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Effect of Solvent on the Rate of Ozonolysis: Development of a Homogeneous Flow Ozonolysis Protocol

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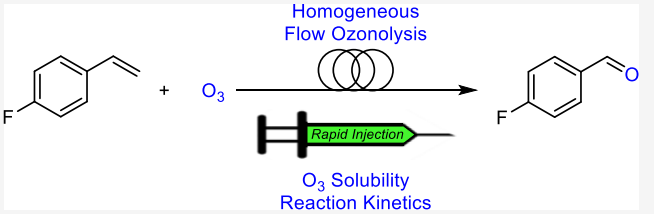
ABSTRACT: Herein, we describe the effect of organic solvents on ozone solubility and the rate of ozonolysis reactions using rapid injection NMR spectroscopy. The tabulated solubility and kinetic data allowed for the design of a homogeneous ozonolysis flow reactor capable of delivering precise quantities of dissolved ozone to various olefin substrates.



INTRODUCTION

Ozonolysis is a powerful method to oxidize olefins and is frequently employed in the synthesis of pharmaceuticals and agrochemicals (Figure 1).[1,2] The efficiency for ozone (O_3) to cleave and convert carbon−carbon (C═C) double bonds into oxygen-rich functional groups remains unparalleled compared to similar transition-metal-mediated transformations.[3,4] However, safety concerns regarding the accumulation of peroxidic intermediates during large-scale pursuits occasionally limit its application. To circumvent these issues, continuous flow reactors have shown promising results in the large-scale preparation of several small molecules, such as azelaic acid **4** (Figure 1).[5,6] The use of heterogeneous annular, slug, membrane, and solid supported flow systems has enabled significant progress in this regard. However, several drawbacks limit the utilization of these processes (Figure 2A).[7−13] For instance, ineffective mixing of gaseous O_3/O_2 mixtures with the dissolved substrate in the liquid phase often results in low conversions.[14] An alternative approach is the employment of homogeneous flow reactors using solutions of predissolved O_3/O_2 mixtures (Figure 2B).

The design of optimized, safe, and homogeneous systems requires quantitative data regarding the solubility of O_3 in organic solvents. Numerous studies on O_3 solubility in aqueous solutions are available yet there are limited reports on the solubility of O_3 in organic solvents.[15−18] UV−vis spectroscopy and iodometry are popular methods to measure O_3 solubility and while these are reliable, the experimental setup and technique have significant influence on the observed O_3 concentration. These factors become especially important when interpreting kinetic results and implementing solubility data for successful oxidative cleavage in continuous flow on ms/s time scales.[19]

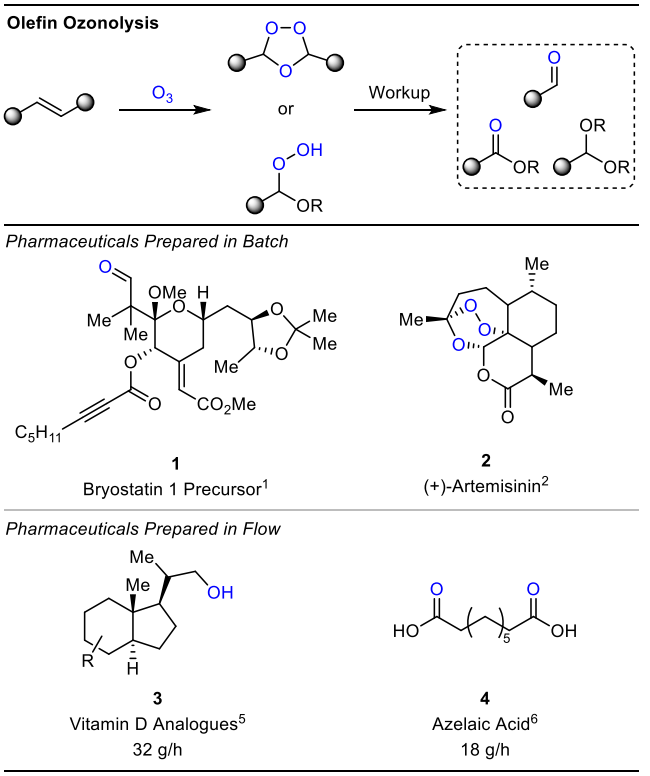


Figure 1. Applications of ozonolysis in batch and continuous flow in the synthesis of pharmaceutically relevant compounds.

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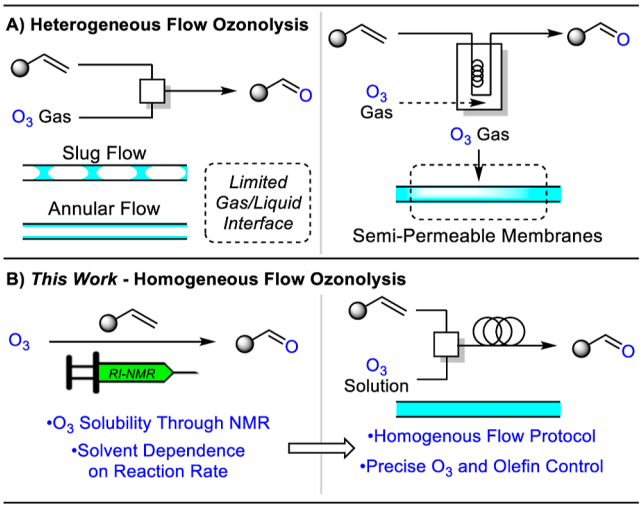


Figure 2. Approaches of ozonolysis in flow. (A) Heterogeneous flow reactors utilize gas/liquid mixing inside the reactor or through semipermeable membranes. (B) Solubility and solvent dependence on reaction rate enabled by RI-NMR led to a homogeneous ozonolysis flow reactor.

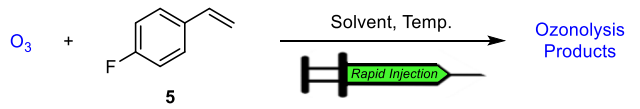
RESULTS AND DISCUSSION

Given our interest in developing new homogeneous flow ozonolysis protocols, it was necessary to obtain a general understanding of the effects of organic solvents on the solubility of O_3 as well as the rates of ozonolysis.[20] To gain this mechanistic information, we sought physical organic techniques that can titrate O_3 solutions and measure the kinetics under realistic reaction conditions. Specifically, rapid-injection nuclear magnetic resonance (RI-NMR) spectroscopy has proven to be a powerful tool in the observation and characterization of reactions with relatively short half-lives ($t_{1/2}$ = < 1 s).[21−24] Herein, we report a simple RI-NMR method that allowed for insights into the effect of various solvents on the solubility of O_3 and rate of ozonolysis with 4-fluorostyrene **5** (Figure 2B). These insights were leveraged in the development of a simple, homogeneous flow protocol for the ozonolysis of various olefin substrates with broad functionality.[25]

Mechanistic investigations into ozonolysis reactions have mainly focused on observing and determining the lifetimes of intermediates formed along the reaction pathway such as primary ozonides or Criegee intermediates.[20,26,27] Although substitution patterns about the olefin substrate are well-known to influence reaction rates of ozonolysis, the effect of solvent on these processes remains largely unexplored.[28] We sought to study the effect of the solvent on the rate of olefin ozonolysis using RI-NMR spectroscopy. However, prior to measuring the reaction rates, we needed to first determine and standardize the solubility of O_3 in organic solvents over a range of synthetically useful temperatures.

We began by studying the reaction of O_3 with 4-fluorostyrene **5** by RI-NMR such that the solubility of O_3 could be quantified by comparing the ^{19}F NMR signal of unreacted **5** against an internal standard (Table 1).[29] At the outset, we investigated the four most employed solvents for olefin ozonolysis reactions at −80 °C: dichloromethane (DCM), pentane, methanol (MeOH), and ethyl acetate (EtOAc).[30] Pentane and EtOAc were found to have appreciable concentrations of O_3 (ca. 70−80 mM) at −80 °C, although significantly less of the O_3 could be detected in DCM (47 mM) at this temperature. MeOH was found to have significantly higher [O_3] (164 mM) compared with the other three solvents. To gain a deeper understanding of the O_3 solubility, we expanded our solvent scope to include several readily available organic solvents at −80 °C (Table 1). Our combined results indicated that the solubility of O_3 ranges from roughly 50 to 160 mM with *tert*-butyl methyl ether (TBME) and MeOH having the highest O_3 concentrations (160.8 and 164.6 mM, respectively). These results are notable because DCM is the most employed solvent in ozonolysis reactions, yet the concentration of O_3 was among the lowest compared to other solvents in this series.

Table 1. O_3 Solubility in Various Organic Solvents



entry	temp.(°C)	solvent	O_3 conc. (mM)[a]
1	−80	2-methyl tetrahydrofuran	0.0 ± 0.0
2		DCM	47.1 ± 2.0
3		heptane	73.7 ± 2.4
4		pentane	73.9 ± 2.4
5		EtOAc	81.8 ± 2.6
6		CF_2Cl_2	84.1 ± 2.4[b]
7		toluene	85.8 ± 2.7
8		CPME	92.9 ± 2.8
9		acetone	144.1 ± 3.8
10		TBME	160.8 ± 4.2
11		MeOH	164.6 ± 4.3
12	−40	pyridine	34.6 ± 1.9
13		MeCN	47.0 ± 2.0
14		DME	48.2 ± 2.0
15		$CHCl_3$	117.1 ± 3.3
16	25	ethylene glycol	0.0 ± 0.0
17		benzene	83.8 ± 2.6
18		CCl_4	108.7 ± 3.1
19		DMSO	147.7 ± 3.9

[a]All reactions were conducted using 500 μL of solvent which was ozonized for 10 min in an 5 mm NMR tube. 4-Fluorostyrene 5 (84 μmol) was then promptly injected via RI-NMR, and the O_3 concentration was determined from unreacted 5 compared against fluorobenzene by ^{19}F NMR. [b]4-Fluorostyrene 5 was dissolved in DCM and injected into 656 μL of CF_2Cl_2.

To further investigate the solubility of O_3, we also examined pyridine, acetonitrile (MeCN), 1,2-dimethoxyethane (DME), and chloroform ($CHCl_3$) by RI-NMR (vide supra) at −40 °C (Table 1, entries 12−15). Pyridine exhibited the lowest O_3 concentration in the series. Both MeCN and DME displayed similar solubilities of 47.0 and 48.2 mM, respectively. Of note, $CHCl_3$ was found to dissolve the most O_3, leading to a concentration 117.1 mM.

Next, the solubility of O_3 in ethylene glycol, benzene, carbon tetrachloride (CCl_4), and dimethyl sulfoxide (DMSO) was explored by RI-NMR (vide supra) at 25 °C. Interestingly, ethylene glycol did not provide any detectible O_3 under the employed reaction conditions. Benzene and CCl_4 resulted in 83.8 and 108.7 mM solutions of O_3. Switching from CCl_4 to DMSO resulted in higher concentrations (147.7 mM) of O_3. With a clearer understanding of the effect of solvent on the solubility of O_3, we next turned our investigations toward

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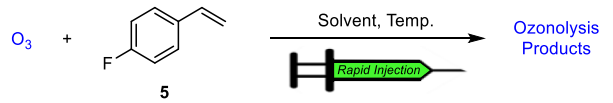
kinetically quantifying the influence of the solvent on the rate of the reaction.

Our kinetic studies began with RI-NMR injection of **5** into O_3 solutions such that the decay of **5** could be monitored by ^{19}F NMR spectroscopy until completion. Characteristic second-order decay kinetic profiles were fitted using eq 1 which allowed for accurate k_{obs} values for ozonolysis to be extracted (Table 2).[31,32] The use of RI-NMR proved to be crucial in obtaining kinetic data for these reactions as O_3 was consumed within seconds at −80 °C. For example, injection of **5** into O_3 solutions in toluene and cyclopentyl methyl ether (CPME) at −80 °C resulted in the complete consumption of O_3 in roughly 30 s.

Table 2. Kinetic Data for the Ozonolysis of 5



entry	temp. (°C)	solvent	k_{obs} [a,b] (M^{-1} s^{-1})	k_{rel}
1	−80	toluene	0.78 ± 0.06	1.0
2		CPME	1.03 ± 0.06	1.3
3		EtOAc	1.08 ± 0.06	1.4
4		MeOH	1.59 ± 0.14	2.0
5		acetone	1.93 ± 0.11	2.5
6		heptane	1.94 ± 0.12	2.5
7		TBME	3.12 ± 0.38	4.0
8		pentane	10.22 ± 0.81	13.1
9		DCM[c]	<1 s	
10		CF_2Cl_2[c,d]	<1 s	
11	−40	$CHCl_3$[c]	<1 s	
12		MeCN[c]	<1 s	
13		DME[c]	<1 s	
14		pyridine[c]	<1 s	
15	25	benzene[c]	<1 s	
16		DMSO[c]	<1 s	
17		CCl_4[c]	<1 s	

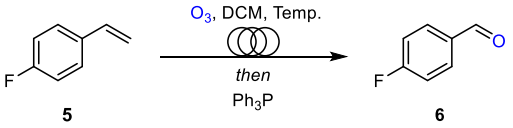
[a]All reactions were conducted using 500 μL of solvent which was ozonized for 10 min in an NMR tube. 4-fluorostyrene **5** (84 μmol) was then promptly injected via RI-NMR. [b]Average of two injections. [c]Reaction was complete in less than 1 s. [d]656 μL of CF_2Cl_2 and 93 μL of DCM were used for the injection.

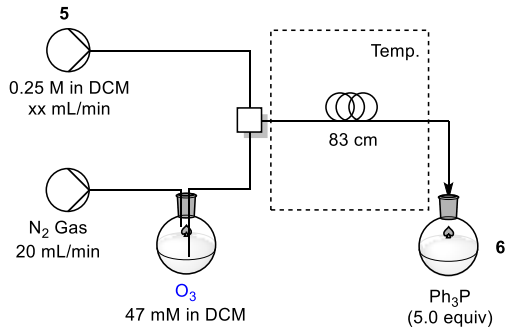
$$[5] = \frac{[5]_\infty}{1 - \frac{[5]_o - [5]_\infty}{[5]_o}\exp(-k_{obs}t[5]_\infty)} \quad (1)$$

The rates of ozonolysis in EtOAc, MeOH, acetone, heptane, and TBME were all shown to be comparable to each other and faster than toluene and CPME (ca. 15 s). Pentane was shown to be an order of magnitude faster than toluene with the ozonolysis complete in less than 10 s. The ozonolysis of **5** in DCM and dichlorodifluoromethane (CF_2Cl_2) at −80 °C resulted in complete consumption of O_3 in less than a second. For solvents limited by their melting point, which could only be tested experimentally above −80 °C such as chloroform ($CHCl_3$), acetonitrile (MeCN), and carbon tetrachloride (CCl_4), the kinetic data concluded that ozonolysis was complete in less than a second. This kinetic data gave key insights into solvents in which the rate of ozonolysis is faster and others in which the rate is lightly diminished. These insights provided us an avenue to develop a continuous flow reactor such that the substrate residence time inside the reactor could be easily telescoped.

With the solubility of O_3 in organic solvents established and the dependence of solvent on the rate of ozonolysis, we developed a homogeneous flow reactor that allowed for precise control of O_3 delivery to olefins. With many solvents to choose from we opted to employ DCM for this continuous flow reactor as it is a nonflammable and nonexplosive solvent[33] that has a high reaction rate with olefins at −80 °C. While the O_3 concentration in DCM at −80 °C was much lower than other solvents, we saw this as an opportunity to showcase the reagent control that continuous flow reactors can achieve over some batch systems with dilute O_3 solutions. Solutions of O_3 in DCM were prepared on mmol scale and immediately fed into the continuous flow reactor at controlled flow rates.[34,35] A quick screen of O_3 equivalence in the homogeneous flow reactor showed low conversion at −78 °C with 3.0 equiv of O_3 giving 62% conversion of **5** (Table 3, entry 3). To increase the conversion of **5** into **6** under mild conditions, we warmed the reactor to 0 °C. Of note, high conversions (97%) were quickly achieved by slightly optimizing the flow rates (see the Supporting Information for details).

Table 3. Optimization for the Homogeneous Ozonolysis Flow Reactor





entry[a]	T (°C)	flow rate **5** (mL/min)	O_3 equiv	conversion[b] (%)
1	−78	2.56	1.0	30
2	−78	1.28	2.0	61
3	−78	0.85	3.0	62
4	0	2.56	1.0	38
5	0	1.28	2.0	67
6	0	0.85	3.0	97

[a]All reactions were performed using 83 cm of PTFE tubing equivalent to 12 s reactor residence time and 0.50 mmol **5**. [b]Measured through ^{19}F NMR using fluorobenzene as an internal standard.

The simple design of our optimized flow reactor maintained efficacy for the oxidative cleavage of many olefins, including those with O_3 labile functional groups (Figure 3). Various terminal olefins were ozonized in high conversion, including 4-fluorostyrene **5** to provide 4-fluorobenzaldehyde **6** in 92% yield. Substrates with allyloxy groups (**8**, 77% and **12**, 45%) and those with oxidizable benzylic carbons such as **7**, **9**, **10**, and **14** were selectively cleaved at the olefin in high yields (93, 95, 81, and 88%, respectively). A protected BINOL derivative

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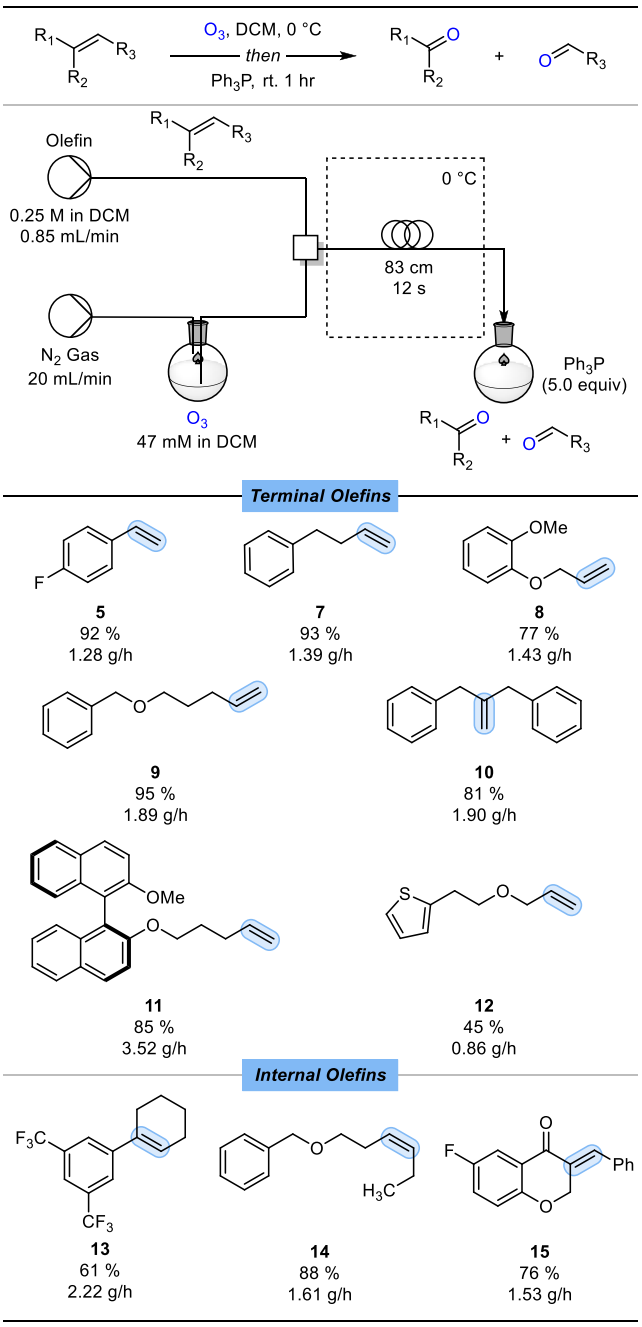

Figure 3. Substrate scope for the homogeneous continuous flow ozonolysis reactor. All reactions were performed using 0.5 mmol olefin with 3.0 equiv of O_3 and 5.0 equiv of Ph_3P.

11 was selectively ozonized with the olefin in 85% yield. Thiophene substrates underwent overoxidation at the heterocycle under batch conditions;[36] however, under continuous flow, it was observed that overoxidation was minimized with substrate **12** which gave the corresponding aldehyde in 45%. Internal olefins were also ozonized using this method to give the corresponding ketones or aldehydes in good yield, exemplified by **13** and **14** in 61 and 88% yields, respectively. Substrate **15** was ozonized to the ketone in good yield (76%) which tautomerized to the corresponding enol upon isolation. We envision that this approach to continuous flow ozonolysis will be beneficial and compatible for many olefins, especially those of interest in pharmaceutical syntheses and industrial settings.

CONCLUSIONS

In conclusion, we developed a general and practical method to measure the O_3 solubility and rates of ozonolysis in organic solvents using RI-NMR spectroscopy. Furthermore, this information proved useful in the design of homogeneous flow reactors. We envision that the solubility and kinetic data provided will be of great use to various fields of chemistry and the physical organic RI-NMR method presented to be valuable in the determination of the O_3 solubility in other organic solvents.

EXPERIMENTAL SECTION

General Information. Reactions were conducted using glassware that had been oven-dried (150 °C) for a minimum of 1 h unless otherwise noted. All reactions were conducted under an inert atmosphere using nitrogen connected to a drying tube equipped with phosphorus pentoxide, calcium sulfate, and sodium hydroxide, unless otherwise noted. Solvents used for ozone dissolution and rapid injection experiments were commercially available and purified accordingly. Heptane (Sigma-Aldrich, ReagentPlus grade), pentane (Fisher Scientific, ACS grade), and benzene (Sigma-Aldrich, ACS grade) were distilled over sodium. DCM (Fisher Scientific, HPLC grade), toluene (Fischer Scientific, HPLC grade), and acetonitrile (Sigma-Aldrich, HPLC grade) were purified by passage through alumina and distilled over calcium hydride. Ethyl acetate (Fisher Scientific, ACS grade), triethyl amine (Sigma-Aldrich, ≥99%), pyridine (Fisher Scientific, certified ACS grade), and 1,2-DME (Sigma-Aldrich) were distilled over calcium hydride. Methanol (Sigma-Aldrich, HPLC grade) was passed through 4 Å molecular sieves and distilled over calcium hydride. Tetrahydrofuran (Sigma-Aldrich, HPLC grade) was distilled over sodium/benzophenone. Cyclopentyl methyl ether (Sigma-Aldrich, contains 50 ppm BHT as an inhibitor, *ReagentPlus* grade, ≥99.90%) and 2-methyl tetrahydrofuran (Sigma-Aldrich, contains 250 ppm BHT as a stabilizer) were distilled over potassium. Acetone (Fisher, ACS grade) and ethylene glycol (VWR, Semi grade) were distilled over calcium sulfate. Diethyl ether (VWR, inhibitor-free, for spectroscopy) was passed through alumina and distilled over sodium/benzophenone. TBME (Sigma-Aldrich, ACS grade) and DMSO (Oakwood chemical, ACS grade) were passed through alumina. Chloroform (VWR, ACS grade) and carbon tetrachloride (Acros-organics, 99%) were distilled over phosphorus pentoxide. Dichlorodifluoromethane was purified by passage through 4 M NaOH, a 0 °C cold trap, and then over calcium sulfate.

Ozone and Ozonolysis Safety. Ozone has a distinctive odor, yet the smell should not be used as a warning of high ozone concentrations. Ozone acts as a primary irritant affecting the eyes, upper respiratory tract, and lungs and could cause a reduction in lung function due to scar tissue formation over prolonged exposure. All ozonolysis experiments were performed in a fume hood to prevent both accumulation and exposure to ozone. Ozonolysis will generate peroxidic intermediates such as primary and secondary ozonides, which can undergo rapid decomposition resulting in an explosion. Extra care must be taken when performing and working on an ozonolysis reaction. Potassium iodide/starch strips were crucial to the workup of all ozonolysis reactions described. Upon reaction quenching if peroxides were still present, additional quenching agents were added until no peroxides could be detected.

General Procedure for the Operation of the Ozonolysis Flow Reactor. The continuous-flow ozonolysis reactor consists of two separate lines, as shown in Figure S19. A 0.25 M stock solution of olefin was charged into feed line A (one-eighth in. OD × 0.09 in. ID) of 75 cm and attached to a 20 mL Chemyx stainless-steel syringe loaded with 20 mL of dry DCM using a Tefzel Luer adapter and flangeless ferrules. The feeder line for B consisted of a siphon

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mechanism using two 60 mL plastic syringes connected to a 100 mL round-bottomed flask via PTFE tubing segments and an airtight plastic cap (Figure S20). The feeder line from line B was connected to a T-joint (Mixer 1) along with the feeder line from syringe A (alkene solution). The outlet of mixer 1 consists of 83 cm of PTFE tubing serving as the reactor and feeds directly into the quench. The reactor was coiled and tied together by using zip ties and submerged into a 0 °C bath (ice). The reactor outlet was fed into the bottom of a 200 mL round-bottomed flask. The flask was equipped with a stir bar and charged with triphenylphosphine (656 mg, 2.5 mmol, 5.0 equiv) and DCM (5 mL). Less than 5.0 equiv of triphenylphosphine may be used, although excess should be considered if the flow reactor was to empty all components (including excess peroxides) into the collection flask. The syringes in line B were loaded with nitrogen gas, and all syringes were placed into their respective syringe pumps and the rates adjusted accordingly (A: 0.85 mL/min, 0.21 mmol/min, B: 20 mL/min). The stock solution of ozone in DCM was prepared by cooling 100 mL of dry DCM to −78 °C (dry ice/acetone) and flowing ozone just above the liquid for 15 min. The solution was then connected to the reactor by using the siphoning cap shown below. The O_3 solution flow parameters (13.56 mL/min, 0.64 mmol/min, 3.0 equiv) were calibrated to a syringe pump rate of 20 mL/min using 47 mM as the bulk concentration. Syringe A was started until the liquid reached 10 cm before reaching mixer 1. The O_3 solution was pushed through the entire reactor length to prime the reactor before starting flow of Syringe A. Once all the preloaded olefin solution from line A has passed through the reactor, additional O_3 solution is passed through the reactor for ca. 20 s. The 200 mL collection flask is then concentrated in vacuo to ca. 10 mL and left to quench for 1 h. Excess O_3 solution may be quenched with triphenylphosphine or dimethyl sulfide to release O_2. Upon completion, the crude residue is purified on column chromatography to yield the purified product.

*4-Fluorobenzaldehyde (**6**).* 4-Fluorobenzaldehyde **6** was prepared using the general procedure using a solution of 4-fluorostyrene **5** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (5% Et_2O in Pentane) to yield **6** (57 mg, 92%) as a clear oil. Spectral data are in accordance with literature reports.[37] TLC (5% Et_2O in Pentane): R_f = 0.55 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.0 (s, 1H), 8.1−7.7 (m, 2H), 7.5−6.9 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 190.6, 166.7 (d, J = 256.9 Hz), 133.1 (d, J = 2.9 Hz), 132.4 (d, J = 9.8 Hz), 116.5 (d, J = 22.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −102.14.

*3-Phenylpropionaldehyde (**7a**).* 3-Phenylpropionaldehyde **7a** was prepared using the general procedure using a solution of 4-phenyl-1-butene **7** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (5% EtOAc in hexanes) to yield **7a** (62 mg, 93%) as a clear oil. Spectral data are in accordance with literature reports.[38] TLC (10% EtOAc in hexanes): R_f = 0.30 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.83 (t, J = 1.4 Hz, 1H), 7.36−7.28 (m, 2H), 7.24−7.19 (m, 3H), 2.97 (t, J = 7.5 Hz, 2H), 2.85−2.70 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 201.6, 140.4, 128.7, 128.4, 126.4, 45.3, 28.2.

*2-(2-Methoxyphenoxy)acetaldehyde (**8a**).* 2-(2-Methoxyphenoxy)acetaldehyde **8a** was prepared using the general procedure using a solution of olefin **8** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (20% EtOAc in hexanes) to yield **8a** (64 mg, 77%) as a white solid. Spectral data are in accordance with literature reports.[39] TLC (20% EtOAc in hexanes): R_f = 0.50 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.89 (t, J = 1.2 Hz, 1H), 7.07−6.79 (m, 4H), 4.59 (d, J = 1.3 Hz, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 200.3, 149.8, 147.4, 123.1, 121.0, 115.0, 112.3, 74.3, 55.9.

*4-(Benzyloxy)butanal (**9a**).* 4-(Benzyloxy)butanal **9a** was prepared using the general procedure using a solution of olefin **9** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (30% EtOAc in hexanes) to yield **9a** (85 mg, 95%) as a clear oil. Spectral data are in accordance with literature reports.[40] TLC (30% EtOAc in hexanes): R_f = 0.30 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (s, 1H), 7.32−7.19 (m, 5H), 4.43 (s, 2H), 3.45 (t, J = 6.1 Hz, 2H), 2.48 (t, J = 7.1 Hz, 2H), 1.94−1.83 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 202.4, 138.4, 128.5, 127.7, 73.1, 69.3, 41.0, 22.7.

*1,3-Diphenylpropan-2-one (**10a**).* 1,3-Diphenylpropan-2-one **10a** was prepared using the general procedure using a solution of olefin **10** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (5% EtOAc in hexanes) to yield **10a** (85 mg, 81%) as a white solid. Spectral data are in accordance with literature reports.[41] TLC (5% EtOAc in hexanes): R_f = 0.40 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.23 (m, 6H), 7.17−7.12 (m, 4H), 3.71 (s, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 205.8, 134.1, 129.6, 128.9, 127.2, 49.2.

*(S)-4-((2′-Methoxy-[1,1′-binaphthalen]-2-yl)oxy)butanal (**11a**).* (*S*)-4-((2′-Methoxy-[1,1′-binaphthalen]-2-yl)oxy)butanal **11a** was prepared using general procedure using a solution of olefin **11** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (30% EtOAc in hexanes) to yield **11a** (157 mg, 85%) as a clear oil. TLC (30% EtOAc in hexanes): R_f = 0.53 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 7.97 (dd, J = 12.1, 8.9 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 19.5, 9.0 Hz, 2H), 7.37−7.28 (m, 2H), 7.24−7.15 (m, 3H), 7.09 (d, J = 8.5 Hz, 1H), 4.06 (ddd, 1H), 3.90 (ddd, J = 9.3, 6.9, 5.0 Hz, 1H), 3.76 (s, 3H), 1.87 (q, J = 6.6 Hz, 2H), 1.77−1.65 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 201.9, 155.0, 154.0, 134.1, 134.0, 129.6, 129.4, 129.4, 129.1, 128.0, 127.9, 126.4, 126.4, 125.4, 125.2, 123.8, 123.5, 120.9, 119.5, 116.1, 114.0, 68.7, 56.7, 39.9, 22.0. IR (Diamond ATR, neat): $\tilde{\nu}_{max}$: 3053, 2937, 2837, 2723, 1720, 1620, 1591, 1506, 1251, 1242. HRMS (ESI) calcd $C_{25}H_{22}O_3$ $[M + H]^+$, 371.1642; found, 371.1637.

*2-(2-(Thiophen-2-yl)ethoxy)acetaldehyde (**12a**).* 2-(2-(Thiophen-2-yl)ethoxy)acetaldehyde **12a** was prepared using the general procedure using a solution of **12** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (10% EtOAc in hexanes) to yield **12a** (38 mg, 45%) as a clear oil. TLC (10% EtOAc in hexanes): R_f = 0.2 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (t, J = 0.9 Hz, 1H), 7.15 (dd, J = 5.1, 1.2 Hz, 1H), 6.94 (dd, J = 5.1, 3.4 Hz, 1H), 6.91−6.85 (m, 1H), 4.10 (d, J = 0.9 Hz, 2H), 3.79 (t, J = 6.6 Hz, 2H), 3.17 (td, J = 6.7, 0.9 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 200.8, 140.6, 126.9, 125.5, 124.0, 76.5, 72.6, 30.5. IR (Diamond ATR, neat): $\tilde{\nu}_{max}$: 2920, 2858, 1734, 1118, 1037, 910, 848, 731, 690. HRMS: (ESI) calcd $C_8H_{10}O_2S$ $[M + H]^+$, 171.0474; found, 171.0474.

*6-(3,5-Bis(trifluoromethyl)phenyl)-6-oxohexanal (**13a**).* 6-(3,5-Bis(trifluoromethyl)phenyl)-6-oxohexanal **13a** was prepared using the general procedure using a solution of olefin **13** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (20% EtOAc in hexanes) to yield **13a** (109 mg, 61%) as a white solid. TLC (20% EtOAc in hexanes): R_f = 0.33 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.77 (t, J = 1.5 Hz, 1H), 8.36 (d, J = 1.7 Hz, 2H), 8.05 (s, 1H), 3.06 (t, J = 7.0 Hz, 2H), 2.52 (td, J = 7.0, 1.5 Hz, 2H), 1.94−1.56 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 202.0, 196.8, 138.4, 132.39 (q, J = 33.9 Hz), 128.07 (d, J = 4.0 Hz), 126.26 (p, J = 3.7 Hz), 123.00 (q, J = 272.9 Hz), 43.7, 38.4, 23.1, 21.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −64.02. IR (Diamond ATR, neat) $\tilde{\nu}_{max}$: 3088, 2943, 2725, 1724, 1699, 1354, 1238, 1172, 1111, 906, 844, 698, 680. HRMS (ESI) calcd $C_{14}H_{12}F_6O_2$ $[M + H]^+$, 327.0814; found, 327.0799.

*3-(Benzyloxy)propanal (**14a**).* 3-(Benzyloxy)propanal **14a** was prepared using the general procedure using a solution of olefin **14** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (20% EtOAc in hexanes) to yield **14a** (72 mg, 88%) as a clear oil. Spectral data are in accordance with literature reports.[42] TLC (20% EtOAc in hexanes): R_f = 0.45 (UV) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.76 (t, J = 1.8 Hz, 1H), 7.54−6.95 (m, 5H), 4.50 (s, 2H), 3.78 (t, J = 6.1 Hz, 2H), 2.66 (td, J = 6.1, 1.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 201.2, 137.9, 128.5, 127.8, 127.8, 73.3, 63.9, 43.9.

*6-Fluoro-3-hydroxy-4H-chromen-4-one (**15a**).* 6-Fluoro-3-hydroxy-4*H*-chromen-4-one **15a** was prepared using the general

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procedure using a solution of olefin **15** in DCM (2.0 mL, 0.50 mmol, 0.25 M). After standard workup, the residue was purified by flash-column chromatography on silica gel (10% to 90% EtOAc in hexanes) to yield **15a** (68 mg, 76%, contains 20 mol % H_2O) as a pale-yellow solid. Spectral data are in accordance with literature reports.[43] TLC (50% EtOAc in hexanes): R_f = 0.5 (UV) ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.27 (s, 1H), 8.29 (s, 1H), 7.76 (m, J = 18.1, 9.0, 3.7 Hz, 2H), 7.67 (td, J = 8.7, 3.0 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 172.94, 160.29, 158.36, 152.70, 142.43, 142.13, 124.69, 122.76, 122.56, 122.16, 110.13, 109.95. ^{19}F NMR (DMSO-d_6, 471 MHz): δ −116.58.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01372.

Solubility data, kinetic experiments, synthetic procedures, characterization data, and NMR spectra of these synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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