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Highly efficient biphasic ozonolysis of alkenes using a high-throughput film-shear flow reactor

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ABSTRACT

A new method for ozonolysis of alkenes using a continuous flow film-shear reactor was developed. The reactor uses a shearing microfluidic mixing chamber to provide biphasic mixing of an organic phase and aqueous phase with ozone gas. The H₂O acts as an in situ reducing agent for the carbonyl oxide intermediate, providing ketones and aldehydes directly from the reaction mixture. Flow rates of up to 1.0 mmol/min (alkene) with an ozone reaction efficiency of >70% were achieved. Aryl conjugated olefins reacted to form carbonyl species in good yields on a multi-gram scale; however, alkyl olefins reacted with ozone to predominantly form secondary ozonides. The discrepancy in product distributions between alkyl and aryl olefins likely originates from the electronic stability of the carbonyl oxide intermediate, which is longer lived for aryl derivatives due to conjugation.

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The use of ozone to oxidize alkenes (ozonolysis) is a powerful tool in modern organic chemistry.^{1–3} Ozone has many advantages over other common strong oxidants: high atom economy, absence of metals or hyper-valent iodine, and the straightforward synthesis of ozone from O₂. These factors make ozonolysis ideal for many industrial processes.⁴ However, the use of ozonolysis both industrially and in research labs is limited because of the cryogenic temperatures (–40 °C) typically required, dangerous intermediates and byproducts that are produced stoichiometrically, and the necessity of a secondary reduction step (using Me₂S, PPh₃, Pt/H₂, BH₃, NaBH₄, Zn/HOAc, LiAlH₄, etc.) to form ketones, aldehydes, or alcohols.³ Several approaches have been developed to address these inherent drawbacks. Flow chemistry has been used to minimize the concentration of dangerous intermediates and cryogenic temperatures; however, the reactions still require a secondary quench step of the reaction mixture.^{5–10} Another approach, pioneered by Dussault et al., prevents secondary ozonide (SOZ) formation using an in situ reduction of the carbonyl oxide intermediate with water as the reductant (Fig. 1).^{11,12} This approach allows for a single-step reaction using ozone and water to oxidize alkenes into aldehydes and ketones directly while avoiding a secondary step and strong reducing agents that may be incompatible with the rest of the molecule. Batch reactions and water-miscible polar organic solvents (containing 5% water) were used by Dussault and

coworkers, limiting the usefulness of this method for large scale syntheses. Also, when a biphasic system using phase transfer catalysis was attempted, in situ water reduction was never observed.¹⁴

To expand the approach of in situ carbonyl oxide reduction with water, while taking advantage of the safety and scalability of flow ozonolysis, we developed a high-throughput, flow method using a Synthetron™ S3T1 film-shear reactor.¹⁵ A film-shear reactor is a device with a rotating disk (the rotor) placed at an adjustable distance 20–300 μm from a stationary disk (the stator). The rotor spins at speeds up to 10⁴ rpm, and two streams containing the reactants are introduced between the two disks. Contact of the reactants within the narrow gap results in intense shear with consequent intimate mixing of the reactants.

As shown in Figure 2, the reaction system is comprised of a plug-flow organic/aqueous mixture that is sheared in the reaction chamber with ozone. The shear force increases the interface of H₂O and the organic phase.^{16–20} In addition, the mass-transport of ozone into solution benefits from the reactor microfluidics and shear mixing.^{21–23} Upon exiting the reactor, the reaction mixture self-separates, with the desired products in the organic phase and H₂O₂ in the aqueous phase.

Preliminary optimizations using isoeugenol found that EtOAc was an excellent solvent and that quantitative conversion to vanillin was achieved at a molar flow rate of 1.0 mmol/min (S.I. Fig. S2). This molar flow rate is approximately eight times faster than has been previously reported in more conventional microfluidic systems.²⁴ It is also notable that the residence time in the reactor is

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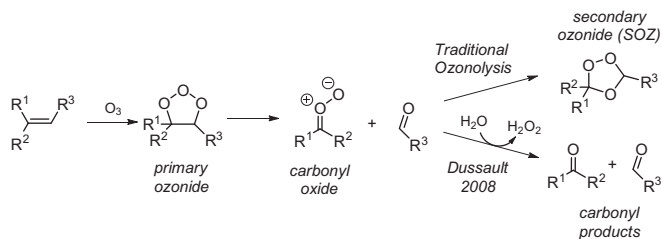


Figure 1. Criegee mechanism¹³ of ozonolysis showing traditional ozonolysis product pathway (top route) and the Dussault modification¹¹ of in situ H₂O reduction (bottom route).

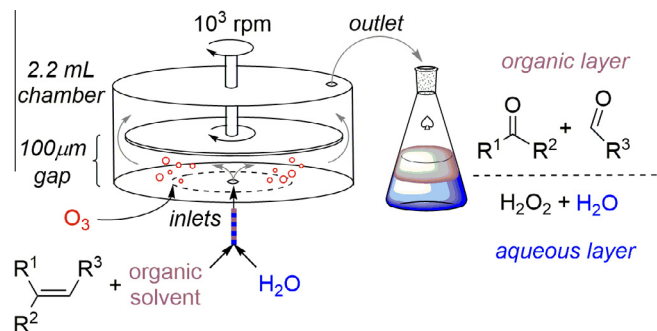


Figure 2. General setup of biphasic ozonolysis using the film-shear reactor. A more detailed diagram of the reactor setup is provided in Supplemental information (S.I.) Figure S1.

Table 1
Gram/multi-gram scale ozonolysis of aryl alkenes²⁶

Entry	Substrate	Product	Yield ^a (%)
1			49
2			81
3			72
4			64
5			79
6			35

^a Isolated yields.

8 s. Even with a very short residence time, ozone reacted with greater than 70% efficiency (1.4 equiv of O₃ per 1.0 equiv of isoeugenol, see S.I.).

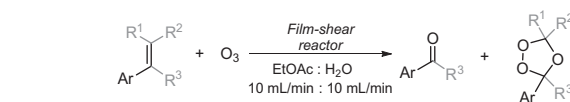
The substrate scope of the film-shear ozonolysis system was determined next. When aryl conjugated alkenes were screened

predominantly aldehyde or ketone products were observed. We were then able to run six substrates on the gram/multi-gram scale with good yields of the aldehyde or ketone (Table 1). Note that no secondary quench was used before these isolations. These results demonstrate several important attributes of our ozonolysis method: (1) it can effectively mix biphasic media to react the carbonyl oxide with water during ozonolysis, (2) it is scalable to multi-gram reaction scale while retaining good yields, (3) aldehydes and ketones can be directly attained from alkenes in flow without a secondary quench step, and (4) reaction times of <10 s.

To further understand the reaction profile with the aryl substrates, we screened an additional four aryl alkenes to determine the ratio of SOZ to carbonyl (Table 2). These data help determine how effective the in situ water reduction is for each substrate. In addition, 1-decene was screened under a variety of conditions (Table 3). The aryl alkenes afforded much higher ratios of carbonyl to SOZ compared to alkyl alkenes. In fact, the dominant product of the reaction with 1-decene was SOZ under a variety of conditions (Table 3). (Even with aqueous oxidants, various acids, phase transfer catalysts, and alcohol solvents, SOZ was the predominant product.)

The discrepancy between the alkyl and aryl alkene ozonolysis products is likely due to a difference in the stabilities of the

Table 2
Product distributions for ozonolysis of aryl alkenes²⁶



Entry	Substrate	Ratio of carbonyl:SOZ ^a
1		>99:1
2		>99:1
3		7.6:1
4		33:1
5		2.8:1
6		3.4:1
7		3.5:1
8		3.6:1
9		1:1.8
10		1:17

^a Determined by ¹H NMR from the crude reaction mixture.

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