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Articles

Peroxycarbenium-Mediated C−C Bond Formation: Applications to the Synthesis of Hydroperoxides and Peroxides

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The Lewis acid-mediated reaction of alkene nucleophiles with peroxyacetals provides an effective route for the synthesis of homologated peroxides and hydroperoxides. In the presence of Lewis acids such as $TiCl_4$, $SnCl_4$, and trimethylsilyl triflate, peroxyacetals and peroxyketals undergo reaction with allyltrimethylsilane, silyl enol ethers, and silyl ketene acetals to afford homoallyl peroxides, 3-peroxyketones, and 3-peroxyalkanoates, respectively. Reactions of peroxyacetals are Lewis acid dependent; $TiCl_4$ promotes formation of ethers while $SnCl_4$ and trimethylsilyl triflate promote formation of peroxides. Lewis acid-promoted reactions of silylated hydroperoxyacetals furnish silylated hydroperoxides, which can be deprotected to homologated hydroperoxides. Hydroperoxyketals undergo Lewis acid-mediated allylation to furnish 1,2-dioxolanes via attack of hydroperoxide on the intermediate carbocation. Lewis acid-mediated cyclization of unsaturated peroxyacetals furnishes 1,2-dioxanes, 1,2-dioxepanes, and 1,2-dioxacanes through 6-*endo*/*exo*, 7-*endo*/*endo*, and 8-*endo*/*endo* pathways. The corresponding reactions involving 6-*endo*/*endo* and 5-*endo*/*exo* pathways were unsuccessful.

The growing number of bioactive peroxide natural products has led to increased awareness of the need for improved synthetic methodology.[1−3] We recently reported a new strategy for peroxide synthesis based upon Lewis acid-mediated reactions of monoperoxyacetals with electron-rich alkenes, a process involving intermediate peroxycarbenium ions (Scheme 1).[4] The corresponding chemistry of nonperoxidic acetals is an important method for synthesis of ethers, and we were curious whether reactions of peroxyacetals might offer a similarly versatile approach to functionalized peroxides.[5−9] This paper demonstrates the scope of the peroxycarbenium ion chemistry for construction of acyclic and cyclic ethers, peroxides, and hydroperoxides and illustrates the influence of Lewis acid, substrate, and nucleophile on reaction selectivity (Scheme 1).

Substrates. The majority of monoperoxyacetal substrates were prepared through ozonolysis of alkenes or enol ethers, followed by alkylation or silylation of the

(1) Dussault, P. H. In *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie A & P: London, 1995; p 141.
(2) Porter, N. A. In *Organic Peroxides*; Ando, W., Ed.; John Wiley & Sons: Chichester, 1992; p 101.
(3) Sheldon, R. A. In *Chemistry of Peroxides*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1983; Vol. 1, p 161.
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(6) Majetich, G. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, CT, 1989; Vol. 1, p 173.
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Scheme 1. Peroxycarbenium Ion Disconnection

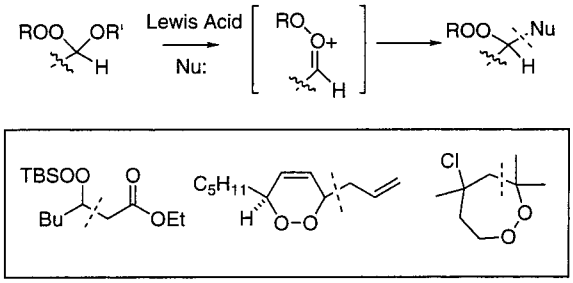
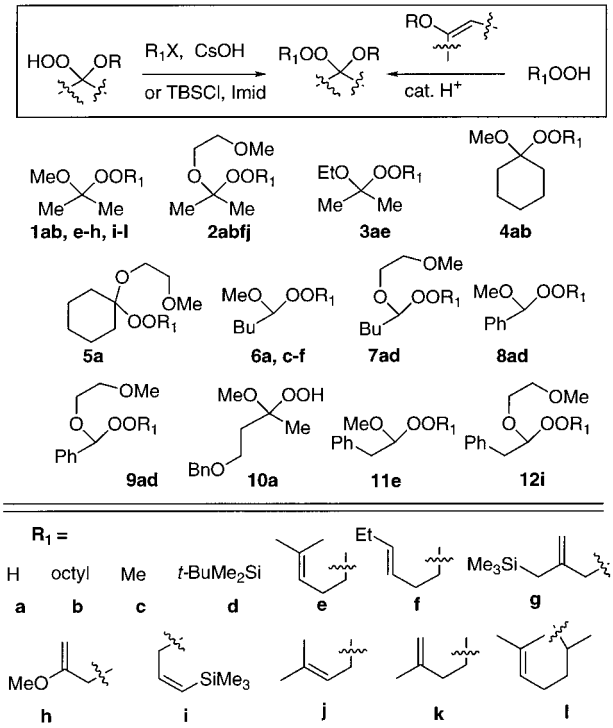


Table 1. Substrate Preparation

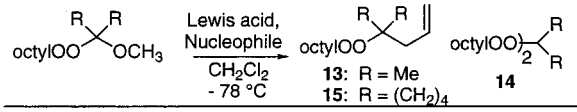


resulting hydroperoxyacetals (Table 1).[10−13] Substrates **4b**, **11e**, and **12i** were obtained from acid-catalyzed acetalization of hydroperoxides.[14,15]

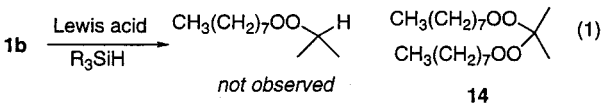
Allylation of Monoperoxyketals. Allylation of monoperoxyketals was initially investigated under conditions analogous to those reported for nonperoxidic acetals.[5,16] Addition of $TiCl_4$ to a solution of allyltrimethylsilane and peroxyketal **1b** led to the rapid formation of homoallyl peroxide **13** (Table 2); premixing the peroxyketal and $TiCl_4$ resulted in a slight improvement. Moderate to good yields were also obtained in the presence of $SnCl_4$ and BCl_3. Use of $BF_3{\cdot}OEt_2$ resulted in formation of a bisperoxyketal dimer (**14**).[17] The corresponding $SnCl_4$- or $TiCl_4$-mediated allylation of cyclohexanone monoperoxyketal **4b** provided good yields of peroxide **15**.

Attempted Reduction of Peroxyketals. The reduction of acetals in the presence of Lewis acids and a mild hydride source is an important method for synthesis of ethers.[18] The stability of the peroxyketals toward hydride-transfer agents (ketal **1b**, for example, is unaffected by brief treatment with Et_3SiH or *n*-Bu_3SnH and related ketals are known to survive reduction of aldehydes by aluminum hydrides)[19,20] led us to investigate Lewis acid-mediated reduction as an approach to secondary peroxides. However, attempted reduction under conditions similar to those employed for nonperoxidic acetals led only to decomposition or disproportionation (eq 1).[21,22]

Table 2. Allylation of Monoperoxyketals



Lewis acid	Nucleophile	Product	Yield
1b $TiCl_4$	$allylSiMe_3$	**13**	86
1b $TiCl_4$	$allylSnBu_3$	**13**	82
1b $SnCl_4$	$allylSiMe_3$	**13**	50
1b Et_2AlCl	$allylSiMe_3$	**13**	10
1b $BF_3{\cdot}OEt_2$	$allylSiMe_3$	**14**	60
1b BCl_3	$allylSiMe_3$	**13**	45
4b $TiCl_4$	$allylSiMe_3$	**15**	85
4b $TiCl_4$	$allylSnBu_3$	**15**	80
4b $SnCl_4$	$allylSiMe_3$	**15**	80



Reactions of Peroxyacetals: Synthesis of Secondary Peroxides and Hydroperoxides. The allylation of peroxyacetals, investigated as an approach to secondary peroxides and hydroperoxides, displayed a strong dependence on Lewis acid (Table 3). For example, $TiCl_4$-mediated allylation of **6c** occurred at −78 °C to afford homoallyl ether **16**. $SnCl_4$-mediated reaction did not occur at −78 °C; however, warming to 0 °C resulted in highly selective formation of peroxide **17**. Addition at 0 °C resulted in a mixture of ether and peroxide. Other promoters were less effective. A similar Lewis acid dependence was observed for acetals **6d** and **8d**. The tendency of $TiCl_4$ to promote formation of ether (loss of peroxide) could be reversed by the use of methoxyethoxy acetals **7d** and **9d**.[23−25] The use of allyltributyltin gave lower yields, implying a competition between allylation and transmetalation to a less nucleophilic allylstannane.[26]

Deprotection of the allylated silyl peroxide (**19**) provided hydroperoxide **22**,[12,27] with the overall four-step procedure (ozonolysis, silylation, allylation, and depro-

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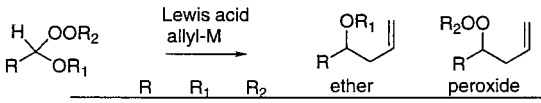
(27) Adam, W.; Catalani, L. H.; Saha-Möller, C. R. *Synthesis* **1989**, 121.

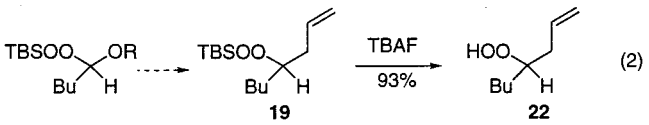
Table 3. Allylation of Peroxyacetals



	R	R_1	R_2	ether	peroxide
6c	Bu	Me	Me	**16**	**17**
6d	Bu	Me	TBS	**16**	**19**
7d	Bu	EtOMe	TBS	**18**	**19**
8d	Ph	Me	TBS	**20**	**21**
9d	Ph	EtOMe	TBS	-	**21**

Acetal	L. acid	M	T (°C)	Time (h)	ether (%)	peroxide (%)
6c	$TiCl_4$	$SiMe_3$	-78	1	67	0
6c	$SnCl_4$	$SiMe_3$	0	1	32	35
6c	$SnCl_4$	$SiMe_3$	-78 - 0	> 2	9	68
6d	$TiCl_4$	$SiMe_3$	-78	1	70	-
6d	$TiCl_4$	$SiMe_3$	-25	0.25	62	trace
6d	$SnCl_4$	$SiMe_3$	0 - 10	0.25	-	83
7d	$TiCl_4$	$SiMe_3$	-78	1	-	64
7d	$TiCl_4$	$SiMe_3$	-50	1	-	61
7d	$TiCl_4$	$SiMe_3$	-25	0.25	-	69
7d	$SnCl_4$	$SiMe_3$	-78	>2	-	-
7d	$SnCl_4$	$SiMe_3$	-40	>2	-	-
7d	$SnCl_4$	$SiMe_3$	0 - 10	1.5	-	84
7d	$SnCl_4$	$SnBu_3$	0-25	15	-	18
8d	$TiCl_4$	$SiMe_3$	-78	1	69	<5
8d	$SnCl_4$	$SiMe_3$	-78	1	NR	-
8d	$SnCl_4$	$SiMe_3$	-78 - 0	2	-	70
9d	$TiCl_4$	$SiMe_3$	-78	1	-	62
9d	$SnCl_4$	$SiMe_3$	-78	1	NR	-
9d	$SnCl_4$	$SiMe_3$	-78 - 0	2	-	83

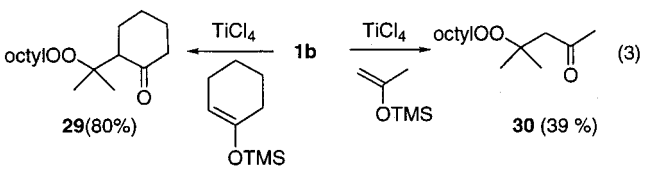
tection) offering a new protocol for conversion of an alkene into a homologated hydroperoxide (eq 2).



(2)

Reaction of peroxyacetal **6d** with an 85:15 *E*/*Z*-mixture of crotyltrimethylsilane in the presence of stoichometric $SnCl_4$ or catalytic TMSOTf produced methallyl peroxide **23** as a 2:1 syn/anti mixture (Table 4); similar results were observed for the $TiCl_4$-mediated reactions of methoxyethoxy peroxyacetal **7d**. Improved syn diastereoselection was observed with benzylic peroxyacetal **8d**, paralleling results reported for nonperoxidic acetals.[28] The magnitude of the diastereoselection was determined by ^1H NMR, while configurational assignments are based upon conversion of **23** and **24** to alcohols **26** and **28**.[29]

Synthesis of 3-Peroxyketones. Reaction of peroxyketal **1b** with silyl enol ethers cleanly furnished 3-peroxyketones (eq 3).



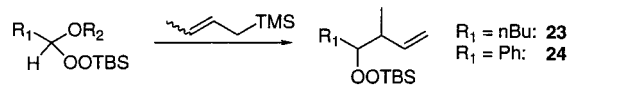
(3)

The corresponding reactions of peroxyacetals **6d**, **7d**, and **8d** furnished peroxyketones **31** and **32** (Table 5), with the best results obtained in the presence of catalytic TMSOTf.

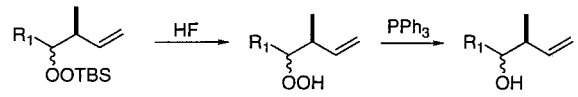
Synthesis of 3-Peroxyesters. Reactions of aliphatic peroxyacetal **6d** with trimethylsilyl ketene acetals (SKAs) of ethyl acetate or ethyl thioacetate failed to produce

(28) Hosomi, A.; Ando, M.; Sakurai, H. *Chem. Lett.* **1986**, 365.
(29) Hoffmann, R. W.; Zeib, H.-J. *J. Org. Chem.* **1981**, *46*, 1309.

Table 4. Crotylation of Peroxyacetals

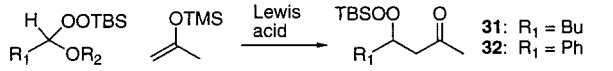


Acetal	Reactants	T (°C)	Time (h)	Product	Yield(%)	*syn* : *anti*
6d	$SnCl_4$	0	0.3	**23**	67	66:34
6d	TMSOTf	0	6	**23**	29	70:30
7d	$TiCl_4$	-50	0.5	**23**	73	60:40
7d	$TiCl_4$	-30	0.5	**23**	86	60:40
7d	$TiCl_4$	0	0.5	**23**	57	66:33
8d	$TiCl_4$	-78	0.5	**24**	82	79:21
8d	$SnCl_4$	-78-> 0	2	**24**	86	81:19



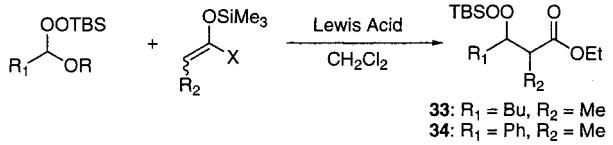
23: R_1 = *n*-Bu **25** **26**
24: R_1 =Ph **27** **28**

Table 5. Reaction of Peroxyacetals with an Enol Ether



Acetal	Reagent	T (°C)	Time (h)	Product	Yield (%)
6d	$SnCl_4$	0	2	**31**	43
6d	TMSOTf	0	5	**31**	73
7d	$TiCl_4$	-45	1	**32**	39
8d	TMSOTf	0	6	**32**	78

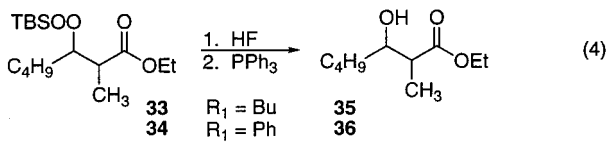
Table 6. Synthesis of 3-Peroxy-2-methylalkanoates



subs.	R_2	X	L. acid	T (°C)	t (h)	Prod.	(%)	syn/anti
6d	H	OEt	$SnCl_4$ (1.0)	-30	1	-	-	-
6d	H	OEt	TMSOTf (0.1)	-30	1	-	-	-
6d	H	SEt	TMSOTf (0.1)	-30	1	-	-	-
6d	Me (E)	OEt	$SnCl_4$ (1.0)	0	6	**33**	-	-
6d	Me (E)	OEt	TMSOTf (0.1)	0	6	**33**	85	30:70
6d	Me (Z)	OEt	TMSOTf (0.1)	0	6	**33**	35	33:66
7d	Me (E)	OEt	$TiCl_4$ (1.0)	-78 - 0	4	**33**	79	29:71
7d	Me (E)	OEt	TMSOTf (0.1)	0	24	**33**	52	30:70
8d	Me (E)	OEt	TMSOTf (0.1)	0	6	**34**	90	1:1
9d	Me (E)	OEt	$TiCl_4$ (1.0)	-78 - 0	6	**34**	92	1:1

3-peroxyalkanoates (Table 6). In contrast, reaction with SKAs derived from ethyl propionate furnished 3-peroxy-2-methylalkanoates (**33**); a similar mixture of syn and anti diastereomers was obtained regardless of whether the (*E*)- or (*Z*)-SKA was used. Reaction of the propionate SKAs with the benzylic peroxyacetals **8d** and **9d** proceeded in higher yield but without diastereoselection.

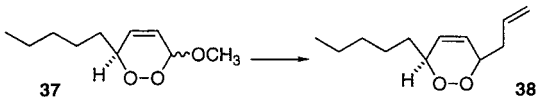
The stereochemistry of *syn*- and *anti*-**33** was assigned following deprotection and reduction to furnish a 70:30 mixture of *anti*- and *syn*-3-hydroxy-2-methylalkanoates **35** (eq 4).



(4)

Deprotection with *n*-Bu_4NF proceeded in good yield but resulted in formation of **34** as a 50:50 mixture of *syn* and *anti* diastereomers, based upon conversion to *syn*- and

Table 7. Allylation of a 1,2-Dioxine



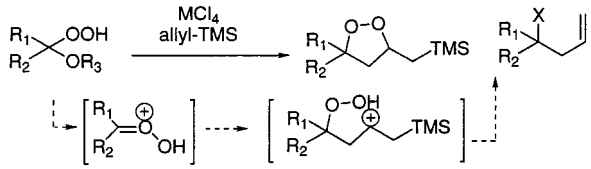
Conditions	Yield(%)
$TiCl_4$ / allyl-$SiMe_3$	41
$TiCl_4$ / allyl-$SnBu_3$	30
$SnCl_4$ / allyl-$SiMe_3$	59

anti-**36**.[30,31] The ability to achieve epimerization without decomposition, a surprising outcome given the intermediacy of β-peroxyenolates in nucleophilic epoxidations,[32,33] offers a potential means of selectively obtaining either *syn*- or *anti*-peroxypropionates.

Allylation of Cyclic Peroxyacetals: Synthesis of 1,2-Dioxines. Allylation of cyclic peroxyacetals was investigated as a potential approach to the 1,2-dioxane core of a number of natural products.[34,35] Allylation of alkoxydioxine **37** in the presence of either $TiCl_4$ or $SnCl_4$ produced moderate yields of allylated dioxine (Table 7). The product was invariably isolated as a 3:2 *cis*/*trans* mixture, regardless of the stereochemistry of **37**. Diastereomers were identified by comparison of the H_3-H_4 coupling constants against reported values for simple endoperoxides.[36] Dioxine **37** failed to react with several silyl ketene acetals, even though the presence of a reactive intermediate could be verified by trapping with allytrimethylsilane. Attempted allylation of a saturated analog[37] led only to ring-opened products.

Displacement of Hydroperoxyacetals: Synthesis of Dioxolanes. The 1,2-dioxolane moiety forms the core of prostaglandins, oxidized lipids, and the plakinic acid family of marine natural products.[34,35,38] An otherwise attractive approach to this substructure based upon 1,3-dipolar addition[39−42] is limited by the compatibility of alkenes with ozonolysis, the most common method for the generation of carbonyl oxides.[43] Protonated and metalated carbonyl oxides capable of 1,3-dipolar addition have been generated via acid-catalyzed decomposition of ozonides (1,2,4-trioxolanes).[39,44] We were interested in employing Lewis acid-mediated ionization of hydroperoxyacetals to furnish reactive hydroperoxycarbenium ions which would react with alkenes to form 1,2-dioxolanes (Table 8).[45,46] In particular, we were curious about selective activation of an alkoxide in the presence of a free hydroperoxide and in the relative rate of the desired transformation versus acid-catalyzed disproportionation.[47]

Table 8. Synthesis of 1,2-Dioxolanes



	R_1, R_2	R_3	M	dioxolane	byproducts (X, yield)
1a	Me,Me	Me	Ti	**39** (31%)	-
2a	Me,Me	-EtOMe	Sn	**39** (56%)	-
2a	Me,Me	-EtOMe	Ti	**39**(12%)	**40** (-OOH, 23%)
4a	4-*t*BuC	Me	Ti	-	**41** (- $O)_2$, 31%)
4a	4-*t*BuC	Me	Sn	**42**(42%)	-
5a	4-*t*BuC	-EtOMe	Sn	**42** (59%)	-
10a	Me, BnOEt-	Me	Ti	**43** (12%)	ketone (62%)
6a	Bu, H	Me	Ti	**44** (7%)	**16** (OMe, 63%)
7a	Bu, H	-EtOMe	Ti	**44** (15%)	**18**

4-*t*BuC = 4-*t*-Butylcyclohexyl

As illustrated in Table 8, $SnCl_4$-promoted reactions of hydroperoxyketals **1a**, **4a**, and **5a** furnished trimethylsilylmethyl-1,2-dioxolanes in moderate to good yield. However, reaction of hydroperoxyacetals **6a** or **7a** furnished little or no dioxolane. A more functionalized hydroperoxyketal (**10a**), prepared as a model for the plakinic acid class of 1,2-dioxolane natural products, furnished mostly ketone.[48,49] $TiCl_4$-mediated reactions tended to favor alternate pathways. Hydroperoxyketal **2a**, for example, produced allylated peroxide, implying that the presence of a bidentate leaving group is able to influence the product distribution. $TiCl_4$-mediated reactions of acetals **6a** and **7a** furnished allyl ethers via loss of the hydroperoxide, while cyclohexane hydroperoxyacetal **4a** reacted to form a bisallylated peroxide, presumably via 2-fold allylation of an intermediate 1,1′-bisalkoxyperoxide. The allylated products derived from **4a** and **5a** were each isolated as a single diastereomer (^{13}C), suggesting predominant equatorial attack on the hydroperoxycarbenium or peroxycarbenium intermediate.[48] All examples reported are based upon rapid addition of Lewis acid to a chilled mixture of alkoxyhydroperoxide and allylsilane; slow addition of Lewis acid or premixing of the hydroperoxide and Lewis acid gave much lower yields. Attempts to employ allyltributylstannane, enol ethers, or enamines as nucleophiles were unsuccessful.

Intramolecular Additions. Intramolecular additions to activated carbonyl and acetal groups have been widely used for construction of carbocycles and cyclic ethers.[50,51] We were interested in corresponding additions to peroxycarbenium ions as a new approach to cyclic peroxides. In particular, we hoped the entropic advantages of an intramolecular reaction might permit the use of simple alkenes as nucleophiles.[52] Intramolecular attack of alkenes onto peroxycarbenium ions, much like reactions of corresponding oxycarbenium ions, can be classified by

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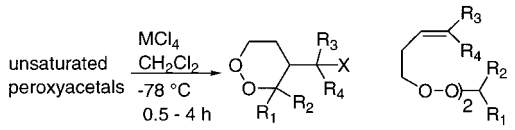
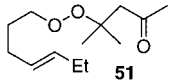
Table 9. 6-*Endo*/*Exo* Cyclizations

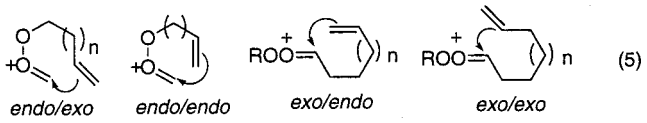


Subs	R_1	R_2	R_3	R_4	M	X	Dioxane	Byproduct
1e	Me	Me	Me	Me	Ti	Cl	**45** (64%)	
1e	Me	Me	Me	Me	Sn	Cl	**45** (73%)	
3e	Me	Me	Me	Me	Ti	Cl	**45** (46%)	
6e	Bu	H	Me	Me	Sn	OMe	**46** (68%, *72:28*)	
11e	Bn	H	Me	Me	Ti	OMe	**47** (20%, *85:15*)	
						Cl	**48** (2%, all cis)	
6f	Bu	H	Et	H	Sn	-	-	**49** (90%)
2f	Me	Me	Et	H	Sn	-	-	**50** (59%)
								51 (16%)



51

the *exo* or *endo* relationship of both the electrophilic peroxycarbenium ion and the nucleophilic alkene to the newly forming ring (eq 5).[53]



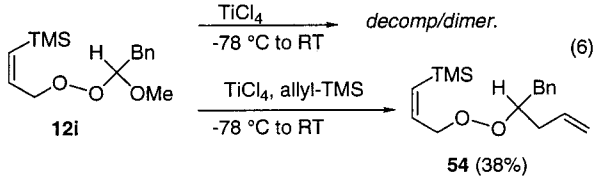
(5)

The large number of natural products containing 1,2-dioxane or 1,2-dioxine ring systems led to an initial emphasis on six-membered ring construction.[34,35]

Addition of either $TiCl_4$ or $SnCl_4$ to a −78 °C solution of peroxyketal **1e** afforded dioxane **45** in good yield through a 6-*endo*/*exo* pathway (Table 9). The same product was obtained, albeit in slightly reduced yield, from the ethoxy analogue **3e**. In pleasant contrast to the corresponding intermolecular reactions, low-temperature cyclization was successful for less-stabilized peroxycarbenium ions; monoperoxyacetal **6e** underwent cyclization to a 2.6:1 *cis*/*trans* mixture of dioxanes **46**. A similar cyclization of acetal **11e** furnished a 5:1 *cis*/*trans* mixture of dioxanes **47** in which the displaced methoxyl leaving group also acts as a cation trapping agent; only a trace of the tertiary chloride **48** was isolated. Stereochemical assignments are based upon the J_{3-4} coupling constants. Nucleophilicity is clearly important as disubstituted alkenes **6f** and **2f** failed to undergo cyclization, instead furnishing dimers. Attempted cyclization of **2f** also produced a 3-peroxyketone (**51**) presumably arising from intermolecular reaction between a peroxycarbenium ion and the methoxypropenyl ether derived from decomposition of the peroxyketal.

We also investigated the relative rate of 6-*endo*/*exo* cyclizations compared with intermolecular allylation (Table 10). In each case investigated, addition of stoichometric allyltrimethylsilane completely suppressed cyclization.

The 6-*endo*/*endo* class of cyclizations was anticipated to open the door to a variety of 1,2-dioxane-containing natural products. Unfortunately, the addition of Lewis acids to unsaturated peroxyketals **1g**−**i** and **12i** resulted only in decomposition. In the latter case, the successful formation of a reactive intermediate was confirmed by intermolecular trapping product with allylsilane (eq 6).



12i **54** (38%) (6)

Given the substantial precedent for 6-*endo*/*endo* cyclizations of oxycarbenium ions,[23,51,54−57] our results imply stereochemical constraints unique to unsaturated monoperoxycarbenium ions.

We next investigated cyclization through a 6-*exo*/*exo* pathway (Scheme 2). Ozonolysis of methylcyclohexene in methoxyethanol afforded an unstable hydroperoxyaldehyde which was directly alkylated to form peroxide **55**. Wittig olefination produced the unsaturated peroxyketal **56** which underwent cyclization to afford dioxanes bearing an exocyclic chloride (**57**) as well as an alkene (**58**). The differing diastereoselection observed in the formation of **57** and **58** implies the presence of different reaction pathways.

Although 5-*endo*-*trig* closures are well-precedented in cyclizations of acetal-derived oxycarbenium ions,[23,56,58] attempts to synthesize 1,2-dioxolanes through 5-*endo*/*exo* cyclizations of monoperoxyketals were unsuccessful (Table 11). Peroxyketal **1j** decomposed upon treatment with Lewis acid, and no allylation was observed in the presence of allylsilane. Curiously, the methoxyethoxy ketal **2j** reacted to form a 1,3-dioxane in the presence or absence of allylsilane. A possible mechanism involves a very rapid 6-*endo* cyclization to an unstable 1,2-dioxane followed by Lewis-acid mediated Hock fragmentation.[59]

Peroxycarbenium ion cyclizations were also investigated as an entry to medium ring peroxides. Cyclization of monoperoxyacetal **1k** with $TiCl_4$ proceeded via the expected 7-*endo*/*endo* pathway to afford a dioxepane. (Scheme 3). However, in a result reminiscent of the 5-*endo*/*exo* attempts, peroxide **1l** did not cyclize via the expected 7-*endo*/*exo* mode, instead closing via an 8-*endo*/*endo* pathway to furnish a 16% yield of a 1,2-dioxocane as a 2.4:1 ratio of diastereomers. A similar outcome in reactions of unsaturated oxycarbenium ions has been rationalized through transannular stabilization of the developing charge by the remote oxygen.[60]

Discussion

The Lewis acid-mediated addition of nucleophiles to peroxyacetals, peroxyketals, hydroperoxyketals, and silylated hydroperoxyacetals provides a new and general approach to the synthesis of acyclic and cyclic hydroperoxides and peroxides. The starting materials are readily available and relatively stable. The products, homoallyl peroxides or 3-peroxycarbonyls, are common

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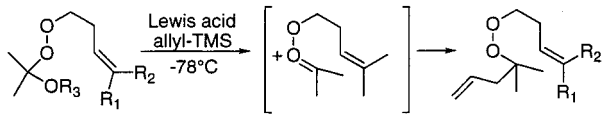
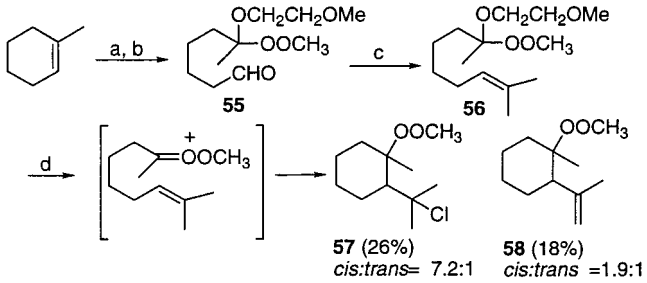
Table 10



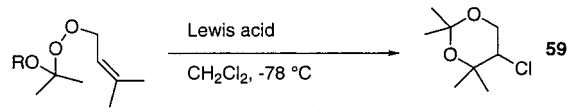
Substrate	Lewis acid	Time (h)	R_1	R_2	R_3	Product	Yield(%)
1e	$TiCl_4$	0.5	Me	Me	Me	**52**	49
3e	$TiCl_4$	0.5	Me	Me	Et	**52**	49
2f	$SnCl_4$	0.5	Et	H	CH_2CH_2OMe	**53**	71
2f	$TiCl_4$	0.16	Et	H	CH_2CH_2OMe	**53**	92
1f	$TiCl_4$	0.33	Et	H	Me	**53**	75 (88% convs)

Scheme 2. 6-*Exo*/*Exo* Cyclization[a]

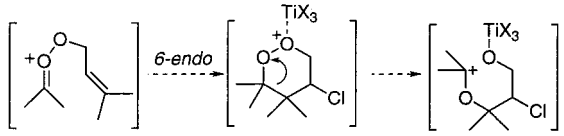


[a] a. Ozone, 2-methoxyethanol (43%); b. CsOH, MeI (29%); c. isopropylidene triphenylphosphorane (37%); $TiCl_4$, −78 °C, 5 min.

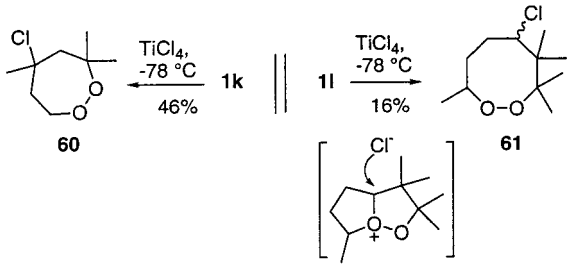
Table 11. Attempted 5-Exo/Endo Cyclizations



subs	R	L. acid	allylSiMe$_3$?	**59** (%)
1j	Me	Sn	no	-
1j	Me	Ti	yes	-
1j	Me	Sn	no	-
1j	Me	Ti	yes	-
2j	-EtOMe	Ti	no	32%
2j	-EtOMe	Ti	yes	24%

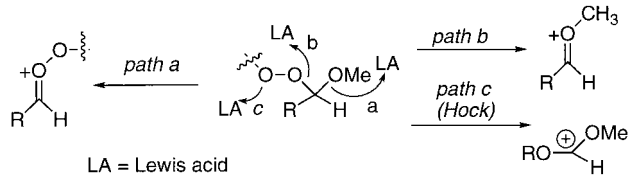


Scheme 3. Medium-Ring Cyclization



subunits in many peroxide-containing natural products. Many aspects of the reaction (stereoselection, reactivity vs substrate structure) support the intermediacy of species with significant transition state dissociation of the carbon−alkoxide bond. Peroxycarbenium ions have been previously postulated as intermediates in reactions of peroxyacetals and similar structures[17,39,61] and are analogous to the oxycarbenium ions postulated for the related displacements of acetals.[62] However, significant

Scheme 4. Available Ionization Modes



practical differences exist between the reactions described in this paper and corresponding reactions of acetals. More forcing reaction conditions are generally required as compared with reactions of acetals. Once formed, the presumed peroxycarbenium ion appear to be less reactive toward alkenes than corresponding oxycarbenium ion. Another difference from the chemistry of acetals is that peroxyacetals are able to enter into three different modes of ionization (Scheme 4). Although Hoch cleavage (O−O heterolysis)[59] was rarely observed in our studies, both C−O and C−OO ionization can clearly occur.

Our results demonstrate that reaction selectivity is influenced by nucleophile, Lewis acid, and substrate structure. In the presence of good nucleophiles, monoperoxyketals invariably react via selective loss of the alkoxide unit to form new peroxides. Depending upon the choice of Lewis acid, peroxyacetals can furnish either ether or peroxide products; the origin of this selectivity will be addressed in detail in a separate paper. Finally, in the absence of an effective nucleophile, either the peroxyacetals or the derived peroxycarbenium ions readily disproportionate to bisperoxyacetals.

In conclusion, we have demonstrated a fundamentally new method for the synthesis of peroxides and hydroperoxides which provides a practical method for the synthesis of allylated peroxides, peroxyketones, and peroxyesters.

Experimental Section

Caution: As in any work involving peroxides, standard precautions (minimal scale; avoidance of heat, light, or metal salts; use of safety shields) should be faithfully observed.[63−67]

2-(2-Methoxy)prop-2-yl hydroperoxide (**1a**),[10] (2-methoxypropy-2-yl)octyl peroxide (**1b**),[10] 2-(2-methoxyethoxy)prop-2-yl hydroperoxide (**2a**),[11] (2-methoxyethoxy)prop-2-yloctyl per-

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oxide (**2b**)[11] and (3*R*,6*S*)- and (3*S*,6*S*)-3-methoxy-6-pentyl-3,6,dihydro-1,2-dioxine (**40**)[20] were prepared using reported procedures.

General Procedure for Synthesis of Hydroperoxyacetals. 4-*tert*-Butyl-1-methoxycyclohexyl Hydroperoxide (4a). Into a −78 °C solution of 1-(methoxymethylene)-4-*tert*-butylcyclohexane (63 mg, 0.35 mmol) in methanol (20 mL) was passed a gaseous stream of O_3/O_2 until a blue color persisted. The reaction mixture was then flushed with O_2 to dissipate the blue color and concentrated behind a shield. The residue was purified by flash chromatography with 10% EA/hexanes to yield 66 mg (95%) of hydroperoxyacetal **4a** as a 2:1 mixture of diastereomers: Major diastereomer (from mixture): $R_f = 0.3$ in 11% EA/hexanes; ^{1}H NMR δ 7.42 (s, 1H, −OOH), 3.29 (s, 3H), 2.12 (m, 2H), 1.63 (m, 2H), 1.31 (m, 2H), 1.07−1.23 (m, 2H), 0.95 (m, 2H), 0.87 (s, 9H); ^{13}C NMR δ 105.5, 48.1, 47.5, 31.4, 30.9, 27.5, 23.4; IR (neat) 3353 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.32; H, 10.95. Found C, 65.50; H, 10.77. Minor diastereomer (from mixture): $R_f = 0.3$ in 11% EA/hexanes; ^{1}H NMR δ 7.44 (s, 1H, OOH), 3.33 (s, 3H), 2.22 (m, 2H), 1.63 (m, 2H), 1.31 (m, 2H), 1.07−1.23 (m, 2H), 0.95 (m, 2H), 0.87 (s, 9H); ^{13}C NMR δ 105.3, 48.4, 47.4, 32.2, 30.9, 27.5, 23.6.

Synthesis of Peroxyacetals via Alkylation of Hydroperoxyacetals. 2-Methoxyprop-2-yl-4-methyl-3-pentenyl peroxide (1e). To a 0 °C solution of 5-bromo-2-methyl-2-pentene (2.0 g, 12 mmol) in DMF (20 mL) under N_2 was added a solution of crude 2-methoxyprop-2-yl hydroperoxide **1a** (2.7 g, 20 mmol) in DMF (5 mL) followed by CsOH (2.4 g, 14 mmol). The resulting solution was stirred for 2 h at 0 °C and then quenched with water (150 mL). The mixture was extracted with ether (3 × 150 mL), and the combined organic layers were dried over Na_2SO_4. After removal of solvent in vacuo, the residue was subjected to flash chromatography (5% EA/hex) to afford the peroxide (1.7 g, 75%) as a colorless oil: $R_f = 0.38$ (5% EA/hex); ^{1}H NMR δ 5.12 (app t of hept, 1 H, $J = 7.2, 1.4$), 3.98 (t, 2 H, $J = 7.6$), 3.32 (s, 3 H), 2.33 (q, 2 H, $J = 7.2$), 1.70 (s, 3 H), 1.63 (s, 3 H), 1.40 (s, 6 H); ^{13}C NMR δ 133.9, 119.6, 104.6, 74.7, 49.1, 26.9, 25.6, 22.7, 17.7. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 64.00; H, 10.56.

Synthesis of Silyl Peroxyacetals from Hydroperoxyacetals. To a 0 °C solution of hydroperoxyacetal (1 equiv) in DMF/CH_2Cl_2 (1:5, 1.0 M) was added imidazole (1.1 equiv) followed by TBDMS-Cl (1.5 equiv). The reaction was monitored by thin-layer chromatography and was quenched with water. The dried hexane extract was concentrated and purified by flash chromatography (5% EA/hex) to give the silylated hydroperoxy acetals.

((1,1-Dimethylethyl)dimethylsilyl)-1-methoxypentyl peroxide (6d): $R_f = 0.76$ in 10% EA/hex; ^{1}H NMR δ 4.73 (t, 1H, $J = 5.5$), 3.54 (s, 3H), 1.60−0.85 (9H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR δ 109.1, 57.1, 31.8, 26.9, 26.1, 22.5, 18.1, 13.9, −5.7. Anal. Calcd for $C_{12}H_{28}O_3Si$: C, 58.02; H, 11.36. Found: C, 58.14; H, 11.51.

Synthesis of Peroxyacetals via Acetalization of Enol Ethers. 1-(1-Methoxycyclohexyl)octyl Peroxide (4b). To a solution of octyl hydroperoxide (1.46 g, 10 mmol)[10] in CH_2Cl_2 was added 1-methoxy-1-cyclohexene (1.23 g, 1.1 equiv) and pyridinium *p*-toluenesulfonate (30 mg). After stirring for 2 h, the reaction was quenched with water and extracted with hexane. The organic layer was dried, and the solvent was removed. The residue was subjected to flash chromatography (5% EA/hex) to afford peroxide **4b** (2.38 g, 92%): $R_f = 0.50$ in 10% EA/hex; ^{1}H NMR δ 4.00 (t, 2H, $J = 6.7$), 3.29 (s, 3H), 1.71−1.26 (m, 22H), 0.86 (t, 3H, $J = 6.7$); ^{13}C NMR δ 104.5, 74.8, 47.9, 31.7, 31.5, 29.3, 29.0, 27.8, 26.0, 25.4, 22.6, 22.4, 13.8. Anal. Calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.50; H, 11.90.

General Procedure for Allylation of Monoperoxyketals. (2-Methyl-4-penten-2-yl)octyl Peroxide (13). To a −78 °C solution of perketal **1b** (87 mg, 0.4 mmol) in CH_2Cl_2 (3 mL) was added $TiCl_4$ (0.4 mmol) under N_2. After 3 min, a solution of allyltrimethylsilane (59 mg, 1.3 equiv) in CH_2Cl_2 (1 mL) was added. The solution was stirred for 1 h and then quenched with water. The hexane extract was dried and concentrated in vacuo. Purification by flash chromatography (5% EA/hex) afforded peroxide **13** (79 mg, 86%: $R_f = 0.65$ in 10% EA/hex; ^{1}H NMR δ 5.85 (m, 1H), 5.07−5.01 (m, 2H), 3.92 (t, 2H, $J = 6.7$), 2.31 (d, 2H, $J = 7.4$), 1.59 (m, 2H), 1.35−1.20 (m, 10H), 1.18 (s, 6H), 0.86 (t, 3H, $J = 6.7$); ^{13}C NMR δ 134.4, 117.5, 81.7, 74.9, 43.6, 31.8, 29.4, 29.2, 27.8, 26.2, 24.2, 22.6, 14.0. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.68; H, 12.40.

Bis(1,1-dioxyoctyl)-2-propane (14): $R_f = 0.55$ in 10% EA/hex; ^{1}H NMR δ 4.04 (t, 2H, $J = 6.7$), 1.59 (m, 4H), 1.42 (s, 6H), 1.33−1.25 (20H), 0.87 (t, 6H, $J = 6.7$): ^{13}C NMR δ 108.5, 75.4, 31.8, 29.4, 29.2, 27.8, 26.1, 21.4, 14.0. Anal. Calcd for $C_{12}H_{26}O_3$: C, 68.63; H, 12.12. Found: C, 68.37; H, 12.05.

Allylation of Peroxyacetals. Method A. To a −78 °C 0.1 M solution of peroxyacetal in dry CH_2Cl_2 was added $TiCl_4$ (75 μL) followed, after 1−2 min, by allyltrimethylsilane (0.33 mL, 1.9 mmol). The reaction mixture was stirred for 30 min at −78 °C and quenched with saturated aqueous NH_4Cl. Workup and purification were conducted as for the monoperoxyketals. **Method B.** Lewis acid was added at −78 °C, followed by warming to desired temperature.

((1,1-Dimethylethyl)dimethylsilyl)-1-octen-4-yl peroxide (19): $R_f = 0.70$ in EA/hex; ^{1}H NMR δ 5.80 (tdd, 1H, $J = 7.2, 10.3, 17.2$), 5.07 (dd, 1H, $J = 10.2, 1.4$), 5.02 (dd, 1H, $J = 17.2, 1.4$), 3.90 (tt, 1H, $J = 6.2, 5.5$), 2.42 (td, 1H, $J = 5.2, 1.2$), 2.29 (tt, 1H, $J = 6.2, 1.2$), 1.60−0.85 (9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR δ 134.8, 116,8, 84.7, 36.9, 31.4, 27.6, 26.2, 22.8, 13.2, 13.9, −5.7. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.33; H, 11.63.

Deprotection of Silyl Peroxides. 1-Octen-3-yl Hydroperoxide (24). To a solution of silylated peroxide (**19**) (115 mg, 1.0 equiv) in THF (0.4 mL, 1 M) was added tetrabutylammonium fluoride (0.42 mL, 1.0 equiv, 1 M in THF). The reaction was quenched after 20 min with saturated NH_4Cl. The ethyl acetate extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration, followed by flash chromatography (10% EA/hex), furnished 56.5 mg (93.5%) of hydroperoxide **22**: $R_f = 0.78$ in 10% EA/hex; ^{1}H NMR δ 7.80 (s, 1H), 5.85 (m, 1H), 5.10 (m, 2H), 3.99 (p, 1H, $J = 6.7$), 2.40 (m, 2H), 1.65−1.25 (6H), 0.92 (t, 3H, $J = 6.9$); ^{13}C NMR δ 134.6, 117.2, 84.9, 36.9, 31.3, 27.6, 22.7, 13.9; IR (neat) 3405 cm^{-1}.

Reaction of Peroxyacetals with Silyl Enol Ethers. To a 0.1 M solution of peroxyacetal (1 equiv) and silyl enol ether (1 equiv) in CH_2Cl_2 at the indicated temperature was added $TiCl_4$ (1 equiv), $SnCl_4$ (1 equiv), or TMSOTf (5−10 mol %). After 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The hexane extract was dried over Na_2SO_4 and concentrated. The peroxides were purified by flash chromatography.

4-Methyl-4-octyldioxy-2-pentanone (30): $R_f = 0.35$ in 20% EA/hex; ^{1}H NMR δ 3.89 (t, 2H, $J = 6.6$), 2.68 (s, 2H), 2.17 (s, 3H), 1.55 (m, 2H), 1.26−1.24 (16 H), 0.86 (t, $J = 6.7$, terminal Me); ^{13}C NMR δ 207.5, 80.9, 74.9, 51.8, 31.9, 31.8, 29.4, 29.1, 27.7, 26.1, 24.6, 22.6, 14.0; IR (neat) 1712 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{33}O_3$ (M + H) 245.2117, found 245.2114. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81: H, 11.55. Found: C, 68.63; H, 11.63.

Reaction of Peroxyacetals with Silyl Ketene Acetals. To a 0 °C solution of peroxyacetal (1 equiv) in CH_2Cl_2 (0.1 M) was added the silyl ketene acetal (1 equiv, prepared by reported procedures) followed by TMSOTf (0.1 equiv). The reaction was monitored by TLC and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with ethyl acetate, and the organic layers were washed with brine and dried over anhydrous Na_2SO_4. The concentrated residue was purified by flash chromatography with EA/hexanes.

Ethyl 2-methyl-3-[((1,1-Dimethylethyl)dimethylsilyl)-dioxy]heptanoate (33): $R_f = 0.53$ in 10% EA/hex. Anal. Calcd for $C_{15}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.24; H, 10.74. *Anti* (determined from mixture): ^{1}H NMR δ 4.23 (m, 1H), 4.10 (m, 2H), 3.08 (qd, 1H, $J = 7.16, 5.60$), 1.08 (d, 3H, $J = 7.16$), 1.40−0.80 (18H), 0.8 (s, 6H). *Syn* (determined from mixture): $R_f = 0.53$ in 10% EA/hex; ^{1}H NMR δ 4.10 (m, 2H + 1H, OC**H**$_2$-

CH_3, C**H**(OOTBS)), 2.64 (qd, 1H, J = 7.2, 4.4), 1.15 (d, 3H, J = 7.2), 1.40−0.80 (18H), 0.8 (s, 6H).

Synthesis of 1,2-Dioxolanes via Allylation of Hydroperoxyacetals. Method A. To a −78 °C solution of freshly prepared 2-methoxyprop-2-yl hydroperoxide **1a** (10.2 mmol) and allyltrimethylsilane (4.2 mL, 26.5 mmol) in CH_2Cl_2 (150 mL) was rapidly added $TiCl_4$ (10.2 mL of a 1 M CH_2Cl_2 solution). The reaction mixture was stirred for 25 min, quenched with water (5 mL), and allowed to warm to RT. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography with 2% EA/hexanes afforded 595 mg (31%) of dioxolane. Addition of $TiCl_4$ prior (3 min) to allyltrimethylsilane furnished the same product in 14% yield. Slow addition (10 min) of $TiCl_4$ resulted in a 4% yield. **Method B.** To a −78 °C solution of freshly prepared 2-(2-methoxyethoxy)prop-2-yl hydroperoxide **2a** (1.566 gm, 10.44 mmol) and allyltrimethylsilane (4.5 mL, 28.2 mmol) in CH_2Cl_2 (150 mL) was rapidly added $SnCl_4$ (10.4 mL of a 1 M solution in CH_2Cl_2). The reaction mixture was stirred for 4 h, worked up, and purified, as before, to afford 1.1 g (56%) of dioxolane **39**.

3,3-Dimethyl-5-trimethylsilylmethyl-1,2-dioxolane (39): R_f = 0.4 in 11% EA/hexanes; ^{1}H NMR (500 MHz) δ 4.35 (m, 1H), 2.41 (dd, 1H, J = 6.8, 11.2), 1.88 (dd, 1H, J = 8.0, 11.6), 1.35 (s, 3H), 1.31 (s, 3H), 1.08 (dd, 1H, J = 5.2, 14.1), 0.88 (dd, 1H, J = 9.6, 14.1), 0.03 (s, 9H); ^{13}C NMR (125 MHz) δ 83.5, 80.1, 54.5, 27.6, 25.7, 21.3, −1.0; IR (neat) 1182 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_2Si$: C, 57.28; H, 10.05. Found C, 57.30; H, 10.55.

Cyclization of Unsaturated Peroxyacetals. *cis*- and *trans*-3-Butyl-4-(2-chloroprop-2-yl)-1,2-dioxane (46). To a −78 °C solution of 5-(1-methoxypentyl)dioxy-2-methyl-2-pentene **6e** (220.0 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) under N_2 was added a solution of $SnCl_4$ in CH_2Cl_2 (2.0 mL, 1.0 M, 2.0 mmol). The resulting solution was stirred for 4 h at −78 °C. Workup as before was followed by flash chromagraphy (5% EA/hex) to furnish a mixture of diastereomers, which could be separated by HPLC (5% EA/hex) to afford *cis*-**46** (107.4 mg, 49%, retention time 9.1 min) followed by *trans*-**46** (41.6 mg, 19%, retention time 10.2 min). *Cis*: R_f = 0.43 (5% EA/hex); ^{1}H NMR δ 4.34−4.26 (m, 1 H), 4.21−4.08 (m, 2 H), 2.08−1.77 (m, 5 H), 1.66 (s, 3 H), 1.63 (s, 3 H), 1.58−1.25 (m, 4 H), 0.91 (t, 3 H, J = 7.2); ^{13}C NMR δ 82.9, 72.8, 70.9, 47.6, 32.7, 32.4, 30.6, 27.7, 24.2, 22.6, 14.0. Anal. Calcd for $C_{11}H_{21}O_2Cl$: C, 59.85; H, 9.59. Found: C, 59.91; H, 9.62. *Trans*: R_f = 0.41 (5% EA/hex); ^{1}H NMR (300 MHz) δ 4.31 (m, 1 H), 4.24−4.15 (m, 2 H), 2.36 (m, 1 H), 2.25−2.10 (m, 2 H), 1.74−1.55 (m, 2 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.50−1.25 (m, 4 H), 0.93 (t, 3 H, J = 7.2); ^{13}C NMR δ 82.5, 72.5, 70.4, 49.2, 31.6, 30.7, 27.8, 26.6, 22.5, 22.4, 14.1.

Competititon between Cyclization and Allylation. 1-(2-Methyl-5-pentenyl)-4-methyl-3-pentenyl Peroxide (52). To a −78 °C solution of peroxyacetal **1e** or **3e** in CH_2Cl_2 under N_2 was added allyltrimethylsilane (1 equiv), followed by a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1 equiv). The resulting solution was stirred for 30 min at −78 °C. Workup as before followed by flash chromatography (2.5% EA/hex) afforded **52**: R_f = 0.65 (2.5% EA/hex); ^{1}H NMR (500 MHz) δ 5.81 (m, 1 H), 5.11 (t, 1 H, J = 6.9), 5.06 (s, 1 H), 5.03 (d, 1 H, J = 5.6), 3.90 (t, 2 H, J = 7.1), 2.31 (d, 2 H, J = 7.3), 2.28 (app. q, 2 H, J = 6.8), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.19 (s, 6 H); ^{13}C NMR (125 MHz) δ 134.4, 133.8, 119.9, 117.4, 81.8, 74.5, 43.7, 26.9, 25.7, 24.2, 17.7. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.64; H, 11.37.

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Supporting Information Available: Standard experimental procedures, selected preparations, and spectral listings (^{1}H, ^{13}C, and IR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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