

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

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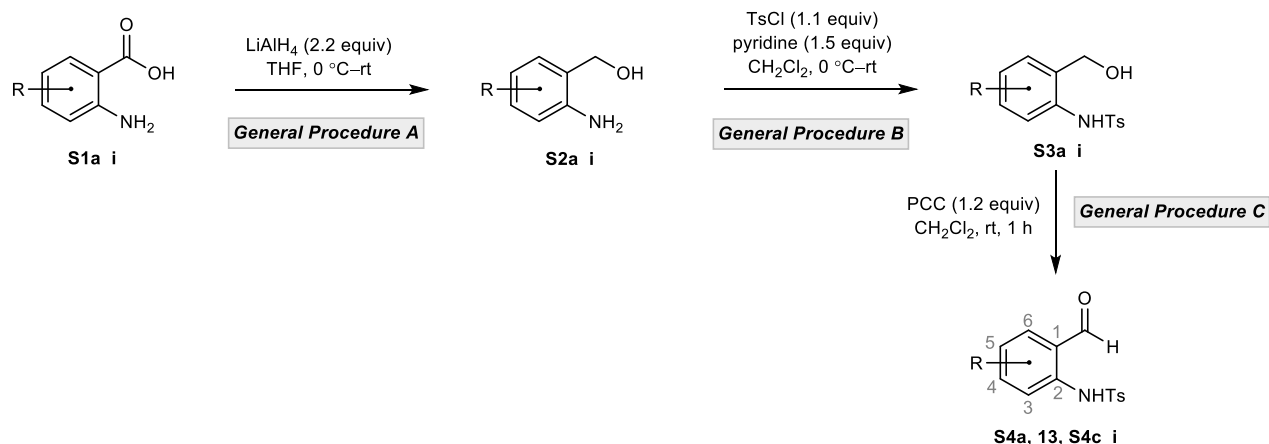
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## **1. General Synthesis and Characterization Methods**

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  $\mu m$ ). 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 ( $^1H$ :  $\delta$  = 0.00 ppm).  $^1H$  NMR spectra acquired in  $CD_3OD$  are reported relative to solvent resonance ( $^1H$ :  $\delta$  = 3.31 ppm).  $^1H$  NMR spectra acquired in  $(CD_3)_2SO$  are reported relative to solvent resonance ( $^1H$ :  $\delta$  = 2.50 ppm).  $^{13}C$  NMR (proton decoupled) spectra acquired in  $CDCl_3$  are reported relative to solvent resonance ( $^{13}C$ :  $\delta$  = 77.16 ppm).  $^{13}C$  NMR (proton decoupled) spectra acquired in  $CD_3OD$  are reported relative to solvent resonance ( $^{13}C$ :  $\delta$  = 49.00 ppm).  $^{13}C$  NMR (proton decoupled) spectra acquired in  $(CD_3)_2SO$  are reported relative to solvent resonance ( $^{13}C$ :  $\delta$  = 39.52 ppm).  $^{19}F$  NMR (proton decoupled) spectra acquired in  $CDCl_3$  are reported relative to fluorobenzene ( $^{19}F$ :  $\delta$  = -112.96 ppm).<sup>S1</sup>  $^1H$  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

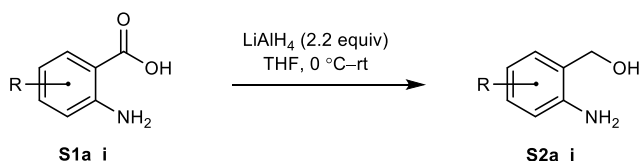
- Most of the required aldehyde starting materials (**S4a**, **13**, **S4c–i**) were prepared according to the scheme below, using *General Procedures A–C*. For the aldehydes not prepared in this way (**S4j–l**), specific schemes and procedures are given at the end of this section.



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

<sup>a</sup> Compound number in manuscript is **13**.

### 2.1. Reduction

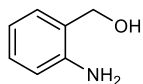


**General Procedure A (Reduction):** Based on a literature procedure,<sup>S2</sup> to a solution of the corresponding commercially available anthranilic acid **S1a–i** (1.0 equiv) in anhydrous THF (~1.0 M) cooled to 0 °C was added a solution of LiAlH<sub>4</sub> (2.2 equiv) in anhydrous THF (~3.0 M) 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 MgSO<sub>4</sub> added and then the mixture was stirred for a further 15 minutes. The crude mixture was then filtered, extracted generously with EtOAc and



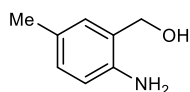
the extract concentrated under reduced pressure. The product was then precipitated from small amount of hot EtOAc and excess *n*-pentane, filtered and washed with cold *n*-pentane to reveal the corresponding alcohol **S2a–i**.

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



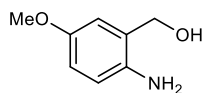
This compound was prepared using *General Procedure A* to afford the title compound as a pale brown solid (1.115 g, 62% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 7.4, 0.5 Hz, 1H), 6.71 (td, *J* = 7.4, 0.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.62 (s, 3H), 3.43 (bs, 2H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 146.1, 129.5, 129.3, 125.0, 118.3, 116.2, 64.4 ppm. NMR data matches literature values.<sup>S3</sup>

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



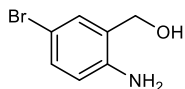
This compound was prepared using *General Procedure A* to afford the title compound as an orange/yellow solid (2.011 g, 98% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.88 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.61 (s, 2H), 2.23 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 143.5, 129.93, 129.89, 127.6, 125.2, 116.4, 64.5, 20.5 ppm. NMR data matches literature values.<sup>S4</sup>

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

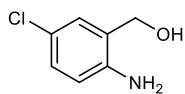


This compound was prepared using *General Procedure A* to afford the title compound as an orange/brown solid (2.066 g, 90% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 6.72 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.69–6.68 (m, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 4.61 (s, 2H), 3.74 (s, 3H) ppm. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 139.3, 126.7, 117.5, 115.1, 114.6, 64.2, 55.9 ppm. NMR data matches literature values.<sup>S5</sup>

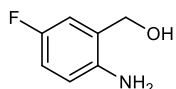
#### (2-Amino-5-bromophenyl)methanol (**S2d**)



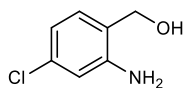
This compound was prepared using *General Procedure A* to afford the title compound as a bright yellow solid (2.926 g, 97% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.22–7.18 (m, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.60 (s, 2H), 4.16 (bs, 2H), 1.76 (bs, 1H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 145.2, 132.0, 131.7, 126.7, 117.7, 109.7, 63.9 ppm. NMR data matches literature values.<sup>S4</sup>

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

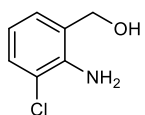
This compound was prepared using *General Procedure A* to afford the title compound as a pale yellow solid (1.827 g, 78% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.09–7.05 (m, 2H), 6.62 (d,  $J$  = 8.0 Hz, 1H), 4.61 (s, 2H), 4.17 (bs, 1H), 1.61 (bs, 1H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  144.7, 129.1, 128.9, 126.2, 122.7, 117.2, 64.0 ppm. NMR data matches literature values.<sup>S6</sup>

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

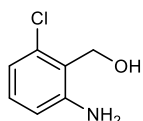
This compound was prepared using *General Procedure A* to afford the title compound as a beige solid (1.647 g, 78% yield). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  6.86–6.81 (m, 2H), 6.65–6.60 (m, 1H), 4.62 (s, 2H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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  $\times$  ArC), 63.9 ppm. NMR data matches literature values.<sup>S6</sup>

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

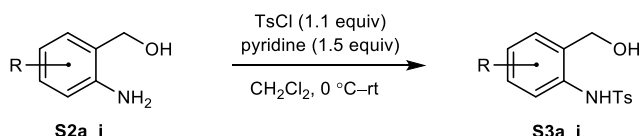
This compound was prepared using *General Procedure A* to afford the title compound as a beige solid (1.618 g, 69% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  6.97 (d,  $J$  = 8.0 Hz, 1H), 6.69–6.66 (m, 2H), 4.64 (s, 2H), 4.27 (bs, 2H), 1.58 (bs, 1H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  147.4, 134.9, 130.3, 123.1, 118.0, 115.7, 64.0 ppm. NMR data matches literature values.<sup>S6</sup>

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

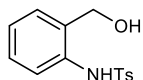
This compound was prepared using *General Procedure A* to afford the title compound as a white “needle-like” solid (1.012 g, 43% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.23 (d,  $J$  = 8.0 Hz, 1H), 6.97 (d,  $J$  = 7.0 Hz, 1H), 6.33 (t,  $J$  = 7.5 Hz, 1H), 4.67 (s, 2H), 4.65 (bs, 2H), 1.72 (bs, 1H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  142.8, 129.5, 127.6, 125.8, 120.1, 118.0, 64.6 ppm. NMR data matches literature values.<sup>S5</sup>

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

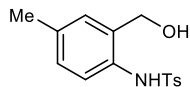
This compound was prepared using *General Procedure A* to afford the title compound as a brown crystalline solid (1.347 g, 57% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.01 (t, *J* = 8.0 Hz, 1H), 6.76 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 4.28 (bs, 2H), 1.66 (bs, 1H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 148.2, 134.3, 129.8, 122.2, 119.2, 114.8, 59.7 ppm. NMR data matches literature values.<sup>S5</sup>

**2.2. *N*-Tosylation**

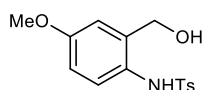
**General Procedure B (*N*-Tosylation):** Based on a literature procedure,<sup>S2</sup> to a solution of corresponding amine **S2a-i** (1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.3 M) was added pyridine (1.5 equiv). The resultant solution was cooled to 0 °C before addition of TsCl (1.1 equiv). The resultant reaction mixture was then allowed to warm to room temperature and allowed to stir overnight. The reaction was then quenched using saturated NaHCO<sub>3</sub> (30 mL), the aqueous layer was extracted using CH<sub>2</sub>Cl<sub>2</sub> (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)**

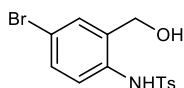
This compound was prepared using *General Procedure B* to afford the title compound as a pale-yellow solid (1.911 g, 77% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.90 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.26–7.23 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.09–7.06 (m, 2H), 4.39 (s, 2H), 2.38 (s, 3H), 2.21 (bs, 1H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 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.<sup>S7</sup>

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

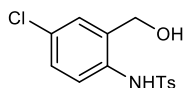
This compound was prepared using *General Procedure B* to afford the title compound as an orange solid (3.746 g, 88% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.63 (bs, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 7.23–7.20 (m, 3H), 7.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 2.27 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 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.<sup>S8</sup>

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

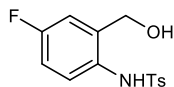
This compound was prepared using *General Procedure B* to afford the title compound as a brown solid (4.150 g, 99% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.33 (bs, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.74–6.71 (m, 2H), 4.30 (s, 2H), 3.76 (s, 3H), 2.39 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 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.<sup>S9</sup>

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

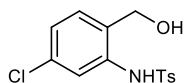
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (4.578 g, 88% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.38–7.31 (m, 2H), 7.24–7.23 (m, 3H), 4.34 (s, 2H), 2.39 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 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.<sup>S10</sup>

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

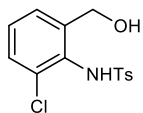
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (3.272 g, 91% yield). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.95 (s, 1H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 6.4 Hz, 2H), 7.22–7.19 (m, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 4.33 (s, 2H), 2.39 (s, 3H), 1.60 (bs, 1H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** 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.<sup>S8</sup>

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

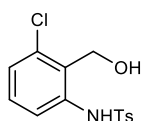
This compound was prepared using *General Procedure B* to afford the title compound as a yellow/orange solid (2.956 g, 86% yield). **Mp**: 150–153 °C. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 7.60 (d, *J* = 8.5 Hz, 2H), 7.31 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.96 (ddd, *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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: δ 160.5 (d, *J*<sub>C-F</sub> = 232.8 Hz), 144.2, 136.5, 135.7 (d, *J*<sub>C-F</sub> = 7.3 Hz), 131.7 (d, *J*<sub>C-F</sub> = 3.0 Hz), 129.9, 127.2, 127.0 (d, *J*<sub>C-F</sub> = 8.3 Hz), 116.0 (d, *J*<sub>C-F</sub> = 22.8 Hz), 115.8 (d, *J*<sub>C-F</sub> = 22.1 Hz), 63.2 (d, *J*<sub>C-F</sub> = 1.0 Hz), 21.7 ppm. **IR (ATR, cm<sup>-1</sup>)**: ν̃ 3446, 3080, 1595, 1491, 1323, 1154, 918, 880, 663, 554. **HRMS (ESI)**: calcd for C<sub>14</sub>H<sub>13</sub>FNO<sub>3</sub>S [M – H]<sup>–</sup> 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). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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.<sup>S9</sup>

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

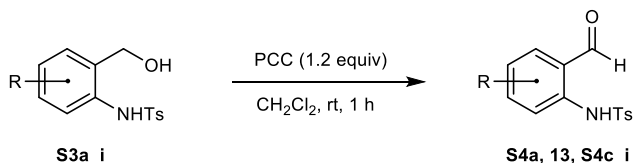
This compound was prepared using *General Procedure B* to afford the title compound as a yellow solid (1.017 g, 58% yield). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 7.53 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.27–7.18 (m, 4H), 6.48 (bs, 1H), 4.86 (s, 2H), 2.24 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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.<sup>S11</sup>

***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. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\tilde{\nu}$  3450, 3356, 3250, 3064, 2922, 1671, 1457, 995, 771. HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{13}\text{ClNO}_3\text{S}$  [ $\text{M} - \text{H}$ ] $^-$  310.0305, found 310.0316.

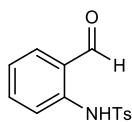
### 2.3. Oxidation



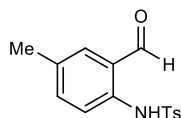
**General Procedure C (Oxidation):** Based on a literature procedure,<sup>S2</sup> to a solution of the corresponding alcohol **S3a–i** (1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.1 M) at room temperature was added PCC (1.2 equiv). The resultant reaction solution was stirred at room temperature and monitored via TLC (typically 1–2 h). To the reaction mixture was then added  $\text{MgSO}_4$  to form a suspension that was then directly filtered through a sintered glass funnel, with the residue washed generously with extra  $\text{CH}_2\text{Cl}_2$ . 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  $\text{MgSO}_4$  was added when celite was used.

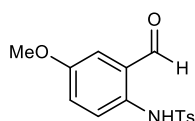
#### ***N*-(2-Formylphenyl)-4-methylbenzenesulfonamide (**S4a**)**



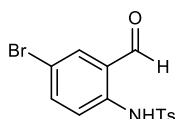
This compound was prepared using *General Procedure C* to afford the title compound as a white solid (1.585 g, 84% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.79 (bs, 1H), 9.82 (s, 1H), 7.77 (d,  $J$  = 8.3 Hz, 2H), 7.68 (d,  $J$  = 8.4 Hz, 1H), 7.59 (dd,  $J$  = 7.6, 0.6 Hz, 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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.<sup>S12</sup>

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

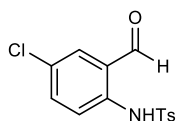
This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (3.398 g, 91% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.59 (s, 1H), 9.77 (s, 1H), 7.74 (d,  $J$  = 8.0 Hz, 2H), 7.60 (d,  $J$  = 8.5 Hz, 1H), 7.37–7.36 (m, 1H), 7.32 (dd,  $J$  = 8.5, 1.5 Hz, 1H), 7.22 (d,  $J$  = 8.5 Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H) ppm. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  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.<sup>S13</sup>

***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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  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.<sup>S9</sup>

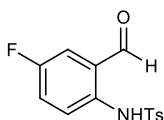
***N*-(4-Bromo-2-formylphenyl)-4-methylbenzenesulfonamide (S4d)**

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. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3126, 3049, 2865, 1669, 1479, 1375, 1159, 856, 684. **HRMS (ESI):** calcd for C<sub>14</sub>H<sub>11</sub>(<sup>79</sup>Br)NO<sub>3</sub>S [M – H]<sup>–</sup> 351.96485, found 351.96505.

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

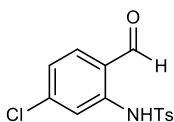
This compound was prepared using *General Procedure C* to afford the title compound as a brown solid (2.848 g, 88% yield). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.62 (bs, 1H), 9.77 (s, 1H), 7.75 (d,  $J$  = 8.0 Hz, 2H), 7.68 (d,  $J$  = 9.0 Hz, 1H), 7.56 (s, 1H), 7.46 (d,  $J$  = 8.5 Hz, 1H), 7.25 (d,  $J$  = 8.5 Hz, 2H), 2.38 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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.<sup>S9</sup>

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



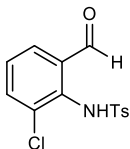
This compound was prepared using *General Procedure C* to afford the title compound as a brown solid (2.785 g, 96% yield). **Mp:** 135–137 °C. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.45 (s, 1H), 9.76 (s, 1H), 7.74–7.71 (m, 3H), 7.29–7.26 (m, 2H), 7.24 (d,  $J$  = 8.0 Hz, 2H), 2.37 (s, 3H) ppm. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3713, 3072, 2873, 1670, 1588, 1495, 1342, 1159, 905, 770, 542. **HRMS (ESI):** calcd for C<sub>14</sub>H<sub>11</sub>FNO<sub>3</sub>S [M – H]<sup>–</sup> 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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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.<sup>S14</sup>

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

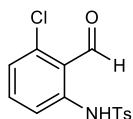


This compound was prepared using *General Procedure C* to afford the title compound as a yellow solid (0.478 g, 47% yield). **Mp:** 143–146 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  10.32 (d,  $J$  = 0.8 Hz, 1H), 7.92 (dd,  $J$  = 7.6, 1.6 Hz, 1H), 7.49 (dd,  $J$  = 8.0, 1.6 Hz, 1H), 7.43 (d,  $J$  = 8.4 Hz, 2H), 7.34 (td,  $J$  = 7.8, 0.8 Hz, 1H), 7.20 (d,  $J$  =



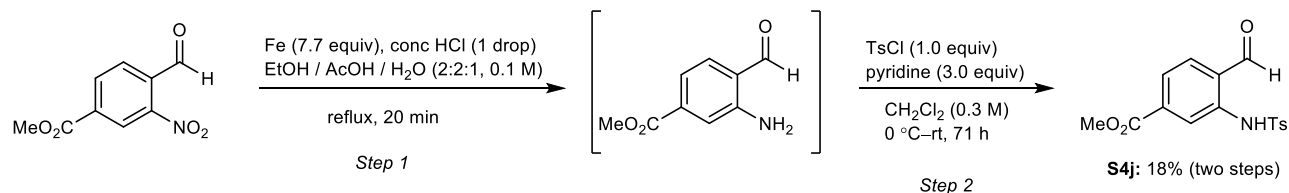
8.0 Hz, 2H), 2.41 (s, 3H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  189.2, 144.9, 135.5, 134.92, 134.85, 134.3, 131.6, 129.8, 128.3, 128.1, 127.6, 21.8 ppm. IR (ATR,  $\text{cm}^{-1}$ ):  $\tilde{\nu}$  = 3366, 3102, 2895, 1671, 1466, 1395, 1163, 883, 796, 721, 576. HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{12}\text{ClNO}_3\text{SNa}$   $[\text{M} + \text{Na}]^+$  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).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.<sup>S13</sup>

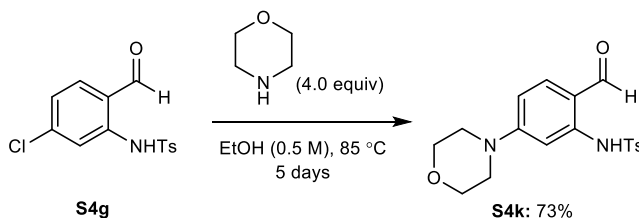
#### ***N*-(5-Carbomethoxy-2-formylphenyl)-4-methylbenzenesulfonamide (S4j)**



**Step 1:** Based on a literature procedure,<sup>S15</sup> 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  $\text{K}_2\text{CO}_3$  (180 mL) was added slowly over 10 min ( $\text{CO}_2$  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  $\text{NaHCO}_3$  (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) 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).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  194.1, 166.5, 149.5, 135.8, 135.6, 121.0, 117.8, 116.7, 52.6 ppm.

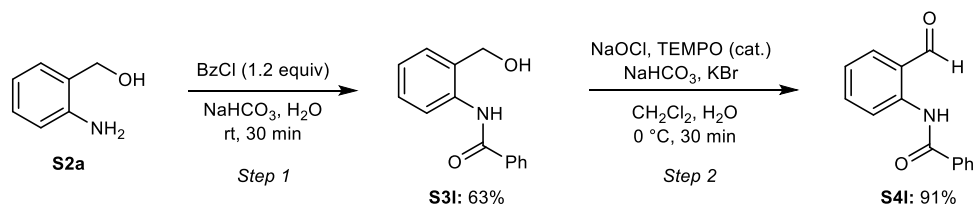
**Step 2:** To a solution of the above aniline (925.5 mg crude,  $\leq 5.00$  mmol) in reagent grade  $\text{CH}_2\text{Cl}_2$  (16.7 mL) at 0 °C under air was added pyridine (0.61 mL, 7.50 mmol) followed by solid TsCl (953.2 mg, 5.00 mmol). The mixture was allowed to warm to room temperature with stirring 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 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 ( $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  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,  $\text{CDCl}_3$ ):**  $\delta$  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,  $\text{cm}^{-1}$ ):**  $\tilde{\nu}$  = 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.<sup>S16</sup>

***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 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 EtOAc/ $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  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,  $\text{CDCl}_3$ ):**  $\delta$  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,  $\text{cm}^{-1}$ ):**  $\tilde{\nu}$  = 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-Benzoylamino benzaldehyde (**S4I**)



**Step 1:** To a solution of amino alcohol **S2a** (0.80 g, 6.45 mmol, 1.0 equiv) in saturated  $\text{NaHCO}_3$  (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.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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.  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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.<sup>S17</sup>

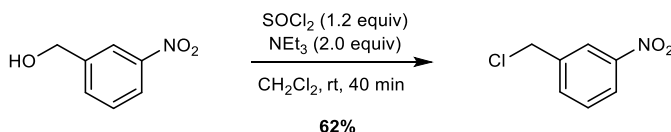
**Step 2:** To a solution of alcohol **S3I** (0.50 g, 2.22 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (14.8 mL) was added saturated  $\text{NaHCO}_3$  (7.4 mL), KBr (0.26 g, 2.21 mmol, 1.0 equiv) and TEMPO (17.5 mg, 0.11 mmol, 0.05 equiv). The solution was cooled to 0 °C and a commercial aqueous ‘bleach’ solution (7.86 mL) was added dropwise over 30 min (containing sodium hypochlorite [42 g/L in  $\text{H}_2\text{O}$ , 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  $\text{CH}_2\text{Cl}_2$  ( $\times$  3), and the combined organic phases dried over  $\text{Na}_2\text{SO}_4$ . 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.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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.  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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.<sup>S17</sup>

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

#### 3.1. Synthesis of Nitro-Substituted Benzyl Chlorides

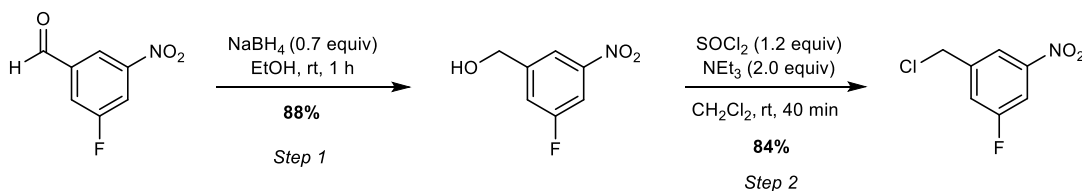
- 3-Nitrobenzyl chloride and 3-fluoro-5-nitrobenzylchloride (for preliminary studies) were prepared from the corresponding aldehyde or alcohol as described below. 3,5-Dinitrobenzyl chloride was obtained commercially.

##### 3-Nitrobenzyl chloride



To a solution of 3-nitrobenzyl alcohol (500.0 mg, 3.26 mmol, 1.0 equiv) and  $\text{NEt}_3$  (0.82 mL, 5.88 mmol, 1.8 equiv) in reagent grade  $\text{CH}_2\text{Cl}_2$  (6.5 mL) at room temperature under air was added dropwise over 10 min neat  $\text{SOCl}_2$  (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  $\text{NaHCO}_3$  (20 mL) and further  $\text{CH}_2\text{Cl}_2$  (20 mL). The organic layer was washed with water (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Polar impurities were removed via flash chromatography (eluting with  $\text{CH}_2\text{Cl}_2$ ) to give 3-nitrobenzyl chloride as an orange solid (346.8 mg, 62% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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

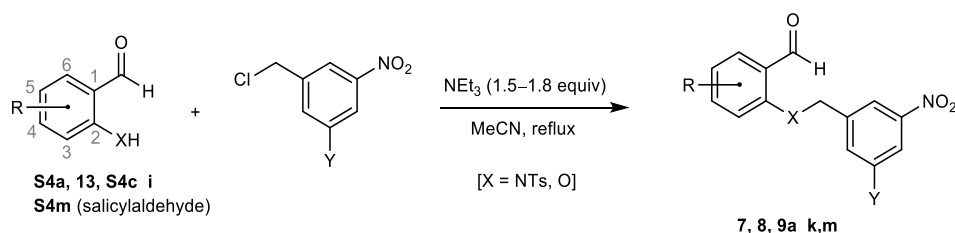


**Step 1:** To a solution of 3-fluoro-5-nitrobenzaldehyde (500.0 mg, 2.96 mmol, 1.0 equiv) in reagent grade EtOH (2 mL) under air at room temperature was added a suspension of  $\text{NaBH}_4$  (79.6 mg, 2.10 mmol, 0.7 equiv) in EtOH (3 mL) via glass pipette. The residual  $\text{NaBH}_4$  was rinsed 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  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic extracts were washed sequentially with  $\text{NaHCO}_3$  (20 mL) and water (20 mL), then dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give 3-fluoro-5-nitrobenzyl alcohol as a yellow solid (444.0 mg, 88% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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), NEt<sub>3</sub> (0.64 mL, 4.59 mmol, 1.8 equiv), CH<sub>2</sub>Cl<sub>2</sub> (5.4 mL) and SOCl<sub>2</sub> (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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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	<b>S4a</b>	H	NTs	H	<b>7</b>	43
2	<b>S4a</b>	H	NTs	F	<b>8</b>	31
3	<b>S4a</b>	H	NTs	NO <sub>2</sub>	<b>9a</b>	89
4	<b>13</b>	5-Me	NTs	NO <sub>2</sub>	<b>9b</b>	79
5	<b>S4c</b>	5-OMe	NTs	NO <sub>2</sub>	<b>9c</b>	71
6	<b>S4d</b>	5-Br	NTs	NO <sub>2</sub>	<b>9d</b>	84
7	<b>S4e</b>	5-Cl	NTs	NO <sub>2</sub>	<b>9e</b>	81
8	<b>S4f</b>	5-F	NTs	NO <sub>2</sub>	<b>9f</b>	79
9	<b>S4g</b>	4-Cl	NTs	NO <sub>2</sub>	<b>9g</b>	54
10	<b>S4h</b>	3-Cl	NTs	NO <sub>2</sub>	<b>9h</b>	55
11	<b>S4i</b>	6-Cl	NTs	NO <sub>2</sub>	<b>9i</b>	17
12	<b>S4j</b>	4-CO <sub>2</sub> Me	NTs	NO <sub>2</sub>	<b>9j</b>	45
13	<b>S4k</b>	4-morpholino	NTs	NO <sub>2</sub>	<b>9k</b>	52
14 <sup>a</sup>	<b>S4l</b>	H	NBz	NO <sub>2</sub>	<b>9l</b>	34
15 <sup>b</sup>	<b>S4m</b>	H	O	NO <sub>2</sub>	<b>9m</b>	77

<sup>a</sup> Using NaH (3.0 equiv) in THF at 0 °C to rt

<sup>b</sup> Using 2.0 equiv of the aldehyde and Cs<sub>2</sub>CO<sub>3</sub> (1.0 equiv) instead of NEt<sub>3</sub>

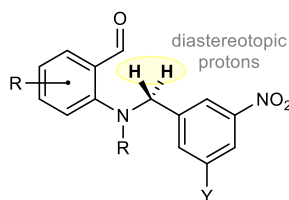
**Note:** A detailed experimental procedure for the larger scale example (product **9b**, 5 mmol scale) is also given in Section 6.

**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 Et<sub>3</sub>N

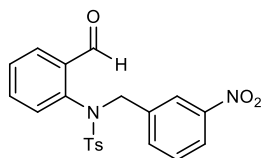
(1.5–1.8 equiv) in anhydrous MeCN (0.5 M). The resultant reaction mixture was heated to reflux and allowed to stir typically overnight. After which time, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was then diluted with water (equal to reaction volume), extracted thrice using CH<sub>2</sub>Cl<sub>2</sub>, then the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, 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 <sup>1</sup>H NMR spectra from the methylene protons (spectra provided in Section 9). No other broadening or splitting/doubling of signals was observed in the <sup>1</sup>H or <sup>13</sup>C NMR spectra. X-ray crystal structures of **9a** and **9j** (see below) showed significant sp<sup>3</sup>-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).

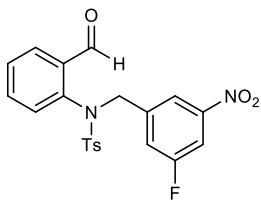


#### *N*-(3-Nitrobenzyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (**7**)



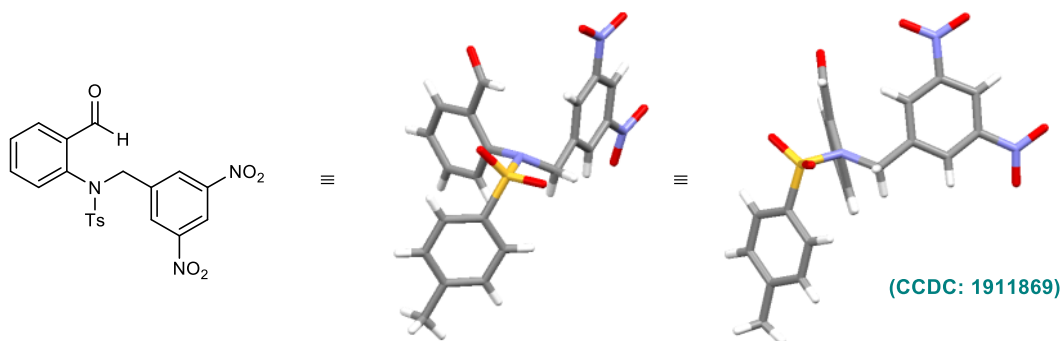
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (137.0 mg, 43% yield). **Mp**: 140–142 °C. **TLC**: *R*<sub>F</sub> = 0.30 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 10.11 (d, *J* = 0.8 Hz, 1H), 8.09 (ddd, *J* = 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 1687, 1596, 1528, 1452, 1349, 1273, 1162, 1089, 1045, 897, 866, 808, 774, 726, 664, 611, 566, 527. **HRMS (ESI)**: calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>SNa [M + Na]<sup>+</sup> 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). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**:  $\delta$  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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**:  $\delta$  (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. **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)**:  $\delta$  –107.2 ppm. **IR (ATR, cm<sup>–1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>21</sub>H<sub>18</sub>FN<sub>2</sub>O<sub>5</sub>S [M + H]<sup>+</sup> 429.0920, found 429.0933.

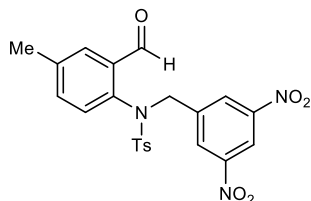
***N*-(3,5-Dinitrobenzyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (9a)**



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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  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<sup>–1</sup>)**:  $\tilde{\nu}$  = 3310, 3085, 2982, 1691, 1595, 1495, 1339, 1270, 1161, 1089, 909, 822, 808, 777, 664, 569. **HRMS (ESI)**: calcd for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>7</sub>SN<sub>a</sub> [M + Na]<sup>+</sup> 478.06849, found 478.06776. **CCDC**: 1911869.

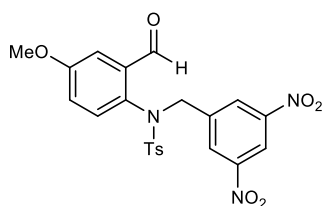
Crystals of **9a** suitable for X-ray analysis were obtained by the following solvent-diffusion method: **9a** (3–5 mg) was dissolved in ~0.7 mL of CH<sub>2</sub>Cl<sub>2</sub> in a 2 mL glass vial. This vial was placed (uncapped) inside an empty 12 mL glass vial and then pentane (~5 mL) was carefully 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**)**



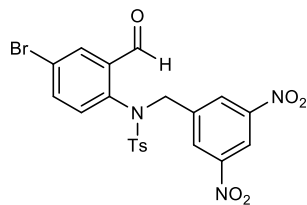
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.814 g, 79% yield). **TLC:**  $R_F$  = 0.29 (30:70 EtOAc/*n*-hexane). **Mp:** 180–183 °C. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.06 (s, 1H), 8.91 (d,  $J$  = 2.0 Hz, 1H), 8.43 (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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3086, 2866, 1688, 1540, 1340, 1087, 942, 857, 696, 666, 571. **HRMS (ESI):** calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>7</sub>SNa [M + Na]<sup>+</sup> 492.0841, found 492.0858.

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

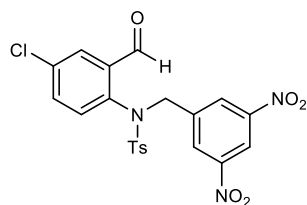


This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.729 g, 71% yield). **Mp:** 215–217 °C. **TLC:**  $R_F$  = 0.25 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  10.02 (s, 1H), 8.93 (t,  $J$  = 2.0 Hz, 1H), 8.42 (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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3118, 3089, 2973, 2866, 1693, 1597, 1539, 1495, 1341, 1277, 1161, 853, 699, 573. **HRMS (ESI):** calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>8</sub>SNa [M + Na]<sup>+</sup> 508.0791, found 508.0793.

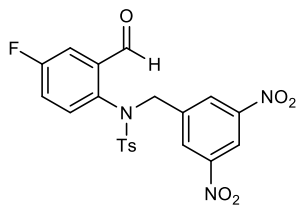


***N*-(4-Bromo-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9d)**

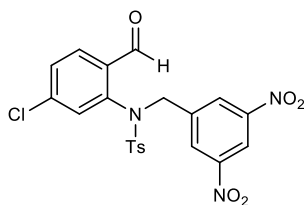
This compound was prepared using *General Procedure D* to afford the title compound as a white solid (0.819 g, 84% yield). **Mp:** 171–172 °C. **TLC:**  $R_F$  = 0.36 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.07 (s, 1H), 8.94 (s, 1H), 8.44 (d,  $J$  = 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3122, 3089, 2866, 1696, 1538, 1475, 1343, 1253, 1161, 1089, 846, 723, 680, 567. **HRMS (ESI):** calcd for C<sub>21</sub>H<sub>16</sub>(<sup>79</sup>Br)N<sub>3</sub>O<sub>7</sub>SNa [M + Na]<sup>+</sup> 555.9790, found 555.9799.

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

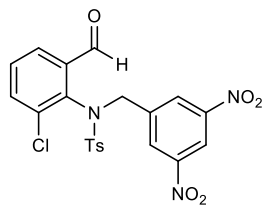
This compound was prepared using *General Procedure D* to afford the title compound as a yellow solid (0.832 g, 81% yield). **Mp:** 180–182 °C. **TLC:**  $R_F$  = 0.30 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  10.07 (s, 1H), 8.93 (t,  $J$  = 2.0 Hz, 1H), 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3093, 2905, 1689, 1539, 1447, 1337, 1211, 1161, 1090, 909, 857, 725, 630, 570. **HRMS (ESI):** calcd for C<sub>21</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>7</sub>S [M – H]<sup>–</sup> 488.03247, found 488.03289.

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

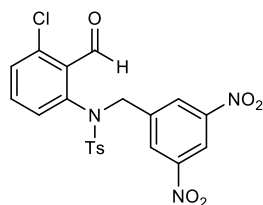
This compound was prepared using *General Procedure D* to afford the title compound as a yellowish solid (0.828 g, 79% yield). **Mp**: 170–174 °C. **TLC**:  $R_F$  = 0.30 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  10.04 (d,  $J$  = 2.8 Hz, 1H), 8.93 (t,  $J$  = 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**:  $\delta$  187.5, 162.4 (d,  $J_{C-F}$  = 252.2 Hz), 148.7, 145.5, 140.0, 137.5 (d,  $J_{C-F}$  = 6.9 Hz), 136.1 (d,  $J_{C-F}$  = 3.4 Hz), 133.6, 130.32 (d,  $J_{C-F}$  = 7.7 Hz), 130.31, 128.8, 128.1, 121.9 (d,  $J_{C-F}$  = 23.2 Hz), 118.4, 116.4 (d,  $J_{C-F}$  = 23.3 Hz), 54.9, 21.8 ppm. **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)**:  $\delta$  –108.2 ppm. **IR (ATR, cm<sup>-1</sup>)**:  $\tilde{\nu}$  3097, 2876, 1691, 1541, 1488, 1342, 1261, 1151, 1057, 883, 771, 674, 577, 535. **HRMS (ESI)**: calcd for C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>7</sub>FS [M – H]<sup>–</sup> 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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3112, 3086, 2872, 1691, 1539, 1344, 1154, 1086, 915, 725, 668, 545. **HRMS (ESI)**: calcd for C<sub>21</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>7</sub>S [M – H]<sup>–</sup> 488.03247, found 488.03285.

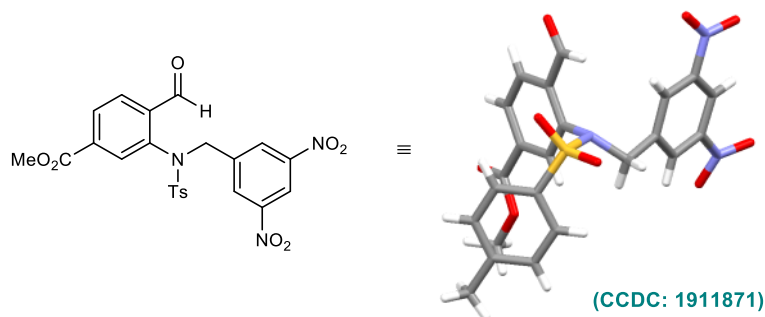
***N*-(2-Chloro-6-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (9h)**

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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3095, 2879, 1685, 1537, 1449, 1343, 1243, 1158, 1086, 918, 856, 727, 658, 565. **HRMS (ESI):** calcd for C<sub>21</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>7</sub>SNa [M + Na]<sup>+</sup> 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). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3121, 3088, 2918, 2772, 1702, 1585, 1449, 1341, 1156, 1087, 905, 828, 726, 657, 578. **HRMS (ESI):** calcd for C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>7</sub>S [M – H]<sup>–</sup> 488.03247, found 488.03282.

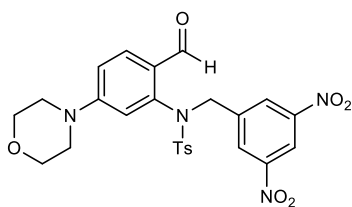
***N*-(5-Carbomethoxy-2-formylphenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (**9j**)**



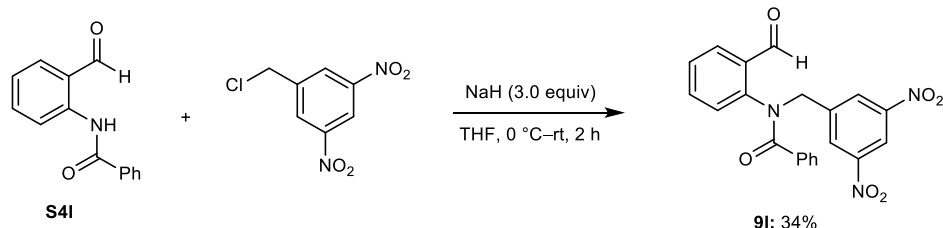
This compound was prepared using *General Procedure D* to afford the title compound as a pale yellow solid (173.1 mg, 45% yield). **Mp**: 162–164 °C. **TLC**:  $R_F$  = 0.26 (35:65 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  10.21 (d,  $J$  = 0.8 Hz, 1H), 8.91 (t,  $J$  = 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>9</sub>SNa [M + Na]<sup>+</sup> 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**.

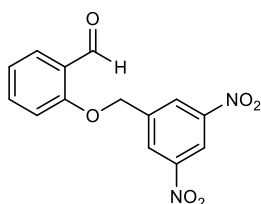
***N*-(2-Formyl-5-morpholinophenyl)-*N*-(3,5-dinitrobenzyl)-4-methylbenzenesulfonamide (**9k**)**



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/CH<sub>2</sub>Cl<sub>2</sub>). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**:  $\delta$  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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**:  $\delta$  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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>25</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub>SNa [M + Na]<sup>+</sup> 563.1213, found 563.1213.

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

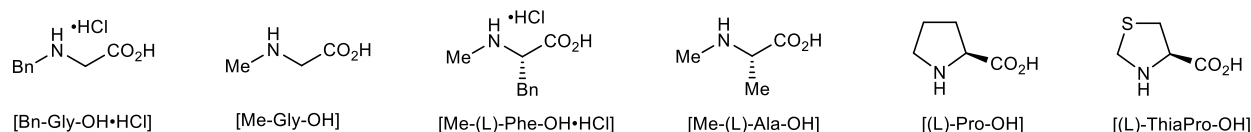
To a solution of NaH (60% in mineral oil, 53.3 mg, 1.33 mmol, 3.0 equiv) in anhydrous THF (4.4 mL) was added aldehyde **S4l** (99.9 mg, 0.44 mmol, 1.0 equiv) at 0 °C. The solution was left to stir at 0 °C for 10 min, before 3,5-dinitrobenzyl chloride (96.3 mg, 0.44 mmol, 1.0 equiv) was added, and the reaction mixture left to stir at room temperature for 2 h. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$ , the aqueous layer extracted with ethyl acetate ( $\times 3$ ), and the combined organic phases dried over  $\text{Na}_2\text{SO}_4$ . 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 **9l** 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).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$ : 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.  **$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**  $\delta$ : 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,  $\text{cm}^{-1}$ )**:  $\tilde{\nu}$  = 1701, 1633, 1531, 1341, 983, 910, 723, 574. **HRMS (ESI)**: calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_6$   $[\text{M} - \text{H}]^-$  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,  $\text{Cs}_2\text{CO}_3$  (1.0 equiv) was used (instead of  $\text{NEt}_3$ ) 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 ( $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$ : 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.  **$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**  $\delta$ : 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,  $\text{cm}^{-1}$ )**:  $\tilde{\nu}$  = 3110, 2890, 2770, 1685, 1597, 1534, 1492, 1344, 1287, 1186, 1154, 908, 870, 763, 728, 649. **HRMS (ESI)**: calcd for  $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_6$   $[\text{M} + \text{H}]^+$  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:

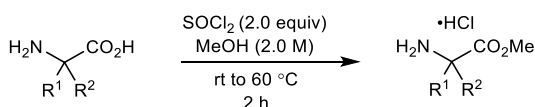


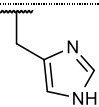
- All other *N*-benzyl- and *N*-methyl amino acid substrates were prepared in the laboratory as described below.

**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:

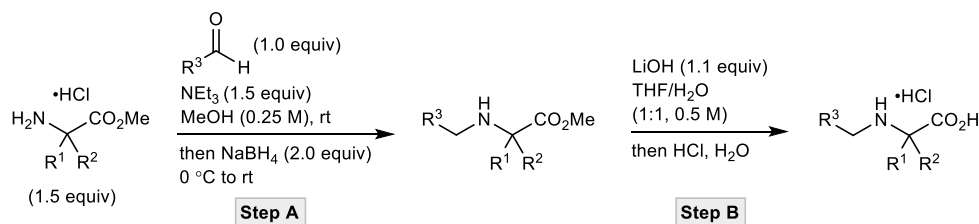


Entry	Starting Material	R <sup>1</sup> , R <sup>2</sup>	Product	Yield (%)
1	-	H, H	H-Gly-OMe·HCl	obtained commercially
2	H-L-Phe-OH	H, Bn	H-L-Phe-OMe·HCl	93
3	H-(D/L)-Phg-OH	H, Ph	H-(D/L)-Phg-OMe·HCl	98
4	H-L-Val-OH	H, <i>i</i> -Pr	H-L-Val-OMe·HCl	92
5	-	H, 	H-L-His-OMe·2HCl	obtained commercially
6	H-Aib-OH	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 SOCl<sub>2</sub> (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 Et<sub>2</sub>O (5 mL) and the resulting precipitate/solid was broken up with a spatula, collected and washed with Et<sub>2</sub>O (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

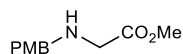
• The required *N*-benzylated amino acids were prepared from the corresponding amino esters by reductive alkylation with benzaldehydes, followed by ester saponification, according to the scheme below. The final products were isolated by trituration (various methods described further on) – differing solubility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



Entry	Starting Material	R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup>	Step A Yield (%) <sup>a</sup>	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

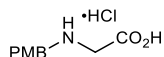
<sup>a</sup> Yield based on aldehyde (R<sup>3</sup>CHO) used for the reductive alkylation.

### *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 N<sub>2</sub> was added NEt<sub>3</sub> (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 NaBH<sub>4</sub> (756.6 mg, 20.00 mmol, 2.0 equiv) was added portionwise over 10 min under a positive pressure of N<sub>2</sub> (H<sub>2</sub> 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 Et<sub>2</sub>O (50 mL, then 30 mL). The aqueous phase was basified to pH 9–10 by the addition of solid Na<sub>2</sub>CO<sub>3</sub> and the product freebase was extracted with Et<sub>2</sub>O (2 × 60 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give PMB-Gly-OMe (1.43 g, 68%, based on 4-methoxybenzaldehyde) as a pale yellow, cloudy oil. **TLC:** *R*<sub>F</sub> = 0.26 (60:40 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** 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.

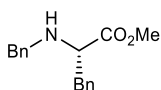
- Note that the above reaction can be performed under air with equal efficiency (see examples below for *Step A*).



**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 Et<sub>2</sub>O (30 mL) and dried to give PMB-Gly-OH·HCl (1.244 g, 79%) as a white solid. **<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):** 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. **<sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD):** δ 168.8, 162.3, 132.7, 123.9, 115.6, 55.8, 51.6, 47.4 ppm.

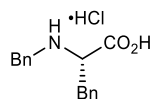
- Note that this reaction produces ‘NMR silent’ LiCl as a stoichiometric by-product. Therefore, trituration of the crude product with *i*-PrOH was performed to remove LiCl from the otherwise pure product.

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



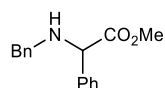
**Step A [Bn-L-Phe-OMe]:** This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe (except that the entire reaction was performed under air) using H-L-Phe-OMe·HCl (1.004 g, 4.66 mmol, 1.5 equiv), MeOH (12.4 mL), NEt<sub>3</sub> (0.65 mL, 4.66 mmol, 1.5 equiv), benzaldehyde (0.32 mL, 3.10 mmol, 1.0 equiv), NaBH<sub>4</sub> (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*<sub>F</sub> = 0.57 (25:75 EtOAc/*n*-hexane).



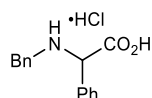


**Step B [Bn-L-Phe-OH·HCl]:** This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OH·HCl using Bn-L-Phe-OMe (682.1 mg, 2.53 mmol, 1.0 equiv), THF (2.5 mL), water (2.5 mL) and LiOH (66.7 mg, 2.79 mmol, 1.1 equiv) with a 4 h reaction time, followed by the addition 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. CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>). The suspension was filtered and the undissolved solids were again subjected to the sonication procedure with CH<sub>2</sub>Cl<sub>2</sub>. 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. **<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):** 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 CD<sub>2</sub>HOD), 3.24 (dd, *J* = 14.3, 7.5 Hz, 1H) ppm. **<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):** 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]**



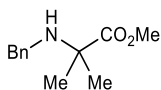
**Step A [Bn-(D/L)-Phg-OMe]:** This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe (except that the entire reaction was performed under air) using H-(D/L)-Phg-OMe·HCl (988.4 mg, 4.90 mmol, 1.5 equiv), MeOH (13.1 mL), NEt<sub>3</sub> (0.68 mL, 4.90 mmol, 1.5 equiv), benzaldehyde (0.33 mL, 3.27 mmol, 1.0 equiv), NaBH<sub>4</sub> (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*<sub>F</sub> = 0.54 (25:75 EtOAc/*n*-hexane).



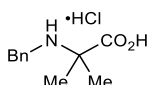
**Step B [Bn-(D/L)-Phg-OH·HCl]:** This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OH·HCl using Bn-(D/L)-Phg-OMe (661.1 mg, 2.59 mmol, 1.0 equiv), THF (2.6 mL), water (2.6 mL) and LiOH (68.2 mg, 2.85 mmol, 1.1 equiv) with a 4 h reaction time, followed by the addition 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. **<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** 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. **<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):** 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]**



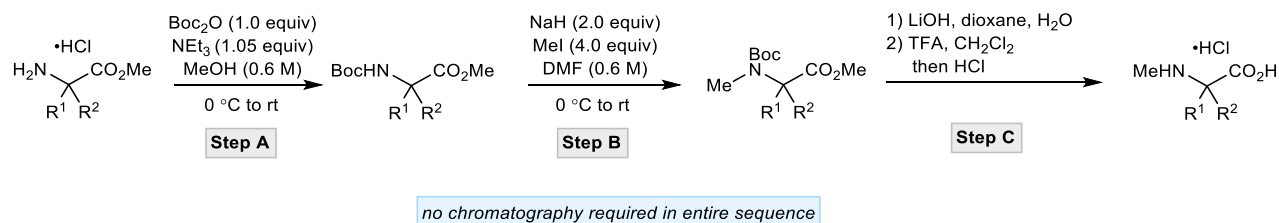
**Step A [Bn-Aib-OMe]:** This reaction was performed according to the above procedure for the synthesis of PMB-Gly-OMe using H-Aib-OMe·HCl (726.9 mg, 4.73 mmol, 1.5 equiv), MeOH (12.6 mL), NEt<sub>3</sub> (0.66 mL, 4.73 mmol, 1.5 equiv), benzaldehyde (0.32 mL, 3.15 mmol, 1.0 equiv), NaBH<sub>4</sub> (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*<sub>F</sub> = 0.62 (40:60 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 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. **<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):** δ 7.59–7.56 (m, 2H), 7.50–7.45 (m, 3H), 4.22 (s, 2H), 1.71 (s, 6H) ppm. **<sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD):** δ 173.5, 132.9, 131.3, 130.7, 130.2, 63.7, (CH<sub>2</sub> overlapping with solvent peak between 49.5–48.5), 22.6 ppm. **IR (ATR, cm<sup>-1</sup>):**  $\tilde{\nu}$  = 2722, 2565, 2394, 1751, 1562, 1454, 1396, 1196, 1152, 973, 844, 762, 742, 697, 607, 531, 499, 375. **HRMS (ESI):** calcd for C<sub>11</sub>H<sub>16</sub>NO<sub>2</sub> [M + H]<sup>+</sup> 194.1181, found 194.1178.

### 4.3. Synthesis of *N*-Methylated Amino Acids

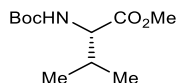
• The required *N*-methylated amino acids were prepared according to the scheme below. This sequence provides the products in reasonable overall yields without any requirement for chromatography or recrystallisation. An exception was *N*-methyl-2-phenylglycine hydrochloride [Me-Phg-OH·HCl] which could 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.



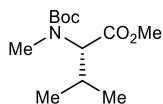
• **Note:** In entries 2 and 4, R<sup>1</sup> and/or R<sup>2</sup> (above) do not stay constant. Therefore, the actual structures of the intermediates and products have been drawn in the table.

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 <sup>a</sup> (91%) <sup>a</sup>	 (38%) <sup>b</sup>	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%) <sup>c</sup>	Me-(D/L)-(α-Me)-Phg-OH·HCl

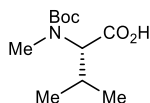
<sup>a</sup> Using Boc<sub>2</sub>O (2.0 equiv) and NEt<sub>3</sub> (2.1 equiv). Yield is of the doubly *N*-Boc-protected intermediate as an inconsequential 4.3:1 mixture of regioisomers with respect to the regiochemistry of the imidazole *N*-Boc group (structure of major/minor regioisomer undetermined). <sup>b</sup> Final Boc-deprotection performed with HCl instead of TFA. <sup>c</sup> Both *N*- and *C*-methylation occurred with NaH/MeI giving the fully substituted product.

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

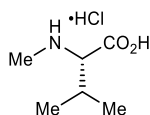
**Step A** [*Boc-L-Val-OMe*]: To a solution/suspension of H-L-Val-OMe·HCl (502.9 mg, 3.00 mmol, 1.0 equiv) and NEt<sub>3</sub> (0.44 mL, 3.15 mmol, 1.05 equiv) in reagent grade MeOH (2.5 mL) at 0 °C under air was added a solution of Boc<sub>2</sub>O (654.7 mg, 3.00 mmol, 1.0 equiv) in MeOH (2.5 mL) and the mixture was allowed to warm to room temperature with stirring over 13 h. CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added and stirring continued at room temperature for a further 6 h. The solvents were then removed under reduced pressure. Et<sub>2</sub>O (20 mL) and 1 M aqueous HCl (15 mL) were added and the layers separated. The organic phase was washed with 1 M K<sub>2</sub>CO<sub>3</sub> (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give Boc-L-Val-OMe (586.3 mg, 84%) as a colorless oil, which contained 9 mol% of unreacted Boc<sub>2</sub>O as an impurity. This material was used in the next step without complications. **TLC:** *R*<sub>F</sub> = 0.43 (15:85 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ (excluding residual Boc<sub>2</sub>O) 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.



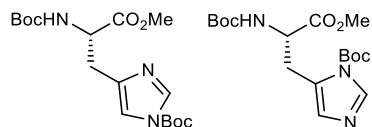
**Step B** [*(Boc,Me)-L-Val-OMe*]: To a solution of Boc-L-Val-OMe (574.4 mg, 2.48 mmol, 1.0 equiv, containing 9 mol% of Boc<sub>2</sub>O as an impurity) in anhydrous DMF (4.1 mL) in a Schlenk flask under N<sub>2</sub> at 0 °C was added MeI (0.62 mL, 9.93 mmol, 4.0 equiv). Under a positive pressure of N<sub>2</sub>, 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 (H<sub>2</sub> 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 NH<sub>4</sub>Cl (10 mL). The product was extracted with Et<sub>2</sub>O (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*<sub>F</sub> = 0.51 (15:85 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 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.



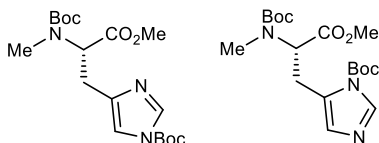
**Step C [(Boc,Me)-L-Val-OH]: Part 1: saponification.** A solution of ‘crude’ (Boc,Me)-L-Val-OMe (547.5 mg total, containing  $\leq 2.23$  mmol, 1.0 equiv) and LiOH (532.3 mg, 22.23 mmol,  $\geq 10$  equiv) in dioxane (6.7 mL) and water (4.4 mL) was heated at 50 °C under air for 45 min, then cooled to 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  $\text{CH}_2\text{Cl}_2$  (11.2 mL) and water (0.20 mL, 11.15 mmol,  $\geq 5$  equiv) and TFA (1.71 mL, 22.23 mmol,  $\geq 10$  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 ( $\geq 5$  min) under high vacuum to remove residual TFA. The residue was re-dissolved in  $\text{CH}_2\text{Cl}_2$ /*i*-PrOH (1:1, 6 mL) and the solution was transferred to a vial of known weight. With stirring, ethereal HCl (2 M in  $\text{Et}_2\text{O}$ , 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  $\text{Et}_2\text{O}$ /*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  $\text{Et}_2\text{O}$ /*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  $\text{Boc}_2\text{O}$  in the original starting material) as an off-white solid.  **$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  3.86 (d,  $J$  = 3.8 Hz, 1H), 2.75 (s, 3H), 2.35 (sepd,  $J$  = 7.0, 3.8 Hz, 1H), 1.15 (d,  $J$  = 7.0 Hz, 3H), 1.07 (d,  $J$  = 6.9 Hz, 3H) ppm.  **$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  170.1, 67.9, 33.4, 30.4, 19.2, 17.5 ppm.

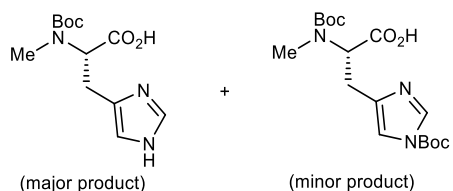
**(S)-N-Methyl-histidine dihydrochloride** [Me-L-His-OH·2HCl]4.3:1 mixture of *N*-Boc regioisomers

**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 NEt<sub>3</sub> (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 Boc<sub>2</sub>O (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. Et<sub>2</sub>O (40 mL) and water (40 mL) were added and the layers separated. The organic phase was washed with saturated NaHCO<sub>3</sub> (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give Boc-L-His(*Boc*)-OMe (3.379 g, 91%) as a colorless gum. Consistent with previous reports,<sup>S18</sup> 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*<sub>F</sub> = 0.34 [major], 0.22 [minor] (50:50 EtOAc/*n*-hexane). **Major regioisomer:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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

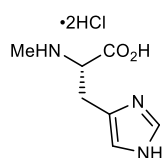
**Step B** [(*Boc*,Me)-L-His(*Boc*)-OMe]: This reaction was performed according to the above procedure for the synthesis of (*Boc*,Me)-L-Val-OMe using Boc-L-His(*Boc*)-OMe (3.379 g, 9.15 mmol, 1.0 equiv), anhydrous DMF (15.2 mL), MeI (2.28 mL, 36.59 mmol, 4.0 equiv) and NaH (731.7 mg of 60% suspension = 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 NH<sub>4</sub>Cl (30 mL) over ~2 min. The product was extracted with Et<sub>2</sub>O (60 mL). The organic layer was washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) 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*<sub>F</sub> = 0.31 (50:50 EtOAc/*n*-hexane). **Major regioisomer:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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 Et<sub>2</sub>O (40 mL, then 20 mL) and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) 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. **<sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):**  $\delta$  (~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.

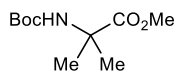
The aqueous layer (pH 4–5) was concentrated under reduced pressure to give the *major product* [(Boc,Me)-L-His-OH] (1.327 g) which was necessarily contaminated with the LiCl by-product. It was also uncertain whether this material was the HCl salt (protonated by HCl at imidazole) or the neutral zwitterion (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). **<sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):**  $\delta$  (~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

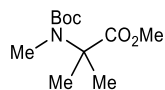
air for 19 h, then sonicated at room temperature for 5 min. The supernatant liquid was decanted from the immobilized solids [the supernatant was concentrated to give 91.0 mg of a white solid; theoretical maximum amount of LiCl present = 195.4 mg]. To ensure most (or all) of the LiCl was removed, MeOH (4 mL) was added to the THF-insoluble material in the original flask and to the resulting free suspension was rapidly added Et<sub>2</sub>O (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<sup>+</sup> 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. **<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** 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. **<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):** 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]**

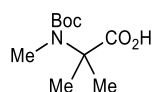


**Step A [Boc-Aib-OMe]:** This reaction was performed according to the above procedure for the synthesis of Boc-L-Val-OMe using H-Aib-OMe·HCl (315.0 mg, 2.05 mmol, 1.0 equiv), NEt<sub>3</sub> (0.30 mL, 2.15 mmol, 1.05 equiv), Boc<sub>2</sub>O (447.6 mg, 2.05 mmol, 1.0 equiv) and MeOH (2 × 1.7 mL) with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

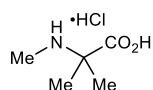




**Step B [(Boc,Me)-Aib-OMe]:** This reaction was performed according to the above procedure for the synthesis of (Boc,Me)-L-Val-OMe using Boc-Aib-OMe (328.3 mg, 1.51 mmol, 1.0 equiv), anhydrous DMF (2.5 mL), MeI (0.38 mL, 6.04 mmol, 4.0 equiv) and NaH (120.9 mg of 60% suspension = 72.5 mg of NaH, 3.02 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,  $\text{CDCl}_3$ ):**  $\delta$  3.70 (s, 3H), 2.91 (s, 3H), 1.430 (s, 6H), 1.425 (s, 9H) ppm.

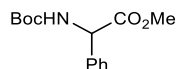


**Step C [(Boc,Me)-Aib-OH]: Part 1: saponification.** A solution of ‘crude’ (Boc,Me)-Aib-OMe (487.7 mg total, containing  $\leq 1.51$  mmol, 1.0 equiv) and LiOH (361.6 mg, 15.10 mmol,  $\geq 10$  equiv) in dioxane (4.5 mL) and water (3.0 mL) was heated at 50 °C under air for 45 min, then cooled to rt 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).

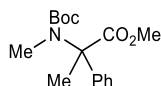


**Step C [Me-Aib-OH·HCl]: Part 2: Boc deprotection.** This reaction was performed according to the procedure above for the synthesis of Me-L-Val-OH·HCl using (Boc,Me)-Aib-OH (189.8 mg, 0.87 mmol, 1.0 equiv),  $\text{CH}_2\text{Cl}_2$  (4.4 mL), water (78  $\mu\text{L}$ , 4.33 mmol,  $\geq 5$  equiv) and TFA (0.67 mL, 8.76 mmol,  $\geq 10$  equiv). Work-up, then treatment with ethereal HCl (2 M in  $\text{Et}_2\text{O}$ , 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,  $\text{CD}_3\text{OD}$ ):**  $\delta$  2.68 (s, 3H), 1.59 (s, 6H) ppm.  **$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  173.6, 62.7, 28.4, 21.8 ppm.

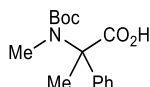
- In this case, further purification of the final product by trituration with  $\text{Et}_2\text{O}/n$ -hexane (1:1, 8 mL) was not required because trituration had been performed in the previous saponification step (thus removing the grease carried over from the NaH).

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

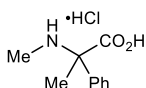
**Step A** [*Boc*-(D/L)-Phg-OMe]: This reaction was performed according to the above procedure for the synthesis of Boc-L-Val-OMe using H-(D/L)-Phg-OMe·HCl (552.6 mg, 2.74 mmol, 1.0 equiv), NEt<sub>3</sub> (0.40 mL, 2.88 mmol, 1.05 equiv), Boc<sub>2</sub>O (598.1 mg, 2.74 mmol, 1.0 equiv) and MeOH (2 × 2.3 mL) with a 19 h reaction time (note that no CH<sub>2</sub>Cl<sub>2</sub> 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*<sub>F</sub> = 0.35 (15:85 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** 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*<sub>F</sub> = 0.40 (15:85 EtOAc/*n*-hexane).

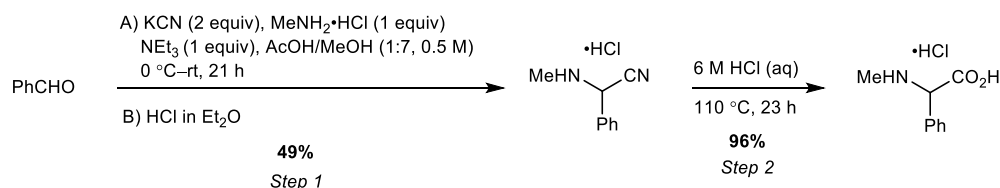


**Step C** [(*Boc,Me*)-(D/L)-(α-Me)-Phg-OH]: **Part 1: saponification.** A solution of ‘crude’ (Boc,Me)-(D/L)-(α-Me)-Phg-OMe (containing ≤2.00 mmol, 1.0 equiv) and LiOH (239.5 mg, 10.00 mmol, ≥5 equiv) in reagent grade THF (2.0 mL) and water (2.0 mL) was stirred at room temperature under air for 42 h. 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 (Na<sub>2</sub>SO<sub>4</sub>) 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), CH<sub>2</sub>Cl<sub>2</sub> (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 Et<sub>2</sub>O, 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 Et<sub>2</sub>O/*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 Et<sub>2</sub>O/*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. **<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** δ 7.59–7.50 (m, 5H), 2.45 (s, 3H), 2.02 (s, 3H) ppm. **<sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):** δ 172.9, 134.7, 131.3, 130.6, 127.9, 67.8, 28.3, 18.3 ppm. **IR (ATR, cm<sup>-1</sup>):**  $\tilde{\nu}$  = 2864, 2750, 2729, 2574, 2440, 1729, 1586, 1454, 1368, 1218, 1194, 1121, 1049, 836, 716, 693, 653, 558, 360. **HRMS (ESI):** calcd for C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub> [M + H]<sup>+</sup> 180.1025, found 180.1033.

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



**Step 1:** Based on a literature procedure,<sup>S19</sup> 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 MeNH<sub>2</sub>·HCl (337.6 mg, 5.00 mmol, 1.0 equiv, dried in a 120 °C oven before use) and NEt<sub>3</sub> (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 K<sub>2</sub>CO<sub>3</sub> (50 mL) was slowly added, followed by water (30 mL). The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic layer was washed with saturated NaHCO<sub>3</sub> (30 mL) and brine (30 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give a yellow oil (freebase of product with minor impurities). This was taken up in Et<sub>2</sub>O (15 mL) and ethereal HCl (2 M in Et<sub>2</sub>O, 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 Et<sub>2</sub>O (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

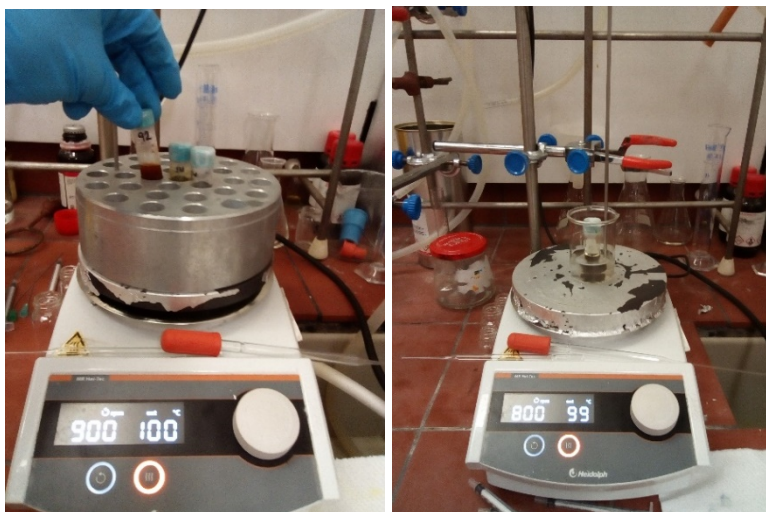
salt (448.8 mg, 49%) as a pale yellow gum which solidified on standing overnight. <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 7.78–7.71 (m, 2H), 7.58–7.51 (m, 3H), 6.06 (s, 1H), 2.58 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) δ 130.8, 129.34, 129.30, 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 Et<sub>2</sub>O (20 mL) and broken up with a spatula. The suspension was sonicated for ~2 min. The solid was collected by filtration, washed with Et<sub>2</sub>O (40 mL) and dried to give Me-(D/L)-Phg-OH·HCl (456.1 mg, 96%) as a pale yellow solid. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.53–7.51 (m, 5H), 5.08 (s, 1H), 2.63 (s, 3H) ppm. <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD): 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**

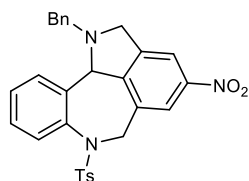
### **5.1. General Points and Observations**

- The anhydrous toluene used for the cycloaddition was sparged with N<sub>2</sub> for ~30 min and stored under N<sub>2</sub>. 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.

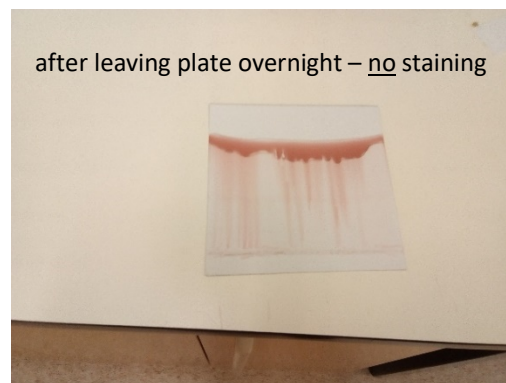
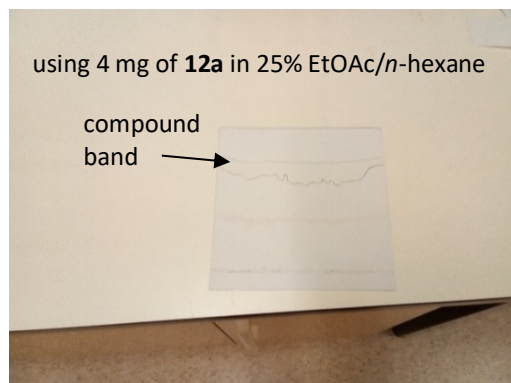
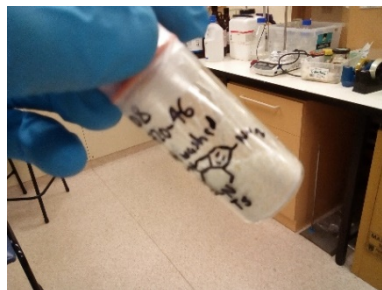


- The products **12** are poorly soluble in EtOAc/*n*-hexane and although TLC analyses proceeded without complications with this developing system, attempts to use an EtOAc/*n*-hexane binary solvent system as the eluent for flash chromatography consistently gave poor results. For example, when minimal CH<sub>2</sub>Cl<sub>2</sub> (<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<sub>F</sub>* **12a** = 0.22) significant ‘fronting’ (i.e., immediate partial elution) of the product was observed due to apparent carry-through with the CH<sub>2</sub>Cl<sub>2</sub>. This appeared to be an anomalous solubility effect, as running a column with CH<sub>2</sub>Cl<sub>2</sub> 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 NEt<sub>3</sub> 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**).



**12a**: white solid

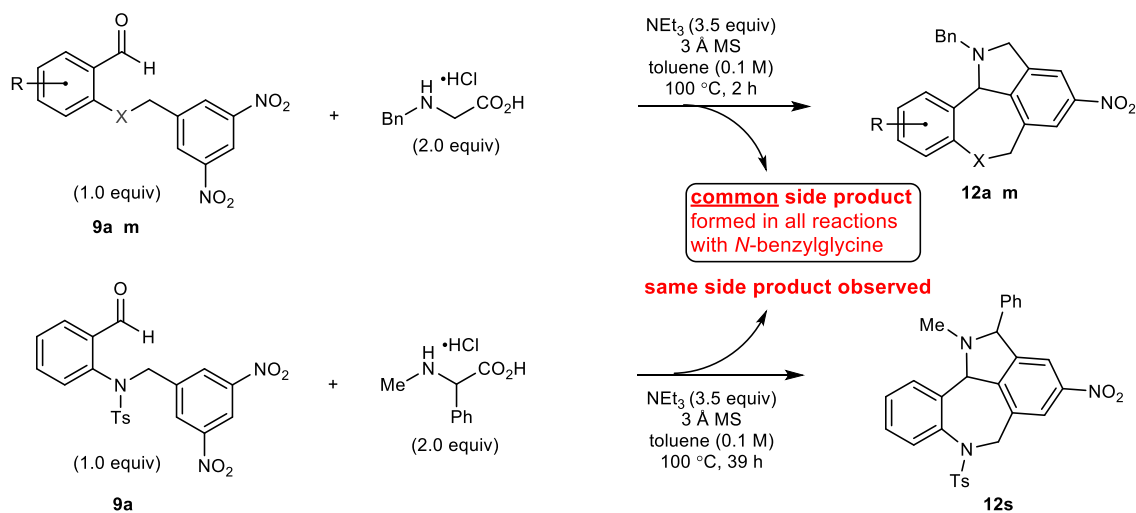


- Related to the above points, oxidation/degradation of the products (**12**) appeared to be catalyzed/accelerated to some extent by silica gel. However, this effect appeared to be largely dependent on the solvent system used, especially for preparative work (i.e., flash chromatography). For instance, 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 CH<sub>2</sub>Cl<sub>2</sub> under otherwise identical conditions did not cause any measurable degradation/oxidation. The obvious solubility and stability benefit of performing flash chromatography with CH<sub>2</sub>Cl<sub>2</sub> 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 N<sub>2</sub> (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.

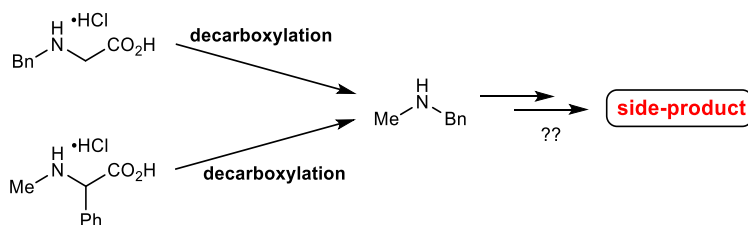
- Once purified and obtained as solids, the products (**12**) have not shown any evidence of decomposition or oxidation to the isoindole. Products are typically stored in capped vials under air in a freezer, but samples left in capped vials at room temperature for extended periods (e.g., 7 days) likewise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

## 5.2. Notes on Unidentified Side Product Derived from *N*-Benzylglycine (and *N*-methyl- $\alpha$ -phenylglycine)

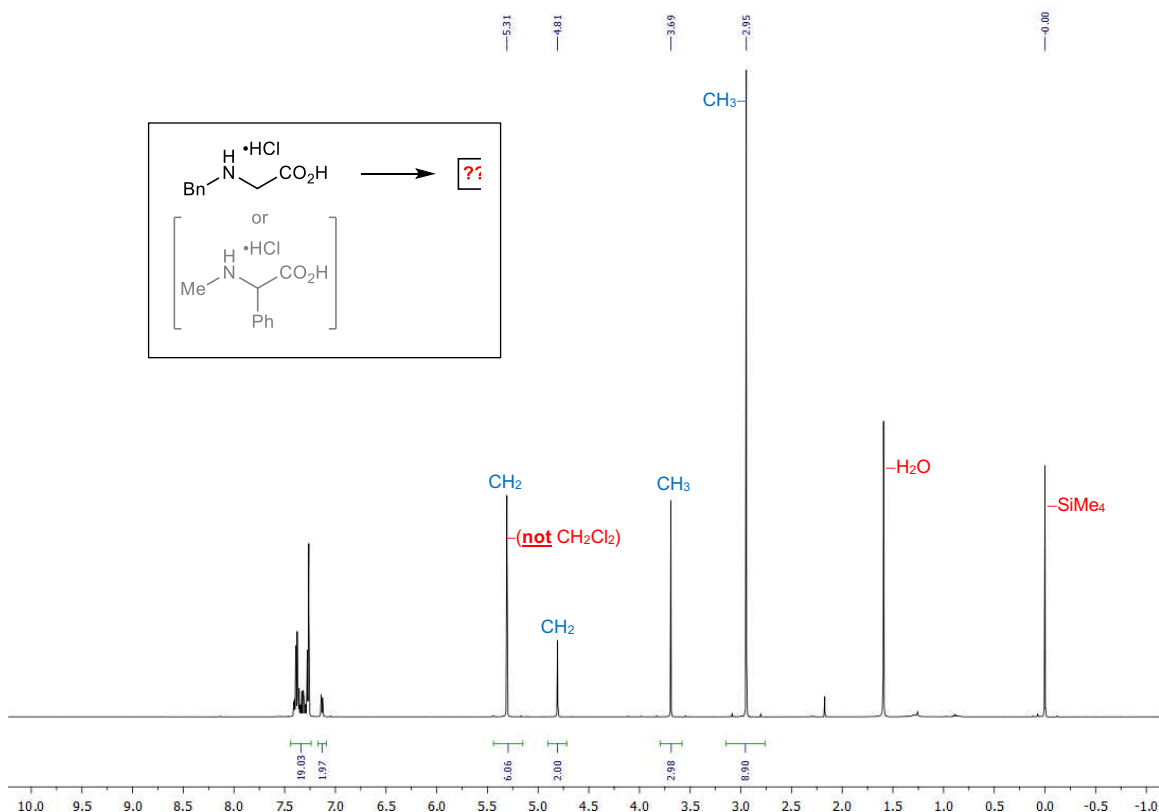
- In all reactions with *N*-benzylglycine, regardless of the identity of the benzaldehyde (**9**) used, the same unidentified side product derived solely from the amino acid was observed. This side product typically co-eluted (to some extent) with **12** during flash chromatography which was the main 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- $\alpha$ -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:

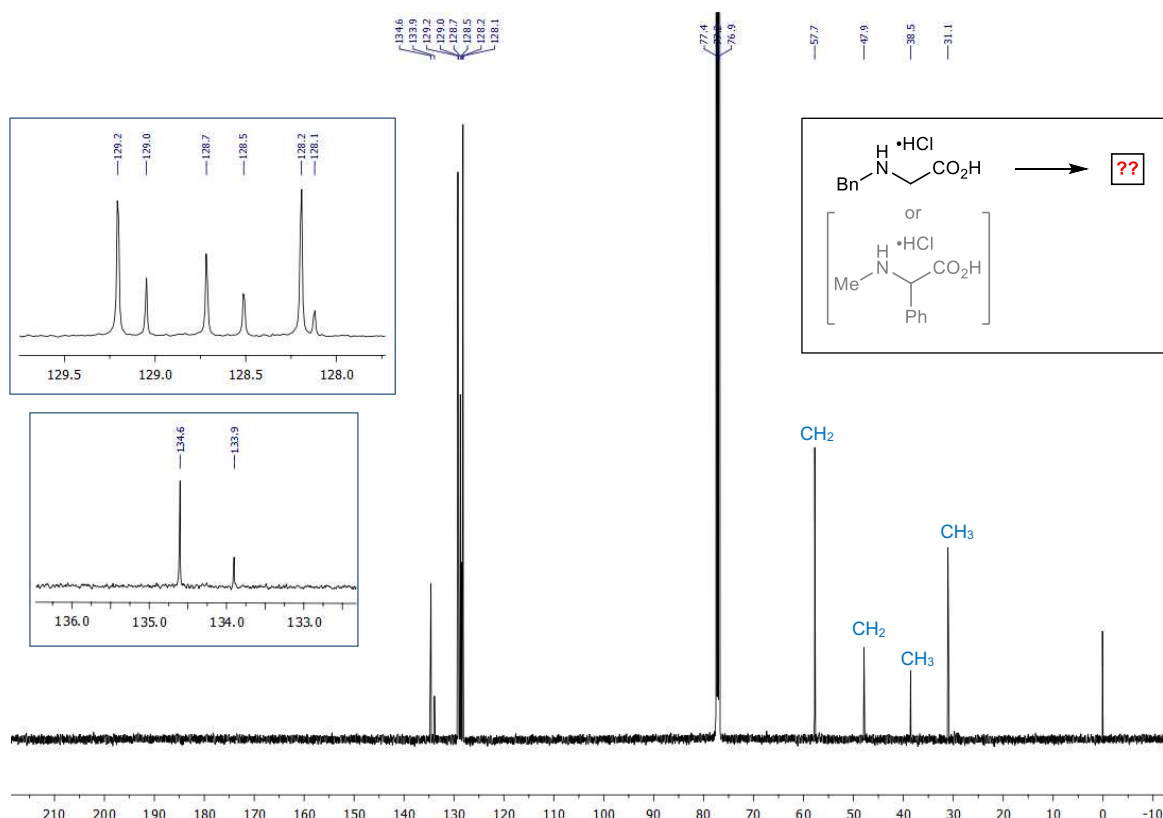


- In one case, the side product was isolated cleanly and quantitatively (3.0 mg) by flash chromatography during the purification of **12k** (the lower  $R_F$  value of **12k** compared to most other products enabled earlier elution of the pure side product). See Section 5.4.2 for details, as well as 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)
- $^1\text{H}$  NMR spectrum of the persistent, unidentified side product (3.0 mg) in  $\text{CDCl}_3$  (500 MHz):

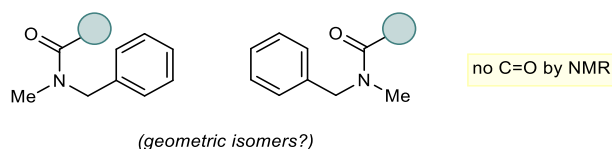




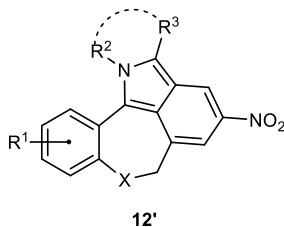
- $^{13}\text{C}$  NMR spectrum of the persistent, unidentified side product (3.0 mg) in  $\text{CDCl}_3$  (125 MHz):



- 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  $\text{CH}_2$  and  $\text{CH}_3$  peaks (NMR above). However, no carbonyl peak was observed by  $^{13}\text{C}$  NMR, ruling out this possibility:

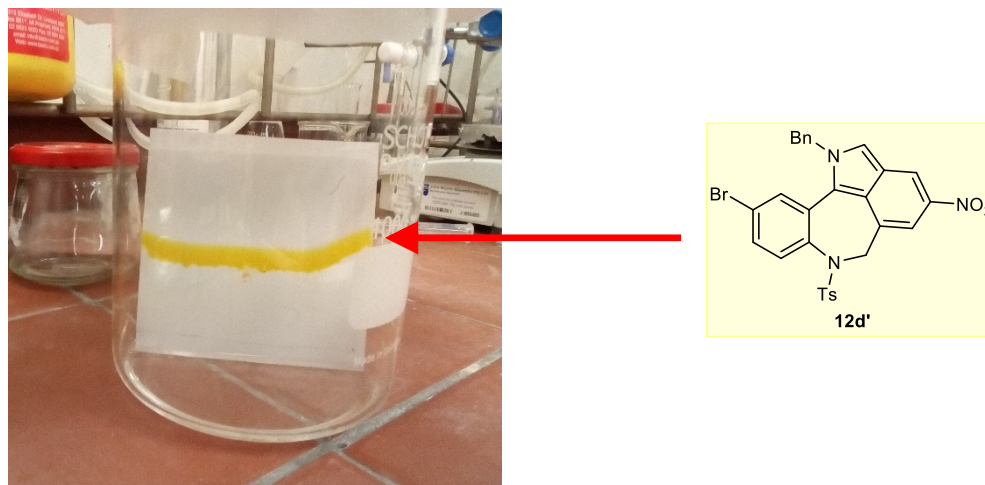


### 5.3. Notes on Isoindole Side Product (12')



- 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.<sup>S20</sup> For our system, all

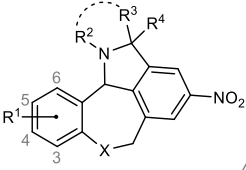
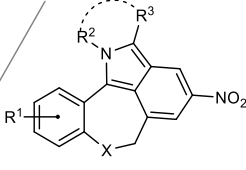
reactions were carried out under N<sub>2</sub> and in several cases the corresponding isoindole form of **12** (**12'**), was observed as a minor side product. This isoindole scaffold exhibited a bright yellow to red color, consistent with previously reported nitro-substituted isoindoles.<sup>S20</sup> The isoindole (**12'**) typically has a higher polarity (i.e., lower *R<sub>F</sub>*) 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 image below shows the typical color of an isoindole side product on TLC.



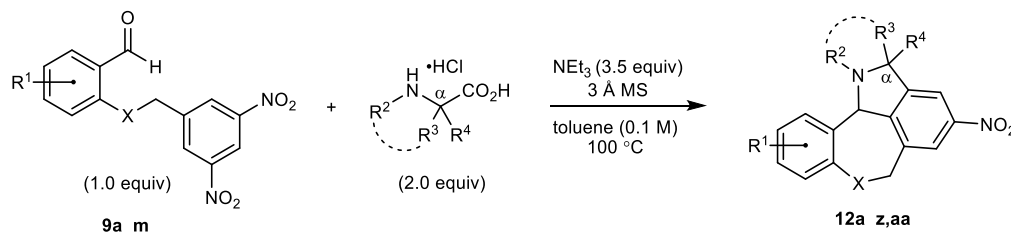
- The ratio isoindoline/isoindole (**12:12'**) in all crude samples directly after work-up (filtration only) was quantified by <sup>1</sup>H NMR spectroscopy and are listed in the table below (Section 5.3.1). The propensity for **12** to undergo (partial) oxidation during the reaction was dependent on 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 <sup>1</sup>H 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 <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Crude ratio 12:12'	
							 12	 12' (where R <sup>4</sup> = 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 <sub>2</sub> Me	Bn	H	H	2.8:1	
10	12k	NTs	4-morpho- lino	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		
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		
23	12y	NTs	H	Me	Me	Ph	oxidation to 12' not possible	
24	12z	NTs	H	–CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> –	H	H	10.0:1	
25	12aa	NTs	H	–CH <sub>2</sub> –S–CH <sub>2</sub> –	H	H	7.1:1	

## 5.4. Cycloaddition Experimental



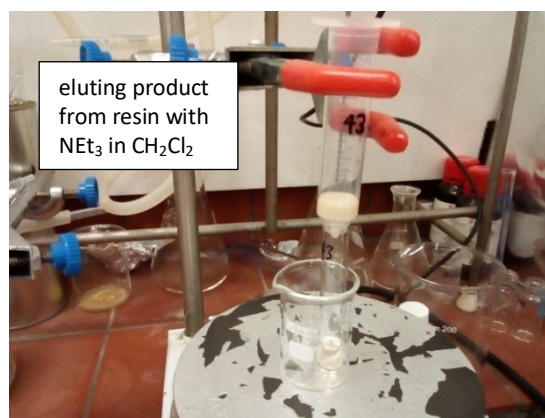
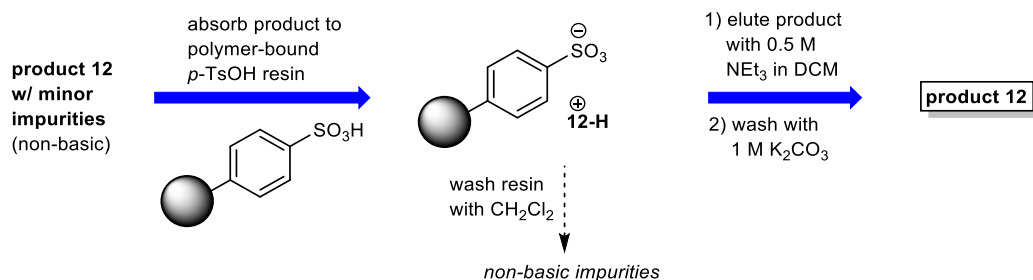
**Note:** A detailed experimental procedure for the larger scale example (product **12b**, 4 mmol scale) is also given in Section 6.

**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 N<sub>2</sub> via an outlet needle. The outlet needle was removed and anhydrous, deoxygenated toluene (1.0 mL, 0.1 M) was then added, followed by NEt<sub>3</sub> (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 N<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and filtered. The reaction vial and the filter cake were rinsed with further CH<sub>2</sub>Cl<sub>2</sub> (5 × 2 mL), then the filtrate was concentrated under reduced pressure. The residue was analyzed by <sup>1</sup>H 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 CH<sub>2</sub>Cl<sub>2</sub>-based eluent under a positive pressure of N<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (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<sub>F</sub>* 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 CH<sub>2</sub>Cl<sub>2</sub>-rinse (20 mL). The dry resin was washed with further CH<sub>2</sub>Cl<sub>2</sub> (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 NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (~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

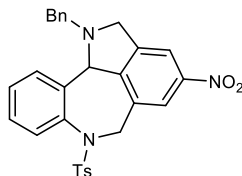
product was then concentrated under reduced pressure to dryness. The residue, which contained what appeared to be  $\text{NEt}_3$  salt impurities by NMR (but not free  $\text{NEt}_3$  nor  $\text{NEt}_3 \cdot p\text{-TsOH}$ ) was taken back up in  $\text{CH}_2\text{Cl}_2$  (20 mL) and washed with 1 M  $\text{K}_2\text{CO}_3$  (25 mL). The aqueous phase was back-extracted with  $\text{CH}_2\text{Cl}_2$  (15 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) 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  $\text{CH}_2\text{Cl}_2$  (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 °C,  $\geq 200$  mbar) to selectively remove the  $\text{CH}_2\text{Cl}_2$ . 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**.

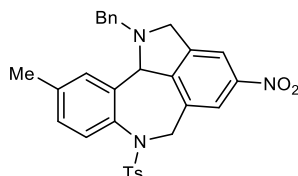
### 5.4.2. Products from Benzaldehyde Scope (12a–m)

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



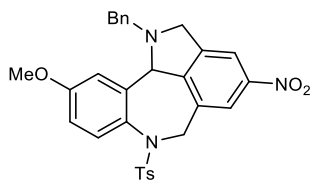
This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and further purification with polymer-bound *p*-TsOH (*General Procedure E'*) gave **12a** (37.7 mg, 74%) as a white solid. **Mp**: 121–125 °C. **TLC**:  $R_F$  = 0.51 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3099, 3030, 2922, 2829, 1598, 1526, 1482, 1342, 1159, 1091, 895, 785, 702, 572. **HRMS (ESI)**: calcd for C<sub>29</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 512.16440, found 512.16374.

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



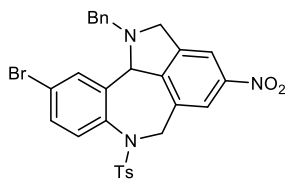
This compound was prepared according to *General Procedure E* using aldehyde **9b** (46.9 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and further purification with polymer-bound *p*-TsOH (*General Procedure E'*) gave **12b** (42.0 mg, 80%) as a pale yellow solid. **Mp**: 205–209 °C. **TLC**:  $R_F$  = 0.59 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3034, 2921, 2852, 2795, 1599, 1528, 1496, 1342, 1157, 1116, 866, 746, 695, 612, 537. **HRMS (ESI)**: calcd for C<sub>30</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 526.1801, found 526.1812.

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



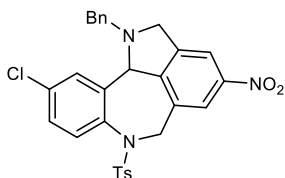
This compound was prepared according to *General Procedure E* using aldehyde **9c** (48.5 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12c** (39.0 mg, 72%) as a pale yellow solid. **Mp**: 216–218 °C. **TLC**: *R*<sub>F</sub> = 0.53 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3068, 3031, 2921, 2851, 2798, 1725, 1600, 1523, 1491, 1334, 1091, 902, 839, 810, 667, 525. **HRMS (ESI)**: calcd for C<sub>30</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub>SNa [M + Na]<sup>+</sup> 564.1569, found 564.1567.

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



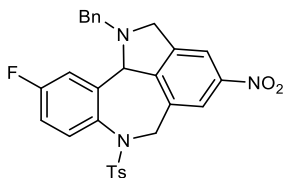
This compound was prepared according to *General Procedure E* using aldehyde **9d** (53.4 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12d** (39.9 mg, 68%) as a yellow solid. **Mp**: 207–209 °C. **TLC**: *R*<sub>F</sub> = 0.70 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3078, 3030, 2921, 2851, 2787, 1751, 1523, 1453, 1336, 1154, 1095, 864, 767, 687, 575. **HRMS (ESI)**: calcd for C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>S(<sup>79</sup>Br) [M + H]<sup>+</sup> 590.0749, found 590.0762.

**(±)-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 (CH<sub>2</sub>Cl<sub>2</sub>) 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*<sub>F</sub> = 0.58 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3081, 3030, 2922, 2801, 1718, 1523, 1350, 1324, 1268, 1154, 1090, 813, 722, 658, 578, 544. **HRMS (ESI)**: calcd for C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>SCl [M + H]<sup>+</sup> 546.1254, found 546.1230.

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

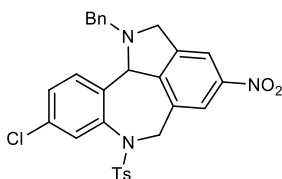


This compound was prepared according to *General Procedure E* using aldehyde **9f** (47.3 mg, 0.10 mmol) and Bn-Gly-OH·HCl (40.3 mg, 0.20 mmol) with a 2 h reaction time. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and further purification with polymer-bound *p*-TsOH (*General Procedure E*) gave **12f** (33.2 mg, 63%) as a yellow solid. **Mp**: 206–209 °C. **TLC**: *R*<sub>F</sub> = 0.59 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: δ ([164.2, 162.3], d, *J*<sub>C-F</sub> = 249.0 Hz), 148.2, ([145.1, 145.0], d, *J*<sub>C-F</sub> = 8.2 Hz), 144.2, 143.1, 141.6, 138.2, 138.1, 134.4, ([133.04, 133.02], d, *J*<sub>C-F</sub> = 2.7 Hz), ([130.73, 130.66], d, *J*<sub>C-F</sub> = 8.8 Hz), 130.1, 128.9, 128.5, 127.7, 127.3, 120.6, 116.4, ([115.3, 115.2], d, *J*<sub>C-F</sub> = 23.9 Hz), ([113.6, 113.4], d, *J*<sub>C-F</sub> = 24.9 Hz), 67.4, 59.2, 57.8, 50.6, 21.7 ppm. **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)**: δ –109.8 ppm. **IR (ATR, cm<sup>-1</sup>)**:  $\tilde{\nu}$  = 2887, 2811,



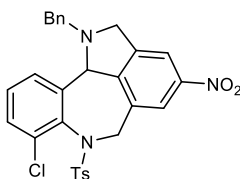
1593, 1530, 1483, 1343, 1314, 1290, 1259, 1157, 1120, 1087, 967, 903, 866, 811, 754, 734, 701, 667, 614, 591, 559, 532, 484. **HRMS (ESI):** calcd for  $C_{29}H_{25}FN_3O_4S$   $[M + H]^+$  530.1550, found 530.1537.

**(±)-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,  $CDCl_3$ ):**  $\delta$  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,  $CDCl_3$ ):**  $\delta$  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.

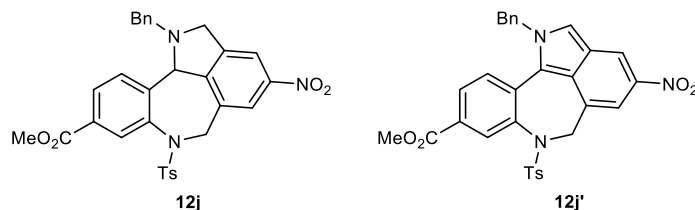
**(±)-10-Benzyl-6-chloro-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12h)**



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,  $CDCl_3$ ):**  $\delta$  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,  $CDCl_3$ ):**  $\delta$  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**

$\text{cm}^{-1}$ ):  $\tilde{\nu}$  = 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.

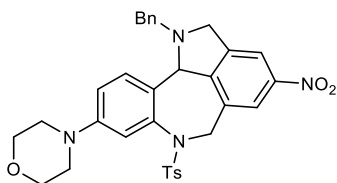
( $\pm$ )-10-Benzyl-7-carbomethoxy-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (**12j**) and 10-Benzyl-7-carbomethoxy-2-nitro-5-tosyl-5,10-dihydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (**12j'**)



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,  $\text{CDCl}_3$ )**:  $\delta$  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,  $\text{CDCl}_3$ )**:  $\delta$  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,  $\text{cm}^{-1}$ )**:  $\tilde{\nu}$  = 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.

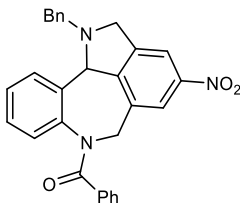
Further elution (0:100 to 1:99 EtOAc/ $\text{CH}_2\text{Cl}_2$ ) gave **12j'** (6.7 mg, 12%) as a bright orange/red solid. **Mp**: 165–170 °C. **TLC**:  $R_F$  = 0.26 (35:65 EtOAc/ $n$ -hexane).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  8.42–8.39 (m, 2H), 7.92 (dd,  $J$  = 8.3, 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,  $\text{CDCl}_3$ )**:  $\delta$  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,  $\text{cm}^{-1}$ )**:  $\tilde{\nu}$  = 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.

(±)-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 (CH<sub>2</sub>Cl<sub>2</sub>) 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/CH<sub>2</sub>Cl<sub>2</sub>) gave **12k** (35.5 mg, 59%) as an off-white solid. **Mp**: 220–232 °C. **TLC**:  $R_F$  = 0.56 (5:95 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>33</sub>H<sub>33</sub>N<sub>4</sub>O<sub>5</sub>S [M + H]<sup>+</sup> 597.2172, found 597.2182.

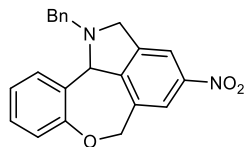
(±)-10-Benzyl-2-nitro-5-benzoyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (**12l**)



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), NEt<sub>3</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>/*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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>):**  $\tilde{\nu}$  = 2800, 1646, 1522, 1483, 1454, 1378, 1340, 1298, 1258, 1153, 1078, 906, 778, 731, 698, 588, 483. **HRMS (ESI):** calcd for C<sub>29</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 462.1818, found 462.1812.

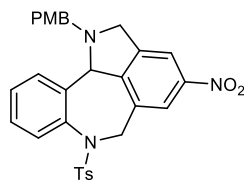
**(±)-10-Benzyl-2-nitro-4,9b,10,11-tetrahydrobenzo[6,7]oxepino[5,4,3-*cd*]isoindole (12m)**



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 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane) gave **12m** (8.8 mg, 25%) as a white solid. **Mp:** 130–134 °C. **TLC:** *R*<sub>F</sub> = 0.57 (75:25 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 3056, 1701, 1529, 1481, 1343, 1266, 1222, 1045, 895, 773, 734, 699. **HRMS (ESI):** calcd for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na [M + Na]<sup>+</sup> 381.1215, found 381.1227.

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

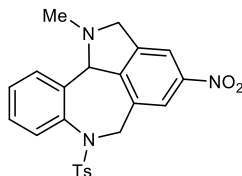
**(±)-10-(4-Methoxybenzyl)-2-nitro-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (12n)**



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 (CH<sub>2</sub>Cl<sub>2</sub>) 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*<sub>F</sub> = 0.54 (30:70 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  159.0, 147.9,

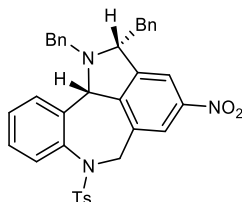
144.1, 143.9, 141.9, 141.6, 138.4, 137.5, 134.5, 130.4, 130.1, 129.63, 129.57, 128.59, 128.56, 127.2, 126.0, 120.5, 116.3, 114.2, 67.4, 58.4, 57.6, 55.5, 50.7, 21.8 ppm. **IR (ATR, cm<sup>-1</sup>):**  $\tilde{\nu}$  = 2783, 1612, 1530, 1512, 1484, 1452, 1337, 1304, 1251, 1154, 1129, 1093, 1037, 912, 898, 846, 813, 783, 719, 688, 670, 649, 572, 547, 514, 476. **HRMS (ESI):** calcd for C<sub>30</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub>SNa [M + Na]<sup>+</sup> 564.1569, found 564.1553.

**(±)-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/CH<sub>2</sub>Cl<sub>2</sub>) 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 CDCl<sub>3</sub> relative to other analogues of **12**]. **Mp:** 193–199 °C. **TLC:** *R*<sub>F</sub> = 0.54 (35:65 EtOAc/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 2821, 2847, 2787, 1684, 1532, 1482, 1341, 1117, 1089, 1017, 888, 783, 681, 572. **HRMS (ESI):** calcd for C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 436.1331, found 436.1335.

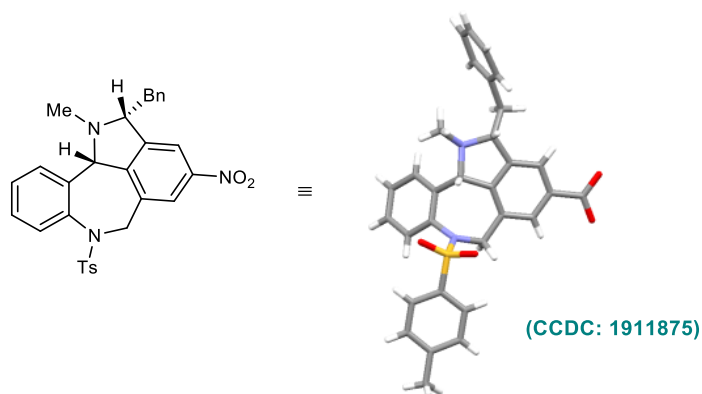
**(±)-[(9b*R*,11*R*)/(9b*S*,11*S*)]-10,11-Dibenzyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-cd]isoindole (12p)**



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 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane) gave **12p** (26.4 mg, 44%, dr *cis/trans* = 2.9:1) as a pale yellow solid,

which contained  $\leq 10$  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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  (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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  (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<sup>-1</sup>)**:  $\tilde{\nu}$  = 2923, 1597, 1525, 1454, 1340, 1156, 1115, 1093, 1029, 907, 862, 816, 754, 701, 672, 649, 570, 544, 479. **HRMS (ESI)**: calcd for C<sub>36</sub>H<sub>32</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 602.2114, found 602.2116.

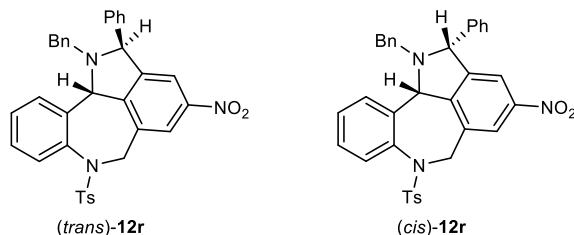
**(±)-[(9*bR*,11*R*)/(9*bS*,11*S*)]-11-Benzyl-10-methyl-2-nitro-5-tosyl-5,9*b*,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (**12q**)**



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 (CH<sub>2</sub>Cl<sub>2</sub>) 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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**:  $\delta$  (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<sup>-1</sup>)**:  $\tilde{\nu}$  = 3088, 3064, 3028, 2920, 2854, 2800, 1702, 1525, 1341, 1161, 1010, 787, 701, 648, 584. **HRMS (ESI)**: calcd for C<sub>30</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 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).

(±)-[(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*)-**12r**) and (±)-[(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*)-**12r**)



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<sub>3</sub> (21 μL, 0.15 mmol) and toluene (0.2 mL). The vial was purged again with N<sub>2</sub> then heated at 100 °C for a further 23 h (crude dr of **12r** *trans/cis* = 1.1:1). Flash chromatography (70:30 CH<sub>2</sub>Cl<sub>2</sub>/*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 <sup>1</sup>H 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).

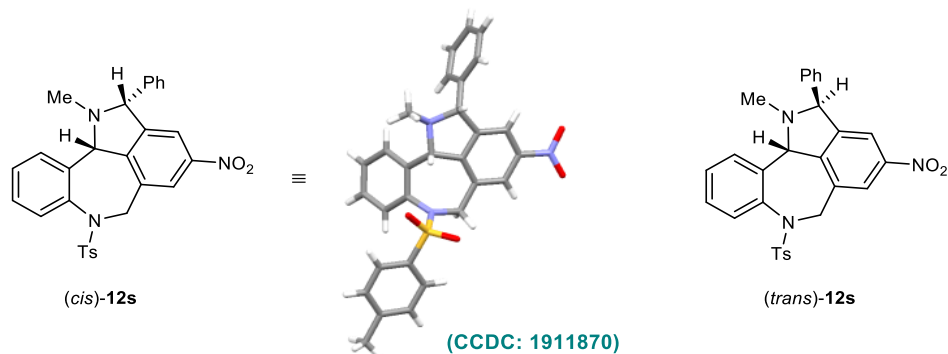
Data for Sample A enriched in (*trans*)-**12r** (dr *trans/cis* = 2.1:1). **Mp**: 121–127 °C. **TLC**: *R*<sub>F</sub> = 0.50 [*cis*], 0.44 [*trans*] (75:25 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ (data for *trans* diastereomer only) 7.90 (s, 1H), 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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  $CH_2Cl_2/n$ -hexane).  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  (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.  **$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):**  $\delta$  (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.

( $\pm$ )-[(9*bR*,11*R*)/(9*bS*,11*S*)]-10-Methyl-11-phenyl-2-nitro-5-tosyl-5,9*b*,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole ((*cis*)-**12s**) and ( $\pm$ )-[(9*bR*,11*S*)/(9*bS*,11*R*)]-10-Methyl-11-phenyl-2-nitro-5-tosyl-5,9*b*,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  $CH_2Cl_2/n$ -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  $CH_2Cl_2/n$ -hexane).  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  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),

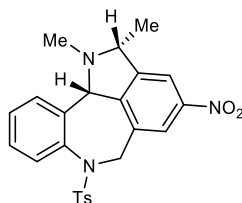


5.60 (d,  $J = 17.7$  Hz, 1H), 5.21 (s, 1H), 4.85 (d,  $J = 3.0$  Hz, 1H), 4.44 (d,  $J = 17.7$  Hz, 1H), 2.51 (s, 3H), 2.48 (s, 3H) ppm.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2, 145.7, 144.1, 143.3, 141.9, 141.4, 138.4, 137.4, 134.3, 130.1, 129.7, 128.9, 128.6, 128.55, 128.46, 128.4, 127.2, 126.2, 120.7, 117.1, 74.6, 68.1, 50.7, 39.3, 21.8 ppm. IR (ATR,  $\text{cm}^{-1}$ ):  $\tilde{\nu} = 2787, 1598, 1524, 1483, 1455, 1339, 1157, 1116, 1099, 1022, 904, 865, 836, 801, 743, 713, 669, 649, 565, 541, 516$ . 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).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{cm}^{-1}$ ):  $\tilde{\nu} = 2919, 2850, 1597, 1528, 1454, 1338, 1158, 1097, 1021, 904, 866, 833, 814, 801, 744, 723, 701, 667, 648, 565, 543, 503, 481$ . 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).

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

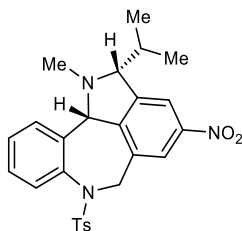


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(L)-Ala-OH [freebase] (20.6 mg, 0.20 mmol) with a 16 h reaction time (single diastereomer of **12t** observed in crude sample). Flash chromatography (70:30 to 75:25  $\text{CH}_2\text{Cl}_2/n$ -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).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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  $\text{cm}^{-1}$ ):  $\tilde{\nu}$  = 3065, 2963, 2921, 2845, 2789, 2598, 1523, 1482, 1341, 1115, 915, 811, 776, 705, 651, 568.

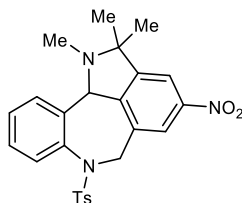
HRMS (ESI): calcd for  $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$  450.1488, found 450.1489.

(±)-[(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  $\text{CH}_2\text{Cl}_2/n$ -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).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**:  $\delta$  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.  **$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**:  $\delta$  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,  $\text{cm}^{-1}$ )**:  $\tilde{\nu}$  = 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  $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$  478.1801, found 478.1808.

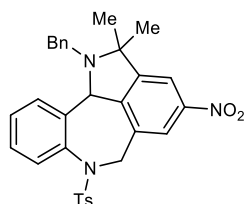
(±)-10,11,11-Trimethyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (**12w**)



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  $\text{CH}_2\text{Cl}_2/n$ -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).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  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)

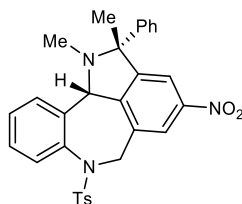
ppm.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  151.3, 148.3, 144.0, 142.4, 141.6, 138.7, 137.4, 134.1, 130.0, 129.4, 129.0, 128.3, 127.2, 126.2, 120.4, 115.3, 66.3, 65.4, 50.8, 33.1, 27.4, 23.9, 21.6 ppm. IR (ATR,  $\text{cm}^{-1}$ ):  $\tilde{\nu}$  = 2968, 1594, 1532, 1481, 1455, 1340, 1312, 1238, 1154, 1108, 1015, 972, 910, 870, 815, 795, 764, 728, 674, 648, 572, 545, 463. HRMS (ESI): calcd for  $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$  464.1644, found 464.1634.

(±)-10-Benzyl-11,11-dimethyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-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  $\text{CH}_2\text{Cl}_2/n$ -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).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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,  $\text{cm}^{-1}$ ):  $\tilde{\nu}$  = 2967, 1598, 1528, 1451, 1337, 1155, 1116, 910, 870, 818, 746, 700, 676, 647, 564, 543, 483. HRMS (ESI): calcd for  $\text{C}_{31}\text{H}_{30}\text{N}_3\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$  540.1957, found 540.1963.

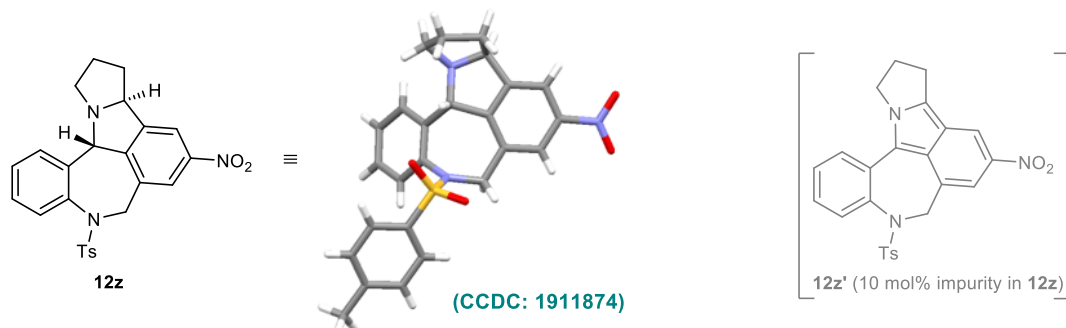
(±)-[(9*bR*,11*R*)/(9*bS*,11*S*)]-10,11-Dimethyl-11-phenyl-2-nitro-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (**12y**)



This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and Me-(D/L)-( $\alpha$ -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  $\text{CH}_2\text{Cl}_2/n$ -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):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{cm}^{-1}$ ):  $\tilde{\nu} = 2975, 1597, 1527, 1481, 1456, 1340, 1279, 1236, 1156, 1098, 908, 871, 806, 755, 724, 702, 675, 647, 568, 544, 484$ . 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.

(±)-[(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**)

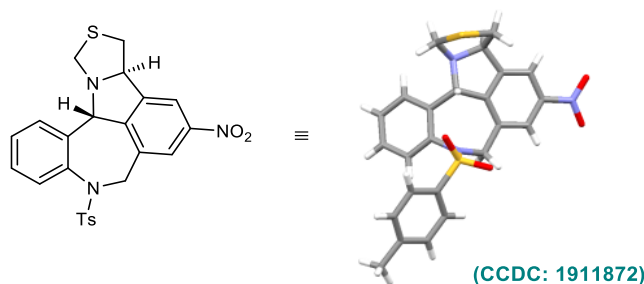


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and (L)-Pro-OH [freebase] (23.0 mg, 0.20 mmol) with a 15 h reaction time (single diastereomer of **12z** observed in crude sample). Flash chromatography (77.5:22.5 to 100:0  $\text{CH}_2\text{Cl}_2/n$ -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):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  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): **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  (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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  (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<sup>-1</sup>):**  $\tilde{\nu}$  = 3075, 2954, 2919, 2853, 1594, 1530, 1452, 1341, 1155, 878, 778, 725, 677, 579. **HRMS (ESI):** calcd for **12z**: C<sub>25</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 462.1488, found 462.1502. **HRMS (ESI):** calcd for **12z'**: C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>SNa [M + Na]<sup>+</sup> 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.

(±)-[(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**)

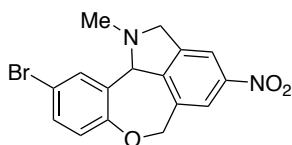


This compound was prepared according to *General Procedure E* using aldehyde **9a** (45.5 mg, 0.10 mmol) and (L)-ThiaPro-OH [freebase] (26.6 mg, 0.20 mmol) with a 15 h reaction time (single diastereomer of **12aa** observed in crude sample) [note that **12aa**, like **12o**, has a very low solubility in CDCl<sub>3</sub> relative to other analogues, thus determination of an accurate NMR yield by complete dissolution of the crude sample in CDCl<sub>3</sub> was not possible]. Flash chromatography (88:12 CH<sub>2</sub>Cl<sub>2</sub>/*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). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  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<sup>-1</sup>):**  $\tilde{\nu}$  = 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.

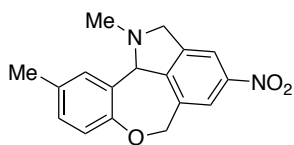
Crystals of **12aa** suitable for X-ray analysis were obtained by the same crystallization procedure as described for **9a** (Section 3.2).

**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,  $CDCl_3$ ):**  $\delta$  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.  **$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):**  $\delta$  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)**

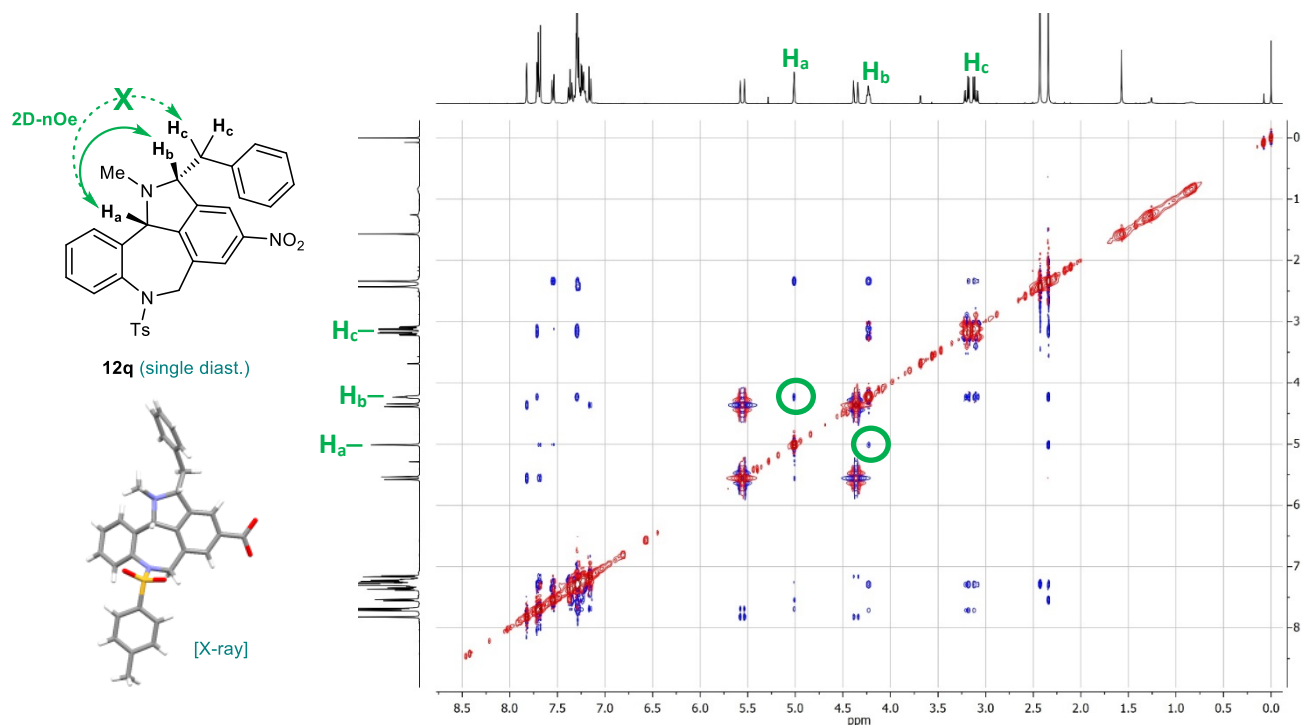


The compound was prepared according to *General Procedure E* using 2-((3,5-dinitrobenzyl)oxy)-5-methylbenzaldehyde and sarcosine (**9a**) with a 12-hour reaction time. Flash chromatography (EtOAc/*n*-hexanes) gave **12cc** (11.4 mg, 23% yield) as a yellow residue. **TLC:**  $R_F$  = 0.29 (20/80 EtOAc/*n*-hexanes).  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  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.  **$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):**  $\delta$  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.

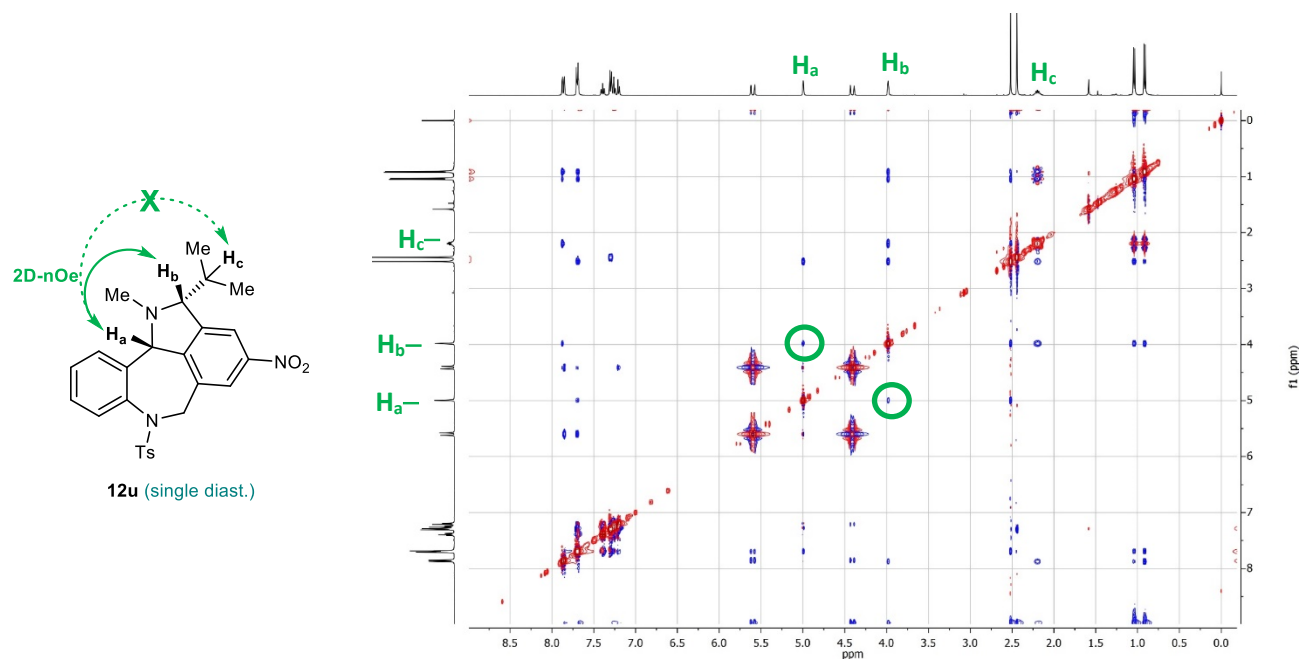
## 5.5. Determination of Relative Stereochemistry of 12p, 12t, 12u and 12y by nOe NMR Spectroscopy

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

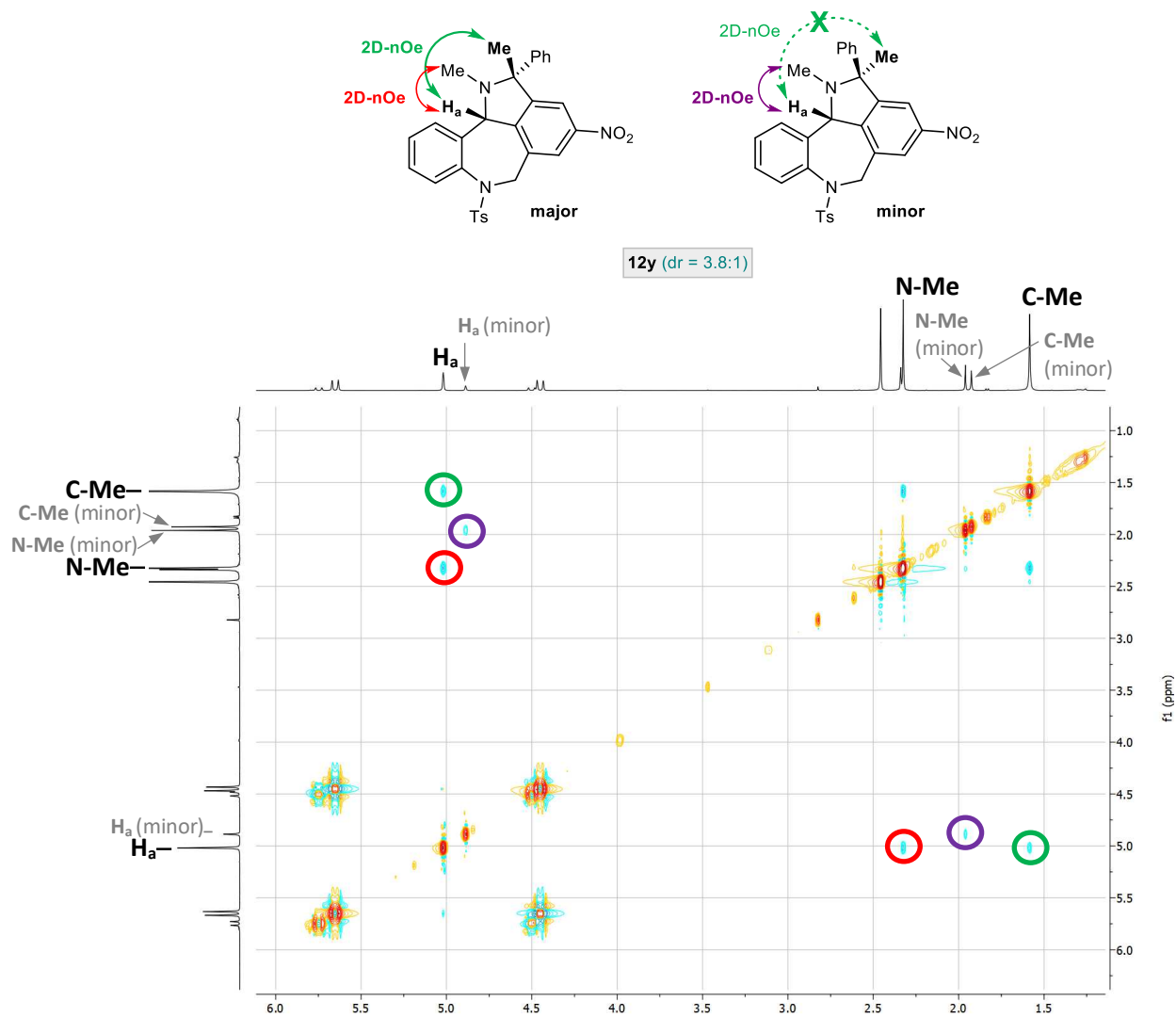
- **Compound 12q** of known *cis*-configuration (X-ray) was used as a positive control to confirm a 2D-nOe correlation between  $\text{H}_a$  and  $\text{H}_b$ . Note that no correlation between  $\text{H}_a$  and  $\text{H}_c$  was observed, as expected for the *cis* stereochemistry.



- **Compound 12u** exhibited an analogous 2D-nOe correlation between  $\text{H}_a$  and  $\text{H}_b$ . Further evidence for the assigned *cis* stereochemistry was the absence of a  $\text{H}_a$ – $\text{H}_c$  correlation.

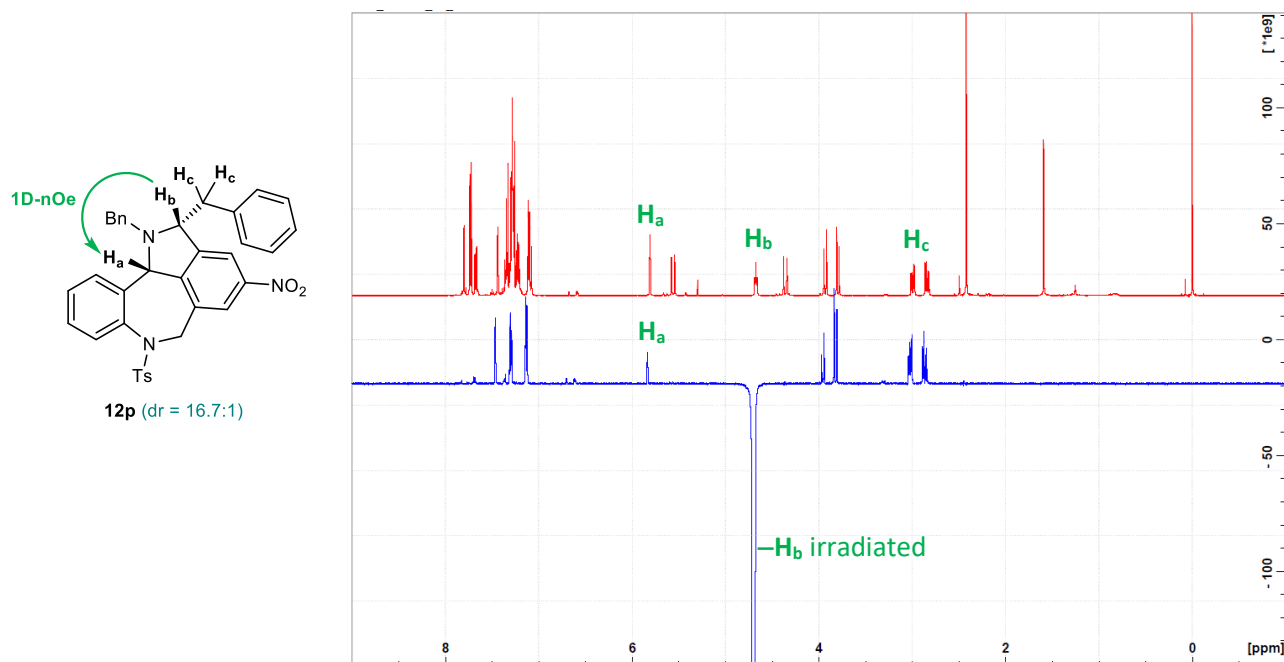
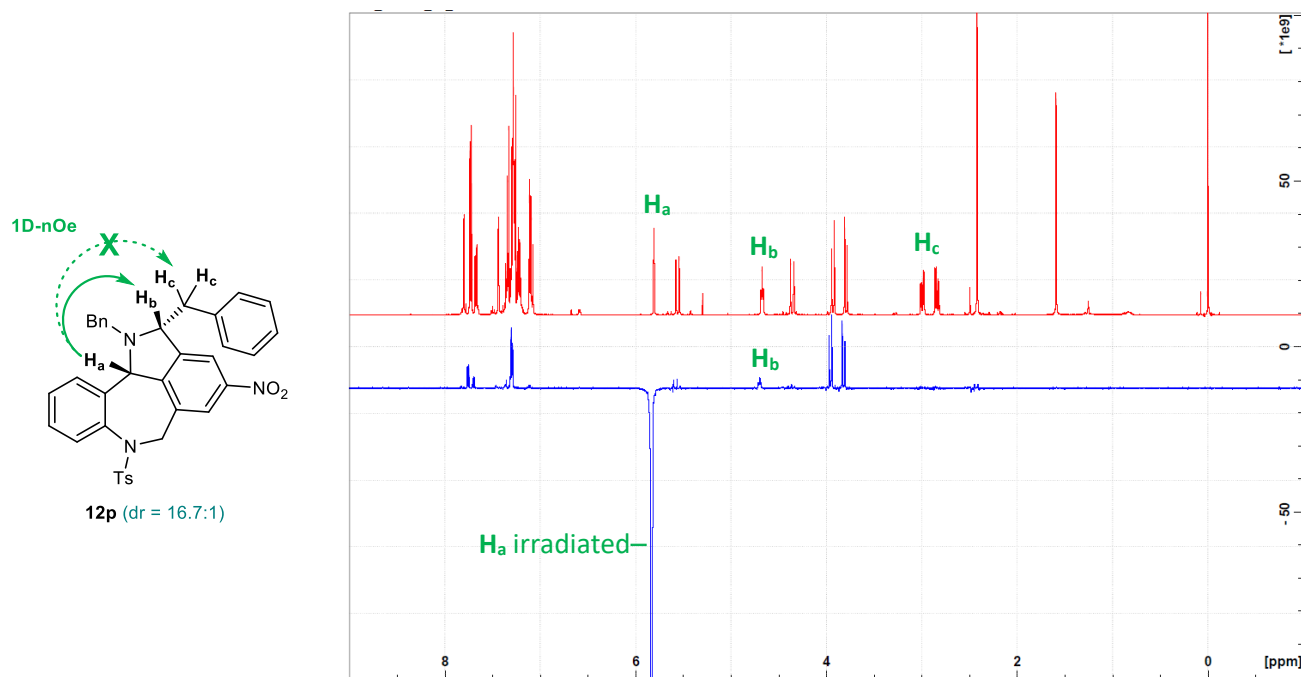


- **Compound 12y** was analyzed as a mixture of diastereomers (dr = 3.8 :1). All key proton signals were resolved which enabled nOe analysis to determine the relative stereochemistry. The major diastereomer (*cis*) exhibited a 2D-nOe correlation between the methine hydrogen ( $H_a$ ) and the C-methyl 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).

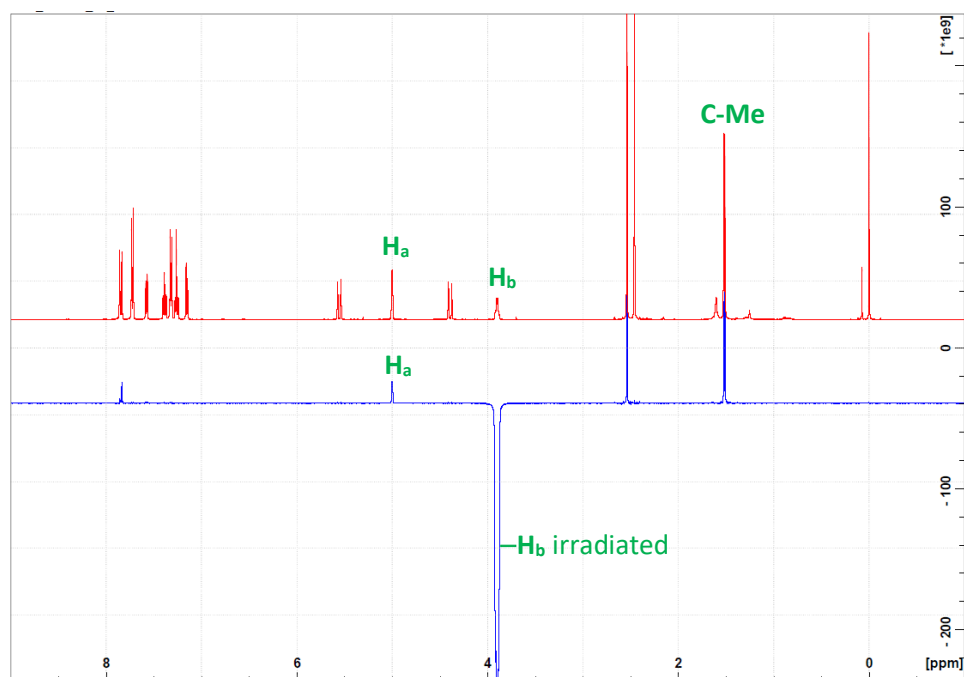
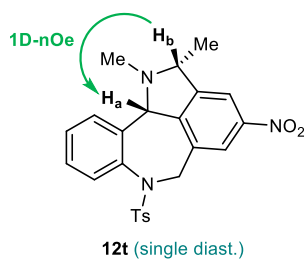
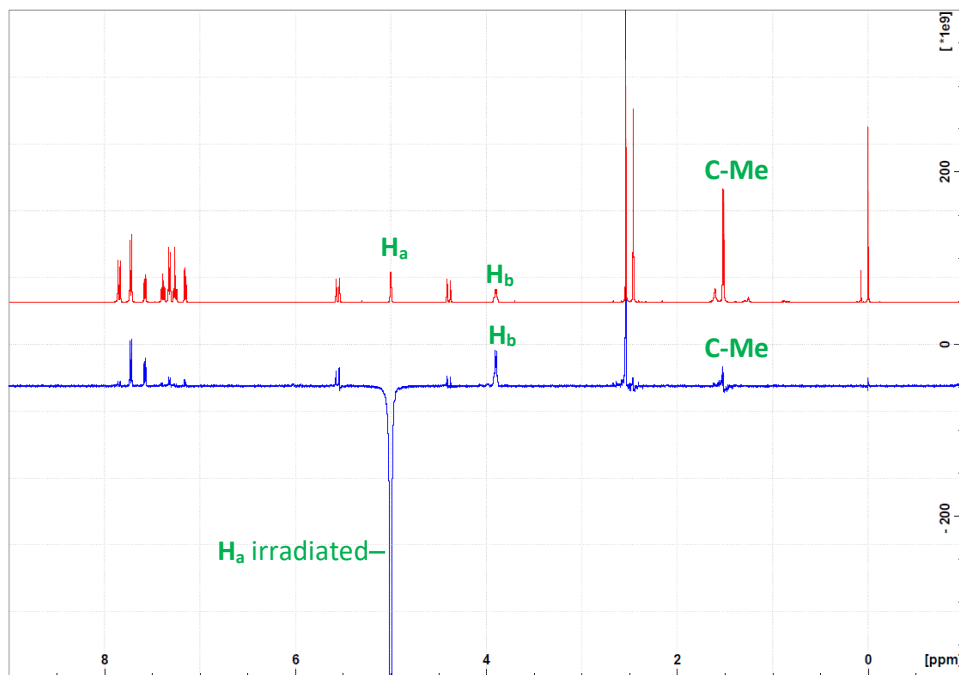
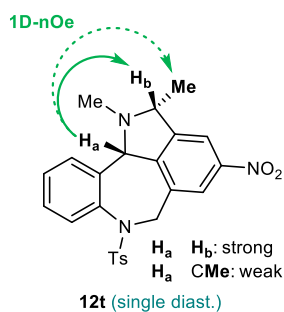




• **Compound 12p** was analyzed as a diastereoenriched sample ( $dr = 16.7:1$ , see Section 5.4.3). This sample was enriched in the same diastereomer as the crude mixture (and originally isolated sample). Although no conclusive 2D-nOe data could be obtained, 1D-nOe experiments involving separate irradiation 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.



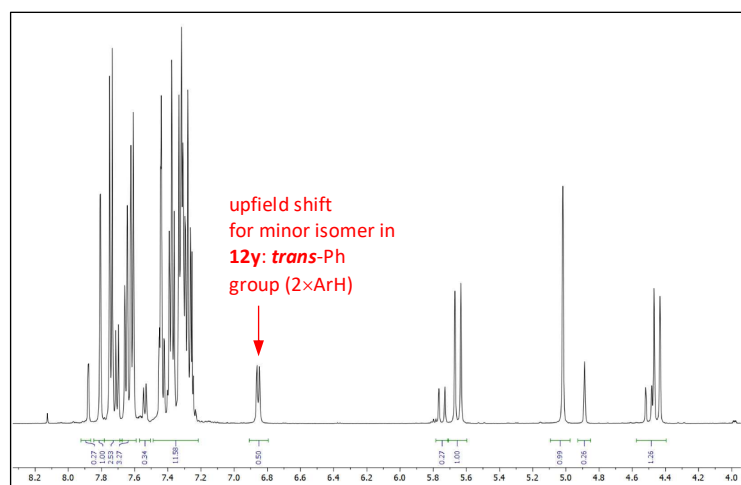
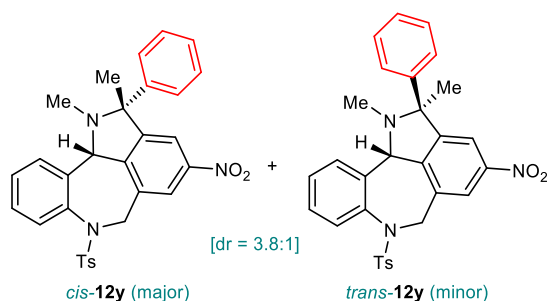
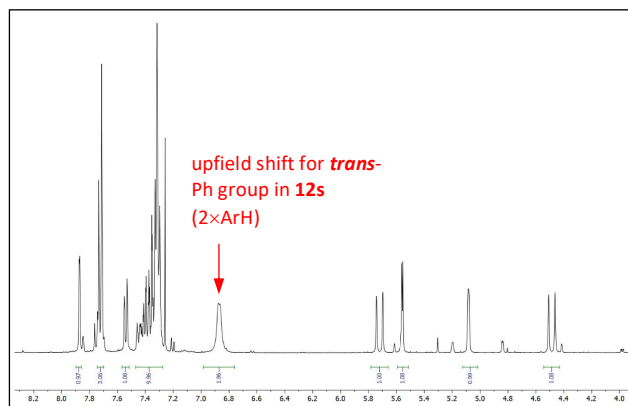
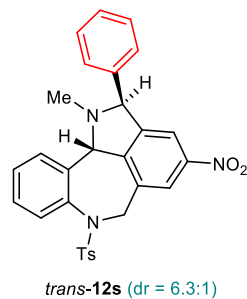
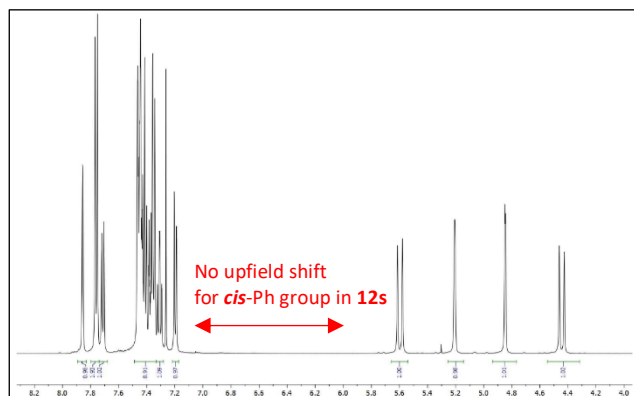
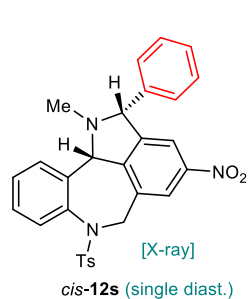
- **Compound 12t** was assigned as the *cis* isomer by analogous 1D-nOe experiments ( $H_a$ – $H_b$  correlations). Further evidence for the assigned *cis* stereochemistry was a much stronger correlation between  $H_a$  and  $H_b$  relative to  $H_a$  and the C-methyl group (weak signal observed).



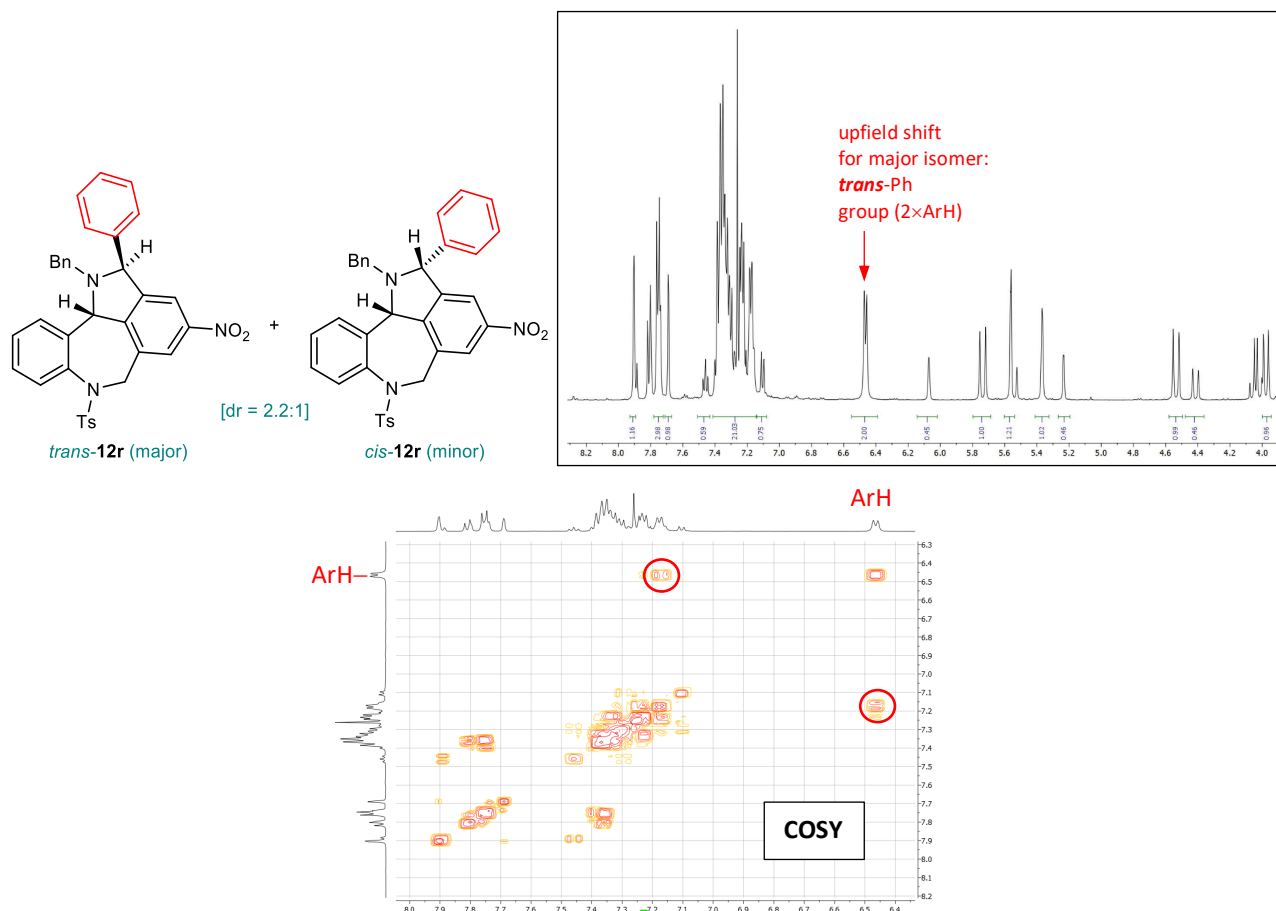
## 5.6. Determination of Relative Stereochemistry of **12r** (by $^1\text{H}$ NMR spectral comparison with **12s** and **12y**)

**Note:** Full  $^1\text{H}$  and  $^{13}\text{C}$  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 ( $2\times\text{ArH}$ , *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.

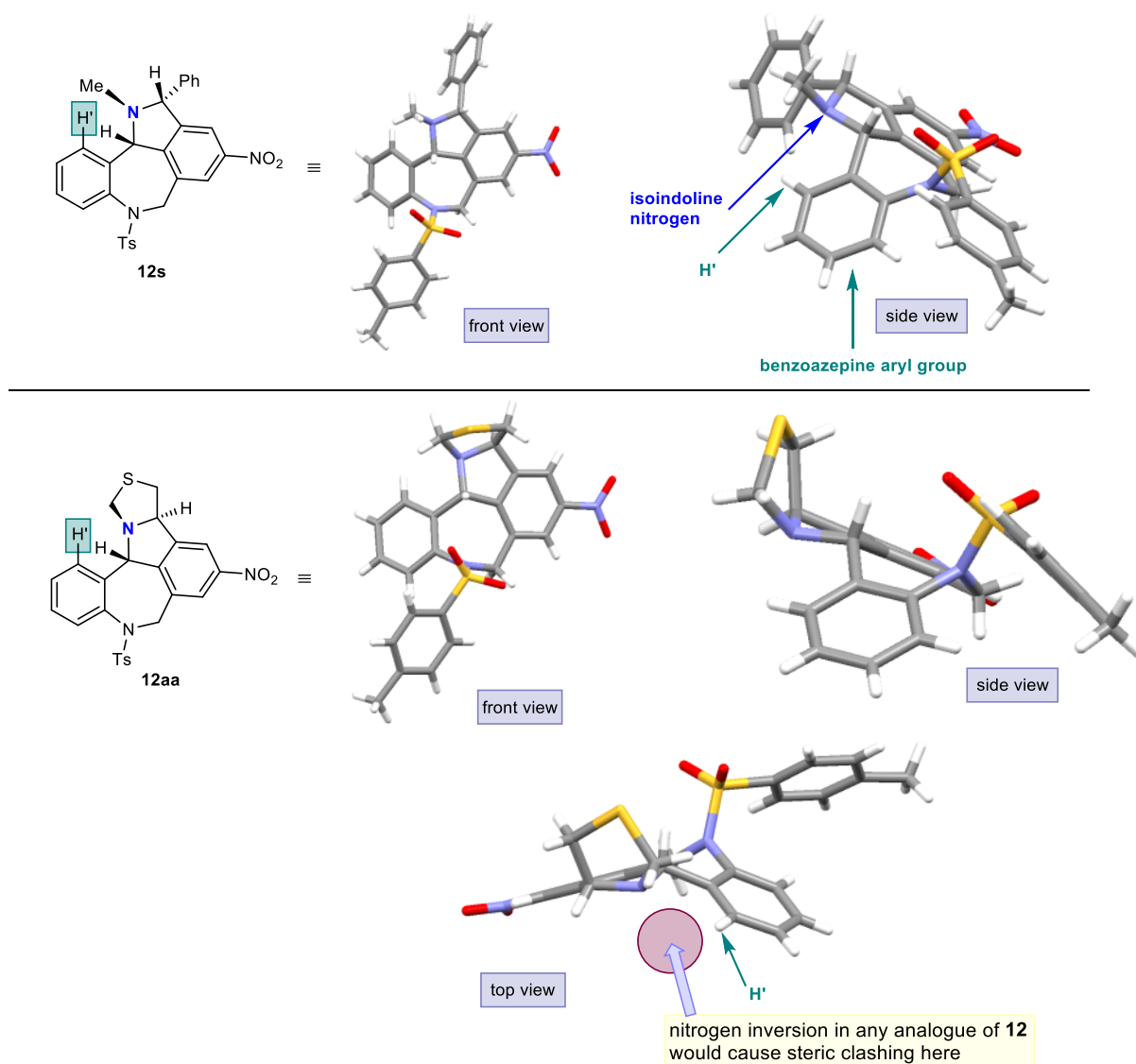


- Further 2D-NMR analyses of all above samples (*trans*-**12s**, **12r** and **12y**) using COSY, nOe, HSQC and HMBC (COSY for **12r** shown above) confirmed in each case that this diagnostic signal from the phenyl group (ArH) was not an impurity nor a deshielded sp<sup>3</sup>-C–H proton.

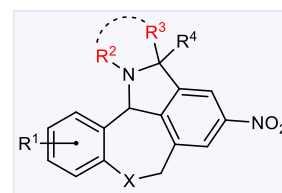
### 5.7. Further Discussions on Diastereoselectivity Switch with Cyclic Amino Acid Substrates

- *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<sup>3</sup>-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<sub>2</sub> 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

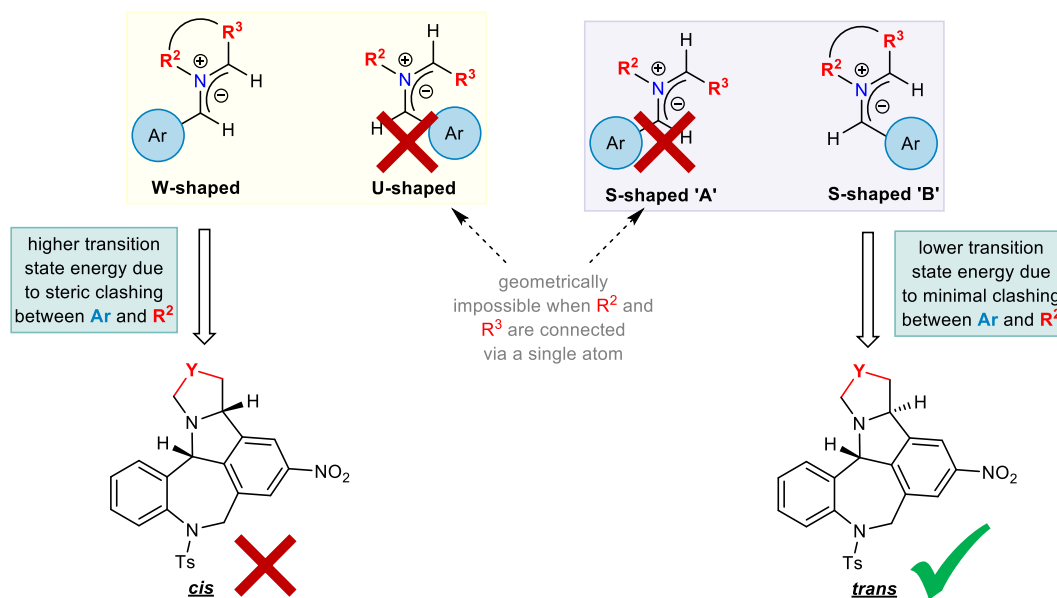
isoindoline nitrogen relative to the configurations in the crystal structures shown) would clearly be higher in energy as a result of steric interactions.



• 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 ( $\underline{C}-Ar$ ,  $\underline{N}-R^2$  and  $\underline{C}-R^3$ ) 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-

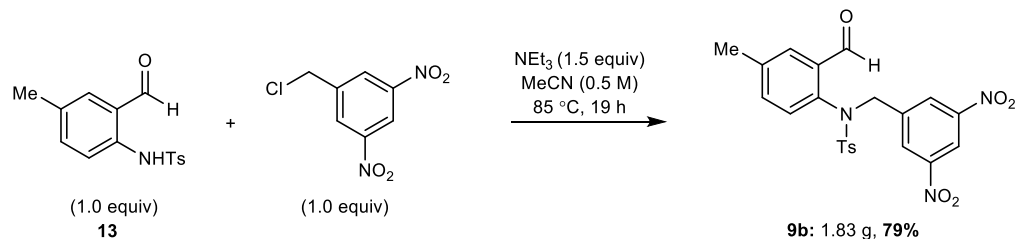


Shaped ylide 'B', which projects Ar and R<sup>2</sup> in opposite directions in the cycloaddition transition state, prevails for these systems.



## 6. Larger Scale Examples

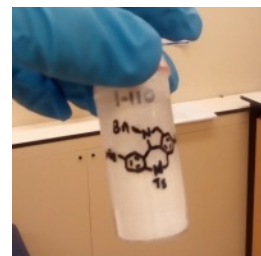
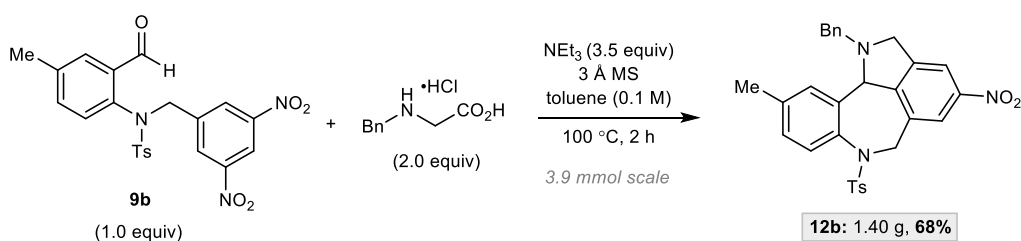
### *N*-(3,5-Dinitrobenzyl)-*N*-(2-formyl-4-methylphenyl)-4-methylbenzenesulfonamide (**9b**)



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 N<sub>2</sub>. Anhydrous MeCN (9.9 mL, 0.5 M) was added, followed by NEt<sub>3</sub> (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 NEt<sub>3</sub>·HCl and polar impurities, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (~20 mL) and adsorbed to a silica column (31 g silica, wet-packed with 5:95 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>). The product was then rapidly eluted with 5:95 EtOAc/CH<sub>2</sub>Cl<sub>2</sub> (~300 mL) and the fractions containing **9b** were concentrated under reduced pressure [**9b**: *R*<sub>F</sub> = 0.31 (30:70 EtOAc/*n*-hexane)]. The remaining solid (containing **9b**, residual **13** and other minor impurities) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (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  $\text{CH}_2\text{Cl}_2$  (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.

**(±)-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.

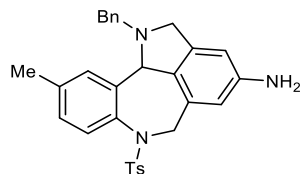


An oven-dried, two neck 100 mL round-bottom flask was charged in air with **9b** (1.829 g, 3.90 mmol, 1.0 equiv), Bn-Gly-OH·HCl (1.571 g, 7.79 mmol, 2.0 equiv) and powdered 3 Å molecular sieves (1.87 g). A reflux condenser was attached and the system was purged with  $\text{N}_2$  via flow through the 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  $\text{NEt}_3$  (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 EtOAc/*n*-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  $\text{CH}_2\text{Cl}_2$ ) with the aid of  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL) to rinse the reaction flask. The product was then eluted with  $\text{CH}_2\text{Cl}_2$  (<500 mL required) and the fractions containing **12b** (with minor impurities) were concentrated under reduced pressure [**12b**:  $R_f$  = 0.59 (30:70 EtOAc/*n*-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 ( $2 \times 20$  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

### (±)-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)

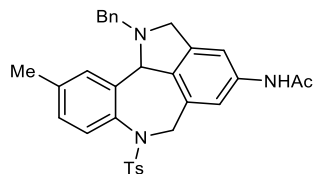


- The MeOH used as solvent for this experiment was de-oxygenated by N<sub>2</sub>-sparging for 20 min before use. Subsequent experiments have shown that this precaution is not necessary to obtain high yields (>90%).

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 N<sub>2</sub> 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 N<sub>2</sub>, 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/CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and filtered. The filtrate was concentrated under reduced pressure. CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and 1 M K<sub>2</sub>CO<sub>3</sub> (40 mL) were added. The resulting sticky inorganic precipitate was removed by vacuum filtration, rinsing the flask and filter cake with CH<sub>2</sub>Cl<sub>2</sub> (4 × 15 mL). The filtrate was poured into a separating funnel and the organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (4 g silica, 0:100 to 5:95 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave **14** (245.1 mg, 99%) as a white solid. **Mp**: 235–239 °C. **TLC**: *R*<sub>F</sub> = 0.36 (2.5:97.5 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>30</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 496.2059, found 496.2061.

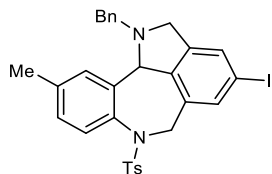


**(±)-2-Acetylamino-10-benzyl-8-methyl-5-tosyl-5,9b,10,11-tetrahydro-4H-benzo[6,7]azepino[5,4,3-*cd*]isoindole (15)**



To solid **14** (29.7 mg, 0.060 mmol, 1.0 equiv) was added a solution of Ac<sub>2</sub>O (7.4 mg weighed, 0.072 mmol, 1.2 equiv) in reagent grade CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL, 0.1 M) and the solution was stirred under at room temperature for 2 h. CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and 1 M K<sub>2</sub>CO<sub>3</sub> (2 mL) were added and the biphasic mixture was stirred rapidly at room temperature for 5 min. Additional 1 M K<sub>2</sub>CO<sub>3</sub> (15 mL) was added and the product was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> (25 mL, then 15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give **15** (32.4 mg, 100%) as an off-white solid. **Mp**: 226–232 °C. **TLC**: *R*<sub>F</sub> = 0.16 (7.5:92.5 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>32</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 538.2164, found 538.2168.

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

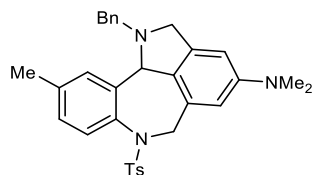


To a suspension of **14** (45.5 mg, 0.092 mmol, 1.0 equiv) in reagent grade MeCN (1.0 mL, 0.09 M) at –10 °C (ice/salt bath) under air was added solid *p*-TsOH·H<sub>2</sub>O (69.8 mg, 0.37 mmol, 4.0 equiv) to give a near homogenous solution. A solution of KI (76.2 mg, 0.46 mmol, 5.0 equiv) in water (0.20 mL) was added, followed by the dropwise addition of a solution of NaNO<sub>2</sub> (12.7 mg, 0.18 mmol, 2.0 equiv) in water (0.20 mL) over 1 min (N<sub>2</sub> 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 K<sub>2</sub>CO<sub>3</sub> (3 mL) and 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (25 mL, then 10 mL). The combined (dark purple) organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (4.4 g silica, 75:25 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane)

gave **16** (33.2 mg, 60%) as a white solid. **Mp**: 228–234 °C. **TLC**:  $R_F$  = 0.58 (75:25 CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**: 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<sup>-1</sup>)**:  $\tilde{\nu}$  = 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 C<sub>30</sub>H<sub>28</sub>IN<sub>2</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 607.0916, found 607.0923.

• One earlier run with only 2.5 equiv of KI at 0 °C with an inverse addition order of NaNO<sub>2</sub> 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.

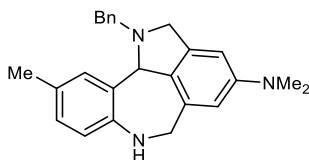
**(±)-10-Benzyl-2-dimethylamino-8-methyl-5-tosyl-5,9b,10,11-tetrahydro-4*H*-benzo[6,7]azepino[5,4,3-*cd*]isoindole (**17**)**



To a suspension of **14** (49.6 mg, 0.10 mmol, 1.0 equiv) and NaBH<sub>3</sub>CN (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 μL = 9.0 mg of CH<sub>2</sub>O, 0.30 mmol, 3.0 equiv) and AcOH (29 μL, 0.50 mmol, 5.0 equiv). The resulting solution was stirred under at room temperature for 1.5 h, then quenched with 1 M K<sub>2</sub>CO<sub>3</sub> (2 mL). Additional 1 M K<sub>2</sub>CO<sub>3</sub> (15 mL) was added and the product was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> (25 mL, then 15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) 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 (CH<sub>2</sub>Cl<sub>2</sub>). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: 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. **<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**: 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,  $\text{cm}^{-1}$ ):**  $\tilde{\nu}$  = 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  $\text{C}_{32}\text{H}_{34}\text{N}_3\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$  524.2372, found 524.2385.

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



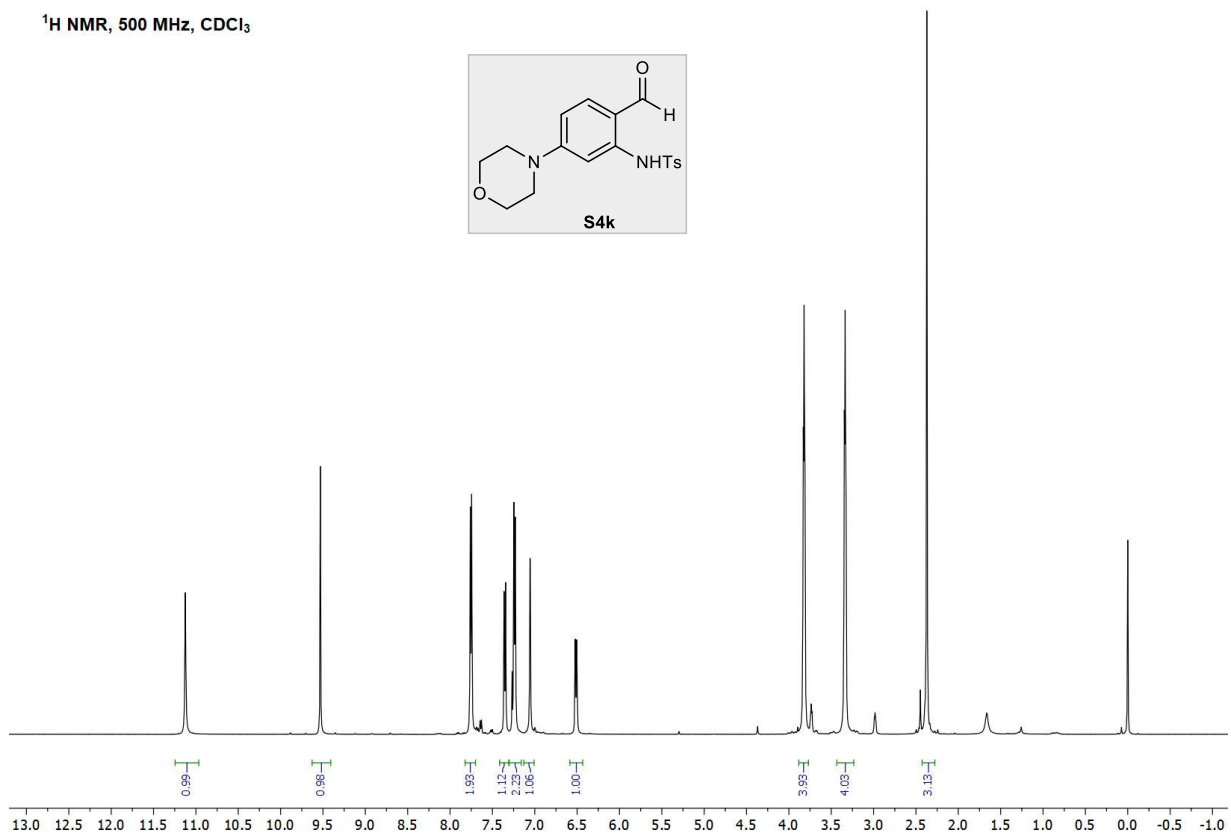
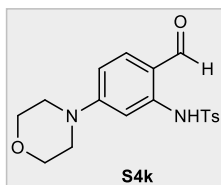
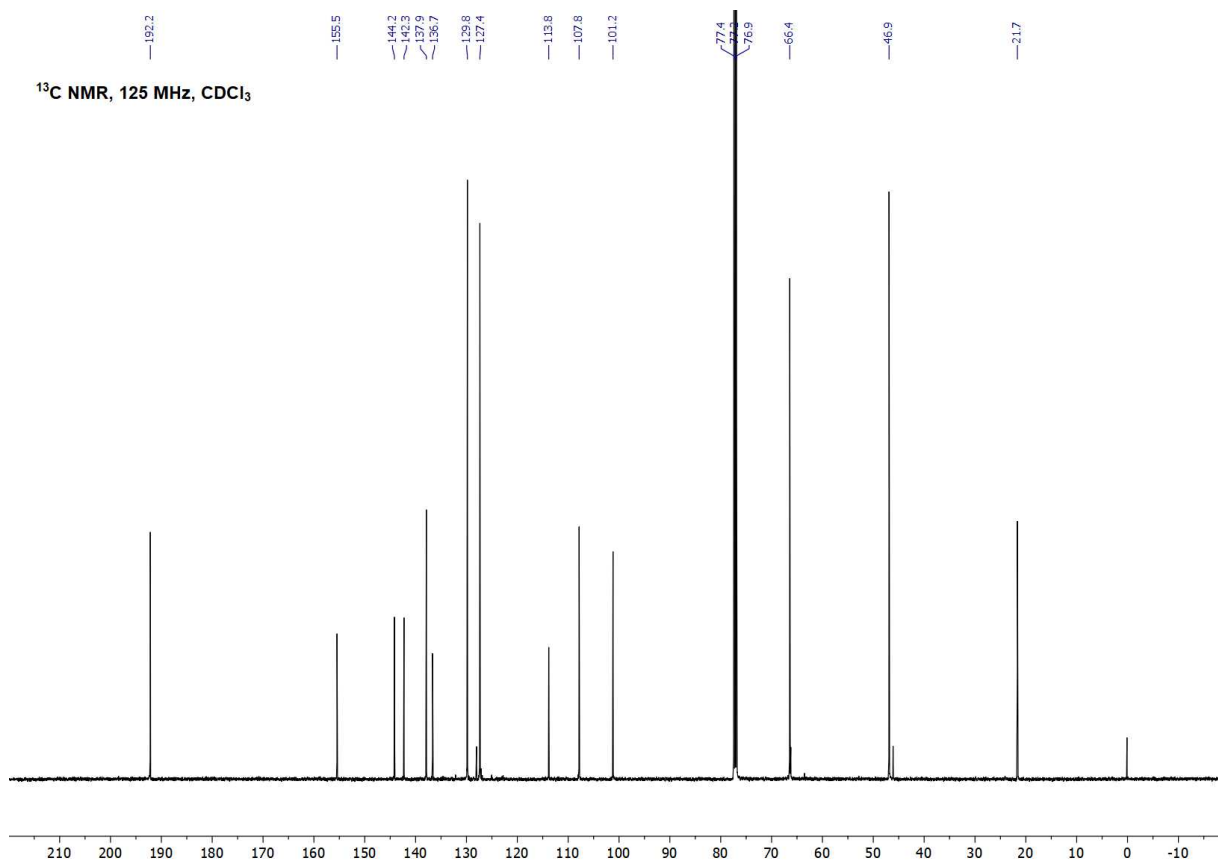
• Note that this reaction work-up procedure is unoptimized. An alternative Fieser work-up<sup>S21</sup> is recommended in subsequent runs, especially on larger scale to avoid complications from aluminum emulsions encountered in the small scale aqueous work-up described here. It is also recommended as a safety precaution on larger scale to add the substrate (as a solid) to a suspension of  $\text{LiAlH}_4$  in THF under  $\text{N}_2$ , 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  $\text{LiAlH}_4$  powder (22.8 mg, 0.60 mmol, 10.0 equiv). A reflux condenser was attached and the system was purged with  $\text{N}_2$ . 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  $\text{LiAlH}_4$  was quenched by slow addition of 1 M NaOH (5 mL,  $\text{H}_2$  evolution observed). The mixture was diluted further with water (10 mL),  $\text{CH}_2\text{Cl}_2$  (8 mL) and EtOAc (20 mL). The organic layer (top) was washed with brine (15 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Flash chromatography (~2 g silica, 0:100 to 5:95 EtOAc/ $\text{CH}_2\text{Cl}_2$ ) gave **18** (13.7 mg, 62%) as a light brown solid. **Mp:** 86–92 °C. **TLC:**  $R_F$  = 0.27 (1:99 EtOAc/ $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  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.  **$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  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,  $\text{cm}^{-1}$ ):**  $\tilde{\nu}$  = 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  $\text{C}_{25}\text{H}_{28}\text{N}_3$   $[\text{M} + \text{H}]^+$  370.2283, found 370.2284.

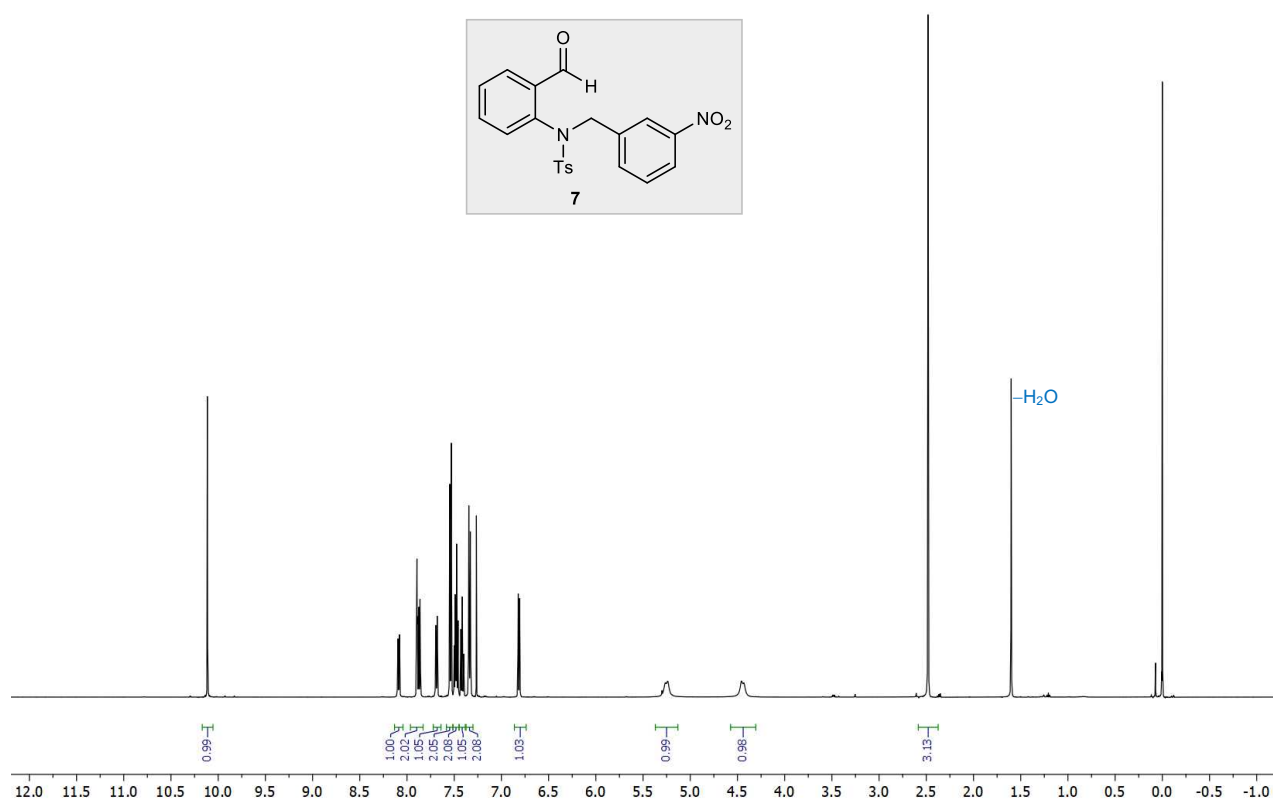
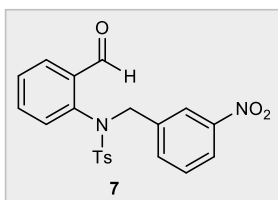
- Other conditions attempted (once) for the de-tosylation process with **17** included:
  - Mg powder (2 × 20 equiv), MeOH (0.05 M), 60 °C, 2 h: recovered **17**/unknown product = 85:15 (molar ratio). The sparing solubility of **17** in MeOH is the likely reason for the poor reactivity (significant H<sub>2</sub> 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

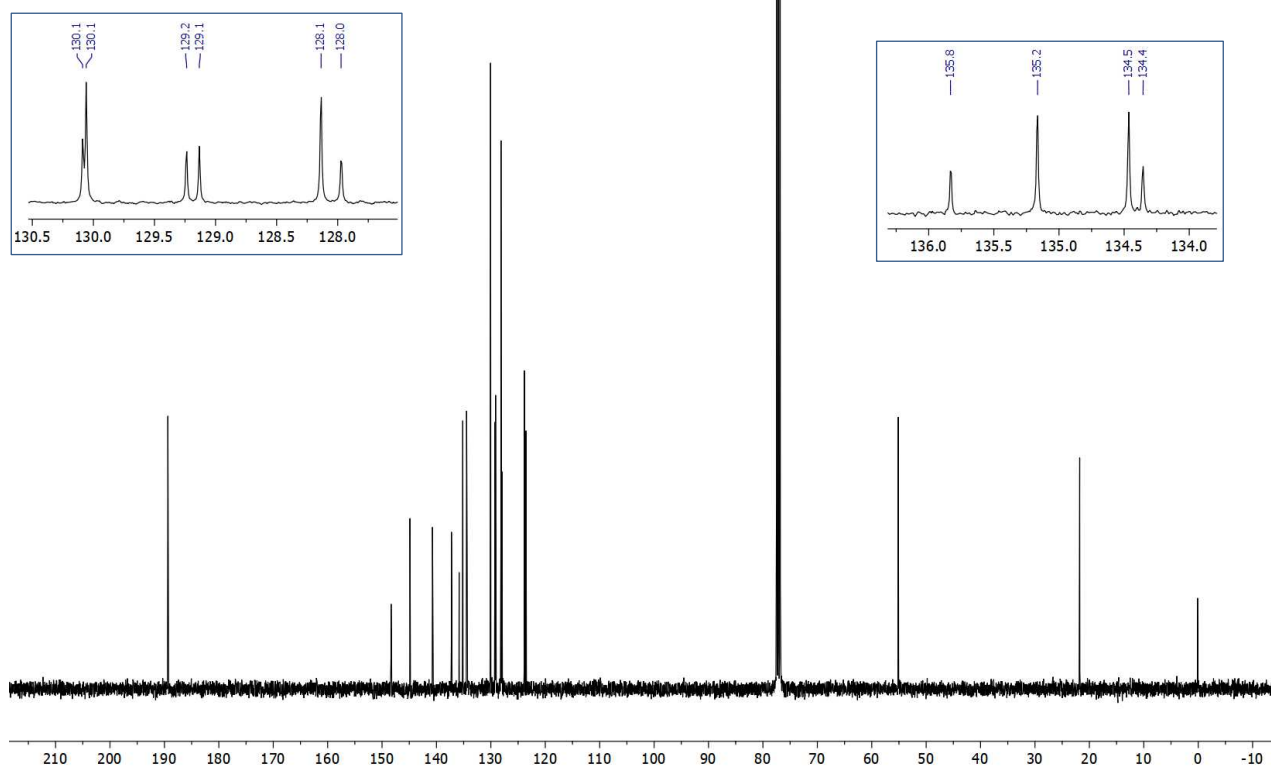
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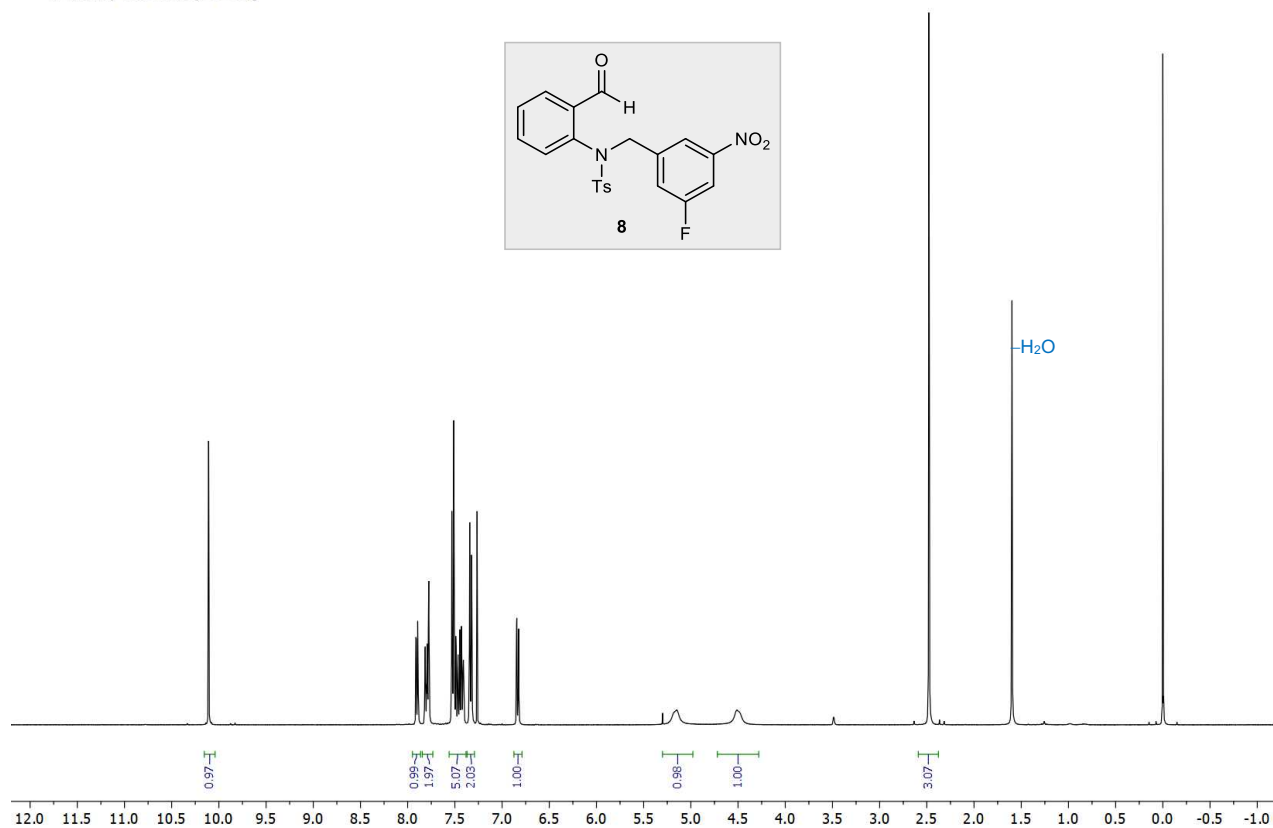
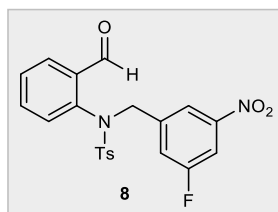
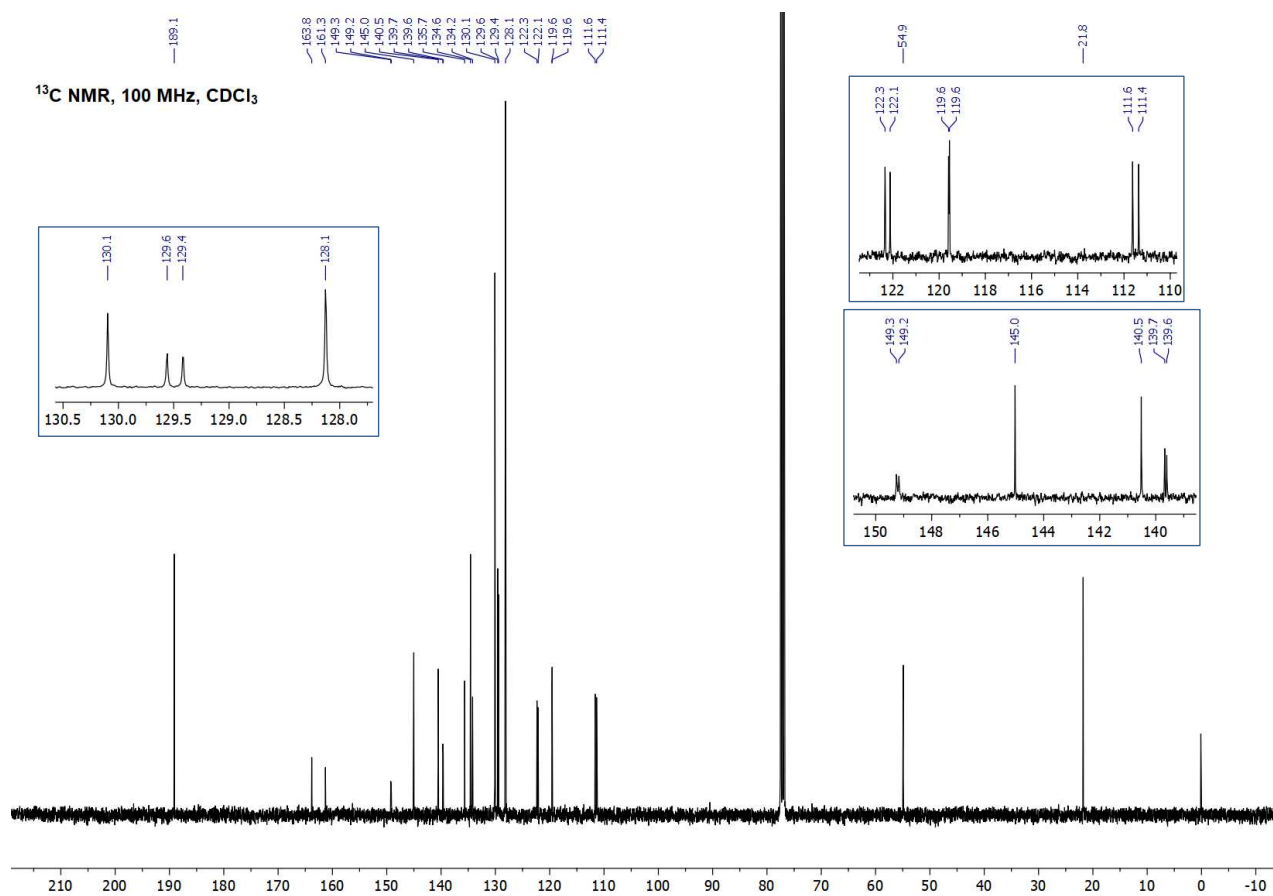
**9. NMR Spectra of Novel Compounds**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

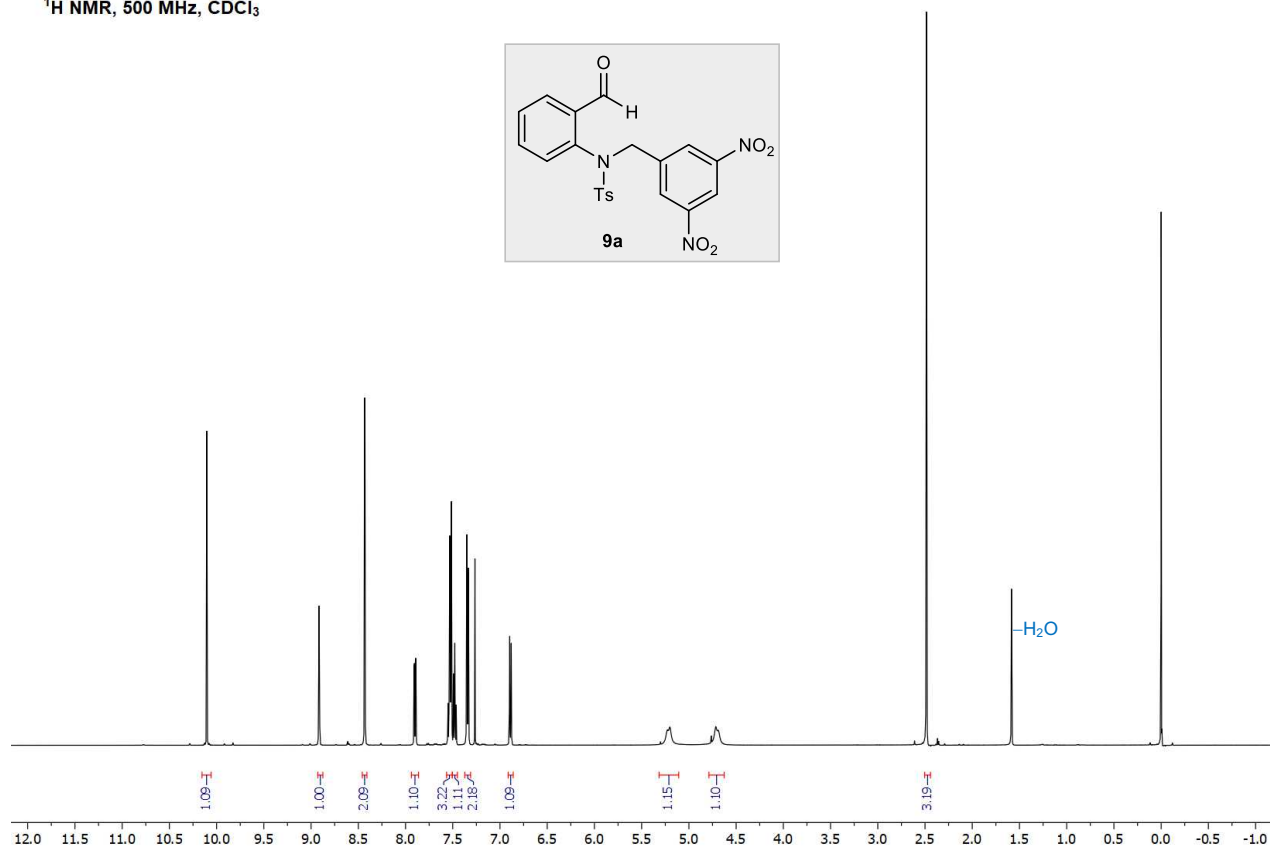
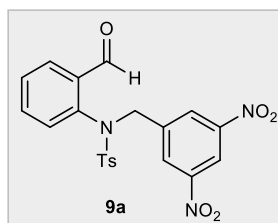
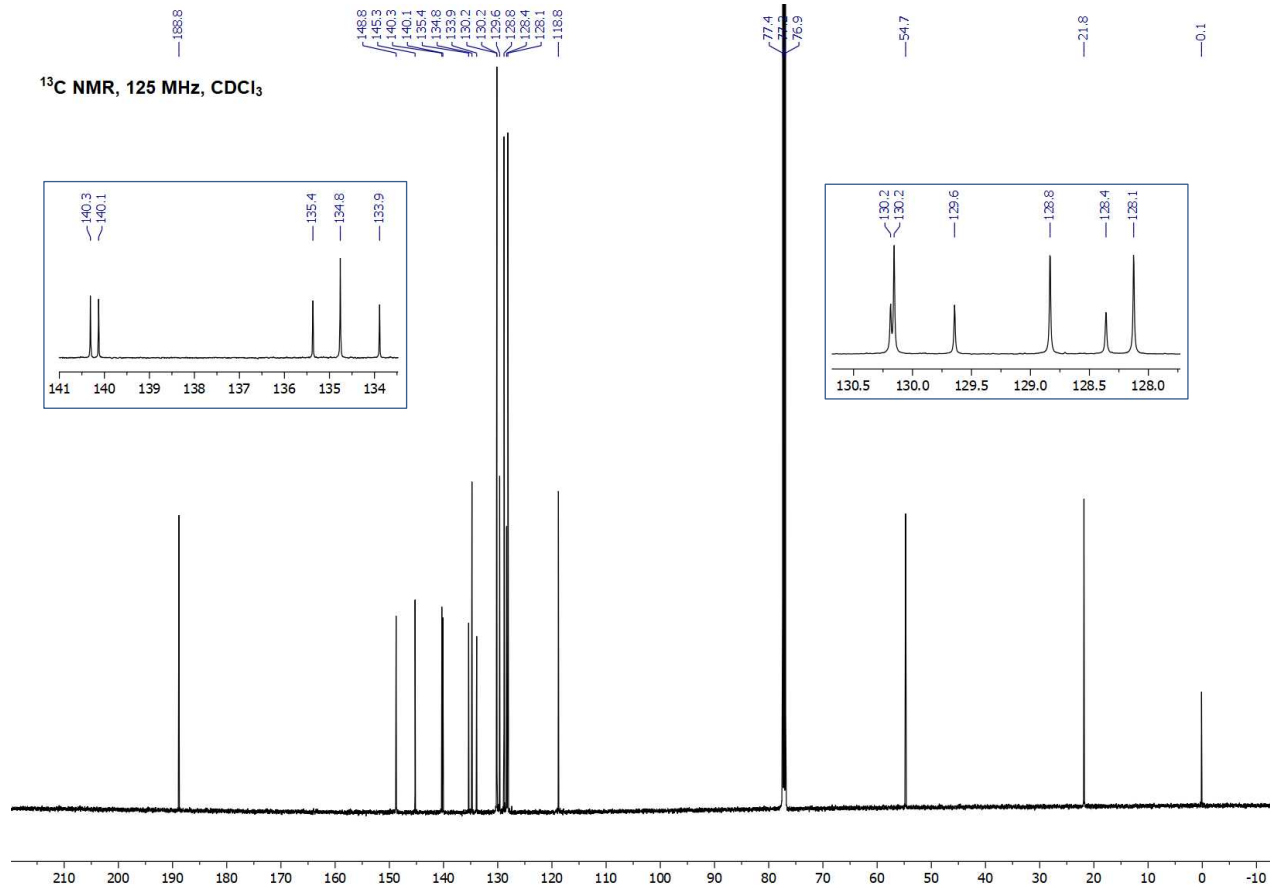
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$



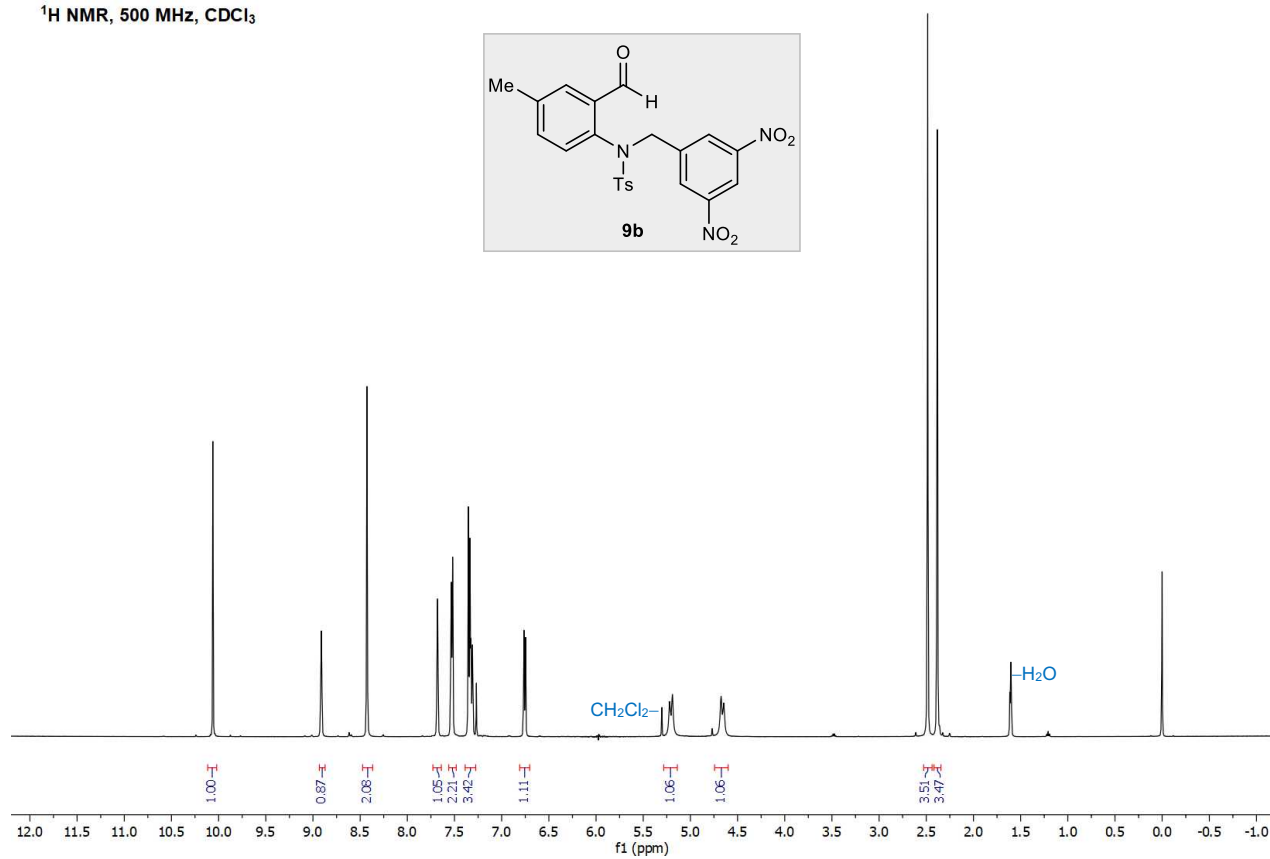
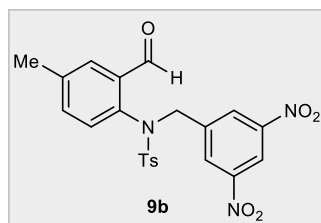
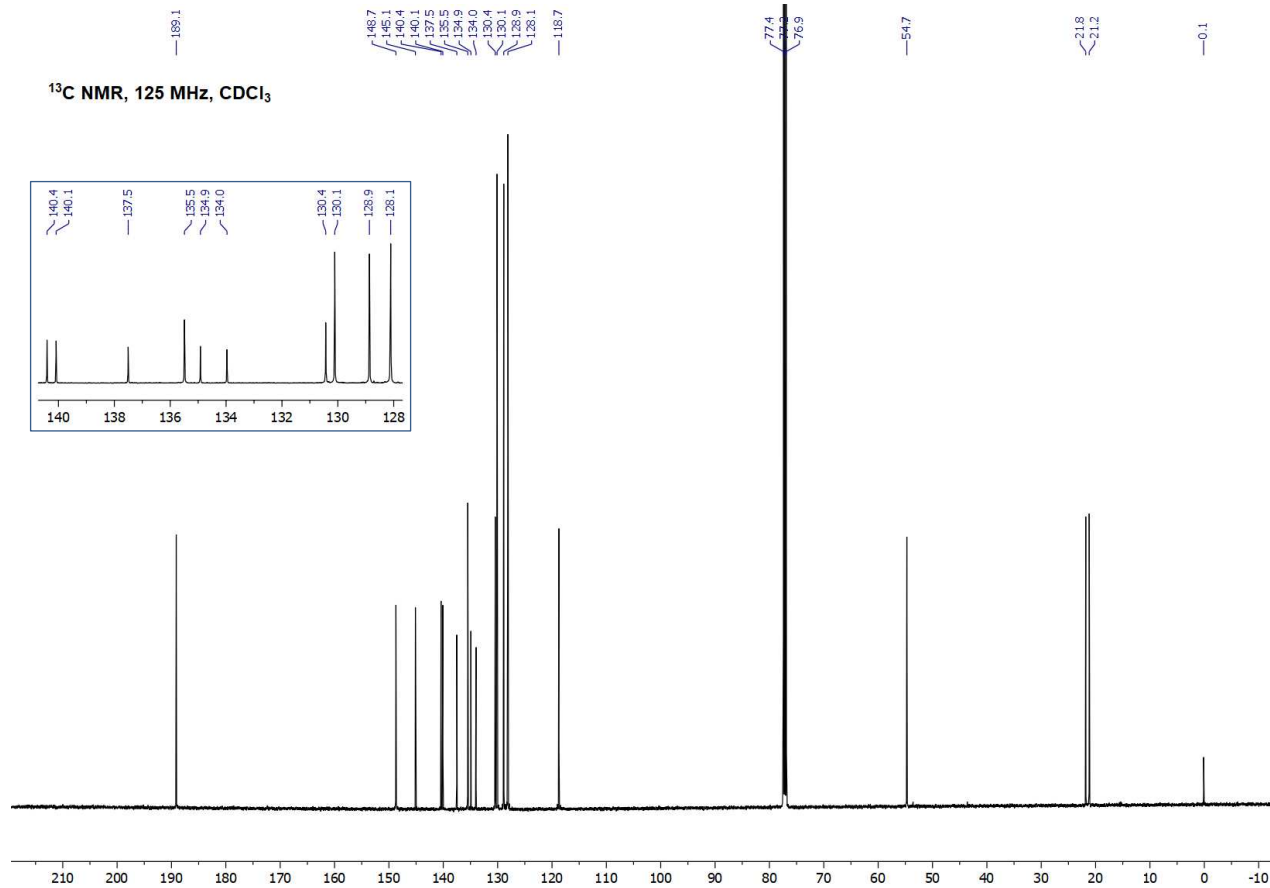
$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$

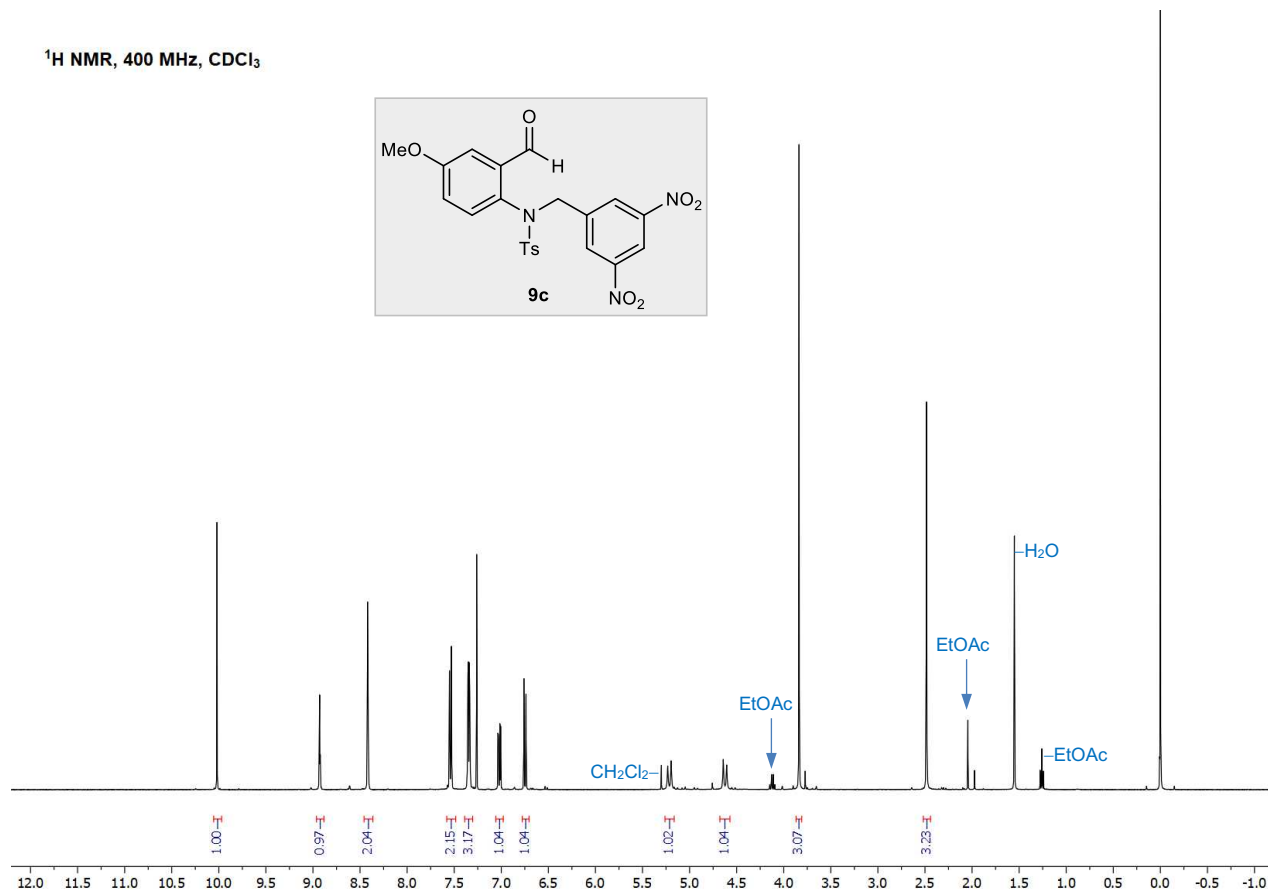
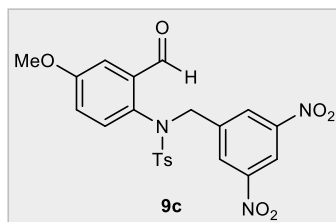
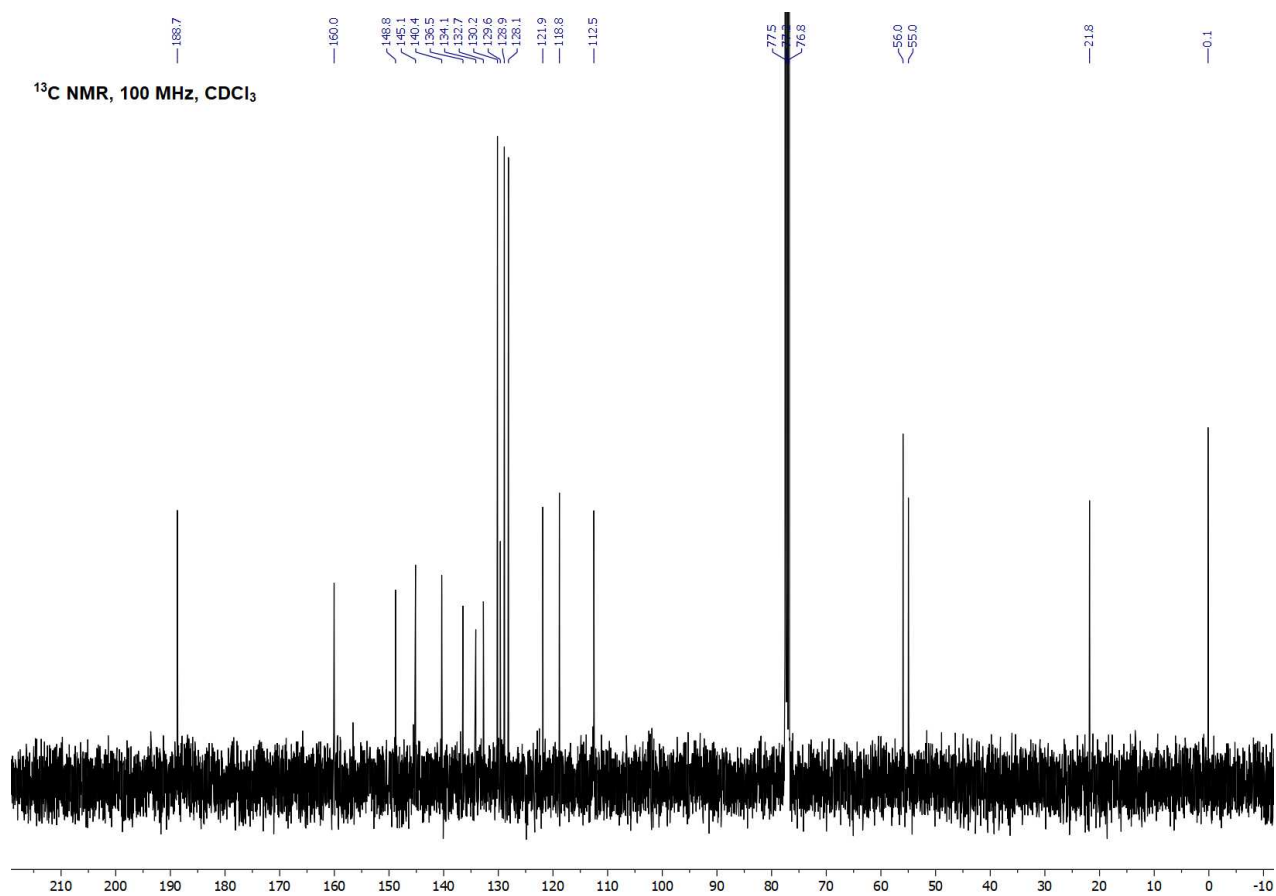


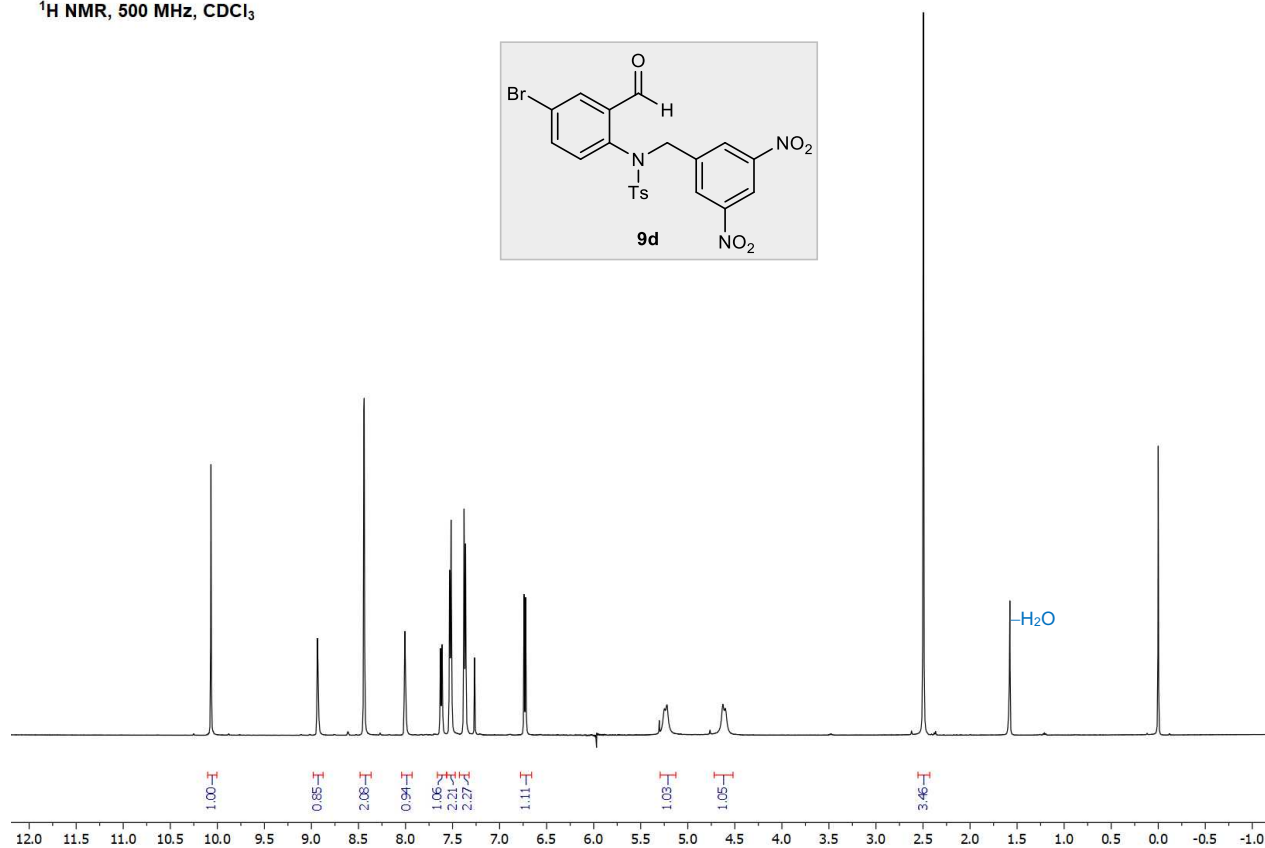
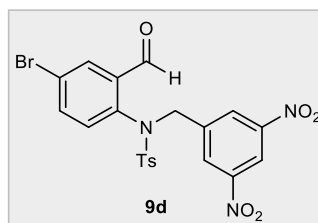
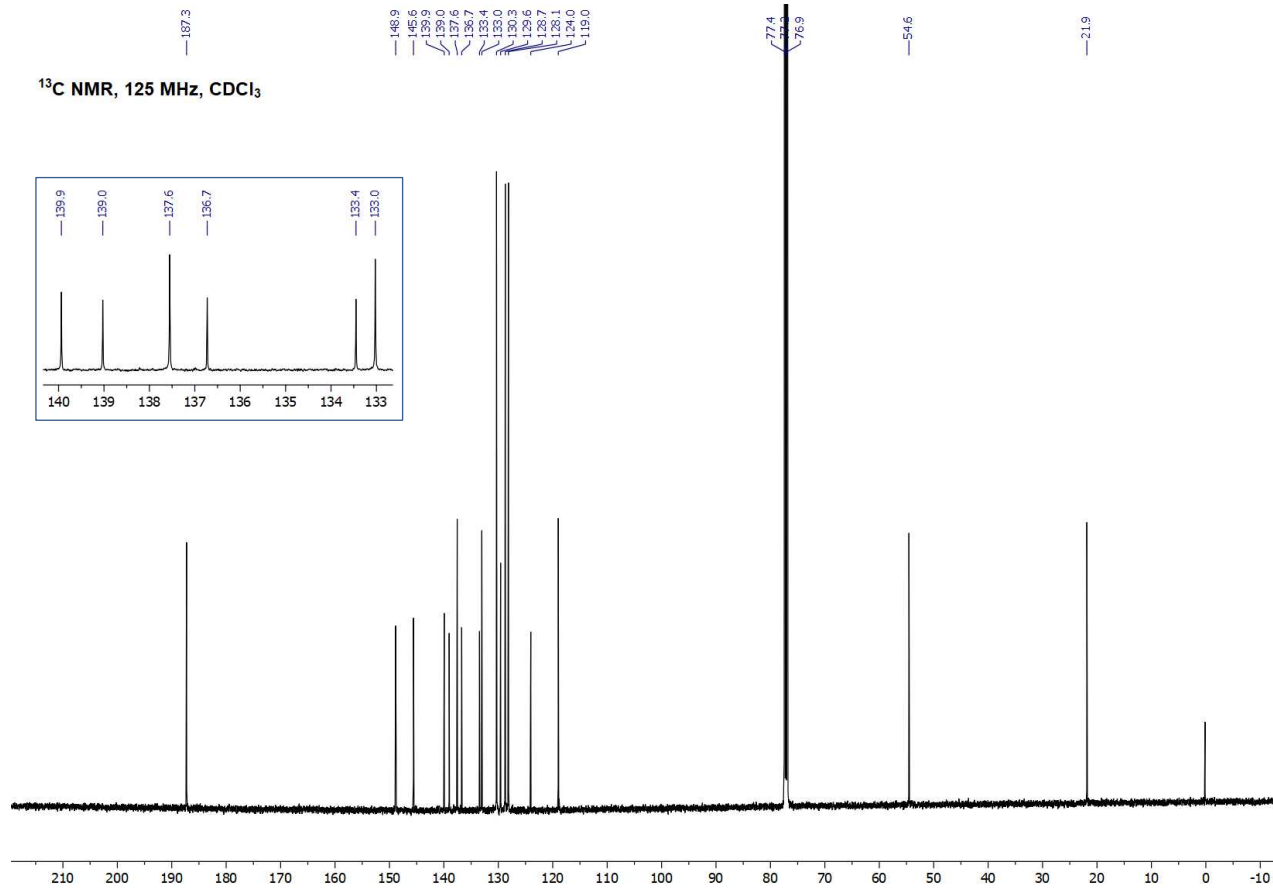
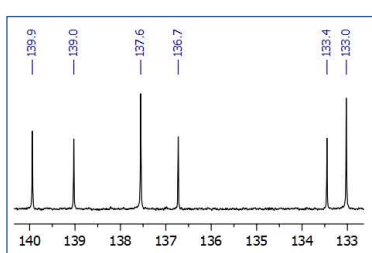
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

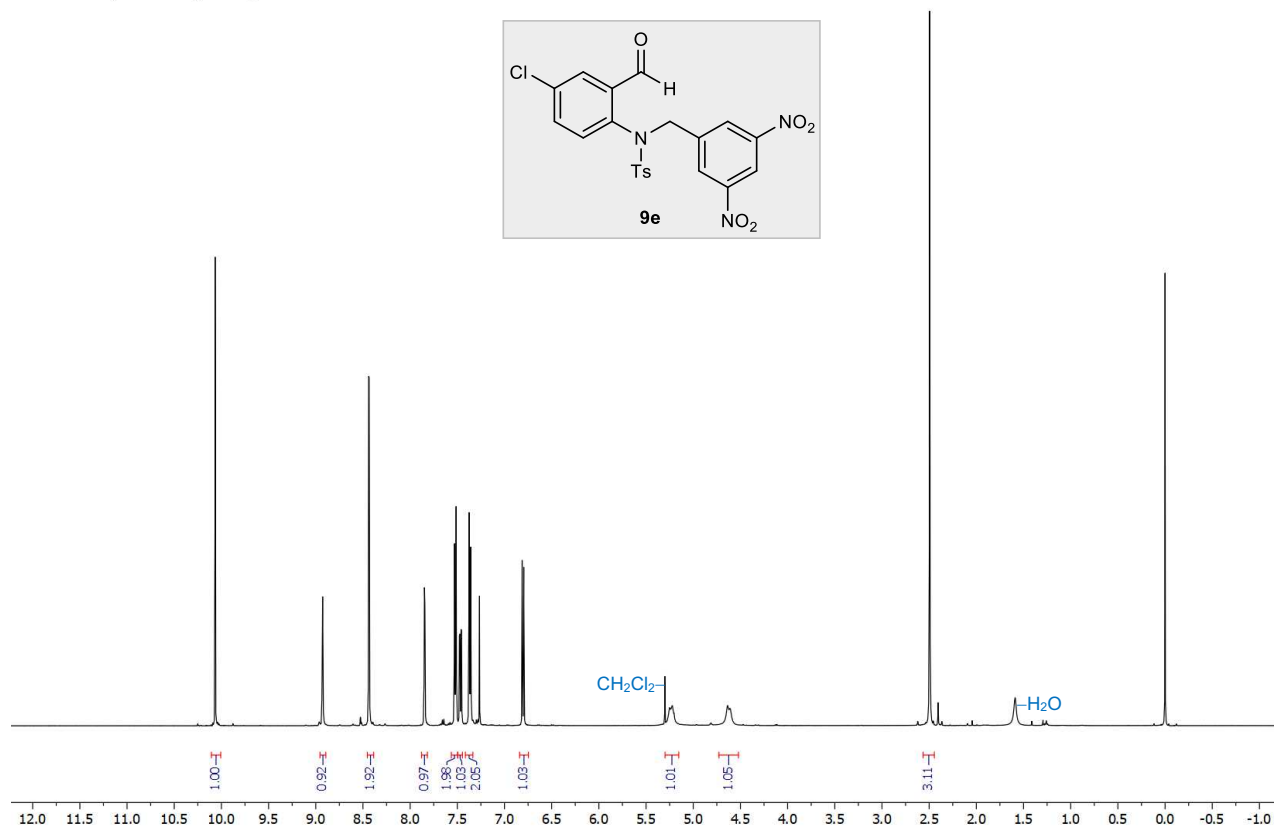
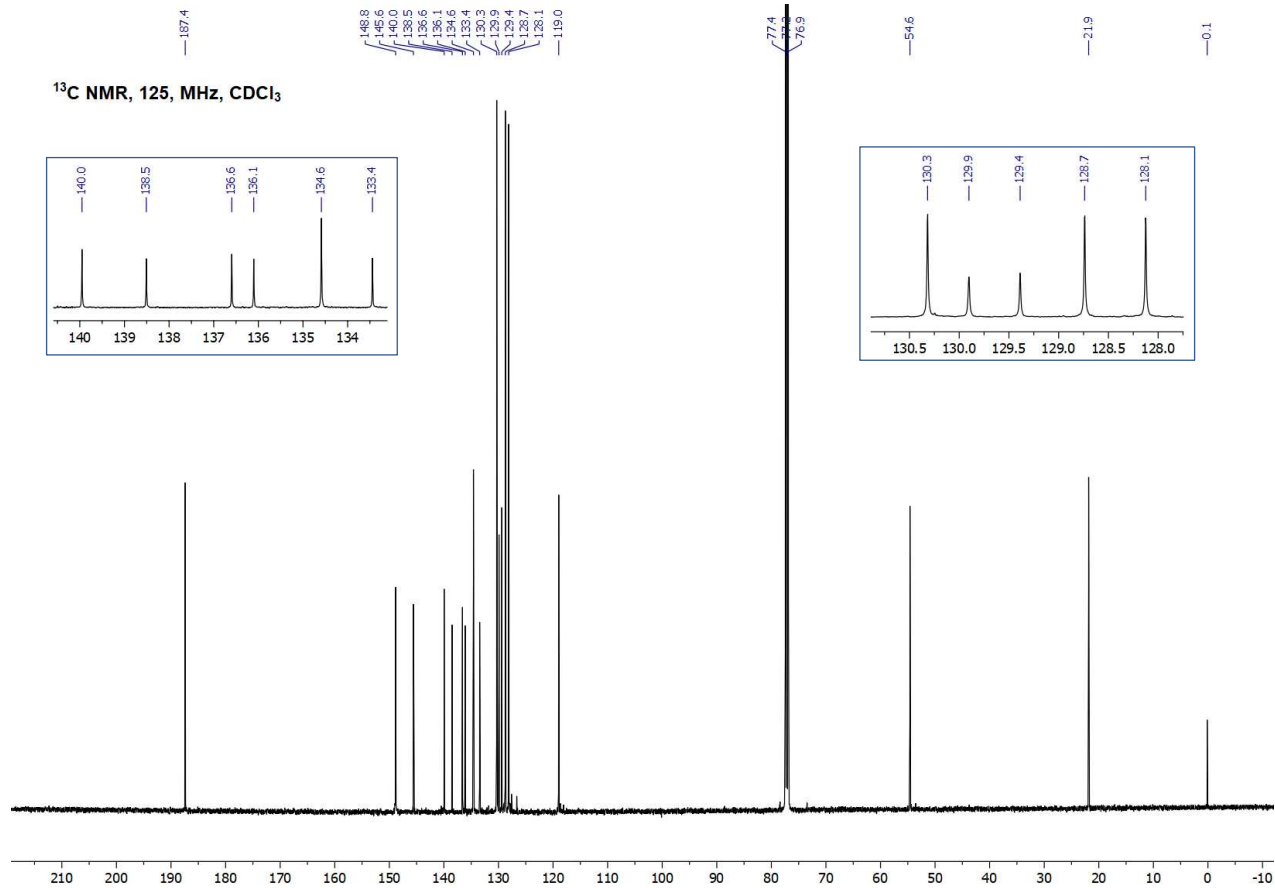
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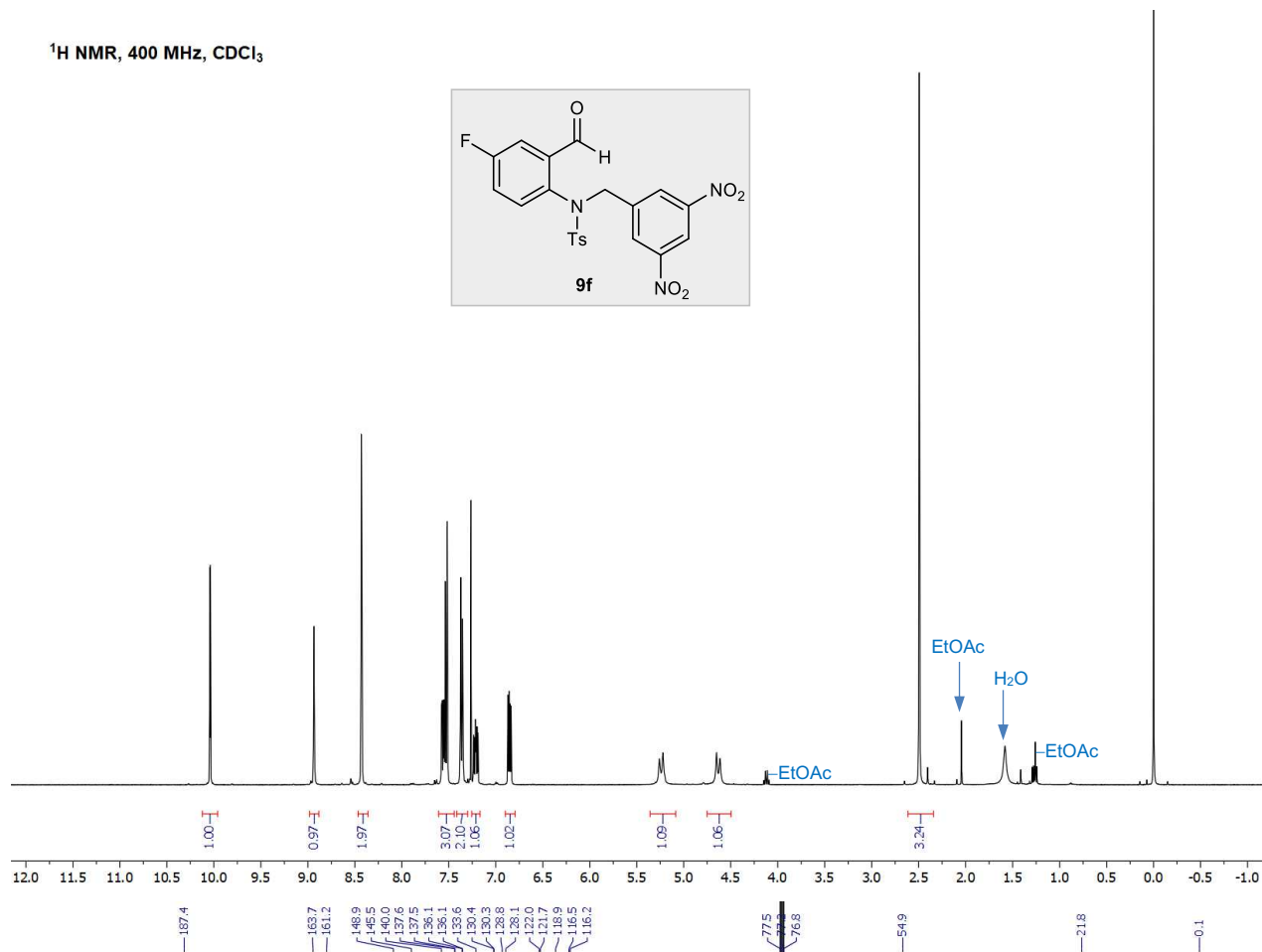
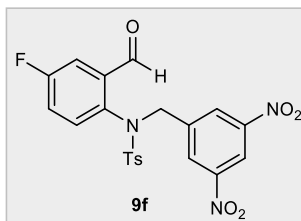
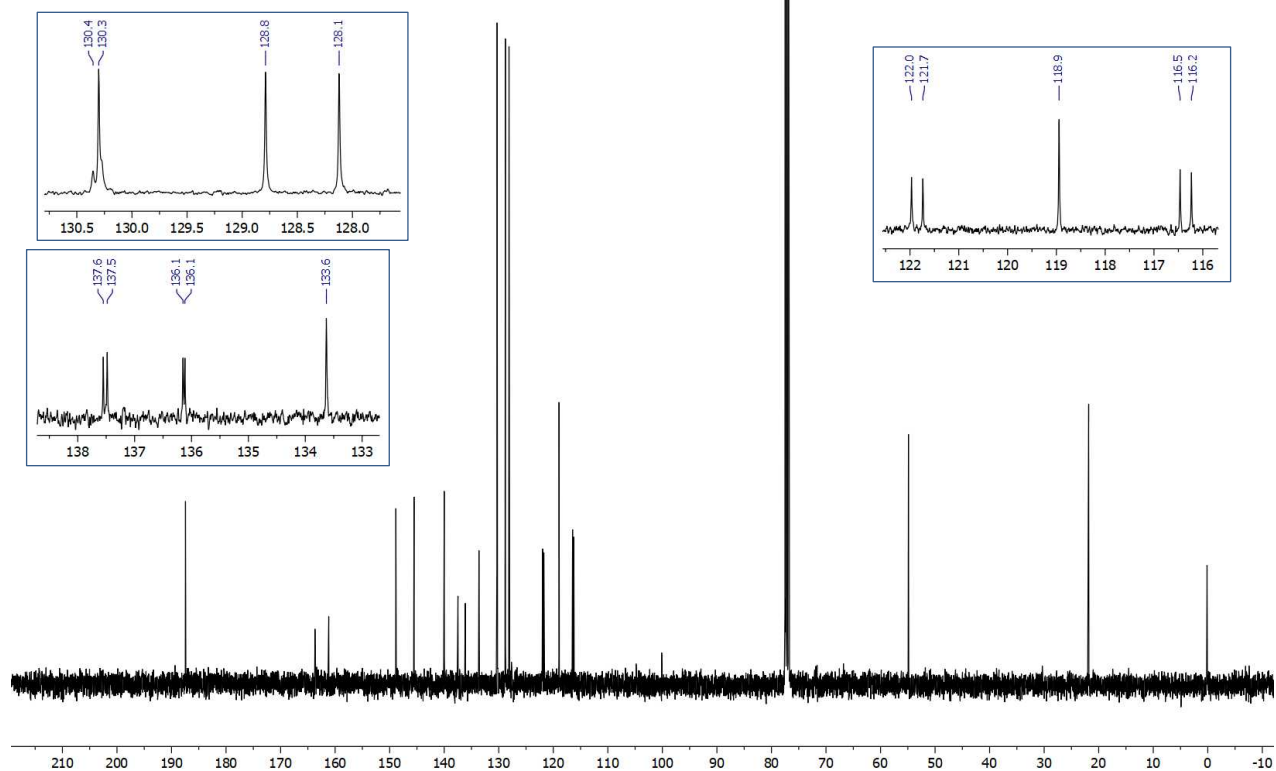


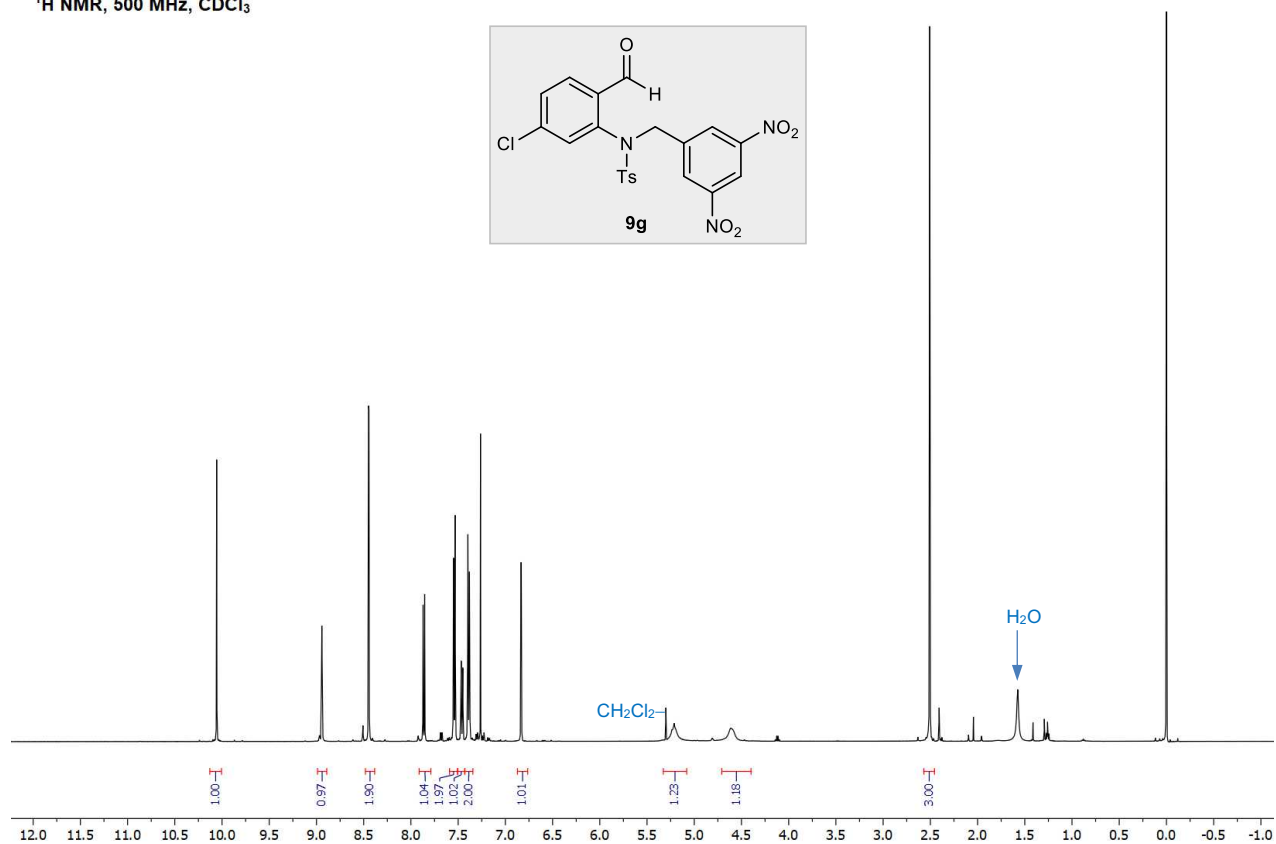
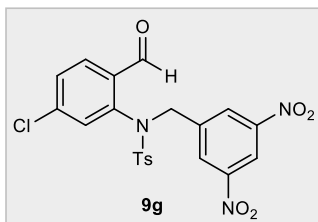
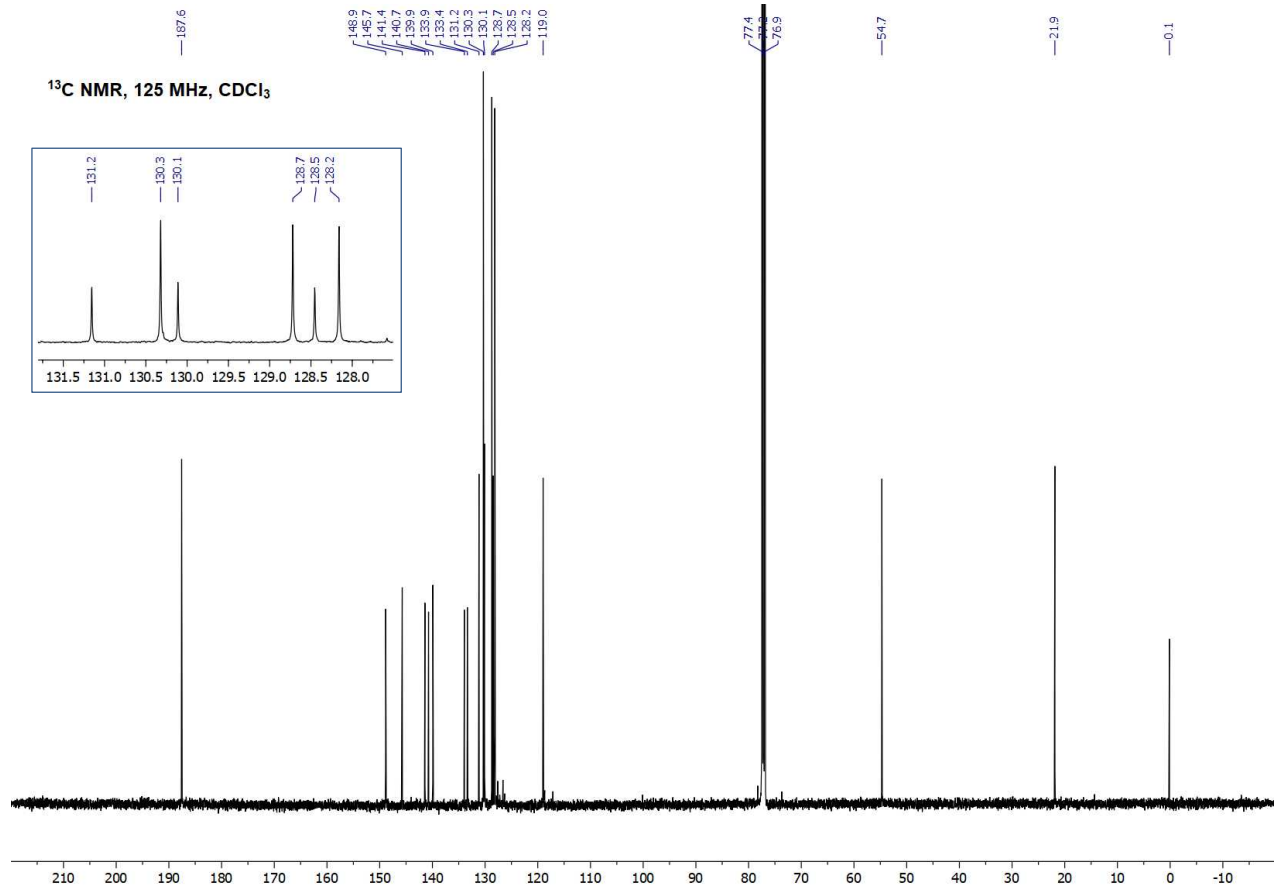
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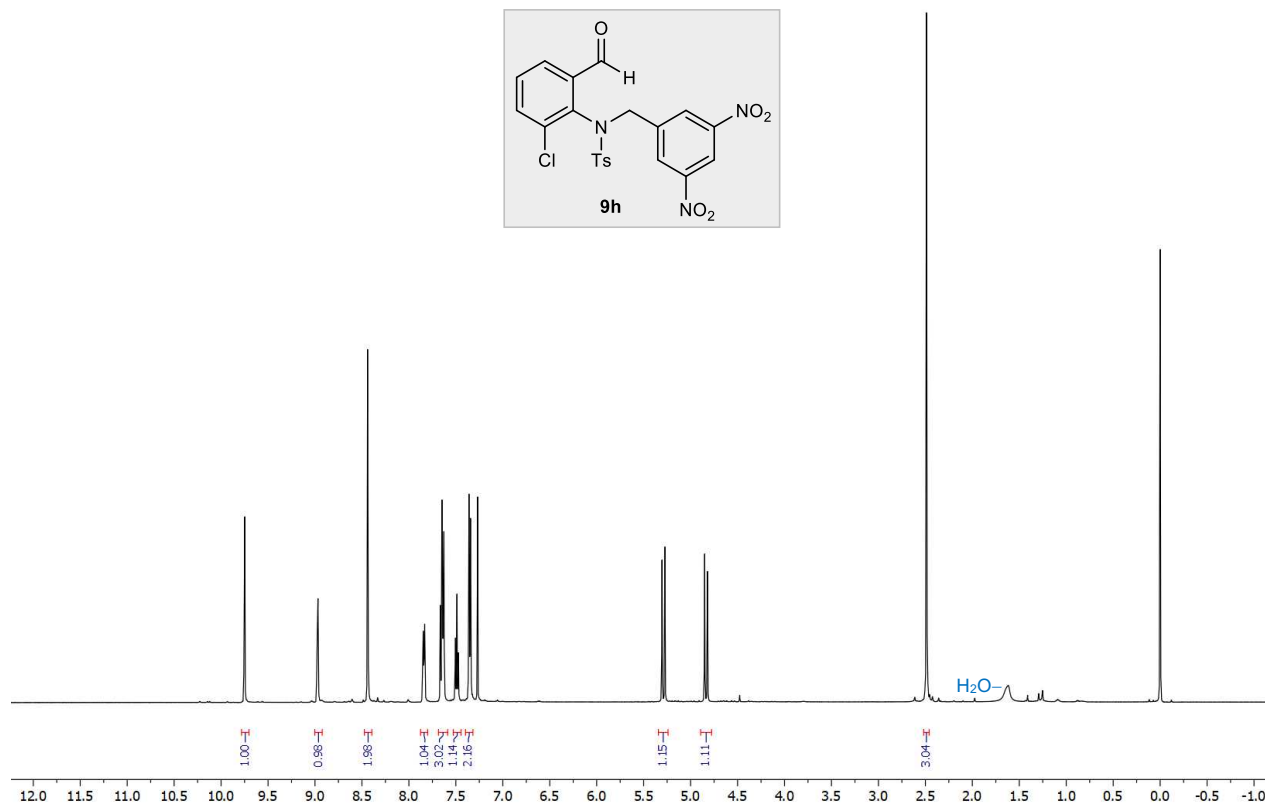
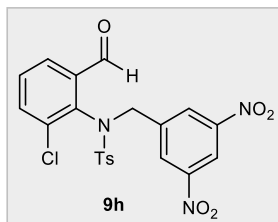
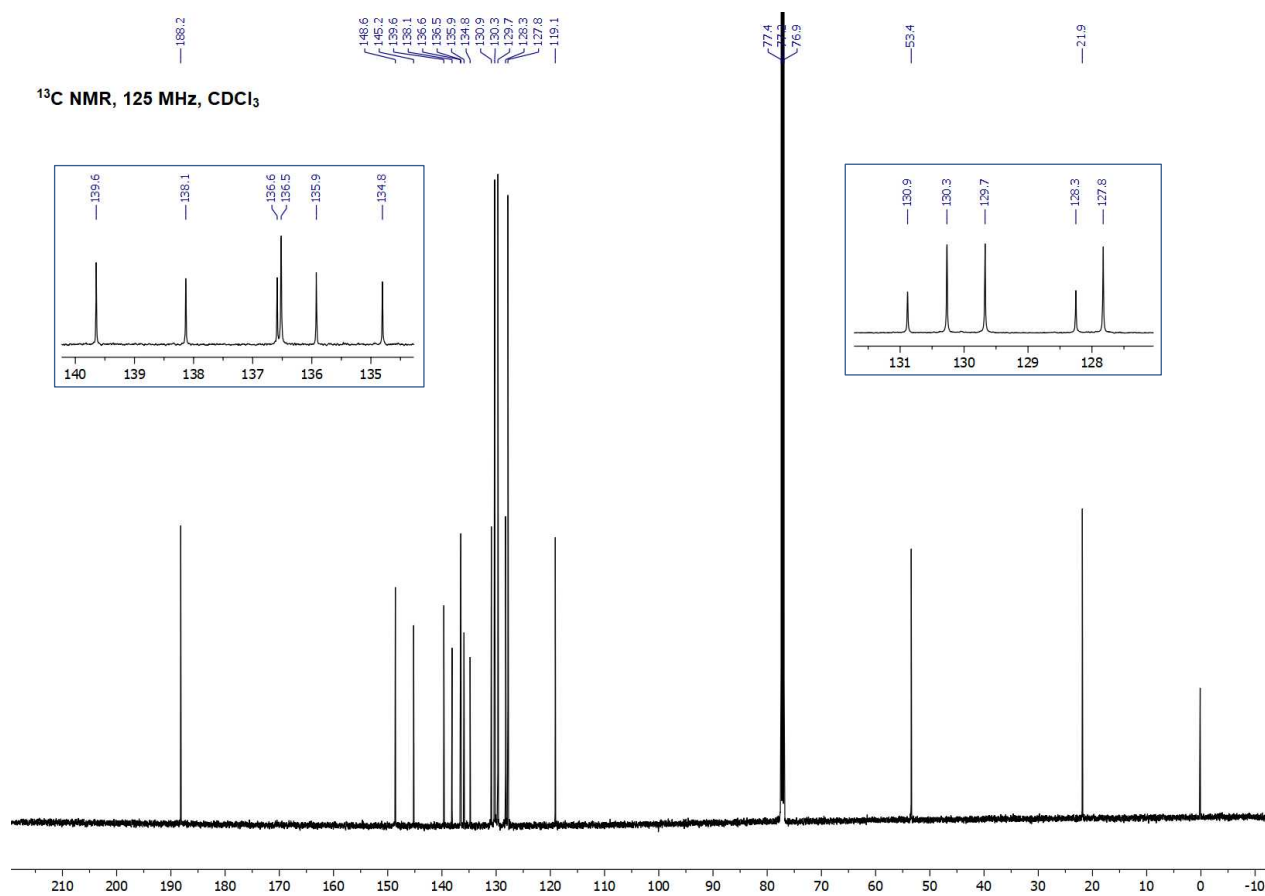
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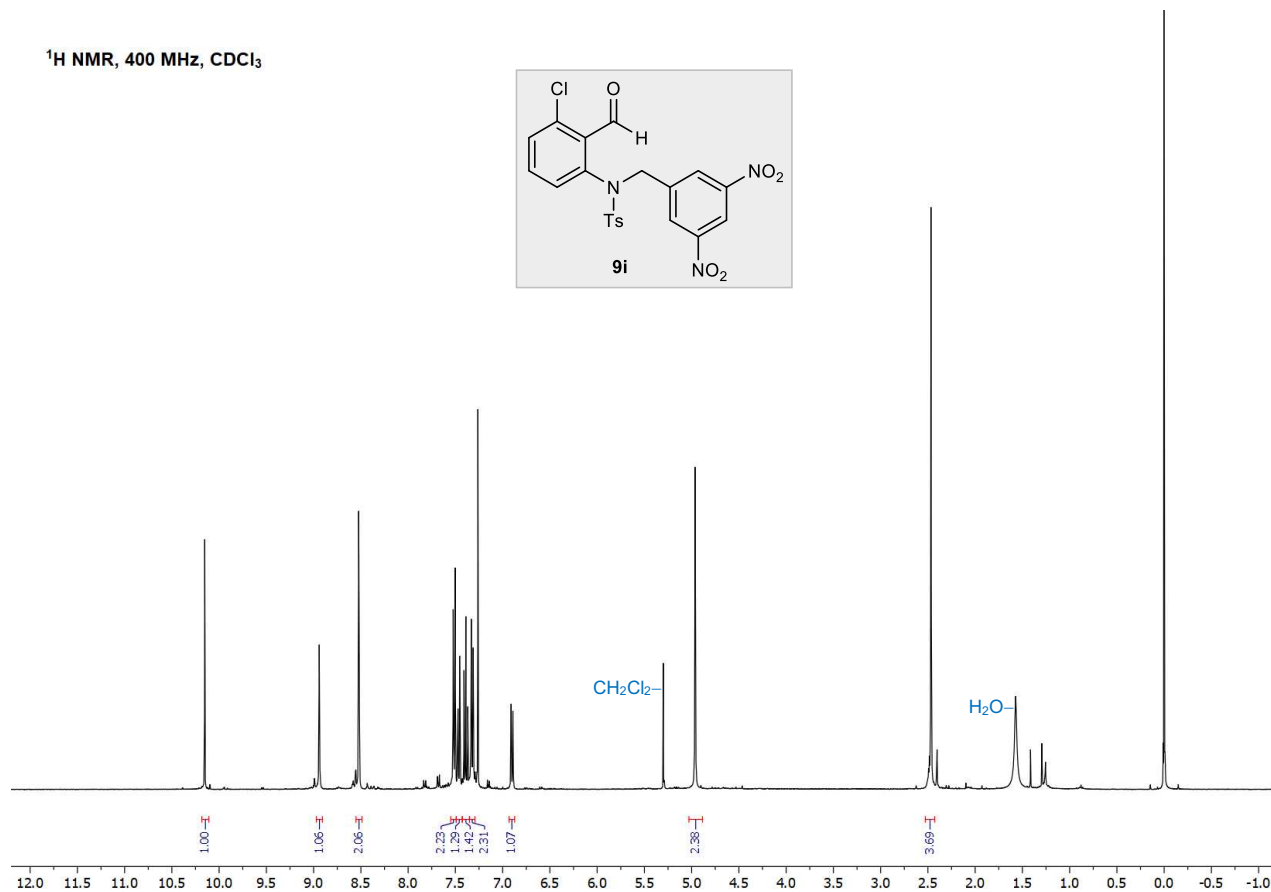
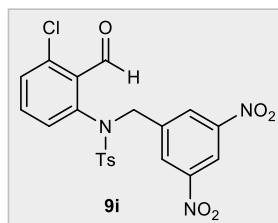
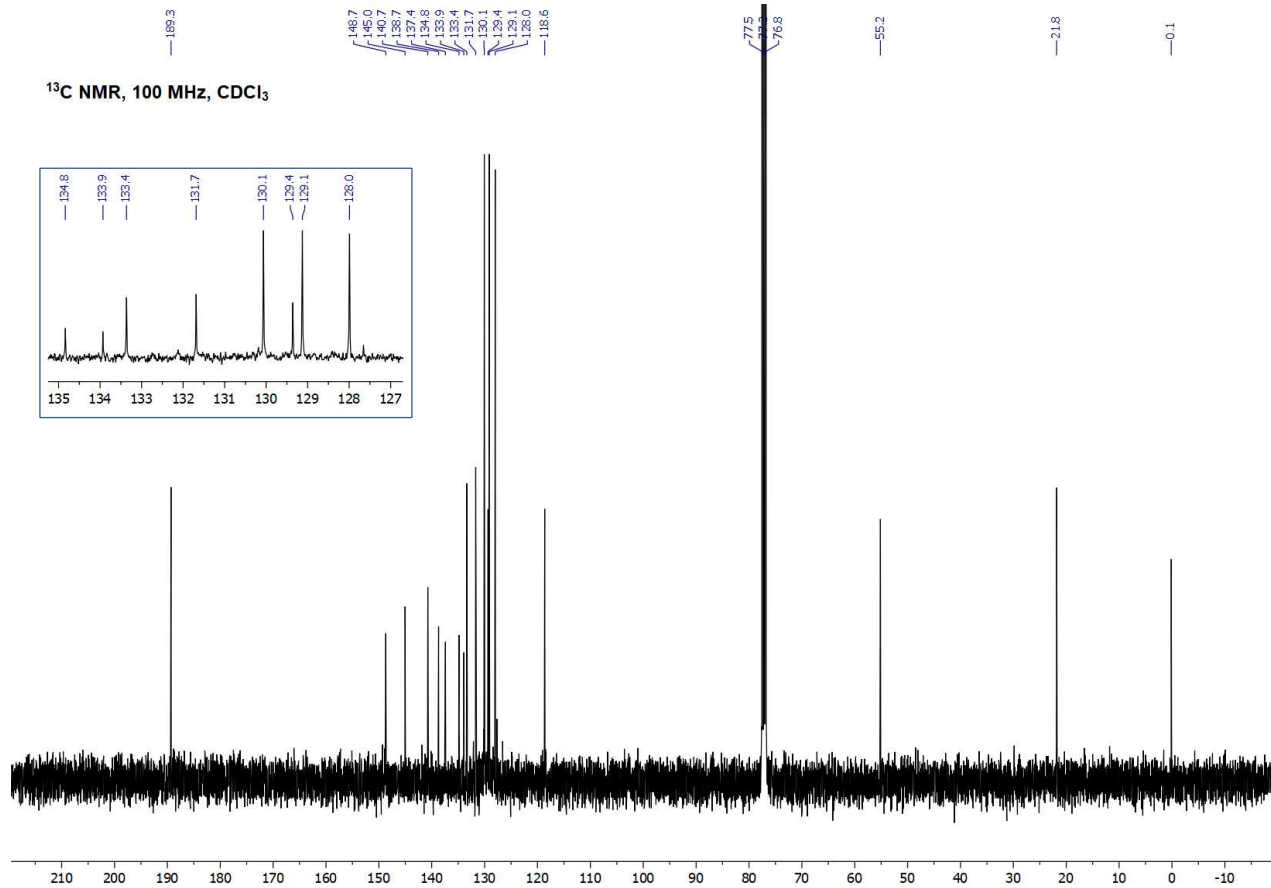
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125, MHz, CDCl<sub>3</sub>

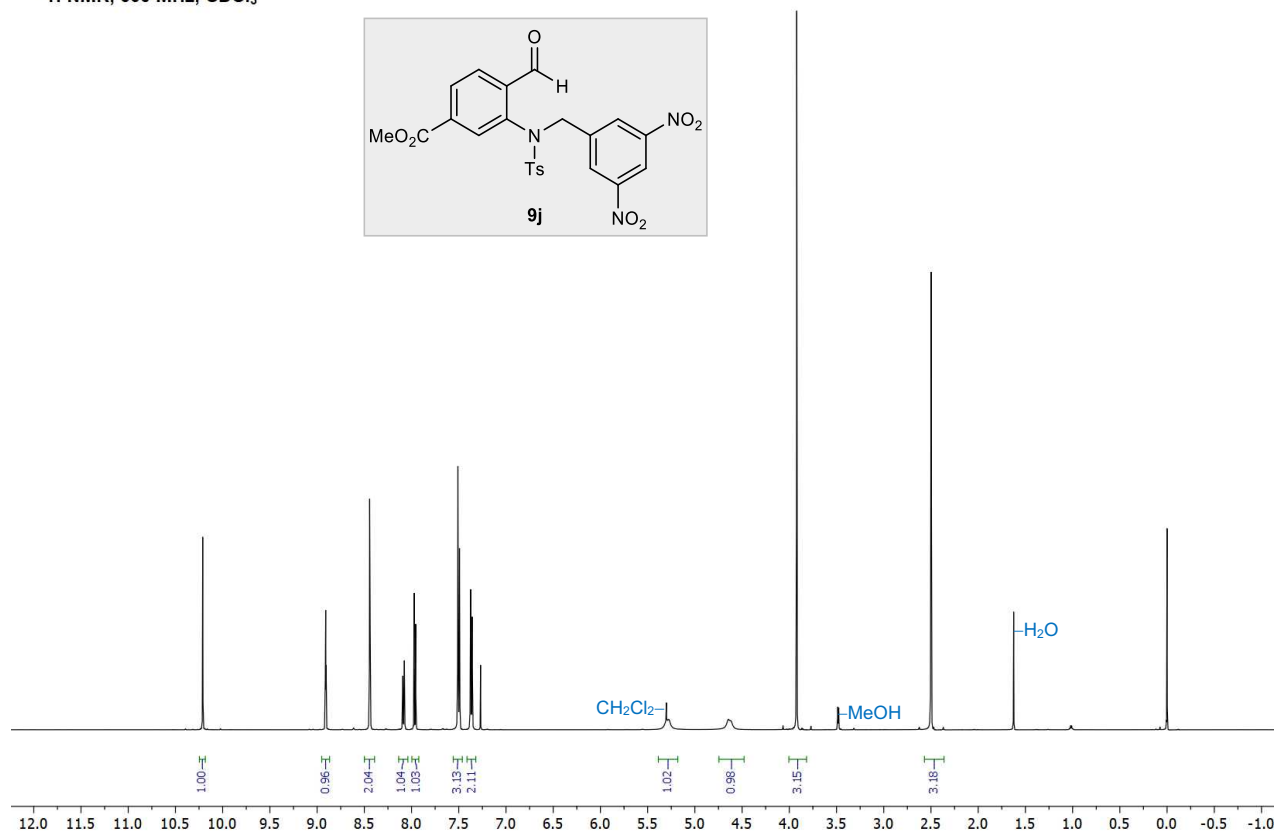
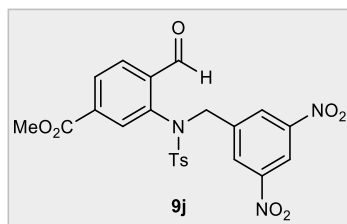
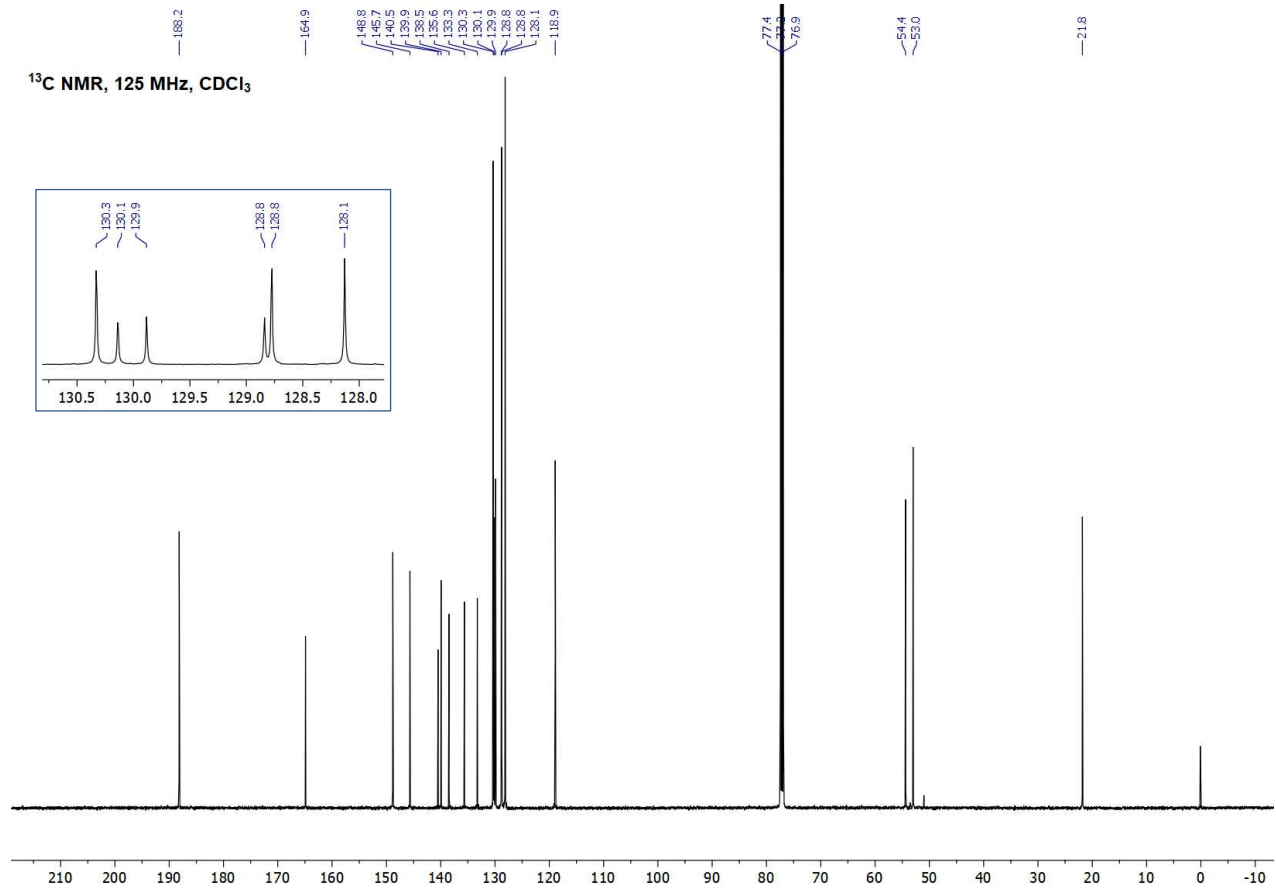
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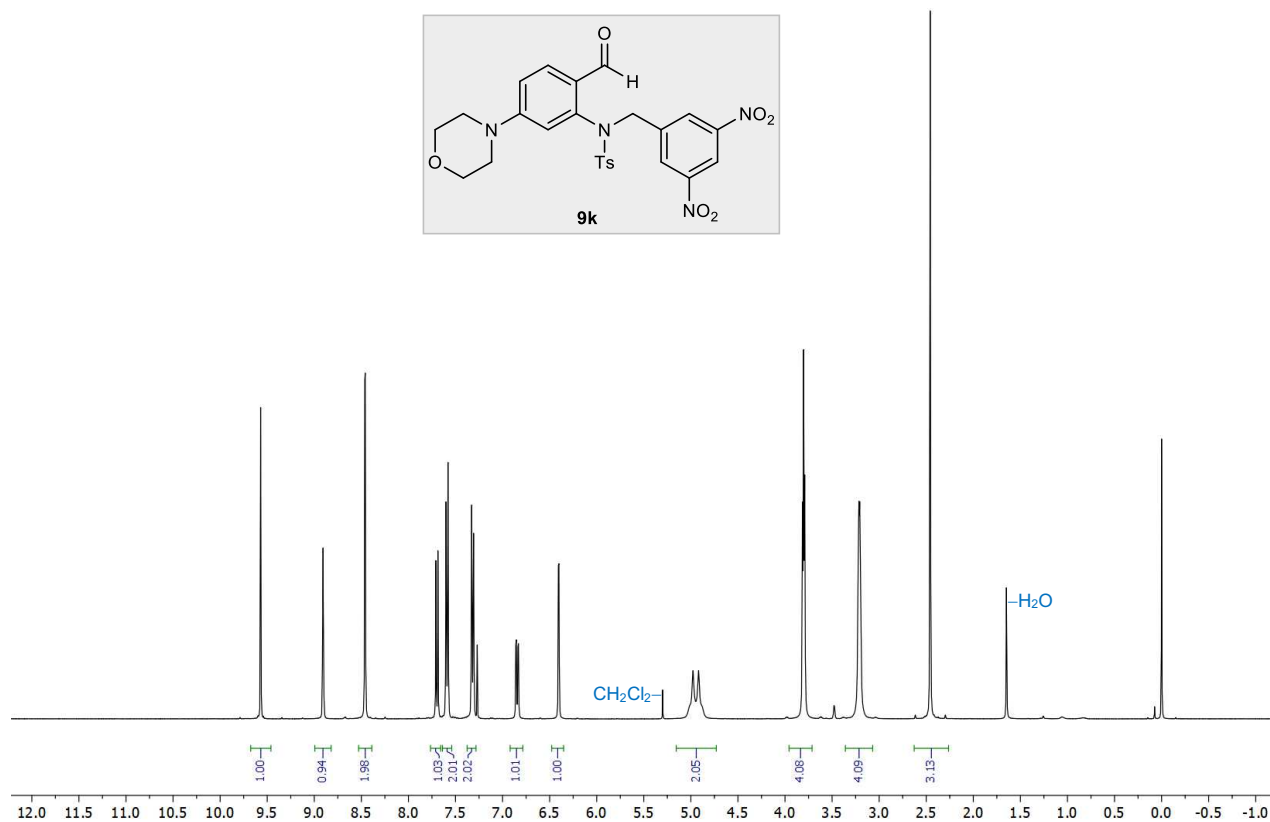
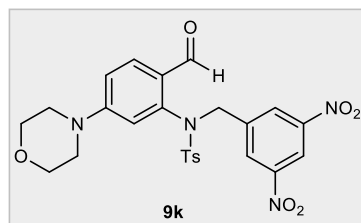
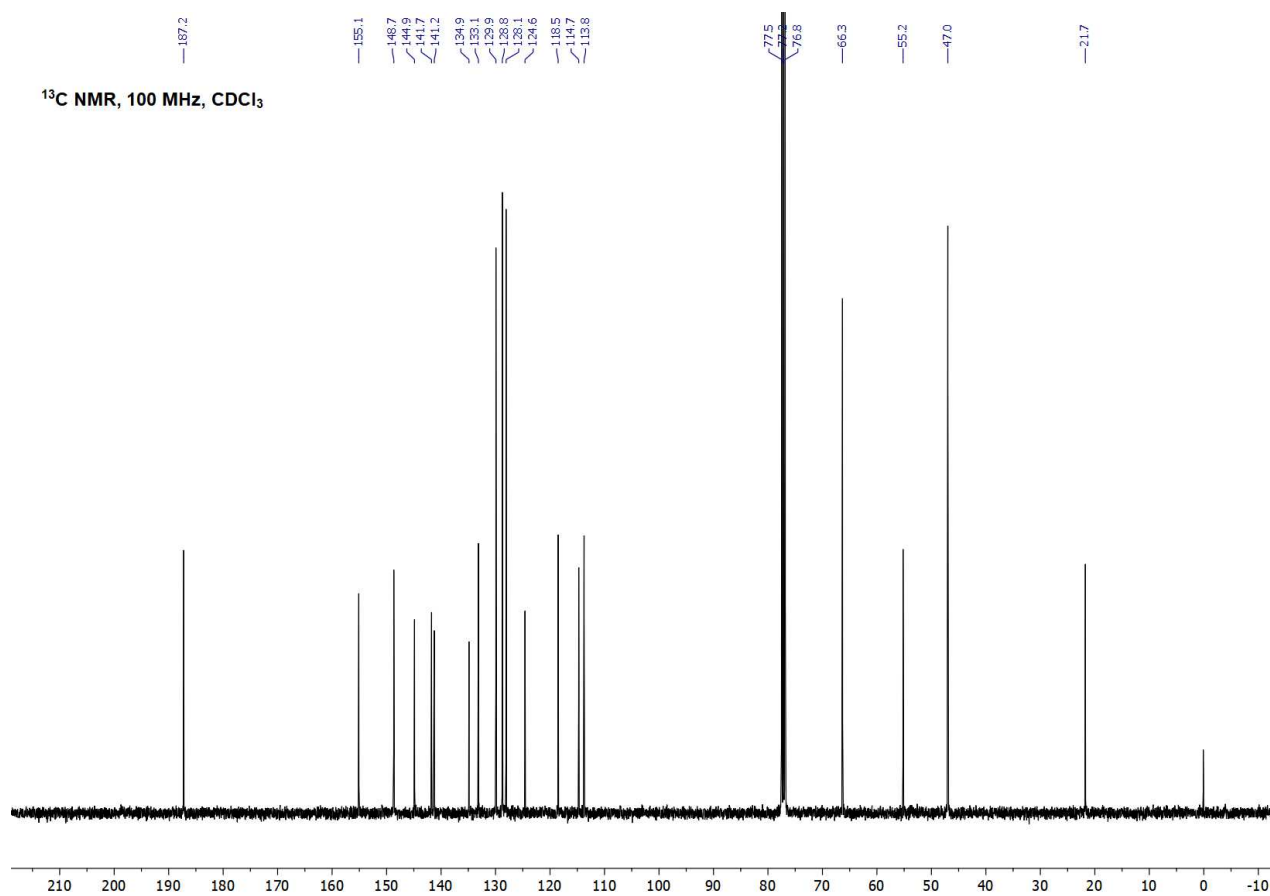
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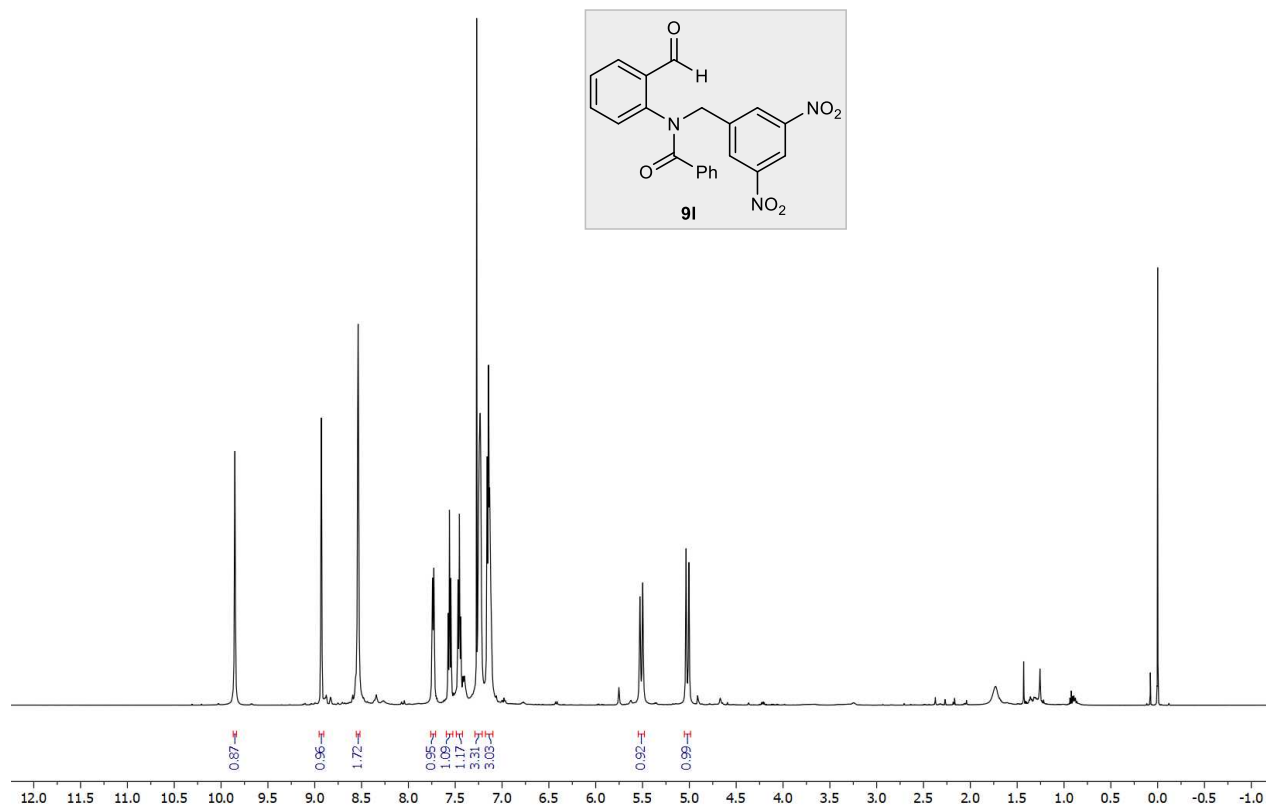
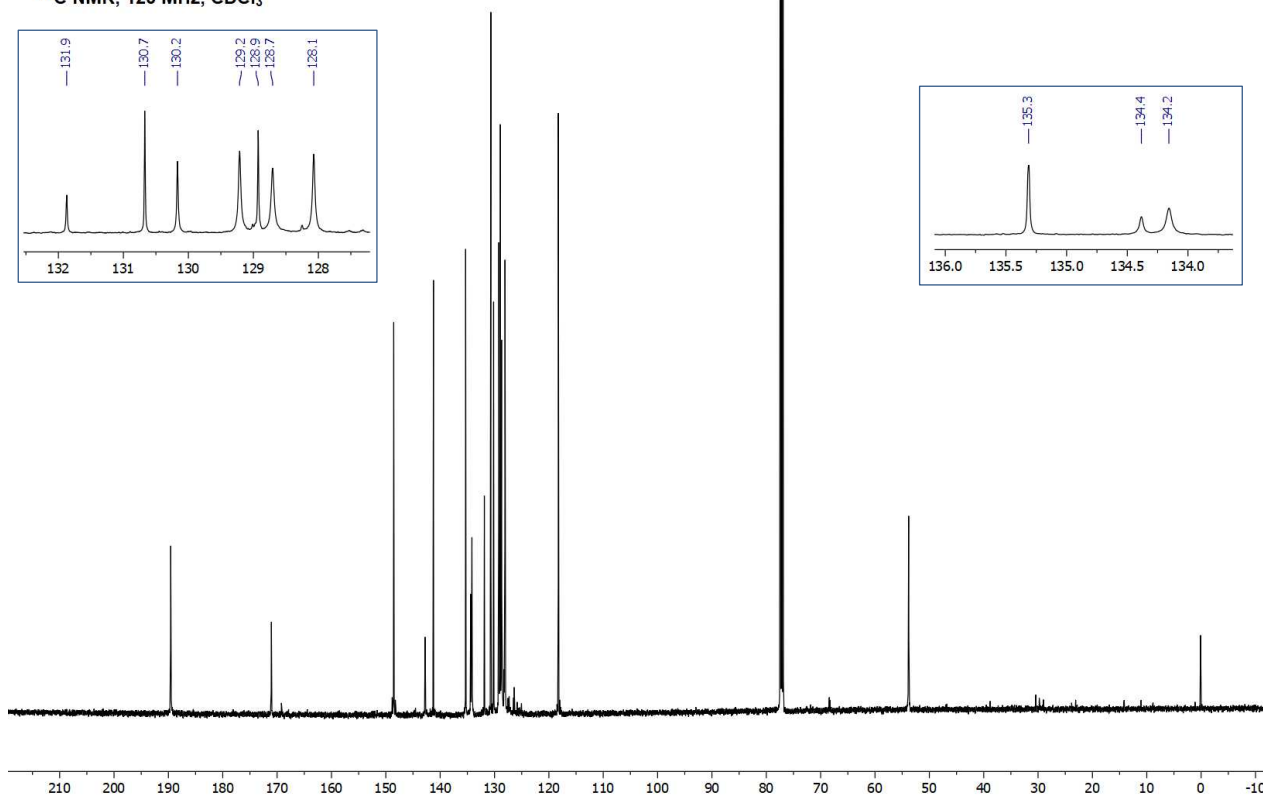
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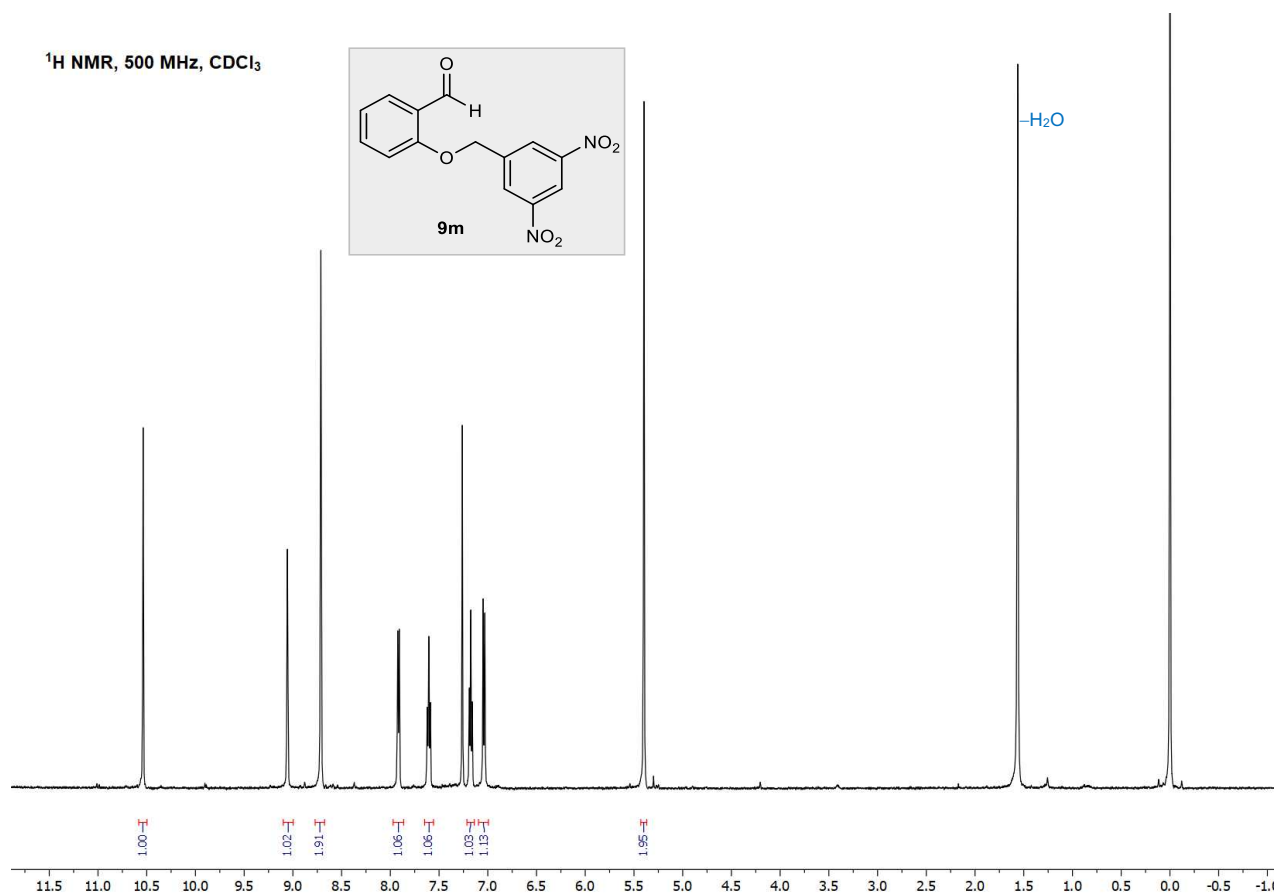
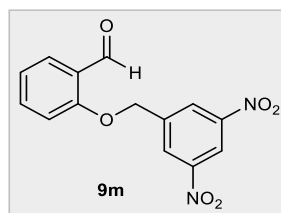
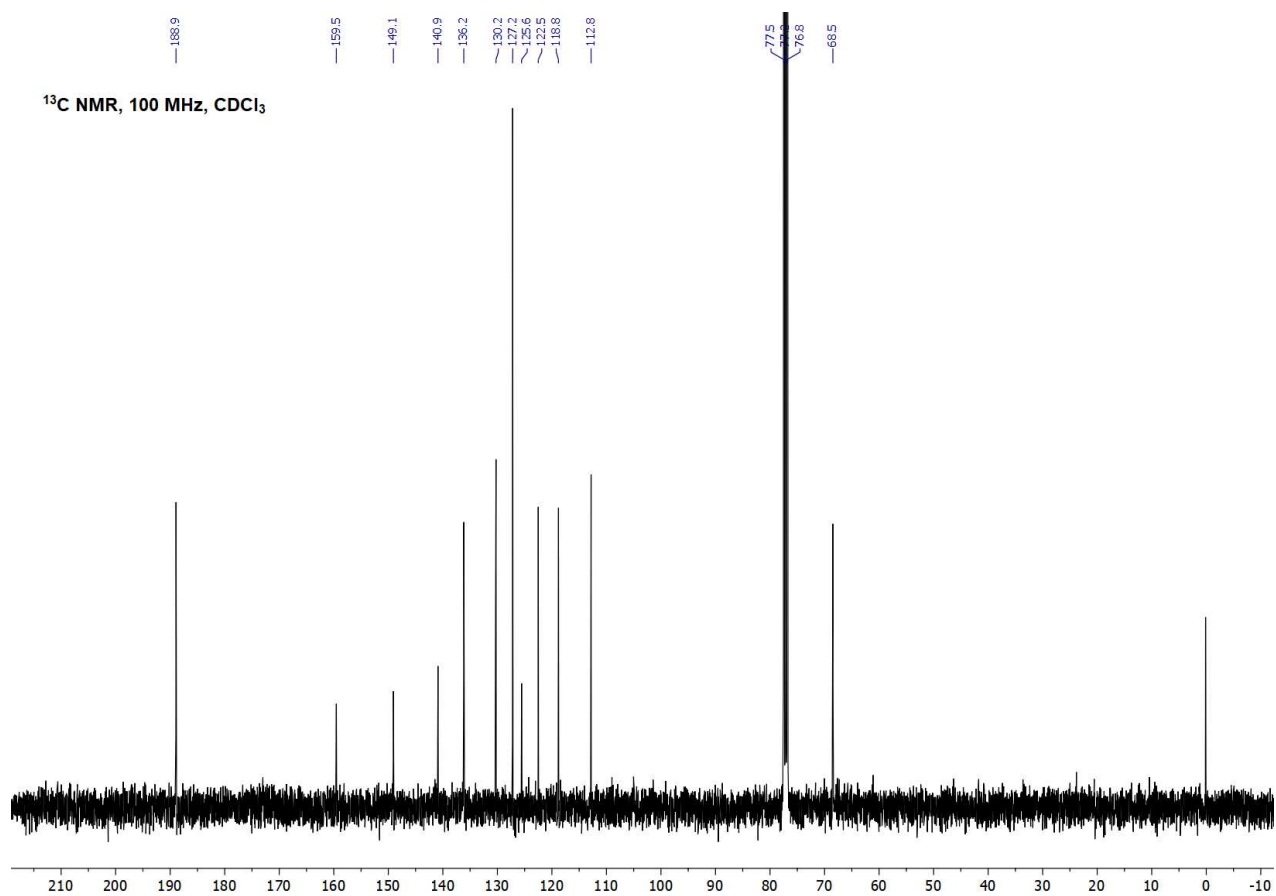
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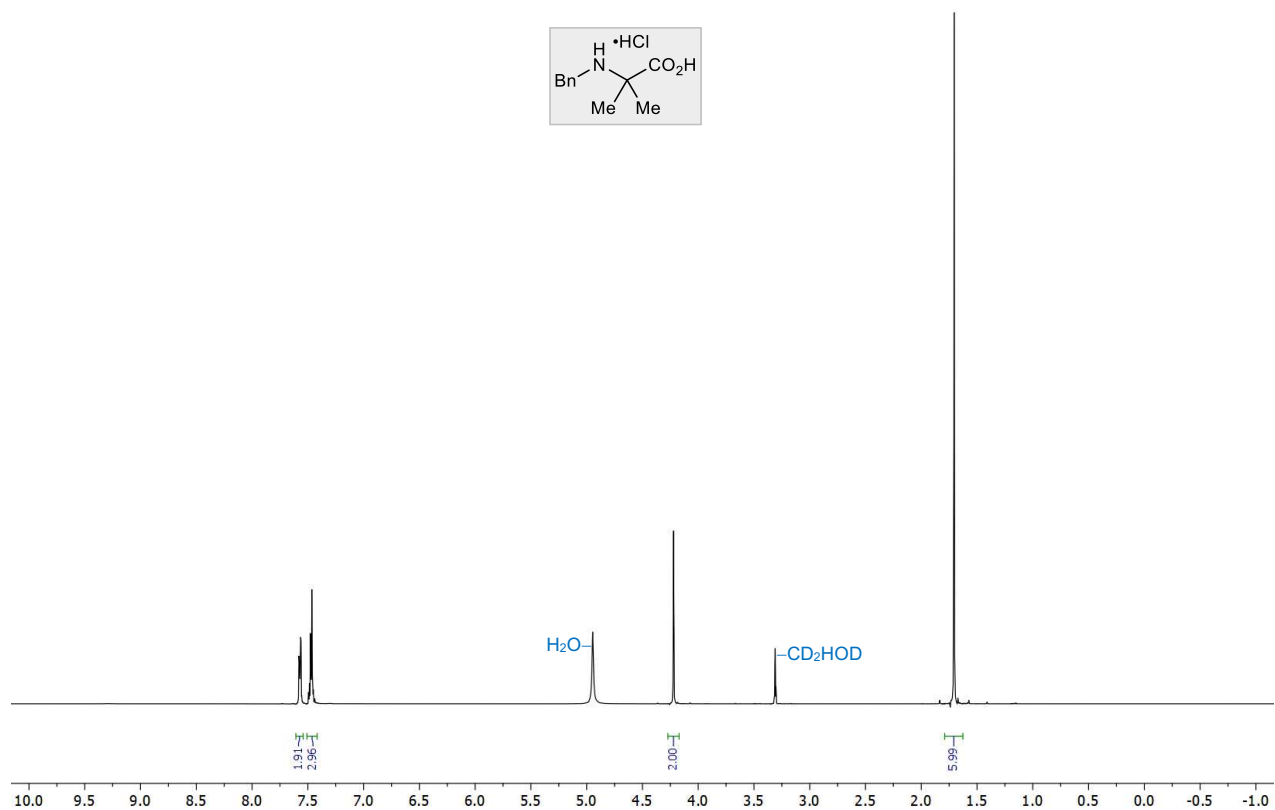
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<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

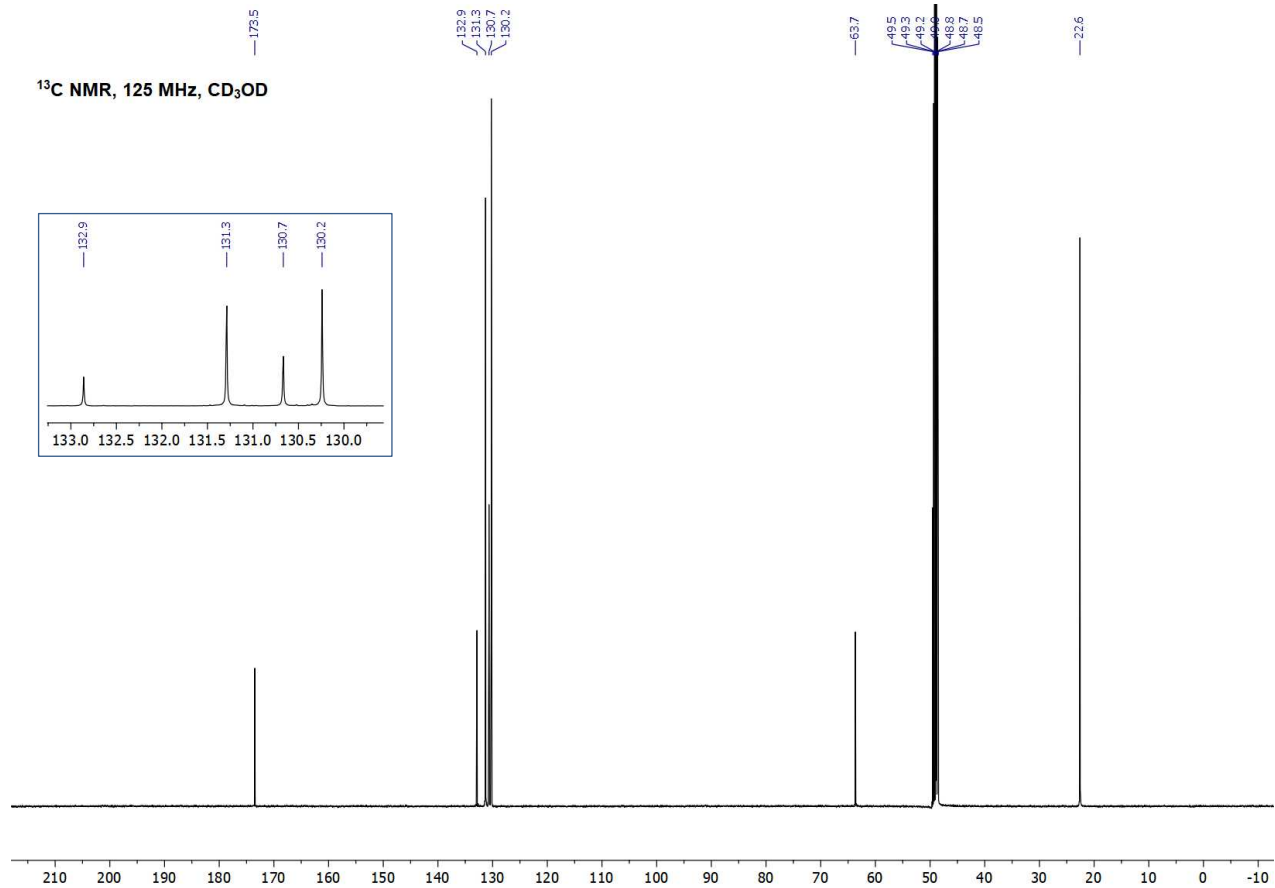
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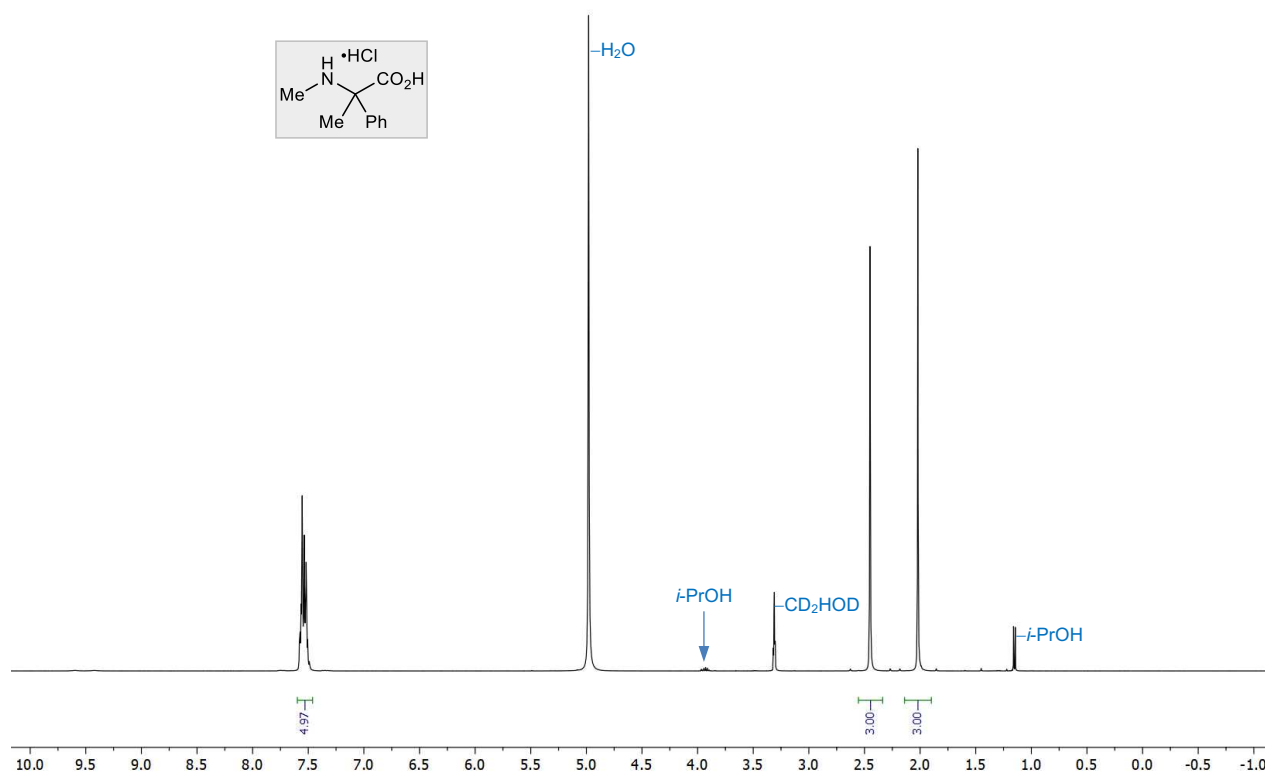
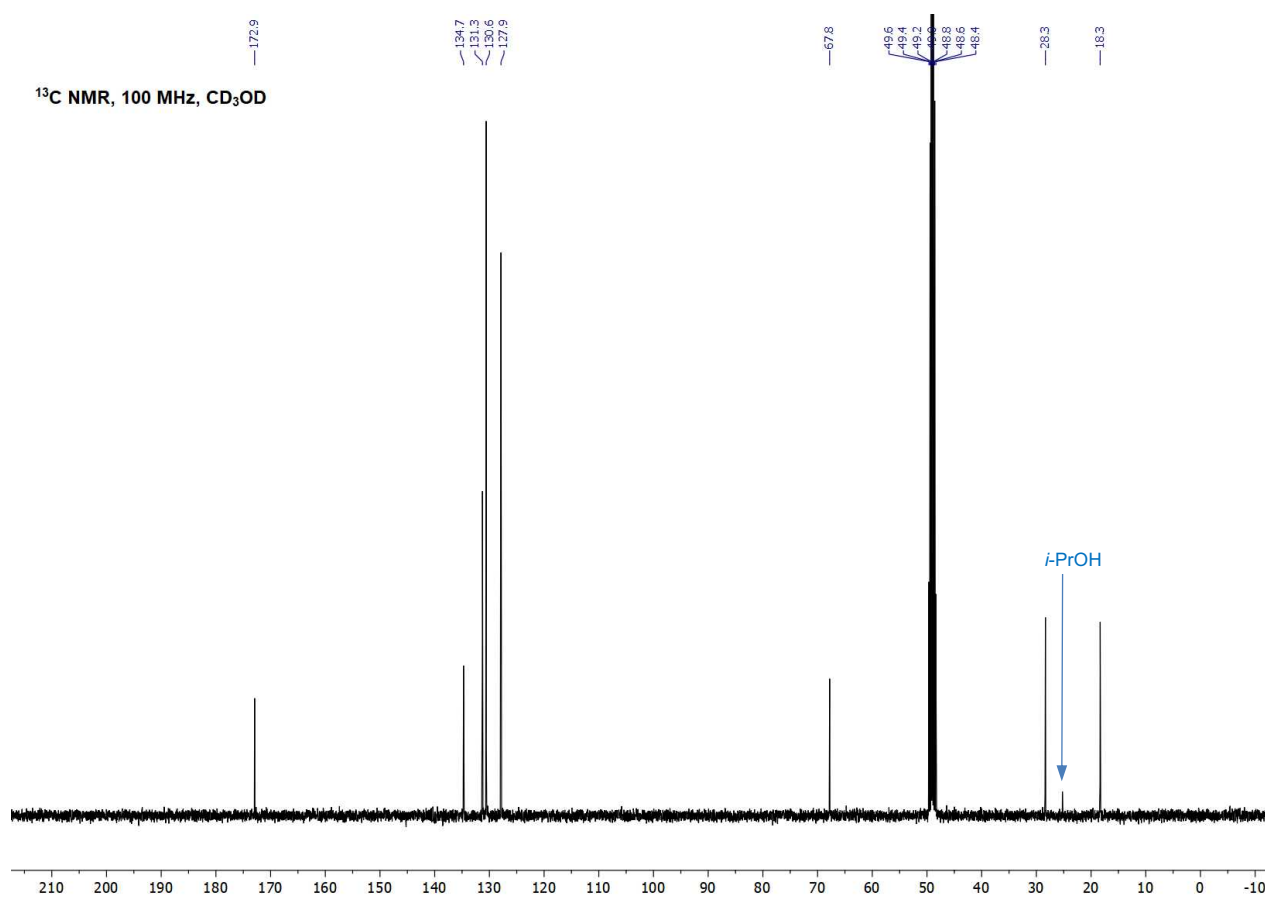
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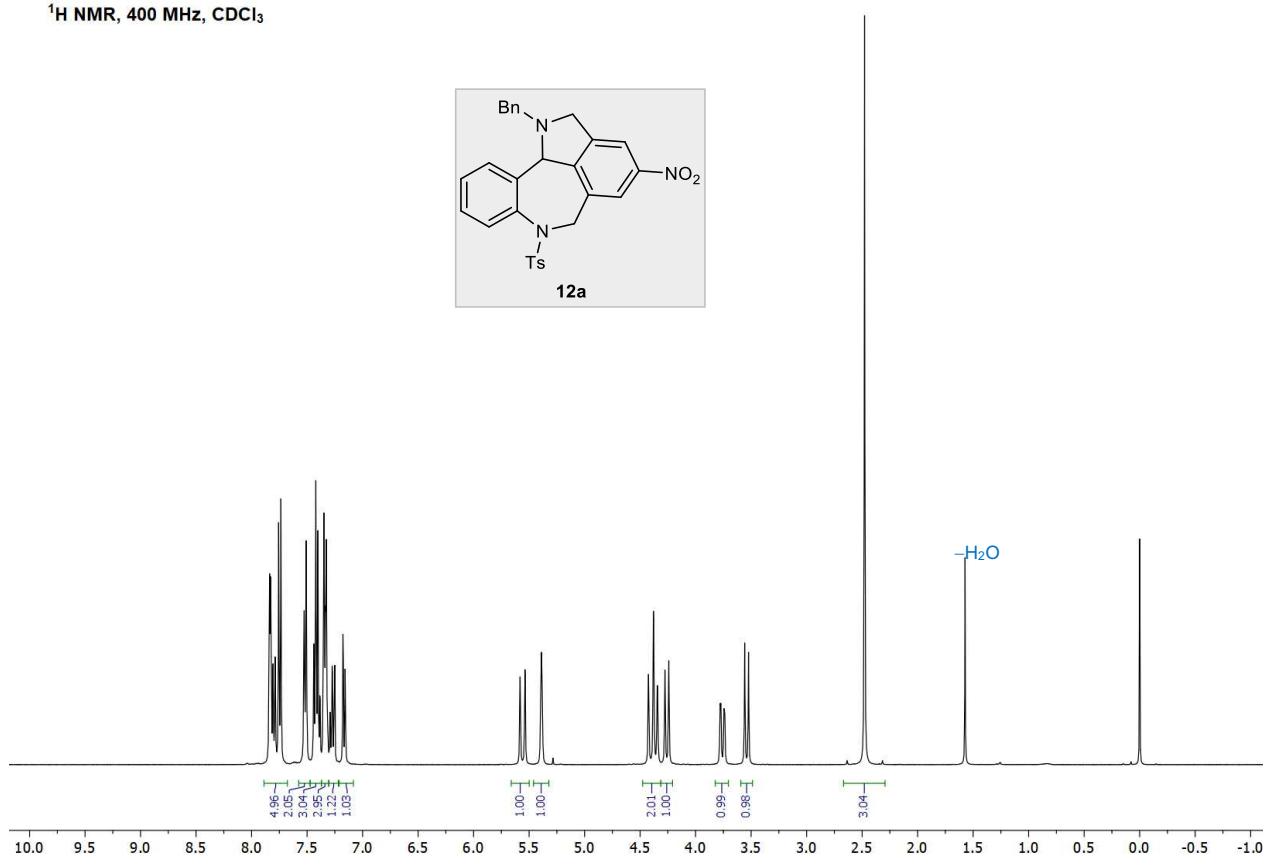
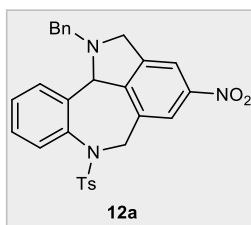
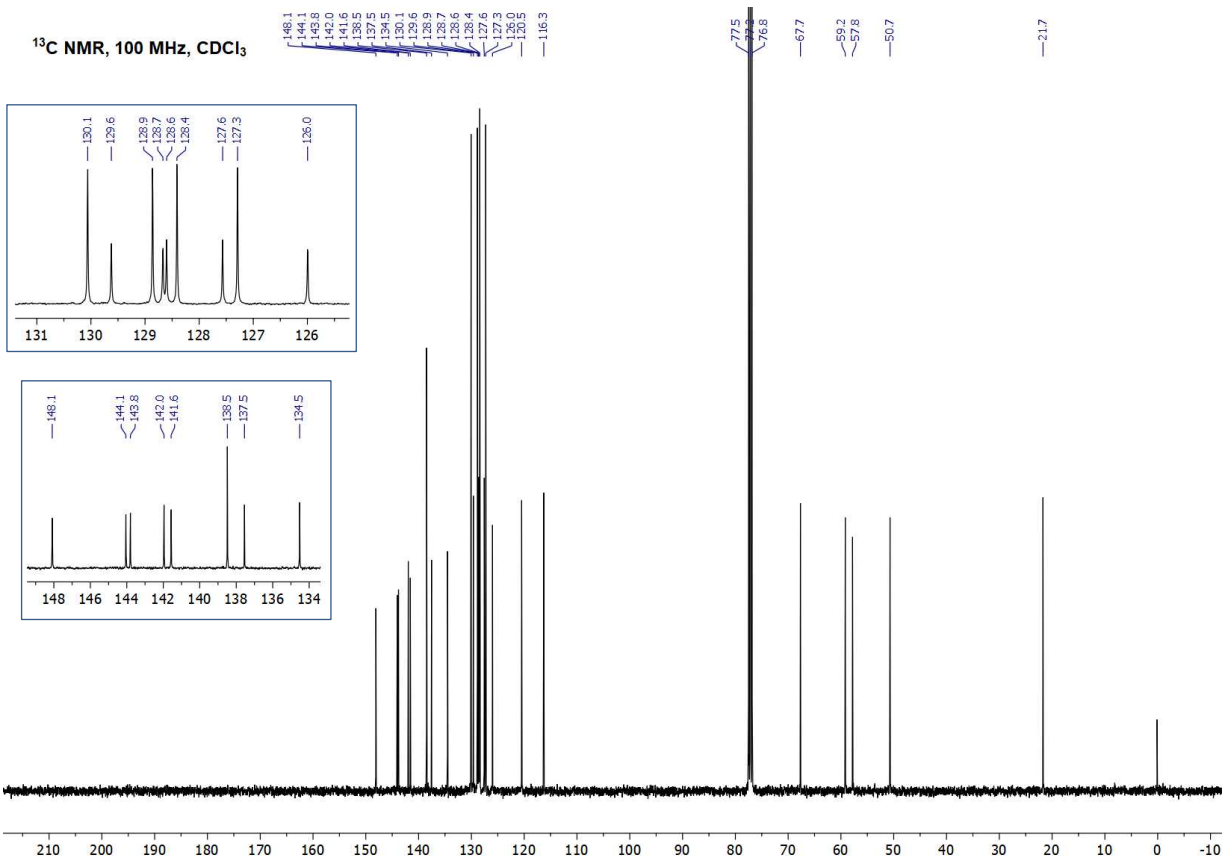
$^1\text{H}$  NMR, 500 MHz,  $\text{CD}_3\text{OD}$

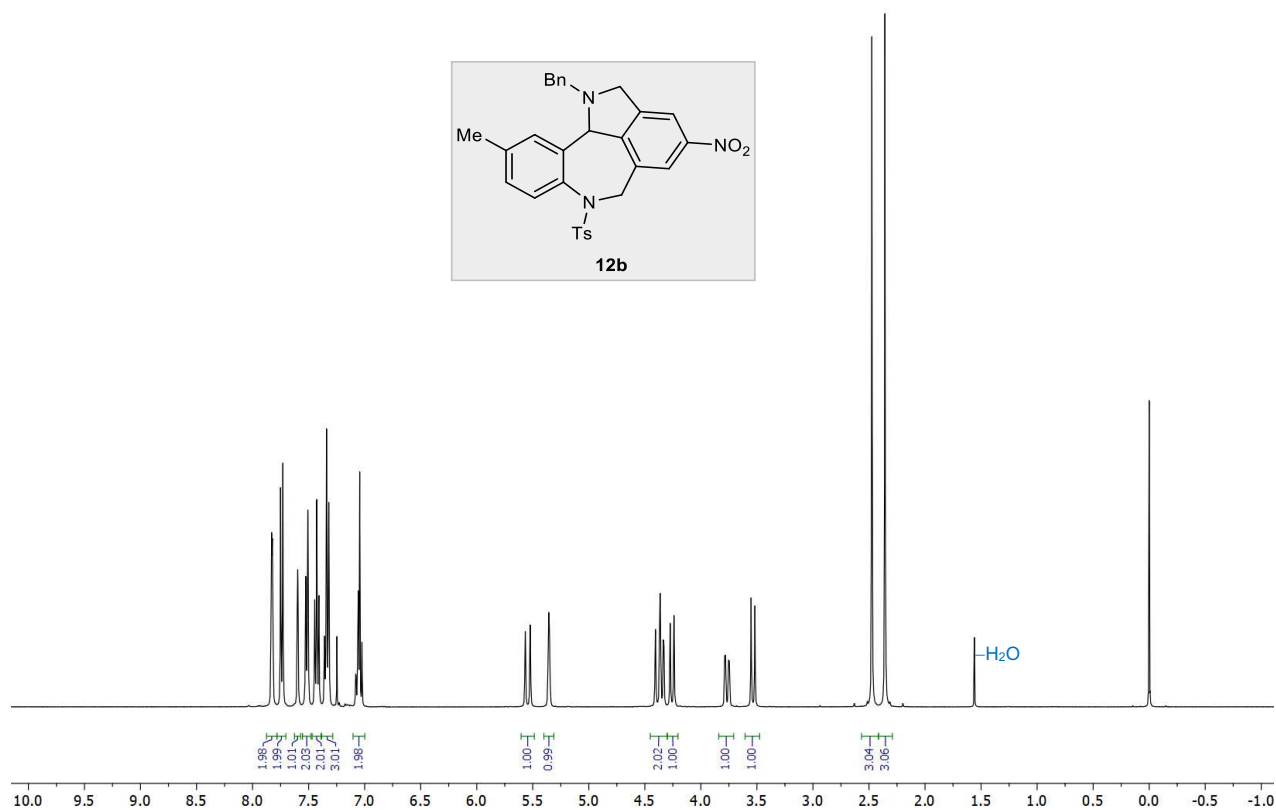
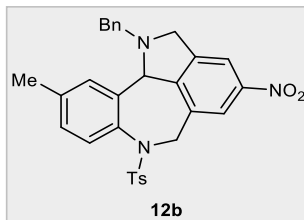
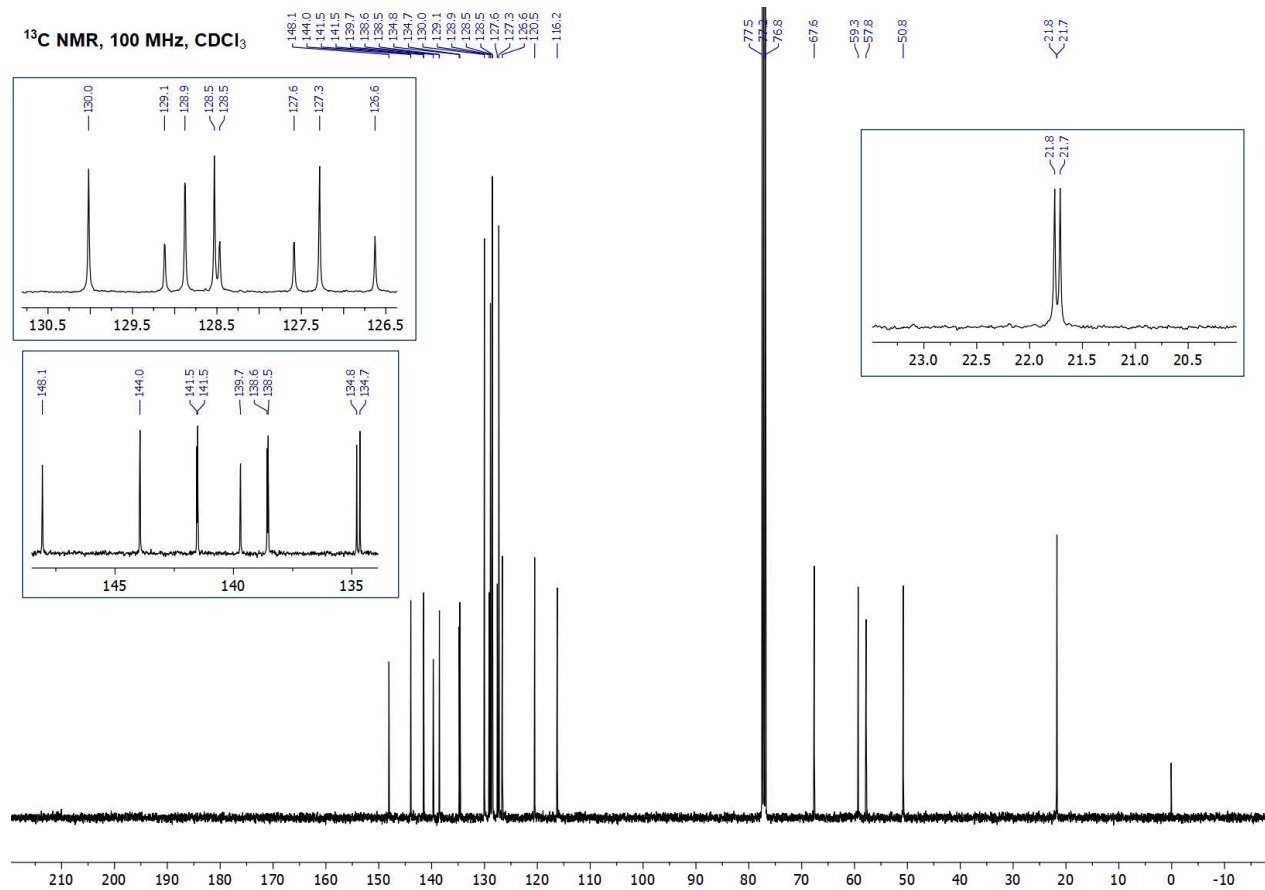


$^{13}\text{C}$  NMR, 125 MHz,  $\text{CD}_3\text{OD}$

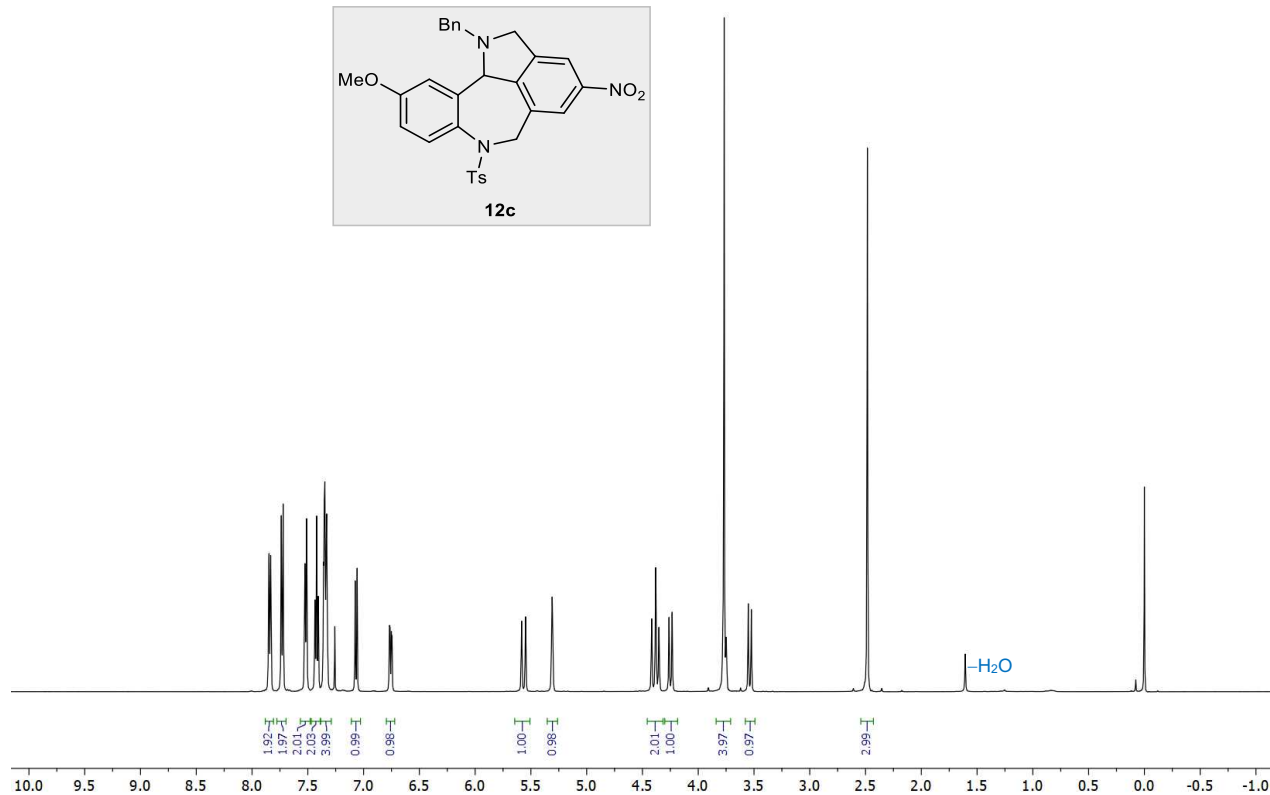
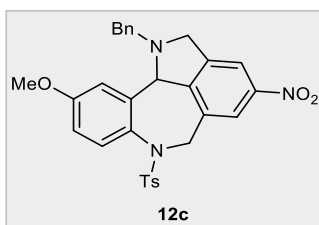
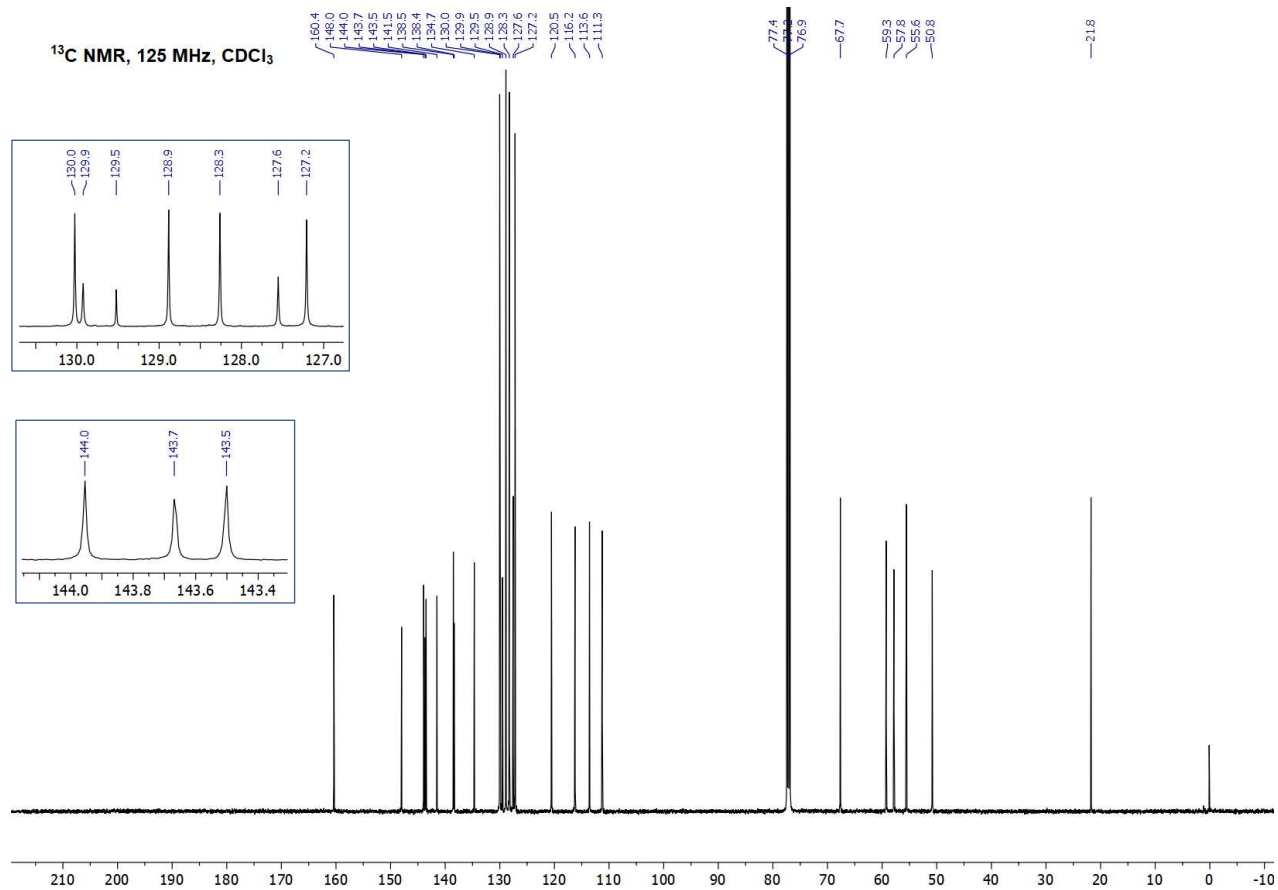


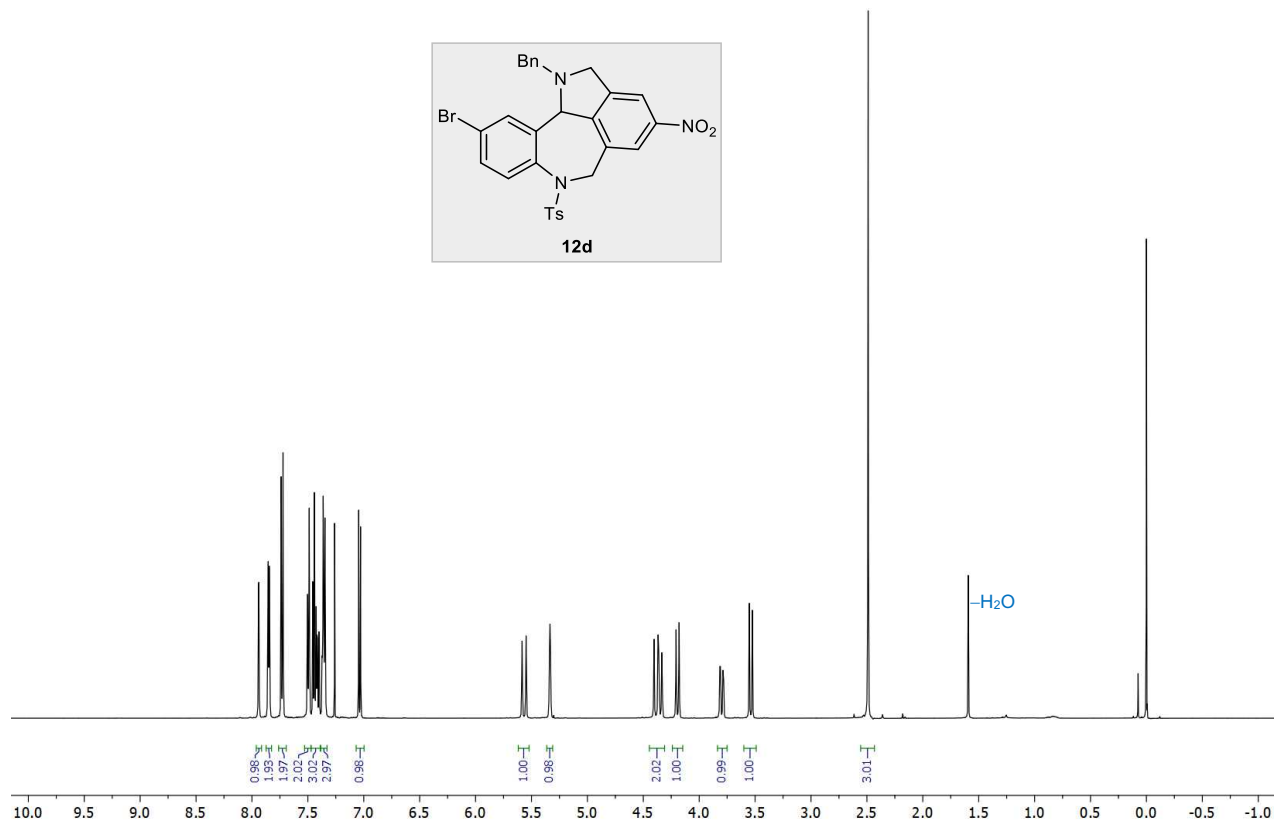
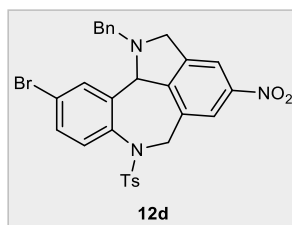
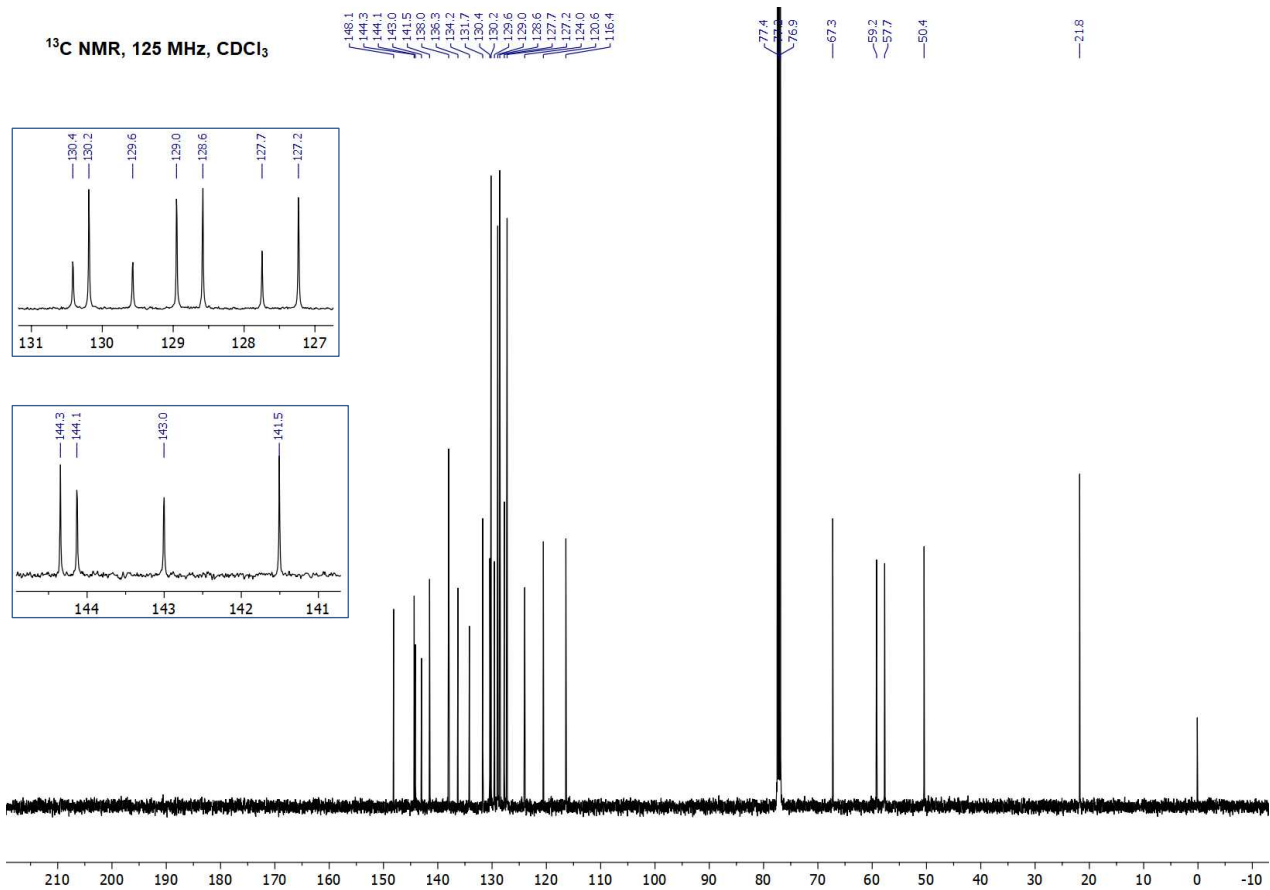
<sup>1</sup>H NMR, 400 MHz, CD<sub>3</sub>OD<sup>13</sup>C NMR, 100 MHz, CD<sub>3</sub>OD

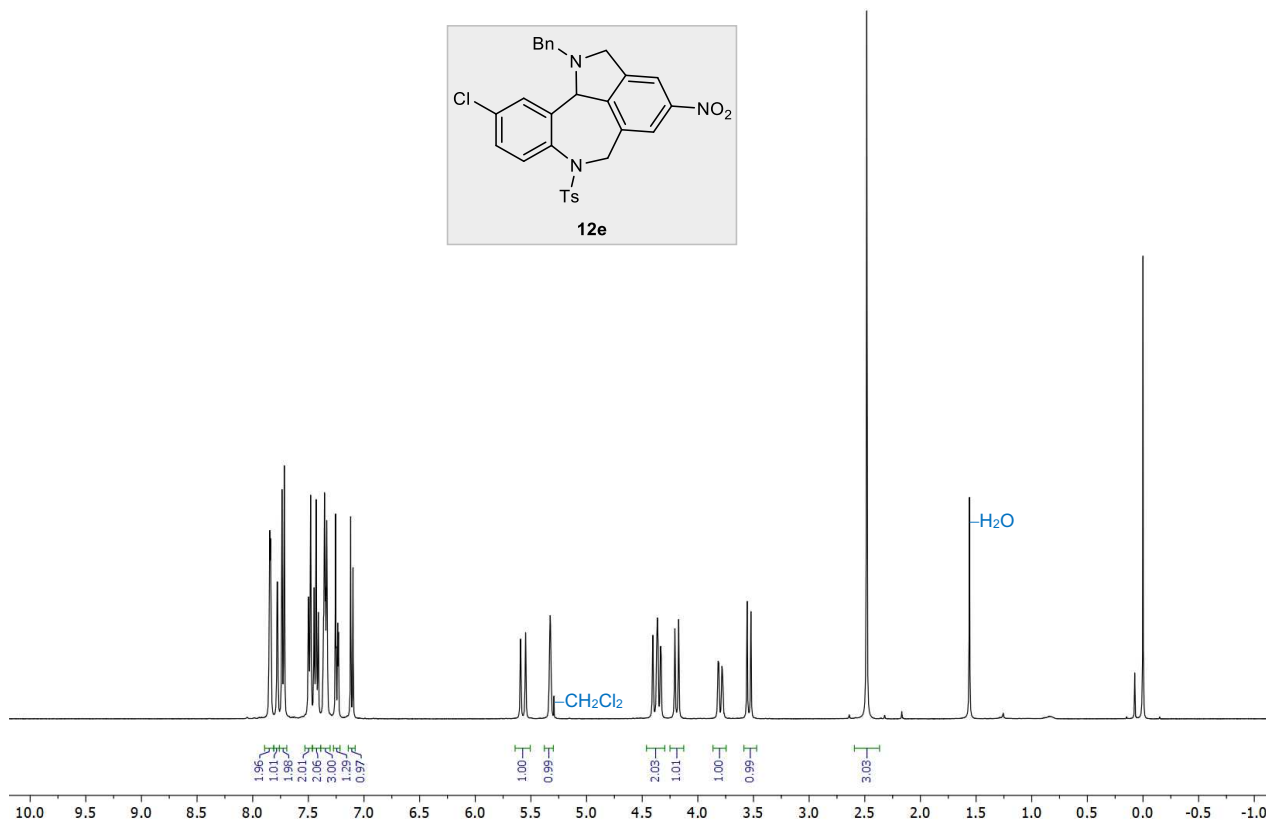
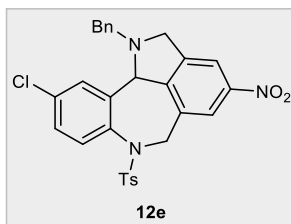
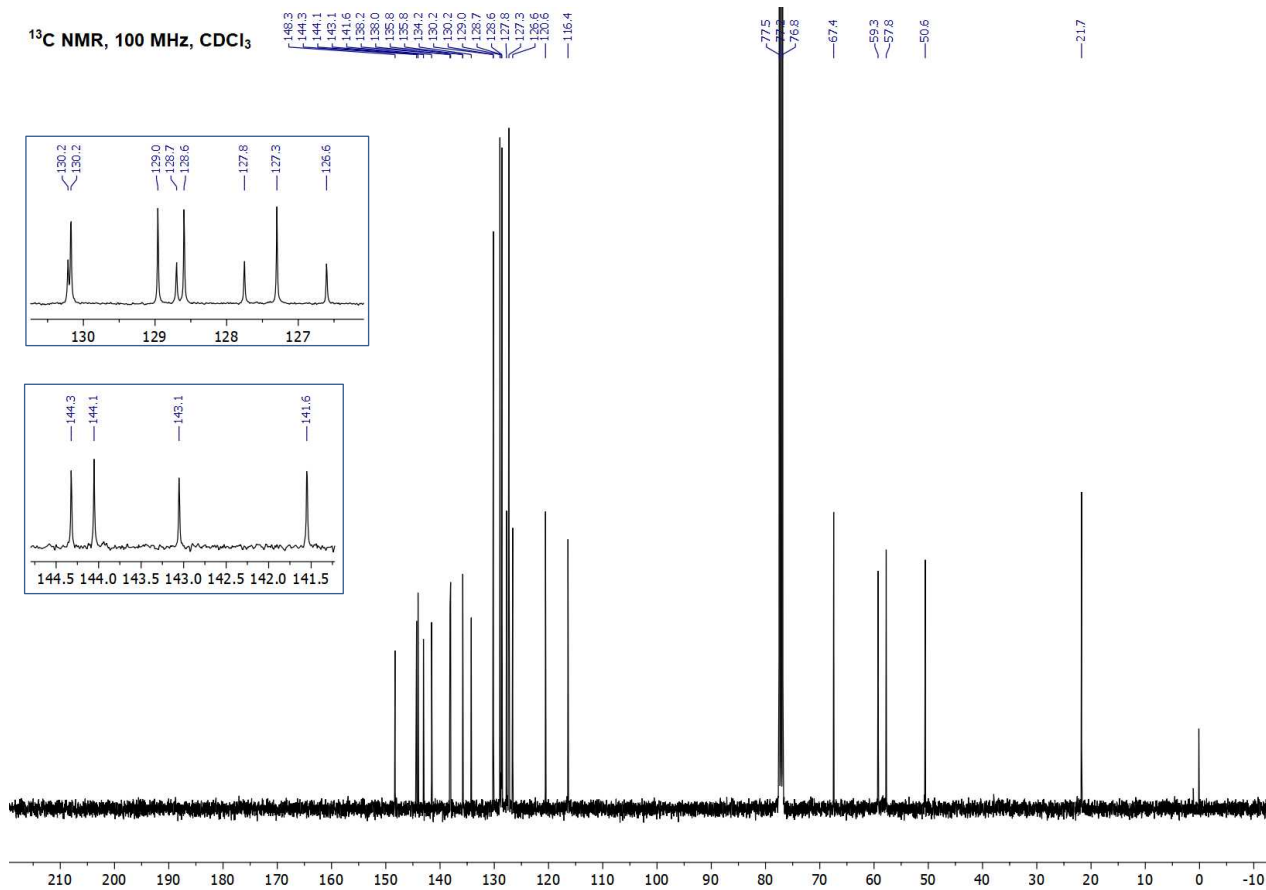
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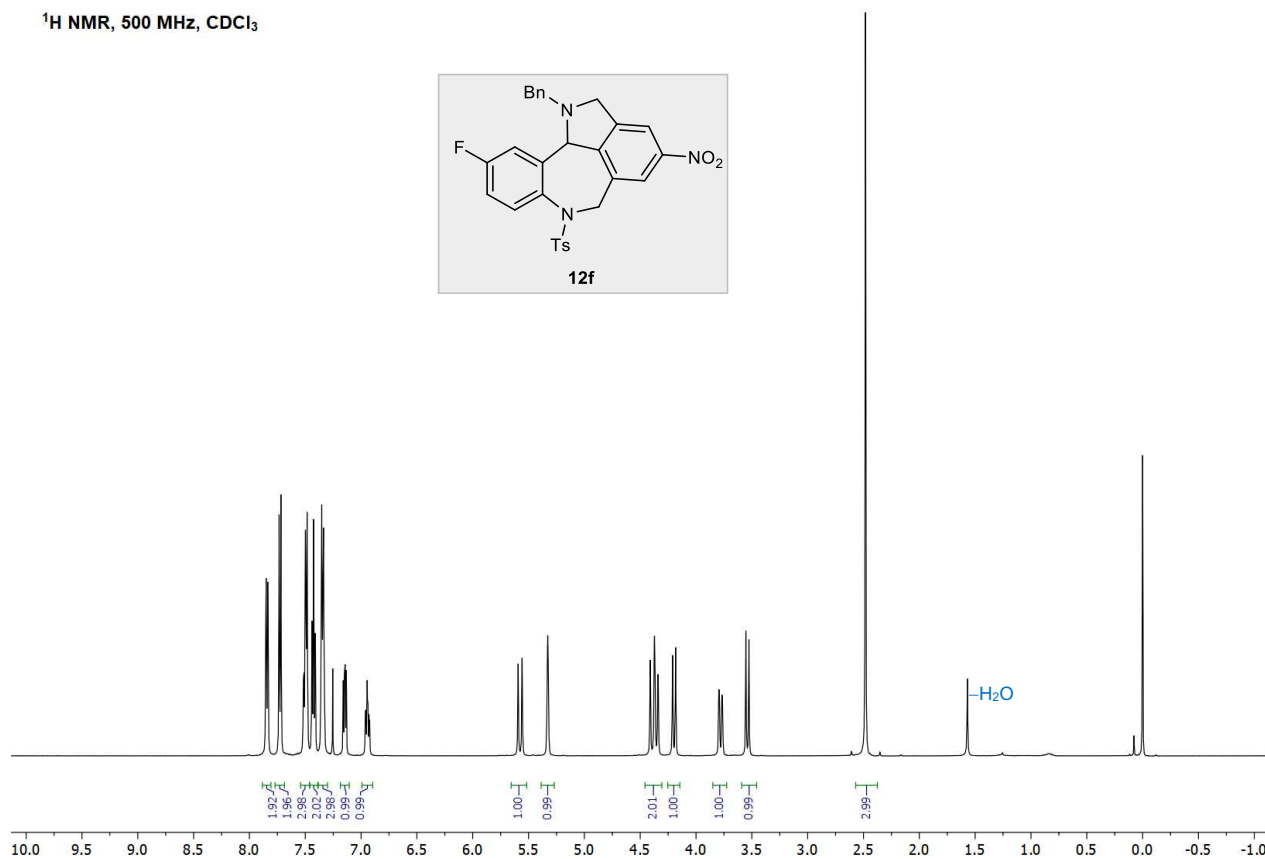
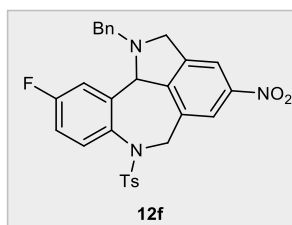
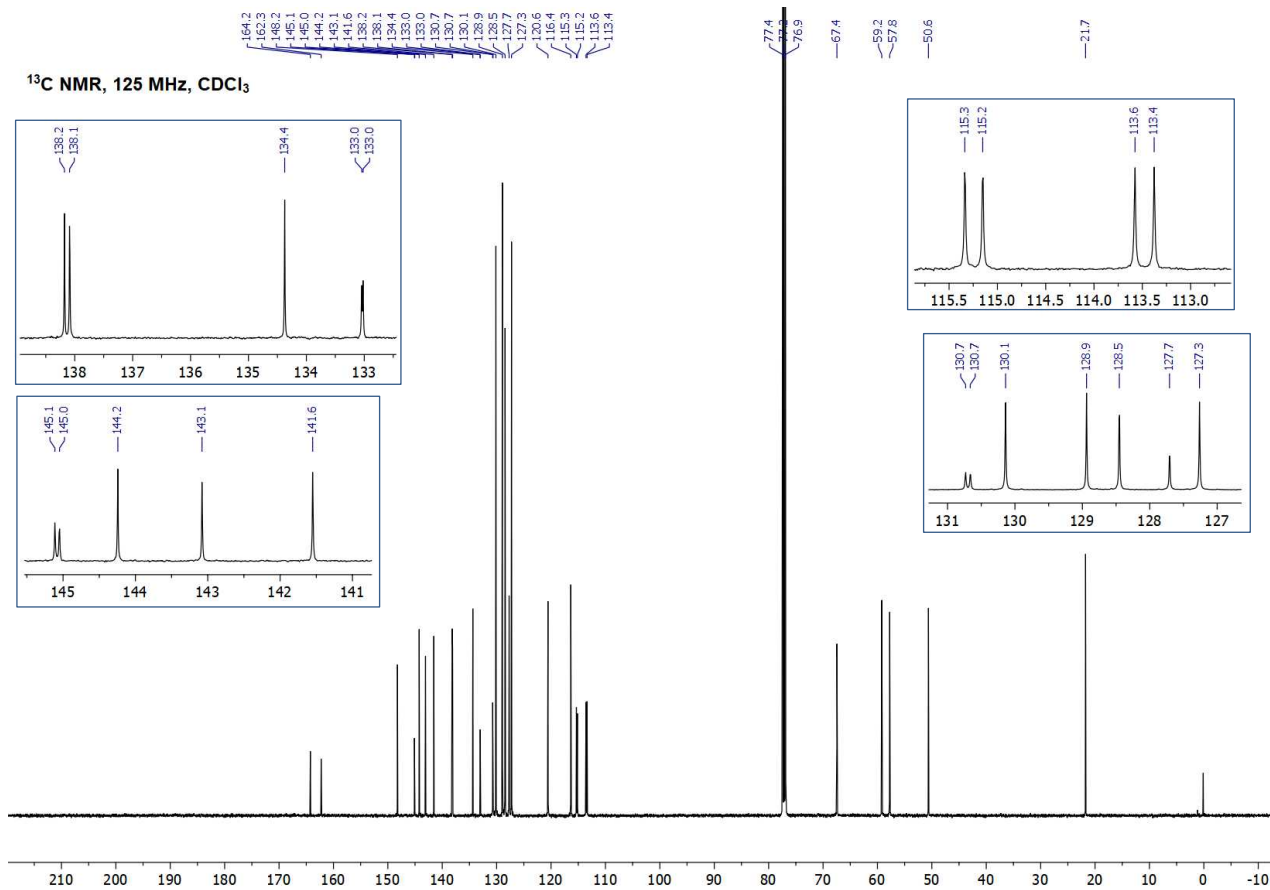
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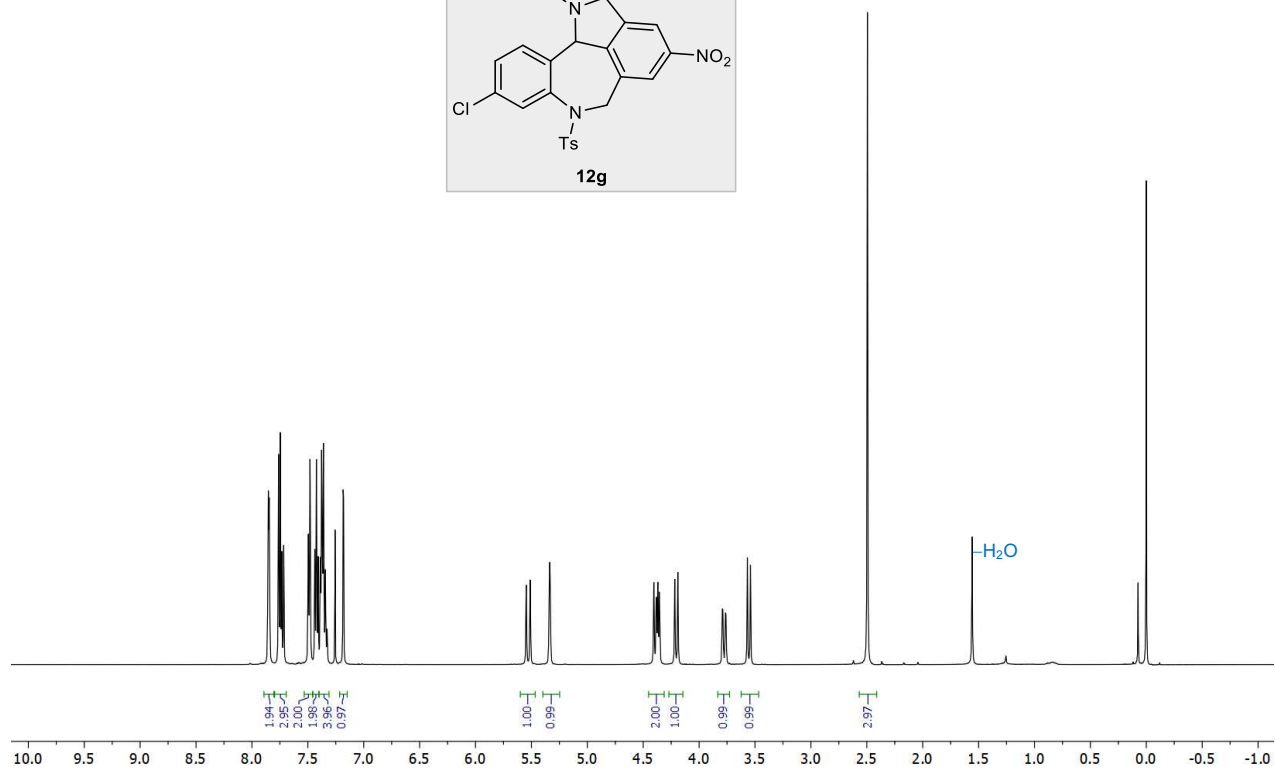
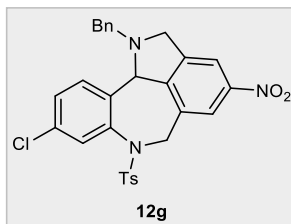
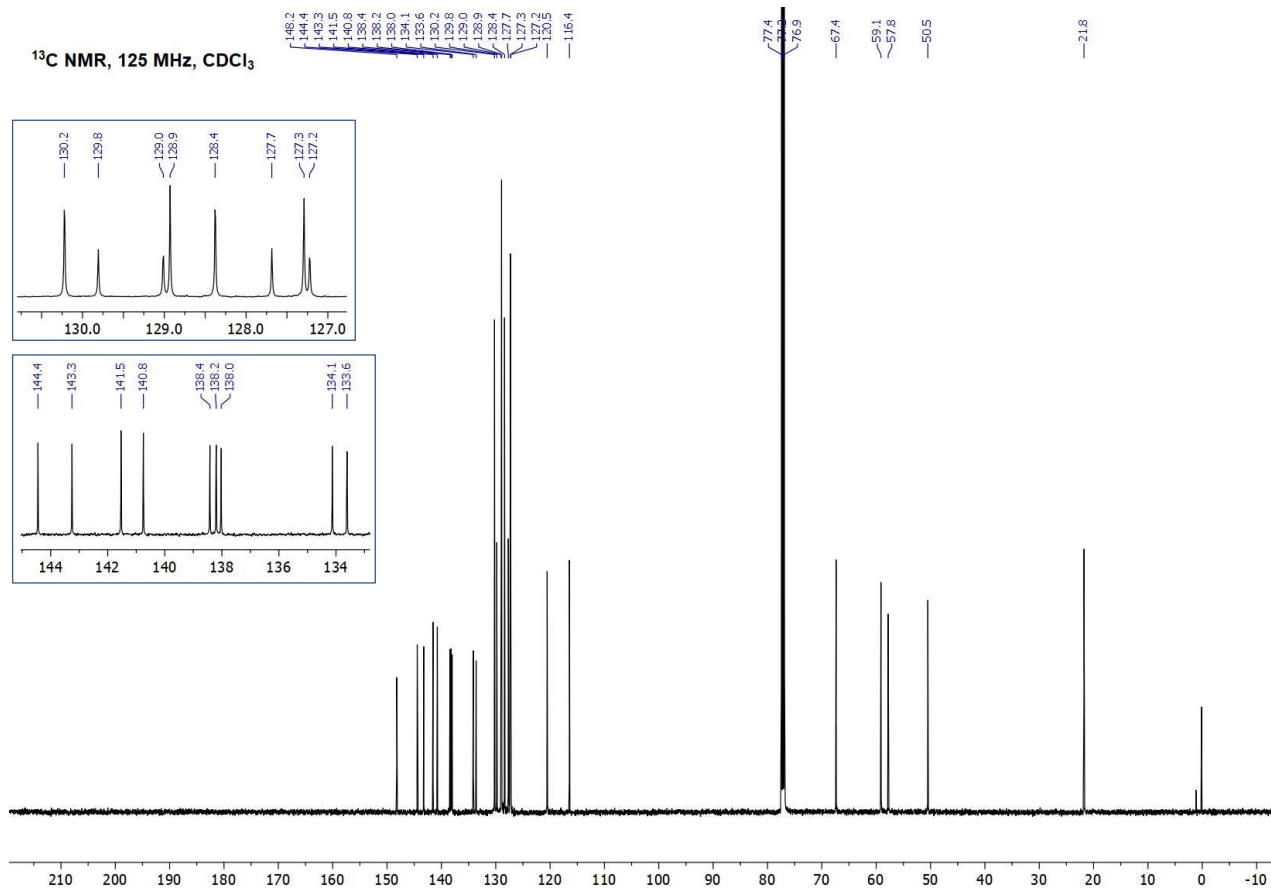


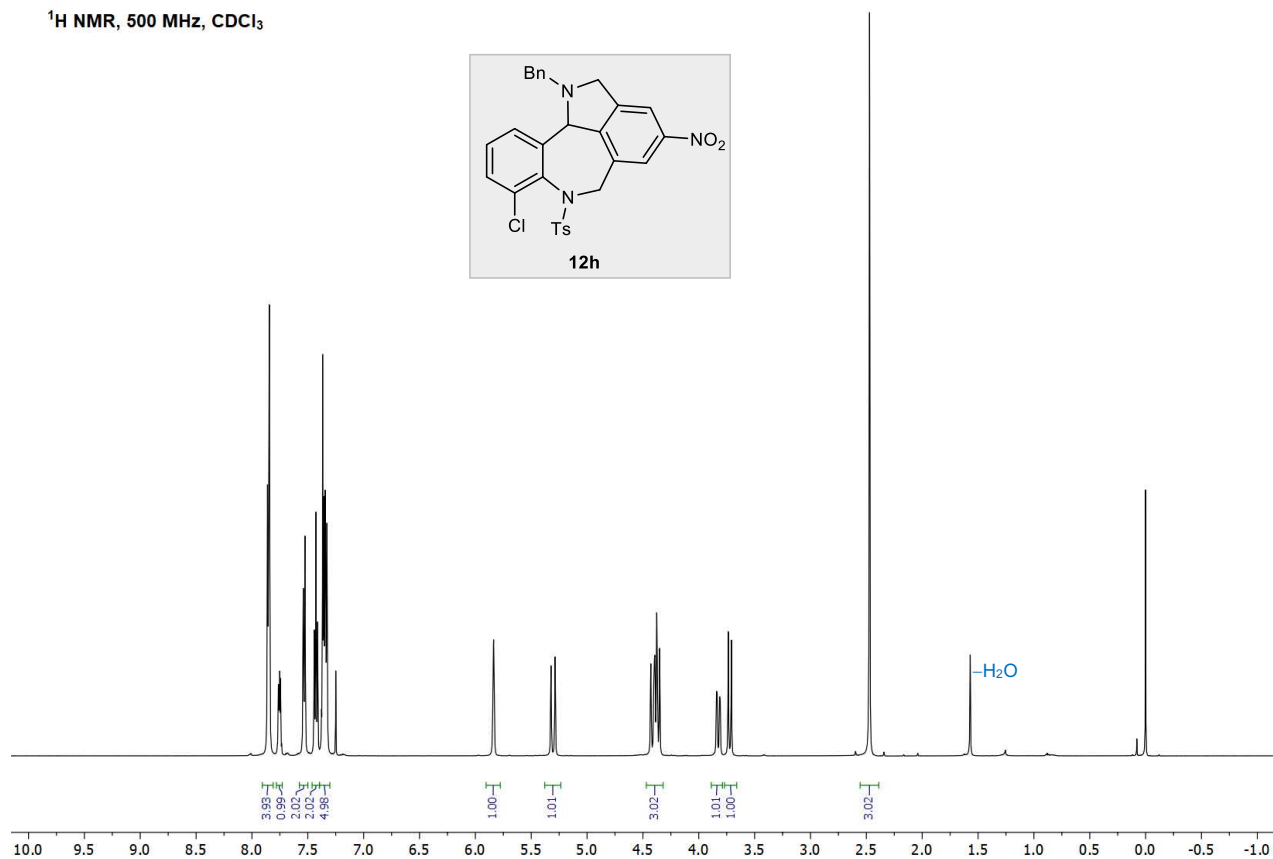
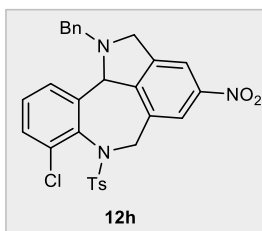
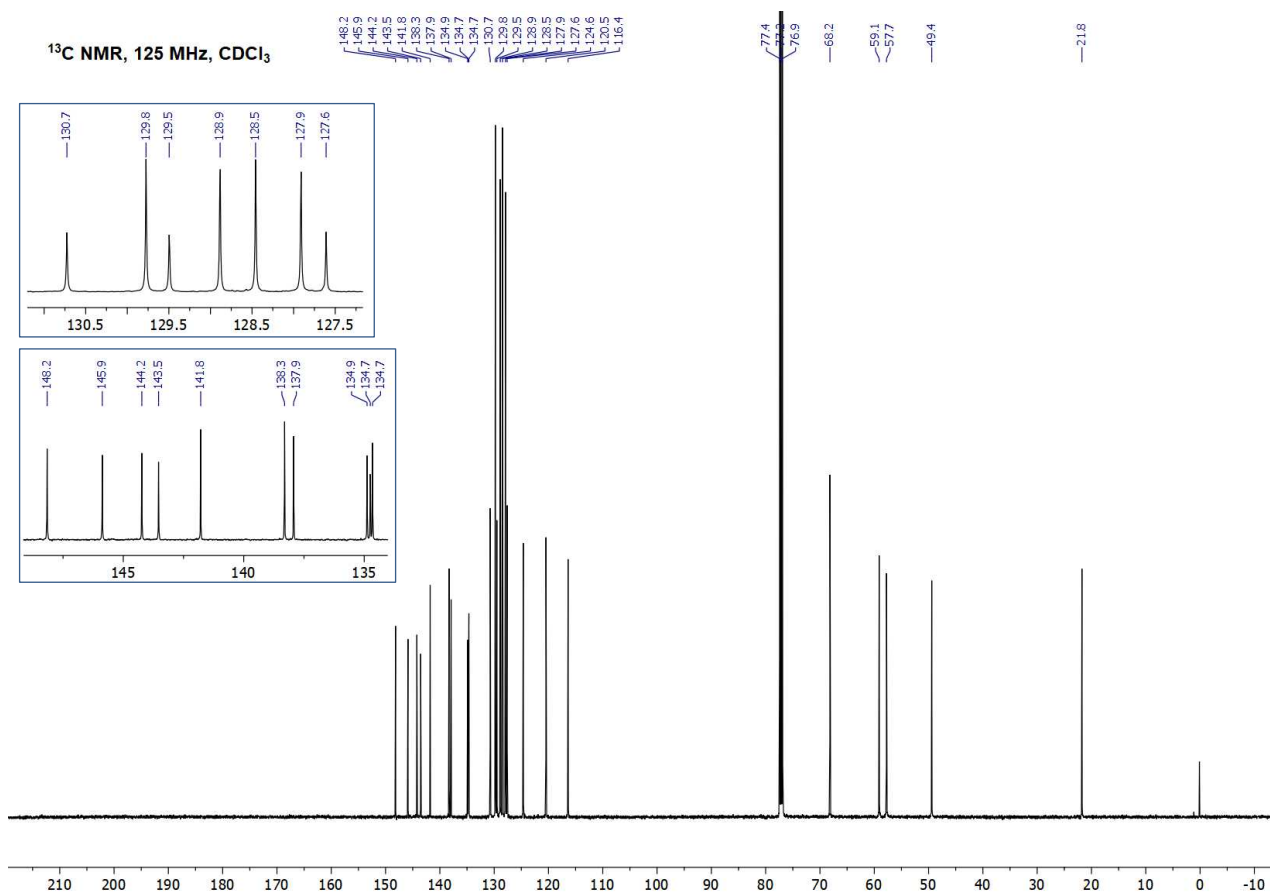
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

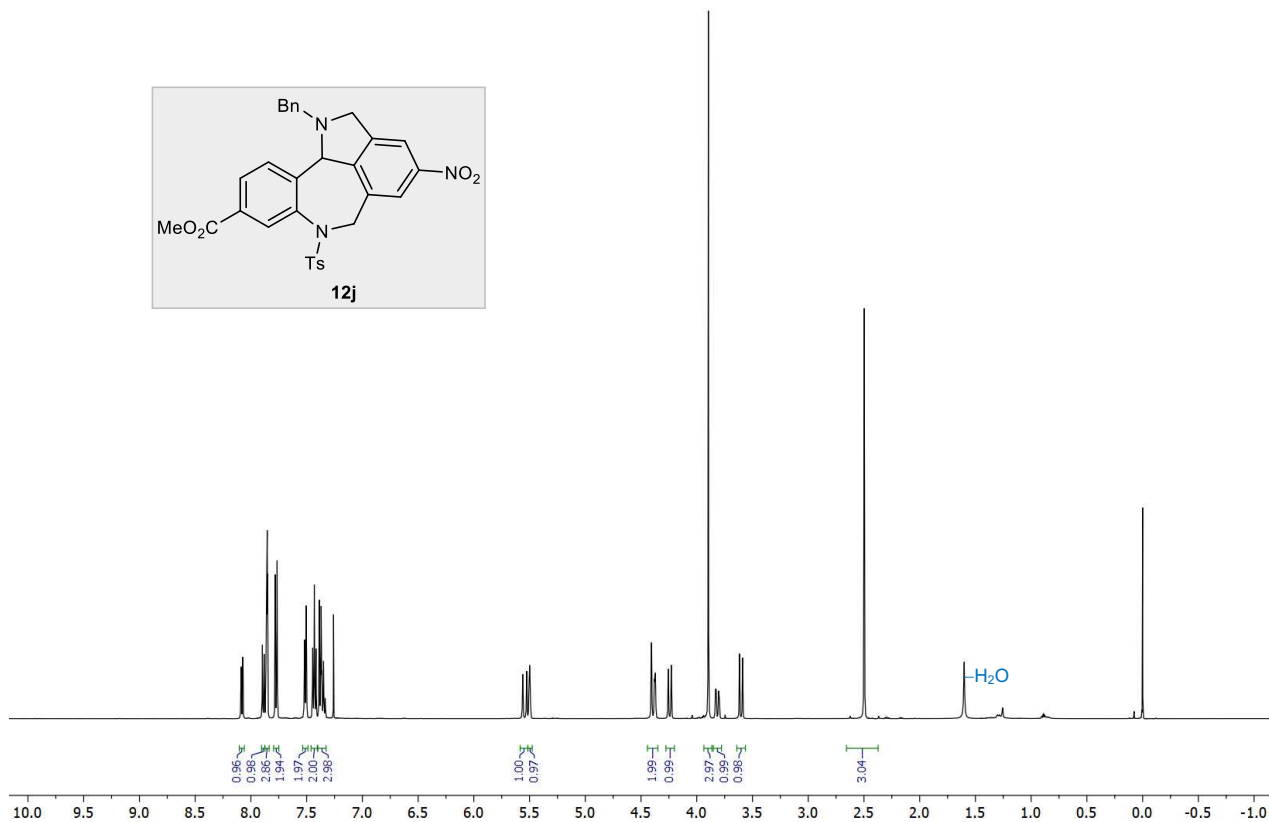
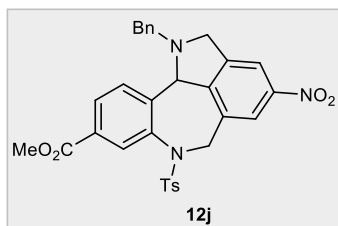
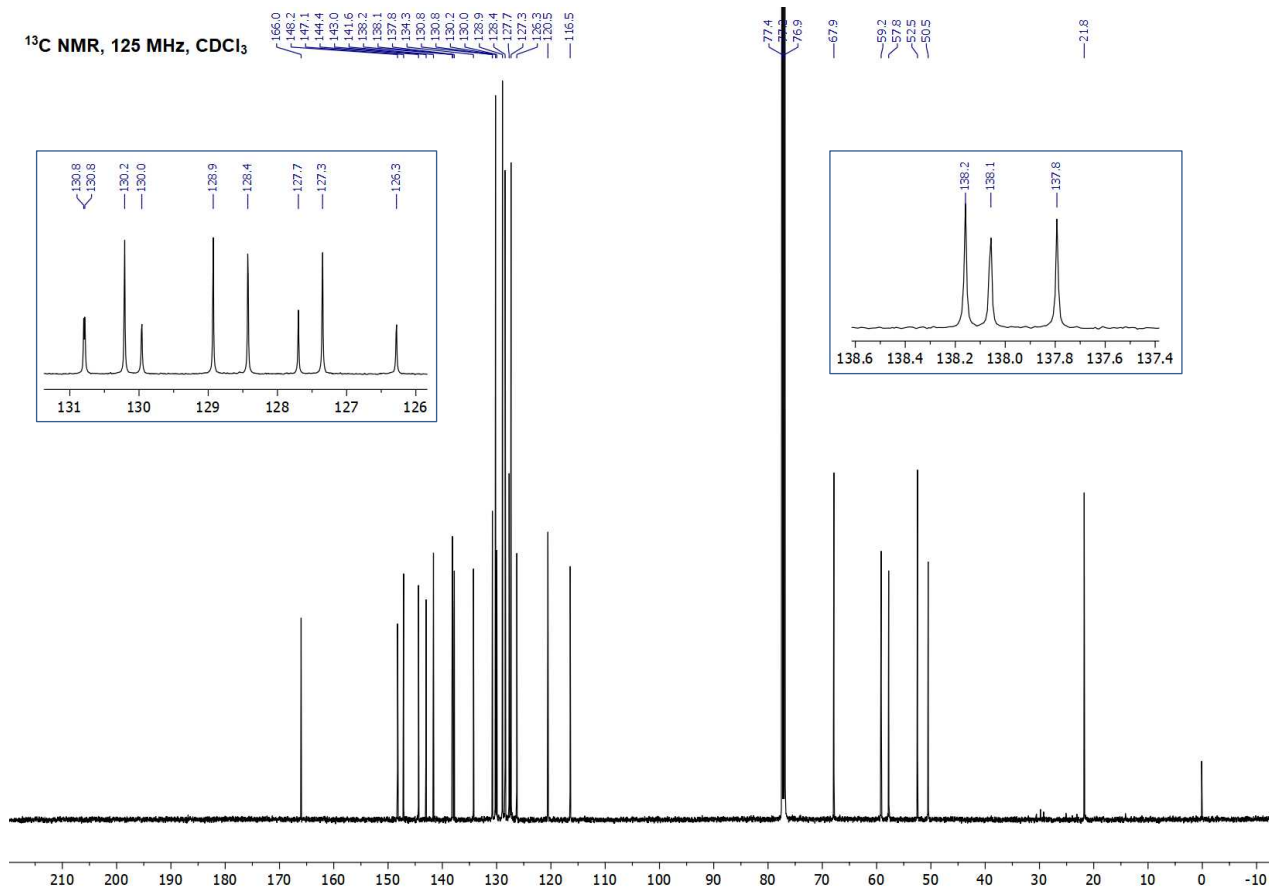
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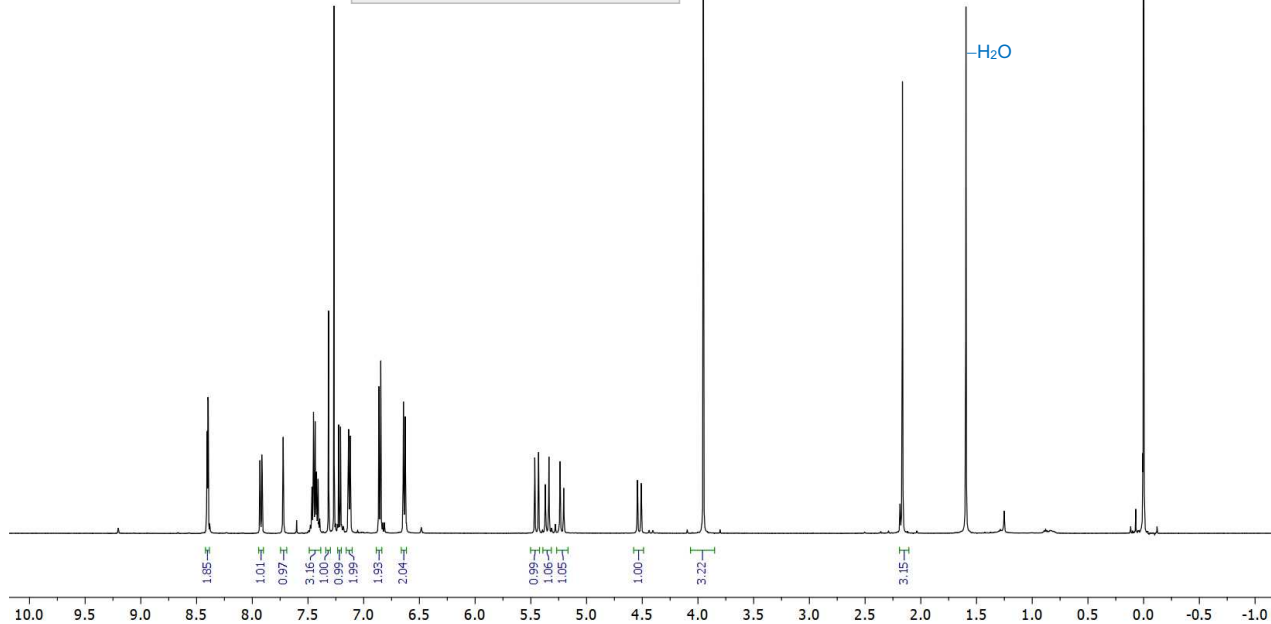
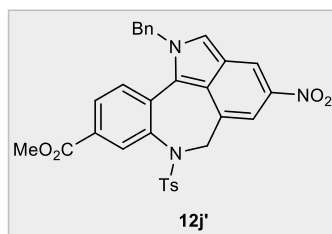
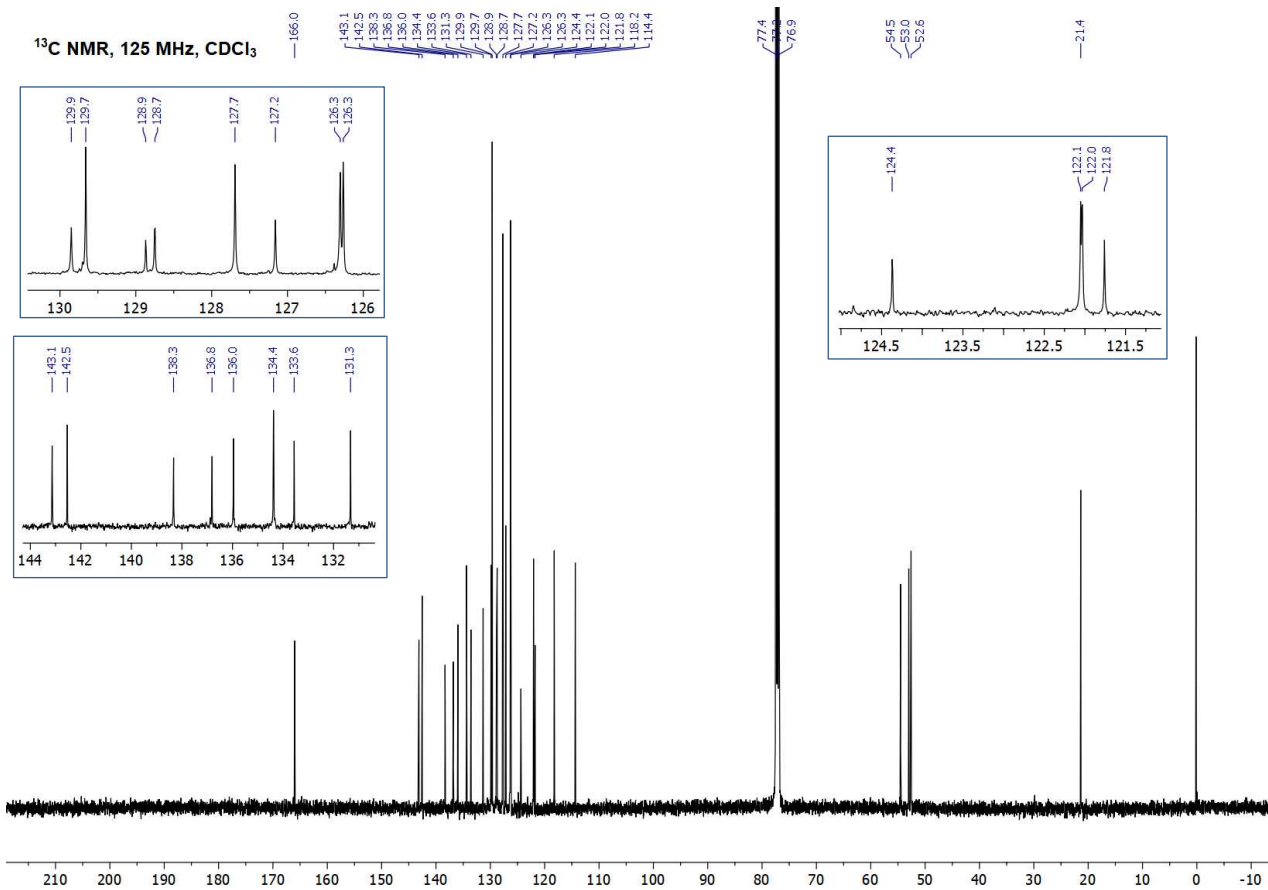
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

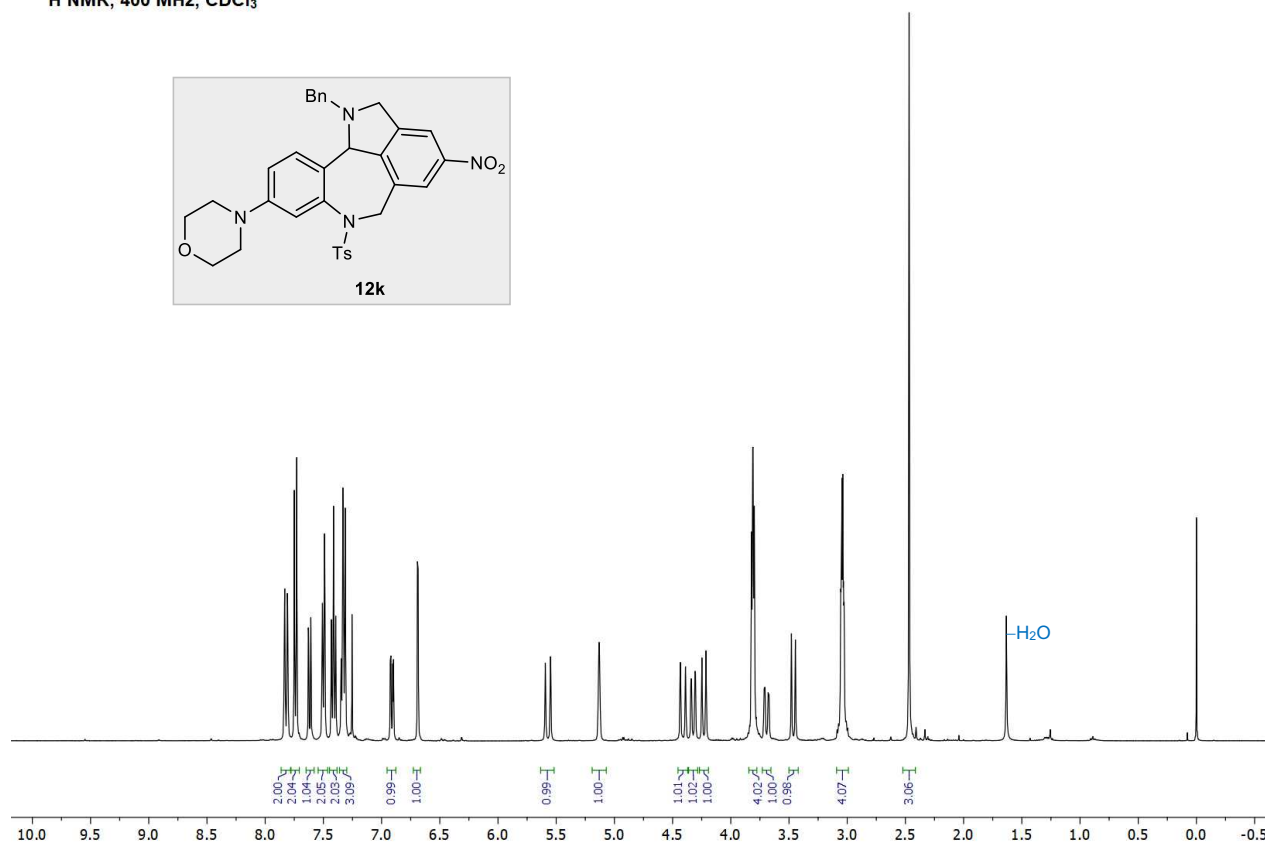
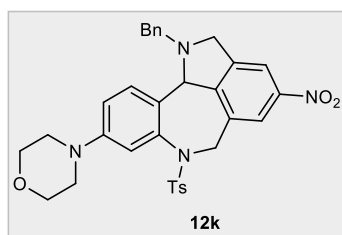
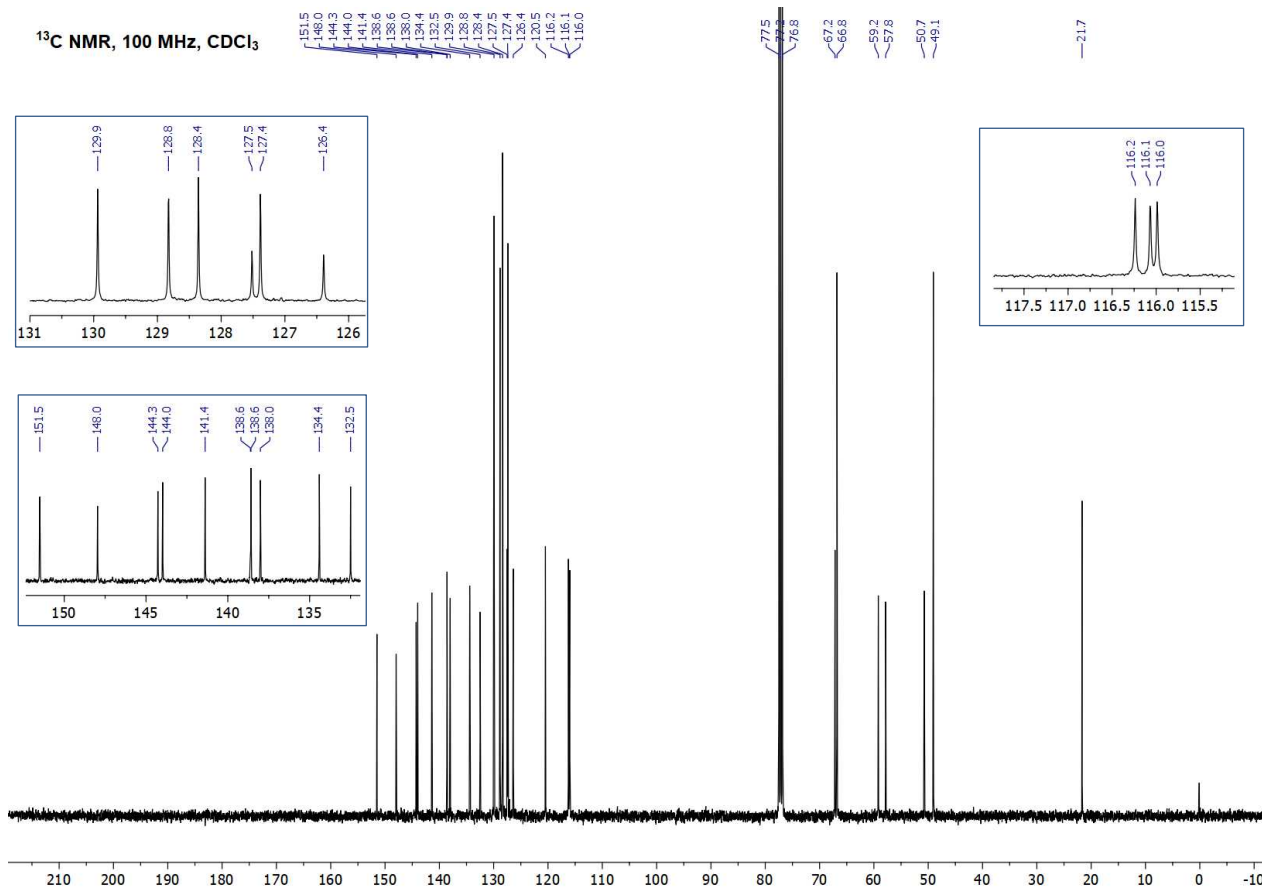
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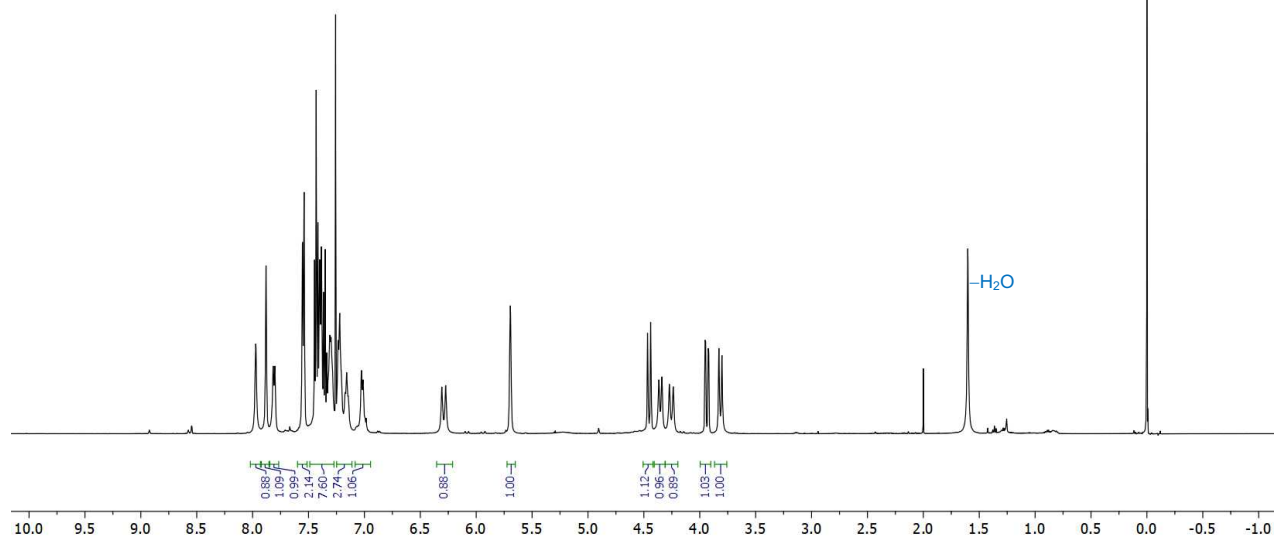
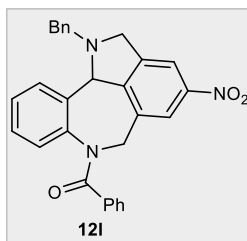
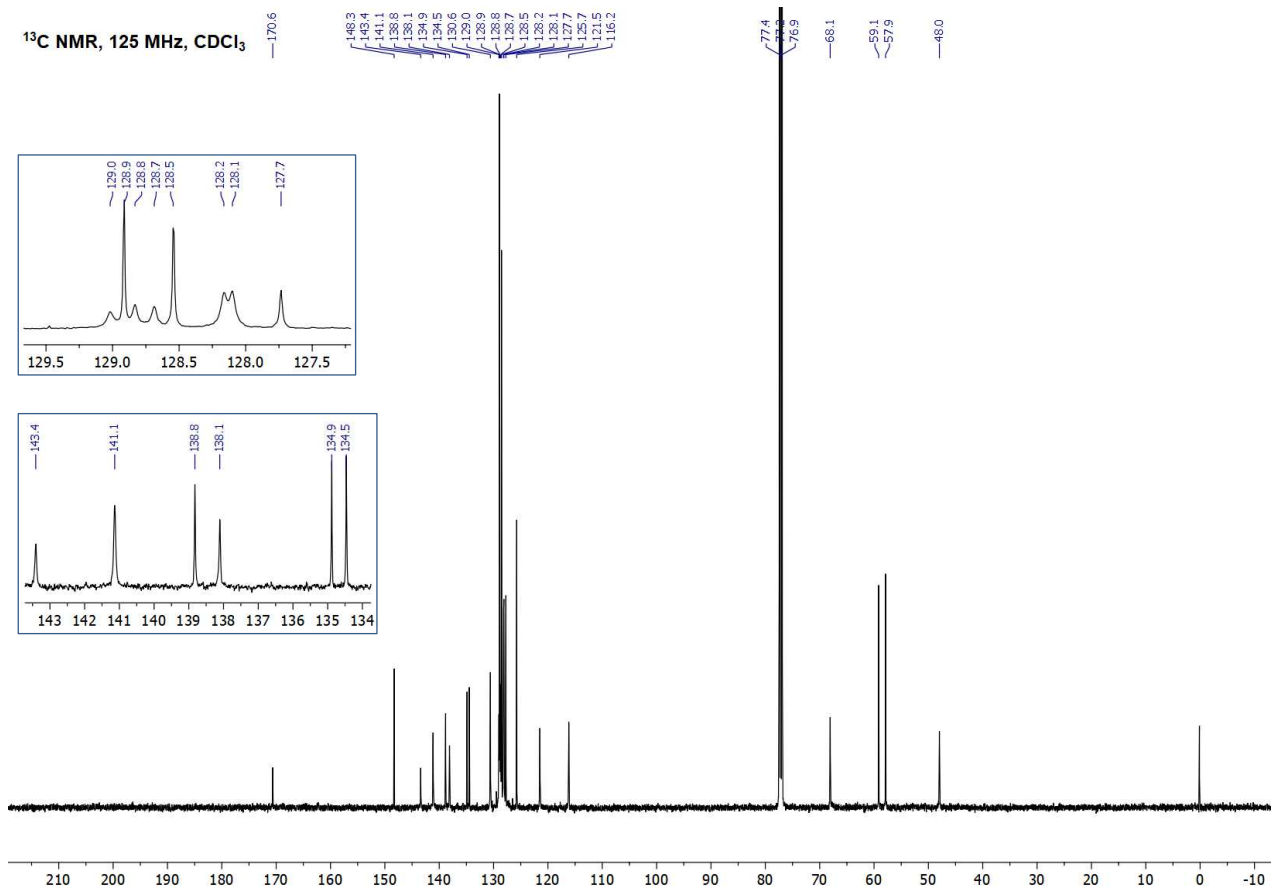
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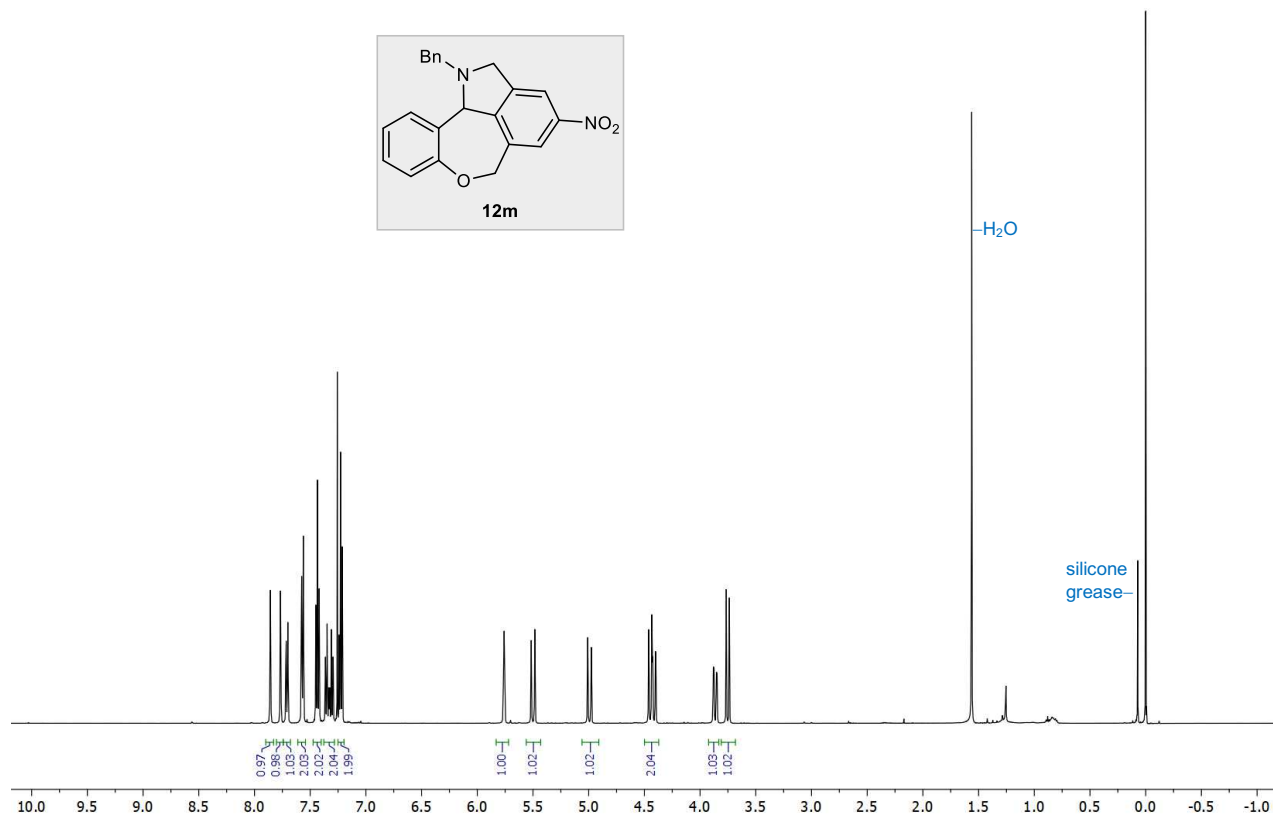
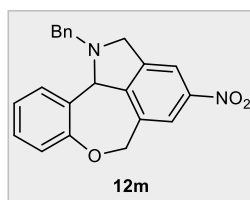
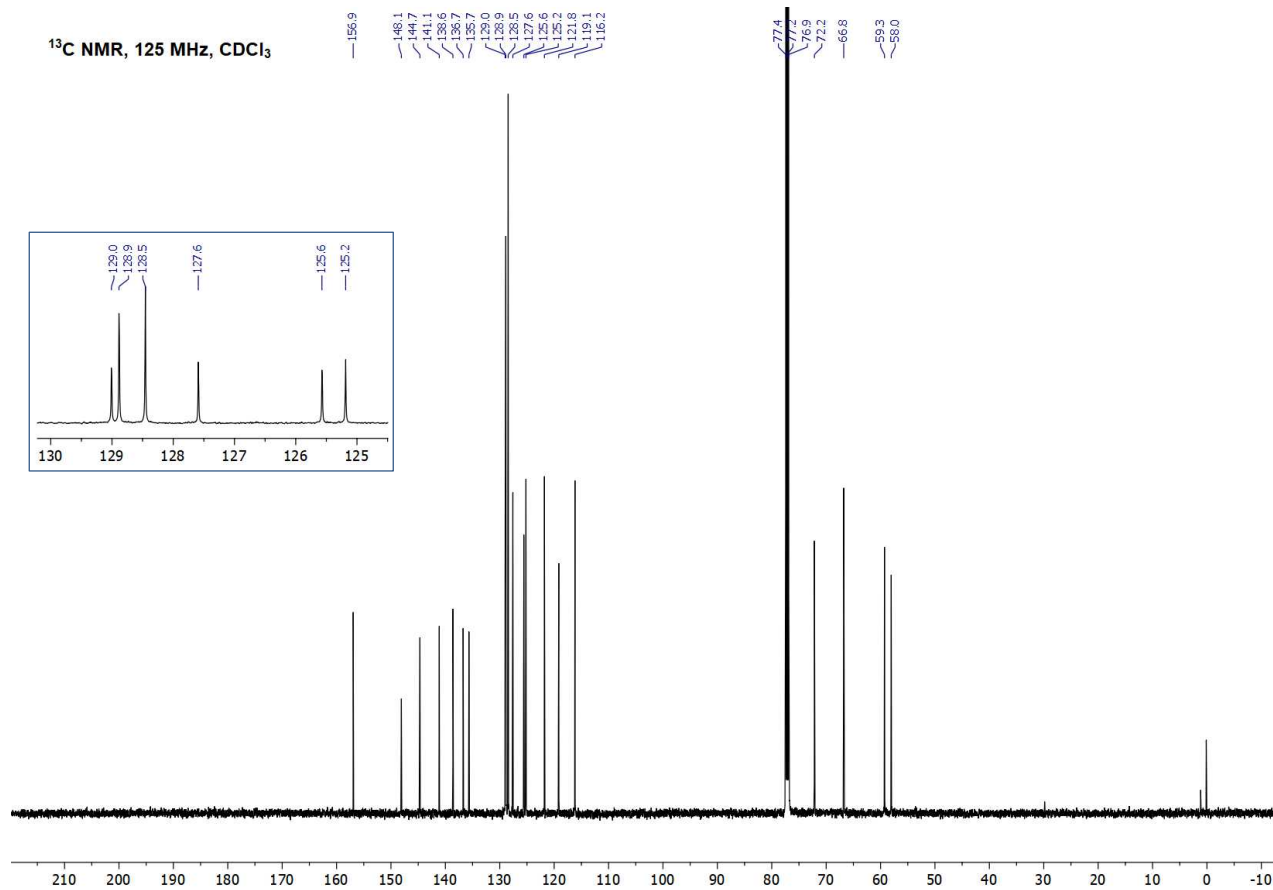
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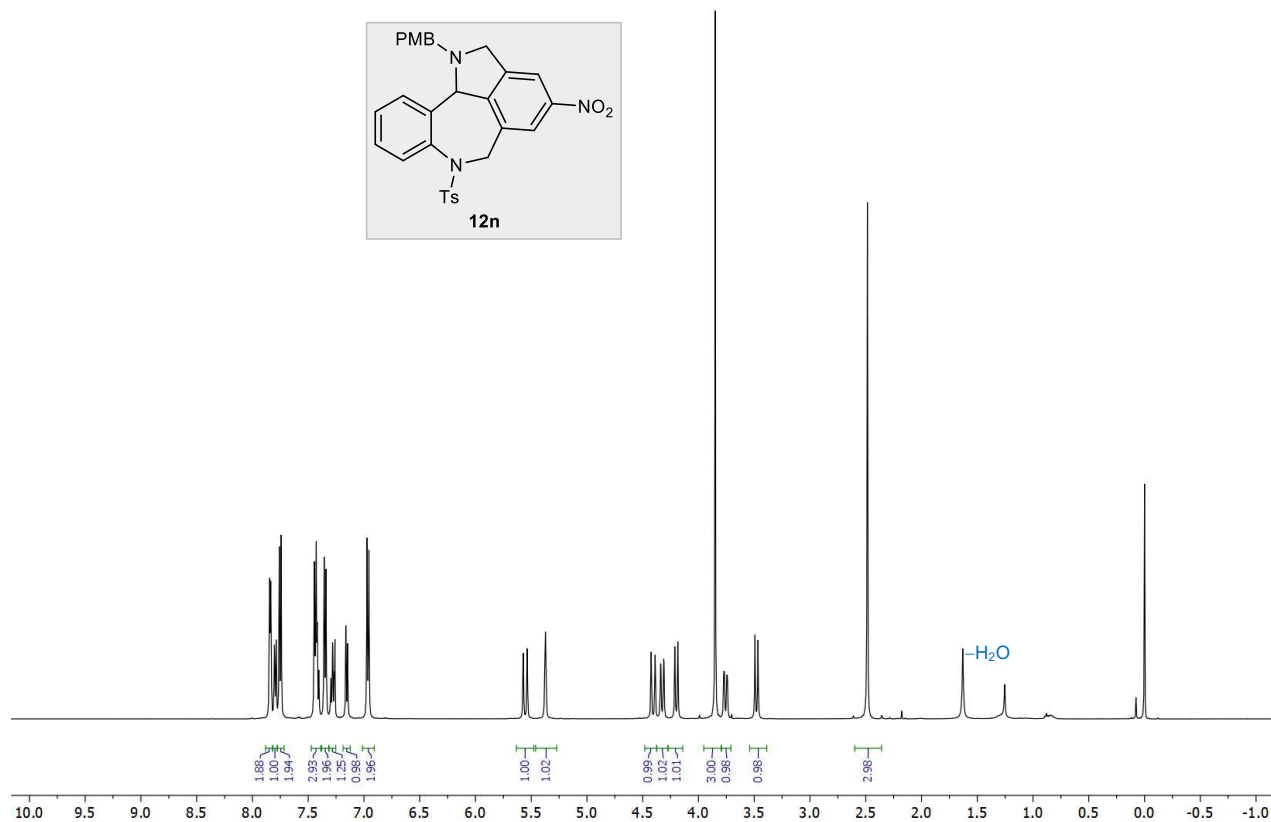
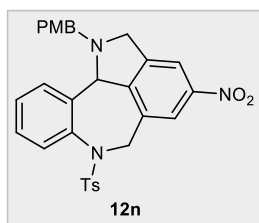
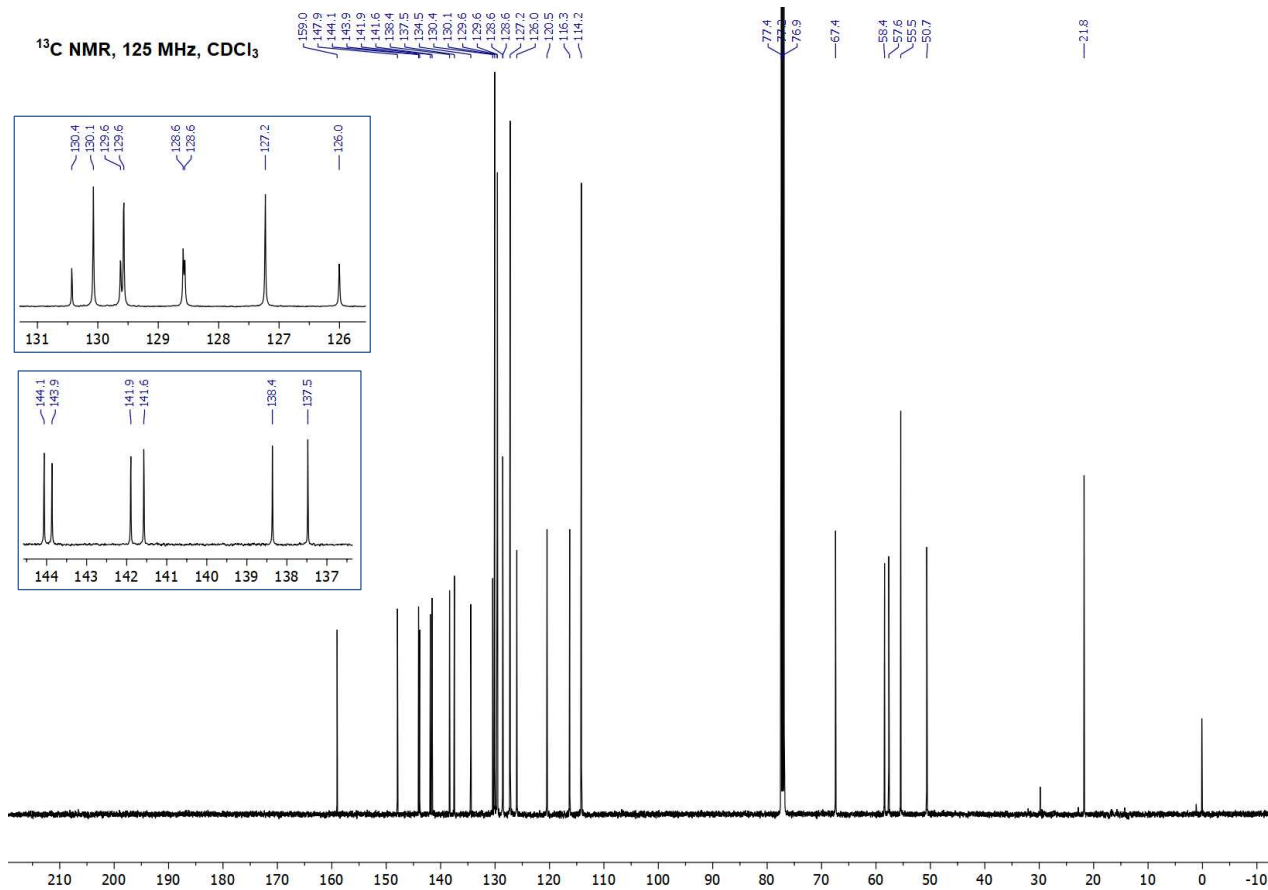
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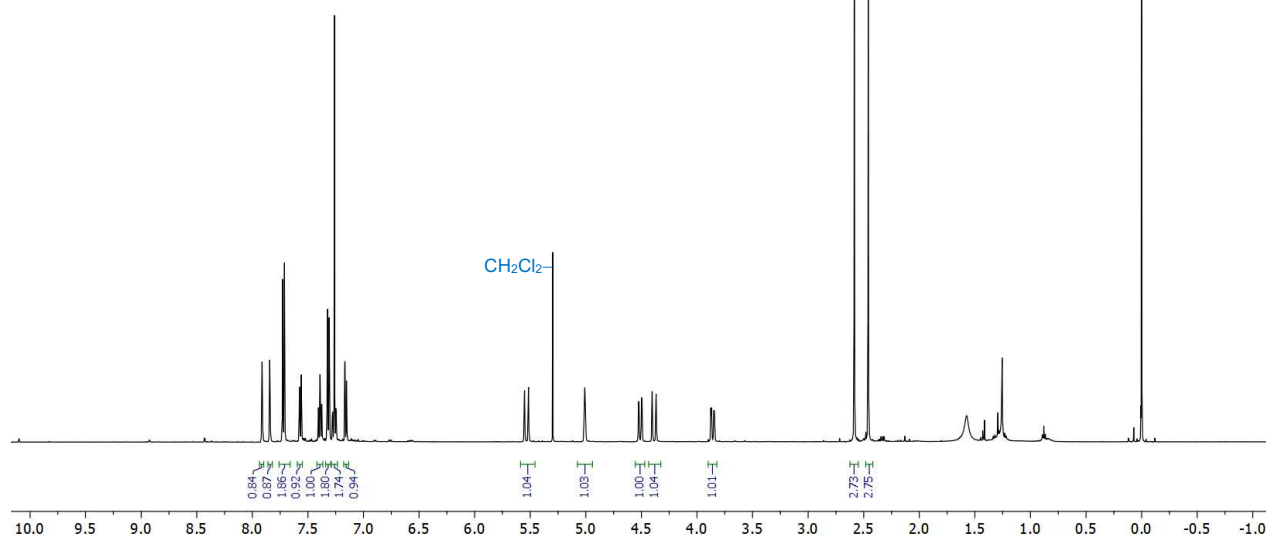
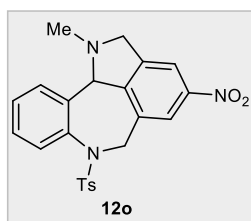
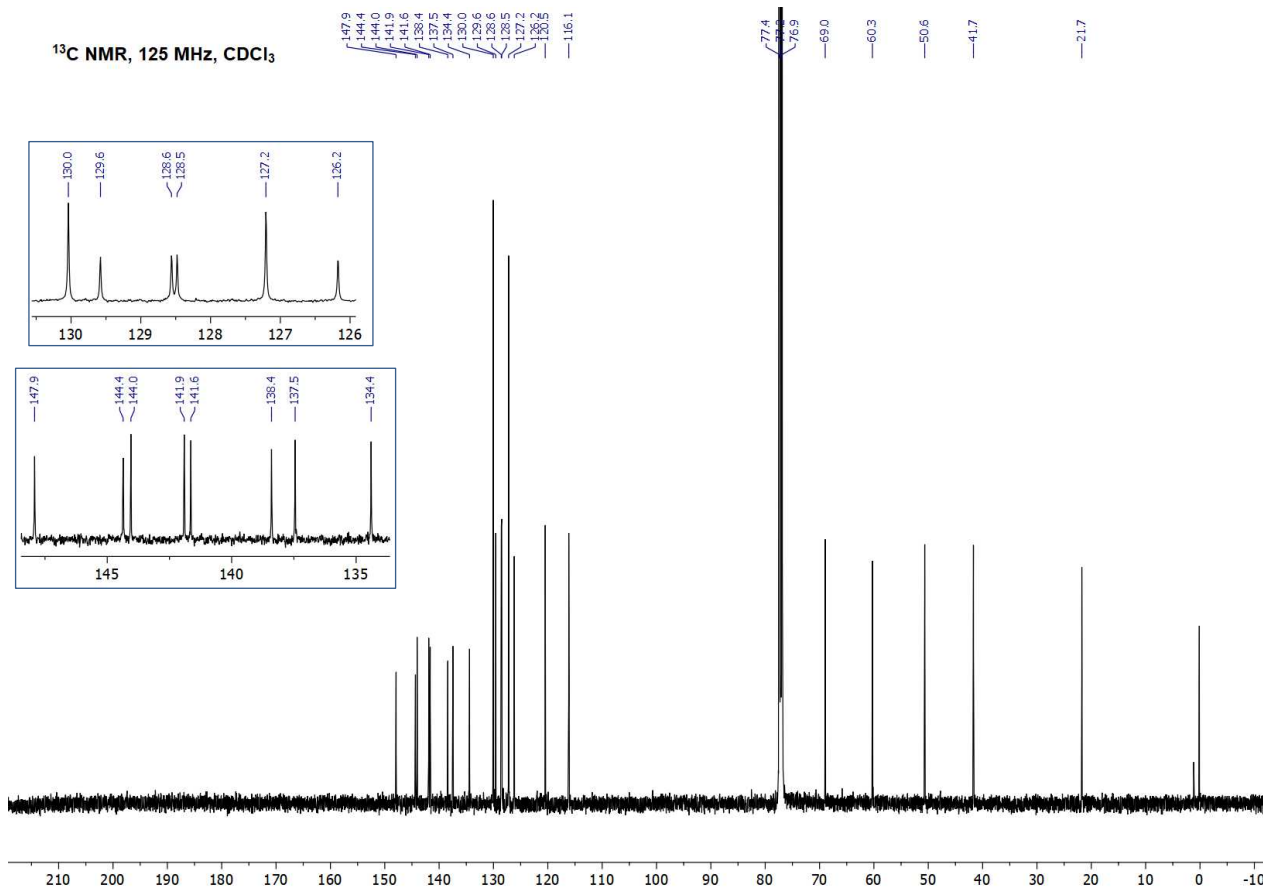


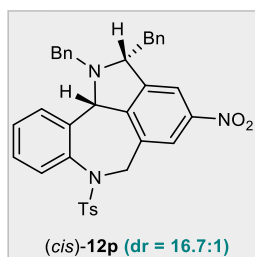
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

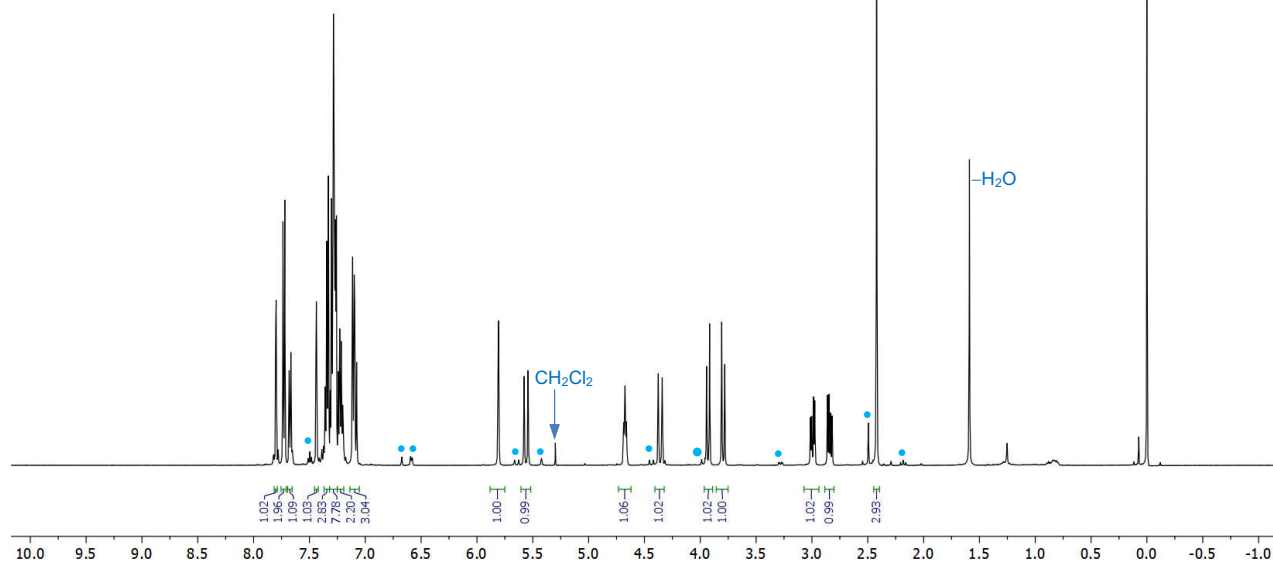
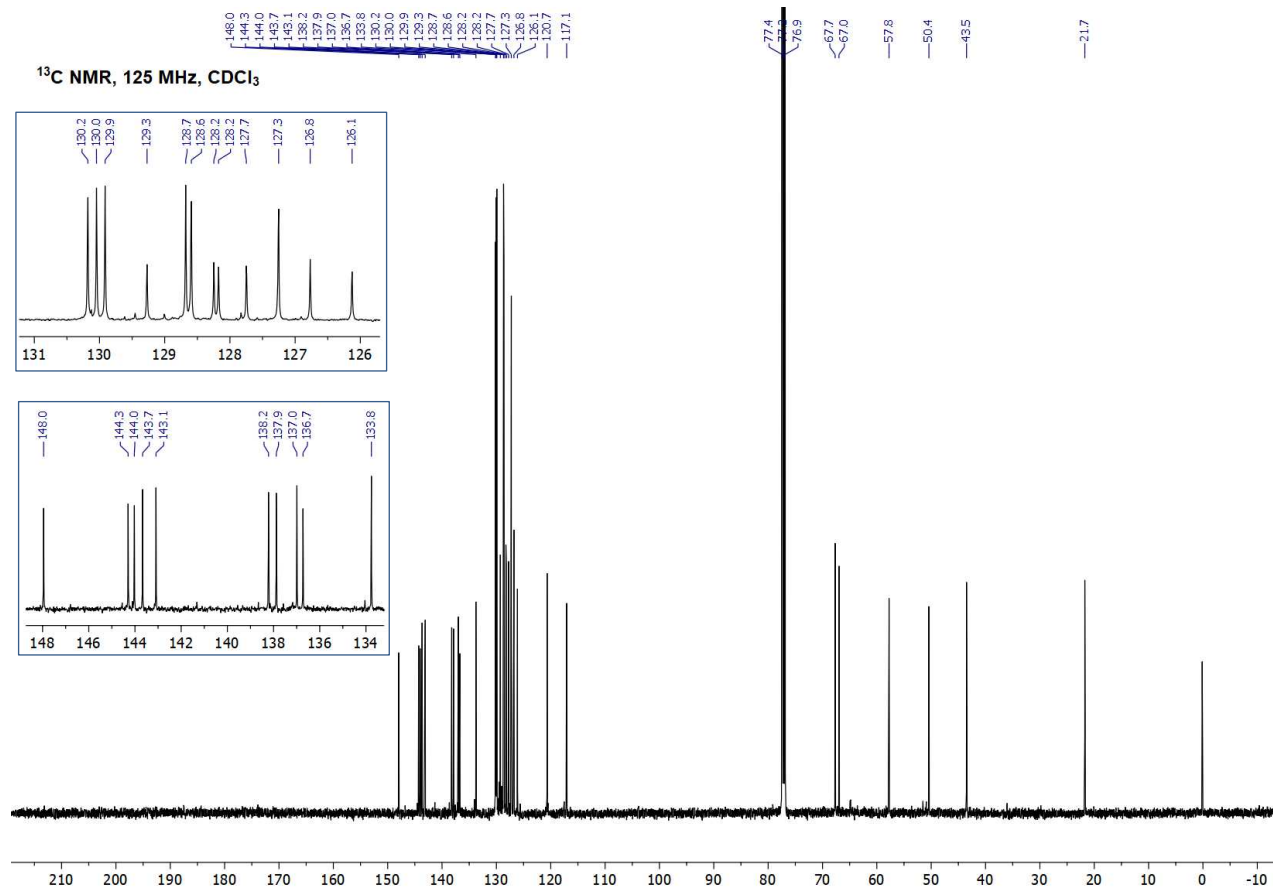
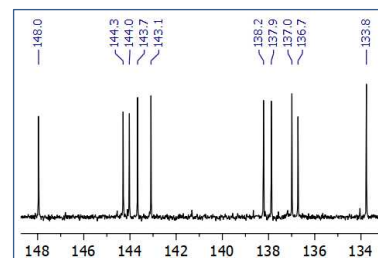
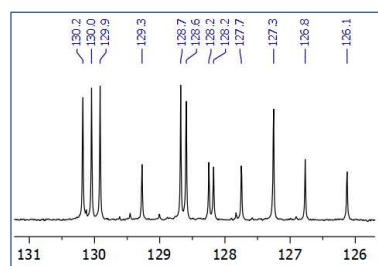
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

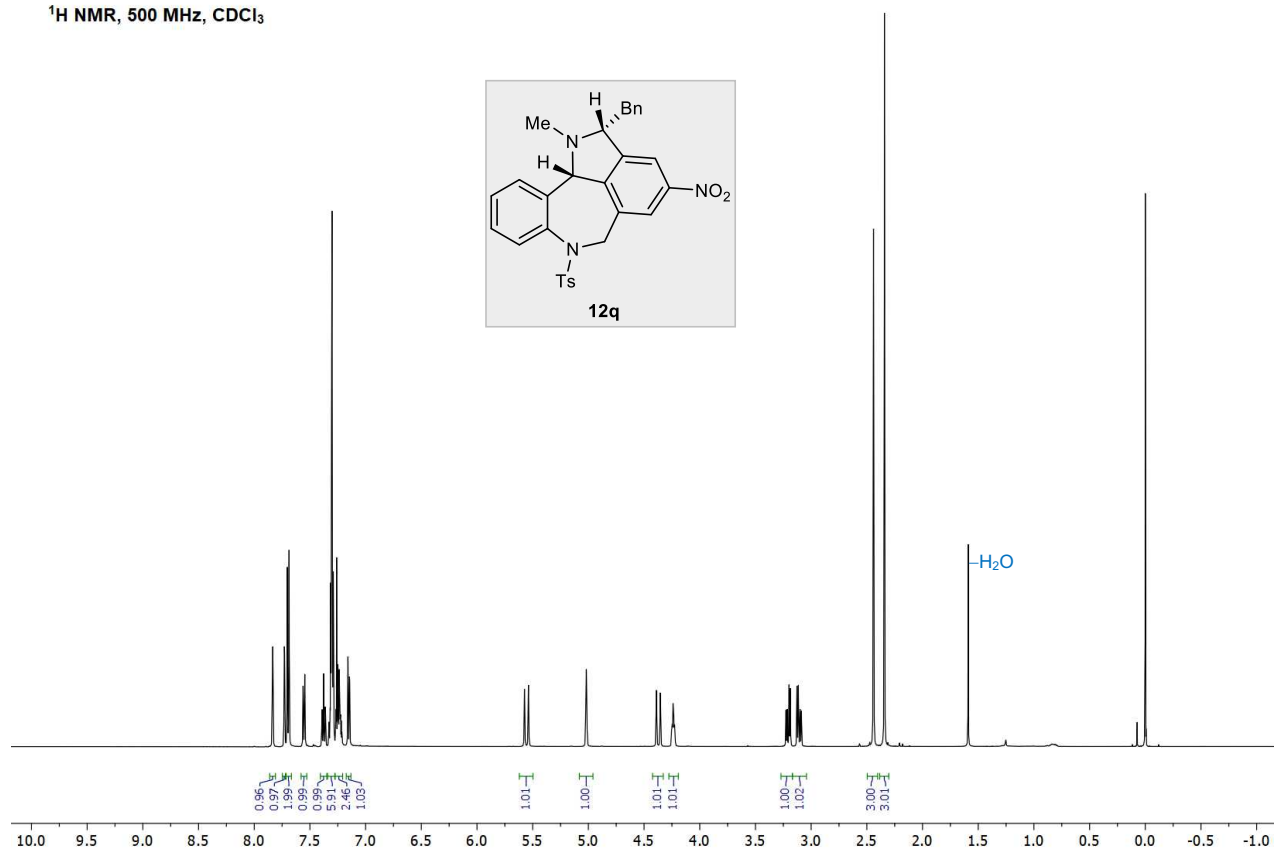
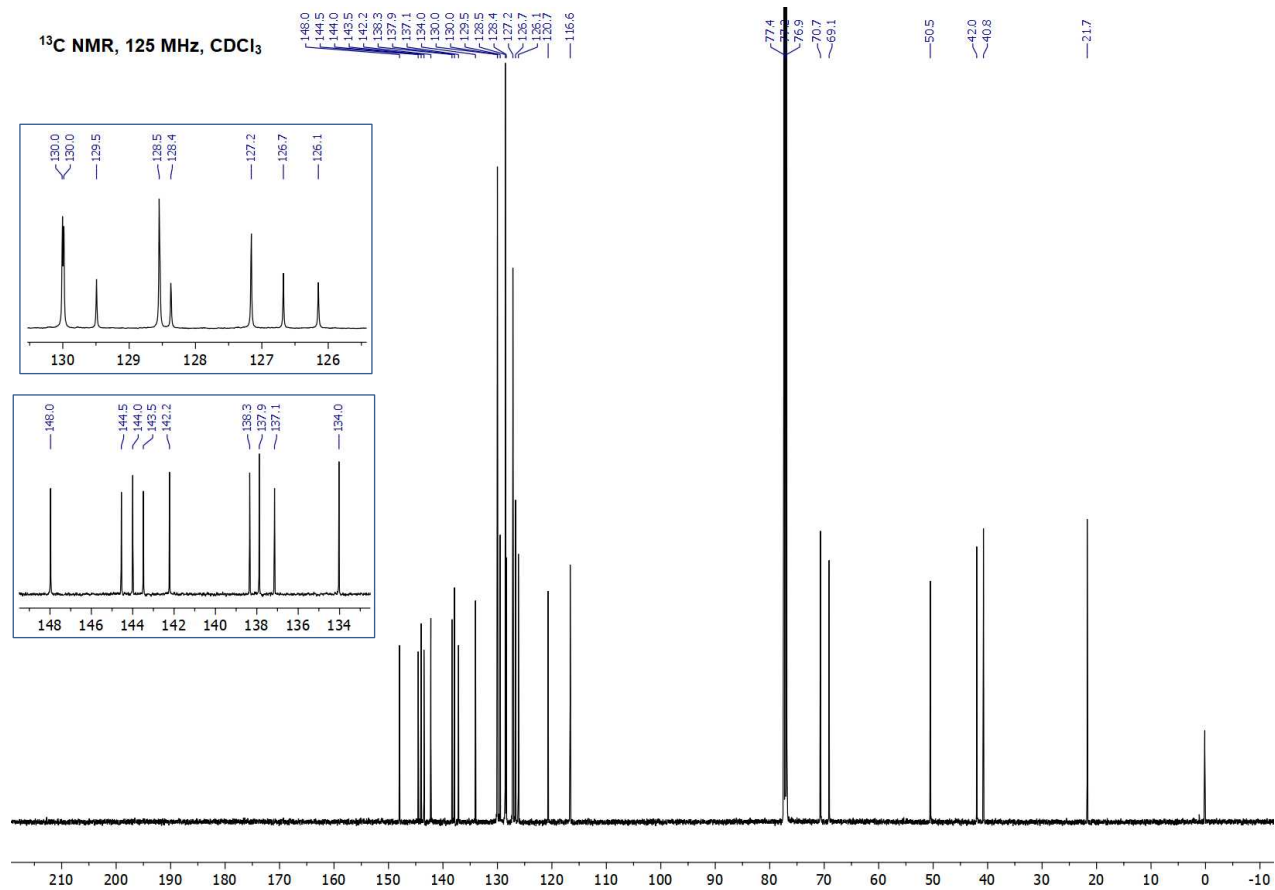
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

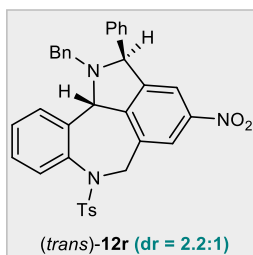
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

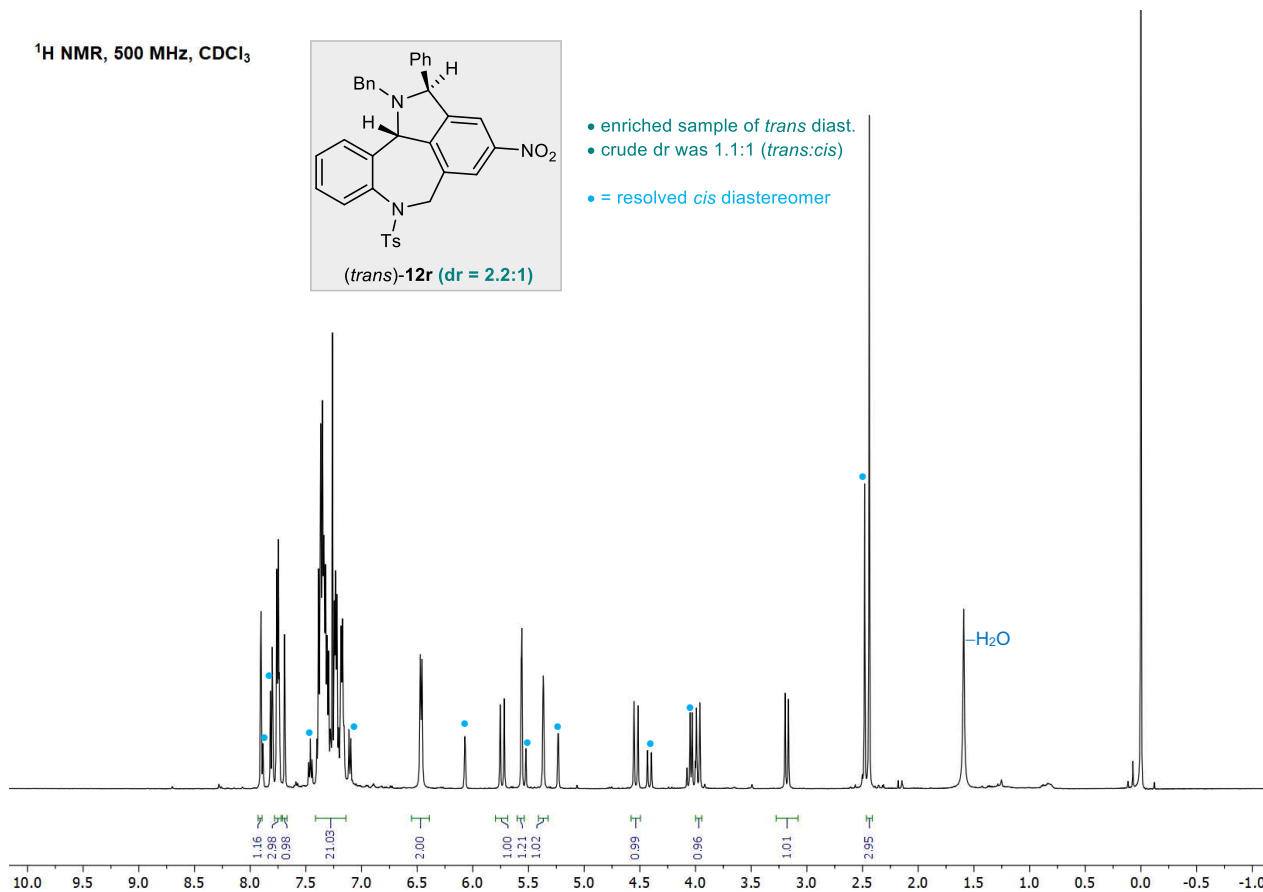
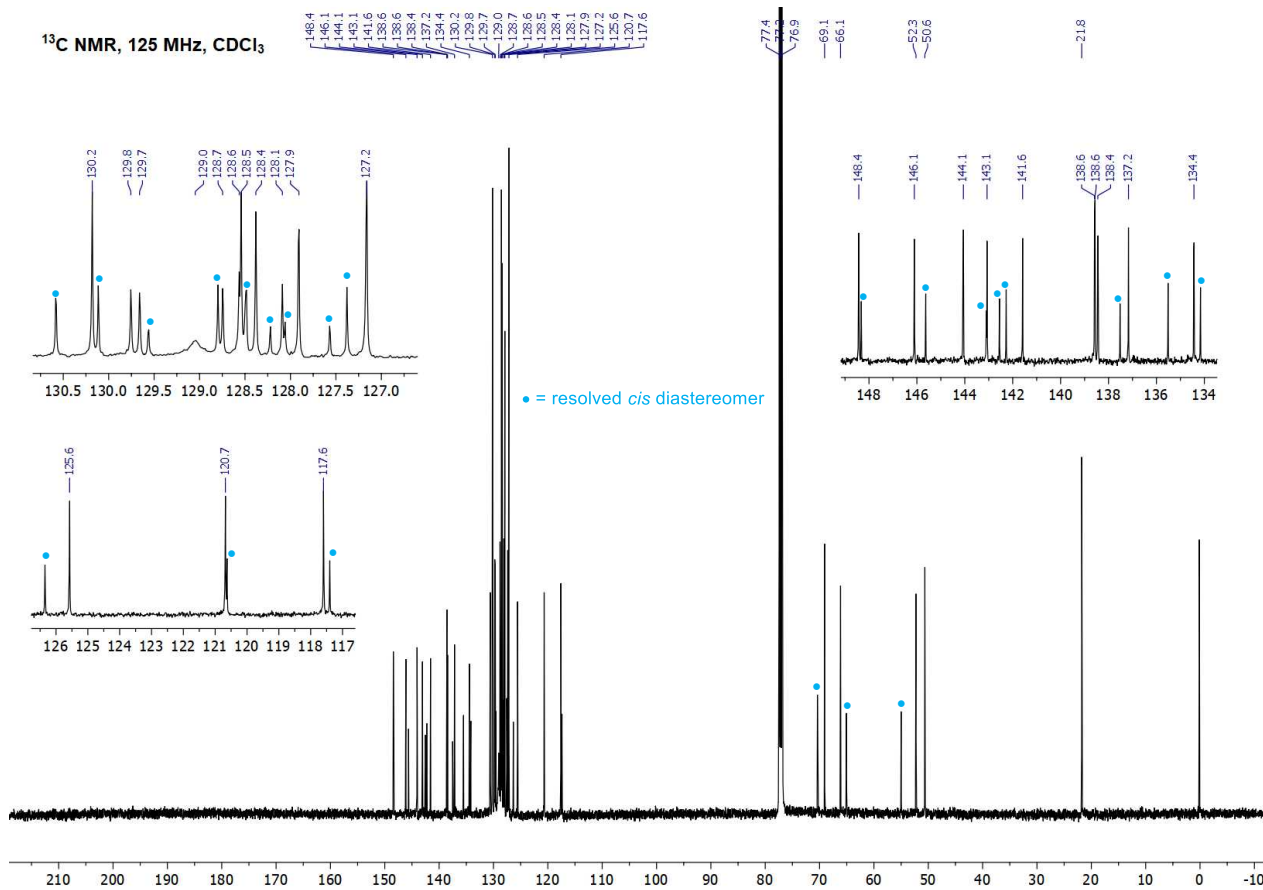
- enriched sample of *cis* diast.
- crude dr was 2.2:1 (*cis:trans*)
- = resolved *trans* diastereomer

 $^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ 

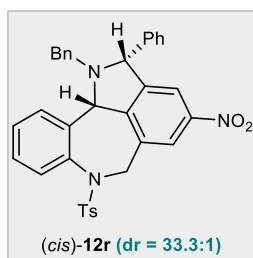
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$  $^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ 

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

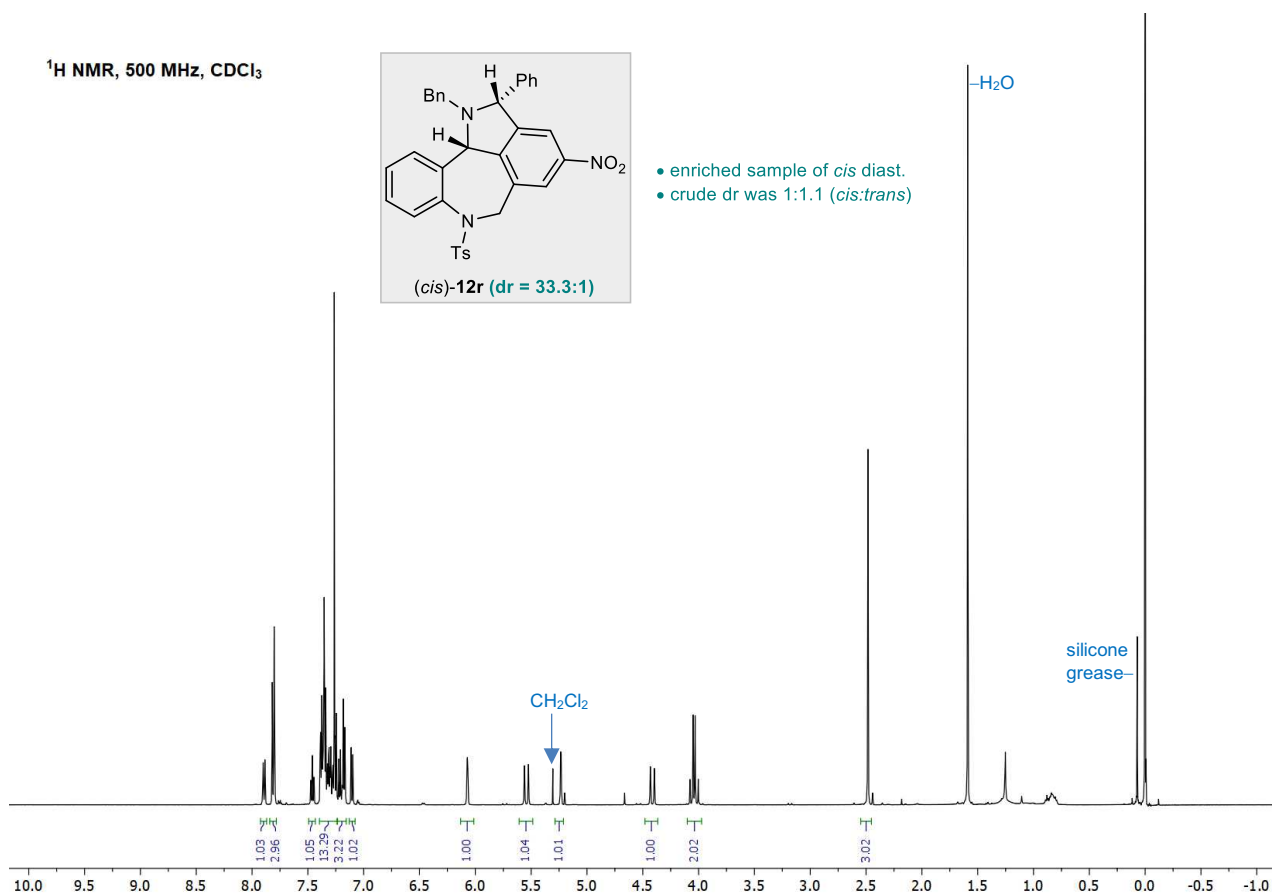
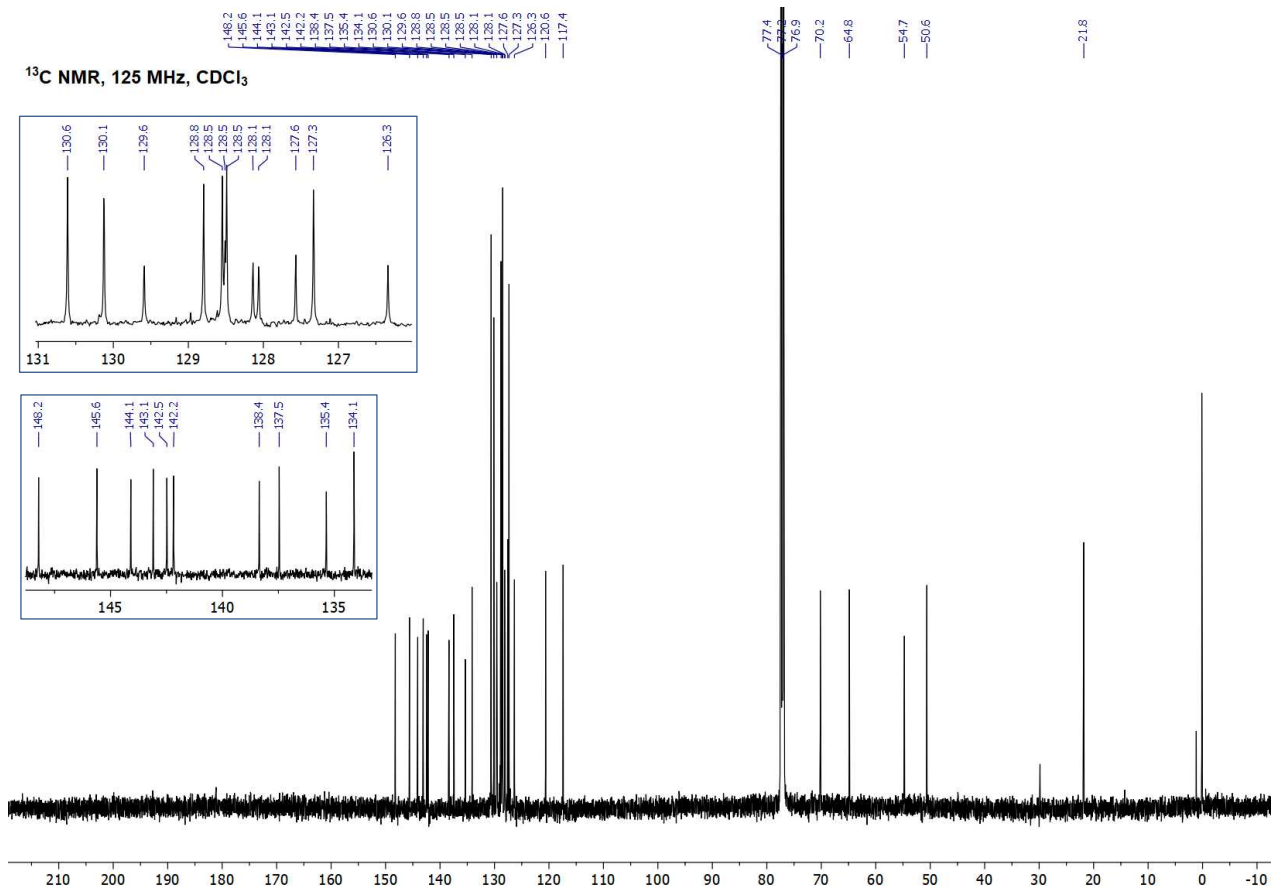
- enriched sample of *trans* diast.
- crude dr was 1.1:1 (*trans*:*cis*)
- = resolved *cis* diastereomer

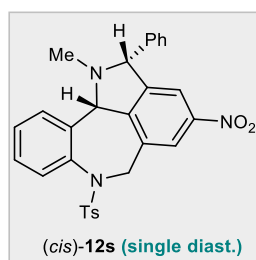
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



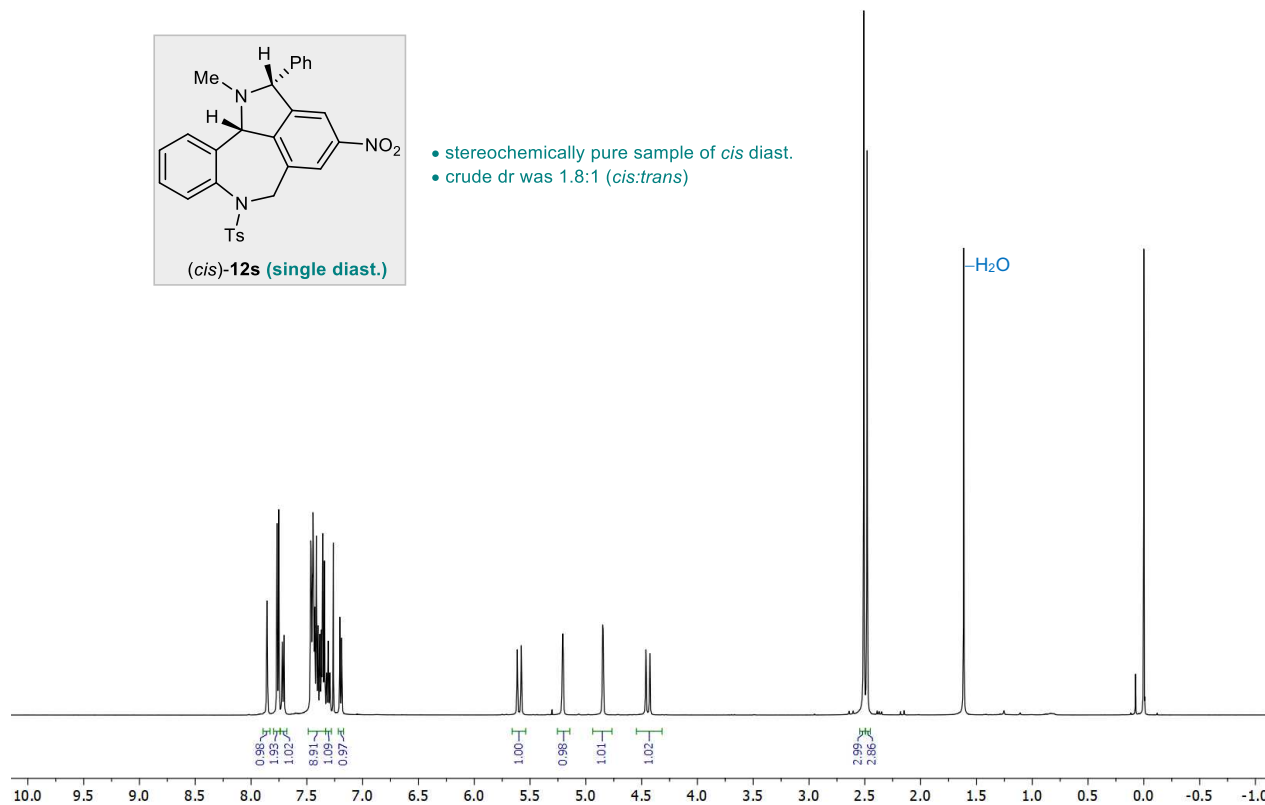
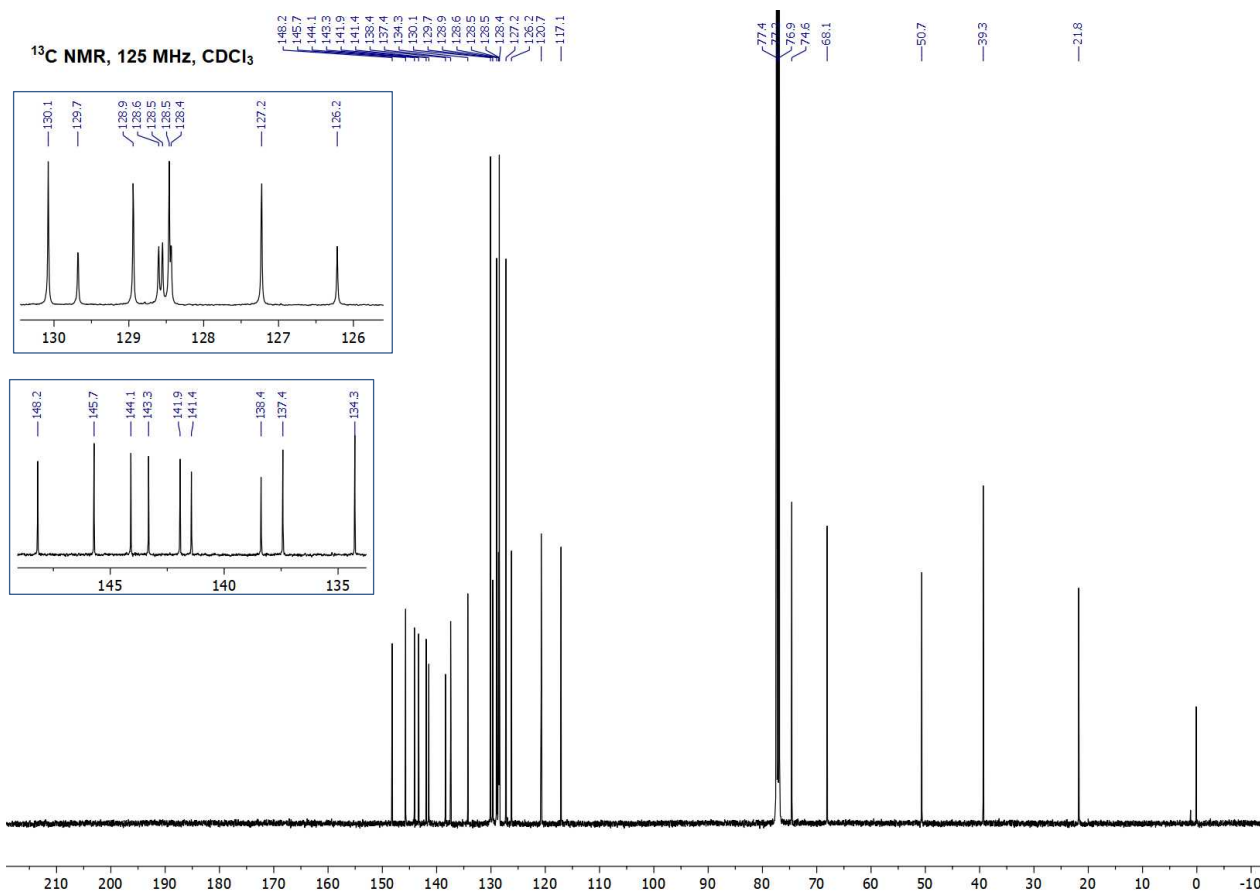
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

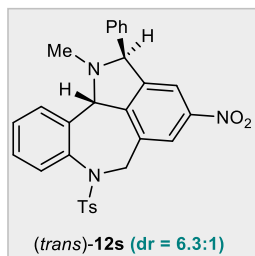
- enriched sample of *cis* diast.
- crude dr was 1:1.1 (*cis:trans*)

<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

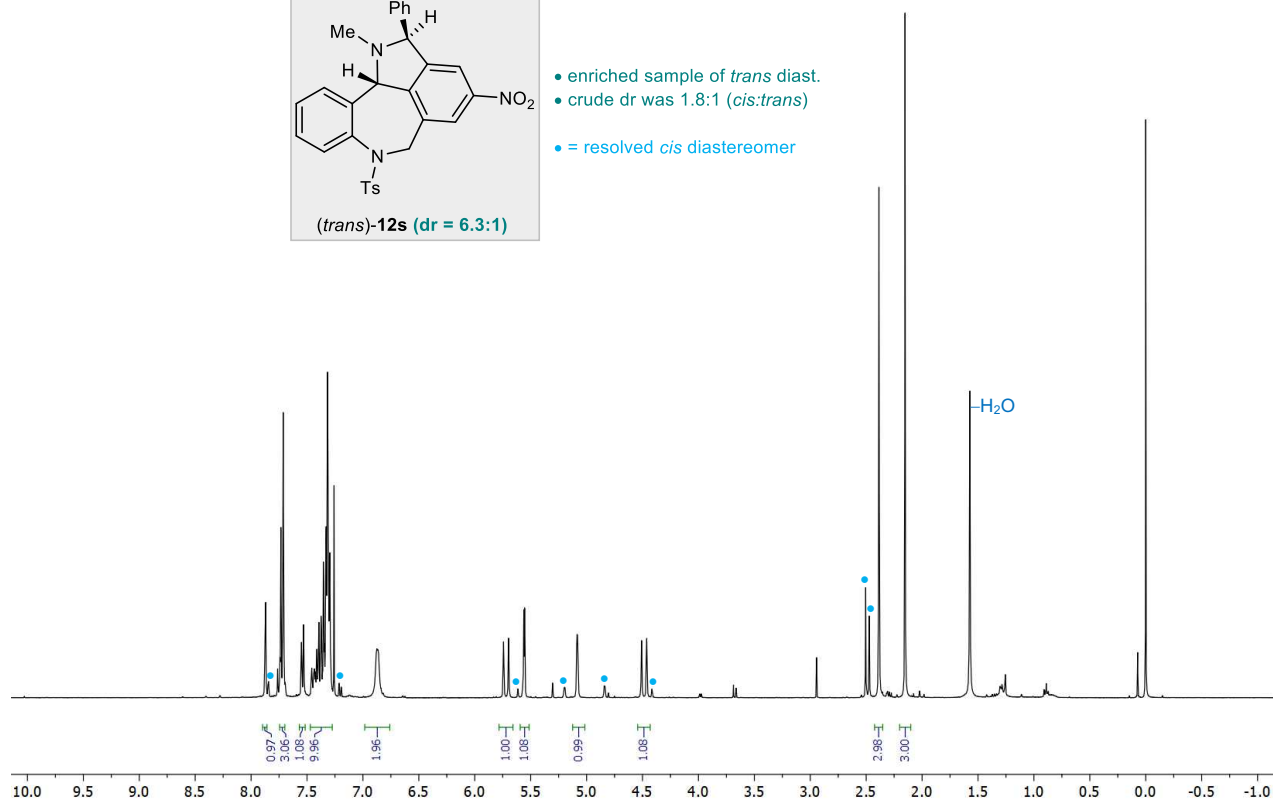
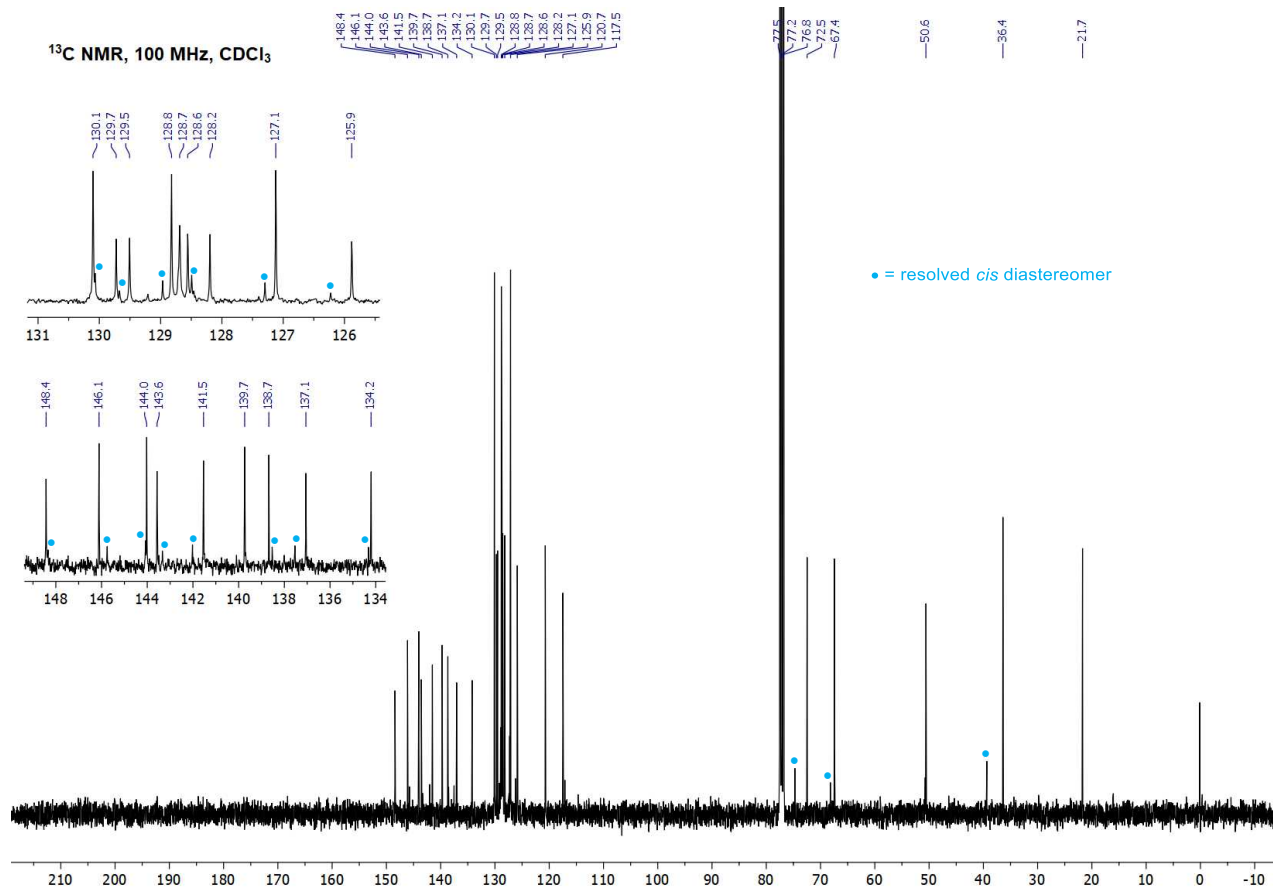
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

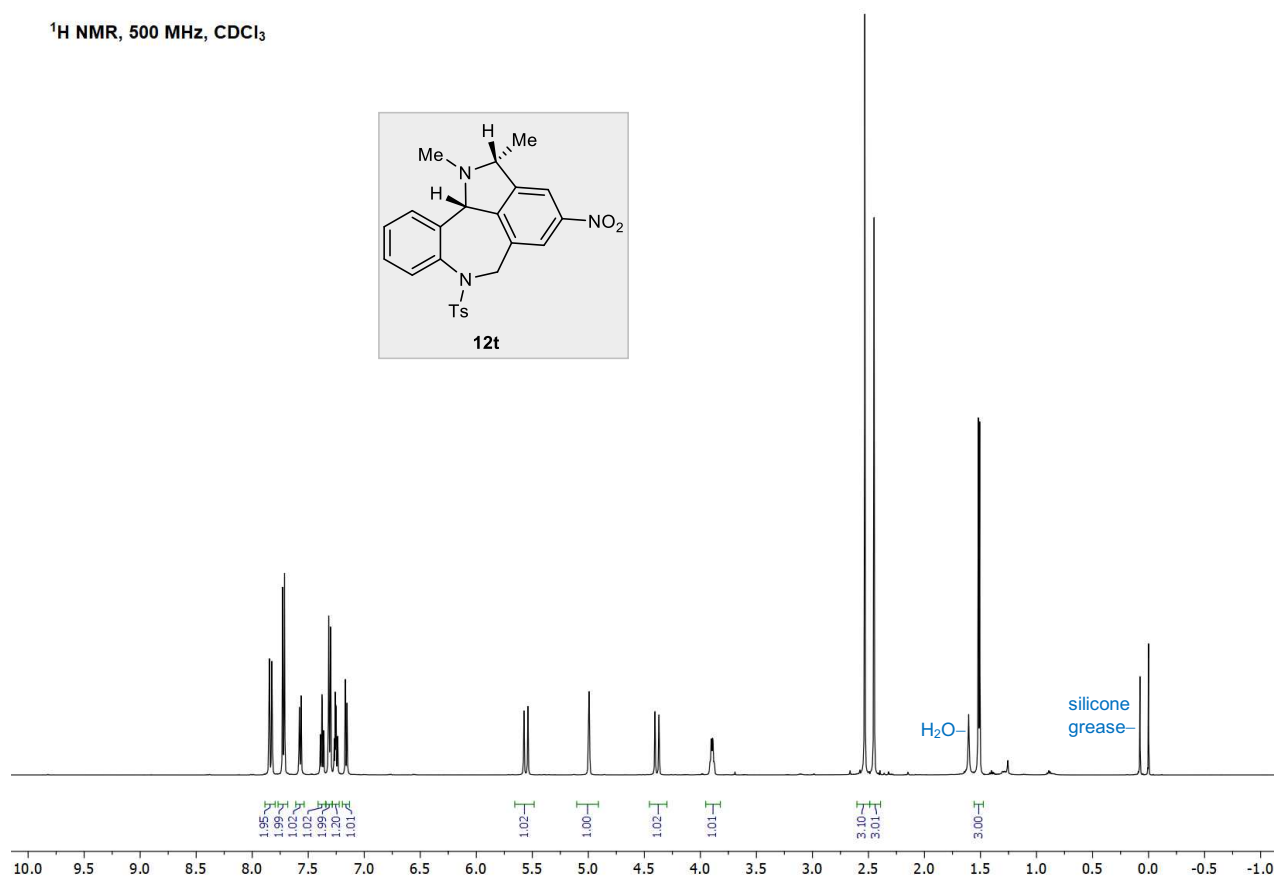
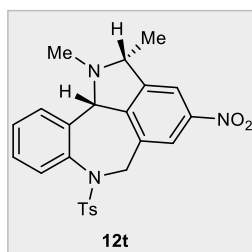
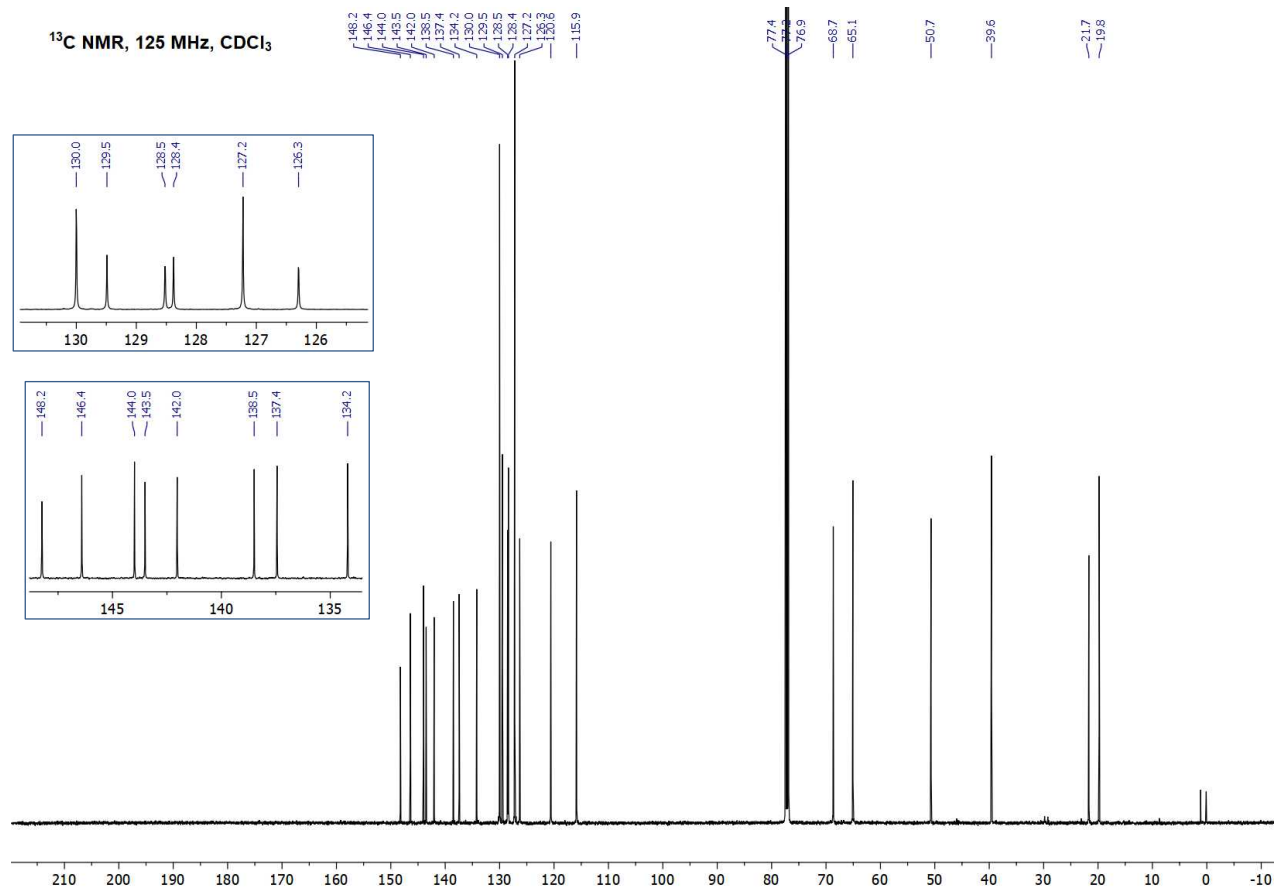
- stereochemically pure sample of *cis* diast.
- crude dr was 1.8:1 (*cis*:*trans*)

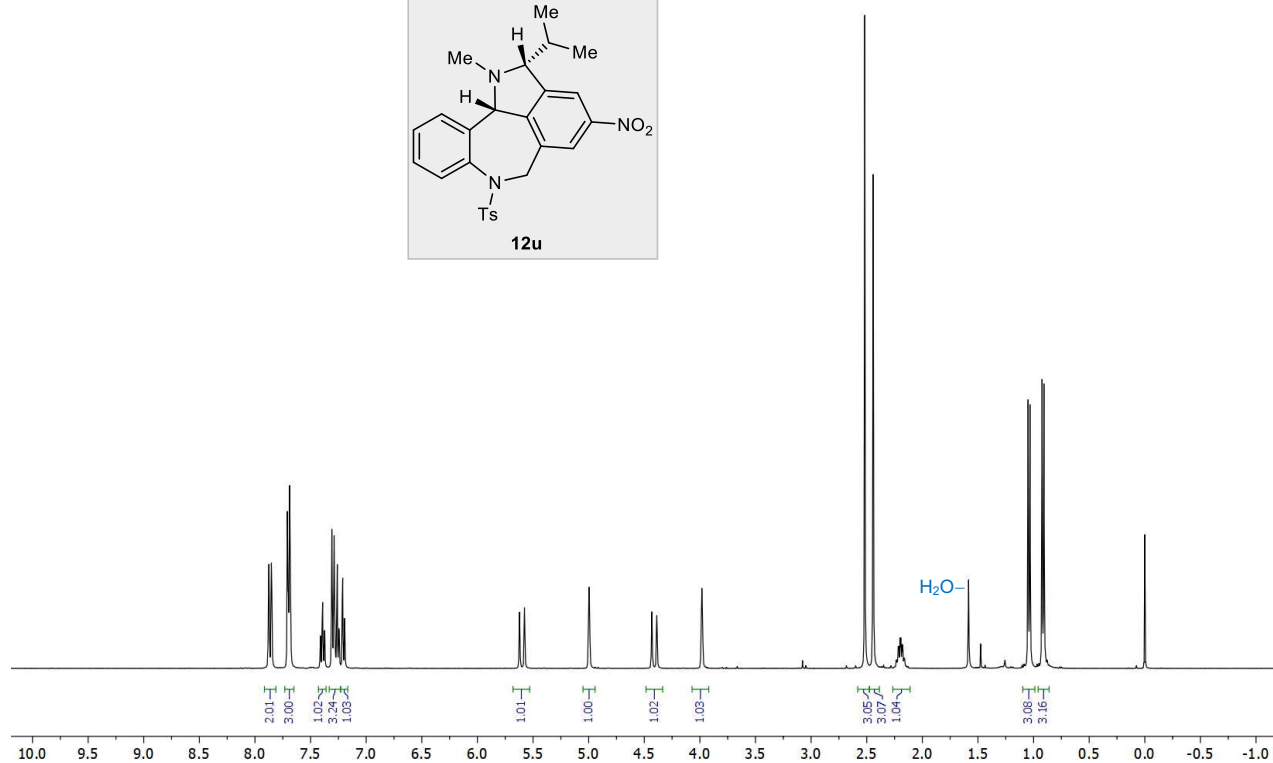
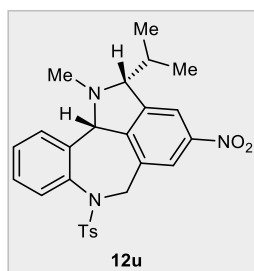
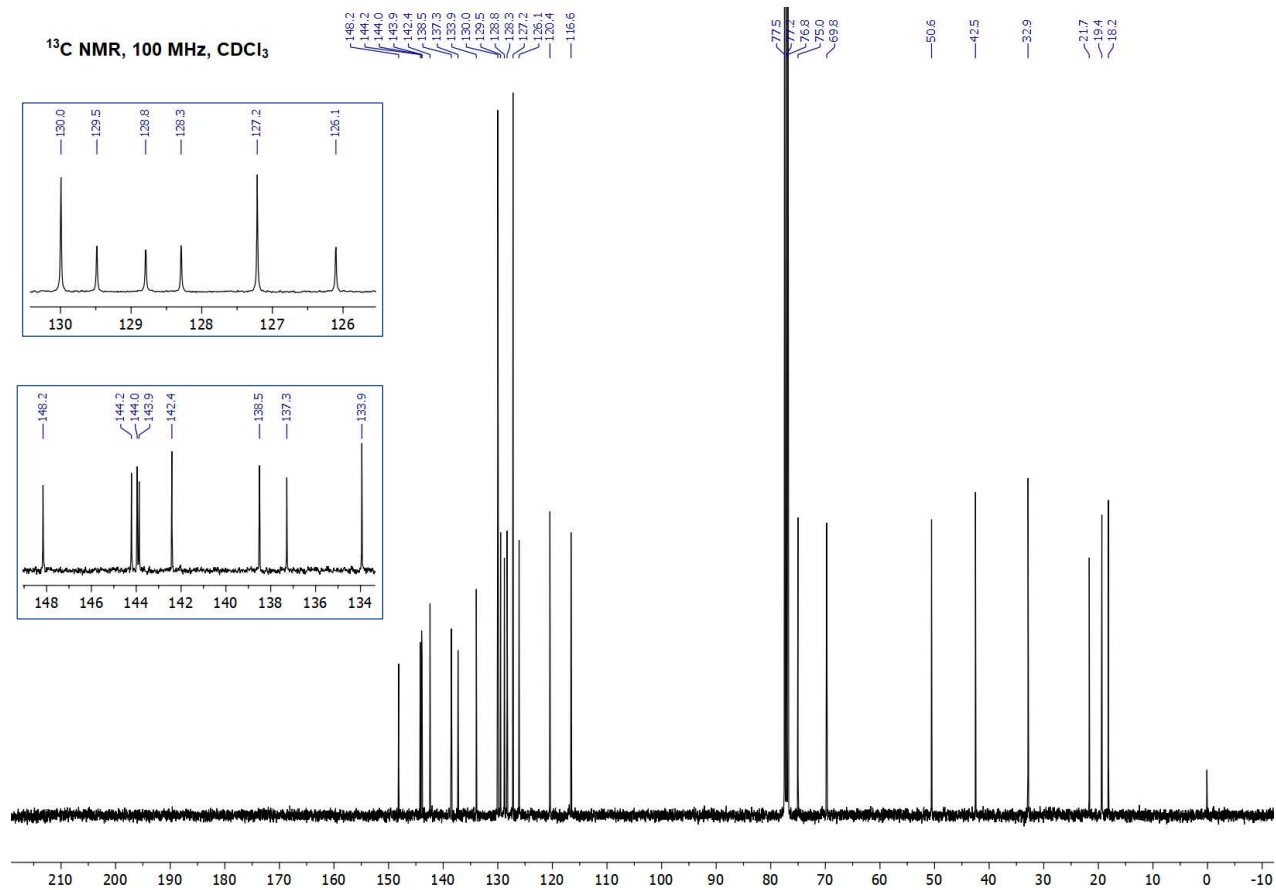
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

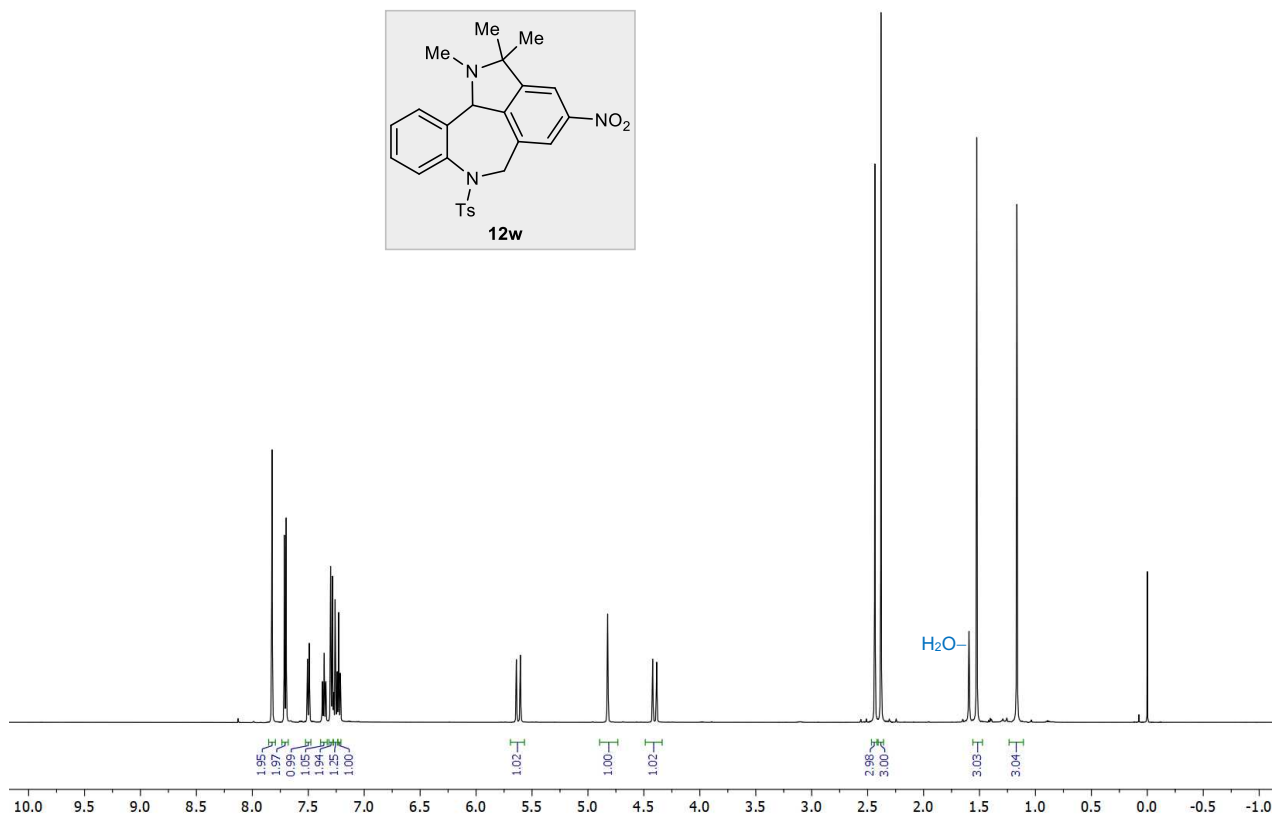
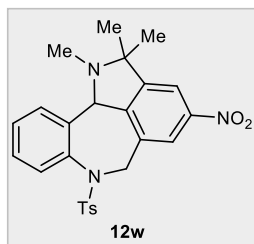
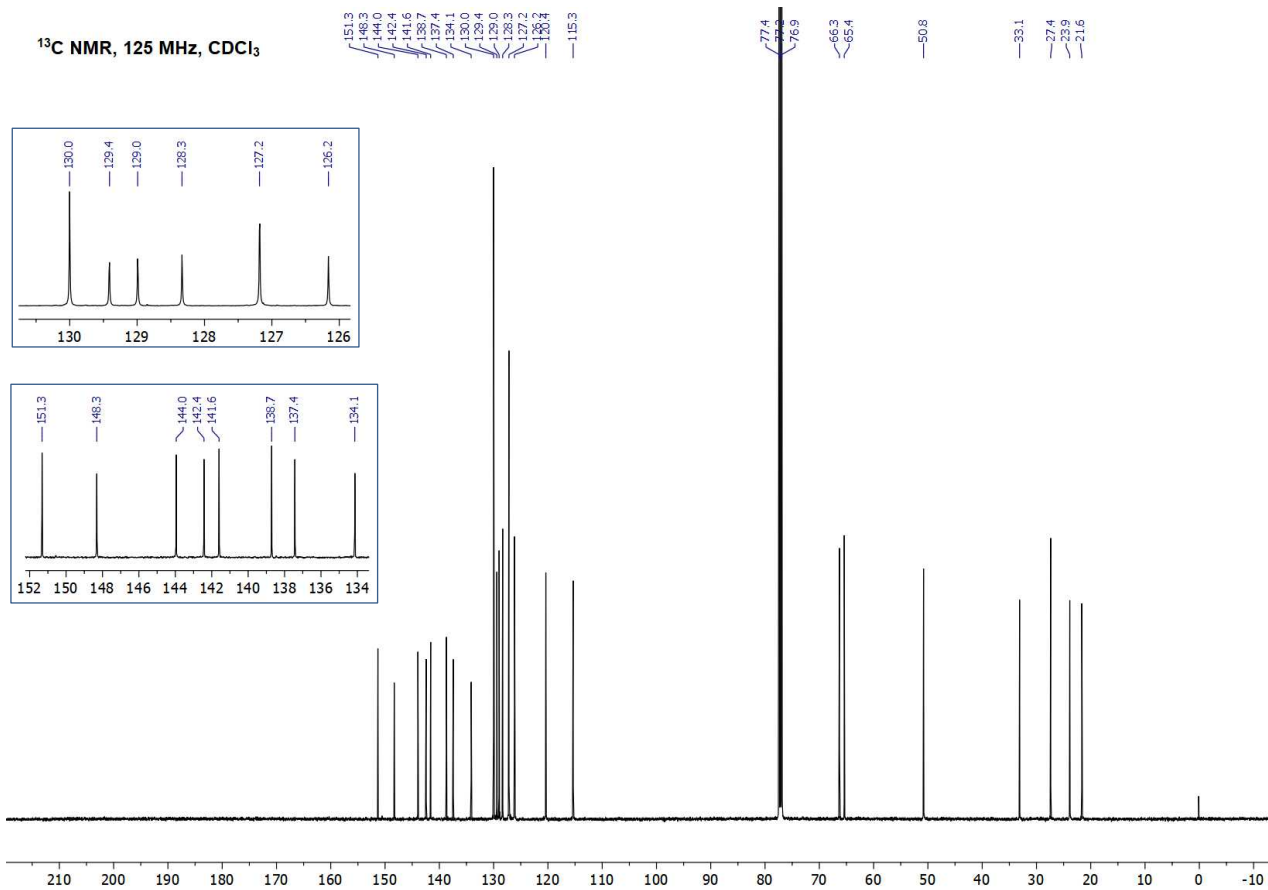
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

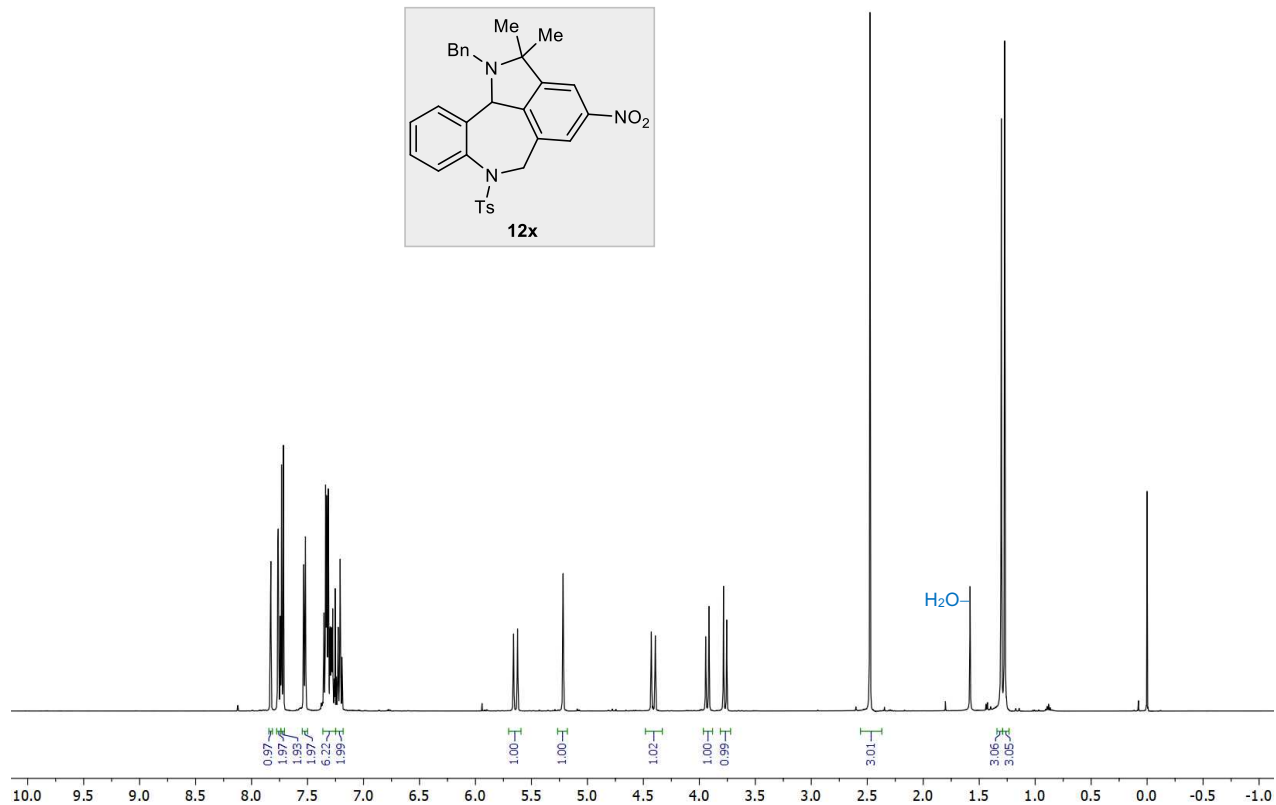
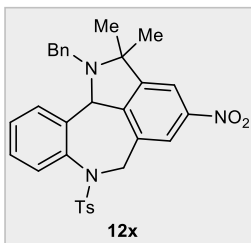
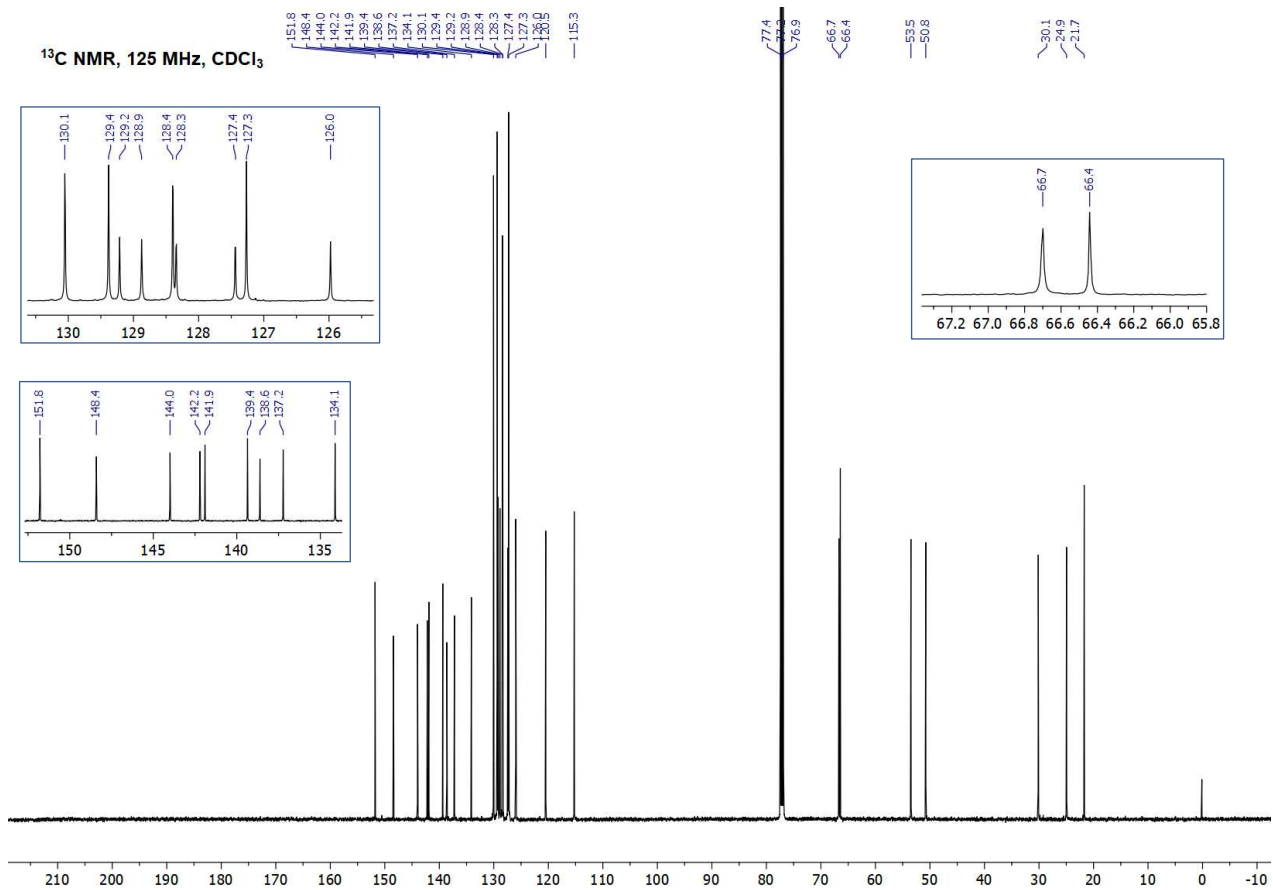
- enriched sample of *trans* diast.
- crude dr was 1.8:1 (*cis:trans*)
- = resolved *cis* diastereomer

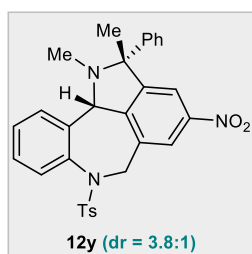
<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

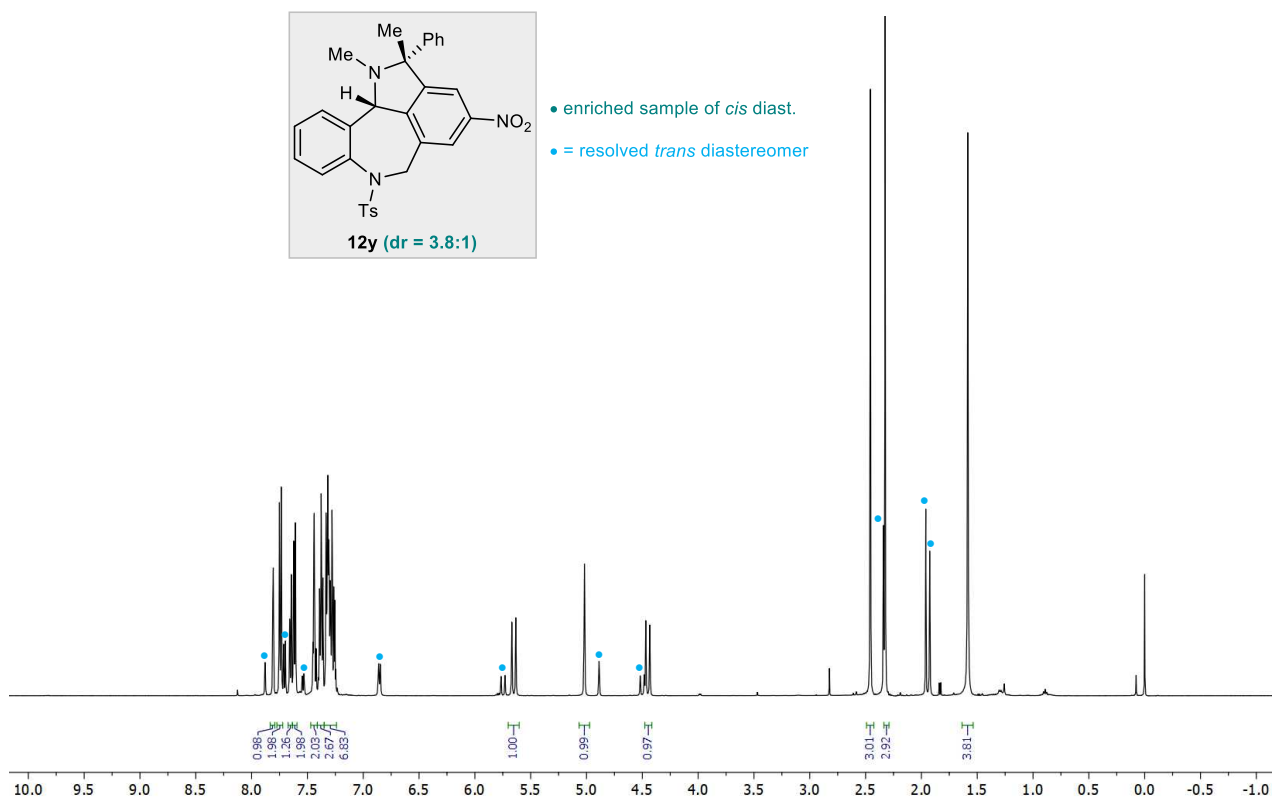
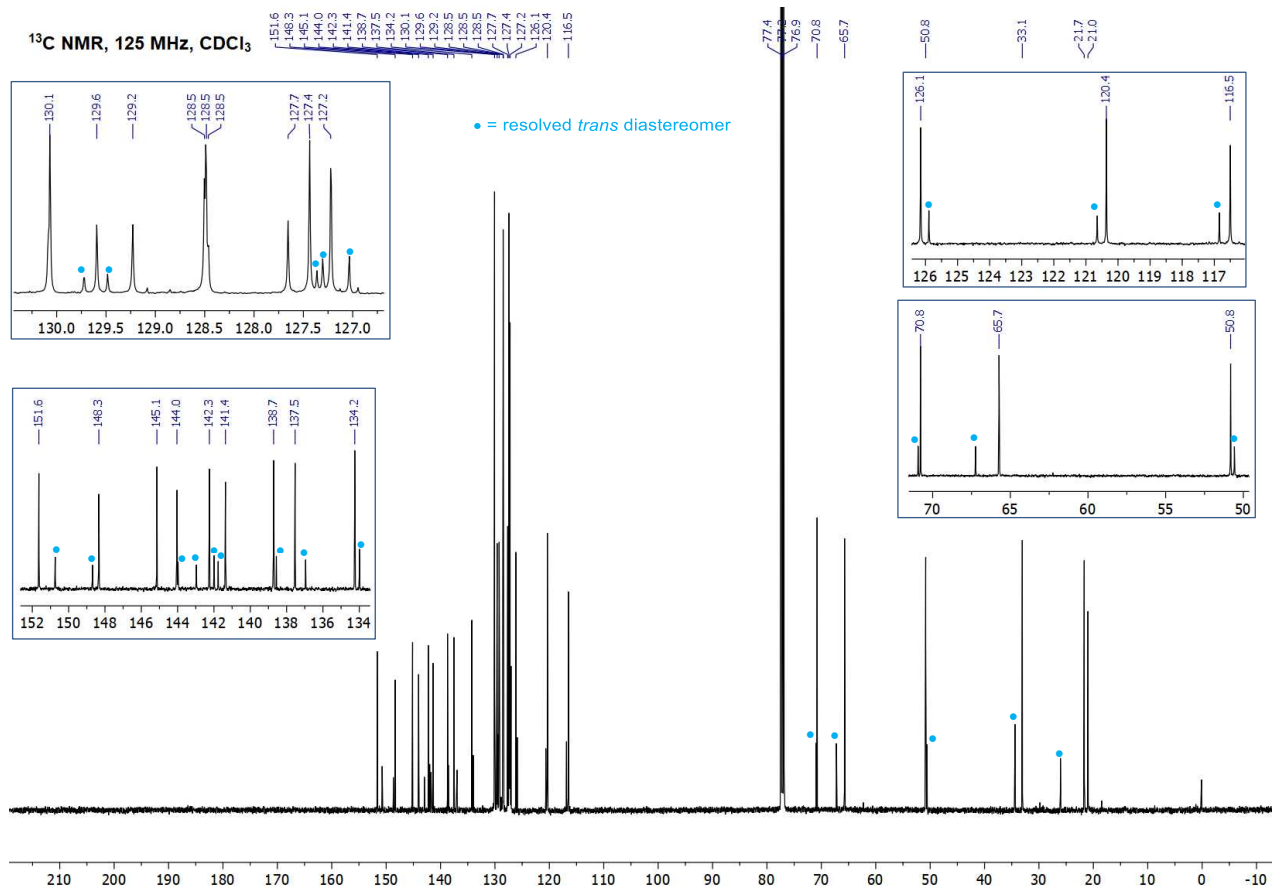
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

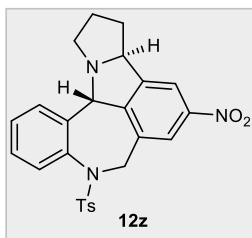
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

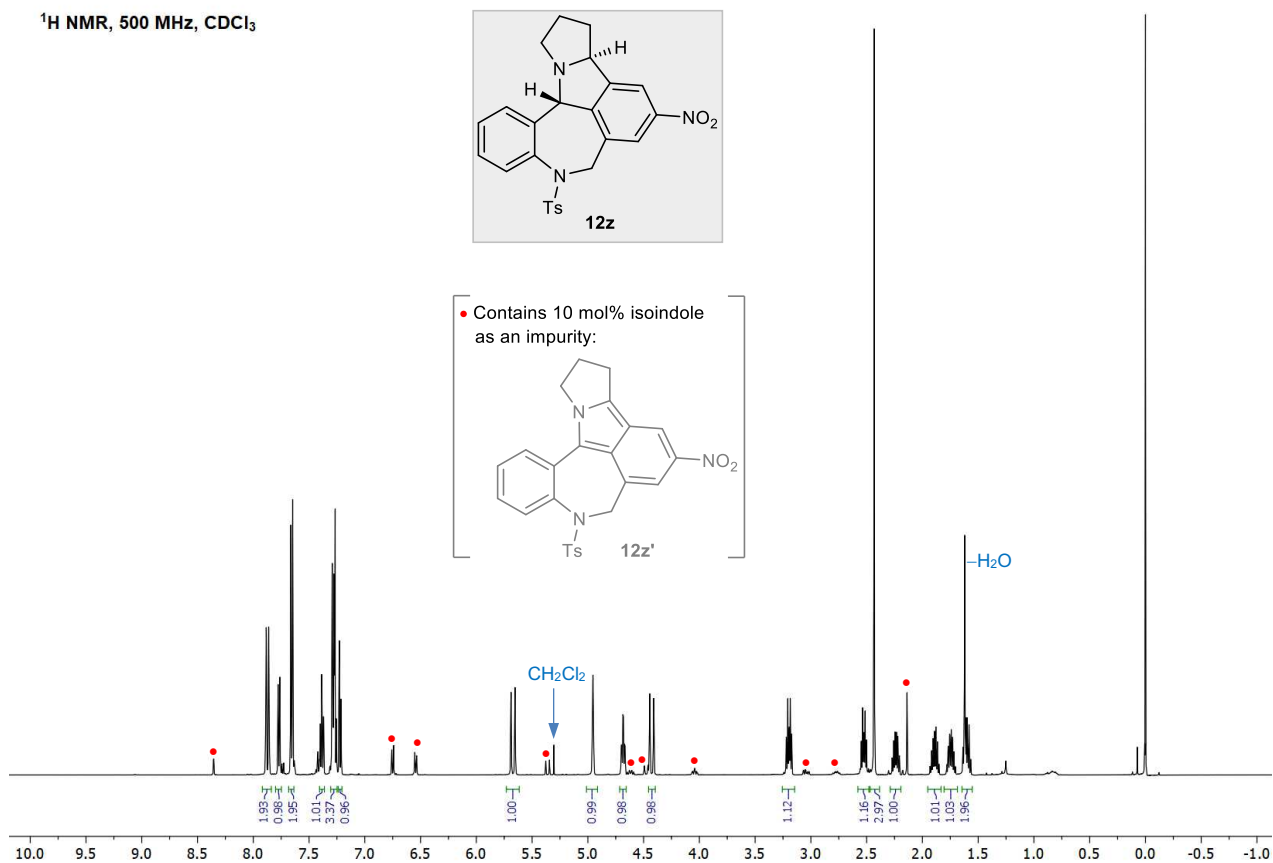
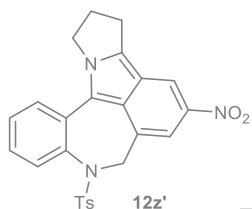
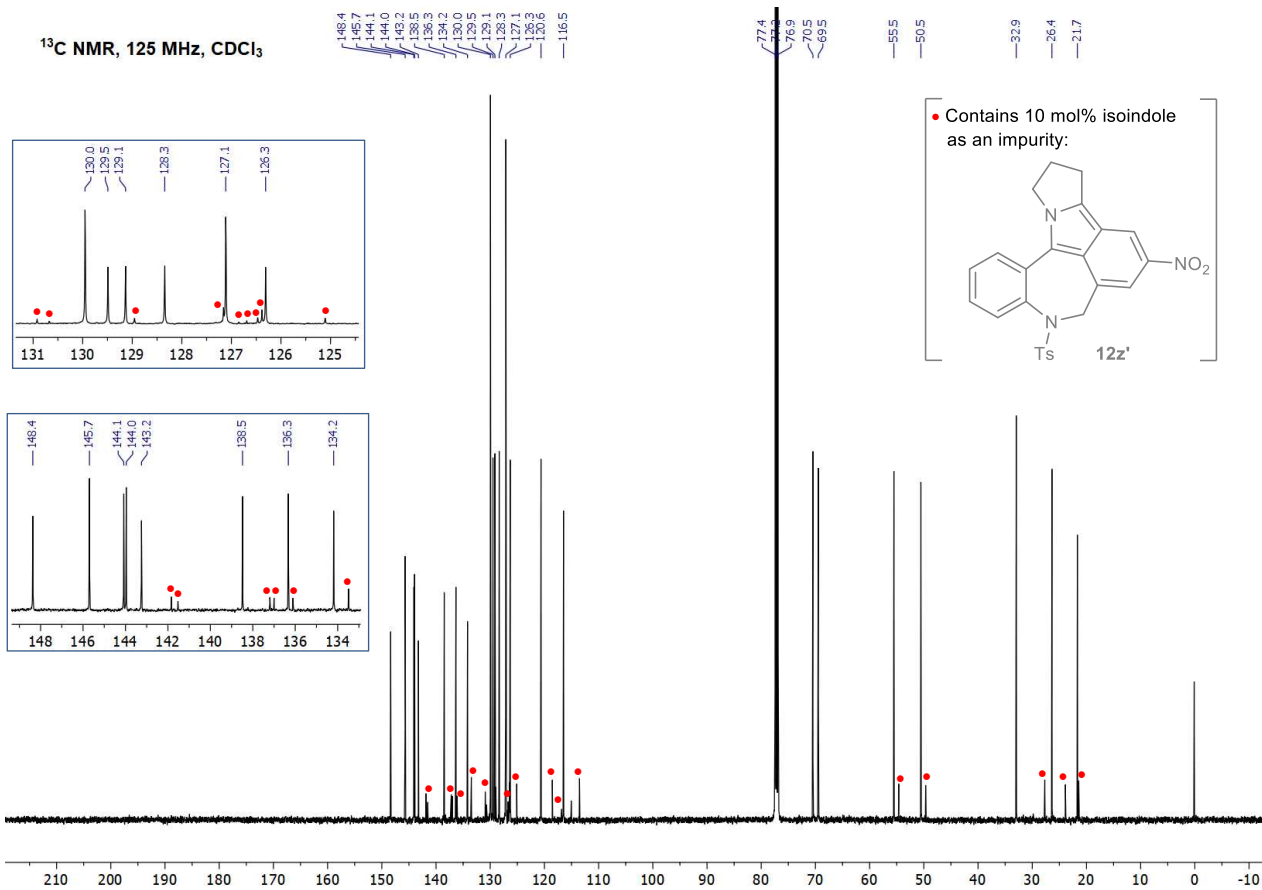
- enriched sample of *cis* diast.
- = resolved *trans* diastereomer

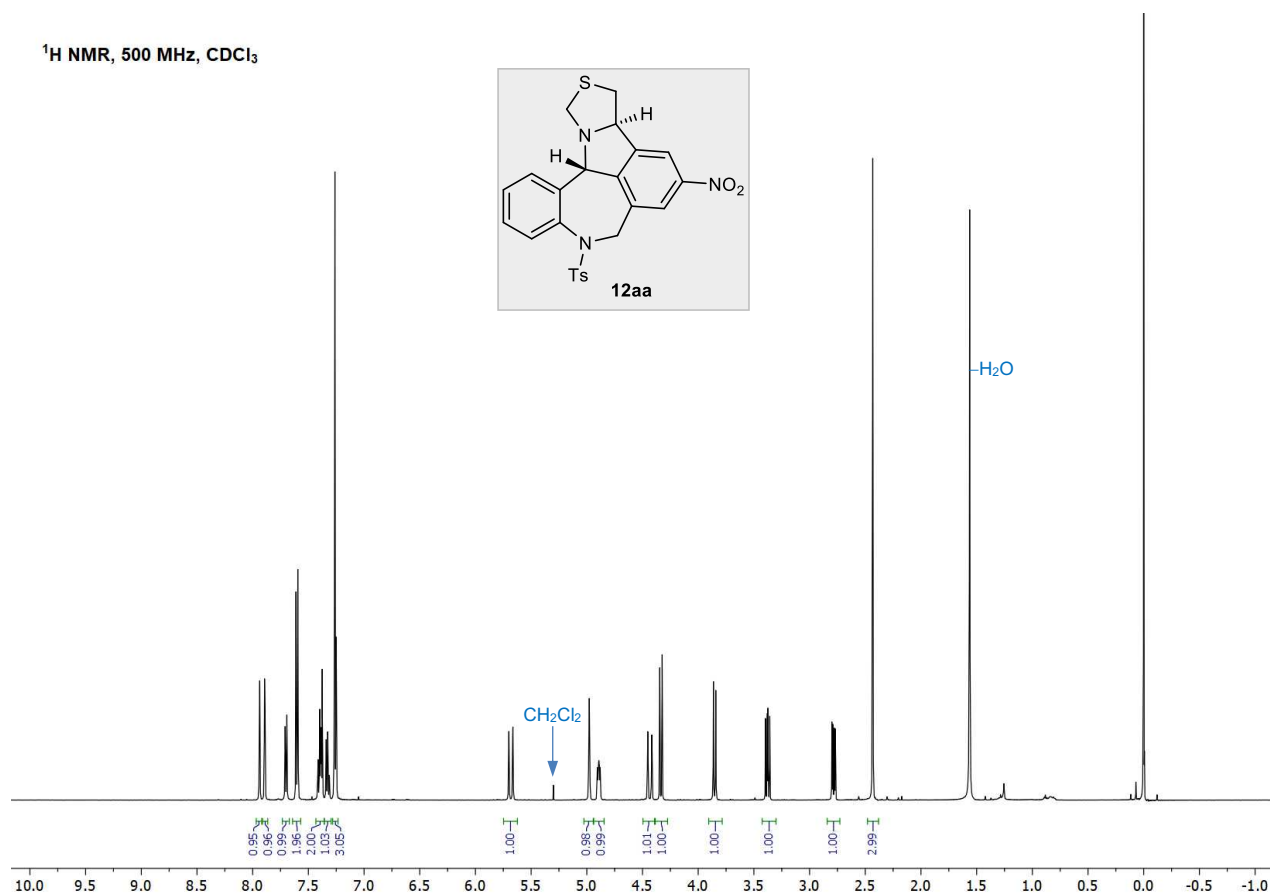
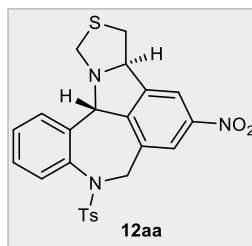
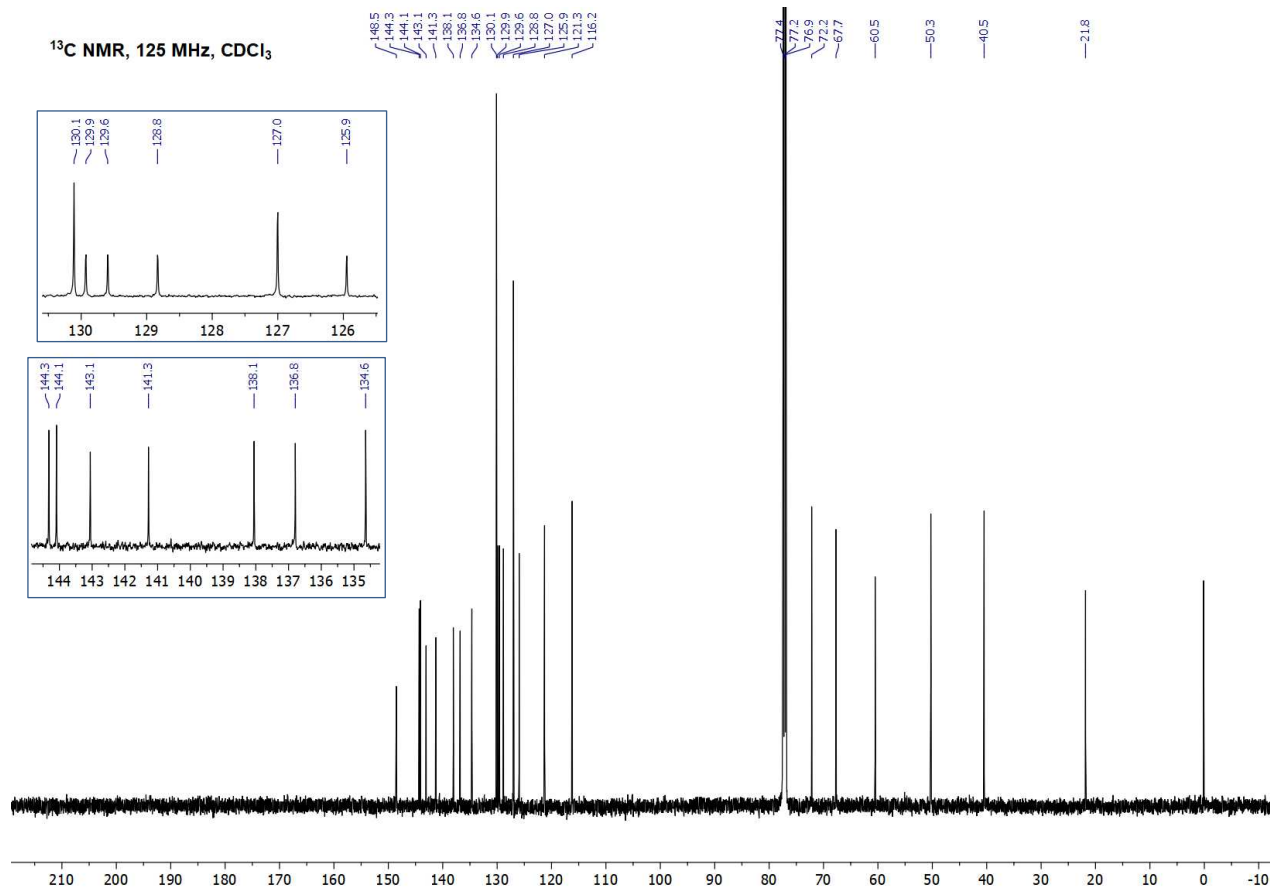
 $^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ 

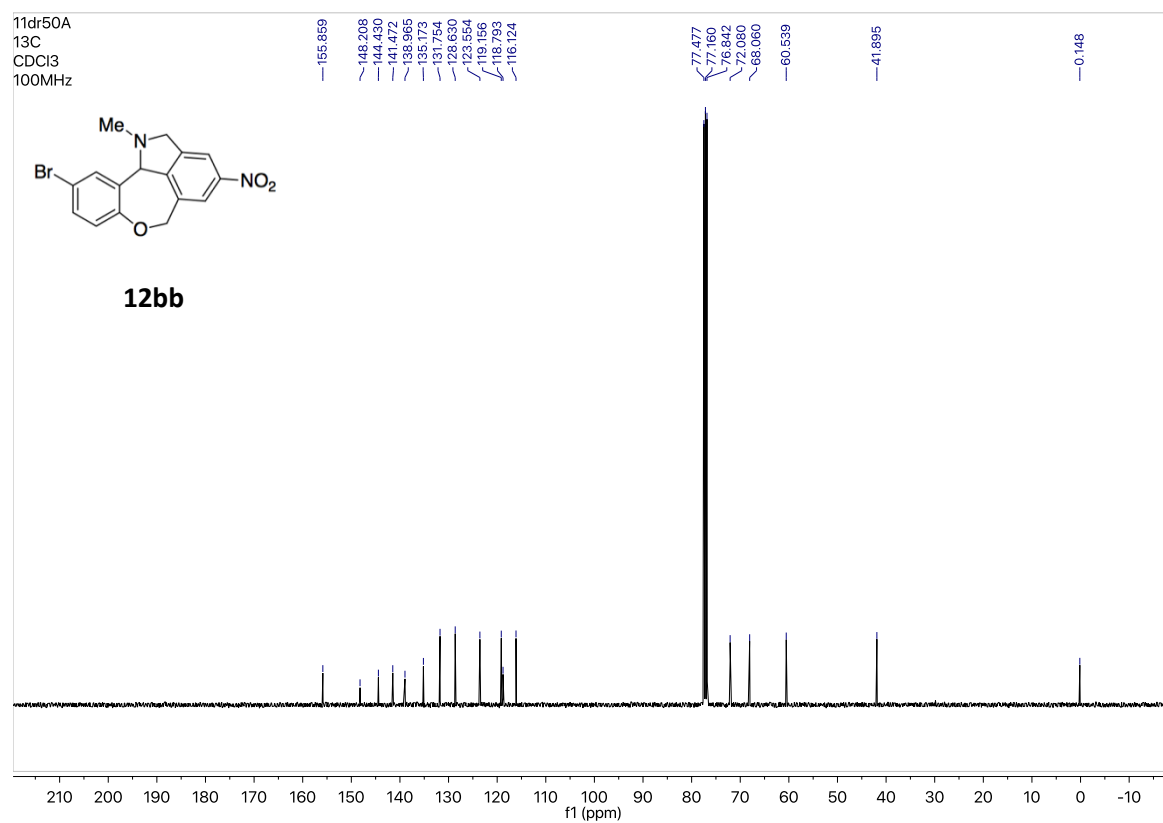
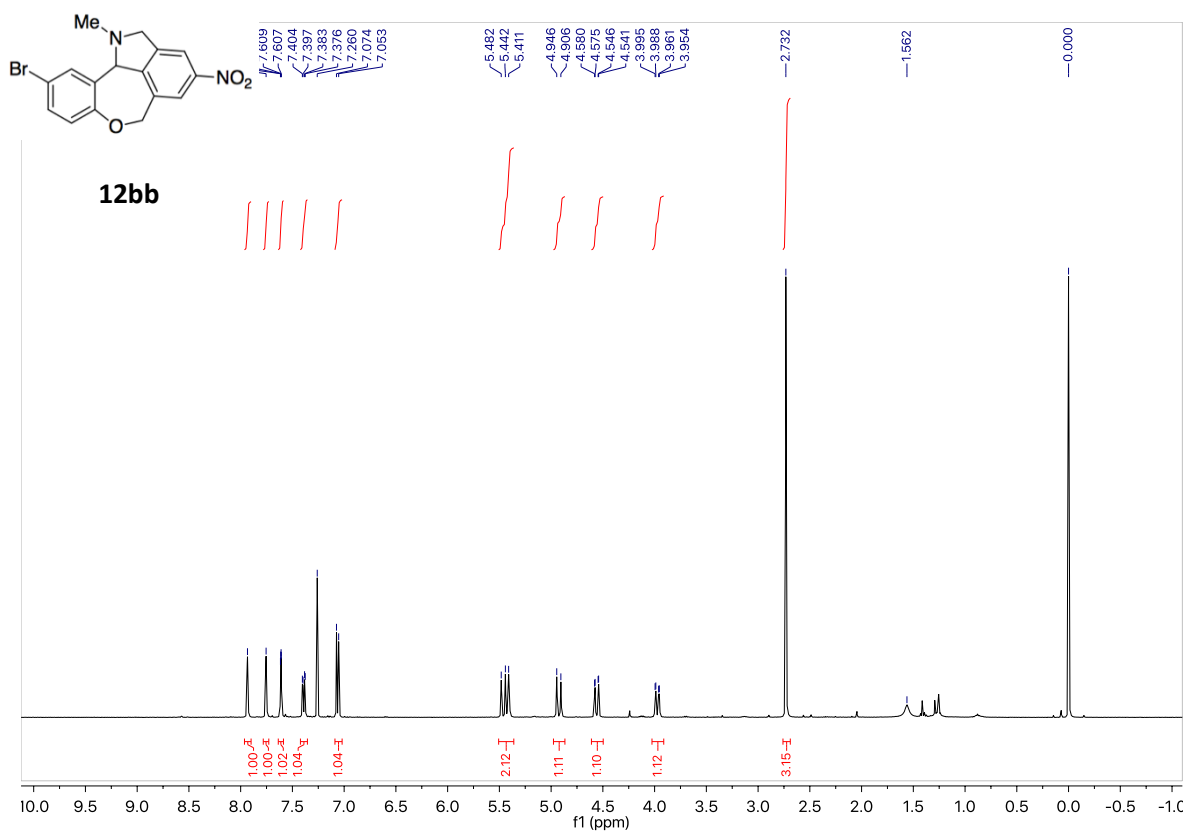


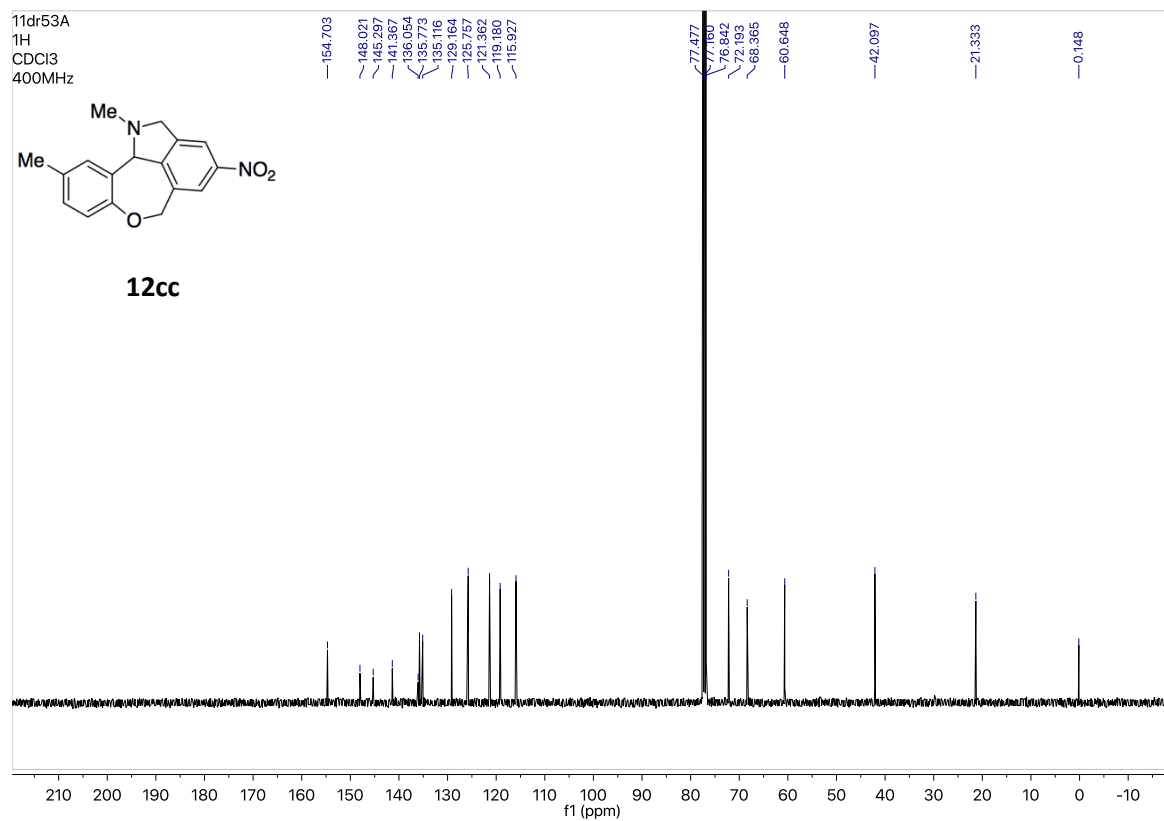
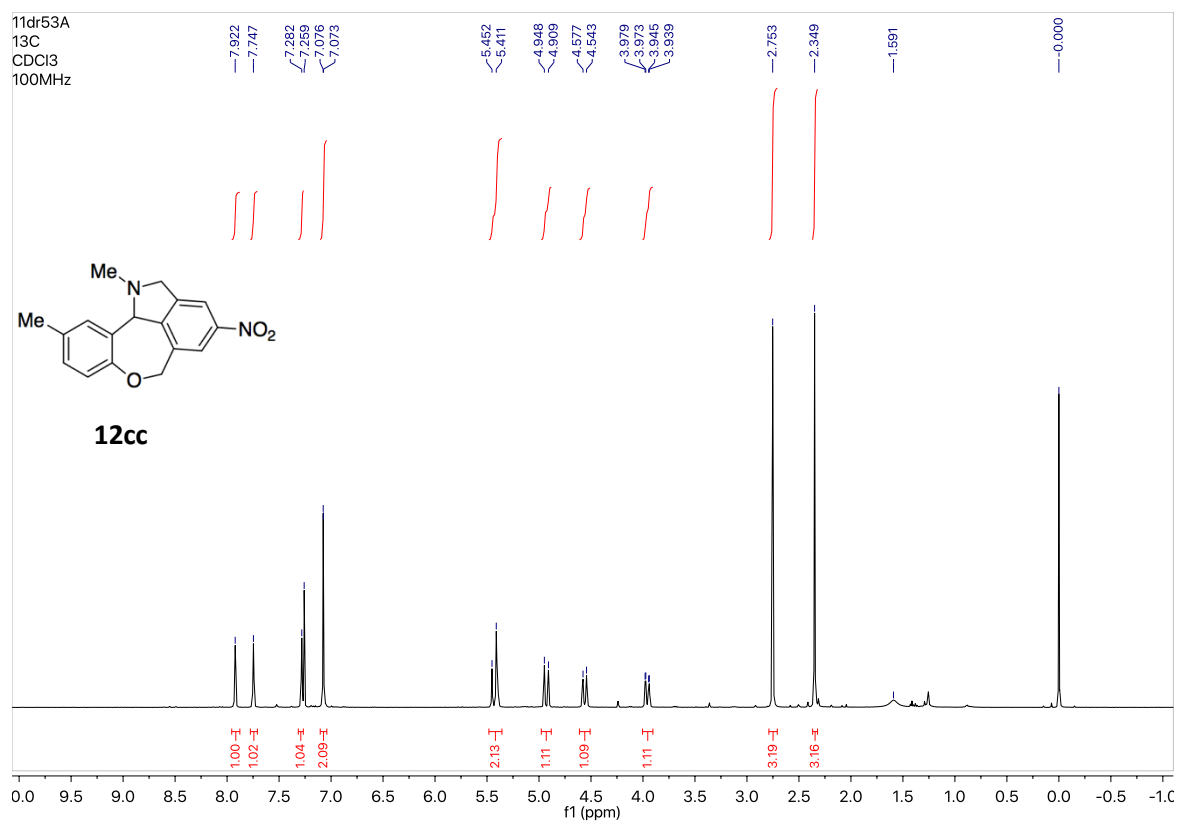
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>

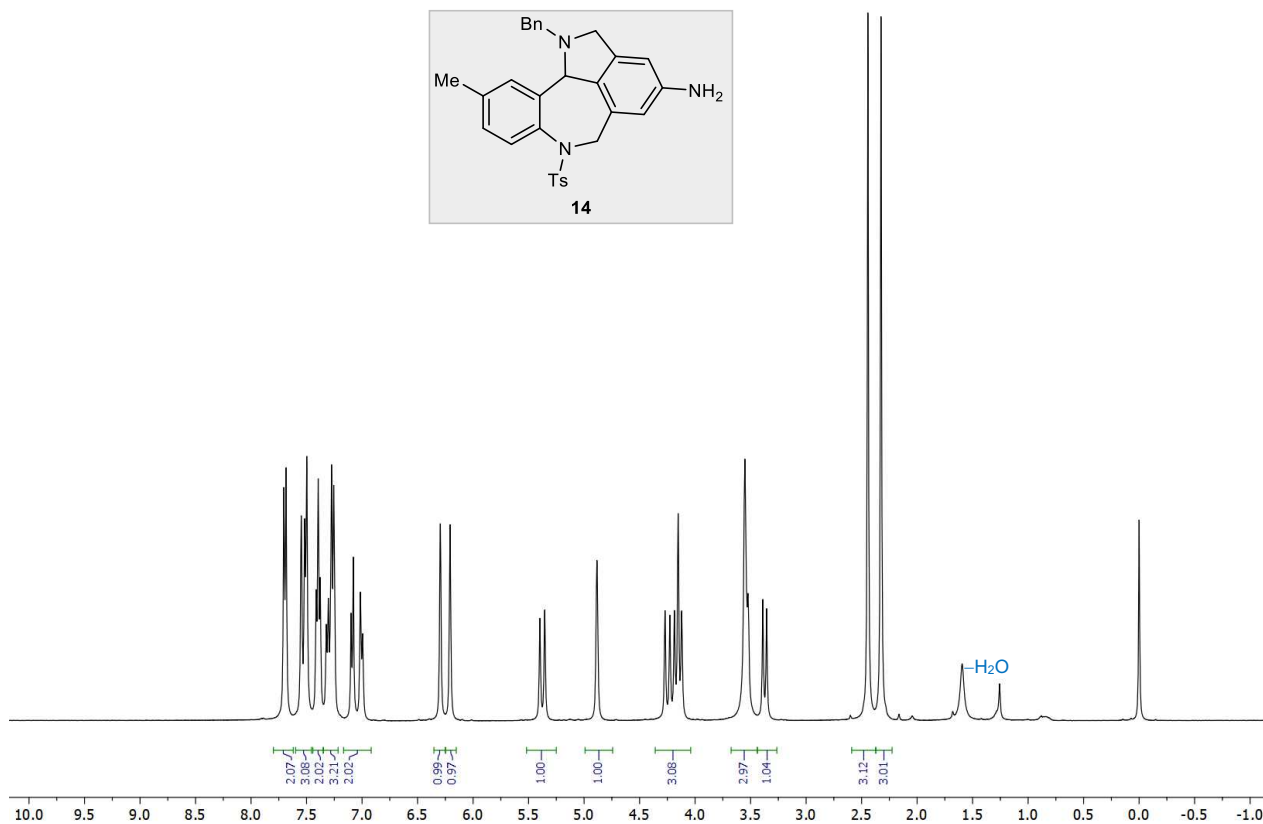
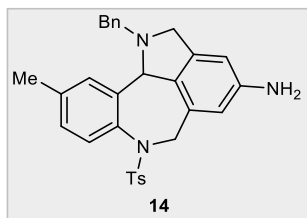
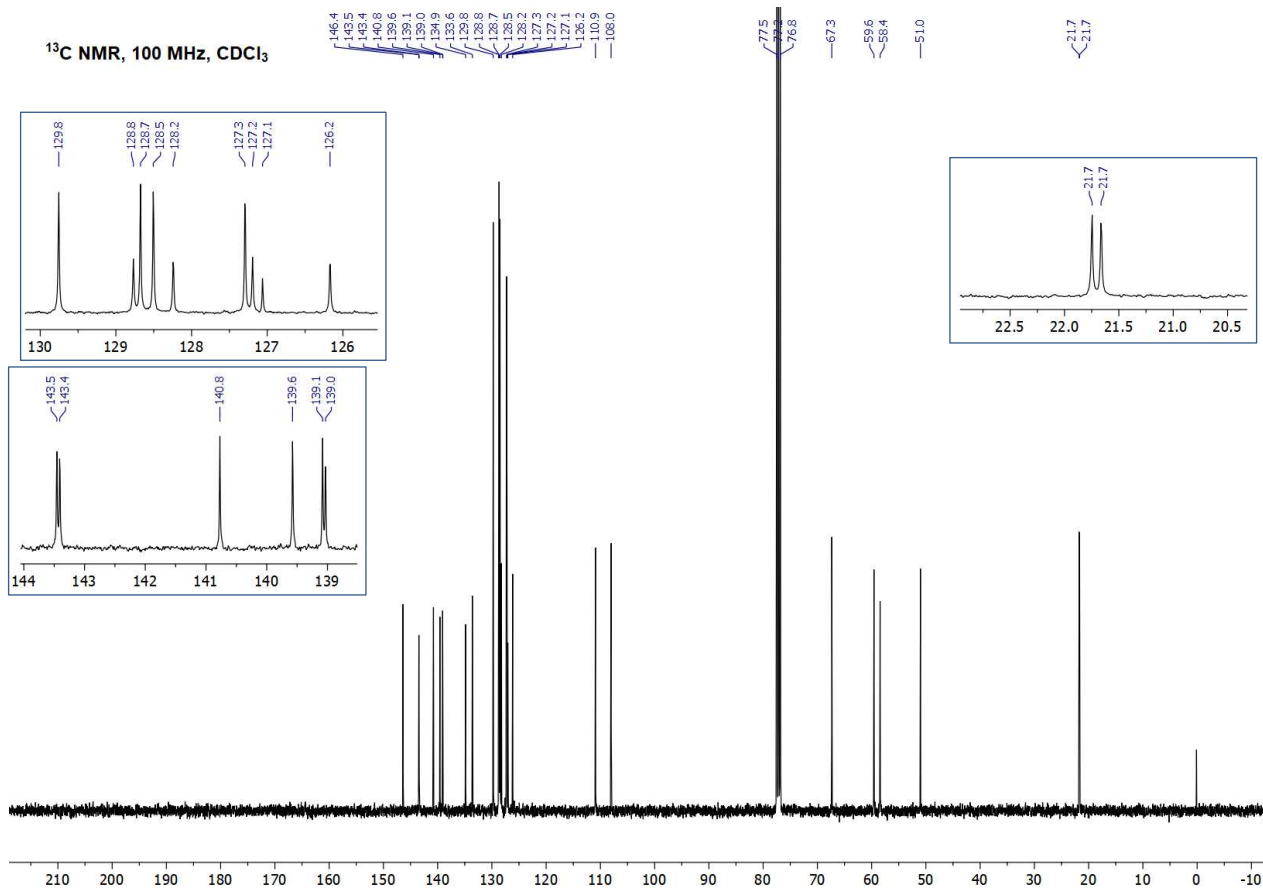
• Contains 10 mol% isoindole as an impurity:

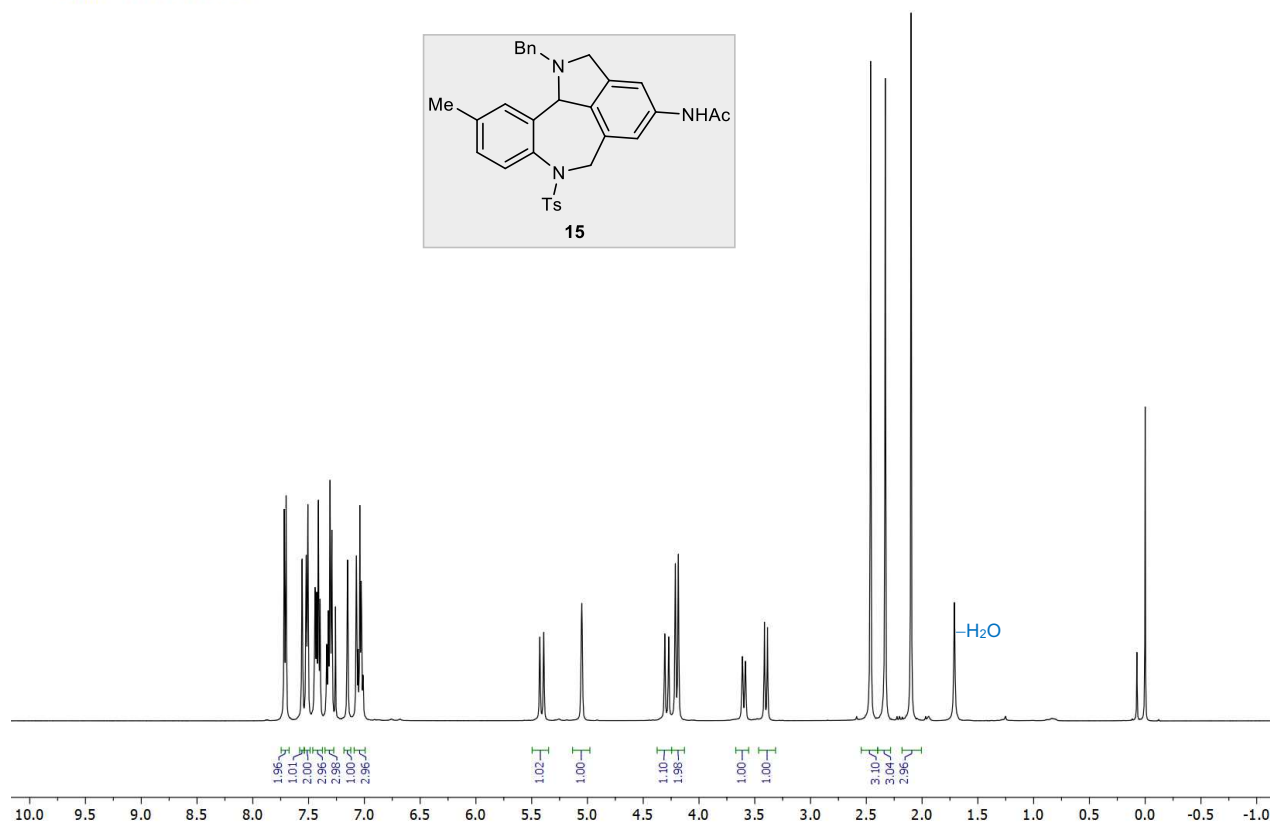
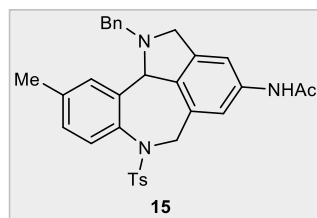
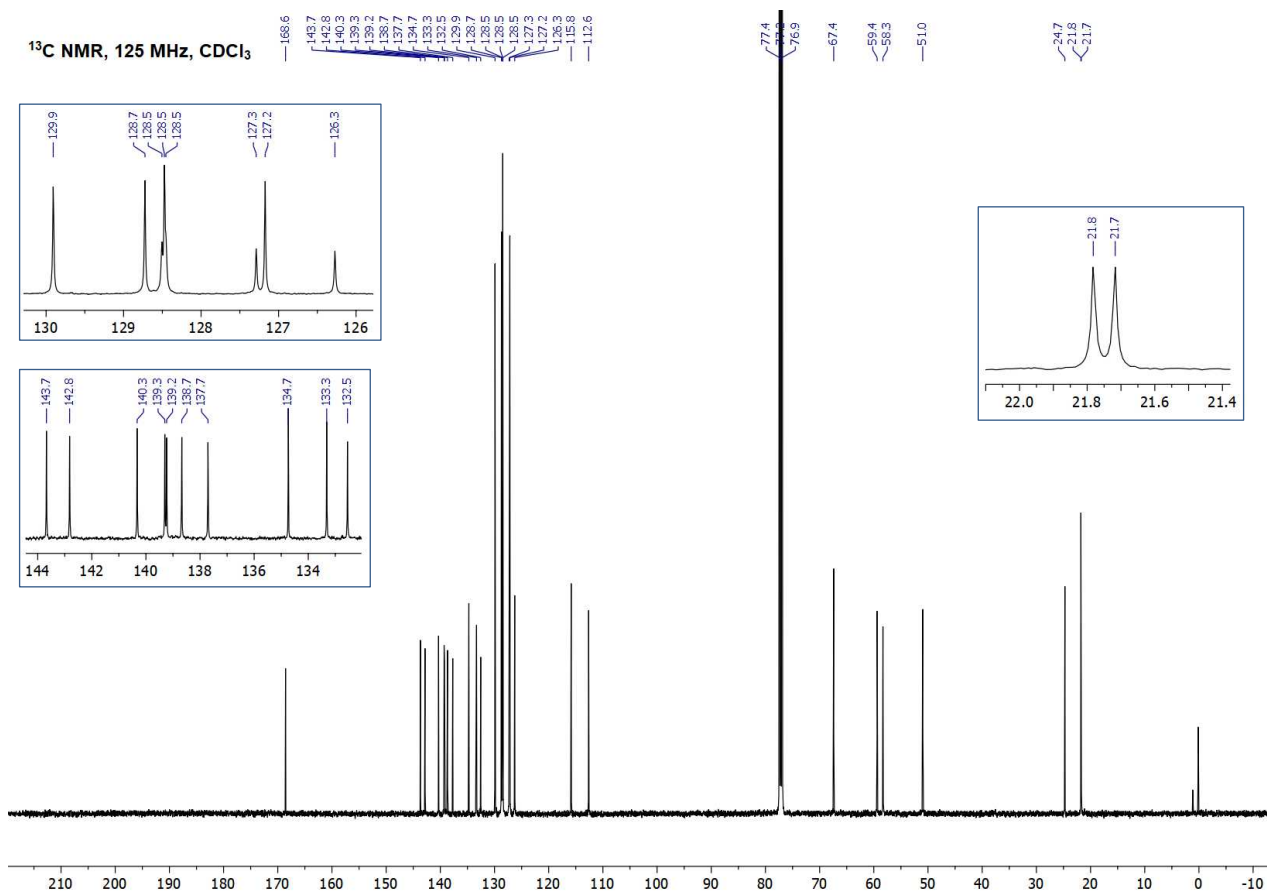
<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

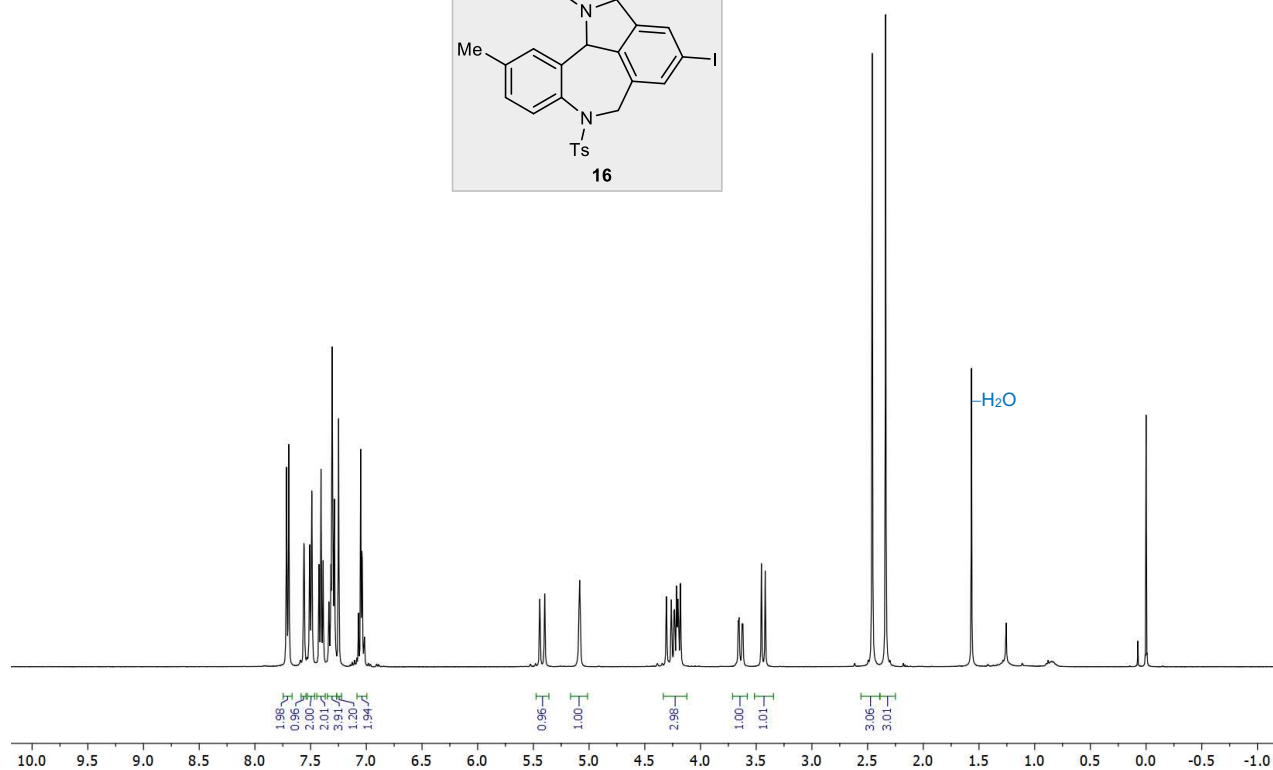
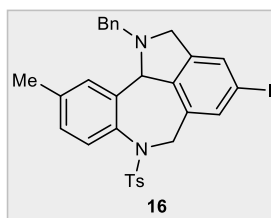
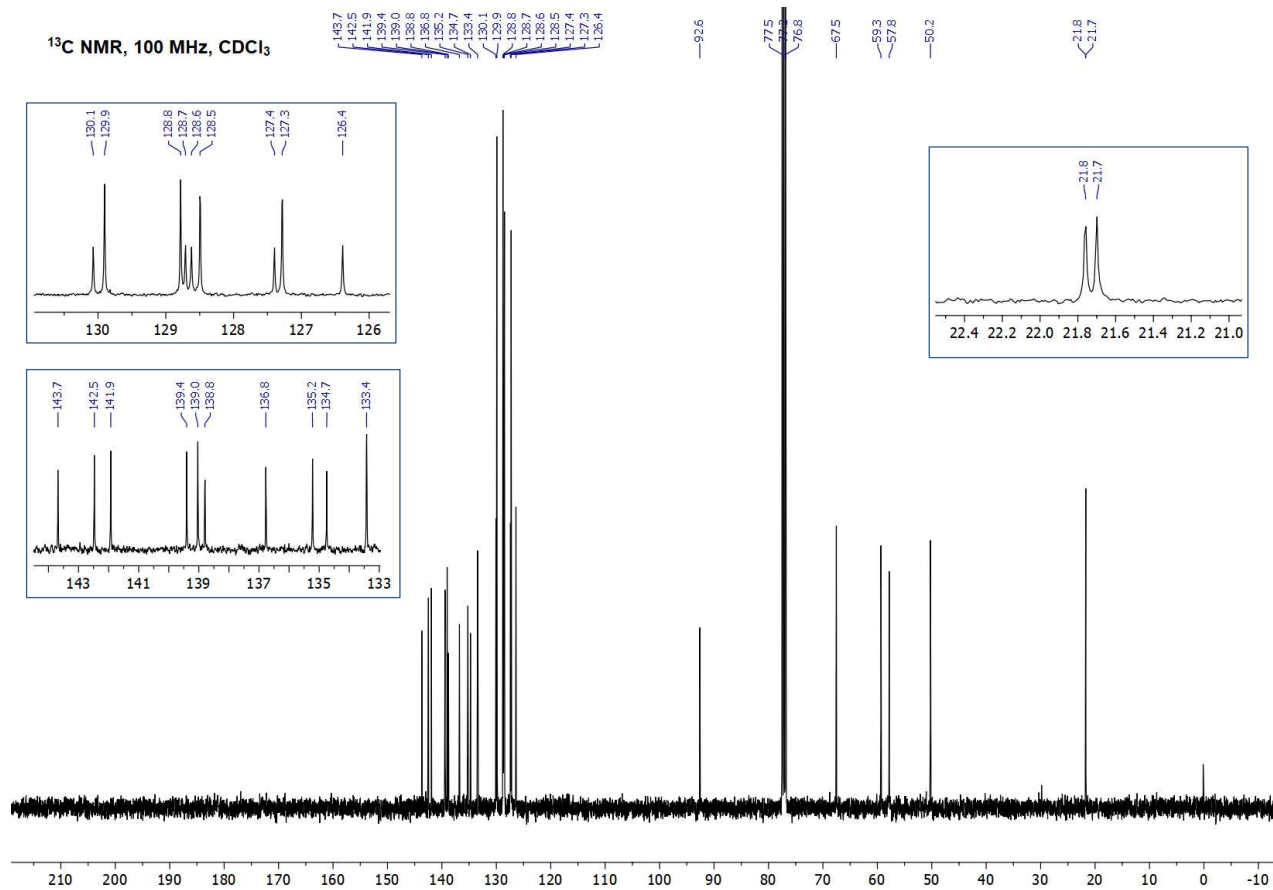
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

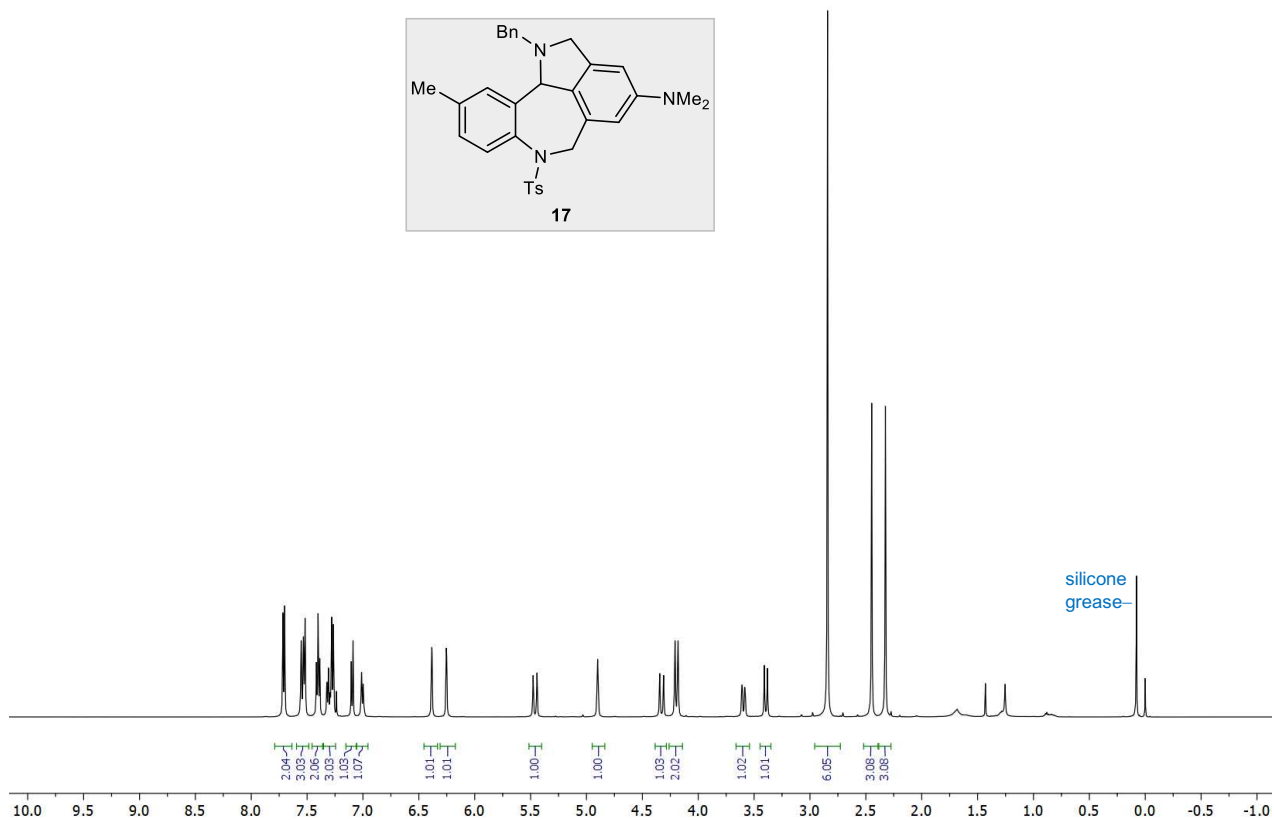
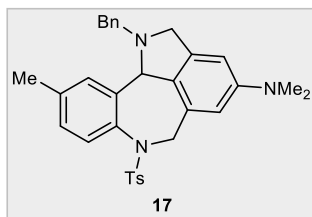
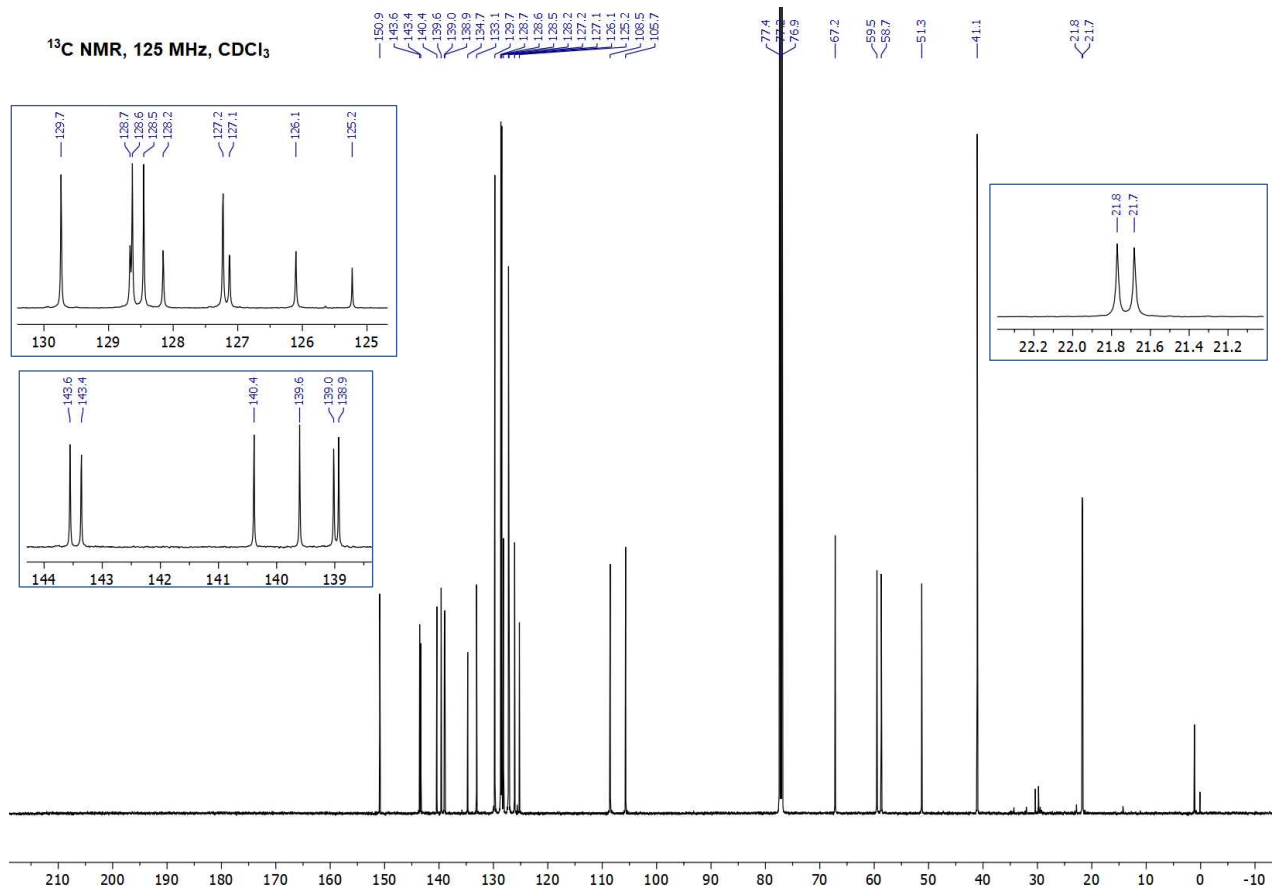




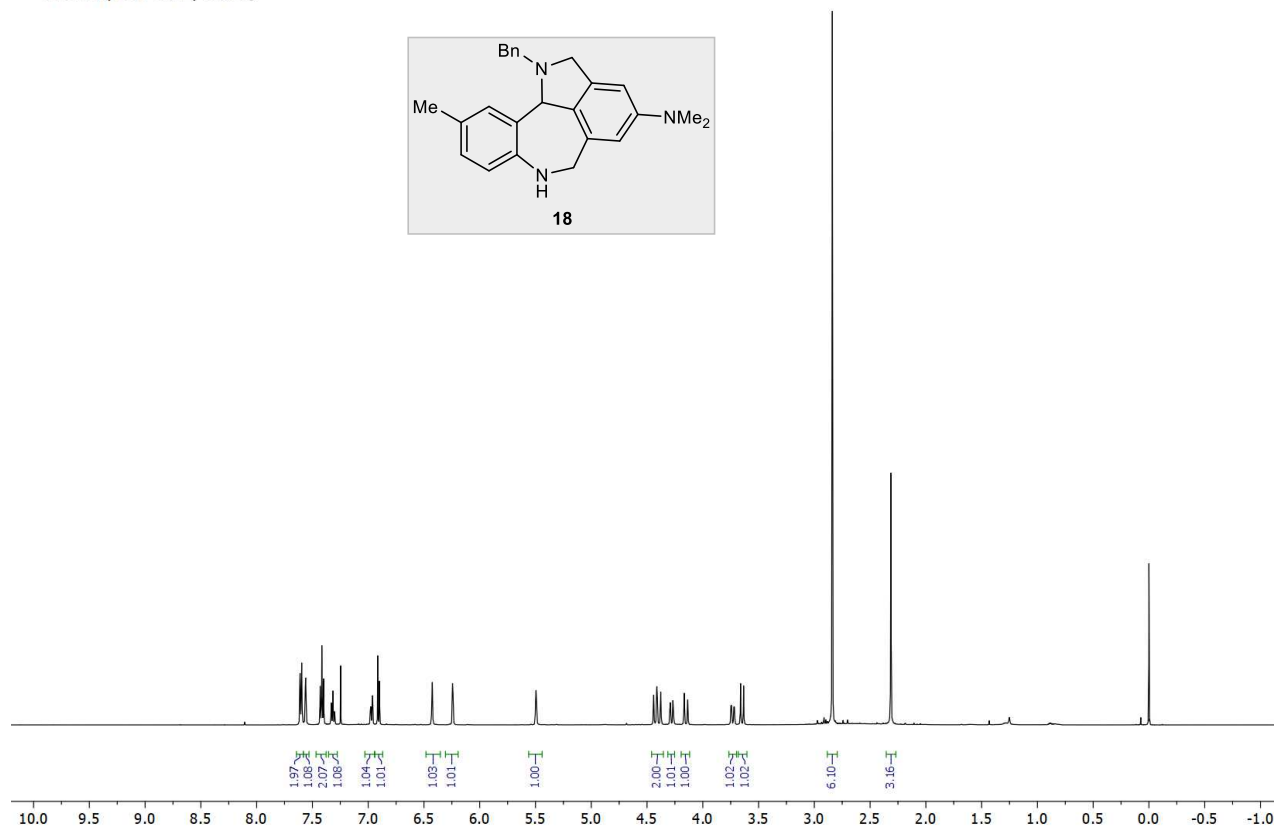
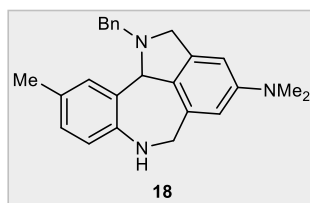
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>

$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$  $^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ 

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>



<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>