Supporting Information

Sustainable Continuous Catalytic Epoxidation of Biorenewable Terpene Feedstocks Using H_2O_2 as Oxidant in Flow Microreactors

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General experimental details

All reagents were purchased from commercial suppliers and microreactors were purchased from Little Things Factory. All solutions of alkene/catalyst and H_2O_2/Na_2SO_4 were prepared in air. Nuclear magnetic resonance spectra were recorded using either a Bruker Avance 300, 400 or 500 MHz spectrometer, or an Agilent Technologies 500 MHz spectrometer. All ^{13}C spectra were proton decoupled ($^{13}C\{^1H\}$) and all spectra run in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to residual solvent peaks. Representative NMR spectra used to analyse the mixtures of alkene/epoxide/diols produced in this study are shown below.

General procedure for carrying out alkene epoxidation reactions in flow

Two Little Things Factory (LTF) GmbH XXL-ST-04 microreactors were connected in series as shown below using PTFE 1/16 inch tubing. The sampling ports have valves which can be opened or closed to allow the reaction mixture to exit the reactor at these ports. Underneath the reactor channels are channels containing ethylene glycol that was heated to 50 °C and continuously pumped through the reactor using an external heating unit. Reactions were carried out by dissolving the $PW_4O_{24}[PTC]_3$ catalyst in the alkene substrate (1 equiv.) and loading this into a 24 mL Henke NORM-JECT syringe connected to the input of the first reactor by PTFE tubing. 30 wt% aqueous hydrogen peroxide (1.6 equiv.) with optional Na_2SO_4 (0.3 equiv.) dissolved in it was basified to pH 7.0 using 3 M NaOH and loaded into a second 24 mL Henke NORM-JECT syringe connected to the other input of the reactor by PTFE tubing. The syringes were pumped into the 50 °C heated reactor using Harvard apparatus PHD ULTRA syringe pumps at the desired flow rates and samples taken from after a combined 7.5 mL of reaction mixture had passed through the static mixer (to allow for steady state equilibration). ^{1}H NMR spectroscopic analysis of the top organic layer allowed conversions and selectivities to be calculated, with the organic layer then purified by column chromatography or vacuum distillation as required. This method of analysis was verified for limonene by analysing product compositions using an Agilent Technologies GCMS system (GC: 7890B, MS: 5977A, column: capillary nitroterephthalic acid-modified polyethylene glycol column of high polarity DB-FFAP 30 m × 0.250 mm × 0.25 µm).

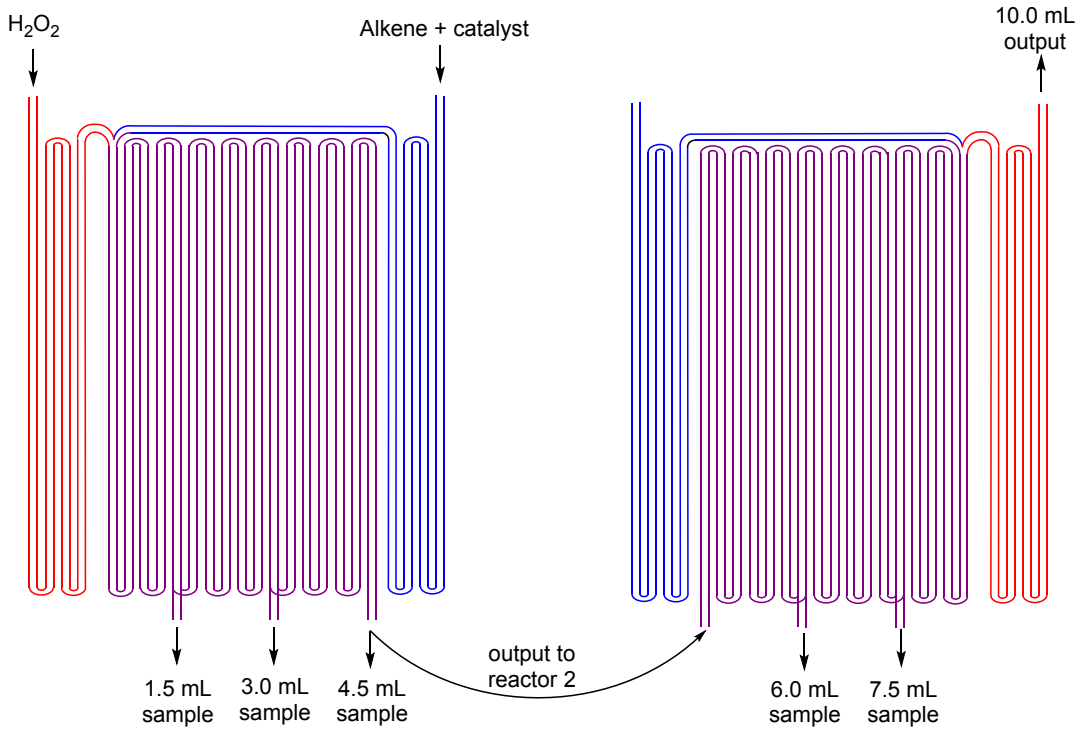


Figure SI1 Schematic diagram of flow microreactors used in alkene epoxidations. Red and blue sections correspond to heated channels whose flow streams are not mixed. Purple channels are combined flow streams which are heated and mixed in static mixing channels.

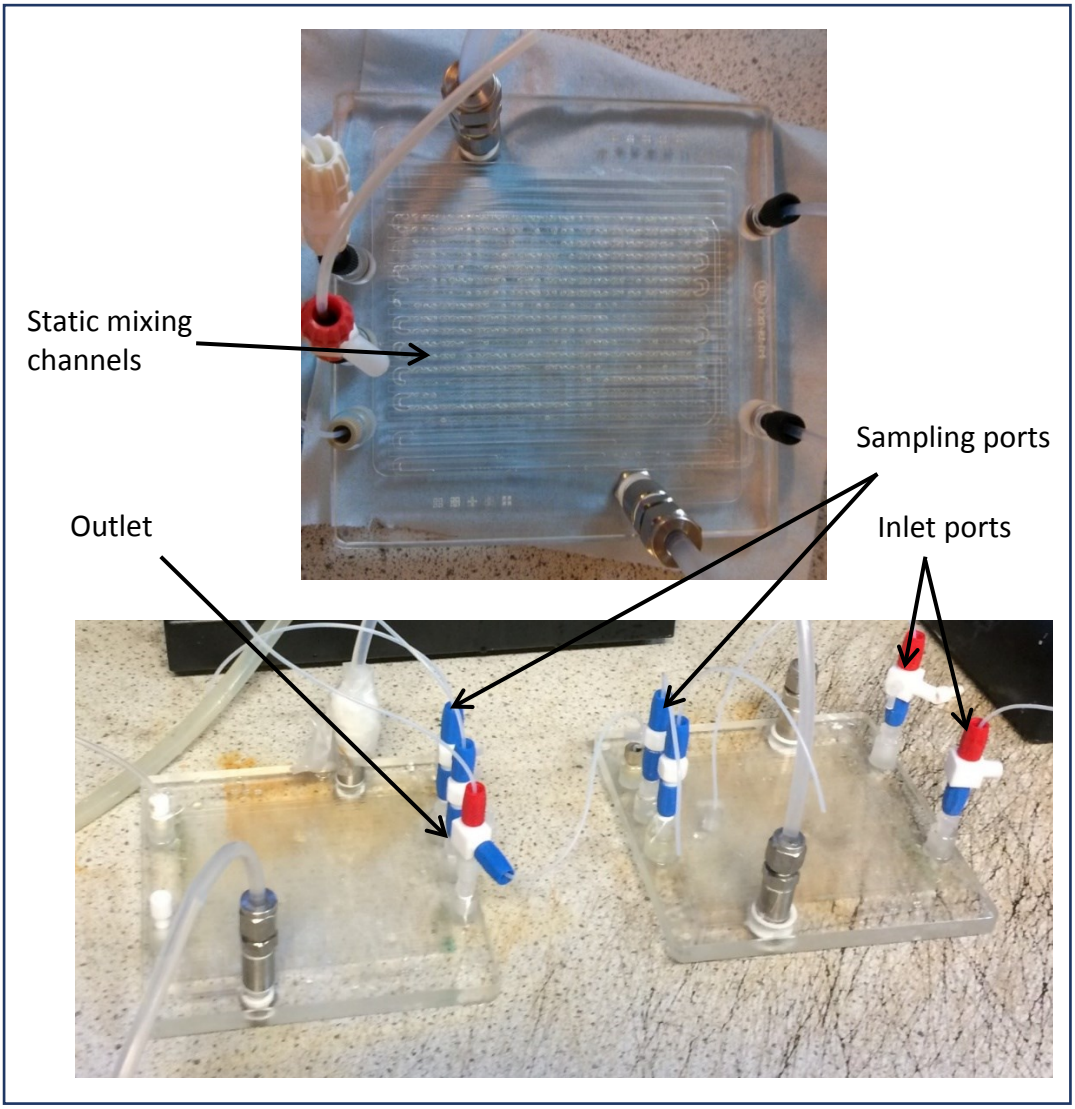


Figure SI2 (Top) Close-up of LTF flow microreactor showing static mixing channels; (bottom) LTF static mixer setup used for alkene epoxidation reactions showing inlet, outlet and sampling ports.

Optimisation of conditions for flow epoxidation of limonene

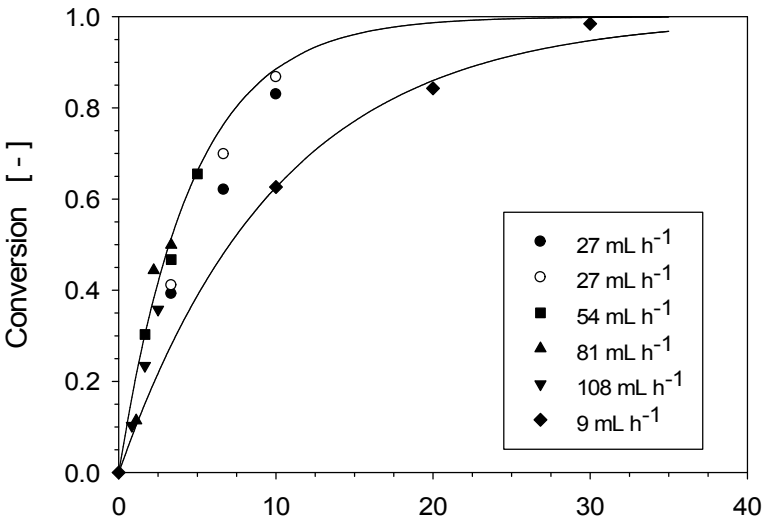


Figure SI3 Effect of flow rate on limonene conversion rates under biphasic VPTC/H_2O_2 flow conditions. T = 50 °C. 1 equiv. 30 mol% $H_2O_{2(aq)}$. c_{cat} = 1 mol%.

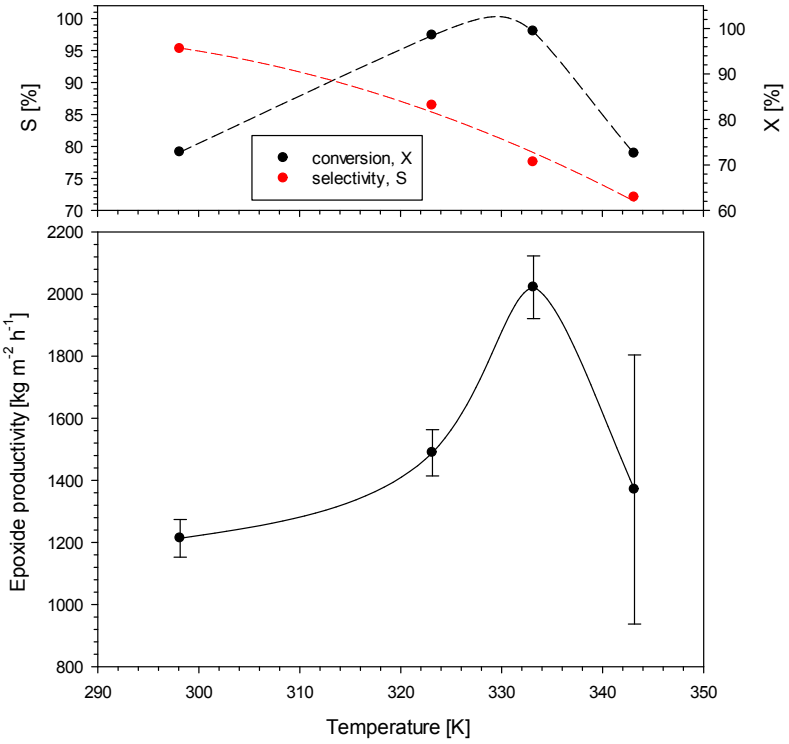


Figure SI4 Effect of temperature on limonene conversion rates and selectivities for formation of limonene 1,2-oxide. 1 equiv. 30 mol% $H_2O_{2(aq)}$. c_{cat} = 1 mol%. Flow-rate = 27 ml h^{-1}.

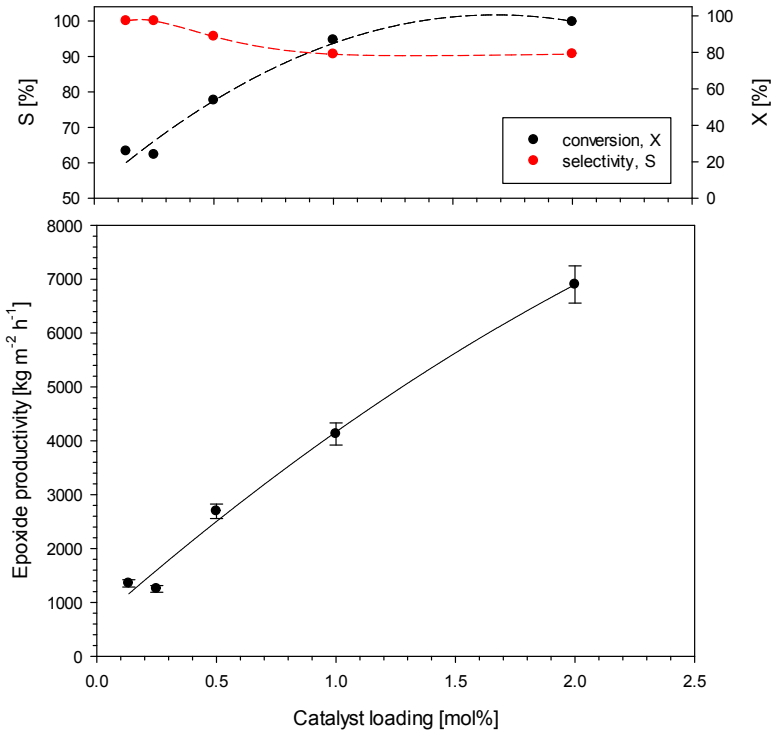


Figure SI5 Effect of catalyst loading on limonene conversion rates and selectivities for formation of limonene 1,2-oxide. 1 equiv. 30 mol% $H_2O_{2(aq)}$. T = 50 °C. Flow-rate = 27 mL h^{-1}.

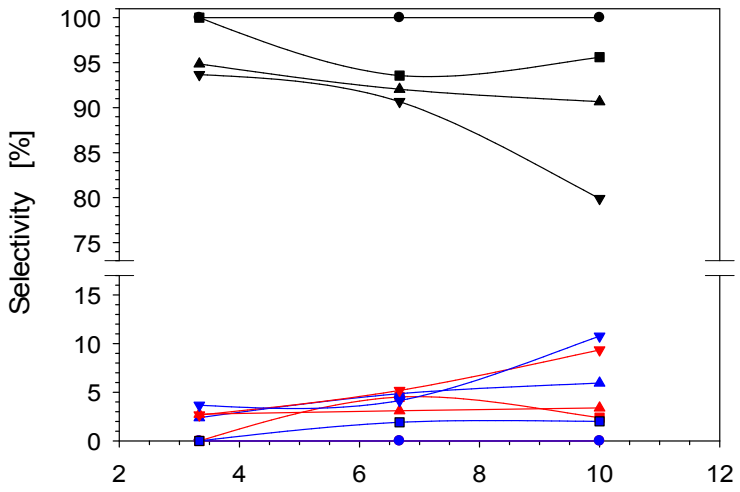


Figure SI6 Effect of catalyst loading on product distribution for flow epoxidation of limonene. 1 equiv. 30 mol% $H_2O_{2(aq)}$. T = 50 °C. Flow-rate = 27 mL h^{-1}. Legend: Black = epoxide, Red = 1,2-anti-diol, Blue = bis-epoxide, Circle = c_{cat} = 0.25 mol% , Square = c_{cat} = 0.50 mol%, Triangle Up = c_{cat} = 1.00 mol%, Triangle Down = c_{cat} = 2.00 mol%.

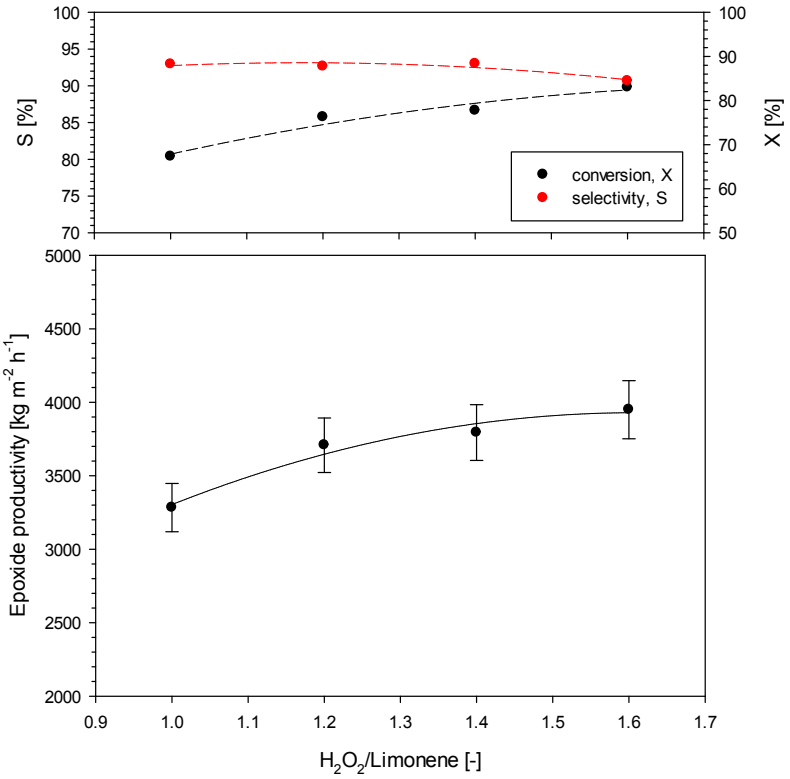
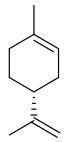
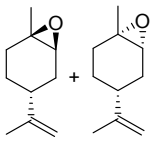
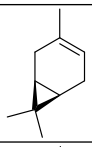
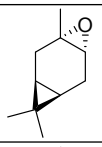
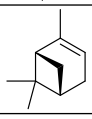
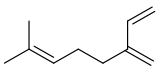
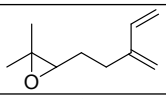
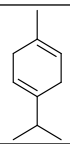
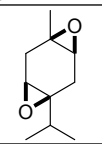
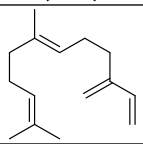
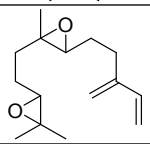
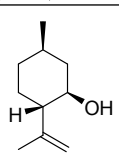
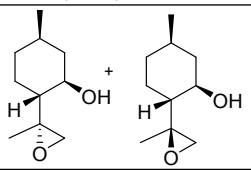
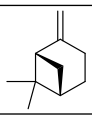
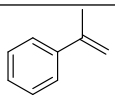
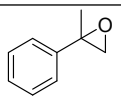
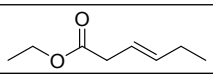
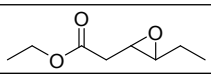
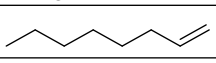
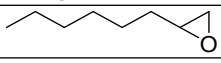


Figure SI7 Effect of H_2O_2 concentration on limonene conversion rates and selectivities for formation of limonene-1,2-oxide. 1 equiv. 30 mol% $H_2O_{2(aq)}$. c_{cat} = 1.00 mol%. Flow-rate = 27 mL h^{-1}.

Experimental details for carrying alkene epoxidation reactions in flow

Table SI1 Conditions used in flow epoxidation reactions of alkene substrates. [a]1.6 equivalents of H_2O_2 (pH 7.0) were used *for each* alkene bond present. [b]50 wt% H_2O_2 (pH 7.0) used instead of 30 wt% H_2O_2.

Substrate	Product	Catalyst loading (mol %)	Alkene flow rate (mL/hr)	H_2O_2 flow rate[a] (mL/hr)	Na_2SO_4 (mol%)	Temperature (°C)	Residence time (min.)	Conversion	Selectivity
		1 %	13.5 (1)	13.5 (1.6)	0%	50	16.7	89%	90%
		2%	13.5	13.5	0%	50	16.7	97%	98%
		3%	13.5	13.5	30%	50	16.7	95%	96%
		3%	13.5	13.5	0%	50	16.7	92%	97%
		1%	9	18	0%	50	16.7	100%	60%
		1%	9.5	13	0%	50	20	99%	72%
		2%	13.5	13.5	30%	50	16.7	92%	97%
		5%	34.6	19.4[a]	0%	75	1.65	55%	99%
		2%	10.1	16.9	0%	50	16.7	93%	98%
		2%	12	15	30%	50	16.7	55%	89%
		2%	13.5	13.5	0%	50	16.7	26%	100%
		2%	13.5	13.5	0%	50	16.7	<5%	-

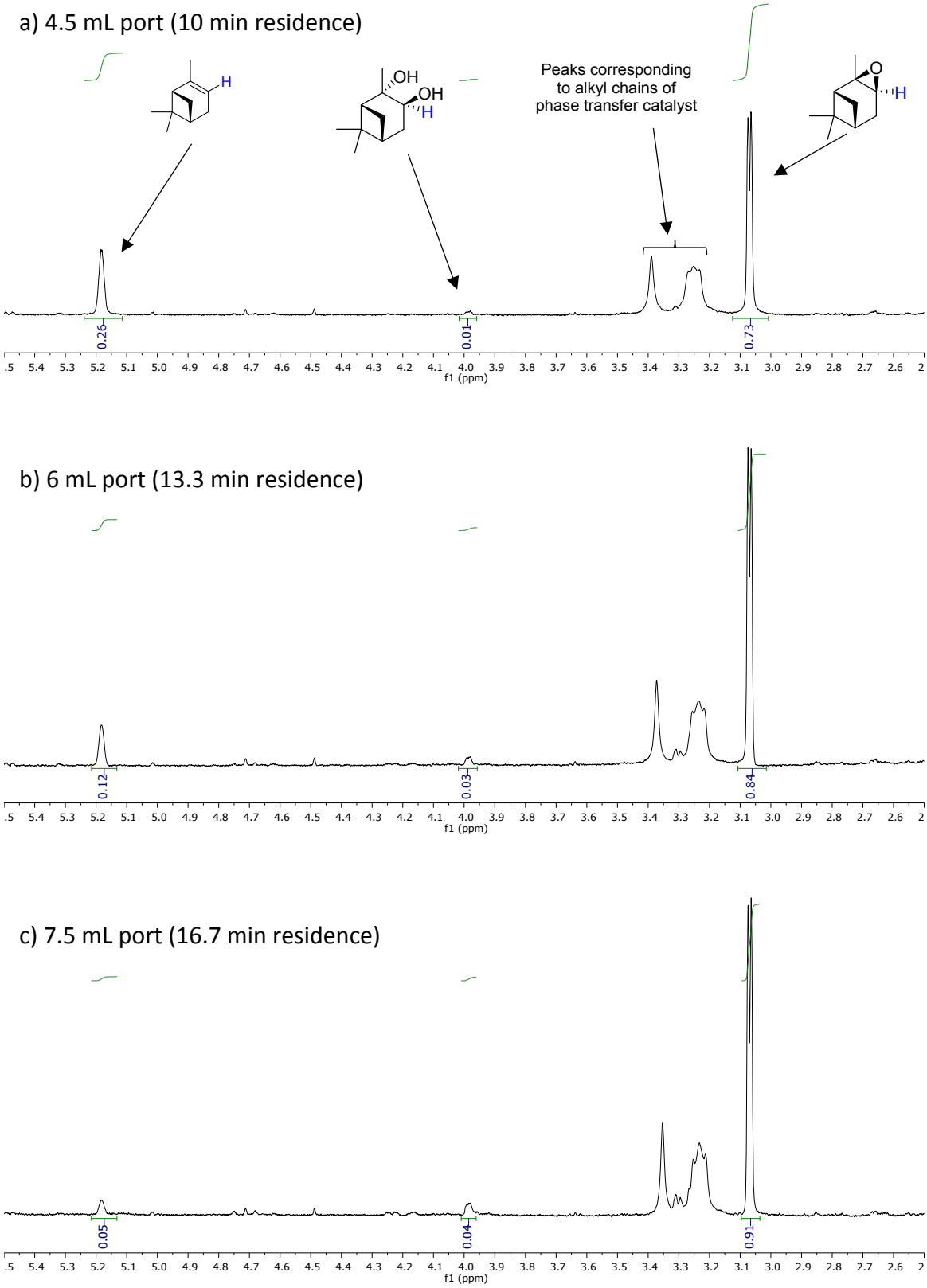


Figure SI8 Representative ^{1}H NMR spectra showing conversion of α-pinene to its epoxide and diol at different sampling ports of the flow reactor.

All of the integrals in Figure SI8 correspond to a single proton (shown in blue) from each of the products formed. Conversion is therefore calculated as the ratio of oxidation product integrals to the sum of oxidation products and remaining alkene integrals. Selectivity is calculated as the ratio of the epoxide integral to the total sum of the oxidation product integrals.

For example, for the 7.5 mL (16.7 min residence) sampling port the conversion is calculated as follows:

$$\frac{\int epoxide + \int diol}{\int epoxide + \int diol + \int alkene} = \frac{0.91 + 0.04}{0.91 + 0.04 + 0.05} = 95\%$$

A selectivity value is then calculated as follows:

$$\frac{\int epoxide}{\int epoxide + \int diol} = \frac{0.91}{0.91 + 0.04} = 96\%$$

The same calculation was carried out for the other sampling ports to give the conversions and selectivities for α-pinene oxide formation shown below in Figure SI9.

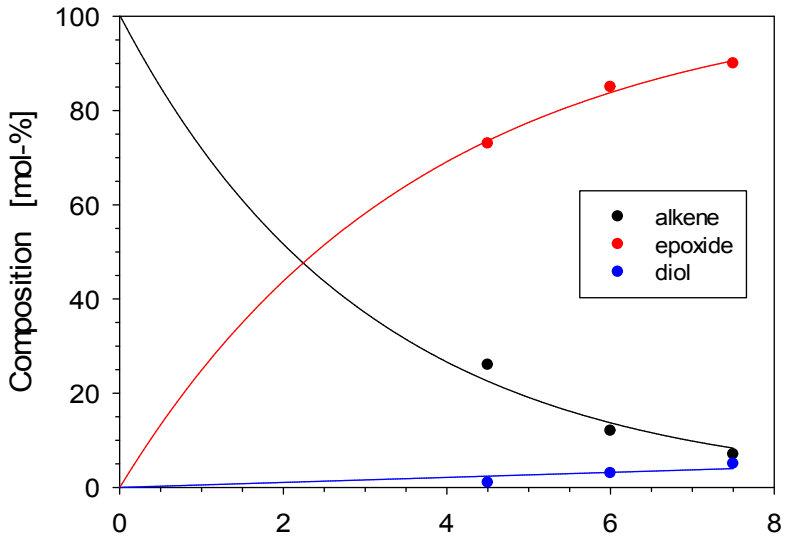
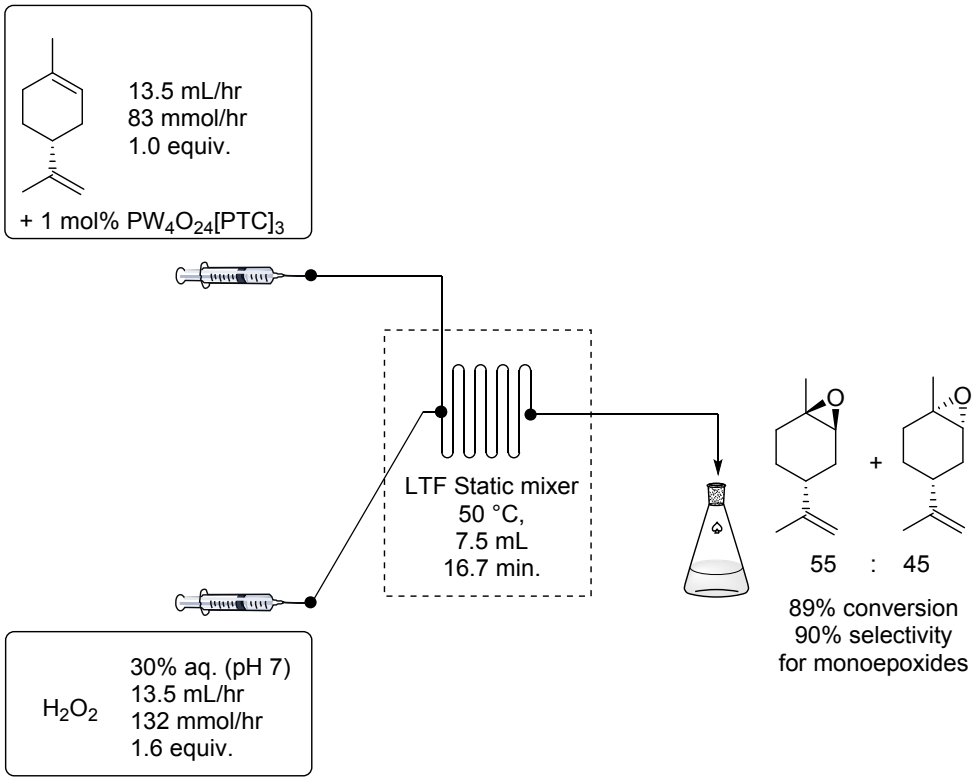


Figure SI9 Graph showing consumption of α-pinene and formation of epoxide/diol during flow epoxidation.

Experimental details and characterisation data for epoxides

Limonene 1,2-oxide 1a/1b



The general flow epoxidation procedure was followed using the conditions described above to produce limonene 1,2-oxide (55:45 diastereomeric ratio), which could be purified according to previously reported procedures (distillation under reduced pressure or silica flash column chromatography).[1]

Major isomer data

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.65 (m, 2H), 3.05 (s, 1H), 2.00 – 2.15 (m, 2H), 1.75 – 1.86 (m, 2H), 1.61 – 1.70 (m, 4 H), 1.47 – 1.53 (m, 1 H), 1.26 (s, 3H), 1.14 – 1.22 (m, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 149.2, 109.2, 60.7, 57.5, 36.4, 30.9, 28.8, 26.1, 24.4, 21.2.

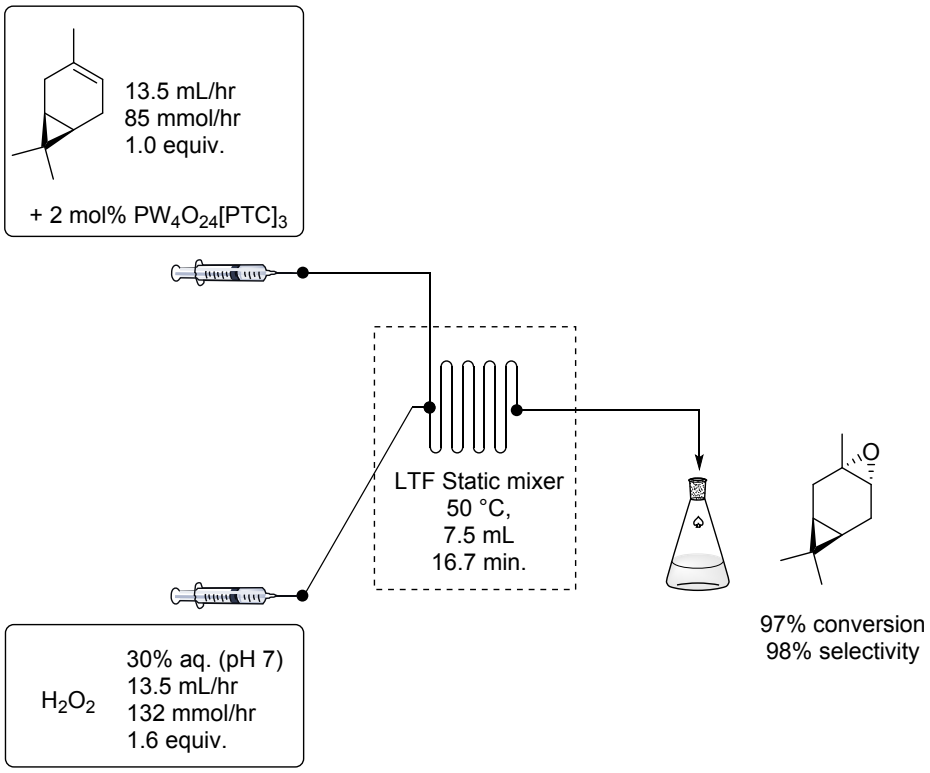
Minor isomer data

^{1}H NMR (101 MHz, $CDCl_3$): δ (ppm) 4.67 (m, 2H), 2.98 – 3.00 (m, 1H), 1.99 – 2.07 (m, 2H), 1.82 – 1.92 (m, 1H), 1.66 – 1.74 (m, 5 H), 1.35 – 1.41 (m, 2 H), 1.32 (s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 149.4, 109.2, 59.4, 57.7, 40.9, 30.9, 30.0, 24.5, 23.3, 20.4.

NMR spectra in accordance with previously reported data.[1]

3-Carene oxide 4



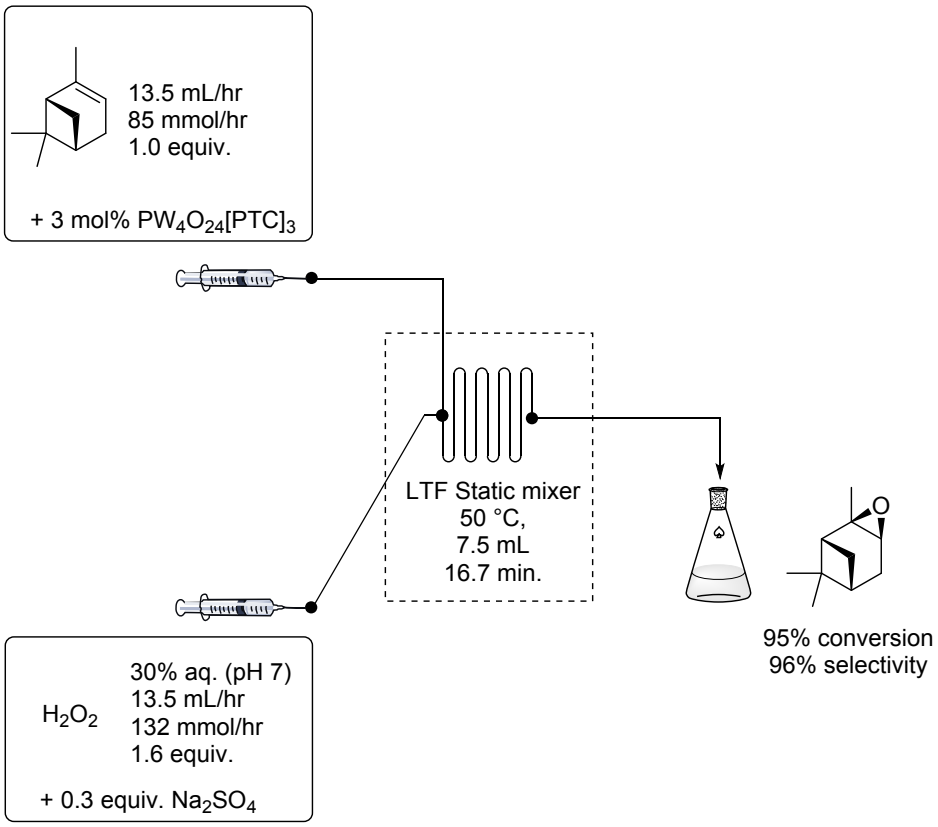
The general flow epoxidation procedure was followed using the conditions described above to produce 3-carene oxide, which could be purified according to previously reported procedures (distillation under reduced pressure or silica flash column chromatography).[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.82 (s, 1H), 2.31 - 2.26 (m, 1H), 2.16 – 2.11 (m, 1H), 1.65 – 1.61 (m, 1H), 1.50 – 1.46 (m, 1H), 1.25 (s, 3H), 1.00 (s, 3H), 0.72 (s, 3 H), 0.54 – 0.50 (m, 1H), 0.46 – 0.42 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) δ 58.4, 56.0, 27.9, 23.5, 23.2, 19.3, 19.4 16.1, 14.8, 14.0.

NMR spectra in accordance with previously reported data.[1]

α-Pinene oxide 5



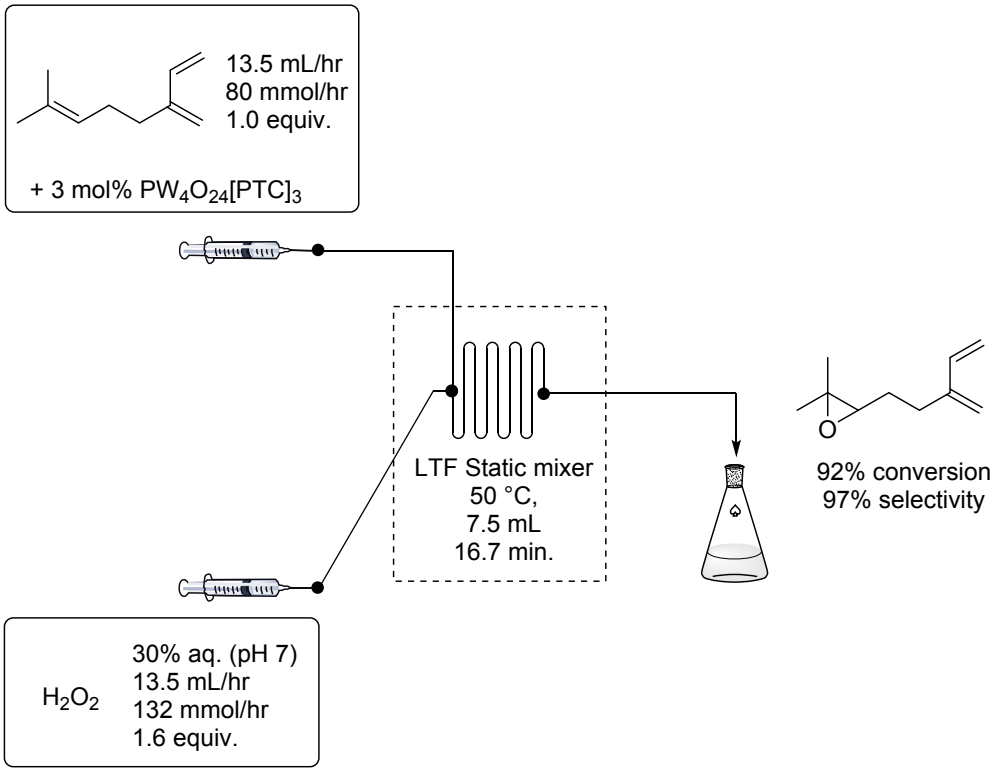
The general flow epoxidation procedure was followed using the conditions described above to produce α-pinene oxide, which could be purified according to previously reported procedures (distillation under reduced pressure or silica flash column chromatography).[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.07 (d, *J* = 7 Hz, 1H), 2.05 - 1.87 (m, 4H), 1.75 - 1.69 (m, 1H), 1.65 – 1.60 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 60.5, 57.1, 45.2, 40.7, 39.9, 27.8, 26.9, 26.0, 22.6, 20.3

NMR spectra in accordance with previously reported data.[1]

Myrcene 6,7-oxide 6



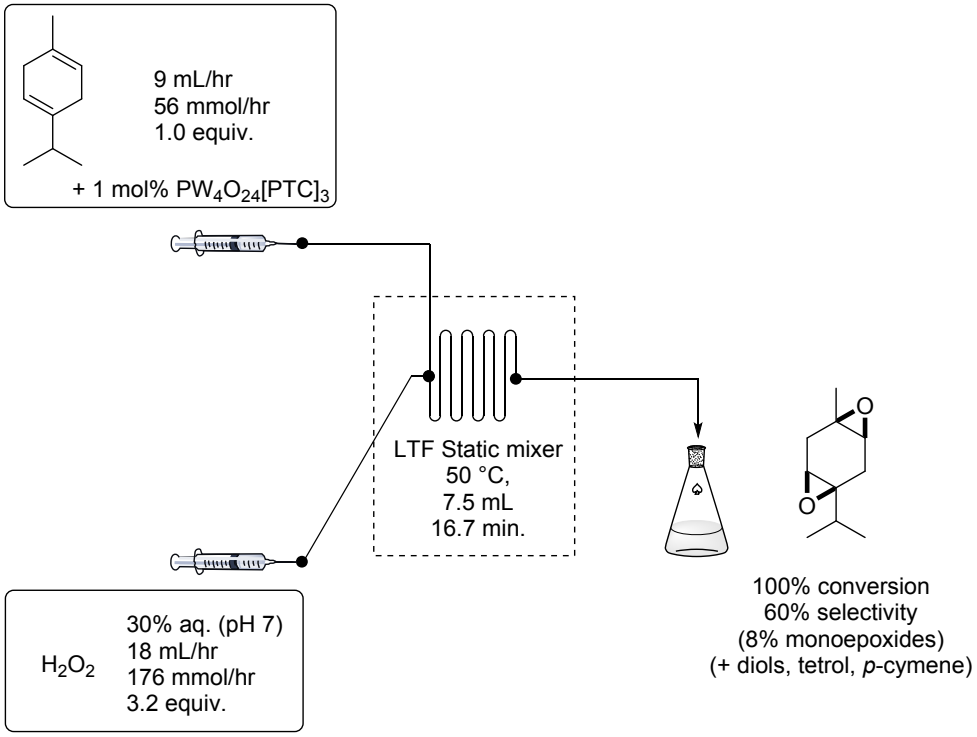
The general flow epoxidation procedure was followed using the conditions described above to produce myrcene 6,7-oxide, which could be purified according to previously reported procedures (silica flash column chromatography).[1]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.43 – 6.33 (m, 1H), 5.28 – 5.20 (d, *J* = 18 Hz, 1H), 5.11 - 5.01 (m, 3H), 2.76 (t, *J* = 7 Hz, 1H), 2.28 – 2.47 (m, 2H), 1.78 - 1.65 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) 145.5, 138.6, 116.3, 113.5, 64.2, 58.6, 28.2, 27.6, 25.0, 18.9.

NMR spectra in accordance with previously reported data.[1]

γ-Terpinene bis-epoxide 7



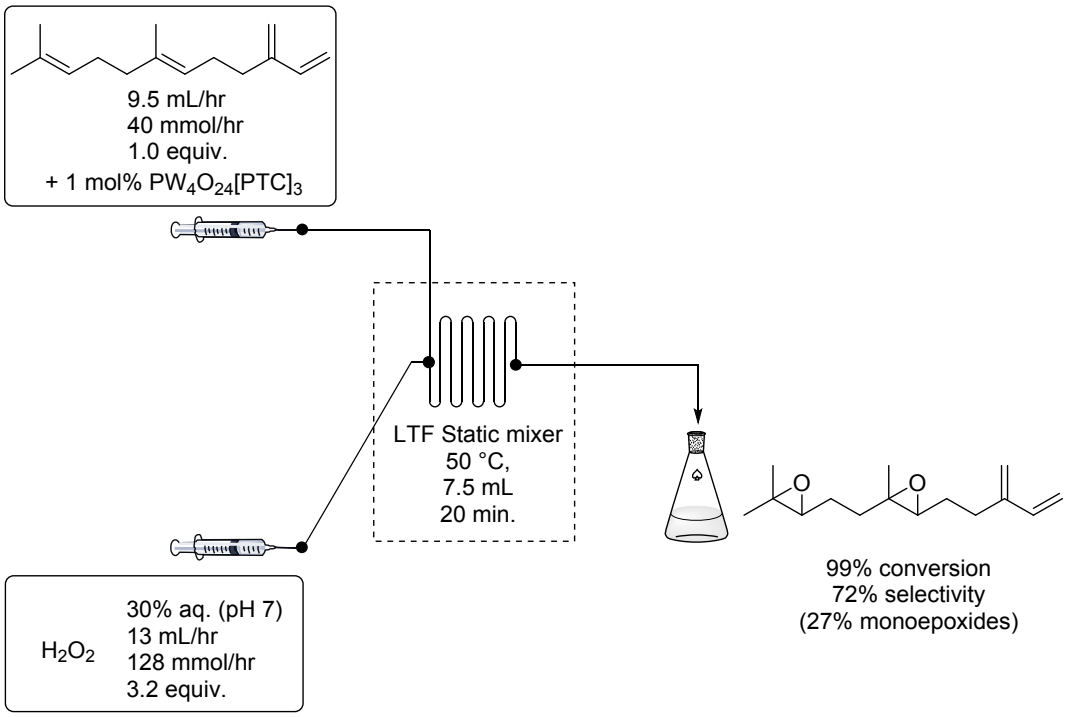
The general flow epoxidation procedure was followed using the conditions described above to produce γ-terpinene bis-epoxide, which could be purified according to previously reported procedures (silica flash column chromatography).[1]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.93 (d, *J* = 3 Hz, 1H), 2.85 (d, *J* = 4 Hz, 1H), 2.32 – 2.08 (m, 4H), 1.47 (m, 1H), 1.31 (s, 3H), 0.96 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 61.2, 57.5, 56.2, 55.4, 35.0, 30.2, 24.9, 23.5, 18.4, 17.4.

NMR spectra in accordance with previously reported data.[1]

Farnesene bis-epoxides 8



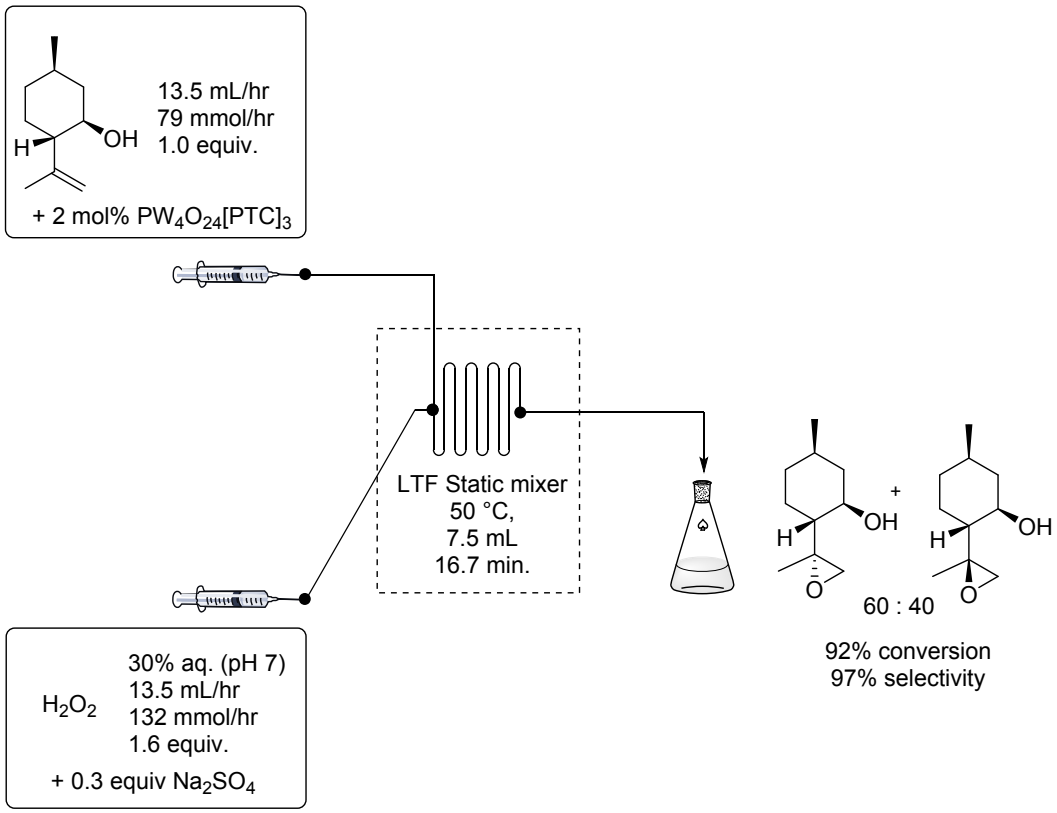
The general flow epoxidation procedure was followed using the conditions described above to produce farnesene bis-epoxide (mixture of *syn*- and *anti*-epoxides (50:50)), which could be purified according to previously reported procedures (silica flash column chromatography).[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.35 (dd, *J* = 18, 11 Hz, 1H), 5.21 (d, *J* = 18Hz, 1H), 5.11 – 4.95 (m, 3H), 2.75 (t, *J* = 6 Hz, 1H), 2.71 - 2.63 (m, 1H), 2.48 – 2.22 (m, 2H), 1.78 – 1.49 (m, 6H), 1.30 – 1.20 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.4, 138.6, 116.2, 113.5, 64.0, 63.9, 63.5, 63.0, 60.6, 60.5, 58.5, 58.4, 35.7, 35.3, 28.2, 27.3, 24.9, 24.8, 24.6, 18.7, 16.8, 16.6.

NMR spectra in accordance with previously reported data.[1]

Isopulegol epoxides 9a/9b



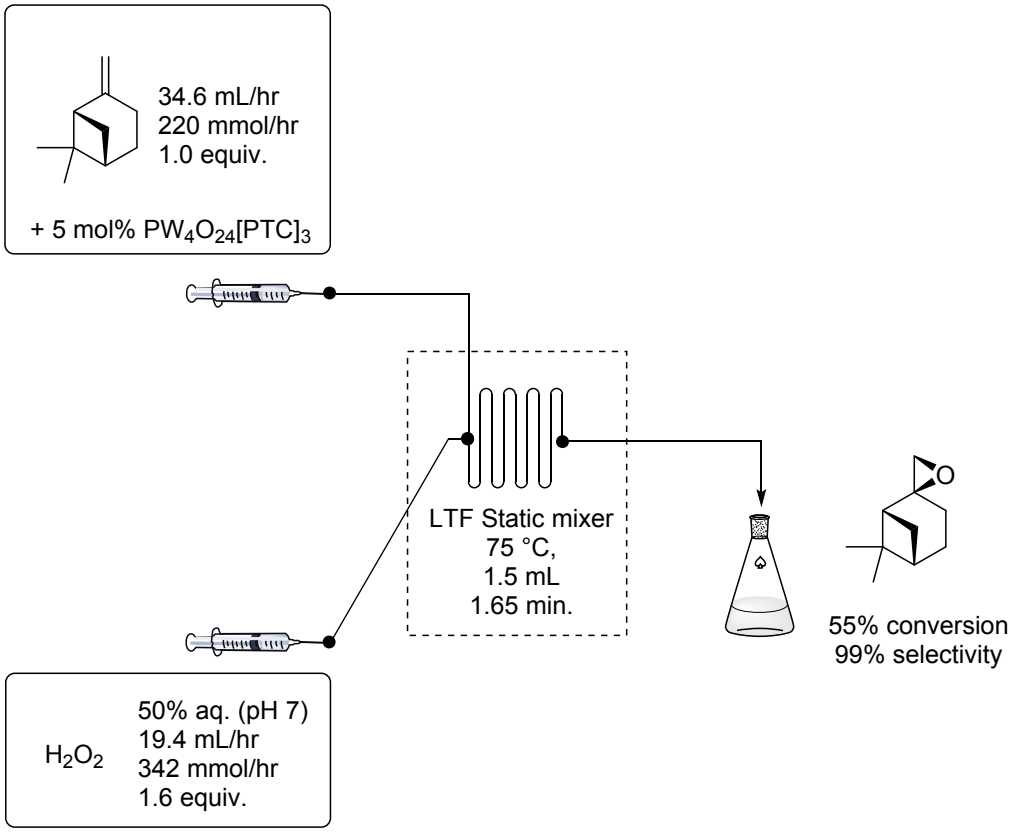
The general flow epoxidation procedure was followed using the conditions described above to produce isopulegol epoxide (mixture of diastereomers (60:40)), which could be purified according to previously reported procedures (silica flash column chromatography).[1]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.71 (td, *J* = 11, 4 Hz, 1H, major), 3.35 (d, *J* = 2 Hz, 1H, minor), 3.28 (td, *J* = 11, 5 Hz, 1H, minor), 2.92 (d, *J* = 4 Hz, 1H, minor), 2.81 (d, *J* = 2 Hz, 1H, major), 2.66 (d, *J* = 4 Hz, 1H, minor), 2.59 (d, *J* = 5 Hz, 1H, major), 2.53 (dq, *J* = 5, 1 Hz, 1H, major), 2.08 – 1.98 (m, 1H, major), 1.97 – 1.81 (m, 2H, minor), 1.75 – 1.61 (m, 3H, 2 x major and 1 x minor), 1.54 – 1.38 (m, 3H, 1 x major and 2 x minor), 1.36 (d, *J* = 1 Hz, 3H, minor), 1.31 (d, *J* = 1 Hz, 3H, major), 1.26 – 1.05 (m, 2H, 1 x major and 1 x minor) 1.03 – 0.80 (m, 11H, 6 x major and 5 x minor)

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 71.4, 70.6, 60.5, 59.3, 53.0, 52.3, 51.3, 49.0, 43.6, 42.9, 34.0, 34.0, 31.3, 31.0, 27.8, 22.2, 21.1, 17.0.

NMR spectra in accordance with previously reported data.[1]

β-Pinene oxide 10



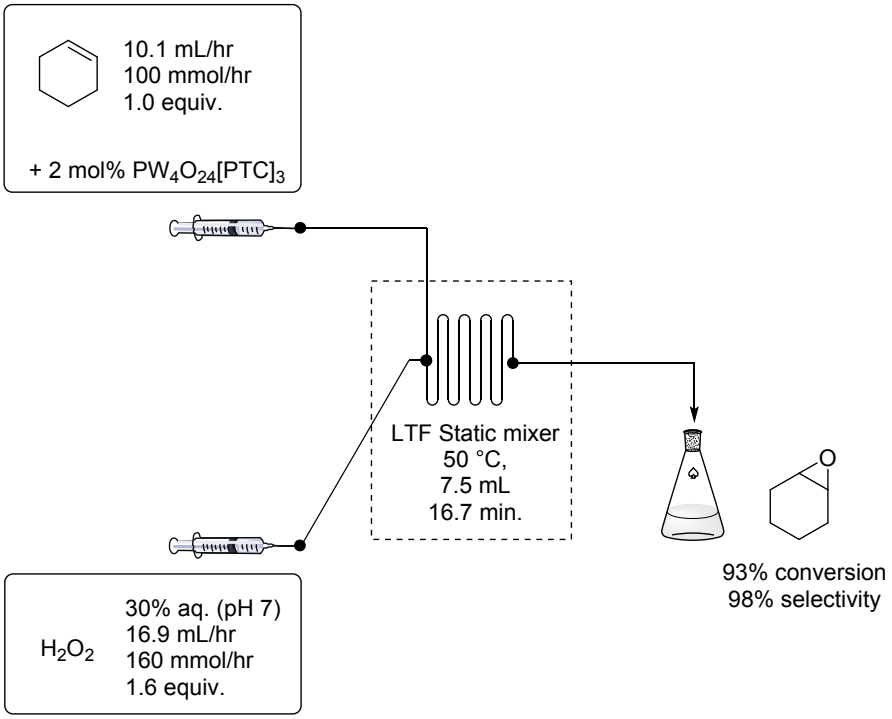
The general flow epoxidation procedure was followed using the conditions described above to produce β-pinene oxide, which could be purified according to previously reported procedures (distillation under reduced pressure or flash column chromatography on basic alumina).[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.74 (d, *J* = 5.0 Hz, 1H), 2.57 (d, *J* = 4.9 Hz, 1H), 2.31 – 2.09 (m, 2H), 2.00 – 1.60 (m, 5H), 1.47 (t, *J* = 5 Hz, 1H), 1.21 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 61.7, 56.6, 48.9, 40.9, 40.2, 26.2, 25.3, 23.7, 22.4, 21.3.

NMR spectra in accordance with previously reported data.[1]

Cyclohexene oxide 11



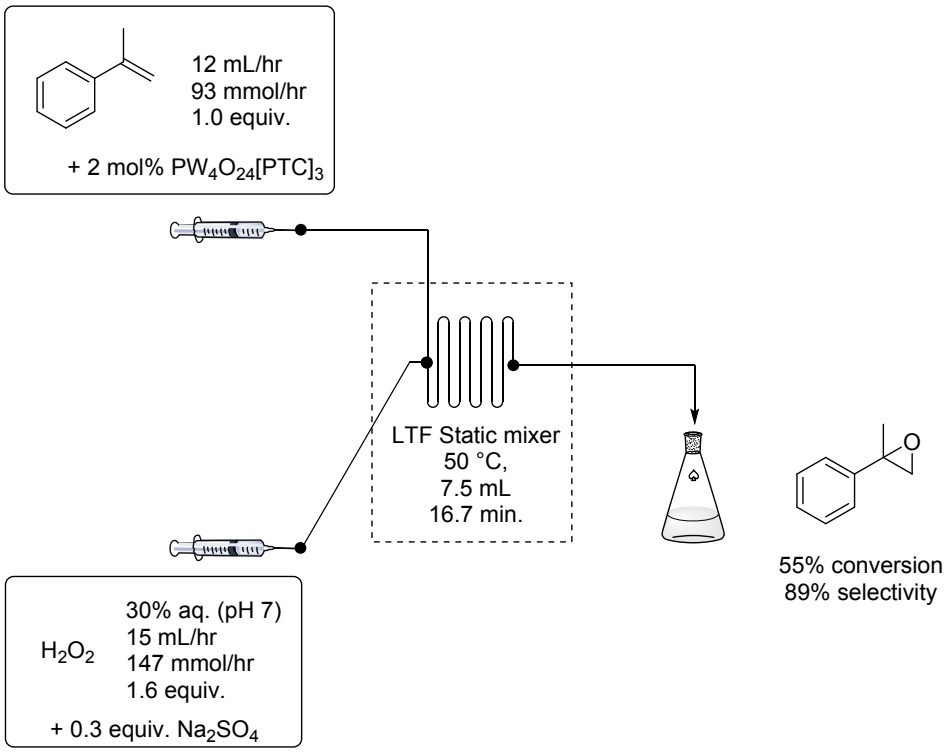
The general flow epoxidation procedure was followed using the conditions described above to produce cyclohexene oxide, which could be purified by passing through a plug of silica (0 to 10% ethyl acetate in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.12 (s, 2H), 1.94 (m, 2H), 1.86 – 1.74 (m, 2H), 1.48 – 1.36 (m, 2H), 1.29 – 1.17 (m, 2H).

^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 52.3, 24.6, 19.6

Spectra in accordance with previously reported data.[2]

α-Methylstyrene oxide 12



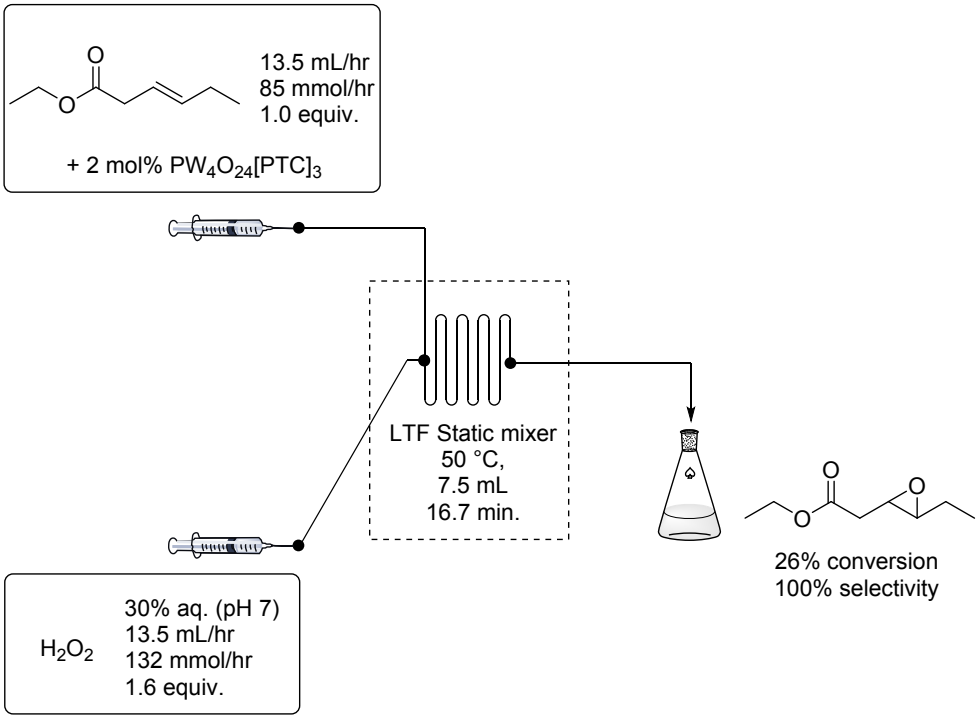
The general flow epoxidation procedure was followed using the conditions described above to produce α-methylstyrene oxide, which could be purified by passing through a plug of silica (0 to 10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 – 6.77 (m, 5H), 2.88 (d, *J* = 5 Hz, 1H), 2.71 (d, *J* = 5 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 141.3, 128.5, 127.6, 125.4, 57.2, 56.9, 22.0

Spectra in accordance with previously reported data.[3]

Ethyl 2-(3-ethyloxiran-2-yl)-acetate 13



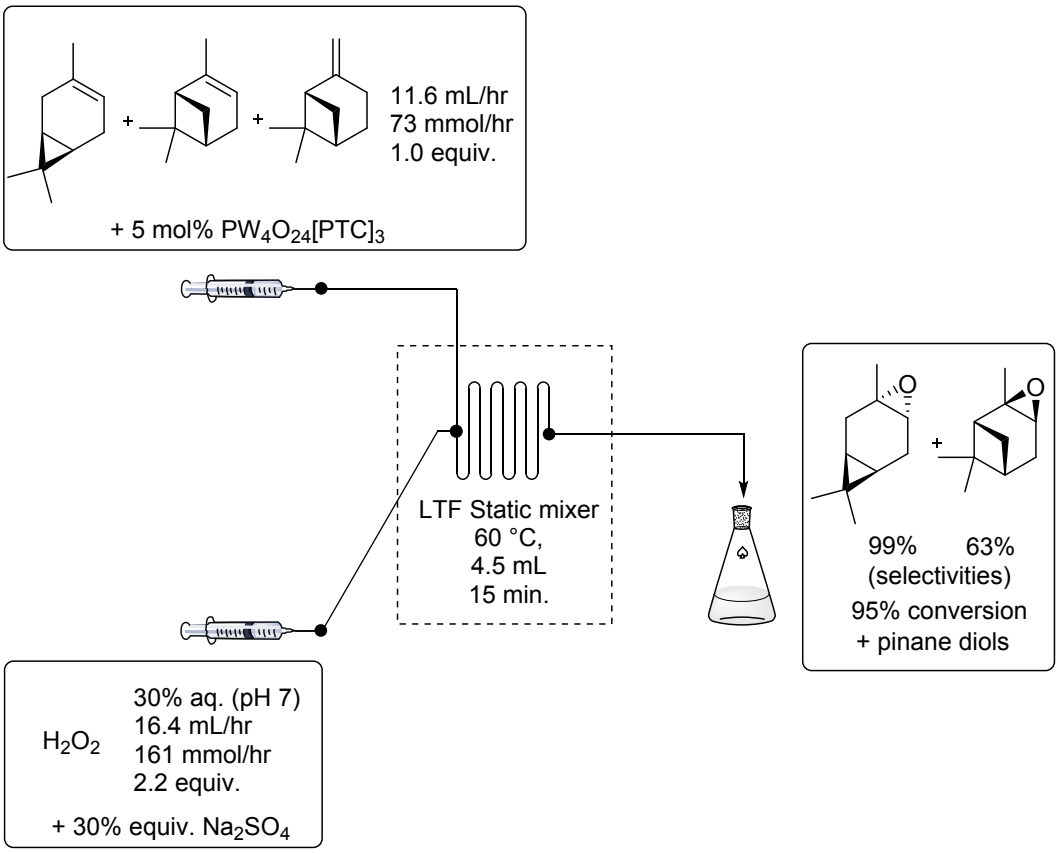
The general flow epoxidation procedure was followed using the conditions described above to produce ethyl 2-(3-ethyloxiran-2-yl)-acetate, which could be purified by silica flash column chromatography (20% ethyl acetate in petroleum ether, R_f = 0.40).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.17 (q, *J* = 7 Hz, 2H), 3.08 – 3.01 (m, 1H), 2.76 – 2.70 (m, 1H,), 2.59 (dd, *J* = 16, 6 Hz, 1H), 2.50 (dd, *J* = 16, 6 Hz, 1H), 1.66 – 1.54 (m, 2H), 1.27 (t, *J* = 7 Hz, 3H), 1.00 (t, *J* = 7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.6, 61.0, 59.8, 53.9, 38.0, 25.0, 14.3, 9.9.

Spectra in accordance with previously reported data.[4]

Crude Sulfate Turpentine (CST) flow epoxidation conditions



The general flow epoxidation procedure was followed using the conditions described above to produce a mixture of α-pinene oxide and 3-carene oxide (see representative ^{1}H NMR spectra shown below that were used to calculate conversions and selectivities relative to an internal standard of 1,3,5-trimethoxybenzene).

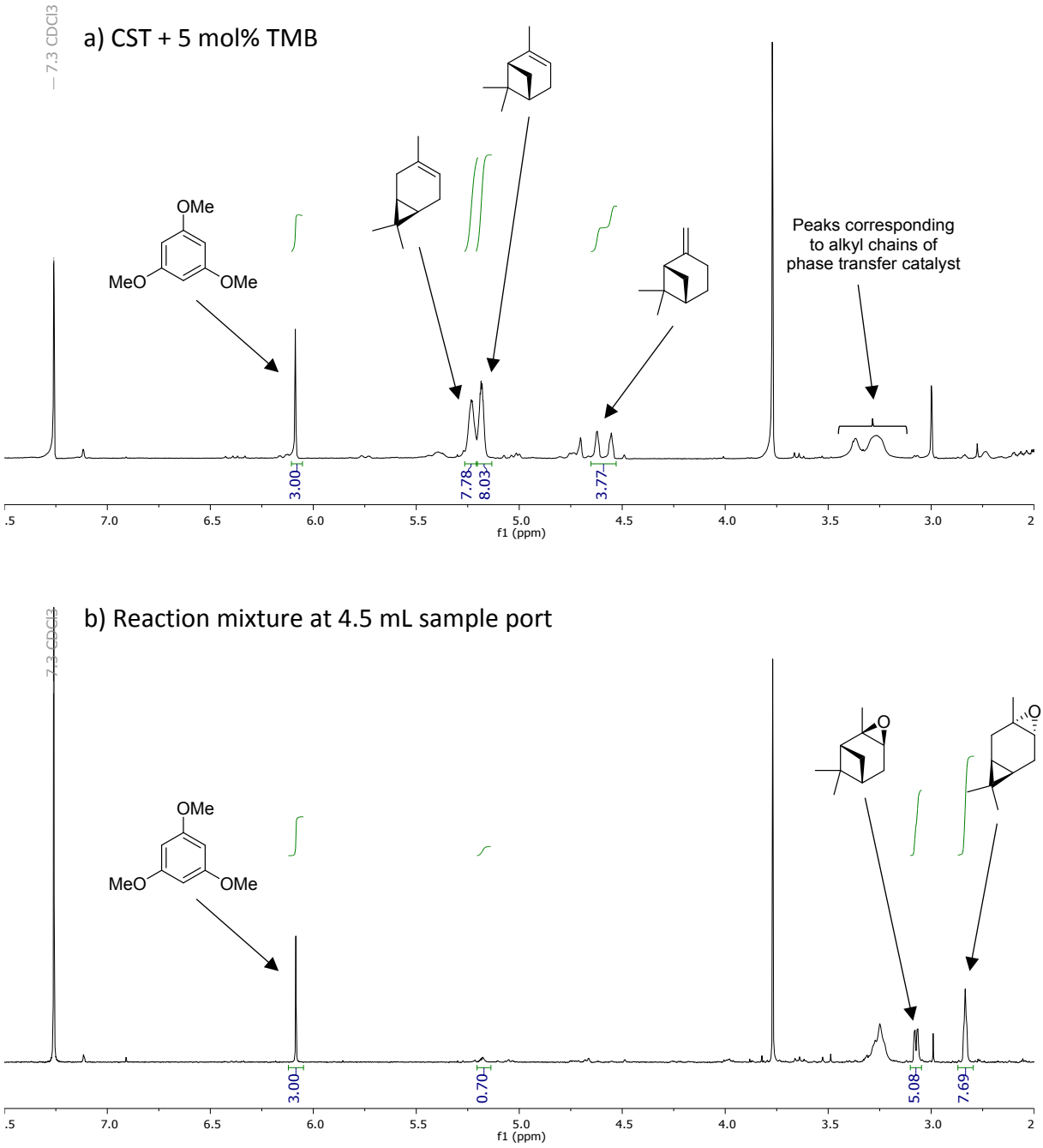


Figure SI10 Representative ^{1}H NMR spectra of: (a) CST containing 5 mol% 1,3,5-trimethoxybenzene (TMB): b) Sample of flow epoxidized CST collected at the 4.5 mL sampling port.

Yield of 3-carene oxide = $\frac{7.69}{7.78} = 99\%$

Yield of α-pinene oxide = $\frac{5.08}{8.03} = 63\%$

VPTC recycling in flow epoxidation of limonene

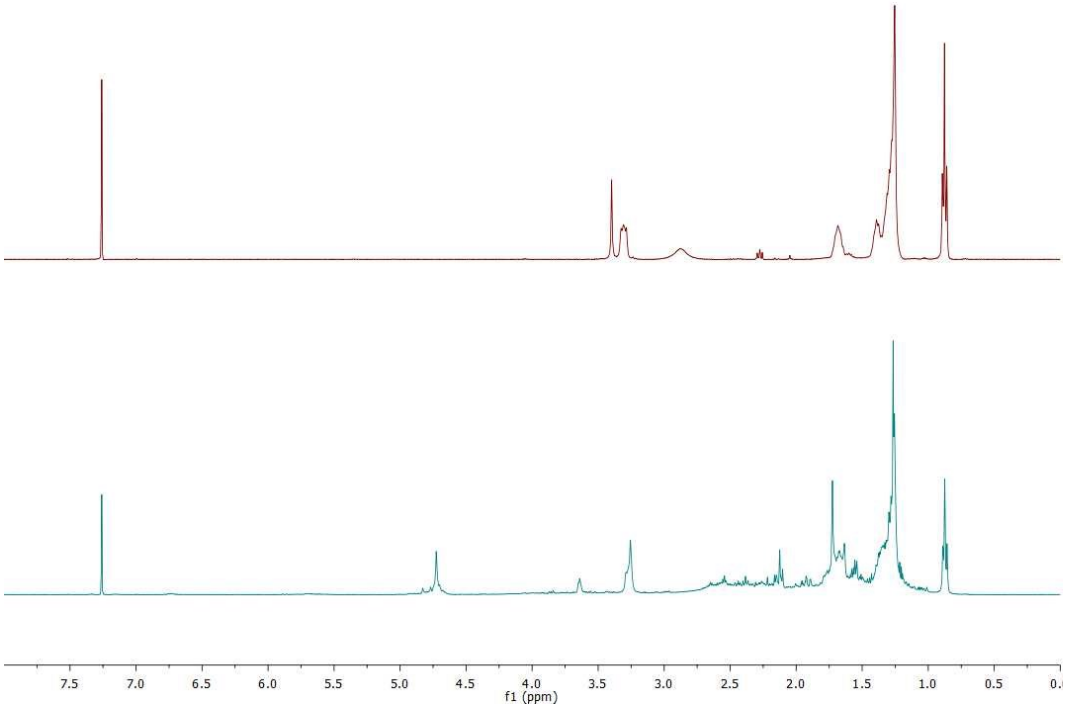


Figure SI11 ^{1}H NMR spectra of fresh VPTC used in initial flow epoxidation of limonene (top) and VPTC residue recovered after distillation of 1,2-limonene oxide from crude reaction output stream (bottom). Additional peaks are due to the presence of 1,2-limonene-diols formed via hydrolysis during distillation.

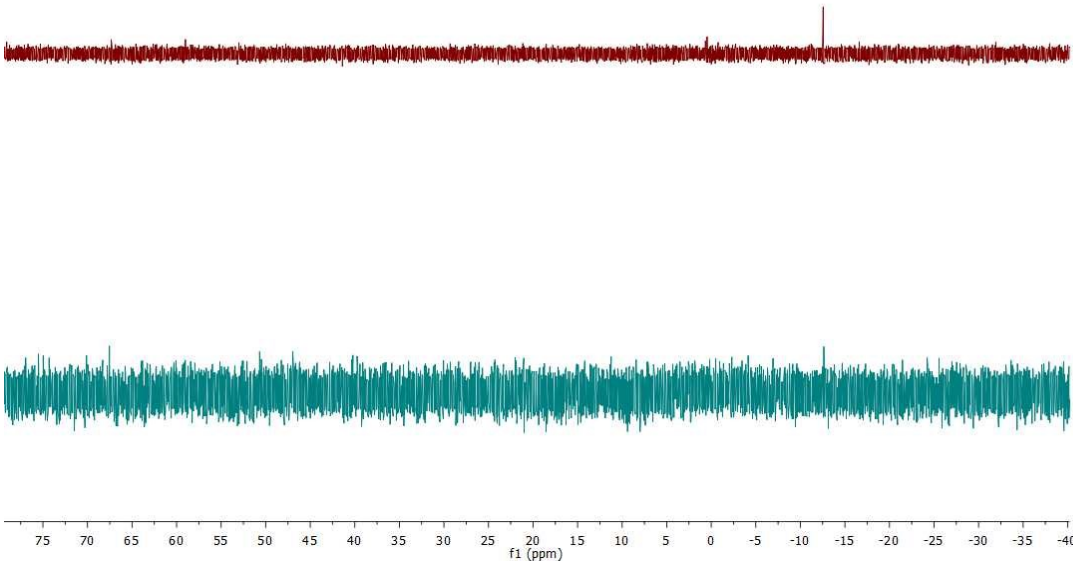


Figure SI12 ^{31}P NMR spectra of fresh VPTC used in initial flow epoxidation of limonene (top) and VPTC residue recovered after distillation of 1,2-limonene oxide from crude reaction output stream (bottom).

References

[1] W. B. Cunningham, J. D. Tibbetts, M. Hutchby, K. A. Maltby, M. G. Davidson, U. Hintermair, P. Plucinski and S. D. Bull, *Green Chem.*, 2020, **22**, 513 —524.
[2] P. Battioni, J. P. Renaud, J. F. Bartoli, M. Reina-Artiles, M. Fort and D. Mansuy, *J. Am. Chem. Soc.*, 1988, **110**, 8462–8470.
[3] H. Hachiya, Y. Kon, Y. Ono, K. Takumi, N. Sasagawa, Y. Ezaki and K. Sato, *Synthesis*, 2012, **44**, 1672–1678.
[4] J. Izquierdo, S. Rodríguez and F. V. González, *Org. Lett.*, 2011, **13**, 3856–3859.