Preparation of Stereodefined Homoallylic Amines from the Reductive Cross-Coupling of Allylic Alcohols with Imines

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Supporting Information

Experimental Procedures and Spectral Data

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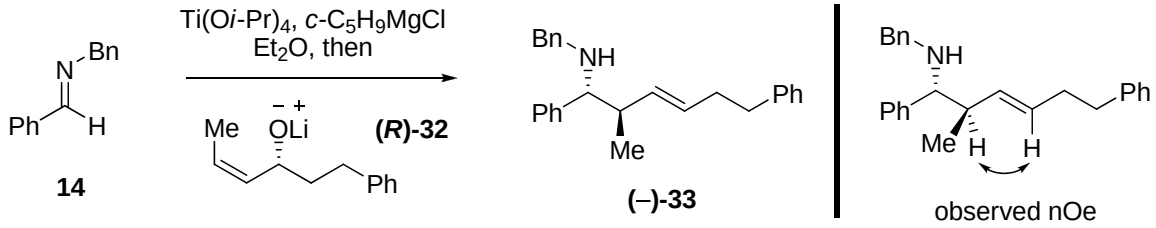
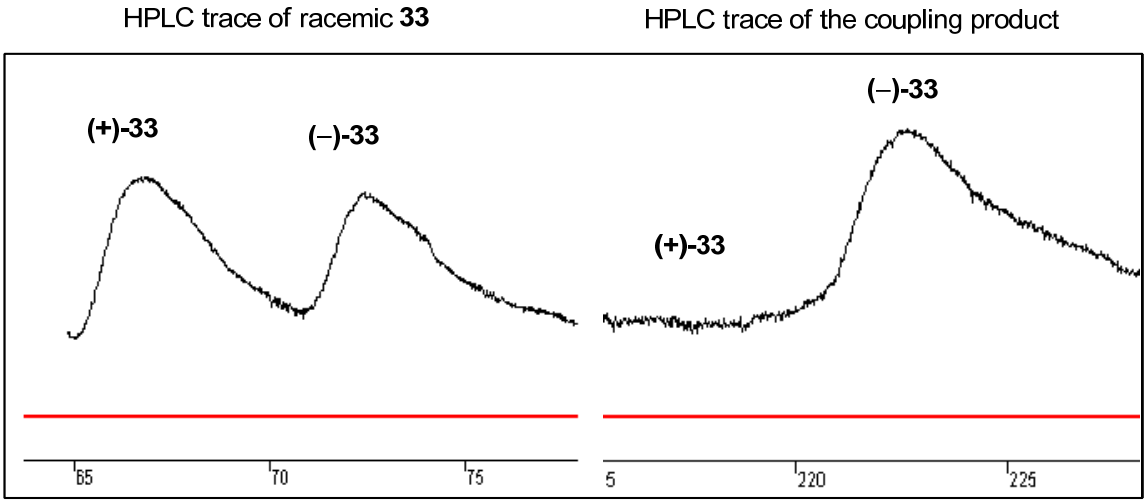
General. All reactions were conducted in flame-dried glassware under an argon atmosphere with anhydrous solvents, unless otherwise noted. Anhydrous diethyl ether (Et_2O), dichloromethane (DCM) and tetrahydrofuran (THF) were obtained by passing HPLC grade solvents through activated alumina columns. Acetonitrile (CH_3CN) was distilled over calcium hydride. Titanium(IV) tetraisopropoxide (Ti(O*i*-Pr)$_4$) was purified prior to use by distillation at 250 millitorr. *c*-C_5H_9MgCl, *n*-C_4H_9MgCl and *n*-BuLi were titrated using 1,10-phenanthroline/*sec*-butanol.[1] Imines **14**[2]**, 44** and ***ent*-44**[3] were prepared according to literature procedures. Propargylic alkyne **S-3**[4], α,β-unsaturated ketone **S-4**[5,6], and chiral allylic alcohols **(*R*)-28** and **(*R*)-32**[7-9] were prepared by adaptation of literature procedures for similar compounds. Enantiomeric excess of chiral alcohols **(*R*)-28**, **(*R*)-32**, **47**, **49**, **51** and **53** was determined using Mosher's ester analysis.[10] Enantiomeric excess of homoallylic amine **(+)-36** was determined using Mosher's amide analysis.[11] Enantiomeric excess of homoallylic amine **(–)-37** was determined by first subjecting it to *N*-debenzylation via catalytic transfer hydrogenolysis[12] followed by Mosher's amide analysis.[11] All other commercially available reagents were used as received. Thin-layer chromatography was performed on 250 μm E. Merck silica gel plates (60F-254). Silica gel for flash column chromatography was purchased from Silicycle (P60, particle size 40-63 μm). All compounds purified by chromatography were sufficiently pure for use in further experiments except otherwise indicated. ^{1}H NMR and ^{13}C NMR data were recorded at 400 MHz and 100 MHz, respectively. ^{1}H NMR chemical shifts were reported relative to residual $CHCl_3$ (7.26 ppm) or TMS (0.00 ppm). ^{13}C NMR chemical shifts were reported relative to the central line of $CDCl_3$ (77.23 ppm). High-resolution mass spectrometry was performed at the Mass Spectrometry Facility at University of Illinois at Urbana-Champaign. Low-resolution mass spectrometry was performed using electrospray ionization. Optical rotations were measured using a quartz cell with a 0.5 mL capacity and a 10 cm path length. Relative stereochemistry was defined using the R*/S* convention proposed by IUPAC.

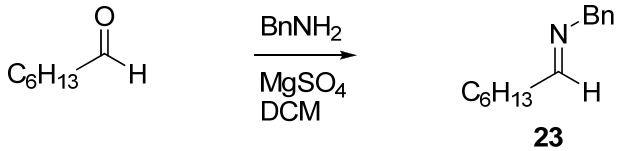


Synthesis of (1*R*,2*R*,*E*)-*N*-benzyl-2-methyl-1,6-diphenylhex-3-en-1-amine (33): To a solution of imine **14** (55.3 μL, 59.7 mg, 0.306 mmol) and Ti(O*i*-Pr)$_4$ (136 μL, 130 mg, 0.459 mmol) in Et_2O (1.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 0.918 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for 1 h. A solution of lithium alkoxide **(*R*)-32** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (96% ee by Mosher's ester, 27 mg, 0.153 mmol) with *n*-BuLi (2.54 M in hexane, 0.168 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (2→4% EtOAc/hexanes) to afford homoallylic amines **33** (d.r. ≥ 20:1, *E*:*Z* ≥ 20:1, ee ≥ 95%, 38 mg, 69%,) as a colorless oil. No evidence for minor isomer was observed by ^{1}H NMR. The absolute stereochemistry was assigned based on a mechanistic course that follows *syn*-carbometalation and *syn*-elimination. The spectral data correspond to that of previously reported racemic material.[7]

$[\alpha]_D^{20}$ –58.0 (*c* 0.10, Et_2O).

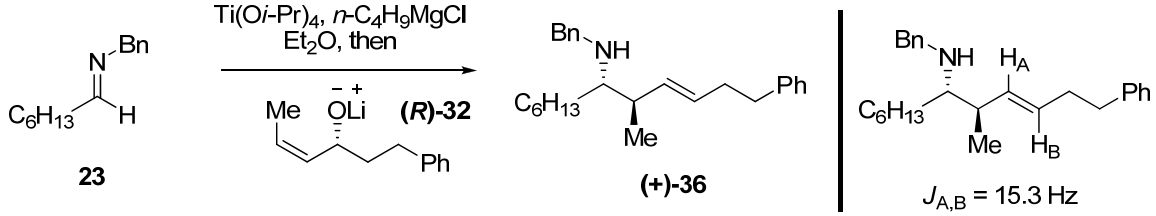
HPLC analysis of the product: CHIRALPAK IA column; solvent system: 0.1% EtOAc in hexanes; flow rate: 0.7 mL/min; retention times: 18.0 min for **(+)-33**, 22.4 min for **(–)-33.**





23

Synthesis of (*E*)-*N*-heptylidene-1-phenylmethanamine (23): To a suspension of anhydrous $MgSO_4$ in DCM (10 mL) was added successively heptanal (1.40 mL, 1.14 g, 10 mmol) and benzylamine (1.09 mL, 1.07 g, 10 mmol) via syringe. The reaction was stirred at ambient temperature and monitored by NMR. Upon completion, the mixture was filtered and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation to afford imine **23** as a colorless oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, J = 4.9 Hz, 1H), 7.35-7.21 (m, 5H), 4.56 (s, 2H), 2.35-2.26 (m, 2H), 1.62-1.50 (m, 2H), 1.40-1.22 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 139.6, 128.6, 128.1, 127.1, 65.3, 36.2, 31.8, 29.2, 26.2, 22.7, 14.2; IR (thin film, NaCl) ν_{max} 3086, 3064, 2925, 2856, 1668, 1604, 1495, 1454, 1377, 1028, 732, 697 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{22}N$ $[M + H]^+$ 204.2, found 204.2.



Synthesis of (5*R*,6*S*,*E*)-*N*-benzyl-5-methyl-1-phenyldodec-3-en-6-amine (36): To a solution of imine **23** (244 mg, 1.20 mmol) and Ti(O*i*-Pr)$_4$ (355 μL, 341 mg, 1.20 mmol) in Et_2O (6.0 mL) at –78 °C was added dropwise *n*-C_4H_9MgCl (2.02 M in Et_2O, 2.40 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and

stirred at this temperature for 1.5 h. A solution of lithium alkoxide **(*R*)-32** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (85% ee by Mosher's ester, 53 mg, 0.30 mmol) with *n*-BuLi (2.39 M in hexane, 0.33 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to afford homoallylic amines **36** (d.r. ≥ 20:1, *E*:*Z* ≥ 20:1, ee = 85% by Mosher's amide, 62 mg, 57%,) as a pale yellow oil. No evidence for minor isomer was observed by ^{1}H NMR. The absolute stereochemistry was assigned based on a mechanistic course that follows *syn*-carbometalation and *syn*-elimination. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.10 (m, 10H), 5.46 (dt, *J* =15.3, 6.6 Hz, 1H), 5.29 (dd, *J* = 15.3, 7.7 Hz, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.36-2.21 (m, 4H), 1.54 (br, 1H), 1.40-1.20 (m, 10H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.4, 134.6, 130.0, 128.7, 128.5, 128.4, 128.3, 126.9, 126.0, 61.3, 52.0, 39.7, 36.3, 34.7, 32.1, 30.9, 30.0, 25.9, 22.9, 16.8, 14.3; IR (thin film, NaCl) ν_{max} 3086, 3027, 2926, 2856, 1942, 1689, 1604, 1495, 1454, 1377, 1102, 1028, 972, 744, 698 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{26}H_{38}N$ $[M + H]^+$ 364.3, found 364.4; $[\alpha]_D^{20}$ +9.6 (*c* 0.25, $CHCl_3$).

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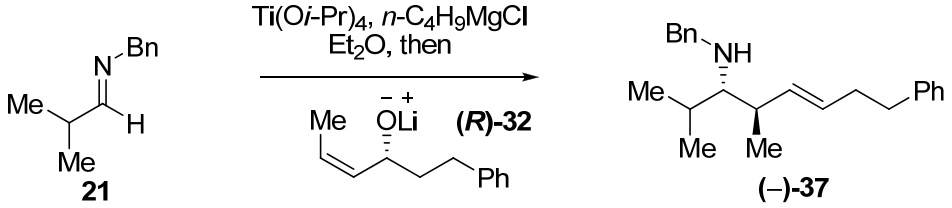
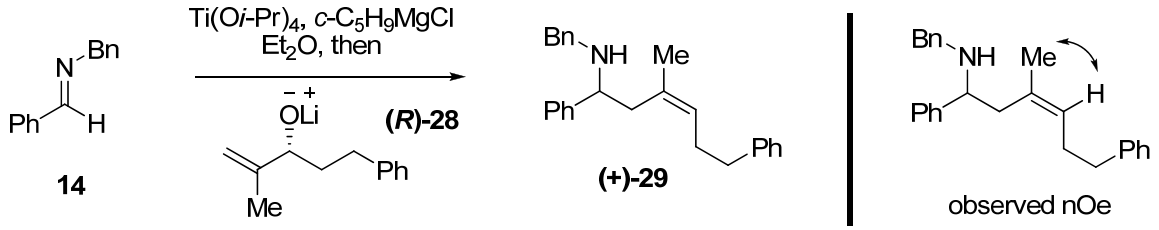
Synthesis of (*E*)-*N*-(2-methylpropylidene)-1-phenylmethanamine (21): To a suspension of anhydrous $MgSO_4$ in DCM (10 mL) was added successively isobutyraldehyde (0.91 mL, 0.72 g, 10 mmol) and benzylamine (1.09 mL, 1.07 g, 10 mmol) via syringe. The reaction was stirred at ambient temperature and monitored by

NMR. Upon completion, the mixture was filtered and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation to afford imine **21** as a colorless oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 5.0 Hz, 1H), 7.39-7.34 (m, 2H), 7.32-7.25 (m, 3H), 4.60 (s, 2H), 2.60-2.49 (m, 1H), 1.16 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 139.6, 128.5, 127.9, 126.9, 64.9, 34.3, 19.5; IR (thin film, NaCl) ν_{max} 3086, 3028, 2964, 2871, 2827, 1670, 1604, 1495, 1453, 1366, 1029, 733, 697 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{11}H_{16}N$ $[M + H]^+$ 162.1, found 162.2.



Synthesis of (3*S*,4*R*,*E*)-*N*-benzyl-2,4-dimethyl-8-phenyloct-5-en-3-amine (37): To a solution of imine **21** (145 mg, 0.90 mmol) and Ti(O*i*-Pr)$_4$ (266 μL, 256 mg, 0.90 mmol) in Et_2O (6.0 mL) at –78 °C was added dropwise *n*-C_4H_9MgCl (2.02 M in Et_2O, 2.40 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for 1.5 h. A solution of lithium alkoxide **(*R*)-32** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (85% ee by Mosher's ester, 53 mg, 0.30 mmol) with *n*-BuLi (2.39 M in hexane, 0.33 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes) to afford homoallylic amines **37** (d.r. ≥ 20:1, *E*:*Z* ≥ 20:1, ee = 85% by Mosher's amide, 46 mg, 48%,) as a pale yellow oil. No evidence for minor isomer was observed by ^{1}H NMR. The absolute stereochemistry was assigned based on a mechanistic course that follows *syn*-carbometalation and *syn*-elimination. The olefin geometry was assigned by analogy based on the cross-coupling of **(*R*)-32** with aryl and alkyl imines. ^{1}H NMR (400 MHz,

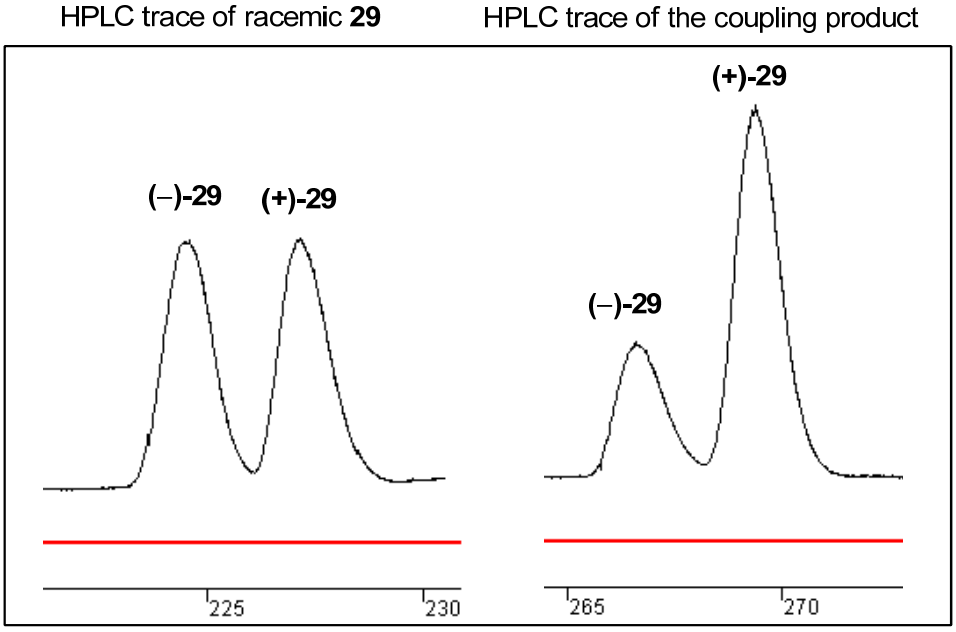
$CDCl_3$) δ 7.39-7.09 (m, 10H), 5.50-5.33 (m, 2H), 3.74 (s, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.35-2.22 (m, 3H), 2.07 (dd, *J* = 5.5, 5.5 Hz, 1H), 1.78-1.66 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 141.7, 134.6, 129.7, 128.7, 128.5, 128.4, 127.0, 125.9, 67.8, 55.7, 40.3, 36.3, 34.8, 31.0, 21.0, 19.1, 18.3; IR (thin film, NaCl) ν_{max} 3340, 3086, 3063, 3027, 2958, 2871, 1943, 1803, 1604, 1495, 1454, 1381, 974, 745, 698 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{23}H_{31}N$ $[M + H]^+$ 322.3, found 322.4; $[\alpha]_D^{20}$ –4.3 (*c* 0.44, $CHCl_3$).

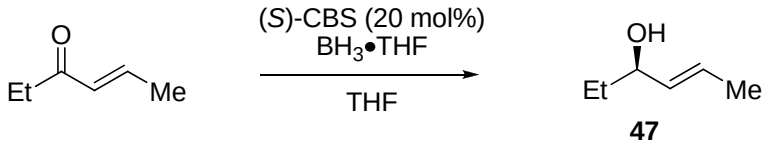


Synthesis of (*Z*)-*N*-benzyl-3-methyl-1,6-diphenylhex-3-en-1-amine (29): To a solution of imine **14** (108 μL, 117 mg, 0.60 mmol) and Ti(O*i*-Pr)$_4$ (266 μL, 256 mg, 0.90 mmol) in Et_2O (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 1.8 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for 1 h. A solution of lithium alkoxide **(*R*)-28** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (80% ee by Mosher's ester, 53 mg, 0.30 mmol) with *n*-BuLi (2.07 M in hexane, 0.33 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to afford homoallylic amines **29** (*E*:*Z* ≥ 20:1, ee = 46%, 80 mg, 75%) as a colorless oil. No evidence for minor isomer was observed by ^{1}H NMR. The absolute stereochemistry of the major product was not assigned. The spectral data correspond to that of previously reported racemic material.[7]

$[\alpha]_D^{20}$ +15.0 (*c* 0.10, Et_2O).

HPLC analysis of the product: CHIRALPAK IA column; solvent system: 0.1% EtOAc in hexanes; flow rate: 1.0 mL/min; retention times: 19.8 min for **(–)-29**, 22.1 min for **(+)-29.**

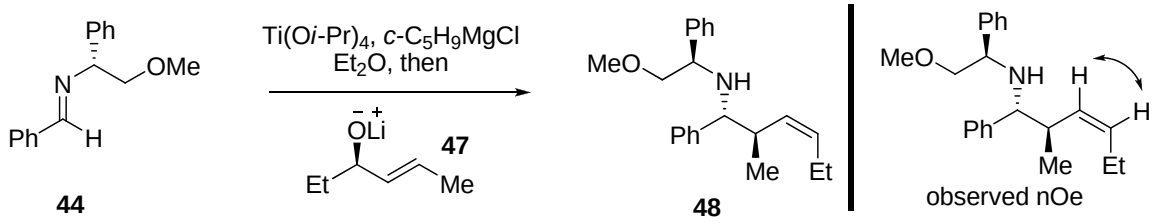




47

Synthesis of (*R*,*E*)-hex-4-en-3-ol (47): To a solution of (*S*)-Corey-Bakshi-Shibata (CBS) catalyst (554 mg, 2.0 mmol) in THF (100 mL) was added BH_3•THF (1.0 M in THF, 11 mmol). The resultant solution was stirred rapidly at ambient temperature for 1 h. The reaction was then cooled down to –40 °C, and a solution of (*E*)-hex-4-en-3-one (981 mg, 10 mmol) in THF (20 mL) was added slowly via cannula over 3 h. After stirring at the same temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl and allowed to warm up to ambient temperature. The reaction was diluted with Et_2O (200 mL) and washed with saturated aqueous NH_4Cl. The combined NH_4Cl washes were back extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **47** (93% ee by Mosher's ester, 788 mg, 79%) as a colorless oil. ^1H NMR (400 MHz,

$CDCl_3$) δ 5.66 (dq, *J* = 15.2, 7.5 Hz, 1H), 5.48 (dd, *J* = 15.2, 7.0 Hz, 1H), 3.97 (app q, *J* = 6.6 Hz, 1H), 1.70 (d, *J* = 5.6 Hz, 3H), 1.63-1.43 (m, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 127.1, 74.7, 30.3, 17.9, 10.0; IR (thin film, NaCl) ν_{max} 3351 (br), 2964, 2935, 2877, 1673, 1454, 1377, 1328, 1074, 1008, 964, 921, 885, 779 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_6H_{11}O$ $[M - H]^+$ 99.0810, found 99.0806; $[\alpha]_D^{20}$ +4.0 (*c* 0.32, $CHCl_3$), (Lit[13] $[\alpha]_D^{20}$ +2.1 (*c* 0.85, $CHCl_3$)).

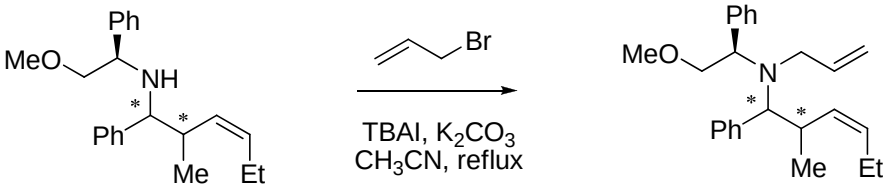


Synthesis of (1*R*,2*R*,*Z*)-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (48): To a solution of imine **44** (239 mg, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **47** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (50 mg, 0.5 mmol) with *n*-BuLi (2.54 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (3% EtOAc/hexane) to afford homoallylic amine **48** (d.r. ≥ 20:1, *Z*:*E* ≥ 20:1, 126 mg, 78%) as a pale yellow oil. No evidence for minor isomer was observed by ^{1}H NMR. See **48→S-1→S-2** for the assignment of absolute stereochemistry. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-6.96 (m, 10H), 5.45 (app dt, *J* = 10.8, 7.3 Hz, 1H), 5.13 (dd, *J* = 10.8, 10.8 Hz, 1H), 3.67 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.44-3.34 (m, 2H), 3.28 (d, *J* = 8.5 Hz, 1H), 3.26 (s, 3H), 2.72-2.60 (m, 1H), 2.35 (br, 1H), 2.08-1.97 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5,

142.2, 133.3, 133.1, 128.7, 128.0, 127.8, 127.8, 126.8, 126.7, 76.6, 67.5, 61.0, 59.1, 38.8, 21.2, 18.1, 14.6; IR (thin film, NaCl) ν_{max} 3320, 3063, 2962, 2874, 2823, 1946, 1806, 1602, 1493, 1455, 1194, 1110, 757, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2327, found 324.2317; $[\alpha]_D^{20}$ +19.8 (*c* 0.69, $CHCl_3$).

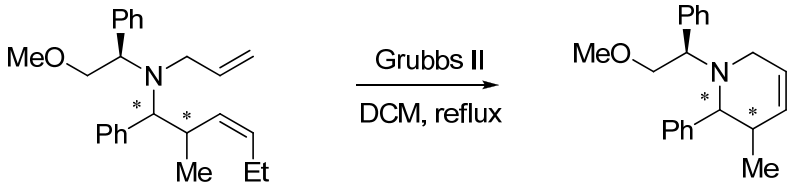
Structure proof: While the absolute stereochemistry of the phenylglycine auxiliary was known, the relative stereochemistry of the homoallylic amine with respect to the auxiliary was assigned based on the following experiments and analyses.

I. Conversion of homoallylic amine to piperidine.



48 **S-1**

Synthesis of (1*R*,2*R*,*Z*)-*N*-allyl-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (S-1): To a solution of homoallylic amine **48** (37.6 mg, 0.116 mmol) in CH_3CN (0.5 mL) was added allyl bromide (140 mg, 98 μL, 1.16 mmol), tetrabutylammonium iodide (86 mg, 0.232 mmol), and potassium carbonate (160 mg, 1.16 mmol). The resultant mixture was refluxed for 24 h. After cooling down to ambient temperature, the reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford **S-1** (17.9 mg, 43%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.15 (m, 10H), 5.91-5.77 (m, 1H), 5.28 (app dt, *J* = 11.3, 7.2 Hz, 1H), 5.20-5.08 (m, 3H), 4.19 (dd, *J* = 8.2, 3.6 Hz, 1H), 3.49 (d, *J* = 10.3 Hz, 1H), 3.47-3.40 (m, 1H), 3.33 (dd, *J* = 9.5, 8.4 Hz, 1H), 3.23-3.08 (m, 2H), 3.06 (s, 3H), 3.03 (dd, *J* = 9.5, 3.7 Hz, 1H), 2.10-1.87 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.8, 139.1, 138.1, 128.6, 127.9, 126.7, 116.8, 72.5, 67.4, 59.7, 58.7; IR (thin film, NaCl) ν_{max} 3062, 3003, 2963, 2926, 2809, 1948, 1810, 1639, 1600, 1493, 1454, 1108, 917, 701 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{25}H_{34}NO$ $[M + H]^+$ 364.2640, found 364.2639; $[\alpha]_D^{20}$ –7.6 (*c* 0.43, $CHCl_3$).

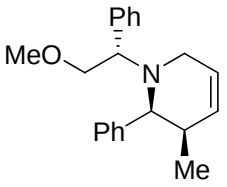


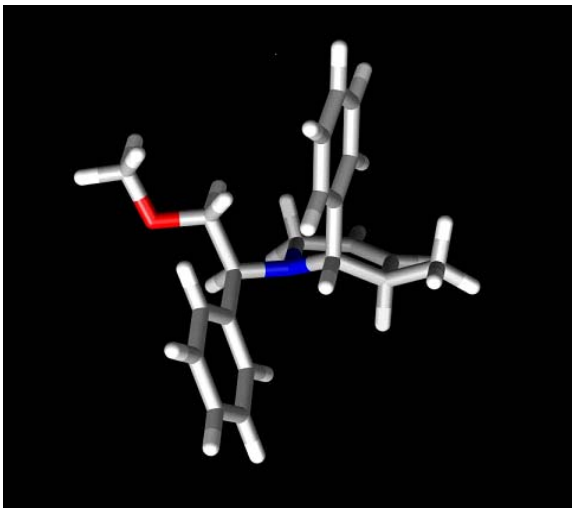
S-1 **S-2**

Synthesis of (2*R*,3*R*)-1-((*R*)-2-methoxy-1-phenylethyl)-3-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (S-2): To a solution of **S-1** (49.5 mg, 0.136 mmol) in DCM (7.0 mL) was added Grubbs II catalyst (2.3 mg, 0.003 mmol). The resultant mixture was refluxed for 10 h. After cooling down to ambient temperature, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford piperidine **S-2** (25.6 mg, 61%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.10 (m, 10H), 5.68-5.57 (m, 2H), 3.94 (app t, *J* = 6.4 Hz, 1H), 3.82 (app s, 1H), 3.81 (d, *J* = 1.2 Hz, 1H), 3.58 (d, *J* = 8.0 Hz, 1H), 3.22 (s, 3H), 3.22-3.14 (m, 1H), 3.10-3.01 (m, 1H), 2.55-2.45 (m, 1H), 0.79 (d, *J* = 7.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.3, 131.1, 129.2, 128.6, 128.3, 128.2, 127.5, 126.7, 124.6, 70.1, 69.6, 59.4, 59.1, 45.4, 39.8, 19.0; IR (thin film, NaCl) ν_{max} 3062, 3030, 2926, 1660, 1651, 1602, 1494, 1454, 1258, 1197, 1113, 761, 700 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{21}H_{26}NO$ $[M + H]^+$ 308.2014, found 308.2012; $[\alpha]_D^{20}$ –55.0 (*c* 0.14, $CHCl_3$).

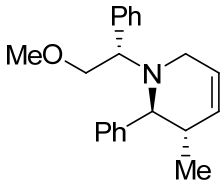
II. Assignment of the relative stereochemistry of the piperidines began with conformational analysis. The lowest energy conformers of three possible piperidine diastereomers were calculated using AM1 stochastic search with BOSS v. 4.6.[14]

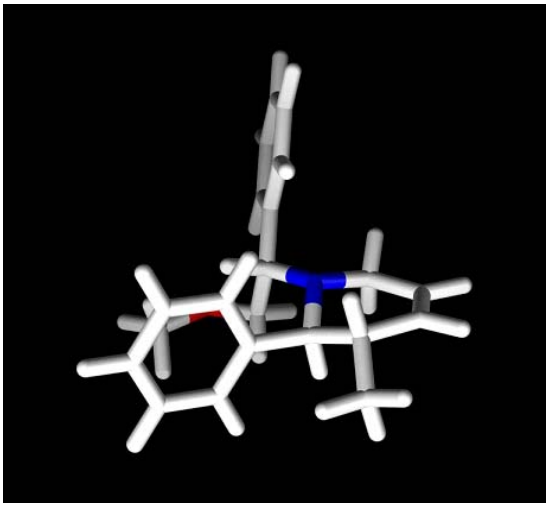
A.



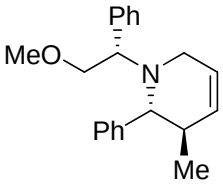


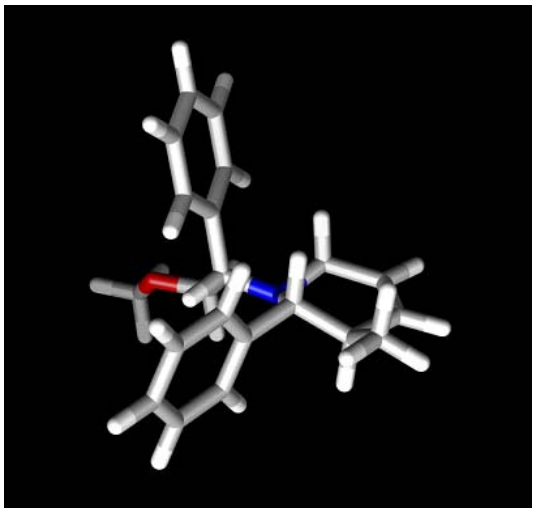
B.



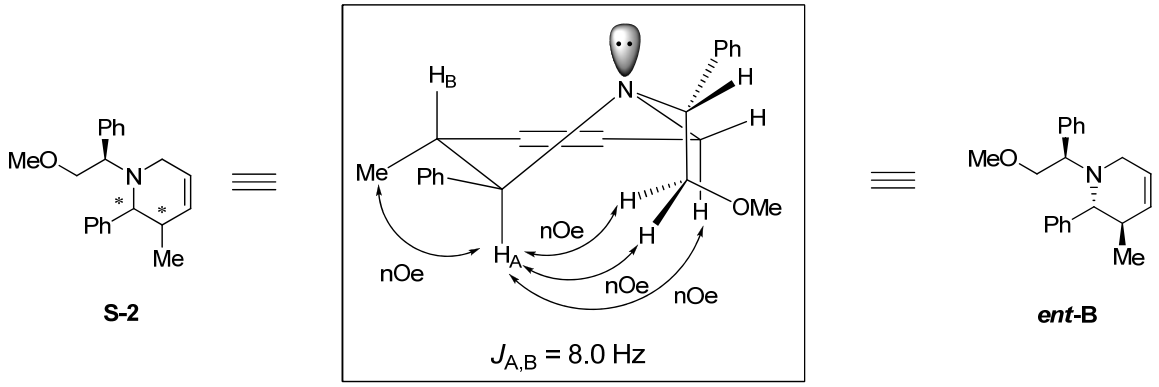


C.

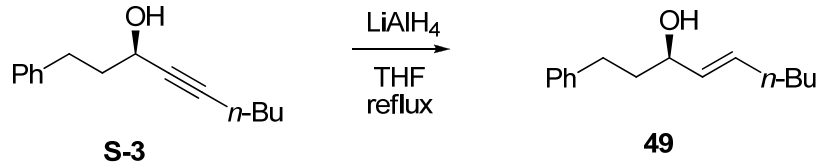




III. [1]H NMR and nOe data were used to assign the stereochemistry of each piperidine.

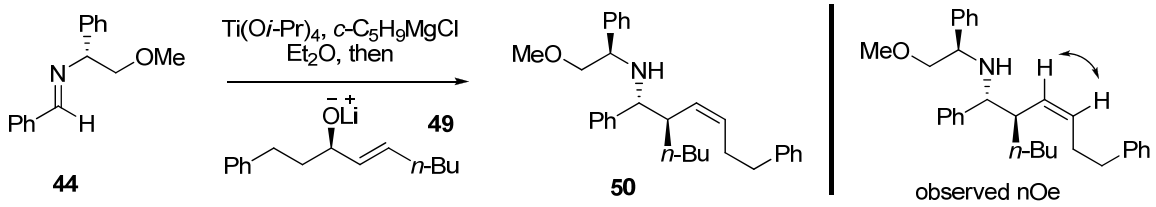


The [1]H NMR and nOe data of **S-2** are most consistent with the conformation shown for ***ent*-B**. Thus, the stereochemistry of the corresponding homoallylic amine was assigned as shown for **48**.



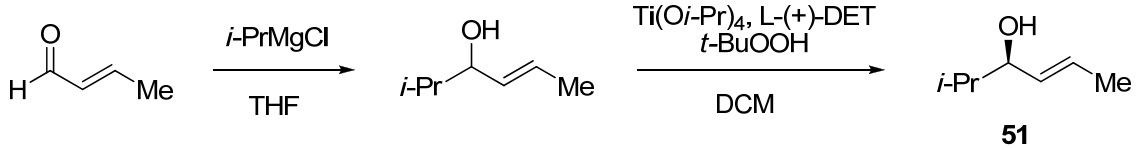
Synthesis of (*R*,*E*)-1-phenylnon-4-en-3-ol (49): To a stirred suspension of lithium aluminum hydride (57 mg, 1.5 mmol) in THF (6.5 mL) at –20 °C was added dropwise a solution of propargylic alcohol **S-3** (560 mg, 2.5 mmol) in THF (2.0 mL) via cannula. After warming up to ambient temperature, the reaction was refluxed overnight. Then the reaction was cooled down and quenched successively with H_2O (0.1 mL), 10 wt% aqueous NaOH (0.1 mL), and H_2O (0.3 mL). The resultant mixture was stirred until it became milky white, and then filtered through a pad of Celite and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10→15% EtOAc/Hexane) to afford allylic alcohol **49** (91% ee by Mosher's ester) as a pale yellow oil in quantitative yield. [1]H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 3H), 7.22-7.16 (m, 2H), 5.66 (app dt, *J* = 15.5, 7.0 Hz, 1H), 5.49 (dd, *J* = 15.5, 7.0 Hz, 1H), 4.12-4.03 (m, 1H), 2.76-2.61 (m, 2H), 2.04 (app q, *J* = 6.8 Hz, 2H), 1.94-1.75 (m, 2H), 1.42-1.25 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H); [13]C NMR (100 MHz, $CDCl_3$) δ 142.3, 132.9, 132.8, 128.7, 128.6, 126.0, 72.7, 39.1, 32.1, 32.0, 31.5, 22.4, 14.1; IR (thin film, NaCl) ν_{max} 3350 (br), 3086, 3063, 3027, 2924, 2858, 1941, 1869, 1801, 1603, 1495, 1454, 1378, 1055, 970 cm^{-}

[1]; HRMS (EI, H) *m/z* calc'd for $C_{15}H_{22}O$ $[M]^+$ 218.1671, found 218.1661; $[\alpha]_D^{20}$ +9.0 (*c* 0.30, $CHCl_3$), (Lit[15] $[\alpha]_D^{20}$ +6.1 (*c* 0.95, $CHCl_3$), 64 % ee).



Synthesis of (3*S*,4*R*,*Z*)-*N*-((*R*)-2-methoxy-1-phenylethyl)-4-methyl-1-phenyldec-5-en-3-amine (50): To a solution of imine **44** (239 mg, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4.0 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **49** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (109 mg, 0.5 mmol) with *n*-BuLi (2.07 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (3→4% EtOAc/hexane) to afford homoallylic amine **50** (d.r. ≥ 20:1, *Z*:*E* ≥ 20:1, 184 mg, 83%) as a pale yellow oil. No evidence for minor isomer was observed by crude ^{1}H NMR. A small amount of inseparable mixture of two *E*-isomers (8.0 mg, 4%) with trace impurity was also isolated. The stereochemistry was assigned by analogy based on the cross-coupling of imine **44** with allylic alcohol **47**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 2H), 7.21-7.04 (m, 13H), 5.62 (app dt, *J* = 10.9, 7.3 Hz, 1H), 5.17 (dd, *J* = 10.9, 10.9 Hz, 1H), 3.72 (dd, *J* = 6.5, 5.0 Hz, 1H), 3.51-3.40 (m, 3H), 3.32 (s, 3H), 2.67-2.54 (m, 3H), 2.44-2.25 (m, 3H), 1.29-0.93 (m, 6H), 0.75 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 142.3, 132.7, 132.0, 128.7, 128.6, 128.5, 128.0, 127.8, 126.8, 126.6, 126.0, 76.7, 66.2, 60.9, 59.1, 44.6, 36.2, 30.0, 29.8, 22.9, 14.3; IR (thin film, NaCl) ν_{max} 3319, 3085, 3062, 3027, 2928, 2857, 1944, 1603,

1494, 1454, 1378, 1194, 1108, 739, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{31}H_{40}NO$ $[M + H]^+$ 442.3110, found 442.3105; $[\alpha]_D^{20}$ –6.0 (*c* 0.38, $CHCl_3$).

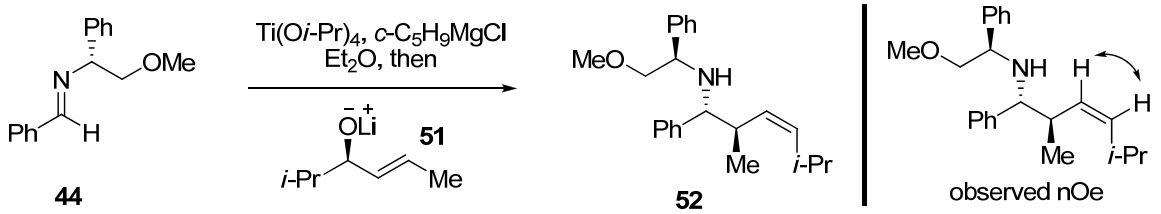


51

Synthesis of (*R,E*)-2-methylhex-4-en-3-ol (51): To a solution of *trans*-crotonaldehyde (1.75 g, 25 mmol) in THF (50 mL) at 0 °C was added slowly *i*-PrMgCl (2.0 M in THF, 27.5 mmol) via a gas-tight syringe. The reaction was allowed to warm up to ambient temperature and stirred for one additional hour. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (7% EtOAc/hexane) to afford the racemic allylic alcohol as a colorless oil (1.47 g, 52%).

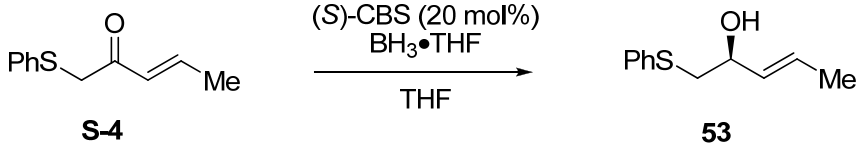
A flame-dried 25-mL RBF was charged with Ti(O*i*-Pr)$_4$ (1.48 mL, 5.0 mmol), L-diethyl tartrate (1.03 mL, 6.0 mmol), powdered 4 Å molecular sieves, and dichloromethane (3.5 mL). The mixture was stirred at –5 °C for 30 min. Then *t*-BuOOH (6.0 M in decane, 3.0 mmol) was added. After additional 10 min, the racemic allylic alcohol (571 mg, 5.0 mmol) was added via a syringe. The resultant mixture was stirred at –5 °C for 3 h. Then the reaction mixture was poured into a stirred solution of iron (II) sulfate heptahydrate (3.5 g) and tartaric acid (1.5 g) in H_2O (11 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were stirred with NaOH (1.5 g) in brine (5 mL) at 0 °C for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford allylic alcohol **51** as a colorless oil (95% ee by Mosher's ester). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dq, *J* = 16.2, 6.4 Hz, 1H), 5.48 (dd, *J* = 16.2, 6.7 Hz, 1H), 3.77 (appd. t, *J* = 6.7 Hz, 1H), 1.75-1.63 (m, 4H), 1.48-1.38 (br, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 127.9, 78.5, 34.0, 18.4, 18.3, 18.0; IR (thin film, NaCl) ν_{max} 3369 (br), 2960, 2874, 1714, 1672, 1469, 1448, 1379, 1331, 1262, 1148, 1074, 1014,

967, 928 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_7H_{13}O$ $[M - H]^+$ 113.0967, found 113.0965; $[\alpha]_D^{20}$ –11.3 (*c* 0.30, $CHCl_3$), (Lit[16] $[\alpha]_D^{20}$ –8.39 (*c* 0.41, $CHCl_3$)).



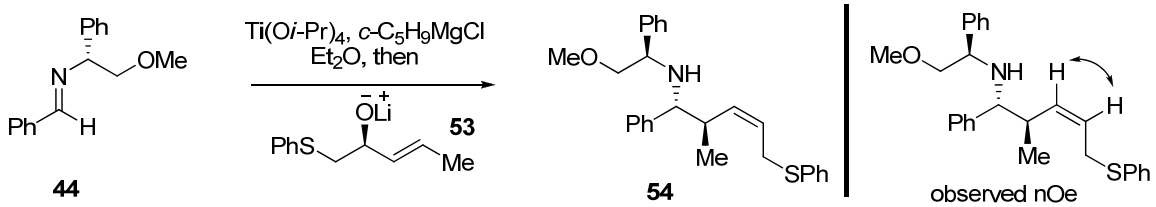
Synthesis of (1*R*,2*R*,*Z*)-*N*-((*R*)-2-methoxy-1-phenylethyl)-2,5-dimethyl-1-phenylhex-3-en-1-amine (52): To a solution of imine **44** (239 mg, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4.0 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **51** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (48 mg, 0.42 mmol) with *n*-BuLi (2.07 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (3% EtOAc/hexane) to afford homoallylic amine **52** (d.r. ≥ 20:1, *Z*:*E* = 13:1, 101 mg, 71%) as a pale yellow oil. A small amount of inseparable mixture of two *E*-isomers (7.7 mg, 5%) with trace impurity was also isolated. The stereochemistry was assigned by analogy based on the cross-coupling of imine **44** with allylic alcohol **47**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.02 (m, 10H), 5.33 (dd, *J* = 10.6, 10.6 Hz, 1H), 5.10 (dd, *J* = 10.6, 10.6 Hz, 1H), 3.75 (dd, *J* = 6.9, 4.7 Hz, 1H), 3.52-3.40 (m, 2H), 3.34 (d, *J* = 8.3 Hz, 1H), 3.33 (s, 3H), 2.79-2.59 (m, 2H), 2.44 (br, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.2, 139.1, 131.2, 128.7, 127.9, 127.8, 127.8, 126.8, 126.6, 76.7, 67.6, 61.2, 59.0, 39.1, 27.2, 23.4, 18.3; IR (thin film, NaCl) ν_{max} 3319, 3063, 2958, 2871, 1945, 1740, 1463, 1455,

1195, 1110, 757, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{23}H_{32}NO$ $[M + H]^+$ 338.2484, found 338.2479; $[\alpha]_D^{20}$ +23.7 (*c* 0.16, $CHCl_3$).



S-4 **53**

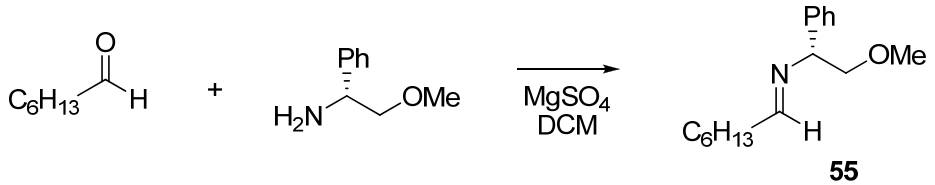
Synthesis of (*S*,*E*)-1-(phenylthio)pent-3-en-2-ol (53): To a solution of (*S*)-Corey-Bakshi-Shibata (CBS) catalyst (559 mg, 2.02 mmol) in THF (100 mL) was added BH_3•THF (1.0 M in THF, 11.1 mmol). The resultant solution was stirred rapidly at ambient temperature for 1 h. The reaction was then cooled down to –40 °C, and a solution of ketone **S-4** (1.94 g, 10.1 mmol) in THF (20 mL) was added slowly via cannula over 3 h. After stirring at the same temperature for 30 min, the reaction was quenched cold with saturated aqueous NH_4Cl and allowed to warm up to ambient temperature. The reaction was diluted with Et_2O (200 mL) and washed with saturated aqueous NH_4Cl. The combined NH_4Cl washes were back extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford allylic alcohol **53** (96% ee by Mosher's ester, 1.89 g, 96%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 2H), 7.33-7.17 (m, 3H), 5.74 (dq, *J* = 15.3, 6.4 Hz, 1H), 5.49 (dd, *J* = 15.3, 6.8 Hz, 1H), 4.19-4.10 (m, 1H), 3.14 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.95 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.40 (s, 1H), 1.69 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 131.7, 130.3, 129.3, 128.7, 126.8, 70.6, 42.3, 17.9; IR (thin film, NaCl) ν_{max} 3391 (br), 3058, 2963, 2917, 2855, 1673, 1584, 1480, 1439, 1371, 1088, 1025, 965, 739, 691 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{11}H_{14}OS$ $[M]^+$ 194.0765, found 194.0751; $[\alpha]_D^{20}$ +5.2 (*c* 0.82, $CHCl_3$).



44 **54**

Synthesis of (1*R*,2*R*,*Z*)-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenyl-5-(phenylthio)pent-3-en-1-amine (54): To a solution of imine **44** (239 mg, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4.0 mL) at –78 °C was added dropwise

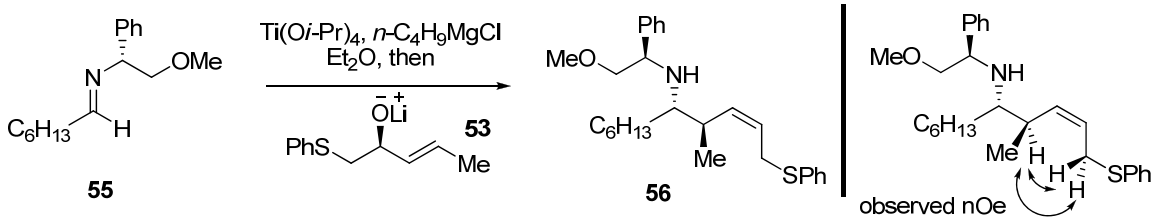
c-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **53** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (97 mg, 0.5 mmol) with *n*-BuLi (2.54 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (3→5% EtOAc/Hexane) to afford homoallylic amine **54** (d.r. ≥ 20:1, *Z*:*E* ≥ 20:1, 182 mg, 87%) as a pale yellow oil. No evidence for minor isomer was observed by ^1H NMR. The stereochemistry was assigned by analogy based on the cross-coupling of imine **44** with allylic alcohol **47.** ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (app d, *J* = 7.6 Hz, 2H), 7.28 (app d, *J* = 7.5 Hz, 2H), 7.23-7.10 (m, 11H), 5.66 (app dt, *J* = 10.5, 7.6 Hz, 1H), 5.39 (dd, *J* = 10.5, 10.5 Hz, 1H), 3.77 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.68 (dd, *J* = 13.3, 8.5 Hz, 1H), 3.55-3.44 (m, 4H), 3.36 (s, 3H), 2.78-2.67 (m, 1H), 2.32 (br, 1H), 0.71 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 142.1, 137.1, 136.6, 130.1, 128.1, 127.9, 127.8, 127.0, 126.9, 126.4, 126.1, 76.7, 66.9, 60.7, 59.1, 38.9, 31.7, 17.6; IR (thin film, NaCl) ν_{max} 3320, 3060, 3025, 2961, 2823, 1947, 1601, 1584, 1479, 1453, 1193, 1102, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{27}H_{32}NOS$ $[M + H]^+$ 418.2205, found 418.2202; $[\alpha]_D^{20}$ – 66.6 (*c* 0.21, $CHCl_3$).



55

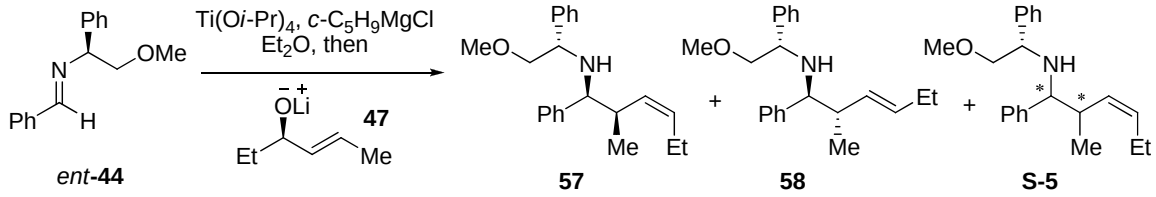
Synthesis of (*R*,*E*)-*N*-heptylidene-2-methoxy-1-phenylethanamine (55): To a suspension of anhydrous $MgSO_4$ in DCM (10 mL) was added successively heptanal (1.40 mL, 1.14 g, 10 mmol) and (*R*)-2-methoxy-1-phenylethanamine (1.51 g, 10 mmol) via

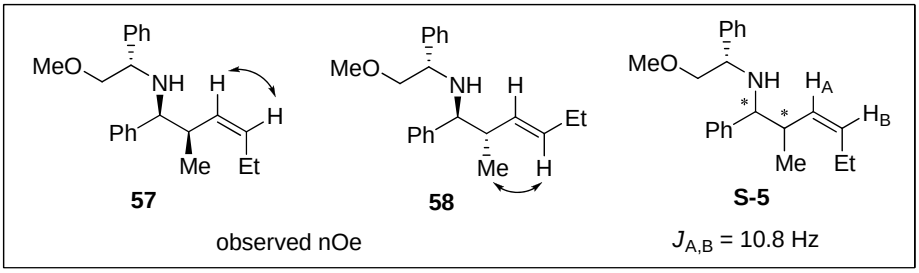
syringe. The reaction was stirred at ambient temperature and monitored by NMR. Upon completion, the mixture was filtered and concentrated *in vacuo* to afford imine **55** as a colorless oil. The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 5.1 Hz, 1H), 7.40-7.29 (m, 4H), 7.28-7.22 (m, 1H), 4.29 (dd, *J* = 8.4, 4.6 Hz, 1H), 3.69-3.58 (m, 2H), 3.35 (s, 3H), 2.35-2.27 (m, 2H), 1.58-1.47 (m, 2H), 1.37-1.24 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 141.3, 128.6, 127.4, 77.5, 59.1, 36.1, 31.8, 29.0, 26.2, 22.7, 14.2; IR (thin film, NaCl) ν_{max} 3318, 3063, 3029, 2925, 2856, 1668, 1603, 1493, 1454, 1380, 1196, 1119, 758, 700 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{16}H_{26}NO$ $[M + H]^+$ 248.2, found 248.3.



Synthesis of (4*R*,5*S*,*Z*)-*N*-((*R*)-2-methoxy-1-phenylethyl)-4-methyl-1-(phenylthio) undec-2-en-5-amine (56): To a solution of imine **55** (223 mg, 0.90 mmol) and Ti(O*i*-Pr)$_4$ (4266 μL, 256 mg, 0.9 mmol) in Et_2O (5.0 mL) at –78 °C was added dropwise *n*-C_4H_9MgCl (2.02 M in Et_2O, 1.8 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **53** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (58 mg, 0.30 mmol) with *n*-BuLi (2.54 M in hexane, 0.33 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (2→3% EtOAc/Hexane) to afford homoallylic amine **56** (d.r. ≥ 20:1, *Z*:*E* ≥ 20:1, 76 mg, 60%) as a pale yellow oil. No evidence for minor isomer was observed by ^{1}H NMR. The stereochemistry was assigned by analogy based on the cross-coupling of imine **44** with

allylic alcohol **47.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.12 (m, 10H), 5.45-5.31 (m, 2H), 4.01 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.43-3.31 (m, 6H), 3.20 (dd, *J* = 13.1, 5.4 Hz, 1H), 2.80-2.70 (m, 1H), 2.31-2.23 (m, 1H), 1.74 (br, 1H), 1.47-1.38 (m, 1H), 1.29-1.03 (m, 9H), 0.89-0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.8, 136.7, 130.0, 128.9, 128.5, 128.1, 127.6, 126.3, 124.4, 78.5, 59.7, 59.0, 58.5, 32.5, 32.1, 31.2, 30.8, 29.7, 26.5, 22.9, 14.3, 14.1; IR (thin film, NaCl) ν_{max} 3344, 3062, 3023, 2927, 2873, 1689, 1640, 1585, 1480, 1455, 1378, 1194, 1115, 737, 701 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{27}H_{40}NOS$ $[M + H]^+$ 426.3, found 426.4; $[\alpha]_D^{20}$ –95.2 (*c* 0.80, $CHCl_3$).

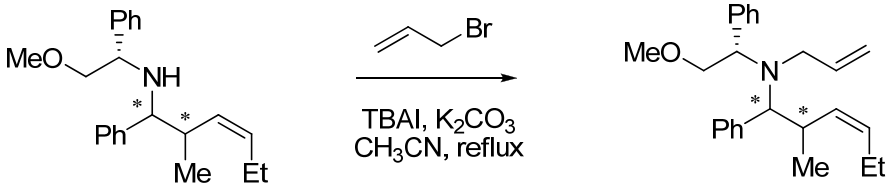




Synthesis of (1*S*,2*R*,*Z*)-*N*-((*S*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (57) and (1*S*,2*S*,*E*)-*N*-((*S*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (58): To a solution of imine *ent*-**44** (239 mg, 1.0 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4.0 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **47** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (50 mg, 0.5 mmol) with *n*-BuLi (2.54 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated

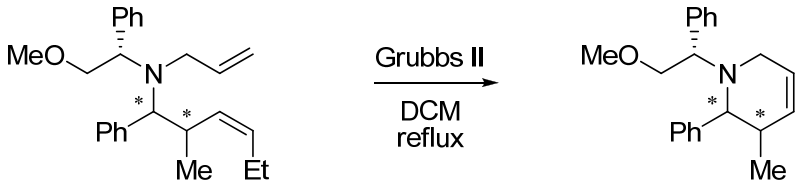
aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (3% EtOAc/Hexane) to afford an isomeric mixture of homoallylic amines (**57**:**58**:**S-5** = 2.3:1:0.3, 133 mg, 82%) as a pale yellow oil. The isomeric ratio was determined by the integration of methyl signals (doublet) at 0.95 ppm (**57**), 0.72 ppm (**58**) and 0.67 ppm (**S-5**). The mixture was subjected to semi-preparative HPLC purifications to isolate pure isomers **57** and **58**. Attempted isolation of pure isomer **S-5** was not successful. Its olefin geometry was determined based on the coupling constant (J = 10.8 Hz) of the vinylogous protons. Data for **57:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.07 (m, 10H), 5.27 (app dt, J = 11.3, 7.3 Hz, 1H), 5.02, (dd, J = 11.3, 11.3 Hz, 1H), 3.83 (app t, J = 6.3 Hz, 1H), 3.58 (d, J = 6.0 Hz, 1H), 3.54-3.44 (m, 2H), 3.31 (s, 3H), 2.94-2.80 (m, 1H), 2.18 (br, 1H), 2.08-1.89 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.4, 132.2, 131.5, 128.4, 128.3, 127.8, 127.7, 127.2, 126.6, 77.4, 66.0, 60.7, 59.2, 37.7, 21.2, 18.5, 14.6; IR (thin film, NaCl) ν_{max} 3351, 3062, 3027, 2962, 2929, 2875, 1602, 1493, 1454, 1194, 1110, 757, 699 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2327, found 324.2317; $[\alpha]_D^{20}$ –8.8 (*c* 0.61, $CHCl_3$). Data for **58**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-6.98 (m, 10H), 5.65 (app dt, J = 15.3, 6.7 Hz, 1H), 5.31 (dd, J = 15.3, 8.8 Hz, 1H), 3.73 (dd, J = 6.7, 5.0 Hz, 1H), 3.48-3.42 (m, 2H), 3.33 (s, 3H), 3.32 (d, J = 8.7 Hz, 1H), 2.55 (br, 1H), 2.41-2.30 (m, 1H), 2.12-2.02 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 142.2, 134.0, 132.9, 128.6, 127.9, 127.8, 127.7, 126.8, 126.6, 76.6, 67.7, 61.6, 59.0, 44.4, 25.9, 18.3, 14.1; IR (thin film, NaCl) ν_{max} 3322, 3063, 3027, 2963, 2927, 2874, 1602, 1494, 1454, 1194, 1107, 757, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2327, found 324.2321; $[\alpha]_D^{20}$ –43.8 (*c* 0.29, $CHCl_3$).

Structure proof: The stereochemistry of homoallylic amines **57** and **58** were assigned in the same manner as done for homoallylic amine **48**.



57 **S-6**

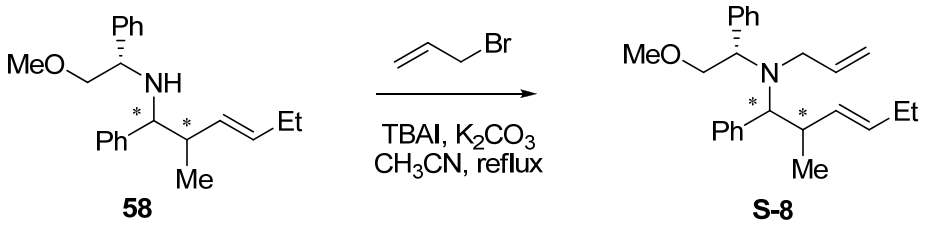
Synthesis of (1*S*,2*R*,*Z*)-*N*-allyl-*N*-((*S*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (S-6): To a solution of homoallylic amine **57** (46.3 mg, 0.143 mmol) in CH_3CN (1.0 mL) was added allyl bromide (346 mg, 242 μL, 2.86 mmol), tetrabutylammonium iodide (106 mg, 0.286 mmol), and potassium carbonate (198 mg, 1.43 mmol). The resultant mixture was refluxed for 24 h. After cooling down to ambient temperature, the reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford **S-6** (30.9 mg, 60%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (app d, *J* = 7.3 Hz, 2H), 7.36-7.16 (m, 8H), 5.96-5.82 (m, 1H), 5.24-5.13 (m, 2H), 4.99 (app dt, *J* = 10.8, 7.2 Hz, 1H), 4.82 (dd, *J* = 10.8, 10.8 Hz, 1H), 4.24 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.53-3.45 (m, 2H), 3.34-3.08 (m, 3H), 3.04 (s, 3H), 2.94 (dd, *J* = 9.5, 3.7 Hz, 1H), 2.04-1.81 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.4, 138.6, 130.4, 128.3, 127.9, 126.8, 117.1, 72.9, 66.9, 59.8, 58.7, 50.2, 30.1 (residual acetone), 24.1, 21.1, 20.1, 14.3; IR (thin film, NaCl) ν_{max} 3062, 3027, 2962, 2924, 2873, 2810, 1640, 1600, 1493, 1451, 1109, 916, 701 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{25}H_{34}NO$ $[M + H]^+$ 364.2640, found 364.2643; $[\alpha]_D^{20}$ –97.2 (*c* 0.11, $CHCl_3$).



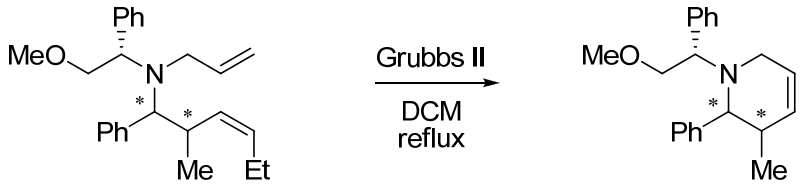
S-6 **S-7**

Synthesis of (2*S*,3*S*)-1-((*S*)-2-methoxy-1-phenylethyl)-3-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (S-7): To a solution of **S-6** (11.9 mg, 0.033 mmol) in DCM (3.3 mL) was added Grubbs II catalyst (2.8 mg, 0.003 mmol). The resultant mixture was refluxed for 10 h. After cooling down to ambient temperature, the solvent was removed *in vacuo*,

and the residue was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford piperidine **S-7** (9.5 mg, 94%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.14 (m, 10H), 5.72-5.61 (m, 2H), 4.15 (d, *J* = 5.9 Hz, 1H), 3.79-3.63 (m, 3H), 3.21 (s, 3H), 3.18-2.96 (m, 2H), 2.94-2.82 (m, 1H), 0.73 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.6, 130.8, 130.4, 128.7, 128.3, 128.1, 127.2, 127.1, 125.4, 74.2, 64.4, 63.3, 59.1, 46.6, 34.7, 17.7; IR (thin film, NaCl) ν_{max} 3085, 3060, 3026, 2962, 2927, 2873, 2807, 1951, 1601, 1493, 1453, 1190, 1113, 765, 702 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{21}H_{26}NO$ $[M + H]^+$ 308.2014, found 308.2017; $[\alpha]_D^{20}$ –21.1 (*c* 0.17, $CHCl_3$).

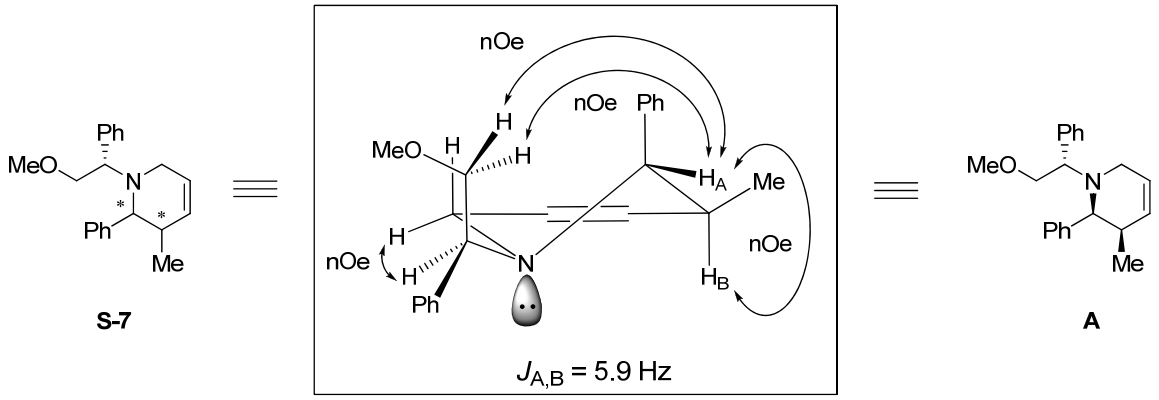


Synthesis of (1*S*,2*S*,*E*)-*N*-allyl-*N*-((*S*)-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (S-8): To a solution of homoallylic amine **58** (14.7 mg, 0.045 mmol) in CH_3CN (0.5 mL) was added allyl bromide (109 mg, 76 μL, 0.90 mmol), tetrabutylammonium iodide (33 mg, 0.090 mmol), and potassium carbonate (62 mg, 0.45 mmol). The resultant mixture was refluxed for 24 h. After cooling down to ambient temperature, the reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford **S-8** (9.6 mg, 59%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (app d, *J* = 7.9 Hz, 2H), 7.36-7.17 (m, 8H), 5.91-5.77 (m, 1H), 5.40-5.21 (m, 2H), 5.21-5.07 (m, 2H), 4.21 (dd, *J* = 8.3, 3.7 Hz, 1H), 3.53-3.45 (m, 1H), 3.45 (d, *J* = 10.4 Hz, 1H), 3.35 (app t, *J* = 8.3 Hz, 1H), 3.21 (dd, *J* = 14.4, 8.5 Hz, 1H), 3.06 (s, 3H), 3.06-3.01 (m, 1H), 2.82-2.70 (m, 1H), 2.04-1.95 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.9, 138.9, 134.5, 128.6, 127.9, 126.6, 116.9, 72.6, 67.3, 59.6, 58.6, 50.1, 39.4, 30.1 (residual acetone), 25.8, 19.6, 13.9; IR (thin film, NaCl) ν_{max} 3062, 3027, 2962, 2919, 2873, 2850, 1640, 1493, 1452, 1249, 1109, 964, 701 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{25}H_{34}NO$ $[M + H]^+$ 364.2640, found 364.2631; $[\alpha]_D^{20}$ +106.8 (*c* 0.44, $CHCl_3$).

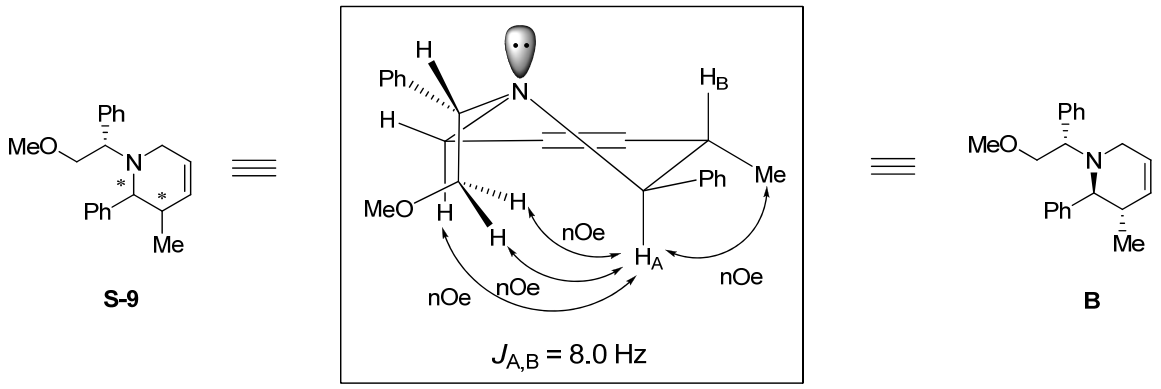


S-8 **S-9**

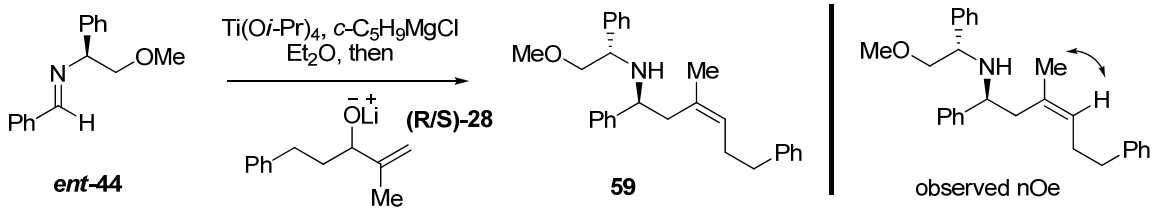
Synthesis of (2*S*,3*S*)-1-((*S*)-2-methoxy-1-phenylethyl)-3-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (S-9): To a solution of **S-8** (5.2 mg, 0.014 mmol) in DCM (1.4 mL) was added Grubbs II catalyst (1.2 mg, 0.001 mmol). The resultant mixture was refluxed for 10 h. After cooling down to ambient temperature, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (2% EtOAc/hexane) to afford piperidine **S-9** (3.8 mg, 88%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.14 (m, 10H), 5.69-5.57 (m, 2H), 3.94 (app t, J = 6.5 Hz, 1H), 3.82 (app s, 1H), 3.81 (d, J = 1.7 Hz, 1H), 3.58 (d, J = 7.9 Hz, 1H), 3.23 (s, 3H), 3.23-3.16 (m, 1H), 3.09-3.02 (m, 1H), 2.55-2.46 (m, 1H), 0.79 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.4, 131.1, 129.2, 128.6, 128.3, 128.2, 127.5, 126.8, 124.7, 70.1, 69.6, 59.4, 59.1, 45.4, 39.8, 19.1; IR (thin film, NaCl) ν_{max} 3030, 2927, 1652, 1601, 1494, 1454, 1378, 1260, 1197, 1115, 1030, 972, 701 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{21}H_{26}NO$ [M + H]$^+$ 308.2014, found 308.2011; $[\alpha]_D^{20}$ +38.8 (*c* 0.43, $CHCl_3$).



The ^{1}H NMR and nOe data of **S-7** are most consistent with the conformation shown for **A**. Thus, the stereochemistry of the corresponding homoallylic amine was assigned as shown for **57**.



The ^{1}H NMR and nOe data of **S-9** are most consistent with the conformation shown for **B**. Thus, the stereochemistry of the corresponding homoallylic amine was assigned as shown for **58**.



Synthesis of (*S*,*Z*)-N-((*S*)-2-methoxy-1-phenylethyl)-3-methyl-1,6-diphenylhex-3-en-1-amine (59): To a solution of imine ***ent*-44** (143 mg, 0.6 mmol) and Ti(O*i*-Pr)$_4$ (266 μL, 256 mg, 0.9 mmol) in Et$_2$O (2.5 mL) at –78 °C was added dropwise *c*-C$_5$H$_9$MgCl (2.0 M in Et$_2$O, 1.8 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **(R/S)-28** in Et$_2$O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (53 mg, 0.3 mmol) with *n*-BuLi (2.54 M in hexane, 0.33 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at –30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous NaHCO$_3$, and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous NaHCO$_3$ and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford homoallylic amine **59** (d.r. ≥ 20:1, *Z*:*E* ≥ 20:1, 107 mg, 89%) as a pale yellow oil. No evidence for minor isomer was observed by crude ^{1}H NMR. The stereochemistry was assigned by analogy based on the

cross-coupling of imine **44** with allylic alcohol **47.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.08 (m, 15H), 5.20 (app t, *J* = 6.6 Hz, 1H), 3.89 (dd, *J* = 7.0, 4.4 Hz, 1H), 3.78 (app t, *J* = 7.2 Hz, 1H), 3.53-3.42 (m, 2H), 3.32 (s, 3H), 2.58 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.54-2.36 (m, 2H), 2.25-2.06 (m, 4H), 1.57 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.5, 142.0, 132.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.5, 127.5, 127.2, 126.9, 125.9, 60.5, 59.5, 59.1, 40.9, 36.2, 30.0, 23.9; IR (thin film, NaCl) ν_{max} 3324, 3084, 3062, 3027, 2922, 2854, 1946, 1602, 1494, 1453, 1377, 1194, 1103, 756, 698 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{28}H_{34}NO$ $[M + H]^+$ 400.3, found 400.3; $[\alpha]_D^{20}$ –4.3 (*c* 0.23, $CHCl_3$).

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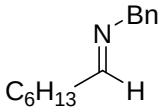

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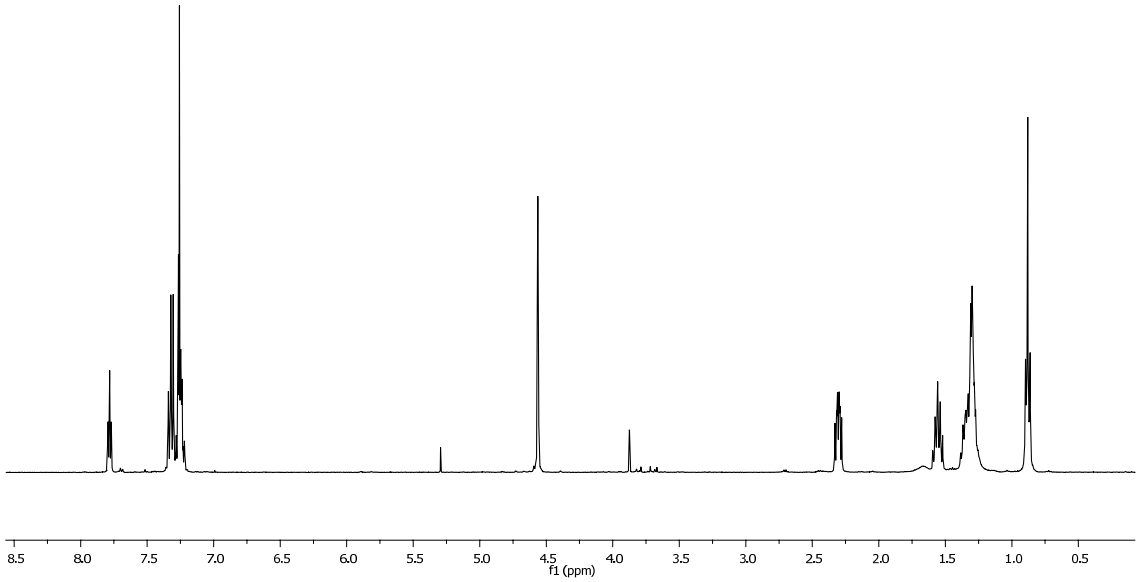
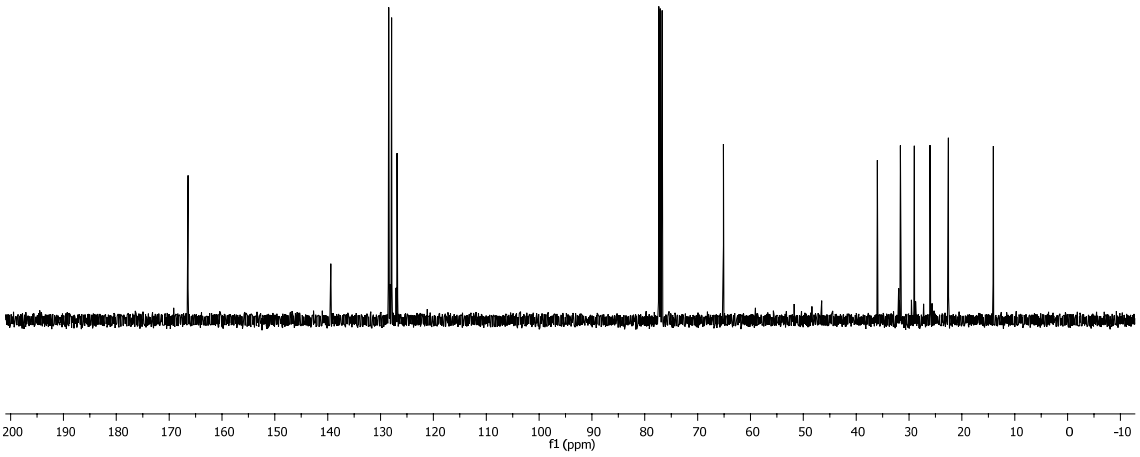
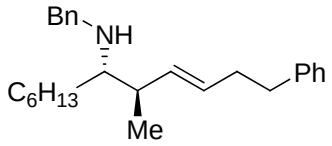
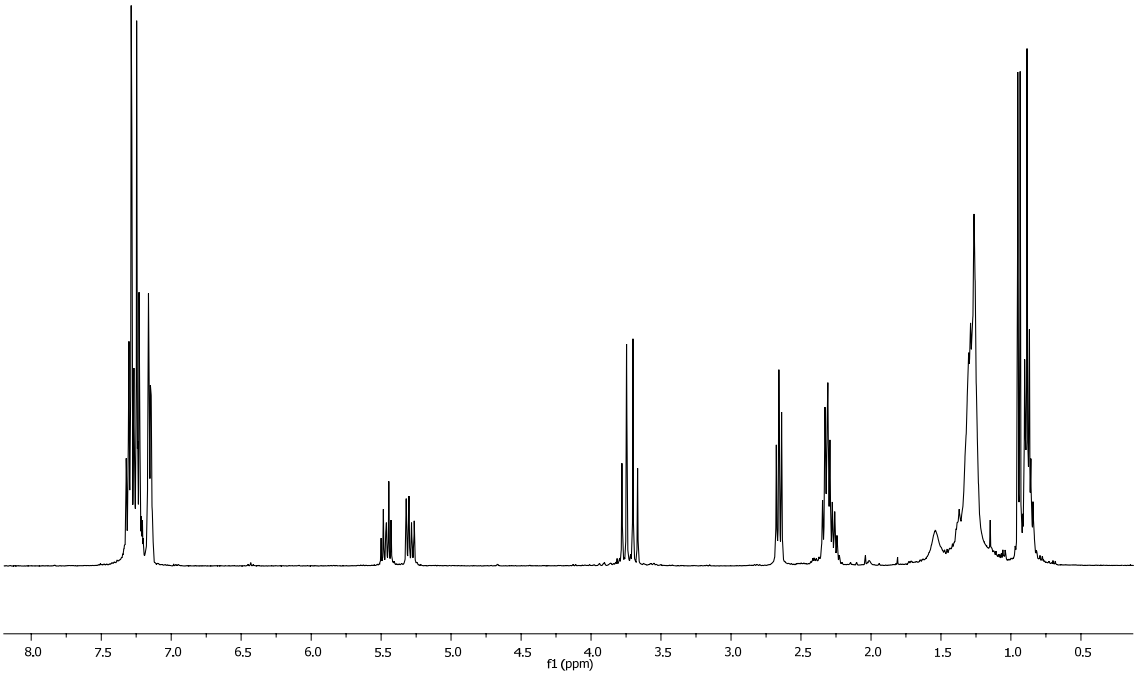


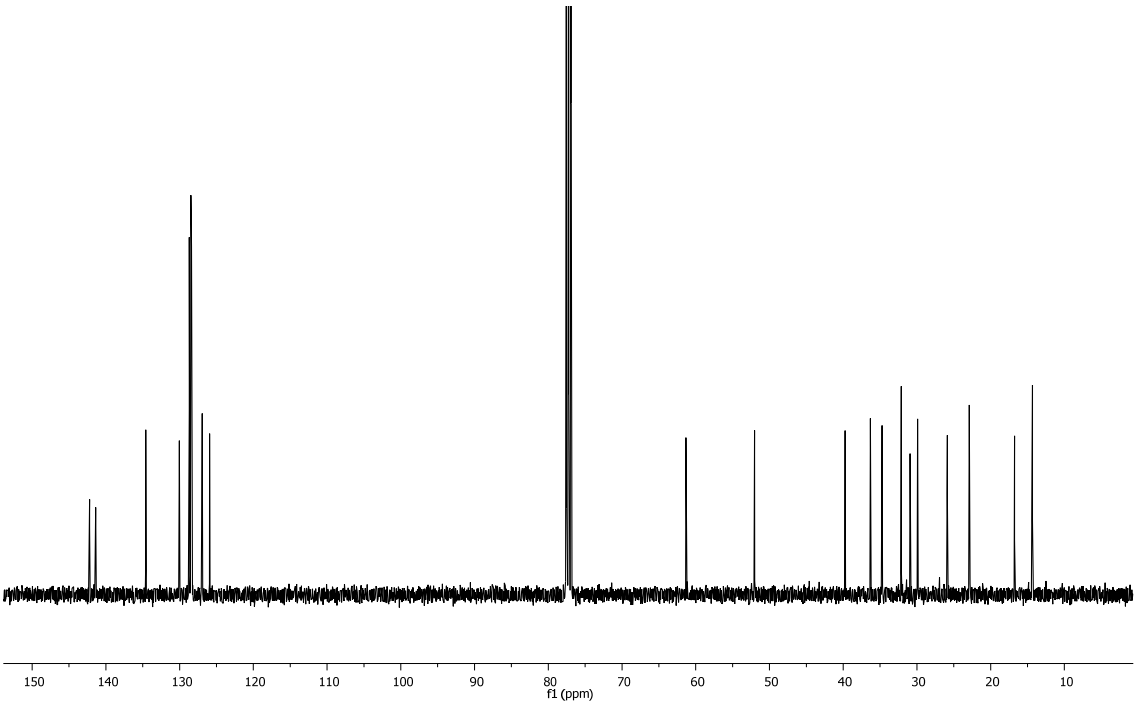


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **23**

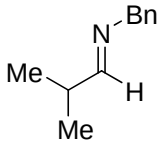


(+)-36





^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **36**



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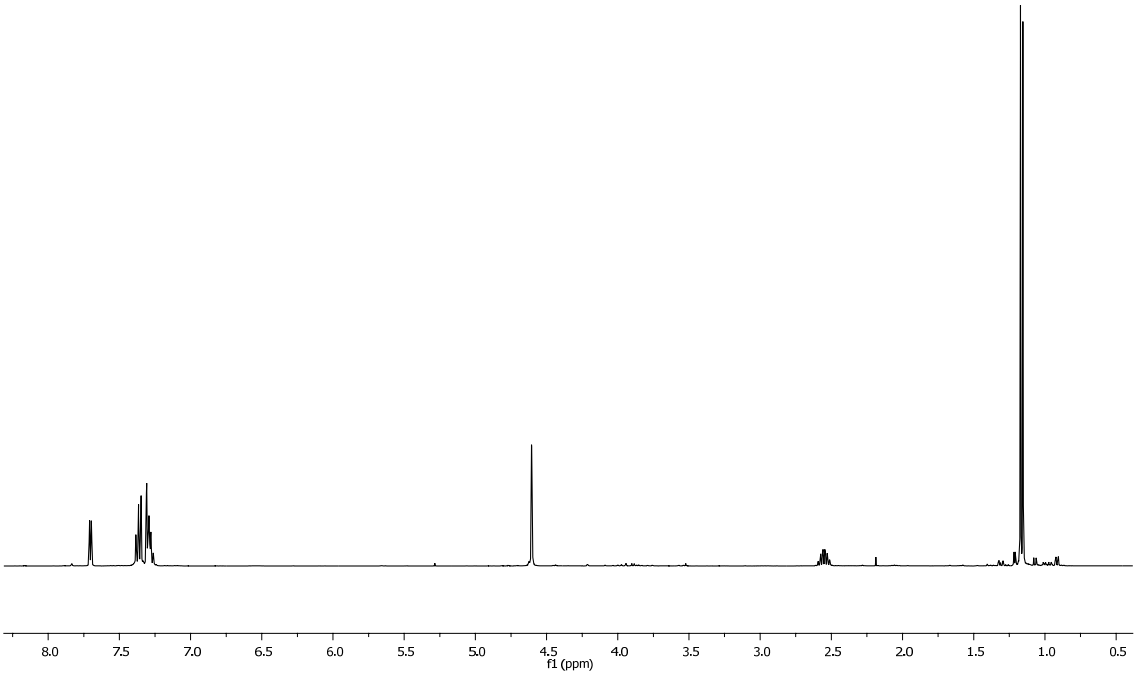
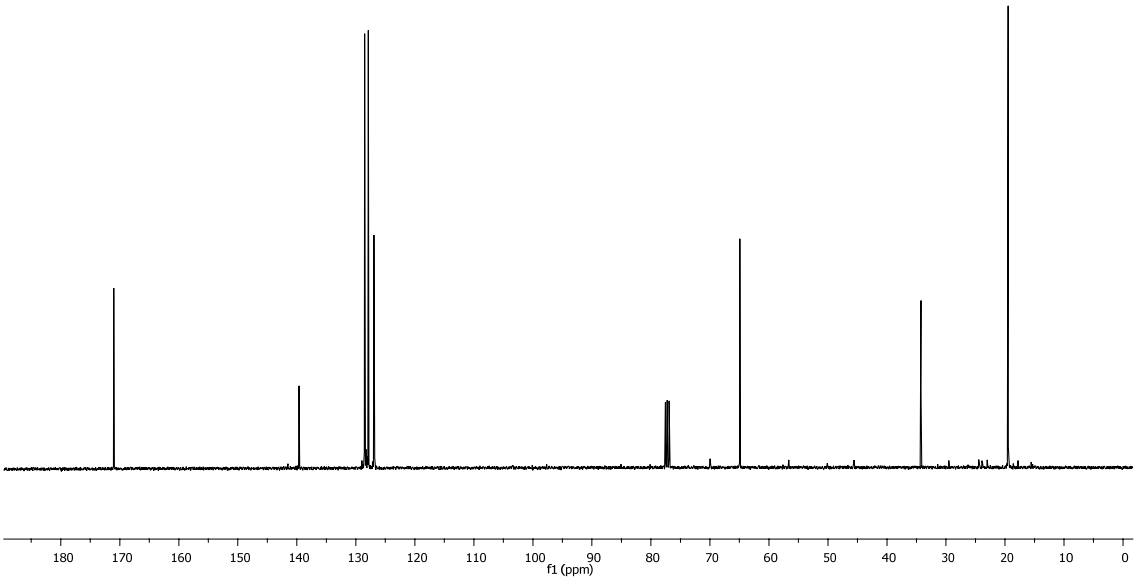
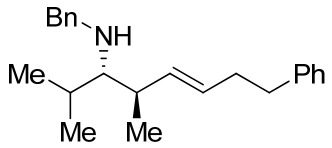
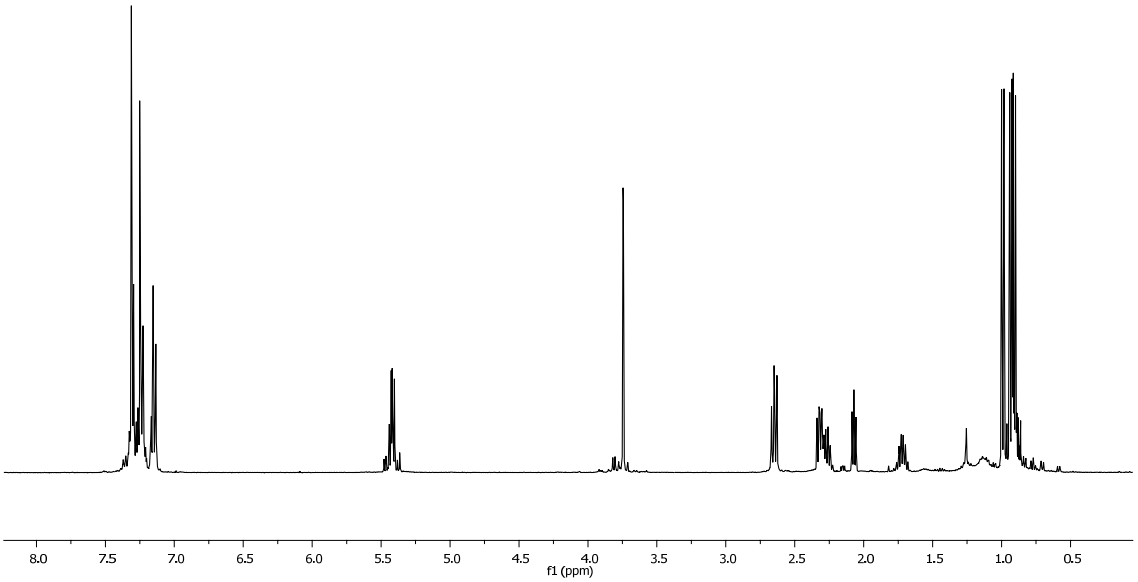


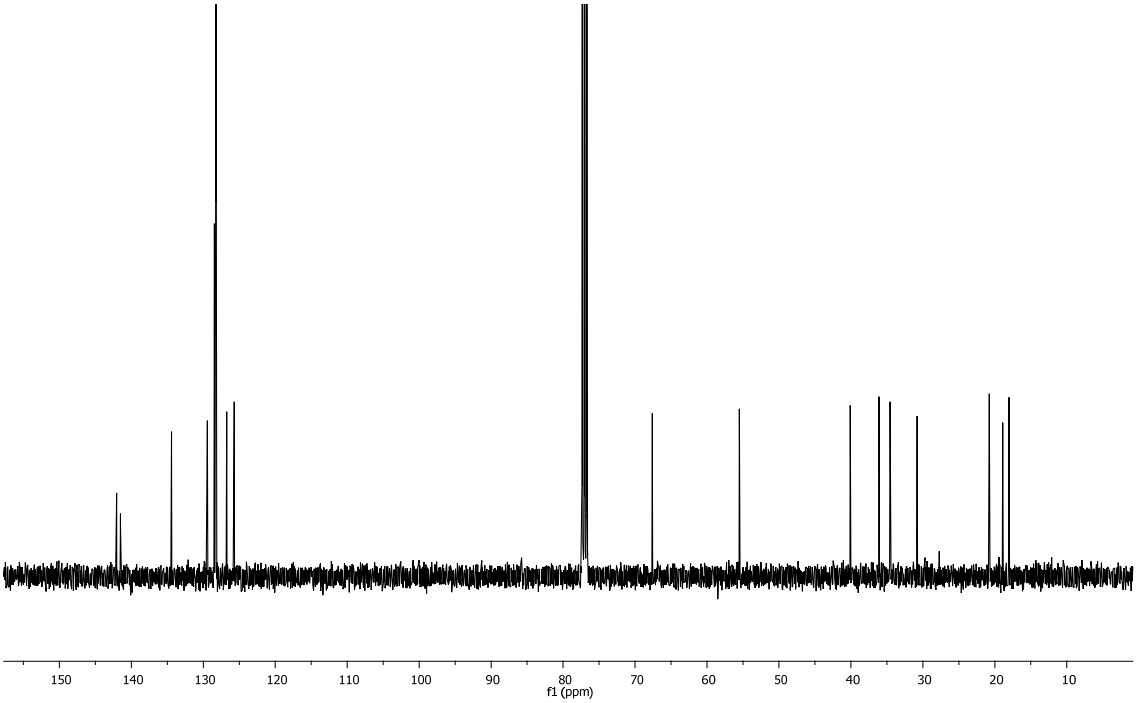


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **21**

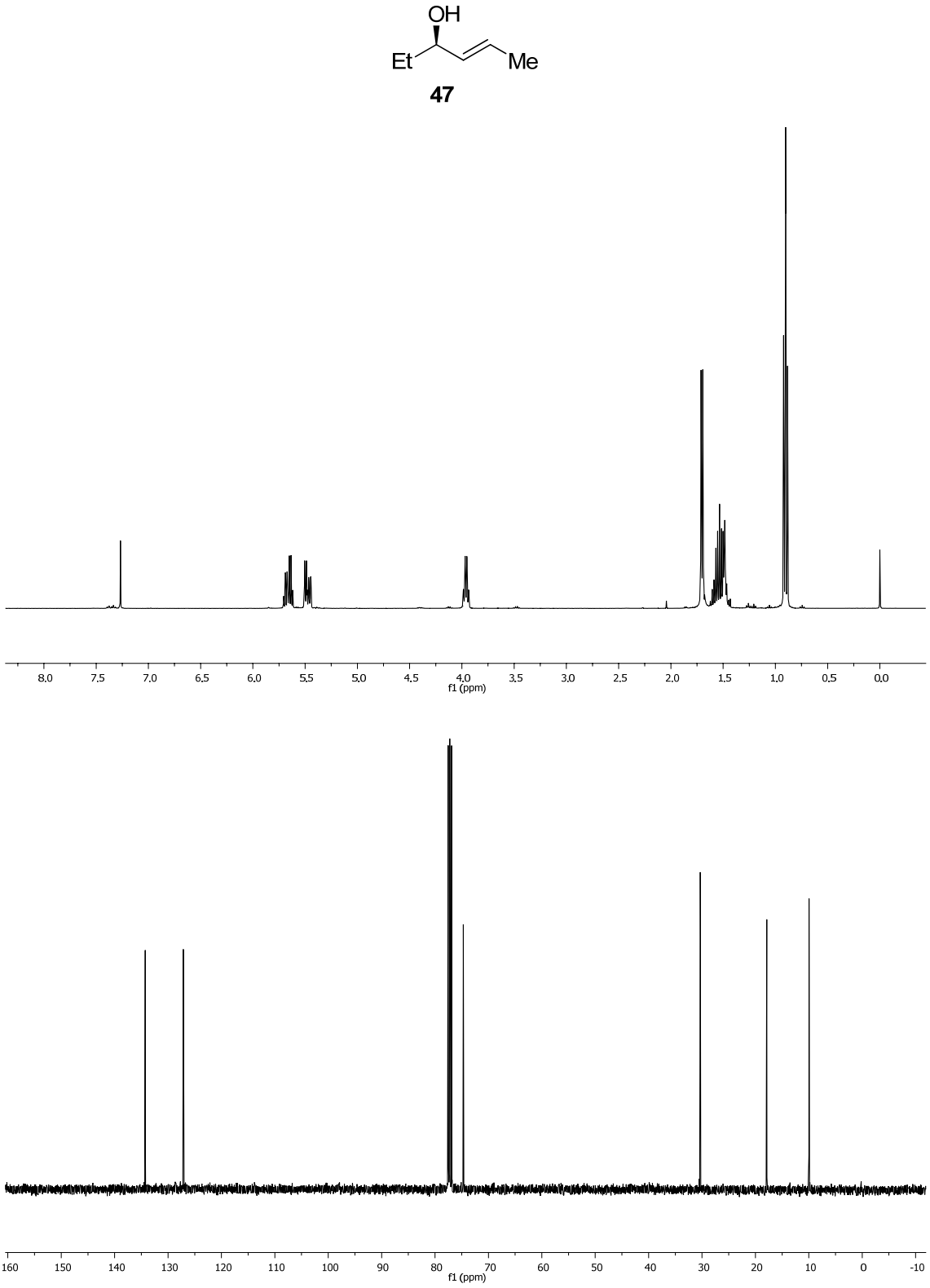


(–)-37

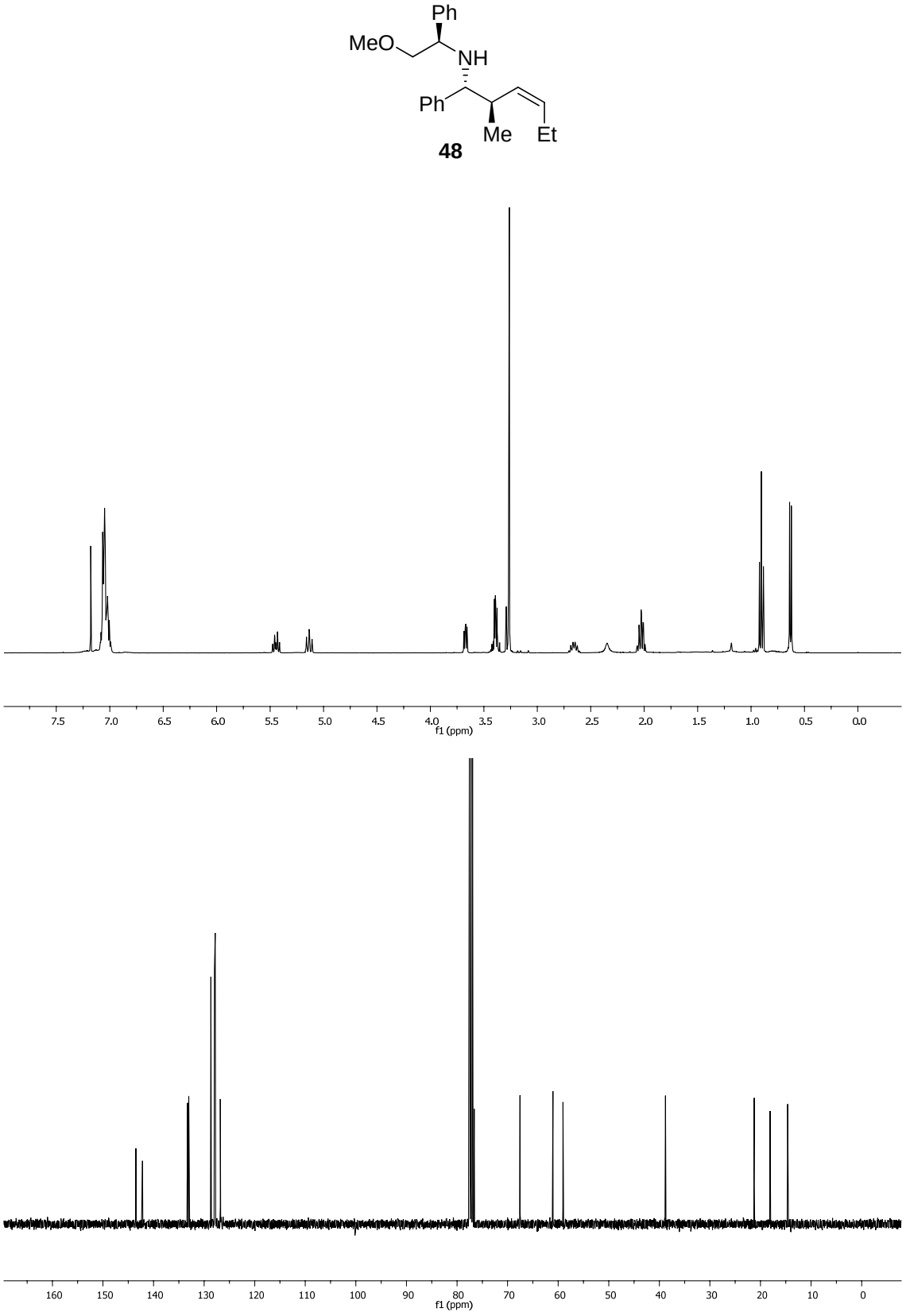




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **37**

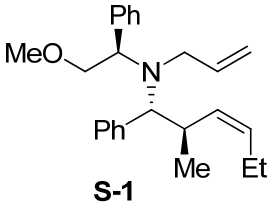


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **47**

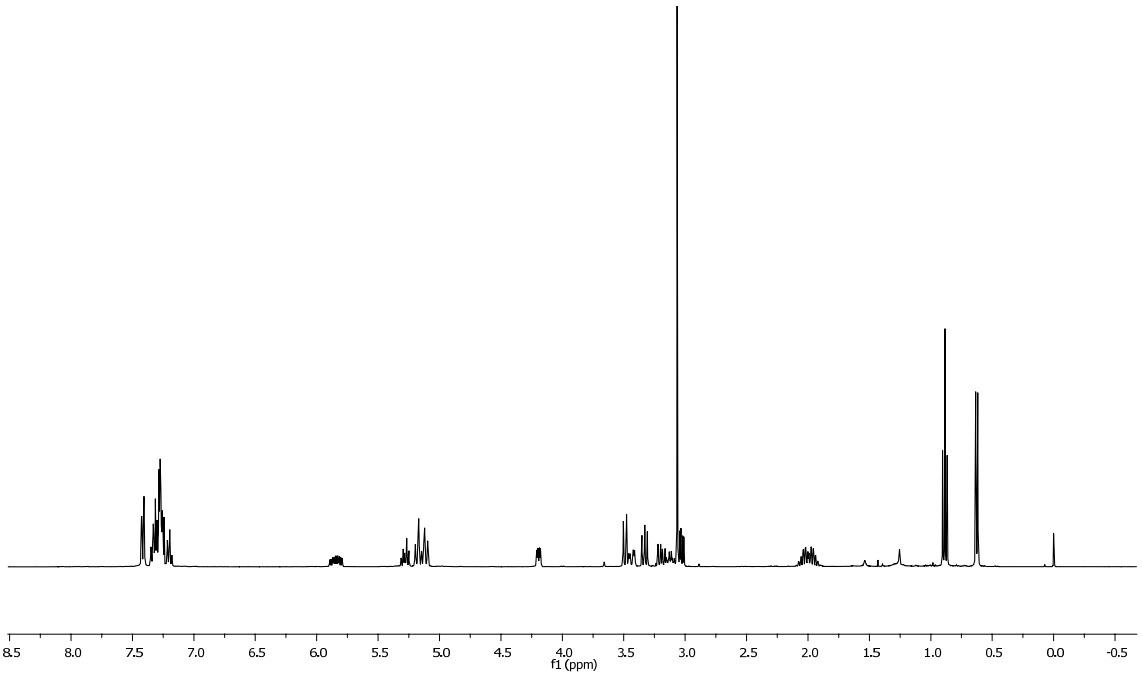


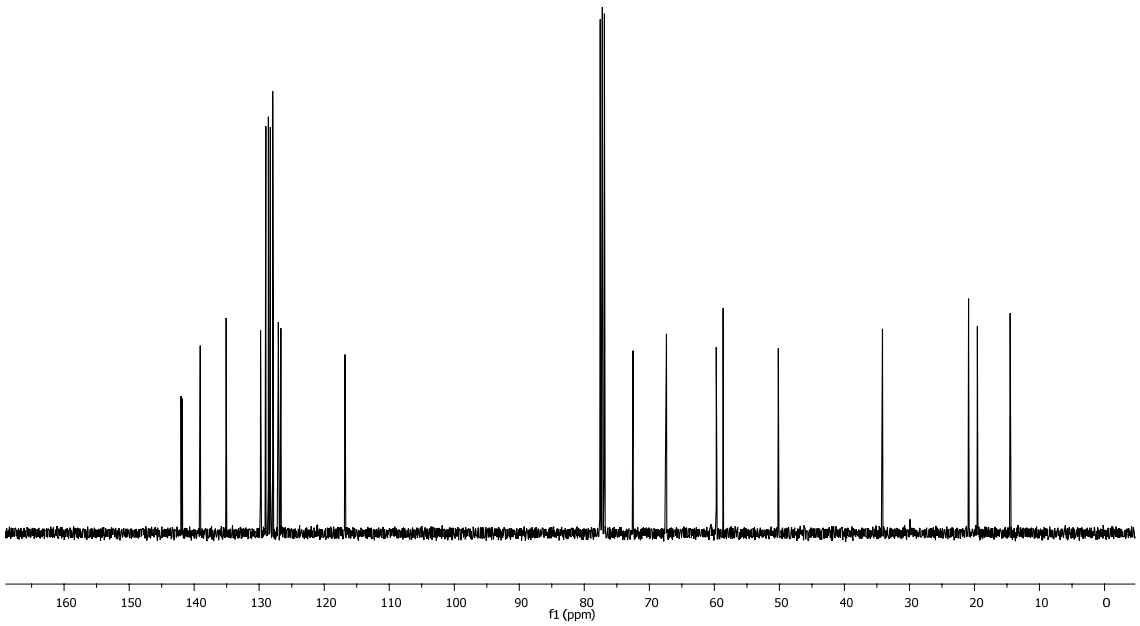
48

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **48**

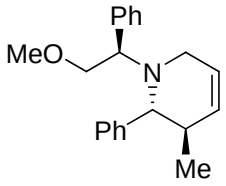


S-1

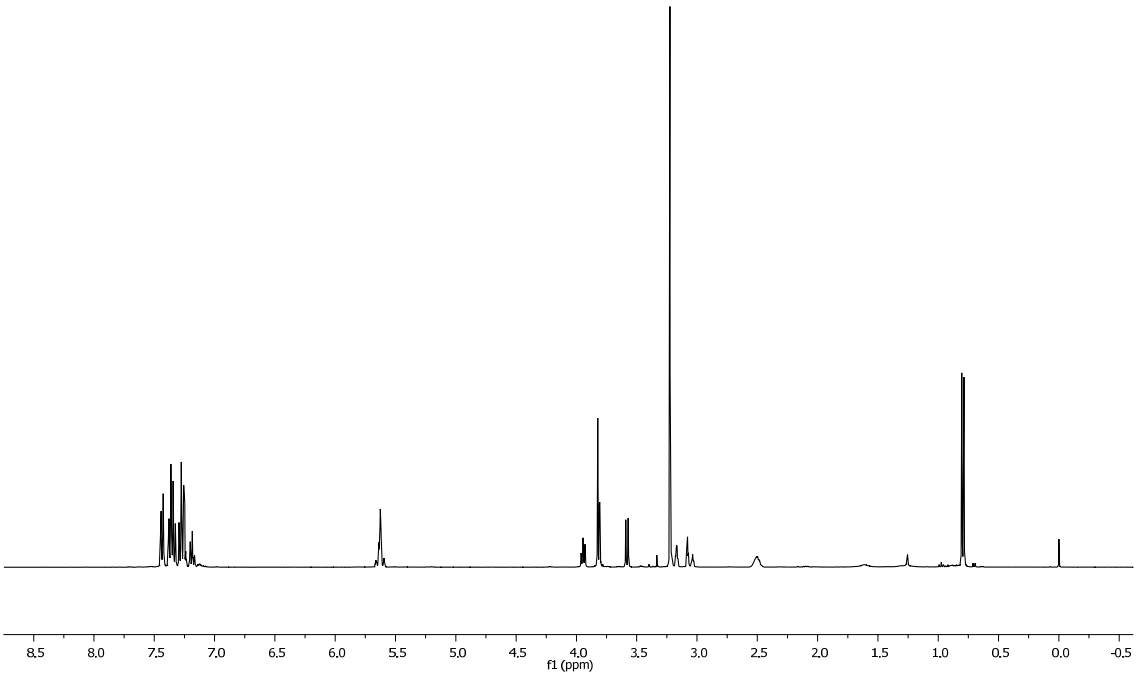


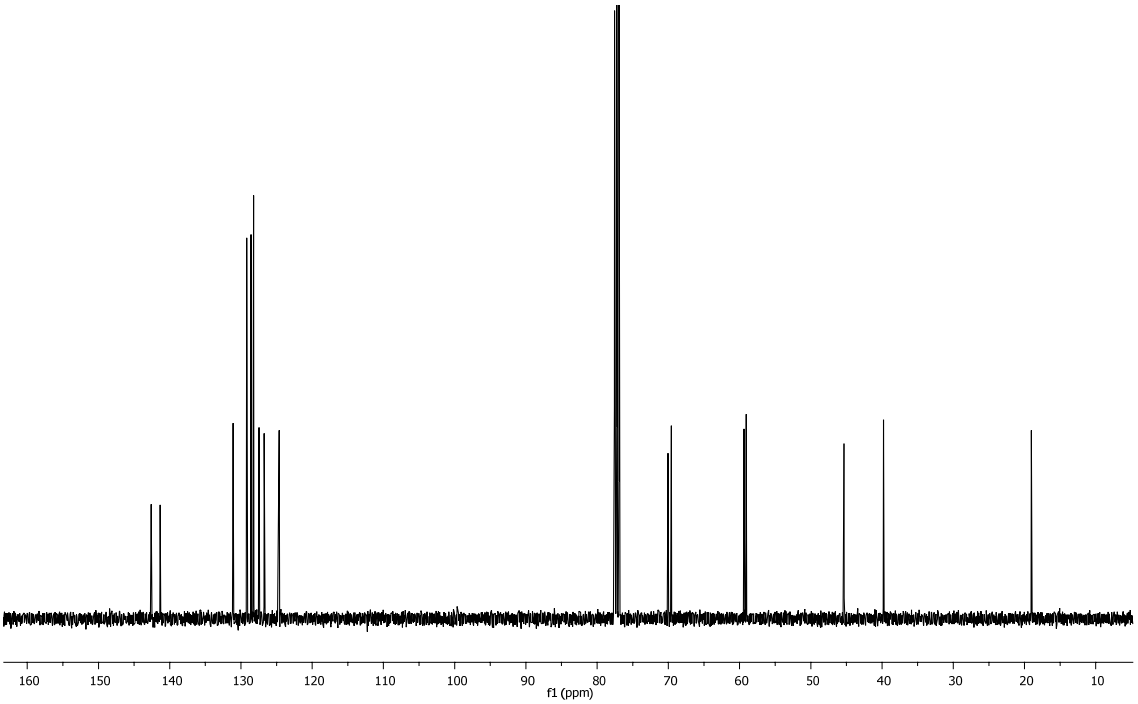


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-1**

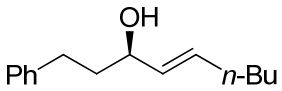


S-2





^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-2**



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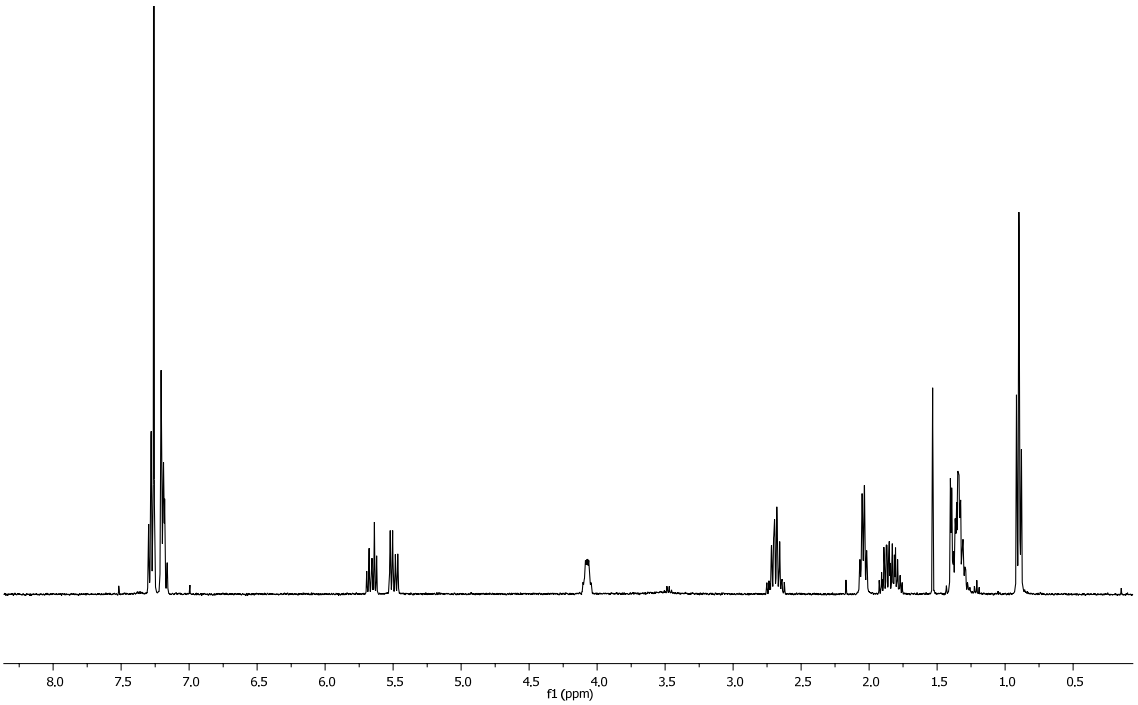
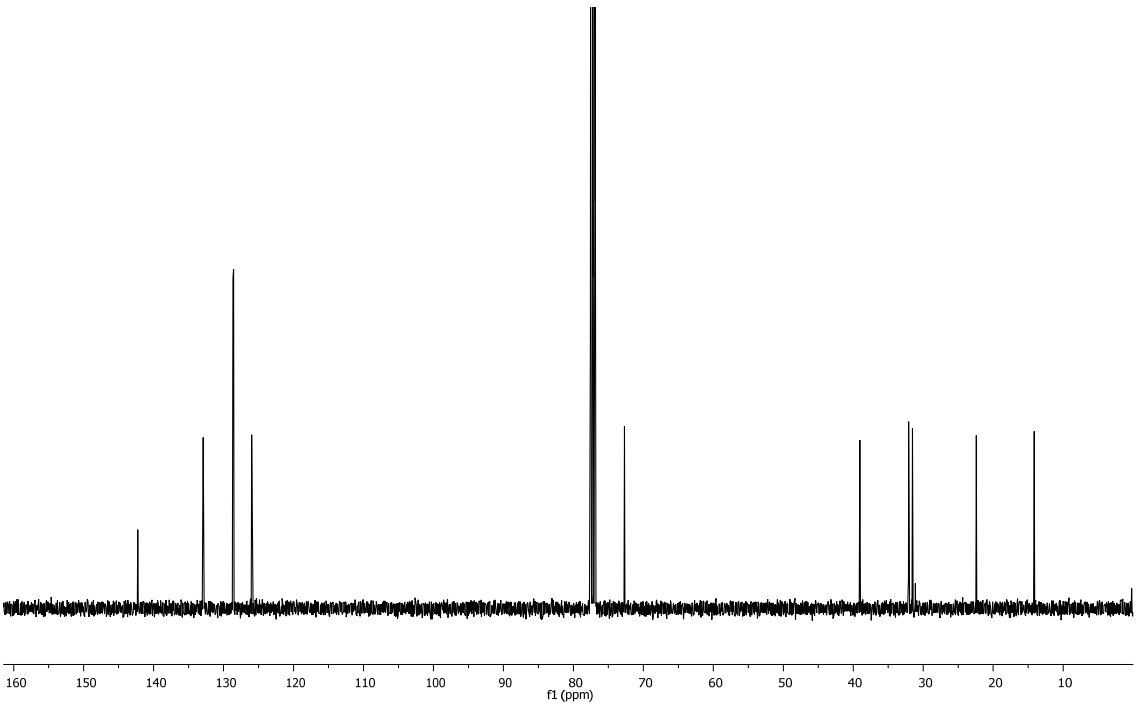
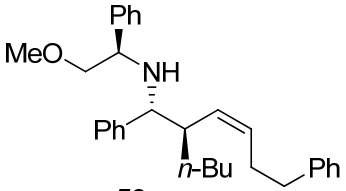




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **49**



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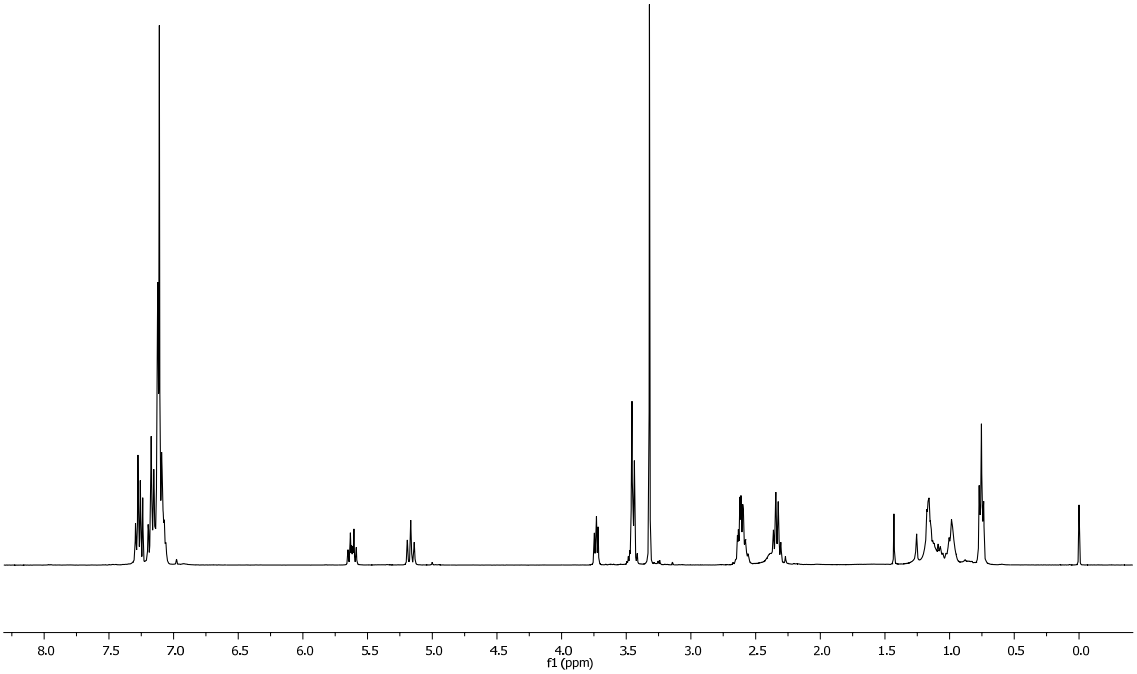
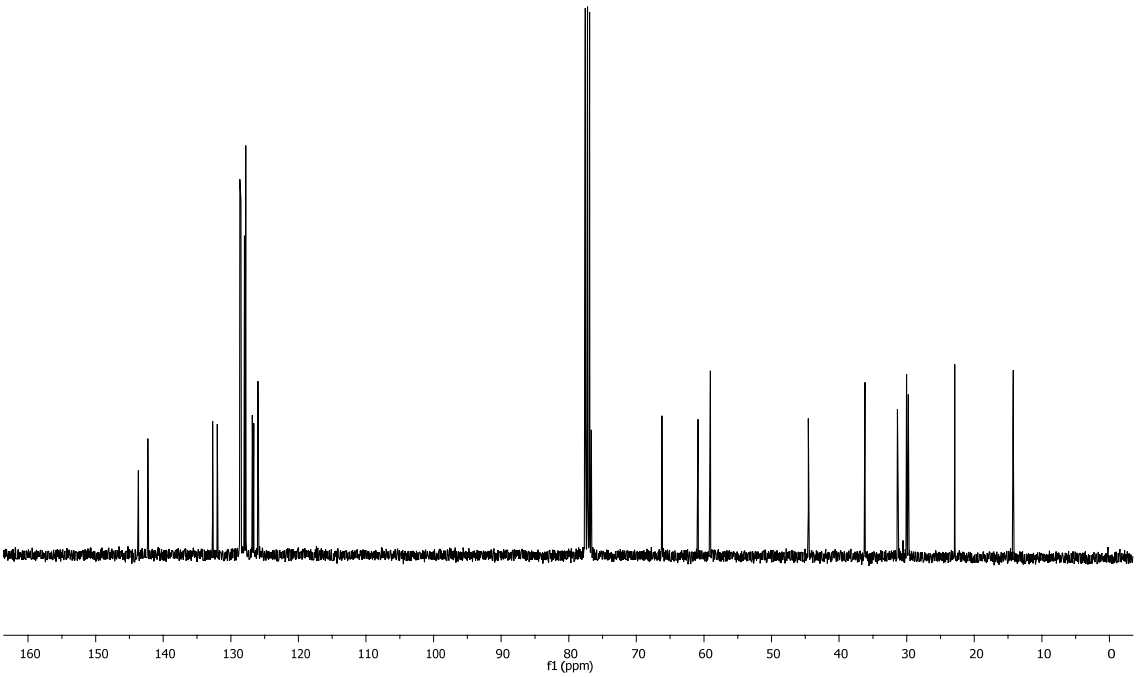
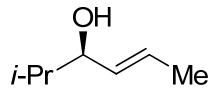




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **50**



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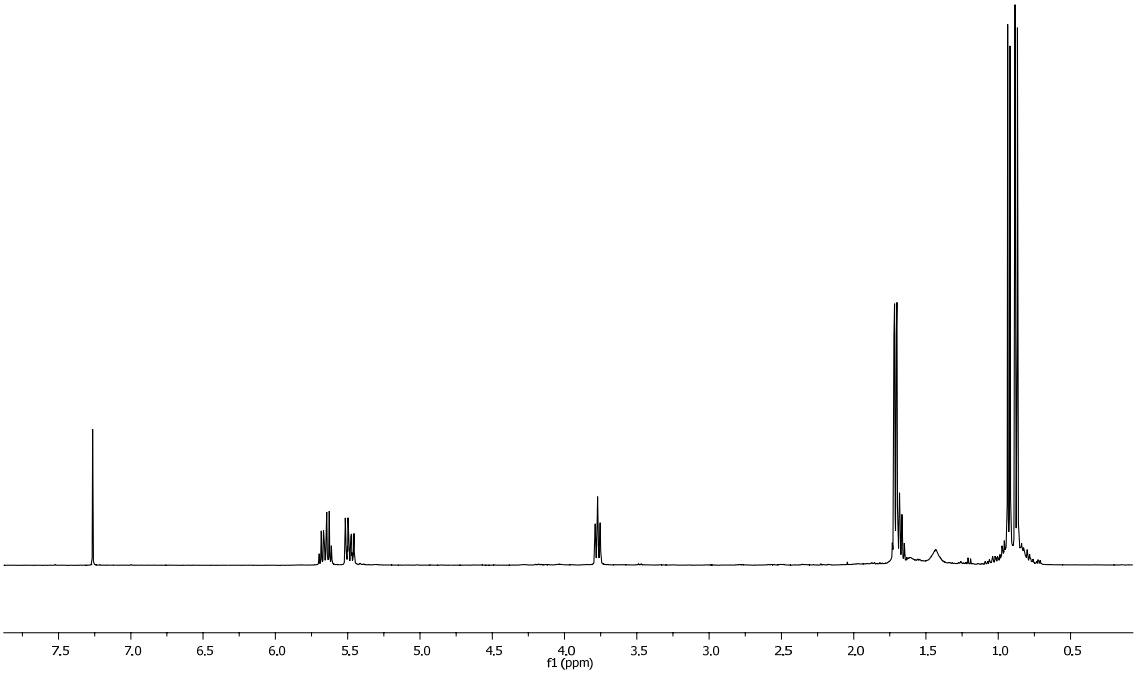
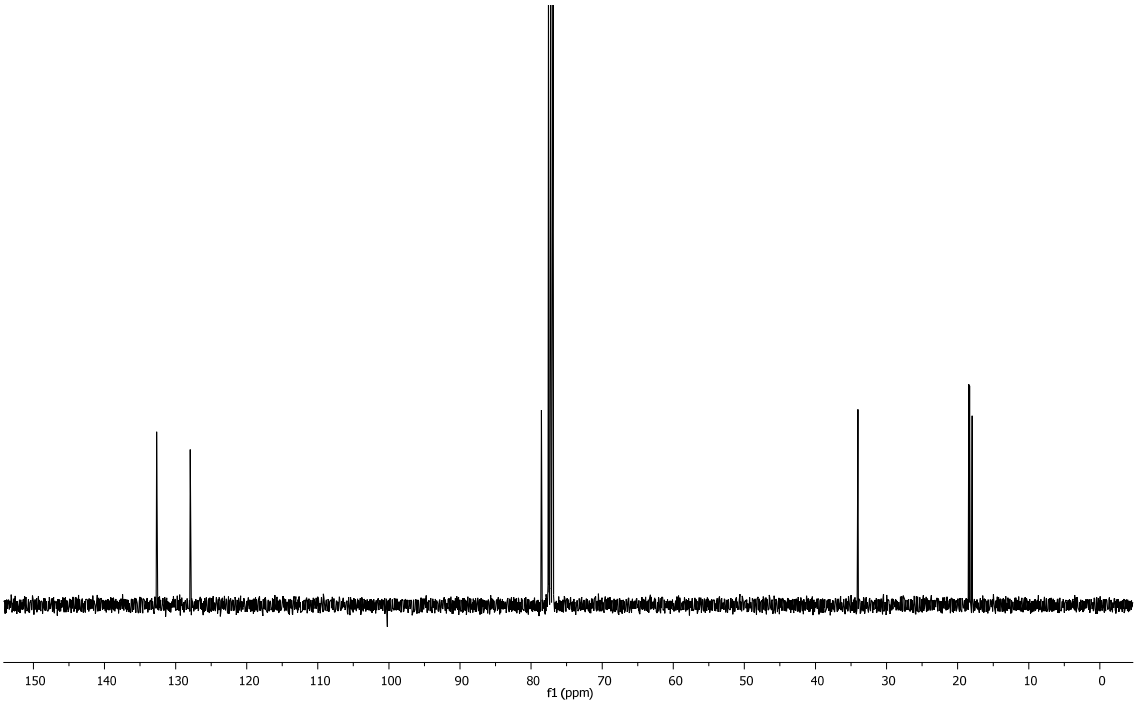
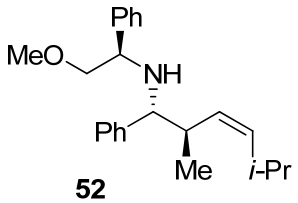




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **51**



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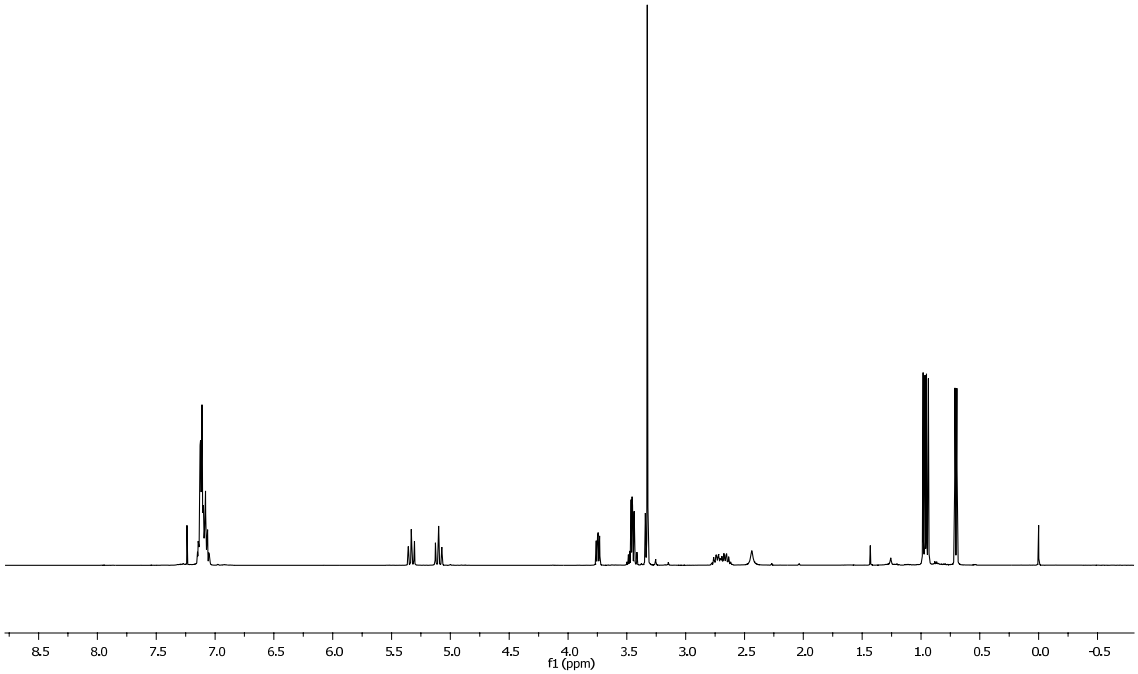
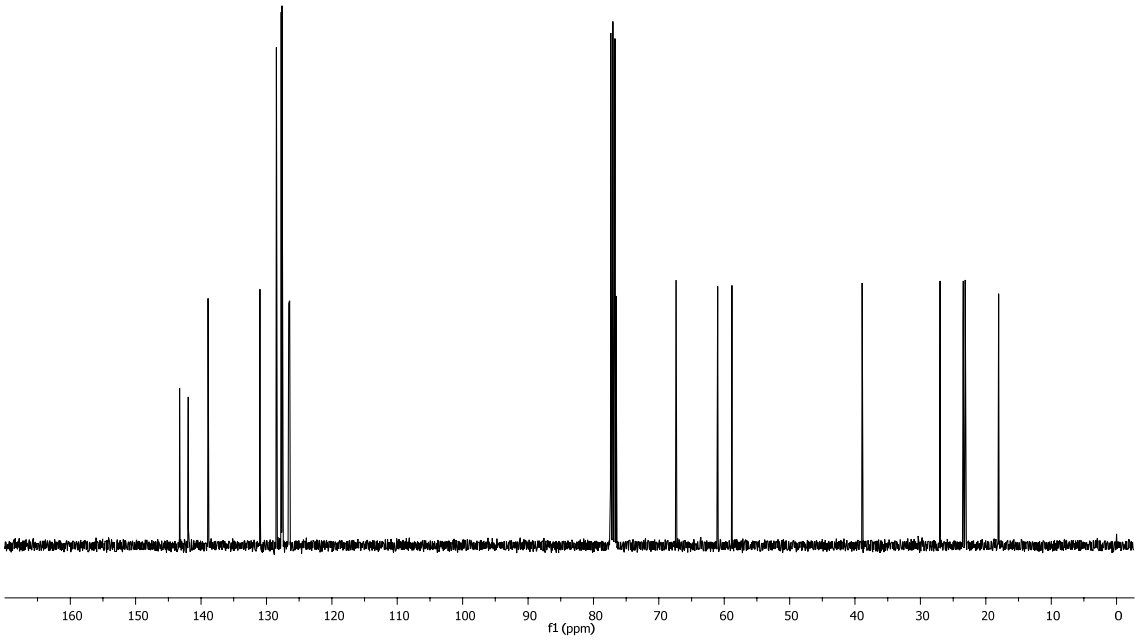
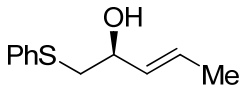




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **52**



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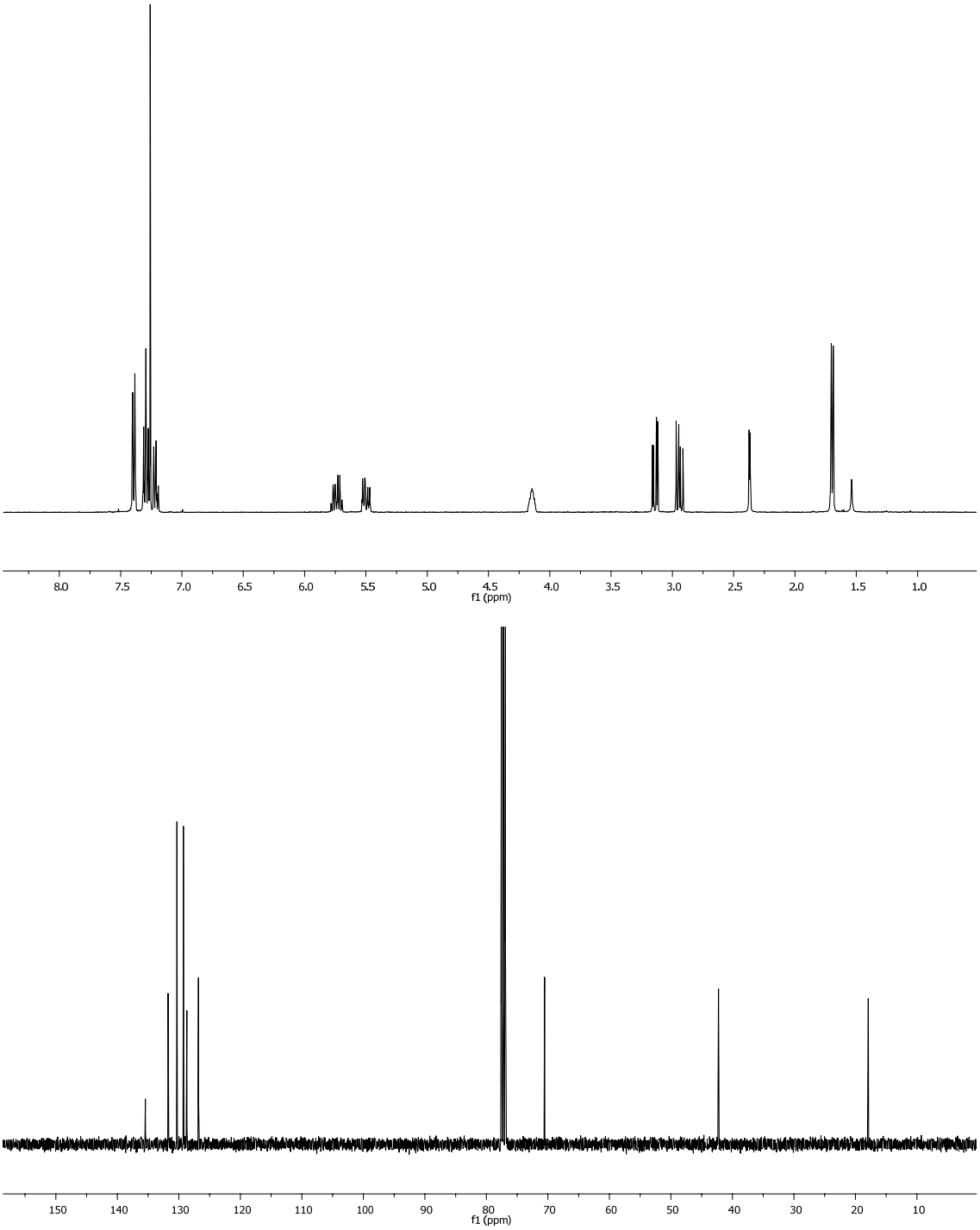
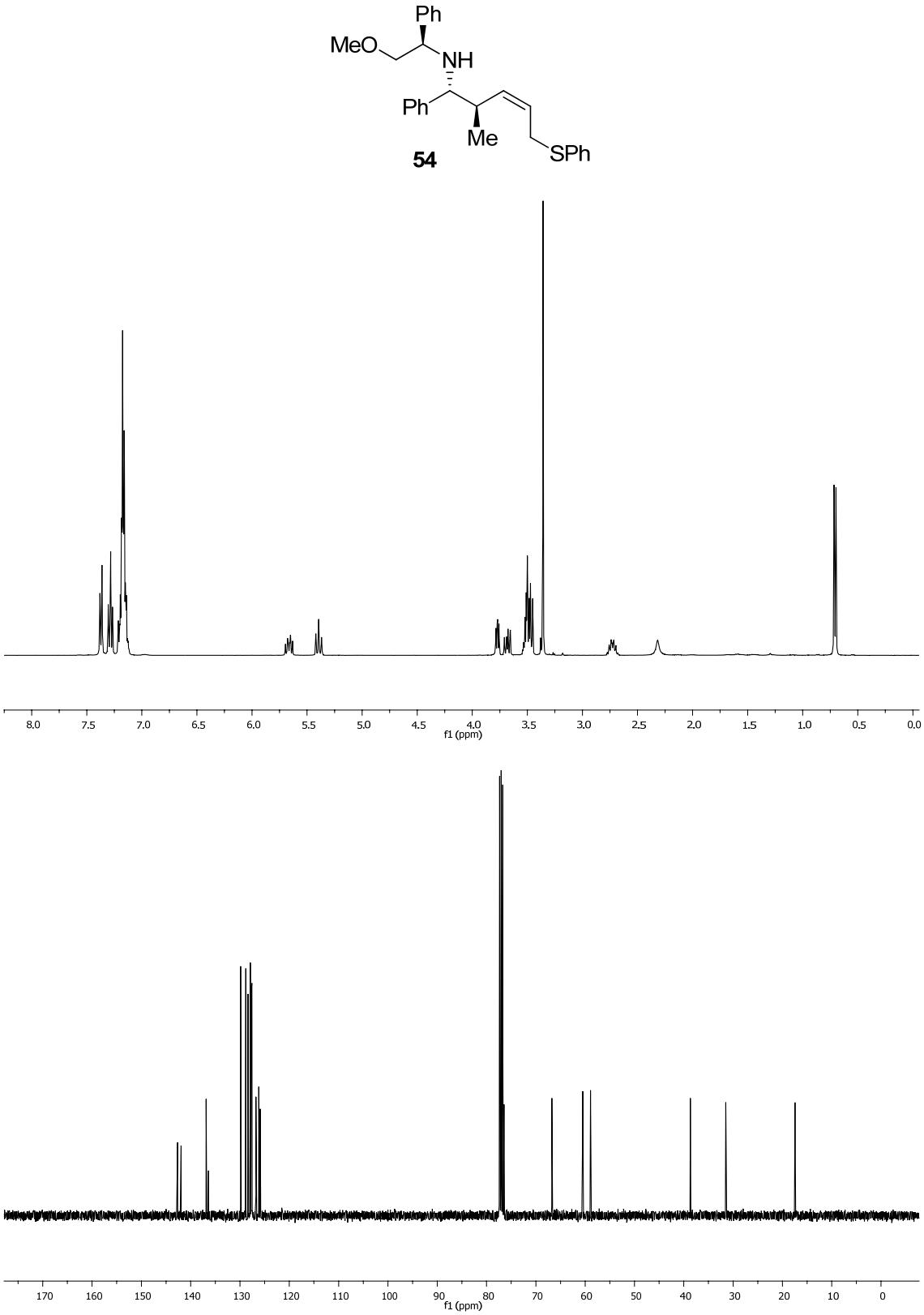
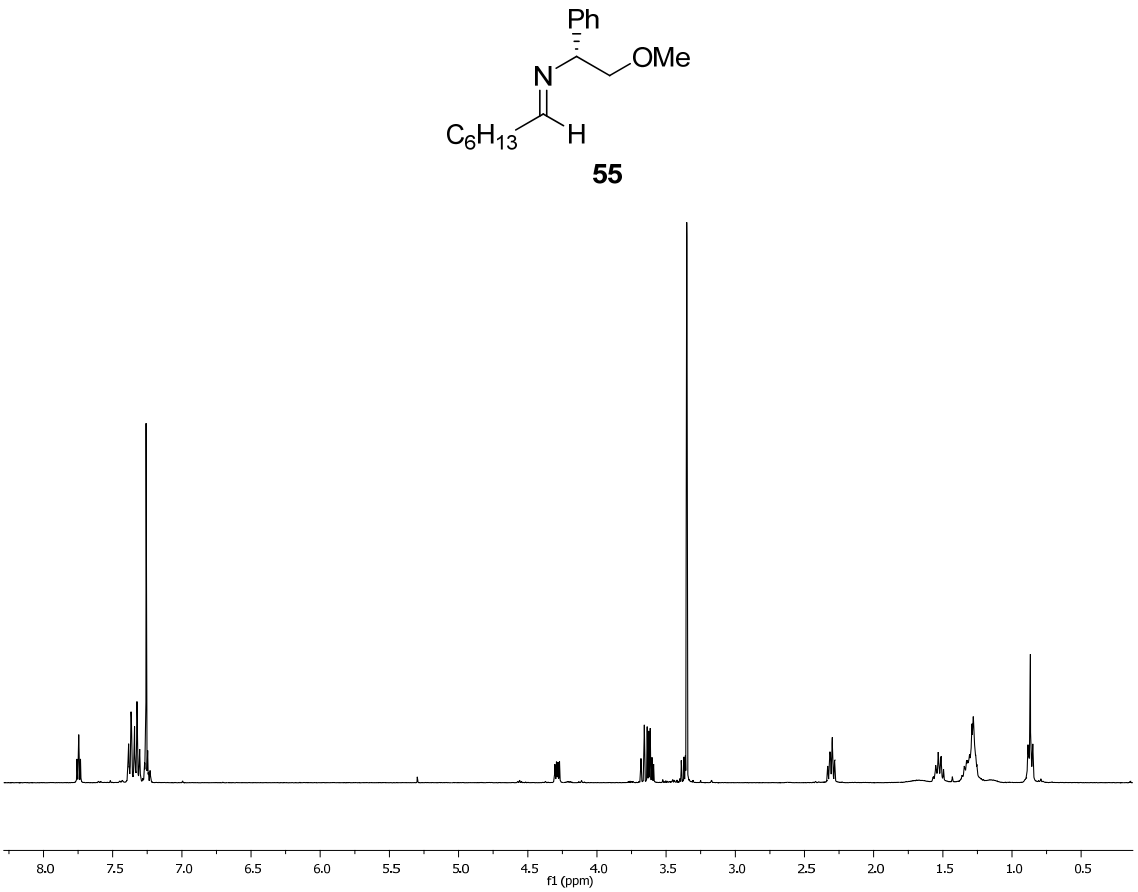


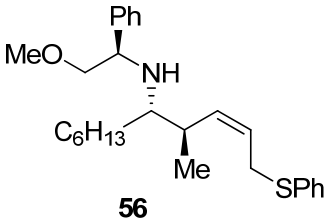
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **53**



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **54**



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **55**



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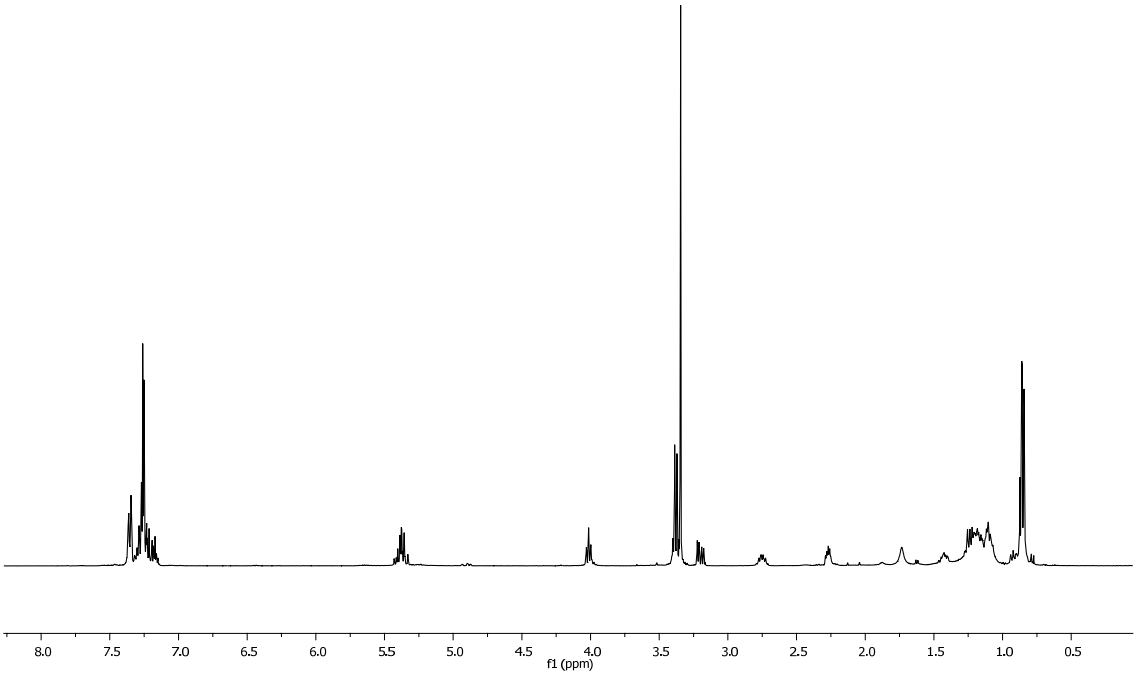
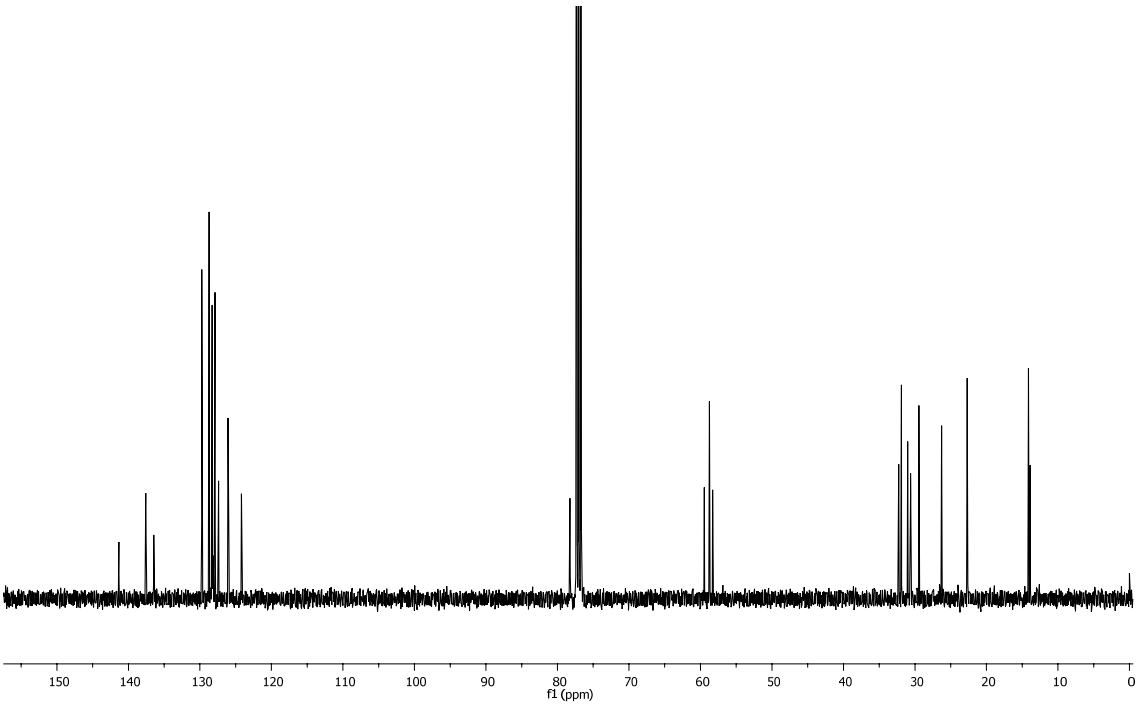
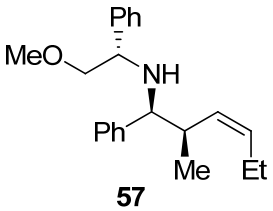




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **56**



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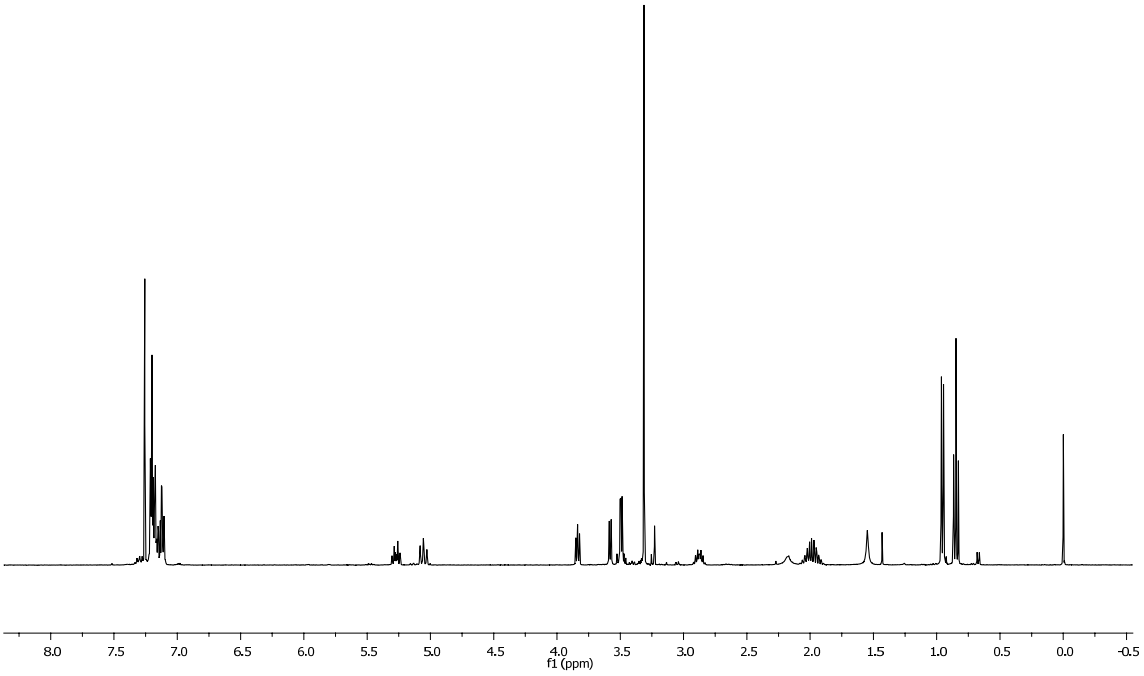
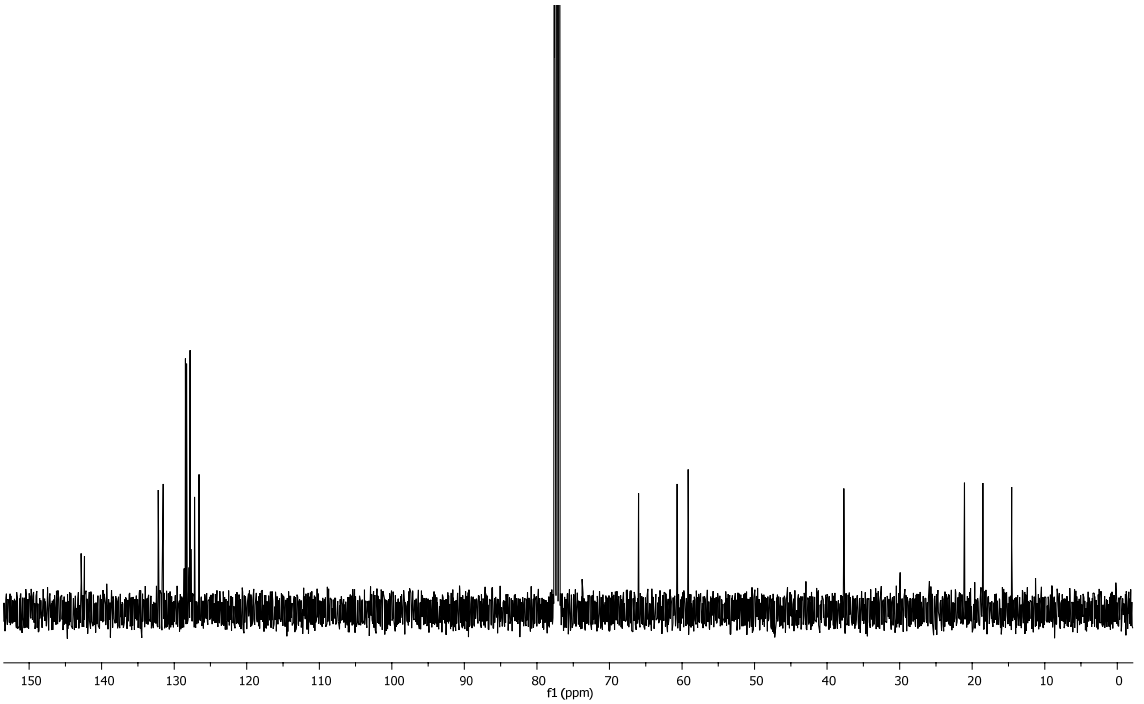
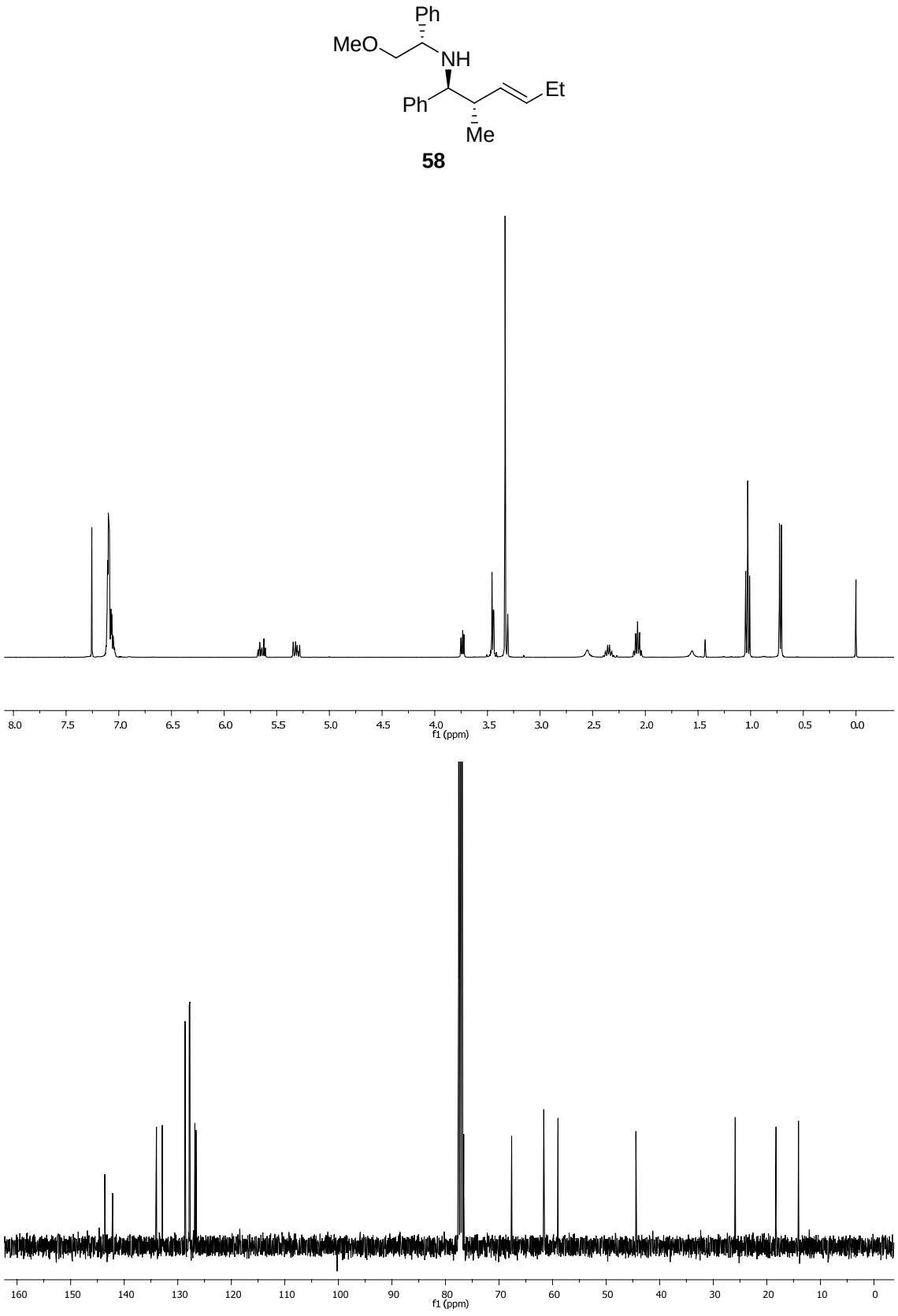


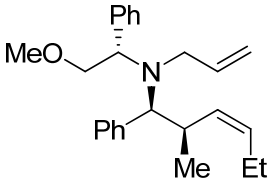


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **57**

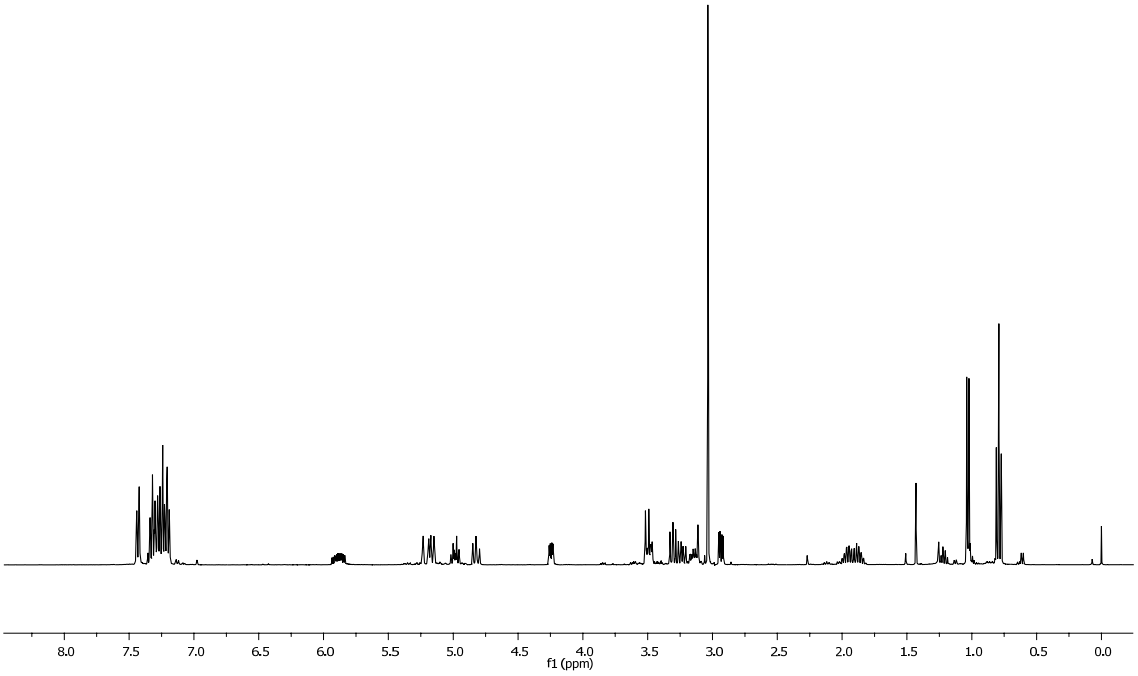


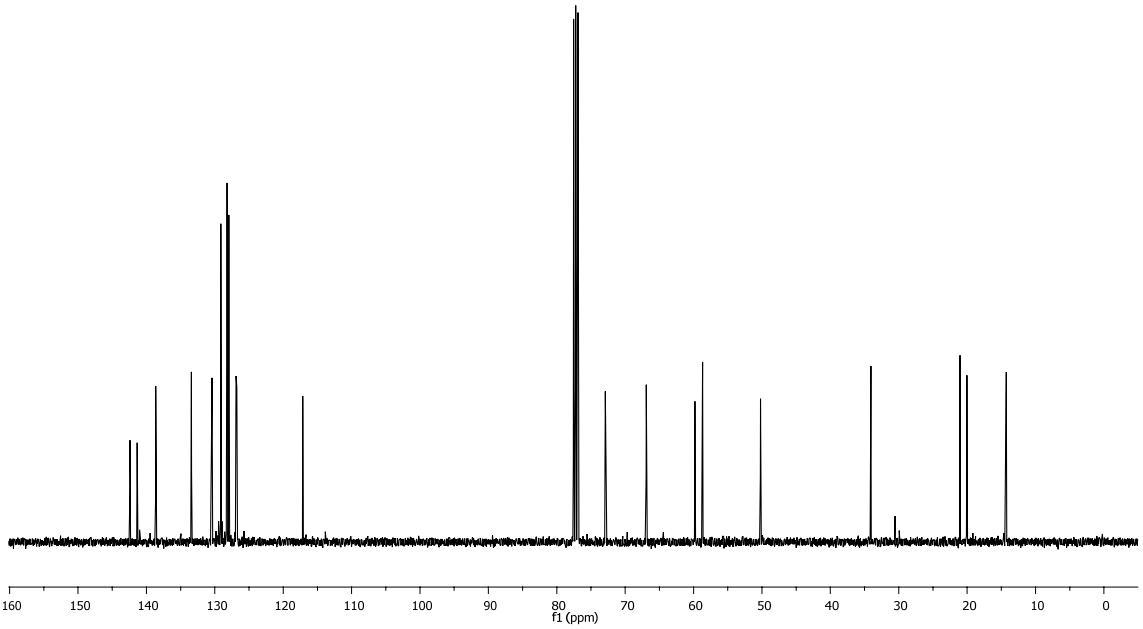
58

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **58**

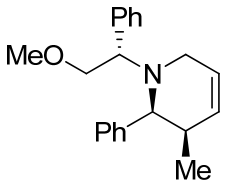


S-6

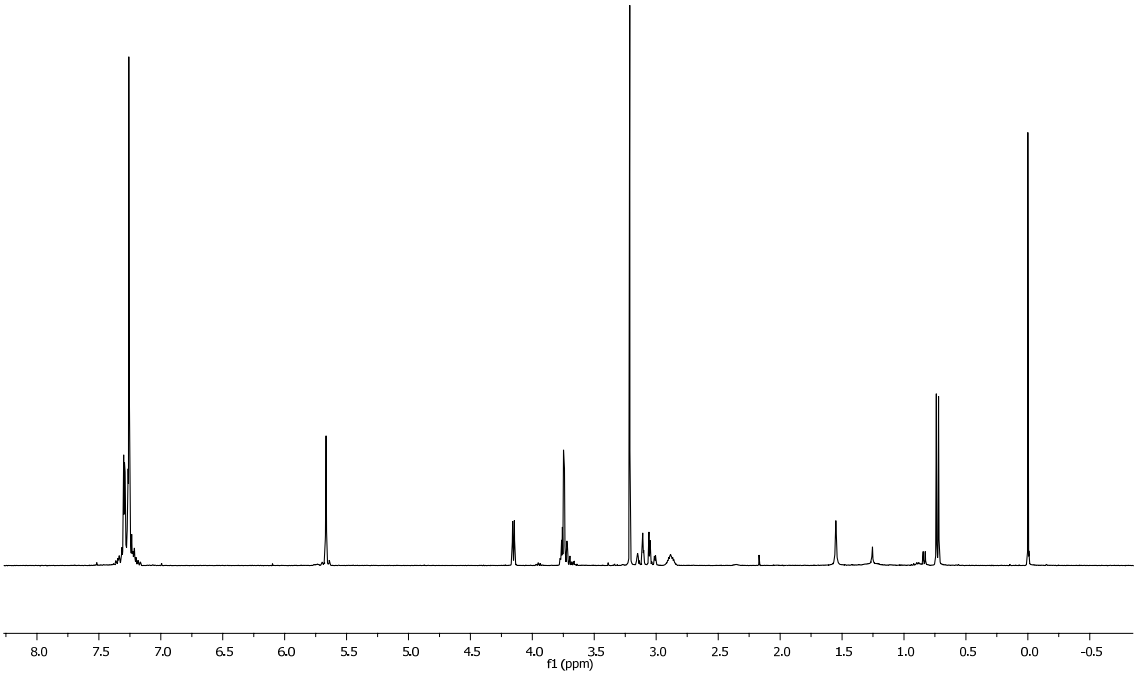


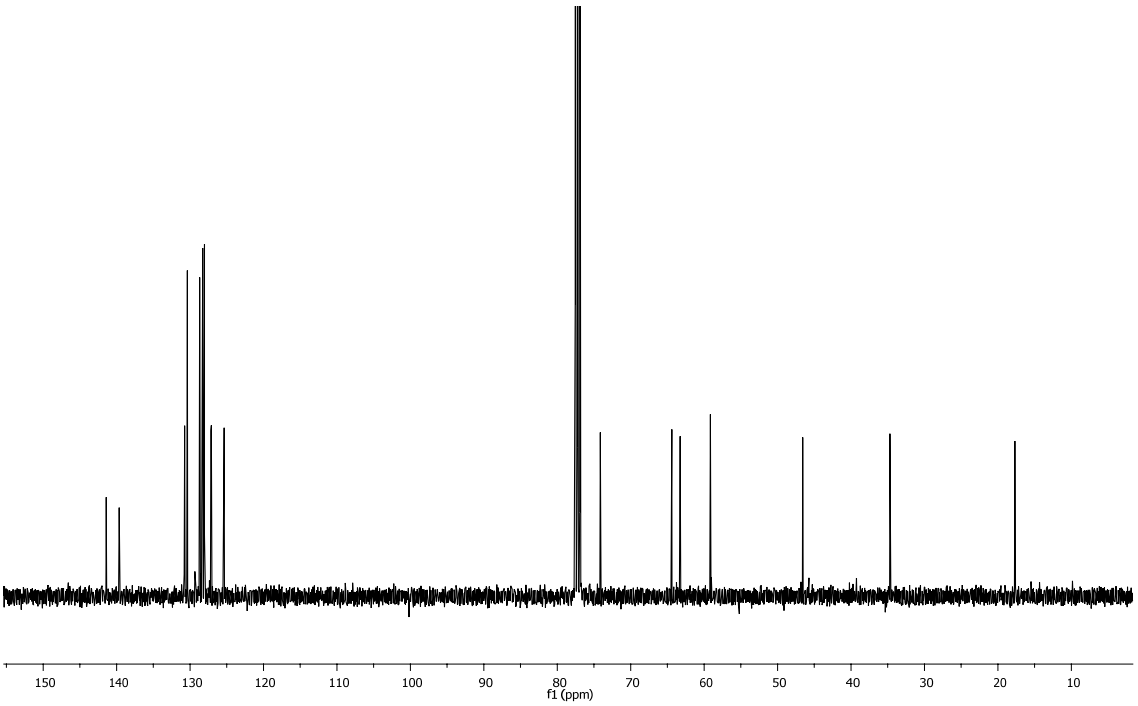


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-6**

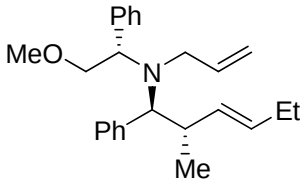


S-7

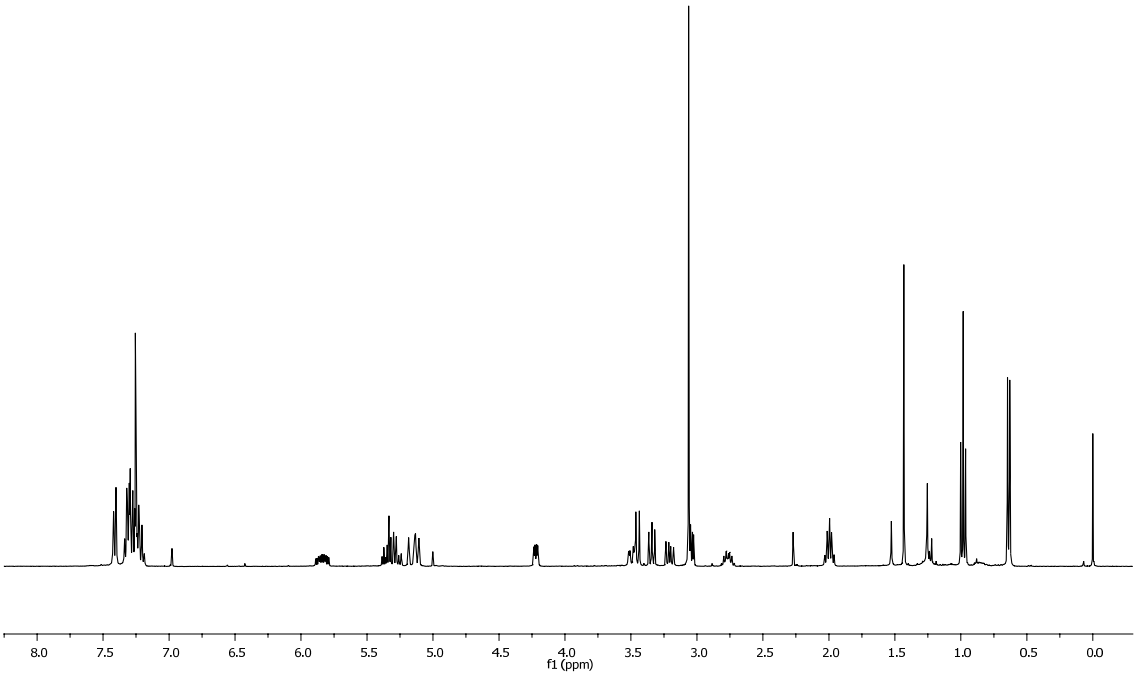


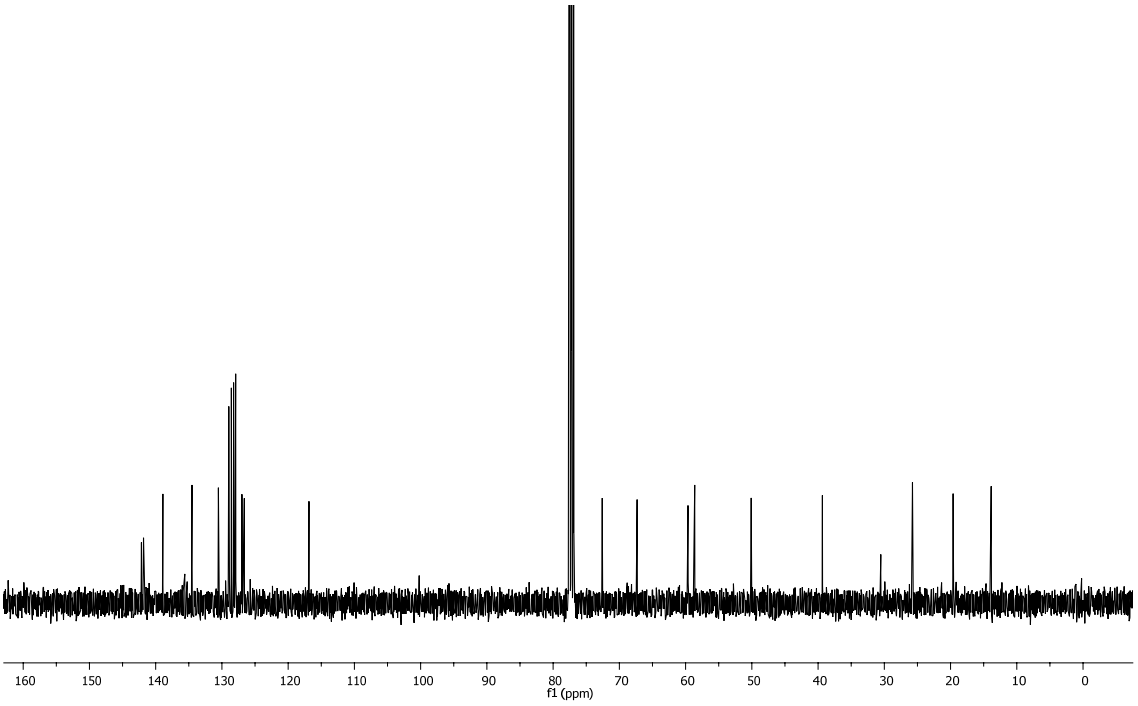


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-7**

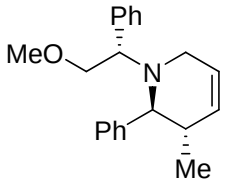


S-8

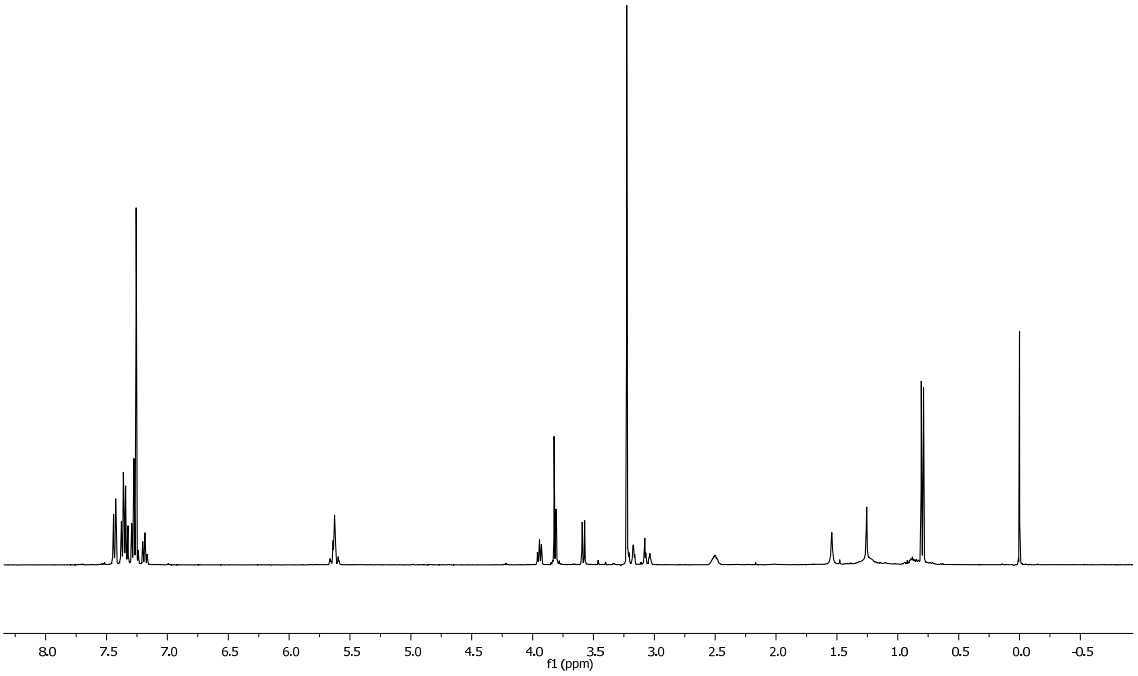


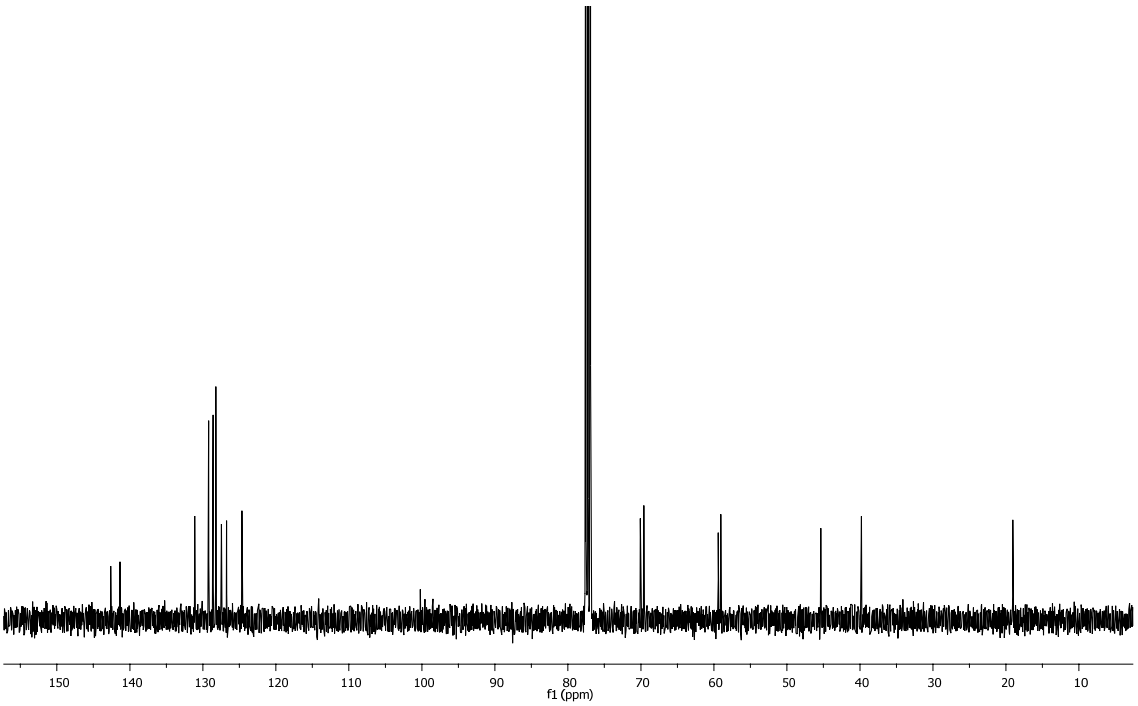


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-8**

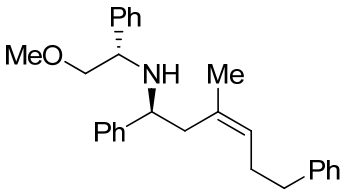


S-9

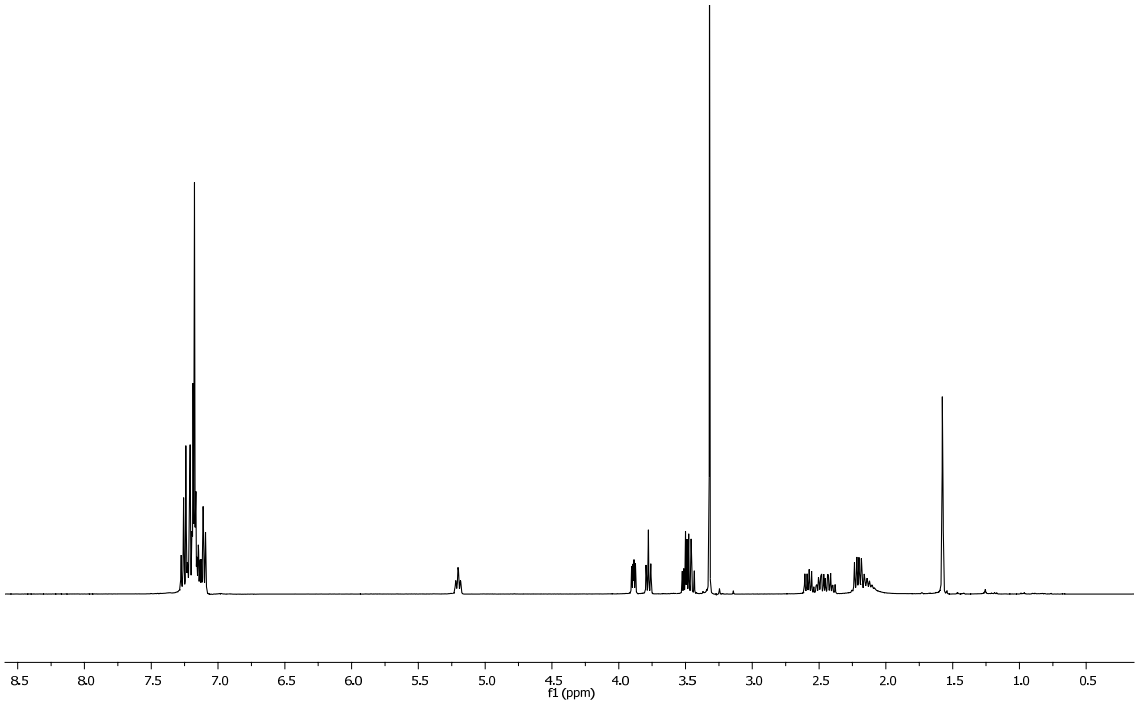


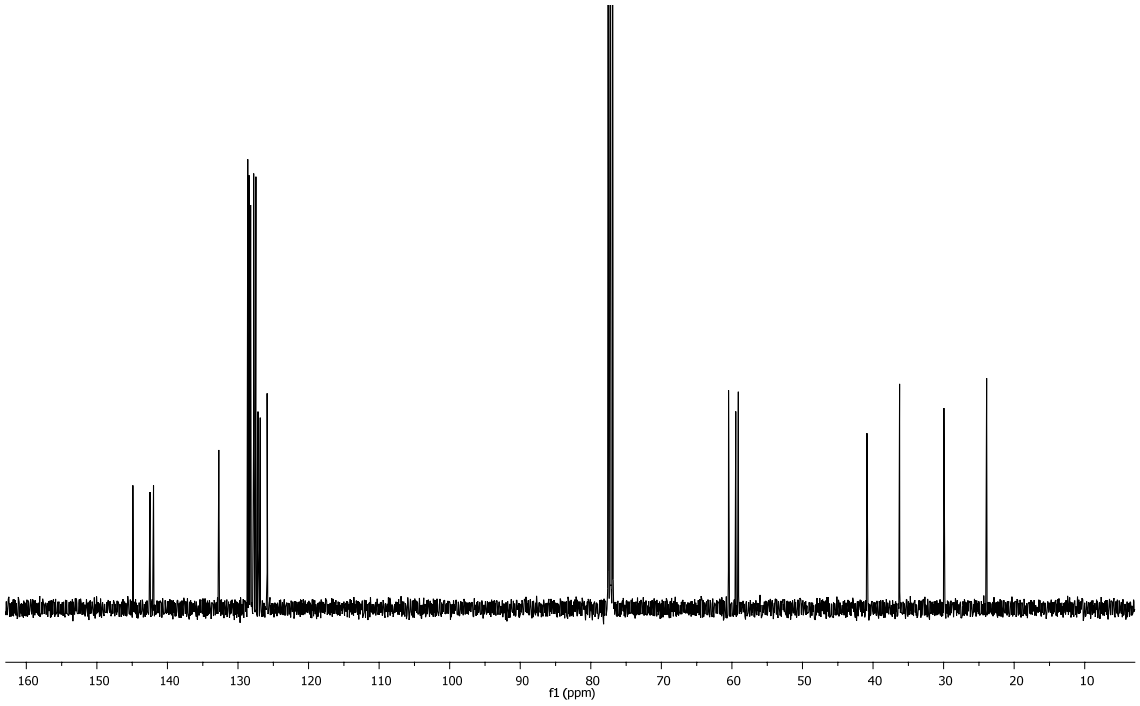


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **S-9**



59





^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **59**