Dichotomous Mechanistic Behavior in Narasaka-Heck Cyclizations: Electron Rich Pd-Catalysts Generate Iminyl Radicals

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Electronic Supplementary Information

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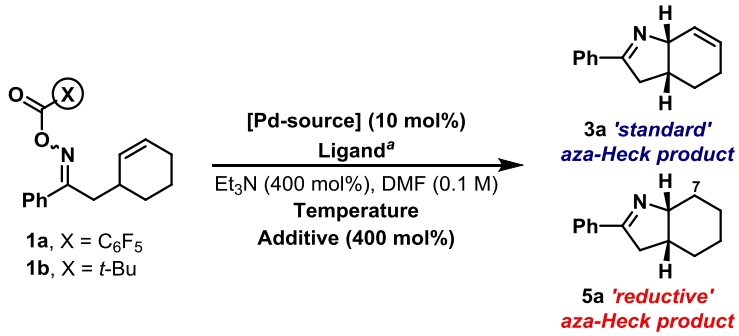
General Experimental Details. Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Dry solvents, where necessary, were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering based on the Grubb's design. The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at r.t.. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen or argon; glassware, syringes and needles were either flame dried immediately prior to use or placed in an oven (200 °C) for at least 2 h and allowed to cool either in a desiccator or under an atmosphere of nitrogen or argon; liquid reagents, solutions or solvents were added *via* syringe through rubber septa; solid reagents were added *via* Schlenk type adapters. Commercially available Merck Kieselgel $60F_{254}$ aluminium backed plates were used for TLC analysis. Visualization was achieved by either UV fluorescence or basic $KMnO_4$ solution and heat. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). The crude material was applied to the column as a solution in CH_2Cl_2 or by pre-adsorption onto silica, as appropriate. Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window. NMR spectra were recorded using either a Varian 400 MHz or JOEL ECS 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), coupling constants (*J*) are given in Hz to the nearest 0.5 Hz. Other abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet) and br. (broad). ^{1}H and ^{13}C NMR spectra were referenced to the appropriate residual solvent peak. Assignments of ^{1}H NMR and ^{13}C NMR signals were made, where possible, using COSY, DEPT, HMQC, HMBC and NOE experiments. Where mixtures of isomers (*e.g.* diastereomers and/or rotamers) have been characterized together, they are referred to as A and B. *Numbering systems for NMR signal assignments are specified on the structure and are not related to those used for the compound names.* Mass spectra were determined by the University of Bristol mass spectrometry service by either electron impact (EI^+) or chemical ionization (CI^+) using a Fisons VG Analytical Autospec spectrometer, or by electrospray ionization (ESI^+) using a Brüker Daltonics Apex IV spectrometer.

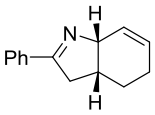
Experimental procedures and Data.

Ligand effects on the cyclization of oxime esters 1a/b

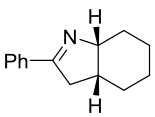


Entry	X	Pd-source/Ligand	Temp/°C	Additive	3a (%)[d]	5a (%)[d]
1	C_6F_5	$Pd_2(dba)_3/PPh_3$	100	none	30	<5
2	C_6F_5	$Pd_2(dba)_3/P(2\text{-furyl})_3$	100	none	38	<5
3	C_6F_5	$Pd_2(dba)_3/P(4\text{-}FC_6H_4)_3$	100	none	76	<5
4	C_6F_5	$Pd_2(dba)_3/P(4\text{-}CF_3C_6H_4)_3$	100	none	85	<5
5	C_6F_5	$Pd_2(dba)_3/P(3,5\text{-}(CF_3)_2C_6H_3)_3$	120	none	90	<5
6	C_6F_5	$Pd_2(dba)_3/P(3,5\text{-}(CF_3)_2C_6H_3)_3$[c]	60	none	93	<5
7	C_6F_5	$Pd_2(dba)_3/P(C_6F_5)_3$	100	none	10	<5
8	C_6F_5	(d*t*-bpf)$PdCl_2$[b]	120	none	<5	72
9	*t*-Bu	(d*t*-bpf)$PdCl_2$[b]	120	none	<5	72
10	*t*-Bu	$Pd_2(dba)_3$/S-Phos	120	none	<5	10
11	*t*-Bu	$Pd_2(dba)_3/P(1\text{-Ad})_2n\text{-Bu}$	120	none	<5	29
12	*t*-Bu	$Pd_2(dba)_3/P(Cy)_3$	120	none	<5	30
13	*t*-Bu	$Pd_2(dba)_3/P(t\text{-Bu})_3$	120	none	<5	50
14	*t*-Bu	PEPPSI-*i*-Pr	120	none	<5	27
15	*t*-Bu	(d*t*-bpf)$PdCl_2$[b,c]	70	none	<5	67
16	*t*-Bu	(d*t*-bpf)$PdCl_2$[b,c]	70	HCO_2H	<5	<5
17	*t*-Bu	(d*t*-bpf)$PdCl_2$[b,c]	70	*i*-PrOH	<5	61
18	*t*-Bu	(d*t*-bpf)$PdCl_2$[b,c]	70	1,4-CHD	<5	80
19	*t*-Bu	(d*t*-bpf)$PdCl_2$[b,c]	70	γ-terpinene	<5	88

[a] 1:2 [Pd]:ligand for monodentate systems, 1:1 [Pd]:ligand for bidentate systems. [b] d*t*-bpf = 1,1'-bis(di-*tert*-butylphosphino)ferrocene. [c] 5 mol% Pd/L used. [d] Isolated yield.



(3a*R,7a*S**)-2-Phenyl-3a,4,5,7a-tetrahydro-3*H*-indole 3a:** The optimized procedure for the cyclization of oxime ester **1a** to dihydropyrrole **3a** has been reported previously.[1]

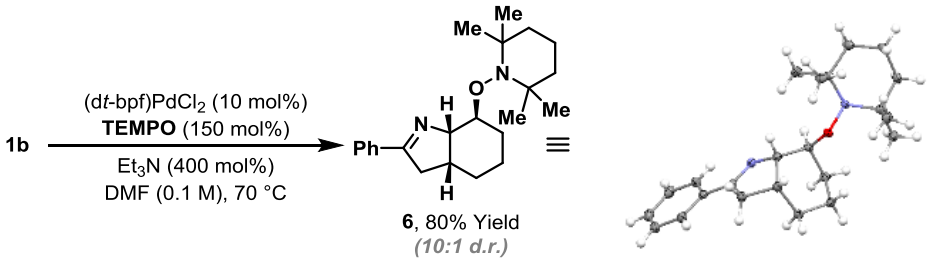


(3a*R,7a*R**)-2-Phenyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole 5a:** An oven-dried reaction tube, fitted with magnetic stirrer, was charged with (d*t*-bpf)$PdCl_2$ (6.3 mg, 5 mol%) and oxime ester **1b** (58 mg,

0.19 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. DMF (1.90 mL, 0.1 M), Et_3N (108 μL, 400 mol%) and γ-terpinene (124 μL, 400 mol%) were then added sequentially *via* syringe. The mixture was placed in a preheated heating block (70 °C) and stirred for 24 hours. The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was purified by FCC (4:1 hexane-EtOAc) to afford dihydropyrrole **5a** (34 mg, 88%) as a pale yellow oil. *The reaction proceeds with equal facility from oxime ester **1a**.* υ_{max} / cm^{-1} (film) 2928, 2853, 1604, 1574, 1448; δ_H (400 MHz, $CDCl_3$) 7.90-7.83 (2H, m), 7.46-7.39 (3H, m), 4.02-3.96 (1H, m), 2.90 (1H, dddd, *J* = 16.0, 9.0, 7.0 and 2.0 Hz), 2.74 (1H, dddd, *J* = 16.0, 11.5, 4.5, and 1.0 Hz), 2.46-2.36 (1H, m), 1.96-1.89 (2H, m), 1.67-1.59 (1H, m), 1.54-1.44 (3H, m), 1.37-1.26 (2H, m); δ_C (100 MHz, $CDCl_3$) 173.5, 135.4, 130.3, 128.5, 127.5, 70.1, 41.6, 37.0, 29.3, 27.5, 23.1, 22.2; HRMS (CI^+) Found $[M+H]^+$: 200.1434, $C_{14}H_{18}N$ requires 200.1434.

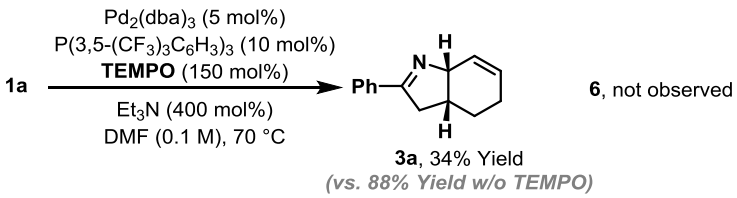
*The relative stereochemistry of **5a** was assigned by analogy to compounds **3a**, **6** and **22b** (vide infra).*

TEMPO trapping experiments



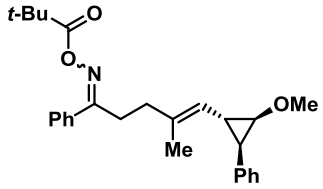
(3a*R,7*S**,7a*S**)-2-Phenyl-7-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3a,4,5,6,7,7a-hexahydro-3*H*-indole 6:** An oven-dried reaction tube, fitted with magnetic stirrer, was charged with (d*t*-bpf)$PdCl_2$ (12.8 mg, 10 mol%), oxime ester **1b** (58 mg, 0.19 mmol, 100 mol%) and TEMPO (45 mg, 0.29 mmol, 150 mol%). The tube was fitted with a rubber septum and purged with argon. DMF (1.90 mL, 0.1 M) and Et_3N (108 μL, 400 mol%) were then added sequentially *via* syringe. The mixture was placed in a preheated heating block (70 °C) and stirred for 24 hours. The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was purified by FCC (8:1 hexane-EtOAc) to afford dihydropyrrole **6** (54 mg, 80%, 10:1 d.r.) as a colorless, crystalline solid. Under these conditions, compound **5a** was not detected. υ_{max} / cm^{-1} (film) 2935, 1604, 1571, 1447; δ_H (400 MHz, $CDCl_3$) 7.90-7.85 (2H, m), 7.45-7.35 (3H, m), 4.34-4.25 (1H, m), 4.21-4.15 (1H, m), 2.95 (1H, ddd, *J* = 16.0, 7.0, 2.0), 2.69 (1H, ddd, *J* = 16.0, 4.0, 1.0), 2.65-2.53 (1H, m), 1.84-1.73 (1H, m), 1.73-1.26 (11H, m), 1.23 (6H, s), 1.19 (6H, s); δ_C (100 MHz, $CDCl_3$) 173.5, 135.2, 130.4, 128.5, 127.7, 80.9, 73.7, 60.1, 42.1, 40.6, 36.1, 34.6, 27.8, 27.3 (2 signals), 20.6, 18.7, 17.4; HRMS (ESI^+) Found $[M+H]^+$: 355.2760, $C_{23}H_{35}N_2O$ requires 355.2744.

The structure of the major diastereomer of this compound was confirmed by single crystal X-ray diffraction (see above) of crystals grown from CH_2Cl_2-hexane.

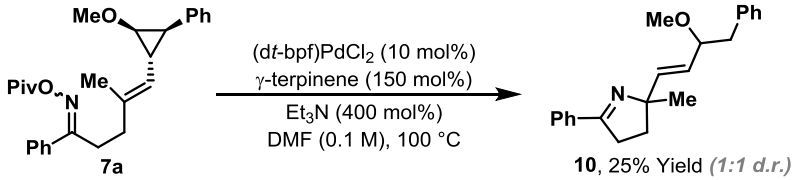


(3a*R,7a*S**)-2-Phenyl-3a,4,5,7a-tetrahydro-3*H*-indole 3a:** An oven-dried reaction tube, fitted with magnetic stirrer, was charged with $Pd_2(dba)_3$ (6.8 mg, 5 mol%), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20.0 mg, 20 mol%), oxime ester **1a** (61 mg, 0.15 mmol, 100 mol%) and TEMPO (36 mg, 0.23 mmol, 150 mol%). The tube was fitted with a rubber septum and purged with argon. DMF (1.50 mL, 0.1 M) and Et_3N (84 μL, 400 mol%) were then added sequentially *via* syringe. The mixture was placed in a preheated heating block (70 °C) and stirred for 22 hours. The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was purified by FCC (8:1 hexane-EtOAc) to afford dihydropyrrole **3a** (12 mg, 41%, >19:1 d.r.) as a colorless oil. Oxime ester **1a** was recovered in 34% yield. Compound **6** was not detected. *Spectroscopic data for dihydropyrrole **3a** have been reported previously.*[1]

Cyclopropane mechanistic experiments

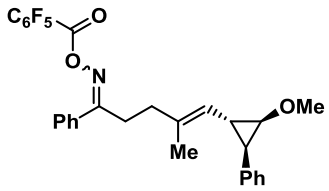


(*E*)-5-(1*S,2*R**,3*R**)-2-Methoxy-3-phenylcyclopropyl)-4-methyl-1-phenylpent-4-en-1-one *O*-pivaloyl oxime 7a:** This was synthesised according to our previously reported route.[2]

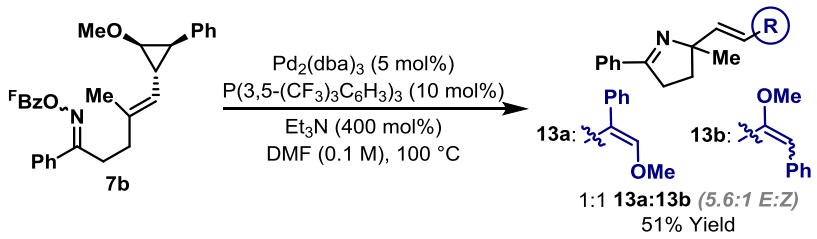


(*E*)-2-(4-Methoxy-3-phenylbut-1-en-1-yl)-5-phenyl-3,4-dihydro-2*H*-pyrrole 10: A flame-dried reaction tube, fitted with a magnetic stirrer bar, was charged with [d*t*-bpf]$PdCl_2$ (15.6 mg, 10 mol%) and oxime ester **7a** (100 mg, 0.239 mmol). The tube was fitted with a rubber septum and purged with argon. γ-Terpinene (153 μL, 0.955 mmol), Et_3N (133 μL, 0.955 mmol) and argon-sparged DMF (2.4 mL) were added sequentially *via* syringe and the reaction mixture was heated at 90 °C. Upon consumption of starting material (TLC analysis, approximately 5 hours) the reaction mixture was cooled

to room temperature and concentrated *in vacuo* (approximately 0.1 mmHg). Purification of the residue by FCC (10:1 – 3:1 hexane-EtOAc) afforded the title compound **10** (19 mg, 25%, 1:1 d.r.) as a yellow oil. υ_{max} / cm^{-1} (film) 1722, 1612, 1575, 1495; δ_H (400 MHz, $CDCl_3$) 7.87-7.83 (2H, m), 7.44-7.38 (3H, m), 7.25-7.13 (5H, m), 5.74 (1H, dd, *J* = 16.0, 2.5 Hz), 5.43-5.34 (1H, m), 3.79-3.73 (1H, m,), 3.24 (3H, d, *J* = 2.0 Hz), 3.05-2.69 (4H, m), 2.01-1.79 (2H, m), 1.40 (3H, app. d, *J* = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 171.4, 140.1, 139.7, 138.4, 134.6, 130.4, 129.6, 128.4, 128.0, 127.7, 126.5, 126.0, 83.2, 83.1, 75.9, 56.3, 56.2, 42.3, 35.8, 35.7, 34.8, 27.5, 27.4; HRMS (ESI^+) Found $[M+H]^+$: 320.2022, $C_{22}H_{26}NO$ requires 320.2009.

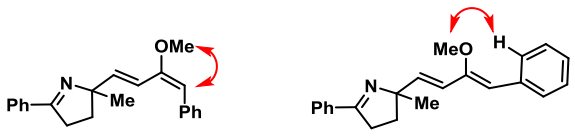


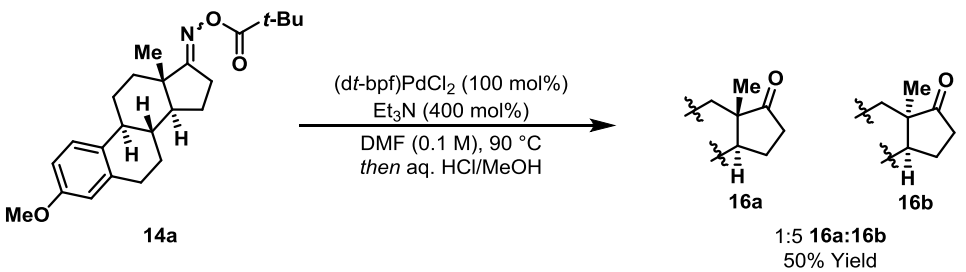
(4*E*)-5-((1*S,2*R**,3*R**)-2-Methoxy-3-phenylcyclopropyl)-4-methyl-1-phenylpent-4-en-1-one *O*-perfluorobenzoyl oxime 7b:** To a solution of (4*E*)-5-((1*S**,2*R**,3*R**)-2-methoxy-3-phenylcyclopropyl)-4-methyl-1-phenylpent-4-en-1-one oxime[2] (1.37 g, 3.95 mmol) and Et_3N (1.38 mL, 7.90 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added pentafluorobenzoyl chloride (0.68 mL, 4.74 mmol) dropwise over 5 minutes. The mixture was then warmed to room temperature and stirred until the reaction was complete as observed by TLC. MeOH (1 mL) was then added and the mixture stirred for a further 10 minutes. The mixture was diluted with CH_2Cl_2 (20 mL), washed with aq. 1 M HCl (15 mL), saturated aq. Na_2CO_3 (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by FCC (20:1 – 10:1 hexane-EtOAc) afforded the title compound **7b** (1.74 g, 83%, 12.5:1 mixture of oxime isomers) as a pale yellow oil. υ_{max} / cm^{-1} (film) 1764, 1649, 1523, 1494, 1321, 1189, 1000; δ_H (400 MHz, $CDCl_3$) 7.74-7.71 (1.80H, m), 7.51-7.41 (3H, m), 7.32-7.16 (5.2H, m), 4.79-4.73 (1H, m), 3.36 (0.08H, dd, *J* = 6.5, 3.5 Hz), 3.33 (0.92H, m, dd, *J* = 6.5, 3.5 Hz), 3.18 (0.24H, s), 3.17 (2.76H, s), 3.06-2.95 (1.84H, m), 2.89-2.85 (0.16H, m), 2.29-2.19 (2H, m), 2.01 (1H, ddd, *J* = 8.5, 6.5, 3.5 Hz), 1.91 (1H, app. t, *J* = 6.5 Hz), 1.73 (3H, s); δ_C (100 MHz, $CDCl_3$) *Signals for the major isomer only:* 168.5, 156.6, 137.1, 134.3, 133.2, 131.0, 128.8, 128.0, 127.7, 127.4, 125.7, 67.1, 58.2, 36.0, 32.3, 27.7, 26.5, 16.5; -136.9 (2F), -137.3 (0.16F), -147.4 (1F), -148.1 (0.08F), -159.8 (2F), -160.2 (0.16F); HRMS (ESI^+) Found $[M+H]^+$: 530.1747, $C_{29}H_{25}F_5NO_3$ requires 530.1749.



2-((1*E*,3*E*)-4-Methoxy-3-phenylbuta-1,3-dien-1-yl)-2-methyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 13a *and* 2-((1*E*)-3-Methoxy-4-phenylbuta-1,3-dien-1-yl)-2-methyl-5-phenyl-3,4-dihydro-2*H*-pyrrole 13b: A flame-dried reaction tube, fitted with a magnetic stirrer bar, was charged with oxime ester **7b** (150 mg, 0.284 mmol), $Pd_2(dba)_3$ (6.5 mg, 7.1 μmol) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (19 mg, 0.0284 mmol). The tube was fitted with a rubber septum and purged with argon. Et_3N (158 μL, 1.13 mmol) and argon-sparged DMF (2.8 mL) were added sequentially *via* syringe and the reaction mixture was heated at 90 °C. Upon consumption of starting material (TLC analysis) the reaction mixture was cooled to room temperature and concentrated *in vacuo* (approximately 0.1 mmHg). Purification of the residue by FCC (50:1 – 30:1 toluene-EtOAc) afforded an inseparable mixture of the title compounds (46 mg, 51% yield, 1:1, **13a**:**13b**) as a yellow oil. **13b** was formed as a 5.6:1 mixture of *E*:*Z* alkene isomers. *Due to product instability, characterization was only possible by ^1H and ^{13}C NMR, and assignments were made by 2D NMR techniques (see pages S20-21).* δ_H (400 MHz, $CDCl_3$) 7.88-7.79 (2H, m), 7.44-7.10 (8H, m), 6.74 (0.50H, dd, *J* = 16.5, 1.0 Hz), 6.49 (0.43H, d, *J* = 15.5 Hz), 6.46 (0.43H, d, *J* = 15.5 Hz), 6.25 (0.07H, d, *J* = 15.5 Hz), 6.01 (0.07H, *J* = 15.5 Hz), 6.00 (0.5H, m), 5.82-5.74 (1H, m), 3.72 (1.27H, s), 3.69 (1.5H, s), 3.63 (0.21H, s), 3.08-2.86 (2H, m), 2.12-2.04 (1H, m), 1.93-1.86 (1H, m), 1.50 (0.21H, s), 1.46 (1.27H, s), 1.43 (1.5H, s); δ_C (100 MHz, $CDCl_3$) 171.6 (2C), 170.8 (3C), 155.5, 153.9, 146.6, 138.3, 138.1, 137.4, 136.8, 136.8, 135.7, 134.8, 134.6 (2C), 130.5, 130.4, 130.2, 129.5, 129.2, 128.6, 128.4, 128.3 (3C), 128.2, 128.1, 128.0, 127.8 (2C), 126.6, 126.5, 125.5, 123.3, 120.9, 119.9, 119.8, 116.3, 103.2, 76.8, 76.2, 76.2, 60.2, 58.5, 54.8, 36.2, 36.0, 35.9, 35.0 (2C), 34.9, 27.6, 27.5, 27.2.

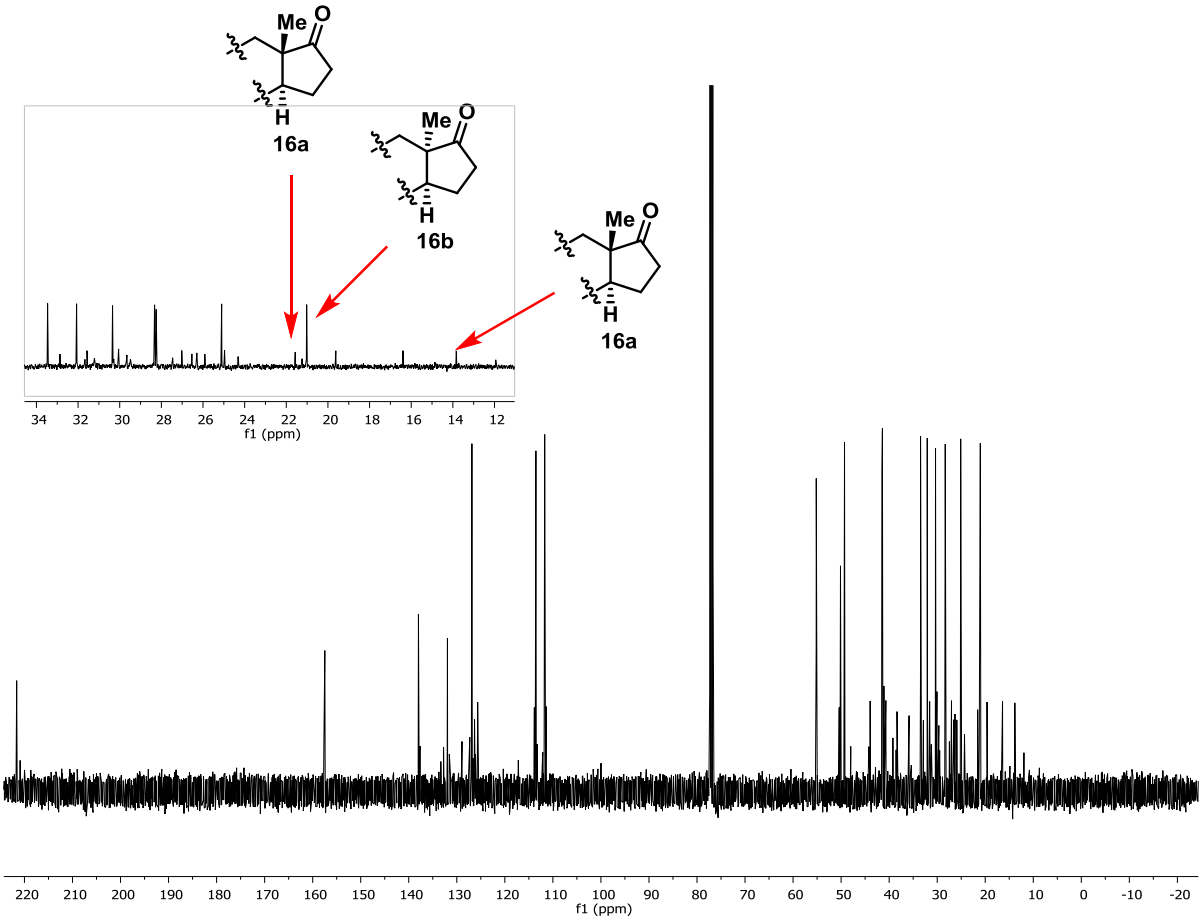
*The relative stereochemistry of **(E)-13b** and **(Z)-13b** was determined by nOe analysis, as indicated on the compound structures below.*

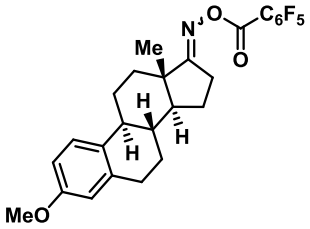




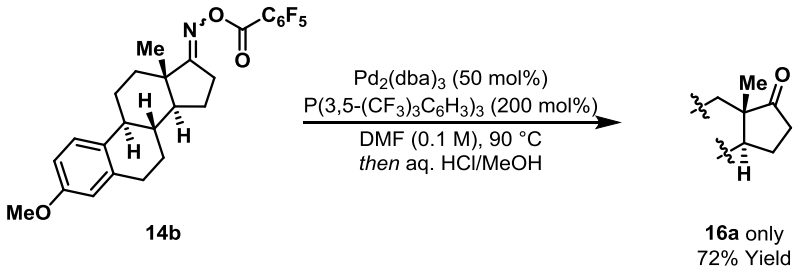
Estrone-3-methylether 16a *and* 13*α*-estrone-3-methylether 16b: An oven-dried reaction tube, fitted with magnetic stirrer, was charged with (d*t*-bpf)$PdCl_2$ (51 mg, 0.078 mmol) and oxime ester **14a**[2] (30 mg, 0.078 mmol). The tube was fitted with a rubber septum and purged with argon. Et_3N (22 μL, 0.156 mmol) and DMF (0.8 mL) were then added sequentially *via* syringe. The mixture was then placed in a

preheated heating block (90 °C) and stirred for 18 hours. The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was re-dissolved in MeOH (4 mL) and 1 M HCl (2 mL) was added. The mixture was heated at 75 °C in a sealed tube for 2 hours. After cooling to room temperature the mixture was diluted with Et_2O (10 mL) and washed with Na_2CO_3 (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue (5:1 hexane-EtOAc) afforded the title compounds as an inseparable mixture (11 mg, 50% yield, 1:5, **16a**:**16b**). This material was contaminated with approx. 5% of an unidentified impurity. δ_H (400 MHz, $CDCl_3$) Diagnostic signals for **16a**: 0.91 (0.16H, s); Diagnostic signals for **16b**: 1.06 (0.84H, s); δ_C (100 MHz, $CDCl_3$) Diagnostic signals for **16a**: 21.6, 13.8; Diagnostic signals for **16b**: 21.0. *The spectroscopic properties of these compounds were consistent with the data previously reported in the literature*.[3] *The most diagnostic method for characterizing the mixture was* ^{13}C *NMR (shown below).*



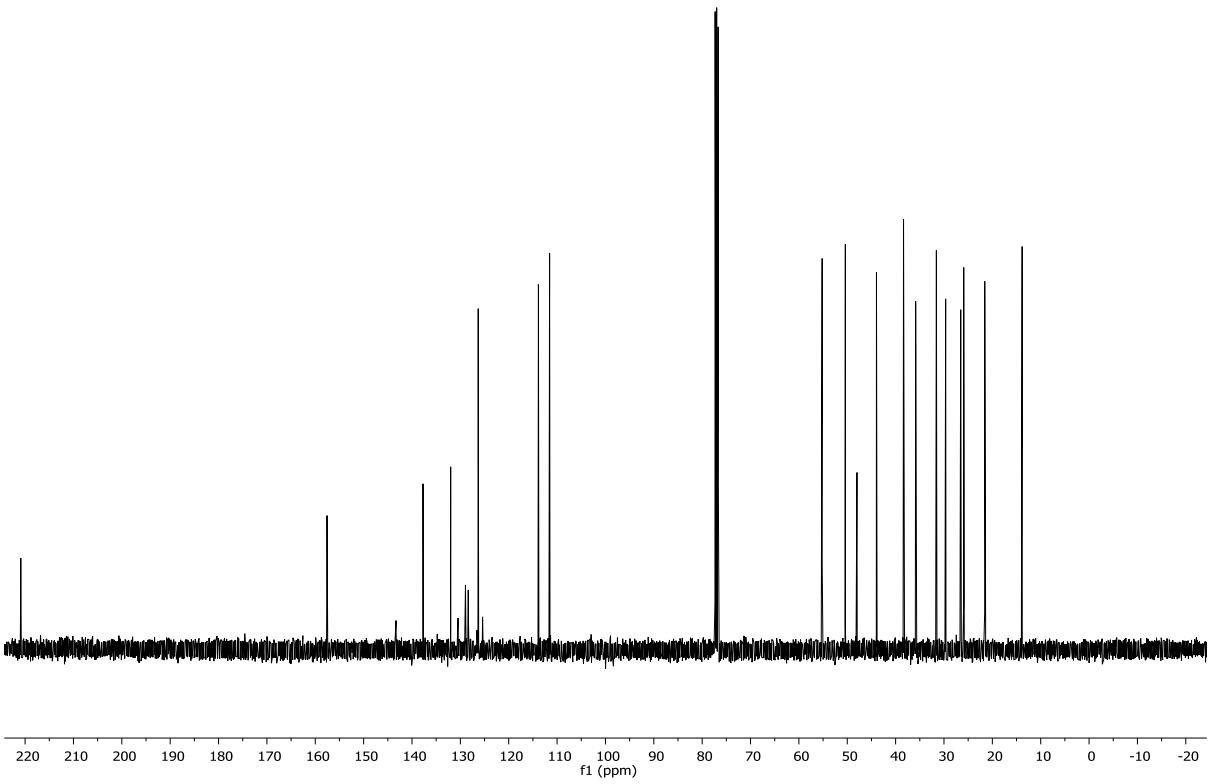


Estrone 3-methyl ether *O*-pentafluorobenzoyl oxime 14b: To a solution of estrone-3-methylether oxime[2] (500 mg, 1.67 mmol) and Et_3N (0.58 mL, 3.34 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added pentafluorobenzoyl chloride (0.29 mL, 2.00 mmol) dropwise over 5 minutes. The mixture was then warmed to room temperature and stirred until the reaction was complete as observed by TLC. MeOH (1 mL) was then added and the mixture stirred for a further 10 minutes. The mixture was diluted with CH_2Cl_2 (10 mL), washed with 1 M HCl (10 mL), saturated aq. Na_2CO_3 (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by FCC (10:1 hexane-EtOAc) afforded the title compound **14b** (552 mg, 67%, >19:1 mixture of oxime isomers) as a colorless waxy solid. υ_{max} / cm^{-1} (film) 1756, 1612, 1523, 1494, 1321, 1189, 1000; δ_H (400 MHz, $CDCl_3$) 7.22 (1H, dd, *J* = 8.5, 1.0 Hz), 6.73 (1H, dd, *J* = 8.5, 3.0 Hz), 6.64 (1H, d, *J* = 3.0 Hz), 3.78 (3H, s), 2.92-2.87 (2H, m), 2.80-2.60 (2H, m), 2.46-2.40 (1H, m), 2.35-2.23 (2H, m), 1.99-1.93 (2H, m), 1.80 (1H, td, *J* = 13.5, 4.0 Hz), 1.63-1.40 (5H, m), 1.08 (3H, s); δ_C (100 MHz, $CDCl_3$) 180.8, 157.6, 137.6, 131.9, 126.3, 113.9, 111.6, 55.2, 52.9, 46.0, 43.7, 38.2, 33.6, 29.6, 27.8, 27.2, 26.0, 22.8, 17.1; δ_F (376 MHz, $CDCl_3$) -137.0 (2F), -147.4 (1F), -159.7 (2F); HRMS (ESI^+) Found $[M+Na]^+$: 516.1555, $C_{26}H_{24}F_5NO_3Na$ requires 516.1569.



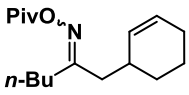
Estrone-3-methylether 16a: An oven-dried reaction tube, fitted with magnetic stirrer, was charged with $Pd_2(dba)_3$ (42 mg, 0.046 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (122 mg, 0.182 mmol) and oxime ester **14b** (45 mg, 0.091 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous DMF (1 mL) was then added *via* syringe. The mixture was then placed in a preheated heating block (90 ^oC) until complete consumption of starting material was observed (TLC analysis). The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was redissolved in MeOH (4 mL) and 1 M HCl (2 mL) was added. The mixture was heated at 75 °C in a sealed tube for 2 hours. After cooling to room temperature, the mixture was diluted with Et_2O (20 mL) and washed with $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue (10:1 – 5:1 hexane-EtOAc) afforded the title

compound **16a** (19 mg, 72%) as a colorless solid. The product was contaminated with approx. 2 mg of dibenzylideneacetone; the yield of **16a** has been adjusted accordingly. δ_H (400 MHz, $CDCl_3$) 7.21 (1H, d, *J* = 8.5 Hz), 6.73 (1H, dd, *J* = 8.5, 3.0 Hz), 6.65 (1H, d, *J* = 3.0 Hz), 3.78 (3H, s), 2.94-2.88 (2H, m), 2.54-2.47 (1H, m), 2.43-2.38 (1H, m), 2.29-2.23 (1H, m), 2.19-1.94 (4H, m), 1.68-1.39 (6H, m), 0.91 (3H, s); δ_C (100 MHz, $CDCl_3$) 220.9, 157.4, 137.7, 132.0 126.3, 113.9, 111.5, 55.2, 50.4, 48.0, 44.0, 38.4, 35.9, 31.6, 29.7, 26.5, 25.9, 21.6, 13.8. *The spectroscopic properties of this compound were consistent with the available in the literature*.[3] ***16b*** *was not observed in this reaction, see the* ^{13}C *NMR spectrum below.*

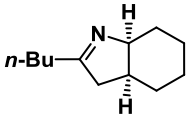


Iminyl radical cyclization scope

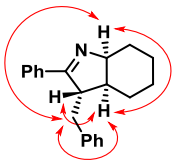
General Procedure A: for 'reductive' aza-Heck cyclizations: An oven-dried reaction tube, fitted with magnetic stirrer, was charged with (d*t*-bpf)$PdCl_2$ (5 mol%) and oxime ester substrate (100 mol%). The tube was fitted with a rubber septum and purged with argon. DMF (0.1 M w.r.t oxime ester), Et_3N (400 mol%) and γ-terpinene (400 mol%) were then added sequentially *via* syringe. The mixture was placed in a preheated heating block (70-95 ^oC as noted) and stirred for 20-24 hours (as noted). The mixture was then cooled to room temperature and concentrated *in vacuo* (40 °C, approximately 1.0 mmHg). The residue was purified by FCC, under the conditions noted, to afford the target dihydropyrrole.



1-(Cyclohex-2-en-1-yl)hexan-2-one *O*-pivaloyl oxime 21a: To a room temperature solution of 1-(cyclohex-2-en-1-yl)hexan-2-one oxime (515 mg, 2.64 mmol)[1] in anhydrous CH_2Cl_2 (7.80 mL) was added pivaloyl chloride (0.40 mL, 3.21 mmol) and Et_3N (0.73 mL, 5.25 mmol). The mixture was stirred at room temperature for 22 hours. MeOH (5 mL) was added and the mixture was diluted with Et_2O (50 mL). The mixture was washed with saturated aq. $NaHCO_3$ (2 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by FCC (6:1 hexane-EtOAc) afforded oxime ester **21a** (688 mg, 96%, 1:1 mixture of isomers) as a colorless oil. υ_{max} / cm^{-1} (film) 2932, 1755, 1702, 1114;δ_H (400 MHz, $CDCl_3$) 5.77-5.70 (2H, m), 5.57 (1H, m), 5.50 (1H, m), 2.55-2.25 (10H, m), 2.03-1.95 (4H, m), 1.85-1.68 (4H, m), 1.63-1.45 (6H, m), 1.45-1.25 (6H, m), 1.29 (9H, s), 1.27 (9H, s), 0.97-0.90 (6H, m); δ_C (100 MHz, $CDCl_3$) 175.4, 175.3, 169.5, 169.3, 130.2, 130.1, 128.4, 128.3, 40.6, 38.8 (2 signals), 35.5, 34.5, 33.0, 32.6, 29.6, 29.3, 29.0, 28.8, 28.3, 27.4, 26.6, 25.2, 25.1, 23.1, 22.7, 21.2, 21.1, 13.9 (2 signals); HRMS (ESI^+) Found $[M+H]^+$: 280.2274, $C_{17}H_{30}NO_2$ requires 280.2271.



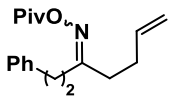
(3*aS,7*aS**)-2-Butyl-3*a*,4,5,6,7,7*a*-hexahydro-3*H*-indole 22a:** General procedure A: Oxime ester **21a** (50 mg, 0.18 mmol) was employed. The reaction was heated at 95 °C for 24 hours. FCC (2:1 to 1:1 hexane-EtOAc) afforded the title compound **22a** (15 mg, 47%) as a yellow oil. υ_{max} / cm^{-1} (film) 2927, 1633, 1450, 1295; δ_H (400 MHz, $CDCl_3$) 3.75 (1H, m), 2.46 (1H, ddd, *J* = 17.0, 8.0, 2.0 Hz), 2.35 (2H, t, *J* = 8.0 Hz), 2.25-2.17 (2H, m), 1.89-1.73 (2H, m), 1.60-1.50 (2H, m), 1.50-1.09 (8H, m), 0.93 (3H, t, *J* = 7.5 Hz); δ_C (100 MHz, $CDCl_3$) 179.2, 69.0, 43.8, 36.9, 34.4, 29.0, 28.7, 27.6, 23.2, 22.8, 21.9, 14.0; HRMS (EI^+) Found $[M]^+$: 289.1838, $C_{21}H_{23}N$ requires 289.1830. *N.B. Compound **22a** is relatively volatile and appropriate care must be taken.*



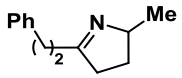
(3*S,3*aS**,7*aS**)-3-Benzyl-2-phenyl-3*a*,4,5,6,7,7*a*-hexahydro-3*H*-indole 22b:** General procedure A: Oxime ester **21b** (71 mg, 0.18 mmol)[2] was employed. The reaction was heated at 80 °C for 22 hours. FCC (5:1 hexane-EtOAc) afforded the title compound **22b** (38 mg, 73%, >19:1 d.r.) as a colorless oil.υ_{max} / cm^{-1} (film) 2925, 1603, 1572, 1495, 1447; δ_H (400 MHz, $CDCl_3$) 7.97-7.90 (2H, m), 7.49-7.44 (3H, m), 7.35-7.30 (2H, m), 7.27-7.20 (3H, m), 4.05 (1H, m), 3.30 (1H, dd, *J* = 10.5, 4.0 Hz), 2.91 (1H, dd, *J* = 14.5, 4.0 Hz), 2.65 (1H, dd, *J* = 14.5, 11.0 Hz), 2.40 (1H, m), 2.11 (1H, dddd, *J* = 5.5, 5.5, 5.5, 4.0 Hz), 1.82-1.71 (1H, m), 1.60-1.47 (3H, m), 1.31 (1H, m), 1.15 (1H, m), 1.02 (1H, m); δ_C (100 MHz,

$CDCl_3$) 176.0, 140.5, 134.3, 130.4, 128.8, 128.7, 128.6, 128.0, 126.3, 67.7, 57.3, 41.1, 34.7, 29.1, 28.7, 24.0, 21.8. HRMS (EI^+) Found $[M]^+$: 289.1838, $C_{21}H_{23}N$ requires 289.1830.

The relative stereochemistry of this compound was determined by nOe analysis, as indicated on the compound structure.

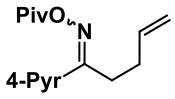


1-Phenylhept-6-en-3-one *O*-pivaloyl oxime 21c: To a solution of the corresponding oxime[4] (500 mg, 2.46 mmol) and pivaloyl chloride (593 mg, 4.92 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (1.13 mL, 8.12 mmol) at r.t.. After 20 hours the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue purified by FCC (EtOAc-hexane 1:1) to afford **21c** (619 mg, 88 %, 1:1 d.r. *A*:*B*) as a colorless oil. υ_{max} / cm^{-1} (film) 2933, 1754, 1107, 1027, 912, 699; δ_H (400 MHz, $CDCl_3$) 7.33-7.18 (5H, *A and B*), 5.87-5.74 (1H, *A and B*), 5.09-4.99 (2H, *A and B*), 2.95-2.91 (2H, m, *A*), 2.87-2.83 (2H, m, *B*), 2.68-2.63 (2H, m, *A and B*), 2.51-2.47 (2H, m, *A*), 2.41-2.26 (4H, m, *A and B*), 1.29 (9H, s, *A and B*); δ_C (100 MHz, $CDCl_3$) 175.2 (*A and B*), 168.9 (*A*), 168.7 (*B*), 140.9 (*A*), 140.3 (*B*), 136.9 (*A*), 136.6 (*B*), 128.8, 128.7, 128.4 and 128.3 (*A and B*), 126.7 (*A*), 126.4 (*B*), 116.1 (*A*), 115.8 (*B*), 38.9 (*A*), 38.8 (*B*), 36.6, 34.2, 32.5 and 32.2, (*A and B*), 31.9, 30.3, 30.2 and 29.5 (*A and B*), 27.4 (*A and B*); HRMS (ESI^+) Found: $[M+Na]^+$ 310.1777, $C_{18}H_{25}NO_2Na$ requires 310.1783.



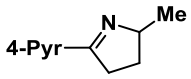
2-Methyl-5-phenethyl-3,4-dihydro-2*H*-pyrrole 22c: General procedure A: Oxime ester **21c** (53 mg, 0.18 mmol) was employed. The reaction was heated at 80 °C for 24 hours. FCC (EtOAc) afforded the title compound **22c** (19 mg, 58%) as a pale brown oil. δ_H (400 MHz, $CDCl_3$) 7.33-7.28 (2H, m), 7.26-7.19 (3H, m), 4.12-4.02 (1H, m), 3.02-2.88 (2H, m), 2.68-2.62 (2H, m), 2.55 (1H, dddd, *J* = 17.0, 10.0, 5.0, 2.0 Hz), 2.49-2.39 (1H, m), 2.14-2.05 (1H, m), 1.44-1.34 (1H, m), 1.27 (3H, d, *J* = 7.0 Hz); δ_C (100 MHz, $CDCl_3$) 176.3, 141.6, 128.5, 128.4, 126.1, 67.8, 37.9, 35.6, 32.9, 30.8, 22.2.

The spectroscopic properties of this compound were consistent with the data available in the literature.[5]

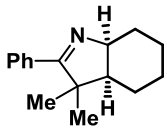


1-(Pyridin-4-yl)pent-4-en-1-one *O*-pivaloyl oxime 21d: In a re-sealable tube, 1-(pyridin-4-yl)pent-4-en-1-one[6] (499 mg, 3.10 mmol), $NH_2OH{\cdot}HCl$ (253 mg, 3.64 mmol) and NaOAc (298 mg, 3.63 mmol) were suspended in MeOH (9.00 mL). The tube was sealed and the mixture was heated at 80 °C for 16 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL), washed with saturated aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried

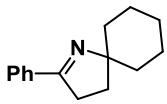
(Na_2SO_4) and concentrated *in vacuo* to afford the corresponding oxime (515 mg, 94%) as a pale yellow solid, which was used directly without purification. To a room temperature solution of the oxime (515 mg, 2.91 mmol)[1] in anhydrous CH_2Cl_2 (9.00 mL) was added pivaloyl chloride (0.42 mL, 3.41 mmol) and Et_3N (0.81 mL, 5.82 mmol). The mixture was stirred at room temperature for 22 hours. MeOH (5 mL) was added and the mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (50 mL), and washed sequentially with water (50 mL), saturated aq. $NaHCO_3$ (2 × 25 mL) and brine (50 mL). The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by FCC (1:3 hexane-EtOAc) afforded oxime ester **21d** (696 mg, 92%, 10:1 mixture of isomers) as a pale yellow oil. υ_{max} / cm^{-1} (film); 2978, 1699, 1482, 1197; δ_H (400 MHz, $CDCl_3$) *Signals for the major isomer:* 8.69-8.67 (2H, m), 7.62-7.60 (2H, m), 5.79 (1H, ddt, *J* = 17.0, 10.0, 6.5), 5.09-5.01 (2H, m), 2.94-2.89 (2H, m), 2.37-2.29 (2H, m), 1.33 (9H, s). *Characteristic signal for the minor isomer:* 2.77 (0.2H, t, *J* = 7.5); δ_C (100 MHz, $CDCl_3$) *Signals for the major isomer only:* 174.6, 164.0, 150.3, 141.6, 135.9, 121.3, 116.4, 38.8, 30.5, 27.4, 27.2; HRMS: (ESI^+) Found $[M+H]^+$ 261.1599, $C_{15}H_{21}N_2O_2$ requires 261.1598.



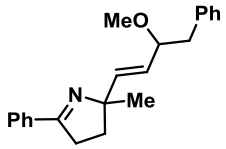
4-(2-Methyl-3,4-dihydro-2*H*-pyrrol-5-yl)pyridine 22d: General procedure A: Oxime ester **21d** (49 mg, 0.19 mmol) was employed. The reaction was heated at 90 °C for 24 hours. FCC (10:1 EtOAc-MeOH) afforded the title compound **22d** (25 mg, 82%) as a yellow oil. υ_{max} / cm^{-1} (film) 2926, 1595, 1408; δ_H (400 MHz, $CDCl_3$) 8.66 (2H, d, *J* = 5.5), 7.66-7.65 (2H, m), 4.36-4.26 (1H, m), 3.02 (1H, dddd, *J* = 17.0, 10.0, 5.0, 2.5), 2.86 (1H, dddd, *J* = 17.0, 10.0, 7.5, 2.5), 2.27 (1H, dddd, *J* = 12.5, 10.0, 7.5, 5.0), 1.58 (1H, dddd, *J* = 12.5, 10.0, 7.5, 6.5), 1.36 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 170.3, 150.2, 141.6, 121.7, 69.0, 35.0, 30.5, 21.9; HRMS: (CI^+) Found $[M+H]^+$ 161.1077, $C_{10}H_{13}N_2$ requires 161.1079.



(3*aS,7*aS**)-3,3-Dimethyl-2-phenyl-3*a*,4,5,6,7,7*a*-hexahydro-3*H*-indole 22e:** General procedure A: Oxime ester **21e** (60 mg, 0.18 mmol)[2] was employed. The reaction was heated at 90 °C for 21 hours. FCC (4:1 hexane-EtOAc) afforded the title compound **22e** (29 mg, 71%) as a colorless oil. υ_{max} / cm^{-1} (film) 2927, 1597, 1445, 1299; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, m), 7.31-7.25 (3H, m), 4.01 (1H, ddd, *J* = 5.5, 5.5, 4.0), 2.17 (1H, dddd, *J* = 14.0, 4.0, 4.0, 4.0), 1.82 (1H, m), 1.73 (1H, m), 1.55-1.44 (3H, m), 1.35-1.25 (1H, m), 1.25 (3H, s), 1.15-1.07 (5H, m); δ_C (125 MHz, $CDCl_3$) 180.4, 135.9, 129.1, 128.0, 127.5, 65.9, 53.4, 49.7, 29.4, 24.3, 24.2, 24.0, 22.2, 21.2; HRMS: (ESI^+) Found $[M+H]^+$ 228.1751, $C_{16}H_{22}N$ requires 228.1747.



2-Phenyl-1-azaspiro[4.5]dec-1-ene 22f: General procedure A: Oxime ester **21f** (60 mg, 0.19 mmol)[2] was employed. The reaction was heated at 70 °C for 24 hours. FCC (12:1 hexane-EtOAc) afforded the title compound **22f** (32 mg, 80%) as a pale brown oil. υ_{max} / cm^{-1} (film) 2926, 2853, 1616, 1447, 1335; δ_H (400 MHz, $CDCl_3$) 7.84 (2H, m), 7.41-7.38 (3H, m), 2.98 (2H, t, *J* = 8.0), 1.86 (2H, t, *J* = 8.0), 1.79 (4H, m), 1.50-1.38 (5H, m), 1.65 (1H, m); δ_C (100 MHz, $CDCl_3$) 169.5, 135.2, 130.2, 128.4, 127.8, 76.9, 37.8, 34.5, 32.8, 25.9, 23.7; HRMS: (CI^+) Found $[M+H]^+$ 214.1588, $C_{15}H_{19}N$ requires 214.1596.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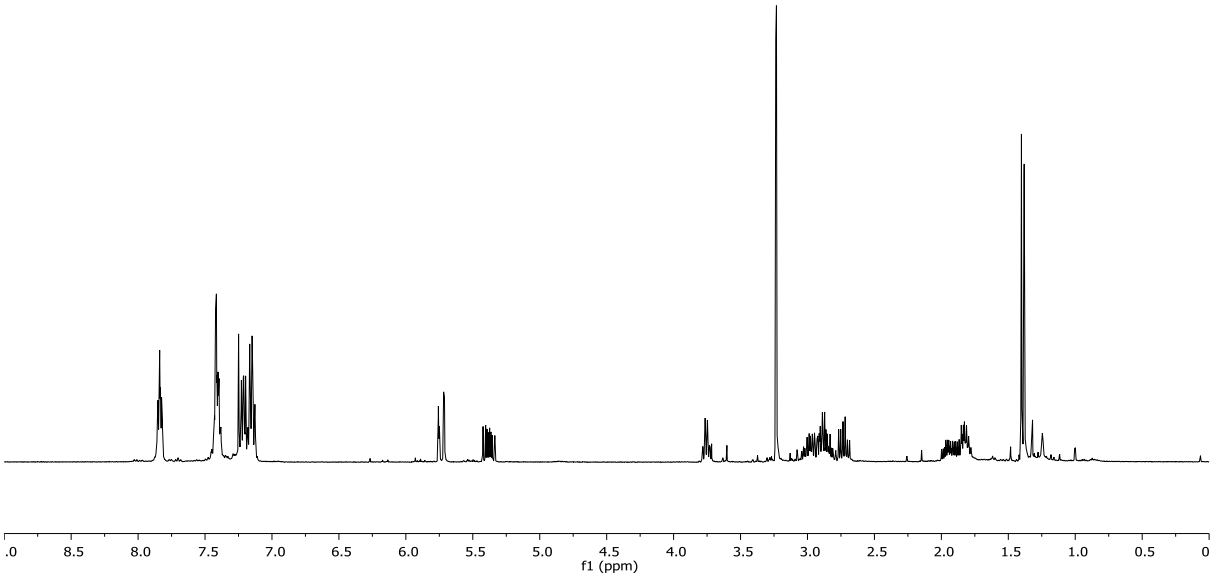
Ph
N
Me
Ph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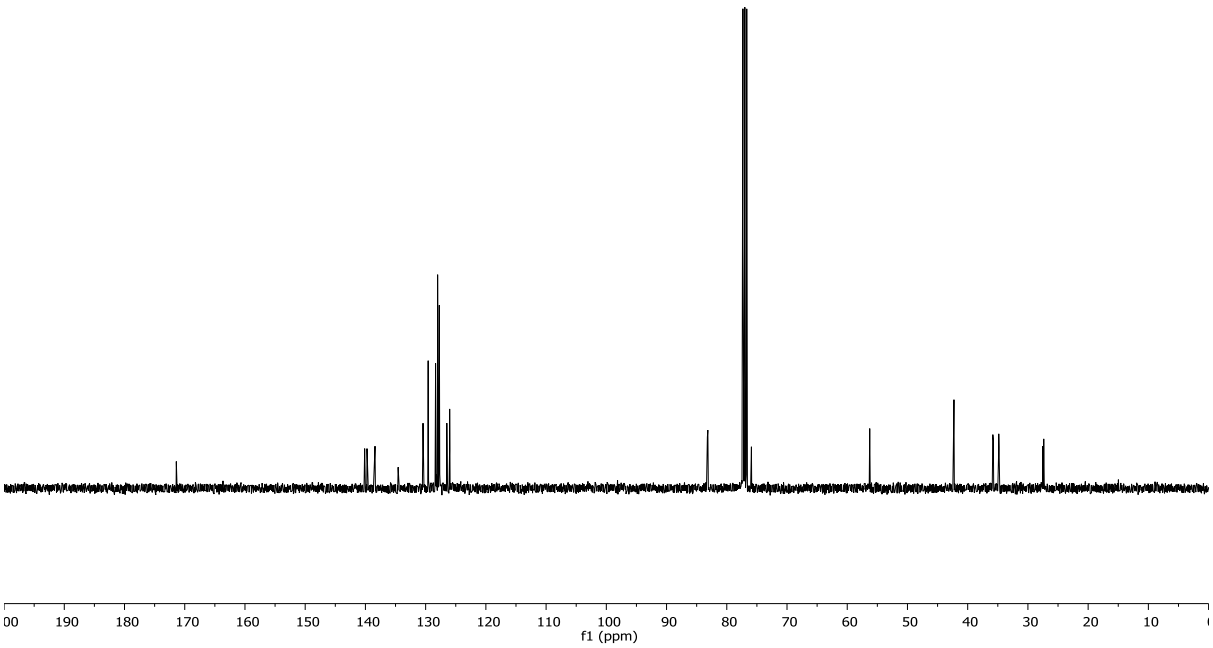
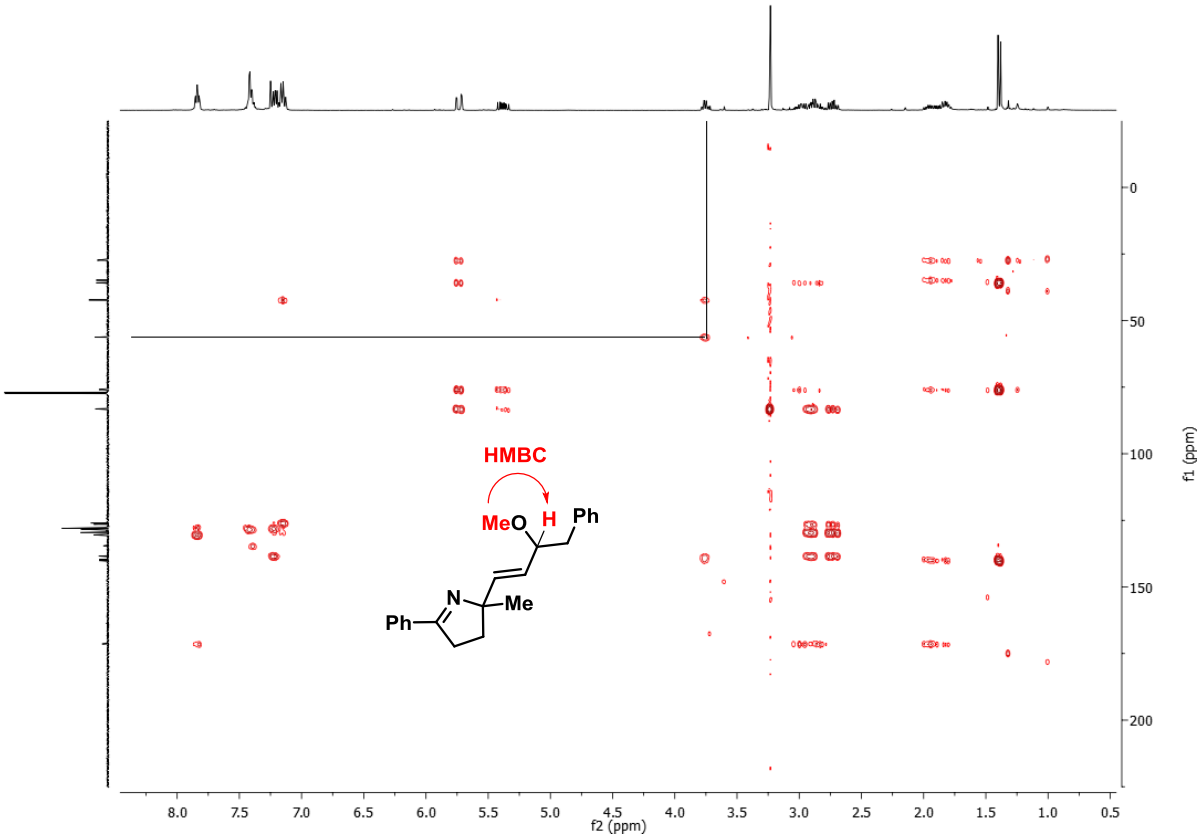
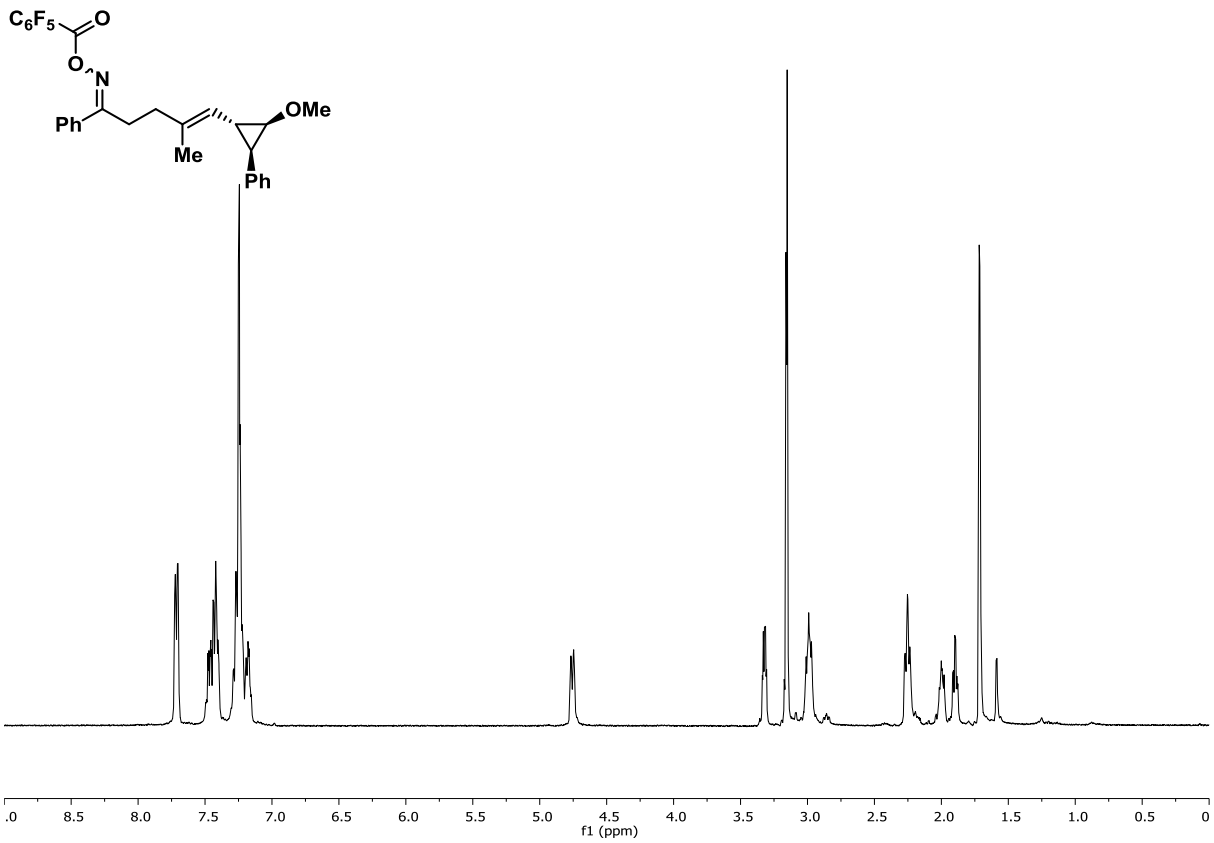
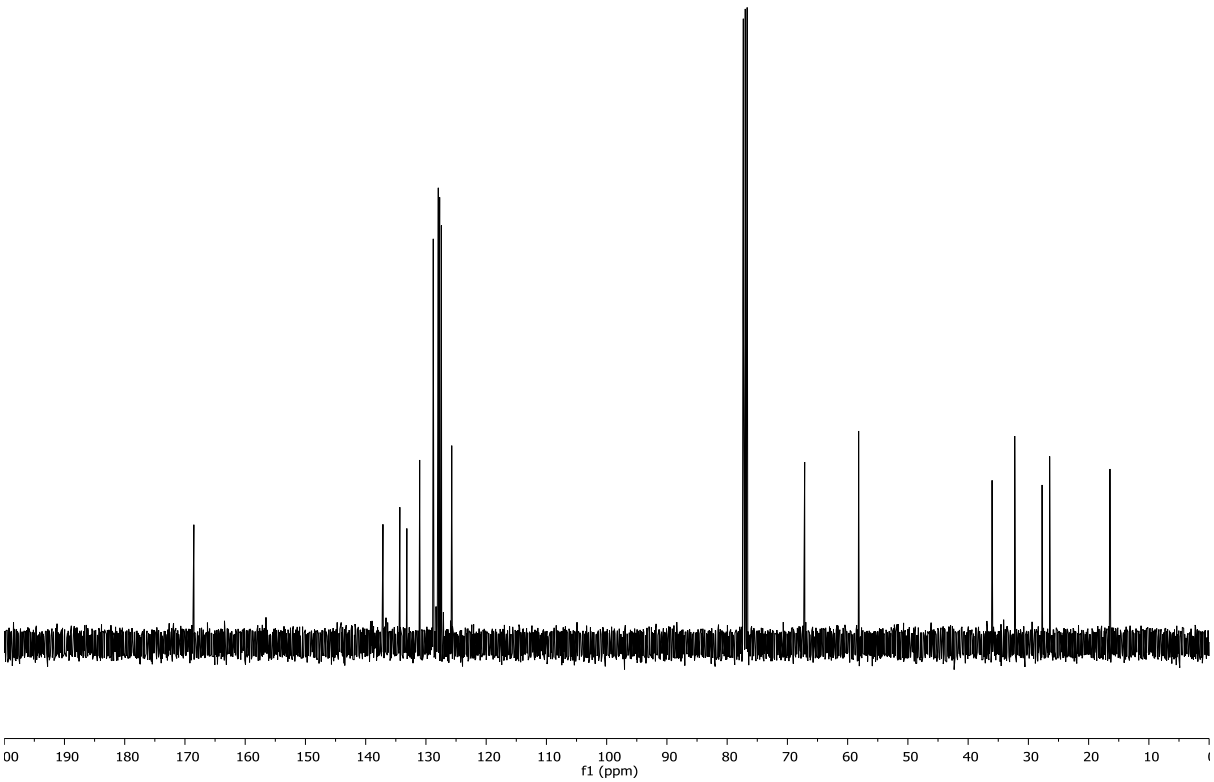
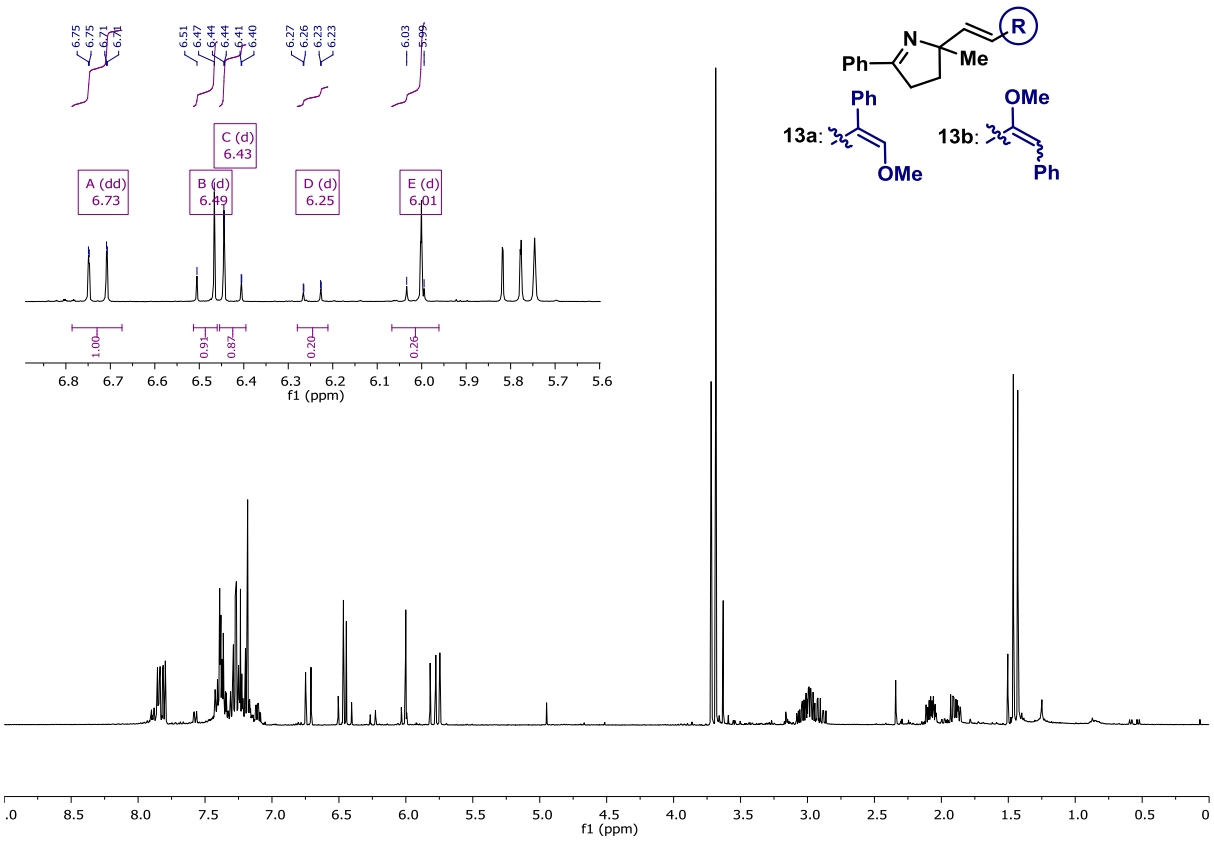
f1 (ppm)


00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


HMBC
MeO
H
Ph
N
Me
Ph
f2 (ppm)
f1 (ppm)


C6F5
O
O
N
Ph
Me
OMe
Ph
f1 (ppm)


f1 (ppm)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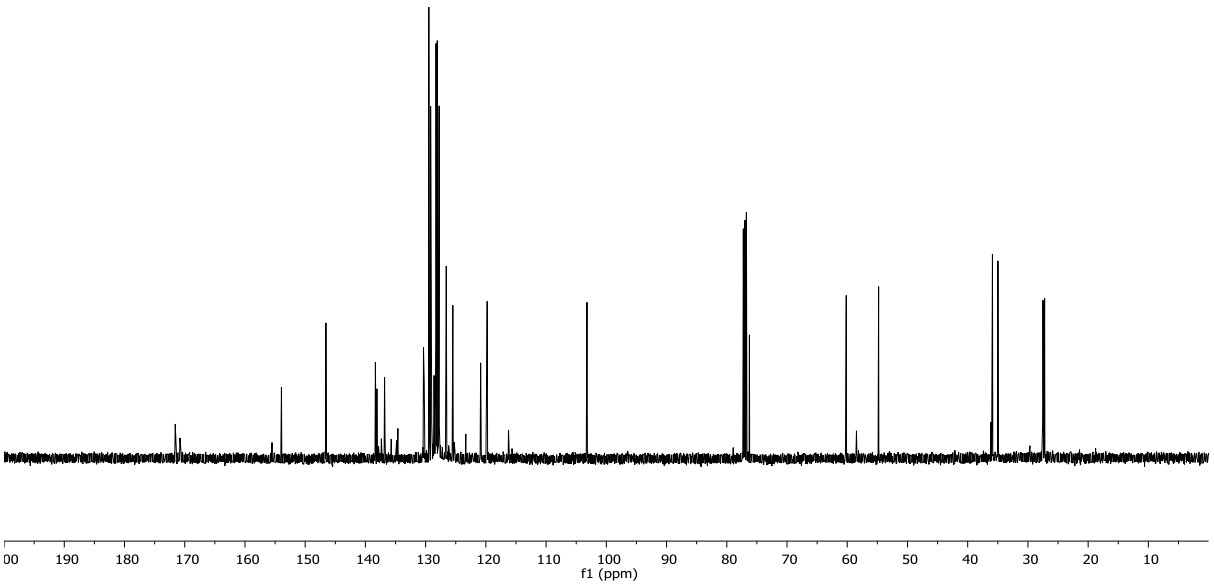
6.75
6.71
6.71
6.51
6.47
6.44
6.44
6.41
6.40
6.27
6.26
6.23
6.23
6.03
5.99
A (dd)
6.73
B (d)
6.49
C (d)
6.43
D (d)
6.25
E (d)
6.01
1.00
0.91
0.87
0.20
0.26
f1 (ppm)
N
Ph
Me
R
13a:
Ph
OMe
13b:
OMe
Ph
f1 (ppm)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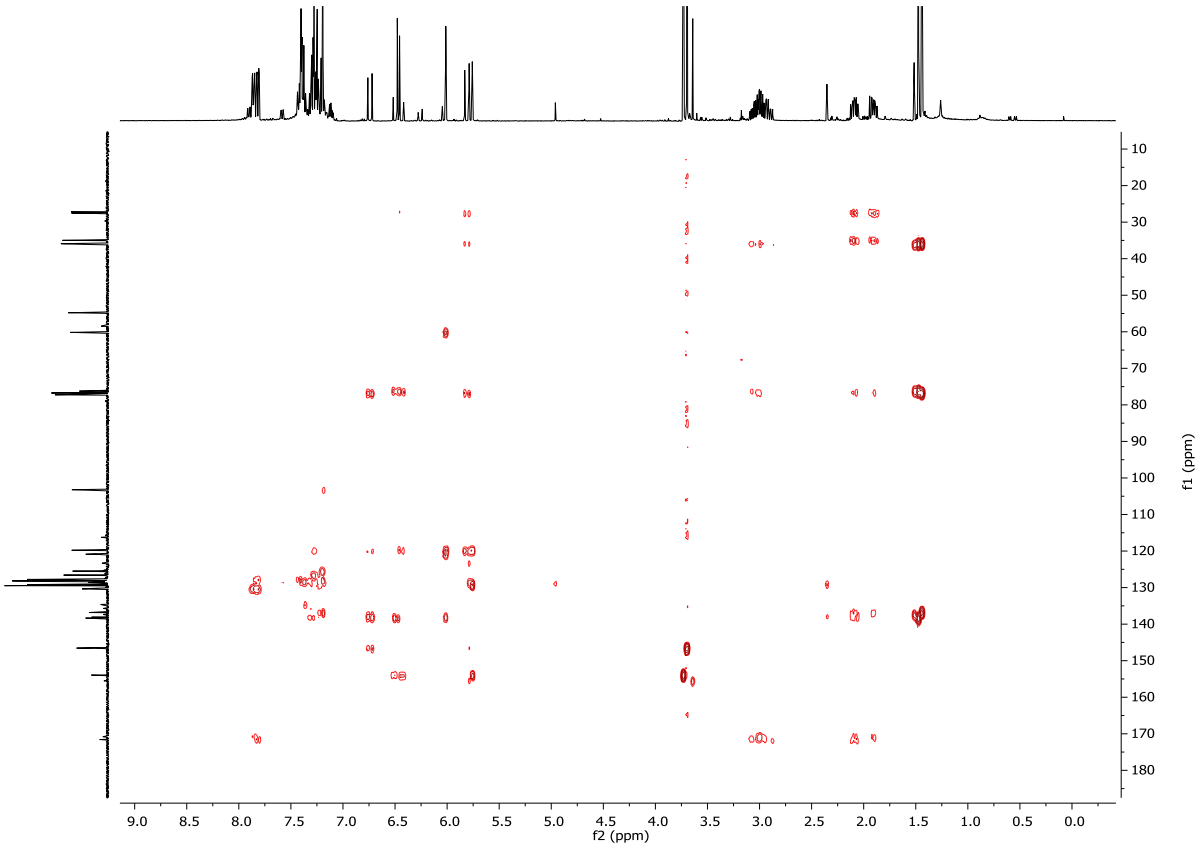
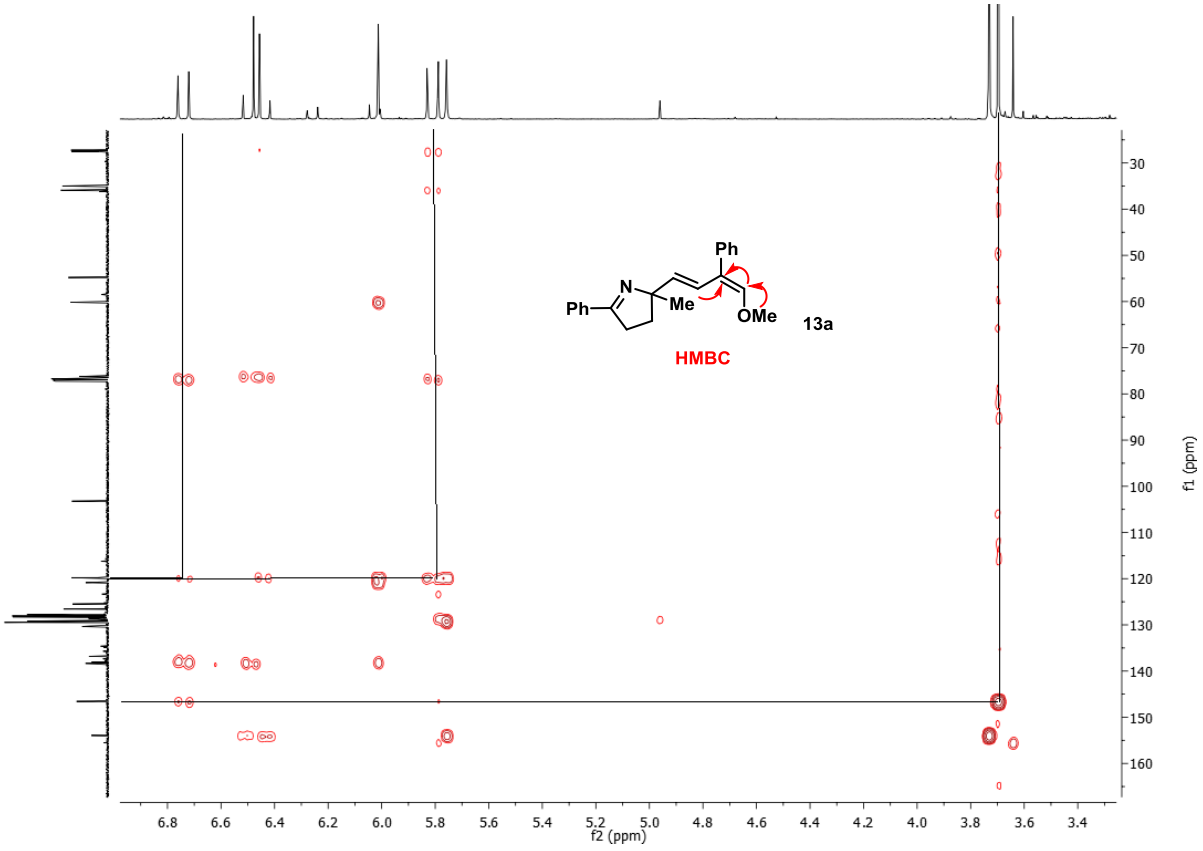
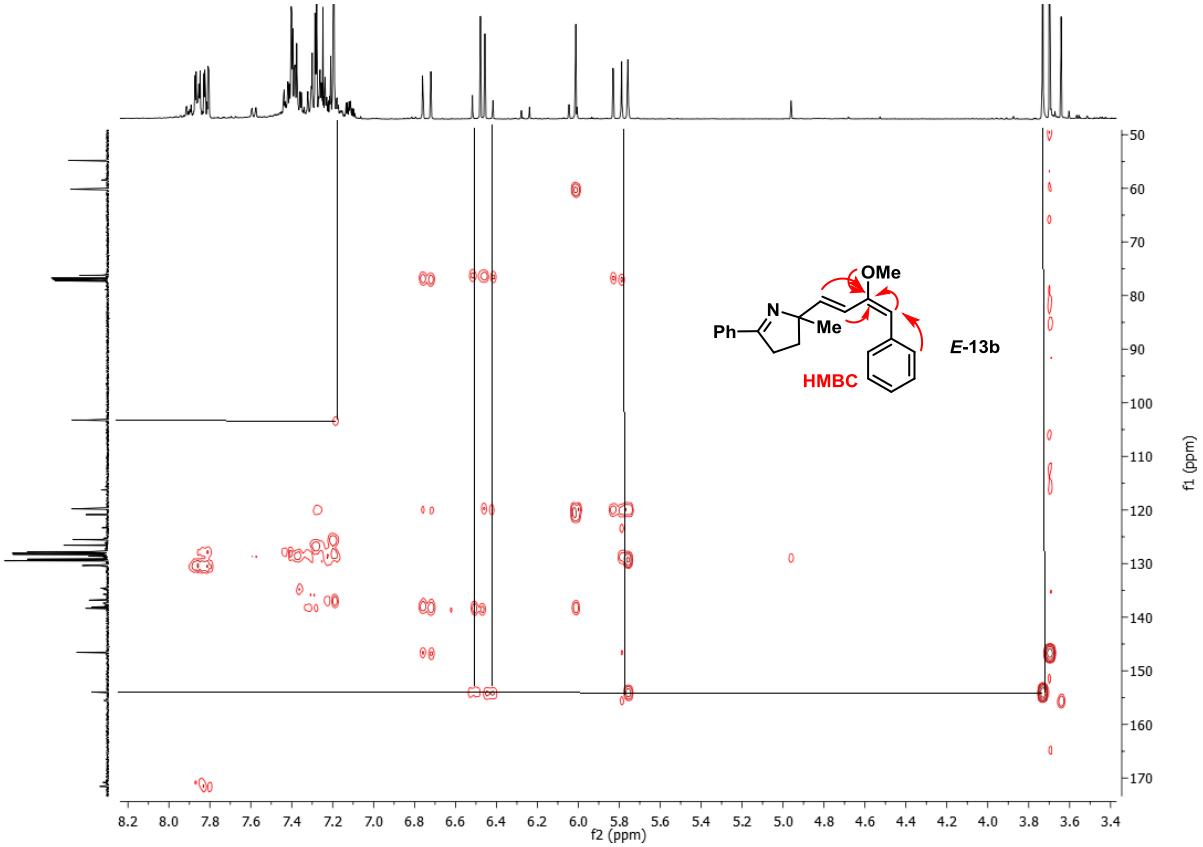

f2 (ppm)
f1 (ppm)


Ph
N
Me
OMe
Ph
13a
HMBC
f2 (ppm)
f1 (ppm)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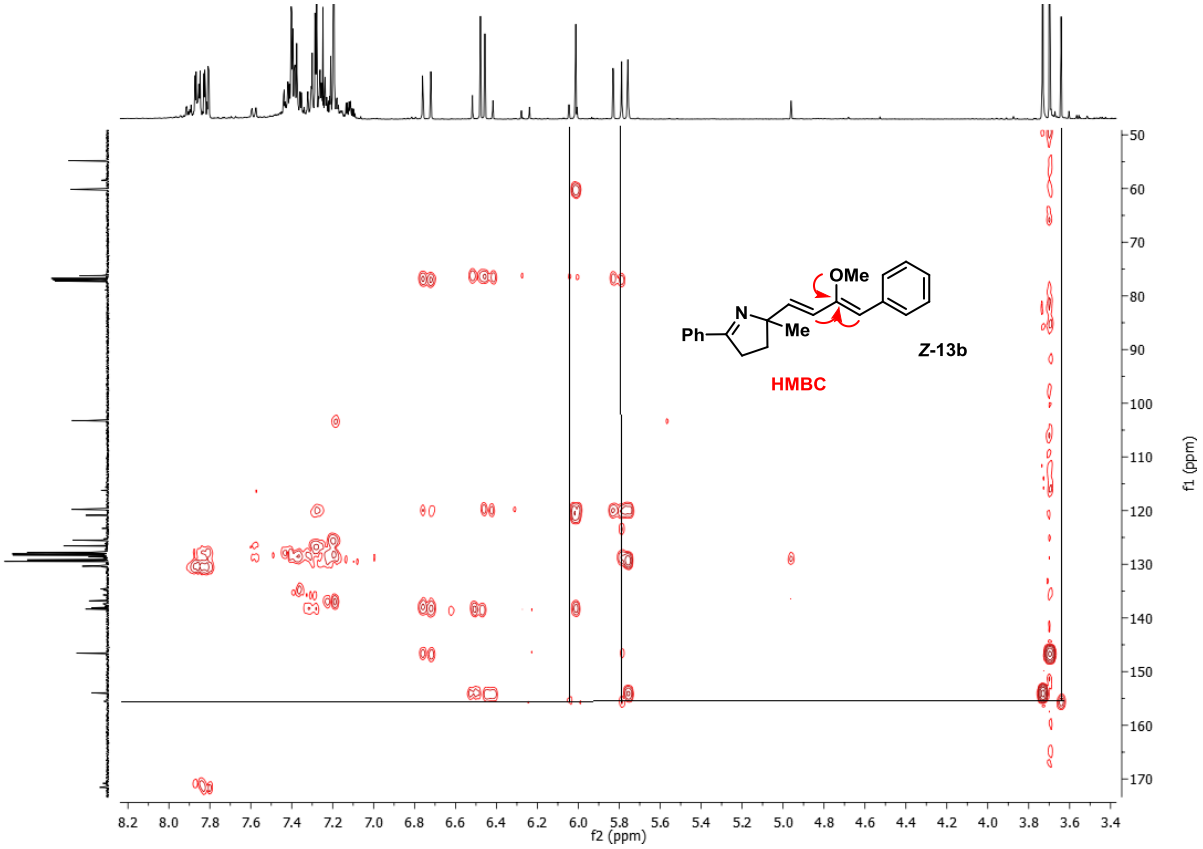
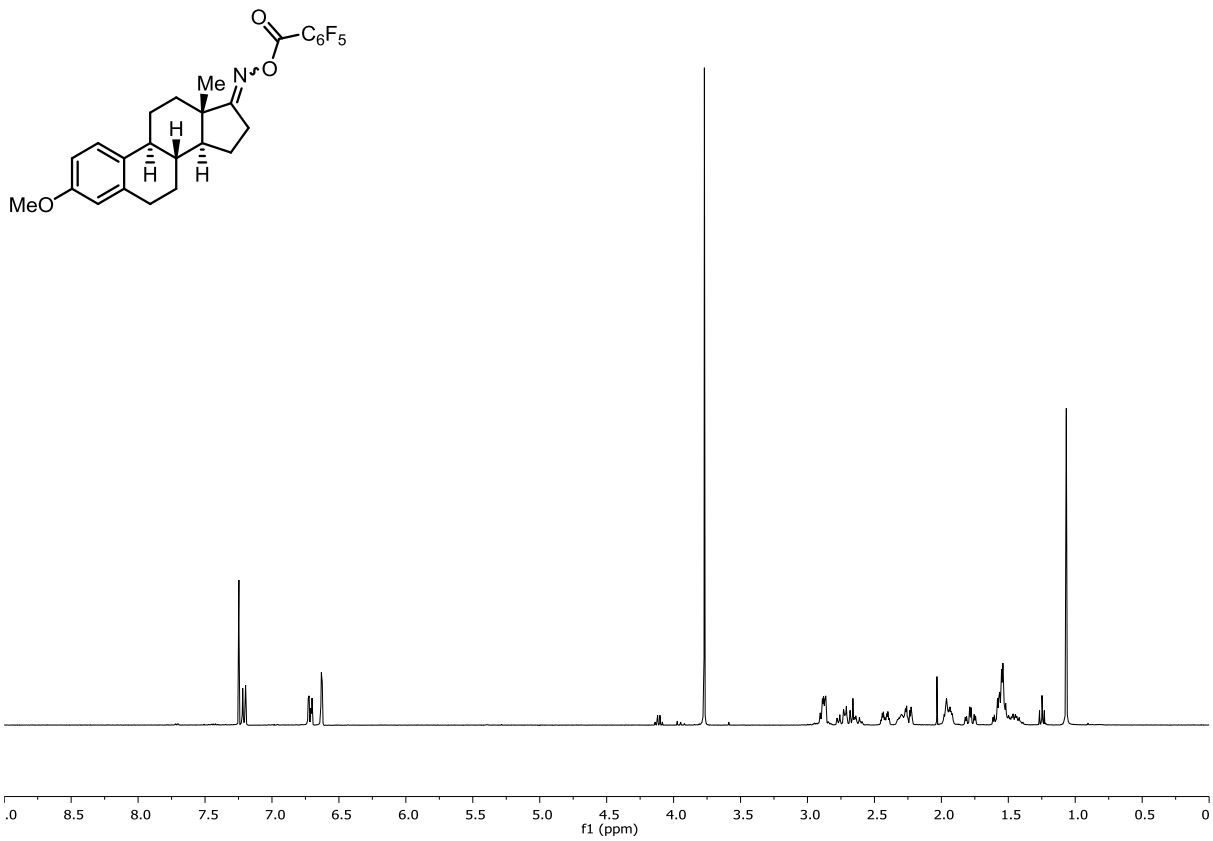
N
Ph
Me
HMBC
E-13b
f2 (ppm)
f1 (ppm)


OMe
N
Ph
Me
HMBC
Z-13b
f2 (ppm)
f1 (ppm)


O
C6F5
Me
N
O
H
H
H
MeO
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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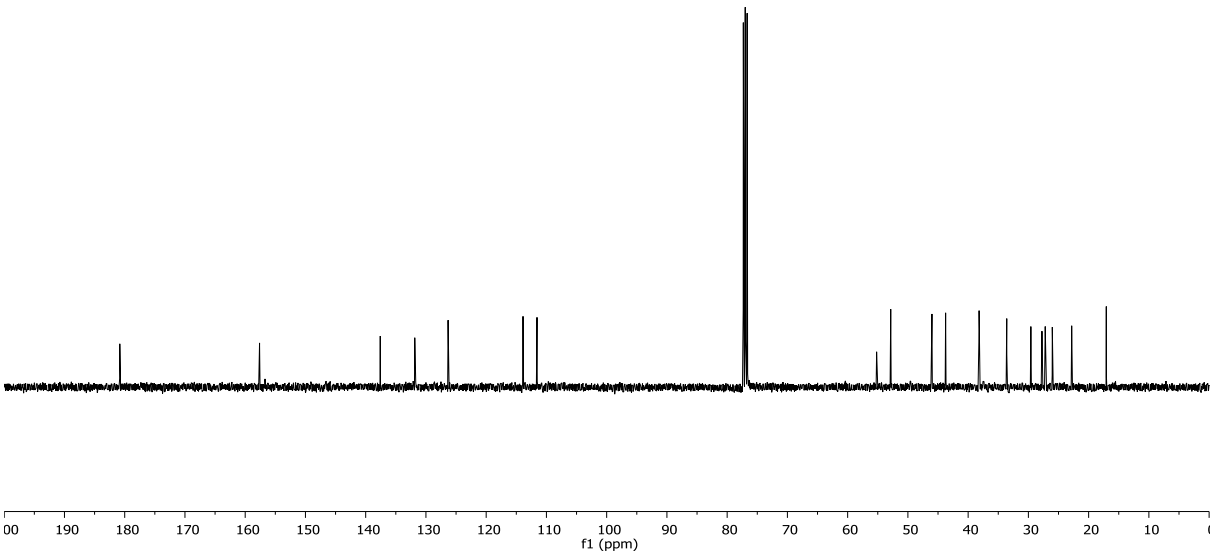
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


00
190
180
170
160
150
140
130
120
110
100
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80
70
60
50
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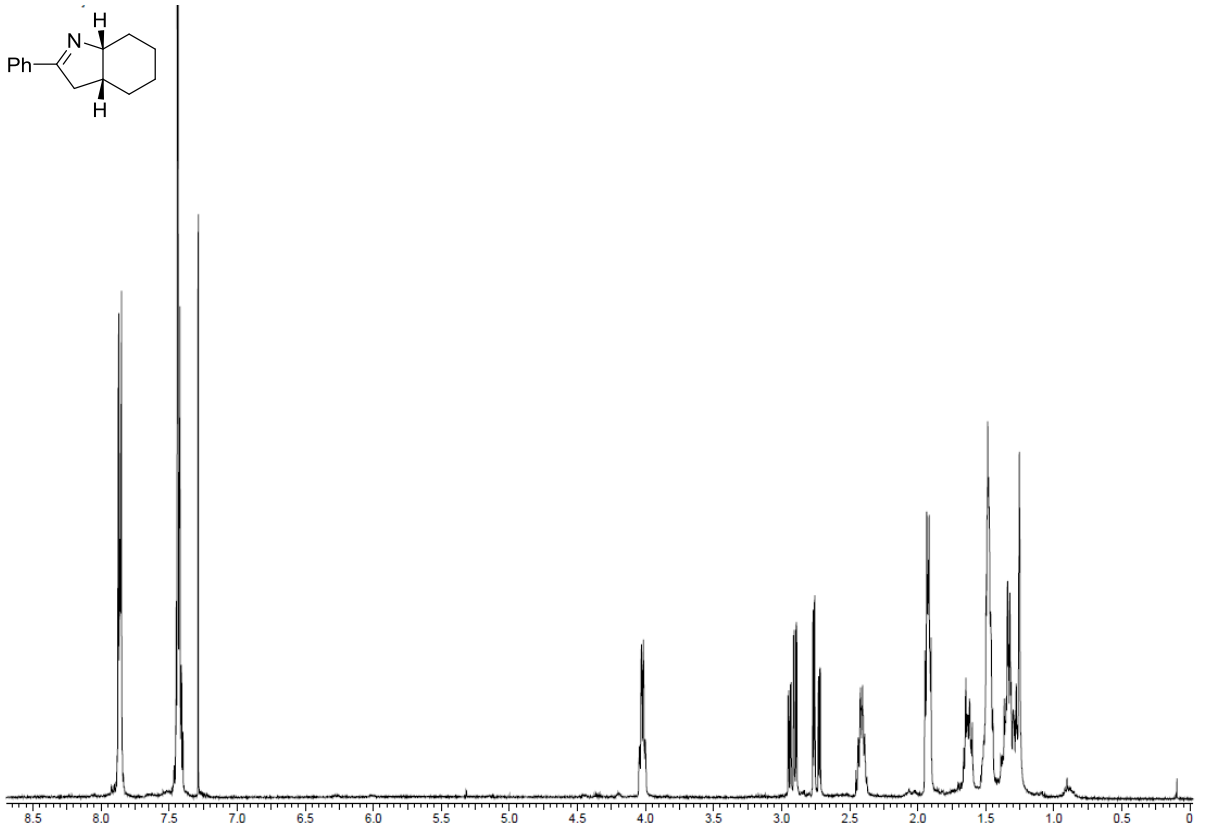
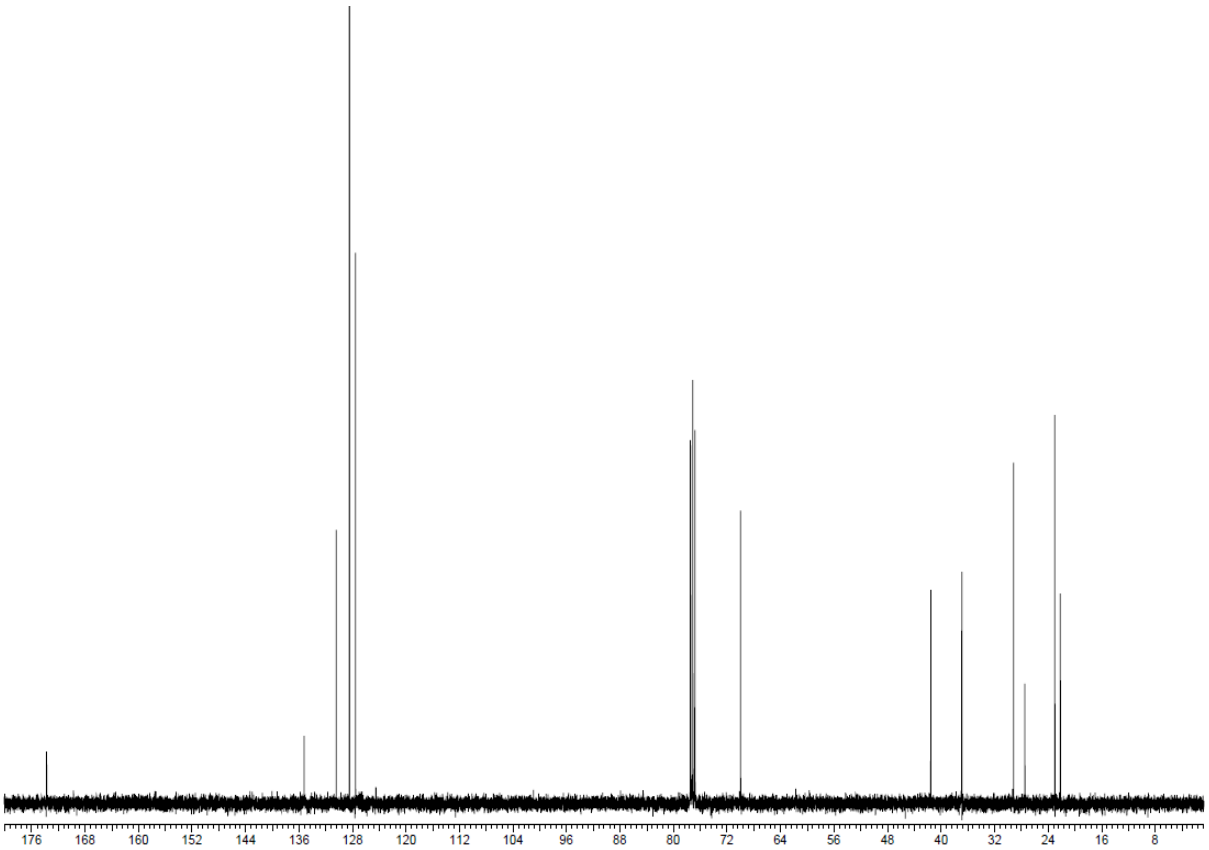
30
20
10
f1 (ppm)


H
N
Ph
H
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0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16
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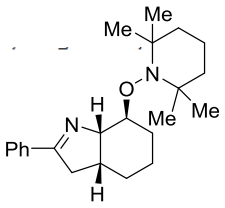
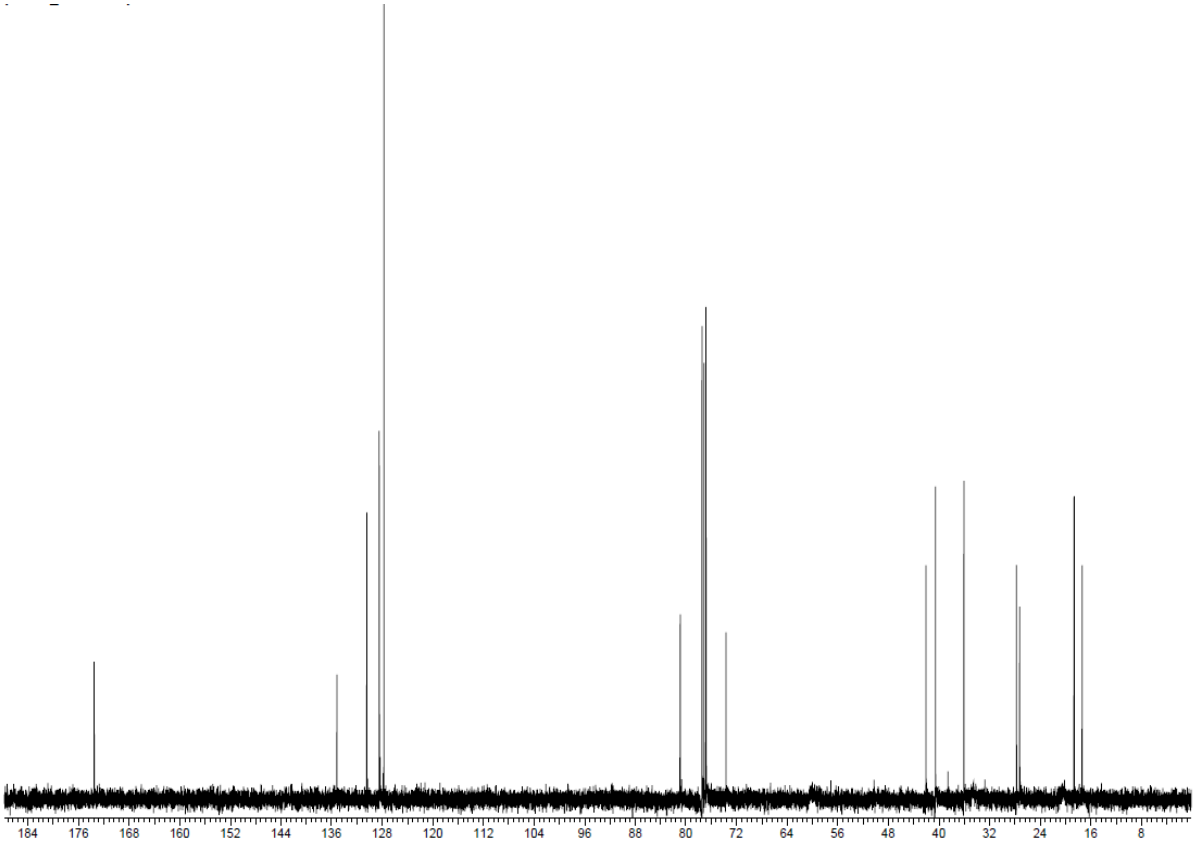

Me
Me
N
O
H
N
Ph
Me
Me
H

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5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16
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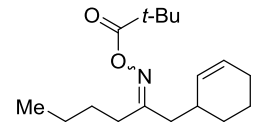
O
t-Bu
O
N
Me

7.5
7.0
6.5
6.0
5.5
5.0
4.5
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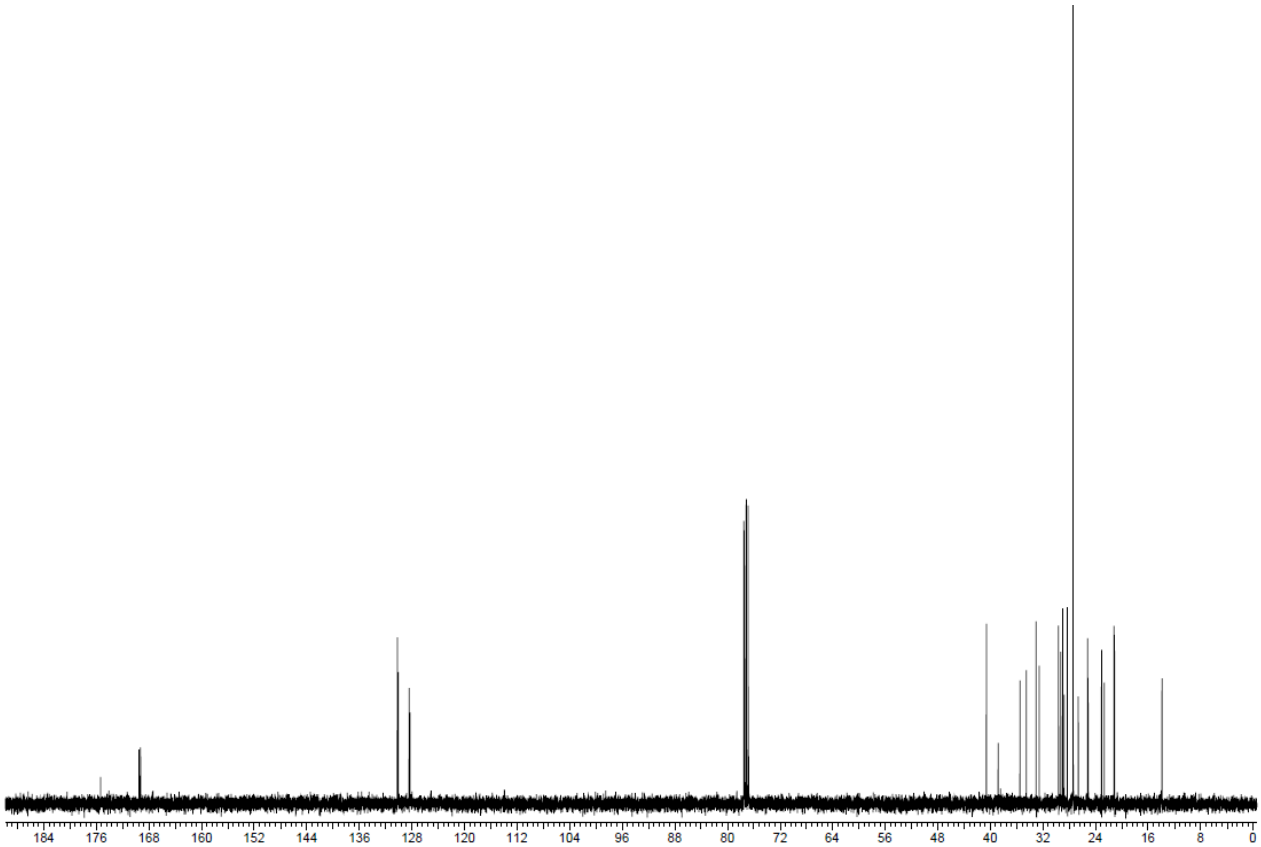
3.5
3.0
2.5
2.0
1.5
1.0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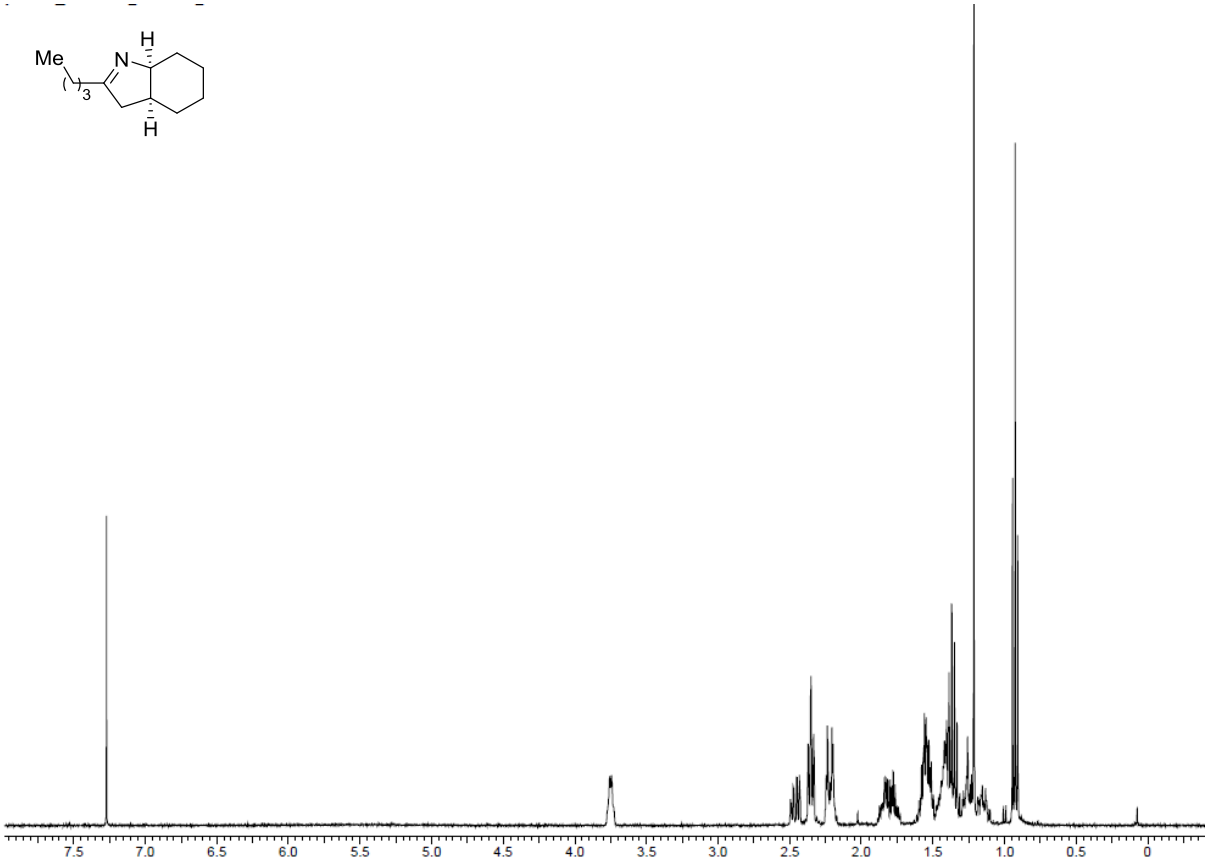
Me
3
N
H
H
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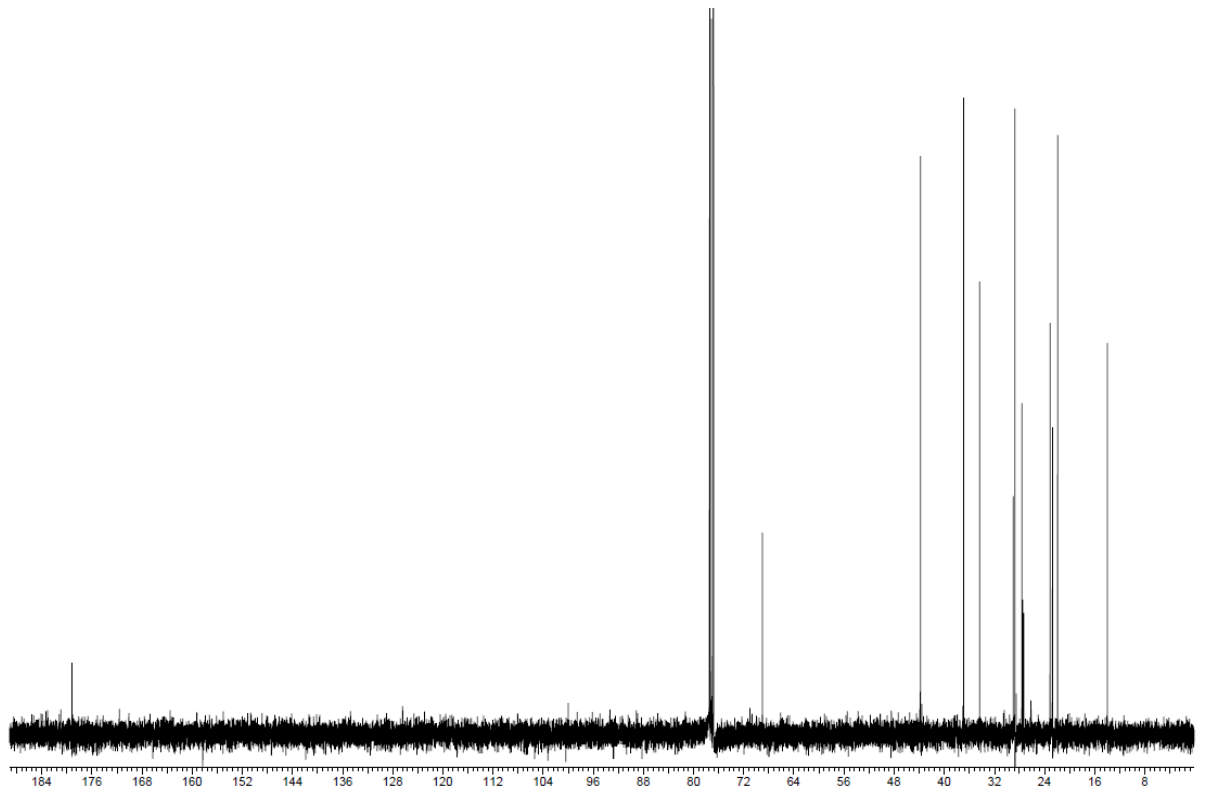
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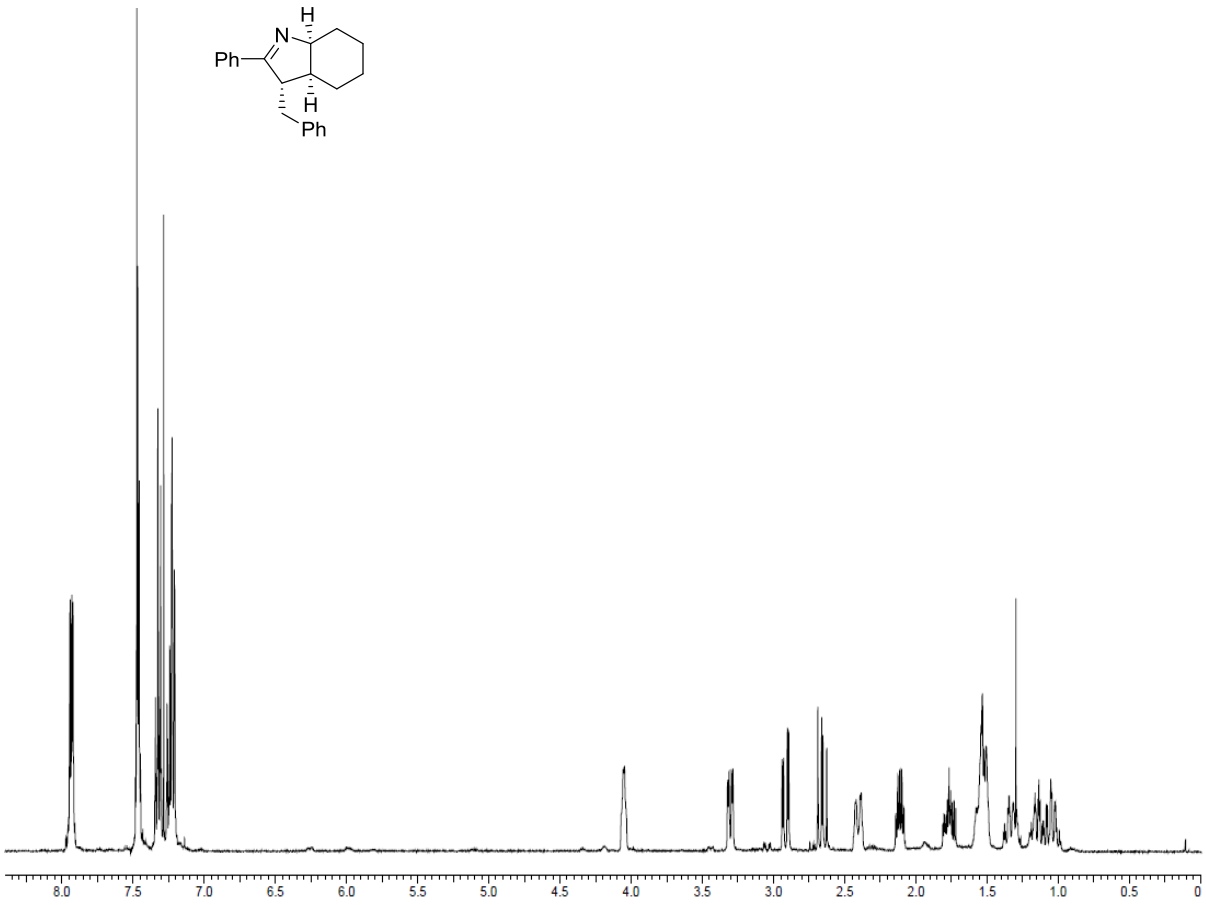
H
N
Ph
H
Ph
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6.0
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1.0
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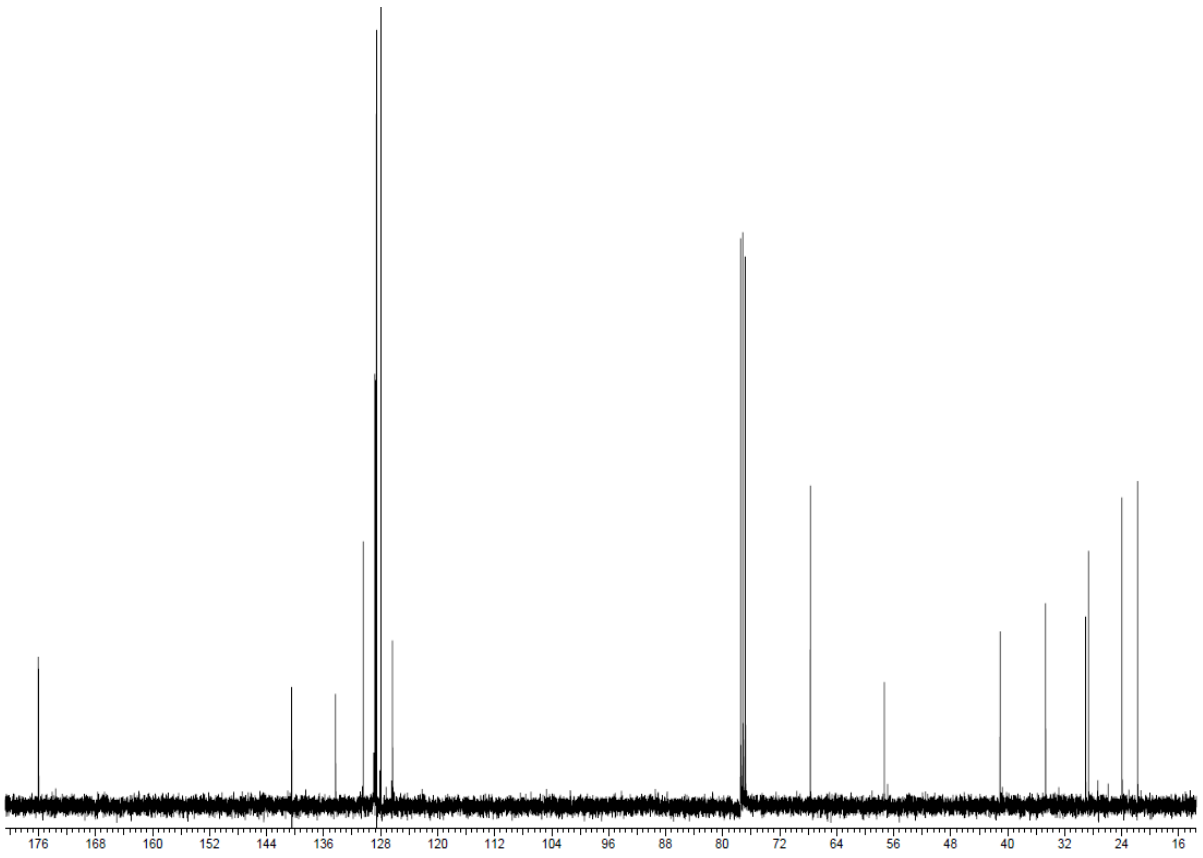
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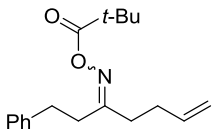
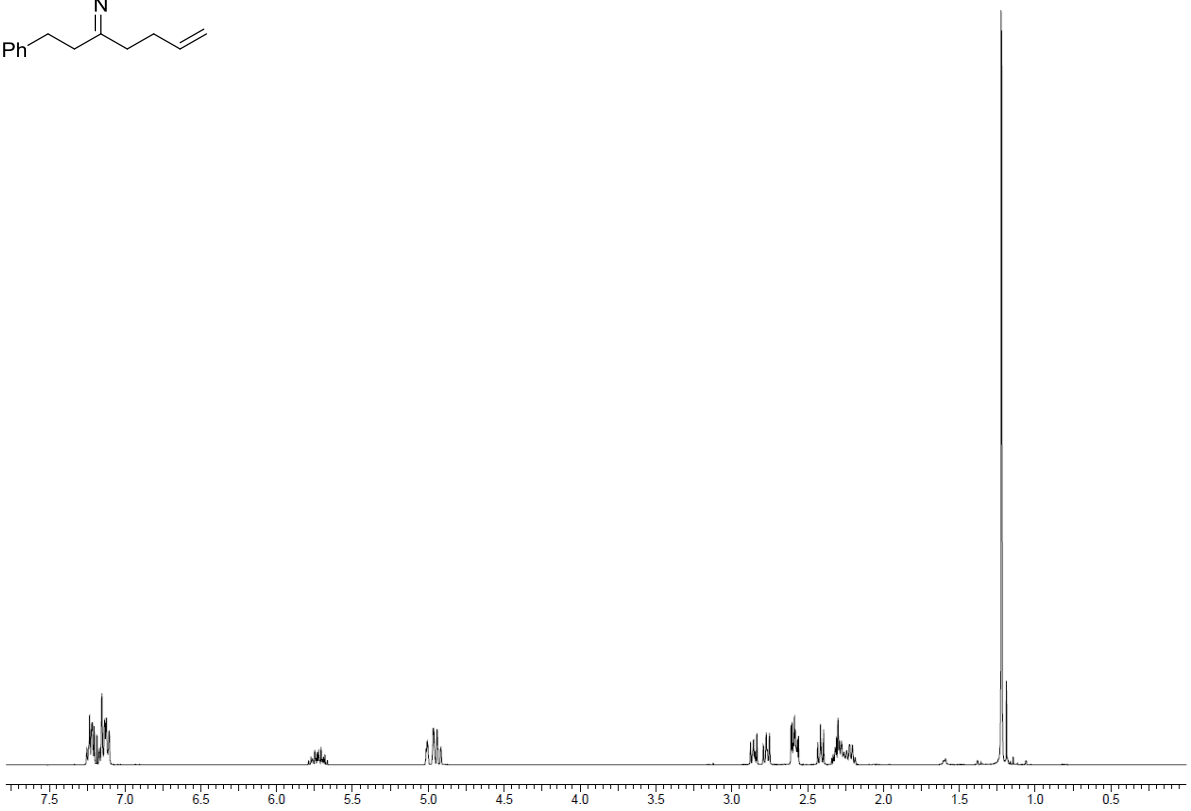

O
t-Bu
O
N
Ph


7.5
7.0
6.5
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5.5
5.0
4.5
4.0
3.5
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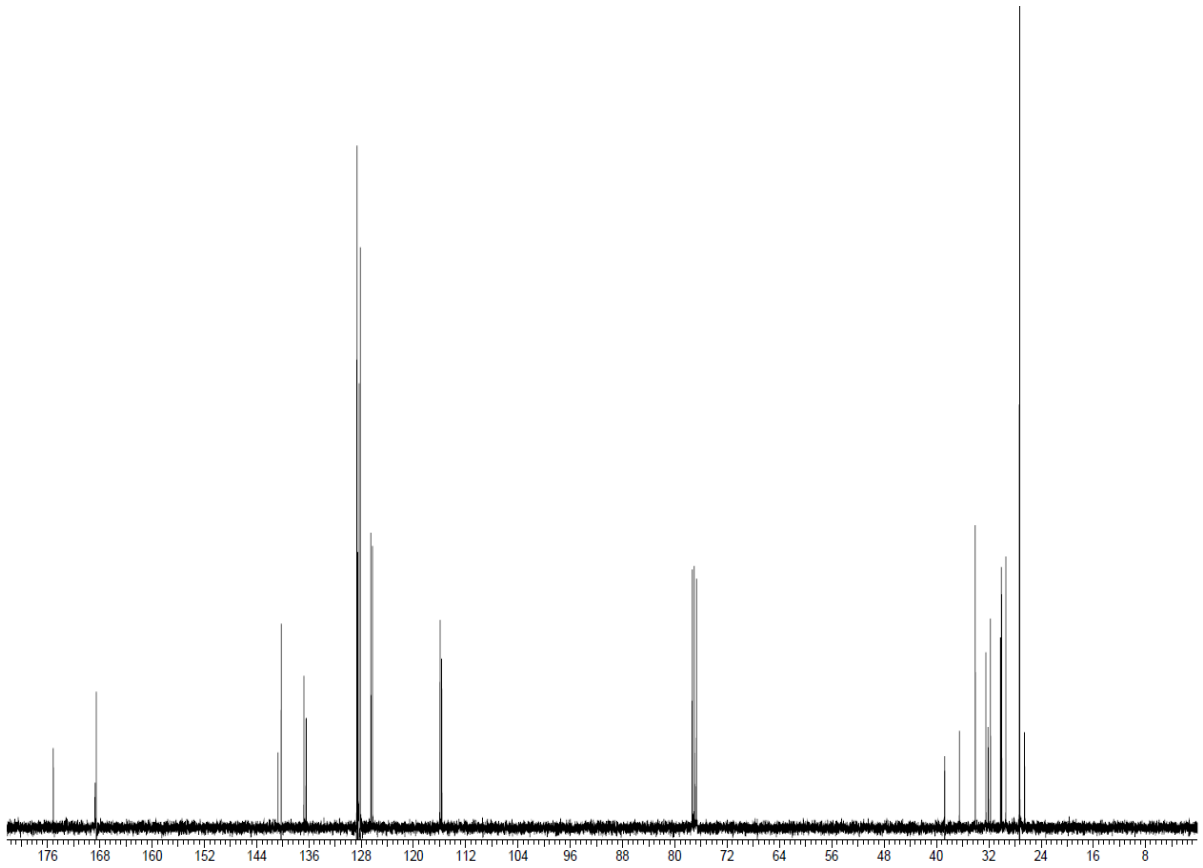
2.5
2.0
1.5
1.0
0.5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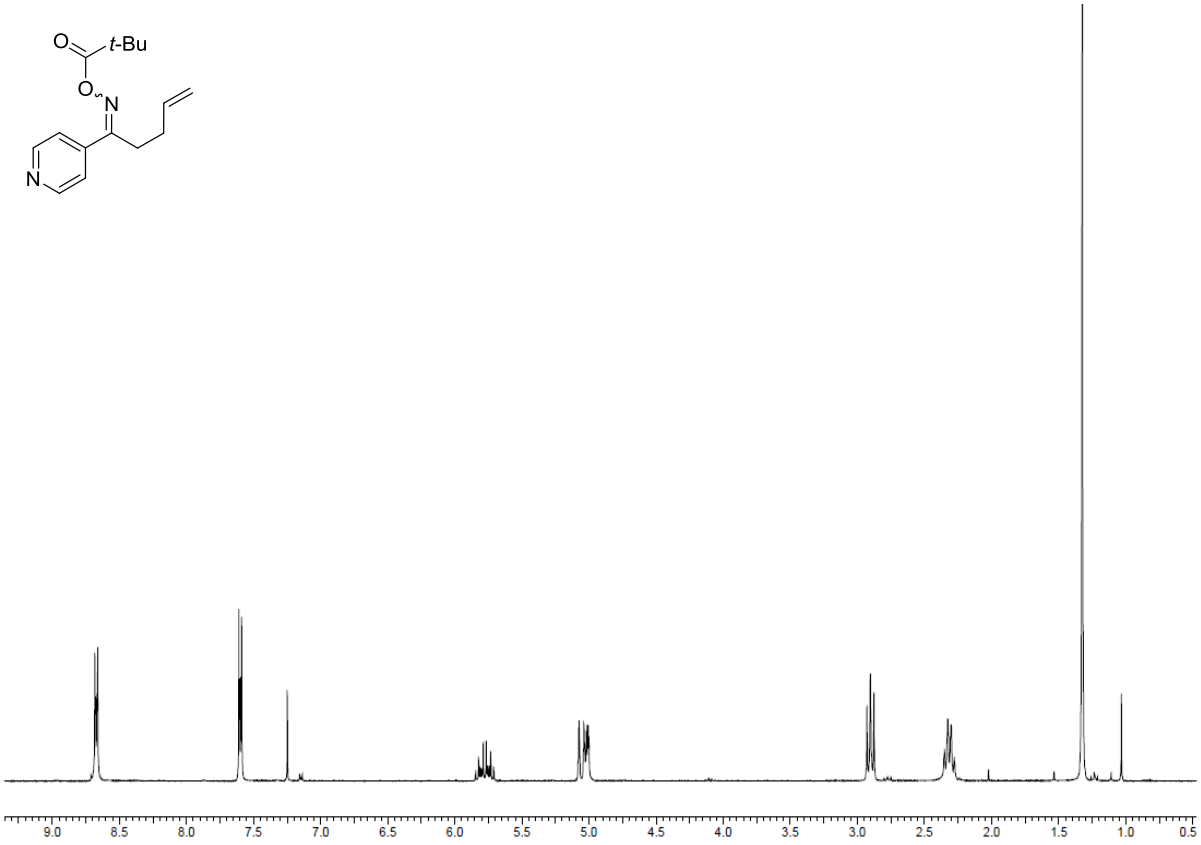
O
t-Bu
O
N
N
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8.5
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
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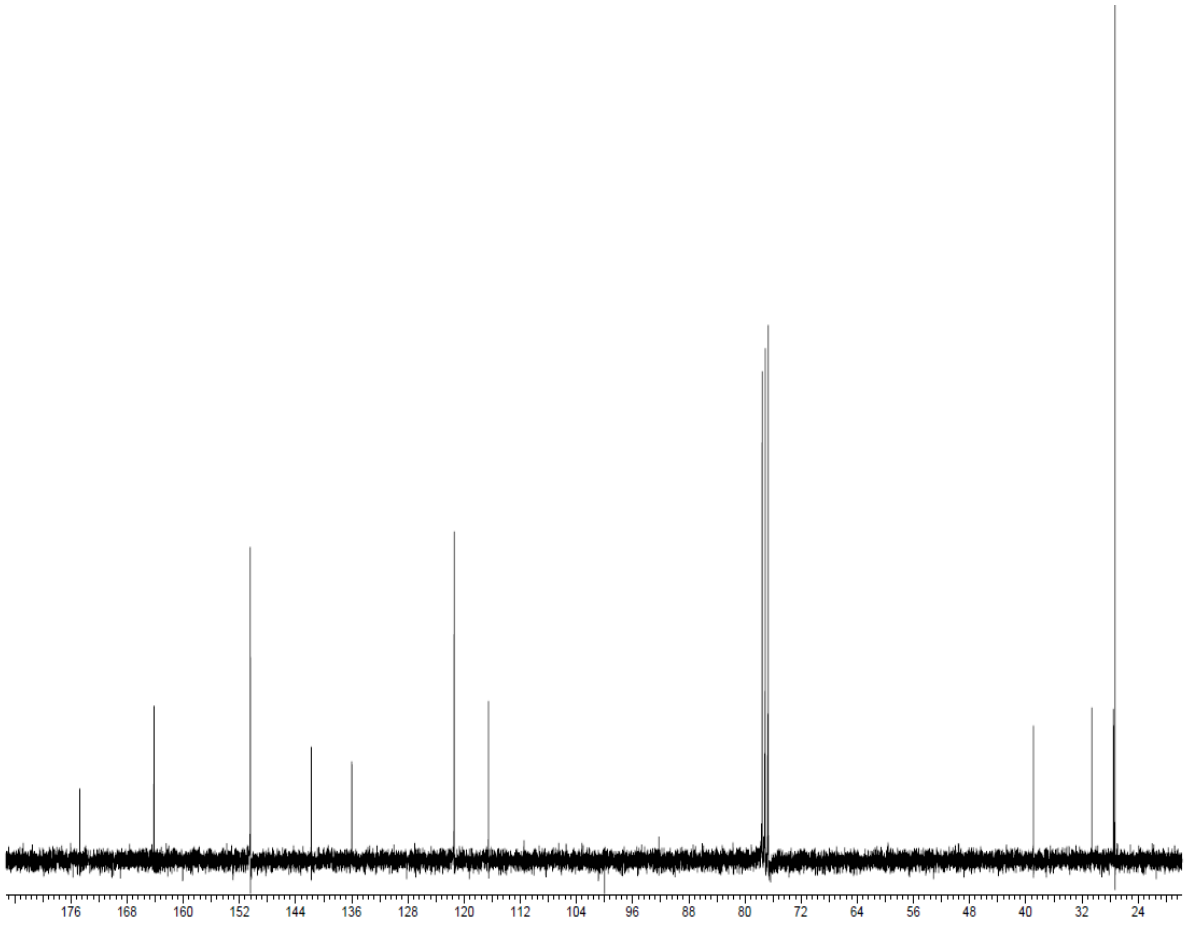
1.5
1.0
0.5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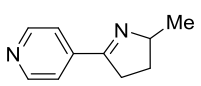
N
N
Me

9.0
8.5
8.0
7.5
7.0
6.5
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1.0
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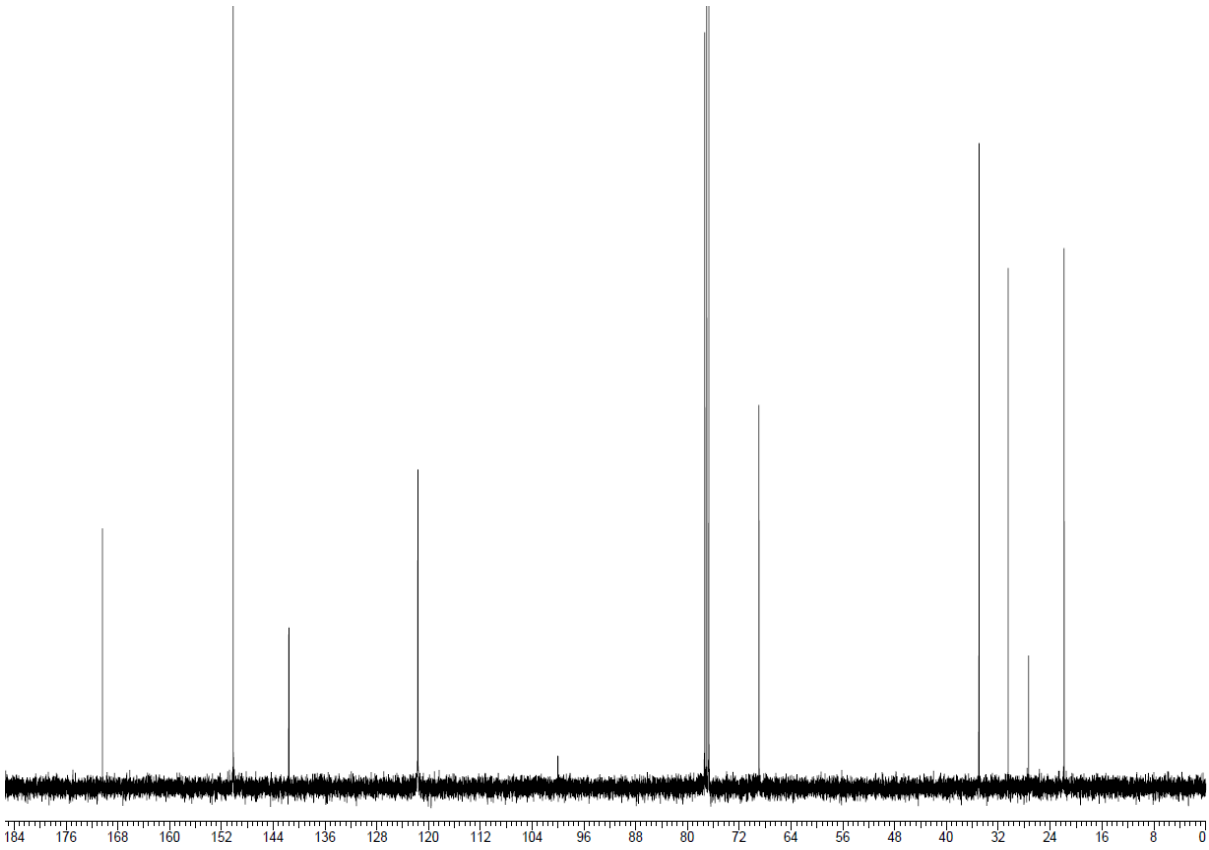
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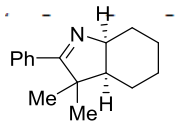
N
H
Ph
Me
Me
H

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2.0
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1.0
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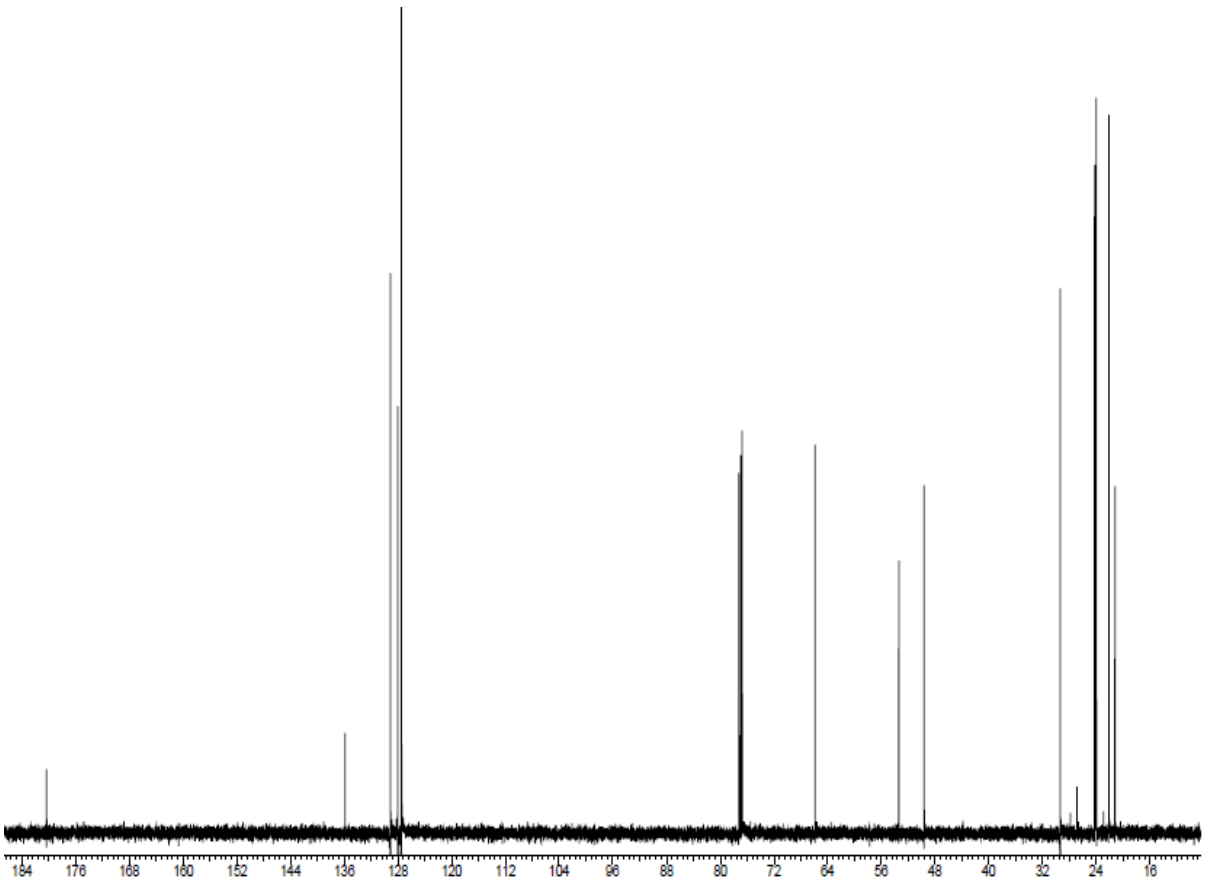
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(1) Faulkner, A.; Bower, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 1675.
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