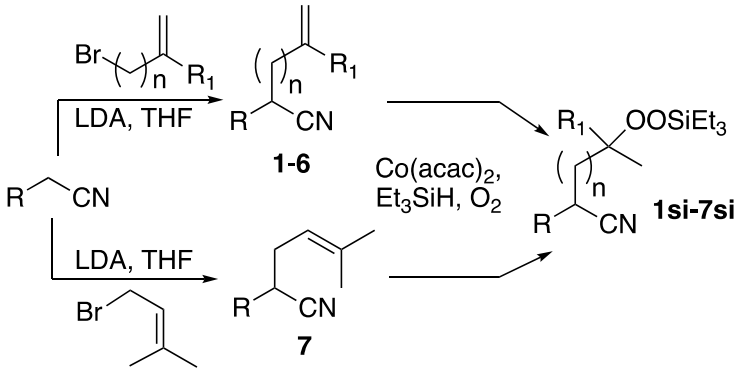


R = H, *t*-Bu; EWG = acyl, CN, SO_2Ph

Results: A series of secondary and tertiary peroxyalkylnitrile substrates were prepared via monoalkylation of phenylacetonitrile or octanenitrile with bromoalkenes, followed by reductive

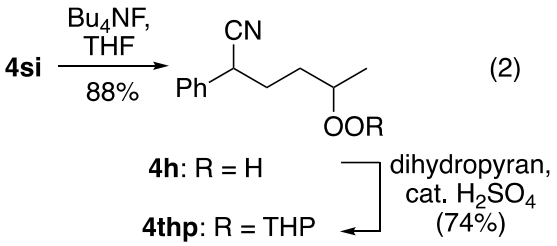
oxygenation in the presence of Co(II) and triethylsilane (Table 1).[13] Yields for the peroxidation were lower than those later observed with substrates lacking a nitrile group *(vide infra*).

Table 1. Syntheses of peroxy-substituted nitriles.



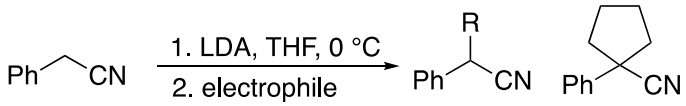
R	R_1	n	nitrile (%)	peroxide (%)
hexyl	H	2	**1** (97)	**1si** (41)
" "	CH_3	2	**2** (92)	**2si** (30)
Ph	H	1	**3** (98)	**3si** (35)
Ph	H	2	**4** (97)	**4si** (47)
Ph	H	3	**5** (98)	**5si** (41)
Ph	H	4	**6** (96)	**6si** (42)
Ph	CH_3	-	**7** (98)	**7si** (36)

Deprotection of silyl peroxide **4si** furnished hydroperoxide **4h** (eq 2), which was subjected to acid-promoted acetalization with dihydropyran to furnish monoperoxyacetal **4thp**.[14]

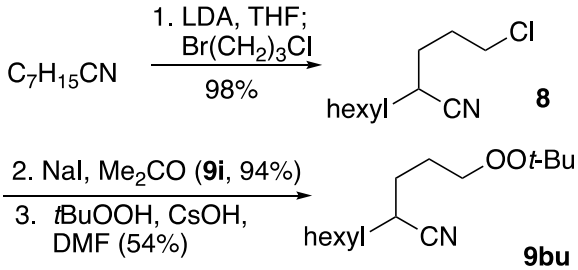


Preparation of the corresponding dialkyl peroxide substrates proved more challenging (Scheme 1). Although monoalkylation of phenylacetonitrile with 1,*n*-dihalides has been reported, we found that reaction with 1-bromo-4-chlorobutane furnished a mixture of the desired chloroalkylnitrile and a spirocyclopentane.[15,16] An alternative route based upon alkylation with 1-iodo-4-*t*-butylperoxybutane proceeded slowly and in low yield. The unexpectedly low reactivity of the iodoalkyl peroxide was confirmed by a competition reaction with 4-bromo-1-butene. In contrast, monoalkylation of octanenitrile with 1-chloro-3-bromopropane provided chloronitrile **8** in high

yield, offering a simple pathway, via the iodide **9i**, for synthesis of a dialkyl peroxide-substituted alkyl nitrile (**9bu**).

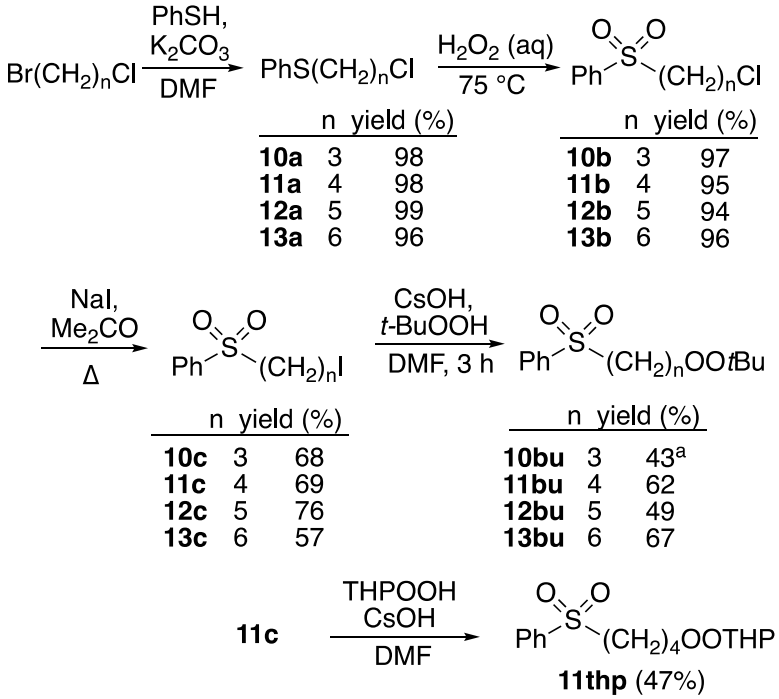


Electrophile(s)	R	yield	
n-BuI	Bu	98%	na
$Br(CH_2)_4Cl$	$(CH_2)_4Cl$	49%	42%
$I(CH_2)_4OOt$-Bu	$(CH_2)_4OOtBu$	23%[a]	na
$I(CH_2)_4OOt$-Bu + 4–Br-1-butene	$(CH_2)_2CH=CH_2$	92%	na



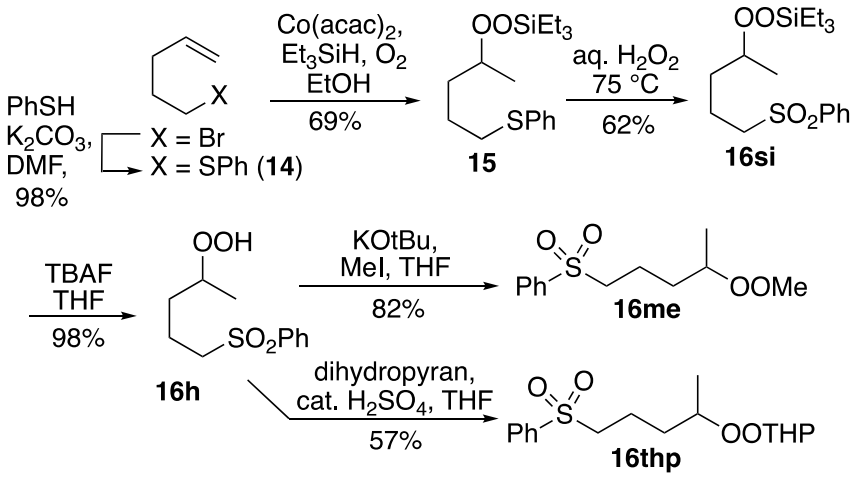
Scheme 1. Approaches to alkylperoxy nitriles.
[a] approx. 50% recovered iodoperoxide

Clean alkylation of lithiated methyl phenyl sulfone with a 1,3-diodide or a 4-iodoperoxide also proved unsuccessful despite precedent for similar reactions.[17] A series of *t*-butyl/primary alkyl peroxysulfones was instead prepared using the sequence shown in Scheme 2. Monoalkylation of thiophenol with 1,*n*-chlorobromides furnished thioethers **10a**-**13a**. Oxidation of the thioethers to generate sulfones **10b**-**13b** was followed by Finkelstein exchange to generate iodosulfones **10c**-**13c.** Alkylation of *t*-butyl hydroperoxide with the iodosulfones furnished the corresponding peroxysulfones, **10bu-13bu**. Reaction of iodide **11c** with 2-tetrahydropyranyl hydroperoxide, generated from dihydropyran,[18] generated peroxyacetal **11thp** (Scheme 2). The reaction of **10c** to furnish peroxide **10bu** was accompanied by spiroalkylation to form a cyclopropyl sulfone (not shown).



Scheme 2. Synthesis of *t*-butylperoxyalkyl sulfones.
[a]$PhSO_2$*cyclo*C_3H_5 also formed (46%)

Preparation of a series of secondary peroxides on a common sulfone framework is illustrated in Scheme 3. Alkylation of thiophenol with 5-bromo-1-pentene generated the unsaturated thioether **14**, which underwent Co(II)-promoted oxygenation in the presence of triethylsilane to produce triethylsilyl peroxide **15**; this appears to be the first application of Mukaiyama/Nojima peroxidation in the presence of a thioether.[13,19] Oxidation of the thioether with neat hydrogen peroxide furnished sulfone **16si**. Fluoride-mediated desilylation furnished hydroperoxide **16h**, which underwent methylation to furnish **16me** or acetalization to produce monoperoxyacetal **16thp**.

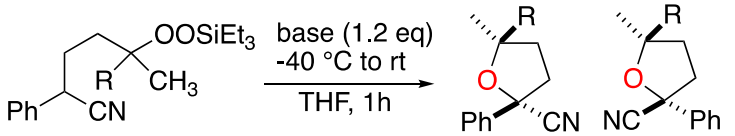


Scheme 3. Synthesis of secondary peroxyalkylsulfones.

Reactivity of nitriles

Table 2 illustrates base-promoted reactions of substrates combining a benzylic nitrile and 2° or 3° trialkylsilyl peroxides. The secondary peroxide (**4si**) underwent cyclization in good and sometimes excellent yields to form tetrahydrofurans **17** with moderate selectivity for generation of the diastereomer (**17a**) possessing a *trans* relationship of the C_2 phenyl and C_5 methyl (*vide infra*); the only reagent that was unsuccessful was a phosphazene "superbase". Encouragingly, fragmentation of the peroxide to the ketone (Kornblum-De la Mare reaction) was not observed in any of these reactions.[20] Cyclizations of the corresponding tertiary peroxide (**7si**) were also successful, generating the tertiary/tertiary ether **18** in yields only slightly lower yields than observed with **4si**.

Table 2. Influence of base on a selected cyclization



4si R = H (S,R*) **17a** (R,R*) **17b**

7si R = Me **18**

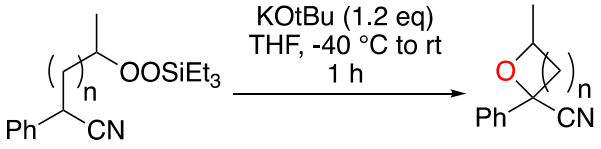
subs	R	base	product (% yield)	*S,R*/ R,R**
4si	H	KO*t*Bu	**17** (95)	8:1
4si	H	KDA	**17** (93)	6.5:1
4si	H	KH	**17** (91)	6:1
4si	H	LDA	**17** (72)	3.5:1
4si	H	*n*-BuLi	**17** (83)	3:1
4si	H	PhLi	**17** (30)	3.1:1

4si	H	NaH	**17** (94)	4.7:1
4si	H	BTPP*	nr	na
7si	Me	KO*t*Bu	**18** (75)	na
7si	Me	KDA	**18** (71)	na
7si	Me	KH	**18** (59)	na
7si	Me	LDA	**18** (57)	na
7si	Me	*n*-BuLi	**18** (67)	na
7si	Me	PhLi	**18** (25)	na
7si	Me	NaH	**18** (21)	na

* *tert*-butylimino-tri(pyrrolidino)phosphorane

Table 3 compares the application of a common set of cyclizations across a homologous series of secondary triethylsilyl peroxides. Cyclizations to form the oxetane **(19**), tetrahydrofuran (**17**) and tetrahydropyran (**20**) all proceeded at similar rates, but with major differences in yields. In each case, one diastereomer predominated (^{1}H NMR). Cyclization of **6si** to form an oxepane was unsuccessful, generating a mixture of recovered starting materials and byproducts (TLC).

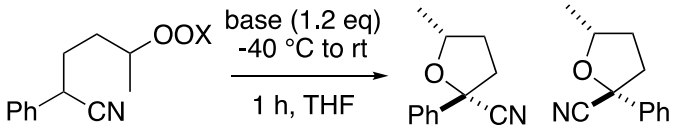
Table 3. Cyclization yields vs. ring size.



subs	n	ring size	product (% yield)
3si	1	4	**19** (58)
4si	2	5	**17** (95)
5si	3	6	**20** (37)
6si	4	7	nr (62% recov **6i**)

We next explored the influence of the peroxide group on cyclizations generating a common tetrahydrofuran (Table 4). Although superior yields were consistently obtained with the triethylsilyl peroxide (**4si**), cyclizations of the peroxyacetal (**4thp**) gave good yields under some conditions (KO*t*Bu, NaH). The few trials attempted using the free hydroperoxide (**4h**) gave poor yields. Interestingly, reactions of the silyl peroxide generally proceeded with moderate stereoselectivity while the corresponding reactions of the hydroperoxide and monoperoxyacetal proceeded with minimal diastereoselection.

Table 4. Influence of the class of peroxide on cyclization.



4si: X = $SiEt_3$
4h: X = H
4thp: X = THP

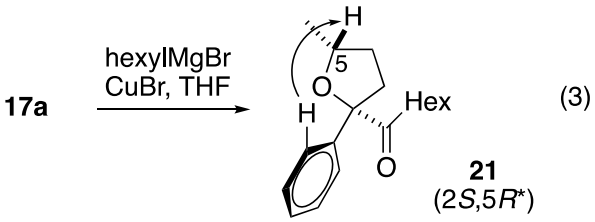
17a *(S,R*)*

17b *(R,R*)*

subs	base	yield (%)	**17a**/**17b**
4si		95	8:1
4h[a]	KO*t*Bu	15	1.5:1
4thp		85	1.1:1
4si		72	3.5:1
4h[a]	LDA	28	1.6:1
4thp		39	1.4:1
4si	*n*-BuLi	83	3:1
4thp		47	1.6:1
4si	KH	91	6:1
4thp		71	1.1:1
4si	NaH	94	4.7:1
4thp		78	1.2:1

[a]2.0 equiv of base

The configuration of the major diastereomer was assigned based upon observation of nOe enhancements between the *ortho* arene hydrogens and the tetrahydrofuranyl C_5-hydrogen in butyl ketone **21** (eq. 3). Addition details can be found in Table S1.

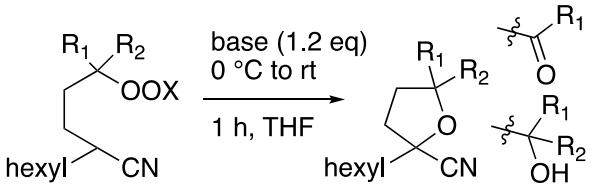


(3)

Analogous cyclizations of the alkyl-peroxide in the nitrile series proved to be strongly dependent upon choice of base (Table 5). The best yields, whether for reaction of a primary dialkyl peroxide (**9bu**), a secondary silyl peroxide (**1si**), or a tertiary alkyl/silyl peroxide (**2si**), were obtained using strong lithium bases. Use of KO*t*Bu produced fragmentation of the primary dialkyl and secondary alky/silyl peroxide substrates to form complex mixtures containing aldehydes and ketones.[20] Reactions of tertiary alkyl/silyl peroxides proceeded with remarkable

sensitivity to base: LDA gave the best yield yet seen, while use of KO*t*-Bu or KH resulted in complex product mixtures containing significant amounts (^{1}H NMR) of the tertiary alcohol. Interestingly, reactions of **1si** appeared to generate one major diastereomer.

Table 5. Cyclization of peroxy-substituted alkyl nitriles.



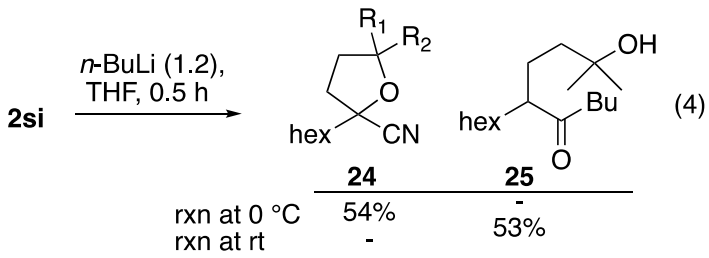
s. mat	X	R_1	R_2	prod
9bu	*t*-Bu	H	H	**22**
1si	$SiEt_3$	H	CH_3	**23**
2si	$SiEt_3$	CH_3	CH_3	**24**

subs	base	product (% yield)
9bu	KO*t*Bu	decomp[a]
9bu	KDA	decomp[a]
9bu	LDA	**22** (27)
9bu	*n*-BuLi	**22** (46)
9bu	PhLi	**22** (60)
1si	KO*t*-Bu	decomp[a]
1si	KDA	decomp[a]
1si	KH	decomp[a]
1si	LDA	**23** (67)
1si	*n*-BuLi	**23** (22)
1si	NaH	recov **1si** (82)
2si	KO*t*Bu	decomp[b]
2si	KH	decomp[b]
2si	LDA	**24** (85)
2si	*n*-BuLi	**24** (54)
2si	PhLi	**24** (29)
2si	NaH	recov **2si** (86)

[a]mixture including aldehyde or ketone;
[b]mixture including 3° alcohol

The reactions described in Table 5 were conducted by mixing substrate and base at 0 °C, followed by removal of the cooling bath. A seemingly minor change, addition of a hexane solution of *n*-BuLi into a room temperature solution of tertiary peroxide **2si** gave no cyclization

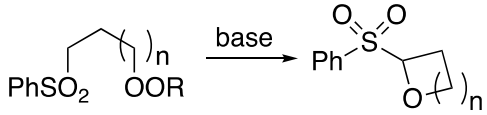
product; instead we observed the hydroxyketone (**25**) derived from cleavage of the peroxide and attack on the nitrile (eq 4).



(4)

Cyclizations of *t*-butyl peroxyalkylsulfones were successful in the case of 4-, 5- and 6-membered rings, but failed to generate an oxepane (Table 6). The cyclizations, which demonstrated a strong and seemingly substrate-specific base dependence, were generally slower than had been observed for the nitriles and significant amounts of starting materials were often recovered. Although the use of a slight excess of base gave improved yields, continued increase in base stoichiometry led to increased formation of decomposition products. Application of some of the successful cyclization conditions to monoperoxyacetal **11thp** resulted only in decomposition.

Table 6: Cyclizations of peroxy- and monoperoxyacetal-substituted sulfones.



10bu n = 1, R = *t*-Bu **26**
11bu n = 2, R = *t*-Bu **27**
11thp n = 2, R = THP -
12bu n = 3, R = *t*-Bu **28**
13bu n = 4, R = *t*-Bu -

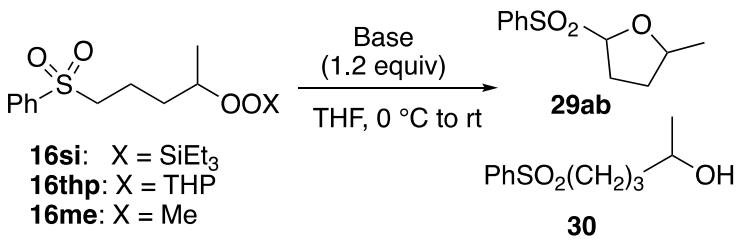
sub	base	eq.	T (°C)	t (h)	prod (%)	recov s. mat (%)
10bu	KO*t*Bu	1.5	rt	1	**26** (13)	43
		1.8	rt	2	(25)	40
10bu	PhLi	1.1	0	0.5	**26** (24)	32
		1.2	0	0.25	(29)	25
10bu	*n*-BuLi	1.2	0	1	**26** (41)	10
11bu	KO*t*Bu	1.5	rt	0.5	**27** (34)	-
		1.7	rt	1	(67)	-
11bu	PhLi	1.1	0	0.25	**27** (33)	-
		1.2	"	0.25	(22)	-
		1.6	"	0.17	(14)	-

11bu	*n*-BuLi	1.1	"	1	**27** (<1)	55
		1.5	"	"	(27)	31
		1.8	"	"	(33)	21
		2.2	"	"	dec	-
11bu	LDA	1.0	"	"	**27** (9)	45
		1.2	"	"	(21)	41
		1.5	"	"	(47)	33
11bu	LiHMDS	1.5	"	"	**27** (52)	11
11bu	KH	2.0	rt	3	-	79
11bu	NaH	2.0	rt	5	-	83
11thp	KO*t*Bu	1.6	rt	0.5	dec	-
11thp	PhLi	1.2	0	0.25	dec	-
11hp	*n*-BuLi	1.3	0	0.75	dec	-
12bu	KO*t*Bu	1.5	rt	1	**28** (9)	42
		1.5	66	"	(11)	32
		2.0	rt	"	**(**18)	37
12bu	PhLi	1.1	0	0.25	**28** (64)	24
12bu	*n*-BuLi	1.2	0	1	**28** (11)	31
		1.5	0	"	(44)	15
12bu	NaH	2.6	rt	3	-	77
12bu	CsOH	2.5	rt	3	-	81
13bu	PhLi	1.2	0		-	74[a]
13bu	*n*-BuLi	1.2	0		-	76[a]

a. Some decomp observed

Table 7 compares cyclizations of three different secondary peroxides on a common sulfone framework. All attempts to achieve closure from the triethylsilyl peroxide (**16si**) were unsuccessful, invariably generating the corresponding alcohol (**30**). Reaction of the monoperoxyacetal (**16thp**) generated a complex mixture of products. The dialkyl peroxide (**16me**) underwent successful cyclization in the presence of a number of bases, but yields were generally modest or poor. The reactions generated inseparable mixtures of diastereomers, with the same major product generated from reaction with KO*t*Bu (69:31) and PhLi (80:20). Changing the solvent had limited impact on reaction yield.

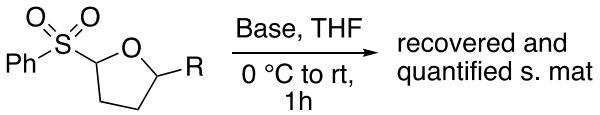
Table 7. Influence of peroxide electrophile



subs	base	eq.	T	t (h)	Prod (% yield)
16si	KO*t*Bu	1.5	rt	0.5	**30** (98)
16si	*n*-BuLi	1.2	0°C	0.5	**30** (97)
16si	LDA	1.5	0	1	**30** (94)
16si	KDA	1.5	rt	"	**30** (71)
16thp	KO*t*Bu	1.5	rt	0.5	decomp
16thp	*n*-BuLi	1.2	0°C	0.5	decomp
16me	KO*t*Bu	1.2	rt	1	**29** (13)
	"	1.5	"	"	**29** (33)
	CH_3CN	1.3	"	"	**29** (9)
	DMSO	1.3	"	"	**29** (7)
	DMF	1.4	"	"	**29** (10)
16me	PhLi	1.0	0°C	0.5	**29** (18)
		1.1	0°C	"	**29** (19)
		1.3		"	**29** (21)
16me	*n*-BuLi	1.0	0°C	0.5	**29** (10)
		1.2	0°C	0.5	**29** (37)
16me	LDA	1.5	0°C	1	**29** (48)
16me	KDA	1.2	0°C	2	decomp
16me	KH	2.0	rt	18	nr
16me	NaH	2.0	rt	18	nr

The reduction in yields seen at increased base stoichiometry led us to investigate the stability of alkoxysulfones **27** and **29** to typical cyclization conditions (Table 8). Both were rapidly degraded by phenyl lithium, which had proved effective as a base (Tables 6 and 7); **29** was recovered in good yield following treatment with excess KO*t*Bu.

Table 8. Stability of sulfonyl ether products.



27: R = H
29: R = Me

subs	base (equiv)	T	yield
27	PhLi (1.3)	0 °C	32%
29	KO*t*Bu(1.5)	rt	85%
"	PhLi (1.3)	0 °C	39%

Discussion:

Nitriles and sulfones are capable of a rich suite of transformations, including generation and functionalization of adjacent carbanions and used as precursors to other functional groups, radicals, and hydrocarbons.[6, 21,22,23] α-Alkoxy nitriles and α-Alkoxysulfones are both versatile classes of synthetic intermediates.[9, 24, 25 26] Cyanoethers have also been used as components in fluorescent probes [27] and the core of a class of anti-viral nucleoside analogs.[28]

Nitrile and sulfone stabilized anions have been applied to intermolecular reactions with a variety of heteroatom electrophiles, including some activated peroxides.[8, 29,30] Our results demonstrate that this class of anions undergoes intramolecular reaction with peroxides to generate functionalized oxetanes,[31] tetrahydrofurans,[32] and tetrahydropyrans.[33] However, as discussed in the following paragraphs, yields vary greatly depending upon substrates and conditions.

Nature of the peroxide: Subject to limitations discussed below in relation to peroxide decomposition, the reactions show no obvious dependence upon the nature of the peroxide. For example, ring closures involving the benzylic nitrile were rapid and high-yielding for nearly all peroxides tested, including one in which the electrophilic oxygen is effectively neopentyl. This is a significant departure from reactions with highly reactive organometallics such as *n*-BuLi or PhMgX, where reactivity of monoperoxyacetals > dialkyl peroxides >> alkyl trialkylsilyl peroxides.[14] However, the limited influence of the nature of the peroxide is consistent with the successful reaction of dialkyl peroxide intermediates during nucleophilic epoxidations and in cyclizations of peroxide-substituted ketone enolates.[5,10-12]

Peroxide stability. The rate of peroxide decomposition appears to play a major factor in the success or failure of the cyclizations. Base-promoted Kornblum fragmentation, an often exothermic analog of the E_1cb or E_2 reactions involving elimination across a H-C-O-O unit of peroxides,[20] requires a C–H bond alpha to the peroxide. The Kornblum reaction is also favored by a basic medium and/or activation of the peroxides by a conjugated electron-withdrawing

group.[34] In our experience, dialkyl peroxides and monoperoxyacetals are often relatively stable towards fragmentation.[14] In the current work, Kornblum fragmentation products were never observed in reactions of involving derivatives of benzyl nitrile (pKa ~22) but were observed for the more basic anions derived from the alkyl nitrile (pKa ~ 32); a similar phenomenon is discussed below for the phenylsulfones. The observation of moderate yields from a reaction of a silyl/tertiary alkyl peroxide (**2si**, see Table 5) may reflect in part the inability of this substrate to enter into Kornblum fragmentation. The corresponding reactions of alkyl nitriles were successful in at least some cases for both dialkyl peroxides and triethylsilyl peroxides. Cyclizations involving a sulfone-stabilized anion were successful only for dialkyl peroxides; as discussed below, the failure to successfully cyclize onto silyl peroxides or monoperoxyacetals may reflect less on the rate of cyclization than on the rate of peroxide decomposition. The formation of alcohol during reactions of some triethylsilyl peroxides with anions derived from an alkyl nitrile or phenylsulfones (pKa ~ 29) makes clear that a different class of fragmentation is open for these substrates. We note that analogous products have been reported from reactions of organometallics with a hindered alkyl silyl peroxide.[14]

Nucleophile reactivity and basicity: Cycloalkylation of nitriles bearing ω-halo or sulfonate groups has been shown to generate good yields of 4-, 5-, and 6-membered rings.[15] There are fewer reports describing comparable cyclizations of sulfones,[35] but 3-*exo* attack of sulfone-stabilized carbanions on sp^3 C-Cl or C-Br linkage to form cyclopropanes is known.[36] While there is obvious risk in evaluating the reaction of carbanions and peroxides using scales developed for carbon electrophiles, it is clear that the anions derived from benzylic nitriles are strong and highly polarizable nucleophiles,[37,38] whereas the anions derived from alkyl nitriles and alkyl sulfones are more localized and more basic.[39] However, the superior yields obtained with the benzyl nitriles may also reflect their greater acidity, which results in a less basic reaction medium and a higher effective concentration of nucleophile. Cyclizations of alkyl nitriles were successful in the presence of bases (*n*-BuLi, PhLi, LDA) capable of rapidly generating significant concentrations of the nitrile-stabilized carbanions; KO*t*Bu, one of the most effective bases with the benzyl nitriles, generated a mixture of recovered starting material and decomposition byproducts. Cyclizations of sulfones were successful with multiple bases, with some of the best yields coming from KO*t*Bu; however, this may relate to the stability of the sulfone products in the presence of this base.

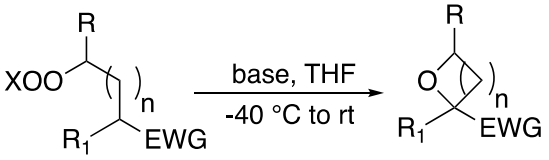
During reactions of the benzyl nitriles, we observed successful cyclization in the presence of different counterions (Table 2, Li, Na, or K), but no major differences in diastereoselection. This

is in contrast to reports describing base-dependent diastereoselection of carbocyclizations involving nitrile-stabilized anions.[39] Attempts to achieve cyclizations of sulfone-stabilized carbanions onto secondary alkyl silyl peroxides were unsuccessful regardless of base. The role of the counterion remains to some degree a mystery. In our earlier work with ketones, potassium enolates were found to be far more active than the corresponding sodium or lithium species. However, for some substrates (e.g., the cyclization of **10si**) all bases work well and there is almost no difference between KH or NaH. For other substrates, for example peroxyacetal **4thp**, KO*t*Bu is far more effective than either LDA or *n*-BuLi. Comparison of diastereoselection within a common framework (Table 2), makes clear that the nature of the base and counterion, while less impactful than the nature of the peroxide leaving group (Table 4), does have a discernible influence.

Steric influences: For the reactions of benzylic nitriles, the degree of substitution adjacent to the electrophilic oxygen has little influence on either reactivity or yields. In the alkyl nitrile series, superior yields were observed with a tertiary peroxide, perhaps as a consequence of removing a pathway for Kornblum fragmentation. Within the sulfone series, somewhat better yields were observed for reaction at a primary vs. secondary oxygen, although this may have also reflected different stabilities towards fragmentation.

Ring size: Cyclizations of peroxide-substituted benzyl nitriles successfully generated four- to six-membered oxacycles, with yields decreasing 5>4>6 (Table 9). Yields for cyclizations involving sulfone-stabilized anions with dialkyl peroxides followed a trend of 5 ~ 6 > 4; different bases were optimal in each case. Cyclizations to form seven-membered rings were not successful in either series, again consistent with results from ketone enolates.[5]

Table 9. Relative yields of ring closures in nitrile and sulfones



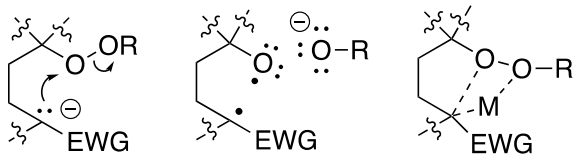
EWG	n	R	R_1	X	base	yield
CN	1	Me	Ph	$SiEt_3$	KO*t*Bu	58%
CN	2	Me	Ph	$SiEt_3$	KO*t*Bu	95%
CN	3	Me	Ph	$SiEt_3$	KO*t*Bu	37%
CN	4	Me	Ph	$SiEt_3$	KO*t*Bu	nr
SO_2Ph	1	H	H	*t*-Bu	*n*-BuLi	41%
SO_2Ph	2	H	H	*t*-Bu	KO*t*Bu	67%
SO_2Ph	3	H	H	*t*-Bu	PhLi	64%

SO_2Ph	4	H	H	*t*-Bu	PhLi	nr

Stability of the reaction products: Evaluation of the relative efficiency of cyclization in the sulfone series is complicated by decomposition of the products in the presence of an organolithium reagent, an unreported variant of a known transformation.[26] The only example of similar decomposition in the nitrile series (equation 4) involves the use of a strong nucleophile (*n*-BuLi) under conditions in which intermolecular attack by the reagent appears to compete with deprotonation of the substrate.

Mechanism: Several pathways can be envisaged for intramolecular reactions of peroxides with carbanions (Figure 2). Early work on cleavage of a series of dialkyl peroxides with organometallics displayed trends consistent with S_N2-type pathways,[14] and the 3-*exo* closure of 3-peroxy-2-enols/enolates during nucleophilic epoxidation has been described as a low-barrier substitution.[40] However, a direct displacement is not consistent with the high yields observed for attack of a nitrile-stabilized anion on the isobutyl and neopentyl-like oxygen atoms of secondary and tertiary peroxides. Reactions of organometallic reagents with peroxides have often been interpreted in terms of intermediate alkoxy radicals derived through single-electron transfer (SET).[41] Earlier work in our lab on intermolecular reactions of organolithium and -magnesium reagents with dialkyl and alkyl silyl peroxides incorporating alkoxy radical "clocks" gave some evidence for SET processes; whereas reactions of more reactive THP monoperoxyacetals appeared to involve direct insertion.[14]

Figure 2. Possible mechanisms/intermediates

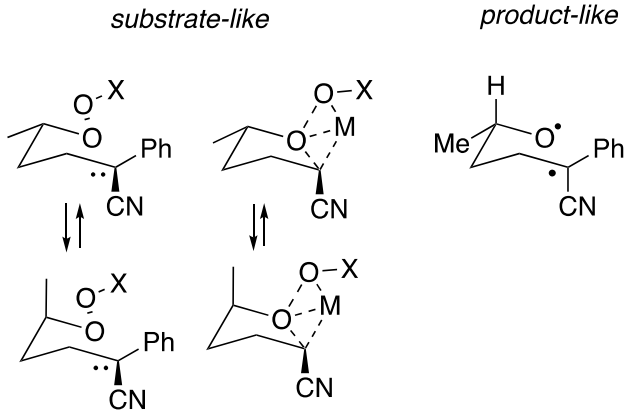


S_N2-like *SET* *insertion*

Our results, and in particular, the observation of peroxide-dependent diastereoselection, suggests the possibility of multiple mechanisms. Although the data on conformational preferences in 2,2,5-trisubstituted tetrahydrofurans is limited,[42] there is evidence that the major diastereomer observed in our reactions is also the thermodynamically favored product, placing the C_5-methyl group *trans* to the C_2-phenyl and *cis* to the C_2 nitrile. The contrast between the moderate diastereoselection observed during cyclizations of triethylsilyl peroxides and the

minimal diastereoselection observed during reactions of the more reactive acetals or peroxyanions, may support reactions of the silyl peroxides via SET and a product-like diradical intermediate, whereas the more reactive peroxyanion and peroxyacetal substrates might react through an early transition state involving an S_N2 or insertion (Figure 3).[14,43] Similar levels of diastereoselection were observed in the sulfone series, but we were not able to assign the relative stereochemistry.

Figure 3. Possible intermediates and products



Dampening effect of peroxide: We were surprised by the unexpectedly low intermolecular reactivity of electrophiles attached to a peroxide-containing alkyl chain. For example, 4-iodoalkyl *t*-butyl peroxide, a substrate we had employed in tandem C-C/C-O bond-forming reaction,[5] is poorly reactive towards a deprotonated nitrile and fails to react with lithiated phenyl methyl sulfone. The reduced rate of nucleophilic substitution on carbons adjacent to sigma electron-withdrawing groups is well-known (e.g. trifluoroethyl);[44] however we are unaware when this effect has been observed across a three- or four-methylene span.

Conclusion:

Intramolecular reactions of peroxides with nitrile- and sulfone-stabilized carbanions offer a new approach to a range of functionalized oxacycles, including oxetanes, tetrahydrofurans, and tetrahydropyrans. The cyclizations, which can be conducted using several different classes of peroxide, enable synthesis of secondary or tertiary ether linkages. Key factors in the success of the reaction are the basicity of the reagents required and the propensity of the peroxide towards decomposition. The nature of the substituent on the departing peroxide oxygen also appears to strongly influence the reaction mechanism.

Experimental:

General Methods: All reagents and solvents were used as purchased except for DMF, which was distilled from CaH_2 at reduced pressure, and THF, which was distilled from Na/benzophenone. Except as noted, all reactions were conducted under an atmosphere of N_2 in flame-dried glassware. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica plates visualized with a UV lamp or by developing with one of the following dips: 2.5% ammonium molybdate and 0.5% ceric sulfate in 10% aqueous sulfuric acid (general stain, after heating); 1% potassium permanganate in water (general stain, heating sometimes required); 1% *N,N*-dimethyl-*p*-phenylenediamine in 1:20:100 acetic acid/ water/ methanol (hydroperoxides give a color change upon contact; other peroxides can be visualized after heating);[45] or a solution composed of 3 g of vanillin and 3 mL sulfuric acid in 97 mL ethanol (general stain requiring heating). Unless otherwise described, column chromatography refers to flash column chromatography on silica gel. Unless noted, ^{1}H NMR and ^{13}C NMR spectra were acquired in $CDCl_3$. Chemical shifts are reported relative to residual chloroform (7.26/77.16 ppm). ^{1}H spectra are reported as chemical shift (multiplicity, J couplings in, number of protons). IR spectra were recorded as neat films on a ZrSe crystal; selected absorbances are reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained at the Nebraska Center for Mass Spectrometry at UNL. Melting points are uncorrected. Abbreviations: hexane = Hex; THF = tetrahydrofuran; EtOH = ethanol; DCM = dichloromethane; EA = ethyl acetate; *n*-BuLi = *n*-butyl lithium; KO*t*Bu = potassium *tert*-butoxide; LDA = lithium diisopropyl amide; LHMDS = lithium hexamethyldisilazide; TBAF = tetra-*n*-butylammonium fluoride; sat = saturated.

Preparation of LDA (example: actual scale varies): To a solution of diisopropylamine (5.90 mL, 42.1 mmol, 1.0 equiv) in THF 100 mL was added *n*-BuLi (26.0 mL, 41.6 mmol, 1.0 equiv, 1.6 M

in hexanes) at -78 °C. The resulting solution, nominally, 0.33 M in LDA was stirred for 30 min at -78 °C and immediately used.

Nitrile alkylation was based upon an adaptation of a reported procedure.[15a] To a solution of benzyl cyanide (4.0 mL, 35 mmol) in THF (50 mL) was added freshly prepared LDA (42 mmol, 1.2 equiv), followed by bromoalkene (41.6 mmol, 1.2 equiv). After stirring for 1 h, the reaction was quenched with sat. aq. NH_4Cl (50 mL) and the resulting mixture extracted with DCM (50 mL x 3). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (typically 5% EA/Hex).

2-(But-3-en-1-yl)octanenitrile (1) was prepared as a yellow-orange oil (4.52 g, 97%) from octanenitrile (4.0 mL, 25.9 mmol) and 4-bromobutene (3.17 mL, 31.2 mmol, 1.2 equiv) using the nitrile alkylation procedure described above: R_f = 0.53 (10% EA/Hex); ^1H (400 MHz) δ 5.77 (dddd, J = 6.6, 10.1, 13.3, 16.7, 1H), 5.09 (d, J = 17.1, 1H), 5.04 (d, J = 11.0, 1H), 2.54 (ddd, J = 4.9, 9.3, 14.0, 1H), 2.31 (m, 1H), 2.19 (m, 1H), 1.50-1.68 (4H), 1.21-1.38 (8H), 0.89 (t, J = 6.6, 3H); $^{13}C\{^1H\}$ (100 MHz) δ 136.6, 122.3, 116.4, 32.3, 31.6, 31.5, 31.3, 31.1, 28.9, 2.2, 22.6, 14.1; IR: 2928, 2859, 2237, 1642, 1456, 1379, 994, 914, 724, 647, 554 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{12}H_{21}NNa$ $(M + Na)^+$: 202.1572; found: 202.1575.

2-(3-Methylbut-3-en-1-yl)octanenitrile (**2)** was prepared as a light yellow/orange oil (4.63 g, 92%) from octanenitrile (4.0 mL, 26.0 mmol) and 4-iodo-2-methylbutene (5.61 g, 28.6 mmol, 1.1 equiv) using the general procedure described above: R_f = 0.55 (10% EA/Hex); ^1H (400 MHz) δ 4.78 (s, 1H), 4.73 (s, 1H), 2.52 (ddd, J = 5.2, 9.0, 14.1, 1H), 2.18 (m, 2H), 1.73 (s, 3H), 1.49-1.64 (4H), 1.24-1.38 (8H), 0.89 (t, J = 7.0, 3H); $^{13}C\{^1H\}$ (100 MHz) δ 143.7, 122.2, 111.3, 35.1, 32.2, 31.5, 31.1, 30.3, 28.8, 27.1, 22.5, 22.2, 14.0; IR: 2928, 2858, 2238, 1650, 1456, 1377, 889, 724 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{13}H_{23}NNa$ $(M + Na)^+$: 216.1728; found: 216.1733.

2-Phenylpent-4-enenitrile (3) was prepared (5.35 g, 98%) from 3-bromo-1-propene (41.6 mmol, 5.03 g) by the procedure described above. Spectral details matched those previously reported:[46] R_f = 0.45 (10% EA/Hex); ^{1}H (400 MHz) δ 7.29-7.42 (m, 5H), 5.83 (m, 1H), 5.23 (m, 1H), 5.20 (m, 1H), 3.86 (t, J = 7.2, 1H), 2.67 (m, 2H); ^{13}C{^{1}H} (100 MHz) δ 135.3, 132.7, 129.2, 128.3, 127.5, 120.4, 119.5, 40.0, 37.7.

2-Phenylhex-5-enenitrile (4) was prepared (5.74 g, 97%) from 4-bromo-1-butene (41.6 mmol, 5.62 g) by the procedure described above. Spectral details matched those previously reported:[47] R_f = 0.46 (10% EA/Hex); ^{1}H (400 MHz_3) δ 7.31-7.41 (m, 5H), 5.78 (ddt, J = 6.7, 10.2, 17.0, 1H), 5.09 (m, 2H), 3.81 (dd, J = 6.3, 8.6, 1H), 2.25 (q, J = 7.1, 2H), 2.00 (m, 2H); ^{13}C{^{1}H} (100 MHz) δ 136.1, 135.8, 129.1, 128.1, 127.3, 120.7, 116.7, 36.5, 34.9, 30.9

2-Phenylhept-6-enenitrile (5) was prepared (6.28 g, 98%) from 5-bromo-1-pentene (41.6 mmol, 6.20 g) by the procedure described above: R_f = 0.48 (10% EA/Hex); ^{1}H (400 MHz) δ 7.30-7.40 (m, 5H), 5.78 (m, 1H), 5.02 (m, 2H), 3.78 (dd, J = 6.4, 8.4, 1H), 2.13 (app q, J = 7.2, 2H), 1.93 (m, 2H), 1.61 (m, 2H); ^{13}C{^{1}H} (100 MHz) δ 137.7, 136.0, 129.2, 128.2, 127.3, 120.9, 115.6, 37.4, 35.3, 33.0, 26.2; IR: 3065, 2930, 2861, 2239, 1640, 1495, 1455, 994, 911, 755, 698, 519 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{13}H_{15}NNa$ $(M + Na)^+$: 208.1102; found: 208.1102.

2-Phenyloct-7-enenitrile (6) was prepared (6.64 g, 96%) from 6-bromo-1-hexene (41.6 mmol, 6.78 g) by the procedure described above: R_f = 0.49 (10% EA/Hex); ^{1}H (400 MHz) δ 7.30-7.40 (m, 5H), 5.80 (m, 1H), 4.89-5.02 (m, 2H), 3.77 (dd, J = 6.4, 8.4, 1H), 2.08 (app q, J = 6.7, 2H), 1.93 (m, 2H), 1.27-1.59 (4H); ^{13}C{^{1}H} (100 MHz) δ 138.4, 136.1, 129.2, 128.1, 127.3, 121.0, 115.0, 37.5, 35.9, 33.5, 28.3, 26.6; IR: 3065, 2930, 2861, 2239, 1640, 1495, 994, 911, 755, 698, 519; HRMS (ESI$^+$, TOF) calcd for $C_{14}H_{17}NNa$ $(M + Na)^+$: 222.1259; found: 222.1266.

5-Methyl-2-phenylhex-5-enenitrile (7) was prepared as a light yellow oil (6.30 g, 98%) from benzyl cyanide (4.0 mL, 34.7 mmol) and 1-bromo-3-methyl-2-butene (38.1 mmol, 1.1 equiv) using the general procedure for alkylation: R_f = 0.50 (10% EA/Hex); ^{1}H (400 MHz) δ 7.29-7.41 (m, 5H), 5.21 (t, J= 7.4, 1H), 3.79 (t, J = 7.1, 1H), 2.64 (m, 2H), 1.75 (s, 3H), 1.69 (s, 3H); ^{13}C{^{1}H} (100 MHz) δ 136.8, 135.8, 129.1, 128.1, 127.5, 120.9, 118.6, 38.0, 34.6, 25.9, 18.0; IR: 2971, 2915, 2240, 1673, 1600, 1497, 1454, 1378, 844, 755, 697, 515 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{13}H_{15}NNa$ (M + Na)$^+$: 208.1102; found 208.1104.

Reductive deoxygenation to form triethylsilylperoxides: The reductive dioxygenation of alkenes to generate the corresponding triethylsilyl peroxides was adapted from reported procedures.[13ab] To a solution of alkene (10.0 mmol) in EtOH (80 mL) was added triethylsilane (20.0 mmol, 2 equiv), followed by $Co(acac)_2$ (1.0 mmol, 0.1 equiv). The reaction was stirred at room temperature under O_2 (1 atm, balloon) for 18 hrs. The reaction solution was concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield a colorless oil.

2-(3-((Triethylsilyl)peroxy)butyl)octanenitrile (1si) was prepared as an inseparable 1:1 mixture of diastereomers (1.67 g, 41%) from nitrile **1** (2.22 g, 12.4 mmol) using the procedure described above. The product was a colorless oil: R_f = 0.56 (10% EA/Hex); ^{1}H (400 MHz) δ 4.03-4.11 (m, 2H), 2.51-2.62 (m, 2H), 1.51-1.76 (14H), 1.41-1.49 (m, 2H), 1.26-1.40 (m, 12H), 1.22-1.25 (m, 6H), 0.98-1.04 (m, 18H), 0.89-0.92 (m, 6H), 0.67-0.74 (m, 12H); ^{13}C{^{1}H} (100 MHz) δ 122.4, 122.3, 80.9, 80.2, 32.4, 32.3, 32.2, 32.0, 31.8, 31.7, 28.9, 28.7, 27.9, 27.2, 22.6, 18.6, 18.4, 14.1, 6.9, 3.9; IR: 2955, 2931, 2876, 2237, 1459, 1377, 1239, 1006, 795, 727 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{18}H_{37}NNaO_2Si$ (M + Na)$^+$: 350.2491; found: 350.2495.

2-(3-Methyl-3-((triethylsilyl)peroxy)butyl)octanenitrile (2si) was prepared as a colorless oil (1.05 g, 30%) from nitrile **2 (**2.0 g, 10 mmol) using the reductive dioxygenation procedure described above: R_f = 0.57 (10% EA/Hex); ^{1}H (400 MHz) δ 2.52 (m, 1H), 1.59-1.70 (m, 4H), 1.51-.159 (m, 2H), 1.23-1.38 (8H), 1.19 (s, 3H), 1.17 (s, 3H), 0.98 (t, J = 7.9, 9H), 0.89 (t, J = 6.9, 3H), 0.66 (q, J = 7.9, 6H); ^{13}C (100 MHz) δ 122.6, 81.6, 36.1, 32.4, 32.0, 31.7, 28.9, 27.2, 26.8, 24.8, 24.2, 22.6, 14.1, 6.9, 4.0**;** IR: 2955, 2932, 2876, 2237, 1458, 1413, 1379, 1364, 1239, 1006, 855, 804, 728 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{19}H_{39}NNaO_2Si$ $(M + Na)^+$: 364.2648; found: 364.2654.

(*R,R* and R*,S) 2-Phenyl-4-((triethylsilyl)peroxy)pentanenitrile (3si)** was prepared as a nearly inseparable 1:1 mixture of diastereomers (1.65 g, 35%) from 2-phenylpent-4-enenitrile (**3**, 15.4 mmol, 2.42 g) using the reductive dioxygenation procedure described above. The product was a colorless oil*:* R_f = 0.58 (10% EA/Hex); IR: 2956, 2913, 2877, 2241, 1456, 1375, 1239, 1005, 823, 793, 730, 697 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{17}H_{27}NNaO_2Si$ $(M + Na)^+$: 328.1709; found 328.1711. Individual peak assignments are based upon the isolation of a very small quantity of one diastereomer in pure form.

Diastereomer 1: ^{1}H (400 MHz) δ 7.37 (d, J = 6.5, 2H), 7.34 (t, J = 6.9, 2H), 7.32 (t, J = 6.9, 1H), 4.02 (t, J = 6.8, 1H), 3.96 (m, 1H), 2.44 (ddd, J = 6.7, 7.5, 14.2, 2H), 1.98 (ddd, J =4.8, 8.6, 13.5, 1H), 1.24 (d, J = 6.3, 3H), 1.00 (t, J = 8.0, 9H), 0.71 (q, J = 8.1, 6H) ^{13}C{^{1}H} (100 MHz) δ 135.7, 129.2, 128.3, 127.8, 121.4, 78.5, 40.2, 33.2, 18.4, 6.8, 3.9.

Diastereomer 2: ^{1}H (400 MHz) δ 7.41 (d, J = 7.7, 2H), 7.39 (t, J = 7.3, 2H), 7.35 (t, J = 7.4, 1H), 4.38 (m, 1H), 4.21 (dd, J = 4.6, 11.1, 1H), 2.17 (ddd, J = 4.7, 9.5, 14.3, 2H), 2.00 (ddd, J =4.5, 8.1, 13.6, 1H), 1.30 (d, J = 6.2, 3H), 1.04 (t, J = 8.0, 9H), 0.76 (q, J = 8.0, 6H); ^{13}C{^{1}H} (100 MHz) δ 136.3, 129.3, 128.1, 127.2, 120.9, 78.5, 41.9, 34.8, 18.4, 6.9, 3.9.

(*R,R and *R*,S**) 2-Phenyl-5-((triethylsilyl)peroxy)hexanenitrile (4si)** was prepared as an inseparable 1:1 mixture of diastereomers (2.04 g, 47%) from nitrile **4** (13.6 mmol, 2.33 g) using

the reductive dioxygenation procedure described above: R_f = 0.59 (10% EA/Hex); ^{1}H (400 MHz) δ 7.37-7.40 (m, 4H), 7.31-7.34 (m, 6H), 3.99-4.13 (m, 2H), 3.81-3.89 (m, 2H), 1.92-2.09 (m, 4H), 1.63-1.81 (m, 4H), 1.20 (d, J = 6.1, 3H), 1.19 (d, J = 6.2, 3H), 0.96-1.00 (m, 18H), 0.65-0.70 (m, 12H); ^{13}C{^{1}H} (100 MHz) δ 135.9, 129.2, 128.2, 127.4, 120.9, 80.7, 80.2, 37.5, 37.3, 32.0, 31.9, 31.7, 31.6, 18.6, 18.4, 6.9, 3.9; IR: 2956, 2877, 2241, 1495, 1455, 1413, 1375, 1239, 1005, 836, 792, 729, 697 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{18}H_{29}NNaO_2Si$ (M + Na)$^+$: 342.1865; found 342.1866.

(*R,R* and R*,S**) **2-Phenyl-6-((triethylsilyl)peroxy)heptanenitrile (5si)** was prepared as an inseparable 1:1 mixture of diastereomers (1.68 g, 41%) from nitrile **5** (12.3 mmol, 2.28 g) using the reductive dioxygenation procedure described above: R_f = 0.55 (10% EA/Hex); ^{1}H (400 MHz) δ 7.36-7.39 (m, 4H), 7.32-7.33 (m, 6H), 3.95-4.02 (m, 2H), 3.77-3.80 (m, 2H), 1.83-2.01 (m, 4H), 1.39-1.70 (m, 8H), 1.18 (d, J = 6.0, 3H), 1.18 (d, J = 6.1, 3H), 0.95-0.99 (m, 18H), 0.64-0.70 (m 12H); ^{13}C{^{1}H} (100 MHz) δ 135.9, 129.2, 128.2, 127.3, 120.9, 81.2, 81.0, 37.4, 36.0, 35.9, 33.7, 33.3, 33.2, 23.1, 23.0, 18.4, 18.2, 6.9, 6.7, 5.9, 3.9; IR: 2954, 2912, 2876, 2240, 1495, 1456, 1414, 1375, 1239, 1005, 826, 729, 698, 509 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{19}H_{31}NNaO_2Si$ (M + Na)$^+$: 356.2022; found 356.2025.

(*R,R* and R*,S**) **2-Phenyl-7-((triethylsilyl)peroxy)octanenitrile (6si)** was prepared as an inseparable 1:1 mixture of diastereomers (872.9 mg, 42%) from nitrile **6** (5.99 mmol, 1.19 g) using the reductive dioxygenation procedure described above: R_f = 0.57 (10% EA/Hex); ^{1}H (400 MHz) δ 7.37-7.40 (m, 4H), 7.31-7.34 (m, 6H), 3.75-4.01 (m, 2H), 3.76-3.79 (m, 2H), 1.83-1.99 (m, 4H), 1.46-1.66 (m, 4H), 1.33-1.46 (m, 8H), 1.18 (d, J = 6.1, 6H), 0.97-1.01 (m, 18H), 0.65-0.71 (m, 12H); ^{13}C{^{1}H} (100 MHz) δ 136.0, 129.2, 128.1, 127.3, 121.0, 81.2, 81.2, 37.5, 35.9, 34.1, 34.1, 27.2, 24.9, 24.9, 6.9, 6.7, 5.9, 3.9; IR: 2952, 2876, 2240, 1494, 1456, 1413, 1374,

1239, 1005, 832, 794, 728, 698, 509 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{20}H_{33}NNaO_2Si$ $(M + Na)^+$: 370.2178; found: 370.2180.

5-Methyl-2-phenyl-5-((triethylsilyl)peroxy)hexanenitrile (7si) was prepared as a colorless oil (1.24 g, 36%) from nitrile **7** (1.91 g, 10.3 mmol) using the general procedure for reductive deoxygenation described earlier: R_f = 0.63 (10% EA/Hex); ^1H (400 MHz) δ 7.30-7.40 (m, 5H), 3.82 (t, J = 7.3, 1H), 1.94-2.00 (m, 2H), 1.71-1.75 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 0.97 (t, J = 7.9, 9H), 0.65 (q, J = 7.9, 6H); $^{13}C\{^1H\}$ (100 MHz) δ 136.2, 129.1, 128.1, 127.4, 121.1, 81.6, 37.7, 35.9, 30.5, 24.8, 24.3, 6.9, 4.0; IR: 2956, 2876, 2241, 1739, 1495, 1455, 1412, 1364, 1239, 1046, 1006, 856, 802, 730, 697, 525 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{19}H_{31}NNaO_2Si$ $(M + Na)^+$: 356.2022; found: 356.2026.

(*R,R* and R*,S**) **5-Hydroperoxy-2-phenylhexanenitrile (4h)** was prepared using an adaptation of reported procedures.[48] To a solution of alkene **4si** (896.2 mg, 2.8 mmol) in THF (40 mL) was added TBAF (3.4 mL, 3.4 mmol, 1.2 equiv, nominally 1.0 M in THF). The reaction was stirred at room temperature for 10 min. The reaction was diluted with water (15 mL) and extracted with EA (20 mL x 3). The combined organic layers were dried with Na_2SO_4 and filtered. The residue obtained after concentration under reduced pressure and purified by column chromatography (10% EA/Hex) to yield 505.6 mg (88%) of hydroperoxide **4h** as a colorless oil; the product was formed as an inseparable 1:1 mixture of diastereomers: R_f = 0.20 (20% EA/Hex); ^1H (400 MHz) δ 8.27 (s, 2H), 7.32-7.40 (m, 10H), 4.06-4.15 (m, 2H), 3.81-3.87 (m, 2H), 1.93-2.07 (m, 2H), 1.65-1.82 (m, 2H), 1.23 (d, J = 6.2, 3H), 1.22 (d, J = 6.3, 3H); $^{13}C\{^1H\}$ (100 MHz) δ 135.7, 135.7, 129.3, 128.3, 127.4, 127.4, 80.8, 80.4, 37.5, 37.2, 31.9, 31.5, 31.5, 31.3, 18.3, 18.2; IR: 3376, 2977, 2935, 2243, 1492, 1455, 1375, 1185, 1095, 1057, 915, 761, 743, 698 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{12}H_{15}NNaO_2$ $(M + Na)^+$: 228.1000; found: 228.1004.

(*R,R* and R*,S**) **2-Phenyl-5-(tetrahydro-2*H*-pyran-2-yl)peroxy hexanenitrile (4thp):** The conversion of the hydroperoxide to the tetrahydropyranyl peroxyacetal employed a reported procedure.[14] To hydroperoxide **4h** (768.4 mg, 3.74 mmol) was added dihydropyran (0.35 mL, 4.16 mmol, 1.1 equiv), followed by a solution of 10% H_2SO_4 in THF (0.1 mL). The reaction was stirred at room temperature for 18 h. The reaction was diluted with EA (30 mL) and the organic layer was extracted with water (25 mL x 3). The dried organic layer (Na_2SO_4) was concentrated under reduced pressure and the residue purified by column chromatography (10-20% EA/Hex) to yield 802.9 mg (74%) of the tetrahydropyranyl peroxyacetal as a light orange oil as an inseparable 1 : 1.14 mixture of diastereomers: R_f = 0.33 (20% EA/Hex); ^{1}H (400 MHz) δ 7.30-7.39 (10H), 5.11 (m, 1H), 5.06 (m, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 3.60 (m, 2H), 1.97-2.08 (m, 4H), 1.65-1.83 (8H), 1.46-1.63 (8H), 1.21-1.25 (6H); ^{13}C{^{1}H} (100 MHz) δ 135.9, 129.2, 128.2, 127.4, 120.9, 101.4, 101.0, 79.8, 79.1, 62.8, 37.5, 37.4, 37.2, 36.9, 32.1, 32.0, 31.9, 31.8, 31.7, 31.6, 31.5, 28.0, 25.2, 19.9; IR: 2955,2925, 2877, 2243, 1496, 1454, 1202, 1131, 1105, 1078, 996, 969, 904, 874, 814, 738, 698, 430 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{17}H_{23}NNaO_3$ $(M + Na)^+$: 312.1576; found: 312.1578.

2-(3-Chloropropyl)octanenitrile (9) was prepared using a modification of a reported procedure.[49] To a solution of octanenitrile (3.0 mL, 19.5 mmol) in THF (20 mL) was added a freshly prepared solution of LDA in THF (23.6 mmol, 1.2 equiv; prepared as described earlier), followed by 1-bromo-3-chloropropane (2.3 mL, 23.3 mmol, 1.2 equiv). The reaction was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with DCM (60 mL X 3). The combined organic layers were dried with Na_2SO_4 and the residue concentrated under reduced pressure to yield 3.86 g (98%) of the chloroalkyl nitrile as a yellow oil: R_f = 0.52 (10% EA/Hex); ^{1}H (400 MHz) δ 3.58 (t, J = 6.4, 2H), 2.57 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.77 (m, 2H), 1.59 (m, 2H), 1.45 (m, 2H), 1.23-1.38 (6H), 0.89 (t, J = 6.8, 3H);

$^{13}C\{^{1}H\}$ (100 MHz) δ 121.9, 44.2, 32.4, 31.6, 31.2, 30.0, 29.7, 28.8, 27.2, 22.6, 14.1; IR: 2955, 2928, 2858, 2237, 1459, 1379, 1308, 725, 654 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{11}H_{20}ClNNa$ $(M + Na)^+$: 224.1182; found: 224.1182.

2-(3-(*tert*-Butylperoxy)propyl)octanenitrile (9bu) was prepared via the intermediate iodide.[50] To a solution of 2-(3-chloropropyl)octanenitrile (3.81 g, 18.9 mmol) in acetone (150 mL) was added sodium iodide (15.58 g, 104.0 mmol, 5.5 equiv); the reaction was held at reflux for 18 h. The cooled reaction was then diluted with water (50 mL) and extracted with hexanes (50 mL X 3). The combined organic layers were dried with Na_2SO_4 and the residue concentrated under reduced pressure to yield 5.22 g (94%) of 2-(3-iodopropyl)octanenitrile **(9i**) as a yellow/orange oil which was used without purification: R_f = 0.53 (10% EA/Hex); ^1H (400 MHz) δ 3.23 (t, J = 6.6, 2H), 2.57 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.50-1.79 (4H), 1.23-1.40 (8H), 0.91 (t, J = 6.3, 3H); $^{13}C\{^{1}H\}$ (100 MHz) δ 121.9, 33.1, 32.3, 31.6, 30.9, 30.7, 28.8, 27.2, 22.6, 14.1, 5.2**;** IR: 2927, 2857, 2236, 1457, 1378, 1291, 1223, 1174, 724, 505 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{11}H_{20}INNa$ $(M + Na)^+$: 316.0538; found: 316.0539.

The conversion of the iodide to peroxide **9bu** was based upon reported procedures.[5, 51] To a solution of CsOH monohydrate (2.18 g, 14.7 mmol, 1.2 equiv) in DMF (125 mL) at 0 °C was added dropwise *tert*-butyl hydroperoxide (3.33 mL, 18.3 mmol, 1.5 equiv, nominally 5.5 M in decane). After the solution had stirred for 30 min, 2-(3-iodopropyl)octanenitrile (3.58 g, 12.2 mmol) was added. The reaction was allowed to slowly warm to room temperature. After 5 h, the reaction was quenched with water (50 mL) and extracted with hexanes (50 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) pressure to yield 1.68 g (54%) of peroxide **9bu** as a colorless oil: R_f = 0.55 (10% EA/Hex); ^1H (400 MHz) δ 3.96 (m, 2H), 2.55 (m, 1H), 1.62-1.78 (4H), 1.47-1.60, 4H), 1.25-1.36 (6H), 1.23 (s, 9H), 0.88 (t, J = 6.6, 3H); $^{13}C\{^{1}H\}$ (100 MHz) δ 122.3, 80.4, 74.1, 32.4, 31.7, 31.6, 29.4, 28.9, 27.2, 26.4, 25.9, 22.6, 14.1; IR:

2929, 2860, 2237, 1458, 1385, 1362, 1242, 1196, 1059, 1023, 878, 756, 724, 546 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{15}H_{29}NNaO_2$ $(M + Na)^+$: 278.2096: found; 278.2099.

Syntheses of [(chloroalkyl)thio]benzenes was based upon a modification of a reported procedure.[52] To a solution of thiophenol (4.69 mL, 46 mmol) in DMF (100 mL) was added K_2CO_3 (8.29 g, 60 mmol, 1.3 equiv), followed by the 1,*n*-bromochloroalkane (46 mmol). The reaction was stirred at room temperature for 1 h and then diluted with water (30 mL). The combined hexane extracts (3 x 25 mL) were dried with Na_2SO_4 and the residue concentrated under reduced pressure to yield a colorless oil which was used without further purification.

3-Chloropropyl-phenyl sulfide (10a) was prepared (8.40 g, 98%) from 1-bromo-3-chloropropane (4.55 mL, 46.0 mmol) using the general procedure described above. Spectral details matched those previously reported:[53] R_f = 0.66 (10% EA/Hex); ^{1}H (400 MHz) δ 7.39 (d, J = 7.1, 2H), 7.33 (t, J = 7.4, 2H) 7.23 (t, J = 7.3, 1H), 3.70 (t, J = 6.3, 2H), 3.11 (t, J = 7.0, 2H), 2.10 (p, J = 6.6, 2H); ^{13}C{^{1}H} (100 MHz) δ 135.7, 129.6, 129.0, 126.3, 43.4, 31.7, 30.8.

4-Chlorobutyl-phenyl sulfide (11a) was prepared (9.03 g, 98%) from 1-bromo-4-chlorobutane (5.30 mL, 46.0 mmol) using the procedure described above. Spectral details matched those previously reported.[52] R_f = 0.65 (10% EA/Hex); ^{1}H (400 MHz) δ 7.36 (d, J = 7.8, 2H), 7.31 (t, J = 7.4, 2H), 7.21 (t, J = 7.2, 1H), 3.57 (t, J = 6.5, 2H), 2.97 (t, J = 7.1, 2H), 1.95 (app tt, J = 6.3, 7.6, 2H), 1.82 (app tt, J = 7.0, 7.6, 2H); ^{13}C{^{1}H} (100 MHz) δ 136.6, 129.7, 129.3, 126.4, 44.8, 33.4, 31.7, 26.7.

5-Chloropentyl-phenyl sulfide (12a) was prepared (9.79 g, 99%) from 1-bromo-5-chloropentane (6.06 mL, 46.0 mmol) using the general procedure described above. Spectral details matched those previously reported.[54] R_f = 0.66 (10% EA/Hex); ^{1}H (400 MHz) δ 7.39 (d, J

= 7.8, 2H), 7.34 (t, J = 7.6, 2H), 7.23 (t, J = 7.3, 1H), 3.55 (t, J = 6.7, 2H), 2.97 (t, J = 7.2, 2H), 1.82 (p, J = 7.3, 2H), 1.72 (app tt, J = 7.2, 7.6, 2H), 1.62 (app tt, J = 6.7, J = 7.6, 2H); $^{13}C\{^{1}H\}$ (100 MHz) δ 136.8, 129.1, 129.0, 44.9, 33.4, 32.2, 28.8, 28.5, 26.2.

6-Chlorohexyl-phenyl sulfide (13a) was prepared (10.1 g, 96%) from 1-bromo-6-chlorohexane (6.86 mL, 46.0 mmol) using the procedure described above. Spectral details matched those previously reported.[54] R_f = 0.66 (10% EA/Hex); ^{1}H (400 MHz) δ 7.36 (d, J = 7.3, 2H), 7.31 (t, J = 7.3, 2H), 7.20 (t, 7.2, 1H), 3.55 (t, J = 6.7, 2H), 2.95 (t, J = 7.2, 2H), 1.79 (p, J = 6.9, 2H), 1.70 (p, J = 7.3, 2H), 1.47-1.52 (m, 4H); $^{13}C\{^{1}H\}$ (100 MHz) δ 136.9, 129.0, 128.9, 125.8, 45.0, 33.5, 32.3, 29.0, 28.0, 26.5.

Syntheses of chloroalkyl sulfonyl benzenes: Oxidation of the sulfides followed a published procedure.[55] To the neat sulfide (6.0 mmol) was added 30% aq. H_2O_2 (30 mmol, 5.0 equiv). The stirred mixture was heated to 75 °C for 5 h. The reaction was allowed to cool and was then diluted with water (20 mL). The combined EA extracts (20 mL X 3) were dried with Na_2SO_4 and the residue concentrated under reduced pressure to yield a colorless oil which was used without further purification.

3-Chloropropyl-sulfonyl benzene (10b) was prepared (1.60 g, 97%) from 3-chloropropyl-phenyl sulfide (1.40 g, 7.5 mmol) by the procedure described above. Spectral details matched those previously reported:[52] R_f = 0.36 (25% EA/Hex); ^{1}H (400 MHz) δ 7.92 (d, J = 7.7, 2H), 7.68 (t, J = 7.3, 1H), 7.59 (t, J = 7.3, 2H), 3.62 (t, J = 6.2, 2H), 3.27 (t, J = 7.6, 2H), 2.22 (app p, J = 6.6, 2H); $^{13}C\{^{1}H\}$ (100 MHz) δ 139.0, 134.1, 129.6, 128.1, 53.7, 42.8, 25.9.

4-Chlorobutyl-sulfonyl benzene (11b) was prepared (1.58 g, 95%) from 4-chlorobutyl-phenyl sulfide (1.41 g, 7.0 mmol) by the procedure described above. Spectral details matched those

previously reported:[52] R_f = 0.35 (25% EA/Hex); ^{1}H (400 MHz) δ 7.92 (d, J = 7.7, 2H), 7.68 (t, J = 7.4, 1H), 7.59 (t, J = 7.6, 2H), 3.52 (t, J = 5.5, 2H), 3.13 (t, J = 7.1, 2H), 1.89-1.91 (m, 4H); ^{13}C{^{1}H} (100 MHz) δ 139.3, 134.2, 129.7, 128.4, 55.7, 44.2, 31.2, 20.7.

5-Chloropentyl-sulfonyl benzene (12b) was prepared (1.35 g, 94%) from 5-chloropentyl-phenyl sulfide (1.25 g, 5.8 mmol) by the procedure described above. Spectral details matched those previously reported:[52] R_f = 0.36 (25 % EA/Hex); ^{1}H (400 MHz) δ 7.88 (d, J = 7.9, 2H), 7.64 (t, J = 7.3, 1H), 7.55 (t, J = 7.6, 2H), 3.46 (t, J = 6.5, 2H), 3.08 (t, J = 8.0, 2H), 1.72 (app p, J = 6.9, 4H), 1.49 (m, 2H) ; ^{13}C{^{1}H} (100 MHz) δ 139.0, 133.8. 129.4, 128.0, 56.1, 44.4, 31.9, 25.6, 22.0.

6-Chlorohexyl-sulfonyl benzene (13b) was prepared (1.52 g, 96%) from 6-chlorohexyl-phenyl sulfide (1.37 g, 6.0 mmol) by the procedure described above. Spectral details matched those previously reported:[56] R_f = 0.36 (25% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 7.3, 2H), 7.66 (t, J = 7.5, 1H), 7.57 (t, J = 7.6, 2H), 3.49 (t, J = 6.6, 2H), 3.09 (app dt, J = 5.5, 7.9, 2H), 1.70-1.77 (m, 4H), 1.38-1.43 (m, 4H); ^{13}C{^{1}H} (100 MHz) δ 139.3, 133.8, 129.4, 128.1, 56.3, 44.9, 32.2, 27.7, 26.4, 22.7.

Syntheses of [iodoalkylsulfonyl] benzenes was performed as described for the synthesis of **9bu**. To a solution of chloroalkyl sulfonyl benzene (30.0 mmol) in acetone (165 mL) was added sodium iodide (24.7 g, 165 mmol, 5.5 equiv). The reaction was stirred under reflux for 18 h. The reaction was allowed to cool and then diluted with water (50 mL). The combined hexane extracts (60 mL X 3) were dried over Na_2SO_4 and the residue concentrated under reduced pressure to yield a yellow solid.

3-Iodopropylsulfonyl benzene (10c) was prepared (8.50 g, 68%) as a yellow solid (mp 30.5-31.5 ° C) from 3-chloropropyl-sulfonyl benzene (8.75 g, 40 mmol) by the procedure described above. Spectral details matched those previously reported:[57] R_f = 0.39 (25% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 5.9, 2H), 7.68 (t, J = 5.9, 1H), 7.59 (t, J = 6.1, 2H), 3.22 (t, J = 6.6, 2H), 3.21 (t, J = 7.6, 2H), 2.24 (app tt, J = 6.6, 7.6, 2H); ^{13}C{^{1}H} (100 MHz) δ 139.1, 134.1, 129.6, 128.1, 56.9, 26.6, 2.9.

4-Iodobutylsulfonyl benzene (11c) was prepared (6.59 g, 69%) as a yellow solid (mp = 52-54 °C) from 4-chlorobutyl-sulfonyl benzene (6.98 g, 30 mmol) using a version of a known procedure:[58] R_f = 0.39 (25% EA/Hex); ^{1}H (400 MHz) δ 7.92 (d, J = 7.6, 2H), 7.68 (t, J = 7.4, 1H), 7.59 (t, J = 7.5, 2H), 3.14 (t, J = 6.5, 2H), 3.12 (t, J = 7.5, 2H), 1.82-1.96 (m, 4H); ^{13}C{^{1}H} (100 MHz) δ 139.2, 134.0, 129.6, 128.3, 55.2, 31.8, 24.0, 4.8; IR (ν [cm^{-1}]) 446, 1282, 1144, 1085, 861, 754, 691, 561, 530, 446 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{10}H_{13}INaO_2S$ $(M + Na)^+$: 346.9579; found: 346.9581.

5-Iodopentylsulfonyl benzene (12c) was prepared (5.74 g, 76%) as a yellow solid (mp = 57-59 °C) from 5-chloropentyl-sulfonyl benzene (5.43 g, 22 mmol) by the procedure described above: R_f = 0.38 (25% EA/Hex); ^{1}H (400 MHz) δ 7.90 (d, J = 5.8, 2H), 7.66 (t, J = 5.9, 1H), 7.57 (t, J = 6.1, 2H), 3.13 (t, J = 5.4, 2H), 3.09 (t, J = 6.4, 2H), 1.72-1.82 (m, 4H), 1.45-1.52 (m, 2H); ^{13}C{^{1}H} (100 MHz) δ 139.2, 133.9, 129.4, 128.1, 56.1, 32.8, 29.2, 21.8, 5.9; IR 1446, 1282, 1143, 1085, 861, 754, 691, 561, 530, 446 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{11}H_{15}INaO_2S$ $(M + Na)^+$: 360.9735; found: 360.9731.

6-Iodohexylsulfonyl benzene (13c) was prepared (9.04 g, 57%) as a yellow solid (mp = 62-64 °C) from 6-chlorohexyl-sulfonyl benzene (11.73 g, 45 mmol) by the procedure described above: R_f = 0.38 (25% EA/Hex); ^{1}H (400 MHz) δ 7.90 (d, J = 7.6, 2H), 7.66 (t, J = 7.5, 1H), 7.57 (t, J =

7.3, 2H), 3.06-3.20 (4H), 1.69-1.82 (m, 4H), 1.37-1.42 (m, 4H); $^{13}C\{^{1}H\}$ (100 MHz) δ 139.3, 133.8, 129.4, 128.1, 56.2, 33.0, 29.9, 27.3, 22.6, 6.7; IR 1446, 1295, 1284, 1144, 1084, 755, 690, 599, 560, 534, 450 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{12}H_{17}INaO_2S$ $(M + Na)^+$: 374.9892; found: 374.9894.

Synthesis of peroxyalkyl sulfonyl benzenes was adapted from a reported procedure.[51] To a 0 °C solution of CsOH monohydrate (1.01 g, 6.0 mmol, 1.2 equiv) in DMF (40 mL) was added dropwise *tert*-butyl hydroperoxide (1.36 mL, 7.5 mmol, 1.5 equiv, ~5.5 M solution in decane). The solution was stirred for 30 min, whereupon the iodoalkyl sulfonyl benzene (5.0 mmol) was added. The reaction was allowed to slowly warm to room temperature. After 5 h, the reaction was quenched with water (20 mL) and the mixture extracted with hexanes (20 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield a light yellow oil.

3-(*tert*-Butylperoxy)propyl-sulfonyl benzene (10bu) was prepared (139 mg, 43%) from 3-iodopropyl-sulfonyl benzene (372 mg, 1.2 mmol) by the procedure described above. The product was formed as a mixture with cyclopropyl phenyl sulfone (light yellow solid, 98.6 mg, 46%); the two could be separated during chromatography:

10bu: R_f = 0.48 (25% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 7.3, 2H), 7.65 (t, J = 7.5, 1H), 7.56 (t, J = 7.4, 2H), 3.96 (t, J = 5.9, 2H), 3.21 (ddd, J = 10.3, 4.9, 5.5, 2H), 2.03 (app tt, J = 4.5, 5.5, 2H), 1.17 (s, 9H); $^{13}C\{^{1}H\}$ (100 MHz) δ 139.1, 133.9, 129.4, 128.2, 80.5, 72.5, 53.6, 26.4, 22.1; IR 2975, 1306, 1143, 1084, 752, 689, 534 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{13}H_{20}NaO_4S$ $(M + Na)^+$: 295.0980; found: 295.0983.

Cyclopropyl phenyl sulfone: R_f = 0.33 (25% EA/Hex); mp = 32-34 °C; ^{1}H (400 MHz) 7.90 (d, J = 7.3, 2H), 7.63 (t, J = 7.5, 1H), 7.55 (t, J = 7.5, 2H), 2.46 (ttt, J= 4.8, 8.0, 12.9, 1H), 1.34 (ddd, J = 2.0, 6.0, 8.0, 2H), 1.02 (ddd, J = 1.2, 4.8, 6.0, 2H); $^{13}C\{^{1}H\}$ (100 MHz) δ 140.8, 133.5, 129.3,

127.6, 33.0, 6.06; IR 1316, 1287, 1190, 1140, 1088, 1063, 780, 730, 694, 680, 582, 540, 436 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_9H_{10}NaO_2S$ $(M + Na)^+$: 205.0299; found: 205.0303. Spectral details matched those previously reported.[59]

4-(*tert*-Butylperoxy)butyl-sulfonyl benzene (11bu) was prepared (1.68 g, 62%) from 4-iodobutyl-sulfonyl benzene (3.05 g, 9.4 mmol) by the general procedure described above: R_f = 0.46 (25% EA/Hex); ^1H (400 MHz) δ 7.91 (d, J = 7.4, 2H), 7.66 (t, J = 7.4, 1H), 7.57 (t, J = 7.6, 2H), 3.90 (t, J = 6.0, 2H), 3.13 (t, J = 7.9, 2H), 1.81 (app tt, J = 7.2, 7.9, 2H), 1.68 (m, 2H), 1.18 (s, 9H); $^{13}C\{^1H\}$ (100 MHz) δ 139.3, 133.9, 129.5, 128.3, 80.4, 74.0, 56.3, 26.9, 26.5, 20.2; IR 2976, 1363, 1307, 1194, 1153, 1089, 877, 811, 734, 592, 569, 547 cm^{-1}. HRMS (ESI^+, TOF) calcd for $C_{14}H_{22}NaO_4S$ $(M + Na)^+$: 309.1136; found: 309.1141.

5-(*tert*-Butylperoxy)pentyl-sulfonyl benzene (12bu) was prepared (710 mg, 49%) from 5-iodopentyl-sulfonyl benzene (1.66 g, 4.9 mmol) by the procedure described above: R_f = 0.47 (25% EA/Hex); ^1H (400 MHz) δ 7.90 (d, J = 7.4, 2H), 7.65 (t, J = 7.5, 1H), 7.56 (t, J = 7.9, 2H), 3.89 (t, J = 6.3, 2H), 3.08 (ddd, J = 10.6, 5.3, 5.6, 2H), 1.73 (p, J = 7.8, 2H), 1.57 (app tt, J = 6.5, 7.3, 2H), 1.43 (app tt, J = 7.1, 8.0, 2H), 1.19 (s, 9H); $^{13}C\{^1H\}$ (100 MHz) δ 139.2, 133.7, 129.3, 128.1, 80.2, 74.3, 56.2, 27.4, 26.3, 25.1, 22.6IR (ν [cm^{-1}]) 2937, 1302, 1141, 1086, 755, 687, 583, 533 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{15}H_{24}NaO_4S$ $(M + Na)^+$: 323.1293; found: 323.1299.

6-(*tert*-Butylperoxy)hexyl-sulfonyl benzene (13bu) was prepared (1.85 g, 67%) from 6-iodohexyl-sulfonyl benzene (3.10 g, 8.8 mmol) by the procedure described above. R_f = 0.47 (25% EA/Hex); ^1H (400 MHz) δ 7.90 (d, J = 9.6, 2H), 7.65 (t, J = 9.7, 1H), 7.56 (t, J = 9.6, 2H), 3.88 (t, J = 8.6, 2H), 3.07 (ddd, J = 10.8, 5.1, 5.5, 2H), 1.71 (app tt, J = 7.2, 7.7, 2H), 1.54 (p, J = 6.7, 2H), 1.28-1.43 (m, 4H), 1.21 (s, 9H); $^{13}C\{^1H\}$ (100 MHz) δ 139.3, 133.7, 129.4, 128.1, 80.2,

74.7, 56.3, 28.2, 27.6, 26.4, 25.8, 22.7; IR 2937, 1305, 1143, 1086, 743, 727, 689, 594, 564, 533 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{16}H_{26}NaO_4S$ $(M + Na)^+$: 337.1449; found: 337.1454.

2-((4-Phenylsulfonyl)butyl)peroxy)tetrahydro-2*H*-pyran (11thp) was prepared by alkylation of 2-hydroperoxytetrahydropyran with **11i** following a reported procedure.[14, 51]

2-Hydroperoxytetrahydro-2*H*-pyran [CAUTION-low molecular weight hydroperoxide] was prepared using an adaptation of reported procedures.[18, 60] To a solution of 50% aqueous hydrogen peroxide (26 mmol, 2.0 equiv) at 0 °C was added 10% aqueous sulfuric acid (0.1 ml). After the mixture had stirred for 10 min at 0 °C, dihydropyran (1.0 g, 12 mmol) was added over a period of 3 min. The reaction was allowed to slowly warm to room temperature. After 3 h, the reaction was diluted with sat. aq. NH_4Cl (15 mL) and extracted with diethyl ether (50 mL X 3). The organic layer was washed with sat. aq. ammonium sulfate (15 mL X 5). The resulting solution was dried with Na_2SO_4, carefully concentrated under reduced pressure and the residue purified by column chromatography (5-25% EA/Hex) to yield 427 mg (47%) of 2-hydroperoxytetrahydro-2*H*-pyran as a colorless oil (CAUTION-low molecular weight hydroperoxide). Spectral details matched those previously reported.[60]

To a solution of CsOH monohydrate (571 mg, 3.4 mmol, 1.2 equiv) in DMF (15 mL) at 0 °C was added dropwise 2-hydroperoxytetrahydro-2*H*-pyran (508 mg, 4.3 mmol, 1.5 equiv; majority added neat; final portion transferred within small volume of DMF). The solution was stirred for 30 min, whereupon iodosulfone **11i** (940 mg, 2.9 mmol) was added. The reaction was allowed to slowly warm to room temperature. After 5 h, the reaction was quenched with water (10 mL) and extracted with hexanes (15 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 427 mg (47%) of the peroxyacetal **11thp** as a colorless oil: R_f = 0.22 (25% EA/Hex); ^1H (400 MHz) δ 7.94 (d, J = 7.4, 2H), 7.68 (t, J = 7.4, 1H), 7.59 (t, J = 7.4, 2H), 5.09 (t,

J = 3.7, 1H), 4.09 (t, J = 6.0, 2H), 3.97 (t, J = 8.0, 1H), 3.61 (t, J = 6.9, 1H), 3.17 (t, J = 7.4, 2H), 1.54-1.95 (m, 10H); $^{13}C\{^{1}H\}$ (100 MHz) δ 139.2, 133.8, 129.4, 128.2, 101.1, 74.4, 62.9, 56.1, 28.0, 26.7, 25.2, 20.0, 19.9; IR 2923, 1733, 1304, 1240, 1143, 1039, 690, 593, 564, 533 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{15}H_{22}NaO_5S$ $(M + Na)^+$: 337.1086; found: 337.1096.

Pent-4-en-1-yl(phenyl)sulfide (14): To a solution of thiophenol (5.0 mL, 49.0 mmol) in DMF (120 mL) was added K_2CO_3 (8.3 g, 60.0 mmol, 1.2 equiv), followed by 5-bromo-1-pentene (5.8 mL, 49.0 mmol, 1.0 equiv).[52] After stirring at rt for 1 h, the reaction was diluted with water (50 mL) and extracted with hexanes (50 mL X 3). The combined organic layers were dried with Na_2SO_4 and the residue concentrated under reduced pressure to yield 8.67 g (99%) of thioether **14** as a yellow oil, which was used without further purification. Spectral details matched those previously reported:[61] R_f = 0.68 (10% EA/Hex); ^{1}H (400 MHz) δ 7.37 (d, J = 7.2, 2H), 7.31 (t, J = 7.3, 2H), 7.20 (tt, J = 1.3, 7.3, 1H), 5.82 (ddt, J = 7.0, 10.9, 16.8, 1H), 5.07 (td, J = 2.0, 16.8, 1H), 5.03 (td, J = 1.0, 10.9, 1H), 2.96 (td, J = 1.8, 7.3, 2H), 2.23 (m, 2H), 1.78 (tt, J = 1.8, 7.3, 2H); $^{13}C\{^{1}H\}$ (100 MHz) 137.7, 136.9, 129.2, 129.0, 125.9, 115.5, 33.1, 32.8, 28.4.

Triethyl (5-phenylthiopentan-2-yl)peroxysilane (15): The synthesis of the triethylsilyl peroxide followed a similar procedure as described for reactions of unsaturated nitriles. To a solution of unsaturated thioether **14** (1.42 g, 0.67 mmol) in EtOH (40 mL) was added triethylsilane (2.2 mL, 13.8 mmol, 2 equiv), followed by $Co(acac)_2$ (213 mg, 0.83 mmol, 0.1 equiv). The reaction was stirred at room temperature under O_2 for 18 h. The reaction solution was concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 1.52 g (69%) of peroxide **15** as a yellow oil: R_f = 0.65 (10% EA/Hex); ^{1}H (400 MHz) δ 7.36 (d, J = 7.4, 2H), 7.30 (t, J = 7.4, 2H), 7.19 (t, J = 7.2, 1H), 4.04 (sextet, J = 6.1, 1H), 2.95 (t, J = 7.0, 2H), 1.82-1.59 (m, 4H), 1.21 (d, J = 6.2, 3H), 1.00 (t, J = 8.0, 9H), 0.70 (q, J = 7.9, 6H); $^{13}C\{^{1}H\}$ (100 MHz) δ 136.7, 129.4, 129.0, 126.0, 81.0, 33.9, 33.6, 25.3, 18.6, 6.9, 3.9; IR (ν [cm^{-1}]) 2954,

2875, 1073, 1004, 735, 690 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{17}H_{30}NaO_2SSi$ $(M + Na)^+$: 349.1633; found: 349.1638.

Triethyl (5-phenylsulfonylpentan-2-yl peroxy) silane (16si): The oxidation of thioether **15** (868.6 mg, 2.66 mmol) was conducted using a similar procedure as described above for the syntheses of chloroalkyl sulfonyl benzenes to furnish 592.2 mg (62%) of the triethylsilylperoxy alkyl phenyl sulfone (**16si**) as an opaque, viscous oil: R_f = 0.40 (30% EA/Hex); ^1H (400 MHz) δ 7.93 (d, J = 7.6, 2H), 7.68 (t, J = 7.4, 1H), 7.60 (t, J = 7.9, 2H), 4.08 (sextet, J = 6.2, 1H), 3.18 (app td, J = 3.3, 7.2, 2H), 1.86 (app tt, J = 7.2, 8.0, 2H), 1.66-1.74 (m, 2H), 1.22 (d, J = 6.3, 3H), 0.95 (t, J = 7.9, 9H), 0.53 (q, J = 8.0, 6H); $^{13}C\{^1H\}$ (100 MHz) δ 139.1, 133.9, 129.5, 128.1, 80.8, 56.1, 32.1, 18.8, 18.1, 6.9, 6.5; IR 2929, 1683, 1415, 1288, 1139, 747, 718, 534 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{11}H_{16}NaO_4S$ $(M+Na - Et_3Si)^+$: 267.0667; found 267.0667.

(4-Hydroperoxypentyl)sulfonylbenzene (16h): Fluoride-promoted desilylation was conducted using an adaptation of a reported procedure.[48a] To a solution of the triethylsilyl peroxide (435.2 g, 1.2 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (0.4 mL, 1.4 mmol, 1.2 equiv, 1.0 M in THF). The reaction was stirred at room temperature for 10 min. The reaction was diluted with water (5 mL) and the resulting mixture extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography (5% EA/Hex) to yield 288.8 mg (98%) of the hydroperoxide as a colorless oil: R_f = 0.28 (30% EA/Hex); ^1H (400 MHz) δ 7.92 (d, J = 7.1, 2H), 7.67 (t, J = 7.4, 1H), 7.58 (t, J = 7.6, 2H), 4.07 (sextet, J = 6.2, 1H), 3.16 (apparent td, J = 3.2, 9.6, 2H), 1.83-1.91 (m, 2H), 1.67-1.73 (m, 2H), 1.20 (d, J = 8.4, 3H); $^{13}C\{^1H\}$ (100 MHz) 139.2, 133.9, 129,5, 128.2, 80.8, 56.1, 32.0, 18.8, 18.1; IR 3397, 2933, 1447, 1285, 1138, 1084, 731, 688, 532 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{11}H_{16}NaO_4S$ $(M + Na)^+$: 267.0667; found: 267.0670.

4-(Methylperoxy)pentylsulfonyl benzene (16me): To a solution of the hydroperoxy sulfone (695.2 mg, 2.85 mmol) in THF (70 mL) was added potassium *tert*-butoxide (400 mg, 3.56 mmol, 1.25 equiv), followed by methyl iodide (0.25 mL, 4.0 mmol, 1.4 equiv). The reaction was stirred at room temperature for 30 min and then quenched with water (20 mL). The resulting mixture was extracted with EA (25 mL x 3) and the combined organic layers were dried with Na_2SO_4. The residue obtained following concentration under reduced pressure was purified by column chromatography (5% EA/Hex) to yield 601.2 mg (82%) of methyl peroxide **16me** as a light yellow oil: R_f = 0.53 (25% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 7.3, 2H), 7.66 (t, J = 7.2, 1H), 7.57 (t, J = 7.8, 2H), 4.05 (sextet, J = 6.2, 1H), 3.74 (s, 3H), 3.11 (t, J = 7.9, 2H), 1.76-1.85 (m, 2H), 1.51-1.65 (m, 2H), 1.16 (d, J = 6.2, 3H); ^{13}C{^{1}H} (100 MHz) δ 139.2, 133.8, 129.4, 128.1, 78.4, 62.5, 56.3, 32.9, 19.0, 18.6; IR 2954, 1447, 1303, 1141, 1086, 730, 689, 533 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{12}H_{18}NaO_4S$ (M + Na)$^+$: 281.0823; found: 281.0827.

(*R,R and *R*,S**) 5-(Phenylsulfonyl)pentan-2-yl tetrahydro-2*H*-pyran-2-yl peroxide (16thp)**: The conversion of the hydroperoxide to the tetrahydropyranyl peroxyacetal was based upon a reported procedure.[62] To a solution of hydroperoxide **16h** (122.3 mg, 0.50 mmol) in THF (6 mL) was added dihydropyran (0.1 mL, ~1.1 mmol, 2.2 equiv), followed by 0.1 mL of a solution of 10% H_2SO_4 in THF (0.1 mL). The reaction, after stirring for 18 h, was diluted with EA (30 mL) and the organic layer was extracted with water (25 mL X 3). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (10-20% EA/Hex) to yield 93.6 mg (57%) of peroxyacetal **16thp** as a light yellow oil; the peroxyacetal was formed as a inseparable 1:1 mixture of diastereomers: R_f = 0.26 (25% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 7.5, 2H), 7.65 (t, J = 7.4, 1H), 7.56 (t, J = 7.6, 2H), 5.02 (d, J = 8.8, 1H), 4.09-4.18 (m, 1H), 3.92-3.97 (m, 1H), 3.58-3.61(m, 1H), 3.11-3.20 (m, 2H), 1.82-1.90 (m, 2H), 1.68-1.75 (m, 2H), 1.55-1.66 (m, 6H), 1.22 (d, J = 6.2, 3H); ^{13}C{^{1}H} (100 MHz) δ 139.3, 133.8, 129.4, 128.2, 101.0, 79.6, 62.9, 56.1 33.0, 32.9, 28.0, 25.2, 20.0, 19.1; IR

2939, 2870, 1447, 1304, 1143, 1085, 1038, 689, 533 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{16}H_{24}NaO_5S$ $(M + Na)^+$: 351.1242; found: 351.1243.

Cyclization of peroxide-containing nitriles: To a solution of the peroxide-substituted nitrile (1.0 mmol) in THF (5 mL) at -40 °C was added base (unless noted, 1.2 mmol, 1.2 equiv). The reaction was allowed to come to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield a light yellow oil.

From triethylsilyl peroxide:

5-Methyl-2-phenyltetrahydrofuran-2-carbonitrile (17ab) was prepared (148.2 mg, 95%) as a mixture of nearly inseparable diastereomers from 2-phenyl-5-((triethylsilyl)peroxy)hexanenitrile (**4si**, 0.833 mmol, 266.2 mg) and KO*t*Bu by the procedure described above. Spectral details matched those previously reported:[63] R_f = 0.47 (10% EA/Hex); IR: 2974, 1493, 1449, 1382, 1238, 1067, 1005, 877, 758, 697, 522, 476 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{12}H_{13}NNaO$ $(M + Na)^+$: 210.0895; found: 210.0897. The isolation of a small amount of major diastereomer in pure form was used to establish NMR signals for each individual diastereomer.

Major diastereomer (**17a**): ^1H (400 MHz) δ 7.53 (d, J = 7.7, 2H), 7.40 (t, J = 7.7, 2H), 7.37 (t, J = 7.1, 1H), 4.48 (m, 1H), 2.79 (app q, J = 6.2, 1H), 2.31 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H); $^{13}C\{^1H\}$ (100 MHz) δ 139.3, 129.0, 128.9, 124.9, 121.7, 80.3, 79.2, 43.1, 34.1, 21.7.

Minor diastereomer (**17b**): ^1H (400 MHz) δ 7.56 (d, J = 7.6, 2H), 7.41 (t, J = 7.6, 2H), 7.38 (t, J = 6.9, 1H), 4.56 (m, 1H), 2.75 (app q, J = 6.1, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 1.75 (m, 1H); $^{13}C\{^1H\}$ (100 MHz) δ 139.0, 128.9, 128.9, 125.1, 121.0, 80.9, 79.2, 41.7, 32.3, 20.9;

5,5-Dimethyl-2-phenyltetrahydrofuran-2-carbonitrile (18): To a solution of 5-methyl-2-phenyl-5-((triethylsilyl)peroxy)hexanenitrile (**10si**, 112.7 mg, 0.338 mmol) in THF (5 mL) at -40 °C was added KO*t*Bu (50.2 mg, 0.447 mmol, 1.3 equiv). The reaction was allowed to come to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 51.1 mg (75%) of tetrahydrofuran **18** as a light yellow oil: R_f = 0.48 (10% EA/Hex); ^{1}H (400 MHz) δ 7.54 (d, J = 7.6, 2H), 7.40 (t, J = 7.6, 2H), 7.37 (t, J = 6.9, 1H), 2.74 (m, 1H), 2.28 (m, 2H), 2.05 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H);^{13}C{^{1}H} (100 MHz) δ 139.3, 128.9, 128.8, 124.9, 121.7, 85.4, 80.7, 42.5, 38.5, 28.9, 28.9; IR: 2973, 2874, 1493, 1449, 1384, 1370, 1227, 1163, 1127, 1045, 1008, 859, 753, 696 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{13}H_{15}NNaO$ $(M + Na)^+$: 224.1051; found: 224.1053.

4-Methyl-2-phenyloxetane-2-carbonitrile (9) was prepared (113.2 mg, 58%) from 2-phenyl-4-((triethylsilyl)peroxy)pentanenitrile (**3si**, 1.13 mmol, 345.2 mg) and KO*t*Bu by the procedure described above (as an 1:1 mixture of diastereomers). Spectral details matched those previously reported:[15a] R_f = 0.38 (10% EA/Hex); ^{1}H (400 MHz) δ 7.48 (d, J = 7.9, 2H), 7.36-7.40 (m, 5H), 7.29-7.32 (m, 3H), 4.73 (m, 1H), 4.13 (m, 1H), 2.71 (m, 1H), 2.38 (m, 1H), 2.06 (m, 1H), 2.00 (m, 1H), 1.53 (d, J = 6.2, 3H), 1.61 (m, 3H), 1.53 (d, J = 6.2, 3H); ^{13}C{^{1}H} (100 MHz) δ 139.5, 138.9, 129.5, 129.1, 128.9, 125.5, 124.8, 120.9, 118.1, 74.5, 69.6, 41.7, 40.7, 21.3; IR: 2932, 1689, 1495, 1448, 1373, 1241, 1045, 913, 757 731, 696, 515 cm^{-1}.

7-methyl-2-phenyloxepane-2-carbonitrile (20) was prepared (44.7 mg, 37%) from peroxide **6si** (0.597 mmol, 199.1 mg) and KO*t*Bu as one major diastereomer by the procedure described above: R_f = 0.53 (10% EA/Hex); ^{1}H (400 MHz) δ 7.54 (d, J = 7.3, 2H), 7.45 (tt, J = 7.1, 2H), 7.38 (t, J = 7.3, 1H), 3.60 (tq, J = 2.8, 6.3, 1H), 2.58 (dt, J = 3.6, 9.8, 1H), 2.27 (ddd, J = 4.1, 11.7,

13.9, 1H), 1.84 (ddd, J = 4.5, 8.6, 12.9, 1H), 1.55 (m, 2H), 1.44 (m, 1H), 1.26 (d, J = 6.2, 3H); $^{13}C\{^{1}H\}$ (100 MHz) δ 136.9, 129.3, 129.1, 126.7, 121.3, 72.7, 68.8, 32.3, 31.7, 21.5, 18.7; IR: 2972, 2941, 2916, 2867, 1492, 1447, 1380, 1373, 1222, 1211, 1180, 1157, 1055, 1031, 990, 914, 761, 699, 608, 472 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{13}H_{15}NNaO$ $(M + Na)^+$: 224.1051; found: 224.1052.

Cyclization to form **17ab** from hydroperoxide **4h**: To a solution of 5-hydroperoxy-2-phenylhexanenitrile (**4h**,1 41.1 mg, 0.687 mmol) in THF (5 mL) at -40 °C was added freshly prepared LDA (0.824 mmol, 1.2 equiv). The reaction was allowed to come to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 36.6 mg (28%) of 24ab (light yellow oil) as a 1.5 : 1 mixture of diastereomers: R_f = 0.47 (10% EA/Hex).

Cyclization to form **17ab** from hydroperoxide **4thp**: To a solution of peroxide **4thp** (147.5 mg, 0.510 mmol) in THF (5 mL) at -40 °C was added KO*t*Bu (72.9 mg, 0.65 mmol, 1.3 equiv). The reaction was allowed to come to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 81.0 mg (85%) of 5-methyl-2-phenyltetrahydrofuran-2-carbonitrile (light yellow oil) as an inseparable 1.1 : 1 mixture of diastereomers: R_f = 0.47 (10% EA/Hex).

(*S*,R)-1-(5-Methyl-2-phenyltetrahydrofuran-2-yl)heptan-1-one** (**21**): Conversion of nitrile **17a** into ketone **21** was based upon a reported procedure.[24a] To a solution of (*2S*, 5R*)-5-methyl-2-phenyltetrahydrofuran-2-carbonitrile (326.4 mg, 1.74 mmol) in THF (10 mL) was added

hexylmagnesium bromide (1.1 mL, 2.2 mmol, 1.3 equiv, 2.0 M in diethyl ether), followed by CuBr (21.4 mg, 0.15 mmol, 0.85 equiv). The reaction was refluxed for 14 hrs. It was then cooled to room temperature and quenched by sequential addition of water (5 mL) and 15% aq. H_2SO_4 (30 mL). The resulting mixture was stirred for 2 h and then extracted with ether (2 x 15 mL). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 370.1 mg (78%) of ketone **21** as a light yellow oil: R_f = 0.75 (10% EA/Hex); ^{1}H (400 MHz) δ 7.45 (d, J = 7.5, 2H), 7.34 (t, J = 7.5, 2H), 7.27 (t, J = 7.5, 1H), 4.30 (m, 1H), 2.99 (dd, J = 7.5, 8.4, 1H), 2.71 (ddd, J =6.1, 8.4, 17.6, 1H), 2.38 (ddd, J = 6.4, 8.4, 17.6, 1H), 1.99 (m, 2H), 1.38-1.52 (m, 3H), 1.35 (d, J = 6.1, 3H), 1.14-1.23 (m, 6H), 0.84 (t, J = 7.3, 3H); ^{13}C{^{1}H} (100 MHz) δ 211.4, 142.3, 128.5, 127.4, 124.9, 92.8, 76.9, 36.7, 36.2, 33.9, 31.6, 28.5, 23.8, 22.6, 21.4, 14.1; IR: 2957, 2928, 2859, 1715, 1490, 1446, 1379, 1098, 1073, 889, 756, 700, 538 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{18}H_{26}NaO_2$ (M + Na)$^+$: 297.1830; found: 297.1833.

2-Hexyltetrahydrofuran-2-carbonitrile (22): To a solution of 2-(3-(*tert*-butylperoxy)propyl)octanenitrile (**9bu**, 206.8 mg, 0.81 mmol) in THF (5 mL) at 0 °C was added PhLi (0.47 mL, 0.893 mmol, 1.1 equiv, 1.9 M in dibutyl ether), The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) pressure to yield 88.1 mg (60%) of nitrile **22** as a light yellow oil: R_f = 0.48 (10% EA/Hex); ^{1}H (400 MHz) δ 3.99 (t, J = 6.8, 2H), 2.37 (ddd, J = 3.9, 8.0, 12.2, 1H), 2.16 (m, 1H), 2.02 (m, 1H), 1.70-1.89 (3H), 1.59 (m, 2H), 1.49 (m, 1H), 1.25-1.39 (6H), 0.89 (t, J = 6.8, 3H); ^{13}C{^{1}H} (100 MHz) δ 121.2, 80.0, 68.9, 38.9, 37.6, 31.7, 29.2, 25.1, 25.0, 22.6, 14.1; IR: 2929, 2860, 1459, 1197, 1125, 1057, 1021, 937, 923, 876, 726 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{11}H_{19}NNaO$ (M + Na)$^+$: 204.1364; found: 204.1367.

(R*,R*, and R*,S*) 2-Hexyl-5-methyltetrahydrofuran-2-carbonitrile (23)

To a solution of 2-(3-(triethylsilyl)peroxy)butyl)octanenitrile (**1si**, 200.8 mg, 0.613 mmol) in THF (2 mL) at 0 °C was added freshly prepared LDA (0.72 mmol, 1.2 equiv) of diisopropylamine and *n*-BuLi (0.46 mL, 0.736 mmol, 1.2 equiv in 3 mL THF). The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) pressure to yield 80.8 g (67%) of nitrile as a light yellow oil which proved to be a single diastereomer of nitrile **23**: R_f = 0.58 (10% EA/Hex); ^{1}H (400 MHz) δ 4.24 (m, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 1.83 (td, J = 4.7, 12.0, 1H), 1.74 (td, J = 4.7, 12.0, 1H), 1.60 (m, 1H), 1.49 (m, 1H), 1.28-1.35 (m, 8H), 0.91 (t, J = 6.7, 3H); ^{13}C{^{1}H} (100 MHz) δ 122.2, 79.4, 78.0, 39.5, 38.9, 33.7, 31.8, 29.3, 24.9, 22.7, 21.6, 14.2; IR: 2955, 2928, 2859, 1459, 1379, 1070, 888, 727 cm^{-1}; HRMS (ESI$^+$, TOF) calcd for $C_{12}H_{21}NNaO$ $(M + Na)^+$: 218.1521; found: 218.1521.

2-Hexyl-5,5-dimethyltetrahydrofuran-2-carbonitrile (24).

To a solution of 2-(3-methyl-3-((triethylsilyl)peroxy)butyl)octanenitrile (**2si**, 197.1 mg, 0.577 mmol) in THF (2 mL) at 0 °C was added freshly prepared LDA (0.688 mmol, 1.2 equiv). The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) pressure to yield 102.7 mg (85%) of the cyanotetrahydrofuran as a light yellow oil: R_f = 0.53 (10% EA/Hex); ^{1}H (400 MHz) δ 2.38 (m, 1H), 2.05 (m, 2H), 1.89 (m, 1H), 1.74 (m, 2H), 1.41 (s, 3H), 1.25-1.38 (m, 8H), 1.23 (s, 3H), 0.89 (t, J = 7.1, 3H); ^{13}C{^{1}H} (100 MHz) δ 122.3, 84.3, 79.5, 40.1, 38.0, 37.8, 31.7, 29.2, 29.1, 28.7,

24.7, 22.6, 14.1; IR: 2955, 2929, 2860, 1682, 1458, 1383, 1369, 1305, 1266, 1134, 1058, 1039, 893, 854, 763, 726, 701, 464 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{13}H_{23}NNaO$ $(M + Na)^+$: 232.1677; found: 232.1680.

6-(3-Hydroxy-3-methylbutyl)dodecan-5-one (25): To a solution of 2-(3-methyl-3-((triethylsilyl)peroxy)butyl)octanenitrile (85.6 mg, 0.25 mmol) in THF (3 mL) at 0 °C was added *n*-BuLi (0.19 mL, 0.3 mmol, 1.2 equiv). The reaction was stirred at room temperature for 1 h. The reaction was quenched with water (5 mL) and extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) pressure to yield 35.8 mg (53%) 6-(3-hydroxy-3-methylbutyl)dodecan-5-one as a light yellow oil: R_f = 0.24 (10% EA/Hex); ^1H (400 MHz) δ 2.40-2.48 (3H), 1.44-1.69 (m, 6H), 1.31-1.42 (4H), 1.22-1.31 (m, 8H), 1.20 (s, 6H), 0.86-0.94 (6H); $^{13}C\{^1H\}$ (100 MHz) δ 215.0, 70.8, 52.6, 42.1, 41.4, 32.0, 31.8, 29.5, 29.4, 29.2, 27.5, 26.1, 25.7, 22.7, 22.5, 14.1, 14.0; IR: 3437, 2957, 2928, 2857, 1705, 1465, 1378, 1217, 1155, 1033, 908, 725, 469 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{17}H_{34}NaO_2$ $(M + Na)^+$: 293.2457; found: 293.2460.

General procedure for cyclization of peroxyalkylsulfones to sulfonyl oxacycles:

To a solution of the peroxide-substituted sulfone (0.70 mmol) in THF (1.5 mL) was added base (unless noted, 0.84 mmol, 1.2 equiv; in a number of cases, additional base was employed). The reaction was stirred at rt for 1 h and then quenched with water (3 mL). The combined EA extracts (10 mL X 3) were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (typically 5% EA/Hex) to yield a light yellow oil.

2-(Phenylsulfonyl)oxetane (26) was prepared (56.3 mg, 41%) from 3-(*tert*-butylperoxy)propyl-sulfonyl benzene (**10bu**, 190.7 mg, 0.70 mmol) and *n*-BuLi by the procedure described above.

Spectral details matched those previously reported:[64] R_f = 0.35 (25% EA/Hex); ^{1}H (400 MHz) δ 7.98 (dd, J = 7.2, ^{4}J = 1.0, 2H), 7.69 (tt, J = 7.2, ^{4}J = 1.0, 1H), 7.58 (t, J = 7.6, 2H), 5.39 (t, J = 6.0, 1H), 4.78 (td, J = 5.5, 8.3, 1H), 4.64 (ddd, J = 2.1, 5.5, 7.6, 1H), 3.08-3.12 (m, 2H); ^{13}C{^{1}H} (100 MHz) δ 135.3, 134.3, 129.5, 129.3, 94.1, 71.4, 22.4

2-(Phenylsulfonyl)tetrahydrofuran (27) was prepared (96.8 mg, 67%) from 4-(*tert*-butylperoxy)butyl-sulfonyl benzene (**11bu**, 200.5 mg, 0.70 mmol) and KO*t*Bu by the procedure described above. Spectral details matched those previously reported:[32a] R_f = 0.40 (25% EA/Hex); ^{1}H (400 MHz) δ 7.94 (dd, J = 7.1, ^{4}J = 1.2, 2H), 7.67 (tt, J = 7.4, ^{4}J = 1.2, 1H), 7.57 (t, J = 7.3, 2H), 4.89 (dd, J = 3.9, 4.2, 1H), 4.14 (dd, J = 7.4, 7.5, 1H), 3.99 (td, J = 5.7, 7.8, 1H), 2.69 (dddd, J = 3.9, 5.8, 8.8, 14.0, 1H), 2.31 (ddd, J = 6.9, 8.5, 15.2, 1H), 2.17 (m, 1H), 1.96 (m, 1H); ^{13}C{^{1}H} (100 MHz) δ 137.1, 133.9, 129.2, 129.0, 94.2, 71.0, 26.0, 25.0.

2-(Phenylsulfonyl)tetrahydro-2*H*-pyran (28) was prepared (95.7 mg, 64%) from 5-(*tert*-butylperoxy)pentyl-sulfonyl benzene (**12bu**, 198.3 mg, 0.66 mmol) and *n*-BuLi by the procedure described above. Spectral details matched those previously reported:[32b] R_f = 0.38 (10% EA/Hex); ^{1}H (400 MHz) δ 7.91 (d, J = 7.3, 2H), 7.65 (t, J = 7.5, 1H), 7.54 (t, J = 7.6, 2H), 4.39 (dd, J = 3.1, 9.7, 1H), 4.10 (m, 1H), 3.46 (m, 1H), 2.10-2.14 (m, 1H), 1.99-2.06 (m, 1H), 1.75-1.85 (m, 1H), 1.50-1.61 (m, 3H); ^{13}C{^{1}H} (100 MHz) δ 136.4, 133.9, 129.5, 129.0, 91.3, 68.7, 24.8, 23.7, 21.5.

(*R*,R** and *R*,S**) **2-Methyl-5-phenylsulfonyl tetrahydrofuran (29ab)**

from methyl peroxide: Tetrahydrofuran **29ab** was prepared (14.9 mg, 14%) from reaction of methyl phenylsulfonyl)pentan-2-yl peroxide (**16me**, 116.8 mg, 0.452 mmol) and LDA using the procedure described above, except that the reactants were mixed at 0 °C and then allowed to warm to rt. The product was a light yellow oil containing an incompletely separated mixture of

diastereomers in an approximately 2:1 ratio: IR 2922, 2853, 1447, 1307, 1285, 1149, 1072, 728, 689, 592, 541 cm^{-1}; HRMS (ESI^+, TOF) calcd for $C_{11}H_{14}NaO_3S$ $(M + Na)^+$: 249.0561; found: 249.0568.

Higher R_f diastereomer: R_f = 0.51 (25% EA/Hex); ^1H (400 MHz) δ 7.92 (d, J = 4.8, 2H), 7.66 (t, J = 4.8, 1H), 7.57 (4.5, 2H), 4.84 (dd, J = 5.0, 8.1, 1H), 4.25 (ddq, J = 2.3, 6.0, 9.5, 1H), 2.74 (ddt, J = 1.8, 7.5, 13.9, 1H), 2.31 (tdd, J = 8.3, 9.2, 11.5, 1H), 2.04 (dddd, J = 1.7, 5.6, 7.8, 14.0, 1H), 1.76 (dddd, J = 2.7, 8.3, 8.8, 11.5, 1H), 1.35 (d, J = 3.5, 3H) $^{13}C\{^1H\}$ (100 MHz) δ 136.8, 133.8, 129.5, 129.0, 94.6, 80.4, 32.1, 27.6, 20.8.

Lower R_f diastereomer: R_f = 0.48 (25% EA/Hex); ^1H (400 MHz) δ 7.93 (d, J = 4.2, 2H), 7.66 (t, J = 4.3, 1H), 7.56 (4.5, 2H), 4.93 (dd, J = 2.1, 8.6, 1H), 4.47 (ddq, J = 1.8, 6.0, 7.8, 1H), 2.66 (dddd, J = 4.9, 8.4, 8.4, 16.7, 1H), 2.39 (dddd (app dtd), J = 4.5, 9.1, 13.7, 1H), 2.24 (ddd, J = 5.8, 8.8, 12.6, 1H), 1.53 (ddt, J = 8.5, 8.5,12.0, 1H), 1.22 (d, J = 3.5, 3H); $^{13}C\{^1H\}$ (100 MHz) δ 137.2, 133.8, 129.2, 129.1, 94.1, 78.7, 32.4, 25.8, 20.4.

5-(Phenylsulfonyl)pentan-2-ol (30). Attempted cyclization of **16si** afforded good yields of alcohol **30** under several sets of conditions (see Table 7); for brevity, only the reaction with KOtBu is described. Reaction of **16s**i (183.6 mg, 0.512 mmol) with KOtBu (1.3 equiv) using the general procedure described for peroxy-substituted sulfones followed by warming to rt. To a solution of triethyl))5-(phenylsulfonyl)pentan-2-yl)peroxy)silane (183.6 mg, 0.512 mmol) in THF (5 mL) at 0 °C was added KO*t*Bu (72.4 mg, 0.645 mmol, 1.3 equiv). The reaction was allowed to slowly warm to room temperature. After 1 h, the reaction was quenched with water (5 mL) and the mixture extracted with EA (10 mL X 3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue purified by column chromatography (5% EA/Hex) to yield 115.0 mg (98%) of the alcohol as a light yellow solid (mp = 45-48 °C). Spectral details matched those previously reported.[65] R_f = 0.15 (30% EA/Hex); ^1H (400 MHz) δ 7.90 (d, J = 7.5, 2H), 7.65 (t, J = 7.4, 1H), 7.56 (t, J = 7.6, 2H), 5.29 (s, 1H), 3.77

(sextet, J = 6.1, 1H), 3.13 (t, J = 7.9, 2H), 1.87 (ddt, J = 5.7, 6.1,13.9, 2H), 1.48-1.54 (m, 2H), 1.16 (d, J = 6.2); $^{13}C\{^{1}H\}$ (100 MHz) δ 139.2, 133.8, 129.4, 128.1, 67.4, 56.2, 37.3, 23.7, 19.3; IR 3384, 2960, 2926, 1299, 1278, 1140, 1085, 789, 754, 693, 563, 534, 430 cm^{-1}; HRMS (ESI^{+}, TOF) calcd for $C_{11}H_{16}NaO_3S$ $(M + Na)^{+}$: 251.0718; found: 251.0721.

Acknowledgements: Funding was provided by NSF (CHE 1464914). We thank Prof. Martha Morton for technical assistance and insightful suggestions.

Supporting Information: Supporting Information, available free of charge on the ACS Publications website, includes: ^{1}H and ^{13}C NMR spectra of all new molecules and other selected structures; tables of spectral assignments related to compound **21**.

References:

[1] a. Martin, T.; Padron, J. I.; Martin, V. S. Strategies for the synthesis of cyclic ethers of marine natural products. *Synlett*, **2014**, *25*, 12-32; b. Cossy, J., ed. Chemistry of Saturated Oxygen Heterocycles I, *Topics in Heterocyclic Chemistry v. 35*, Springer-Verlag Berlin Heidelberg **2014**; DOI https://doi.org/10.1007/978-3-642-41473-2; c. Cossy, J., ed. Synthesis of Saturated Oxygen Heterocles II; *Topics in Heterocyclic Chemistry v. 36*, Springer-Verlag: Berlin, **2014**; https://doi.org/10.1007/978-3-642-41470-1; d. Gupta, R. R.; Kumar. M.; Gupta, V. Four-Membered Heterocycles. In: Heterocyclic Chemistry. Springer, Berlin, Heidelberg 1998; e. Wolfe, J.P. ed., Synthesis of Heterocycles via Metal-Catalyzed Reactions that Generate One or More Carbon-Heteroatom Bonds, *Topics in Heterocyclic Chemistry, v. 32*; Springer-Verlag: Berlin Heidelberg, **2013**; https://doi.org/10.1007/978-3-642-38880-4; f. Nasir, N. M.; Ermanis, K.; Clarke, P. A. Strategies for the construction of tetrahydropyran rings in the synthesis of natural products. *Org. Biomol. Chem.* **2014**, *12*, 3323-3335; g. Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. *Chem. Rev.* **2016**, *116*, 12150-12233.

[2] *Substitution:* a. Inoue, M.; Yamashita, S. "Product Class: 5-, 6- and Larger Ring Oxacycloalkanes," *Science of Synthesis,* **2008**, *37*, 584; online at 37.5.1.1.1.1, doi 10.1055/sos-SD-037-00384 (accessed 6/21/2019); b. Boivin, T. L. B. , Synthetic routes to tetrahydrofuran, tetrahydropyran, and spiroketal units of polyether antibiotics and a survey of spiroketals of other natural products. *Tetrahedron*, **1987** *43*, 3309-3362.

[3] *Metal- catalyzed substitution*: a. Palucki, M.; Wolfe, J. P.; Buchwald, S. L., Synthesis of Oxygen Heterocycles via a Palladium-Catalyzed C−O Bond-Forming Reaction. *J. Am. Chem. Soc*. **1996**, *118*, 10333-10334; b. Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem. Int. Ed*, **1998**, *37*, 2046-2067.

[4] *Reaction with halonium and similar electrophiles:* Cardillo, G.; Orena, M.; Stereocontrolled cyclofunctionalizations of double bonds through heterocyclic intermediates. *Tetrahedron* **1990**, *46*, 3321-3408.

[5] Willand-Charnley, R.; Puffer, B. W.; Dussault, P. H. Oxacycle synthesis via intramolecular reaction of carbanions and peroxides. *J. Am. Chem. Soc.* **2014**, *136*, 5821–5823.

[6] a. Fleming, F. F.; Zhang, Z. Cyclic nitriles: tactical advantages in synthesis. *Tetrahedron*, **2005**, *61*, 747-789. b. Fatiadi, A. J. Preparation and synthetic applications of cyano compounds. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S.; Rappoport, Z. eds.; Wiley; 1983. doi:10.1002/9780470771709.ch9 (accessed June 2019).

[7] a. El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. Evolving organic synthesis fostered by the pluripotent phenylsulfone moiety. *Chem. Rev.* **2009**, *109*, 2315-2349; b. Simpkins, N.S.; Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, **1993**.

[8] a. Freerksen, R. W.; Selikson, S. J.; Wroble, R. R.; Kyler, K. S.; Watt, D. S. Oxidative Decyanation of Secondary Nitriles to Ketones. *J. Org. Chem.* **1983**, *48*, 4087–4096; b. Larsen, E. H.; Lawesson, S. O. Diethyl [*O*-benzoyl]ethyltartronate. *Org. Synth.* **1965**, *45*, 37–39.

[9] Chemla, F.; Julia, M.; Uguen, D. Conversion of primary sulfones into α-silyloxysulfones and aldehydes. *Bull. Soc. Chim. Fr.* **1993**, *130*, 547–553.

[10] Yang, N. C.; Finnegan, R. A. A New Method for the Epoxidation of α, β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1958**, 80, 5845-5848.

[11] *Epoxidation of alkenyl nitriles:* a. Payne, G. B.; Williams, P. H. Reactions of Hydrogen Peroxide. VI. Alkaline Epoxidation of Acrylonitrile. *J. Org. Chem*. **1961**, *26*, 651–659; b. Kamata, K.; Sugahara, K.; Yonehara, K.; Ishimoto, R.; Mizuno, N. Efficient Epoxidation of Electron-Deficient Alkenes with Hydrogen Peroxide Catalyzed by $[\gamma\text{-}PW_{10}O_{38}V_2(\mu\text{-}OH)_2]^{3-}$. *Chem. Eur. J.* **2011**, *17*, 7549–7559; c. De Fusco, C.; Tedesco, C.; Lattanzi, A. Organocatalytic stereoselective epoxidation of trisubstituted acrylonitriles. *J. Org. Chem.* **2010**, *76,* 676-679.; d. Tse, M. K.; Klawonn, M.; Bhor, S.; Döbler, C.; Anilkumar, G.; Hugl, H.; Mägerlein, W.; Beller, M. Convenient Method for Epoxidation of Alkenes Using Aqueous Hydrogen Peroxide. *Org. Lett*. **2005**, *7*, 987–990.

[12] *Epoxidation of alkenyl sulfones*: a. Zwanenberg, B.; Ter Wiel, J. α,β-Epoxysulfones by epoxidation of α,β-unsaturated sulfones *Tetrahedron Lett.* **1970**, 935–936; b. Meth-Cohn, O.; Moore, C.; Taljaard, H. C. A Stereocontrolled Approach to Electrophilic Epoxides. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 2663–2674; c. Bäckvall, J. E.; Juntunen, S. K. 2-(Phenylsulfonyl)-1,3-Dienes as Versatile Synthons in Organic Transformations. Functionalizations via Epoxidation Reactions. *J. Org. Chem.* **1988**, *53*, 2398–2400.

[13] a. Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, 1071-1074; b. Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. Co(III)-alkyl complex- and Co(III)-alkylperoxo complex-catalyzed triethylsilylperoxidation of alkenes with molecular oxygen and triethylsilane. *Org. Lett.* **2002**, *4*, 3595–3598.

[14] Kyasa, S. K.; Meier, R. N.; Pardini, R. A.; Truttmann, T. K.; Kuwata, K. T.; Dussault, P. H. Synthesis of Ethers via Reaction of Carbanions and Monoperoxyacetals. *J. Org. Chem.* **2015**, *80*, 12100–12114.

[15] a. Arseniyadis, S.; Kyler, K. S.; Watt, D. S. Addition and Substitution Reactions of Nitrile-Stabilized Carbanions. *Org. React.* **1984**, *31*, 1–364; b. Winterfeld, K.; Kullmar, K.; Gobel, W. 1-(2-Chloroethyl)- 2 chloromethylpiperidine (German). *Chem. Ber.* **1959**, *92*, 1510–1517.

[16] Fleming, F. F.; Gudipati, V.; Steward, O. W. 2003. ω-Halonitriles: Domino Cyclizations to Oxa-and Carbocyclic Nitriles. *J. Org. Chem.* **2003**, *68*, 3943-3946.

[17] Pine, S. H.; Shen, G.; Bautista, J.; Sutton Jr, C.; Yamada, W.; Apodaca, L. Monoalkylation vs. dialkylation of a sulfone-stabilized carbanion. *J. Org. Chem.* **1990**, *55*, 2234-2237.

[18] Milas, N. A.; Peeler, R. L. Jr.; Mageli, O. L. Organic Peroxides. XIX. α-Hydroperoxyethers and Related Peroxides. *J. Am. Chem. Soc*. **1954**, *76*, 2322-2325.

[19] Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912–9000.

[20] a. Kornblum, N.; DeLaMare, H. E. Base catalyzed decomposition of a dialkyl peroxide. *J. Am. Chem. Soc*. **1951**, *73*, 880–881; b. Yaremenko, I. A.; Vil', V. A.; Demchuk, D. V.; Terent'ev, A. O. Rearrangements of organic peroxides and related processes. *Beilstein J. Org. Chem*. **2016**, *12*, 1647–1748.

[21] *Reduction to amines:* a. Amundsen, L. H.; Nelson, L. S. Reduction of Nitriles to Primary Amines with Lithium Aluminum Hydride. *J. Am. Chem. Soc.* **1951**, *73*, 242–244; b. *Addition of organometallics:* Weiberth, F. J.; Hall, S. S. Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines. *J. Org. Chem.* **1987**, *52*, 3901–3904; c. *Ketones via Aldehydes:* Crimmins, M. T.; Jung, D. K.; Gray, J. L. Synthetic Studies on the Ginkgolides: Total Synthesis of Bilobalide. *J. Am. Chem. Soc.* **1993**, *115*, 3146–3155; d. *Decyanation:* Rychnovsky, S. D.; Swenson, S. S. Alkylation and Reductive Decyanation of 4-Cyano-2,2-dimethyl-1,3-dioxanes (Cyanohydrin Acetonides). *J. Org. Chem.* **1997**, *62*, 1333–1340; e. Mattalia, J.-M. R. The reductive decyanation reaction: an overview and recent developments. *Beilstein J. Org. Chem.* **2017**, *13*, 267-284.

[22] Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S.; Modular radical cross-coupling with sulfones enables access to sp3-rich (fluoro) alkylated scaffolds. *Science*, **2018**, *360*, 75-80.

[23] Nájera, C.; Yus, M. Desulfonylation reactions: recent developments. *Tetrahedron*, **1999**, *55*, 10547-10658.

[24] a. Stork, G.; Maldonado, L. Anions of protected cyanohydrins as acyl carbanion equivalents and their use in a new synthesis of ketones. *J. Am. Chem. Soc.* **1971**, *93*, 5286-5287; b. Morin, M. D.; Rychnovsky, S. D. Reductive spiroannulation of nitriles with secondary electrophiles. *Org. Lett.* **2005**, *7*, 2051-2053.

[25] a. Oishi, T.; Suzuki, M.; Watanabe, K.; Murata, M. Convergent synthesis of the CDEF ring fragment of yessotoxin via α-cyano ethers. *Heterocycles*, **2006**, *69*, 91-98; b. Oishi, T.;

Hasegawa, F.; Torikai, K.; Konoki, K.; Matsumori, N.; Murata, M.; Convergent synthesis and biological activity of the WXYZA′ B′ C′ ring system of maitotoxin. *Org. Lett.* **2008**, *10*, 3599-3602;

[26] Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. Use of 2-phenylsulphonyl cyclic ethers in the preparation of tetrahydropyran and tetrahydrofuran acetals and in some glycosidation reactions. *Tetrahedron*, **1991**, *47*, 1329-1342.

[27] Zhang, R.; Kang, K.-D.; Shan, G.; Hammock, B. D. Design, synthesis and evaluation of novel P450 fluorescent probes bearing α-cyanoether. *Tetrahedron Lett.* **2003**, *44*, 4331-4334.

[28] Warren, T. K.; Jordan, R.; Lo, M. K.; Ray, A. S.; Mackman, R. L.; Soloveva, V.; Siegel, D.; Perron, M.; Bannister, R.; Hui, H. C.; Larson, N.; Strickley, R.; Wells, J.; Stuthman, K. S.; Van Tongeren, S. A.; Garza, N. L.; Donnelly, G.; Shurtleff, A. C.; Retterer, C. J.; Gharaibeh, D.; Zamani, R.; Kenny, T.; Eaton, B. P.; Grimes, E.; Welch, L. S.; Gomba, L.; Wilhelmsen, C. L.; Nichols, D. K.; Nuss, J. E.; Nagle, E. R.; Kugelman, J. R.; Palacios, G.; Doerffler, E.; Neville, S.; Carra, E.; Clarke M. O.; Zhang, L.; Lew, W.; Ross, B.; Wang, Q.; Chun, K.; Wolfe, L.; Babusis, D.; Park, Y.; Stray, K. M.; Trancheva, I.; Feng, J. Y.; Barauskas, O.; Xu, Y.; Wong, P.; Braun, M. R.; Flint, M.; McMullan, L. K.; Chen, S. S.; Fearns, R.; Swaminathan, S.; Mayers, D. L.; Spiropoulou, C. F.; Lee, W. A.; Nichol, S. T.; Cihlar, T.; Bavari, S. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*, **2016**, *531*, 381-385.

[29] a. Dembech, P.; Seconi, G.; Ricci, A. The Electrophilic Amination of Carbanions : An Unconventional New Entry to C-N Bond Formation. *Chem. Eur. J.* **2000**, *6*, 1281–1286; b. Armstrong, A.; Atkin, M. A.; Swallow, S. Electrophilic amination of carbanions by *N* -carboxamido oxaziridines. *Tetrahedron Lett.* **2000**, *41*, 2247–2251; c. Erdik, E.; Ay, M. Electrophilic Amination of Carbanions. *Chem. Rev.* **1989**, *89*, 1947–1980; d. Ciganek, E. Electrophilic Amination of Carbannions, Enolates, and their Surrogates. *Org. React.* **2008**, 72, 1–366;

[30] a. Ager, D. J. The Synthesis of Ketones via α-Silyl Sulphides. *J. Chem. Soc. Perkin Trans. 1,* **1986**, 195–204; b. Chemla, F.; Julia, M.; Uguen, D. Conversion of primary sulfones into α-silyloxysulfones and aldehydes. *Bull. Soc. Chim. Fr.* **1993**, *130*, 547–553; c. Parsons, Z. D.; Ruddraraju, K. V.; Santo, N.; Gates, K. S. Sulfone-stabilized carbanions for the reversible covalent capture of a posttranslationally-generated cysteine oxoform found in protein tyrosine phosphatase 1B (PTP1B). *Bioorganic Med. Chem.* **2016**, *24*, 2631–2640; d. Chemla, F. α-Oxy sulfones and sulfoximines: versatile intermediates. *J. Chem. Soc. Perkin Trans. 1*, **2002**, 275-299;

[31] Sulfonyl oxetanes: Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. Studies on the synthesis, stability and conformation of 2-sulfonyl-oxetane fragments. *Org. Biomol. Chem*. **2015**, *13*, 5265–5272.

[32] Sulfonyl tetrahydrofurans: a. Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. Substitution Reactions of 2-Benzenefsulphonyl Cyclic Ethers with Carbon Nucleophiles. *Tetrahedron* **1989**, *45*, 4293–4308; b. Kamijo, S.; Hirota, M.; Tao, K.; Watanabe, M.; Murafuji, T. Photoinduced sulfonylation of cyclic ethers. *Tetrahedron Lett*. **2014**, *55*, 5551–5554.

[33] Sulfonyl tetrahydropyrans: a. Ley, S. V, Lygo, B.; Sternfeld, F.; Wonnacott, A. Alkylation Reactions of Anions Derived From 2-Benzensulphonyl Tetrahydropyran and Their Application to Spiroketal Synthesis. *Tetrahedron*, **1986**, *42*, 4333–4342; b. Chen, G.; Franck, R. W.; Yang, G.; Blumenstein, M. Anomeric effects of sulfones. *Can. J. Chem*. **2002**, *80*, 894–899.

[34] a. Goodman, R. M.; Kishi, Y. Experimental Support for the Primary Stereoelectronic Effect Governing Baeyer-Villiger Oxidation and Criegee Rearrangement *J. Am. Chem. Soc.* **1998**, *120*, 9392-9393; b. Criegee, R. The rearrangement of decahydronaphthalene peroxide esters resulting from cationic oxygen. *Liebigs Ann. Chem.* **1948**, *560*, 127-135; c. Kropf, H. In *Methoden der Organischen Chemie*, 4th ed.; Kropf, H.; Ed.; Thieme: Stuttgart, **1988**; Vol. E13; pp 1095**–**1099;

[35] a. Monteiro, H. J.; Zukerman-Schpector, J. A new practical synthesis of (+)-grandisol from (+)-citronellol using an intramolecular carbenoid cyclization. *Tetrahedron*, **1996**, *52*, 3879-3888; b. Benedetti, F.; Fabrissin, S.; Rusconi, A.; Stirling, C. J. M. Transition States in Intramolecular S_N2 Reactions of Carbanions. The Closure of 3-, 4-and 5-Membered Rings. *Gazz. Chim. Ital*. **1988**, *118*, 233-240; c. Kitagaki, S.; Teramoto, S.; Mukai, C. Ring-closing reaction of allenic/propargylic anions generated by base treatment of sulfonylallenes. *Org. Lett.* **2007**, *9*, 2549-2552.

[36] Mąkosza, M.; Judka, M. New Reactions of γ-Halocarbanions: Simple Synthesis of Substituted Tetrahydrofurans. *Chem. Eur. J.* **2002**, *8*, 4234-4240.

[37] a. Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H. Nucleophilicities of the Anions of Arylacetonitriles and Arylpropionitriles in Dimethyl Sulfoxide. *J. Org. Chem.* **2008**, *74*, 75-81 b. Strzalko, T.; Wartski, L.; Corset, J.; Castellà-Ventura, M.; Froment, F. Study of the Lithiated Phenylacetonitrile Monoanions and Dianions Formed According to the Lithiated Base Used

(LHMDS, LDA, or n-BuLi). 2. Alkylation and Deuteriation Mechanism Study by Vibrational and NMR Spectroscopy and Quantum Chemistry Calculations. *J. Org. Chem.* **2012**, *77*, 6431-6442.

[38] Viteva, L.; Gospodova, T.; Stefanovsky, Y.; Simova, S. Diastereoselectivity in addition of nitrile-stabilized carbanions to Schiff bases and in subsequent alkylation reactions. *Tetrahedron* **2005**, *61*, 5855–5865.

[39] Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W.; C-Metalated Nitriles: Electrophile-Dependent Alkylations and Acylations. *J. Org. Chem*. **2006**, *71*, 1430–1435.

[40] Capobianco, A. , Russo, A. , Lattanzi, A.; Peluso, A. On the Mechanism of Asymmetric Epoxidation of Enones Catalyzed by α,α-*L*-Diarylprolinols: A Theoretical Insight. *Adv. Synth. Catal.* **2012**, *354*, 2789-2796.

[41] Nugent, W. A.; Bertini, F.; Kochi, J. K. Electron transfer from organolithium and Grignard reagents. Reactions with peroxides. *J. Am. Chem. Soc.* **1974**, *96*, 4945-4954.

[42] a. Harmange, J. C.; Figadère, B. Synthetic routes to 2, 5-disubstituted tetrahydrofurans. *Tetrahedron: Asym.* **1993**, *4*, 1711-1754. b. Wolfe, J. P.; Hay, M. B. Recent advances in the stereoselective synthesis of tetrahydrofurans. *Tetrahedron*, **2007**, *63*, 261-290.

[43] Panek, E. J; Kaiser, L. R; Whitesides, G. M. Vinylic radicals are intermediates in the oxidation of vinylic lithium reagents to lithium enolates by dioxygen, but not by lithium tert-butyl peroxide. *J. Am. Chem. Soc,* **1977**, *99*, 3708-13; b. Boche, G.; Bosold, F.; Lohrenz, J. C. W. Oxenoid character of metalated hydroperoxides O(M)OR: oxidation of organometallic compounds R'M' to R'OH under mild conditions. *Angew. Chem. Int. Ed*. **1994,** *106*, 1228-30; c. Minko, Y.; Marek, I. Oxenoids in organic synthesis. *Org. Biomol. Chem.* **2014**, *12*, 1535-1546.

[44] Hine, J.; Ghirardelli, R. The S_N2 Reactivity of β-Fluorethyl Iodides. *J. Org. Chem.* **1958**, *23*, 1550-1552.

[45] a. Knappe, E.; Peteri, D. Düinnschichtchromatographische Identifizierung organischer Peroxide. *Z. Anal. Chem* **1962**, *190*, 386-389. b. Smith, L. L.; Hill, F. L. Detection of sterol hydroperoxides on thin-layer chromatoplates by means of the Wurster dyes. *J. Chrom. A*. **1972**, *66*, 101-109.

[46] Wang, M.-X.; Zhao, S.-M. Synthesis of enantiomerically enriched (*S*)-(+)-2-aryl-4-pentenoic acids and (*R*)-(-)-2-aryl-4-pentenamides via microbial hydrolysis of nitriles, a chemoenzymatic approach to stereoisomers of α,γ-disubstituted γ-butyrolactones. *Tetrahedron Asym.* **2002**, *13*, 1695–1702.

[47] Wu, P. L.; Wang, C. C. The Flash Vacuum Thermolysis of N-Acyl Imidates. *J. Chin. Chem. Soc.* **1991**, *38*, 273–276.

[48] a. Adam, W.; Catalani, L. H.; Saha-Möller, C. R. Synthesis of Trialkylsilylated α-Hydroperoxy Aldehydes and Ketones via Ozonolysis of Protected Allylic Hydroperoxides. *Synthesis* **1989,** 121-3; b. Dussault, P. H.; Lee, I. Q.; Lee, H. J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. Peroxycarbenium-mediated C-C bond formation: Applications to the synthesis of hydroperoxides and peroxides. *J. Org. Chem.* **2000**, *65*, 8407–8414.

[49] Sanaboina, C.; Jana, S.; Chidara, S.; Patro, B.; Raolji, G. B.; Eppakayala, L. Synthesis of indolo[2,3-a]quinolizine and hexahydro-1H-indolizino[8,7-b] indole derivatives by cascade condensation, cyclization, and Pictet-Spengler reaction: An application to the synthesis of (±)-harmicine. *Tetrahedron Lett.* **2012**, *53*, 5027–5029.

[50] a. Jiang, X.-R.; Wang, P.; Smith, C. L.; Zhu, B. T. Synthesis of Novel Estrogen Receptor Antagonists Using Metal-Catalyzed Coupling Reactions and Characterization of Their Biological Activity. *J. Med. Chem.* **2013**, *56*, 2779–2790; b. Siebum, A. H. G.; Tsang, R. K. F.; Van Der Steen, R.; Raap, J.; Lugtenburg, J. Synthesis of (ε-^{13}C-,ε-^{15}N)-enriched L-lysine - Establishing schemes for the preparation of all possible ^{13}C and ^{15}N isotopomers of *L*-lysine, *L*-ornithine, and *L*-proline. *Eur. J. Org. Chem.* **2004**, *21*, 4391–4396.

[51] Dussault, P. H.; Sahli, A. 2-Methoxy-2-propyl hydroperoxide: a convenient reagent for the synthesis of hydroperoxides and peracids. *J. Org. Chem.* **1992**, *57*, 1009-12; safety warning: *Chem. Eng. News.* **1993**, 7*1*(32, 9 Aug), 2.

[52] Martin, R. E.; Plancq, B.; Gavelle, O.; Wanger, B.; Fischer, H.; Bendels, S.; Muller, K. Remote Modulation of Amine Basicity by a Phenylsulfone and a Phenylthio Group. *ChemMedChem.* **2007**, *2*, 285–287.

[53] Yoon, N. M.; Choi, J.; Ahn, J. H. Convenient Synthesis of Phenyl Sulfides by a Borohydride Exchange Resin-Phenyl Disulfide System in Methanol. *J. Org. Chem.* **1994**, *59*, 3490–3493.

[54] Leicht, H.; Gottker-Schnetmann, I.; Mecking, S. Synergetic Effect of Monomer Functional Group Coordination in Catalytic Insertion Polymerization. *J. Am. Chem. Soc.* **2017**, *139*, 6823–6826.

[55] Jereb, M. Highly atom-economic, catalyst- and solvent-free oxidation of sulfides into sulfones using 30% aqueous H_2O_2. *Green Chem.* **2012**, *14*, 3047–3052.

[56] Wodtke, R.; Koenig, J.; Pigorsch, A.; Kocekerling, M.; Mamat, C. Evaluation of novel fluorescence probes for conjugation purposes using the traceless Staudinger ligation. *Dye. Pigment.* **2015**, *113*, 263–273.

[57] Rao, S. A.; Chou, T. S.; Schipor, I.; Knochel, P. Preparation and Reactivity of Polyfunctional Zinc and Copper Organometallics Bearing Sulfur Functionalities. *Tetrahedron* **1992**, *48*, 2025–2043.

[58] Loughlin, W.; Haynes, R. Preparation of Some Novel Butyl, Butenyl, Butadienyl and Butynyl Sulfone Electrophiles for Use in Enolate Trapping Studies. *Aust. J. Chem.* **1996**, *48*, 651–661.

[59] Feng, J-B.; Gong, J-L.; Wu, X-F. The first zinc-catalyzed oxidation of sulfides to sulfones using H_2O_2 as green oxidant. *RSC Adv.* **2014**, *4*, 29273–29275.

[60] Fisher, T. J.; Dussault, P. H. Fragmentation of chloroperoxides; hypochlorite-induced dehydration of hydroperoxyacetals to esters. *Tetrahedron Lett*. **2010**, 51, 5615–5617.

[61] Zhang, Y.; Lee, J.-H.; Danishefsky, S. J. Antarafacial Mediation of Oxygen Delivery by a Phenylsulfinyl Group in the Epoxidation of Proximal Double Bonds : Intramolecular Trapping of an Early Pummerer Intermediate. *J. Am. Chem. Soc.* **2011**, *133*, 752–755.

[62] Rigaudy, J.; Izoret, G. Addition of hydroperoxides to activated double bonds of vinyl ethers. *Compt. Rend*. **1953**, *236*, 2086-8.

[63] Gharpure, S. J.; Vishwakarma, D. S.; Nanda, S. K. Lewis Acid Mediated “endo-dig” Hydroalkoxylation–Reduction on Internal Alkynols for the Stereoselective Synthesis of Cyclic Ethers and 1,4-Oxazepanes. *Org. Lett.* **2017**, *19*, 6534–6537.

[64] Morgan, K.; Hollingsworth, I.; Bull, J. 2-(Aryl-sulfonyl)oxetanes as designer 3-dimensional fragments for fragment screening: synthesis and strategies for functionalisation. *Chem. Commun.* **2014**, *50*, 5203–5205.

[65] Brimble, M. A.; Officer, D. L.; Williams, G. M. A Facile Synthesis of Spiroketals. *Tetrahedron Lett.* **1988**, *29*, 3609–3612.