Synthesis of Diversely Functionalised 2,2-Disubstituted Oxetanes: Fragment Motifs in New Chemical Space

Owen A. Davis, Rosemary A. Croft and James A. Bull*

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

*E-mail: j.bull@imperial.ac.uk

Table of Contents................................................................................................................. S1
Calculated Fragment-Like Properties of Selected Oxetanes .................................................. S2
General Experimental Considerations .................................................................................. S3
Preparation of a 0.61M solution of LiHMDS ....................................................................... S3
Synthesis of Diazo Transfer Reagents Sa–Sc ......................................................................... S4
Synthesis of Activated Methylene Species S1–S8 ................................................................. S5
Synthesis of Disubstituted Diazos 1a–1i ............................................................................... S9
Synthesis of Disubstituted Aryl Diazos 6a–6g ..................................................................... S14
Synthesis of 2,2-Disubstituted Oxetanes 3a–3g ................................................................. S18
Synthesis of Tri- and Tetrasubstituted Oxetanes 5a–5h ...................................................... S24
Optimisation of C–C Bond Forming Cyclisation using Aryl Bromide 7a ............................. S35
Synthesis of 2,2-Disubstituted Aryl Oxetanes 8a–8g ............................................................ S36
Functionalisation of Oxetanes 8a, 3e and 3f ...................................................................... S43
1H and 13C NMR spectra for Selected Compounds ............................................................. S45
NOESY and Selective NOE Spectra for Oxetanes 5a, 5d, 5f and 5h ................................. S120
References............................................................................................................................. S128
Calculated Fragment-Like Properties of Selected Oxetanes

A selection of the oxetanes synthesized were analysed against parameters used to indicate desirable molecular properties, with particular reference to the Astex ‘rule of 3’ for fragments.

Criteria for fragments as defined by Congreve and co-workers:¹
- $M_w < 300$ daltons
- $c\log P < 3^2$
- H-bond donors (HBD) ≤ 3
- H-bond acceptors (HBA) ≤ 3

Klebe and co-workers proposed that HBA ≤ 6 is appropriate for fragments to allow for fragment growing/merging due to appropriate functional groups frequently display properties as hydrogen bond acceptors.³

**Selected Oxetanes**

![Chemical Structures](image)

These oxetanes conform well to fragment guidelines.
General Experimental Considerations
All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware and anhydrous solvents using standard techniques.

Anhydrous solvents were obtained by filtration through drying columns (THF, DMF, CH₂Cl₂) or used as supplied (DMF, benzene).

Flash column chromatography was performed using 230-400 mesh silica or 50-200 µm Brockmann basic alumina (activity IV) 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), aqueous potassium permanganate stain, PMA (phosphomolybdic acid), ninhydrin or vanillin.

Infrared spectra ($\nu_{\text{max}}$, FTIR ATR) were recorded in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra were recorded on either 400 MHz or 500 MHz spectrometers. Chemical shifts for $^1$H NMR spectra are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: $\delta = 7.27$ ppm, DMSO: $\delta = 2.50$ ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, sep = septet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. $^{13}$C 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 ($^{13}$CDCl₃: 77.0 ppm, ($^{13}$CD₃)$_2$SO: 39.5 ppm). $^{19}$F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard monofluorobenzene: $-113.5$ ppm. $J$ values are reported in Hz. Assignments of $^1$H/$^{13}$C spectra were made by the analysis of $\delta/J$ values, and COSY, DEPT-135, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary. 2-Substituted β-bromohydrins were prepared by reported procedures.⁴

Notes:
- Although we have not experienced any problems in the handling of azides or diazo reagents, extreme care should be taken when manipulating them due to their potentially explosive nature.
- For all diazo compounds synthesized (apart from 1a and 1f), the resonance for the fully substituted C=N=N carbon in the $^{13}$C NMR could not be seen due to quadrupole coupling to $^{14}$N. The carbon resonance is not reported.
- Where diastereoisomers were separable by flash chromatography, attempts to determine their relative stereochemistry were conducted using NMR experiments (NOESY and selective NOE). However, this was not possible in all cases. Diastereomers that were not separable by flash chromatography have been characterized as mixtures.
- For β-bromohydrin S9 (derived from N-Boc-2,5-dihydro-1H-pyrrole; pg S40), the carbon resonances in the $^{13}$C NMR are doubled. This is due to the compound existing as rotamers at rt in CDCl₃ on the NMR timescale. The assignment of this compound has taken this into consideration.

Preparation of a 0.61 M solution of LiHMDS
A solution of freshly distilled HMDS (0.31 ml, 1.47 mmol) in THF (1.06 ml) was cooled to $-78$ °C for 5 min then n-butyllithium (1.6 M in hexanes, 0.84 ml, 1.34 mmol) was added dropwise. The solution was stirred at $-78$ °C for 30 min then warmed to 0 °C for 30 min prior to immediate use.
Synthesis of Diazo Transfer Reagents Sa–Sc

4-Toluenesulfonyl azide (Sa)$^5$

![Structure](image)

Sodium azide (6.24 g, 96 mmol) in water (26 mL) was added in one portion to a stirring mixture of 4-toluenesulfonyl chloride (15.25 g, 80 mmol) in isopropyl alcohol (46 mL). The resulting mixture was stirred at 25 °C for 90 min. Water (300 mL) was added and the mixture stirred at 25 °C for 1 h. The aqueous mixture was extracted with CH$_2$Cl$_2$ (4 x 100 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford azide Sa as a colorless oil (15.62 g, 99%); IR (film) / cm$^{-1}$ 2126 (N=N=N), 1596, 1495, 1370, 1298, 1191, 1167, 1086, 814, 747, 703, 661, 592, 540; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89–7.83 (m, 2 H, 2 x Ts-H), 7.45–7.39 (m, 2 H, 2 x Ts-H), 2.50 (s, 3 H, Ts-CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.2 (Ts-C$_q$-SO$_2$), 135.6 (Ts-C$_q$-Me), 130.3 (2 x Ts-CH), 127.5 (2 x Ts-CH), 21.8 (Ts-CH$_3$).

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.$^6,^7$

4-Acetamidobenzene-1-sulfonyl azide ($p$-ABSA, Sb)$^8$

![Structure](image)

Acetylsulfanilyl chloride (1.17 g, 5.0 mmol) was added portionwise over 2 min to a stirring mixture of sodium azide (325 mg, 5.0 mmol) in acetone (117 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 48 h. The reaction mixture was then filtered and concentrated in vacuo to yield azide Sb as a light brown solid (1.19 g, 99%); mp = 107–109 °C; IR (film) / cm$^{-1}$ 3259 (N-H), 3187, 3112, 2118 (N=N=N), 1672 (C=O), 1585, 1529, 1404, 1362, 1314, 1265, 1160, 1086, 1041, 1011, 838, 743, 706; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.94–7.88 (m, 2 H, 2 x Ar-H), 7.80–7.73 (m, 2 H, 2 x Ar-H), 7.57 (br s, 1 H, NH), 2.25 (s, 3 H, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.4 (C=O), 143.8 (Ar-C$_q$-SO$_2$), 129.1 (2 x Ar-CH), 119.5 (2 x Ar-CH), 110.0 (Ar-C$_q$-NH), 24.9 (CH$_3$).

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.$^9$

Trifluoromethanesulfonyl azide solution (Sc)$^{10}$

![Structure](image)

Triflic anhydride (10 g, 5.96 mL, 35.4 mmol) in n-hexane (35 mL) was added dropwise to a stirring mixture of sodium azide (4.95 g, 76.2 mmol) and tetrabutylammonium hydrogen sulfate (241 mg, 0.71 mmol) in water (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min. The layers were separated and the aqueous mixture was extracted with n-hexane (35 mL). The organic extracts were combined, dried over sodium hydroxide pellets and decanted. The n-hexane solution of trifly azide (0.47 M) was either used immediately or was stored at −15 °C for several weeks without significant decomposition. The concentration of the azide was estimated based on the total volume of the solution and assuming a quantitative conversion based on the amount of triflic anhydride used.
Synthesis of Activated Methylene Species S1–S8

Ethyl 3-oxo-3-(pyrrolidin-1-yl)propanoate (S1)

Pyrrrolidine (0.60 mL, 7.2 mmol) was added to a stirring mixture of ethyl potassium malonate (1.02 g, 6.0 mmol), EDC-HCl (1.36 g, 7.2 mmol) and HOBT hydrate (1.10 g, 8.2 mmol) in CH₂Cl₂ (25 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 70 h. A 1 M HCl solution (10 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH₂Cl₂ (3 x 25 mL). The organic extracts were combined, washed with saturated aq. NaHCO₃ (10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (3% MeOH in CH₂Cl₂) afforded amide S1 as a colorless oil (550 mg, 49%); Rf = 0.14 (5% MeOH in CH₂Cl₂); IR (film) / cm⁻¹: 2978, 2877, 1734 (C=O ester), 1638 (C=O amide), 1433, 1367, 1307, 1251, 1151, 1031, 973, 943, 915, 863, 666, 604, 568; ¹H NMR (400 MHz, CDCl₃) δ 4.18 (q, J = 7.1 Hz, 2 H, CO₂H₂CH₃), 3.47 (t, J = 6.9 Hz, 2 H, NCH₂), 3.42 (t, J = 6.8 Hz, 2 H, NCH₂), 3.36 (s, 2 H, CH₂), 1.99–1.90 (m, 2 H, NCH₂CH₂), 1.90–1.81 (m, 2 H, NCH₂CH₂), 1.26 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.5 (C=O), 164.3 (C=O), 61.3 (CO₂CH₂CH₃), 47.1 (NCH₂), 45.8 (NCH₂), 42.4 (CH₂), 26.0 (NCH₂CH₂), 24.4 (NCH₂CH₂), 14.0 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₉H₁₄NO₃⁺ [M+H]⁺: 186.1130, Found: 186.1128.

Observed data (IR) was consistent with that previously reported.¹¹

Ethyl 2-[methoxy(methyl)carbamoyl]acetate (S2)

N,N-Diisopropylethylamine (3.14 mL, 18.0 mmol) was added to a stirring mixture of ethyl potassium malonate (1.02 g, 6.0 mmol), N,N-dimethylhydroxylamine hydrochloride (703 mg, 7.2 mmol) and HATU (2.73 g, 7.2 mmol) in CH₂Cl₂ (30 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 68 h. A 1 M HCl solution (10 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH₂Cl₂ (3 x 30 mL). The organic extracts were combined, washed with saturated aq. NaHCO₃ (20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded Weinreb amide S2 as a colorless oil (852 mg, 81%); Rf = 0.04 (5% EtOAc in hexanes); IR (film) / cm⁻¹: 2978, 2877, 1734 (C=O ester), 1638 (C=O amide), 1465, 1445, 1416, 1385, 1369, 1369, 1323, 1252, 1153, 1123, 1031, 1005, 934, 857, 753, 706, 667, 566; ¹H NMR (400 MHz, CDCl₃) δ 4.13 (q, J = 7.1 Hz, 2 H, CO₂H₂CH₃), 3.66 (s, 3 H, OCH₃), 3.43 (s, 2 H, CH₂), 3.16 (s, 3 H, NCH₃), 1.22 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.2 (CO₂ and CON), 61.2 (OCH₃), 61.1 (CO₂CH₂CH₃), 40.1 (CH₂), 32.0 (NCH₃), 13.9 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₉H₁₄NO₄⁺ [M+H]⁺: 176.0923, Found: 176.0927.

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.¹²

Ethyl 2-(benzenesulfonyl)acetate (S3)

n-Butyllithium (1.62 M in hexanes, 7.78 mL, 12.6 mmol) was added dropwise to a stirring solution of methyl phenyl sulfone (936 mg, 6.0 mmol) in THF (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. Ethyl chloroformate (0.6 mL, 6.3 mmol) was then added and the resulting mixture was stirred at 0 °C for 90 min. Saturated aq. NH₄Cl (60 mL) was added. The layers were separated and the aqueous mixture was
extracted with EtOAc (2 x 60 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (30% EtOAc in hexanes) afforded ethyl 2-(benzenesulfonyl)acetate S₃ as a colorless oil (1.09 g, 80%); Rᵣ = 0.26 (30% EtOAc in hexanes); IR (film) / cm⁻¹ 2986, 2944, 1736 (C=O), 1586, 1478, 1448, 1397, 1368, 1324, 1310, 1275, 1148, 1083, 1024, 999, 910, 844, 810, 760, 741, 721, 686, 619, 555; ¹H NMR (400 MHz, CDCl₃) δ 8.00–7.91 (m, 2 H, 2 x Ph-H), 7.74–7.67 (m, 1 H, Ph-H), 7.64–7.55 (m, 2 H, 2 x Ph-H), 4.14 (q, J = 7.1 Hz, 2 H, CO₂C₆H₄CH₃), 4.12 (s, 2 H, CH₂), 1.19 (t, J = 7.1 Hz, 3 H, CO₂CH₂C₆H₄). ¹³C NMR (101 MHz, CDCl₃) δ 162.3 (CO₂), 138.7 (Ph-Cq), 134.3 (Ph-CH), 129.2 (2 x Ph-CH), 128.5 (2 x Ph-CH), 62.4 (CO₂C₆H₄CH₃), 61.0 (CH₂), 13.8 (CO₂CH₂C₆H₄).

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.

Synthesis of activated methylene species S₄–S₇ from acid derivatives (Table S1).

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Ethyl 2-(3-chlorophenyl)acetate (S₄)

A solution of 2-(3-chlorophenyl)acetic acid (1.02 g, 6.0 mmol) and p-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed in vacuo. Saturated aq. NaHCO₃ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo to afford ester S₄ as a colorless oil which was used without further purification (1.18 g, 99%); Rᵣ = 0.33 (10% EtOAc in hexanes); IR (film) / cm⁻¹ 2983, 1732 (C=O), 1599, 1575, 1477, 1433, 1368, 1335, 1249, 1218, 1155, 1094, 1079, 1029, 1000, 943, 893, 868, 850, 781, 763, 734, 682; ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.16 (m, 4 H, 4 x Ar-H), 4.18 (q, J = 7.1 Hz, 2 H, CO₂CH₂C₆H₄), 3.60 (s, 2 H, CH₂), 1.28 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.3 (CO₂), 136.0 (Ar-CqCH₂), 134.4 (Ar-CqCl), 129.8 (Ar-CH), 129.5 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 61.1 (CO₂CH₂C₆H₄), 41.1 (CH₂), 14.2 (CO₂CH₂C₆H₄).

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.
**Ethyl 2-[4-(trifluoromethyl)phenyl]acetate (S5)**

A solution of 2-[4-(trifluoromethyl)phenyl]acetic acid (1.22 g, 6.0 mmol) and p-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. NaHCO₃ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated *in vacuo* to yield ester S5 as a colorless oil which was used without further purification (1.30 g, 94%); Rₚ = 0.63 (50% EtOAc/hexane); IR (film) / cm⁻¹: 2990, 1720 (C=O), 1619, 1421, 1374, 1225, 1155, 1128, 1068, 1019, 886, 843, 823, 765, 741, 691; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 8.0 Hz, 2 H, 2 x Ar-H), 7.42 (d, J = 8.0 Hz, 2 H, 2 x Ar-H), 4.18 (q, J = 7.1 Hz, 2 H, CO₂C₃H₂), 3.68 (s, 2 H, CH₂), 1.27 (t, J = 7.1 Hz, 3 H, CO₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.8 (CO₂), 138.2 (Ar-C₆H₄), 129.7 (2 x Ar-C₆H₄), 129.5 (q, J₉-F = 33 Hz, Ar-C₆F₃), 125.8 (q, J₉-F = 264 Hz, CH₃), 125.6 (q, J₉-F = 4 Hz, 2 x Ar-C₆H₄), 61.2 (CO₂C₂H₃), 41.2 (CH₂), 14.2 (CO₂C₂H₃); ¹⁹F NMR (376 MHz, CDCl₃) δ –62.6.

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.¹⁵

**Ethyl 2-(4-methoxyphenyl)acetate (S6)**

A solution of 2-(4-methoxyphenyl)acetic acid (1.00 g, 6.0 mmol) and p-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. NaHCO₃ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated *in vacuo* to yield ester S6 as a colorless oil which was used without further purification (1.16 g, 99%); Rₚ = 0.27 (10% EtOAc/hexane); IR (film) / cm⁻¹: 2982, 2837, 1730 (C=O), 1613, 1512, 1464, 1443, 1368, 1300, 1244, 1150, 1029, 946, 880, 820, 790, 765, 723, 693; ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, J = 8.6 Hz, 2 H, 2 x Ar-H), 6.87 (d, J = 8.6 Hz, 2 H, 2 x Ar-H), 4.15 (q, J = 7.1 Hz, 2 H, CO₂C₃H₂), 3.80 (s, 3 H, OCH₃), 3.56 (s, 2 H, CH₂), 1.26 (t, J = 7.1 Hz, 3 H, CO₂C₂H₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.0 (CO₂), 158.7 (Ar-C₆H₄), 130.3 (2 x Ar-C₆H₄), 126.3 (Ar-C₆H₄), 114.0 (2 x Ar-C₆H₄), 60.8 (CO₂C₂H₃), 55.3 (OCH₃), 40.6 (CH₂), 14.3 (CO₂C₂H₃).

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.¹⁶

**Ethyl 2-(6-chloropyridin-3-yl)acetate (S7)**

A solution of 2-(6-chloropyridin-3-yl)acetic acid (1.03 g, 6.0 mmol) and p-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. NaHCO₃ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated *in vacuo* to yield ester S7 as a colorless oil which was used without further purification (1.30 g, 94%); Rₚ = 0.59 (50% EtOAc/hexane); IR (film) / cm⁻¹: 2984, 1730 (C=O), 1589, 1567, 1460, 1385, 1368, 1334, 1262, 1230, 1160, 1140, 1102, 1023, 946, 879, 819, 752, 671; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 2.5 Hz, 1 H, Ar-H), 7.60 (dd, J = 8.1, 2.5 Hz, 1 H, Ar-H), 7.27 (d, J = 8.1 Hz, 1 H, Ar-H), 4.14 (q, J = 7.1 Hz, 2 H, CO₂C₂H₃), 3.58 (s, 2 H, CH₂), 1.23 (t, J = 7.1 Hz, CO₂C₂H₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.2 (C=O), 150.3 (Ar-C₆Cl), 150.2 (Ar-C₆H₄), 139.7 (Ar-C₆H₄), 128.8 (Ar-C₆F₃), 124.1 (Ar-C₆H₄), 61.4 (CO₂C₂H₃), 37.6 (CH₂), 14.1 (CO₂C₂H₃).
Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.  

2-(3-Chlorophenyl)-1-(morpholin-4-yl)ethan-1-one (S8)

$N,N$-Diisopropylethylamine (3.14 mL, 18.0 mmol) was added to a stirring mixture of 2-(3-chlorophenyl)acetic acid (1.02 g, 6.0 mmol), HATU (2.74 g, 7.2 mmol) and morpholine (0.63 mL, 7.2 mmol) in CH$_2$Cl$_2$ (30 mL) at 25 °C. The reaction was stirred at 25 °C for 48 h. A 1 M HCl solution (30 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The organic extracts were combined, dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded amide S8 as a colorless oil (1.26 g, 88%); $R_f$ = 0.13 (50% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2977, 2912, 2852, 1638 (C=O), 1575, 1475, 1436, 1413, 1364, 1319, 1271, 1231, 1190, 1116, 1079, 1036, 1019, 965, 944, 922, 902, 877, 850, 811, 768, 699, 685; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38–7.10 (m, 4 H, 4 x Ar-H), 3.72 (s, 2 H, CH$_2$), 3.69–3.65 (m, 4 H, 2 x OCH$_2$), 3.58–3.53 (m, 2 H, NCH$_2$), 3.49–3.41 (m, 2 H, NCH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.0 (C=O), 136.8 (Ar-C$_r$-CH$_2$), 134.7 (Ar-C$_r$-Cl), 130.1 (Ar-CH), 128.9 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 66.9 (OCH$_2$), 66.6 (OC$'$_H$_2$), 46.6 (NCH$_2$), 42.3 (NC$'$_H$_2$), 40.3 (CH$_2$).

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.
Synthesis of Disubstituted Diazos 1a–1i

Synthesis of disubstituted diazos 1a–1i were adapted from procedures of Lee and co-worker (TsN₃),¹⁹ or procedures of Charette and co-workers (TfN₃).²₀,²¹

Ethyl diazo-3-oxo-3-(pyrrolidin-1-yl)propanoate (1a)

Cesium carbonate (813 mg, 2.5 mmol) was added in one portion to a stirring solution of tosyl azide Sa (496 mg, 2.5 mmol) and amide S₁ (463 mg, 2.5 mmol) in THF (25 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 3 h 30 min. The reaction mixture was diluted with Et₂O (50 mL), and washed with 1 M aq. NaOH (2 x 10 mL) and brine (10 mL). The combined aqueous washes were then re-extracted with Et₂O (20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (30% to 40% EtOAc in pentane) afforded diazo amide 1a as a yellow oil (515 mg, 93%); Rᵣ = 0.34 (50% EtOAc in hexanes); IR (film) / cm⁻¹: 2977, 2881, 2118 (C=N=N out-of-phase), 1707 (C=O ester), 1613 (C=O amide), 1407, 1368 (C=N=N in-phase), 1343, 1283, 1231, 1168, 1096, 1032, 1015, 934, 906, 873, 857, 820, 753, 709, 585, 566, 538; ¹H NMR (400 MHz, CDCl₃) δ 4.26 (q, J = 7.1 Hz, 2 H, CO₂CH₂CH₃), 3.60–3.46 (m, 4 H, 2 x NCH₂), 1.96–1.83 (m, 4 H, 2 x NCH₂CH₂), 1.31 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.0 (C=O), 159.5 (C=O), 66.7 (CqN₂), 61.1 (CO₂CH₂CH₃), 48.3 (br, NCH₂), 47.3 (br, NCH₂), 25.9 (br, NCH₂CH₂), 24.3 (br, NCH₂CH₂), 14.3 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₉H₁₄N₃O₃⁺ [M+H]⁺: 212.1035, Found: 212.1033.

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.²²

Ethyl diazo-2-[methoxy(methyl)carbamoyl]acetate (1b)

Tosyl azide Sa (592 mg, 3.0 mmol) in THF (6 mL) was added dropwise to a stirring suspension of Weinreb amide S₂ (525 mg, 3.0 mmol) and cesium carbonate (981 mg, 3.0 mmol) in THF (24 mL). The resulting mixture was stirred at 25 °C for 2 h 30 min. The reaction mixture was filtered through celite, the precipitate washed with Et₂O (100 mL) and the filtrate concentrated in vacuo. Purification by flash chromatography (40% to 50% EtOAc in pentane) afforded diazo amide 1b as a yellow oil (444 mg, 74%); Rᵣ = 0.32 (50% EtOAc in hexanes); IR (film) / cm⁻¹: 2983, 2940, 2120 (C=N=N out-of-phase), 1728 (C=O ester), 1650 (C=O amide), 1463, 1407, 1369 (C=N=N in-phase), 1282, 1248, 1171, 1137, 1106, 1053, 1014, 967, 889, 749, 705, 665, 555; ¹H NMR (400 MHz, CDCl₃) δ 4.29 (q, J = 7.1 Hz, 2 H, CO₂CH₂CH₃), 3.70 (s, 3 H, OCH₃), 3.21 (s, 3 H, NCH₃), 1.30 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.0 (C=O), 159.5 (C=O), 66.7 (CqN₂), 61.1 (CO₂CH₂CH₃), 61.2 (OCH₃), 33.6 (NCH₃), 14.3 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₇H₁₄N₃O₄⁺ [M+H]⁺: 202.0828, Found: 202.0823.
Ethyl 2-(benzenesulfonyl)-2-diazoacetate (1c)\(^{19}\)

Tosyl azide \(\text{Sa}\) (787 mg, 4.0 mmol) in THF (8 mL) was added dropwise to a stirring suspension of ethyl 2-(benzenesulfonyl)acetate \(\text{S3}\) (911 mg, 4.0 mmol) and cesium carbonate (1.30 g, 4.0 mmol) in THF (32 mL). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through celite, the precipitate washed with \(\text{Et}_2\text{O}\) (100 mL) and the filtrate concentrated in vacuo. Purification by flash chromatography (20% to 30% EtOAc in hexanes) afforded diazo sulfone 1c as an orange solid (746 mg, 73%); \(R_t = 0.47\) (30% EtOAc in hexanes); mp = 49–52 °C; IR (film) / cm\(^{-1}\) 2986, 2124 (C=N=N out of phase), 1711 (C=O), 1584, 1477, 1393, 1370 (C=N=N in-phase), 1336, 1285, 1213, 1156, 1097, 1070, 1000, 909, 855, 804, 720, 684, 607, 557; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.02–7.94 (m, 2 H, 2 x Ph-H), 7.65–7.59 (m, 1 H, Ph-H), 7.56–7.48 (m, 2 H, 2 x Ph-H), 4.17 (q, \(J = 7.1\) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.19 (t, \(J = 7.1\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.3 (CO\(_2\)), 141.3 (Ph-C\(_\text{a}\)), 133.9 (Ph-CH), 128.9 (2 x Ph-CH), 127.6 (2 x Ph-CH), 62.1 (CO\(_2\)CH\(_2\)CH\(_3\)), 13.9 (CO\(_2\)CH\(_2\)CH\(_3\)).

Observed data (mp, IR, \(^1\)H, \(^{13}\)C) was consistent with that previously reported.\(^{13}\)

Ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (1d)\(^{19}\)

Tosyl azide \(\text{Sa}\) (1.18 g, 6.0 mmol) in THF (12 mL) was added dropwise to a stirring suspension of triethyl phosphonoacetate (1.19 mL, 6.0 mmol) and cesium carbonate (1.95 g, 6.0 mmol) in THF (48 mL). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through celite, the precipitate washed with \(\text{Et}_2\text{O}\) (70 mL) and the filtrate concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded diazo phosphonate 1d as a pale yellow oil (1.23 g, 82%); \(R_t = 0.23\) (50% EtOAc in hexanes); IR (film) / cm\(^{-1}\) 2985, 2125 (C=N=N out of phase), 1701 (C=O), 1478, 1446, 1392, 1368 (C=N=N in-phase), 1273 (P=O), 1165, 1095, 1013, 976, 859, 796, 744, 588, 555; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.30–4.09 (m, 6 H, CO\(_2\)CH\(_2\)CH\(_3\) and 2 x OCH\(_2\)CH\(_3\)), 1.36 (t, \(J = 7.1\) Hz, 6 H, 2 x OCH\(_2\)CH\(_3\)), 1.29 (t, \(J = 7.1\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.4 (d, \(J_{\text{C-P}} = 12.1\) Hz, CO\(_2\)), 63.6 (d, \(J_{\text{C-P}} = 5.6\) Hz, 2 x OCH\(_2\)CH\(_3\)), 61.7 (CO\(_2\)CH\(_2\)CH\(_3\)), 16.1 (d, \(J_{\text{C-P}} = 6.9\) Hz, 2 x OCH\(_2\)CH\(_3\)), 14.3 (CO\(_2\)CH\(_2\)CH\(_3\)); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) 10.1.

Observed data (IR, \(^1\)H, \(^{13}\)C, \(^{31}\)P) was consistent with that previously reported.\(^{24}\)

Benzyl cyano(diazo)formate (1e)\(^{20}\)

Pyridine (0.97 mL, 12.0 mmol) was added dropwise over 5 min to a stirring solution of benzyl cyanoacetate (0.92 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution \(\text{Sc}\) (0.47 M in \(n\)-hexane, 19.3 mL, 9.0 mmol) in CH\(_3\)CN (13 mL) at 0 °C. The resulting biphasic mixture was vigorously stirred at 25 °C for 15 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (90% CHCl\(_3\) in hexanes to CHCl\(_3\)) afforded diazo nitrile 1e as a yellow oil (610 mg, 51%); \(R_t = 0.23\) (CHCl\(_3\)); IR (film) / cm\(^{-1}\) 3036, 2957, 2919, 2850, 2229 (C=\(\equiv\)N), 2130 (C=N=N out of-phase), 1712 (C=O), 1584, 1499, 1456, 1381 (C=N=N in-phase), 1317, 1292, 1265, 1243, 1121, 1030, 949, 909, 791, 735, 697, 602, 544; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 (s, 5 H, 5 x Ph-H), 5.31 (s, 2 H, CO\(_2\)CH\(_2\)Ph); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.1 (CO\(_2\)), 134.3 (Ph-C\(_\text{a}\)), 128.9 (Ph-CH), 128.7 (2 x Ph-CH), 128.5 (2 x Ph-CH), 107.1 (C=\(\equiv\)N), 68.6 (CO\(_2\)CH\(_2\)Ph).
Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.  

Reaction performed on a large scale (2 x 12.5 mmol of benzyl cyanoacetate) using the following modified work up procedure: After the reaction time, the reaction mixture was concentrated in vacuo, diluted with EtOAc (100 mL), washed with 1 M aq. NaOH (2 x 20 mL) and brine (20 mL). The combined aqueous washes were then re-extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Combination of the 2 reactions afforded a combined isolated yield of diazo 1e (2.19 g, 44%) after flash chromatography.

**tert-Butyl 4-[cyano(diazo)carbonyl]piperazine-1-carboxylate (1f)**

![Chemical Structure](image)

Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of cyanoacetic acid (427 mg, 5.0 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 1 h then at 25 °C for 1 h. The reaction mixture was concentrated in vacuo, CH$_2$Cl$_2$ (10 mL) was then added to the residue and again concentrated in vacuo. The reaction flask was re-purged with Ar, the residue dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0 °C. N-Boc-piperazine (1.40 g, 7.5 mmol) in CH$_2$Cl$_2$ (2 mL) was added, and the reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH$_4$Cl (10 mL) was added, the layers separated and the aqueous mixture extracted with CH$_2$Cl$_2$ (2 x 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford the $\alpha$-cyano acetamide. Triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution Sc (0.506 M, 11.9 mL, 6.0 mmol) were added to a solution of $\alpha$-cyanoacetamide in CH$_3$CN (10 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated in vacuo and saturated aq. NH$_4$Cl (10 mL) was added to the residue. The aqueous mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford the $\alpha$-cyano acetamide. Purification by flash chromatography (2% to 4% to 6% CH$_3$CN in CH$_2$Cl$_2$) afforded diazo 1f as a yellow solid (523 mg, 37% over 2 steps); $R_f$ = 0.15 (5% CH$_3$CN in CH$_2$Cl$_2$); mp = 92–95 °C; IR (film) / cm$^{-1}$ 2978, 2932, 2216 (C≡N), 2118 (C=N=N out phase), 1694 (C=O), 1634 (C=O), 1456, 1413, 1366 (C=N=N in-phase), 1288, 1242, 1164, 1211, 1011, 996, 887, 861, 770, 721; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.67–3.56 (m, 4 H, 2 x CH$_2$), 3.53–3.44 (m, 4 H, 2 x CH$_2$), 1.47 (s, 9 H, 3 x CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 158.9 (C=O amide), 154.3 (C=O carbamate), 109.5 (C≡N), 80.6 (C$_6$H$_5$), 73.0 (C$_2$H$_5$), 45.1 (2 x CH$_2$), 43.2 (br, 2 x CH$_2$), 28.3 (3 x CH$_3$); HRMS (FTMS +pNSI) m/z Calcd for C$_{12}$H$_{21}$N$_5$O$_9$ $^+[M+NH_4]^+$: 297.1670, Found: 297.1674.

**Diethyl [1-diazo-2-oxo-2-(pyrrolidin-1-yl)ethyl]phosphonate (1g)**

![Chemical Structure](image)

Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of diethylphosphonoacetic acid (0.80 mL, 5.0 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 90 min then at 25 °C for 3 h. The reaction mixture was concentrated in vacuo, CH$_2$Cl$_2$ (10 mL) was then added to the residue and again concentrated in vacuo. The reaction flask was re-purged with Ar, the residue dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0 °C. Pyrrolidine (1.00 mL, 12.0 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 90 min then 25 °C for 1 h. A 1 M HCl solution (10 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH$_2$Cl$_2$ (4 x 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford the $\alpha$-phosphono acetamide.
Cesium carbonate (1.90 g, 5.8 mmol) was added in one portion to a stirring solution of tosyl azide Sa (1.09 g, 5.5 mmol) and α-phosphonoacetamide in THF (50 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 5 h 30 min. The reaction mixture was diluted with EtOAc (100 mL), and washed with 1 M aq. NaOH (2 × 15 mL) and brine (15 mL). The combined aqueous washes were then re-extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (2% MeOH in CH₂Cl₂) afforded diazo phosphonate 1g as a yellow oil (1.27 g, 93% over 2 steps); Rf = 0.29 (5% MeOH in CH₂Cl₂); IR (film) / cm⁻¹ 2980, 2877, 2120 (C≡N=N out-of-phase), 1615 (C=O), 1444, 1389 (C≡N=N in-phase), 1347, 1253 (P=O), 1193, 1162, 1097, 1011, 968, 873, 794, 758, 731, 555; ¹H NMR (400 MHz, CDCl₃) δ 4.33–4.06 (m, 4 H, 2 x OCH₂CH₃), 3.56–3.41 (m, 4 H, 2 x NCH₂), 1.89 (br s, 4 H, 2 x NCH₂CH₃), 1.35 (t, J = 7.1 Hz, 6 H, 2 x CH₃), 1.22 (t, J = 7.1 Hz, 6 H, 2 x CH₃), 1.10 (t, J = 7.1 Hz, 6 H, 2 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.3 (2 x C=O), 110.1 (C≡N), 42.5 (2 x CH₂), 13.6 (br, 2 x CH₃).

Observed data (IR, ¹H, ¹³C) was consistent with that previously reported.⁰

**(Diethylcarbamoyl)methanecarbonimidoyl cyanide (1h)²¹**

Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of cyanoacetic acid (425 mg, 5.0 mmol) in CH₂Cl₂ (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 75 min then at 25 °C for 1 h. The reaction mixture was concentrated in vacuo. CH₂Cl₂ (10 mL) was then added to the residue and again concentrated in vacuo. The reaction flask was re-purged with Ar, the residue dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. Diethylamine (1.0 mL, 10.0 mmol) was added dropwise over 3 min. The reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH₄Cl (10 mL) was added, the layers separated and the aqueous mixture extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo to afford the α-cyano acetamide.

Triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution Sc (0.506 M, 11.9 mL, 6.0 mmol) were added to a solution of the α-cyanoacetamide in CH₂CN (10 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated in vacuo and saturated aq. NH₄Cl (10 mL) added. The aqueous mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (CHCl₃) afforded diazo 1h as a dark yellow liquid (566 mg, 68% over 2 steps); Rf = 0.16 (CHCl₃); IR (film) / cm⁻¹ 2980, 2940, 2215 (C≡N), 2134, 2113 (C≡N=N), 1629 (C=O), 1480, 1459, 1425, 1385, 1363 (C≡N=N), 1312, 1278, 1257, 1215, 1191, 1101, 893, 868, 789, 724, 668, 629; ¹H NMR (400 MHz, CDCl₃) δ 3.44 (q, J = 7.1 Hz, 6 H, 2 x CH₃), 1.22 (t, J = 7.1 Hz, 6 H, 2 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.3 (C=O), 110.1 (C≡N), 42.5 (2 x CH₂), 13.6 (br, 2 x CH₃).

Observe data (IR, ¹H, ¹³C) was consistent with that previously reported.²¹

**(Benzenesulfonyl)methanecarbonimidoyl cyanide (1i)**

Pyridine (0.49 mL, 6.0 mmol) was added dropwise over 5 min to a stirring solution of (phenylsulfonyl)acetonitrile (543 mg, 3.0 mmol) and trifluoromethanesulfonyl azide solution Sc (0.47 M in n-hexane, 7.1 mL, 3.3 mmol) in CH₂CN (6 mL) at 0 °C. The resulting biphasic mixture was vigorously stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (50% to 75% CHCl₃ in toluene) afforded diazo nitrile 1i as a yellow solid (118 mg, 19%); Rf = 0.33 (50% CHCl₃ in toluene); mp = 109–105 °C (decomp.) (lit.²⁶ mp = 103–108 °C (decomp.)); IR (film) / cm⁻¹ 2936, 2256 (C≡N), 2127 (C≡N=N out-of-phase), 1698, 1584, 1449, 1333 (C≡N=N in-phase), 1158, 1068, 976, 907, 808, 726, 660, 555; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 7.1 Hz, 2 x H, 2 x CH₂), 6.93 (d, J = 7.1 Hz, 2 x H, 2 x CH₂), 1.68 (d, J = 7.1 Hz, 2 x H, 2 x CH₂), 1.26 (t, J = 7.1 Hz, 2 x H, 2 x CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 158.3 (2 x C=O), 110.1 (C≡N), 42.5 (2 x CH₂), 13.6 (br, 2 x CH₂).
683, 648, 628, 588, 558; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02–7.89 (m, 2 H, 2 x Ph-H), 7.80–7.73 (m, 1 H, Ph-H), 7.70–7.62 (m, 2 H, 2 x Ph-H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.1 (Ph-Cq), 135.0 (Ph-CH), 130.0 (2 x Ph-CH), 127.1 (2 x Ph-CH), 110.0 (C≡N), 105.7 (C$_2$N$_2$).

Observed data (mp, IR) was consistent with that previously reported.$^{25}$
Synthesis of Disubstituted Aryl Diazos 6a–6g

Synthesis of disubstituted aryl diazos 6a–6g using p-ABSA, adapted from the procedure of Davies and co-workers (Table S2).26

\[
\begin{array}{ccc}
  \text{O} & \text{Ar} & \text{N}_2 \\
  \text{DBU (1.2 equiv)} & \text{MeCN, 24 h} & \text{DBU (1.2 equiv)} \\
  \text{p-ABSA (1.2 equiv)} & & \\
  \end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(X = )</th>
<th>(\text{Ar} = )</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 75 (6a)   |
| 2     | OPr    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 52 (6b)   |
| 3     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 86 (6c)   |
| 4     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 86 (6d)   |
| 5     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 48 (6e)   |
| 6     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 83 (6f)   |
| 7     | OEt    | \(\begin{array}{c}
\text{OEt} \\
\end{array}\) | 15 (6g)   |

Ethyl 2-diazo-2-phenylacetate (6a)

DBU (0.90 mL, 6.0 mmol) was added to a stirred solution of p-ABSA Sb (1.44 g, 6.0 mmol) and ethyl 2-phenylacetate (0.80 mL, 5.0 mmol) in CH\(_3\)CN (8.3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH\(_4\)Cl (30 mL) was added. The aqueous mixture was extracted with Et\(_2\)O (3 x 30 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated in vacuo. The mixture was then taken up with 50% Et\(_2\)O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (3% Et\(_2\)O in petroleum ether) afforded diazo 6a as an orange oil (713 mg, 75%); \(R_f = 0.30\) (5% EtOAc in hexanes); IR (film) / cm\(^{-1}\) 2983, 2079 (C=N=N out-of-phase), 1699 (C=O), 1599, 1499, 1450, 1370 (C=N=N in-phase), 1337, 1242, 1149, 1095, 1048, 1028, 904, 753, 689, 666; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.57–7.45 (m, 2 H, Ph-H), 7.42–7.33 (m, 2 H, Ph-H), 7.22–7.14 (m, 1 H, Ph-H), 4.34 (q, \(J = 7.0\) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.35 (t, \(J = 7.0\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.2 (CO\(_2\)), 128.9 (2 x Ph-H), 125.7 (Ph-CH), 125.6 (Ph-C\(_3\)), 124.0 (2 x Ph-CH), 61.0 (CO\(_2\)CH\(_2\)CH\(_3\)), 14.5 (CO\(_2\)CH\(_2\)CH\(_3\)).
Reaction performed on a large scale (15 mmol ethyl 2-phenylacetate) afforded an isolated yield of diazo 6a (1.83 g, 64%).

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.\(^{27}\)

**Propan-2-yl 2-diazo-2-phenylacetate (6b)**

\[\text{DBU (0.63 mL, 4.2 mmol) was added to a stirred solution of } p\text{-ABSA Sb (1.00 g, 4.2 mmol) and propan-2-yl 2-phenylacetate (0.62 mL, 3.5 mmol) in CH}_3\text{CN (35 mL) at } 0^\circ\text{C. The reaction mixture was stirred at 25 }^\circ\text{C for 24 h. Saturated aq. NH}_4\text{Cl (30 mL) was added. The aqueous mixture was extracted with Et}_2\text{O (3 x 30 mL). The organic extracts were combined, dried (MgSO}_4\text{) and concentrated in vacuo. The mixture was then taken up with 50\% Et}_2\text{O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (3\% Et}_2\text{O in petroleum ether) afforded diazo 6b as a yellow oil (372 mg, 52\%); } R_f = 0.59 (3\% Et}_2\text{O in petroleum ether); IR (film) / cm}^{-1}\text{ 2982, 2935, 2077 (C=N=N out-of-phase), 1695 (C=O), 1599, 1363 (C=N=N in-phase), 1327, 1286, 1243, 1163, 1104, 1008, 996, 906, 753, 689, 664; } ^1\text{H NMR (400 MHz, CDCl}_3\text{) } $\delta$\text{ 7.54–7.45 (m, 2 H, 2 x Ph-H), 7.43–7.34 (m, 2 H, 2 x Ph-H), 7.21–7.13 (m, 1 H, Ph-H), 5.22 (sep, } J = 6.5 \text{ Hz, 1 H, } CO}_2\text{C(CH}_3\text{)_2}; 13\text{C NMR (101 MHz, CDCl}_3\text{) } $\delta$\text{ 164.8 (CO}_2\text{), 128.9 (2 x Ph-CH), 125.8 (Ph-C}, C\text{), 125.7 (Ph-CH) 123.9 (2 x Ph-CH), 68.7 (CO}_2\text{CH(CH}_3\text{)_2}, 22.1 (2 x CH}_3\text{).}

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.\(^{28}\)

**2-(3-Chlorophenyl)-2-diazoacetic acid (6c)**

\[\text{DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of } p\text{-ABSA Sb (865 mg, 3.6 mmol) and ester S4 (596 mg, 3.0 mmol) in CH}_3\text{CN (5.0 mL) at } 0^\circ\text{C. The reaction mixture was extracted with Et}_2\text{O (3 x 30 mL). The organic extracts were combined, dried (MgSO}_4\text{) and concentrated in vacuo. The mixture was then taken up with 50\% Et}_2\text{O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (5\% Et}_2\text{O in pentane) afforded diazo 6c as a yellow solid (581 mg, 86\%); } R_f = 0.47 (5\% diethyl ether in pentane); IR (film) / cm}^{-1}\text{ 2991, 2907, 2089 (C=N=N out-of-phase), 1698 (C=O), 1592, 1559, 1479, 1446, 1425, 1391 (C=N=N in-phase), 1341, 1276, 1241, 1166, 1114, 1097, 1081, 1047, 993, 885, 865, 825, 776, 735, 679, 657; } ^1\text{H NMR (400 MHz, CDCl}_3\text{) } $\delta$\text{ 7.57–7.55 (m, 1 H, Ar-H), 7.36–7.28 (m, 2 H, 2 x Ar-H), 7.17–7.12 (m, 1 H, Ar-H), 4.35 (q, } J = 7.1 \text{ Hz, 2 H, CO}_2\text{CH(CH}_3\text{)_2}; 13\text{C NMR (101 MHz, CDCl}_3\text{) } $\delta$\text{ 164.6 (CO}_2\text{), 135.0 (Ar-C}, C\text{), 130.0 (Ar-CH), 127.9 (Ar-C}, C\text{–Cl), 125.7 (Ar-CH), 123.7 (Ar-CH), 121.6 (Ar-CH), 61.2 (CO}_2\text{CH(CH}_3\text{)_2), 14.5 (CO}_2\text{CH(CH}_3\text{).}

Observed data (IR, $^1$H, $^{13}$C) was consistent with that previously reported.\(^{29}\)
Ethyl 2-diazo-2-[4-(trifluoromethyl)phenyl]acetate (6d)

DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of \( p \)-ABSA Sb (865 mg, 3.6 mmol) and ester S5 (697 mg, 3.0 mmol) in CH\(_3\)CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH\(_2\)Cl (30 mL) was added. The aqueous mixture was extracted with Et\(_2\)O (3 x 30 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated in vacuo. The mixture was then taken up with 50% Et\(_2\)O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (5% Et\(_2\)O in pentane) afforded diazo 6d as a yellow solid (667 mg, 86%); \( R_f = 0.35 \) (5% Et\(_2\)O in pentane); IR (film) / cm\(^{-1}\): 2988, 2092 (C=N=N out-of-phase), 1691 (C=O), 1618, 1572, 1518, 1466, 1450, 1420, 1372 (C=N=N in-phase), 1320, 1297, 1241, 1198, 1153, 1112, 1069, 1040, 1010; \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.62 (s, 4 H, 4 x Ar-H), 4.36 (q, \( J = 7.0 \) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.37 (t, \( J = 7.0 \) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)) \( ^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 164.4 (CO\(_2\)), 130.2 (Ar-C\(_q\)-CN\(_2\)), 127.5 (q, \( J_{C-F} = 33 \) Hz, Ar-C\(_q\)-CF\(_3\)), 125.8 (q, \( J_{C-F} = 4 \) Hz, 2 x Ar-CH), 124.1 (q, \( J_{C-F} = 272 \) Hz, CF\(_3\)), 123.4 (2 x Ar-CH), 61.3 (CO\(_2\)CH\(_2\)CH\(_3\)), 14.4 (CO\(_2\)CH\(_2\)CH\(_3\)) \( ^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) –62.4.

Observed data (IR, \( ^1\)H, \( ^{13}\)C) was consistent with that previously reported.\(^{30}\)

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate (6e)

DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of \( p \)-ABSA Sb (865 mg, 3.6 mmol) and ester S6 (583 mg, 3.0 mmol) in CH\(_3\)CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH\(_2\)Cl (30 mL) was added. The aqueous mixture was extracted with Et\(_2\)O (3 x 30 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated in vacuo. The mixture was then taken up with 50% Et\(_2\)O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (5% Et\(_2\)O in pentane) afforded diazo 6e as a red solid (314 mg, 48%); \( R_f = 0.17 \) (5% Et\(_2\)O in pentane); IR (film) / cm\(^{-1}\): 2983, 2916, 2837, 2089 (C=N=N out-of-phase), 1692 (C=O), 1609, 1574, 1510, 1478, 1468, 1444, 1393, 1367 (C=N=N in-phase), 1343, 1318, 1295, 1252, 1238, 1189, 1162, 1049, 1031, 990, 828, 734, 639, 615, 554; \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.44–7.35 (m, 2 H, 2 x Ar-CH), 7.00–6.91 (m, 2 H, 2 x Ar-H), 4.33 (q, \( J = 7.1 \) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 3.82 (s, 3 H, OCH\(_3\)), 1.34 (t, \( J = 7.1 \) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)) \( ^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 165.7 (CO\(_2\)), 158.0 (Ar-C\(_q\)-OCH\(_3\)), 125.9 (2 x Ar-CH), 117.0 (Ar-C\(_q\)-CN\(_2\)), 114.6 (2 x Ar-CH), 60.9 (CO\(_2\)CH\(_2\)CH\(_3\)), 55.3 (OCH\(_3\)), 14.5 (CO\(_2\)CH\(_2\)CH\(_3\)).

Observed data (IR, \( ^1\)H, \( ^{13}\)C) was consistent with that previously reported.\(^{31}\)

Ethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (6f)

DBU (0.53 mL, 3.6 mmol) was added to a stirred solution of \( p \)-ABSA Sb (865 mg, 3.6 mmol) and ester S7 (599 mg, 3.0 mmol) in CH\(_3\)CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH\(_2\)Cl (30 mL) was added. The aqueous mixture was extracted with Et\(_2\)O (3 x 30 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated in vacuo. The mixture was then taken up with 50%
Et₂O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (10% Et₂O in pentane) afforded diazo 6f as a yellow solid (564 mg, 83%); Rᵣ = 0.18 (10% Et₂O in pentane); IR (film) / cm⁻¹ 2981, 2089 (C=N=N out-of-phase), 1689 (C=O), 1579, 1549, 1471, 1399, 1383 (C=N=N in-phase), 1341, 1307, 1253, 1228, 1166, 1105, 1047, 1018, 988, 842, 832, 814, 741, 725; ¹H NMR (400 MHz, CDCl₃) δ 8.46 (dd, J = 2.7, 0.7 Hz, 1 H, Ar-H), 7.87 (dd, J = 8.5, 2.7 Hz, 1 H, Ar-H), 7.34 (dd, J = 8.5, 0.7 Hz, 1 H, Ar-H), 4.36 (q, J = 7.1 Hz, 2 H, CO₂CH₂CH₃), 1.36 (t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.3 (CO₂), 148.4 (Ar-C₉-Cl) 144.4 (Ar-CH), 133.8 (Ar-CH), 124.2 (Ar-CH), 122.0 (Ar-C₉-C₉), 61.6 (CO₂CH₂CH₃), 14.4 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z calcd for C₉H₉N₃O₂Cl⁺ [M+H]⁺: 226.0383, Found: 226.0390.

2-(3-Chlorophenyl)-2-diazo-1-(morpholin-4-yl)ethan-1-one (6g)

DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of p-ABSA Sb (865 mg, 3.6 mmol) and amide S₈ (719 mg, 3.0 mmol) in CH₃CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH₄Cl (30 mL) was added. The aqueous mixture was extracted with Et₂O (3 x 30 mL). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo. The mixture was then taken up with 50% Et₂O in petroleum ether (50 mL), filtered and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) afforded diazo 6g as a yellow oil (124 mg, 15%); Rᵣ = 0.15 (25% EtOAc in hexanes); IR (film) / cm⁻¹ 2968, 2856, 2059 (C=N=N out-of-phase), 1645, 1625 (C=O), 1591, 1563, 1481, 1456, 1424, 1362 (C=N=N in-phase), 1324, 1299, 1281, 1268, 1254, 1180, 1112, 1085, 1062, 1023, 993, 874, 867, 835, 782, 753, 727, 715, 685; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (t, J = 7.9 Hz, 1 H, Ar-H), 7.24 (t, J = 2.0 Hz, 1 H, Ar-H), 7.15 (dd, J = 8.0, 2.0, 1.0 Hz, 1 H, Ar-H), 7.09 (ddd, J = 8.0, 1.8, 0.9 Hz, 1 H, Ar-H), 3.72–3.64 (m, 4 H, 2 x OCH₂), 3.50–3.45 (m, 4 H, 2 x NCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 164.7 (C=O), 135.3 (Ar-C₉-CN₂), 130.4 (Ar-CH), 129.5 (Ar-C₉-Cl), 126.0 (Ar-CH), 124.1 (Ar-CH), 122.2 (Ar-CH), 66.6 (2 x OCH₂), 46.0 (2 x NCH₂); HRMS (ESI-TOF) m/z calcd for C₁₄H₁₆N₆O₂Cl⁺ [M+CH₃CN+H]⁺: 307.0962, Found: 307.0956.
Synthesis of 2,2-Disubstituted Oxetanes 3a–3g

\[
\begin{align*}
\text{E}_1^1 \text{N}_2 & \quad \text{E}_2 \quad \text{HO} \quad \text{Br} \\
1a \text{–} 1g & \quad \text{Rh}_2(\text{OAc})_4 (0.5 \text{ mol%}) \\
& \quad \text{Benzene or CH}_2\text{Cl}_2 \\
\text{E}_1^1 \text{O} \quad \text{E}_2 & \quad \text{Br} \quad \text{NaH (1.2 equiv)} \\
2a \text{–} 2g & \quad \text{DMF} \\
\text{O} & \quad 3a \text{–} 3g
\end{align*}
\]

\[
\text{(±)-Ethyl 2-(bromoethoxy)-3-oxo-3-(pyrrolidin-1-yl)propanoate (2a)}
\]

\[
\text{EtO}_2\text{C} \quad \text{O} \quad \text{Br}
\]

A mixture of diazo amide 1a (442 mg, 2.1 mmol), 2-bromoethanol (249 mg, 2.0 mmol) and dirhodium(II) tetraacetate (4.4 mg, 0.010 mmol) in benzene (20 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide 2a as a white solid (462 mg, 75%); R$_f$ = 0.16 (50% EtOAc in hexanes); mp = 44–47 °C; IR (film) / cm$^{-1}$ 2976, 2877, 1752 (C=O ester), 1647 (C=O amide), 1430, 1338, 1276, 1204, 1186, 1065, 1027, 915, 865, 715, 661, 568, 523; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.72 (s, 1 H, CH(CO$_2$Et)(CON)), 4.30 (q, J = 7.1 Hz, 2 H, CO$_2$CH$_2$CH$_3$), 3.98 (m, 1 H, OC(O)CH$_3$), 3.58 (m, 1 H, NCH$_2$H), 3.47 (m, 4 H, CH$_2$CO$_2$Et), 3.10 (m, 1 H, NCH$_2$H), 2.90–2.78 (m, 1 H, OCHH), 2.50–2.38 (m, 1 H, OCHH), 2.34–2.18 (m, 2 H, CH$_2$), 1.92–1.83 (m, 2 H, NCH$_2$CH$_2$) 1.31 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.2 (C=O), 163.6 (C=O), 80.0 (CH(CO$_2$Et)(CON)), 70.2 (OCH$_2$), 61.7 (CO$_2$CH$_2$CH$_3$), 46.4 (NCH$_2$), 46.3 (NCH$_2$), 29.9 (CH$_2$Br), 26.1 (NCH$_2$CH$_2$), 23.8 (NCH$_2$CH$_2$), 14.0 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for C$_{11}$H$_{18}$BrNO$_4$ $^+$ [M+H]$^+$: 308.0497, Found: 308.0502.

\[
\text{(±)-Ethyl 2-(pyrrolidine-1-carbonyl)oxetane-2-carboxylate (3a)}
\]

\[
\text{EtO}_2\text{C} \quad \text{O} \quad \text{N}
\]

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide 2a (154 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 0 °C for 1 h then allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded oxetane 3a as a colorless oil (106 mg, 93%); R$_f$ = 0.13 (50% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2977, 2895, 1745 (C=O ester), 1645 (C=O amide), 1440, 1369, 1338, 1276, 1204, 1186, 1065, 1027, 915, 865, 715, 661, 568, 523; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.75–4.65 (m, 1 H OCHH), 4.58–4.49 (m, 1 H, OCHH), 4.31 (q, J = 7.1 Hz, 2 H, CO$_2$CH$_2$CH$_3$), 3.69–3.43 (m, 4 H, NCH$_2$ and NCHH and CHH), 3.22–3.10 (m, 1 H, NCHH), 2.90–2.78 (m, 1 H, CHH), 1.98–1.75 (m, 4 H, 2 x NCH$_2$CH$_2$), 1.31 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.1 (C=O), 166.0 (C=O), 86.1 (C$_6$(CO$_2$Et)(CON)), 67.3 (OCH$_3$), 61.9 (CO$_2$CH$_2$CH$_3$), 46.6 (NCH$_2$), 45.7 (NCH$_2$), 29.0 (CH$_2$), 26.2 (NCH$_2$CH$_2$), 23.4 (NCH$_2$CH$_2$), 14.0 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{18}$NO$_4$ $^+$ [M+H]$^+$: 228.1236, Found: 228.1244.
A mixture of diazo amide 1b (220 mg, 1.1 mmol), 2-bromoethanol (125 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (4% to 5% MeOH in CH₂Cl₂) afforded bromide 2b as a colorless oil (153 mg, 51%); Rₐ = 0.25 (5% MeOH in CH₂Cl₂); IR (film) / cm⁻¹ 2979, 2942, 2874, 1755 (C=O ester), 1670 (C=O amide), 1585, 1175, 1077, 1022, 1000, 859, 836, 760, 721, 565, 541, 514, 489, 461, 448, 424, 392, 380, 362, 341, 321, 303, 283, 253, 241, 228, 216, 204, 192, 180, 168, 156, 144, 132, 120, 108, 96, 84, 72, 60, 48, 36, 24, 12. HRMS (ESI-TOF) m/z Calcd for C₁₇H₁₇BrNO₅⁺ [M+H]⁺: 298.0290, Found: 298.0289.

**(-)-Ethyl 2-(methoxy(methyl)carbamoyl]acetate (3b)**

DMF (10 mL) was added to a flask containing sodium hydride (60% in mineral oil, 16 mg, 0.41 mmol) which had been cooled to 0 °C. Bromide 2b (101 mg, 0.34 mmol) in DMF (3.6 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 1 h then allowed to cool to 25 °C for 1 h. Saturated aq. NH₄Cl (14 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (30% to 40% EtOAc in hexanes) afforded oxetane 3b as a colorless oil (71 mg, 96%); Rₐ = 0.38 (40% EtOAc in hexanes); IR (film) / cm⁻¹ 2980, 2941, 2901, 1757 (C=O ester), 1670 (C=O amide), 1585, 1175, 1077, 1022, 1000, 859, 836, 760, 721, 565, 541, 514, 489, 461, 448, 424, 392, 380, 362, 341, 321, 303, 283, 253, 241, 228, 216, 204, 192, 180, 168, 156, 144, 132, 120, 108, 96, 84, 72, 60, 48, 36, 24, 12. HRMS (ESI-TOF) m/z Calcd for C₂₉H₁₆NO₅⁺ [M+H]⁺: 218.1028, Found: 218.1037.

**(-)-Ethyl 2-(benzenesulfonyl)-2-(bromoethoxy)acetate (2c)**

A mixture of diazo sulfone 1c (280 mg, 1.1 mmol), 2-bromoethanol (124 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.5 mg, 0.006 mmol) in benzene (10 mL) was heated at 80 °C for 90 min. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CHCl₃ (3 x 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) afforded bromide 2c as a white solid (323 mg, 92%); Rₐ = 0.15 (25% EtOAc in hexanes); mp = 47–50 °C; IR (film) / cm⁻¹ 2982, 1745 (C=O), 1585, 1448, 1424, 1394, 1370, 1323, 1310, 1281, 1233, 1186, 1146, 1115, 1077, 1022, 1000, 859, 836, 760, 721. 1H NMR (400 MHz, CDCl₃) δ 4.78 (s, 1 H, CH(C=O)(CON)(Me)(OMe)), 71.0 (OCH₃), 56.2 (OCH₃), 4.22 (m, 2 H, CO₂Et(CH₂CH₃)), 3.67 (s, 3 H, OCH₃), 3.22 (s, 3 H, NCH₂), 2.81–2.71 (m, 1 H, CHH), 1.29 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃); 13C NMR (101 MHz, CDCl₃) δ 169.3 (CO₂ and CON), 85.0 (C₆H₅(C=O)(ET)(CON)), 67.8 (OCH₃), 61.7 (OCH₃), 61.5 (CO₂CH₂CH₃), 32.8 (NCH₃), 27.7 (CH₂), 14.1 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₉H₈NO₅⁺ [M+H]⁺: 218.1028, Found: 218.1037.
686, 631, 563; \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.97–7.87 (m, 2 H, 2 x Ph-H), 7.74–7.67 (m, 1 H, Ph-H), 7.62–7.53 (m, 2 H, 2 x Ph-H), 5.01 (s, 1 H, CH(CO\(_2\)Et)(SO\(_2\)Ph), 4.31 (dt, \( J = 11.1, 5.9 \) Hz, 1 H, OCH\(_2\)H), 4.21 (q, \( J = 7.1 \) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 4.07 (dt, \( J = 11.1, 6.2 \) Hz, 1 H, OCH\(_2\)Ph), 3.51–3.44 (m, 2 H, CH\(_2\)Br), 1.25 (t, \( J = 7.1 \) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 163.1 (CO\(_2\)), 135.4 (Ph-C\(_6\)), 134.6 (Ph-CH), 129.8 (2 x Ph-CH), 129.0 (2 x Ph-CH), 94.3 (CH(CO\(_2\)Et)(SO\(_2\)Ph)), 73.4 (OCH\(_2\)), 62.8 (CO\(_2\)CH\(_2\)CH\(_3\)), 29.0 (CH\(_2\)Br), 13.9 (CO\(_2\)CH\(_2\)CH\(_3\)); HRMS (ESI-TOF) m/z Calcd for C\(_{14}\)H\(_{15}\)BrNO\(_5\)SNa\(^+\) [M+CH\(_3\)CN+Na]\(^+\): 413.9987, Found: 413.9986.

(\( \pm \))-Ethyl 2-(benzenesulfonyl)oxetane-2-carboxylate (3c)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{PhO}_2\text{S} \\
& \quad \text{O} \\
& \quad \text{EtO}_2\text{C} \\
\end{align*}
\]

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide 2c (175 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH\(_4\)Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo}. Purification by flash chromatography (40% EtOAc in hexanes) afforded oxetane 3c as a white solid (117 mg, 87%); \( R_f = 0.30 \) (40% EtOAc in hexanes); mp = 67–70 °C; IR (film) / cm\(^{-1}\) 2980, 2907, 1739 (C=O), 1584, 1477, 1448, 1392, 1369, 1310, 1283, 1233, 1156, 1144, 1115, 1084, 1063, 1013, 964, 931, 886, 855, 759, 723, 689, 584, 559; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.00–7.88 (m, 2 H, 2 x Ph-H), 7.75–7.66 (m, 1 H, Ph-H), 7.62–7.51 (m, 2 H, 2 x Ph-H), 4.84–4.76 (m, 1 H OCH\(_2\)H), 4.57 (dt, \( J = 8.9, 5.5 \) Hz, 1 H, OCH\(_2\)Ph), 4.19 (q, \( J = 7.1 \) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 3.52–3.43 (m, 1 H, CH-H), 3.32–3.22 (m, 1 H, CH-H), 1.18 (t, \( J = 7.1 \) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 165.9 (CO\(_2\)), 134.6 (Ph-CH), 134.1 (Ph-C\(_6\)), 130.2 (2 x Ph-CH), 128.8 (2 x Ph-CH), 98.7 (C\(_8\)(CO\(_2\)Et)(SO\(_2\)Ph)), 68.9 (OCH\(_2\)), 62.8 (CO\(_2\)CH\(_2\)CH\(_3\)), 26.5 (CH\(_2\)), 13.8 (CO\(_2\)CH\(_2\)CH\(_3\)); HRMS (ESI-TOF) m/z Calcd for C\(_{12}\)H\(_{15}\)O\(_5\)S\(^+\) [M+H]\(^+\): 271.0640, Found: 271.0633.

(\( \pm \))-Ethyl 2-(2-bromoethoxy)-2-(diethoxyphosphoryl)acetate (2d)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{O} \\
& \quad \text{Br} \\
& \quad \text{EtO}_2\text{COP} \\
\end{align*}
\]

A mixture of diazo phosphonate 1d (375 mg, 1.5 mmol), 2-bromoethanol (71 \( \mu \)L, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The organic extracts were combined, dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo}. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide 2d as a light yellow oil (267 mg, 77%); \( R_f = 0.21 \) (50% EtOAc in hexanes); IR (film) / cm\(^{-1}\) 2983, 2933, 1746 (C=O), 1445, 1392, 1254 (P=O), 1124, 1016, 974, 857, 794, 737, 667; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.40 (d, \( J_{\text{P-H}} = 18.5 \) Hz, 1 H, CH(CO\(_2\)Et)(PO(OEt\(_2\)))\)), 4.35–4.16 (m, 6 H, CO\(_2\)CH\(_2\)CH\(_3\) and 2 x OCH\(_2\)CH\(_3\)), 4.04 (dt, \( J = 10.5, 6.0 \) Hz, 1 H, OCH\(_2\)H), 3.83 (dt, \( J = 10.5, 6.5 \) Hz, 1 H, OCH\(_2\)H), 3.58–3.46 (m, 2 H, CH\(_2\)Br), 1.41–1.29 (m, 9 H, CO\(_2\)CH\(_2\)CH\(_3\) and 2 x OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 167.0 (CO\(_2\)), 76.9 (d, \( J_{\text{C-P}} = 157.4 \) Hz, CH(CO\(_2\)Et)(PO(OEt\(_2\)))\)), 72.3 (d, \( J_{\text{C-P}} = 12.5 \) Hz, OCH\(_2\)CH\(_3\)Br), 63.9 (d, \( J_{\text{C-P}} = 6.3 \) Hz, OCH\(_2\)CH\(_3\)Br), 63.8 (d, \( J_{\text{C-P}} = 6.3 \) Hz, OCH\(_2\)CH\(_3\)Br), 62.0 (CO\(_2\)CH\(_2\)CH\(_3\)), 29.3 (CH\(_2\)Br), 16.4 (d, \( J_{\text{C-P}} = 6.1 \) Hz, 2 x OCH\(_2\)CH\(_3\)), 14.1 (CO\(_2\)CH\(_2\)CH\(_3\)); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \) 13.4; HRMS (ESI-TOF) m/z Calcd for C\(_{16}\)H\(_{22}\)BrO\(_6\)PNa\(^+\) [M+Na]\(^+\): 369.0079, Found: 369.0091.
(±)-Ethyl 2-(diethoxyphosphoryl)oxetane-2-carboxylate (3d)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide 2d (174 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (50% to 60% EtOAc in hexanes to EtOAc) afforded oxetane 3d as a colorless oil (93 mg, 70%); Rf = 0.11 (60% EtOAc in hexanes); IR (film) / cm⁻¹: 2982, 2905, 1733 (C=O), 1447, 1392, 1369, 1256 (P=O), 1195, 1163, 1100, 1010, 968, 941, 857, 794, 759; ¹H NMR (400 MHz, CDCl₃) δ 4.84–4.75 (m, 1 H, OCH₂), 4.41–4.13 (m, 6 H, CO₂CH₂CH₃ and 2 x OCH₂CH₃), 3.26–3.13 (m, 1 H, CH), 3.12–2.97 (m, 1 H, CHH), 3.19–1.92 (m, 9 H, CO₂CH₂CH₃ and 2 x OCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.0 (d, J_C-P = 12.0 Hz, CO₂), 83.6 (d, J_C-P = 159.0 Hz, C₁(CO₂Et)(PO(OEt)₂), 69.2 (d, J_C-P = 4.5 Hz, OCH₂), 64.2 (d, J_C-P = 7.0 Hz, OCH₂CH₃), 63.8 (d, J_C-P = 7.0 Hz, OCH₂CH₃), 62.0 (CO₂CH₂CH₃), 28.4 (d, J_C-P = 3.5 Hz, CH₂), 16.44 (d, J_C-P = 6.0 Hz, OCH₂CH₃), 16.41 (d, J_C-P = 6.0 Hz, OCH₂CH₃), 14.1 (CO₂CH₂CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 15.3; HRMS (ESI-TOF) m/z Calcd for C₁₀H₂₀O₆P⁺ [M+H]⁺: 267.0998, Found: 267.0989.

(±)-Benzyl 2-(2-bromoethoxy)-2-cyanoacetate (2e)

A mixture of diazo nitrile 1e (221 mg, 1.1 mmol), 2-bromoethanol (125 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in CH₂Cl₂ (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded bromide 2e as a yellow oil (253 mg, 85%); Rf = 0.30 (20% EtOAc in hexanes); IR (film) / cm⁻¹: 3036, 2931, 2877, 2251 (C≡N), 1760 (C=O), 1498, 1456, 1423, 1379, 1282, 1213, 1127, 988, 907, 826, 776, 749, 697, 601, 574; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 5 H, 5 x Ph), 5.33 (d, J = 12.2 Hz, 1 H, CO₂CH₂Ph), 5.29 (d, J = 12.2 Hz, 1 H, CO₂CH₂Ph), 4.99 (s, 1 H, CH(CO₂Bn)(CN)), 4.13–4.04 (m, 1 H, OCH₂), 4.03–3.95 (m, 1 H, OCH₂), 3.52 (t, J = 6.0 Hz, 2 H, CH₂Br); ¹³C NMR (101 MHz, CDCl₃) δ 162.7 (CO₂), 133.9 (Ph-C₆H₅), 128.9 (Ph-CH), 128.7 (2 x Ph-CH), 128.4 (2 x Ph-CH), 113.1 (C≡N), 70.2 (OCH₂), 68.9 (CO₂CH₂Ph), 67.2 (CH(CO₂Bn)(CN)), 28.5 (CH₂Br); HRMS (EI) m/z Calcd for C₁₂H₁₅BrN₂O₅⁺ [M+Br⁻]: 315.0342, Found: 315.0357.

Reaction performed on a large scale (10 mmol 2-bromoethanol, 11 mmol diazo 1e) afforded an isolated yield of bromide 2e (2.79 g, 93%).

(±)-Benzyl 2-cyanooxetane-2-carboxylate (3e)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide 2e (149 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (40% EtOAc in hexanes) afforded oxetane 3e as a yellow oil which solidified upon storage at −20 °C (95 mg, 88%); Rf = 0.47 (40% EtOAc in hexanes); mp = 30–32 °C; IR (film) / cm⁻¹: 3035, 2980, 2909,
2244 (C=N), 1746 (C=O), 1498, 1456, 1379, 1268, 1195, 1161, 1105, 1029, 965, 938, 907, 738, 696, 601, 588; 1H NMR (400 MHz, CDCl₃) δ 7.44–7.35 (m, 5 H, 5 x Ph-H), 5.36 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 5.32 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 4.90–4.82 (m, 1 H, OCH₃), 4.81–4.73 (m, 1 H, OCH₃), 3.32–3.22 (m, 1 H, CH₂), 3.21–3.12 (m, 1 H, CH₂); IR (film) / cm⁻¹: 2978, 2908, 2254 (C≡N), 1746 (C=O), 1661 (C=O), 1629, 1543, 1379, 1269, 1192, 1119, 1096, 950, 940, 917, 878, 801, 770, 594, 548; 13C NMR (101 MHz, CDCl₃) δ 164.5 (CO₂), 134.1 (Ph-C₆), 128.8 (Ph-CH), 128.7 (2 x Ph-CH), 128.3 (2 x Ph-CH), 113.6 (C≡N), 76.5 (C(q)(CO₂Bn)(CN)), 69.4 (OCH₃), 68.8 (CO₂CH₂Ph), 31.5 (CH₂); HRMS (FTMS +pNSI) m/z Calcd for C₁₂H₁₄NO₃Na⁺ [M+Na]⁺: 240.0631, Found: 240.0631.

Reaction performed on a large scale (8 mmol bromide 2e) afforded an isolated yield of oxetane 3e (1.61 g, 93%).

(±)-tert-Butyl 4-[2-(2-bromoethoxy)-2-cyanoacetyl]piperazine-1-carboxylate (2f)

A mixture of diazo amide 1f (336 mg, 1.2 mmol), 2-bromoethanol (71 µL, 1.0 mmol) and dirhodium(II) tetraacetate (2.3 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (3% to 4% to 6% CH₂Cl₂O in hexanes) afforded oxetane 2f as a pale yellow viscous oil (252 mg, 67%); R₂ = 0.11 (4% CH₂Cl₂O in CH₂Cl₂); IR (film) / cm⁻¹: 2977, 2931, 2868, 2223 (C=N), 1664 (C=O), 1460, 1419, 1366, 1286, 1254, 1235, 1167, 1126, 1050, 996, 864, 771, 577, 538; 1H NMR (400 MHz, CDCl₃) δ 5.11 (s, 1 H, (NC)CH(O)), 4.18–4.08 (m, 1 H, OCH₃), 4.05–3.95 (m, 1 H, OCH₃), 3.74–3.46 (m, 10 H, CH₂Br and 4 x CH₂), 1.50 (s, 9 H, 3 x CH₃); 13C NMR (101 MHz, CDCl₃) δ 164.0 (C=O amide), 154.3 (C=O carbamate), 113.6 (C≡N), 80.6 (C(q)(CH₃)₃), 70.4 (OCH₂), 70.1 (NC)CH(O)), 45.9 (2 x CH₂), 42.8 (2 x CH₂), 29.0 (CH₂Br), 28.3 (3 x CH₃); HRMS (FTMS +pNSI) m/z Calcd for C₁₅H₂₆BrN₂O₄⁺ [M+Na⁺]: 393.1132, Found: 393.1131.

(±)-tert-Butyl 4-(2-cyanooxetane-2-carbonyl)piperazine-1-carboxylate (3f)

DMF (20 mL) was added to a flask containing sodium hydride (60% in mineral oil, 30 mg, 0.76 mmol) which had been cooled to 0 °C. Bromide 2f (237 mg, 0.63 mmol) in DMF (5 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (25 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 25 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (70% Et₂O in hexanes) afforded oxetane 3f as a white solid (161 mg, 87%); R₂ = 0.22 (70% Et₂O in hexanes); mp = 76–79 °C; IR (film) / cm⁻¹: 2978, 2908, 2254 (C≡N), 1693 (C=O), 1661 (C=O), 1416, 1366, 1287, 1247, 1234, 1162, 1139, 1018, 995, 940, 917, 846, 770, 728, 669, 647, 594, 548; 1H NMR (400 MHz, CDCl₃) δ 4.82 (td, J = 8.1, 5.8 Hz, 1 H, OCH₃), 4.54 (dt, J = 9.1, 5.8 Hz, 1 H, OCH₃), 3.73–3.35 (m, 9 H, 4 x NCH₂ and CH₂), 3.15–3.03 (m, 1 H, CH₃), 1.46 (s, 9 H, 3 x CH₃); 13C NMR (101 MHz, CDCl₃) δ 162.9 (C≡N amide), 154.4 (C=O carbamate), 117.4 (C≡N), 80.4 (C(q)(CH₃)₃), 68.4 (OCH₂), 45.7 (2 x NCH₂), 42.9 (2 x NCH₂), 30.3 (CH₂), 28.3 (3 x CH₃); HRMS (FTMS +pNSI) m/z Calcd for C₁₄H₂₆N₂O₄⁺ [M+NH₄⁺]: 313.1873, Found: 313.1870.
(±)-Diethyl [1-(2-bromoethoxy)-2-oxo-2-(pyrrolidin-1-yl)ethyl]phosphonate (2g)

A mixture of diazo phosphonate 1g (612 mg, 2.2 mmol), 2-bromoethanol (250 mg, 2.0 mmol) and dirhodium(II) tetraacetate (4.5 mg, 0.010 mmol) in benzene (20 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (6 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (4% MeOH in CH₂Cl₂) afforded bromide 2g as a green oil (623 mg, 84%); Rf = 0.16 (4% MeOH in CH₂Cl₂); IR (film) / cm⁻¹ 2979, 2878, 1642 (C=O), 1433, 1392, 1340, 1250 (P=O), 1163, 1112, 1018, 968, 867, 749, 664, 546; ¹H NMR (400 MHz, CDCl₃) δ 4.54 (d, J_{P-H} = 16.8 Hz, 1 H, CH(CON)(PO(OEt)₂)), 4.27–4.16 (m, 2 H, 2 x OCH₂CH₃), 4.03–3.95 (m, 1 H, OCH₂), 3.80–3.70 (m, 2 H, OCHH and NCHP), 3.69–3.61 (m, 1 H, NCHP), 3.58–3.43 (m, 4 H, CH₂Br and NCH₂), 2.00–1.89 (m, 2 H, NCH₂CH₂), 1.89–1.78 (m, 2 H, NCH₂CH₂) 1.41–1.26 (m, 6 H, 2 x OCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 163.8 (C=O), 77.7 (d, J_{C-P} = 155.3 Hz, CH(CON)(PO(OEt)₂)), 71.7 (d, J_{C-P} = 13.1 Hz, OCH₂CH₂Br), 63.8 (d, J_{C-P} = 5.6 Hz, OCH₂CH₃), 63.6 (d, J_{C-P} = 6.6 Hz, OCH₂CH₃); 46.7 (NCH₂), 46.6 (NCH₂), 29.7 (CH₂Br), 26.2 (NCH₂CH₂), 23.7 (NCH₂CH₂), 16.4 (d, J_{C-P} = 6.1 Hz, 2 x OCH₂CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 14.8; HRMS (ESI-TOF) m/z Calcd for C₁₂H₂₄BrNO₅P⁺ [M+H]⁺: 372.0575, Found: 372.0579.

(±)-Diethyl [2-(pyrrolidine-1-carbonyl)oxetan-2-yl]phosphonate (3g)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol) which had been cooled to 0 °C. Bromide 2g (186 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (5 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc to 5% MeOH in EtOAc) afforded oxetane 3g as a yellow oil (105 mg, 72%); Rf = 0.10 (EtOAc); IR (film) / cm⁻¹ 2976, 2895, 1629 (C=O), 1429, 1392, 1343, 1250 (P=O), 1163, 1098, 1020, 968, 944, 854, 791, 720, 756, 681, 573, 547; ¹H NMR (400 MHz, CDCl₃) δ 4.74–4.46 (m, 1 H OCH₂), 4.55–4.46 (m, 1 H, OCH₂), 4.34–4.23 (m, 2 H, OCH₂CH₃), 4.23–4.12 (m, 2 H, OCH₂CH₃), 3.82–3.71 (m, 1 H, NCHH), 3.69–3.59 (m, 1 H, NCHH), 3.58–3.48 (m, 2 H, NCH₂), 3.29–3.04 (m, 2 H, CH₂), 1.94–1.72 (m, 4 H, 2 x NCH₂CH₂), 1.38 (t, J = 7.1 Hz, 3 H, OCH₂CH₃), 1.32 (t, J = 7.1 Hz, 3 H, OCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.7 (d, J_{C-P} = 12.1 Hz, C=O), 85.3 (d, J_{C-P} = 153.1 Hz, C₉(CON)(PO(OEt)₂)), 68.4 (d, J_{C-P} = 4.1 Hz, OCH₂), 63.7 (d, J_{C-P} = 5.4 Hz, OCH₂CH₃), 63.5 (d, J_{C-P} = 5.7 Hz, OCH₂CH₃), 47.2 (NCH₂), 46.7 (NCH₂), 29.5 (d, J_{C-P} = 3.4 Hz, CH₂), 26.5 (NCH₂CH₂), 23.3 (NCH₂CH₂), 16.5 (d, J_{C-P} = 5.6 Hz, OCH₂CH₃), 16.4 (d, J_{C-P} = 5.6 Hz, OCH₂CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 17.8; HRMS (ESI-TOF) m/z Calcd for C₁₂H₂₃NO₅P⁺ [M+H]⁺: 292.1314, Found: 292.1313.
Synthesis of Tri- and Tetrasubstituted Oxetanes 5a–5h

A mixture of diazo sulfone 1c (279 mg, 1.1 mmol), (±)-1-[(tert-butyl-2-methylsilyl)oxy]-3-chloropropan-2-yl]oxy)acetate (4a)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Chloride 4a (226 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash
chromatography (20% EtOAc in hexanes) afforded major oxetane 5a as a pale yellow oil (104 mg, 51%) followed by minor oxetane 5a’ as a pale yellow oil (86 mg, 41%) (total yield 92%, d.r. 55:45).

**Major Product 5a:** Rf = 0.33 (20% EtOAc in hexanes); IR (film) / cm⁻¹ 2954, 2930, 2857, 1743 (C=O), 1585, 1472, 1448, 1390, 1369, 1323, 1311, 1284, 1254, 1229, 1138, 1108, 1089, 1068, 1020, 995, 834, 778, 758, 722, 687, 580, 567; ¹H NMR (400 MHz, CDCl₃) δ 7.96–7.90 (m, 2 H, 2 x Ph-H), 7.71–7.65 (m, 1 H, Ph-H), 7.58–7.52 (m, 2 H, 2 x Ph-H), 4.95 (tt, J = 7.2, 2.3 Hz, 1 H, OCH(CH₂OTBS)), 4.14 (q, J = 7.1 Hz, 2 H, CO₂CH₂CH₃), 3.83 (dd, J = 12.6, 2.3 Hz, 1 H, CH(OTBS)), 3.57 (dd, J = 12.6, 2.3 Hz, 1 H, CH(OTBS)), 3.38 (dd, J = 12.6, 7.5 Hz, 1 H, CH(H)), 3.31 (dd, J = 12.6, 6.9 Hz, 1 H, CH(H)), 1.14 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 0.86 (s, 9 H, C(C₃H₃)₂), 0.04 (s, 3 H, OSi(C₃H₃)(C₃H₃)(Bu)), 0.02 (s, 3 H, OSi(C₃H₃)(C₃H₃)(Bu)); ¹³C NMR (101 MHz, CDCl₃) δ 165.6 (CO₂), 134.4 (Ph-CH), 134.3 (Ph-C₆), 130.2 (2 x Ph-CH), 128.8 (2 x Ph-CH), 95.9 (CO₂(CH₂)(SO₂Ph)), 79.9 (OCH(CH₂OTBS)), 63.5 (CH₂OTBS), 62.4 (CO₂CH₂CH₃), 26.5 (CH₃), 25.7 (C(CH₃)₃), 18.2 (C(CH₃)₃), 13.7 (CO₂CH₂CH₃), −5.5 (OSi(CH₃)(C₃H₃)(Bu)), −5.7 (OSi(CH₃)(C₃H₃)(Bu)); HRMS (ESI-TOF) m/z Calcd for C₃₁H₅₃NO₃SSINa⁺ [M+CH₃CN+Na⁺]: 478.1696, Found: 478.1712.

**Minor Product 5a’:** Rf = 0.24 (20% EtOAc in hexanes); IR (film) / cm⁻¹ 2954, 2930, 2857, 1742 (C=O), 1585, 1472, 1448, 1390, 1368, 1324, 1275, 1258, 1154, 1099, 1082, 999, 835, 777, 758, 721, 686, 589, 561; ¹H NMR (400 MHz, CDCl₃) δ 7.96–7.87 (m, 2 H, 2 x Ph-H), 7.74–7.65 (m, 1 H, Ph-H), 7.60–7.51 (m, 2 H, 2 x Ph-H), 4.85–4.74 (m, 1 H, OCH(CH₂OTBS)), 4.19 (q, J = 7.1 Hz, 2 H, CO₂CH₂CH₃), 4.10 (dd, J = 11.2, 6.6 Hz, 1 H, CH(OTBS)), 3.86 (dd, J = 11.2, 5.6 Hz, 1 H, CH(OTBS)), 3.27 (dd, J = 13.0, 6.7 Hz, 1 H, CH(H)), 3.17 (dd, J = 13.0, 7.6 Hz, 1 H, CH(H)), 1.17 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₃), 0.91 (s, 9 H, C(C₃H₃)₃), 0.12 (s, 3 H, OSi(CH₃)(C₃H₃)(Bu)), 0.11 (s, 3 H, OSi(CH₃)(C₃H₃)(Bu)); ¹³C NMR (101 MHz, CDCl₃) δ 166.5 (CO₂), 134.5 (Ph-CH), 134.3 (Ph-C₆), 130.3 (2 x Ph-CH), 128.8 (2 x Ph-CH), 95.8 (CO₂(CH₂)(SO₂Ph)), 79.2 (OCH(CH₂OTBS)), 65.4 (CH₂OTBS), 62.8 (CO₂CH₂CH₃), 28.7 (CH₂), 25.9 (C(CH₃)₃), 18.3 (C(CH₃)₃), 13.8 (CO₂CH₂CH₃), −5.27 (OSi(CH₃)(C₃H₃)(Bu)), −5.33 (OSi(CH₃)(C₃H₃)(Bu)); HRMS (ESI-TOF) m/z Calcd for C₃₁H₅₃NO₃SSINa⁺ [M+CH₃CN+Na⁺]: 478.1696, Found: 478.1707.

The relative stereochemistries for the major and minor isomers of oxetane 5a were determined based on NOE studies (see page S119).

(±)-Ethyl 2-(2-bromo-1-phenylethoxy)-2-(diethoxyphosphoryl)acetate (4b)

A mixture of diazo phosphate 1d (500 mg, 2.0 mmol), (±)-2-bromo-1-phenylethanol-1-ol 4d (268 mg, 1.3 mmol) and dirhodium(II) tetraacetate (3.0 g, 0.007 mol) in benzene (13 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide 4b as a mixture of diastereoisomers as a light yellow oil (361 mg, 64%, d.r. 1:2.1:0); Rf = 0.39 (60% EtOAc in hexanes); IR (film) / cm⁻¹ 2982, 1748 (C=O), 1455, 1369, 1257 (P=O), 1162, 1104, 1018, 975, 755, 702; **Major Product:** ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.31 (m, 5 H, 5 x Ph-H), 4.90 (dd, J = 7.5, 5.0 Hz, 1 H, OCH(Ph)), 4.39–4.14 (m, 6 H, CO₂CH₂CH₃ and 2 x OCH₂CH₃), 4.12–4.02 (m, 1 H, CH(CO₂Et)(PO(OEt)₂)), 3.76–3.69 (m, 1 H, CHBr), 3.59–3.47 (m, 1 H, CHBr), 1.42–1.26 (m, 6 H, 2 x OCH₂CH₃), 1.16 (t, J = 7.0 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.9 (CO₂), 137.4 (Ph-C₆), 129.1 (Ph-C₆), 127.4 (2 x Ph-CH), 83.8 (d, J_C-P = 6.1 Hz, OCH(Ph)), 75.0 (d, J_C-P = 156.3 Hz, CH(CO₂Et)(PO(OEt)₂)), 63.9 (d, J_C-P = 6.6 Hz, OCH₂CH₃), 63.5 (d, J_C-P = 6.6 Hz, OCH₂CH₃), 61.6 (CO₂CH₂CH₃), 34.8 (CH₂Br), 16.3 (d, J_C-P = 6.6 Hz, 2 x OCH₂CH₃), 13.9 (CO₂CH₂CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 14.3; **Minor Product:** ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.31 (m, 5 H, 5 x Ph-H), 4.72–4.65 (m, 1 H, OCH(Ph)), 4.39–4.14 (m, 6 H, CO₂CH₂CH₃ and 2 x OCH₂CH₃), 4.12–4.02 (m, 1 H, CH(CO₂Et)(PO(OEt)₂)), 3.76–3.69 (m, 1 H, CHBr), 3.59–3.47 (m, 1 H, CHBr), 1.42–1.26 (m, 9 H, CO₂CH₂CH₃ and 2 x OCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.7 (CO₂), 136.6 (Ph-C₆), 129.2 (Ph-CH),
The relative stereochemistries for the major and minor isomers of oxetane 63.7 (d, J = 7.5 Hz, OCH(Ph)), 63.8 (d, J = 12.1 Hz, CO), 1446, 1392, 1368, 1255, 1163, 1100, 1013, 970, 941, 865, 793, 757, 699, 597, 562; Major Product: 1H NMR (400 MHz, CDCl3) δ 7.63–7.56 (m, 1 H, Ph-H), 7.46–7.28 (m, 4 H, 4 x Ph-H), 5.85 (t, J = 7.5 Hz, 1 H, OCH(Ph)), 4.47–4.09 (m, 6 H, CO2CH2CH3 and 2 x OCH2CH3), 3.59–3.38 (m, 1 H, CHH), 3.06–2.91 (m, 1 H, CHH), 1.43–1.27 (m, 9 H, CO2CH2CH3 and 2 x OCH2CH3); 13C NMR (101 MHz, CDCl3) δ 169.7 (d, JCP = 12.1 Hz, CO2), 140.4 (Ph-Cq), 128.6 (2 x Ph-CH), 128.4 (Ph-CH), 125.8 (2 x Ph-CH), 79.8 (d, JCP = 3.3 Hz, OCH(Ph)), 79.4 (d, JCP = 159.7 Hz, Cq(CO2Et)(PO(OEt)2), 64.4 (d, JCP = 6.6 Hz, OCH2CH3), 63.8 (d, JCP = 6.6 Hz, OCH2CH3), 62.3 (CO2CH2CH3), 36.9 (d, JCP = 2.4 Hz, CH2), 16.53 (d, JCP = 5.2 Hz, OCH2CH3), 16.47 (d, JCP = 5.2 Hz, OCH2CH3), 14.1 (CO2CH2CH3); 31P (162 MHz, CDCl3) δ 16.3; Minor Product: 1H NMR (400 MHz, CDCl3) δ 7.63–7.56 (m, 1 H, Ph-H), 7.46–7.28 (m, 4 H, 4 x Ph-H), 5.88 (t, J = 7.5 Hz, 1 H, OCH(Ph)), 4.47–4.09 (m, 6 H, CO2CH2CH3 and 2 x OCH2CH3), 3.59–3.38 (m, 1 H, CHH), 3.29–3.17 (m, 1 H, CHH), 1.43–1.27 (m, 9 H, CO2CH2CH3 and 2 x OCH2CH3); 13C NMR (101 MHz, CDCl3) δ 170.6 (d, JCP = 12.1 Hz, CO2), 141.1 (Ph-Cq), 128.6 (2 x Ph-CH), 128.5 (Ph-CH), 126.4 (2 x Ph-CH), 81.3 (d, JCP = 8.9 Hz, OCH(Ph)), 80.2 (d, JCP = 161.5 Hz, Cq(CO2Et)(PO(OEt)2), 64.0 (d, JCP = 6.6 Hz, OCH2CH3), 63.7 (d, JCP = 6.6 Hz, OCH2CH3), 62.0 (CO2CH2CH3), 36.7 (d, JCP = 4.4 Hz, CH2), 16.36 (d, JCP = 6.0 Hz, OCH2CH3), 16.34 (d, JCP = 6.0 Hz, OCH2CH3), 14.1 (CO2CH2CH3); 31P (162 MHz, CDCl3) δ 14.5; HRMS (ESI-TOF) m/z calcd for C18H26NO5PNa+ [M+Na]+: 406.1395, Found: 406.1395.

The relative stereochemistries for the major and minor isomers of oxetane 5b were assigned by analogy to that observed for oxetane 5a.

(±)-Benzyl 2-[2-bromo-1-(2-fluorophenyl)ethoxy]-2-cyanoacetate (4c)

A mixture of diazo nitrile 1e (193 mg, 0.96 mmol), (±)-2-bromo-1-(2-fluorophenyl)ethan-1-ol4 (191.4 mg, 0.87 mmol) and dirhodium(II) tetraacetate (1.9 mg, 0.0043 mmol) in CH2Cl2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (70% CH2Cl2 in hexanes) afforded bromide 4c as a mixture of diastereoisomers as a yellow oil (277 mg, 81%, d.r. 1:4:1:0; Rf = 0.30 (70% CH2Cl2 in hexanes); IR (film) / cm−1 3037, 2968, 2244 (C≡N), 1753 (C=O), 1616, 1587, 1489, 1487, 1465, 1374, 1267, 1234, 1162, 986, 948, 917, 801.
DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide 4c (197 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NaOH (20 mL) was added. The aqueous mixture was extracted with EtOAc (20 mL). The organic extracts were combined, dried (Na2SO4) and concentrated in vacuo. Purification by flash chromatography (20% ElOAc in hexanes) afforded oxetane 5c as a mixture of diastereoisomers as a pale yellow oil (126 mg, 80%, d.r. 70:30; Rf = 0.45 (20% ElOAc in hexanes); IR (film) / cm⁻¹ 3037, 2964, 2220 (C=O), 1746 (C=O), 1619, 1588, 1492, 1456, 1377, 1269, 1235, 1170, 1114, 1062, 1030, 967, 929, 817, 751, 696, 599; Major Product: ¹H NMR (400 MHz, CDCl₃) δ 7.76–7.67 (m, 1 H, Ar-H), 7.48–7.35 (m, 6 H, Ar-H and 5 x Ph-H), 7.32–7.25 (m, 1 H, Ar-H), 7.12–6.99 (m, 1 H, Ar-H), 6.15 (t, J = 7.5 Hz, 1 H, OCH(Ar)), 5.42 (d, J = 12.1 Hz, 1 H, CO₂CH₂PhH), 5.39 (d, J = 12.1 Hz, 1 H, CO₂CH₂PhH), 3.52 (dd, J = 12.1, 7.9 Hz, 1 H, CH₂H), 3.29 (dd, J = 12.1, 7.2 Hz, 1 H, CH₂H); ¹³C NMR (101 MHz, CDCl₃) δ 165.8 (CO₂), 159.3 (d, J₇CF = 248 Hz, Ar-C₇F), 134.1 (Ph-C₇H), 130.7 (d, J₇CF = 8 Hz, Ar-CH), 129.0 (Ph-CH), 128.81 (2 x Ph-CH), 128.40 (2 x Ph-CH), 127.2 (d, J₇CF = 3 Hz, Ar-CH), 127.0 (d, J₇CF = 13 Hz, Ar-C₇F(CH₃)), 124.8 (d, J₇CF = 3 Hz, Ar-CH), 116.1 (C=CH), 115.5 (d, J₇CF = 21 Hz, Ar-CH), 75.8 (d, J₇CF = 4 Hz, OCH(Ar)), 72.60 (CO₂(Bn)CN), 69.1 (CO₂CH₂Ph), 39.0 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ −118.5; Minor Product: ¹H NMR (400 MHz, CDCl₃) δ 7.76–7.67 (m, 1 H, Ar-H), 7.48–7.35 (m, 6 H, Ar-H and 5 x Ph-H), 7.21–7.13 (m, 1 H, Ar-H), 7.12–6.99 (m, 1 H, Ar-H), 6.28 (t, J = 7.7 Hz, 1 H, OCH(Ar)), 5.36 (d, J = 12.1 Hz, 1 H, CO₂CH₂PhH), 5.32 (d, J = 12.1 Hz, 1 H, CO₂CH₂PhH), 3.57 (dd, J = 12.1, 7.6 Hz, 1 H, CH₂H), 3.24 (dd, J = 12.1, 7.8 Hz, 1 H, CH₂H); ¹³C NMR (101 MHz, CDCl₃) δ 165.1 (CO₂), 159.1 (d, J₇CF = 248 Hz, Ar-C₇F), 134.0 (Ph-C₇H), 130.6 (d, J₇CF = 8 Hz, Ar-CH), 128.59 (Ph-CH), 128.75 (2 x Ph-CH), 128.44 (2 x Ph-CH), 127.7 (d, J₇CF = 3 Hz, Ar-CH), 126.8 (d, J₇CF = 13 Hz, Ar-C₇F(CH₃)), 124.6 (d, J₇CF = 3 Hz, Ar-CH), 116.6 (C=CH), 115.2 (d, J₇CF = 21 Hz, Ar-CH), 74.5 (d, J₇CF = 4 Hz, OCH(Ar)), 72.58 (CO₂(Bn)CN), 69.0 (CO₂CH₂Ph), 39.2 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ −118.8; HRMS (ESI-TOF) m/z Calcd for C₁₈H₁₉BrF₂N₂O₃⁺ [M+Na⁺]: 409.0558, Found: 409.0556.

The relative stereochemistries for the major and minor isomers of oxetane 5c were assigned by analogy to that observed for oxetane 5d.
A mixture of diazo amide \(1h\) (199 mg, 1.2 mmol), (±)-2-bromo-1-(4-chlorophenyl)ethan-1-ol\(^4\) (236 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CHCl\(_3\) (3 x 10 mL). The organic extracts were combined, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by flash chromatography (35% to 40% Et\(_2\)O in hexanes) afforded bromide 4d as a mixture of diastereoisomers as a colorless oil (235 mg, 63%, d.r. 1.0:1.0); \(R_e\) = 0.61 and 0.50 (75% Et\(_2\)O in hexanes); IR (film) / cm\(^{-1}\) 2975, 2938, 2216 (C=\(\equiv\)N), 1653 (C=O), 1598, 1491, 1463, 1383, 1363, 1312, 1252, 1215, 1145, 1088, 1015, 834, 729, 628, 552; **Diastereoisomer 1**: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45–7.37 (m, 2 H, 2 x Ar-H), 7.34–7.28 (m, 2 H, 2 x Ar-H), 4.92–4.86 (m, 2 H, OCH(\(Ar\)) and CH\((\text{CN})(\text{CONEt}_2)\)), 3.67–3.60 (m, 1 H, CH\(\equiv\)Br), 3.59–3.36 (m, 5 H, CH\(\equiv\)Br and 2 x NCH\(_2\)CH\(_3\)), 1.24 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)), 1.15 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 160.8 (C=O), 135.9 (Ar-C\(_{\equiv}\)CH\((\text{O})\)), 135.0 (Ar-C\(_{\equiv}\)Cl), 129.5 (2 x Ar-CH), 128.5 (2 x Ar-CH), 114.3 (C=\(\equiv\)N), 81.6 (OCH(\(\text{Ar}\))), 68.0 (CH\((\text{CN})(\text{CONEt}_2)\)), 42.2 (NCH\(_2\)CH\(_3\)), 40.9 (NCH\(_2\)CH\(_3\)), 33.7 (CH\(_2\)Br), 14.0 (NCH\(_2\)CH\(_3\)), 12.31 (NCH\(_2\)CH\(_3\)); **Diastereoisomer 2**: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45–7.37 (m, 2 H, 2 x Ar-H), 7.34–7.28 (m, 2 H, 2 x Ar-H), 4.78 (dd, \(J = 8.0, 4.6\) Hz, 1 H, OCH(\(\text{Ar}\))), 4.71 (s, 1 H, CH\((\text{CN})(\text{CONEt}_2)\)), 3.67–3.60 (m, 1 H, CH\(\equiv\)Br), 3.59–3.36 (m, 4 H, 2 x NCH\(_2\)CH\(_3\)), 3.27 (dd, \(J = 13.7, 7.0\) Hz, 1 H, CH\(\equiv\)Br), 1.24 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)), 1.10 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 160.5 (C=O), 135.6 (Ar-C\(_{\equiv}\)CH\((\text{O})\)), 134.1 (Ar-C\(_{\equiv}\)Cl), 129.3 (2 x Ar-CH), 128.4 (2 x Ar-CH), 113.9 (C=\(\equiv\)N), 81.2 (OCH(\(\text{Ar}\))), 68.1 (CH\((\text{CN})(\text{CONEt}_2)\)), 41.9 (NCH\(_2\)CH\(_3\)), 40.8 (NCH\(_2\)CH\(_3\)), 34.2 (CH\(_2\)Br), 13.7 (NCH\(_2\)CH\(_3\)), 12.30 (NCH\(_2\)CH\(_3\)); HRMS (ESI-TOF) m/z Calcd for C\(_{15}\)H\(_{19}\)BrClN\(_2\)O\(_2\)\(^+\)[M+H\(^+\)]: 373.0318, Found: 373.0331.

**DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol) which had been cooled to 0 °C. Bromide 4d (193 mg, 0.52 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH\(_4\)Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by flash chromatography (40% Et\(_2\)O in hexanes) afforded minor oxetane 5d as a white solid (33 mg, 22%) followed by major oxetane 5d’ as a white solid (96 mg, 64%) (total yield 86%, d.r. 74:26).

**Minor Product 5d**: \(R_e\) = 0.50 (50% Et\(_2\)O in hexanes); mp = 86–89 °C; IR (film) / cm\(^{-1}\) 2978, 2939, 2223 (C=\(\equiv\)N), 1655 (C=O), 1599, 1494, 1448, 1383, 1369, 1283, 1218, 1190, 1155, 1091, 1016, 949, 868, 825, 734, 659; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39–7.34 (m, 2 H, 2 x Ar-H), 7.31–7.25 (m, 2 H, 2 x Ar-H), 5.81 (t, \(J = 7.8\) Hz, 1 H, OCH(\(\text{Ar}\))), 3.61 (dd, \(J = 12.4, 8.0\) Hz, 1 H, CH\(\equiv\)H) and 2 x NCH\(_2\)CH\(_3\)), 1.25 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)), 1.22 (t, \(J = 7.1\) Hz, 3 H, NCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.3 (C=O), 138.1 (Ar-C\(_{\equiv}\)CH\((\text{O})\)), 135.1 (Ar-C\(_{\equiv}\)Cl), 129.0 (2 x Ar-CH), 127.7 (2 x Ar-CH), 118.0 (C=\(\equiv\)N), 78.5 (OCH(\(\text{Ar}\))), 72.7 (C\((\text{CN})(\text{CONEt}_2)\)), 42.0 (NCH\(_2\)CH\(_3\)), 40.9 (NCH\(_2\)CH\(_3\)), 38.9 (CH\(_2\)), 13.5
(NCH₂CH₃), 13.2 (NCH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₁₅H₁₈ClN₂O₂⁺ [M+H]⁺: 293.1057, Found: 293.1067.

**Major Product 5d**: Rᵣ = 0.28 (50% Et₂O in hexanes); mp = 89–91 °C; IR (film) / cm⁻¹ 2978, 2938, 2221 (C≡N), 1654 (C=O), 1598, 1493, 1447, 1383, 1364, 1283, 1217, 1188, 1091, 1015, 951, 825, 739, 660; ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.45 (m, 2 H, 2 x Ar-H), 7.45–7.39 (m, 2 H, 2 x Ar-H), 5.67–5.59 (m, 1 H, OCH(Ar)), 4.00 (dd, J = 12.3, 8.1 Hz, 1 H, CH₂H), 3.58–3.37 (m, 4 H, 2 x NCH₂CH₃), 3.09 (dd, J = 12.3, 6.8 Hz, 1 H, CH₂H), 1.28 (t, J = 7.1 Hz, 3 H, NCH₂CH₃), 1.23 (t, J = 7.1 Hz, 3 H, NCH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 163.3 (C=O), 138.5 (Ar-C≡CH(O)), 135.0 (Ar-C≡Cl), 129.1 (2 x Ar-CH), 127.3 (2 x Ar-CH), 117.7 (C≡N), 79.4 (OCH(Ar)), 72.7 (O(CH₂)(CNNEt₂), 42.1 (NCH₂CH₃), 40.9 (NCH₂CH₃), 38.8 (CH₂), 13.4 (NCH₂CH₃), 12.3 (NCH₂CH₃); HRMS (ESI-TOF) m/z Calcd for C₁₅H₁₈ClN₂O₂⁺ [M+H]⁺: 293.1057, Found: 293.1050.

The relative stereochemistries for the major and minor isomers of oxetane 5d were determined based on NOE studies (see page S119).

**(-)2-(Benzenesulfonyl)-2-[2-bromo-1-(3-methoxyphenyl)ethoxy]acetonitrile (4e)**

A mixture of diazo nitrile 1i (110 mg, 0.53 mmol), (-)-2-Bromo-1-(3-methoxyphenyl)ethan-1-ol (112 mg, 0.48 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in CH₂Cl₂ (4.8 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (70% CH₂Cl₂ in hexanes) afforded bromide 4e as a mixture of diastereoisomers as a yellow crystalline solid (158 mg, 80%, d.r. 1.4:1.0); Rᵣ = 0.50 (70% CH₂Cl₂ in hexanes); mp = 100–104 °C; IR (film) / cm⁻¹ 2964, 2838, 2236 (C≡N), 1601, 1586, 1489, 1449, 1436, 1332, 1314, 1287, 1259, 1212, 1145, 1099, 1074, 1041, 995, 909, 872, 791, 754, 725, 704, 684, 609, 587; **Major Product**: ¹H NMR (400 MHz, CDCl₃) δ 8.21–8.16 (m, 1 H, Ph-H), 8.00–7.91 (m, 1 H, Ph-H), 7.86–7.75 (m, 1 H, Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.65–7.58 (m, 1 H, Ph-H), 7.41–7.29 (m, 1 H, Ar-H), 7.02–6.95 (m, 1 H, Ar-H), 6.94–6.89 (m, 1 H, Ar-H), 6.88–6.81 (m, 1 H, Ar-H), 5.36 (dd, J = 8.7, 3.8 Hz, 1 H, OCH(Ar)), 4.91 (s, 1 H, CH(SO₂Ph)(CN)), 3.83 (s, 3 H, OCH₃), 3.65–3.57 (m, 1 H, CH₂HBr), 3.55–3.48 (m, 1 H, CH₂HBr); ¹³C NMR (101 MHz, CDCl₃) δ 160.5 (Ar-C≡Ome), 136.5 (Ar-C≡CH(O)), 135.7 (Ph-CH), 133.3 (Ph-C₆), 130.9 (2 x Ph-CH), 130.8 (Ar-CH), 129.4 (2 x Ph-CH), 119.5 (Ar-CH), 116.2 (Ar-CH), 112.5 (Ar-CH), 112.0 (C≡N), 85.6 (OCH(Ar)), 80.8 (CH(SO₂Ph)(CN)), 55.3 (OCH₃), 33.6 (CH₂Br); **Minor Product**: ¹H NMR (400 MHz, CDCl₃) δ 8.21–8.16 (m, 1 H, Ph-H), 8.00–7.91 (m, 1 H, Ph-H), 7.86–7.75 (m, 1 H, Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.65–7.58 (m, 1 H, Ph-H), 7.41–7.29 (m, 1 H, Ar-H), 7.02–6.95 (m, 2 H, 2 x Ar-H), 6.88–6.81 (m, 2 H, 2 x Ar-H), 5.05 (s, 1 H, CH(SO₂Ph)(CN)), 4.88 (dd, J = 8.4, 4.2 Hz, 1 H, OCH(Ar)), 3.84 (s, 3 H, OCH₃), 3.65–3.57 (m, 1 H, CH₂HBr), 3.55–3.48 (m, 1 H, CH₂HBr); ¹³C NMR (101 MHz, CDCl₃) δ 160.3 (Ar-C≡Ome), 136.2 (Ar-C≡CH(O)), 135.6 (Ph-CH), 133.1 (Ph-CH), 130.7 (2 x Ph-CH), 130.4 (Ar-CH), 129.3 (2 x Ph-CH), 119.3 (Ar-CH), 115.8 (Ar-CH), 112.3 (Ar-CH), 111.7 (C≡N), 83.9 (OCH(Ar)), 81.3 (CH(SO₂Ph)(CN)), 55.4 (OCH₃), 34.0 (CH₂Br); HRMS (ESI-TOF) m/z Calcd for C₁₉H₁₉Br₂O₄SNa⁺ [M+CH₂CN+Na]⁺: 473.0147, Found: 473.0161.
(±)-2-(Benzenesulfonfonyl)-4-(3-methoxyphenyl)oxetane-2-carbonitrile (5e)

DMF (9 mL) was added to a flask containing sodium hydride (60% in mineral oil, 15 mg, 0.37 mmol) which had been cooled to 0 °C. Bromide 4e (127 mg, 0.31 mmol) in DMF (3.4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH₄Cl (10 mL) was added. The aqueous mixture was extracted with EtOAc (4 × 15 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane 5e as a mixture of diastereoisomers a yellow oil (44 mg, 43%, d.r. 70:30); Rₛ = 0.44 (30% EtOAc in hexanes); IR (film) / cm⁻¹ 2941, 2839, 2234 (C≡N), 1602, 1585, 1491, 1448, 1331, 1292, 1263, 1155, 1037, 967, 918, 850, 784, 753, 725, 684, 604, 568;

**Major Product:** ¹H NMR (500 MHz, CDCl₃) δ 8.13–8.09 (m, 2 H, 2 x Ph-H), 7.83–7.76 (m, 1 H, Ph-H), 7.70–7.61 (m, 2 H, 2 x Ph-H), 7.39–7.33 (m, 1 H, Ar-H), 7.04–7.00 (m, 1 H, Ar-H), 7.00–6.96 (m, 1 H, Ar-H), 6.96–6.91 (m, 1 H, Ar-H), 6.00 (t, J = 7.3 Hz, 1 H, OCH(Ar)), 3.94 (dd, J = 13.0, 7.6 Hz, 1 H, CH(Br)), 4.09 (ddd, J = 8.1, 5.6 Hz, 1 H, CH(Br)), 4.17 (d, J = 12.3, 7.9 Hz, 1 H, OCH(Ar)); ¹³C NMR (126 MHz, CDCl₃) δ 160.1 (Ar-C≡N), 140.1 (Ar-C≡N), 135.7 (Ph-CH), 132.1 (Ph-C₆), 130.0 (2 x Ph-CH), 129.4 (Ar-C≡N), 115.4 (Ar-CH), 114.2 (C≡N), 111.2 (Ar-CH), 86.8 (C≡N(SO₂Ph)(CN)), 82.6 (OCH(Ar)), 55.3 (OCH₃), 36.4 (CH₃); **Minor Product:** ¹H NMR (500 MHz, CDCl₃) δ 8.09–8.05 (m, 2 H, 2 x Ph-H), 7.83–7.76 (m, 1 H, Ph-H), 7.70–7.61 (m, 2 H, 2 x Ph-H), 7.39–7.33 (m, 1 H, Ar-H), 7.17–7.13 (m, 1 H, Ar-H), 7.00–6.96 (m, 1 H, Ar-H), 6.96–6.91 (m, 1 H, Ar-H), 6.00 (t, J = 7.3 Hz, 1 H, OCH(Ar)), 3.94 (dd, J = 12.3, 7.9 Hz, 1 H, OCH(Ar)); ¹³C NMR (126 MHz, CDCl₃) δ 160.0 (Ar-C≡N), 139.3 (Ar-C≡N), 135.7 (Ph-CH), 132.0 (Ph-C₆), 130.8 (2 x Ph-CH), 129.8 (Ar-CH), 129.49 (2 x Ph-CH), 119.4 (Ar-CH), 116.1 (Ar-CH), 115.0 (C≡N), 112.2 (Ar-CH), 86.1 (C≡N(SO₂Ph)(CN)), 81.0 (OCH(Ar)), 55.4 (OCH₃), 36.0 (CH₃); HRMS (EI⁺) m/z Calcd for C₁₇H₁₁NO₂S [M+H₂O]: 347.0822, Found: 347.0821.

The relative stereochemistries for the major and minor isomers of oxetane 5e were assigned by analogy to that observed for oxetane 5d.

(±)-2-Bromo-2-phenylethan-1-ol (S9)³²

Ammonium cerium(IV) nitrate (1.64 g, 3.0 mmol) was added portionwise to a stirring mixture of styrene oxide (1.14 mL, 10.0 mmol) and tetrabutylammonium bromide (9.67 g, 30.0 mmol) in CH₂CN (30 mL) at 25 °C. The reaction was stirred at 25 °C for 3 h. The reaction mixture was concentrated in vacuo and water (30 mL) was added to the residue. The aqueous mixture was extracted with Et₂O (3 × 60 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (20% to 30% EtOAc in pentane) afforded β-bromohydryn S9 as a yellow crystalline solid oil (263 mg, 13%); Rₛ = 0.13 (20% EtOAc in pentane); mp = 35–37 °C; IR (film) / cm⁻¹ 3354 (br O-H), 3030, 2921, 1493, 1381, 1235, 1158, 1067, 1024, 840, 760, 696, 591; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.33 (m, 3 H, 3 x Ph-H), 7.41–7.33 (m, 3 H, 3 x Ph-H), 5.08 (dd, J = 7.9, 5.6 Hz, 1 H, CH(Br)), 4.09 (ddd, J = 12.3, 7.9, 5.8 Hz, 1 H, CH(Br(H))), 3.98 (ddd, J = 12.3, 8.1, 5.6 Hz, 1 H, CH(Br(H))), 2.08 (dd, J = 8.1, 5.8 Hz, 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 138.2 (Ph-C₆), 129.0 (Ph-CH), 128.9 (2 x Ph-CH), 127.9 (2 x Ph-CH), 127.9 (2 x Ph-CH), 67.5 (CH₃(OH)), 57.0 (CH(Br)).

Observed data (mp, IR, ¹H, ¹³C) was consistent with that previously reported.³³,³⁴
(±)-Benzy1 2-(2-bromo-2-phenylethoxy)-2-cyanoacetate (4f)

A mixture of diazo nitrile 1e (221 mg, 1.1 mmol), β-bromohydrazin S9 (198 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in CH₂Cl₂ (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (15% EtOAc in hexanes) afforded bromide 4f as a yellow oil (283 mg, 77%, d.r. 1.0:1.0); Rf = 0.18 (15% EtOAc in hexanes); IR (film) / cm⁻¹ 3067, 3033, 2254 (C≡N), 1761 (C=O ester), 1496, 1455, 1379, 1280, 1203, 1128, 1003, 968, 907, 838, 728, 695, 648, 596; Diastereoisomer 1: ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.32 (m, 10 H, 10 x Ph-H), 5.35–5.25 (m, 2 H, CO₂CH₂Ph), 5.16–5.09 (m, 1 H, CH(Br)), 4.99 (s, 1 H, CH(CO₂Bn)(CN)), 4.31–4.17 (m, 2 H, OCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 162.67 (CO₂), 137.72 (Ph-Ca), 133.9 (Ph-Ca), 129.0 (Ph-CH), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.7 (2 x Ph-CH), 128.6 (2 x Ph-CH), 127.8 (2 x Ph-CH), 113.0 (C≡N), 73.9 (OCH₂), 68.9 (CO₂CH₂Ph), 67.2 (CH(CO₂Bn)(CN)), 49.9 (CH(Br)); Diastereoisomer 2: ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.32 (m, 10 H, 10 x Ph-H), 5.35–5.25 (m, 2 H, CO₂CH₂Ph), 5.16–5.09 (m, 1 H, CH(Br)), 4.91 (s, 1 H, CH(CO₂Bn)(CN)), 4.31–4.17 (m, 2 H, OCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 162.66 (CO₂), 137.65 (Ph-Ca), 133.9 (Ph-Ca), 129.0 (Ph-CH), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.7 (2 x Ph-CH), 128.45 (2 x Ph-CH), 127.7 (2 x Ph-CH), 113.0 (C≡N), 73.9 (OCH₂), 68.9 (CO₂CH₂Ph), 67.2 (CH(CO₂Bn)(CN)), 49.6 (CH(Br)); HRMS (CI) m/z Calcd for C₁₈H₂₀Br₂N₂O₃⁺ [M+NH₄]⁺: 391.0657, Found: 391.0660.

(±)-Benzy1 2-cyano-3-phenylxetane-2-carboxylate (5f)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.61 mmol) which had been cooled to 0 °C. Bromide 4f (188 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded minor oxetane 5f as a colorless oil (49 mg, 33%) followed by major oxetane 5f* as a colorless oil (62 mg, 42%) (total yield 75%, d.r. 56:44).

Minor Product 5f: Rf = 0.34 (20% EtOAc in hexanes); IR (film) / cm⁻¹ 3066, 3036, 2972, 2907, 2242 (C≡N), 1761 (C=O ester), 1587, 1498, 1456, 1379, 1270, 1212, 1097, 1069, 1027, 945, 906, 851, 789, 733, 695, 599; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.22 (m, 8 H, 8 x Ph-H), 7.10–6.95 (m, 2 H, 2 x Ph-H), 5.17–5.10 (m, 2 H, OCH₂), 4.93–4.85 (m, 2 H, CH(Ph) and CO₂CH(Ph)H), 4.71 (d, J = 12.0 Hz, 1 H, CO₂CH(Ph)H); ¹³C NMR (101 MHz, CDCl₃) δ 163.7 (CO₂), 133.6 (Ph-C), 132.6 (Ph-C), 129.1 (Ph-CH), 128.9 (2 x Ph-CH), 128.6 (Ph-CH), 128.5 (2 x Ph-CH), 128.4 (2 x Ph-CH), 128.0 (2 x Ph-CH), 116.5 (C≡N), 80.5 (CO₂Bn(CN)), 73.8 (OCH₂), 68.5 (CO₂CH₂Ph), 50.2 (CH(Ph)); HRMS (CI) m/z Calcd for C₁₈H₁₉N₂O₃⁺ [M+NH₄]⁺: 311.1396, Found: 311.1403.

Major Product 5f*: Rf = 0.27 (20% EtOAc in hexanes); IR (film) / cm⁻¹ 3067, 3035, 2979, 2908, 2240 (C≡N), 1764 (C=O), 1499, 1456, 1378, 1265, 1225, 1108, 1086, 1064, 1033, 1003, 954, 904, 750, 696, 601; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.28 (m, 10 H, 10 x Ph-H), 5.44 (d, J = 12.1 Hz, 1 H, CO₂CH(Ph)H), 5.34 (d, J = 12.1 Hz, 1 H, CO₂CH(Ph)H), 5.11 (dd, J = 7.6, 6.2 Hz, 1 H, OCHH), 5.02 (dd, J = 8.5, 6.2 Hz, 1 H, OCHH), 4.53 (t, J = 8.0 Hz, 1 H, CH(Ph)); ¹³C NMR (101 MHz, CDCl₃) δ 165.5 (CO₂), 134.2 (Ph-C), 133.6 (Ph-C), 129.11 (Ph-CH), 129.06 (2 x Ph-CH), 129.0 (Ph-CH), 128.8 (2 x Ph-CH), 128.4 (2 x Ph-CH), 128.0
Purification by flash chromatography (10% EtOAc in hexanes) afforded chloride 4g as a pale yellow oil (114 mg, 40%); Rf = 0.13 (10% EtOAc in hexanes); IR (film) / cm⁻¹: 2982, 2258 (C=O), 1499, 1457, 1389, 1374, 1270, 1213, 1106, 1003, 900, 794, 736, 697, 635; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.35 (m, 5 H, 5 x Ph-H), 5.30 (s, 2 H, CO₂CH₂Ph), 5.01 (s, 1 H, CH(C₂Bn)(CN)), 3.57 (d, J = 11.7 Hz, 1 H, CH), 3.54 (d, J = 11.7 Hz, 1 H, CH₂Cl), 1.43 (s, 3 H, CH₃), 1.41 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 163.7 (CO₂), 134.2 (Ph-C₃H), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.4 (2 x Ph-CH), 115.2 (C=N), 79.7 (OC₆H₅(CH₂)₂), 68.9 (CO₂CH₂Ph), 61.7 (CH(C₂Bn)(CN)), 51.5 (CH₂Cl), 23.8 (CH₃), 23.2 (CH₃); HRMS (CI) m/z Calcd for C₁₄H₂₀ClN₂O₃⁺ [M+NH₄]⁺: 299.1152, Found: 299.1162.

(±)-Benzyl 2-cyano-4,4-dimethyloxetane-2-carboxylate (5g)

DMF (9 mL) was added to a flask containing sodium hydride (60% in mineral oil, 13 mg, 0.33 mmol) which had been cooled to 0°C. Bromide 4g (78 mg, 0.28 mmol) in DMF (3 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0°C over 6 min. The reaction mixture was stirred at 25°C for 16 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane 5g as a yellow oil (37 mg, 54%); Rf = 0.31 (20% EtOAc in hexanes); IR (film) / cm⁻¹: 2974, 2932, 2249 (C=O), 1743 (C=O), 1499, 1456, 1375, 1281, 1166, 1150, 1079, 1048, 1012, 970, 909, 839, 779, 741, 696, 601; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.35 (m, 5 H, 5 x Ph-H), 5.32 (s, 2 H, CO₂CH₂Ph), 2.97 (s, 2 H, CH₂), 1.67 (s, 3 H, CH₃), 1.51 (s, 3 H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 166.2 (CO₂), 134.3 (Ph-C₆H₅), 128.83 (2 x Ph-CH), 128.75 (2 x Ph-CH), 117.4 (C=N), 84.8 (C₆H₅(C₂Bn)(CN)), 69.4 (OC₆H₅(CH₂)₂), 68.8 (CO₂CH₂Ph), 43.1 (CH₂), 29.3 (CH₃), 29.1 (CH₃); HRMS (Cl) m/z Calcd for C₁₄H₁₉N₂O₃⁺ [M+Na⁺]⁺: 263.1384, Found: 263.1390.

(±)-trans-tert-Butyl 3-bromo-4-hydroxypyrrolidine-1-carboxylate (S10)³⁵

N-Bromosuccinimide (1.06 g, 6.0 mmol) was added portionwise to a stirring mixture of N-Boc-2,5-dihydro-1H-pyrrole (845 mg, 5.0 mmol) in DMSO (5 mL) and H₂O (0.75 mL) at 0°C. The reaction was stirred at 25°C for 17 h. Water (20 mL) was added. The aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (60 mL), dried (Na₂SO₄) and
concentrated in vacuo. Purification by flash chromatography (1% NEt₃, 30% EtOAc in hexanes to 1% NEt₃, 40% EtOAc in hexanes) afforded β-bromohydrin S10 as a white crystalline solid (979 mg, 74%); Rₜ = 0.27 (40% EtOAc in hexanes); mp = 55–59 °C; IR (film) / cm⁻¹ 3376 (br O-H), 2977, 2935, 1661 (C=O), 1478, 1416, 1367, 1281, 1255, 1158, 1116, 1083, 1001, 959, 930, 866, 769, 741, 642, 551; ¹H NMR (400 MHz, CDCl₃) δ 4.43 (br s, 1 H, CH(OH)), 4.19–4.14 (m, 1 H, CHBr), 4.14–4.05 (m, 1 H, OH), 4.01 (dd, J = 12.9, 4.9 Hz, 1 H, NCH=H), 3.85–3.66 (m, 2 H, NCHH and NC'H'H), 3.38 (dd, J = 11.9, 2.8 Hz, 1 H, NC'H'H), 1.45 (s, 9 H, 3 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 154.8 and 154.7 (C=O), 80.3 and 80.2 (C₆H₅CH), 76.7 and 75.9 (CH(OH)), 53.0 and 52.4 (NCH₂), 51.4 and 51.1 (NC'H₂), 50.6 and 50.1 (CHBr), 28.4 (3 x CH₃).

Observed data (IR, ¹H) was consistent with that previously reported.³⁶

(±)-trans-tert-Butyl 3-[2-(benzyl oxy)-1-cyano-2-oxoethoxy]-4-bromopyrrolidine-1-carboxylate (4h)

A mixture of diazo nitrile 1e (223 mg, 1.1 mmol), β-bromohydrin S10 (266 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in CH₂Cl₂ (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (15% to 20% EtOAc in hexanes) afforded bromide 4h as a viscous pale yellow oil (286 mg, 65%, d.r. 1:1:1.0); Rₜ = 0.70 (50% EtOAc in hexanes); IR (film) / cm⁻¹ 2977, 2886, 2245 (C≡N), 1764 (C=O ester), 1683 (C=O carbamate), 1456, 1404, 1367, 1213, 1160, 1107, 1002, 960, 869, 769, 749, 697, 652, 549; Diastereoisomer 1: ¹H NMR (400 MHz, DMSO-d₆, 353 K) δ 7.44–7.30 (m, 5 H, 5 x Ph-H), 5.88 (s, 1 H, CH(CO₂Bn)(CN)), 5.33 (d, J = 12.8 Hz, 1 H, CO₂H(Ph)), 5.29 (d, J = 12.8 Hz, 1 H, CO₂CH(Ph)), 4.66–4.62 (m, 1 H, CHBr), 4.58–4.53 (m, 1 H, CH(O)), 3.89–3.82 (m, 1 H, NCH₃), 3.82–3.75 (m, 1 H, NCH₃), 3.70–3.61 (m, 1 H, NCH₃), 3.50–3.41 (m, 1 H, NCH₃), 1.428 (s, 9 H, 3 x CH₃); ¹³C NMR (101 MHz, DMSO-d₆, 353 K) δ 163.0 (C=O ester), 153.2 (C=O carbamate), 134.4 (Ph-C₆H₄), 128.1 (3 x Ph-CH₃), 127.7 (2 x Ph-CH₃), 114.3 (C≡N), 84.1 (br, CH(O)), 78.8 (C₆H₅CH₃), 67.8 (CO₂CH₂Ph), 66.3 (CH(CO₂Bn)(CN)), 52.4 (NCH₂), 49.2 (NCH₂), 47.5 (br, CHBr), 27.7 (3 x CH₃); Diastereoisomer 2: ¹H NMR (400 MHz, DMSO-d₆, 353 K) δ 7.44–7.30 (m, 5 H, 5 x Ph-H), 5.87 (s, 1 H, CH(CO₂Bn)(CN)), 5.33 (d, J = 12.8 Hz, 1 H, CO₂H(Ph)), 5.29 (d, J = 12.8 Hz, 1 H, CO₂CH(Ph)), 4.62–4.59 (m, 1 H, CHBr), 4.58–4.53 (m, 1 H, CH(O)), 3.89–3.82 (m, 1 H, NCH₃), 3.82–3.75 (m, 1 H, NCH₃), 3.70–3.61 (m, 1 H, NCH₃), 3.50–3.41 (m, 1 H, NCH₃), 1.425 (s, 9 H, 3 x CH₃); ¹³C NMR (101 MHz, DMSO-d₆, 353 K) δ 163.0 (C=O ester), 153.1 (C=O carbamate), 134.3 (Ph-C₆H₄), 128.1 (3 x Ph-CH₇), 127.6 (2 x Ph-CH₃), 114.2 (C≡N), 84.1 (br, CH(O)), 78.8 (C₆H₅CH₃), 67.7 (CO₂CH₂Ph), 66.2 (CH(CO₂Bn)(CN)), 52.4 (NCH₂), 49.0 (NCH₂), 47.5 (br, CHBr), 27.7 (3 x CH₃); HRMS (FTMS +pNSI) m/z Calcd for C₁₉H₁₇BrN₃O₅⁺ [M+N⁺]: 456.1124, Found: 456.1129.

(±)-cis-7-Benzyl 3-tert-buty 7-cyano-6-oxa-3-azabicyclo[3.2.0]heptane-3,7-dicarboxylate (5h)

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.61 mmol) which had been cooled to 0 °C. Bromide 4h (223 mg, 0.51 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH₄Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded minor oxetane 5h as a white solid (22 mg, 12%) followed by major oxetane 5h* as a white solid (151 mg, 83%) (total yield 95%, d.r. 83:17).
Minor Product 5h: Rf = 0.61 (60% EtOAc in hexanes); mp = 152–155 °C; IR (film) / cm⁻¹ 2982, 2930, 2876, 2236 (C≡N), 1770 (C=O ester), 1696 (C=O carbamate), 1479, 1455, 1420, 1367, 1239, 1165, 1098, 1031, 1010, 876, 747, 698, 572; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.34 (m, 5 H, 5 x Ph-H), 5.52 (dd, J = 5.8, 3.6 Hz, 1 H, OCH), 5.35 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 5.29 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 4.06 (t, J = 6.1 Hz, 1 H, CH), 3.86–3.76 (m, 2 H, NC₃H₃ and NC'O'H), 3.21 (dd, J = 13.5, 6.6 Hz, 1 H, NCH₂), 3.13 (dd, J = 13.7, 3.6 Hz, 1 H, NC'O'H), 1.43 (s, 9 H, 3 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.8 (C=O ester), 153.0 (C=O carbamate), 134.1 (Ph-C₃q), 128.1 (3 x Ph-C₃q), 127.6 (2 x Ph-CH), 116.4 (C≡N), 83.4 (OCH), 78.8 (C₃(CH₃)₃), 77.6 (C₃(CO₂Bn)(CN)), 75.2 (C₃(CH₃)₃), 67.9 (CO₂CH₂Ph), 51.5 (NC'H₂), 47.4 (CH), 45.4 (NCH₂), 27.7 (3 x CH₃); HRMS (ESI-TOF) m/z Calcd for C₂₁H₂₅N₅O₅Na⁺ [M+CH₃CN+Na⁺]: 422.1692, Found: 422.1685.

Major Product 5h*: Rf = 0.52 (60% EtOAc in hexanes); mp = 120–122 °C; IR (film) / cm⁻¹ 2979, 2931, 2874, 2243 (C≡N), 1749 (C=O ester), 1696 (C=O carbamate), 1456, 1417, 1367, 1237, 1167, 1101, 1077, 1006, 875, 847, 785, 750, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.35 (m, 5 H, 5 x Ph-H), 5.38 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 5.37 (dd, J = 9.1, 5.7 Hz, 1 H, OCH), 5.33 (d, J = 12.3 Hz, 1 H, CO₂CH₂Ph), 4.11–4.06 (m, 1 H, NCH₂), 3.82 (d, J = 13.7 Hz, 1 H, NC'O'H), 3.76 (t, J = 6.0 Hz, 1 H, CH), 3.34 (dd, J = 13.1, 6.5 Hz, 1 H, NCH₂), 3.12 (dd, J = 13.7, 3.4 Hz, NC'O'H), 1.46 (s, 9 H, 3 x CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.8 (C=O ester), 153.2 (C=O carbamate), 134.4 (Ph-C₃q), 128.1 (2 x Ph-CH), 128.0 (Ph-CH), 127.6 (2 x Ph-CH), 113.7 (C≡N), 84.6 (OCH), 78.8 (C₃(CH₃)₃), 77.6 (C₃(CO₂Bn)(CN)), 76.9 (CO₂CH₂Ph), 51.4 (NC'H₂), 47.0 (NCH₂), 45.3 (CH), 27.7 (3 x CH₃); HRMS (ESI-TOF) m/z Calcd for C₂₁H₂₅N₅O₅Na⁺ [M+CH₃CN+Na⁺]: 422.1692, Found: 422.1699.

The relative stereochemistries for the major and minor isomers of oxetane 5h were determined based on NOE studies (see page S119).
Optimisation of C–C Bond Forming Cyclisation using Aryl Bromide 7a

Selected optimization of reaction conditions (Table S3).

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<tr>
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<td>LiHMDS (2.0)</td>
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<td>0</td>
<td>(73)</td>
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</table>

*0.3 mmol bromide 7a. †Yield determined by 1H NMR with respect to an internal standard (1,3,5-trimethoxybenzene). Isolated yield in parentheses.

Initial studies were conducted using 1.2 equivalents of NaH and after 1 hour at 25 °C a 75% yield of desired product was observed (entry 1). Oxetane 8a could not be separated from ether 7a. An extended reaction time of 5 h led to a decrease in yield presumably due to degradation of product at this temperature (entry 2). Decreasing the temperature to 0 °C gave variable yields with up to 88% of oxetane 8a (entries 3 and 4) with the mass balance accounted for by ether 7a. Switching to LiHMDS led to an immediate increase in yield to 95% (entry 5) and increasing the number of equivalents of base to 1.4 led to the highest conversion (99% by 1H NMR) with an isolated yield of 93% (entry 7).
Synthesis of Aryl 2,2-Disubstituted Oxetanes 8a–8g

A mixture of aryl diazo 6a (550 mg, 2.9 mmol), 2-bromoethanol (137 µL, 1.9 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in benzene (19 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide 7a as a light yellow oil (478 mg, 86%); Rᵣ = 0.34 (15% EtOAc in hexanes); IR (film) / cm⁻¹ 2981, 1744 (C=O), 1495, 1454, 1392, 1369, 1272, 1205, 1177, 1105, 1024, 730, 696, 567; ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.32 (m, 5 H, 5 x Ph-H), 4.96 (s, 1 H, CH(CO₂Et)(Ph)), 4.30–4.08 (m, 2 H, CO₂CH₂CH₃), 3.91 (ddd, J = 10.5, 7.0, 6.0 Hz, 1 H, OCH₃), 3.78 (dt, J = 10.5, 6.5 Hz, 1 H, OCH₃), 3.58–3.45 (m, 2 H, CH₂Br), 1.23 (t, J = 7.0 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.4 (C=O₂), 136.0 (Ph-C₆), 128.8 (Ph-CH), 128.7 (2 x Ph-CH), 127.3 (2 x Ph-CH), 81.3 (CH(CO₂Et)(Ph)), 69.5 (OCH₂), 61.4 (CO₂CH₂CH₃), 29.6 (CH₂Br), 14.1 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z calcd for C₁₄H₁₈NaBrO₃⁺ [M+CH₃CN+Na]⁺: 350.0368, Found: 350.0378.

Reaction performed on a large scale (7.5 mmol 2-bromoethanol, 8.3 mmol diazo 6a) afforded an isolated yield of bromide 7a (1.73 g, 80%).

(±)-Ethyl 2-(bromoethoxy)-2-phenylacetate (7a)

LiHMDS (0.61 M in THF, 115 µL, 0.70 mmol) was added dropwise to a stirred solution of bromide 7a (144 mg, 0.5 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane 8a as a colorless oil (95 mg, 93%); Rᵣ = 0.24 (10% EtOAc in hexanes); IR (film) / cm⁻¹ 2980, 2893, 1728 (C=O), 1494, 1448, 1368, 1269, 1107, 1015, 968, 948, 857, 760, 731, 698, 623; ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.32 (m, 5 H, 5 x Ph-H), 7.36–7.28 (m, 1 H, Ph-H), 4.67 (ddd, J = 8.5, 6.5, 6.0 Hz, 1 H, OCH₃), 4.57 (ddd, J = 8.5, 7.0, 6.0 Hz, 1 H, OCH₃), 4.30–4.12 (m, 2 H, CO₂CH₂CH₃), 3.39 (ddd, J = 11.5, 8.5, 7.0 Hz, 1 H, CH₂H), 2.91 (ddd, J = 11.5, 8.5, 6.5 Hz, 1 H, CH₂H), 1.25 (t, J = 7.0 Hz, 3 H, CO₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.8 (C=O₂), 141.1 (Ph-C₆), 128.3 (2 x Ph-CH), 127.8 (Ph-CH), 124.3 (2 x Ph-CH), 86.2 (CO₂Et(Ph)), 65.9 (OCH₂), 61.6 (CO₂CH₂CH₃), 33.2 (CH₂), 14.0 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z calcd for C₁₄H₁₇NNaO₃⁺ [M+CH₃CN+Na]⁺: 270.1106, Found: 270.1115.

Reaction performed on a large scale (5 mmol bromide 7a) afforded an isolated yield of oxetane 8a (784 mg, 76%).
A mixture of aryl diazo \( \text{6b} \) (153 mg, 0.75 mmol), 2-bromoethanol (36 \( \mu \)L, 0.50 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (5 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (2 x 20 mL). The organic extracts were combined, dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo.

Purification by flash chromatography (10% EthOAc in hexanes) afforded bromide \( \text{7b} \) as a colorless oil (131 mg, 87%); \( R_f = 0.29 \) (10% EthOAc in hexanes); IR (film) / cm\(^{-1}\) 2981, 1740 (C=O), 1454, 1375, 1275, 1208, 1177, 1101, 1015, 963, 731, 696; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.48–7.31 (m, 5 H, 5 x Ph-H), 5.05 (sep. \( J = 6.5 \) Hz, 1 H, CO\( _2\)CH(CH\(_3\))\(_2\)), 4.92 (s, 1 H, CH(CO\( _2\)iPr)(Ph)), 3.98 (ddd, \( J = 10.5, 7.0, 6.0 \) Hz, 1 H, OCH\(_2\)), 3.76 (dt, \( J = 10.5, 7.0 \) Hz, 1 H, OCH\(_2\)H), 3.57–3.47 (m, 2 H, CH\(_2\)Br), 1.25 (d, \( J = 6.0 \) Hz, 3 H, CH\(_3\)), 1.12 (d, \( J = 6.0 \) Hz, 3 H, CH\(_3\); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 169.9 (CO\( _2\)), 136.1 (Ph-C\(_3\)), 128.7 (Ph-CH), 128.6 (2 x Ph-CH), 127.2 (2 x Ph-CH), 81.3 (CH(CO\( _2\)iPr)(Ph)), 69.4 (OCH\(_2\)), 69.0 (CO\( _2\)CH(CH\(_3\))\(_2\)), 29.7 (CH\(_2\)Br), 21.8 (CH\(_3\)), 21.5 (CH\(_3\)); HRMS (ESI-TOF) \( m/z \) calcld for C\(_{15}\)H\(_{20}\)BrNNaO\(_3\)\(^+\) [M+CH\(_3\)CN+Na]\(^+\): 364.0519, Found: 364.0527.

**(+)-Propan-2-yl 2-(2-bromoethoxy)-2-phenylacetate (7b)**

\( \text{LiHMDS} (0.61 \text{ M in THF, } 78 \mu\text{L, 0.48 mmol}) \) was added dropwise to a stirring solution of bromide \( \text{7b} \) (100 mg, 0.34 mmol) in THF (12.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH\(_4\)Cl (30 mL) was added. The aqueous mixture was extracted with EthOAc (6 x 30 mL). The organic extracts were combined, dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo.

Purification by flash chromatography (10% EthOAc in hexanes) afforded oxetane \( \text{8b} \) as a colorless oil (54 mg, 72%); \( R_f = 0.26 \) (10% EthOAc in hexanes); IR (film) / cm\(^{-1}\) 2981, 2891, 1743 (C=O), 1724, 1449, 1375, 1277, 1182, 1145, 1099, 970, 950, 887, 828, 759, 697; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54–7.46 (m, 2 H, 2 x Ph-H), 7.44–7.35 (m, 2 H, 2 x Ph-H), 7.34–7.28 (m, 1 H, Ph-H), 5.07 (sep. \( J = 6.5 \) Hz, 1 H, CO\( _2\)CH(CH\(_3\))\(_2\)), 4.66 (ddd, \( J = 8.5, 6.5, 6.0 \) Hz, 1 H, OCH\(_2\)), 4.56 (ddd, \( J = 8.5, 7.0, 6.0 \) Hz, 1 H, OCH\(_2\)H), 3.35 (ddd, \( J = 11.5, 8.5, 7.0 \) Hz, 1 H, CH\(_2\)H), 2.90 (ddd, \( J = 11.5, 8.5, 6.5 \) Hz, 1 H, CH\(_2\)HH), 1.22 (dd, \( J = 9.0, 6.0 \) Hz, 6 H, 2 x CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 172.3 (CO\( _2\)), 141.3 (Ph-C\(_3\)), 128.2 (2 x Ph-CH), 127.8 (Ph-CH), 124.3 (2 x Ph-CH), 86.2 (C\(_6\)(CO\( _2\)iPr)(Ph)), 69.1 (CO\( _2\)CH(CH\(_3\))\(_2\)), 65.9 (OCH\(_2\)), 33.2 (CH\(_2\)), 21.5 (2 x CH\(_3\)); HRMS (ESI-TOF) \( m/z \) calcld for C\(_{15}\)H\(_{19}\)NNaO\(_3\)\(^+\) [M+CH\(_3\)CN+Na]\(^+\): 284.1263, Found: 284.1272.

**(+)-Ethyl 2-(2-bromoethoxy)-2-(3-chlorophenyl)acetate (7c)**

A mixture of aryl diazo \( \text{6c} \) (270 mg, 1.2 mmol), 2-bromoethanol (71 \( \mu\)L, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was
extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (7% EtOAc in hexanes) afforded bromide 7c as a light yellow oil (222 mg, 69%); R$_f$ = 0.13 (7% EtOAc in hexanes); IR (film) cm$^{-1}$ 2982, 1745 (C=O), 1597, 1576, 1475, 1432, 1393, 1369, 1335, 1256, 1204, 1180, 1115, 1079, 1024, 910, 884, 769, 730, 681, 648, 572; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50–7.47 (m, 1 H, Ar-H), 7.38–7.28 (m, 3 H, 3 x Ar-H), 4.92 (s, 1 H, CH(CO$_2$Et)(Ar)), 4.29–4.11 (m, 2H, CO$_2$CH$_2$CH$_3$), 3.92 (td, J = 10.4, 6.3 Hz, 1 H, OCH$_3$), 3.77 (td, J = 10.4, 6.3 Hz, 1 H, OCH$_2$H), 3.53 (td, J = 6.4, 2.0 Hz, 2 H, CH$_2$Br), 1.24 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.8 (CO$_2$), 138.0 (Ar-C$_q$-CH), 134.6 (Ar-C$_q$-Cl), 129.9 (Ar-CH), 129.0 (Ar-CH), 127.3 (Ar-CH), 125.3 (Ar-CH), 80.5 (CH(CO$_2$Et)(Ar)), 69.7 (OCH$_2$), 61.6 (CO$_2$CH$_2$CH$_3$), 29.5 (CH$_2$Br), 14.1 (CO$_2$CH$_2$CH$_3$); HRMS (Cl) m/z calc for C$_{12}$H$_{15}$O$_3$BrCl$^+$ [M+H]$^+$: 320.9888, Found: 320.9893.

(±)-Ethyl 2-(3-chlorophenyl)oxetane-2-carboxylate (8c)

LiHMDS (0.61 M in THF, 115 µL, 0.70 mmol) was added dropwise to a stirring solution of bromide 7c (161 mg, 0.55 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH$_4$Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane 8c as a colorless oil (116 mg, 97%); R$_f$ = 0.12 (10% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2980, 2895, 1730 (C=O), 1596, 1574, 1475, 1448, 1422, 1368, 1230, 1190, 1145, 1109, 1079, 1045, 1015, 969, 948, 857, 777, 697, 682; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55–7.52 (m, 1 H, Ar-H), 7.40–7.28 (m, 3 H, 3 x Ar-H), 4.68 (ddd, J = 8.7, 6.6, 5.9 Hz, 1 H, OCH$_2$H), 4.57 (ddd, J = 8.7, 6.8, 5.9 Hz, 1 H, OCH$_2$H), 4.28–4.18 (m, 2 H, CO$_2$CH$_2$CH$_3$), 3.39 (ddd, J = 11.4, 8.7, 6.8 Hz, 1 H, CH$_2$H), 2.87 (ddd, J = 11.4, 8.7, 6.6 Hz, 1 H, CH$_2$H), 1.26 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.3 (CO$_2$), 143.3 (Ar-C$_q$), 134.5 (Ar-C$_q$-Cl), 129.7 (Ar-CH), 128.1 (Ar-CH), 124.8 (Ar-CH), 122.6 (Ar-CH), 85.7 (C$_q$(CO$_2$Et)(Ar)), 66.1 (OCH$_2$), 61.9 (CO$_2$CH$_2$CH$_3$), 33.3 (CH$_2$), 14.0 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z calc for C$_{12}$H$_{16}$NO$_3$BrCl$^+$ [M+Na]$^+$: 304.0716, Found: 304.0716.

(±)-Ethyl 2-(2-bromoethoxy)-2-[4-(trifluoromethyl)phenyl]acetate (7d)

A mixture of aryl diazo 6d (310 mg, 1.2 mmol), 2-bromoethanol (71 µL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide 7d as a light yellow oil (227 mg, 64%); R$_f$ = 0.20 (10% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2983, 1747 (C=O), 1620, 1420, 1370, 1323, 1277, 1210, 1164, 1120, 1105, 1066, 1018, 841, 810, 789, 757, 720; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72–7.54 (m, 4 H, 4 x Ar-H), 5.02 (s, 1 H, CH(CO$_2$Et)(Ar)), 4.29–4.10 (m, 2 H, CO$_2$CH$_2$CH$_3$), 3.96 (td, J = 10.5, 6.0 Hz, 1 H, OCH$_2$H), 3.78 (td, J = 10.5, 6.5 Hz, 1 H, OCH$_3$), 3.58–3.53 (m, 2 H, CH$_2$Br), 1.25 (t, J = 7.2 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.7 (CO$_2$), 139.9 (Ar-C$_q$-CH), 130.9 (q, J$_{C,F}$ = 32 Hz, Ar-C$_q$-CF$_3$), 127.4 (2 x Ar-CH), 125.6 (q, J$_{C,F}$ = 4 Hz, 2 x Ar-CH), 124.0 (q, J$_{C,F}$ = 272 Hz, CF$_3$).
80.6 (CH(CO$_2$Et)(Ar)), 69.8 (OCH$_2$) 61.7 (CO$_2$CH$_2$CH$_3$), 29.6 (CH$_2$Br), 14.0 (CO$_2$CH$_2$CH$_3$); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.7; HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{17}$NO$_3$NaBrF$_3^+$ [M+CH$_3$CN+Na]$^+$: 418.0242, Found: 418.0236.

(±)-Ethyl 2-[4-(trifluoromethyl)phenyl]oxetane-2-carboxylate (8d)

$\text{LiHMDS (0.61 M in THF, 115 $\mu$L, 0.70 mmol) was added dropwise to a stirring solution of bromide 7d (178 mg, 0.5 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH$_4$Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane 8d as a colorless oil (105 mg, 77%); R$_f$ = 0.17 (10% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2982, 2900, 1732 (C=O), 1618, 1449, 1410, 1369, 1324, 1302, 1263, 1164, 1107, 1072, 1061, 1016, 969, 948, 845, 812, 757, 722; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67–7.62 (m, 4 H, 4 x Ar-H), 4.69 (td, $J$ = 8.7, 6.2 Hz, 1 H, OCH$_3$H), 4.57 (td, $J$ = 8.4, 6.2 Hz, 1 H, OCH$_3$H), 4.26–4.18 (m, 2 H, CO$_2$CH$_2$CH$_3$), 3.42 (ddd, $J$ = 11.5, 8.8, 6.7 Hz, 1 H, CH$_2$), 2.88 (ddd, $J$ = 11.5, 8.7, 6.7 Hz, 1 H, CH$_2$H), 1.25 (t, $J$ = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.1 (CO$_2$), 145.2 (Ar-C$_6$), 130.2 (q, $J$$_{C,F} = 33$ Hz, Ar-C$_F$-CF$_3$), 125.4 (q, $J$$_{C,F} = 4$ Hz, 2 x Ar-CH), 124.9 (2 x Ar-CH), 124.0 (q, $J$$_{C,F} = 272$ Hz, CF$_3$), 85.9 (C$_6$(CO$_2$Et)(Ar)), 66.2 (OCH$_2$) 62.0 (CO$_2$CH$_2$CH$_3$), 33.4 (CH$_3$), 14.0 (CO$_2$CH$_2$CH$_3$); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.6; HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{18}$NO$_3$NaF$_3^+$ [M+CH$_3$CN+Na]$^+$: 338.0980, Found: 338.0988.

(±)-Ethyl 2-(2-bromoethoxy)-2-(4-methoxyphenyl)acetate (7e)

$\text{A mixture of aryl diazo 6e (264 mg, 1.2 mmol), 2-bromoethanol (71 $\mu$L, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide 7e as a light yellow oil (274 mg, 86%); R$_f$ = 0.20 (10% EtOAc in hexanes); IR (film) / cm$^{-1}$ 2980, 2905, 2838, 1743 (C=O), 1611, 1511, 1464, 1444, 1369, 1333, 1304, 1247, 1207, 1173, 1097, 1027, 911, 836, 795, 755, 731, 667, 573; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41–7.35 (m, 2 H, 2 x Ar-H), 6.93–6.87 (m, 2 H, 2 x Ar-H), 4.90 (s, 1 H, CH(CO$_2$Et)(Ar)), 4.29–4.08 (m, 2 H, CO$_2$CH$_2$CH$_3$), 3.92–3.83 (m, 1 H, OCH$_3$H), 3.81 (s, 3 H, OCH$_3$), 3.74 (dt, $J$ = 10.5, 6.7 Hz, 1 H, OCH$_3$H), 3.57–3.42 (m, 2 H, CH$_2$Br), 1.23 (t, $J$ = 7.2 Hz, 3 H, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.6 (CO$_2$), 160.0 (Ar-C$_F$-OCH$_3$), 128.6 (2 x Ar-CH), 128.1 (Ar-C$_F$-CH), 114.0 (2 x Ar-CH), 80.8 (CH(CO$_2$Et)(Ar)), 69.2 (OCH$_3$), 51.3 (CO$_2$CH$_2$CH$_3$), 55.3 (OCH$_3$), 29.7 (CH$_2$Br), 14.1 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{20}$NNaO$_3$Br$^+$ [M+CH$_3$CN+Na]$^+$: 380.0473, Found: 380.0491.
LiHMDS (0.61 M in THF, 92 μL, 0.56 mmol) was added dropwise to a stirring solution of bromide 7e (90 mg, 0.28 mmol) in THF (10.5 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) afforded oxetane 8e as a colorless oil (27 mg, 41%); Rᵣ = 0.26 (25% EtOAc in hexanes); IR (film) / cm⁻¹ 2976, 2894, 2839, 1728 (C=O), 1610, 1583, 1510, 1464, 1445, 1368, 1299, 1243, 1174, 1104, 1028, 968, 949, 856, 834, 804, 731, 634, 582; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.38 (m, 2 H, 2 x Ar-H), 6.95–6.87 (m, 2 H, 2 x Ar-H), 4.65 (ddd, J = 8.7, 6.7, 5.8 Hz, 1 H, OCH₂), 4.56 (ddd, J = 8.7, 6.8, 5.8 Hz, 1 H, OCH₂), 4.29–4.13 (m, 2 H, CO₂CH₂CH₂), 3.82 (s, 3 H, OCH₃), 3.35 (s, 3 H, OCH₃), 1.25 (t, J = 7.1 Hz, 3 H, CO₂CH₂CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 173.1 (C₂), 159.3 (Ar-C₅), 153.2 (Ar-C₅), 125.8 (2 x Ar-CH), 113.7 (2 x Ar-CH), 86.0 (C₆(CO₂Et)(Ar)), 65.9 (OCH₂), 61.5 (CO₂CH₂CH₂), 55.3 (OCH₃), 33.2 (CH₂), 14.0 (CO₂CH₂CH₂); HRMS (ESI-TOF) m/z calcd for C₁₃H₁₇O₄⁺ [M+H]⁺: 237.1127, Found: 237.1121.

(±)-Ethyl 2-(bromoethoxy)-2-(6-chloropyridin-3-yl)acetate (7f)

A mixture of aryl diazo 6f (271 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide 7f as a light yellow oil (175 mg, 54%); Rᵣ = 0.09 (10% EtOAc in hexanes); IR (film) / cm⁻¹ 2982, 1745 (C=O), 1587, 1568, 1468, 1458, 1382, 1330, 1282, 1214, 1181, 1101, 1020, 927, 836, 774, 736, 670; ¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, J = 2.4 Hz, 1 H, Ar-H), 7.80 (dd, J = 8.3, 2.4 Hz, 1 H, Ar-H), 7.35 (d, J = 8.3 Hz, 1 H, Ar-H), 4.97 (s, 1 H, CH(CO₂Et)(Ar)), 4.34–4.11 (m, 2 H, CO₂CH₂CH₂), 4.01 (td, J = 10.5, 5.8 Hz, 1 H, OCH₂), 3.76 (td, J = 10.5, 6.4 Hz, 1 H, OCH₂), 3.52 (t, J = 6.2 Hz, 2 H, CH₂Br), 1.23 (t, J = 7.2 Hz, 3 H, CO₂CH₂CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 169.3 (C₂), 151.8 (Ar-C₅), 148.4 (Ar-CH), 137.3 (Ar-CH), 130.9 (Ar-C₅), 124.3 (Ar-CH), 78.2 (CH(CO₂Et)(Ar)), 70.1 (OCH₂), 61.9 (CO₂CH₂CH₂), 29.5 (CH₂Br), 14.0 (CO₂CH₂CH₂); HRMS (ESI-TOF) m/z calcd for C₁₁H₁₄NO₂ClBr⁺ [M+H]⁺: 321.9846, Found: 321.9854.
(±)-Ethyl 2-(6-chloropyridin-3-yl)oxetane-2-carboxylate (8f)

LiHMDS (0.61 M in THF, 78 µL, 0.48 mmol) was added dropwise to a stirred solution of bromide 7f (110 mg, 0.34 mmol) in THF (12.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane 8f as a colorless oil (62 mg, 76%); Rᵣ = 0.11 (20% EtOAc in hexanes); IR (film) / cm⁻¹: 2981, 2899, 1731, 1586, 1564, 1455, 1366, 1245, 1104, 1054, 1015, 967, 947, 837, 753, 740; ¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, J = 2.5 Hz, 1 H, Ar-H), 7.78 (dd, J = 8.3, 2.5 Hz, 1 H, Ar-H), 7.33 (d, J = 8.3 Hz, 1 H, Ar-H), 4.74–4.64 (m, 1 H, OCH₂), 4.58 (ddd, J = 8.7, 6.8, 5.8 Hz, 1 H, CH₂), 4.29–4.16 (m, 2 H, CO₂CH₂CH₃), 3.38 (ddd, J = 11.5, 8.7, 6.7 Hz, 1 H, CH₂), 2.87 (ddd, J = 11.5, 8.7, 6.7 Hz, 1 H, CH₂CH₂), 1.25 (t, J = 7.1 Hz, 3 H, CH₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.6 (CO₂), 151.1 (Ar-Cₓ-Cl) 146.4 (Ar-CH), 135.8 (Ar-Cₓ), 135.4 (Ar-CH), 123.8 (Ar-CH), 84.3 (Cₓ(CO₂Et)(Ar)), 66.5 (OCH₂) 62.1 (CO₂CH₂CH₃), 33.2 (CH₂), 13.9 (CO₂CH₂CH₃); HRMS (ESI-TOF) m/z calcd for C₁₁H₁₃NO₃Cl⁺ [M+H]⁺: 242.0584, Found: 242.0592.

(±)-2-(2-Bromoethoxy)-2-(3-chlorophenyl)-1-(morpholin-4-yl)ethan-1-one (7g)

A mixture of aryl diazo 6g (111 mg, 0.42 mmol), 2-bromoethanol (27 µL, 0.38 mmol) and dirhodium(II) tetraacetate (0.8 mg, 0.002 mmol) in benzene (3.8 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (40% EtOAc in hexanes) afforded bromide 7g as a light yellow oil (101 mg, 73%); Rᵣ = 0.11 (40% EtOAc in hexanes); IR (film) / cm⁻¹: 2965, 2900, 2856, 1640 (C=O), 1597, 1574, 1458, 1433, 1360, 1299, 1272, 1225, 1192, 1111, 1079, 1033, 1012, 964, 920, 884, 761, 720, 692; ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.41 (m, 1 H, Ar-CH), 7.37–7.29 (m, 3 H, 3 x Ar-CH), 5.21 (s, 1 H, CH(CON)(Ar)), 4.03–3.89 (m, 2 H, OCH₂CH₂Br), 3.72–3.29 (m, 10 H, CH₂Br and 2 x NCH₂ and 2 x OCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 167.9 (C=O), 138.2 (Ar-Cₓ-CH), 134.8 (Ar-Cₓ-Cl), 130.0 (Ar-CH), 128.6 (Ar-CH), 126.1 (Ar-CH), 124.0 (Ar-CH), 82.7 (CH(CON)(Ar)), 70.3 (OCH₂CH₂Br), 66.8 (OCH₂), 66.5 (OCH₂), 45.8 (NCH₂), 42.8 (NC'H₂), 30.2 (CH₂Br); HRMS (ESI-TOF) m/z calcd for C₁₄H₁₈NO₃ClBr⁺ [M+H]⁺: 362.0159, Found: 362.0160.
LiHMDS (0.61 M in THF, 57 μL, 0.35 mmol) was added dropwise to a stirring solution of bromide 7g (91 mg, 0.25 mmol) in THF (9.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH₄Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (30% EtOAc in hexanes) afforded oxetane 8g as a colorless oil (63 mg, 90%); Rₛ = 0.18 (30% EtOAc in hexanes); IR (film) / cm⁻¹ 2966, 2894, 2855, 1638 (C=O), 1594, 1572, 1460, 1436, 1300, 1274, 1259, 1226, 1113, 1067, 1027, 970, 951, 858, 787, 752, 694, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.51 (m, 1 H, Ar-H), 7.40–7.28 (m, 3 H, Ar-H), 4.55 (dd, J = 8.4, 7.1 Hz, 2 H, OCH₂CH₂), 3.77–3.54 (m, 5 H, CH₂ and 2 x OCH₂), 3.54–3.34 (m, 2 H, NCH₂), 3.13 (dd, J = 11.0, 6.3, 3.0 Hz, 1 H, N'CHH), 3.04 (ddd, J = 13.7, 6.5, 3.0 Hz, 1 H, N'CHH), 2.55 (dt, J = 11.5, 7.5 Hz, 1 H, CHH); ¹³C NMR (101 MHz, CDCl₃) δ 170.1 (C=O), 144.3 (Ar-Cα), 135.0 (Ar-CαCl), 130.2 (Ar-CH), 128.0 (Ar-CH), 123.7 (Ar-CH), 121.5 (Ar-CH), 88.8 (Cα(CON)(Ar)), 66.7 (OCH₂), 66.4 (OC'Η₂), 66.1 (OCH₂CH₂), 46.1 (NCH₂), 42.8 (N'CH₂), 34.4 (CH₂); HRMS (ESI-TOF) m/z calcd for C₁₄H₁₇NO₃Cl⁺ [M+H]⁺: 282.0897, Found: 282.0895.
Functionalisation of Oxetanes 8a, 3e and 3f

(±)-4-(2-Phenyloxetane-2-carbonyl)morpholine (10)

A microwave vial (2.0–5.0 mL volume) was charged with oxetane 8a (103 mg, 0.50 mmol). The reaction vial was flushed with argon, sealed with a cap and then further flushed with argon. Anhydrous ethanol (2.4 mL) was added followed by 1 N aq. NaOH (0.55 mL, 0.55 mmol). The reaction mixture was stirred at 30 °C for 22 h. The reaction mixture was concentrated to afford (±)-2-phenyloxetane-2-carboxylate sodium salt 9 as a white solid which was used without further purification: \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.49–7.39 (m, 2 H, 2 x Ph-H), 7.25 (t, \(J = 7.6\) Hz, 2 H, 2 x Ph-H), 7.15 (t, \(J = 7.3\) Hz, 1 H, Ph-H), 4.29–4.14 (m, 2 H, OCH\(_2\)), 3.14–3.09 (m, 1 H, CH\(\equiv\)H), 2.54–2.51 (m, 1 H, CH\(\equiv\)H).

HATU (228 mg, 0.6 mmol) and morpholine (53 \(\mu\)L, 0.60 mmol) were added to a flask containing (±)-2-phenyloxetane-2-carboxylate sodium salt 9 (0.50 mmol) in DMF (2.5 mL). \(N,N\)-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 16 h. The reaction was concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded oxetane 10 as a yellow oil (97 mg, 78% over 2 steps); \(R_f\) = 0.36 (50% EtOAc in hexanes); IR (film) / cm\(^{-1}\) 2968, 2892, 2855, 1692, 1639 (C=O), 1435, 1365, 1300, 1275, 1260, 1225, 1150, 1112, 1066, 1027, 968, 952, 910, 850, 758, 727, 700, 671; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53–7.48 (m, 2 H, 2 x Ph-H), 7.44–7.37 (m, 2 H, 2 x Ph-H), 7.36–7.29 (m, 1 H, Ph-H), 4.66–4.57 (dd, \(J = 8.4, 7.2\) Hz, 2 H, OCH\(_2\)CH\(_2\)), 3.78–3.53 (m, 5 H, CH\(\equiv\)H and OCH\(_2\) and NCH\(_2\)), 3.49–3.36 (m, 2 H, OCH\(_2\)H and NC\(\equiv\)H(H)), 3.14–2.98 (m, 2 H, OCH\(_2\)H and NCH\(_2\)), 2.62–2.50 (m, 1 H, CH\(\equiv\)H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 170.7 (C=O), 142.2 (Ph-C\(_3\)), 128.8 (2 x Ph-CH). 127.8 (Ph-CH), 123.3 (2 x Ph-CH), 89.3 (CON(CON)(Ph)), 66.7 (OCH\(_2\)), 66.3 (OC\(_2\)H), 66.1 (OCH\(_2\)CH\(_2\)), 46.1 (NCH\(_2\)), 42.8 (NCH\(_2\)), 34.5 (CH\(_2\)); HRMS (ESI-TOF) \(m/z\) calcd for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_3\)Na\(^+\) [M+CH\(_3\)CN+Na\(^+\): 311.1372, Found: 311.1365.

(±)-cyano-N-cyclobutylxoxetane-2-carboxamide (12)

Lithium hydroxide monohydrate (23 mg, 0.54 mmol) in H\(_2\)O (2 mL) was added to a solution of oxetane 3e (109 mg, 0.50 mmol) in THF (6 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated in vacuo affording (±)-cyanoxoxetane-2-carboxylate lithium salt 11 as a viscous yellow oil which was used without further purification: \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 4.61–4.52 (m, 1 H, OCH\(_2\)H), 4.45–4.36 (m, 1 H, OCH\(_2\)), 2.99–2.90 (m, 1 H, CH\(\equiv\)H), 2.89–2.79 (m, 1 H, CH\(\equiv\)H). Benzyl alcohol was removed overnight under high vacuum at rt.

HATU (209 mg, 0.55 mmol) and cyclobutylamine (64 \(\mu\)L, 0.75 mmol) were added to a flask containing (±)-cyanoxoxetane-2-carboxylate lithium salt 11 (0.50 mmol) in DMF (2.5 mL). \(N,N\)-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 18 h. The reaction was concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded oxetane 12 as a white crystalline solid (27 mg, 30% over 2 steps); \(R_f\) = 0.22 (50% EtOAc in hexanes); mp = 126–130 °C; IR (film) / cm\(^{-1}\) 3303 (N-H), 2983, 2944, 2908, 2875, 2249 (C≡N), 1664 (C=O), 1524, 1482, 1454, 1275, 1246, 1215, 1196, 1170, 1147, 1121, 1033, 968, 937, 810, 777, 750, 716, 639; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.00 (br s, 1 H, NH), 4.97–4.87 (m, 1 H, OCH\(_2\)), 4.69–4.60 (m, 1 H, OCH\(_2\)), 4.52–4.38 (m, 1 H, NHCH(CH\(_2\))\(_2\)), 3.37–3.25 (m, 1 H, OCH\(_2\)CH\(_2\)), 3.15–3.03 (m, 1 H, OCH\(_2\)CH\(_2\)), 2.49–2.33 (m, 2 H,
2 x NHCH(CH₃), 2.08–1.92 (m, 2 H, 2 x NHCH(CH₃)), 1.86–1.74 (m, 2 H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 164.5 (C=O), 116.9 (C≡N), 76.2 (C₆(CONH)(CN)), 68.9 (OCH₃), 44.6 (NHCH(CH₃)₂), 32.2 (OCH₂CH₂), 30.9 (NHCH(CH₃)), 30.8 (NHCH(CH₃)), 15.0 (CH₂); HRMS (CI) m/z calcd for C₉H₁₈N₃O₂⁺ [M+NH₄]⁺: 198.1243, Found: 198.1240.

(±)-2-cyano-N-(4-methoxyphenyl)oxetane-2-carboxamide (13)

Lithium hydroxide monohydrate (23 mg, 0.54 mmol) in H₂O (2 mL) was added to a solution of oxetane 3e (109 mg, 0.50 mmol) in THF (6 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated in vacuo affording (±)-2-cyanooxetane-2-carboxylate lithium salt 11 as a viscous yellow oil which was used without further purification. Benzyl alcohol was removed overnight under high vacuum at rt.

HATU (209 mg, 0.55 mmol) and p-anisidine (67 mg, 0.55 mmol) were added to a flask containing (±)-2-cyanooxetane-2-carboxylate lithium salt 11 (0.50 mmol) in DMF (2.5 mL). N,N-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 24 h. The reaction was concentrated in vacuo. Purification by flash chromatography on deactivated basic alumina (activity IV) (2% Et₂O in CH₂Cl₂) afforded oxetane 13 as a beige solid (41 mg, 35% over 2 steps); Rf = 0.27 (2% Et₂O in CH₂Cl₂); mp = 84–86 °C; IR (film) / cm⁻¹ 3320 (N=O), 1684, 1648, 1596, 1511, 1465, 1444, 1417, 1302, 1247, 1234, 1180, 1158, 1030, 935, 830, 810, 731, 672, 541; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (br s, 1 H, NH), 7.58–7.46 (m, 2 H, 2 x Ar-H), 6.96–6.86 (m, 2 H, 2 x Ar-H), 5.03–4.93 (m, 1 H, OCH), 4.77–4.68 (m, 1 H, OCH₂), 3.81 (s, 3 H, OCH₃), 3.44–3.33 (m, 1 H, CH₂), 3.25–3.15 (m, 1 H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 163.1 (C=O), 157.2 (Ar-C₆-OMe), 129.0 (Ar-C₆-NH), 121.5 (2 x Ar-CH), 116.7 (C≡N), 77.4 (2 x Ar-CH), 76.4 (C₆(CONH)(CN)), 69.1 (OCH₂), 55.5 (OCH₃), 32.4 (CH₂); HRMS (CI) m/z calcd for C₁₂H₁₈N₃O₃⁺ [M+Na⁺]: 250.1192, Found: 250.1199.

(±)-2-(Piperazine-1-carbonyl)oxetane-2-carbonitrile (14)

Trifluoroacetic acid (78 mL, 1.0 mmol) was added to a solution of oxetane 3f (30 mg, 0.1 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min then 25 °C for 22 h. Toluene (5 mL) was added and the reaction mixture was concentrated in vacuo. Purification by flash chromatography on deactivated basic alumina (activity IV) (2% MeOH in CH₂Cl₂) afforded oxetane 14 as a colorless oil (16 mg, 79%); Rf = 0.36 (10% MeOH in CH₂Cl₂); IR (film) / cm⁻¹ 3323 (br N-H), 2909, 2854, 2249 (C≡N), 1656 (C=O), 1444, 1322, 1269, 1162, 1141, 1122, 1023, 969, 941, 802, 601; ¹H NMR (400 MHz, CDCl₃) δ 4.87–4.79 (m, 1 H, OCH₂), 4.60–4.52 (m, 1 H, OCH₂), 3.71–3.59 (m, 3 H, OCNCH₂ and CH₂), 3.37–3.47 (m, 2 H, OCNCH₂), 3.14–3.04 (m, 1 H, CH₂), 3.00–2.84 (m, 4 H, 2 x HNC₃), 157.2 (C=O), 117.5 (C≡N), 76.1 (C₆(CN)(CON)), 68.4 (OCH₂), 47.2 (OCNCH₂), 45.8 (HNC₃), 45.7 (HNC₃), 44.2 (OCNCH₂), 30.5 (CH₂); HRMS (ESI-TOF) m/z Calcd for C₁₁H₁₁N₃O₂⁺ [M+CH₃CN+H⁺]: 237.1352, Found: 237.1359.
$^1$H and $^{13}$C NMR Spectra of Selected Compounds
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
S2
$^1$H NMR (400 MHz, CDCl$_3$)

S2
$^{13}$C NMR (101 MHz, CDCl$_3$)
S10

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

S10

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
O. A. Davis, R. A. Croft and J. A. Bull

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

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
O. A. Davis, R. A. Croft and J. A. Bull

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

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
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$\text{EtO}_2\text{C}\text{O\text{-}}\text{O\text{-}}\text{Br}$

$\text{MeO}$

$\text{N}$

$\text{Me}$

$2b$

$^1\text{H NMR (400 MHz, CDCl}_3$)

$^1\text{H NMR (400 MHz, CDCl}_3$)

$2b$

$13\text{C NMR (101 MHz, CDCl}_3$)

$13\text{C NMR (101 MHz, CDCl}_3$)

$167.08$

$156.80$
O. A. Davis, R. A. Croft and J. A. Bull

$\text{EtO}_2\text{C} \quad \text{O} \quad \text{Br}$
(\text{EtO})_2\text{OP}

2d

$^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3)$

$\text{ppm}$

166.96

2d

$^13\text{C NMR} \ (101 \text{ MHz, CDCl}_3)$

$\text{ppm}$
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
O. A. Davis, R. A. Croft and J. A. Bull

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

2g

$^{13}$C NMR (101 MHz, CDCl$_3$)

2g
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$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
(EtO)₂OP
O
N

3g

\(^1\)H NMR (400 MHz, CDCl₃)

\(^13\)C NMR (101 MHz, CDCl₃)
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$^{13}$C NMR (101 MHz, CDCl$_3$)

4d

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

4d
d.r. 1:0:1.0
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PhO₂S⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻~-~-

4e

d.r. 1.4:1.0

¹H NMR (400 MHz, CDCl₃)

13C NMR (101 MHz, CDCl₃)
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$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
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$^1$H NMR (400 MHz, DMSO-$d_6$, 353 K)

$^1$C NMR (101 MHz, DMSO-$d_6$, 353 K)
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Major Diastereoisomer
$^1$H NMR (400 MHz, CDCl$_3$)

5a

$^13$C NMR (101 MHz, CDCl$_3$)
Minor Diastereoisomer
(6.5:1 Mixture of Minor : Major)
$^1$H NMR (400 MHz, CDCl$_3$)

5a'
Minor Diastereoisomer
$^{13}$C NMR (101 MHz, CDCl$_3$)
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5b
d.r. 1.2:1.0

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

5b

$^{13}$C NMR (101 MHz, CDCl$_3$)
5c

$d.r. = 2.5:1.0$

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

$^13$C NMR (101 MHz, CDCl$_3$)
Minor Diastereoisomer
$^1$H NMR (400 MHz, CDCl$_3$)

Minor Diastereoisomer
$^{13}$C NMR (101 MHz, CDCl$_3$)
Major Diastereoisomer

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

Major Diastereoisomer

$^{13}$C NMR (101 MHz, CDCl$_3$)
Minor Diastereoisomer
(4.1:1 Mixture of Minor : Major)

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

5f

$^1$C NMR (101 MHz, CDCl$_3$)
Major Diastereoisomer
(7.7:1 Mixture of Major : Minor)
$^1$H NMR (400 MHz, CDCl$_3$)

5f

Major Diastereoisomer
$^{13}$C NMR (101 MHz, CDCl$_3$)
Minor Diastereoisomer

$^1$H NMR (500 MHz, DMSO-$d_6$, 353 K)

$^{13}$C NMR (126 MHz, DMSO-$d_6$, 353 K)
Major Diastereoisomer

$^1$H NMR (500 MHz, DMSO-$d_6$, 353 K)

$^1$C NMR (126 MHz, DMSO-$d_6$, 353 K)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$\text{H NMR (400 MHz, CDCl}_3\text{)}$

$\text{C NMR (101 MHz, CDCl}_3\text{)}$
1H NMR (400 MHz, CDCl₃)

13C NMR (101 MHz, CDCl₃)
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$\text{1H NMR (400 MHz, CDCl}_3\text{)}$

$\text{13C NMR (101 MHz, CDCl}_3\text{)}$
\[ \text{ELO}_2\text{C} \]

8a

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \]

\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \]
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)

8b
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
\( \text{\(^1\)H NMR (400 MHz, CDCl}_3\) } \\

\( \text{\(^{13}\)C NMR (101 MHz, CDCl}_3\) }
O. A. Davis, R. A. Croft and J. A. Bull

\[ 8g \]

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

\[ 8g \]

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, DMSO-$d_6$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, DMSO-$d_6$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
NOESY and Selective NOE Spectra for Oxetanes 5a, 5d, 5f and 5h

NOESY NMR of major oxetane 5a

NOESY NMR of minor oxetane 5a'
Selective NOE of major oxetane 5a – Irradiation at 0.85 ppm

Selective NOE of minor oxetane 5a' – Irradiation at 0.90 ppm
NOESY NMR of minor oxetane 5d

NOESY NMR of major oxetane 5d'
Selective NOE of minor oxetane 5d – Irradiation at 7.27 ppm

Selective NOE of major oxetane 5d' – Irradiation at 1.22 ppm
NOESY NMR of minor oxetane 5f

NOESY NMR of major oxetane 5f'
Selective NOE of minor oxetane 5f – Irradiation at 6.97 ppm

Selective NOE of major oxetane 5f' – Irradiation at 4.52 ppm
Selective NOE of minor oxetane $5h$ – Irradiation at 4.05 ppm

Selective NOE of major oxetane $5h'$ – Irradiation at 3.75 ppm
The relative stereochemistry for the major isomer of oxetane 5b as indicated in table 2 was assigned by analogy to that observed for oxetane 5a.

The relative stereochemistry for the major isomers of oxetanes 5c and 5e as indicated in table 2 were assigned by analogy to that observed for oxetane 5d.
References