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Ozonolysis in the Presence of Lewis Acids: Directed Addition to Carbonyl Oxides

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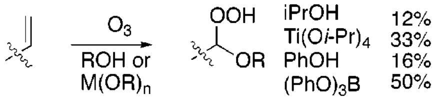
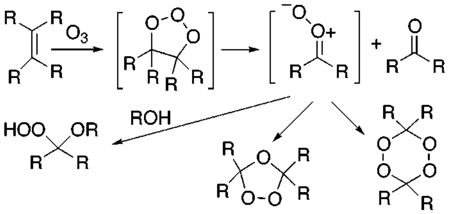
ABSTRACT



The presence of Lewis acids strongly influences the distribution of products from alkene ozonolysis. Delivery of alkoxide and phenoxide ligands to a coordinated carbonyl oxide affords hydroperoxyacetals under aprotic conditions.

Ozonolysis of alkenes is still one of the most popular methods for cleavage of alkenes.[1] The mechanism of this process, elucidated by Criegee more than 50 years ago, consists of dipolar cycloaddition to form a seldom-observed primary ozonide (1,2,3-trioxolane), followed by cycloreversion to carbonyl oxide (CO) and carbonyl fragments (Scheme 1).[2,3] The fate of the short-lived CO is dictated by reaction conditions. Ozonolysis in the presence of protic nucleophiles produces hydroperoxyacetals via addition across the CO.[4] Cycloaddition of the CO with strongly dipolarophilic carbonyl fragments forms 1,2,4-trioxolanes (ozonides).[5] In the absence of these two pathways, dimerization to a 1,2,4,5-tetraoxane or polymerization to larger peroxides (not shown) assume greater importance.

Scheme 1. Overview of Alkene Ozonolysis



Although a large body of research describes the formation and structure of carbonyl oxides,[4] there has been relatively little effort to control their reactivity. We wondered if the presence of Lewis acids would result in complexation of CO's, allowing intramolecular transfer of a nucleophile (Figure 1). We now report that ozonolysis of alkenes in the presence of alkoxide- or phenoxide-bearing Lewis acids proceeds via intramolecular transfer of a nucleophile to a metalated CO to produce the same hydroperoxyacetals observed under more traditional nucleophilic conditions. Our initial studies examined the ozonolysis of 1-methoxy-1-nonene, **1** (Scheme 2). The primary ozonides derived from

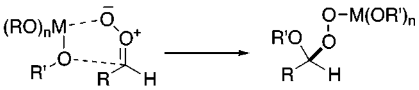


Figure 1. Lewis acid-directed addition.

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(1) Bailey, P. S. *Ozonation in Organic Chemistry. Volume I. Olefinic Compounds*; Academic Press: New York, 1978; Vol. 39.

(2) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 745.

(3) Kuczkowski, R. L. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; p 197.

(4) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335.

(5) Kuczkowski, R. L. *Chem. Soc. Rev.* **1992**, *21*, 79.

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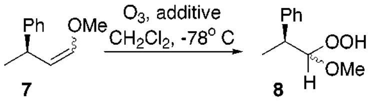
Scheme 2. Addition to a Chiral Carbonyl Oxide



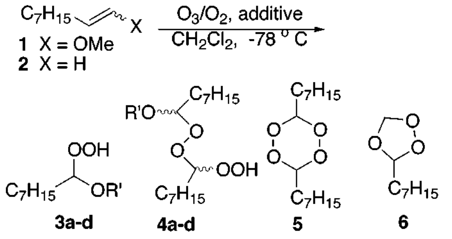
Additive	Diast. Ratio
MeOH	2.5:1
$B(OMe)_3$	1.4:1

enol ethers undergo highly regioselective cycloreversion to produce carbonyl oxides at the original β-carbon.[4] In addition, the low dipolarophilicity of the liberated ester typically precludes ozonide formation. Ozonolysis of **1** in the absence of nucleophile produced mostly polymeric materials, accompanied by a 4% yield of tetraoxane **5** as a 1:1 mixture of diastereomers. A similar ozonolysis in the presence of 2 equiv of methanol resulted in the formation of monomeric hydroperoxyacetal **3a** (75%) accompanied by 8% of a dimeric hydroperoxyacetal (**4a**) presumably arising through reaction of the CO with **3a**. Ozonolysis in CH_2Cl_2 containing 2 equiv of trimethyl borate also led to formation of **3a** and **4a**, albeit in somewhat lower yields. Ozonolysis in the presence of a bulkier nucleophile, 2-propanol, provided a good yield of hydroperoxyacetal **3b** with a modest increase in the relative amount of dimer **4b**. Neither $Al(Oi\text{-}Pr)_3$ nor $B(Oi\text{-}Pr)_3$ produced satisfactory amounts of **3b** or **4b**. However, use of the isopropyl borate resulted in an unusually high yield of tetraoxane **5** as a 2:1 ratio of diastereomers. Use of $Ti(Oi\text{-}Pr)_4$ resulted in isolation of **3b** and **4b** in modest yield.

The primary ozonide derived from a terminal alkene such as nonene (**2**) undergoes cycloreversion with moderate selectivity for production of the more substituted carbonyl oxide and formaldehyde; the alternate cycloreversion to form aldehyde and formaldehyde *O*-oxide occurs to a lesser extent.[1,4] The efficiency of the aldehyde/carbonyl oxide recombinations is evident from the high yield of ozonide obtained in the absence of nucleophiles (Table 1). Reaction in the presence of 2 equiv of MeOH afforded a 66% of hydroperoxyacetal **3a**, 4% of dimer **4a**, and 10% of the ozonide. (The yield of **3** and **4** is ultimately limited by the regioselectivity of the initial cycloreversion.) Reaction in the presence of trimethyl borate gave mixtures of **3a**, **4a**, and **6**. However, reaction in the presence of methyl pinacol borate produced only trace amounts of **3a** and **4a** and a 48% yield of **6**. In an exciting result, the use of titanium isopropoxide furnished hydroperoxyacetal **3b** in superior yield relative to 2-propanol. Additionally, **6** is only formed in 20% with the titanate as compared to 32% for 2-propanol.

In an effort to probe the scope of transferable ligands, we also investigated trapping with phenols/phenoxides (Scheme 2). The low nucleophilicity of phenol toward CO's results in a poor yield of **3c**. The ozonolysis of **1** in the presence of triphenyl borate resulted in a similar yield of **3c** and a sharp increase in the yield of dimer **4c**. Use of triphenyl borate also proved to be much more effective, furnishing 50% of **3c** and 9% of dimer **4c**, with ozonide **6** produced in 13%.

Table 1. Product Distributions from Ozonolyses



a: R' = Me **b**: R' = *i*-Pr **c**: R'=Ph **d**: R'=2-OHPh

subst	additive	R′	yields (%)[a] 3a–d	4a–d	5	6
1	none				4	
1	MeOH	Me	75	8		
1	$(MeO)_3B$	Me	25	39		
1	*i*-PrOH	*i*-Pr	68	11		
1	$(i\text{-}PrO)_3B$	*i*-Pr	tr[b]	tr		
1	$(i\text{-}PrO)_3Al$	*i*-Pr	8	18		
1	$(i\text{-}PrO)_4Ti$	*i*-Pr	20	27		
1	PhOH	Ph	12	20	8	
1	$(PhO)_3B$	Ph	11	39	7	
1	(catechol)BH	2-OHPh			25	
2	none					96
2	MeOH	Me	66	4		10
2	$(MeO)_3B$	Me	27	21		30
2	MeOB(pinacol)	Me	tr	tr		48
2	*i*-PrOH	*i*-Pr	12	32		32
2	$(i\text{-}PrO)_4Ti$	*i*-Pr	33	12		20
2	PhOH	Ph	16	27		14
2	$(PhO)_3B$	Ph	50	9		13
2	$(PhO)_4Ti$	Ph	14	12		13
2	catechol	2-OHPh	17			27
2	(catechol)BH	2-OHPh	57			18

[a] Isolated yields. [b] tr = trace.

Ozonolysis in the presence of tetraphenyl titanate afforded a mixture of **3c**, **4c**, and **6**.

In an attempt to effect the in situ reduction of the CO, **1** was ozonized in the presence of catechol borane. Although no products from hydride transfer were detected, the tetraoxane **5** was isolated in 25% yield as a 1:32 ratio of diastereomers. Surprisingly, ozonolysis of **2** in the presence of catechol borane afforded catechol adduct hydroperoxy acetal **3d**, in 57% yield, a 3-fold improvement relative to trapping with catechol.

The relative diastereoselection for addition of methanol and methyl borate to a chiral carbonyl oxide was used to probe for differences in the transition states of the conventional and Lewis acid-mediated processes. As previously reported from our lab, ozonolysis of enol ether **7** in the presence of methanol proceeds with a Cram–Felkin sense of stereoselection to furnish hydroperoxyacetal **8** as a 2.5:1 mixture of diastereomers.[6] Ozonolysis in the presence of methyl borate provided the same products but in a 1.4:1 ratio (Scheme 2). Control experiments revealed that the difference

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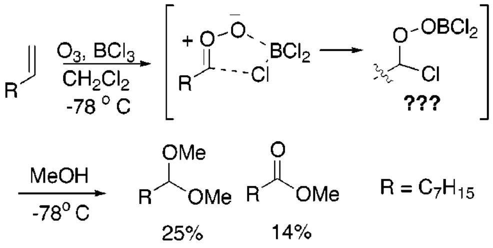
(6) Dussault, P. H.; Zope, U. R. *J. Org. Chem.* **1995**, *60*, 8218.

in product ratios was not due to equilibration of the hydroperoxyacetals.

Finally, the ability of a coordinated Lewis acid to deliver other classes of nucleophiles was investigated. Ozonolysis of **2** in the presence of 2 equiv of BCl_3 until the alkene was no longer visible by thin-layer assay, followed by a low-temperature quench with methanol, produced a mixture of 1,1-dimethoxyoctane and methyl octanoate (Scheme 3). The acetal could arise through acetalization of an aldehyde or transacetalization of a 1-chloroperoxide. However, the formation of an ester clearly suggests the intermediacy of an acid chloride derived from fragmentation of a chloroperoxide.

Scheme 3. Reaction with a Boron Halide



The Lewis acid-mediated delivery of alkoxides and phenoxides to carbonyl oxides offers a dramatic expansion of typical carbonyl oxide reactivity. First, the method provides a means of achieving "protic" ozonolysis products under aprotic conditions. Furthermore, the methodology is clearly superior to traditional conditions for delivery of bulky nucleophiles such as 2-propanol as well as traditionally ineffective nucleophiles such as phenols. Finally, the superior yield obtained for catechol borane mediated delivery of catechol testifies to the potential for delivery of oxidation-sensitive nucleophiles.

Our observations support a mechanism in which Lewis acid complexation is followed by intramolecular delivery of the ligand to the carbonyl oxide (Figure 1). This hypothesis is supported by a number of observations. Hydroperoxyacetals or derived dimers are observed in the absence of the appropriate alcohol. Although free alcohol could in theory arise from adventitious hydrolysis of the Lewis acid, this can be ruled out for several reasons. First, the yields of hydroperoxyacetals obtained from Lewis acid-mediated delivery of 2-propanol, phenol, and catechol are superior (in some cases, dramatically so) to those available using the parent alcohol or phenol. Second, differing diastereoselection is observed for addition to a chiral carbonyl oxide under traditional and Lewis acid-mediated conditions. Finally, the results of the experiment with BCl_3 support the presence of an intermediate with the characteristics of a complexed carbonyl oxide/chloroperoxyacetal.

In conclusion, these experiments demonstrate that the reactivity of carbonyl oxides can be strongly influenced by the presence of Lewis acids. Investigations into the mechanism of these reactions, the possibility of asymmetric induction, and the scope of transferable ligands are in process.

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Supporting Information Available: Sample ozonolysis and spectral listings (^1H, ^{13}C, IR) for **3a−d**, **4a−c**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) **Safety**: No safety problems were encountered in the course of these studies, However, as in any work involving peroxides, use of standard precautions is warranted. (a) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341. (b) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992. (c) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2.