Supporting Information
for DOI: 10.1055/s-0037-1610864
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Supporting Information

Synthesis of chiral triazole-based halogen bond donors

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I) Synthetic procedures

General Information

NMR spectra were measured on a Bruker Avance III 400 MHz instrument. The spectra are reported in parts per million (δ) referenced to the residual solvent signal [CDCl₃ δ = 7.26 ppm, CD₂OD δ = 3.31 ppm, [D₆]DMSO δ = 2.50 ppm, [D₆]Acetone δ = 2.05 ppm (for ¹H NMR), CDCl₃ δ = 77.16 ppm, CD₂OD δ = 49.00 ppm, [D₆]DMSO δ = 39.52 ppm, [D₆]Acetone δ = 29.84 ppm (for ¹³C NMR)]. High resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Single crystal X-ray diffraction data was collected at 123 K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-Kα radiation (1.54178 Å) from a MicroMax™-003 sealed tube microfocus X-ray source. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. Infrared absorption frequencies in wavenumbers are listed, with the relative strength in parentheses (w = weak, m = medium, s = strong, br = broad). Precoated silica gel 60 F₂₅₄ plates from Merck were used for TLC, whereas for column chromatography silica gel Kieselgel 40-63 μm was used. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorous pentoxide and MeOH was dried by distillation over sodium metal. Petroleum ether (PE) has a boiling point of 40-60°C. The reactions were performed without additional moisture elimination unless stated otherwise.

Imidazole-1-sulfonyl Azide Hydrochloride (Cas No. 952234-36-5)

![Chemical structure of Imidazole-1-sulfonyl Azide Hydrochloride]

The azidating agent was prepared starting from imidazole, following the literature procedures,¹ as colourless crystals (9.85 g, 75% yield).

¹H NMR (400 MHz, D₂O) δ 9.14, 7.95, 7.53.

¹³C NMR (101 MHz, D₂O) δ 137.7, 125.1, 119.7.

(Iodoethynyl)benzene (Cas No. 932-88-7)

![Chemical structure of (Iodoethynyl)benzene]

The alkyne was prepared starting from ethynylbenzene, following the literature procedure,² as an orange oil (0.634 g, 70% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.39 (m, 2H), 7.36 – 7.27 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 132.5, 128.9, 128.4, 123.5, 94.3, 6.3.

S2
1-(iodoethynyl)-3,5-bis(trifluoromethyl)benzene (Cas No. 1246224-46-3)

\[
\begin{array}{c}
\text{Br CF}_3 \\
\text{CF}_3 \\
\rightarrow \\
\text{Si} \\
\left.\text{CF}_3\right. \\
\text{Si} \\
\begin{array}{c}
\text{CF}_3 \\
\text{CF}_3 \\
\text{NaOH} \\
99\% \\
\text{for two steps} \\
\rightarrow \\
\text{CF}_3 \\
\text{CF}_3 \\
\rightarrow \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\end{array}
\]

The alkyne was prepared starting from 3,5-bis(trifluoromethyl)bromobenzene, following the literature procedures,\(^6\) as an orange oil (0.854 g, in 87% total yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.87\) (bs, 2H), \(7.81\) (bs, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 132.5 – 132.3\) (m), 132.1 (q, \(J = 33.8\) Hz), 125.7, 123.0 (q, \(J = 272.9\) Hz), 122.4 – 122.2 (m), 91.3, 12.7.

Synthesis of 1,3-bis(iodoethynyl)benzene (Cas No. 1396817-65-4)

\[
\text{I I} \\
\rightarrow \text{TMS} \\
\rightarrow \text{NaOH} \\
96\% \text{for two steps} \\
\rightarrow
\]

The alkyne was prepared starting from 1,3-diiodobenzene, following the literature procedures,\(^4\) as a yellow solid (0.242 g, in 84% total yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.50\) (s, 1H), \(7.40 – 7.35\) (m, 2H), \(7.28 – 7.23\) (m, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 136.2, 132.7, 128.4, 123.8, 93.2, 7.8\).

Synthesis of 2-((1R,2R)-2-aminocyclohexyl)isoindoline-1,3-dione (Cas No. 438588-60-4)

\[
\begin{array}{c}
\text{N} \\
\text{NH}_2 \\
\text{O} \\
\text{O} \\
\text{OH} \\
\rightarrow \\
\text{NH}_2 \\
92\% \\
\rightarrow \\
\text{NH}_2 \\
57\% \\
\text{NaOH} \\
\rightarrow \\
\text{NaHCO}_3 \\
62\% \\
\rightarrow
\end{array}
\]

The monoprotected diamine was prepared starting from the (1R,2R)-cyclohexane-1,2-diamine L-tartaric salt, following the literature procedures,\(^5\) as a grey solid (0.95 g, in 33% total yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.83\) (dd, \(J = 5.4, 3.0\) Hz, 2H), \(7.70\) (dd, \(J = 5.4, 3.1\) Hz, 2H), \(3.80\) (ddd, \(J = 12.4, 10.5, 3.9\) Hz, 1H), \(3.41\) (td, \(J = 10.9, 4.1\) Hz, 1H), \(2.20\) (qd, \(J = 12.5, 3.6\) Hz, 1H), \(2.09 – 1.98\) (m, 1H), \(1.91 – 1.65\) (m, 3H), \(1.51 – 1.29\) (m, 2H), \(1.20\) (tdd, \(J = 12.9, 11.3, 3.5\) Hz, 1H), \(1.10\) (s, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 169.0, 134.0, 132.1, 123.3, 58.8, 51.0, 36.9, 29.5, 25.8, 25.3\).
**N-((1R,2R)-2-(1,3-dioxoisindolin-2-yl)cyclohexyl)acetamide (Cas No. 593284-19-6)**

\[
\text{2-}((1R,2R)-2\text{-aminocyclohexyl})\text{isoindoline-1,3-dione (0.350 g, 1.43 mmol) was dissolved in CH}_2\text{Cl}_2 (9 mL), triethylamine (0.195 mL, 1.40 mmol) and acetyl chloride (0.100 mL, 1.41 mmol) were added and the reaction mixture was stirred at r.t. for 2 hours. The reaction mixture was diluted with CH}_2\text{Cl}_2 (10 mL), after which water (9 mL) was added and the phases separated. The aqueous layer was extracted additionally with CH}_2\text{Cl}_2 (3 x 10 mL) and the combined organic phases were dried over Na}_2\text{SO}_4. Filtration and removal of the solvent under reduced pressure provided the product as a colourless solid (0.38 g, 1.33 mmol, 93% yield).}
\]

Mp 180–183 °C; [\(\alpha\)]\text{D}^20 = −23.5 (c = 0.39, CHCl₃).

\(^1\text{H NMR (400 MHz, CDCl}_3\text{) \(\delta\) 7.81 (dd, \(J = 5.4, 3.0\) Hz, 2H), 7.68 (dd, \(J = 5.5, 3.1\) Hz, 2H), 5.28 (d, \(J = 9.4\) Hz, 1H), 4.49 (tdd, \(J = 11.4, 9.3, 4.4\) Hz, 1H), 3.91 (ddd, \(J = 12.4, 10.8, 4.1\) Hz, 1H), 2.56 (qd, \(J = 12.9, 3.6\) Hz, 1H), 2.18 – 2.04 (m, 1H), 1.92 – 1.74 (m, 3H), 1.72 (s, 3H), 1.48 (qt, \(J = 13.2, 3.4\) Hz, 1H), 1.39 – 1.14 (m, 2H).}

\(^{13}\text{C NMR (101 MHz, CDCl}_3\text{) \(\delta\) 169.6, 168.8, 134.0, 131.9, 123.3, 55.1, 49.9, 33.4, 28.6, 25.6, 24.7, 23.4}


**N-((1R,2R)-2-aminocyclohexyl)acetamide (Cas No. 320778-89-0)**

\[
\text{N-}((1R,2R)-2\text{-amidocyclohexyl})\text{isoindoline-1,3-dione (0.360 g, 1.26 mmol) was dissolved in ethanol (3 mL) and hydrazine monohydrate (0.155 mL, approximately 64\% w/w) was added. The reaction mixture was refluxed for 3 hours during which a white precipitate formed. After cooling to r.t. diethyl ether (6 mL) was added, then the suspension was filtered and washed with diethyl ether (20 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (starting from 2\% MeOH/NH}_3 \text{in CH}_2\text{Cl}_2) to provide the product, after removal of solvent under reduced pressure, as a colourless solid (0.107 g, 0.68 mmol, 54\% yield).}
\]

Mp 117–120 °C.

\(^1\text{H NMR (400 MHz, CDCl}_3\text{) \(\delta\) 5.47 – 5.30 (m, 1H), 3.58 – 3.46 (m, 1H), 2.36 (td, \(J = 10.3, 4.0\) Hz, 1H), 2.06 – 1.93 (m, 5H), 1.77 – 1.67 (m, 2H), 1.51 – 1.01 (m, 6H).}

\(^{13}\text{C NMR (101 MHz, CDCl}_3\text{) \(\delta\) 170.4, 56.3, 55.8, 35.9, 32.8, 25.3, 25.2, 23.9.}


**N-((1R,2R)-2-azidocyclohexyl)acetamide**

\[
\text{N-}((1R,2R)-2\text{-amidocyclohexyl})\text{isoindoline-1,3-dione (0.096 g, 0.614 mmol) was dissolved in a suspensuion of K}_2\text{CO}_3 (0.11 g, 0.80 mmol) and CuSO}_4 \times 5\text{H}_2\text{O (0.007 mg, 0.028 mmol) in MeOH (3 mL). Imidazole-1-sulfonyl azide hydrochloride (0.15 g, 0.72 mmol) was added and the mixture stirred at r.t. for 2 hours. The solvent was removed under reduced pressure, then the solid was dissolved in H}_2\text{O (10 mL), acidified with HCl (30 mL, 1 M) and extracted with CH}_2\text{Cl}_2 (3 x}
\]
10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (starting from 3% MeOH/NH₃ in CH₂Cl₂) to provide the product after removal of solvent under reduced pressure as a colourless oil (0.091 g, 0.500 mmol, 81% yield).

Mp 121–123 °C; [α]D²⁰ = 25.4 (c = 0.07, CHCl₃).

IR (KBr tablet) ν: 3280 (w), 2923 (m), 2855 (w), 2100 (w), 1636 (m), 1555 (w), 1458 (w), 1264 (w), 795 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.45 – 5.28 (m, 1H), 3.83 – 3.71 (m, 1H), 3.11 (td, J = 10.6, 4.2 Hz, 1H), 2.14 – 2.02 (m, 2H), 2.01 (s, 3H), 1.86 – 1.76 (m, 1H), 1.76 – 1.66 (m, 1H), 1.53 – 1.12 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 170.0, 64.1, 52.7, 32.3, 30.8, 24.4, 24.3, 23.7.


N-((1R,2R)-2-(1,3-dioxoisindolin-2-yl)cyclohexyl)benzamide (Cas No. 496924-09-5)

2-((1R,2R)-2-aminocyclohexyl)isoindoline-1,3-dione (0.300 g, 1.23 mmol) was dissolved in CH₂Cl₂ (6 mL), triethylamine (0.172 mL, 1.23 mmol) and benzyl chloride (0.143 mL, 1.23 mmol) were added and the reaction mixture was stirred at r.t. for 3 hours. The reaction mixture was diluted with CH₂Cl₂ (10 mL), after which water (10 mL) was added and the phases separated. The aqueous layer was extracted additionally with CH₂Cl₂ (3 x 10 mL) and the combined organic phases were dried over MgSO₄. Filtration and removal of the solvent under reduced pressure provided the product as a colourless solid (0.408 g, 1.17 mmol, 95% yield).

Mp sublimes above 250 °C; [α]D²⁰ = −108.0 (c = 0.25, CHCl₃).

IR (KBr tablet) ν: 3340 (w), 2936 (w), 2859 (w), 1771 (w), 1705 (s), 1644 (s), 1530 (m), 1491 (w), 1394 (m), 1376 (m), 1161 (w), 1093 (w), 1067 (w), 1048 (w), 716 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, J = 5.2, 2.9 Hz, 2H), 7.64 (dd, J = 5.5, 3.0 Hz, 2H), 7.55 – 7.48 (m, 2H), 7.45 – 7.37 (m, 1H), 7.36 – 7.28 (m, 2H), 5.92 (d, J = 9.2 Hz, 1H), 4.82 – 4.59 (m, 1H), 4.07 (ddd, J = 12.3, 10.9, 4.0 Hz, 1H), 2.67 (qd, J = 13.6, 12.9, 4.4 Hz, 1H), 2.32 – 2.20 (m, 1H), 1.99 – 1.79 (m, 3H), 1.63 – 1.49 (m, 1H), 1.46 – 1.24 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 167.2, 134.6, 134.0, 131.8, 131.4, 128.6, 126.8, 123.4, 55.1, 50.5, 33.4, 28.7, 25.7, 24.7.


N-((1R,2R)-2-aminocyclohexyl)benzamide (Cas No. 151434-96-7)

N-((1R,2R)-2-(1,3-dioxoisindolin-2-yl)cyclohexyl)benzamide (0.408 g, 1.17 mmol) was dissolved in ethanol (10 mL) and hydrazine monohydrate (0.146 mL, approximately 64% w/w) was added. The reaction mixture was refluxed for 3 hours and an additional amount of hydrazine monohydrate (0.075 mL, approximately 64 w%) was added. The reaction mixture was refluxed additionally for 5 hours during which a white precipitate formed. After cooling to r.t. the suspension was filtered and washed with diethyl ether (20 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica
gel (starting from 2% MeOH/NH₃ in CH₂Cl₂) to provide the product, after removal of solvent under reduced pressure, as a colourless solid (0.207 g, 0.948 mmol, 81% yield).

Mp 169–173 °C.

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.75 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 6.16 – 5.96 (m, 1H), 3.82 – 3.62 (m, 1H), 2.50 (td, J = 10.2, 3.9 Hz, 1H), 2.23 – 2.08 (m, 1H), 2.07 – 1.96 (m, 1H), 1.83 – 1.69 (m, 2H), 1.53 – 1.13 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 167.9, 134.9, 131.6, 128.7, 127.0, 56.8, 56.0, 35.9, 32.8, 25.3, 25.2.


N-((1R,2R)-2-azidocyclohexyl)benzamide (Cas No. 210566-55-5)

N-((1R,2R)-2-aminocyclohexyl)benzamide (0.207 g, 0.948 mmol) was dissolved in a suspension of K₂CO₃ (0.165 g, 1.19 mmol) and CuSO₄ x 5H₂O (0.007 mg, 0.028 mmol) in MeOH (6 mL). Imidazole-1-sulfonyl azide hydrochloride (0.24 g, 1.15 mmol) was added and the mixture stirred at r.t. for 3 hours. The solvent was removed under reduced pressure, then the solid was dissolved in H₂O (10 mL), acidified with HCl (20 mL, 1 M) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (starting from 3% MeOH/NH₃ in CH₂Cl₂) to provide the product, after removal of solvent under reduced pressure, as a colourless solid (0.227 g, 0.929 mmol, 98% yield).

Mp 146–148 °C; [α]D²⁰ = −79.6 (c = 0.27, CHCl₃).

IR (KBr tablet) ν: 3320 (m), 2935 (m), 2855 (m), 2078 (s), 1636 (s), 1580 (w), 1532 (s), 1490 (w), 1331 (m), 1259 (m), 1236 (m), 1137 (w), 849 (w), 714 (w), 693 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.75 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.38 (m, 2H), 6.10 (d, J = 8.3 Hz, 1H), 3.97 (tdd, J = 10.3, 8.3, 4.1 Hz, 1H), 3.27 (td, J = 10.7, 4.2 Hz, 1H), 2.24 – 2.07 (m, 2H), 1.90 – 1.67 (m, 2H), 1.60 – 1.21 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 167.6, 134.8, 131.7, 128.7, 127.1, 64.0, 53.2, 32.2, 30.9, 24.4, 24.3.


N-((1R,2R)-2-(1,3-dioxoisooindolin-2-yl)cyclohexyl)pivalamide

2-((1R,2R)-2-aminocyclohexyl)isoindoline-1,3-dione (0.30 g, 1.23 mmol) was dissolved in CH₂Cl₂ (8 mL), triethylamine (0.17 mL, 1.23 mmol) and pivaloyl chloride (0.15 mL, 1.23 mmol) were added and the reaction mixture was stirred at r.t. for 3 hours. The reaction mixture was diluted with CH₂Cl₂ (10 mL), after which water (10 mL) was added and the phases separated. The aqueous layer was extracted additionally with CH₂Cl₂ (3 × 10 mL) and the combined organic phases were dried over Na₂SO₄. Filtration and removal of the solvent under reduced pressure provided the product as a colourless solid (0.32 g, 0.974 mmol, 79% yield).

Mp 165–168 °C; [α]D²⁰ = −5.1 (c = 0.42, CHCl₃).
IR (KBr tablet) ν: 3068 (w), 1714 (w), 1573 (w), 1457 (s), 1435 (m), 1252 (w), 1128 (m), 1035 (s), 749 (s), 659 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.75 (m, 2H), 7.74 – 7.61 (m, 2H), 5.40 (d, J = 9.2 Hz, 1H), 4.60 – 4.38 (m, 1H), 4.01 – 3.81 (m, 1H), 3.68 – 3.32 (m, 1H), 2.34 (td, J = 10.3, 3.9 Hz, 1H), 2.08 – 1.87 (m, 2H), 1.81 – 1.65 (m, 2H), 1.39 – 0.98 (m, 15H).

¹³C NMR (101 MHz, CDCl₃) δ 178.9, 56.1, 55.9, 38.9, 35.5, 32.6, 27.8, 25.3, 25.2.


N-((1R,2R)-2-aminocyclohexyl)pivalamide (Cas No. 1587547-24-7)

N-((1R,2R)-2-(1,3-dioxoisindolin-2-yl)cyclohexyl)pivalamide (0.320 g, 0.974 mmol) was dissolved in ethanol (3 mL) and hydrazine monohydrate (0.120 mL, approximately 64% w/w) was added. The reaction mixture was refluxed for 8 hours during which a white precipitate formed. After cooling to r.t. diethyl ether (6 mL) was added, then the suspension was filtered and washed with diethyl ether (20 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (starting from 2% MeOH/NH₃ in CH₂Cl₂) to provide the product, after removal of solvent under reduced pressure, as a yellow oil (0.174 g, 0.877 mmol, 90% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.74 – 5.30 (m, 1H), 3.68 – 3.32 (m, 1H), 2.34 (td, J = 10.3, 3.9 Hz, 1H), 2.08 – 1.87 (m, 2H), 1.81 – 1.65 (m, 2H), 1.39 – 0.98 (m, 15H).

¹³C NMR (101 MHz, CDCl₃) δ 178.9, 56.1, 55.9, 38.9, 35.5, 32.6, 27.8, 25.3, 25.2.

N-((1R,2R)-2-azidocyclohexyl)pivalamide

N-((1R,2R)-2-aminocyclohexyl)pivalamide (0.174 g, 0.877 mmol) was dissolved in a suspension of K₂CO₃ (0.15 g, 1.10 mmol) and CuSO₄ x 5H₂O (0.007 mg, 0.028 mmol) in MeOH (4 mL). Imidazole-1-sulfonyl azide hydrochloride (0.22 g, 1.05 mmol) was added and the mixture stirred at r.t. overnight. The solvent was removed under reduced pressure, then the solid was dissolved in H₂O (10 mL), acidified with HCl (20 mL, 1 M) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (starting from 0% MeOH/NH₃ in CH₂Cl₂) to provide the product after removal of solvent under reduced pressure as a colourless solid (0.189 g, 0.842 mmol, 96% yield).

Mp 115–118 °C; [α]D²⁰ = −18.25 (c = 0.45, CHCl₃).

IR (KBr tablet) ν: 3345 (m), 2941 (m), 2865 (m), 2096 (s), 1643 (s), 1538 (s), 1367 (w), 1314 (m), 1265 (m), 1200 (m), 990 (w), 909 (w), 669 (m) cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 5.56 (d, J = 8.1 Hz, 1H), 3.82 – 3.65 (m, 1H), 3.17 (td, J = 10.5, 4.2 Hz, 1H), 2.11 – 1.92 (m, 2H), 1.85 – 1.65 (m, 2H), 1.51 – 1.23 (m, 4H), 1.20 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 178.3, 64.1, 52.7, 38.9, 32.2, 31.0, 27.7, 24.4, 24.3.

(1R,2S)-2-azido-1,2-diphenylethan-1-ol (Cas No. 74684-65-4)

(1R,2S)-2-amino-1,2-diphenylethan-1-ol (0.199 g, 0.933 mmol) was dissolved in a suspension of K₂CO₃ (0.164 g, 1.19 mmol) and CuSO₄ x 5H₂O (0.007 mg, 0.028 mmol) in MeOH (3.4 mL). Imidazole-1-sulfonyl azide hydrochloride (0.237 g, 1.13 mmol) was added and the mixture stirred at r.t. for 2 hours. The solvent was removed under reduced pressure, then the solid was dissolved in H₂O (5 mL), acidified with HCl (10 mL, 1 M) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (starting from 5% EtOAc in petroleum ether) to provide the product, after removal of solvent under reduced pressure, as a colourless solid (0.172 g, 0.719 mmol, 77% yield).

1H NMR (400 MHz, CDCl₃) δ 7.40 – 7.29 (m, 6H), 7.29 – 7.21 (m, 4H), 4.82 (dd, J = 6.8, 2.9 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 2.16 – 2.04 (m, 1H).

13C NMR (101 MHz, CDCl₃) δ 139.8, 136.1, 128.8, 128.8, 128.5, 128.4, 128.2, 127.2, 77.1, 71.4.

Cis-(1S,2R)-1,2-aminoindanol (1.006 g, 6.71 mmol) was dissolved in a suspension of K₂CO₃ (1.39 g, 10.065 mmol) and CuSO₄ x 5H₂O (0.017 mg, 0.068 mmol) in MeOH (50 mL). Imidazole-1-sulfonyl azide hydrochloride (0.84 g, 4.00 mmol) was added and the mixture stirred at r.t. for 18 hours. The solvent was removed under reduced pressure, then the solid was dissolved in H₂O (20 mL), acidified with HCl (40 mL, 1 M) and extracted with CH₂Cl₂ (5 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (starting from 10% of EtOAc in petroleum ether) to provide the product, after removal of solvent under reduced pressure, as a clear yellow oil (0.876 g, 5.006 mmol, 75% yield).

[α]D²⁰ = 98.9 (c = 0.425, CHCl₃).

IR (KBr tablet) ν: 3406 (br m), 3027 (w), 2921 (m), 2102 (s), 1610 (w), 1478 (m), 1461 (m), 1432 (w), 1321 (s), 1256 (s), 1206 (m), 1091 (s), 1054 (m), 992 (w), 906 (w), 886 (w), 750 (s) cm⁻¹.

1H NMR (400 MHz, CDCl₃) δ 7.40 (dd, J = 7.1, 1.8 Hz, 1H), 7.37 – 7.26 (m, 3H), 4.79 (d, J = 5.3 Hz, 1H), 4.60 (dq, J = 7.8, 6.0 Hz, 1H), 3.17 (dd, J = 15.9, 6.3 Hz, 1H), 2.94 (dd, J = 15.9, 6.0 Hz, 1H), 2.36 (d, J = 7.9 Hz, 1H).

13C NMR (101 MHz, CDCl₃) δ 140.6, 137.7, 129.6, 127.4, 125.7, 125.2, 74.2, 67.9, 39.1.

HRMS (ESI): m/z [M-N₂+H]+ calcld for C₉H₁₀NO: 148.0757; found 148,0760.

Synthesis of tert-butyl (S)-2-(azidomethyl)pyrrolidine-1-carboxylate (Cas No. 168049-26-1)

The N-Boc protected azide was prepared starting from N-Boc-(S)-prolinol, following the literature procedure,⁵ as a yellow oil (1.984 g, in 70 % total yield).

[α]D²⁰ = −50.0 (c = 0.535, CHCl₃).

IR (KBr tablet) ν: 3068 (w), 2977 (w), 2102 (m), 1692 (s), 1573 (w), 1457 (s), 1435 (m), 1393 (s), 1252 (w), 1169 (m), 1128 (s), 1035 (s), 941 (w), 749 (s), 659 (m) cm⁻¹.
\[^{1}\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}, for a mixture of two conformers) \(\delta\) 4.02 – 3.81 (m, 1H), 3.68 – 3.23 (m, 4H), 2.07 – 1.76 (m, 4H), 1.47 (s, 9H).

\[^{13}\text{C NMR}\] (101 MHz, CDCl\textsubscript{3}, for a mixture of two conformers) \(\delta\) 154.5, 154.2, 79.9, 79.6, 56.5, 53.8, 52.7, 47.1, 46.6, 29.5, 28.6, 28.5, 23.9, 23.0.

HRMS (ESI): \(m/z\) [M+Na\textsuperscript{+}] calcd for C\textsubscript{10}H\textsubscript{18}N\textsubscript{4}O\textsubscript{2}Na: 249.1322; found 249.1324.

The azide was prepared starting from (-)-menthol, following the literature procedure,\textsuperscript{7} as a colourless oil (1.19 g, 51% yield).

\([\alpha]D^{25}\) = 105.4 (c = 0.46, CHCl\textsubscript{3}).

\[^{1}\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.00 – 3.95 (m, 1H), 2.01 (dq, \(J = 14.0, 3.4\) Hz, 1H), 1.78 – 1.61 (m, 3H), 1.51 (ddt, \(J = 13.3, 9.0, 6.3\) Hz, 1H), 1.27 – 1.10 (m, 2H), 0.97 – 0.80 (m – two d on top of the m, 11H).

\[^{13}\text{C NMR}\] (101 MHz, CDCl\textsubscript{3}) \(\delta\) 60.7, 47.5, 39.1, 35.0, 29.6, 26.7, 25.1, 22.3, 21.1, 20.8.

**Synthesis of N-\((15,2S,4R)-2-azido-1-isopropyl-4-methylcyclohexane\) (Cas No. 107535-12-6)**

\(\text{cis-}(15,2R)-1\text{-amino-2-indanol (0.180 g, 1.21 mmol) was dissolved in CH}_2\text{Cl}_2 (6 mL), triethylamine (0.673 mL, 4.84 mmol) and DMAP (0.015 g, 0.121 mmol) were added under argon atmosphere. The reaction mixture was cooled to 0 °C and trifluoroacetic anhydride (0.168 mL, 1.21 mmol) was added dropwise. Then allowed to warm and stirred at r.t. for 2 hours. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL), after which an aqueous solution of saturated NaHCO\(_3\) (10 mL) was added and the phases separated. The aqueous phase was extracted additionally with CH\(_2\)Cl\(_2\) (4 x 10 mL) and the combined organic phases were dried over Na\(_2\)SO\(_4\). Filtration and removal of the solvent under reduced pressure provided the crude product which was purified by column chromatography on silica gel (starting from 20% of EtOAc in petroleum ether) to provide the product as colourless crystals (0.274 g, 1.12 mmol, 93% yield).

Mp 153-154 °C; \([\alpha]D^{20}\) = 143.4 (c = 0.26, CHCl\(_3\)).

IR (KBr tablet) \(\nu\): 3417 (br m), 3271 (s), 3089 (w), 2941 (w), 1698 (s), 1555 (m), 1461 (w), 1340 (w), 1308 (w), 1188 (s), 1094 (m), 1054 (m), 958 (w), 935 (w), 758 (m), 723 (w) cm\(^{-1}\).

\[^{1}\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.34 – 7.26 (m, 4H), 7.12 (s, 1H), 5.41 (dd, \(J = 8.4, 5.1\) Hz, 1H), 4.70 (qd, \(J = 5.2, 1.9\) Hz, 1H), 3.25 (dd, \(J = 16.8, 5.0\) Hz, 1H), 2.99 (dd, \(J = 16.7, 1.8\) Hz, 1H), 2.02 – 1.93 (m, 1H).
\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 157.7 (q, \(J = 37.4\) Hz), 139.5, 138.9, 128.9, 127.6, 125.5, 124.6, 116.0 (q, \(J = 287.9\) Hz), 73.0, 57.5, 40.2.

HRMS (ESI): \(m/z\) [M + H]\textsuperscript{+} calcd for C\textsubscript{11}H\textsubscript{15}F\textsubscript{3}NO\textsubscript{2}: 246.0736; found 246.0748.

\((1S,2R)-1\{2,2,2\text{-trifluoroacetamido}\}-2,3\text{-dihydro-1H-inden-2-yl methanesulfonate}\)

Acetamide (0.266 g, 1.09 mmol) and triethylamine (0.453 mL, 3.26 mmol) were dissolved in CH\textsubscript{3}Cl\textsubscript{2} (8 mL) under argon atmosphere, then the reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (0.127 mL, 1.63 mmol) was added dropwise and the reaction mixture was allowed to warm up to r.t. and stirred for 2 hours. The reaction mixture was diluted with CH\textsubscript{3}Cl\textsubscript{2} (10 mL), after which water (10 mL) was added and the phases separated. The aqueous phase was extracted additionally with CH\textsubscript{3}Cl\textsubscript{2} (3 x 10 mL) and the combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4}. Filtration and removal of the solvent under reduced pressure provided the crude product which was purified by column chromatography on silica gel (starting from 2% of EtOAc in CH\textsubscript{2}Cl\textsubscript{2}) to provide the product as a white solid (0.343 g, 1.06 mmol, 98% yield).

Mp 203-204 °C; [\(\alpha\)]\textsubscript{D}\textsuperscript{20} = -42.1 (c = 0.09, CHCl\textsubscript{3}).

IR (KBr tablet) v: 3291 (s), 3096 (w), 2941 (w), 1715 (s), 1557 (s), 1462 (m), 1431 (w), 1354 (s), 1312 (w), 1269 (m), 1243 (w), 1186 (s), 1152 (s), 932 (w), 881 (w), 736 (w), 707 (w), 683 (w), 532 (m) cm\textsuperscript{-1}.

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.38 – 7.27 (m, 4H), 6.84 (d, \(J = 8.7\) Hz, 1H), 5.66 (dd, \(J = 8.8, 5.1\) Hz, 1H), 5.54 (ddd, \(J = 5.0, 4.3, 2.3\) Hz, 1H), 3.42 – 3.27 (m, 2H), 3.02 (s, 3H).

HRMS (ESI): \(m/z\) [M+H]\textsuperscript{+} calcd for C\textsubscript{12}H\textsubscript{15}F\textsubscript{3}NO\textsubscript{2}: 324.0512; found 324.0525.

\(N\{1S,2S\}-2\text{-azido-2,3\text{-dihydro-1H-inden-1-yl\}}\}2,2,2\text{-trifluoroacetamide}\)

Mesylate (0.340 g, 1.05 mmol) was dissolved in DMF (3 mL) and sodium azide (0.104 g, 1.59 mmol) was added. The reaction mixture was stirred at 100 °C overnight. After cooling to r.t., water (6 mL) was added, the aqueous layer was extracted with EtOAc (4 x 10 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. The crude product was filtrated, concentrated and purified by column chromatography on silica gel (starting from 10% of EtOAc in petroleum ether) to provide the product as colourless crystals (0.245 g, 0.907 mmol, 86% yield).

Mp 155-156 °C; [\(\alpha\)]\textsubscript{D}\textsuperscript{20} = 32.25 (c = 0.16, CHCl\textsubscript{3}).

IR (KBr tablet) v: 3281 (s), 3103 (w), 2105 (s), 1705 (s), 1559 (s), 1483 (w), 1375 (w), 1352 (w), 1311 (w), 1269 (m), 1186 (s), 1152 (s), 984 (w), 932 (w), 753 (m), 707 (m) cm\textsuperscript{-1}.

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.40 – 7.21 (m, 4H), 6.45 (s, 1H), 5.40 (dd, \(J = 8.0, 6.2\) Hz, 1H), 4.16 (q, \(J = 6.8\) Hz, 1H), 3.37 (dd, \(J = 16.1, 7.4\) Hz, 1H), 3.00 (dd, \(J = 16.2, 6.7\) Hz, 1H).

\(^13\)C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 157.3 (q, \(J = 37.5\) Hz), 139.6, 137.6, 129.7, 128.1, 125.3, 124.1, 115.7 (q, \(J = 288.0\) Hz), 67.5, 60.4, 36.2.

HRMS (ESI): \(m/z\) [M-N\textsubscript{2}+H]\textsuperscript{+} calcd for C\textsubscript{12}H\textsubscript{16}F\textsubscript{3}N\textsubscript{2}O: 243.0740; found 243.0737.
Synthesis of 1-[[[(1R,2R)-1-amino-2,3-dihydro-1H-inden-2-yl]oxy]-5-(trifluoromethyl)phenyl]-3-(3,5-bis(trifluoromethyl)phenyl)urea 12

The urea 12 was prepared following the literature procedure.8

tert-buty1 ((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamate (Cas No. 766556-66-5)

Following the literature procedure the carbamate was obtained as a colourless solid (8.14 g, 32.9 mmol, 97%).

1H NMR (400 MHz, CDCl3) δ 7.29 – 7.17 (m, 4H), 5.04 (bs, 1H), 4.91 (t, J = 6.0 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.26 (bs, 1H), 3.29 (dd, J = 15.7, 7.7 Hz, 1H), 2.92 (dd, J = 15.8, 8.2 Hz, 1H), 1.50 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 157.5, 140.2, 139.2, 128.5, 127.2, 125.2, 122.9, 82.3, 80.6, 64.1, 38.4, 28.4.

tert-buty1 ((1R,2R)-2-(2-nitro-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1H-inden-1-yl)carbamate (Cas No. 1402743-80-9)

The compound was obtained as an off-white solid (15.1 g), which was used subsequently in the next reaction step.

1H NMR (400 MHz, CDCl3) δ 8.06 (bs, 1H), 7.84 (t, J = 8.8 Hz, 2H), 7.35 – 7.24 (m, 4H), 5.21 – 5.12 (m, 2H), 4.72 (d, J = 6.0 Hz, 1H), 3.54 (dd, J = 16.8, 6.1 Hz, 1H), 3.18 (d, J = 16.8 Hz, 1H), 1.46 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 155.2, 153.7, 140.2, 140.0, 139.3, 131.0 – 130.8 (m), 129.3, 127.7, 125.2, 124.9, 124.5, 123.40 – 122.95 (m, 2C overlapped), 123.13 (q, J = 271.3 Hz), 117.0, 85.1, 80.3, 61.0, 37.1, 28.3.
**tert-butyl (1R,2R)-2-(2-amino-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1H-inden-1-yl)carbamate 11 (Cas No. 1402743-81-0)**

Compound 11 was obtained as an off-white solid (10.8 g, 26.5 mmol, 79%).

\[
egin{align*}
\text{Mp} & = 182-183 \, ^\circ C; \, [\alpha]_D^{20} = -99.9 \, (c = 0.70, \text{CHCl}_3).
\end{align*}
\]

\[
\begin{align*}
{\text{H}} \text{NMR} (400 \, \text{MHz}, \text{CDCl}_3) \delta & = 7.40 - 7.21 \, (m, 4H), 7.07 - 6.94 \, (m, 2H), 6.92 \, (s, 1H), 5.48 - 5.23 \, (m, 1H), 4.87 - 4.74 \, (m, 2H), 4.02 \, (bs, 2H), 3.51 \, (dd, J = 16.2, 6.7 \, Hz, 1H), 3.06 \, (dd, J = 16.2, 5.6 \, Hz, 1H), 1.47 \, (s, 9H).
\end{align*}
\]

\[
\begin{align*}
{\text{C}} \text{NMR} (101 \, \text{MHz}, \text{CDCl}_3) \delta & = 155.6, 147.8, 139.7, 139.4, 137.6, 128.8, 127.6, 125.2, 124.5 \, (q, J = 271.5 \, Hz), 124.3, 123.9 \, (q, J = 32.3 \, Hz), 115.3 - 115.0 \, (m), 112.7, 111.6 - 111.3 \, (m), 85.8, 80.0, 61.3, 37.0, 28.4.
\end{align*}
\]

1-(2-((1R,2R)-1-amino-2,3-dihydro-1H-inden-2-yl)oxy)-5-(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea 12 (Cas No. 1402743-82-1)

A solution of compound 11 (6.98 g, 17.1 mmol) in THF (21 mL) was cooled to 0 °C and 3,5-bis(trifluoromethylphenyl) isocyanate (4.57 g, 17.9 mmol) was added dropwise. The reaction mixture was allowed to warm up to r.t. and stirred for 2.5 h. Then the reaction mixture was cooled to 0 °C, TFA (34 mL, 444 mmol) was added and stirred for 16 hours at r.t. The reaction mixture was concentrated, a saturated solution of NaHCO$_3$ (170 mL) was added and extracted with CH$_2$Cl$_2$ (4 × 100 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and the solvent was removed in vacuo. The crude solid product was triturated with CHCl$_3$ and hexane, filtered and washed with hexane to give the urea 13 (8.85 g, 15.7 mmol, 92 %) as an off-white solid.

\[
\begin{align*}
\text{Mp} & = 202-203 \, ^\circ C; \, [\alpha]_D^{20} = -78.1 \, (c = 0.51, \text{MeOH}).
\end{align*}
\]

\[
\begin{align*}
{\text{H}} \text{NMR} (400 \, \text{MHz}, [\text{D}_6] \text{DMSO}) \delta & = 10.16 \, (s, 1H), 8.52 \, (d, J = 2.2 \, Hz, 1H), 8.40 \, (bs, 1H), 8.08 \, (s, 2H), 7.67 \, (s, 1H), 7.51 - 7.33 \, (m, 3H), 7.31 - 7.18 \, (m, 3H), 4.89 \, (dt, J = 7.1, 5.3 \, Hz, 1H), 4.52 \, (d, J = 4.7 \, Hz, 1H), 3.60 \, (dd, J = 16.4, 7.1 \, Hz, 1H), 3.35 \, (s, 2H), 2.93 \, (dd, J = 16.3, 5.5 \, Hz, 1H).
\end{align*}
\]

\[
\begin{align*}
{\text{C}} \text{NMR} (101 \, \text{MHz}, [\text{D}_6] \text{DMSO}) \delta & = 152.1, 149.3, 144.4, 141.4, 138.6, 130.8 \, (q, J = 32.6 \, Hz), 129.1, 127.6, 127.0, 124.6, 124.5 \, (q, J = 271.5 \, Hz), 124.2, 123.2 \, (q, J = 272.3 \, Hz), 121.2 \, (q, J = 31.8 \, Hz), 119.8 - 119.5 \, (m), 118.0 - 117.7 \, (m), 115.1 - 114.9 \, (m), 114.8 - 114.6 \, (m), 113.3, 88.1, 62.2, 36.2.
\end{align*}
\]
II) $^1$H NMR and $^{13}$C NMR spectra

Figure S1. $^1$H NMR spectrum of N-((1R,2R)-2-azidocyclohexyl)acetamide (CDCl$_3$, 400 MHz).

Figure S2. $^{13}$C NMR spectrum of N-((1R,2R)-2-azidocyclohexyl)acetamide (CDCl$_3$, 101 MHz).
Figure S3. $^1$H NMR spectrum of N-((1R,2R)-2-azidocyclohexyl)benzamide (CDCl$_3$, 400 MHz).

Figure S4. $^{13}$C NMR spectrum of N-((1R,2R)-2-azidocyclohexyl)benzamide (CDCl$_3$, 101 MHz).
Figure S5. $^1$H NMR spectrum of $N$-((1$R$,2$R$)-2-azidocyclohexyl)pivalamide (CDCl$_3$, 400 MHz).

Figure S6. $^{13}$C NMR spectrum of $N$-((1$R$,2$R$)-2-azidocyclohexyl)pivalamide (CDCl$_3$, 101 MHz).
Figure S7. $^1$H NMR spectrum of (1R,2S)-2-azido-1,2-diphenylethan-1-ol (CDCl$_3$, 400 MHz).

Figure S8. $^{13}$C NMR spectrum of (1R,2S)-2-azido-1,2-diphenylethan-1-ol (CDCl$_3$, 101 MHz).
Figure S9. $^1$H NMR spectrum of (15,2R)-1-azido-2,3-dihydro-1H-inden-2-ol (CDCl$_3$, 400 MHz).

Figure S10. $^{13}$C NMR spectrum of (15,2R)-1-azido-2,3-dihydro-1H-inden-2-ol (CDCl$_3$, 101 MHz).
Figure S11. $^1$H NMR spectrum of tert-butyl (S)-2-(azidomethyl)pyrrolidine-1-carboxylate (CDCl$_3$, 400 MHz).

Figure S12. $^{13}$C NMR spectrum of tert-butyl (S)-2-(azidomethyl)pyrrolidine-1-carboxylate (CDCl$_3$, 101 MHz).
Figure S13. $^1$H NMR spectrum of (1S,2S,4R)-2-azido-1-isopropyl-4-methylcyclohexane (CDCl$_3$, 400 MHz).

Figure S14. $^{13}$C NMR spectrum of (1S,2S,4R)-2-azido-1-isopropyl-4-methylcyclohexane (CDCl$_3$, 101 MHz).
**Figure S15.** $^1$H NMR spectrum of $N$-((1S,2S)-2-azido-2,3-dihydro-1H-inden-1-yl)-2,2,2-trifluoroacetamide (CDCl$_3$, 400 MHz).

**Figure S16.** $^{13}$C NMR spectrum of $N$-((1S,2S)-2-azido-2,3-dihydro-1H-inden-1-yl)-2,2,2-trifluoroacetamide (CDCl$_3$, 101 MHz).
Figure S17. $^1$H NMR spectrum of 4a (CDCl$_3$, 400 MHz).

Figure S18. $^{13}$C NMR spectrum of 4a (CDCl$_3$, 101 MHz).
Figure S19. $^1$H NMR spectrum of 4a-OTf (CD$_3$OD, 400 MHz).

Figure S20. $^{13}$C NMR spectrum of 4a-OTf (CD$_3$OD, 101 MHz).
**Figure S21.** $^1$H NMR spectrum of 4b (CDCl$_3$, 400 MHz).

**Figure S22.** $^{13}$C NMR spectrum of 4b (CDCl$_3$, 101 MHz).
Figure S23. $^1$H NMR spectrum of 4b-OTf (CD$_3$OD, 400 MHz).

Figure S24. $^{13}$C NMR spectrum of 4b-OTf (CD$_3$OD, 101 MHz).
Figure S25. $^1$H NMR spectrum of 4c (CDCl$_3$, 400 MHz).

Figure S26. $^{13}$C NMR spectrum of 4c (CDCl$_3$, 101 MHz).
Figure S27. $^1$H NMR spectrum of 4c-OTf (CDCl$_3$, 400 MHz).

Figure S28. $^{13}$C NMR spectrum of 4c-OTf (CDCl$_3$, 101 MHz).
Figure S29. $^1$H NMR spectrum of 5 (CDCl$_3$, 400 MHz).

Figure S30. $^{13}$C NMR spectrum of 5 (CDCl$_3$, 101 MHz).
Figure S31. $^1$H NMR spectrum of 5-OTf (CD$_3$OD, 400 MHz).

Figure S32. $^{13}$C NMR spectrum of 5-OTf (CD$_3$OD, 101 MHz).
Figure S33. $^1$H NMR spectrum of 6 (CDCl$_3$, 400 MHz).

Figure S34. $^{13}$C NMR spectrum of 6 (CDCl$_3$, 101 MHz).
Figure S35. $^1$H NMR spectrum of 6-OTf (CD$_3$OD, 400 MHz).

Figure S36. $^{13}$C NMR spectrum of 6-OTf (CD$_3$OD, 101 MHz).
Figure S37. $^1$H NMR spectrum of 7 (CDCl$_3$, 400 MHz).

Figure S38. $^{13}$C NMR spectrum of 7 (CDCl$_3$, 101 MHz).
Figure S39. $^1$H NMR spectrum of 8 (CDCl$_3$, 400 MHz).

Figure S40. $^{13}$C NMR spectrum of 8 (CDCl$_3$, 101 MHz).
Figure S41. $^1$H NMR spectrum of 9 ([D$_6$]DMSO, 400 MHz).

Figure S42. $^{13}$C NMR spectrum of 9 ([D$_6$]DMSO, 101 MHz).
Figure S43. $^1$H NMR spectrum of 9-OTf (CD$_3$OD, 400 MHz).

Figure S44. $^{13}$C NMR spectrum of 9-OTf (CD$_3$OD, 101 MHz).
Figure S45. $^1$H NMR spectrum of 10 ([D$_6$]Acetone, 400 MHz).

Figure S46. $^{13}$C NMR spectrum of 10 ([D$_6$]Acetone, 101 MHz).
Figure S47. $^1$H NMR spectrum of 10-OTf ([D$_6$]Acetone, 400 MHz).

Figure S48. $^{13}$C NMR spectrum of 10-OTf ([D$_6$]Acetone, 101 MHz).
Figure S49. $^1$H NMR spectrum of 11 (CDCl$_3$, 400 MHz).

Figure S50. $^{13}$C NMR spectrum of 11 (CDCl$_3$, 101 MHz).
Figure S51. $^1$H NMR spectrum of 12 ([D$_6$]DMSO, 400 MHz).

Figure S52. $^{13}$C NMR spectrum of 12 ([D$_6$]DMSO, 101 MHz).
Figure S5. $^1$H NMR spectrum of 13 ([D$_6$]DMSO, 400 MHz).

Figure S54. $^{13}$C NMR spectrum of 13 ([D$_6$]DMSO, 101 MHz).
Figure S55. $^1$H NMR spectrum of 14 ([D$_6$]DMSO, 400 MHz).

Figure S56. $^{13}$C NMR spectrum of 14 ([D$_6$]DMSO, 101 MHz).
Figure S57. $^1$H NMR spectrum of 14-OTf (CD$_3$OD, 400 MHz).

Figure S58. $^{13}$C NMR spectrum of 14-OTf (CD$_3$OD, 101 MHz).
III) Crystallographic details

Single crystal X-ray diffraction data was collected at 123 K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 941 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-Kα radiation (1.54178 Å) from a MicroMax™-003 sealed tube microfocus X-ray source. The strategy of data collections was calculated using Rigaku CollectionStrategy. Data was collected with ω-scans. CrysAlisPro was used for data reduction and empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm. The structures were solved using SHELXT and refined by full-matrix least-squares method against F² with SHELXL-2014 through OLEX2 program package. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen atoms attached to carbon atoms were treated as riding atoms, using isotropic displacement parameters Uiso(H) = 1.2Uiso(C) for CH and CH₂, Uiso(H) = 1.5Uiso(C) for CH₃. The hydrogen atom of the amide group of 4b-OTf was refined freely. The figures were drawn using the programs Mercury CSD 3.8 and POV-Ray 3.7. The crystallographic data is deposited with the Cambridge Crystallographic Data Centre (CCDC 1885328–1885329) and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic details for 4b-OTf (CCDC 1885328)

Single crystals were obtained by slow cooling of a saturated solution of 4b-OTf in dichloromethane. The crystals were uniform, small colorless blocks.

C₂₃H₂₄F₃IN₄O₄S, M = 636.42 g/mol, triclinic, P1, a = 7.0898(2) Å, b = 9.7861(5) Å, c = 9.9324(4) Å, α = 85.560(4)°, β = 83.909(3)°, γ = 71.438(4)°, V = 648.89(5) Å³, Z = 1, Cu-Kα radiation (λ = 1.54184 Å) at T = 123.0 K, μ(Cu-Kα) = 10.966 mm⁻¹, Dcalc = 1.629 g/cm³, 11970 reflections measured (8.964° ≤ 2θ ≤ 134.196°), of which 4187 unique (4189 with I > 2σ(I)), Rint = 0.0217, R₁[F² > 2σ(F²)] = 0.0194, wR² (all data) = 0.0498, S = 1.04, Flack x = -0.007(4); absolute structure determined by anomalous diffraction effects. The absolute configuration of the compound was determined to be (R,R).

Figure S59. The crystal structure of 4b-OTf. Atomic displacement ellipsoids are drawn at 50% probability level.
Crystallographic details for 8 (CCDC 1885329)

Single crystals were obtained by slow evaporation of a solution of 8 in a 1:1 mixture of CCl₄ and CHCl₃. The crystals were small colorless blocks. Compound 8 crystallized with two moieties in the asymmetric unit and eight molecules in the unit cell. The crystal exhibited twinning by pseudo-merohedry. The twin law (−100 001 001 010), a four-fold rotation around the crystallographic a-axis plus a two-fold rotation around the b-axis, was found using the TwinRotMat tool of PLATON and applied in the refinement. The fraction of the minor twin component refined to 0.159(3). The disordered trifluoromethyl groups were refined with two disorder components per site. The s.o.f. of the relative occupancies were refined freely, resulting in 0.35(4)/0.65(4) and 0.20(7)/0.80(7) for the two disordered CF₃ groups. The geometry of the disordered CF₃ groups was restrained (SADI, SIMU). Further RIGU restraints were applied to the anisotropic displacement parameters of the structure.

C₂₀H₂₂F₆IN₃, Mₚ =545.30 g/mol, orthorhombic, P2₁2₁2₁, a = 14.1110(4) Å, b = 17.6127(5) Å, c = 17.7395(5) Å, V = 4408.8(2) Å³, Z = 8, Cu-Kα radiation (λ = 1.54184 Å) at T = 123.0 K, μ(Cu-Kα) = 11.979 mm⁻¹, Dcalc = 1.643 g/cm³, 49327 reflections measured (4.982° ≤ 2θ ≤ 135.08°), of which 7881 unique (7610 with I > 2σ(I)), Rint = 0.0821, R1([F² > 2σ(F²)]) = 0.0751, wR2 (all data) = 0.2280, S = 1.06, Flack x = 0.016(4); absolute configuration determined by Parsons’ method using 3188 quotients [(|I|−|I|)/(|I|+|I|)]. The absolute configuration of the compound was determined to be (9S, 13R, 16S) as shown on Figure 2.

Figure S60. The crystal structure of 8. Atomic displacement ellipsoids are drawn at 50% probability level.
IV) References


