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Patrick Dussault

University of Nebraska-Lincoln, pdussault1@unl.edu

Prasanta Ghorai

Indian Institute of Science and Education Research, Bhopal, pghorai@iiserbhopal.ac.in

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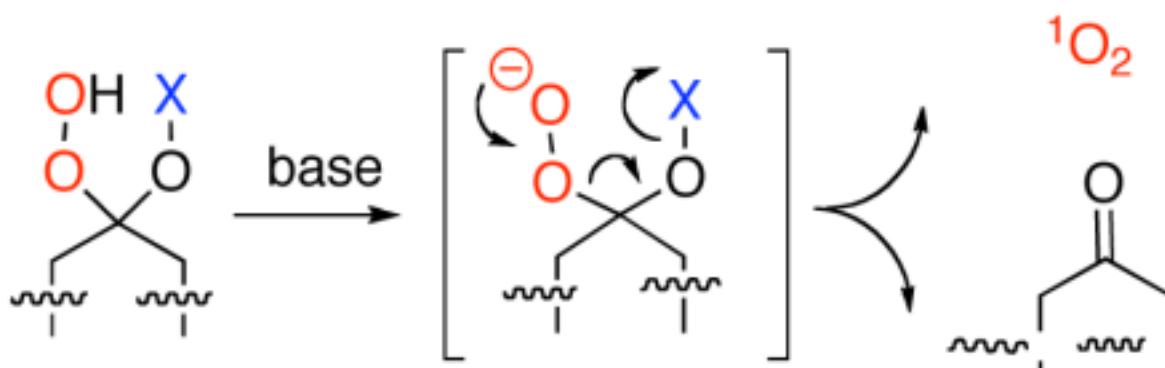
A new peroxide fragmentation: efficient chemical generation of $^1\text{O}_2$ in organic media

Prasanta Ghorai and Patrick H. Dussault

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, NE 68588-0304

Prasanta Ghorai ; Patrick H. Dussault: pdussault1@unl.edu

Abstract



X = acetate, carbonate, sulfonate

Monoactivated derivatives of 1,1-dihydroperoxides undergo an unprecedented base-promoted fragmentation to efficiently generate singlet oxygen ($^1\text{O}_2$) in anhydrous organic solvents.

Singlet molecular oxygen ($^1\text{O}_2$), an important oxidant in chemistry, biology, and medicine, ^{1a,b} is most commonly generated via photosensitized excitation of ground state ($^3\text{O}_2$) dioxygen. ^{1b,2} The discovery that $^1\text{O}_2$ is also produced from reaction of H_2O_2 and HOCl led to the discovery of a number of additional methods for chemical generation. ^{1a,3,4} However, many of these “dark” oxygenations have significant limitations. Due to the short half-life of $^1\text{O}_2$ in aqueous media, ⁵ methods based upon reaction of H_2O_2 with hypohalites, ³ alkaline earth metals, ⁶ transition metals, ⁷ lanthanides, ⁸ or metalloenzymes ⁹ must typically employ biphasic or emulsion conditions for preparative oxidations. ¹⁰ Thermal generation of $^1\text{O}_2$ from phosphite ozonides, ¹¹ silyl hydrotrioxides, ¹² or arene endoperoxides ¹³ can be conducted in organic solvents but requires preparation of unstable precursors. We report an efficient and convenient generation of $^1\text{O}_2$ in organic solvents via an unprecedented fragmentation of derivatives of 1,1-dihydroperoxides (Scheme 1).

Correspondence to: Patrick H. Dussault, pdussault1@unl.edu.

Supporting Information Available: Experimental procedures and spectral characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Our discovery stemmed from earlier research on “reductive” ozonolysis, in which the presence of amine *N*-oxides was found to promote direct ozonolytic conversion of alkenes to aldehydes and ketones.¹⁴ The proposed mechanism, involving formation and fragmentation of a zwitterionic peroxy/oxyammonium acetal, also predicted stoichiometric generation of ¹O₂ (Scheme 1). However, this prediction could not be easily tested within an ozonolysis reaction. In search of more accessible precursors for the putative fragmentation, we discovered that readily available derivatives of 1,1-dihydroperoxides will generate ¹O₂ under preparatively useful conditions.

The precursor 1,1-dihydroperoxides are readily available and possess surprising kinetic stability.^{15,16} The dihydroperoxides of 4-*t*-butylcyclohexanone and 4-phenyl-2-butanone, **1b** and **2b** respectively, were prepared in high yield by Re₂O₇-catalyzed reaction of the ketones with aq. H₂O₂ (Scheme 2).¹⁷ Monoperesters (**1c**, **1e**, **2c**) and a monopercarbonate (**1d**) were prepared by acylation or carboxylation of the dihydroperoxides.¹⁸ The monoesters were stable for several days at room temperature or weeks at -20 °C.¹⁹ In contrast, monopercarbonate **1d** could be isolated and purified but undergoes slow ring-expansion to 4-*t*-butylcaprolactone even at room temperature.²⁰

Addition of KOtBu to a THF solution of **1c** resulted in immediate bubbling, accompanied by disappearance of starting material and formation (TLC) of 4-*t*-butylcyclohexanone. Encouraged by this observation, we repeated the reaction in the presence of ¹O₂ trapping reagents (Table 1 and Figure 1).^{1a} Addition of KOtBu to a THF solution of **1c** and terpinene (**3**) resulted in formation of ketone **1a** (TLC) and endoperoxide **3-O₂**.²¹ A similar result was obtained with percarbonate **1d**. An increased yield of ¹O₂ from **1c** was observed at lower temperature, in acetonitrile (MeCN), or in the presence of diphenylisobenzofuran (DPBF, **4**), a more reactive trap which was completely consumed whether present in 0.5 or 0.75 equivalents relative to the monoperester.²² Efficient ¹O₂ generation was also observed from reaction of monoperester **1c** with Cs₂CO₃, but not K₂CO₃ or KOAc. This disparity drew our attention to the potential importance of ion pairing, and we turned to *n*Bu₄NF (TBAF) as a convenient base which would afford a highly dissociated peroxyanion. Gratifyingly, treatment of **1c** with TBAF led to extremely rapid reaction and a 39% yield of ¹O₂ (as **3-O₂**).

Further exploring the TBAF-promoted reaction (Table 2), we found that the use of excess TBAF and **1c** allowed consumption of furan **4** but failed to oxidize the less reactive **7**. Concerned that overly rapid generation of ¹O₂ might allow escape from a saturated solution, we investigated the decomposition of excess (1.5 – 8 equiv) monoperester in the presence of CsF and Me₄NOAc (TMA). Reactions were allowed to run for 30 min, but were typically complete (TLC) within 10 min. Complete consumption of all substrates was now observed. Citronellol (**7**) reacted to furnish a 91% yield of a 58:28:14 mixture of **7-O₂**, **9-O₂**, and ketone **8**. The formation of the isomeric hydroperoxides is characteristic for reactions of ¹O₂ with **7**;^{6,7} ketone **8** derives from base-promoted fragmentation of **7-O₂**.²³ The CsF protocol was also successfully applied to monoperesters **1e** and **2c**.

Finally, ¹O₂ can be generated via *in situ* formation and decomposition of monoperoxysulfonates. Although we were unable to isolate a monoperoxysulfonate, reaction of **1b** and terpinene (**3**) with toluenesulfonyl chloride (1.0 equiv) and KOtBu resulted in the rapid disappearance (TLC) of the dihydroperoxide and the formation of **3-O₂** (Scheme 3).

The unprecedented fragmentation described above could involve a Grob-like fragmentation,²⁴ or, alternatively, decomposition of an unstable peroxetane derived from 4-*exo tet* attack of the peroxyanion on the activated peroxide (Scheme 4).²⁵ Regardless of pathway, the fragmentation clearly requires both a highly dissociated peroxyanion and a peroxide activated towards heterolytic O-O scission. For example, the monoperesters do not generate oxygen in

the absence of base, while we found the 1,1-dihydroperoxides to be unaffected by the bases employed in these studies.²⁶ The efficiency of ¹O₂ production from the new fragmentation compares very favorably with known oxygen-generating systems.^{4,6,7,8}

In conclusion, we have developed a new heterolytic fragmentation that allows efficient and rapid generation of ¹O₂ in nondeuterated organic solvents from readily available precursors. The clean regeneration of the parent ketone suggests an avenue for possible development of solid-supported or phase-separable reagents while the efficiency and rate of ¹O₂ production points to potential application as a power source for chemical oxygen/iodine lasers.³⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Foote, CS.; Clennan, EL. Active Oxygen in Chemistry. Foote, CS.; Valentine, JS.; Greenberg, A.; Liebman, JF., editors. Blackie Academic and Professional; London: 1995. p. 105 b) Clennan E, Pace A. Tetrahedron 2005;61:6665.
2. Schmidt R. Photochem Photobiol 2006;82:1161. [PubMed: 16683906]
3. Foote CS, Wexler S, Ando W, Higgins RJ. Am Chem Soc 1968;90:975–81. Greer A. Acc Chem Res 2006;39:797. [PubMed: 17115719]
4. Adam W, Kazakov DV, Kazakov VP. Chem Rev 2005;105:3371. [PubMed: 16159156] Wahlen J, De Vos DE, Jacobs PA, Alsters PL. Adv Synth Catal 2004;346:152.
5. The half-life of ¹O₂ ranges from 1–2 usec in H₂O to 60 usec in CH₃CN to nearly msec in perhalogenated solvents. See ref. ^{1a}, and Wilkinson F, Helman WP, Ross AB. J Phys Chem Ref Data 1995;24:663.
6. Pierlot C, Nardello V, Schrive J, Mabelle C, Barbillat J, Sombret B, Aubry JM. J Org Chem 2002;67:2418. [PubMed: 11950282]
7. Sels BF, De Vos DE, Jacobs PE. J Am Chem Soc 2007;129:6916. [PubMed: 17488006] Caron L, Nardello V, Alsters PL, Aubry JM. J Mol Cat, A 2006;251:194.
8. Nardello V, Barbillat J, Marko J, Witte PT, Alsters PL, Aubry JM. Chem Eur J 2003;9:435.
9. Renirie R, Pierlot C, Aubry JM, Hartog AF, Schoemaker HE, Alsters PL, Wever R. Adv Synth Catal 2003;345:849.
10. See, for example: Aubry J-M, Adam W, Alsters PL, Borde C, Queste S, Marko J, Nardello V. Tetrahedron 2006;62:10753.
11. Thompson QE. J Am Chem Soc 1961;83:845. Mendenhall, GD. Advances in Oxygenated Processes. Baumstark, AL., editor. Vol. 2. JAI; Greenwich: Connecticut: 1990. p. 203
12. Corey EJ, Mehrotra MM, Khan AU. J Am Chem Soc 1986;108:2472. Cerkovnik J, Tuttle T, Kraka E, Lendero N, Plesnicar B, Cremer D. J Am Chem Soc 2006;128:4090. [PubMed: 16551118]
13. Wasserman HH, Scheffer JR, Cooper JL. J Am Chem Soc 1972;94:4991. Pellieux C, Dewilde A, Pierlot C, Aubry JM. Meth Enzymol 2000;319:197. [PubMed: 10907511]
14. Schwartz C, Raible J, Mott K, Dussault PH. Tetrahedron 2006;62:10747.
15. Li Y, Hao HD, Zhang Q, Wu Y. Org Lett 2009;11:1615. [PubMed: 19278246] and references therein
16. Dihydroperoxide 1b is not detonated by a hammer blow and melts without decomposition at 78–80 °C. However, even though no hazards were experienced in the course of this work, any preparative work with peroxides should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions. See Supporting Information for references related to safe handling of peroxides.
17. Ghorai P, Dussault PH. Org Lett 2008;10:4577. [PubMed: 18783232] and references therein

18. Cudden RCP, Hewlett C. *J Chem Soc, C* 1968:2983. Van de Bovenkamp-Bouwman AG, Van Gendt JWJ, Meijer J, Hogt AH, Van Swieten AP. Dihydroperoxide monoesters have been investigated as radical initiators. *PCT Int Appl.* 1999WO 9932442 A1 19990701
19. Monoester 1c is not detonated by a hammer blow and melts without decomposition at 37 °C. It is stable for less than a day at 60 °C.
20. Percarbonates of tertiary hydroperoxides and monoperoesters of 1,1-dihydroperoxides are both known to undergo Criegee rearrangement: Villenave JJ, Filliatre C, Maillard B, Jaouhari R. *Bull Soc Chim Belg* 1982;91:301. Velluz L, Amiard G, Martel J, Warnant J. *Compt Rend* 1957;244:1937. We are uncertain as to the basis for the increased stability of 1c vs. 1d.
21. Reported yields are based upon either isolation or quantitative GC/MS of oxidation products relative to an internal standard; see Supporting Information for details. In general, the ketone byproduct (1a or 2a) was recovered in good yield from the decomposition reactions.
22. Due to the facility of self-sensitized oxidation, the use of DPBF for quantitative experiments should include control reactions or take care to exclude light and oxygen. See: Owakowska M. *J Chem Soc, Faraday Trans 1* 1984;80:2119.
23. Kornblum N, DelaMare HE. *J Am Chem Soc* 1951;73:880.
24. Grob CA. *Angew Chem, Int Ed Engl* 1969;8:535.
25. Although 4-*exo/tet* displacements by peroxyanions to form dioxetanes have been observed (Kopecky, K., Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J-Y. *Can. J. Chem.* 1975, 53, 1103), the corresponding closure to peroxetanes is unknown. The intermediacy of peroxetanes could in principle be established by the relative fractions of $^{18}\text{O}^{16}\text{O}$ formed upon decomposition of dihydroperoxides derived from mixtures of $\text{H}^{18}\text{O}^{18}\text{OH}$ and $\text{H}^{16}\text{O}^{16}\text{OH}$. We thank one of the referees for this suggestion.
26. 1,1-Dihydroperoxides have been successfully bisalkylated in the presence of Cs_2CO_3 : Kim HS, Nagai Y, Ono K, Begum K, Wataya Y, Hamada Y, Tsuchiya K, Masuyama A, Nojima M, McCullough KJ. *J Med Chem* 2001;44:2357–61. [PubMed: 11428929]
30. Endo, M *Russ. J Phys Chem A* 2007;81:1497.

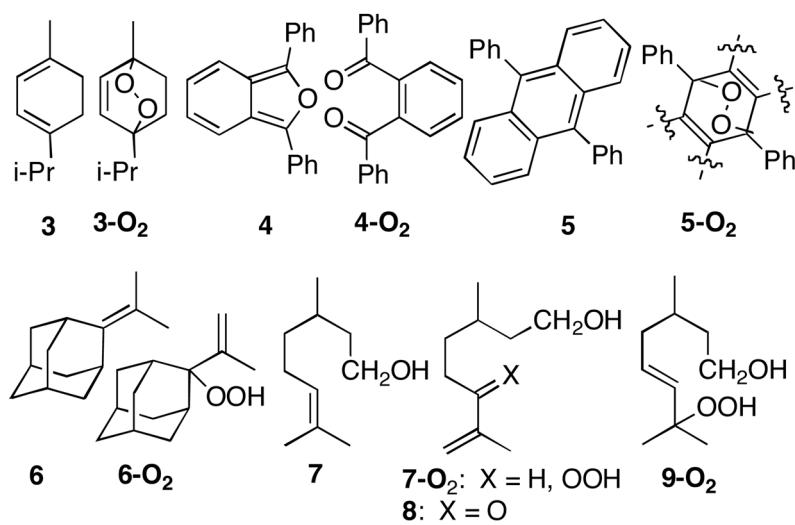
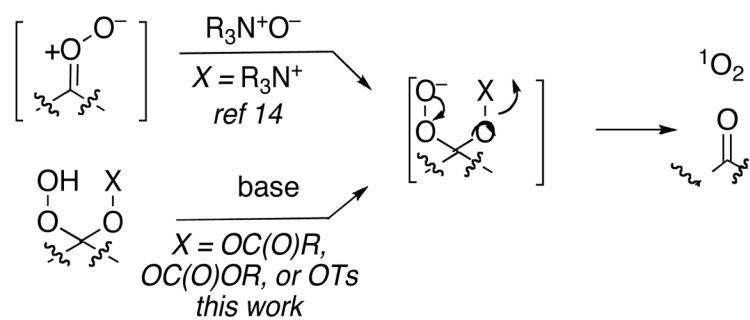
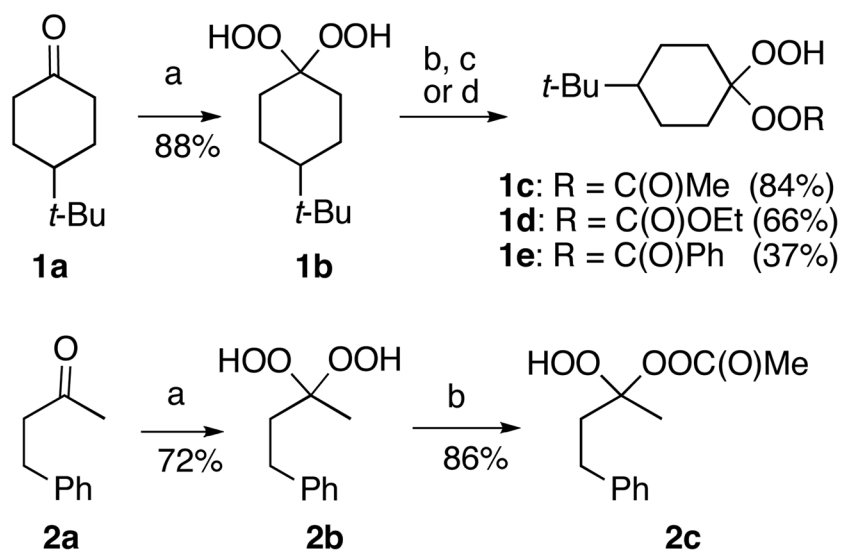
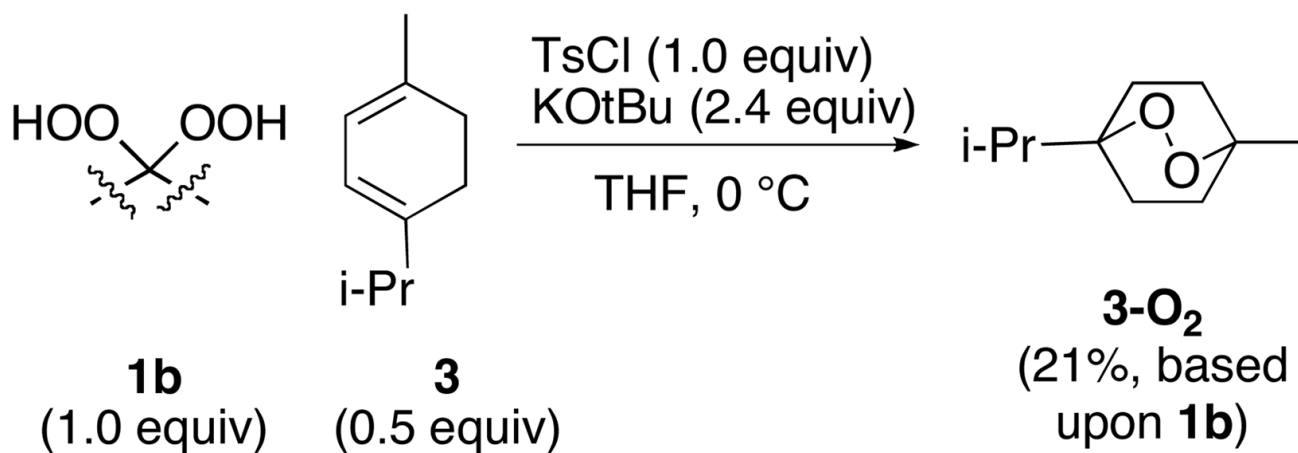


Figure 1.
Trapping substrates and products

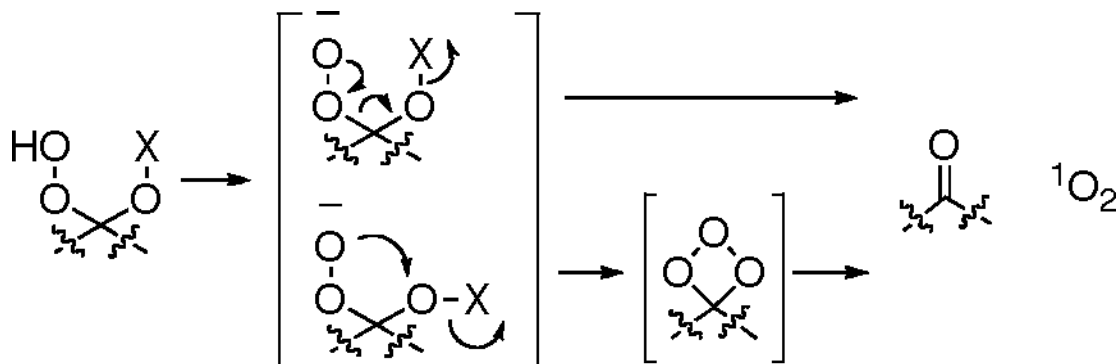


Scheme 1.
Fragmentation of peroxyacetals

**Scheme 2.**Preparation of peroxide substrates^a^a(a) ref ¹⁷ (b) Ac₂O, DMAP (c) EtOC(O)Cl, pyr (d) BzCl, pyr



Scheme 3.
Generation of ¹O₂ from 1,1-dihydroperoxide



Scheme 4.
Potential mechanisms

Table 1

Generation of $^1\text{O}_2$ from **1c** and **1d**^a

reagents	base	sol ^v	time (h)	temp (°C)	prod	yield ^b	Reaction Scheme	
							trapping agent (3 or 4, 0.5 equiv)	base (1.1 equiv) oxidized trap (3-O ₂ or 4-O ₂)
1c	KOtBu ^c	THF	1	0	3-O ₂	15%	<p> $\text{HOO-CH(O)R} \xrightarrow[\text{trapping agent (3 or 4, 0.5 equiv)}]{\text{base (1.1 equiv)}} \text{oxidized trap (3-O}_2 \text{ or 4-O}_2)$ </p> <p> 1c: R = CH₃ 1d: R = OEt (1.0 equiv) </p>	
1c	KOtBu ^c	THF	2	-78	3-O ₂	21%		
1c	KOtBu	MeCN	0.5	0	3-O ₂	30%		
1c	KOtBu	MeCN	1	0	4-O ₂	50% (48%) ^d		
1c	KOtBu	MeCN	1	0	4-O ₂	75% ^e		
1d	KOtBu	MeCN	1	0	3-O ₂	39%		
1c	K ₂ CO ₃	MeCN	1	0	3-O ₂	NR		
1c	C ₅ H ₅ CO ₃	MeCN	1	0	3-O ₂	27%		
1c	KOAc	MeCN	1	0	3-O ₂	NR		
1c	TBAF	MeCN	0.2	0	3-O ₂	39%		

^a Trapping agents shown in Figure 1.^b 3-O₂ or 4-O₂ vs **1c** or **1d**.^c Base added to substrates.^d Isolated yield.^e 0.75 equiv of **4**.

Table 2

Protocols for preparative oxidation

Trap (1.0 equiv) + 1c or 2c (excess) + Promoter (excess)		CH ₃ CN	Oxidized Product(s)	trap	promoter ^a	t (h)	temp (°C)	products (yield) ^b
perester (equiv)								
1c (3)		4	4	TBAF ^c	0.5	0	4-O₂ (91%)	
1c (2)		7	7	TBAF ^c	0.5	0	NR	
1c (4)		3	3	CsF, TMA	0.5	rt	3-O₂ (69%)	
1c (1.5)		4	4	CsF, TMA	0.5	rt	4-O₂ (94%)	
1c (8)		5	5	CsF, TMA	1	rt	5-O₂ (81%)	
1c (6)		6	6	CsF, TMA	0.5	rt	6-O₂ (76%)	
1c (8)		7	7	CsF, TMA	0.5	rt	7-O₂/9-O₂/8 (91%, 58:28:14)	
1e (3)		3	3	CsF, TMA	0.5	rt	3-O₂ (62%)	
2c (3)		3	3	CsF, TMA	0.5	rt	3-O₂ (66%)	

^aPromoter present in 2.4 equiv relative to monoperoester.^bBased upon conversion of trap to product.^cTHF as solvent.