Supplementary Materials for

Strain-release amination

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General Experimental

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Dry tetrahydrofuran (THF) was obtained by passing the previously degassed solvent through an activated alumina column. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by LC-MS or thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using shortwave UV light as the visualizing agent and iodine (mixed with silica gel) or KMnO4 and heat as developing agents. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.043 – 0.063 mm). NMR spectra were recorded on Bruker AVIII-600, DRX-500, AV-400, and DPX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (CDCl3: 7.26 ppm 1H NMR, 77.2 ppm 13C NMR; MeOH-d4: 3.31 ppm 1H NMR, 29.8 ppm 13C NMR; acetone-d6: 2.05 ppm 1H NMR, 29.8 ppm 13C NMR; C6D6: 7.16 ppm 1H NMR, 128.1 ppm 13C NMR; DMSO-d6: 2.50 ppm 1H NMR, 39.5 ppm 13C NMR, CD3CN: 1.94 ppm 1H NMR, 118.3 ppm 13C NMR). For 19F NMR, CF3Cl was referenced at 0 ppm. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LCMS TOF mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and were uncorrected.
Table S1. Selected optimization reactions in the development of Bn$_2$NMgCl•LiCl

| Entry | $R^1$ | Solvent       | $R^2$ | Metal | Equiv. Amide | Temp            | Time | Additives | Yield |%
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*Entry 10 was adapted from Butov’s work on dehydroadamantane (68). †Dioxane used as solvent for amination step; ‡Diethoxymethane was used as the solvent for [1.1.1]propellane formation; §Equivalents of “turbo amide” and number of different solvents reduced for economics on process scale.
Gram-scale preparation of 2

Preparation of “turbo amide” Bn₂NMgCl•LiCl: To a flame dried round bottom flask under argon was added dibenzylamine (5.7 mL, 30 mmol) and dibutyl ether (7.2 mL). To this was added iPrMgCl•LiCl (27 mL, 1.11M in THF) via syringe at room temp (Caution: vigorous gas evolution!) and stirred at room temp for another 2 hours. Mixture turned a progressively darker red over that period of time. Used directly in reaction below. Note: 1.3M solution of iPrMgCl•LiCl can be used to prepare the turbo amide.

Formation of [1.1.1]propellane: A 110 mL flame-dried pressure tube fitted with a septa and under argon (balloon) was charged with 8 (1 g, 3.41 mmol) and dry dibutyl ether (1 mL). The reaction was cooled to −45 °C in a dry ice/isopropanol bath. PhLi (3.79 mL, 6.82 mmol, 1.8M in dibutyl ether) was added slowly via syringe and stirred at the same temperature for ca. 5 min. The reaction temperature was allowed to warm to 0 °C and stirred for 2h in an ice bath (or in cold room) to form A.

Amination of [1.1.1]propellane: The reaction was removed from the cold room and the reaction temperature was allowed to become ambient. Bn₂NMgCl•LiCl (9 mL, 2 equiv., 0.75M) was added slowly via syringe, the septum was removed and the reaction was quickly capped with a Teflon pressure tube cap. The reaction was transferred to an oil bath that was pre-heated to 50 °C and the reaction was stirred at this temperature for 16 h. The reaction was removed from the oil bath and cooled in an ice bath for ca. 10 min and quenched slowly with sat. aq. NH₄Cl. The reaction was then diluted with EtOAc and transferred into a separatory funnel. The layers were separated and the organics were washed with H₂O (2 X 20 mL). The organics were dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The residual solvent was removed by hi-vacuum and the crude material was passed over a silica pad (20 g) while eluting with EtOAc/hexanes (0 to 3%) to yield of ca. 98% of yellow oil 9 which solidified upon cooling to −20 °C (yields range from 50 – 60%). The material could be further purified by recrystallization from EtOH with cooling to −20 °C overnight.
\[N,N\text{-dibenzylbicyclo}[1.1.1]\text{pentan-1-amine}\ (9)\]

**Physical State:** white solid (m.p. = 46-48 °C);

\[R_f = 0.52\ (1:20\ \text{EtOAc:hexanes, vis. KMnO}_4);\]

\[^1\text{H NMR (600 MHz, CDCl}_3\):} \ \delta\ 7.40\ (\text{ddt, } J = 7.7, 1.5, 0.7\ \text{Hz, 4H}),\ 7.32\ –\ 7.28\ (m, 4H),\ 7.24\ –\ 7.20\ (m, 2H),\ 3.66\ (s, 4H),\ 2.31\ (s, 1H),\ 1.71\ (s, 6H);\]

\[^{13}\text{C NMR (151 MHz, CDCl}_3\):} \ \delta\ 140.8\ (2C),\ 128.5\ (4C),\ 128.1\ (4C),\ 126.7\ (2C),\ 61.3,\ 55.1\ (2C),\ 49.7\ (3C),\ 22.9;\]

**HRMS (ESI-TOF):** calc’d for \(C_{19}H_{22}N\) [M+H\(^+\)] 264.1752; found 264.1756.

**Fig. S2.** Crystal structure of \(N,N\text{-dibenzylbicyclo}[1.1.1]\text{pentan-1-amine}\ (9)

**Table S2.** Crystal data and structure refinement for 9

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Temperature: 100(2) K
Wavelength: 0.71073 Å
Crystal system: Orthorhombic
Space group: P 21 21 21
Unit cell dimensions:
- a = 5.8460(4) Å, α = 90°.
- b = 14.9613(9) Å, β = 90°.
- c = 16.7311(12) Å, γ = 90°.
Volume: 1463.37(17) Å³
Z: 4
Density (calculated): 1.195 Mg/m³
Absorption coefficient: 0.069 mm⁻¹
F(000): 568
Crystal size: 0.290 x 0.260 x 0.200 mm³
Theta range for data collection: 1.826 to 28.274°.
Index ranges: -7 ≤ h ≤ 7, -19 ≤ k ≤ 19, -22 ≤ l ≤ 17
Reflections collected: 8634
Independent reflections: 3633 [R(int) = 0.0407]
Completeness to theta = 25.000°: 99.9 %
Absorption correction: Multi-scan
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 3633 / 0 / 181
Goodness-of-fit on F²: 1.022
Final R indices [I>2σ(I)]: R1 = 0.0415, wR2 = 0.1020
R indices (all data): R1 = 0.0455, wR2 = 0.1051
Absolute structure parameter: -0.1(10)
Extinction coefficient: n/a
Largest diff. peak and hole: 0.201 and -0.233 e.Å⁻³

**Deprotection of 9 to bicyclo[1.1.1]pentan-1-amine hydrochloride (2):** To a mixture of N,N-dibenzylbicyclo[1.1.1]pent-1-yl-amine (2.1 g, 8.0 mmol) in methanol (20 mL) was added 20% palladium hydroxide on carbon (45 mg, 50% water) in one portion at 25 °C under nitrogen. The stainless steel vessel was attached to a pressure apparatus, stirring was initiated (900 rpm) and after three 1.5 to 4 bar purges of nitrogen the reaction was pressurized under 4 bar of hydrogen and left at 50 °C. After 72 h, the chamber was de-pressurized and purged with three 1.5 to 4 bar purges of nitrogen. LC/MS gave only product. The crude product was filtered through a glass fiber filter and 3.8 mL of 4M HCl-dioxane (2 eq) was added to the filtrate. The solvent was removed under reduced pressure and a beige solid was isolated from EtOAc (819 mg). The
beige solid was triturated with EtOAc and filtered. A fluffy off-white solid was collected (702 mg, 74% yield). All spectroscopic data matched that which was previously reported in the literature (10).

**Bicyclo[1.1.1]pentan-1-amine hydrochloride (2)**

**Physical State:** off-white solid (m.p. = 241-243 °C; lit: 247-251 °C);

$R_f = 0.70$ (10% MeOH in EtOAc + 0.1% NH$_4$OH, vis. I$_2$);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.94 (s, 3H), 2.58 (s, 1H), 1.98 (s, 6H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 51.0 (3C), 45.5, 23.6;

HRMS (ESI-TOF): calc’d for C$_5$H$_9$N [M$^+$] 83.0735; found 83.0734.

**Graphical Gram-Scale Preparation of 9.**
Fig. S3. **Left.** Tetrahalide 8 is added to a thick walled pressure tube equipped with a stir bar. **Center.** Bu$_2$O is added under an argon balloon sealed with a septum. **Right.** The mixture is cooled to −45 °C with a dry ice/isopropanol bath.

Fig. S4. **Left.** To consistently maintain −45 °C for ca. 20 minutes, the dry ice should be dissolved in isopropanol. The bath should appear homogeneous and not contain any solid pieces of dry ice. **Right.** After addition of the PhLi, the solution will change from a clear colorless/white to clear yellow.
Fig. S5. Left. The reaction was moved to a cold room (ca. 5 °C) and stirred for 2h under argon. **Right.** Close up view of reaction mixture in cold room.

Fig. S6. **Left.** Flask of the “turbo amide” solution (ready to be used). **Center.** Upon addition of the “turbo amide” the color of the reaction mixture changes from yellow to orange/red. **Right.** Close up of the reaction mixture after the addition of the “turbo amide.”
**Fig. S7.** Left. The reaction is heated to 50 °C for ca. 16h. **Right.** Close up view of the heated reaction mixture.

**Fig. S8.** Left. After completion, the mixture is cooled to 0 °C in an ice bath. **Right.** The color changes from red to yellow after slowly quenching with sat. aq. NH₄Cl.
Fig. S9. **Left.** The quenched reaction mixture is diluted with EtOAc. **Right.** The solution is transferred to a separatory funnel and the organics washed with H$_2$O.

Fig. S10. **Left.** The combined organics are dried over Na$_2$SO$_4$. **Right.** The combined organics are filtered through cotton and concentrated *in vacuo.*
Fig. S11. **Left.** The crude material is wet loaded onto silica (ca. 20 g) and eluted in a single flask (no fractions) with 0 to 3% EtOAc in hexanes. **Right.** Alternatively, the crude material was dry loaded onto a silica pad in a sintered glass funnel and eluted in a single flask (no fractions) with 0 to 3% EtOAc in hexanes. Note: this picture is from a 10 g scale run.

Fig. S12. **Left.** The crude material is obtained as yellow oil that solidified upon cooling in a –20 °C freezer. **Right.** The material can be further purified by recrystallization from EtOH at –20 °C followed by collection by filtration, washing with ice cold EtOH, and drying under vacuum.
Multi-decagram Scale Prep of 9 and 2 (conducted at WuXi)

Preparation of “turbo amide” \( \text{Bn}_2\text{NMgCl-LiCl} \): To a stirred colorless solution of dibenzyamine (150.0 g, 0.76 mol) in dibutyl ether (150 mL) was added dropwise \( \text{iPrMgCl-LiCl} \) (450 mL, 0.76 mol, 1.3 M in THF) between 5-10 °C over a period of 50 min. The mixture turned dark red during this time. After the addition, it was slowly warmed to 25 °C and stirred for two hours. This solution was used for the next step directly without further workup.

Amination of [1.1.1]propellane: The reaction was carried out in two parallel batches. To a stirred suspension of compound 8 (112.7 g, 0.38 mol) in dibutyl ether (120 mL) was added dropwise \( \text{PhLi} \) (400 mL, 0.76 mol, 1.9 M in dibutyl ether) between –40 to –45 °C over a period of 1h. After the addition was complete, the dark reaction solution was stirred at 0 °C for two hours. The solution of \( \text{Bn}_2\text{NMgCl-LiCl} \) (0.76 mol) was added dropwise to the above mixture between 5-10 °C over a period of 30 min. After addition, the orange mixture was heated to 60 °C (the oil bath was preheated to 60 °C) and stirred at that temperature for 16 hours. The reaction mixture was cooled to 0 °C and sat. aq. \( \text{NH}_2\text{Cl} \) (200 mL) was added dropwise to the above mixture between 5-15 °C. The combined mixtures from two batches were filtered and the filtrate was extracted with EtOAc (2 x 1.5 L). The combined organic layers were washed with brine (1 L), dried over \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated to give the crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether (100%) to give the desired product as a liquid. The product was triturated with heptane (400 mL) with stirring between –20 to –30 °C for 1h. Many solids were formed and the mixture was filtered immediately. The solid was collected to give compound 9 (91 g, 45.5%) as an off-white solid. The filtrate was evaporated under reduced pressure to give a second batch of crude product that was purified by column chromatography on silica gel eluted with petroleum ether (100%) to give the desired product as a liquid. The product was triturated with heptane (100 mL) with stirring between –20 to –30 °C for 1h. The mixture was filtered as soon as possible and the solid was collected (41 g). Both batches of solid were combined together to give compound 9 as a white solid. 132 g of compound 9 was prepared from 275.4 g of compound 8; the overall yield was 54.0%. The spectroscopic data was identical to that reported above.
Deprotection step: Synthesis of bicyclo[1.1.1]pentan-1-amine hydrochloride (2): The reaction was carried out in three parallel batches. To a mixture of compound 9 (30.0 g, 0.114 mol) in MeOH (600 mL) was added Pd(OH)$_2$/C (2.0 g, 20% Pd(OH)$_2$, 50% H$_2$O) in one portion at 25 °C under argon. After addition, it was degassed with argon two times and purged with H$_2$ two times. The reaction mixture was stirred at 30 °C under 50 psi of H$_2$ for 12 hours. The mixture was allowed to stand for 24 hours before workup. TLC (petroleum ether/EtOAc = 20/1, EtOAc /MeOH = 20/1, UV, I$_2$) showed that the starting material was consumed completely and the desired product was detected. The mixtures from three batches were filtered through a pad of Celite and the filter cake was washed with MeOH (2 x 600 mL). HCl-dioxane (4.0 M, 200 mL) was added dropwise to the above filtrate between 0–3 °C. After addition, it was stirred at 25 °C for 30 min. The mixture was evaporated under reduced pressure to give a crude product, which was triturated with EtOAc (100 mL) with stirring for 30 min. The mixture was filtered and the solid was collected to give 2 (32.0 g, 78.3%) as a light-brown solid. The spectroscopic data was identical to that reported above.

Preparation of [1.1.1]propellane stock solution (10,43)

A 250 mL flame dried flask under argon was charged with 8 (9.51 g, 32.45 mmol) and dry diethyl ether (20 mL). The reaction was cooled to –40 °C in a dry ice/isopropanol bath. PhLi (36 mL, 64.9 mmol, 31.8 M in dibutyl ether) was added slowly via syringe and stirred at the same temperature for ca. 5 min. The reaction temperature was allowed to warm to 0 °C and stirred for 2 h in an ice bath (or in cold room). Upon completion of the reaction, the solvent was removed via rotovap (pump pressure of ca. 4 Torr) in a room temperature rotovap bath and the catch flask of the rotovap was immersed in a –78 °C bath. The product (A) was collected as a clear, colorless solution in diethyl ether in the catch flask and the approximate concentration of the solution was calculated using quantitative NMR.

Quantitative NMR Experiment:

A sample of the solution containing A (200 µL) in diethyl ether was diluted with dichloroethane (DCE) (50 µL) and CDCl$_3$ was added (ca. 0.5 mL). The ratio of the DCE:propellane was determined and used for the calculation of the concentration of the propellane solution. This is run in duplicate and the average of the two runs is used as the final approximated concentration.

Determination of the Concentration of Dichloroethane:

50µl DCE X 1.253g/mL = 62.65mg DCE ÷ 98.96mg/mmol = 0.63mmol DCE
0.63 was then divided by the ratio of DCE:propellane NMR peaks. We obtained ratios of 3.03:1 and 2.74:1.

\[ [\text{propellane stock}] = \left( \frac{0.63}{\text{nmr peak ratio}_{\text{DCE/stock}}} \right) \div 0.2 \text{mL} \]

**Sample 1:** \( 0.63 \text{mmol} \div 3.03 \div 0.2 \text{mL} = 1.035 \text{M} \)

**Sample 2:** \( 0.63 \text{mmol} \div 2.74 \div 0.2 \text{mL} = 1.145 \text{M} \)

**Average = 1.09 M.**

**Overall Yield Calculation:**

Theoretical yield of 10 g solution: \( (10 \text{ g} \div 293 \text{ (MW of tetrahalide 8)} \times 34.13 \text{ mmol}) \times 66 \text{ (mw of propellane A)} = 2.252 \text{ g} \)

Calculated concentration X mL of propellane solution X 66 (Propellane MW) = g propellane in solution.

\( 1.09 \text{ M} \times 25 \text{ mL} \times 66 = 1.798 \text{ g} \) (~ 80% yield)

**Note:** We have obtained yields that range from 78% (6 g scale) to 95% (9.51 g scale) depending on the scale.
Graphical Preparation of [1.1.1]propellane stock solution in Et₂O

Fig. S13. Left. Tetrahalide 8 is dissolved in Bu₂O under argon and sealed with a septum. Right. The reaction is cooled to –45 °C in a dry ice/isopropanol bath.

Fig. S14. Left. To consistently maintain –45 °C for ca. 20 minutes, the dry ice should be dissolved in isopropanol. The bath should appear homogeneous and not contain any solid pieces of dry ice. Right. Addition of PhLi at –45 °C.
Fig. S15. **Left.** After addition of the PhLi, the solution will change from a clear colorless/white to clear yellow. **Right.** Close up view of yellow solution after PhLi addition.

Fig. S16. **Left.** Reaction is transferred to a cold room (*ca.* 5 °C) and stirred for 2h under argon. The clear yellow solution becomes an opaque yellow suspension once warmed to *ca.* 5 °C. **Right.** Close up view of the suspension.
Fig. S17. **Left.** After stirring for 2h, the suspension turns a dark brown color. **Right.** Close up view of the suspension.

Fig. S18. **Left.** The suspension is distilled directly on the rotovap. **Right.** The water bath is maintained at *ca.* 20 °C during the course of the distillation.
Fig. S19. **Left.** The receiving flash is immersed in a dry ice/acetone bath at –78 °C. **Right.** The pressure of the distillation is carefully controlled beginning at *ca.* 10 Torr.

Fig. S20. **Left.** View of the distillation in progress. **Right.** The pressure is reduced to *ca.* 4 Torr to complete the distillation.
Fig. S21. Left. View of the reaction flask at the end of distillation. Do not distill to dryness; the flask should contain a suspension of salts in Bu$_2$O. Right. Stock solution of [1.1.1]propellane in diethyl ether.

**Starting Amines for Strain Release Amination**

Aniline, N-methylaniline, benzylamine, dibenzylamine, diallylamine, morpholine, piperidine, 4-phenylpiperidine, N-benzylmethylamine, N-benzylethylamine, N-benzyl-(cyclobutylmethyl)amine, nornicotine, perhydroisoquinoline, 1,2,3,4-tetrahydroisoquinoline, 1-(3-methoxyphenyl)-2,2-dimethylpiperazine, maprotiline hydrochloride, nortriptyline, sertraline, paroxetine, fluoxetine, lorcaserin, quipazine, and amoxapine were purchased from commercial sources and were used as received. All others are referenced in the appropriate sections.

![Chemical Structure](attachment:image)

(S)-1-benzyl-N-ethyl-3-methylpyrrolidin-3-amine (S8)

In a 100 mL RB flask, (R)-N-(1-benzyl-3-methylpyrrolidin-3-yl)acetamide (44) (683 mg, 2.94 mmol) was diluted with THF (5.00 mL, c=0.588 M) under nitrogen and cooled to 0 °C. Lithium aluminum hydride (2.0 M in THF) (411 mg, 10.3 mmol, 5.14 mL, 2.0 M) was then added drop-
wise (bubbling noted at beginning of addition) and the vessel warmed to ambient temperature followed by fitting with a reflux condenser and heating to reflux temperature overnight (mantle set to 75 °C). After ~21 hours, the reaction was cooled to ambient temperature. LC/MS indicated complete reduction. The reaction was cooled to 0 °C, diluted with diethyl ether and treated sequentially with 0.4 mL water, 0.4 mL 15% KOH and 1.2 mL water) then warmed to ambient temperature. After 10 minutes, magnesium sulfate was added, the mixture stirred for 5 minutes, and then filtered (solids washed with diethyl ether). The filtrate was concentrated to give S8 (466.4 mg, 73% yield).

**Physical State:** colorless oil;

$$R_f = 0.31\ (10:1\ \text{CH}_2\text{Cl}_2:\text{MeOH});$$

$$[\alpha]^{22}_D = -2.6\ (c = 1.3, \text{MeOH});$$

$^1\text{H NMR (400 MHz, DMSO-}d_6\text{):} \delta 7.33 - 7.27\ (m, 4\text{H}), 7.26 - 7.18\ (m, 1\text{H}), 3.60 - 3.50\ (m, 2\text{H}), 2.63 - 2.44\ (m, 5\text{H}), 2.28\ (d, J = 8.9\ Hz, 1\text{H}), 1.80 - 1.70\ (m, 1\text{H}), 1.60 - 1.51\ (m 1\text{H}), 1.25\ (\text{br s, 1H}), 1.16\ (s, 3\text{H}), 0.99\ (t, J = 7.1\ Hz, 3\text{H});$$

$^{13}\text{C NMR (101 MHz, DMSO-}d_6\text{):} \delta 139.3, 128.2\ (2\text{C}), 128.0\ (2\text{C}), 126.6, 65.9, 60.1, 59.7, 53.0, 37.7, 36.9, 26.6, 16.0;$$

**HRMS (ESI-TOF):** calc’d for C$_{14}$H$_{23}$N$_2$ [M+H$^+$] 219.1856; found 219.1859.

![Structure](image)

**N-benzyl-2-(3-methoxyphenyl)ethan-1-amine (S9)**

To a solution of 2-(4-methoxyphenyl)ethan-1-amine (1.48 g, 9.80 mmol, 1.0 equiv.) in dry trifluoroethanol (50 mL) was added benzaldehyde (998 µL, 9.80 mmol, 1.2 equiv.) and the mixture stirred at 40 °C for 5 min. The reaction was cooled to 0 °C and NaBH$_4$ (435 mg, 1.2 equiv.) was added in 3 equal portions and the reaction stirred at room temperature until TLC indicated complete conversion (ca. 60 min.) Water was added and the mixture extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica
gel, 0% to 40% EtOAc:hexanes) to give 1.23 g of S9 (52%).

**Physical State:** colorless oil;

\( R_f = 0.60 \) (100% EtOAc);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.35 – 7.28 (m, 4H), 7.28 – 7.20 (m, 2H), 6.83 – 6.80 (m, 1H), 6.77 (dd, \( J = 6.6, 1.1 \) Hz, 2H), 3.82 (s, 2H), 3.80 (s, 3H), 2.92 (td, \( J = 7.1, 0.8 \) Hz, 2H), 2.82 (t, \( J = 7.1 \) Hz, 2H), no N–H peak observed;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 159.8, 141.8, 140.4, 129.5, 128.5 (2C), 128.2 (2C), 127.0, 121.2, 114.5, 111.6, 55.2, 54.0, 50.5, 36.5;

HRMS (ESI-TOF): calc’d for C\(_{16}\)H\(_{20}\)NO [M+H\(^+\)] 242.1545; found 242.1542.

\[ \text{Bn} \quad \text{N} \quad \text{H} \]

\[ \text{N}} \quad \text{benzyl-2-(pyridin-3-yl)ethan-1-amine (S10)} \]

To a solution of 3-(2-aminoethyl)pyridine in dry MeOH (4 mL) was added benzaldehyde (200 \( \mu \)L, 2 mmol, 1.0 equiv.) and the mixture stirred at 40 °C for 12h. The reaction was cooled to 0 °C and NaBH\(_4\) (100 mg, 1.2 equiv.) was added in 3 equal portions and the reaction stirred at room temperature until TLC indicated complete conversion (ca. 60 min.). Water was added and the mixture extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0% to 20% MeOH in EtOAc) to give 356 mg of S10 (84%).

**Physical State:** yellow oil;

\( R_f = 0.29 \) (3:7 EtOAc:hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 8.49 – 8.45 (m, 2H), 7.54 – 7.50 (m, 1H), 7.34 – 7.28 (m, 4H), 7.26 – 7.23 (m, 1H), 7.21 (ddd, \( J = 7.8, 4.8, 0.9 \) Hz, 1H), 3.83 (s, 2H), 2.92 (td, \( J = 7.2, 1.0 \) Hz, 2H), 2.84 (t, \( J = 7.2 \) Hz, 2H), no N–H peak observed;

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 150.3, 147.9, 136.3, 135.3, 128.6 (2C), 128.5, 128.4 (2C), 127.3, 123.5, 53.8, 50.1, 33.5;
HRMS (ESI-TOF): calc’d for C_{14}H_{17}N_{2} [M+H^+] 213.1392; found 213.1387.

General medicinal chemistry procedure for the propellerization of amines using the propellane stock solution (prepared above)

\( N,N\text{-dibenzylbicyclo[1.1.1]pentylamine (9)} \): To a flame-dried vessel under argon was added dibenzylamine (198 \( \mu \)L, 1.0 mmol) and dry THF (1 mL). To this was added \( iPrMgCl\cdot LiCl \) (0.90 mL, 1.0 mmol, 1.11M in THF) via syringe at room temp (CAUTION: gas evolution) and stirred at room temp for 2h. To this solution was added a stock solution of propellane (0.57 mL, 0.50 mmol, 0.875M in diethyl ether). The vial was sealed and heated to 90 \(^\circ\)C overnight. The reaction was cooled to 0 \(^\circ\)C and quenched with sat. aq. \( \text{NH}_4\text{Cl} \) (2 mL) and \( \text{H}_2\text{O} \) (2 mL) and extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. The residual oil was purified by flash chromatography (SiO\(_2\), 0% hexanes \( \rightarrow \) 20% EtOAc/hexanes) to give the desired product (9, 62%). All spectroscopic data matched previously prepared samples.

Note: Dibenzylamine dihydrochloride can also be used in the above preparation in place of dibenzylamine. Two equivalents of \( iPrMgCl\cdot LiCl \) (1.80 mL, 2.0 mmol, 1.11M in THF) are needed and 9 is obtained in 54% yield. The spectroscopic data was identical to that reported above.

Notes, Troubleshooting, and Limitations for the “Propellerization” of Amines:

1. If the “turbo amide” as prepared above is insoluble, add additional THF to give a homogeneous solution. The solution or suspension may also become homogeneous upon heating to 90 \(^\circ\)C.
2. In some cases, the hydrochloride salt of the starting amine may be used, but the resulting yields may be lower. It is recommended to use the free base wherever possible.
3. Higher yields of products are obtained with increasing equivalents of turbo amide. For precious amines, a stoichiometry of 1:1 amine:propellane should still give product. Alternatively, complex amines have been demonstrated to be recoverable unchanged in high yields (ca. 90%, see 33 – 38) after completion of the reaction.
4. Adding excess propellane to the reaction mixture results in no product formation.
5. Excessive dilution of the reaction mixture results in lower yields.
6. Limitations:
   a. Primary amines cannot be used as the source of “turbo amide.” Instead, a benzyl group can be added to the primary amine and removed after “propellerization.”
b. Turbo amides of 2-pyridyl-substituted amines are generally unreactive with propellane under the above conditions. This is presumed to be due to chelation of the magnesium between the amide nitrogen and pyridine nitrogen.

c. Functional groups such as ketones, amides, carbamates, and free alcohols or thiols are incompatible with “turbo amides.”

Substrates for the “Propellerization” of Amines

1-(bicyclo[1.1.1]pentan-1-yl)-4-phenylpiperidine (12)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 4-phenylpiperidine to 12 in 50% yield.

Physical State: White solid (m.p. = 47-48 °C);

\( R_f = 0.55 \) (1:4 EtOAc:hexanes, vis. KMnO₄);

\(^1\text{H} \text{NMR (400 MHz, CDCl}_3\):} \ \delta \ 7.37 - 7.16 (m, 5H), 3.06 (dt, \( J = 12.5, 3.0 \) Hz, 2H), 2.47 (d, \( J = 5.1 \) Hz, 2H), 2.14 (td, \( J = 11.5, 3.1 \) Hz, 2H), 1.95 – 1.74 (m, 10H);

\(^{13}\text{C NMR (101 MHz, CDCl}_3\):} \ \delta \ 146.6, 128.5 (2C), 127.0 (2C), 126.2, 60.9, 49.0 (3C), 47.9 (2C), 42.7, 33.2 (2C), 22.3;

HRMS (ESI-TOF): calc’d for \( C_{16}H_{22}N \) [M+H\(^+\)] 228.1752; found 228.1755.
**Fig. S22.** Crystal structure of 1-(bicyclo[1.1.1]pentan-1-yl)-4-phenylpiperidine (12)

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</table>
R indices (all data) 
R1 = 0.0552, wR2 = 0.1258
Largest diff. peak and hole 
0.313 and -0.259 eÅ⁻³

\( N\)-benzyl-\(N\)-methylbicyclo[1.1.1]pentan-1-amine (13)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert \( N\)-benzylmethylamine to 13 in 48% yield.

**Physical State:** colorless oil;

\( R_f = 0.68 \) (20% EtOAc in hexanes, vis. KMnO₄);

\( ^1H \) NMR (500 MHz, CDCl₃): \( \delta \) 7.42 – 7.38 (m, 4H), 7.34 – 7.32 (m, 1H), 5.59 (s, 2H), 2.52 (s, 1H), 2.21 (s, 3H), 1.90 (s, 6H);

\( ^{13}C \) NMR (125 MHz, CDCl₃): \( \delta \) 139.5, 129.1 (2C), 128.3 (2C), 127.0, 61.7, 57.5, 48.4 (3C), 37.1, 22.3;

**HRMS (ESI-TOF):** calc’d for C₁₃H₁₈N [M+H⁺] 188.1439; found 188.1441.

\( N\)-benzyl-\(N\)-ethylbicyclo[1.1.1]pentan-1-amine (14)

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert \( N\)-benzylethylamine to 14 in 64% yield.

**Physical State:** colorless oil;
$R_f = 0.50$ (3% MTBE/heptane, vis. KMnO$_4$);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.35 – 7.25 (m, 4H), 7.23 – 7.15 (m, 1H), 3.58 (s, 2H), 2.53 (q, $J = 7.5$ Hz, 2H), 2.33 (s, 1H), 1.72 (s, 6H), 0.93 (t, $J = 7.1$ Hz, 3H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 141.1, 128.5 (2C), 128.4 (2C), 126.9, 61.2, 53.4, 49.9 (3C), 44.1, 22.8, 13.6;

HRMS (ESI-TOF): calc’d for C$_{14}$H$_{20}$N [M+H$^+$] 202.1596; found 202.1597.

![Diagram](image)

$N$-benzyl-$N$-isobutylbicyclo[1.1.1]pentan-1-amine (15)

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert $N$-benzylisobutylamine$^{45}$ to 15 in 72% yield.

Physical State: colorless oil;

$R_f = 0.60$ (5% EtOAc/heptane, vis. I$_2$);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.35 – 7.24 (m, 4H), 7.23 – 7.14 (m, 1H), 3.57 (s, 2H), 2.30 (s, 1H), 2.20 (d, $J = 7.1$ Hz, 2H), 1.67 (s, 6H), 1.56 (dt, $J = 13.5$, 6.7 Hz, 1H), 0.77 (d, $J = 6.6$ Hz, 6H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 140.9, 128.0 (2C), 127.8 (2C), 126.4, 61.0, 58.7, 55.2, 49.0 (3C), 26.9, 22.2, 20.5 (2C);

HRMS (ESI-TOF): calc’d for C$_{16}$H$_{24}$N [M+H$^+$] 230.1909; found 230.1908.
N-Benzyl-N-(2,2-diethoxyethyl)bicyclo[1.1.1]pentan-1-amine (16)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl-(2,2-diethoxyethyl)amine\textsuperscript{46} to 16 in 12% yield.

**Physical State:** colorless oil;

\[ R_f = 0.63 \text{ (19\% EtOAc/hexanes, vis. KMnO}_4\text{);} \]

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\text{): } \delta 7.35 \text{ (d, } J = 7.0 \text{ Hz, 2H), 7.30 - 7.24 \text{ (m, 2H), 7.20 \text{ (t, } J = 7.3 \text{ Hz, 1H), 4.42 \text{ (t, } J = 5.2 \text{ Hz, 1H), 3.74 \text{ (s, 2H), 3.55 \text{ (dq, } J = 9.3, 7.1 \text{ Hz, 2H), 3.43 \text{ (dq, } J = 9.3, 7.0 \text{ Hz, 2H), 2.70 \text{ (d, } J = 5.3 \text{ Hz, 2H), 2.33 \text{ (s, 1H), 1.75 \text{ (s, 6H), 1.15 \text{ (t, } J = 7.1 \text{ Hz, 6H);}}} \]

\[ \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3\text{): } \delta 141.1, 128.7 \text{ (2C), 128.1 \text{ (2C), 126.7, 102.6, 62.1 \text{ (2C), 61.3, 55.7, 53.5, 49.9 \text{ (3C), 22.8, 15.5 \text{ (2C);}}} \]

**HRMS (ESI-TOF):** calc’d for C\textsubscript{18}H\textsubscript{28}NO\textsubscript{2} [M+H\textsuperscript{+}] 290.2120; found 290.2116.

N-Benzyl-N-(2-(benzyloxy)ethyl)bicyclo[1.1.1]pentan-1-amine (17)

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl-(2-(benzyloxy)ethyl)amine\textsuperscript{47} to 17 in 51% yield.

**Physical State:** colorless oil;
$R_f = 0.81$ (3:1 heptane/EtOAc, vis. KMnO₄);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.36 – 7.24 (m, 9H), 7.23 – 7.17 (m, 1H), 4.39 (s, 2H), 3.65 (s, 2H), 3.41 (t, $J = 6.5$ Hz, 2H), 2.68 (t, $J = 6.5$ Hz, 2H), 2.32 (s, 1H), 1.70 (s, 6H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 140.4, 138.5, 128.1 (2C), 128.0 (2C), 127.9 (2C), 127.3 (2C), 127.2, 126.5, 71.9, 68.6, 60.6, 54.3, 49.3, 49.2 (3C), 22.1;


$N$-benzyl-$N$-cyclobutylbicyclo[1.1.1]pentan-1-amine (18)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert $N$-benzylcyclobutylamine (48) to 18 in 42% yield.

Physical State: colorless oil;

$R_f = 0.80$ (3:7 EtOAc:hexanes, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.35 (d, $J = 7.6$ Hz, 2H), 7.30 – 7.23 (m, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 3.57 (s, 2H), 3.37 – 3.28 (m, 1H), 2.24 (s, 1H), 2.03 – 1.89 (m, 4H), 1.67 (s, 8H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 141.8, 128.4 (2C), 128.0 (2C), 126.5, 60.1, 56.5, 51.6, 50.5 (3C), 29.6 (2C), 23.6, 15.3;

HRMS (ESI-TOF): calc'd for $C_{16}H_{22}N$ [M+H$^+$] 228.1752; found 228.1753.
**N-benzyl-N-(cyclobutylmethyl)bicyclo[1.1.1]pentan-1-amine (19)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl(cyclobutylmethyl)amine to 19 in 46% yield.

**Physical State:** colorless oil;

\( R_f = 0.70 \) (3% MTBE/heptane, vis. KMnO₄);

\[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO-}\textsubscript{d₆): } \delta 7.33 - 7.24 \text{ (m, 4H), 7.22 - 7.15 } \text{ (m, 1H), 3.55 (s, 2H), 2.47 (d, } J = 7.3 \text{ Hz, 2H), 2.40 - 2.32 } \text{ (m, 1H), 2.32 (s, 1H), 1.94 - 1.83 } \text{ (m, 2H), 1.81 - 1.61 } \text{ (m, 8H), 1.53 - 1.40 } \text{ (m, 2H);}
\]

\[
\text{\textsuperscript{13}C NMR (101 MHz, DMSO-}\textsubscript{d₆): } \delta 141.5, 128.5 \text{ (2C), 128.3 (2C), 126.9, 61.4, 56.9, 54.7, 49.6 (3C), 34.5, 26.9 (2C), 22.6, 18.4;}
\]

**HRMS (ESI-TOF):** calc’d for C\textsubscript{17}H\textsubscript{24}N \([\text{M+H}^+\]) 242.1909; found 242.1907.

**N-benzyl-N-(thiophen-3-ylmethyl)bicyclo[1.1.1]pentan-1-amine (20)**

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl-(thiophen-3-ylmethyl)amine (49) to 20 in 74% yield.

**Physical State:** colorless oil;

\( R_f = 0.30 \) (1:40 EtOAc:hexanes, vis. KMnO₄);
**1H NMR (600 MHz, CDCl₃):** \(\delta\) 7.35 (d, \(J = 7.1\) Hz, 2H), 7.30 – 7.24 (m, 2H), 7.23 – 7.17 (m, 2H), 7.11 – 7.04 (m, 2H), 3.65 (s, 2H), 3.63 (s, 2H), 2.30 (s, 1H), 1.69 (s, 6H);

**13C NMR (151 MHz, CDCl₃):** \(\delta\) 141.1, 140.2, 127.8 (2C), 127.7, 127.5 (2C), 126.1, 124.5, 121.2, 60.6, 54.2, 49.5, 49.1 (3C), 22.3;

**HRMS (ESI-TOF):** calc’d for C₁₇H₂₀N₅ [M+H⁺] 270.1316; found 270.1312.

![Structure](image)

1-benzyl-N-(bicyclo[1.1.1]pentan-1-yl)-N-ethyl-3-methylpyrrolidin-3-amine (21)

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert (S)-1-benzyl-N-ethyl-3-methylpyrrolidin-3-amine S₈ to 21 in 54% yield.

**Physical State:** light yellow oil;

\(R_f = 0.29\) (3:1 heptane:EtOAc, vis. KMnO₄);

\([\alpha]^{22}_D = -19.0\) (c = 0.60, MeOH);

**1H NMR (400 MHz, DMSO-d₆):** \(\delta\) 7.33 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 3.62 (d, \(J = 13.3\) Hz, 1H), 3.53 (d, \(J = 13.3\) Hz, 1H), 2.73 – 2.66 (m, 1H), 2.65 – 2.38 (m, 5H), 2.25 (s, 1H), 1.94 – 1.85 (m, 7H), 1.66 – 1.58 (m, 1H), 1.19 (s, 3H), 0.96 (t, \(J = 7.1\) Hz, 3H);

**13C NMR (101 MHz, DMSO-d₆):** \(\delta\) 139.2, 128.2 (2C), 128.1 (2C), 126.6, 67.0, 65.2, 59.7, 59.5, 52.5 (3C), 52.3, 41.2, 23.6, 23.5, 18.0 (1 sp³ signal missing due to solvent overlap);

**HRMS (ESI-TOF):** calc’d for C₁₉H₂₉N₂ [M+H⁺] 285.2331; found 285.2325.
(±)-3-(1-(bicyclo[1.1.1]pentan-1-yl)pyrrolidin-2-yl)pyridine (22)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert rac-nornicotine to 22 in 54% yield.

**Physical State:** yellow oil;

$R_f = 0.42$ (3:7 EtOAc:hexanes, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.53 (d, $J = 2.2$ Hz, 1H), 8.48 – 8.40 (m, 1H), 7.71 (dt, $J = 7.8$, 2.1 Hz, 1H), 7.19 (dd, $J = 7.8$, 4.8 Hz, 1H), 3.57 (t, $J = 8.0$ Hz, 1H), 3.15 – 3.02 (m, 1H), 2.59 (q, $J = 8.8$ Hz, 1H), 2.28 – 2.13 (m, 2H), 1.96 – 1.85 (m, 1H), 1.80 – 1.72 (m, 1H), 1.70 – 1.63 (m, 1H), 1.62 – 1.47 (m, 6H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 149.3, 148.3, 140.9, 134.8, 123.3, 62.9, 58.7, 50.4, 49.3 (3C), 36.3, 23.3, 23.1;

HRMS (ESI-TOF): calc’d for C$_{14}$H$_{19}$N$_2$ [M+H$^+$] 215.1548; found 215.1544.

8-(bicyclo[1.1.1]pentan-1-yl)-1,4-dioxa-8-azaspiro[4.5]decane (23)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1,4-dioxa-8-azaspiro[4.5]decane (50) to 23 in 52% yield.

**Physical State:** yellow oil;
$R_f = 0.32$ (3:7 EtOAc:hexanes, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.93 (s, 4H), 2.54 (s, 4H), 2.38 (s, 1H), 1.76 (s, 6H), 1.73 (t, $J$ = 5.8 Hz, 4H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 107.3, 64.3 (2C), 60.5, 48.1 (3C), 46.4 (2C), 34.6 (2C), 22.1;

HRMS (ESI-TOF): calc’d for C$_{12}$H$_{20}$NO$_2$ [M+H$^+$] 210.1494; found 210.1494.

![Image](24)

2-(bicyclo[1.1.1]pentan-1-yl)decahydroisoquinoline (24)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert perhydroisoquinoline to 24 in 32% yield.

Physical State: yellow oil;

$R_f = 0.64$ (3:7 EtOAc:hexanes, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.88 (d, $J$ = 9.6 Hz, 1H), 2.72 (d, $J$ = 10.9 Hz, 1H), 2.38 (s, 1H), 2.00 – 1.92 (m, 1H), 1.74 (s, 6H), 1.70 (d, $J$ = 9.7 Hz, 2H), 1.64 – 1.57 (m, 2H), 1.57 – 1.49 (m, 2H), 1.35 – 1.14 (m, 4H), 1.04 – 0.86 (m, 2H), 0.87 – 0.76 (m, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 60.9, 55.0, 49.0, 47.8 (3C), 41.8, 41.7, 33.2, 32.8, 30.9, 26.7, 26.3, 22.3;

HRMS (ESI-TOF): calc’d for C$_{14}$H$_{24}$N [M+H$^+$] 206.1909; found 206.1912.
2-(bicyclo[1.1.1]pentan-1-yl)-1,2,3,4-tetrahydroisoquinoline (25)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1,2,3,4-tetrahydroisoquinoline to 25 in 57% yield.

**Physical State:** pale yellow oil;

\[ R_f = 0.50 \] (20% EtOAc in hexanes, vis. KMnO₄);

**H NMR (500 MHz, CDCl₃):** \[ δ \text{ 7.16} – \text{7.01 (m, 4H), 3.67 (s, 2H), 2.92 (t, } J = 6.0 \text{ Hz, 2H), 2.76 (t, } J = 6.0 \text{ Hz, 2H), 2.49 (s, 1H), 1.87 (s, 6H);} \]

**C NMR (125 MHz, CDCl₃):** \[ δ \text{ 134.9, 134.5, 129.1, 127.1, 126.5, 126.0, 60.8, 51.1, 48.3 (3C), 46.1, 29.5, 22.8;} \]

**HRMS (ESI-TOF):** calc’d for C₁₄H₁₈N [M+H⁺] 200.1439; found 200.1440.

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2-(bicyclo[1.1.1]pentan-1-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (26)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 2,3,4,5-tetrahydro-1H-benzo[c]azepine (51) to 26 in 53% yield.

**Physical State:** yellow oil;

\[ R_f = 0.53 \] (1:4 EtOAc:hexanes, vis. KMnO₄);

**H NMR (500 MHz, CDCl₃):** \[ δ \text{ 7.19} – \text{7.06 (m, 4H), 3.83 (s, 2H), 3.06 (t, } J = 5.4 \text{ Hz, 2H), 2.96 – 2.82 (m, 2H), 2.37 (s, 1H), 1.81 – 1.77 (s, 8H);} \]

**C NMR (125 MHz, CDCl₃):** \[ δ \text{ 142.9, 140.3, 129.5, 129.0, 127.2, 126.1, 60.9, 56.3, 54.9, 49.8 (3C), 35.8, 27.8, 22.8;} \]
HRMS (ESI-TOF): calc’d for C_{15}H_{20}N [M+H^+] 214.1596; found 214.1599.

1-benzyl-4-(bicyclo[1.1.1]pentan-1-yl)piperazine (27)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzylpiperazine (52) to 27 in 67% yield.

Physical State: pale yellow oil;

\( R_f = 0.53 \) (3:7 EtOAc:hexanes, vis. I2);

\(^1\text{H NMR} \) (600 MHz, CDCl\(_3\)): \( \delta \) 7.33 – 7.27 (m, 4H), 7.24 (td, \( J = 5.7, 2.8 \) Hz, 1H), 3.52 (s, 2H), 2.50 (s, 8H), 2.41 (s, 1H), 1.76 (s, 6H);

\(^{13}\text{C NMR} \) (151 MHz, CDCl\(_3\)): \( \delta \) 138.2, 129.3 (2C), 128.3 (2C), 127.1, 63.3, 60.5, 52.8 (2C), 48.0 (2C), 47.8 (3C), 22.3;

HRMS (ESI-TOF): calc’d for C\(_{16}\)H\(_{23}\)N\(_2\) [M+H^+] 243.1861; found 243.1859.

4-(bicyclo[1.1.1]pentan-1-yl)-1-(3-methoxyphenyl)-2,2-dimethylpiperazine (28)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1-(3-methoxyphenyl)-2,2-dimethylpiperazine to 28 in 69% yield.
Physical State: colorless oil;

$R_f = 0.65$ (1:4 EtOAc:hexanes, vis. KMnO$_4$);

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.15 (t, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.70 – 6.63 (m, 2H), 3.77 (s, 3H), 3.13 (t, $J = 5.0$ Hz, 2H), 2.56 (t, $J = 5.0$ Hz, 2H), 2.42 (s, 1H), 2.33 (s, 2H), 1.77 (s, 6H), 1.08 (s, 6H);

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 159.5, 151.0, 128.5, 120.1, 113.8, 109.6, 61.5, 60.8, 55.3, 54.6, 49.3, 47.7 (3C), 47.6, 23.3 (br s, 2C), 22.3;

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{27}$N$_2$O [M+H$^+$] 287.2123; found 287.2126.

$N$-benzyl-$N$-(3-methoxyphenethyl)bicyclo[1.1.1]pentan-1-amine (29)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert $N$-benzyl-(3-methoxyphenethyl)amine S9 to 29 in 54% yield.

Physical State: yellow oil;

$R_f = 0.79$ (3:7 EtOAc:hexanes, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.35 – 7.32 (m, 2H), 7.31 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.16 (dd, $J = 8.2$, 7.5 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.63 (dd, $J = 2.6$, 1.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 2H), 2.78 – 2.74 (m, 2H), 2.71 – 2.66 (m, 2H), 2.39 (s, 1H), 1.82 (s, 6H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 159.7, 142.5, 140.6, 129.3, 128.6 (2C), 128.2 (2C), 126.8, 121.2, 114.6, 111.2, 61.2, 55.2, 54.5, 52.4, 50.1 (3C), 35.1, 23.0;
**HRMS (ESI-TOF):** calc’d for $\text{C}_{21}\text{H}_{26}\text{NO}$ [M+H$^+$] 308.2014; found 308.2018.

![N-benzyl-N-(pyridin-3-ylmethyl)bicyclo[1.1.1]pentan-1-amine (30)](image)

**N-benzyl-N-(pyridin-3-ylmethyl)bicyclo[1.1.1]pentan-1-amine (30)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert $N$-benzyl-(pyridin-3-ylmethyl)amine to 30 in 60% yield.

**Physical State:** colorless oil;

$R_f = 0.43$ (3:1 heptane/EtOAc; vis. KMnO$_4$);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.51 (d, $J = 1.6$ Hz, 1H), 8.40 (dd, $J = 4.6, 1.2$ Hz, 1H), 7.71 (dt, $J = 7.8, 2.0$ Hz, 1H), 7.37 – 7.26 (m, 5H), 7.23 – 7.17 (m, 1H), 3.62 (s, 4H), 2.30 (s, 1H), 1.65 (s, 6H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 149.3, 147.9, 139.9, 135.7, 135.6, 128.1 (2C), 128.0 (2C), 126.7, 123.1, 60.6, 54.5, 51.6, 49.1 (3C), 22.2;

**HRMS (ESI-TOF):** calc’d for $\text{C}_{18}\text{H}_{21}\text{N}_2$ [M+H$^+$] 265.1699; found 265.1700.

![N-benzyl-N-(2-(pyridin-3-yl)ethyl)bicyclo[1.1.1]pentan-1-amine (31)](image)

**N-benzyl-N-(2-(pyridin-3-yl)ethyl)bicyclo[1.1.1]pentan-1-amine (31)**
For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl-(2-(pyridin-3-yl)ethyl)amine S10 to 31 in 39% yield.

**Physical State:** colorless oil;

\[ R_f = 0.65 \text{ (1:1 EtOAc:hexanes, vis. KMnO}_4) \];

\[ \text{H NMR (500 MHz, CDCl}_3\text{): } \delta 8.49 \text{ (d, } J = 4.7 \text{ Hz, 1H), 8.42 \text{ (s, 1H), 7.42 \text{ (d, } J = 7.8 \text{ Hz, 1H), 7.37 - 7.26 \text{ (m, 5H), 7.21 \text{ (dd, } J = 7.7, 4.9 \text{ Hz, 1H), 3.76 \text{ (s, 2H), 2.82 \text{ (dd, } J = 9.0, 5.6 \text{ Hz, 2H), 2.73 \text{ (dd, } J = 9.0, 6.0 \text{ Hz, 2H), 2.47 \text{ (s, 1H), 1.89 \text{ (s, 6H)}}} \text{);} \]

\[ \text{C NMR (125 MHz, CDCl}_3\text{): } \delta 150.3, 147.3, 140.1, 136.2, 136.1, 128.6 \text{ (2C), 128.2 \text{ (2C), 126.9, 123.2, 61.0, 54.8, 51.7, 49.9 \text{ (3C), 32.3, 22.9;}} \]

**HRMS (ESI-TOF):** calc’d for C\textsubscript{19}H\textsubscript{23}N\textsubscript{2} [M+H\textsuperscript{+}] 279.1861; found 279.1863.

\[ \text{N-benzyl-N-(2-morpholinoethyl)bicyclo[1.1.1]pentan-1-amine (32)} \]

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert N-benzyl-(2-morpholinoethyl)amine (53) to 32 in 48% yield.

**Physical State:** pale yellow oil;

\[ R_f = 0.37 \text{ (50\% EtOAc/hexanes, vis. KMnO}_4) \];

\[ \text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.41 \text{ (d, } J = 6.9 \text{ Hz, 2H), 7.35 \text{ (t, } J = 7.6 \text{ Hz, 2H), 7.28 \text{ (t, } J = 7.3 \text{ Hz, 1H), 3.73-3.72 \text{ (m, 6H), 2.75-2.72 \text{ (m, 2H), 2.47-2.42 \text{ (m, 7H), 1.85 \text{ (s, 6H)}}} \text{);} \]

N-benzyl-N-(2-morpholinoethyl)bicyclo[1.1.1]pentan-1-amine (32)
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 140.5, 128.5 (2C), 128.1 (2C), 126.8, 66.9 (2C), 61.2, 58.0, 55.2, 54.1 (2C), 49.7 (3C), 47.3, 22.8;

HRMS (ESI-TOF): calc’d for C\(_{18}\)H\(_{27}\)N\(_2\)O [M+H\(^+\)] 287.2123; found 287.2133.

\(N\)-(3-((9r,10r)-9,10-ethanoanthracen-9(10H)-yl)propyl)-\(N\)-methylbicyclo[1.1.1]pentan-1-amine, “propellerized” maprotiline (33)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert maprotiline hydrochloride to 33 in 80% yield.

Note 1: Two equivalents of \(i\)PrMgCl•LiCl (1.80 mL, 2.0 mmol, 1.11M in THF) were used.

Note 2: Unreacted maprotiline (170 mg, 86%) was recovered from the reaction.

**Physical State:** colorless oil;

\(R_f = 0.53\) (1:4 EtOAc:hexanes; vis. UV);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.31 (ddd, \(J = 7.3, 6.3, 1.4\) Hz, 4H), 7.14 (dtd, \(J = 23.9, 7.4, 1.4\) Hz, 4H), 4.32 (s, 1H), 2.76 – 2.68 (m, 2H), 2.54 – 2.45 (m, 3H), 2.35 (s, 3H), 2.06 – 1.96 (m, 2H), 1.95 – 1.83 (m, 8H), 1.67 – 1.59 (m, 2H);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 145.6 (2C), 145.1 (2C), 125.3 (2C), 125.3 (2C), 123.4 (2C), 121.4 (2C), 61.5, 53.8, 48.5 (3C), 44.9, 44.6, 37.2, 29.8, 29.1, 27.8, 23.6, 22.4;

HRMS (ESI-TOF): calc’d for C\(_{25}\)H\(_{30}\)N [M+H\(^+\)] 344.2378; found 344.2381.
\[ N-((1S,4S)-4-(3,4\text{-dichlorophenyl})-1,2,3,4\text{-tetrahydronaphthalen}-1\text{-yl})-N\text{-methylbicyclo[1.1.1]pentan-1-amine, “propellerized” sertraline (34)} \]

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert sertraline to 34 in 62% yield.

Note: Unreacted sertraline (239 mg, 93%) was recovered from the reaction.

**Physical State:** colorless oil;

\[ R_f = 0.65 \ (1:1 \ EtOAc:hexanes; \ vis. \ UV); \]

\[ [\alpha]_{D}^{20} = +94.1 \ (c = 1.00, CDCl_3); \]

\[ \text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3): \delta \ 7.76 \ (d, \ J = 7.8 \ Hz, 1H), \ 7.31 \ (d, \ J = 8.3 \ Hz, 1H), \ 7.28 - 7.22 \ (m, 1H), \ 7.16 - 7.09 \ (m, 2H), \ 6.85 \ (ddd, \ J = 32.4, 8.0, 1.7 \ Hz, 2H), \ 4.11 \ (dq, \ J = 9.9, 5.6, 4.4 \ Hz, 2H), \ 2.41 \ (s, 1H), \ 2.18 \ (ddd, \ J = 13.4, 12.4, 5.7, 2.9 \ Hz, 1H), \ 2.13 \ (s, 3H), \ 1.98 \ (dd, \ J = 5.9, 3.3 \ Hz, 1H), \ 1.90 \ (dd, \ J = 9.4, 1.6 \ Hz, 3H), \ 1.80 \ (dd, \ J = 9.4, 1.6 \ Hz, 3H), \ 1.73 \ (tdd, \ J = 12.9, 10.3, 2.8 \ Hz, 1H), \ 1.65 \ (ddt, \ J = 10.5, 8.1, 2.9 \ Hz, 1H); \]

\[ \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3): \delta \ 147.7, \ 139.7, \ 138.2, \ 132.2, \ 130.9, \ 130.2, \ 130.0, \ 129.9, \ 128.7, \ 128.3, \ 127.0, \ 126.8, \ 61.1, \ 57.7, \ 50.5 \ (3C), \ 43.6, \ 30.9, \ 30.5, \ 22.4, \ 18.7; \]

**HRMS (ESI-TOF):** calc’d for C\textsubscript{22}H\textsubscript{24}Cl\textsubscript{2}N \ [M+H\textsuperscript{+}] 372.1286; found 372.1280.
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert paroxetine to 35 in 67% yield.

Note: Unreacted paroxetine (240 mg, 91%) was recovered from the reaction.

**Physical State:** colorless oil;

$R_f = 0.30$ (1:5 EtOAc:hexanes; vis. UV);

$\left[ \alpha \right]_{D}^{20} = –59.6$ (c = 1.00, CDCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.15 (dd, $J = 8.5, 5.4$ Hz, 2H), 6.96 (t, $J = 8.7$ Hz, 2H), 6.62 (d, $J = 8.5$ Hz, 1H), 6.35 (d, $J = 2.5$ Hz, 1H), 6.13 (dd, $J = 8.5, 2.5$ Hz, 1H), 5.87 (s, 2H), 3.58 (dd, $J = 9.4, 2.8$ Hz, 1H), 3.45 (dd, $J = 9.4, 6.7$ Hz, 1H), 3.23 (ddd, $J = 11.4, 3.7, 1.6$ Hz, 1H), 3.04 (d, $J = 11.4$ Hz, 1H), 2.50–2.41 (m, 2H), 2.25–2.06 (m, 3H), 1.83 (s, 8H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 161.6 (d, $^1$J$_{C\text{-}F} = 244$ Hz), 154.5, 148.3, 141.7, 139.8, 129.0 (d, $^3$J$_{C\text{-}F} = 7.9$ Hz, 2C), 115.5 (d, $^2$J$_{C\text{-}F} = 21.1$ Hz, 2C), 108.0, 105.7, 101.2, 98.1, 69.7, 60.7, 52.3, 48.9, 48.0 (3C), 44.0, 41.9, 34.0, 22.3;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –116.8;

**HRMS (ESI-TOF):** calc’d for C$_{24}$H$_{27}$FNO$_3$ [M+H$^+$] 396.1975; found 396.1972.
(R)-3-(bicyclo[1.1.1]pentan-1-yl)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine, “propellerized lorcaserin” (36)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert lorcaserin to 36 in 84% yield. Note: Unreacted lorcaserin (136 mg, 90%) was recovered from the reaction.

**Physical State:** colorless oil;

\[ R_f = 0.60 \text{ (1:5 EtOAc:hexanes; vis. UV)}; \]

\[ [\alpha]_D^{20} = +7.9 \text{ (c = 1.00, CDCl}_3); \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.14 (d, \( J = 2.2 \) Hz, 1H), 7.08 (dd, \( J = 8.0, 2.2 \) Hz, 1H), 7.00 (d, \( J = 8.0 \) Hz, 1H), 3.15 (p, \( J = 7.5 \) Hz, 1H), 3.09 – 3.00 (m, 1H), 3.00 – 2.92 (m, 1H), 2.85 – 2.78 (m, 2H), 2.41 (s, 1H), 2.25 (t, \( J = 11.3 \) Hz, 1H), 2.17 (dd, \( J = 12.3, 8.5 \) Hz, 1H), 1.78 (s, 6H), 1.34 (d, \( J = 7.2 \) Hz, 3H);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 147.0, 139.6, 131.5, 129.9, 125.3, 125.0, 60.9, 56.5, 49.3, 47.9 (3C), 37.2, 35.2, 21.6, 17.9;

**HRMS (ESI-TOF):** calc’d for C\(_{16}\)H\(_{21}\)ClN [M+H\(^+\)] 262.1363; found 262.1364.

2-(4-(bicyclo[1.1.1]pentan-1-yl)piperazin-1-yl)quinoline, “propellerized” quipazine (37)
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert quipazine to 37 in 81% yield. Note: Unreacted quipazine (160 mg, 96%) was recovered from the reaction.

**Physical State**: white solid (m.p. = 143-144 °C);

$R_f = 0.34$ (1:2 EtOAc:hexanes; vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.88 (d, $J = 9.1$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 7.7$ Hz, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.22 (t, $J = 7.4$ Hz, 1H), 6.98 (d, $J = 9.1$ Hz, 1H), 3.83 – 3.76 (m, 4H), 2.63 – 2.58 (m, 4H), 2.46 (s, 1H), 1.81 (s, 6H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 157.5, 148.0, 137.6, 129.6, 127.3, 126.8, 123.2, 122.5, 109.7, 60.5, 48.0 (2C), 47.8 (3C), 44.9 (2C), 22.4;

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{22}$N$_3$ [M+H$^+$] 280.1814; found 280.1811.

11-(4-(bicyclo[1.1.1]pentan-1-yl)piperazin-1-yl)-2-chlorodibenzo[b,f][1,4]oxazepine, “propellerized” amoxapine (38)

For 0.50 mmol scale of [1.1.1.]propellane, the standard procedure was followed to convert amoxapine to 38 in 31% yield. Note: Unreacted amoxapine (286 mg, 89%) was recovered from the reaction.

**Physical State**: colorless oil;

$R_f = 0.35$ (1:4 EtOAc:hexanes; vis. UV);
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.38 (dd, $J$ = 8.6, 2.6 Hz, 1H), 7.31 (d, $J$ = 2.6 Hz, 1H), 7.18 (d, $J$ = 8.7 Hz, 1H), 7.14 (dd, $J$ = 7.9, 1.7 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.98 (td, $J$ = 7.7, 1.7 Hz, 1H), 3.58 (s, 4H), 2.59 (s, 4H), 2.47 (s, 1H), 1.82 (s, 6H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 159.4, 158.9, 151.9, 140.3, 132.6, 130.3, 129.2, 127.2, 125.9, 125.2, 124.6, 122.8, 120.2, 60.4, 47.9 (2C), 47.9 (3C), 47.2 (2C), 22.4;

HRMS (ESI-TOF): calc’d for C$_{22}$H$_{23}$ClN$_3$O [M+H$^+$] 380.1530; found 380.1529.

Synthesis of azetidine hydrobromide precursor on decagram scale (41)

1-Amino-2,3-dibromopropane hydrobromide (41): Following the literature method of Nagao, (54) a solution of Br$_2$ (40 mL, 0.785 mol, 2.1 equiv.) was added very slowly dropwise under vigorous stirring to a solution of ethanol (100 mL) in a 1L round bottom flask at 0 °C (Caution: exothermic, fuming). After the addition was complete, allylamine (S11) (28 mL, 0.374 mol, 1.0 equiv.) was added very slowly dropwise under vigorous stirring at 0 °C (Caution: Fuming!). The mixture was allowed to warm to room temperature and stirred at this temperature overnight (16-18 hours). The precipitate was collected via suction filtration and washed with small portions of ice-cold Et$_2$O. The crude material was recrystallized from MeOH to give 41 as colorless prisms (55.5 g, 50% first crop, 30.6 g 28%, second crop $\rightarrow$ 86.1 g, 78% overall). The spectroscopic data was identical to that reported in the literature. (54)

Sigma-Aldrich Catalog Number: MKE151704;

Physical State: white solid (m.p. = 173-174 °C);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.57 – 4.46 (m, 1H), 4.01 (dd, $J$ = 10.9, 4.6 Hz, 1H), 3.86 (dd, $J$ = 11.0, 8.7 Hz, 1H), 3.70 (dd, $J$ = 14.0, 3.2 Hz, 1H), 3.38 – 3.31 (m, 1H).
General medicinal chemistry procedure for the one-pot “azetidinylation” of amines using 41 (prepared above)

**Turbo amide formation:** To a flame-dried round bottom flask containing the starting amine (1 eq.) was added iPrMgCl•LiCl (1.04M in THF, 1.0 eq) slowly dropwise (Caution: gas evolution) at room temperature. The mixture was stirred for 2 hours at room temperature and used as directed below.

**Azabicyclobutane (ABB) formation and reaction:** To a flame-dried 25 or 50 mL round bottom flask was added amine salt 41 (298 mg, 1.0 mmol, 1.0 eq.) and dry THF (3 mL) with an argon balloon. The resulting suspension was cooled to −78 °C (dry ice/acetone). A solution of PhLi (1.67 mL, 3.0 mmol, 1.8M solution in Bu₂O, 3.0 eq.) was added slowly dropwise and the resulting mixture stirred at −78 °C for 2h. A pre-made solution of turbo amide (1.0 equiv., see above) was then added dropwise at −78 °C. The flask was removed from the dry ice bath and allowed to warm to room temperature overnight (~16h). The reaction was cooled to 0 °C and treated slowly dropwise with a solution of electrophilic trapping agent (e.g. Boc₂O, ClCO₂Et, TsCl) (2.0 eq.) in dry THF (5 mL). The reaction was removed from the bath and stirred at room temperature for 3 hours. The resulting mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography to give the desired product.
Notes, Troubleshooting, and Limitations for the “Azetidinylation” of Amines:

1. Use of a 25 or 50 mL round bottom flask for azabicyclobutane (ABB) formation is preferred to maintain consistent stirring of the suspension.
2. Initial dilution of 3 mL THF per 1 mmol of 41 is optimal.
3. Slow addition of PhLi (during ABB formation) and of the electrophilic solution (during quench) is required for optimal yields.
4. Regarding time:
   a. 2 hours for ABB formation appears optimal for maximum yield (more than 2 hours will result in degradation of the ring system; less time may not give full conversion from 41 to ABB).
   b. 16 hours for the amination reaction and 3 hours for the electrophilic quench are general and meant to cover a full range of substrates; reaction time for individual substrates may be further optimized if desired.
5. Limitations:
   a. Primary amines cannot be used as the source of “turbo amide.” Instead, a benzyl group can be added to the primary amine and removed after “azetidinylation.”
   b. Turbo amides of 2-pyridyl-substituted amines are generally unreactive with ABB under the above conditions. This is presumed to be due to chelation of the magnesium between the amide nitrogen and pyridine nitrogen.
   c. Functional groups such as ketones, amides, carbamates, and free alcohols or thiols are incompatible with “turbo amides.”
Graphical procedure for the one-pot “azetidinylation” of amines

Fig. S24. Left. Suspension of 41 in dry THF is cooled to –78 °C. Right. After addition of PhLi, the color changes from colorless/white to pale yellow.

Fig. S25. Left. Solution of the “turbo amide “ of morpholine (substrate 53). This is added to the solution in Figure S23 (right) at –78 °C then removed from the dry ice bath and stirred at room temperature overnight. Right. TLC of reaction after quench with Boc₂O in THF. From left to right: authentic sample of 53, co-spot, crude reaction mixture.
Substrates for the “Azetidinylation” of Amines

Note on $^{13}$C NMR of protected azetidines: When protected with Boc or CO$_2$Et, C2 and C4 on the azetidine ring typically appear as broad singlets or doublets at 50-55 ppm. These peaks sometimes overlap with other signals and do not resolve well from the baseline. Expanded insets are included where possible in the NMR spectra section. An X-ray crystal structure is provided for 53 and HSQC is included for 46 and 49. Similar observations for these compounds have been reported previously in the literature. (55, 56)

![Chemical structure of 42a](image)

$N,N$-dibenzylazetidin-3-amine (42a)

For 1.0 mmol scale, the standard procedure was followed to convert dibenzyamine to 42a in 53% yield. For $^1$H, $^{13}$C, and $^{19}$F NMR 42a was analyzed as the bis-TFA salt (57).

**Physical State**: yellow solid (m.p. = 138-139 °C);

$R_f = 0.43$ (20:2:1 CHCl$_3$:MeOH:acetone);

$^1$H NMR (600 MHz, MeOD): δ 7.47 – 7.28 (m, 10H), 4.02 (q, $J = 7.7$ Hz, 1H), 3.96 – 3.89 (m, 2H), 3.85 – 3.78 (m, 2H), 3.76 (s, 4H), NH proton not observed;

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 161.8 (q, $^2J_{C\text{-}F} = 37.1$ Hz, from TFA), 130.2 (2 signals overlapping, 6C), 129.3 (4C), 127.9 (2C), 115.6 (q, $^1J_{C\text{-}F} = 290$ Hz, from TFA), 56.9 (2C), 54.6, 48.1 (2C);

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –77.0 (t, $J = 38.5$ Hz), –77.1 (t, $J = 37.9$ Hz) [from TFA];

HRMS (ESI-TOF): calc’d for C$_{17}$H$_{21}$N$_2$ [M+H$^+$] 253.1705; found 253.1701.
Ethyl 3-(dibenzylamino)azetidine-1-carboxylate (42b)

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to 42b in 82% yield.

**Physical State**: pale yellow oil;

$R_f = 0.70 \text{ (1:2 EtOAc/hexanes, vis. KMnO}_4\text{)}$;

$^1\text{H NMR (600 MHz, CDCl}_3\text{): } \delta 7.32 \text{ (dt, } J = 13.1, 7.1 \text{ Hz, 8H), 7.29 – 7.25 (m, 2H), 4.09 (q, } J = 7.1 \text{ Hz, 2H), 3.96 – 3.89 (m, 2H), 3.85 (dd, } J = 9.0, 5.8 \text{ Hz, 2H), 3.66 – 3.59 (m, 1H), 3.56 (s, 4H), 1.23 (t, } J = 7.1 \text{ Hz, 3H);}$

$^{13}\text{C NMR (151 MHz, CDCl}_3\text{): } \delta 156.9, 138.1 \text{ (2C), 129.1 (4C), 128.5 (4C), 127.4 (2C), 61.1, 54.6 (2C), 53.7 (br s, 2C), 52.0, 14.9; }$

HRMS (ESI-TOF): calc’d for C$_{20}$H$_{25}$N$_2$O$_2$ [M+H$^+$] 325.1916; found 325.1919.

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tert-butyI 3-(dibenzylamino)azetidine-1-carboxylate (42c)

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to 42c in 93% yield.

**Physical State**: pale yellow oil;

$R_f = 0.62 \text{ (1:4 EtOAc:hexanes, vis. KMnO}_4\text{)}$;

$^1\text{H NMR (600 MHz, CDCl}_3\text{): } \delta 7.35 – 7.28 \text{ (m, 8H), 7.28 – 7.24 (m, 2H), 3.88 (t, } J = 8.3 \text{ Hz, 2H), 3.80 (dd, } J = 9.0, 5.7 \text{ Hz, 2H), 3.62 – 3.53 (m, 5H), 1.42 (s, 9H);}$
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.4, 138.1 (2C), 129.2 (4C), 128.4 (4C), 127.4 (2C), 79.5, 54.5 (2C), 53.6 (br d, $J = 97.9$ Hz, 2C), 51.6, 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{22}$H$_{29}$N$_2$O$_2$ [M+H$^+$] 353.2229; found 353.2229.

$N,N$-dibenzyl-1-tosylazetidin-3-amine (42d)

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to 42d in 78% yield.

Physical State: pale yellow oil;

$R_f = 0.63$ (1:2 EtOAc/hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.67 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.30 – 7.22 (m, 6H), 7.12 (d, $J = 6.8$ Hz, 4H), 3.69 (q, $J = 6.0$ Hz, 2H), 3.53 – 3.44 (m, 3H), 3.35 (s, 4H), 2.49 (s, 3H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 144.1, 138.1 (2C), 131.4, 129.8 (2C), 128.9 (4C), 128.6 (2C), 128.4 (4C), 127.5 (2C), 55.5 (2C), 54.9 (2C), 51.3, 21.8;

HRMS (ESI-TOF): calc’d for C$_{24}$H$_{27}$N$_2$O$_2$S [M+H$^+$] 407.1793; found 407.1795.

$\underline{43}$

tert-butyl 3-(diallylamino)azetidine-1-carboxylate (43)
For 1.0 mmol scale, the standard procedure was followed to convert diallylamine to 43 in 52% yield.

**Physical State:** pale yellow oil;

$R_f = 0.30$ (1:3 EtOAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, MeOD): $\delta$ 5.89 (ddt, $J = 17.0, 10.1, 6.7$ Hz, 2H), 5.30 – 5.16 (m, 4H), 3.93 (d, $J = 7.5$ Hz, 2H), 3.83 (d, $J = 5.7$ Hz, 2H), 3.56 (ddd, $J = 13.1, 7.3, 5.8$ Hz, 1H), 3.13 (d, $J = 6.7$ Hz, 4H), 1.45 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.5, 134.6 (2C), 118.4 (2C), 79.5, 54.5 (br s, 2C), 53.6 (2C), 51.6, 28.5 (3C);

HRMS (ESI-TOF): calc'd for C$_{14}$H$_{25}$N$_2$O$_2$ [M+H$^+$] 253.1916; found 253.1916.

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**tert-butyl 3-(benzyl(methyl)amino)azetidine-1-carboxylate (44)**

For 1.0 mmol scale, the standard procedure was followed to convert $N$-benzylmethylamine to 44 in 46% yield (58).

**Physical State:** yellow oil;

$R_f = 0.30$ (1:5 EtOAc:hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.36 – 7.26 (m, 5H), 3.95 (dd, $J = 8.7, 7.1$ Hz, 2H), 3.85 (dd, $J = 8.8, 5.5$ Hz, 2H), 3.41 (s, 2H), 3.27 (tt, $J = 7.2, 5.5$ Hz, 1H), 2.08 (s, 3H), 1.46 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.5, 137.7, 129.2 (2C), 128.4 (2C), 127.4, 79.5, 58.9, 53.9, 53.1 (br s, 2C) 38.0, 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{16}$H$_{25}$N$_2$O$_2$ [M+H$^+$] 277.1916; found 277.1914.
**tert-butyl 3-(benzyl(ethyl)amino)azetidine-1-carboxylate (45)**

For 1.0 mmol scale, the standard procedure was followed to N-benzylethylamine to 45 in 44% yield.

**Physical State**: light yellow oil;

\[ R_f = 0.45 \ (3:1 \text{ heptanes:EtOAc, vis. KMnO}_4); \]

\[ ^1H\ \text{NMR (400 MHz, MeCN-d}_3\):} \ \delta 7.35 - 7.30 (m, 4H), 7.28 - 7.23 (m, 1H), 3.84 (t, \text{ } J = 7.9 \text{ Hz, } 2H), 3.72 - 3.66 (m, 2H), 3.59 - 3.48 (m, 3H), 2.46 (q, \text{ } J = 7.1 \text{ Hz, } 2H), 1.40 (s, 9H), 0.96 (t, \text{ } J = 7.1 \text{ Hz, } 3H); \]

\[ ^{13}C\ \text{NMR (101 MHz, CDCl}_3\):} \ \delta 156.5, 138.5, 129.1 (2C), 128.4 (2C), 127.3, 79.5, 54.1, 53.7 (br s, 2C), 51.7, 44.3, 28.5 (3C), 11.6;

**HRMS (ESI-TOF)**: calc’d for C_{17}H_{27}N_{2}O_{2} \ [M+H^+] 291.2067; found 291.2077.

**tert-butyl 3-(benzyl(isobutyl)amino)azetidine-1-carboxylate (46)**

For 1.0 mmol scale, the standard procedure was followed to convert N-benzylisobutylamine (46) to 46 in 42% yield.

**Physical State**: colorless oil;

\[ R_f = 0.66 \ (3:1 \text{ heptanes:EtOAc, vis. KMnO}_4); \]
$^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.36 – 7.21 (m, 5H), 3.79 (br s, 2H), 3.58 (br s, 2H), 3.53, (s, 2H), 3.49 – 3.40 (m, 1H), 2.08 (d, $J = 7.1$ Hz, 2H), 1.69 (dt, $J = 13.4$, 6.6 Hz, 1H), 1.35 (s, 9H), 0.82 (d, $J = 6.6$ Hz, 6H);

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ 156.0, 139.0, 129.4 (2C), 128.6 (2C), 127.4, 79.0, 58.8, 55.8, 53.9 (br d, $J = 95.7$ Hz, 2C), 52.2, 28.5 (3C), 26.0, 21.2 (2C);

HSQC: See pages S258-S259;

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{30}$N$_2$NaO$_2$ [M+Na$^+$] 341.2205; found 341.2202.

<chemical-structure-image>

tert-butyl 3-(benzyl(2-(benzyloxy)ethyl)amino)azetidine-1-carboxylate (47)

For 1.0 mmol scale, the standard procedure was followed to convert N-benzyl-(2-(benzyloxy)ethyl)amine (47) to 47 in 45% yield.

Physical State: colorless oil;

$R_f = 0.40$ (25% EtOAc in heptanes, vis. KMnO$_4$);

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.38 – 7.32 (m, 10H), 4.45 (s, 2H), 3.94 – 3.88 (m, 2H), 3.84 – 3.77 (m, 2H), 3.68 – 3.62 (m, 3H), 3.48 (t, $J = 5.8$ Hz, 2H), 2.72 (t, $J = 5.8$ Hz, 2H), 1.43 (s, 9H);

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 156.4, 138.5, 138.3, 129.1 (2C), 128.5 (2C), 128.4 (2C), 127.8 (2C), 127.7, 127.3, 79.4, 73.4, 68.3, 55.4, 54.0 (br s, 2C), 52.3, 49.9, 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{24}$H$_{33}$N$_2$O$_3$ [M+H$^+$] 397.2486; found 397.2493.
tert-butyl 3-(benzyl(thiophen-3-ylmethyl)amino)azetidine-1-carboxylate (48)

For 1.0 mmol scale, the standard procedure was followed to convert N-benzyl-(thiophen-3-ylmethyl)amine (49) to 48 in 42% yield.

**Physical State:** colorless oil;

\[ R_f = 0.50 \text{ (1:10 EtOAc/hexanes, vis. KMnO}_4\text{);} \]

\( ^1\text{H NMR (600 MHz, CDCl}_3\text{):} \) \( \delta \) 7.38 – 7.22 (m, 6H), 7.07 (d, \( J = 2.0 \text{ Hz, 1H} \)), 7.01 – 6.98 (m, 1H), 3.89 (t, \( J = 8.2 \text{ Hz, 2H} \)), 3.80 (dd, \( J = 8.9, 5.7 \text{ Hz, 2H} \)), 3.62 – 3.51 (m, 5H), 1.43 (s, 9H);

\( ^{13}\text{C NMR (151 MHz, CDCl}_3\text{):} \) \( \delta \) 156.4, 138.6, 138.2, 129.1 (2C), 128.6, 128.5 (2C), 127.4, 125.8, 123.1, 79.6, 54.2, 53.6 (br s, 2C), 51.5, 49.0, 28.5 (3C);

**HRMS (ESI-TOF):** calc’d for \( \text{C}_{20}\text{H}_{27}\text{N}_{2}\text{O}_{2}\text{S} \) [M+H\(^+\)] 359.1793; found 359.1789.

....

tert-butyl 3-(benzyl(cyclobutylmethyl)amino)azetidine-1-carboxylate (49)

For 1.0 mmol scale, the standard procedure was followed to convert \( N\)-benzyl-(cyclobutylmethyl)amine to 49 in 50% yield.

**Physical State:** colorless oil;
$R_f = 0.58$ (3:1 heptanes:EtoAc, vis. KMnO$_4$);

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.34 – 7.20 (m, 5H), 3.82 (br s, 2H), 3.60 (br s, 2H), 3.50 (s, 2H), 3.48 – 3.42 (m, 1H), 2.48 – 2.39 (m, 1H), 2.37 – 2.31 (m, 2H), 1.97 – 1.87 (m, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.65 (m, 1H), 1.59 – 1.47 (m, 2H), 1.41 – 1.30 (m, 9H);

$^{13}$C NMR (151 MHz, DMSO-$d_6$): $\delta$ 156.0, 139.4, 129.1 (2C), 128.6 (2C), 127.3, 79.0, 56.7, 54.8, 54.0 (br d, $J = 103$ Hz, 2C), 52.1, 33.0, 28.5 (3C), 27.1 (2C), 18.5;

HSQC: See pages S266-S267;

HRMS (ESI-TOF): calc’d for C$_{20}$H$_{30}$N$_2$NaO$_2$ [M+Na$^+$] 353.2205; found 353.2199.

**tert-butyl 3-(piperidin-1-yl)azetidine-1-carboxylate (50)**

For 1.0 mmol scale, the standard procedure was followed to convert piperidine to 50 in 56% yield.

**Physical State:** yellow oil;

$R_f = 0.50$ (50% EtoAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.93 – 3.86 (m, 2H), 3.80 (dd, $J = 8.8, 5.6$ Hz, 2H), 2.99 (p, $J = 6.9, 6.4$ Hz, 1H), 2.25 (s, 4H), 1.60 (p, $J = 5.6$ Hz, 4H), 1.51 – 1.43 (m, 2H), 1.42 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.5, 79.4, 54.5, 53.6 (br d, $J = 186$ Hz, 2C), 51.0 (2C), 28.5 (3C), 25.6 (2C), 24.3;

HRMS (ESI-TOF): calc’d for C$_{13}$H$_{25}$N$_2$O$_2$ [M+H$^+$] 241.1916; found 241.1915.
For 1.0 mmol scale, the standard procedure was followed to convert 4-phenylpiperidine to 51 in 65% yield.

Physical State: white solid (m.p. = 72-73 °C);

$R_f = 0.55$ (50% EtOAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30 (t, $J = 7.6$ Hz, 2H), 7.22 (dd, $J = 10.4$, 7.3 Hz, 3H), 3.98 – 3.91 (m, 2H), 3.85 (dd, $J = 8.8$, 5.6 Hz, 2H), 3.08 (p, $J = 7.0$, 6.3 Hz, 1H), 2.94 (d, $J = 10.2$ Hz, 2H), 2.52 (ddt, $J = 12.0$, 7.7, 3.9 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.87 (d, $J = 12.4$ Hz, 2H), 1.80 (qd, $J = 12.6$, 3.6 Hz, 2H), 1.43 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.4, 146.1, 128.6 (2C), 126.9 (2C), 126.4, 79.5, 54.3, 52.9 (br s, 2C), 50.9, 42.6 (2C), 33.0 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{29}$N$_2$O$_2$ [M+H$^+$] 317.2229; found 317.2230.

$\text{tert\-butyl 3\-(4-benzylpiperazin-1-yl)azetidine-1\-carboxylate (52)}$

For 1.0 mmol scale, the standard procedure was followed to convert 4-phenylpiperidine to 51 in 65% yield.

Physical State: white solid (m.p. = 72-73 °C);

$R_f = 0.55$ (50% EtOAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30 (t, $J = 7.6$ Hz, 2H), 7.22 (dd, $J = 10.4$, 7.3 Hz, 3H), 3.98 – 3.91 (m, 2H), 3.85 (dd, $J = 8.8$, 5.6 Hz, 2H), 3.08 (p, $J = 7.0$, 6.3 Hz, 1H), 2.94 (d, $J = 10.2$ Hz, 2H), 2.52 (ddt, $J = 12.0$, 7.7, 3.9 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.87 (d, $J = 12.4$ Hz, 2H), 1.80 (qd, $J = 12.6$, 3.6 Hz, 2H), 1.43 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.4, 146.1, 128.6 (2C), 126.9 (2C), 126.4, 79.5, 54.3, 52.9 (br s, 2C), 50.9, 42.6 (2C), 33.0 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{29}$N$_2$O$_2$ [M+H$^+$] 317.2229; found 317.2230.
For 1.0 mmol scale, the standard procedure was followed to convert 1-benzylpiperazine (52) to 52 in 47% yield.

**Physical State:** colorless oil.

$R_f = 0.40$ (50% EtOAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.41 – 7.15 (m, 5H), 3.94 – 3.86 (m, 2H), 3.79 (dd, $J = 8.8, 5.4$ Hz, 2H), 3.52 (s, 2H), 3.07 (p, $J = 7.0, 6.2$ Hz, 1H), 2.44 (d, $J = 69.7$ Hz, 8H), 1.42 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.4, 137.7, 129.4 (2C), 128.4 (2C), 127.4, 79.5, 63.0, 54.0, 53.8 (br s, 2C), 52.6 (2C), 49.6 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{30}$N$_3$O$_2$ [M+H$^+$] 332.2338; found 332.2337.

---

tert-butyl 3-morpholinoazetidine-1-carboxylate (53)

For 1.0 mmol scale, the standard procedure was followed to convert morpholine to 53 in 58% yield (59).

**Physical State:** white solid (m.p. = 73-74 °C);

$R_f = 0.40$ (4:1 EtOAc/hexanes, vis. KMnO$_4$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.93 – 3.89 (m, 2H), 3.79 (dd, $J = 8.8, 5.3$ Hz, 2H), 3.72 (t, $J = 4.6$ Hz, 4H), 3.06 (ddd, $J = 12.4, 7.0, 5.4$ Hz, 1H), 2.35 (s, 4H), 1.42 (s, 9H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.4, 79.6, 66.7 (2C), 54.1, 52.9 (br d, $J = 167$ Hz, 2C), 50.2 (2C), 28.5 (3C);
HRMS (ESI-TOF): calc’d for C_{12}H_{23}N_{2}O_{3} [M+H⁺] 243.1709; found 243.1703.

Fig. S26. Crystal structure of tert-butyl 3-morpholinoazetidine-1-carboxylate (53)

Table S4. Crystal data and structure refinement for 53

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Absorption correction          Semi-empirical from equivalents  
Max. and min. transmission     0.0916 and 0.0669  
Refinement method             Full-matrix least-squares on F^2  
Data / restraints / parameters 2406 / 0 / 242  
Goodness-of-fit on F^2         1.050  
Final R indices [I>2sigma(I)]  R1 = 0.0395, wR2 = 0.0872  
R indices (all data)           R1 = 0.0544, wR2 = 0.0951  
Extinction coefficient         n/a  
Largest diff. peak and hole    0.152 and -0.244 e.Å^-3

tert-butyl 3-(octahydroisoquinolin-2(1H)-yl)azetidine-1-carboxylate (54)

For 1.0 mmol scale, the standard procedure was followed to convert perhydroisoquinoline to 54 in 60% yield.

Physical State: yellow oil;

R_f = 0.56 (1:2 EtOAc:hexanes vis. KMnO_4);

^1H NMR (600 MHz, CDCl_3): δ 3.93 – 3.85 (m, 2H), 3.85 – 3.76 (m, 2H), 2.99 (p, J = 6.5 Hz, 1H), 2.80 (d, J = 9.9 Hz, 1H), 2.63 (d, J = 10.0 Hz, 1H), 1.79 (s, 1H), 1.71 (d, J = 9.7 Hz, 3H), 1.61 (s, 1H), 1.59 – 1.50 (m, 2H), 1.46 (d, J = 11.0 Hz, 1H), 1.41 (s, 9H), 1.32 – 1.18 (m, 4H), 0.91 (dd, J = 11.9, 8.8 Hz, 2H);

^13C NMR (151 MHz, CDCl_3): δ 156.5, 79.4, 56.9, 54.2, 52.9 (br s, 2C), 50.9, 41.9, 41.6, 33.0, 32.6, 30.8, 28.5 (3C), 26.6, 26.2;

HRMS (ESI-TOF): calc’d for C_{17}H_{31}N_2O_2 [M+H^+] 295.2386; found 295.2382.
tert-buty1 3-(3,4-dihydroisoquinolin-2(1H)-yl)azetidine-1-carboxylate (55)

For 1.0 mmol scale, the standard procedure was followed to convert 1,2,3,4-tetrahydroisoquinoline to 55 in 55% yield.

Physical State: colorless oil;

\[ R_f = 0.57 \text{ (1:2 EtOAc/hexanes, vis. KMnO}_4\text{)}; \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\text{): } \delta 7.12 \text{ (dq, } J = 13.1, 8.0, 6.6 \text{ Hz, 3H), 7.02 \text{ (d, } J = 6.7 \text{ Hz, 1H), 4.05 – 3.98 \text{ (m, 2H), 3.92 \text{ (dd, } J = 8.7, 5.4 \text{ Hz, 2H), 3.54 \text{ (s, 2H), 3.26 \text{ (p, } J = 6.9 \text{ Hz, 1H), 2.92 \text{ (t, } J = 5.9 \text{ Hz, 2H), 2.64 \text{ (s, 2H), 1.43 \text{ (s, 9H)}}; \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3\text{): } \delta 156.5, 134.0, 133.8, 128.1, 126.8, 126.6, 126.0, 79.6, 53.8, 53.6 \text{ (br d, } J = 182 \text{ Hz, 2C), 52.9, 47.4, 28.9, 28.5 \text{ (3C);}} \]

HRMS (ESI-TOF): calc’d for C$_{17}$H$_{25}$N$_2$O$_2$ [M+H$^+$] 289.1916; found 289.1917.

tert-buty1 3-(1,3,4,5-tetrahydro-2H-benzo[c]azepin-2-yl)azetidine-1-carboxylate (56)

For 1.0 mmol scale, the standard procedure was followed to convert 2,3,4,5-tetrahydro-1H-benzo[c]azepine (51) to 56 in 43% yield.

Physical State: yellow oil;

\[ R_f = 0.40 \text{ (3:4 EtOAc/hexanes, vis. KMnO}_4\text{)}; \]
**1H NMR (600 MHz, CDCl₃):** δ 7.20 – 7.09 (m, 3H), 7.09 – 7.02 (m, 1H), 3.91 – 3.84 (m, 2H), 3.81 (dd, J = 8.4, 5.7 Hz, 2H), 3.71 (s, 2H), 3.28 (p, J = 6.8, 6.3 Hz, 1H), 2.91 (br s, 4H), 1.78 – 1.70 (m, 2H), 1.42 (s, 9H);

**13C NMR (151 MHz, CDCl₃):** δ 156.5, 142.8, 138.5, 129.4, 129.1, 127.7, 126.5, 79.5, 57.2, 55.9, 53.9 (br d, J = 187 Hz, 2C), 50.8, 35.8, 28.5 (3C), 26.1;

**HRMS (ESI-TOF):** calc’d for C₁₈H₂₇N₂O₂ [M+H⁺] 303.2073; found 303.2072.

**tert-butyl 3-(4-(quinolin-2-yl)piperazin-1-yl)azetidine-1-carboxylate, “azetidinylated” quipazine (57)**

For 1.0 mmol scale, the standard procedure was followed to convert quipazine to 57 in 51% yield.

**Physical State:** white solid (m.p. = 138 °C, decomposition);

**Rₛ** = 0.50 (20:1:1 CHCl₃:MeOH:acetone, vis. UV);

**1H NMR (600 MHz, CDCl₃):** δ 7.89 (d, J = 9.1 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.25 – 7.20 (m, 1H), 6.97 (d, J = 9.1 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.87 (dd, J = 8.7, 5.4 Hz, 2H), 3.78 (s, 4H), 3.11 (ddd, J = 12.4, 7.0, 5.4 Hz, 1H), 2.53 – 2.44 (m, 4H), 1.44 (s, 9H);

**13C NMR (151 MHz, CDCl₃):** δ 157.4, 156.4, 147.9, 137.7, 129.7, 127.3, 126.8, 123.3, 122.7, 109.6, 79.6, 54.0, 53.2 (br d, J = 161 Hz, 2C), 49.7 (2C), 44.9 (2C), 28.5 (3C);

**HRMS (ESI-TOF):** calc’d for C₂₁H₂₉N₄O₂ [M+H⁺] 369.2291; found 369.2292.
**tert-butyl 3-(((1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl) amino)azetidine-1-carboxylate, “azetidinylated” sertraline (58)**

For 1.0 mmol scale, the standard procedure was followed to convert sertraline to 58 in 45% yield.

**Physical State:** colorless oil;

$R_f = 0.45$ (1:2 EtOAc/hexanes, vis. UV);

$\left[\alpha\right]_{D}^{20} = +57.1$ (c = 1.00, CDCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 7.9$ Hz, 1H), 7.32 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 6.3$ Hz, 1H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.09 (d, $J = 2.0$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 6.79 (dd, $J = 8.3$, 2.0 Hz, 1H), 4.14 (d, $J = 3.1$ Hz, 1H), 3.90 (dq, $J = 10.6$, 5.9, 4.3 Hz, 4H), 3.85 (t, $J = 8.0$ Hz, 1H), 3.68 (p, $J = 6.5$ Hz, 1H), 2.16 (s, 3H), 2.12 (dd, $J = 15.3$, 5.6 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.59 – 1.52 (m, 2H), 1.45 (s, 9H);

$^1$C NMR (151 MHz, CDCl$_3$): $\delta$ 156.6, 147.4, 138.6, 138.2, 132.3, 130.8, 130.4, 130.1, 130.1, 128.4, 128.2, 127.3, 127.2, 79.5, 59.5, 53.5 (br s, 2C), 50.8, 43.5, 31.8, 30.2, 28.6 (3C), 16.5;

HRMS (ESI-TOF): calc’d for C$_{25}$H$_{31}$Cl$_2$N$_2$O$_2$ [M+H$^+$] 461.1763; found 461.1761.
tert-butyl 3-((3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)propyl)(methyl)amino)azetidine-1-carboxylate, “azetidinylated” nortriptyline (59)

For 1.0 mmol scale, the standard procedure was followed to convert nortriptyline to 59 in 45% yield.

**Physical State**: pale yellow oil;

\[ R_f = 0.65 \text{ (1:1 EtOAc:hexanes, vis. KMnO}_4\text{)}; \]

**\( ^1H \text{ NMR (600 MHz, CDCl}_3\):}** \( \delta \) 7.30 – 7.27 (m, 1H), 7.24 – 7.11 (m, 6H), 7.06 – 7.02 (m, 1H), 5.84 (t, \( J = 7.2 \) Hz, 1H), 3.85 (d, \( J = 7.9 \) Hz, 2H), 3.75 (dd, \( J = 8.7, 5.5 \) Hz, 2H), 3.36 (d, \( J = 63.7 \) Hz, 2H), 3.17 – 3.09 (m, 1H), 2.98 (d, \( J = 15.8 \) Hz, 1H), 2.77 (d, \( J = 14.7 \) Hz, 1H), 2.40 – 2.24 (m, 4H), 2.04 (s, 3H), 1.44 (s, 9H);

**\( ^{13}C \text{ NMR (151 MHz, CDCl}_3\):}** \( \delta \) 156.4, 144.2, 141.1, 140.0, 139.4, 137.1, 130.1 (2C), 128.6, 128.1 (2C), 127.6, 127.2, 126.1, 125.8, 79.4, 54.0, 53.9, 52.9 (br s, 2C), 37.7, 33.8, 32.1, 28.5 (3C), 27.0;

**HRMS (ESI-TOF):** calc’d for C\(_{27}H_{35}N_2O_2\) [M+H\(^{+}\)] 419.2699; found 419.2702.
Synthesis of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (C7)

![Chemical structure of C7]

**Fig. S27.** Overall scheme for the synthesis of C7

2-(2-((3,5-difluorophenyl)sulfonyl)ethyl)oxirane (S12)

A 500 mL round bottom flask was charged with 3,5-difluorobenzenesulfonyl chloride (10 g, 47 mmol, 1 equiv.), H$_2$O (100 mL), Na$_2$SO$_3$ (12 g, 95.2 mmol, 2 equiv.), and heated to 80 °C. NaHCO$_3$ (8 g, 95.2 mmol, 2 equiv.) was added portionwise over 30 minutes (watch for vigorous bubbling) and the flask was fitted with a reflux condenser. The reaction was stirred for 16 h at 80 °C and was then removed from the heating bath and allowed to reach ambient temperature. The reaction was concentrated under reduced pressure and the residual water was azeotroped with toluene (ca. 100 mL). The residual solvent was removed under hi-vacuum to obtain a yellowish solid. Hot MeOH (50 mL) was added to flask and the suspension was filtered to leave behind a yellow cake. The filtrate was concentrated under reduced pressure to give a white solid and used directly in the next reaction without further purification.
The sulfinate salt was dissolved in DMF (100 mL) at room temperature and 4-bromobut-1-ene (5.72 mL, 56.4 mmol, 1.2 equiv.) was added. A septum was placed on the round bottom flask and the reaction was warmed to 60 °C for 2 h. The reaction was removed from the heating bath and the reaction was diluted with EtOAc and H₂O was added. The layers were separated and the aqueous layer was extracted with EtOAc. The organics were combined and washed with LiCl (5% aqueous solution), dried with Na₂SO₄ and passed over a pad of silica while eluting with EtOAc. The organics were concentrated under reduced pressure and used directly in the next reaction without further purification.

The crude alkene was diluted in acetone (100 mL) and H₂O (100 mL) and the flask was charged with oxone (9.3 g, 61.1 mmol, 1.3 eq) and NaHCO₃ (19.7 g, 235 mmol, 5 eq). The solution was stirred at room temperature for 20 h and monitored by TLC (Note: a second portion of oxone (1.3 eq.) and NaHCO₃ (5 eq.) along with acetone (100mL) and H₂O (100mL) was added and stirred for another 3h until TLC indicated the reaction reached completion. The recharge step was added on large scale for safety purposes). The reaction was filtered through a fritted funnel, EtOAc was added, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na₂SO₄, filtered over a pad of silica and concentrated under reduced pressure. The crude material was purified (silica gel) with the following gradient of EtOAc:hexanes (0%→20%→30%) to afford the S12 as a white solid (3.61 g, 31%).

**Physical State:** pale yellow solid (m.p. = 44-45 °C);

\[ R_f = 0.38 \text{ (3:7 EtOAc: hexanes);} \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\text{): } \delta 7.48 – 7.43 \text{ (m, 2H), 7.12 (tt, } J = 8.3, 2.3 \text{ Hz, 1H), 3.30 – 3.20 (m, 2H), 3.02 (dtd, } J = 6.6, 3.9, 2.5 \text{ Hz, 1H), 2.80 (dd, } J = 4.7, 3.9 \text{ Hz, 1H), 2.52 (dd, } J = 4.8, 2.6 \text{ Hz, 1H), 2.21 (ddd, } J = 14.3, 8.5, 7.1, 4.0 \text{ Hz, 1H), 1.81 (ddt, } J = 13.9, 9.0, 6.9 \text{ Hz, 1H);} \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3\text{): } \delta 163.1 \text{ (dd, } ^1J_{C,F} = 245, 11.4 \text{ Hz, 2C), 142.3 (t, } ^3J_{C,F} = 7.8 \text{ Hz), 111.8 (q, } ^2J_{C,F} = 6.7 \text{ Hz, 2C), 109.8 (t, } ^2J_{C,F} = 25.2 \text{ Hz), 52.8, 50.0, 47.2, 25.8;} \]

\[ ^19F \text{ NMR (376 MHz, CDCl}_3\text{): } \delta –104.7; \]

**HRMS (ESI-TOF):** calc’d for C₁₀H₁₁F₂O₃S [M+H⁺] 249.0397; found 249.0391.

S73
1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (C7)

Epoxide S12 (3.61 g, 14.55 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. n-BuLi (10.2 mL, 14.3 mmol, 1.40 M, 1 eq.) was added slowly and the solution turned from colorless to orange to red. After stirring for 5 minutes, TLC (7:3 hexanes:EtOAc) indicated that the reaction was complete. Sat. aq. NH₄Cl was added and the solution was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and passed over a pad of silica while eluting with EtOAc. The material obtained was used directly in the next reaction without further purification.

The crude alcohol was diluted in CH₂Cl₂ (100 mL) and cooled to 0 °C. Et₃N (2.43 mL, 17.46 mmol, 1.2 eq.) was added followed by methanesulfonyl chloride (1.351 mL, 17.46 mmol, 1.2 eq). The reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was diluted with CH₂Cl₂, H₂O was added, and the layers were separated. The combined organic layers were dried over Na₂SO₄ and passed over a pad of silica to obtain a solid that contained minor impurities. This material was used directly in the next step without further purification.

The mesylate was dissolved in THF (100 mL) and cooled to 0 °C. n-BuLi (5.65 mL, 7.91 mmol, 1.40 M, 1 eq.) was added slowly and the reaction monitored by TLC (EtOAc/hexanes 4:1). The reaction was quenched after 5 minutes by addition of sat. aq. NH₄Cl. CH₂Cl₂ and H₂O were added and the layers were separated (a thick emulsion appears in the aqueous layer). The aqueous phase was extracted with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄ and filtered over a pad of silica. The crude material was purified by silica gel chromatography (0→20% EtOAc in hexanes) to obtain the final product (1 g, 30% from S12).

(Alternative purification: The reaction was quenched with sat. aq. NH₄Cl (ca. 2 mL), passed over a pad of silica and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (EtOAc/hexanes 0→20%) to obtain the final product).

Sigma-Aldrich Catalog Number: MKE151703;

Physical State: white solid (m.p. = 60-62 °C);
$R_f = 0.93$ (30% EtOAc in hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.50 – 7.45 (m, 2H), 7.06 (tt, $J = 8.4$, 2.3 Hz, 1H), 2.69 (tt, $J = 3.7$, 2.9 Hz, 1H), 2.55 (dt, $J = 3.7$, 1.1 Hz, 2H), 1.45 (dt, $J = 2.9$, 1.0 Hz, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $^1J_{C,F} = 243$, 11.3 Hz, 2C), 145.5 (t, $^3J_{C,F} = 7.9$ Hz), 110.8 (q, $^2J_{C,F} = 7.3$ Hz, 2C), 108.8 (t, $^2J_{C,F} = 25.3$ Hz), 38.9 (2C), 22.6, 13.7;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –105.7;

HRMS (ESI-TOF): calc’d for C$_{10}$H$_9$F$_2$O$_2$S [M+H$^+$] 231.0286; found 231.0283.

Graphical preparation of Designer Sulfone C7

Fig. S28. Left. Conversion of 3,5-difluorobenzensulfonyl chloride to sodium 3,5-difluorobenzensulfinate after heating at 80 °C for 16h. Right. The crude product was azeotroped with toluene to remove residual H$_2$O.
Fig. S29. **Left.** Crude sodium 3,5-difluorobenzenesulfinate after azeotrope. **Right.** Crude sodium 3,5-difluorobenzenesulfinate after hi-vacuum.

Fig. S30. **Left.** Hot MeOH was added to the crude sodium 3,5-difluorobenzenesulfinate and the suspension filtered. **Right.** Pure sodium 3,5-difluorobenzenesulfinate collected by filtration.
Fig. S31. **Left.** Purified sodium 3,5-difluorobenzenesulfinate was transferred to a round bottom flask. **Center.** DMF was added. **Right.** 4-Bromobut-1-ene was added.

Fig. S32. **Left.** The reaction was heated at 60 °C for 2h. **Center.** The reaction was diluted with EtOAc and H₂O. The organic layers were combined and washed with 5% aqueous LiCl. **Right.** The combined organics were dried over Na₂SO₄.
Fig. S33. Left. The combined organics were passed over silica. Right. The crude material was collected in a single flask and used in the next reaction without further purification.

Fig. S34. Left. The crude alkene was dissolved in 1:1 acetone and H$_2$O. Oxone was added. Center. NaHCO$_3$ was added. Right. The mixture was stirred at room temperature for 20h.
**Fig. S35. Left.** The reaction was recharged with acetone, H₂O, oxone, and NaHCO₃. **Right.** TLC (on left) indicates reaction after 20h and before recharge. All lanes are crude reaction mixture. Top most spot is starting olefin. Bottom spot is product S12. TLC (on right) indicated completion of the reaction after recharge and stirring for another 3h. All lanes are crude reaction mixture. Starting material consumed. Bottom spot is product S12 (1:1 EtOAc:hexanes).

**Fig. S36. Left.** The mixture was directly filtered through a fritted funnel. **Center.** The crude product was purified by column chromatography (0%→20%→30% EtOAc in hexanes). **Right.** TLC of purified fractions; 30% EtOAc in hexanes; 14-16 = S12.
Fig. S37. **Left.** Pure epoxide (white solid). **Center.** The epoxide was dissolved in THF and cooled to 0 °C. **Right.** *n*-BuLi was slowly added to the reaction mixture.

Fig. S38. **Left.** During the addition of *n*-BuLi, the reaction turns orange. **Center.** By the end of the *n*-BuLi addition, the mixture turns red. **Right.** After 5 minutes, TLC shows complete consumption of the starting material. Lanes: Left = Starting epoxide; Center = Co-spot; Right = Crude reaction mixture (solvent system = 7:3 EtOAc:hexanes).
**Fig. S39. Left.** The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc. **Right.** The dried, combined organic layer was passed over silica gel.

**Fig. S40. Left.** The crude alcohol was dissolved in CH₂Cl₂ and cooled to 0 °C. **Center.** Et₃N was added. **Right.** Methanesulfonyl chloride was added.
Fig. S41. **Left.** After stirring for 16h at room temperature, the reaction was diluted with CH$_2$Cl$_2$ and washed with H$_2$O. **Center.** The combined organics were dried over Na$_2$SO$_4$, concentrated, and passed over silica gel to obtain the mesylated product. **Right.** TLC of mesylate (all lanes); solvent system – 1:1 EtOAc:hexanes.

Fig. S42. **Left.** Crude mesylated product obtained as a pale yellow solid. **Center.** The mesylate was dissolved in THF and cooled to 0 ºC.
Fig. S43. **Left.** $n$-BuLi was added slowly and the reaction darkened. **Right.** After 5 minutes, TLC indicated complete consumption of the starting material. Lanes: Left = Starting mesylate; Center = Co-spot; Right = Crude reaction mixture (solvent system = 4:1 EtOAc:hexanes).

Fig. S44. **Left.** The reaction was quenched with sat. aq. NH$_4$Cl and extracted with CH$_2$Cl$_2$. **Right.** The aqueous layer was extracted with CH$_2$Cl$_2$ (note: thick emulsion in aqueous layer).
Fig. S45. **Left.** The combined organics were dried over Na$_2$SO$_4$ and filtered through a pad of silica gel. **Center.** The crude bicycle was purified by column chromatography (0%→20% EtOAc in hexanes). **Right.** 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (C7) was obtained as a white solid.

**Synthesis of other substituted phenylsulfonylcyclobutanes: General scheme for the synthesis of designer sulfones C3 – C6:**

![Chemical reaction diagram]

**Fig. S46.** Overall scheme for the synthesis of sulfones C3-C6
Note: The reaction sequence from the starting sulfonyl chloride to the final bicycles (C1-C7) can be telescoped in a variety of ways. Our optimal approach to C7 is described above (both in text and graphics). The sulfone bicycles described below and in the literature (60,61) demonstrate other ways these reactions can be run either stepwise or telescoped.

![C1](image)

1-(phenylsulfonyl)bicyclo[1.1.0]butane (C1) (see (60))

Physical State: white solid (m.p. = 75 °C);

$R_f = 0.80$ (1:1 EtOAc:hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.96 – 7.92 (m, 2H), 7.64 – 7.60 (m, 1H), 7.59 – 7.53 (m, 2H), 2.56 (tt, $J = 3.9, 2.7$ Hz, 1H), 2.51 (dt, $J = 3.7, 0.9$ Hz, 2H), 1.38 (dt, $J = 2.7, 0.9$ Hz, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 142.0, 133.1, 129.2 (2C), 127.2 (2C), 38.3 (2C), 23.1, 12.7;

HRMS (ESI-TOF): calc’d for C$_{10}$H$_{11}$O$_2$S [M+H$^+$] 195.0474; found 195.0475.

![Crystal structure](image)

**Fig. S47.** Crystal structure of 1-(phenylsulfonyl)bicyclo[1.1.0]butane (C1)
Table S5. Crystal data and structure refinement for C1

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1-tosylbicyclo[1.1.0]butane (C2) (see (61))

Physical State: white solid (m.p. = 82-84 °C);

$R_f = 0.58$ (3:7 EtOAc:hexanes, vis. UV);

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.84 – 7.79 (m, 2H), 7.35 (dt, $J = 7.1$, 0.9 Hz, 2H), 2.53 – 2.47 (m, 3H), 2.44 (s, 3H), 1.38 – 1.34 (m, 2H);

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.0, 139.1, 129.9 (2C), 127.3 (2C), 38.2 (2C), 23.4, 21.7, 12.6;

HRMS (ESI-TOF): calc’d for C$_{11}$H$_{13}$O$_2$S [M+H$^+$] 209.0631; found 209.0631.

1-(but-3-en-1-ylsulfonyl)-4-methoxybenzene (S13)

4-Methoxybenzenesulfonyl chloride (10.0 g, 4.8 mmol) was added to a solution of Na$_2$SO$_3$ (15.5 g, 2.0 equiv) and NaHCO$_3$ (8.0 g, 2.0 equiv) in H$_2$O (50 mL) portionwise at room temperature. The mixture was heated at 80 °C for 5h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (100 mL) and allowed to react with 4-bromo-1-butene (5.8 mL, 1.2 equiv) at 50 °C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with brine (3 x 25 mL), dried with Na$_2$SO$_4$, and evaporated in vacuo to give alkene S13 (6.46 g, 60%).

Physical State: colorless oil;

$R_f = 0.46$ (3:7 EtOAc:hexanes, vis. UV);
$^1$H NMR (600 MHz, CDCl$_3$): δ 7.86 – 7.73 (m, 2H), 7.05 – 6.93 (m, 2H), 5.70 (ddtd, $J$ = 16.7, 10.2, 6.5, 0.9 Hz, 1H), 5.09 – 4.94 (m, 2H), 3.85 (s, 3H), 3.17 – 3.06 (m, 2H), 2.48 – 2.36 (m, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 163.8, 133.9, 130.4, 130.2 (2C), 117.0, 114.5 (2C), 55.7, 55.6, 27.0;

HRMS (ESI-TOF): calc’d for C$_{11}$H$_{15}$O$_3$S [M+H$^+$] 227.0736; found 227.0736.

\[
\text{MeO} \quad \text{S14}
\]

2-(2-((4-methoxyphenyl)sulfonyl)ethyl)oxirane (S14)

Alkene S13 (6.3 g, 27.7 mmol) and NaHCO$_3$ (11.6 g, 5.0 equiv) were dissolved in acetone (90 mL) and H$_2$O (90 mL). Oxone (22.1 g, 2.6 equiv) was added portionwise during a period of 4 hours at room temperature. After stirring for another 6h, the mixture was evaporated in vacuo to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na$_2$SO$_4$, and evaporated in vacuo to give epoxide S14 (6.7 g, quant.).

Physical State: colorless oil;

$R_f$ = 0.14 (3:7 EtOAc:hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.78 – 7.72 (m, 2H), 6.99 – 6.92 (m, 2H), 3.80 (s, 3H), 3.13 (dd, $J$ = 8.3, 6.6, 1.2 Hz, 2H), 2.92 (ddt, $J$ = 6.7, 4.1, 2.6 Hz, 1H), 2.68 (dd, $J$ = 4.8, 3.9 Hz, 1H), 2.41 (dd, $J$ = 4.8, 2.6 Hz, 1H), 2.03 (dddd, $J$ = 14.3, 8.6, 7.0, 4.3 Hz, 1H), 1.77 – 1.70 (m, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 163.8, 130.2, 130.1 (2C), 114.5 (2C), 55.7, 52.8, 50.0, 47.0, 26.0;

HRMS (ESI-TOF): calc’d for C$_{11}$H$_{15}$O$_3$S [M+H$^+$] 243.0691; found 243.0687.

S88
(2-((4-methoxyphenyl)sulfonyl)cyclopropyl)methyl methanesulfonate (S15)

Epoxide S14 (6.3 g, 26 mmol) was dissolved in THF (130 mL) and n-BuLi (1.97 M in hexane, 13.2 mL, 1.0 equiv) was added dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 45 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give intermediate alcohol (5.1 g, 81%) which was used directly in the next step. To a solution of the intermediate alcohol (4.9 g, 20.2 mmol) in CH₂Cl₂ (30 mL) was added Et₃N (3.1 mL, 1.1 equiv) and methanesulfonyl chloride (1.7 mL, 1.1 equiv) successively at room temperature. After stirring for 2h, the reaction mixture was washed with brine twice, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (3:2 hexanes:EtOAc) to give mesylate S15 (6.26 g, 97%).

**Physical State:** colorless oil;

\(R_f = 0.42\) (1:1 EtOAc:hexanes, vis. UV);

\(^1^H\text{ NMR (}600\text{ MHz, CDCl}_3\): } \delta 7.81 - 7.78 \text{ (m, 2H), 7.02 - 6.99 \text{ (m, 2H), 4.24 (dd, } J = 11.3, 6.1 \text{ Hz, 1H), 3.98 (dd, } J = 11.3, 7.6 \text{ Hz, 1H), 3.86 (s, 3H), 2.95 (s, 3H), 2.54 (ddd, } J = 8.5, 5.2, 4.3 \text{ Hz, 1H), 2.12 (ddtd, } J = 9.4, 7.5, 6.1, 4.3 \text{ Hz, 1H), 1.58 (dt, } J = 9.4, 5.5 \text{ Hz, 1H), 1.12 (dt, } J = 8.5, 6.0 \text{ Hz, 1H);}

\(^1^C\text{ NMR (}151\text{ MHz, CDCl}_3\): } \delta 163.9, 131.6, 129.9 \text{ (2C), 114.6 \text{ (2C), 69.3, 55.8, 38.2, 38.1, 18.5, 10.9;}

**HRMS (ESI-TOF):** calc’d for C₁₂H₁₆O₆NaO₆S₂ [M+Na\(^+\)] 343.0286; found 343.0285.
1-((4-methoxyphenyl)sulfonyl)bicyclo[1.1.0]butane (C3)

To mesylate S15 (5.9 g, 18.4 mmol) in THF (100 mL) was added n-BuLi (1.97 M in hexane, 8.9 mL, 0.95 equiv) dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (15:1 hexanes:EtoAc) to give bicyclobutane sulfone C₃ (2.63 g, 64%).

**Physical State:** white solid (m.p. = 63 °C);

$R_f = 0.73$ (1:1 EtOAc:hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl₃): δ 7.88 – 7.84 (m, 2H), 7.03 – 7.00 (m, 2H), 3.88 (s, 3H), 2.51 – 2.45 (m, 3H), 1.37 – 1.32 (m, 2H);

$^{13}$C NMR (151 MHz, CDCl₃): δ 163.3, 133.6, 129.5 (2C), 114.4 (2C), 55.8, 38.1 (2C), 23.7, 12.5;

HRMS (ESI-TOF): calc’d for C₁₁H₁₃O₃S [M+H⁺] 225.0585; found 225.0581.

1-(but-3-en-1-ylsulfonyl)-4-chlorobenzene (S16)

4-Chlorobenzenesulfonyl chloride (10.0 g, 46 mmol) was added to a solution of Na₂SO₃ (11.6 g, 2.0 equiv) and NaHCO₃ (7.7 g, 2.0 equiv) in H₂O (50 mL) portionwise at room temperature. The mixture was heated at 80 °C for 6h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (63 mL) and allowed to react with 4-bromo-1-butene (3.9 mL, 1.2 equiv) at 50 °C for 2h. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with brine (3 x 25 mL), dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (8:1 hexanes:EtoAc) to give alkene S16 (4.9 g, 46%).

S90
Physical State: colorless oil;

\[ R_f = 0.58 \ (3:7 \ \text{EtOAc}:\text{hexanes, vis. UV}); \]

\(^1\text{H NMR (600 MHz, CDCl}_3\): \( \delta 8.44 - 8.40 \ (m, 2H), 8.15 - 8.11 \ (m, 2H), 5.71 \ (ddt, J = 16.9, 10.3, 6.5 \ Hz, 1H), 5.12 - 5.04 \ (m, 2H), 3.27 - 3.18 \ (m, 2H), 2.54 - 2.44 \ (m, 2H); \]

\(^{13}\text{C NMR (151 MHz, CDCl}_3\): \( \delta 151.1, 144.8, 133.2, 129.8 \ (2C), 124.7 \ (2C), 117.9, 55.4, 26.8; \)

HRMS (ESI-TOF): calc’d for C\(_{10}\)H\(_{12}\)ClO\(_2\)S [M+H\(^+\)] 231.0247; found 231.0249.

![Image](S17)

2-(2-((4-chlorophenyl)sulfonyl)ethyl)oxirane (S17)

Alkene S16 (4.9 g, 21.2 mmol) and NaHCO\(_3\) (8.9 g, 5.0 equiv) were dissolved in acetone (70 mL) and H\(_2\)O (70 mL). Oxone (16.9 g, 2.6 equiv) was added portionwise during a period of 4 hours at room temperature. After stirring for another 1h, the mixture was evaporated \textit{in vacuo} to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na\(_2\)SO\(_4\), evaporated \textit{in vacuo}, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give epoxide S17 (4.71 g, 90%).

Physical State: colorless oil;

\[ R_f = 0.75 \ (1:1 \ \text{EtOAc}:\text{hexanes}); \]

\(^1\text{H NMR (600 MHz, CDCl}_3\): \( \delta 8.47 - 8.39 \ (m, 2H), 8.19 - 8.09 \ (m, 2H), 3.29 \ (dd, J = 8.7, 7.0 \ Hz, 2H), 3.03 \ (ddt, J = 6.7, 3.9, 2.6 \ Hz, 1H), 2.81 \ (dd, J = 4.7, 3.9 \ Hz, 1H), 2.52 \ (dd, J = 4.7, 2.5 \ Hz, 1H), 2.26 \ (dddd, J = 14.3, 8.3, 7.2, 3.9 \ Hz, 1H), 1.87 - 1.76 \ (m, 1H); \]

\(^{13}\text{C NMR (151 MHz, CDCl}_3\): \( \delta 151.2, 144.6, 129.8 \ (2C), 124.8 \ (2C), 52.9, 50.0, 47.3, 25.8; \)

HRMS (ESI-TOF): calc’d for C\(_{10}\)H\(_{12}\)ClO\(_2\)S [M+H\(^+\)] 247.0196; found 247.0194.
1-((4-chlorophenyl)sulfonyl)bicyclo[1.1.0]butane (C4)

Epoxide S17 (4.71 g, 19.1 mmol) was dissolved in THF (100 mL) and n-BuLi (1.97 M in hexane, 9.7 mL, 1.05 equiv) was added dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and filtered through a pad of silica gel. This material was used directly in the next reaction.

To a solution of the sulfone alcohol (2.85 g, 11.5 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (1.8 mL, 1.1 equiv) and methanesulfonyl chloride (1.0 mL, 1.1 equiv) successively at room temperature. After stirring for 1h, the reaction mixture was washed with brine twice, dried with Na₂SO₄, evaporated in vacuo, and filtered through a pad of silica gel. This material was used directly in the next reaction.

To the sulfone mesylate (3.70 g, 11.4 mmol) in THF (60 mL) was added n-BuLi (1.97 M in hexane, 5.5 mL, 0.95 equiv) dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (15:1 hexanes:EtOAc) to give bicyclobutane sulfone C4 (1.23 g, 28% over three steps).

**Physical State:** white powder (m.p. = 83-84 °C);

\[ R_f = 0.53 \text{ (3:7 EtOAc:hexanes, vis. UV);} \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{):} \delta 7.90 – 7.84 \text{ (m, 2H), 7.55 – 7.49 (m, 2H), 2.60 (ddd, } J = 6.4, 3.7, 2.8 \text{ Hz, 1H), 2.51 (dt, } J = 3.7, 1.0 \text{ Hz, 2H), 1.39 (dt, } J = 2.8, 1.0 \text{ Hz, 2H);} \]

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\text{):} \delta 140.6, 139.7, 129.6 \text{ (2C), 128.7 (2C), 38.5 (2C), 23.1, 13.1;} \]

**HRMS (ESI-TOF):** calc’d for C₁₀H₁₀ClO₂S [M+H⁺] 229.0085; found 229.0084.
A 500 mL round bottom flask was charged with 4-fluorobenzenesulfonyl chloride (10 g, 51.55 mmol, 1 equiv.), H₂O (100 mL), Na₂SO₃ (13 g, 103.1 mmol, 2 equiv.), and heated to 80 °C. NaHCO₃ (8.66 g, 103.1 mmol, 2 equiv.) was added portionwise over 30 minutes (watch for vigorous bubbling) and the flask was fitted with a reflux condenser. The reaction was stirred for 16 h at 80 °C and was then removed from the heating bath and allowed to reach ambient temperature. The reaction was concentrated under reduced pressure and the residual water was azeotroped with toluene (ca. 100 mL). The residual traces of solvent were removed under high vacuum to obtain a yellowish solid. Hot MeOH (50 mL) was added to flask and the suspension was filtered to leave behind a yellow cake. The filtrate was concentrated under reduced pressure to give a white solid and used directly in the next reaction without further purification.

The sulfinate salt was dissolved in DMF (100 mL) at room temperature and 4-bromobut-1-ene (6.3 mL, 61.7 mmol, 1.2 equiv.) was added. A septum was placed on the round bottom flask and the reaction was warmed to 60 °C for 2 h. The reaction was removed from the heating bath and the reaction was diluted with EtOAc and H₂O was added. The layers were separated and the aqueous layer was extracted with EtOAc. The organics were combined and washed with LiCl (5% aqueous solution), dried with Na₂SO₄ and passed over a pad of silica while eluting with EtOAc. The organics were concentrated under reduced pressure and used directly in the next reaction without further purification.

The crude alkene was diluted in acetone (200 mL) and H₂O (200 mL) and the flask was charged with oxone (47.5 g, 155 mmol, 3 eq) and NaHCO₃ (21.6 g, 257 mmol, 5 eq). The solution was stirred at room temperature for 20 h and monitored by TLC. The reaction was filtered through a fritted funnel, EtOAc was added, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na₂SO₄, filtered over a pad of silica and concentrated under reduced pressure. The crude material was purified (silica gel) with the following gradient of EtOAc:hexanes (0%→20%→40%) to afford the S18 as a white solid (6.48 g, 56%).

**Physical State:** colorless oil;

*R*ₚ = 0.55 (1:1 EtOAc:hexanes, vis. UV);
$^1$H NMR (600 MHz, CDCl$_3$): δ 7.96 – 7.91 (m, 2H), 7.28 – 7.23 (m, 2H), 3.28 – 3.18 (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), 2.18 (dddd, $J = 14.3$, 8.7, 6.9, 4.2 Hz, 1H), 1.86 – 1.77 (m, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 166.0 (d, $^1J_{C-F} = 257$ Hz), 135.0 (d, $^4J_{C-F} = 3.2$ Hz), 131.1 (d, $^3J_{C-F} = 9.7$ Hz, 2C), 116.9 (d, $^2J_{C-F} = 22.8$ Hz, 2C), 53.0, 50.1, 47.2, 26.0;

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –103.3;

HRMS (ESI-TOF): calc’d for C$_{10}$H$_{12}$FO$_3$S [M+H$^+$] 231.0491; found 231.0486.

The epoxide (6.0 g, 26 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. n-BuLi (3.32 mL, 26 mmol, 1.97M, 1.0 eq.) was added slowly and the solution turned from colorless to orange to red. After stirring for 5 minutes, TLC (7:3 hexanes:EtOAc) indicated that the reaction was complete. Sat. aq. NH$_4$Cl was added and the solution was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and passed over a pad of silica while eluting with EtOAc. The material obtained was used directly in the next reaction without further purification.

The crude alcohol was diluted in CH$_2$Cl$_2$ (150 mL) and cooled to 0 °C. Et$_3$N (5.1 mL, 36.8 mmol, 1.2 eq.) was added followed by methanesulfonyl chloride (2.85 mL, 36.8 mmol, 1.2 eq). The reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was diluted with CH$_2$Cl$_2$, H$_2$O was added, and the layers were separated. The combined organic layers were dried over Na$_2$SO$_4$ and passed over a pad of silica to obtain a solid that contained minor impurities. This material was used directly in the next step without further purification.

The mesylate was dissolved in THF (150 mL) and cooled to 0 °C. n-BuLi (8.23 mL, 16.23 mmol, 1.97 M, 1.0 eq) was added slowly and the reaction monitored by TLC (EtOAc/hexanes 4:1). The reaction was quenched after 5 minutes by addition of sat. aq. NH$_4$Cl. CH$_2$Cl$_2$ and H$_2$O were added and the layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried over Na$_2$SO$_4$ and filtered over a pad of
silica. The crude material was purified by silica gel chromatography (0→20%→40% EtOAc in hexanes) to obtain the final product (1.0 g, 12% from S18).

**Physical State**: white solid (m.p. = 71-72 °C);

\[ R_f = 0.48 \] (3:7 EtOAc:hexanes, vis. UV);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.97 – 7.93 (m, 2H), 7.26 – 7.20 (m, 2H), 2.58 (p, \( J = 3.2 \) Hz, 1H), 2.51 (dd, \( J = 3.7, 0.9 \) Hz, 2H), 1.39 (dd, \( J = 2.7, 0.9 \) Hz, 2H);

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 165.5 (d, \( ^1J_{C-F} = 255 \) Hz), 138.2 (d, \( ^4J_{C-F} = 3.7 \) Hz), 130.0 (d, \( ^3J_{C-F} = 9.7 \) Hz, 2C), 116.5 (d, \( ^2J_{C-F} = 22.8 \) Hz, 2C), 38.4 (2C), 23.2, 13.0;

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –105.0;

**HRMS (ESI-TOF)**: calc’d for C\(_{10}\)H\(_{10}\)FO\(_2\)S \([M+H^+]\) 213.0386; found 213.0382.

\[
\text{1-(but-3-en-1-ylsulfonyl)-4-(trifluoromethyl)benzene (S19)}
\]

4-(Trifluoromethyl)benzenesulfonyl chloride (4.89 g, 20 mmol) was added to a solution of Na\(_2\)SO\(_3\) (5.04 g, 2.0 equiv) and NaHCO\(_3\) (3.36 g, 2.0 equiv) in H\(_2\)O (20 mL) portionwise at room temperature. The mixture was heated at 50 °C for 2h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (30 mL) and allowed to react with 4-bromo-1-butene (4.06 mL, 2.0 equiv) at 50 °C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with brine (3 x 25 mL), dried with Na\(_2\)SO\(_4\), evaporated *in vacuo*, and purified by silica gel flash chromatography (8:1 hexanes:EtOAc) to give alkene S19 (3.88 g, 73%).

**Physical State**: colorless oil;

\[ R_f = 0.70 \] (1:3 EtOAc:hexanes, vis. UV);
\[ ^1H \text{ NMR (500 MHz, CDCl}_3\]: \delta 8.11 – 8.02 (m, 2H), 7.85 (d, \(J = 8.2 \text{ Hz}, 2H\)), 5.72 (ddt, \(J = 16.8, 10.2, 6.5 \text{ Hz}, 1H\)), 5.12 – 5.01 (m, 2H), 3.23 – 3.16 (m, 2H), 2.52 – 2.45 (m, 2H); 

\[ ^13C \text{ NMR (125 MHz, CDCl}_3\]: \delta 142.7, 135.7 (q, \(^2J_{C-F} = 33.5 \text{ Hz}\)), 133.4, 129.0 (2C), 126.6 (q, \(^3J_{C-F} = 3.8 \text{ Hz}, 2C\)), 123.2 (q, \(^1J_{C-F} = 273 \text{ Hz}\)), 117.6, 55.4, 26.8; 

\[ ^19F \text{ NMR (376 MHz, CDCl}_3\]: \delta –63.5; 

HRMS (ESI-TOF): calc’d for C\(_{11}\)H\(_{12}\)F\(_3\)O\(_2\)S [M+H\(^+\)] 265.0505; found 265.0507.

2-(2-((4-(trifluoromethyl)phenyl)sulfonyl)ethyl)oxirane (S20) 

Alkene S19 (3.88 g, 14.6 mmol) and NaHCO\(_3\) (6.18 g, 5.0 equiv) were dissolved in acetone (37 mL) and H\(_2\)O (37 mL). Oxone (11.75 g, 2.6 equiv) was added portionwise during a period of 4 hours at room temperature. After stirring for another 1h, the mixture was evaporated \textit{in vacuo} to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na\(_2\)SO\(_4\), evaporated \textit{in vacuo}, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give epoxide S20 (3.96 g, 96%).

Physical State: white solid (m.p. = 60-63 °C);

\[ R_f = 0.20 \text{ (1:3 EtOAc:hexanes, vis. UV)}; \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\]: \delta 8.06 (d, \(J = 8.2 \text{ Hz}, 2H\)), 7.86 (d, \(J = 8.2 \text{ Hz}, 2H\)), 3.25 (ddd, \(J = 8.5, 6.6, 1.4 \text{ Hz}, 2H\)), 3.02 (ddt, \(J = 6.7, 4.0, 2.6 \text{ Hz}, 1H\)), 2.79 (dd, \(J = 4.7, 3.9 \text{ Hz}, 1H\)), 2.51 (dd, \(J = 4.7, 2.5 \text{ Hz}, 1H\)), 2.21 (ddddd, \(J = 14.4, 8.7, 6.9, 4.0 \text{ Hz}, 1H\)), 1.81 (ddt, \(J = 13.7, 9.1, 6.8 \text{ Hz}, 1H\)); 

\[ ^13C \text{ NMR (151 MHz, CDCl}_3\]: \delta 142.5, 135.8 (q, \(^2J_{C-F} = 33.0 \text{ Hz}\)), 128.9 (2C), 126.7 (q, \(^3J_{C-F} = 3.4 \text{ Hz}, 2C\)), 123.2 (q, \(^1J_{C-F} = 273 \text{ Hz}\)), 52.8, 50.1, 47.2, 25.8; 

\[ ^19F \text{ NMR (376 MHz, CDCl}_3\]: \delta –63.5;
HRMS (ESI-TOF): calc’d for C_{11}H_{12}F_{3}O_{3}S [M+H^+] 281.0459; found 281.0454.

(2-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopropyl)methyl methanesulfonate (S21)

Epoxide S20 (2.56 g, 9.1 mmol) was dissolved in THF (60 mL) and n-BuLi (1.97 M in hexane, 4.85 mL, 1.05 equiv) was added dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give the desired alcohol (2.30 g, 90%).

To a solution of the alcohol (2.30 g, 8.2 mmol) in CH₂Cl₂ (30 mL) was added Et₃N (2.27 mL, 2.0 equiv) and methanesulfonyl chloride (0.95 mL, 1.5 equiv) successively at room temperature. After stirring for 1h, the reaction mixture was washed with brine twice, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (3:2 hexanes:EtOAc) to give mesylate S21 (2.80 g, 95%).

Physical State: colorless oil;

\[ R_f = 0.30 \] (1:1 EtOAc:hexanes, vis. UV);

\(^1\text{H NMR (600 MHz, CDCl}_3\): } \delta 8.04 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 4.32 (dd, J = 11.4, 5.7 Hz, 1H), 3.95 (dd, J = 11.4, 7.8 Hz, 1H), 2.93 (s, 3H), 2.66 – 2.58 (m, 1H), 2.18 (ddtd, J = 10.0, 7.8, 6.0, 4.4 Hz, 1H), 1.67 (dt, J = 9.5, 5.6 Hz, 1H), 1.21 (dt, J = 8.4, 6.1 Hz, 1H);

\(^{13}\text{C NMR (151 MHz, CDCl}_3\): } \delta 143.5, 135.5 (q, \(^3J_{C,F} = 33.0\) Hz), 128.5 (2C), 126.6 (q, \(^3J_{C,F} = 3.6\) Hz, 2C), 123.2 (q, \(^1J_{C,F} = 273\) Hz), 68.8, 38.1, 37.7, 19.0, 11.0;

\(^{19}\text{F NMR (376 MHz, CDCl}_3\): } \delta –63.5;

HRMS (ESI-TOF): calc’d for C_{12}H_{13}F_{3}NaO_{5}S_{2} [M+Na^+] 381.0054; found 381.0055.
1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane (C6)

To mesylate S21 (2.69 g, 7.5 mmol) in THF (75 mL) was added n-BuLi (1.97 M in hexane, 3.8 mL, 1.0 equiv) dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH₄Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography (15:1 hexanes:EtOAc) to give bicyclobutane sulfone C6 (0.81 g, 41%, 68% brsm).

**Physical State**: white solid (m.p. = 68-72 °C);

\[ R_f = 0.75 \text{ (2:3 EtOAc:hexanes, vis. UV)} \]

\[ ^1H\ NMR\ (600\ MHz,\ CDCl_3):\ δ\ 8.08\ (d,\ J = 8.1\ Hz,\ 2H),\ 7.83\ (d,\ J = 8.2\ Hz,\ 2H),\ 2.69\ (ddd,\ J = 6.5,\ 3.7,\ 2.9\ Hz,\ 1H),\ 2.56\ (dt,\ J = 3.8,\ 1.0\ Hz,\ 2H),\ 1.44\ (dd,\ J = 2.6,\ 1.3\ Hz,\ 2H);\]

\[ ^13C\ NMR\ (151\ MHz,\ CDCl_3):\ δ\ 145.7,\ 134.8\ (q,\ ^2J_{C,F} = 33.0\ Hz),\ 127.8\ (2C),\ 126.5\ (q,\ ^3J_{C,F} = 4.3\ Hz,\ 2C),\ 123.4\ (q,\ ^1J_{C,F} = 273\ Hz),\ 38.8\ (2C),\ 22.8,\ 13.5;\]

\[ ^19F\ NMR\ (376\ MHz,\ CDCl_3):\ δ\ −63.4;\]

**HRMS (ESI-TOF)**: calc’d for C₁₁H₁₀F₃O₂S [M+H⁺] 263.0348; found 263.0348.

**Characterization of aminated sulfone intermediates (cis and trans isomers)**
N-Methylbenzylamine (S22, 61 mg, 0.5 mmol), sulfone C7 (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12 h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na2SO4, evaporated in vacuo, and purified by silica gel chromatography (8:1 to 3:1 hexanes:EtOAc) to give cis-isomer S23 (88 mg, 50% yield) and trans-isomer S24 (76 mg, 43% yield).

\[
\text{ cis-N-benzyl-3-((3,5-difluorophenyl)sulfonyl)-N-methylcyclobutan-1-amine (S23) } 
\]

**Physical State**: white solid (m.p. = 81-83 °C);

\[ R_f = 0.55 \text{ (1:2 EtOAc:hexanes, vis. I}_2) \];

\[ \text{H NMR (600 MHz, CDCl}_3\text{): } \delta 7.48 - 7.40 \text{ (m, 2H), 7.37 – 7.23 (m, 5H), 7.11 (tt, } J = 8.4, 2.4 \text{ Hz, 1H), 3.53 – 3.44 (m, 1H), 3.42 (s, 2H), 2.95 (tt, } J = 8.8, 7.0 \text{ Hz, 1H), 2.49 (qd, } J = 9.3, 2.7 \text{ Hz, 2H), 2.37 – 2.26 (m, 2H), 2.08 (s, 3H); } \]

\[ \text{C NMR (151 MHz, CDCl}_3\text{): } \delta 163.0 \text{ (dd, } J_{C-F} = 244, 11.4 \text{ Hz, 2C), 141.8 (t, } J_{C-F} = 8.0 \text{ Hz, 2C), 138.1, 129.1 \text{ (2C), 128.4 (2C), 127.3, 111.9 (q, } J_{C-F} = 8.2 \text{ Hz, 2C), 109.5 (t, } J_{C-F} = 25.0 \text{ Hz, 2C), 58.4, 54.1, 50.5, 37.6, 28.9 (2C); } \]

\[ \text{F NMR (376 MHz, CDCl}_3\text{): } \delta -105.2; \]

**HRMS (ESI-TOF)**: calc’d for C18H20F2NO2S [M+H\(^+\)] 352.1183; found 352.1184.
**Fig. S48.** Crystal structure of cis-N-benzyl-3-((3,5-difluorophenyl)sulfonyl)-N-methylocyclobutan-1-amine (S23)

**Table S6.** Crystal data and structure refinement for S23

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S100
trans-N-benzyl-3-((3,5-difluorophenyl)sulfonyl)-N-methycyclobutan-1-amine (S24)

Physical State: white solid (m.p. = 47-50 °C);

$R_f = 0.45$ (1:2 EtOAc:hexanes, vis. $I_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.51 – 7.43 (m, 2H), 7.37 – 7.23 (m, 5H), 7.12 (tt, $J = 8.4$, 2.3 Hz, 1H), 3.74 (tt, $J = 9.2$, 4.2 Hz, 1H), 3.38 (s, 2H), 3.28 (p, $J = 7.4$ Hz, 1H), 2.70 – 2.59 (m, 2H), 2.41 – 2.30 (m, 2H), 2.03 (s, 3H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $^1J_{C-F} = 244$, 11.4 Hz, 2C), 141.5 (t, $^3J_{C-F} = 8.0$ Hz), 138.1, 129.2 (2C), 128.4 (2C), 127.3, 112.0 (q, $^2J_{C-F} = 8.3$ Hz, 2C), 109.5 (t, $^2J_{C-F} = 25.1$ Hz), 58.6, 56.9, 53.2, 37.9, 28.5 (2C);

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –105.2;

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{20}$F$_3$NO$_2$S [M+H$^+$] 352.1183; found 252.1185.
General medicinal chemistry preparations for the “cyclobutylation” of amines using C7 (prepared above)

General procedure A: (Compounds 62, 63, 64, 67, 68, 69, 70, 71)
The free amine (1.0 equiv), sulfone C7 (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h (36 hours for 62 and 64). After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄ and evaporated in vacuo. The crude product was dissolved in MeOH (0.04 M) and refluxed with freshly activated (62) Mg turnings (40 equiv). After completion of the reaction (typically < 2 hours), the mixture was cooled to room temperature, diluted with EtOAc, washed successively with sat. aq. NH₄Cl and brine, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography to give the desired products.

General procedure B: (Compounds 61, 65, 66)
The free amine (1.0 equiv), sulfone C7 (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄ and evaporated in vacuo. The crude product was purified by silica gel flash chromatography to give the intermediate aminated cyclobutylsulfones. The product above was dissolved in MeOH (0.04 M) and refluxed with freshly activated (62) Mg turnings (40 equiv). After completion of the reaction (typically < 2 hours), the mixture was cooled to room temperature, diluted with EtOAc, washed successively with sat. aq. NH₄Cl and brine, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography to give the desired products.

General procedure C: (Compounds 72, 73, 74, 75)
The free amine (1.0 equiv), sulfone C7 (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄ and evaporated in vacuo. The crude product was dissolved in MeOH (0.04 M) and freshly activated (62) Mg turnings (40 equiv) were added. After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc, washed successively with sat. aq. NH₄Cl and brine, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography to give the desired products.

Notes, Troubleshooting, and Limitations for the “Cyclobutylation” of Amines:
1. The desulfonylation reaction must be initiated by 1 of 3 methods (after initial activation of the Mg turnings): (62)
   a. Reflux at 80 °C until the mixture turns opaque or muddy.
b. Sonication until bubbling is observed.
c. Washing the Mg turnings again with dilute HCl.

2. Limitations for the amination of primary amines:
   a. Benzylamine: low isolated yield (40%) due to bis-addition of C7.
   b. 4-Aminopyridine: mostly bis-addition of C7 observed.
   c. 2-Aminopyridine: low conversion (mixture of mono- and bis-addition of C7).

3. Limitations for the reduction:
   a. Amoxapine: The amination proceeds well, but a mixture of reduction products is observed.
   b. Quipazine: The amination proceeds well, but a mixture of reduction products is observed.
   c. Preliminary studies have been conducted which suggest SmI$_2$ or Raney nickel can serve as alternative reduction procedures.

**Graphical preparation for the “cyclobutylation” of amines**

![Graphical preparation](image_url)

**Fig. S49.** Left. Addition of stir bar and dibenzylamine to a reaction tube. Center. Addition of sulfone C7 and LiCl to reaction tube. Right. Addition of DMSO to reaction tube.
Fig. S50. Left. Reaction after stirring for 2 min. Right. Reaction after stirring for 12h.

Fig. S51. Left. TLC under UV visualization (1:6 EtOAc:hexanes). Lane 1 = Bn$_2$NH; Lane 2 = co-spot of Bn$_2$NH and crude reaction mixture; Lane 3 = crude reaction mixture; Lane 4 = co-spot of crude reaction mixture and sulfone C7; Lane 5 = pure sulfone C7. Right. Same TLC plate with I$_2$ development.
Fig. S52. **Left.** The reaction was dissolved in EtOAc and washed with brine. **Right.** The organic layers were dried over Na\(_2\)SO\(_4\) and concentrated on the rotovap.

Fig. S53. **Left.** The crude product (same flask as rotovap) was dissolved in MeOH and activated Mg turnings added. **Right.** The Mg/MeOH reduction after heating at 80 °C for 2h.
**Fig. S54. Left.** TLC under UV visualization (1:10 EtOAc:hexanes). Lane 1 = Bn₂N cyclobutylsulfone 76; Lane 2 = co-spot of 76 and crude reaction mixture; Lane 3 = crude reaction mixture. **Right.** Same TLC plate with I₂ development.

**Graphical Preparation for Reduction Step of Complex Example 72**

**Fig. S55. Left.** Aminated sulfone intermediate of 72 dissolved in MeOH with activated Mg turnings added. **Left-Center.** Sonication of reaction for 5 min. **Right-Center.** Reaction after stirring with MeOH/Mg until completion. **Right.** TLC with I₂ development (1:6 MeOH:CH₂Cl₂). Lane 1 = nortriptyline cyclobutylsulfone; Lane 2 = co-spot of nortriptyline cyclobutylsulfone and crude reaction mixture; Lane 3 = crude reaction mixture.
Substrates for the “Cyclobutylation” of Amines

\[ \text{Bn}_2\text{N} \]\n\[ 61 \]

\( N,N\)-dibenzyleicylobutanamine (61)

For 0.5 mmol scale, general procedure B was followed to convert dibenzylamine to 61 in 97% and 72% yield (for the amination and reduction, respectively).

**Physical State:** colorless oil;

\( R_f = 0.70 \) (1:10 EtOAc:hexanes, vis. I₂);

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \delta 7.41 – 7.30 (m, 8H), 7.30 – 7.23 (m, 2H), 3.53 (s, 4H), 3.26 – 3.14 (m, 1H), 2.06 – 1.86 (m, 4H), 1.74 – 1.54 (m, 2H);

\(^{13}\text{C NMR (101 MHz, CDCl}_3\):} \delta 139.5 (2C), 129.3 (4C), 128.1 (4C), 126.8 (2C), 58.2, 54.3 (2C), 28.3 (2C), 14.6;

**HRMS (ESI-TOF):** calc’d for C\(_{18}\)H\(_{22}\)N \([\text{M+H}^+]\) 252.1752; found 252.1753.

\[ \text{Ph} \]\n\[ -\text{N} \]\n\[ 62 \]

\( N\)-cyclobutylaniline (62)

For 0.5 mmol scale, general procedure A was followed to convert aniline to 62 in 61% yield (over two steps) (63).

**Physical State:** light yellow oil;

\( R_f = 0.75 \) (1:5 EtOAc:hexanes, vis. I₂);
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.23 – 7.14 (m, 2H), 6.72 (t, $J = 7.4$ Hz, 1H), 6.61 – 6.55 (m, 2H), 4.00 – 3.89 (m, 1H), 3.83 (br s, 1H), 2.52 – 2.37 (m, 2H), 1.93 – 1.74 (m, 4H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 147.3, 129.3 (2C), 117.4, 113.1 (2C), 49.1, 31.4 (2C), 15.4;

HRMS (ESI-TOF): calc’d for C$_{10}$H$_{14}$N [M+H$^+$] 148.1126; found 148.1126.

$N$-benzylcyclobutanamine (63)

For 0.5 mmol scale, general procedure A was followed to convert benzylamine to 63 in 40% yield (over two steps) (48).

Physical State: colorless oil;

$R_f$ = 0.40 (1:6 MeOH:CH$_2$Cl$_2$, vis. I$_2$);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 3.71 (s, 2H), 3.36 – 3.25 (m, 1H), 2.27 – 2.17 (m, 2H), 2.01 (s, 1H), 1.80 – 1.59 (m, 4H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 140.1, 128.5 (2C), 128.4 (2C), 127.1, 53.6, 51.1, 31.1 (2C), 15.0;

HRMS (ESI-TOF): calc’d for C$_{11}$H$_{16}$N [M+H$^+$] 162.1283; found 162.1279.
**N-cyclobutyl-N-methylaniline (64)**

For 0.5 mmol scale, general procedure A was followed to convert N-methylaniline to 64 in 73% yield (over two steps) (64).

**Physical State:** colorless oil;

*R* = 0.75 (1:6 EtOAc:hexanes, vis. I₂);

**1H NMR (400 MHz, CDCl₃):** δ 7.33 – 7.25 (m, 2H), 6.89 – 6.78 (m, 3H), 4.07 – 3.97 (m, 1H), 2.89 (s, 3H), 2.37 – 2.25 (m, 2H), 2.23 – 2.09 (m, 2H), 1.83 – 1.70 (m, 2H);

**13C NMR (101 MHz, CDCl₃):** δ 150.4, 129.0 (2C), 117.9, 115.2 (2C), 55.3, 34.8, 29.0 (2C), 14.6;

**HRMS (ESI-TOF):** calc’d for C₁₁H₁₆N [M+H⁺] 162.1283; found 162.1278.

![N-benzyl-N-methylcyclobutanamine (65)](image)

**N-benzyl-N-methylecyclobutanamine (65)**

For 0.5 mmol scale (step 1) and 0.2 mmol scale (step 2), general procedure B was followed to convert N-benzylmethylaniline to 65 in 93% and 71% yield (for the amination and reduction, respectively).

**Physical State:** colorless oil;

*R* = 0.50 (1:10 MeOH:CH₂Cl₂, vis. I₂);

**1H NMR (600 MHz, CDCl₃):** δ 7.33 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 3.36 (s, 2H), 2.89 – 2.81 (m, 1H), 2.09 – 2.02 (m, 2H), 2.00 (s, 3H), 1.97 – 1.88 (m, 2H), 1.76 – 1.60 (m, 2H);

**13C NMR (101 MHz, CDCl₃):** δ 138.8, 129.5 (2C), 128.3 (2C), 127.0, 60.5, 58.6, 37.9, 28.0 (2C), 14.1;
HRMS (ESI-TOF): calc’d for C_{12}H_{18}N [M+H^+] 176.1439; found 176.1433.

[Chemical structure image]

**tert-butyl (3-(cyclobutyl(methyl)amino)propyl)(methyl)carbamate (66)**

For 0.5 mmol scale, general procedure B was followed to convert tert-butyl methyl(3-(methylamino)propyl)carbamate to 66 in 95% and 82% yield (for the amination and reduction, respectively) (65).

**Physical State:** colorless oil;

\[ R_f = 0.40 \ (1:8 \text{ MeOH:CH}_2\text{Cl}_2, \text{ vis. I}_2) \];

\[ ^1H \text{ NMR (600 MHz, CDCl}_3 + \text{NH}_4\text{OH)}: \delta 3.20 \ (s, 2H), 2.82 \ (s, 3H), 2.75 – 2.67 \ (m, 1H), 2.22 – 2.14 \ (m, 2H), 2.06 \ (s, 3H), 2.04 – 1.95 \ (m, 2H), 1.87 – 1.77 \ (m, 2H), 1.72 – 1.56 \ (m, 4H), 1.43 \ (s, 9H); \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3): \delta 155.9, 79.3, 60.8, 51.6, 47.2, 37.9, 34.3, 28.6 \ (3C), 28.0 \ (2C), 25.6, 14.1; \]

**HSQC:** See page S300 for correlations of doubled peaks;

**HRMS (ESI-TOF):** calc’d for C_{14}H_{29}N_{2}O_2 [M+H^+] 257.2229; found 257.2231.

[Chemical structure image]

**2-cyclobutyl-1,2,3,4-tetrahydroisoquinoline (67)**
For 0.5 mmol scale, general procedure A was followed to convert 1,2,3,4-tetrahydroisoquinoline to 67 in 68% yield (over two steps).

**Physical State**: light yellow oil;

\[ R_f = 0.40 \ (1:1 \text{ EtOAc:hexanes, vis. I}_2); \]

\[ \text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\text{):} \delta \ 7.14 – 7.06 \ (m, 3H), 7.01 \ (dd, J = 6.6, 2.0 \ Hz, 1H), 3.50 \ (s, 2H), 2.89 \ (q, J = 7.5, 6.7 \ Hz, 3H), 2.60 \ (t, J = 6.0 \ Hz, 2H), 2.17 – 2.10 \ (m, 2H), 2.03 – 1.94 \ (m, 2H), 1.80 – 1.71 \ (m, 2H); \]

\[ \text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3\text{):} \delta \ 134.6, 134.4, 128.8, 126.8, 126.2, 125.7, 60.1, 52.6, 47.0, 28.9, 27.6 \ (2C), 14.6; \]

**HRMS (ESI-TOF)**: calc’d for C\textsubscript{13}H\textsubscript{18}N [M+H\textsuperscript{+}] 188.1439; found 188.1436.

2-cyclobutyldecahydroisoquinoline (68)

For 0.5 mmol scale, general procedure A was followed to convert perhydroisoquinoline to 68 in 71% yield (over two steps).

**Physical State**: colorless oil;

\[ R_f = 0.40 \ (1:6 \text{ MeOH:CH}_2\text{Cl}_2, \text{vis. I}_2); \]

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):} \delta \ 2.92 \ (d, J = 11.1 \ Hz, 1H), 2.80 – 2.62 \ (m, 2H), 2.07 – 1.87 \ (m, 4H), 1.78 – 1.47 \ (m, 8H), 1.43 – 1.16 \ (m, 5H), 1.03 – 0.80 \ (m, 3H); \]

\[ \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{):} \delta \ 60.6, 56.5, 50.5, 41.8, 41.2, 33.0, 32.3, 30.8, 27.4, 27.3, 26.6, 26.2, 14.4; \]

**HRMS (ESI-TOF)**: calc’d for C\textsubscript{13}H\textsubscript{24}N [M+H\textsuperscript{+}] 194.1909; found 194.1912.
**N-benzyl-N-(furan-2-ylmethyl)cyclobutanamine (69)**

For 0.2 mmol scale, general procedure A was followed to convert \(N\)-benzyl-\(N\)-(furan-2-ylmethyl)amine to \(69\) in 60% yield (over two steps) (66).

**Physical State**: colorless oil;

\[ R_f = 0.75 \text{ (1:4 EtOAc:hexanes, vis. I2)}; \]

\[ ^1H\text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 7.45 – 7.31 \text{ (m, 5H), 7.31 – 7.23 \text{ (m, 1H), 6.34 (dd, } J = 3.1, 1.8 \text{ Hz, 1H), 6.14 (d, } J = 3.1 \text{ Hz, 1H), 3.55 (s, 2H), 3.50 (s, 2H), 3.19 – 3.08 \text{ (m, 1H), 2.15 – 2.02 (m, 2H), 2.02 – 1.86 \text{ (m, 2H), 1.78 – 1.60 \text{ (m, 2H)};}} \]

\[ ^{13}C\text{ NMR (101 MHz, CDCl}_3\text{)}: \delta 152.6, 141.9, 139.1, 129.5 \text{ (2C), 128.2 (2C), 126.9, 110.1, 108.8, 57.6, 53.5, 45.0, 28.4 \text{ (2C), 14.3;}} \]

**HRMS (ESI-TOF)**: calc’d for \(C_{16}H_{20}NO\) [M+H\(^+\)] 242.1545; found 242.1546.

**1-benzyl-4-cyclobutylpiperazine (70)**

For 0.5 mmol scale, general procedure A was followed to convert \(N\)-benzylpiperazine to \(70\) in 76% yield (over two steps) (52).
Physical State: colorless oil;

\[ R_f = 0.60 \text{ (1:10 MeOH:CH}_2\text{Cl}_2, \text{ vis. I}_2); \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta 7.32 - 7.27 \) (m, 4H), 7.23 (tt, \( J = 5.1, 3.3 \) Hz, 1H), 3.52 (s, 2H), 2.79 – 2.71 (m, 1H), 2.49 (s, 8H), 2.05 – 1.97 (m, 2H), 1.95 – 1.84 (m, 2H), 1.75 – 1.61 (m, 2H);

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \( \delta 138.1, 129.3 \) (2C), 128.3 (2C), 127.1, 63.2, 60.4 (2C), 52.7, 49.5 (2C), 27.1 (2C), 14.4;

HRMS (ESI-TOF): calc’d for \( \text{C}_{15}\text{H}_{23}\text{N}_2 [\text{M+H}^+] \) 231.1861; found 231.1864.

![Image](otbdps_71)

4-((tert-butyldiphenylsilyl)oxy)-1-cyclobutylpiperidine (71)

For 0.2 mmol scale, general procedure C was followed to convert 4-((tert-butyldiphenylsilyl)oxy)piperidine to 71 in 75% yield (over two steps) (67).

Physical State: colorless oil;

\[ R_f = 0.60 \text{ (1:1 EtOAc:hexanes, vis. UV}); \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta 7.66 \) (dt, \( J = 6.7, 1.5 \) Hz, 4H), 7.43 – 7.39 (m, 2H), 7.39 – 7.34 (m, 4H), 3.78 (s, 1H), 2.65 (p, \( J = 7.9 \) Hz, 1H), 2.54 (s, 2H), 1.99 (dddt, \( J = 11.4, 9.4, 4.3, 2.1 \) Hz, 3H), 1.92 – 1.78 (m, 3H), 1.73 – 1.58 (m, 6H), 1.06 (s, 9H);

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \( \delta 135.9 \) (4C), 134.7 (2C), 129.6 (2C), 127.6 (4C), 68.7, 60.6, 46.8 (2C), 34.0 (2C), 27.6 (2C), 27.1 (3C), 19.4, 14.3;

HRMS (ESI-TOF): calc’d for \( \text{C}_{25}\text{H}_{36}\text{NOSi} [\text{M+H}^+] \) 394.2561; found 394.2556.
Alternatively, 71 can be prepared from 4-hydroxypiperidine:

4-Hydroxypiperidine (51 mg, 0.5 mmol), sulfone C7 (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12 hours. The reaction was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄ and concentrated under reduced pressure. The crude aminated product was dissolved in MeOH (12.5 mL) and activated Mg turning 62 (40 equiv) were added. After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. To the mixture was added sat. aq. NH₄Cl and solid NaCl until saturation. To remove the water-soluble product, the mixture was extracted with CH₂Cl₂ (10 times), dried with Na₂SO₄, and concentrated under reduced pressure. To the crude cyclobutylated product was added DMF (3 mL), imidazole (68 mg) and TBDPSCI (0.19 mL) sequentially and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄, concentrated under reduced pressure, and purified by silica gel chromatography (1:1 hexanes:EtOAc) to give the 71 (85 mg, 43% yield). The spectroscopic data matched that from 71 as prepared above.

N-(3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)propyl)-N-methylcyclobutanamine, “cyclobutylated” nortriptyline (72)

For 0.2 mmol scale (step 1) and 0.08 mmol scale (step 2), general procedure C was followed to convert nortriptyline to 72 in 83% and 72% yield (for the amination and reduction, respectively).
Physical State: colorless oil;

$R_f = 0.40$ (1:6 MeOH:CH$_2$Cl$_2$, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30 – 7.24 (m, 2H), 7.21 – 7.10 (m, 5H), 7.05 – 7.01 (m, 1H), 5.84 (t, $J = 7.2$ Hz, 1H), 3.36 (br d, $J = 57.1$ Hz, 2H), 2.96 (br s, 1H), 2.82 – 2.67 (m, 2H), 2.39 – 2.21 (m, 3H), 2.00 (s, 3H), 1.96 (d, $J = 8.4$ Hz, 1H), 1.80 (p, $J = 10.6$, 9.9 Hz, 2H), 1.69 – 1.52 (m, 4H);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 8.7$ Hz, 2H), 7.38 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 5.27 (dd, $J = 8.4$, 4.6 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.44 (ddd, $J = 12.4$, 8.4, 6.6 Hz, 1H), 2.35 (ddd, $J = 12.4$, 8.5, 5.2 Hz, 1H), 2.15 (ddt, $J = 13.7$, 8.4, 5.2 Hz, 1H), 2.10 (s, 3H), 2.02 – 1.93 (m, 3H), 1.89 – 1.72 (m, 2H), 1.68 – 1.54 (m, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 143.6, 141.5, 140.2, 139.4, 137.2, 130.1, 129.6, 128.7, 128.3, 128.1, 127.5, 127.1, 126.1, 125.9, 60.4, 53.8, 37.8, 33.9, 32.2, 28.0 (2C), 27.3, 14.1;

HRMS (ESI-TOF): calc’d for C$_{23}$H$_{28}$N $[M+H]^+$ 318.2222; found 318.2223.

(rac)-N-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)cyclobutanamine, “cyclobutylated” fluoxetine (73)

For 0.1 mmol scale, general procedure C was followed to convert fluoxetine to 73 in 61% yield (over two steps).

Physical State: colorless oil;

$R_f = 0.25$ (1:15 MeOH:CH$_2$Cl$_2$, vis. I$_2$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 8.7$ Hz, 2H), 7.38 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 5.27 (dd, $J = 8.4$, 4.6 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.44 (ddd, $J = 12.4$, 8.4, 6.6 Hz, 1H), 2.35 (ddd, $J = 12.4$, 8.5, 5.2 Hz, 1H), 2.15 (ddt, $J = 13.7$, 8.4, 5.2 Hz, 1H), 2.10 (s, 3H), 2.02 – 1.93 (m, 3H), 1.89 – 1.72 (m, 2H), 1.68 – 1.54 (m, 2H);
\[ ^{13}\text{C NMR (151 MHz, CDCl}_3\text{): } \delta 160.8, 141.4, 128.9 \text{ (2C), 127.9, 126.8 (q, } ^3J_{\text{C-F}} = 4.2 \text{ Hz, 2C), 126.0, (2C) 124.5 (q, } ^1J_{\text{C-F}} = 271 \text{ Hz), 122.8 (q, } ^2J_{\text{C-F}} = 33.0 \text{ Hz), 115.9 (2C), 78.8, 60.8, 50.2, 38.0, 36.4, 28.0 \text{ (2C), 14.1);} \]

\[ ^{19}\text{F NMR (376 MHz, CDCl}_3\text{): } \delta -61.8; \]

\[ \text{HRMS (ESI-TOF): calc’d for C}_{21}\text{H}_{25}\text{F}_3\text{NO [M+H}^+] \text{ 364.1888; found 364.1892.} \]

(3S,4R)-3-((benzo[d][1,3]dioxol-5-yl oxy)methyl)-1-cyclobutyl-4-(4-fluorophenyl)piperidine, “cyclobutylated” paroxetine (74)

For 0.1 mmol scale, general procedure C was followed to convert paroxetine to 74 in 70% yield (over two steps).

**Physical State:** colorless oil;

\[ R_f = 0.25 \text{ (1:15 MeOH:CH}_2\text{Cl}_2, \text{ vis. I}_2); \]

\[ [\alpha]_D^{20} = -70.1 \text{ (c = 0.76, CHCl}_3); \]

\[ ^1\text{H NMR (600 MHz, CDCl}_3\text{): } \delta 7.16 \text{ (dd, } J = 8.4, 5.5 \text{ Hz, 2H), 6.96 (t, } J = 8.7 \text{ Hz, 2H), 6.61 (d, } J = 8.5 \text{ Hz, 1H), 6.34 (d, } J = 2.6 \text{ Hz, 1H), 6.12 (dd, } J = 8.5, 2.5 \text{ Hz, 1H), 5.87 (s, 2H), 3.57 (dd, } J = 9.4, 2.9 \text{ Hz, 1H), 3.44 (dd, } J = 9.4, 6.7 \text{ Hz, 1H), 3.21 (ddd, } J = 11.4, 3.8, 1.7 \text{ Hz, 1H), 3.07 – 2.97 (m, 1H), 2.79 (p, } J = 8.0 \text{ Hz, 1H), 2.53 – 2.44 (m, 1H), 2.24 – 2.13 (m, 1H), 2.13 – 2.03 (m, 2H), 2.03 – 1.90 (m, 2H), 1.91 – 1.79 (m, 4H), 1.79 – 1.65 \text{ (m, 2H);} \]

\[ ^{13}\text{C NMR (151 MHz, CDCl}_3\text{): } \delta 161.6 \text{ (d, } ^1J_{\text{C-F}} = 244 \text{ Hz), 154.5, 148.2, 141.7, 139.8 \text{ (d, } ^4J_{\text{C-F}} = 3.2 \text{ Hz), 129.0 (d, } ^3J_{\text{C-F}} = 7.6 \text{ Hz, 2C), 115.5 \text{ (d, } ^2J_{\text{C-F}} = 21.0 \text{ Hz, 2C), 108.0, 105.7, 101.2, 98.1, 97.2, 60.7, 53.8, 50.4, 44.2, 41.8, 34.0, 27.5, 27.5, 14.4);} \]

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$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –117.0;


(1S,4S)-N-cyclobutyl-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine, “cyclobutylated” sertraline (75)

For 0.1 mmol scale, general procedure C was followed to convert sertraline to 75 in 67% yield (over two steps).

**Physical State:** colorless oil;

$R_f$ = 0.50 (1:10 EtOAc:hexanes, vis. I$_2$);

$[\alpha]_{D}^{20}$ = + 97.8 (c = 1.22, CHCl$_3$);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.84 (dt, $J$ = 7.9, 1.2 Hz, 1H), 7.31 (d, $J$ = 8.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.13 (tt, $J$ = 7.5, 1.1 Hz, 1H), 7.11 (d, $J$ = 2.1 Hz, 1H), 6.88 (dd, $J$ = 7.7, 1.3 Hz, 1H), 6.82 (dd, $J$ = 8.3, 2.2 Hz, 1H), 4.12 (td, $J$ = 4.7, 4.0, 2.5 Hz, 1H), 3.90 (dd, $J$ = 9.6, 6.5 Hz, 1H), 3.30 – 3.21 (m, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 1.87 (m, 8H), 1.74 – 1.53 (m, 4H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 147.8, 139.9, 138.2, 132.2, 130.9, 130.2, 130.0, 129.9, 128.6, 128.4, 127.1, 126.7, 57.5, 57.1, 43.7, 31.8, 30.4, 28.8, 28.1, 15.7, 14.4;

HRMS (ESI-TOF): calc’d for C$_{21}$H$_{24}$Cl$_2$N [M+H$^+$] 360.1286; found 360.1288.
(cis/trans)-N,N-dibenzyl-3-((3,5-difluorophenyl)sulfonyl)cyclobutan-1-amine (76)

N-methylbenzyl-amine (99 mg, 0.5 mmol), sulfone C7 (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12h. The reaction was diluted with EtOAc, washed with brine twice, dried with Na$_2$SO$_4$, evaporated in vacuo, and purified by silica gel chromatography (15:1 hexanes:EtOAc) to give an inseparable mixture of cis/trans 76 (207 mg, 97% yield, ~1:1 ratio).

Physical State: white solid (inseparable mixture of cis/trans isomers);

$R_f = 0.35$ (1:6 EtOAc/hexanes, vis. UV);

Major isomer (trans):

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.45 (ddd, $J = 5.0$, 2.3, 1.1 Hz, 2H), 7.38 – 7.25 (m, 10H), 7.15 – 7.07 (m, 1H), 3.66 (ttd, $J = 9.7$, 4.0, 1.1 Hz, 1H), 3.52 (s, 4H), 3.39 (tt, $J = 9.6$, 7.7 Hz, 1H), 2.55 (ddddd, $J = 11.8$, 8.0, 4.0, 2.7 Hz, 2H), 2.37 – 2.28 (m, 2H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $^1J_{C,F} = 255$, 11.1 Hz, 2C), 141.5 (t, $^3J_{C,F} = 7.8$ Hz), 138.5 (2C), 129.1 (4C), 128.4 (4C), 127.2 (2C), 112.0 (q, $^2J_{C,F} = 6.6$ Hz, 2C), 109.5 (t, $^2J_{C,F} = 24.6$ Hz), 54.6 (2C), 54.4, 51.9, 29.0 (2C);

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –105.2;

Minor isomer (cis):

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.43 – 7.38 (m, 2H), 7.38 – 7.25 (m, 10H), 7.15 – 7.07 (m, 1H), 3.61 (qd, $J = 7.9$, 1.2 Hz, 1H), 3.58 (s, 4H), 3.23 (tt, $J = 9.1$, 7.1 Hz, 1H), 2.49 (qd, $J = 9.4$, 2.7 Hz, 2H), 2.23 (dtq, $J = 11.4$, 6.8, 2.0 Hz, 2H);
\( ^{13}C \) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 163.0 (dd, \( ^1J_{CF} = 255 \), 11.5 Hz, 2C), 141.8 (t, \( ^3J_{CF} = 7.7 \) Hz), 138.6 (2C), 129.0 (4C), 128.4 (4C), 127.2 (2C), 111.9 (q, \( ^2J_{CF} = 6.5 \) Hz, 2C), 109.4 (t, \( ^2J_{CF} = 25.2 \) Hz), 55.2 (2C), 53.6, 50.9, 29.1 (2C);

\( ^{19}F \) NMR (376 MHz, CDCl\(_3\)): \( \delta \) –105.2;

HRMS (ESI-TOF): calc’d for C\(_{24}\)H\(_{24}\)F\(_2\)NO\(_2\)S \([\text{M}+\text{H}^+]\) 428.1496; found 428.1496.

Note: Assignments for cis and trans isomers were made by comparison to cis-S\(_{23}\) and trans-S\(_{24}\) which were able to be separated and individually characterized.

\[ \text{N,N-dibenzyloyclobutane-1-amine-3,3-D}_2 \] (77)

Amine 76 (40 mg, 0.094 mmol) was dissolved in CD\(_3\)OD (5 mL) and added to CD\(_3\)ONa in CD\(_3\)OD (freshly prepared from Na and CD\(_3\)OD) and stirred at 60 °C for 5h. The reaction was cooled to room temperature, Na/Hg (4-5%, 240 mg, 5 equiv) was added and the suspension stirred at room temperature for another 1h. The reaction was diluted with EtOAc, washed successively with sat. aq. NH\(_4\)Cl and brine, dried with Na\(_2\)SO\(_4\), evaporated in vacuo and purified by silica gel flash chromatography to give 77 (13 mg, 55%).

Physical State: colorless oil;

\( R_f = 0.60 \) (1:15 EtOAc/hexanes, vis. I\(_2\));

\( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.34 – 7.27 (m, 8H), 7.25 – 7.20 (m, 2H), 3.49 (s, 4H), 3.15 (tt, \( J = 9.0 \), 7.0 Hz, 1H), 1.94 (ddd, \( J = 9.5 \), 7.0, 2.8 Hz, 2H), 1.86 (t, \( J = 9.9 \) Hz, 2H);

\( ^{13}C \) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 139.5 (2C), 129.3 (4C), 128.1 (4C), 126.8 (2C), 58.1, 54.3 (2C), 28.1 (2C) [CD\(_2\) peak at ~14ppm almost imperceptible];

HRMS (ESI-TOF): calc’d for C\(_{18}\)H\(_{20}\)D\(_2\)N \([\text{M}+\text{H}^+]\) 254.1878; found 254.1872.
(cis)-3-allyl-N,N-dibenzycyclobutan-1-amine (78)

To a solution of amine 76 (40 mg, 0.094 mmol) in THF (1 mL) was added LHMDS (1.0 M in THF, 0.14 mL, 1.5 equiv) at –78 °C. The mixture was stirred for 30 min before allyl bromide (24 µL, 3 equiv) was added. The resulting mixture was stirred at –78 °C for 2h before being quenched by sat. aq. NH₄Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄, evaporated in vacuo and purified by silica gel flash chromatography to give the allylated product (38 mg, 87%). This allylated product was dissolved in MeOH (2 mL) and treated with activated Mg (62) Mg turnings (78 mg, 40 equiv). After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc, washed successively with sat. aq. NH₄Cl and brine, dried with Na₂SO₄, evaporated in vacuo and purified by silica gel flash chromatography to give 78 (19 mg, 80%). Note: The reaction gave a 2.7:1 mixture of cis:trans diastereomers. After purification with prep TLC, a ratio of 3.8:1 mixture of cis:trans diastereomers was shown in the spectra.

**Physical State:** colorless oil;

\[ R_f = 0.60 \ (1:15 \ \text{EtOAc:hexanes, vis. I}_2) \];

\(^1\)H NMR for cis isomer (600 MHz, CDCl₃): \( \delta 7.33 - 7.28 \ (m, 8\text{H}), 7.23 \ (\text{ddd, } J = 8.6, 5.5, 2.5 \ \text{Hz, 2H}), 5.73 \ (\text{ddt, } J = 17.0, 10.2, 6.7 \ \text{Hz, 1H}), 5.03 - 4.91 \ (m, 2\text{H}), 3.49 \ (s, 4\text{H}), 3.00 \ (tt, J = 9.0, 6.9 \ \text{Hz, 1H}), 2.22 - 2.10 \ (m, 4\text{H}), 1.90 \ (tp, J = 9.6, 7.3 \ \text{Hz, 1H}), 1.51 \ (qd, J = 9.0, 2.7 \ \text{Hz, 2H}) \);

\(^{13}\)C NMR for cis isomer (151 MHz, CDCl₃): \( \delta 139.3 \ (2\text{C}), 136.9, 129.3 \ (4\text{C}), 128.1 \ (4\text{C}), 126.8 \ (2\text{C}), 115.0, 54.6, 54.3 \ (2\text{C}), 41.2, 34.3 \ (2\text{C}), 27.6 \);

**2D NOESY:** See page S328;

**HRMS (ESI-TOF):** calc’d for C\(_{21}\)H\(_{26}\)N \([M+H^+]\) 292.2065; found 292.2062.
(cis)-N,N-dibenzyl-3-fluorocyclobutan-1-amine (79)

To a solution of amine 76 (47 mg, 0.11 mmol) in THF (2 mL) was added LHMDS (1.0 M in THF, 0.13 mL, 1.2 equiv) at –40 °C. The reaction was stirred for 10 min before N-fluorobenzenesulfinimide (NFSI) (32 mg, 1.0 equiv) in THF (0.5 mL) was added. The resulting mixture was stirred at –40 °C for 2h before being quenched by sat. aq. NH₄Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na₂SO₄ and evaporated in vacuo. The crude product was dissolved in MeOH (2 mL) and Na/Hg (4-5%, 310 mg, 6 equiv) was added and the suspension stirred at room temperature for 1h. The mixture was diluted with EtOAc, washed successively with sat. aq. NH₄Cl and brine, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel flash chromatography to give 79 (15 mg, 51% for 2 steps). Note: the reaction gave a 7:1 mixture of cis:trans diastereomers. After purification with prep TLC, the cis isomer (the major product) was shown in the spectra.

Physical State: white solid (m.p. = 67-69 °C);

R_f = 0.70 (1:6 EtOAc/hexanes, vis. I₂);

¹H NMR (600 MHz, CDCl₃): δ 7.34 – 7.28 (m, 8H), 7.24 (ddt, J = 8.6, 5.6, 2.8 Hz, 2H), 4.69 (dp, J = 56.1, 7.0 Hz, 1H), 3.51 (s, 4H), 2.67 (tttd, J = 8.5, 6.6, 1.6 Hz, 1H), 2.51 – 2.40 (m, 2H), 2.17 – 2.03 (m, 2H);

¹³C NMR (151 MHz, CDCl₃): δ 138.9 (2C), 129.2 (4C), 128.3 (4C), 127.1 (2C), 81.8 (d, ¹J_C-F = 211 Hz), 54.9 (2C), 47.7 (d, ²J_C-F = 22.1 Hz, 2C), 19.7 (d, ³J_C-F = 19.7 Hz);

2D NOESY: See page S332;

¹⁹F NMR (376 MHz, CDCl₃): δ –168.3;

HRMS (ESI-TOF): calc’d for C₁₈H₂₁FN [M+H⁺] 270.1658; found 270.1659.
\( N,N\text{-dibenzyl-3-benzylidencyclobutan-1-amine (80)} \)

To a solution of amine 76 (76 mg, 0.18 mmol) and benzaldehyde (36 \( \mu \)L, 2.0 equiv) in THF (5 mL) was added a solution of \( t \)BuOK (0.75 M in THF, 0.48 mL, 2.0 equiv) dropwise at 0 \( ^\circ \)C. The reaction was stirred for 1h at 0 \( ^\circ \)C before being quenched by sat. aq. NH\(_4\)Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na\(_2\)SO\(_4\) and evaporated \textit{in vacuo}. The crude product was dissolved in CH\(_2\)Cl\(_2\) (5 mL), and then DMAP (2 mg), Et\(_3\)N (74 \( \mu \)L, 3 equiv) and Ac\(_2\)O (33 \( \mu \)L, 2 equiv) were added successively. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with brine twice, dried with Na\(_2\)SO\(_4\) and evaporated \textit{in vacuo}. The crude product was dissolved in MeOH (5 mL) and Na/Hg (4-5%, 546 mg, 6 equiv) was added and the suspension stirred at room temperature for 1h. The mixture was diluted with EtOAc, washed successively with sat. aq. NH\(_4\)Cl and brine, dried with Na\(_2\)SO\(_4\), evaporated \textit{in vacuo} and purified by silica gel flash chromatography to give 80 (38 mg, 63% for 3 steps).

\textbf{Physical State}: colorless oil;

\[ R_f = 0.50 \text{ (1:20 EtOAc:hexanes, vis. UV)}; \]

\( ^1H \text{ NMR (600 MHz, CDCl}_3\): } \delta 7.40 – 7.27 \text{ (m, 12H)}, 7.26 – 7.22 \text{ (m, 2H)}, 7.20 \text{ (td, } J = 7.3, 1.4 \text{ Hz, 1H)}, 6.21 \text{ (t, } J = 2.4 \text{ Hz, 1H)}, 3.62 \text{ (q, } J = 14.0 \text{ Hz, 4H}), 3.40 \text{ (p, } J = 7.3 \text{ Hz, 1H)}, 3.13 – 3.01 \text{ (m, 2H)}, 2.87 \text{ (dt, } J = 7.4, 2.1 \text{ Hz, 2H)}; \]

\( ^{13}C \text{ NMR (151 MHz, CDCl}_3\): } \delta 138.9 \text{ (2C)}, 138.0, 137.4, 129.3 \text{ (4C)}, 128.5 \text{ (2C)}, 128.3 \text{ (4C)}, 127.2 \text{ (2C)}, 127.0 \text{ (2C)}, 126.1, 121.7, 54.8, 54.3 \text{ (2C)}, 38.7, 38.4; \]

\textbf{HRMS (ESI-TOF)}: calc’d for C\(_{25}\)H\(_{26}\)N [M+H\(^+\)] 340.2065; found 340.2067.
Comparison of two-step, one-pot (with DMSO/MeOH), and one-pot (MeOH only) prep. For the “cyclobutylation” of N-benzylmethylamine (to give 65)

Two step protocol: For 0.5 mmol scale (step 1) and 0.2 mmol scale (step 2), general procedure B was followed to convert N-benzylmethylamine to 65 in 93% and 71% yield (for the amination and reduction, respectively). Overall yield was 66%.

One-pot with DMSO and MeOH: N-Methylbenzylamine (24 mg, 0.2 mmol), sulfone C7 (48 mg, 1.05 equiv) and LiCl (25 mg, 3.0 equiv) were dissolved in DMSO (0.5 mL) stirred at room temperature for 12h. Activated (62) Mg turnings (480 mg, 100 equiv) were added, the suspension diluted with MeOH (5 mL), and then heated to reflux. After TLC indicated completion of the reaction, the mixture was diluted with EtOAc, washed with sat. aq. NH₄Cl and brine successively, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel chromatography (30:1 CH₂Cl₂:MeOH) to give 65 (19 mg, 59% yield).

One-pot with MeOH only: N-Methylbenzylamine (24 mg, 0.2 mmol), sulfone C7 (48 mg, 1.05 equiv) and LiCl (25 mg, 3.0 equiv) were added to MeOH (0.5 mL) and the mixture stirred at room temperature for 60h. Activated (62) Mg turnings (192 mg, 40 equiv) were added, the suspension diluted with MeOH (5 mL), and then heated to reflux. After TLC indicated completion of the reaction, the mixture was diluted with EtOAc, washed with sat. aq. NH₄Cl and brine successively, dried with Na₂SO₄, evaporated in vacuo, and purified by silica gel chromatography (30:1 CH₂Cl₂:MeOH) to give 65 (24 mg, 74% yield).

Preparation of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (82)

3-((3,5-difluorophenyl)sulfonyl)cyclopentyl methanesulfonate (S25)

Cyclopentenone (1.67 mL, 20 mmol, 1.0 equiv.) was dissolved in H₂O (30 mL) and sodium 3,5-difluorobenzensulfinate (5 g, 24.98 mmol, 1.25 equiv.) was added followed by the dropwise addition of HCl (30 mL, 1.0 M). A white precipitate appeared and the solution was stirred for 16 h at room temperature. The reaction was filtered, the residual H₂O was azeotroped
with toluene, and residual solvent was removed under reduced pressure to yield the ketone as a white solid which was used directly in the next reaction without further purification.

The ketone was dissolved in MeOH (100 mL) and the reaction was cooled to 0 °C. NaBH₄ (690 mg, 18.22 mmol, 1.0 equiv.) was added and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. NH₄Cl (ca. 10 mL), CH₂Cl₂ was added, the layers were separated and the combined organic layers were dried over Na₂SO₄. The crude material was passed over a pad of silica gel to yield a white solid which was used directly in the next reaction without further purification.

The alcohol was dissolved in CH₂Cl₂ (100 mL) and the reaction was cooled to 0 °C. The flask was then charged with Et₃N (3.05 mL, 21.86 mmol, 1.2 equiv.) and methanesulfonyl chloride (1.70 mL, 21.86 mmol, 1.2 equiv.) and the temperature of the reaction was allowed to become ambient over 16 h. The reaction was quenched with H₂O, the layers were separated, the organic layer was dried over Na₂SO₄, passed over a pad of silica gel, and concentrated under reduced pressure to afford S25 as a white solid which was further purified by recrystallization from CH₂Cl₂ (5.75 g, 82% from cyclopentenone).

**Physical State:** white solid (m.p. = 99-100 °C);

\[ R_f = 0.31 \text{ (1:1 EtOAc:hexanes, vis. UV)}; \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3\text{): } \delta \text{ 7.47} - \text{7.42 (m, 2H), 7.13 (tt, } J = 8.3, 2.3 \text{ Hz, 1H), 5.16} - \text{5.11 (m, 1H), 3.55 (dq, } J = 9.2, 8.2 \text{ Hz, 1H), 3.04 (s, 3H), 2.44} - \text{2.39 (m, 2H), 2.33} - \text{2.24 (m, 1H), 2.21} - \text{2.15 (m, 1H), 2.02} - \text{1.93 (m, 2H)}; \]

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\text{): } \delta \text{ 163.1 (dd, } ^1J_{C-F} = 256, 11.7 \text{ Hz, 2C), 141.7 (t, } ^3J_{C-F} = 7.9 \text{ Hz), 112.3 (q, } ^2J_{C-F} = 6.6 \text{ Hz, 2C), 109.8 (t, } ^2J_{C-F} = 25.1 \text{ Hz), 80.0, 62.1, 38.8, 33.7, 33.1, 24.9; \]

\[ ^{19}F \text{ NMR (376 MHz, CDCl}_3\text{): } \delta \text{ –104.8;} \]

**HRMS (ESI-TOF):** calc’d for C₁₂H₁₄F₂NaO₅S₂ [M+Na⁺] 363.0148; found 363.0149.

![Chemical Structure](attachment:image.png)

1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (82)
Mesylate S25 (2.0 g, 5.88 mmol, 1.0 equiv.) was dissolved in THF (30 mL) and cooled to –10 °C in a NaCl/H2O bath. n-BuLi (3 mL, 5.88 mmol, 1.97 M) was added in one portion, the reaction was stirred for 5 minutes, and quenched with sat. aq. NH4Cl (ca. 3 mL). CH2Cl2 was added, the layers were separated and the aqueous layer was extracted with CH2Cl2 (2 X 50 mL). The combined organic layers were dried over Na2SO4, concentrated under reduced pressure, and purified with column chromatography (silica gel, 0→20% EtOAc in hexanes) to yield 82 as a white solid (720 mg, 50%)

**Physical State**: white solid (m.p. = 59-60 °C);

**Sigma-Aldrich Catalog Number**: MKE151701;

$R_f = 0.25$ (1:4 EtOAc:hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl3): $\delta$ 7.42 – 7.35 (m, 2H), 7.07 (tt, $J = 8.5$, 2.3 Hz, 1H), 2.69 (ddd, $J = 6.6$, 4.2, 1.9 Hz, 1H), 2.55 (tdd, $J = 11.0$, 4.1, 1.9 Hz, 1H), 2.24 (ttdd, $J = 11.0$, 4.7, 1.4 Hz, 1H), 1.80 (td, $J = 6.5$, 5.7, 2.4 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.43 (ddd, $J = 10.9$, 6.3, 4.1 Hz, 1H), 1.31 (dd, $J = 4.8$, 2.4 Hz, 1H);

$^{13}$C NMR (151 MHz, CDCl3): $\delta$ 163.0 (dd, $^1J_{CF} = 255$, 11.6 Hz, 2C), 143.4 (t, $^3J_{CF} = 7.9$ Hz), 111.3 (q, $^2J_{CF} = 6.7$ Hz, 2C), 109.0 (t, $^2J_{CF} = 25.3$ Hz), 40.0, 26.1, 22.5, 22.4, 20.4;

$^{19}$F NMR (376 MHz, CDCl3): $\delta$ –105.7;

**HRMS (ESI-TOF)**: calc’d for C$_{11}$H$_{11}$F$_2$O$_2$S [M+H$^+$] 245.0448; found 245.0442.

**Substrates for the “Cyclopentylation” of Amines**

\[
\text{cis-2-((3,5-difluorophenyl)sulfonyl)cyclopentyl-1,2,3,4-tetrahydroisoquinoline (83)}
\]
On a 0.5 mmol scale, “cyclobutylation” General Procedure A (sans reduction) was followed to convert 1,2,3,4-tetrahydroisoquinoline to 83 in 55% yield as a single isolated diastereomer.

**Physical State:** white solid (unstable at room temperature);

$R_f = 0.60$ (1:1 EtOAc:hexanes, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.49 – 7.43 (m, 2H), 7.10 (dt, $J = 10.9$, 6.3, 5.5, 2.3 Hz, 4H), 7.02 – 6.98 (m, 1H), 3.67 (s, 2H), 3.56 (tt, $J = 9.8$, 7.0 Hz, 1H), 2.93 – 2.82 (m, 3H), 2.82 – 2.71 (m, 2H), 2.24 (tt, $J = 13.8$, 8.3 Hz, 2H), 2.03 (ddt, $J = 15.9$, 12.4, 9.0 Hz, 2H), 1.93 (dq, $J = 13.8$, 8.7 Hz, 1H), 1.80 (dq, $J = 12.2$, 9.5 Hz, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $^1J_{C-F} = 256$, 11.3 Hz, 2C), 142.0 (t, $^3J_{C-F} = 7.8$ Hz), 134.2, 134.1, 128.7, 126.7, 126.3, 125.8, 112.2 (q, $^2J_{C-F} = 6.8$ Hz, 2C), 109.5 (t, $^2J_{C-F} = 24.9$ Hz), 65.6, 62.4, 54.7, 49.1, 31.5, 29.1, 29.0, 24.6;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –105.2;

2D NOESY: See pages S341-S342;

HRMS (ESI-TOF): calc’d for C$_{20}$H$_{22}$F$_2$NOS$_2$ [M+H$^+$] 378.1339; found 378.1339.

cis-1-benzyl-4-(3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperazine (85)

On a 0.5 mmol scale, “cyclobutylation” General Procedure A (sans reduction) was followed to convert N-benzylpiperazine (52) to 85 in 42% yield with ~12:1 d.r. Note: Major isomer tentatively assigned as cis.

**Physical State:** white solid (m.p. = 122-124 °C);
$R_f = 0.41$ (100% EtOAc, vis. UV);

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.46 – 7.40 (m, 2H), 7.29 (d, $J = 5.0$ Hz, 4H), 7.24 (q, $J = 5.0$, 4.5 Hz, 1H), 7.08 (tt, $J = 8.3$, 2.3 Hz, 1H), 3.49 (s, 3H), 2.65 – 2.57 (m, 1H), 2.48 (s, 8H), 2.18 (dtd, $J = 13.6$, 6.7, 3.9 Hz, 1H), 2.11 (dt, $J = 13.2$, 6.8 Hz, 1H), 1.95 – 1.82 (m, 3H), 1.72 – 1.61 (m, 1H);

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $^1J_{C-F} = 256$, 11.5 Hz, 2C), 142.1 (t, $^3J_{C-F} = 7.8$ Hz), 138.0, 129.3 (2C), 128.3 (2C), 127.2, 112.2 (q, $^2J_{C-F} = 6.5$ Hz, 2C), 109.4 (t, $^2J_{C-F} = 25.0$ Hz), 66.2, 63.1, 62.4, 53.0 (2C), 51.8 (2C), 31.4, 29.0, 24.4;

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –105.3 (minor diastereomer at –105.2 (~12:1 ratio);

2D NOESY: See pages S346-S347;

HRMS (ESI-TOF): calc’d for C$_{22}$H$_{27}$F$_2$N$_2$O$_2$S [M+H$^+$] 421.1761; found 421.1762.
Methods for peptide synthesis and cysteine labeling:

Analytical reverse-phase HPLC was performed on a Hitachi D-7000 separations module equipped with a L-4500A photodiode array detector. Peptides were analyzed using a Venusil ASB C18 column (5 µm, 4.6 x 150 mm, Bonna-Agela Technologies) at a flow rate of 1.5 mL min\(^{-1}\) using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B). Results were analyzed using Hitachi Model D-7000 Chromatography Data Station Software.

Preparative reverse-phase HPLC was performed using a Hitachi system comprised of an L-7150 pump and L-4000 programmable UV detector operating at a wavelength of 230 nm coupled to a Hitachi D-2500 Chromato-Integrator. Peptides were purified on a Thermo Scientific Bio-basic C18 10 µm preparative column operating at a flow rate of 12 mL min\(^{-1}\) using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B) and a linear gradient as specified. Peptides were isolated as the corresponding TFA salts and as white solids (unless otherwise noted) following lyophilization.
Preparation of peptides 86 and 87:

![Diagram of Fmoc-SPPS on 2-chlorotrityl chloride resin]

Fig. S56. Preparation of peptides 86 and 87 using Fmoc-SPPS on 2-chlorotrityl chloride resin.

Solid-phase peptide synthesis

Preloading 2-chloro-trityl chloride resin

2-chloro-trityl chloride resin (265 mg, 1.51 mmol/g loading) was swollen in dry DCM for 30 min then washed with CH$_2$Cl$_2$ (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-Lys(Boc)-OH (210 µmol) and N,N-diisopropylethylamine (DIEA) (420 µmol) in DMF (2 mL) was added and the resin agitated on an orbital shaker at rt for 18 h. The resin was washed with DMF (5 x 3 mL) and CH$_2$Cl$_2$ (5 x 3 mL) and treated with a solution of CH$_2$Cl$_2$/CH$_3$OH/DIEA (17:2:1 v/v/v, 3 mL)
for 0.5 h. The resin washed with DMF (5 x 3 mL), CH₂Cl₂ (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

The loading efficiency was evaluated through treatment of the resin with 20% piperidine/DMF (3 mL, 2 x 3 min) to deprotect the Fmoc group. The combined deprotection solutions were diluted to 10 mL with 20% piperidine/DMF. An aliquot of this mixture (50 µL) was diluted 200-fold with 20% piperidine/DMF and the UV absorbance of the piperidine-fulvene adduct was measured ($\lambda = 301$ nm, $\varepsilon = 7800$ M$^{-1}$ cm$^{-1}$) to quantify the amount of amino acid loaded onto the resin.

**General iterative peptide assembly (Fmoc-SPPS)**

Peptides were elongated using iterative Fmoc-solid-phase peptide synthesis (Fmoc-SPPS), according to the following general protocols:

**Deprotection:** The resin was treated with 20% piperidine/DMF (3 mL, 2 x 3 min) and washed with DMF (5 x 3 mL), CH₂Cl₂ (5 x 3 mL) and DMF (5 x 3 mL).

**General amino acid coupling:** A preactivated solution of protected amino acid (4 eq.), PyAOP (4 eq.) and N-methylmorpholine (8 eq.) in DMF (final concentration 0.1 M) was added to the resin. After 1 h, the resin was washed with DMF (5 x 3 mL), CH₂Cl₂ (5 x 3 mL) and DMF (5 x 3 mL).

**Capping:** Acetic anhydride/pyridine (1:9 v/v) was added to the resin (3 mL). After 3 min the resin was washed with DMF (5 x 3 mL), CH₂Cl₂ (5 x 3 mL) and DMF (5 x 3 mL).

**Cleavage:** A mixture of TFA, triisopropylsilane (TIS) and water (90:5:5 v/v/v) was added to the resin. After 2 h, the resin was washed with TFA (3 x 2 mL).

**Work-up:** The combined cleavage solution and TFA washes were concentrated under a stream of nitrogen. The residue was treated with cold Et₂O to precipitate the crude peptide, which was subsequently dissolved in water containing 0.1% TFA, filtered and purified by reverse-phase HPLC.
Peptide 86: H-WTPYCGHNK-OH

Peptide 86 was prepared using iterative Fmoc-SPPS (50 µmol scale) and purified by reverse-phase HPLC (gradient: 10% B for 5 min, 10% to 40% B over 35 min) to afford the target compound as a white solid following lyophilization (3 x TFA salt). Note: for clarity, TFA salts have been omitted from the condensed structure.

Analytical HPLC (0 to 100% B over 25 min, λ = 230 nm, R_t = 10.6 min) of purified peptide 86.
Peptide 86: HRMS

HRMS (ESI-TOF): calc'd for C_{50}H_{69}N_{14}O_{13}S [M+H]^+ 1105.4884, found 1105.4865 [M+H]^+, 553.2473 [M+2H]^{2+}
Peptide 87: H-WTPYAGHNK-OH

Peptide 87 was prepared using iterative Fmoc-SPPS (50 µmol scale) and purified by reverse-phase HPLC (gradient: 15% B for 5 min, 15% to 45% B over 25 min) to afford the target compound as a white solid following lyophilization (3 x TFA salt). Note: for clarity, TFA salts have been omitted from the condensed structure.

Analytical HPLC (0 to 100% B over 25 min, λ = 230 nm, Rf = 10.3 min) of purified peptide 87.
Peptide 87: HRMS

HRMS (ESI-TOF): calc’d for $\text{C}_{50}\text{H}_{69}\text{N}_{14}\text{O}_{13} [\text{M+H}]^+$ 1073.5163, found 1073.5128 [M+H]^+, 537.2605 [M+2H]^2+
Fig. S57. General protocol for the reaction of cysteine-containing peptides with bicyclobutane sulfone reagents C.

Note: Stock solutions of K₂CO₃ may also be prepared in aqueous denaturing buffer (6 M guanidine hydrochloride/0.2 M phosphate, pH = 7.0).

**General procedure:**

To a solution of thiol-containing peptide (1.0 equiv.) in degassed 0.2 M K₂CO₃ (2.6 equiv. K₂CO₃) was added a 0.2 M solution of sulfone C in DMF (1.3 equiv. reagent C) to give a final concentration of 0.05 M with respect to the peptide. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and the reaction
quenched by the addition of water containing 0.1% TFA upon consumption of the starting peptide. The crude mixture was immediately purified by reverse-phase HPLC and lyophilized to afford the cysteine-labeled peptide as a white solid.

**Notes, Troubleshooting, and Limitations for cysteine tagging:**

1. **Solvent and concentration:**
   a. Aqueous denaturing buffer (6 M guanidine hydrochloride, 0.2 M phosphate) may be readily employed in place of H₂O as a suitable reaction medium.
   b. The reaction may also be performed at higher dilution. Suitable tagging was observed in aqueous denaturing buffer (6 M guanidine hydrochloride, 0.2 M phosphate) at a concentration of 10 mM with respect to the cysteine-containing peptide – see Fig. S58.

2. **Addition of base and pH considerations:**
   a. Varying equivalents of K₂CO₃ were employed based on the relative number of basic side-chains (e.g. lysine, arginine, and histidine, which are protonated in TFA buffer upon HPLC purification) in the starting amino acid or peptide. Reaction of cysteine methyl ester hydrochloride S32 and C1 in the absence of base did not proceed. The addition of 1.0 equiv. of K₂CO₃ facilitated rapid and efficient tagging. The tagging of glutathione also proceeded efficiently in the presence of 1.0 equiv. of K₂CO₃. In the case of peptide 86 (a tri TFA salt), the addition of 2.6 equiv. of K₂CO₃ facilitated efficient cysteine tagging.
   b. The pH of the reaction mixture following addition of an appropriate amount of K₂CO₃ was measured to be between approximately 9-10, allowing for deprotonation of the cysteine thiol (pKa = 8.14). It is anticipated that reactions may be run with similar efficiency in the absence of K₂CO₃ in aqueous buffer maintained at a pH of approximately 8 or above.

3. **Degassing:**
   a. Solvents were degassed prior to use by bubbling argon through the solutions (~3 min of sparging per solution). The exclusion of oxygen is important to keep thiols in reduced form.
   b. Alternatively, tris(carboxyethyl)phosphine (TCEP) may be employed as a water-soluble reductant. Sulfone reagent C7 (1.0 equiv.) is stable to the presence of TCEP (2.0 equiv.) in 2:1 (v/v) 0.2 M aqueous K₂CO₃/DMF:
Stability of reagent C7 to TCEP: Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of C7 after treatment with TCEP. A) t = 1 h 40 min; B) t = 4 h 40 min; C) t = 26 h.

4. Limitations:
   a. Designer sulfone reagents C1-C7 are not water-soluble. The reaction must therefore be performed with a suitable organic cosolvent (e.g. DMF) to solubilize the strain release reagent. THF may also be employed as an organic cosolvent, although rates of cysteine tagging in the presence of THF were observed to be substantially slower than with DMF.
   b. Thiol reductants (e.g. dithiothreitol, β-mercaptoethanol) should be avoided to prevent competitive tagging of the reductants.
Peptide 88:

To a solution of peptide 86 (3.25 mg, 2.25 µmol) in degassed 0.2 M K₂CO₃ (29.4 µL, 2.6 equiv. K₂CO₃) was added a 0.2 M solution of sulfone C7 in DMF (14.6 µL, 2.94 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 86. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and then quenched at t = 5 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 55% B over 30 min) and lyophilized to afford peptide 88 as a white solid (3 x TFA salt, 3.3 mg, 91% yield).
Fig. S58. A) Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of peptide 86 with sulfone C7 at $t = 2$ h and B) $t = 3.5$ h; C) Purified peptide product 88 ($R_t = 13.5$ min).
Peptide 88: HRMS

HRMS (ESI-TOF): calc’d for $C_{60}H_{77}F_2N_{14}O_{15}S_2$ [M+H]$^+$ 1335.5097, found 1335.5056 [M+H]$^+$, 668.2579 [M+2H]$^{2+}$
Preparation of \textbf{88} in denaturing buffer (0.01 M concentration):

The reaction of peptide \textbf{86} and reagent \textbf{C7} could also be performed in aqueous denaturing buffer. Peptide \textbf{86} (2.1 mg, 1.45 µmol) was dissolved in a degassed solution of 0.039 M K$_2$CO$_3$ prepared in aqueous 6 M guanidine hydrochloride/0.2 M Na$_2$HPO$_4$ (97 µL, 2.6 equiv. K$_2$CO$_3$). A 0.039 M solution of sulfone \textbf{C7} in DMF (48 µL, 1.89 µmol, 1.3 equiv.) was added to the peptide to give a final concentration of 0.01 M with respect to peptide \textbf{86}. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.
**Fig. S59.** A) Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of peptide 86 with sulfone C7 at t = 0 h, B) t = 2.75 h, and C) t = 20.5 h.

Peptide Control Studies:

To a solution of peptide 87 (3.59 mg, 2.54 µmol) in degassed 0.2 M K$_2$CO$_3$ (33.3 µL, 2.6 equiv. K$_2$CO$_3$) was added a 0.2 M solution of sulfone C7 in DMF (16.7 µL, 3.35 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 87. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.
**Fig. S60.** Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of peptide 87 with sulfone C7 at A) $t = 0$ h and B) $t = 24$ h.
To a solution of peptide 87 (1.98 mg, 1.40 µmol) in degassed 0.2 M K$_2$CO$_3$ (18.4 µL, 2.6 equiv. K$_2$CO$_3$) was added a 0.2 M solution of N-ethylmaleimide 89 in DMF (9.2 µL, 1.84 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 87. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

**Fig. S61.** Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of peptide 87 with N-ethylmaleimide 89 at A) t = 0 h, B) t = 1 h, and C) t = 24 h.
To a solution of peptide 87 (3.27 mg, 2.31 µmol) in degassed 0.2 M K₂CO₃ (30.0 µL, 2.6 equiv. K₂CO₃) was added a 0.2 M solution of iodoacetamide in DMF (15.0 µL, 3.04 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 87. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

Fig. S62. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide 87 with iodoacetamide at A) t = 0 h and B) t = 24 h.
Peptide S26:

To a solution of peptide 86 (4.29 mg, 2.96 µmol) in degassed 0.2 M K₂CO₃ (39.0 µL, 2.6 equiv. K₂CO₃) was added a 0.2 M solution of sulfone C1 in DMF (19.0 µL, 3.88 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 86. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and then quenched at t = 24 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 50% B over 30 min) and lyophilized to afford peptide S26 as a white solid (3 x TFA salt, 3.7 mg, 76% yield).
Fig. S63. A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide 86 with sulfone C1 at t = 24 h; and B) purified peptide product S26 (R_t = 12.7 min)

Peptide S26: HRMS

HRMS (ESI-TOF): calc’d for C_{60}H_{79}N_{14}O_{15}S_{2} [M+H]^+ 1299.5285, found 1299.5265 [M+H]^+, 650.2681 [M+2H]^{2+}
To a solution of peptide 87 (3.47 mg, 2.45 µmol) in degassed 0.2 M K$_2$CO$_3$ (32.0 µL, 2.6 equiv. K$_2$CO$_3$) was added a 0.2 M solution of sulfone C1 in DMF (16.0 µL, 3.23 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 87. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

![Chemical structure and diagram](image)

**Fig. S64.** Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of peptide 87 with sulfone C1 at A) t = 0 h and B) t = 24 h.


**Reaction Kinetics:**

The rates of reaction between peptide 86 and bicyclobutane arylsulfones (reagent C) were evaluated by peak integration of analytical HPLC chromatograms (0 to 100% B over 25 min, $\lambda = 280$ nm). Reactions were performed under the conditions previously described. Aliquots (0.8 µL) were removed at various time points and quenched by dilution with water containing 0.1% TFA (360 µL) and immediately frozen. Prior to analysis, the samples were thawed and treated with a 10 mg/mL solution of TCEP in water containing 0.1% TFA (120 µL) to reduce any peptide disulfides. Chromatograms were integrated at $\lambda = 280$ nm (corresponding to the $\lambda_{\text{max}}$ of the phenolic tyrosine side-chain). At this wavelength, bicyclobutane arylsulfones C exhibited minimal absorbance (<10%) relative to the peptide starting material. The peak area of the bicyclobutane labeled product relative to the unfunctionalized peptide starting material was used to approximate relative percent conversion at each time point.
Fig. S65. Kinetic plot depicting the relative rate of reaction between peptide 86 and sulfone reagents C1, C3, and C5-7.
Fig. S66. Crude analytical HPLC traces (0 to 100% B over 25 min, λ = 280 nm) depicting the reaction of peptide 86 with sulfone reagents C1, C3, and C5-C7 at various time points.
Peptide S27:

Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm, R_t = 13.5 min) of peptide S27.
Peptide S27: HRMS

HRMS (ESI-TOF): calc’d for C_{61}H_{78}F_{3}N_{14}O_{15}S_{2} [M+H]^+ 1367.5159, found 1367.5156 [M+H]^+, 684.2626 [M+2H]^{2+}
Peptide S28:

Analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm, $R_t = 12.1$ min) of peptide S28.
Peptide S28: HRMS

HRMS (ESI-TOF): calc’d for C$_{60}$H$_{78}$FN$_{14}$O$_{15}$S$_2$ [M+H]$^+$ 1317.5191, found 1317.5174 [M+H]$^+$, 659.2639 [M+2H]$^{2+}$
Peptide S29:

![Chemical structure of S29]

Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm, R_t = 12.1 min) of peptide S29.
Peptide S29: HRMS

HRMS (ESI-TOF): calc'd for $\text{C}_{61}\text{H}_{81}\text{N}_{14}\text{O}_{16}\text{S}_{2}$ $[\text{M+H}]^+$ 1329.5391, found 1329.5389 $[\text{M+H}]^+$, 665.2744 $[\text{M+2H}]^{2+}$
Compound S30:

To a solution of glutathione (10.0 mg, 32.5 µmol) in degassed 0.2 M K$_2$CO$_3$ (162 µL, 1.0 equiv. K$_2$CO$_3$) was added a 0.2 M solution of sulfone C7 in DMF (162 µL, 1.0 equiv.) to give a final concentration of 0.1 M with respect to glutathione. The reaction vial was flushed with Ar(g) and stirred at rt. The reaction was monitored by analytical HPLC, and then quenched at $t = 5$ h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 30 min) and lyophilized to afford S30 as a white solid (1 x TFA salt, 18.5 mg, 89% yield).
**Fig. S67.** Crude analytical HPLC trace (0 to 100% B over 25 min, \( \lambda = 230 \text{ nm} \)) of the reaction of glutathione with sulfone C7 at A) \( t = 2 \text{ h} \) and B) \( t = 4 \text{ h} \); C) purified product S30.
S30 (TFA salt):

![Chemical Structure]

3.7:1 dr;

**Physical state:** fluffy white solid (following lyophilization);

**$^1$H NMR** (600 MHz, D$_2$O) *major diastereomer:* $\delta$ 7.58 – 7.54 (m, 2H), 7.37 (tt, $^3J_{H-F} = 8.8$, $^4J_{H-H} = 2.3$ Hz, 1H), 4.58 – 4.47 (m, 1H), 4.26 (m, 1H), 4.07 (t, $J = 6.6$ Hz, 1H), 4.00 (d, $J = 1.9$ Hz, 2H), 3.73 – 3.63 (m, 1H), 3.01 (dd, $J = 14.1$, 5.3 Hz, 1H), 2.93 – 2.81 (m, 3H), 2.58 (m, $J = 8.2$ Hz, 2H), 2.32 (m, 2H), 2.23 (m, 2H) ppm;

*minor diastereomer:* $\delta$ 7.55 – 7.51 (m, 2H), 7.37 (tt, $^3J_{H-F} = 8.8$, $^4J_{H-H} = 2.3$ Hz, 1H), 4.58 – 4.47 (m, 1H), 4.15 – 4.08 (m, 2H), 4.00 (d, $J = 1.9$ Hz, 2H), 3.58 – 3.49 (m, 1H), 3.06 (dd, $J = 14.1$, 5.3 Hz, 1H), 2.92 – 2.80 (m, 1H), 2.71 – 2.63 (m, 2H), 2.62 – 2.52 (m, 2H), 2.44 – 2.36 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

**$^{13}$C NMR** (151 MHz, D$_2$O) *major diastereomer:* $\delta$ 173.7, 172.3, 172.0, 171.1, 162.4 (dd, $^1J_{C-F} = 253.7$ Hz, $^3J_{C-C} = 12.0$ Hz, 2C), 162.4 (q, $^2J_{C-C} = 35.4$ Hz), 138.2 (t, $^3J_{C-C} = 8.3$ Hz), 115.8 (q, $^1J_{C-C} = 291.4$ Hz), 111.4 (dd, $^2J_{C-C} = 22.0$ Hz, $^4J_{C-C} = 7.4$ Hz, 2C), 109.9 (t, $J = 25.6$ Hz), 53.8, 52.6, 51.8, 40.6, 34.2, 31.8, 30.4, 29.3, 29.3, 24.9 ppm;

**HRMS** (ESI-TOF): calc’d for C$_{20}$H$_{26}$F$_2$N$_3$O$_6$S$_2$ [M+H]$^+$ 538.1124, found 538.1120.
Compound **S31**: 

![Chemical structures](image)

To a solution of glutathione (10.1 mg, 32.9 µmol) in degassed 0.2 M K$_2$CO$_3$ (162 µL, 1.0 equiv. K$_2$CO$_3$) was added a 0.2 M solution of sulfone C1 in DMF (162 µL, 1.0 equiv.) to give a final concentration of 0.1 M with respect to glutathione. The reaction vial was flushed with Ar(g) and stirred at rt. The reaction was monitored by analytical HPLC, and then quenched at t = 24 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 40 min) and lyophilized to afford **S31** as a white solid (1 x TFA salt, 16.2 mg, 81% yield).
**Fig. S68.** Crude analytical HPLC trace (0 to 100% B over 25 min, $\lambda = 230$ nm) of the reaction of glutathione with sulfone C1 at A) $t = 6$ h and B) $t = 24$ h; C) purified peptide product S31.
S31 (TFA salt):

4.8:1 dr;

Physical state: fluffy white solid (following lyophilization);

$^1$H NMR (600 MHz, D$_2$O) major diastereomer: $\delta$ 7.93 (dd, $J = 8.5, 1.3$ Hz, 2H), 7.87 – 7.77 (m, 1H), 7.75 – 7.65 (m, 2H), 4.63 – 4.45 (m, 1H), 4.35 – 4.15 (m, 1H), 4.16 – 4.02 (m, 1H), 4.02 (s, 2H), 3.74 – 3.59 (m, 1H), 3.02 (dd, $J = 14.2, 5.4$ Hz, 1H), 2.93 – 2.80 (m, 3H), 2.66 – 2.53 (m, 2H), 2.35 – 2.27 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

minor diastereomer: $\delta$ 7.90 (dd, $J = 8.4, 1.3$ Hz, 2H), 7.87 – 7.77 (m, 1H), 7.75 – 7.65 (m, 2H), 4.63 – 4.45 (m, 1H), 4.16 – 4.02 (m, 2H), 4.02 (s, 2H), 3.59 – 3.44 (m, 1H), 3.09 – 3.03 (m, 1H), 2.93 – 2.86 (m, 1H), 2.70 – 2.62 (m, 2H), 2.62 – 2.52 (m, 2H), 2.43 – 2.36 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

$^{13}$C NMR (151 MHz, D$_2$O) major diastereomer: $\delta$ 174.2, 172.8, 172.5, 171.7, 162.9 (q, $J = 35.5$ Hz), 135.3, 134.9, 129.7 (2C), 128.0 (2C), 116.3 (q, $J = 291.5$ Hz), 54.3, 53.1, 52.3, 41.0, 34.6, 32.2, 30.9, 29.8, 29.8, 25.4 ppm;

HRMS (ESI-TOF): calc’d for C$_{20}$H$_{28}$N$_3$O$_8$S$_2$ [M+H]$^+$ 502.1312, found 502.1301.
Compound S33:

Amino acid S32 (30 mg, 0.17 mmol) was dissolved in degassed 0.2 M K₂CO₃ (0.87 mL, 1.0 equiv. K₂CO₃). A solution of C1 (34 mg, 0.17 mmol) in DMF (0.87 mL) was prepared and added to the reaction mixture to give a final concentration of 0.1 M with respect to S32. The reaction vial was flushed with Ar(g) and stirred at rt for 8 h. The DMF was removed under a stream of N₂ and the resultant solution diluted in water containing 0.1% TFA and purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 30 min) and lyophilized to afford S33 as a clear oil (TFA salt, 68 mg, 88% yield).

S33 (TFA salt):

5.3:1 dr;

Physical state: clear oil;

¹H NMR (500 MHz, CD₃OD) major diastereomer: δ 7.94 – 7.89 (m, 2H), 7.73 (td, J = 7.3, 1.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 4.28 (dd, J = 6.4, 5.0 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.86 (s, 3H), 3.76 – 3.64 (m, 1H), 3.11 – 3.04 (m, 2H), 2.93 – 2.81 (m, 2H), 2.34 – 2.22 (m, 2H) ppm;
minor diastereomer: δ 7.89 – 7.86 (m, 2H), 7.73 (td, J = 7.3, 1.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 4.34 – 4.23 (m, 1H), 3.96 – 3.88 (m, 1H), 3.84 (s, 3H), 3.56 – 3.43 (m, 1H), 3.17 (dd, J = 14.7, 4.8 Hz, 1H), 3.13 – 3.04 (m, 1H), 2.60 – 2.51 (m, 2H), 2.48 – 2.38 (m, 2H) ppm;

13C NMR (151 MHz, CD3OD) major diastereomer: δ 169.5, 162.0 (q, 2J_{C-F} = 36.9 Hz), 138.9, 135.2, 130.6 (2C), 129.3 (2C), 117.6 (q, 1J_{C-F} = 291 Hz), 55.5, 53.9, 53.4, 36.4, 32.1, 31.5, 31.2 ppm;

minor diastereomer: δ 169.4, 162.0 (q, 2J_{C-F} = 36.9 Hz), 139.1, 135.2, 130.6 (2C), 129.2 (2C), 117.6 (q, 1J_{C-F} = 291 Hz), 53.9, 53.7, 53.5, 34.6, 32.7, 32.2, 32.0 ppm;

HRMS (ESI-TOF): calc’d for C_{14}H_{20}NO_{4}S_{2} [M+H]^+ 330.0828, found 330.0822.
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2 TFA

\[
\begin{align*}
\text{HN} & \quad \text{N'} \\
\text{Bn} & \quad \text{Bn} \\
42a & \\
\end{align*}
\]
• 2 TFA

\[
\begin{align*}
HN & \quad N' \\
\text{Bn} & \quad \text{Bn}
\end{align*}
\]

![NMR Spectrogram]
S305
[inseparable mixture of cis/trans isomers]
[inseparable mixture of cis/trans isomers]
[inseparable mixture of cis/trans isomers]
Bn₂N

78

[+ minor amt. of trans isomer]
[+ minor amt. of trans isomer]
[+ minor amt. of other inseparable diastereomer]
[+ minor amt. of other inseparable diastereomer]
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S391