Chiral Aniline Synthesis via Stereospecific C(sp³)–C(sp³) Coupling of Boronic Esters with Aryl Hydrazines

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1. General Information

Solvents and Reagents:

All air and water-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere using the standard Schlenk manifold technique. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Bristol. Petroleum ether (pet. ether) refers to the fraction collected between 40 – 60 °C. n-BuLi was purchased from Acros and the molarity was determined by titration using N-benzyl benzamide as an indicator. All other reagents were purchased from commercial sources and used as sold unless noted.

Chromatography and Spectroscopy:

Flash column chromatography (FCC) was carried out using fluorochem silica gel LC60A-40 (63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica which was visualized under UV light or by staining with aqueous basic potassium permanganate or phosphomolybdic acid.

1H and 13C NMR spectra were recorded using Jeol ECP(Eclipse) 300 MHz, Jeol ECS 400 MHz and Varian VNMR 500 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The 1H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sx = sextet, sp = septet, m = multiplet, dd = doublet of doublets, etc.

High-resolution mass spectra (HRMS) were recorded on a VG Analytical Autospec by Electron Ionisation (EI) or on a Brüker Daltonics Apex IV by Electrospray Ionisation (ESI) or on Brüker Daltonics UltrafleXtreme (MALDI). The hydrazine starting materials show the M+ peak in some cases with ESI and MALDI techniques. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Only selected absorption maxima (νmax) are reported in wavenumbers (cm⁻¹). Melting points were recorded in degrees Celsius (°C), using a Kofler hot-stage microscope apparatus and are reported uncorrected. Optical rotation ([α]D) was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter and is quoted in (° ml)(g
Chiral HPLC was performed on an HP Agilent 1100 with Chiralpak columns and monitored by DAD (Diode Array Detector). Chiral SFC was performed on a Waters TharSFC system using a Diacel Chiralpak columns (4.6 m × 250 mm × 5 μm) and monitored by DAD (Diode Array Detector). GC-MS was performed on an Agilent 7820A using an HP-5MS UI column (30 m x 0.25 mm x 0.25 μm).

The naming of compounds:
Compound names are those generated by ChemDraw Pro 16.0 software (PerkinElmer), following the IUPAC nomenclature.

Boronic ester substrates:
All boronic ester substrates are either commercially available or were synthesized according to literature procedures.1-10
2. Optimization Studies

Evaluation of activators for the reaction of para-lithiated phenyl hydrazines:

\[
\text{entry} \quad \text{activator} \quad \text{\textsuperscript{1}H NMR yield} \quad \text{comment}
\]
\[
\begin{array}{cccc}
1^a & \text{Me:Troc-Cl} & 54\% & - \\
2^a & \text{Boc:O} & <5\% & \text{borinic ester (\textsuperscript{11}B NMR)} \\
3^a & \text{Nosyl chloride} & 23\% & - \\
4 & \text{Me:Troc-Cl} & 60\%* & - \\
5 & \text{Troc-Cl} & 52\% & - \\
6 & \text{acetyl chloride} & 13\% & - \\
7 & \text{pivaloyl chloride} & 42\% & - \\
8 & \text{triflic anhydride} & 52\% & - \\
9 & \text{p-toluenesulfonic isocyanate} & \text{polymerization of THF} & - \\
10 & \text{trichloromethyl chloroformate} & <5\% & - \\
11 & \text{trichloroacetyl chloride} & 13\% & - \\
12 & \text{TFAA} & 82\%* & - \\
\end{array}
\]

\(^a\) With 1.5 equiv of activator. * Isolated Yield.

Evaluation of activators for the reaction of ortho-lithiated phenyl hydrazines:

\[
\text{entry} \quad \text{activator} \quad \text{\textsuperscript{1}H NMR yield} \quad \text{comment}
\]
\[
\begin{array}{cccc}
1 & \text{TFAA} & <5\% & \text{Very messy crude \textsuperscript{1}H NMR} \\
2 & \text{Me:Troc-Cl} & 75\%* & - \\
\end{array}
\]

* Isolated Yield.
3. Substrate Synthesis

3.1. Bromophenyl Hydrazines

I. General Procedure for the Synthesis of ortho- and para-bromophenyl hydrazines

\[
\begin{array}{c}
\text{NH}_2 \\
\text{Br} \\
\text{R} \\
\end{array}
\xrightarrow{1. \text{NaNO}_2/\text{HCl, 0 } ^\circ\text{C, 30 min}}
\begin{array}{c}
\text{NH}_2 \\
\text{Br} \\
\text{R} \\
\end{array}
\xrightarrow{2. \text{SnCl}_2\cdot2\text{H}_2\text{O, 0 } ^\circ\text{C to rt, 5 h}}
\begin{array}{c}
\text{NH}_2 \\
\text{Br} \\
\text{R} \\
\end{array}
\]

To a stirred solution of o-/p-bromoaniline (1.74 mmol) in concentrated aq. HCl (3.4 ml) and H₂O (1.2 ml) at 0 °C a solution of sodium nitrite (120 mg, 1.74 mmol) in H₂O (1.2 ml) was added over a period of 30 minutes. The reaction mixture was stirred for a further 30 minutes then added dropwise to a solution of tin chloride hydrate (1.97 g, 8.71 mmol) in concentrated aq. HCl (3 ml) at 0 °C. After the addition is complete, the reaction was stirred at room temperature for 5 hours. Then the reaction was basified with 40% aqueous NaOH at 0 °C until the pH was 13. The mixture was then extracted with DCM (25 mL x 3) and water (30 mL). The organic phase was separated and dried over Na₂SO₄ and concentrated in vacuo. The crude product was further purified by column chromatography with silica gel using pentane/EtOAc as eluents.

(2-Bromo-4-methoxyphenyl)hydrazine:

The starting o-bromoaniline (2.01 g; 10 mmol) was reacted according to the above general procedure I to afford the title compound (1.56 g; 72%) as gummy liquid. Rf (30% EtOAc/pet. ether): 0.3; IR (film) νmax/cm⁻¹: 3367, 3318, 3217, 1609, 1495, 1290, 1028, 827, 779; ¹H NMR (500 MHz, Chloroform-d) 7.05 (m, 2H), 6.87 (dd, J = 8.8, 2.9 Hz, 1H), 3.75 (s, 3H); ¹³C NMR (126 MHz, Chloroform-d) 153.0, 142.0, 118.0, 114.4, 113.6, 108.4, 55.9; HRMS (ESI⁺) mass calculated for [M+H]⁺ C₈H₉BrN₂O requires m/z 216.9971, found m/z 216.9961.

(2-Bromo-5-fluorophenyl)hydrazine:

The starting o-bromoaniline (2.1 g; 10.3 mmol) was reacted according to the above general procedure I to afford the title compound (1.69 g; 78%) as gummy liquid. Rf (30% EtOAc/pet. ether): 0.4; ¹H NMR (400 MHz, Chloroform-d) 7.22
(dd, J = 8.6, 5.8 Hz, 1H), 6.77 (dd, J = 11.2, 2.9 Hz, 1H), 6.28 (td, J = 8.3, 2.9 Hz, 1H), 5.67 (s, 1H),
3.49 (s, 2H); $^{13}$C NMR (101 MHz, Chloroform-d) 163.4 (d, J = 243.7 Hz), 148.9 (d, J = 10.7 Hz),
132.9 (d, J = 9.7 Hz), 105.9 (d, J = 23.3 Hz), 101.3 (d, J = 2.8 Hz), 99.8 (d, J = 28.5 Hz); $^{19}$F NMR
(377 MHz, Chloroform-d) -112.7 (ddd, J = 11.2, 8.0, 5.8 Hz). The characterization data matched
with that of commercially available material (Fluorochem).

(5-Bromo-2-iodophenyl)hydrazine:

The starting o-idoaniline (2.0 g; 6.73 mmol) was reacted according to the above
general procedure 1 to afford the title compound (1.02 g; 49%) as gummy liquid.
IR (film) $\nu_{\text{max}}$/cm$^{-1}$: 3368, 3218, 1609, 1495, 1290, 1028, 780; R$_f$ (30% EtOAc/pet.
ether): 0.4; $^1$H NMR (500 MHz, Chloroform-d) 7.72 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.7, 2.2 Hz,
1H), 6.91 (d, J = 8.7 Hz, 1H), 5.52 (s, 1H), 3.61 (s, 2H); $^{13}$C NMR (126 MHz, Chloroform-d) 148.7,
140.1, 132.0, 113.0, 110.6, 82.0; HRMS (ESI$^+$) mass calculated for [M+H]+$^+$ C$_6$H$_7$BrIN$_2$ requires
m/z 312.8832, found m/z 312.8838.
2.2. Permethylated Bromophenyl Hydrazines

II. General Procedures for the Synthesis of Permethylated Hydrazines

IIA. General procedure for Route 1:

To a stirred solution of o-/p-bromohydrazine or its hydrochloride salt (2 mmol, 1 equiv.) in THF (10 mL) and H$_2$O (10 mL) at 0 °C was added a 30% w/v aqueous solution of sulfuric acid (0.6 mmol, 0.3 equiv.). To this stirred solution, a 37% aqueous solution of formaldehyde (16.0 mmol, 8 equiv.) was added followed by a portion-wise addition of NaBH$_4$ (8.0 mmol, 4 equiv.). After the addition was complete, the reaction was stirred at room temperature for 5 hours. Then the reaction mixture was basified with 40% aqueous NaOH at 0 °C until the pH was 13. The mixture was then extracted with DCM (25 mL x 3) and water (30 mL). The organic phase was separated and dried over Na$_2$SO$_4$ and concentrated in vacuo. The success of the permethylation was judged by crude $^1$H NMR. The crude product was then purified by column chromatography with silica gel using pentane/EtOAc as eluents.

IIB. General procedure for Route 2:

To a stirred solution of o-/p-bromohydrazine or its hydrochloride salt (2 mmol, 1 equiv.) in THF (10 mL) and H$_2$O (10 mL) at 0 °C was added a 30% w/v aqueous solution of sulfuric acid (0.6 mmol, 0.3 equiv.). To this stirred solution, a 37% aqueous solution of formaldehyde (16.0 mmol, 8 equiv.) was added followed by a portion-wise addition of NaBH$_4$ (8.0 mmol, 4 equiv.). After the addition was complete, the reaction was stirred at room temperature for 5 hours. Then the reaction mixture was basified with 40% aqueous NaOH at 0 °C until the pH was 13. The mixture was then extracted with DCM (25 mL x 3) and water (30 mL). The organic phase
was separated and dried over Na$_2$SO$_4$ and concentrated in vacuo. The success of the permethylation was judged by crude $^1$H NMR. If the permethylation was not complete, the dimethylation product was purified by column chromatography with silica gel using pentane/EtOAc as eluents. **Methylation of Dimethylated Hydrazine:** To a stirred solution of dimethyl-o-/p-bromohydrazine (1 mmol, 1 equiv.) in DMF (10 mL) at 0 °C was added 40% sodium hydride in mineral oil (1.5 mmol, 1.5 equiv.). The reaction mixture was allowed to stir for 20 min and then methyl iodide (1.05 mmol, 1.05 equiv.) was added dropwise at 0 °C. After the addition is complete, the reaction was warmed to room temperature and stirred for 1 hour after which excess NaH was quenched by the addition of water at 0 °C. The mixture was then extracted with DCM (25 mL x 2) and water (30 mL). The organic phase was separated and dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was then purified by column chromatography with silica gel using pentane/EtOAc as eluents.

1-(4-Bromophenyl)-1,2,2-trimethylhydrazine (4a)

The starting p-bromophenyl hydrazine hydrochloride (2.5 g; 11 mmol) was reacted according to the above general procedure IIA to afford the title compound (1.6 g; 52%) as pale yellow oil. R$_f$ (5% EtOAc/pet. ether): 0.6; IR (film) $\nu_{max}/$cm$^{-1}$: 2943, 2845, 2769, 1585, 1474, 1152, 1025, 753, 549; $^1$H NMR (400 MHz, Chloroform-d) 7.21 (d, $J$ = 9.1 Hz, 2H), 6.81 (d, $J$ = 9.1 Hz, 2H), 2.67 (s, 3H), 2.37 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 149.3, 131.5, 114.5, 109.4, 41.0, 26.6; HRMS (ESI$^+$) mass calculated for [M+H]$^+$ C$_9$H$_{14}$BrN$_2$ requires m/z 229.0335, found m/z 229.0333.

1-(4-Bromonaphthalen-1-yl)-1,2,2-trimethylhydrazine (4b)

The starting 4-bromonaphthyl hydrazine (0.85 g; 3.6 mmol) was reacted according to the above general procedure IIA to afford the title compound (0.81 g; 81%) as pale yellow oil; IR (film) $\nu_{max}/$cm$^{-1}$: 2942, 2846, 1453, 1376, 952, 753, 516; $^1$H NMR (400 MHz, Chloroform-d) 8.29 – 8.17 (m, 1H), 8.12 – 8.03 (m, 1H), 7.54 (d, $J$ = 8.1 Hz, 1H), 7.49 – 7.37 (m, 2H), 6.71 (d, $J$ = 8.0 Hz, 1H), 2.74 (s, 3H), 2.43 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 147.0, 132.9, 130.9, 128.8, 127.1, 127.0, 126.0, 125.4, 117.3, 114.6, 40.1, 27.3; HRMS (ESI$^+$) mass calculated for [M+H]$^+$ C$_{13}$H$_{16}$BrN$_2$ requires m/z 279.0491, found m/z 279.0492.
5-Bromo-1,2-dimethyl-2,3-dihydro-1H-indazole (4c)

Following a modified literature procedure for the methylation of indazole, bromoindazole was methylated.11 To a stirred solution of bromoindazole (1.2 g, 6.12 mmol, 1 equiv.) in MeOH (20 mL) in sealed tube, MeI (2 mL) and solid NaOH (245 mg, 6.12 mmol, 1 equiv.) were added. The reaction was stirred at 100 °C overnight resulting in a white precipitate. Copious amounts of ether were added, and the precipitate was collected after filtration. The iodide salt was suspended in a dilute aqueous solution of HClO₄ and stirred overnight at room temperature to yield perchlorate salt as a precipitate. The perchlorate salt was collected by filtration to give 1,2-dimethyl-1H-indazol-2-ium perchlorate (1.38 g, 92%) as white solid; ¹H NMR (500 MHz, CD₃OD) 8.32 – 7.81 (m, 4H), 4.43 (s, 3H), 4.29 (s, 3H); ¹³C NMR (126 MHz, CD₃OD) 139.4, 136.3, 131.9, 124.6, 120.6, 118.0, 112.5, 37.1, 32.4. The salt was taken forward to the reduction step with NaBH₄ following the literature procedure.11 The starting indazolium salt (300 mg; 0.93 mmol) was stirred in MeOH (6 mL) at 0 °C, then NaBH₄ (53 mg, 1.4 mmol, 1.5 equiv.) was added portion-wise. The reaction mixture was slowly warmed to rt and stirred for 1 h before being quenched by the addition of water (20 mL). The mixture was extracted into EtOAc (3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was then purified by column chromatography with silica gel (5% EtOAc/pet. ether) to afford the title compound (126 mg; 60%) as pale yellow oil; Rᵣ (5% EtOAc/pet. ether): 0.4; IR (film) ν₁max/cm⁻¹: 2993, 2854, 1345, 1150, 764; ¹H NMR (500 MHz, Chloroform-d) 7.26 – 7.14 (m, 2H), 6.47 (dd, J = 8.3, 1.3 Hz, 1H), 4.10 (s, 2H), 2.82 (s, 3H), 2.65 (s, 3H); ¹³C NMR (126 MHz, Chloroform-d) 150.7, 130.6, 130.1, 125.5, 112.8, 111.7, 59.4, 44.3, 40.8; Not observed by ESI or MALDI.

5-Bromo-N,N-dimethylindolin-1-amine (4d)

Following the literature procedure, 5-bromoindoline (620 mg) was converted to 5-bromoindolin-1-amine.12 To a stirred solution of 5-bromoindoline (620 mg, 3.15 mmol, 1
equiv.) in EtOH (3 mL) at 0 °C Conc. HCl (0.33 mL) was added. A freshly prepared solution of aqueous sodium nitrite solution (0.26 g, 3.78 mmol, 1.2 equiv.) in 2mL of water was added dropwise. After the addition is complete, the reaction mixture was allowed to stir for 1 h at 0 °C. After checking complete consumption of substrate material by TLC analysis, a solution of NaOH (2 g, 50 mmol) in H₂O (4 mL) and Na₂S₂O₄ (75%, 1.64 g, 9.45 mmol, 3 equiv.) was added at 0 °C. The suspension was refluxed at 80 °C for 2 h, and then the reaction mixture was cooled to room temperature. After addition of H₂O (25 mL) to the reaction mixture followed by extraction with DCM (25 mL x 2), the organic layer was dried over anhydrous Na₂SO₄ and concentrated to give crude material. The crude product of 5-bromoindolin-1-amine thus obtained was methylated without purification according to the literature procedure to afford the title compound (92 mg; 8%) as pale yellow liquid; Rf (5% EtOAc/pet. ether): 0.6; IR (film) νmax/cm⁻¹: 2984, 2944, 2846, 1474, 1152, 1025, 753, 649; ¹H NMR (400 MHz, Chloroform-d) 7.12 (dd, J = 8.3, 2.0 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.60 (d, J = 8.1 Hz, 1H), 3.30 (t, J = 8.1 Hz, 2H), 2.83 (t, J = 8.1 Hz, 2H), 2.44 (s, 6H); ¹³C NMR (101 MHz, Chloroform-d) 149.8, 130.1, 129.7, 127.4, 111.4, 110.7, 42.4, 40.9, 27.1; HRMS (ESI⁺) mass calculated for [M+H]⁺ C₁₀H₁₄BrN₂ requires m/z 241.0335, found m/z 241.0334.

2-(2-Bromophenyl)-1,1-dimethylhydrazine (8a’)

The o-bromophenyl hydrazine (2.88 g; 15.4 mmol) was reacted according to the above general procedure IIB to afford the title compound (1.53 g; 49%) as an oil along with 1-(2-bromophenyl)-1,2,2-trimethylhydrazine (673 mg; 22%); Rf (5% EtOAc/pet. ether): 0.7; IR (film) νmax/cm⁻¹: 3259, 2950, 2773, 1594, 1491, 1458, 1017, 745; ¹H NMR (400 MHz, Chloroform-d) 7.41 (dd, J = 7.9, 1.3 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.67 (dd, J = 7.9, 6.8, 2.1 Hz, 1H), 4.88 (s, 1H), 2.60 (s, 6H); ¹³C NMR (126 MHz, Chloroform-d) 144.4, 132.2, 128.4, 119.6, 114.9, 107.8, 47.8; MS (EI⁺) mass calculated for [M⁺]⁺ C₁₀H₁₄BrN₂ requires m/z 214.0, found m/z 214.0.

1-(2-Bromophenyl)-1,2,2-trimethylhydrazine (8a)

2-(2-Bromophenyl)-1,1-dimethyl hydrazine (1.53 g; 7.15 mmol) was further methylated according to the above general procedure IIB to afford the title compound (1.48 g; 93%) as pale yellow liquid; Rf (5% EtOAc/pet. ether): 0.6; IR
(film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2945, 2845, 1590, 753; $^1$H NMR (400 MHz, Chloroform-d) 7.61 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.24 (td, $J = 7.9, 1.5$ Hz, 1H), 7.04 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.90 (td, $J = 7.7, 1.5$ Hz, 1H), 2.78 (s, 3H), 2.52 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 149.0, 134.3, 127.1, 124.0, 120.4, 120.2, 40.3, 27.1; HRMS (ESI$^+$) mass calculated for $[\text{M+H}]^+$ $\text{C}_9\text{H}_14\text{BrN}_2$ requires $m/z$ 229.0335, found $m/z$ 229.0334.

2-(2-Bromo-5-(trifluoromethyl)phenyl)-1,1-dimethylhydrazine (8b$'$)

The starting hydrazine (1 g; 3.44 mmol) was reacted according to the above general procedure IIB to afford the title compound (850 mg; 88%) as an oil; $R_f$ (5% EtOAc/pet. ether): 0.4; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3293, 2947, 1333, 1121, 1081, 884, 538; $^1$H NMR (400 MHz, Chloroform-d) 7.40 (d, $J = 2.2$ Hz, 1H), 7.39 – 7.35 (m, 1H), 6.78 – 6.73 (m, 1H), 4.94 (s, 1H), 2.48 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 144.8, 132.6, 131.0 (q, $J = 32.3$ Hz), 124.1 (q, $J = 272.4$ Hz), 115.5 (q, $J = 3.9$ Hz), 111.1 (q, $J = 4.0$ Hz), 110.5 (d, $J = 1.5$ Hz), 47.7; $^{19}$F NMR (377 MHz, Chloroform-d) -62.8. Not observed with ESI$^+$ or MALDI.

1-(2-Bromo-5-(trifluoromethyl)phenyl)-1,2,2-trimethylhydrazine (8b)

The starting hydrazine (850 mg; 3.0 mmol) was reacted according to the above general procedure IIB to afford the title compound (696 mg; 78%) as an oil; $R_f$ (5% EtOAc/pet. ether): 0.6; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2947, 2775, 1333, 1119, 1081, 884, 537; $^1$H NMR (400 MHz, Chloroform-d) 7.73 – 7.55 (m, 1H), 7.19 (d, $J = 1.6$ Hz, 1H), 7.14 – 7.04 (m, 1H), 2.80 (s, 3H), 2.50 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 149.7, 134.9, 129.6 (q, $J = 32.5$ Hz), 125.4 (q, $J = 272.1$ Hz), 123.2 (q, $J = 1.3$ Hz), 120.0 (q, $J = 3.7$ Hz), 116.2 (q, $J = 3.5$ Hz), 40.5, 27.1; $^{19}$F NMR (377 MHz, Chloroform-d) -62.6; HRMS (ESI$^+$) mass calculated for $[\text{M}]^+$ $\text{C}_{10}\text{H}_{12}\text{BrF}_3\text{N}_2$ requires $m/z$ 296.0130, found $m/z$ 296.0138.

1-(2-Bromo-4-methoxyphenyl)-1,2,2-trimethylhydrazine (8c)

(2-bromo-4-methoxyphenyl)hydrazine (1.56 g; 7.2 mmol) was reacted according to the above general procedure IIA to afford the title compound (1.49 g; 80%) as pale yellow oil; $R_f$ (10% EtOAc/pet. ether): 0.6; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2944, 1490, 1286, 1038, 807; $^1$H NMR (400 MHz, Chloroform-d) 7.11 (d, $J = 2.8$ Hz, 1H), 6.89 (d, $J = 8.8$ Hz, 1H), 6.69 (dd, $J = 8.7, 2.8$ Hz, 1H), 3.68 (s, 3H), 2.62 (s, 3H), 2.39 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-d) 149.7, 134.9, 129.6 (q, $J = 32.5$ Hz), 125.4 (q, $J = 272.1$ Hz), 123.2 (q, $J = 1.3$ Hz), 120.0 (q, $J = 3.7$ Hz), 116.2 (q, $J = 3.5$ Hz), 40.5, 27.1; $^{19}$F NMR (377 MHz, Chloroform-d) -62.6; HRMS (ESI$^+$) mass calculated for $[\text{M}]^+$ $\text{C}_{10}\text{H}_{12}\text{BrF}_3\text{N}_2$ requires $m/z$ 296.0130, found $m/z$ 296.0138.
Chloroform-d) 156.0, 142.2, 121.9, 120.9, 119.7, 112.3, 55.6, 40.0, 27.6; HRMS (ESI+) mass calculated for [M+Na]+ C_{10}H_{15}BrN_{2}NaO requires m/z 281.0260, found m/z 281.0265.

2-(2-Bromo-5-fluorophenyl)-1,1-dimethylhydrazine (8d')

(2-Bromo-5-fluorophenyl)hydrazine (1.0 g; 4.9 mmol) was reacted according to the above general procedure IIb to afford the title compound (1.09 mg; 94%) as an oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) ν_{max}/cm^{-1}: 2953, 2818, 2776, 1608, 1435, 1141, 855, 784, 585; ^{1}H NMR (400 MHz, Chloroform-d) 7.21 (dd, J = 8.7, 5.8 Hz, 1H), 6.89 (dd, J = 11.4, 3.0 Hz, 1H), 6.27 (ddd, J = 8.6, 8.0, 3.0 Hz, 1H), 4.84 (s, 1H), 2.47 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-d) 163.48 (d, J = 243.1 Hz), 145.94 (d, J = 11.2 Hz), 132.89 (d, J = 9.6 Hz), 106.15 (d, J = 23.6 Hz), 101.76 (d, J = 28.6 Hz), 101.35 (d, J = 2.8 Hz), 47.69; ^{19}F NMR (377 MHz, Chloroform-d) -113.3 (dddd, J = 11.3, 7.7, 5.8, 1.8 Hz); HRMS (ESI+) mass calculated for [M+H]+ C_{8}H_{10}BrFNa requires m/z 233.0084, found m/z 233.0093.

1-(2-Bromo-5-fluorophenyl)-1,2,2-trimethylhydrazine (8d)

The starting hydrazine (0.99 g; 4.26 mmol) was reacted according to the above general procedure IIb to afford the title compound (0.87 g; 83%) as an oil; Rf (5% EtOAc/pet. ether): 0.6; IR (film) ν_{max}/cm^{-1}: 2946, 2818, 1603, 1488, 1148, 823, 697, 487; ^{1}H NMR (400 MHz, Chloroform-d) 7.51 (dd, J = 8.7, 6.2 Hz, 1H), 6.76 (dd, J = 10.8, 2.9 Hz, 1H), 6.62 (ddd, J = 8.8, 7.5, 2.9 Hz, 1H), 2.76 (s, 3H), 2.51 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-d) 162.0 (d, J = 245.5 Hz), 150.7 (d, J = 8.3 Hz), 134.8 (d, J = 9.3 Hz), 113.3 (d, J = 3.7 Hz), 110.1 (d, J = 22.4 Hz), 107.6 (d, J = 24.5 Hz), 40.6, 27.3; ^{19}F NMR (377 MHz, Chloroform-d) -114.6 (q, J = 6.9 Hz); HRMS (ESI+) mass calculated for [M]+ C_{9}H_{12}BrFN_{2} requires m/z 246.0162, found m/z 246.0168.

2-(2-Bromo-5-chlorophenyl)-1,1-dimethylhydrazine (8e')

The starting hydrazine (1 g; 4.5 mmol) was reacted according to the above general procedure IIb to afford the title compound (900 mg; 81%) as an oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) ν_{max}/cm^{-1}: 3271, 2951, 2775, 1589, 1081, 874; ^{1}H NMR (500 MHz, Chloroform-d) 7.29 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 2.5 Hz, 1H), 6.62 (dd, J = 8.4, 2.5 Hz, 1H), 2.58 (s, 6H); ^{13}C NMR (126 MHz, Chloroform-d) 145.3, 134.6, 132.9, 119.2,
114.4, 105.1, 47.7; HRMS (ESI+) mass calculated for [M+H]+ C₈H₁₁BrClN₂ requires m/z 248.9789, found m/z 248.9799.

1-(2-Bromo-5-chlorophenyl)-1,2,2-trimethylhydrazine (8e)

The starting hydrazine (900 mg; 4.5 mmol) was reacted according to the above general procedure IIB to afford the title compound (913 mg; 96%) as an oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2945, 2847, 1576, 1462, 1025, 875, 560; ¹H NMR (400 MHz, Chloroform-d) 7.46 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H), 2.74 (s, 3H), 2.48 (s, 6H); ¹³C NMR (101 MHz, Chloroform-d) 150.2, 135.0, 132.9, 123.4, 120.2, 117.4, 40.5, 27.2; HRMS (ESI+) mass calculated for [M]+ C₉H₁₂BrClN₂ requires m/z 261.9867, found m/z 261.9877.

1-(5-Bromo-2-iodophenyl)-1,2,2-trimethylhydrazine (8f)

The starting hydrazine (1.0 g; 3.2 mmol) was reacted according to the above general procedure IIB. The crude product 2-(2-iodo-4-bromophenyl)-1,1-dimethylhydrazine (920 mg; 2.7 mmol) thus obtained after the first step was methylated without purification according to the above general procedure IIB to afford the title compound (900 mg; 79% over two steps) as pale yellow liquid; Rf (5% EtOAc/pet. ether): 0.6; IR (film) νmax/cm⁻¹: 2926, 2852, 1714, 1360, 1153, 799; ¹H NMR (400 MHz, Chloroform-d) 8.00 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.5, 2.3 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 2.70 (s, 3H), 2.46 (s, 6H); ¹³C NMR (101 MHz, Chloroform-d) 150.8, 142.9, 130.8, 120.3, 115.7, 96.4, 40.4, 27.0; HRMS (ESI+) mass calculated for [M+H]+ C₉H₁₃BrI₂N₂ requires m/z 354.9301, found m/z 354.9300; [M]+ was also observed [M]+ C₉H₁₂BrI₂N₂ requires m/z 353.9223, found m/z 353.9224.
4. Aniline Synthesis

4.1. Coupling with para-Bromophenyl Hydrazines (Tables 1 and 3)

III. General Procedure for Coupling of Boronic Esters with p-bromophenyl hydrazines:
A solution of p-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) in THF (1 mL, 0.2 M) was cooled to –78 °C and treated with n-BuLi (0.125 mL, 0.20 mmol, 1.1 equiv., 1.6 M in hexanes), and the mixture was stirred at –78 °C for 1 h. To the resulting solution, the boronic ester (0.18 mmol, 1.0 equiv.) was added as a solution in THF (0.2 mL x 3) and the mixture was stirred at –78 °C for 1 h. A solution of trifluoroacetic anhydride (0.06 mL, 0.42 mmol, 2.1 equiv.) in THF (0.2 mL) was added at –78 °C and the reaction was allowed to warm slowly to rt overnight (12 h). The reaction mixture was then quenched with sat. aqueous NaHCO₃ solution (1 mL) and diluted with DCM (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel eluting with a gradient of pet. ether:EtOAc.

N-(4-Cyclohexylphenyl)-2,2,2-trifluoro-N-methylacetamide (7a)

The starting p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) and Cy-Bpin (38 mg, 0.18 mmol) were reacted according to the above general procedure III to afford the title compound (42 mg; 82%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) ν_max/cm⁻¹: 2926, 2853, 1698, 1199, 1151, 836, 674;¹H NMR (400 MHz, Chloroform-d) 7.17 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 3.26 (s, 3H), 2.54 – 2.34 (m, 1H), 1.89 – 1.62 (m, 5H), 1.42 – 1.10 (m, 5H);¹³C NMR (101 MHz, Chloroform-d) 156.8 (q, J = 35.6 Hz), 149.0, 138.2, 127.8, 127.1, 116.4 (q, J = 286.0 Hz), 44.2, 39.7, 34.3, 26.8, 26.1;¹⁹F NMR (283 MHz, Chloroform-d) -67.0; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₅H₁₈F₃NNaO requires m/z 308.1233, found m/z 308.1244.

* The formation of ‘ate’ complex could be monitored by ¹¹B NMR spectroscopy [¹¹B NMR (96 MHz, THF) ~8 ppm]. During optimization, it was found that this was complete within 1 h.
The synthesis of product 7a was also performed on a 1.2 mmol scale:
A solution of p-bromophenyl hydrazine (300 mg, 1.31 mmol, 1.10 equiv.) in THF (6.5 mL, 0.20 M) was cooled to –78 °C and n-BuLi (0.818 mL, 1.31 mmol, 1.10 equiv., 1.6 M in hexanes) was added dropwise over 30 min using a syringe pump. The solution was stirred at –78 °C for 1 h before the boronic ester (250 mg, 1.19 mmol, 1.0 equiv.) was added as a solution in THF (0.4 mL x 3) dropwise over 5 min. The mixture was stirred at –78 °C for 1 h before a solution of trifluoroacetic anhydride (0.347 mL, 2.50 mmol, 2.10 equiv.) in THF (0.5 mL) was added dropwise over 5 min. The reaction was allowed to warm slowly to rt overnight (12 h). The reaction mixture was then quenched with sat. aqueous NaHCO₃ solution (7 mL) and diluted with DCM (30 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, 5% EtOAc/pet. ether) to give compound 7a (268 mg; 79%) as a gummy oil.

N-(4-Cyclohexylnaphthalen-1-yl)-2,2,2-trifluoro-N-methylacetamide (7b)

The starting p-bromophenyl hydrazine (55.6 mg; 0.2 mmol) and Cy-Bpin (38 mg, 0.18 mmol) were reacted according to the above general procedure III to afford the title compound (56 mg; 87%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2929, 2853, 1699, 1205, 1152, 766; ¹H NMR (400 MHz, Chloroform-d) 8.20 (dd, J = 5.8, 3.8 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.63 – 7.54 (m, 2H), 7.37 (dd, J = 7.7 Hz, 7.7 Hz, 2H), 3.44 (s, 3H), 3.40 – 3.28 (m, 1H), 2.06 (d, J = 9.0 Hz, 2H), 2.00 – 1.81 (m, 3H), 1.68 – 1.48 (m, 4H), 1.45 – 1.29 (m, 1H); ¹³C NMR (101 MHz, Chloroform-d) 158.0 (q, J = 35.7 Hz), 146.1, 134.7, 132.3, 130.1, 126.9, 126.4, 125.6, 124.1, 122.8, 121.7, 116.4 (q, J = 288.1 Hz), 39.5, 39.2, 34.5, 33.9, 27.2, 27.1, 26.4; ¹⁹F NMR (377 MHz, Chloroform-d) -68.6; HRMS (ESI⁺) mass calculated for [M+H]⁺ C₁₉H₂₁F₃NO requires m/z 336.1570, found m/z 336.1572.
N-(4-Cyclohexyl-2-((2,2,2-trifluoro-N-methylacetamido)methyl)phenyl)-2,2-trifluoro-N-methylacetamide (7c)

The starting p-bromophenyl hydrazine (45 mg; 0.2 mmol) and Cy-Bpin (38 mg, 0.18 mmol) were reacted according to the above general procedure III to afford the title compound (47 mg; 62%) as a gummy oil; Rf (10% EtOAc/pet. ether): 0.6; IR (film) ν_max/cm^-1: 2927, 2854, 1697, 1197, 1144, 1088, 757; ^1H NMR and ^19F NMR at rt showed the existence of four rotamers (See below for ^1H NMR at rt and 100 °C). ^1H NMR (500 MHz, DMSO-d_6, 100 °C) 7.45 – 6.96 (m, 3H), 4.78 – 4.40 (m, 2H), 3.22 (s, 3H), 3.11 – 2.83 (m, 3H), 2.56 (s, 1H), 1.88 – 1.65 (m, 5H), 1.44 – 1.19 (m, 5H); ^13C NMR (126 MHz, DMSO-d_6, 100 °C) 156.4 (q, J = 35.6 Hz), 149.6, 137.3, 132.7, 129.3, 128.3, 127.5, 116.9 (q, J = 288.5 Hz), 116.6 (q, J = 288.6 Hz), 48.6, 39.1, 35.0, 34.1, 26.6, 26.0; ^19F NMR (377 MHz, Chloroform-d, 25 °C) -68.4, -68.7, -69.6 (d, J = 1.3 Hz), -69.7 (d, J = 1.0 Hz), -69.98 (d, J = 1.3 Hz), -70.01 (d, J = 1.3 Hz); HRMS (ESI^+*) mass calculated for [M+Na]^+ C_{19}H_{22}F_{6}N_{2}NaO_2 requires m/z 447.1478, found m/z 447.1481.

1-(5-Cyclohexylindolin-1-yl)-2,2,2-trifluoroethan-1-one (7d)

The starting p-bromophenyl hydrazine (48 mg; 0.2 mmol) and Cy-Bpin (38 mg, 0.18 mmol) were reacted according to the above general procedure III to afford the title compound (49 mg; 92%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) ν_max/cm^-1: 2927, 2855, 1675, 1195, 1148, 824; ^1H NMR (400 MHz, Chloroform-d) 8.02 (d, J = 9.0 Hz, 1H), 7.03 (s, 1H), 7.03 (d, J = 7.3 Hz, 1H), 4.31 – 4.06 (m, 2H), 3.15 (t, J = 8.2 Hz, 2H), 2.53 – 2.30 (m, 1H), 1.86 – 1.62 (m, 5H), 1.40 – 1.09 (m, 5H); ^13C NMR (101 MHz, Chloroform-d) 153.9 (q, J = 37.2 Hz), 146.3, 139.6, 131.7, 126.3, 123.1, 117.7, 116.2 (q, J = 287.8 Hz), 47.9 (q, J = 4.1 Hz), 44.3, 34.6, 28.5, 26.9, 26.1; ^19F NMR (377 MHz, Chloroform-d) -72.5; HRMS (ESI^+*) mass calculated for [M+Na]^+ C_{16}H_{18}F_{3}NNaO requires m/z 320.1233, found m/z 320.1246.
2,2,2-Trifluoro-N-methyl-N-(4-phenethylphenyl)acetamide (11)

The starting boronic ester (42 mg, 0.18 mmol) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (44 mg; 79%) as a gummy oil; R\text{f} (5% EtOAc/pet. ether): 0.4; IR (film) \( \nu_{\text{max}}/\text{cm}^{-1} \): 2928, 1698, 1512, 1200, 1151, 699; \(^1\)H NMR (400 MHz, Chloroform-d) 7.37 – 7.06 (m, 9H), 3.35 (s, 3H), 2.95 (m, 4H); \(^1^3\)C NMR (126 MHz, Chloroform-d) 157.0 (q, \( J = 35.4 \) Hz), 142.8, 141.0, 138.5, 129.6, 128.5, 128.4, 127.1, 126.1, 116.4 (q, \( J = 288.0 \) Hz), 39.7, 37.6, 37.4; \(^1^9\)F NMR (377 MHz, Chloroform-d) -67.0; HRMS (ESI\(^+\)) mass calculated for [M+Na]\(^+\) \( \text{C}_{17}\text{H}_{16}\text{F}_{3}\text{NNaO} \) requires m/z 330.1076, found m/z 330.1074.

\( \text{N-} (4\text{-Cyclododecylphenyl})\text{-2,2,2-trifluoro-N-methylacetamide (12)} \)

The starting boronic ester (53 mg; 0.18 mmol) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (48 mg; 76%) as a gummy oil; R\text{f} (5% EtOAc/pet. ether): 0.4; IR (film) \( \nu_{\text{max}}/\text{cm}^{-1} \): 2931, 2861, 1701, 1509, 1199, 1152, 1111, 756; \(^1\)H NMR (400 MHz, Chloroform-d) 7.22 (d, \( J = 8.4 \) Hz, 2H), 7.13 (d, \( J = 8.2 \) Hz, 2H), 3.34 (s, 3H), 2.80 (m, 1H), 1.91 – 1.69 (m, 2H), 1.51 – 1.25 (m, 20H); \(^1^3\)C NMR (126 MHz, Chloroform-d) 157.0 (q, \( J = 35.6 \) Hz), 148.7, 138.1, 128.6, 126.9, 116.4 (q, \( J = 288.0 \) Hz), 39.7, 39.5, 31.4, 23.9, 23.8, 23.5, 23.3, 22.5; \(^1^9\)F NMR (377 MHz, Chloroform-d) -67.1; MS (ESI\(^+\)) mass calculated for [M+Na]\(^+\) \( \text{C}_{21}\text{H}_{30}\text{F}_{3}\text{NNaO} \) requires m/z 392.2, found m/z 392.2.

tert-Butyl 4-(4-(2,2,2-trifluoro-N-methylacetamido)phenyl)piperidine-1-carboxylate (13)

The starting boronic ester (56 mg; 0.18 mmol) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (46 mg; 66%) as a gummy oil; R\text{f} (30% EtOAc/pet. ether): 0.4; IR (film) \( \nu_{\text{max}}/\text{cm}^{-1} \): 2933, 1693, 1200, 1199, 1154, 1015, 757; \(^1\)H NMR (400 MHz, Chloroform-d) 7.22 – 7.06 (m, 4H), 4.19 (d, \( J = 13.2 \) Hz, 2H), 3.27 (s, 3H), 2.82 – 2.52 (m, 3H), 1.77 (d, \( J = 12.7 \) Hz, 2H), 1.54 (m, 2H), 1.41 (s, 9H); \(^1^3\)C NMR (101 MHz, Chloroform-d) 156.9 (q, \( J = 35.7 \) Hz), 154.8, 146.7, 138.8, 127.8, 127.4, 116.4 (q, \( J = 287.9 \) Hz), 79.6, 44.3, 42.3, 39.7, 33.0, 28.5; \(^1^9\)F NMR (377 MHz, Chloroform-d) -67.0; MS (ESI\(^+\)) mass calculated for [M+Na]\(^+\) \( \text{C}_{21}\text{H}_{30}\text{F}_{3}\text{NNaO} \) requires m/z 392.2, found m/z 392.2.
(S)-2,2,2-Trifluoro-N-(4-(4-(4-methoxyphenyl)butan-2-yl)phenyl)-N-methylacetamide (14)

The starting boronic ester (52 mg; 0.18 mmol; 96.0:4.0 er) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (52 mg; 79%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D23 = -8.52 (c 1.76, CHCl3); IR (film) νmax/cm⁻¹: 2931, 1697, 1510, 1198, 1150, 1036, 843; 1H NMR (400 MHz, Chloroform-d) 7.19 – 7.04 (m, 4H), 6.95 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.70 (s, 3H), 3.27 (s, 3H), 2.68 (m, 1H), 2.54 – 2.21 (m, 2H), 1.80 (q, J = 7.7 Hz, 2H), 1.20 (d, J = 6.9 Hz, 3H); 13C NMR (101 MHz, Chloroform-d) 157.8, 157.0 (q, J = 35.5 Hz), 148.5, 138.4, 134.2, 129.2, 128.1, 127.2, 116.4 (q, J = 287.9 Hz), 113.8, 55.3, 40.1, 39.7, 39.0, 32.9, 22.2; 19F NMR (377 MHz, Chloroform-d) -67.1; HRMS (ESI⁺) mass calculated for [M+Na]+ C20H22F3NNaO2 requires m/z 388.1495, found m/z 388.1508. The er was determined by chiral HPLC [chiralpak IB, 99.9:0.1 hexane/isopropanol, 1.0 mL/min, rt, t(major) = 37.4 min, t(minor) = 41.8 min] to be 95.8:4.2 (100% es).

(R)-N-(4-(7-Azido-1-phenylheptan-3-yl)phenyl)-2,2,2-trifluoro-N-methylacetamide (15)

The starting boronic ester (62 mg; 0.18 mmol; 98.0:2.0 er) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (43 mg; 57%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D23 = +12.85 (c 2.1, CHCl3); IR (film) νmax/cm⁻¹: 2934, 2860, 2095, 1698, 1217, 1199, 1151, 1112, 755, 700; 1H NMR (400 MHz, Chloroform-d) 7.39 – 7.05 (m,
7H), 7.00 (d, J = 7.2 Hz, 2H), 3.30 (s, 3H), 3.10 (td, J = 6.8, 3.1 Hz, 2H), 2.58 – 2.20 (m, 3H), 2.05 – 1.73 (m, 2H), 1.69 – 1.38 (m, 4H), 1.23 – 1.01 (m, 2H); \(^{13}\)C NMR (101 MHz, Chloroform-d) 157.1 (q, J = 34.9 Hz), 146.3, 142.0, 138.6, 128.7, 128.4, 128.3, 127.4, 125.8, 116.4 (d, J = 288.0 Hz), 51.3, 45.1, 39.7, 38.3, 36.3, 33.7, 28.8, 24.7; \(^{19}\)F NMR (377 MHz, Chloroform-d) -67.1; HRMS (ESI\(^{+}\)) mass calculated for [M+Na]\(^{+}\) C\(_{22}\)H\(_{25}\)F\(_{3}\)N\(_{4}\)NaO requires m/z 441.1873, found m/z 441.1882. The er was determined by chiral HPLC [chiralpak IB, 99.5:0.5 hexane/isopropanol, 1.0 mL/min, rt, t(minor) = 18.2 min, t(minor) = 24.0 min] to be 98.5:1.5 (100% es).

\(\textbf{(R)-2,2,2-Trifluoro-N-methyl-N-(4-(1-phenylhept-6-en-3-yl)phenyl)acetamide (16)}\)

The starting boronic ester\(^3\) (54 mg; 0.18 mmol; 97.5:2.5 er) and \(p\)-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure to afford the title compound (47 mg; 70%) as a gummy oil; R\(_f\) (5% EtOAc/pet. ether): 0.4; [\(\alpha\)]\(_D\)\(^{23}\) = +16.25 (c 0.8, CHCl\(_3\)); IR (film) \(\nu_{\max}/\text{cm}^{-1}\): 2987, 1700, 1491, 1200, 1152, 1066; \(^{1}\)H NMR (500 MHz, Chloroform-d) 7.28 – 7.17 (m, 7H), 7.09 (d, J = 7.7 Hz, 2H), 5.83 – 5.64 (m, 1H), 5.03 – 4.80 (m, 2H), 3.38 (s, 3H), 2.63 (tt, J = 9.6, 5.0 Hz, 1H), 2.45 (t, J = 7.9 Hz, 2H), 2.07 – 1.95 (m, 1H), 1.93-1.85 (m, 3H), 1.84 – 1.74 (m, 1H), 1.74 – 1.62 (m, 1H); \(^{13}\)C NMR (126 MHz, Chloroform-d) 157.0 (q, J = 36.0 Hz), 146.3, 142.1, 138.5, 138.3, 128.8, 128.3, 128.3, 127.3, 125.8, 116.4 (q, J = 288.6 Hz), 114.7, 44.6, 39.6, 38.3, 35.9, 33.7, 31.6; \(^{19}\)F NMR (377 MHz, Chloroform-d) -67.1; HRMS (ESI\(^{+}\)) mass calculated for [M+Na]\(^{+}\) C\(_{22}\)H\(_{25}\)F\(_{3}\)N\(_{4}\)NaO requires m/z 398.1702, found m/z 398.1690. The er was determined by chiral HPLC [chiralpak IB, 99.9:0.1 hexane/isopropanol, 1.0 mL/min, rt, t (major) = 25.2 min, t(minor) = 28.6 min] to be 96.2:3.8 (97% es).
(R)-2,2,2-Trifluoro-N-methyl-N-(4-(1-phenylethyl)phenyl)acetamide (17)

The starting boronic ester (42 mg; 0.18 mmol; 97.0:3.0 er) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (47 mg; 85%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D23 = -13.5 (c 2.0, CHCl3); IR (film) νmax/cm⁻¹: 2970, 1698, 1511, 1200, 1150, 700; ¹H NMR (500 MHz, Chloroform-d) 7.36 – 7.25 (m, 4H), 7.22 (t, J = 6.8 Hz, 3H), 7.14 (d, J = 8.2 Hz, 2H), 4.19 (q, J = 7.2 Hz, 1H), 3.33 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H); ¹³C NMR (126 MHz, Chloroform-d) 157.0 (q, J = 35.9 Hz), 147.4, 145.5, 138.5, 128.6, 128.5, 127.6, 127.2, 126.3, 116.4 (q, J = 288.1 Hz), 44.4, 39.7, 21.8; ¹⁹F NMR (377 MHz, Chloroform-d) -66.9; HRMS (ESI⁺) mass calculated for [M+Na]+ C₁₇H₁₆F₃NNaO requires m/z 330.1076, found m/z 330.1076. The er was determined by chiral HPLC [2 x chiralpak IB with guard on the first one, 99.9:0.1 hexane/isopropanol, 1.0 mL/min, 10 °C, t (major) = 45.1 min, t(minor) = 46.6 min] to be >95:5 (>95% es). *The separation of enantiomers by HPLC proved challenging and was complicated by significant peak broadening, which prevented complete resolution of the enantiomers. Furthermore, in the enantioenriched product, the minor enantiomer could not be observed as it was masked by the tail of the major enantiomer peak, which prevented accurate measurement of the er. However, qualitative analysis of the HPLC traces suggests an er of >95:5. Therefore, we have tentatively reported the es as >95%.
The starting boronic ester 5 (52 mg; 0.18 mmol; 99.0:1.0 er) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (46 mg; 70%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D 23 = -17.5 (c 1.2, CHCl3); IR (film) νmax/cm⁻¹: 2967, 1699, 1200, 1151, 699; ¹H NMR (400 MHz, Chloroform-d) 7.31 (d, J = 8.6 Hz, 2H), 7.23 – 7.03 (m, 5H), 6.99 (d, J = 7.1 Hz, 2H), 3.29 (s, 3H), 2.38 (td, J = 12.8, 5.0 Hz, 1H), 2.13 (td, J = 12.9, 4.3 Hz, 1H), 1.92 (td, J = 13.1, 4.4 Hz, 1H), 1.85 – 1.65 (m, 2H), 1.62-1.51 (m, 1H), 1.30 (s, 3H), 0.63 (t, J = 7.4 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-d) 157.1 (q, J = 35.8 Hz), 148.6, 142.8, 138.0, 128.4, 128.2, 127.6, 126.9, 125.7, 116.4 (q, J = 288.0 Hz), 45.3, 41.4, 39.6, 35.6, 30.9, 23.1, 8.6; ¹⁹F NMR (377 MHz, Chloroform-d) -67.1; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₃₂H₂₄F₃NNaO requires m/z 386.1702, found m/z 386.1708. The er was determined by chiral HPLC [chiralpak IB, 99.5:0.5 hexane/isopropanol, 1.0 mL/min, rt, t(major) = 9.8 min, t(minor) = 10.7 min] to be 99.2:0.8 (100% es).

The starting boronic ester 6 (70.6 mg; 0.18 mmol; >95:5 dr) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (57 mg; 68%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.3; IR (film) νmax/cm⁻¹: 2915, 1700, 1509, 1199, 1151, 1111, 831, 738; ¹H NMR (500 MHz, Chloroform-d) 7.59 – 7.31 (m, 5H), 7.20 – 6.93 (m, 7H), 6.69 (d, J = 7.7 Hz, 1H), 4.08 (d, J = 8.4 Hz, 1H), 3.34 (s, 3H), 2.86 (m, 2H), 2.12 – 1.98 (m, 1H), 1.72 (ddt, J = 18.7, 9.8, 5.5 Hz, 1H), 1.59 – 1.46 (m, 1H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (126 MHz, Chloroform-d) 157.0 (q, J = 35.8
Hz), 148.9, 139.4, 138.5, 138.0, 137.3, 134.0, 130.2, 129.9, 129.0, 127.7, 127.1, 125.9, 125.8, 116.4 (q, J = 288.0 Hz), 46.4, 39.7, 30.9, 30.1, 23.1, -3.2, -4.3; 19F NMR (377 MHz, Chloroform-d) -66.9; HRMS (ESI+) mass calculated for [M+Na]+ C27H28F3NNaOSi requires m/z 490.1784, found m/z 490.1789. The dr was determined by 1H NMR analysis to be >95:5.

2,2,2-Trifluoro-N-(4-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)phenyl)-N-methylacetamide (20)

The starting boronic ester7 (48 mg; 0.18 mmol; >95:5 dr) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to the above general procedure III to afford the title compound (42 mg; 68%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D23 = +7.5 (c 0.8, CHCl3); IR (film) νmax/cm⁻¹: 2954, 1701, 1210, 1153, 1110, 840; 1H NMR (400 MHz, Chloroform-d) 7.12 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 3.27 (s, 3H), 2.40 (ddd, J = 11.7, 11.7, 3.4 Hz, 1H), 1.89 – 1.57 (m, 3H), 1.34 (m, 3H), 1.16 – 0.87 (m, 3H), jj0.83 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.60 (d, J = 6.9 Hz, 3H); 13C NMR (126 MHz, Chloroform-d) 157.1 (q, J = 35.6 Hz), 147.8, 138.1, 128.4, 127.1, 116.4 (q, J = 288.0 Hz), 47.7, 47.5, 45.2, 39.7, 35.2, 33.2, 27.5, 24.6, 22.5, 21.4, 15.5; 19F NMR (377 MHz, Chloroform-d) -67.1; HRMS (ESI+) mass calculated for [M+Na]+ C19H26F3NNaO requires m/z 364.1859, found m/z 364.1877. The dr was determined by 1H NMR analysis to be >95:5.

Cholesterol-derived product 21

The starting boronic ester4 (113 mg; 0.18 mmol; >95:5 dr) and p-bromophenyl hydrazine (45.6 mg; 0.2 mmol) were reacted according to a modified general procedure III – with a reduced amount of TFFA (56 μL, 0.19 mmol) – to afford the title compound (58 mg; 46%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; [α]D23 = +19.0 (c 2.1, CHCl3); IR (film) νmax/cm⁻¹: 2931, 2853, 1702, 1510, 1470, 1220, 1200, 1154, 1098, 1082, 836, 775; 1H NMR (500 MHz, Chloroform-d) 7.14 (m, 4H), 3.33 (m, 4H), 2.48 (td, J = 12.0, 3.6 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.77 (m, 3H), 1.70 – 1.62 (m, 1H), 1.60 – 0.96 (m, 24H), 0.96 – 0.89 (m, 6H), 0.86 (d, J = 2.2 Hz,
3H), 0.85 (d, J = 2.2 Hz, 3H), 0.75 (s, 9H), 0.68 (s, 3H), -0.14 (s, 3H) -0.13 (s, 3H); \(^1^3^C\) NMR (126 MHz, Chloroform-d) 157.1 (q, J = 35.6 Hz), 147.3, 138.3, 130.9, 127.2, 116.4 (q, J = 288.0 Hz), 72.3, 56.3 (d, J = 4.9 Hz), 54.4, 49.8, 44.4, 42.6, 41.0, 40.0, 39.7, 39.5, 37.4, 36.2, 36.1, 35.8, 35.3, 34.9, 31.7, 28.3, 28.0, 25.8, 24.2, 23.9, 22.8, 22.6, 21.3, 18.7, 18.2, 13.2, 12.1, -4.9, -5.0; \(^1^9^F\) NMR (377 MHz, Chloroform-d) -67.0; HRMS (MALDI\(^+\)) mass calculated for [M+Na]\(^+\) C\(_{42}\)H\(_{68}\)NNaO\(_2\)F\(_3\)Si requires m/z 726.4864, found m/z 726.4869. The dr was determined by \(^1^H\) NMR analysis to be >95:5.
4.1. Coupling with ortho-Bromophenyl Hydrazines (Tables 2 and 3)

IV. General Procedure for coupling boronic esters to o-bromophenyl hydrazines

A solution of o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) in THF (1 mL, 0.2 M) was cooled to –78 °C and treated with n-BuLi (0.125 mL, 0.20 mmol, 1.1 equiv., 1.6 M in hexanes), and the mixture was stirred at –78 °C for 1 h. To the resulting solution, the boronic ester (0.18 mmol, 1.0 equiv.) was added as a solution in THF (0.2 mL x 3) and the mixture was stirred at –78 °C for 1 h.† Then solid 2,2,2-trichloro-1,1-dimethylethyl chloroformate (100 mg, 0.42 mmol, 2.1 equiv.) was added at –78 °C and the reaction was allowed to warm slowly to rt overnight (12 h). The reaction mixture was then quenched with sat. aqueous NaHCO₃ solution (1 mL) and diluted with DCM (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel eluting with a gradient of pet. ether:EtOAc.

1,1,1-Trichloro-2-methylpropan-2-yl (2-cyclohexylphenyl)(methyl)carbamate (10a)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and Cy-Bpin (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (53 mg; 75%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2925, 2851, 1711, 1366, 1152, 799, 749;¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.33 – 7.21 (m, 2H), 7.15 (m, 2H), 3.13 (s, 3H), 2.57 (t, J = 10.4 Hz, 1H), 2.10 – 1.57 (m, 10H), 1.57 – 0.73 (m, 6H);¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 153.2, 144.9, 134.3, 128.4, 128.2, 127.3, 126.8, 107.0, 88.4, 39.2, 38.7*, 34.6, 33.5, 27.1, 26.1, 22.1, 22.0 [the rotameric peaks that did not coalesce at 100 °C are marked with an asterisk*]; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₃₈H₃₆Cl₃NNaO₂ requires m/z 414.0765, found m/z 414.0746.

† The formation of ‘ate’ complex could be monitored by ¹¹B NMR spectroscopy [¹¹B NMR (96 MHz, THF) ~8 ppm]. During optimization, it was found that this was complete within 1 h.
1,1,1-Trichloro-2-methylpropan-2-yl (2-cyclohexyl-5-(trifluoromethyl)phenyl)(methyl) carbamate (10b)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and Cy-Bpin (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (39.5 mg; 48%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.6; IR (film) νmax/cm⁻¹: 2928, 2854, 1716, 1334, 1157, 1125, 800; ¹H NMR (500 MHz, DMSO-d6, 100 °C) 7.65 – 7.41 (m, 3H), 3.16 (s, 3H), 2.64 (t, J = 11.3 Hz, 1H), 2.04 – 1.60 (m, 10H), 1.58 – 1.00 (m, 6H); ¹³C NMR (126 MHz, DMSO-d6, 100 °C) 152.9, 149.7, 141.5, 128.7, 128.1 (q, J = 31.8 Hz), 125.9, 124.9 (d, J = 3.6 Hz), 124.3 (q, J = 271.9 Hz), 106.8, 88.7, 39.3, 38.3, 34.1, 33.3, 26.9, 25.9, 22.0; ¹⁹F NMR (377 MHz, Chloroform-d, 25 °C) -62.5; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₉H₂₃Cl₃F₃NNaO₂ requires m/z 482.0639, found m/z 482.0642.

1,1,1-Trichloro-2-methylpropan-2-yl (2-cyclohexyl-4-methoxyphenyl)(methyl)carbamate (10c)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and Cy-Bpin (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (67.5 mg; 89%) as a gummy oil; Rf (10% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2926, 1713, 1155, 797; ¹H NMR (500 MHz, DMSO-d6, 100 °C) 7.04 (d, J = 8.5 Hz, 1H), 6.79 (s, 1H), 6.76 – 6.67 (m, 1H), 3.75 (s, 3H), 3.10 (s, 3H), 2.56 – 2.49 (m, 1H), 1.93 – 1.64 (m, 11H), 1.54 – 1.18 (m, 5H); ¹³C NMR (126 MHz, DMSO-d6, 100 °C) 159.3, 153.5, 146.2, 134.1, 129.3, 113.0, 112.3, 107.1, 88.3, 55.8, 39.4, 38.9, 34.5, 33.4, 27.1, 27.1*, 26.1, 22.1, 21.9 [the rotameric peaks that did not coalesce at 100 °C are marked with an asterisk*]; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₀H₁₃ClF₃NNaO₂ requires m/z 444.0870, found m/z 444.0869.

1,1,1-Trichloro-2-methylpropan-2-yl (2-cyclohexyl-5-fluorophenyl)(methyl)carbamate (10d)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (45 mg; 61%) as a
gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2926, 2852, 1714, 1360, 1153, 799;
¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.36 – 7.26 (m, 1H), 7.12 – 6.95 (m, 2H), 3.13 (s, 3H), 2.59 – 2.50 (m, 1H), 2.02 – 1.54 (m, 10H), 1.49 – 1.21 (m, 6H); ¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 160.7 (d, J = 243.3 Hz), 152.9, 142.1 (d, J = 10.8 Hz), 141.2, 128.8 (d, J = 8.7 Hz), 115.4 (d, J = 21.6 Hz), 115.1 (d, J = 20.7 Hz), 106.9, 88.6, 38.7, 38.4", 34.6, 33.6, 27.1, 26.0, 22.0 [the rotameric peaks that did not coalesce at 100 °C are marked with an asterisk*]; ¹⁹F NMR (377 MHz, Chloroform-d, 25 °C) -116.0 (td, J = 8.7, 6.3 Hz), -116.9 (td, J = 8.6, 6.4 Hz); HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₈H₂₃Cl₃FNNaO₂ requires m/z 432.0671, found m/z 432.0672.

1,1,1-Trichloro-2-methylpropan-2-yl (2-cyclohexyl-5-fluorophenyl)(methyl)carbamate (10e)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (42 mg; 55%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.5; IR (film) νmax/cm⁻¹: 2927, 1716, 1358, 1157, 1066, 799;
¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.36 – 7.27 (m, 2H), 7.24 (s, 1H), 3.13 (s, 3H), 2.60 – 2.50 (m, 1H), 2.04 – 1.56 (m, 11H), 1.50 – 1.09 (m, 5H); ¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 152.9, 144.0, 142.1, 130.7, 129.0, 128.7, 128.3, 106.9, 88.7, 38.9, 38.4, 34.2, 33.4, 27.0, 26.0, 22.0; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₈H₂₃Cl₃FNNaO₂ requires m/z 448.0375, found m/z 448.0382.

1,1,1-Trichloro-2-methylpropan-2-yl (5-bromo-2-cyclohexylphenyl)(methyl)carbamate (10f)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (44 mg; 52%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2927, 1715, 1367, 1155, 1066, 798; ¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.44 (d, J = 1.9 Hz, 1H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 3.12 (s, 3H), 2.54 (t, J = 11.2 Hz, 1H), 2.18 – 0.86 (m, 16H); ¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 153.0, 147.7, 140.4, 130.8, 130.3, 129.9, 121.3, 106.9, 88.6, 39.3, 38.5, 34.3, 33.2, 27.0, 25.9, 22.0; HRMS (ESI⁺) mass calculated for [M+Na]⁺ C₁₈H₂₅BrCl₃NNaO₂ requires m/z 491.9870, found m/z 491.9846.
1,1,1-Trichloro-2-methylpropan-2-yl (2-(1,3-dioxolan-2-yl)ethyl)phenyl)(methyl) carbamate (22)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (41 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (52 mg; 71%) as a gummy oil; Rf (15% EtOAc/pet. ether): 0.4; IR (film) νmax/cm⁻¹: 2953, 1712, 1367, 1153, 1046, 799; ¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.33 – 7.09 (m, 4H), 4.94 – 4.77 (m, 1H), 3.98 – 3.69 (m, 4H), 3.14 (s, 3H), 2.69 – 2.55 (m, 2H), 2.00 – 1.70 (m, 8H); ¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 153.0, 141.8, 139.3, 129.8, 128.3, 128.0, 127.2, 106.9, 103.8, 88.4, 64.8, 38.0, 34.3, 25.3, 21.9; HRMS (ESI⁺) mass calculated for [M+Na⁺] C₁₇H₂₂Cl₃NNaO₄ requires m/z 432.0507, found m/z 432.0523.

1,1,1-trichloro-2-methylpropan-2-yl (2-(but-3-en-1-yl)phenyl)(methyl)carbamate (23)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (41 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (38 mg; 58%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.5; IR (film) νmax/cm⁻¹: 2951, 2096, 1713, 1384, 1161, 794; ¹H NMR (500 MHz, DMSO-d₆, 100 °C) 7.34 – 7.08 (m, 4H), 5.93 – 5.78 (m, 1H), 5.09 – 4.91 (m, 2H), 3.14 (s, 3H), 2.62 (t, J = 7.7 Hz, 2H), 2.39 – 2.27 (m, 2H), 1.84 (s, 6H); ¹³C NMR (126 MHz, DMSO-d₆, 100 °C) 153.0, 141.8, 139.1, 138.6, 129.8, 128.2, 127.9, 127.2, 115.3, 106.9, 88.4, 38.1, 33.7, 30.4, 22.0; HRMS (ESI⁺) mass calculated for [M+Na⁺] C₁₆H₂₀Cl₃NNaO₂ requires m/z 386.0452, found m/z 386.0466.

1,1,1-Trichloro-2-methylpropan-2-yl (2-(4-azidobutyl)phenyl)(methyl)carbamate (24)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (40.5 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (47 mg; 64%) as a gummy oil; Rf (10% EtOAc/pet. ether): 0.3; IR (film) νmax/cm⁻¹: 2951, 2096, 1713, 1384, 1161, 794; ¹H NMR (500 MHz, Chloroform-d, rt) 7.30 – 7.04 (m, 4H), 3.38 – 3.12 (m, 5H), 2.60 (d, J = 7.2 Hz, 2H), 1.95 (d, J = 44.0 Hz, 6H), 1.81 – 1.51 (m, 4H); ¹³C NMR (126 MHz, Chloroform-d, rt) 153.5, 153.2*, 141.6, 141.1*, 139.1, 138.9*, 129.9, 129.3*, 128.0, 127.9*, 127.9, 127.7*, 127.4, 126.9*, 106.7, 106.1*, 88.8, 88.6*, 51.3, 38.5, 37.6*, 30.6, 30.5*, 29.0,
28.9*, 27.2, 27.1*, 21.6, 21.6 [the rotameric peaks are marked with an asterisk*]; HRMS (ESI+) mass calculated for [M+Na]+ C_{16}H_{21}Cl_{3}N_{4}NaO_{2} requires m/z 429.0622, found m/z 429.0626.

**tert-Butyl 4-(2-(methyl(((1,1,1-trichloro-2-methylpropan-2-yl)oxy)carbonyl)amino)phenyl)piperidine-1-carboxylate (25)**

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (56 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (70 mg; 79%) as a gummy oil; Rf (5% EtOAc/pet. ether): 0.4; IR (film) ν_{max}/cm^{-1}: 2974, 1711, 1659, 1651, 1024, 993; ^1H NMR (500 MHz, DMSO-d_{6}, 100 °C) 7.49 – 7.25 (m, 2H), 7.25 – 7.02 (m, 2H), 4.11 (d, J = 13.0 Hz, 2H), 3.16 (s, 3H), 2.92 – 2.58 (m, 3H), 2.01 – 1.62 (m, 8H), 1.60 – 1.48 (m, 2H), 1.44 (s, 9H); ^13C NMR (126 MHz, DMSO-d_{6}, 100 °C) 154.5, 153.2, 143.1, 141.2, 128.6, 128.4, 127.4, 127.3, 126.3, 128.4, 127.4, 127.3, 106.9, 88.5, 79.0, 44.8, 38.7, 37.3, 33.2, 32.5, 28.7, 22.1, 21.9; HRMS (ESI+) mass calculated for [M+Na]+ C_{22}H_{31}Cl_{3}N_{4}O_{4} requires m/z 515.1242, found m/z 515.1238.

**1,1,1-Trichloro-2-methylpropan-2-yl methyl(2-(thiophen-2-yl)phenyl)carbamate (26)**

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester (38 mg; 0.18 mmol) were reacted according to the above general procedure IV to afford the title compound (48 mg; 67%) as a gummy oil; Rf (toluene): 0.4, flash column chromatography was performed using toluene as the eluent; IR (film) ν_{max}/cm^{-1}: 2987, 1714, 1367, 1156, 1066, 798; ^1H NMR (500 MHz, DMSO-d_{6}, 100 °C) 7.70 – 7.60 (m, 1H), 7.60 – 7.50 (m, 1H), 7.43 – 7.23 (m, 4H), 7.17 – 7.04 (m, 1H), 3.04 (s, 3H), 2.03 – 1.55 (m, 6H); ^13C NMR (126 MHz, DMSO-d_{6}, 100 °C) 152.8, 139.7, 132.2, 129.6, 128.8, 128.3, 127.6, 127.2, 126.3, 106.8, 88.5, 37.4, 21.9 [two of the aromatic carbon signals seem to be overlapped]; HRMS (ESI+) mass calculated for [M+Na]+ C_{16}H_{16}Cl_{3}NNaO_{2} requires m/z 413.9859, found m/z 413.9863.
1,1,1-Trichloro-2-methylpropan-2-yl (S)-(2-(4-(4-methoxyphenyl)butan-2-yl)phenyl)(methyl)carbamate (27)

The o-bromophenyl hydrazine (0.20 mmol, 1.1 equiv.) and the starting boronic ester\(^2\) (52 mg; 0.18 mmol; 96.0:4.0 er) were reacted according to the above general procedure IV to afford the title compound (69.5 mg; 82%) as a gummy oil; \(R\) (5\% EtOAc/pet. ether): 0.4; \([\alpha]_D^{23} = +43.15\) (c 1.9, CHCl\(_3\)); IR (film) \(\nu_{\text{max}}/\text{cm}^{-1}\): 2929, 1716, 1365, 1153, 1060, 776; \(^1\)H NMR (500 MHz, DMSO-\(d_6\), 100 °C) 7.37 – 7.31 (m, 1H), 7.31 – 7.23 (m, 1H), 7.21 – 7.14 (m, 1H), 7.14 – 7.09 (m, 1H), 7.04 (d, \(J = 7.8\) Hz, 2H), 6.86 – 6.75 (m, 2H), 3.72 (m, 3H), 3.08 (s, 3H), 2.95 – 2.84 (m, 1H), 2.66 – 2.53 (m, 1H), 2.43 (tdd, \(J = 8.8, 3.5, 1.7\) Hz, 1H), 1.85 (d, \(J = 7.1\) Hz, 8H), 1.30 – 1.17 (m, 3H); \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\), 100 °C) 158.3, 153.3, 145.2, 141.3, 134.5, 129.3, 128.5, 128.3, 127.1, 126.8, 114.6, 107.1, 88.6, 55.7, 39.6, 38.6, 33.1, 22.2, 21.3 (one of the aliphatic carbon peak merged with the solvent peak); HRMS (ESI\(^+\)) mass calculated for \([\text{M+Na}]^+\) \(C_{23}H_{28}Cl_3NNaO_3\) requires m/z 494.1027, found m/z 494.1017. The \(\text{er}\) was determined by chiral HPLC [2 x chiralpak IB with a guard column on the first one, 99.9:0.1 hexane/isopropanol, 0.5 mL/min, rt, t(major) = 108.6 min, t(minor) = 118.3 min] to be >95:5* (>97% es). *Due to the fluxional nature of these molecules, the HPLC separation was found to be very difficult to achieve, and significant peak broadening prevented complete resolution of the enantiomers. Thus, accurate measurement of the \(\text{er}\) was not possible. However, qualitative analysis of the HPLC traces indicates that the minor enantiomer appears as a small shoulder on the tail of the major enantiomer, which suggests an \(\text{er}\) of >95:5. Therefore, we have tentatively reported the \(\text{es}\) as >97%.
5. References

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6. NMR Spectra

6.1. Substrates

![NMR Spectra Image]

- 4a

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S31
8e'

8e
6.2. *para*-Substituted Aniline Products from Scheme 2
6.3. *ortho*-Substituted Aniline Products from Scheme 3

10a
NMR @ 100 °C
10b
NMR @ 100 °C
10b
NMR @ 25 °C

10c
NMR @ 100 °C
$\text{Cl}_3\text{C} = \text{O} - \text{N} - \text{O} - \text{C}_6\text{H}_5$

10c

NMR @ 100 °C

$\text{Cl}_3\text{C} = \text{O} - \text{N} - \text{O} - \text{C}_6\text{H}_5\text{F}$

10d

NMR @ 100 °C
10d
NMR @ 100 °C

10d
NMR @ 25 °C
6.4. *para*-Substituted Aniline Products from Scheme 4
6.5. *ortho*-Substituted Aniline Products from Scheme 4

![Chemical structure image]

NMR @ 100 °C
NMR @ 100 °C
