

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

Josep Mas-Roselló^a, Mary Okoh^a and Jonathan Clayden^{*a}

^aSchool of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK

*Corresponding author: j.clayden@bristol.ac.uk

Supporting Information

CONTENTS

Page S2	General Information
Page S3-S29	Experimental Procedures and Characterisation Data
Page S30-S59	¹ H, ¹³ C and ¹⁹ F NMR Spectra
Page S60	References

General Information

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, Et₂O and CH₂Cl₂ were obtained from a purification column composed of activated alumina (A-2).^[1] CH₃CN, MeOH and EtOH were purchased from Acros as extra dry solvent over 3Å molecular sieves. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) and 2,2,6,6-tetramethylpiperidine (HTMP) were distilled under reduced pressure from CaH₂ 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*-benzylbenamide.^[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 (KHMDs) were used as a solution in THF (1.0 M from Sigma-Aldrich). Et₃N 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 F₂₅₄). 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.

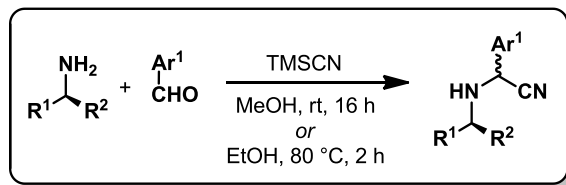
¹H, ¹³C and ¹⁹F NMR spectra were recorded on Jeol ECS (400 MHz), Varian VNMR (400 MHz or 500 MHz) or Bruker Ultrashield (400 MHz) spectrometers. Chemical shifts (δ_H, δ_C and δ_F) are quoted in parts per million (ppm) and referenced to the appropriate NMR residual solvent peak(s). For CDCl₃ (δ_H: 7.26 ppm; δ_C: 77.16 ppm), CD₂Cl₂ (δ_H: 5.32 ppm; δ_C: 54.00 ppm) and CD₃OD (δ_H: 3.31 ppm; δ_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^T) were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter where *c* is given in g/100 mL.

Experimental Procedures and Characterisation Data

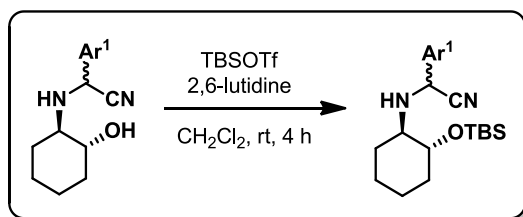
General Procedure 1: Strecker synthesis of *N*-alkyl amino nitriles from chiral primary amines and aromatic aldehydes.



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.

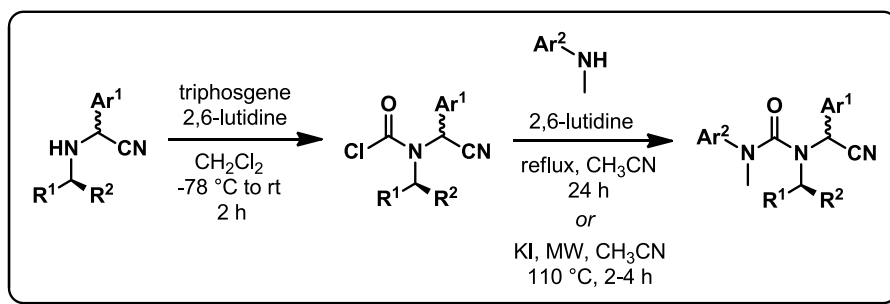
Note: all the apparatus that stayed in contact with TMSCN was quenched with bleach.

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



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.

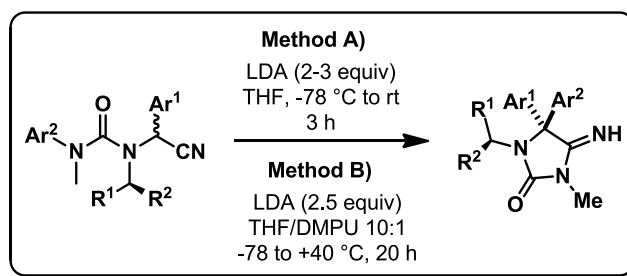
General Procedure 3: Synthesis of *N'*-aryl ureido nitriles from *N*-alkyl amino nitriles



Step 1: Triphosgene (0.4 equiv) was dissolved in dry CH_2Cl_2 (0.4 M). The solution was cooled to $-78\text{ }^\circ\text{C}$. 2,6-lutidine (1.2 equiv) was added dropwise and the reaction mixture was left to stir for 10 min. The *N*-alkyl amino nitrile was added dropwise as a solution in CH_2Cl_2 . The mixture was warmed to room temperature and left to stir for 2 h. The reaction was quenched by addition of HCl (1 M, aq.), washed with HCl (1 M, aq.), NaHCO_3 (sat. aq.), brine, dried over Na_2SO_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 *N*-methylaniline (1.0–2.0 equiv) were added to a solution of the carbamoyl chloride (1.0 equiv) in dry CH_3CN (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 $110\text{ }^\circ\text{C}$ in a microwave reactor for 2–4 h. The solvent was removed under reduced pressure and the resulting residue was partitioned between EtOAc and HCl (1 M, aq.). The aqueous phase was further extracted (x2) in EtOAc and the combined organic phase was washed with NaHCO_3 (sat. aq.), brine, dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

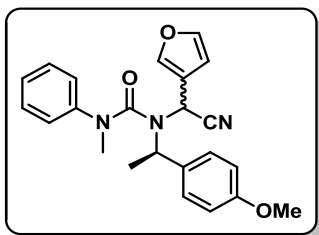
General Procedure 4: Synthesis of 5,5-diaryl-4-iminohydantoin from *N'*-aryl ureido nitriles



In a flame-dried round-bottom flask, the *N'*-aryl ureido nitrile (1.0 equiv) was dissolved in anhydrous THF (0.1 M) under a nitrogen atmosphere. The mixture was cooled to $-78\text{ }^\circ\text{C}$ and LDA (2–3 equiv, 2.0 M in THF/heptane/ethylbenzene) was added dropwise. The reaction mixture was stirred for 10 minutes at $-78\text{ }^\circ\text{C}$ 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 THF at room temperature before cooling to $-78\text{ }^\circ\text{C}$ and adding the LDA) heating to $+40\text{ }^\circ\text{C}$ stirring for 20 h (Method B). The reaction mixture was quenched at room temperature by addition of NH_4Cl (sat. aq.) and then partitioned between H_2O and EtOAc. The aqueous layer was

further extracted (x2) in EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

(R)-1-(Cyano(furan-3-yl)methyl)-1-(1-(4-methoxyphenyl)ethyl)-3-methyl-3-phenylurea (6a)



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 $^1\text{H-NMR}$) was purified by flash column chromatography (SiO_2 , *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; **R_f** 0.45 (SiO_2 ; *n*-Hex:EtOAc 70:30); **IR** (neat, cm^{-1}): ν_{max} = 3320, 2836, 1511, 1241, 1022, 600; **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ_{H} = 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 $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}$]⁺ 257.1285, found 257.1292. **Minor diast.**: brown oil; **R_f** 0.50 (SiO_2 ; *n*-Hex:EtOAc 70:30); **IR** (neat, cm^{-1}): ν_{max} = 3321, 2836, 1611, 1512, 1244, 601; **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ_{H} = 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 $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}$]⁺ 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 CH_2Cl_2 (37 mL). The crude was purified by flash column chromatography (SiO_2 , *n*-Hex to *n*-Hex:Et₂O 50:50) to afford the corresponding carbamoyl chloride (2.36 g, 99%; 80:20 *dr*) as a yellow oil. **R_f** 0.40 (SiO_2 ; *n*-Hex: Et₂O 50:50); **$^1\text{H NMR}$** (500 MHz, CDCl_3) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): δ_{H} = 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).

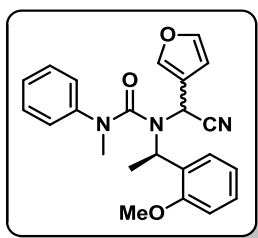
Following a similar method to general procedure 3 (step 2), the carbamoyl chloride (2.00 g, 6.27 mmol), was reacted with triethylamine (0.96 mL, 6.90 mmol) and *N*-methylaniline (0.75 mL, 6.90 mmol) in dry CH_3CN (16 mL) at reflux for 16 h. The crude product (50:50 *dr* by $^1\text{H-NMR}$) was purified by flash column chromatography (SiO_2 ; *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; **R_f** 0.25 (SiO_2 ; *n*-Hex:Et₂O 50:50); **IR** (neat, cm^{-1}): ν_{max} = 2930 (C–H), 2241 ($\text{C}\equiv\text{N}$), 1661 (C=O), 1513, 1374, 1251; **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ_{H} = 7.45 (d, J =0.8 Hz, 1 H, $\text{C}_{\text{Ar}}\text{H}$), 7.41 (td, J =7.3, 1.8 Hz, 2 H, $2\times\text{C}_{\text{Ar}}\text{H}$), 7.34 – 7.27 (m, 2 H, $2\times\text{C}_{\text{Ar}}\text{H}$), 7.07 (dd, J =8.3, 1.0 Hz, 2 H, $2\times\text{C}_{\text{Ar}}\text{H}$), 6.74 (d, J =8.8 Hz, 2 H, $2\times\text{C}_{\text{Ar}}\text{H}$), 6.63 (d, J =8.6 Hz, 2 H, $2\times\text{C}_{\text{Ar}}\text{H}$), 6.02 (d, J =1.0 Hz, 1 H, $\text{C}_{\text{Ar}}\text{H}$), 4.94 (q, J =6.9 Hz, 1 H, NCHCH_3), 4.65 (s, 1 H, NCHCN), 3.77 (s, 3 H, OCH_3), 3.21 (s, 3 H, NCH_3), 1.66 (d, J =7.1 Hz, 3 H, NCHCH_3); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ_{C} = 161.3 (C=O), 159.3 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 146.1 (C_{Ar}), 143.0 ($\text{C}_{\text{Ar}}\text{H}$), 142.2

(C_{Ar}H), 130.6 (C_{Ar}), 129.9 (2xC_{Ar}H), 128.8 (2xC_{Ar}H), 126.6 (C_{Ar}H), 126.2 (2xC_{Ar}H), 119.3 (C_{Ar}), 118.8 (C≡N), 113.9 (2xC_{Ar}H), 110.0 (C_{Ar}H), 57.1 (NCH(CH₃)Ar), 55.3 (OCH₃), 40.4 (NCH₃), 40.0 (NCHCN), 16.6 (NCH(CH₃)Ar); **HRMS** (ESI⁺): *m/z* calcd for C₂₃H₂₄N₃O₃ [M+H]⁺ 390.1812, found 390.1803.

Diast B: Orange oil. *R_f* 0.15 (SiO₂; *n*-Hex:Et₂O 50:50); **IR** (neat, cm⁻¹): ν_{max} = 2930 (C–H), 2249 (C≡N), 1655 (C=O), 1513, 1393, 1251; **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.64 (d, *J*=0.8 Hz, 1 H, C_{Ar}H), 7.43 (t, *J*=1.6 Hz, 1 H, C_{Ar}H), 7.38 (t, *J*=7.8 Hz, 2 H, 2xC_{Ar}H), 7.26 (t, *J*=7.6 Hz, 1 H, C_{Ar}H), 7.20 (d, *J*=8.6 Hz, 2 H, 2xC_{Ar}H), 7.03 (d, *J*=7.6, 2 H, 2xC_{Ar}H), 6.91 (d, *J*=8.6 Hz, 2 H, 2xC_{Ar}H), 6.37 (d, *J*=1.0 Hz, 1 H, C_{Ar}H), 4.95 (q, *J*=7.1 Hz, 1 H, NCHCH₃), 4.72 (s, 1 H, NCHCN), 3.81 (s, 3 H, OCH₃), 3.23 (s, 3 H, NCH₃), 0.95 (d, *J*=7.1 Hz, 3 H, NCHCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 160.8 (C=O), 159.5 (C_{Ar}OCH₃), 146.0 (C_{Ar}), 143.4 (C_{Ar}H), 142.3 (C_{Ar}H), 130.5 (C_{Ar}), 129.8 (2xC_{Ar}H), 128.6 (2xC_{Ar}H), 126.3 (C_{Ar}H), 126.0 (2xC_{Ar}H), 119.6 (C_{Ar}), 116.6 (C≡N), 114.1 (2xC_{Ar}H), 109.7 (C_{Ar}H), 56.8 (NCH(CH₃)Ar), 55.2 (OCH₃), 41.2 (NCH₃), 40.3 (NCHCN), 15.6 (NCH(CH₃)Ar); **HRMS** (ESI⁺): *m/z* calcd for C₂₃H₂₄N₃O₃ [M+H]⁺ 390.1812, found 390.1807.

(*R*)-1-(Cyano(furan-3-yl)methyl)-1-(1-(2-methoxyphenyl)ethyl)-3-methyl-3-phenylurea (6b)



Following the general procedure 1, (*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 (*R*)-2-(furan-3-yl)-2-((1-(2-methoxyphenyl)ethyl)amino)acetonitrile product (0.70 g; 70:30 *dr* by ¹H-NMR; *relative stereochemistry undetermined*) was used in the next step without further purification. Yellow oil; *R_f* 0.45 (SiO₂; *n*-Hex:EtOAc 70:30); **IR** (neat, cm⁻¹): ν_{max} = 3320, 2836, 1512, 1243, 600; **¹H NMR** (400 MHz, CD₂Cl₂) (mixture of diastereoisomers A:B in a 0.7:0.3 ratio): δ_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); **¹³C NMR** (101 MHz, CD₂Cl₂) δ_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), 122.21 (diast B), 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⁺): *m/z* calcd for C₁₅H₁₇N₂O₂ [M+H]⁺ 257.1285, found 257.1288.

Following a similar method to general procedure 3 (step 1), the *N*-alkyl amino nitrile (650 mg, 2.536 mmol; 70:30 *dr*) was reacted with triphosgene (301 mg, 1.014 mmol) and pyridine (0.25 mL, 3.043 mmol) in dry CH₂Cl₂ (13 mL). The crude was purified by flash column chromatography (SiO₂, *n*-Hex to *n*-Hex:Et₂O 50:50) to afford the corresponding carbamoyl chloride (614 mg, 76% over 2 steps; 70:30

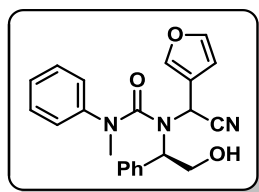
dr) as a yellow oil. **R_f** 0.40 (SiO₂; *n*-Hex: Et₂O 50:50); **¹H NMR** (400 MHz, CD₂Cl₂) (mixture of diastereoisomers A:B in a 0.7:0.3 ratio): δ_H = 7.51 (q, *J* = 1.1 Hz, 0.7H, diast A), 7.48 – 7.40 (m, 2.0H, diast A+B), 7.37 (d, *J* = 7.6 Hz, 0.7H, diast A), 7.17 (t, *J* = 1.7 Hz, 0.3H, diast B), 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; **R_f** 0.15 (SiO₂; *n*-Hex:Et₂O 50:50); **IR** (neat, cm⁻¹): ν_{max} = 2926 (C–H), 2239 (C≡N), 1659 (C=O), 1512, 1379, 1250; **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.62 (dt, *J* = 1.8, 1.0 Hz, 1H, C_{Ar}H), 7.41 (t, *J* = 1.7 Hz, 1H, C_{Ar}H), 7.40 – 7.33 (m, 3H, 3x C_{Ar}H), 7.24 (tt, *J* = 7.9, 1.3 Hz, 1H, C_{Ar}H), 7.15 (ddd, *J* = 7.8, 1.7, 0.7 Hz, 1H, C_{Ar}H), 7.09 – 7.04 (m, 2H, 2x C_{Ar}H), 6.95 (dtd, *J* = 7.6, 4.0, 3.5, 1.1 Hz, 2H, 2x C_{Ar}H), 6.33 (dd, *J* = 1.9, 0.9 Hz, 1H, C_{Ar}H), 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, NCH₃), 0.72 (d, *J* = 7.1 Hz, 3H, NCHCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 161.41 (C=O), 158.61 (C_{Ar}OCH₃), 146.37 (C_{Ar}), 143.31 (C_{Ar}H), 142.35 (C_{Ar}H), 130.36 (C_{Ar}H), 129.68 (2x C_{Ar}H), 126.86 (2x C_{Ar}H), 126.82 (C_{Ar}H), 126.29 (C_{Ar}H), 126.21 (C_{Ar}), 120.55 (C_{Ar}H), 120.09 (C_{Ar}), 116.75 (C≡N), 110.96 (C_{Ar}H), 109.77 (C_{Ar}H), 56.09 (OCH₃), 53.24 (NCH(CH₃)Ar), 41.00 (NCHCN), 39.90 (NCH₃), 15.09 (NCH(CH₃)Ar); **HRMS** (ESI⁺): *m/z* calcd for C₂₃H₂₄N₃O₃ [M+H]⁺ 390.1812, found 390.1815.

Diast B: Yellow oil. **R_f** 0.25 (SiO₂; *n*-Hex:Et₂O 50:50); **IR** (neat, cm⁻¹): ν_{max} = 2930 (C–H), 2245 (C≡N), 1657 (C=O), 1512, 1384, 1250; **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.39 – 7.33 (m, 2H, 2x C_{Ar}H), 7.27 – 7.16 (m, 5H, 5x C_{Ar}H), 7.10 (ddd, *J* = 7.7, 1.7, 0.7 Hz, 1H, C_{Ar}H), 6.97 (dt, *J* = 1.6, 0.9 Hz, 1H, C_{Ar}H), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H, C_{Ar}H), 6.70 (dd, *J* = 8.2, 1.2 Hz, 1H, C_{Ar}H), 6.14 (dd, *J* = 1.9, 0.8 Hz, 1H, C_{Ar}H), 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, NCH₃), 1.03 (d, *J* = 7.1 Hz, 3H, NCHCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 161.87 (C=O), 158.04 (C_{Ar}OCH₃), 146.47 (C_{Ar}), 142.42 (C_{Ar}H), 142.23 (C_{Ar}H), 129.82 (C_{Ar}H), 129.72 (2x C_{Ar}H), 127.60 (C_{Ar}H), 127.42 (C_{Ar}), 126.10 (C_{Ar}H), 125.98 (2x C_{Ar}H), 120.30 (C_{Ar}), 119.79, 117.63 (C_{Ar}H), 110.88 (C_{Ar}H), 110.54 (C_{Ar}H), 55.36 (OCH₃), 52.99 (NCH(CH₃)Ar), 41.68 (NCHCN), 40.68 (NCH₃), 15.74 (NCH(CH₃)Ar); **HRMS** (ESI⁺): *m/z* calcd for C₂₃H₂₄N₃O₃ [M+H]⁺ 390.1812, found 390.1807.

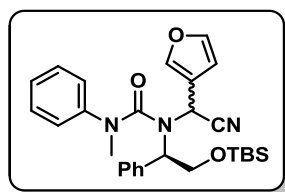
(*R*)-1-(cyano(furan-3-yl)methyl)-1-(2-hydroxy-1-phenylethyl)-3-methyl-3-phenylurea (6c)



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. **R_f** 0.20 (SiO₂; *n*-Hex:EtOAc 50:50); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 3323 (br.), 2858 (C–H), 2238 (C≡N), 1670 (C=O), 1493, 1256; **¹H NMR** (500 MHz, CD₂Cl₂): δ_{H} = 7.42 (dt, *J* = 1.8, 1.0 Hz, 1H, C_{Ar}H), 7.41 – 7.36 (m, 2H, 2xC_{Ar}H), 7.33 (t, *J* = 1.7 Hz, 1H, C_{Ar}H), 7.32 (s, 1H, C_{Ar}H), 7.30 – 7.26 (m, 1H, C_{Ar}H), 7.24 – 7.18 (m, 3H, 2xC_{Ar}H + OH), 7.08 – 7.04 (m, 2H, 2xC_{Ar}H), 6.67 – 6.63 (m, 2H, 2xC_{Ar}H), 5.98 (dd, *J* = 1.9, 0.9 Hz, 1H, C_{Ar}H), 4.90 – 4.85 (m, 2H, NCHCN + NCHCH₂OH), 4.36 (ddd, *J* = 11.7, 8.4, 5.9 Hz, 1H, NCH(CH_AH_B)OH), 4.19 (dt, *J* = 11.7, 5.4 Hz, 1H, NCH(CH_AH_B)OH), 3.18 (s, 3H, NCH₃); **¹³C NMR** (126 MHz, CD₂Cl₂) δ_{C} = 161.51 (C=O), 146.29 (C_{Ar}), 143.79 (C_{Ar}H), 142.94 (C_{Ar}), 142.92 (C_{Ar}H), 130.46 (2xC_{Ar}H), 129.16 (2xC_{Ar}H), 128.87 (C_{Ar}H), 128.52 (2xC_{Ar}H), 127.03 (C_{Ar}H), 126.88 (2xC_{Ar}H), 119.65 (C_{Ar}), 119.07 (C≡N), 110.51 (C_{Ar}H), 63.61 (NCHCH₂OH), 62.46 (NCHCH₂OH), 41.75 (NCHCN), 40.64 (NCH₃). **HRMS** (ESI⁺): *m/z* calcd for C₂₂H₂₂N₃O₃ [M+H]⁺ 376.1656, found 376.1663.

(*R*)-1-(2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethyl)-1-(cyano(furan-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; **R_f** 0.60 (SiO₂; *n*-Hex:EtOAc 50:50); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 3324 (br.), 2874, 1454, 1160, 1022; **¹H NMR** (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): δ_{H} = 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) δ_{C} = 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 C₁₄H₁₅N₂O₂ [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 CH₃CN (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 CH₂Cl₂ and water and the aqueous phase was further extracted in CH₂Cl₂ (x2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude (80:20 *dr* by ¹H-NMR; *relative stereochemistry undetermined*) was purified by flash column chromatography (SiO₂; *n*-Hex to *n*-Hex:EtOAc 95:05) to afford (*R*)-2-((2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)-2-(furan-3-yl)acetonitrile (1.92 g, 85%; 80:20 *dr*) as a yellow liquid; *R*_f 0.30 (SiO₂; *n*-Hex:EtOAc 95:05); ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): δ_H = 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 C₂₀H₂₉N₂O₂Si [M+H]⁺ 357.1993, found 357.1999.

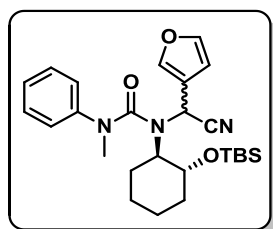
Following a similar method to general procedure 3 (step 1), the *N*-alkyl-OTBS amino nitrile (1.88 g, 5.26 mmol; 80:30 *dr*) was reacted with triphosgene (0.64 g, 2.10 mmol) and pyridine (0.51 mL, 6.31 mmol) in dry CH₂Cl₂ (26 mL). The crude was purified by flash column chromatography (SiO₂, *n*-Hex:Et₂O 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 (SiO₂; *n*-Hex:Et₂O 95:05); ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.8:0.2 ratio): δ_H = 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 B), 0.85 (s, 7.2H, diast A), 0.20 (s, 0.6H, diast B), 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 CH₃CN (28 mL) at reflux for 16 h. The crude product (60:40 *dr* by ¹H-NMR) was purified by flash column chromatography (SiO₂; *n*-Hex to *n*-Hex:EtOAc 80:20) to afford the title compound (0.86 g, 32%; 60:40 *dr*, *relative stereochemistry undetermined*).

Diast. A: Brown oil; *R*_f 0.40 (SiO₂; *n*-Hex:EtOAc 80:20); IR (neat, cm⁻¹): ν_{max} = 2856 (C–H), 2240 (C≡N), 1668 (C=O), 1495, 1258, 1109, 837; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.43 (dt, *J*=1.8, 0.8 Hz, 1 H, C_{Ar}H), 7.38 (s, 2 H, 2xC_{Ar}H), 7.30 – 7.25 (m, 2 H, 2xC_{Ar}H), 7.23 – 7.14 (m, 3 H, 3xC_{Ar}H), 7.06 – 7.03 (m, 2xC_{Ar}H), 6.61 – 6.58 (m, 2 H, 2xC_{Ar}H), 5.94 (dd, *J*=1.8, 1.0 Hz, 1 H, C_{Ar}H), 4.91 – 4.94 (m, 2 H, NCHCN + NCHCH₂OTBS), 4.29 (dd, *J*=10.6, 8.3 Hz, 1 H, NCH(CH_AH_B)OTBS), 4.09 (dd, *J*=10.6, 5.3 Hz, 1 H, NCH(CH_AH_B)OTBS), 3.18 (s, 3 H, NCH₃), 0.95 (s, 9 H, Si(CH₃)₃), 0.17 (s, 3 H, Si(CH₃)_A(CH₃)_B), 0.16 (s, 3 H, Si(CH₃)_A(CH₃)_B); HRMS (ESI⁺): *m/z* calcd for C₂₈H₃₆N₃O₃Si [M+H]⁺ 490.2520, found 490.2518.

Diast. B: Brown oil. *R*_f 0.30 (SiO₂; *n*-Hex:EtOAc 80:20); IR (neat, cm⁻¹): ν_{max} = 2856 (C–H), 2241 (C≡N), 1665 (C=O), 1595, 1496; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.65 (dt, *J*=1.6, 0.9 Hz, 1 H, C_{Ar}H), 7.43 (t, *J*=1.6 Hz, 1 H, C_{Ar}H), 7.31 – 7.41 (m, 7 H, 7xC_{Ar}H), 7.03 (d, *J*=1.3 Hz, 1 H, C_{Ar}H), 7.00 – 7.02 (m, 2 H, 2xC_{Ar}H), 6.45 (dd, *J*=1.5, 0.8 Hz, 1 H, C_{Ar}H), 5.49 (d, *J*=0.8 Hz, 1 H, NCHCN), 4.60 (t, *J*=5.0 Hz, 1 H, NCHCH₂OTBS),

3.68 (dd, $J=10.8, 4.8$ Hz, 1 H, $\text{NCH}(\text{CH}_\text{A}\text{H}_\text{B})\text{OTBS}$), 3.42 (dd, $J=11.1, 5.3$ Hz, 1 H, $\text{NCH}(\text{CH}_\text{A}\text{H}_\text{B})\text{OTBS}$), 3.13 (s, 3 H, NCH_3), 0.80 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), -0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$), -0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_\text{A}(\text{CH}_3)_\text{B}$); **HRMS** (ESI^+): m/z calcd for $\text{C}_{28}\text{H}_{36}\text{N}_3\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 490.2520, found 490.2512.

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



Following the general procedure 1, (1*R*,2*R*)-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 (SiO_2 ; Pet. Ether:EtOAc 100:0 to Pet. Ether:EtOAc 60:40) to afford 2-(Furan-3-yl)-2-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)acetonitrile (1.30 g, 61%; 65:35 *dr*) as a colourless solid. R_f 0.34 (SiO_2 ; Pet. Ether:EtOAc 60:40); **IR** (neat, cm^{-1}): ν_{max} = 3600 – 3200 (O–H, br.), 3323 (N–H), 2932 (C–H), 2859 (C–H), 2233 ($\text{C}\equiv\text{N}$); **^1H NMR** (400 MHz, CDCl_3) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δ_H = 7.60 (0.65H, dt, $J=1.8, 1.0$, $\text{C}_\text{Ar}\text{H}$, diast A), 7.58 (0.35H, dt, $J=1.8, 1.0$, $\text{C}_\text{Ar}\text{H}$, diast B), 7.44 (0.65H, t, $J=1.7$, $\text{C}_\text{Ar}\text{H}$, diast A), 7.43 – 7.39 (0.35H, m, $\text{C}_\text{Ar}\text{H}$, diast B), 6.50 (1H, dt, $J=1.9, 1.0$, $\text{C}_\text{Ar}\text{H}$, diast A+B), 4.92 (0.35H, s, $\text{NCH}(\text{Ar})\text{CN}$, diast B), 4.79 (0.65H, s, $\text{NCH}(\text{Ar})\text{CN}$, diast A), 3.31 (1H, ddt, $J=13.7, 9.1, 4.1$, NHCHCHOH , diast A+B), 2.65 (0.65H, ddd, $J=11.1, 9.1, 4.1$, NHCHCHOH , diast A), 2.55 (0.35H, ddd, $J=11.2, 9.0, 4.2$, NHCHCHOH , diast B), 2.47 – 1.93 (3H, m, NH , diast A+B, $2\times\text{CH}$, diast A+B), 1.94 – 1.53 (3H, m, OH , diast A+B, $2\times\text{CH}$, diast A+B), 1.41 – 1.22 (3H, m, $3\times\text{CH}$, diast A+B), 1.21 – 1.02 (1H, m, CH , diast A+B); **^{13}C NMR** (126 MHz, CDCl_3) δ_C = 144.3 ($\text{C}_\text{Ar}\text{H}$, diast A), 144.2 ($\text{C}_\text{Ar}\text{H}$, diast B) 140.8 ($\text{C}_\text{Ar}\text{H}$, diast A), 140.6 ($\text{C}_\text{Ar}\text{H}$, diast B), 121.8 (C_Ar , diast B), 121.3 (C_Ar , diast A), 120.0 ($\text{C}\equiv\text{N}$, diast B), 118.8 ($\text{C}\equiv\text{N}$, diast A), 109.4 ($\text{C}_\text{Ar}\text{H}$, diast A), 109.3 ($\text{C}_\text{Ar}\text{H}$, diast B), 75.5 (NHCHCHOH , diast B), 74.1 (NHCHCHOH , diast A), 62.8 (NHCHCHOH , diast B), 61.3 (NHCHCHOH , diast A), 46.0 ($\text{NCH}(\text{Ar})\text{CN}$, diast B), 43.6 ($\text{NCH}(\text{Ar})\text{CN}$, diast A), 34.3 (CH_2 , diast A), 33.9 (CH_2 , diast B), 31.6 (CH_2 , diast B), 29.9 (CH_2 , diast A), 25.0 (CH_2 , diast B) 24.5 (CH_2 , diast A), 24.4 (CH_2 , diast A), 24.3 (CH_2 , diast B); **HRMS** (ESI^+): m/z calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 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 CH_2Cl_2 (20 mL). Purification by flash column chromatography (SiO_2 ; *n*-Hex:EtOAc 100:0 to *n*-Hex:EtOAc 90:10) afforded 2-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(furan-3-yl)acetonitrile (0.80 g, 52%; 65:35 *dr*) as a yellow oil. R_f 0.29 (90:10 *n*-Hex:EtOAc); **IR** (neat, cm^{-1}): ν_{max} = 3329 (N–H), 2929 (C–H), 2857 (C–H), 2346 ($\text{C}\equiv\text{N}$); **^1H NMR** (400 MHz, CDCl_3) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δ_H = 7.60 – 7.53 (1H, m, $\text{C}_\text{Ar}\text{H}$, diast A+B), 7.43 (0.65H, dq, $J=2.6, 1.6$, $\text{C}_\text{Ar}\text{H}$, diast A), 7.40 (0.35H, 1d, $J=1.7$, $\text{C}_\text{Ar}\text{H}$, diast B), 6.58 – 6.39 (1H, m, $\text{C}_\text{Ar}\text{H}$, diast A+B), 4.93 (0.35H, s, $\text{NCH}(\text{Ar})\text{CN}$, diast B), 4.72

(0.65H, s, NCH(Ar)CN, diast A), 3.50 – 3.34 (1H, m, NHCHCHOTBS, diast A+B), 2.76 (0.65H, ddd, $J=11.9$, 8.8, 3.9, NHCHCHOTBS, diast A), 2.63 (0.35H, ddd, $J=9.9$, 8.9, 4.0, NHCHCHOTBS, diast B), 2.34 (0.65H, br. d, $J=11.4$, NH, diast A), 2.05 – 1.82 (1.65H, m, 2xCH, diast A; CH, diast B), 1.81 – 1.59 (2.70H, m, 2xCH, diast A; 2xCH + CH₂, diast B), 1.48 – 1.15 (3.35H, 3xCH, diast A; 3xCH + NH, diast B), 1.07 (0.65H, qd, $J=13.2$, 12.7, CH, diast A), 0.86 (5.85H, s, SiC(CH₃)₃, diast A), 0.79 (3.15H, s, SiC(CH₃)₃, diast B), 0.07 (1.95H, s, Si(CH_{3,A})(CH_{3,B}), diast A), 0.05 (1.05H, s, Si(CH_{3,A})(CH_{3,B}), diast B), 0.03 (1.95H, s, Si(CH_{3,A})(CH_{3,B}), diast A), 0.01 (1.05H, Si(CH_{3,A})(CH_{3,B}), diast B); ¹³C NMR (100 MHz, CDCl₃): δ_c = 144.15 (C_{Ar}H, diast A), 143.92 (C_{Ar}H, diast B), 140.48 (C_{Ar}H, diast B), 140.40 (C_{Ar}H, diast A), 121.8 (C_{Ar}, diast B), 121.6 (C_{Ar}, diast A), 120.0 (C $\equiv$ N, diast B), 118.4 (C $\equiv$ N, diast A), 109.22 (2xC_{Ar}H, diast A+B), 76.8 (NHCHCHOTBS, diast B), 75.3 (NHCHCHOTBS, diast A), 61.8 (NHCHCHOTBS, diast B), 61.1 (NHCHCHOTBS, diast A), 46.1 (NCH(Ar)CN, diast B), 43.6 (NCH(Ar)CN, diast A), 34.3 (CH₂, diast A), 32.8 (CH₂, diast B), 31.4 (CH₂, diast B), 29.1 (CH₂, diast A), 25.96 (SiC(CH₃)₃, diast B), 25.91 (SiC(CH₃)₃, diast A), 24.8 (CH₂, diast B), 24.5 (CH₂, diast A), 24.3 (CH₂, diast B), 24.1 (CH₂, diast A), 18.09 (SiC(CH₃)₃, diast A), 18.07 (SiC(CH₃)₃, diast B), -3.66 (Si(CH_{3,A})(CH_{3,B}), diast A), -3.85 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.43 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.67 (Si(CH_{3,A})(CH_{3,B}), diast A); HRMS (ESI⁺): m/z calcd for C₁₈H₃₁N₂O₂Si [M+H]⁺ 335.2149. Found 335.2137.

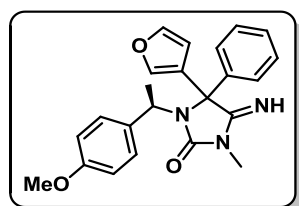
Following the general procedure 3 (step 1), the *N*-alkyl-OTBS amino nitrile (800 mg, 2.390 mmol; 65:35 *dr*) was reacted with triphosgene (284 mg, 0.956 mmol) and 2,6-lutidine (0.33 mL, 2.871 mmol) in dry CH₂Cl₂ (13 mL). The crude carbamoyl chloride (1.00 g, brown oil) was used in the next step without 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 CH₃CN (6.0 mL) in a microwave reactor at 110 °C for 4 h. The crude product was purified by flash column chromatography (SiO₂; *n*-Hex:Et₂O 100:0 to *n*-Hex:Et₂O 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:Et₂O 70:30); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 2929 (C–H), 2857 (C–H), 2243 (C $\equiv$ N), 1657 (C=O); ¹H NMR (400 MHz, CDCl₃): δ_H = 7.61 (1H, dt, $J=1.7$, 0.9, C_{Ar}H), 7.37 (1H, t, $J=1.7$, C_{Ar}H), 7.36 – 7.31 (2H, m, 2xC_{Ar}H), 7.20 – 7.15 (1H, m, C_{Ar}H), 7.14 – 7.10 (2H, m, 2xC_{Ar}H), 6.50 (1H, dd, $J=1.8$, 1.1, C_{Ar}H), 5.77 (1H, s, NCH(Ar)CN), 4.10 – 3.96 (1H, m, NCHCHOTBS), 3.22 – 3.15 (1H, m, NCHCHOTBS), 3.21 (3H, s, NCH₃), 1.98 – 1.89 (1H, m, CH), 1.70 – 1.61 (1H, m, CH), 1.60 – 1.49 (2H, m, 2xCH), 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, SiC(CH₃)₃), 0.80 – 0.68 (1H, m, CH), 0.06 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.01 (3H, s, Si(CH_{3,A})(CH_{3,B})); ¹³C NMR (126 MHz, CDCl₃): δ_c = 161.26 (C=O), 146.13 (C_{Ar}), 143.36 (C_{Ar}H), 142.13 (C_{Ar}H), 129.78 (2xC_{Ar}H), 125.83 (C_{Ar}H), 124.93 (2xC_{Ar}H), 120.53 (C_{Ar}), 118.14 (C $\equiv$ N), 110.61 (C_{Ar}H), 71.94 (NCHCHOTBS), 65.11 (NCHCHOTBS), 41.91 (NCH(Ar)CN), 40.38 (NCH₃), 36.97 (CH₂), 29.20 (CH₂), 26.13 (SiC(CH₃)₃), 25.74 (CH₂), 24.47 (CH₂), 18.23 (SiC(CH₃)₃), -3.60 (Si(CH_{3,A})(CH_{3,B})), -3.82 (Si(CH_{3,A})(CH_{3,B})); HRMS (ESI⁺): m/z calcd for C₂₆H₃₈N₃O₃Si [M+H]⁺ 468.2677. Found 468.2676.

Diast. B: orange oil; **R_f** 0.21 (*n*-Hex:Et₂O 70:30); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 2929 (C–H), 2857 (C–H), 2243 (C $\equiv$ N), 1661 (C=O); ¹H NMR (400 MHz, CDCl₃): δ_H = 7.71 (1H, s, C_{Ar}H), 7.42 (1H, t, $J=1.7$, C_{Ar}H), 7.34 – 7.28 (2H, m, 2xC_{Ar}H), 7.19 – 7.14 (1H, m, C_{Ar}H), 6.97 – 6.93 (2H, m, 2xC_{Ar}H), 6.39 (1H, d, $J=1.5$, C_{Ar}H),

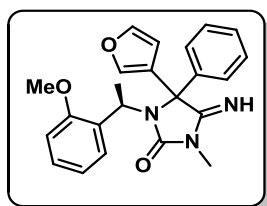
4.97 (1H, s, NCH(Ar)CN), 3.67 (1H, dt, $J=10.4, 3.8$, NCHCHOTBS), 3.28 (1H, ddd, $J=12.9, 9.3, 4.0$, NCHCHOTBS), 3.16 (3H, s, NCH₃), 2.10 – 1.97 (1H, m, CH), 1.62 – 1.50 (1H, m, CH), 1.46 – 1.37 (1H, m, CH), 1.20 – 1.10 (1H, m, CH), 1.07 – 0.96 (3H, m, 3xCH), 0.95 (9H, s, SiC(CH₃)₃), 0.57 (1H, td, $J=12.0, 11.6, 5.9$, CH), 0.23 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.14 (3H, s, Si(CH_{3,A})(CH_{3,B})); ¹³C NMR (126 MHz, CDCl₃): δ_C = 160.47 (C=O), 146.41 (C_{Ar}), 143.32 (C_{Ar}H), 142.66 (C_{Ar}H), 129.57 (2xC_{Ar}H), 125.77 (C_{Ar}H), 125.51 (2xC_{Ar}H), 119.98 (C_{Ar}), 118.03 (C $\equiv$ N), 110.06 (C_{Ar}H), 71.58 (NCHCHOTBS), 64.91 (NCHCHOTBS), 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(CH_{3,A})(CH_{3,B})), -3.89 (Si(CH_{3,A})(CH_{3,B})); HRMS (ESI⁺): m/z calcd for C₂₆H₃₈N₃O₃Si [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)



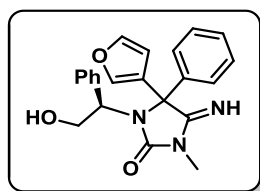
Following the general procedure 4 (method A), the *N'*-aryl ureido nitrile **6a** (50 mg, 0.128 mmol; 50:50 *dr*) was reacted with LDA (0.13 mL, 2.0 M in THF/heptane/ethylbenzene, 0.256 mmol) in anhydrous THF (1.1 mL) at room temperature for 3 h. The crude product (77:23 *dr* by NMR) was purified by 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; *R_f* 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): δ_H = 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) δ_C = 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, C_{Ar}OCH₃), [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 C₂₃H₂₄N₃O₃ [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)



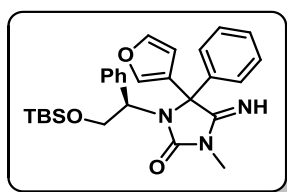
Following the general procedure 4 (method A), the *N'*-aryl ureido nitrile **6b** (100 mg, 0.256 mmol; 50:50 *dr*) was reacted with LDA (0.26 mL, 2.0 M in THF/heptane/ethylbenzene, 0.512 mmol) in anhydrous THF (2.2 mL) at room temperature for 3 h. ¹H-NMR analysis of the reaction crude showed a 60:40 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; *R*_f 0.30 (SiO₂; EtOAc); ¹H NMR (400 MHz, CD₂Cl₂) (mixture of diastereoisomers A:B in a 0.65:0.35 ratio): δ_H = 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.

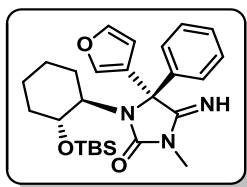
3-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethyl)-4-(furan-3-yl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (7d)



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

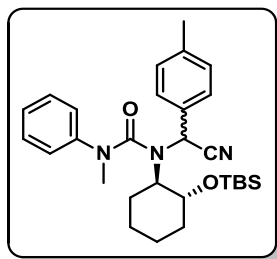
purified by flash column chromatography (SiO₂; *n*-Hex:EtOAc 80:20 to 60:40) to afford the title compound (96 mg, 96%; 75:25 *dr*, *relative stereochemistry undetermined*) as a yellow oil; **R_f** 0.25 (SiO₂; *n*-Hex:EtOAc 60:40); **IR** (neat, cm⁻¹): ν_{max} = 2928 (C–H), 1733 (C=NH), 1660 (C=O), 1450, 1101; **¹H NMR** (500 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.75:0.25 ratio): δ_{H} = 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 C₂₈H₃₆N₃O₃Si [M+H]⁺ 490.2520, found 490.2529.

(*R*)-3-((1*R*,2*R*)-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**: **R_f** 0.19 (SiO₂; *n*-Hex:EtOAc 70:30); **IR** (neat, cm⁻¹): ν_{max} = 3311 (N–H), 2929 (C–H), 2856 (C–H), 1732 (C=N), 1659 (C=O); **¹H NMR** (400 MHz, CDCl₃): δ_{H} = 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, NCHCHOTBS), 3.11 (3H, s, NCH₃), 3.00 – 2.86 (1H, m, NCHCHOTBS), 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, SiC(CH₃)₃), 0.92 – 0.87 (1H, m, CH), 0.19 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.08 (3H, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (101 MHz, CDCl₃): δ_{C} = 167.26 (C=N), 155.86 (C=O), 143.85 (C_{Ar}H), 142.47 (C_{Ar}H), 137.84 (C_{Ar}), 128.85 (2xC_{Ar}H), 128.69 (C_{Ar}H), 128.27 (2xC_{Ar}H), 126.20 (C_{Ar}), 110.96 (C_{Ar}H), 72.48 (NCHCHOTBS), 69.05 (NC(Ar)Ph), 61.16 (NCHCHOTBS), 37.48 (CH₂), 29.87 (CH₂), 26.23 (SiC(CH₃)₃), 25.65 (NCH₃), 25.48 (CH₂), 24.76 (CH₂), 18.33 (SiC(CH₃)₃), -3.75 (Si(CH_{3,A})(CH_{3,B})), -5.54 (Si(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for [C₂₆H₃₈N₃O₃Si]⁺ [M+H]⁺ 468.2677. Found 468.2680.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(*p*-tolyl)methyl)-3-methyl-3-phenylurea (8a)



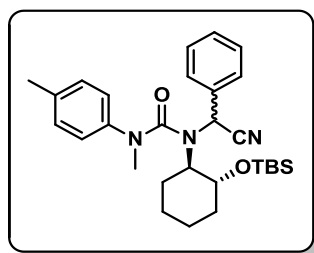
Following the general procedure 1, (1*R*,2*R*)-trans-2-aminocyclohexanol (500 mg, 4.341 mmol) was reacted with *p*-tolualdehyde (0.52 mL, 4.341 mmol) and TMSCN (0.65 mL, 5.209 mmol) in MeOH (20 mL) for 16 h at room temperature. The crude was purified by flash column chromatography (SiO₂; *n*-Hex to *n*-Hex:EtOAc 70:30) to afford 2-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-2-(*p*-tolyl)acetonitrile (636 mg, 60%; 70:30 *dr*) as a colourless solid. *R*_f 0.3 (SiO₂; *n*-Hex:EtOAc 70:30); **IR** (neat, cm⁻¹): *v*_{max} = 3600 – 3200 (O–H, br.), 3320 (N–H), 2928 (C–H), 2236 (C≡N); **¹H NMR** (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.70:0.30 ratio): δ_H = 7.44 – 7.38 (m, 2.0H, 2x*C*_{Ar}*H*, diast A+B), 7.23 (d, *J* = 7.9 Hz, 2.0H, 2x*C*_{Ar}*H*, diast A+B), 4.94 (s, 0.3H, NCH(Ar)CN, diast B), 4.84 (s, 0.7H, NCH(Ar)CN, diast A), 3.38 – 3.26 (m, 1.0H, NHCHCHOH, diast A+B), 2.70 (ddd, *J* = 11.2, 9.0, 4.1 Hz, 0.7H, NHCHCHOH, diast A), 2.56 (ddd, *J* = 11.2, 9.0, 4.1 Hz, 0.3H, NHCHCHOH, diast B), 2.38 (s, 3H, *C*_{Ar}CH₃, diast A+B), 2.26 – 1.89 (3.0H, m, NH, diast A+B, 2xCH, diast A+B), 1.84 – 1.69 (m, 2.0H, 2xCH, diast A+B), 1.43 – 1.23 (m, 3.0H, OH, diast A+B, 2xCH, diast A+B), 1.21 – 1.03 (m, 1.0H, CH, diast A+B); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 139.11 (*C*_{Ar}, diast B), 139.09 (*C*_{Ar}, diast A), 132.82 (*C*_{Ar}, diast B), 132.47 (*C*_{Ar}, diast A), 129.83 (2x*C*_{Ar}*H*, diast A+B), 127.38 (2x*C*_{Ar}*H*, diast A), 127.21 (2x*C*_{Ar}*H*, diast B), 120.56 (C≡N, diast B), 119.24 (C≡N, diast A), 75.27 (NHCHCHOH, diast B), 74.04 (NHCHCHOH, diast A), 62.86 (NHCHCHOH, diast B), 61.56 (NHCHCHOH, diast A), 53.39 (NCH(Ar)CN, diast B), 51.35 (NCH(Ar)CN, diast A), 34.20 (CH₂, diast A), 33.80 (CH₂, diast B), 31.48 (CH₂, diast B), 29.96 (CH₂, diast A), 25.04 (CH₂, diast B), 24.48 (CH₂, diast A), 24.46 (CH₂, diast A), 24.29 (CH₂, diast B), 21.27 (*C*_{Ar}CH₃, diast A+B); **HRMS** (ESI⁺): *m/z* calcd for C₁₅H₂₁N₂O [M+H]⁺ 245.1648, found 245.1653.

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 CH₂Cl₂ (7.2 mL). Purification by flash column chromatography (SiO₂; *n*-Hex:Et₂O 95:5 to 80:20) afforded 2-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(*p*-tolyl)acetonitrile (258 mg, 50%; 80:20 *dr*) as a clear oil. *R*_f 0.3 (SiO₂; *n*-Hex:Et₂O 90:10); **IR** (neat, cm⁻¹): *v*_{max} = 3330 (N–H), 2932 (C–H), 2341 (C≡N); **¹H NMR** (400 MHz, CDCl₃) (mixture of diastereoisomers A:B in a 0.80:0.20 ratio): δ_H = 7.36 (d, *J* = 8.0 Hz, 2.0H, 2x*C*_{Ar}*H*, diast A+B), 7.23 – 7.16 (m, 2.0H, 2x*C*_{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, *C*_{Ar}CH₃, diast A+B), 2.11 – 1.55 (m, 5H, 4xCH, diast A+B; NH, diast A+B), 1.49 – 0.98 (m, 4H, 4xCH, diast A+B), 0.86 (s, 7.2H, Si(CH₃)₃, diast A), 0.84 (s, 1.8H, Si(CH₃)₃, diast B), 0.06 (s, 3.0H, Si(CH₃,A)(CH₃,B), diast A+B), 0.04 (s, 0.6H, Si(CH₃,A)(CH₃,B), diast B), -0.01 (s, 2.4H, Si(CH₃,A)(CH₃,B), diast A); **¹³C NMR** (101 MHz, CDCl₃): δ_C = 138.88 (*C*_{Ar}, diast B), 138.83

(C_{Ar}, diast A), 133.07 (C_{Ar}, diast B), 132.81 (C_{Ar}, diast A), 129.84(2xC_{Ar}H, diast B), 129.77 (2xC_{Ar}H, diast A), 127.13 (2xC_{Ar}H, diast A+B), 120.53 (C≡N, diast B), 118.96 (C≡N, diast A), 76.16 (NHCHCHOTBS, diast B), 75.25 (NHCHCHOTBS, diast A), 62.06 (NHCHCHOTBS, diast B), 61.35 (NHCHCHOTBS, diast A), 53.33 (NCH(Ar)CN, diast B), 51.26 (NCH(Ar)CN, diast A), 34.45 (CH₂, diast A), 34.37 (CH₂, diast B), 31.04 (CH₂, diast B) 29.24 (CH₂, diast A), 25.93 (SiC(CH₃)₃ diast A+B), 24.52 (CH₂, diast A) 24.30 (CH₂, diast B), 24.28 (CH₂, diast A+B), 21.28 (SiC(CH₃)₃, diast A), 18.08 (SiC(CH₃)₃, diast B), -3.63 (Si(CH_{3,A})(CH_{3,B}), diast A), -3.78 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.45 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.69 (Si(CH_{3,A})(CH_{3,B}), diast A); **HRMS** (ESI⁺): *m/z* calcd for C₂₁H₃₅N₂OSi [M+H]⁺ 359.2513. Found 359.2523.

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 CH₃CN (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. **R_f** 0.25 (*n*-Hex:Et₂O 80:20); **IR** (neat, cm⁻¹): ν_{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, 4xC_{Ar}H), 7.36 – 7.28 (m, 4H, 4xC_{Ar}H), 7.24 – 7.14 (m, 6H, 6xC_{Ar}H), 7.14 – 7.07 (m, 2H, 2xC_{Ar}H), 6.94 – 6.87 (m, 2H, 2xC_{Ar}H), 5.85 (s, 1H, NCH(Ar)CN), 5.08 (s, 1H, NCH(Ar)CN), 4.09 (td, *J* = 9.9, 4.2 Hz, 1H, NCHCHOTBS), 3.79 – 3.68 (m, 1H, NCHCHOTBS), 3.38 – 3.21 (m, 2H, 2xNCHCHOTBS), 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, SiC(CH₃)₃), 0.86 (s, 9H, SiC(CH₃)₃), 0.67 – 0.53 (m, 1H, CH), 0.26 (s, 3H, Si(CH_{3,A})(CH_{3,B})), 0.15 (s, 3H, Si(CH_{3,A})(CH_{3,B})), 0.08 (s, 3H, Si(CH_{3,A})(CH_{3,B})), 0.03 (s, 3H, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 161.44 (C=O), 160.42 (C=O), 146.27 (C_{Ar}), 145.90 (C_{Ar}), 138.35 (C_{Ar}), 138.28 (C_{Ar}), 131.78 (C_{Ar}), 131.21 (C_{Ar}), 129.69 (2xC_{Ar}H), 129.45 (2xC_{Ar}H), 129.24 (2xC_{Ar}H), 129.08 (2xC_{Ar}H), 128.27 (2xC_{Ar}H), 127.72 (2xC_{Ar}H), 125.74 (C_{Ar}H), 125.66 (C_{Ar}H), 125.55 (2xC_{Ar}H), 124.97 (2xC_{Ar}H), 118.76 (C≡N), 118.32 (C≡N), 71.92 (NCHCHOTBS), 71.60 (NCHCHOTBS), 65.25 (NCHCHOTBS), 64.97 (NCHCHOTBS), 49.03 (NCH(Ar)CN), 47.51 (NCH(Ar)CN), 40.26 (NCH₃), 39.64 (NCH₃), 36.96 (CH₂), 36.87 (CH₂), 29.71 (CH₂), 29.54 (CH₂), 26.33 (SiC(CH₃)₃), 26.23 (SiC(CH₃)₃), 25.76 (CH₂), 25.28 (CH₂), 24.43 (CH₂), 24.34 (CH₂), 21.28 (ArCH₃), 21.25 (ArCH₃), 18.34 (SiC(CH₃)₃), 18.30 (SiC(CH₃)₃), -3.26 (Si(CH_{3,A})(CH_{3,B})), -3.54 (Si(CH_{3,A})(CH_{3,B})), -3.72 (2xSi(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for C₂₉H₄₂N₃O₂Si [M+H]⁺ 492.3041, found 492.3042.

1-(((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-methyl-3-(*p*-tolyl)urea (8b)



Following the general procedure 1, (1*R*,2*R*)-trans-2-aminocyclohexanol (1.00 g, 8.68 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-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-2-phenylacetonitrile (1.20 g, 60%; 74:26 *dr*) as a colourless solid; **IR** (neat, cm⁻¹): $\nu_{\max}$ = 3294 (br. N–H, O–H), 2933 (C–H), 2228 (C≡N), 1449; **¹H NMR** (400 MHz, CDCl₃) (mixture of diast A:B in a 0.74:0.26 ratio): δ_{H} = 7.55 – 7.48 (2 H, m, 2x*C*_{Ar}*H*, diast A+B), 7.44 – 7.34 (3 H, m, 3x*C*_{Ar}*H*, 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; 2xCH diast A+B), 1.84 – 1.64 (2 H, m, 2xCH diast A+B), 1.41 – 1.21 (3 H, m, 3xCH diast A+B), 1.20 – 1.01 (1 H, m, CH diast A+B); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} = 135.8 (*C*_{Ar}*H*, diast B), 135.4 (*C*_{Ar}*H*, diast A), 129.18 (2x*C*_{Ar}*H*, diast A), 129.15 (2x*C*_{Ar}*H*, diast B), 128.7 (*C*_{Ar}, diast B), 128.4 (*C*_{Ar}, diast A), 127.5 (2x*C*_{Ar}*H*, diast A), 127.3 (2x*C*_{Ar}*H*, 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 (NCHCHOH, 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 C₁₄H₁₈N₂NaO₂ [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-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-phenylacetonitrile (1.52 g, 92%; 80:20 *dr*) as a colourless oil; **R_f** 0.25 (SiO₂; *n*-Hex:EtOAc 90:10); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 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): δ_{H} = 7.52 – 7.46 (2 H, m, 2x*C*_{Ar}*H*, diast A+B), 7.43 – 7.33 (3 H, m, 3x*C*_{Ar}*H*, 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, NCHCHOTBS, diast A+B), 2.81 (0.80 H, ddd, *J* = 11.1, 8.6, 4.0 Hz, NCHCHOTBS, diast A), 2.63 (0.20 H, ddd, *J* = 10.1, 8.4, 4.0 Hz, NCHCHOTBS, diast B), 2.37 (0.80 H, br. s, NH, diast A), 2.13 – 1.58 (4.20 H, m, NH, diast A; 4xCH, diast A+B), 1.51 – 1.04 (4 H, m, 4xCH, diast A+B), 0.85 (7.20 H, s, SiC(CH₃)₃, diast A), 0.84 (1.80 H, s, SiC(CH₃)₃, diast B), 0.06 (3 H, s, Si(CH_{3,A})(CH_{3,B}), diast A+B), 0.03 (0.60 H, s, Si(CH_{3,A})(CH_{3,B}), diast B), -0.01 (2.40 H, s, Si(CH_{3,A})(CH_{3,B}), diast A); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} = 136.05 (*C*_{Ar}*H*, diast B), 135.77 (*C*_{Ar}*H*, diast A), 129.11 (2x*C*_{Ar}*H*, diast A), 128.96 (2x*C*_{Ar}*H*, diast B), 128.53 (*C*_{Ar}, diast B), 128.30 (*C*_{Ar}, diast A), 127.25 (2x*C*_{Ar}*H*, diast A),

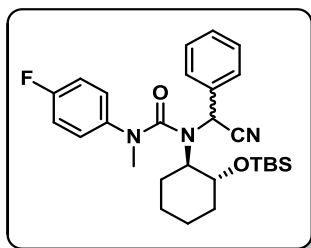
127.22 (2xC_{Ar}H, diast B), 120.36 (C≡N, diast B), 118.78 (C≡N, diast A), 76.19 (NCHCHOTBS, diast B), 75.27 (NCHCHOTBS, diast A), 62.19 (NCHCHOTBS, diast B), 61.37 (NCHCHOTBS, diast A), 53.67 (NCH(Ar)CN, diast B), 51.52 (NCH(Ar)CN, diast A), 34.45 (CH₂, diast B), 34.35 (CH₂, diast A), 31.08 (SiC(CH₃)₃, diast B), 29.23 (SiC(CH₃)₃, diast A), 25.93 (SiC(CH₃)₃, diast B), 25.90 (SiC(CH₃)₃, 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(CH_{3,A})(CH_{3,B}), diast A), -3.78 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.47 (Si(CH_{3,A})(CH_{3,B}), diast B), -4.73 (Si(CH_{3,A})(CH_{3,B}), diast A); **HRMS** (ESI⁺): *m/z* calcd for C₂₀H₃₃N₂OSi [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 CH₃CN (2.0 mL) 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. *R_f* 0.30 (SiO₂; *n*-Hex:Et₂O 80:20); **IR** (neat, cm⁻¹): ν_{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, 2xC_{Ar}H), 7.43 – 7.30 (3 H, m, 3xC_{Ar}H), 7.16 – 7.08 (2 H, m, 2xC_{Ar}H), 6.82 – 6.74 (2 H, m, 2xC_{Ar}H), 5.10 (1 H, s, NCH(Ar)CN), 3.75 (1 H, td, *J* = 9.4, 4.6 Hz, NCHCHOTBS), 3.37 (1 H, ddd, *J* = 12.7, 9.3, 3.9 Hz, NCHCHOTBS), 3.06 (3 H, s, NCH₃), 2.33 (3 H, s, ArCH₃), 2.10 – 2.02 (1 H, m, CH), 1.61 – 1.44 (2 H, m, 2xCH), 1.35 – 1.19 (2 H, m, 2xCH), 1.14 – 1.04 (2 H, m, 2xCH), 0.96 (9 H, s, SiC(CH₃)₃), 0.71 – 0.56 (1 H, m, CH), 0.26 (3 H, s, Si(CH_{3,A})(CH_{3,B})), 0.16 (3 H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 160.5 (C=O), 143.6 (C_{Ar}), 135.6 (C_{Ar}), 134.3 (C_{Ar}), 130.0 (2xC_{Ar}), 128.4 (C_{Ar}H), 128.3 (2xC_{Ar}), 128.3 (2xC_{Ar}), 125.6 (2xC_{Ar}), 118.2 (C≡N), 71.6 (NCHCHOTBS), 64.9 (NCHCHOTBS), 47.8 (NCH(Ar)CN), 39.8 (NCH₃), 36.8 (CH₂), 29.6 (CH₂), 26.3 (SiC(CH₃)₃), 25.3 (CH₂), 24.3 (CH₂), 21.0 (ArCH₃), 18.3 (SiC(CH₃)₃), -3.4 (Si(CH_{3,A})(CH_{3,B})), -3.8 (Si(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for C₂₉H₄₂N₃O₂Si [M+H]⁺ 492.3041, found 492.3040.

Diast B: Purple oil. *R_f* 0.20 (SiO₂; *n*-Hex:Et₂O 80:20); **IR** (neat, cm⁻¹): ν_{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, 2xC_{Ar}H), 7.40 – 7.28 (3 H, m, 3xC_{Ar}H), 7.15 – 7.08 (2 H, m, 2xC_{Ar}H), 7.03 – 6.96 (2 H, m, 2xC_{Ar}H), 5.85 (1 H, s, NCH(Ar)CN), 4.07 (1 H, td, *J* = 9.8, 4.2 Hz, NCHCHOTBS), 3.26 (1 H, td, *J* = 12.7, 9.7, 3.1 Hz, NCHCHOTBS), 3.16 (3 H, s, NCH₃), 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, 3xCH), 1.24 – 1.08 (1 H, m, CH), 1.04 – 0.72 (11 H, m, 2xCH + SiC(CH₃)₃), 0.08 (3 H, s, Si(CH_{3,A})(CH_{3,B})), 0.02 (3 H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (101 MHz, CDCl₃) δ_C = 161.5 (C=O), 143.3 (C_{Ar}), 135.8 (C_{Ar}), 134.9 (C_{Ar}), 130.3 (2xC_{Ar}), 128.5 (C_{Ar}H), 128.4 (2xC_{Ar}), 127.7 (2xC_{Ar}), 125.2 (2xC_{Ar}), 118.8 (C≡N), 72.0 (NCHCHOTBS), 65.3 (NCHCHOTBS), 49.2 (NCH(Ar)CN), 40.5 (NCH₃), 37.0 (CH₂), 29.8 (CH₂), 26.2 (SiC(CH₃)₃), 25.8 (CH₂), 24.5 (CH₂), 21.0 (ArCH₃), 18.3 (SiC(CH₃)₃), -3.3 (Si(CH_{3,A})(CH_{3,B})), -3.6 (Si(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for C₂₉H₄₂N₃O₂Si [M+H]⁺ 492.3041, found 492.3042.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-(4-fluorophenyl)-3-methylurea (8c)

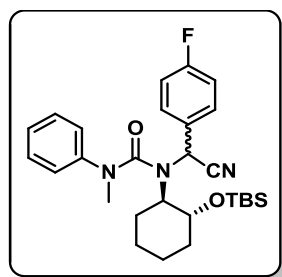


Following the general procedure 3 (step 2), the corresponding carbamoyl chloride (see compound **8b** for the synthetic procedure; 412 mg) was reacted with 2,6-lutidine (0.12 mL, 1.06 mmol) and 4-fluoro-*N*-methyl aniline (0.12 mL, 0.97 mmol) in dry CH₃CN (1.0 mL) at reflux for 24 h. The crude product 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. *R*_f 0.25 (Pet. Ether:Et₂O 80:20); **IR** (neat, cm⁻¹): *v*_{max} = 2926 (C–H), 2855 (C–H), 2253 (C≡N) 1661 (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, 2xCH), 1.07 – 0.98 (1H, m, CH), 0.87 (9H, s, SiC(CH₃)₃), 0.09 (3H, s, Si(CH₃,_A)(CH₃,_B)), 0.04 (3H, s, Si(CH₃,_A)(CH₃,_B)); **¹³C NMR** (126 MHz, CDCl₃): δ_C = 161.57 (C=O), 160.57 (C_{Ar}, d, ¹*J*^{C-F} = 246.2), 141.84 (C_{Ar}, d, ⁴*J*^{C-F} = 3.1), 134.71 (C_{Ar}), 128.62 (3xC_{Ar}H, overlap), 127.67 (2xC_{Ar}H), 126.98 (2xC_{Ar}H, d, ³*J*^{C-F} = 8.3), 118.68 (C≡N), 116.47 (2xC_{Ar}H, d, ²*J*^{C-F} = 22.6), 71.98 (NCHCHOTBS), 65.71 (NCHCHOTBS), 49.23 (NCH(Ar)CN), 40.57 (NCH₃), 37.00 (CH₂), 29.86 (CH₂), 26.24 (SiC(CH₃)₃), 25.88 (CH₂), 24.44 (CH₂), 18.34 (SiC(CH₃)₃), -3.26 (Si(CH₃,_A)(CH₃,_B)) -3.53 (Si(CH₃,_A)(CH₃,_B)); **¹⁹F NMR** (377 MHz, CDCl₃) δ_F -116.01; **HRMS** (EI⁺): *m/z* calcd for [C₂₈H₃₈FN₃NaO₂Si]⁺ [M+Na]⁺ 518.2609. Found 518.2595.

Diast. B: yellow oil. *R*_f 0.22 (Pet. Ether:Et₂O 80:20); **IR** (neat, cm⁻¹): *v*_{max} = 2926 (C–H), 2855 (C–H), 2240 (C≡N), 1662 (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*), 7.04 – 6.98 (2H, m, 2xAr-*H*), 6.87 – 6.81 (2H, m, 2xAr-*H*), 5.09 (1H, s, NCH(Ar)CN), 3.76 (1H, td, *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, 2xCH), 1.32 – 1.18 (1H, m, CH), 1.12 – 1.05 (3H, m, 3xCH), 0.95 (9H, s, SiC(CH₃)₃), 0.74 – 0.66 (1H, m, CH), 0.26 (3H, s, Si(CH₃,_A)(CH₃,_B)), 0.16 (3H, s, Si(CH₃,_A)(CH₃,_B)); **¹³C NMR** (126 MHz, CDCl₃): δ_C = 160.58 (C=O), 160.47 (C_{Ar}, d, ¹*J*^{C-F} = 246.10), 142.34 (C_{Ar}, d, ⁴*J*^{C-F} = 3.2), 134.08 (C_{Ar}), 128.63 (C_{Ar}H), 128.47 (2xC_{Ar}H), 128.39 (2xC_{Ar}H), 127.42 (2xC_{Ar}H, d, ³*J*^{C-F} = 8.2), 118.07 (C≡N), 116.31 (2xC_{Ar}H, d, ²*J*^{C-F} = 22.6), 71.63 (NCHCHOTBS), 65.23 (NCHCHOTBS), 47.71 (NCH(Ar)CN), 40.00 (NCH₃), 36.92 (CH₂), 29.72 (CH₂), 26.34 (SiC(CH₃)₃), 25.42 (CH₂), 24.33 (CH₂), 18.36 (SiC(CH₃)₃), -3.44 (Si(CH₃,_A)(CH₃,_B)), -3.76 (Si(CH₃,_A)(CH₃,_B)); **¹⁹F NMR** (377 MHz, CDCl₃) δ_F -116.11; **HRMS** (EI⁺): *m/z* calcd for [C₂₈H₃₉FN₃O₂Si]⁺ [M+H]⁺ 496.2790. Found 496.2777.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(4-fluorophenyl)methyl)-3-methyl-3-phenylurea (8d)



Following the general procedure 1, (1*R*,2*R*)-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-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)acetonitrile (colourless solid; 2.70 g, 63:37 *dr*) was used in the next step without further purification.

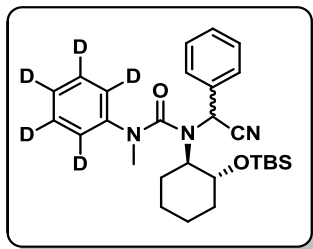
Following the general procedure 2, the *N*-alkyl-OH amino nitrile (2.56 g, 10.25 mmol) was reacted with 2,6-lutidine (1.80 mL, 15.38 mmol) and TBSOTf (2.80 mL, 12.30 mmol) in anhydrous CH₂Cl₂ (47 mL). Purification by flash column chromatography (SiO₂; *n*-Hex to *n*-Hex:Et₂O 90:10) afforded 2-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(4-fluorophenyl)acetonitrile (1.41 g, 38% over 2 steps; 75:25 *dr*) as a pale yellow oil. **R_f** (*n*-Hex:EtOAc 70:30) 0.23; **IR** (neat, cm⁻¹): ν_{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): δ_H = 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, *CH*, diast. A), 1.98 – 1.82 (1.50H, m, *CH* + *NH*, diast. B; *CH*, diast. A + B), 1.79 – 1.67 (2H, *CH*₂, diast. A+B), 1.50 – 1.17 (3.25H, m, *CH* + *CH*₂, diast. A+B; *CH*, diast. B), 1.18 – 0.97 (0.75H, m, *CH*, diast. A) 0.84 (9H, s, Si(CH₃)₃, diast. A+B), 0.06 (3H, s, Si(CH_{3,A})(CH_{3,B}), diast. A + B), 0.03 (0.75H, s, Si(CH_{3,A})(CH_{3,B}), diast. B), -0.02 (2.25H, s, Si(CH_{3,A})(CH_{3,B}), diast. A), **¹³C NMR** (101 MHz, CDCl₃): δ_C = 164.16 (C_{Ar}, d, *J*=249.9, diast. B), 162.98 (C_{Ar}, d, *J*=248.0, diast. A), 131.96 (C_{Ar}, d, *J*=3.3, diast. B), 131.66 (C_{Ar}, d, *J*=3.3, diast. A), 129.08 (2xC_{Ar}H, d, *J*=8.4, diast. A), 129.02 (2xC_{Ar}H, d, *J*=8.3, diast. B), 120.14 (C≡N, diast. B), 118.57 (C≡N, diast. A), 116.05 (2xC_{Ar}H, d, *J*=21.8, diast. A), 115.60 (2xC_{Ar}H, 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(CH_{3,A})(CH_{3,B}), diast. A), -3.78 (Si(CH_{3,A})(CH_{3,B}), diast. B) -4.47 (Si(CH_{3,A})(CH_{3,B}), diast. B), -4.75 (Si(CH_{3,A})(CH_{3,B}), diast. A); **HRMS** (EI⁺): *m/z* calcd for [C₂₀H₃₂FN₂OSi]⁺ [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 CH₃CN (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. *R*_f 0.3 (Pet. Ether:Et₂O 80:20); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 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, NCH₃), 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(CH_{3,A})(CH_{3,B})), 0.01 (3H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (126 MHz, CDCl₃): δ_{C} = 162.76 (C_{Ar}, d, ¹*J*^{C-F}=247.5), 161.38 (C=O), 145.75 (C_{Ar}), 130.74 (C_{Ar}), 129.79 (2xC_{Ar}H), 129.67 (2xC_{Ar}H, d, ³*J*^{C-F}=8.3), 126.04 (C_{Ar}H), 125.17 (2xC_{Ar}H), 118.58 (C≡N), 115.55 (2xC_{Ar}H, d, ²*J*^{C-F}=21.8), 72.09 (NCHCHOTBS), 65.37 (NCHCHOTBS), 48.57 (NCH(Ar)CN), 40.36 (NCH₃), 36.92 (CH₂), 29.86 (CH₂), 26.24 (Si(CH₃)₃), 25.74 (CH₂), 24.46 (CH₂), 18.37 (Si(CH₃)₃), -3.17 (Si(CH_{3,A})(CH_{3,B})) -3.48 (Si(CH_{3,A})(CH_{3,B})); **¹⁹F NMR** (377 MHz, CDCl₃) δ_{F} -113.49; **HRMS** (EI⁺): *m/z* calcd for [C₂₈H₃₉FN₃O₂Si]⁺ [M+H]⁺ 496.2790 Found 496.2771.

Diast. B: pale yellow oil. *R*_f 0.29 (Pet. Ether:Et₂O 80:20); **IR** (neat, cm⁻¹): $\nu_{\max}$ = 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(CH_{3,A})(CH_{3,B})), 0.15 (3H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (126 MHz, CDCl₃): δ_{C} = 162.73 (C_{Ar}, d, ¹*J*^{C-F}=246.9), 160.46 (C=O), 146.19 (C_{Ar}), 130.31 (2xC_{Ar}H, d, ³*J*^{C-F}=8.3), 130.10 (C_{Ar}, d, ⁴*J*^{C-F}= 3.2), 129.56 (2xC_{Ar}H), 125.93 (C_{Ar}H), 125.70 (2xC_{Ar}H), 118.07 (C≡N), 115.41 (2xC_{Ar}H, d, ²*J*^{C-F}=21.9), 71.63 (NCHCHOTBS), 65.06 (NCHCHOTBS), 47.11 (NCH(Ar)CN), 39.76 (NCH₃), 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(CH_{3,A})(CH_{3,B})) -3.74 (Si(CH_{3,A})(CH_{3,B})); **¹⁹F NMR** (377 MHz, CDCl₃) δ_{F} -113.44; **HRMS** (EI⁺): *m/z* calcd for [C₂₈H₃₉FN₃O₂Si]⁺ [M+H]⁺ 496.2790 Found 496.2777.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-methyl-3-(phenyl-*d*₅)urea (8e)

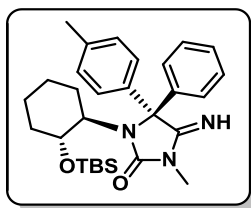


Following the general procedure 3 (step 2), the corresponding carbamoyl chloride (*see compound 8b for the synthetic procedure*; 528 mg) was reacted with 2,6-lutidine (0.18 mL, 1.56 mmol) and *N*-methylaniline-2,3,4,5,6-*d*₅ (160 mg, 1.43 mmol) in dry CH₃CN (3.2 mL) at reflux for 24 h. The crude product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

Diast. A: yellow oil. *R*_f 0.24 (SiO₂; *n*-Hex:Et₂O 80:20); **IR** (neat, cm⁻¹): *v*_{max} = 2929 (C–H), 2856 (C–H), 2250 (C≡N), 1661 (C=O); **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.59 – 7.54 (2H, m, 2xAr-*H*), 7.39 – 7.31 (3H, m, 3xAr-*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, 3xCH), 1.20 – 1.07 (1H, m, CH), 1.04 – 0.93 (1H, m, CH), 0.86 (9H, s, SiC(CH₃)₃), 0.82 – 0.75 (1H, m, CH) 0.09 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.03 (3H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (126 MHz, CDCl₃): δ_C = 161.49 (C=O), 145.71 (*C*_{Ar}), 134.83 (*C*_{Ar}), 129.21 (2x*C*_{ArD}, t, ¹*J*_{C-D}=23.94), 128.59 (2x*C*_{ArH}), 128.55 (*C*_{ArH}), 127.76 (2x*C*_{ArH}), 125.67 – 124.35 (3x*C*_{ArD}, m), 118.70 (C≡N), 71.98 (NCHCHOTBS), 65.40 (NCHCHOTBS), 49.21 (NCH(Ar)CN), 40.31 (NCH₃), 36.97 (CH₂), 29.79 (CH₂), 26.25 (SiC(CH₃)₃), 25.78 (CH₂), 24.45 (CH₂), 18.34 (SiC(CH₃)₃), -3.25 (Si(CH_{3,A})(CH_{3,B})) -3.62 (Si(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for [C₂₈H₃₄D₅N₃NaO₂Si]⁺ [M+Na]⁺ 505.3018 Found 505.3014.

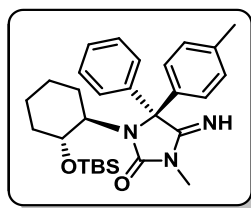
Diast. B: yellow oil. *R*_f 0.17 (SiO₂; *n*-Hex:Et₂O 80:20); **IR** (neat, cm⁻¹): *v*_{max} = 2930 (C–H), 2856 (C–H), 2278 (C≡N), 1659 (C=O); **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.60 – 7.53 (2H, m, 2xAr-*H*), 7.45 – 7.33 (3H, m, 3xAr-*H*), 5.11 (1H, s, NCH(Ar)CN), 3.80 – 3.71 (1H, m, NCHCHOTBS), 3.34 (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, 3xCH), 0.96 (9H, s, SiC(CH₃)₃), 0.68 – 0.57 (1H, m, CH), 0.26 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.16 (3H, s, Si(CH_{3,A})(CH_{3,B})); **¹³C NMR** (126 MHz, CDCl₃): δ_C = 160.48 (C=O), 146.13 (*C*_{Ar}), 134.22 (*C*_{Ar}), 129.01 (2x*C*_{ArD}, t, ¹*J*_{C-D}=23.94), 128.53 (*C*_{ArH}), 128.45 (2x*C*_{ArH}), 128.37 (2x*C*_{ArH}), 125.63 – 124.92 (3x*C*_{ArD}, 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 (SiC(CH₃)₃), 25.30 (CH₂), 24.36 (CH₂), 18.37 (SiC(CH₃)₃), -3.51 (Si(CH_{3,A})(CH_{3,B})) -3.69 (Si(CH_{3,A})(CH_{3,B})); **HRMS** (ESI⁺): *m/z* calcd for [C₂₈H₃₅D₅N₃O₂Si]⁺ [M+H]⁺ 483.3198 Found 483.3198.

(*R*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-5-imino-1-methyl-4-phenyl-4-(*p*-tolyl)imidazolidin-2-one (9a)



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. *R_f* 0.25 (SiO₂; *n*-Hex:EtOAc 60:40); *IR* (neat, cm⁻¹): $\nu_{\max}$ = 3320 (N–H), 2943 (C–H), 1732 (C=N), 1657 (C=O), 1458; ¹H NMR (400 MHz, CDCl₃): δ_{H} = 7.88 – 7.82 (2 H, m, 2x*C_{Ar}H*), 7.41 – 7.32 (3 H, m, 3x*C_{Ar}H*), 7.17 – 7.09 (4 H, m, 4x*C_{Ar}H*), 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, 5x*CH*), 0.96 (9 H, s, SiC(*CH₃*)₃), 0.77 – 0.62 (1 H, m, *CH*), 0.20 (3 H, s, Si(*CH_{3,A}*)(*CH_{3,B}*)), 0.08 (3 H, s, Si(*CH_{3,A}*)(*CH_{3,B}*)); ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 168.0 (C=N), 155.7 (C=O), 138.8 (*C_{Ar}*), 138.6 (*C_{Ar}*), 137.8 (*C_{Ar}*), 129.3 (2x*C_{Ar}H*), 128.9 (2x*C_{Ar}H*), 128.6 (*C_{Ar}H*), 128.5 (2x*C_{Ar}H*), 128.2 (2x*C_{Ar}H*), 75.0 (NC(*Ar*)Ph), 72.4 (*NCHCHOTBS*), 60.9 (*NCHCHOTBS*), 37.4 (*CH₂*), 29.3 (SiC(*CH₃*)₃), 26.1 (SiC(*CH₃*)₃), 25.4 (*CH₂*), 25.3 (*NCH₃*), 24.6 (*CH₂*), 21.1 (*ArCH₃*), 18.2 (*CH₂*), -3.9 Si(*CH_{3,A}*)(*CH_{3,B}*), -5.8 Si(*CH_{3,A}*)(*CH_{3,B}*); *HRMS* (ESI⁺): *m/z* calcd for C₂₉H₄₁N₃NaO₂Si [*M*+Na]⁺ 514.2860, found 514.2857.

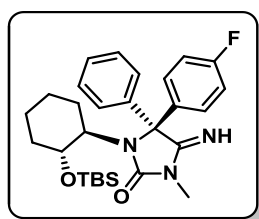
(*S*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-5-imino-1-methyl-4-phenyl-4-(*p*-tolyl)imidazolidin-2-one (9b)



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. *R_f* 0.25 (SiO₂; *n*-Hex:EtOAc 60:40); *m.p.* = 93 – 95 °C; [α]_D²⁵ = -212 (*c* = 1.0, CHCl₃); *IR* (neat, cm⁻¹): $\nu_{\max}$ = 3318 (N–H), 2928 (C–H), 1731 (C=N), 1659 (C=O), 1460; ¹H NMR (500 MHz, CDCl₃): δ_{H} = 7.75 – 7.69 (2 H, m, 2x*C_{Ar}H*), 7.37 – 7.31 (3 H, m, 3x*C_{Ar}H*), 7.27 – 7.23 (2 H, m, 2x*C_{Ar}H*), 7.21 – 7.17 (2 H, m, 2x*C_{Ar}H*), 6.90 (1 H, br. s, *NH*), 4.83 – 4.72 (1

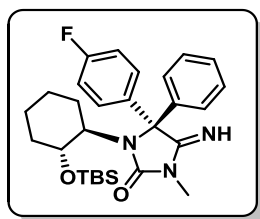
H, m, NCHCHOTBS), 3.13 (3 H, s, NCH_3), 2.90 (1 H, ddd, $J = 12.4, 9.7, 3.0$ Hz, NCHCHOTBS), 2.37 (3 H, s, ArCH_3), 1.96 – 1.87 (1 H, m, CH), 1.56 – 1.48 (1 H, m, CH), 1.36 – 1.14 (5 H, m, $5\times\text{CH}$), 0.97 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.75 – 0.62 (1 H, m, CH), 0.20 (3 H, s, $\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$), 0.08 (3 H, s, $\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$); ^{13}C NMR (126 MHz, CDCl_3) $\delta_{\text{C}} = 168.2$ (C=N), 155.8 (C=O), 141.1 (C_{Ar}), 138.2 (C_{Ar}), 135.5 (C_{Ar}), 129.4 ($2\times\text{C}_{\text{ArH}}$), 129.1 ($2\times\text{C}_{\text{ArH}}$), 129.0 (C_{ArH}), 128.8 ($2\times\text{C}_{\text{ArH}}$), 128.7 ($2\times\text{C}_{\text{ArH}}$), 75.2 (NC(Ar)Ph), 72.5 (NCHCHOTBS), 61.0 (NCHCHOTBS), 37.6 (CH_2), 29.4 ($\text{SiC}(\text{CH}_3)_3$), 26.3 ($\text{SiC}(\text{CH}_3)_3$), 25.6 (CH_2), 25.4 (NCH_3), 24.7 (CH_2), 21.2 (ArCH_3), 18.4 (CH_2), -3.8 ($\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$), -5.6 ($\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$); HRMS (ESI $^+$): m/z calcd for $\text{C}_{29}\text{H}_{41}\text{N}_3\text{NaO}_2\text{Si}$ [M+Na] $^+$ 514.2860, found 514.2860.

(S)-3-((1R,2R)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4-(4-fluorophenyl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (9c)



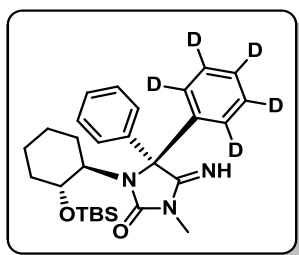
Following the general procedure 4 (method B), the *N'*-aryl ureido nitrile **8c** (53 mg, 0.108 mmol; 50:50 *dr*) was reacted with LDA (0.13 mL, 2.0 M in THF/heptane/ethylbenzene, 0.270 mmol) in a mixture of anhydrous THF (1.0 mL) and DMPU (0.1 mL) at +40 °C for 20 h. The crude product (94:6 *dr* by ^{19}F -NMR) was purified by flash column chromatography (SiO_2 ; Pet. Ether:Et $_2$ O 100:0 to 70:30) to afford the title compound (27 mg, 51%, 94:6 *dr*) as a yellow oil. R_f 0.25 (SiO_2 ; Pet. Ether:Et $_2$ O 70:30); IR (neat, cm^{-1}): $\nu_{\text{max}} = 3321$ (N–H), 2930 (C–H), 2856 (C–H), 1737 (C=N), 1660 (C=O); ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 7.89$ – 7.83 (2H, m, $2\times\text{Ar-H}$), 7.40 – 7.32 (3H, m, $3\times\text{Ar-H}$), 7.25 – 7.21 (2H, m, $2\times\text{Ar-H}$), 7.10 – 7.03 (2H, m, $2\times\text{Ar-H}$), 4.78 (1H, dt, $J = 10.2, 5.2$, NCHCHOTBS), 3.14 (3H, s, NCH_3), 2.87 (1H, ddd, $J = 11.9, 9.7, 3.0$, NCHCHOTBS), 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, $3\times\text{CH}$), 0.96 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.76 – 0.64 (1H, m, CH), 0.20 (3H, s, $\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$), 0.07 (3H, $\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$), 0.06 – (-0.03) (1H, m, CH); ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 167.83$ (C=N), 162.91 (C_{Ar} , d, $^1J^{\text{C-F}} = 248.0$), 155.67 (C=O), 140.82 (C_{Ar}), 134.32 (C_{Ar} , d, $^4J^{\text{C-F}} = 3.1$), 130.78 ($2\times\text{C}_{\text{ArH}}$, d, $^3J^{\text{C-F}} = 8.0$), 129.22 (C_{ArH}), 129.00 ($2\times\text{C}_{\text{ArH}}$), 128.95 ($2\times\text{C}_{\text{ArH}}$), 115.58 ($2\times\text{C}_{\text{ArH}}$, d, $^2J^{\text{C-F}} = 21.4$), 74.81 (NC(Ar)Ph), 72.56 (NCHCHOTBS), 61.15 (NCHCHOTBS), 37.59 (CH_2), 29.34 (CH_2), 26.21 ($\text{SiC}(\text{CH}_3)_3$), 25.59 (NCH_3), 25.37 (CH_2), 24.71 (CH_2), 18.36 ($\text{SiC}(\text{CH}_3)_3$), -3.77 ($\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$), -5.61 ($\text{Si}(\text{CH}_{3,\text{A}})(\text{CH}_{3,\text{B}})$); ^{19}F NMR (377 MHz, CDCl_3) $\delta_{\text{F}} -114.09$; HRMS (ESI $^+$): m/z calcd for $[\text{C}_{28}\text{H}_{39}\text{FN}_3\text{O}_2\text{Si}]^+ [\text{M}+\text{H}]^+$ 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}F -NMR) was purified by flash column chromatography (SiO_2 ; Pet. Ether:Et₂O 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:Et₂O 60:40); IR (neat, cm^{-1}): ν_{max} = 3315 (N–H), 2929 (C–H), 2856 (C–H), 1732 (C=N), 1656 (C=O); ^1H NMR (400 MHz, CDCl_3): δ_{H} = 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, NCHCHOTBS), 3.13 (3H, s, NCH₃), 2.89 (1H, ddd, *J* = 11.9, 9.6, 3.0 NCHCHOTBS), 1.97 – 1.89 (1H, m, CH), 1.58 – 1.51 (1H, m, CH), 1.39 – 1.21 (2H, m, 2xCH), 1.23 – 1.15 (2H, m, 2xCH), 0.96 (9H, s, Si(CH₃)₃), 0.78 – 0.66 (1H, m, CH), 0.20 (3H, s, Si(CH_{3,A})(CH_{3,B})), 0.12 (1H, br. s, CH), 0.08 (3H, Si(CH_{3,A})(CH_{3,B})); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 167.79 (C=N), 162.95 (C_{Ar}, d, $^1J^{\text{C-F}}$ = 249.8), 155.69 (C=O), 138.35 (C_{Ar}), 137.06 (C_{Ar}), 131.05 (2xC_{Ar}H, d, $^3J^{\text{C-F}}$ = 8.2), 128.80 (2xC_{Ar}H), 128.70 (2xC_{Ar}H), 128.53 (C_{Ar}H), 115.84 (2xC_{Ar}H, d, $^2J^{\text{C-F}}$ = 21.5), 74.67 (NC(Ar)Ph), 72.52 (NCHCHOTBS), 61.09 (NCHCHOTBS), 37.59 (CH₂), 29.56 (CH₂), 26.23 (Si(CH₃)₃), 25.63 (NCH₃), 25.40 (CH₂), 24.70 (CH₂), 18.35 (Si(CH₃)₃), -3.78 (Si(CH_{3,A})(CH_{3,B})), -5.59 (Si(CH_{3,A})(CH_{3,B})); ^{19}F NMR (377 MHz, CDCl_3) δ_{F} -112.09; HRMS (ESI⁺): *m/z* calcd for [C₂₈H₃₉FN₃O₂Si]⁺ [M+H]⁺ 496.2790. Found 496.2811.

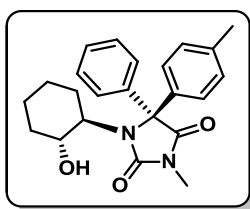
(S)-3-((1R,2R)-2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)-5-imino-1-methyl-4-phenyl-4-(phenyl-d₅)imidazolidin-2-one (9e)



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:Et₂O 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:Et₂O 50:50); IR (neat, cm^{-1}): ν_{max} = 3314 (N–H), 2928 (C–H), 2855 (C–H), 1731 (C=N), 1658 (C=O); ^1H NMR (400 MHz, CDCl_3): δ_{H} = 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

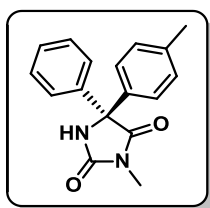
(3H, s, NCH_3), 2.91 (1H, ddd, $J = 11.9, 9.6, 3.0$, NCHCHOTBS), 1.96 – 1.89 (1H, m, CH), 1.55 – 1.49 (1H, m, CH), 1.33 – 1.27 (1H, m, CH), 1.25 – 1.15 (3H, m, $3\times\text{CH}$), 0.97 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.75 – 0.62 (1H, m, CH), 0.20 (3H, s, $\text{Si}(\text{CH}_3)_2(\text{CH}_3)_2$), 0.09 (3H, $\text{Si}(\text{CH}_3)_2(\text{CH}_3)_2$), 0.06 – (-0.01) (1H, m, CH); ^{13}C NMR (126 MHz, CDCl_3) $\delta_{\text{C}} = 167.99$ ($\text{C}=\text{N}$), 155.80 ($\text{C}=\text{O}$), 140.99 (C_{Ar}), 138.31 (C_{Ar}), 129.11 ($2\times\text{C}_{\text{ArH}}$), 129.07 (C_{ArH}), 128.83 ($2\times\text{C}_{\text{ArH}}$), 128.80 – 127.64 ($5\times\text{C}_{\text{ArD}}$, m), 75.27 ($\text{NC}(\text{Ar})\text{Ph}$), 72.52 (NCHCHOTBS), 61.11 (NCHCHOTBS), 37.59 (CH_2), 29.36 (CH_2), 26.22 ($\text{SiC}(\text{CH}_3)_3$), 25.61 (NCH_3), 25.37 (CH_2), 24.72 (CH_2), 18.35 ($\text{SiC}(\text{CH}_3)_3$), -3.79 ($\text{Si}(\text{CH}_3)_2(\text{CH}_3)_2$), -5.61 ($\text{Si}(\text{CH}_3)_2(\text{CH}_3)_2$); **HRMS** (ESI^+): m/z calcd for $[\text{C}_{28}\text{H}_{35}\text{D}_5\text{N}_3\text{O}_2\text{Si}]^+ [\text{M}+\text{H}]^+$ 483.3198. Found 483.3198.

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

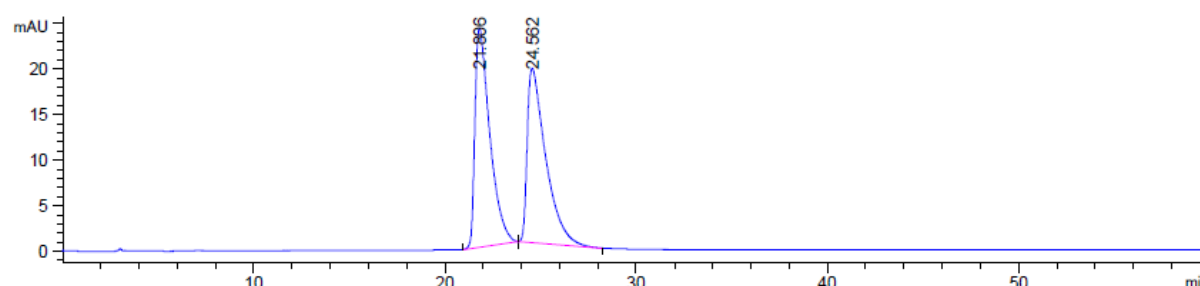


HCl (2.0 mL, 2 M, aq.) was added to a solution of the 4-iminohydantoin **9b** (100 mg, 0.203 mmol, 95:5 *dr*) in MeOH (2.0 mL) and the reaction mixture was heated to reflux for 72 h (progress monitored by TLC). The acidic media was neutralised by addition of NaHCO_3 (sat. aq.). The mixture was partitioned between H_2O and EtOAc. The aqueous phase was further extracted ($\times 2$) in EtOAc, and the combined organic phase was washed with brine, dried over Na_2SO_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; $[\alpha]_{\text{D}}^{25} = -190$ ($c = 0.5$, CHCl_3); **IR** (neat, cm^{-1}): $\nu_{\text{max}} = 3463$ (br. O–H), 2938 (C–H), 1764 ($\text{C}=\text{O}$), 1697 ($\text{C}=\text{O}$), 1450; ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 7.68$ – 7.59 (2 H, m, $2\times\text{C}_{\text{ArH}}$), 7.40 – 7.34 (3 H, m, $3\times\text{C}_{\text{ArH}}$), 7.29 – 7.25 (2 H, m, $2\times\text{C}_{\text{ArH}}$), 7.22 – 7.17 (2 H, m, $2\times\text{C}_{\text{ArH}}$), 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_3), 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, $2\times\text{CH}$), 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) $\delta_{\text{C}} = 174.2$ ($\text{C}=\text{O}$)_{amide}, 156.1 ($\text{C}=\text{O}$)_{urea}, 138.8 (C_{Ar}), 138.7 (C_{Ar}), 133.8 (C_{Ar}), 129.3 ($2\times\text{C}_{\text{ArH}}$), 129.2 ($2\times\text{C}_{\text{ArH}}$), 129.2 (C_{ArH}), 129.0 ($2\times\text{C}_{\text{ArH}}$), 128.8 ($2\times\text{C}_{\text{ArH}}$), 75.8 ($\text{NC}(\text{Ar})\text{Ph}$), 71.0 (NCHCHOTBS), 61.7 (NCHCHOTBS), 36.0 (CH_2), 29.7 (CH_2), 25.4 (CH_2), 25.2 (NCH_3), 24.6 (CH_2), 21.3 (ArCH_3); **HRMS** (ESI^+): m/z calcd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 379.2016, found 379.2019.

(S)-3-Methyl-5-phenyl-5-(p-tolyl)imidazolidine-2,4-dione (11b)

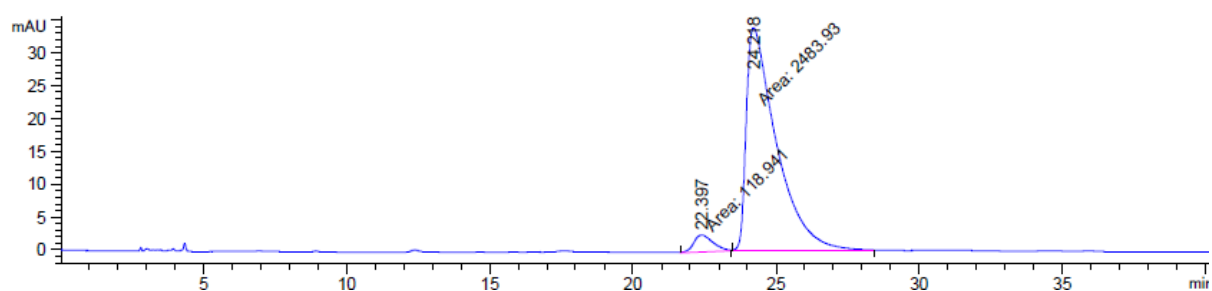


In a sealed tube, an emulsion of the hydantoin **10b** (50 mg, 0.132 mmol) in neat polyphosphoric acid (PPA, 2 mL) was heated at 100 °C stirring for 16 h. After cooling down to room temperature, the reaction mixture was partitioned between H₂O (exothermic!) and CH₂Cl₂. The aqueous phase was further extracted (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; *R_f* 0.35 (SiO₂; *n*-Hex:EtOAc 70:30); $[\alpha]_D^{25} = +10$ (*c* = 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H = 7.42 – 7.32 (6 H, m, 5x*C_{Ar}H*+NH), 7.29 – 7.23 (2 H, m, 2x*C_{Ar}H*), 7.19 – 7.13 (2 H, m, 2x*C_{Ar}H*), 3.07 (3 H, s, NCH₃), 2.34 (3 H, s, ArCH₃); ¹³C NMR (101 MHz, CDCl₃) δ_C = 173.8 (C=O)_{amide}, 157.2 (C=O)_{urea}, 139.4 (*C_{Ar}*), 138.5 (*C_{Ar}*), 136.4 (*C_{Ar}*), 129.6 (2x*C_{Ar}H*), 128.8 (2x*C_{Ar}H*), 128.6 (*C_{Ar}H*), 126.9 (2x*C_{Ar}H*), 126.8 (2x*C_{Ar}H*), 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., λ = 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]



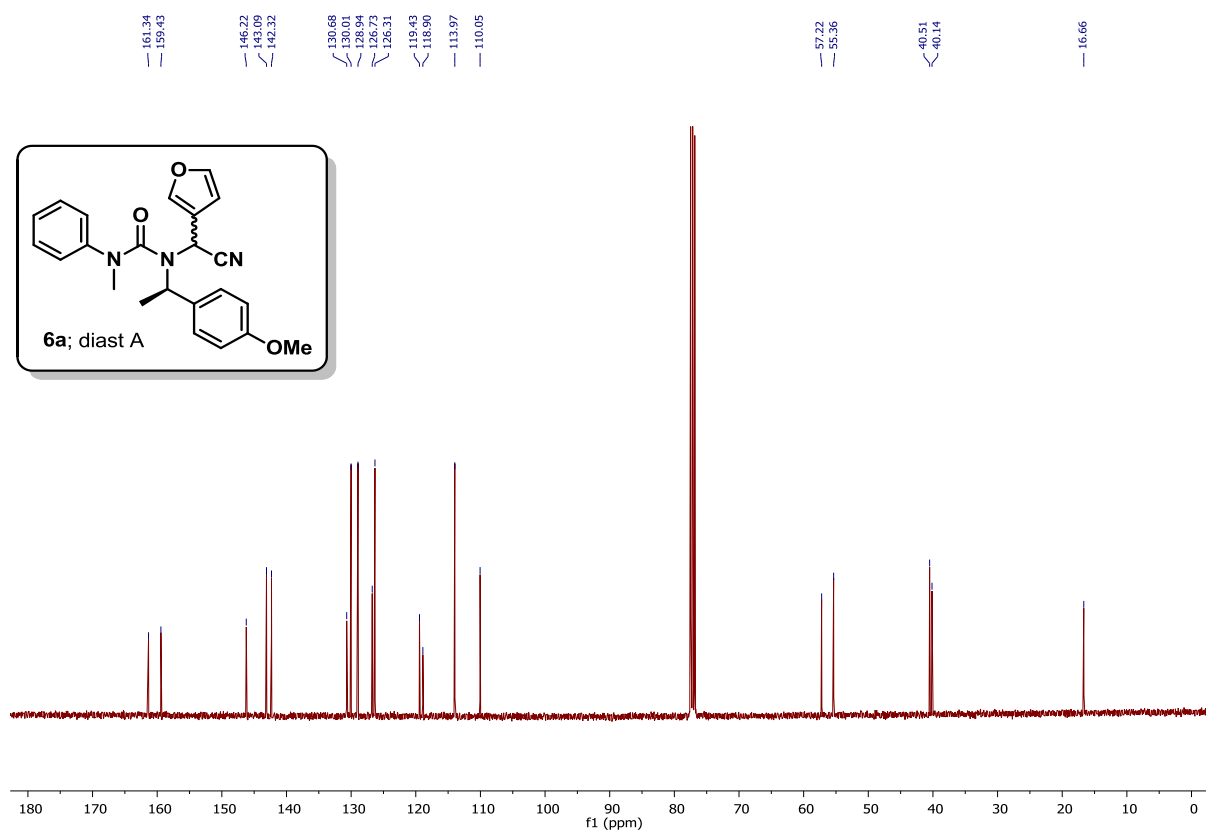
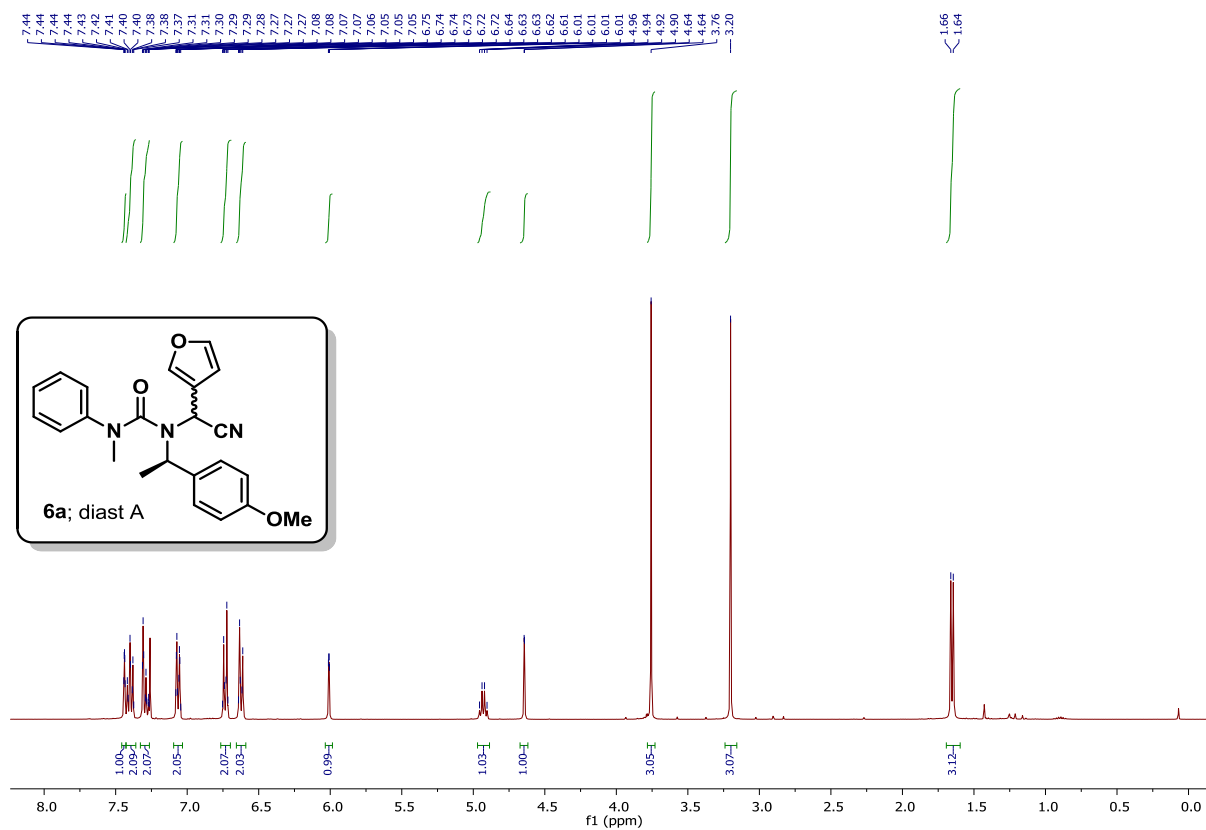
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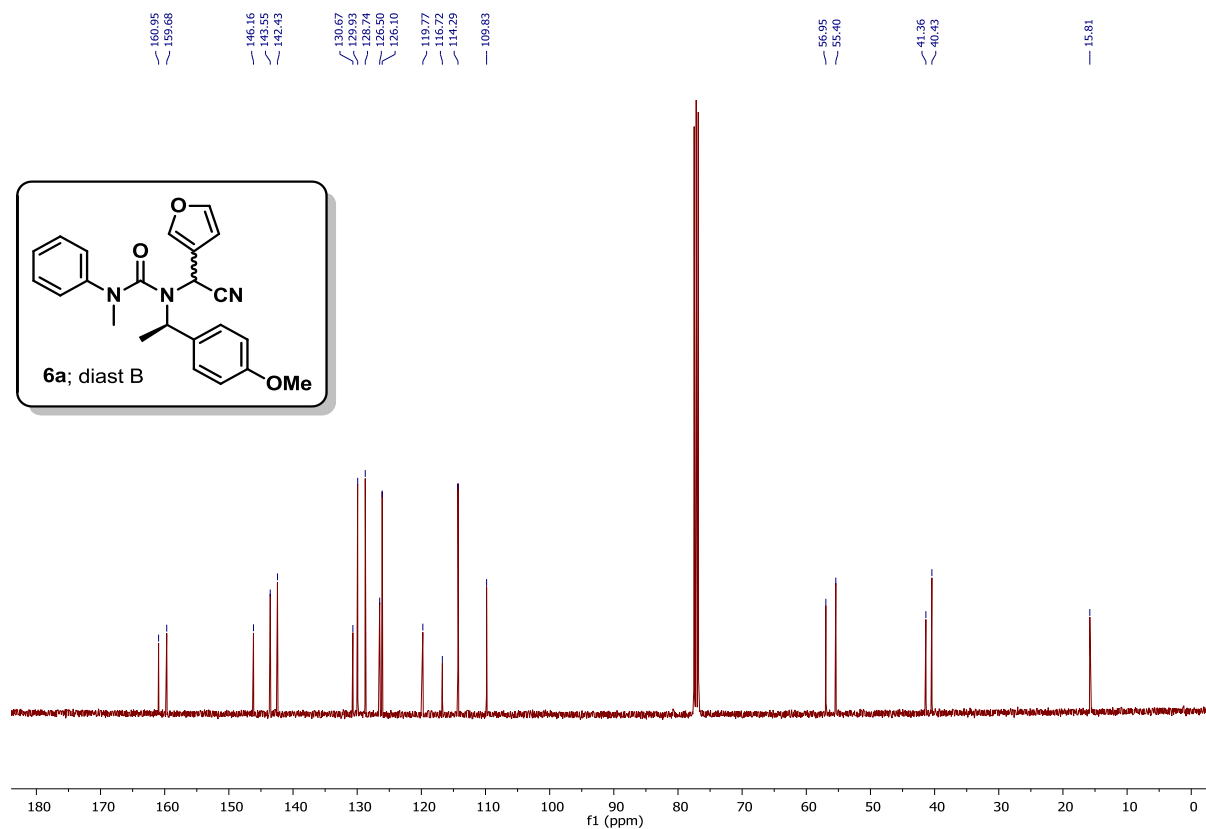
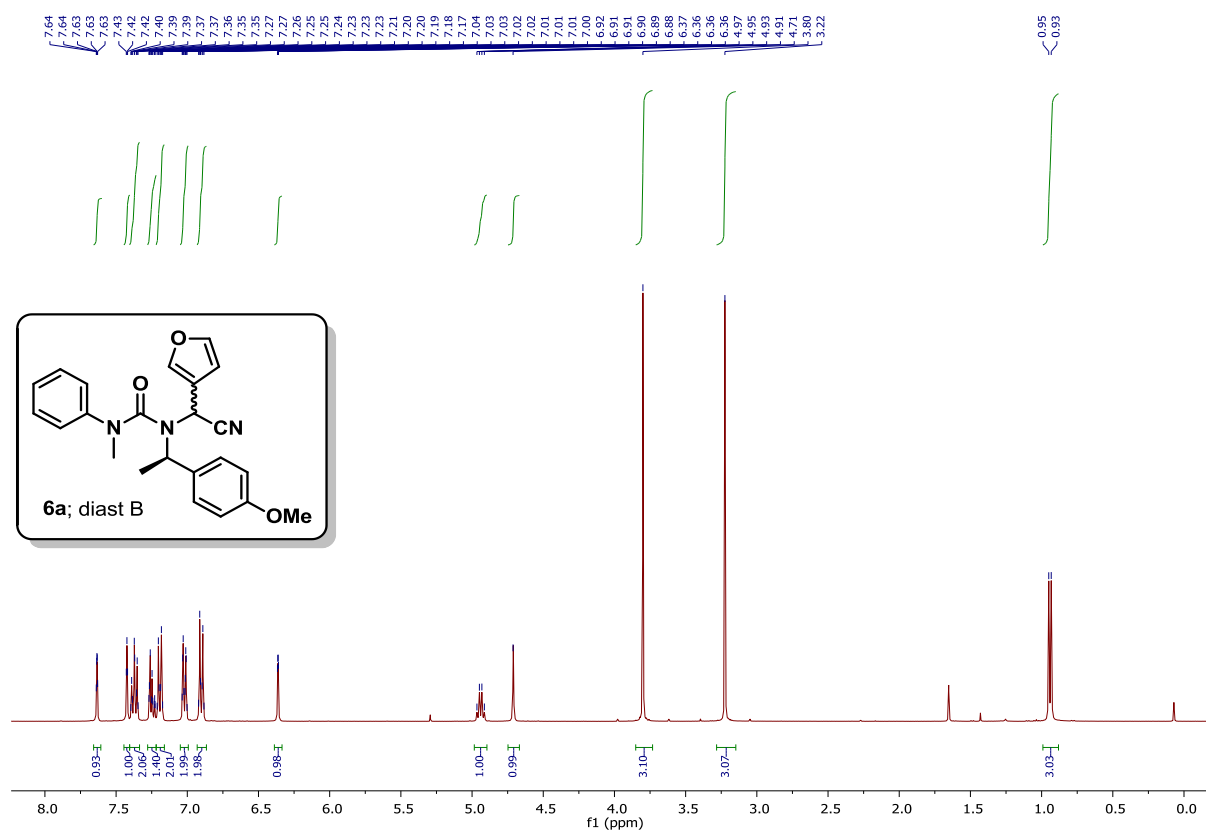
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2	24.562	BB	0.9581	1287.37354	19.15393	49.7436

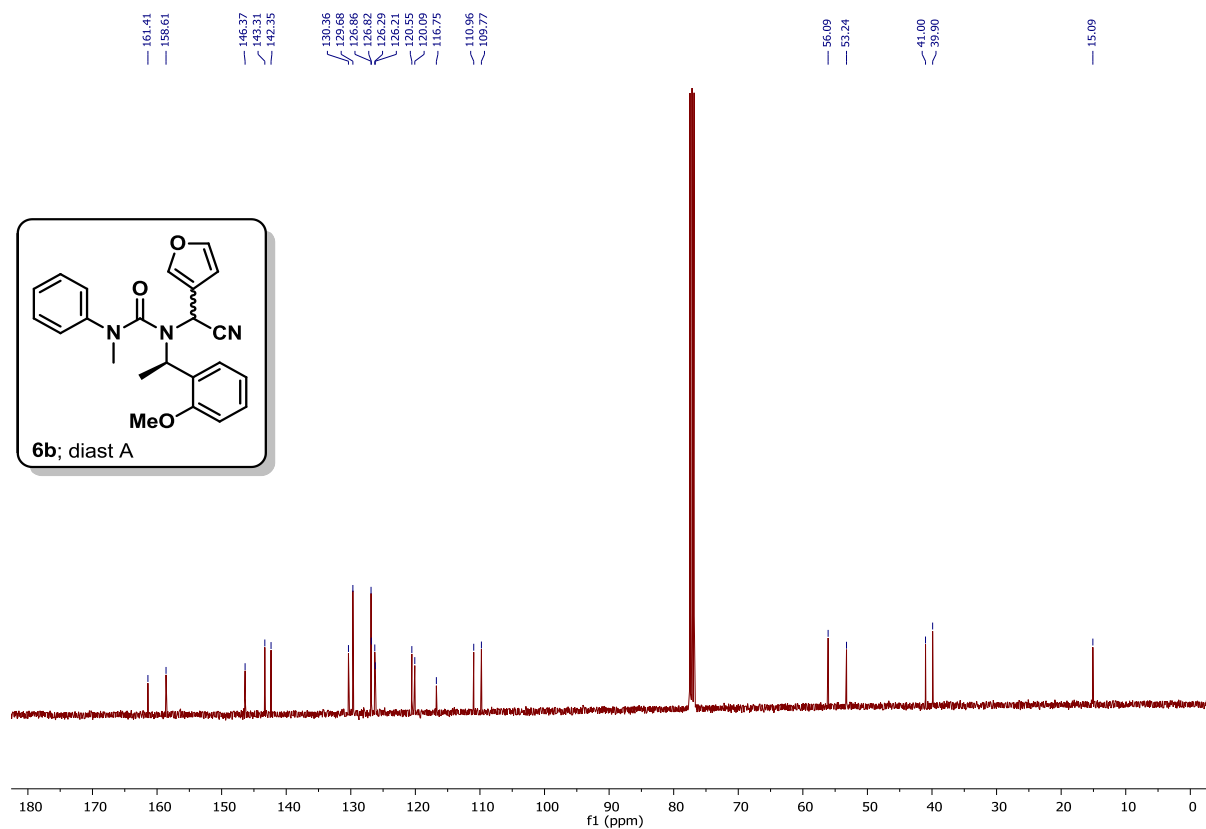
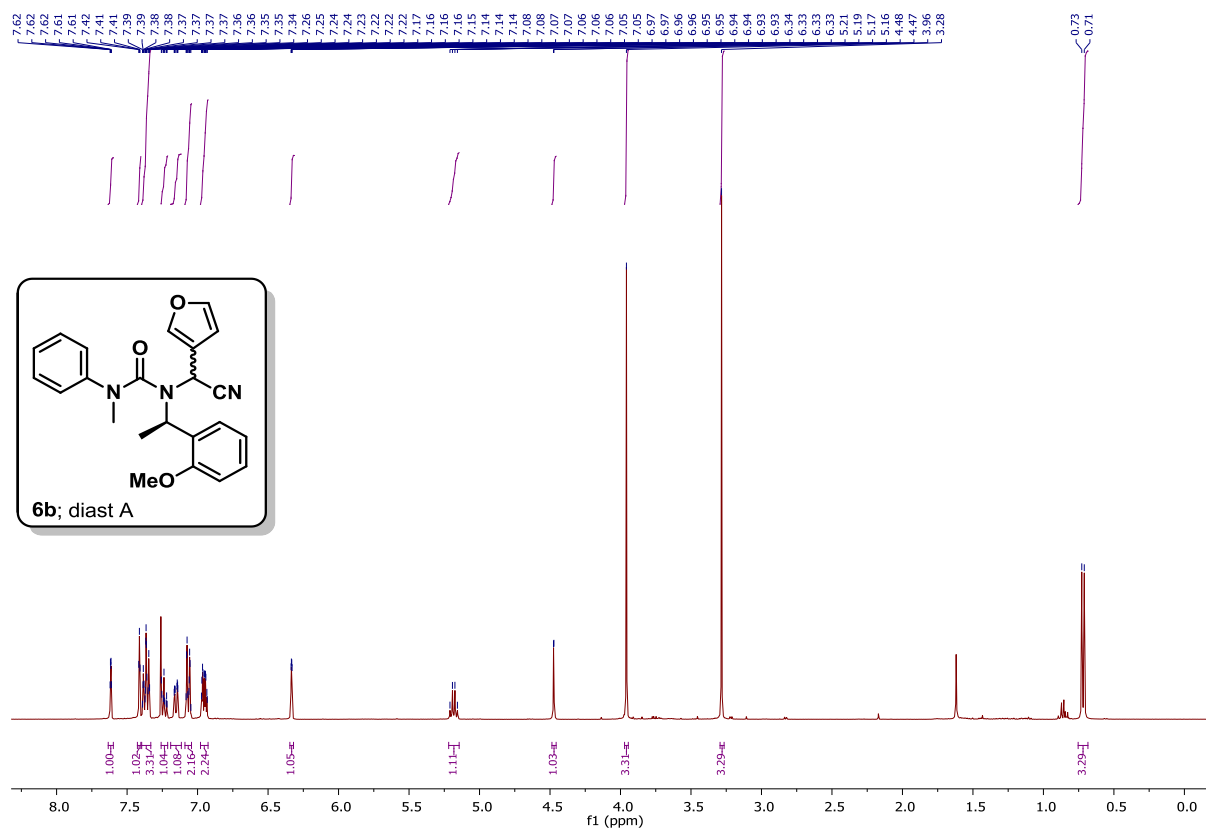


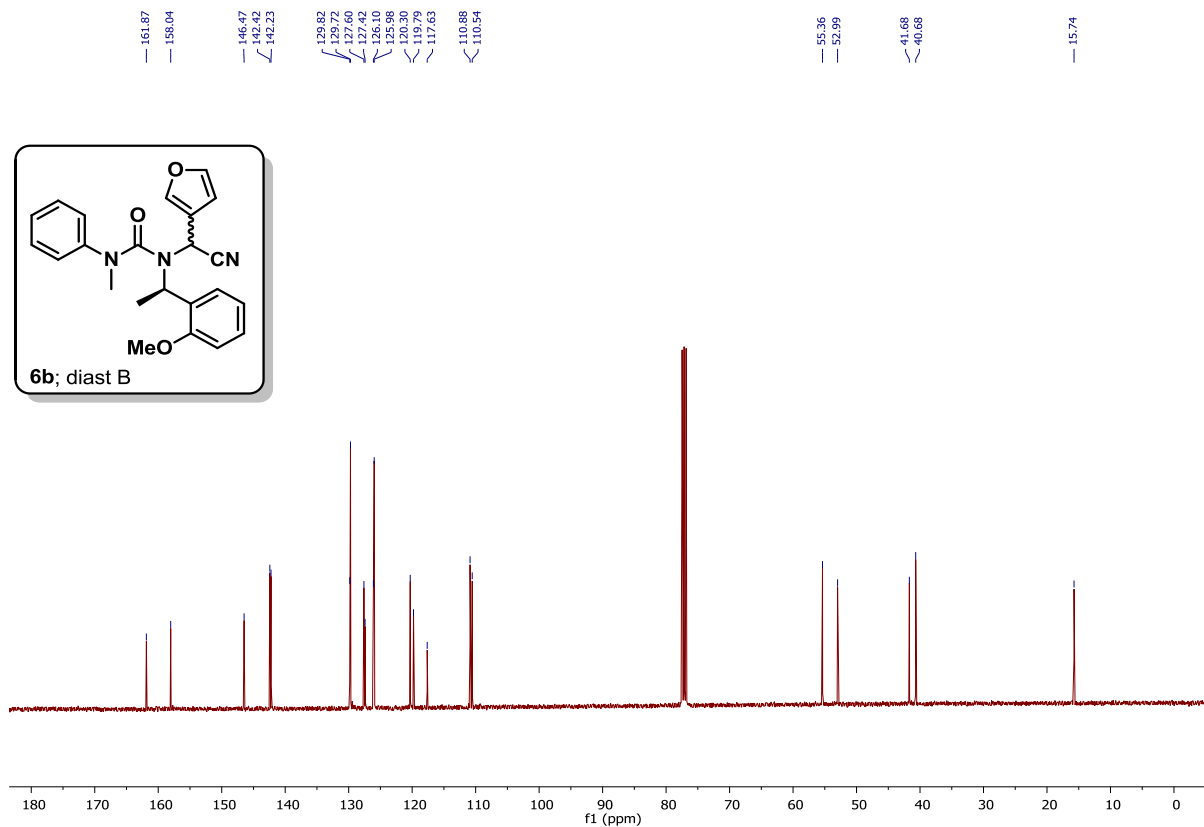
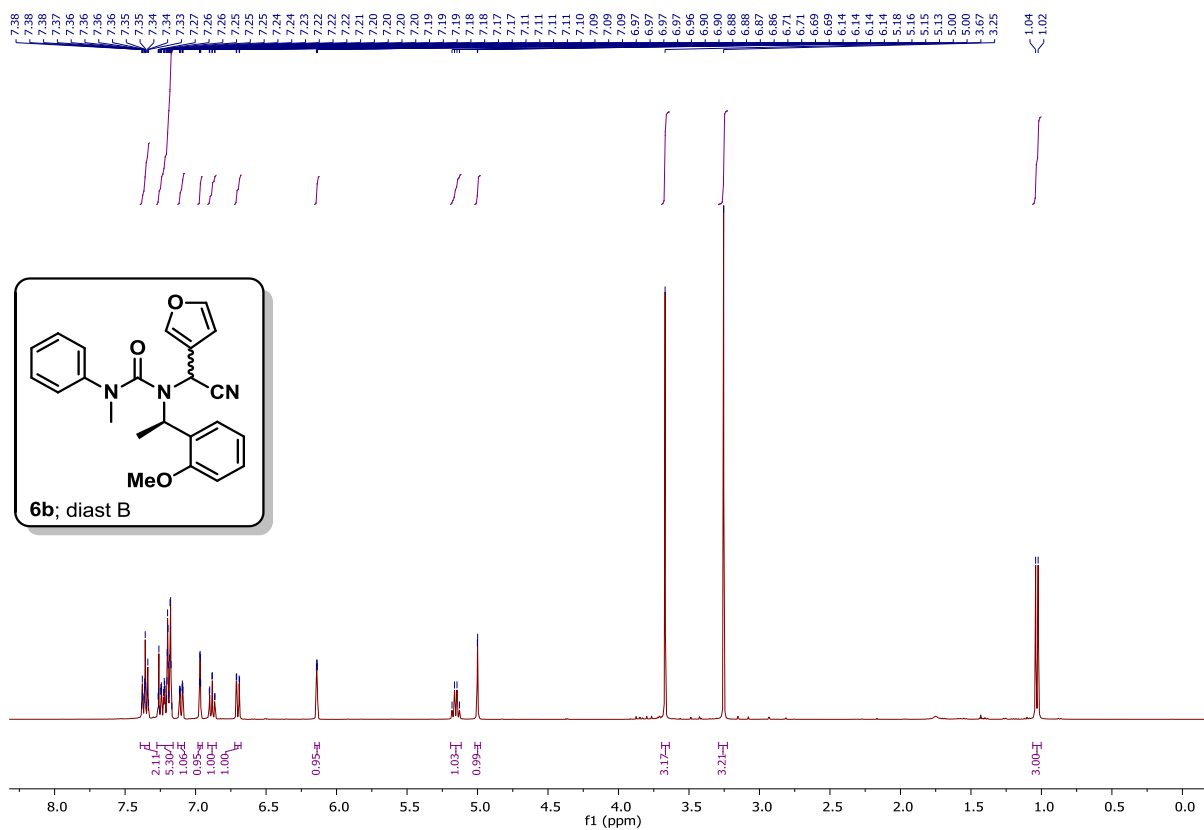
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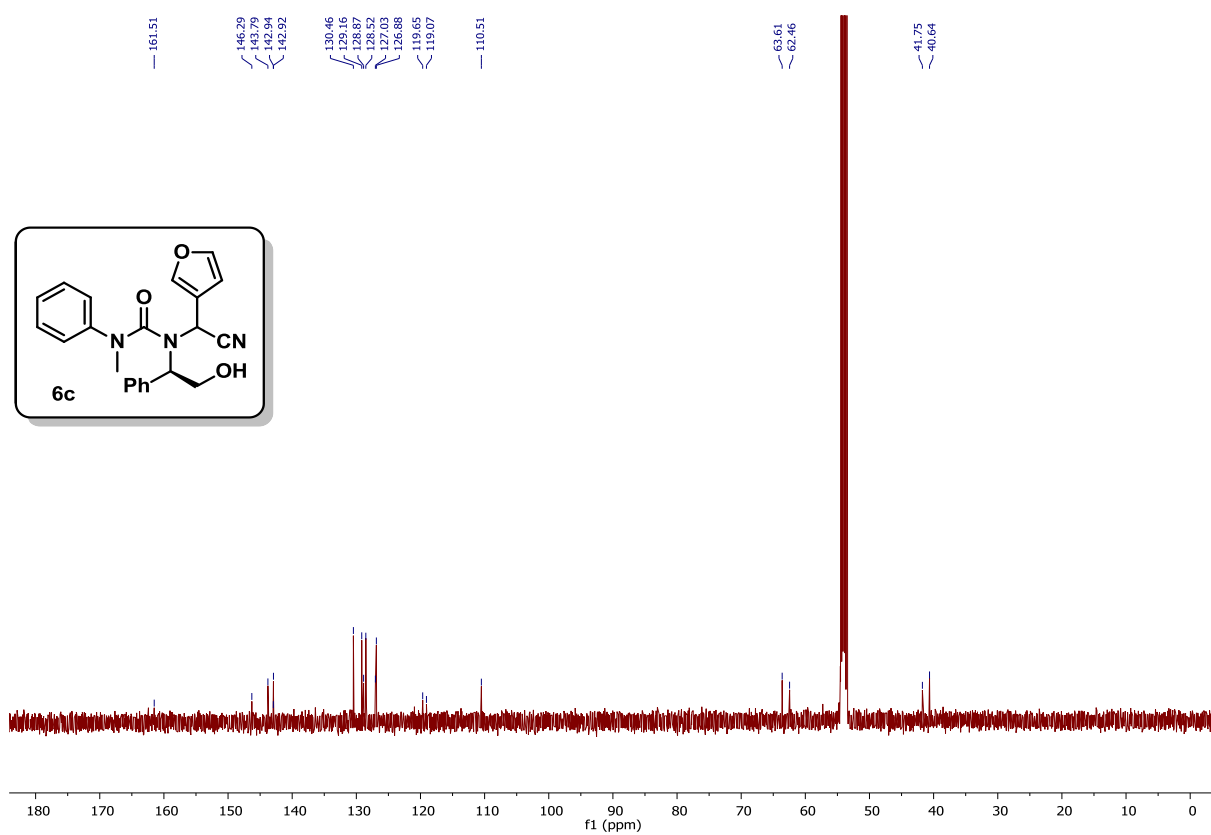
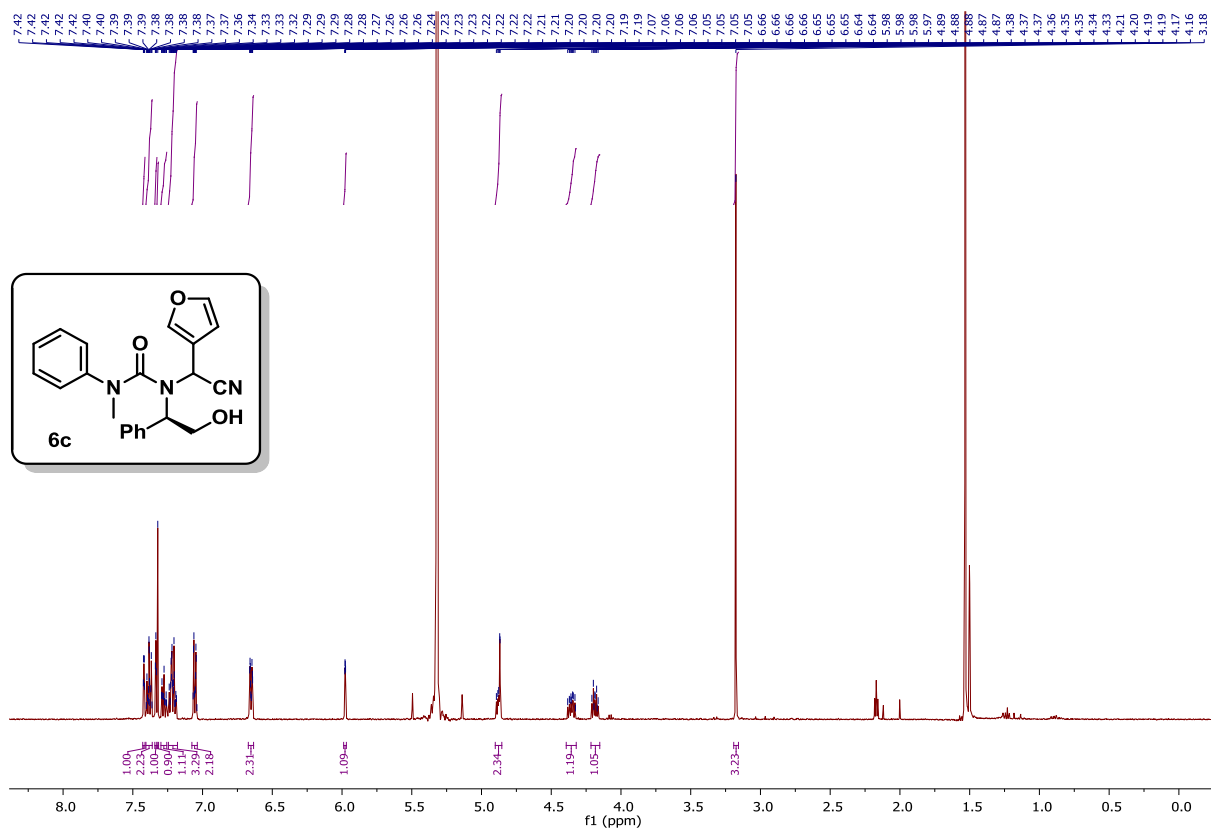
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2	24.218	MM	1.2206	2483.93457	33.91676	95.4304

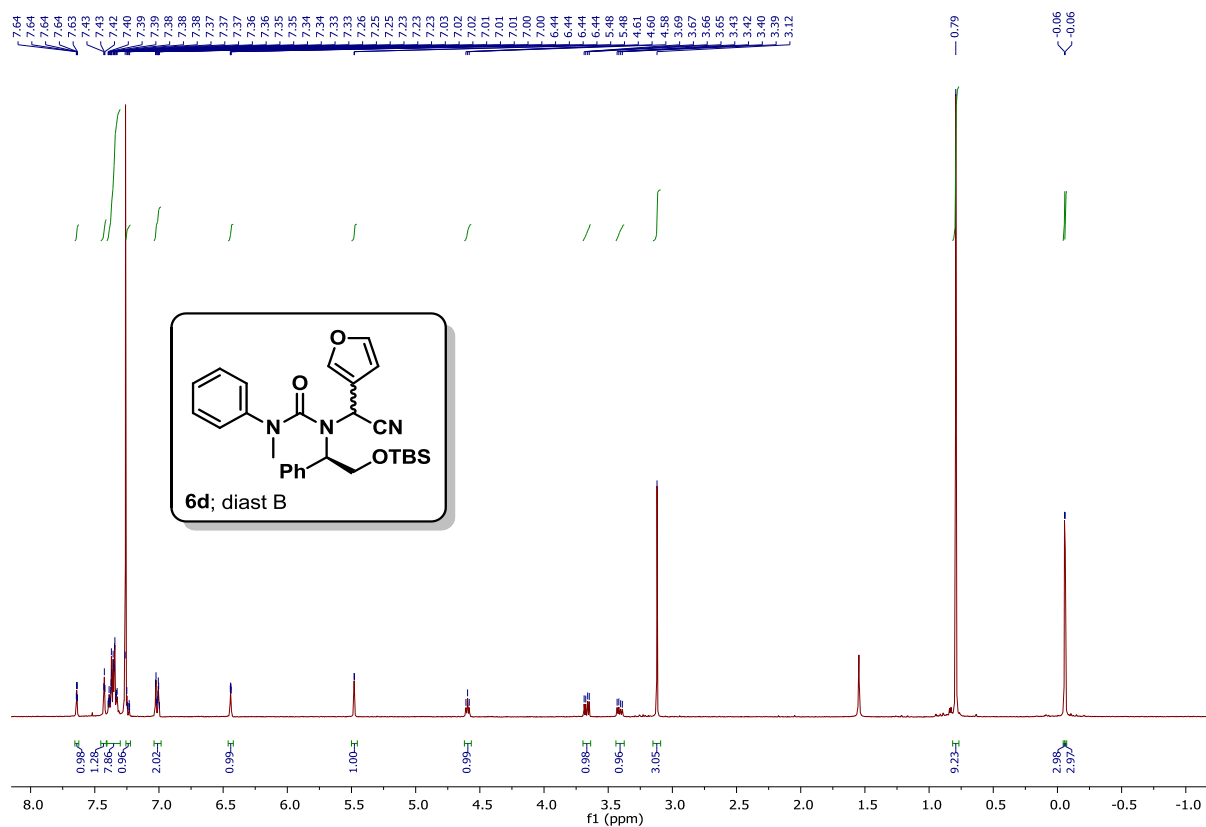
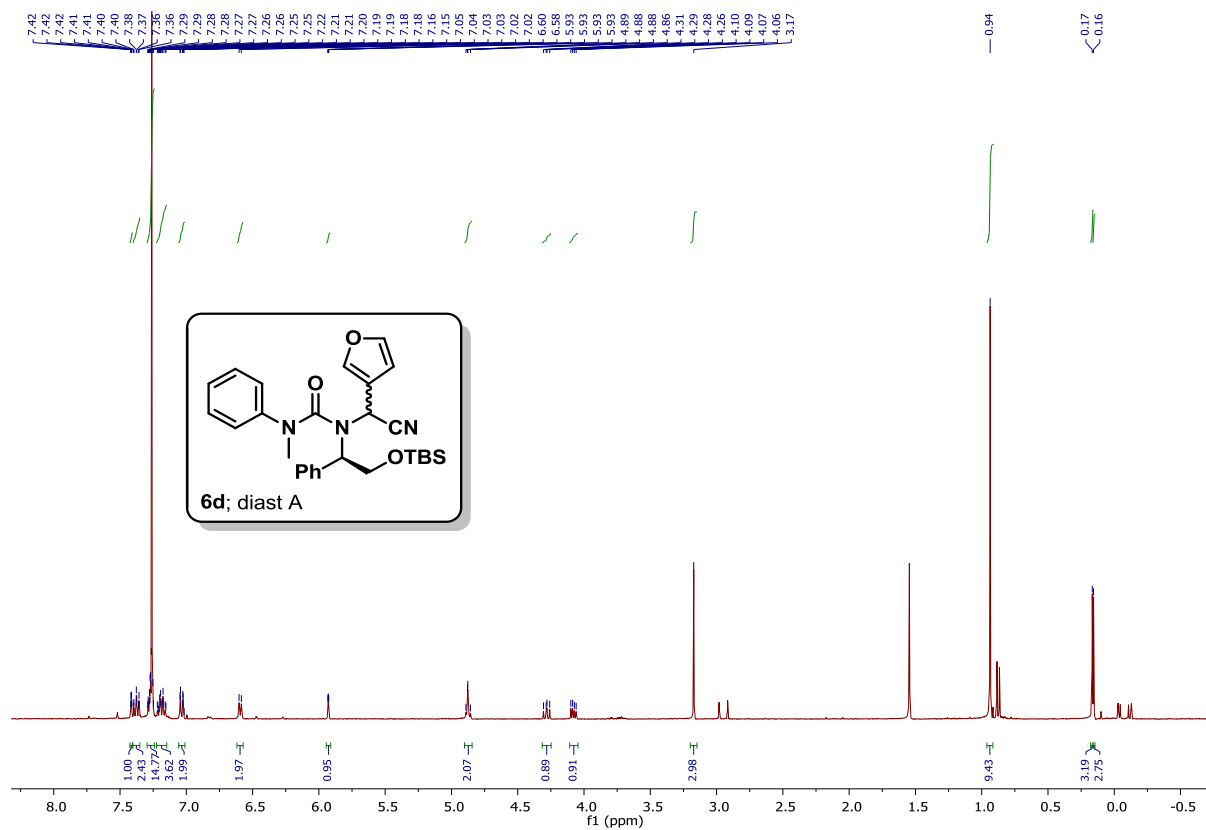


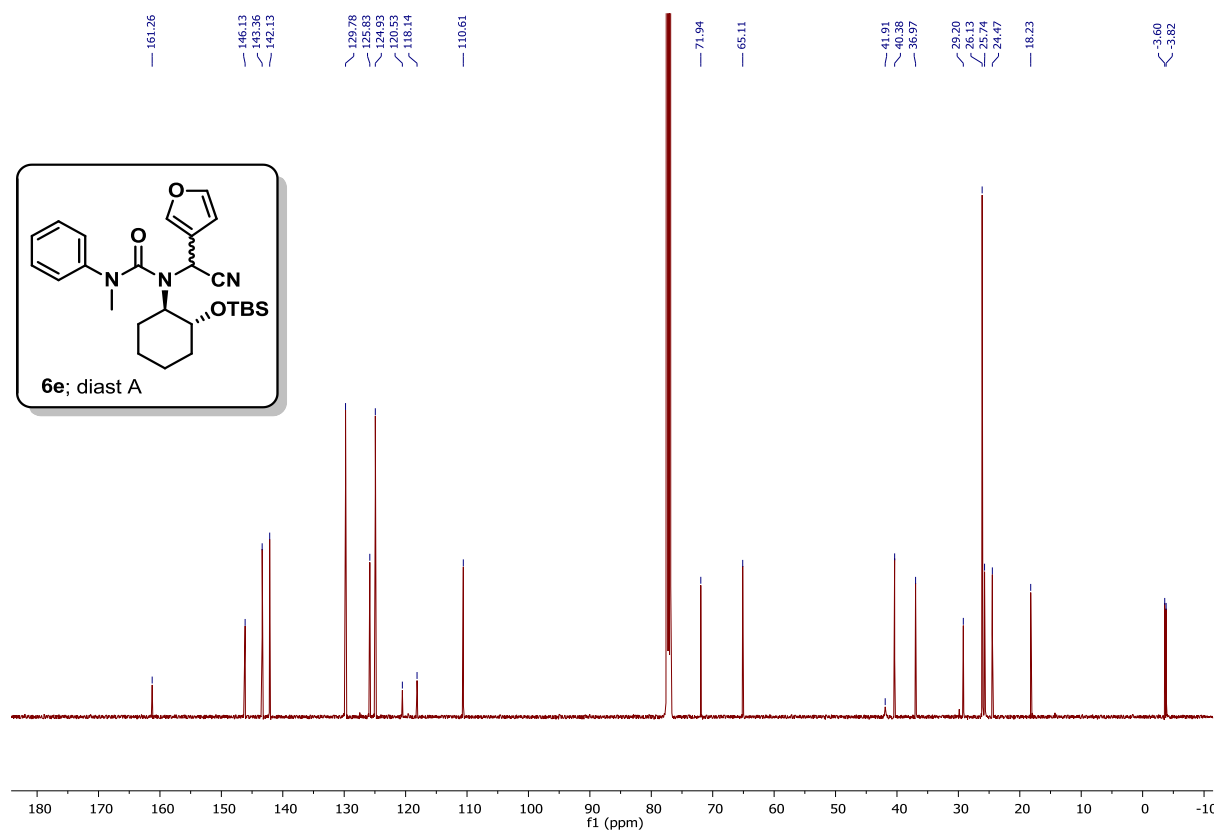
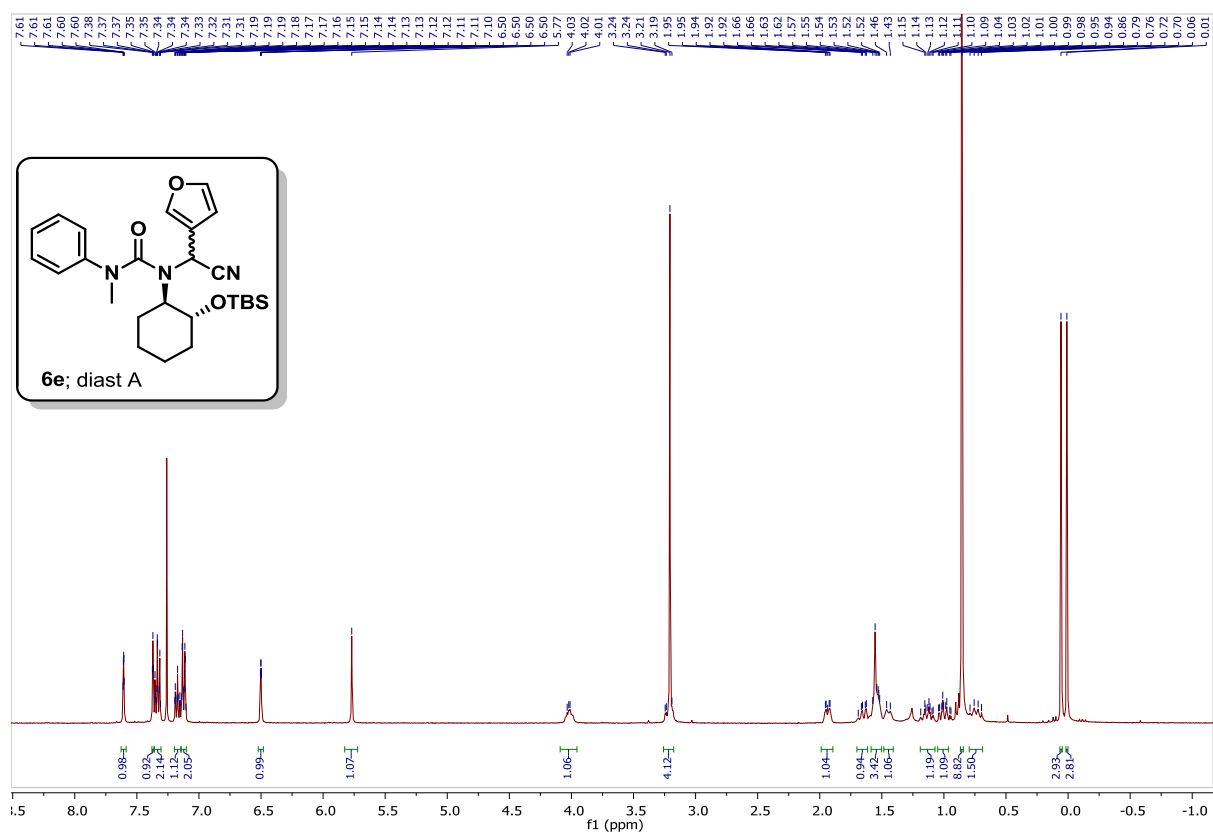


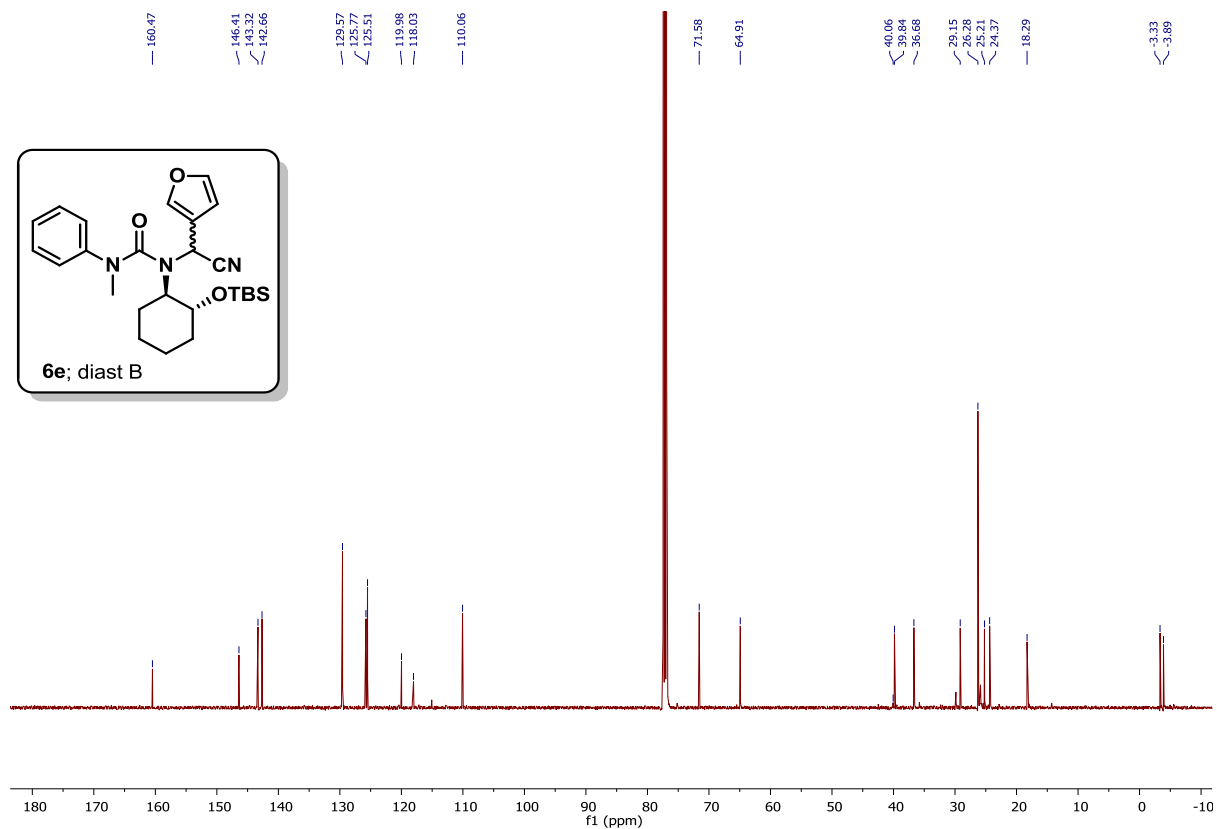
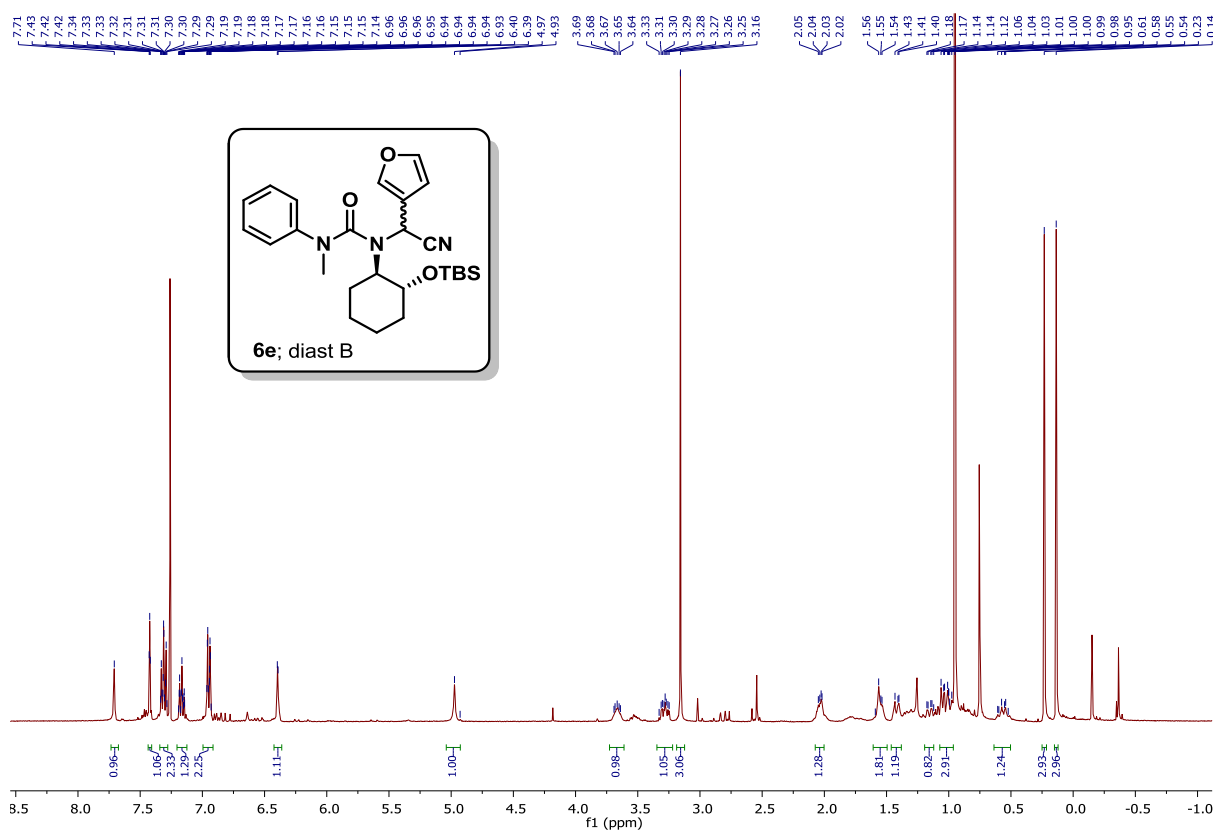


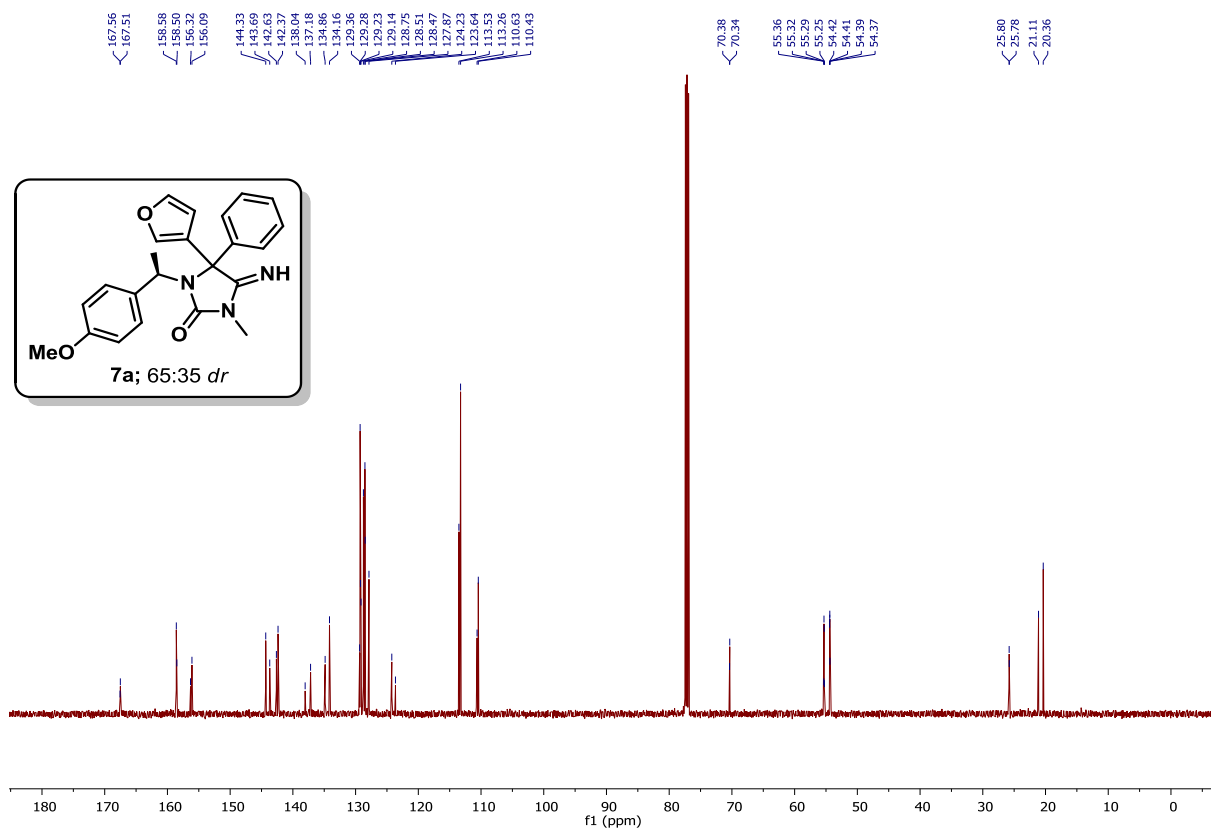
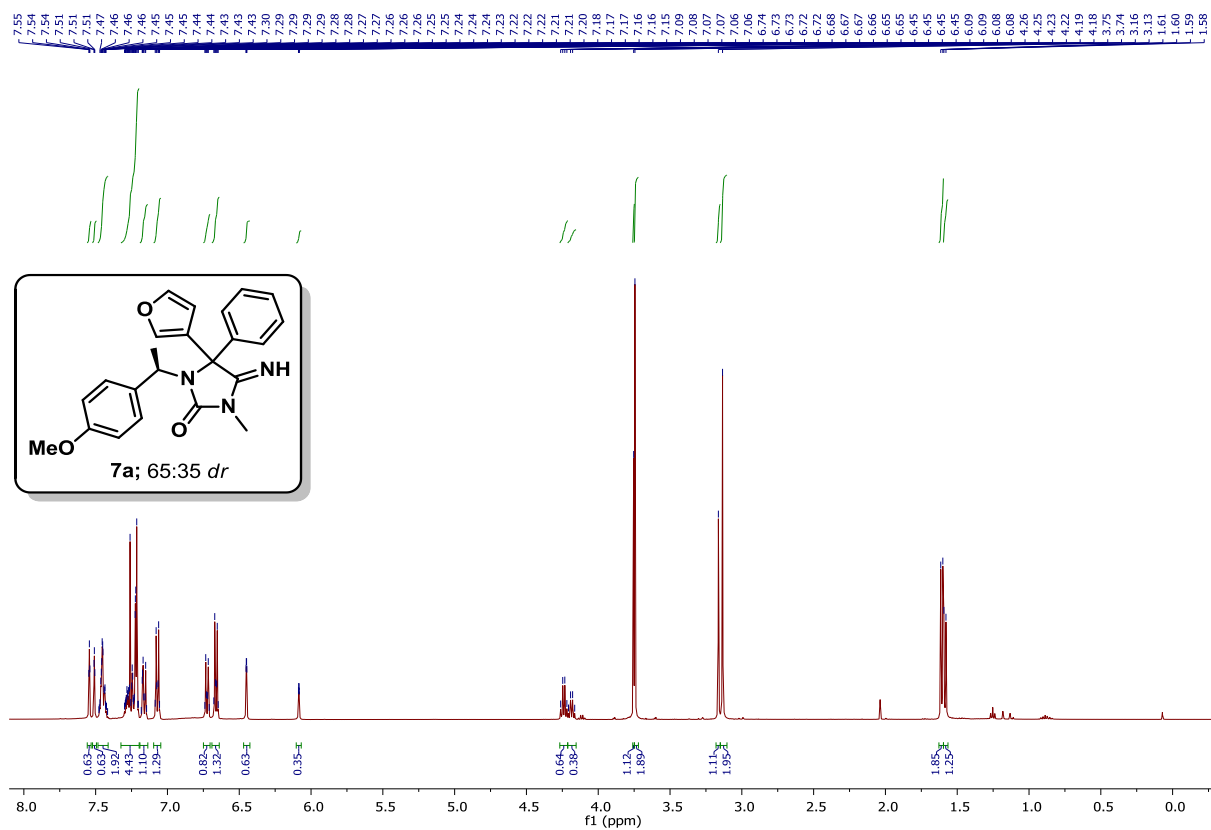


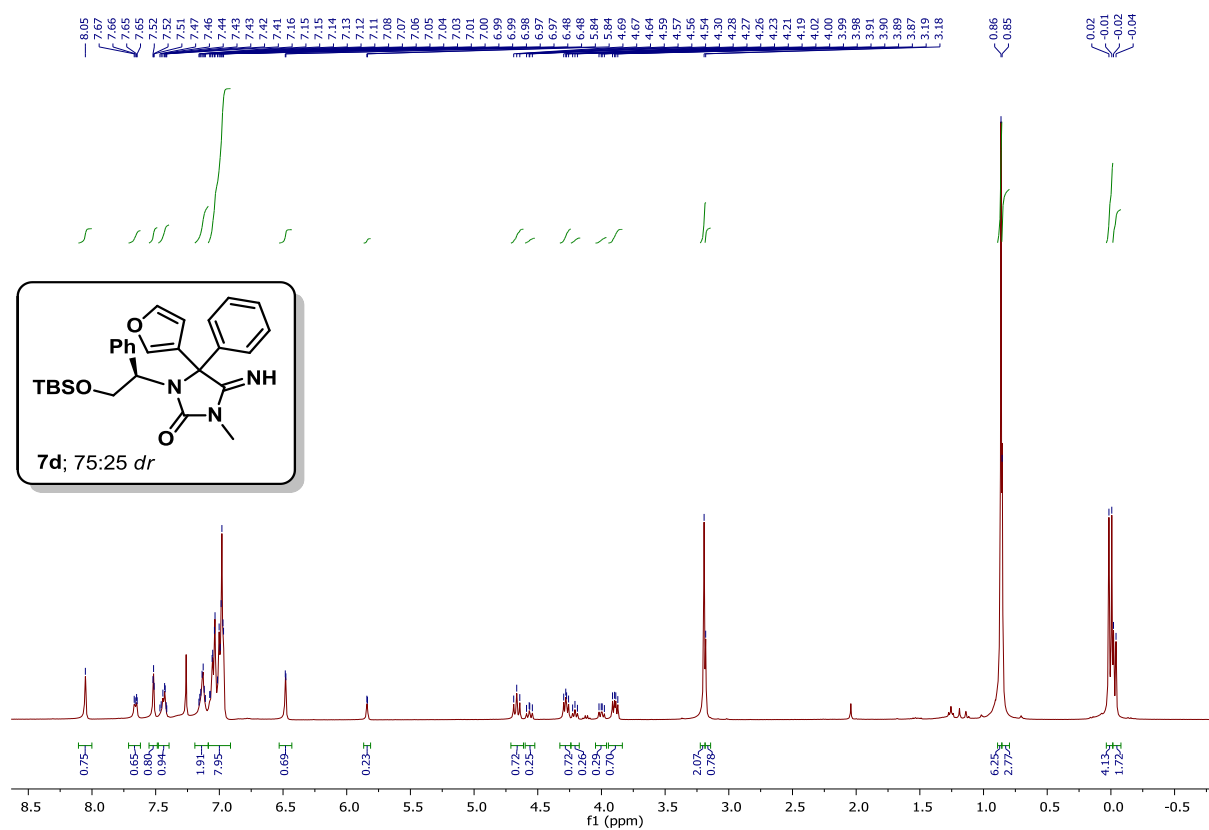
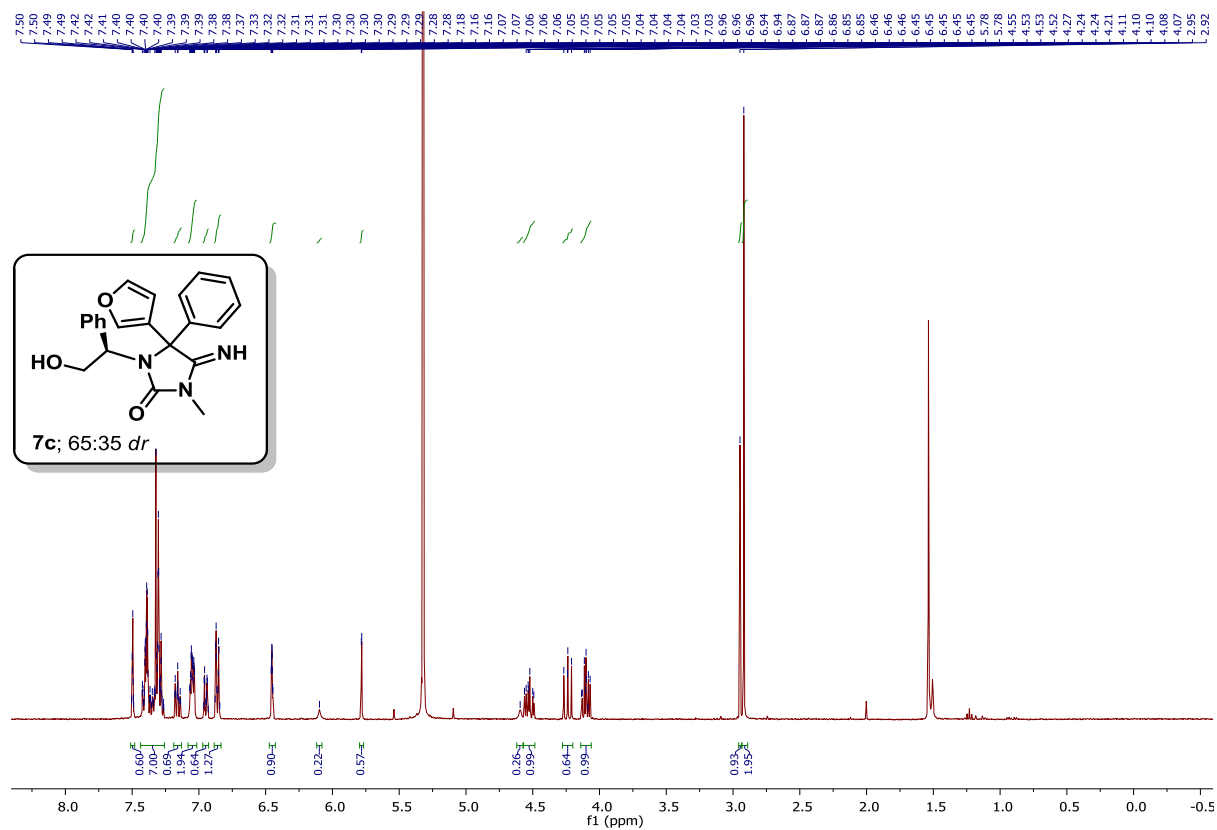


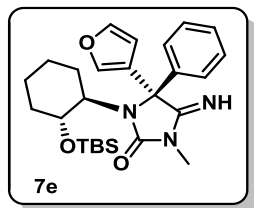
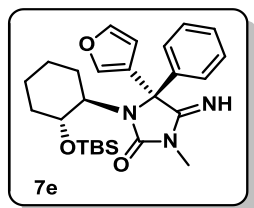


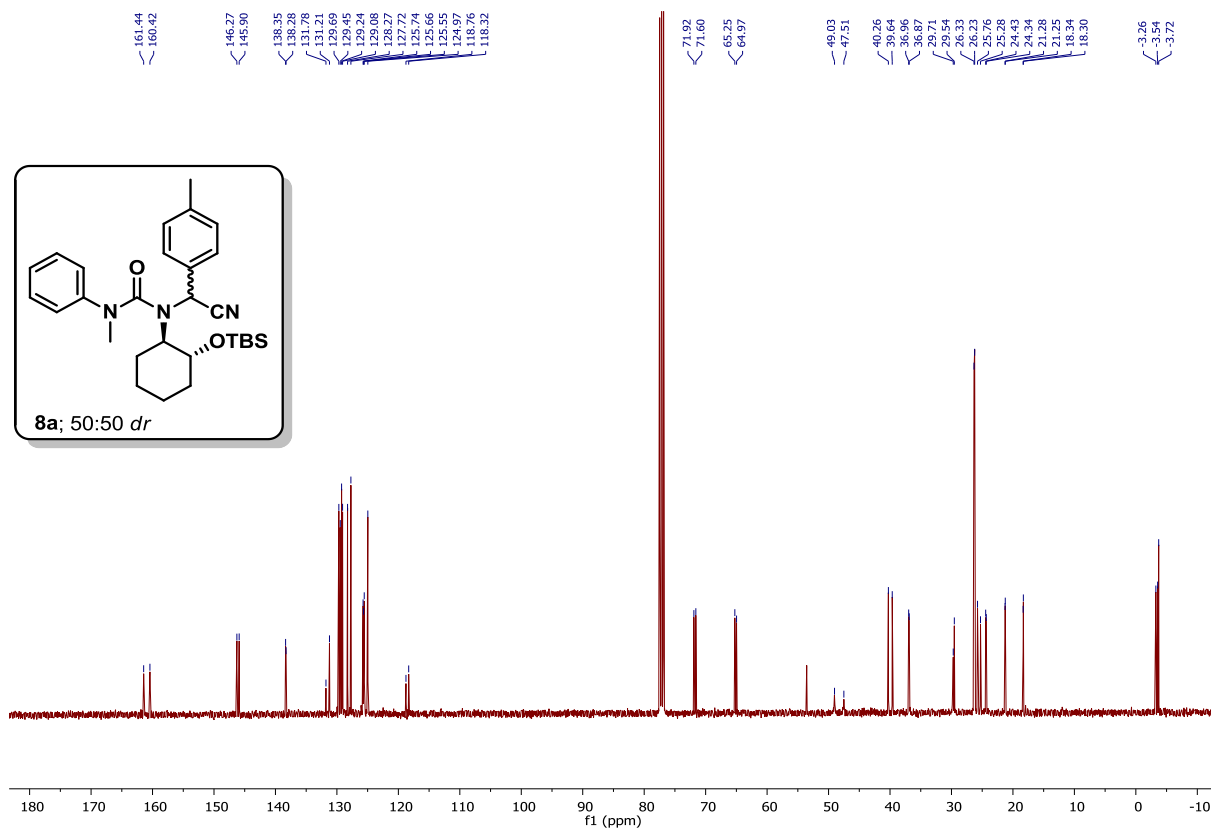
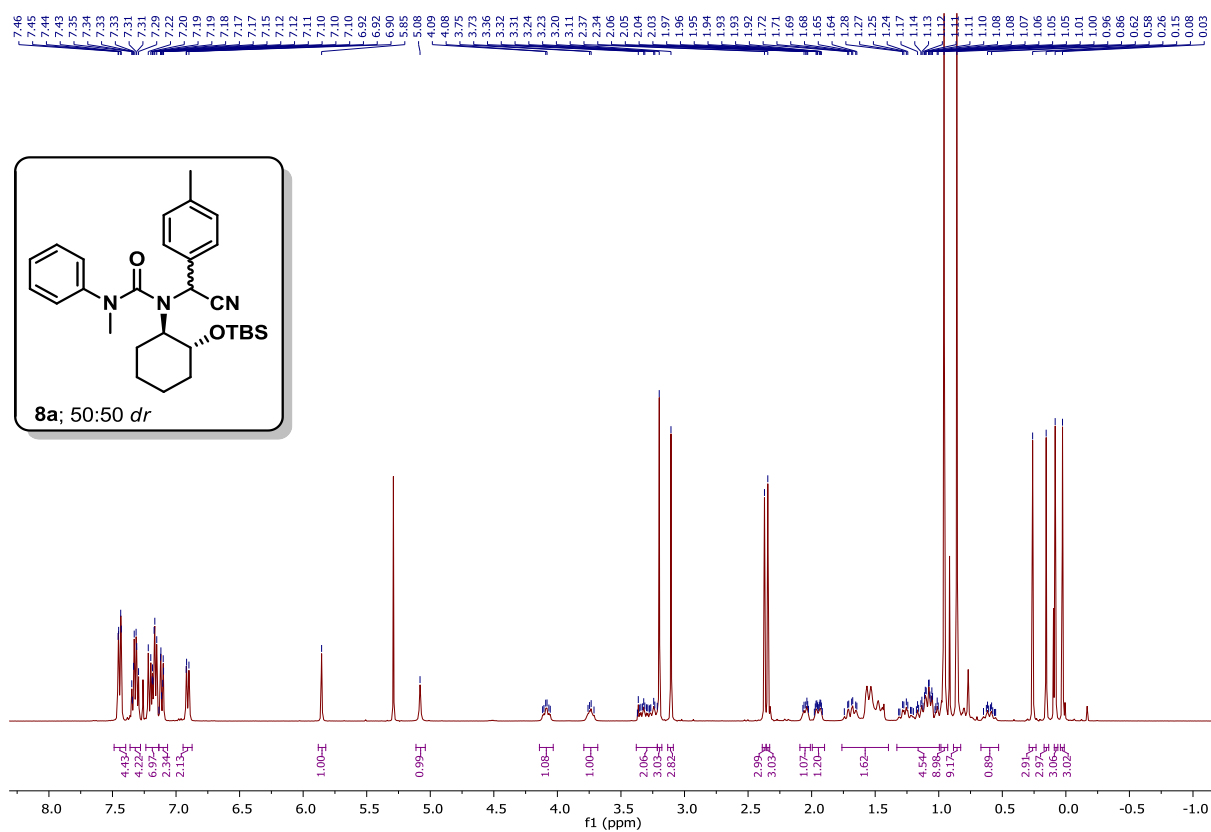


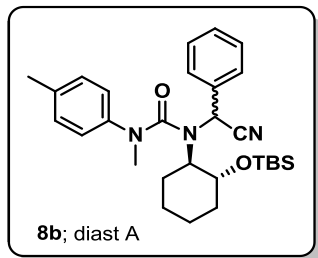
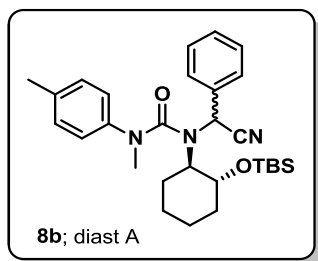


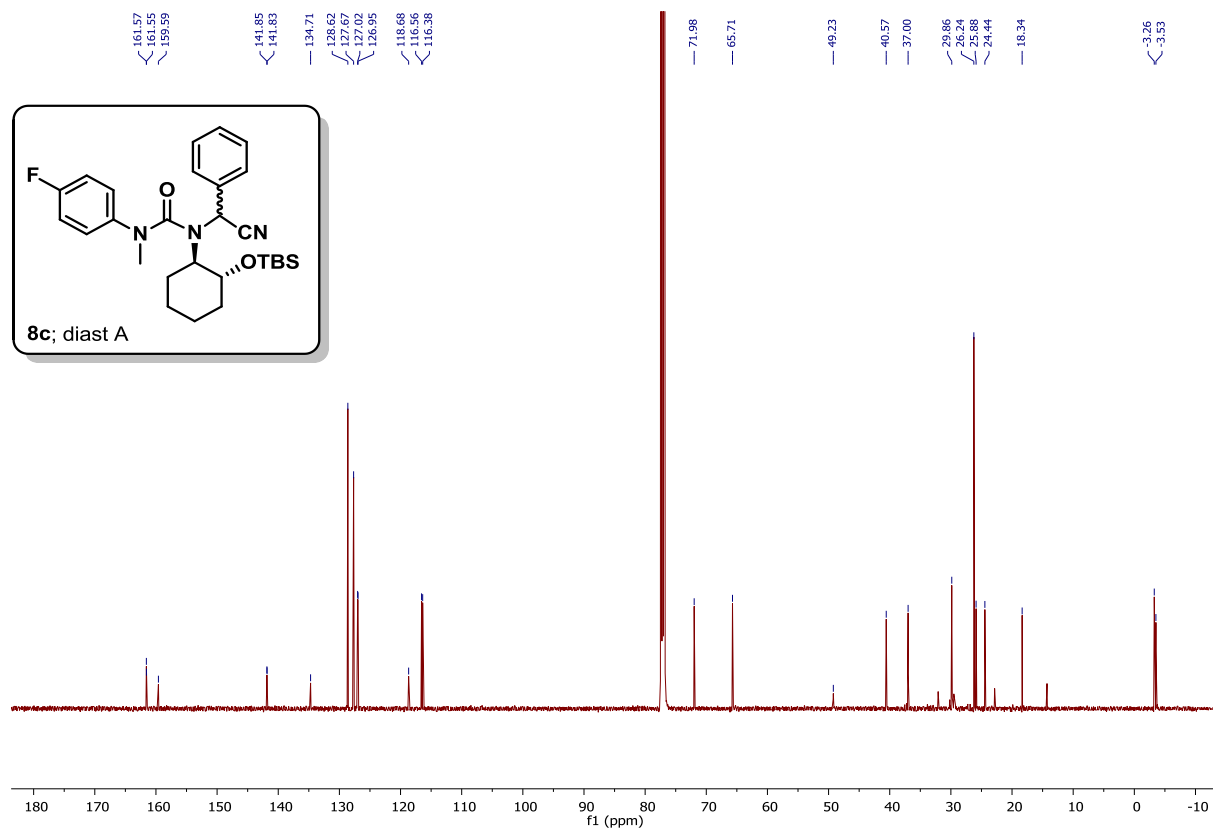
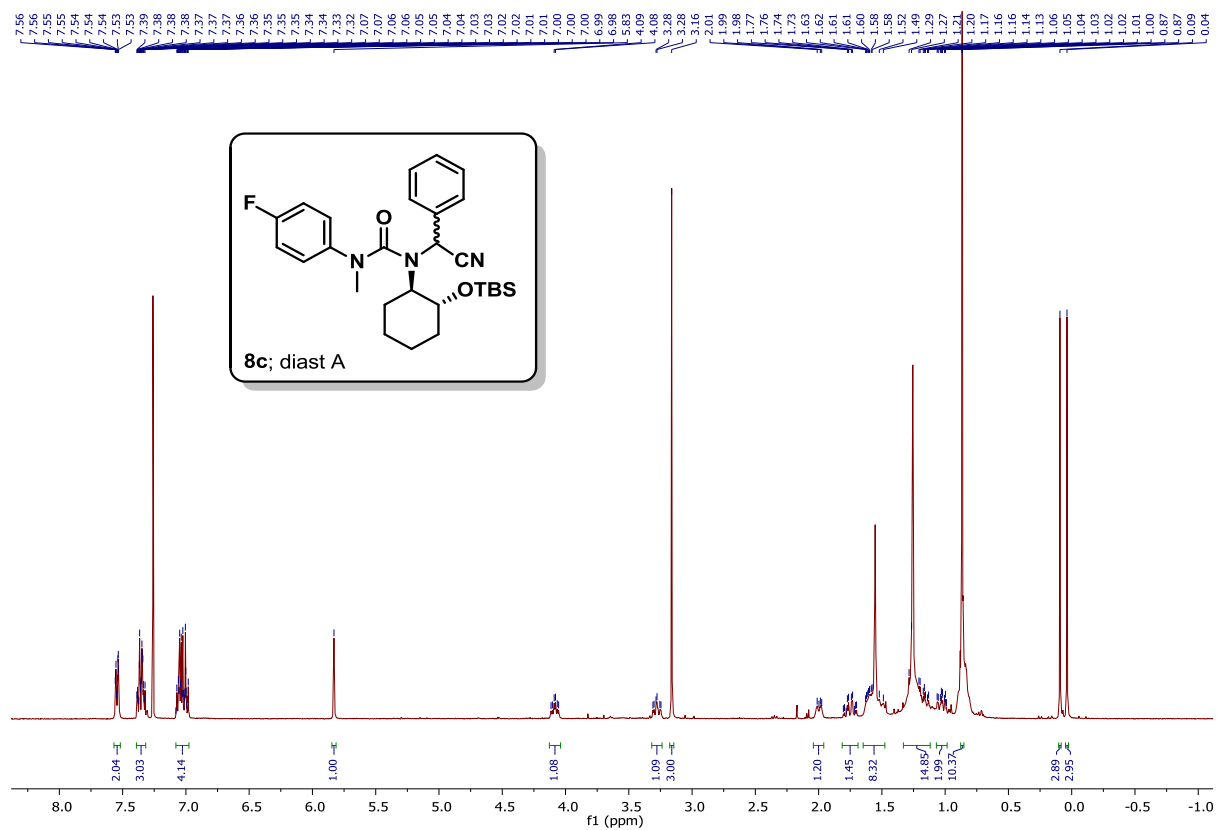


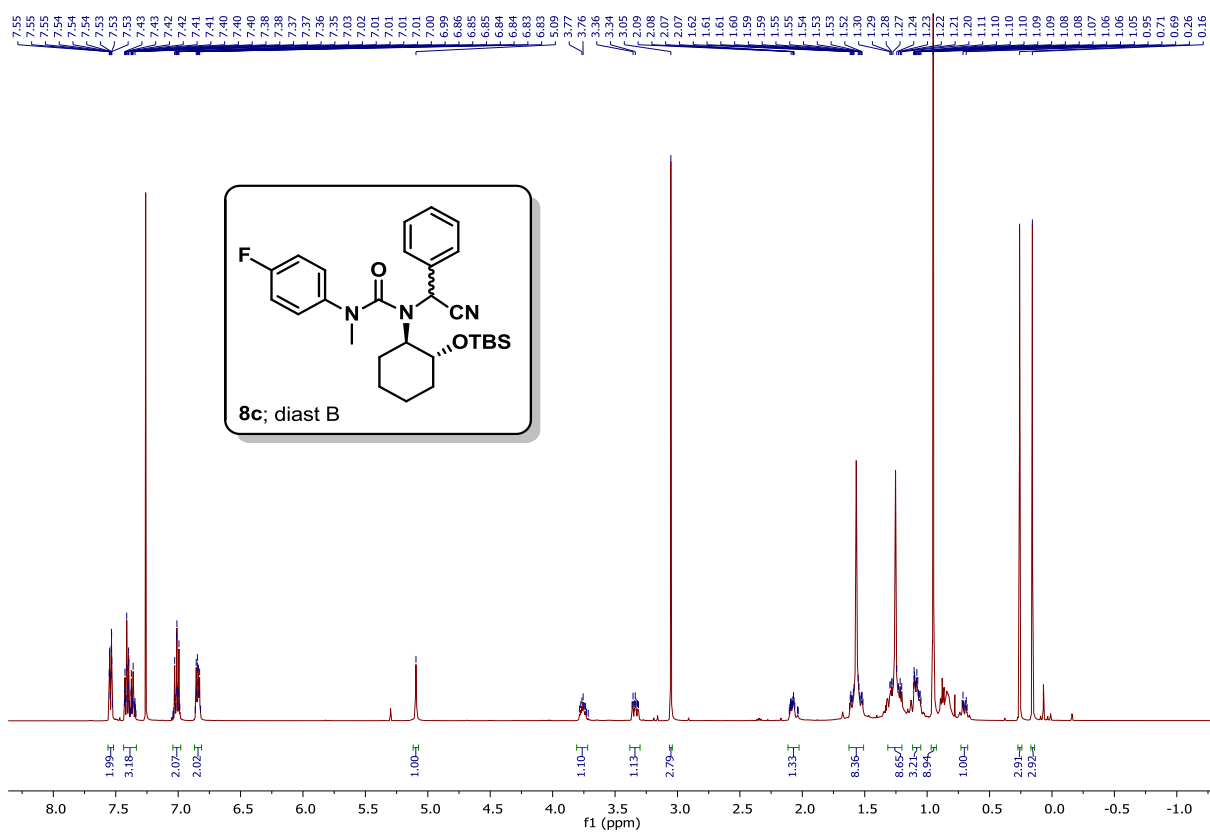
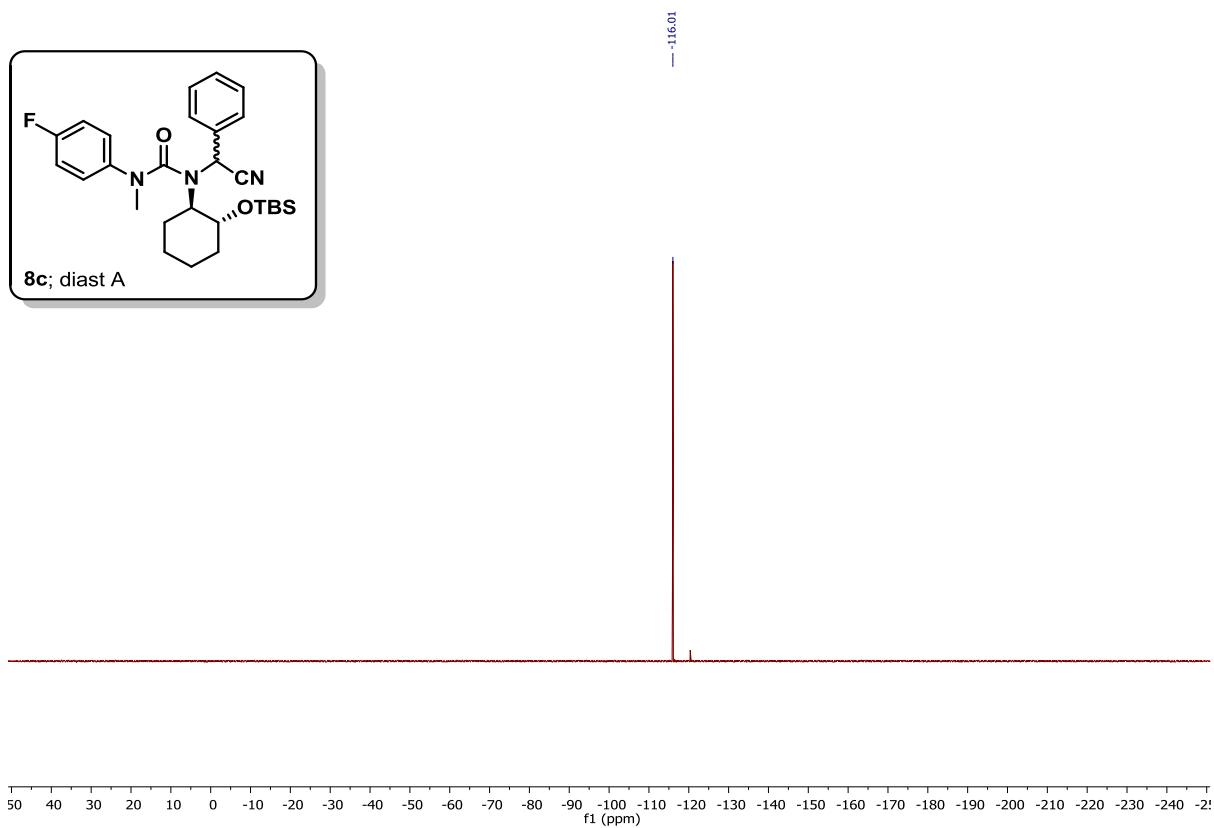


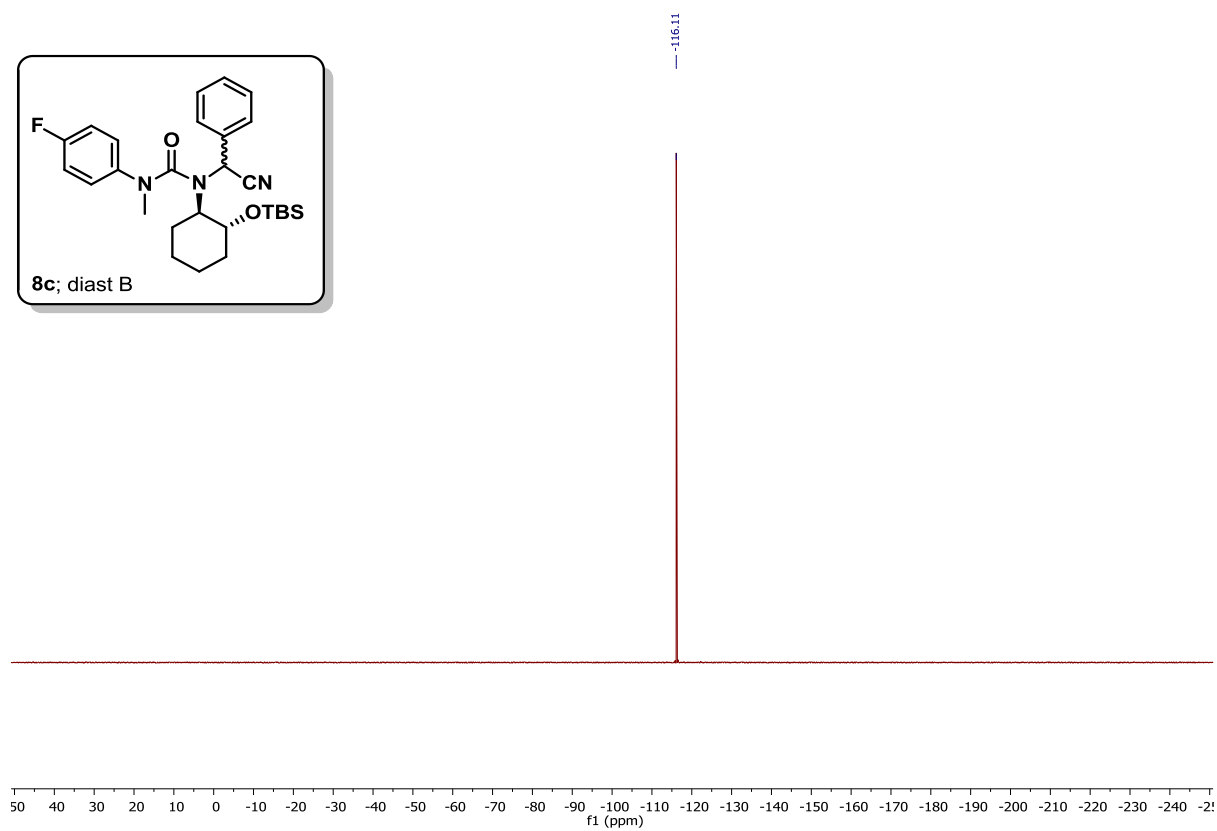
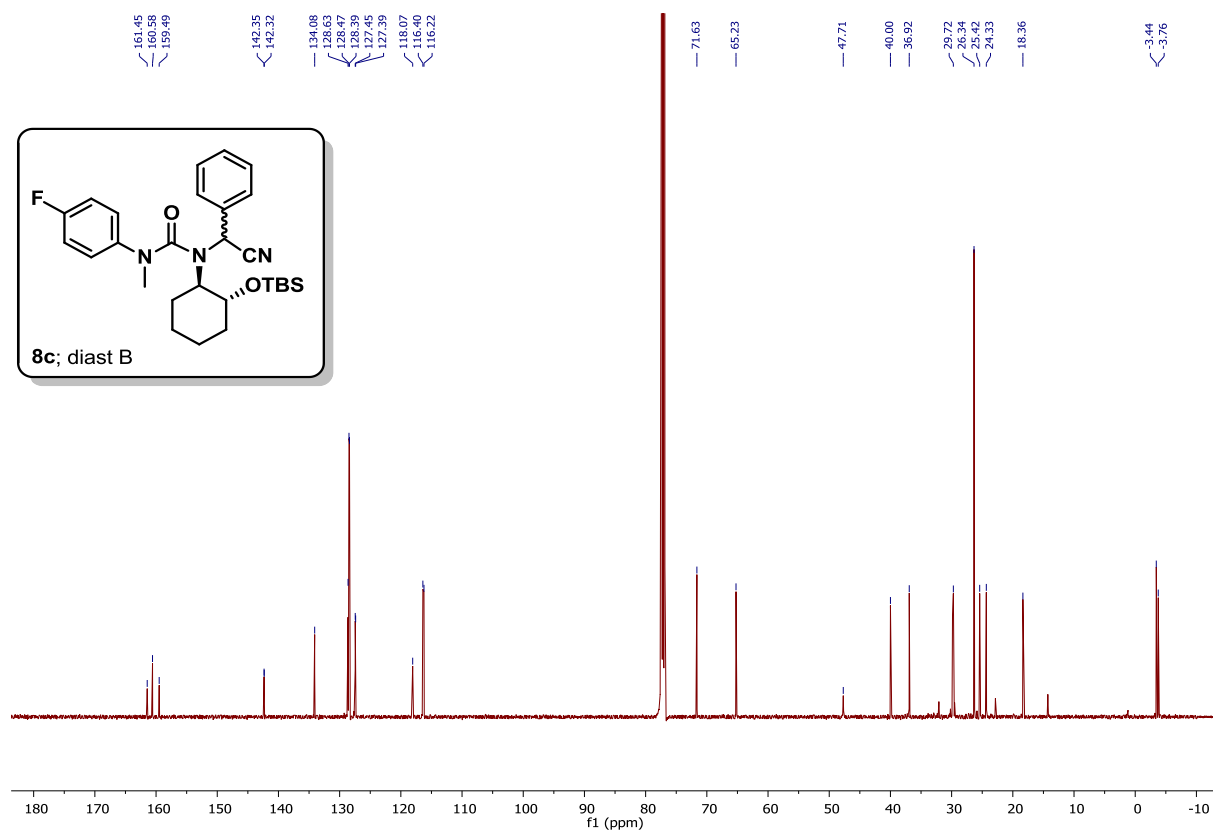


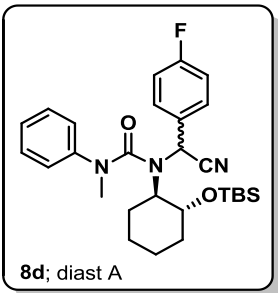
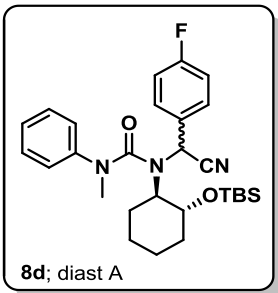


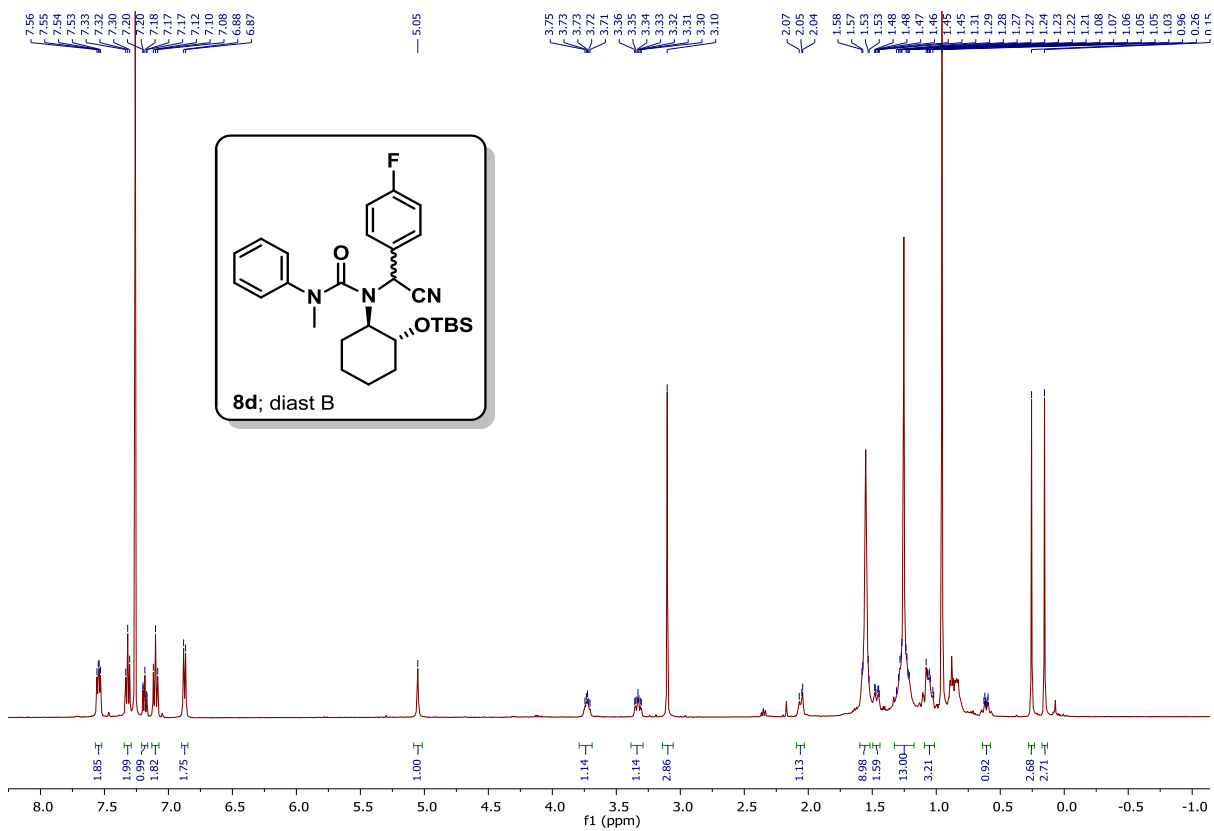
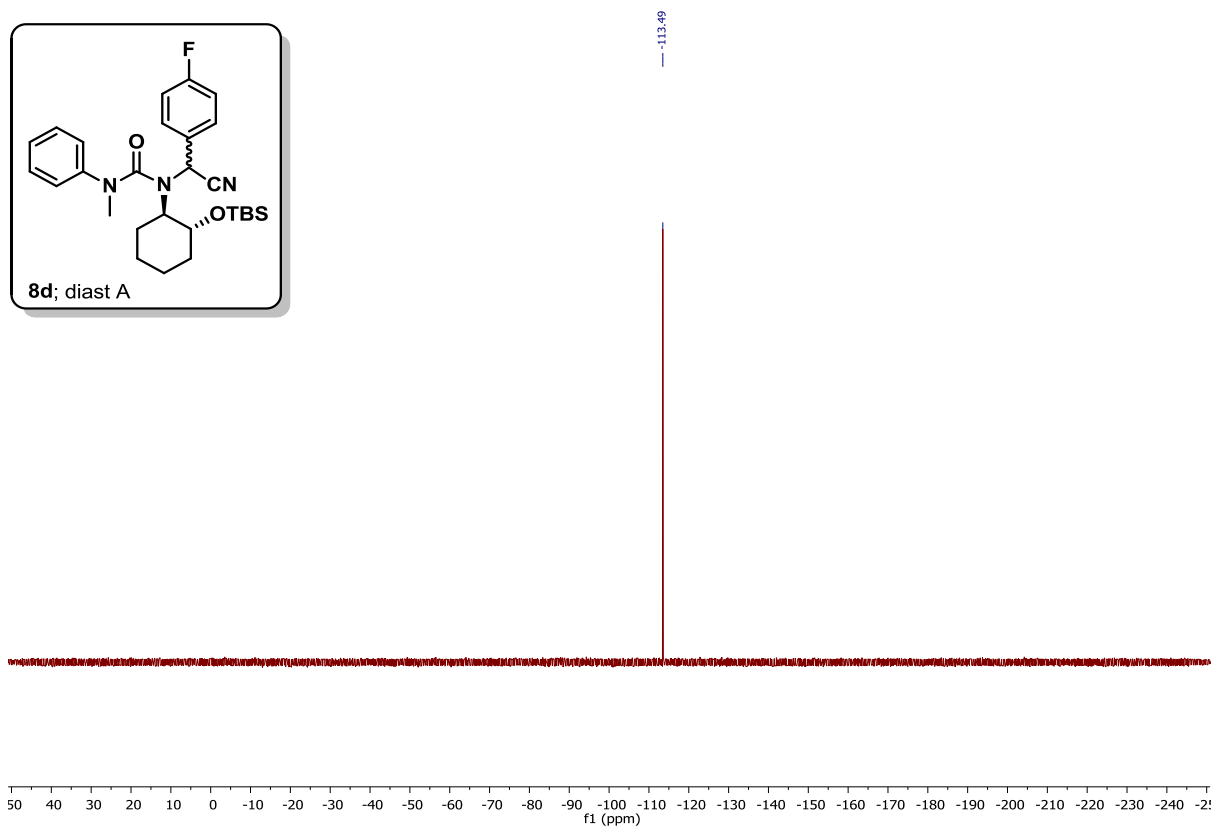


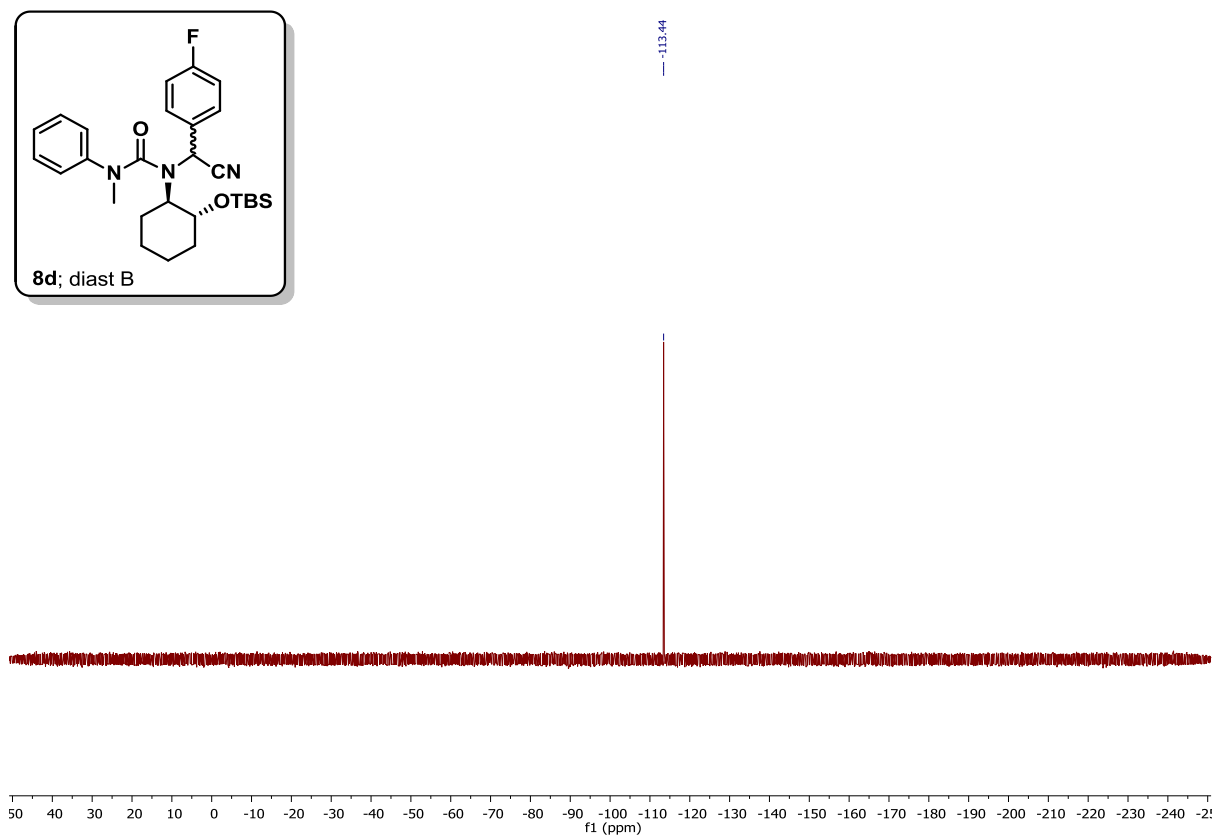
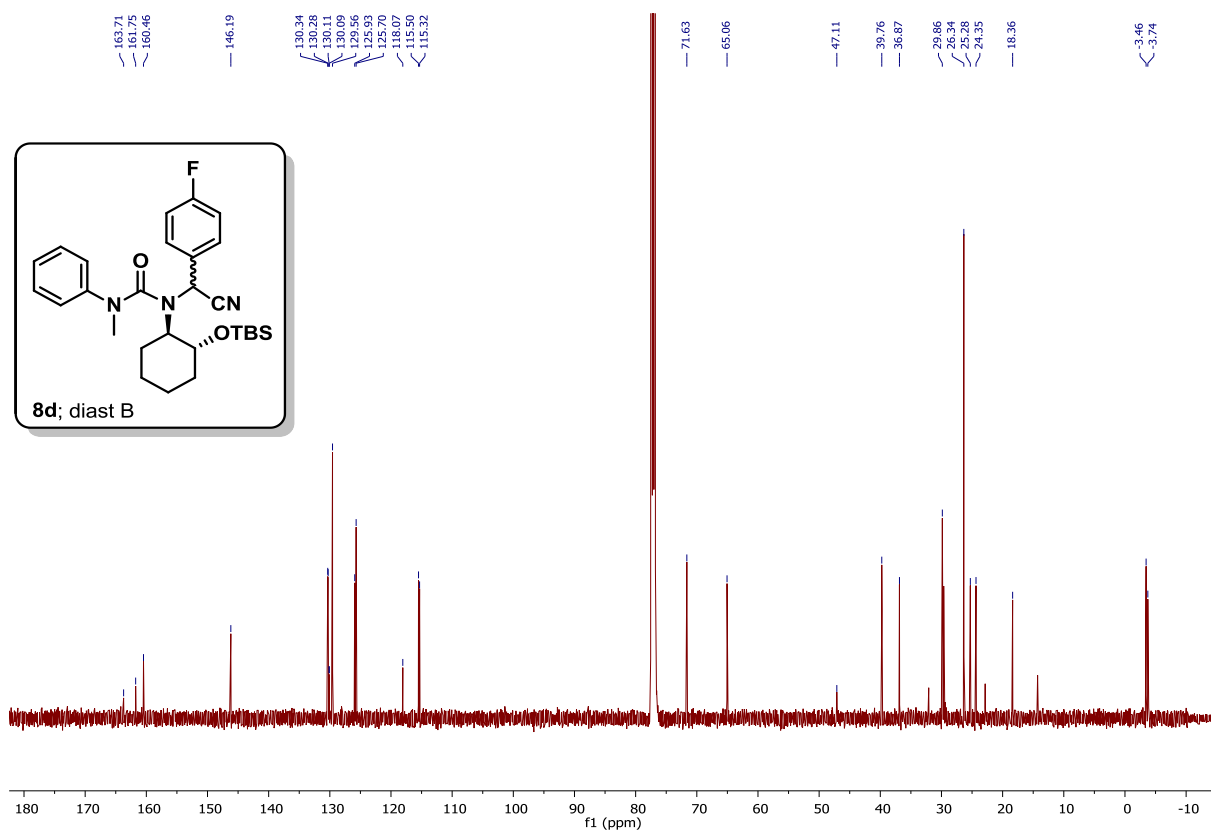


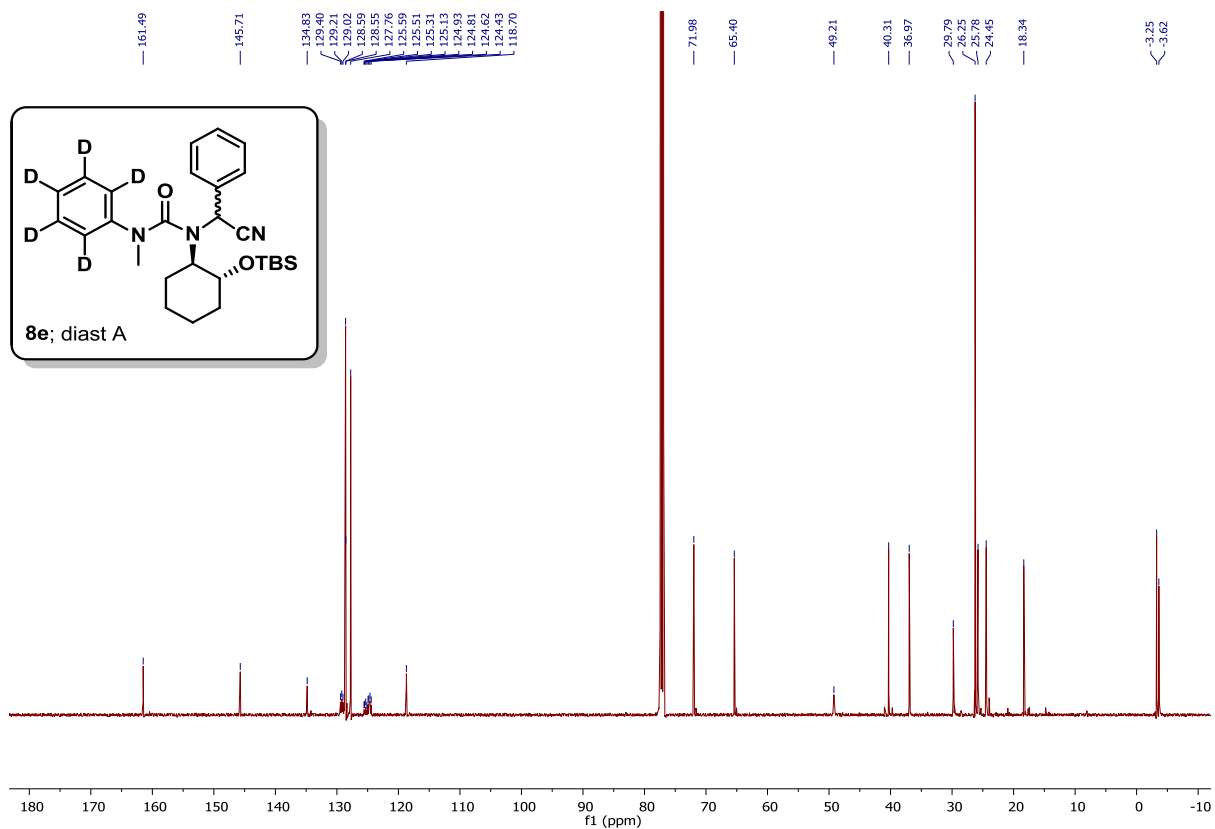
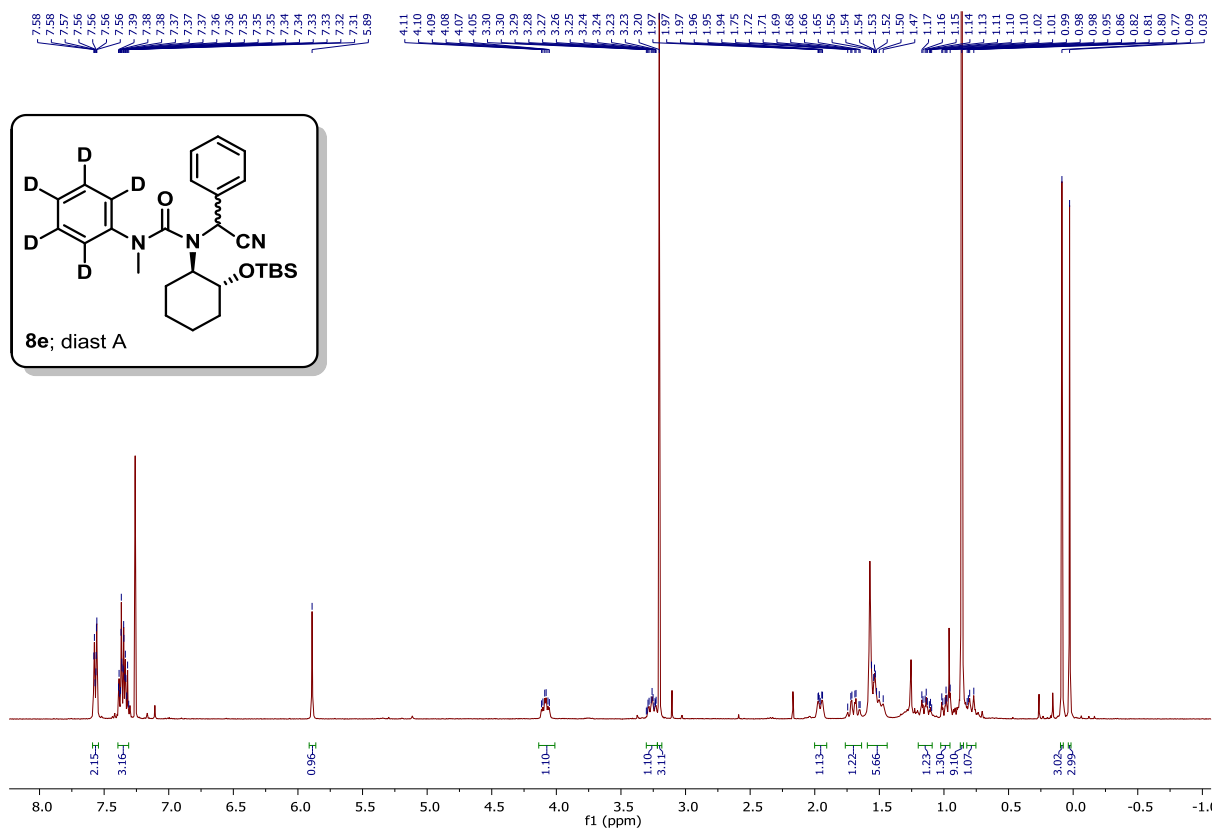


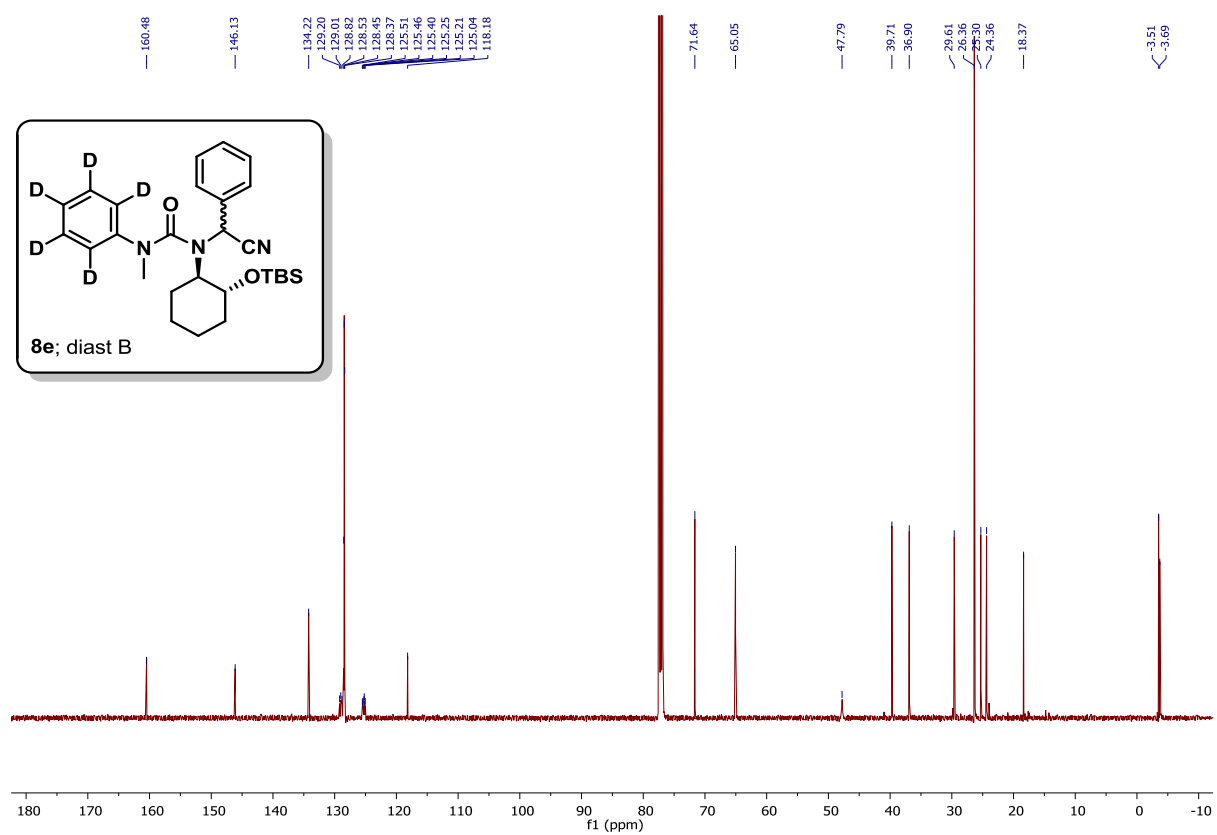
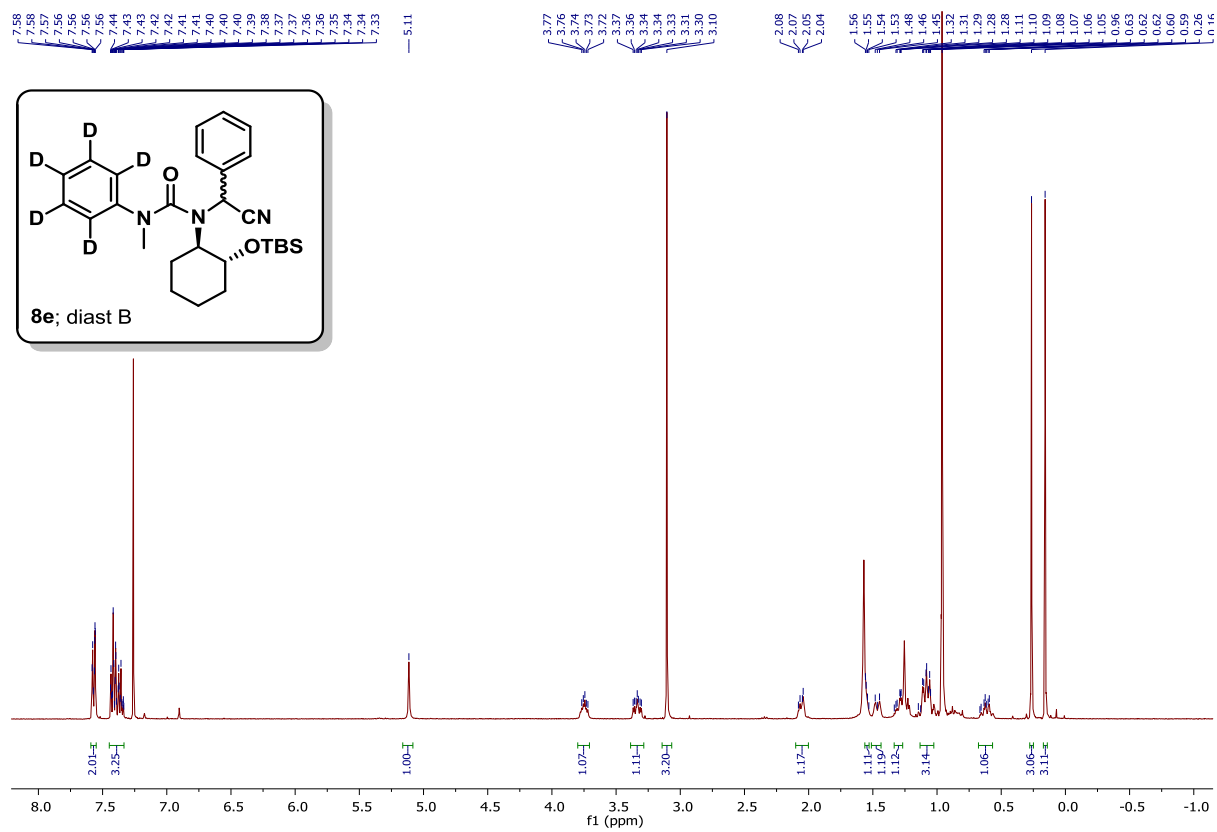


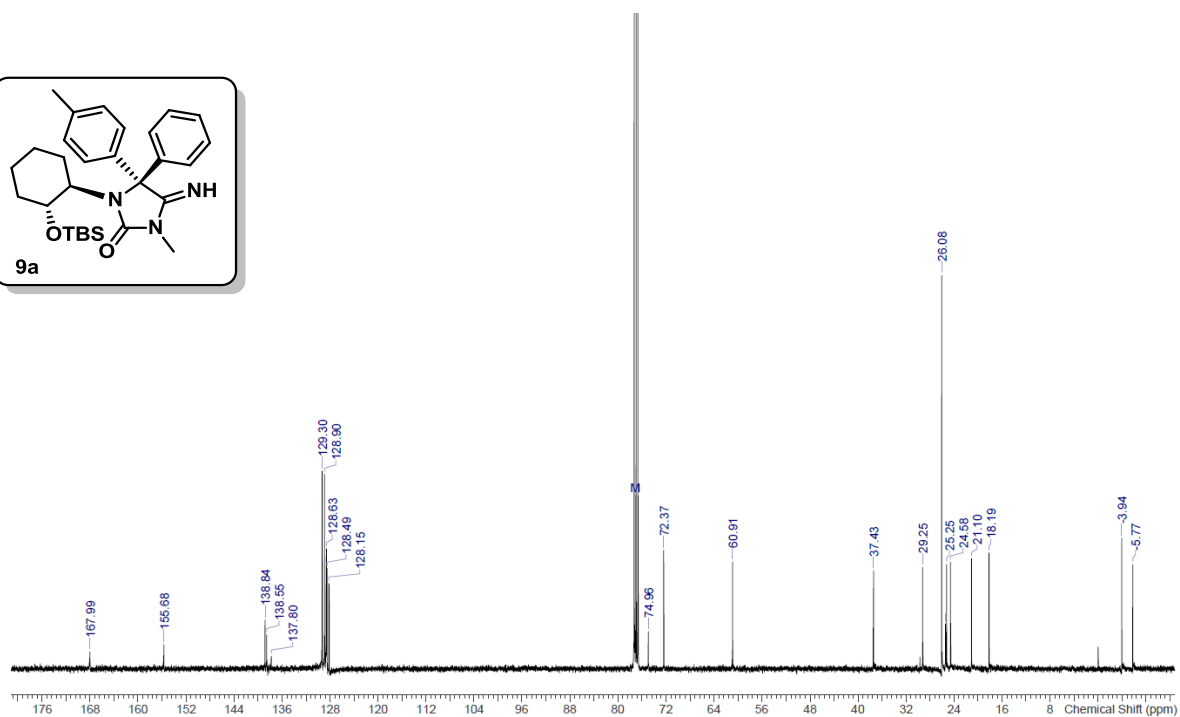
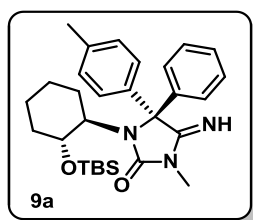
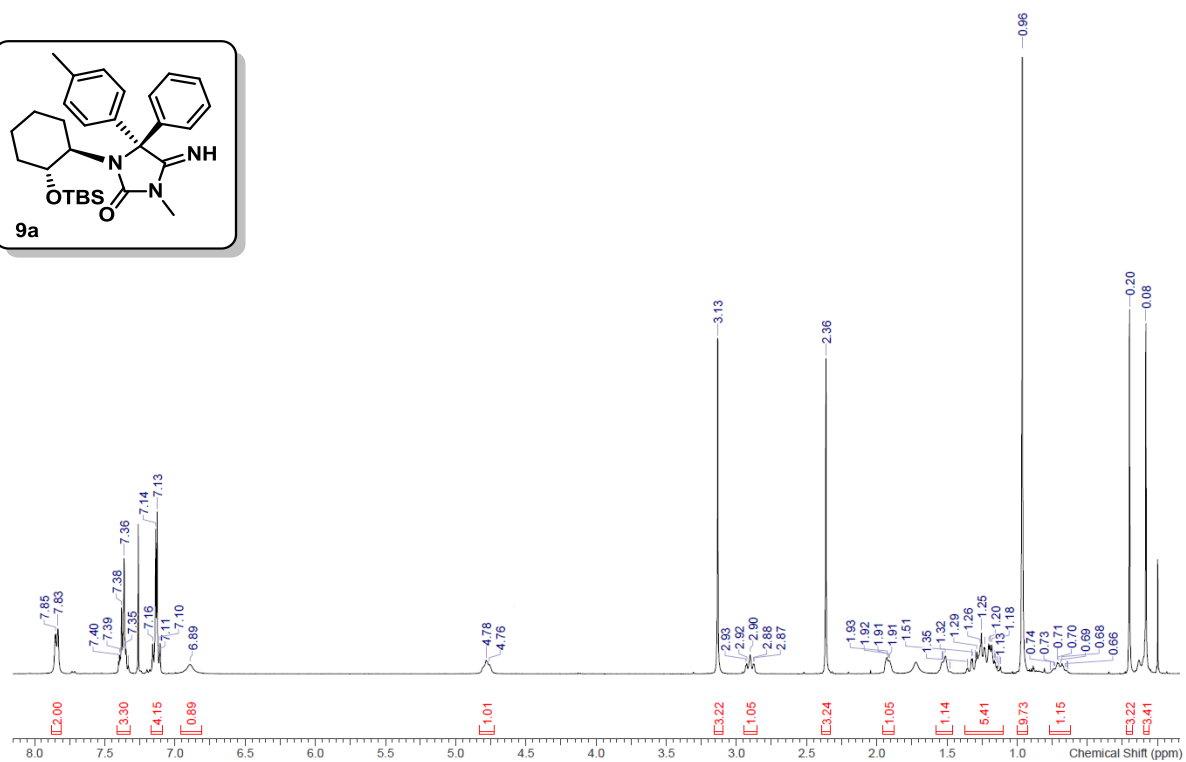
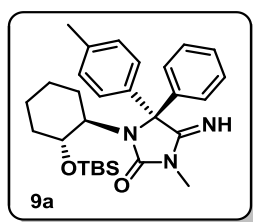


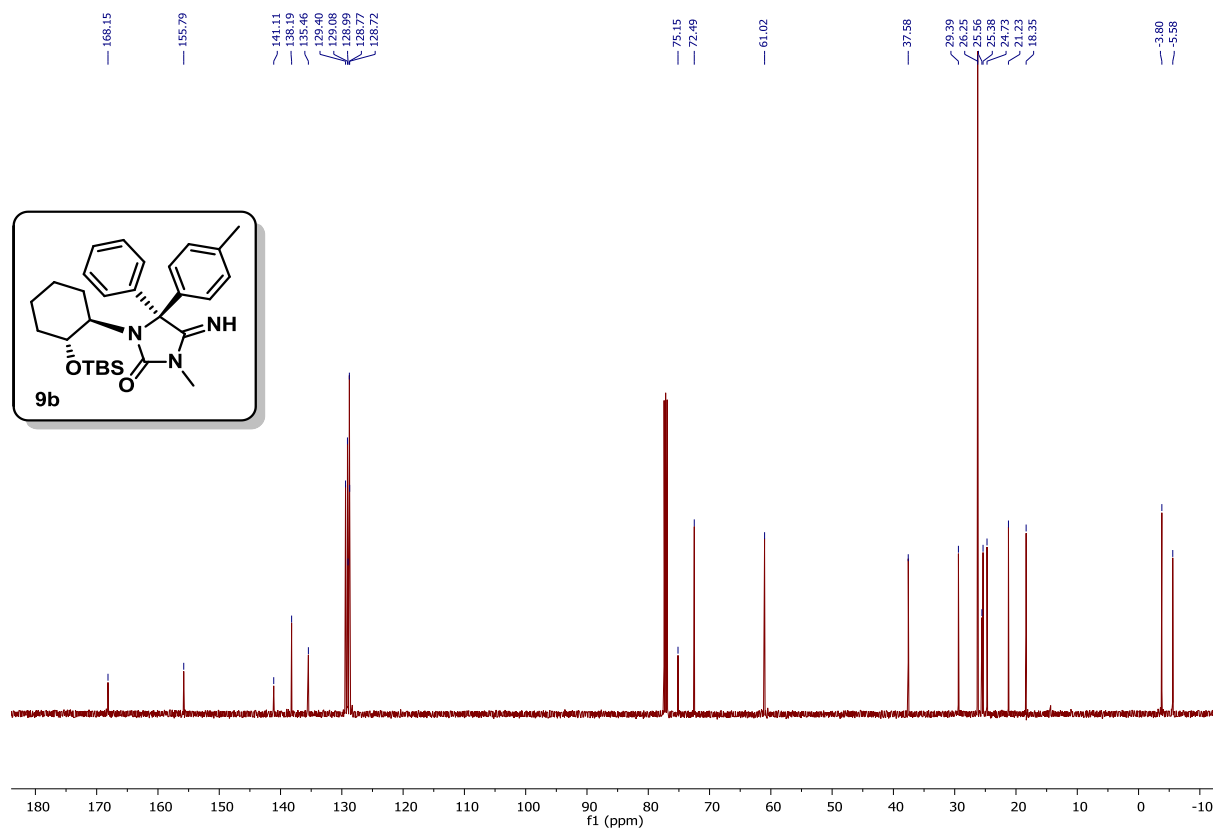
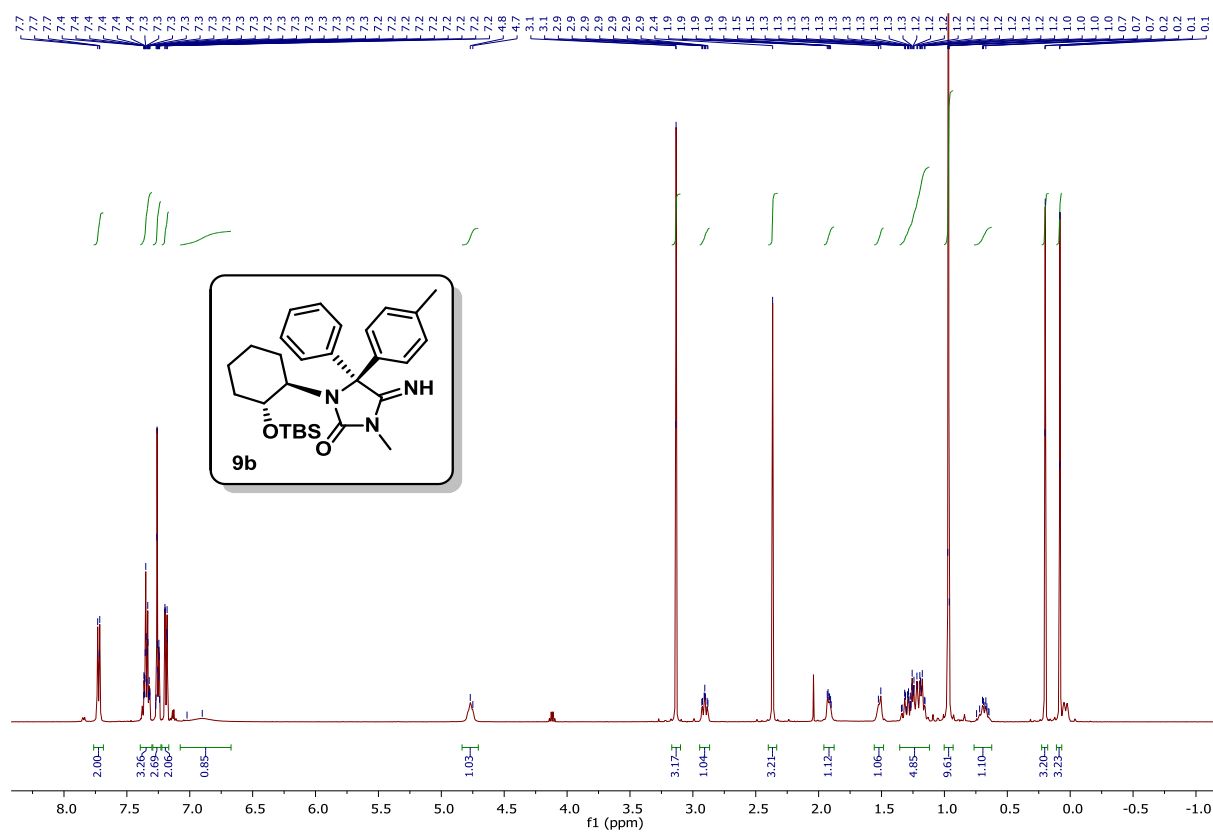


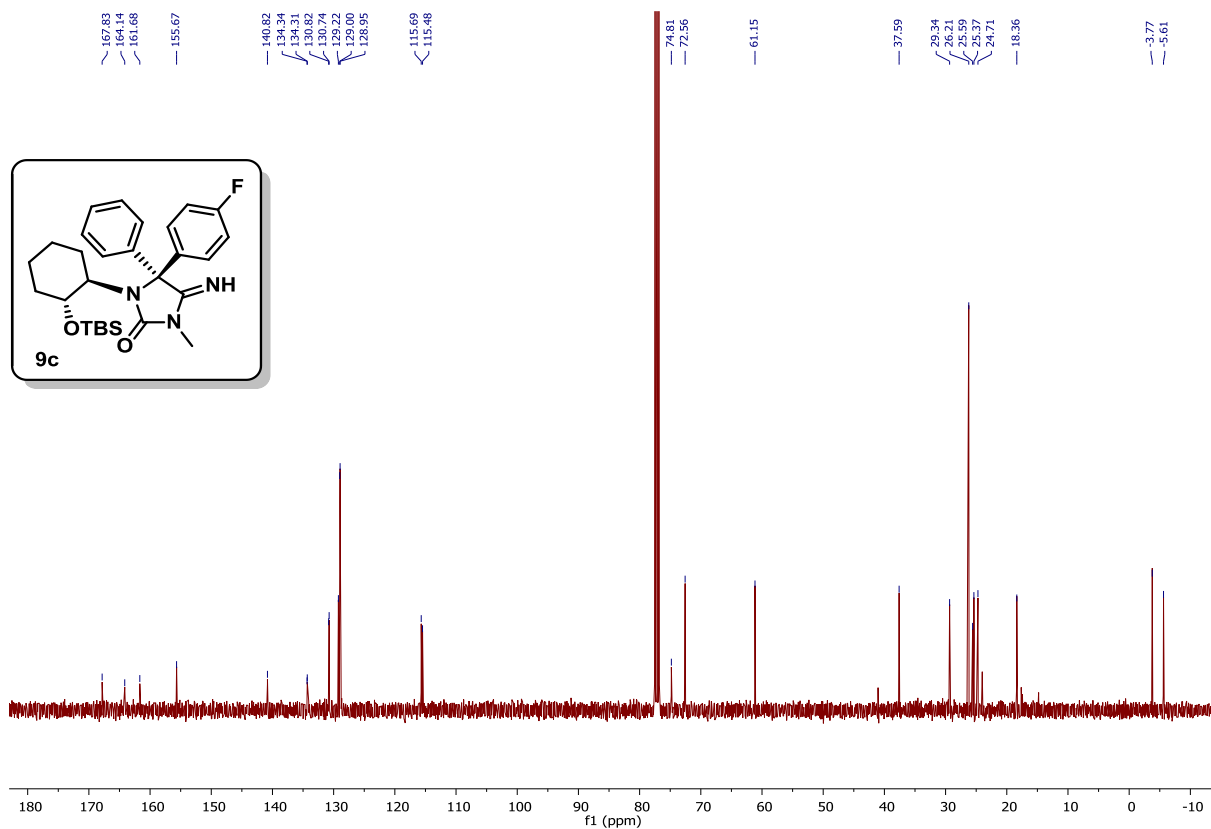
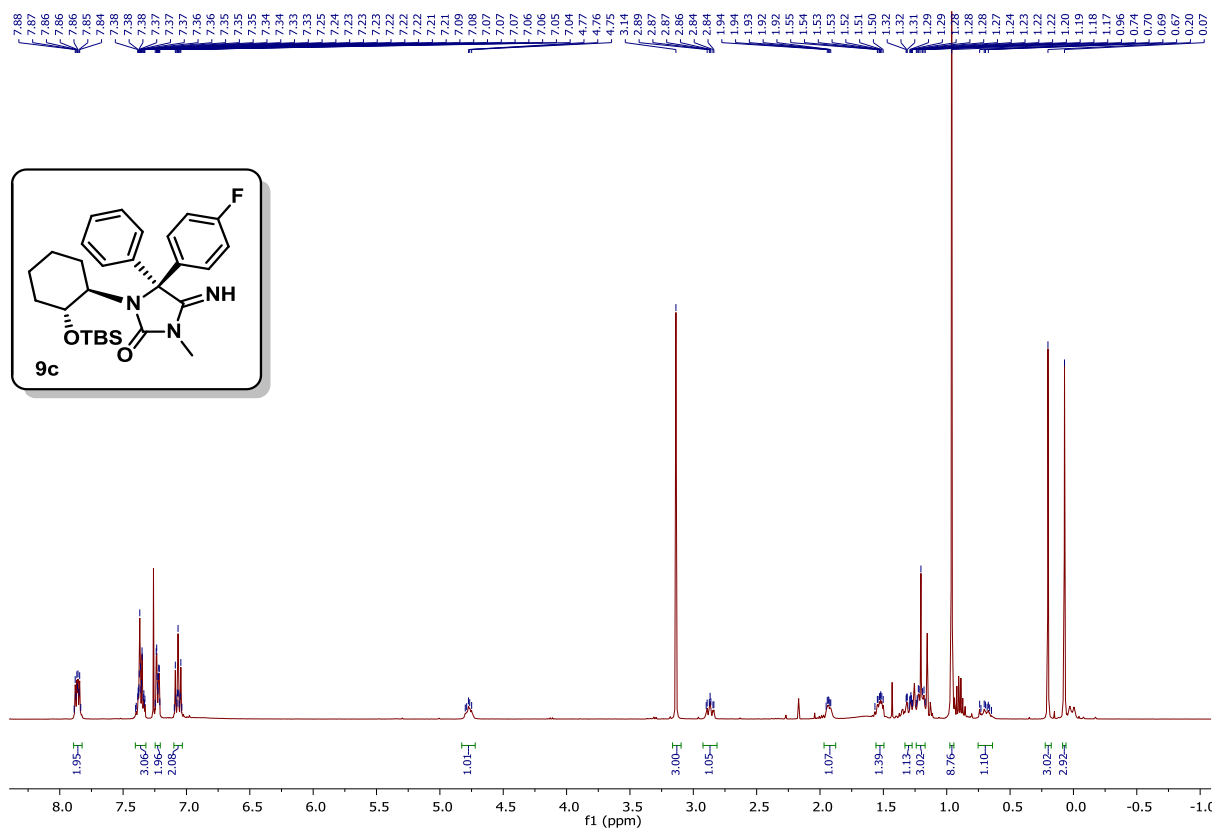


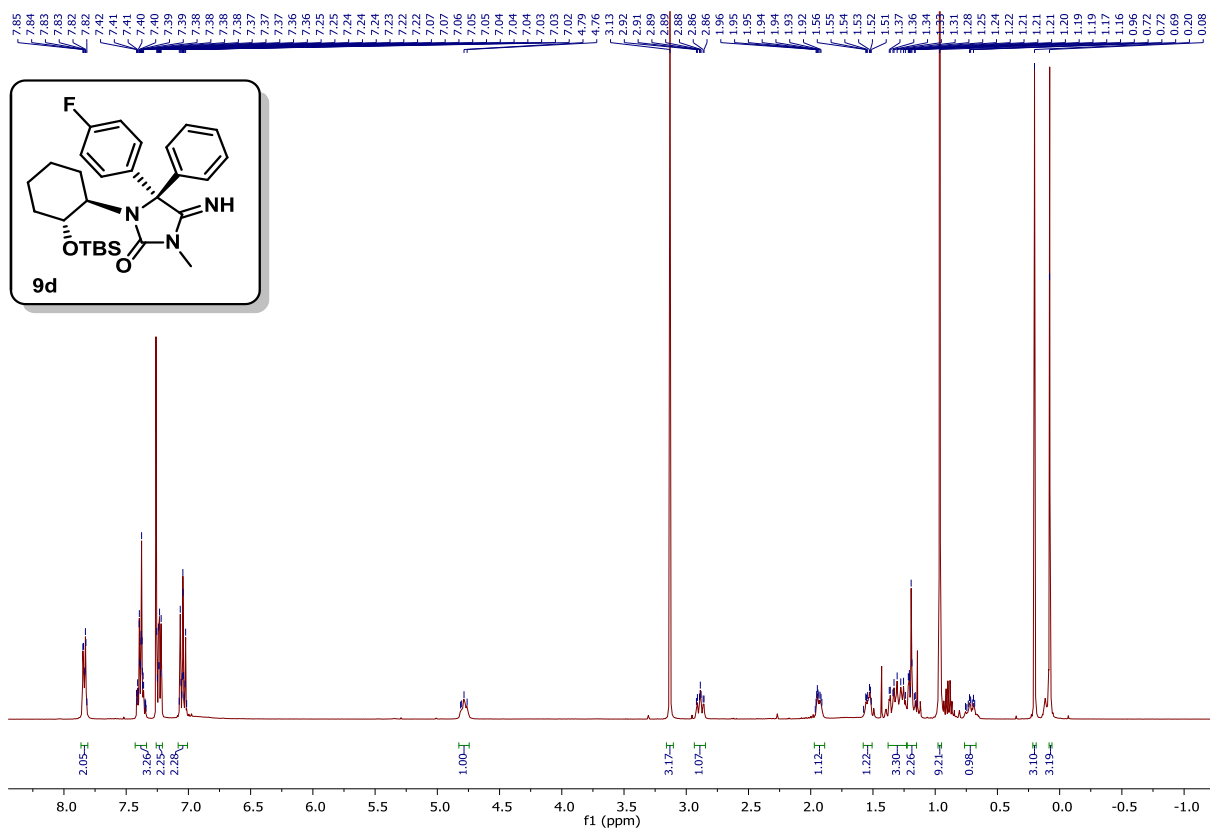
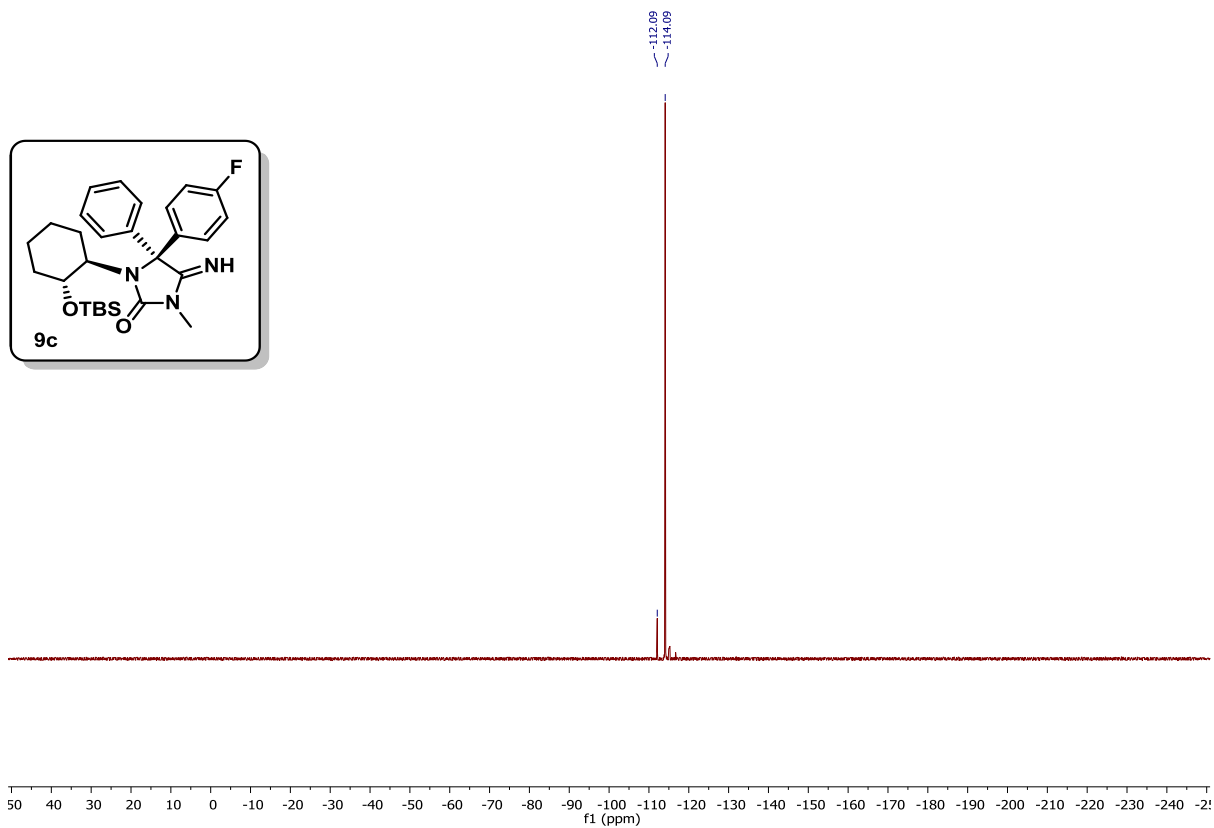


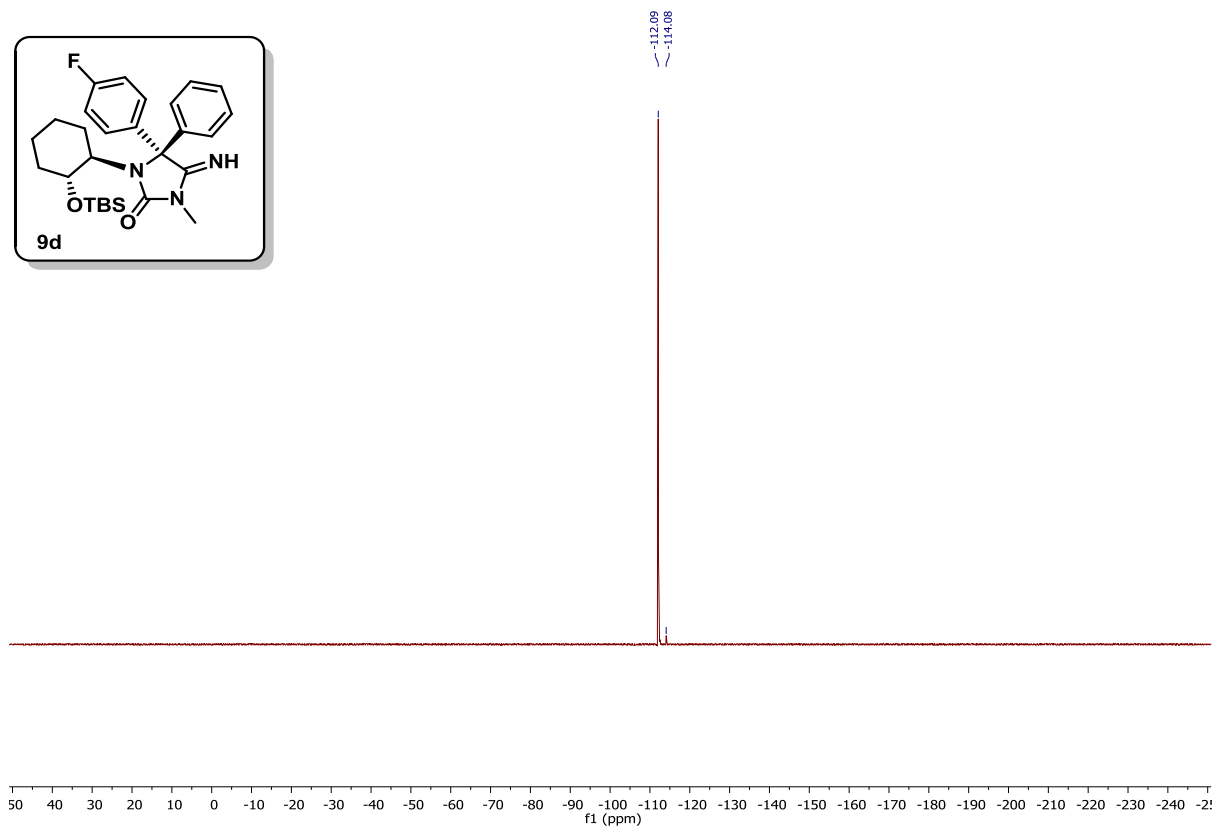
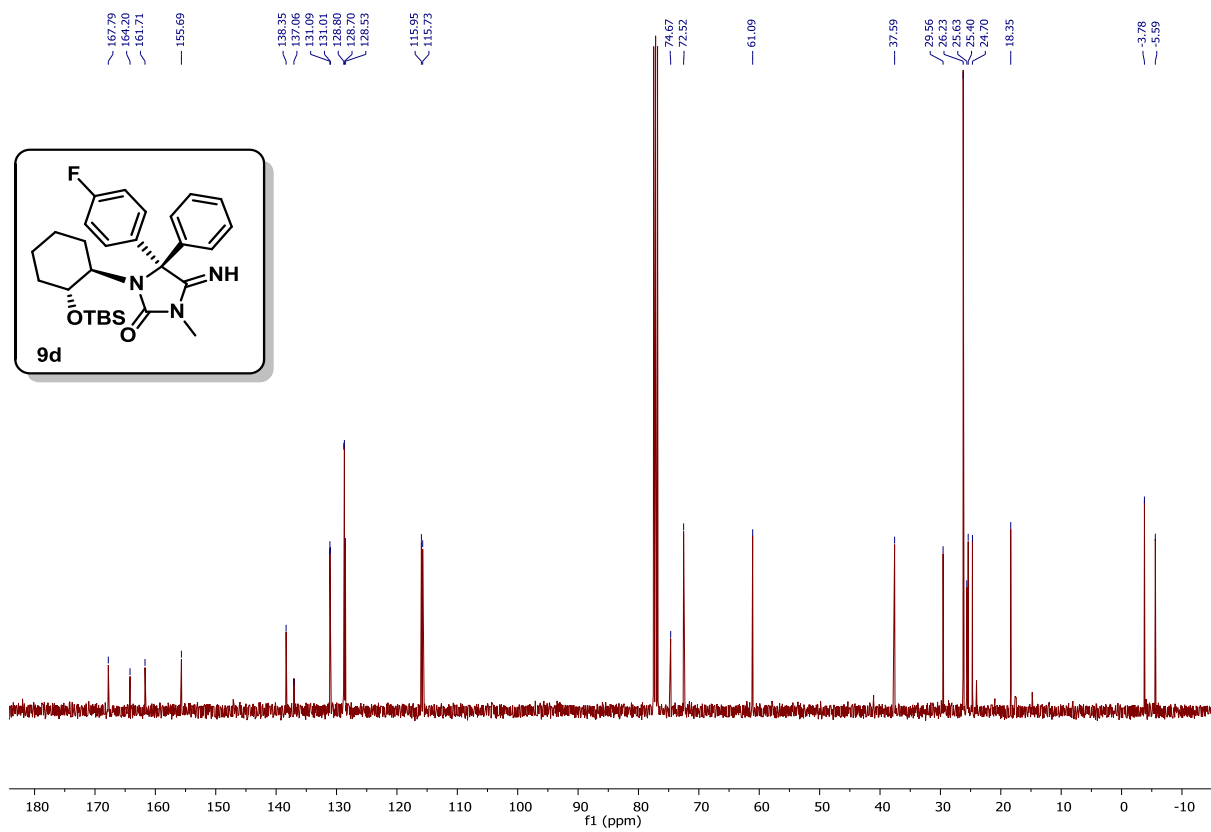


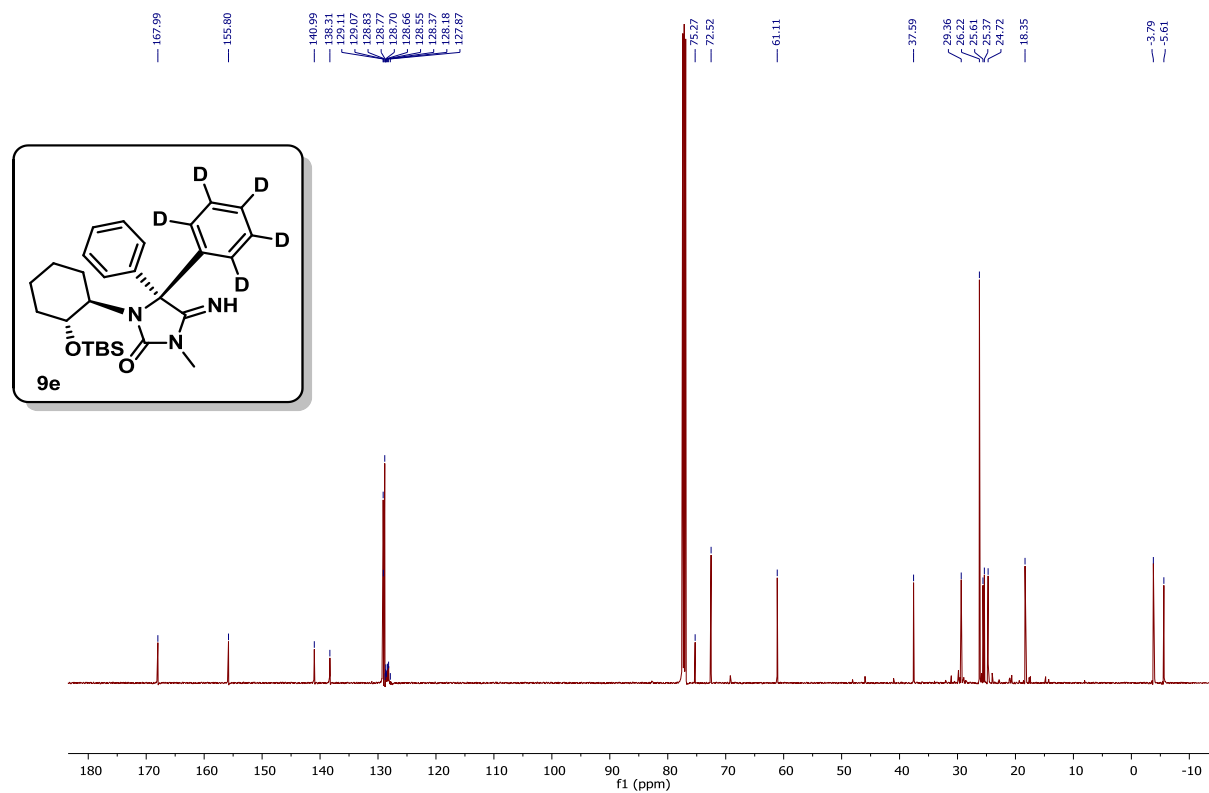
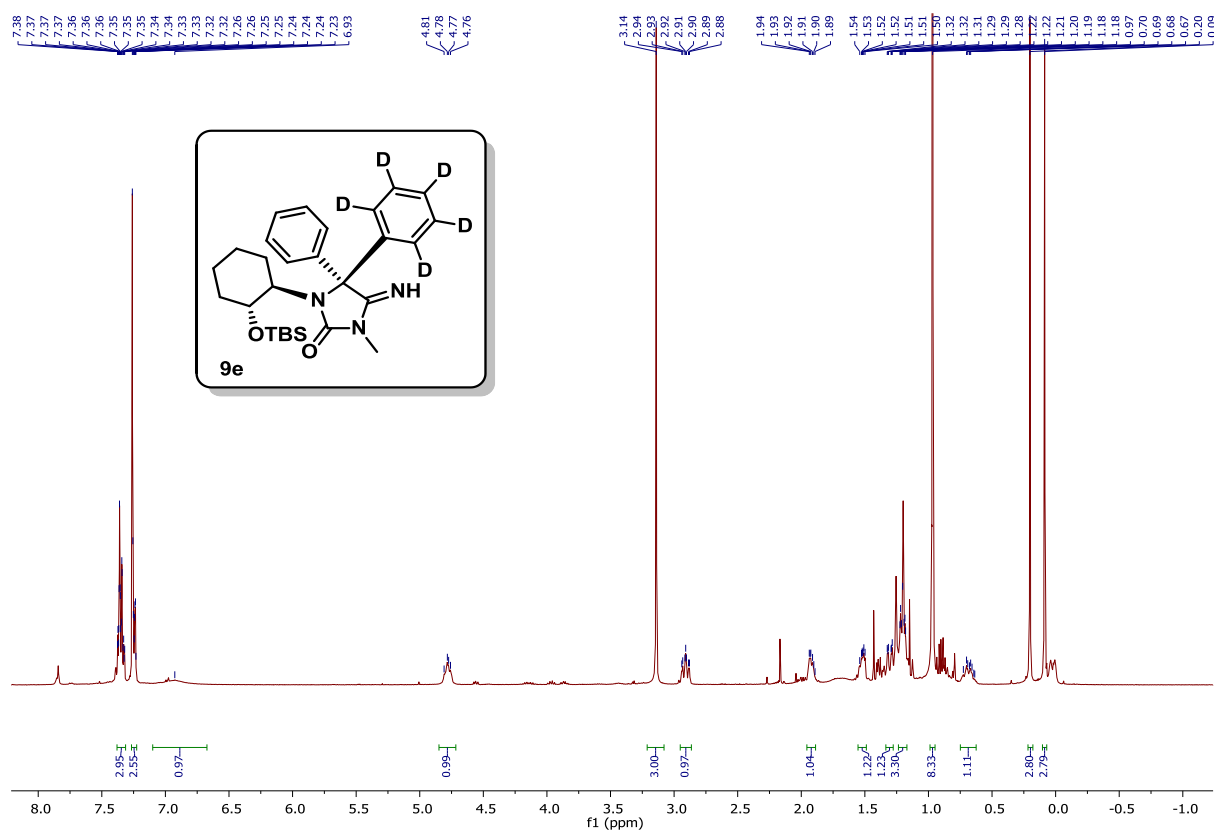


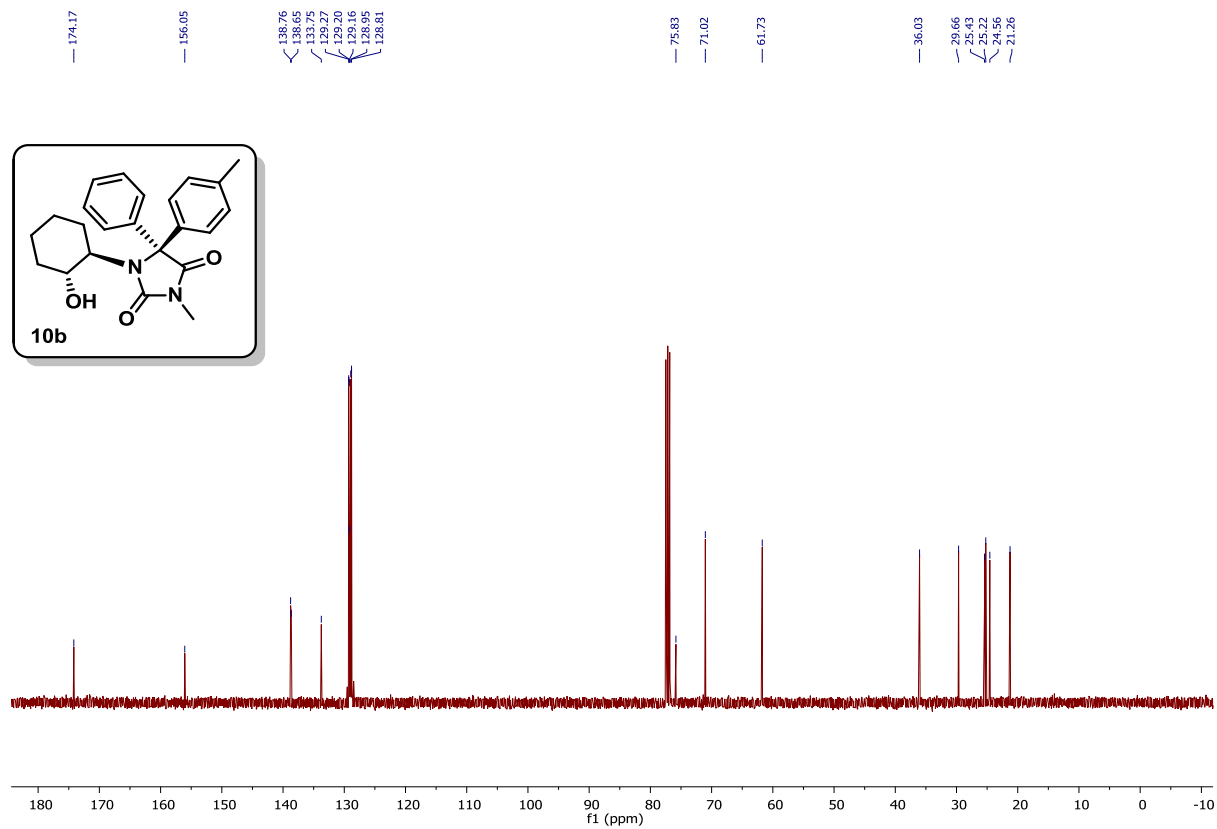
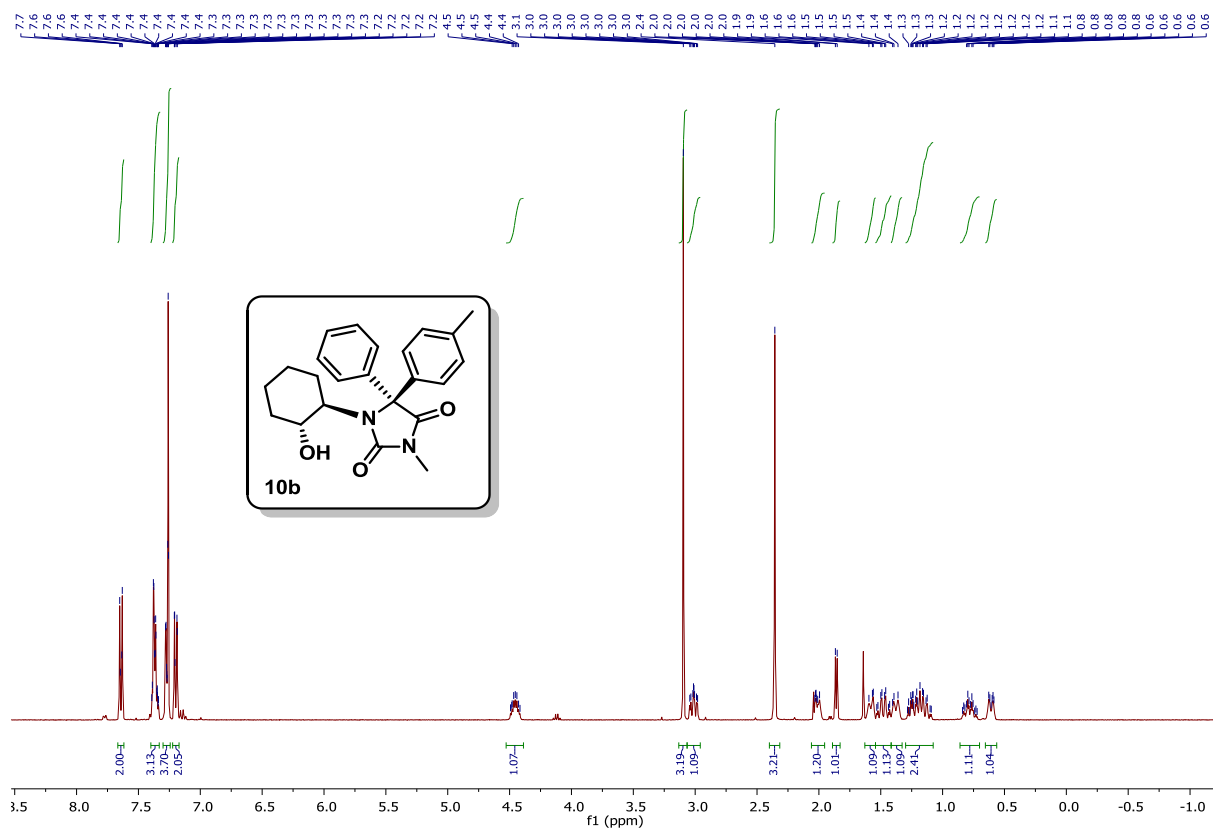


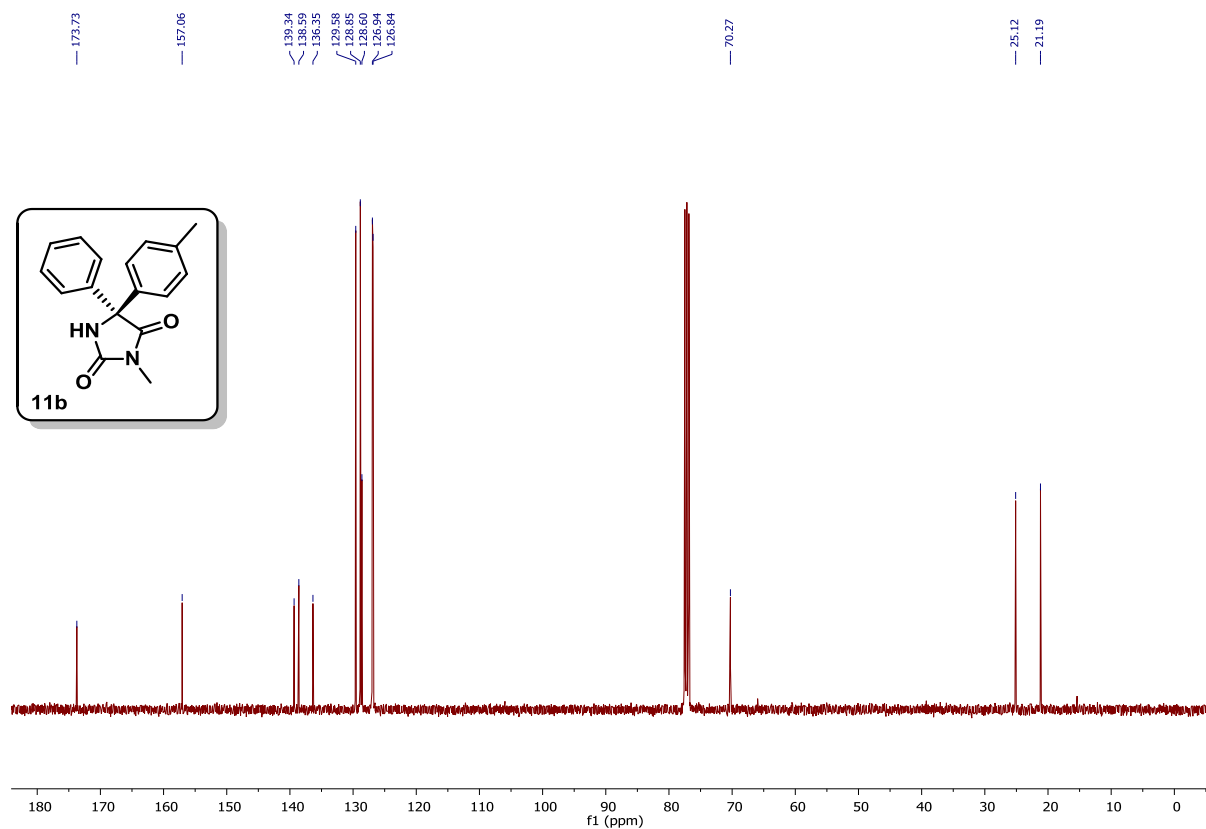
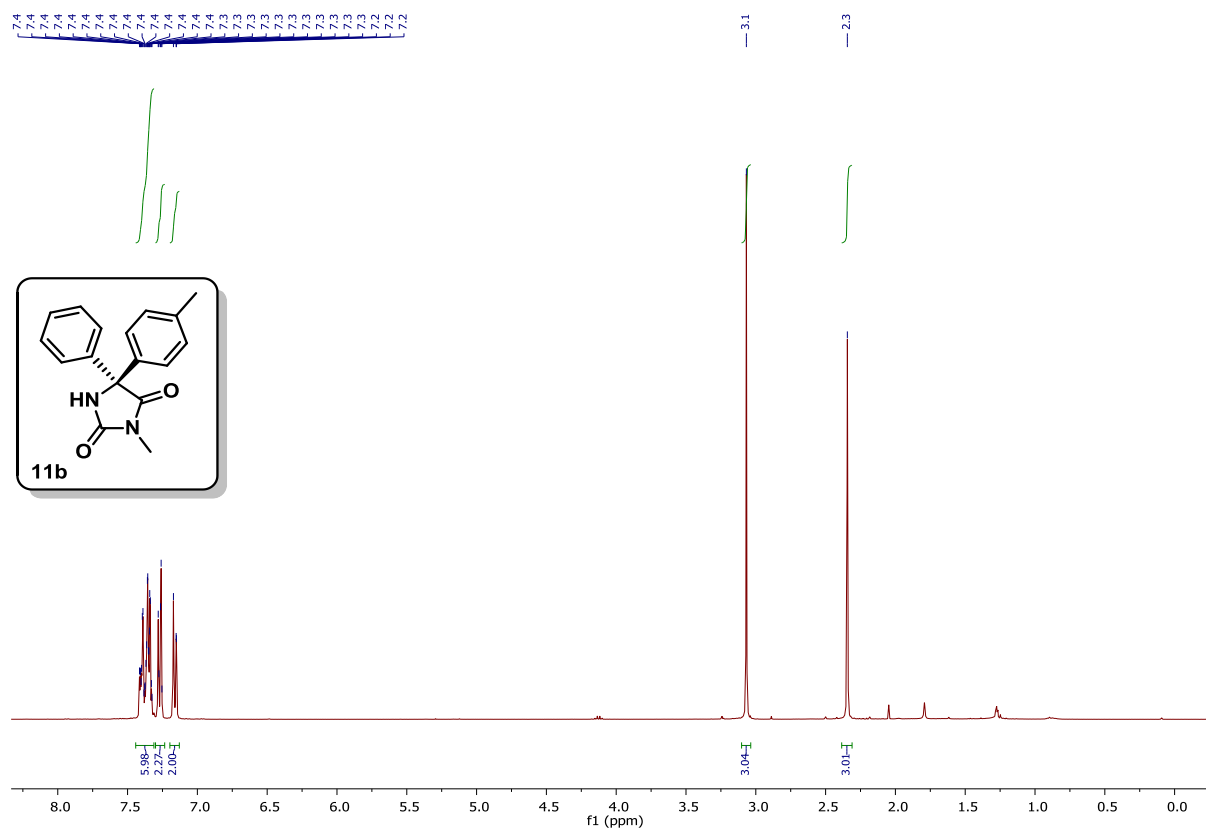












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2. A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281.
3. F. Fernández-Nieto, J. Mas-Roselló, S. Lenoir, S. Hardy, J. Clayden, *Org. Lett.* **2015**, *17*, 3838.