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SUPPLEMENTARY INFORMATION

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$FINO_2$ initiates ferroptosis through GPX4 inactivation and iron oxidation

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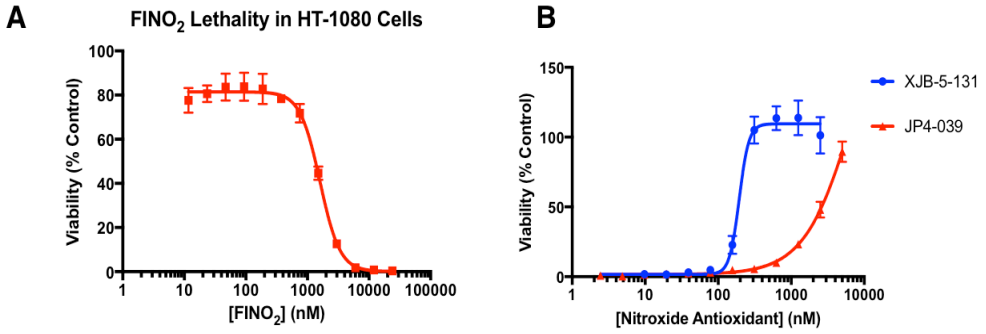
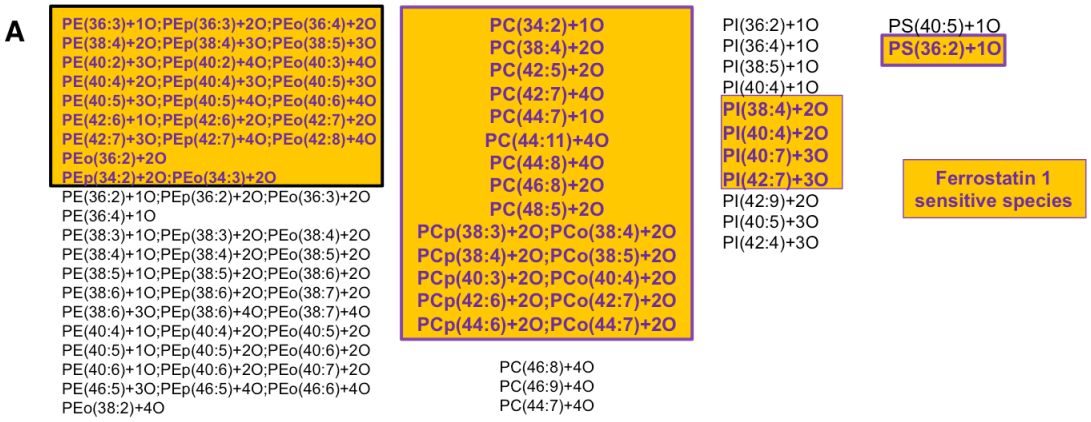
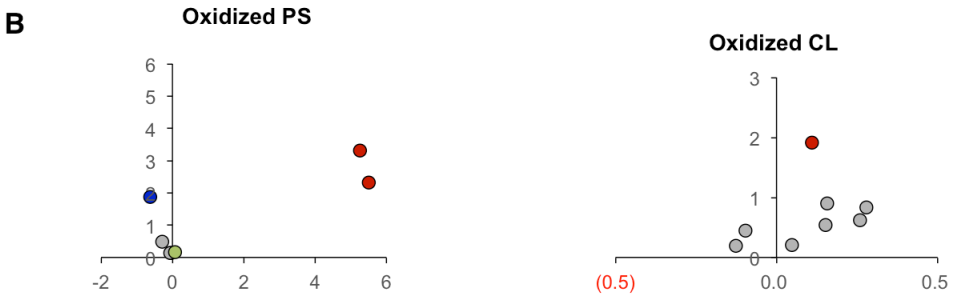
Supplementary Figures

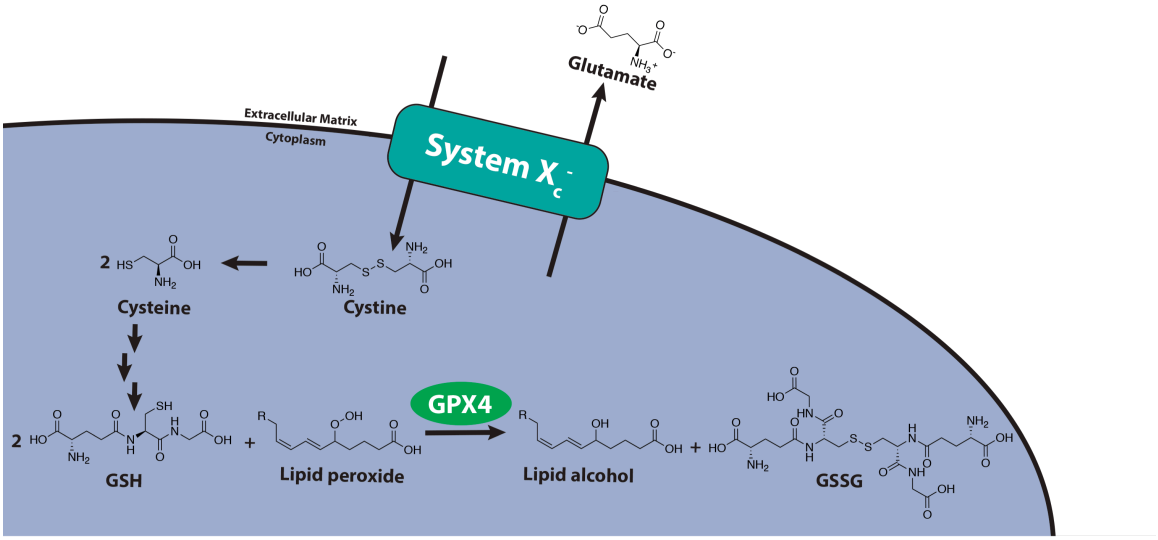


Supplementary Figure 1. (A) Dose-dependent lethality of $FINO_2$ in HT-1080 cells. Experiments were performed in biological triplicate. (B) Dose-dependent rescue of ferroptosis-suppressing nitroxides on HT-1080 cells treated with $FINO_2$ (10 μM). Viability for (A) and (B) was measured 24 h after compound addition using presto blue. Experiments were performed in biological triplicate. Data are plotted as the mean ± s.d..

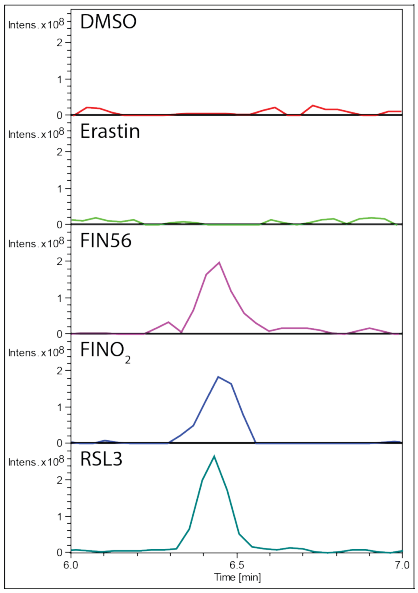




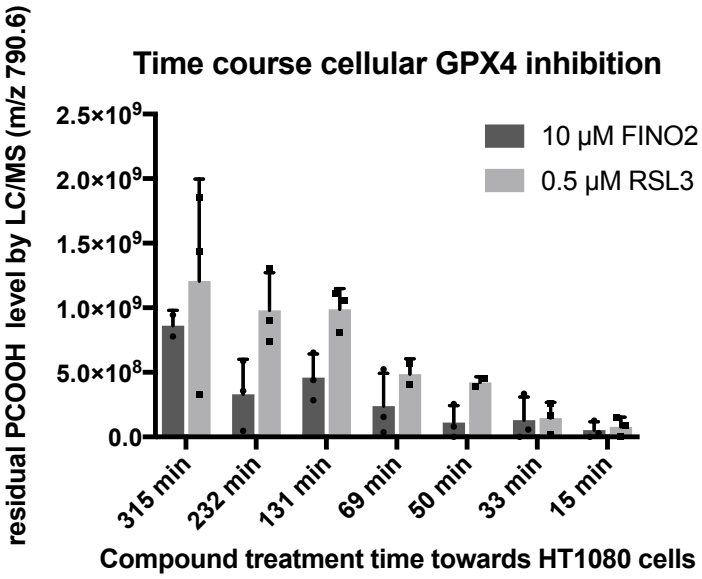
Supplementary Figure 2. (A) Lipids oxidized in HT-1080 cells treated with $FINO_2$ (10 μM). Lipids that were not upregulated when co-treated with ferroptosis suppressor ferrostatin (2 μM) are boxed in orange. PE: Phosphatidylethanolamine, PC: Phosphatidylcholine, PI: Phosphotidylinositol, PS: Phosphatidylserine. (B) Change in oxidized phosphatidylserine (PS) and cardiolipin (CL) following $FINO_2$ treatment in HT-1080 cells (10 μM). Green and gray circles indicate no change, red circles indicate an increase in abundance and blue circles indicate depletion.

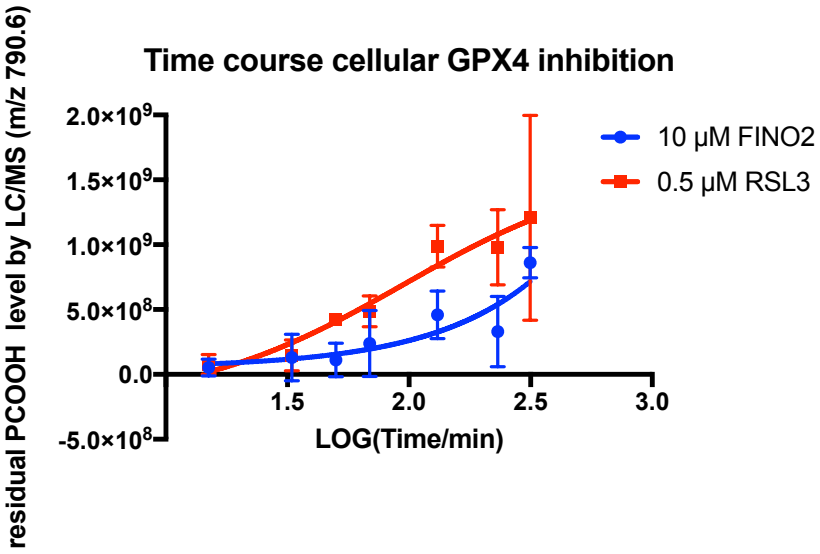


Supplementary Figure 3. Cystine import via system x_c^- provides cysteine required for synthesis of glutathione (GSH), a necessary cofactor for the lipid peroxide-reducing enzyme GPX4.

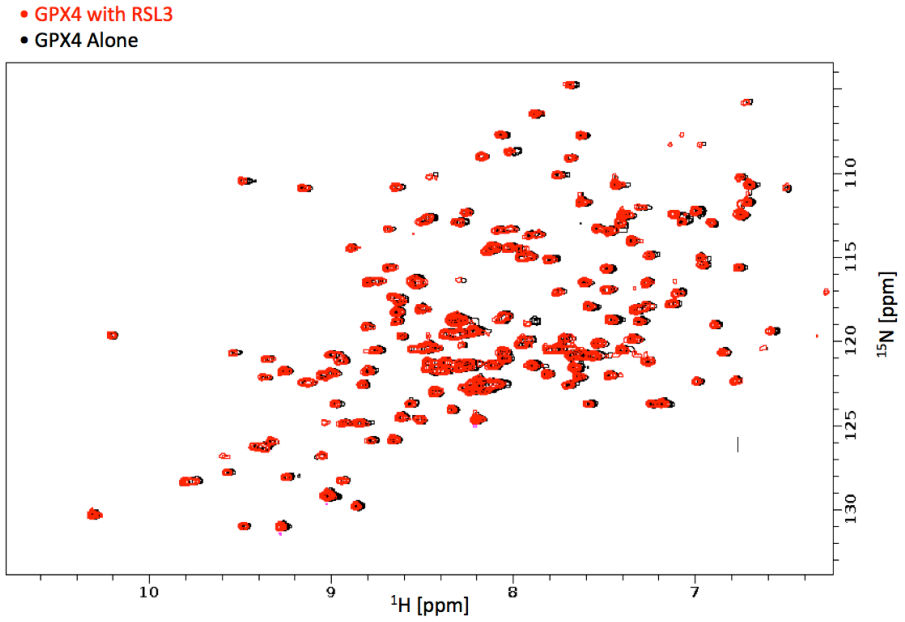


Supplementary Figure 4. Effect of ferroptosis inducers on the *in vitro* activity of GPX4 from treated HT-1080 cells. Cells were treated with DMSO, erastin (10 μM), FIN56 (5 μM), or $FINO_2$ (10 μM) for 6 h or RLS3 (0.5 μM) for 2 h. Cells were lysed and lysates were treated with PCOOH and GSH; after incubation (45 min) mixtures were extracted for lipids and the abundance of PCOOH was measured by LC-MS. Three independent experiments were performed with similar results.

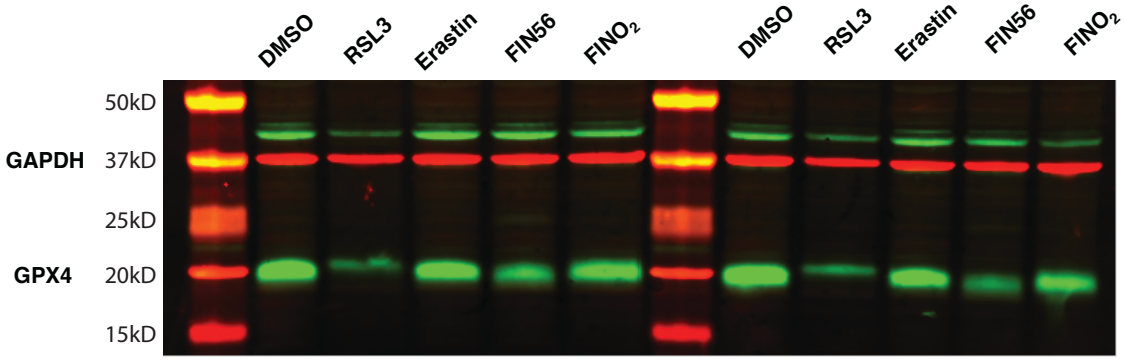




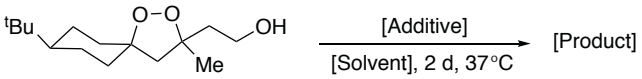
Supplementary Figure 5. Time dependent inhibition of GPX4-mediated PCOOH reduction by RSL3 and $FINO_2$. Data are plotted as the mean ± s.d.. Experiments were performed in triplicate with biologically independent samples.



Supplementary Figure 6. HSQC NMR of GPX4^{U46C} (10 μM) with RSL3 (100 μM).

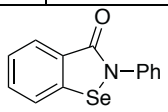


Supplementary Figure 7. Representative blot image from figure 3E.



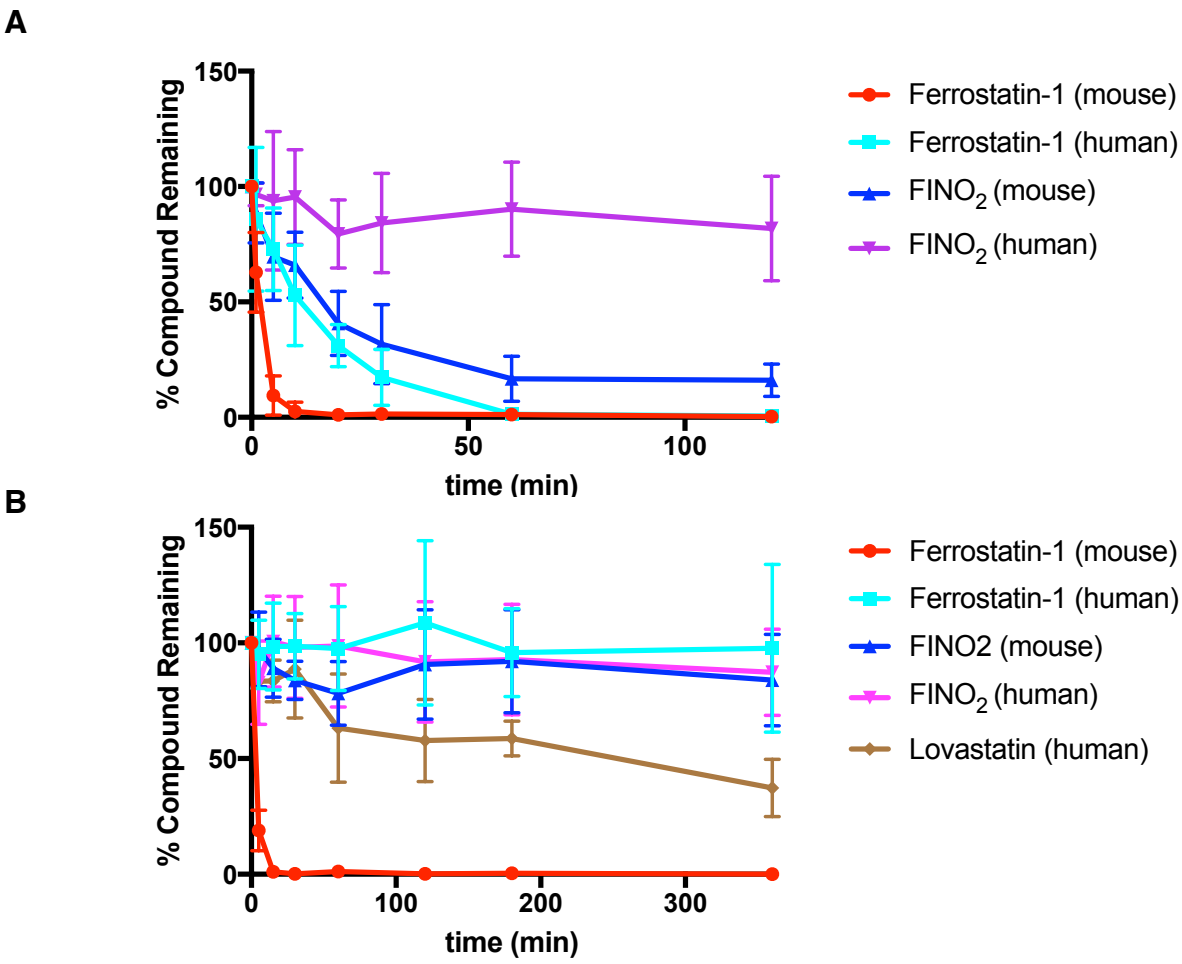
$FINO_2$ (**4**)

Entry	[Additive][a]	[Solvent]	[Product]
1	cysteine	DMSO-d_6	no reaction
2	GSH	DMSO-d_6	no reaction
3	arachadonic acid	CD_3CN	no reaction
4	selenocysteine	DMSO-d_6	no reaction
5	ebselen	DMSO-d_6	no reaction
6	Et_3N	DMSO-d_6	no reaction
7	KOH	DMSO-d_6	no reaction
8	DCl, KCl, NaCl	D_2O/DMSO-d_6	no reaction

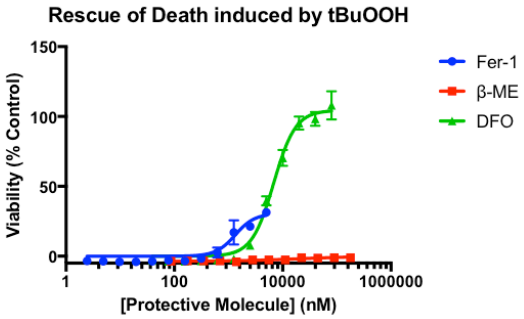


ebselen (**43**)

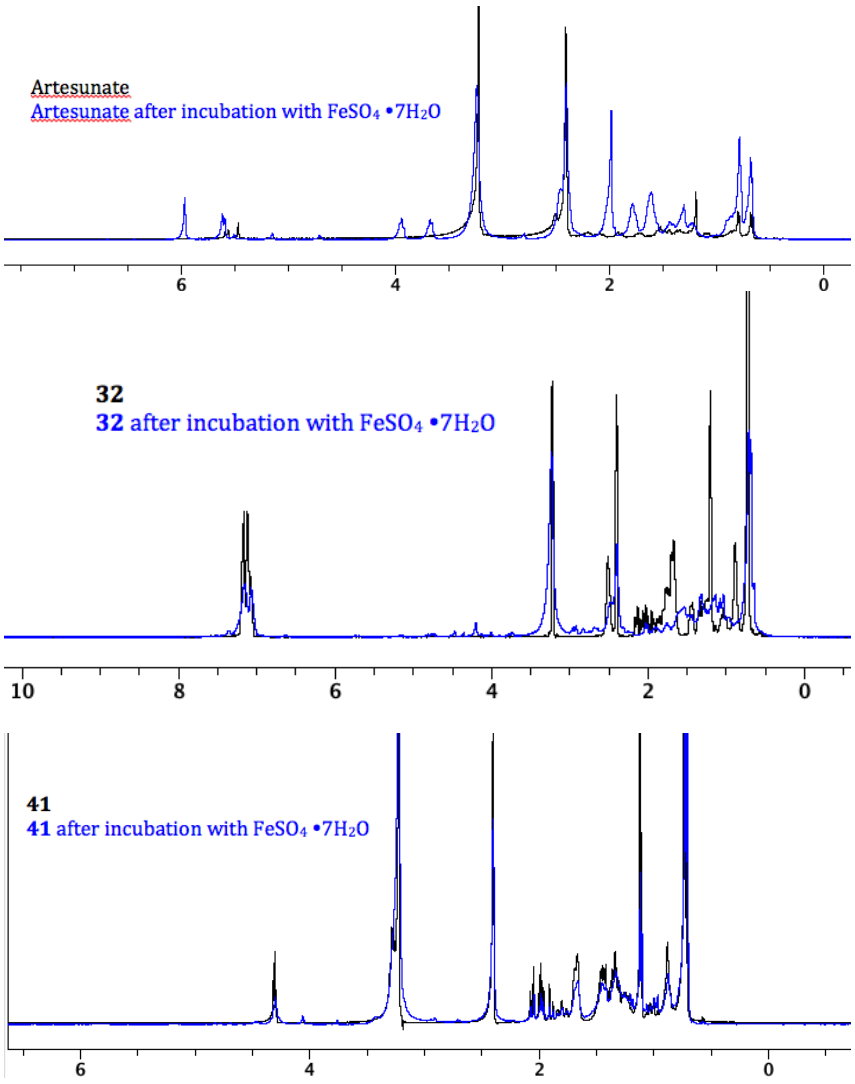
Supplementary Figure 8. Stability of $FINO_2$ under various reactive conditions.



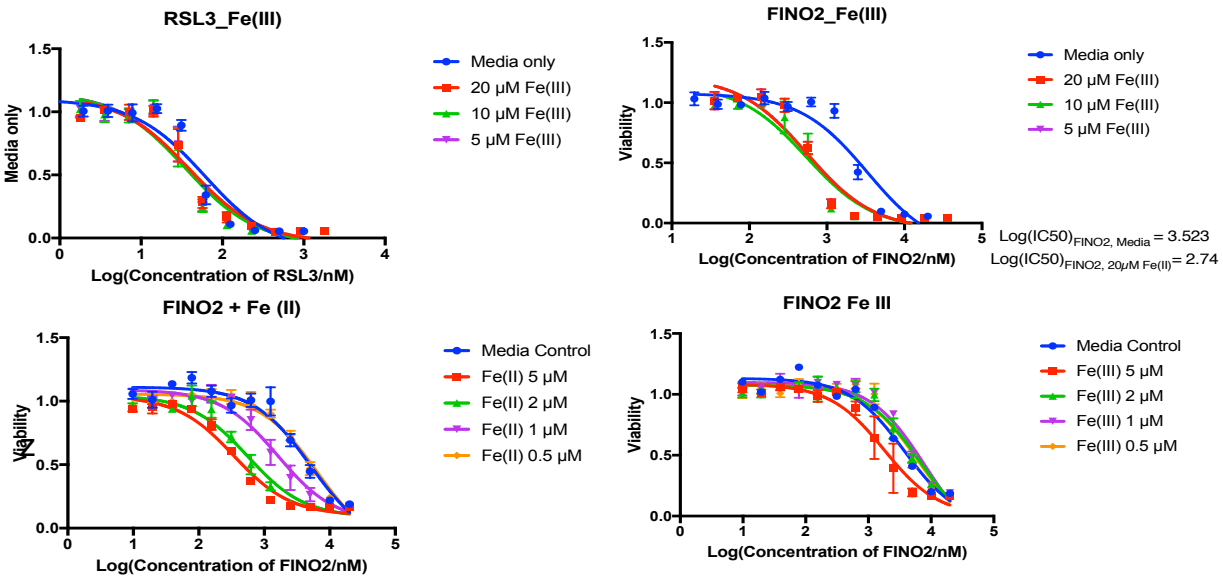
Supplementary Figure 9. Metabolic stability of $FINO_2$. (A) Stability of $FINO_2$ in mouse and human liver microsomes. (B) Stability of $FINO_2$ in mouse and human plasma. Experiments were performed in biological triplicate. Data are plotted as the mean ± s.d..



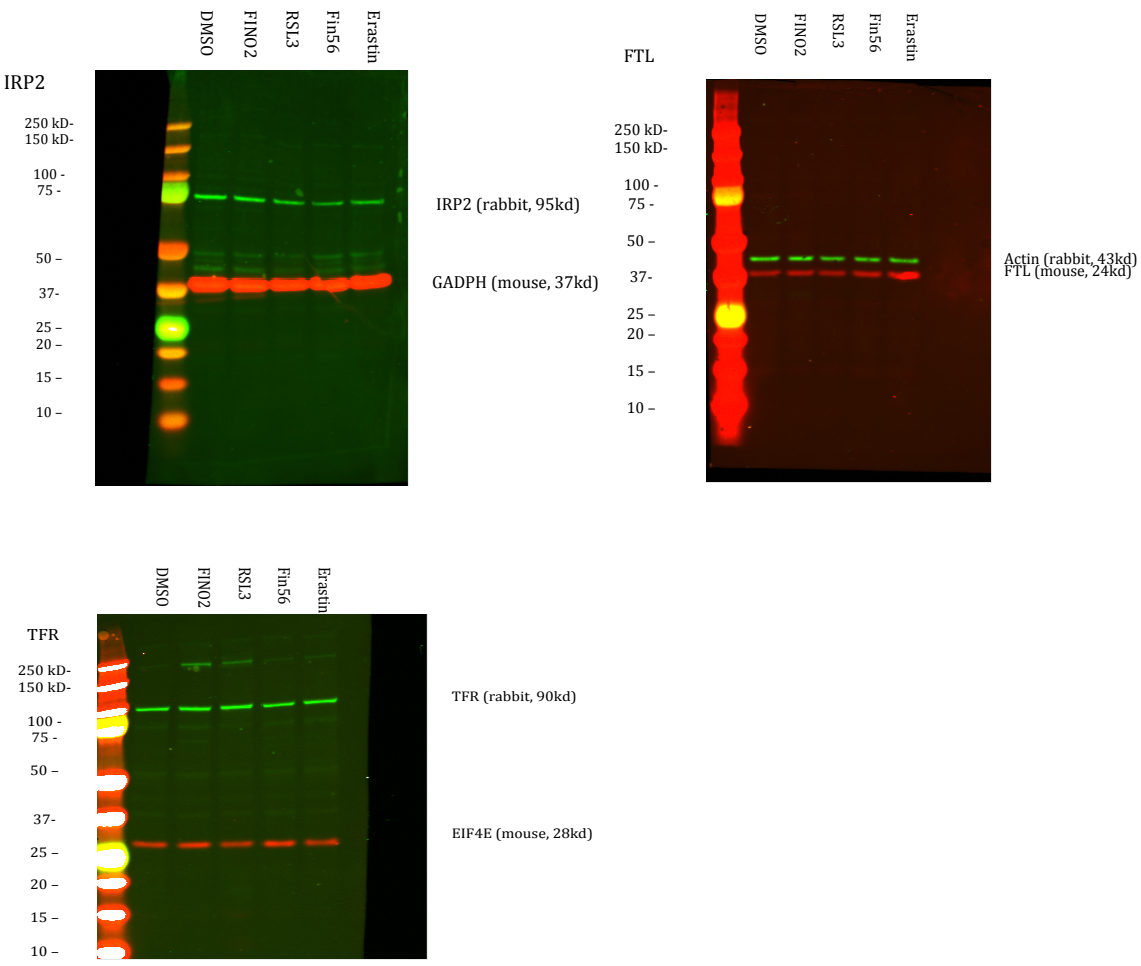
Supplementary Figure 10. Dose-dependent effect of ferroptosis-suppressing compounds on lethality initiated by *t*BuOOH (150 µM). Viability was measured 24 h after compound addition using presto blue. Experiments were performed in biological triplicate. Data are plotted as the mean ± s.d..



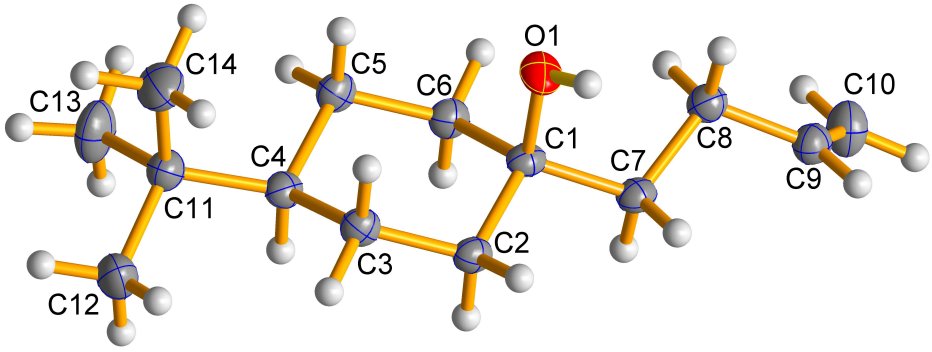
Supplementary Figure 11. Stability of Artesunate and $FINO_2$ analogues in the presence of $FeSO_4$



Supplementary Figure 12. Potency changes ferroptosis induction by $FINO_2$ and RSL3 in the presence of iron salts. Experiments were done in biological triplicate. Data are plotted as the mean ± s.d..



Supplementary Figure 13. Western blots of iron regulatory proteins in cells treated with vehicle (DMSO) or ferroptosis inducers. Experiments were performed in biological triplicate.



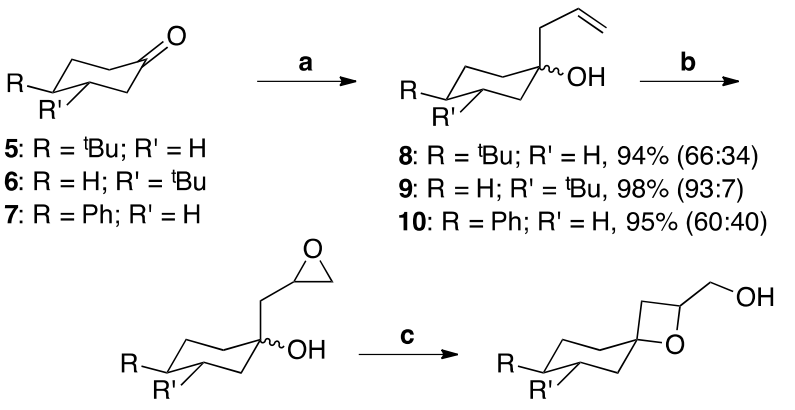
Supplementary figure 14. Crystal structure of **17a**

Supplementary table 1 Retention times and m/z for LC-MS analysis of in vitro Pharmacokinetic studies.

Compound	**Retention time**	**m/z**
Terfenadine	3.1 min	472.3
Ferrostatin-1	3.3 min	263.1
$FINO_2$	3.6 min	279.2
Lovastatin	3.7 min	405.2

Synthetic Procedures

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 400 MHz, 500 MHz, or 600 MHz spectrometers as indicated. The data are reported as follows: chemical shift in ppm are referenced from residual solvent (^{1}H NMR: $(CD_3)_2SO$, δ 2.50; C_6D_6, δ 7.16; $CDCl_3$, δ 7.26; ^{13}C NMR: $(CD_3)_2SO$, δ 39.52; C_6D_6, δ 128.39; $CDCl_3$, δ 77.23) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Structures were assigned using HSQC experiments. ^{13}C NMR spectra were collected with broadband decoupling on the proton channel. High resolution mass spectra (HRMS) were acquired on a time-of-flight spectrometer with atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI), as indicated, and were obtained by peak matching. Infrared (IR) spectra were obtained using attenuated total reflectance (ATR). Microanalyses were performed by Atlantic Microlabs Inc., Norcross, GA. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on silica gel 60 Å F_{254} plates. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on silica gel (SiO_2) 60 (230-400 mesh). All reactions were run under an atmosphere of nitrogen or oxygen in glassware that was flame-dried under a stream of nitrogen unless otherwise stated. Solvents used in reactions were dried and degassed using a solvent purification system before use. Aqueous solutions were prepared from nanopure water with a resistivity over 18 MΩ-cm. Unless otherwise noted, all reagents and substrates were commercially available. The following compounds were synthesized according to known literature procedures and their analytical data matched reported characterization: **4**,[1] **6**,[2] **8**,[3] **10**,[4] **23**,[1] **26**,[1] **29**,[1] **30**,[5] **35**,[4] **36**,[3] and **42**.[6] Ebselen (**43**) was prepared according to the method of Engman[7] and its analytical data matched reported characterization.[8]



5: R = ^{t}Bu; R' = H
6: R = H; R' = ^{t}Bu
7: R = Ph; R' = H

8: R = ^{t}Bu; R' = H, 94% (66:34)
9: R = H; R' = ^{t}Bu, 98% (93:7)
10: R = Ph; R' = H, 95% (60:40)

11: R = ^{t}Bu; R' = H, 70% (63:37)
12: R = H; R' = ^{t}Bu, 64% (61:39)
13: R = Ph; R' = H, 68% (50:50)

14: R = ^{t}Bu; R' = H, 48%
15: R = H; R' = ^{t}Bu, 47% (60:40)
16: R = Ph; R' = H, 49%

Figure 4a. a. allylMgCl, THF, 0 °C; **b.** *m*CPBA, CH_2Cl_2; **c.** LiOH•H_2O, DMSO, 150 °C.

1-Allyl-3-(*tert*-butyl)cyclohexan-1-ol (9). To a solution of ketone **6** (0.100 g, 0.648 mmol) in THF (1 mL) at 0 °C was added allylmagnesium chloride (0.39 mL, 0.78 mmol, 2 M in THF), dropwise. To the reaction mixture was then added 5% HCl (5 mL) and the product was extracted with EtOAc (3 X 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (5:95 EtOAc:hexanes) afforded **9** (0.125 g, 98%) in a 93:7 mixture of diastereomers as a clear oil. The data were collected for a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.82 (m, 2H), 5.19–5.09 (m, 4H), 2.38–2.33 (m, 2H), 2.21 (m, 2H), 1.80–1.71 (m, 4H), 1.67–1.54 (m, 6H), 1.43–1.36 (m, 2H), 1.30–1.23 (m, 2H), 1.22–1.09 (m, 2H), 1.08–0.95 (m, 2H), 0.89 (s, 1.2H) 0.85 (s, 16.8 H); ^{13}C NMR (100 MHz, $CDCl_3$) 134.0, 133.9, 119.0, 118.9, 73.1 (minor), 71.8 (major), 50.1, 49.4, 45.2, 42.8, 41.8, 39.7, 38.6, 38.5, 37.0, 32.4, 27.7, 27.6, 27.1, 26.7, 23.6, 22.1; IR (ATR) 3386, 2940, 2865, 1368, 1016 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{13}H_{23}$ $(M + H - H_2O)^+$ 179.1794, found 179.1800.

Representative Procedure for the Synthesis of 11–13: To a solution of alkene **8**, **9**, or **10** (1.0 equiv) in CH_2Cl_2 (4 mL/1 mmol ketone) was added *m*CPBA (1.5 equiv). The reaction mixture was allowed to stir for 2 h. To the reaction mixture was then added saturated aqueous $Na_2S_2O_3$ (5 mL/1 mmol ketone) and saturated aqueous KOH (5 mL/1 mmol ketone). The product was extracted with CH_2Cl_2 (3 X 5 mL/1 mmol of ketone). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (10:90 EtOAc:hexanes) afforded the epoxide product as a clear oil.

4-(*tert*-Butyl)-1-(oxiran-2-ylmethyl)cyclohexan-1-ol (11). Following the representative procedure for the epoxidation of alkenes, alkene **8** (0.180 g, 0.917 mmol), *m*CPBA (0.237 g, 1.38 mmol), and CH_2Cl_2 (4 mL) were combined to afford epoxide **11** (0.136 g, 70%) in a 60:40 mixture of diastereomers as a white solid. The data were collected for a mixture of diastereomers: mp = 51–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18–3.15 (m, 2H), 2.81–2.77 (m, 2H), 2.50–2.45 (m, 2H), 1.96–1.88 (m, 3H), 1.81–1.71 (m, 5H), 1.66 (br s, 1H), 1.63–1.59 (m, 3H), 1.56–1.48 (m, 3H), 1.44–1.31 (m, 7H), 1.08–0.98 (m, 2H), 0.86 (s, 11.4H), 0.84 (s, 6.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.7, 70.9, 49.3, 49.1, 47.9, 47.7, 47.0, 46.5, 39.5, 39.2, 39.1, 38.1, 37.9, 32.6, 32.4, 27.8, 27.7, 27.6, 24.7, 24.6, 22.5, 22.4; IR (ATR) 3442, 2960, 2867, 1366, 1136 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{13}H_{23}O$ $(M + H - H_2O)^+$ 195.1743, found 195.1744.

3-(*tert*-Butyl)-1-(oxiran-2-ylmethyl)cyclohexan-1-ol (12). Following the representative procedure for the epoxidation of alkenes, alkene **9** (0.228 g, 1.16 mmol), *m*CPBA (0.306 g, 1.74 mmol), and CH_2Cl_2 (5 mL) were combined to afford epoxide **12** (0.158 g, 64%) in a 60:40 mixture of diastereomers as a clear oil. The data were collected for a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18–3.15 (m, 2H), 2.82–2.79 (m, 2H), 2.51–2.47 (m, 2H), 2.01–1.92 (m, 2H), 1.81–1.72 (m, 8H), 1.66–1.51 (m, 4H), 1.45–1.37 (m, 2H), 1.34–1.25 (m, 3H), 1.15–1.05 (m, 3H), 0.93–0.89 (m, 2H), 0.86 (s, 7H), 0.85 (s, 11H); ^{13}C NMR (150 MHz, $CDCl_3$) 72.8, 71.0, 49.4, 49.1, 48.0, 47.7, 47.01, 47.00, 46.5, 39.6, 39.2, 39.1, 38.2, 32.6, 32.5, 27.81, 27.75, 24.8, 24.6, 22.50, 22.46; IR (ATR)

3464, 2930, 2868, 1365, 1139 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{13}H_{23}O$ (M + H – H_2O)$^+$ 195.1743, found 195.1747.

1-(Oxiran-2-ylmethyl)-4-phenylcyclohexan-1-ol (**13).** Following the representative procedure for the epoxidation of alkenes, alkene **10** (0.186 g, 0.860 mmol), *m*CPBA (0.226 g, 1.29 mmol), and CH_2Cl_2 (3 mL) were combined to afford epoxide **13** (0.136 g, 68%) in a 1:1 mixture of diastereomers as a white solid. The following data is for a mixture of diastereomers: mp = 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 5H), 7.24–7.17 (m, 5H), 3.23–3.18 (m, 2H), 2.85–2.81 (m, 2H), 2.60–2.49 (m, 2H), 2.13–2.01 (m, 4H), 1.95–1.90 (m, 4H), 1.88–1.82 (m, 4H), 1.79–1.71 (m, 2H), 1.70–1.65 (m, 2H), 1.64–1.61 (m, 3H), 1.59–1.55 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) 147.0, 146.2, 128.41, 128.37, 126.9, 126.8, 126.2, 126.0, 72.3, 70.6, 49.1, 48.9, 46.9, 46.8, 46.4, 43.9, 43.4, 39.3, 39.0, 38.7, 37.9, 37.4, 31.3, 30.9, 29.1, 29.0; IR (ATR) 3430, 2930, 2859, 1494, 1139 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{15}H_{19}O$ (M + H – H_2O)$^+$ 215.1430, found 215.1439.

Representative Procedure for the Synthesis of Oxetanes 14–16: To a solution of epoxide **11**, **12**, or **13** (1.0 equiv) in H_2O (10 mL/1 mmol epoxide) and DMSO (30 mL/1 mmol epoxide) was added LiOH•H_2O (10 equiv). The reaction mixture was then heated to 150 °C for 15 min. The reaction mixture was then cooled and diluted with ice-water (30 mL/1 mmol of epoxide) and the product was extracted with EtOAc (3 X 30 mL/1 mmol of epoxide). The combined organic layers were washed with brine (1 X 30 mL/1 mmol of epoxide), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (25:75 EtOAc:hexanes) afforded the epoxide product as either a white solid or yellow oil.

((4*r*,7*r*)-7-(*tert*-Butyl)-1-oxaspiro[3.5]nonan-2-yl)methanol (**14).** Following the representative procedure for the synthesis of oxetanes, epoxide **11** (0.010 g, 0.05 mmol), H_2O (0.5 mL), DMSO (2 mL) and LiOH•H_2O (0.020 g, 0.47 mmol) were combined to afford oxetane **14** (0.005 g, 48%) as a white solid: mp = 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73–4.67 (m, 1H), 3.76–3.71 (m, 1H), 3.58–3.52 (m, 1H), 2.24–2.15 (m, 3H), 2.07 (br s, 1H), 2.02–1.99 (m, 1H), 1.75–1.67 (m, 2H), 1.53–1.38 (m, 2H), 0.98–0.94 (m, 3H), 0.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.5, 75.0, 65.7, 47.1, 41.9, 39.5, 38.7, 32.4, 27.7, 24.2, 23.6; IR (ATR) 3427, 2946, 2919, 2853, 1210, 1055 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{13}H_{23}O$ (M + H – H_2O)$^+$ 195.1743, found 195.1748.

(4*S*,6*R*)-6-(*tert*-Butyl)-1-oxaspiro[3.5]nonan-2-yl)methanol (15). Following the representative procedure for the synthesis of oxetanes, epoxide **12** (0.158 g, 0.744 mmol), H_2O (7 mL), DMSO (25 mL), and LiOH•H_2O (0.312 g, 7.44 mmol) were combined to afford oxetane **15** (0.074 g, 47%) in a 60:40 mixture of diastereomers as a clear oil. The following data is for a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76–4.70 (m, 2H), 3.78–3.73 (m, 2H), 3.61–3.54 (m, 2H), 2.25–2.20 (m, 4H), 2.18–2.12 (m, 1H), 2.05–1.97 (m, 4H) 1.82–1.71 (m, 2H), 1.66 (s, 1H), 1.64 (s, 1H), 1.45–1.29 (m, 3H), 1.28–1.10 (m, 6H), 1.04–0.95 (m, 2H), 1.01–0.93 (m, 1H), 0.88 (s, 6.9H), 0.86 (s, 11.1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 84.5, 84.4, 75.33, 75.29, 65.9, 65.8, 45.5, 44.9, 41.0, 40.1, 39.4, 38.4, 32.79, 32.75, 32.5, 32.3, 27.79, 27.75, 26.28, 26.27 23.0, 22.4; IR (ATR) 3418,

2929, 2857, 1365 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{13}H_{25}O_2$ $(M + H)^+$ 213.1849, found 213.1854.

((4*r*,7*r*)-7-Phenyl-1-oxaspiro[3.5]nonan-2-yl)methanol (**16**)**.** Following the representative procedure for the synthesis of oxetanes, epoxide **13** (0.097 g, 0.42 mmol), H_2O (4 mL), DMSO (13 mL), and LiOH•H_2O (0.175 g, 4.18 mmol) were combined to afford oxetane **16** (0.11 g, 49%) as a white solid: mp = 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.17 (m, 5H), 4.74–4.72 (m, 1H), 3.79–3.77 (m, 1H), 3.62–3.58 (m, 1H), 2.49–2.45 (m, 1H), 2.37–2.34 (m, 2H), 2.33–2.25 (m, 1H), 2.17–2.15 (m, 1H), 2.06–2.04 (m, 1H), 1.85–1.81 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 128.6, 127.1, 126.2, 81.5, 75.1, 65.7, 43.5, 39.1, 38.1, 33.7, 29.5, 29.2; IR (ATR) 3410, 2928, 2850, 1438, 1037 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{15}H_{19}O$ $(M + H - H_2O)^+$ 215.1430, found 215.1441.

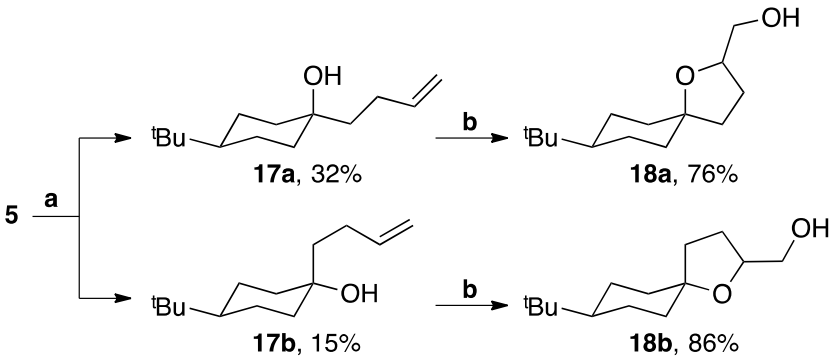


Figure 4b. a. $CH_2CHCH_2CH_2Br$, Mg, I_2, THF, 0 °C; **b**. *m*CPBA, CH_2Cl_2.

(1*s*,4*r*)-1-(But-3-en-1-yl)-4-(*tert*-butyl)cyclohexan-1-ol and (1*r*,4*s*)-1-(But-3-en-1-yl)-4-(*tert*-butyl)cyclohexan-1-ol (17a and 17b). To a solution of magnesium (0.215 g, 8.84 mmol) and iodine (5 mg) in Et_2O (5 mL) at 0 °C was added homoallyl bromide (0.50 mL, 4.9 mmol). The reaction mixture was stirred for 30 min. The reaction mixture was transferred by cannula to a flask containing a solution of ketone **5** (0.250 g, 1.62 mmol) in Et_2O (1 mL) at 0 °C and the reaction mixture was stirred for 3 h. To the reaction mixture was then added H_2O (5 mL) and the product was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1 M HCl (10 mL) and H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (10:90 EtOAc:hexanes) yielded alkenes **17a** (0.110 g, 32%) and **17b** (0.052 g, 15%) as white solids.

17a: mp = 72–73 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89–5.82 (m, 1H), 5.03 (dd, *J* = 17.1, 1.7, 1H), 4.94 (dd, *J* = 10.1, 1.5, 1H), 2.18–2.14 (m, 2H), 1.70–1.69 (m, 2H), 1.60–1.58 (m, 2H), 1.52–1.49 (m, 2H), 1.35–1.27 (m, 4H), 1.15 (s, 1H), 0.96–0.91 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 114.5, 70.8, 48.2, 43.4, 37.7, 32.6, 27.9, 27.8, 22.7; IR (ATR) 3385, 2936, 1639 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{14}H_{26}NaO$ $(M + Na)^+$ 233.1876, found 233.1878.

17b: mp = 80–81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92–5.84 (m, 1H), 5.08–5.05 (m, 1H), 4.98–4.96 (m, 1H), 2.15–2.12 (m, 2H), 1.83–1.80 (m, 2H), 1.69–1.67 (m, 2H), 1.62–1.59 (m, 2H), 1.38–1.33 (m, 2H), 1.27 (br s, 1H), 1.10–1.00

(m, 3H), 0.85 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 114.7, 72.4, 47.8, 39.1, 35.7, 32.5, 27.9, 27.5, 24.6; IR (ATR) 3289, 2938, 1641 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{14}H_{26}NaO$ (M + Na)$^+$ 233.1876, found 233.1878.

((5*s*,8*s*)-(8-(*tert*-Butyl)-1-oxaspiro[4.5]decan-2-yl)methanol (18a). To a solution of alkene **17a** (0.066 g, 0.31 mmol) in CH_2Cl_2 (10 mL) was added *m*CPBA (0.183 g, 0.738 mmol) and the reaction mixture was stirred for 16 h. To the reaction mixture was then added saturated aqueous $Na_2S_2O_3$ (5 mL) and the product was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1 M NaOH (5 mL) and H_2O (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (15:85 EtOAc:hexanes) afforded **18a** (0.054 g, 76%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.08–4.04 (m, 1H), 3.68–3.65 (m, 1H), 3.46–3.42 (m, 1H), 2.06 (t, *J* = 6.3, 1H), 1.93–1.88 (m, 1H), 1.78–1.71 (m, 2H), 1.70–1.65 (m, 3H), 1.60–1.55 (m, 2H), 1.41–1.24 (m, 4H), 0.96–0.91 (m, 1H), 0.85 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.0, 78.5, 65.5, 48.0, 38.7, 38.6, 37.2, 32.6, 27.8, 27.1, 23.9, 23.8; IR (ATR) 3421, 2867, 1036 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{14}H_{26}NaO_2$ (M + Na)$^+$ 249.1825, found 249.1825.

((5*r*,8*r*)-(8-(*tert*-Butyl)-1-oxaspiro[4.5]decan-2-yl)methanol (18b). To a solution of alkene **17b** (0.022 g, 0.10 mmol) in CH_2Cl_2 (5 mL) was added *m*CPBA (0.071 g, 0.28 mmol and the reaction mixture was stirred for 16 h. To the reaction mixture was then added saturated aqueous $Na_2S_2O_3$ (5 mL) and the product was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1 M NaOH (5 mL) and H_2O (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (30:70 EtOAc:hexanes) afforded **18b** (0.020 g, 86%) as a white solid: mp = 68–69 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.11–4.07 (m, 1H), 3.68–3.67 (m, 1H), 3.48–3.44 (m, 1H), 2.01 (br s, 1H), 1.95–1.89 (m, 1H), 1.79–1.73 (m, 6H), 1.64–1.61 (m, 1H), 1.54–1.43 (m, 2H), 1.06–0.95 (m, 3H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 84.5, 78.1, 65.4, 47.6, 38.8, 38.1, 34.1, 32.5, 27.8, 27.5, 25.9, 25.4; IR (ATR) 3415, 2937, 1033 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{14}H_{26}NaO_2$ (M + Na)$^+$ 249.1825, found 249.1825.

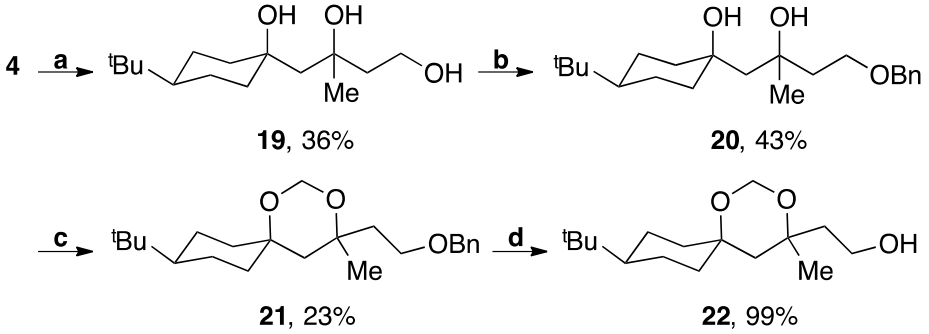


Figure 4c. a. H_2, Pd/C, THF; **b.** NaH, BnBr, THF; **c.** NaH, CH_2Br_2, TBAI, DMF; **d.** H_2, Pd/C, THF.

4-((1*s*,4*s*)-(4-(*tert*-Butyl)-1-hydroxycyclohexyl)-3-methylbutane-1,3-diol (19). To a solution of **5** (0.054 g, 0.21 mmol) in THF (2 mL) was added 10% Pd/C

(0.015 g, 0.14 mmol). The reaction mixture was purged with H_2 for 1 min. After 16 h, the reaction mixture was filtered through a plug of Celite, washed with EtOAc (10 mL), and concentrated. Purification by flash chromatography (50:50 EtOAc:hexanes) afforded **19** (0.020 g, 36%) as a white solid: mp = 69–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 3.95–3.90 (m, 1H), 3.86–3.82 (m, 1H), 3.41 (br s, 1H), 3.23 (br s, 1H), 2.09–2.06 (m, 1H), 1.97–1.87 (m, 2H), 1.80 (d, *J* = 14.8, 1H), 1.65–1.54 (m, 4H), 1.38 (s, 3H), 1.37–1.25 (m, 4H), 0.97–0.89 (m, 1H), 0.85 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 75.2, 72.9, 60.1, 52.3, 47.7, 44.3, 40.6, 39.5, 32.6, 29.3, 27.7, 22.6, 22.5; IR (ATR) 3477, 3299, 2938, 1364 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{15}H_{30}NaO_3$ $(M + Na)^+$ 281.2087, found 281.2089.

(1*s*,4*s*)-1-(4-(Benzyloxy)-2-hydroxy-2-methylbutyl)-4-(*tert*-butyl)cyclohexan-1-ol (20). To a solution of **19** (0.060 g, 0.23 mmol) in THF (2 mL) was added NaH (0.029 g, 0.73 mmol, 60% dispersion in mineral oil) and the reaction mixture was stirred for 15 min. Benzyl bromide (0.032 mL, 0.27 mmol) was then added and the reaction mixture stirred for 14 h. To the reaction mixture was then added saturated aqueous NH_4Cl (5 mL) and the product was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (10:90 EtOAc:hexanes) afforded **20** (0.035 g, 43%) as a white solid: mp = 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.52 (s, 2H), 4.07 (br s, 1H), 3.97 (br s, 1H), 3.78–3.73 (m, 1H), 3.71–3.67 (m, 1H), 2.12–2.06 (m, 1H), 2.04–2.00 (m, 1H), 1.88–1.84 (m, 1H), 1.72–1.65 (m, 2H), 1.57–1.50 (m, 3H), 1.44–1.22 (m, 4H), 1.33 (s, 3H), 0.94–0.88 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 128.7, 128.1, 128.0, 74.5, 73.7, 71.7, 67.7, 52.6, 48.0, 42.6, 40.7, 39.9, 32.6, 29.2, 27.8, 22.8, 22.7; IR (ATR) 3414, 2938, 1454, 1364 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{22}H_{36}NaO_3$ $(M + Na)^+$ 371.2557, found 371.2560.

(6*s*,9*s*)-4-(2-(Benzyloxy)ethyl)-9-(*tert*-butyl)-4-methyl-1,3-dioxaspiro[5.5]undecane (21). To a solution of **20** (0.025 g, 0.072 mmol) in DMF (1 mL) was added CH_2Br_2 (0.025 mL, 0.36 mmol), TBAI (0.003 g, 0.001 mmol), and then NaH (0.032 g, 0.80 mmol). The reaction mixture stirred for 16 h. To the reaction mixture was added H_2O (5 mL) and the product was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography (5:95 EtOAc:hexanes) afforded **21** (0.006 g, 23%) as a white solid: mp = 77–79 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.90 (d, *J* = 7.1, 1H), 4.86 (d, *J* = 7.1, 1H), 4.50 (s, 2H), 3.60 (t, *J* = 7.1, 2H), 2.20–2.17 (m, 1H), 2.06–1.99 (m, 2H), 1.90–1.89 (m, 1H), 1.59 (d, *J* = 14.0, 1H), 1.51–1.49 (m, 2H), 1.42 (d, *J* = 13.9, 1H), 1.38–1.29 (m, 2H), 1.30 (s, 3H), 1.23–1.15 (m, 2H), 0.97–0.92 (m, 1H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 128.6, 127.9, 127.8, 82.5, 73.3, 71.9, 70.7, 66.5, 47.9, 46.1, 41.9, 38.2, 36.9, 32.6, 27.8, 26.8, 22.4, 22.3; IR (ATR) 3010, 2942, 1365 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{23}H_{37}O_3$ $(M + H)^+$ 361.2737, found 361.2744.

2-((6*s*,9*s*)-9-(*tert*-Butyl)-4-methyl-1,3-dioxaspiro[5.5]undecan-4-yl)ethan-1-ol (22). To a solution of **21** (0.006 g, 0.02 mmol) in THF (0.5 mL) was added 10%

Pd/C (0.003 g, 0.03 mmol). The reaction mixture was purged with H_2 for 1 min. After 14 h, the reaction mixture was filtered through a 1 cm plug of Celite, washed with EtOAc (20 mL), and concentrated. Purification by flash chromatography (25:75 EtOAc:hexanes) afforded pure **22** (0.005 g, 99%) as a white solid: mp = 77–79 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.94 (d, *J* = 10.6, 1H), 4.85 (d, *J* = 10.6, 1H), 3.87–3.77 (m, 2H), 2.61 (br s, 1H), 2.40–2.34 (m, 1H), 1.95–1.87 (m, 2H), 1.73–1.67 (m, 2H), 1.54–1.50 (m, 2H), 1.39 (s, 3H), 1.44–1.13 (m, 5H), 0.97–0.94 (m, 1H), 0.85 (s, 9H); ^{13}C (150 MHz, $CDCl_3$) δ 82.3, 73.8, 70.8, 59.4, 47.8, 45.9, 44.8, 39.8, 35.3, 32.6, 27.8, 25.4, 22.4, 22.3; IR (ATR) 3409, 2965, 1365 cm^{-1}; HRMS (APCI) *m* / *z* calcd for $C_{16}H_{31}O_3$ $(M + H)^+$ 271.2268, found 271.2264.

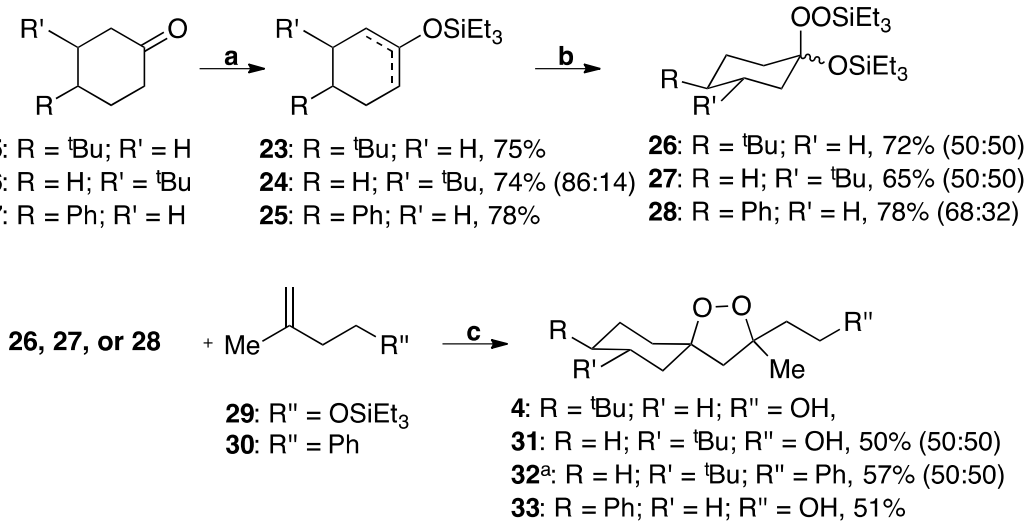


Figure 5a. a. (1) ^{i}Pr$_2$NH, ^{n}BuLi, THF, −78 °C (2) Et_3SiCl, THF, −78 °C; **b.** $Co(thd)_2$, Et_3SiH, $PhCF_3$, O_2 (balloon); **c.** (1) $SnCl_4$, CH_2Cl_2, −78 °C (2) TBAF, THF, rt. [a]deprotection with TBAF not necessary.

Representative Procedure for the Synthesis of Silyl Enol Ethers 24 and 25: To a solution of ^{i}Pr$_2$NH (2.0 equiv) in THF (2 mL/1 mmol ketone) at –78 °C was added ^{n}BuLi (2.0 equiv). The reaction mixture was allowed to stir for 20 min. To this solution was added a solution of ketone (1.0 equiv) in THF (0.75 mL/1 mmol ketone), dropwise. The reaction mixture was allowed to stir for 20 min. To this solution was then added triethylsilyl chloride (1.5 equiv), dropwise. The reaction mixture was allowed to warm to room temperature and the reaction mixture was stirred for 6 h. The reaction mixture was then quenched by the addition of H_2O (10 mL/1 mmol ketone). The product was extracted with hexanes (3 X 10 mL/1 mmol ketone). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes) afforded the silyl enol ether as a clear oil.

((5-(*tert*-Butyl)cyclohex-1-en-1-yl)oxy)triethylsilane (24a) and **((3-(*tert*-Butyl)cyclohex-1-en-1-yl)oxy)triethylsilane** (**24b**). Following the representative procedure for the synthesis of silyl enol ethers, ketone **7** (0.250 g, 1.62 mmol), ^{i}Pr$_2$NH (0.45 mL, 3.2 mmol), ^{n}BuLi (1.3 mL, 3.2 mmol, 2.5 M in hexanes), Et_3SiCl

(0.40 mL, 2.4 mmol), and THF (4 mL) were combined to afford silyl enol ethers **24a** and **24b** (0.322 g, 74%) in an 86:14 mixture as a clear oil. The following data is for the major isomer (**24a**), only: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90–4.85 (m, 1H), 2.05–1.71 (m, 6H), 1.37–1.30 (m, 1H), 0.97 (t, *J* = 8.0, 9H), 0.88 (s, 9H), 0.70 (q, *J* = 8.0, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.0, 103.5, 45.2, 32.3, 31.9, 27.5, 27.4, 24.7, 7.0, 5.3; IR (ATR) 2954, 2912, 2876, 1192, 1005 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{16}H_{33}OSi$ $(M + H)^+$ 269.2295, found 269.2303.

Triethyl((1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)oxy)silane (25). Following the representative procedure for the synthesis of silyl enol ethers, 4-phenylcyclohexanone (0.250 g, 1.44 mmol), $^{i}Pr_2NH$ (0.40 mL, 2.88 mmol), ^{n}BuLi (1.2 mL, 2.9 mmol, 2.5 M in hexanes), Et_3SiCl (0.36 mL, 2.15 mmol), and THF (4 mL) were combined to afford silyl enol ether **25** (0.323 g, 78%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.25–7.18 (m, 3H), 4.96–4.95 (m, 1H), 2.79–2.73 (m, 1H), 2.30–2.16 (m, 3H), 2.11–2.06 (m, 1H), 1.98–1.94 (m, 1H), 1.91–1.84 (m, 1H), 1.02 (t, *J* = 8.0, 9H), 0.70 (q, *J* = 8.0, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.2, 146.5, 128.1, 126.7, 125.8, 103.1, 39.8, 31.8, 30.02, 29.97, 6.6, 4.9; IR (ATR) 3005, 2950, 2913, 1179, 740 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{18}H_{29}OSi$ $(M + H)^+$ 289.1982, found 289.1988.

Representative Procedure for the Synthesis of Mixed Peroxyketals 27 and 28: To a solution of silyl enol ether (1.0 equiv) in $PhCF_3$ (5 mL/1 mmol silyl enol ether) under a balloon of oxygen was added Et_3SiH (2.0 equiv) followed by $Co(thd)_2$ (0.20 equiv). Upon completion of the reaction by TLC, the reaction mixture was filtered through a 1–2 cm plug of Davisil. The plug was then washed with hexanes (5 mL/1 mmol silyl enol ether). The reaction mixture was then concentrated to afford a dark green oil that was used without further purification.

((3-(*tert*-Butyl)-1-((triethylsilyl)oxy)cyclohexyl)peroxy)triethylsilane (27). Following the representative procedure for the synthesis of mixed peroxyketals, silyl enol ethers **24a** and **24b** (0.132 g, 0.492 mmol), $Co(thd)_2$ (0.021 g, 0.049 mmol), Et_3SiH (0.16 mL, 0.98 mmol), and $PhCF_3$ (2 mL) were combined to afford mixed peroxyketal **27** (0.082 g, 65%) as a 1:1 mixture of diastereomers as a dark green oil that was used without further purification. The data were collected for the crude reaction mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23–2.03 (m, 2H), 1.88–1.85 (m, 2H), 1.69–1.55 (m, 6H), 1.35–1.18 (m, 6H), 0.99–0.84 (m, 30H), 0.82 (s, 9H), 0.81 (s, 9H), 0.71–0.58 (m, 10H), 0.55–0.46 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 105.7, 104.9, 44.4, 44.3, 37.2, 36.8, 35.9, 35.6, 32.3, 32.1, 27.6, 27.5, 26.8, 26.2, 23.2, 23.1, 7.2, 7.1, 7.0, 6.8, 6.5, 6.2, 4.1, 3.9; IR (ATR) 2955, 2877, 1320, 1005 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{22}H_{49}O_3Si_2$ $(M + H)^+$ 417.3215, found 417.3220.

Triethyl((4-phenyl-1-((triethylsilyl)oxy)cyclohexyl)peroxy)silane (28). Following the representative procedure for the synthesis of mixed peroxyketals, silyl enol ether **25** (0.134 g, 0.464 mmol), $Co(thd)_2$ (0.020 g, 0.046 mmol), Et_3SiH (0.15 mL, 0.93 mmol), and $PhCF_3$ (2 mL) were combined to afford mixed peroxyketal **28** (0.158 g, 78%) as a 68:32 mixture of diastereomers as a dark green oil that was used without further purification. The data were collected for the crude reaction mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 4H), 7.22–7.16 (m, 6H), 2.53–2.48 (m, 2H), 2.28–2.25 (m, 2.6H), 2.03–2.00 (m, 1.3H),

1.83–1.76 (m, 2H), 1.73–1.51 (m, 10H), 1.06–0.91 (m, 30H), 0.78–0.61 (m, 25H), 0.56–0.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.16, 147.15, 128.53, 128.52, 127.02, 126.97, 126.2, 126.1, 103.33, 103.32, 44.2, 43.6, 36.1, 35.8, 31.3, 30.9, 7.4, 7.2, 7.05, 6.96, 6.4, 4.2, 4.1, 4.0; IR (ATR) 2953, 2876, 1458, 1237, 1132 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{24}H_{45}O_3Si_2$ $(M + H)^+$ 437.2902, found 437.2908.

Representative Procedure for the Synthesis of 1,2-Dioxolanes 31–33, 37, 39, and 41:

To a solution of mixed peroxyketal (1.0 equiv) in CH_2Cl_2 (3 mL/1 mmol mixed peroxyketal) at –78 °C was added $SnCl_4$ (0.05 equiv) followed by the alkene (2.0 equiv). Upon completion of the reaction by TLC, the reaction mixture was warmed to room temperature and a saturated aqueous solution of Rochelle's salt (5 mL/1 mmol mixed peroxyketal) was added. The reaction mixture was allowed to stir at room temperature for 1 h. The product was extracted with CH_2Cl_2 (3 X 5 mL/1 mmol mixed peroxyketal). The combined organic layers were washed with H_2O (1 X 5 mL/1 mmol mixed peroxyketal), dried over $MgSO_4$, filtered, and concentrated to afford a viscous oil.

The crude reaction mixture was immediately diluted with THF (2 X 5 mL/1 mmol mixed peroxyketal) and treated with TBAF (1 M in THF, 2 mL/1 mmol mixed peroxyketal). Upon completion of the reaction by TLC, H_2O (5 mL/1 mmol mixed peroxyketal) was added, and the product was extracted with EtOAc (3 X 5 mL/1 mmol mixed peroxyketal). The combined organic layers were washed with H_2O (2 X 5 mL/1 mmol mixed peroxyketal), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (10:90 EtOAc:hexanes) afforded the 1,2–dioxolane as a white solid, clear oil, or yellow oil.

2-((5*R*,7*R*)-7-(*tert*-Butyl)-3-methyl-1,2-dioxaspiro[4.5]decan-3-yl)ethan-1-ol (**31**). Following the representative procedure for the synthesis of 1,2-dioxolanes, mixed peroxyketal **27** (0.165 g, 0.378 mmol), alkene **29** (0.151 g, 0.756 mmol), $SnCl_4$ (0.019 mL, 0.019 mmol, 1 M in CH_2Cl_2), CH_2Cl_2 (1 mL), TBAF (0.76 mL, 0.76 mmol, 1 M in THF), and THF (0.75 mL) were combined to afford **31** (0.052 g, 50%) as a 1:1 mixture of diastereomers as a clear oil. The data were collected for a mixture of diastereomers: ^{1}H NMR (600 MHz, C_6D_6) δ 3.66–3.59 (m, 4H), 2.05–1.90 (m, 6H), 1.87–1.80 (m, 2H), 1.77–1.74 (m, 2H), 1.69–1.55 (m, 7H), 1.52–1.42 (m, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.08–0.94 (m, 5H), 0.82 (s, 9H), 0.80 (s, 9H), 0.70–0.67 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 85.92, 85.86, 85.1, 85.0, 59.6, 59.5, 58.91, 58.87, 44.5, 44.4, 42.3, 42.1, 37.5, 37.2, 36.0, 35.8, 32.51, 32.48, 27.79, 27.76, 26.76, 26.75, 25.1, 24.9, 23.8, 23.7; IR (ATR) 3338, 2970, 2912, 1430, 1056 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{15}H_{27}O_2$ $(M + H - H_2O)^+$ 239.2006, found 239.2003.

(5*R*,7*R*)-7-(*tert*-Butyl)-3-methyl-3-phenethyl-1,2-dioxaspiro[4.5]decane (**32**). Following the representative procedure for the synthesis of 1,2-dioxolanes, mixed peroxyketal **27** (0.212 g, 0.508 mmol), alkene **30** (0.149 g, 1.02 mmol), $SnCl_4$ (0.025 mL, 0.025 mmol, 1 M in CH_2Cl_2), and CH_2Cl_2 (2 mL) were combined to afford **32** (0.091 g, 57%) in a 1:1 mixture of diastereomers as a clear, viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4H), 7.27–7.22 (m, 6H), 2.80–2.69 (m, 4H), 2.25–2.20 (m, 2H), 2.17–2.00 (m, 7H), 1.98–1.87 (m, 2H), 1.85–1.76 (m,

2H), 1.70–1.55 (m, 5H), 1.44 (s, 3H), 1.42 (s, 3H), 1.39–1.16 (m, 6H), 1.09–1.04 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.4, 142.3, 128.61, 128.60, 128.52, 128.49, 126.03, 126.02, 85.80, 85.77, 85.0, 84.9, 58.6, 58.5, 44.1, 44.0, 41.7, 41.4, 37.1, 36.9 35.7, 35.6, 32.34, 32.33, 31.2, 31.1, 27.51, 27.48, 26.31, 26.30, 24.4, 24.0, 23.3, 23.1; IR (ATR) 2943, 2865, 1496, 1453, 1365 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{21}H_{33}O_2$ $(M + H)^+$ 317.2475, found 317.2470.

2-((5*s*,8*s*)-3-Methyl-8-phenyl-1,2-dioxaspiro[4.5]decan-3-yl)ethan-1-ol (33). Following the representative procedure for the synthesis of 1,2-dioxolanes, mixed peroxyketal **28** (0.200 g, 0.458 mmol), alkene **29** (0.188 g, 0.938 mmol), $SnCl_4$ (0.023 mL, 0.023 mmol, 1 M in CH_2Cl_2), CH_2Cl_2 (3 mL), TBAF (0.92 mL, 0.92 mmol, 1 M in THF), and THF (3 mL) were combined to afford mixed peroxyketal **33** (0.061 g, 51%) as a white solid: mp = 77–79 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2H), 7.21–7.17 (m, 3H), 3.86–3.78 (m, 2H), 2.52–2.47 (m, 1H), 2.21 (d, *J* = 12.0, 1H), 2.16 (m, 1H and d, *J* = 12.0, 1H), 2.12–2.08 (m, 1H), 2.07–2.03 (m, 1H), 1.87–1.81 (m, 2H), 1.80–1.73 (m, 3H), 1.70–1.65 (m, 1H), 1.58 (td, *J* = 13.7, 4.2, 1H), 1.40 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 147.5, 129.1, 127.6, 126.7, 85.2, 84.3, 59.6, 58.0, 44.1, 42.2, 36.3, 35.9, 31.3, 31.2, 24.9; IR (ATR) 3397, 3026, 2930, 1451 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{17}H_{25}O_3$ $(M + H)^+$ 277.1795, found 277.1798.

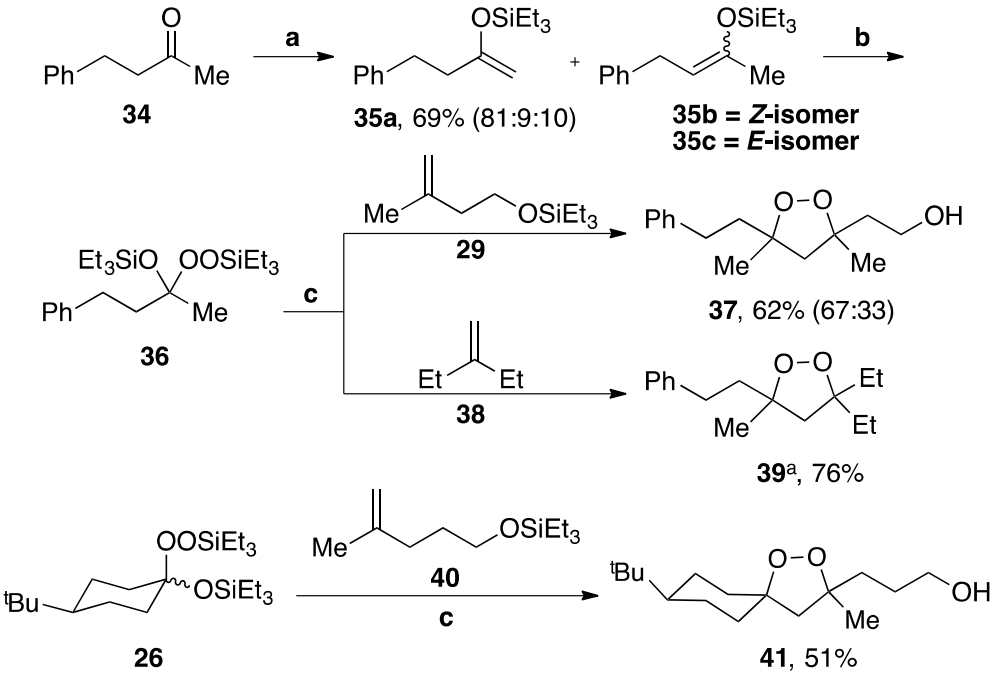


Figure 5b. a. (1) ^{i}Pr$_2$NH, ^{n}BuLi, THF, −78 °C (2) Et_3SiCl, THF, −78 °C; **b.** $Co(thd)_2$, Et_3SiH, $PhCF_3$, O_2 (balloon); **c.** (1) $SnCl_4$, CH_2Cl_2, −78 °C (2) TBAF, THF, rt. [a]deprotection with TBAF not necessary.

2-(3,5-Dimethyl-5-phenethyl-1,2-dioxolan-3-yl)ethan-1-ol (**37**). Following the representative procedure for the synthesis of 1,2-dioxolanes, mixed peroxyketal **36** (0.377 g, 0.918 mmol), alkene **29** (0.367 g, 1.84 mmol), $SnCl_4$ (0.046 mL,

0.046 mmol, 1 M in CH_2Cl_2), CH_2Cl_2 (3 mL), TBAF (1.8 mL, 1.8 mmol, 1 M in THF), and THF (0.75 mL) were combined to afford **37** (0.142 g, 62%) in a 67:33 mixture of diastereomers as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.25 (m, 4H), 7.20–7.17 (m, 6H), 3.87–3.73 (m, 4H), 2.76–2.60 (m, 4H), 2.39–2.30 (m, 2H), 2.28–2.15 (m, 2H), 2.10–1.96 (m, 5H), 1.92–1.79 (m, 5H), 1.42 (s, 3.3H), 1.40 (s, 3.2H), 1.40 (s, 2.5H), 1.37 (s, 2.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.9, 128.65, 128.64, 128.47, 128.45, 126.13, 126.09, 86.18, 86.15, 86.1, 86.0, 59.5, 59.4, 57.0, 56.9, 41.7, 41.6, 41.24, 41.21, 31.2, 31.0, 24.6, 24.4, 24.3, 23.6; IR (ATR) 3429, 2973, 2933, 1454, 1052 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{15}H_{26}NO_3$ $(M + NH_4)^+$ 268.1907, found 268.1902.

3,3-Diethyl-5-methyl-5-phenethyl-1,2-dioxolane (39). Following the representative procedure for the synthesis of 1,2-dioxolanes, mixed peroxyketal **36** (0.060 g, 0.25 mmol), alkene **38** (0.036 mL, 0.29 mmol), $SnCl_4$ (0.013 mL, 0.013 mmol, 1 M in CH_2Cl_2), and CH_2Cl_2 (1 mL) were combined to afford **39** (0.027 g, 76%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.21–7.19 (m, 3H), 2.73 (td, *J* = 13.2, 4.8, 1H), 2.64 (td, *J* = 13.2, 4.8, 1H), 2.20 (d, *J* = 12.0, 1H), 2.11 (d, *J* = 12.0, 1H), 2.03 (td, *J* = 13.6, 5.2, 1H), 1.88–1.70 (m, 3H), 1.61–1.48 (m, 2H), 1.44 (s, 3H), 0.95–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.7, 128.5, 126.1, 89.2, 85.5, 54.5, 41.6, 31.2, 28.5, 28.4, 24.2, 8.9, 8.8; IR (ATR) 2952, 2898, 1481, 1404, 1217 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{16}H_{24}KO_2$ $(M + K)^+$ 248.1807, found 248.1810.

Triethyl((4-methylpent-4-en-1-yl)oxy)silane (40). To a solution of 4-methyl-4-penten-1-ol (1.17 mL, 11.6 mmol) in CH_2Cl_2 (13 mL) was added imidazole (1.74 g, 23.2 mmol) followed by Et_3SiCl (3.9 mL, 23.2 mmol). The reaction mixture was allowed to stir overnight. The reaction mixture was quenched by the addition of 5% aqueous HCl (20 mL). The product was extracted into CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (1 X 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexanes) afforded **40** as a clear oil (0.120 g, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.69 (d, *J* = 12.6, 1H), 4.67 (d, *J* = 12.6, 1H), 3.60 (t, *J* = 6.6, 2H), 2.05 (t, *J* = 7.8, 2H), 1.72 (s, 3H), 1.65 (p, *J* = 7.8, 6.6, 2H), 0.95 (t, *J* = 3.6, 9H), 0.59 (q, *J* = 3.6, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 109.9, 62.7, 34.1, 31.0, 22.6, 6.9, 4.5; IR (ATR) 2950, 2912, 2877, 1095, 725 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{12}H_{27}OSi$ $(M + H)^+$ 215.1831, found 215.1830.

3-((5*s*,8*s*)-8-(*tert*-Butyl)-3-methyl-1,2-dioxaspiro[4.5]decan-3-yl)propan-1-ol (41). Following the representative procedure for the synthesis of 1,2–dioxolanes, mixed peroxyketal **26** (0.100 g, 0.229 mmol), alkene **30** (0.066 mg, 0.308 mmol), $SnCl_4$ (0.095 mL, 1 M in CH_2Cl_2), CH_2Cl_2 (2 mL), THF (2 mL), and TBAF (0.700 mL, 1 M in THF) were combined to afford **41** (0.031 g, 23%) as a single diastereomer as a white solid: mp = 64–66 °C; ^{1}H NMR (600 MHz, C_6D_6) δ 3.35 (t, *J* = 6.1, 2H), 2.04 (dq, *J* = 13.6, 2.7, 2H), 1.87 (d, *J* = 11.8, 1H), 1.72 (d, *J* = 11.8, 1H), 1.69–1.66 (m, 1H), 1.53–1.40 (m, 7H), 1.19 (s, 3H), 1.21–1.14 (m, 2H), 0.83 (s, 9H), 0.87–0.79 (m, 2H); ^{13}C (150 MHz, $CDCl_3$) δ 85.1, 84.3, 63.2, 58.0, 47.8, 36.6, 36.5, 36.3, 32.7, 28.5, 28.0, 24.6, 24.5, 24.4; IR (ATR) 3353, 2942, 1365 cm^{-1}; HRMS (APCI) *m / z* calcd for $C_{16}H_{29}O_2$ $(M + H - H_2O)^+$ 253.2162, found 253.2157.

Synthesis of Arachidonic Acids

All deuterated arachadonic acids were synthesized according to a known literature procedure.[9, 10]

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