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Pyridine Is an Organocatalyst for the Reductive Ozonolysis of Alkenes

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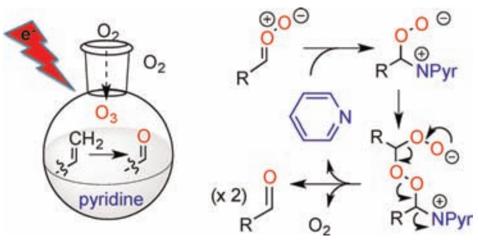
ABSTRACT



Whereas the cleavage of alkenes by ozone typically generates peroxide intermediates that must be decomposed in an accompanying step, ozonolysis in the presence of pyridine directly generates ketones or aldehydes through a process that neither consumes pyridine nor generates any detectable peroxides. The reaction is hypothesized to involve nucleophile-promoted fragmentation of carbonyl oxides via formation of zwitterionic peroxyacetals.

The ozonolysis of alkenes, a widely used and environmentally sustainable oxidative transformation, is nearly always accompanied by a reaction to decompose the ozonides or other peroxide intermediates.[1] However, the proclivity of ozonides toward exothermic and self-accelerating decomposition reactions, combined with their low rate of reaction with many reducing agents, can create serious hazards.[2−4] An attractive alternative to a traditional stepwise approach would involve *in situ* capture and decomposition of the carbonyl oxide intermediates. We recently described two approaches to "reductive" ozonolyses based upon trapping of carbonyl oxides by amine *N*-oxides or water.[5] However, the first of these requires basic conditions while the latter generates hydrogen peroxide as a stoichiometric byproduct. We became interested in a handful of reports describing the direct formation of carbonyl groups for ozonolyses conducted in the presence of pyridine.[6,7] This mechanistically unexplained process has received little synthetic attention.[8,9] We now report that ozonolysis in the presence of pyridine involves an unprecedented organocatalyzed decomposition of carbonyl oxides via the formation and fragmentation of zwitterionic peroxyacetals. The overall process offers a fast, general, and high-yielding route to aldehydes and/or ketones.

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(1) (a) Bailey, P. S. *Ozonation in Organic Chemistry: Vol. 1: Olefinic Compounds*; Academic Press: New York, 1978. (b) McGuire, J.; Bond, G.; Haslam, P. J. Ozonolysis in the Production of Chiral Fine Chemicals. *Handbook of Chiral Chemicals*, 2nd ed.; Taylor & Francis: Boca Raton, FL, 2006; pp 165−184. (c) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990.

(2) Kula, J. *Chem. Health Safety* **1999**, *6*, 21.

(3) (a) Gordon, P. M. *Chem. Eng. News.* **1990**, *68*, 2. (b) Lavallee, P; Bouthillier, G. *J. Org. Chem.* **1986**, *51*, 1362–5; see note 27 and references within. (c) Ferreira, J. T. B. *Chem. Eng. News.* **1990**, *68*, 4.

(4) (a) See: Hida, T.; Kikuchi, J.; Kakinuma, M.; Nogusa, H. *Org. Process Res. Dev.* **2010**, *14*, 1485. For discussions of membrane- or flow-through reactors, see: (b) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596. (c) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *Org. Lett.* **2010**, *13*, 984.

(5) (a) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Org. Lett.* **2006**, *8*, 3199. (b) *Tetrahedron* **2006**, *62*, 10747. (c) Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688. See also: (d) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558.

(6) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.

(7) Lutidine has been employed as an additive for ozonolyses (Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320), but the substrates in this study would be expected to generate aldehydes regardless of conditions or additives.

(8) Griesbaum, K. *Chem. Commun.* **1966**, 920.

(9) Pyridine has been applied as an additive to enhance the chemoselectivity of ozonolysis within polyunsaturated systems. See ref 6 and: Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.

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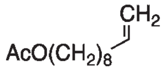
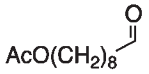
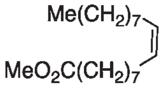
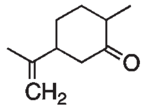
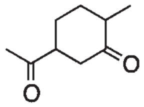
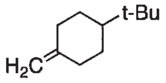
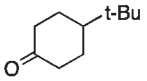
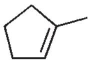
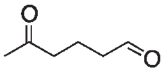
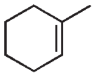
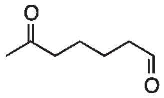
Table 1. O_3/Pyridine versus a Standard Two-Step Procedure[a]

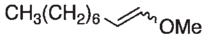
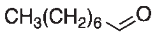
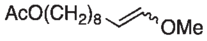
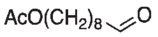
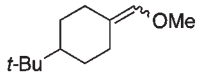
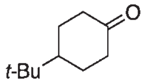
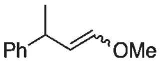
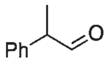
substrate	cond	product	yield(s)
	A		78%
	B		83%
	A	$Me(CH_2)_7CHO$ + $MeO_2C(CH_2)_7CHO$	90, 75%
	B		82, 78%
	A		80%
	C		81%
	A		79%
	B		85%
	A		70%
	B		77%
	A		87%
	B		93%

[a] Conditions: (A) O_3, CH_2Cl_2, −78 °C; Ph_3P, 24 h; (B) O_3, 2−3 equiv of pyridine, CH_2Cl_2, −78 °C, 2−3 min; (C) As per "B" but 1 equiv of pyridine.

Our initial investigations, illustrated in Table 1, directly compared ozonolysis in pyridine against a traditional two-step protocol.[10,11] For example, ozonolysis of the acetate of 9-decenol, followed by reduction of the intermediate ozonide with Ph_3P, furnished the aldehyde in 78% yield. The same product was available in 83% yield, in only 2−3 min and without any reductive workup, if ozonolysis was conducted in the presence of pyridine. Performing the reaction in the presence of substoichiometric pyridine resulted in the isolation of significant amounts of ozonide, and the best yields of aldehyde or ketone were generally obtained in the presence of ≥ 2 equiv of pyridine. In control reactions, we demonstrated that isolated ozonides were unreactive toward pyridine under the reaction conditions.

We next investigated ozonolysis of enol ethers (Table 2); the carbonyl oxide/ester pair derived from cycloreversion of the primary ozonide does not readily undergo cycloaddition to ozonides. As a result, enol ethers typically generate monomeric products only in the presence of an added alcohol or aldehyde able to capture the carbonyl oxide.[12] However, ozonolysis of enol ethers **1a**−**4a** in the presence of pyridine furnished good yields of the carbonyl products (**1b**−**4b**); neither carbonyl products nor ozonides were obtained in the absence of pyridine (not shown).

Table 2. Reductive Ozonolysis of Enol Ethers[a]

	substrate	product		yield
1a			**1b**	74%
2a			**2b**	86%
3a			**3b**	83%
4a			**4b**	70%

[a] Conditions: O_3/O_2, −78 °C, 2−3 equiv of pyridine in CH_2Cl_2.

The influence of pyridine electronic and steric factors was further investigated using enol ether **3a** (Table 3). Similar yields of ketone **3b** were obtained in the presence of electron-rich and -poor pyridines.[13] However, the presence of steric bulk adjacent to the pyridine nitrogen suppresses formation of carbonyl product. Similar results were obtained with alkene substrates (not shown); for example, terminal alkenes furnish aldehydes in the presence of pyridine or 2,6-lutidine but not 2,6-di-*tert*-butylpyridine. The replacement of pyridine with other heterocyclic bases (thiophene, imidazole, 1-methylimidazole) led to much lower yields of reduction products, and this theme was not pursued.

Table 3. Probing Steric and Electronic Influences

$$\mathbf{3a} \xrightarrow[\text{CH}_2\text{Cl}_2,\ -78\ °\text{C}]{\text{O}_3,\ \text{additive (3 equiv)}} \mathbf{3b}$$

additive	ketone (%)[a]
pyridine	83
3-nitropyridine	53
N,N′-dimethylaminopyridine	65
2,6-lutidine	traces
2,6-di-*tert*-butylpyridine	traces

[a] Isolated yield.

The synthetic utility of the reductive ozonolysis can be seen in the ability to directly apply the products to reaction with a stoichiometric amount of an organometallic

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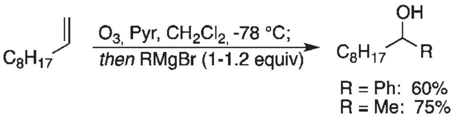
(10) The alkene substrate (1−3 mmol) and dry pyridine (3−9 mmol) were dissolved in dry CH_2Cl_2 (15−20 mL) in a flame-dried flask under N_2. The solution was cooled to −78 °C, and a stream of O_3/O_2 was introduced through a disposable pipet for a period varying with the amount of alkene (typically ~1 min/mmol). Once judged to be complete (TLC, in situ IR, or time), the reaction was sparged with O_2 and then N_2. The crude reaction mixture was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$, and the separated aqueous layer was extracted with additional CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered through a cotton plug. The residue obtained upon concentration was purified via flash chromatography with ethyl acetate/hexanes to furnish the aldehyde or ketone. Comparable yields were obtained on a 10 mmol scale or when the sparged reaction mixture was directly concentrated and submitted to chromatography.

(11) The best yields of aldehydes are obtained if reactions were stopped immediately upon consumption of alkene. Although direct monitoring (NMR) revealed formation of only small amounts (~5%) of carboxylic acids under typical reaction conditions, allowing reactions to proceed longer than necessary can result in significant overoxidation. Control reactions demonstrated that ozonolysis of mixtures of purified aldehydes and pyridine resulted in the slow formation of carboxylic acids.

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

reagent, a transformation typically performed on the *purified* products of ozonolysis (eq 1).



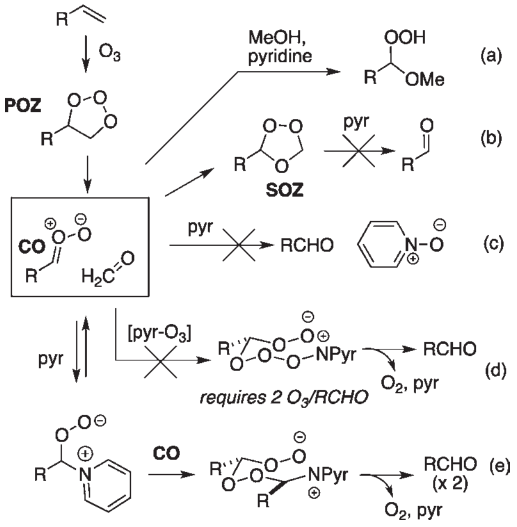
(1)

As illustrated in Scheme 1, reductive ozonolysis could in principle involve reaction of pyridine with the primary ozonide (**POZ**), the carbonyl oxide (**CO**), or the secondary ozonide (**SOZ**).[12] Unhindered alcohols are known to be effective carbonyl oxide trapping reagents,[12,14] and we investigated the reaction of several substrates in the presence of pyridine and added methanol. In each case, we observed hydroperoxyacetals (path a), demonstrating that the reductions involve either the **CO** or a downstream species.[12] Control reactions demonstrated that the carbonyl products did not arise from pyridine-promoted E$_1$cB fragmentation of the **SOZ** (path b).[15] These observations implied the intermediacy of the **CO**[1a,12] but did little to explain the mechanism. The absence of hydrogen peroxide in crude reaction mixtures ruled out trapping of the **CO** by traces of solubilized water (not shown),[5b] while NMR monitoring of a reaction conducted in CD$_2$Cl$_2$ observed only carbonyl products and recovered pyridine, excluding a redox process (path c).[8]

Given the inabilty to explain the observed products via traditional reaction pathways, we next considered whether attack of a pyridine–ozone complex[6a,9] on the **CO** could generate zwitterionic peroxyacetals able to fragment to pyridine, oxygen, and a carbonyl (path d). However, this mechanism requires 2 equiv of O$_3$ per molecule of carbonyl product, something not supported by experimental observations.[16] A more viable mechanism involves addition of pyridine to the **CO** to generate a zwitterion which can react with another molecule of carbonyl oxide (path e).[17] The resulting zwitterionic bisperoxyacetal would be highly activated toward fragmentation to generate a molecule of O$_2$, two carbonyl groups, and pyridine.

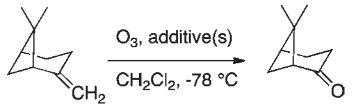
The proposed mechanism is consistent with the observed steric influences on the reduction process and suggested that reductive ozonolysis of bulky substrates might be enhanced by an unhindered "helper" **CO** which could trap pyridine to generate the nucleophilic zwitterion.

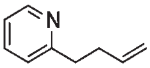
Scheme 1. Mechanistic Possibilities



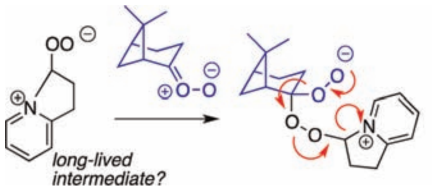
As illustrated in Table 4, this hypothesis was tested on β-pinene. This hindered substrate predominantly generates ozonides or polymeric peroxides even in the presence of pyridine.[18] However, the performance of ozonolysis in the presence of pyridine and ethyl vinyl ether, the latter a source of formaldehyde *O*-oxide, produced an improved yield of the ketone. More intriguingly, ozonolysis of pinene in the presence of an unsaturated pyridine designed to generate a pyridine-stabilized carbonyl oxide (eq 2) resulted in a dramatically improved yield of ketone.

Table 4. Influence of Added Carbonyl Oxide Sources



additive A	additive B	ketone (%)[a]
-	-	traces
-	pyridine (3 equiv)	12
	pyridine (3 equiv)	30
	-	65

[a] Isolated yield.



(2)

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(13) Addition of ozone to CH$_2$Cl$_2$ solutions of pyridine and alkene often resulted in a yellowish tint which dissipated once the alkene substrate was consumed; the color varied with substrate and with different pyridines. We have been unable to isolate or to detect the colored intermediates (TLC, in situ IR, or ^{1}H NMR on reactions conducted in CD$_2$Cl$_2$), which we assume are small amounts of pyridine-derived byproducts possessing a high extinction coefficient and which are consumed by excess ozone. Further investigations of this phenomenon are in progress.

(14) Yamamoto, Y.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2677.

(15) In contrast, trialkylamines readily decompose terminal ozonides to an aldehyde and formate. See Hon, Y. S.; Wu, K. C. *Tetrahedron* **2003**, *59*, 493 and references within.

(16) The effective delivery of ozone to a given substrate under a given set of conditions is easily calibrated; our experience has been that the rate of consumption of a given substrate is very similar in the presence or absence of pyridine. An example is provided in the Supporting Information.

(17) Barton, M.; Ebdon, J. R.; Foster, A. B.; Rimmer, S. *Org. Biomol. Chem.* **2005**, *3*, 1323.

(18) The ozonolytic cleavage of β-pinene to nopinone is notorious for the formation of explosive ozonides and peroxides which are decomposed only slowly by mild reductants. See ref 3.

In conclusion, we demonstrate a high-yielding and convenient procedure for the direct ozonolytic generation of anhydrous solutions of aldehydes and ketones. The reaction provides the first example of organocatalysis in ozonolysis and suggests the existence of yet unglimpsed avenues of carbonyl oxide reactivity.

Note on Safety. Although the process described above largely precludes formation of peroxides or ozonides, ozonolyses should always be conducted with an awareness of the potential for spontaneous and exothermic decompositions.[4a] In particular, experimenters should verify the absence of significant amounts of peroxides before concentrating crude reaction mixtures.[19]

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Supporting Information Available. Experimental protocols, spectral characterization, and ^{1}H NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Smith, L. L.; Hill, F. L. *J. Chromatogr.* **1972**, *66*, 101.

The authors declare no competing financial interest.