SUPPORTING INFORMATION

2-(Aryl-Sulfonyl)Oxetanes as Designer 3-Dimensional Fragments for Fragment Screening: Synthesis and Strategies for Functionalisation

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General Experimental Conditions

All non-aqueous reactions were run under an inert atmosphere (argon or nitrogen) with flame-dried or oven-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns or obtained from commercial suppliers and used without further purification (THF, CH₂Cl₂, toluene, DMF).

Flash column chromatography was performed using 230-400 mesh silica, 70-290 mesh basic alumina modified to activity IV or ISCO Flash Silica cartridges with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), or aqueous potassium permanganate stain.

Infrared spectra (FTIR) were recorded in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm) or using chloroform with 1% tetramethylsilane as the internal standard. Data is reported as follows: chemical shift [integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz]. ¹³C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (¹³CDCl₃: 77.0 ppm) or using chloroform with 1% tetramethylsilane as the internal standard.

Assignments of ¹H and ¹³C spectra were made by the analysis of δ/J values and COSY, HSQC and HMBC experiments as appropriate.

Melting points are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary.

Compound Handling/Purification/Storage:
All synthetic intermediates were stored under argon at −20 °C for short periods. Oxetanes 1a-d were bench stable; oxetane 1a was stored at rt for 3 months without degradation.

Where required for purification, the activity of basic alumina was altered by the addition of water to commercial basic alumina (activity I) and evenly distributed (activity IV: 10% w/w water).¹

Preparation of a 0.61M solution of LiHMDS.
A solution of HMDS (0.14 ml, 0.67 mmol) in THF (0.48 mL) was cooled to −78 °C for 5 min then nBuLi (0.38 mL, 0.61 mmol, 1.6 M in hexane) was added dropwise. Solution stirred at −78 °C for 30 min then warmed to 0 °C for 30 min prior to use.
Initial investigations treated sulfone 4a (0.52 mmol) with base (2 equiv.) in THF at 0 °C for 1 h then warmed to rt for 1 h (Table S1, entries 1-7). Amine bases were generally successful in promoting cyclisation, with LiHMDS the most effective, especially when freshly prepared (entries 7 and 8).

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^a Conditions A, addition of the substrate to a solution of the base; Conditions B, addition of the base to a solution of the substrate. ^b Yield determined by 1H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard. ^c Base made immediately prior to use. ^d Reaction run at –78 °C as opposed to 0 °C. ^e Reaction time of 1 h.

The order of addition of the base and substrate was examined next using LiHMDS and nBuLi as they were the two most effective bases under the original conditions adding a solution of tosyl sulfone 4a to a solution of base in THF. Reversing the addition, base added to sulfone, resulted in a marked increase in yield using LiHMDS to 89% by 1H NMR (entries 8 and 10). Under these conditions the amount of LiHMDS could be reduced to 1.2 equiv affording a further increase in yield (entry 11). The concentration of the reaction was next investigated, maintaining relatively dilute conditions to favour intramolecular cyclisation. Increasing the concentration from 0.025 M to 0.05 M gave a notable reduction in yield (entry 12). More dilute conditions (entry 13) gave a marginal increase in yield and 0.025 M was chosen as optimal. The reaction time could be reduced to 1 h at 0 °C (entry 14). Further reduction of the amount of base to 1.1 equiv gave the optimal reaction conditions (entry 15) which afforded a quantitative conversion to the oxetane product; decreasing the equivalents further resulted in a decrease in yield (entry 16).

Under these conditions, the synthesis was scaled up to 6.5 mmol to give 1.2 g oxetane 1a with a 93% isolated yield (Scheme 1).
Electronic Supplementary Material (ESI) for Chemical Communications

K. F. Morgan, I. A. Hollingsworth, J. A. Bull

**Synthesis of 2-[(4-methylphenyl)sulfonyl]oxetane 1a**

**p-Methylphenyl chloromethyl sulfide (2a)**

Potassium carbonate (122.2 g, 885 mmol) was added to a solution of 4-methyl benzene thiol S1 (100 g, 805 mmol) in acetone (1 L) followed by Mel (52.6 mL, 845 mmol) and the reaction stirred at rt for 14 h. The reaction was filtered through celite and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with ether (150 mL) then the combined organics were washed with brine (100 mL), dried (Na2SO4) and solvent removed under reduced pressure to afford p-tolyl methyl sulfide S2 (109.3 g, 98%) as a yellow liquid which was used without further purification. 1H NMR (400 MHz, CDCl3) δ 7.20 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.11 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 2.48 (3 H, s, SCH3), 2.33 (3 H, s, CH3). 13C NMR (100 MHz, CDCl3) δ 135.0 (Ar-C), 134.6 (Ar-C), 129.6 (2 × Ar-C), 127.22 (2 × Ar-C), 21.0 (Ar-CH3), 16.5 (CH3). The observed data (1H, 13C) was consistent with that reported in the literature.2

N-Chlorosuccinimide (33.4 g, 250 mmol) was added portionwise to a solution of p-tolyl methyl sulfide (S2) (34.6 g, 228 mmol) in carbon tetrachloride (250 mL). The reaction was stirred at rt for 14.5 h then filtered through a short pad of silica, eluting with CCl4 (30 mL) and the solvent removed under reduced pressure. Purification by vacuum distillation afforded chloromethyl sulfide 2a (36.9 g, 94%) as an orange oil. b.p. = 98 °C at 2.1 mbar (lit. b.p. = 88 °C at 0.2 Torr).3 1H NMR (400 MHz, CDCl3) δ 7.46 (2 H, d, J = 8.5 Hz, 2 × Ph-H), 7.21 (2 H, d, J = 8.5 Hz, 2 × Ph-H), 4.95 (2 H, s, CH2), 2.39 (3 H, s, CH3). 13C NMR (100 MHz, CDCl3) δ 138.3 (Ar-C), 131.6 (2 × Ar-C), 129.9 (2 × Ar-C), 129.4 (Ar-C), 51.9 (CH2), 21.1 (CH3). The observed data (1H, 13C) was consistent with that reported in the literature.4

**p-Tolyl sulfanylmethoxy-ethanol (3a)**

Sodium hydride (60% in mineral oil, 2.57 g, 64.2 mmol) was added to ethylene glycol (400 mL) at 0 °C and stirred for 1 h 15 min. Sodium iodide (9.62 g, 64.2 mmol) was added followed by a solution of sulfide 2a (10.04 g, 58.4 mmol) in ethylene glycol (5 mL). The resulting solution was stirred at 0 °C for 1 h then warmed to rt for 4 h. H2O (300 mL) was added and the product was extracted with ethyl acetate (10 × 50 mL). The combined organic layers were dried (MgSO4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% ETOAc/hexane) afforded alcohol 3a (9.60 g, 83%) as a yellow oil. Rf = 0.34 (50% ETOAc/hexane). IR (film)/cm⁻¹ 3449, 2926, 2782, 1734, 1493, 1461, 1373, 1250, 1052, 806, 734. 1H NMR (400 MHz, CDCl3) δ 7.38 (2 H, d, J = 8.1 Hz, 2 × Ar-H), 7.13 (2 H, d, J = 8.1 Hz, 2 × Ar-H), 5.00 (2 H, s, SCH3O), 3.78–3.72 (4 H, m, OCH2CH2), 2.34 (3 H, s, CH3). 13C NMR (100 MHz, CDCl3) δ 137.2 (Ar-C), 131.5 (Ar-C), 131.1 (2 × Ar-C), 129.8 (2 × Ar-C), 77.0 (SCH2O), 69.7 (OCH2), 61.7 (OCH2), 21.1 (CH3). HRMS (ESI) m/z Calculated for C10H14Na2O2S2⁺ [M+Na]⁺: 221.0607; Found: 221.0607 [M+Na]⁺.

**Toluene-4-sulfonic acid 2-p-tolylsulfanylmethoxy ethyl ester (S3)**

Triethylamine (3.14 mL, 22.5 mmol) and trimethylamine hydrochloride (70 mg, 0.75 mmol) were added to a solution of sulfide 3a (1.50 g, 7.5 mmol) in toluene (10 mL) at 0 °C and stirred for 10 min. A suspension of 4-toluenesulfonyl chloride (2.86 g, 15 mmol) in toluene (10 mL) was added dropwise. The mixture was stirred at 0°C for 30 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 20 min. H2O (100 mL) was added to the reaction and the product was extracted with EtOAc (4 × 50 mL). The
combined organic layers were washed with brine (50 mL) and H$_2$O (30 mL) then dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded tosylate S$_3$ (2.50 g, 97%) as a yellow oil. R$_f$ = 0.34 (40% EtOAc/hexane). IR (film)/cm$^{-1}$ 2984, 2891, 1596,1499, 1362, 1237, 1175, 1095, 1011, 915, 807. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.79 (2 H, d, J = 8.2 Hz, 2 × Ts-H), 7.34–7.30 (4 H, m, 2 × Ts-H + 2 × Tol-H), 7.10 (2 H, d, J = 8.2 Hz, 2 × Tol-H), 4.90 (2 H, s, SCH$_2$O), 4.22–4.18 (2 H, m, TsOCH$_2$), 3.83–3.78 (2 H, m, CH$_2$OCH$_2$), 2.45 (3 H, s, Ts-CH$_3$), 2.33 (3 H, s, Tol-CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 132.7 (2 C, C), 129.7 (4 C, Ar), 129.5 (2 × Ar-C), 129.7 (2 × Ar-C), 127.9 (2 × Ar-C), 127.9 (2 × Ar-C), 76.8 (SCH$_2$O), 68.7 (SCH$_2$OCH$_2$), 65.5 (TsOCH$_2$), 21.6 (Ts-CH$_3$), 21.0 (Tol-CH$_3$). HRMS (ESI) m/z Calculated for C$_{17}$H$_{23}$NO$_5$S$_2^+$ [M+NH$_4$]$^+$: 370.1141; Found: 370.1134 [M+NH$_4$]$^+$.  

Toluene-4-sulfonic acid 2–toluene 4-sulfonylmethoxy ethyl ester (4a)  

meta-Chloroperbenzoic acid (1.47 g, 8.50 mmol) was added to a solution of sulfide S$_3$ (1.00 g, 2.84 mmol) in dichloromethane (15 mL) at 0 ºC and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with Na$_2$SO$_3$ (25 mL) and extracted with dichloromethane (6 × 20 mL). The combined organic layers were washed with 1 M NaOH (3 × 15 mL) and sat. aq. NH$_4$Cl (50 mL) then dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone 4a (1.04 g, 96%) as a white solid; mp = 73–79 ºC. R$_f$ = 0.65 (EtOAc). IR (film)/cm$^{-1}$ 2992, 2926, 2885, 1599, 1461, 1350, 1327, 1300, 1170, 1170, 1130, 1080, 813. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81–7.79 (13 H, m, 4 × Ar-H), 4.52 (2 H, s, SCH$_2$O), 4.19–4.15 (2 H, m, TsOCH$_2$), 4.12–4.08 (2 H, m, TsOCH$_2$CH$_2$), 2.49 (3 H, s, Ts-CH$_3$), 2.48 (3 H, s, Tol-CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.4 (Ar-C$_{3}$), 145.0 (Ar-C$_{3}$), 133.9 (Ar-C$_{3}$), 132.7 (Ar-C$_{3}$), 130.0 (2 × Ar-C), 129.9 (2 × Ar-C), 128.9 (2 × Ar-C), 127.9 (2 × Ar-C), 86.2 (SCH$_2$O), 70.6 (TsOCH$_2$CH$_2$), 68.5 (TsOCH$_2$), 21.7 (CH$_3$), 21.7 (CH$_3$). HRMS (ESI) m/z Calculated for C$_{17}$H$_{23}$NO$_5$S$_2^+$ [M+NH$_4$]$^+$: 402.1040; Found: 402.1040 [M+NH$_4$]$^+$.  

2-[(4-Methylphenyl)sulfonyl] oxetane (1a)  

A solution of LiHMDS (0.61 M in THF, 11.7 mL, 7.16 mmol) was added dropwise to a solution of sulfone 4a (2.50 g, 6.51 mmol) in THF (250 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH$_4$Cl (200 mL) and extracted with CHCl$_3$ (8 × 30 mL). The combined organics were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane 1a (1.28 g, 93%) as a white solid; mp = 106–108 ºC. R$_f$ = 0.26 (40% EtOAc/hexane). IR (film)/cm$^{-1}$ 2977, 2901, 1596, 1447, 1406, 1310, 1147, 1089, 1030, 984, 909, 816, 717. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.39 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 5.37 (1 H, dd, J = 7.4, 5.6 Hz, OCHS), 4.80–4.74 (1 H, m, OCH/H), 4.67–4.61 (1 H, m, OCH/H), 3.17–3.05 (2 H, m, OCH$_2$CH$_2$), 2.47 (3H, s, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.4 (Ar-C$_{3}$), 132.2 (Ar-C$_{3}$), 129.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (OCHS), 71.3 (OCH$_2$), 22.4 (OCH$_2$CH$_2$), 21.7 (CH$_3$). HRMS (APCI) m/z Calculated for C$_{16}$H$_{15}$O$_2$S$^+$ [M+H]$^+$: 213.0580; Found: 213.0580 [M+H]$^+$. 

Electronic Supplementary Material (ESI) for Chemical Communications  

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**Synthesis of 2-((phenyl)sulfonyl)oxetane 1b**

2-((Phenylothio)methoxy)ethanol (3b)

Sodium hydride (60% in mineral oil, 0.70 g, 17.6 mmol) was added to ethylene glycol (100 mL) at 0 °C and stirred for 1 h 15 min. Sodium iodide (2.60 g, 17.3 mmol) was added followed by sulfide 2b (2.50 g, 15.7 mmol). The resulting solution was stirred at 0 °C for 1 h then warmed to rt for 5 h. H₂O (100 mL) was added and the product was extracted with ethyl acetate (6 × 40 mL). The combined organic layers were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded alcohol 3b (2.54 g, 87%) as a colourless oil. Rf = 0.42 (50%, EtOAc/hexane). IR (film/cm⁻¹) 3402, 2927, 1583, 1480, 1370, 1304, 1102, 1053, 887, 823, 690, 673. ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.46 (2 H, m, 2 × Ar-H), 7.33–7.27 (2 H, m, 2 × Ar-H), 7.20.65 (3 H, m, 3 × Ph). ²H NMR (400 MHz, CDCl₃) δ 5.03 (2 H, s, SCH₂), 3.74–3.69 (4 H, m, OCH₂CH₂), 2.32 (1 H, s, OH). ³C NMR (100 MHz, CDCl₃) δ 144.9 (Ar-C₂), 137.4 (Ar-C₃), 130.1 (2 × Ar-C), 129.8 (2 × Ar-C), 127.4 (Ar-C), 76.4 (SCH₂O), 69.9 (OCH₂), 61.6 (OCH₂). HRMS (EI) m/z Calculated for C₁₆H₁₂O₂S⁺ [M⁺]: 284.0553; Found: 284.0550 [M⁺].

2-((Phenylothio)methoxy)ethyl 4-methylbenzenesulfonate (S4)

Triethylamine (5.54 mL, 39.7 mmol) and trimethylamine (2.11 mL, 15.7 mmol) were added to a solution of sulfide 2b (2.44 g, 13.2 mmol) in toluene (20 mL) at 0 °C and stirred for 20 min. A suspension of 4-toluenesulfonyl chloride (5.05 g, 26.5 mmol) in toluene (15 mL) was added dropwise. The mixture was stirred at 0 °C for 35 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 30 min. H₂O (150 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with H₂O (20 mL) and brine (10 mL) then dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded tosylate S4 (4.40 g, 98%) as a colourless oil. Rf = 0.49 (40% EtOAc/hexane). IR (film/cm⁻¹) 2972, 2903, 1593, 1566, 1468, 1443, 1389, 1314, 1270, 1231, 1185, 1064, 1029, 938, 908, 859, 829, 737, 722, 697, 677. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.43–7.39 (2 H, m, 2 × Ph-H), 7.30 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.29–7.19 (3 H, m, 3 × Ph-H), 4.93 (2 H, s, SCH₂O), 4.21–4.18 (2 H, m, TsOCH₂), 3.81–3.79 (2 H, m, CH₂OCH₂), 2.43 (3 H, s, CH₃). ³C NMR (100 MHz, CDCl₃) δ 144.8 (Ts-C₂), 135.3 (Ph-C₃), 130.0 (Ts-C₄), 129.8 (2 × Ar-C), 129.8 (2 × Ar-C), 127.9 (2 × Ar-C), 126.9 (Ar-C), 76.3 (SCH₂O), 68.7 (SCH₂OCH₂), 65.7 (TsOCH₂), 21.6 (CH₃). HRMS (Cl) m/z Calculated for C₁₈H₂₂NO₄S₂⁺ [M+N₂H⁺]: 356.0990; Found: 356.0997 [M+N⁺].

2-((Phenylothio)methoxy)ethyl 4-methylbenzenesulfonate (4b)

meta-Chloroperbenzoic acid (8.34 g, 37.2 mmol) was added to a solution of sulfide S4 (4.20 g, 12.4 mmol) in dichloromethane (65 mL) at 0 °C and the mixture stirred at 0 °C for 4 h. The reaction was quenched with Na₂SO₃ (60 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic layers were washed with 2 M NaOH (3 × 30 mL) and sat.aq. NH₄Cl (60 mL) then dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone 4b (4.27 g, 93%) as a white solid, mp = 82–83 °C. Rf = 0.19 (40% EtOAc/hexane). IR (film/cm⁻¹) 3071, 1594, 1493, 1445, 1419, 1323, 1296, 1251, 1149, 1127, 1080, 1016, 927, 939, 893, 818, 803, 705. ¹H NMR (400 MHz, CDCl₃) δ 7.93–7.90 (2 H, m,
2 x Ts-H), 7.77 (2 H, dt, J = 8.3, 2.1 Hz, 2 x Ph-H), 7.70 (1 H, tt, J = 7.4, 1.3 Hz, Ph-H), 7.61–7.56 (2 H, m, 2 x Ph-H), 7.35–7.31 (2 H, m, 2 x Ts-H), 4.52 (2 H, s, SCH₂O), 4.18–4.15 (2 H, m, TsOCH₂), 4.10–4.08 (2 H, m, CH₂OCH₂), 2.45 (3 H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 145.0 (Ar-C), 137.0 (Ar-C), 134.2 (Ph-C), 132.8 (Ar-C), 129.9 (2 x Ar-C), 129.3 (2 x Ar-C), 128.8 (2 x Ar-C), 127.9 (2 x Ar-C), 86.2 (SCH₂O), 70.7 (SCH₂OCH₂), 68.4 (TsOCH₂), 21.6 (CH₃).

HRMS (ESI) m/z Calculated for C₁₆H₁₈O₆S₂Na⁺ [M+Na⁺]: 393.0442; Found: 393.0451 [M+Na⁺].

2-(Phenylsulfonyl)oxetane (1b)

A solution of LiHMDS (0.61 M in THF, 12.2 mL, 7.4 mmol) was added dropwise to a solution of sulfone 4b (2.50 g, 6.75 mmol) in THF (240 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH₄Cl (150 mL) and extracted with CH₂Cl₂ (5 x 50 mL). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/heptane) afforded oxetane 1b (1.01 g, 75%) as a white solid, mp = 87–88 ºC. Rf = 0.23 (40% EtOAc/heptane). IR (film)/cm⁻¹ 2996, 2980, 2908, 1583, 1478, 1445, 1301, 1288, 1266, 1144, 1084, 1026, 977, 901, 762, 730. ¹H NMR (400 MHz, CDCl₃) δ 8.01–7.97 (2 H, m, 2 x Ar-H), 7.70 (1 H, tt, J = 7.5, 1.4 Hz, Ar-H), 7.62–7.56 (2 H, m, 2 x Ar-H), 5.39 (1 H, dd, J = 7.1, 6.0 Hz, OCH₂S), 4.81–4.76 (1 H, m, OCH₂H), 4.67–4.62 (1 H, m, OCH₂H). ¹³C NMR (100 MHz, CDCl₃) δ 135.5 (Ar-C), 134.2 (Ar-C), 129.5 (2 x Ar-C), 129.2 (2 x Ar-C), 94.1 (OCHS), 71.4 (OCH₂), 22.4 (OCH₂CH₂). HRMS (APCI) m/z Calculated for C₉H₁₁O₃S⁺ [M+H⁺]: 199.0423; Found: 199.0423 [M+H⁺].

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Synthesis of 2-[(4-chlorophenyl)sulfonyl] oxetane 1c

![Chemical Structure](image)

Chloromethyl 4-chlorophenyl sulfide (2c)

Potassium carbonate (109.7 g, 795 mmol) was added to a solution of 4-chlorobenzene thiol S5 (95 g, 722 mmol) in acetone (1.1 L) followed by Mel (50.5 mL, 811 mmol) and the mixture stirred at rt for 4 h. The reaction was filtered through celite and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with ether (2 × 100 mL) then the combined organics were washed with brine (100 mL), dried (Na₂SO₄) and solvent removed under reduced pressure to afford 4-chlorophenyl methyl sulfide S6 (96.5 g, 84%) as a yellow liquid which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (2 H, m, 2 × Ar-H), 7.20 (2 H, m, 2 × Ar-H), 2.49 (3 H, s, SCH₃). N-Chlorosuccinimide (9.26 g, 69 mmol) was added portionwise to a solution of 4-chlorophenyl methyl sulfide S6 (10 g, 63 mmol) in carbon tetrachloride (65 mL). The reaction was stirred at rt for 19 h then filtered through a short pad of silica, eluting with CCl₄ (30 mL), and the solvent removed under reduced pressure to afford chloromethyl 4-chlorophenyl sulfide 2c (11.5 g, 94%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (2 H, d, J = 8.9 Hz, 2 × Ar-H), 7.36 (2 H, d, J = 8.9 Hz, 2 × Ar-H), 4.94 (2 H, s, SCH₂Cl). The observed data (¹H) was consistent with that reported in the literature.

2-(((4-Chlorophenyl)thio)methoxy)ethanol (3c)

Sodium hydroxide (60% in mineral oil, 1.56 g, 38.9 mmol) was added to ethylene glycol (200 mL) at 0 °C and stirred for 30 min. Sodium iodide (5.83 g, 38.9 mmol) was added followed by chloromethyl 4-chlorophenyl sulfide 2c (6.26 g, 32.4 mmol) using DMF (5 mL) to aid transfer. The resulting solution was stirred at 0 °C for 3 h then warmed to rt for 12 h. The reaction was quenched by the addition of sat. aq. NH₂Cl (200 mL) and the mixture extracted with EtOAc (4 × 75 mL). The combined organic layers were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded alcohol 3c (5.27 g, 74%) as a colourless oil. Rₚ = 0.31 (50% EtOAc/hexane). IR (film)/cm⁻¹ 3388, 2934, 2872, 1481, 1392, 1313, 1095, 1059, 1013, 816, 683. ¹H NMR (400 MHz, CDCl₃) δ 7.45–7.36 (2 H, m, 2 × Ar-H), 7.31–7.23 (2 H, m, 2 × Ar-H), 5.01 (2 H, s, SCH₂O), 3.80–3.69 (4 H, m, OCH₂CH₂), 2.08 (1 H, s, OH). ¹³C NMR (100 MHz, CDCl₃) δ 133.9 (Ar-Cₗ), 133.0 (Ar-C₂), 131.6 (2 × Ar-C), 129.1 (2 × Ar-C), 76.4 (SCH₂O), 69.8 (OCH₂), 61.5 (OCH₃). HRMS (ESI) m/z Calculated for C₉H₁₁ClNaO₂S⁺ [M+Na⁺]: 241.0060; Found: 241.0060 [M+Na⁺].

2-(((4-Chlorophenyl)thio)methoxy)ethyl 4-methylbenzenesulfonate (S7)

Triethylamine (6.19 mL, 44.4 mmol) and trimethylenemethane hydrochloride (141 mg, 1.48 mmol) were added to a solution of alcohol 3c (3.24 g, 14.8 mmol) in toluene (40 mL) at 0 °C and stirred for 20 min. 4-Toluenesulfonyl chloride (5.65 g, 29.6 mmol) was added to a solution of alcohol 3c (3.24 g, 14.8 mmol) in toluene (40 mL) at 0 °C and stirred for 20 min. The reaction was quenched by the addition of sat. aq. NaHCO₃ (200 mL) and the mixture extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. NH₂Cl (100 mL) then dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded tosylate S7 (5.39 g, 98%) as a colourless oil. Rₚ = 0.24 (20% EtOAc/hexane). IR (film)/cm⁻¹ 2920, 1601,1482, 1358, 1180, 1095, 1093, 1017, 922, 820, 776, 668, 559. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (2 H, d,
2-(((4-Chlorophenyl)sulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (4c)

(meta-Chloroperbenzoic acid (7.5 g 43.5 mmol) was added to a solution of sulfide S7 (5.39 g, 14.5 mmol) in dichloromethane (75 mL) at 0 ºC and the mixture stirred at 0 ºC for 5 h. The reaction was quenched with Na2SO3 (125 mL) and extracted with dichloromethane (6 × 35 mL). The combined organic layers were washed with 1 M NaOH (3 × 25 mL) and sat. aq. NH4Cl (100 mL) then dried (MgSO4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone 4c (5.58 g, 95%) as a white solid, mp = 87–88 ºC. Rf = 0.19 (40% EtOAc/hexane). IR (film)/cm⁻¹ 3130, 2952, 2892, 1578, 1495, 1474, 1423, 1397, 1357, 1323, 1291, 1135, 1108, 1040, 1017, 948, 804, 728, 701, 686. ¹H NMR (400 MHz, CDCl₃) δ 7.84 (2 H, d, J = 9.0 Hz, 2 × Ts-H), 7.77 (2 H, d, J = 7.8 Hz, 2 × Ar-H), 7.54 (2 H, d, J = 9.0 Hz, 2 × Ts-H), 7.42 (2 H, d, J = 7.8 Hz, 2 × Ar-H), 4.53 (2 H, s, SCH₂), 3.91–4.40 (4 H, m, 2 × CH₂), 2.46 (3 H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 145.1 (Ts-C), 141.1 (Ar-C), 135.2 (Ts-C), 132.6 (Ar-C), 130.4 (2 × Ar-C), 129.9 (2 × Ar-C), 129.6 (2 × Ar-C), 127.9 (2 × Ar-C), 86.0 (SCH₂O), 70.6 (TsOCH₂CH₂), 68.4 (TsOCH₂), 21.7 (CH₃). HRMS (ESI) m/z Calculated for C₁₆H₁₇ClNaO₆S₂⁺ [M+Na]⁺: 427.0044 Found: 427.0047 [M+Na]⁺.

2-(((4-Chlorophenyl)sulfonyl)oxetane (1c)

A solution of LiHMDS (0.61 M in THF, 4.45 mL, 2.72 mmol) was added dropwise to a solution of sulfone 4c (0.99 g, 2.47 mmol) in THF (100 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH₄Cl (100 mL) and extracted with CHCl₃ (8 × 20 mL). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane 1c (0.48 g, 84%) as a white solid, mp = 91–93 ºC. Rf = 0.36 (40% EtOAc/hexane). IR (film)/cm⁻¹ 3092, 2977, 2927, 1654, 1581, 1474, 1393, 1312, 1273, 1144, 1087, 1010, 976, 940, 897, 843, 712. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (2 H, d, J = 8.6 Hz, 2 × Ar-H), 7.56 (2 H, d, J = 8.6 Hz, 2 × Ar-H), 5.37 (1 H, dd, J = 7.6, 5.4 Hz, OCHS), 4.83–4.77 (1 H, m, OCH₃), 4.66 (1 H, dt, J = 8.6, 6.1 Hz, OCHH), 3.18–3.05 (2 H, m, OCH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 141.2 (Ar-C), 133.7 (Ar-C), 130.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (OCHS), 71.5 (OCH₂), 22.2 (OCH₂CH₂). HRMS (APCI) m/z Calculated for C₉H₁₀ClO₃S⁺ [M+H]⁺: 233.0034 Found: 233.0034 [M+H]⁺.

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J = 8.6 Hz, 2 × Ts-H), 7.38–7.31 (4 H, m, 2 × Ts-H + 2 × Ar-H), 7.26–7.20 (2 H, m, 2 × Ar-H), 4.92 (2 H, s, SCH₂O), 4.24–4.19 (2 H, m, TsOCH₂), 3.84–3.80 (2 H, m, CH₂OCH₂), 2.45 (3 H, s, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 144.9 (Ts-C), 133.7 (Ar-C), 133.0 (Ts-C), 132.8 (Ar-C), 131.7 (2 × Ar-C), 129.8 (2 × Ar-C), 129.0 (2 × Ar-C), 127.9 (2 × Ar-C), 76.3 (SCH₂O), 68.6 (SCH₂OCH₂), 65.6 (TsOCH₂), 21.7 (CH₃). HRMS (ESI) m/z Calculated for C₁₆H₂₁ClNO₃S₂⁺ [M+NH₄]⁺: 390.0595; Found: 390.0595 [M+NH₄]⁺.
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Synthesis of 2-(Oxetan-2-ylsulfonyl)pyridine 1d

2-((Chloromethly)thio)pyridine (2d)
Sodium hydride (60% in mineral oil, 0.79 g, 19.8 mmol) was added to a solution of 2-mercaptopyridine S8 (2.0 g, 18.0 mmol) in DMF (50 mL) at −5 °C and stirred for 10 min. A solution of chloroiodomethane (1.96 mL, 27 mmol) in DMF (7 mL) was added in one portion and stirred for 1 h 45 min at rt. The reaction was quenched by the addition of sat. aq. NH4Cl (100 mL) and diluted with EtOAc (30 mL) then extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with H2O (3 × 20 mL) and brine (20 mL) then dried (MgSO4), filtered and the solvent removed under reduced pressure to give an orange oil. The crude product was purified by flash chromatography (0-80% EtOAc/hexanes) to afford alcohol 3d (1.46 g, 63% yield) as a colourless oil. Rf = 0.59 (80% EtOAc/heptane).

2-(Pyridine-2-ylthio)methoxyethanol (3d)
Sodium hydride (60% in mineral oil, 0.55 g, 13.78 mmol) was added to ethylene glycol (120 mL) at 0 °C and stirred for 55 min. Sodium iodide (2.06 g, 13.78 mmol) was added followed by 2-((chloromethly)thio)pyridine 2d (2.0 g, 12.53 mmol) using ethylene glycol (1 mL) to aid transfer. The resulting solution was stirred at 0 °C for 25 min then warmed to rt for 1 h 20 min. The reaction was quenched by the addition of water (150 mL) and the mixture extracted with EtOAc (10 × 35 mL). The combined organic layers were dried (MgSO4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0-80% EtOAc/heptane) afforded alcohol 3d (1.46 g, 63%) as a colourless oil. Rf = 0.59 (80% EtOAc/heptane).

2-((Pyridin-2-ylthio)methoxy)ethyl 4-methylbenzenesulfonate (S9)
Triethylamine (4.06 mL, 29.22 mmol) and trimethylamine hydrochloride (93 mg, 0.97 mmol) were added to a solution of alcohol 3d (0.90 g, 4.86 mmol) in toluene (30 mL) at 0 °C and stirred for 30 min. A solution of 4-toluenesulfonyl chloride (3.71 g, 19.44 mmol) in toluene (10 mL) was added and the mixture was stirred at 0 °C for 35 min then at rt for 2 h 35 min. The reaction was quenched by the addition of water (50 mL) and the mixture extracted with EtOAc (7 × 30 mL). The combined organic layers were washed with H2O (30 mL) and brine (30 mL) then dried (MgSO4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0-40% EtOAc/heptane) afforded tosylate S9 (1.57 g, 95%) as a colourless oil. Rf = 0.36 (40% EtOAc/heptane).

IR (film)/cm−1: 3071, 2924, 1610, 1533, 1494, 1453, 1419, 1353, 1281, 1216, 1172, 1119, 1032, 1009, 916, 816, 767, 680. 1H NMR (400 MHz, CDCl3) δ 8.43–8.41 (1 H, m, Py-H), 7.76 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.50 (1 H, ddd, J = 8.0, 7.4, 1.9 Hz, Py-H), 7.31 (2 H, d, J = 8.3 Hz, 2 × Ts-H), 7.24 (1 H, dt, J = 8.0, 1.0 Hz, Py-H), 7.02 (1 H,
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2-((Pyridin-2-ylsulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (4d)

A solution of LiHMDS (0.61 M in THF, 4.08 mL, 2.49 mmol) was added dropwise to a solution of sulfone 4d (0.56 g, 1.52 mmol) in THF (70 mL) at 0 °C and stirred for 1 h. Reaction quenched with sat. aq. NH₄Cl (50 mL) and extracted with CH₂Cl₂ (5 × 30 mL). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/heptane) afforded oxetane 1d (0.25 g, 81%) as a white solid, mp = 64–65 ºC. Rᵣ = 0.16 (40% EtOAc/heptane). IR (film)/cm⁻¹: 3101, 3051, 2974, 2904, 1580, 1426, 1415, 1311, 1272, 1230, 1108, 1040, 1024, 991, 906, 792, 734, 682. ³¹H NMR (400 MHz, CDCl₃) δ 8.77–8.75 (1 H, m, Py-H), 8.17 (1 H, dt, J = 7.8, 1.0 Hz, Py-H), 7.97 (1 H, td, J = 7.8, 1.8 Hz, Py-H), 7.56 (1 H, ddd, J = 7.7, 4.7, 1.2, Py-H), 5.96 (1 H, dd, J = 8.0, 5.2 Hz, OCH₅), 4.93–4.87 (1 H, m, OCHH), 4.71–4.66 (1 H, m, OCHH), 3.31–3.15 (2 H, OCH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 155.1 (Py-C₆), 150.4 (Py-C), 138.0 (Py-C), 127.6 (Py-C), 124.3 (Py-C), 91.9 (OCH₅), 72.0 (OCH₂), 21.9 (OCH₂CH₂). HRMS (ESI) m/z Calculated for C₈H₁₃NO₃S²⁺ [M+H]⁺: 200.0386; Found: 200.0389 [M+H]⁺.
Optimisation of Deprotonation of 1a for Reaction with Electrophiles

With LiHMDS (Conditions A, Table 1)

Under the initial conditions oxetane 1a was treated with various bases at T1 for time 1 prior to the addition of MeI to form oxetane 5. The reaction was then warmed to T2 over time 2. Entries 1-4 in table S2 show that under these conditions LiHMDS was the best base affording a yield of 76%. Warming to 0 °C was required; quenching the reaction at −78 °C afforded a much lower yield (entry 5). Increasing the deprotonation time to 30 min did increase the yield to 84% (entry 6). The equivalents of LiHMDS employed were also investigated however it was found that increasing the equivalents to 1.3 and 1.5 did not affect the reaction yield. The addition of the substrate in THF to a solution of the base was favourable over the addition of the base to the substrate (entries 6 and 7).

Finally we investigated the addition of MeI immediately after the addition of base. Pleasingly this increased the yield of the reaction with MeI to 90% (entry 8), and provided our optimised set of conditions A.

**Table S2**: Selected optimisation: deprotonation of oxetane 1a to form oxetanes 5.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>order of addition</th>
<th>temperature 1 (T1, °C)</th>
<th>temperature 2 (T2 °C)</th>
<th>time 1 (min)</th>
<th>time 2 (min)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td>B</td>
<td>−78</td>
<td>−78 to 0</td>
<td>15</td>
<td>45</td>
<td>62</td>
</tr>
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<td>B</td>
<td>−78</td>
<td>−78 to 0</td>
<td>15</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>sBuLi</td>
<td>B</td>
<td>−78</td>
<td>−78 to 0</td>
<td>15</td>
<td>45</td>
<td>20</td>
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<td>4</td>
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<td>−78 to 0</td>
<td>15</td>
<td>45</td>
<td>76</td>
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<td>22</td>
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<td>−78 to 0</td>
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<td>45</td>
<td>84</td>
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<td>7</td>
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*Conditions: oxetane 1a (0.24 mmol), base (1.1 equiv), at temp 1 for time 1; MeI (2 equiv) added then warmed to temp 2 for time 2. *Order of addition. A: addition of the base to a solution of the substrate; B: addition of the substrate to a solution of the base. *Yield determined by 1H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard.
During the course of this work, Capriati and co-workers reported the deprotonation of 2-phenyl-oxetane with sBuLi. Consequently sBuLi was further examined to deprotonate the sulfonyl oxetane. A summary of the results is shown in Table S3.

**Table S3**: Selected optimisation: deprotonation of oxetane 1a to form oxetanes 5.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>equiv.</th>
<th>time 1 (min)</th>
<th>time 2 (min)</th>
<th>Temperature 2 (ºC)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; 5</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; 1a</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; 10</th>
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<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: base added to oxetane 1a (0.24 mmol), at −78 ºC for time 1; Mel (2 equiv) added then warmed to temp 2 for time 2.

<sup>b</sup> Yield determined by 1H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard.

The initial conditions employed 1.1 equivalents of sBuLi followed by the addition of 2 equivalents of Mel after 5 min. (table S3, entry 1). Two products were obtained, the desired methylated oxetane 5 but also 1% of the double methylated oxetane 10, along with remaining 1a. Increasing the equivalents of sBuLi employed from 1.1 to 1.2 and 1.4 increased the yield of the desired product however unreacted starting material and double methylated oxetane were also observed (table S3, entries 2 and 3). This implies that the second methylation occurs before all 1a is consumed. Increasing the deprotonation time (time 1) afforded an increase in formation of oxetane 10 (entry 4). Using 1.1 equiv base with the longer deprotonation did reduce the formation of 10 but decreased the yield of the desired oxetane 5 as well (entry 5). Warming the reaction to rt immediately after addition of Mel significantly increased the amount of oxetane 10 formed and decreased the yield of oxetane 5, however for the first time no unreacted starting material was observed (entry 6). The addition of Mel immediately after the addition of sBuLi was investigated (entry 7) but this was not an improvement on previous reaction conditions.

As a result we further investigated the use of nBuLi (entries 9-10), which displayed reduced formation of 10. The optimal yield of oxetane 5 was achieved using 1.3 equiv nBuLi which limited the amounts of starting material and double methylated product whilst improving the yield of desired product to 86% (entry 9). This provided the second set of optimised conditions (conditions B).
Synthesis of 2,2-disubstituted oxetanes 5-9 from oxetane 1a

General Procedure A (Table S2, entry 9; Conditions B Table S2)

A solution of oxetane 1a (50 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (0.95 mL) at −78 °C. The electrophile (for Mel: 0.03 mL, 0.47 mmol) was then added immediately and the reaction was stirred at −78 °C for 1 h, before being warmed to 0 °C in an ice bath for 15 min. The reaction was quenched by the addition of sat. aq. NH$_4$Cl (6 mL) and extracted with CHCl$_3$ (5 × 5 mL). The combined organic layers were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with EtOAc (15 mL) afforded oxetane 5.

General Procedure B (Table S3, entry 8; Conditions B Table S2)

nBuLi (1.60 M in hexane, 0.18 mL, 0.28 mmol) was added dropwise to a solution of oxetane 1a (50 mg, 0.22 mmol) in THF (1.2 mL) at −78 °C and stirred at −78 °C for 5 min. The electrophile (for Mel: 0.03 mL, 0.47 mmol) was added and the reaction stirred at −78 °C for 25 min. The reaction was quenched by the addition of sat. aq. NH$_4$Cl (6 mL) and extracted with CHCl$_3$ (5 × 5 mL). The combined organic layers were dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) or by filtration through a pad of basic alumina (activity IV) eluting with EtOAc (15 mL) afforded oxetane 5.

2-Methyl-2-[(4-methylphenyl)sulfonyl]oxetane (5)

Prepared according to the General Procedure A described above using methyl iodide (0.03 mL, 0.47 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with EtOAc (15 mL) afforded oxetane 5 (51 mg, 93%) as a yellow solid. R$_f$ = 0.27 (20% EtOAc/hexane). IR (film)/cm$^{-1}$: 3064, 2978, 2906, 1602, 1444, 1375, 1287, 1141, 1113, 1075, 973, 941, 864, 749. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 4.56–4.51 (1 H, m, OCH$_3$), 4.45 (1 H, t, J = 8.5, 5.4 Hz, OCH$_2$CHH$_2$), 3.25 (1 H, ddd, J = 12.4, 8.5, 5.4 Hz, OCH$_2$CHH$_2$), 2.76 (1 H, m, OCH$_2$CHH$_2$), 2.45 (3 H, s, Ar-CH$_3$), 1.64 (3 H, s, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.1 (Ar-CH$_3$), 130.9 (Ar-CH$_3$), 130.3 (2 × Ar-C), 129.6 (2 × Ar-C), 100.3 (C$_q$), 67.3 (OCH$_2$), 28.6 (OCH$_2$CH$_2$), 22.1 (CH$_3$), 21.7 (Ar-CH$_3$). HRMS (APCI) m/z Calculated for C$_{11}$H$_{15}$O$_3$S$^+$ [M+H]$^+$: 227.0736; Found: 227.0736 [M+H]$^+$.

2-Ethyl-2-[(4-methylphenyl)sulfonyl]oxetane (6)

Prepared according to the General Procedure A described above using ethyl iodide (0.04 mL, 0.46 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with EtOAc (15 mL) afforded oxetane 6 (47 mg, 85%) as a white solid. R$_f$ = 0.44 (40% EtOAc/hexane). IR (film)/cm$^{-1}$: 3071, 2971, 2899, 1596, 1460, 1309, 1299, 1288, 1237, 1113, 1076, 1035, 967, 952, 931, 853, 813, 707. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 4.55–4.50 (1 H, m, OCH$_2$CHH$_2$), 4.38 (1 H, t, J = 8.7, 5.6 Hz, OCH$_2$CHH$_2$), 3.16–3.09 (1 H, m, OCH$_2$CHH$_2$), 2.91–2.84 (1 H, m, OCH$_2$CHH$_2$), 2.45 (3 H, s, Ar-CH$_3$), 2.00–1.91 (1 H, m, CH$_2$CHH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.0 (Ar-CH$_3$), 131.5 (Ar-CH$_3$), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 103.5 (C$_q$), 67.8 (OCH$_2$), 26.2 (C$_{12}$H$_{15}$O$_3$S$^+$ [M+H]$^+$: 241.0893; Found: 241.0894 [M+H]$^+$).
2-Allyl-2-tosyloxytane (7)
Prepared according to the General Procedure A described above using allyl bromide (0.04 mL, 0.48 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with EtO (15 mL) afforded oxetane 7 (54 mg, 91%) as an orange solid. Rf = 0.28 (20% EtOAc/hexane). IR (film/cm⁻¹) 2970, 2899, 1641, 1597, 1403, 1300, 1288, 1235, 1156, 1106 1070, 944, 857, 814, 710.¹H NMR (400 MHz, CDCl₃) δ 7.88 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 7.38 (2 H, d, J = 8.2 Hz, 2 × Ar-H), 6.08–6.89 (1 H, m, CH=), 5.33–5.24 (2 H, m, =CH₂), 4.46 (1 H, ddd, J = 8.6, 7.5, 5.5 Hz, OCH₂), 4.32 (1 H, ddd, J = 8.9, 5.7, 5.5 Hz, OCH₂), 3.06 (1 H, ddd, J = 12.7, 8.6, 5.7 Hz, OCH₂CH₂CH₂), 2.87 (1 H, ddd, J = 12.7, 8.9, 7.5 Hz, OCH₂CH₂H), 2.61 (1 H, dd, J = 14.6, 8.8 Hz, CHHCH=CH₂), 2.47–2.41 (4 H, m, CH₃ + CHHCH=CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 145.2 (Ar-C), 131.0 (Ar-C), 130.4 (2 × Ar-C), 130.1 (CH=), 129.6 (2 × Ar-C), 121.0 (=CH₂), 101.9 (C), 67.7 (OCH₂), 37.5 (CH₂CH₂=CH₂), 24.3 (OCH₂CH₂), 21.7 (CH₃). HRMS (ESI) m/z Calculated for C₁₃H₁₇O₃S⁺ [M+H⁺]: 253.0893; Found: 253.0899 [M+H⁺].

2-(3-Fluorobenzyl)-2-tosyloxytane (8)
Prepared according to the General Procedure B described above using 3-fluorobenzyl bromide (0.06 mL, 0.48 mmol). Purification by flash chromatography on basic alumina (activity IV) (10–50% EtOAc/hexane) afforded oxetane 8 (68 mg, 90%) as a white solid. Rf = 0.26 (40% EtOAc/hexane). IR (film/cm⁻¹) 2970, 2899, 2255, 1616, 1590, 1487, 1449, 1301, 1255, 1155, 1104, 952, 941, 906, 861, 725, 703.¹H NMR (400 MHz, CDCl₃) δ 7.93 (2 H, d, J = 8.3 Hz, 2 × Ar-H), 7.40 (2 H, d, J = 8.3 Hz, 2 × Ar-H), 7.33–7.27 (1 H, m, Ar-H), 7.09–6.98 (3 H, m, 3 × Ar-H), 4.28–4.23 (1 H, m, OCH₂H), 3.83 (1 H, dt, J = 9.0, 5.5 Hz, OCH₂H), 3.14 (1 H, d, J = 14.3 Hz, CHH), 3.04–2.97 (1 H, m, OCH₂CH₂H), 2.93 (1 H, d, J = 14.3 Hz, CCH₂), 2.54–2.47 (1 H, m, OCH₂CH₂H) 2.48 (3 H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 162.6 (d, J = 245.0 Hz, Ar-C), 145.3 (Ar-C), 136.7 (d, J = 7.0 Hz, Ar-C), 131.1 (Ar-C), 130.4 (2 × Tol-C), 129.8 (d, J = 8.2 Hz, Ar-C), 129.7 (2 × Tol-C), 126.3 (d, J = 2.6 Hz, Ar-C), 117.4 (d, J = 21.3 Hz, Ar-C), 114.3 (d, J = 21.3 Hz, Ar-C) 102.1 (C), 67.5 (OCH₂), 38.1 (CH₂), 24.2 (OCH₂CH₂), 21.7 (CH₃). HRMS (ESI) m/z Calculated for C₁₇H₁₉F₂O₃S⁺ [M+H⁺]: 321.0955; Found: 321.0978 [M+H⁺].

2-Methyl-1-(2-tosyloxetan-2-yl)propan-1-ol (9)
Prepared according to the General Procedure B using isobutylaldehyde (0.04 mL, 0.48 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with EtO (15 mL) afforded oxetane 9 (57 mg, 86%, dr 1: 0.9). Rf = 0.28 (20% EtOAc/hexane). IR (film/cm⁻¹) 3504, 2966, 2905, 1596, 1493, 1448, 1365, 1311, 1299, 1287, 1154, 1134, 1067, 935, 815, 713. Major ¹H NMR (400 MHz, CDCl₃) δ 7.91 (2 H, d, J = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, J = 8.0 Hz, 2 × Ar-H), 4.30 (1 H, dt, J = 9.0, 5.7 Hz, OCH₂H), 4.14–4.03 (1 H, m, OCH₂H), 3.72–3.67 (1 H, m, HOCH₂H), 3.24 (1 H, dt, J = 12.4, 8.6, OCH₂CH₂H), 2.92–2.85 (1 H, m, OCH₂CH₂H), 2.48 (3 H, s, Ar-CH₃), 2.42–2.36 (1 H, m, (CH₂)₂CH), 1.02 (3 H, d, J = 6.6 Hz, CHHCH₂), 0.97 (3 H, d, J = 6.6 Hz, CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 145.3 (C₉), 132.0 (C₈), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 104.5 (C₈), 74.4 (HOCH₂), 69.0 (OCH₂), 29.0 (CH₂)₂CH, 23.9 (OCH₂CH₂), 21.7 (Ar-CH₃), 20.8 (CH₃), 15.5 (CH₃). Minor ¹H NMR (400 MHz, CDCl₃) δ 7.90 (2 H, d, J = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, J = 8.0 Hz, 2 × Ar-H), 4.50–4.38 (2 H, m, OCH₂), 3.72–3.68 (1 H, m, HOCH₂H), 3.19–2.98 (3 H, m, OCH₂CH₂ + (CH₂)₂CH₂), 2.48 (3 H, s, Ar-CH₃), 1.03 (3 H, d, J = 6.6 Hz, CHHCH₂), 0.94 (3 H, d, J = 6.6 Hz, CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 145.4 (C₉), 132.6 (C₈), 130.5 (2 × Ar-C), 129.5 (2 × Ar-C), 103.7 (C₈), 74.4 (HOCH₂), 68.7 (OCH₂), 29.8 (CH₂)₂CH, 23.8 (OCH₂CH₂), 21.7 (Ar-CH₃), 20.9 (CH₃), 17.5 (CH₃). HRMS (ESI) m/z Calculated for C₉H₁₃O₂S⁺ [M+H⁺]: 285.1161; Found: 285.1179 [M+H⁺].
Preparation of oxetane 10 by Directed ortho-Metallation

nBuLi (1.60 M in hexane, 0.16 mL, 0.26 mmol) was added dropwise to a solution of oxetane 5 (50.0 mg, 0.22 mmol) in THF (1.2 mL) at −78 °C and stirred at −78 °C for 30 min. Mel (0.027 mL, 0.44 mmol) was added and the reaction stirred at −78 °C for 2 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (6 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) (25% Et₂O/hexane) afforded oxetane 10 as a colourless oil. Rf = 0.28 (20% EtOAc/hexane). IR (film)/cm⁻¹ 2974, 2931, 2900, 1602, 1567, 1440, 1373, 1294, 1212, 1174, 1107, 1050, 973, 948, 865, 744, 675. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (1 H, d, J = 8.7 Hz, Ar-H), 7.19–7.14 (2 H, m, 2 x Ar-H), 4.57–4.50 (1 H, m, OCH₂H), 4.49–4.43 (1 H, m, OCH₂H), 3.31–3.22, (1 H, m, OCH₂CH₂H), 2.78 (1 H, dt, J = 12.6, 8.4 Hz, OCH₂CH₂H), 2.73 (3 H, s, Ar-CH₃), 2.39 (3 H, s, Ar-CH₃), 1.65 (3 H, s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 144.9 (Ar-C₢), 141.3 (Ar-Cₐ), 133.6 (Ar-Cₐ), 132.6 (Ar-C), 129.6 (Ar-Cₐ) 126.8 (Ar-C), 101.6 (C₀), 67.3 (OCH₂), 29.0 (OCH₂CH₂), 22.1 (CH₃), 21.4 (Ar-CH₃), 21.3 (Ar-CH₃). HRMS (ESI) m/z Calculated for C₁₂H₁₇O₃S⁺ [M+H]⁺: 241.0893; Found: 241.0927 [M+H]⁺.
Preparation of Oxetanes 11–12 by Fe-Catalysed Cross-Coupling of Oxetane 1c with Grignard Reagents

Conditions reported by Fürstner were employed.\(^8\)

2-((4-Hexylphenyl)sulfonyl)oxetane (11)

\(n\)Hexylmagnesium bromide (0.16 mL, 0.25 mmol) was added dropwise to a solution of oxetane 1c (48 mg, 0.21 mmol) and Fe(acac)\(_3\) (3.6 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et\(_2\)O (10 mL) and quenched with 1M HCl (10 mL) then extracted with Et\(_2\)O (5 × 7 mL). Combined organics were dried (MgSO\(_4\)), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20–80% EtOAc/heptane) afforded oxetane 11 (41 mg, 70%) as a colourless oil. \(R_f = 0.18\) (20% EtOAc/heptane).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 (2 H, d, \(J = 8.5\) Hz, 2 × Ar-H), 7.38 (2 H, d, \(J = 8.5\) Hz, 2 × Ar-H), 5.37 (1 H, dd, \(J = 6.7, 6.2\) Hz, OCH\(_3\)), 4.80–4.75 (1 H, m, OCH\(_2\)), 4.66–4.61 (1 H, m, OCH\(_2\)), 3.13–3.08 (2 H, m, OCH\(_2\)CH\(_2\)), 2.70 (2 H, t, \(J = 7.6\) Hz, Ar-CH\(_2\)CH\(_2\)), 1.64 (2 H, q, \(J = 7.6\) Hz, Ar-CH\(_2\)CH\(_2\)), 1.36–1.28 (6 H, m, 3 × CH\(_2\)), 0.89 (3 H, t, \(J = 6.9\) Hz, CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 150.3 (C\(_9\)), 132.5 (C\(_3\)), 129.5 (2 × Ar-C), 129.2 (2 × Ar-C), 94.1 (OCH\(_3\)), 71.3 (OCH\(_3\)), 36.0 (CH\(_2\)), 31.6 (CH\(_2\)), 30.9 (CH\(_3\)), 28.9 (CH\(_2\)), 22.5 (CH\(_2\)), 22.4 (CH\(_3\)), 14.0 (CH\(_3\)). HRMS (APCI) \(m/z\) Calculated for C\(_{13}\)H\(_{26}\)NO\(_3\)S\(_2\) [M+NH\(_4\)]\(^+\): 300.1628; Found: 300.1627 [M+NH\(_4\)]\(^+\).

2-((4-Hexylphenyl)sulfonyl)oxetane (12)

\(n\)Propylmagnesium chloride (1 M in MeTHF, 0.25 mL, 0.25 mmol) was added dropwise to a solution of oxetane 1c (50 mg, 0.21 mmol) and Fe(acac)\(_3\) (4 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et\(_2\)O (10 mL) and quenched with 1M HCl (10 mL) then extracted with Et\(_2\)O (5 × 7 mL). Combined organics were dried (MgSO\(_4\)), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane 12 (37 mg, 71%) as a colourless oil. \(R_f = 0.19\) (20% EtOAc/hexane).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38 (1 H, dd, \(J = 6.9, 6.0\) Hz, OCH\(_3\)), 4.81–4.75 (1 H, m, OCH\(_2\)), 4.67–4.62 (1 H, m, OCH\(_2\)), 3.16–3.07 (2 H, m, OCH\(_2\)CH\(_2\)), 2.69 (2 H, t, \(J = 7.4\) Hz, Ar-CH\(_2\)CH\(_2\)), 1.68 (2 H, q, \(J = 7.5, 7.4\) Hz, Ar-CH\(_2\)CH\(_2\)), 0.96 (3 H, t, \(J = 7.4\) Hz, CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 150.0 (C\(_9\)), 133.3 (C\(_3\)), 129.5 (2 × Ar-C), 129.3 (2 × Ar-C), 94.0 (OCH\(_3\)), 71.4 (OCH\(_3\)), 38.0 (CH\(_3\)), 24.1 (CH\(_2\)), 22.4 (OCH\(_2\)CH\(_2\)), 13.7 (CH\(_3\)). HRMS (APCI) \(m/z\) Calculated for C\(_{12}\)H\(_{26}\)NO\(_3\)S\(_2\) [M+NH\(_4\)]\(^+\): 258.1158; Found: 258.1158 [M+NH\(_4\)]\(^+\).
Preparation of Oxetanes 13–16 by Suzuki Cross-Coupling of Oxetane 1c

Conditions related to those reported by Buchwald were employed, using the S-Phos ligand.9

2-[[1,1′-Biphenyl]-4-ylsulfonyl]oxetane (13)
Phenylboronic acid (38 mg, 0.31 mmol) and oxetane 1c (54 mg, 0.23 mmol) were added to Pd(OAc)₂ (3 mg, 0.012 mmol), S-Phos (9 mg, 0.023 mmol) and K₂CO₃ (64 mg, 0.46 mmol) and the reaction vessel was placed under N₂. The mixture was dissolved in dioxane:water (4:1, 2.5 mL) and heated to 65°C for 3 h 30 min. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H₂O (10 mL). The organic layer was separated, dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–100% EtOAc/heptane) afforded oxetane 13 (55 mg, 86%) as a white solid. Rₐ = 0.39 (40% EtOAc/heptane). IR (film)/cm⁻¹: 3066, 2980, 2909, 1592, 1563, 1479, 1446, 1396, 1302, 1144, 1091, 900, 838, 762, 720, 657. ¹H NMR (400 MHz, CDCl₃) δ 8.05 (2 H, d, J = 8.7 Hz, 2 × Ar-H), 7.79 (2 H, d, J = 8.7 Hz, 2 × Ar-H), 7.64–7.59 (2 H, m, 2 × Ar-H), 7.52–7.42 (3 H, m, 3 × Ar-H), 5.43 (1 H, dd, J = 7.0, 6.5 Hz, OCH₃), 4.86–4.81 (1 H, m, OCH₂CH₂), 4.70–4.65 (1 H, m, OCHH), 3.18–3.12 (2 H, m, OCH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 147.3 (C₉), 139.2 (C₈), 133.9 (C₇), 130.0 (2 × C₆), 129.1 (2 × C₅), 128.7 (Ar-C), 127.8 (2 × C₄), 127.4 (2 × C₃), 94.1 (OCH₃), 71.4 (OCH₂), 22.4 (OCH₂CH₂). HRMS (APCI) m/z: Calculated for C₁₅H₁₆NO₃S⁺ [M+NH₄]⁺: 292.1002; Found 292.1001 [M+NH₄]⁺.

2-[[3′,5′-Dimethylbiphenyl]-4-ylsulfonyl]oxetane (14)
3,5-Dimethylbenzenesulfonyl acid (60 mg, 0.42 mmol) and oxetane 1c (75 mg, 0.32 mmol) were added to Pd(OAc)₂ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K₂CO₃ (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65°C for 5 h. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H₂O (10 mL). The organic layer was separated, dried (MgSO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane 14 as a colourless oil (83 mg, 86%). Rₐ = 0.53 (40% EtOAc/hexane). IR (film)/cm⁻¹: 2972, 2903, 1593, 1443, 1389, 1314, 1270, 1231, 1185 1064, 1029, 982, 908, 829, 737, 722, 697. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (2 H, d, J = 8.4 Hz, 2 × Ar-H), 7.77 (2 H, d, J = 8.4 Hz, 2 × Ar-H), 7.23 (2 H, s, 2 × Ar-H), 7.09 (1 H, s, Ar-H), 5.43 (1 H, dd, J = 7.4, 6.0 Hz, OCH₃), 4.84–4.77 (1 H, m, OCH₂), 4.70–4.63 (1 H, m, OCH₃), 3.19–3.08 (2 H, m, OCH₃CH₂), 2.40 (6 H, s, 2 × CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 147.5 (C₉), 139.0 (C₈), 138.6 (2 × C₇), 133.4 (C₆), 130.3 (Ar-C), 129.8 (2 × Ar-C), 127.7 (2 × Ar-C), 125.2 (2 × Ar-C), 94.0 (OCH₃), 71.4 (OCH₂), 22.4 (OCH₂CH₂), 21.3 (2 × CH₃). HRMS (EI) m/z: Calculated for C₁₇H₁₆O₃S⁺ [M⁺]: 302.0971; Found 302.0973 [M⁺].
2-[(4'-Methoxybiphenyl)-4-ylsulfonylo]xetane (15)
4-Methoxyphenylboronic acid (64 mg, 0.42 mmol) and oxetane 1c (75 mg, 0.32 mmol) were added to Pd(OAc)$_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K$_2$CO$_3$ (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65 ºC for 5 h 30 min. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H$_2$O (10 mL). The organic layer was separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane 15 as a white solid (92 mg, 95%). R$_f$ = 0.34 (40% EtOAc/hexane). IR (film)/cm$^{-1}$ 2980, 2909, 2839, 1603, 1591, 1523, 1457, 1425, 1396, 1294, 1136, 1091, 1063, 1012, 982, 936, 907, 849, 819, 751, 712, 682. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (2 H, d, $J$ = 8.6 Hz, 2 × Ar-H), 7.75 (2 H, d, $J$ = 8.6 Hz, 2 × Ar-H), 7.58 (2 H, d, $J$ = 8.6 Hz, 2 × Ar-H), 7.02 (2 H, d, $J$ = 8.6 Hz, 2 × Ar-H), 5.42 (1 H, dd, $J$ = 7.0, 6.4 Hz, OCHS), 4.85–4.79 (1 H, m, OCHH), 4.70–4.64 (1 H, m, OCHH), 3.88 (3 H, s, CH$_3$), 3.19–3.09 (2 H, m, OCH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.3 (C$_{Ar}$), 146.8 (C$_{O}$), 133.0 (C$_{O}$), 131.4 (C$_{O}$), 130.0 (2 × Ar-C), 128.6 (2 × Ar-C), 127.2 (2 × Ar-C), 114.5 (2 × Ar-C), 94.1 (OCH$_2$), 71.4 (OCH$_2$), 55.4 (CH$_3$), 22.4 (OCH$_2$CH$_2$). HRMS (EI) m/z Calculated for C$_{16}$H$_{10}$O$_4$S$^+$ [M$^+$]: 304.0769; Found 304.0744 [M$^+$].

2-[(1,1'-Biphenyl)-3-carboxaldehyde-4-ylsulfonylo]xetane (16)
3-Formylphenylboronic acid (60 mg, 0.42 mmol) and oxetane 1c (75 mg, 0.32 mmol) were added to Pd(OAc)$_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K$_2$CO$_3$ (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65 ºC for 20 h. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H$_2$O (10 mL). The organic layer was separated, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane 16 as a colourless oil (57 mg, 59%). R$_f$ = 0.13 (40% EtOAc/hexane). IR (film)/cm$^{-1}$ 2973, 2902, 2827, 1694, 1595, 1585, 1442, 1398, 1360, 1314, 1232, 1180, 1090, 1064, 1028, 937, 868, 843, 769, 761, 660. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.09 (1 H, s, CHO), 8.13–8.11 (1 H, m, Ar-H), 8.06 (2 H, d, $J$ = 8.5 Hz, 2 × Ar-H), 7.93 (1 H, dt, $J$ = 7.5, 1.4 Hz, Ar-H), 7.87 (1 H, dt, $J$ = 7.7, 1.4 Hz, Ar-H), 7.81 (2 H, d, $J$ = 8.5 Hz, 2 × Ar-H), 7.67 (1 H, t, $J$ = 7.7 Hz, Ar-H), 5.43 (1 H, dd, $J$ = 7.2, 5.5 Hz, OCHS), 4.85–4.79 (1 H, m, OCHH), 4.70–4.64 (1 H, m, OCHH), 3.21–3.07 (2 H, m, OCH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 191.8 (C=O), 145.6 (C$_{Ar}$), 140.0 (C$_{O}$), 137.0 (C$_{O}$), 134.5 (C$_{O}$), 133.1 (Ar-C), 130.1 (2 × Ar-C), 129.8 (Ar-C), 128.1 (Ar-C), 127.8 (2 × Ar-C), 94.0 (OCH$_2$), 71.5 (OCH$_2$), 22.3 (OCH$_2$CH$_2$). HRMS (APCI) m/z Calculated for C$_{16}$H$_{18}$NO$_4$S$^+$ [M+NH$_4$]$^+$: 320.0951; Found 320.0951 [M+NH$_4$]$^+$. 

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Calculated fragment-like and lead-like properties of oxetanes 1a-d, 5-9 and 10-16

The scope of oxetanes prepared were analysed against parameters used to indicate desirable molecular properties, with particular reference to the Astex 'rule of 3' for fragments, and lead-likeness criteria recently proposed by Churcher and co-workers.

Criteria as defined by Congreve et al. for fragments: 10
- $\text{cLogP} < 3$ 11
- Three or fewer H-bond donors (HBD)
- Three or fewer H-bond acceptors (HBA)
- $\text{MW} < 300$ daltons

Secondary criteria include: Number of rotatable bonds (NROT) ≤ 3; Polar surface area (PSA) ≤ 60. Köster et al. recently proposed six or fewer HBA to be a more appropriate guideline. 12

Criteria as defined by Churcher et al. for lead-like compound: 13
- $14 \leq \text{heavy atoms} \leq 26$ ($200 \leq \text{Molecular weight (MW)} \leq 300$ Da)
- $-1 \leq \text{cLogP} \leq 3$
- more 3D shape/sp$^3$ content favoured

**Compounds 1a-d**

These compounds conform well to the fragment guidelines.

To illustrate the 3-dimensional shape of the oxetane fragments we calculated the minimum energy structure of 1a using Gaussian 09 (GaussView 5), 14 up to the B3LYP/3-21G level of theory with default solvation (water; scrf = pcm).
**Oxetanes 5-9**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (E⁺)</th>
<th>Conditions</th>
<th>Oxetane</th>
<th>Yield (%)</th>
<th>Calculated molecular properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mel</td>
<td>A</td>
<td><img src="image1.png" alt="Image" /></td>
<td>93%</td>
<td>MW = 226, clogP = 0.80 ± 0.4, HAC = 15, HBD/A = 0/3</td>
</tr>
<tr>
<td>2</td>
<td>MeI</td>
<td>B</td>
<td><img src="image2.png" alt="Image" /></td>
<td>71%</td>
<td>MW = 240, clogP = 0.80 ± 0.4, HAC = 15, HBD/A = 0/3</td>
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<tr>
<td>3</td>
<td>EtI</td>
<td>A</td>
<td><img src="image3.png" alt="Image" /></td>
<td>85%</td>
<td>MW = 252, clogP = 1.33 ± 0.4, HAC = 16, HBD/A = 0/3</td>
</tr>
<tr>
<td>4</td>
<td>allyl bromide</td>
<td>A</td>
<td><img src="image4.png" alt="Image" /></td>
<td>91%</td>
<td>MW = 252, clogP = 1.64 ± 0.4, HAC = 17, HBD/A = 0/3</td>
</tr>
<tr>
<td>5</td>
<td>F-Br</td>
<td>B</td>
<td><img src="image5.png" alt="Image" /></td>
<td>90%</td>
<td>MW = 320, clogP = 2.62 ± 0.5, HAC = 22, HBD/A = 0/4</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>B</td>
<td><img src="image6.png" alt="Image" /></td>
<td>86% b</td>
<td>MW = 284, clogP = 1.59 ± 0.5, HAC = 19, HBD/A = 1/4</td>
</tr>
</tbody>
</table>

DFT calculation of minimum energy structure of oxetane 5 (B3LYP/3-21G, water). 

![Image](image7.png)
The physicochemical properties of these compounds conform well to lead-like guidelines.
$^1$H and $^{13}$C NMR spectra of selected compounds
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3a
$^1$H NMR (400 MHz, CDCl$_3$)

3a
$^{13}$C NMR (100 MHz, CDCl$_3$)
S3

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)

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$^1$H NMR (400 MHz, CDCl₃)

$^{13}$C NMR (100 MHz, CDCl₃)
$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_3$)
S4

$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

S4

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_3$)
3c
$^1$H NMR (400 MHz, CDCl$_3$)

3c
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
\(^1\)H NMR (400 MHz, CDCl\(_3\))

\(^{13}\)C NMR (100 MHz, CDCl\(_3\))
$2d$

$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_3$)
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5

$^1$H NMR (400 MHz, CDCl$_3$)

5

$^{13}$C NMR (100 MHz, CDCl$_3$)
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$^1$H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)

$^{13}$C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
9

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
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1H NMR (400 MHz, CDCl₃, 1% SiMe₄)

13C NMR (100 MHz, CDCl₃, 1% SiMe₄)
Electronic Supplementary Material (ESI) for Chemical Communications
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$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100 MHz, CDCl$_3$)
References


11. cLogP values were determined using ACDlabs LogP calculator, [http://www.acdlabs.com/resources/freeware/chemsketch/logp](http://www.acdlabs.com/resources/freeware/chemsketch/logp).

