Enantioselectively functionalised phenytoin derivatives by diastereoselective intramolecular arylation of lithiated α-amino nitriles

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Supporting Information

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Reactions requiring anhydrous conditions and inert atmosphere were carried out under dry nitrogen in flame-dried apparatus. Air- and moisture-sensitive solvents and reagents were transferred via plastic syringe into the reaction vessels through rubber septa. Reactions carried out in a microwave reactor were completed on a Biotage Initiator+. All reagents were bought from chemical suppliers and used without further purification (unless otherwise stated). Anhydrous THF, Et$_2$O and CH$_2$Cl$_2$ were obtained from a purification column composed of activated alumina (A-2).[1] CH$_3$CN, MeOH and EtOH were purchased from Acros as extra dry solvent over 3Å molecular sieves. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) and 2,2,6,6-tetramethylpiperidine (HTMP) were distilled under reduced pressure from CaH$_2$ and stored under nitrogen over 3Å molecular sieves in a Young’s tube. n-Butyllithium (n-BuLi) was used as a solution in hexanes (2.5 M from Sigma-Aldrich) and sec-butyllithium (sec-BuLi) was used as a solution in cyclohexane (1.5 M from Sigma-Aldrich). Both organolithium reagents were titrated prior to use against N-benzylbenzamide.[2] Lithium diisopropylamide (LDA) was used as a solution in THF/heptane/ethylbenzene (2.0 M from Sigma-Aldrich). Lithium bis(trimethylsilyl)amide (LiHMDS) and potassium bis(trimethylsilyl)amide (KHMD) were used as a solution in THF (1.0 M from Sigma-Aldrich). Et$_3$N and 2,6-lutidine were stored over KOH. Potassium iodide (KI) was dried in a vacuum oven (T = 80 °C) prior to use.

Thin layer chromatography (TLC) was performed using commercially available aluminium backed silica plates (0.2 mm, 60 F$_{254}$). Visualisation was done under UV light (254 nm), or by staining with phosphomolybdic acid, ‘Seebach’ dip or potassium permanganate.

Flash chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elutions on pre-packed silica gel Biotage® SNAP Ultra/ZIP Sphere columns.

Melting points were measured on a Stuart Scientific melting point SMP 10 apparatus and are uncorrected.

FT-IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer, using a Universal ATR sampling accessory. Only strong and relevant absorptions are reported.

$^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded on Jeol ECS (400 MHz), Varian VNMR (400 MHz or 500 MHz) or Bruker Ultrashield (400 MHz) spectrometers. Chemical shifts (δ$_{\text{H}},$ δ$_{\text{C}},$ and δ$_{\text{F}}$) are quoted in parts per million (ppm) and referenced to the appropriate NMR residual solvent peak(s). For CDCl$_3$ (δ$_{\text{H}}$: 7.26 ppm; δ$_{\text{C}}$: 77.16 ppm), CD$_2$Cl$_2$ (δ$_{\text{H}}$: 5.32 ppm; δ$_{\text{C}}$: 54.00 ppm) and CD$_3$OD (δ$_{\text{H}}$: 3.31 ppm; δ$_{\text{C}}$: 49.00 ppm). 2D-NMR experiments COSY, HSQC and HMBC were used where necessary to assign NMR spectra. Coupling constants (J) are quoted in Hertz (Hz).

High resolution mass spectra were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI) with only molecular ions [M+H]$^+$ and [M+Na]$^+$ reported.

Optical rotations ([α]$_D^\text{c}$) were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter where c is given in g/100 mL.
**Experimental Procedures and Characterisation Data**

**General Procedure 1:** Strecker synthesis of N-alkyl amino nitriles from chiral primary amines and aromatic aldehydes.

![Chemical Reaction](attachment:reaction.png)

The amine (1.0 equiv) was added to a solution of the aldehyde (1.1 equiv) in MeOH or EtOH (0.2 – 1.0 M). After stirring for 15 min at room temperature, TMSCN (1.2 eq.) was added dropwise and the reaction mixture was stirred for 16 h at room temperature (progress monitored by TLC) or for 2 h at 80 °C. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

*Note: all the apparatus that stayed in contact with TMSCN was quenched with bleach.*

**General Procedure 2:** O-silylation of (1R,2R)-aminocyclohexanol-derived amino nitriles.

![Chemical Reaction](attachment:reaction2.png)

2,6-Lutidine (1.5 equiv) was added to a solution of the amino nitrile (1.0 equiv) in anhydrous CH₂Cl₂ (0.2 M). Upon cooling to −78 °C and under a nitrogen atmosphere, tert-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf, 1.2 equiv) was added dropwise to the solution. After stirring for 5 min, the reaction mixture was warmed to room temperature and left to stir for 4 h. The reaction mixture was quenched by addition of NaHCO₃ (aq., sat.). The organic phase was washed with H₂O, brine, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.
**General Procedure 3:** Synthesis of \( N' \)-aryl ureido nitriles from \( N \)-alkyl amino nitriles

**Step 1:** Triphosgene (0.4 equiv) was dissolved in dry \( \text{CH}_2\text{Cl}_2 \) (0.4 M). The solution was cooled to \(-78^\circ\text{C}\). 2,6-lutidine (1.2 equiv) was added dropwise and the reaction mixture was left to stir for 10 min. The \( \text{N} \)-alkyl amino nitrile was added dropwise as a solution in \( \text{CH}_2\text{Cl}_2 \). The mixture was warmed to room temperature and left to stir for 2 h. The reaction was quenched by addition of \( \text{HCl} \) (1 M, aq.), washed with \( \text{HCl} \) (1 M, aq.), \( \text{NaHCO}_3 \) (sat. aq.), brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered and the solvent was removed under reduced pressure. The crude product was used without further purification unless otherwise stated.

**Step 2:** 2,6-lutidine (1.1 equiv) and the corresponding \( \text{N} \)-methylaniline (1.0–2.0 equiv) were added to a solution of the carbamoyl chloride (1.0 equiv) in dry \( \text{CH}_3\text{CN} \) (0.4 M). The reaction mixture was refluxed for 24 h (progress monitored by TLC). Alternatively, the urea coupling was also performed in the presence of dry potassium iodide (1.2 equiv) at 110 °C in a microwave reactor for 2-4 h. The solvent was removed under reduced pressure and the resulting residue was partitioned between \( \text{EtOAc} \) and \( \text{HCl} \) (1 M, aq.). The aqueous phase was further extracted (x2) in \( \text{EtOAc} \) and the combined organic phase was washed with \( \text{NaHCO}_3 \) (sat. aq.), brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

**General Procedure 4:** Synthesis of 5,5-diaryl-4-iminohydantoins from \( N' \)-aryl ureido nitriles

In a flame-dried round-bottom flask, the \( N' \)-aryl ureido nitrile (1.0 equiv) was dissolved in anhydrous \( \text{THF} \) (0.1 M) under a nitrogen atmosphere. The mixture was cooled to \(-78^\circ\text{C}\) and \( \text{LDA} \) (2-3 equiv, 2.0 M in \( \text{THF/heptane/ethylbenzene} \)) was added dropwise. The reaction mixture was stirred for 10 minutes at \(-78^\circ\text{C}\) before leaving it to warm to room temperature stirring for 3 h (Method A). Alternatively, the reaction was carried out in the presence of anhydrous DMPU (10% v/v; pre-mixed with the substrate in \( \text{THF} \) at room temperature before cooling to \(-78^\circ\text{C}\) and adding the \( \text{LDA} \)) heating to +40 °C stirring for 20 h (Method B). The reaction mixture was quenched at room temperature by addition of \( \text{NH}_4\text{Cl} \) (sat. aq.) and then partitioned between \( \text{H}_2\text{O} \) and \( \text{EtOAc} \). The aqueous layer was
further extracted (x2) in EtOAc. The combined organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.
Following the general procedure 1, (R)-1-(4-methoxyphenyl)ethylamine (3.70 mL, 24.55 mmol) was reacted with 3-furaldehyde (2.10 mL, 24.55 mmol) and TMSCN (3.80 mL, 29.46 mmol) in EtOH (61 mL) at 80 °C for 2 h. The crude product (80:20 dr by 1H-NMR) was purified by flash column chromatography (SiO2, n-Hex to n-Hex:Et2O 75:25) to afford (R)-2-(furan-3-yl)-2-((1-(4-methoxyphenyl)ethyl)amino)acetonitrile (5.07 g, 80%, 80:20 dr; relative stereochemistry undetermined). Major diast.: yellow solid; m.p. = 84 – 86 °C; Rf 0.45 (SiO2; n-Hex:EtOAc 70:30); IR (neat, cm−1): νmax = 3320, 2836, 1511, 1241, 1022, 600; 1H NMR (400 MHz, CDCl3): δH = 7.57 (d, J=0.6 Hz, 1 H), 7.42 (t, J=1.7 Hz, 1 H), 7.35 (d, J=8.6 Hz, 2 H), 6.92 (d, J=8.7 Hz, 2 H), 6.46 (d, J=1.0 Hz, 1 H), 4.28 (br. s., 1 H), 4.15 (q, J=6.5 Hz, 1 H), 3.82 (s, 3 H), 1.41 ppm (d, J=6.5 Hz, 3 H); HRMS (ESI+): m/z calcd for C18H17N2O2 [M+H]+ 257.1285, found 257.1292. Minor diast.: brown oil; Rf 0.50 (SiO2; n-Hex:EtOAc 70:30); IR (neat, cm−1): νmax = 3321, 2836, 1611, 1512, 1244, 601; 1H NMR (400 MHz, CDCl3): δH = 7.52 (s, 1 H), 7.44 (t, J=1.6 Hz, 1 H), 7.29 (d, J=8.7 Hz, 2 H), 6.89 (d, J=8.7 Hz, 2 H), 6.50 (s, 1 H), 4.66 (s, 1 H), 4.00 (q, J=6.5 Hz, 1 H), 3.82 (s, 3 H), 1.39 ppm (d, J=6.5 Hz, 3 H); HRMS (ESI+): m/z calcd for C18H17N2O2 [M+H]+ 257.1285, found 257.1288.

Following a similar method to general procedure 3 (step 1), the N-alkyl amino nitrile (2.00 g, 7.41 mmol; 80:20 dr) was reacted with triphosgene (0.88 g, 2.96 mmol) and pyridine (0.72 mL, 8.89 mmol) in dry CH2Cl2 (37 mL). The crude product was purified by flash column chromatography (SiO2, n-Hex:Et2O 50:50) to afford the corresponding carbamoyl chloride (2.36 g, 99%; 80:20 dr) as a yellow oil. Rf 0.40 (SiO2; n-Hex: Et2O 50:50); 1H NMR (500 MHz, CDCl3) (mixture of diastereoisomers A:B in a 8:0.2 ratio): δH = 7.63 (s, 1 H, diast A+B), 7.44 (s, 1 H, diast A+B), 7.37 (d, J=8.8 Hz, 2 H, diast A+B), 7.02 – 6.91 (m, 2 H, diast A+B), 6.47 (s, 1 H, diast A+B), 5.86 – 5.47 (br. m, 2 H, diast A+B), 3.85 (s, 3 H, diast A+B), 1.80 (d, J=6.9 Hz, 0.6 H, diast B), 1.65 (d, J=6.9 Hz, 2.4 H, diast A).

Following a similar method to general procedure 3 (step 2), the carbamoyl chloride (2.00 g, 6.27 mmol), was reacted with triethylamine (0.96 mL, 6.90 mmol) and N-methylaniline (0.75 mL, 6.90 mmol) in dry CH3CN (16 mL) at reflux for 16 h. The crude product (50:50 dr by 1H-NMR) was purified by flash column chromatography (SiO2; n-Hex to n-Hex:Et2O 50:50) to afford the title compound (2.14 g, 88%; 50:50 dr, relative stereochemistry undetermined).

Diast. A: Yellow oil; Rf 0.25 (SiO2; n-Hex:Et2O 50:50); IR (neat, cm−1): νmax = 2930 (C–H), 2241 (C≡N), 1661 (C=O), 1513, 1374, 1251; 1H NMR (400 MHz, CDCl3): δH = 7.45 (d, J=0.8 Hz, 1 H, Cα,H), 7.41 (td, J=7.3, 1.8 Hz, 2 H, 2xCα,H), 7.34 – 7.27 (m, 2 H, 2xCα,H), 7.07 (dd, J=8.3, 1.0 Hz, 2 H, 2xCα,H), 6.74 (d, J=8.8 Hz, 2 H, 2xCα,H), 6.63 (d, J=8.6 Hz, 2 H, 2xCα,H), 6.02 (d, J=1.0 Hz, 1 H, Cα,H), 4.94 (q, J=6.9 Hz, 1 H, NCH3), 4.65 (s, 1 H, NCHCN), 3.77 (s, 3 H, OCH3), 3.21 (s, 3 H, NCH3), 1.66 (d, J=7.1 Hz, 3 H, NCH3); 13C NMR (101 MHz, CDCl3) δC = 161.3 (C=O), 159.3 (Cα,OCH3), 146.1 (Cα), 143.0 (Cα,H), 142.2
(C\textsubscript{8}H\textsubscript{10}), 130.6 (C\textsubscript{8}H), 129.9 (2xC\textsubscript{8}H), 128.8 (2xC\textsubscript{8}H), 126.6 (C\textsubscript{8}H), 126.2 (2xC\textsubscript{8}H), 119.3 (C\textsubscript{8}H), 118.8 (C=N), 113.9 (2xC\textsubscript{8}H), 110.0 (C\textsubscript{8}H), 57.1 (NCH(CH\textsubscript{3})Ar), 55.3 (OCH\textsubscript{3}), 40.4 (NCH\textsubscript{3}), 40.0 (NCHCN), 16.6 (NCH(CH\textsubscript{3})Ar); HRMS (ESI\textsuperscript{*}): \textit{m/z} calcd for C\textsubscript{23}H\textsubscript{24}N\textsubscript{3}O\textsubscript{3} [M+H]\textsuperscript{+} 390.1812, found 390.1803.

\textbf{Diat B}: Orange oil. \textbf{Rf} 0.15 (SiO\textsubscript{2}; n-Hex:EtO 50:50); \textbf{IR} (neat, cm\textsuperscript{-1}): \nu\textsubscript{max} = 2930 (C–H), 2249 (C=N), 1655 (C=O), 1513, 1393, 1251; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}): \delta\textsubscript{H} = 7.64 (d, J=0.8 Hz, 1 H, C\textsubscript{8}H), 7.43 (t, J=1.6 Hz, 1 H, C\textsubscript{8}H), 7.38 (t, J=7.8 Hz, 2 H, 2xC\textsubscript{8}H), 7.26 (t, J=7.6 Hz, 1 H, C\textsubscript{8}H), 7.20 (d, J=8.6 Hz, 2 H, 2xC\textsubscript{8}H), 7.03 (d, J=7.6, 2 H, 2xC\textsubscript{8}H), 6.91 (d, J=8.6 Hz, 2 H, 2xC\textsubscript{8}H), 6.37 (d, J=1.0 Hz, 1 H, C\textsubscript{8}H), 4.95 (q, J=7.1 Hz, 1 H, NCHCH\textsubscript{3}), 4.72 (s, 1 H, NCHCN), 3.81 (s, 3 H, OCH\textsubscript{3}), 3.23 (s, 3 H, NCH\textsubscript{3}), 0.95 (d, J=7.1 Hz, 3 H, NCHCH\textsubscript{3}); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \delta\textsubscript{C} = 160.8 (C=O), 159.5 (C\textsubscript{8}CH\textsubscript{3}), 146.0 (C\textsubscript{8}H), 143.4 (C\textsubscript{8}H), 130.5 (C\textsubscript{8}H), 128.9 (2xC\textsubscript{8}H), 128.6 (2xC\textsubscript{8}H), 126.3 (C\textsubscript{8}H), 126.0 (2xC\textsubscript{8}H), 119.6 (C\textsubscript{8}H), 116.6 (C=N), 114.1 (2xC\textsubscript{8}H), 109.7 (C\textsubscript{8}H), 56.8 (NCH(CH\textsubscript{3})Ar), 55.2 (OCH\textsubscript{3}), 41.2 (NCH\textsubscript{3}), 40.3 (NCHCN), 15.6 (NCH(CH\textsubscript{3})Ar); HRMS (ESI\textsuperscript{*}): \textit{m/z} calcd for C\textsubscript{23}H\textsubscript{24}N\textsubscript{3}O\textsubscript{3} [M+H]\textsuperscript{+} 390.1812, found 390.1807.

\textbf{(R)-1-(Cyano(furan-3-yl)methyl)-1-(1-(2-methoxyphenyl)ethyl)-3-methyl-3-phenylurea (6b)}

![Diagram of the molecule]

Following the general procedure 1, \textbf{(R)}-1-(2-methoxyphenyl)ethylamine (0.37 g, 2.46 mmol) was reacted with 3-furaldehyde (0.21 mL, 2.46 mmol) and TMSCN (0.38 mL, 2.95 mmol) in EtOH (6.1 mL) at 80 °C for 2 h. The crude \textbf{(R)}-2-(furan-3-yl)-2-[(1-(2-methoxyphenyl)ethyl)amino]acetonitrile product (0.70 g; 70:30 \textit{dr} by \textbf{\textsuperscript{1}H-NMR}; relative stereochemistry undetermined) was used in the next step without further purification. Yellow oil; \textbf{Rf} 0.45 (SiO\textsubscript{2}; n-Hex:EtOAc 70:30); \textbf{IR} (neat, cm\textsuperscript{-1}): \nu\textsubscript{max} = 3320, 2836, 1512, 1243, 600; \textbf{\textsuperscript{1}H NMR} (400 MHz, CD\textsubscript{3}Cl\textsubscript{2}) (mixture of diastereoisomers A:B in a 0.7:0.3 ratio): \delta\textsubscript{H} = 7.57 (dt, J = 1.9, 1.0 Hz, 0.7H, diast A), 7.51 (dt, J = 1.8, 0.9 Hz, 0.3H, diast B), 7.46 – 7.42 (m, 1.7H, diast A+B), 7.34 (dd, J = 7.5, 1.8 Hz, 0.3H, diast B), 7.29 – 7.23 (m, 1H, diast A+B), 7.00 – 6.89 (m, 2H, diast A+B), 6.52 – 6.49 (m, 1H, diast A+B), 4.64 (d, J = 1.1 Hz, 0.3H, diast B), 4.55 (q, J = 6.6 Hz, 0.7H, diast A), 4.40 (d, J = 1.1 Hz, 0.7H, diast A), 4.31 (q, J = 6.6 Hz, 0.3H, diast B), 3.86 (s, 2.1H, diast A), 3.85 (s, 0.9H, diast B), 1.94 (br. s, 1H, diast A+B), 1.39 (d, J = 6.8 Hz, 0.9H, diast B), 1.38 (d, J = 6.8 Hz, 2.1H, diast A); \textbf{\textsuperscript{13}C NMR} (101 MHz, CD\textsubscript{3}Cl\textsubscript{2}) \delta\textsubscript{C} = 158.12 (diast A), 157.65 (diast B), 144.55 (diast A), 144.51 (diast B), 141.27 (diast B), 140.99 (diast A), 132.06 (diast B), 131.47 (diast A), 128.90 (diast B), 128.79 (diast A), 127.78 (diast B), 127.17 (diast A), 122.31 (diast A), 121.41 (diast A), 121.23 (diast B), 119.65 (diast A), 119.51 (diast B), 111.37 (diast A), 111.21 (diast B), 109.81 (diast A+B), 55.91 (diast A), 55.82 (diast B), 51.18 (diast B), 50.80 (diast A), 44.99 (diast A), 44.60 (diast B), 23.15 (diast A), 21.31 (diast B); HRMS (ESI\textsuperscript{*}): \textit{m/z} calcd for C\textsubscript{32}H\textsubscript{32}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+} 527.1285, found 527.1288.

Following a similar method to general procedure 3 (step 1), the N-alkyl amino nitrile (650 mg, 2.536 mmol; 70:30 \textit{dr}) was reacted with triphosgene (301 mg, 1.014 mmol) and pyridine (0.25 mL, 3.043 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (13 mL). The crude was purified by flash column chromatography (SiO\textsubscript{2}; n-Hex to n-Hex:EtO 50:50) to afford the corresponding carbamoyl chloride (614 mg, 76% over 2 steps; 70:30
dr) as a yellow oil. Rf 0.40 (SiO2; n-Hex: Et2O 50:50); 1H NMR (400 MHz, CD2Cl2) (mixture of diastereoisomers A:B in a 0.7:0.3 ratio): δH = 7.51 (q, J = 1.1 Hz, 0.7H, diast A), 7.48 – 7.40 (m, 2.0H, diast A+B), 7.37 (d, J = 7.6 Hz, 0.7H, diast A), 7.17 (t, J = 1.7 Hz, 0.3H, diast B), 7.11 – 7.03 (m, 1.0H, diast A+B), 6.99 (d, J = 8.3 Hz, 0.7H, diast A), 6.86 (d, J = 8.5 Hz, 0.3H, diast B), 6.78 (s, 0.3H, diast B), 6.43 – 6.40 (m, 0.7H, diast A), 5.94 (q, J = 7.2 Hz, 0.3H, diast B), 5.87 (br. s, 0.7H, diast A), 5.72 (br. s, 0.3H, diast B), 5.02 (br. s, 0.3H, diast B), 4.91 (br. s, 0.7H, diast A), 3.91 (s, 2.1H, diast A), 3.66 (s, 0.9H, diast B), 1.72 (d, J = 7.1 Hz, 0.9H, diast B), 1.68 (d, J = 7.1 Hz, 2.1H, diast A).

Following a similar method to general procedure 3 (step 2), the carbamoyl chloride (400 mg, 1.255 mmol), was reacted with triethylamine (0.21 mL, 1.506 mmol) and N-methylaniline (0.15 mL, 1.381 mmol) in dry CH3CN (6.3 mL) at reflux for 16 h. The crude product (50:50 dr by 1H-NMR) was purified by flash column chromatography (SiO2; n-Hex to n-Hex:Et2O 50:50) to afford the title compound (439 mg, 90%; 50:50 dr, relative stereochemistry undetermined).

Diast A: Yellow oil; Rf 0.15 (SiO2; n-Hex:Et2O 50:50); IR (neat, cm⁻¹): νmax = 2926 (C=H), 2239 (C≡N), 1659 (C=O), 1512, 1379, 1250; 1H NMR (400 MHz, CDCl3): δH = 7.62 (dt, J = 1.8, 10.0 Hz, 1H, CαH), 7.41 (t, J = 1.7 Hz, 1H, CαH), 7.40 – 7.33 (m, 3H, 3xCαH), 7.24 (tt, J = 7.9, 1.3 Hz, 1H, CαH), 7.15 (ddd, J = 7.8, 1.7, 0.7 Hz, 1H, CαH), 7.09 – 7.04 (m, 2H, 2xCαH), 6.95 (ddt, J = 7.6, 4.0, 3.5, 1.1 Hz, 2H, 2xCαH), 6.33 (dd, J = 1.9, 0.9 Hz, 1H, CαH), 5.18 (q, J = 7.1 Hz, 1H, NCHCH3), 4.47 (d, J = 1.1 Hz, NCHCN), 3.96 (s, 3H, OCH3), 3.28 (s, 3H, NCH2), 0.72 (d, J = 7.1 Hz, 3H, NCH2CH3); 13C NMR (101 MHz, CDCl3) δC = 161.41 (C=O), 158.61 (CαOCH3), 146.37 (Cα), 143.31 (CαH), 142.35 (CαH), 130.36 (CβH), 129.68 (2xCαH), 126.86 (2xCαH), 126.29 (CβH), 126.21 (Cα), 120.55 (CαH), 120.09 (Cα), 116.75 (C≡N), 110.96 (CαH), 109.77 (CαH), 56.09 (OCH3), 53.24 (NCH(2)Ar), 41.00 (NCHCN), 39.90 (NCH3), 15.09 (NCH(3)Ar);

HRMS (ESI⁺): m/z calcd for C22H22N2O3 [M+H]+ 390.1812, found 390.1815.

Diast B: Yellow oil. Rf 0.25 (SiO2; n-Hex:Et2O 50:50); IR (neat, cm⁻¹): νmax = 2930 (C=H), 2245 (C≡N), 1657 (C=O), 1512, 1384, 1250; 1H NMR (400 MHz, CDCl3): δH = 7.39 – 7.33 (m, 2H, 2xCαH), 7.27 – 7.16 (m, 5H, 5xCαH), 7.10 (ddd, J = 7.7, 1.7, 0.7 Hz, 1H, CαH), 6.97 (dt, J = 1.6, 0.9 Hz, 1H, CαH), 6.88 (td, J = 7.5, 1.1 Hz, 1H, CαH), 6.70 (dd, J = 8.2, 1.2 Hz, 1H, CαH), 6.14 (dd, J = 1.9, 0.8 Hz, 1H, CαH), 5.15 (q, J = 7.1 Hz, 1H, NCHCH3), 5.00 (d, J = 0.8 Hz, 1H, NCHCN), 3.67 (s, 3H, OCH3), 3.25 (s, 3H, NCH2), 1.03 (d, J = 7.1 Hz, 3H, NCH2CH3); 13C NMR (101 MHz, CDCl3) δC = 161.87 (C=O), 158.04 (CαOCH3), 146.47 (Cα), 142.42 (CαH), 142.23 (CαH), 129.82 (CαH), 129.72 (2xCαH), 127.60 (CβH), 127.42 (Cα), 126.10 (CαH), 125.98 (2xCαH), 120.30 (Cα), 119.79, 117.63 (CαH), 110.88 (CαH), 110.54 (CαH), 55.36 (OCH3), 52.99 (NCH(3)Ar), 41.68 (NCHCN), 40.68 (NCH3), 15.74 (NCH(2)Ar); HRMS (ESI⁺): m/z calcd for C22H22N2O3 [M+Na]+ 390.1812, found 390.1807.

(R)-1-(cyano(furan-3-yl)methyl)-1-(2-hydroxy-1-phenylethyl)-3-methyl-3-phenylurea (6c)

HCl (aq., 1 m, 1.0 mL) was added to a solution of urea 6d (Diast. B, 123 mg, 0.251 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 72 h. The reaction
mixture was partitioned between EtOAc and water. The aqueous phase was further extracted in EtOAc (x2). The combined organic layers were washed with NaHCO₃ (sat., aq.), brine, dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO₂; n-Hex:EtOAc 50:50) afforded the title compound (53 mg, 56%; >95:5 dr by NMR) as a pink oil. Rf 0.20 (SiO₂; n-Hex:EtOAc 50:50); IR (neat, cm⁻¹): ν-max = 3323 (br.), 2858 (C–H), 2238 (C=O), 1670 (C=O), 1493, 1256; ¹H NMR (500 MHz, CD₂Cl₂): δH = 7.42 (dt, J = 1.8, 10.0 Hz, 1H, C₆H), 7.41 – 7.36 (m, 2H, 2xC₆H), 7.33 (t, J = 1.7 Hz, 1H, C₆H), 7.32 (s, 1H, C₆H), 7.30 – 7.26 (m, 1H, C₆H), 7.24 – 7.18 (m, 3H, 2xC₆H + OH), 7.08 – 7.04 (m, 2H, 2xC₆H), 6.67 – 6.63 (m, 2H, 2xC₆H), 5.98 (dd, J = 1.9, 0.9 Hz, 1H, C₆H), 4.90 – 4.85 (m, 2H, NCH₂ + NCH₂OH), 4.36 (ddd, J = 11.7, 8.4, 5.9 Hz, 1H, NCH(CH₂H)₆OH), 4.19 (dt, J = 11.7, 5.4 Hz, 1H, NCH(CH₂H)₆OH), 3.18 (s, 3H, NCH₃); ¹³C NMR (126 MHz, CD₂Cl₂) δC = 161.51 (C=O), 146.29 (C₆H), 143.79 (C₆H), 142.94 (C₆H), 142.92 (C₆H), 130.46 (2xC₆H), 129.16 (2xC₆H), 128.87 (C₆H), 128.52 (2xC₆H), 127.03 (C₆H), 126.88 (2xC₆H), 119.65 (C₆H), 119.07 (C=O), 110.51 (C₆H), 63.61 (NCH₂OH), 62.46 (NCH₂OH), 41.75 (NCHCN), 40.64 (NCH₃). HRMS (ESI⁺): m/z calcd for C₂₃H₂₂N₃O₃ [M+H]⁺ 376.1656, found 376.1663.

(R)-1-(2-((tert-Butyldimethylsilyloxy)-1-phenylethyl)-1-(cyanofuran-3-yl)methyl)-3-methyl-3-phenylurea (6d)

Following the general procedure 1, (R)-2-phenylglycinol (2.00 g, 14.29 mmol) was reacted with 3-furaldehyde (1.24 mL, 14.29 mmol) and TMSCN (2.24 mL, 17.15 mmol) in MeOH (50 mL) at room temperature for 16 h. The crude (80:20 dr by ¹H-NMR; relative stereochemistry undetermined) was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:EtOAc 60:40) to afford (R)-2-(furan-3-yl)-2-((2-hydroxy-1-phenylethyl)amino)acetonitrile (3.19 g, 92%; 80:20 dr) as a pale yellow oil; Rf 0.60 (SiO₂; n-Hex:EtOAc 50:50); IR (neat, cm⁻¹): ν-max = 3324 (br.), 2874, 1454, 1160, 1022; ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): δH = 7.60 (s, 0.8H, diast A), 7.51 – 7.29 (m, 6.2H, diast A+B), 6.50 (s, 1H, diast A+B), 4.74 (s, 0.2H, diast B), 4.42 (s, 0.8H, diast A), 4.22 (dd, J=9.2, 3.9 Hz, 0.8H, diast A), 3.95 (dd, J=8.0, 4.3 Hz, 0.2H, diast B), 3.83 (dd, J=11.0, 4.0 Hz, 0.8H, diast A), 3.80 – 3.75 (m, 0.2H, diast B), 3.73 – 3.67 (m, 0.2H, diast B), 3.64 (dd, J=10.8, 9.3 Hz, 0.8H, diast A), 2.57 (br. s, 1.0H, diast A+B), 2.36 – 1.75 (m, 1.0H, diast A+B); ¹³C NMR (101 MHz, CDCl₃) δC = 144.3 (diast B), 144.0 (diast A), 140.8 (diast B), 140.4 (diast A), 138.7 (diast B), 137.8 (diast A), 129.0 (diast A), 128.9 (diast B), 128.5 (diast A), 128.3 (diast B), 127.6 (diast A), 127.5 (diast B), 121.0 (diast A), 120.5 (diast B), 118.8 (diast B), 118.4 (diast A), 109.2 (diast A), 109.0 (diast B), 67.2 (diast A), 66.6 (diast B), 62.9 (diast A), 62.0 (diast B), 44.2 (diast A), 43.9 (diast B); HRMS (ESI⁺): m/z calcd for C₄₆H₅₁N₂O₂ [M+H]⁺ 243.1128, found 243.1131.

tert-Butyldimethylsilyl chloride (1.05 g, 6.93 mmol) was added to a solution of the N-alkyl-OH amino nitrile (1.53 g, 6.30 mmol), triethylamine (1.32 mL, 9.46 mmol) and 4-dimethylaminopyridine (77 mg,
0.63 mmol) in CH$_3$CN (21 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature and the solvent was removed under reduced pressure. The residue was partitioned between CH$_2$Cl$_2$ and water and the aqueous phase was further extracted in CH$_2$Cl$_2$ (x2). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and the solvent removed under reduced pressure. The crude (80:20 dr by $^1$H-NMR; *relative stereochemistry undetermined*) was purified by flash column chromatography (SiO$_2$; n-Hex to n-Hex:EtOAc 95:05) to afford (R)-2-((2-( tert-butyldimethylsilyl)oxy)-1-phenylethylamino)-2-(furan-3-yl)acetanitrile (1.92 g, 85%; 80:20 dr) as a yellow liquid; $R_f$ 0.30 (SiO$_2$; n-Hex:EtOAc 95:05); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): $\delta_{HH} = 7.63 - 7.59$ (m, 0.8H, diast A), 7.47 - 7.29 (m, 6.2H diast A+B), 6.50 (dd, $J=1.9$, 0.6 Hz, 0.8H, diast A), 6.48 - 6.46 (m, 0.2H, diast B), 4.72 (d, $J=9.6$ Hz, 0.2H, diast B), 4.38 (d, $J=0.8$ Hz, 0.8H, diast A), 4.20 (dd, $J=9.6$, 3.8 Hz, 0.8H, diast A), 3.90 (dd, $J=8.8$, 3.8 Hz, 0.2H, diast B), 3.74 (dd, $J=10.3$, 4.0 Hz, 0.8H, diast A), 3.70 - 3.55 (m, 1.2H diast A+B), 2.62 (d, $J=12.9$ Hz, 0.8H, diast A), 2.48 (d, $J=10.6$ Hz, 0.2H, diast B), 0.92 (s, 7.2H, diast A), 0.90 (s, 1.8H, diast B), 0.09 (d, $J=9.3$ Hz, 4.8H, diast A), 0.04 (d, $J=7.1$ Hz, 1.2H, diast B); HRMS (ESI$^+$): $m/z$ calcd for C$_{20}$H$_{26}$N$_2$O$_5$Si [M+H]$^+$ 357.1993, found 357.1999.

Following a similar method to general procedure 3 (step 1), the N-alkyl-OTBS amino nitrile (1.88 g, 5.26 mmol; 80:30 dr) was reacted with triphosgene (0.64 g, 2.10 mmol) and pyridine (0.51 mL, 6.31 mmol) in dry CH$_2$Cl$_2$ (26 mL). The crude was purified by flash column chromatography (SiO$_2$, n-Hex:EtOAc 95:05 to 90:10) to afford the corresponding carbamoyl chloride (1.94 g, 88%; 80:20 dr) as a yellow oil. $R_f$ 0.15 (SiO$_2$; n-Hex:EtOAc 95:05); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): $\delta_{HH} = 7.66$ (s, 0.8H, diast A), 7.42 (dt, $J=14.2$, 7.6 Hz, 6.0H, diast A+B), 7.16 (s, 0.2H, diast B), 7.00 (s, 0.2H, diast B), 6.54 (dd, $J=1.9$, 0.9 Hz, 0.8H, diast B), 5.87 - 4.98 (br. m, 2.0H, diast A+B), 4.43 - 3.96 (br. m, 2.0H, diast A+B), 0.97 (s, 1.8H, diast A), 0.85 (s, 7.2H, diast A), 0.20 (s, 0.6H, diast B), 0.06 (s, 2.4H, diast A), 0.03 (s, 2.4H, diast A). Then, following a similar method to general procedure 3 (step 2), the carbamoyl chloride (1.88 g, 5.56 mmol) was reacted with triethylamine (0.93 mL, 6.67 mmol) and N-methylaniline (0.68 mL, 6.12 mmol) in dry CH$_3$CN (28 mL) at reflux for 16 h. The crude product (60:40 dr by $^1$H-NMR) was purified by flash column chromatography (SiO$_2$; n-Hex to n-Hex:EtOAc 80:20) to afford the title compound (0.86 g, 32%; 60:40 dr, *relative stereochemistry undetermined*).

**Dia$t.$ A:** Brown oil; $R_f$ 0.40 (SiO$_2$; n-Hex:EtOAc 80:20); IR (neat, cm$^{-1}$): $v_{max} = 2856$ (C–H), 2240 (C≡N), 1668 (C=O), 1495, 1258, 1109, 837; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_{HH} = 7.43$ (dt, $J=1.8$, 0.8 Hz, 1 H, C$_6$H), 7.38 (s, 2 H, 2xC$_6$H), 7.30 - 7.25 (m, 2 H, 2xC$_6$H), 7.23 - 7.14 (m, 3 H, 3xC$_6$H), 7.06 - 7.03 (m, 2xC$_6$H), 6.61 - 6.58 (m, 2 H, 2xC$_6$H), 5.94 (dd, $J=1.8$, 1.0 Hz, 1 H, C$_6$H), 4.91 - 4.94 (m, 2 H, NCHCN + NCH$_2$OTBS), 4.29 (dd, $J=10.6$, 8.3 Hz, 1 H, NCH(CH$_3$H)$_2$OTBS), 4.09 (dd, $J=10.6$, 5.3 Hz, 1 H, NCH(CH$_3$H)$_2$OTBS), 3.18 (s, 3 H, NCH$_3$), 0.95 (s, 9 H, Si(C$_3$H)$_3$)$_3$, 0.17 (s, 3 H, Si(C$_3$H)$_3$), 0.16 (s, 3 H, Si(C$_3$H)$_3$); HRMS (ESI$^+$): $m/z$ calcd for C$_{38}$H$_{46}$N$_2$O$_5$Si [M+H]$^+$ 490.2520, found 490.2518.

**Dia$t.$ B:** Brown oil. $R_f$ 0.30 (SiO$_2$; n-Hex:EtOAc 80:20); IR (neat, cm$^{-1}$): $v_{max} = 2856$ (C–H), 2241 (C≡N), 1665 (C=O), 1595, 1496; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_{HH} = 7.65$ (dt, $J=1.6$, 0.9 Hz, 1 H, C$_6$H), 7.43 (t, $J=1.6$ Hz, 1 H, C$_6$H), 7.31 - 7.41 (m, 7 H, 7xC$_6$H), 7.03 (d, $J=1.3$ Hz, 1 H, C$_6$H), 7.00 - 7.02 (m, 2 H, 2xC$_6$H), 6.45 (dd, $J=1.5$, 0.8 Hz, 1 H, C$_6$H), 5.49 (d, $J=0.8$ Hz, 1 H, NCHCN), 4.60 (t, $J=5.0$ Hz, 1 H, NCH$_2$OTBS),

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3.68 (dd, J=10.8, 4.8 Hz, 1 H, NCH(CH₃)CH₃)OTBS), 3.42 (dd, J=11.1, 5.3 Hz, 1 H, NCH(CH₃)CH₃)OTBS), 3.13 (s, 3 H, NCH₃), 0.80 (s, 9 H, Si(CH₃)₃), -0.05 (s, 3 H, Si(CH₃)₃), -0.06 (s, 3 H, Si(CH₃)₃). HRMS (ESI⁺): m/z calcd for C₂₉H₃₀N₃O₃Si [M+H]⁺ 490.2520, found 490.2512.

1-((1R,2R)-2-(((tert-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(furan-3-yl)methyl)-3-methyl-3-pheny lurea (6e)

Following the general procedure 1, (1R,2R)-trans-2-aminocyclohexanol (1.13 g, 9.79 mmol) was reacted with 3-furaldehyde (0.93 mL, 10.77 mmol) and TMSCN (1.47 mL, 11.75 mmol) in MeOH (56 mL) for 16 h at room temperature. The crude was purified by flash column chromatography (SiO₂; Pet. Ether:EtOAc 100:0 to Pet. Ether:EtOAc 60:40) to afford 2-(Furan-3-yl)-2-(((1R,2R)-2-hydroxy(cyclohexyl)amino)acetonitrile (1.30 g, 61%; 65:35 dr) as a colourless solid. Rf 0.34 (SiO₂; Pet. Ether:EtOAc 60:40); IR (neat, cm⁻¹): vₘₐₓ = 3600 – 3200 (O–H, br.), 3323 (N–H), 2959 (C–H), 2233 (C≡N); ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δₘₛ = 7.60 (0.65H, dt, J=1.8, 1.0, C₆H, diast A), 7.58 (0.35H, dt, J=1.8, 1.0, C₆H, diast B), 7.44 (0.65H, t, J=1.7, C₆H, diast A), 7.43 – 7.39 (0.35H, m, C₆H, diast B), 6.50 (1H, dt, J=1.9, 1.0, C₆H, diast A+B), 4.92 (0.35H, s, NCH(Ar)CN, diast B), 4.79 (0.65H, s, NCH(Ar)CN, diast A), 3.31 (1H, ddt, J=13.7, 9.1, 4.1, NHCH(OH), diast A+B), 2.65 (0.65H, tdd, J=11.1, 9.1, 4.1, NHCH(OH), diast A), 2.55 (0.35H, dd, J=11.2, 9.0, 4.2, NHCH(OH), diast B), 2.47 – 1.93 (3H, m, NH, diast A+B, 2xCH, diast A+B), 1.94 – 1.53 (3H, m, OH, diast A+B, 2xCH, diast A+B), 1.41 – 1.22 (3H, m, 3xCH, diast A+B), 1.21 – 1.02 (1H, m, CH, diast A+B); ¹³C NMR (126 MHz, CDCl₃) δₐₛ = 144.3 (C₆H, diast A), 144.2 (C₆H, diast B) 140.8 (C₆H, diast A), 140.6 (C₆H, diast B), 121.8 (C₆H, diast A), 121.3 (C₆H, diast A), 120.0 (C≡N, diast B), 118.8 (C≡N, diast A), 109.4 (C₆H, diast A), 109.3 (C₆H, diast B), 75.5 (NHCH(OH), diast B), 74.1 (NHCH(OH), diast A), 62.8 (NHCH(OH), diast A), 61.3 (NHCH(OH), diast A), 46.0 (NCH(Ar)CN, diast B), 43.6 (NCH(Ar)CN, diast A), 34.3 (CH₂, diast A), 33.9 (CH₂, diast B), 31.6 (CH₂, diast B), 29.9 (CH₂, diast A), 25.0 (CH₂, diast B) 24.5 (CH₂, diast A), 24.4 (CH₂, diast A), 24.3 (CH₂, diast B); HRMS (ESI⁺): m/z calcd for C₁₂H₁₃N₃O₂ [M+H]⁺ 221.1284, found 257.1291.

Following the general procedure 2, the N-alkyl-OH amino nitrile (1.00 g, 4.54 mmol) was reacted with 2,6-lutidine (0.79 mL, 6.81 mmol) and TBSOTf (1.30 mL, 5.45 mmol) in anhydrous CH₂Cl₂ (20 mL). Purification by flash column chromatography (SiO₂; n-Hex:EtOAc 100:0 to n-Hex:EtOAc 90:10) afforded 2-(((1R,2R)-2-(((tert-Butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(furan-3-yl)acetonitrile (0.80 g, 52%; 65:35 dr) as a yellow oil. Rf 0.29 (90:10 n-Hex:EtOAc); IR (neat, cm⁻¹): vₘₐₓ = 3329 (N–H), 2929 (C–H), 2857 (C–H), 2346 (C≡N); ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δₘₛ = 7.60 – 7.53 (1H, m, C₆H, diast A+B), 7.43 (0.65H, dq, J=2.6, 1.6, C₆H, diast A), 7.40 (0.35H, 1d, J=1.7, C₆H, diast B), 6.58 – 6.39 (1H, m, C₆H, diast A+B), 4.93 (0.35H, s, NCH(Ar)CN, diast B), 4.72
Following the general procedure 3 (step 1), the N-alkyl-OTBS amino nitrile (800 mg, 2.390 mmol; 65:35 dr) was reacted with trisphosgene (284 mg, 0.956 mmol) and 2,6-lutidine (0.33 mL, 2.871 mmol) in dry CH$_2$Cl$_2$ (13 mL). The crude carbamoyl chloride (1.00 g, brown oil) was used in the next step without further purification. Following the general procedure 3 (step 2), the carbamoyl chloride (1.00 g), was reacted with 2,6-lutidine (0.33 mL, 2.868 mmol), potassium iodide (476 mg, 2.868 mmol) and N-methylaniline (0.28 mL, 2.629 mmol) in dry CH$_3$CN (6.0 mL) in a microwave reactor at 110 °C for 4 h. The crude product was purified by flash column chromatography (SiO$_2$; n-Hex:Et$_2$O 100:0 to n-Hex:Et$_2$O 70:30) to afford the title compound (279 mg, 25% over 2 steps; 50:50 dr, relative stereochemistry undetermined).

**Diast. A:** yellow solid; m.p. = 119 – 121 °C; R$_f$ 0.34 (n-Hex:Et$_2$O 70:30); IR (neat, cm$^{-1}$): ν$_{max}$ = 2929 (C–H), 2857 (C–H), 2243 (C≡N), 1657 (C=O); $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.61 (1H, dt, J=1.7, 0.9, C$_6$H), 7.37 (1H, t, J=1.7, C$_6$H), 7.36 – 7.31 (2H, m, 2xC$_6$H), 7.20 – 7.15 (1H, m, C$_6$H), 7.14 – 7.10 (2H, m, 2xC$_6$H), 6.50 (1H, dd, J=1.8, 1.1, C$_6$H), 5.77 (1H, s, N(CH$_3$)CN), 4.10 – 3.96 (1H, m, NHCCHOTBS), 3.22 – 3.15 (1H, m, NHCCHOTBS), 3.21 (3H, s, NCH$_3$), 1.98 – 1.89 (1H, m, CH), 1.70 – 1.61 (1H, m, CH), 1.60 – 1.49 (2H, m, 2xC$^\equiv$C), 1.49 – 1.41 (1H, m, CH), 1.20 – 1.08 (1H, m, CH), 1.06 – 0.93 (1H, m, CH), 0.86 (9H, s, Si(CH$_3$)$_3$), 0.80 – 0.68 (1H, m, CH), 0.06 (3H, s, Si(CH$_3$)$_3$), 0.01 (3H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$): δ$_C$ = 161.26 (C=O), 146.13 (C$_6$H), 143.36 (C$_6$H), 142.13 (C$_6$H), 129.78 (2xC$_6$H), 125.83 (C$_6$H), 124.93 (2xC$_6$H), 120.53 (C$_6$H), 118.14 (C≡N), 110.61 (C$_6$H), 71.94 (NHCCHOTBS), 65.11 (NHCCHOTBS), 41.91 (N(CH$_3$)CN), 40.38 (NCH$_3$), 36.97 (CH$_3$), 29.20 (CH$_3$), 26.13 (Si(CH$_3$)$_3$), 25.74 (CH$_3$), 24.47 (CH$_3$), 18.23 (Si(CH$_3$)$_3$), -3.60 (Si(CH$_3$)$_3$); HRMS (ESI$^+$): m/z calcd for C$_{28}$H$_{33}$N$_2$O$_2$Si [M+H]$^+$ 468.2677. Found 468.2676.

**Diast. B:** orange oil; R$_f$ 0.21 (n-Hex:Et$_2$O 70:30); IR (neat, cm$^{-1}$): ν$_{max}$ = 2929 (C–H), 2857 (C–H), 2243 (C≡N) 1661 (C=O); $^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.71 (1H, s, C$_6$H), 7.42 (1H, t, J=1.7, C$_6$H), 7.34 – 7.28 (2H, m, 2xC$_6$H), 7.19 – 7.14 (1H, m, C$_6$H), 6.97 – 6.93 (2H, m, 2xC$_6$H), 6.39 (1H, d, J=1.5, C$_6$H),

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4.97 (1H, s, NCH(Ar)CN), 3.67 (1H, dt, J=10.4, 3.8, NCHCOTBS), 3.28 (1H, ddd, J=12.9, 9.3, 4.0, NCHCOTBS), 3.16 (3H, s, NCH₃), 2.10 – 1.97 (1H, m, CH), 1.62 – 1.50 (1H, m, CH), 1.46 – 1.37 (1H, m, CH), 1.20 – 1.10 (1H, m, CH), 1.07 – 0.96 (3H, m, 3xCH), 0.95 (9H, s, SiC(CH₃)₃), 0.57 (1H, td, J=12.0, 11.6 5.9, CH), 0.23 (3H, s, Si(CH₃)₂(CH₃)₃), 0.14 (3H, s, Si(CH₃)₂(CH₃)₃); ¹³C NMR (126 MHz, CDCl₃): δC = 160.47 (C=O), 146.41 (C₆H), 143.32 (C₆-H), 142.66 (C₆-H), 129.57 (2xC₆-H), 125.77 (C₆-H), 125.51 (2xC₆-H), 119.98 (C₆H), 118.03 (C=Ν) 110.06 (C₆-H), 71.58 (NCHCOTBS), 40.06 (NCH(Ar)CN) 39.84 (NCH₃), 36.68 (CH₂), 29.15 (CH₂), 26.28 (SiC(CH₃)₃), 25.21 (CH₂), 24.37 (CH₂), 18.29 (SiC(CH₃)₃), -3.33 (Si(CH₃)₂(CH₃)₃) -3.89 (Si(CH₃)₂(CH₃)₃); HRMS (ESI⁺): m/z calcd for C₂₆H₃₇N₃O₃Si [M+H]⁺ 468.2677. Found 468.2657.

4-(Furan-3-yl)-5-imino-3-(((R)-1-(4-methoxyphenyl)ethyl)-1-methyl-4-phenylimidazolidin-2-one (7a)

Following the general procedure 4 (method A), the N'-aryl ureido nitrile 6a (50 mg, 0.128 mmol; 50:50 dr) was reacted with LDA (0.13 mL, 2.0 m in THF/heptane/ethylbenzene, 0.256 mmol) in anhydrous THF (1.1 mL) at room temperature for 3 h. The crude product (77:23 dr by NMR) was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:EtOAc 60:40) to afford the title compound (47 mg, 93%; 65:35 dr, relative stereochemistry undetermined) as a yellow oil; Rf 0.50 (SiO₂; n-Hex:EtOAc 50:50); ¹H NMR (500 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δHH = 7.54 (t, J = 1.7 Hz, 0.65H, diast A), 7.51 (t, J = 1.3 Hz, 0.65H, diast A), 7.48 – 7.41 (m, 2.0H, diast A+B), 7.32 – 7.20 (m, 3.35H, diast A+B), 7.19 – 7.14 (m, 1.05H, diast B), 7.09 – 7.05 (m, 1.30H, diast A), 6.75 – 6.70 (m, 0.70H, diast B), 6.69 – 6.63 (m, 1.30H, diast A), 6.45 (dd, J = 1.9, 1.0 Hz, 0.65H, diast A), 6.08 (dd, J = 1.9, 0.9 Hz, 0.35H, diast B), 4.24 (q, J = 7.2 Hz, 0.65H, diast A), 4.19 (q, J = 7.2 Hz, 0.35H, diast B), 3.75 (s, 1.05H, diast B), 3.74 (s, 1.95H, diast A), 3.16 (s, 1.05H, diast B), 3.13 (s, 1.95H, diast A), 1.61 (d, J = 7.2 Hz, 1.95H, diast A), 1.59 (d, J = 7.2 Hz, 1.05H, diast B); ¹³C NMR (126 MHz, CDCl₃) δC = 167.56 (diast B), 167.51 (diast A), 158.58 (diast A), 158.50 (diast B), 156.32 (diast B), 156.09 (diast A), 144.33 (diast A), 143.69 (diast B), 142.63 (diast B), 142.37 (diast A), 138.04 (diast B), 137.18 (diast A), 134.86 (diast B), 134.16 (diast A), 129.36, 129.28, 129.23, 129.14, 128.75, 128.51, 128.47, 127.87, 124.23 (diast A), 123.64 (diast B), 113.53 (diast B), 113.26 (diast A), 110.63 (diast B), 110.43 (diast A), 70.38 (diast B), 70.34 (diast A), [55.36 + 55.32 + 55.29 + 55.25] (diast A+B, C₆OCH₃), [54.42 + 54.41 + 54.39 + 54.37] (diast A+B, NCH(Ar)CH₃), 25.80 (diast A), 25.78 (diast B), 21.11 (diast B), 20.36 (diast A); HRMS (ESI⁺): m/z calcd for C₂₆H₃₇N₃O₃Si [M+H]⁺ 390.1812, found 390.1819.
4-{Furan-3-yl}-5-imino-3-{((R)-1-{2-methoxyphenyl}ethyl)-1-methyl-4-phenylimidazolidin-2-one (7b)

Following the general procedure 4 (method A), the N'-aryl ureido nitrile 6b (100 mg, 0.256 mmol; 50:50 dr) was reacted with LDA (0.26 mL, 2.0 M in THF/heptane/ethylbenzene, 0.512 mmol) in anhydrous THF (2.2 mL) at room temperature for 3 h. 1H-NMR analysis of the reaction crude showed a 60:40 diastereomeric mixture of the product (87% NMR yield using hexamethylbenzene as internal standard; peaks corresponding to the product assigned by analogy to 7a).

4-{Furan-3-yl}-3-{((R)-2-hydroxy-1-phenylethyl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (7c)

Following the general procedure 4 (method A), the N'-aryl ureido nitrile 6c (46 mg, 0.123 mmol; >95:5 dr) was reacted with LDA (0.19 mL, 2.0 M in THF/heptane/ethylbenzene, 0.374 mmol) in anhydrous THF (1.1 mL) at room temperature for 3 h. The crude product (60:40 dr by NMR) was purified by flash column chromatography (SiO2; EtOAc) to afford the title compound (35 mg, 76%; 60:40 dr, relative stereochemistry undetermined) as a yellow oil; Rf 0.30 (SiO2; EtOAc); 1H NMR (400 MHz, CD2Cl2) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δH = 7.51 – 7.48 (m, 0.65H), 7.44 – 7.25 (m, 7.0H), 7.19 – 7.13 (m, 0.70H), 7.09 – 7.01 (m, 2.0H), 6.98 – 6.92 (m, 0.7H), 6.89 – 6.83 (m, 1.3H), 6.45 (ddd, J = 2.5, 1.7, 1.2 Hz, 1.0H), 6.10 (br. s, 0.20H), 5.78 (d, J = 1.2 Hz, 0.65H), 4.59 (br. s), 4.57 – 4.48 (m, 1.0H), 4.24 (dd, J = 12.1, 11.1 Hz, 0.65H), 4.14 – 4.06 (m, 1.0H), 2.95 (s, 1.05H, diast B), 2.92 (s, 1.95H, diast A); HRMS (ESI+): m/z calcd for C22H22N3O3 [M+H]+ 376.1656, found 376.1649.

3-{((R)-2-{(tert-Butyldimethylsilyl)oxy}-1-phenylethyl)-4-{(furan-3-yl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (7d)

Following the general procedure 4 (method A), the N'-aryl ureido nitrile 6d (100 mg, 0.204 mmol; 50:50 dr) was reacted with LDA (0.20 mL, 2.0 M in THF/heptane/ethylbenzene, 0.408 mmol) in anhydrous THF (2.0 mL) at room temperature for 3 h. The crude product (75:25 dr by NMR) was
purified by flash column chromatography (SiO₂; n-Hex:EtOAc 80:20 to 60:40) to afford the title compound (96 mg, 96%; 75:25 dr, relative stereochemistry undetermined) as a yellow oil; Rf 0.25 (SiO₂; n-Hex:EtOAc 60:40); IR (neat, cm⁻¹): νmax = 2928 (C–H), 1733 (C=NH), 1660 (C=O), 1450, 1101; ¹H NMR (500 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.75:0.25 ratio): δH = 8.05 (s, 0.75H, diast A), 7.69 – 7.64 (m, 0.50H, diast B), 7.52 (t, J = 1.8 Hz, 0.75H, diast A), 7.44 (h, J = 3.6, 3.1 Hz, 1.0H, diast A+B), 7.17 – 6.93 (m, 10H, diast A+B), 6.48 (d, J = 1.8 Hz, 0.75H, diast A), 5.84 (d, J = 1.9 Hz, 0.25H, diast B), 4.67 (t, J = 9.6 Hz, 0.75H, diast A), 4.57 (dd, J = 10.0, 8.3 Hz, 0.25H, diast B), 4.28 (dd, J = 9.0, 6.4 Hz, 0.75H, diast A), 4.21 (t, J = 7.6 Hz, 0.25H, diast B), 4.00 (dd, J = 10.0, 7.0 Hz, 0.25H, diast B), 3.89 (dd, J = 10.2, 6.4 Hz, 0.75H, diast A), 3.19 (s, 2.25H, diast A), 3.18 (s, 0.75H, diast B), 0.86 (s, 6.75H, diast A), 0.85 (s, 2.25H, diast B), 0.00 (d, J = 8.9 Hz, 4.5H, diast A), -0.03 (d, J = 8.0 Hz, 1.5H, diast B); HRMS (ESI⁺): m/z calcd for C₂₉H₃₈N₅O₅Si [M+H]⁺ 490.2520, found 490.2529.

(R)-3-(((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-4-(furan-3-yl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (7e)

Following the general procedure 4 (method A), the N'-aryl ureido nitrile 6e (53 mg, 0.113 mmol; diast A, >95:5 dr) was reacted with LDA (0.17 mL, 2.0 m in THF/heptane/ethylbenzene, 0.339 mmol) in anhydrous THF (1.0 mL) at room temperature for 3 h. The crude product (>95:5 dr by NMR) was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:EtOAc 70:30) to afford the title compound (34 mg, 68%; >95:5 dr, absolute configuration assigned by analogy to 9b) as a yellow oil. The same diastereoisomer of 7e was obtained (85%, >95:5 dr by ¹H-NMR) after performing the reaction from 6e (diast B, >95:5 dr). 7e: Rf 0.19 (SiO₂; n-Hex:EtOAc 70:30); IR (neat, cm⁻¹): νmax = 3311 (N–H), 2929 (C–H), 2856 (C–H), 1732 (C=N), 1659 (C=O); ¹H NMR (400 MHz, CDCl₃): δH = 7.83 – 7.77 (2H, m, 2xAr-H), 7.45 (1H, t, J = 1.7, Ar-H), 7.41 – 7.33 (4H, m, 4xAr-H), 6.25 (1H, dd, J = 2.0, 0.9, Ar-H), 4.76 (1H, br. s, NCHOTBS), 3.11 (3H, s, NCH₂), 3.00 – 2.86 (1H, m, NCHOTBS), 1.98 – 1.89 (1H, m, CH), 1.63 – 1.53 (2H, m, 2xCH), 1.50 – 1.40 (1H, m, CH), 1.31 – 1.21 (1H, m, CH), 1.21 – 1.15 (1H, m, CH), 1.06 – 0.95 (1H, m, CH), 0.94 (9H, s, Si(CH₃)₃), 0.92 – 0.87 (1H, m, CH), 0.19 (3H, s, Si(CH₃)₃(CH₃),), 0.08 (3H, Si(CH₃)₃(CH₃)), 0.08 (3H, Si(CH₃)₃(CH₃)); ¹³C NMR (101 MHz, CDCl₃): δC = 167.26 (C=N), 155.86 (C=O), 143.85 (CaH), 142.47 (CaH), 137.84 (Ca), 128.85 (2xCaH), 128.69 (CaH), 128.27 (2xCaH), 126.20 (CaH), 120.96 (CaH), 72.48 (NCHOTBS), 69.05 (NC(Ar)Ph), 61.16 (NCHOTBS), 37.48 (CH₃), 29.87 (CH₃), 26.23 (Si(CH₃)₃), 25.65 (NCCH₃), 25.48 (CH₂), 24.76 (CH₃), 18.33 (Si(CH₃)₃). -3.75 (Si(CH₃)₃(CH₃)), -5.54 (Si(CH₃)₃(CH₃)); HRMS (ESI⁺): m/z calcd for [C₂₉H₃₈N₅O₅Si]⁺ [M+H]⁺ 468.2677. Found 468.2680.
Following the general procedure 1, (1R,2R)-trans-2-aminocyclohexanol (500 mg, 4.341 mmol) was reacted with p-tolualdehyde (0.52 mL, 4.341 mmol) and TMSCN (0.65 mL, 5.209 mmol) in MeOH (20 mL) for 16 h at room temperature. The crude was purified by flash column chromatography (SiO$_2$; n-Hex to n-Hex:EtOAc 70:30) to afford 2-(((1R,2R)-2-hydroxycyclohexyl)amino)-2-(p-tolyl)acetonitrile (636 mg, 60%; 70:30 dr) as a colourless solid. $R_f$ 0.3 (SiO$_2$; n-Hex:EtOAc 70:30); IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ = 3600 – 3200 (O–H, br.), 3320 (N–H), 2928 (C–H), 2236 (C≡N); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers A:B in a 0.70:0.30 ratio): $\delta_{\text{H}}$ = 7.44 - 7.38 (m, 2.0H, 2xC$_{Ar}$H, diast A+B), 7.23 (d, J = 7.9 Hz, 2.0H, 2xC$_{Ar}$H, diast A+B), 4.94 (s, 0.20H, s, $\text{CH}_2$), 3.84 (s, 3.38 - 3.26 (m, 1.0H, NHCHCHOH, diast A+B), 2.70 (ddd, J = 11.2, 9.0, 4.1 Hz, 2xC$_{CH}$H, diast A+B), 1.43 - 1.23 (m, 3.0H, $\text{CH}_2$), diast A+B, 2.81 (ddd, J = 11.0, 8.6, 4.0 Hz, 0.8H, NHCHCHOTBS, diast A+B), 2.61 (ddd, J = 12.5, 8.9, 4.1 Hz, 0.2H, NHCHCHOTBS, diast B), 2.36 (s, 3H, $\text{C}_3\text{H}_5$, diast A+B), 2.11 - 1.55 (m, 5H, 4xC$_{CH}$H, diast A+B; NH, diast A+B), 1.49 - 0.98 (m, 4H, 4xC$_{CH}$H, diast A+B), 0.86 (s, 7.2H, Si(CH$_3$)$_3$, diast A), 0.84 (s, 1.8H, Si(CH$_3$)$_3$, diast B), 0.06 (s, 3.0H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast A+B), 0.04 (s, 0.6H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast B), -0.01 (s, 2.4H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast A); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta_{\text{C}}$ = 138.88 (C$_{Ar}$, diast B), 138.83

Following the general procedure 2, the N-alkyl-OH amino nitrile (350 mg, 1.432 mmol) was reacted with 2,6-lutidine (0.25 mL, 2.148 mmol) and TBSOTf (0.40 mL, 1.718 mmol) in anhydrous CH$_2$Cl$_2$ (7.2 mL). Purification by flash column chromatography (SiO$_2$; n-Hex:EtOAc 95:5 to 80:20) afforded 2-(((1R,2R)-2-((tert-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(p-tolyl)acetonitrile (258 mg, 50%; 80:20 dr) as a clear oil. $R_f$ 0.3 (SiO$_2$; n-Hex:EtOAc 90:10); IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ = 3330 (N–H), 2932 (C–H), 2341 (C≡N); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers A:B in a 0.80:0.20 ratio): $\delta_{\text{H}}$ = 7.36 (d, J = 8.0 Hz, 2.0H, 2xC$_{Ar}$H, diast A+B), 7.23 - 7.16 (m, 2.0H, 2xC$_{Ar}$H, diast A+B), 4.87 (s, 0.20H, s, NCH(Ar)CN, diast B), 4.73 (s, 0.80H, s, NCH(Ar)CN, diast A), 3.50 - 3.37 (m, 1.0H, NHCHCHOTBS, diast A+B), 2.80 (ddd, J = 11.0, 8.6, 4.0 Hz, 0.8H, NHCHCHOTBS, diast A), 2.61 (ddd, J = 12.5, 8.9, 4.1 Hz, 0.2H, NHCHCHOTBS, diast B), 2.36 (s, 3H, $\text{C}_3\text{H}_5$, diast A+B), 2.11 - 1.55 (m, 5H, 4xC$_{CH}$H, diast A+B; NH, diast A+B), 1.49 - 0.98 (m, 4H, 4xC$_{CH}$H, diast A+B), 0.86 (s, 7.2H, Si(CH$_3$)$_3$, diast A), 0.84 (s, 1.8H, Si(CH$_3$)$_3$, diast B), 0.06 (s, 3.0H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast A+B), 0.04 (s, 0.6H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast B), -0.01 (s, 2.4H, Si(CH$_3$)$_3$(CH$_3$)$_2$, diast A); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta_{\text{C}}$ = 138.88 (C$_{Ar}$, diast B), 138.83...
Following the general procedure 3 (step 1), the N-alkyl-OTBS amino nitrile (200 mg, 0.558 mmol; 80:20 dr) was reacted with triphosgene (66 mg, 0.223 mmol) and 2,6-lutidine (78 µL, 0.670 mmol) in dry CH₂Cl₂ (5.6 mL). The crude carbamoyl chloride (240 mg, yellow oil) was used in the next step without further purification. Following the general procedure 3 (step 2), the carbamoyl chloride (240 mg), was reacted with 2,6-lutidine (78 µL, 0.670 mmol) and N-methylaniline (91 µL, 0.837 mmol) in dry CH₂CN (2.0 mL) in a sealed tube at 100 °C for 24 h. The crude product was purified by flash column chromatography (SiO₂; n-Hex:Et₂O 80:20) to afford the title compound (90 mg, 33% over 2 steps; 50:50 dr, relative stereochemistry undetermined) as a clear oil. Rf 0.25 (n-Hex:Et₂O 80:20); IR (neat, cm⁻¹): v_max = 2930 (C=H), 2241 (C≡N), 1656 (C=O), 1104; ¹H NMR (400 MHz, CDCl₃) (unassigned mixture of diastereoisomers in a 1:1 ratio): δ_H = 7.49 – 7.40 (m, 4H, 4xC₆H), 7.36 – 7.28 (m, 4H, 4xC₆H), 7.24 – 7.14 (m, 6H, 6xC₆H), 7.14 – 7.07 (m, 2H, 2xC₆H), 6.94 – 6.87 (m, 2H, 2xC₆H), 5.85 (s, 1H, NCH(Ar)CN), 5.08 (s, 1H, NCH(Ar)CN), 4.09 (td, J = 9.9, 4.2 Hz, 1H, NCHOTBS), 3.79 – 3.68 (m, 1H, NCHOTBS), 3.38 – 3.21 (m, 2H, 2xNCHOTBS), 3.20 (s, 3H, NCH₃), 3.11 (s, 3H, NCH₃), 2.37 (s, 3H, ArCH₃), 2.34 (s, 3H, ArCH₃), 2.09 – 2.01 (m, 1H, CH), 1.94 (ddt, J = 12.6, 5.1, 2.6 Hz, 1H, CH), 1.76 – 1.40 (m, 7H, 7xCH), 1.33 – 1.00 (m, 6H, 6xCH), 0.96 (s, 9H, Si(CH₃)₃), 0.86 (s, 9H, Si(CH₃)₃), 0.67 – 0.53 (m, 1H, CH), 0.26 (s, 3H, Si(CH₃)₃(CH₃B)), 0.15 (s, 3H, Si(CH₃)₃(CH₃B)), 0.08 (s, 3H, Si(CH₃)₃(CH₃B)), 0.03 (s, 3H, Si(CH₃)₃(CH₃B)); ¹³C NMR (101 MHz, CDCl₃) δ_C = 161.44 (C=O), 160.42 (C=O), 146.27 (C₆H), 145.90 (C₆H), 138.35 (C₆H), 138.28 (C₆H), 131.78 (C₆H), 131.21 (C₆H), 129.69 (2xC₆H), 129.45 (2xC₆H), 129.24 (2xC₆H), 129.08 (2xC₆H), 128.27 (2xC₆H), 127.72 (2xC₆H), 125.74 (C₆H), 125.66 (C₆H), 125.55 (2xC₆H), 124.97 (2xC₆H), 118.76 (C≡N), 118.32 (C≡N), 71.92 (NCHOTBS), 71.60 (NCHOTBS), 65.25 (NCHOTBS), 64.97 (NCHOTBS), 49.03 (NCH(Ar)CN), 47.51 (NCH(Ar)CN), 40.26 (NCH₃), 39.64 (NCH₃), 36.96 (CH₂), 36.87 (CH₃), 29.71 (CH₃), 29.54 (CH₃), 26.33 (Si(CH₃)₃), 26.23 (Si(CH₃)₃), 25.76 (CH₂), 25.28 (CH₂), 24.43 (CH₂), 24.34 (CH₂), 21.28 (ArCH₃), 21.25 (ArCH₃), 18.34 (Si(CH₃)₃), 18.30 (Si(CH₃)₃), -3.26 (Si(CH₃)₃(CH₃B)), -3.54 (Si(CH₃)₃(CH₃B)), -3.72 (2xSi(CH₃)₃(CH₃B)); HRMS (ESI⁺): m/z calcd for C₂⁹H₄₂N₂O₃Si [M+H]⁺ 492.3041, found 492.3042.
Following the general procedure 1, (1R,2R)-trans-2-aminocyclohexanol (1.00 g, 4.78 mmol) was reacted with benzaldehyde (0.88 mL, 8.68 mmol) and TMSCN (1.3 mL, 10.42 mmol) in MeOH (50 mL) for 16 h at room temperature. The crude was purified by flash column chromatography (SiO2; n-Hex to n-Hex:EtOAc 70:30) to afford 2-(((1R,2R)-2-hydroxycyclohexyl)amino)-2-phenylacetanilide (1.20 g, 60%; 74:26 dr) as a colourless solid; IR (neat, cm⁻¹): νmax = 3294 (br. N–H, O–H), 2933 (C–H), 1449; ¹H NMR (400 MHz, CDCl₃) (mixture of diast A:B in a 0.74:0.26 ratio): δH = 7.55 – 7.48 (2 H, m, 2xC₆H, diast A+B), 7.44 – 7.34 (3 H, m, 3xC₆H, diast A+B), 4.98 (0.26 H, s, NCH(Ar)CN, diast B), 4.85 (0.74 H, s, NCH(Ar)CN, diast A), 3.37 – 3.25 (1 H, m, NCHCHOH, diast A+B), 2.69 (0.74 H, ddd, J = 11.2, 9.1, 4.1 Hz, NCHCHOH, diast A), 2.57 (0.26 H, ddd, J = 11.2, 9.0, 4.1 Hz, NCHCHOH, diast B), 2.47 (0.26 H, br. s, NH, diast B), 2.36 – 1.91 (3.74 H, m, NH, diast B; OH, diast A+B; 2xC₇H diast A+B), 1.84 – 1.64 (2 H, m, 2xC₇H diast A+B), 1.41 – 1.21 (3 H, m, 3xC₇H diast A+B), 1.20 – 1.01 (1 H, m, CH diast A+B).; ¹³C NMR (101 MHz, CDCl₃) δC = 135.8 (C₆H, diast B), 135.4 (C₆H, diast A), 129.15 (2xC₆H, diast B), 128.7 (C₆H, diast B), 128.4 (C₆H, diast A), 127.5 (2xC₆H, diast A), 127.3 (2xC₆H, diast B), 120.4 (C≡N, diast B), 119.1 (C≡N, diast A), 75.4 (NCHCHOH, diast B), 74.1 (NCHCHOH, diast A), 62.9 (NCHCOH, diast B), 61.6 (NCHCHOH, diast A), 53.7 (NCH(Ar)CN, diast B), 51.6 (NCH(Ar)CN, diast A), 34.3 (CH₂, diast A), 33.9 (CH₂, diast B), 31.5 (CH₂, diast B), 29.9 (CH₂, diast A), 25.0 (CH₂, diast B), 24.5 (CH₂, diast A), 24.4 (CH₂, diast A), 24.3 (CH₂, diast B); HRMS (ESI⁺): m/z calcd for C₁₄H₁₄N₂NaO₄ [M+Na⁺]: 253.1311, found 253.1318.

Following the general procedure 2, the N-alkyl-OH amino nitrile (1.10 g, 4.78 mmol) was reacted with 2,6-lutidine (0.83 mL, 7.16 mmol) and TBSOTf (1.3 mL, 5.74 mmol) in anhydrous CH₂Cl₂ (24 mL). Purification by flash column chromatography (SiO2; n-Hex to n-Hex:EtOAc 90:10) afforded 2-(((1R,2R)-2-(tert-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-phenylacetanilide (1.52 g, 92%; 80:20 dr) as a colourless solid; IR (neat, cm⁻¹): νmax = 3330 (br. N–H), 2930 (C–H), 2232 (C≡N); ¹H NMR (400 MHz, CDCl₃) (mixture of diast A:B in a 0.80:0.20 ratio): δH = 7.52 – 7.46 (2 H, m, 2xC₆H, diast A+B), 7.43 – 7.33 (3 H, m, 3xC₆H, diast A+B), 4.93 (0.20 H, s, NCH(Ar)CN, diast B), 4.77 (0.80 H, s, NCH(Ar)CN, diast A), 3.51 – 3.37 (1 H, m, NCHCHOH, diast A+B), 2.81 (0.80 H, ddd, J = 11.1, 8.6, 4.0 Hz, NCHCHOH, diast A), 2.63 (0.20 H, ddd, J = 10.1, 8.4, 4.0 Hz, NCHCHOH, diast B), 2.37 (0.80 H, br. s, NH, diast A), 2.13 – 1.58 (4.20 H, m, NH, diast A; 4xC₇H, diast A+B), 1.51 – 1.04 (4 H, m, 4xC₇H, diast A+B), 0.85 (7.20 H, s, Si(CH₃)₃, diast A), 0.84 (1.80 H, s, Si(CH₃)₃, diast B), 0.06 (3 H, s, Si(CH₃,)(CH₃,)(CH₃,)), diast A+B), 0.03 (0.60 H, s, Si(CH₃,)(CH₃,)(CH₃,), diast B), -0.01 (2.40 H, s, Si(CH₃,)(CH₃,)(CH₃,), diast A); ¹³C NMR (101 MHz, CDCl₃) δC = 136.05 (C₆H, diast B), 135.77 (C₆H, diast A), 129.11 (2xC₆H, diast A), 128.96 (2xC₆H, diast B), 128.53 (C₆H, diast B), 128.30 (C₆H, diast A), 127.25 (2xC₆H, diast A),
127.22 (2xC₅H, diast B), 120.36 (C=N, diast B), 118.78 (C=N, diast A), 76.19 (NCHCHTBS, diast B), 75.27 (NCHCHTBS, diast A), 62.19 (NCHCHTBS, diast B), 61.37 (NCHCHTBS, diast A), 53.67 (NCH(Ar)CN, diast B), 51.52 (NCH(Ar)CN, diast A), 34.45 (CH₃, diast B), 34.35 (CH₃, diast A), 31.08 (Si(CH₃)₂, diast B), 29.23 (Si(CH₃)₂, diast A), 25.93 (Si(CH₃)₂, diast B), 25.90 (Si(CH₃)₂, diast A), 24.51 (CH₂, diast A), 24.31 (CH₂, diast B), 24.26 (CH₂, diast B), 24.06 (CH₂, diast A), 18.07 (CH₂, diast A), 18.05 (CH₂, diast B), -3.64 (Si(CH₃)(CH₃)(CH₃), diast A), -3.78 (Si(CH₃)(CH₃)(CH₃), diast B), -4.47 (Si(CH₃)(CH₃)(CH₃), diast B), -4.73 (Si(CH₃)(CH₃)(CH₃), diast A); **HRMS (ESI⁺):** m/z calcd for C₉₀H₇₃N₂O₅Si [M+H]⁺ 345.2357, found 345.2356.

Following the general procedure 3 (step 1), the N-alkyl-OTBS amino nitrile (1.50 g, 4.36 mmol; 80:20 dr) was reacted with triphosgene (517 mg, 1.74 mmol) and 2,6-lutidine (0.61 mL, 5.23 mmol) in dry CH₂Cl₂ (20 mL). The crude carbamoyl chloride (1.80 g, pale yellow oil) was used in the next step without further purification. Following the general procedure 3 (step 2), the carbamoyl chloride (1.80 g), was reacted with 2,6-lutidine (0.61 mL, 5.23 mmol), KI (868 mg, 5.23 mmol) and N-methyl-p-toluidine (0.61 mL, 4.80 mmol) in dry CH₂CN (2.0 mL) in a in a microwave reactor at 110 °C for 4 h. The crude product was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:Et₂O 70:30) to afford the title compound (1.15 g, 54% over 2 steps; 50:50 dr, relative stereochemistry undetermined).

**Diast A:** Pale yellow oil. Rf 0.30 (SiO₂; n-Hex:Et₂O 80:20); IR (neat, cm⁻¹): v max = 2928 (C–H), 2239 (C=N), 1657 (C=O), 1104; ¹H NMR (400 MHz, CDCl₃): δ H = 7.59 – 7.53 (2 H, m, 2xC₅H), 7.43 – 7.30 (3 H, m, 3xC₅H), 7.16 – 7.08 (2 H, m, 2xC₅H), 6.82 – 6.74 (2 H, m, 2xC₅H), 5.10 (1 H, s, NCH(Ar)CN), 3.75 (1 H, td, J = 9.4, 4.6 Hz, NCHCHTBS), 3.37 (1 H, ddd, J = 12.7, 9.3, 3.9 Hz, NCHCHTBS), 3.06 (3 H, s, NCH), 2.33 (3 H, s, ArCH₃), 2.10 – 2.02 (1 H, m, CH), 1.61 – 1.44 (2 H, m, 2xC₅H), 1.35 – 1.19 (2 H, m, 2xC₅H), 1.14 – 1.04 (2 H, m, 2xC₅H), 0.96 (9 H, s, Si(CH₃)₃), 0.71 – 0.56 (1 H, m, CH), 0.26 (3 H, s, Si(CH₃)(CH₃)(CH₃)); ¹³C NMR (101 MHz, CDCl₃) δ C = 160.5 (C=O), 143.6 (C₅H), 135.6 (C₅H), 134.3 (C₅H), 130.0 (2xC₅H), 128.4 (C₅H), 128.3 (2xC₅H), 128.3 (2xC₅H), 125.6 (2xC₅H), 118.2 (C=H), 71.6 (NCHCHTBS), 64.9 (NCHCHTBS), 47.8 (NCH(Ar)CN), 39.8 (N(CH₃)), 36.8 (CH₂), 29.6 (CH₂), 26.3 (Si(CH₃)₃), 25.3 (CH₂), 24.3 (CH₂), 21.0 (ArCH₃), 18.3 (Si(CH₃)₃), -3.4 (Si(CH₃)(CH₃)(CH₃)), -3.8 (Si(CH₃)(CH₃)(CH₃)); **HRMS (ESI⁺):** m/z calcd for C₂₉H₄₂N₂O₅Si [M+H]⁺ 942.3041, found 942.3040.

**Diast B:** Purple oil. Rf 0.20 (SiO₂; n-Hex:Et₂O 80:20); IR (neat, cm⁻¹): v max = 2929 (C–H), 2239 (C=N), 1655 (C=O), 1100; ¹H NMR (400 MHz, CDCl₃): δ H = 7.59 – 7.52 (2 H, m, 2xC₅H), 7.40 – 7.28 (3 H, m, 3xC₅H), 7.15 – 7.08 (2 H, m, 2xC₅H), 7.03 – 6.96 (2 H, m, 2xC₅H), 5.85 (1 H, s, NCH(Ar)CN), 4.07 (1 H, td, J = 9.8, 4.2 Hz, NCHCHTBS), 3.26 (1 H, td, J = 12.7, 9.7, 3.1 Hz, NCHCHTBS), 3.16 (3 H, s, NCH), 2.32 (3 H, s, ArCH₃), 2.01 – 1.90 (1 H, m, CH), 1.78 – 1.65 (1 H, m, CH), 1.61 – 1.46 (3 H, m, 3xC₅H), 1.24 – 1.08 (1 H, m, CH), 1.04 – 0.72 (11 H, m, 2xC₅H + Si(CH₃)₃), 0.08 (3 H, s, Si(CH₃)(CH₃)(CH₃)), 0.02 (3 H, s, Si(CH₃)(CH₃)(CH₃)); ¹³C NMR (101 MHz, CDCl₃) δ C = 161.5 (C=O), 143.3 (C₅H), 135.8 (C₅H), 134.9 (C₅H), 130.3 (2xC₅H), 128.5 (C₅H), 128.4 (2xC₅H), 127.7 (2xC₅H), 125.2 (2xC₅H), 118.8 (C=H), 72.0 (NCHCHTBS), 65.3 (NCHCHTBS), 49.2 (NCH(Ar)CN), 40.5 (N(CH₃)), 37.0 (CH₂), 29.8 (CH₂), 26.2 (Si(CH₃)₃), 25.8 (CH₂), 24.5 (CH₂), 21.0 (ArCH₃), 18.3 (Si(CH₃)₃), -3.3 (Si(CH₃)(CH₃)(CH₃)), -3.6 (Si(CH₃)(CH₃)(CH₃)); **HRMS (ESI⁺):** m/z calcd for C₂₉H₄₂N₂O₅Si [M+H]⁺ 942.3041, found 942.3042.
1-((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-(4-fluorophenyl)-3-methylurea (8c)

Following the general procedure 3 (step 2), the corresponding carbamoyl chloride (see compound 8b for the synthetic procedure; 412 mg) was reacted with 2,6-lutidine (0.12 mL, 1.06 mmol) and 4-fluorophenyl-N-methyl aniline (0.12 mL, 0.97 mmol) in dry CH₂CN (1.0 mL) at reflux for 24 h. The crude product was purified by flash column chromatography (SiO₂; Pet. Ether to Pet. Ether:Et₂O 80:20) to afford the title compound (391 mg, 58% over the last 2 steps; 50:50 dr, relative stereochemistry undetermined).

**Diast. A**: orange oil. Rf 0.25 (Pet. Ether:Et₂O 80:20); IR (neat, cm⁻¹): ν max = 2926 (C–H), 2855 (C–H), 2253 (C=O) 1616 (C=O); ¹H NMR (500 MHz, CDCl₃): δ_H = 7.58 – 7.51 (2H, m, 2xAr-H), 7.39 – 7.32 (3H, m, 3xAr-H), 7.08 – 6.98 (4H, m, 4xAr-H), 5.83 (1H, s, NCH(Ar)CN), 4.08 (1H, td, J = 9.9, 4.3, NCHCHOTBS), 3.28 (1H, td, J = 9.9, 3.5, NCHCHOTBS), 3.16 (3H, s, NCH₃), 2.04 – 1.95 (1H, m, CH), 1.83 – 1.68 (1H, m, CH), 1.65 – 1.46 (3H, m, 3xCH), 1.33 – 1.11 (2H, m, 2xCH₂), 1.07 – 0.98 (1H, m, CH), 0.87 (9H, s, Si(CH₃)₃), 0.09 (3H, s, Si(CH₃)(CH₂)₂), 0.04 (3H, s, Si(CH₃)(CH₂)₂); ¹³C NMR (126 MHz, CDCl₃): δ_c = 161.57 (C=O), 160.57 (C=O, d, J=146.2), 141.84 (C=O, d, J=3.1), 134.71 (C=O), 128.62 (3xC₆H, overlap), 127.67 (2xC₆H), 126.98 (2xC₆H, d, J=8.3), 118.68 (C=O, N), 116.47 (2xC₆H, d, J=22.6), 71.98 (NCHCHOTBS), 65.71 (NCHCHOTBS), 49.23 (NCH(AR)CN), 40.57 (NCH₃), 37.00 (CH₂), 29.86 (CH₂), 26.24 (Si(CH₃)₃), 25.88 (CH₂), 24.44 (CH₂), 18.34 (Si(CH₃)₃), -3.26 (Si(CH₃)(CH₂)₂) -3.53 (Si(CH₃)(CH₂)₂); ¹⁹F NMR (377 MHz, CDCl₃) δ_F -116.01; HRMS (EI⁺): m/z calcd for [C₂₈H₃₈FN₃NaO₃Si]⁺ [M+Na]⁺ 518.2609. Found 518.2595.

**Diast. B**: yellow oil. Rf 0.22 (Pet. Ether:Et₂O 80:20); IR (neat, cm⁻¹): ν max = 2926 (C–H), 2855 (C–H), 2240 (C=O), 1616 (C=O); ¹H NMR (500 MHz, CDCl₃): δ_H = 7.56 – 7.52 (2H, m, 2xAr-H), 7.44 – 7.33 (3H, m, 3xAr-H), 7.10 – 6.98 (2H, m, 2xAr-H), 6.87 – 6.81 (2H, m, 2xAr-H), 5.09 (1H, s, NCH(AR)CN), 3.76 (1H, m, J=9.5, 4.7, NCHCHOTBS), 3.34 (1H, ddd, J=12.9, 9.3, 4.0, NCHCHOTBS), 3.05 (3H, s, NCH₃), 2.12 – 2.02 (1H, m, CH), 1.64 – 1.49 (2H, m, 2xCH₂), 1.32 – 1.18 (1H, m, CH), 1.12 – 1.05 (3H, m, 3xCH), 0.95 (9H, s, Si(CH₃)₃), 0.74 – 0.66 (1H, m, CH), 0.26 (3H, s, Si(CH₃)(CH₂)₂), 0.16 (3H, s, Si(CH₃)(CH₂)₂); ¹³C NMR (126 MHz, CDCl₃): δ_c = 160.58 (C=O), 160.47 (C=O, d, J=146.10), 142.34 (C=O, d, J=3.2), 134.08 (C₆H), 128.63 (C₆H), 128.47 (2xC₆H), 128.39 (2xC₆H, d, J=22.6), 118.07 (C=O, N), 116.31 (2xC₆H, d, J=22.6), 71.63 (NCHCHOTBS), 65.23 (NCHCHOTBS), 47.71 (NCH(AR)CN), 40.00 (NCH₃), 36.92 (CH₂), 29.72 (CH₂), 26.34 (Si(CH₃)₃), 25.42 (CH₂), 24.33 (CH₂), 18.36 (Si(CH₃)₃), -3.44 (Si(CH₃)(CH₂)₂), -3.76 (Si(CH₃)(CH₂)₂); ¹⁹F NMR (377 MHz, CDCl₃) δ_F -116.11; HRMS (EI⁺): m/z calcd for [C₂₈H₃₈FN₃NaO₃Si]⁺ [M+Na]⁺ 496.2790. Found 496.2777.
Following the general procedure 1, (1R,2R)-trans-2-aminocyclohexanol (1.18 g, 10.25 mmol) was reacted with 4-fluorobenzaldehyde (1.20 mL, 11.28 mmol) and TMSCN (1.50 mL, 12.30 mmol) in MeOH (59 mL) for 16 h at room temperature. The crude 2-(4-fluorophenyl)-2-(((1R,2R)-2-hydroxycyclohexyl)amino)acetonitrile (colourless solid; 2.70 g, 63:37 dr) was used in the next step without further purification.

Following the general procedure 2, the N-alkyl-OH amino nitrile (2.56 g, 10.25 mmol) was reacted with 2,6-lutidine (1.80 mL, 15.38 mmol) and TBSOTf (2.80 mL, 12.30 mmol) in anhydrous CH₂Cl₂ (47 mL). Purification by flash column chromatography (SiO₂; n-Hex to n-Hex:Et₃O 90:10) afforded 2-(((1R,2R)-2-(((tert-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(4-fluorophenyl)acetonitrile (1.41 g, 38% over 2 steps; 75:25 dr) as a pale yellow oil. Rₓ (n-Hex:EtOAc 70:30) 0.23; IR (neat, cm⁻¹): νₓ max = 3327 (N-H), 2930 (C-H), 2858 (C-H); ¹H NMR (400 MHz, CDCl₃) (mixture of diast A:B in a 0.75:0.25 ratio): δₓ = 7.54 – 7.39 (2H, m (Ar-H, diast. A+B), 7.08 (2H, ddt, J=8.6, 6.7, 2.0 Ar-H, diast. A+B), 4.93 (0.25H, s, NCH(Ar)CN, diast. B), 4.75 (0.75H, s, NCH(Ar)CN, diast. A), 3.43 (1H, dddd, J=19.4, 10.8, 8.5, 4.2 NHCHCHOTBS, diast. A+B), 2.79 (0.75H, ddd, J=11.1, 8.6, 4.0, NHCHCHOTBS, diast. A), 2.62 (0.25H, ddd, J=10.4, 8.3, 3.9, NHCHCHOTBS, diast. B), 2.33 (0.75H, br. d, J=12.0, NH, diast. A), 2.03 (0.75H, ddt, J=12.6, 5.3, 2.6, CH₃, diast. A), 1.98 – 1.82 (1.50H, m, CH + NH, diast. B; CH₃, diast. A+B), 1.79 – 1.67 (2H, CH₂, diast. A+B), 1.50 – 1.17 (3.25H, m, CH + CH₂, diast. A+B; CH, diast. B), 1.18 – 0.97 (0.75H, m, CH₃, diast. A) 0.84 (9H, s, Si(CH₃)₃, diast. A+B), 0.06 (3H, s, Si(CH₃)₃(CH₃)₃, diast. A + B), 0.03 (0.75H, s, Si(CH₃)₃(CH₃)₃, diast. B), -0.02 (2.25H, s, Si(CH₃)₃(CH₃)₃, diast. A). ¹³C NMR (101 MHz, CDCl₃): δ_c = 164.16 (Cₛ, d, J=249.9, diast. B), 162.98 (Cₛ, d, J=248.0, diast. A), 131.96 (Cₛ, d, J=3.3, diast. B), 131.66 (Cₛ, d, J=3.3, diast. A), 129.08 (2xCₛH, d, J=8.4, diast. A), 129.02 (2xCₛH, d, J=8.3, diast. B), 120.14 (C≡N, diast. B), 118.57 (C≡N, diast. A), 116.05 (2xCₛH, d, J=21.8, diast. A), 115.60 (2xCₛH, d, J=21.7, diast. B), 76.29 (NHCHCHOTBS, diast. B), 75.27 (NHCHCHOTBS, diast. A), 62.15 (NHCHCHOTBS, diast. B), 61.36 (NHCHCHOTBS, diast. A), 53.04 (NCH(Ar)CN, diast. B), 50.83 (NCH(Ar)CN, diast. A), 34.47 (CH₂, diast. B), 34.32 (CH₂, diast. A), 31.17 (CH₂, diast. B) 29.20 (CH₂, diast. A), 25.91 (Si(CH₃)₃, diast. B) 25.88 (Si(CH₃)₃, diast. A), 24.49 (CH₂, diast. A) 24.32 (CH₂, diast. B), 24.24 (CH₂, diast. B), 24.04 (CH₂, diast. A), 18.07 (Si(CH₃)₃, diast. A), 18.04 (Si(CH₃)₃, diast. B) -3.65 (Si(CH₃)₃(CH₃)₃, diast. A), -3.78 (Si(CH₃)₃(CH₃)₃, diast. B) -4.47 (Si(CH₃)₃(CH₃)₃, diast. B), -4.75 (Si(CH₃)₃(CH₃)₃, diast. A); HRMS (EI⁺): m/z calcd for [C₂₀H₂₃FN₂OSi]⁺ [M+H]⁺ 363.2262. Found 363.2278.
Following the general procedure 3 (step 1), the N-alkyl-OTBS amino nitrile (1.31 g, 3.60 mmol; 75:25 dr) was reacted with triphosgene (428 mg, 1.44 mmol) and 2,6-lutidine (0.50 mL, 4.32 mmol) in dry CH₂Cl₂ (18 mL). The crude carbamoyl chloride (1.39 g, yellow oil) was used in the next step without further purification. Following the general procedure 3 (step 2), the corresponding carbamoyl chloride (1.28 g) was reacted with 2,6-lutidine (0.42 mL, 3.61 mmol), potassium iodide (600 mg, 3.61 mmol) and N-methyl aniline (0.36 mL, 3.31 mmol) in dry CH₂CN (8.0 mL) in a microwave reactor at 110 °C for 4 h. The crude product was purified by flash column chromatography (SiO₂; Pet. Ether to Pet. Ether:Et₂O 80:20) to afford the title compound (194 mg, 11% over 2 steps; 50:50 dr, relative stereochemistry undetermined).

**Diast. A:** pale yellow oil. Rₗ 0.3 (Pet. Ether:Et₂O 80:20); IR (neat, cm⁻¹): ν max = 2926 (C–H), 2855 (C–H), 2242 (C≡N), 1660 (C=O); ¹H NMR (500 MHz, CDCl₃): δ H = 7.59 – 7.54 (2H, m, 2xAr-H), 7.37 – 7.31 (2H, m, 2xAr-H), 7.22 – 7.16 (1H, m, Ar-H), 7.11 – 7.02 (4H, m, 4xAr-H), 5.76 (1H, s, NCH(Ar-CN)), 4.06 – 3.99 (1H, m, NCHCHOTBS), 3.29 – 3.21 (1H, m, NCHCHOTBS), 3.19 (3H, s, CH₃), 2.00 – 1.94 (1H, m, CH), 1.76 – 1.67 (1H, m, CH), 1.61 – 1.48 (3H, m, 3xCH), 1.34 – 1.15 (1H, m, CH), 1.18 – 1.10 (1H, m, CH), 0.99 – 0.95 (1H, m, CH), 0.85 (9H, s, Si(CH₃)₃), 0.08 (3H, s, Si(CH₃)₃(CH₂CH₃)), 0.01 (3H, s, Si(CH₃)₃CH₂S); ¹³C NMR (126 MHz, CDCl₃): δ C = 162.76 (C₆H₅, d, J_C-F=247.5), 161.38 (C=O), 145.75 (C₆H₅), 130.74 (C₆H₅), 129.79 (2xC₆H₅), 129.67 (2xC₆H₅, d, J_C-F=8.3), 126.04 (C₆H₅), 125.17 (2xC₆H₅), 118.58 (C≡N), 115.55 (2xC₆H₅, d, J_C-F=21.8), 72.09 (NCHCHOTBS), 65.37 (NCHCHOTBS), 48.57 (NCH(Ar-CN)), 40.36 (NCH₂), 36.92 (CH₃), 29.86 (CH₂), 26.24 (Si(CH₃)₃), 25.74 (CH₂), 24.46 (CH₂), 18.37 (Si(CH₃)₃), -3.17 (Si(CH₃)₃(CH₂CH₃)) -3.48 (Si(CH₃)₃(CH₂CH₃)); ¹⁹F NMR (377 MHz, CDCl₃) δ F -113.49; HRMS (EI⁺): m/z calcld for [C₂₈H₃₉FN₃O₂Si⁺][M+H]⁺ 496.2790 Found 496.2777.

**Diast. B:** pale yellow oil. Rₗ 0.29 (Pet. Ether:Et₂O 80:20); IR (neat, cm⁻¹): ν max = 2925 (C–H), 2854 (C–H), 2242 (C≡N), 1661 (C=O); ¹H NMR (500 MHz, CDCl₃): δ H = 7.54 (2H, dd, J = 8.5, 5.2, 2xAr-H), 7.32 (2H, t, J = 7.7, 2xAr-H), 7.21 – 7.16 (1H, m, Ar-H), 7.10 (2H, t, J = 8.5, 2xAr-H), 6.87 (2H, d, J = 7.9, 2xAr-H), 5.05 (1H, s, NCH(Ar-CN)), 3.81 – 3.65 (1H, m, NCHCHOTBS), 3.33 (1H, ddd, J = 12.9, 9.3, 4.0, NCHCHOTBS), 3.10 (3H, s, NCH₃), 2.09 – 2.03 (1H, m, CH), 1.60 – 1.51 (1H, m, CH), 1.50 – 1.43 (1H, m, CH), 1.33 – 1.17 (1H, m, CH), 1.10 – 1.00 (3H, m, 3xCH), 0.96 (9H, s, Si(CH₃)₃), 0.65 – 0.57 (1H, m, CH), 0.26 (3H, s, Si(CH₃)₃(CH₂CH₃)), 0.15 (3H, s, Si(CH₃)₃(CH₃CH₂)); ¹³C NMR (126 MHz, CDCl₃): δ C = 162.73 (C₆H₅, d, J_C-F=246.9), 160.46 (C=O), 146.19 (C₆H₅), 130.31 (2xC₆H₅, d, J_C-F=8.3), 130.10 (C₆H₅, d, J_C-F=3.2), 129.56 (2xC₆H₅), 125.93 (C₆H₅), 125.70 (2xC₆H₅), 118.07 (C≡N), 115.41 (2xC₆H₅, d, J_C-F=21.9), 71.63 (NCHCHOTBS), 65.06 (NCHCHOTBS), 47.11 (NCH(Ar-CN)), 39.76 (NCH₂), 36.87 (CH₂), 29.86 (CH₂), 26.34 (Si(CH₃)₃), 25.28 (CH₂), 24.35 (CH₂), 18.36 (Si(CH₃)₃), -3.46 (Si(CH₃)₃(CH₂CH₃)) -3.74 (Si(CH₃)₃(CH₂CH₃)); ¹⁹F NMR (377 MHz, CDCl₃) δ F -113.44; HRMS (EI⁺): m/z calcld for [C₂₈H₃₈FN₃O₂Si⁺][M+H]⁺ 496.2790 Found 496.2777.
1-((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-methyl-3-(phenyl-d5)urea (8e)

Following the general procedure 3 (step 2), the corresponding carbamoyl chloride (see compound 8b for the synthetic procedure; 528 mg) was reacted with 2,6-lutidine (0.18 mL, 1.56 mmol) and N-methylaniline-2,3,4,5,6-d5 (160 mg, 1.43 mmol) in dry CH3CN (3.2 mL) at reflux for 24 h. The crude product was purified by flash column chromatography (SiO2; Pet. Ether to Pet. Ether:Ether:Et2O 80:20) to afford the title compound (391 mg, 51 % over 2 steps; 50:50 dr, relative stereochemistry undetermined).

**Diast. A:** yellow oil. Rf 0.24 (SiO2; n-Hex:Et2O 80:20); IR (neat, cm⁻¹): νmax = 2929 (C=H), 2856 (C=H), 2250 (C≡N), 1661 (C=O); 1H NMR (400 MHz, CDCl3): δH = 7.59 – 7.54 (2H, m, 2×Ar-H), 7.39 – 7.31 (3H, m, 3×Ar-H), 5.89 (1H, s, NCH(Ar)CN), 4.08 (1H, td, J=9.9, 4.3, NCHCHOTBS), 3.32 – 3.20 (1H, m, NCHCHOTBS), 3.20 (3H, s, NCH3), 2.00 – 1.91 (1H, m, CH), 1.77 – 1.63 (1H, m, CH), 1.59 – 1.44 (3H, m, 3×CH), 1.20 – 1.07 (1H, m, CH), 1.04 – 0.93 (1H, m, CH), 0.86 (9H, s, SiCH3), 0.82 – 0.75 (1H, m, CH) 0.09 (3H, s, Si(CH2)2(CH3)), 0.03 (3H, s, Si(CH2)2(CH3)); 13C NMR (126 MHz, CDCl3): δC = 161.49 (C=O), 145.71 (CAr), 134.83 (CAr), 129.21 (2×C6D6ArD, t, J=C-D=23.94), 128.59 (2×C6ArD), 128.55 (C6H), 127.76 (2×C6D6ArD), 125.67 – 124.35 (3×C6D6ArD, m), 118.70 (C6N), 71.98 (NCHCHOTBS), 65.40 (NCHCHOTBS), 49.21 (NCH(Ar)CN), 40.31 (NCH3), 36.97 (CH2), 29.79 (CH2), 26.25 (SiCH3), 25.78 (CH2), 24.45 (CH2), 18.34 (SiCH3), -3.25 (Si(CH2)2(CH3)), -3.62 (Si(CH2)2(CH3)); HRMS (ESI⁺): m/z calcd for [C28H33D5N3NaO2Si]⁺ [M+Na]⁺ 505.3018 Found 505.3014.

**Diast. B:** yellow oil. Rf 0.17 (SiO2; n-Hex:Et2O 80:20); IR (neat, cm⁻¹): νmax = 2930 (C=H), 2856 (C=H), 2278 (C≡N), 1659 (C=O); 1H NMR (400 MHz, CDCl3): δH = 7.60 – 7.53 (2H, m, 2×Ar-H), 7.45 – 7.33 (3H, m, 3×Ar-H), 5.11 (1H, s, NCH(Ar)CN), 3.80 – 3.71 (1H, m, NCHCHOTBS), 3.34 (1H, ddd, J=12.9, 9.3, 4.0, NCHCHOTBS), 3.10 (3H, s, NCH3), 2.10 – 2.01 (1H, m, CH), 1.59 – 1.51 (1H, m, CH), 1.52 – 1.42 (1H, m, CH), 1.34 – 1.27 (1H, m, CH), 1.17-1.03 (3H, m, 3×CH), 0.96 (9H, s, SiCH3), 0.68 – 0.57 (1H, m, CH), 0.26 (3H, s, Si(CH2)2(CH3)), 0.16 (3H, s, Si(CH2)2(CH3)); 13C NMR (126 MHz, CDCl3): δC = 160.48 (C=O), 146.13 (C6H6D5), 143.22 (C6), 129.01 (2×C6D6ArD, t, J=C-D=23.94), 129.53 (C6H), 128.45 (2×C6ArD), 128.37 (2×C6ArD), 125.63 – 124.92 (3×C6D6ArD, m), 118.18 (C≡N), 71.64 (NCHCHOTBS), 65.05 (NCHCHOTBS), 47.79 (NCH(Ar)CN), 39.71 (NCH3), 36.90 (CH2), 29.61 (CH2), 26.36 (SiCH3), 25.30 (CH2), 24.36 (CH2), 18.37 (SiCH3), -3.51 (Si(CH2)2(CH3)), -3.69 (Si(CH2)2(CH3)); HRMS (ESI⁺): m/z calcd for [C28H33D5N3NaO2Si]⁺ [M+H]⁺ 483.3198 Found 483.3198.
Following the general procedure 4 (method A), the N'-aryl ureido nitrile **8a** (200 mg, 0.407 mmol; 50:50 dr) was reacted with LDA (0.51 mL, 2.0 m in THF/heptane/ethylbenzene, 1.017 mmol) in anhydrous THF (3.6 mL) at room temperature for 3 h. The crude product (>95:5 dr by NMR) was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:EtOAc 80:20 to 50:50) to afford the title compound (169 mg, 85%, 95:5 dr; absolute configuration assigned by analogy to 9b) as a yellow oil. Rf 0.25 (SiO₂; n-Hex:EtOAc 60:40); IR (neat, cm⁻¹): νmax = 3320 (N=H), 2943 (C=H), 1732 (C=O), 1457; ¹H NMR (400 MHz, CDCl₃); δH = 7.78 – 7.68 (2 H, m, 2xC₆H), 7.41 – 7.32 (3 H, m, 3xC₆H), 7.17 – 7.09 (4 H, m, 4xC₆H), 6.89 (1 H, br. s, NH), 4.77 (1 H, br. d, J = 9.1 Hz, NCHCHOTBS), 3.13 (3 H, s, NCH₃), 2.94 – 2.85 (1 H, m, NCHCHOTBS), 2.36 (3 H, s, ArCH₃), 1.92 (1 H, br. dd, J = 5.1, 2.5 Hz, CH), 1.58 – 1.46 (1 H, m, CH), 1.38 – 1.10 (5 H, m, 5xC₆H), 0.96 (9 H, s, Si(C₃H₃)₃), 0.77 – 0.62 (1 H, m, CH), 0.20 (3 H, s, Si(CH₃)(CH₃,8)), 0.08 (3 H, s, Si(CH₃)(CH₃,8)); ¹³C NMR (101 MHz, CDCl₃) δC = 168.0 (C=N), 155.7 (C=O), 138.8 (C₆H), 138.6 (C₆H), 137.8 (C₆H), 129.3 (2xC₆H), 128.9 (2xC₆H), 128.6 (C₆H), 128.5 (2xC₆H), 128.2 (2xC₆H), 75.0 (NC(Ph), 72.4 (NCHCHOTBS), 60.9 (NCHCHOTBS), 37.4 (CH₃), 29.3 (Si(CH₃)₃), 26.1 (Si(CH₃)₃), 25.4 (CH₂), 25.3 (NCH₃), 24.6 (CH₂), 21.1 (ArCH₃), 18.2 (CH₂), -3.9 Si(CH₃)(CH₃,8), -5.8 Si(CH₃)(CH₃,8); HRMS (ESI⁺): m/z calcd for C₂₀H₂₁N₂NaO₂Si [M+Na]⁺ 514.2860, found 514.2857.

Following the general procedure 4 (method B), the N'-aryl ureido nitrile **8b** (200 mg, 0.407 mmol; 50:50 dr) was reacted with LDA (0.51 mL, 2.0 m in THF/heptane/ethylbenzene, 1.017 mmol) in a mixture of anhydrous THF (3.6 mL) and DMPU (0.36 mL) at 40 °C for 20 h. The crude product (95:5 dr by ¹H-NMR) was purified by flash column chromatography (SiO₂; n-Hex:EtOAc 80:20 to 50:50) to afford the title compound (169 mg, 74%, 95:5 dr) as a beige solid. Rf 0.25 (SiO₂; n-Hex:EtOAc 60:40); m.p. = 93 – 95 °C; [α]D²⁵ = -212 (c = 1.0, CHCl₃); IR (neat, cm⁻¹): νmax = 3318 (N=H), 2928 (C=H), 1731 (C=N), 1659 (C=O), 1460; ¹H NMR (500 MHz, CDCl₃); δH = 7.75 – 7.69 (2 H, m, 2xC₆H), 7.37 – 7.31 (3 H, m, 3xC₆H), 7.27 – 7.23 (2 H, m, 2xC₆H), 7.21 – 7.17 (2 H, m, 2xC₆H), 6.90 (1 H, br. s, NH), 4.83 – 4.72 (1
Following the general procedure 4 (method B), the N'-aryl ureido nitrile 8c (53 mg, 0.108 mmol; 50:50 dr) was reacted with LDA (0.13 mL, 2.0 M in THF/heptane/ethylbenzene, 0.270 mmol) in a mixture of anhydrous THF (1.0 mL) and DMPU (0.1 mL) at +40 °C for 20 h. The crude product (94:6 dr by 19F-NMR) was purified by flash column chromatography (SiO2; Pet. Ether:Et2O 100:0 to 70:30) to afford the title compound (27 mg, 51%, 94:6 dr) as a yellow oil. Rf 0.25 (SiO2; Pet. Ether:Et2O 70:30); IR (neat, cm⁻¹):  νmax = 3321 (N=H), 2930 (C–H), 2856 (C–H), 1737 (C=N), 1660 (C=O) ppm; ¹H NMR (400 MHz, CDCl₃): δH = 7.89 – 7.83 (2H, m, 2xAr-H), 7.40 – 7.32 (3H, m, 3xAr-H), 7.25 – 7.21 (2H, m, 2xAr-H), 7.10 – 7.03 (2H, m, 2xAr-H), 4.78 (1H, dt, J= 10.2, 5.2, NCHOTBS), 3.14 (3H, s, NCOTBS), 2.87 (1H, ddd, J= 11.9, 9.7, 3.0 NCHOTBS), 1.97 – 1.88 (1H, m, CH), 1.57 – 1.48 (1H, m, CH), 1.33 – 1.27 (1H, m, CH), 1.24 – 1.17 (3H, m, 3xCH), 0.96 (9H, s, Si(CH₃)₃), 0.76 – 0.64 (1H, m, CH), 0.20 (3H, s, Si(CH₃)₃(CH₃,8)), 0.07 (3H, Si(CH₃)₃(CH₃,8)), 0.06 – (-0.03) (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δC = 167.83 (C=N), 162.91 (C=Ar, d, δC,F=248.0), 155.67 (C=O), 140.82 (C=Ar), 134.32 (C=Ar, d, δC,F=3.1), 130.78 (2xAr-H, d, δC,F=8.0), 129.22 (C=Ar), 129.00 (2xAr-H), 128.95 (2xAr-H), 115.58 (2xAr-H, d, δC,F=21.4), 74.81 (NC(=N)Ph), 72.56 (NCHOTBS), 61.15 (NCHOTBS), 37.59 (CH₂), 29.34 (CH₂), 26.21 (Si(CH₃)₃), 25.59 (NCH₃), 25.37 (CH₂), 24.71 (CH₂), 18.36 (Si(CH₃)₃), -3.77 (Si(CH₃)₃(CH₃,8)), -5.61 (Si(CH₃)₃(CH₃,8)); 19F NMR (377 MHz, CDCl₃) δF = -114.09; HRMS (ESI⁺): m/z calcd for [C₂₉H₄₁F₇N₃O₇Si]⁺ [M+H⁺]⁺ 496.2790. Found 496.2806.
(R)-3-((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-4-(4-fluorophenyl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (9d)

Following the general procedure 4 (method A), the \( N' \)-aryl ureido nitrile 8d (48 mg, 0.096 mmol; 50:50 dr) was reacted with LDA (0.14 mL, 2.0 m in THF/heptane/ethylbenzene, 0.288 mmol) in anhydrous THF (0.96 mL) at room temperature for 3 h. The crude product (98:2 dr by \( ^{19}\text{F-NMR} \)) was purified by flash column chromatography (SiO\(_2\); Pet. Ether:Et\(_2\)O 100:0 to 60:40) to afford the title compound (44 mg, 93%, 98:2 dr) as a colourless oil. R\(_f\) 0.17 (SiO\(_2\); Pet. Ether:Et\(_2\)O 60:40); IR (neat, cm\(^{-1}\)): \( \nu_{\text{max}} = 3315 \) (N–H), 2928 (C–H), 2855 (C–H), 1731 (C=O), 1656 (C=O); \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \)= 7.86 – 7.81 (2H, m, 2xAr-H), 7.43 – 7.33 (3H, m, 3xAr-H), 7.26 – 7.21 (2H, m, 2xAr-H), 7.08 – 7.01 (2H, m, 2xAr-H), 4.83 – 4.74 (1H, m, C=N), 4.59 (2xCH, d, \( J=11.8, 9.5 \)), 2.99 (1H, d, \( J=10.8 \)) as a colourless oil. R\(_f\) 0.20 (THF/methylene chloride, 0.288 mL, 2.0 m). HRMS: m/z calcd for [\( \text{C}_{35}\text{H}_{35}\text{FNO}_5\text{Si} \]+ [M+H]+ 496.2790. Found 496.2811.

(S)-3-((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-5-imino-1-methyl-4 phenyl-4-(phenyl d\(_3\))imidazolidin-2-one (9e)

Following the general procedure 4 (method A), the \( N' \)-aryl ureido nitrile 8e (65 mg, 0.135 mmol; 50:50 dr) was reacted with LDA (0.20 mL, 2.0 m in THF/heptane/ethylbenzene, 0.405 mmol) in anhydrous THF (1.2 mL) at room temperature for 16 h. The crude product was purified by flash column chromatography (SiO\(_2\); Pet. Ether:Et\(_2\)O 100:0 to 50:50) to afford the title compound (49 mg, 75%, 95:5 dr by 2D-NMR) as an orange oil. R\(_f\) 0.17 (SiO\(_2\); Pet. Ether:Et\(_2\)O 50:50); IR (neat, cm\(^{-1}\)): \( \nu_{\text{max}} = 3314 \) (N–H), 2928 (C–H), 2855 (C–H), 1731 (C=O), 1658 (C=O); \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) = 7.38 – 7.31 (3H, m, 3xAr-H), 7.27 – 7.23 (2H, m, 2xAr-H), 6.93 (br. s, 1H, NH), 4.87 – 4.68 (1H, m, NCHCHOTBS), 3.14
(3H, s, NCH$_3$), 2.91 (1H, ddd, J= 11.9, 9.6, 3.0, NCHOTBS), 1.96 – 1.89 (1H, m, CH), 1.55 – 1.49 (1H, m, CH), 1.33 – 1.27 (1H, m, CH), 1.25 – 1.15 (3H, m, 3xCH), 0.97 (9H, s, Si(CH$_3$)$_3$), 0.75 – 0.62 (1H, m, CH), 0.20 (3H, s, Si(CH$_3$)$_3$)(CH$_3$)$_2$), 0.09 (3H, Si(CH$_3$)$_3$)(CH$_3$)$_2$), 0.06 – (-0.01) (1H, m, CH); $^{13}$C NMR (126 MHz, CDCl$_3$) δ C = 167.99 (C=N), 155.80 (C=O), 140.99 (C$_{Ar}$), 138.31 (C$_{Ar}$), 129.11 (2xC$_{Ar}$H), 129.07 (C$_{Ar}$H), 128.83 (2xC$_{Ar}$H), 128.80 – 127.64 (5xC$_{Ar}$D, m), 75.27 (NCArPh), 72.52 (NCHOTBS), 61.11 (NCHCHOTBS), 37.59 (CH$_2$), 29.36 (CH$_3$), 26.22 (Si(CH$_3$)$_3$), 25.61 (NCH$_3$), 25.37 (CH$_2$) 24.72 (CH$_2$), 18.35 (Si(CH$_3$)$_3$), -3.79 (Si(CH$_3$)$_3$)(CH$_3$)$_2$), -5.61 (Si(CH$_3$)$_3$)(CH$_3$)$_2$); HRMS (ESI$^+$): m/z calcd for [C$_{29}$H$_{35}$D$_3$N$_2$O$_3$Si]$^+$ [M+H]$^+$ 483.3198. Found 483.3198.

(5)-1-((1R,2R)-2-Hydroxycyclohexyl)-3-methyl-5-phenyl-5-(p-tolylimidazolidine-2,4-dione (10b)

HCl (2.0 mL, 2 M, aq.) was added to a solution of the 4-iminothydantoin 9b (100 mg, 0.203 mmol, 95:5 dr) in MeOH (2.0 mL) and the reaction mixture was heated to reflux for 72 h (progress monitored by TLC). The acidic media was neutralised by addition of NaHCO$_3$ (sat. aq.). The mixture was partitioned between H$_2$O and EtOAc. The aqueous phase was further extracted (x2) in EtOAc, and the combined organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$; n-Hex:EtOAc 90:10 to 50:50) to afford the title compound (66 mg, 86%, 95:5 dr) as a colourless solid; R$_f$ 0.70 (SiO$_2$; EtOAc); m.p. = 172 – 173 °C; [α]$_D^{25} = -190$ (c = 0.5, CHCl$_3$); IR (neat, cm$^{-1}$): $\nu_{max}$ = 3463 (br. O–H), 2938 (C–H), 1764 (C=O), 1697 (C=O), 1450; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ H = 7.68 – 7.59 (2 H, m, 2xC$_{Ar}$H), 7.40 – 7.34 (3 H, m, 3xC$_{Ar}$H), 7.29 – 7.25 (2 H, m, 2xC$_{Ar}$H), 7.22 – 7.17 (2 H, m, 2xC$_{Ar}$H), 4.45 (1 H, tt, J = 10.0, 5.0 Hz, NCHCHOTBS), 3.10 (3 H, s, NCH$_3$), 3.01 (1 H, ddd, J = 11.7, 9.9, 3.4 Hz, NCHCHOTBS), 2.36 (3 H, s, ArCH$_2$), 2.04 – 1.97 (1 H, m, CH), 1.86 (1 H, d, J = 5.9 Hz, OH), 1.62 – 1.54 (1 H, m, CH), 1.48 (1 H, qd, J = 12.8, 3.6 Hz, CH), 1.42 – 1.32 (1 H, m, CH), 1.30 – 1.07 (2 H, m, 2xCH), 0.78 (1 H, qt, J = 13.2, 3.9 Hz, CH), 0.65 – 0.57 (1 H, m, CH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ C = 174.2 (C=O)$_{amide}$, 156.1 (C=O)$_{urea}$, 138.8 (C$_{Ar}$), 138.7 (C$_{Ar}$), 133.8 (C$_{Ar}$), 129.3 (2xC$_{Ar}$H), 129.2 (2xC$_{Ar}$H), 129.2 (C$_{Ar}$H), 129.0 (2xC$_{Ar}$H), 128.8 (2xC$_{Ar}$H), 128.8 (NCArPh), 71.0 (NCHOTBS), 61.7 (NCHCHOTBS), 36.0 (CH$_2$), 29.7 (CH$_2$), 25.4 (CH$_3$), 25.2 (NCH$_3$), 24.6 (CH$_3$), 21.3 (ArCH$_3$); HRMS (ESI$^+$): m/z calcd for [C$_{23}$H$_{27}$N$_2$O$_3$][M+H]$^+$ 379.2016, found 379.2019.
(S)-3-Methyl-5-phenyl-5-(p-tolyl)imidazolidine-2,4-dione (11b)

In a sealed tube, an emulsion of the hydantoin 10b (50 mg, 0.132 mmol) in neat polyphosphoric acid (PPA, 2 mL) was heated at 100 °C stirring for 16 h. After cooling down to room temperature, the reaction mixture was partitioned between H₂O (exothermic!) and CH₂Cl₂. The aqueous phase was further extracted (x2) in CH₂Cl₂, and the combined organic phase was washed with H₂O, NaHCO₃ (aq., sat.), brine, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂; n-Hex to n-Hex:EtOAc 70:30) to afford the title compound (19 mg, 52%, 95:5 er) as a colourless solid; \( [\alpha]_D^{25} = +10 \) (c = 0.3, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta_H = 7.42 – 7.32 \) (6 H, m, 5xCₐH+NH), 7.29 – 7.23 (2 H, m, 2xCₐH), 7.19 – 7.13 (2 H, m, 2xCₐH), 3.07 (3 H, s, NC₃H₃), 2.34 (3 H, s, ArC₃H₃); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta_C = 173.8 \) (C=O)amide, 157.2 (C=O)urea, 139.4 (Cₐ), 138.5 (Cₐ), 136.4 (Cₐ), 129.6 (2xCₐH), 128.8 (2xCₐH), 128.6 (Cₐ), 126.9 (2xCₐH), 126.8 (2xCₐH), 70.3 (NC(Ar)Ph), 25.1 (NCH₃), 21.2 (ArCH₃); HRMS (ESI\(^+\)): m/z calcd for C₁₇H₁₆N₂NaO₂ [M+Na\(^+\)] 303.1104, found 303.1108. Chiral HPLC: (R,R) Whelk-O\(^*\) 1, n-Hexane:IPA = 90:10, T = 25 °C, flow = 1.0 mL/min., \( \lambda = 254 \) nm; \( t_{R,A} = 22.4 \) min (minor), \( t_{R,B} = 24.2 \) min (major); 95:5 er. The racemic sample was prepared by \( N \)-methylation of commercial 5-(4-methylphenyl)-5-phenylhydantoin (CAS: 51169-17-6).\(^{[3]}\)
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