Organic Oxidations Promoted in Vortex Driven Thin Films Under Continuous Flow

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General considerations.

All NMR was performed on either 600 or 400 MHz Bruker advance spectrometers using $CDCl_3$ or D_2O as the solvent, as specified. Spectra were acquired using a relaxation delay time of 4 seconds. All chemical shifts are presented in ppm using residual solvent as the internal standard. All solvents and reagents were used as received from commercial suppliers, except for allyl phenyl sulfide which was synthesized from the method stated, using solvents and reagents as supplied from commercial source. Infrared (IR) spectra were recorded on a Perkin Elmer ATR Fourier Transform spectrometer as liquid films, or solid crystals. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

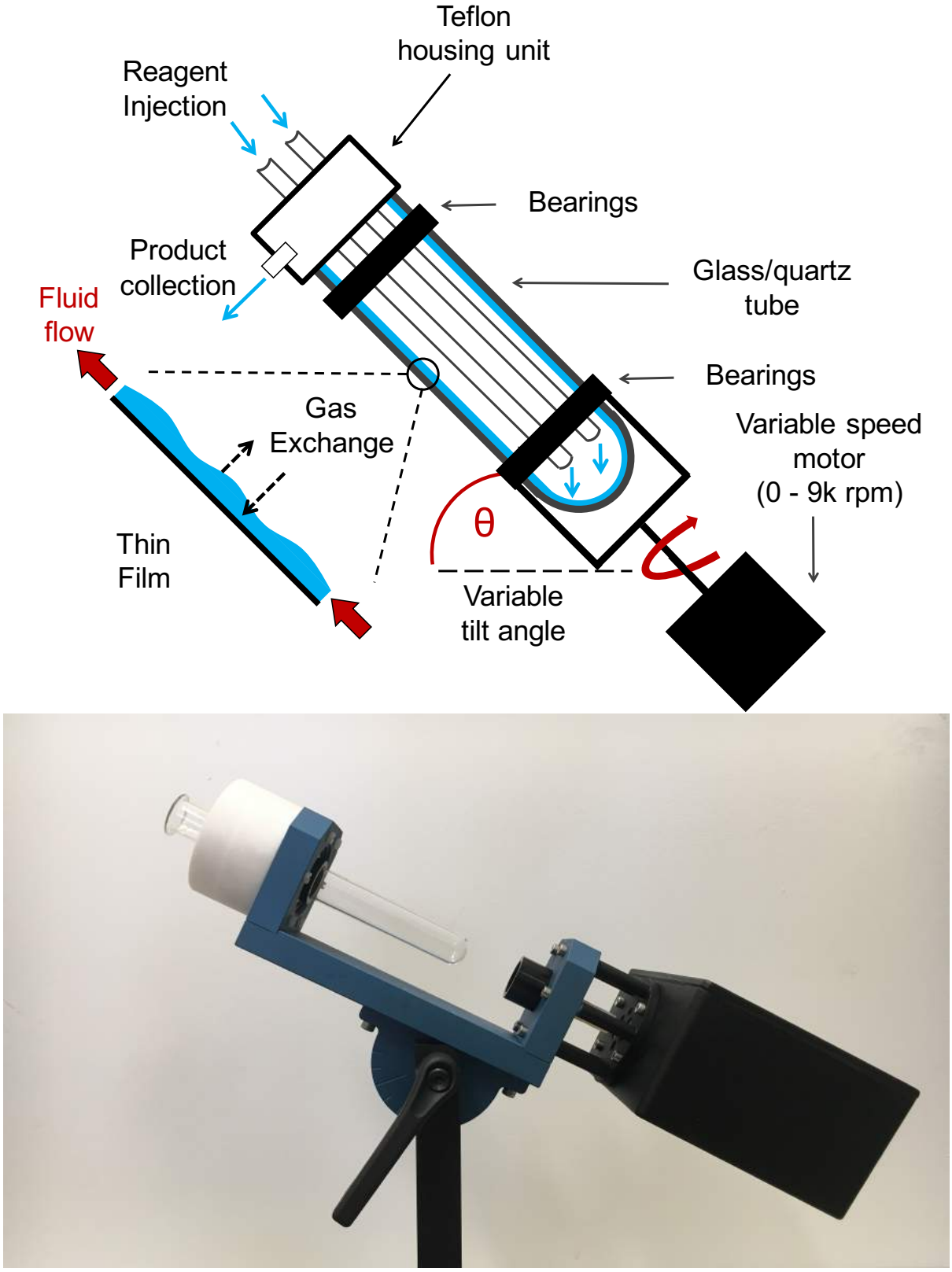
The vortex fluidic device (VFD) shown in figure S1 is modular in nature, thus this device can have many configurations. Unless otherwise specified, throughout this report the following specifications were used. The tube used was a borosilicate glass, 19 cm long with a 20 mm outer diameter (OD). "Confined mode" refers to the mode of operation where a finite amount of reagent is reacted within the tube, "continuous flow" refers to mode of operation where reagents are delivered via stainless steal jet feed (2 mm OD) to the base of the rotating tube, and reaction mixture is collected after exiting the tube. Liquid reagents were delivered using syringe pumps, with a borosilicate glass syringe and plunger, and stainless steal 17 G needles. Rotating tube was always operated at a 45˚ tilt angle (θ).

Thin layer chromatography (TLC) was carried out using aluminum backed sheets coated with 60F254 silica gel. Visualization of the silica plates was achieved using a UV lamp ("max = 254 nm) and/or potassium permanganate (5% $KMnO_4$ in 1M NaOH with 5% potassium carbonate). Flash column chromatography was carried out using 40-60 mm silica gel, wet packed to a height of 15 cm in a 30 mm OD column.

For crystal diffraction studies, single crystals were grown and a suitable crystal was selected in each case and mounted on a Bruker APEX-II CCD diffractometer using paratone oil and a loop. The crystals were kept at 100(2) K during respective data collections. Using Olex2 [1], the structures were solved with the XT [2] structure solution program using Intrinsic Phasing and refined with the XL [3] refinement package using Least Squares minimisation.

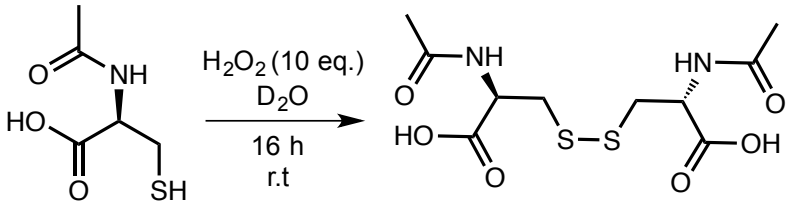
[1] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
[2] Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
[3] Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Figure S1. Schematic representation and photograph of the vortex fluidic device (VFD).



Aerobic oxidation of *N*-acetyl-L-cysteine.

Obtaining reference sample of disulfide 2

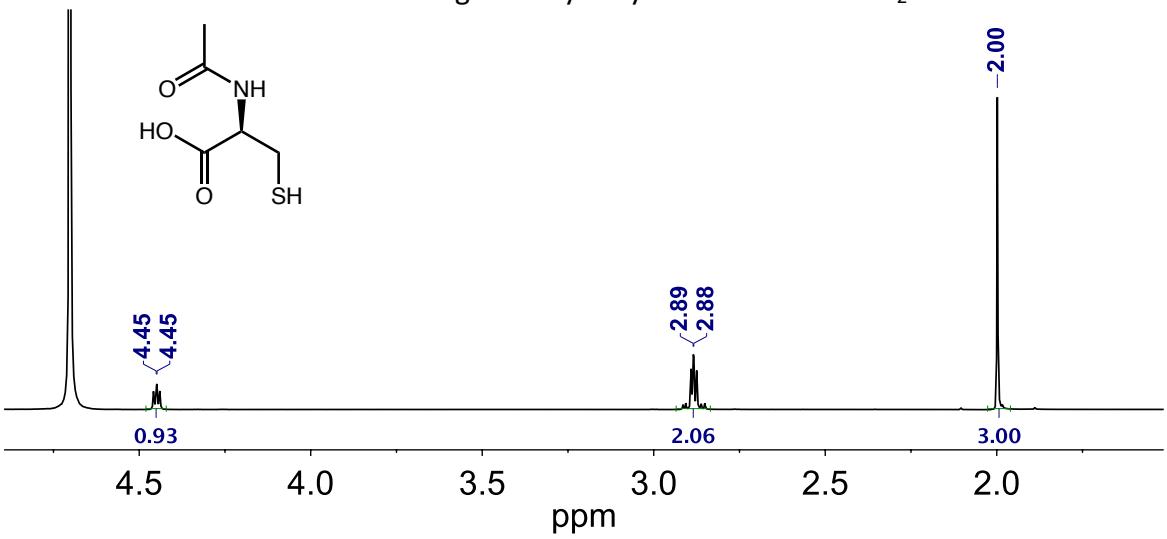


1 **2**

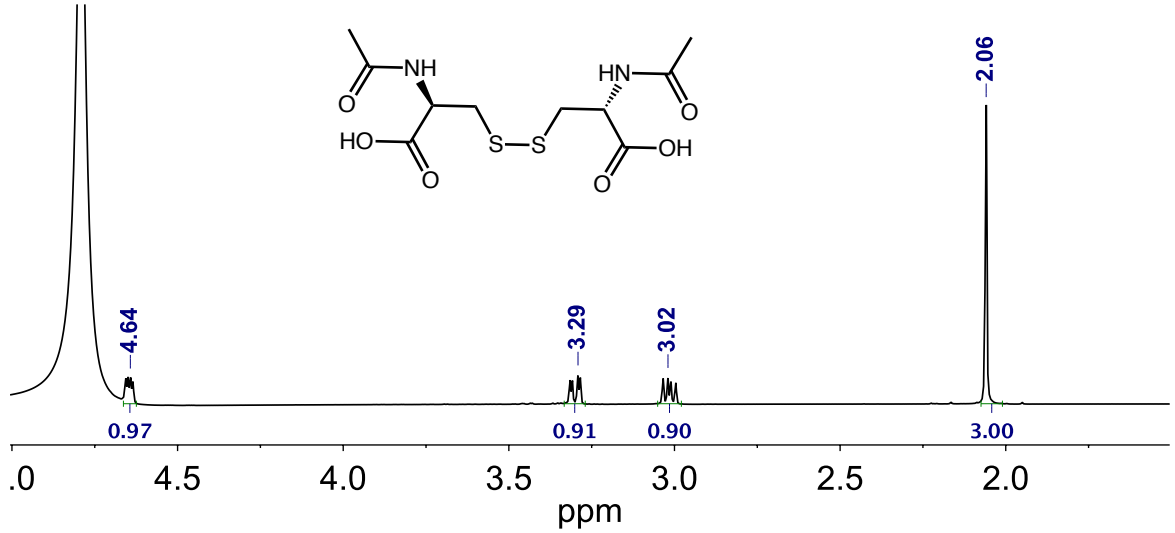
A reference sample of disulfide **2** was prepared by adding 30% w/w H_2O_2 (20 μL, 1.2 mmol) to *N*-acetyl-L-cysteine (20 mg, 0.12 mmol) in D_2O (2 mL) in a small vial. Reaction took place over 16 hours, ^{1}H-NMR and MS analysis showed disulfide **2** in high purity without need for further purification. The resulting spectra can be found on the following page.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 4.64 (2H, q, J = 3.95 Hz, NHC<u>H</u>) 3.29 (2H, m S-SCH<u>H</u>'), 3.02 (2H, m, S-SC<u>H</u>H'), 2.06 (6H, s, O=CC<u>H</u>$_3$).

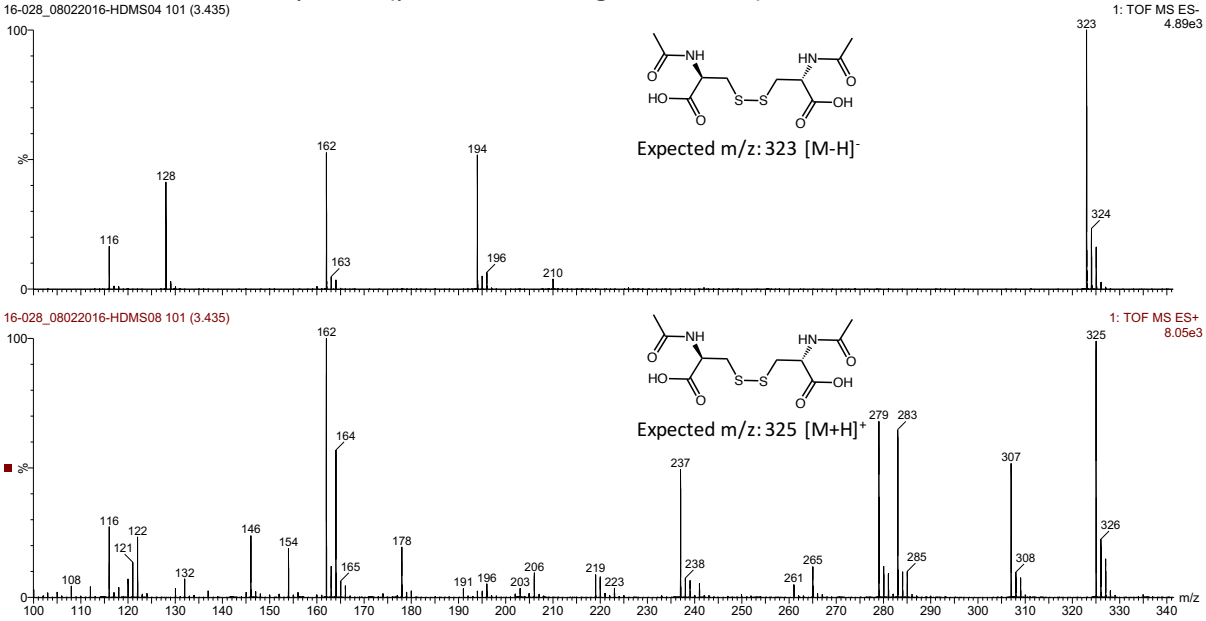
H-NMR of Starting *N*-acetyl-L-cysteine material in D_2O.



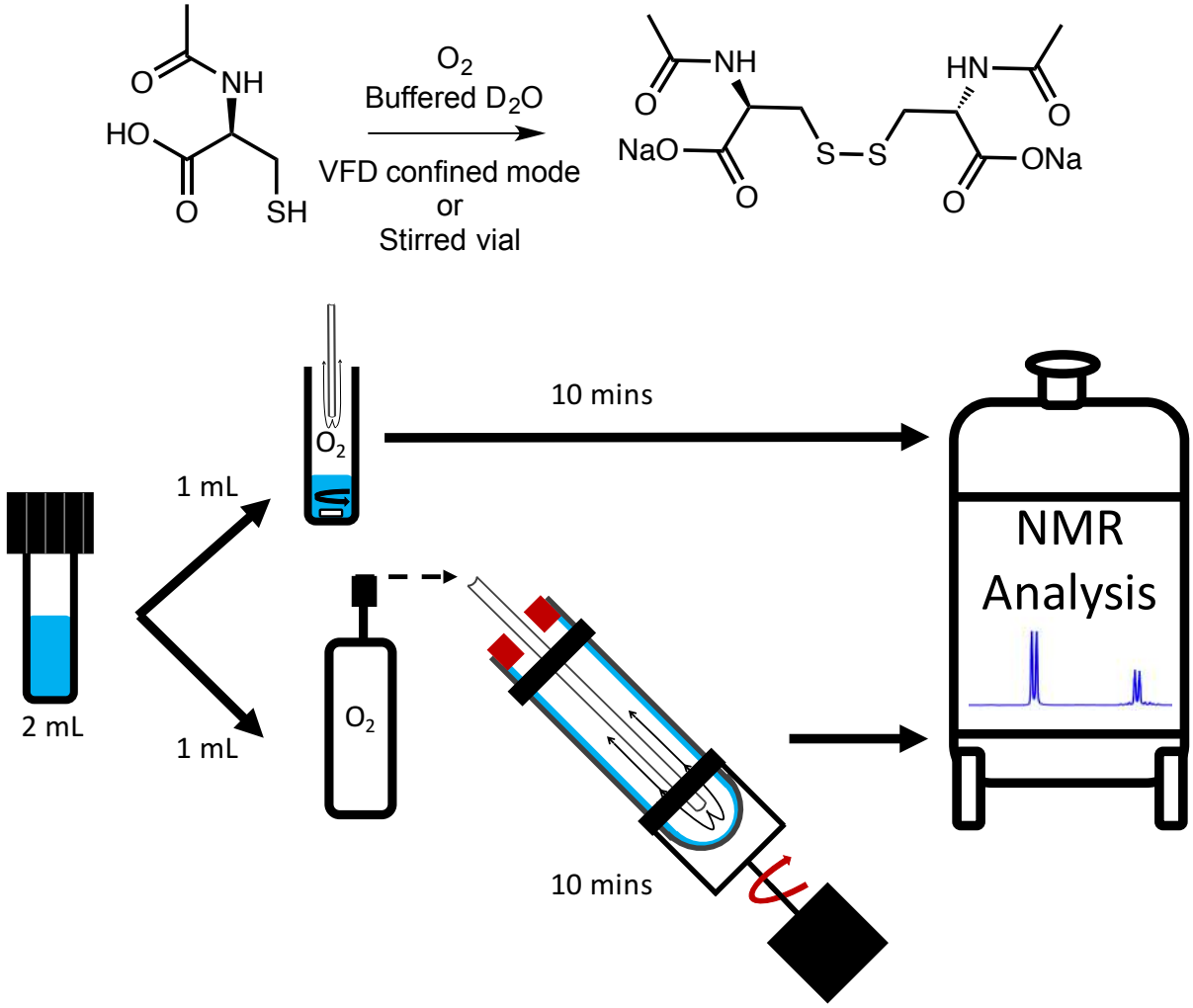
H-NMR of product **2** formed through peroxide treatment of compound **1**. D_2O solvent



Mass spectra (positive and negative mode) of the disulfide **2**.



Small scale batch and confined mode VFD processing.

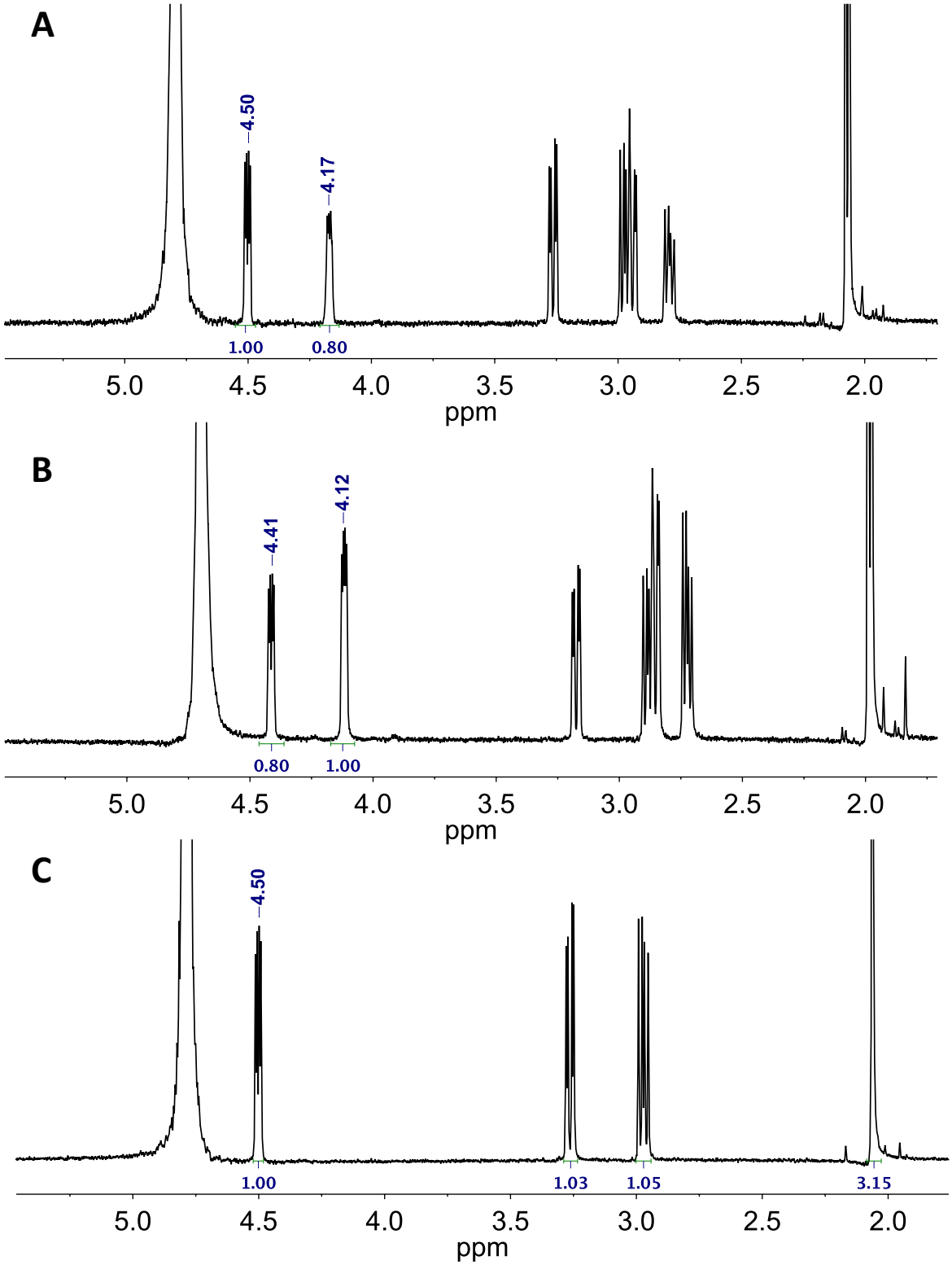


Comparisons between small scale confined mode VFD and batch were made. First a buffered stock solution of *N*-acetyl-L-cysteine in D_2O was prepared by addition of sodium carbonate (2.12 mg, 0.02mmol) and sodium bicarbonate (16.8 mg, 0.2 mmol) to 2 mL of D_2O, followed by the addition of *N*-acetyl-L-cysteine (3.28 mg, 0.02 mmol). The pH of this solution was measured to be 9.8. Then, 1 mL of this was transferred to a 20 mm VFD tube and operated at 7k rpm, whilst simultaneously the other 1 mL was transferred to a 20 mm VFD tube and stirred with a magnetic stirrer bar under a stream of O_2 gas. After 10 minutes of elapsed reaction time these samples analyzed by H NMR. This experiment was performed in duplicate. The batch sample was also then left in the NMR tube for 3 days and re-analyzed. This showed conversion times were moderately faster in the VFD on these 1 mL scale volumes and that the reaction will continue until completion.

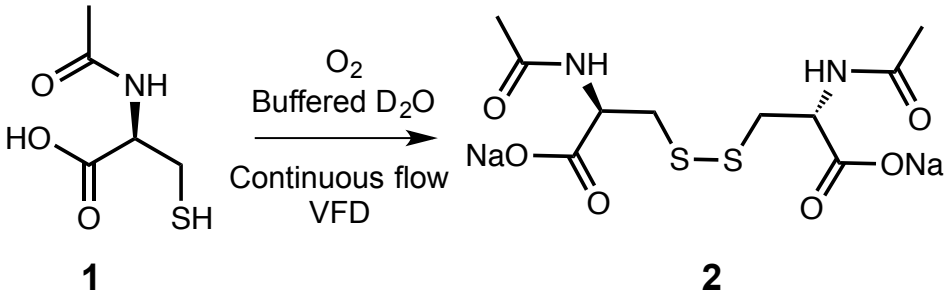
Table S1. Comparisons of conversion of 1 mL scale *N*-acetyl-L-cysteine to disulfide **2** in batch vs VFD.

Entry	Reaction Vessel	Conversion (%)
1	Batch	25 (+/- 2.7)
2	VFD	40 (+/- 0.7)

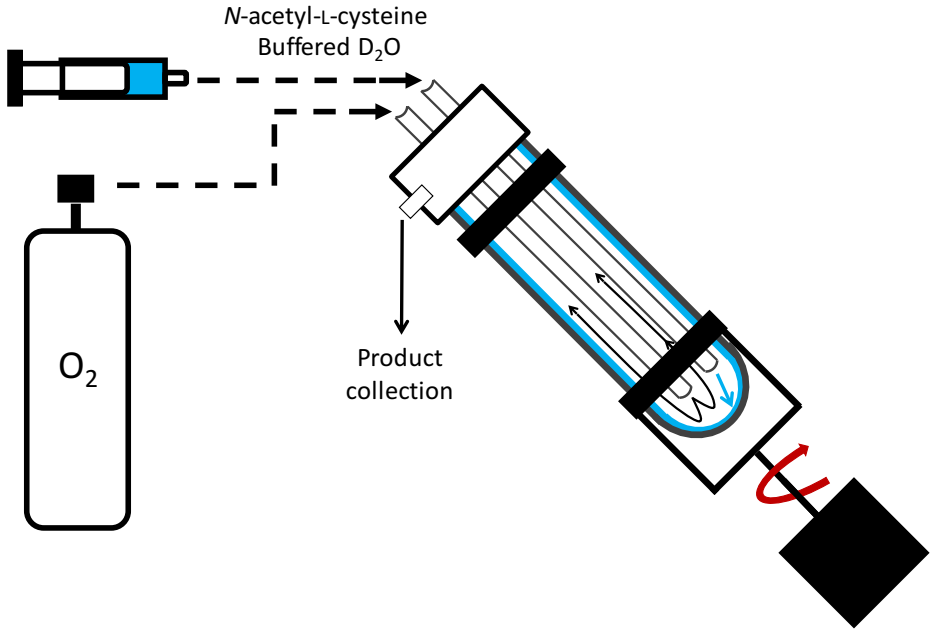
Figure S2. Representative ^{1}H NMR spectra from above graph, from reaction at pH 9.78 in A) confined mode VFD operation, B) batch comparison and C) batch sample left for 3 days.



Large scale continuous flow VFD processing with atmosphere of O_2 vs air.



1 **2**



A buffered solution of D_2O was prepared by the addition sodium carbonate (150 mg, 1.42 mmol) and sodium bicarbonate (420 mg, 5.00 mmol) to 50 mL of D_2O. *N*-acetyl-L-cysteine (82 mg, 0.50 mmol) was then added to the buffered solution and the initial pH was 9.9, as measured using a pH meter. This solution was then injected via syringe pump at the desired 0.5 mL/min into the base of the VFD tube, operating at 7 krpm with a 45˚ tilt angle. In another jet feed of the VFD, a stream of O_2 gas was introduced so that flow rate was no more than 0.5 L/min. The device was operated for a total of 2h, over which time the collection vessel was changed every 30 mins giving 4 fractions of reaction product. Fractions were analyzed by ^{1}H-NMR upon collection. A final pH was also recorded for the fractions. A control experiment was also carried out where air was used instead of O_2 gas. Reaction conversions were calculated based on the relative integration of the alpha protons for the starting material and product. The results are tabulated in figure S3 for each fraction. It was found that the average conversion across the 3 fractions was 55% when O_2 gas was used, compared to 7% when air was used, indicating O_2 is required for useful conversions. Representative NMR data for this set of experiments can be found in figure S5.

Figure S3. Conversion of *N*-acetyl-L-cysteine to disulfide **2** under continuous flow in the VFD. A) With an atmosphere of O_2 gas and B) With an atmosphere of air within the reaction vessel.

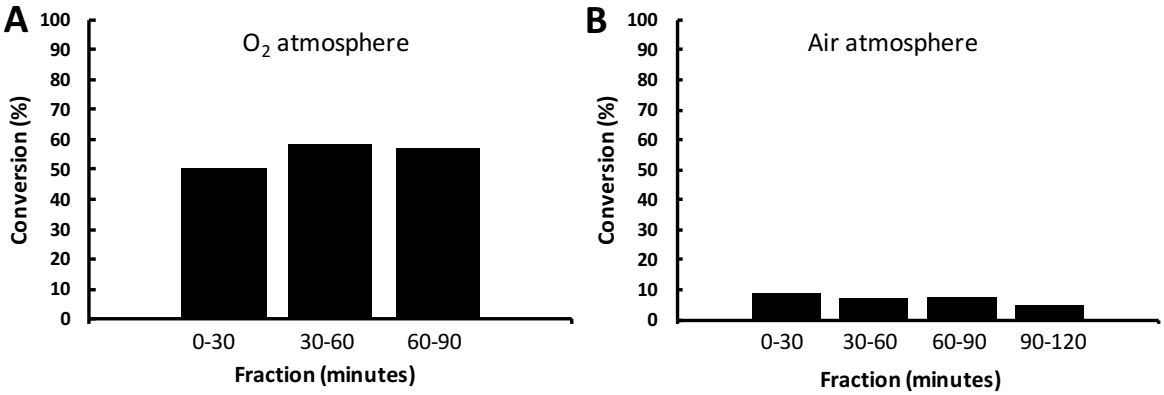


Figure S4. ^{1}H-NMR spectrum from continuous flow VFD with **O_2 atmosphere**. Samples at A) t = 0 (before VFD mediation) and B) from fraction collected between 60-90 minutes of operation. D_2O solvent.

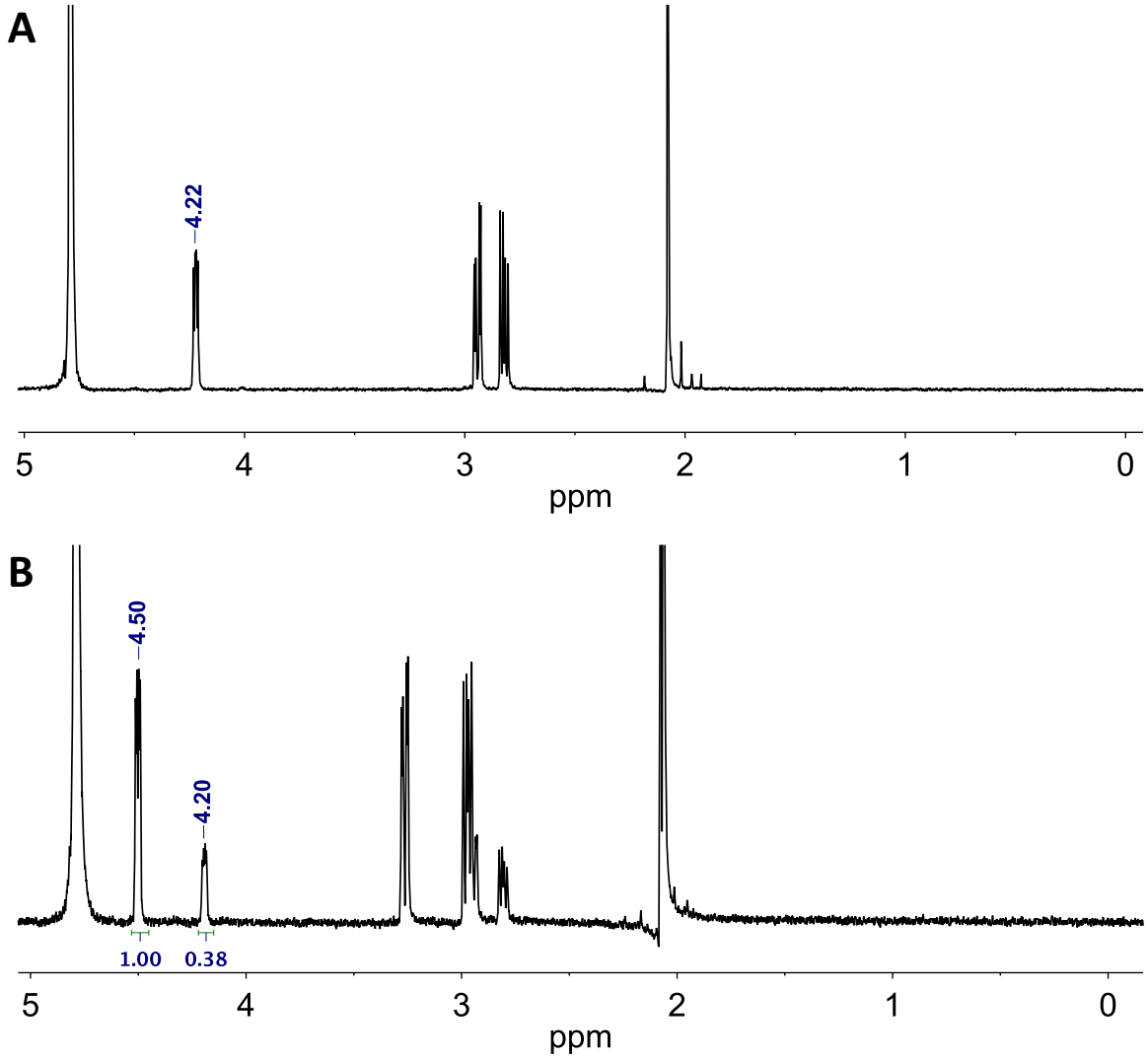
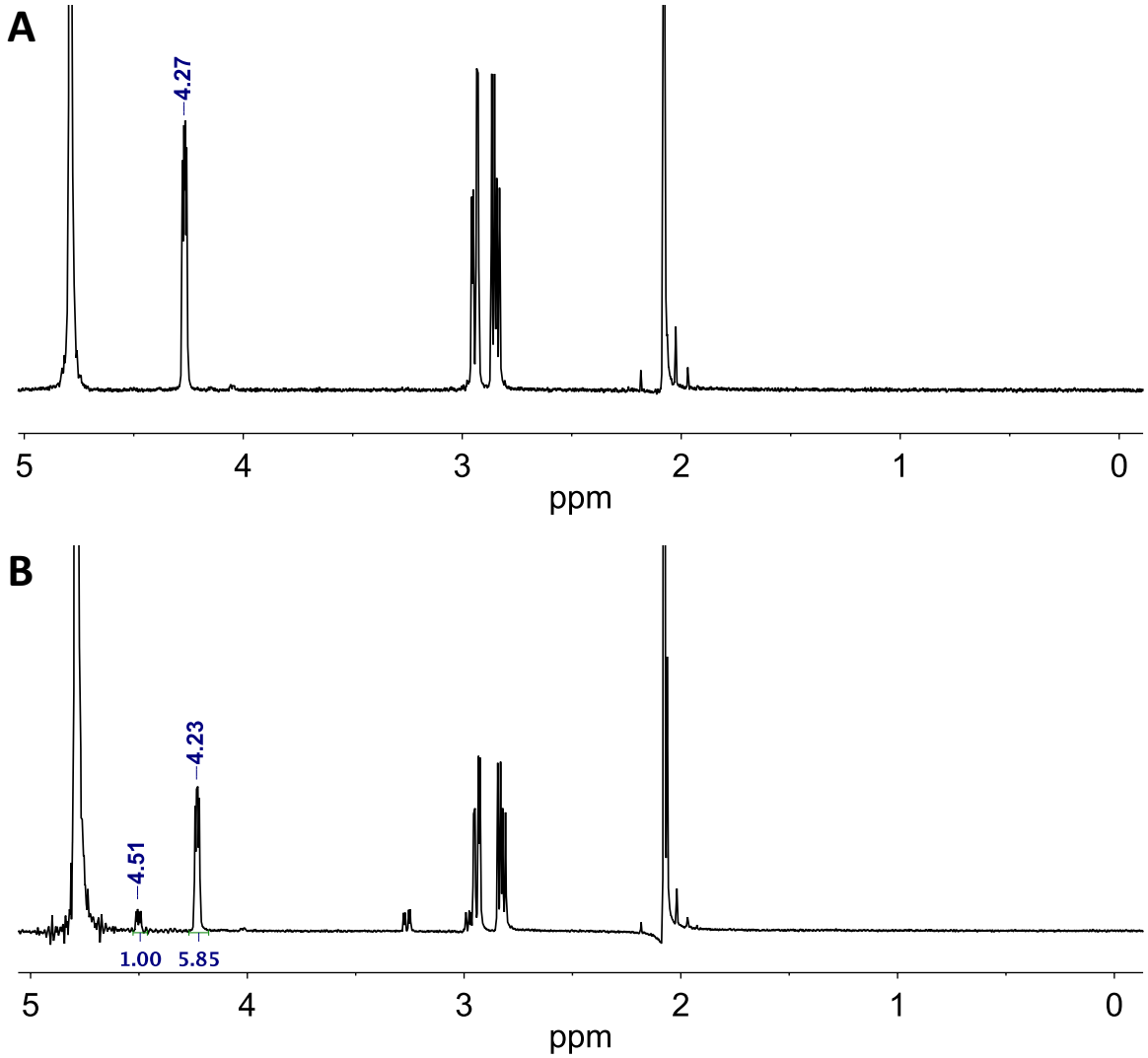


Figure S5. ^{1}H-NMR spectrum from continuous flow VFD with **air atmosphere**. Samples at A) t = 0 (before VFD mediation) and B) from fraction collected between 60-90 minutes of operation. D_2O solvent.



Large scale batch processing.

Three control experiments were carried out using batch conditions to determine if running the reaction in the VFD confers a benefit in reaction rate. A) A buffered *N*-acetyl-L-cysteine solution stirred with a with headspace of air. B) A buffered *N*-acetyl-L-cysteine solution stirred with a sealed headspace of O_2. C) A buffered *N*-acetyl-L-cysteine solution with stream of O_2 gas bubbled through. Accordingly, a buffered solution of D_2O was prepared by the addition sodium carbonate (300 mg, 2.84 mmol) and sodium bicarbonate (842 mg, 10.0 mmol) to 100 mL of D_2O. *N*-acetyl-L-cysteine (164 mg, 1.00 mmol) was added to the buffered solution and the initial pH was 9.9, as measured using a pH meter. This solution was then stirred with either a headspace of air (open flask), O_2 (1 atm, sealed flask) or a stream of O_2 bubbling through continuously at no more than 0.5 L/min. NMR samples were taken at times of 0, 5, 10, 20, 40 and 60 minutes, with conversions determined directly by ^{1}H NMR analysis. The results are tabulated below, with NMR data on the following page. It is interesting to note that while only a small difference was observed in VFD vs batch processing for small scale processing, major differences in conversion were observed on up-scaling.

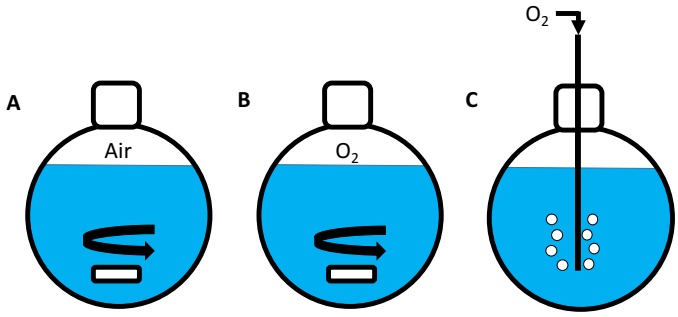


Table S2. Conversions of the *N*-acetyl-L-cysteine to disulfide **2** for the three batch controls

	Conversion (%)		
t (min)	Headspace of air	Headspace of O_2	Bubbling O_2
0	0	0	0
5	0	0	0
10	0	0	0
20	0	0	0
40	<1	5	4
60	3	5	4
960	12	-	-

Figure S6. ^{1}H NMR spectra for the open air batch experiment

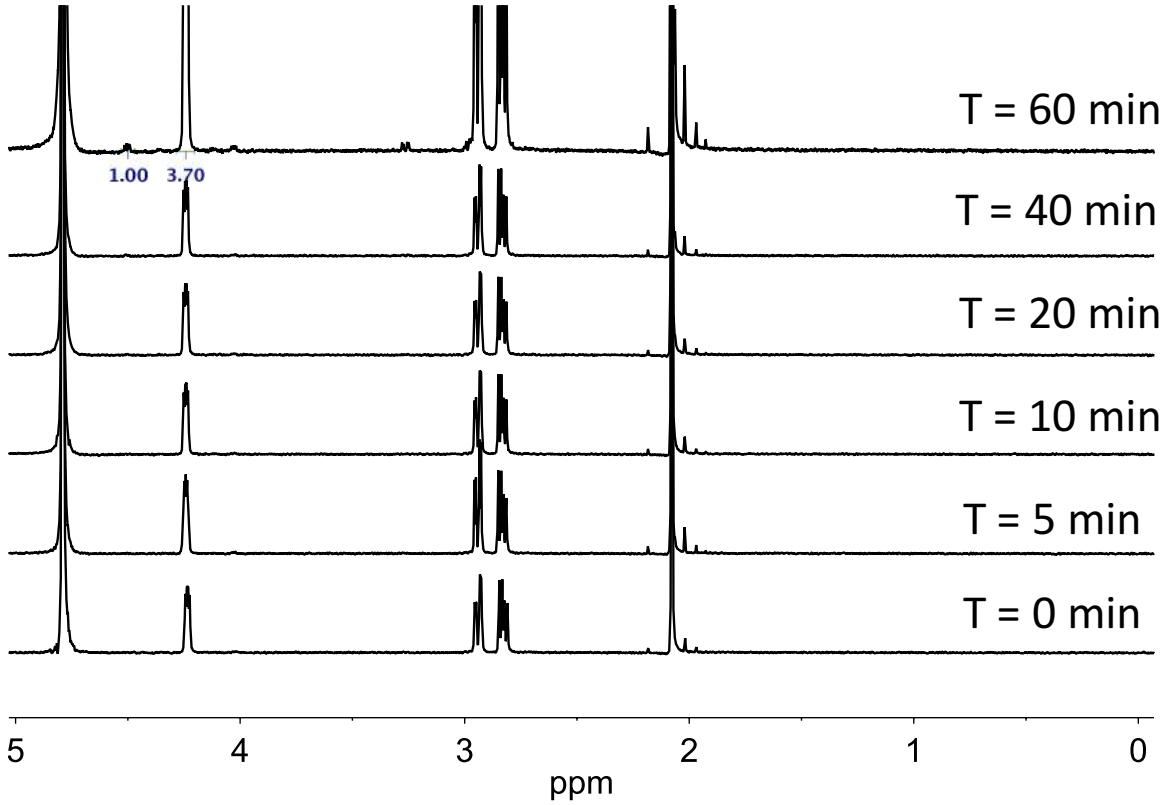


Figure S7. ^{1}H NMR spectra for the batch experiment under 1 atm oxygen

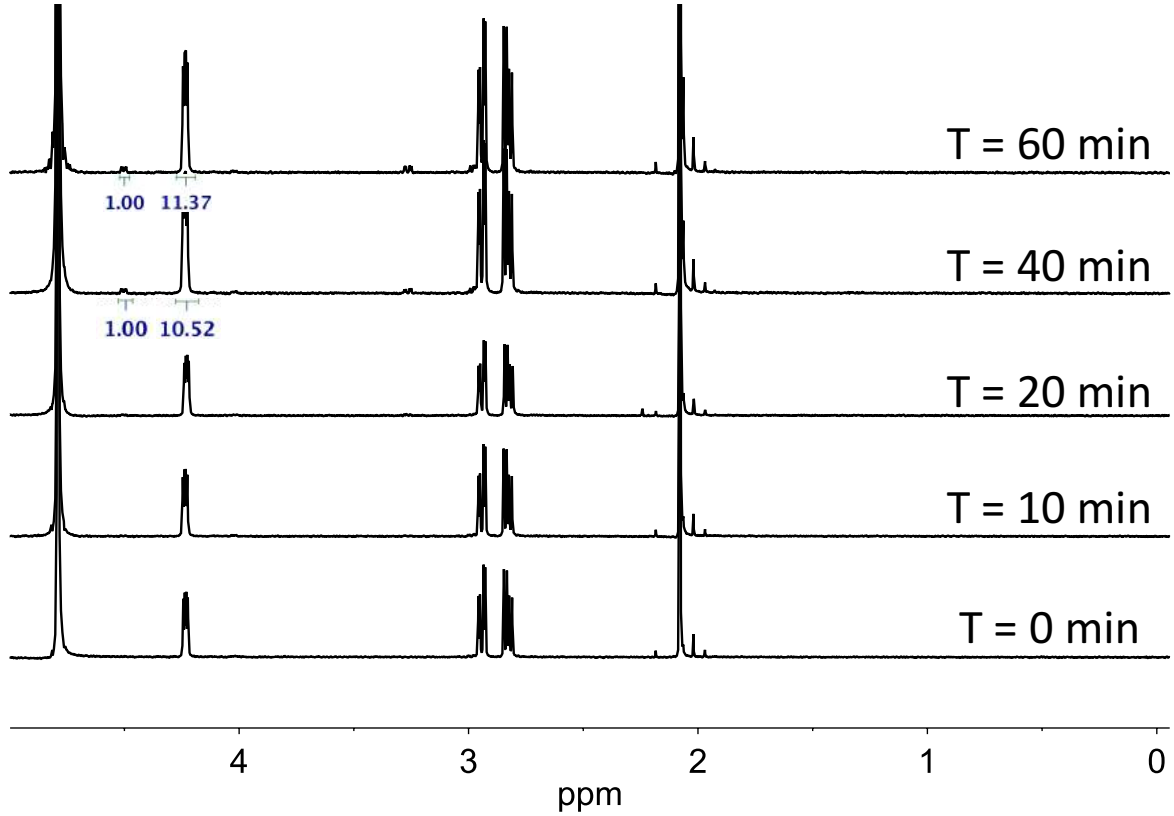
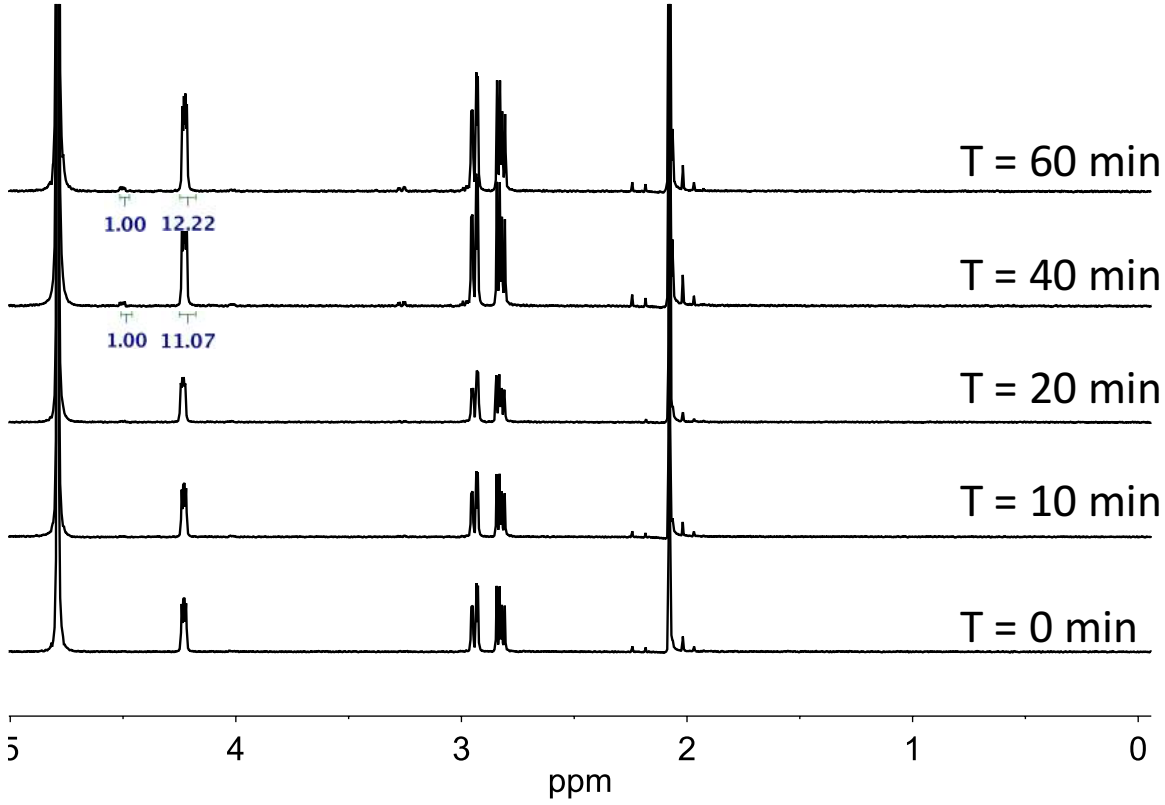
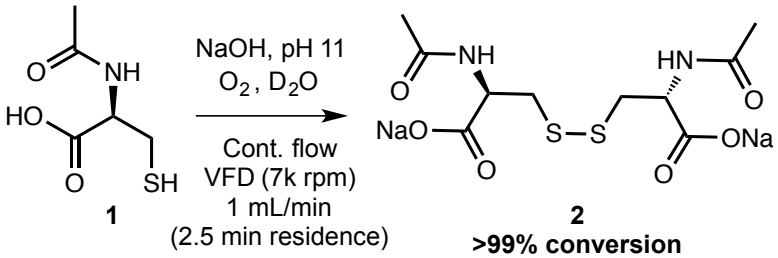
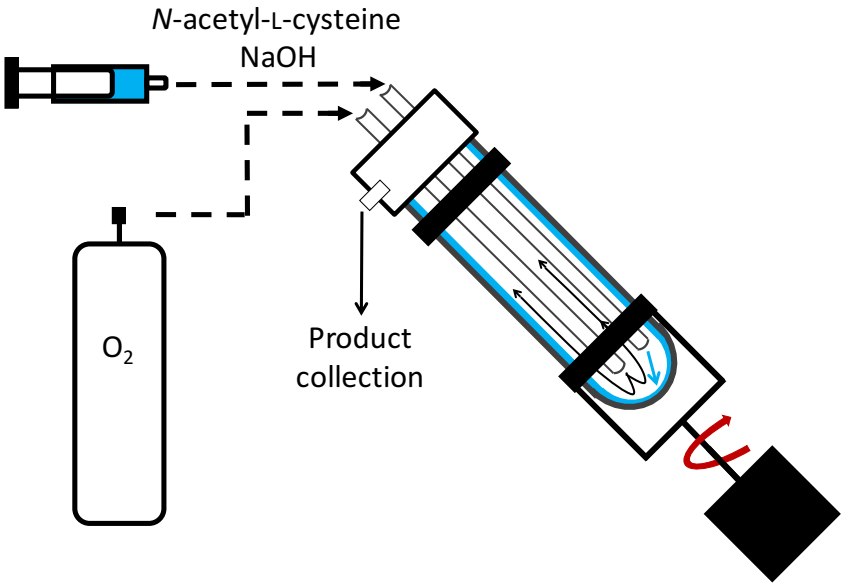


Figure S8. ^{1}H NMR spectra for the batch experiment with oxygen bubbled through the reaction



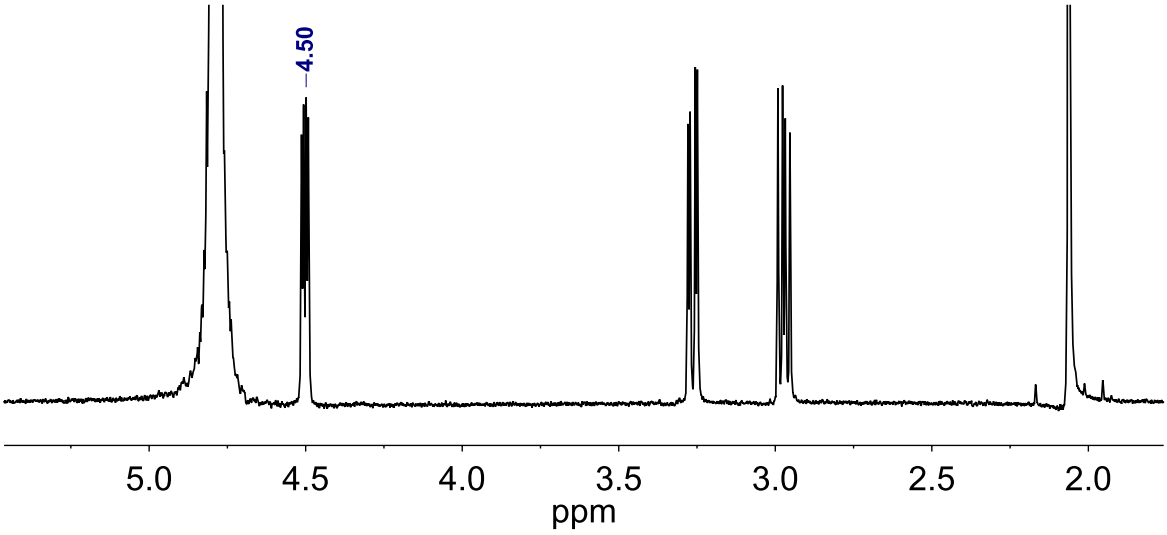
Continuous flow VFD processing at pH 11.





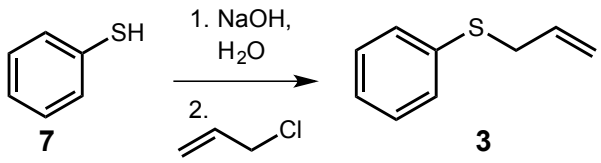
A 5 M NaOH (0.5 mL, 2.5 mol) was added to 20 mL D_2O. *N*-acetyl-L-cysteine (82 mg, 0.50 mmol) was then added to the solution. This solution was then injected via syringe pump at the 1 mL/min into the base of the VFD tube, operating at 7k rpm with a 45˚ tilt angle. In another jet feed of the VFD, a stream of O_2 gas was introduced so that the flow rate was no more than 0.5 L/min. The device was operated for a total of 20 mins, over which time the collection vessel was changed every 5 mins giving 4 fractions of reaction product. Fractions were analyzed by ^{1}H-NMR upon collection. Average conversion across all 4 fraction showed a conversion >99 % to the disulfide. Representative ^{1}H NMR spectra can be found below.

^{1}H NMR spectra of fraction 1 of the continuous flow process



Oxidation of allyl phenyl sulfide with sodium hypochlorite.

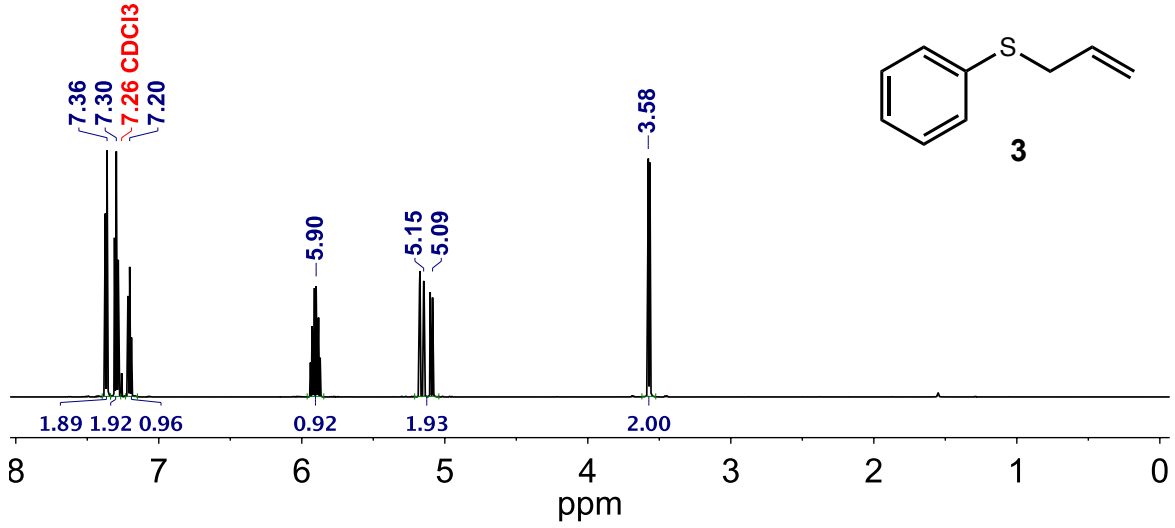
Synthesis of allyl phenyl sulfide 3.



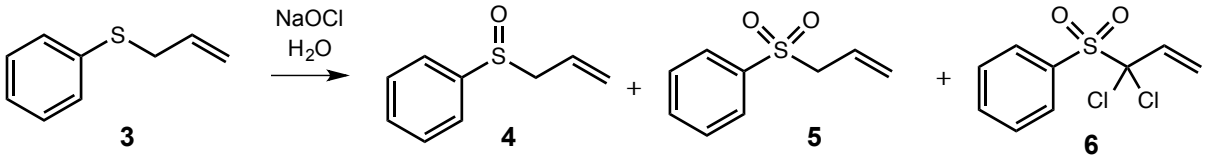
NaOH (1.56 g, 39.0 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of deionized H_2O. The stirred solution was cooled to 0 ˚C and thiophenol (4.0 mL, 39.0 mmol) was added. After 5 minutes of stirring, allyl chloride (3.3 mL, 42.9 mmol) was added. The resulting cloudy reaction mixture was stirred vigorously for 6 hours at room temperature. TLC (10% EtOAc in hexane) indicated the formation of a single product. The reaction was diluted with 250 mL Et_2O and washed successively with 0.1 M NaOH (3 × 100 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **3** as a clear oil that required no purification. Reaction was performed to provide compound **3** as needed, resulting in a typical yield of 90 - 95 %.

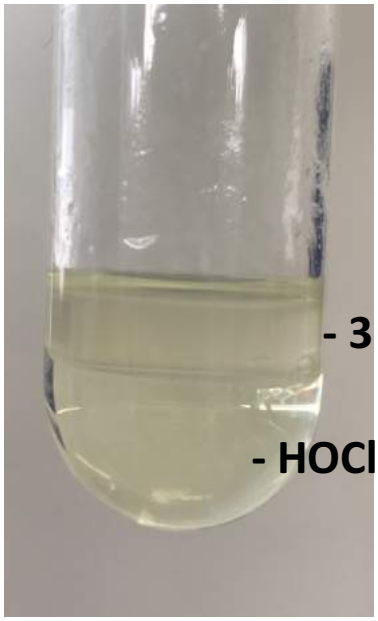
^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.35-7.38 (2H, m, Ar), 7.28-7.32 (2H, m, Ar), 7.2 (1H, tt, J= 7 Hz, 1 Hz, Ar), 5.87-5.94 (1H, m, C<u>H</u>=CH_2), 5.14-5.18 (1H, m, CH=C<u>H</u>H'), 5.08-5.11 (1H, m, CH=CH<u>H</u>'), 3.58 (2H, dt, J = 7 Hz, 1 Hz, PhSC<u>H_2</u>).

^{1}H NMR spectrum of allyl phenyl sulfide **3**.



Comparisons between VFD and batch processing.





Allyl phenyl sulfide (20 mg, 0.067 mmol), and a solution of 4% active chlorine bleach (2.45 mL, 0.67 mmol NaOCl) were transferred into a 20 mm VFD tube. The reaction mixture appears as two phases (see figure at left). This tube was then placed into a VFD and operated in confined mode at 7k rpm with a tilt angle of 45˚ for 40 minutes. After rotation had stopped, extraction was performed using $CDCl_3$ and NMR analysis was undertaken on the crude extract. All experiments were all repeated where the VFD tube was not rotated, these are noted as "batch" controls. Experiments were also performed for 20 eq. of bleach, in which case the amount of allyl phenyl sulfide was halved (10 mg, 0.033 mmol). All experiments were performed in duplicate (Tables S3 & 4). Reaction conversions were determined by relative integration of the allylic protons for **4** and **5** and the C<u>H</u>=CH_2 peak for **6** (3.5 , 3.8, 6.3 δ_H ppm shifts respectively).

Here, since the oxidative ability of bleach is the focus, the E-factor was calculated assuming all oxidation products are desired products. The waste is the generated NaCl (assuming 1:1 conversion from NaOCl) and the unreacted starting material. Note that since compounds are in separate phases, pipetting of the product is the only purification step required. Separation of the oxidation products requires further purification, such as the column chromatography method reported on page S19 of this document.

Batch, 20 eq.

$$E_{(batch)} = \frac{390\ mg}{0.47\ mg} = 91$$

VFD, 20 eq.

$$E_{(VFD)} = \frac{386\ mg}{6.8\ mg} = 6$$

Noting that the majority of waste in the VFD processing is innocuous NaCl .

Figure S9. Conversion from starting allyl phenyl sulfide to chlorinated compound **6** and sulfone **5** after 40 minutes, for both 10 and 20 bleach equivalents. A) for VFD and B) for batch processing.

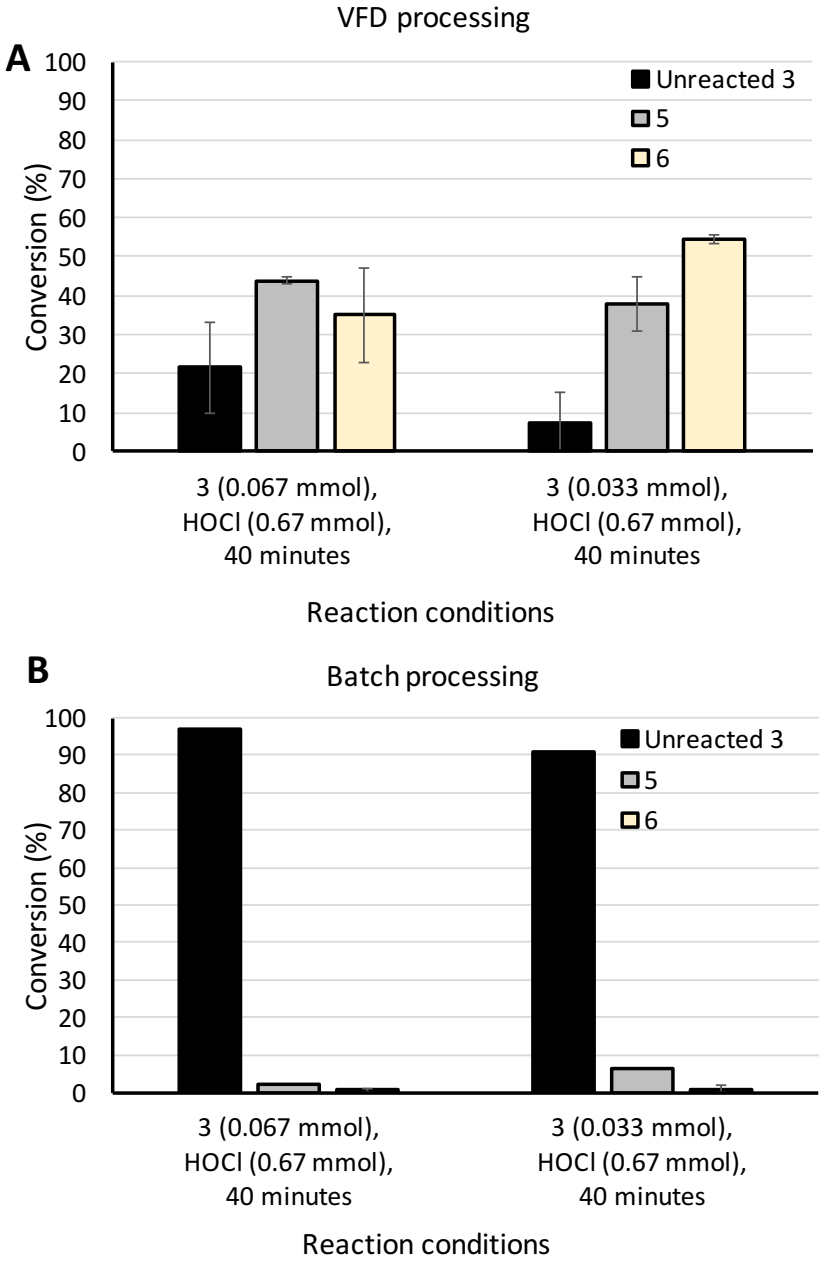


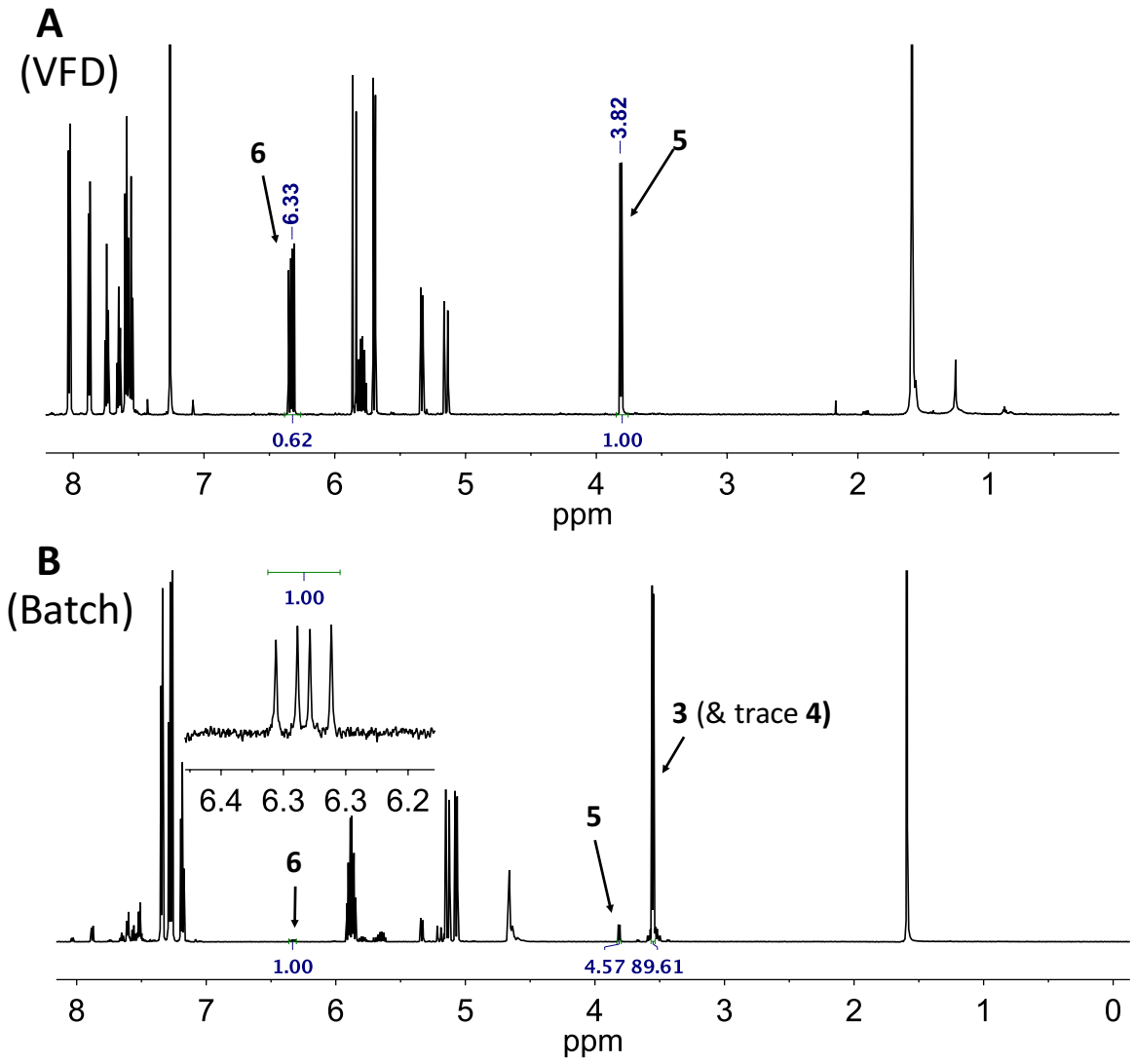
Table S3. **Conversion screening when using VFD**, from starting allyl phenyl sulfide to chlorinated compound **6** and sulfone **5** after 40 minutes, for both 10 and 20 bleach equivalents. (*sample spectra can be found on the following page*)

Entry	Bleach eq.	Time (min)	Conversion to Dichloride **6** (%)	Conversion to Sulfone **5** (%)	Unreacted starting material **3** (%)
1	10	40	35 (+/- 12)	43.8 (+/- 0.2)	21.5 (+/- 11.5)
2	20	40	54.5 (+/- 0.05)	38 (+/- 7)	7.5 (+/- 7.5)

Table S4. **Conversion screening in batch**, from starting allyl phenyl sulfide to chlorinated compound **6** and sulfone **5** after 40 minutes, for both 10 and 20 bleach equivalents. (*sample spectra can be found on the below*)

Entry	Bleach eq.	Time (min)	Conversion to Dichloride **6** (%)	Conversion to Sulfone **5** (%)	Unreacted starting material **3** (%)
1	10	40	0.65 (+/- 0.35)	2.15 (+/- 0.85)	97 (+/- 1)
2	20	40	1 (+/- 1)	6.5 (+/- 1.5)	91 (+/- 2)

Figure S10. ^{1}H-NMR spectrum from VFD mediated bleach oxidation of **3**. Key peaks from compounds **3** ($C\underline{H}_2CH=CH_2$), **5** ($C\underline{H}_2CH=CH_2$) and **6** ($CH_2C\underline{H}=CH_2$) are annotated. Representative spectra from replicates that formed A) table S3 entry 2 and from B) table S4 entry 2.



VFD synthesis and Isolation of compound 6.

Allyl phenyl sulfide (60 µL, 0.40 mmol), and a solution of 8-12 % active chlorine bleach (2.45 mL, 2.6 – 3.9 mmol, 6.5 - 10 eq.) were transferred into a 20 mm VFD tube. This tube was then placed into a VFD and operated in confined mode at 7k rpm for 3 h. NMR analysis of crude product showed 71 % conversion to compound **6**. Flash column chromatography was performed with a mobile phase of 30% EtOAc in hexane (≈ 50 mL). This resulted in separation of compound **6** (63.3 mg) in yield of 63 %. ^{1}H NMR, ^{13}C NMR, IR and MS were performed on this isolated compound and spectra can be found below. The E-factor for the formation of compound **6** is calculated below, noting that the vast majority of waste in the crude mixture is innocuous NaCl.

$$E_{(crude)} = \frac{0.239\ g}{0.071\ g} = 3 \qquad E_{(isolated)} = \frac{45\ g}{0.063\ g} = 715$$

Melting point: 64-68 ˚C

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.01 (2H, dd, J= 8, 1 Hz, Ar), 7.73 (1H, tt, J= 8, 1 Hz, Ar), 7.58, (2H, m, Ar), 6.3 (1 H, dd, J = 16, 10 Hz, C<u>H</u>=CH_2) 5.83 (1H, d, J = 16 Hz, CH=C<u>H</u>H') , 5.68 (1H, d, J= 10 Hz, CH=CH<u>H</u>').

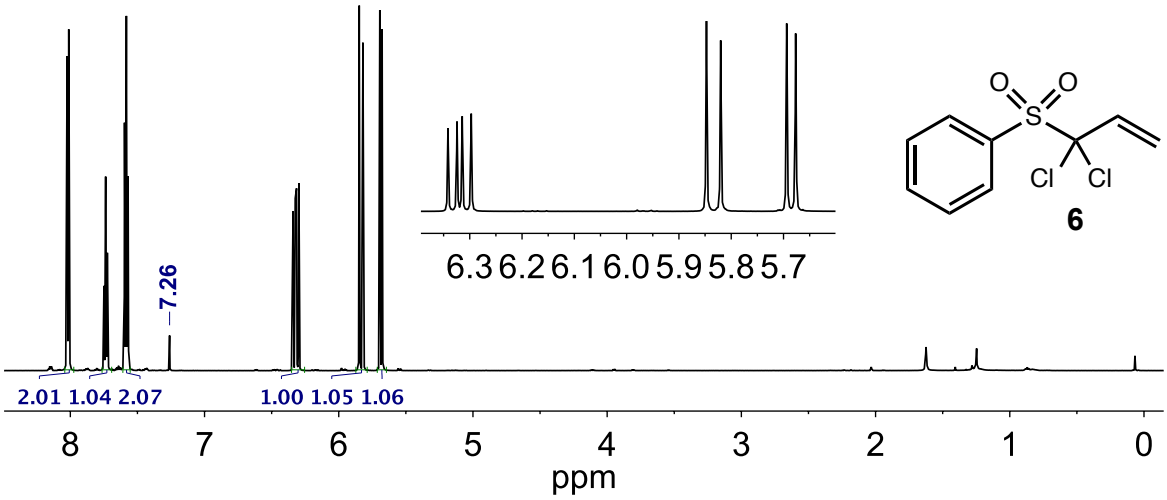
^{13}C NMR (600 MHz, $CDCl_3$): δ_C = 135.35 (Ar), 132.32 (Ar), 131.91 (<u>C</u>H=CH_2), 131.56 (Ar), 128.82 (Ar), 125.11 (CH=<u>C</u>H_2), 96.84 ($PhSO_2$<u>C</u>Cl_2).

IR (υ_{max}, crystals ATR): 1581, 1475, 1446, 1399, 1333, 1313, 1289, 1155, 1111, 1083, 1026, 998, 972, 953, 808, 759, 722, 687.

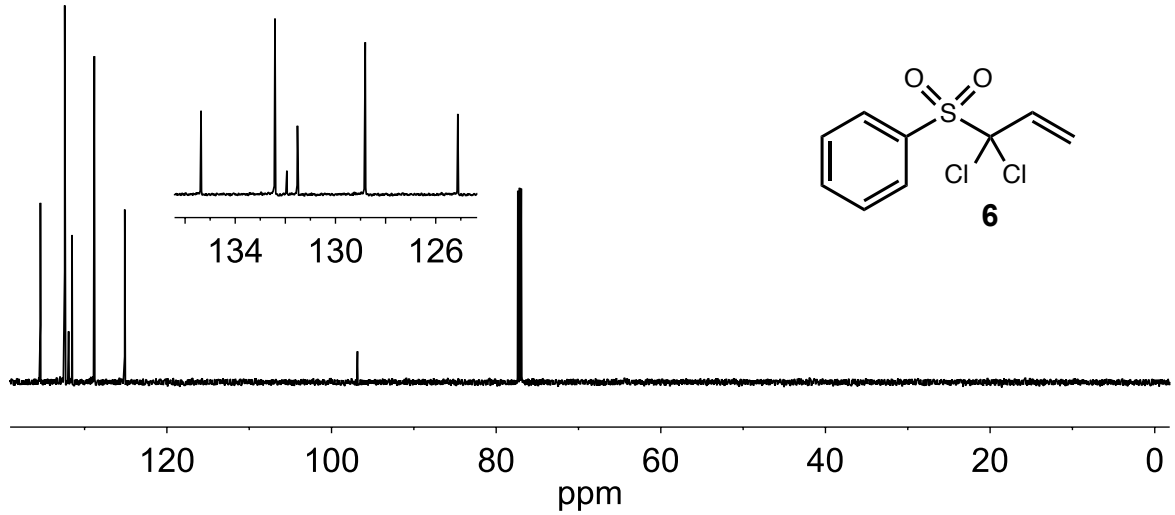
LR-MS: 251 $[M+H]^+$.

Crystal Data for 6 (CCDC 1552986): $C_9H_8Cl_2O_2S$, *M* =251.11 g/mol, monoclinic, space group $P2_1$ (no. 4), *a* = 7.3712(4) Å, *b* = 10.3338(6) Å, *c* = 13.8683(8) Å, *β* = 93.683(3)°, *V* = 1054.20(10) Å^3, *Z* = 4, *T* = 100(2) K, µ(MoKα) = 0.782 mm^{-1}, *Dcalc* = 1.582 g/cm^3, 4177 reflections measured (2.94° ≤ 2Θ ≤ 66.48°), 4177 unique (R_{int} = 0.0000, merged due to twin refinement, R_{sigma} = 0.0204) which were used in all calculations. The final R_1 was 0.0239 (>2sigma(I)) and wR_2 was 0.0580 (all data).

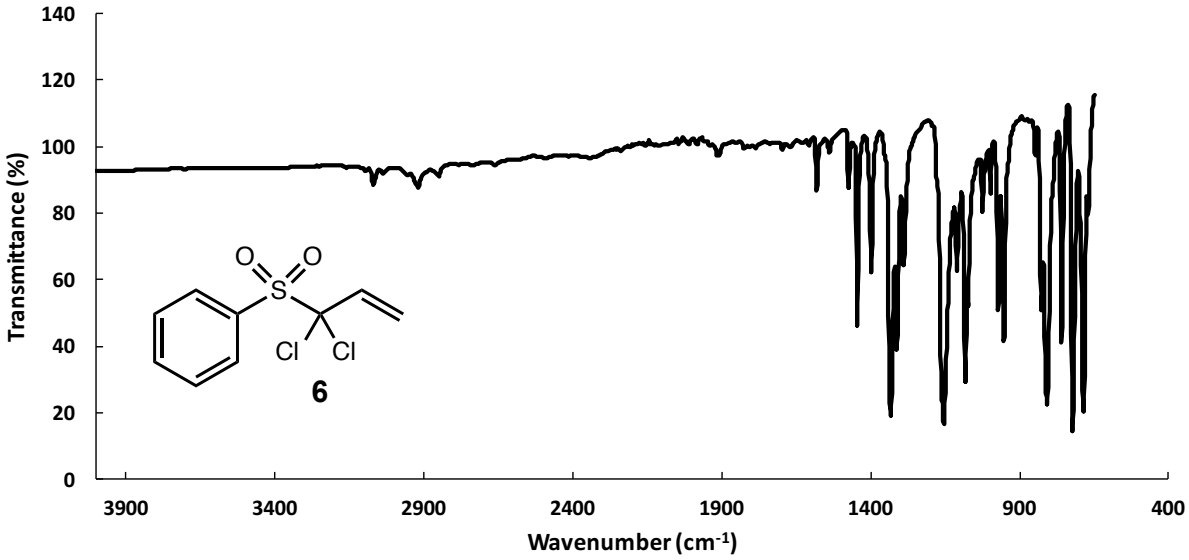
^{1}H NMR spectrum of isolated compound **6**.



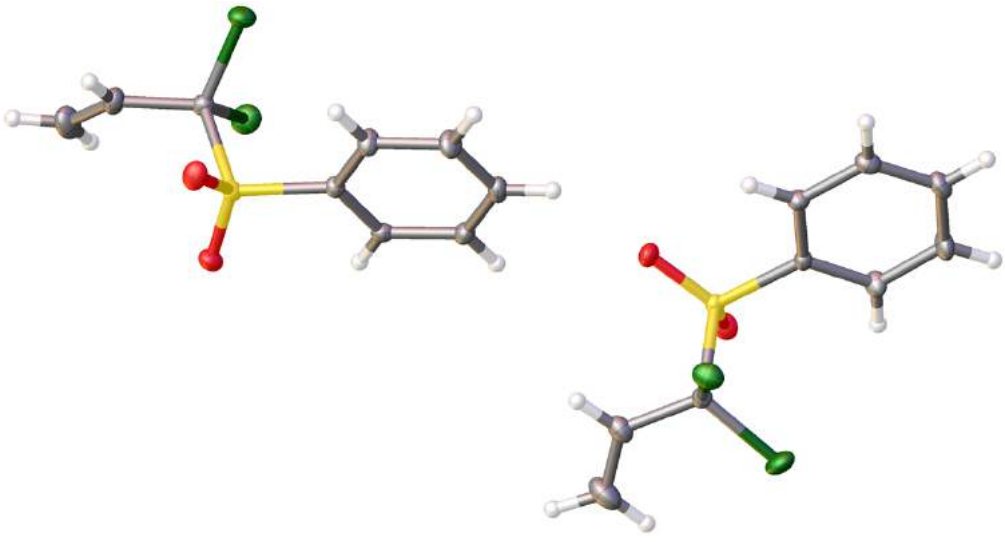
^{13}C NMR spectrum of isolated compound **6**.



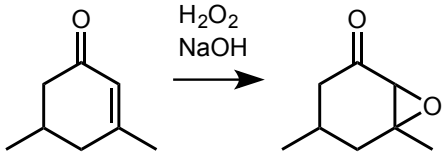
ATR IR spectrum of isolated compound **6**.



Crystal structure of compound **6**. Shown is the asymmetric unit containing 2 molecules.



Epoxidation of compound 8 with H_2O_2.



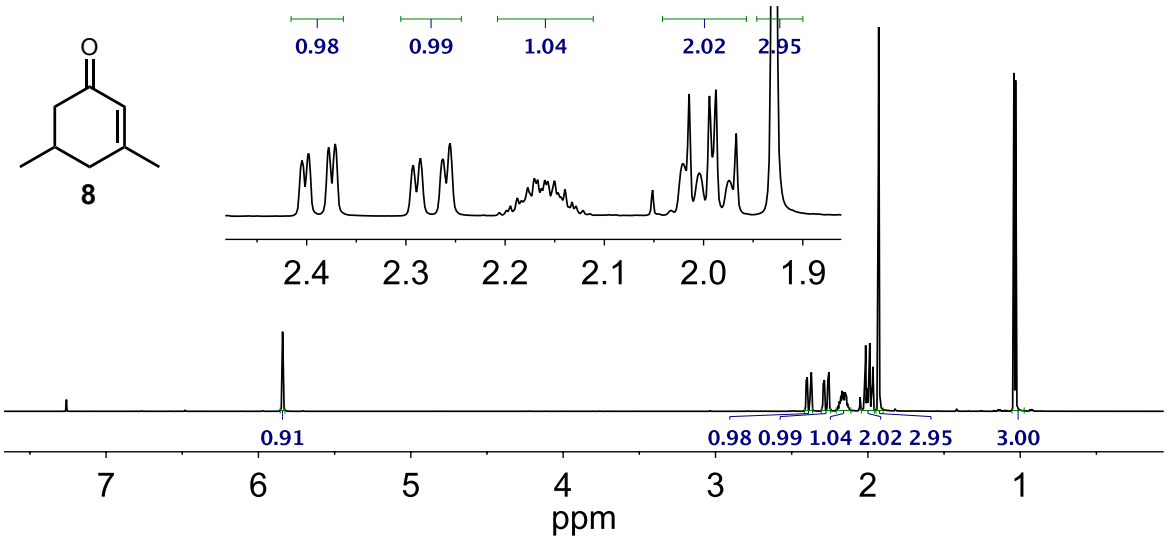
8 **9**

First, a NaOH solution (5 M, 0.7 mL, 3.5 mmol) was mixed with a H_2O_2 solution (30% aq. v/v, 1.2 mL, 17.5 mmol) over an ice bath and cooled for 15 minutes. This was then removed from ice and transferred to a 20 mm VFD tube. Following this, Compound **8** (0.5 mL, 3.5 mmol) was added to the reaction mixture and was operated at 7k rpm in a VFD for 1 hour. Crude NMR in $CDCl_3$ at this point revealed a conversion of 99 %. Further purification of this compound was performed for analytical purposes, since the structure of the respective minor and major diasteriomers have not been previously reported. The organic material was extracted from the aqueous hydrogen peroxide using chloroform (3 x 10 mL extractions). This extract was then combined with the NMR sample and dried (magnesium sulfate, ≈3 g), filtered and concentrated under a stream of compressed air. Flash column chromatography was then performed using a mobile phase of 20% EtOAc in toluene (≈50 mL), giving compound **9** (417 mg) as a yellow/clear oil in 85 % yield (d.r 22:1). NMR, GC-MS, and IR analysis were performed on this extract as reported below, with spectra found on the following page. E-factor calculations, are shown below. Since the terminal products are water, and the NaOH is catalytic, no purification is required in cased where full conversion is observed. Also shown is the E-factor of the purification process that was performed for analytical purposes, this was important as the diasteriomer of this process is unknown.

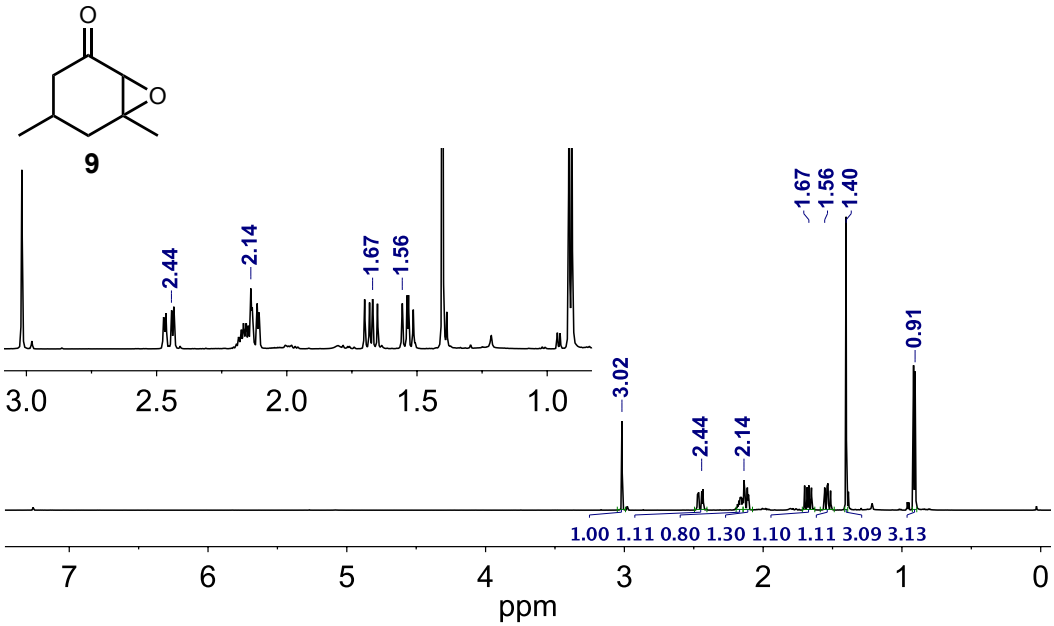
$$E = \frac{0.026\ g}{0.486\ g} = 0.05 \qquad E_{(isolated)} = \frac{95.68\ g}{0.417\ g} = 229$$

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 3.02 (1H, s), 2.44 (1H, dd, J= 5.2 Hz, 18.1 Hz, C<u>H</u>H'C=O), 2.16-2.24 (m, 1H, C<u>H</u>CH_3), 2.14 (1H, dd, J= 4.1 Hz, 18.4 Hz, CH<u>H'</u>), 1.67 (1H, dd, J = 11.0 Hz, 18.3 Hz, C<u>H</u>H'), 1.56 (1H, dd, J= 10.5 Hz, 14.2 Hz, CH<u>H'</u>), 1.40 (s, 3H, CH_3), 0.94 (3H, d, J= 6.7 Hz, HC-C<u>H$_3$</u>).
^{13}C NMR (600 MHz, $CDCl_3$): δ_C = 206.3 (<u>C</u>=O), 61.5 (O-<u>C</u>H), 61.2 (O-<u>C</u>CH_3), 44.3 (<u>C</u>H_2C=O), 37.2 (<u>C</u>H_2CCH_3), 23.4 (<u>C</u>HCH_3), 22.0(<u>C</u>H_3C-O), 21.1 (<u>C</u>H_3CH).
IR (υ_{max}, liquid ATR): 2963, 2933, 2877, 1713, 1461, 1425, 1400, 1366, 1281, 1260, 1097, 1029, 913, 877, 807, 707.
LR-MS: 141 $[M+H]^+$.

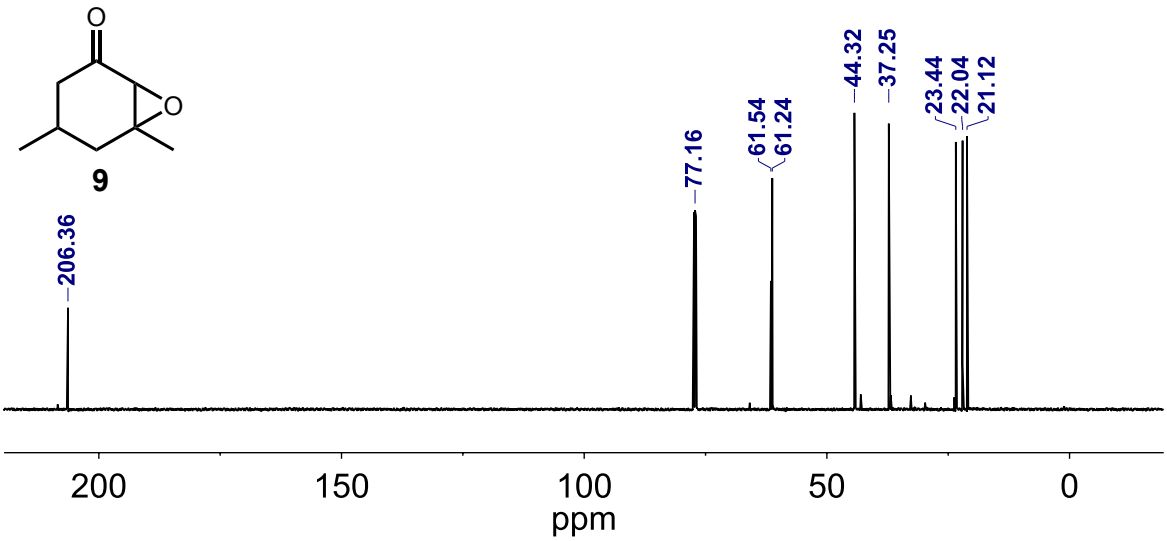
^{1}H NMR spectrum of starting material **8** in $CDCl_3$.



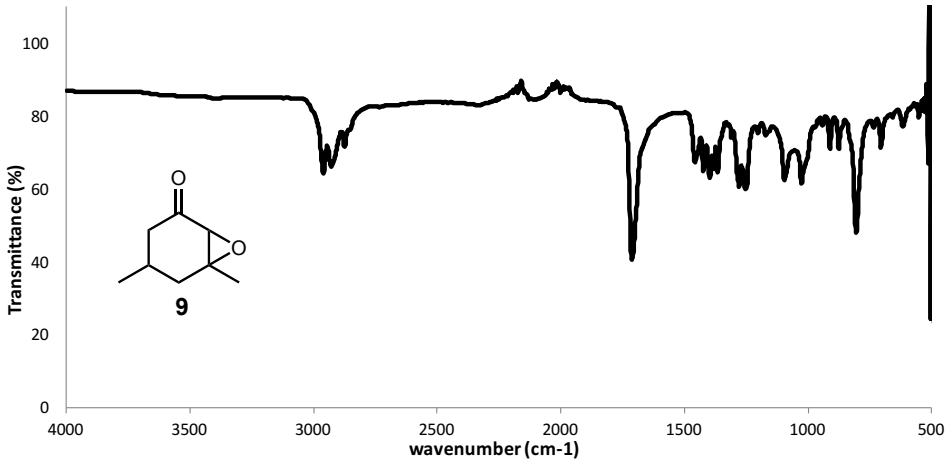
^{1}H NMR spectrum of isolated compound **9** in $CDCl_3$.



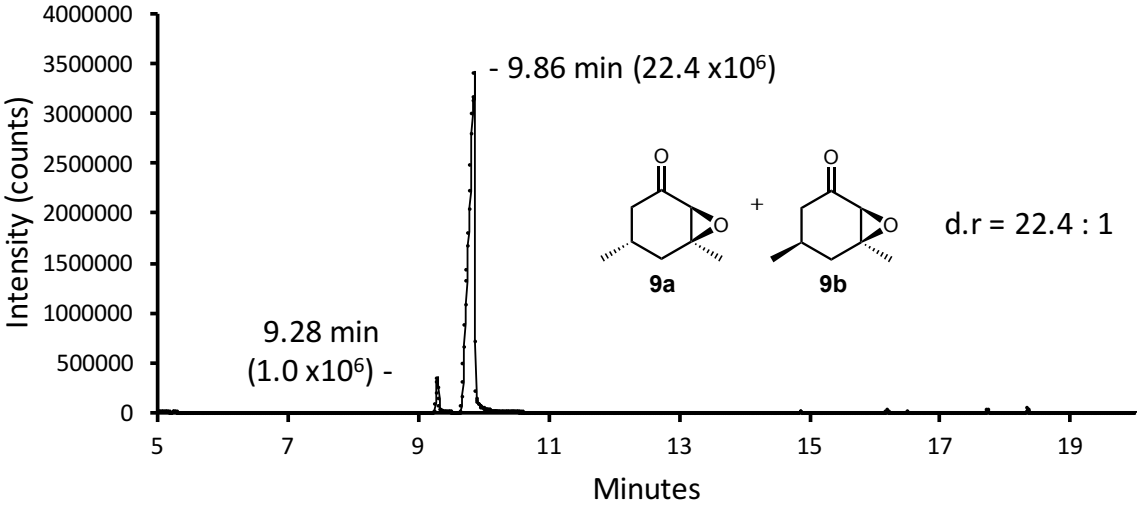
^{13}C NMR spectrum of isolated compound **9** in $CDCl_3$.



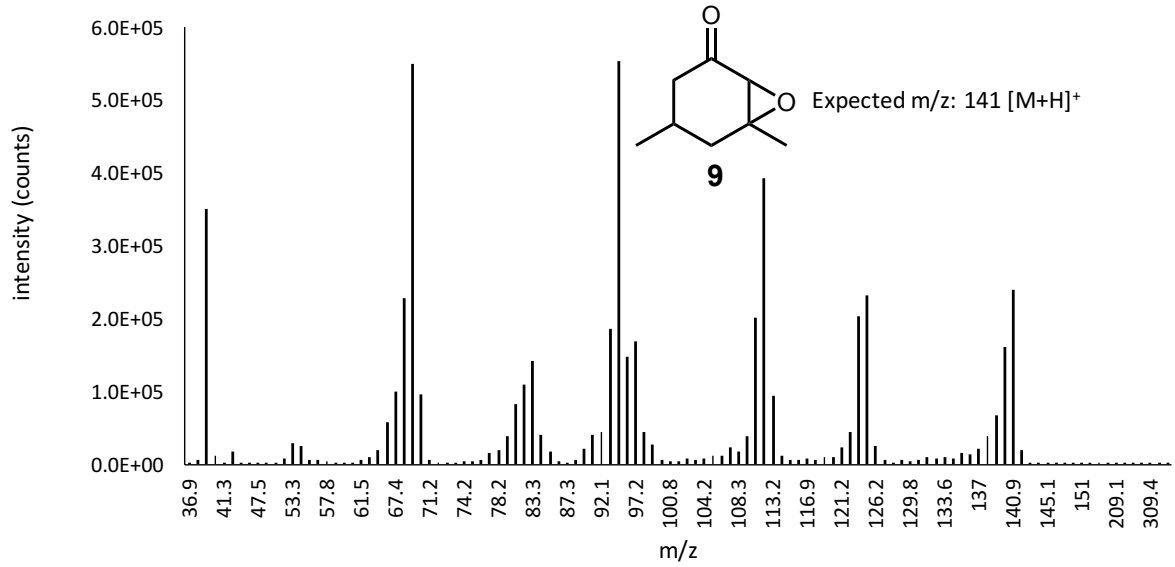
ATR IR spectrum for isolated compound **9**.



GC trace for the isolated product. (peak labels indicate retention time and peak area)



LR-MS fragmentation pattern for isolated compound **9** (identical spectra for both peaks, 9.2 min & 9.86 min).



Comparisons between batch and VFD processing

For both VFD and batch experiments, a NaOH solution (5 M, 0.7 mL, 3.5 mmol) was mixed with a H_2O_2 solution (30% aq. v/v, 1.2 mL, 17.5 mmol) over an ice bath and cooled for 15 minutes. This vial was then removed from ice and allowed to return to room temperature. Following this, compound **8** (0.5 mL, 3.5 mmol) was added to the reaction mixture. Stirring was then begun (7000 rpm in VFD, and 500 rpm for the magnetic stirrer bead batch control). After 15 minutes of reaction time $CDCl_3$ (≈1.5 mL) was used to extract the crude reaction mixture for NMR and GC-MS analysis. The experiment was performed in duplicate for each the batch and VFD processing. Conversions and d.r were determined by comparing the integration of the CHC<u>H</u>$_3$ in the ^{1}H NMR spectrum for the starting material and the product isomers (table S5). Representative spectra can be found on the following page. The E-factor calculations are shown below.

Batch

$$E_{(batch)} = \frac{0.14\ g}{0.368\ g} = 0.38$$

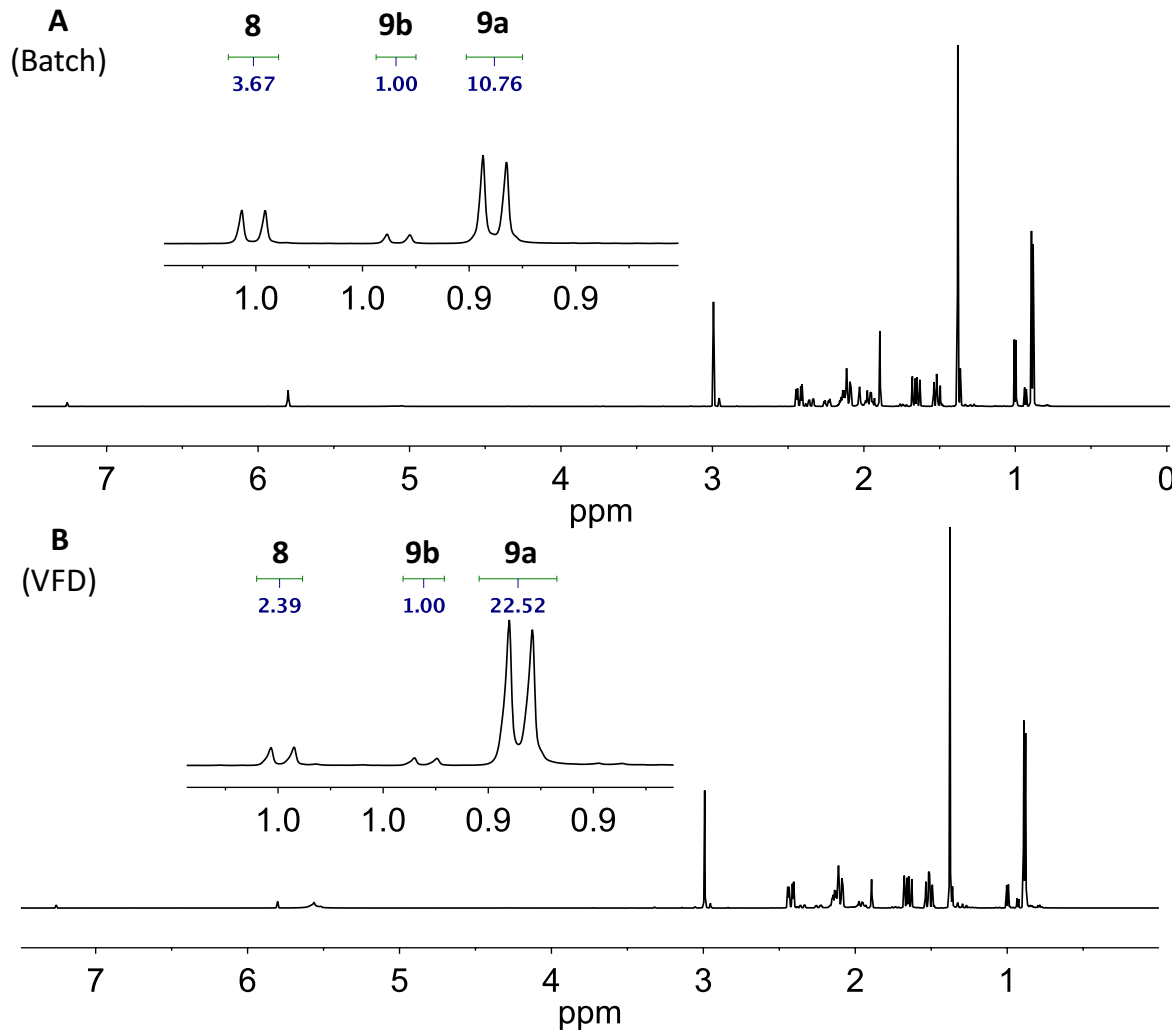
VFD

$$E_{(VFD)} = \frac{0.06\ g}{0.442\ g} = 0.14$$

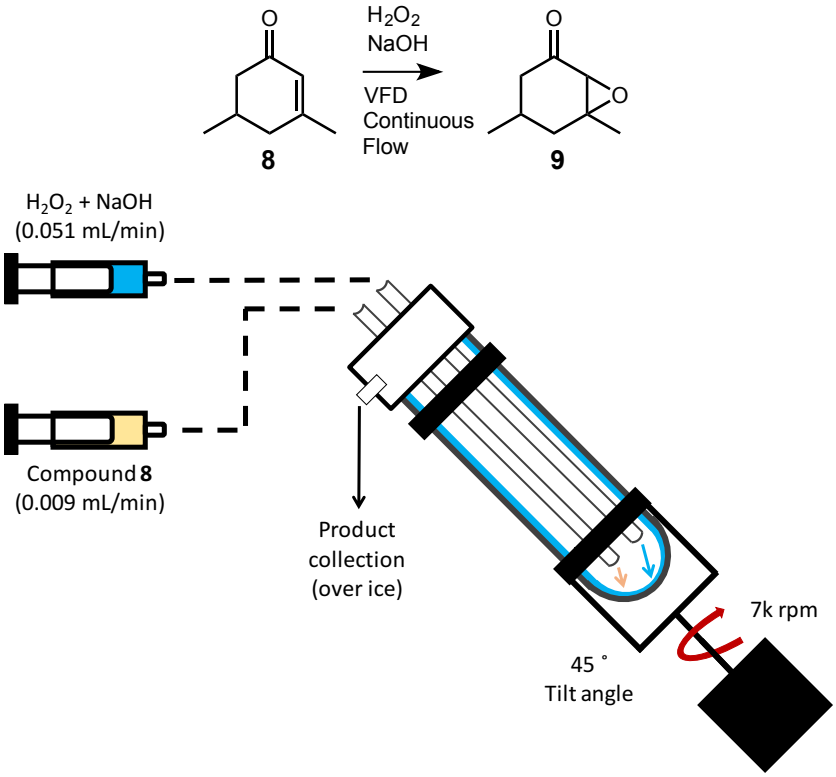
Table S5. ^{1}H NMR conversions to **9a**, diasteriomer ratio (d.r) and E-factor after **30 minutes** of reaction time for batch and VFD processing methods.

Entry		batch	VFD
1	Conversion (%)	75 (+/- 1.4)	90 (+/- 0.6)
2	d.r	11 : 1	22 : 1
3	E-Factor	0.170	0.213

Figure S11. Representative crude 1H NMR from A) Batch and B) VFD processing. The major and minor diasteriomers of compound **9** are denoted **9a** and **9b** respectively.



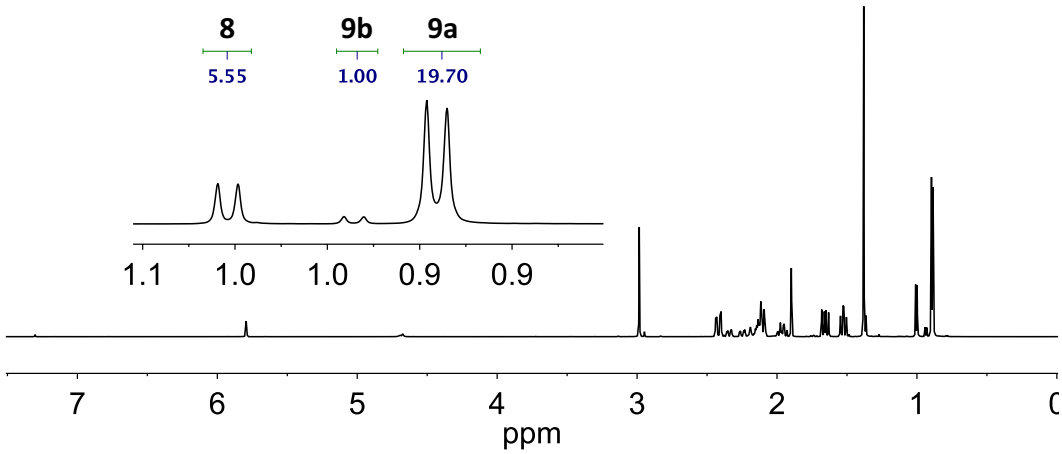
Continuous flow VFD synthesis of compound 9.



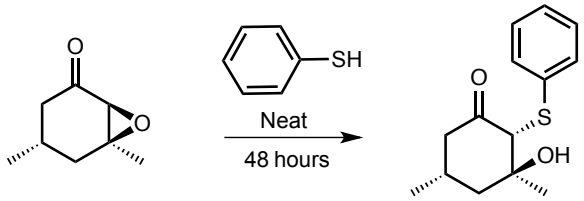
Two syringe pumps were used to pump the liquid reagents through the continuous flow set up. A solution of NaOH (5 M, 3.6 mL, 18.3 mmol) and aqueous H_2O_2 (30% v/v, 7.14 mL, 91.4 mmol) was prepared and cooled to 0 ˚C over ice for 15 minutes. This solution was then removed from ice and transferred into 1 of the 2 syringes. This syringe was set to deliver contents at 0.051 mL/min. The other syringe contained compound **8** (2 mL, 18.3 mmol) and was set to deliver contents at 0.009 mL/min. This resulted in a total flow rate of 0.06 mL/min, which relates to ≈ 30-minute residence time (time for the liquid delivered to the base of the rotating tube to leave the top). Once exiting from the vortex, the reaction mixture was collected over ice. The total reaction time was 3.5 hours, over which time the collection vessel was changed every 30 mins giving 7 fractions of reaction product. The organic material was extracted form these fractions with $CDCl_3$ and analyzed by ^{1}H-NMR upon collection. Averaging these fraction gave a conversion of 84 % and a d.r of 20 : 1. A representative ^{1}H NMR can be found on the following page. The E-Factor calculation for this experiment is shown below.

$$E = \frac{0.471\ g}{2.15\ g} = 0.219$$

^{1}H NMR spectrum of fraction 4 collected from the continuous flow processing



Structure determination of 9a (via crystallographic analysis of 10).



9
(major diasteriomer **9a** shown**)**

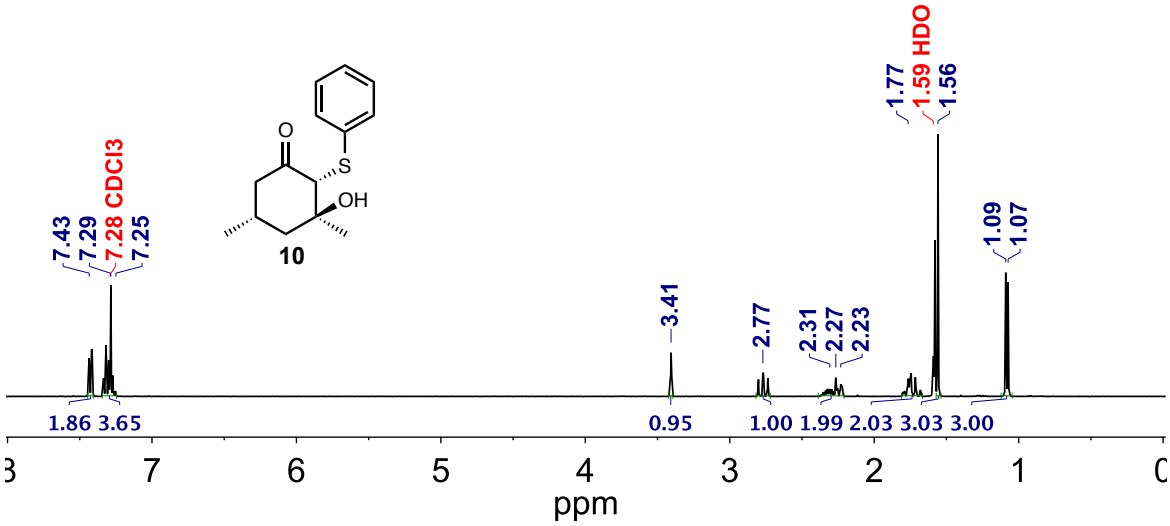
10
86 % yield

Epoxide **9** is an oil and standard NMR analysis was not sufficient for determining the relative stereochemistry for the major diastereomer **9a**. Epoxide **9** was therefore converted to crystalline derivative **10** using a regio- and stereospecific ring-opening reaction. The major diastereomer of **10** crystallised directly from the mixture and X-ray crystallographic analysis confirmed the relative stereochemistry. Protocol for conversion of **9** to **10**: Epoxide **9** (0.36 mmol, 50 µL) was reacted directly with thiophenol (0.36 mmol, 37 µL) (neat reaction, no solvent). Over 48 hours, the product crystallised directly from the mixture. The crystals were isolated by filtration and then washed with water (3 x 5 mL) and hexane (3 x 5 mL), providing compound **10** in 86% yield (76 mg, 0.307 mmol).

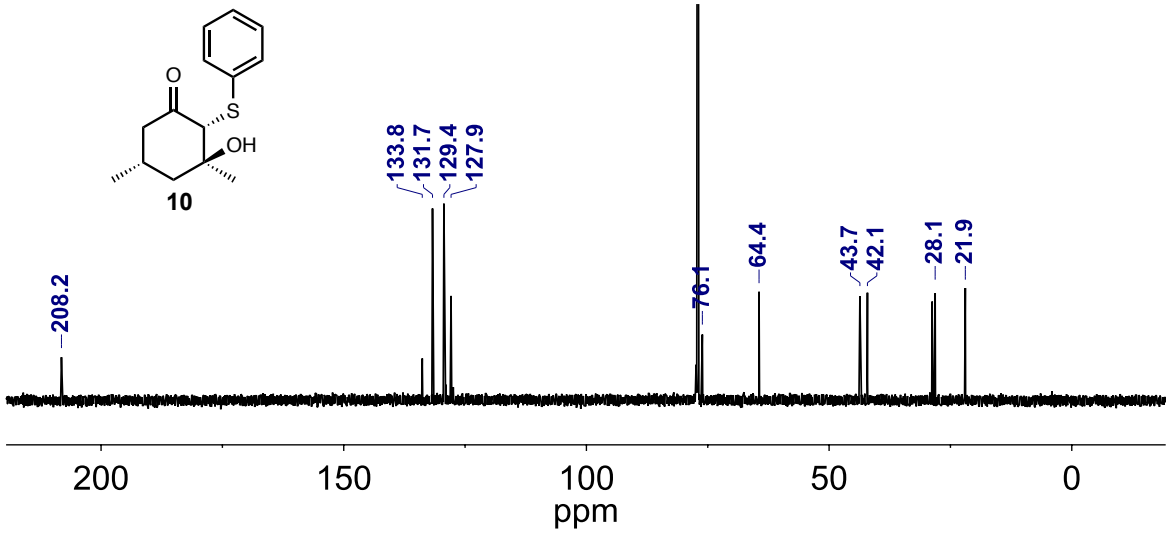
Melting point: 74 ˚C
^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.44 - 7.40 (2H, m, Ar), 7.34 - 7.24 (3H, m, Ar), 3.41 (1H, s, C<u>H</u>S), 2.77 (1H, t, J= 12.4 & 14 Hz, C<u>H</u>HC=O), 2.26-2.17 (1H, m, C<u>H</u>CH_3), 2.14 (1H, dd J = 14, 4.7 Hz, CH<u>H</u>C=O), 1.8-1.7 (3H, m, $C\underline{H_2}COH$), 1.56 (3H, s, $HOCC\underline{H_3}$), 1.08 (3H, d, 6.4 Hz, $HCC\underline{H_3}$)
^{13}C NMR (600 MHz, $CDCl_3$): δ_C = 208.2 (<u>C</u>=O), 133.8 (Ar 4˚), 131.7, 129.4, 127.9 (Ar, CHx3), 76.1 (<u>C</u>OH), 64.4 (<u>C</u>SPh), 43.7 ($\underline{C}H_2C$=O), 42.1 ($\underline{C}H_2COH$), 28.1 ($\underline{C}H_3COH$), 21.9 ($\underline{C}H_3CH$)
IR (υ_{max}, crystals ATR):3414, 2958, 2933, 1699, 1455, 1441, 1435, 1401, 1379, 1300, 1254, 1233, 1177, 1117, 1096, 1045, 1021, 948, 856, 819, 765, 741, 696

Crystal Data for 10 (CCDC 1552987): $C_{14}H_{18}O_2S$, *M* =250.34 g/mol, monoclinic, space group $P2_1/n$ (no. 14), *a* = 7.8477(5) Å, *b* = 7.9550(5) Å, *c* = 20.8582(11) Å, *β* = 96.801(2)°, *V* = 1292.98(13) Å^3, *Z* = 4, *T* = 100(2) K, µ(MoKα) = 0.238 mm^{-1}, *Dcalc* = 1.286 g/cm^3, 11046 reflections measured (5.36° ≤ 2Θ ≤ 53.46°), 2733 unique (R_{int} = 0.0211, R_{sigma} = 0.0188) which were used in all calculations. The final R_1 was 0.0283 (I > 2σ(I)) and wR_2 was 0.0755 (all data).

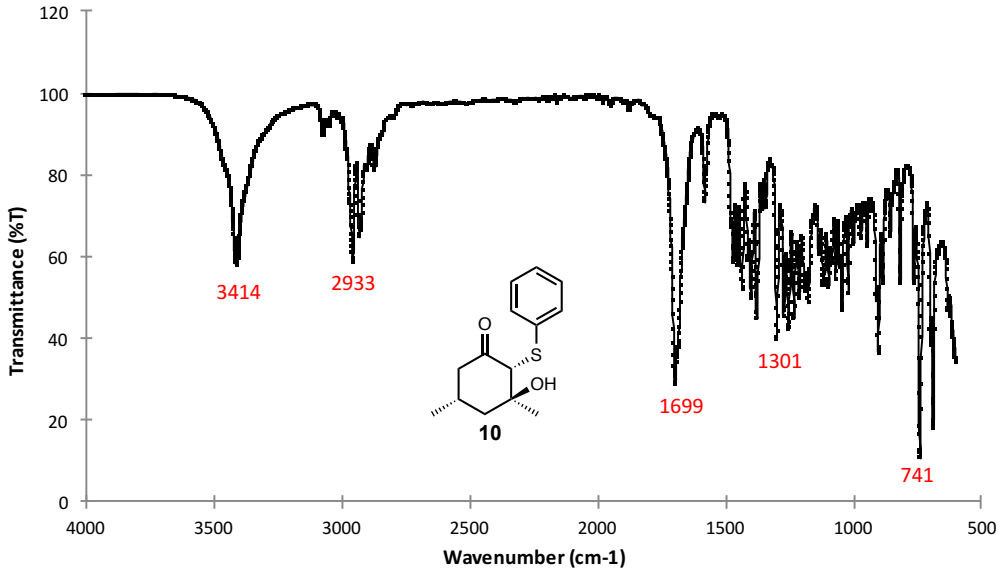
^{1}HNMR spectrum of compound **10**



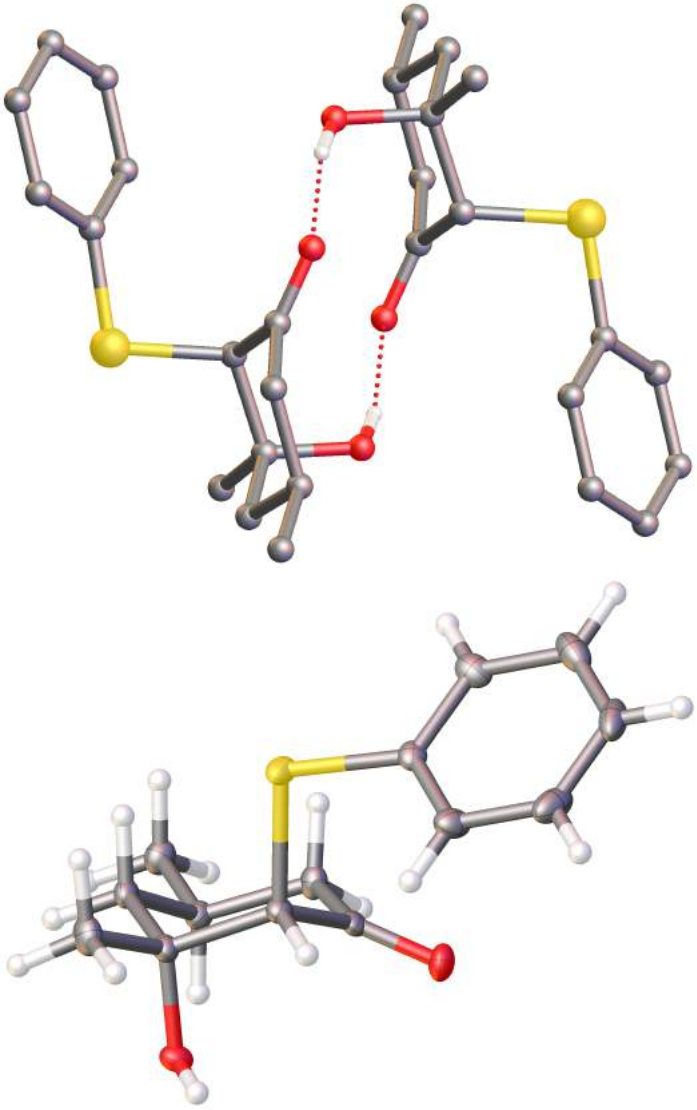
^{13}CNMR spectrum of compound **10**



I.R spectra of compound **10**



Crystal structure of compound **10** (shown as both the hydrogen bonding dimer and single molecule)

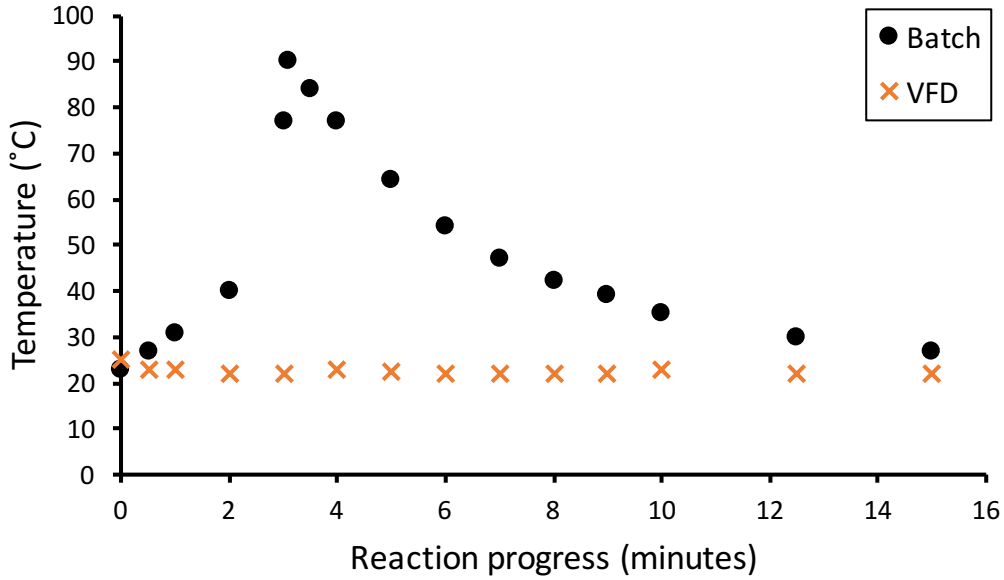


Thermal monitoring, comparing confined mode VFD vs batch processing.
For both VFD and batch experiments, a NaOH solution (5 M, 0.7 mL, 3.5 mmol) was mixed with a H_2O_2 solution (30% aq. v/v, 1.2 mL, 17.5 mmol) over an ice bath and cooled for 15 minutes. This vial was then removed from ice and allowed to return to room temperature. Following this, Compound **8** (0.5 mL, 3.5 mmol) was added to the reaction mixture. Stirring was then begun (7k rpm in VFD, and 500 rpm for the magnetic stirrer bead batch control). During this time, thermal imaging of the reaction mixture was performed at set intervals (Figure S12). After 15 minutes of reaction time $CDCl_3$ was used to extract the crude reaction mixture for NMR and GC-MS analysis. Interestingly, comparing the integration of the $CHC\underline{H_3}$ in the ^{1}H NMR spectrum for the starting material and the product isomers (table S6), it was still observed that the reaction progressed further in the VFD at 7k rpm compared to the batch sample in 15 minutes, despite not reaching temperatures over 23 ˚C.

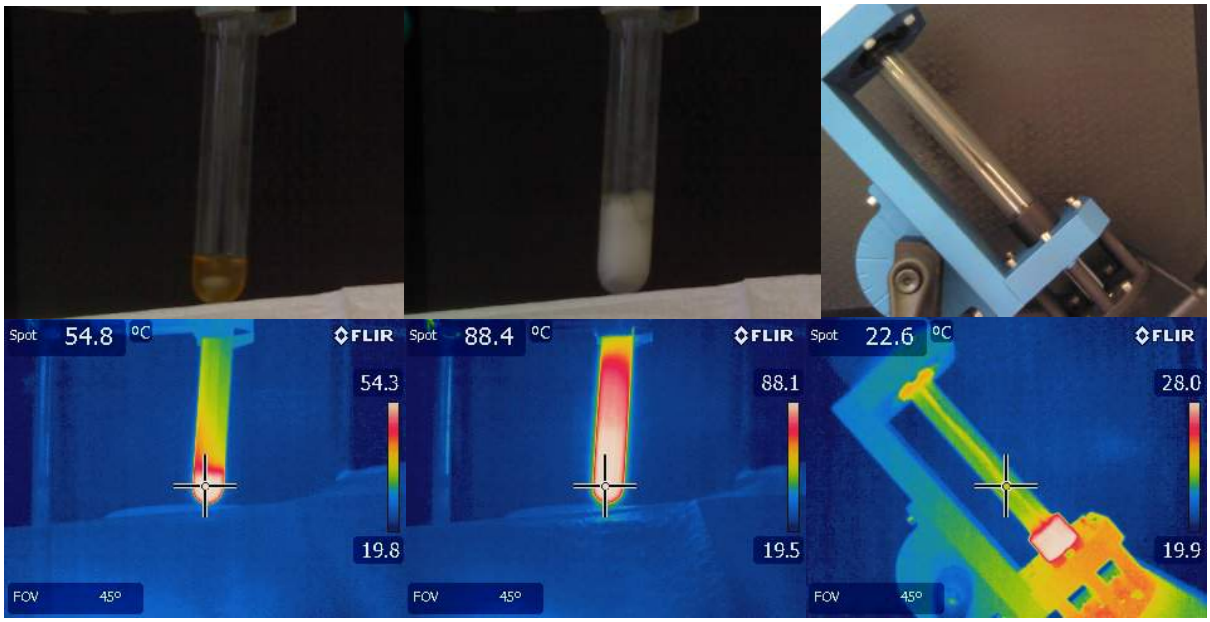
Table S6. ^{1}H NMR conversions and d.r. after the elapsed **15 minutes** of reaction time.

	Batch	VFD
conversion (%)	55.4	68.3
d.r. (%)	12.9 : 1	22 : 1

Figure S12. IR thermal monitoring of the reaction progress of the epoxidation of **8**, comparison of VFD and batch processing.



Representative photographs and corresponding IR thermal image for batch (500 rpm magnetically stirred) and VFD (7000 rpm).



NaOH recycling in the epoxidation of 8

A NaOH solution (5 M, 0.7 mL, 3.5 mmol) was mixed with a H_2O_2 solution (30% aq. v/v, 1.2 mL, 17.5 mmol) over an ice bath and cooled for 15 minutes. This was then removed from ice and returned to room temperature. Following this, compound **8** (0.5 mL, 3.5 mmol) was added to the reaction mixture, followed by operation at 7k rpm in the VFD for 30 minutes. Upon completion, the aqueous layer was separated by pipette, and the organic layer was collected for crude NMR analysis. The aqueous layer, containing the NaOH was then re-used, mixing with fresh H_2O_2 solution over ice, followed by the addition of compound **8**, and then operated in the VFD at 7k rpm for 30 mins. This was repeated for a total of 3 cycles, with the organic layer being analyzed by H-NMR for conversion. Because the addition of H_2O_2 dilutes the reaction mixture with each cycle, the conversion decreases under the same time frame. To ensure the same molar ratio of reagents, 0.7 mL of the aqueous layer was re-used each cycle, using reduced amounts of H_2O_2 and compound **8**. As can be seen in figure S13 below, the NaOH acts catalytically and remains active, with reduced conversion from the resulting dilution in each reaction. Another experiment was performed where the recycled aqueous layer (1.9 mL) was mixed with solid NaOH (160 mg, 4 mmol) and H_2O_2 (30% aq. v/v, 1.2 mL, 17.5 mmol) and compound **8** (0.5 mL, 3.5 mmol). This was repeated for a total of 3 cycles. In this recycling protocol, all reagent concentrations are the same as in the original process. It can be seen in figure S14 that

Figure S13. Recycling of aqueous layer. Also shown is the corresponding reduction in concentration of NaOH in the aqueous layer with each cycle, from the addition of aqueous H_2O_2.

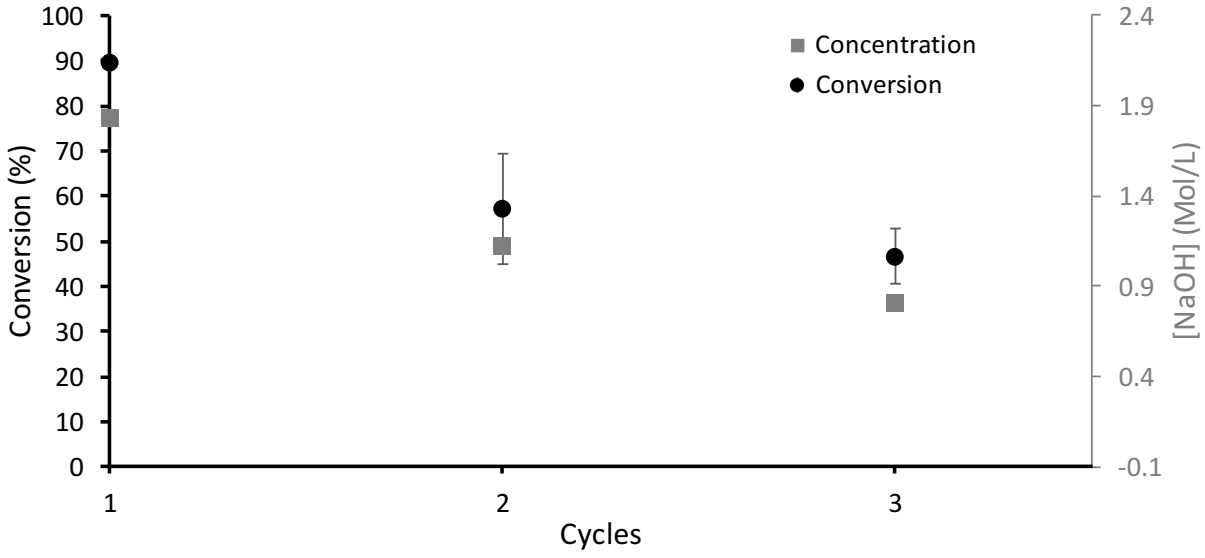


Figure S14. Recycling of aqueous layer, and running reactions under original concentrations of all reagents.