

Supporting Information**Benzoazepine-Fused Isoindolines via Intramolecular (3+2)-Cycloadditions of Azomethine Ylides with Dinitroarenes**

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Contents

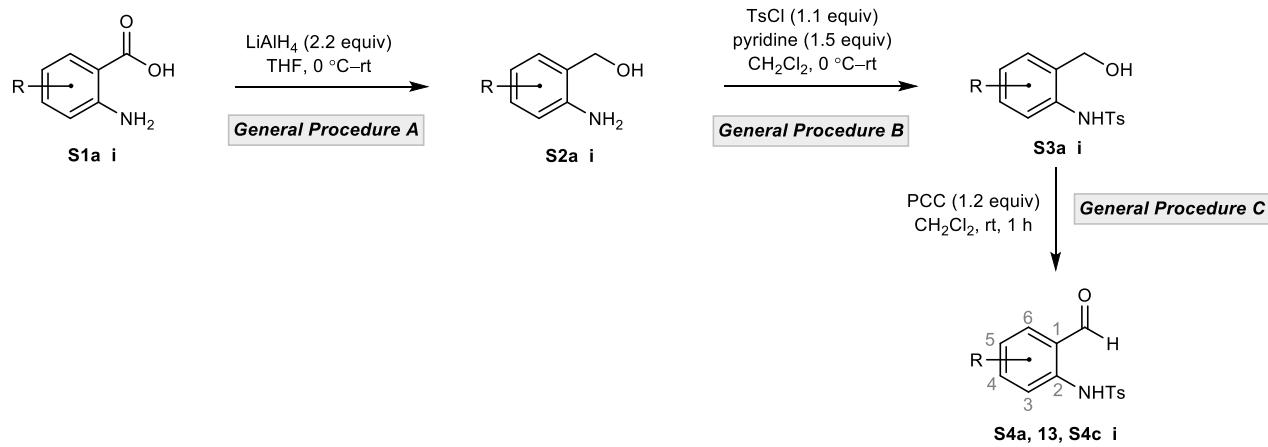
- 1. General Synthesis and Characterization Methods**
- 2. Synthesis of Aldehyde Starting Materials**
 - 2.1. Reduction (General Procedure A)**
 - 2.2. *N*-Tosylation (General Procedure B)**
 - 2.3. Oxidation (General Procedure C)**
- 3. Synthesis of Aldehyde Substrates by Benzylation (7, 8, 9a–m)**
 - 3.1. Synthesis of Nitro-Substituted Benzyl Chlorides**
 - 3.2. Benzylation (General Procedure D)**
 - 3.2.1. Note on NMR Spectra of Amino-Linked Substrates**
- 4. Synthesis of Amino Acid Substrates**
 - 4.1. Synthesis of Amino Acid Methyl Ester Starting Materials**
 - 4.1.1 Esterification Procedure**
 - 4.2. Synthesis of *N*-Benzylated Amino Acids**
 - 4.3. Synthesis of *N*-Methylated Amino Acids**
- 5. Synthesis of Benzoazepine-Fused Isoindolines (12) via Cycloaddition**
 - 5.1. General Points and Observations**
 - 5.2. Notes on Unidentified Side Product Derived from *N*-Benzylglycine**
 - 5.3. Notes on Isoindole Side Product (12')**
 - 5.3.1. Crude Ratios of Isoindoline (12) to Isoindole (12')**
 - 5.4. Cycloaddition Experimental**
 - 5.4.1. General Procedure E (Cycloaddition)**
 - 5.4.2. Products from Benzaldehyde Scope (12a–m)**
 - 5.4.3. Products from Amino Acid Scope (12n–z,aa–cc)**
 - 5.5. Determination of Relative Stereochemistry of 12p, 12t, 12u and 12y by *n*OE NMR Spectroscopy**
 - 5.6. Determination of Relative Stereochemistry of 12r**
 - 5.7. Furthers Discussions on Diastereoselectivity Switch with Cyclic Amino Acid Substrates**
- 6. Larger Scale Examples**
- 7. Further Manipulations**
- 8. References**
- 9. NMR Spectra of Novel Compounds**

1. General Synthesis and Characterization Methods

Reagents and solvents were purchased reagent grade and used as received unless otherwise noted. Anhydrous solvents and inert reaction atmospheres (N_2) were used when indicated in the procedures. Anhydrous solvents (toluene, CH_2Cl_2 , THF, MeCN, DMF) were obtained from commercial sources. All reactions were carried out in standard laboratory glassware with magnetic stirring and were monitored by thin layer chromatography (TLC). TLC was performed on aluminum-backed Silica Gel 60 plates with fluorescent indicator F254. Visualization was accomplished with UV light and/or a phosphomolybdic acid in ethanol staining solution. Flash chromatography was performed under positive air pressure or N_2 (where specified) using Silica Gel 60 of 230–400 mesh (40–63 μ m). Melting points were determined using a Buchi Melting Point M-560 apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker 400 MHz or 500 MHz spectrometers as specified. 1H NMR spectra acquired in $CDCl_3$ are reported relative to tetramethylsilane (1H : δ = 0.00 ppm). 1H NMR spectra acquired in CD_3OD are reported relative to solvent resonance (1H : δ = 3.31 ppm). 1H NMR spectra acquired in $(CD_3)_2SO$ are reported relative to solvent resonance (1H : δ = 2.50 ppm). ^{13}C NMR (proton decoupled) spectra acquired in $CDCl_3$ are reported relative to solvent resonance (^{13}C : δ = 77.16 ppm). ^{13}C NMR (proton decoupled) spectra acquired in CD_3OD are reported relative to solvent resonance (^{13}C : δ = 49.00 ppm). ^{13}C NMR (proton decoupled) spectra acquired in $(CD_3)_2SO$ are reported relative to solvent resonance (^{13}C : δ = 39.52 ppm). ^{19}F NMR (proton decoupled) spectra acquired in $CDCl_3$ are reported relative to fluorobenzene (^{19}F : δ = -112.96 ppm).⁵¹ 1H NMR data are reported as follows: chemical shift, multiplicity, coupling constant (Hz) and integration. The following abbreviations are used for multiplicity: s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets, ddt = doublet of doublets of triplets, t = triplet, app t = apparent triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, qd = quartet of doublets, pd = pentet of doublets, ABq = AB quartet, sep = septet, sepd = septet of doublets, m = multiplet, bm = broad multiplet. Infrared (IR) spectra were obtained on a Bruker Vertex 70 FTIR Spectrometer with neat samples. High resolution mass spectrometry (HRMS) was performed on a Waters Xevo G1 QTOF mass spectrometer with electrospray ionization. Cambridge Crystallographic Data Centre (CCDC) deposition numbers for compounds **9a**, **9j**, **12q**, **12s**, **12z** and **12aa** can be found along with the experimental procedure and characterization data for each compound.

2. Synthesis of Aldehyde Starting Materials

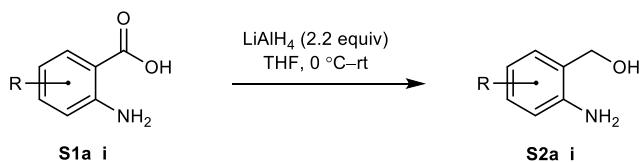
- Most of the required aldehyde starting materials (**S4a, 13, S4c–i**) were prepared according to the scheme below, using *General Procedures A–C*. For the aldehydes not prepared in this way (**S4j–l**), specific schemes and procedures are given at the end of this section.



Entry	R (in S4)	Yield of S2 (%)	Yield of S3 (%)	Yield of S4 (%)
1	a: H	62	77	84
2	b: 5-Me	98	88	91 ^a
3	c: 5-OMe	90	99	56
4	d: 5-Br	97	88	90
5	e: 5-Cl	78	91	88
6	f: 5-F	78	86	96
7	g: 4-Cl	69	97	86
8	h: 3-Cl	43	58	47
9	i: 6-Cl	57	47	99

^a Compound number in manuscript is **13**.

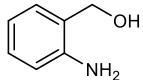
2.1. Reduction



General Procedure A (Reduction): Based on a literature procedure,^{S2} to a solution of the corresponding commercially available anthranilic acid **S1a–i** (1.0 equiv) in anhydrous THF (~1.0 M) cooled to 0 °C was added a solution of LiAlH₄ (2.2 equiv) in anhydrous THF (~3.0 M) dropwise. After complete addition the reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The next day, the reaction mixture was cooled to 0 °C, quenched with crushed ice (slowly), then by addition of 15% NaOH solution (2 mL) forming a gel-like suspension which was stirred for 15 minutes, then MgSO₄ added and then the mixture was stirred for a further 15 minutes. The crude mixture was then filtered, extracted generously with EtOAc and

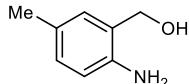
the extract concentrated under reduced pressure. The product was then precipitated from small amount of hot EtOAc and excess *n*-pentane, filtered and washed with cold *n*-pentane to reveal the corresponding alcohol **S2a–i**.

(2-Aminophenyl)methanol (**S2a**)



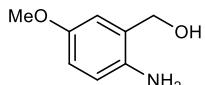
This compound was prepared using *General Procedure A* to afford the title compound as a pale brown solid (1.115 g, 62% yield). **1H NMR (500 MHz, CDCl₃)**: δ 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 7.4, 0.5 Hz, 1H), 6.71 (td, *J* = 7.4, 0.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.62 (s, 3H), 3.43 (bs, 2H) ppm. **13C NMR (125 MHz, CDCl₃)**: δ 146.1, 129.5, 129.3, 125.0, 118.3, 116.2, 64.4 ppm. NMR data matches literature values.⁵³

(2-Amino-5-methylphenyl)methanol (**S2b**)



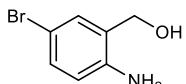
This compound was prepared using *General Procedure A* to afford the title compound as an orange/yellow solid (2.011 g, 98% yield). **1H NMR (500 MHz, CDCl₃)**: δ 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.88 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.61 (s, 2H), 2.23 (s, 3H) ppm. **13C NMR (125 MHz, CDCl₃)**: δ 143.5, 129.93, 129.89, 127.6, 125.2, 116.4, 64.5, 20.5 ppm. NMR data matches literature values.⁵⁴

(2-Amino-5-methoxyphenyl)methanol (**S2c**)



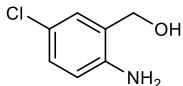
This compound was prepared using *General Procedure A* to afford the title compound as an orange/brown solid (2.066 g, 90% yield). **1H NMR (500 MHz, CDCl₃)**: δ 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.69–6.68 (m, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 4.61 (s, 2H), 3.74 (s, 3H) ppm. **13C NMR (100 MHz, CDCl₃)**: δ 152.7, 139.3, 126.7, 117.5, 115.1, 114.6, 64.2, 55.9 ppm. NMR data matches literature values.⁵⁵

(2-Amino-5-bromophenyl)methanol (**S2d**)



This compound was prepared using *General Procedure A* to afford the title compound as a bright yellow solid (2.926 g, 97% yield). **1H NMR (500 MHz, CDCl₃)**: δ 7.22–7.18 (m, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.60 (s, 2H), 4.16 (bs, 2H), 1.76 (bs, 1H) ppm. **13C NMR (125 MHz, CDCl₃)**: δ 145.2, 132.0, 131.7, 126.7, 117.7, 109.7, 63.9 ppm. NMR data matches literature values.⁵⁴

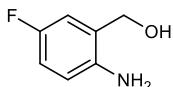
(2-Amino-5-chlorophenyl)methanol (**S2e**)



This compound was prepared using *General Procedure A* to afford the title compound as a pale yellow solid (1.827 g, 78% yield). **¹H NMR (500 MHz, CDCl₃):** δ 7.09–7.05 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.61 (s, 2H), 4.17 (bs, 1H), 1.61 (bs, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 144.7, 129.1, 128.9, 126.2, 122.7, 117.2, 64.0 ppm.

NMR data matches literature values.⁵⁶

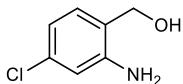
(2-Amino-5-fluorophenyl)methanol (**S2f**)



This compound was prepared using *General Procedure A* to afford the title compound as a beige solid (1.647 g, 78% yield). **¹H NMR (400 MHz, CDCl₃):** δ 6.86–6.81 (m, 2H), 6.65–6.60 (m, 1H), 4.62 (s, 2H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 156.0 (d, *J*_{C-F} = 235.1 Hz), 141.9, 126.3 (d, *J*_{C-F} = 6.3 Hz), 117.0 (d, *J*_{C-F} = 7.4 Hz), 115.6 (d, *J*_{C-F} = 22.1 Hz, 2 × ArC), 63.9 ppm.

NMR data matches literature values.⁵⁶

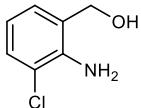
(2-Amino-4-chlorophenyl)methanol (**S2g**)



This compound was prepared using *General Procedure A* to afford the title compound as a beige solid (1.618 g, 69% yield). **¹H NMR (500 MHz, CDCl₃):** δ 6.97 (d, *J* = 8.0 Hz, 1H), 6.69–6.66 (m, 2H), 4.64 (s, 2H), 4.27 (bs, 2H), 1.58 (bs, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 147.4, 134.9, 130.3, 123.1, 118.0, 115.7, 64.0 ppm.

NMR data matches literature values.⁵⁶

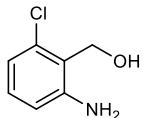
(2-Amino-3-chlorophenyl)methanol (**S2h**)



This compound was prepared using *General Procedure A* to afford the title compound as a white “needle-like” solid (1.012 g, 43% yield). **¹H NMR (500 MHz, CDCl₃):** δ 7.23 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.33 (t, *J* = 7.5 Hz, 1H), 4.67 (s, 2H), 4.65 (bs, 2H), 1.72 (bs, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 142.8, 129.5, 127.6, 125.8, 120.1, 118.0, 64.6 ppm.

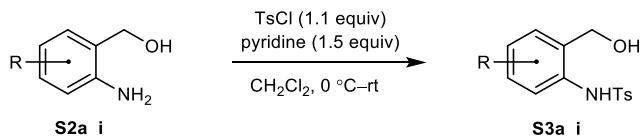
NMR data matches literature values.⁵⁵

(2-Amino-6-chlorophenyl)methanol (S2i**)**



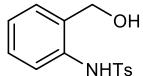
This compound was prepared using *General Procedure A* to afford the title compound as a brown crystalline solid (1.347 g, 57% yield). **1H NMR (500 MHz, CDCl₃)**: δ 7.01 (t, J = 8.0 Hz, 1H), 6.76 (dd, J = 8.0, 0.5 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.88 (s, 2H), 4.28 (bs, 2H), 1.66 (bs, 1H) ppm. **13C NMR (125 MHz, CDCl₃)**: δ 148.2, 134.3, 129.8, 122.2, 119.2, 114.8, 59.7 ppm. NMR data matches literature values.^{S5}

2.2. N-Tosylation



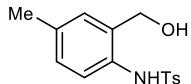
General Procedure B (N-Tosylation): Based on a literature procedure,^{S2} to a solution of corresponding amine **S2a–i** (1.0 equiv) in anhydrous CH₂Cl₂ (0.3 M) was added pyridine (1.5 equiv). The resultant solution was cooled to 0 °C before addition of TsCl (1.1 equiv). The resultant reaction mixture was then allowed to warm to room temperature and allowed to stir overnight. The reaction was then quenched using saturated NaHCO₃ (30 mL), the aqueous layer was extracted using CH₂Cl₂ (3 × 20 mL) and the solvent removed under reduced pressure. The crude material was then dissolved in EtOAc (30 mL), washed thrice using 2 M HCl solution (30 mL), and then concentrated under reduced pressure to reveal the corresponding *N*-tosylated product **S3a–i**. The corresponding *N*-tosylated product was then clean enough to be used in the next reaction or purified via recrystallisation if required.

N-(2-(Hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3a**)**



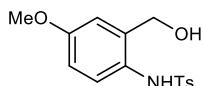
This compound was prepared using *General Procedure B* to afford the title compound as a pale-yellow solid (1.911 g, 77% yield). **1H NMR (500 MHz, CDCl₃)**: δ 7.90 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.26–7.23 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.09–7.06 (m, 2H), 4.39 (s, 2H), 2.38 (s, 3H), 2.21 (bs, 1H) ppm. **13C NMR (125 MHz, CDCl₃)**: δ 143.9, 137.1, 136.5, 131.8, 129.8, 129.4, 129.2, 127.2, 125.5, 123.6, 64.0, 21.7 ppm. NMR data matches literature values.^{S7}

N-(2-(Hydroxymethyl)-4-methylphenyl)-4-methylbenzenesulfonamide (S3b)



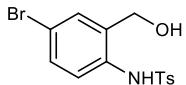
This compound was prepared using *General Procedure B* to afford the title compound as an orange solid (3.746 g, 88% yield). **¹H NMR (500 MHz, CDCl₃):** δ 7.63 (bs, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 7.23–7.20 (m, 3H), 7.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 2.27 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 143.8, 137.0, 135.8, 133.4, 132.8, 130.0, 129.8, 129.7, 127.2, 124.5, 63.7, 21.7, 20.9 ppm. NMR data matches literature values.⁸⁸

N-(2-(Hydroxymethyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (S3c)



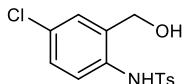
This compound was prepared using *General Procedure B* to afford the title compound as a brown solid (4.150 g, 99% yield). **¹H NMR (500 MHz, CDCl₃):** δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.33 (bs, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.74–6.71 (m, 2H), 4.30 (s, 2H), 3.76 (s, 3H), 2.39 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 158.1, 143.9, 136.7, 136.6, 129.7, 128.0, 127.6, 127.3, 114.8, 114.0, 63.2, 55.6, 21.7 ppm. NMR data matches literature values.⁸⁹

N-(4-Bromo-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3d)



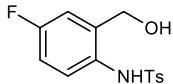
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (4.578 g, 88% yield). **¹H NMR (500 MHz, CDCl₃):** δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.38–7.31 (m, 2H), 7.24–7.23 (m, 3H), 4.34 (s, 2H), 2.39 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 144.2, 136.8, 135.6, 133.8, 132.2, 132.0, 129.9, 127.2, 125.2, 118.5, 63.4, 21.7 ppm. NMR data matches literature values.⁸¹⁰

N-(4-Chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3e)



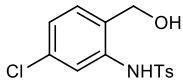
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (3.272 g, 91% yield). **¹H NMR (400 MHz, CDCl₃):** δ 7.95 (s, 1H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 6.4 Hz, 2H), 7.22–7.19 (m, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 4.33 (s, 2H), 2.39 (s, 3H), 1.60 (bs, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 144.2, 136.6, 134.9, 133.8, 130.8, 129.9, 129.1 (2 × ArC), 127.2, 125.2, 63.3, 21.7 ppm. NMR data matches literature values.⁸⁸

N-(4-Fluoro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3f)



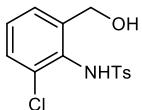
This compound was prepared using *General Procedure B* to afford the title compound as a yellow/orange solid (2.956 g, 86% yield). **Mp:** 150–153 °C. **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 7.60 (d, $J = 8.5$ Hz, 2H), 7.31 (dd, $J = 9.0, 5.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.96 (ddd, $J = 9.0, 8.0, 3.0$ Hz, 1H), 6.89 (dd, $J = 8.5, 3.0$ Hz, 1H), 4.32 (s, 2H), 2.40 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 160.5 (d, $J_{\text{C-F}} = 232.8$ Hz), 144.2, 136.5, 135.7 (d, $J_{\text{C-F}} = 7.3$ Hz), 131.7 (d, $J_{\text{C-F}} = 3.0$ Hz), 129.9, 127.2, 127.0 (d, $J_{\text{C-F}} = 8.3$ Hz), 116.0 (d, $J_{\text{C-F}} = 22.8$ Hz), 115.8 (d, $J_{\text{C-F}} = 22.1$ Hz), 63.2 (d, $J_{\text{C-F}} = 1.0$ Hz), 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ 3446, 3080, 1595, 1491, 1323, 1154, 918, 880, 663, 554. **HRMS (ESI):** calcd for $\text{C}_{14}\text{H}_{13}\text{FNO}_3\text{S}$ [$\text{M} - \text{H}$]⁺ 294.0606, found 294.0608.

N-(5-Chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3g)



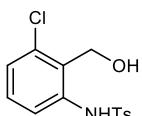
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (3.098 g, 97% yield). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 8.14 (bs, 1H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.03–6.98 (m, 2H), 4.37 (s, 2H), 2.49 (bs, 1H), 2.39 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 144.3, 137.7, 136.6, 134.8, 130.1, 129.9, 129.5, 127.1, 125.1, 122.8, 63.4, 21.7 ppm. NMR data matches literature values.⁵⁹

N-(6-Chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3h)



This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (1.017 g, 58% yield). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 7.53 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.27–7.18 (m, 4H), 6.48 (bs, 1H), 4.86 (s, 2H), 2.24 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 144.6, 142.6, 135.8, 132.2, 130.8, 130.1, 129.7, 129.1, 129.0, 127.8, 62.0, 21.8 ppm. NMR data matches literature values.⁵¹

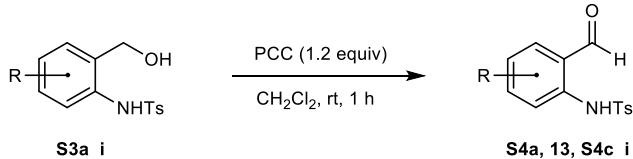
N-(3-Chloro-2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (S3i)



This compound was prepared using *General Procedure B* to afford the title compound as a brown solid (1.256 g, 47% yield). **Mp:** 115–120 °C. **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 7.66 (d, $J = 8.4$ Hz, 2H), 7.32 (dd, $J = 5.8, 3.4$

Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.15–7.14 (m, 2H), 4.65 (s, 2H), 2.39 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ 144.2, 138.3, 136.8, 133.9, 129.9, 129.65, 129.55, 127.2, 126.7, 122.2, 59.8, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ 3450, 3356, 3250, 3064, 2922, 1671, 1457, 995, 771. **HRMS (ESI):** calcd for $\text{C}_{14}\text{H}_{13}\text{ClNO}_3\text{S}$ [M – H] – 310.0305, found 310.0316.

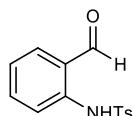
2.3. Oxidation



General Procedure C (Oxidation): Based on a literature procedure,^{S2} to a solution of the corresponding alcohol **S3a–i** (1.0 equiv) in anhydrous CH_2Cl_2 (0.1 M) at room temperature was added PCC (1.2 equiv). The resultant reaction solution was stirred at room temperature and monitored via TLC (typically 1–2 h). To the reaction mixture was then added MgSO_4 to form a suspension that was then directly filtered through a sintered glass funnel, with the residue washed generously with extra CH_2Cl_2 . The solvent was removed under reduced pressure to afford crude material that was then purified via recrystallization or flash column chromatography to reveal the corresponding aldehydes **S4a, 13** and **S4c–i**.

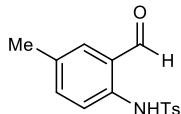
- Note that in some cases, celite (3× weight of PCC used) was also added at the start of the reaction. This greatly simplified the work-up and filtration (and subsequent cleaning of the reaction vessel) by absorbing the chromium by-product during its formation. No MgSO_4 was added when celite was used.

N-(2-Formylphenyl)-4-methylbenzenesulfonamide (**S4a**)



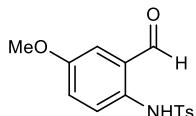
This compound was prepared using *General Procedure C* to afford the title compound as a white solid (1.585 g, 84% yield). **^1H NMR (500 MHz, CDCl_3):** δ 10.79 (bs, 1H), 9.82 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 7.6, 0.6 Hz, 1H), 7.52–7.49 (m, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.16 (t, J = 7.5, Hz, 1H), 2.36 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 195.1, 144.3, 140.0, 136.5, 136.2, 135.9, 129.9, 127.4, 123.1, 122.0, 117.8, 21.6 ppm. NMR data matches literature values.^{S12}

***N*-(2-Formyl-4-methylphenyl)-4-methylbenzenesulfonamide (13)**



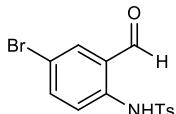
This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (3.398 g, 91% yield). **¹H NMR (500 MHz, CDCl₃):** δ 10.59 (s, 1H), 9.77 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.37–7.36 (m, 1H), 7.32 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 195.1, 144.0, 137.5, 136.6, 136.5, 136.3, 132.9, 129.7, 127.3, 122.1, 118.3, 21.6, 20.4 ppm. NMR data matches literature values.⁸¹³

***N*-(2-Formyl-4-methoxyphenyl)-4-methylbenzenesulfonamide (S4c)**



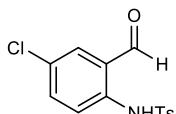
This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (2.323 g, 56% yield). **¹H NMR (500 MHz, CDCl₃):** δ 10.22 (s, 1H), 9.74 (dd, *J* = 0.5 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.68–7.67 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 194.6, 155.9, 144.1, 136.5, 133.1, 129.8, 127.4, 123.7, 122.2, 121.2, 119.5, 55.9, 21.7 ppm. NMR data matches literature values.⁸⁹

***N*-(4-Bromo-2-formylphenyl)-4-methylbenzenesulfonamide (S4d)**



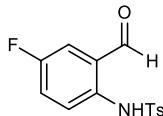
This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (4.116 g, 90% yield). **Mp:** 135–139 °C. **¹H NMR (500 MHz, CDCl₃):** δ 10.64 (s, 1H), 9.76 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.63–7.58 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 193.7, 144.6, 139.0, 138.6, 138.2, 136.2, 130.0, 127.3, 123.3, 119.9, 115.5, 21.7 ppm. **IR (ATR, cm⁻¹):** ̄ = 3126, 3049, 2865, 1669, 1479, 1375, 1159, 856, 684. **HRMS (ESI):** calcd for C₁₄H₁₁(⁷⁹Br)NO₃S [M – H][–] 351.96485, found 351.96505.

***N*-(4-Chloro-2-formylphenyl)-4-methylbenzenesulfonamide (S4e)**



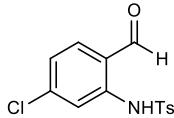
This compound was prepared using *General Procedure C* to afford the title compound as a brown solid (2.848 g, 88% yield). **1H NMR (500 MHz, CDCl₃):** δ 10.62 (bs, 1H), 9.77 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 2.38 (s, 3H) ppm. **13C NMR (125 MHz, CDCl₃):** δ 193.9, 144.6, 138.6, 136.2, 135.8, 135.3, 130.0, 128.5, 127.4, 123.0, 119.7, 21.7 ppm. NMR data matches literature values.⁵⁹

***N*-(4-Fluoro-2-formylphenyl)-4-methylbenzenesulfonamide (S4f)**



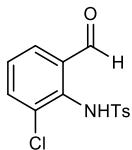
This compound was prepared using *General Procedure C* to afford the title compound as a brown solid (2.785 g, 96% yield). **Mp:** 135–137 °C. **1H NMR (500 MHz, CDCl₃):** δ 10.45 (s, 1H), 9.76 (s, 1H), 7.74–7.71 (m, 3H), 7.29–7.26 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H) ppm. **13C NMR (125 MHz, CDCl₃):** δ 193.7, 158.3 (d, *J*_{C-F} = 244.4 Hz), 144.4, 136.2, 136.2 (d, *J*_{C-F} = 2.4 Hz), 129.9, 127.3, 123.21 (d, *J*_{C-F} = 22.6 Hz), 123.2, 121.3 (d, *J*_{C-F} = 22.4 Hz), 120.7 (d, *J*_{C-F} = 7.0 Hz), 21.7 ppm. **IR (ATR, cm⁻¹):** ̄ = 3713, 3072, 2873, 1670, 1588, 1495, 1342, 1159, 905, 770, 542. **HRMS (ESI):** calcd for C₁₄H₁₁FNO₃S [M – H][–] 292.0449, found 292.0451.

***N*-(5-Chloro-2-formylphenyl)-4-methylbenzenesulfonamide (S4g)**



This compound was prepared using *General Procedure C* to afford the title compound as a brown solid (2.591 g, 86% yield). **1H NMR (500 MHz, CDCl₃):** δ 10.88 (s, 1H), 9.79 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 2.39 (s, 3H) ppm. **13C NMR (125 MHz, CDCl₃):** δ 194.0, 144.7, 142.7, 141.1, 137.2, 136.2, 130.1, 127.4, 123.3, 120.2, 117.8, 21.7 ppm. NMR data matches literature values.⁵¹⁴

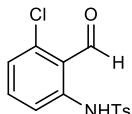
***N*-(6-Chloro-2-formylphenyl)-4-methylbenzenesulfonamide (S4h)**



This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (0.478 g, 47% yield). **Mp:** 143–146 °C. **1H NMR (400 MHz, CDCl₃):** δ 10.32 (d, *J* = 0.8 Hz, 1H), 7.92 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (td, *J* = 7.8, 0.8 Hz, 1H), 7.20 (d, *J* =

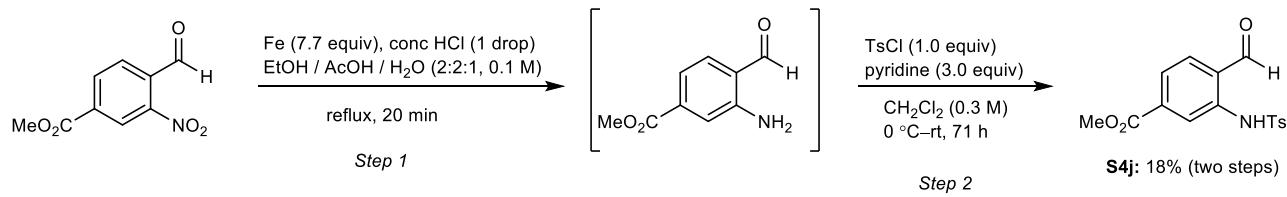
8.0 Hz, 2H), 2.41 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 189.2, 144.9, 135.5, 134.92, 134.85, 134.3, 131.6, 129.8, 128.3, 128.1, 127.6, 21.8 ppm. **IR (ATR, cm⁻¹):** ν = 3366, 3102, 2895, 1671, 1466, 1395, 1163, 883, 796, 721, 576. **HRMS (ESI):** calcd for C₁₄H₁₂ClNO₃SNa [M + Na]⁺ 332.0124, found 332.0132.

N-(3-Chloro-2-formylphenyl)-4-methylbenzenesulfonamide (S4i)



This compound was prepared using *General Procedure C* to afford the title compound as a white solid (1.844 g, 99% yield). **¹H NMR (500 MHz, CDCl₃):** δ 11.33 (bs, 1H), 10.45 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 2.38 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 193.9, 144.6, 142.4, 140.5, 136.5, 136.3, 130.0, 127.4, 124.6, 117.7, 116.8, 21.7 ppm. NMR data matches literature values.^{S13}

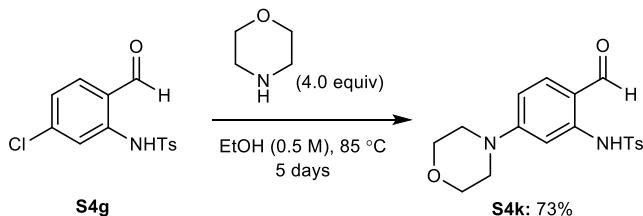
N-(5-Carbomethoxy-2-formylphenyl)-4-methylbenzenesulfonamide (S4j)



Step 1: Based on a literature procedure,^{S15} to a suspension of commercially obtained methyl 4-formyl-3-nitrobenzoate (1.046 g, 5.00 mmol) in a mixture of EtOH (20 mL), AcOH (20 mL) and water (10 mL) under air at room temperature was added Fe powder (2.144 g, 38.39 mmol) followed by concentrated HCl (32%, 4 drops from glass pipette). The suspension was placed in a pre-heated oil bath at 80 °C and heated to 100 °C (over 5 min) and maintained at 100 °C for a further 20 min (the reaction flask was fitted with a condenser opened to the air but no water flow was required). The mixture was cooled to rt and stirred for a further 30 min. The suspension was vacuum filtered and the reaction flask and filter cake were washed with EtOAc (70 mL). The filtrate was cooled in an ice bath with stirring and 1 M K₂CO₃ (180 mL) was added slowly over 10 min (CO₂ evolution). EtOAc (50 mL) was added and the organic layer was separated. The aqueous phase was further extracted with EtOAc (70 mL). The combined organic extracts were washed with saturated NaHCO₃ (50 mL), dried (Na₂SO₄) and concentrated to give the intermediate aniline (925.5 mg, 103% of theoretical) as a yellow solid, which contained only minor impurities by NMR and was used directly in the next step. **TLC:** *R*_F = 0.46 (25:75 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 9.95 (d, *J* = 0.7 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.36–7.33 (m, 2H), 6.23 (bs, 2H), 3.92 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 194.1, 166.5, 149.5, 135.8, 135.6, 121.0, 117.8, 116.7, 52.6 ppm.

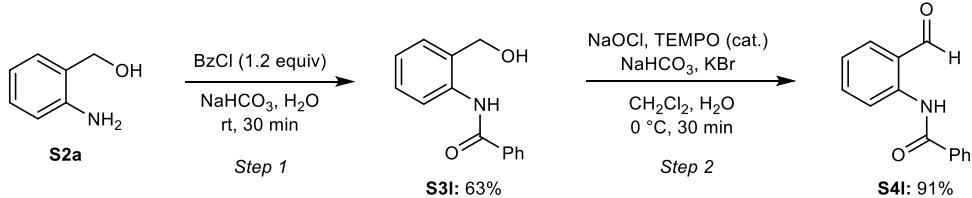
Step 2: To a solution of the above aniline (925.5 mg crude, ≤ 5.00 mmol) in reagent grade CH_2Cl_2 (16.7 mL) at 0 °C under air was added pyridine (0.61 mL, 7.50 mmol) followed by solid TsCl (953.2 mg, 5.00 mmol). The mixture was allowed to warm to room temperature with stirring over 7 h. Additional pyridine (0.61 mL, 7.50 mmol) was added and stirring continued for a further 64 h, after which time TLC analysis indicated complete consumption of TsCl and only a trace of the aniline remaining (several more polar side products were present). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (30.6 g silica, 0:100 to 1:99 $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to give **S4j** (302.3 mg, 18% over two steps) as a pale yellow solid. **Mp:** 169–173 °C. **TLC:** $R_F = 0.38$ (CH_2Cl_2). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.72 (bs, 1H), 9.91 (d, $J = 0.8$ Hz, 1H), 8.33 (s, 1H), 7.83–7.77 (m, 3H), 7.69 (d, $J = 7.9$ Hz, 1H), 7.26 (d, $J = 8.2$ Hz, 2H), 3.96 (s, 3H), 2.37 (s, 3H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CDCl_3):** δ 194.8, 165.5, 144.6, 140.0, 136.3, 136.2, 136.1, 130.0, 127.5, 124.1, 123.6, 118.9, 53.0, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 3161, 2967, 1721, 1672, 1571, 1502, 1430, 1397, 1349, 1302, 1250, 1189, 1167, 1087, 986, 870, 824, 807, 672, 667, 568, 545, 526, 425. **HRMS (ESI):** calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_5\text{S} [\text{M} - \text{H}]^-$ 332.0593, found 332.0598. NMR data for this compound was previously reported using DMSO-d_6 as solvent.^{S16}$

***N*-(2-Formyl-5-morpholinophenyl)-4-methylbenzenesulfonamide (**S4k**)**



A solution of **S4g** (216.8 mg, 0.70 mmol) and morpholine (0.24 mL, 2.80 mmol) in reagent grade EtOH (1.5 mL) under air was heated at 85 °C for 5 days. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (10.4 g silica, 2.5:97.5 to 3:97 $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to give **S4k** (183.5 mg, 73%) as a yellow solid, which contained an unidentified 5 mol% impurity by NMR and was used in the subsequent benzylation step without any complications. **Mp:** 192–196 °C. **TLC:** $R_F = 0.34$ (2.5:97.5 $\text{EtOAc}/\text{CH}_2\text{Cl}_2$). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 11.12 (bs, 1H), 9.53 (s, 1H), 7.75 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 8.8, 2.5$ Hz, 1H), 3.86–3.78 (m, 4H), 3.39–3.30 (m, 4H), 2.37 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 192.2, 155.5, 144.2, 142.3, 137.9, 136.7, 129.8, 127.4, 113.8, 107.8, 101.2, 66.4, 46.9, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 2959, 2842, 1610, 1555, 1518, 1447, 1360, 1270, 1216, 1158, 1109, 1089, 1045, 990, 923, 883, 848, 834, 793, 709, 661, 578, 560, 542, 469, 456. **HRMS (ESI):** calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4\text{S} [\text{M} - \text{H}]^-$ 359.1066, found 359.1060.$

2-Benzoylaminobenzaldehyde (S4I)



Step 1: To a solution of amino alcohol **S2a** (0.80 g, 6.45 mmol, 1.0 equiv) in saturated NaHCO₃ (30 mL) was added benzoyl chloride (1.10 g, 7.78 mmol, 1.2 equiv) dropwise at room temperature. The reaction mixture was left to stir at room temperature for 30 min, before the precipitate was collected by filtration and washed with a mixture of hexane and ether (20:1) to yield the intermediate alcohol **S3I** as a white solid in 63% yield (0.92 g, 4.07 mmol). **Mp:** 93–95 °C. **¹H NMR (400 MHz, CDCl₃) δ:** 9.58 (bs, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 2H), 7.60–7.52 (m, 1H), 7.51–7.44 (m, 2H), 7.38 (td, *J* = 7.8, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 4.80 (d, *J* = 5.9 Hz, 2H), 2.47 (t, *J* = 5.9 Hz, 1H) ppm. **¹³C NMR (100 MHz, CDCl₃) δ:** 165.6, 138.1, 134.9, 132.0, 129.5, 129.4, 128.93, 128.85, 127.3, 124.4, 122.4, 65.1 ppm. This data matches that previously reported.^{S17}

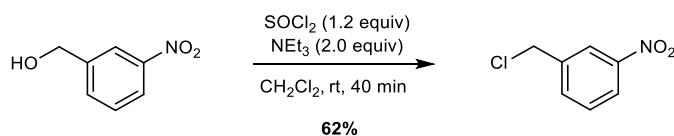
Step 2: To a solution of alcohol **S3I** (0.50 g, 2.22 mmol, 1.0 equiv) in CH₂Cl₂ (14.8 mL) was added saturated NaHCO₃ (7.4 mL), KBr (0.26 g, 2.21 mmol, 1.0 equiv) and TEMPO (17.5 mg, 0.11 mmol, 0.05 equiv). The solution was cooled to 0 °C and a commercial aqueous ‘bleach’ solution (7.86 mL) was added dropwise over 30 min (containing sodium hypochlorite [42 g/L in H₂O, 7.86 mL aliquot = 0.33 g of NaOCl, 4.42 mmol, 2.0 equiv] and NaOH [4 g/L, 7.86 mL aliquot = 31.4 mg of NaOH, 0.79 mmol, 0.36 equiv]). The reaction mixture was diluted with saturated sodium thiosulfate (0.30 M), the aqueous layer extracted with CH₂Cl₂ (× 3), and the combined organic phases dried over Na₂SO₄. The solvent was evaporated under reduced pressure to yield aldehyde **S4I** as a white solid in 91% yield (0.46 g, 2.02 mmol). **Mp:** 70–71 °C. **¹H NMR (500 MHz, CDCl₃) δ:** 12.10 (bs, 1H), 10.01 (s, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 6.8 Hz, 2H), 7.74 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.7, 7.4, 1.7 Hz, 1H), 7.62–7.57 (m, 1H), 7.56–7.52 (m, 2H), 7.30–7.25 (m, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃) δ:** 196.1, 166.3, 141.4, 136.6, 136.4, 134.5, 132.4, 129.0, 127.7, 123.2, 122.2, 120.2 ppm. This data matches that previously reported.^{S17}

3. Synthesis of Aldehyde Substrates by Benzylation (7, 8, 9a–m)

3.1. Synthesis of Nitro-Substituted Benzyl Chlorides

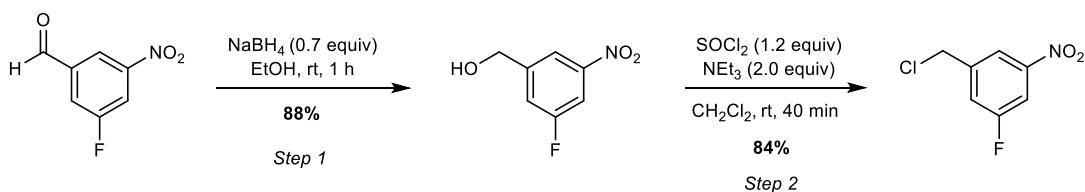
- 3-Nitrobenzyl chloride and 3-fluoro-5-nitrobenzylchloride (for preliminary studies) were prepared from the corresponding aldehyde or alcohol as described below. 3,5-Dinitrobenzyl chloride was obtained commercially.

3-Nitrobenzyl chloride



To a solution of 3-nitrobenzyl alcohol (500.0 mg, 3.26 mmol, 1.0 equiv) and NEt_3 (0.82 mL, 5.88 mmol, 1.8 equiv) in reagent grade CH_2Cl_2 (6.5 mL) at room temperature under air was added dropwise over 10 min neat SOCl_2 (0.29 mL, 3.92 mmol, 1.2 equiv). After complete addition, the solution was stirred at room temperature for 40 min. Water was slowly added (5 mL), followed by saturated NaHCO_3 (20 mL) and further CH_2Cl_2 (20 mL). The organic layer was washed with water (20 mL), dried (Na_2SO_4) and concentrated. Polar impurities were removed via flash chromatography (eluting with CH_2Cl_2) to give 3-nitrobenzyl chloride as an orange solid (346.8 mg, 62% yield). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 8.29–8.27 (m, 1H), 8.20 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.75–7.72 (m, 1H), 7.56 (t, J = 7.9 Hz, 1H), 4.66 (s, 2H) ppm.

3-Fluoro-5-nitrobenzyl chloride

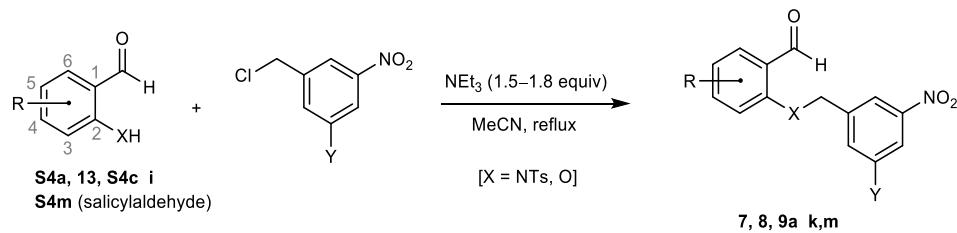


Step 1: To a solution of 3-fluoro-5-nitrobenzaldehyde (500.0 mg, 2.96 mmol, 1.0 equiv) in reagent grade EtOH (2 mL) under air at room temperature was added a suspension of NaBH_4 (79.6 mg, 2.10 mmol, 0.7 equiv) in EtOH (3 mL) via glass pipette. The residual NaBH_4 was rinsed into the reaction vessel with further EtOH (0.5 mL) and the mixture was stirred at room temperature for 1 h. The reaction was quenched by the dropwise addition of 1 M NaOH until the mixture became a homogenous solution. Most of the EtOH was then removed under reduced pressure. Water (20 mL) was added and the product was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed sequentially with NaHCO_3 (20 mL) and water (20 mL), then dried (Na_2SO_4) and concentrated to give 3-fluoro-5-nitrobenzyl alcohol as a yellow solid (444.0 mg, 88% yield). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 8.05 (dt, J = 2.1, 1.0 Hz, 1H), 7.83 (dt, J = 8.2, 2.3 Hz, 1H), 7.46 (ddd, J = 8.5, 2.3, 1.3 Hz, 1H), 4.83 (d, J = 3.8 Hz, 2H), 2.28 (s, 1H) ppm.

Step 2: Chlorination was performed according to the procedure for the synthesis of 3-nitrobenzyl chloride above using 3-fluoro-5-nitrobenzyl alcohol (436.2 mg, 2.55 mmol, 1.0 equiv), NEt₃ (0.64 mL, 4.59 mmol, 1.8 equiv), CH₂Cl₂ (5.4 mL) and SOCl₂ (0.22 mL, 3.06 mmol, 1.2 equiv). Work-up and purification as described above gave the title compound as an orange liquid (405.0 mg, 84% yield). ¹H NMR (500 MHz, CDCl₃): δ 8.10–8.08 (m, 1H), 7.90 (dt, J = 8.1, 2.2 Hz, 1H), 7.51–7.48 (m, 1H), 4.64 (d, J = 0.6 Hz, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 162.5 (d, J_{C-F} = 252.1 Hz), 149.3 (d, J_{C-F} = 9.2 Hz), 141.5 (d, J_{C-F} = 8.1 Hz), 121.9 (d, J_{C-F} = 22.2 Hz), 119.3 (d, J_{C-F} = 2.8 Hz), 111.4 (d, J_{C-F} = 26.3 Hz), 44.1 (d, J_{C-F} = 1.8 Hz) ppm.

3.2. Benzylation

- Most of the required aldehyde substrates (**7**, **8**, **9a–k,m**) were prepared according to the benzylation procedure below (*General Procedure D*). The reaction conditions for the synthesis of aldehyde **9l** were different (entry 14), and thus a specific scheme and procedure is given at the end of this section.



Entry	Starting Aldehyde	R	X	Y	Product	Yield (%)
1	S4a	H	NTs	H	7	43
2	S4a	H	NTs	F	8	31
3	S4a	H	NTs	NO ₂	9a	89
4	13	5-Me	NTs	NO ₂	9b	79
5	S4c	5-OMe	NTs	NO ₂	9c	71
6	S4d	5-Br	NTs	NO ₂	9d	84
7	S4e	5-Cl	NTs	NO ₂	9e	81
8	S4f	5-F	NTs	NO ₂	9f	79
9	S4g	4-Cl	NTs	NO ₂	9g	54
10	S4h	3-Cl	NTs	NO ₂	9h	55
11	S4i	6-Cl	NTs	NO ₂	9i	17
12	S4j	4-CO ₂ Me	NTs	NO ₂	9j	45
13	S4k	4-morpholino	NTs	NO ₂	9k	52
14 ^a	S4l	H	NBz	NO ₂	9l	34
15 ^b	S4m	H	O	NO ₂	9m	77

^a Using NaH (3.0 equiv) in THF at 0 °C to rt

^b Using 2.0 equiv of the aldehyde and Cs₂CO₃ (1.0 equiv) instead of NEt₃

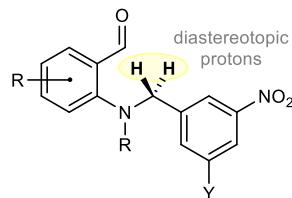
Note: A detailed experimental procedure for the larger scale example (product **9b**, 5 mmol scale) is also given in Section 6.

General Procedure D (Benzylation): In a round bottom flask equipped with condenser was loaded the appropriate nitro-substituted benzyl chloride (1.0 equiv), the corresponding aldehyde (1.0–1.2 equiv) and Et₃N

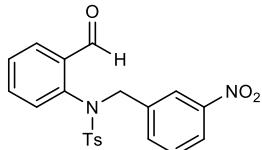
(1.5–1.8 equiv) in anhydrous MeCN (0.5 M). The resultant reaction mixture was heated to reflux and allowed to stir typically overnight. After which time, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was then diluted with water (equal to reaction volume), extracted thrice using CH_2Cl_2 , then the combined organic phases were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was then purified via recrystallisation or flash column chromatography to reveal the corresponding *N*-benzylated product **9a–k,m**.

3.2.1. Note on NMR Spectra of Amino-Linked Substrates

- All tethered substrates bearing an amino linker (**7**, **8**, **9a–l**) exhibited diastereotopic signals in their ^1H NMR spectra from the methylene protons (spectra provided in Section 9). No other broadening or splitting/doubling of signals was observed in the ^1H or ^{13}C NMR spectra. X-ray crystal structures of **9a** and **9j** (see below) showed significant sp^3 -character to the adjacent nitrogen linker. Therefore, we tentatively attribute the observed diastereotopic splitting to either a slow (or restricted) inversion of the nitrogen atom on the NMR timescale, or alternatively, an atropisomeric N–aryl bond (at least on the NMR timescale).

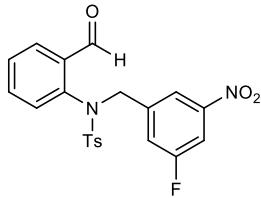


N-(3-Nitrobenzyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (**7**)



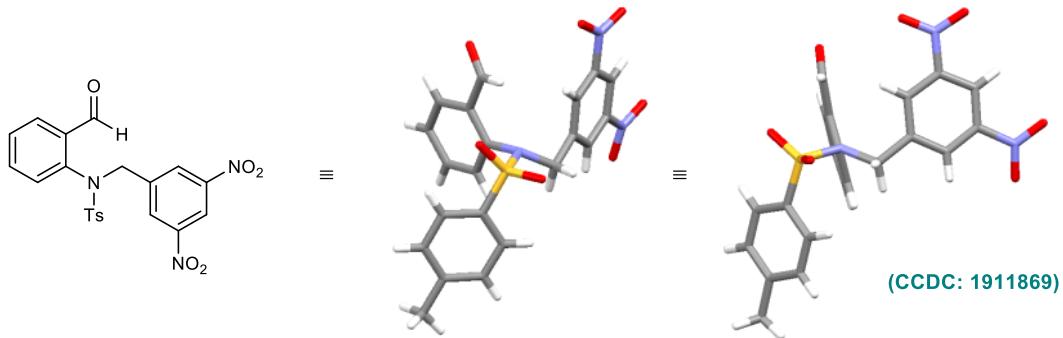
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (137.0 mg, 43% yield). **Mp:** 140–142 °C. **TLC:** $R_F = 0.30$ (30:70 EtOAc/*n*-hexane). **^1H NMR (500 MHz, CDCl_3):** δ 10.11 (d, $J = 0.8$ Hz, 1H), 8.09 (ddd, $J = 8.2, 2.3, 1.1$ Hz, 1H), 7.89 (t, $J = 2.0$ Hz, 1H), 7.87 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.51–7.46 (m, 2H), 7.41 (tt, $J = 7.4, 1.0$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), 6.81 (dd, $J = 8.0, 1.2$ Hz, 1H), 5.25 (bd, $J = 14.0$ Hz, 1H), 4.44 (bd, $J = 13.9$ Hz, 1H), 2.48 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ 189.4, 148.3, 144.9, 140.7, 137.2, 135.8, 135.2, 134.5, 134.4, 130.09, 130.06, 129.2, 129.1, 128.1, 128.0, 123.9, 123.5, 55.1, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 1687, 1596, 1528, 1452, 1349, 1273, 1162, 1089, 1045, 897, 866, 808, 774, 726, 664, 611, 566, 527$. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_5\text{SNa} [\text{M} + \text{Na}]^+$ 433.0834, found 433.0835.

***N*-(3-Fluoro-5-nitrobenzyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (8)**



This compound was prepared using *General Procedure D* to afford the title compound as a white solid (108.7 mg, 31% yield). **Mp:** 135–137 °C. **TLC:** R_F = 0.31 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 10.11 (d, J = 0.8 Hz, 1H), 7.90 (dd, J = 7.6, 1.8 Hz, 1H), 7.83–7.76 (m, 2H), 7.55–7.39 (m, 5H), 7.33 (d, J = 8.0 Hz, 2H), 6.84 (dd, J = 7.8, 1.3 Hz, 1H), 5.25–5.07 (bm, 1H), 4.58–4.43 (bm, 1H), 2.48 (s, 3H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CDCl_3):** δ (one ArC ‘missing’ due to overlap) 189.1, 162.5 (d, J = 253.2 Hz), 149.2 (d, J = 8.7 Hz), 145.0, 140.5, 139.6 (d, J = 7.2 Hz), 135.7, 134.6, 134.2, 130.1, 129.6, 129.4, 128.1, 122.2 (d, J = 22.0 Hz), 119.6 (d, J = 3.5 Hz), 111.5 (d, J = 26.5 Hz), 54.9 (d, J = 1.5 Hz), 21.8 ppm. **$^{19}\text{F NMR}$ (376 MHz, CDCl_3):** δ –107.2 ppm. **IR (ATR, cm^{–1}):** $\tilde{\nu}$ = 3092, 1688, 1595, 1538, 1447, 1340, 1281, 1213, 1194, 1157, 1091, 1013, 970, 891, 843, 815, 777, 743, 727, 661, 644, 573. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{18}\text{FN}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 429.0920, found 429.0933.

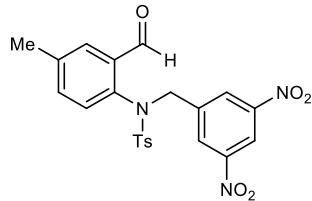
***N*-(3,5-Dinitrobenzyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (9a)**



This compound was prepared using *General Procedure D* to afford the title compound as a white solid (1.683 g, 89% yield). **Mp:** 156–160 °C. **TLC:** R_F = 0.24 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.10 (s, 1H), 8.92 (s, 1H), 8.43 (d, J = 2.0 Hz, 2H), 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.53–7.52 (m, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 13.5 Hz, 1H), 4.70 (d, J = 13.0 Hz, 1H), 2.49 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 188.8, 148.8, 145.3, 140.3, 140.1, 135.4, 134.8, 133.9, 130.19, 130.16, 129.6, 128.8, 128.4, 128.1, 118.8, 54.7, 21.8 ppm. **IR (ATR, cm^{–1}):** $\tilde{\nu}$ = 3310, 3085, 2982, 1691, 1595, 1495, 1339, 1270, 1161, 1089, 909, 822, 808, 777, 664, 569. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_7\text{SNa}$ $[\text{M} + \text{Na}]^+$ 478.06849, found 478.06776. **CCDC:** 1911869.

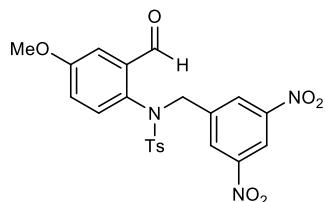
Crystals of **9a** suitable for X-ray analysis were obtained by the following solvent-diffusion method: **9a** (3–5 mg) was dissolved in ~0.7 mL of CH_2Cl_2 in a 2 mL glass vial. This vial was placed (uncapped) inside an empty 12 mL glass vial and then pentane (~5 mL) was carefully added to the outer vial (avoiding spill-over into the smaller vial). The outer vial was sealed with a screw cap and left to stand at room temperature for 1–5 days. The resulting crystals were obtained by rinsing them out of the smaller vial onto filter paper with MeOH (5–10 mL) and allowing them to dry in air.

N-(3,5-Dinitrobenzyl)-N-(2-formyl-4-methylphenyl)-4-methylbenzenesulfonamide (9b)



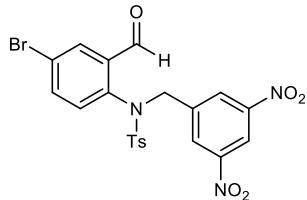
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.814 g, 79% yield). **TLC:** R_F = 0.29 (30:70 $\text{EtOAc}/n\text{-hexane}$). **Mp:** 180–183 °C. **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.06 (s, 1H), 8.91 (d, J = 2.0 Hz, 1H), 8.43 (s, 2H), 7.68 (s, 1H), 7.53 (d, J = 7.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.34–7.31 (m, 1H), 6.76 (d, J = 14.5 Hz, 1H), 5.21 (d, J = 14.5 Hz, 1H), 4.66 (d, J = 14.5 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 189.1, 148.7, 145.1, 140.4, 140.1, 137.5, 135.5, 134.9, 134.0, 130.4, 130.1, 128.9, 128.1 (2 \times ArC), 118.7, 54.7, 21.8, 21.2 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3086, 2866, 1688, 1540, 1340, 1087, 942, 857, 696, 666, 571. **HRMS (ESI):** calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_7\text{SNa}$ $[\text{M} + \text{Na}]^+$ 492.0841, found 492.0858.

N-(3,5-Dinitrobenzyl)-N-(2-formyl-4-methoxyphenyl)-4-methylbenzenesulfonamide (9c)



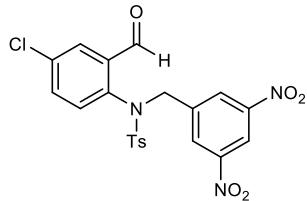
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.729 g, 71% yield). **Mp:** 215–217 °C. **TLC:** R_F = 0.25 (30:70 $\text{EtOAc}/n\text{-hexane}$). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 10.02 (s, 1H), 8.93 (t, J = 2.0 Hz, 1H), 8.42 (d, J = 2.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.35–7.33 (m, 3H), 7.02 (dd, J = 8.8, 3.2 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.21 (d, J = 14.4 Hz, 1H), 4.62 (d, J = 14.8 Hz, 1H), 3.84 (s, 3H), 2.48 (s, 3H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CDCl_3):** δ 188.7, 160.0, 148.8, 145.1, 140.4, 136.5, 134.1, 132.7, 130.2, 129.6, 128.9, 128.1, 121.9, 118.8, 112.5, 56.0, 55.0, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3118, 3089, 2973, 2866, 1693, 1597, 1539, 1495, 1341, 1277, 1161, 853, 699, 573. **HRMS (ESI):** calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_8\text{SNa}$ $[\text{M} + \text{Na}]^+$ 508.0791, found 508.0793.

***N*-(4-Bromo-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9d)**



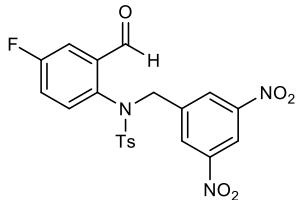
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.819 g, 84% yield). **Mp:** 171–172 °C. **TLC:** R_F = 0.36 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.07 (s, 1H), 8.94 (s, 1H), 8.44 (d, J = 1.5 Hz, 2H), 8.01 (s, 1H), 7.62 (dd, J = 8.5, 2.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.5 Hz, 1H), 5.23 (d, J = 13.5 Hz, 1H), 4.61 (d, J = 13.5 Hz, 1H), 2.50 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 187.3, 148.9, 145.6, 139.9, 139.0, 137.6, 136.7, 133.5, 133.0, 130.3, 129.6, 128.7, 128.1, 124.0, 119.0, 54.6, 21.9 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3122, 3089, 2866, 1696, 1538, 1475, 1343, 1253, 1161, 1089, 846, 723, 680, 567. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{16}({}^{79}\text{Br})\text{N}_3\text{O}_7\text{SNa}$ [M + Na]⁺ 555.9790, found 555.9799.

***N*-(4-Chloro-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9e)**



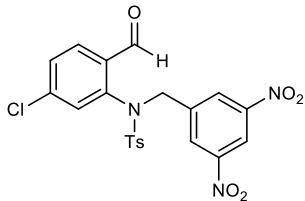
This compound was prepared using *General Procedure D* to afford the title compound as a yellow solid (0.832 g, 81% yield). **Mp:** 180–182 °C. **TLC:** R_F = 0.30 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.07 (s, 1H), 8.93 (t, J = 2.0 Hz, 1H), 8.44 (d, J = 2.0 Hz, 2H), 7.85 (d, J = 2.5 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.47 (dd, J = 8.5, 2.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.24 (d, J = 14.0 Hz, 1H), 4.62 (d, J = 13.0 Hz, 1H), 2.49 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 187.4, 148.8, 145.6, 140.0, 138.5, 136.6, 136.1, 134.6, 133.4, 130.3, 129.9, 129.4, 128.7, 128.1, 119.0, 54.6, 21.9 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3093, 2905, 1689, 1539, 1447, 1337, 1211, 1161, 1090, 909, 857, 725, 630, 570. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{15}\text{ClN}_3\text{O}_7\text{S}$ [M – H][–] 488.03247, found 488.03289.

***N*-(3,5-Dinitrobenzyl)-*N*-(4-fluoro-2-formylphenyl)-4-methylbenzenesulfonamide (9f)**



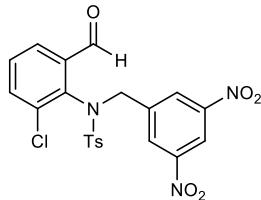
This compound was prepared using *General Procedure D* to afford the title compound as a yellowish solid (0.828 g, 79% yield). **Mp:** 170–174 °C. **TLC:** R_F = 0.30 (30:70 EtOAc/n-hexane). **^1H NMR (500 MHz, CDCl_3):** δ 10.04 (d, J = 2.8 Hz, 1H), 8.93 (t, J = 2.1 Hz, 1H), 8.43 (d, J = 2.1 Hz, 2H), 7.56 (dd, J = 8.2, 3.1 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.21 (ddd, J = 8.2, 7.2, 3.1 Hz, 1H), 6.85 (dd, J = 8.8, 4.4 Hz, 1H), 5.24 (d, J = 14.9 Hz, 1H), 4.63 (d, J = 14.8 Hz, 1H), 2.49 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ 187.5, 162.4 (d, $J_{\text{C}-\text{F}}$ = 252.2 Hz), 148.7, 145.5, 140.0, 137.5 (d, $J_{\text{C}-\text{F}}$ = 6.9 Hz), 136.1 (d, $J_{\text{C}-\text{F}}$ = 3.4 Hz), 133.6, 130.32 (d, $J_{\text{C}-\text{F}}$ = 7.7 Hz), 130.31, 128.8, 128.1, 121.9 (d, $J_{\text{C}-\text{F}}$ = 23.2 Hz), 118.4, 116.4 (d, $J_{\text{C}-\text{F}}$ = 23.3 Hz), 54.9, 21.8 ppm. **^{19}F NMR (376 MHz, CDCl_3):** δ -108.2 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ 3097, 2876, 1691, 1541, 1488, 1342, 1261, 1151, 1057, 883, 771, 674, 577, 535. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_7\text{FS}$ [M – H][–] 472.0615, found 472.0622.

***N*-(5-Chloro-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9g)**



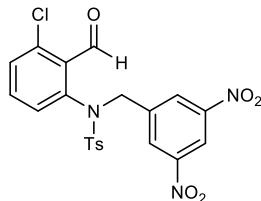
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.552 g, 54% yield). **Mp:** 197–200 °C. **TLC:** R_F = 0.36 (30:70 EtOAc/n-hexane). **^1H NMR (500 MHz, CDCl_3):** δ 10.06 (s, 1H), 8.94 (s, 1H), 8.45 (d, J = 2.0 Hz, 2H), 7.86 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.46 (dd, J = 8.3, 1.9 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 6.83 (d, J = 1.9 Hz, 1H), 5.21 (bs, 1H), 4.61 (bs, 1H), 2.51 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 187.6, 148.9, 145.7, 141.4, 140.7, 139.9, 133.9, 133.4, 131.2, 130.3, 130.1, 128.7, 128.5, 128.2, 119.0, 54.7, 21.9 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3112, 3086, 2872, 1691, 1539, 1344, 1154, 1086, 915, 725, 668, 545. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{15}\text{ClN}_3\text{O}_7\text{S}$ [M – H][–] 488.03247, found 488.03285.

***N*-(2-Chloro-6-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9h)**



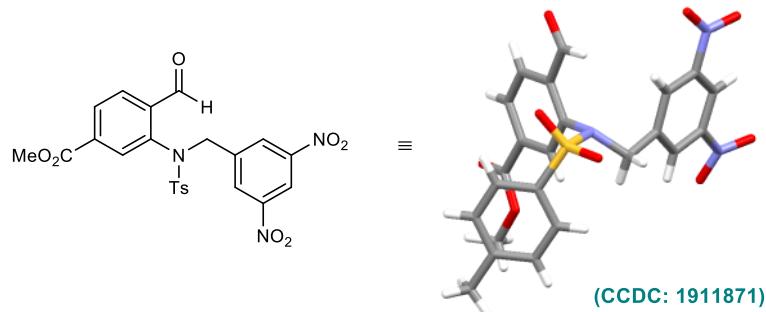
This compound was prepared using *General Procedure D* to afford the title compound as a yellow solid (0.300 g, 55% yield). **Mp:** 189–191 °C. **TLC:** R_F = 0.33 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 9.75 (s, 1H), 8.97 (d, J = 1.5 Hz, 1H), 8.44 (d, J = 1.5 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.67–7.63 (m, 3H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 5.29 (d, J = 15.5 Hz, 1H), 4.83 (d, J = 15.5 Hz, 1H), 2.49 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 188.2, 148.6, 145.2, 139.6, 138.1, 136.6, 136.5, 135.9, 134.8, 130.9, 130.3, 129.7, 128.3, 127.8, 119.1, 53.4, 21.9 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3095, 2879, 1685, 1537, 1449, 1343, 1243, 1158, 1086, 918, 856, 727, 658, 565. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{16}\text{ClN}_3\text{O}_7\text{SNa}$ [M + Na]⁺ 512.0295, found 512.0284.

***N*-(3-Chloro-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9i)**



This compound was prepared using *General Procedure D* to afford the title compound as a yellow solid (0.171 g, 17% yield). **Mp:** 192–195 °C. **TLC:** R_F = 0.27 (30:70 EtOAc/n-hexane). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 10.15 (s, 1H), 8.94 (t, J = 2.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.46 (dd, J = 8.0, 1.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 7.6 Hz, 1H), 4.96 (s, 2H), 2.47 (s, 3H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CDCl_3):** δ 189.3, 148.7, 145.0, 140.7, 138.7, 137.4, 134.8, 133.9, 133.4, 131.7, 130.1, 129.3, 129.1, 128.0, 118.6, 55.2, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3121, 3088, 2918, 2772, 1702, 1585, 1449, 1341, 1156, 1087, 905, 828, 726, 657, 578. **HRMS (ESI):** calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_7\text{S}$ [M – H][–] 488.03247, found 488.03282.

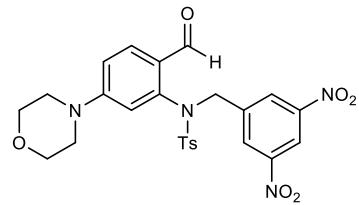
N-(5-Carbomethoxy-2-formylphenyl)-N-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9j)



This compound was prepared using *General Procedure D* to afford the title compound as a pale yellow solid (173.1 mg, 45% yield). **Mp:** 162–164 °C. **TLC:** R_F = 0.26 (35:65 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 10.21 (d, J = 0.8 Hz, 1H), 8.91 (t, J = 2.1 Hz, 1H), 8.44 (d, J = 2.1 Hz, 2H), 8.08 (ddd, J = 8.1, 1.6, 0.8 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.52–7.49 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 5.37–5.21 (bm, 1H), 4.72–4.56 (bm, 1H), 3.92 (s, 3H), 2.50 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 188.2, 164.9, 148.8, 145.7, 140.5, 139.9, 138.5, 135.6, 133.3, 130.3, 130.1, 129.9, 128.84, 128.77, 128.1, 118.9, 54.4, 53.0, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3110, 2865, 1731, 1687, 1596, 1538, 1433, 1343, 1274, 1203, 1162, 1087, 1056, 972, 913, 835, 807, 766, 723, 667, 569, 544. **HRMS (ESI):** calcd for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_9\text{SNa}$ $[\text{M} + \text{Na}]^+$ 536.0740, found 536.0742. **CCDC:** 1911871.

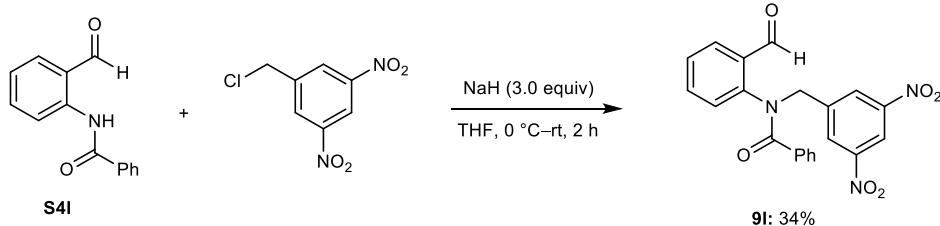
Crystals of **9j** suitable for X-ray analysis were obtained by the same crystallization procedure as described for **9a**.

N-(2-Formyl-5-morpholinophenyl)-N-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9k)



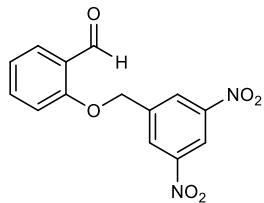
This compound was prepared using *General Procedure D* to afford the title compound as a pale yellow solid (129.1 mg, 52% yield). **Mp:** 188–190 °C. **TLC:** R_F = 0.35 (5:95 EtOAc/CH₂Cl₂). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 9.57 (s, 1H), 8.91 (t, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 2H), 7.70 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.85 (dd, J = 8.9, 2.5 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 5.07–4.85 (m, 2H), 3.80 (t, J = 4.9 Hz, 4H), 3.26–3.16 (m, 4H), 2.46 (s, 3H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CDCl_3):** δ 187.2, 155.1, 148.7, 144.9, 141.7, 141.2, 134.9, 133.1, 129.9, 128.8, 128.1, 124.6, 118.5, 114.7, 113.8, 66.3, 55.2, 47.0, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 2855, 1654, 1593, 1539, 1450, 1345, 1251, 1224, 1161, 1109, 1088, 1047, 955, 892, 865, 808, 769, 725, 703, 662, 577, 542, 521, 486. **HRMS (ESI):** calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_8\text{SNa}$ $[\text{M} + \text{Na}]^+$ 563.1213, found 563.1213.

2-((Benzoyl)(3,5-dinitrobenzyl)amino)benzaldehyde (**9I**)



To a solution of NaH (60% in mineral oil, 53.3 mg, 1.33 mmol, 3.0 equiv) in anhydrous THF (4.4 mL) was added aldehyde **S4I** (99.9 mg, 0.44 mmol, 1.0 equiv) at 0 °C. The solution was left to stir at 0 °C for 10 min, before 3,5-dinitrobenzyl chloride (96.3 mg, 0.44 mmol, 1.0 equiv) was added, and the reaction mixture left to stir at room temperature for 2 h. The reaction mixture was quenched with saturated NH₄Cl, the aqueous layer extracted with ethyl acetate (\times 3), and the combined organic phases dried over Na₂SO₄. The solvent was evaporated under reduced pressure to yield the crude product, which was purified via flash column chromatography (20% ethyl acetate:*n*-hexane) to yield aldehyde **9I** as an orange solid in 34% yield (61.8 mg, 0.15 mmol). **Mp:** 157–159 °C. **TLC:** R_F = 0.26 (30:70 EtOAc/*n*-hexane). **¹H NMR (500 MHz, CDCl₃)** δ: 9.85 (s, 1H), 8.93 (s, 1H), 8.54 (s, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.56 (td, *J* = 7.6, 1.7 Hz, 1H), 7.46 (app t, *J* = 7.6 Hz, 1H), 7.27–7.20 (m, 3H), 7.16–7.12 (m, 3H), 5.51 (d, *J* = 15.1 Hz, 1H), 5.02 (d, *J* = 14.9 Hz, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃)** δ: 189.6, 171.1, 148.5, 142.8, 141.2, 135.3, 134.4, 134.2, 131.9, 130.7, 130.2, 129.2, 128.9, 128.7, 128.1, 118.3, 53.8 ppm. **IR (ATR, cm⁻¹)**: $\tilde{\nu}$ = 1701, 1633, 1531, 1341, 983, 910, 723, 574. **HRMS (ESI)**: calcd for C₂₁H₁₅N₃O₆ [M – H][–] 404.0896, found 404.0883.

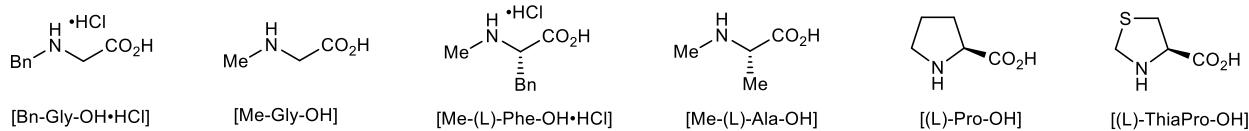
2-((3,5-Dinitrobenzyl)oxy)benzaldehyde (**9m**)



This compound was prepared using *General Procedure D* with the following modifications: 2.0 equiv of the aldehyde (commercial salicylaldehyde) was used, Cs₂CO₃ (1.0 equiv) was used (instead of NEt₃) and no filtration was performed after cooling to room temperature before concentration and aqueous work-up. The crude product was recrystallised from MeOH to afford the title compound as a white solid (0.272 g, 77% yield). **Mp:** 173–176 °C. **TLC:** R_F = 0.47 (CH₂Cl₂). **¹H NMR (400 MHz, CDCl₃)**: δ 10.54 (s, 1H), 9.06 (s, 1H), 8.71 (s, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 5.40 (s, 2H) ppm. **¹³C NMR (100 MHz, CDCl₃)**: δ 188.9, 159.5, 149.0, 140.8, 136.2, 130.2, 127.2, 125.5, 122.5, 118.8, 112.7, 68.4 ppm. **IR (ATR, cm⁻¹)**: $\tilde{\nu}$ = 3110, 2890, 2770, 1685, 1597, 1534, 1492, 1344, 1287, 1186, 1154, 908, 870, 763, 728, 649. **HRMS (ESI)**: calcd for C₁₄H₁₁N₂O₆ [M + H]⁺ 303.0617, found 303.0608.

4. Synthesis of Amino Acid Substrates

- The following *N*-benzyl-, *N*-methyl- and cyclic amino acid substrates were obtained commercially:

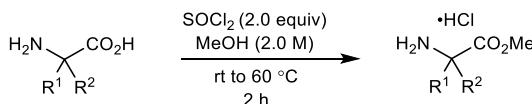


- All other *N*-benzyl- and *N*-methyl amino acid substrates were prepared in the laboratory as described below.

Note: Although three of the substrates below were synthesized from commercially available L-amino acids, we did not check whether any racemization had occurred during these synthetic sequences as this was inconsequential for this study.

4.1. Synthesis of Amino Acid Methyl Ester Starting Materials

- The required methyl ester starting materials were prepared by esterification or obtained commercially as indicated:

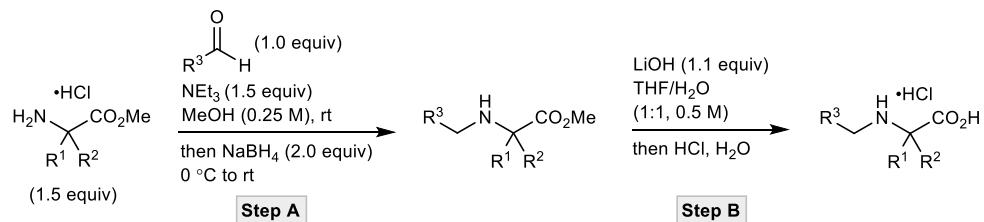


Entry	Starting Material	R ¹ , R ²	Product	Yield (%)
1	-	H, H	H-Gly-OMe·HCl	obtained commercially
2	H-L-Phe-OH	H, Bn	H-L-Phe-OMe·HCl	93
3	H-(D/L)-Phg-OH	H, Ph	H-(D/L)-Phg-OMe·HCl	98
4	H-L-Val-OH	H, <i>i</i> -Pr	H-L-Val-OMe·HCl	92
5	-	H,	H-L-His-OMe·2HCl	obtained commercially
6	H-Aib-OH	Me, Me	H-Aib-OMe·HCl	95

4.1.1. Esterification procedure: To a suspension of the amino acid (5.00 mmol, 1.0 equiv) in reagent grade MeOH (2.5 mL) at room temperature under air was added cautiously dropwise over 5 min neat SOCl₂ (0.73 mL, 10.00 mmol, 2.0 equiv) [note: addition is exothermic]. After complete addition, the mixture was heated at 60 °C open to the air for 2 h during which time the suspension turned to a homogenous solution (a further 0.5 mL of MeOH was also added during heating to rinse any deposited solids back in to the reaction solution). The mixture was then concentrated under reduced pressure. The residue was treated with Et₂O (5 mL) and the resulting precipitate/solid was broken up with a spatula, collected and washed with Et₂O (3×10 mL). Drying under vacuum gave the amino ester hydrochloride salts as white solids in the yields given above.

4.2. Synthesis of *N*-Benzylated Amino Acids

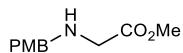
- The required *N*-benzylated amino acids were prepared from the corresponding amino esters by reductive alkylation with benzaldehydes, followed by ester saponification, according to the scheme below. The final products were isolated by trituration (various methods described further on) – differing solubility profiles resulted in variable isolated yields during this step (B).



Entry	Starting Material	R ¹ , R ² , R ³	Step A Yield (%) ^a	Step B Yield (%)	Product
1	H-Gly-OMe·HCl	H, H, 4-OMePh	68	79	PMB-Gly-OH·HCl
2	H-L-Phe-OMe·HCl	H, Bn, Ph	82	38	Bn-L-Phe-OH·HCl
3	H-(D/L)-Phg-OMe·HCl	H, Ph, Ph	79	70	Bn-(D/L)-Phg-OH·HCl
4	H-Aib-OMe·HCl	Me, Me, Ph	78	55	Bn-Aib-OH·HCl

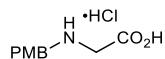
^a Yield based on aldehyde (R³CHO) used for the reductive alkylation.

N-(4-Methoxybenzyl)glycine hydrochloride [PMB-Gly-OH·HCl]



Step A [PMB-Gly-OMe]: To a solution of H-Gly-OMe·HCl (1.883 g, 15.00 mmol, 1.5 equiv) in reagent grade MeOH (40 mL) under N₂ was added NEt₃ (2.09 mL, 15.00 mmol, 1.5 equiv) followed by 4-methoxybenzaldehyde (1.22 mL, 10.00 mmol, 1.0 equiv) and the mixture was stirred at room temperature for 16 h. The mixture was cooled in an ice bath and solid NaBH₄ (756.6 mg, 20.00 mmol, 2.0 equiv) was added portionwise over 10 min under a positive pressure of N₂ (H₂ evolution observed). After complete addition, the mixture was allowed to warm to room temperature with stirring over 2.5 h. After re-cooling in an ice bath, 2 M aqueous HCl (20 mL, 40 mmol) was slowly added. Most of the methanol was then removed under reduced pressure (total volume reduced to ~30 mL). The solution was diluted with water (30 mL) and washed twice with Et₂O (50 mL, then 30 mL). The aqueous phase was basified to pH 9–10 by the addition of solid Na₂CO₃ and the product freebase was extracted with Et₂O (2 × 60 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to give PMB-Gly-OMe (1.43 g, 68%, based on 4-methoxybenzaldehyde) as a pale yellow, cloudy oil. **TLC:** R_F = 0.26 (60:40 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.24 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 2H), 3.73 (s, 3H), 3.41 (s, 2H), 1.77 (bs, 1H) ppm.

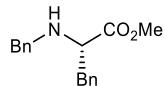
- Note that the above reaction can be performed under air with equal efficiency (see examples below for *Step A*).



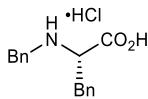
Step B [PMB-Gly-OH·HCl]: To a solution of PMB-Gly-OMe (1.42 g, 6.79 mmol, 1.0 equiv) in reagent grade THF (8.5 mL) was added water (8.5 mL) and solid LiOH (178.8 mg, 7.46 mmol, 1.1 equiv) and the mixture was stirred under air at room temperature for 70 min. The solvents were removed under reduced pressure and the residue was treated with 4 M aqueous HCl (5 mL, 20.00 mmol). The solution was again concentrated under reduced pressure. To remove residual water, MeCN (50 mL) was added and the solvent was again removed under reduced pressure (this process of adding MeCN and concentrating was performed twice). The resulting white solid was further dried under high vacuum. To this was added *i*-PrOH (30 mL) and the suspension was sonicated for 1 min, then stirred at room temperature for 10 min. The solid was collected by gravity filtration, washed with *i*-PrOH (10 mL) and Et₂O (30 mL) and dried to give PMB-Gly-OH·HCl (1.244 g, 79%) as a white solid. ¹H NMR (500 MHz, CD₃OD): δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.20 (s, 2H), 3.88 (s, 2H), 3.82 (s, 3H) ppm. ¹³C NMR (125 MHz, CD₃OD): δ 168.8, 162.3, 132.7, 123.9, 115.6, 55.8, 51.6, 47.4 ppm.

- Note that this reaction produces ‘NMR silent’ LiCl as a stoichiometric by-product. Therefore, trituration of the crude product with *i*-PrOH was performed to remove LiCl from the otherwise pure product.

N-Benzyl-(S)-phenylalanine hydrochloride [Bn-L-Phe-OH·HCl]

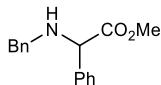


Step A [Bn-L-Phe-OMe]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe (except that the entire reaction was performed under air) using H-L-Phe-OMe·HCl (1.004 g, 4.66 mmol, 1.5 equiv), MeOH (12.4 mL), NEt₃ (0.65 mL, 4.66 mmol, 1.5 equiv), benzaldehyde (0.32 mL, 3.10 mmol, 1.0 equiv), NaBH₄ (234.8 mg, 6.21 mmol, 2.0 equiv) and quenching with 4 M aqueous HCl (3.9 mL, 15.6 mmol). In this case, work-up as described above gave a mixture of the product (Bn-L-Phe-OMe) and excess amine starting material (H-L-Phe-OMe) due to the lower volatility/higher organic solubility of the starting amine freebase (compared with H-Gly-OMe above). Flash chromatography (21.5 g silica, 30:70 EtOAc/*n*-hexane) gave Bn-L-Phe-OMe (682.1 mg, 82%, based on benzaldehyde) as a pale yellow oil. TLC: R_F = 0.57 (25:75 EtOAc/*n*-hexane).

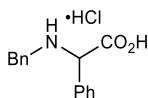


Step B [Bn-L-Phe-OH·HCl]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OH·HCl using Bn-L-Phe-OMe (682.1 mg, 2.53 mmol, 1.0 equiv), THF (2.5 mL), water (2.5 mL) and LiOH (66.7 mg, 2.79 mmol, 1.1 equiv) with a 4 h reaction time, followed by the addition of 4 M aqueous HCl (2.0 mL, 8.0 mmol). Work-up as described above gave the product as a white solid containing the LiCl by-product. In this case, the product could not be effectively purified by trituration with *i*-PrOH (~8 mL) due to its higher solubility in this solvent (only 19% isolated yield was obtained using this method). Therefore, the entire sample was recovered and concentrated. CH₂Cl₂ (60 mL) was added and the suspension was sonicated at 30 °C for 20 min to partially dissolve the desired product (LiCl is insoluble in CH₂Cl₂). The suspension was filtered and the undissolved solids were again subjected to the sonication procedure with CH₂Cl₂. The combined filtrates were concentrated to give a LiCl-free sample of Bn-L-Phe-OH·HCl (282.0 mg, 38%) as a white solid. **¹H NMR (500 MHz, CD₃OD):** δ 7.47–7.45 (m, 5H), 7.38–7.27 (m, 5H), 4.23 (d, *J* = 3.1 Hz, 2H), 4.21–4.16 (m, 1H), 3.36–3.31 (m, 1H, overlapping with CD₂HOD), 3.24 (dd, *J* = 14.3, 7.5 Hz, 1H) ppm. **¹³C NMR (100 MHz, CD₃OD):** δ 170.6, 135.5, 132.0, 131.3, 130.9, 130.5, 130.3, 130.0, 128.9, 61.9, 51.6, 36.8 ppm.

(±)-N-Benzyl-2-phenylglycine hydrochloride [Bn-(D/L)-Phg-OH·HCl]



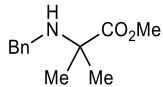
Step A [Bn-(D/L)-Phg-OMe]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe (except that the entire reaction was performed under air) using H-(D/L)-Phg-OMe·HCl (988.4 mg, 4.90 mmol, 1.5 equiv), MeOH (13.1 mL), NEt₃ (0.68 mL, 4.90 mmol, 1.5 equiv), benzaldehyde (0.33 mL, 3.27 mmol, 1.0 equiv), NaBH₄ (247.2 mg, 6.54 mmol, 2.0 equiv) and quenching with 4 M aqueous HCl (4.2 mL, 16.8 mmol). In this case, work-up as described above gave a mixture of the product (Bn-(D/L)-Phg-OMe) and excess amine starting material (H-(D/L)-Phg-OMe) due to the lower volatility/higher organic solubility of the starting amine freebase (compared with H-Gly-OMe above). Flash chromatography (16.9 g silica, 30:70 EtOAc/*n*-hexane) gave Bn-(D/L)-Phg-OMe (661.1 mg, 79%, based on benzaldehyde) as a yellow oil. **TLC:** *R*_F = 0.54 (25:75 EtOAc/*n*-hexane).



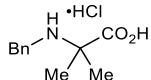
Step B [Bn-(D/L)-Phg-OH·HCl]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OH·HCl using Bn-(D/L)-Phg-OMe (661.1 mg, 2.59 mmol, 1.0 equiv), THF (2.6 mL), water (2.6 mL) and LiOH (68.2 mg, 2.85 mmol, 1.1 equiv) with a 4 h reaction time, followed by the addition of

4 M aqueous HCl (2.0 mL, 8.0 mmol). Work-up, followed by trituration with *i*-PrOH (~8 mL) as described above gave Bn-(D/L)-Phg-OH·HCl (506.7 mg, 70%) as a white solid. **¹H NMR (400 MHz, CD₃OD):** δ 7.55–7.48 (m, 5H), 7.46–7.43 (m, 5H), 5.01 (s, 1H), 4.22 (d, *J* = 13.0 Hz, 1H), 4.11 (d, *J* = 13.0 Hz, 1H) ppm. **¹³C NMR (100 MHz, CD₃OD):** δ 170.3, 132.5, 132.0, 131.4, 131.3, 130.8, 130.7, 130.3, 129.9, 64.7, 51.5 ppm.

N-Benzyl-2-aminoisobutyric acid hydrochloride [Bn-Aib-OH·HCl]



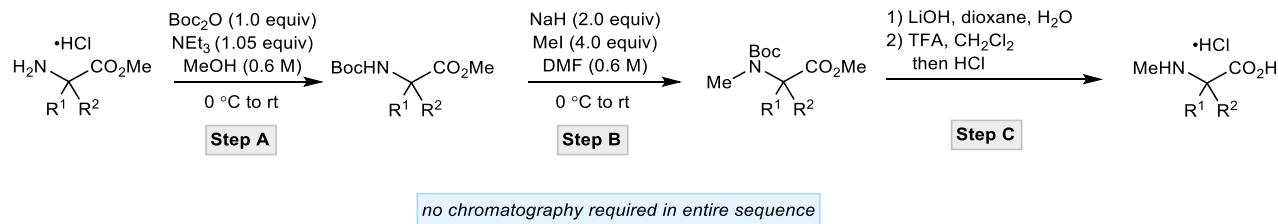
Step A [Bn-Aib-OMe]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe using H-Aib-OMe·HCl (726.9 mg, 4.73 mmol, 1.5 equiv), MeOH (12.6 mL), NEt₃ (0.66 mL, 4.73 mmol, 1.5 equiv), benzaldehyde (0.32 mL, 3.15 mmol, 1.0 equiv), NaBH₄ (238.7 mg, 6.30 mmol, 2.0 equiv) and quenching with 4 M aqueous HCl (4.0 mL, 16.0 mmol). Work-up as described above gave Bn-Aib-OMe (513.1 mg, 78%, based on benzaldehyde) as a colorless oil. **TLC:** *R*_F = 0.62 (40:60 EtOAc/n-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.36–7.29 (m, 4H), 7.27–7.22 (m, 1H), 3.74 (s, 3H), 3.62 (s, 2H), 1.80 (bs, 1H), 1.38 (s, 6H) ppm.



Step B [Bn-Aib-OH·HCl]: This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OH·HCl using Bn-Aib-OMe (508.3 mg, 2.45 mmol, 1.0 equiv), THF (2.45 mL), water (2.45 mL) and LiOH (64.6 mg, 2.70 mmol, 1.1 equiv) with a 65 h reaction time [reaction had reached completion but was not monitored during this time], followed by the addition of 4 M aqueous HCl (2.3 mL, 9.2 mmol). Work-up, followed by trituration with *i*-PrOH (~7 mL) as described above gave Bn-Aib-OH·HCl (309.4 mg, 55%) as a white solid. This compound (as the hydrochloride salt) has not been previously reported. **Mp:** 271–275 °C. **¹H NMR (500 MHz, CD₃OD):** δ 7.59–7.56 (m, 2H), 7.50–7.45 (m, 3H), 4.22 (s, 2H), 1.71 (s, 6H) ppm. **¹³C NMR (125 MHz, CD₃OD):** δ 173.5, 132.9, 131.3, 130.7, 130.2, 63.7, (CH₂ overlapping with solvent peak between 49.5–48.5), 22.6 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2722, 2565, 2394, 1751, 1562, 1454, 1396, 1196, 1152, 973, 844, 762, 742, 697, 607, 531, 499, 375. **HRMS (ESI):** calcd for C₁₁H₁₆NO₂ [M + H]⁺ 194.1181, found 194.1178.

4.3. Synthesis of *N*-Methylated Amino Acids

• The required *N*-methylated amino acids were prepared according to the scheme below. This sequence provides the products in reasonable overall yields without any requirement for chromatography or recrystallisation. An exception was *N*-methyl-2-phenylglycine hydrochloride [Me-Phg-OH·HCl] which could not be prepared by the below route because both *N*- and *C*-methylation occurred with excess NaH/MeI (see entry 4). Instead, Me-Phg-OH·HCl was prepared via Strecker chemistry as described further on.

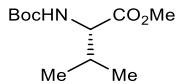


• **Note:** In entries 2 and 4, R¹ and/or R² (above) do not stay constant. Therefore, the actual structures of the intermediates and products have been drawn in the table.

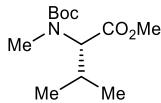
Entry	Starting Material	Step A (Yield)	Step B + C (Yield)	Product Name
1	H-L-Val-OMe·HCl	(84%)	(70%)	Me-L-Val-OH·HCl
2	H-L-His-OMe·2HCl	+ regioisomer ^a (91%) ^a	(38%) ^b	Me-L-His-OH·2HCl
3	H-Aib-OMe·HCl	(81%)	(59%)	Me-Aib-OH·HCl
4	H-(D/L)-Phg-OMe·HCl	(87%)	(69%) ^c	Me-(D/L)-(α-Me)-Phg-OH·HCl

^a Using Boc₂O (2.0 equiv) and NEt₃ (2.1 equiv). Yield is of the doubly *N*-Boc-protected intermediate as an inconsequential 4.3:1 mixture of regioisomers with respect to the regiochemistry of the imidazole *N*-Boc group (structure of major/minor regioisomer undetermined). ^b Final Boc-deprotection performed with HCl instead of TFA. ^c Both *N*- and *C*-methylation occurred with NaH/MeI giving the fully substituted product.

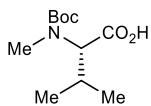
(S)-N-Methyl-valine hydrochloride [Me-L-Val-OH·HCl]



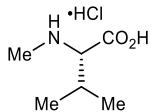
Step A [Boc-L-Val-OMe]: To a solution/suspension of H-L-Val-OMe·HCl (502.9 mg, 3.00 mmol, 1.0 equiv) and NEt₃ (0.44 mL, 3.15 mmol, 1.05 equiv) in reagent grade MeOH (2.5 mL) at 0 °C under air was added a solution of Boc₂O (654.7 mg, 3.00 mmol, 1.0 equiv) in MeOH (2.5 mL) and the mixture was allowed to warm to room temperature with stirring over 13 h. CH₂Cl₂ (5 mL) was added and stirring continued at room temperature for a further 6 h. The solvents were then removed under reduced pressure. Et₂O (20 mL) and 1 M aqueous HCl (15 mL) were added and the layers separated. The organic phase was washed with 1 M K₂CO₃ (15 mL), dried (Na₂SO₄) and concentrated to give Boc-L-Val-OMe (586.3 mg, 84%) as a colorless oil, which contained 9 mol% of unreacted Boc₂O as an impurity. This material was used in the next step without complications. **TLC:** R_F = 0.43 (15:85 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ (excluding residual Boc₂O) 5.02 (d, J = 9.3 Hz, 1H), 4.22 (dd, J = 9.1, 4.8 Hz, 1H), 3.74 (s, 3H), 2.18–2.07 (m, 1H), 1.45 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H) ppm.



Step B [(Boc,Me)-L-Val-OMe]: To a solution of Boc-L-Val-OMe (574.4 mg, 2.48 mmol, 1.0 equiv, containing 9 mol% of Boc₂O as an impurity) in anhydrous DMF (4.1 mL) in a Schlenk flask under N₂ at 0 °C was added MeI (0.62 mL, 9.93 mmol, 4.0 equiv). Under a positive pressure of N₂, unwashed NaH (198.7 mg of 60% suspension = 119.2 mg of NaH, 4.97 mmol, 2.0 equiv) was slowly added as a solid through the main neck of the flask over a period of 10 min (H₂ evolution). After complete addition, the ice bath was removed and the thick slurry was stirred at room temperature for 1 h (stirring may be impeded at first but increases when reaction begins to warm). After re-cooling in an ice bath, the reaction was quenched by the slow addition of saturated NH₄Cl (10 mL). The product was extracted with Et₂O (30 mL). The organic layer was concentrated under reduced pressure to give ‘crude’ (Boc,Me)-L-Val-OMe (547.5 mg) as a yellow oil, containing residual DMF and grease from the NaH but otherwise pure. This material was used in the next step without further purification (an overall yield is given below). **TLC:** R_F = 0.51 (15:85 EtOAc/n-hexane). **¹H NMR (400 MHz, CDCl₃):** δ (~1:1 mixture of Boc rotamers, *indicates resolved rotamers) [4.46* (d, J = 10.6 Hz) & 4.10* (d, J = 10.4 Hz), 1H in total], 3.70 (s, 3H), [2.85* (s) & 2.82* (s), 3H in total], 2.28–2.10 (m, 1H), 1.46 (s, 9H), 0.97 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H) ppm.

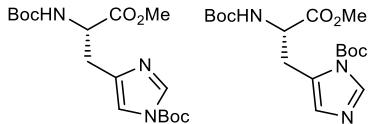


Step C [(Boc,Me)-L-Val-OH]: Part 1: saponification. A solution of ‘crude’ (Boc,Me)-L-Val-OMe (547.5 mg total, containing ≤ 2.23 mmol, 1.0 equiv) and LiOH (532.3 mg, 22.23 mmol, ≥ 10 equiv) in dioxane (6.7 mL) and water (4.4 mL) was heated at 50 °C under air for 45 min, then cooled to rt and stirred for a further 17.5 h. The reaction was cooled in an ice bath and acidified with 2 M aqueous HCl (~ 15 mL). The product was extracted with EtOAc (30 mL) and the organic extract was concentrated under reduced pressure to give the intermediate (Boc,Me)-L-Val-OH (481.1 mg).



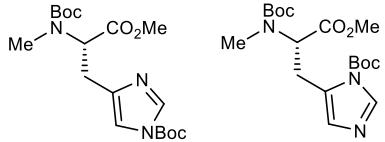
Step C [Me-L-Val-OH·HCl]: Part 2: Boc deprotection. The above (Boc,Me)-L-Val-OH (481.1 mg) was dissolved in reagent grade CH₂Cl₂ (11.2 mL) and water (0.20 mL, 11.15 mmol, ≥ 5 equiv) and TFA (1.71 mL, 22.23 mmol, ≥ 10 equiv) were added. The solution was stirred at room temperature under air for 6.5 h. The solvents were removed under reduced pressure and the residue was further dried (≥ 5 min) under high vacuum to remove residual TFA. The residue was re-dissolved in CH₂Cl₂/i-PrOH (1:1, 6 mL) and the solution was transferred to a vial of known weight. With stirring, ethereal HCl (2 M in Et₂O, 3.35 mL, 6.70 mmol) was rapidly added and the solution/suspension was stirred at room temperature for 5 min. Most of the solvent was then removed by carefully blowing a stream of air into the vial over 30 min (this method for solvent removal was chosen over rotary evaporation at 40 °C to avoid any possible formation of the isopropyl ester under the acidic conditions). After removal of residual solvent under high vacuum, a mixture of Et₂O/n-hexane (1:1, 8 mL) was added. In this case, the product precipitated as a sticky solid and could not be obtained via conventional filtration. Therefore, the solid was allowed to settle to the bottom of the vial and the supernatant liquid was carefully pipetted away. This process of adding Et₂O/n-hexane (1:1, 8 mL) and removing the supernatant liquid was repeated three times. The remaining solid was dried to give Me-L-Val-OH·HCl (293.4 mg, 70%, over Steps B and C, uncorrected for residual Boc₂O in the original starting material) as an off-white solid. **¹H NMR (400 MHz, CD₃OD):** δ 3.86 (d, *J* = 3.8 Hz, 1H), 2.75 (s, 3H), 2.35 (sep, *J* = 7.0, 3.8 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H) ppm. **¹³C NMR (100 MHz, CD₃OD):** δ 170.1, 67.9, 33.4, 30.4, 19.2, 17.5 ppm.

(S)-N-Methyl-histidine dihydrochloride [Me-L-His-OH·2HCl]



4.3:1 mixture of N-Boc regioisomers

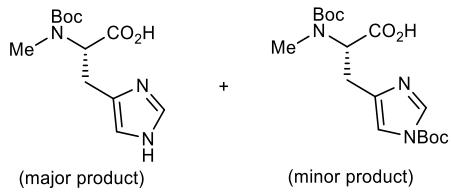
Step A [Boc-L-His(Boc)-OMe]: To a solution/suspension of H-L-His-OMe·2HCl (2.421 g, 10.00 mmol, 1.0 equiv) and NEt₃ (2.93 mL, 21.00 mmol, 2.1 equiv) in reagent grade MeOH (8.3 mL) at 0 °C under air was added a solution of Boc₂O (4.365 g, 20.00 mmol, 2.0 equiv) in MeOH (8.3 mL) and the mixture was allowed to warm to room temperature with stirring over 17.5 h. The solvent was removed under reduced pressure. Et₂O (40 mL) and water (40 mL) were added and the layers separated. The organic phase was washed with saturated NaHCO₃ (30 mL), dried (Na₂SO₄) and concentrated to give Boc-L-His(Boc)-OMe (3.379 g, 91%) as a colorless gum. Consistent with previous reports,^{S18} this material was an inconsequential 4.3:1 mixture of regioisomers with respect to the regiochemistry of the imidazole N-Boc group (structure of major/minor regioisomer undetermined). **TLC:** R_F = 0.34 [major], 0.22 [minor] (50:50 EtOAc/n-hexane). **Major regioisomer:** **¹H NMR (500 MHz, CDCl₃):** δ 7.98 (d, J = 1.3 Hz, 1H), 7.14 (d, J = 1.2 Hz, 1H), 5.71 (d, J = 8.4 Hz, 1H), 4.61–4.54 (m, 1H), 3.73 (s, 3H), 3.12–2.98 (m, 2H), 1.61 (s, 9H), 1.44 (s, 9H) ppm. **Minor regioisomer:** **¹H NMR (500 MHz, CDCl₃):** δ 8.02 (d, J = 1.1 Hz, 1H), 6.83 (s, 1H), 5.10 (d, J = 8.8 Hz, 1H), 4.67–4.61 (m, 1H), 3.73 (s, 3H), 3.41 (dd, J = 15.0, 5.3 Hz, 1H), 3.16 (dd, J = 15.0, 8.7 Hz, 1H), 1.64 (s, 9H), 1.38 (s, 9H) ppm.



11:1 mixture of N-Boc regioisomers

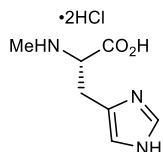
Step B [(Boc,Me)-L-His(Boc)-OMe]: This reaction was performed according to the above procedure for the synthesis of (Boc,Me)-L-Val-OMe using Boc-L-His(Boc)-OMe (3.379 g, 9.15 mmol, 1.0 equiv), anhydrous DMF (15.2 mL), MeI (2.28 mL, 36.59 mmol, 4.0 equiv) and NaH (731.7 mg of 60% suspension = 439.0 mg of NaH, 18.29 mmol, 2.0 equiv) with a 1 h reaction time. After re-cooling in an ice bath, the reaction was quenched by addition of saturated NH₄Cl (30 mL) over ~2 min. The product was extracted with Et₂O (60 mL). The organic layer was washed with brine (30 mL), dried (Na₂SO₄) and concentrated to give ‘crude’ (Boc,Me)-L-His(Boc)-OMe (2.253 g) as a yellow oil, which was an inconsequential 11:1 mixture of regioisomers with respect to the regiochemistry of the imidazole N-Boc group (structure of major/minor regioisomer undetermined). This material also contained residual DMF and grease from the NaH. NMR analysis of a portion of this sample with respect to mesitylene as internal standard, enabled the purity to be calculated at 75% w/w. This material was used in the next step without further purification (an overall yield is given below). **TLC:** R_F = 0.31 (50:50 EtOAc/n-hexane). **Major regioisomer:** **¹H NMR (500 MHz, CDCl₃):** δ (~1:1 mixture of Boc rotamers, *indicates resolved rotamers) 7.99 (s, 1H), [7.15* (s) & 7.11* (s), 1H in total], [4.95* (dd, J = 10.8, 4.9 Hz) &

4.66* (dd, $J = 10.5, 4.8$ Hz), 1H in total], 3.74 (s, 3H), 3.23 (dd, $J = 14.6, 6.2$ Hz, 1H), 3.03 (td, $J = 16.1, 15.4, 10.6$ Hz, 1H), [2.81* (s) & 2.79* (s), 3H in total], 1.62–1.59 (m, 9H), [1.43* (s) & 1.41* (s), 9H in total] ppm.



Step C [(Boc,Me)-L-His-OH]: Part 1: saponification. A solution of ‘crude’ (Boc,Me)-L-His(Boc)-OMe (2.253 g total, 75% w/w purity, containing 4.39 mmol, 1.0 equiv) and LiOH (110.4 mg, 4.61 mmol, 1.05 equiv) in dioxane (5.3 mL) and water (3.5 mL) was heated at 50 °C under air for 2 h. After cooling to room temperature, water (40 mL) and *n*-hexane (50 mL) were added. The aqueous layer was separated and washed with further *n*-hexane (20 mL) [the *n*-hexane washings were concentrated down to give 688.3 mg of a colorless oil, which contained some unreacted starting material by TLC and grease carried over from the use of NaH]. The pH of the aqueous solution was lowered to 4–5 by the dropwise addition of 2 M aqueous HCl (~2.5 mL). The aqueous layer was extracted twice with Et₂O (40 mL, then 20 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated to give the *minor product* (Boc,Me)-L-His(Boc)-OH (105.4 mg, ~6%, corrected for impurities in the starting material) as a colorless gum. **¹H NMR (400 MHz, (CD₃)₂SO):** δ (~1:1 mixture of Boc rotamers; *indicates resolved rotamers) [8.12* (s) & 8.09* (s), 1H in total], [7.26* (s) & 7.20* (s), 1H in total], [4.81* (dd, $J = 11.0, 4.6$ Hz) & 4.64* (dd, $J = 10.7, 4.5$ Hz), 1H in total], 3.06–2.88 (m, 2H), [2.69* (s) & 2.66* (s), 3H in total], 1.55 (s, 9H), [1.34* (s) & 1.29* (s), 9H in total] ppm.

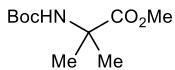
The aqueous layer (pH 4–5) was concentrated under reduced pressure to give the *major product* [(Boc,Me)-L-His-OH] (1.327 g) which was necessarily contaminated with the LiCl by-product. It was also uncertain whether this material was the HCl salt (protonated by HCl at imidazole) or the neutral zwitterion (as drawn above), although this was ultimately inconsequential. This material was used in the next step without further purification (an overall yield is given below). **¹H NMR (400 MHz, (CD₃)₂SO):** δ (~1:1 mixture of Boc rotamers; *indicates resolved rotamers) [8.17* (s) & 8.15* (s), 1H in total], 7.03 (s, 1H), [4.79* (dd, $J = 10.7, 5.0$ Hz) & 4.61* (dd, $J = 10.7, 4.7$ Hz), 1H in total], 3.15–2.97 (m, 2H), [2.69* (s) & 2.66* (s), 3H in total], [1.32* (s) & 1.28* (s), 9H in total] ppm.



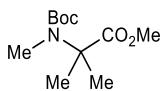
Step C [Me-L-His-OH·2HCl]: Part 2: Boc deprotection. The above impure (Boc,Me)-L-His-OH (1.32 g, containing <4.32 mmol) was dissolved in 2 M aqueous HCl (10 mL) and the solution was heated at 45 °C under air for 22 h. The mixture was concentrated under reduced pressure to dryness. To selectively dissolve the LiCl by-product carried through from above, THF (120 mL) was added and the suspension was heated at 70 °C under

air for 19 h, then sonicated at room temperature for 5 min. The supernatant liquid was decanted from the immobilized solids [the supernatant was concentrated to give 91.0 mg of a white solid; theoretical maximum amount of LiCl present = 195.4 mg]. To ensure most (or all) of the LiCl was removed, MeOH (4 mL) was added to the THF-insoluble material in the original flask and to the resulting free suspension was rapidly added Et₂O (100 mL) resulting in the product turning to a sticky white gum. The supernatant was decanted into the flask containing the original LiCl extract, and the solution was again concentrated (mass now 131.0 mg). The remaining product was re-dissolved/suspended in MeOH (8 mL) and transferred to a vial via pipette. Most of the solvent was then removed by carefully blowing a stream of air into the vial over 30 min. Further drying under high vacuum gave Me-L-His-OH·2HCl (843.8 mg, 38%, over Steps B and C) as an off-white foam. This material was ultimately found to be contaminated with 12 mol% of the corresponding methyl ester Me-L-His-OMe·2HCl. This impurity was traced back to the saponification step, in which a small percentage of (Boc,Me)-L-His-OMe (having the ester still intact but imidazole Boc group cleaved) was detected in the (Boc,Me)-L-His-OH obtained from the aqueous phase. In order to obtain a pure sample of the desired product, a portion of the sample (619.9 mg, ~2.56 mmol) was dissolved in 6 M aqueous HCl (8 mL) and the solution was heated at 100 °C under air for 19 h, then at 110 °C for 3.5 h to ensure complete ester hydrolysis (monitored by ES⁺ MS). After cooling to rt, the mixture was filtered through cotton and the filtrate was washed with EtOAc (20 mL). The aqueous layer was concentrated under reduced pressure, then the residue was transferred to a new vial in minimal MeOH (~3 mL). Blowing off the solvent as before and drying gave pure Me-L-His-OH·2HCl (570.2 mg, 92% mass recovery) as a white foam. This could be broken up into a coarse, hygroscopic powder which turned to a sticky gum when exposed to moist air. **¹H NMR (400 MHz, CD₃OD):** δ 8.94 (d, *J* = 1.4 Hz, 1H), 7.58 (d, *J* = 1.2 Hz, 1H), 4.39 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.59–3.45 (m, 2H), 2.84 (s, 3H) ppm. **¹³C NMR (100 MHz, CD₃OD):** δ 169.6, 135.7, 128.4, 119.7, 60.7, 32.6, 25.3.

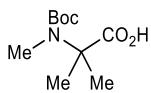
***N*-Methyl-2-aminoisobutyric acid hydrochloride [Me-Aib-OH·HCl]**



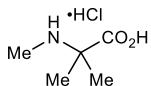
Step A [Boc-Aib-OMe]: This reaction was performed according to the above procedure for the synthesis of Boc-L-Val-OMe using H-Aib-OMe·HCl (315.0 mg, 2.05 mmol, 1.0 equiv), NEt₃ (0.30 mL, 2.15 mmol, 1.05 equiv), Boc₂O (447.6 mg, 2.05 mmol, 1.0 equiv) and MeOH (2 × 1.7 mL) with a 19 h reaction time (note that no CH₂Cl₂ was added in this case). Work-up as described above gave Boc-Aib-OMe (360.3 mg, 81%) as a white solid. **TLC:** *R*_F = 0.39 (15:85 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 5.02 (bs, 1H), 3.74 (s, 3H), 1.50 (s, 6H), 1.43 (s, 9H) ppm.



Step B [(Boc,Me)-Aib-OMe]: This reaction was performed according to the above procedure for the synthesis of (Boc,Me)-L-Val-OMe using Boc-Aib-OMe (328.3 mg, 1.51 mmol, 1.0 equiv), anhydrous DMF (2.5 mL), MeI (0.38 mL, 6.04 mmol, 4.0 equiv) and NaH (120.9 mg of 60% suspension = 72.5 mg of NaH, 3.02 mmol, 2.0 equiv) with a 3.5 h reaction time. Quenching and work-up as described above gave ‘crude’ (Boc,Me)-Aib-OMe (487.7 mg) as a pale yellow oil, containing residual DMF and grease from the NaH but otherwise pure. This material was used in the next step without further purification (an overall yield is given below). **TLC:** R_F = 0.39 (15:85 EtOAc/n-hexane). **$^1\text{H NMR}$ (400 MHz, CDCl_3):** δ 3.70 (s, 3H), 2.91 (s, 3H), 1.430 (s, 6H), 1.425 (s, 9H) ppm.



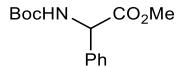
Step C [(Boc,Me)-Aib-OH]: Part 1: saponification. A solution of ‘crude’ (Boc,Me)-Aib-OMe (487.7 mg total, containing \leq 1.51 mmol, 1.0 equiv) and LiOH (361.6 mg, 15.10 mmol, \geq 10 equiv) in dioxane (4.5 mL) and water (3.0 mL) was heated at 50 °C under air for 45 min, then cooled to rt and stirred for a further 17.5 h. TLC analysis showed some unreacted starting material. Therefore, the mixture was re-heated at 50 °C for an additional 24 h. The reaction was cooled in an ice bath and acidified with 2 M aqueous HCl (\sim 10 mL). The product was extracted with EtOAc (30 mL) and the organic extract was concentrated under reduced pressure. The product was further purified by trituration: n-hexane (20 mL) was added and the undissolved solid was collected and dried to give the intermediate (Boc,Me)-Aib-OH (189.8 mg, single crop).



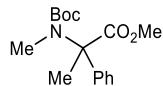
Step C [Me-Aib-OH·HCl]: Part 2: Boc deprotection. This reaction was performed according to the procedure above for the synthesis of Me-L-Val-OH·HCl using (Boc,Me)-Aib-OH (189.8 mg, 0.87 mmol, 1.0 equiv), CH_2Cl_2 (4.4 mL), water (78 μ L, 4.33 mmol, \geq 5 equiv) and TFA (0.67 mL, 8.76 mmol, \geq 10 equiv). Work-up, then treatment with ethereal HCl (2 M in Et_2O , 1.31 mL, 2.61 mmol) and removal of the solvents with air as described above gave Me-Aib-OH·HCl (137.7 mg, 59%, over Steps B and C) as a light pink solid. **$^1\text{H NMR}$ (400 MHz, CD_3OD):** δ 2.68 (s, 3H), 1.59 (s, 6H) ppm. **$^{13}\text{C NMR}$ (100 MHz, CD_3OD):** δ 173.6, 62.7, 28.4, 21.8 ppm.

- In this case, further purification of the final product by trituration with Et_2O /n-hexane (1:1, 8 mL) was not required because trituration had been performed in the previous saponification step (thus removing the grease carried over from the NaH).

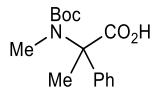
(\pm)-*N*-Methyl-2-methyl-2-phenylglycine hydrochloride [Me-(D/L)-(α-Me)-Phg-OH·HCl]



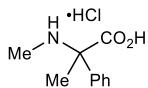
Step A [Boc-(D/L)-Phg-OMe]: This reaction was performed according to the above procedure for the synthesis of Boc-L-Val-OMe using H-(D/L)-Phg-OMe·HCl (552.6 mg, 2.74 mmol, 1.0 equiv), NEt₃ (0.40 mL, 2.88 mmol, 1.05 equiv), Boc₂O (598.1 mg, 2.74 mmol, 1.0 equiv) and MeOH (2 × 2.3 mL) with a 19 h reaction time (note that no CH₂Cl₂ was added in this case). Work-up as described above gave Boc-(D/L)-Phg-OMe (634.4 mg, 87%) as a white solid. **TLC:** R_F = 0.35 (15:85 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.38–7.30 (m, 5H), 5.61–5.49 (m, 1H), 5.32 (d, J = 7.6 Hz, 1H), 3.72 (s, 3H), 1.43 (s, 9H) ppm.



Step B [(Boc,Me)-(D/L)-(α-Me)-Phg-OMe]: This reaction was performed according to the above procedure for the synthesis of (Boc,Me)-L-Val-OMe using Boc-(D/L)-Phg-OMe (530.6 mg, 2.00 mmol, 1.0 equiv), anhydrous DMF (3.0 mL), MeI (0.50 mL, 8.00 mmol, 4.0 equiv) and NaH (160.0 mg of 60% suspension = 96.0 mg of NaH, 4.00 mmol, 2.0 equiv) with a 1 h reaction time. Quenching and work-up as described above gave ‘crude’ (Boc,Me)-(D/L)-(α-Me)-Phg-OMe containing residual DMF and grease from the NaH. This material was used in the next step without further purification (an overall yield is given below). **TLC:** R_F = 0.40 (15:85 EtOAc/n-hexane).

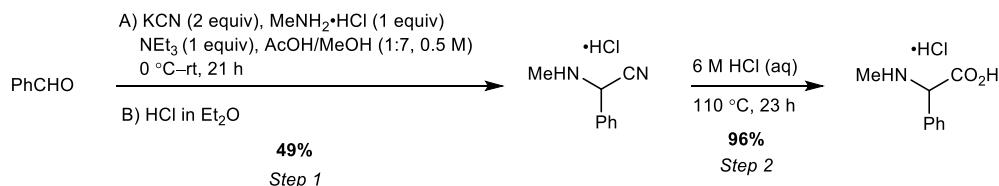


Step C [(Boc,Me)-(D/L)-(α-Me)-Phg-OH]: Part 1: saponification. A solution of ‘crude’ (Boc,Me)-(D/L)-(α-Me)-Phg-OMe (containing \leq 2.00 mmol, 1.0 equiv) and LiOH (239.5 mg, 10.00 mmol, \geq 5 equiv) in reagent grade THF (2.0 mL) and water (2.0 mL) was stirred at room temperature under air for 42 h. TLC analysis showed significant unreacted starting material. Dioxane (1.0 mL) and further THF (4.0 mL) and water (4.0 mL) were added (to aid in solubilizing the suspended solids) and the mixture was heated at 80 °C (oil bath temperature) opened to the air for a further 6 days (a reflux condenser was attached but no water flow was used). The reaction was cooled in an ice bath and acidified with 2 M aqueous HCl (12 mL). The product was extracted with EtOAc (30 mL) and the organic extract was concentrated under reduced pressure. To purify the product from a small amount of unreacted starting material, LiOH (50.0 mg, 2.09 mmol) was again added, followed by water (20 mL). The flask was placed on a rotary evaporator for 20 min to re-form the water-soluble lithium carboxylate salt (the flask was rotated in the water bath at 40 °C but no vacuum was applied). The resulting cloudy solution was diluted with water (20 mL) and washed with *n*-hexane (40 mL). The aqueous phase was acidified with 2 M aqueous HCl (12 mL). The product was extracted with EtOAc (30 mL), dried (Na₂SO₄) and concentrated to give the intermediate (Boc,Me)-(D/L)-(α-Me)-Phg-OH (427.9 mg) as a colorless semi-solid.



Step C [Me-(D/L)-(α-Me)-Phg-OH·HCl]: Part 2: Boc deprotection. This reaction was performed according to the procedure above for the synthesis of Me-L-Val-OH·HCl using (Boc,Me)-(D/L)-(α-Me)-Phg-OH (427.9 mg, 1.53 mmol, 1.0 equiv), CH₂Cl₂ (8.1 mL), water (0.15 mL, 8.06 mmol, 5.3 equiv) and TFA (1.24 mL, 16.13 mmol, 10.5 equiv). Work-up, then treatment with ethereal HCl (2 M in Et₂O, 2.42 mL, 4.83 mmol) and removal of the solvents with air as described above gave a residue which was precipitated by addition of Et₂O/n-hexane (1:1, 8 mL). The solids were broken-up with a spatula and collected by filtration. The original vial and filter cake were rinsed/washed with Et₂O/n-hexane (1:1, 30 mL). The solid was transferred back to the original vial (containing residual product) and dried to give *Me*-(D/L)-(α-Me)-Phg-OH·HCl (295.9 mg, 69%, over Steps B and C) as a white solid. This compound (as the hydrochloride salt) has not been previously reported. **Mp:** 266–274 °C. **¹H NMR (400 MHz, CD₃OD):** δ 7.59–7.50 (m, 5H), 2.45 (s, 3H), 2.02 (s, 3H) ppm. **¹³C NMR (100 MHz, CD₃OD):** δ 172.9, 134.7, 131.3, 130.6, 127.9, 67.8, 28.3, 18.3 ppm. **IR (ATR, cm⁻¹):** ̄ = 2864, 2750, 2729, 2574, 2440, 1729, 1586, 1454, 1368, 1218, 1194, 1121, 1049, 836, 716, 693, 653, 558, 360. **HRMS (ESI):** calcd for C₁₀H₁₄NO₂ [M + H]⁺ 180.1025, found 180.1033.

(±)-*N*-Methyl-2-phenylglycine hydrochloride [Me-(D/L)-Phg-OH·HCl]



Step 1: Based on a literature procedure,^{S19} to a suspension of benzaldehyde (0.51 mL, 5.00 mmol, 1.0 equiv) and KCN (651.2 mg, 10.00 mmol, 2.0 equiv) in reagent grade MeOH (5.1 mL) at 0 °C under air was added a solution of MeNH₂·HCl (337.6 mg, 5.00 mmol, 1.0 equiv, dried in a 120 °C oven before use) and NEt₃ (0.70 mL, 5.00 mmol, 1.0 equiv) in MeOH (4.0 mL). To this mixture was added AcOH (1.3 mL) dropwise over 10 min, then the mixture was allowed to warm to room temperature with stirring over 21 h. After cooling in an ice bath, 1 M K₂CO₃ (50 mL) was slowly added, followed by water (30 mL). The product was extracted with CH₂Cl₂ (50 mL). The organic layer was washed with saturated NaHCO₃ (30 mL) and brine (30 mL), then dried (Na₂SO₄) and concentrated to give a yellow oil (freebase of product with minor impurities). This was taken up in Et₂O (15 mL) and ethereal HCl (2 M in Et₂O, 4.0 mL, 8.00 mmol) was added, immediately forming a sticky white solid. The supernatant liquid was decanted off and the residue was washed with Et₂O (20 mL) then EtOAc (20 mL), each time by swirling and decanting the supernatant (each time the decanted supernatant was passed through filter paper to collect any suspended solids). The filter cake and remaining majority of product in the flask were recombined after dissolution in MeOH (15 mL). This solution was concentrated to give the α-aminonitrile HCl

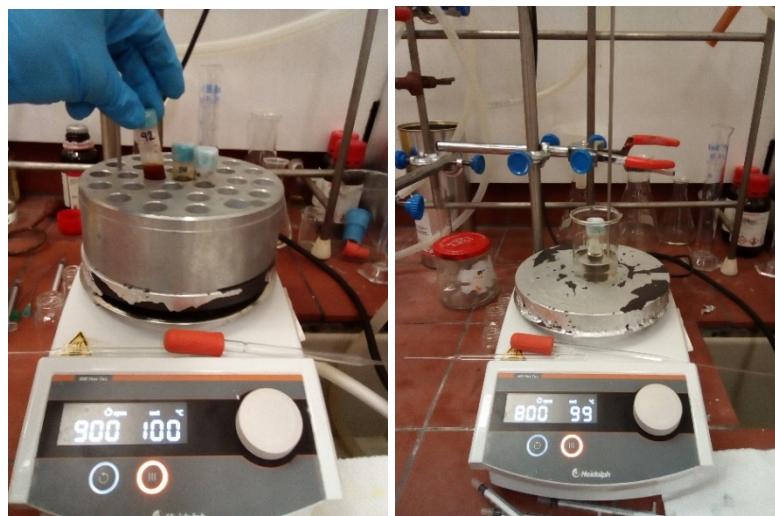
salt (448.8 mg, 49%) as a pale yellow gum which solidified on standing overnight. **¹H NMR (400 MHz, (CD₃)₂SO):** δ 7.78–7.71 (m, 2H), 7.58–7.51 (m, 3H), 6.06 (s, 1H), 2.58 (s, 3H) ppm. **¹³C NMR (100 MHz, (CD₃)₂SO):** δ 130.8, 129.34, 129.30, 128.5, 115.1, 50.9, 30.8 ppm.

Step 2: A solution of the above α-aminonitrile salt (428.5 mg, 2.35 mmol) in 6 M aqueous HCl (8 mL) was heated at 110 °C (oil bath temperature) under air for 23 h. The solution was cooled to room temperature and concentrated under reduced pressure. The remaining solid was treated with Et₂O (20 mL) and broken up with a spatula. The suspension was sonicated for ~2 min. The solid was collected by filtration, washed with Et₂O (40 mL) and dried to give Me-(D/L)-Phg-OH·HCl (456.1 mg, 96%) as a pale yellow solid. **¹H NMR (500 MHz, CD₃OD):** δ 7.53–7.51 (m, 5H), 5.08 (s, 1H), 2.63 (s, 3H) ppm. **¹³C NMR (125 MHz, CD₃OD):** δ 170.2, 131.9, 131.5, 130.7, 129.8, 65.3, 31.8 ppm.

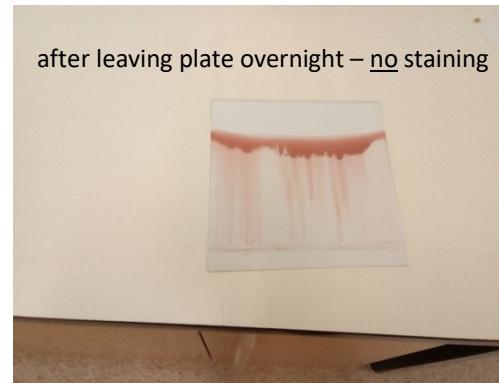
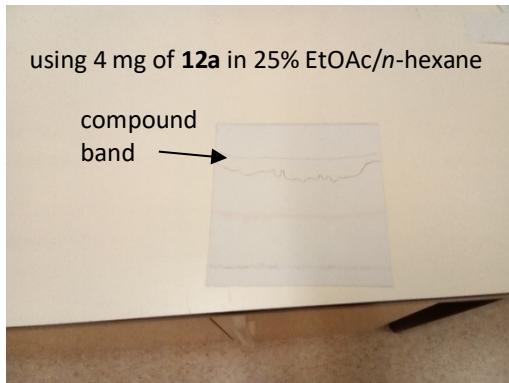
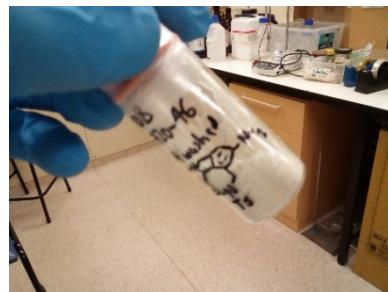
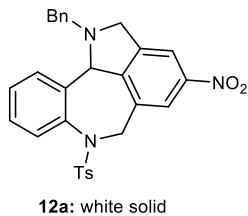
5. Synthesis of Benzoazepine-Fused Isoindolines (12) via Cycloaddition

5.1. General Points and Observations

- The anhydrous toluene used for the cycloaddition was sparged with N₂ for ~30 min and stored under N₂. Aliquots from a given batch of deoxygenated toluene were used in reactions for up to 2 weeks without the need to freshly sparge each time.
- Powdered 3 Å molecular sieves were activated by heating in a 300 °C oven for 16 h, then ‘cooled’ in a 100 °C oven for 1 h before being stored in a desiccator.
- As stated in the manuscript, preliminary studies with cycloaddition product **12a** showed that 2.0 equiv of the amino acid (Bn-Gly-OH·HCl) was optimal. As such, 2.0 equiv of the amino acid was employed throughout this study without optimizing the stoichiometry for each substrate. Indeed, full consumption of the benzaldehyde was observed even in reactions that required >60 h. In one example (product **12r**), an additional 1.0 equiv of the amino acid was added arbitrarily at the midpoint of the reaction (24 h out of 43 h total) as specified in Section 5.4.3. This was merely a precaution to ensure enough amino acid was still present to consume the aldehyde [TLC monitoring for the presence (or absence) of the amino acid component was generally not attempted due to its polar, zwitterionic nature].
- In most cases a heating block with vial inserts was used for reaction heating as shown (left image). In a few cases, stirring was not sufficient using this set-up and therefore a ‘mini’ oil bath in a beaker was used (right image), which brought the vial closer to the magnet.



- The products **12** are poorly soluble in EtOAc/*n*-hexane and although TLC analyses proceeded without complications with this developing system, attempts to use an EtOAc/*n*-hexane binary solvent system as the eluent for flash chromatography consistently gave poor results. For example, when minimal CH₂Cl₂ (<2 mL) was used to dissolve and load a compound (e.g., **12a**) to a column ran with 10:90 EtOAc/*n*-hexane (e.g., *R*_F **12a** = 0.22) significant ‘fronting’ (i.e., immediate partial elution) of the product was observed due to apparent carry-through with the CH₂Cl₂. This appeared to be an anomalous solubility effect, as running a column with CH₂Cl₂ with the same compound (under otherwise identical conditions) did not result in this immediate ‘fronting’.
- After TLC analysis, the product spots (**12**) typically start to turn dark brown/purple within 10–20 min (without staining). An attempt was made to determine the identity of the derived colored material: a ‘mini’ prep-TLC was performed with 4 mg of **12a** using 25:75 EtOAc/*n*-hexane, then the plate was left overnight in air (see images below). The resultant dark brown band (derived from the previously colorless product) was recovered and analyzed by NMR. Other than a trace of the isoindole **12a'**, no significant product/s were observed, indicating predominant decomposition. Note that ‘deactivating’ a TLC plate with NEt₃ prior to developing did not prevent the product from colorizing on the TLC plate after standing. The images below show the typical color change observed by TLC with a representative product (**12a**).

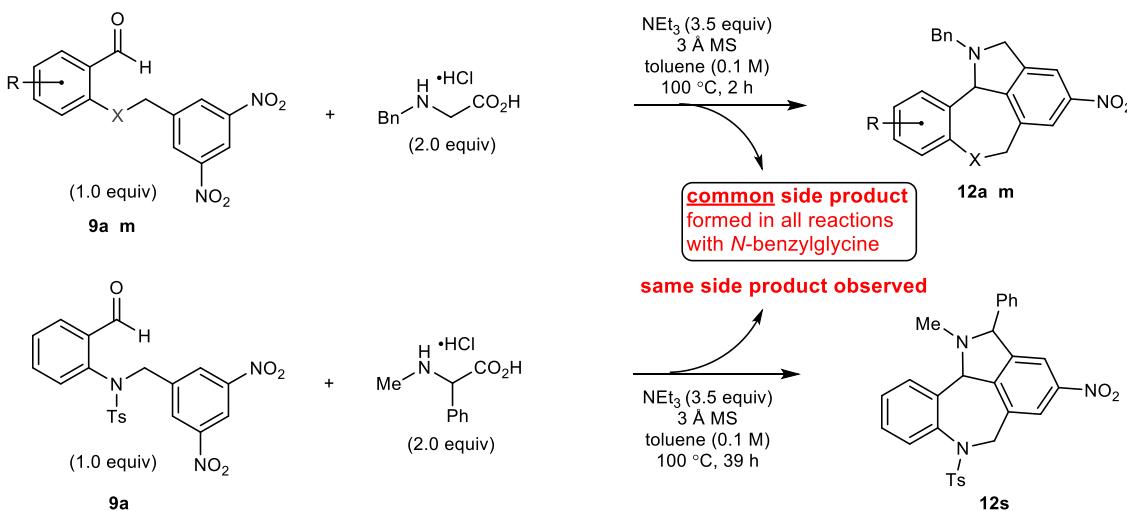


- Related to the above points, oxidation/degradation of the products (**12**) appeared to be catalyzed/accelerated to some extent by silica gel. However, this effect appeared to be largely dependent on the solvent system used, especially for preparative work (i.e., flash chromatography). For instance, attempts to purify the products using an EtOAc/n-hexane eluent (in addition to the solubility problems described above) resulted in the appearance of new product/s containing an aldehyde proton, indicative of oxidation. However, running the same compound through a column with CH₂Cl₂ under otherwise identical conditions did not cause any measurable degradation/oxidation. The obvious solubility and stability benefit of performing flash chromatography with CH₂Cl₂ for this class of compounds led us to the general procedure given (Section 5.4.1). As an additional precaution, flash chromatography was generally performed under a positive pressure of N₂ (rather than air).
- In some cases, further purification or diastereoenrichment of the product (after flash chromatography) was achieved by selective adsorption to polymer-bound *p*-TsOH or by precipitation from methanol. In fact, the low methanol-solubility of the aldehyde substrates (**9**) and tetracyclic products (**12**) appears to be general and can be exploited as a practical means for purification, particularly at scale (see Section 6). General procedures for these additional purification methods for reactions performed at 0.10 mmol scale are given in Section 5.4.1.
- Isolated yields of analytically pure products using the general procedure (Section 5.4.1) were generally only 2–10% lower than NMR yields determined from the crude mixture, consistent with mechanical losses during purification on small scale (0.10 mmol) rather than any product degradation.

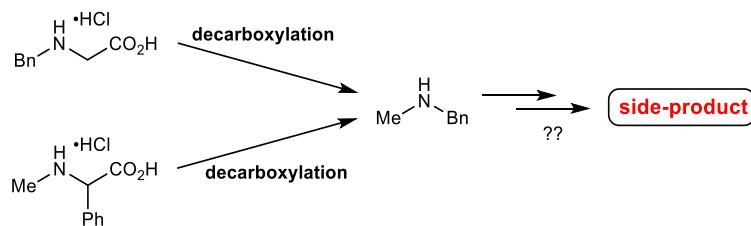
- Once purified and obtained as solids, the products (**12**) have not shown any evidence of decomposition or oxidation to the isoindole. Products are typically stored in capped vials under air in a freezer, but samples left in capped vials at room temperature for extended periods (e.g., 7 days) likewise do not show any sign of decomposition/oxidation.

5.2. Notes on Unidentified Side Product Derived from *N*-Benzylglycine (and *N*-methyl- α -phenylglycine)

- In all reactions with *N*-benzylglycine, regardless of the identity of the benzaldehyde (**9**) used, the same unidentified side product derived solely from the amino acid was observed. This side product typically co-eluted (to some extent) with **12** during flash chromatography which was the main reason why most reaction products **12a–m** derived from *N*-benzylglycine required further purification with polymer-bound *p*-TsOH. The desired products **12a–m** could also be effectively purified by precipitation (or trituration) from methanol in which the side product remains in solution. The latter purification method works particularly well on larger scale (see Section 6), but on smaller scale (e.g., 0.10 mmol), some product yield (~10–20%) is inevitably lost and therefore the former method (polymer-bound *p*-TsOH) was preferred at 0.10 mmol scale.

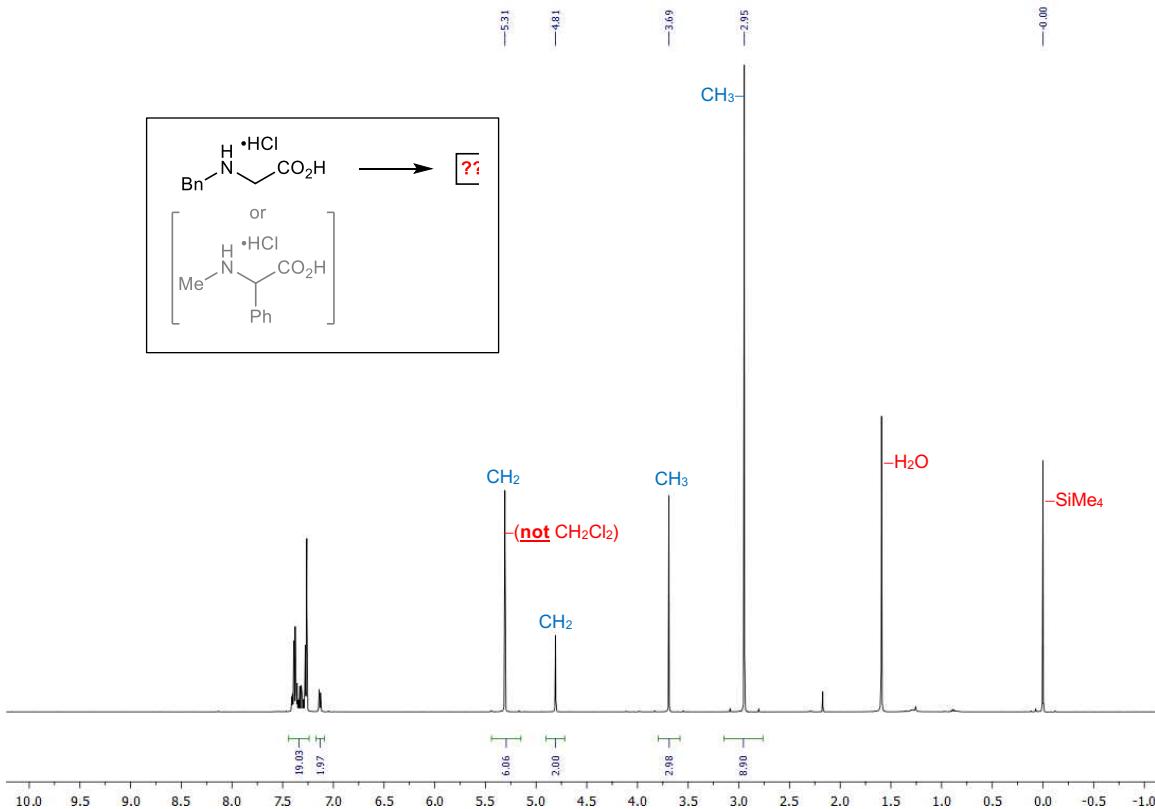


- One other amino acid, *N*-methyl- α -phenylglycine, which is a constitutional isomer of *N*-benzylglycine, also produced the exact same side product (Scheme above). This strongly suggests decarboxylation to a common amine intermediate is operative:

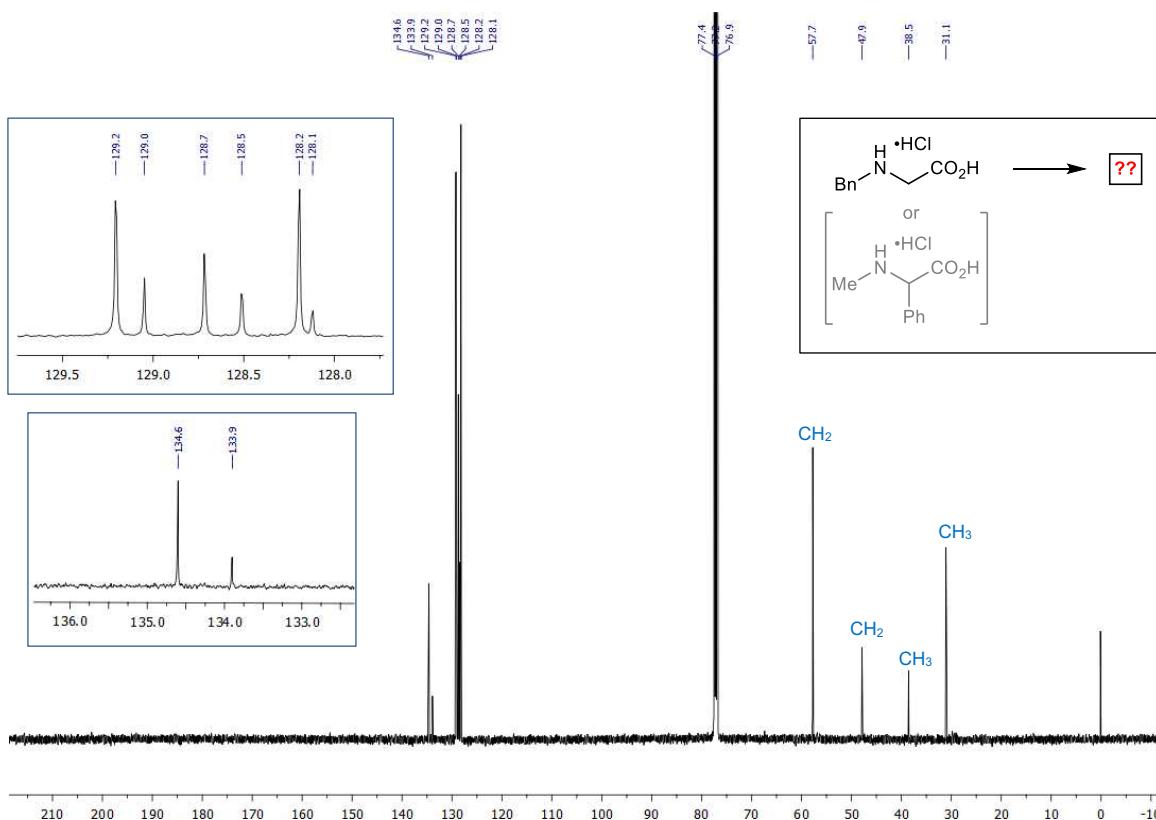


- In one case, the side product was isolated cleanly and quantitatively (3.0 mg) by flash chromatography during the purification of **12k** (the lower R_F value of **12k** compared to most other products enabled earlier elution of the pure side product). See Section 5.4.2 for details, as well as observations and NMR spectra below.

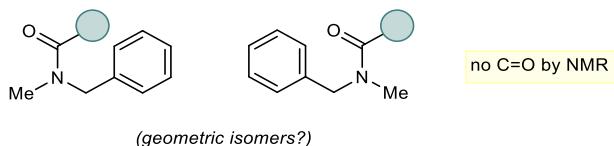
- Observations on pure sample obtained of side product: • Colorless gum • UV active • single spot by TLC
- $R_F = 0.46$ (25:75 EtOAc/n-hexane) • no basic groups (does not adsorb on to polymer-bound *p*-TsOH)
- ^1H NMR spectrum of the persistent, unidentified side product (3.0 mg) in CDCl_3 (500 MHz):



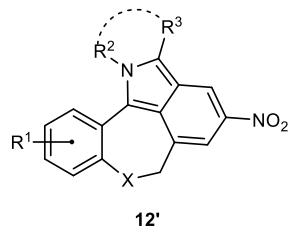
- ^{13}C NMR spectrum of the persistent, unidentified side product (3.0 mg) in CDCl_3 (125 MHz):



- Originally it was postulated that the compound was an amide with unequally populated *cis* and *trans* configurations by NMR, which could cause the apparent ‘doubling’ of CH_2 and CH_3 peaks (NMR above). However, no carbonyl peak was observed by ^{13}C NMR, ruling out this possibility:

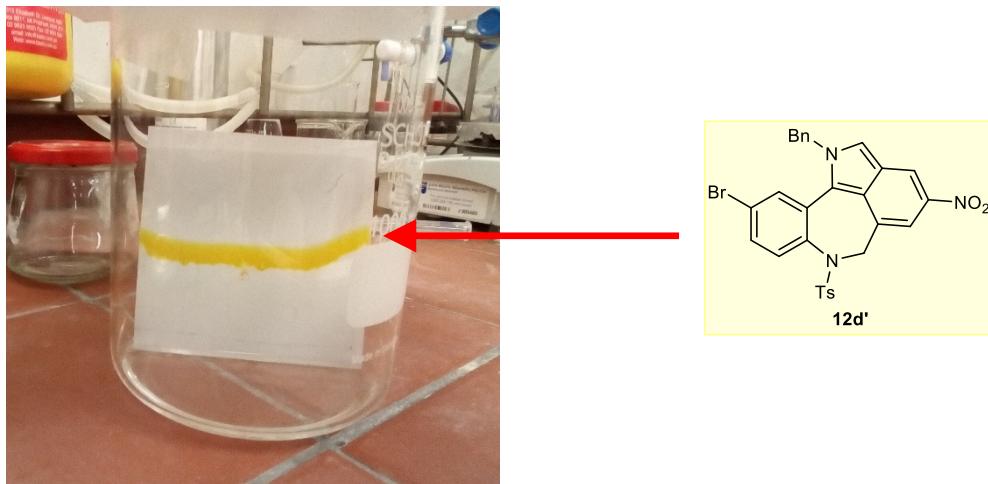


5.3. Notes on Isoindole Side Product (12')



- In previous work by Starosotnikov on related intermolecular thermal cycloadditions (Scheme 1b, manuscript), an isoindole was formed regardless of whether their reaction was under air or an inert atmosphere, suggesting a competing role of the starting polynitroarene (or the nitrite by-product) as an oxidant.^{S20} For our system, all

reactions were carried out under N_2 and in several cases the corresponding isoindole form of **12** (**12'**), was observed as a minor side product. This isoindole scaffold exhibited a bright yellow to red color, consistent with previously reported nitro-substituted isoindoles.^{S20} The isoindole (**12'**) typically has a higher polarity (i.e., lower R_F) than the desired isoindoline product and was easily separated in most cases by flash chromatography. The image below shows the typical color of an isoindole side product on TLC.



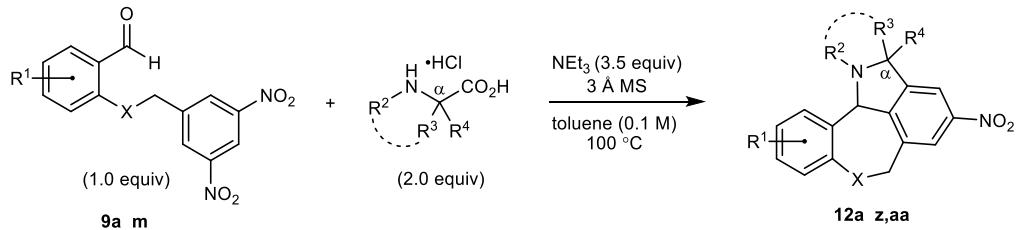
- The ratio isoindoline/isoindole (**12:12'**) in all crude samples directly after work-up (filtration only) was quantified by 1H NMR spectroscopy and are listed in the table below (Section 5.3.1). The propensity for **12** to undergo (partial) oxidation during the reaction was dependent on both the aldehyde and amino acid precursors, however, in general, products derived from *N*-Bn (or PMB) amino acids (Schemes 3 and 4) were the least susceptible to oxidation (ratios of **12:12'** ranged from 10.7:1 to >25:1), while products derived from *N*-Me or cyclic amino acids gave ratios of **12:12'** of 4.2:1 to 10.1:1. One notable exception to these trends was compound **12j** (crude ratio **12:12'** = 2.7:1). In this case, the isoindole (**12j'**) was isolated in 12% yield and fully characterized (see Section 5.4.2). The only compounds that could not be separated from their derived isoindoles by flash chromatography were **12o** and **12z** (Scheme 4), which were obtained with 5 and 10 mol% of **12o'** and **12z'**, respectively. No further oxidation to the isoindole (**12'**) was generally observed during the conditions used for purification, analysis and storage.

5.3.1. Crude Ratios of Isoindoline (**12**) to Isoindole (**12'**)

- The following table lists the ratios of **12:12'** in the crude reaction mixtures for the 25 successful examples. Ratios were determined by 1H NMR spectroscopy and are from reactions performed at 0.10 mmol scale. Note that where **12** was a mixture of diastereomers, the ratio represents that of the combined diastereomers : **12j'**.

Entry	Prod	X	R ¹	R ²	R ³	R ⁴	Crude ratio 12:12'	
							12	12' (where R ⁴ = H)
1	12a	NTs	H	Bn	H	H	>25:1	
2	12b	NTs	5-Me	Bn	H	H	>25:1	
3	12c	NTs	5-OMe	Bn	H	H	>25:1	
4	12d	NTs	5-Br	Bn	H	H	10.7:1	
5	12e	NTs	5-Cl	Bn	H	H	23:1	
6	12f	NTs	5-F	Bn	H	H	13.6:1	
7	12g	NTs	4-Cl	Bn	H	H	13.6:1	
8	12h	NTs	3-Cl	Bn	H	H	>25:1	
9	12j	NTs	4-CO ₂ Me	Bn	H	H	2.8:1	
10	12k	NTs	4-morpholino	Bn	H	H	>25:1	
11	12l	NBz	H	Bn	H	H	>25:1	
12	12m	O	H	Bn	H	H	>25:1	
13	12n	NTs	H	PMB	H	H	>25:1	
14	12o	NTs	H	Me	H	H	not determined [isolated ratio = 19:1]	
15	12p	NTs	H	Bn	Bn	H	>25:1	
16	12q	NTs	H	Me	Bn	H	4.2:1	
17	12r	NTs	H	Bn	Ph	H	>25:1	
18	12s	NTs	H	Me	Ph	H	10.1:1	
19	12t	NTs	H	Me	Me	H	7.9:1	
20	12u	NTs	H	Me	<i>i</i> -Pr	H	6.8:1	
21	12w	NTs	H	Me	Me	Me	oxidation to 12' not possible	
22	12x	NTs	H	Bn	Me	Me	oxidation to 12' not possible	
23	12y	NTs	H	Me	Me	Ph	oxidation to 12' not possible	
24	12z	NTs	H	—CH ₂ CH ₂ CH ₂ —	H		10.0:1	
25	12aa	NTs	H	—CH ₂ —S—CH ₂ —	H		7.1:1	

5.4. Cycloaddition Experimental



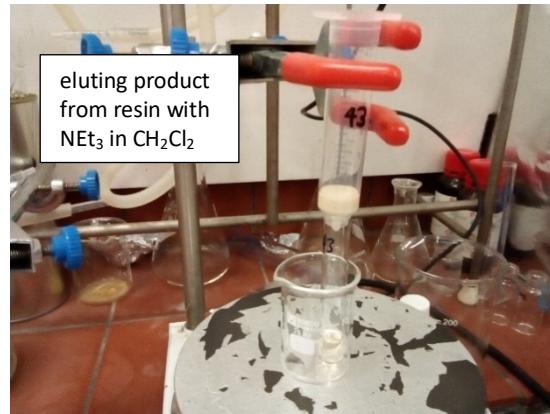
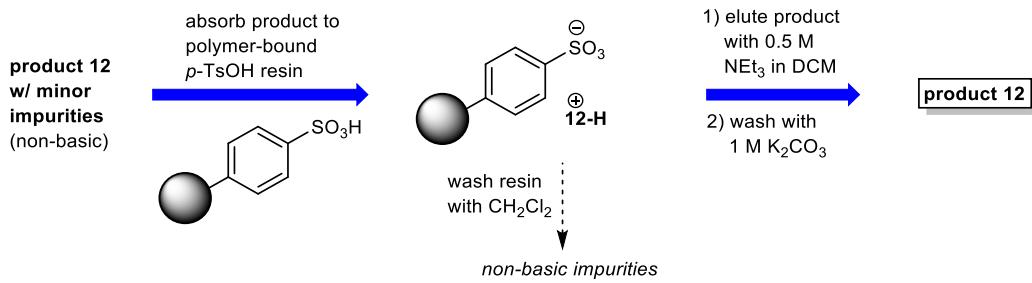
Note: A detailed experimental procedure for the larger scale example (product **12b**, 4 mmol scale) is also given in Section 6.

5.4.1. General Procedure E (Cycloaddition): An oven-dried 3 mL screw-top vial was charged in air with the appropriate benzaldehyde **9a–m** (0.10 mmol, 1.0 equiv), amino acid hydrochloride salt or freebase (0.20 mmol,

2.0 equiv) and powdered 3 Å molecular sieves (45.0 mg). The vial was fitted with a teflon cap and purged with N₂ via an outlet needle. The outlet needle was removed and anhydrous, deoxygenated toluene (1.0 mL, 0.1 M) was then added, followed by NEt₃ (49 µL, 0.35 mmol, 3.5 equiv for reactions using an amino acid hydrochloride salt or 21 µL, 0.15 mmol, 1.5 equiv for reactions using an amino acid freebase). The N₂ inlet needle was removed and parafilm was wrapped around and over the vial cap. [For reactions requiring longer than 9 h, as specified, the teflon cap was replaced (in quick fashion) with a plastic screw-cap to avoid any potential loss of solvent during the overnight reaction. Parafilm was also used in these cases]. The reaction was then heated from room temperature to 100 °C during 10–15 min, then maintained at 100 °C for the times specified (1–68 h). After cooling to room temperature, the reaction was diluted with CH₂Cl₂ (2 mL) and filtered. The reaction vial and the filter cake were rinsed with further CH₂Cl₂ (5 × 2 mL), then the filtrate was concentrated under reduced pressure. The residue was analyzed by ¹H NMR spectroscopy with mesitylene as an internal standard to determine (1) the conversion of the aldehyde [100% in all cases except for substrates **7** and **8**], (2) the NMR yield of **12** [typically <10% higher than the isolated yields given] (3) the product ratio of isoindoline/isoindole [**12:12'**, tabulated in Section 5.3.1] and (4) the crude diastereomeric ratio [listed in the experimental and manuscript], where applicable. Purification by flash chromatography (4.4 g silica) with the specified CH₂Cl₂-based eluent under a positive pressure of N₂ gave the cycloaddition products **12a–z,aa**. In some cases, where stated, further purification or diastereoenrichment of the product was carried out using the following methods:

General Procedure E' (Further purification with polymer-bound p-TsOH): [Before use, the commercially obtained polymer-bound p-TsOH was washed with MeOH and CH₂Cl₂ (then dried under vacuum) as a precaution to remove any potentially unbound p-TsOH.] To a solution of the product obtained after flash chromatography (0.10 mmol theoretical yield) in reagent grade CH₂Cl₂ (3 mL) was added polymer-bound p-TsOH (Macroporous, 30–60 mesh, 2.0–3.0 mmol/g loading, 300 mg used = 0.6–0.9 mmol p-TsOH, 6–9 equiv) and the suspension was stirred under air (capped vial) arbitrarily for ~16 h after which time TLC analysis showed no isoindoline product (**12**) remaining in the supernatant liquid (the only exception where complete resin adsorption was not achieved was product **12r**, as specified in Section 5.4.3). Note that in many cases the non-basic impurity/impurities had a similar R_F value to the desired product, however the distinct color change of the desired product on TLC serves as a good indicator for its presence or absence (see Section 5.1 for more information). The resin was collected by pouring the suspension into a 10 mL syringe cartridge containing a plug of cotton with the aid of a CH₂Cl₂-rinse (20 mL). The dry resin was washed with further CH₂Cl₂ (5 × 3 mL) [note that during collecting and washing the resin, the syringe plunger was inserted each time and used to increase the rate of solvent flow through the cartridge, ensuring that the plunger did not come in to contact with the resin]. The product was then slowly eluted by gravity from the resin (without the use of the plunger) by applying ~0.5 mL aliquots of 0.5 M NEt₃ in CH₂Cl₂ (~10–15 mL total required). This elution process avoided the resin spreading out up the syringe barrel and ensured adequate missing time. The eluent containing the

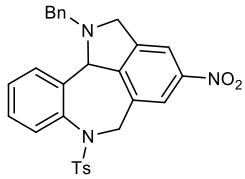
product was then concentrated under reduced pressure to dryness. The residue, which contained what appeared to be NEt_3 salt impurities by NMR (but not free NEt_3 nor $\text{NEt}_3\cdot p\text{-TsOH}$) was taken back up in CH_2Cl_2 (20 mL) and washed with 1 M K_2CO_3 (25 mL). The aqueous phase was back-extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the purified product **12**.



General Procedure E'' (Further purification by precipitation from methanol): To the solid product (0.10 mmol theoretical yield) in a 12 mL vial was added CH_2Cl_2 (0.5–2 mL). Once all (or most) of the product has dissolved, MeOH (~5 mL) was added. The resulting solution/suspension was placed on a rotary evaporator ($40\text{ }^\circ\text{C}$, ≥ 200 mbar) to selectively remove the CH_2Cl_2 . Once the total volume had reduced to 3–5 mL, the vial containing the precipitated product was stood at room temperature for 10–15 min. The precipitate was collected, washed with cold MeOH (5 mL, pre-cooled in a freezer), then dried to give the purified product **12**.

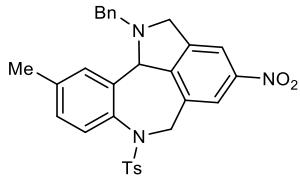
5.4.2. Products from Benzaldehyde Scope (12a–m)

(\pm)-10-Benzyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12a)



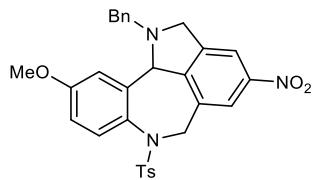
This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12a** (37.7 mg, 74%) as a white solid. **Mp:** 121–125 °C. **TLC:** R_F = 0.51 (30:70 EtOAc/*n*-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.86–7.82 (m, 2H), 7.80 (dt, J = 7.8, 1.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.55–7.49 (m, 2H), 7.46–7.37 (m, 3H), 7.37–7.30 (m, 3H), 7.28 (dd, J = 7.8, 0.9 Hz, 1H), 7.17 (dd, J = 7.8, 1.3 Hz, 1H), 5.56 (d, J = 17.7 Hz, 1H), 5.39 (s, 1H), 4.44–4.33 (m, 2H), 4.26 (d, J = 13.8 Hz, 1H), 3.76 (dd, J = 14.0, 3.0 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 2.48 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ (one ArC ‘missing’ due to overlap) 148.1, 144.1, 143.8, 142.0, 141.6, 138.5, 137.5, 134.5, 130.1, 129.6, 128.9, 128.7, 128.6, 128.4, 127.6, 127.3, 126.0, 120.5, 116.3, 67.7, 59.2, 57.8, 50.7, 21.7 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3099, 3030, 2922, 2829, 1598, 1526, 1482, 1342, 1159, 1091, 895, 785, 702, 572. **HRMS (ESI):** calcd for C₂₉H₂₆N₃O₄S [M + H]⁺ 512.16440, found 512.16374.

(\pm)-10-Benzyl-8-methyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12b)



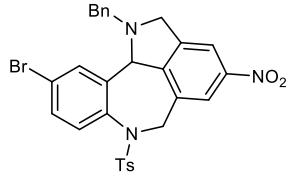
This compound was prepared according to *General Procedure E* using aldehyde **9b** (46.9 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12b** (42.0 mg, 80%) as a pale yellow solid. **Mp:** 205–209 °C. **TLC:** R_F = 0.59 (30:70 EtOAc/*n*-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.86–7.81 (m, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.53–7.50 (m, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.37–7.30 (m, 3H), 7.09–7.02 (m, 2H), 5.54 (d, J = 17.7 Hz, 1H), 5.36 (s, 1H), 4.43–4.31 (m, 2H), 4.26 (d, J = 13.6 Hz, 1H), 3.77 (dd, J = 13.9, 3.0 Hz, 1H), 3.54 (d, J = 13.6 Hz, 1H), 2.47 (s, 3H), 2.36 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ (one ArC ‘missing’ due to overlap) 148.1, 144.0, 141.55, 141.51, 139.7, 138.6, 138.5, 134.8, 134.7, 130.0, 129.1, 128.9, 128.53, 128.47, 127.6, 127.3, 126.6, 120.5, 116.2, 67.6, 59.3, 57.8, 50.8, 21.8, 21.7 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3034, 2921, 2852, 2795, 1599, 1528, 1496, 1342, 1157, 1116, 866, 746, 695, 612, 537. **HRMS (ESI):** calcd for C₃₀H₂₈N₃O₄S [M + H]⁺ 526.1801, found 526.1812.

(\pm)-10-Benzyl-8-methoxy-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12c)



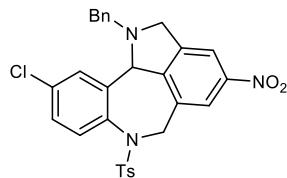
This compound was prepared according to *General Procedure E* using aldehyde **9c** (48.5 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12c** (39.0 mg, 72%) as a pale yellow solid. **Mp:** 216–218 °C. **TLC:** R_F = 0.53 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.86–7.82 (m, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.53–7.51 (m, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.37–7.31 (m, 4H), 7.07 (d, J = 8.6 Hz, 1H), 6.76 (dd, J = 8.7, 3.0 Hz, 1H), 5.57 (d, J = 17.7 Hz, 1H), 5.31 (s, 1H), 4.44–4.34 (m, 2H), 4.25 (d, J = 13.8 Hz, 1H), 3.78–3.74 (m, 1H) overlapping with 3.77 (s, 3H), 3.54 (d, J = 13.9 Hz, 1H), 2.48 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 160.4, 148.0, 144.0, 143.7, 143.5, 141.5, 138.5, 138.4, 134.7, 130.0, 129.9, 129.5, 128.9, 128.3, 127.6, 127.2, 120.5, 116.2, 113.6, 111.3, 67.7, 59.3, 57.8, 55.6, 50.8, 21.8 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3068, 3031, 2921, 2851, 2798, 1725, 1600, 1523, 1491, 1334, 1091, 902, 839, 810, 667, 525. **HRMS (ESI):** calcd for C₃₀H₂₇N₃O₅SnA [M + Na]⁺ 564.1569, found 564.1567.

(\pm)-10-Benzyl-8-bromo-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12d)



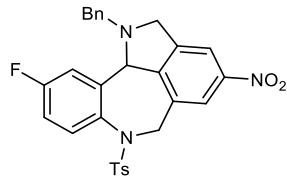
This compound was prepared according to *General Procedure E* using aldehyde **9d** (53.4 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12d** (39.9 mg, 68%) as a yellow solid. **Mp:** 207–209 °C. **TLC:** R_F = 0.70 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.94 (dd, J = 2.4, 1.0 Hz, 1H), 7.87–7.84 (m, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.51–7.48 (m, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.41 (dd, J = 8.3, 2.4 Hz, 1H), 7.38–7.34 (m, 3H), 7.04 (d, J = 8.3 Hz, 1H), 5.57 (d, J = 17.1 Hz, 1H), 5.33 (s, 1H), 4.42 – 4.32 (m, 2H), 4.19 (d, J = 13.5 Hz, 1H), 3.80 (dd, J = 13.8, 2.9 Hz, 1H), 3.54 (d, J = 13.5 Hz, 1H), 2.49 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ (one ArC ‘missing’ due to overlap) 148.1, 144.3, 144.1, 143.0, 141.5, 138.0, 136.3, 134.2, 131.7, 130.4, 130.2, 129.6, 129.0, 128.6, 127.7, 127.2, 124.0, 120.6, 116.4, 67.3, 59.2, 57.7, 50.4, 21.8 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3078, 3030, 2921, 2851, 2787, 1751, 1523, 1453, 1336, 1154, 1095, 864, 767, 687, 575. **HRMS (ESI):** calcd for C₂₉H₂₅N₃O₄S(⁷⁹Br) [M + H]⁺ 590.0749, found 590.0762.

(\pm)-10-Benzyl-8-chloro-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12e)



This compound was prepared according to *General Procedure E* using aldehyde **9e** (49.0 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12e** (35.4 mg, 65%) as a pale yellow solid. **Mp:** 218–221 °C. **TLC:** R_F = 0.58 (30:70 EtOAc/n-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.87–7.82 (m, 2H), 7.78 (dd, J = 2.5, 1.0 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.52–7.47 (m, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.38–7.32 (m, 3H), 7.27–7.22 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.57 (d, J = 17.8 Hz, 1H), 5.33 (s, 1H), 4.42–4.32 (m, 2H), 4.19 (d, J = 13.5 Hz, 1H), 3.80 (dd, J = 14.0, 2.9 Hz, 1H), 3.54 (d, J = 13.6 Hz, 1H), 2.48 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 148.3, 144.3, 144.1, 143.1, 141.6, 138.2, 138.0, 135.83, 135.81, 134.2, 130.21, 130.17, 129.0, 128.7, 128.6, 127.8, 127.3, 126.6, 120.6, 116.4, 67.4, 59.3, 57.8, 50.6, 21.7 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3081, 3030, 2922, 2801, 1718, 1523, 1350, 1324, 1268, 1154, 1090, 813, 722, 658, 578, 544. **HRMS (ESI):** calcd for C₂₉H₂₅N₃O₄SCl [M + H]⁺ 546.1254, found 546.1230.

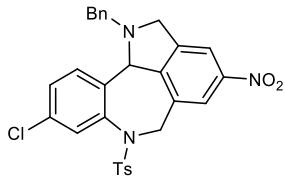
(\pm)-10-Benzyl-8-fluoro-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12f)



This compound was prepared according to *General Procedure E* using aldehyde **9f** (47.3 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12f** (33.2 mg, 63%) as a yellow solid. **Mp:** 206–209 °C. **TLC:** R_F = 0.59 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.87–7.82 (m, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.53–7.46 (m, 3H), 7.43 (t, J = 7.5 Hz, 2H), 7.38–7.31 (m, 3H), 7.15 (dd, J = 8.7, 5.0 Hz, 1H), 6.94 (td, J = 8.2, 3.0 Hz, 1H), 5.58 (d, J = 17.7 Hz, 1H), 5.33 (s, 1H), 4.45–4.32 (m, 2H), 4.20 (d, J = 13.6 Hz, 1H), 3.78 (dd, J = 14.0, 2.9 Hz, 1H), 3.54 (d, J = 13.7 Hz, 1H), 2.48 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ ([164.2, 162.3], d, J_{C-F} = 249.0 Hz), 148.2, ([145.1, 145.0], d, J_{C-F} = 8.2 Hz), 144.2, 143.1, 141.6, 138.2, 138.1, 134.4, ([133.04, 133.02], d, J_{C-F} = 2.7 Hz), ([130.73, 130.66], d, J_{C-F} = 8.8 Hz), 130.1, 128.9, 128.5, 127.7, 127.3, 120.6, 116.4, ([115.3, 115.2], d, J_{C-F} = 23.9 Hz), ([113.6, 113.4], d, J_{C-F} = 24.9 Hz), 67.4, 59.2, 57.8, 50.6, 21.7 ppm. **¹⁹F NMR (376 MHz, CDCl₃):** δ –109.8 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2887, 2811,

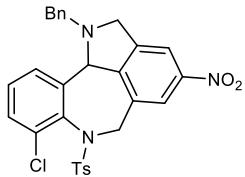
1593, 1530, 1483, 1343, 1314, 1290, 1259, 1157, 1120, 1087, 967, 903, 866, 811, 754, 734, 701, 667, 614, 591, 559, 532, 484. **HRMS (ESI):** calcd for $C_{29}H_{25}FN_3O_4S$ $[M + H]^+$ 530.1550, found 530.1537.

(\pm)-10-Benzyl-7-chloro-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12g)



This compound was prepared according to *General Procedure E* using aldehyde **9g** (49.0 mg, 0.10 mmol) and Bn-Gly-OH-HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH_2Cl_2) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12g** (30.7 mg, 56%) as a pale yellow solid. **Mp:** 161–162 °C. **TLC:** R_F = 0.64 (30:70 EtOAc/*n*-hexane). **1H NMR (500 MHz, $CDCl_3$):** δ 7.88–7.83 (m, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.52–7.46 (m, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.40–7.31 (m, 4H), 7.18 (d, J = 2.1 Hz, 1H), 5.53 (d, J = 17.6 Hz, 1H), 5.34 (s, 1H), 4.44–4.33 (m, 2H), 4.20 (d, J = 13.8 Hz, 1H), 3.78 (dd, J = 13.8, 3.0 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H), 2.49 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 148.2, 144.4, 143.3, 141.5, 140.8, 138.4, 138.2, 138.0, 134.1, 133.6, 130.2, 129.8, 129.0, 128.9, 128.4, 127.7, 127.3, 127.2, 120.5, 116.4, 67.4, 59.1, 57.8, 50.5, 21.8 ppm. **IR (ATR cm^{-1}):** $\tilde{\nu}$ = 3062, 2922, 2852, 1715, 1547, 1431, 1343, 1131, 1027, 913, 744, 697, 582, 539. **HRMS (ESI):** calcd for $C_{29}H_{25}N_3O_4SCl$ $[M + H]^+$ 546.1254, found 546.1238.

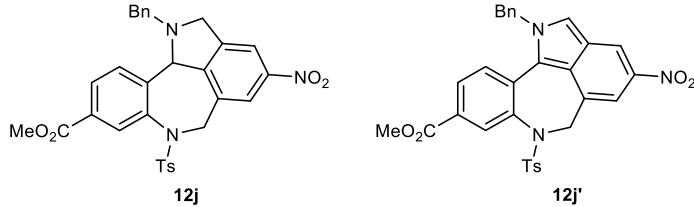
(\pm)-10-Benzyl-6-chloro-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12h)



This compound was prepared according to *General Procedure E* using aldehyde **9h** (49.0 mg, 0.10 mmol) and Bn-Gly-OH-HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH_2Cl_2) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **9h** (38.8 mg, 71%) as a pale yellow solid. **Mp:** 229–230 °C. **TLC:** R_F = 0.60 (30:70 EtOAc/*n*-hexane). **1H NMR (500 MHz, $CDCl_3$):** δ 7.88–7.83 (m, 4H), 7.78–7.73 (m, 1H), 7.56–7.51 (m, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.39–7.31 (m, 5H), 5.84 (s, 1H), 5.30 (d, J = 18.2 Hz, 1H), 4.46–4.33 (m, 3H), 3.82 (dd, J = 13.8, 3.0 Hz, 1H), 3.72 (d, J = 13.8 Hz, 1H), 2.47 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 148.2, 145.9, 144.2, 143.5, 141.8, 138.3, 137.9, 134.9, 134.75, 134.66, 130.7, 129.8, 129.5, 128.9, 128.5, 127.9, 127.6, 124.6, 120.5, 116.4, 68.2, 59.1, 57.7, 49.4, 21.8 ppm. **IR (ATR**

cm^{-1}): $\tilde{\nu} = 3094, 3032, 2922, 2852, 2903, 1737, 1597, 1452, 1341, 1157, 1088, 909, 776, 677, 567$. **HRMS (ESI):** calcd for $\text{C}_{29}\text{H}_{25}\text{N}_3\text{O}_4\text{SCl} [\text{M} + \text{H}]^+$ 546.1254, found 546.1251.

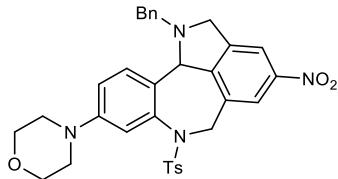
(\pm)-10-Benzyl-7-carbomethoxy-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12j) and 10-Benzyl-7-carbomethoxy-2-nitro-5-tosyl-5,10-dihydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12j')



This reaction was performed according to *General Procedure E* using aldehyde **9j** (51.3 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (85:15 to 100:0 $\text{CH}_2\text{Cl}_2/n$ -hexane) gave **12j** (21.6 mg, 38%) as a pale yellow solid. **Mp:** 205–207 °C. **TLC:** $R_F = 0.48$ (35:65 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 8.08 (dd, $J = 8.1, 1.7$ Hz, 1H), 7.89 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.87–7.84 (m, 3H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.53–7.49 (m, 2H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.40–7.33 (m, 3H), 5.54 (d, $J = 17.8$ Hz, 1H), 5.50 (s, 1H), 4.43–4.36 (m, 2H), 4.24 (d, $J = 13.7$ Hz, 1H), 3.90 (s, 3H), 3.81 (dd, $J = 13.8, 2.7$ Hz, 1H), 3.60 (d, $J = 13.7$ Hz, 1H), 2.50 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 166.0, 148.2, 147.1, 144.4, 143.0, 141.6, 138.2, 138.1, 137.8, 134.3, 130.80, 130.78, 130.2, 130.0, 128.9, 128.4, 127.7, 127.3, 126.3, 120.5, 116.5, 67.9, 59.2, 57.8, 52.5, 50.5, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 1724, 1599, 1526, 1434, 1347, 1312, 1283, 1234, 1156, 1096, 1028, 894, 836, 816, 742, 703, 673, 657, 619, 580, 541, 523, 483$. **HRMS (ESI):** calcd for $\text{C}_{31}\text{H}_{28}\text{N}_3\text{O}_6\text{S} [\text{M} + \text{H}]^+$ 570.1699, found 570.1698.

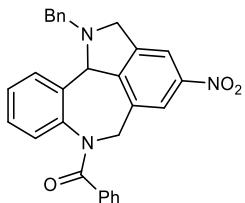
Further elution (0:100 to 1:99 EtOAc/ CH_2Cl_2) gave **12j'** (6.7 mg, 12%) as a bright orange/red solid. **Mp:** 165–170 °C. **TLC:** $R_F = 0.26$ (35:65 EtOAc/n-hexane). **$^1\text{H NMR}$ (500 MHz, CDCl_3):** δ 8.42–8.39 (m, 2H), 7.92 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.72 (t, $J = 1.4$ Hz, 1H), 7.47–7.39 (m, 3H), 7.32 (s, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.13 (d, $J = 6.6$ Hz, 2H), 6.86 (d, $J = 8.3$ Hz, 2H), 6.64 (d, $J = 8.0$ Hz, 2H), 5.45 (d, $J = 16.8$ Hz, 1H), 5.35 (d, $J = 16.4$ Hz, 1H), 5.22 (d, $J = 16.4$ Hz, 1H), 4.53 (d, $J = 16.4$ Hz, 1H), 3.95 (s, 3H), 2.16 (s, 3H) ppm. **$^{13}\text{C NMR}$ (125 MHz, CDCl_3):** δ 166.0, 143.1, 142.5, 138.3, 136.8, 136.0, 134.4, 133.6, 131.3, 129.9, 129.7, 128.9, 128.7, 127.7, 127.2, 126.30, 126.26, 124.4, 122.1, 122.0, 121.8, 118.2, 114.4, 54.5, 53.0, 52.6, 21.4 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 1716, 1603, 1497, 1435, 1409, 1336, 1308, 1290, 1244, 1160, 1095, 1071, 1013, 894, 814, 767, 744, 692, 674, 578, 541, 459$. **HRMS (ESI):** calcd for $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_6\text{SNa} [\text{M} + \text{Na}]^+$ 590.1362, found 590.1365.

(\pm)-10-Benzyl-7-morpholino-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12k)



This reaction was performed according to *General Procedure E* using aldehyde **9k** (54.1 mg, 0.10 mmol) and Bn-Gly-OH-HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH₂Cl₂) gave an initial fraction (3.0 mg) containing the unidentified side product common to all reactions with Bn-Gly-OH-HCl (see Section 5.2 for NMR spectra and additional notes). Further elution (0:100 to 5:95 EtOAc/CH₂Cl₂) gave **12k** (35.5 mg, 59%) as an off-white solid. **Mp:** 220–232 °C. **TLC:** R_F = 0.56 (5:95 EtOAc/CH₂Cl₂). **¹H NMR (400 MHz, CDCl₃):** δ 7.85–7.80 (m, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.62 (dd, J = 8.7, 1.0 Hz, 1H), 7.52–7.48 (m, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.36–7.30 (m, 3H), 6.91 (dd, J = 8.6, 2.6 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 5.57 (d, J = 17.7 Hz, 1H), 5.13 (s, 1H), 4.41 (dd, J = 17.7, 1.4 Hz, 1H), 4.32 (dd, J = 13.9, 2.0 Hz, 1H), 4.23 (d, J = 13.8 Hz, 1H), 3.85–3.77 (m, 4H), 3.69 (dd, J = 13.6, 2.8 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.11–2.99 (m, 4H), 2.47 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 151.5, 148.0, 144.3, 144.0, 141.4, 138.62, 138.59, 138.0, 134.4, 132.5, 129.9, 128.8, 128.4, 127.5, 127.4, 126.4, 120.5, 116.2, 116.1, 116.0, 67.2, 66.8, 59.2, 57.8, 50.7, 49.1, 21.7 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2956, 2839, 1610, 1531, 1496, 1451, 1342, 1308, 1226, 1158, 1116, 960, 910, 812, 744, 699, 669, 653, 589, 546, 523. **HRMS (ESI):** calcd for C₃₃H₃₃N₄O₅S [M + H]⁺ 597.2172, found 597.2182.

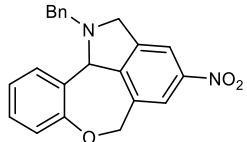
(\pm)-10-Benzyl-2-nitro-5-benzoyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12l)



This compound was prepared according to *General Procedure E* except that the reaction was performed on a slightly reduced scale using aldehyde **9l** (28.1 mg, 0.069 mmol), Bn-Gly-OH-HCl (28.0 mg, 0.14 mmol), 3 Å MS (31.2 mg), NEt₃ (34 µL, 0.24 mmol) and toluene (0.69 mL) with a 3 h reaction time. Flash chromatography (3.5 g silica, 85:15 to 90:10 CH₂Cl₂/n-hexane) gave **12l** (14.4 mg, 45%) as a pale yellow solid. **Mp:** 198–202 °C. **TLC:** R_F = 0.50 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.97 (s, 1H), 7.88 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.46–7.27 (m, 7H), 7.25–7.13 (m, 3H), 7.02 (d, J = 7.8 Hz, 1H), 6.29 (d, J = 17.3 Hz, 1H), 5.69 (s, 1H), 4.45 (dd, J = 13.8, 2.3 Hz, 1H), 4.35 (d, J = 13.5 Hz, 1H), 4.25 (d, J = 17.3 Hz, 1H), 3.94 (dd, J = 13.8, 2.7 Hz, 1H), 3.81 (d, J = 13.5 Hz, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ

(one ArC ‘missing’ due to overlap) 170.6, 148.3, 143.4, 141.1, 138.8, 138.1, 134.9, 134.5, 130.6, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 128.1, 127.7, 125.7, 121.5, 116.2, 68.1, 59.1, 57.9, 48.0 ppm. **IR (ATR, cm⁻¹)**: $\tilde{\nu}$ = 2800, 1646, 1522, 1483, 1454, 1378, 1340, 1298, 1258, 1153, 1078, 906, 778, 731, 698, 588, 483. **HRMS (ESI)**: calcd for C₂₉H₂₄N₃O₃ [M + H]⁺ 462.1818, found 462.1812.

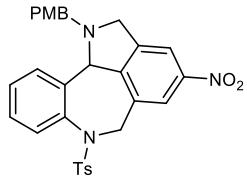
(\pm)-10-Benzyl-2-nitro-4,9b,10,11-tetrahydrobenzo[6,7]oxepino[5,4,3-*cd*]isoindole (12m)



This compound was prepared according to *General Procedure E* using aldehyde **9m** (30.2 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (50:50 CH₂Cl₂/n-hexane) gave **12m** (8.8 mg, 25%) as a white solid. **Mp**: 130–134 °C. **TLC**: R_F = 0.57 (75:25 CH₂Cl₂/n-hexane). **¹H NMR (500 MHz, CDCl₃)**: δ 7.86 (s, 1H), 7.77 (s, 1H), 7.73–7.69 (m, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.46–7.41 (m, 2H), 7.35 (t, 1H), 7.33–7.29 (m, 1H), 7.24–7.21 (m, 2H), 5.76 (s, 1H), 5.49 (d, J = 16.1 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.47–4.39 (m, 2H), 3.86 (dd, J = 13.8, 2.7 Hz, 1H), 3.75 (d, J = 13.8 Hz, 1H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 156.9, 148.1, 144.7, 141.1, 138.6, 136.7, 135.7, 129.0, 128.9, 128.5, 127.6, 125.6, 125.2, 121.8, 119.1, 116.2, 72.2, 66.8, 59.3, 58.0 ppm. **IR (ATR cm⁻¹)**: $\tilde{\nu}$ = 3056, 1701, 1529, 1481, 1343, 1266, 1222, 1045, 895, 773, 734, 699. **HRMS (ESI)**: calcd for C₂₂H₁₈N₂O₃Na [M + Na]⁺ 381.1215, found 381.1227.

5.4.3. Products from Amino Acid Scope (12n–z,aa)

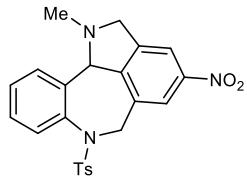
(\pm)-10-(4-Methoxybenzyl)-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12n)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and PMB-Gly-OH·HCl (46.3 mg, 0.20 mmol) with a 1 h reaction time. Flash chromatography (CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12n** (35.1 mg, 65%) as a pale yellow solid. **Mp**: 192–198 °C. **TLC**: R_F = 0.54 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃)**: δ 7.86–7.82 (m, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.47–7.39 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.30–7.26 (m, 1H), 7.15 (dd, J = 7.8, 1.3 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 5.55 (d, J = 17.7 Hz, 1H), 5.37 (s, 1H), 4.41 (d, J = 17.7 Hz, 1H), 4.33 (dd, J = 13.9, 2.2 Hz, 1H), 4.20 (d, J = 13.5 Hz, 1H), 3.85 (s, 3H), 3.76 (dd, J = 13.8, 3.0 Hz, 1H), 3.48 (d, J = 13.5 Hz, 1H), 2.49 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 159.0, 147.9,

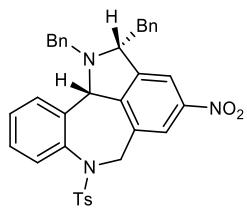
144.1, 143.9, 141.9, 141.6, 138.4, 137.5, 134.5, 130.4, 130.1, 129.63, 129.57, 128.59, 128.56, 127.2, 126.0, 120.5, 116.3, 114.2, 67.4, 58.4, 57.6, 55.5, 50.7, 21.8 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2783, 1612, 1530, 1512, 1484, 1452, 1337, 1304, 1251, 1154, 1129, 1093, 1037, 912, 898, 846, 813, 783, 719, 688, 670, 649, 572, 547, 514, 476. **HRMS (ESI):** calcd for C₃₀H₂₇N₃O₅SnNa [M + Na]⁺ 564.1569, found 564.1553.

(\pm)-10-Methyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12o)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-Gly-OH [freebase] (24.0 mg, 0.27 mmol) with a 9 h reaction time. Flash chromatography (0.75:99.25 EtOAc/CH₂Cl₂) and further purification with polymer-bound *p*-TsOH (*General Procedure E'*) gave **12o** (30.3 mg, 70%) as a yellow solid, which contained 5 mol% of the corresponding isoindole **12o'** as an impurity. Further purification by precipitation from MeOH (*General Procedure E'*) gave a sample of **12o** (23.0 mg) containing <2 mol% of **12o'** for characterization purposes [note that **12o** has a very low solubility in CDCl₃ relative to other analogues of **12**]. **Mp:** 193–199 °C. **TLC:** R_F = 0.54 (35:65 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.91 (s, 1H), 7.84 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.57 (dt, J = 7.8, 1.3 Hz, 1H), 7.39 (td, J = 7.6, 1.3 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.28–7.24 (m, 1H), 7.16 (dd, J = 7.8, 1.3 Hz, 1H), 5.53 (d, J = 17.7 Hz, 1H), 5.01 (s, 1H), 4.51 (dd, J = 13.4, 2.1 Hz, 1H), 4.39 (d, J = 17.7 Hz, 1H), 3.86 (dd, J = 13.4, 3.2 Hz, 1H), 2.58 (s, 3H), 2.46 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 147.9, 144.4, 144.0, 141.9, 141.6, 138.4, 137.5, 134.4, 130.0, 129.6, 128.6, 128.5, 127.2, 126.2, 120.5, 116.1, 69.0, 60.3, 50.6, 41.7, 21.7 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 2821, 2847, 2787, 1684, 1532, 1482, 1341, 1117, 1089, 1017, 888, 783, 681, 572. **HRMS (ESI):** calcd for C₂₃H₂₂N₃O₄S [M + H]⁺ 436.1331, found 436.1335.

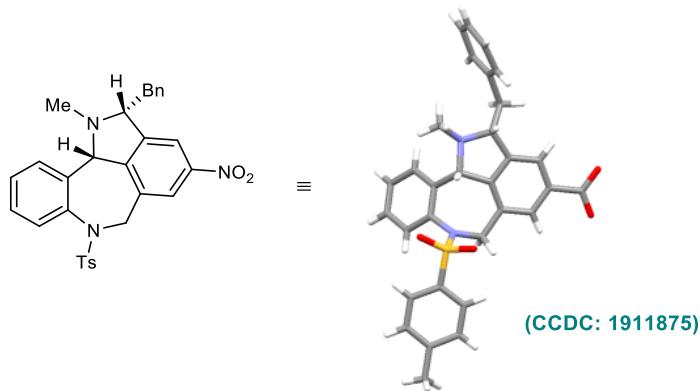
(\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10,11-Dibenzyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12p)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Bn-(L)-Phe-OH·HCl (58.4 mg, 0.20 mmol) with a 23 h reaction time (crude dr of **12p** *cis/trans* = 2.2:1). Flash chromatography (70:30 CH₂Cl₂/n-hexane) gave **12p** (26.4 mg, 44%, dr *cis/trans* = 2.9:1) as a pale yellow solid,

which contained ≤ 10 mol% of an unidentified impurity (relative to the combined diastereomers of **12p**). Precipitation from MeOH (*General Procedure E'*) removed the impurity and gave a diastereoenriched sample of (*cis*)-**12p** (11.1 mg, dr *cis/trans* = 16.7:1) for characterization purposes. **Mp:** 221–224 °C. **TLC:** R_F = 0.55 (30:70 EtOAc/*n*-hexane). **¹H NMR (500 MHz, CDCl₃):** δ (data for *cis* diastereomer only) 7.80 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.67 (dt, J = 7.8, 1.2 Hz, 1H), 7.44 (s, 1H), 7.37–7.32 (m, 3H), 7.32–7.26 (m, 7H), 7.25–7.19 (m, 2H), 7.13–7.07 (m, 3H), 5.81 (s, 1H), 5.56 (d, J = 17.6 Hz, 1H), 4.67 (t, J = 6.4 Hz, 1H), 4.36 (d, J = 17.6 Hz, 1H), 3.93 (d, J = 13.6 Hz, 1H), 3.79 (d, J = 13.6 Hz, 1H), 2.99 (dd, J = 13.7, 5.5 Hz, 1H), 2.84 (dd, J = 13.7, 7.1 Hz, 1H), 2.42 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ (data for *cis* diastereomer only) 148.0, 144.3, 144.0, 143.7, 143.1, 138.2, 137.9, 137.0, 136.7, 133.8, 130.2, 130.0, 129.9, 129.3, 128.7, 128.6, 128.25, 128.17, 127.7, 127.3, 126.8, 126.1, 120.7, 117.1, 67.7, 67.0, 57.8, 50.4, 43.5, 21.7 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2923, 1597, 1525, 1454, 1340, 1156, 1115, 1093, 1029, 907, 862, 816, 754, 701, 672, 649, 570, 544, 479. **HRMS (ESI):** calcd for C₃₆H₃₂N₃O₄S [M + H]⁺ 602.2114, found 602.2116.

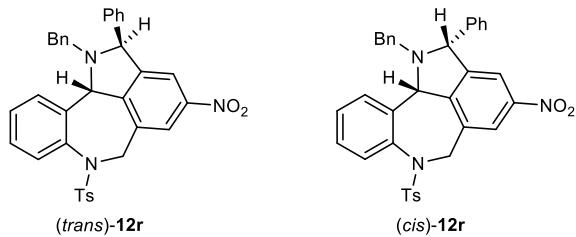
(\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-11-Benzyl-10-methyl-2-nitro-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12q**)**



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(L)-Phe-OH·HCl (43.1 mg, 0.20 mmol) with a 18 h reaction time (single diastereomer of **12q** observed in crude sample). Flash chromatography (CH₂Cl₂) gave **12q** (27.7 mg, 53%, single diastereomer) as a pale yellow solid. **Mp:** 181–184 °C. **TLC:** R_F = 0.58 (30:70 EtOAc/*n*-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.83 (dd, J = 2.1, 1.0 Hz, 1H), 7.73 (dd, J = 2.1, 1.1 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.55 (dt, J = 7.7, 1.3 Hz, 1H), 7.38 (td, J = 7.6, 1.3 Hz, 1H), 7.34–7.28 (m, 6H), 7.27–7.21 (m, 2H), 7.15 (dd, J = 7.8, 1.3 Hz, 1H), 5.56 (d, J = 17.0 Hz, 1H), 5.02 (s, 1H), 4.37 (d, J = 17.6 Hz, 1H), 4.24 (td, J = 6.2, 2.7 Hz, 1H), 3.21 (dd, J = 13.8, 5.7 Hz, 1H), 3.11 (dd, J = 13.8, 6.3 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ (one ArC ‘missing’ due to overlap) 148.0, 144.5, 144.0, 143.5, 142.2, 138.3, 137.9, 137.1, 134.0, 130.01, 129.99, 129.5, 128.5, 128.4, 127.2, 126.7, 126.1, 120.7, 116.6, 70.7, 69.1, 50.5, 42.0, 40.8, 21.7 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu}$ = 3088, 3064, 3028, 2920, 2854, 2800, 1702, 1525, 1341, 1161, 1010, 787, 701, 648, 584. **HRMS (ESI):** calcd for C₃₀H₂₈N₃O₄S [M + H]⁺ 526.1801, found 526.1779. **CCDC:** 1911875.

Crystals of **12q** suitable for X-ray analysis were obtained by the same crystallization procedure as described for **9a** (Section 3.2).

(\pm)-[(9b*R*,11*S*)/(9b*S*,11*R*)]-10-Benzyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (*(trans)*-12*r*) and (\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10-Benzyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (*(cis)*-12*r*)



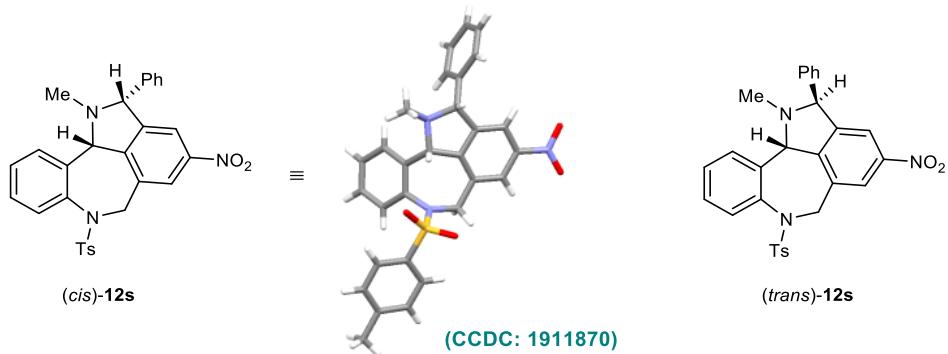
This reaction was performed according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Bn-(D/L)-Phg-OH·HCl (55.5 mg, 0.20 mmol) with a 24 h initial reaction time. After cooling to room temperature, an additional portion of solid Bn-(D/L)-Phg-OH·HCl (27.8 mg, 0.10 mmol) was added, followed by additional NEt_3 (21 μL , 0.15 mmol) and toluene (0.2 mL). The vial was purged again with N_2 then heated at 100 °C for a further 23 h (crude dr of **12r** *trans/cis* = 1.1:1). Flash chromatography (70:30 $\text{CH}_2\text{Cl}_2/n$ -hexane) resulted in partial separation of the diastereomers (marginally resolved by TLC) but the product fractions also contained an unidentified impurity (the impurity exhibited singlets at 5.19 ppm and 4.65 ppm of equal integration in the ^1H NMR spectrum). Therefore, all fractions containing **12r** were combined (44.7 mg) and treated with polymer-bound *p*-TsOH (*General Procedure E'*: stirring time = 24 h). In this case, incomplete adsorption of **12r** was observed and two separate samples ('A' and 'B') containing **12r** were obtained: (A) purified product recovered from the resin (28.2 mg, 48%, dr *trans/cis* = 2.1:1) as an off-white solid and (B) impure product recovered from the filtrate/resin-washings (15.9 mg, dr *cis/trans* = 7:1). Note that the recovered diastereomeric ratios indicated that partial selectivity for adsorption of the *trans* diastereoisomer to the resin had occurred. Sample B was further purified by precipitation from MeOH (*General Procedure E''* with cooling in a freezer instead of room temperature before filtration) to give an additional portion of pure **12r** (Sample B') highly enriched in the *cis*-diastereomer (3.1 mg, 5%, dr *cis/trans* = 33:1) as a pale pink solid. Note that the manuscript lists the combined yield and dr of isolated samples A and B' (31.3 mg, 53%, dr *trans/cis* = 1.6:1).

Data for Sample A enriched in (*trans*)-**12r** (dr *trans/cis* = 2.1:1). **Mp:** 121–127 °C. **TLC:** R_F = 0.50 [*cis*], 0.44 [*trans*] (75:25 CH₂Cl₂/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ (data for *trans* diastereomer only) 7.90 (s, 1H), 7.78–7.73 (m, 3H), 7.69 (s, 1H), 7.42–7.14 (m, 13H), 6.46 (d, J = 7.5 Hz, 2H), 5.74 (d, J = 18.0 Hz, 1H), 5.57 (s, 1H), 5.37 (s, 1H), 4.53 (d, J = 18.0 Hz, 1H), 3.98 (d, J = 15.0 Hz, 1H), 3.18 (d, J = 15.0 Hz, 1H), 2.44 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ (data for *trans* diastereomer only) 148.4, 146.1, 144.1, 143.1, 141.6, 138.59, 138.56, 138.4, 137.2, 134.4, 130.2, 129.8, 129.7, 129.0, 128.7, 128.6*, 128.5, 128.4, 128.1, 127.9, 127.2, 125.6, 120.7, 117.6, 69.1, 66.1, 52.3, 50.6, 21.8 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2921, 1598, 1529, 1494, 1453,

1339, 1241, 1161, 1094, 1028, 904, 866, 833, 806, 744, 723, 698, 671, 647, 566, 543, 506, 483. **HRMS (ESI):** calcd for $C_{35}H_{29}N_3O_4SNa$ $[M + Na]^+$ 610.1776, found 610.1784. *Tentative assignment of *trans* isomer due to poor resolution with *cis* epimer.

Data for Sample B' highly enriched in (*cis*)-**12r** (dr *cis/trans* = 33:1). **Mp:** 108–114 °C. **TLC:** R_F = 0.50 [*cis*] (75:25 CH₂Cl₂/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ (data for *cis* diastereomer only) 7.89 (dt, J = 7.7, 1.3 Hz, 1H), 7.83–7.79 (m, 3H), 7.46 (td, J = 7.6, 1.3 Hz, 1H), 7.40–7.24 (m, 11H), 7.23–7.16 (m, 3H), 7.10 (dd, J = 7.8, 1.2 Hz, 1H), 6.07 (s, 1H), 5.54 (d, J = 17.7 Hz, 1H), 5.23 (d, J = 2.8 Hz, 1H), 4.41 (d, J = 17.7 Hz, 1H), 4.04 (ABq, $\Delta\delta_{AB}$ = 0.05, J = 14.1 Hz, 2H), 2.48 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ (data for *cis* diastereomer only) 148.2, 145.6, 144.1, 143.1, 142.5, 142.2, 138.4, 137.5, 135.4, 134.1, 130.6, 130.1, 129.6, 128.8, 128.55, 128.51, 128.49, 128.14, 128.06, 127.6, 127.3, 126.3, 120.6, 117.4, 70.2, 64.8, 54.7, 50.6, 21.8 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2921, 2851, 1598, 1528, 1453, 1339, 1159, 1095, 1028, 904, 834, 800, 754, 699, 673, 566, 542, 505, 481. **HRMS (ESI):** calcd for $C_{35}H_{30}N_3O_4S$ $[M + H]^+$ 588.1957, found 588.1974.

(\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10-Methyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole ((*cis*)-12s**) and (\pm)-[(9b*R*,11*S*)/(9b*S*,11*R*)]-10-Methyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole ((*trans*)-**12s**)**



This reaction was performed according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(D/L)-Phg-OH·HCl (40.3 mg, 0.20 mmol) with a 39 h reaction time (crude dr of **12s** *cis/trans* = 1.7:1). Flash chromatography (70:30 CH₂Cl₂/n-hexane) gave an initial fraction of **12s** highly enriched in the *cis*-diastereomer (16.5 mg, 32%, dr *cis/trans* = 25:1) as a pale pink solid. Further elution gave an additional sample of **12s** enriched in the *trans*-diastereomer (10.2 mg, 20%, dr *trans/cis* = 6.3:1) as a pale pink solid. Both these samples contained a trace of the unidentified side product discussed in Section 5.2. Note that the manuscript states the combined yield and dr of the two isolated samples (26.7 mg, 52%, dr *cis/trans* = 1.8:1).

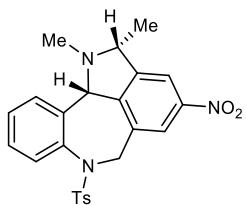
Precipitation of the *cis*-diastereoenriched sample from MeOH (*General Procedure E''* with cooling in a freezer instead of room temperature before filtration) provided a diastereomerically pure sample of (*cis*)-**12s** (11.1 mg, single diastereomer) for characterization purposes. Data for (*cis*)-**12s**. **Mp:** 247–254 °C. **TLC:** R_F = 0.54 [*cis*] (75:25 CH₂Cl₂/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.86 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.71 (dt, J = 7.7, 1.4 Hz, 1H), 7.48–7.33 (m, 9H), 7.31 (td, J = 7.7, 1.6 Hz, 1H), 7.20 (dd, J = 7.9, 1.3 Hz, 1H),

5.60 (d, $J = 17.7$ Hz, 1H), 5.21 (s, 1H), 4.85 (d, $J = 3.0$ Hz, 1H), 4.44 (d, $J = 17.7$ Hz, 1H), 2.51 (s, 3H), 2.48 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 148.2, 145.7, 144.1, 143.3, 141.9, 141.4, 138.4, 137.4, 134.3, 130.1, 129.7, 128.9, 128.6, 128.55, 128.46, 128.4, 127.2, 126.2, 120.7, 117.1, 74.6, 68.1, 50.7, 39.3, 21.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 2787, 1598, 1524, 1483, 1455, 1339, 1157, 1116, 1099, 1022, 904, 865, 836, 801, 743, 713, 669, 649, 565, 541, 516$. **HRMS (ESI):** calcd for $\text{C}_{29}\text{H}_{26}\text{N}_3\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 512.1644, found 512.1631. **CCDC [(*cis*)-12s]:** 1911870.

Data for diastereoenriched (*trans*)-12s (dr *trans/cis* = 6.3:1). **Mp:** 124–140 °C. **TLC:** $R_F = 0.48$ [*trans*] (75:25 $\text{CH}_2\text{Cl}_2/n$ -hexane). **^1H NMR (400 MHz, CDCl_3):** δ (data for *trans* diastereomer only) 7.87 (d, $J = 2.0$ Hz, 1H), 7.74–7.70 (m, 3H), 7.54 (dt, $J = 7.5, 1.4$ Hz, 1H), 7.47–7.27 (m, 8H), 6.92–6.83 (m, 2H), 5.71 (d, $J = 18.0$ Hz, 1H), 5.56 (d, $J = 3.2$ Hz, 1H), 5.08 (s, 1H), 4.49 (d, $J = 18.1$ Hz, 1H), 2.39 (s, 3H), 2.15 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ (data for *trans* diastereomer only) 148.4, 146.1, 144.0, 143.6, 141.5, 139.7, 138.7, 137.1, 134.2, 130.1, 129.7, 129.5, 128.8, 128.7, 128.6, 128.2, 127.1, 125.9, 120.7, 117.5, 72.5, 67.4, 50.6, 36.4, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} = 2919, 2850, 1597, 1528, 1454, 1338, 1158, 1097, 1021, 904, 866, 833, 814, 801, 744, 723, 701, 667, 648, 565, 543, 503, 481$. **HRMS (ESI):** calcd for $\text{C}_{29}\text{H}_{26}\text{N}_3\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 512.1644, found 512.1662.

Crystals of (*cis*)-12s suitable for X-ray analysis were obtained by the same crystallization procedure as described for 9a (Section 3.2).

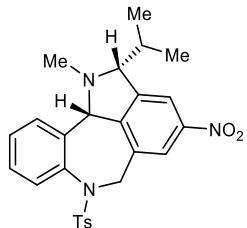
(\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10,11-Dimethyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12t)



This compound was prepared according to *General Procedure E* using aldehyde 9a (45.5 mg, 0.10 mmol) and Me-(L)-Ala-OH [freebase] (20.6 mg, 0.20 mmol) with a 16 h reaction time (single diastereomer of 12t observed in crude sample). Flash chromatography (70:30 to 75:25 $\text{CH}_2\text{Cl}_2/n$ -hexane) gave 12t (25.1 mg, 56%, single diastereomer) as a light pink solid. **Mp:** 186–188 °C. **TLC:** $R_F = 0.54$ (30:70 EtOAc/n-hexane). **^1H NMR (500 MHz, CDCl_3):** δ 7.85 (s, 1H), 7.82 (s, 1H), 7.72 (d, $J = 8.3$ Hz, 2H), 7.57 (dt, $J = 7.8, 1.4$ Hz, 1H), 7.38 (td, $J = 7.6, 1.3$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.25 (td, $J = 7.7, 1.1$ Hz, 1H), 7.16 (dd, $J = 7.8, 1.3$ Hz, 1H), 5.56 (d, $J = 18.0$ Hz, 1H), 4.99 (s, 1H), 4.39 (d, $J = 17.7$ Hz, 1H), 3.90 (qd, $J = 6.3, 2.4$ Hz, 1H), 2.53 (s, 3H), 2.45 (s, 3H), 1.51 (d, $J = 6.3$ Hz, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 148.2, 146.4, 144.0, 143.5, 142.0, 138.5, 137.4, 134.2, 130.0, 129.5, 128.5, 128.4, 127.2, 126.3, 120.6, 115.9, 68.7, 65.1, 50.7, 39.6, 21.7, 19.8 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu} =$

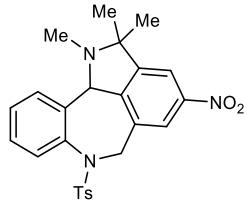
(ATR cm⁻¹): $\tilde{\nu}$ = 3065, 2963, 2921, 2845, 2789, 2598, 1523, 1482, 1341, 1115, 915, 811, 776, 705, 651, 568. **HRMS (ESI):** calcd for C₂₄H₂₄N₃O₄S [M + H]⁺ 450.1488, found 450.1489.

(\pm)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10-Methyl-11-isopropyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12u)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(L)-Val-OH·HCl (33.5 mg, 0.20 mmol) with a 39 h reaction time (single diastereomer of **12u** observed in crude sample). Flash chromatography (70:30 CH₂Cl₂/n-hexane) gave **12u** (26.9 mg, 56%, single diastereomer) as an off-white solid. **Mp:** 194–198 °C. **TLC:** R_F = 0.58 (30:70 EtOAc/n-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.88 (s, 1H), 7.85 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.33–7.24 (m, 3H), 7.20 (dd, J = 7.8, 1.4 Hz, 1H), 5.60 (d, J = 17.8 Hz, 1H), 5.00 (s, 1H), 4.41 (d, J = 17.7 Hz, 1H), 3.98 (s, 1H), 2.52 (s, 3H), 2.44 (s, 3H), 2.20 (pd, J = 7.0, 2.6 Hz, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 148.2, 144.2, 144.0, 143.9, 142.4, 138.5, 137.3, 133.9, 130.0, 129.5, 128.8, 128.3, 127.2, 126.1, 120.4, 116.6, 75.0, 69.8, 50.6, 42.5, 32.9, 21.7, 19.4, 18.2 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2959, 2798, 1597, 1529, 1484, 1454, 1341, 1313, 1155, 1125, 1094, 1038, 912, 867, 814, 784, 744, 716, 672, 647, 570, 542, 517, 478. **HRMS (ESI):** calcd for C₂₆H₂₈N₃O₄S [M + H]⁺ 478.1801, found 478.1808.

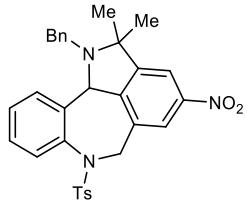
(\pm)-10,11,11-Trimethyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12w)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-Aib-OH·HCl (30.7 mg, 0.20 mmol) with a 64 h reaction time. Flash chromatography (75:25 CH₂Cl₂/n-hexane) gave **12w** (25.7 mg, 55%) as a pale yellow solid. **Mp:** 225–227 °C. **TLC:** R_F = 0.59 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.82 (s, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.50 (dt, J = 7.7, 1.3 Hz, 1H), 7.36 (td, J = 7.4, 1.5 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.28–7.24 (m, 1H), 7.22 (dd, J = 7.8, 1.5 Hz, 1H), 5.62 (d, J = 17.8 Hz, 1H), 4.82 (s, 1H), 4.40 (d, J = 17.8 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H), 1.52 (s, 3H), 1.17 (s, 3H)

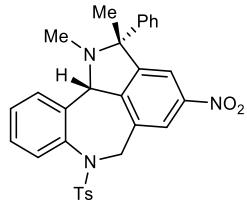
ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 151.3, 148.3, 144.0, 142.4, 141.6, 138.7, 137.4, 134.1, 130.0, 129.4, 129.0, 128.3, 127.2, 126.2, 120.4, 115.3, 66.3, 65.4, 50.8, 33.1, 27.4, 23.9, 21.6 ppm. **IR (ATR, cm⁻¹):** ̄ = 2968, 1594, 1532, 1481, 1455, 1340, 1312, 1238, 1154, 1108, 1015, 972, 910, 870, 815, 795, 764, 728, 674, 648, 572, 545, 463. **HRMS (ESI):** calcd for C₂₅H₂₆N₃O₄S [M + H]⁺ 464.1644, found 464.1634.

(±)-10-Benzyl-11,11-dimethyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12x)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Bn-Aib-OH·HCl (45.9 mg, 0.20 mmol) with a 68 h reaction time. Flash chromatography (75:25 CH₂Cl₂/n-hexane) gave **12x** (25.4 mg, 47%) as a white solid. **Mp:** 237–239 °C. **TLC:** *R*_F = 0.65 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃):** δ 7.84–7.82 (m, 1H), 7.77–7.74 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.36–7.25 (m, 6H), 7.25–7.19 (m, 2H), 5.63 (d, *J* = 17.7 Hz, 1H), 5.22 (s, 1H), 4.41 (dd, *J* = 17.7, 1.4 Hz, 1H), 3.93 (d, *J* = 14.3 Hz, 1H), 3.77 (d, *J* = 14.2 Hz, 1H), 2.48 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 151.8, 148.4, 144.0, 142.2, 141.9, 139.4, 138.6, 137.2, 134.1, 130.1, 129.4, 129.2, 128.9, 128.4, 128.3, 127.4, 127.3, 126.0, 120.5, 115.3, 66.7, 66.4, 53.5, 50.8, 30.1, 24.9, 21.7 ppm. **IR (ATR, cm⁻¹):** ̄ = 2967, 1598, 1528, 1451, 1337, 1155, 1116, 910, 870, 818, 746, 700, 676, 647, 564, 543, 483. **HRMS (ESI):** calcd for C₃₁H₃₀N₃O₄S [M + H]⁺ 540.1957, found 540.1963.

(±)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10,11-Dimethyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12y)

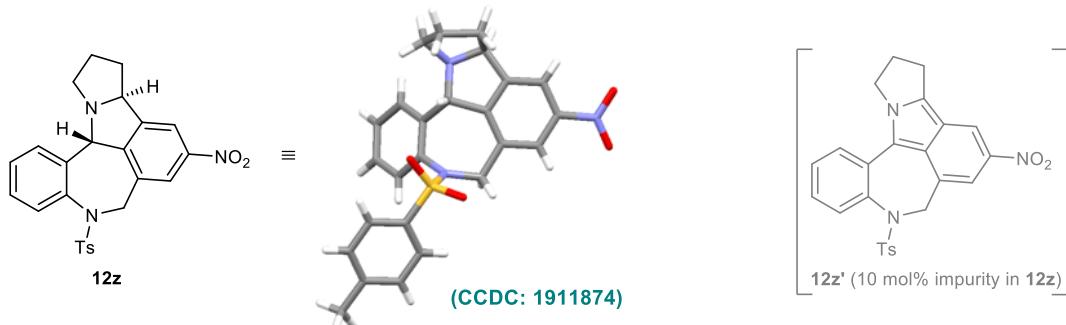


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(D/L)-(α-Me)-Phg-OH·HCl (43.1 mg, 0.20 mmol) with a 68 h reaction time (crude dr of **12y** *cis/trans* = 3.7:1). Flash chromatography (65:35 to 70:30 CH₂Cl₂/n-hexane) gave **12y** (19.9 mg, 38%, dr *cis/trans* = 3.8:1) as a white solid. **Mp:** 216–222 °C. **TLC:** *R*_F = 0.61 (30:70 EtOAc/n-hexane). NMR data for *cis*-diastereomer only (major): **¹H NMR (500 MHz, CDCl₃):** δ 7.81 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.65 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.63–7.60 (m, 2H), 7.46–7.41 (m, 2H), 7.40–7.35 (m, 2H), 7.34–7.24 (m, 5H), 5.65 (d, *J* =

17.8 Hz, 1H), 5.02 (s, 1H), 4.45 (d, J = 17.9 Hz, 1H), 2.46 (s, 3H), 2.32 (s, 3H), 1.58 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 151.6, 148.3, 145.1, 144.0, 142.3, 141.4, 138.7, 137.5, 134.2, 130.1, (129.6)*, (129.2)*, (128.50)*, 128.48, (128.46)*, (127.7)*, 127.4, 127.2, 126.1, 120.4, 116.5, 70.8, 65.7, 50.8, 33.1, 21.7, 21.0 ppm.

*One of the five peaks listed in brackets is from the *trans* isomer; unable to assign with certainty in this region in the absence of a more diastereoenriched sample. NMR data for *trans*-diastereomer only (minor): **^1H NMR (500 MHz, CDCl_3):** δ 7.88 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.67–7.64 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.41–7.35 (m, 2H), 7.35–7.24 (m, 6H), 6.85 (d, J = 6.9 Hz, 2H), 5.75 (d, J = 18.1 Hz, 1H), 4.89 (s, 1H), 4.50 (d, J = 18.7 Hz, 1H), 2.34 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ (three ArC's unassigned between 127–130 ppm due to overlap with *cis*-diastereomer) 150.7, 148.7, 144.0, 143.0, 142.0, 141.8, 138.6, 137.0, 134.0, 129.7, 129.5, 127.4, 127.3, 127.0, 125.9, 120.6, 116.8, 70.9, 67.2, 50.6, 34.4, 26.0, 21.7 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 2975, 1597, 1527, 1481, 1456, 1340, 1279, 1236, 1156, 1098, 908, 871, 806, 755, 724, 702, 675, 647, 568, 544, 484. **HRMS (ESI):** calcd for $\text{C}_{30}\text{H}_{28}\text{N}_3\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 526.1801, found 526.1805.

(\pm)-[(9b*R*,13a*S*)/(9b*S*,13a*R*)]-2-Nitro-5-tosyl-5,9b,11,12,13,13a-hexahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]pyrrolo[2,1-*a*]isoindole (12z)

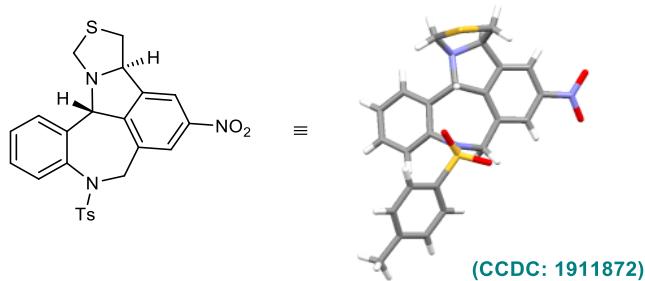


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and (L)-Pro-OH [freebase] (23.0 mg, 0.20 mmol) with a 15 h reaction time (single diastereomer of **12z** observed in crude sample). Flash chromatography (77.5:22.5 to 100:0 $\text{CH}_2\text{Cl}_2/n$ -hexane) gave **12z** (17.8 mg, 39%, single diastereomer) as a pink solid, which contained 10 mol% of the corresponding isoindole **12z'** as an impurity. Note that precipitation from MeOH (*General Procedure E'*) resulted in no change in sample composition (15.1 mg returned). Characterization was therefore performed on the mixed sample. **Mp:** 201–203 °C. **TLC:** R_F = 0.60 (30:70 EtOAc/n-hexane). NMR data for **12z** only (major component of mixture): **^1H NMR (500 MHz, CDCl_3):** δ 7.88 (s, 1H), 7.86 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.30–7.25 (m, 3H), 7.22 (dd, J = 7.8, 1.4 Hz, 1H), 5.67 (d, J = 17.8 Hz, 1H), 4.95 (s, 1H), 4.68 (td, J = 7.5, 2.7 Hz, 1H), 4.43 (d, J = 17.8 Hz, 1H), 3.20 (dt, J = 11.0, 6.6 Hz, 1H), 2.52 (dt, J = 11.0, 6.4 Hz, 1H), 2.43 (s, 3H), 2.28–2.20 (m, 1H), 1.93–1.85 (m, 1H), 1.78–1.70 (m, 1H), 1.64–1.56 (m, 1H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 148.4, 145.7, 144.1, 144.0, 143.2, 138.5, 136.3, 134.2, 130.0, 129.5, 129.1, 128.3, 127.1, 126.3, 120.6,

116.5, 70.5, 69.5, 55.5, 50.5, 32.9, 26.4, 21.7 ppm. NMR data for **12z'** only (minor component of mixture): **¹H NMR (500 MHz, CDCl₃)**: δ (resolved signals only) 8.36 (d, *J* = 1.6 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 5.36 (d, *J* = 16.5 Hz, 1H), 4.62 (dt, *J* = 11.4, 8.1 Hz, 1H), 4.48 (d, *J* = 17.1 Hz, 1H), 4.04 (ddd, *J* = 11.5, 9.0, 2.7 Hz, 1H), 3.04 (ddd, *J* = 16.2, 9.2, 2.6 Hz, 1H), 2.82–2.73 (m, 1H), 2.14 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ (resolved signals only) 141.8, 141.5, 137.2, 137.0, 136.1, 133.5, 130.9, 130.7, 129.0, 127.2, 126.5, 126.4, 125.1, 118.5, 115.1, 113.5, 54.6, 49.7, 27.7, 23.9, 21.4 ppm. **IR (ATR cm⁻¹)**: $\tilde{\nu}$ = 3075, 2954, 2919, 2853, 1594, 1530, 1452, 1341, 1155, 878, 778, 725, 677, 579. **HRMS (ESI)**: calcd for **12z**: C₂₅H₂₄N₃O₄S [M + H]⁺ 462.1488, found 462.1502. **HRMS (ESI)**: calcd for **12z'**: C₂₅H₂₁N₃O₄Na [M + Na]⁺ 482.1150, found 482.1145. **CCDC (12z)**: 1911874.

Crystals of **12z** suitable for X-ray analysis were obtained by the same crystallization procedure as described for **9a** (Section 3.2), except that MeOH was used as the diffusion solvent instead of pentane.

(\pm)-[(9b*R*,13a*R*)/(9b*S*,13a*S*)]-2-Nitro-5-tosyl-5,9b,13,13a-tetrahydro-4*H*-11*H*-benzo[6,7]azepino[5,4,3-*cd*]thiazolo[4,3-*a*]isoindole (12aa)

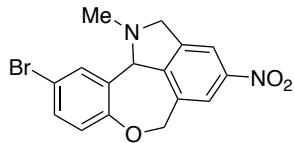


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and (L)-ThiaPro-OH [freebase] (26.6 mg, 0.20 mmol) with a 15 h reaction time (single diastereomer of **12aa** observed in crude sample) [note that **12aa**, like **12o**, has a very low solubility in CDCl₃ relative to other analogues, thus determination of an accurate NMR yield by complete dissolution of the crude sample in CDCl₃ was not possible]. Flash chromatography (88:12 CH₂Cl₂/n-hexane) gave **12aa** (32.4 mg, 68%, single diastereomer) as a light orange solid, which contained \leq 3 mol% of the corresponding isoindole **12aa'** as an impurity. Precipitation from MeOH (*General Procedure E'*) gave a pure sample of **12aa** for characterization purposes. **Mp**: 245–253 °C. **TLC**: *R_F* = 0.57 (30:70 EtOAc/n-hexane). **¹H NMR (500 MHz, CDCl₃)**: δ 7.94 (d, *J* = 1.1 Hz, 1H), 7.89 (d, *J* = 1.1 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.42–7.37 (m, 2H), 7.35–7.31 (m, 1H), 7.28–7.24 (m, 2H), 5.68 (d, *J* = 18.0 Hz, 1H), 4.98 (s, 1H), 4.89 (dd, *J* = 9.3, 4.1 Hz, 1H), 4.43 (d, *J* = 18.1 Hz, 1H), 4.33 (d, *J* = 10.7 Hz, 1H), 3.85 (d, *J* = 10.7 Hz, 1H), 3.38 (dd, *J* = 11.0, 8.0 Hz, 1H), 2.78 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.43 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 148.5, 144.3, 144.1, 143.1, 141.3, 138.1, 136.8, 134.6, 130.1, 129.9, 129.6, 128.8, 127.0, 125.9, 121.3, 116.2, 72.2, 67.7, 60.5, 50.3, 40.5, 21.8 ppm. **IR (ATR, cm⁻¹)**: $\tilde{\nu}$ = 2925, 1594, 1529, 1483, 1341, 1314, 1156, 1118, 1099, 901, 822, 780, 743, 715,

671, 651, 579, 565, 543, 519, 479. **HRMS (ESI):** calcd for $C_{24}H_{21}N_3O_4S_2Na$ $[M + Na]^+$ 502.0871, found 502.0870. **CCDC:** 1911872.

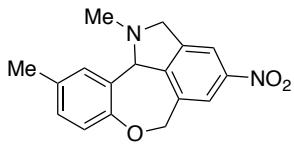
Crystals of **12aa** suitable for X-ray analysis were obtained by the same crystallization procedure as described for **9a** (Section 3.2).

8-bromo-10-methyl-2-nitro-4,9b,10,11-tetrahydrobenzo[6,7]oxepino[5,4,3-cd]isoindole (12bb)



The compound was prepared according to *General Procedure E* using 5-bromo-2-((3,5-dinitrobenzyl)oxy)benzaldehyde and sarcosine (**9a**) with a 12-hour reaction time. Flash chromatography (EtOAc/n-hexanes) gave **12bb** (7.1 mg, 15% yield) as a pale red residue. **TLC:** $R_F = 0.30$ (20:80 EtOAc/n-hexanes). **¹H NMR (400 MHz, CDCl₃):** δ 7.93 (s, 1H), 7.75 (s, 1H), 7.61 (dd, $J = 2.3, 1.1$ Hz, 1H), 7.39 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 5.46 (d, $J = 16.0$ Hz, 1H), 5.41 (s, 1H), 4.93 (d, $J = 16.0$ Hz, 1H), 4.56 (dd, $J = 13.7, 2.3$ Hz, 1H), 3.97 (d, $J = 23.6$ Hz, 1H), 2.73 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 155.9, 148.2, 144.3, 141.5, 139.0, 135.2, 131.8, 128.6, 123.6, 119.2, 118.8, 116.1, 72.1, 68.1, 60.5, 41.9 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu} = 1700$ (m), 1534 (m), 1483 (w), 1343 (s), 1264 (s), 1047 (m), 895 (m), 732 (s), 702 (s). **HRMS (ESI):** calcd for $C_{16}H_{14}N_2O_3Br$ $[M + H]^+$ 361.0188, found 361.0185.

8,10-dimethyl-2-nitro-4,9b,10,11-tetrahydrobenzo[6,7]oxepino[5,4,3-cd]isoindole (12cc)

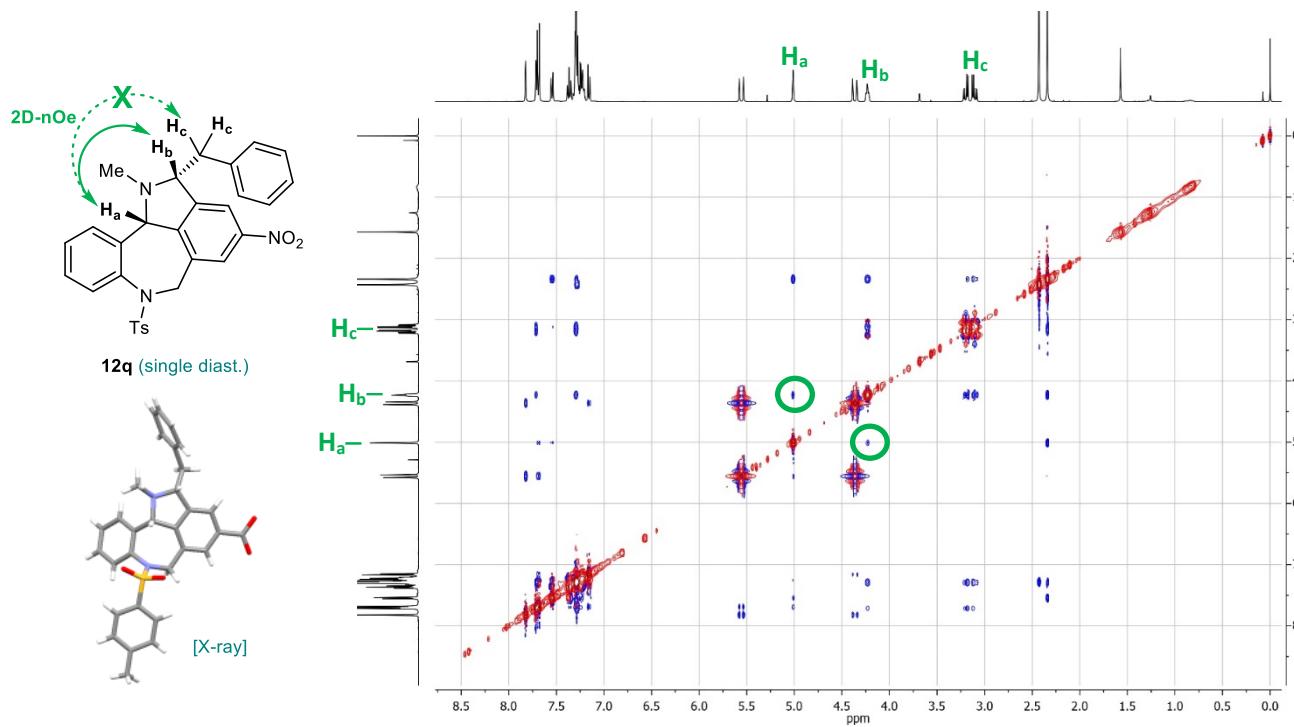


The compound was prepared according to *General Procedure E* using 2-((3,5-dinitrobenzyl)oxy)-5-methylbenzaldehyde and sarcosine (**9a**) with a 12-hour reaction time. Flash chromatography (EtOAc/n-hexanes) gave **12cc** (11.4 mg, 23% yield) as a yellow residue. **TLC:** $R_F = 0.29$ (20:80 EtOAc:n-hexanes). **¹H NMR (500 MHz, CDCl₃):** δ 7.92 (s, 1H, CH_{Ar}), 7.75 (s, 1H), 7.28 (s, 1H), 7.11-7.04 (m, 2H), 5.45-5.41 (m, 2H), 4.93 (d, $J = 15.8$ Hz), 4.56 (d, $J = 13.5$ Hz, 1H), 3.96 (dd, $J = 13.5, 2.3$ Hz, 1H), 2.75 (s, 3H), 2.35 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 154.7, 148.0, 145.3, 141.4, 136.1, 135.8, 135.1, 129.2, 125.8, 121.4, 119.2, 115.9, 72.2, 68.4, 60.6, 42.1, 21.3 ppm. **IR (ATR cm⁻¹):** $\tilde{\nu} = 1700$ (m), 1534 (m), 1483 (w), 1343 (s), 1264 (s), 1047 (m), 895 (m), 732 (s), 702 (s). **HRMS (ESI):** calcd for $C_{17}H_{17}N_2O_3$ $[M + H]^+$ 297.1239, found 297.1235.

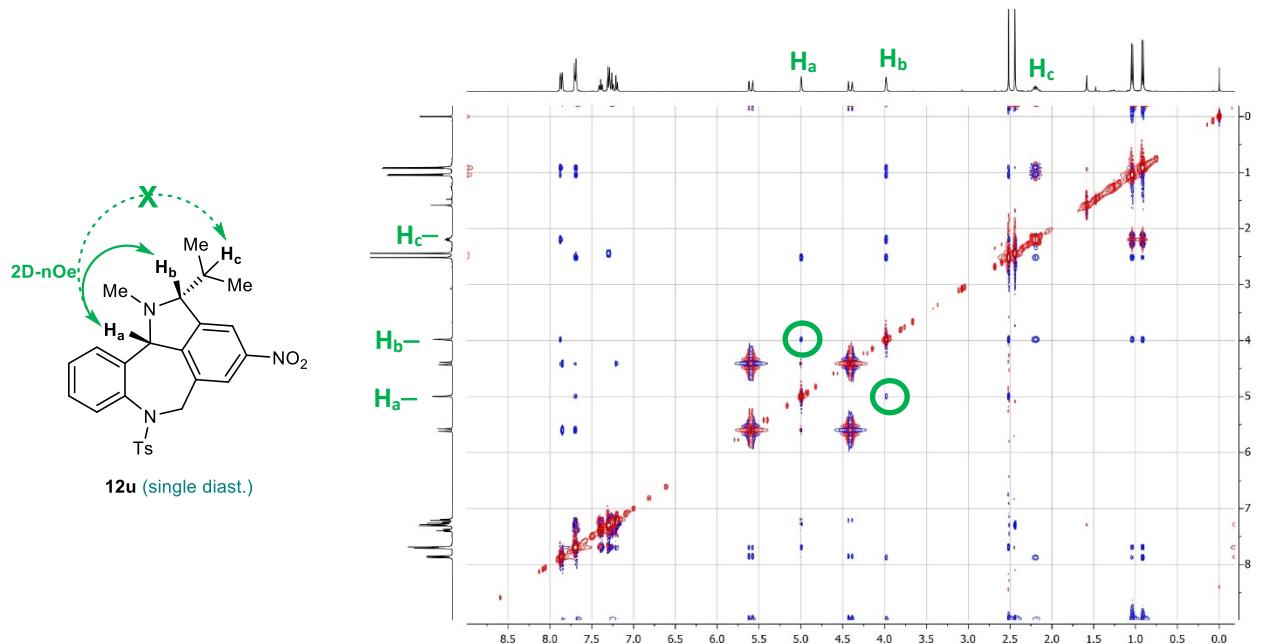
5.5. Determination of Relative Stereochemistry of 12p, 12t, 12u and 12y by nOe NMR Spectroscopy

Note: Full ^1H and ^{13}C spectra for each compound are given in Section 9.

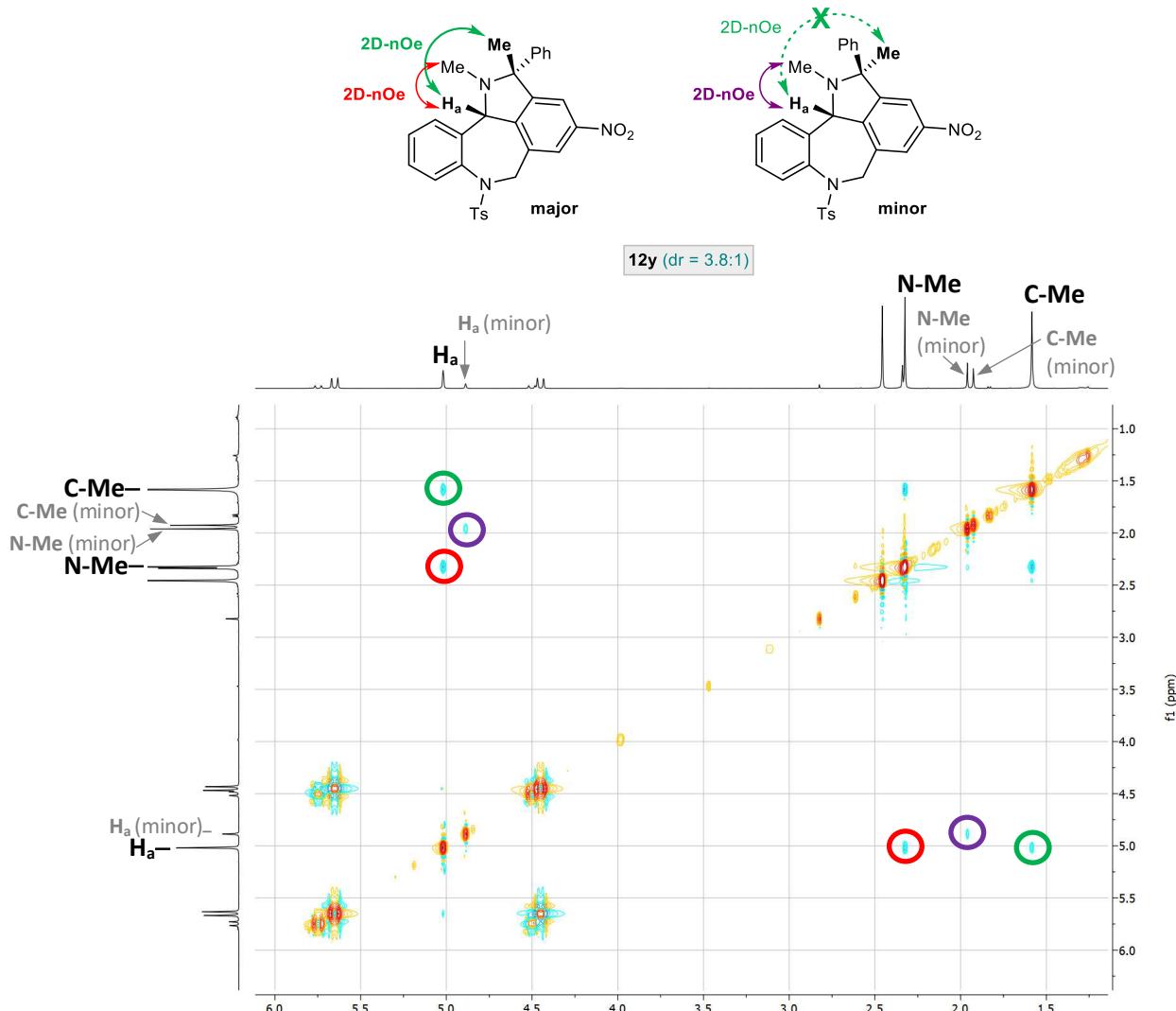
- **Compound 12q** of known *cis*-configuration (X-ray) was used as a positive control to confirm a 2D-nOe correlation between H_a and H_b . Note that no correlation between H_a and H_c was observed, as expected for the *cis* stereochemistry.



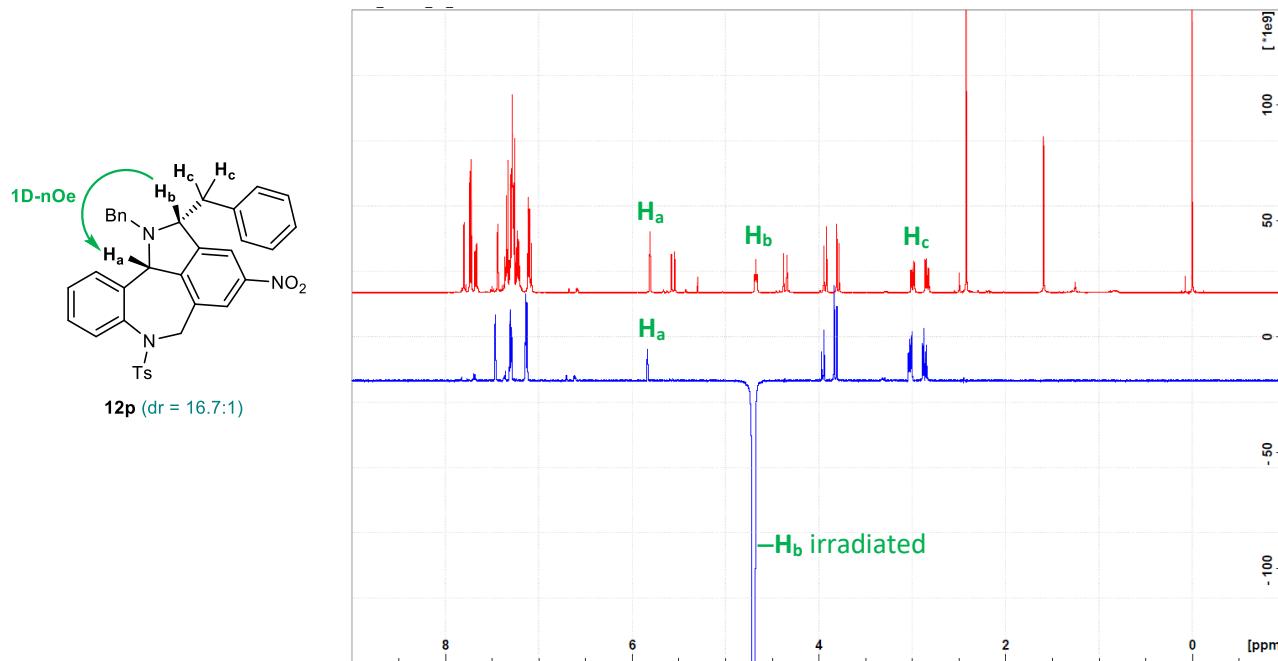
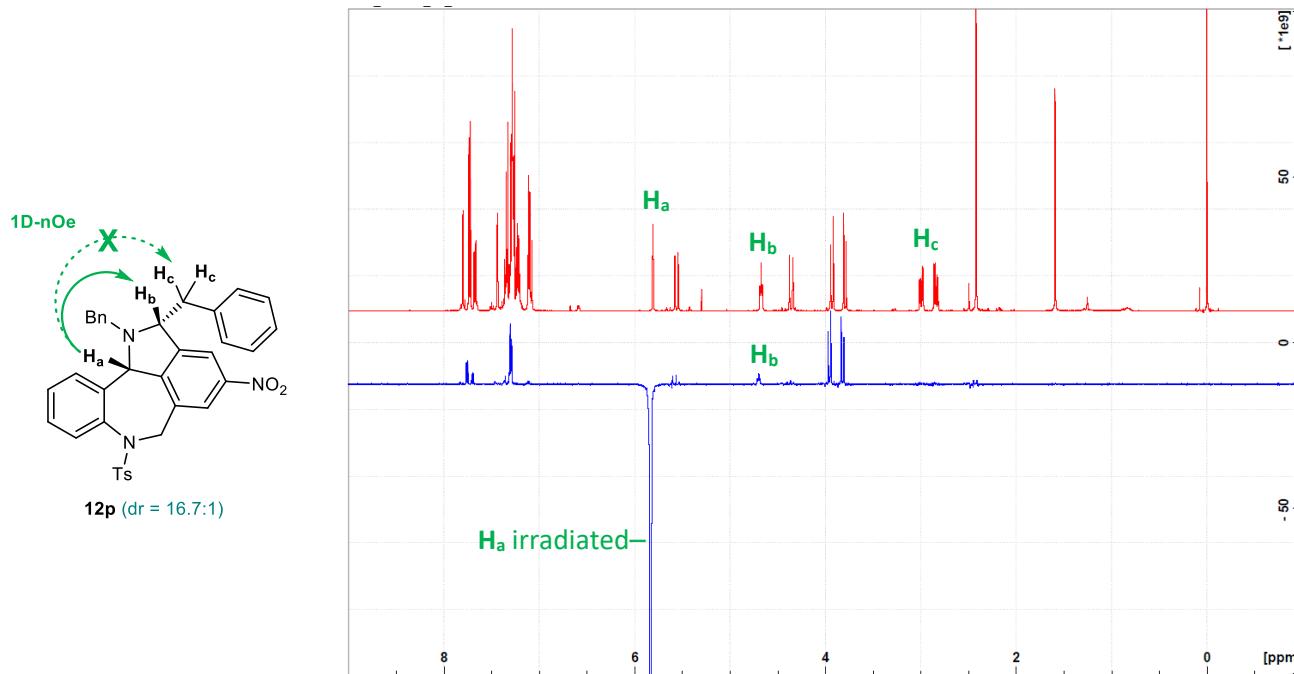
- **Compound 12u** exhibited an analogous 2D-nOe correlation between H_a and H_b . Further evidence for the assigned *cis* stereochemistry was the absence of a H_a – H_c correlation.



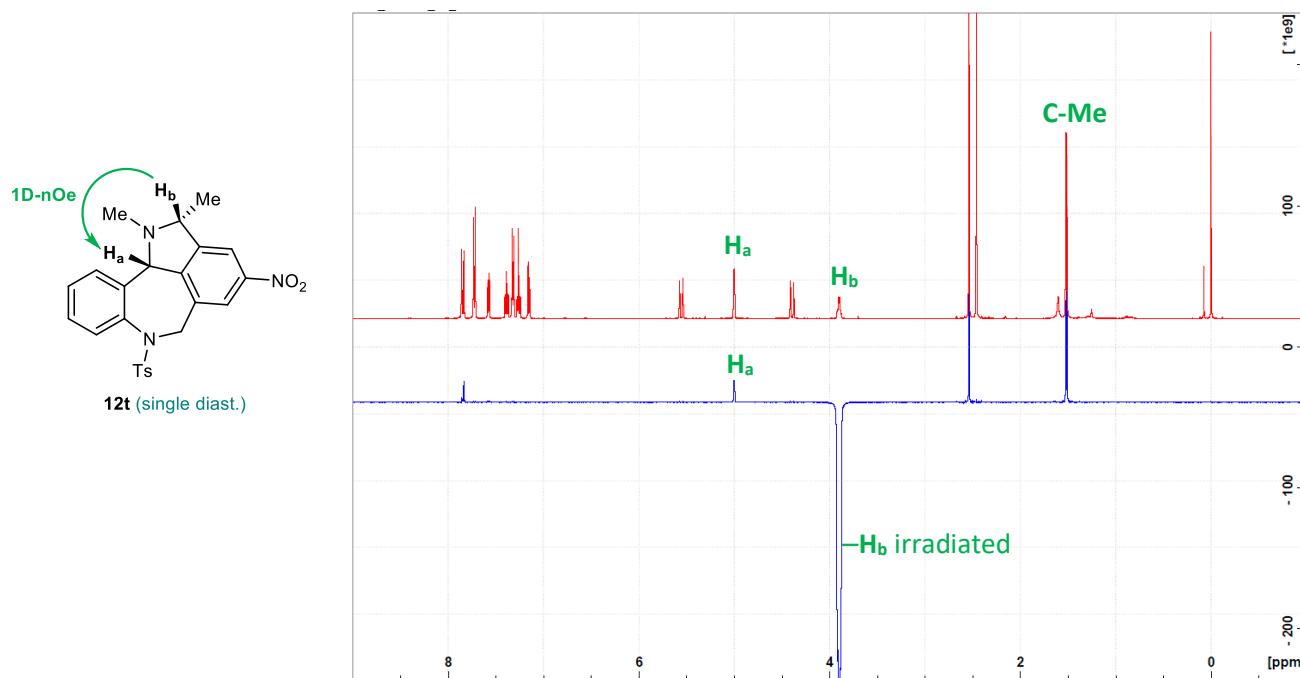
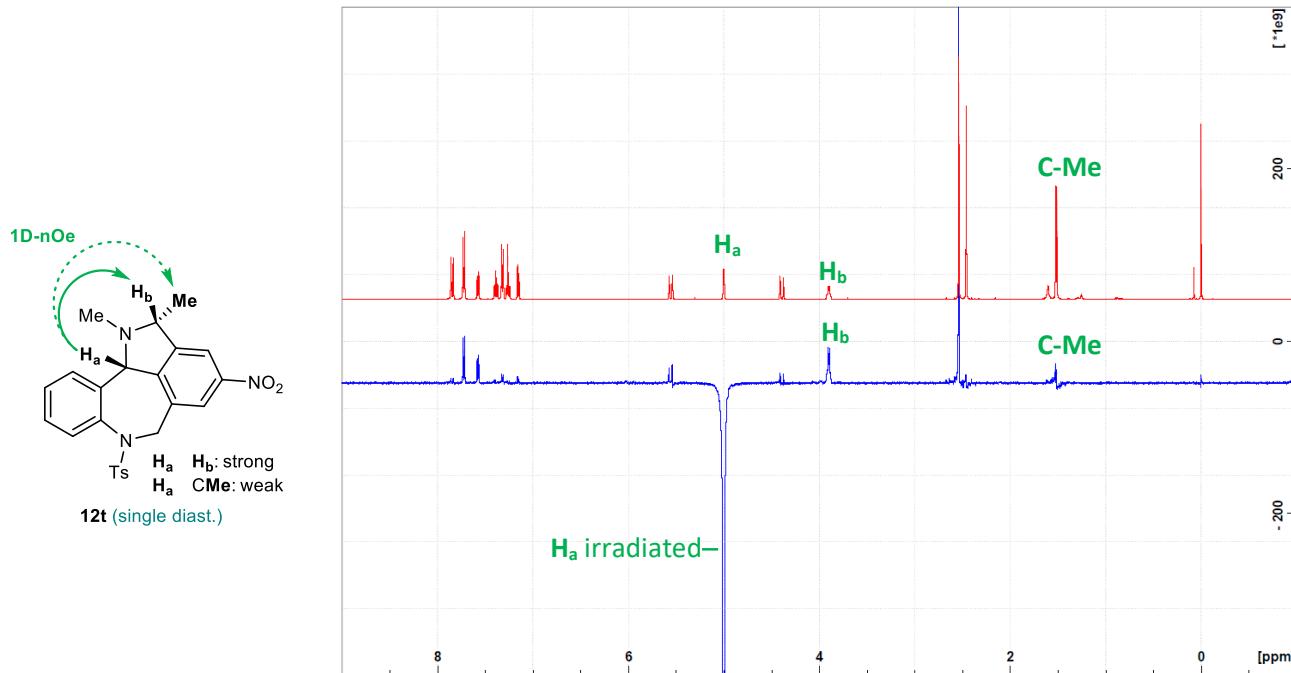
- **Compound 12y** was analyzed as a mixture of diastereomers ($dr = 3.8 : 1$). All key proton signals were resolved which enabled nOe analysis to determine the relative stereochemistry. The major diastereomer (*cis*) exhibited a 2D-nOe correlation between the methine hydrogen (H_a) and the C-methyl group indicated by the green circles on the spectrum. The minor diastereomer (*trans*) did not exhibit a correlation between H_a (minor) and its C-methyl group. Both isomers exhibited a nOe correlation between the methine hydrogen (H_a) and the *N*-methyl group (red circles for major isomer; purple circles for minor isomer).



- **Compound 12p** was analyzed as a diastereoenriched sample ($dr = 16.7:1$, see Section 5.4.3). This sample was enriched in the same diastereomer as the crude mixture (and originally isolated sample). Although no conclusive 2D-nOe data could be obtained, 1D-nOe experiments involving separate irradiation of each methine proton pointed convincingly to the *cis* isomer (H_a – H_b through-space correlations). Further evidence for the assigned *cis* stereochemistry was the absence of a H_a – H_c correlation.



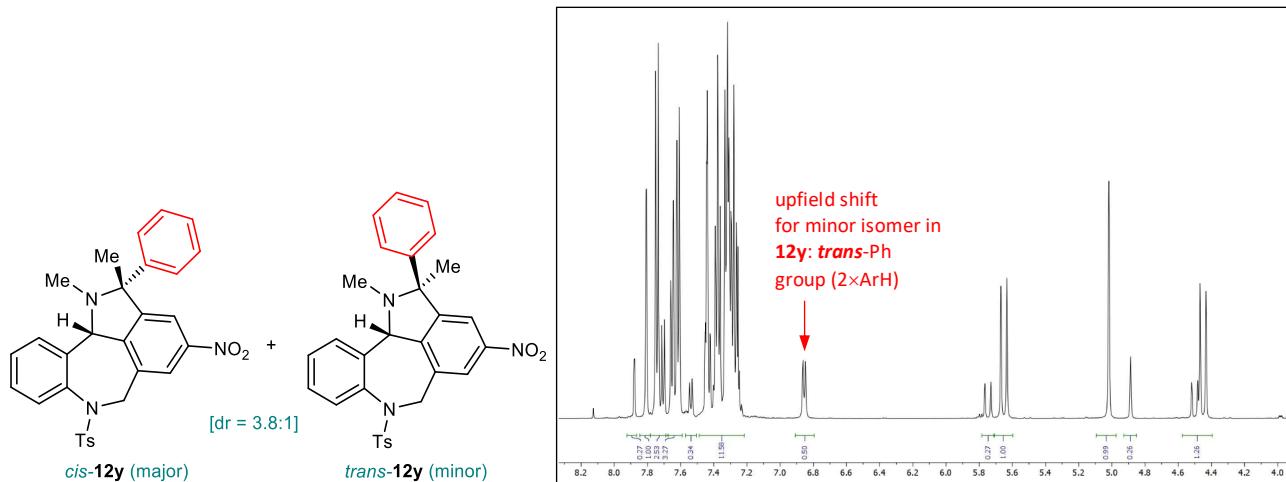
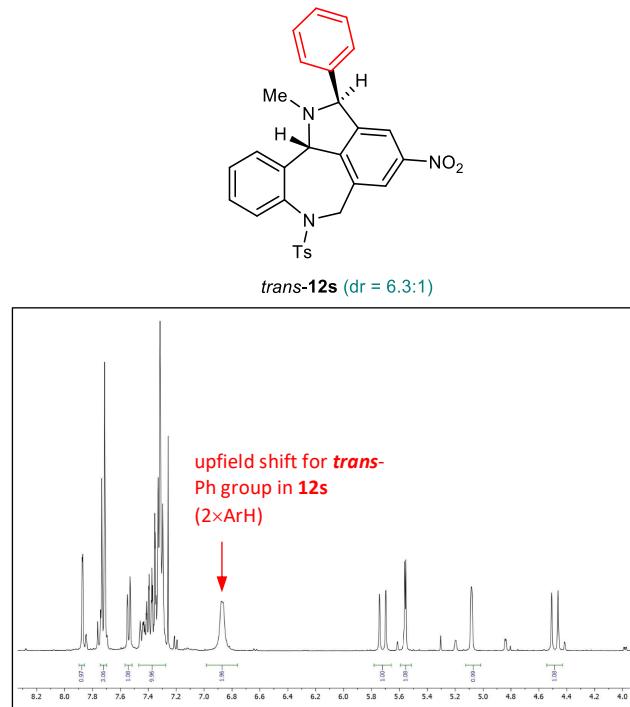
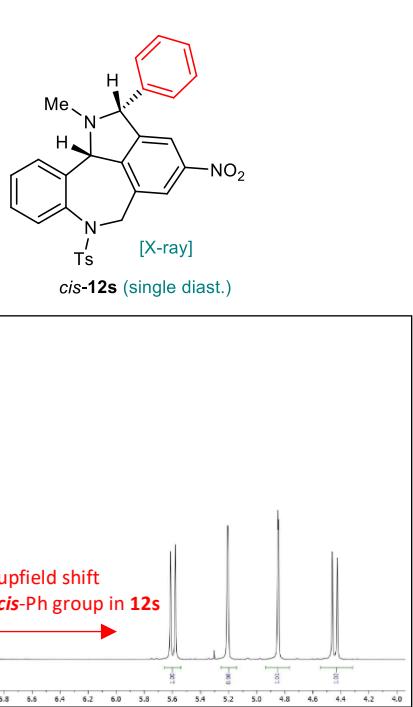
- **Compound 12t** was assigned as the *cis* isomer by analogous 1D-nOe experiments (H_a – H_b correlations). Further evidence for the assigned *cis* stereochemistry was a much stronger correlation between H_a and H_b relative to H_a and the C-methyl group (weak signal observed).



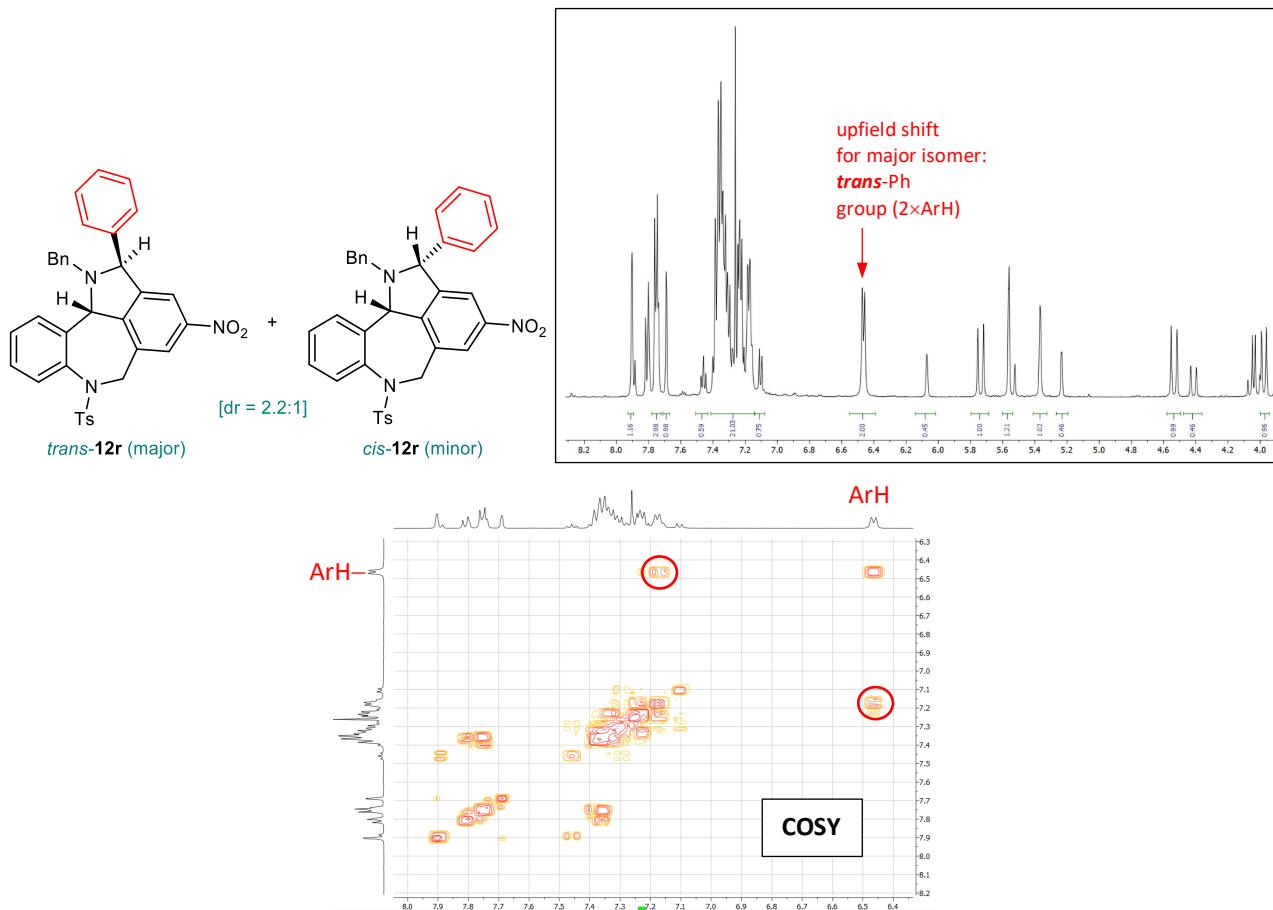
5.6. Determination of Relative Stereochemistry of 12r (by ^1H NMR spectral comparison with 12s and 12y)

Note: Full ^1H and ^{13}C spectra for each compound are given in Section 9.

- Products **12s** and **12y** both bear a phenyl group at the second C-stereocenter and the NMR spectra of **12r** was therefore compared with these compounds. Since the major diastereomers of **12s** and **12y** were determined to have *cis* configurations by X-ray crystallography and nOe, respectively, the minor diastereomers were assigned as *trans* isomers. Relative to their *cis* diastereomers, the *trans* epimers [*trans*-**12s** and *trans*-**12y**] both displayed a characteristic upfield ArH signal (<7 ppm) arising from the phenyl group (2×ArH, *ortho*); this upfield shift was only observed for the *trans* isomer where the phenyl group is *syn* to the distal methine hydrogen.



- The same distinctive upfield shift of the phenyl group was also observed for the major diastereomer of **12r** (dr of sample = 2.2:1, see Section 5.4.3). Therefore, the major diastereomer of **12r** was assigned as the *trans* diastereomer.

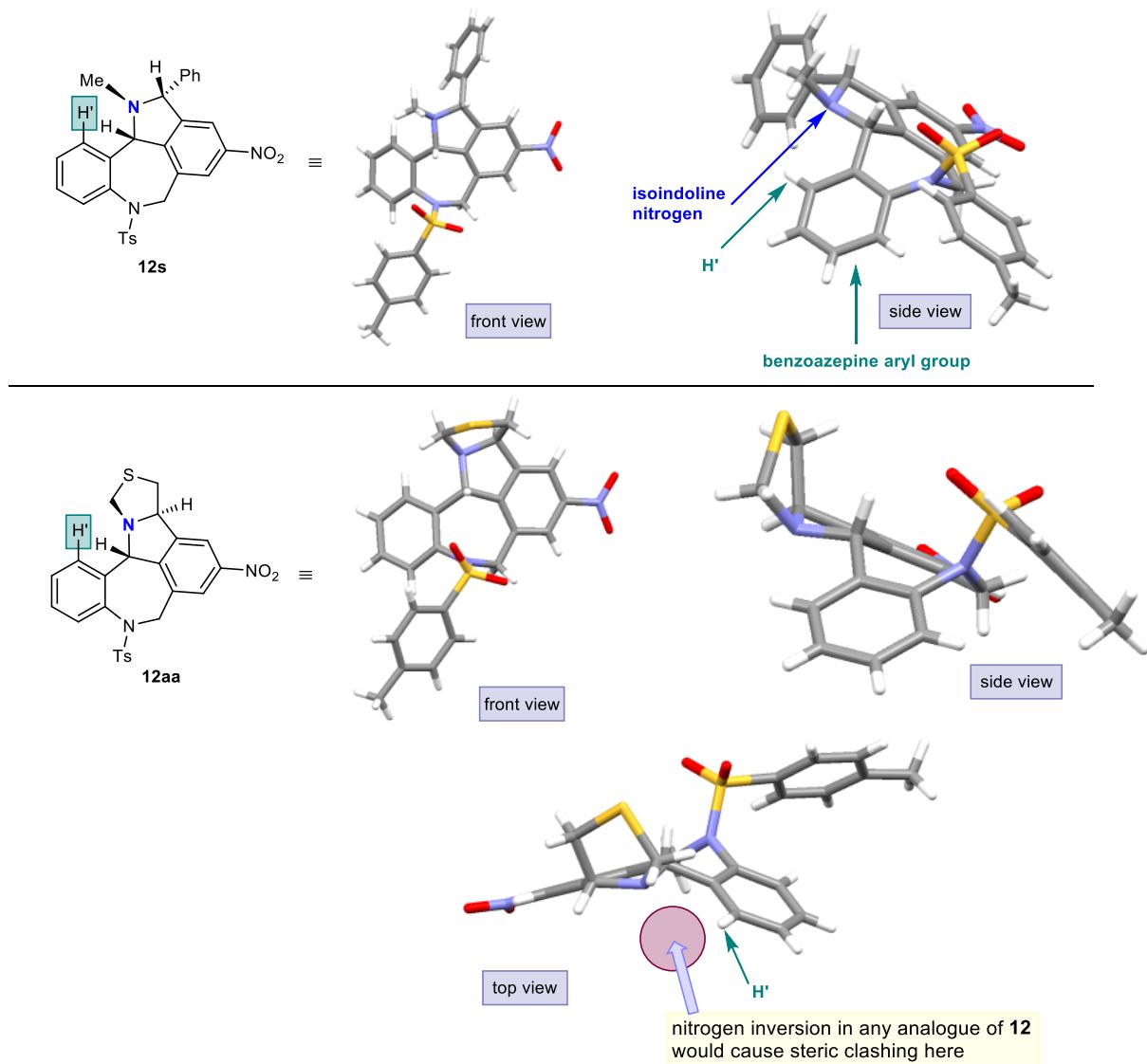


- Further 2D-NMR analyses of all above samples (*trans*-**12s**, **12r** and **12y**) using COSY, nOe, HSQC and HMBC (COSY for **12r** shown above) confirmed in each case that this diagnostic signal from the phenyl group (ArH) was not an impurity nor a deshielded sp^3 -C–H proton.

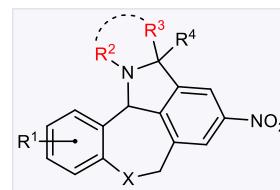
5.7. Further Discussions on Diastereoselectivity Switch with Cyclic Amino Acid Substrates

- Background comments:* For all products in which a crystal structure was obtained (e.g., **12s** and **12aa** below), regardless of whether the product was derived from an acyclic or cyclic amino acid, the sp^3 -hybridized isoindoline nitrogen appears to have a thermodynamic preference to orientate its lone pair *syn* to the α -aryl group of the benzoazepine ring. This stereochemical arrangement places the *N*-substituent (e.g., Me group or CH_2 of the (thia)pyrrolidine ring) *anti* to the benzoazepine ring and minimizes steric interactions that would otherwise occur with the *ortho* hydrogen H'. The question of whether the isoindoline nitrogen atom in products **12** (particularly *trans*-fused pentacycles **12z** and **12aa**) is a bonafide stereocenter at room temperature is a separate issue, but even if dynamic nitrogen inversion does occur, the corresponding *N*-epimers (epimeric at the

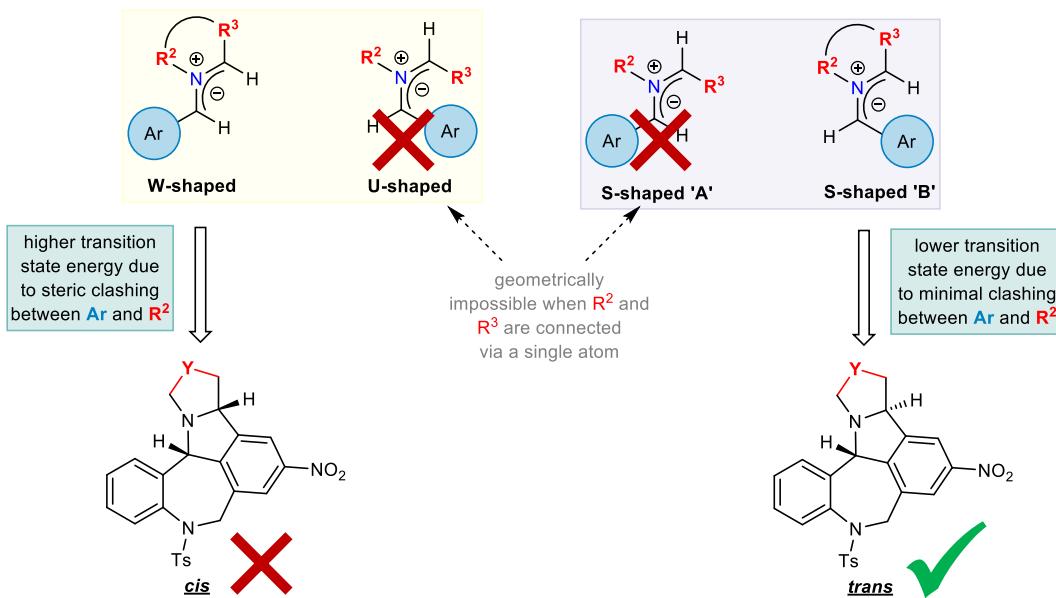
isoindoline nitrogen relative to the configurations in the crystal structures shown) would clearly be higher in energy as a result of steric interactions.



- For the cyclic amino acids substrates used in this study (proline and thiaproline), R^2 and R^3 of the derived azomethine ylides are connected via a single atom (i.e., as part of a 5-membered ring system). Therefore, geometrical constraints require that R^2 and R^3 reside on the same side of the azomethine ylide. This leaves two possible reactive ylide conformations: W-Shaped and S-Shaped 'B' (shown below). During cycloaddition, the three atoms of the azomethine ylide ($C-Ar$, $N-R^2$ and $C-R^3$) must undergo a hybridization change from sp^2 to sp^3 . Since these are constrained cyclic systems, a new requirement arises in that R^2 and R^3 must be projected to the same face during cycloaddition. The consequence of this, in contrast to acyclic systems, is that the transition state leading to the product from the usually preferred W-shaped ylide now suffers from the (aforementioned) steric clashes between R^2 and the aryl group (Ar). Accordingly, the reaction of alternative S-

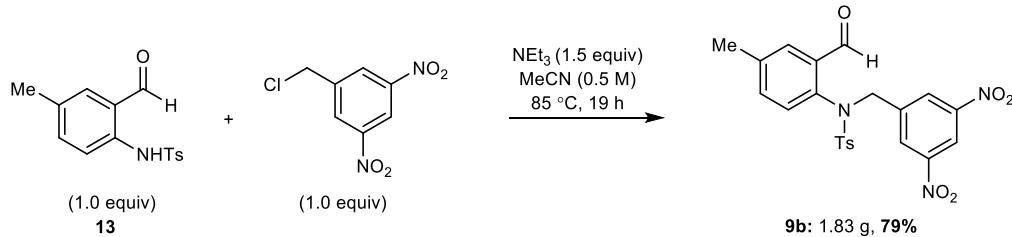


Shaped ylide 'B', which projects Ar and R² in opposite directions in the cycloaddition transition state, prevails for these systems.



6. Larger Scale Examples

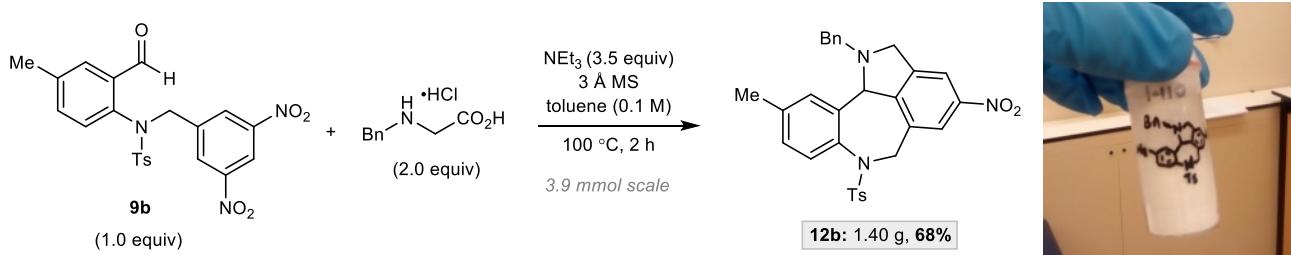
N-(3,5-Dinitrobenzyl)-*N*-(2-formyl-4-methylphenyl)-4-methylbenzenesulfonamide (**9b**)



An oven-dried 50 mL round-bottom flask was charged in air with sulfonamide **13** (1.436 g, 4.96 mmol, 1.0 equiv) and 3,5-dinitrobenzyl chloride (1.075 g, 4.96 mmol, 1.0 equiv). A reflux condenser was attached and the system was purged with N₂. Anhydrous MeCN (9.9 mL, 0.5 M) was added, followed by NEt₃ (1.04 mL, 7.44 mmol, 1.5 equiv). The solution was heated to 85 °C and maintained at this temperature for 19 h (no water flow through the condenser was necessary to maintain the solvent volume). TLC analysis (25:75 EtOAc/n-hexane) after this time showed complete consumption of 3,5-dinitrobenzyl chloride and a small amount of unreacted **13**. After cooling to room temperature, the solvent was removed under reduced pressure. To remove NEt₃·HCl and polar impurities, the residue was dissolved in CH₂Cl₂ (~20 mL) and adsorbed to a silica column (31 g silica, wet-packed with 5:95 EtOAc/CH₂Cl₂). The product was then rapidly eluted with 5:95 EtOAc/CH₂Cl₂ (~300 mL) and the fractions containing **9b** were concentrated under reduced pressure [**9b**: $R_F = 0.31$ (30:70 EtOAc/n-hexane)]. The remaining solid (containing **9b**, residual **13** and other minor impurities) was dissolved in CH₂Cl₂ (10 mL), then MeOH (30 mL) was added. The resulting solution was placed on a rotary evaporator (40 °C, ≥ 300

mbar) to selectively remove the CH_2Cl_2 (roughly judged by the point when condensation of the solvent in the receiving trap virtually ceased and/or the solvent volume in the initial flask had reduced to 25–30 mL). The resulting precipitate was collected and washed with ice-cold MeOH (~10 mL, pre-cooled in a freezer), then dried under vacuum to give **9b** (1.833 g, 79%) as an off-white solid. Characterization data for **9b** is given above in Section 3.2.

(\pm)-10-Benzyl-8-methyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12b)



- See Section 5.1 for notes on the activation of molecular sieves and de-oxygenation of toluene.



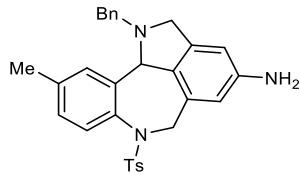
An oven-dried, two neck 100 mL round-bottom flask was charged in air with **9b** (1.829 g, 3.90 mmol, 1.0 equiv), Bn-Gly-OH·HCl (1.571 g, 7.79 mmol, 2.0 equiv) and powdered 3 \AA molecular sieves (1.87 g). A reflux condenser was attached and the system was purged with N_2 via flow through the condenser and out the side neck of the flask. The side neck was sealed with a rubber septum and anhydrous toluene (39.0 mL, 0.1 M) was added, followed by NEt_3 (1.90 mL, 13.64 mmol, 3.5 equiv). The reaction was then heated from room temperature to 100°C during 20 min, then maintained at 100°C for 2.33 h (no water flow through the condenser was necessary to maintain the solvent volume). TLC analysis (30:70 $\text{EtOAc}/n\text{-hexane}$) after this time showed complete consumption of **9b**. After cooling to room temperature, the entire reaction mixture (including suspended molecular sieves and toluene) was

absorbed on to a silica column (38 g silica, wet-packed with CH_2Cl_2) with the aid of CH_2Cl_2 (2×5 mL) to rinse the reaction flask. The product was then eluted with CH_2Cl_2 (<500 mL required) and the fractions containing **12b** (with minor impurities) were concentrated under reduced pressure [**12b**: $R_F = 0.59$ (30:70 $\text{EtOAc}/n\text{-hexane}$)]. To the remaining solid was added MeOH (40 mL). Most of the residual solid on the flask walls was scraped into the MeOH with a spatula, then the suspension was sonicated briefly (~2 min) to ensure dissolution of impurities. After standing at room temperature for 10 min, the insoluble product was collected and washed with ice-cold MeOH (2×20 mL, pre-cooled in a freezer), then dried under vacuum to give **12b** (1.398 g, 68%) as a white solid. Characterization data for **12b** is given above in Section 5.4.2.

7. Further Manipulations

(\pm)-2-Amino-10-benzyl-8-methyl-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole

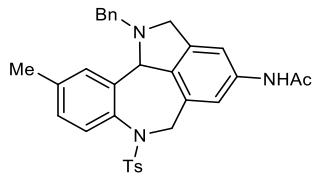
(14)



- The MeOH used as solvent for this experiment was de-oxygenated by N₂-sparging for 20 min before use. Subsequent experiments have shown that this precaution is not necessary to obtain high yields (>90%).

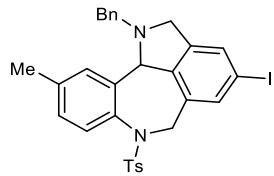
To a suspension of **12b** (262.8 mg, 0.50 mmol, 1.0 equiv) in reagent grade, de-oxygenated MeOH (10 mL, 0.05 M) under N₂ in a Schlenk flask at 0 °C was added TMSCl (1.27 mL, 10.00 mmol, 20 equiv) dropwise over 2 min, giving a homogenous solution. Under a positive pressure of N₂, Zn powder (653.8 mg, 10.00 mmol, 20 equiv) was added portionwise through the main neck over 45 min, while maintaining the temperature between 0–5 °C. After stirring at 0–5 °C for a total of 3 h (significant undissolved Zn powder remained present in the reaction throughout), the reaction was diluted with 1:1 MeOH/CH₂Cl₂ (30 mL) and filtered. The filtrate was concentrated under reduced pressure. CH₂Cl₂ (40 mL) and 1 M K₂CO₃ (40 mL) were added. The resulting sticky inorganic precipitate was removed by vacuum filtration, rinsing the flask and filter cake with CH₂Cl₂ (4 × 15 mL). The filtrate was poured into a separating funnel and the organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography (4 g silica, 0:100 to 5:95 EtOAc/CH₂Cl₂) gave **14** (245.1 mg, 99%) as a white solid. **Mp:** 235–239 °C. **TLC:** *R*_F = 0.36 (2.5:97.5 EtOAc/CH₂Cl₂). **¹H NMR (400 MHz, CDCl₃):** δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.58–7.48 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34–7.23 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.29 (s, 1H), 6.21 (s, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 4.88 (s, 1H), 4.25 (d, *J* = 17.5 Hz, 1H), 4.15 (t, *J* = 13.2 Hz, 2H), 3.62–3.49 (m, 3H), 3.37 (d, *J* = 13.7 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 146.4, 143.5, 143.4, 140.8, 139.6, 139.1, 139.0, 134.9, 133.6, 129.8, 128.8, 128.7, 128.5, 128.2, 127.3, 127.2, 127.1, 126.2, 110.9, 108.0, 67.3, 59.6, 58.4, 51.0, 21.75, 21.66 ppm. **IR (ATR, cm⁻¹):** ̄ = 3482, 3388, 3026, 1623, 1489, 1371, 1326, 1253, 1209, 1153, 1093, 1027, 999, 892, 859, 814, 709, 694, 669, 588, 548. **HRMS (ESI):** calcd for C₃₀H₃₀N₃O₂S [M + H]⁺ 496.2059, found 496.2061.

(\pm)-2-Acetylamo-10-benzyl-8-methyl-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (15)



To solid **14** (29.7 mg, 0.060 mmol, 1.0 equiv) was added a solution of Ac₂O (7.4 mg weighed, 0.072 mmol, 1.2 equiv) in reagent grade CH₂Cl₂ (0.6 mL, 0.1 M) and the solution was stirred under at room temperature for 2 h. CH₂Cl₂ (2 mL) and 1 M K₂CO₃ (2 mL) were added and the biphasic mixture was stirred rapidly at room temperature for 5 min. Additional 1 M K₂CO₃ (15 mL) was added and the product was extracted twice with CH₂Cl₂ (25 mL, then 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to give **15** (32.4 mg, 100%) as an off-white solid. **Mp:** 226–232 °C. **TLC:** *R*_F = 0.16 (7.5:92.5 EtOAc/CH₂Cl₂). **¹H NMR (500 MHz, CDCl₃):** δ 7.71 (d, *J* = 7.9 Hz, 2H), 7.56 (s, 1H), 7.53–7.50 (m, 2H), 7.46–7.38 (m, 3H), 7.36–7.28 (m, 3H), 7.15 (s, 1H), 7.09–7.00 (m, 3H), 5.41 (d, *J* = 17.5 Hz, 1H), 5.05 (s, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 4.20 (d, *J* = 13.5 Hz, 2H), 3.60 (d, *J* = 12.8 Hz, 1H), 3.40 (d, *J* = 13.7 Hz, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 2.10 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 168.6, 143.7, 142.8, 140.3, 139.3, 139.2, 138.7, 137.7, 134.7, 133.3, 132.5, 129.9, 128.7, 128.50, 128.47, 128.45, 127.3, 127.2, 126.3, 115.8, 112.6, 67.4, 59.4, 58.3, 51.0, 24.7, 21.8, 21.7 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 3272, 2917, 1662, 1612, 1557, 1485, 1421, 1374, 1344, 1261, 1156, 1097, 1016, 896, 871, 813, 739, 669, 618, 586, 554, 540, 472. **HRMS (ESI):** calcd for C₃₂H₃₂N₃O₃S [M + H]⁺ 538.2164, found 538.2168.

(\pm)-10-Benzyl-2-iodo-8-methyl-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (16)

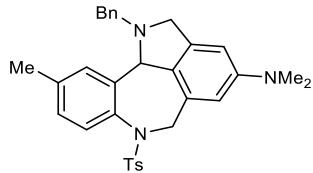


To a suspension of **14** (45.5 mg, 0.092 mmol, 1.0 equiv) in reagent grade MeCN (1.0 mL, 0.09 M) at –10 °C (ice/salt bath) under air was added solid *p*-TsOH·H₂O (69.8 mg, 0.37 mmol, 4.0 equiv) to give a near homogenous solution. A solution of KI (76.2 mg, 0.46 mmol, 5.0 equiv) in water (0.20 mL) was added, followed by the dropwise addition of a solution of NaNO₂ (12.7 mg, 0.18 mmol, 2.0 equiv) in water (0.20 mL) over 1 min (N₂ evolution observed immediately). The resulting dark purple/brown mixture was maintained below 0 °C over 30 min, then quenched by sequential addition of 1 M K₂CO₃ (3 mL) and 1 M Na₂S₂O₃ (3 mL). The mixture was partially concentrated under reduced pressure to remove (most) of the MeCN, then the product was extracted twice from the remaining aqueous phase with CH₂Cl₂ (25 mL, then 10 mL). The combined (dark purple) organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (4.4 g silica, 75:25 CH₂Cl₂/n-hexane)

gave **16** (33.2 mg, 60%) as a white solid. **Mp:** 228–234 °C. **TLC:** R_F = 0.58 (75:25 CH₂Cl₂/n-hexane). **¹H NMR (400 MHz, CDCl₃):** δ 7.71 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.52–7.48 (m, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.35–7.27 (m, 4H), 7.27–7.23 (m, 1H), 7.08–7.01 (m, 2H), 5.42 (d, J = 17.6 Hz, 1H), 5.09 (s, 1H), 4.31 (d, J = 17.7 Hz, 1H), 4.25–4.17 (m, 2H), 3.64 (dd, J = 13.6, 2.9 Hz, 1H), 3.44 (d, J = 13.7 Hz, 1H), 2.46 (s, 3H), 2.34 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 143.7, 142.5, 141.9, 139.4, 139.0, 138.8, 136.8, 135.2, 134.7, 133.4, 130.1, 129.9, 128.8, 128.7, 128.6, 128.5, 127.4, 127.3, 126.4, 92.6, 67.5, 59.3, 57.8, 50.2, 21.8, 21.7 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2920, 2795, 1584, 1495, 1454, 1342, 1310, 1251, 1160, 1113, 1100, 1029, 897, 863, 813, 749, 729, 710, 701, 663, 639, 606, 581, 557, 534, 519, 472. **HRMS (ESI):** calcd for C₃₀H₂₈IN₂O₂S [M + H]⁺ 607.0916, found 607.0923.

- One earlier run with only 2.5 equiv of KI at 0 °C with an inverse addition order of NaNO₂ and KI gave a 38% yield of **16** (with 100% conversion of **14**). These results indicate that excess KI (5.0 equiv) combined with a lower temperature (−10 °C) is important for increasing the yield, presumably by minimizing side reactions of the intermediate diazonium salt, which appears to be highly reactive. No further optimization was carried out.

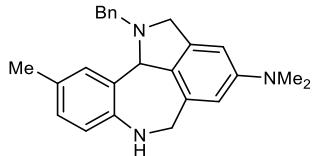
(±)-10-Benzyl-2-dimethylamino-8-methyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (17)



To a suspension of **14** (49.6 mg, 0.10 mmol, 1.0 equiv) and NaBH₃CN (12.6 mg, 0.20 mmol, 2.0 equiv) in reagent grade THF (1.0 mL, 0.1 M) at room temperature under air was sequentially added aqueous formaldehyde (37% w/w in water, 22 μ L = 9.0 mg of CH₂O, 0.30 mmol, 3.0 equiv) and AcOH (29 μ L, 0.50 mmol, 5.0 equiv). The resulting solution was stirred under at room temperature for 1.5 h, then quenched with 1 M K₂CO₃ (2 mL). Additional 1 M K₂CO₃ (15 mL) was added and the product was extracted twice with CH₂Cl₂ (25 mL, then 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to give **17** (42.7 mg) which contained 10 mol% of the *N*-mono-methylated intermediate as confirmed by NMR and MS analysis (R_F is essentially the same as the desired product). To fully convert the material to the desired product, the sample was resubjected to the same reaction and work-up conditions as above (with the same reagent quantities and reaction time), giving full conversion to **17** (41.7 mg, 80%) as a pale yellow solid. **Mp:** 224–231 °C. **TLC:** R_F = 0.49 (CH₂Cl₂). **¹H NMR (500 MHz, CDCl₃):** δ 7.71 (d, J = 8.1 Hz, 2H), 7.57–7.51 (m, 3H), 7.40 (t, J = 7.5 Hz, 2H), 7.34–7.25 (m, 3H), 7.10 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.38 (s, 1H), 6.25 (s, 1H), 5.46 (d, J = 17.3 Hz, 1H), 4.90 (s, 1H), 4.33 (d, J = 17.3 Hz, 1H), 4.19 (d, J = 13.4 Hz, 2H), 3.60 (d, J = 12.6 Hz, 1H), 3.39 (d, J = 13.7 Hz, 1H), 2.84 (s, 6H), 2.45 (s, 3H), 2.32 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 150.9, 143.6, 143.4, 140.4, 139.6, 139.0, 138.9, 134.7, 133.1, 129.7, 128.7, 128.6, 128.5, 128.2, 127.2, 127.1, 126.1, 125.2,

108.5, 105.7, 67.2, 59.5, 58.7, 51.3, 41.1, 21.8, 21.7 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 2890, 2794, 1618, 1494, 1433, 1372, 1342, 1306, 1254, 1159, 1134, 1101, 1027, 981, 889, 814, 746, 716, 696, 670, 586, 556, 539, 480. **HRMS (ESI):** calcd for C₃₂H₃₄N₃O₂S [M + H]⁺ 524.2372, found 524.2385.

(\pm)-10-Benzyl-2-dimethylamino-8-methyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (18)



- Note that this reaction work-up procedure is unoptimized. An alternative Fieser work-up^{S21} is recommended in subsequent runs, especially on larger scale to avoid complications from aluminum emulsions encountered in the small scale aqueous work-up described here. It is also recommended as a safety precaution on larger scale to add the substrate (as a solid) to a suspension of LiAlH₄ in THF under N₂, rather than combining the two reactants in the absence of solvent (**17** may not fully dissolve initially in THF and therefore addition as a solid may be preferred).

To a flask containing solid **17** (31.4 mg, 0.060 mmol, 1.0 equiv) in air was added LiAlH₄ powder (22.8 mg, 0.60 mmol, 10.0 equiv). A reflux condenser was attached and the system was purged with N₂. Anhydrous THF (2.4 mL, 0.025 M) was added. The reaction mixture was heated to 70 °C and maintained at this temperature for 14 h (no water flow through the condenser was necessary to maintain the solvent volume). After cooling to rt, excess LiAlH₄ was quenched by slow addition of 1 M NaOH (5 mL, H₂ evolution observed). The mixture was diluted further with water (10 mL), CH₂Cl₂ (8 mL) and EtOAc (20 mL). The organic layer (top) was washed with brine (15 mL), dried (Na₂SO₄) and concentrated. Flash chromatography (~2 g silica, 0:100 to 5:95 EtOAc/CH₂Cl₂) gave **18** (13.7 mg, 62%) as a light brown solid. **Mp:** 86–92 °C. **TLC:** R_F = 0.27 (1:99 EtOAc/CH₂Cl₂). **¹H NMR (500 MHz, CDCl₃):** δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34–7.29 (m, 1H), 6.97 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 5.49 (s, 1H), 4.45–4.36 (m, 2H), 4.28 (dd, *J* = 13.0, 2.1 Hz, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 3.73 (dd, *J* = 13.1, 2.8 Hz, 1H), 3.65 (d, *J* = 13.7 Hz, 1H), 2.84 (s, 6H), 2.31 (s, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 150.9, 144.6, 140.0, 139.9, 138.4, 134.7, 133.4, 128.61, 128.59, 127.6, 127.0, 126.8, 125.6, 122.6, 109.7, 105.5, 67.7, 59.7, 58.9, 51.4, 41.3, 21.4 ppm. **IR (ATR, cm⁻¹):** $\tilde{\nu}$ = 3334, 2792, 1616, 1599, 1495, 1450, 1368, 1339, 1263, 1154, 1119, 1096, 1063, 1027, 969, 907, 816, 728, 698, 648, 570, 463. **HRMS (ESI):** calcd for C₂₅H₂₈N₃ [M + H]⁺ 370.2283, found 370.2284.

- Other conditions attempted (once) for the de-tosylation process with **17** included:

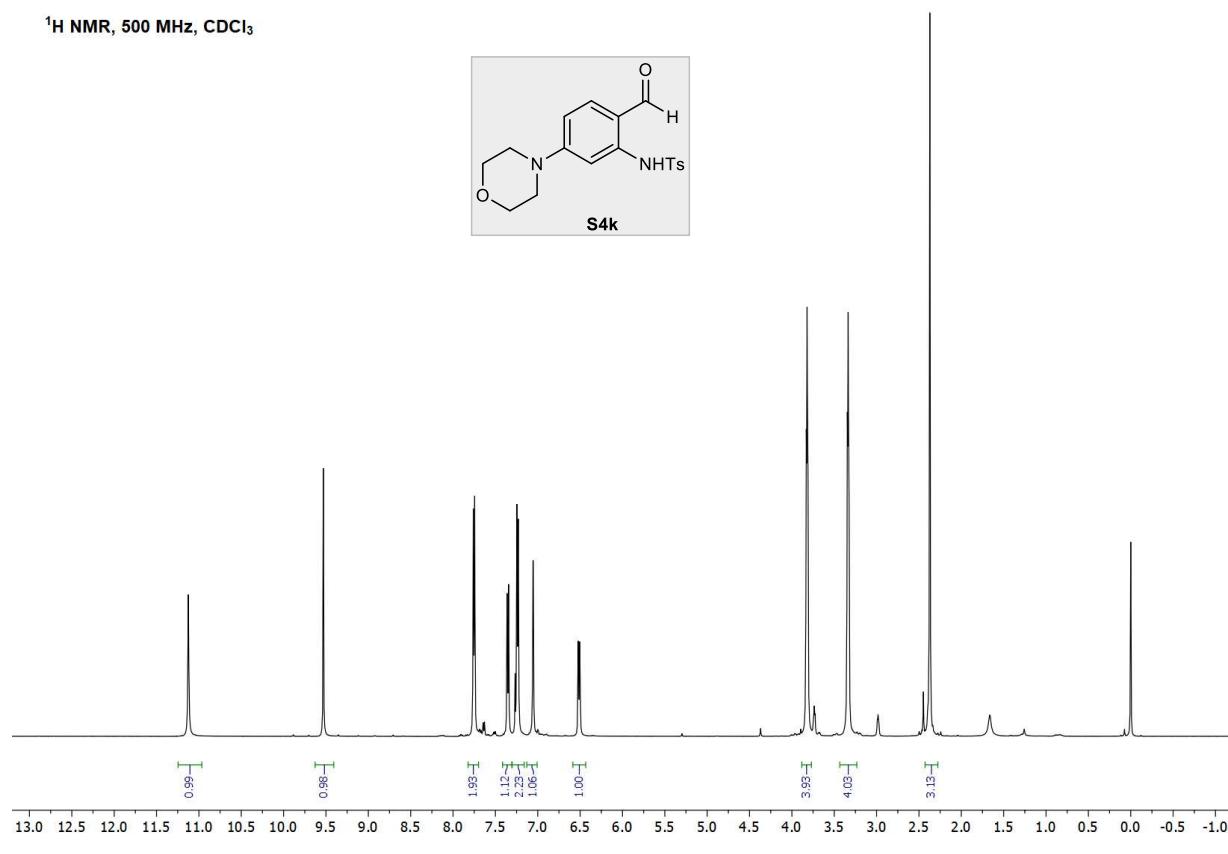
- Mg powder (2×20 equiv), MeOH (0.05 M), 60 °C, 2 h: recovered **17**/unknown product = 85:15 (molar ratio). The sparing solubility of **17** in MeOH is the likely reason for the poor reactivity (significant H₂ evolution from reduction of MeOH by Mg was observed in the reaction).
- TMSCl (2 equiv), NaI (2 equiv), 3 Å MS, MeCN (0.03 M), 90 °C, 24 h, dark: 81% recovery of **17**, no products observed.

8. References

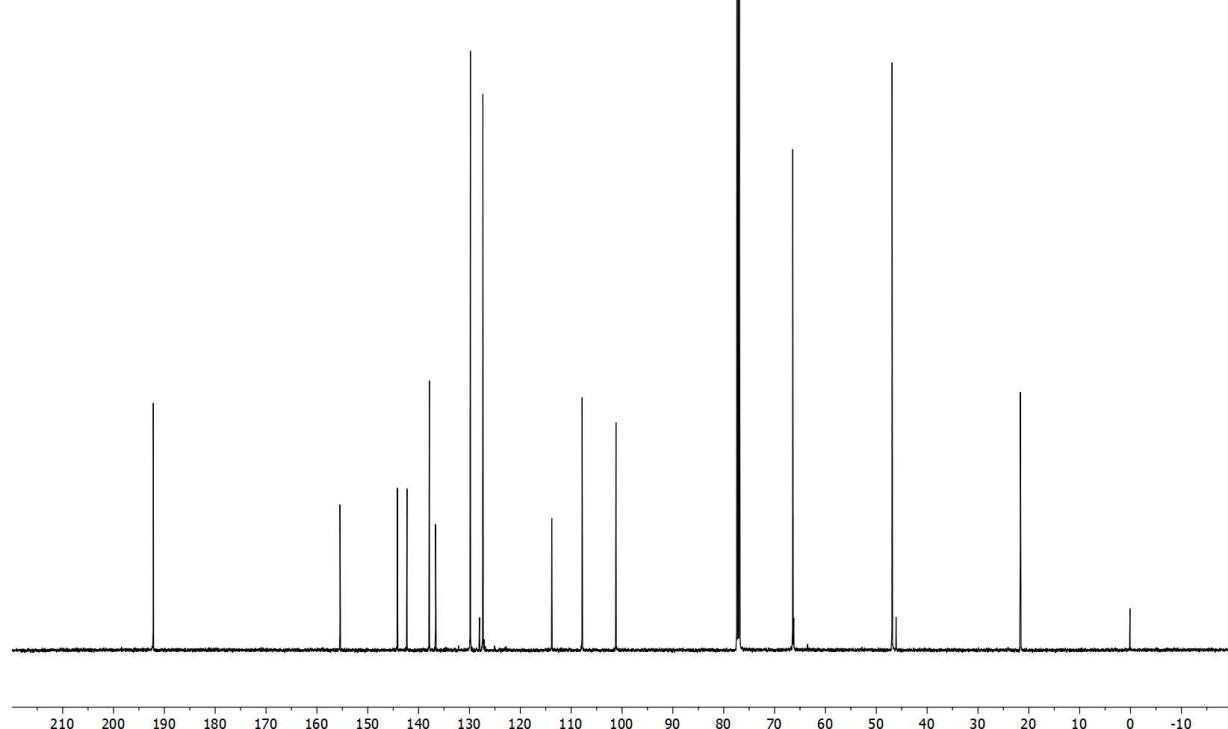
- S1) Rosenau, C. P.; Jelier, B. J.; Gossert, A. D.; Togni, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 9528–9533.
- S2) Cao, B.; Simaan, M.; Marek, I.; Wei, Y.; Shi, M. *Chem. Commun.* **2017**, *53*, 216–219.
- S3) Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887–4890.
- S4) Aebley, A. H.; Rainey, T. J. *Tetrahedron Lett.* **2017**, *58*, 3795–3799.
- S5) Ida, Y.; Matsubara, A.; Nemoto, T.; Saito, M.; Hirayama, S.; Fujii, H.; Nagase, H. *Bioorg. Med. Chem.* **2012**, *20*, 5810–5831.
- S6) Jarrige, L.; Merad, J.; Zaied, S.; Blanchard, F.; Masson, G. *Synlett* **2017**, *28*, 1724–1728.
- S7) Bernárdez, R.; Suárez, J.; Fañanás-Mastral, M.; Varela, J. A.; Saá, C. *Org. Lett.* **2016**, *18*, 642–645.
- S8) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257–2260.
- S9) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035.
- S10) Sriramurthy, V.; Kwon, O. *Org. Lett.* **2010**, *12*, 1084–1087.
- S11) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron* **2011**, *67*, 1501–1505.
- S12) Zhang, Y.-F.; Wu, B.; Shi, Z.-J. *Chem. –Eur. J.* **2016**, *22*, 17808–17812.
- S13) Mu, D.; Wang, X.; Chen G.; He, G. *J. Org. Chem.* **2017**, *82*, 4497–4503.
- S14) Li, Y.; Feng, Y.; Xu, L.; Wang, L.; Cui, X. *Org. Lett.* **2016**, *18*, 4924–4927.
- S15) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417.
- S16) Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K. S.; Zhang, F. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 888–896.
- S17) Selig, P.; Raven, W. *Org. Lett.* **2014**, *16*, 5192–5195.
- S18) Chalker, J. M.; Gunnoo, S. B.; Boutureira, O.; Gerstberger, S. C.; Fernández-González, M.; Bernardes, G. J. L.; Griffin, L.; Hailu, H.; Schofield, C. J.; Davis, B. G. *Chem. Sci.* **2011**, *2*, 1666–1676.
- S19) Emsermann, J.; Arduengo, A. J. III.; Opatz, T. *Synthesis* **2013**, *45*, 2251–2264.
- S20) Starosotnikov, A. M.; Bastrakov, M. A.; Kachala, V. V.; Belyakov, P. A.; Fedyanin, I. V.; Shevelev, S. A. *Synlett* **2012**, *23*, 2400–2404.
- S21) http://chem.chem.rochester.edu/~nvd/pages/magic_formulas.php?page=aluminum_hydride_reduction

9. NMR Spectra of Novel Compounds

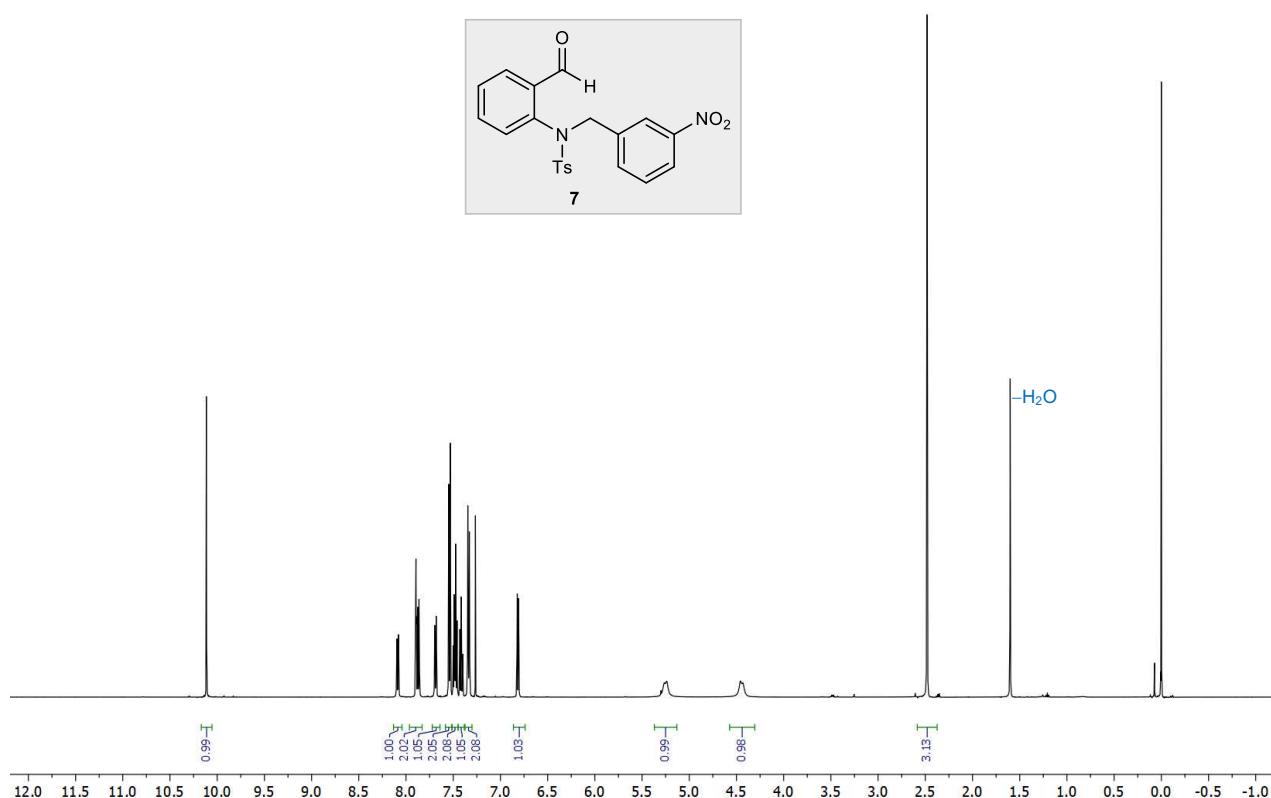
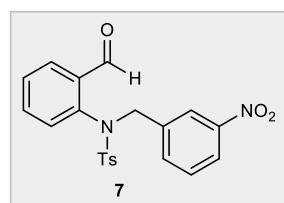
¹H NMR, 500 MHz, CDCl₃



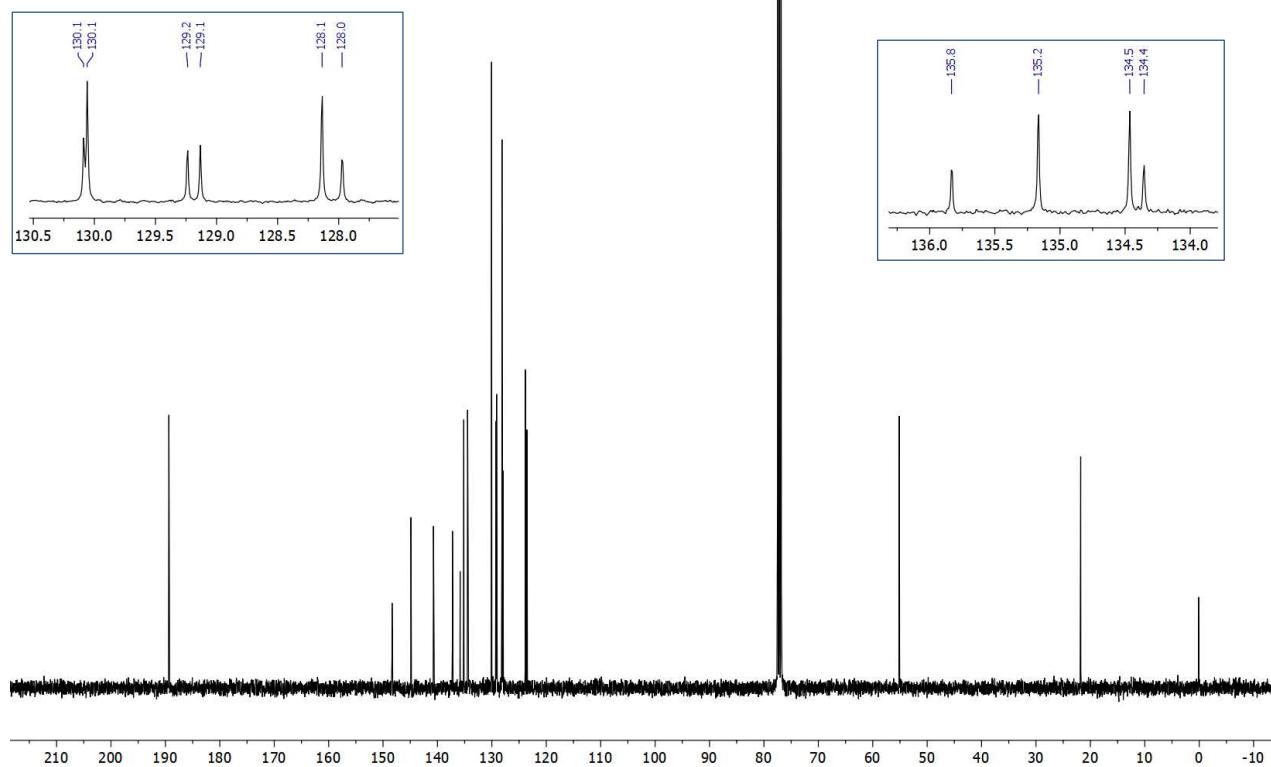
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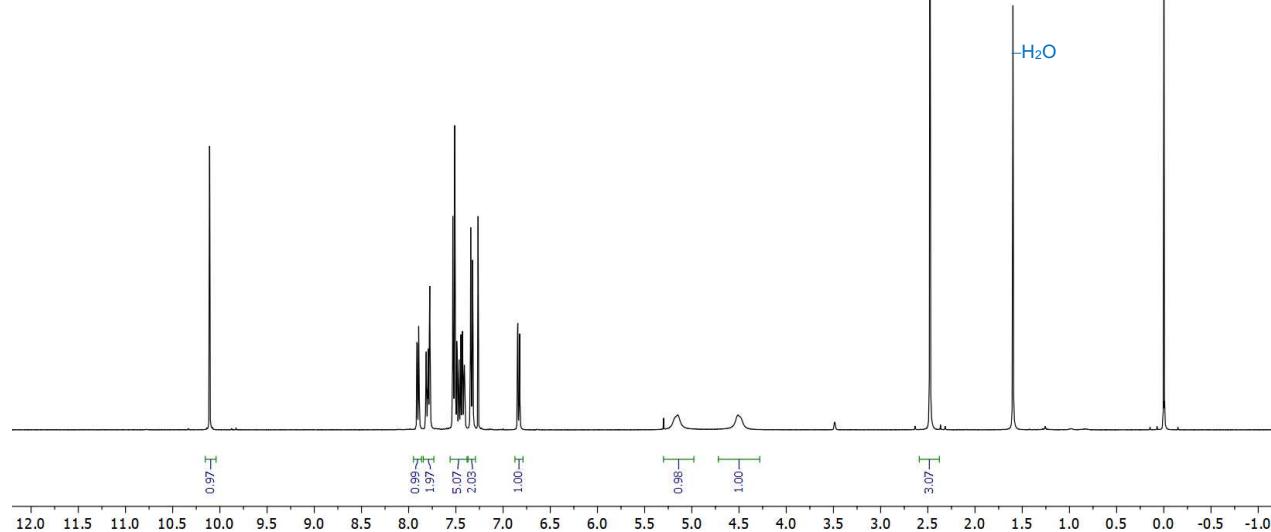
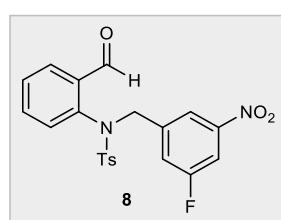
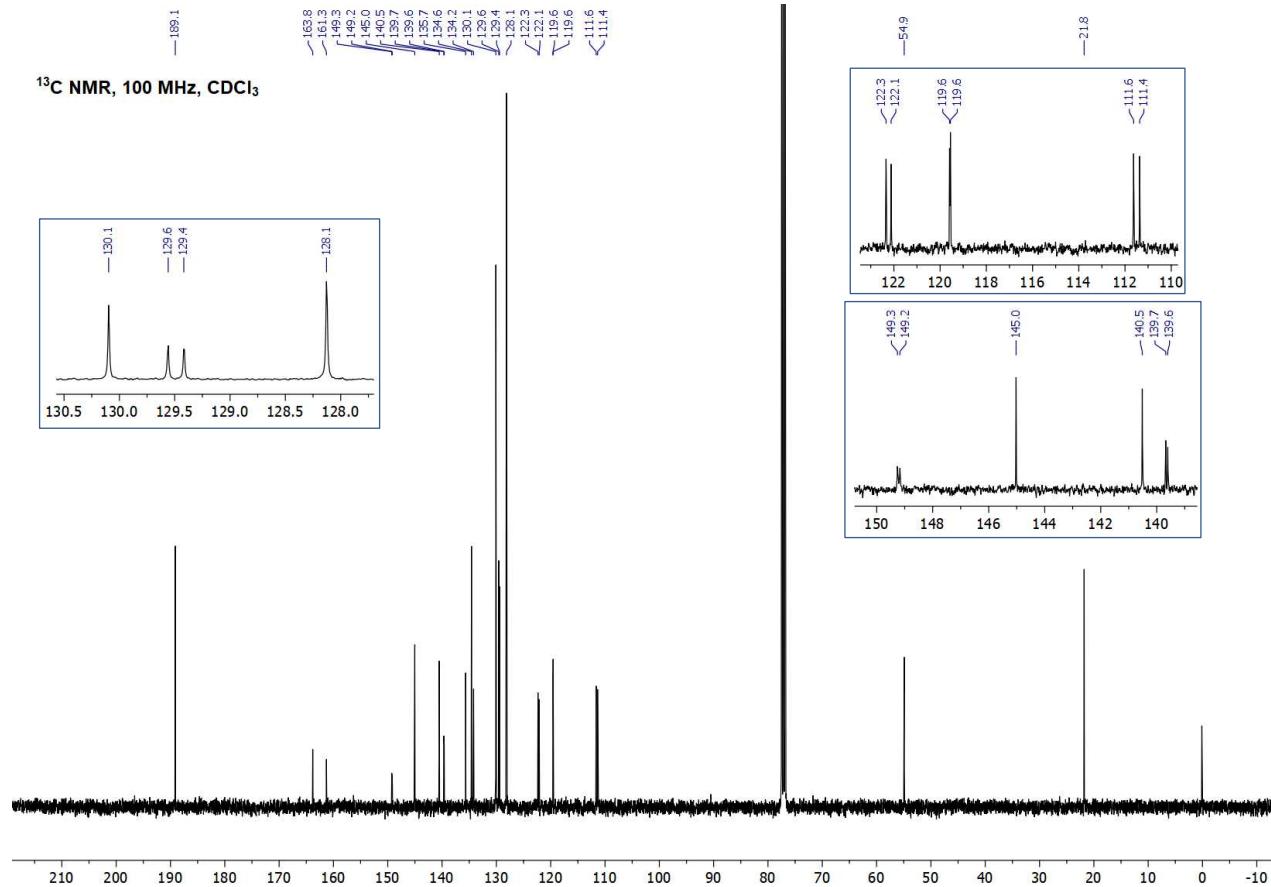


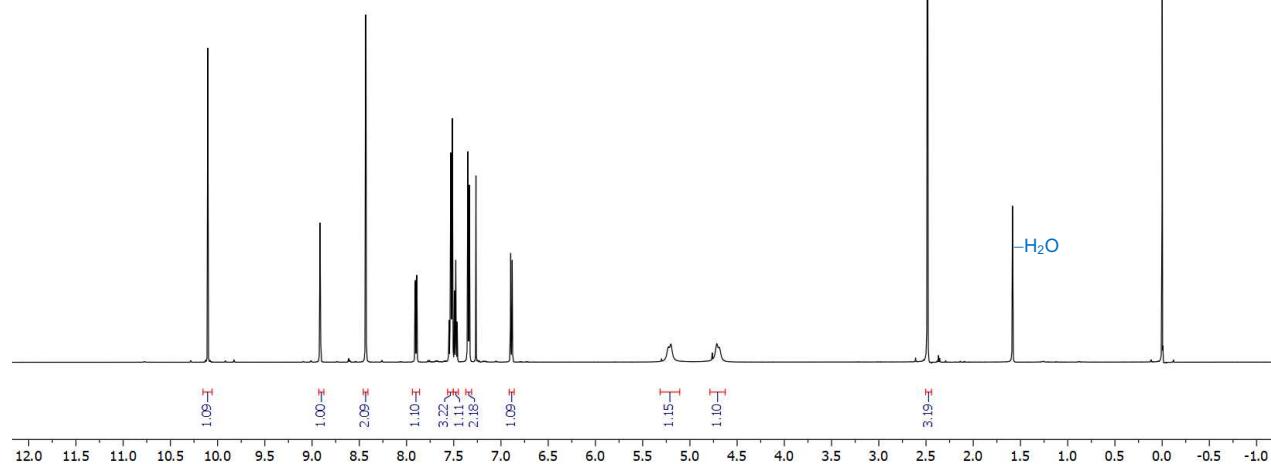
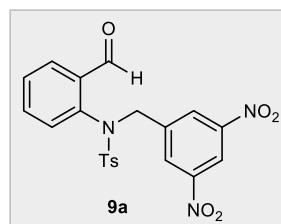
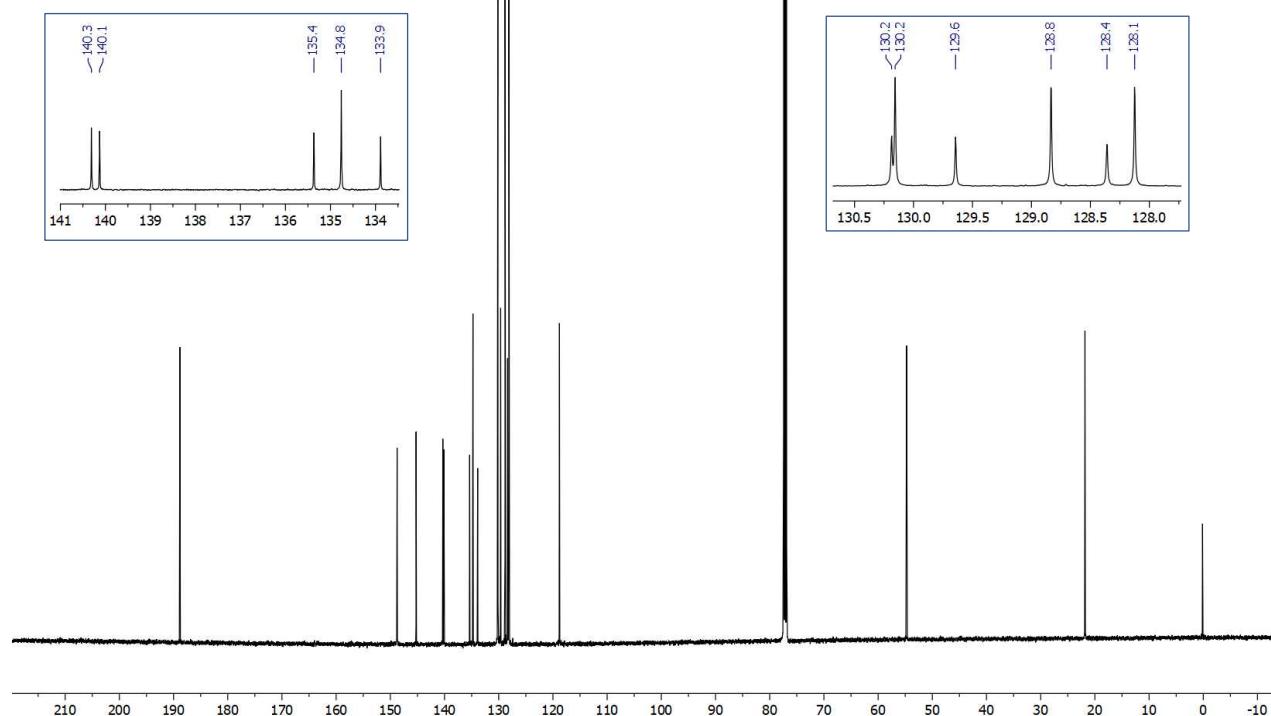
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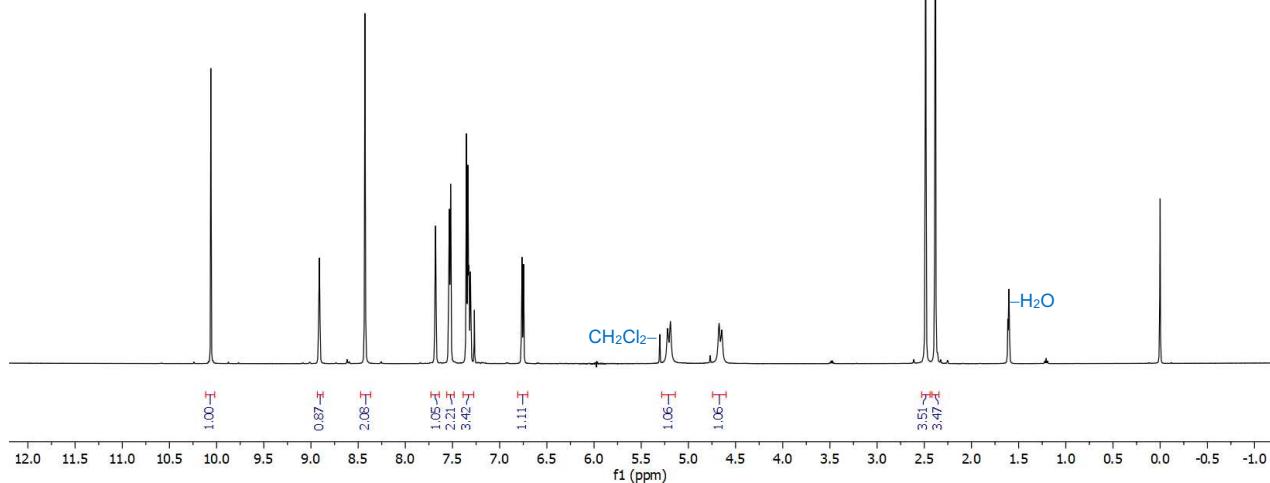
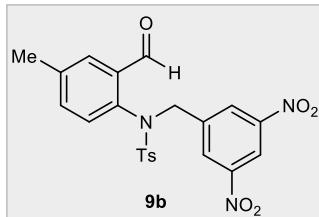
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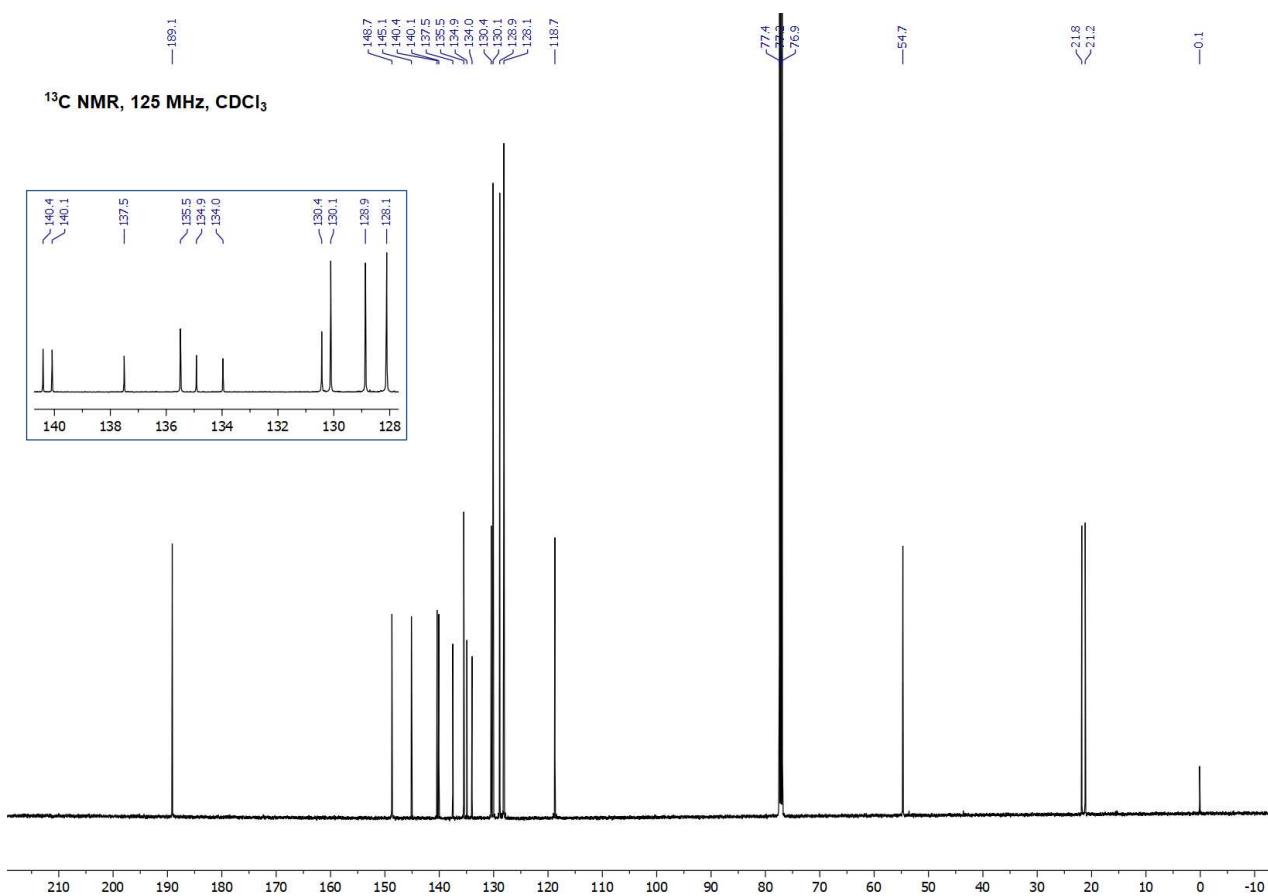
¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

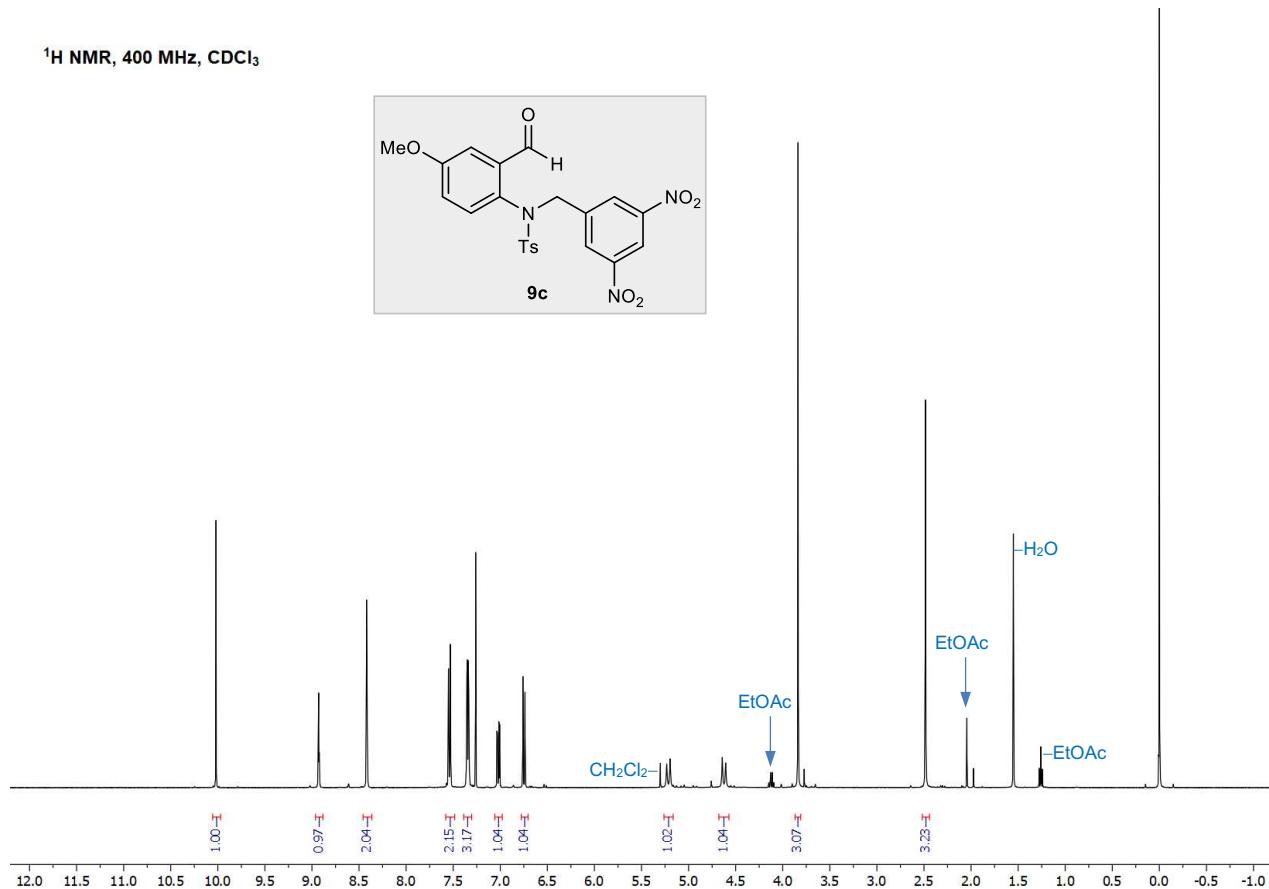
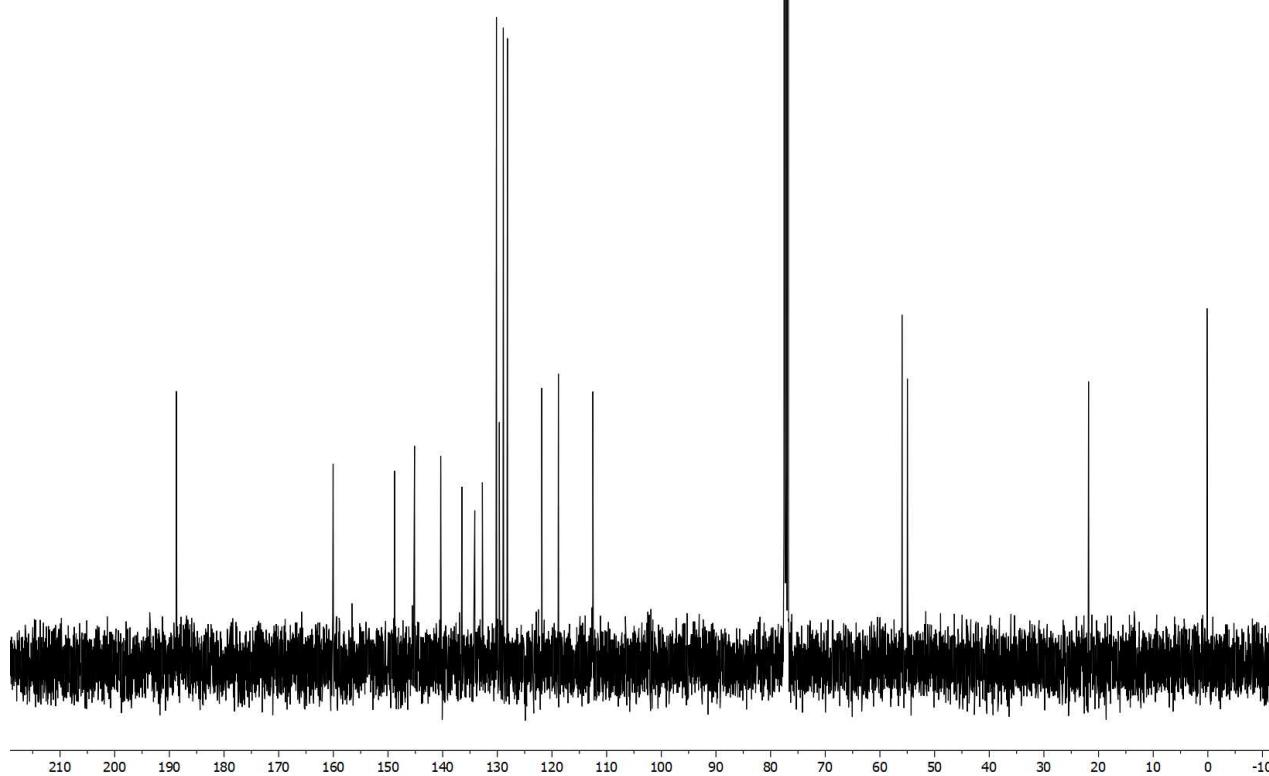
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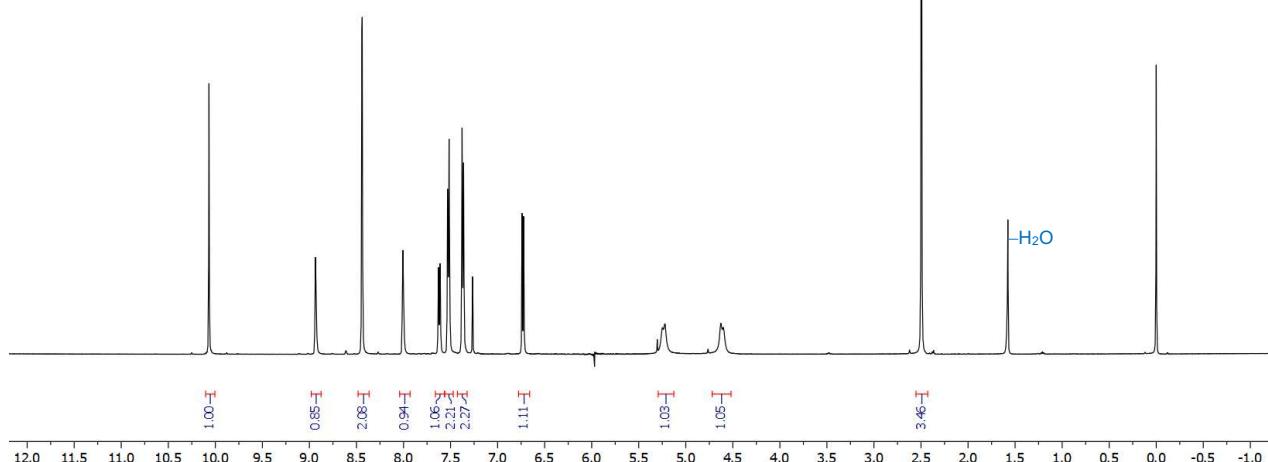
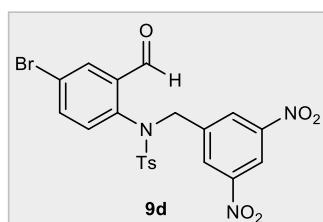
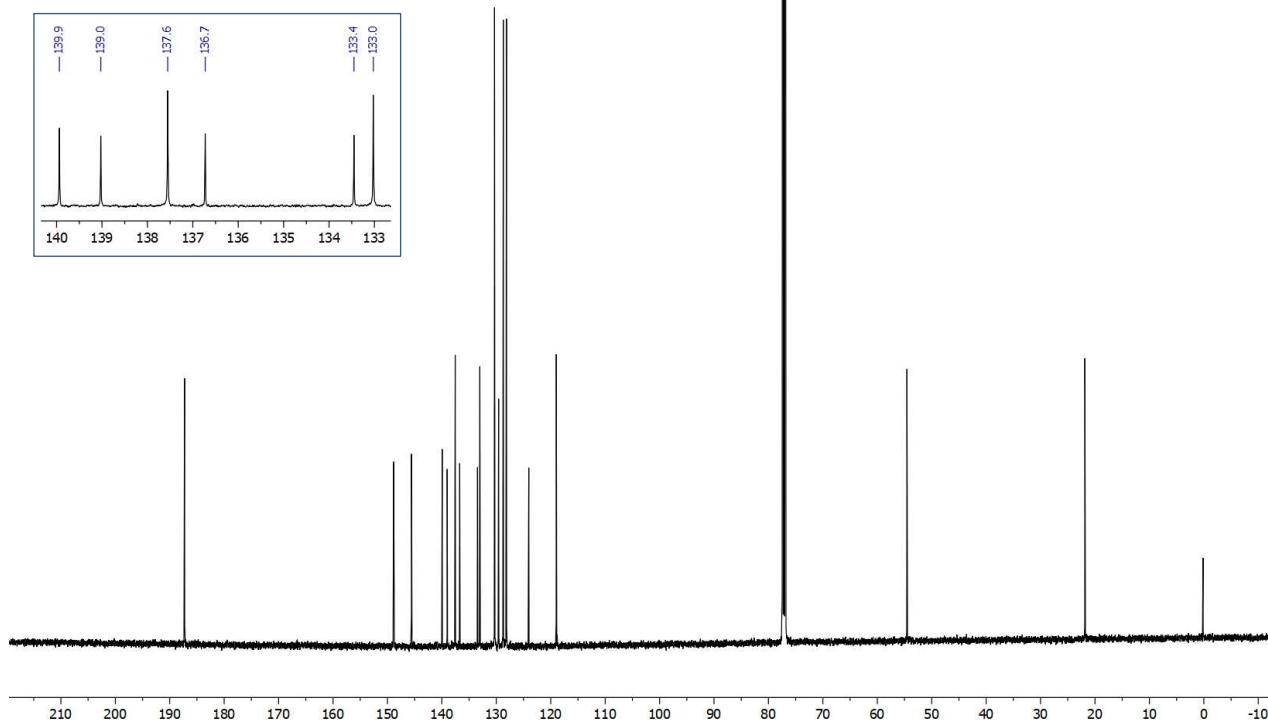
¹H NMR, 500 MHz, CDCl₃

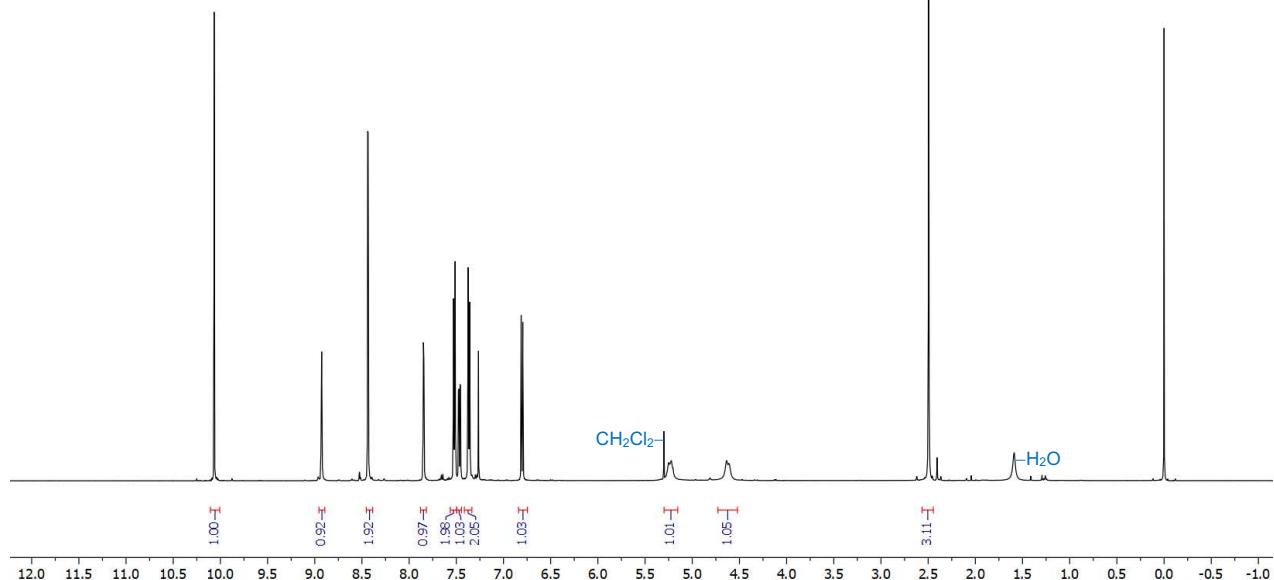
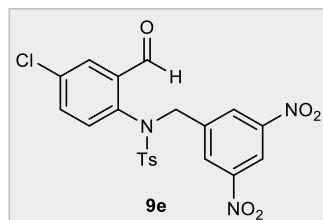
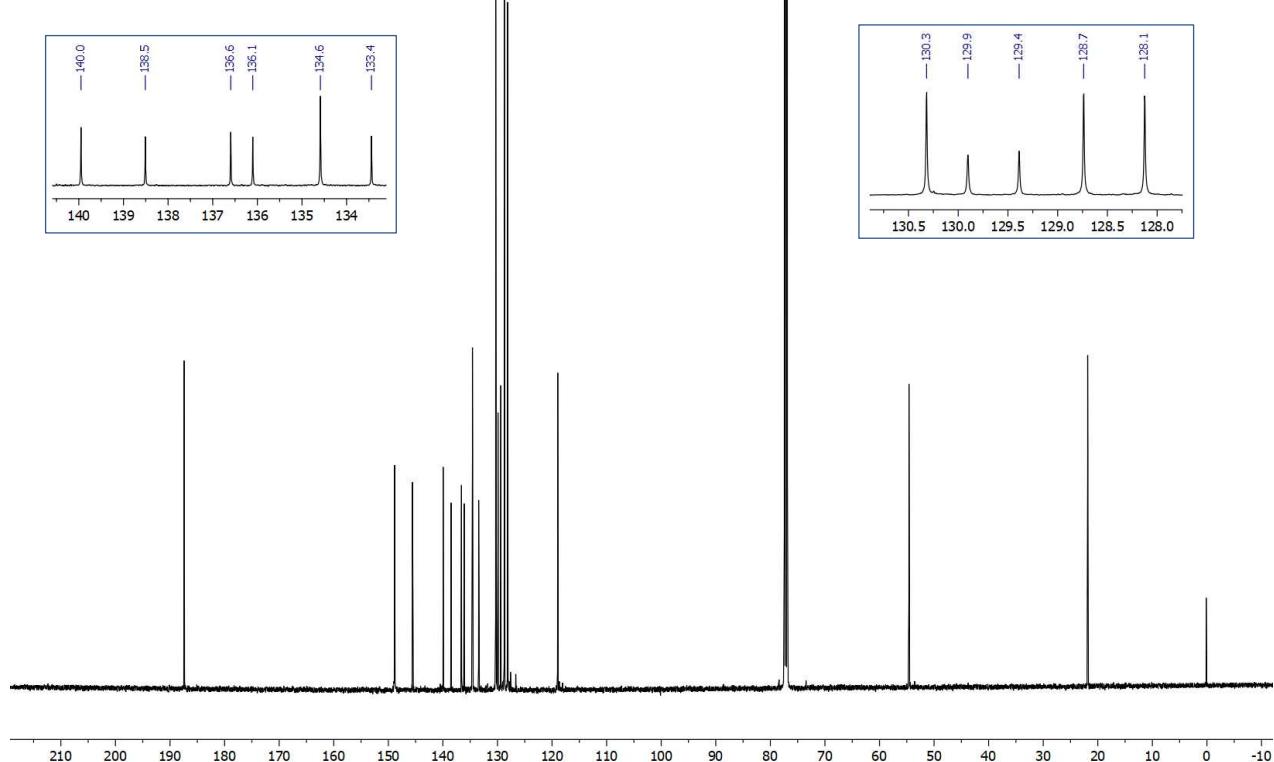


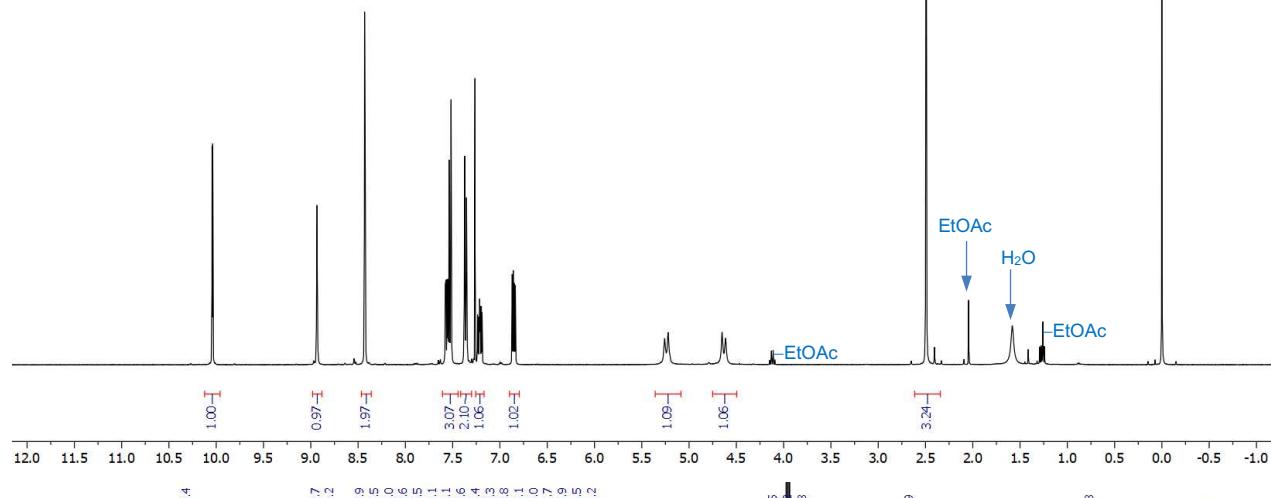
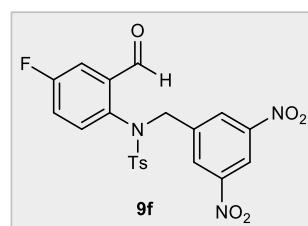
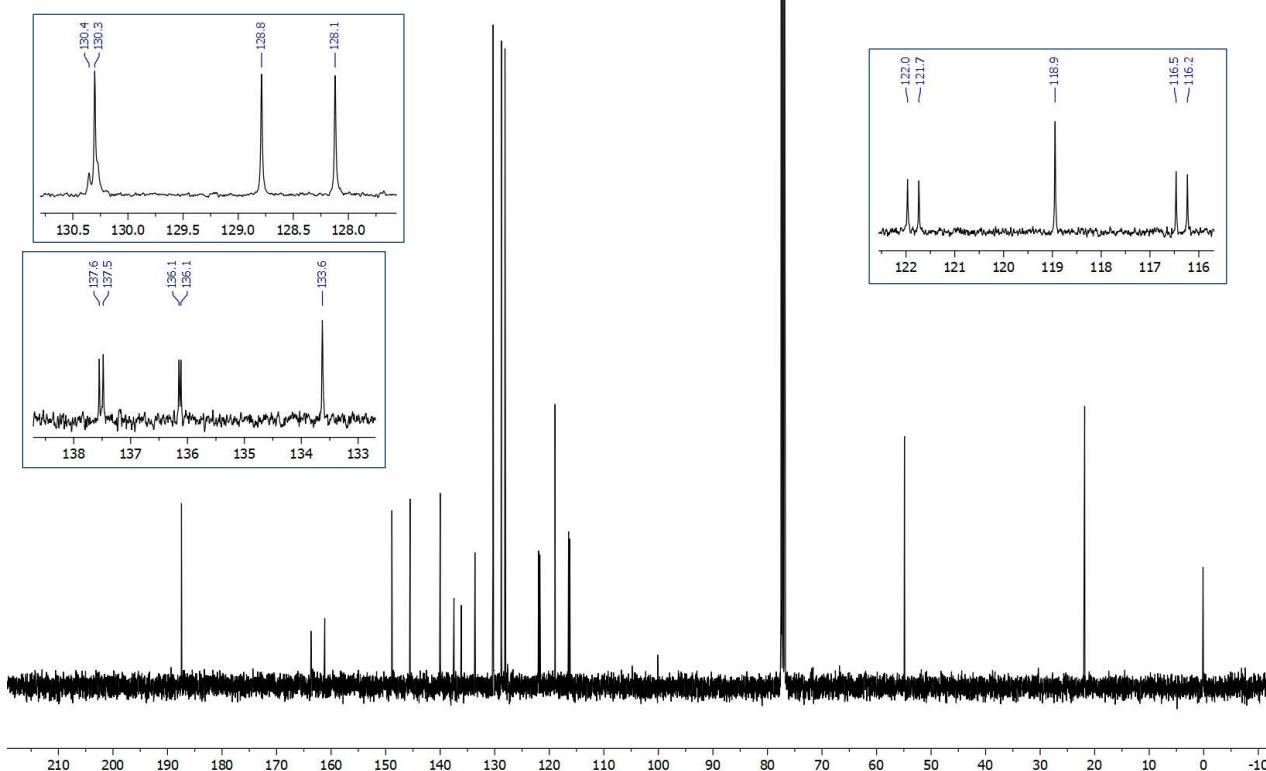
¹³C NMR, 125 MHz, CDCl₃

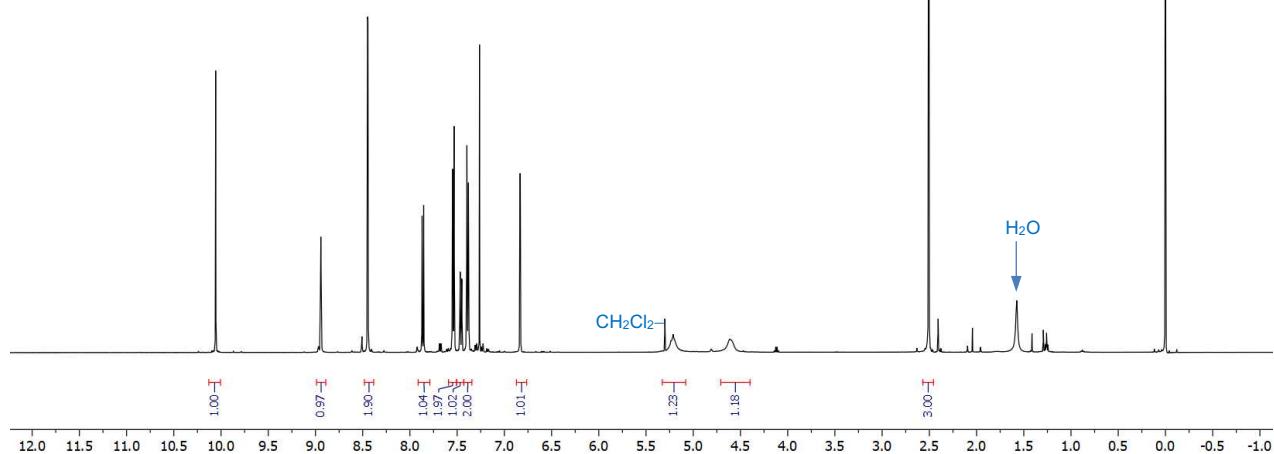
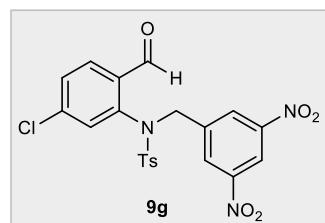
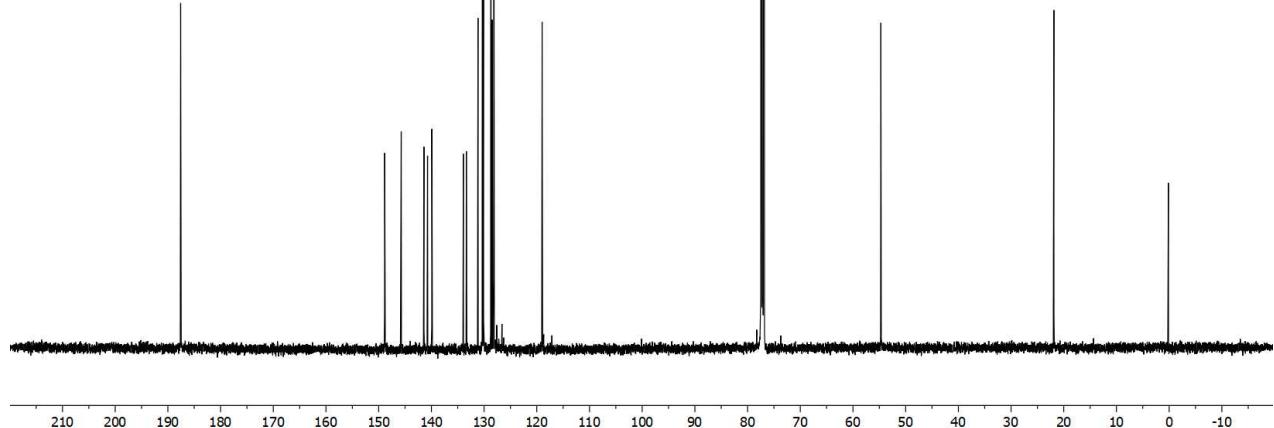
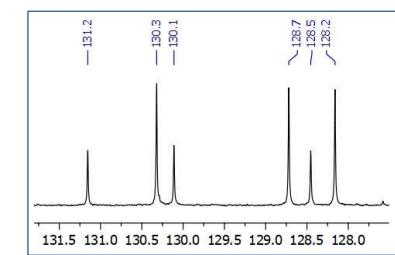


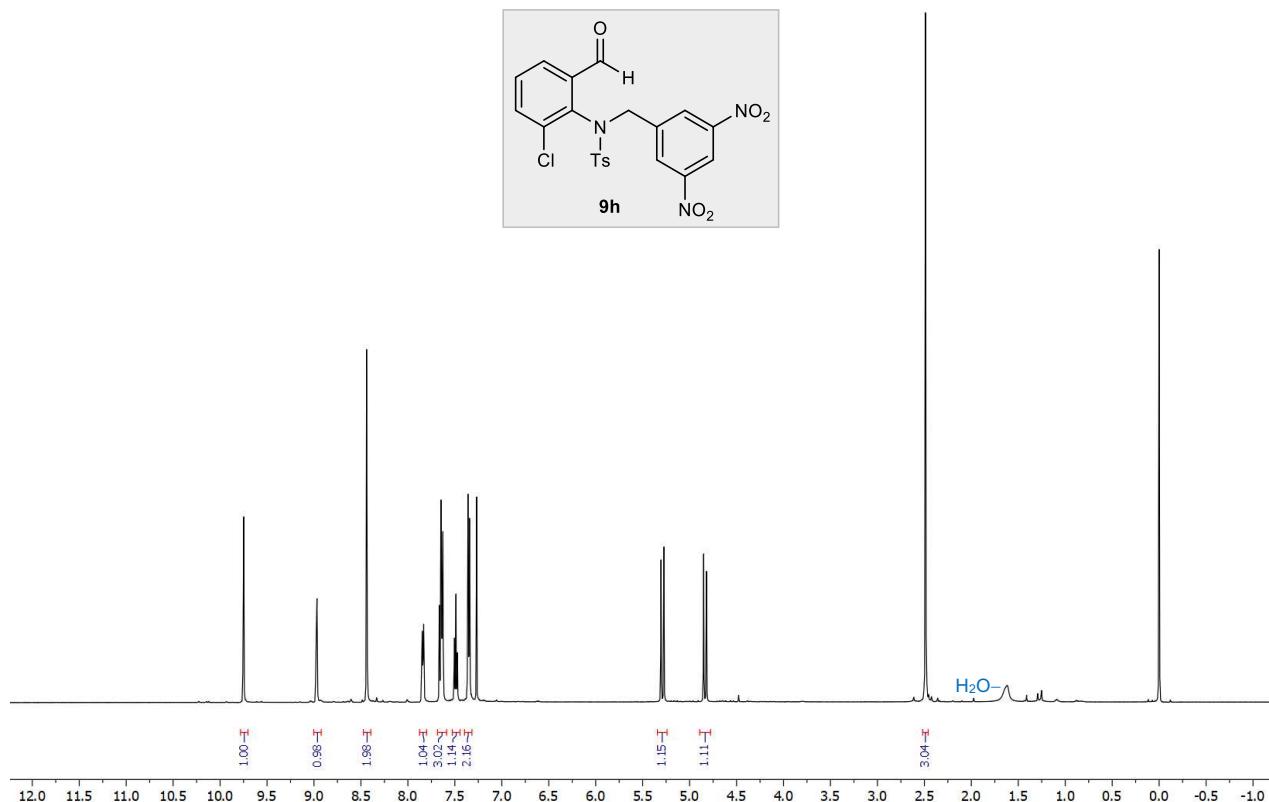
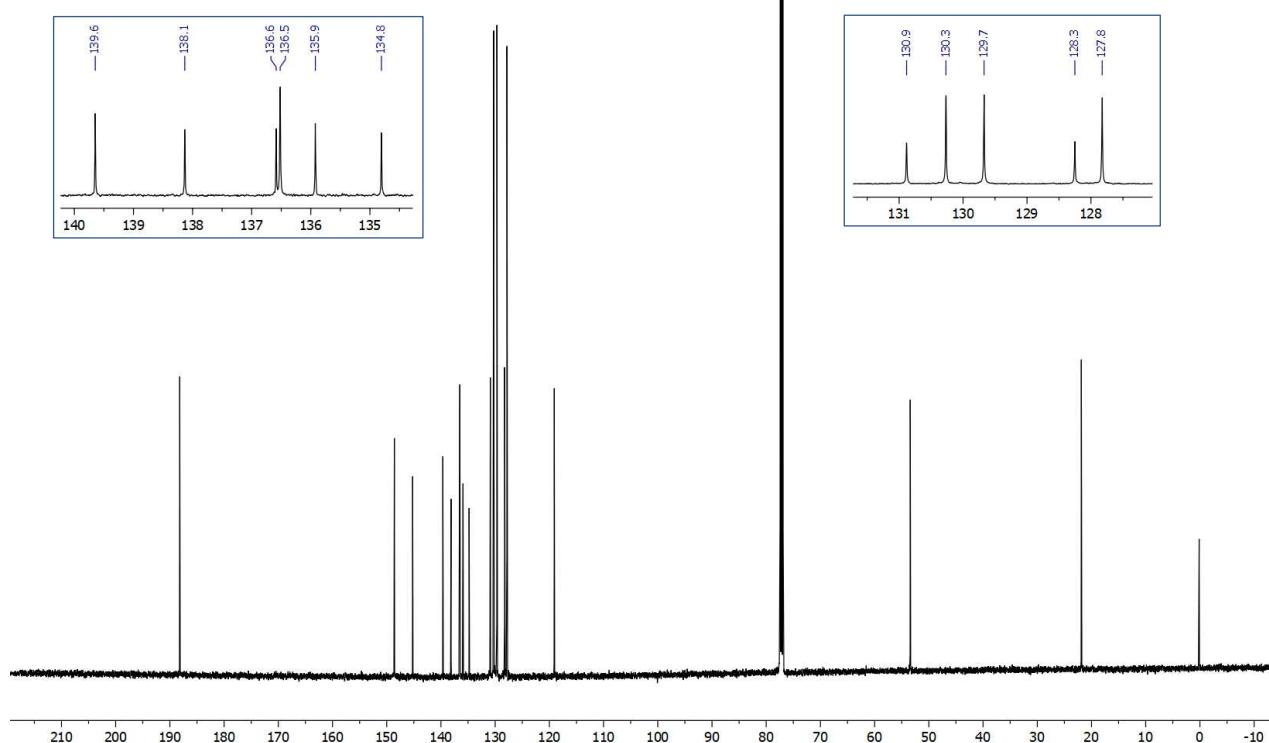
¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

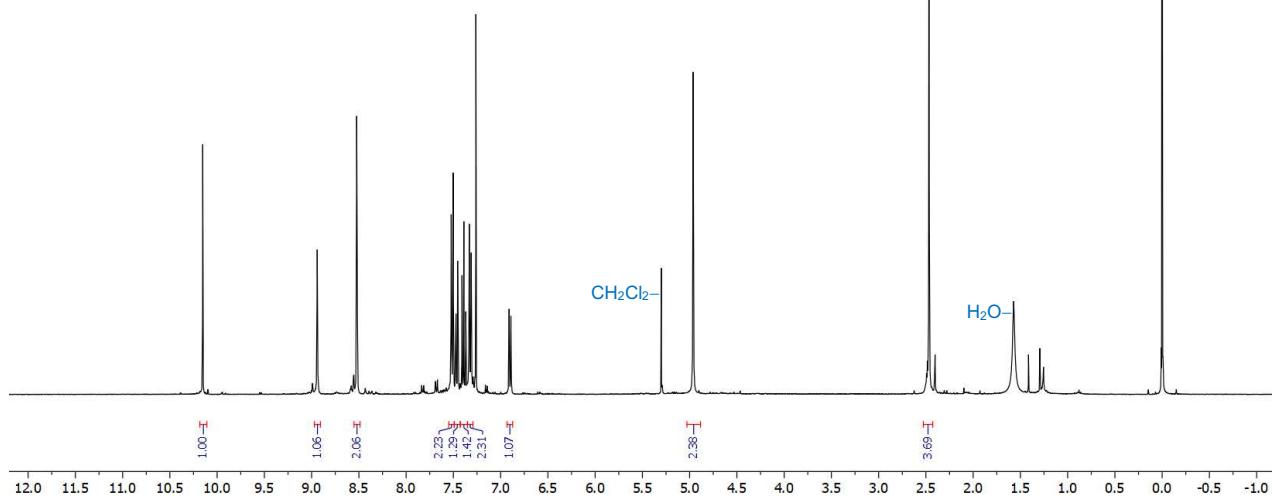
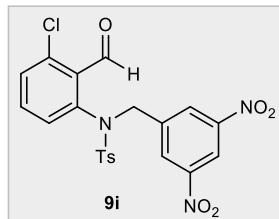
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

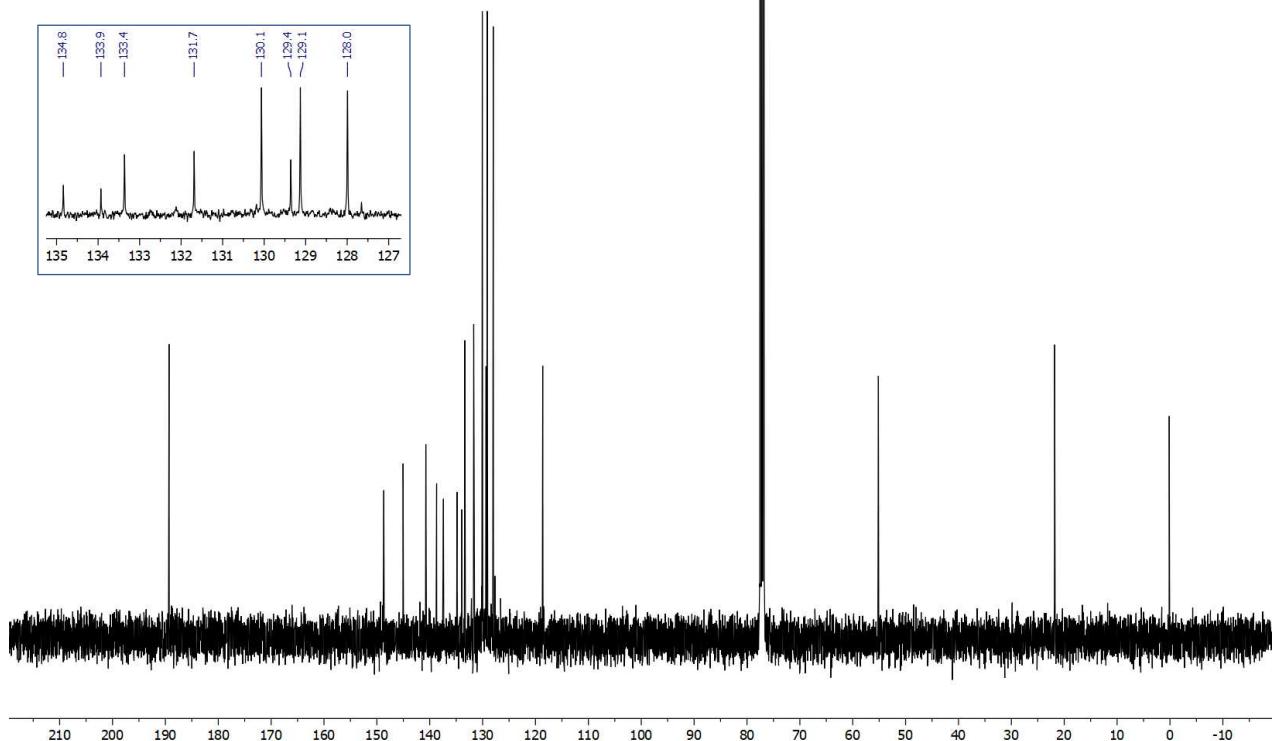
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

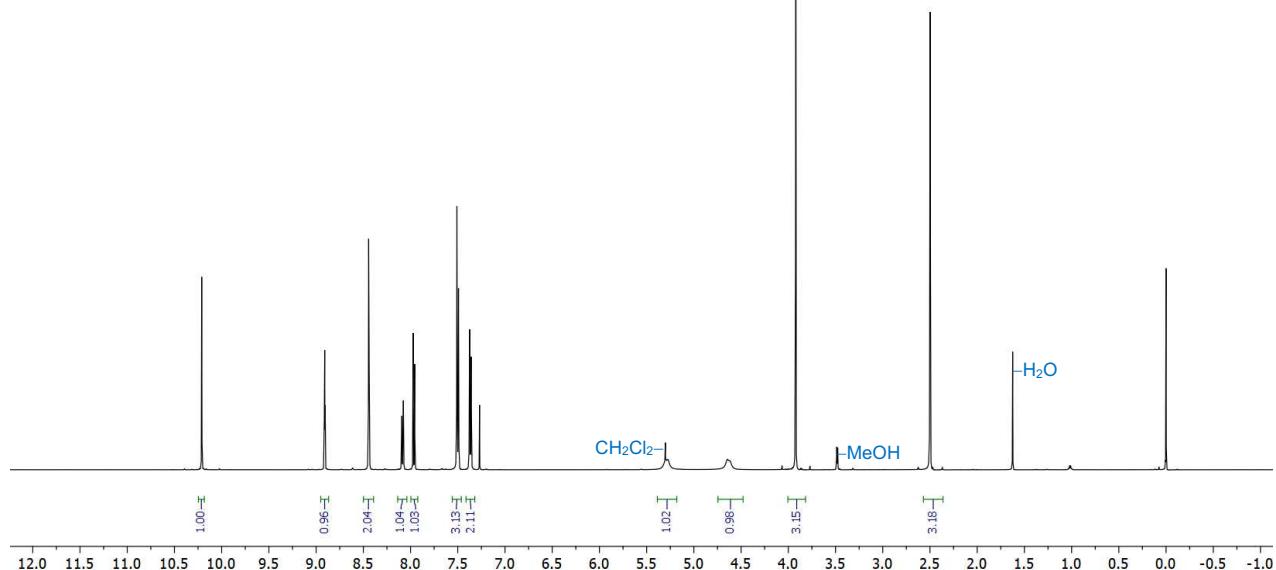
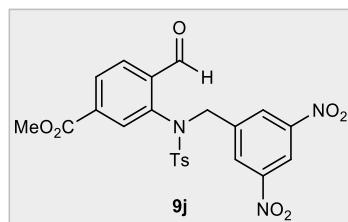
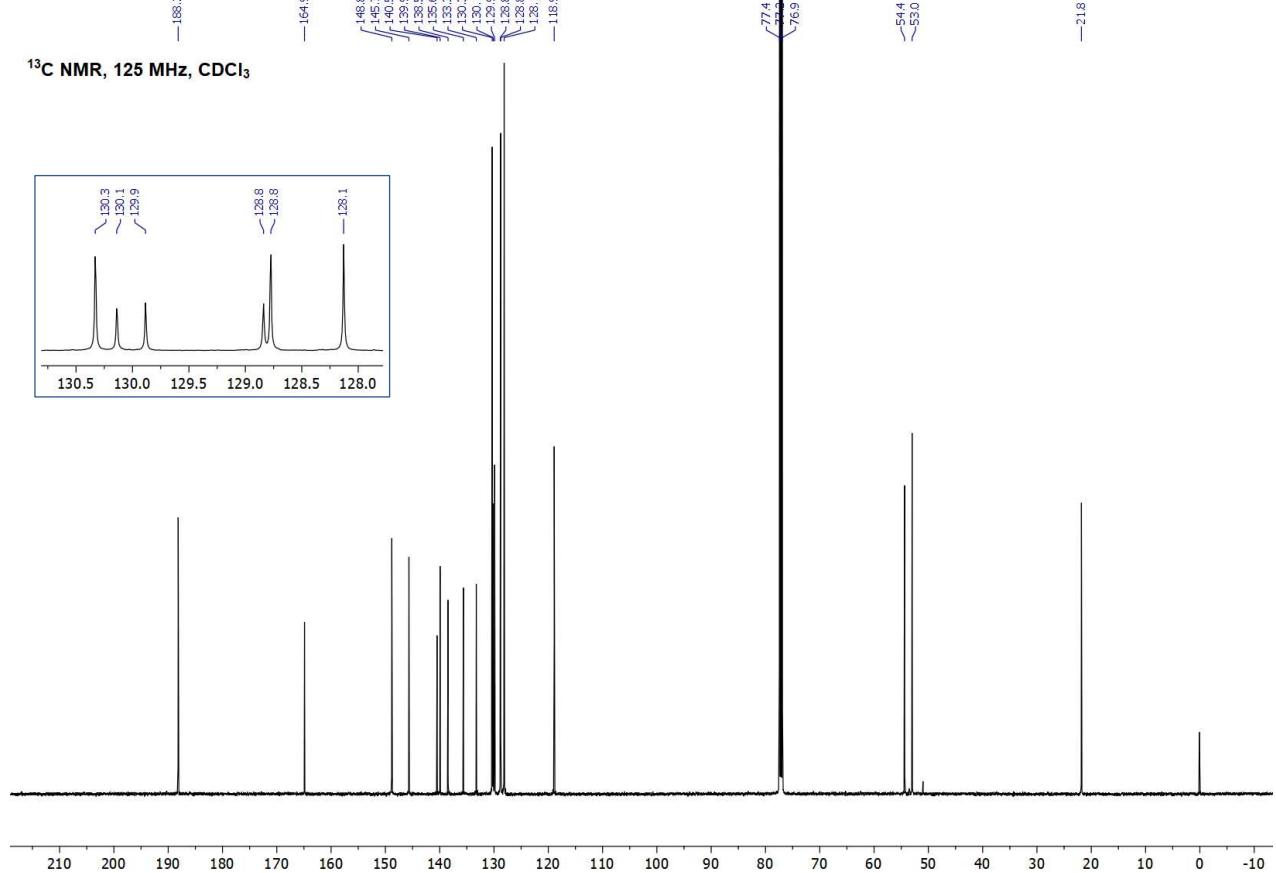
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

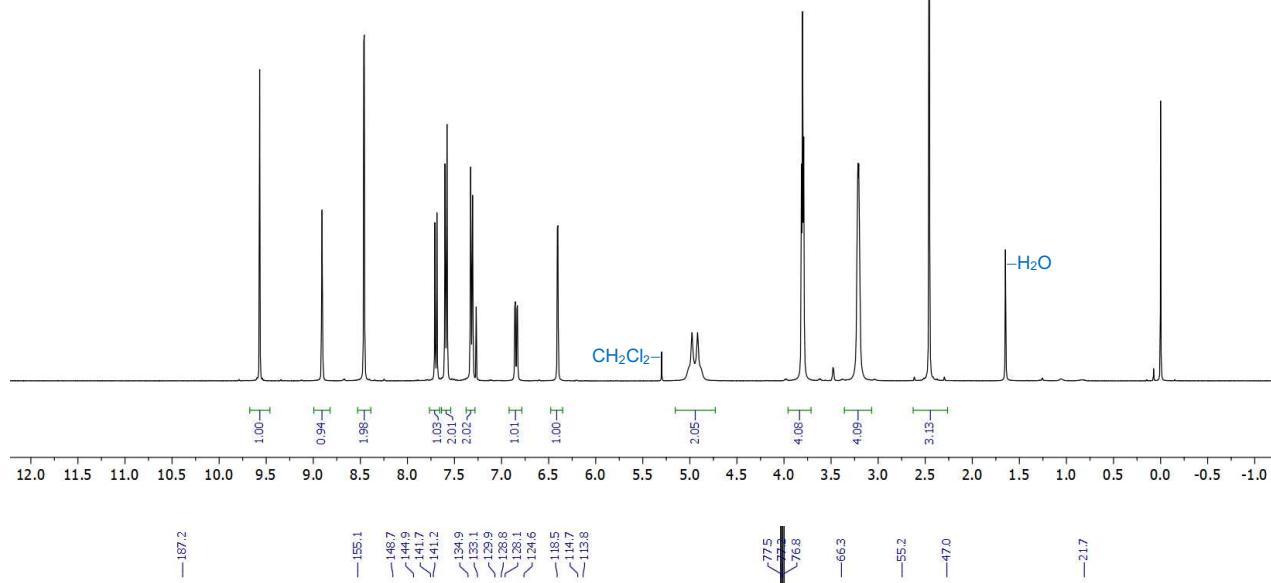
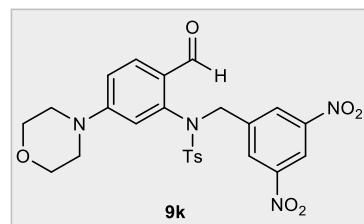
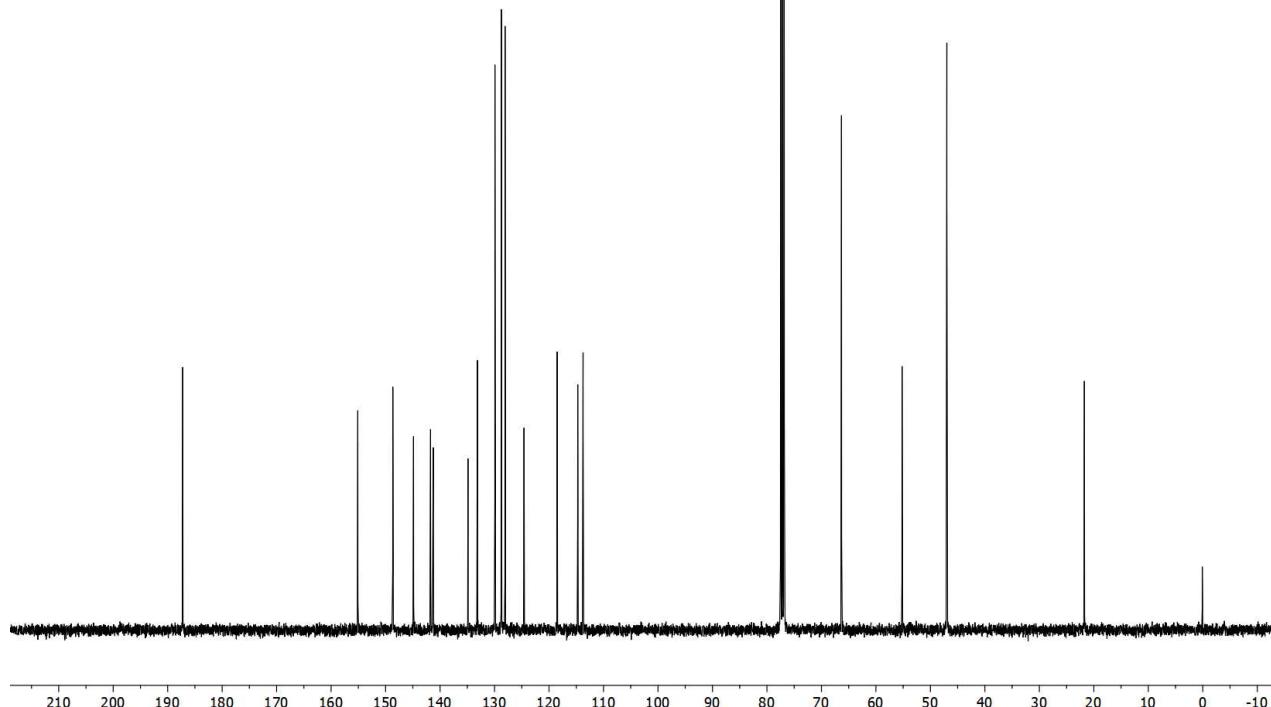
¹H NMR, 400 MHz, CDCl₃

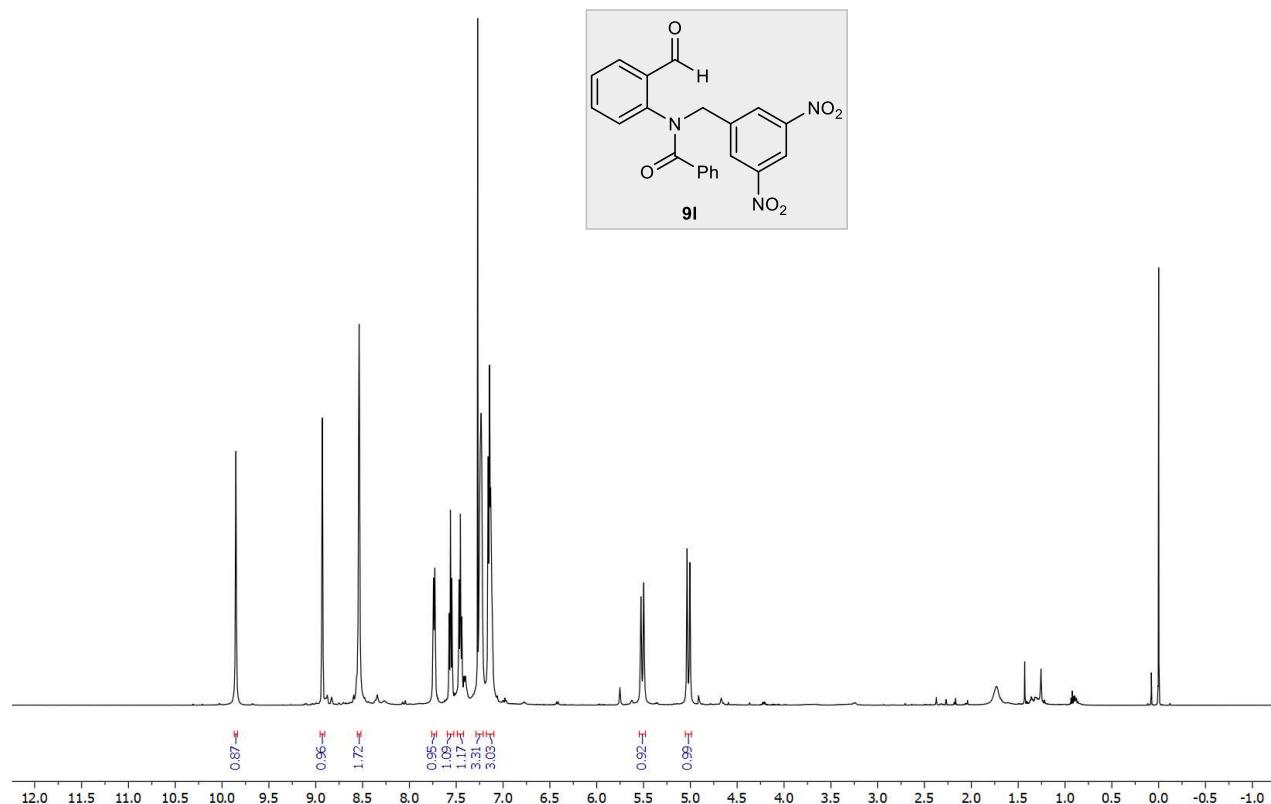
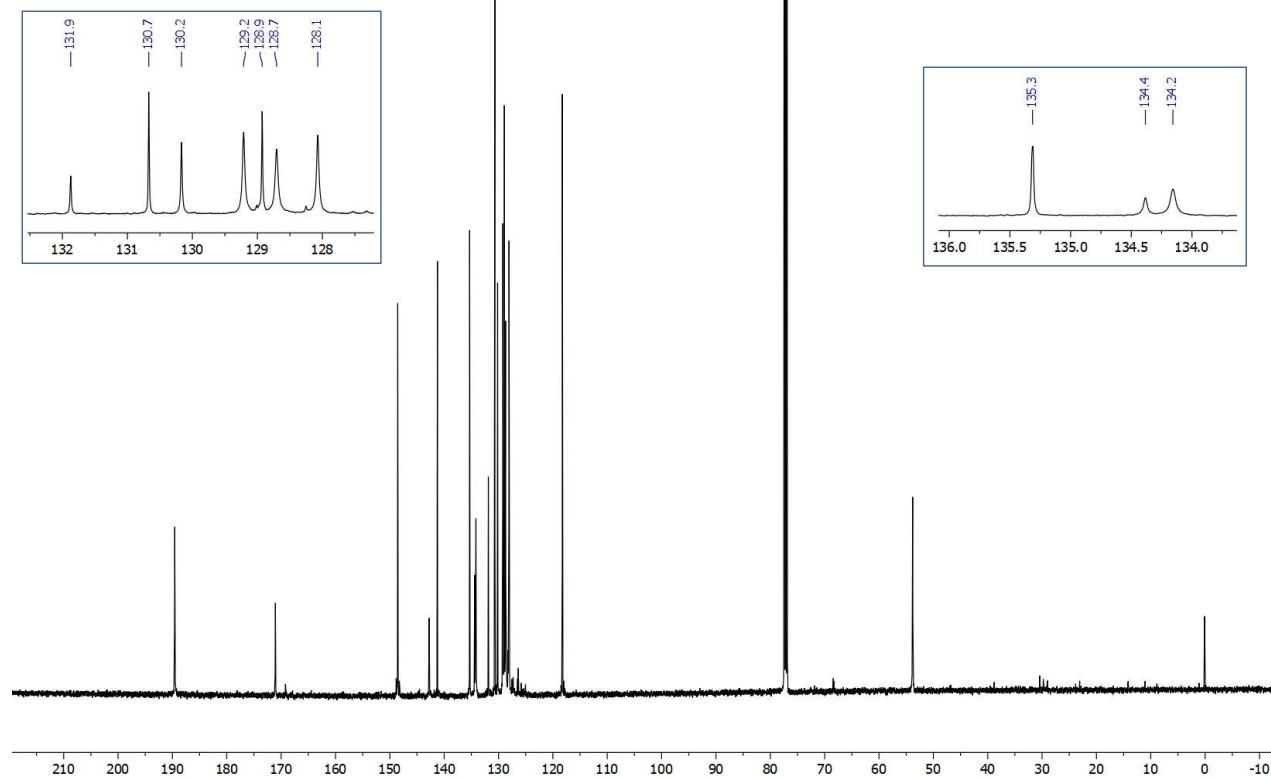


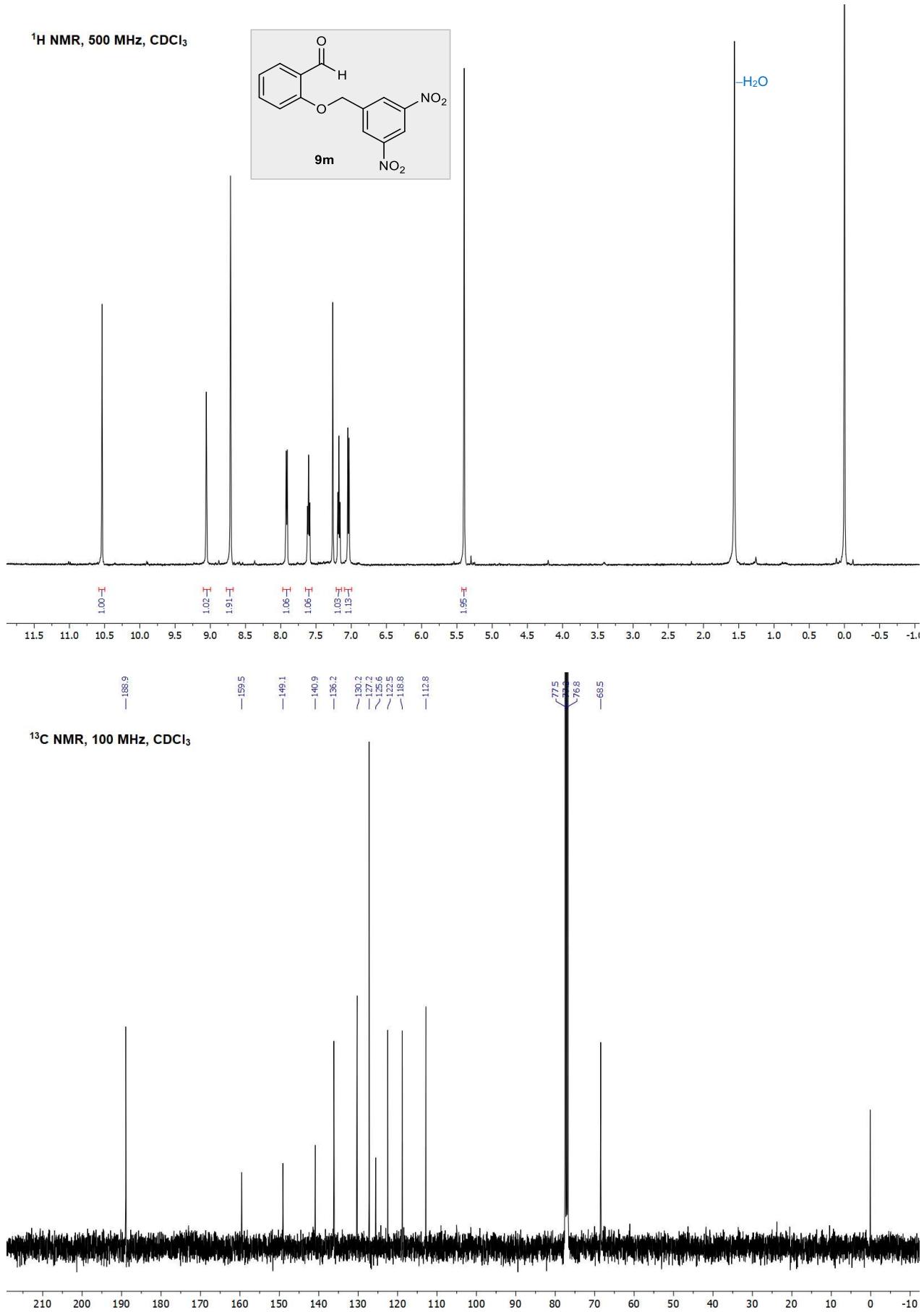
¹³C NMR, 100 MHz, CDCl₃



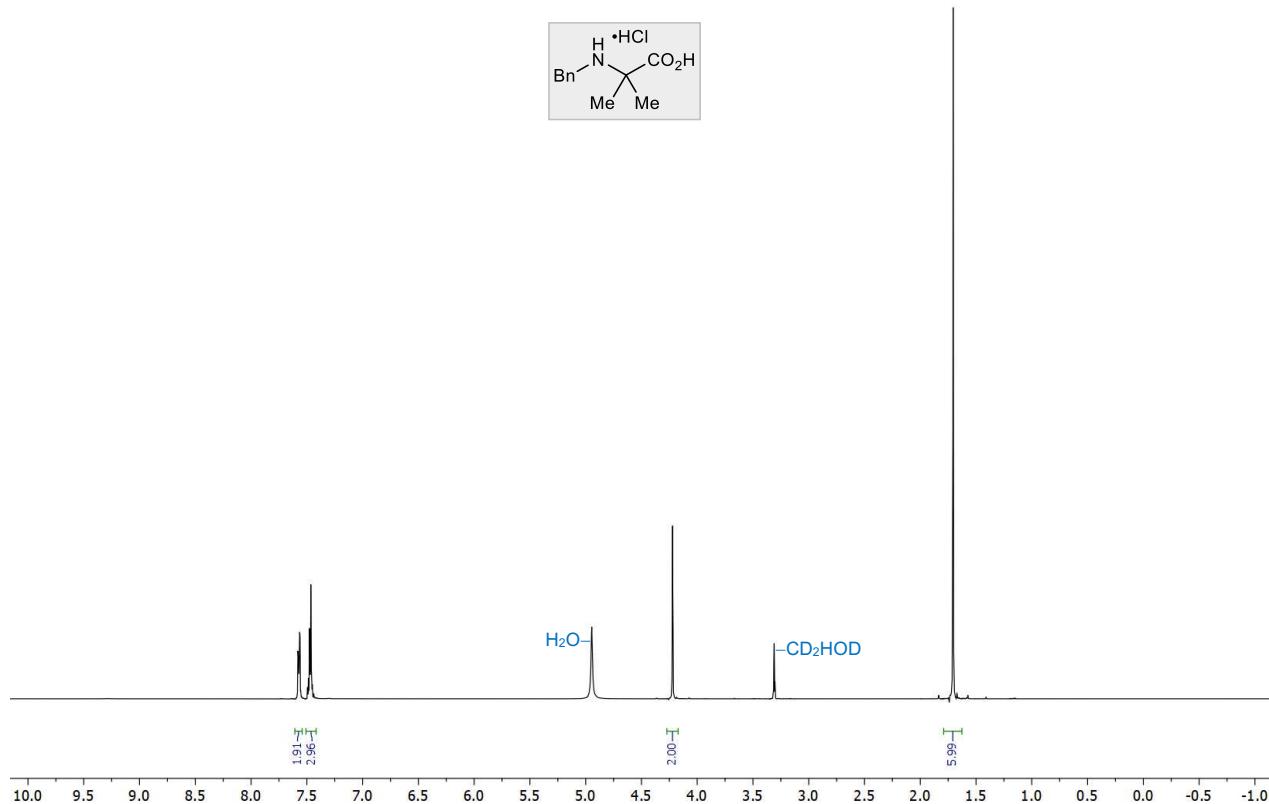
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

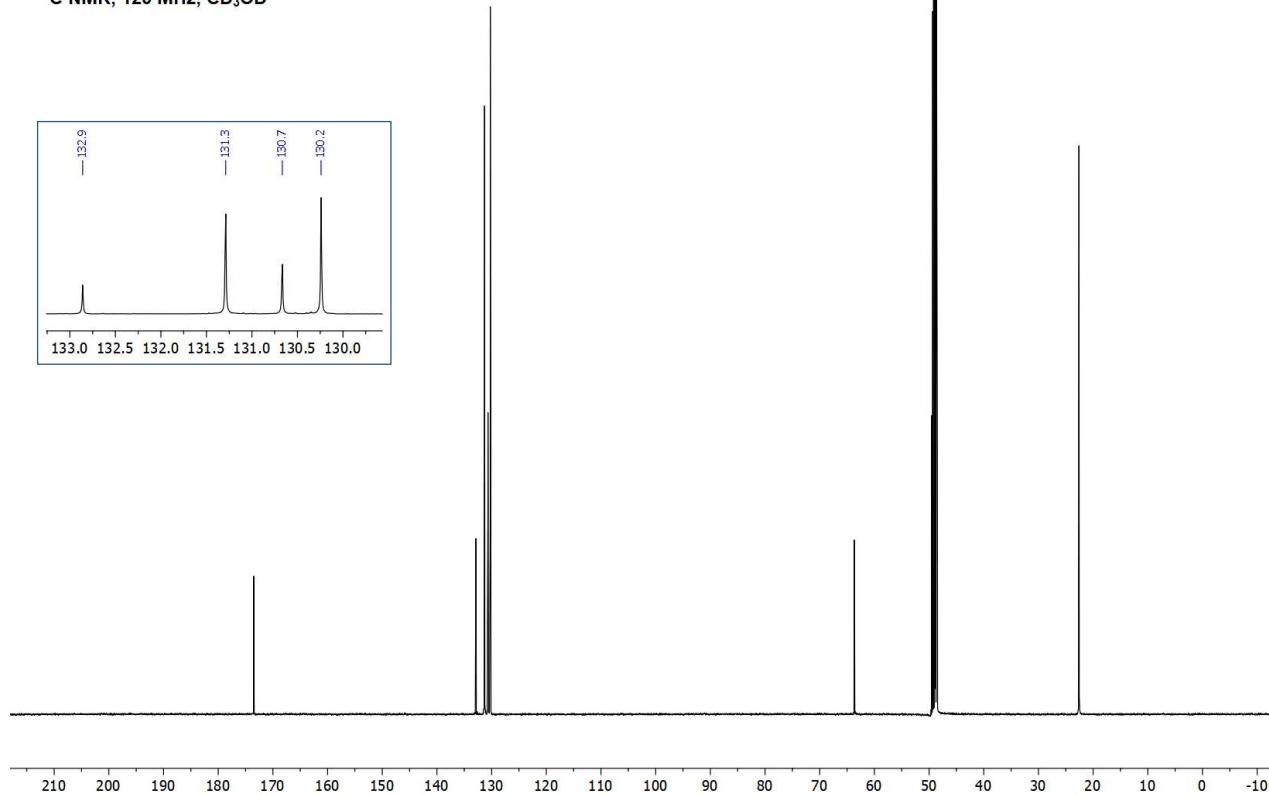
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

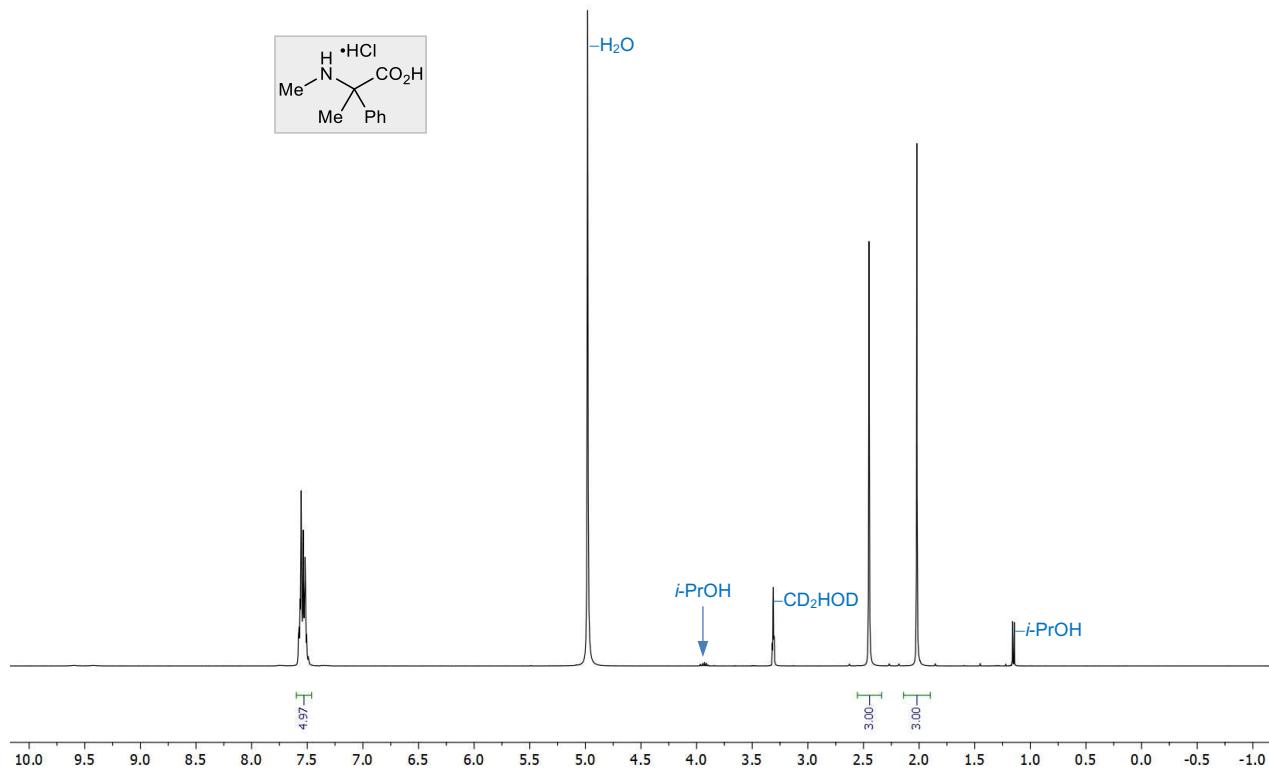
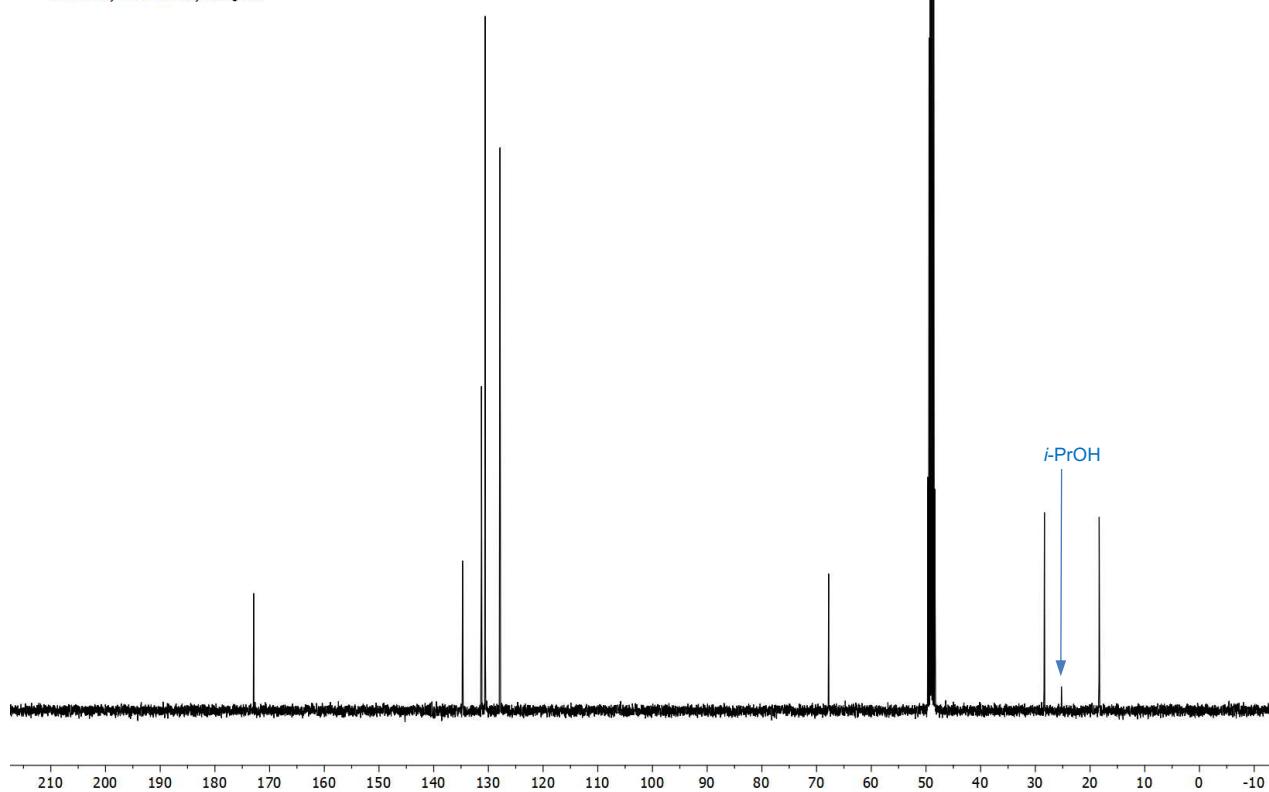


¹H NMR, 500 MHz, CD₃OD

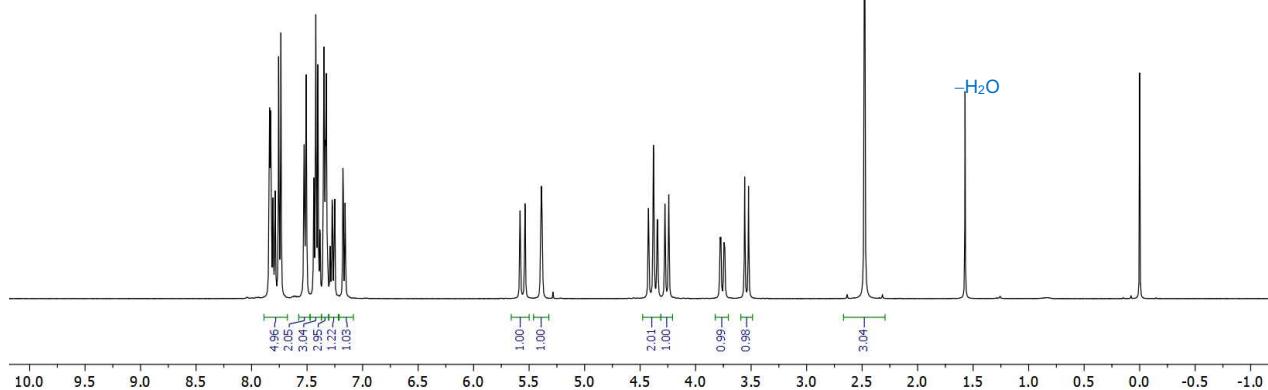
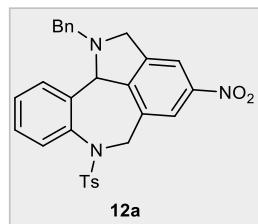


¹³C NMR, 125 MHz, CD₃OD

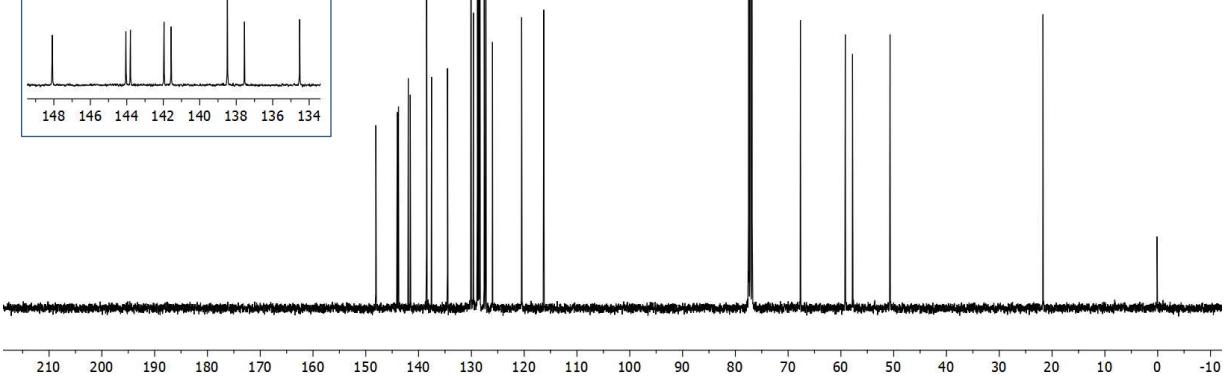
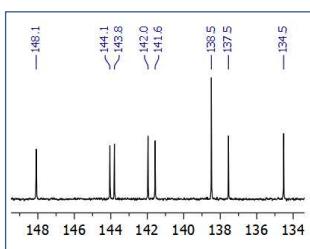
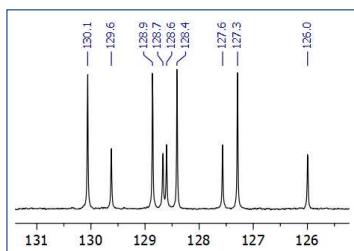


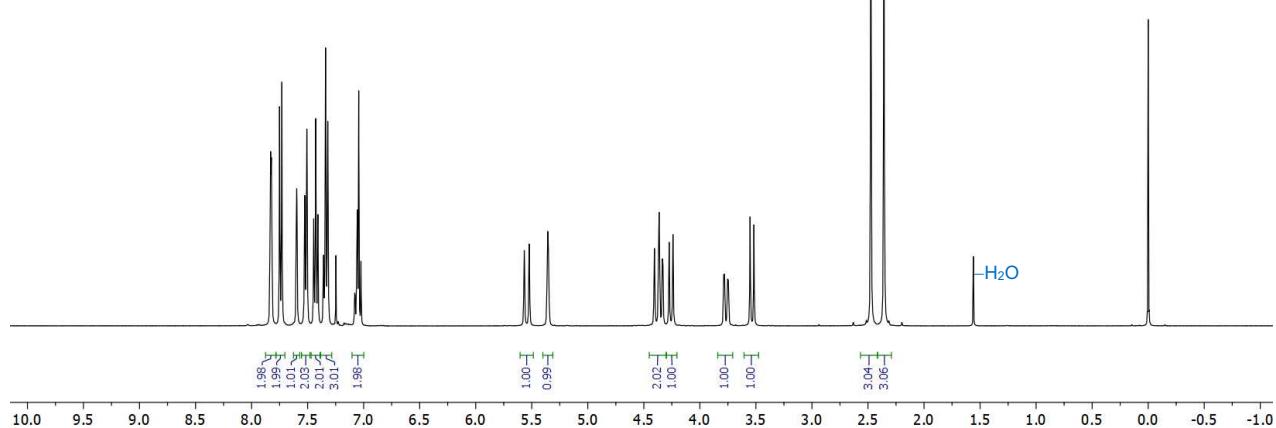
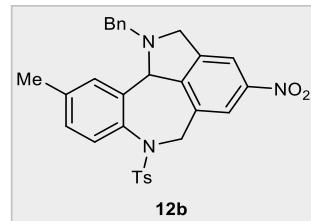
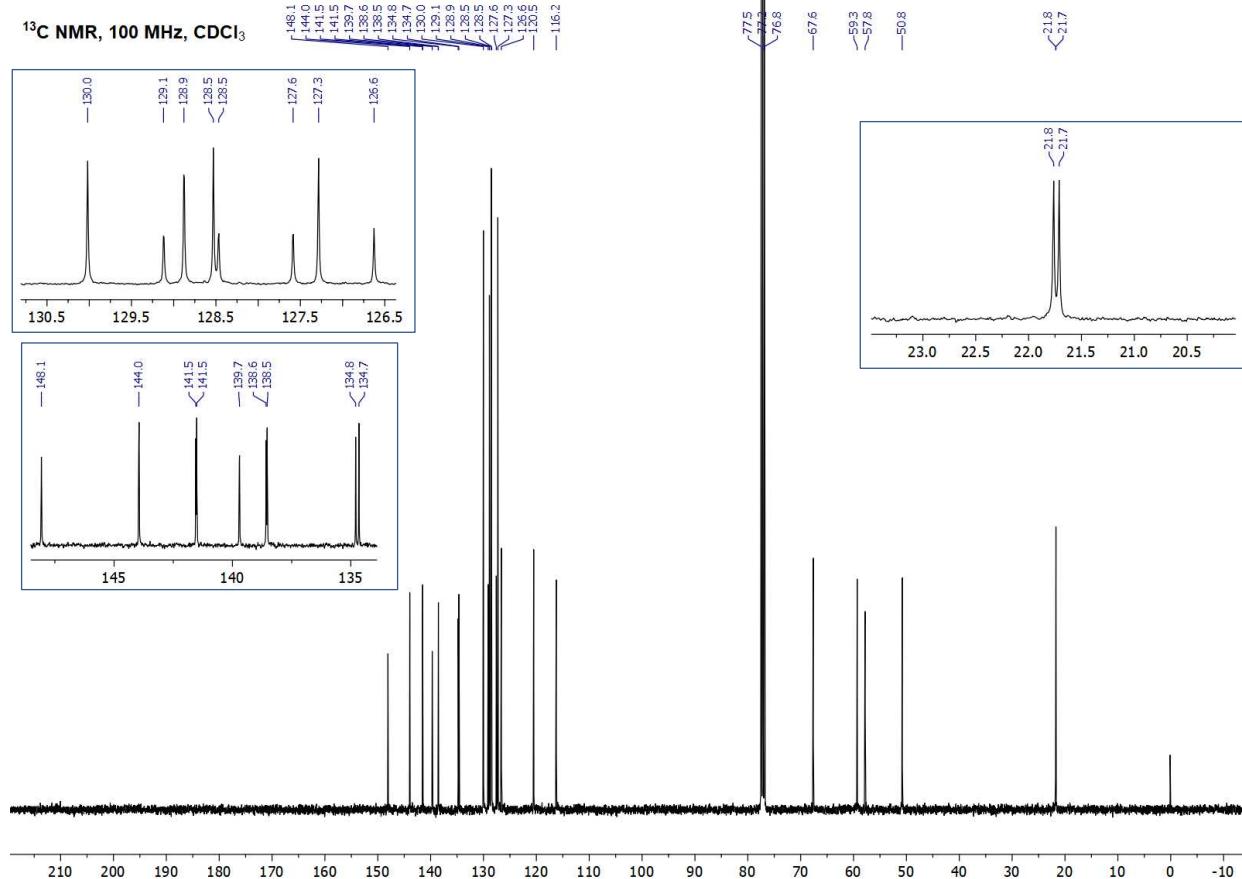
¹H NMR, 400 MHz, CD₃OD¹³C NMR, 100 MHz, CD₃OD

¹H NMR, 400 MHz, CDCl₃

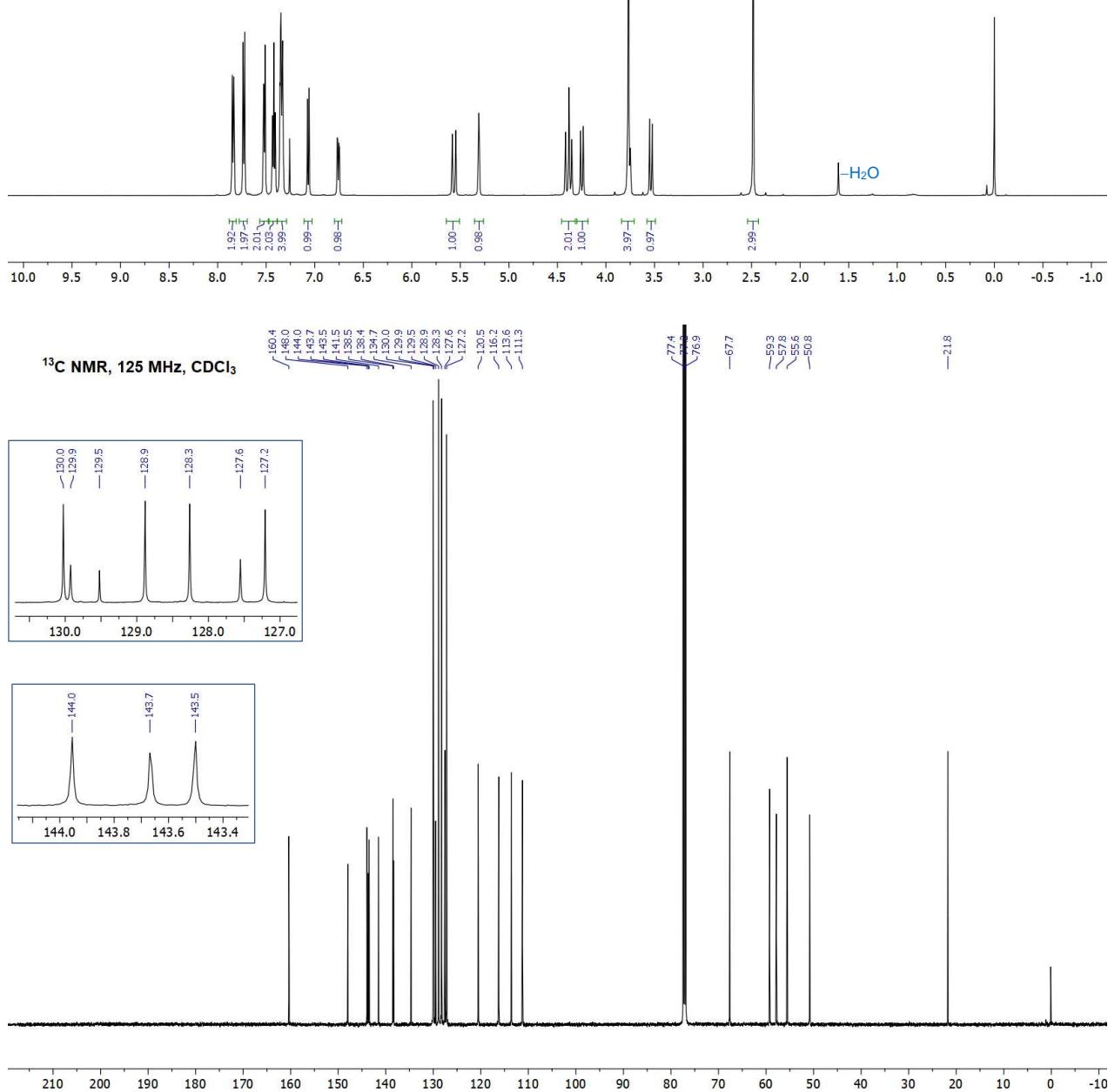
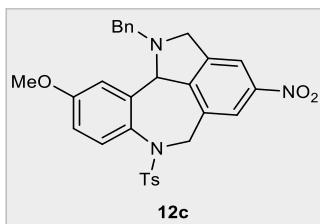


¹³C NMR, 100 MHz, CDCl₃

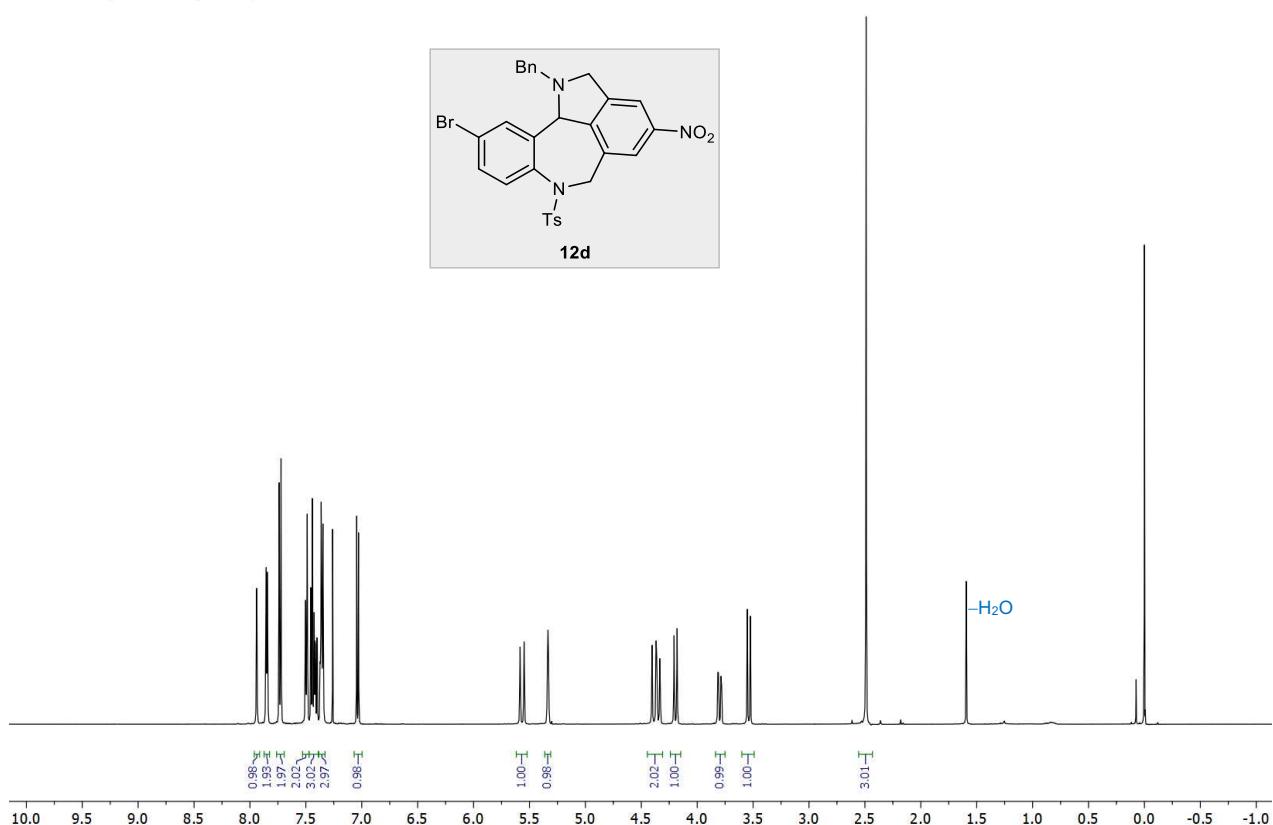
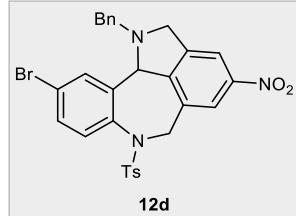


¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

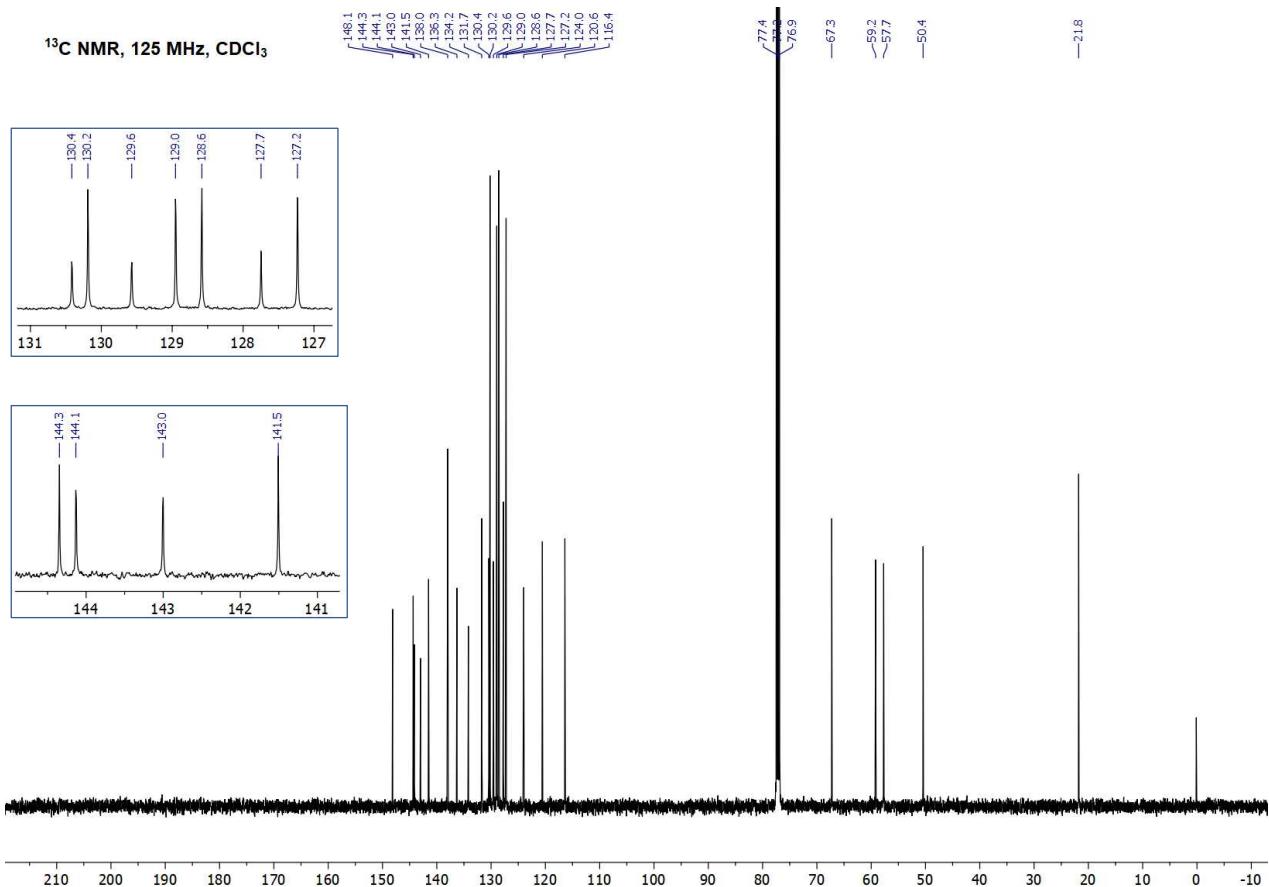
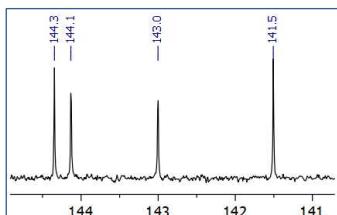
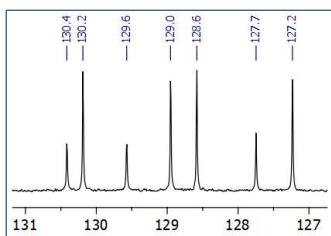
¹H NMR, 500 MHz, CDCl₃

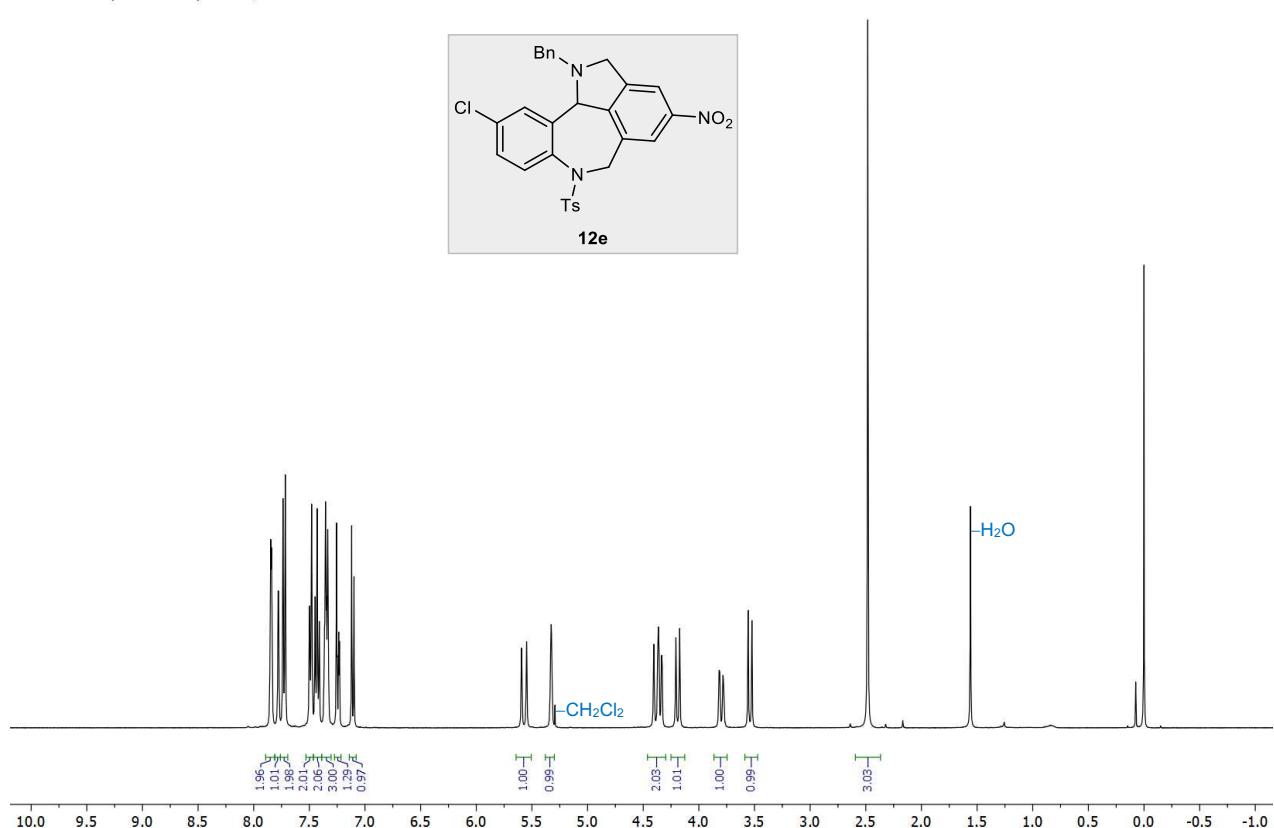
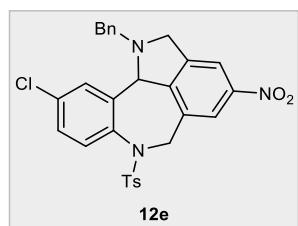
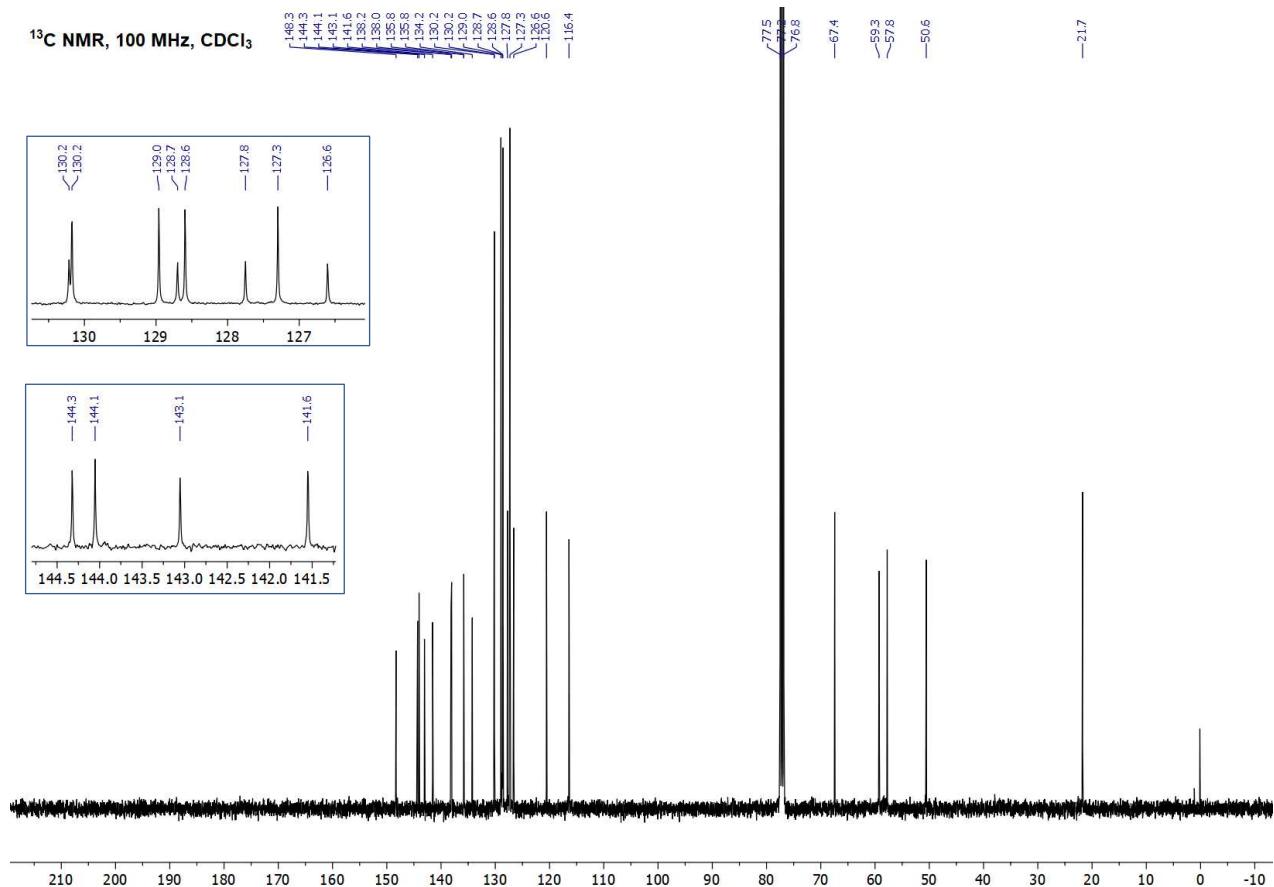
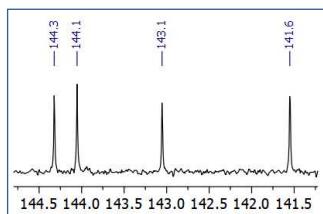
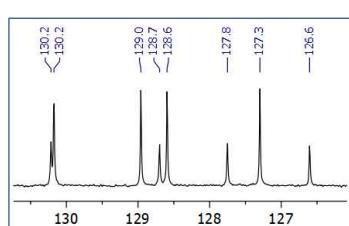


¹H NMR, 500 MHz, CDCl₃

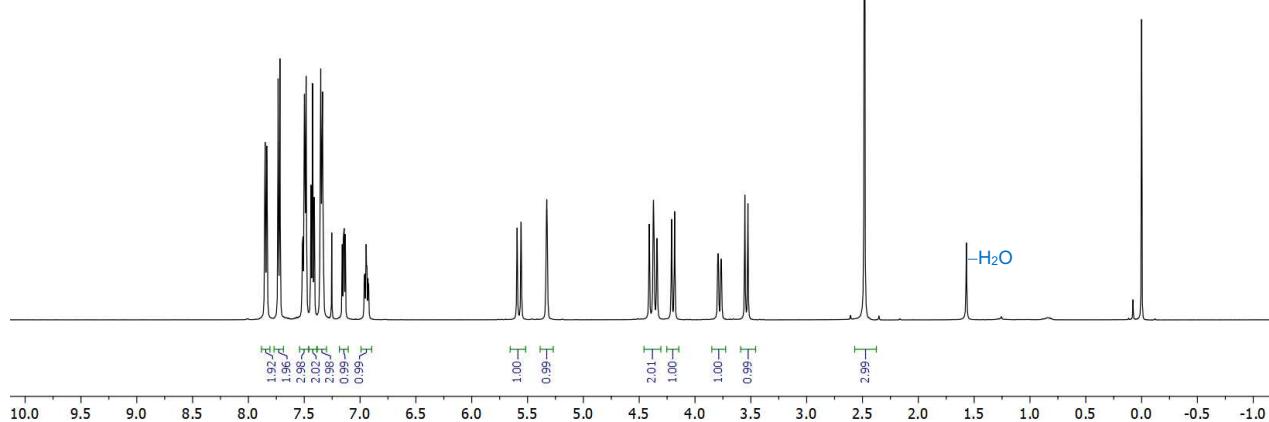
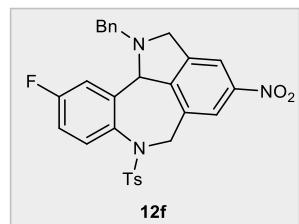


¹³C NMR, 125 MHz, CDCl₃

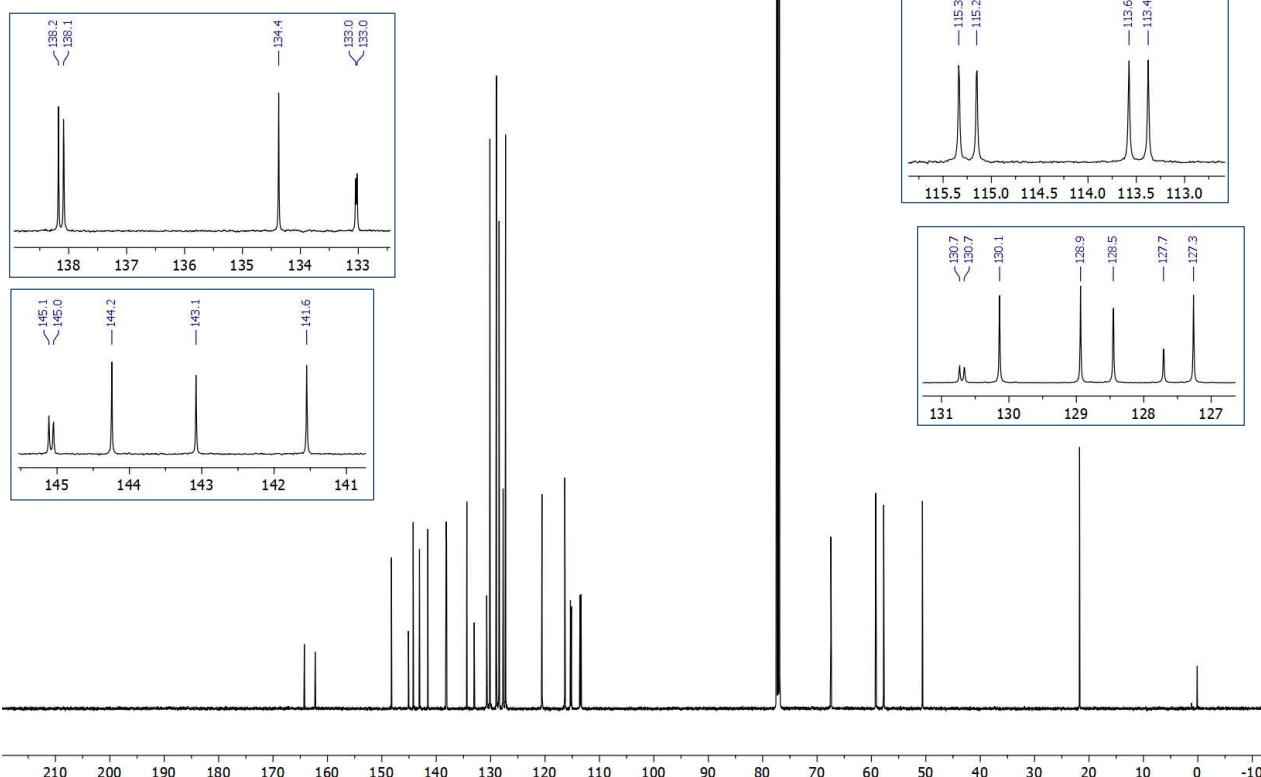


¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

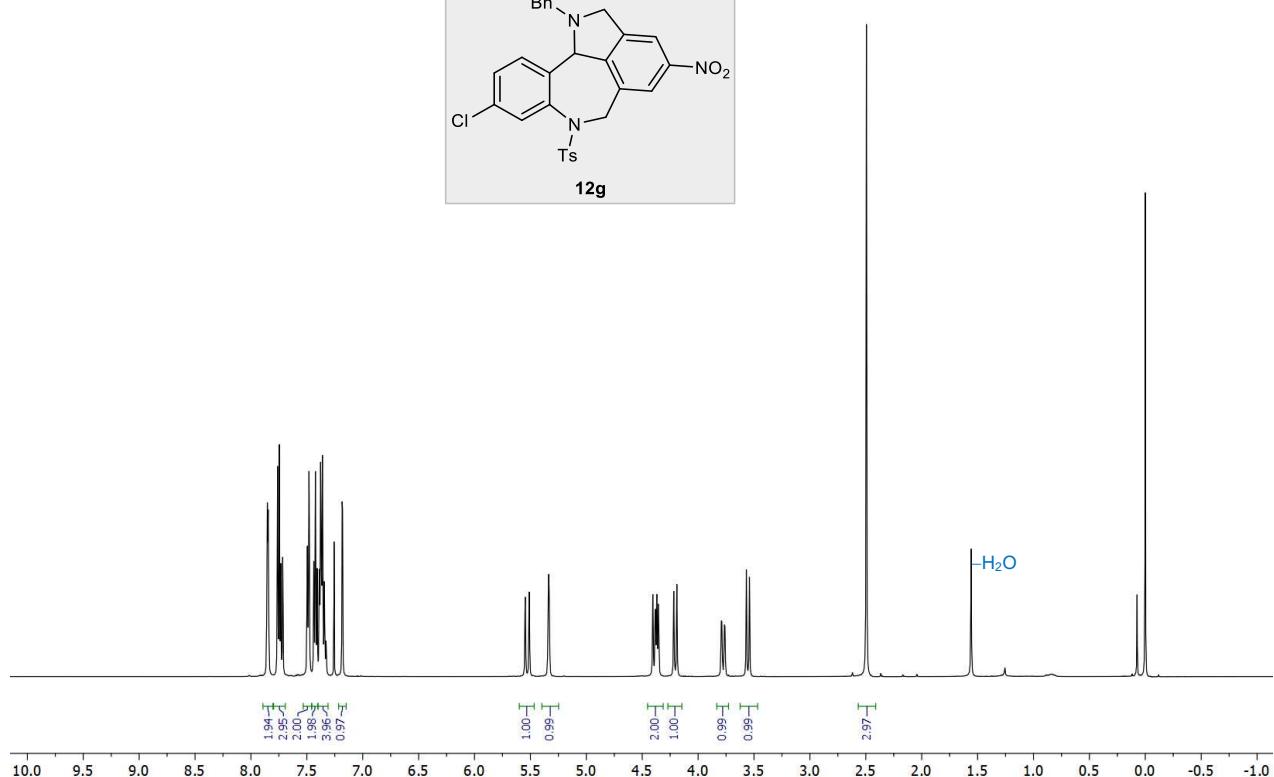
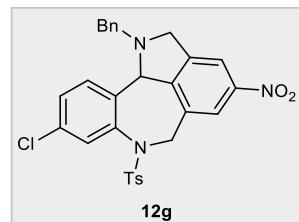
¹H NMR, 500 MHz, CDCl₃



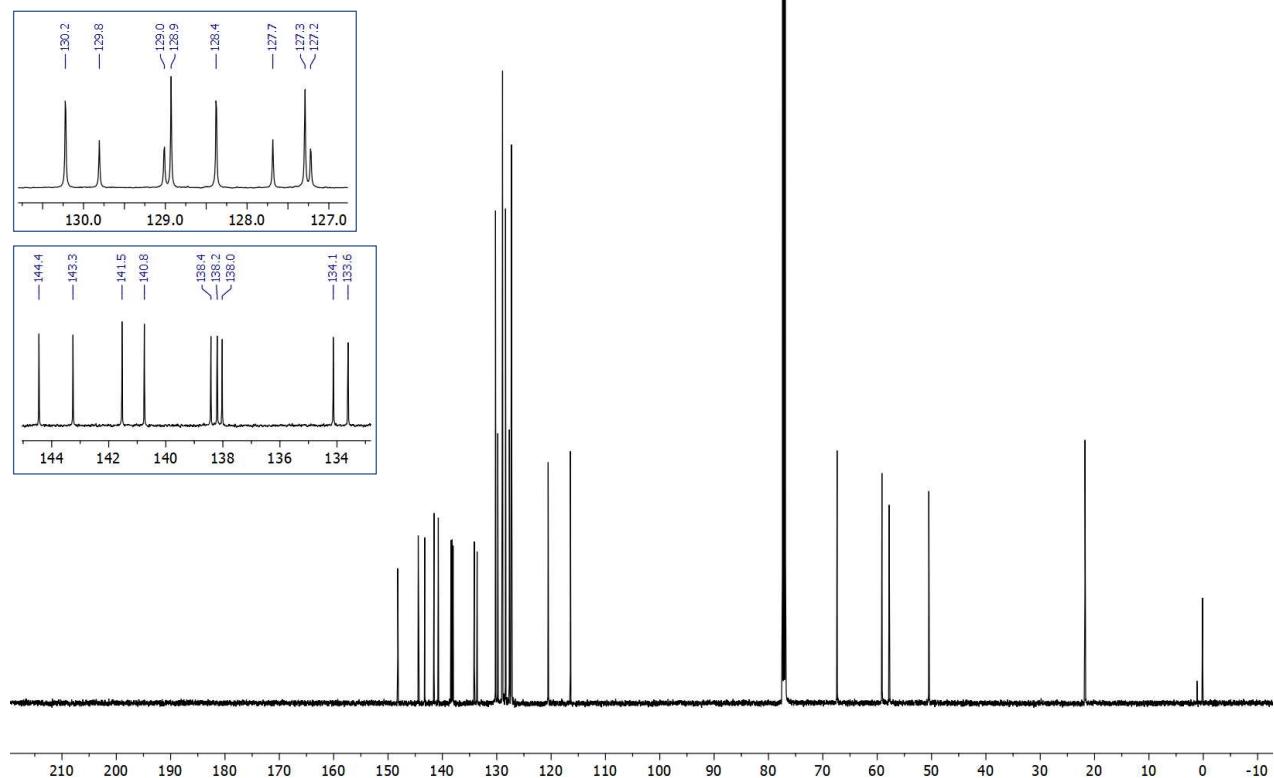
¹³C NMR, 125 MHz, CDCl₃

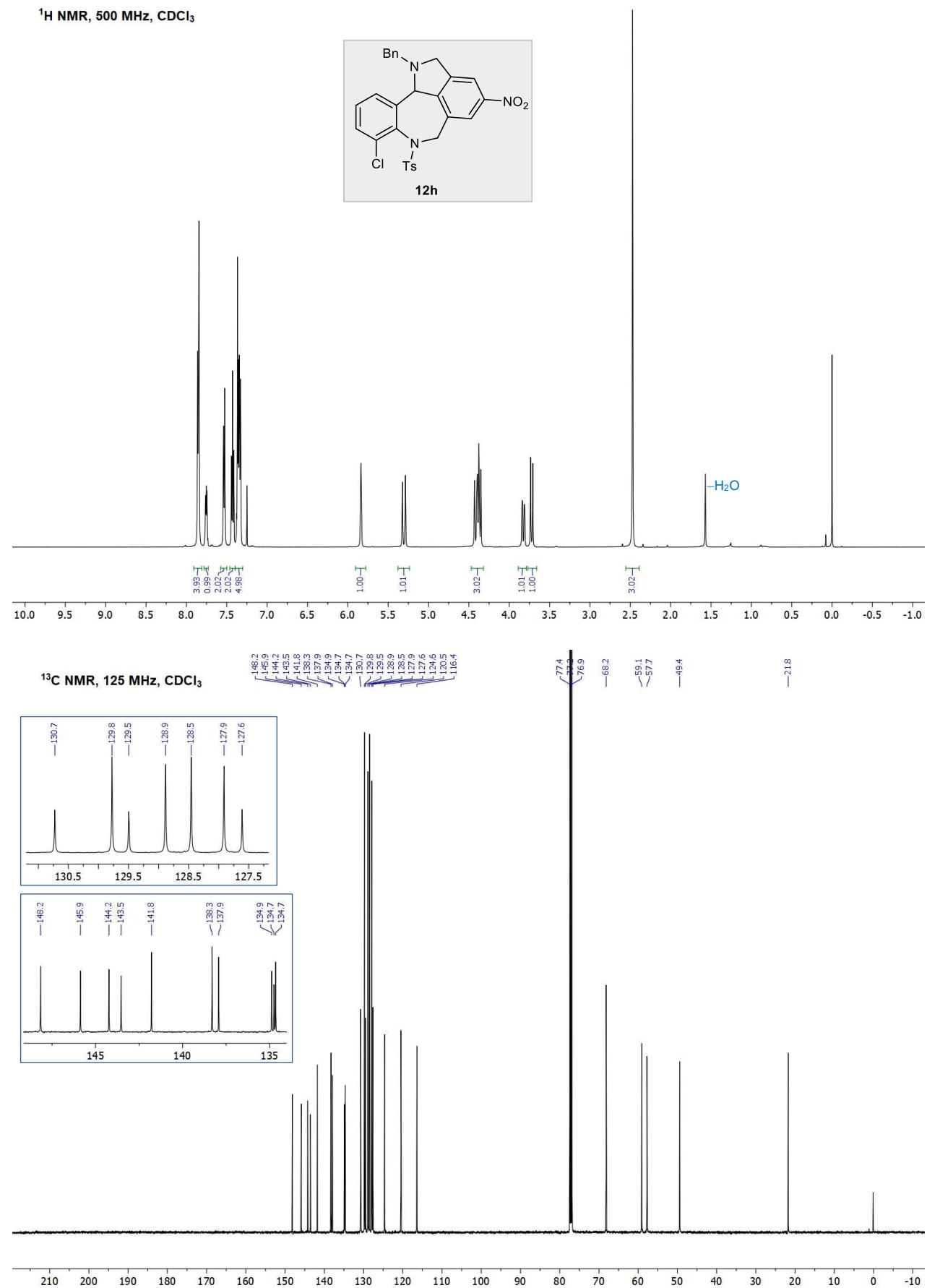


¹H NMR, 500 MHz, CDCl₃

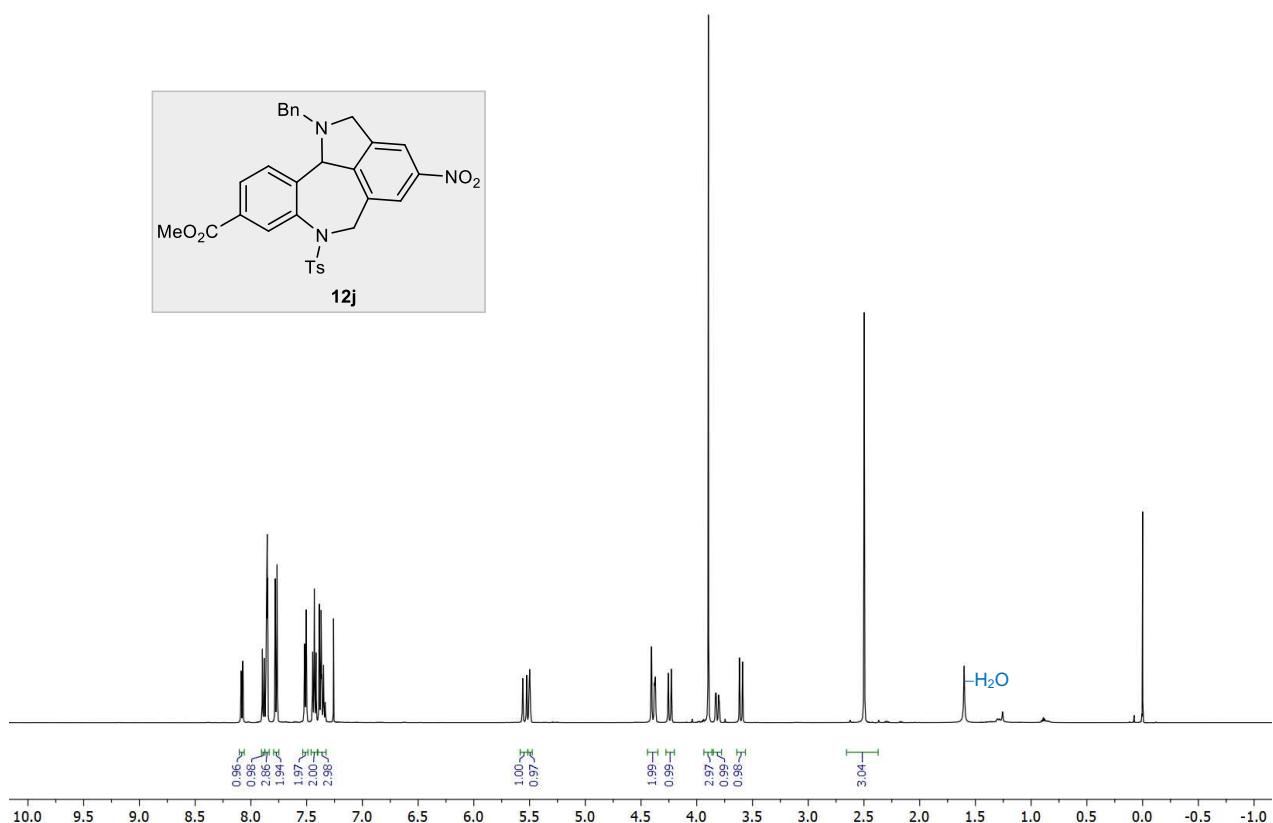
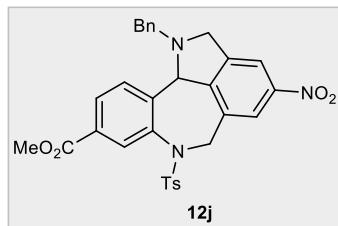


¹³C NMR, 125 MHz, CDCl₃

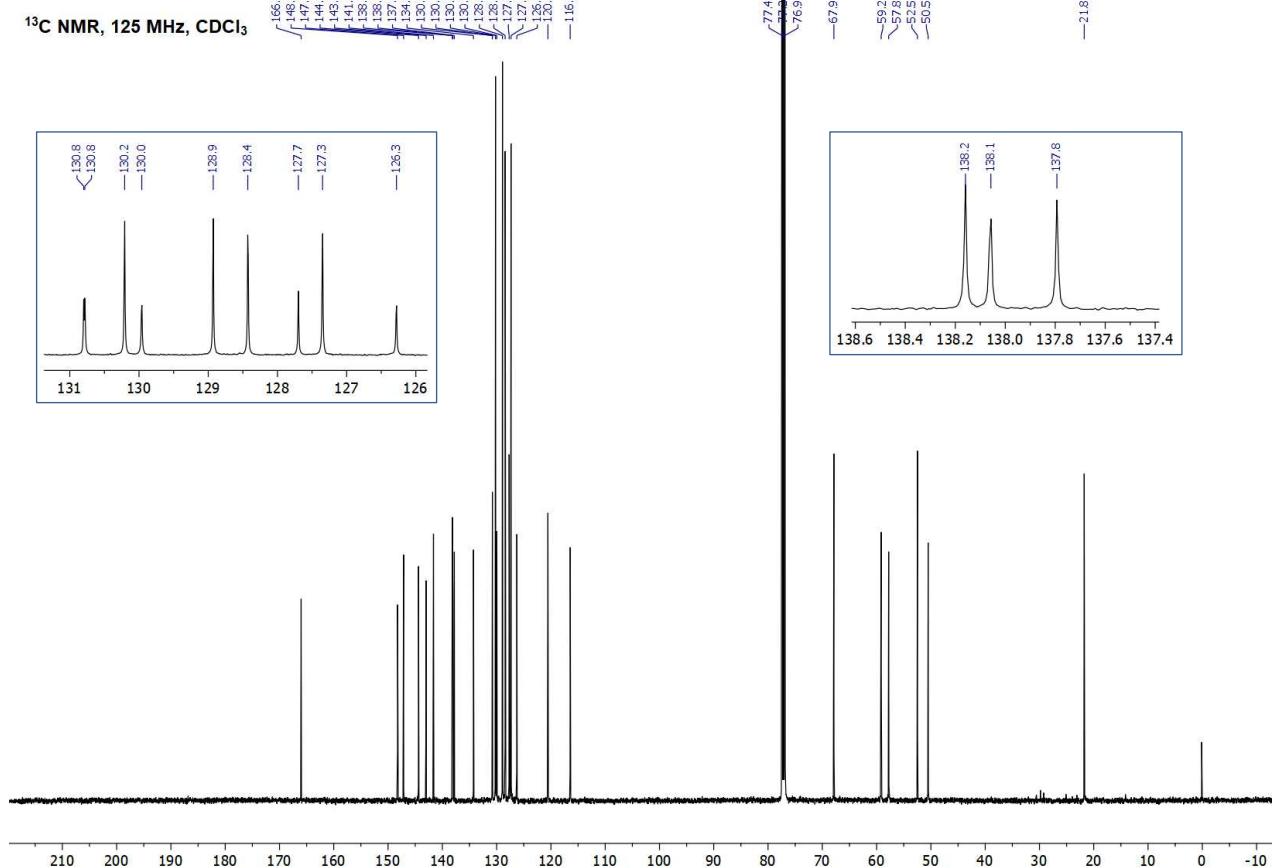


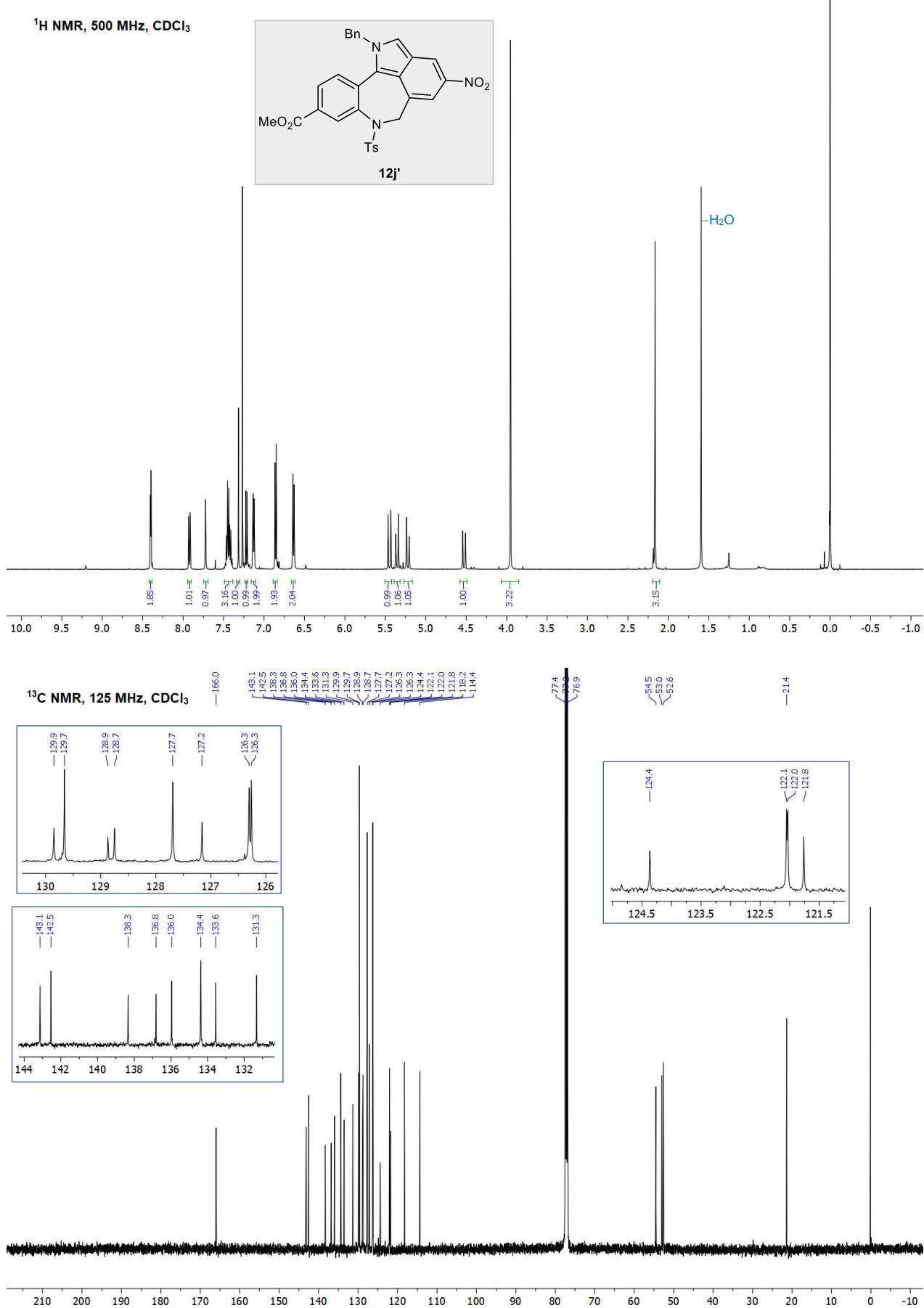


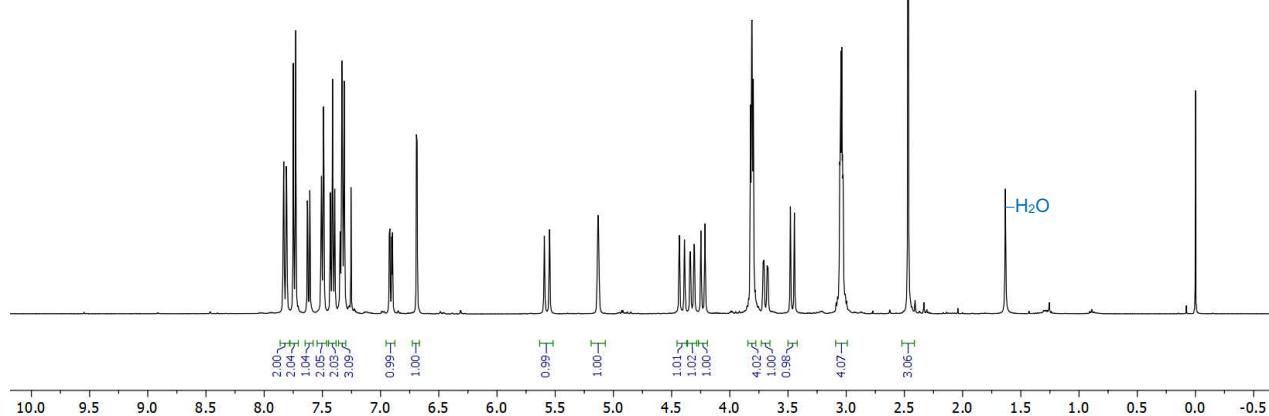
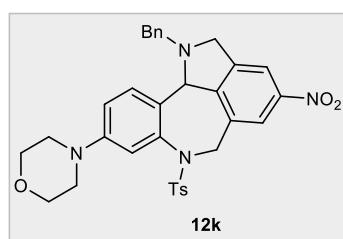
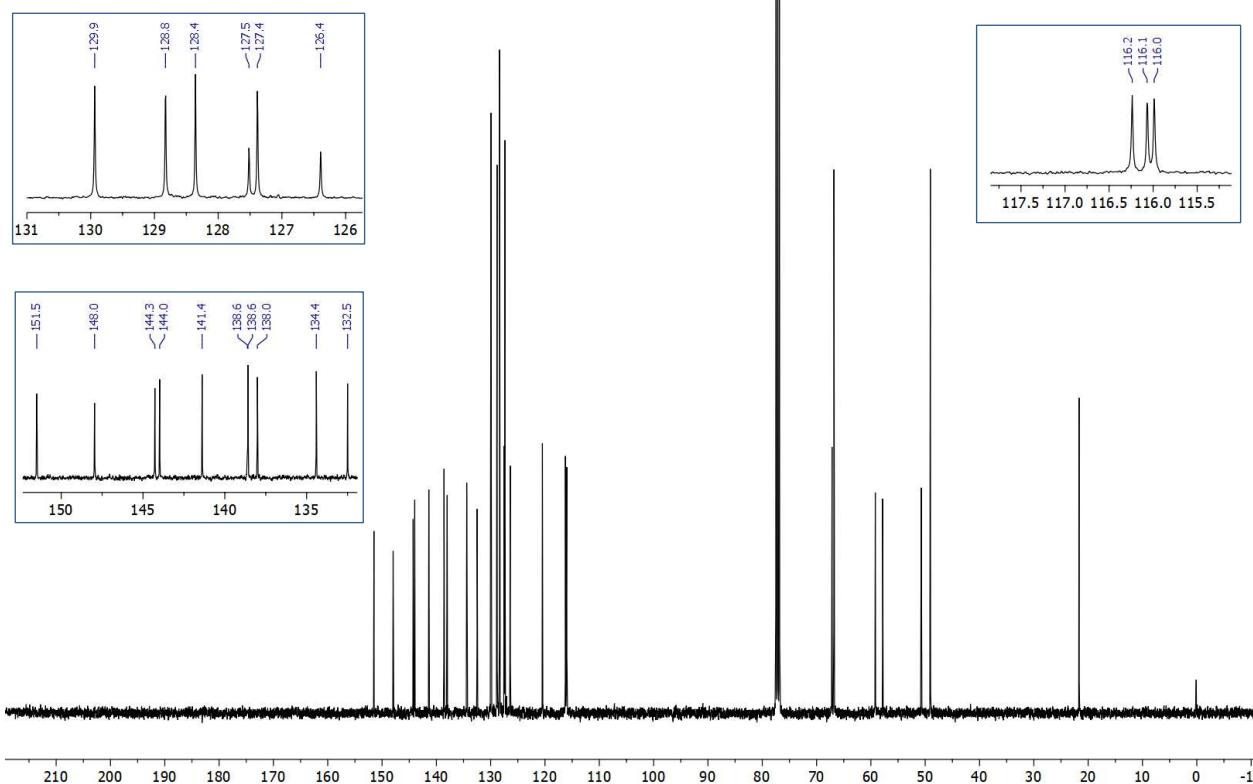
¹H NMR, 500 MHz, CDCl₃

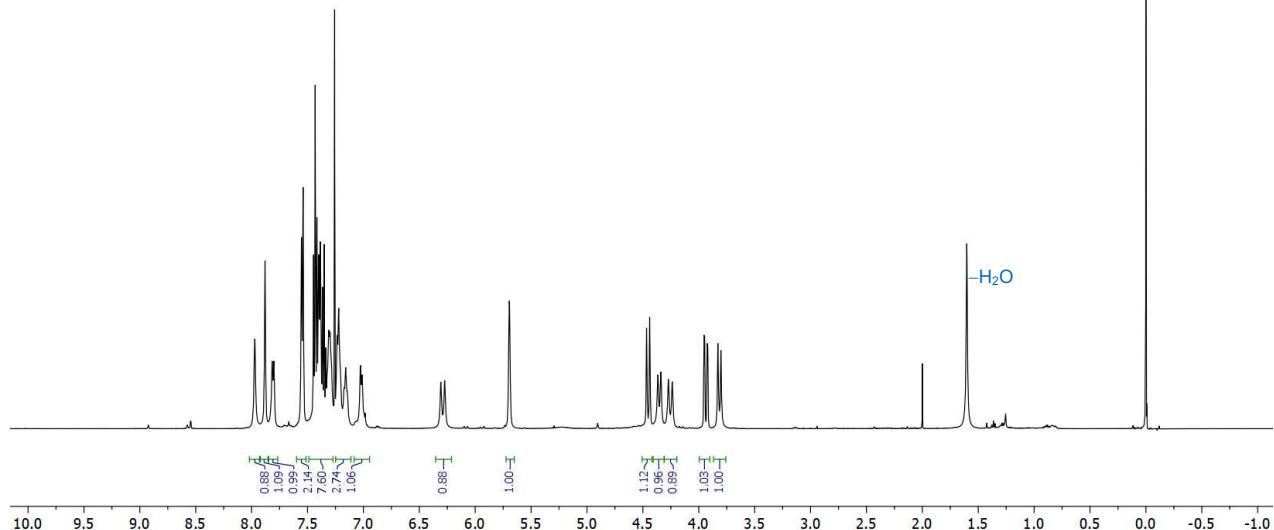
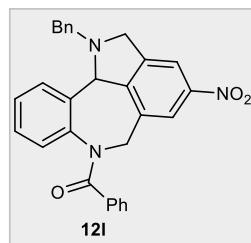
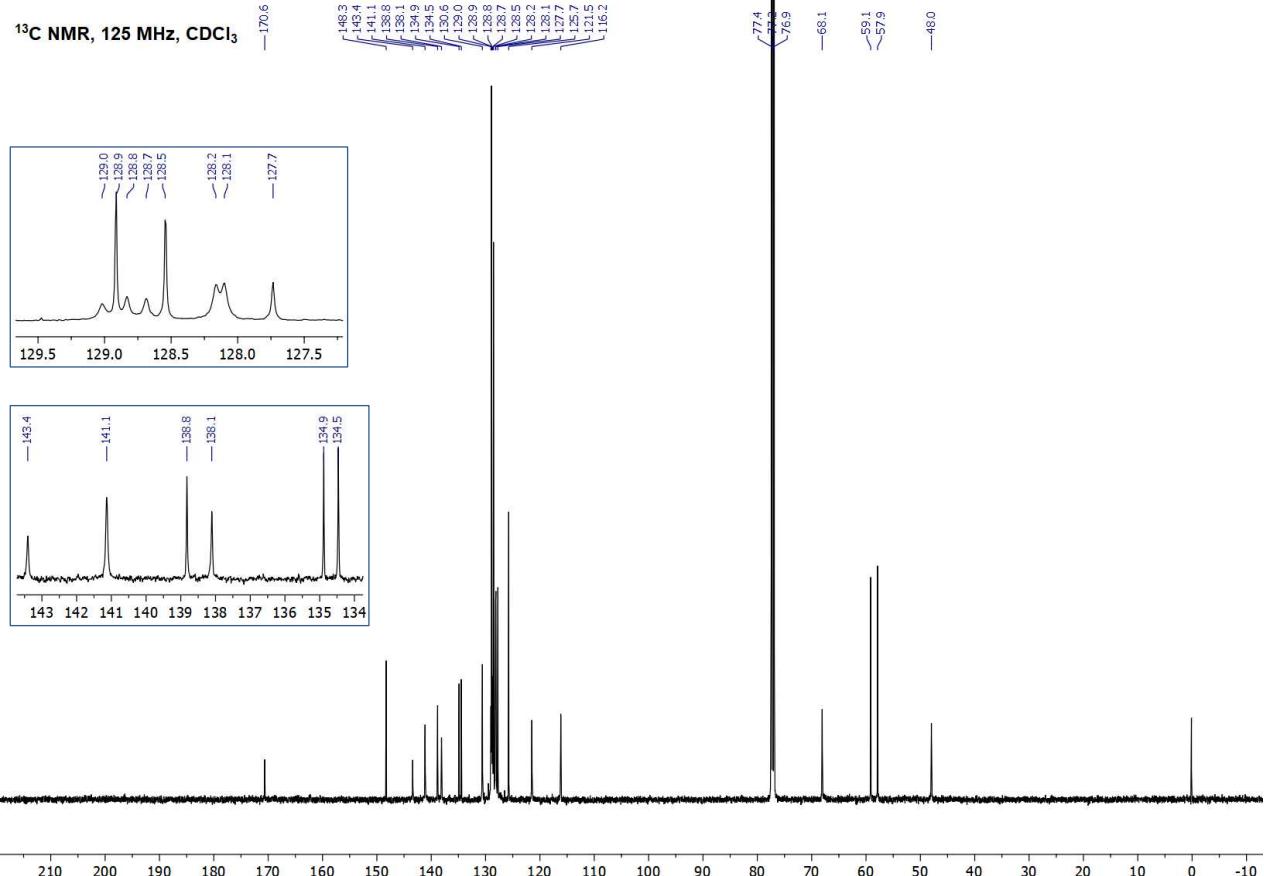


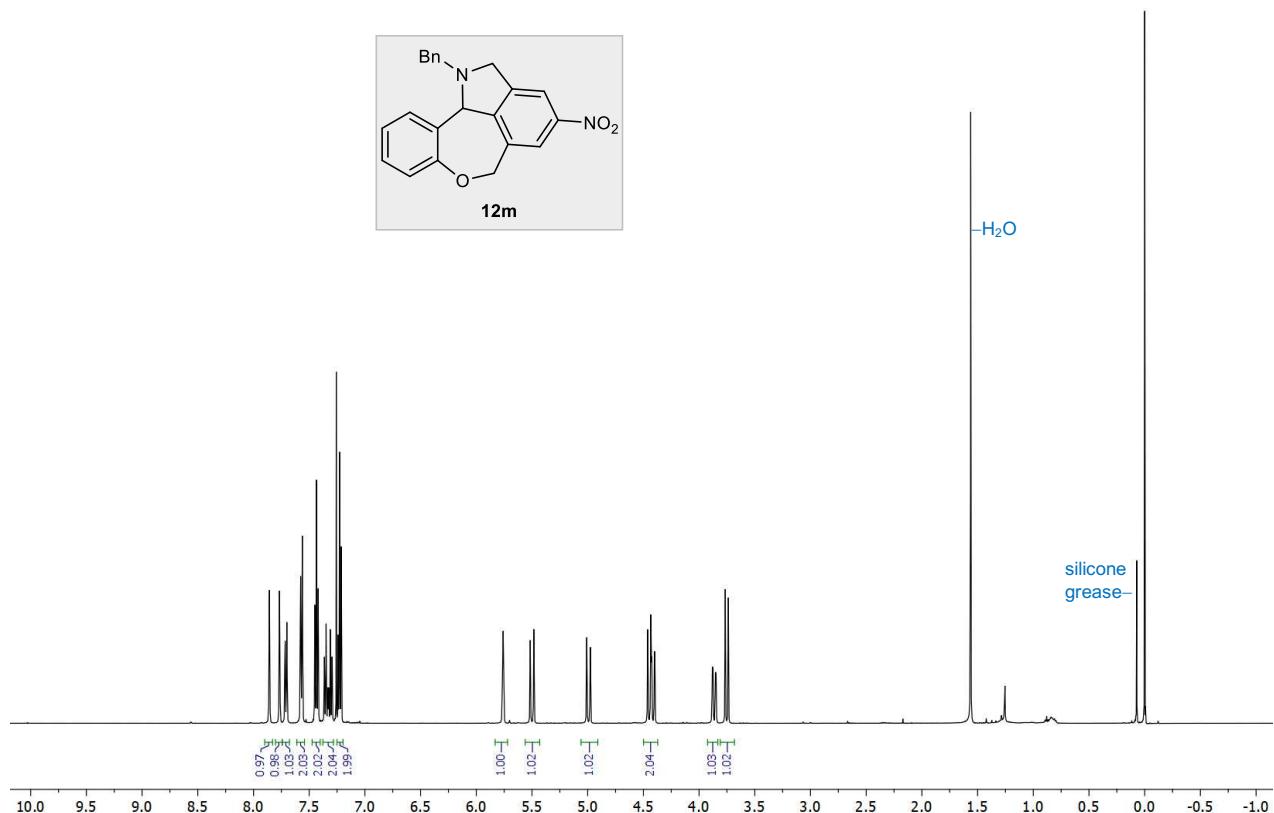
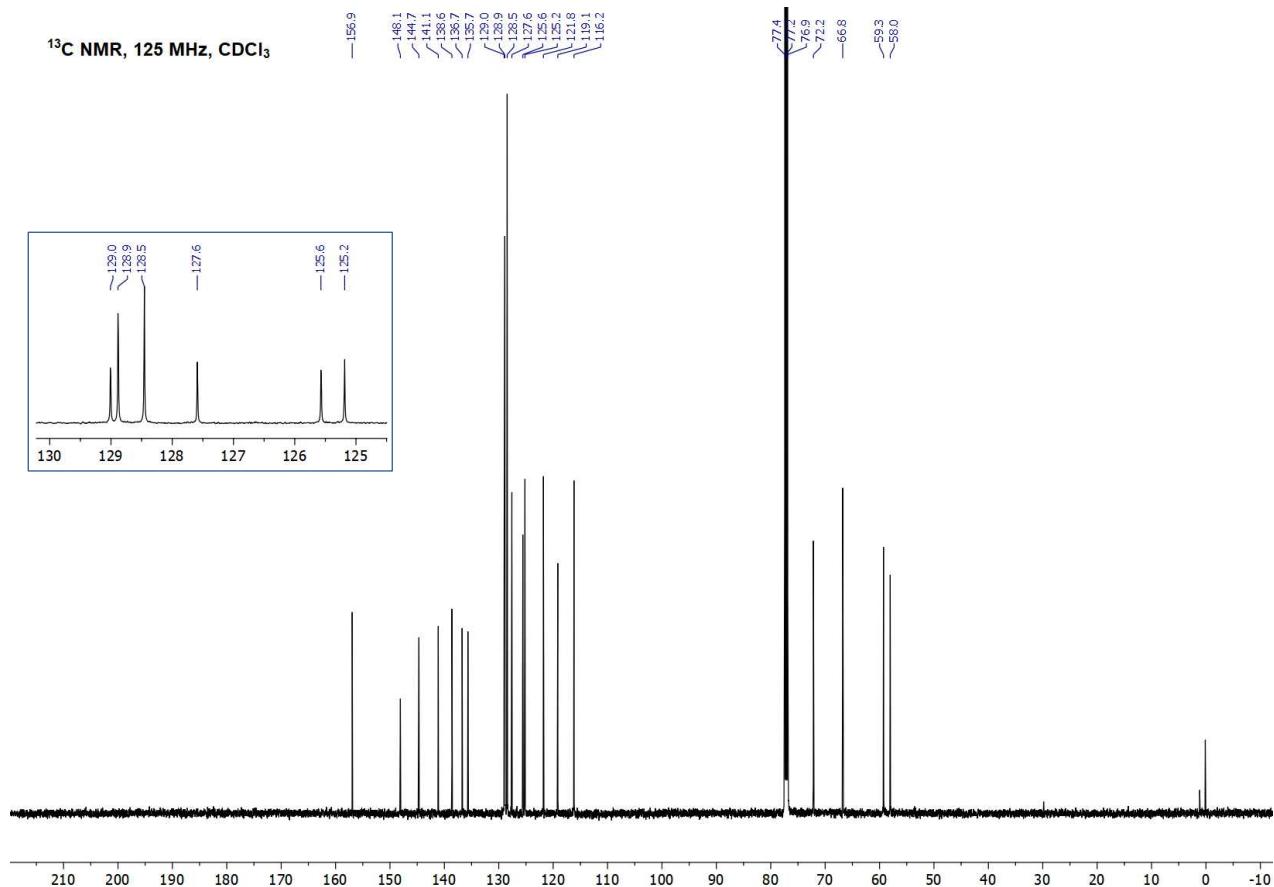
¹³C NMR, 125 MHz, CDCl₃

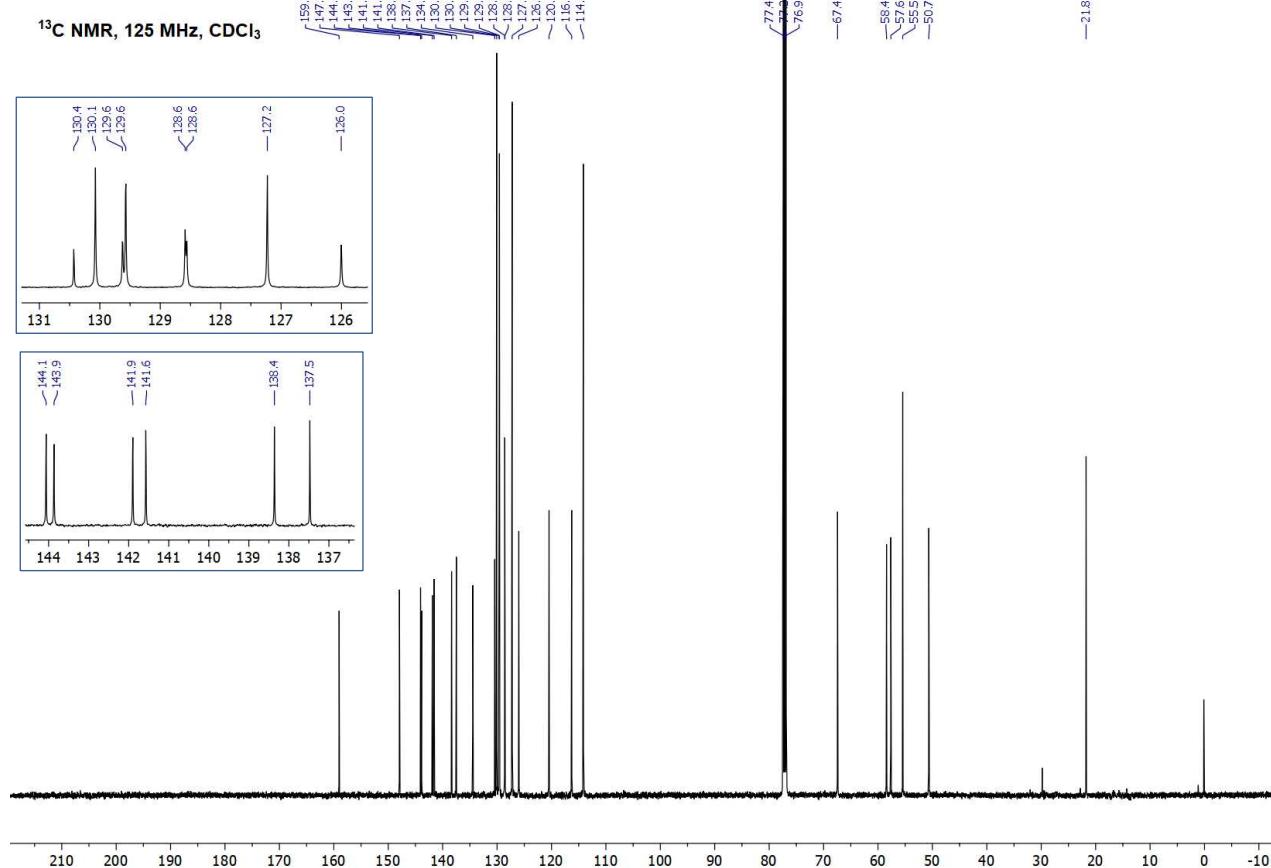
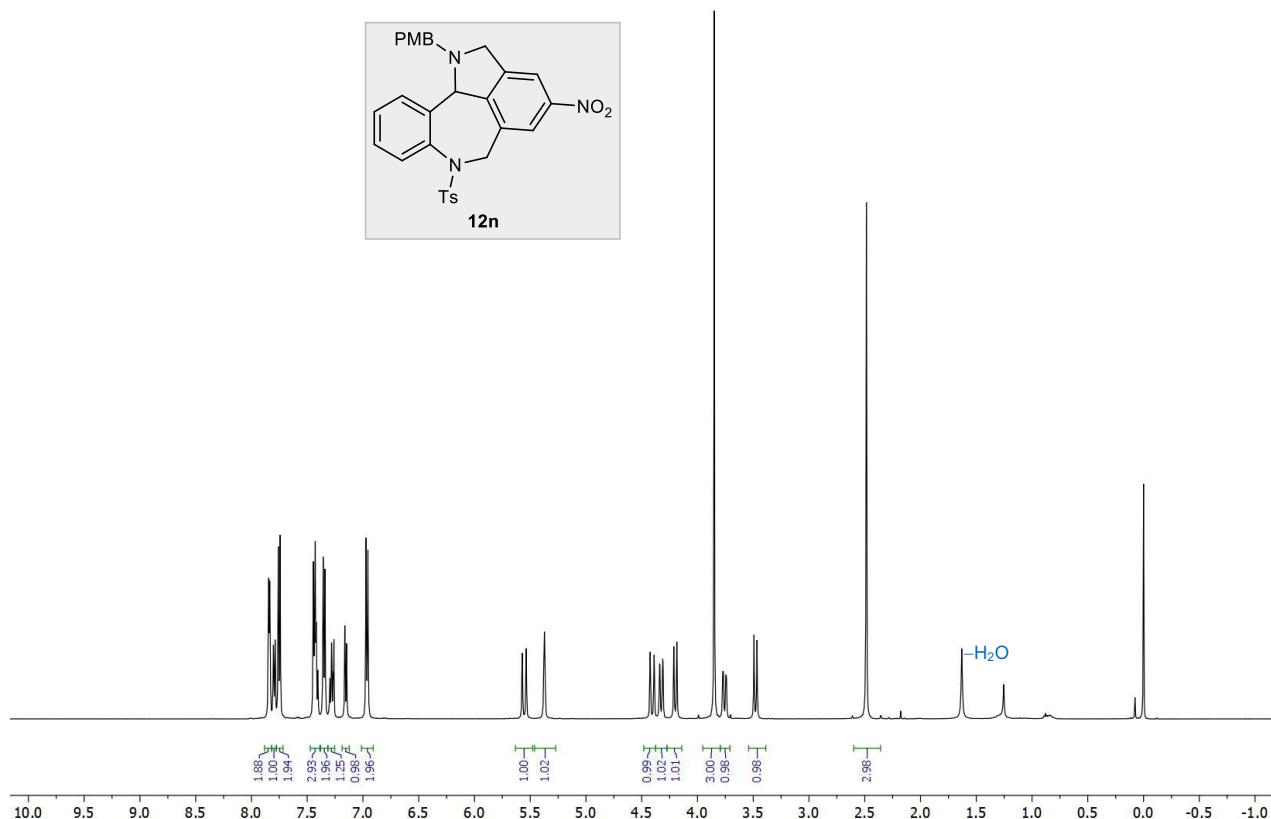




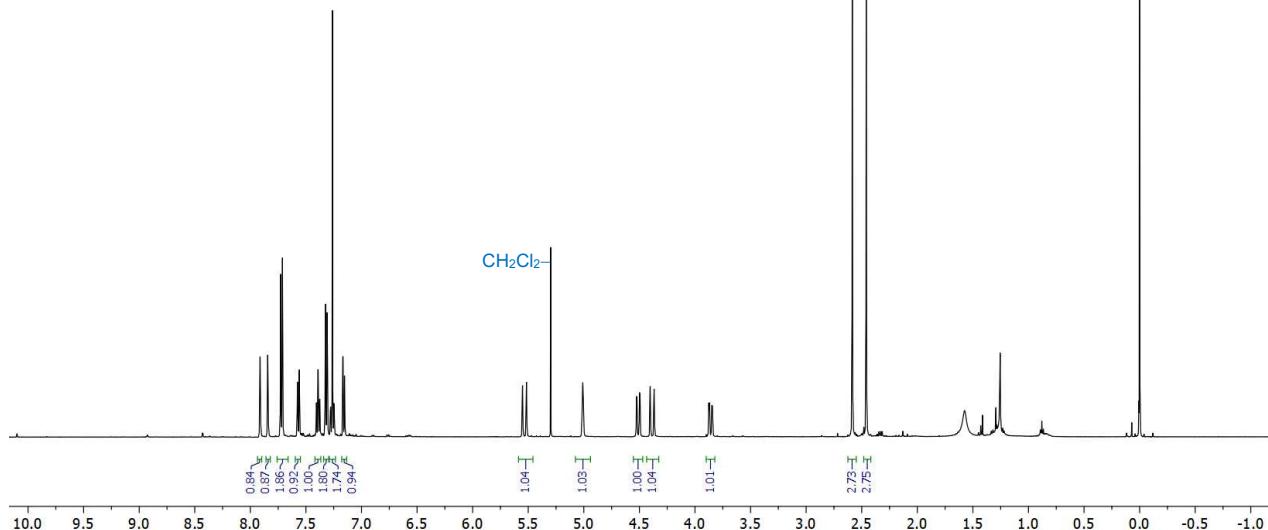
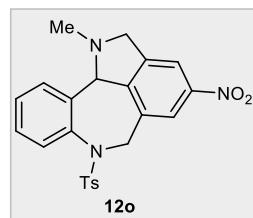
¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

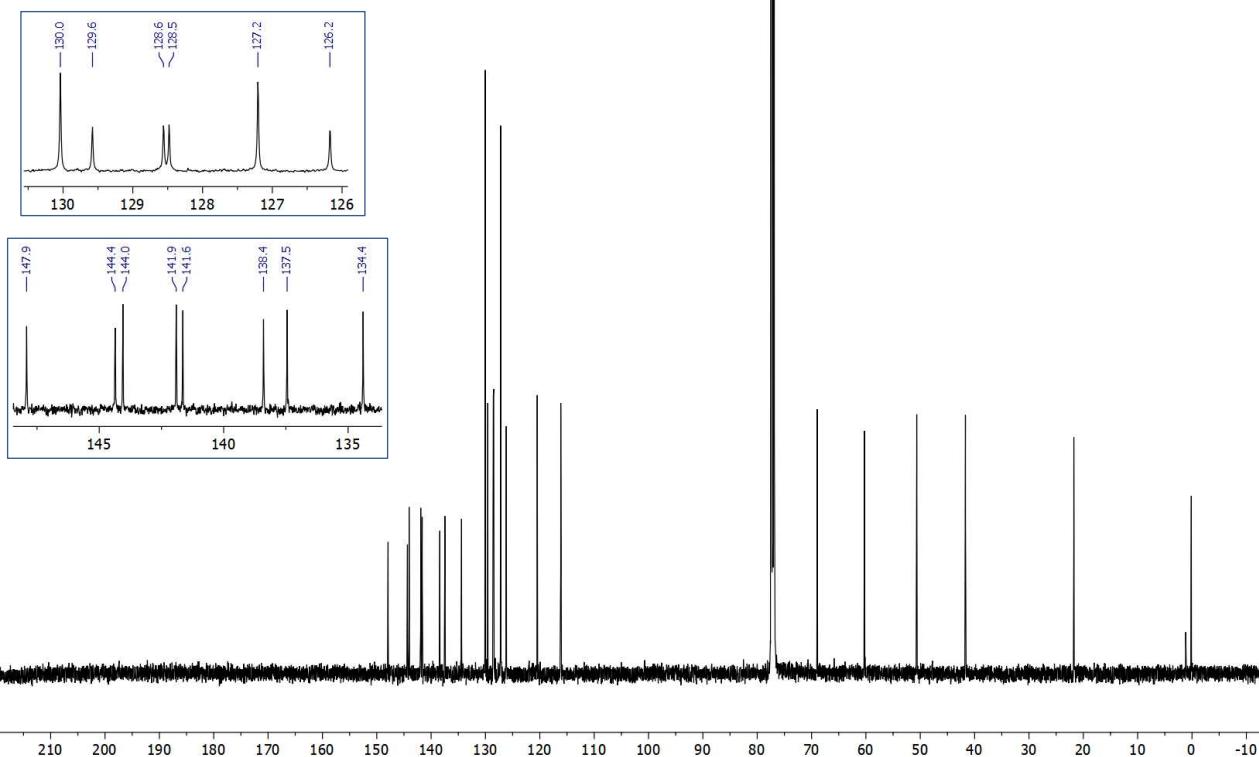
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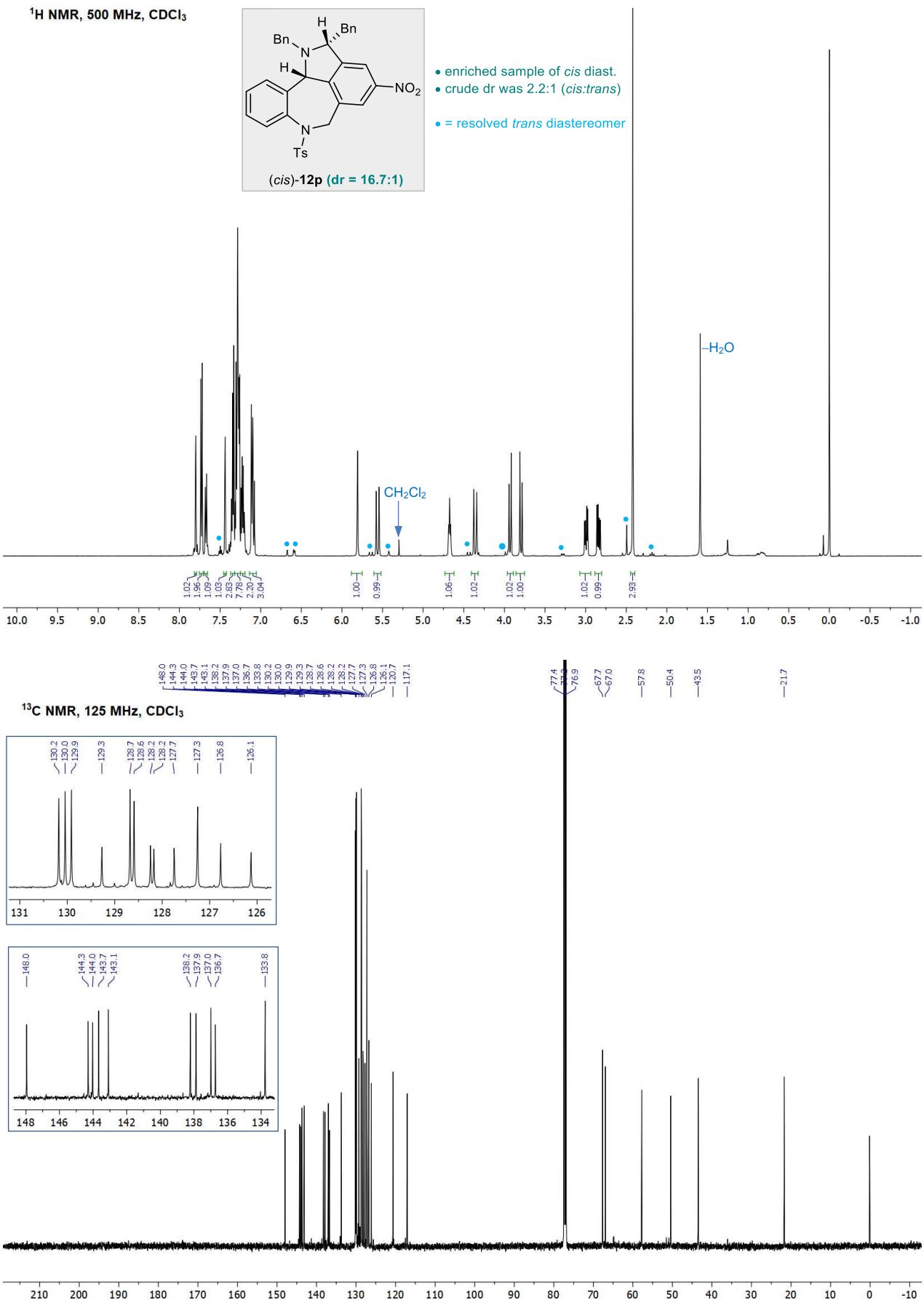
¹H NMR, 500 MHz, CDCl₃

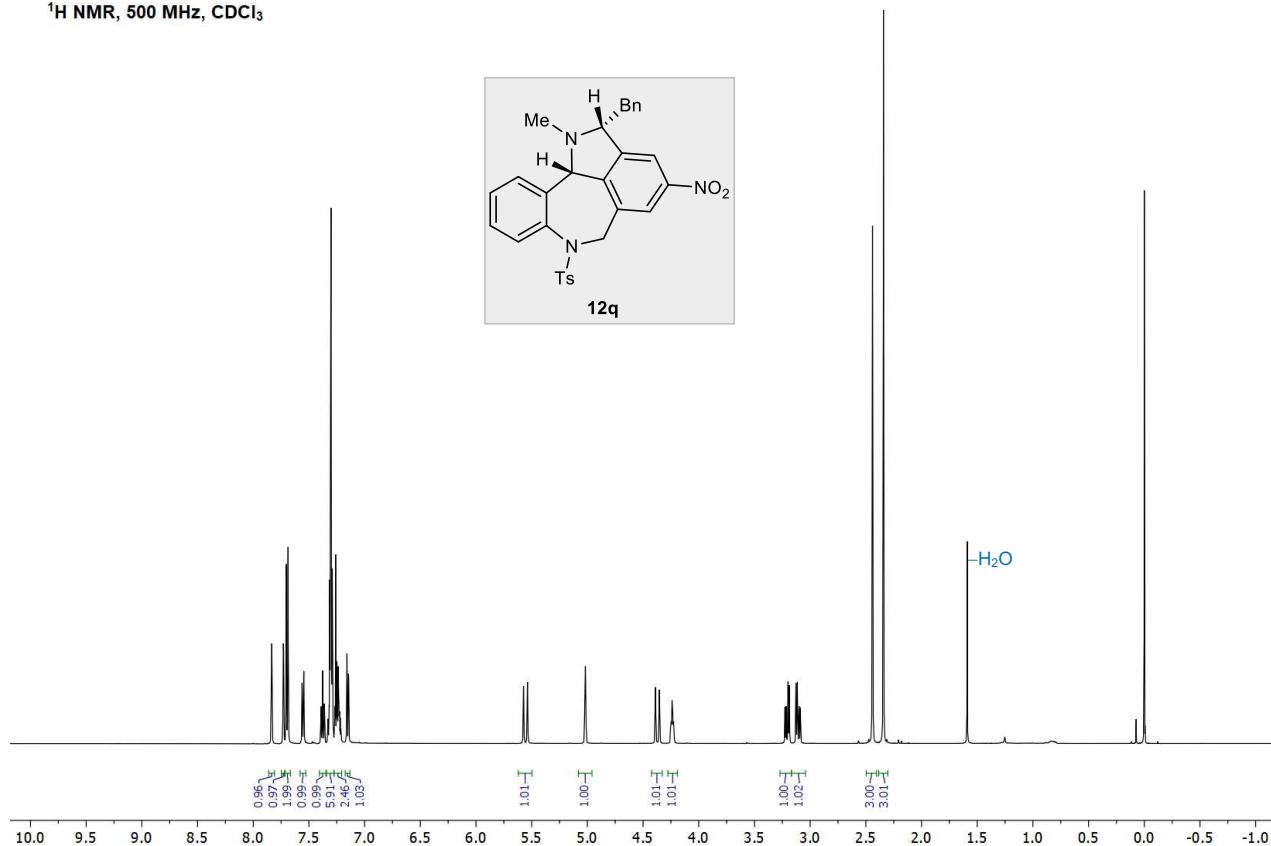
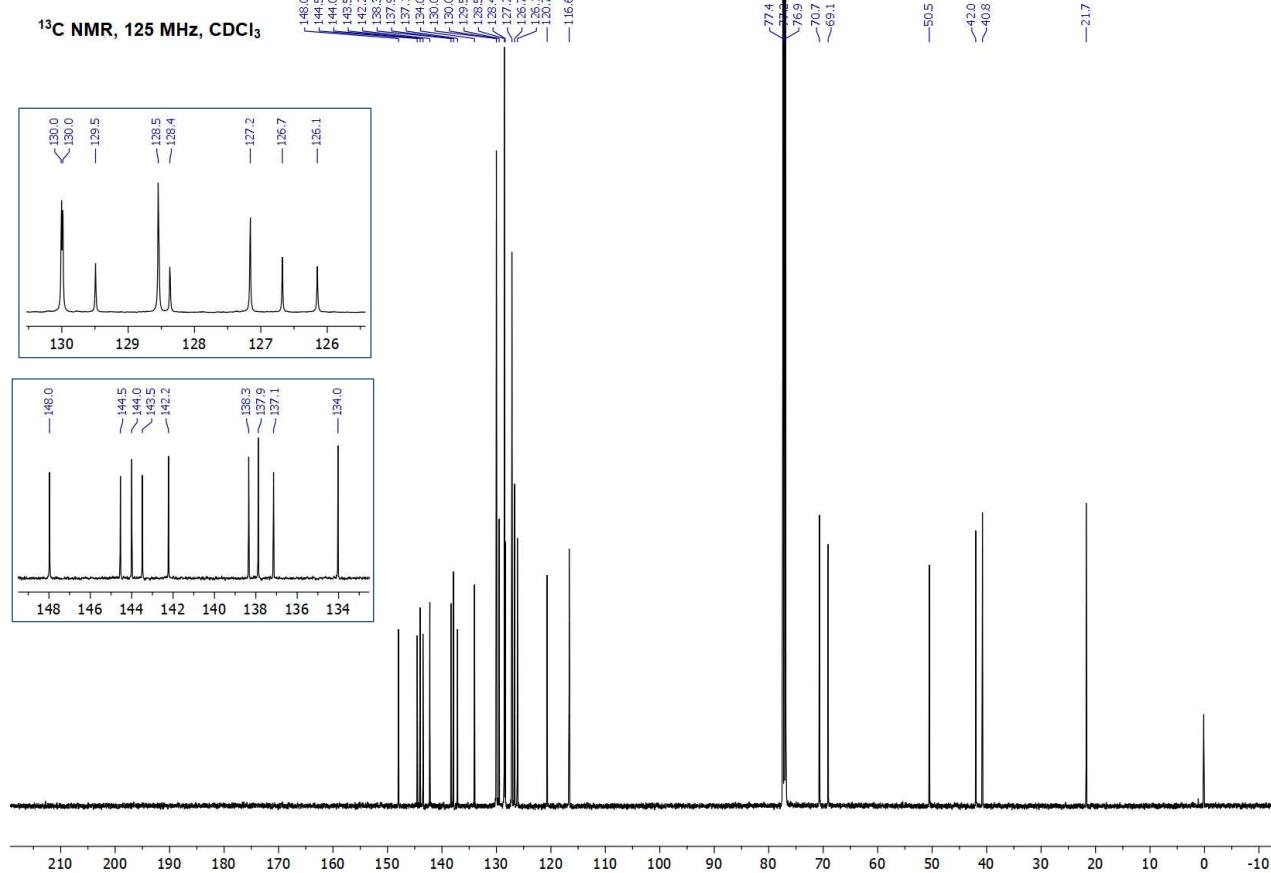
¹H NMR, 500 MHz, CDCl₃

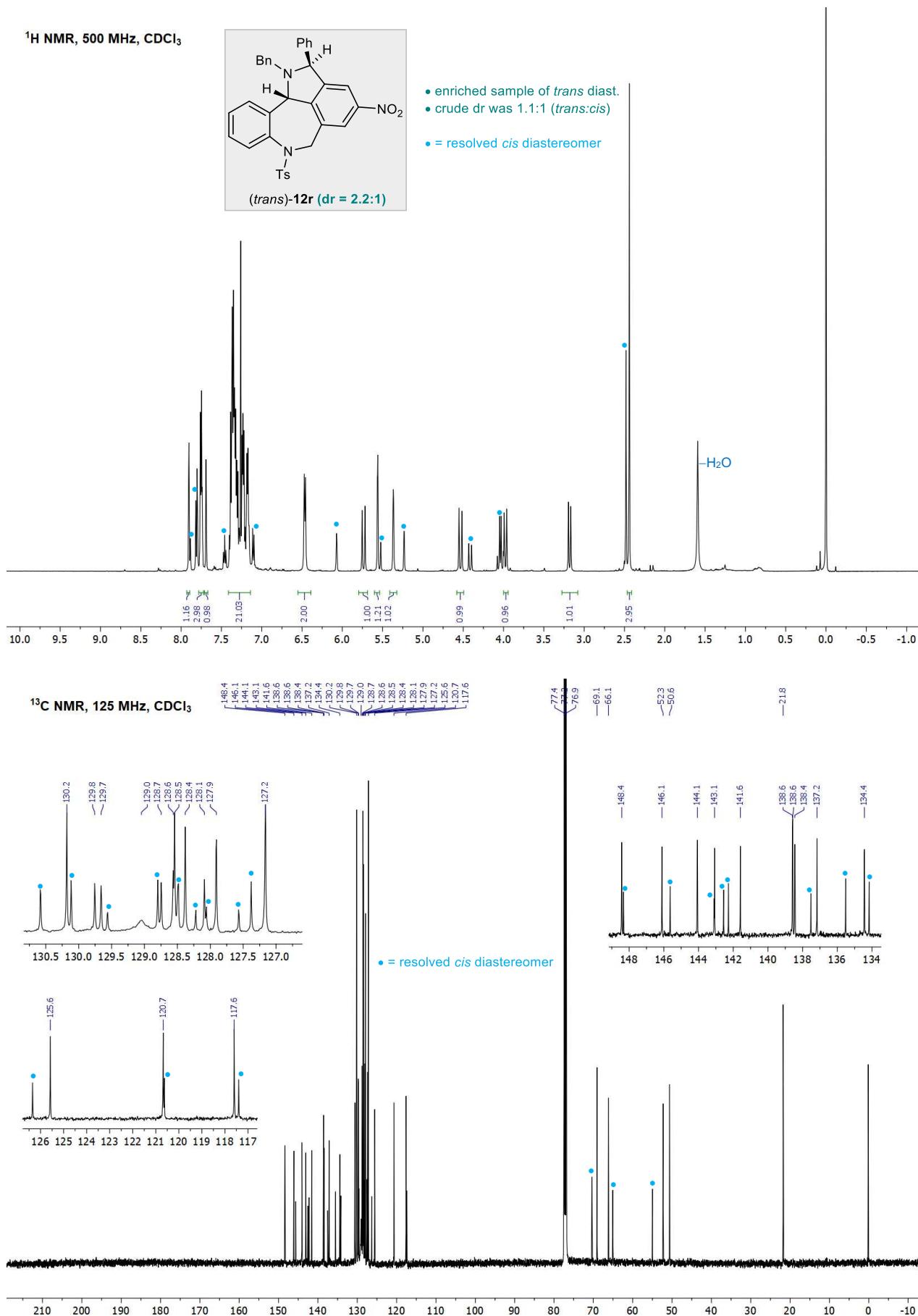


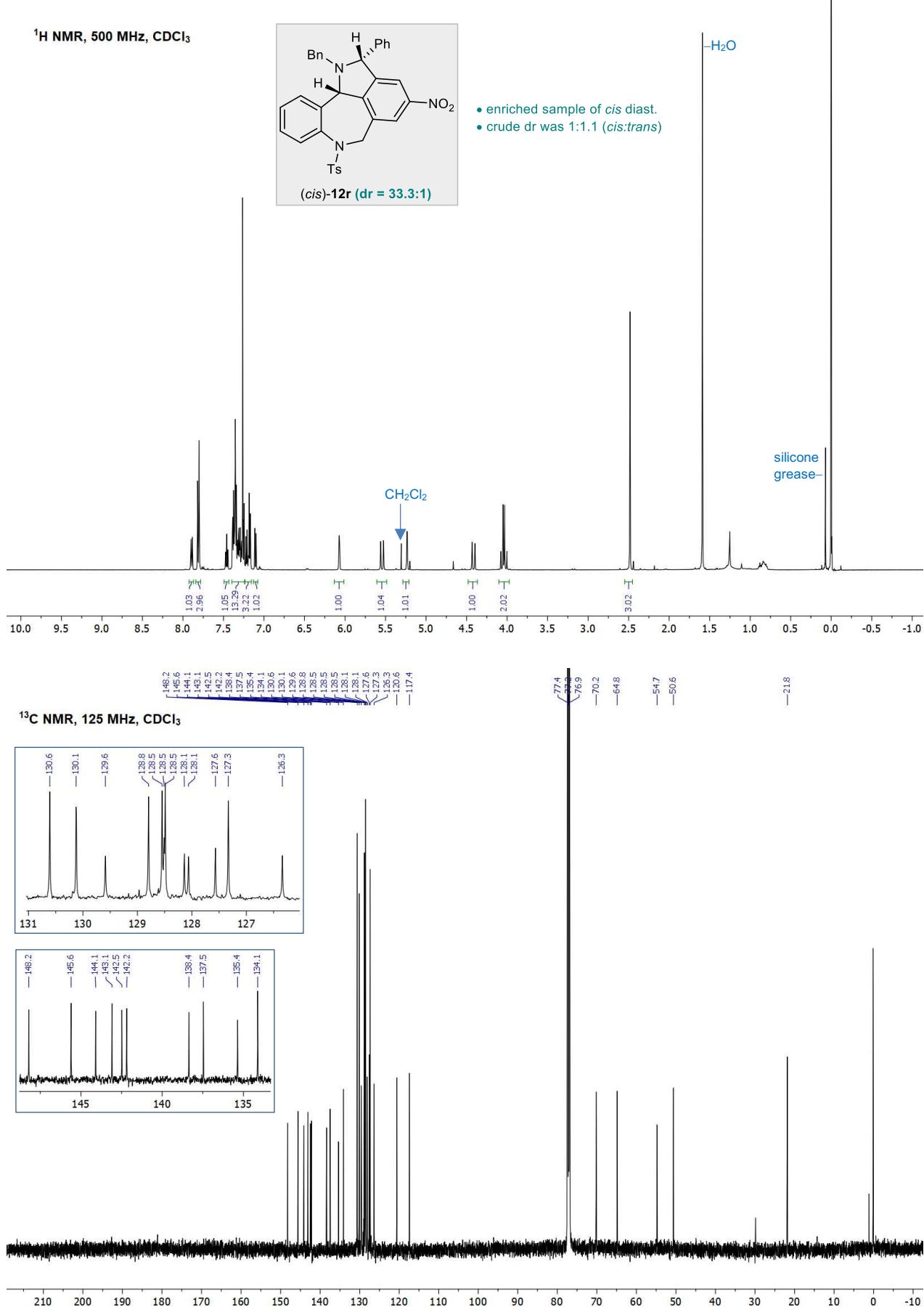
¹³C NMR, 125 MHz, CDCl₃



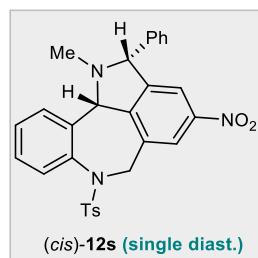


¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

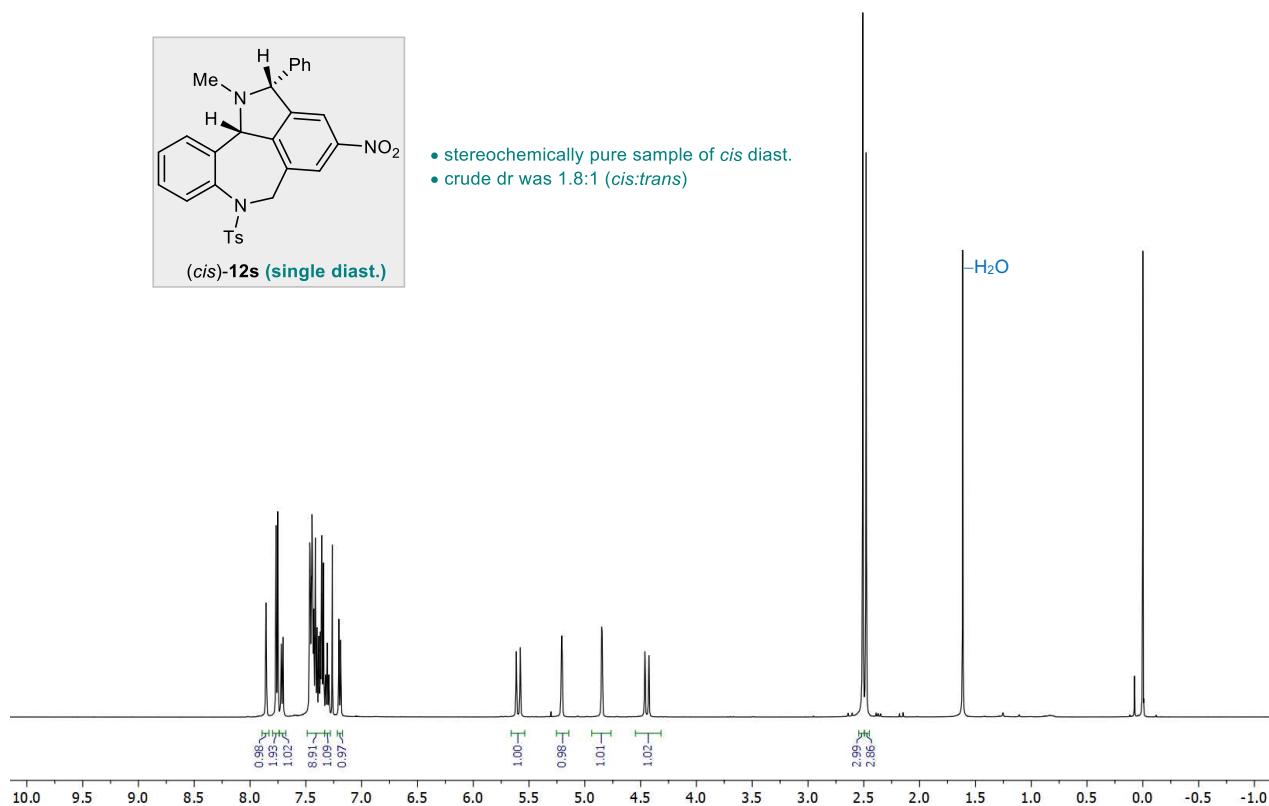




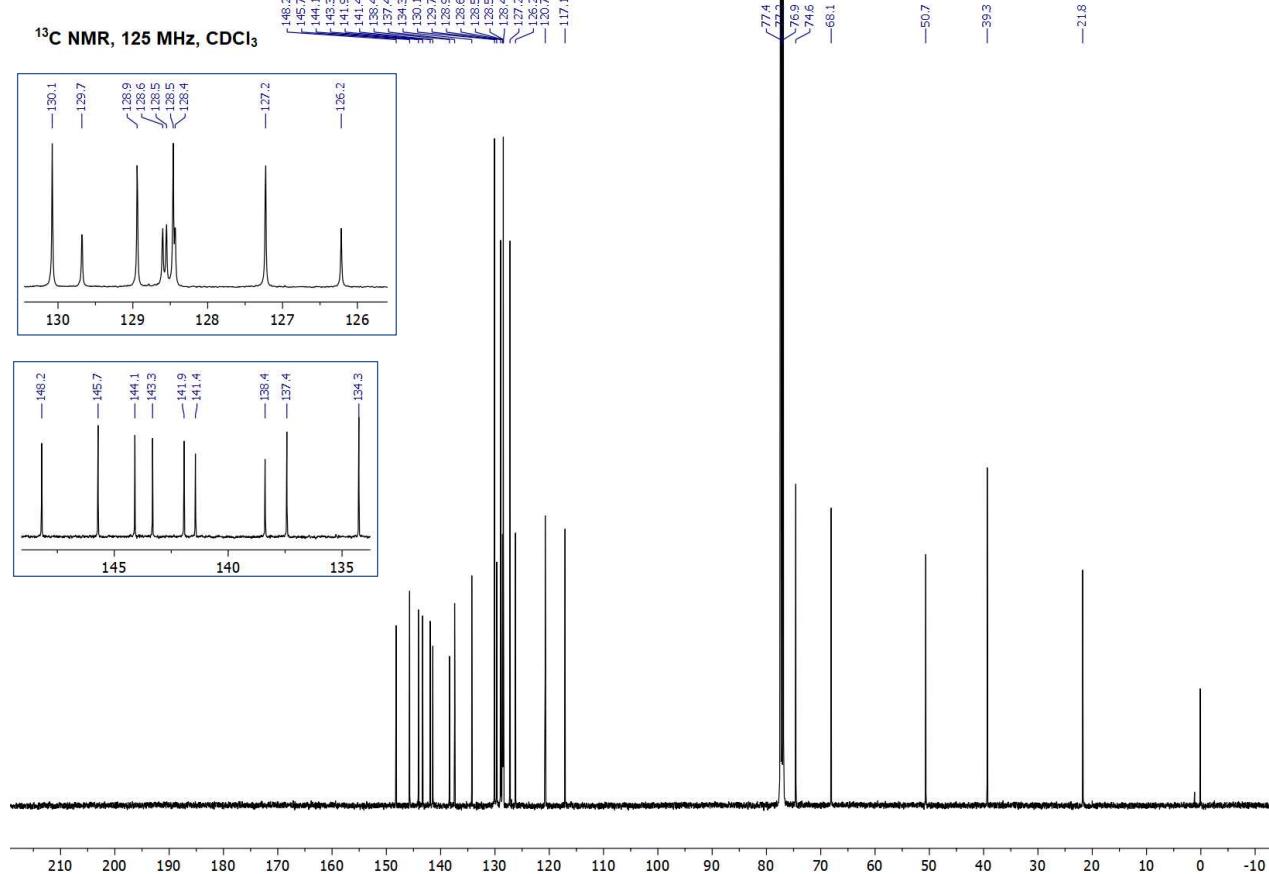
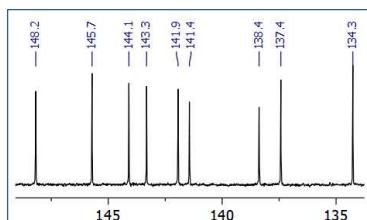
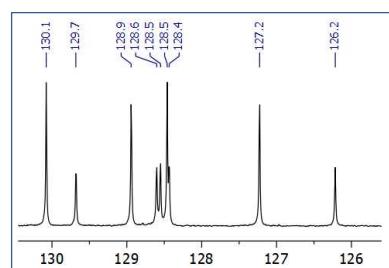
¹H NMR, 500 MHz, CDCl₃

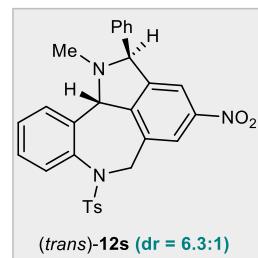


- stereochemically pure sample of *cis* diast.
- crude dr was 1.8:1 (*cis*:*trans*)

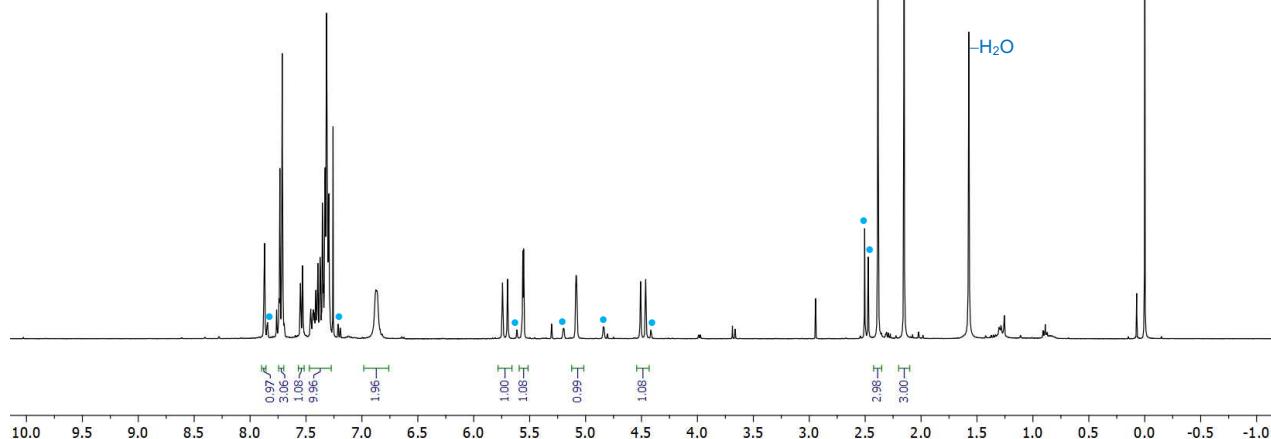
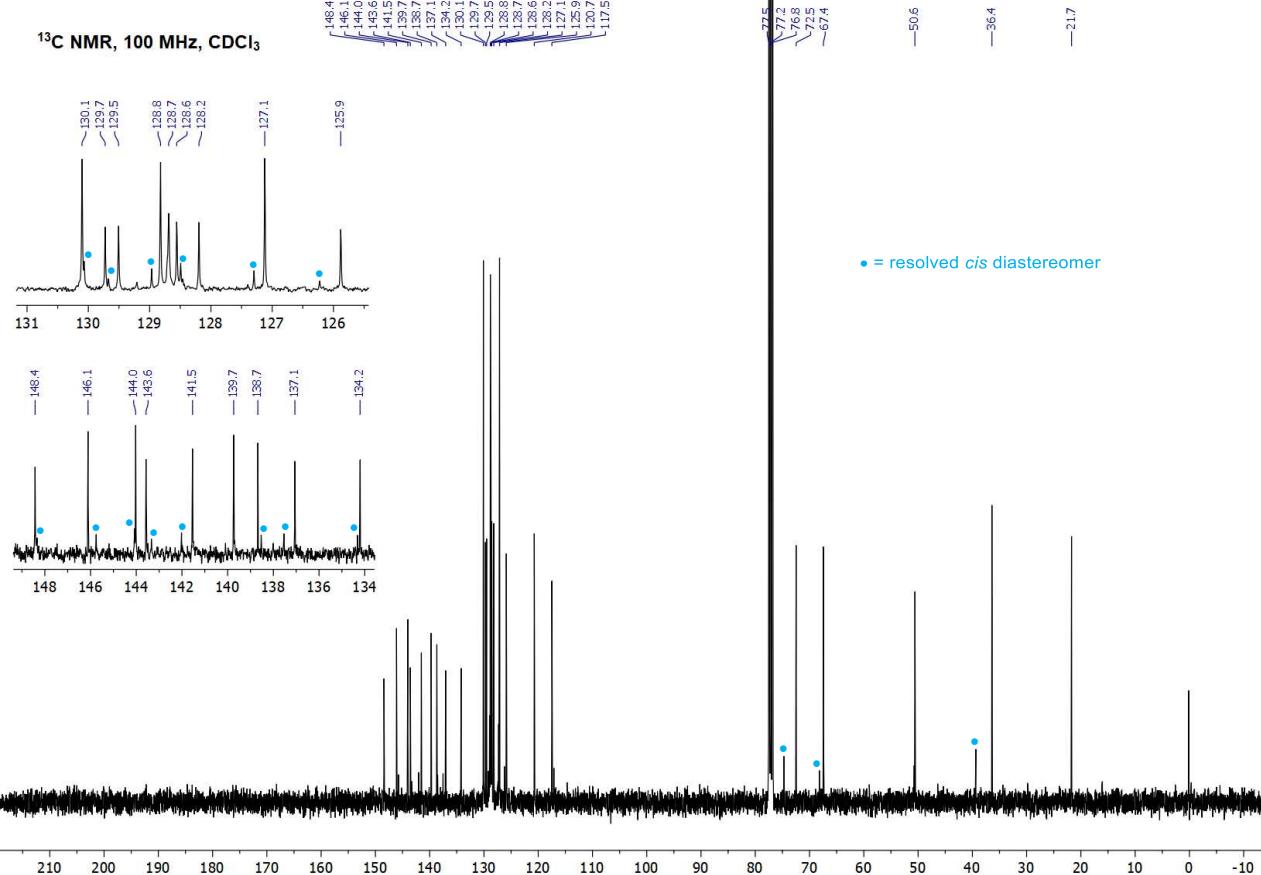


¹³C NMR, 125 MHz, CDCl₃

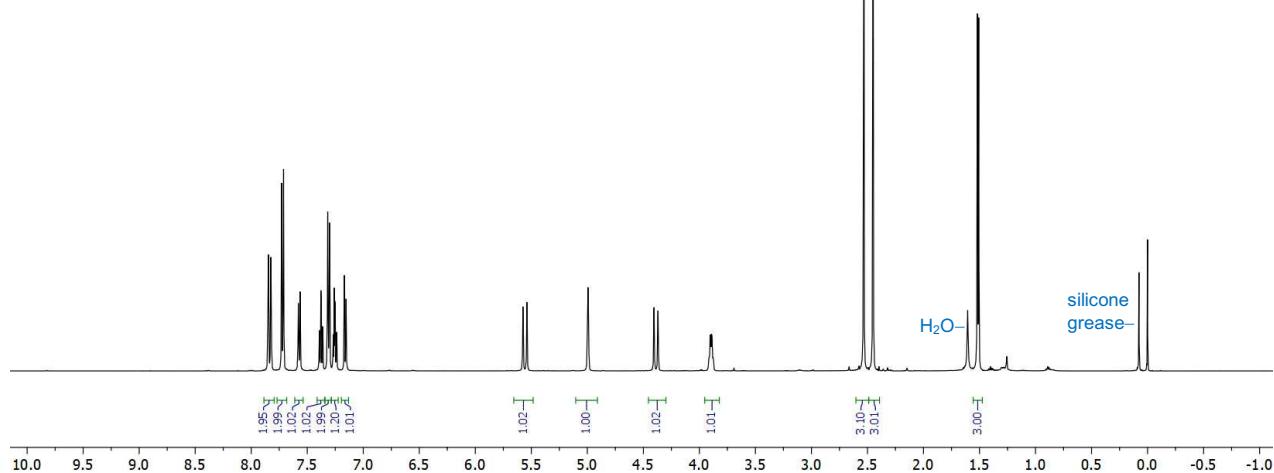
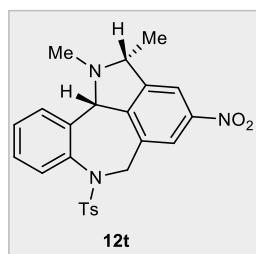


¹H NMR, 500 MHz, CDCl₃

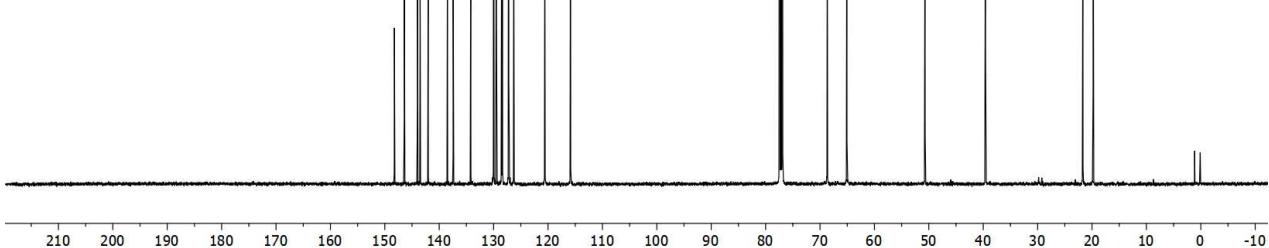
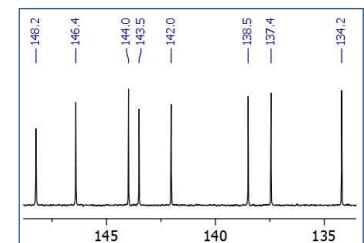
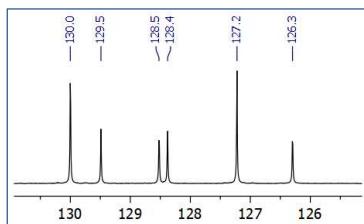
- enriched sample of *trans* diast.
- crude dr was 1.8:1 (*cis*:*trans*)
- = resolved *cis* diastereomer

¹³C NMR, 100 MHz, CDCl₃

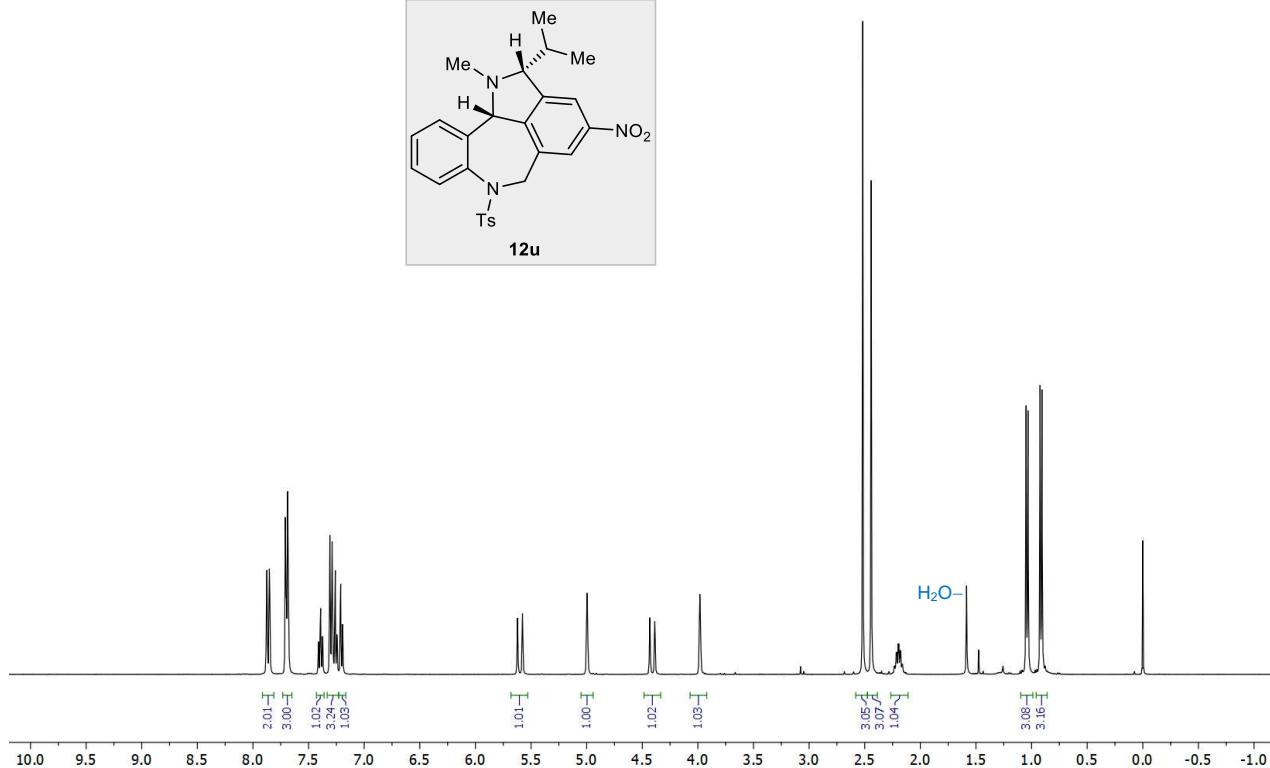
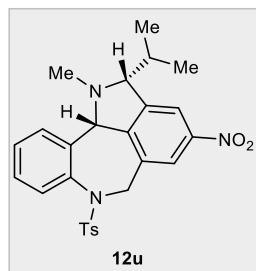
¹H NMR, 500 MHz, CDCl₃



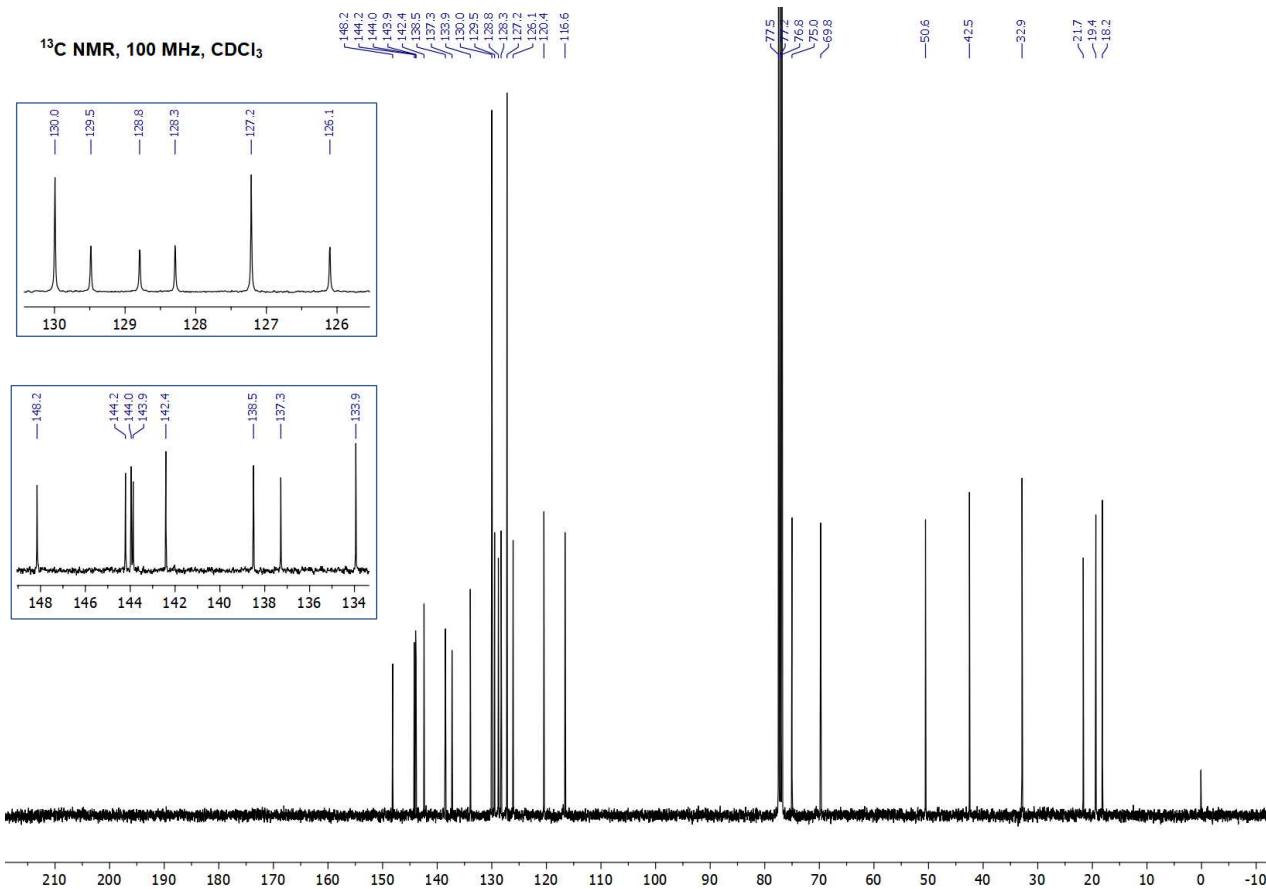
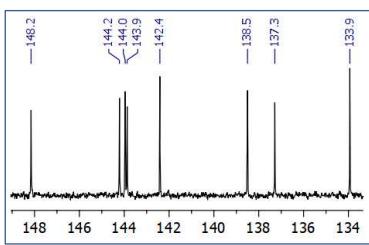
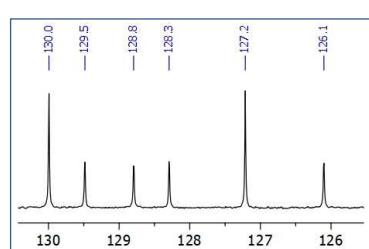
¹³C NMR, 125 MHz, CDCl₃

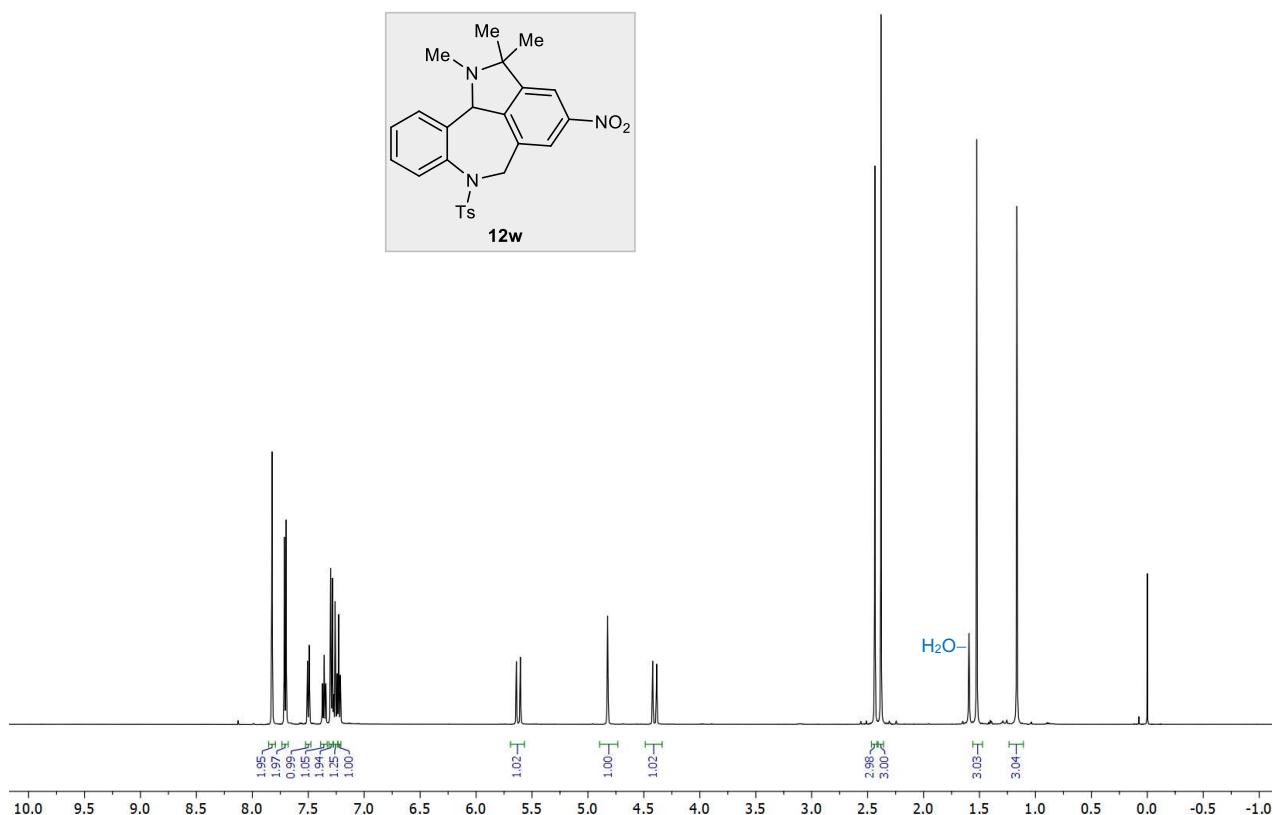
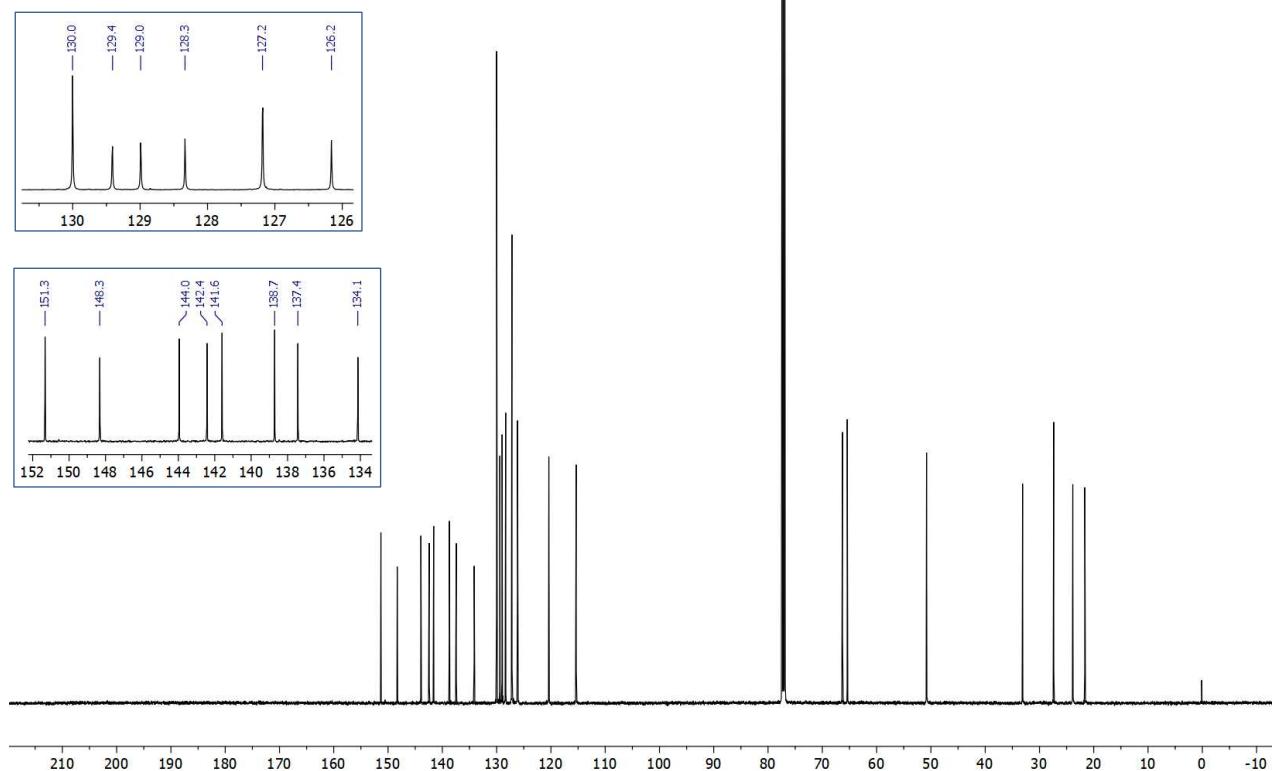


¹H NMR, 400 MHz, CDCl₃

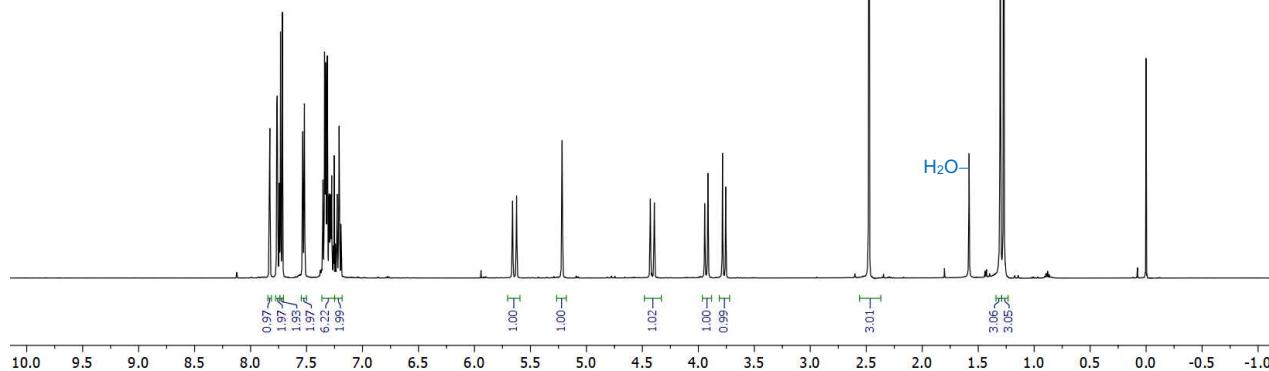
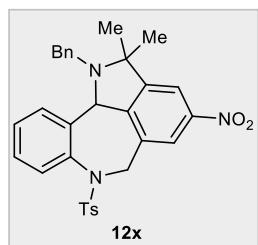


¹³C NMR, 100 MHz, CDCl₃

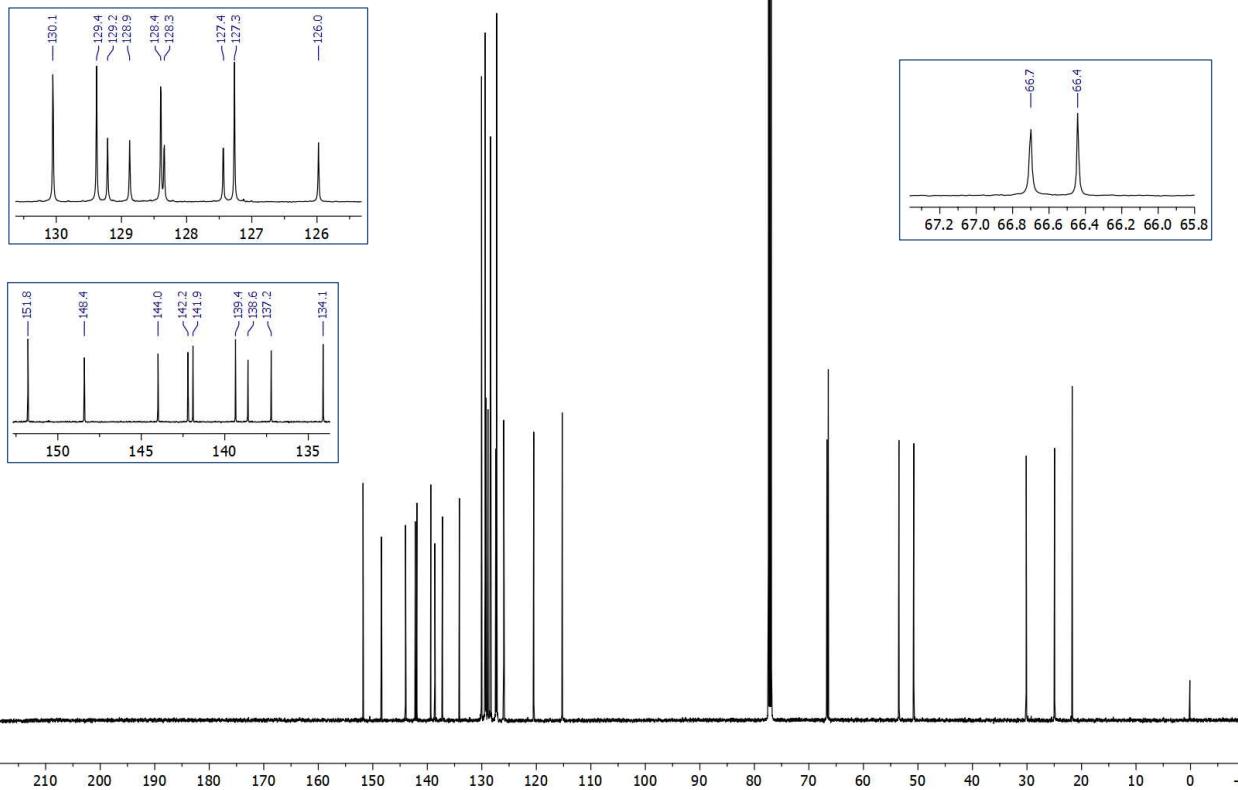


¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

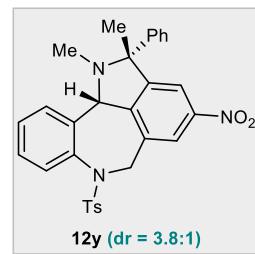
¹H NMR, 500 MHz, CDCl₃



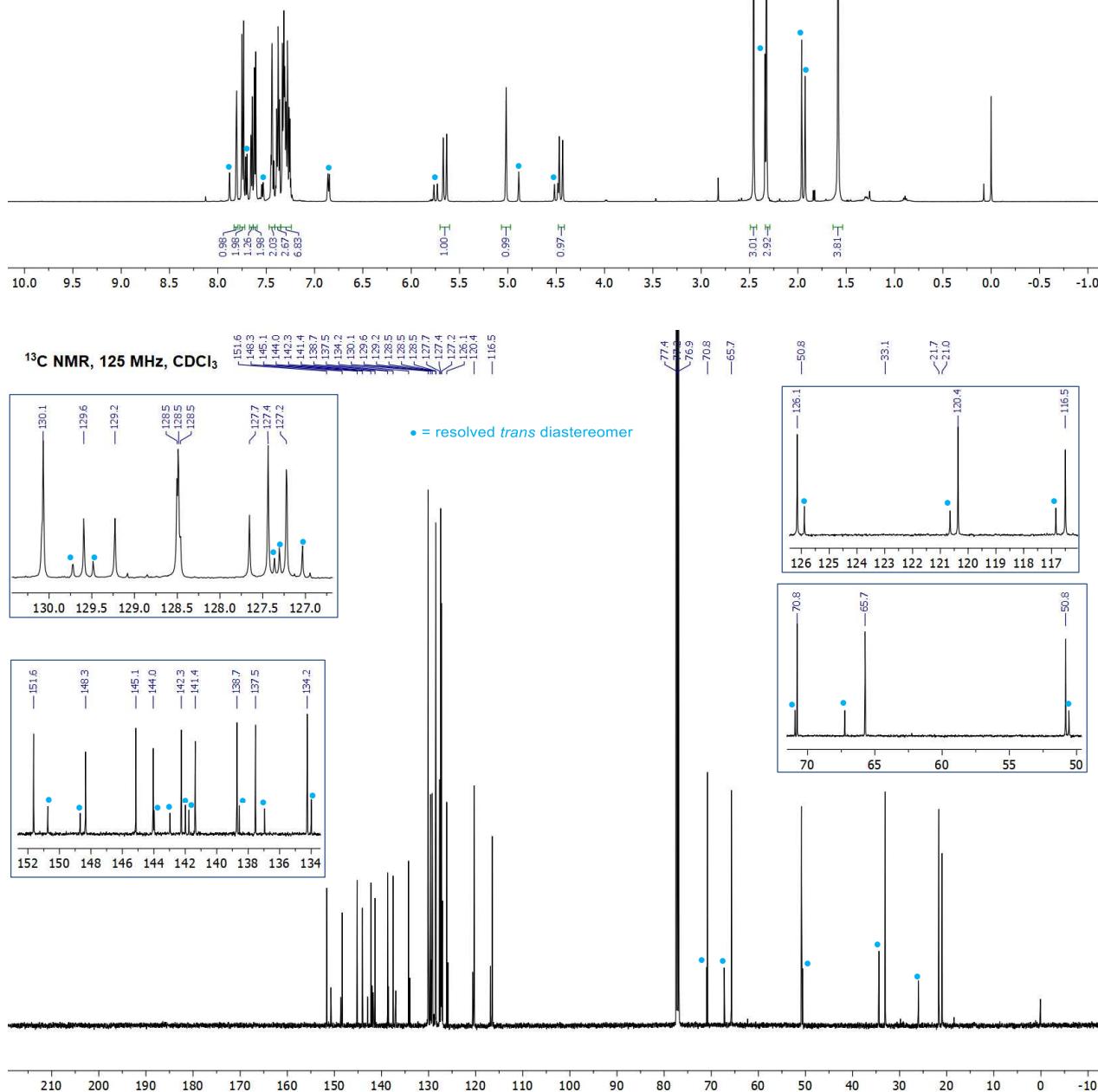
¹³C NMR, 125 MHz, CDCl₃

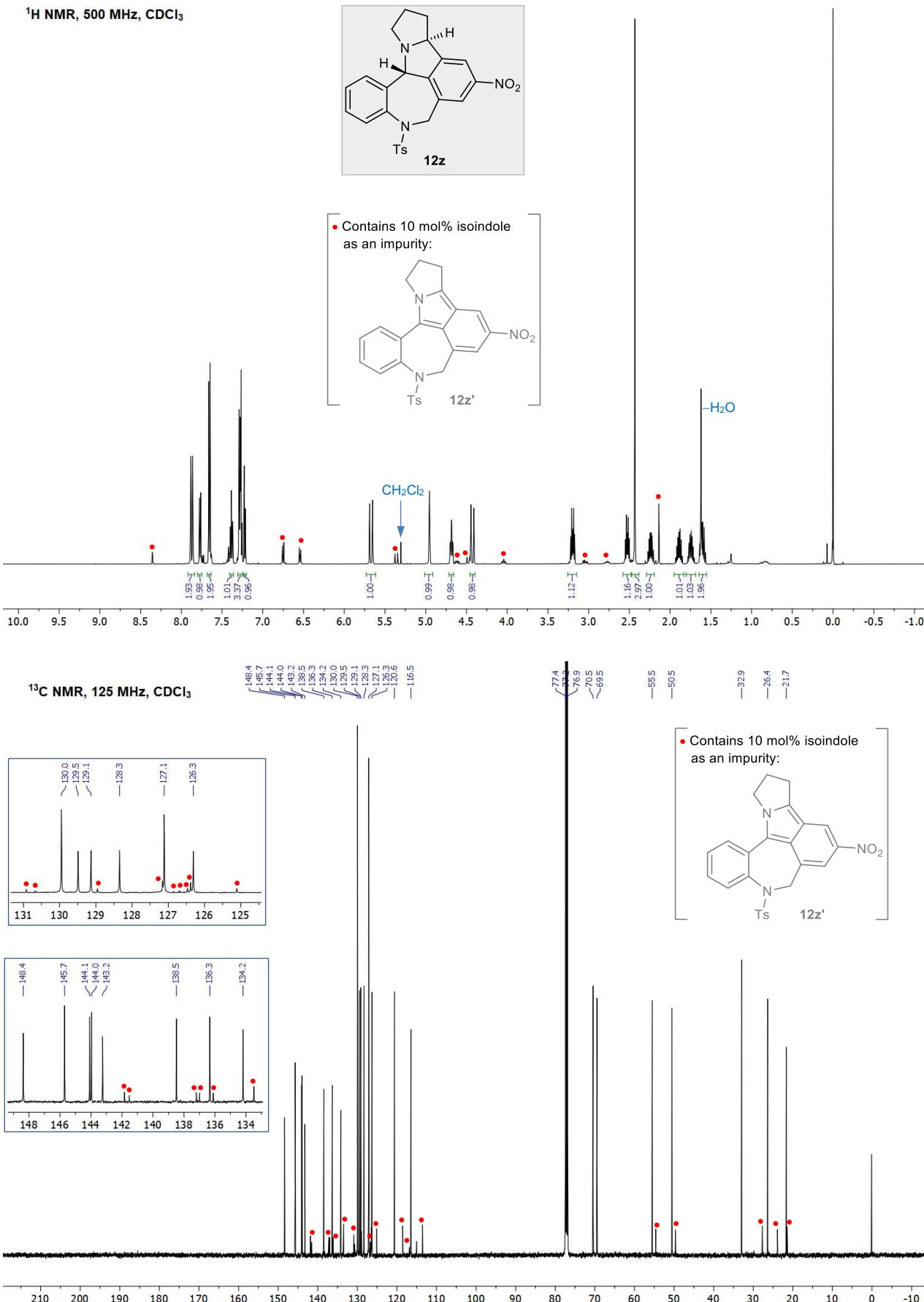


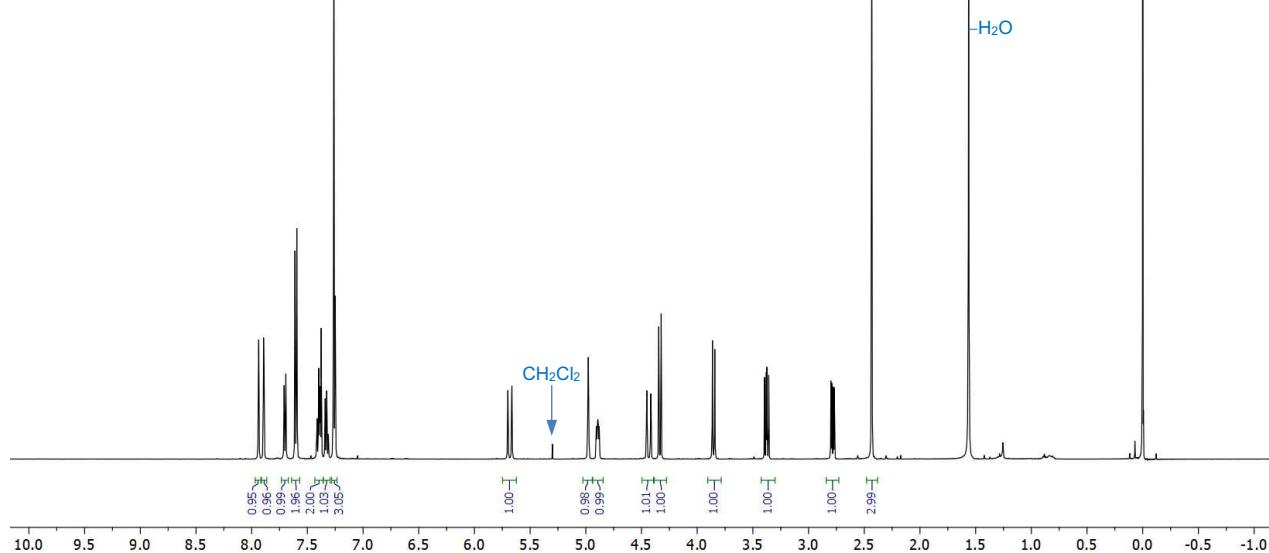
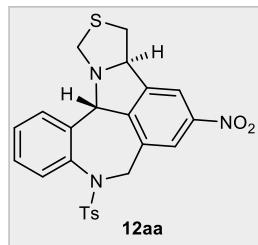
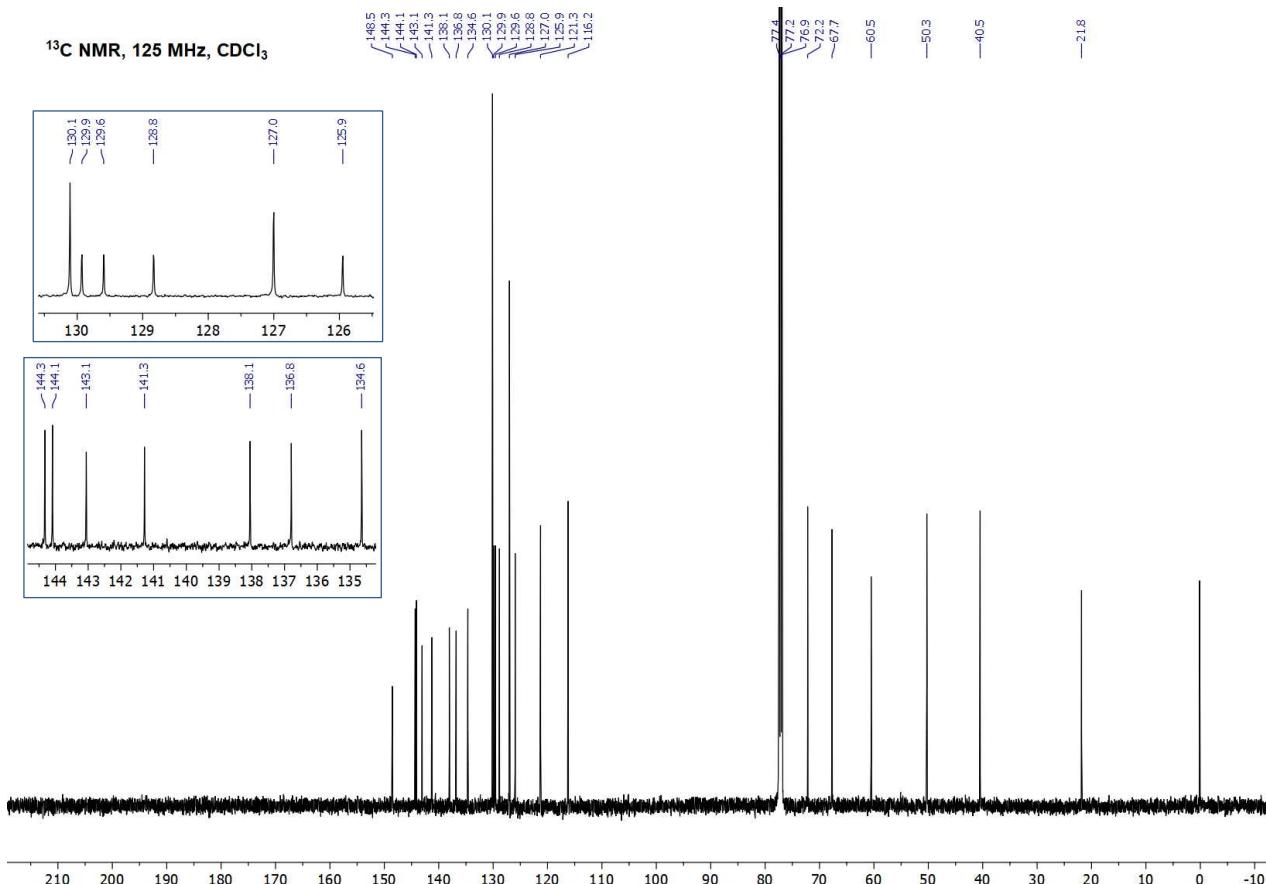
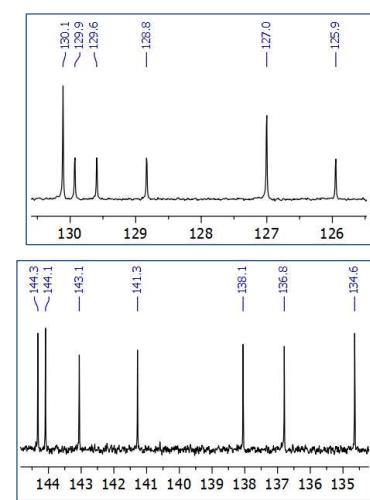
¹H NMR, 500 MHz, CDCl₃

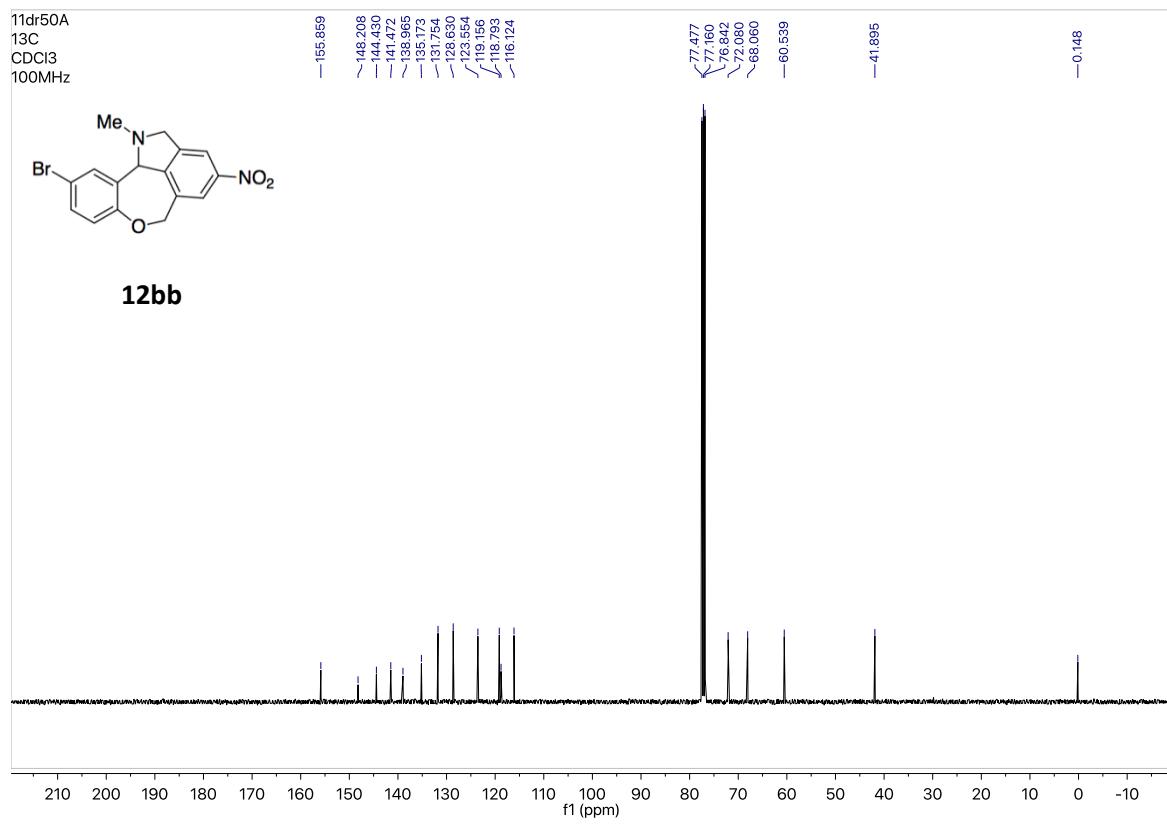
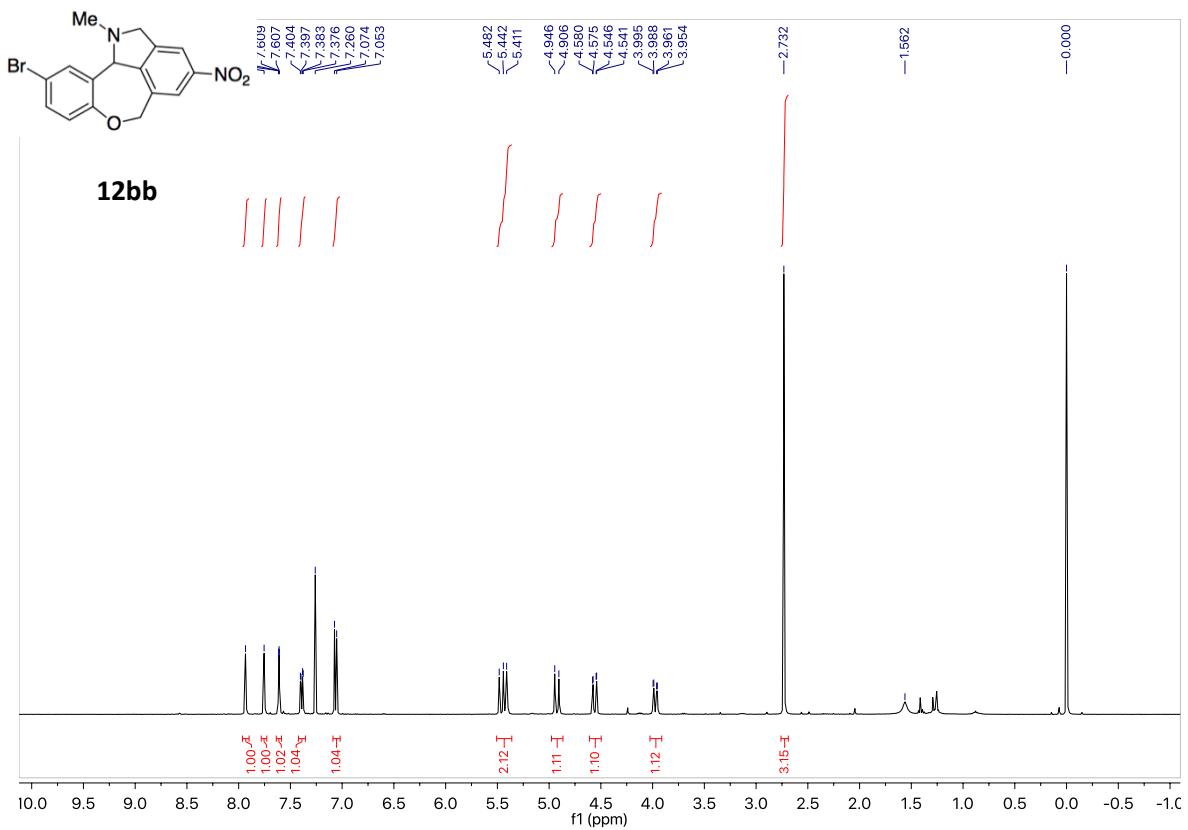


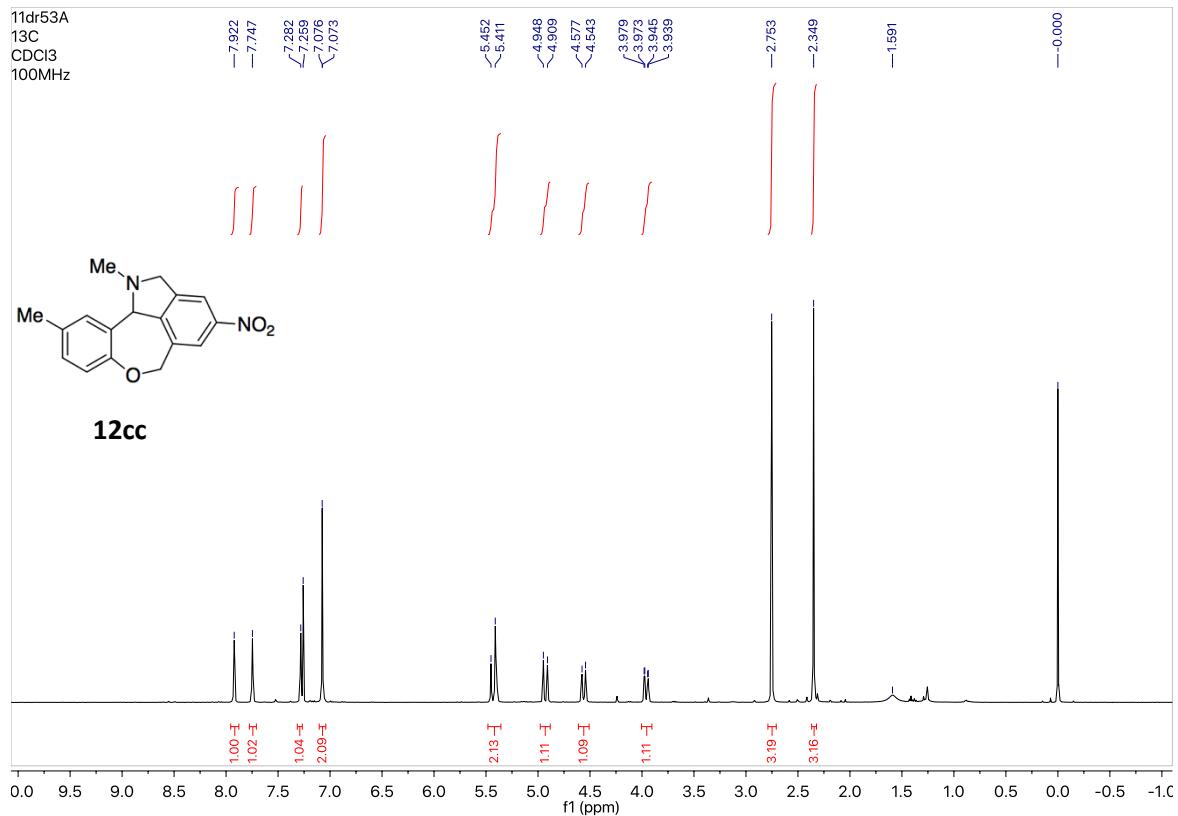
- enriched sample of *cis* diast.
- = resolved *trans* diastereomer



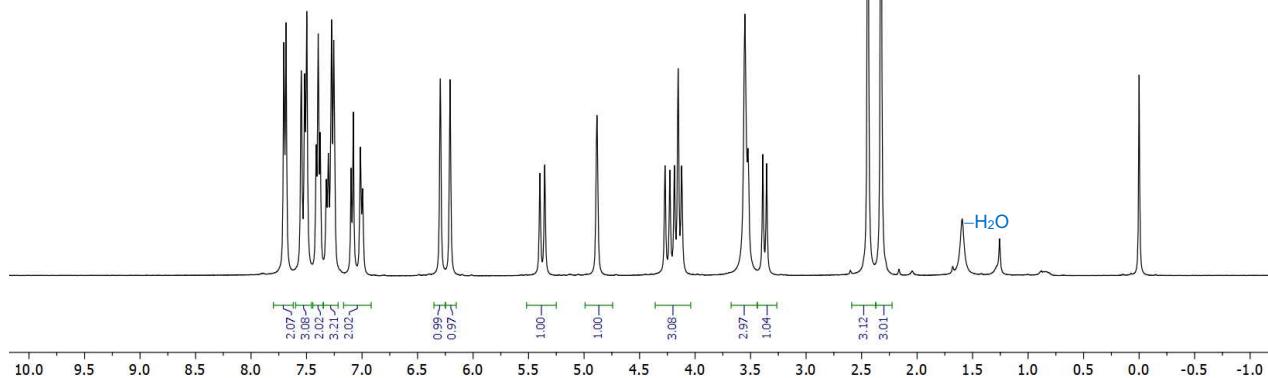
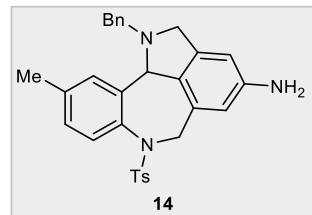


¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

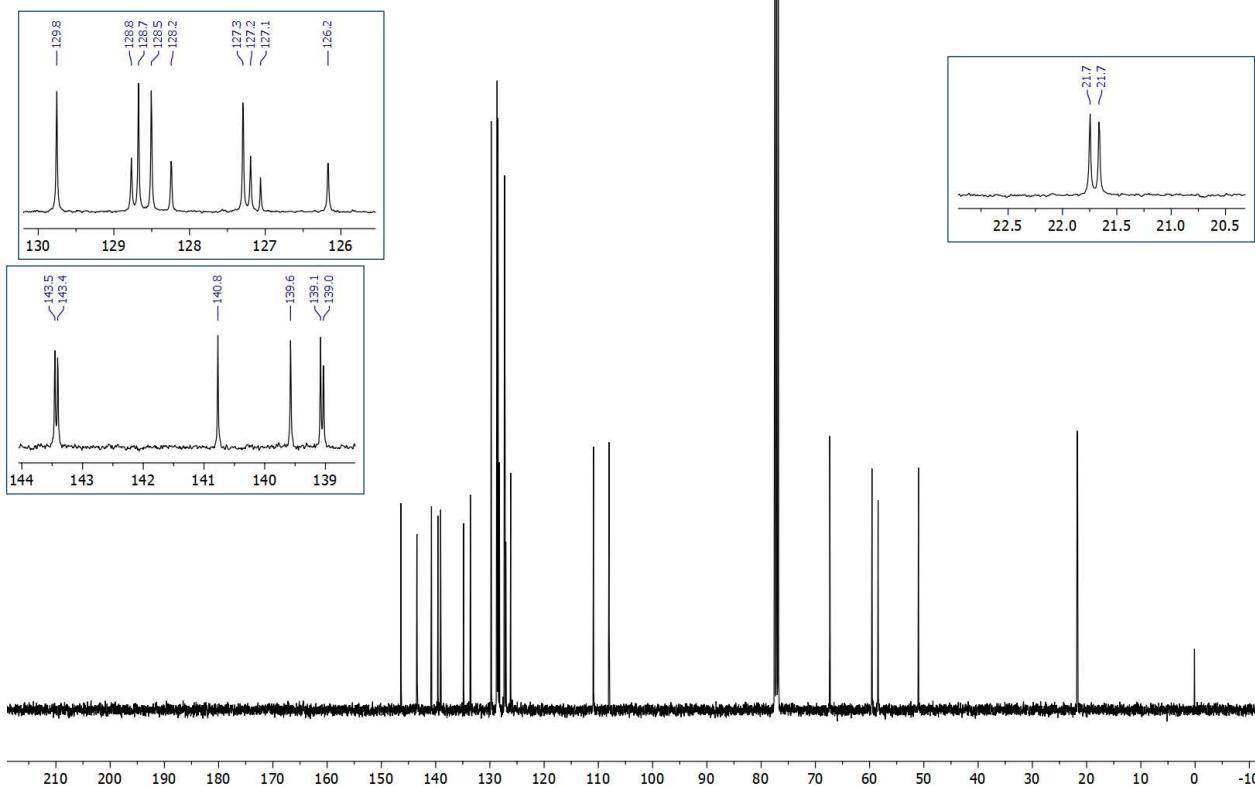


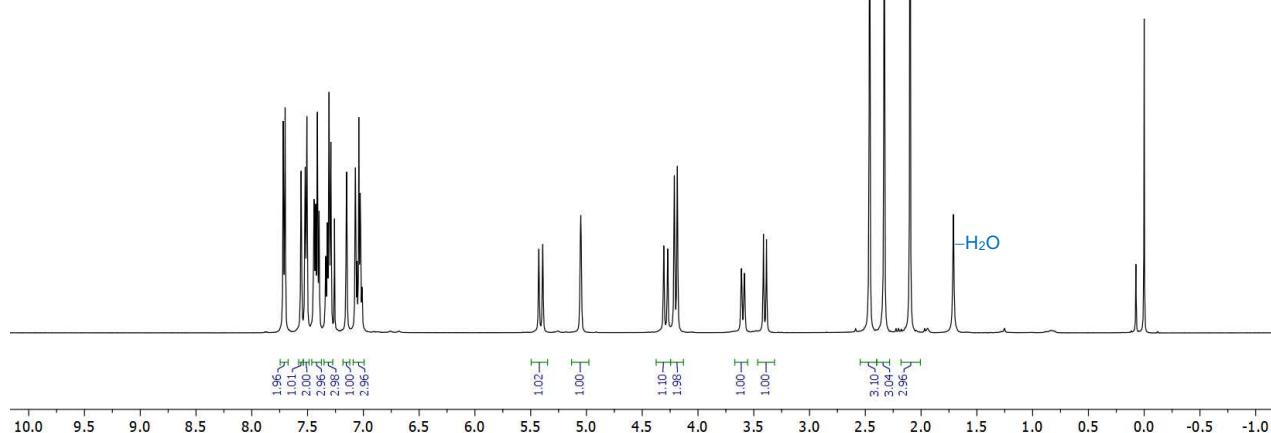
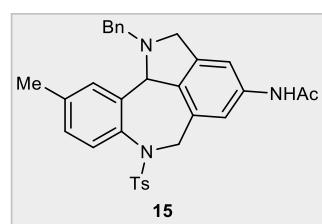
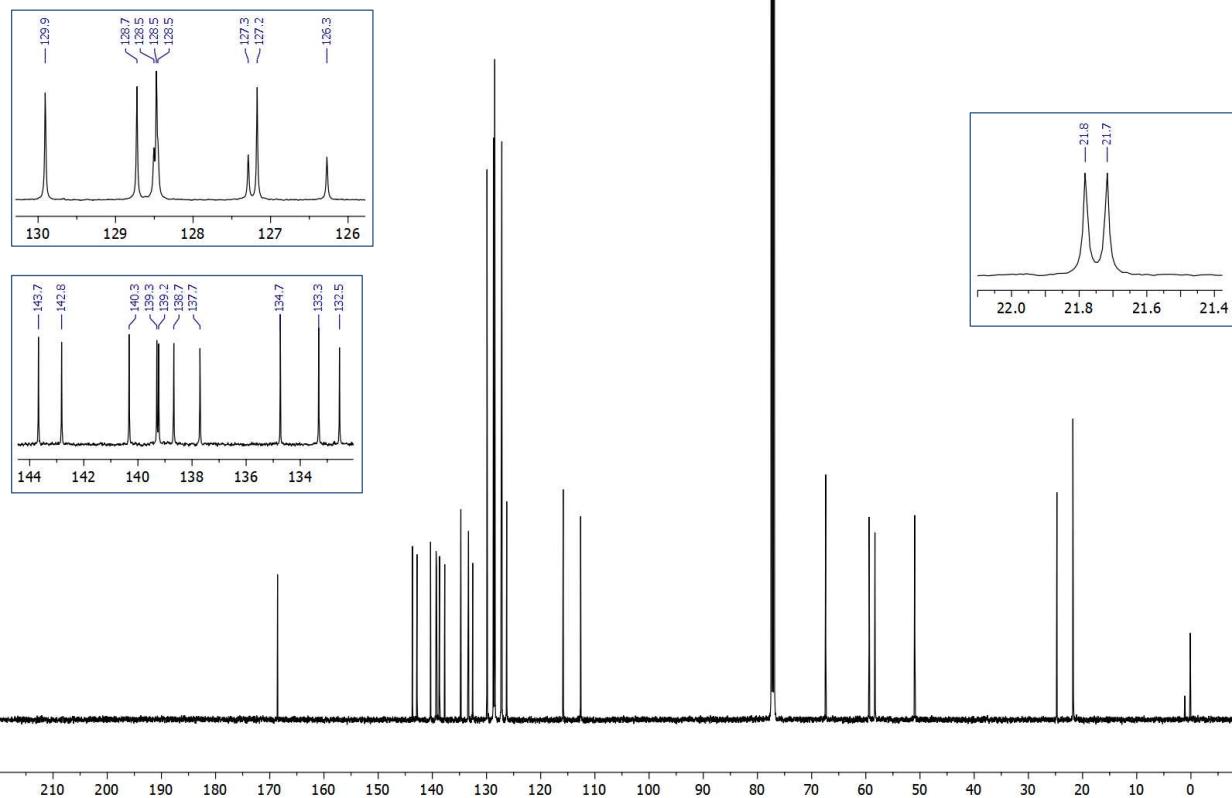


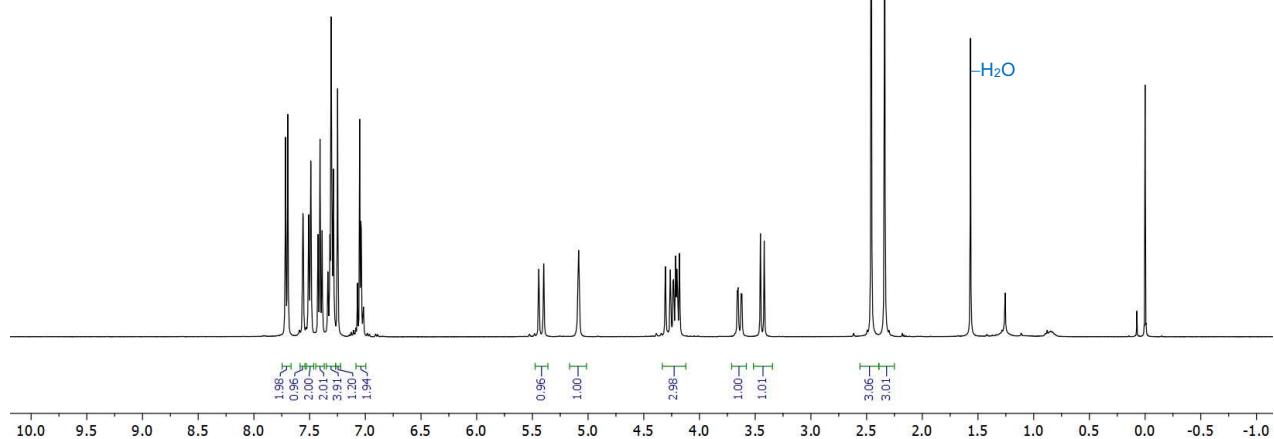
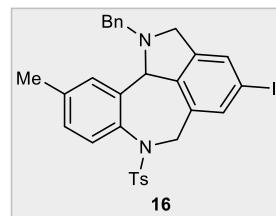
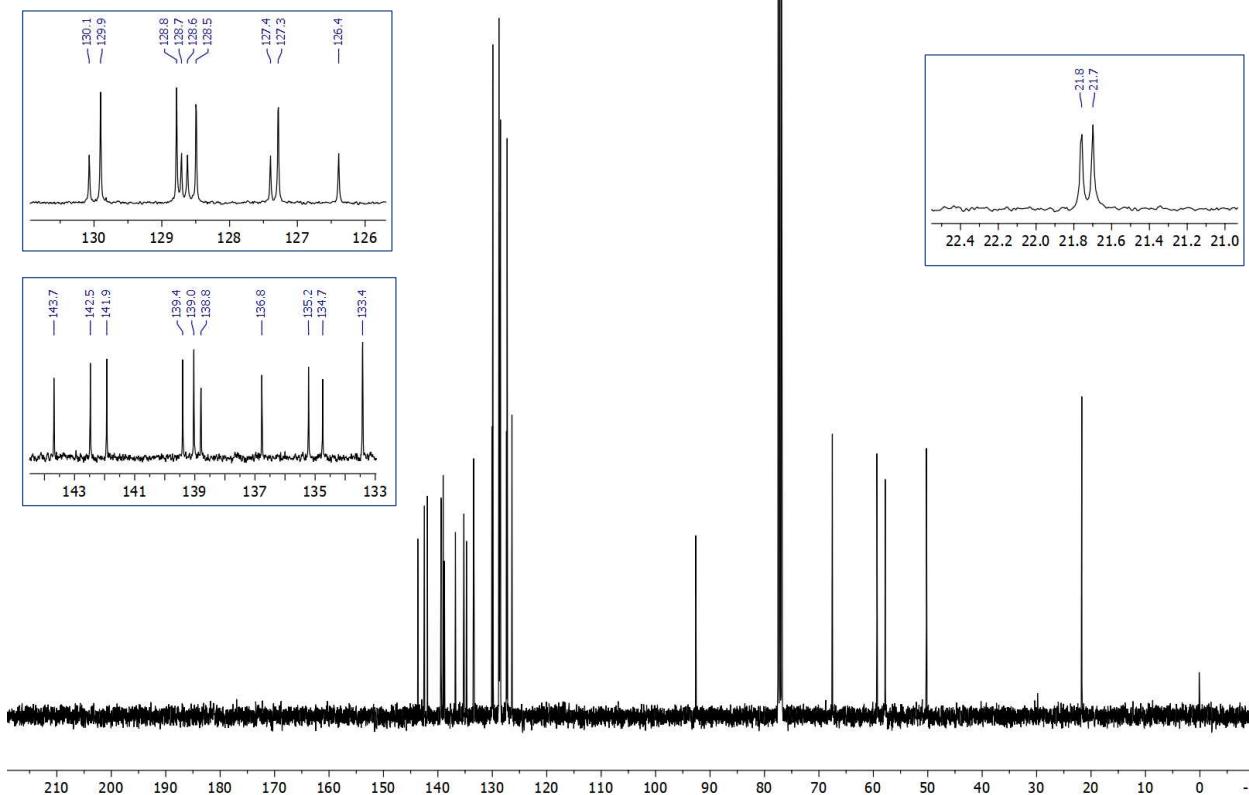
¹H NMR, 400 MHz, CDCl₃



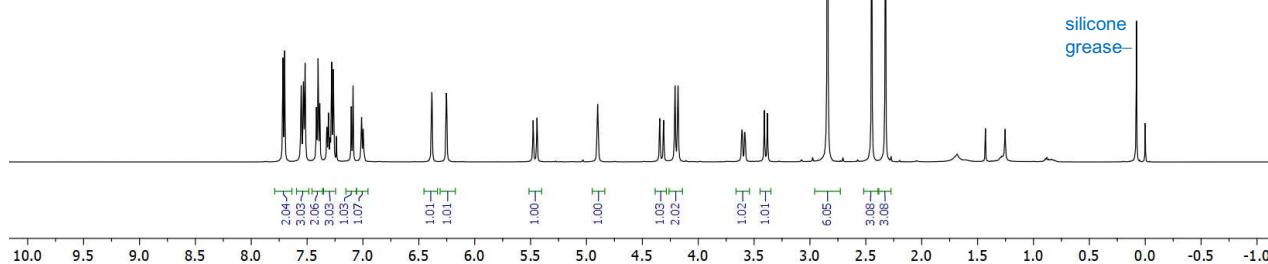
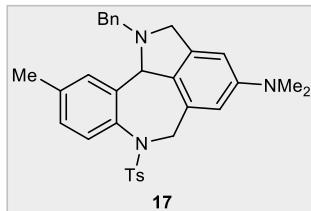
¹³C NMR, 100 MHz, CDCl₃



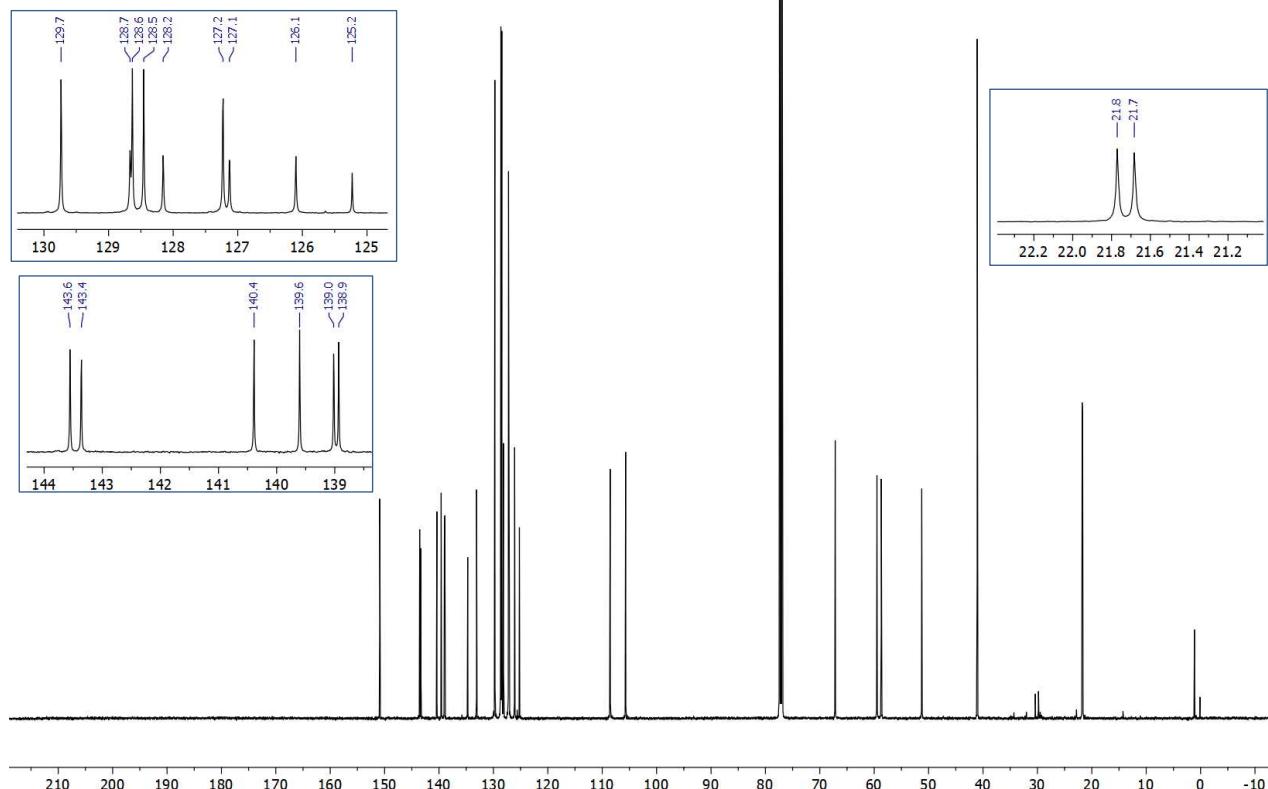
¹H NMR, 500 MHz, CDCl₃¹³C NMR, 125 MHz, CDCl₃

¹H NMR, 400 MHz, CDCl₃¹³C NMR, 100 MHz, CDCl₃

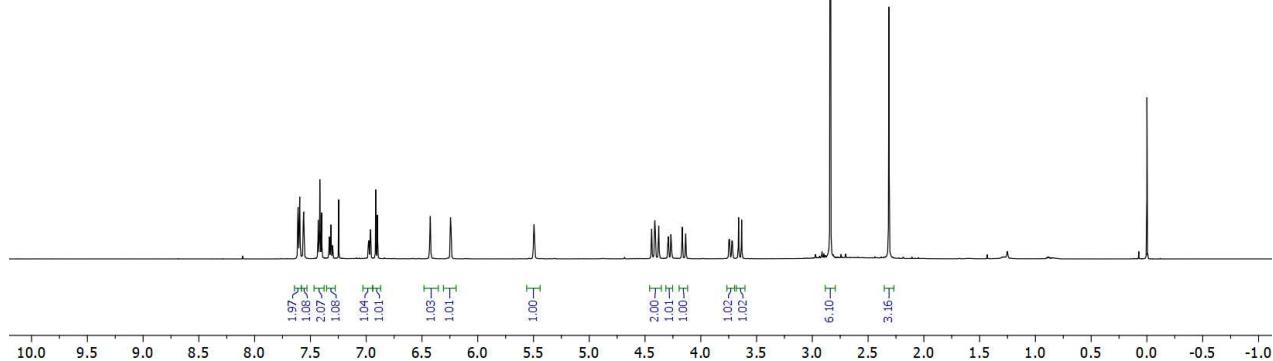
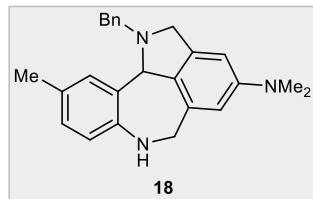
^1H NMR, 500 MHz, CDCl_3



¹³C NMR, 125 MHz, CDCl₃



¹H NMR, 500 MHz, CDCl₃



¹³C NMR, 125 MHz, CDCl₃

