Supporting Information

Synthesis of 1,3-Disubstituted Bicyclo[1.1.0]butanes via Directed Bridgehead Functionalization

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1. Experimental procedures

1.1 General comments

**NMR Spectroscopy:** Proton (^1H), carbon (^13C) and fluorine (^19F) NMR spectra were recorded on a Bruker AVIII HD 400, NEO 400, AVIII HD 500 or AVII 500 spectrometer. Proton, carbon and fluorine chemical shifts (δ) are quoted in parts per million (ppm). ^1H NMR spectra were recorded using an internal deuterium lock for the residual protons in chloroform-d (δ = 7.26) or benzene-d6 (δ = 7.16). ^13C NMR spectra were recorded using an internal deuterium lock in chloroform-d (δ = 77.16) or benzene-d6 (δ = 128.06). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC and/or NOESY experiments. Peak multiplicities are defined as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J) are reported to the nearest 0.1 Hz.

**Mass Spectroscopy:** High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Scientific Exactive Mass Spectrometer (using a Waters Equity autosampler and pump) for electrospray ionization (ESI) and an Agilent 7200 Accurate Mass QTOF GCMS (using a SiM Direct Insertion Probe) for electron ionization (EI) and chemical ionization (CI). High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

**Infrared Spectroscopy:** Infrared spectra were obtained as a thin film, by evaporation of a dichloromethane solution of the sample, on a diamond ATR module on a Bruker Tensor 27 FT-IR spectrometer. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}. Only selected, characteristic IR absorption data are provided for each compound.

**Melting Points:** Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

**Polarimetry:** Optical rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). [α]_D are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/100 mL. Temperatures are reported in °C.

**X-ray crystallography:** Details of instrumentation and techniques are reported in Section 3.

**Chromatography:** Column chromatography refers to normal phase column chromatography and was performed on silica gel obtained from Merck (Silica gel Si 60, 0.040-0.063 mm) under a positive pressure of nitrogen, using the stated solvent system. Analytical thin-layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F254 plates) with visualization by ultraviolet light (254 nm) and/or by staining with phosphomolybdic acid and potassium permanganate. Retention factors (Rf) are reported with the solvent system in parentheses.

**Materials/procedures:** All air- or moisture-sensitive reactions were carried out with anhydrous solvents in flame-dried glassware under an inert atmosphere of argon or nitrogen. Light sensitive reactions were carried out under aluminium foil protection. Heating was performed using an oil. Dry tetrahydrofuran (THF), DCM, pyridine (py) and diethyl ether (Et2O) were collected fresh from an mBraun SPS-800 solvent purification system, having been passed through anhydrous alumina columns. All other commercially available reagents and solvents, where appropriate, were dried and purified before use using standard procedures.
1.3 Synthesis of monosubstituted BCBs

(But-3-en-1-ylsulfonyl)benzene, S1

To a suspension of sodium benzenesulfinate (5.00 g, 30.5 mmol, 1.0 eq.) in DMF (50 mL) was added 4-bromobutene (3.70 mL, 36.5 mmol, 1.2 eq.) dropwise at rt. The reaction mixture was heated to 60 °C and stirred for 2.5 h before diluting with water (150 mL) and extracting with EtOAc (150 mL x 3). The organics were combined, washed with 5% aq. LiCl solution (50 mL x 3), dried with anhydrous Na$_2$SO$_4$, filtered and evaporated in vacuo to afford a yellow oil. The oil was purified via flash chromatography (10→20% EtOAc in pentane) to afford S1 as a clear oil (5.00 g, 25.4 mol, 83%). Data identical to literature values.$^1$

$R_f = 0.24$ (20% EtOAc in pentane)

$^1$H NMR (400 MHz, Chloroform-d): $\delta$ 7.94-7.90 (m, 2H), 7.70-7.64 (m, 1H), 7.61-7.55 (m, 2H), 5.73 (ddt, $J = 16.8, 10.2, 6.5$ Hz, 1H), 5.09-5.02 (m, 2H), 3.20-3.14 (m, 2H), 2.51-2.42 (m, 2H)

$^{13}$C NMR (101 MHz, Chloroform-d): $\delta$ 139.2, 133.9, 133.9, 129.5, 128.7, 117.3, 56.1, 25.3

2-(2-(Phenylsulfonyl)ethyl)oxirane, S2

To a solution of S1 (5.00 g, 25.4 mmol, 1.0 eq.) in acetone/water (1:1, 100 mL) was added NaHCO$_3$ (21.3 g, 0.25 mol, 10.0 eq.), followed by Oxone (20.3 g, 66.0 mmol, 2.6 eq.) at rt. The suspension was stirred for 18 h at rt before filtering, reducing in vacuo (removing acetone) and extracting with EtOAc (100 mL x 2). The organics were combined, dried with anhydrous Na$_2$SO$_4$, filtered and evaporated to afford a yellow oil. The oil was purified via flash chromatography (20→30% EtOAc in pentane) to afford S2 as a clear oil (5.10 g, 23.8 mol, 94%). Data identical to literature values.$^1$

$R_f = 0.24$ (40% EtOAc in pentane)

$^1$H NMR (400 MHz, Chloroform-d): $\delta$ 7.96-7.88 (m, 2H), 7.72-7.63 (m, 1H), 7.59 (ddt, $J = 8.2, 6.7, 1.2$ Hz, 2H), 3.29-3.16 (m, 2H), 3.01 (dt, $J = 6.7, 4.0, 2.6$ Hz, 1H), 2.78 (dd, $J = 4.8, 3.9$ Hz, 1H), 2.50 (dd, $J = 4.8, 2.6$ Hz, 1H), 2.17 (dddd, $J = 14.3, 8.7, 7.0, 4.2$ Hz, 1H), 1.89-1.77 (m, 1H)

$^{13}$C NMR (101 MHz, Chloroform-d): $\delta$ 138.2, 134.1, 129.6, 128.2, 53.4, 50.8, 44.8, 26.0
(2-(Phenylsulfonyl)cyclopropyl)methanol, S3

To a solution of S2 (5.10 g, 23.8 mmol, 1.0 eq.) in THF (150 mL) was added n-BuLi (12.6 mL, 1.9 M in hexane, 23.8 mmol, 1.0 eq.) dropwise over 10 min at 0 °C. The reaction mixture was stirred for 15 min at 0 °C before quenching with sat. aq. NH₄Cl (5 mL). The mixture was partitioned between EtOAc (150 mL) and water (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (100 mL x 2). The combined organic phases were dried with anhydrous Na₂SO₄, filtered and concentrated to afford a yellow oil. The oil was purified via flash chromatography (50→70% EtOAc in pentane) to afford S3 as a clear oil (4.90 g, 22.8 mmol, 96%). Data identical to literature values.¹

Rf = 0.26 (80% EtOAc in pentane)

¹H NMR (400 MHz, Chloroform-d): δ 7.94-7.87 (m, 2H), 7.68-7.61 (m, 1H), 7.61-7.52 (m, 2H), 3.71 (dt, J = 11.2, 5.5 Hz, 1H), 3.54 (dt, J = 11.4, 5.7 Hz, 1H), 2.47 (dt, J = 8.3, 4.7 Hz, 1H), 2.11-2.00 (m, 1H), 1.54-1.45 (m, 2H), 1.10 (ddd, J = 8.3, 6.5, 5.4 Hz, 1H)

¹³C NMR (101 MHz, Chloroform-d): δ 140.7, 133.6, 129.4, 127.7, 62.2, 37.0, 21.7, 10.2

(2-(Phenylsulfonyl)cyclopropyl)methyl methanesulfonate, S4

To a solution of S3 (4.90 g, 22.8 mmol, 1.0 eq.) and NEt₃ (3.80 mL, 27.4 mmol, 1.2 eq.) in dichloromethane (150 mL) was added MsCl (2.10 mL, 27.4 mmol, 1.2 eq.) dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, then warmed to rt and stirred for an additional 9 h. The reaction mixture was concentrated, and the residue dissolved in Et₂O (100 mL) and washed with water (50 mL x 2). The organic phase was dried with anhydrous Na₂SO₄, filtered and evaporated to yield S4 as a yellow oil (6.60 g, 22.8 mmol, 99%). Data identical to literature values.¹

¹H NMR (400 MHz, Chloroform-d): δ 7.95-7.88 (m, 2H), 7.71-7.64 (m, 1H), 7.63-7.54 (m, 2H), 4.30 (dd, J = 11.3, 5.9 Hz, 1H), 3.98 (dd, J = 11.3, 7.7 Hz, 1H), 2.95 (s, 3H), 2.59 (ddd, J = 8.5, 5.3, 4.3 Hz, 1H), 2.18 (ddtd, J = 9.5, 7.7, 6.1, 4.3 Hz, 1H), 1.66 (ddd, J = 9.5, 5.9, 5.3 Hz, 1H), 1.17 (dt, J = 8.5, 6.0 Hz, 1H)

¹³C NMR (101 MHz, Chloroform-d): δ 140.2, 134.8, 128.8, 127.9, 69.0, 38.3, 38.0, 18.7, 11.4
1-(Phenylsulfonyl)bicyclo[1.1.0]butane, 8a

To a solution of S4 (5.90 g, 20.4 mmol, 1.0 eq.) in THF (150 mL) was added n-BuLi (10.7 mL, 1.9 M in hexane, 20.4 mmol, 1.0 eq.) over 1 min at 0 °C. The reaction mixture was stirred for 5 min at 0 °C before quenching with sat. aq. NH₄Cl (5 mL). The mixture was partitioned between Et₂O (100 mL) and water (100 mL), the phases were separated, and the aqueous phase was extracted with Et₂O (100 mL x 2). The organic phases were combined, dried with anhydrous Na₂SO₄, filtered and evaporated to afford a yellow oil. The oil was purified via flash chromatography (5→10% EtOAc in pentane) to afford 8a as a colourless solid (2.60 g, 13.4 mmol, 65%). Data identical to literature values.

**Note A:** n-BuLi must be added as a gentle stream to S4. If added too slowly the SM can polymerise.

\[ R_f = 0.26 \text{ (15\% EtOAc in pentane), 0.23 (40\% Et}_2\text{O in pentane)} \]

**1H NMR** (400 MHz, Chloroform-­d): δ 7.97-7.93 (m, 2H), 7.66-7.60 (m, 1H), 7.61-7.52 (m, 2H), 2.57 (dq, J = 4.0, 2.7 Hz, 1H), 2.52 (dt, J = 3.7, 1.0 Hz, 2H), 1.39 (dt, J = 2.7, 0.9 Hz, 2H)

**13C NMR** (101 MHz, Chloroform-­d): δ 142.1, 134.8, 130.6, 127.3, 36.6, 23.2, 13.9

1,1-Dibromo-2-(chloromethyl)cyclopropane, S5

To a solution of dibenzo-18-crown-6 (1.80 g, 5.00 mmol, 0.05 eq.), allyl chloride (12.2 mL, 0.15 mol, 1.5 eq.), pinacol (0.47 g, 4.00 mmol, 0.04 eq.), and bromoform (8.80 mL, 0.10 mol, 1.0 eq.) in DCM (65 mL) was added a solution of NaOH in water (50% wt, 50 mL, 1.00 mol, 10.0 eq.). The reaction vessel was equipped with a reflux condenser, heated to 40 °C and stirred for 20 h. The reaction mixture was cooled, then poured into a beaker containing 200 mL of pentane, stirred and sonicated. The suspension was left to settle, and the solution was decanted. This was repeated twice followed by combining the organic extracts, filtering through a silica pad, and evaporating in vacuo to yield a yellow oil. The oil was purified via flash chromatography (pentane) to afford S5 as a yellow oil (11.0 g, 0.44 mol, 44%). Data identical to literature values.

\[ R_f = 0.28 \text{ (pentane)} \]

**1H NMR** (400 MHz, Chloroform-­d): δ 3.65 (d, J = 7.4 Hz, 2H), 2.04 (dq, J = 10.3, 7.4 Hz, 1H), 1.93 (dd, J = 10.3, 7.5 Hz, 1H), 1.48 (t, J = 7.5 Hz, 1H)

**13C NMR** (101 MHz, Chloroform-­d): δ 46.3, 32.3, 29.1, 25.8
1-(Phenylsulfinyl)bicyclo[1.1.0]butane, 8b

To a solution of 55 (60 mg, 0.24 mmol, 1.2 eq.) in Et₂O (1.3 mL) was added methylmagnesium iodide (1.4 M in Et₂O, 170 µL, 0.24 mmol, 1.2 eq.) dropwise at −78 °C. The reaction was stirred for 30 min at −78 °C followed by 1 h at −50 °C. The solution was then cooled back to −78 °C and a high vacuum was applied for 5 min (removing MeBr). t-BuLi (1.5 M in Et₂O, 160 µL, 0.24 mmol, 1.2 eq.) was then added dropwise and stirred for 20 min. A solution of freshly prepared MgBr₂•Et₂O was added via syringe. After stirring for 2 h at −78 °C, methyl 4-methylbenzenesulfinyl (26 µL, 0.20 mmol, 1.0 eq.) was added dropwise and the reaction was stirred for 5 min at −78 °C, and finally for 30 min at rt. The solution was quenched with sat. aq. NH₄Cl (2 mL), the phases were separated, and the aqueous phases was extracted with Et₂O (5 mL). The combined organic phases were dried with anhydrous MgSO₄, filtered, and concentrated to afford a yellow oil. The oil was purified via flash chromatography (20% → 40% EtOAc in pentane) to afford 8b as a light yellow oil (23 mg, 0.13 mmol, 64%). Data identical to literature values.

Note A: MgBr₂•Et₂O was prepared during the 1 h stir at −50 °C as follows: To Et₂O (1 mL) containing magnesium turnings (47 mg, 1.9 mmol, 9.6 eq.) and was added dropwise 1,2-dibromoethane (42 µL, 0.50 mmol, 2.4 eq.) until reflux was initiated. The suspension was then cooled to 0 °C and the remaining 1,2-dibromoethane was added dropwise. After gas evolution had ceased, the mixture was stirred for an additional 30 min at rt.

¹H NMR (400 MHz, Chloroform-d): δ 7.69-7.65 (m, 2H), 7.48-7.46 (m, 3H), 2.37 (ddd, J = 6.1, 3.5, 1.5 Hz, 1H), 2.13 (ddd, J = 6.0, 3.5, 1.7 Hz, 1H), 2.08 (tt, J = 3.5, 2.3 Hz, 1H), 1.40 (dt, J = 2.6, 1.3 Hz, 1H), 1.19 (dt, J = 2.5, 1.3 Hz, 1H)

¹³C NMR (101 MHz, Chloroform-d): δ 144.9, 131.0, 129.3, 124.6, 37.7, 34.0, 25.1, 8.7
3-Chlorocyclobutanecarboxylic acid, S6

\[
\begin{align*}
\text{CO}_2\text{H} & \quad i) \text{SO}_2\text{Cl}_2, (\text{PhCO}_2)_2 \\
\text{PhH, 80 °C, 1 d.} & \quad \text{ii) 180 - 200 °C, 45 min, 1:1 dr, 44 %}
\end{align*}
\]

Sulfuryl chloride (34.1 mL, 0.42 mol, 1.05 eq.) was added dropwise via a dropping funnel over 30 min to a stirred solution of cyclobutane-1,1-dicarboxylic acid (57.7 g, 0.40 mol, 1.0 eq.) in benzene (500 mL) at 80 °C. During this addition was added, in two portion at 15 min internals, benzoyl peroxide (1.00 g, 4.10 mmol, 1 mol%) from the top of the condenser. The reflux condenser was fitted with a drying tube and stirred for 1 d at 80 °C. The reaction mixture was cooled and concentrated to yield a colourless solid, which was heated to 180-200 °C for 45 min. The resulting dark oil was distilled (90 °C, 2 mbar) to afford S6 as a colourless oil (23.9 g, 0.18 mol, 44%, 1:1 dr).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)): \(\delta\) 4.61 (ttd, \(J = 7.6, 6.5, 1.0\) Hz, 0.5H), 4.32 (tt, \(J = 8.6, 7.2\) Hz, 0.5H), 3.45-3.30 (m, 0.5H), 3.30-3.15 (m, 0.5H), 2.98-2.77 (m, 2H), 2.68-2.53 (m, 2H)

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)): \(\delta\) 181.4, 179.6, 51.0, 49.4, 47.7, 37.7, 37.1, 34.4

Data identical to literature values.\(^3\)

\(N,N\)-Diisopropylbicyclo[1.1.0]butane-1-carboxamide, 8c

\[
\begin{align*}
\text{CO}_2\text{H} & \quad i) (\text{COCl})_2, \text{DCM, rt} \\
& \quad \text{DMF cat. then (i-Pr)}_2\text{NH, 74 %} \\
& \quad \text{ii) LHMDS, THF, 0 °C, 43 %}
\end{align*}
\]

To a solution of S6 (1.35 g, 10.0 mmol, 1.0 eq.) in DCM (30 mL) was added oxalyl chloride (1.00 mL, 12.0 mmol, 1.2 eq.) and DMF (2 drops) at rt. The reaction was stirred for 1 h at rt before concentrating in vacuo and placing under high vacuum for 5 min. The crude acyl chloride was dissolved in DCM (20 mL) and a solution of (i-Pr)_2NH (1.54 mL, 11.0 mmol, 1.1 eq.) in DCM (20 mL) was added slowly at rt. The solution was stirred for 1 d at rt, followed by washing with aq. HCl (1 M, 50 mL), sat. aq. NaHCO\(_3\) (50 mL), and brine (50 mL). The organic phase was dried with anhydrous MgSO\(_4\), filtered, concentrated and purified by a silica pad filtration (Et\(_2\)O/pentane, 1:1) to yield 3-chloro-\(N,N\)-diisopropylcyclobutanecarboxamide as a clear yellow oil (1.43 g, 6.60 mmol, 74%, 1:1 dr).

To a solution of 3-chloro-\(N,N\)-diisopropylcyclobutanecarboxamide (0.70 g, 3.24 mmol, 1.0 eq.) in THF (8 mL) was added a solution of LHMDS in THF (0.46 M, 8.0 mL, 3.65 mmol, 1.1 eq.) at 0 °C. The reaction was stirred for 4 h at 0 °C before diluting with DCM and quenching with a few drops of water. The mixture was evaporated in vacuo, and the residue was purified by flash column chromatography (1% NEt\(_3\), 10→20% EtOAc in pentane) to afford 8c as a colourless solid (0.28 g, 1.60 mmol, 43%).

\(R_f = 0.29\) (20% EtOAc in pentane)
MP: 55 °C

IR (thin film, \(v_{\text{max}}/\text{cm}^{-1}\)): 2999, 1627, 1482, 1383, 1283

HRMS (ESI+) calc. for \(\text{C}_{11}\text{H}_{20}\text{ON} [\text{M+H}]^+\) 182.1539, found 182.1541

\(^1\text{H NMR} (500 \text{ MHz, Chloroform-}d)\): \(\delta\) 4.86 (s, 1H), 3.41 (s, 1H), 2.16 (d, \(J = 3.3 \text{ Hz, 2H}\)), 1.87 (tt, \(J = 3.4, 2.2 \text{ Hz, 1H}\)), 1.50-1.31 (m, 6H), 1.30-1.12 (m, 6H), 1.05 (d, \(J = 2.2 \text{ Hz, 2H}\))

\(^{13}\text{C NMR} (126 \text{ MHz, Chloroform-}d)\): \(\delta\) 170.0, 49.6, 46.0, 36.5, 21.3, 20.9, 11.6, 9.5

**Methyl bicyclo[1.1.0]butane-1-carboxylate, S7**

![](image)

To a solution of S6 (13.5 g, 0.10 mol, 1.0 eq.) in 2,2-dimethoxypropane (18 mL) was added a solution of methanesulfonic acid (50.0 µL, 0.77 mmol, 0.77 mol%) in MeOH (3 mL). The solution was heated at 70 °C for 19 h before being cooled to room temperature and diluted with Et\(_2\)O (150 mL). The organic phase was washed with sat. aq. \(\text{Na}_2\text{CO}_3\) solution (100 mL), brine (100 mL), dried with anhydrous MgSO\(_4\) and filtered. The organic phase was passed through a silica pad with a further 100 mL of Et\(_2\)O, and the filtrate was evaporated in vacuo to yield the intermediate methyl 3-chlorocyclobutanecarboxylate as a yellow oil (13.9 g, 93.5 mmol, 94%, 1:1 dr).

\(^1\text{H NMR} (400 \text{ MHz, Chloroform-}d)\): \(\delta\) 4.60 (ttd, \(J = 7.5, 6.4, 1.0 \text{ Hz, 0.5H}\)), 4.30 (tt, \(J = 8.6, 7.2 \text{ Hz, 0.5H}\)), 3.71 (s, 1.5H), 3.70 (s, 1.5H), 3.31 (ttd, \(J = 9.7, 5.3, 4.8, 1.0 \text{ Hz, 0.5H}\)), 3.26-3.10 (m, 0.5H), 2.92-2.73 (m, 2H), 2.63-2.50 (m, 2H).

To a suspension of NaH (65% in mineral oil, 3.94 g, 98.4 mmol, 1.05 eq.) in THF (80 mL) was added a solution of methyl 3-chlorocyclobutanecarboxylate (13.9 g, 93.6 mmol, 1.0 eq.) in THF (20 mL) dropwise. The reaction was heated to reflux and stirred for 3 h. The mixture was then cooled to rt, diluted with Et\(_2\)O (200 mL) washed with water (100 mL), brine (100 mL) and dried with anhydrous MgSO\(_4\). The organic phase was filtered and evaporated to yield a yellow oil. The oil was purified by distillation (39-41 °C, 13.0 mbar) to afford S7 as a colourless oil (6.15 g, 50.4 mmol, 59%). Data identical to literature values.³

\(^1\text{H NMR} (400 \text{ MHz, Chloroform-}d)\): \(\delta\) 3.69 (s, 3H), 2.35 (dt, \(J = 3.5, 1.0 \text{ Hz, 2H}\)), 2.07 (tt, \(J = 3.5, 2.8 \text{ Hz, 1H}\)), 1.14 (dt, \(J = 2.8, 1.0 \text{ Hz, 2H}\))

\(^{13}\text{C NMR} (101 \text{ MHz, Chloroform-}d)\): \(\delta\) 173.6, 52.0, 35.6, 16.5, 9.0

³
Tert-butyl bicyclo[1.1.0]butane-1-carboxylate, 8d

To a solution of S7 (1.00 g, 8.92 mmol, 1.0 eq.) in Et₂O (100 mL) was added t-BuOK (2.00 g, 17.8 mmol, 2.0 eq.). The mixture was stirred for 10 min before filtering through a thin alumina bed and concentrating to yield 8d as a clear oil (1.05 g, 6.81 mmol, 78%). Data identical to literature values.⁴

¹H NMR (400 MHz, Chloroform-d): δ 2.29 (dt, J = 3.4, 1.0 Hz, 2H), 1.97 (tt, J = 3.4, 2.8 Hz, 1H), 1.45 (s, 9H), 1.07 (dt, J = 2.8, 0.9 Hz, 2H)

¹³C NMR (101 MHz, Chloroform-d): δ 172.2, 80.5, 35.5, 28.3, 15.9, 10.2
1.4 Deprotonation screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>BCB</th>
<th>conditions</th>
<th>Base equiv.</th>
<th>d-8 (Conversion, %)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>n-BuLi, -78 °C, 5 min</td>
<td>1.10</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>PhLi, -78 °C, 0.5 h</td>
<td>1.10</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>LiTMP, -78 °C, 2.0 h</td>
<td>2.00</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>8a</td>
<td>LDA, -78 °C, 2.0 h</td>
<td>2.00</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>8b</td>
<td>LiTMP, 0 °C, 2 h</td>
<td>3.00</td>
<td>72(^b)</td>
</tr>
<tr>
<td>6</td>
<td>8b</td>
<td>LiTMP, -78 °C, 5.5 h</td>
<td>3.00</td>
<td>65(^b)</td>
</tr>
<tr>
<td>7</td>
<td>8b</td>
<td>LDA, -78 °C, 3 h</td>
<td>3.00</td>
<td>75(^b)</td>
</tr>
<tr>
<td>8</td>
<td>8c</td>
<td>PhLi, -78 °C, 0.5 h</td>
<td>1.10</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>8c</td>
<td>n-BuLi, -78 °C, 0.5 h</td>
<td>1.10</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>8c</td>
<td>s-BuLi, -78 °C, 0.5 h</td>
<td>1.10</td>
<td>23</td>
</tr>
<tr>
<td>11</td>
<td>8c</td>
<td>t-BuLi, -78 °C, 0.5 h</td>
<td>1.10</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>8d</td>
<td>ZnCl(_2), then LiTMP, -78 °C(^5)</td>
<td>1.10</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>8d</td>
<td>TMP(_2)Mg, LiCl, 0 °C to rt(^6)</td>
<td>1.10</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>8d</td>
<td>n-BuLi, -78 °C, 5 min</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>8d</td>
<td>t-BuLi, -78 °C, 5 min</td>
<td>1.00</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 1.** \(^a\) Reactions conducted on 0.1 mmol scale, quenched with D\(_2\)O at the indicated temperature; \(^b\) Conversion based on ratio of d-8 as determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture; \(^c\) Conversion as judged by integration of C3 in 8b vs. C2/C4 integration of 8b, 8b and 9 in the \(^1\)H NMR spectrum of the crude reaction mixture; analysis complicated by diastereomers of 9; \(^d\) n.r. = no reaction; \(^e\) 1:1 mixture of 8d and 10.
1.5 Coupling screen

![Chemical diagram](image)

Table 2. a Cross-couplings run on 0.1 mmol scale with 1.0 equiv. of PhI; b Isolated yields. Values in parentheses indicate conversion based on the ratio of 11 to 8a and 12 as determined by 1H NMR spectroscopic analysis of the crude reaction mixture; c 10 mol% catalyst; d n.d. = not determined; e 2.0 eq. of PhI; f 0.25 mmol scale using 8a (1.2 eq.), PhLi (1.2 eq.) and PhI (1.0 eq.). tfp = 2-trifurylphosphine. rt = room temperature.
1.6 Synthesis of disubstituted BCBs

General BCB Cross-coupling Procedure

To a solution of BCB (0.30 mmol, 1.2 eq.) in THF (0.40 mL) was added PhLi (1.6-1.8 M in n-Bu₂O, 0.19-0.17 mL, 1.2 eq.) dropwise at –78 °C. The mixture was stirred for 30 min, then a solution of ZnCl₂ (41 mg, 0.30 mmol, 1.2 eq.) in THF (0.5 mL) was added, and the reaction was stirred for 5 min at –78 °C before bringing to rt, and stirred for a further 5-10 min. The solution of organozinc was transferred via syringe to a vial containing Pd(dba)₂ (7.5 mg, 13.0 µmol, 5 mol%), trifurylphosphine (tfp, 5.8 mg, 25.0 µmol, 10 mol%) and the coupling partner A (0.25 mmol, 1.0 eq.). The reaction mixture was stirred for 1 d at 40 °C, then it was diluted with DCM or Et₂O (5 mL), washed with water (5 mL), dried with anhydrous MgSO₄ and filtered. The filtrate was evaporated in vacuo and the residue purified by flash chromatography with an appropriate gradient.

Note A: If coupling partner is a solid, or liquid with unknown density, it was added to the vial before addition of the organozinc. If the liquid had a known density it was added after addition of the organozinc.

Note B: Compounds found to readily isomerise to their respective cyclobutenes should be chromatographed on neutralised silica (1% NEt₃ with eluting solvent) and analysed (NMR) in benzene-d₆. Such compounds include: 18, 19, 20, 22, 24, 26, (E/Z)-29, 37, 39, 40, 42 and 45.

Note C: If column chromatography does not afford sufficient purity, trituration with Et₂O was found to be effective at further purifying products. Crystallisations were also performed by layering Et₂O solutions of BCBs with pentane, or heating and cooling BCB solutions in Et₂O.

1-Phenyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 11

Prepared according to the general procedure using iodobenzene (28 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20-40% Et₂O in pentane), and isolated as a colourless solid (66 mg, 0.24 mmol, 98%).

Large scale: 8a (1.70 g, 8.76 mmol, 1.20 eq.), PhLi (1.8 M in n-Bu₂O, 4.87 mL, 8.76 mmol, 1.20 eq.), ZnCl₂ (1.19 g, 8.76 mmol, 1.20 eq.), Pd(dba)₂ (0.21 g, 0.38 mmol, 5 mol%), tfp (0.17 g, 0.73 mmol, 10 mol%) and iodobenzene (0.82 mL, 7.30 mmol, 1.0 eq.) afforded 11 as a light yellow solid (1.89 g, 7.00 mmol, 96%).

Rf = 0.28 (40% Et₂O in pentane)

MP: 119 °C (recrystallized from Et₂O)

IR (thin film, νmax / cm⁻¹): 3061, 2924, 2852, 1483, 1306, 1147, 879, 760, 727, 691, 624
**HRMS** (ESI⁺) calc. for C₁₆H₁₄O₂²³Na²²⁵S [M+Na]⁺ 293.0607, found 293.0608

**¹H NMR** (400 MHz, Chloroform-d): δ 8.19 (d, J = 8.9 Hz, 2H), 7.75 (d, J = 8.5, 1.2 Hz, 1H), 7.61 (tt, J = 7.5, 1.2 Hz, 2H), 7.35-7.23 (m, 5H), 2.90 (s, 2H), 1.66 (s, 2H)

**¹³C NMR** (101 MHz, Chloroform-d): δ 140.3, 133.2, 130.5, 129.0, 128.6, 127.6, 127.5, 127.1, 35.5, 34.8, 31.0

**1-(4-Nitrophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 13**

![Chemical structure](image)

Prepared according to the general procedure using 1-iodo-4-nitrobenzene (62 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by trituration with Et₂O, and isolated as an off-white solid (63 mg, 0.20 mmol, 80%).

**MP**: 180 °C (recrystallized from DCM/Et₂O)

**IR** (thin film, νmax / cm⁻¹): 1598, 1510, 1342, 1296, 1143, 878, 855, 758, 691, 634

**HRMS** (ESI⁺) calc. for C₁₆H₁₄O₂²³Na²²⁵S [M+H]⁺ 32, 316.0638, found 316.0639

**¹H NMR** (400 MHz, Chloroform-d): δ 8.19 (d, J = 8.9 Hz, 2H), 7.75 (dd, J = 8.4, 1.3 Hz, 2H), 7.61 (tt, J = 7.5, 1.2 Hz, 1H), 7.53-7.46 (m, 4H), 3.06 (s, 2H), 1.80 (s, 2H)

**¹³C NMR** (101 MHz, Chloroform-d): δ 147.2, 140.7, 139.3, 133.7, 129.3, 127.9, 127.5, 123.9, 37.1, 36.8, 30.1

**Methyl 4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzoate, 14**

![Chemical structure](image)

Prepared according to the general procedure using methyl 4-iodobenzoate (58 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% Et₂O in pentane), and isolated as a colourless solid (64 mg, 0.20 mmol, 78%).

**Rf**: 0.19 (50% Et₂O in pentane)

**MP**: 141 °C (recrystallized from Et₂O)

**IR** (thin film, νmax / cm⁻¹): 3062, 2951, 1718, 1609, 1279, 1253, 1118, 858, 773, 729, 629
HRMS (ESI+) calc. for C_{18}H_{17}O_{3}S [M+Na]^+ 329.0842, found 329.0842

^1^H NMR (400 MHz, Chloroform-d): δ 7.96 (d, J = 8.5 Hz, 2H), 7.64 (dd, J = 8.4, 1.3 Hz, 1H), 7.54 (tt, J = 7.5, 1.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 3.91 (s, 3H), 2.96 (s, 2H), 1.71 (s, 2H)

^13^C NMR (101 MHz, Chloroform-d): δ 166.8, 140.2, 136.3, 133.4, 129.8, 129.1, 127.6, 127.0, 52.2, 36.2, 36.0, 30.4

1-(4-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenyl)ethan-1-one, 15

![Structure](image)

Prepared according to the general procedure using 1-(4-iodophenyl)ethan-1-one (62 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→40% Et_2O in pentane), and isolated as a brown solid (65 mg, 0.20 mmol, 83%).

R_f = 0.28 (40% EtOAc in pentane)

MP: 118 °C (recrystallized from Et_2O)

IR (thin film, ν_{max} / cm⁻¹): 1679, 1565, 1318, 1306, 1115, 785

HRMS (ESI+) calc. for C_{18}H_{17}O_3S [M+H]^+ 313.0893, found 313.0892

^1^H NMR (500 MHz, Chloroform-d): δ 7.91 (d, J = 8.5 Hz, 2H), 7.70 (dd, J = 8.5, 1.2 Hz, 2H), 7.58 (tt, J = 7.5, 1.2 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H) 7.41 (d, J = 8.5 Hz, 2H), 3.01 (s, 2H), 2.61 (s, 3H), 1.74 (s, 2H)

^13^C NMR (126 MHz, Chloroform-d): δ 197.6, 140.7, 136.6, 136.1, 133.4, 129.2, 128.6, 127.5, 127.2, 36.3, 36.3, 30.6, 26.8

1-(4-Fluorophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 16

![Structure](image)

Prepared according to the general procedure using 1-fluoro-4-iodobenzene (29 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et_2O in pentane), and isolated as a colourless solid (66 mg, 0.23 mmol, 91%).

R_f = 0.37 (50% Et_2O in pentane)
**MP**: 114 °C (recrystallized from Et₂O)

**IR** (thin film, ν_{max} / cm⁻¹): 1523, 1305, 1229, 1147, 883, 836, 812, 729

**HRMS** (ESI⁺) calc. for C₁₆H₁₃O₂F₂ClNa⁺ [M+Na]⁺ 311.0512, found 311.0511

\(^1\text{H NMR}\) (400 MHz, Chloroform-d): δ 7.69 (d, J = 8.4, 1.3 Hz, 2H), 7.49 (tt, J = 7.5, Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.24-7.18 (m, 2H), 7.01 (t, J = 8.7 Hz, 2H), 2.81 (t, J = 0.9 Hz, 2H), 1.59 (t, J = 0.9 Hz, 2H)

\(^{13}\text{C NMR}\) (101 MHz, Chloroform-d): δ 162.5 (d, J = 246.8 Hz), 140.7, 133.3, 129.1, 128.8 (d, J = 8.3 Hz), 127.5, 126.4 (d, J = 3.2 Hz), 115.7 (d, J = 21.9 Hz), 35.9, 34.2, 30.7

\(^{19}\text{F NMR}\) (376 MHz, Chloroform-d) δ -114.5

1-(4-Chlorophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 17

Prepared according to the general procedure using 1-chloro-4-iodobenzene (60 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et₂O in pentane), and isolated as a colourless solid (63 mg, 0.21 mmol, 89%).

\(R_f\) = 0.32 (50% Et₂O in pentane)

**MP**: 91 °C (recrystallized from Et₂O)

**IR** (thin film, ν_{max} / cm⁻¹): 1317, 1147, 879, 883, 631

**HRMS** (ESI⁺) calc. for C₁₆H₁₄O₂ClS [M+H]⁺ 305.0398, found 305.0399

\(^1\text{H NMR}\) (400 MHz, Chloroform-d): δ 7.71 (dd, J = 8.5, 1.2 Hz, 2H), 7.6 (tt, J = 7.5, 1.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 8.7 Hz, 2H) 7.27 (t, J = 8.7 Hz, 2H), 2.93 (s, 2H), 1.71 (s, 2H)

\(^{13}\text{C NMR}\) (101 MHz, Chloroform-d): δ 140.6, 133.7, 133.3, 129.3, 129.1, 128.8, 128.4, 127.5, 35.9, 34.9, 30.5
1-(Phenylsulfonyl)-3-(p-tolyl)bicyclo[1.1.0]butane, 18

![Chemical Structure]

Prepared according to the general procedure using 1-iodo-4-methylbenzene (55 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et₂O in pentane), and isolated as a colourless solid (65 mg, 0.23 mmol, 91%).

\[ R_f = 0.28 \text{ (40\% Et}_2\text{O in pentane)} \]

\[ \text{MP: } 86^\circ \text{C (recrystallized from Et}_2\text{O)} \]

\[ \text{IR (thin film, } \nu_{\text{max}} / \text{cm}^{-1}: 3064, 2921, 1446, 1305, 1111, 882, 728, 689, 627 \]

\[ \text{HRMS (ESI\(^+\)) calc. for C}_{17}\text{H}_{17}\text{O}_2\text{S} [M+H]\^+ 285.0944, \text{found 285.0946} \]

\[ ^1\text{H NMR (400 MHz, Chloroform-}d\text{: } \delta 7.66 (dd, } J = 8.5, 1.2 \text{ Hz, 2H), 7.54 (tt, } J = 7.5, 1.2 \text{ Hz, 1H), 7.40 (t, } J = 7.8 \text{ Hz, 2H), 7.19 (d, } J = 8.3 \text{ Hz, 2H), 7.11 (d, } J = 8.0 \text{ Hz, 2H), 2.90 (s, 2H), 2.35 (s, 3H), 1.64 (s, 2H) } \]

\[ ^{13}\text{C NMR (101 MHz, Chloroform-}d\text{: } \delta 142.0, 137.4, 133.1, 129.4, 129.0, 127.5, 127.3, 127.0, 35.7, 34.3, 31.3, 21.3 \]

1-(4-Methoxyphenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 19

![Chemical Structure]

Prepared according to the general procedure using 1-iodo-4-methoxybenzene (59 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et₂O in pentane, 1% NEt₃), and isolated as a colourless solid (53 mg, 0.17 mmol, 70%).

\[ R_f = 0.21 \text{ (50\% Et}_2\text{O in pentane)} \]

\[ \text{MP: } 100^\circ \text{C (recrystallized from Et}_2\text{O)} \]

\[ \text{IR (thin film, } \nu_{\text{max}} / \text{cm}^{-1}: 2962, 1304, 1248, 1146, 883, 758 \]

\[ \text{HRMS (ESI\(^+\)) calc. for C}_{17}\text{H}_{16}\text{O}_3\text{S} [M+Na]\^+ 323.10712, \text{found 323.0713} \]

\[ ^1\text{H NMR (500 MHz, Benzene-}d\text{: } \delta 7.84 (d, } J = 6.9 \text{ Hz, 2H), 7.30 (d, } J = 8.8 \text{ Hz, 2H), 7.00 (m, 1H), 6.97 (m, 2H), 6.81 (d, } J = 8.8 \text{ Hz, 2H) 3.38 (s, 3H), 2.80 (s, 2H), 1.18 (s, 2H) } \]

\[ ^{13}\text{C NMR (126 MHz, Benzene-}d\text{: } \delta 159.4, 142.2, 132.1, 128.5, 128.5, 127.3, 122.4, 114.0, 54.4, 35.3, 33.5, 31.0 \]

S17
1-(3-Bromophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 20

Prepared according to the general procedure using 1-bromo-3-iodobenzene (32 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et₂O in pentane), and isolated as a colourless solid (78 mg, 0.22 mmol, 89%).

R_f = 0.30 (50% Et₂O in pentane)

**MP**: 148 °C (recrystallized from Et₂O)

**IR** (thin film, ν_{max} / cm⁻¹): 1318, 1148, 887, 782, 687, 625

**HRMS** (ESI⁺) calc. for C_{16}H_{14}O_2BrS [M+H]^+ 348.9892, found 348.9894

**¹H NMR** (500 MHz, Benzene-d): δ 7.59 (dd, J = 8.3, 1.3 Hz, 2H), 7.25 (t, J = 1.8 Hz, 1H), 7.11 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.00 (ddd, J = 7.8, 1.7, 0.9 Hz, 1H), 6.93 (t, J = 7.5, 1.3 Hz, 1H), 6.83 (t, J = 8.0 Hz, 2H), 6.66 (t, J = 7.9 Hz, 1H), 2.48 (s, 2H), 0.93 (s, 2H)

**¹³C NMR** (126 MHz, Benzene-d): δ 141.3, 133.8, 132.9, 130.5, 130.4, 130.1, 128.9, 127.6, 125.8, 122.8, 35.6, 35.4, 29.6

3-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenyl trifluoromethanesulfonate, 21

Prepared according to the general procedure using 3-iodophenyl trifluoromethanesulfonate S8 (88 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% Et₂O in pentane), and isolated as a yellow solid (84 mg, 0.20 mmol, 80%).

R_f = 0.24 (50% Et₂O in pentane)

**MP**: 78 °C (recrystallized from Et₂O)

**IR** (thin film, ν_{max} / cm⁻¹): 1422, 1209, 1139, 931, 871, 802, 782, 652, 625

**HRMS** (ESI⁺) calc. for C_{17}H_{14}F_2O_5S_2 [M+H]^+ 419.0229, found 419.0230

**¹H NMR** (500 MHz, Chloroform-d): δ 7.70 (dd, J = 8.5, 1.2 Hz, 2H), 7.58 (tt, J = 7.5, 1.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.36 (dt, J = 7.9, 1.3 Hz, 1H) 7.22-7.16 (m, 2H), 2.93 (s, 2H), 1.73 (s, 2H)
$^{13}$C NMR (126 MHz, Chloroform-d): $\delta$ 149.6, 140.2, 134.2, 133.4, 130.3, 129.1, 127.4, 126.9, 120.2, 120.1, 118.7 (q, $J = 320.9$ Hz), 36.0, 35.7, 29.8

_Tert-butyl(dimethyl)silyl(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenoxy)silane, 22_

Prepared according to the general procedure using _tert-butyl_(3-iodophenoxy)dimethylsilane _S9_ (84 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (10–30% Et$_2$O in pentane), and isolated as a colourless solid (91 mg, 0.23 mmol, 91%).

$R_f = 0.47$ (50% Et$_2$O in pentane)

**MP:** 52 °C (recrystallized from Et$_2$O)

**IR** (thin film, $v_{\text{max}}$ / cm$^{-1}$): 2956, 2929, 2857, 1601, 1581, 1307, 1253, 1113, 959, 877, 783

**HRMS** (ESI$^+$) calc. for C$_{22}$H$_{29}$O$_3$Si [M+H]$^+$ 401.1601, found 401.1597

$^1$H NMR (500 MHz, Benzene-d$_6$): $\delta$ 7.72-7.68 (d, $J = 7.1$ 2H), 7.09 (t, $J = 2.1$ Hz, 1H), 7.00 (t, $J = 7.9$ Hz, 1H), 6.96-6.84 (m, 4H), 6.78 (ddd, $J = 8.1$, 2.4, 1.0 Hz, 1H), 2.67 (s, 2H), 1.02 (s, 9H), 0.21 (s, 6H)

$^{13}$C NMR (126 MHz, Benzene-d$_6$): $\delta$ 156.2, 142.2, 132.9, 132.6, 129.7, 128.9, 127.7, 121.1, 119.7, 119.4, 35.7, 34.8, 30.8, 25.9, 18.4, -4.2

_1-(Phenylsulfonyl)-3-(2-(trifluoromethyl)phenyl)bicyclo[1.1.0]butane, 23_

Prepared according to the general procedure using _1-iodo-2-(trifluoromethyl)benzene_ (35 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (10–30% Et$_2$O in pentane), and isolated as a colourless solid (43 mg, 0.13 mmol, 51%).

$R_f = 0.47$ (50% Et$_2$O in pentane)

**MP:** 78 °C (recrystallized from Et$_2$O)

**IR** (thin film, $v_{\text{max}}$ / cm$^{-1}$): 1315, 1149, 1127, 1102, 1048, 887, 770, 755, 647

**HRMS** (ESI$^+$) calc. for C$_{17}$H$_{13}$O$_2$F$_3$NaS [M+Na]$^+$ 361.0481, found 361.0480
**1H NMR** (500 MHz, Chloroform-\(d\)): δ 8.01 (d, \(J = 7.9\) Hz, 1H), 7.94 (dd, \(J = 7.1, 1.5\) Hz, 2H), 7.71 (d, \(J = 8.1\) Hz, 1H), 7.64 (tt, \(J = 7.5, 1.3\) Hz, 1H), 7.62-7.53 (m, 3H), 7.44 (t, \(J = 1.1\) Hz, 1H), 2.64 (s, 2H), 1.64 (s, 2H).

**13C NMR** (101 MHz, Chloroform-\(d\)): δ 141.9, 133.5, 132.3, 131.7 (q, \(J = 30.5\) Hz), 130.5, 130.3, 129.4, 128.2, 127.4, 126.5 (q, \(J = 5.5\) Hz), 124.4 (q, \(J = 273.7\) Hz), 34.0, 33.8, 30.9.

**1F NMR** (471 MHz, Chloroform-\(d\)): δ -58.78

1-(Phenylsulfonyl)-3-(o-toly)bicyclo[1.1.0]butane, 24

Prepared according to the general procedure using 1-iodo-2-methylbenzene (32 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et\(_2\)O in pentane), and isolated as a colourless solid (57 mg, 0.20 mmol, 80%).

\(R_f = 0.35\) (50% Et\(_2\)O in pentane)

**MP:** 102 °C (recrystallized from Et\(_2\)O)

**IR** (thin film, \(\nu_{\text{max}} / \text{cm}^{-1}\)): 1317, 1147, 888, 798, 758, 689, 629

**HRMS** (ESI\(^+\)) calc. for C\(_{17}\)H\(_{17}\)O\(_2\)S [M+H\(^+\)]\(^+\) 285.0944, found 285.0944

**1H NMR** (400 MHz, Chloroform-\(d\)): δ 7.89 (dd, \(J = 7.8, 1.4\) Hz, 2H), 7.67-7.63 (m, 1H), 7.61 (tt, \(J = 7.4, 1.2\) Hz, 1H), 7.52 (t, \(J = 7.5\) Hz, 2H), 7.24-7.15 (m, 3H), 2.64 (s, 2H), 2.40 (s, 3H), 1.63 (s, 2H).

**13C NMR** (101 MHz, Chloroform-\(d\)): δ 141.9, 139.1, 133.2, 130.7, 129.5, 129.2, 128.6, 128.0, 127.4, 126.4, 39.1, 33.6, 31.4, 20.7

2-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzonitrile, 25

Prepared according to the general procedure using 2-iodobenzonitrile (57 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et\(_2\)O in pentane), and isolated as a colourless solid (71 mg, 0.24 mmol, 96%).

\(R_f = 0.32\) (50% Et\(_2\)O in pentane)

**MP:** 138 °C (recrystallized from Et\(_2\)O)
IR (thin film, ν<sub>max</sub> / cm<sup>-1</sup>): 2224, 1319, 1148, 883, 759, 725, 689, 626

HRMS (ESI<sup>+</sup>) calc. for C<sub>17</sub>H<sub>14</sub>O<sub>2</sub>NaS [M+H]<sup>+</sup> 296.0740, found 296.0738

<sup>1</sup>H NMR (500 MHz, Chloroform-d): δ 7.83 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.67-7.62 (m, 2H), 7.60 (td, J = 7.8, 1.4 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 3.06 (s, 2H), 1.86 (s, 2H)

<sup>13</sup>C NMR (126 MHz, Chloroform-d): δ 141.1, 135.5, 133.9, 133.7, 132.8, 129.4, 128.5, 128.1, 127.5, 118.3, 113.7, 39.1, 36.3, 29.1

1-(4-Bromo-2-fluorophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 26

Prepared according to the general procedure using 4-bromo-2-fluoro-1-iodobenzene (75 mg, 0.25 mmol, 1.0 eq.) as a coupling partner. The title compound was purified by flash chromatography (20→30% Et<sub>2</sub>O in pentane), and isolated as colourless solid (75 mg, 0.20 mmol, 82%).

<sup>1</sup>H NMR (500 MHz, Benzene-d): δ 7.74-7.70 (d, J = 7.1 Hz 2H), 6.96-6.89 (m, 2H), 6.88-6.84 (m, 4H), 2.72 (s, 2H), 1.04 (s, 2H)

<sup>13</sup>C NMR (126 MHz, Benzene-d): δ 161.5 (d, J = 253.2 Hz), 141.8, 132.5, 130.7, 128.7, 127.3 (d, J = 3.6 Hz), 127.2, 121.2 (d, J = 9.5 Hz), 119.5 (d, J = 25.4 Hz), 118.1 (d, J = 12.0 Hz), 37.3, 34.0, 25.5

19F NMR (470 MHz, Benzene-d): δ -111.9

1-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)naphthalene, 27

Prepared according to the general procedure using 1-iodonaphthalene (37 µl, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et<sub>2</sub>O in pentane), and isolated as a colourless solid (63 mg, 0.20 mmol, 82%).
\[ R_f = 0.31 \text{ (50\% Et}_2\text{O in pentane)} \]

**MP:** 121 °C (recrystallized from Et\(_2\)O)

**IR** (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)): 3062, 1317, 1149, 801, 729, 625

**HRMS** (ESI\(^+\)) calc. for C\(_{20}\)H\(_{17}\)O\(_2\)S \([\text{M+Na}]^+\) 321.0944, found 321.0942

**\(^1\)H NMR** (500 MHz, Chloroform-d): \( \delta 8.20-8.18 \text{ (m, 1H)}, \ 8.01 \text{ (dd, } J = 7.2, 1.2 \text{ Hz, 1H)}, \ 7.96 \text{ (d, } J = 7.2 \text{ Hz, 2H)}, \ 7.91-7.87 \text{ (m, 1H)}, \ 7.85 \text{ (d, } J = 8.3 \text{ Hz, 1H)}, \ 7.62 \text{ (tt, } J = 7.5, 1.2 \text{ Hz, 1H)}, \ 7.57-7.48 \text{ (m, 5H)}, \ 2.75 \text{ (s, 2H)}, \ 1.84 \text{ (s, 2H)} \)

**\(^{13}\)C NMR** (126 MHz, Chloroform-d): \( \delta 142.2, 134.5, 133.9, 133.3, 129.3, 128.9, 128.6, 127.7, 127.4, 126.6, 126.3, 125.9, 125.8, 124.7, 40.0, 33.3, 31.2 \)

**Ethyl (Z)-3-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)acrylate, 28**

Prepared according to the general procedure using ethyl (Z)-3-iodoacrylate (32 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40\% Et\(_2\)O in pentane), and isolated as a green-yellow oil (40 mg, 0.13 mmol, 54%).

\[ R_f = 0.29 \text{ (50\% Et}_2\text{O in pentane)} \]

**IR** (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)): 1719, 1638, 1318, 1217, 1149, 1147, 909, 735, 690, 615

**HRMS** (ESI\(^+\)) calc. for C\(_{15}\)H\(_{17}\)O\(_4\)S \([\text{M+H}]^+\) 293.0842, found 293.0841

**\(^1\)H NMR** (500 MHz, Chloroform-d): \( \delta 7.94 \text{ (d, } J = 7.1 \text{ Hz, 2H)}, \ 7.66 \text{ (tt, } J = 7.5, 1.2 \text{ Hz 1H)}, \ 7.59 \text{ (t, } J = 7.6 \text{ Hz, 2H)}, \ 6.57 \text{ (d, } J = 11.4 \text{ Hz, 1H)}, \ 6.15 \text{ (d, } J = 11.4 \text{ Hz, 1H)}, \ 4.21 \text{ (q, } J = 7.1 \text{ Hz, 2H)}, \ 2.84 \text{ (s, 2H)}, \ 1.89 \text{ (s, 2H)}, \ 1.32 \text{ (t, } J = 7.1 \text{ Hz, 3H)} \)

**\(^{13}\)C NMR** (126 MHz, Chloroform-d): \( \delta 165.4, 141.6, 137.8, 133.6, 129.2, 127.3, 125.1, 60.3, 41.8, 35.2, 28.4, 14.2 \)

**(E)-1-(Oct-1-en-1-yl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, (E)-29**

Prepared according to the general procedure using (E)-1-iodooct-1-ene (58 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (10→30\% Et\(_2\)O in pentane), and isolated as a yellow oil (46 mg, 0.15 mmol, 61%).
\( R_f = 0.5 \) (40 \% Et\(_2\)O in pentane)

IR (thin film, \( \nu_{\text{max}} \) / cm\(^{-1}\)): 2926, 1317, 1146, 623

HRMS (ESI\(^+\)) calc. for C\(_{18}\)H\(_{24}\)O\(_2\)Na\(_2\) [M+Na\(^+\)]\(^{2+}\) 327.1388, found 327.1390

\(^1\)H NMR (400 MHz, Benzene-\( d_6 \)): \( \delta \) 7.96-7.86 (m, 2H), 7.00-6.88 (m, 3H), 5.92 (d, \( J = 15.1 \) Hz, 1H), 5.78 (dt, \( J = 15.0, 6.9 \) Hz, 1H), 2.54 (s, 2H), 1.99 (q, \( J = 7.2 \) Hz, 2H), 1.40-1.16 (m, 8H), 1.00 (s, 2H), 0.91 (t, \( J = 7.1 \) Hz, 3H)

\(^{13}\)C NMR (126 MHz, Benzene-\( d_6 \)): \( \delta \) 143.3, 136.2, 132.1, 128.8, 127.2, 120.6, 37.2, 32.6, 31.7, 31.1, 29.5, 29.1, 28.8, 22.7, 14.0

\((Z)-1\)-(Oct-1-en-1-yl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, (Z)-29

Prepared according to the general procedure using (Z)-1-iodooct-1-ene \( S10 \) (58 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (10\( \rightarrow \)30\% Et\(_2\)O in pentane), and isolated as a yellow oil (56 mg, 0.18 mmol, 74\%).

\( R_f = 0.5 \) (40 \% Et\(_2\)O in pentane)

IR (thin film, \( \nu_{\text{max}} \) / cm\(^{-1}\)): 2926, 1316, 1146, 622

HRMS (ESI\(^+\)) calc. for C\(_{18}\)H\(_{24}\)O\(_2\)Na\(_2\) [M+Na\(^+\)]\(^{2+}\) 327.1389, found 327.1390

\(^1\)H NMR (500 MHz, Benzene-\( d_6 \)): \( \delta \) 7.94-7.88 (m, 2H), 6.97-6.93 (m, 3H), 5.98 (d, \( J = 10.9 \) Hz, 1H), 5.67 (dt, \( J = 10.8, 7.5 \) Hz, 1H), 2.54 (s, 2H), 2.17 (qd, \( J = 7.5, 1.6 \) Hz, 2H), 1.35-1.16 (m, 8H), 1.13 (s, 2H), 0.89 (t, \( J = 7.1 \) Hz, 3H)

\(^{13}\)C NMR (126 MHz, Benzene-\( d_6 \)): \( \delta \) 143.6, 137.5, 132.6, 128.7, 127.4, 119.9, 39.8, 32.1, 30.1, 29.4, 29.2, 28.4, 27.9, 23.0, 14.3

1,3-Dimethyl-5-(3-(phenylsulfonyl)cyclobut-1-en-1-yl)pyrimidine-2,4(1H,3H)-dione, 30

Prepared according to the general procedure using 5-iodo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (67 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (80\( \rightarrow \)100\% EtOAc in pentane), and isolated as a colourless oil (43 mg, 0.13 mmol, 53%).
$R_f = 0.28$ (EtOAc)

IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 1706, 1664, 1598, 1446, 1303, 1146, 726

HRMS (ESI$^+$) calc. for C$_{16}$H$_{17}$O$_2$SN$_2$ [M+H]$^+$ 333.0904, found 333.0903

$^1$H NMR (500 MHz, Chloroform-$d$): 6 7.92 (d, $J = 7.9$ Hz, 2H), 7.66 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.56 (t, $J = 7.8$ Hz, 2H), 7.12 (s, 1H), 6.24 (d, $J = 1.1$ Hz, 1H), 4.33 (dt, $J = 4.6$, 1.4 Hz, 1H), 3.45 (s, 3H), 3.35 (s, 3H), 3.07 (dd, $J = 13.2$, 1.7 Hz, 1H), 2.93 (dd, $J = 13.2$, 4.5 Hz, 1H)

$^{13}$C NMR (126 MHz, Chloroform-$d$): δ 161.2, 151.1, 142.7, 140.1, 138.1, 133.9, 129.4, 128.7, 124.4, 108.0, 61.7, 37.6, 30.0, 28.0

4-((3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)ethynyl)benzonitrile, 31

Prepared according to the general procedure using 4-(iodoethyl)benzonitrile $S_{11}$ (80 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% Et$_2$O in pentane), and isolated as a yellow solid (14 mg, 0.04 mmol, 17%).

$R_f = 0.25$ (50% Et$_2$O in pentane)

MP: 148 °C (recrystallized from Et$_2$O)

IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 2852, 2226, 1603, 1500, 1318, 1146, 1106, 837, 754, 629

HRMS (ESI$^+$) calc. for C$_{19}$H$_{13}$O$_2$NNaS [M+Na]$^+$ 342.0559, found 342.0557

$^1$H NMR (500 MHz, Chloroform-$d$): 6 7.96 (d, $J = 7.1$ Hz, 2H), 7.67-7.62 (m, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 2.75 (s, 2H), 1.75 (s, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$): δ 140.3, 133.8, 132.6, 132.1, 129.3, 127.9, 127.6, 118.6, 111.9, 86.2, 83.1, 41.3, 33.7, 16.0
2-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)pyridine, 32

Prepared according to the general procedure using 2-iodopyridine (27 μL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (40→70% EtOAc in pentane), and isolated as a yellow solid (67 mg, 0.25 mmol, 99%).

R_f = 0.13 (50% EtOAc in pentane)

MP: 118 °C (recrystallized from Et_2O/EtOAc)

IR (thin film, ν_max / cm⁻¹): 1588, 1318, 1149, 878, 784, 729, 628

HRMS (ESI⁺) calc. for C_{15}H_{14}O_2NS [M+H]^+ 272.0740, found 272.0740

¹H NMR (400 MHz, Chloroform-d): δ 8.50 (dd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.69-7.63 (m, 3H), 7.58 (tt, J = 7.4, 1.2 Hz, 1H), 7.46-7.41 (t, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 7.5, 4.8, 1.1 Hz, 1H), 3.21 (s, 2H), 1.80 (s, 2H)

¹³C NMR (101 MHz, Chloroform-d): δ 151.4, 149.7, 140.4, 136.4, 133.3, 129.1, 127.6, 122.1, 121.5, 36.5, 36.3, 31.8

3-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)pyridine, 33

Prepared according to the general procedure using 3-iodopyridine (51 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et_2OAc in pentane), and isolated as a colourless solid (63 mg, 0.23 mmol, 93%).

R_f = 0.08 (50% Et_2O in pentane)

MP: 121 °C (recrystallized from Et_2O/EtOAc)

IR (thin film, ν_max / cm⁻¹): 1317, 1147, 879, 730, 630

HRMS (ESI⁺) calc. for C_{15}H_{14}O_2NS [M+H]^+ 272.0740, Found 272.0742

¹H NMR (400 MHz, Chloroform-d): δ 8.54 (dd, J = 4.8, 1.6 Hz, 1H), 8.51 (dd, J = 2.4, 0.8 Hz, 1H), 7.72-7.67 (m, 3H), 7.59 (tt, J = 7.5, 1.2, 1H), 7.46 (t, J = 7.4, 2H), 7.26 (dd, J = 8.1, 4.8 Hz, 1H), 2.97 (s, 2H), 1.73 (s, 2H)
13C NMR (101 MHz, Chloroform-d): δ 148.8, 148.6, 140.5, 134.2, 133.6, 129.2, 127.5, 127.1, 123.3, 36.0, 34.6, 28.4

4-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)pyridine, 34

Prepared according to the general procedure using 4-iodopyridine (51 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by trituration with Et2O, and isolated as a light-yellow solid (64 mg, 0.24 mmol, 95%).

MP: 160 °C (recrystallized from DCM/Et2O)

IR (thin film, νmax / cm⁻¹): 1599, 1307, 1148, 879, 879, 728, 624

HRMS (ESI⁺) calc. for C₁₅H₁₄O₂NS [M+H⁺] 272.0740, found 272.0739

1H NMR (400 MHz, Chloroform-d): δ 8.52 (d, J = 4.6, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.59 (tt, J = 7.5, 1.2, 1H), 7.46 (t, J = 7.9 Hz, 2H), 7.21-7.16 (d, J = 4.6, 2H), 2.98 (s, 2H), 1.74 (s, 2H)

13C NMR (101 MHz, Chloroform-d): δ 149.8, 140.7, 140.1, 133.6, 129.3, 127.5, 121.9, 37.0, 36.0, 28.9

7-Chloro-4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)quinolone, 35

Prepared according to the general procedure using 7-chloro-4-iodoquinoline (72 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% EtOAc in pentane), and isolated as an off-white solid (70 mg, 0.21 mmol, 83%).

Rf = 0.14 (50% Et2O in pentane)

MP: 168 °C (recrystallized from Et2O/EtOAc)

IR (thin film, νmax / cm⁻¹): 1582, 1319, 1143, 1080, 865, 730, 615

HRMS (ESI⁺) calc. for C₁₉H₁₅O₂NCIS [M+H⁺] 356.0507 and 358.0476, found 356.0510 and 358.0480
**1H NMR** (400 MHz, Chloroform-\(d\)): \(\delta\) 8.91 (d, \(J = 4.6\) Hz, 1H), 8.15 (d, \(J = 2.2\) Hz, 1H), 8.13 (d, \(J = 9.0\) Hz, 1H), 7.92-7.88 (m, 2H), 7.81 (d, \(J = 4.6\) Hz, 1H), 7.63 (tt, \(J = 7.5, 1.3\) Hz, 1H), 7.54 (t, \(J = 7.9\) Hz, 2H), 7.52 (dd, \(J = 9.10, 2.2\) Hz, 1H) 2.90 (s, 2H), 1.93 (s, 2H)

**13C NMR** (101 MHz, Chloroform-\(d\)): \(\delta\) 151.2, 149.2, 141.7, 138.3, 135.5, 133.7, 129.5, 129.4, 127.9, 127.7, 127.5, 125.9, 120.6, 40.1, 34.9, 28.0

1-(3-(Phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)isoquinoline, 36

![Structure](image1)

Prepared according to the general procedure using 1-iodoisoquinoline (64 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% EtOAc in pentane), and isolated as an off-white solid (31 mg, 0.09 mmol, 38%).

**R<sub>f</sub>** = 0.15 (50% Et<sub>2</sub>O in pentane)

**MP**: 169 °C (recrystallized from Et<sub>2</sub>O)

**IR** (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)): 1320, 1153, 893, 818, 727, 686, 625

**HRMS** (ESI\(^{+}\)) calc. for C<sub>19</sub>H<sub>16</sub>O<sub>2</sub>N [M+H]<sup>+</sup> 322.0896, found 322.0894

**1H NMR** (500 MHz, Chloroform-\(d\)): \(\delta\) 8.48 (d, \(J = 5.6\) Hz, 1H), 8.29 (d, \(J = 8.6\) Hz, 1H), 7.82 (d, \(J = 8.3\) Hz, 1H), 7.74-7.70 (dd, \(J = 8.5, 1.3\) Hz, 2H), 7.66 (ddd, \(J = 8.1, 6.8, 1.2\) Hz, 1H), 7.58-7.53 (m, 2H), 7.48 (tt, \(J = 7.4, 1.2\) Hz, 1H), 7.37 (t, \(J = 8.1\) Hz, 2H), 3.33 (s, 2H), 1.98 (s, 2H)

**13C NMR** (126 MHz, Chloroform-\(d\)): \(\delta\) 151.4, 142.2, 140.8, 136.8, 133.2, 130.1, 128.9, 128.7, 127.8, 127.6, 127.3, 125.5, 120.2, 39.3, 36.3, 30.3

**Tert-butyl 5-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)-1H-indole-1-carboxylate, 37**

![Structure](image2)

Prepared according to the general procedure using tert-butyl 5-iodo-1H-indole-1-carboxylate S12 (86 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% Et<sub>2</sub>O in pentane, 1% NEt<sub>3</sub>), and isolated as a colourless solid (92 mg, 0.23 mmol, 91%).

**R<sub>f</sub>** = 0.34 (50% Et<sub>2</sub>O in pentane)
MP: 110 °C (recrystallized from Et$_2$O)

IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 3062, 2979, 1731, 1396, 1138, 864, 766, 727

HRMS (ESI$^+$) calc. for C$_{23}$H$_{24}$O$_4$NS [M+H]$^+$ 410.1421, found 410.1423

$^1$H NMR (500 MHz, Benzene-$d_6$): $\delta$ 8.34 (br, 1H), 7.70 (d, $J$ = 6.9 Hz, 2H), 7.53 (br, 1H), 7.47 (d, $J$ = 1.9 Hz, 1H), 7.31 (d, $J$ = 7.9 Hz, 1H), 6.88 (t, $J$ = 7.4 Hz, 1H), 6.81 (t, $J$ = 7.5 Hz, 2H), 6.24 (d, $J$ = 3.6 Hz, 1H), 2.80 (s, 2H), 1.37 (s, 9H), 1.14 (s, 2H)

$^{13}$C NMR (126 MHz, Benzene-$d_6$): $\delta$ 149.7, 142.2, 135.3, 132.5, 131.3, 128.3, 127.9, 126.6, 125.7, 123.9, 120.2, 115.7, 107.5, 83.2, 35.6, 34.7, 31.7, 27.9

2,6-Bis(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)pyridine, 38

![Chemical Structure](image)

Prepared according to the general procedure using 2,6-diiodopyridine (40 mg, 0.12 mmol, 0.48 eq.) as coupling partner. The title compound was purified by flash chromatography (30→50% Et$_2$O in pentane), and isolated as a light-brown solid (33 mg, 0.07 mmol, 59%).

$R_f$ = 0.60 (80% EtOAc in pentane)

MP: 167 °C (recrystallized from Et$_2$O)

IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 2959, 1589, 1446, 1262, 1108, 1067, 876, 750, 659, 624

HRMS (ESI$^+$) calc. for C$_{25}$H$_{22}$O$_4$N$_2$S$_2$ [M+H]$^+$ 464.0985, found 464.0980

$^1$H NMR (500 MHz, Chloroform-$d$): $\delta$ 7.64 (dd, $J$ = 7.4, 1.2 Hz, 4H), 7.51 (tt, $J$ = 7.5, 1.2 Hz, 2H), 7.42 (t, $J$ = 7.9 Hz, 1H), 7.39 (t, $J$ = 7.9 Hz, 4H), 7.09 (d, $J$ = 7.8 Hz, 2H), 3.11 (s, 4H), 1.73 (s, 4H)

$^{13}$C NMR (126 MHz, Chloroform-$d$): $\delta$ 151.2, 140.2, 136.5, 133.3, 129.1, 127.7, 119.7, 37.0, 36.3, 32.0

$N$-Diisopropyl-3-phenylbicyclo[1.1.0]butane-1-carboxamide, 39

![Chemical Structure](image)
Prepared according to the general procedure using iodobenzene (28 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et$_2$O in pentane, 1% NEt$_3$), and isolated as a colourless solid (47 mg, 0.18 mmol, 73%).

$R_f = 0.54$ (20% EtOAc in pentane)

**MP:** 56 °C (recrystallized from Et$_2$O)

**IR** (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 2965, 2930, 1622, 1484, 1346

**HRMS** (ESI$^+$) calc. for C$_{17}$H$_{24}$ON [M+H]$^+$ 258.1852, found 258.1851

$^1$H NMR (500 MHz, Chloroform-$d$): $\delta$ 7.32–7.27 (m, 4H), 7.17 (t, $J = 8.6, 1.8$ Hz, 1H), 4.70 (br, 1H), 3.23 (br, 1H), 2.81 (s, 2H), 1.52 (s, 2H), 1.19 (br, H6), 1.15 (br, H6)

$^{13}$C NMR (126 MHz, Chloroform-$d$): $\delta$ 167.6, 134.4, 128.1, 126.2, 49.3, 45.9, 36.3, 30.3, 22.3, 21.5, 20.8

$N,N$-Diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.0]butane-1-carboxamide, 40

Prepared according to the general procedure using 1-iodo-4-(trifluoromethyl)benzene (54 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→40% Et$_2$O in pentane, 1% NEt$_3$), and isolated as a colourless solid (76 mg, 0.23 mmol, 93%).

Large scale: 8c (1.00 g, 5.52 mmol, 1.20 eq.), PhLi (1.8 M in n-Bu$_2$O, 3.07 mL, 5.52 mmol, 1.20 eq.), ZnCl$_2$ (0.75 g, 5.52 mmol, 1.20 eq.), Pd(dba)$_2$ (132 mg, 0.26 mmol, 5 mol%), tfp (107 mg, 0.46 mmol, 10 mol%) and 1-iodo-4-(trifluoromethyl)benzene (0.68 mL, 4.60 mmol, 1.0 eq.) afforded 40 as a colourless solid (1.35 g, 4.15 mmol, 96%).

$R_f = 0.31$ (40% EtOAc in pentane)

**MP:** 57 °C (recrystallized from Et$_2$O)

**IR** (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 2963, 2934, 1630, 1483, 1341

**HRMS** (ESI$^+$) calc. for C$_{18}$H$_{23}$ONF$_3$ [M+H]$^+$ 326.1726, found 326.1724

$^1$H NMR (500 MHz, Chloroform-$d$): $\delta$ 7.52 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 4.69 (sep, $J = 6.6$ Hz, 1H), 3.26 (sep, $J = 6.7$ Hz, 1H), 2.82 (s, 2H), 1.59 (s, 2H), 1.21 (d, $J = 6.7$ Hz, 6H), 1.14 (d, $J = 6.8$ Hz, 6H)

$^{13}$C NMR (126 MHz, Chloroform-$d$): $\delta$ 166.9, 139.3, 128.2 (q, $J = 32.3$ Hz), 126.5, 125.1 (q, $J = 3.8$ Hz), 124.5 (q, $J = 270.2$ Hz), 49.6, 46.2, 36.7, 29.2, 23.9, 21.6, 20.8
$^{19}$F NMR (471 MHz, Chloroform-d): $\delta$ -62.4
1-Phenyl-3-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane, 41

Prepared according to the general procedure using iodobenzene (28 µL, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (20→30% Et₂O in pentane, 1% NEt₃), and isolated as a colourless solid (64 mg, 0.19 mmol, 76%).

R₇ = 0.44 (30% Et₂O in pentane)

MP: 104 °C (recrystallized from Et₂O)

IR (thin film, ν max / cm⁻¹): 1449, 1304, 1133, 765

HRMS (ESI⁺) calc. for C₁₇H₁₃O₂F₃NaS [M+Na]⁺ 361.0481, found 361.0479

¹H NMR (500 MHz, Benzene-d): δ 7.41 (d, J = 8.1 Hz, 2H), 7.05-7.01 (m, 2H), 7.01-6.95 (m, 5H), 2.58 (s, 2H), 1.05 (s, 2H)

¹³C NMR (126 MHz, Benzene-d): δ 144.4, 134.0 (q, J = 32.8 Hz), 128.7, 128.4, 128.0, 127.7, 127.2, 125.9 (q, J = 3.6 Hz), 123.9 (d, J = 272.9 Hz), 35.4, 34.5, 31.6

¹⁹F NMR (470 MHz, Benzene-d) δ -63.0

Methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenyl)propanoate, 42

Prepared according to the general procedure using methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate S13 (101 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→40% EtOAc in pentane), and isolated as a light-orange solid (72 mg, 0.15 mmol, 61%).

R₇ = 0.10 (50% Et₂O in pentane)

[α]D²⁵⁻₃₀ (c = 1.0, CHCl₃)

MP: 64 °C (recrystallized from Et₂O/EtOAc)

IR (thin film, ν max / cm⁻¹): 3400, 2978, 2976, 1712, 1494, 1306, 1147, 882, 690

HRMS (ESI⁺) calc. for C₂₅H₃₀O₆NS [M+H]⁺ 472.1788, found 472.1781
$^1$H NMR (500 MHz, Chloroform-d): δ 7.61 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 4.99 (d, J = 6.7 Hz, 1H), 4.58 (q, J = 6.7 Hz, 1H), 3.72 (s, 3H), 3.08 (qd, J = 13.7, 6.1 Hz, 2H), 2.87 (s, 2H), 1.65 (s, 2H), 1.44 (s, 9H)

$^{13}$C NMR (126 MHz, Chloroform-d): δ 172.4, 155.2, 140.2, 135.5, 133.3, 129.3, 129.1, 127.6, 127.3, 80.2, 54.6, 52.4, 38.2, 35.6, 34.9, 30.7, 28.5

(5)-2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzoate, 43

Prepared according to the general procedure using (S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 4-iodobenzoate S14 (112 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (30→40% EtOAc in pentane), and isolated as a colourless solid (31 mg, 0.06 mmol, 24%).

$R_f$ = 0.55 (80% EtOAc in pentane)

$[a]_D^{35} +37 \text{ (c = 1.0, CHCl}_3\text{)}$

MP: 109 °C (recrystallized from Et$_2$O/EtOAc)

IR (thin film, ν$_{max}$ / cm$^{-1}$): 3450, 2978, 1719, 1307, 1273, 1148, 879, 771, 729, 629

HRMS (ESI$^+$) calc. for C$_{23}$H$_{24}$O$_4$NS [M+2H-Boc]$^+$ 416.1168, found 416.1157

$^1$H NMR (500 MHz, Chloroform-d): δ 7.94 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 6.9 Hz, 2H), 7.58 (tt, J = 7.5, 1.2 Hz, 1H), 7.45 (t, J = 7.8, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.39 (d, J = 8.5 Hz, 1H), 4.72 (dt, J = 8.1, 3.7 Hz, 1H), 4.68–4.57 (m, 2H), 3.80 (s, 3H), 3.01 (s, 2H), 1.74 (s, 2H), 1.46 (s, 9H)

$^{13}$C NMR (126 MHz, Chloroform-d): δ 170.4, 165.7, 155.2, 140.5, 136.8, 133.3, 129.9, 129.1, 128.3, 127.3, 127.0, 80.5, 65.0, 53.0, 52.9, 36.2, 30.4, 30.3, 28.3

((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl 4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzoate, 44

S32
Prepared according to the general procedure using \(((3aR,5R,5aS,8aS,8bR)-2,2,7,7\text{-}\text{tetramethyltetrahydro}\text{-}5H\text{-}bis\{(1,3)\text{dioxolo\}[4,5-b:4',5'\text{-}d\}\text{pyran}-5\text{-}y\text{l}\})\text{methyl 4-iodobenzoate S15}\) (123 mg, 0.25 mmol, 1.0 eq.) as coupling partner. The title compound was purified by flash chromatography (40\text{–}70\%\text{ Et}_2\text{O in pentane}), and isolated as a light-orange solid (120 mg, 0.22 mmol, 86%).

\(R_f = 0.10\) (50\%\text{ Et}_2\text{O in pentane})

\text{MP: 89 °C (recrystallized from Et}_2\text{O/EtOAc)}

\(\alpha\) \text{D}^5 -41 (c = 1.0, CHCl}_3\)

\text{IR (thin film, }\nu\text{max / cm}^{-1}): 1715, 1253, 1211, 1148, 1067, 1004, 879, 772, 730, 629

\text{HRMS (ESI') calc. for } C_{29}H_{33}O_9S [M+H]^+ 557.1840, \text{ found 557.1835}

\text{1H NMR (400 MHz, Chloroform-d): } \delta 7.98 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 7.1, 1.2 Hz, 2H), 7.56 (tt, J = 7.5, 1.2 Hz, 1H), 7.41 (t, J = 7.9 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 5.58 (d, J = 5.0 Hz, 1H), 4.66 (dd, J = 7.9, 2.5 Hz, 1H), 4.54 (ddd, J = 11.5, 4.9 Hz, 1H), 4.44 (dd, J = 11.4, 7.6 Hz, 1H), 4.37-4.32 (m, 2H), 4.19 (ddd, J = 7.1, 4.9, 1.9 Hz, 1H), 2.99-2.95 (m, 2H), 1.73 (s, 2H), 1.53 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H)

\text{13C NMR (126 MHz, Chloroform-d): } \delta 166.2, 140.2, 136.4, 133.4, 123.0, 129.1, 129.1, 127.5, 127.0, 109.9, 109.0, 96.5, 71.3, 70.9, 70.7, 66.3, 64.1, 36.3, 36.0, 30.5, 26.2, 26.1, 25.2, 24.7

(8R,9S,13S,14S)-13-Methyl-3-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one, 45

\text{Prepared according to the general procedure using estrone triflate S16 (101 mg, 0.25 mmol, 1.0 eq.) as coupling partner and Pd(PPh}_3\text{)}_4 (29 mg, 0.03 mmol, 10 mol%) as catalyst. The title compound was purified by flash chromatography (30\text{–}60\%\text{ Et}_2\text{O in pentane}), and isolated as a colourless solid (32 mg, 0.07 mmol, 29%).}

\(R_f = 0.28\) (50\%\text{ Et}_2\text{O in pentane})

\(\alpha\) \text{D}^5 + 105 (c = 1.0, CHCl}_3\)

\text{MP: 147 °C (recrystallized from Et}_2\text{O/EtOAc)}

\text{IR (thin film, }\nu\text{max / cm}^{-1}): 2934, 1736, 1317, 1147, 758

\text{HRMS (ESI') calc. for } C_{28}H_{33}O_3S [M+H]^+ 447.1988, \text{ found 447.1991}
\(^1\)H NMR (500 MHz, Chloroform-\(d\)): \(\delta\) 7.69 (dd, \(J = 7.1, 1.3\) Hz, 2H), 7.56 (tt, \(J = 7.5, 1.2\) Hz, 1H), 7.42 (t, \(J = 7.5\) Hz, 2H), 7.23 (d, \(J = 8.2\) Hz, 1H), 7.12 (dd, \(J = 8.1, 2.1\) Hz, 1H), 6.99 (d, \(J = 2.0\) Hz, 1H), 2.89-2.83 (m, 2H), 2.56-2.47 (m, 1H), 2.46-2.39 (m, 1H), 2.35-2.26 (m, 1H), 2.21-1.94 (m, 4H), 1.70-1.39 (m, 8H), 0.93 (s, 3H)

\(^13\)C NMR (126 MHz, Chloroform-\(d\)): \(\delta\) 221.0, 141.0, 139.3, 136.7, 133.0, 129.0, 127.7, 127.7, 127.5, 125.7, 124.5, 50.7, 48.1, 44.5, 38.3, 36.0, 35.8, 35.7, 34.3, 31.7, 31.4, 29.4, 26.6, 25.9, 21.8, 14.0

1.6.1 Failed coupling reactions

Coupling partners that failed to couple or resulted in decomposition.

![Failed coupling reactions](image)

1.7 Diversification of BCBs

General BCB to cyclobutene procedure

To a solution of BCB (0.05-0.40 mmol, 1.0 eq.) in CHCl\(_3\) (0.50-1.50 mL) was added 1 drop of 1M HCl in Et\(_2\)O at rt. The reaction was stirred for 30 min at rt before evaporating in vacuo to afford pure cyclobutene.

\(((3\text{-Phenylcyclobut-2-en-1-yl)sulfonyl)benzene, 12\)

![Image of compound](image)

Prepared according to the general procedure using 11 (150 mg, 0.55 mmol, 1.0 eq.) to afford the title compound as a clear oil (150 mg, 0.55 mmol, quant.).

IR (thin film, \(\nu_{\max}\) / cm\(^{-1}\)): 1446, 1304, 1146, 1084, 765, 728, 692

HRMS (ESI\(^+\)) calc. for C\(_{16}\)H\(_{14}\)O\(_2\)Na\(_{2}\)S [M+Na\(^+\)] 293.0607, found 293.0608

\(^1\)H NMR (500 MHz, Chloroform-\(d\)): \(\delta\) 7.98 (d, \(J = 7.2\) Hz, 2H), 7.68 (tt, \(J = 7.5, 1.2\) Hz, 1H), 7.60 (t, \(J = 8.4\) Hz, 2H), 7.39-7.3 (m, 5H), 6.16 (d, \(J = 1.2\) Hz, 1H), 4.36 (dt, \(J = 4.3, 1.6\) Hz, 1H), 3.14 (dd, \(J = 13.6, 1.9\) Hz, 1H), 3.08 (dd, \(J = 13.6, 4.3\) Hz, 1H)

\(^13\)C NMR (126 MHz, Chloroform-\(d\)): \(\delta\) 151.6, 138.2, 133.8, 132.6, 129.5, 129.3, 128.7, 128.6, 125.3, 120.2, 60.4, 31.0
1-Methoxy-4-(3-(phenylsulfonyl)cyclobut-1-en-1-yl)benzene, 46

![Chemical structure image]

Prepared according to the general procedure using 19 (40 mg, 0.55 mmol, 1.0 eq.) to afford the title compound as a clear oil (40 mg, 0.13 mmol, quant.).

IR (thin film, νmax / cm⁻¹): 2956, 1507, 1304, 1146, 727, 673

HRMS (ESI⁺) calc. for C₁₇H₁₆O₃NaS [M+Na]⁺ 323.0712, found 323.0713

¹H NMR (400 MHz, Chloroform-d): δ 7.95 (dd, J = 7.1, 1.4 Hz, 2H), 7.65 (tt, J = 7.5, 1.3, 1H), 7.56 (t, J = 7.8, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.90 (d, J = 1.1 Hz, 1H), 4.24 (dt, J = 4.1, 1.6 Hz, 1H), 3.74 (s, 3H), 3.00 (dd, J = 13.6, 2.0 Hz, 1H), 2.94 (dd, J = 13.6, 4.3 Hz, 1H)

¹³C NMR (101 MHz, Chloroform-d): δ 160.7, 150.2, 138.3, 133.8, 129.2, 128.7, 126.9, 125.7, 117.45, 114.8, 60.7, 55.5, 31.0

Tert-butyldimethyl(3-(3-(phenylsulfonyl)cyclobut-1-en-1-yl)phenoxy)silane, 47

![Chemical structure image]

Prepared according to the general procedure using 22 (10 mg, 0.03 mmol, 1.0 eq.) to afford the title compound as a clear oil (10 mg, 0.03 mmol, quant.).

IR (thin film, νmax / cm⁻¹): 2956, 2929, 2857, 1601, 1581, 1476, 1320, 1113, 959, 840, 783

HRMS (ESI⁺) calc. for C₂₂H₂₉O₃Si [M+H]⁺ 401.1601, found 401.1597

¹H NMR (500 MHz, Chloroform-d): δ 7.85 (d, J = 8.5 Hz, 2H), 7.55 (tt, J = 7.5, 1.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.83 (dt, J = 7.7, 1.3 Hz, 1H), 6.70 (ddd, J = 8.0, 2.4, 1.0 Hz, 1H), 6.67 (t, J = 2.0 Hz, 2H), 6.00 (d, J = 1.2 Hz, 1H), 4.22 (dt, J = 4.3, 1.5 Hz, 1H), 2.98 (dd, J = 13.6, 1.9 Hz, 1H), 2.91 (dd, J = 13.6, 4.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 6H)

¹³C NMR (126 MHz, Chloroform-d): δ 156.0 151.5, 138.2, 134.1, 133.8, 129.7, 129.3, 128.7, 121.3, 120.3, 118.5, 116.8, 60.3, 31.0, 25.8, 18.4, -4.2
Ethyl (1S*,3S*,5R*)-1-phenyl-3-(phenylsulfonyl)bicyclo[2.1.0]pentane-5-carboxylate, 48

To a solution of 6 (54 mg, 0.20 mmol, 1.0 eq.) in DCM (1 mL) was added a solution of ethyl diazoacetate (≥13 wt% in dichloromethane, 42 µL, 0.40 mmol, 2.00 eq.) in DCM (1 mL) dropwise via syringe pump over 1 h at rt. The solvent was removed \textit{in vacuo} to afford a yellow oil which was purified \textit{via} flash chromatography (1\textsuperscript{st} column: 20% Et\textsubscript{2}O in pentane, 2\textsuperscript{nd} column: 100% DCM) to afford 48 as a colourless waxy solid (19 mg, 0.05 mmol, 26%).

\( R_f = 0.37 \) (50% Et\textsubscript{2}O in pentane), 0.24 (100% DCM)

\textbf{IR} (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)): 1726, 1446, 1307, 1186, 1148, 730, 695

\textbf{HRMS} (ESI\textsuperscript{+}) calc. for C\textsubscript{20}H\textsubscript{20}O\textsubscript{4}NaS [M+Na]\textsuperscript{+} 379.0975, found 379.0968

\textbf{\textsuperscript{1}H NMR} (400 MHz, Chloroform-d): \( \delta \) 7.96 (dd, \( J = 8.5, 1.4 \) Hz, 2H), 7.66 (tt, \( J = 7.4, 1.3 \) Hz, 1H), 7.56 (t, \( J = 7.9 \) Hz, 2H), 7.38-7.29 (m, 4H), 7.28-7.22 (m, 1H), 4.20 (qd, \( J = 7.1, 2.3 \) Hz, 2H), 4.07 (dd, \( J = 5.2, 3.5 \) Hz, 1H, H\textsubscript{2}), 2.94 (ddd, \( J = 12.3, 3.5, 1.1 \) Hz, 1H, H\textsubscript{1}), 2.70 (dd, \( J = 6.0, 1.0 \) Hz, 1H, H3), 2.60 (ddd, \( J = 12.4, 5.3, 1.1 \) Hz, 1H, H1), 2.38 (dd, \( J = 6.0, 1.0 \) Hz, 1H, H4), 1.30 (t, \( J = 7.1 \) Hz, 3H)

\textbf{\textsuperscript{13}C NMR} (101 MHz, Chloroform-d): \( \delta \) 170.3, 138.4, 138.0, 134.0, 129.5, 128.8, 128.6, 127.6, 61.0, 55.4, 37.2, 31.2, 28.6, 28.1, 14.4

\textbf{[(3-Phenylcyclobutyl)sulfonyl]benzene, 49}

To a solution of 11 (27 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added a solution of LiAlH\textsubscript{4} in Et\textsubscript{2}O (4 M, 50.0 µL, 0.20 mmol, 2.00 eq.) at 0 °C. The reaction was stirred for 8 h at 0 °C and quenched with methanol. The solution was diluted with Et\textsubscript{2}O (2 mL) mixture and passed through a silica plug. The organics were evaporated in \textit{vacuo} and purified \textit{via} flash chromatography (DCM) to yield an off-white solid (13-22 mg, 0.05-0.08 mmol, 46-81\%, 2:3 \textit{dr}, major anti/trans). Data identical to literature values.\textsuperscript{7}

\( R_f = 0.22 \) (100% DCM)

\textbf{\textsuperscript{1}H NMR} (400 MHz, Chloroform-d): \( \delta \) 7.97-7.93 (m, 0.25H, \textit{trans} 2H), 7.93-7.88 (m, 0.75H, \textit{cis} 2H), 7.70-7.63 (m, 2H, \textit{trans + cis} 2H), 7.61-7.53 (m, 2H, \textit{trans + cis} 4H), 7.36-7.28 (m, 2H, \textit{trans + cis} 4H), 7.28-7.17 (m, 3H, \textit{trans + cis} 6H), 3.90-3.72 (m, 1.25H, \textit{trans + cis} 3H), 3.41 (tt, \( J = 10.0, 8.2 \) Hz, 0.75H, \textit{cis} 1H), 3.03-2.94 (m, 0.5H, \textit{trans} 2H), 2.75 (qd, \( J = 9.8, 2.6 \) Hz, 1.5H, \textit{cis} 2H), 2.62-2.41 (m, 2H, \textit{trans + cis} 4H)
**13C NMR** (101 MHz, Chloroform-\(d\)): \(\delta\) 144.1 (trans), 143.2 (cis), 138.4 (cis), 138.2 (trans), 133.8 (cis & trans), 129.4 (cis & trans), 128.7 (cis & trans), 128.5 (trans), 128.4 (cis), 126.9 (cis), 126.8 (cis), 126.7 (trans), 126.3 (trans), 54.9 (trans), 53.2 (cis), 35.6 (trans), 34.3 (cis), 30.8 (cis), 29.8 (trans).

3-Chloro-1-methoxy-3-(phenylsulfonyl)cyclobutyl]benzene, 50

To a solution of 11 (27 mg, 0.10 mmol, 1.0 eq.) in MeOH (0.5 mL) at rt was added N-chlorosuccinimide (13 mg, 0.10 mmol, 1.0 eq.). The mixture was stirred at rt for 6 h before evaporating in vacuo. The resulting residue was purified by flash chromatography (0→20% Et\(2\)O in pentane) to afford 50 as a colourless oil (26 mg, 0.08 mmol, 77%).

**Rf** = 0.37 (10% Et2O in pentane)

**IR** (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)): 2948, 1496, 1398, 727

**HRMS** (ESI\(^+\)) calc. for C\(_{17}\)H\(_{17}\)ClO\(_3\)\(_2\)Na\(_3\)S \([\text{M+Na}]^+\) 359.0484, found 359.0479.

**1H NMR** (500 MHz, Chloroform-\(d\)): \(\delta\) 8.05-7.86 (m, 2H), 7.75-7.64 (m, 1H), 7.64-7.51 (m, 2H), 7.48-7.33 (m, 5H), 3.76-3.65 (m, 2H), 3.02 (s, 3H), 2.91-2.83 (m, 2H)

**13C NMR** (126 MHz, Chloroform-\(d\)): \(\delta\) 140.3, 134.6, 134.2, 130.7, 129.1, 128.7, 128.3, 126.1, 76.8, 75.4, 51.2, 44.0

1-(2-Fluorophenyl)sulfonyl]-3-phenylbicyclo[1.1.0]butane, 52

To a solution of 5 (32 mg, 0.12 mmol, 1.20 eq.) in THF (0.4 mL) was added \(n\)-BuLi in pentane (1.9 M, 64.0 \(\mu\)L, 0.12 mmol, 1.2 eq.) at \(-78\) °C. The reaction was stirred for 2 h before addition of a solution of NFSI (16 mg, 0.12 mmol, 1.2 eq.) in THF (0.5 mL) at \(-78\) °C, and stirred for 2 h before quenching by addition of 2 drops of water. The organic phase was diluted with DCM, dried with anhydrous MgSO\(_4\), filtered and evaporated in vacuo. The residue was purified via flash chromatography (1\(^{st}\) column: 20% Et\(2\)O in pentane, 2\(^{nd}\) column: 100% DCM) to yield 52 as an off-white solid (21 mg, 0.07 mmol, 73%).

**Rf** = 0.28 (40% Et\(2\)O in pentane)

**MP**: 110 °C (recrystallized from Et\(2\)O)

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**S37**
IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 1474, 1322, 1264, 1146, 879, 826, 760, 690, 622

HRMS (ESI$^+$) calc. for C$_{16}$H$_{14}$O$_2$FNaS [M+H]$^+$ 311.0512, found 311.0512

$^1$H NMR (500 MHz, Chloroform-d): $\delta$ 7.74-7.69 (m, 1H), 7.60-7.54 (m, 1H), 7.45-7.41 (m, 2H), 7.36-7.27 (m, 3H), 7.23-7.17 (m, 2H), 3.10 (s, 2H), 1.74 (s, 2H)

$^{13}$C NMR (126 MHz, Chloroform-d): $\delta$ 159.4 (d, $J$ = 256.5 Hz), 135.3 (d, $J$ = 8.4 Hz), 130.3, 129.6 (d, $J$ = 14.3 Hz), 129.5, 129.1, 128.5, 127.6, 124.4 (d, $J$ = 3.8 Hz), 117.1 (d, $J$ = 21.0 Hz), 36.6, 34.2, 32.4

$^{19}$F NMR (377 MHz, Chloroform-d): $\delta$ -108.6

Methyl 2'-(3-phenylbicyclo[1.1.0]butan-1-yl)sulfonyl)-[1,1'-biphenyl]-4-carboxylate, 53

To a solution of 5 (32 mg, 0.12 mmol, 1.2 eq.) in THF (0.4 mL) at −78 °C was added n-BuLi (1.9 M in pentane, 64 µL, 0.12 mmol, 1.2 eq.). The reaction was stirred for 2 h before addition of a solution of ZnCl$_2$ (16 mg, 0.12 mmol, 1.20 eq.) in THF (0.5 mL) at −78 °C, and stirred for 5 min before bringing to rt. The solution of organozinc was transferred via syringe to a vial containing Pd(dba)$_2$ (11.5 mg, 0.02 mmol, 10 mol%), tfp (9.2 mg, 0.04 mmol, 20 mol%) and methyl 4-iodobenzoate (26 mg, 0.10 mmol, 1.0 eq.). The reaction mixture was stirred for 1 d at 40 °C, followed by cooling to room temperature, diluting with DCM (5 mL) and filtering. The organic phase was evaporated in vacuo and purified via flash chromatography (30-50% Et$_2$O in pentane) to afford 53 as a light yellow solid (36 mg, 0.07 mmol, 74%).

$R_f$ = 0.33 (50% Et$_2$O in pentane)

MP: 120 °C (recrystallized from Et$_2$O)

IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$): 1721, 1277, 1252, 1147, 1101, 859, 766, 643

HRMS (ESI$^+$) calc. for C$_{24}$H$_{21}$O$_4$S [M+H]$^+$ 401.1601, found 401.1597

$^1$H NMR (500 MHz, Chloroform-d): $\delta$ 8.25 (d, $J$ = 8.3 Hz, 2H), 7.75 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.71-7.65 (m, 3H), 7.50-7.35 (m, 7H), 4.10 (s, 3H), 2.67 (s, 2H), 1.34 (s, 2H)

$^{13}$C NMR (101 MHz, Chloroform-d): $\delta$ 167.0, 144.2, 141.7, 140.4, 132.6, 132.3, 130.7, 130.7, 129.8, 128.9, 128.5, 128.3, 128.01, 127.7, 127.3, 52.4, 37.0, 33.9, 33.7
2,2-Difluoro-\(N,N\)-diisopropyl-3-phenylbicyclo[1.1.1]pentane-1-carboxamide, 54

\[
\begin{align*}
\text{O} & \quad \text{Ph}_{3} \text{PCF}_2 \text{CO}_2 \quad \text{Ph} \\
80 \degree \text{C}, 2.5 \text{h} & \quad \text{43}\% \\
\end{align*}
\]

To a solution of 37 (26 mg, 0.10 mmol, 1.0 eq.) in mesitylene (1 mL) was added \(\text{Ph}_3\text{PCF}_2\text{CO}_2\) (107 mg, 0.3 mmol, 3.0 eq.). The suspension was heated to 80 °C and stirred for 2.5 h before evaporating in vacuo and purifying via flash chromatography (5-15% EtOAc in pentane) to yield a colourless solid (13.3 mg, 0.04 mmol, 43%).

\(R_f = 0.50\) (15% EtOAc in pentane)

\(\text{MP}: 99 \degree \text{C}\) (recrystallized from Et\(_2\)O)

\(\text{IR}\) (thin film, \(\nu_{\text{max}}\) \(\text{cm}^{-1}\)): 2968, 1631, 1439, 1373, 1213, 1100, 711

\(\text{HRMS (ESI)}^{+}\) calc. for \(\text{C}_{18}\text{H}_{24}\text{ONF}_2\) \([\text{M+H}]^+\) 308.1820, found 308.1817

\(\text{\textsuperscript{1}H NMR}\) (500 MHz, Chloroform-d): \(\delta\) 7.39-7.31 (m, 3H), 7.29 (dd, \(J = 8.0, 1.7\) Hz, 2H), 4.26 (sep, \(J = 6.6\) Hz, 1H), 3.42 (sep, \(J = 6.8\) Hz, 1H), 2.62 (s, 2H), 2.11 (t, \(J = 10.6\) Hz, 1H), 1.44 (d, \(J = 6.8\) Hz, 6H), 1.23 (d, \(J = 6.7\) Hz, 6H)

\(\text{\textsuperscript{13}C NMR}\) (126 MHz, Chloroform-d): \(\delta\) 163.8, 132.6, 128.7, 128.3, 127.3, 123.7, 123.9 (t, \(J = 296.6\) Hz), 54.2 (t, \(J = 19.0\) Hz), 53.3 (t, \(J = 19.5\) Hz), 48.6, 46.4, 44.0 (t, \(J = 7.3\) Hz), 21.1, 20.6.

2,2-Difluoro-\(N,N\)-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxamide, 56; 2,2-Difluoro-\(N,N\)-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxamide, 57

\[
\begin{align*}
\text{O} & \quad \text{Ph}_{3} \text{PCF}_2 \text{CO}_2 \quad \text{Ph} \\
80 \degree \text{C}, 3.5 \text{h} & \quad \text{56, 33}\% \\
\end{align*}
\]

To a solution of 40 (1.20 g, 3.67 mmol, 1.0 eq.) in mesitylene (37 mL) was added \(\text{Ph}_3\text{PCF}_2\text{CO}_2\) (3.92 g, 11.0 mmol, 3.0 eq.). The suspension was heated to 80 °C and stirred for 3.5 h before cooling to rt, diluting with EtOAc (200 mL) and washing with water (100 mL x 2). The organic phase was dried with anhydrous MgSO\(_4\), filtered and concentrated in vacuo to remove EtOAc (residual mesitylene). The residue was purified using a 1% NEt\(_3\), 5% Et\(_2\)O in pentane preconditioned silica column, with 1% NEt\(_3\), 5→30% Et\(_2\)O in pentane eluent, to afford 56 as a white solid (0.45 g, 1.21 mmol, 33%) and 57 as a yellow-green oil (0.55 g, 1.47 mmol, 40%).

2,2-Difluoro-\(N,N\)-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxamide, 56
$R_f = 0.39$ (40% Et$_2$O in pentane)

**MP**: 135 °C (recrystallized from Et$_2$O)

**IR** (thin film, $v_{max}$ / cm$^{-1}$): 2971, 1632, 1450, 1325, 1128

**HRMS (ESI$^+$)** calc. for C$_{19}$H$_{23}$ONF$_5$ [M+H]$^+$ 376.1694, found 376.1693

$^1$H NMR (500 MHz, Chloroform-d): $\delta$ 7.62 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 4.24 (sep, $J = 6.7$ Hz, 1H, H2), 3.43 (sep, $J = 6.7$ Hz, 1H, H2), 2.65 (s, 2H, H4), 2.15 (t, $J = 10.9$ Hz, 2H, H4), 1.44 (d, $J = 6.8$ Hz, 6H, H1), 1.24 (d, $J = 6.7$ Hz, 6H, H1)

$^{13}$C NMR (126 MHz, Chloroform-d): $\delta$ 163.4, 136.5, 130.6 (q, $J = 32.5$ Hz), 127.7, 125.7 (q, $J = 3.8$ Hz), 123.7 (t, $J = 296.3$ Hz, C5), 123.0 (q, $J = 272.8$ Hz, C7), 54.4 (t, $J = 18.9$ Hz, C3), 52.9 (t, $J = 19.6$ Hz, C6), 48.7 (C2), 46.5 (C2), 44.0 (C4), 21.1 (C1), 20.5 (C1).

$^{19}$F NMR (470 MHz, Chloroform-d): $\delta$ -62.7, -83.0 (d, $J = 39.7$ Hz), -91.8 (d, $J = 39.7$ Hz)

2,2-Difluoro-N,N-diisopropyl-3-[4-(trifluoromethyl)phenyl]bicyclo[1.1.1]pentane-1-carboxamide, 57

$R_f = 0.52$ (40% Et$_2$O in pentane)

**IR** (thin film, $v_{max}$ / cm$^{-1}$): 2971, 1632, 1450, 1325, 1128

**HRMS (ESI$^+$)** calc. for C$_{19}$H$_{23}$ONF$_5$ [M+H]$^+$ 376.1694, found 376.1693

$^1$H NMR (500 MHz, Chloroform-d): $\delta$ 7.59 (d, $J = 8.7$ Hz, 2H), 7.56 (d, $J = 8.7$ Hz, 2H), 5.54 (s, 1H, H7), 5.34 (s, 1H, H7), 3.69 (sep, $J = 6.9$ Hz, 1H, H2), 3.51 (s, 2H, H5), 3.31 (sep, $J = 6.7$ Hz, 1H, H2), 1.37 (d, $J = 6.8$ Hz, 6H, H1), 0.93 (br, 6H, H1)

$^{13}$C NMR (126 MHz, Chloroform-d): $\delta$ 163.4 (dd, $J = 7.4$, 2.0 Hz), 153.0 (dd, $J = 292.8$, 288.1 Hz, C4), 142.9 (C6 or 8), 142.5 (C6 or 8), 130.1 (q, $J = 32.6$ Hz, C11), 126.4 (C9), 125.6 (q, $J = 3.8$ Hz, C10), 124.2 (q, $J = 271.9$ Hz, C12), 117.7 (C7), 88.9 (dd, $J = 19.5$, 16.2 Hz, C3), 50.8 (C2), 46.3 (C2), 31.8 (d, $J = 2.4$ Hz, C5), 20.9 (C1), 20.3 (C1)

$^{19}$F NMR (470 MHz, Chloroform-d): $\delta$ -62.7, -83.0 (d, $J = 39.7$ Hz), -91.8 (d, $J = 39.7$ Hz)

2,2-Difluoro-3-[4-(trifluoromethyl)phenyl]bicyclo[1.1.1]pentane-1-carboxylic acid, 58

LiAlH$_4$ (7.6 mg, 0.2 mmol, 2.0 eq.) was suspended in THF (0.5 mL) and transferred to vial containing BCP (38 mg, 0.10 mmol, 1.0 eq.) via syringe at rt. The resulting suspension was heated to 60 °C for 5 h before cooling to room
temperature and diluting with THF (0.5 mL). Sat. aq. Na₂SO₄ (0.5 mL) was added dropwise with vigorous stirring. The mixture was stirred for 10 min before diluting with Et₂O and drying with anhydrous MgSO₄. The solution was filtered and solvent removed in vacuo to afford a clear oil, which was dissolved in 30% Et₂O in pentane and passed through a pipette of silica. The solvent was removed in vacuo to afford 56-amine as a clear oil (36 mg, 0.10 mmol, 99%).

\[ R_f = 0.6 \text{(40\% Et}_2\text{O in pentane)} \]

\[ ^1\text{H NMR (400 MHz, Chloroform}-d\text{):} \delta 7.63-7.56 (m, 2H), 7.41-7.35 (m, 2H), 2.97 (sept, J = 6.6 Hz, 2H), 2.73 (s, 2H), 2.26 (s, 2H), 1.72 (t, J = 10.7, 10.2 Hz, 2H), 1.00 (d, J = 6.6 Hz, 12H); ^19\text{F NMR (377 MHz, Chloroform}-d\text{):} \delta -62.6, -123.3 \]

To a vigorously stirred solution of 56-amine (36 mg, 0.10 mmol, 1.0 eq.) in aq. NaOH (1%, 1 mL) was slowly added a solution of KMnO₄ (318 mg, 2.00 mmol, 20 eq.) in water (4 mL). After stirring for 4 h, sat. aq. Na₂S₂O₃ (1 mL) was added dropwise followed by dilution with water (25 mL) and filtering through Celite®. The filtrate was acidified to pH 1-2 with aq. HCl (1.2 M) and extracted with ethyl acetate (25 mL x 3). The combined organic phases were dried with anhydrous MgSO₄, filtered, and concentrated to afford a cream solid. The solid was tritivated with a small amount of cold pentane (1 mL x 2) to yield 58 as a colourless solid (26 mg, 0.09 mmol, 89%).

\[ \text{MP: 179 °C (recrystallized from acetone)} \]

\[ ^1\text{H NMR (500 MHz, Chloroform}-d\text{):} \delta 7.64 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 7.7 Hz, 2H), 2.72 (s, 2H), 2.21 (t, J = 10.1 Hz, 2H) \]

\[ ^13\text{C NMR (126 MHz, Chloroform}-d\text{):} \delta 169.3, 135.7, 130.9 (q, J = 32.6 Hz), 127.7, 125.8 (q, J = 3.8 Hz), 124.0 (q, J = 272.2 Hz), 122.7 (t, J = 243.5 Hz), 54.7 (t, J = 19.4 Hz), 50.2 (t, J = 19.6 Hz), 43.5 (t, J = 6.9 Hz) \]

\[ ^19\text{F NMR (471 MHz, Chloroform}-d\text{):} \delta -62.8, -120.7 (t, J = 10.2 Hz) \]
1.8 Synthesis of coupling partners and reagents

2,2-Difluoro-2-(triphenylphosphonio)acetate, S5

To a cooled solution of potassium hydroxide (2.76 g, 49.3 mmol, 1.0 eq.) in methanol (45 mL) at 0 °C was added ethyl bromodifluoroacetate (6.30 mL, 49.3 mmol, 1.0 eq.). The mixture was stirred at rt for 16 h then concentrated to give the potassium salt as a white powder, which was used without further purification. The salt was dissolved in DMF (56 mL) and PPh3 (12.9 g, 49.3 mmol, 1.0 eq.) was added and the mixture stirred at rt for 3 d. The mixture was suction filtered, and the residual solid washed with DMF (2 x 5 mL), water (2 x 5 mL), Et2O (2 x 5 mL) and dried under high vacuum to give S5 as a white solid (13.5 g, 37.8 mmol, 77%). Data identical to literature values.8

1H NMR (400 MHz, methanol-d) δ 7.97-7.83 (m, 9H), 7.79-7.70 (m, 6H)

13C NMR (101 MHz, methanol-d) 161.3 (d, J = 15.0 Hz), 135.6 (d, J = 3.2 Hz), 134.6 (d, J = 10.1 Hz), 130.1 (d, J = 13.1 Hz), 117.0 (d, J = 80.8 Hz), 115.2 (d, J = 85.9 Hz)

19F NMR (377 MHz, methanol-d) δ -96.0 (d, J = 96.9 Hz)

31P NMR (162 MHz, methanol-d) δ 27.1 (t, J = 96.6 Hz)

3-Iodophenyl trifluoromethanesulfonate, S8

To a solution of 3-iodophenol (442 mg, 2.00 mmol, 1.0 eq.) in pyridine (2 mL) was added Tf2O (0.38 mL, 2.20 mmol, 1.10 eq.) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, warmed to rt and stirred for 16 h. The reaction mixture was diluted with Et2O (25 mL), washed with aq. 1 M HCl (20 mL x 2) and the aqueous phase was extracted with Et2O. The organic was combined, dried with anhydrous MgSO4, filtered, and concentrated to afford a dark oil. The oil was purified via flash chromatography (Et2O in pentane) to yield S8 as a yellow oil (700 mg, 1.98 mmol, 99%). Data identical to literature values.9

1H NMR (400 MHz, Chloroform-d): δ 7.74 (dt, J = 7.8, 1.3 Hz, 1H), 7.63 (dd, J = 2.4, 1.6 Hz, 1H), 7.28 (dd, J = 8.4, 2.4 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H).

13C NMR (101 MHz, Chloroform-d): δ 149.4, 137.8, 131.6, 130.6, 121.0, 118.9 (q, J = 320.7 Hz), 94.0.
Tert-butyl(3-iodophenoxy)dimethylsilane, S9

To a solution of 3-iodophenol (442 mg, 2.00 mmol, 1.0 eq.) and imidazole (136 mg, 2.00 mmol, 1.0 eq.) in DMF (2 ml) was added a solution of TBSCI (301 mg, 2.00 mmol, 1.0 eq.) in DMF (2 ml) dropwise at rt. The mixture was stirred for 16 h, then diluted with Et₂O (20 ml). The organic phase was washed with water (10 ml x 2), brine (10 ml), dried with anhydrous MgSO₄, filtered and concentrated to afford a yellow oil. The oil was purified via flash chromatography (10% Et₂O in pentane) to yield S9 as a clear oil (532 mg, 1.96 mmol, 98%). Data identical to literature values.¹⁰

¹H NMR (400 MHz, Chloroform-d): δ 7.29 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.21 (dd, J = 2.3, 1.6 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.79 (ddd, J = 8.2, 2.4, 1.0 Hz, 1H), 0.98 (s, 9H), 0.20 (s, 6H).

¹³C NMR (101 MHz, Chloroform-d): δ 156.6, 130.9, 130.7, 129.7, 119.7, 94.3, 26.0, 18.4, -4.2

(Z)-1-iodooct-1-ene, S9

A solution of NaHMDS in THF (2.20 ml, 1.00 M, 2.20 mmol, 1.10 eq.) was added to a suspension of Ph₃PCH₂I₂ (1.17 g, 2.20 mmol, 1.10 eq.) in THF (10 ml) at rt. The reaction was stirred for 20 min before addition of HMPA (1.80 ml, 10.0 mmol, 5.00 eq.). The reaction was stirred for 10 min before cooling to -78 °C and addition of n-heptanal (285 µl, 2.00 mmol, 1.0 eq.). The mixture was stirred for 1 h at -78 °C before warming to rt and stirring for an additional 20 h at rt. The reaction was quenched by addition of sat. aq. NaHCO₃ (50 ml), then the aqueous phase was extracted with Et₂O (50 ml x 2). The combined organic phases were dried with anhydrous MgSO₄, filtered and concentrated to afford a yellow oil. The oil was purified via flash chromatography (pentane) to yield S9 as a clear oil (251 mg, 1.05 mmol, 53%). Data identical to literature values.¹¹

¹H NMR (400 MHz, Chloroform-d): δ 6.20-6.14 (m, 2H), 2.19-2.09 (m, 2H), 1.48-1.23 (m, 8H), 0.95-0.83 (m, 3H).

¹³C NMR (101 MHz, Chloroform-d): δ 141.7, 82.2, 34.9, 31.8, 28.9, 28.1, 22.7, 14.2
4-(Iodoethynyl)benzonitrile, S11

To a solution of 4-ethynylbenzonitrile (200 mg, 1.57 mmol, 1.0 eq.) and AcOH (0.12 mL, 2.00 mmol, 1.30 eq.) in MeCN (7.5 mL) was added 4 Å MS (200 mg) and N-iodosuccinimide (389 mg, 1.73 mmol, 1.10 eq.) at rt. The reaction mixture was heated to 80 °C for 3 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (10 mL), dried with anhydrous MgSO₄, filtered and evaporated in vacuo to afford a brown oil. The oil was purified via flash chromatography (10→20% Et₂O in pentane) to yield the title compound as a colourless solid (281 mg, 1.11 mmol, 71%). Data identical to literature values.

1H NMR (400 MHz, Chloroform-d): δ 7.60 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H)

13C NMR (101 MHz, Chloroform-d): δ 133.0, 132.1, 128.2, 118.4, 112.3, 92.7, 13.1

Tert-butyl 5-iodo-1H-indole-1-carboxylate, S12

To a solution of 5-iodoindole (242 mg, 1.00 mmol, 1.0 eq.) in THF (8 mL) was added DMAP (12.0 mg, 0.1 mmol, 10 mol%) and Boc₂O (290 µL, 1.1 mmol, 1.10 eq.) at rt. The reaction was stirred for 1 d at rt before quenching with water (20 mL) and extracting with Et₂O (20 mL x 3). The combined organic phases were dried with anhydrous MgSO₄, filtered, and evaporated in vacuo. The residue was purified via flash chromatography (10% Et₂O in pentane) to yield S12 as a clear oil (323 mg, 0.94 mmol, 94%). Data identical to literature values.

1H NMR (400 MHz, Chloroform-d): δ 7.91 (d, J = 8.5 Hz, 1H), 7.90-7.89 (m, 1H), 7.57 (dd, J = 8.8, 1.8 Hz, 1H), 7.55 (d, J = 3.8 Hz, 1H), 6.49 (dd, J = 3.7, 0.8 Hz, 1H), 1.67 (s, 9H)

13C NMR (101 MHz, Chloroform-d): δ 149.6, 134.6, 133.0, 132.8, 129.9, 126.8, 117.2, 106.4, 86.8, 84.3, 28.3

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate, S13

AcCl (2.5 mL, 35.2 mmol, 10.2 eq.) was added dropwise to MeOH (15 mL) at 0 °C and stirred for 10 min before addition of 4-iodo-L-phenylalanine (1.00 g, 3.44 mmol, 1.0 eq.). The reaction mixture was stirred for 17 h at rt,
then concentrated to afford a colourless solid which was redissolved in DCM (15 mL). To this solution was added NEt$_3$ (1.20 mL, 8.60 mmol, 2.50 eq.) and Boc anhydride (1.10 g, 5.22 mmol, 1.50 eq.) and the reaction was stirred for 16 h at room temperature. The mixture was then diluted with DCM, washed with water and extracted with DCM. The combined organic phases were washed with brine, dried with anhydrous MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/pentane) to yield S13 as a yellow oil (1.40 g, 3.41 mmol, 99%). Data identical to literature values.$^{14}$

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 7.61 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.3$ Hz, 2H), 4.97 (d, $J = 8.3$ Hz, 1H), 4.56 (q, $J = 6.7$ Hz, 1H), 3.71 (s, 3H), 3.18-2.87 (m, 2H), 1.42 (s, 9H)

$^{13}$C NMR (101 MHz, Chloroform-$d$): $\delta$ 172.2, 155.2, 137.8, 135.9, 131.5, 92.7, 80.2, 54.3, 52.5, 38.1, 28.4

(S)-2-((Tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 4-iodobenzoate, S14

![Chemical structure](image)

To a solution of 4-iodobenzoic acid (298 mg, 1.20 mmol, 1.0 eq.) in DCM (5 mL) was added oxalyl chloride (375 µL, 4.40 mmol, 3.70 eq.), followed by 2 drops of DMF. The reaction was stirred for 45 min at room temperature, then the volatiles were removed under a stream of nitrogen. The residue was placed under high vacuum for 15 min. The crude acyl chloride was dissolved in DCM (5 mL), taken up via syringe and added dropwise to a solution of Boc-Ser-OMe (438 mg, 2.00 mmol, 1.70 eq.) and NEt$_3$ (0.56 mL, 4.00 mmol, 3.30 eq.) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 20 h, before being diluted with EtOAc (50 mL), and washed with water (25 mL x 2) and sat. aq. NaHCO$_3$ (25 mL). The organic phase was dried with anhydrous MgSO$_4$, filtered, and evaporated in vacuo to yield a yellow oil. The oil was purified via flash chromatography (20% EtOAc in pentane) to yield S14 a yellow oil (0.74 g, 0.98 mmol, 82%). Data identical to literature values.$^{15}$

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 7.83-7.76 (dt, $J = 8.6$ Hz, 1.8, 2H), 7.73-7.65 (dt, $J = 8.6$ Hz, 1.9, 2H), 5.37 (d, $J = 8.2$ Hz, 1H), 4.74-4.66 (m, 1H), 4.59 (d, $J = 4.0$ Hz, 1H), 3.77 (s, 3H), 1.44 (s, 9H)

$^{13}$C NMR (101 MHz, Chloroform-$d$): $\delta$ 170.4, 165.7, 155.2, 138.0, 131.2, 129.0, 101.4, 80.6, 65.3, 53.1, 53.0, 28.4
To a suspension of D-(+)-galactose (1.80 g, 10.0 mmol, 1.0 eq.) in acetone (40 mL) was added ZnCl₂ (1.85 g, 13.6 mmol, 1.40 eq.) followed by P₂O₅ (370 mg, 2.6 mmol, 0.3 eq.) and H₃PO₄ (730 mg, 7.4 mmol, 0.7 eq.), and the mixture was stirred at room temperature for 20 h. The reaction was quenched by addition of sat. aq. Na₂CO₃ (100 mL) and reduced in vacuo (removing acetone). The residual aqueous phase was extracted with Et₂O (100 mL x 2), the organic phases were combined, dried with anhydrous MgSO₄ and evaporated in vacuo to yield a yellow oil (D-(+)-Galactose-diketal) (2.26 g, 8.68 mmol, 87%).

To a solution of 4-Iodobenzoic acid (595 mg, 2.40 mmol, 1.20 eq.) in DCM (15 mL) was added oxalyl chloride (375 µL, 4.00 mmol, 2.00 eq.), followed by 2 drops of DMF, and the mixture was stirred for 45 min at room temperature. The volatiles were removed under a stream of nitrogen, and the residue placed under high vacuum for 15 min. The crude acyl chloride was dissolved in DCM (5 mL), taken up via syringe and added dropwise to a solution of D-(+)-galactose diketal (520 mg, 2.00 mmol, 1.0 eq.), DMAP (49.0 mg, 0.40 mmol, 20 mol%) and NEt₃ (0.56 mL, 4.00 mmol, 4.00 eq.) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 18 h before being diluted with EtOAc (50 mL), washed with water (20 mL x 2) and sat. aq. NaHCO₃ (20 mL). The organic phase was dried with anhydrous MgSO₄, filtered, and concentrated to yield a yellow oil. The oil was purified via flash chromatography (15% EtOAc in pentane) to yield S15 as a colourless solid (700 mg, 1.42 mmol, 71%). Data identical to literature values.¹⁶

¹H NMR (400 MHz, Chloroform-d): δ 7.79 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 5.56 (d, J = 4.9 Hz, 1H), 4.65 (dd, J = 7.9, 2.5 Hz, 1H), 4.52 (dd, J = 11.6, 4.7 Hz, 1H), 4.41 (dd, J = 11.5, 7.6 Hz, 1H), 4.34 (dd, J = 5.0, 2.5 Hz, 1H), 4.31 (dd, J = 7.9, 1.9 Hz, 1H), 4.16 (ddd, J = 7.7, 4.6, 1.9 Hz, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H)

¹³C NMR (101 MHz, Chloroform-d): δ 166.1, 137.9, 131.3, 129.7, 109.9, 109.0, 101.0, 96.5, 71.3, 70.9, 70.7, 66.3, 64.3, 26.2, 26.1, 25.1, 24.7
To a suspension of estrone (270 mg, 1.00 mmol, 1.0 eq.) in DCM (5 mL) at 0 °C was added py (81 µL, 1.00 mmol, 1.0 eq.) followed by TfCl (128 µl, 1.20 mmol, 1.20 eq.) dropwise. The reaction was stirred for 15 min at 0 °C before warming to rt and stirring for 20 h. The reaction mixture was diluted with EtOAc (20 mL), washed with aq. 1 M HCl (10 mL) and sat. aq. NaHCO₃ (10 mL). The organic phase was dried with anhydrous MgSO₄, filtered and evaporated in vacuo to afford a yellow oil. The oil was purified via flash chromatography (20→40% EtOAc in pentane) to yield S16 (329 mg, 0.82 mmol, 82%) as a colourless solid. Data identical to literature values.¹⁷

³¹H NMR (400 MHz, Chloroform-d): δ 7.34 (d, J = 1.2 Hz, 1H), 7.04 (dd, J = 8.6, 2.8 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 2.98-2.90 (m, 2H), 2.52 (dd, 1H), 2.45-2.37 (m, 1H), 2.30 (td, J = 10.6, 4.3 Hz, 1H), 2.21-2.01 (m, 3H), 2.01-1.95 (m, 1H), 1.71-1.38 (m, 6H), 0.92 (s, 3H)

³¹C NMR (101 MHz, Chloroform-d): δ 220.5, 147.7, 140.4, 139.4, 127.3, 121.4, 118.8 (q, J = 322.3 Hz), 118.5, 50.5, 48.0, 44.2, 37.9, 36.0, 31.6, 29.5, 26.2, 25.8, 21.7, 13.9

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate, S16
2. X-Ray crystallography

For 11, 14, 16 and 18: Single crystal X-ray diffraction data were collected using an Rigaku Oxford Diffraction SuperNova diffractometer fitted with an Oxford Cryosystems Cryostream 700 plus open flow nitrogen cooling device.\textsuperscript{18} The CrysAlisPro software was used for data collection and integration. The structure was solved using charge flipping\textsuperscript{19} with SuperFlip method\textsuperscript{20} within the CRYSTALS suite.\textsuperscript{21} The structures were then modified, improved and optimised by full-matrix least squares on $F^2$ as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2074459-63) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

Compound 11 has a phase transition between 300 K and 150 K. At 300 K there is a single molecule in the asymmetric cell, \textit{i.e.} $Z'=1$. At 150 K the cell has tripled along the $b$-axis and there are three molecules in the asymmetric cell, \textit{i.e.} $Z'=3$. No further studies were performed to find the exact phase transition temperature.
2.1 Crystal data and structure refinement for 11 collected at 300K

Empirical formula C16 H14 O2 S
Formula weight 270.35
Temperature 300 K
Wavelength 1.54184 Å
Crystal system Orthorhombic
Space group P 21 21 21
Unit cell dimensions
\[ a = 6.2560(3) \text{ Å} \] \[ \alpha = 90^\circ. \]
\[ b = 7.6732(3) \text{ Å} \] \[ \beta = 90^\circ. \]
\[ c = 28.1296(8) \text{ Å} \] \[ \gamma = 90^\circ. \]

Volume 1350.32(9) \text{ Å}^3
Z 4
Density (calculated) 1.330 Mg/m³
Absorption coefficient 2.081 mm⁻¹
F(000) 568
Crystal size 0.14 x 0.10 x 0.08 mm³
Theta range for data collection 3.142 to 77.094°.
Index ranges \[-6 \leq h \leq 7, -9 \leq k \leq 8, -35 \leq l \leq 25\]
Reflections collected 4335
Independent reflections 2516 [R(int) = 0.018]
Completeness to theta = 74.781° 99.5 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.85 and 0.82
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2515 / 0 / 174
Goodness-of-fit on F² 1.0021
Final R indices [I>2sigma(I)] R1 = 0.0343, wR2 = 0.0884
R indices (all data) R1 = 0.0389, wR2 = 0.0947
Absolute structure parameter -0.032(12)
Extinction coefficient 20(4)
Largest diff. peak and hole 0.13 and -0.13 e.Å⁻³
### 2.2 Crystal data and structure refinement for 11 collected at 150K

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<td>Density (calculated)</td>
<td>1.377 Mg/m³</td>
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<td>Absorption coefficient</td>
<td>2.156 mm⁻¹</td>
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<td>F(000)</td>
<td>1704</td>
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<td>Crystal size</td>
<td>0.22 x 0.18 x 0.04 mm³</td>
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<tr>
<td>Theta range for data collection</td>
<td>3.744 to 76.292°</td>
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<tr>
<td>Index ranges</td>
<td>-7 ≤ h ≤ 7, -28 ≤ k ≤ 27, -34 ≤ l ≤ 34</td>
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<td>Reflections collected</td>
<td>22609</td>
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<td>Independent reflections</td>
<td>8095 [R(int) = 0.033]</td>
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<td>Completeness to theta = 74.767°</td>
<td>99.6 %</td>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Max. and min. transmission</td>
<td>0.92 and 0.83</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0314, wR2 = 0.0783</td>
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<td>R1 = 0.0342, wR2 = 0.0824</td>
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<td>Absolute structure parameter</td>
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<td>Largest diff. peak and hole</td>
<td>0.32 and -0.26 e.Å⁻³</td>
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### Crystal data and structure refinement for 14

<table>
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<th>Property</th>
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<td>Temperature</td>
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<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
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<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>P 21/c</td>
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<tr>
<td>Unit cell dimensions</td>
<td>a = 7.22830(10) Å, b = 19.74990(10) Å, c = 21.88370(10) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>3123.99(5) Å³</td>
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<tr>
<td>Z</td>
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<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<td>Index ranges</td>
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<tr>
<td>Independent reflections</td>
<td>6514 [R(int) = 0.028]</td>
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<td>Completeness to theta = 76.500°</td>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Max. and min. transmission</td>
<td>0.82 and 0.71</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Goodness-of-fit on F²</td>
<td>0.9991</td>
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<td>Final R indices [I&gt;2σ(I)]</td>
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<td>R indices (all data)</td>
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<td>Extinction coefficient</td>
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<td>Largest diff. peak and hole</td>
<td>0.30 and -0.37 e.Å⁻³</td>
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</table>
2.4 Crystal data and structure refinement for 16

Empirical formula C16 H13 F O2 S
Formula weight 288.34
Temperature 150 K
Wavelength 1.54184 Å
Crystal system Monoclinic
Space group P c
Unit cell dimensions
a = 7.5201(2) Å \[\alpha = 90^\circ.\]
b = 6.1363(2) Å \[\beta = 93.778(2)^\circ.\]
c = 29.1109(7) Å \[\gamma = 90^\circ.\]
Volume 1340.42(7) Å^3
Z 4
Density (calculated) 1.429 Mg/m^3
Absorption coefficient 2.245 mm\(^{-1}\)
F(000) 600
Crystal size 0.20 x 0.10 x 0.05 mm^3
Theta range for data collection 3.043 to 77.111°.
Index ranges -7<=h<=9, -7<=k<=7, -36<=l<=33
Reflections collected 11889
Independent reflections 3740 [R(int) = 0.033]
Completeness to theta = 75.569° 99.6 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.89 and 0.86
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 3738 / 2 / 362
Goodness-of-fit on F^2 1.0019
Final R indices [I>2sigma(I)] R1 = 0.0295, wR2 = 0.0734
R indices (all data) R1 = 0.0318, wR2 = 0.0754
Absolute structure parameter 0.008(14)
Largest diff. peak and hole 0.18 and -0.21 e.Å\(^{-3}\)
2.5 Crystal data and structure refinement for 18

Empirical formula C17H16O2 S
Formula weight 284.38
Temperature 150 K
Wavelength 1.54184 Å
Crystal system Monoclinic
Space group P 21/n
Unit cell dimensions
a = 5.91440(10) Å \(\alpha = 90^\circ\).
b = 16.5154(2) Å \(\beta = 95.2702(14)^\circ\).
c = 14.7712(2) Å \(\gamma = 90^\circ\).
Volume 1436.73(4) Å³
Z 4
Density (calculated) 1.315 Mg/m³
Absorption coefficient 1.981 mm⁻¹
F(000) 600
Crystal size 0.25 x 0.10 x 0.08 mm³
Theta range for data collection 4.025 to 77.086°.
Index ranges -7 ≤ h ≤ 7, -13 ≤ k ≤ 20, -18 ≤ l ≤ 18
Reflections collected 11872
Independent reflections 3022 [R(int) = 0.022]
Completeness to theta = 75.545° 99.6 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.85 and 0.77
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3022 / 0 / 182
Goodness-of-fit on F² 1.0022
Final R indices [I>2σ(I)] R1 = 0.0295, wR2 = 0.0806
R indices (all data) R1 = 0.0308, wR2 = 0.0820
Extinction coefficient 24(4)
Largest diff. peak and hole 0.35 and -0.33 e.Å⁻³
3. References


4. Copies of NMR spectra

1-(phenylsulfonyl)bicyclo[1.1.0]butane, 8a

$^1$H NMR (400 MHz, Chloroform-$d$)

$^{13}$C NMR (101 MHz, Chloroform-$d$)
1-(phenylsulfinyl)bicyclo[1.1.0]butane, 8b

$^1$H NMR (400 MHz, Chloroform-$d$)

$^{13}$C NMR (101 MHz, Chloroform-$d$)
$N,N$-diisopropylbicyclo[1.1.0]butane-1-carboxamide, 8c

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1H$ COSY (500 MHz, Chloroform-$d$)

$^1H$/$^{13}C$ HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-$d$)
Tert-butylbicyclo[1.1.0]butane-1-carboxylate, 8d

\( ^1H \text{ NMR} \) (400 MHz, Chloroform-\( d \))

\( ^{13}C \text{ NMR} \) (101 MHz, Chloroform-\( d \))

S60
1-phenyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 11

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
((3-phenylcyclobut-2-en-1-yl)sulfonyl)benzene, 12

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)
1-(4-nitrophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 13

$^1$H NMR (500 MHz, Chloroform-<i>d</i>)

$^{13}$C NMR (126 MHz, Chloroform-<i>d</i>)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^13$C HSQC (500/126 MHz, Chloroform-$d$)
$^1\text{H}/^{13}\text{C}$ HMBC (500/126 MHz, Chloroform-$d$)
Methyl 4-[(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]benzoate, 14

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
$^{1}H$ COSY (400 MHz, Chloroform-d)

$^{1}H/^{13}C$ HSQC (400/101 MHz, Chloroform-d)
1-(4-{3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl}phenyl)ethan-1-one, 15

$^{1}H$ NMR (500 MHz, Chloroform-d)

$^{13}C$ NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$^1\text{H}/^{13}\text{C}\text{ HMBC}$ (500/126 MHz, Chloroform-$d$)
1-(4-fluorophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 16

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
$^1$H COSY (400 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (400/101 MHz, Chloroform-$d$)
$^{19}$F NMR (377 MHz, Chloroform-$d$)
1-{4-chlorophenyl}-3-{phenylsulfonyl}bicyclo[1.1.0]butane, 17

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1\text{H} \text{COSY} (500 \text{ MHz, Chloroform-d})$

$^1\text{H}/^\text{13C} \text{ HSQC} (500/126 \text{ MHz, Chloroform-d})$
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)
1-(phenylsulfonyl)-3-(p-toly)lbicyclo[1.1.0]butane, 18

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
$^1$H COSY (400 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (400/101 MHz, Chloroform-$d$)
1-(4-methoxyphenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 19

$^1$H NMR (500 MHz, Benzene-d$_6$)

$^{13}$C NMR (126 MHz, Benzene-d$_6$)
$^1$H COSY (500 MHz, Benzene-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Benzene-$d$)
$^1\text{H}/^{13}\text{C} \text{ HMBC}$ (500/126 MHz, Benzene-$d$)
1-(3-bromophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 20

$^1$H NMR (500 MHz, Benzene-d)

$^{13}$C NMR (126 MHz, Benzene-d)
$^1$H COSY (500 MHz, Benzene-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Benzene-$d$)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Benzene-$d$)
3-[(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]phenyl trifluoromethanesulfonate, 21

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-d)

$^{19}$F NMR (470 MHz, Chloroform-d)
Tert-butyldimethyl(3-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenoxy)silane, 22

$^1$H NMR (500 MHz, Benzene-d)

$^{13}$C NMR (126 MHz, Benzene-d)
$^1$H COSY (500 MHz, Benzene-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Benzene-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Benzene-d$_6$)
1-(phenylsulfonyl)-3-(2-(trifluoromethyl)phenyl)bicyclo[1.1.0]butane, 23

^1H NMR (500 MHz, Chloroform-d)

^13C NMR (126 MHz, Chloroform-d)
\(^1\text{H COSY}\) (500 MHz, Chloroform-\(d\))

\(^1\text{H}/^{13}\text{C HSQC}\) (500/126 MHz, Chloroform-\(d\))
$^1\text{H}/^{13}\text{C} \text{ HMBC}$ (500/126 MHz, Chloroform-$d$)

$^{19}\text{F} \text{ NMR}$ (470 MHz, Chloroform-$d$)
1-(phenylsulfonyl)-3-(o-toly) bicyclo[1.1.0]butane, 24

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$$^1$$^H$ COSY (500 MHz, Chloroform-$d$)

$^1$$^H$/$^{13}$$^C$ HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)
2-[(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]benzonitrile, 25

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Chloroform-$d$)
1-(4-bromo-2-fluorophenyl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, 26

$^1$H NMR (500 MHz, Benzene-$d$)

$^{13}$C NMR (126 MHz, Benzene-$d$)
$^{1}H$ COSY (500 MHz, Benzene-$d$)

$^{1}H/^{13}C$ HSQC (500/126 MHz, Benzene-$d$)
$^1$H/$^{13}$C HMBC (500/126 MHz, Benzene-$d$)

$^{19}$F NMR (470 MHz, Benzene-$d$)
1-{3-[phenylsulfonyl]bicyclo[1.1.0]butan-1-yl}naphthalene, 27

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Chloroform-\textit{d})
Ethyl (Z)-3-{3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl}acrylate, 28

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1H/^13C$ HMBC (500/126 MHz, Chloroform-$d$)
(E)-1-(oct-1-en-1-yl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, (E)-29

$^1$H NMR (500 MHz, Benzene-<em>d</em>)

![Image of H NMR spectrum]

$^{13}$C NMR (126 MHz, Benzene-<em>d</em>)

![Image of C NMR spectrum]
$^1$H COSY (500 MHz, Benzene-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Benzene-$d$)
$^1\text{H}/^{13}\text{C} \text{ HMBC}$ (500/126 MHz, Benzene-$d$)
(Z)-1-(oct-1-en-1-yl)-3-(phenylsulfonyl)bicyclo[1.1.0]butane, (Z)-29

$^1$H NMR (500 MHz, Benzene-$d$)

$^{13}$C NMR (126 MHz, Benzene-$d$)
$^1\text{H COSY}$ (500 MHz, Benzene-\textit{d})

$^1\text{H}/^{13}\text{C}$ HSQC (500/126 MHz, Benzene-\textit{d})
$^{1}$H/$^{13}$C HMBC (500/126 MHz, Benzene-$d$)
1,3-dimethyl-5-(3-(phenylsulfonyl)cyclobut-1-en-1-yl)pyrimidine-2,4(1H,3H)-dione, 30

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-d)
4-[(3-{Phenylsulfonyl}bicyclo[1.1.0]butan-1-yl)ethynyl]benzonitrile, 31

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^1$C HSQC (500/126 MHz, Chloroform-$d$)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Chloroform-$d$)
2-(3-[phenylsulfonyl]bicyclo[1.1.0]butan-1-yl)pyridine, 32

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1H$ COSY (500 MHz, Chloroform-d)

$^1H/^13C$ HSQC (500/126 MHz, Chloroform-d)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Chloroform-$d$)
3-[(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]pyridine, 33

$^1$H NMR (500 MHz, Chloroform- $d$)

$^{13}$C NMR (126 MHz, Chloroform- $d$)
$^1$H COSY (500 MHz, Chloroform-d$_2$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d$_2$)
$^1H/^13C\text{ HMBC}$ (500/126 MHz, Chloroform-$d$)
4-[2-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]pyridine, 34

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$\textsuperscript{1}H/\textsuperscript{13}C$ HMBC (500/126 MHz, Chloroform-$d$)
7-chloro-4-[(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]quinolone, 35

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$^1\text{H}/^{13}\text{C} \text{ HMBC}$ (500/126 MHz, Chloroform-$d$)
1-{3-[phenylsulfonyl]bicyclo[1.1.0]butan-1-yl}isoquinoline, 36

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$$^H$/$^{13}C$ HMBC (500/126 MHz, Chloroform-d)
Tert-butyl 5-(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)-1H-indole-1-carboxylate, 37

$^1$H NMR (500 MHz, Benzene-d)

$^{13}$C NMR (126 MHz, Benzene-d)
$^1$H COSY (500 MHz, Benzene-d)

$^1$H/$^13$C HSQC (500/126 MHz, Benzene-d)
$^1\text{H}/^{13}\text{C} \text{ HMBC}$ (500/126 MHz, Benzene -d)}
2,6-bis[3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl]pyridine, 38

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
\[ ^1H/^{13}C \text{ HMBC} (500/126 \text{ MHz, Chloroform-}d) \]
$N,N$-diisopropyl-3-phenylbicyclo[1.1.0]butane-1-carboxamide, 39

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^{1}H/^{13}C$ HMBC (500/126 MHz, Chloroform-$d$)
$N,N$-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.0]butane-1-carboxamide, 40

$^1$H NMR (500 MHz, Chloroform-d)

![1H NMR Spectrum](image1)

$^{13}$C NMR (126 MHz, Chloroform-d)

![13C NMR Spectrum](image2)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-$d$)

$^{19}$F NMR (471 MHz, Chloroform-$d$)
1-phenyl-3-[(4-(trifluoromethyl)phenyl)sulfonyl]bicyclo[1.1.0]butane, 41

$^1$H NMR (400 MHz, Benzene-$d_6$)

$^{13}$C NMR (126 MHz, Benzene-$d_6$)
$^1$H COSY (500 MHz, Benzene-$d$)

$^1$H/$^{13}$C HMBC (500/126 MHz, Benzene-$d$)
$^1$H/$^{13}$C HSQC (500/126 MHz, Benzene-d$_6$)

$^{19}$F NMR (470 MHz, Benzene-d$_6$)
Methyl (2S)-2-[(tert-butoxycarbonylamino)-3-(4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)phenyl)propanoate, 42

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-$d$)
(S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 4-(3-(phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzoate, 43

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-d)
$\text{H}^{1}{\text{H}}^{1}{\text{C}}^{12} \text{HMBC}$ (500/126 MHz, Chloroform-\textit{d})
(3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-5-yl)methyl 4-(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)benzoate, 44

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)
(8R,9S,13S,14S)-13-methyl-3-(3-phenylsulfonyl)bicyclo[1.1.0]butan-1-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one, 45

$^1$H NMR (400 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^13$C HMBC (500/126 MHz, Chloroform-$d$)
1-methoxy-4-[(3-phenylsulfonyl)cyclobut-1-en-1-yl]benzene, 46

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
$^1$H COSY (400 MHz, Chloroform-d)

$^1$H/$^{13}$C HSQC (400/101 MHz, Chloroform-d)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-d)
**Tert-butyldimethyl(3-((phenylsulfonyl)cyclobut-1-en-1-yl)phenoxy)silane, 47**

**$^1$H NMR (500 MHz, Chloroform-$d$)**

**$^{13}$C NMR (126 MHz, Chloroform-$d$)**
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)
Ethyl (1S*,3S*,5R*)-1-phenyl-3-(phenylsulfonyl)bicyclo[2.1.0]pentane-5-carboxylate, 48

$^1$H NMR (400 MHz, Chloroform- $d$)

$^{13}$C NMR (101 MHz, Chloroform- $d$)
$^1$H COSY (400 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (400/101 MHz, Chloroform-$d$)
$^1$H/$^1$C HSQC (500/126 MHz, Chloroform-d) *contains Et$_2$O

$^1$H NOESY (500 MHz, Chloroform-d) *contains Et$_2$O
((3-phenylcyclobuty)sulfonyl)benzene, 49

$^1$H NMR (400 MHz, Chloroform-d)

$^{13}$C NMR (101 MHz, Chloroform-d)
3-chloro-1-methoxy-3-(phenylsulfonyl)cyclobutyl)benzene, 50

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

S175
$^1$H COSY (500 MHz, Chloroform-d)

$^1$H/$^1$C HSQC (500/126 MHz, Chloroform-d)
$^1$H/$^{13}$C HMQC (500/126 MHz, Chloroform-d)

$^1$H NOSEY (400 MHz, Chloroform-d)
1-[[2-fluorophenyl]sulfonyl]-3-phenylbicyclo[1.1.0]butane, 52

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^13$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-$d$)

$^{19}$F NMR (470 MHz, Chloroform-$d$)
Methyl 2'-(3-phenylbicyclo[1.1.0]butan-1-yl)sulfonyl)-[1,1'-biphenyl]-4-carboxylate, 53

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-\textit{d})

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-\textit{d})

S183
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-d)
2,2-difluoro-\(N,N\)-diisopropyl-3-phenylbicyclo[1.1.1]pentane-1-carboxamide, 54

\(^1\text{H NMR}\) (500 MHz, Chloroform-\(d\))

\(^{13}\text{C NMR}\) (126 MHz, Chloroform-\(d\))
\(^1\)H COSY (500 MHz, Chloroform-\(d\))

\(^1\)H/\(^{13}\)C HSQC (500/126 MHz, Chloroform-\(d\))
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)

$^{19}$F NMR (470 MHz, Chloroform-$d$)
2,2-difluoro-N,N-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxamide, 56

$^1$H NMR (500 MHz, Chloroform-d)

$^{13}$C NMR (126 MHz, Chloroform-d)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^13$C HMBC (500/126 MHz, Chloroform-\textit{d})

$^{19}$F NMR (470 MHz, Chloroform-\textit{d})
2,2-difluoro-N,N-diisopropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxamide, 57

$^1$H NMR (500 MHz, Chloroform-$d$)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^{13}$C HMBC (500/126 MHz, Chloroform-$d$)

$^{19}$F NMR (470 MHz, Chloroform-$d$)
2,2-difluoro-3-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pent-1-ene-1-carboxylic acid, 58

**$^1$H NMR (500 MHz, Chloroform-d)**

![H NMR spectrum](image)

**$^{13}$C NMR (126 MHz, Chloroform-d)**

![C NMR spectrum](image)
$^1$H COSY (500 MHz, Chloroform-$d$)

$^1$H/$^{13}$C HSQC (500/126 MHz, Chloroform-$d$)
$^1$H/$^1$C HMBC (500/126 MHz, Chloroform-$d$)

$^{19}$F NMR (470 MHz, Chloroform-$d$)