Graphical Abstract

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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 by using an *in situ* reduction of the carbonyl oxide intermediate with water as the reductant (Figure 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

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

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.

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

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

Table 1. Gram/multi-gram scale ozonolysis of aryl alkenes.[†]

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

^aIsolated yields.

Table 2. Product distributions for ozonolysis of aryl alkenes.[†]

Entry	Substrate	Ratio of carbonyl : SOZ ^a
	$\text{Ar}-\text{C}(\text{R}^1)(\text{R}^2)=\text{C}(\text{R}^3)-\text{R}^4 + \text{O}_3 \xrightarrow[\text{EtOAc}:\text{H}_2\text{O}]{\text{Film-shear reactor}} \text{Ar}-\text{C}(\text{R}^1)(\text{R}^2)=\text{O} + \text{SOZ}(\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4)$ <p style="text-align: center;">10 mL/min : 10 mL/min</p>	
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

^aDetermined by ¹H NMR from the crude reaction mixture.

vanillin was achieved at a molar flow rate of 1.0 mmol/min (S.I. Figure 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 8 seconds. Even with a very short residence time, ozone reacted with greater than 70% efficiency (1.4 eq. of O₃ per 1.0 eq. of isoeugenol, see S.I.).

The substrate scope of the film-shear ozonolysis system was

Table 3. Screening conditions for alkyl olefin ozonolysis.

100 mM

Entry	Phases			Flow Rates ^b (mL/min)			Conversion (%) ^c	Yield (%) ^c	
	Organic	Aqueous	Additives ^a	Organic	Aqueous	Shear RPM (x1000)		Aldehyde	SOZ
1	EtOAc	H ₂ O	-	10	80	2.0	>99	10	38
2	EtOAc	H ₂ O	-	15	80	2.0	>99	8	37
3	EtOAc	H ₂ O	-	20	80	2.0	>99	7	36
4	Hexanes	H ₂ O	-	10	80	2.0	>99	11	38
5	Hexanes	0.1 M H ₂ SO _{4(aq)}	-	10	80	3.6	>99	10	35
6	Hexanes	1.0 M H ₂ SO _{4(aq)}	-	10	80	3.6	>99	4	41
7	Hexanes	H ₂ O	3 eq. TEABr	10	10	3.6	>99	11	44
8	Hexanes	H ₂ O	50% MeOH	10	10	3.6	>99	1	36
9	Hexanes	H ₂ O	3 eq. TBABr	10	10	3.6	>99	13	65
10	Hexanes	H ₂ O	50% EtOH	10	10	3.6	>99	3	40
11	Hexanes	0.1 M H ₂ SO _{4(aq)}	50% EtOH	10	10	3.6	>99	3	42

^a TEABr = tetraethylammonium bromide. ^b See Experimental section and S.I. Fig. S1 for details on method. ^c As determined by ¹H NMR with 1,1,2,2-tetrachloroethane or hexamethyl benzene as an internal standard.

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 seconds.

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 carbonyl oxide intermediates. Although the rate-determining step in ozonolysis is the initial attack of the alkene on the ozone, the nature of the intermediates that follow determine which product(s) form. It is likely that the lifetime of the carbonyl oxide (10^{-3} to 10^{-5} seconds)²⁵ plays a dominant role in product distributions observed in these cases. For alkyl carbonyl oxides, rearrangement to SOZ is preferred due to the short lifetime of the carbonyl oxide intermediate. However, with aryl conjugated alkenes, benzylic resonance stabilization (Figure 3) of the carbonyl oxide may contribute to a more persistent intermediate, allowing enough time for the intermediate to react with water, thus making the product-determining step favor carbonyl

Figure 3. Resonance stabilization of aryl conjugated carbonyl oxide.

products. This rationale also explains the large bias for isoeugenol and anethole (Table 2, entries 1 and 2) toward carbonyl products over SOZs, because they have electron rich aryl rings that provide additional stabilization of the delocalized cation of the carbonyl oxide intermediate.

Most of the aryl alkenes in Table 2 have a ratio biasing strongly towards aldehyde or ketone as products. Notably, cyclic alkenes (Entries 8-10) are more prone to form SOZs with decreasing degrees of freedom (from entries 8 to 10) for the corresponding carbonyl oxide intermediate. The tethered carbonyl and carbonyl oxide pair favor SOZ formation if there is a strong enough entropic bias preferring intramolecular reaction (leading to SOZ) over intermolecular reduction (leading to carbonyl products directly). Notably, phenanthrene (Table 2, entry 8) still produces a majority of carbonyl products even though it is a tethered alkene.

In conclusion, we have developed a method for flow ozonolysis using a film-shear reactor. H₂O acts as a mild *in situ* reductant of the carbonyl oxide intermediate, yielding ketones and aldehydes directly. This flow reactor has a molar flow rate eight times faster than previously reported flow ozonolysis systems and is currently only limited by the rate of ozone production, with reaction times of 8 seconds. The excellent reaction rates and molar flow rates are attributed to superb mixing of the reactants within the film-shear reaction chamber. Alkyl olefins likely produce a carbonyl oxide intermediate that is too short lived to effectively react with water, preferring the formation of SOZs. The longer lifetimes of aryl conjugated carbonyl oxides are responsible for the excellent selectivity and reactivity of aryl conjugated olefins, which generally prefer

carbonyl products from aryl alkenes without any secondary quench with scalable (multi-gram) flow chemistry.

We are currently using this method to investigate aryl alkyne ozonolysis, as well as stoichiometric ozone delivery to multi-olefin substrates.

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References and notes

- † *Standard ozonolysis procedure.* The syringe pumps and the film-shear reactor were primed by running 50 mL EtOAc at 10 mL/min and 50 mL deionized H₂O at 10 mL/min with the rotor running at 2000 RPM. This procedure was repeated with pure oxygen also flowing at 0.8 L/min. The film-shear reaction chamber was cooled to 0°C with a recirculator. Both a 0.10 M solution of alkene in EtOAc at 0°C and deionized water at 0°C were pumped into a “T” valve (10 mL/min each) generating the plug-flow mixture that entered the film-shear reactor. Ozone was sparged through the reaction chamber at 0.8 L/min. A product flask was primed with 2 molar equivalents of a sodium sulfite solution to quench any hydrogen peroxide produced. The resulting product mixture was collected in a fume hood (CAUTION! residual ozone, formaldehyde, and hydrogen peroxide may be present as an aerosol; perform only in a well ventilated hood). The pH was adjusted to 3 using 3 M HCl_(aq). The two resulting layers were separated. The aqueous layer was washed three times with 15 mL of EtOAc, then the organic layers were combined, dried over Na₂SO₄, filtered, and the solvent was removed under vacuum. The products were purified as noted in the Supplemental Information.
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