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Acid-Catalyzed Activation of Peroxyketals: Tunable Radical Initiation at Ambient Temperature and Below

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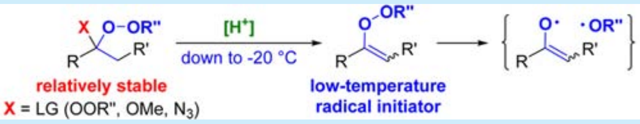
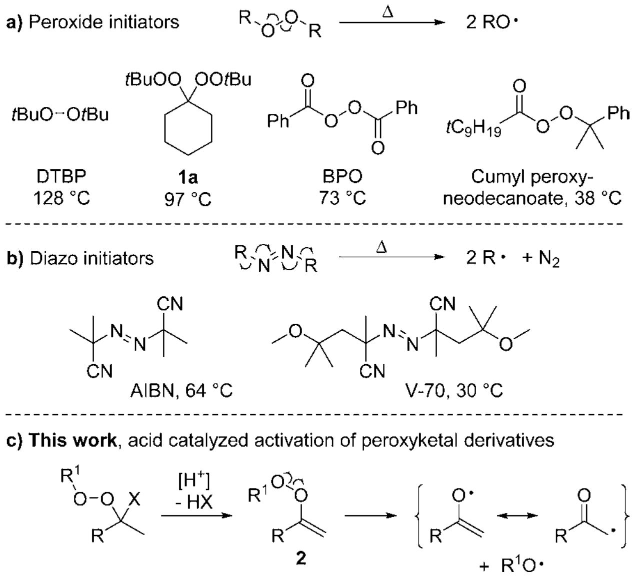
Supporting Information



ABSTRACT: This study details how peroxyketals, commercially available thermal initiators, and structurally related peroxides are activated in the presence of an acid catalyst to generate radicals at room temperature and below. This simple combination of two substrates was shown to efficiently initiate a variety of radical processes. This phenomenon is rationalized by the acid-catalyzed in situ formation of highly unstable alkenyl peroxides which readily decompose into initiating radical species.

Radical chemistry offers unique reaction pathways, often giving products that are inaccessible by ionic mechanisms.[1] To initiate radical-chain reactions, compounds that generate radical species by the homolytic scission of a weak bond are commonly used, for example, peroxides like *tert*-butylperoxide and **1a** (Scheme 1a) and diazo compounds like AIBN (Scheme 1b).[2] Thermal bond homolysis is usually achieved at elevated temperatures, and many initiators have been developed to vary the rate of initiation at a given temperature (Scheme 1).

Scheme 1. Selected Radical Initiators, Including 10 h Half-Life Temperatures[2c,d,3]



Designing low-temperature radical initiators requires compromises. The desired compound has to be sufficiently unstable to decompose at low temperature but needs to be stable enough to be produced, transported, and handled. Examples of commercial low temperature initiators are cumyl peroxyneodecanoate and the diazo compound V-70, which have 10 h half-life temperatures of only 38 and 30 °C, respectively.[2c,3] While these are commercial and useful products, it is evident that a cold chain must be strictly followed throughout transport and storage. To alleviate the associated safety hazards, other strategies have been developed to generate radicals at low temperature.[2b,e] Activation of peroxides by UV light, metal salts, or amines is a common method.[4] Other strategies rely on photoinitiation[5] or on the instability of organoborane and zinc compounds toward molecular oxygen.[6] However, storage of the latter reagents requires strictly inert conditions, and control of the initiation rate can be difficult.[6d]

Here, we show that the combination of geminal bisperoxides and derivatives with an acid catalyst initiates radical reactions at ambient temperature and below (Scheme 1c).

We recently reported that ketones and hydroperoxides generate oxyl and α-keto alkyl radicals in the presence of acid.[7] These radicals can be exploited synthetically for addition reactions to olefins to give low molecular weight products[7a,8] or polymers.[9] We postulated alkenyl peroxides **2** as intermediates that rapidly decompose due to their very weak O–O bonds.[7] In polymerization reactions, we observed that geminal bisperoxide **1a** can be used instead of the combination of ketone and hydroperoxide and leads to increased rates.[9] Interestingly, peroxyketals like **1a** are common thermal initiators[2e,10] but also potentially explosive (Figure 1).[11]

It has been shown that thermal runaway hazards of peroxyketals are dramatically increased in the presence of strong acids[12] and that acid addition shortens curing times when they are used.[2e] We hypothesized that this phenomenon is due to the in situ formation of unstable alkenyl peroxides, and that this behavior could be exploited in a controlled manner for radical initiation purposes (Scheme 1c). We therefore evaluated the potential of geminal bisperoxides as

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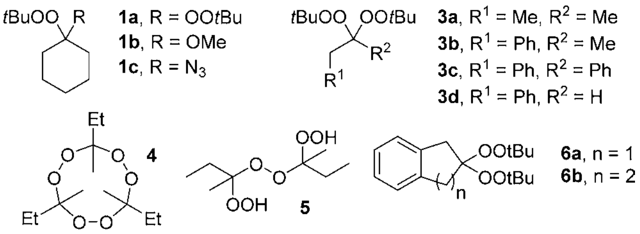
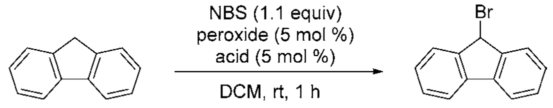


Figure 1. Geminal bisperoxides and related compounds used in this study.

radical initiators at ambient temperature in reactions that do not incorporate fragments of the initiator. For this purpose, we selected the radical bromination of fluorene **7** by *N*-bromosuccinimide (NBS) at room temperature as a benchmark reaction (Table 1).

Table 1. Wohl−Ziegler Bromination of Fluorene at Ambient Temperature.[a]



7 **8**

entry	peroxide	acid (pK_a)[b]	yield[c] (%)
1	**1a**	H_2SO_4 (−8)	72
2	**1a**	*p*-TsOH (−2.8)	67
3	**1a**	CH_3SO_3H (−1.9)	45
4	**1a**	HNO_3 (−1.4)	96
5	**1a**	CF_3CO_2H (0.23)	22
6	**1a**	CCl_3CO_2H (0.66)	18
7	**1a**	AcOH (4.76)	0
8	**1a**	$Sc(OTf)_3$	69[d]
9	**1b**	CH_3SO_3H (−1.9)	21
10	**1c**	CH_3SO_3H (−1.9)	47
11	**3a**	CH_3SO_3H (−1.9)	10; 76[e]
12	**3b**	CH_3SO_3H (−1.9)	20
13	**3c**	CH_3SO_3H (−1.9)	0; 33[e]
14	**3d**	CH_3SO_3H (−1.9)	0; 9[e]
15	**4**	CH_3SO_3H (−1.9)	0; 8[e]
16	**5**	CH_3SO_3H (−1.9)	1; 12[e]
17	**6a**	CH_3SO_3H (−1.9)	50
18	**6b**	CH_3SO_3H (−1.9)	74

[a] All reactions were performed on a 0.5 mmol scale in 5 mL of dichloromethane under an argon atmosphere at room temperature (22−23 °C) and with exclusion of light for 1 h. [b] pK_a value in water given in parentheses. [c] Yields determined by ^1H NMR using CH_2Br_2 as an internal standard. [d] Reaction performed in acetonitrile. [e] After 48 h of reaction.

The bromination proceeded efficiently using a commercial solution of peroxyketal **1a** (Trigonox 22, 50% weight in mineral oil) in combination with different Brønsted acids. Control experiments confirmed the requirement for both acid and peroxyketal, with no conversion being observed after 24 h if either one of these components was omitted. A clear trend following the pK_a value of the acid catalyst can be seen: stronger acids give faster conversion. Sulfuric and *p*-toluenesulfonic acid display similar behavior with 72% and 67% of **8** after 1 h, respectively (entries 1 and 2). Methanesulfonic acid gave a slightly lower yield (45%; entry 3), and only the activated carboxylic acids trifluoroacetic acid (22%, entry 5) and trichloroacetic acid (18%, entry 6) gave reasonable conversions, while acetic acid was inactive (entry 7). Nitric acid falls out of this trend and is more efficient than its pK_a value would suggest, possibly due to alternative pathways involving its oxidizing properties (96%; entry 4).[13] Eventually, all reactions gave high yields when allowed to reach full conversion (80−95% yield of **8** after 24 to 72 h), showing that the acid catalyst only influences the initiation rate, formation of the alkenyl peroxide intermediate presumably being the rate-controlling step. Scandium(III) triflate, a Lewis acid, was also found to be competent (69%; entry 8).

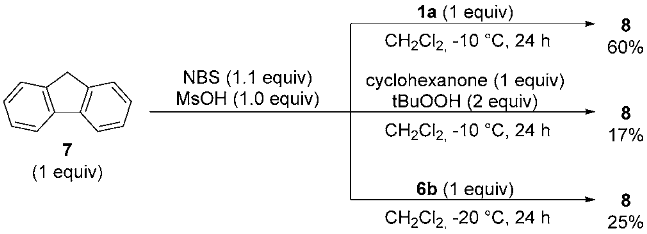
Different commercial peroxyketal solutions were then evaluated using methanesulfonic acid as a standard catalyst of medium reactivity. Compound **3a** (Trigonox D; 50% weight) proved to be less efficient than **1a** (45%, entry 3), giving only 10% of product **8** after 1 h and 76% after 48 h (entry 11). Compound **4** (Trigonox 301; 41% weight) only showed low conversion after 2 days of reaction (8%, entry 15). Compound **5** (Luperox DHD-9, 32% weight) was found to be slightly more reactive than **4**, giving a trace amount of **8** after 1 h and 12% after 48 h (entry 16).

Based on this strong influence of the peroxyketal structure on its reactivity, we decided to synthesize structural analogues, hoping to design more reactive ones toward acid activation. The synthesis of these compounds is easily accomplished by reaction of ketones, ketals, and aldehydes, respectively, with hydroperoxides (see the Supporting Information). We first looked at the effect of the leaving group. Compound **1b** proved to be less reactive than **1a** (21%, entry 9). Interestingly, the azide containing **1c** was as efficient as **1a**, giving 47% of **8** after 1 h (entry 10). We then evaluated aromatic substituents around the peroxyketal moiety to enhance the driving force of elimination toward alkenyl peroxides. Compound **3b** was indeed more effective than **3a** (20%, entry 12 compared to entry 11), while **3c** was much less efficient (33% after 48 h, entry 13), showing that a benzyl substituent is beneficial while an aromatic substituent is highly detrimental. Peroxyacetal **3d** was very unreactive, only giving small amounts of product after 48 h (9%, entry 14), showing the requirement of a ketone-derived bisperoxide for efficient acid activation. In light of these results and the increased reactivity of cyclic **1a** compared to the acyclic **3a**, we reasoned that a cyclic and benzylic peroxyketal would be very reactive. Indeed, **6a** was found to be slightly more reactive than **1a** (50%, entry 17), while **6b** was the most efficient of the structures evaluated, giving 74% of **8** after 1 h of reaction (entry 18).

We were then interested in finding the limits of reactivity with regard to temperature (Scheme 2).

Lowering the temperature had a detrimental effect on the efficiency of the reaction (see the Supporting Information for

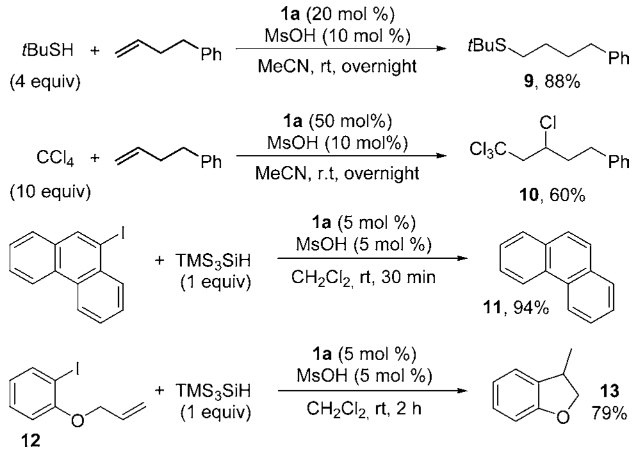
Scheme 2. Wohl−Ziegler Bromination at Cryogenic Temperatures



additional details). However, when the reaction was performed at −10 °C with stoichiometric amounts of **1a** and methanesulfonic acid, a satisfying 60% yield of **8** was obtained after 24 h. We compared this result with our original combination of ketone and hydroperoxide[7a] and found that, while it is still a competent system, its efficiency is considerably lower than using the preformed peroxyketal **1a** (60% vs 17%). Lowering the temperature to −20 °C showed only trace conversion with this combination, while the more reactive **6b** still gave 25% of **2** after 24 h.

We evaluated a selection of classical radical reactions using the commercial solution of peroxyketal **1a** and methanesulfonic acid for initiation (Scheme 3).

Scheme 3. Application of the 3a/Acid Combination for Selected Radical Reactions at Room Temperature

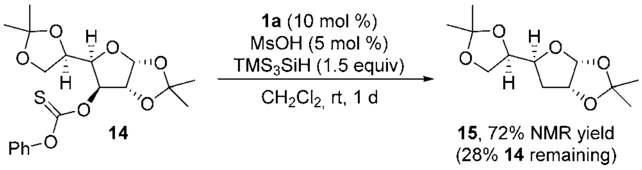


Addition of a thiol to a terminal olefin proceeded smoothly in the presence of 20 mol % of **1a** and 10 mol % methanesulfonic acid to give product **9** in 88% yield. Similarly, an atom-transfer radical addition (ATRA) of carbon tetrachloride was successfully initiated. Although it required a larger amount of **1a**, 60% of product **10** was obtained. The TMS_3SiH-mediated reduction of 9-iodophenanthrene was performed, giving phenanthrene **11** in an excellent 94% yield, requiring only low amounts of peroxyketal and acid. The reductive cyclization of **12** was similarly successful, giving benzofurane **13** in 79% yield. Disappointingly, *n*-Bu_3SnH seemed incompatible with this initiation system, and no conversion was observed in these two reactions when it replaced TMS_3SiH. However, TMS_3SiH has proven to be a suitable replacement for *n*-Bu_3SnH-mediated reactions and avoids most toxicity and purification problems associated with stannane reagents.[14]

Obviously, the reaction conditions involving a strong acid will be incompatible for some compounds. We investigated this in more detail by performing a Barton−McCombie deoxygenation on an acid-sensitive ketal, **14**.[15] While longer reaction times generally led to decomposition, the reaction could be performed successfully with 72% yield of product **15** and 28% of leftover starting material after 1 day, as determined by NMR spectroscopy using an internal standard (Scheme 4, also see the Supporting Information).

This outcome illustrates that acid-sensitive substrates or products can be compatible with this method, especially given that reaction time, acid strength, and concentration can be further fine-tuned.

Scheme 4. Radical Decarboxylation with an Acid-Sensitive Compound



The supposed in situ generation of unstable alkenyl peroxides and the corresponding radicals (Scheme 1C) was supported by a trapping experiment in the presence of styrene, which led to a γ-peroxyketone, indicative of the formation of α-keto-alkyl and oxyl radicals (see the Supporting Information). No attempt was made yet to observe alkenyl peroxide intermediates spectroscopically, which might be difficult since these compounds are believed to be highly reactive. In fact, only a single characterization study is known for a special type of heterocyclic alkenylperoxides.[16]

These different reactions demonstrate the generality of this initiation system. Abstraction of a hydrogen atom from suitable substrates, presumably by a *tert*-butoxyl radical, is possible, as shown by the success of the Wohl−Ziegler and thiol−ene reactions. Direct abstraction of halogen atoms, presumably by the complementary carbon centered radical formed, is also possible, as in the ATRA of CCl_4. If the radicals generated are not reactive enough to initiate chains themselves, they are competent in initiating reactions relying on the use of a hydride mediator like TMS_3SiH. The exact mechanism of initiation and fate of the initiating radicals will not be obvious in many reactions, since hydrogen atom transfer, for example, will generate cyclohexanone and *tert*-butyl alcohol, which would also form by hydrolysis and O−O bond homolysis via any other mechanism, respectively. Detailed studies to clarify this issue are planned for a later stage.

In conclusion, we describe how peroxyketals and related compounds, normally used as thermal initiators, can be activated in the presence of an acid catalyst to efficiently initiate a wide variety of radical processes at room temperature and down to −20 °C. The rate of radical formation was shown to depend on the strength and concentration of the activating acid as well as the structure of the peroxide. Both parameters offer the opportunity to fine-tune the reaction rate. This method of generating radical initiators in situ, believed to be alkenyl peroxides, has the advantage that the substrates are commercially available and easily synthesized, respectively, tolerant to air and moisture, and thermally quite stable. It can be envisioned that even more reactive peroxyketals or combinations with special catalysts can be developed to further lower the initiation temperatures.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02419.

Experimental details including synthesis and characterization of starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; John Wiley & Sons, 2012. (b) *Radicals in Synthesis I & II*; Gansäuer, A., Ed.; Springer: Berlin, 2006; Vols. *263–264*. (c) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003. (d) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH, Weinheim, 2001. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (f) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986; Vol. *5*.

(2) (a) Androvič, L.; Bartáček, J.; Sedlák, M. *Res. Chem. Intermed.* **2016**, *42*, 5133. (b) Lalevée, J.; Fouassier, J. P. Overview of Radical Initiation. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, Ltd., 2012. (c) Sheppard, C. S. Peroxy Compounds. In *Encyclopedia of Polymer Science and Engineering*; John Wiley & Sons, Inc., 1985; Vol. *11*, p 1. (d) Sheppard, C. S. Azo Compounds. In *Encyclopedia of Polymer Science and Engineering*; John Wiley & Sons, Inc., 1985; Vol. 2, p 143. (e) Sheppard, C. S.; Kamath, V. R. *Polym. Eng. Sci.* **1979**, *19*, 597.

(3) Kita, Y.; Gotanda, K.; Murata, K.; Suemura, M.; Sano, A.; Yamaguchi, T.; Oka, M.; Matsugi, M. *Org. Process Res. Dev.* **1998**, *2*, 250.

(4) Kwon, T.-Y.; Bagheri, R.; Kim, Y. K.; Kim, K.-H.; Burrow, M. F. *J. Investig. Clin. Dent.* **2012**, *3*, 3.

(5) (a) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152. (b) Fouassier, J.-P.; Morlet-Savary, F.; Lalevée, J.; Allonas, X.; Ley, C. *Materials* **2010**, *3*, 5130.

(6) (a) Zaremski, M. Y.; Garina, E. S.; Gurskii, M. E.; Bubnov, Y. N. *Polym. Sci., Ser. B* **2013**, *55*, 304. (b) Akindele, T.; Yamada, K.-i.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. (c) Renaud, P.; Beauseigneur, A.; Brecht-Forster, A.; Becattini, B.; Darmency, V.; Kandhasamy, S.; Montermini, F.; Ollivier, C.; Panchaud, P.; Pozzi, D.; Scanlan, E. M.; Schaffner, A.-P.; Weber, V. *Pure Appl. Chem.* **2007**, *79*, 223. (d) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

(7) (a) Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klussmann, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8737. (b) Schweitzer-Chaput, B.; Kurtén, T.; Klussmann, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11848.

(8) (a) Boess, E.; Karanestora, S.; Bosnidou, A.-E.; Schweitzer-Chaput, B.; Hasenbeck, M.; Klussmann, M. *Synlett* **2015**, *26*, 1973. (b) Xia, X.-F.; Zhu, S.-L.; Zeng, M.; Gu, Z.; Wang, H.; Li, W. *Tetrahedron* **2015**, *71*, 6099.

(9) Vandenbergh, J.; Schweitzer-Chaput, B.; Klussmann, M.; Junkers, T. *Macromolecules* **2016**, *49*, 4124.

(10) (a) Watanabe, Y.; Ishigaki, H.; Suyama, S. *Polym. J.* **1992**, *24*, 257. (b) Drumright, R. E.; Kastl, P. E.; Priddy, D. B. *Macromolecules* **1993**, *26*, 2246.

(11) Although we never experienced any problems in the experiments as described in this work, precautions should be taken when working with neat peroxides. Neat **4** and **5** are described as explosive; see: Milas, N. A.; Golubović, A. *J. Am. Chem. Soc.* **1959**, *81*, 5824 The commercial bisperoxides **1a**, **3a**, **4**, and **5** come as solutions in mineral oil which were used as such and are safe to be shipped and stored. See the Supporting Information for further details..

(12) Hsueh, K.-H.; Chen, W.-T.; Chu, Y.-C.; Tsai, L.-C.; Shu, C.-M. *J. Therm. Anal. Calorim.* **2012**, *109*, 1253.

(13) Control experiments revealed that nitric acid alone does not promote any reaction but that, in the presence of tBuOOH, significant conversion is achieved after 24 h (80%).

(14) (a) Chatgilialoglu, C.; Timokhin, V. I. Silanes as Reducing Reagents in Radical Chemistry. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, Ltd, 2012. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, *2002*, 835.

(15) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949.

(16) Kropf, H.; Ball, M. *Justus Liebigs Ann. Chem.* **1976**, *1976*, 2331.

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