Palladium-catalyzed stereospecific cross-coupling of enantioenriched allylic alcohols with boronic acids

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Supporting information

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General information

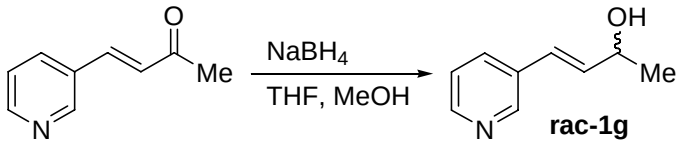
^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-400 FT spectrometer (400 MHz and 100 MHz, respectively) using tetramethylsilane as an internal reference. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. High resolution mass spectra (HRMS) were recorded on a LC-TOF spectrometer (Micromass). High pressure liquid chromatography (HPLC) analyses were performed on a Hewlett-Packard 1200 Series instrument equipped with an isostatic pump using a Daicel Chiralpak column (AD, OD, OD-H, or OJ, 250 x 4.6 mm) with isopropanol/hexanes as mobile phase, and the UV detection was monitored at 254 or 220 nm. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured on a Perkin-Elmer 343 polarimeter with a sodium lamp at λ = 589 nm and reported as $[\alpha]_D^{T\,^\circ C}$ (c = g/100 mL, solvent). Melting points are uncorrected.

Except alcohol **1g**, the chiral allylic alcohols we used are known compounds. Alcohols **1a-i**, **1l**, and **1m** were prepared by sharpless kinetic resolution,[1] and alcohols **ent-1j** and **ent-1k** were synthesized from (*S*)-ethyl lactate[2] according to literature procedures. Their absolute configuration was assigned by comparison of the optical rotation (or the chiral HPLC trace) with that reported in the literature.[1b-c,3,4] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Meryer, Acros, Alfa Aesar, and TCI, and used as received.

Abbreviations: Ac = acetyl, Am = amyl, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, BINOL = 1,1'-binaphthol, dba = dibenzylideneacetone, DIPT = diisopropyl tartrate, DMAP = 4-dimethylamiopryidine, DMF = *N*,*N*-dimethyl-formamide, DMSO = dimethyl sulfoxide, dppb = 1,4-bis(diphenylphosphino)butane, MS = molecular sieves, TBHP = *tert*-butyl hydroperoxide, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Ts = *p*-toluenesulfonyl.

Preparation of alcohol 1g

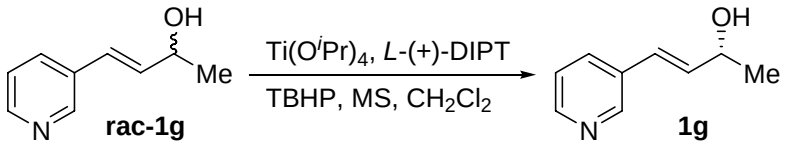
(1) Preparation of rac-1g



To a solution of (*E*)-4-pyridinylbut-3-en-2-one[5] (1.47 g, 10.0 mmol) in a mixed solvent of tetrahydrofuran and methanol (1:1, 20 mL) at 0 °C was added portionwise sodium borohydride (454 mg, 12.0 mmol). After being stirred for 30 min, the mixture was warmed slowly to room temperature and stirred for 1 h. The mixture was quenched with water (10 mL), evaporated to remove the organic solvents, and extracted with ethyl acetate (50 mL). The organic phase was washed successively with water (20 mL) and brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (dichloromethane/methanol,

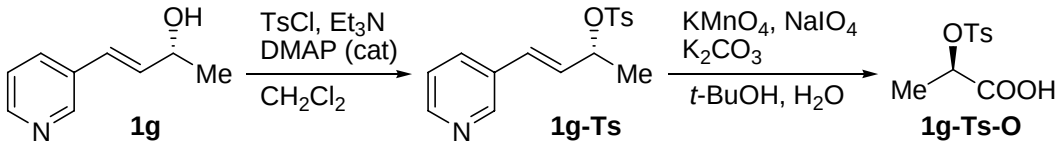
15:1) to give **rac-1g** (1.24 g, 83%) as a yellow oil.[6]

(2) Resolution of rac-1g



A mixture of **rac-1g** (746 mg, 5.0 mmol), *L*-(+)-DIPT (703 mg, 3.0 mmol), and 4 Å molecular sieves (1.00 g) in dichloromethane (20 mL) was cooled to -20 ºC under nitrogen and stirred for 30 min. Ti(O^{i}Pr)$_4$ (852 mg, 0.88 mL, 3.0 mmol) and TBHP (5.0-6.0 M in dichloromethane,1.0 mL) was added subsequently. After being stirred for 2 h, the mixture was added an aqueous solution (15 mL) of $FeSO_4 \cdot 7H_2O$ (1.39 g), filtered under vacuum, and washed with dichloromethane (20 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated to give a residue, which was purified by silica gel chromatography (dichloromethane/methanol, 15:1) to give chiral alcohol **1g (**162 mg, 22%) as a yellow oil.[6] The ee was determined to be 93% by HPLC analysis (Chiralpak AD, λ = 254 nm, *i*-PrOH/hexane = 15/85, flow rate = 1.0 mL/min): t_R (minor) = 9.8 min, t_R (major) = 11.9 min. $[\alpha]_D^{20}$ = -15 (*c* = 6.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.48-8.41 (m, 1H), 7.72-7.65 (m, 1H), 7.27-7.21 (m, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.56-4.47 (m, 1H), 2.60 (s, br, 1H), 1.39 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 148.2, 136.4, 133.0, 132.6, 125.3, 123.5, 68.4, 23.4.

(3) Assignment of the absolute configuration of alcohol 1g

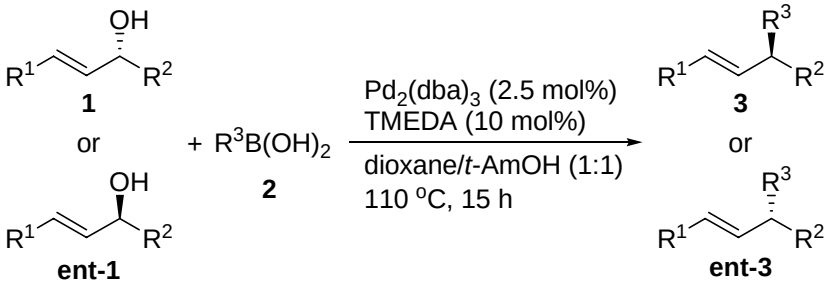


To a solution of chiral alcohol **1g** (74.6 mg, 0.50 mmol), triethylamine (75.9 mg, 0.11 mL, 0.75 mmol), and DMAP (3.1 mg, 5 mol %) in dichloromethane (10 mL) was added portionwise *p*-toluenesulfonyl chloride (114 mg, 0.60 mmol) at 0 ºC. The mixture was warmed to room temperature, stirred overnight, and filtered. The filtrate was washed with water, dried over anhydrous sodium sulfate, and evaporated under vacuum to give crude **1g-Ts**.

To a mixture of crude **1g-Ts** and potassium carbonate (34.6 mg, 0.25 mmol) in *t*-butyl alcohol (25 mL) and water (5 mL) at 0 ºC was added dropwise an aqueous solution (20 mL) of potassium permanganate (20.5 mg, 0.13 mmol), potassium carbonate (34.6 mg, 0.25 mmol), and sodium metaperiodate (535 mg, 2.50 mmol). The resulting mixture was stirred at 0 ºC for 30 min and warmed to room temperature. The mixture was stirred at room temperature for 48 h, cooled to 0 ºC, and quenched

with aqueous HCl (1 M, 3.0 mL). Solid sodium pyrosulfite was added until the reddish color disappeared and then the mixture was evaporated to remove *t*-butyl alcohol. The resulting aqueous solution was extracted with dichloromethane (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue, which was purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:3) to give acid **1g-Ts-O** (21.2 mg, 17%, two steps) as a yellowish solid.[4] m.p. 126-127 °C; $[\alpha]_D^{20}$ = +29 (*c* = 1.00, $CHCl_3$), lit.[4]: $[\alpha]_D^{25}$ = -34.9 (1% solution in chloroform, *S*-enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, br, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.97 (q, *J* = 6.8 Hz, 1H), 2.45 (s, 3H), 1.55 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 145.4, 133.1, 129.9, 128.0, 73.2, 21.7, 18.3.

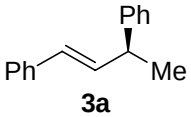
General procedure for the stereospecific cross-coupling of enantioenriched allylic alcohols with boronic acids



A mixture of enantioenriched allylic alcohol **1** (or **ent-1**, 0.50 mmol), boronic acid **2** (0.60 mmol), TMEDA (5.8 mg, 10 mol %), and $Pd_2(dba)_3$ (11.5 mg, 2.5 mol %) in a mixed solvent of dioxane and *tert*-amyl alcohol (1:1, 3.5 mL) was stirred vigorously under nitrogen at room temperature for 5 min and then heated at 110 ºC for 15 h. The mixture was cooled to room temperature and purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (0:100 ~ 1:5) or ethyl acetate/dichloromethane (1:100 ~ 1:25), to give alkene **3** (or **ent-3**).

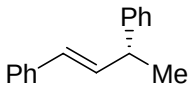
The purified products were found to have the same α/γ and *E*/*Z* ratios for their regioisomers and stereoisomers (if any), respectively, as the crude ones according to ^{1}H NMR spectrometric analysis. The absolute configuration of products **3a**, **3b**, **3e**, **ent-3j**, **ent-3k**, **3n**, **3o**, and **3t** was assigned by comparison of the optical rotation with that reported in the literature, and that of the rest of products was assigned by analogy.

Analytical data for the products



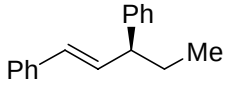
3a,[7] colorless oil; $[\alpha]_D^{20}$ = -37 (*c* = 1.02, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +34 (*c* = 1.0, $CHCl_3$, *R*-enantiomer, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (m, 10H),

6.45-6.33 (m, 2H), 3.68-3.59 (m, 1H), 1.46 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 137.6, 135.2, 128.5, 127.3, 127.0, 126.2, 126.1, 42.6, 21.2. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 0.5/99.5, flow rate = 0.5 mL/min): t_R (major) = 15.6 min, t_R (minor) = 18.1 min.



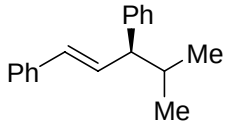
ent-3a

ent-3a,[7] colorless oil; $[\alpha]_D^{20}$ = +35 (c = 0.98, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +34 (c = 1.0, $CHCl_3$, *R*-enantiomer, 95% ee). The ee was determined to be 97% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 0.5/99.5, flow rate = 0.5 mL/min): t_R (minor) = 16.1 min, t_R (major) = 18.4 min.



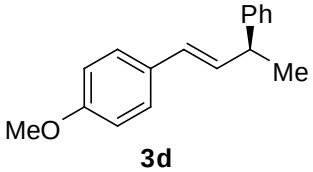
3b

3b,[7] colorless oil; $[\alpha]_D^{20}$ = -47 (c = 1.02, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +44 (c = 1.0, $CHCl_3$, *R*-enantiomer, 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.13 (m, 10H), 6.40 (d, J = 16.0 Hz, 1H), 6.32 (dd, J = 16.0, 7.2 Hz, 1H), 3.34-3.27 (m, 1H), 1.88-1.76 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 137.6, 134.2, 129.5, 128.4, 127.7, 127.0, 126.2, 126.1, 51.0, 28.8, 12.3. The ee was determined to be 97% by HPLC analysis (Chiralpak OJ, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 11.9 min, t_R (minor) = 18.2 min.



3c

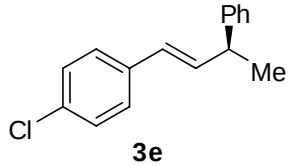
3c,[8] colorless oil; $[\alpha]_D^{20}$ = -36 (c = 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.13 (m, 10H), 6.44-6.33 (m, 2H), 3.09-2.98 (m, 1H), 2.10-1.97 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 137.7, 133.2, 130.3, 128.4, 128.0, 127.0, 126.1, 126.0, 57.6, 33.2, 21.2, 20.9. The ee was determined to be 91% by HPLC analysis (Chiralpak AD, λ = 254 nm, *i*-PrOH/hexane = 1/99, flow rate = 1.0 mL/min): t_R (minor) = 5.1 min, t_R (major) = 5.6 min.



3d

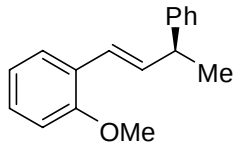
3d,[9] colorless oil; $[\alpha]_D^{20}$ = -16 (c = 1.28, $CHCl_3$); H NMR (400 MHz, $CDCl_3$) δ

7.34-7.16 (m, 7H), 6.85-6.79 (m, 2H), 6.35 (d, J = 16.0 Hz, 1H), 6.24 (dd, J = 16.0, 6.8 Hz, 1H), 3.78 (s, 3H), 3.65-3.57 (m, 1H), 1.45 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 145.9, 133.2, 130.4, 128.4, 127.9, 127.3, 127.2, 126.1, 113.9, 55.3, 42.5, 21.3. The ee was determined to be 94% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 6.2 min, t_R (minor) = 6.6 min.



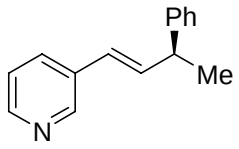
3e

3e,[7] colorless oil; $[\alpha]_D^{20}$ = -36 (c = 1.00, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +33 (c = 1.0, $CHCl_3$, *R*-enantiomer, 91% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (m, 9H), 6.40-6.30 (m, 2H), 3.68-3.56 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 136.1, 136.0, 132.6, 128.6, 128.5, 127.4, 127.3, 127.3, 126.3, 42.6, 21.1. The ee was determined to be 96% by HPLC analysis (Chiralpak OD, λ = 254 nm, hexane, flow rate = 0.8 mL/min): t_R (major) = 16.5 min, t_R (minor) = 18.6 min.



3f

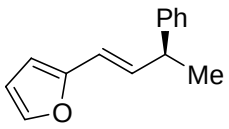
3f, colorless oil; $[\alpha]_D^{20}$ = -12 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.6, 2.0 Hz, 1H), 7.34-7.23 (m, 4H), 7.21-7.13 (m, 2H), 6.93-6.72 (m, 3H), 6.37 (dd, J = 16.0, 6.8 Hz, 1H), 3.82 (s, 3H), 3.70-3.60 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 146.0, 135.7, 128.4, 128.0, 127.3, 126.6, 126.5, 126.1, 123.1, 120.6, 110.8, 55.5, 43.0, 21.4; HRMS (EI) calcd for $C_{17}H_{18}O$ (M) 238.1358, found 238.1359. The ee was determined to be 96% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 5.2 min, t_R (minor) = 5.8 min.



3g

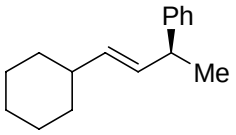
3g, colorless oil; $[\alpha]_D^{20}$ = -59 (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.42 (d, J = 4.0 Hz, 1H), 7.68-7.62 (m, 1H), 7.36-7.16 (m, 6H), 6.46 (dd, J = 16.0, 6.4 Hz, 1H), 6.37 (d, J =16.0 Hz, 1H), 3.70-3.61 (m, 1H), 1.48 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 148.1, 145.0, 137.7, 133.1, 132.6, 128.6, 127.3, 126.4, 125.0, 123.3, 42.7, 21.0; HRMS (EI) calcd for $C_{15}H_{15}N$ (M) 209.1204, found 209.1206. The ee was determined to be 92% by HPLC analysis (Chiralpak OD,

λ = 254 nm, *i*-PrOH/hexane = 10/90, flow rate = 1.0 mL/min): t_R (major) = 12.1 min, t_R (minor) = 16.2 min.



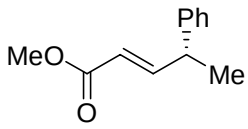
3h

3h, obtained as a 97:3 mixture of α/γ isomers , yellow oil; $[\alpha]_D^{20}$ = -48 (*c* = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.37-7.16 (m, 6H), 6.42-6.28 (m, 2H), 6.22-6.12 (m, 2H), 3.65-3.54 (m, 1H), 1.44 (d, *J* = 7.2 Hz 3H); Partial ^{1}H NMR for the minor *γ*-isomer: *δ* 6.03 (d, *J* = 3.6 Hz, 1H), 5.89-5.79 (m, 1H), 5.56-5.45 (m, 1H), 4.67 (d, *J* = 7.6 Hz, 1H), 1.72 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 153.1, 145.4, 141.4, 134.2, 128.5, 127.3, 126.3, 117.4, 111.1, 106.7, 42.3, 21.1; HRMS (EI) calcd for $C_{14}H_{14}O$ (M) 198.1045, found 198.1049. The ee was determined to be 95% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 9.9 min, t_R (minor) = 11.6 min.



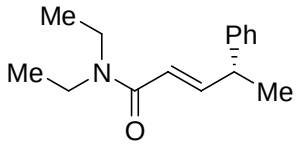
3i

3i,[9] obtained as a 88:12 mixture of α/γ isomers, colorless oil; $[\alpha]_D^{20}$ = -9.8 (*c* = 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32-7.10 (m, 5H), 5.55 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.41 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.45-3.33 (m, 1H), 1.98-1.86 (m, 1H), 1.78-1.60 (m, 4H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.29-0.99 (m, 6H); Partial ^{1}H NMR for the minor *γ*-isomer: *δ* 2.91-2.78 (m, 1H). The ee was determined to be 97% by HPLC analysis (Chiralpak OJ, λ = 220 nm, *i*-PrOH/hexane = 1/99, flow rate = 1.0 mL/min): t_R (minor) = 16.1 min, t_R (major) = 17.5 min.



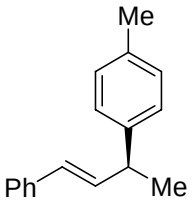
ent-3j

ent-3j,[10] colorless oil; $[\alpha]_D^{20}$ = +19 (*c* = 1.01, $CHCl_3$), lit.[10]: $[\alpha]_D^{25}$ = +15.5 (*c* = 0.3, $CHCl_3$ for *R*-enantiomer, 85% ee, 95:5 *E/Z*); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.35-7.28 (m, 2H), 7.25-7.16 (m, 3H), 7.12 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.81 (dd, *J* = 15.6, 1.6 Hz, 1H), 3.72 (s, 3H), 3.66-3.57 (m, 1H), 1.43 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.2, 152.9, 143.3, 128.7, 127.3, 126.8, 119.7, 51.5, 42.1, 20.2. The ee was determined to be 96% by HPLC analysis (Chiralpak OD, λ = 220 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 5.8 min, t_R (minor) = 6.9 min.



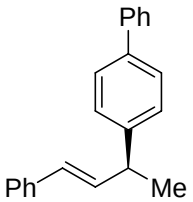
ent-3k

ent-3k,[2] colorless oil; $[\alpha]_D^{20}$ = -6.2 (*c* = 0.80, $CHCl_3$), lit.[2]: $[\alpha]_D^{24}$ = +4.85 (*c* = 0.79, $CHCl_3$, *S*-enantiomer, 83% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.26-7.15 (m, 3H), 7.07 (dd, *J* = 15.2, 6.8 Hz, 1H), 6.13 (dd, *J* = 15.2, 1.6 Hz, 1H), 3.68-3.57 (m, 1H), 3.45-3.28 (m, 4H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.18-1.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 149.5, 144.1, 128.5, 127.3, 126.5, 119.5, 42.3, 42.2, 40.8, 20.8, 14.8, 13.2. The ee was determined to be 97% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 10.1 min, t_R (minor) = 11.1 min.



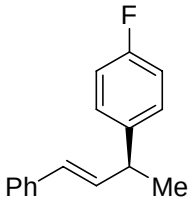
3l

3l,[11] colorless oil; $[\alpha]_D^{20}$ = -29 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.30-7.22 (m, 2H), 7.20-7.08 (m, 5H), 6.43-6.32 (m, 2H), 3.64-3.53 (m, 1H), 2.32 (s, 3H), 1.44 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 137.6, 135.7, 135.5, 129.2, 128.4, 128.3, 127.2, 127.0, 126.1, 42.1, 21.3, 21.0. The ee was determined to be 99% by HPLC analysis (Chiralpak OJ, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (major) = 11.8 min, t_R (minor) = 16.7 min.



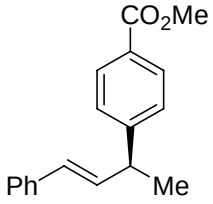
3m

3m, white solid, m.p. 58-59 °C; $[\alpha]_D^{20}$ = -28 (*c* = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.50 (m, 4H), 744-7.24 (m, 9H), 7.21-7.15 (m, 1H), 6.49-6.34 (m, 2H), 3.73-3.60 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 141.0, 139.2, 137.5, 135.1, 128.7, 128.5, 127.7, 127.2, 127.1, 127.0, 126.2, 42.2, 21.2; HRMS (EI) calcd for $C_{22}H_{20}$ (M) 284.1565, found 284.1563. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 1.0 mL/min): t_R (minor) = 8.7min, t_R (major) = 11.1 min.



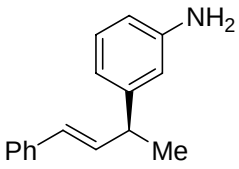
3n

3n,[7] colorless oil; $[\alpha]_D^{20}$ = -39 (*c* = 1.09, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +29 (*c* = 1.0, $CHCl_3$, *R*-enantiomer, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.17 (m, 7H), 7.04-6.95 (m, 2H), 6.43-6.30 (m, 2H), 3.67-3.58 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, $J_{C\text{-}F}$ = 242.3 Hz), 141.2 (d, $J_{C\text{-}F}$ = 3.2 Hz), 137.4, 135.0, 128.7 (d, $J_{C\text{-}F}$ = 7.5 Hz), 128.5, 127.1, 126.1, 115.2 (d, $J_{C\text{-}F}$ = 21.0 Hz), 41.8, 21.3. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, hexane, flow rate = 0.3 mL/min): t_R (minor) = 55.7 min, t_R (major) = 64.3 min.



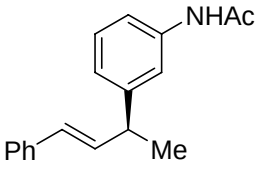
3o

3o,[7] colorless oil; $[\alpha]_D^{20}$ = -33 (*c* = 1.00, $CHCl_3$), lit.[7]: $[\alpha]_D^{20}$ = +29 (*c* = 1.0, $CHCl_3$, *R*-enantiomer, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.37-7.17 (m, 7H), 6.45-6.31 (m, 2H), 3.90 (s, 3H), 3.74-3.65 (m, 1H), 1.47 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.0, 137.3, 134.2, 129.9, 129.2, 128.5, 128.2, 127.3, 126.2, 52.0, 42.6, 21.0. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 2/98, flow rate = 0.8 mL/min): t_R (minor) = 12.4 min, t_R (major) = 13.8 min.



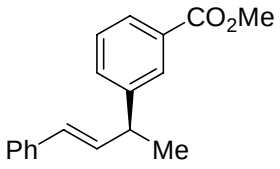
3p

3p,[12] brown oil; $[\alpha]_D^{20}$ = -19 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (m, 5H), 7.13-7.03 (m, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.58 (s, 1H), 6.55-6.48 (m, 1H), 6.44-6.31 (m, 2H), 3.75-3.33 (m, 3H), 1.42 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 146.4, 137.6, 135.3, 129.4, 128.5, 128.3, 127.0, 126.1, 117.7, 114.1, 113.1, 42.5, 21.1. The ee of compound **3p** was determined to be 99% after being converted to compound **3q** by acylation (see below).



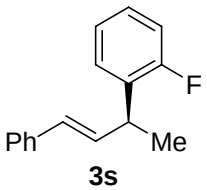
3q

3q, obtained as a 98:2 mixture of α/γ isomers , colorless oil; $[\alpha]_D^{20}$ = -14 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.46-7.15 (m, 9H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.44-6.31 (m, 2H), 3.65-3.56 (m, 1H), 2.13 (s, 3H), 1.44 (d, *J* = 7.2 Hz, 3H); Partial ^{1}H NMR for the minor *γ*-isomer: *δ* 1.72 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.3, 146.7, 138.1, 137.5, 134.9, 129.1, 128.7, 128.5, 127.1, 126.2, 123.3, 118.8, 117.9, 42.5, 24.6, 21.1; HRMS (EI) calcd for $C_{18}H_{19}NO$ (M) 265.1467, found 265.1474. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 10/90, flow rate = 1.0 mL/min): t_R (major) = 11.6 min, t_R (minor) = 14.1 min.



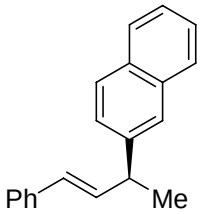
3r

3r, colorless oil; $[\alpha]_D^{20}$ = -8.4 (*c* = 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.97-7.94 (m, 1H), 7.91-7.86 (m, 1H), 7.48-7.43 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.31-7.25 (m, 2H), 7.22-7.17 (m, 1H), 6.45-6.31 (m, 2H), 3.90 (s, 3H), 3.73-3.65 (m, 1H), 1.48 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.2, 146.0, 137.4, 134.5, 132.0, 130.4, 129.1, 128.5, 128.4, 127.6, 127.2, 126.2, 52.1, 42.5, 21.2; HRMS (EI) calcd for $C_{18}H_{18}O_2$ (M) 266.1307, found 266.1306. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 1/99, flow rate = 0.8 mL/min): t_R (major) = 18.2 min, t_R (minor) = 21.2 min.



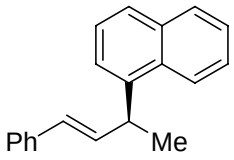
3s

3s, colorless oil; $[\alpha]_D^{20}$ = -46 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.38-7.33 (m, 2H), 7.30-7.23 (m, 3H), 7.21-7.15 (m, 2H), 7.12-7.06 (m, 1H), 7.05-6.98 (m, 1H), 6.48-6.34 (m, 2H), 4.00-3.91 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.6 (d, $J_{C\text{-}F}$ = 243.8 Hz), 137.5, 133.6, 132.5 (d, $J_{C\text{-}F}$ = 14.5 Hz), 129.1, 128.5, 128.4 (d, $J_{C\text{-}F}$ = 4.8 Hz), 127.7 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.1, 126.2, 124.1 (d, $J_{C\text{-}F}$ = 3.5 Hz), 115.5 (d, $J_{C\text{-}F}$ = 22.5 Hz), 35.7 (d, $J_{C\text{-}F}$ = 2.4 Hz), 20.2; HRMS (EI) calcd for $C_{16}H_{15}F$ (M) 226.1158, found 226.1157. The ee was determined to be 99% by HPLC analysis (Chiralpak OD, λ = 254 nm, hexane, flow rate = 0.8 mL/min): t_R (minor) = 13.9 min, t_R (major) = 14.8 min.



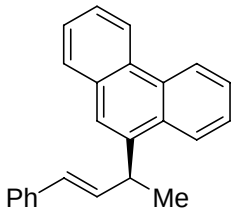
3t

3t,[13] white solid, m.p. 55-56 °C; $[\alpha]_D^{20}$ = -29 (*c* = 2.10, $CHCl_3$), lit.[13]: $[\alpha]_D^{24}$ = -21 (*c* = 8.40, $CHCl_3$, *S*-enantiomer, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.72 (m, 3H), 7.69 (s, 1H), 7.48-7.15 (m, 8H), 6.55-6.34 (m, 2H), 3.87-3.70 (m, 1H), 1.55 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 137.5, 135.1, 133.7, 132.3, 128.8, 128.5, 128.0, 127.6, 127.1, 126.3, 126.2, 125.9, 125.3, 125.2, 42.6, 21.1. The ee was determined to be 99% by HPLC analysis (Chiralpak OD + Chiralpak OD-H), λ = 254 nm, *i*-PrOH/hexane = 0.8/99.2 flow rate = 1.0 mL/min): t_R (major) = 19.0 min, t_R (minor) = 20.0 min.



3u

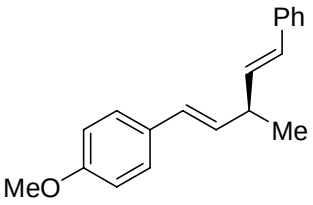
3u,[9] white solid, m.p. 52-54 °C; $[\alpha]_D^{20}$ = -186 (*c* = 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.75-7.70 (m, 1H), 7.54-7.40 (m, 4H), 7.37-7.32 (m, 2H), 7.30-7.24 (m, 2H), 7.21-7.14 (m, 1H), 6.55 (dd, *J* = 16.0, 5.6 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.51-4.41 (m, 1H), 1.61 (d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.6, 135.0, 134.0, 131.4, 128.9, 128.5, 127.0, 126.9, 126.1, 125.9, 125.6, 125.4, 123.8, 123.5, 37.3, 20.8. The ee was determined to be 98% by HPLC analysis (Chiralpak OD, λ = 254 nm, *i*-PrOH/hexane = 1/99, flow rate = 0.8 mL/min): t_R (minor) = 23.5 min, t_R (major) = 24.8 min.



3v

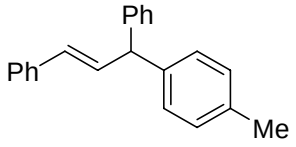
3v, white solid, m.p. 58-60 °C; $[\alpha]_D^{20}$ = -66 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 7.2 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.67 (s, 1H), 7.65-7.51 (m, 4H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.28-7.23 (m, 2H), 7.19-7.15 (m, 1H), 6.59 (dd, *J* = 16.0, 6.0 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 4.49-4.38 (m, 1H), 1.66 (d, *J* = 6.8 Hz ,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 137.6, 134.8, 131.8, 130.8, 129.6, 129.3, 128.5, 128.4, 127.1, 126.6,

126.5, 126.2, 126.1, 124.5, 124.3, 123.3, 122.4, 37.5, 20.6; HRMS (EI) calcd for $C_{24}H_{20}$ (M), 308.1565, found 308.1556. The ee was determined to be 99% by HPLC analysis (Chiralpak AD, λ = 254 nm, *i*-PrOH/hexane = 0.7/99.3, flow rate = 1.0 mL/min): t_R (minor) = 9.7 min, t_R (major) = 10.5 min.



3w

3w, colorless oil; $[\alpha]_D^{20}$ = -13 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 2H), 7.33-7.15 (m, 5H), 6.87-6.81 (m, 2H), 6.45-6.33 (m, 2H), 6.28-6.20 (m, 1H), 6.13-6.05 (m, 1H), 3.79 (s, 3H), 3.23-3.13 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 137.7, 134.5, 132.1, 130.4, 128.6, 128.5, 128.2, 127.2, 127.0, 126.1, 113.9, 55.3, 40.0, 20.3; HRMS (EI) calcd for $C_{19}H_{20}O$ (M), 264.1514, found 264.1510. The ee was determined to be 94% by HPLC analysis (Chiralpak AD, λ = 254 nm, *i*-PrOH/hexane = 1/99, flow rate = 1.0 mL/min): t_R (major) = 8.6 min, t_R (minor) = 9.7 min.



3x

3x,[14] colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.17 (m, 10H), 7.15-7.10 (m, 4H), 6.66 (dd, *J* = 16.0, 7.6 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.85 (d, *J* = 7.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.6, 137.4, 136.0, 132.8, 131.2, 129.2, 128.6 128.5, 127.3, 126.4, 126.3, 53.8, 21.0.

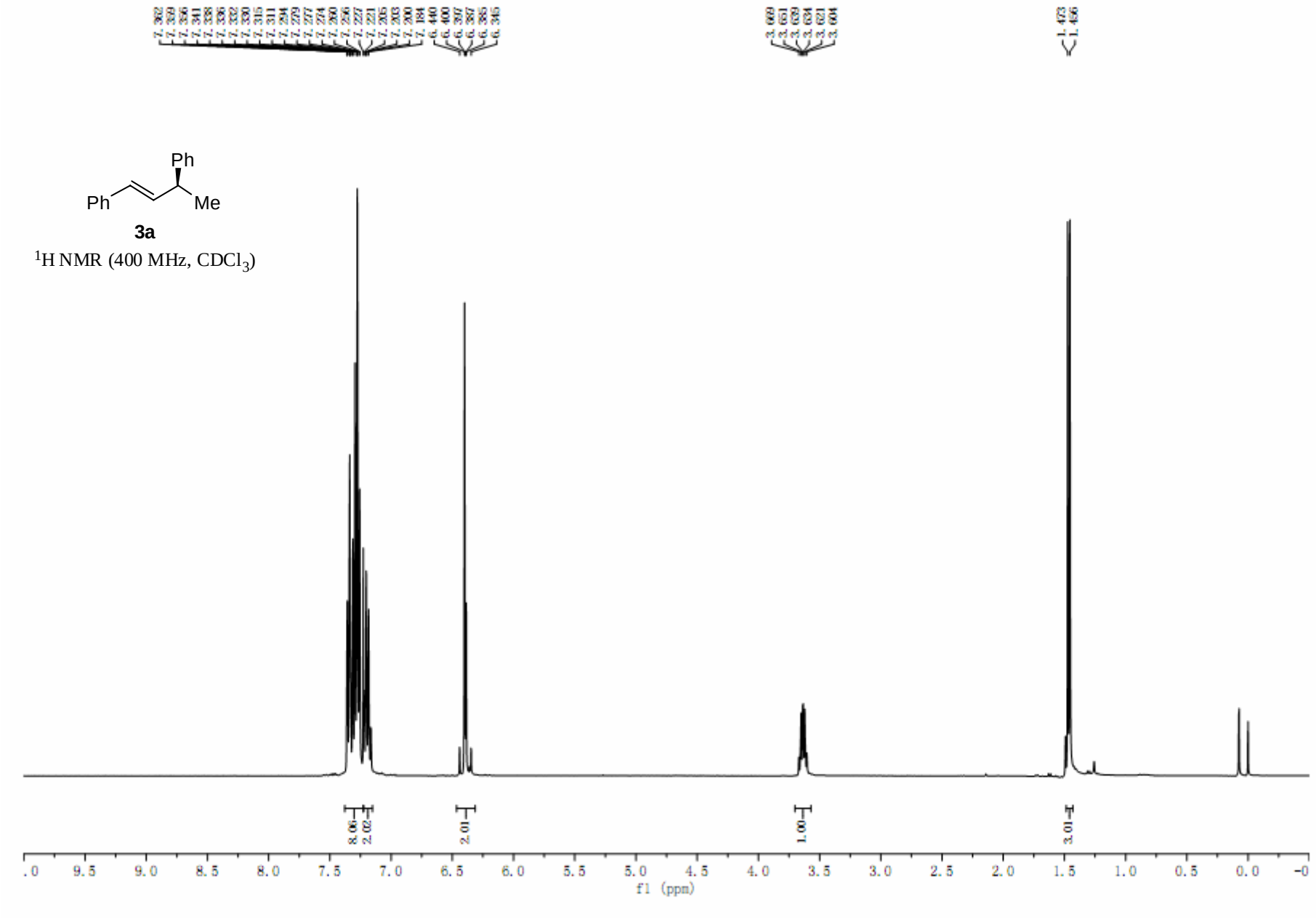
References

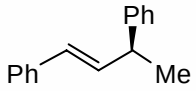
1 (*a*) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765; (*b*) M. Sasaki, H. Ikemoto, M. Kawahata, K. Yamaguchi and K. Takeda, *Chem. Eur. J.*, 2009, **15**, 4663; (*c*) G. H. P. Roos and A. R. Donovan, *Synlett*, 1996, 1189.

2 T. Hata, R. Bannai, M. Otsuki and H. Urabe, *Org. Lett.*, 2010, **12**, 1012.

3 (*a*) E. Brenna, C. D. Negri, C. Fuganti, F. G. Gatti and S. Serra, *Tetrahedron: Asymmetry*, 2004, **15**, 335; (*b*) V. B. Birman and H. Jiang, *Org. Lett.*, 2005, **7**, 3445; (*c*) S. Sgalla, G. Fabrizi, R. Cirilli, A. Macone, A. Bonamore, A. Boffi and S. Cacchi, *Tetrahedron: Asymmetry*, 2007, **18**, 2791; (*d*) C. M. Binder, A. Bautista, M. Zaidlewicz, M. P. Krzemiński, A. Oliver and B. Singaram, *J. Org. Chem.*, 2009, **74**, 2337; (*e*) S. Akai, R. Hanada, N. Fujiwara, Y. Kita and M. Egi, *Org. Lett.*, 2010, **12**, 4900.

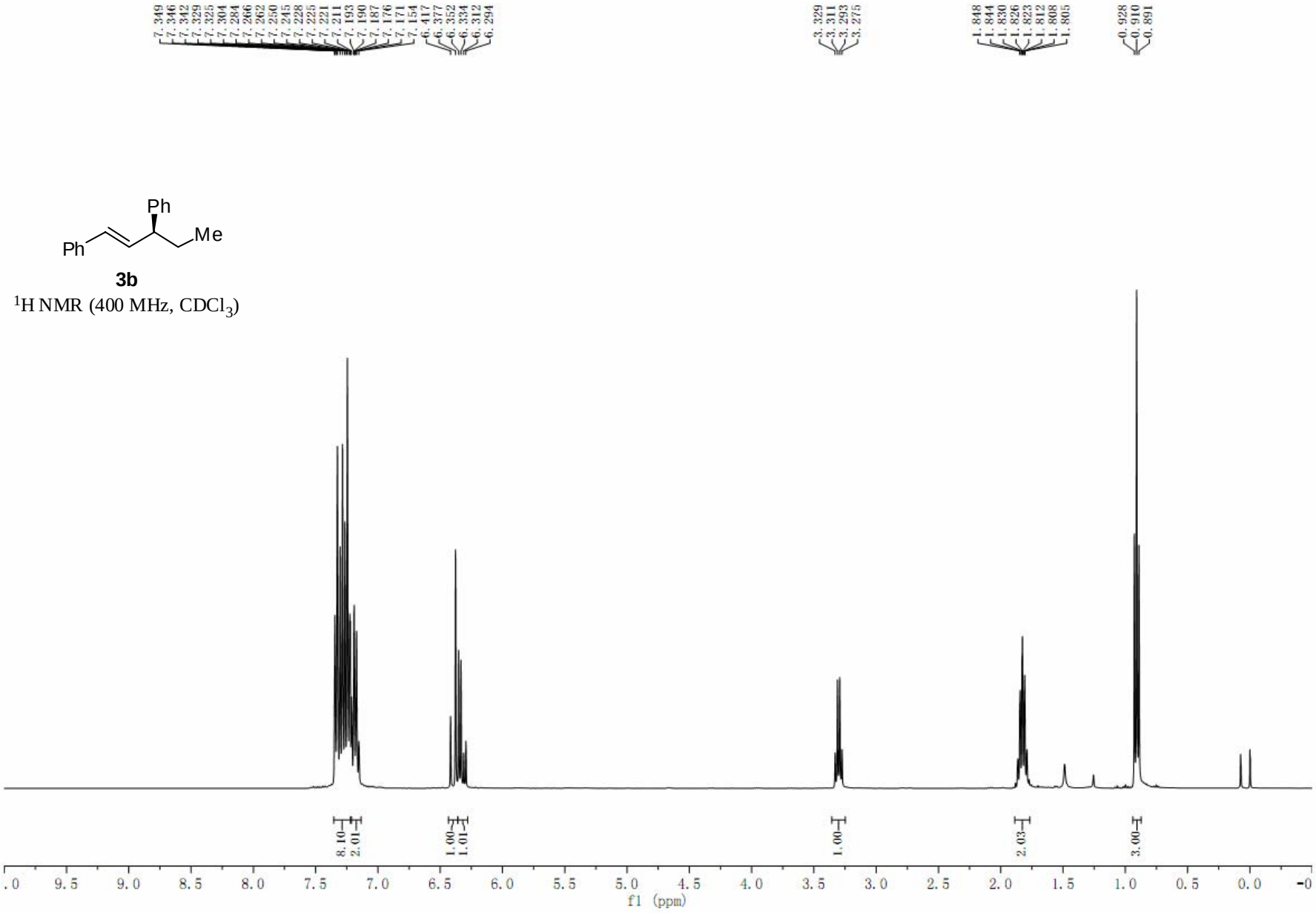
4 A. V. Kurkin, D. S. Belov and M. A Yurovskaya, *Chem. Heterocycl. Compd*., 2008, **44**, 1123.
5 K. Zumbansen, A. Döhring and B. List, *Adv. Synth. Catal*., 2010, **352**, 1135.
6 For a racemic form, see: Y. Tamaru, Y. Yamada, Z. Yoshida, *J. Org. Chem.*, 1978, **43**, 3396.
7 M.-B. Li, Y, Wang and S.-K. Tian, *Angew. Chem. Int. Ed.*, 2012, **51**, 2968.
8 For a racemic form, see: Y. Uozumi, H. Danjo and T. Hayashi, *J. Org. Chem.*, 1999, **64**, 3384.
9 For a racemic form, see: C. Li, J. Xing, J. Zhao, P. Huynh, W. Zhang, P. Jiang and Y. J. Zhang, *Org. Lett.*, 2012, **14**, 390.
10 A. Baeza, C. Nájera and J. M. Sansano, *Eur. J. Org. Chem*., 2007, 1101.
11 For a racemic form, see: Z.-Q. Liu, Y. Zhang, L. Zhao, Z. Li, J. Wang, H. Li and L.-M. Wu, *Org. Lett.*, 2011, **13**, 2208.
12 For a racemic form, see: B. J. Stokes, S. M. Opra and M. S. Sigman, *J. Am. Chem. Soc.*, 2012, **134**, 11408.
13 P. Maity, D. M. Shacklady–McAtee, G. P. A. Yap, E. R. Sirianni and M. P. Watson, *J. Am. Chem. Soc*., 2013, **135**, 280.
14 G. W. Kabalka, G. Dong and B. Venkataiah, *Org. Lett*., 2003, **5**, 893.


Ph
Ph
Me
3a
1H NMR (400 MHz, CDCl3)
f1 (ppm)



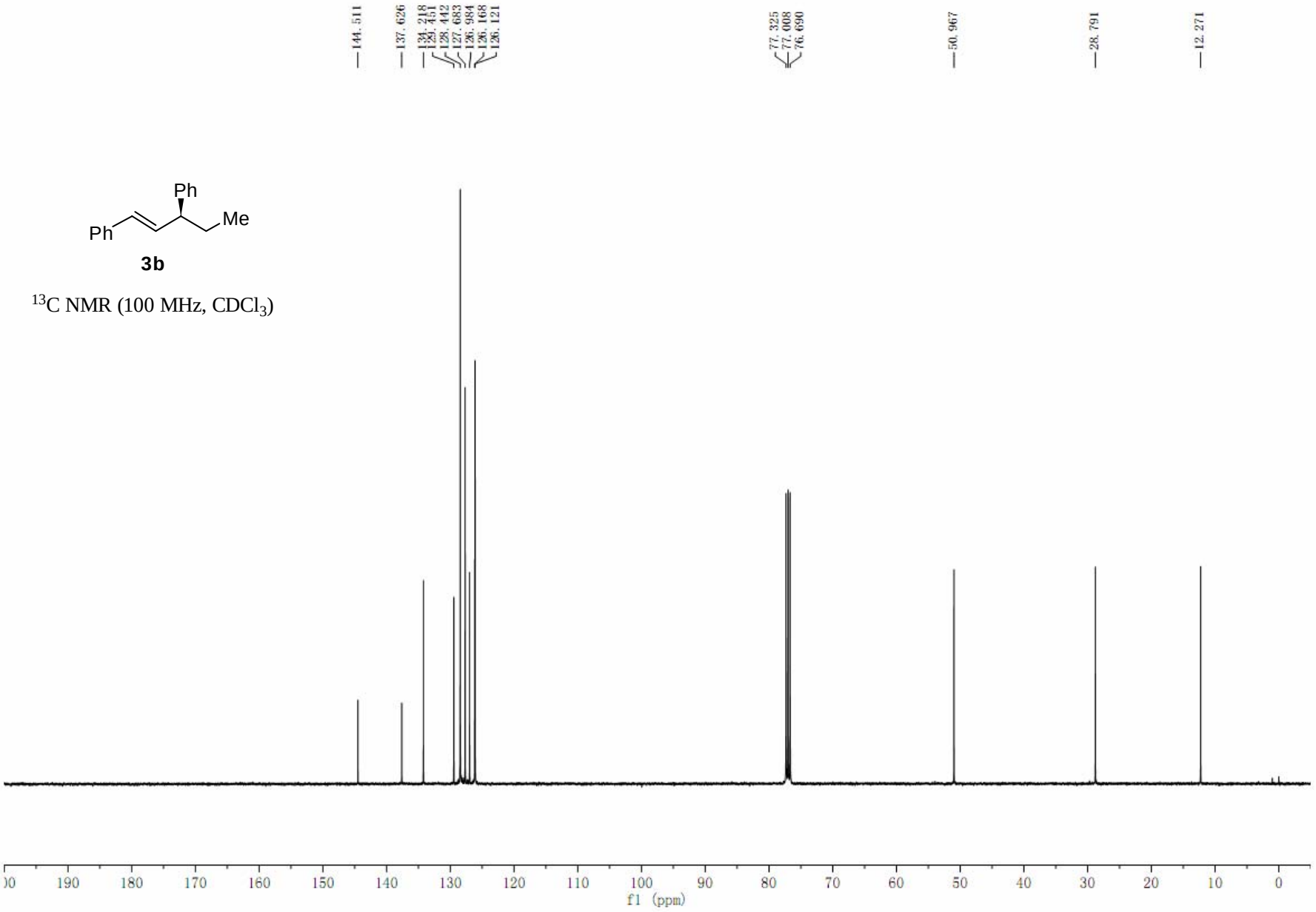
3a

^{13}C NMR (100 MHz, $CDCl_3$)



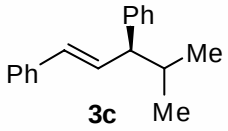
3b

^{1}H NMR (400 MHz, $CDCl_3$)



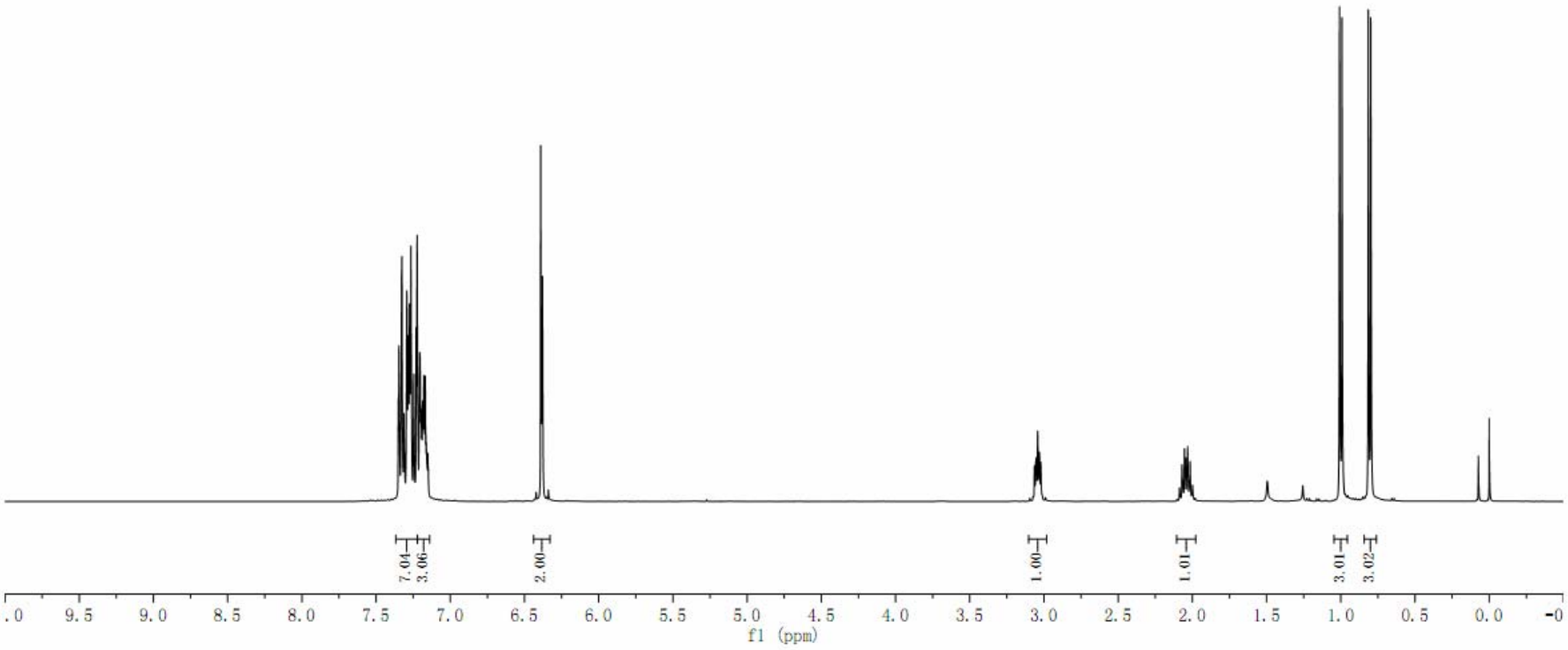
3b

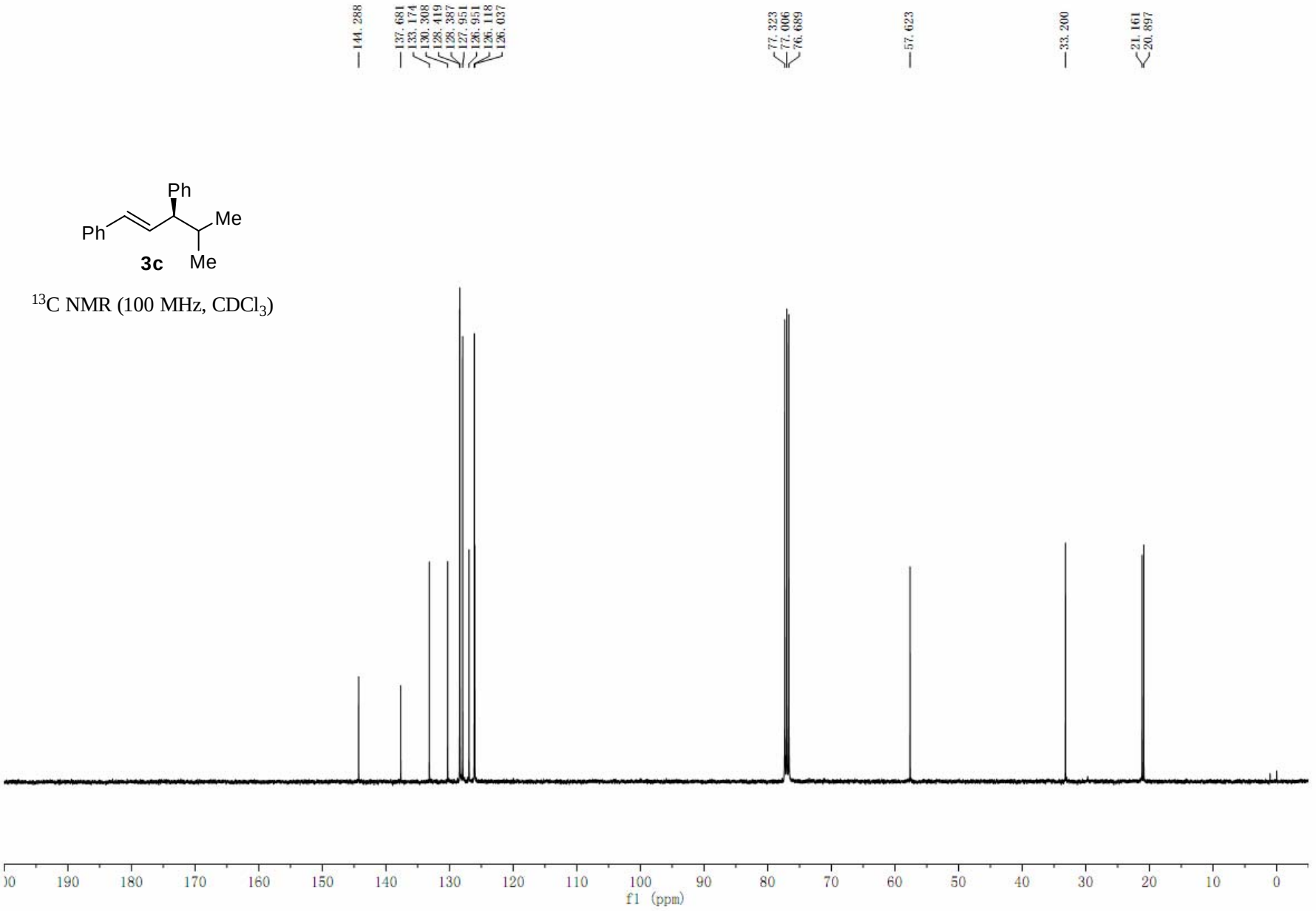
^{13}C NMR (100 MHz, $CDCl_3$)



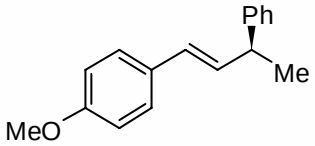
3c

^{1}H NMR (400 MHz, $CDCl_3$)



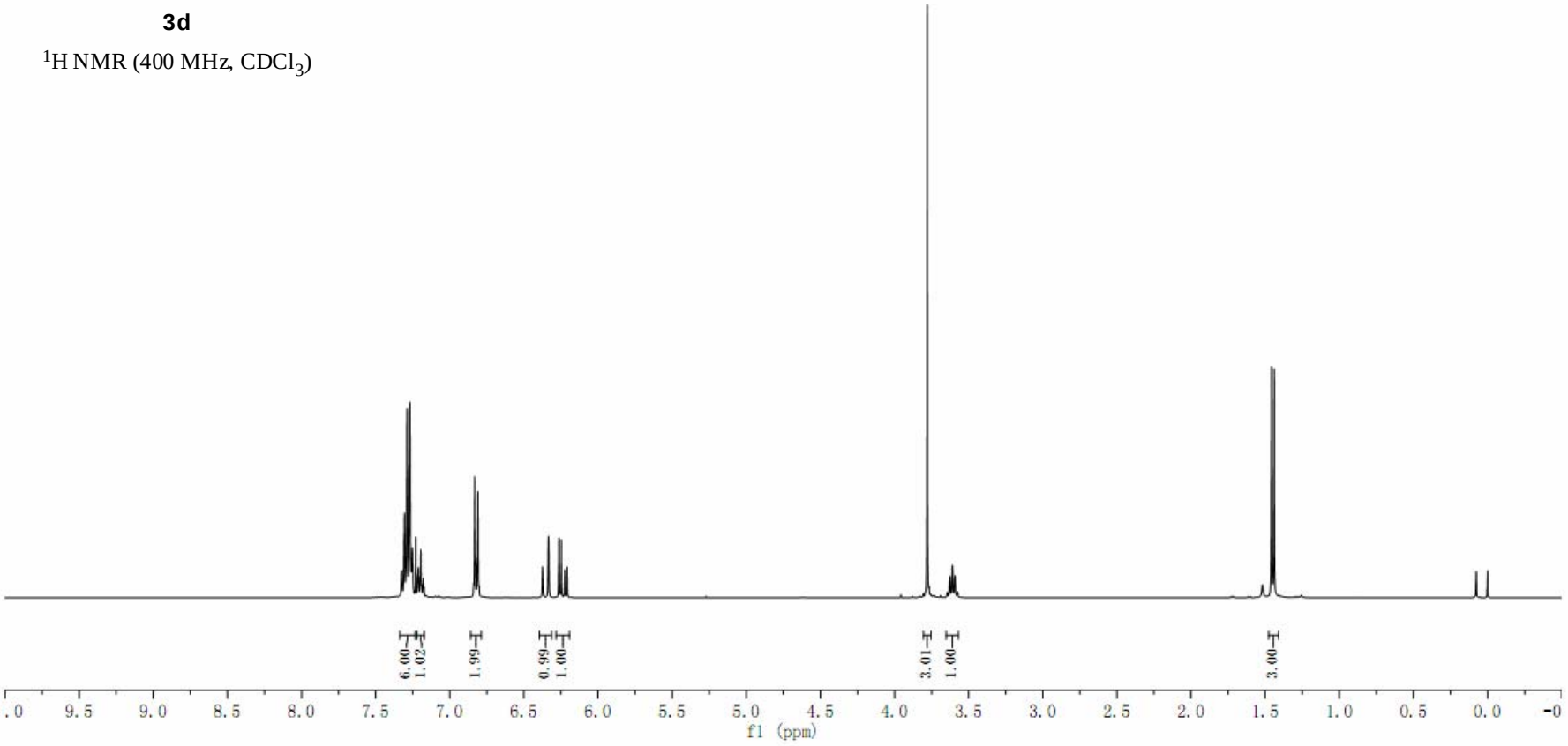


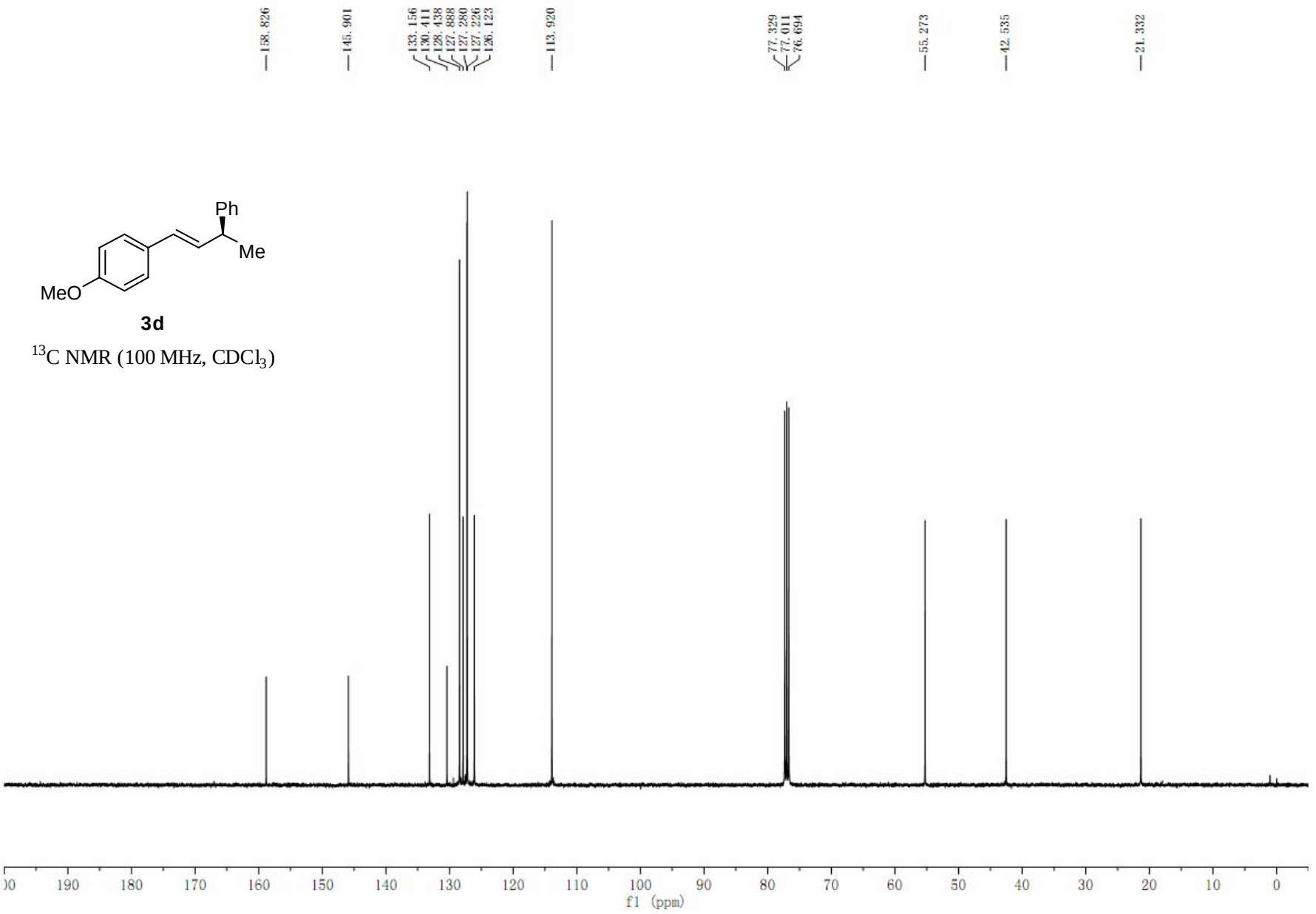
^{13}C NMR (100 MHz, $CDCl_3$)



3d

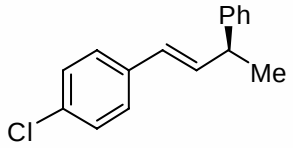
^{1}H NMR (400 MHz, $CDCl_3$)





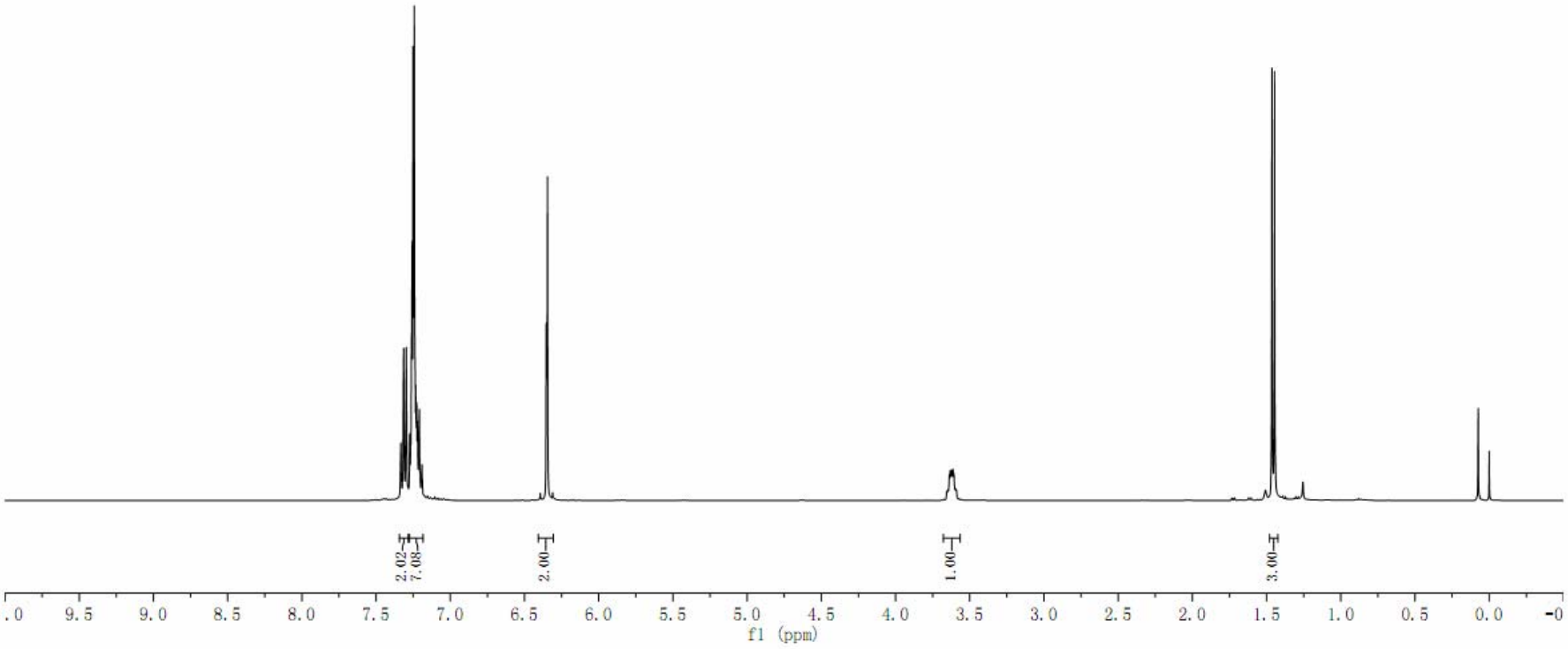
3d

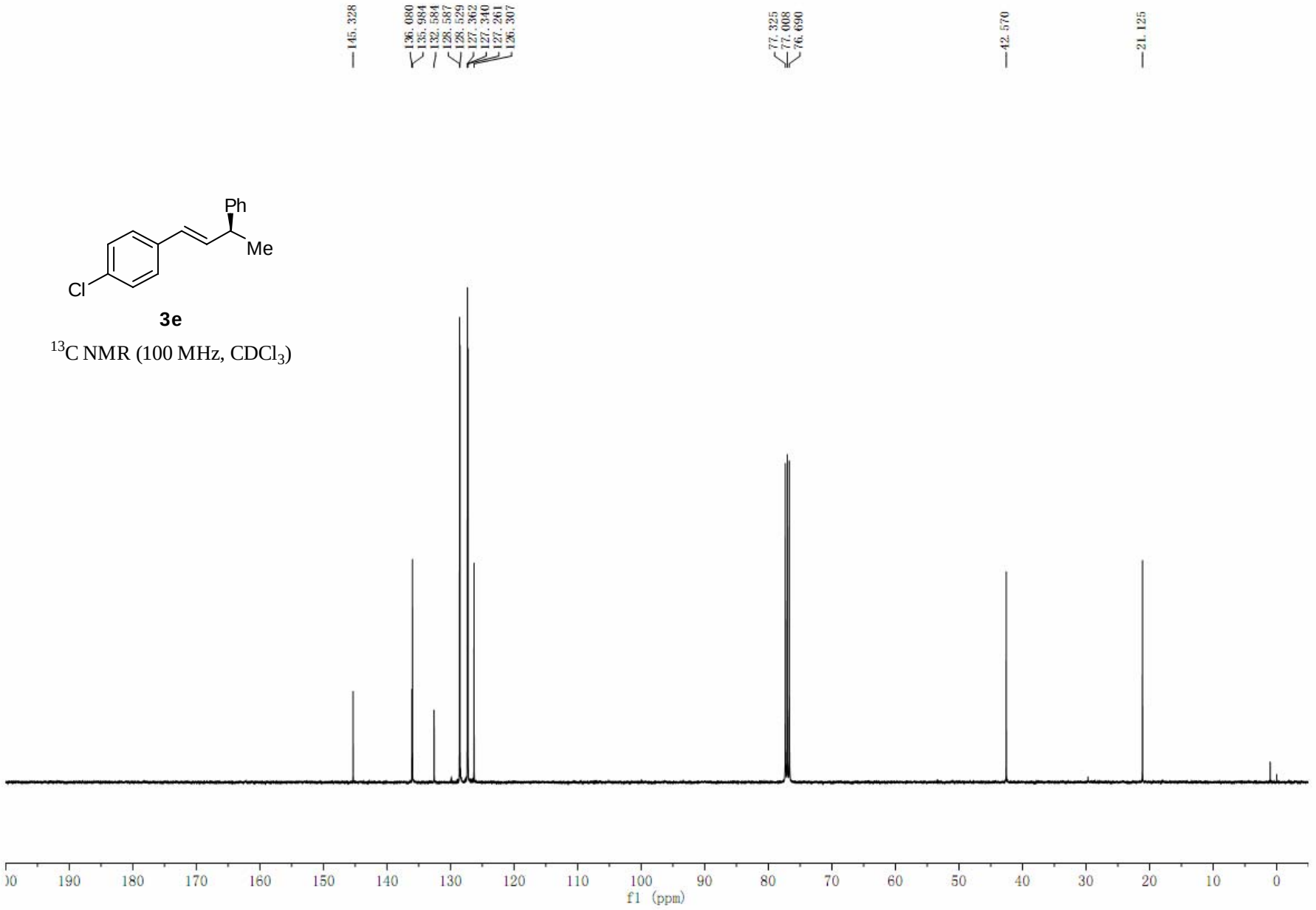
^{13}C NMR (100 MHz, $CDCl_3$)



3e

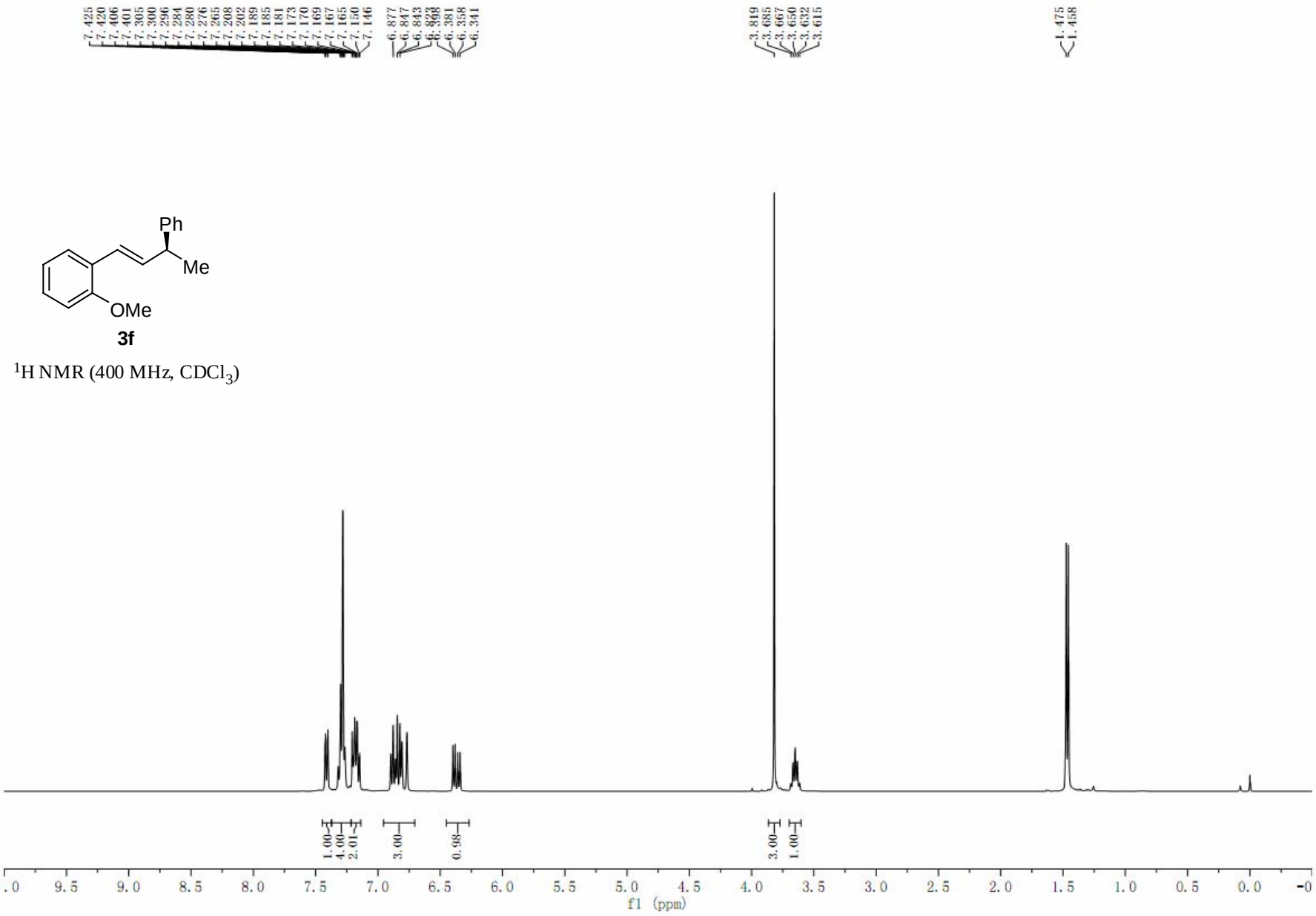
^{1}H NMR (400 MHz, $CDCl_3$)





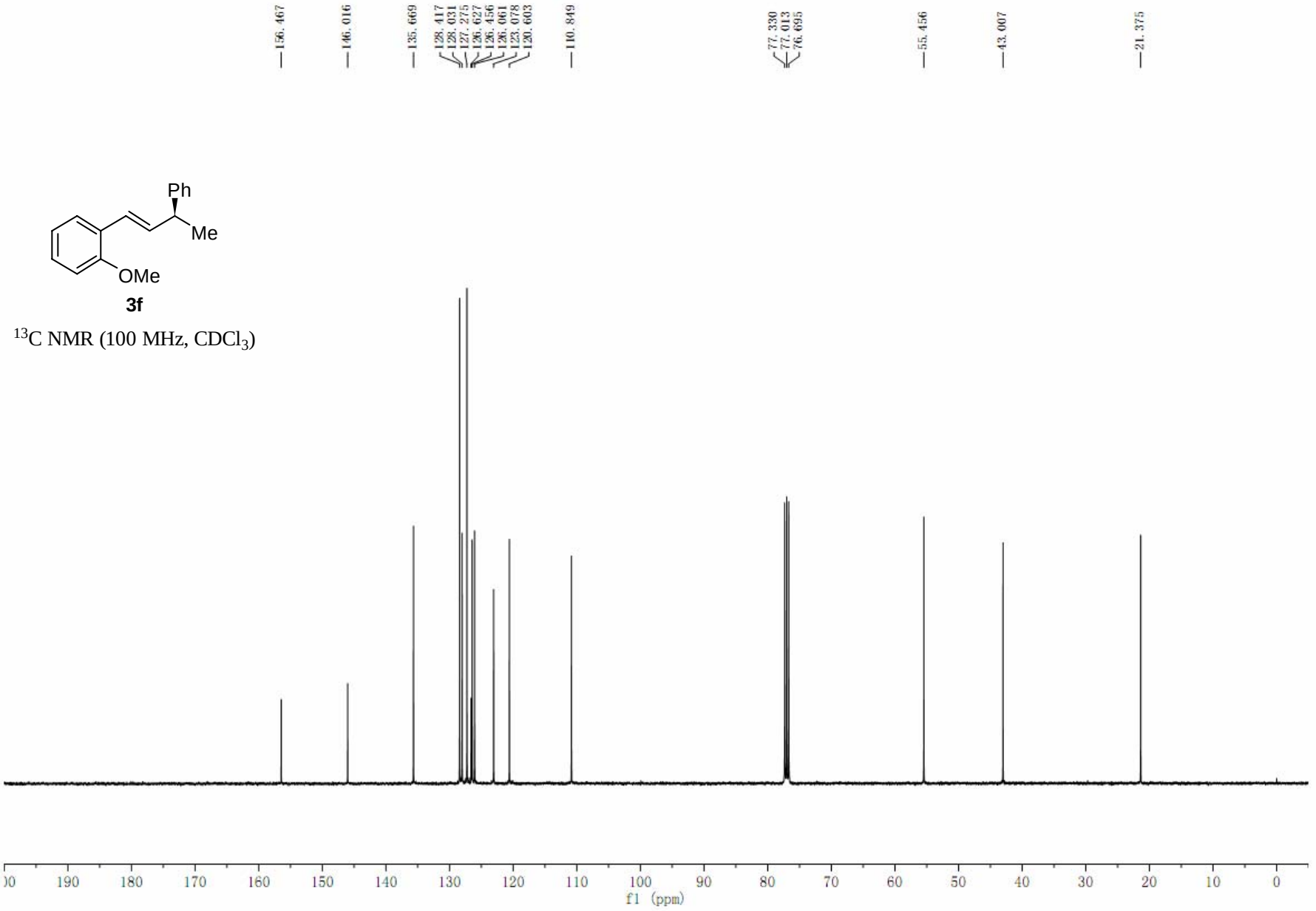
3e

^{13}C NMR (100 MHz, $CDCl_3$)



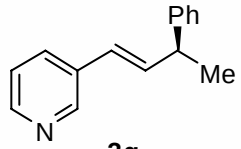
3f

^{1}H NMR (400 MHz, $CDCl_3$)



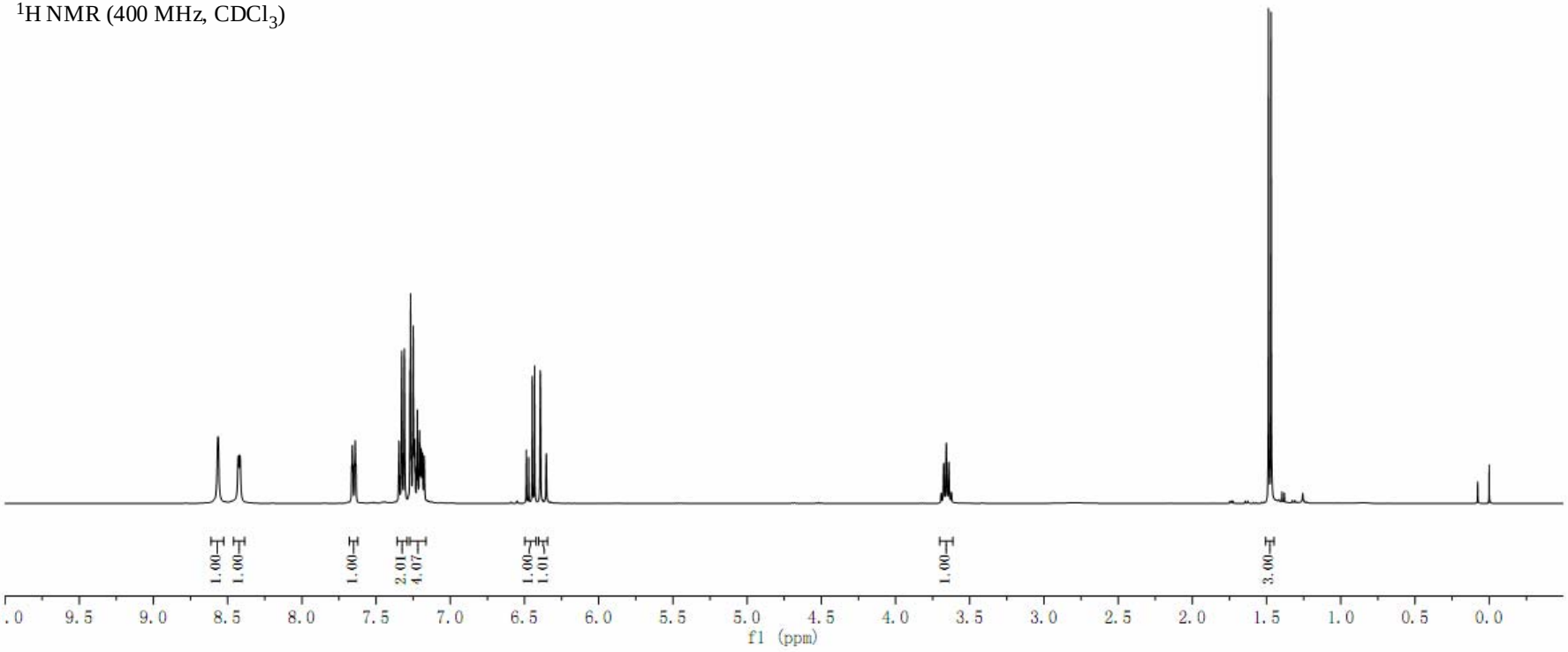
3f

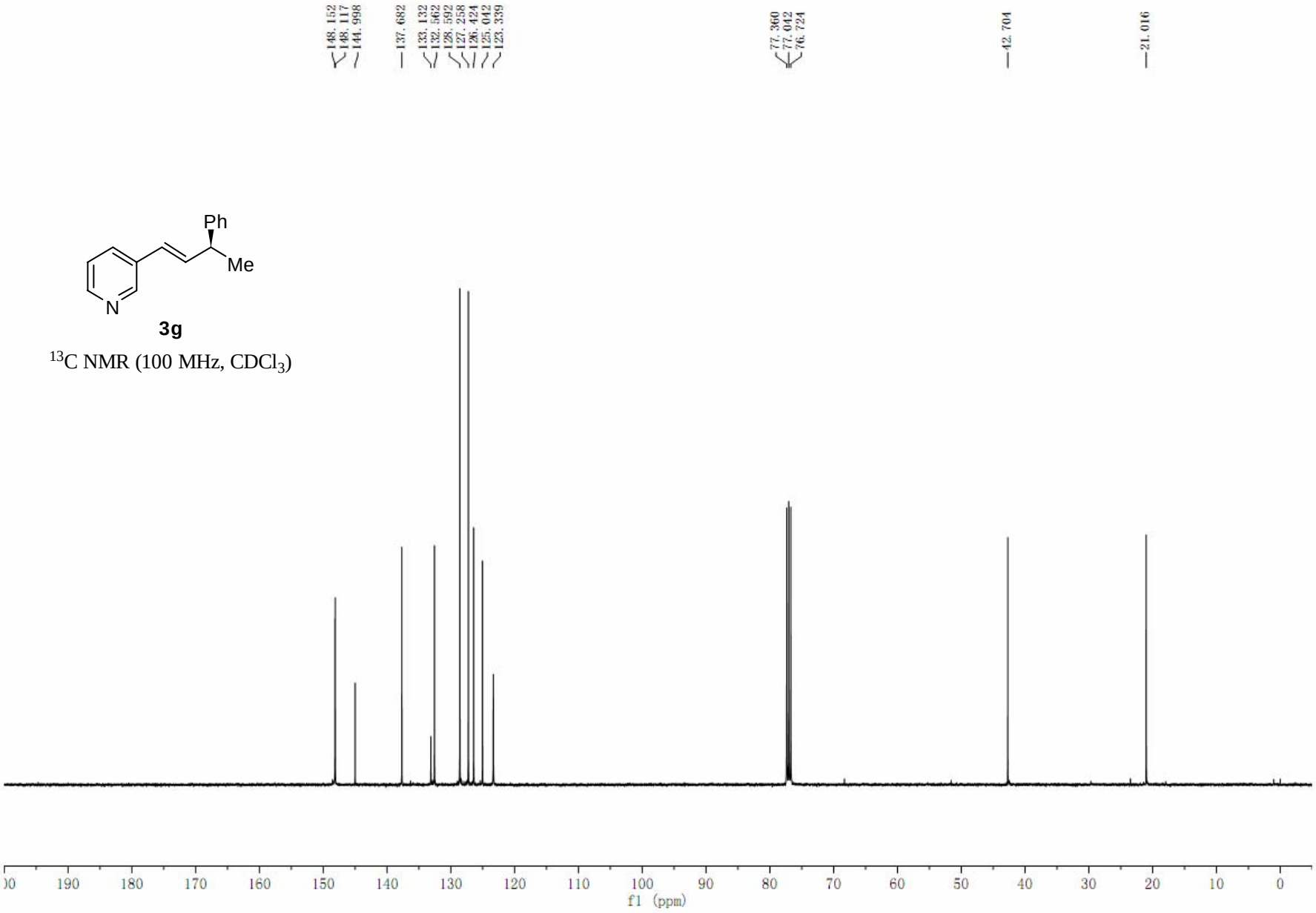
^{13}C NMR (100 MHz, $CDCl_3$)



3g

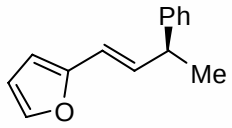
^{1}H NMR (400 MHz, $CDCl_3$)





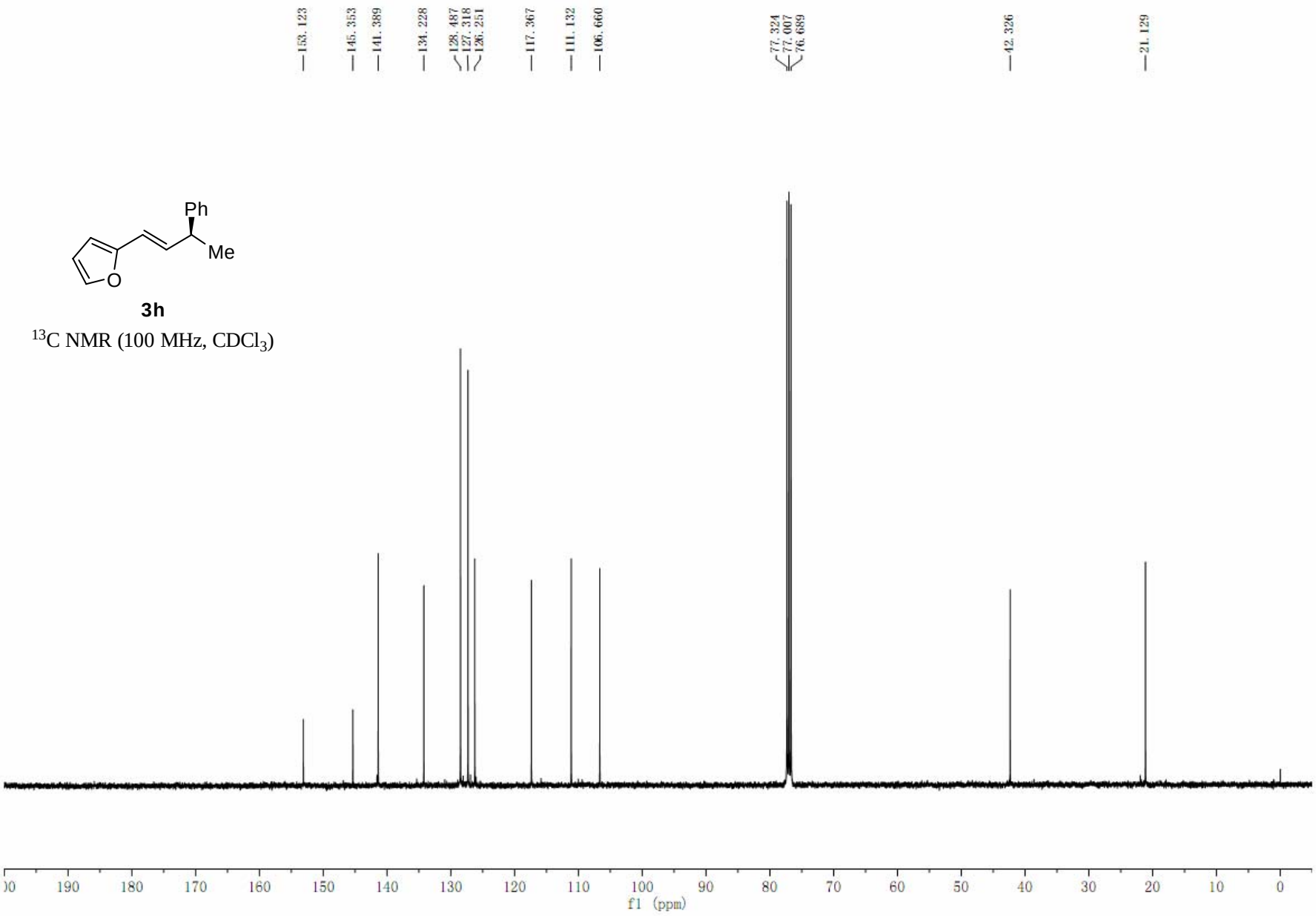
3g

^{13}C NMR (100 MHz, $CDCl_3$)



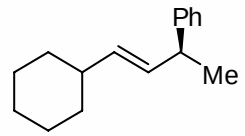
3h

^{1}H NMR (400 MHz, $CDCl_3$)



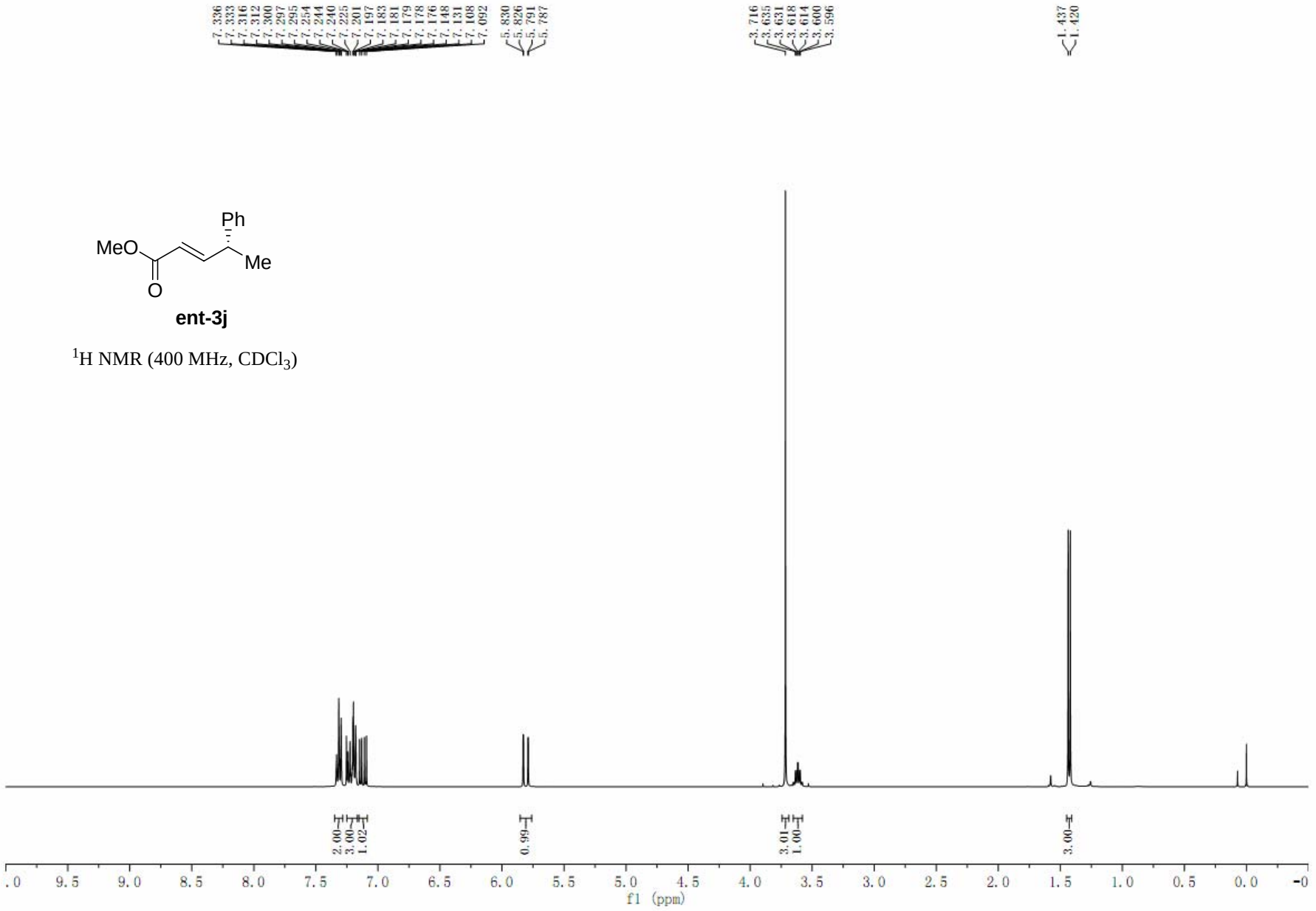
3h

^{13}C NMR (100 MHz, $CDCl_3$)



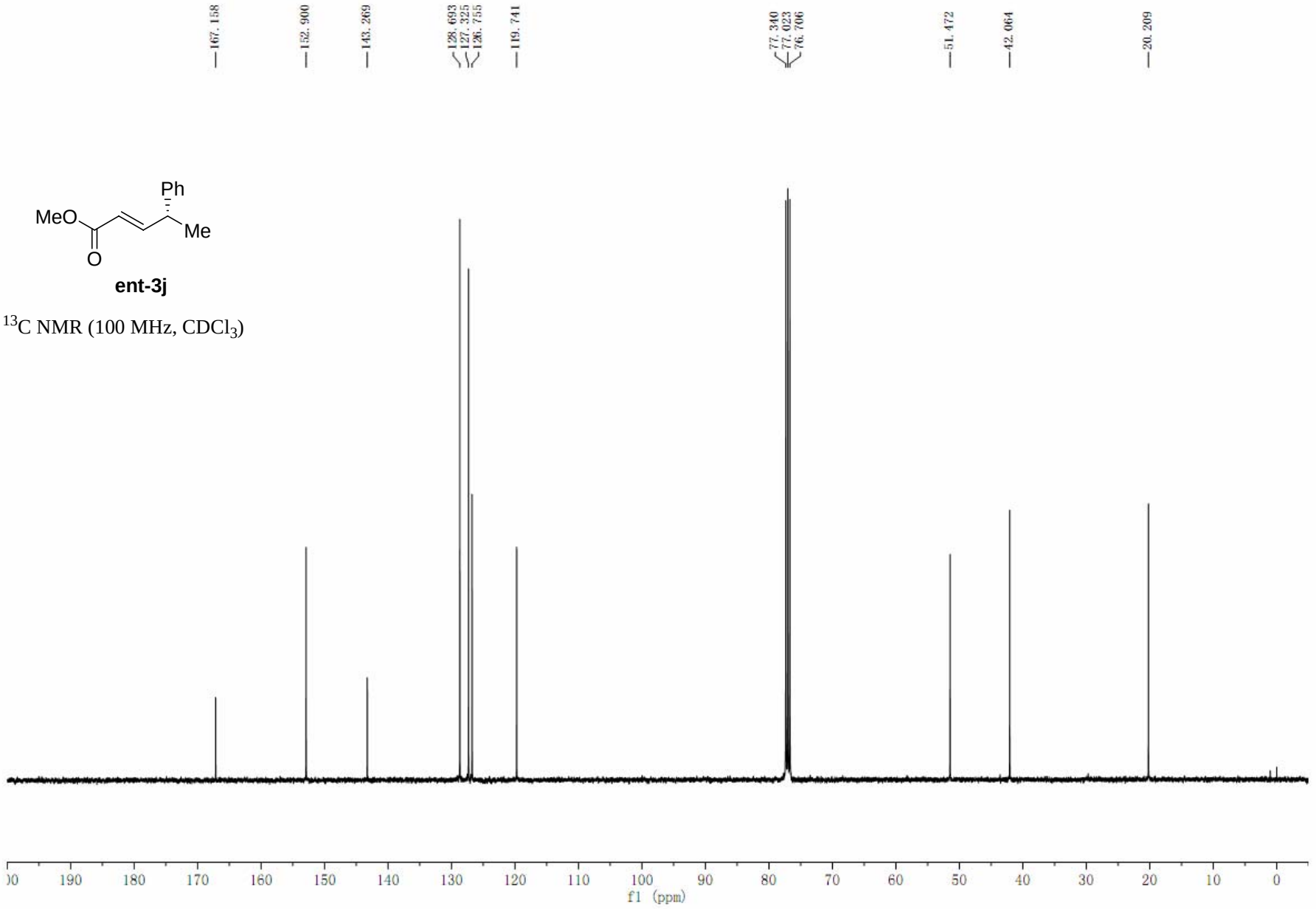
3i

^{1}H NMR (400 MHz, $CDCl_3$)



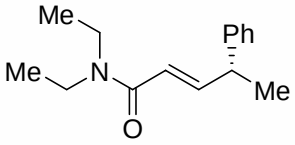
ent-3j

^{1}H NMR (400 MHz, $CDCl_3$)



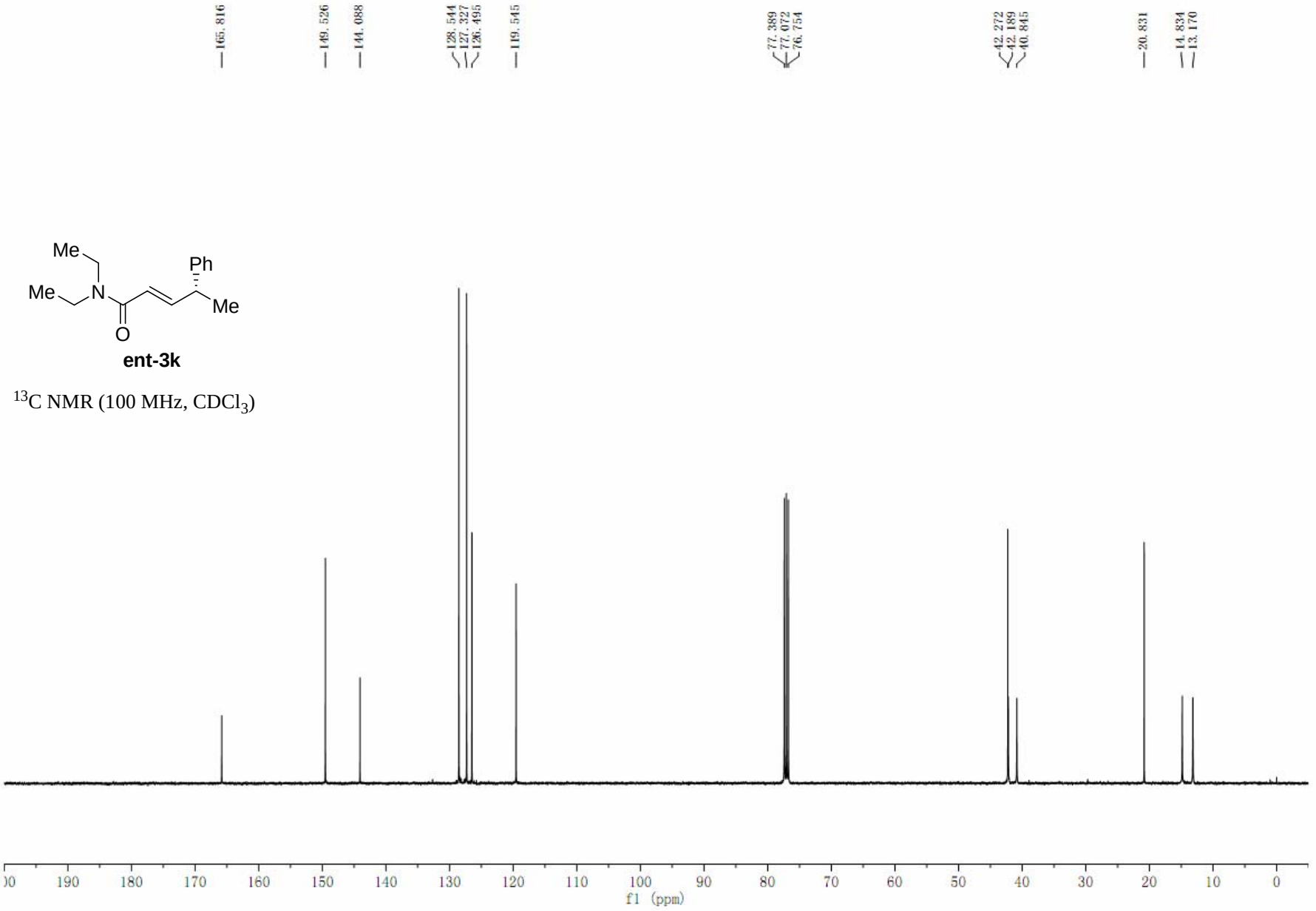
ent-3j

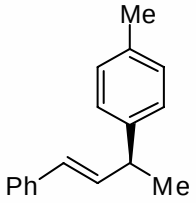
^{13}C NMR (100 MHz, $CDCl_3$)



ent-3k

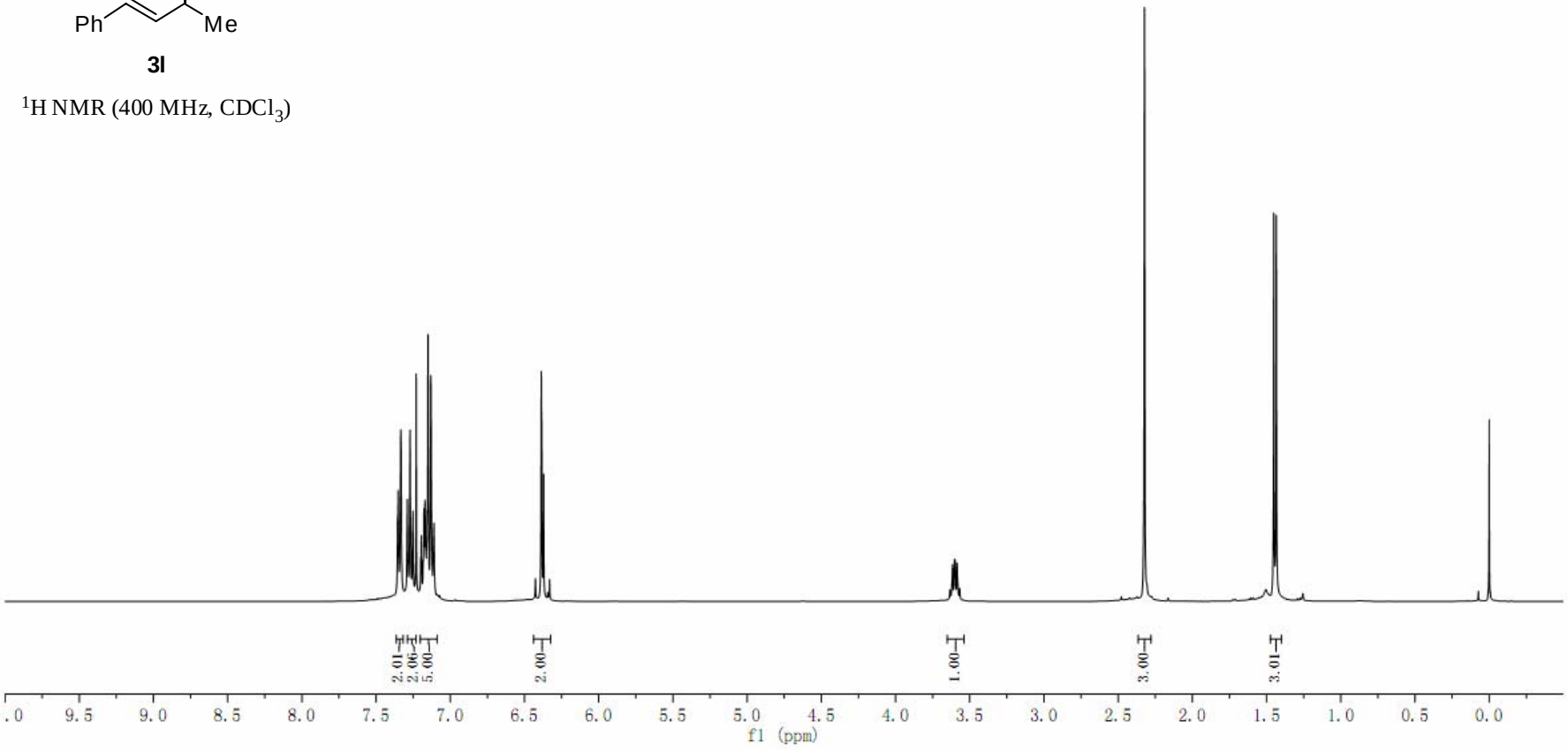
^{1}H NMR (400 MHz, $CDCl_3$)

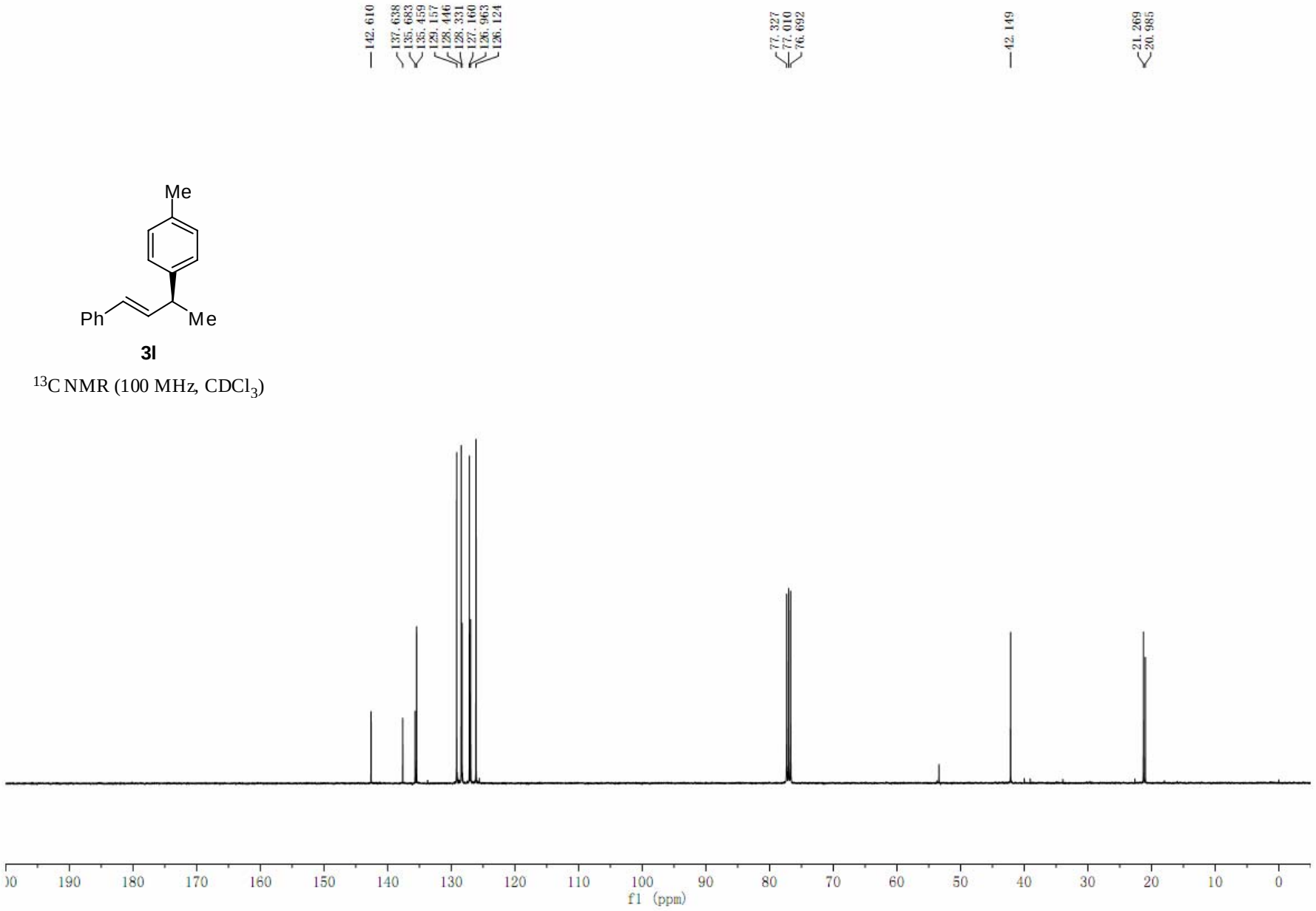

165.816
149.526
144.088
128.544
127.327
126.495
119.545
77.389
77.072
76.754
42.272
42.189
40.845
20.831
14.834
13.170
Me
Me
N
O
Ph
Me
ent-3k
13C NMR (100 MHz, CDCl3)
f1 (ppm)



3l

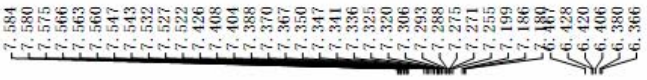
^{1}H NMR (400 MHz, $CDCl_3$)

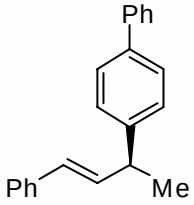




3l

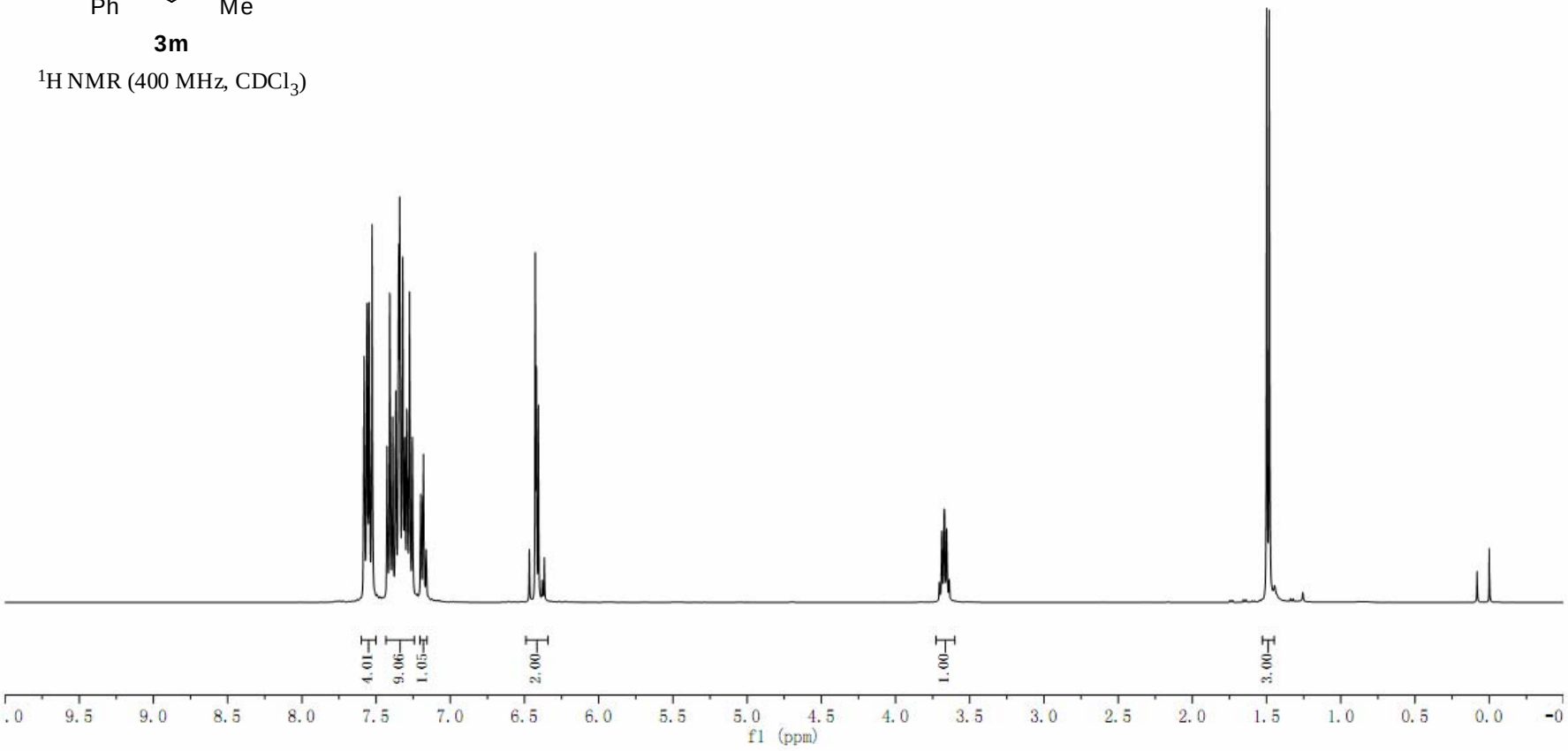
^{13}C NMR (100 MHz, $CDCl_3$)

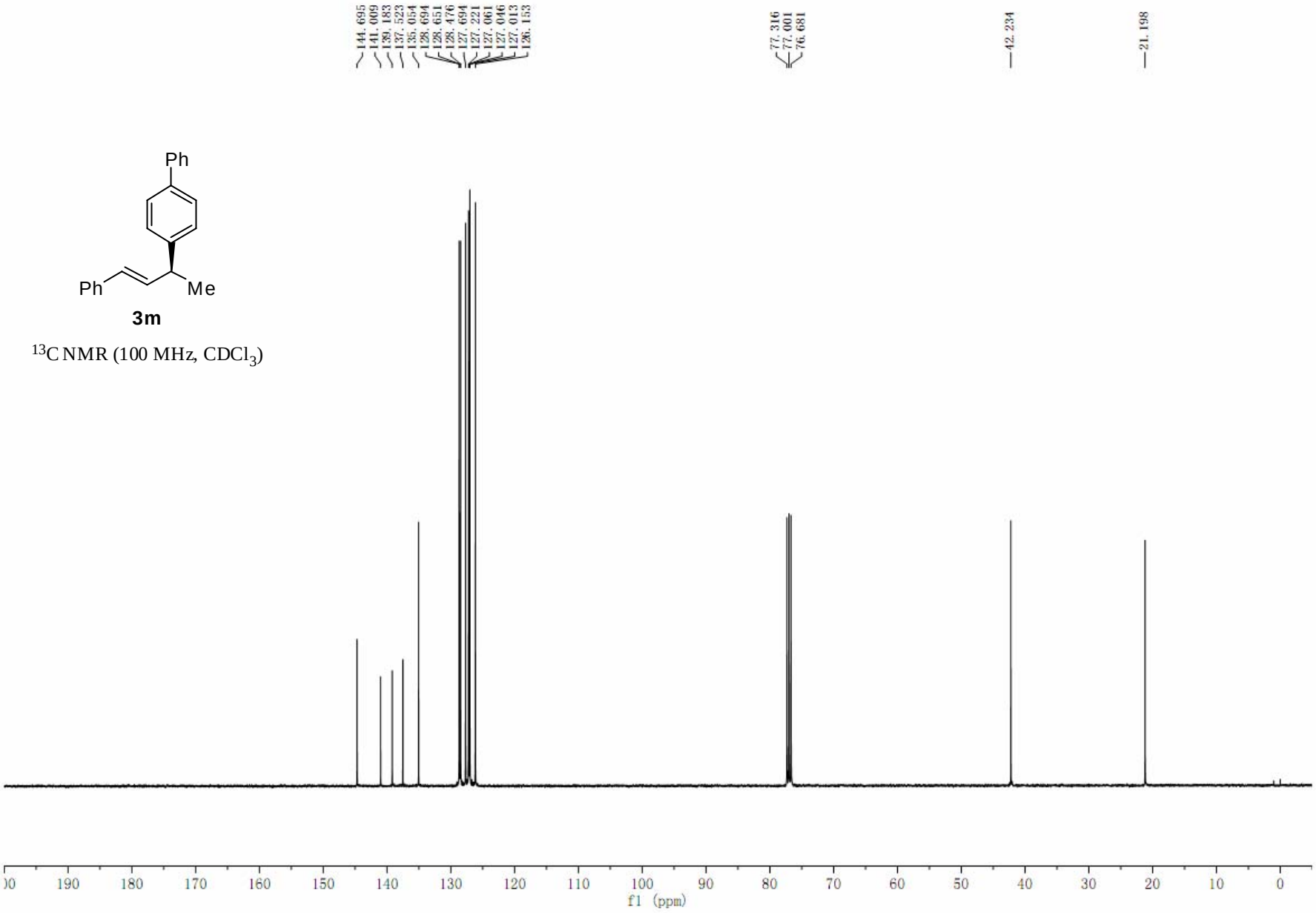


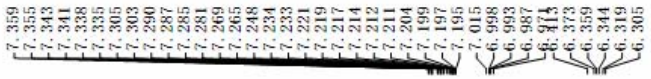


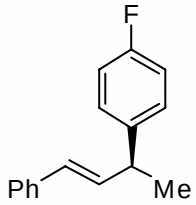
3m

^{1}H NMR (400 MHz, $CDCl_3$)



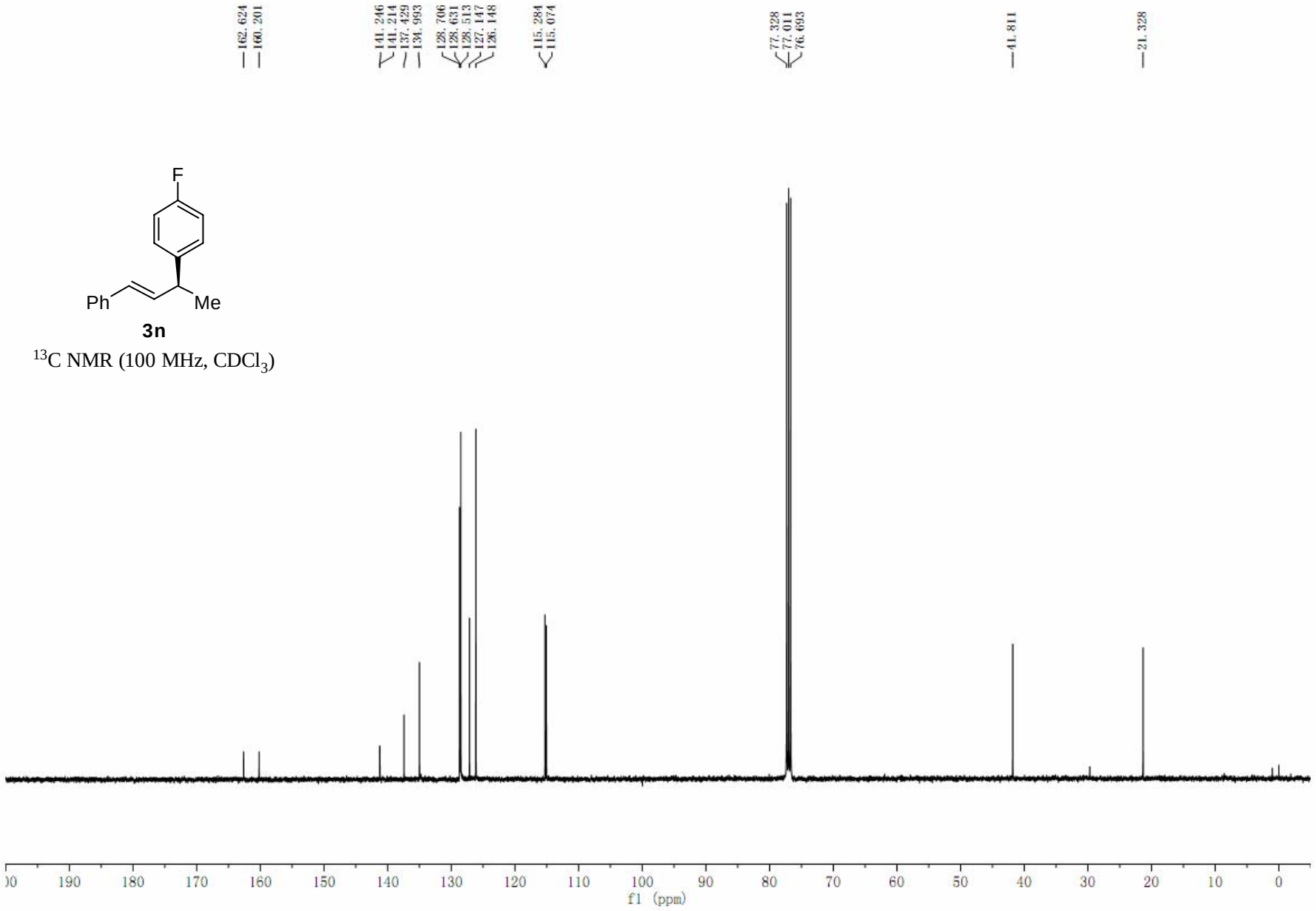

144.695
141.009
139.183
137.523
135.054
128.694
128.651
128.476
127.694
127.221
127.061
127.046
127.013
126.153
77.316
77.001
76.681
42.234
21.198
Ph
Ph
Me
3m
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)





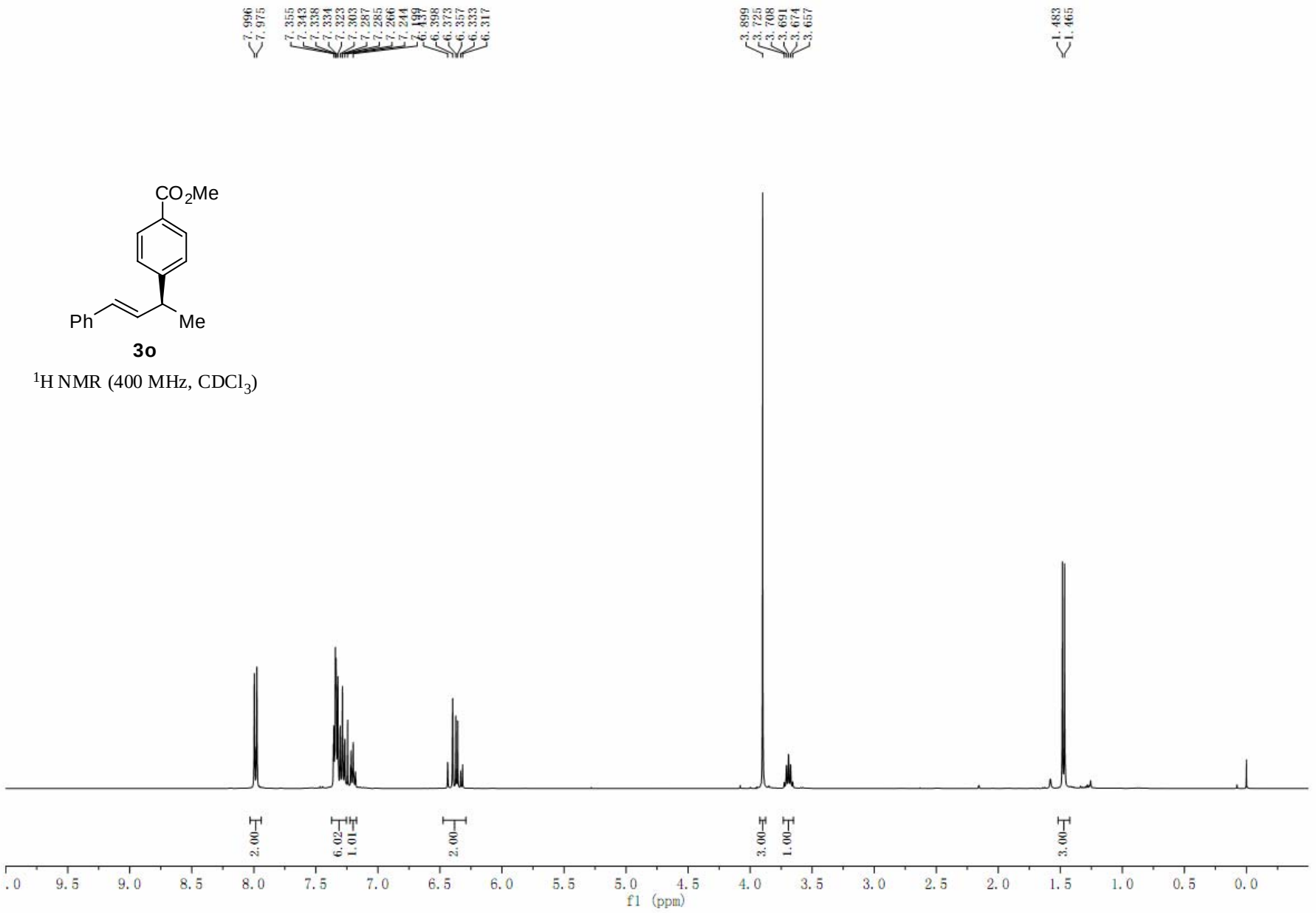
3n

^{1}H NMR (400 MHz, $CDCl_3$)



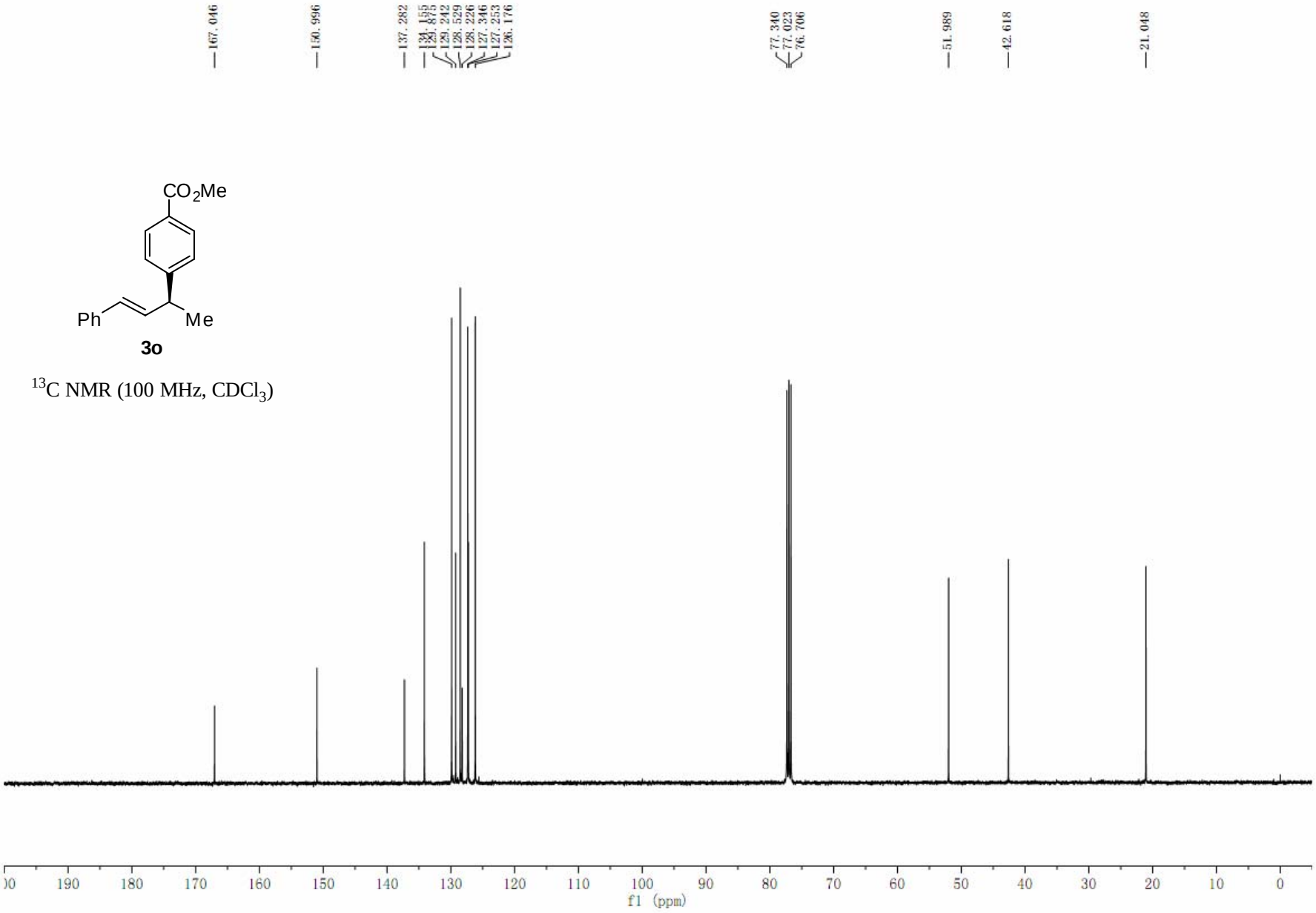
3n

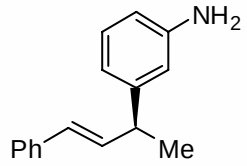
^{13}C NMR (100 MHz, $CDCl_3$)



3o

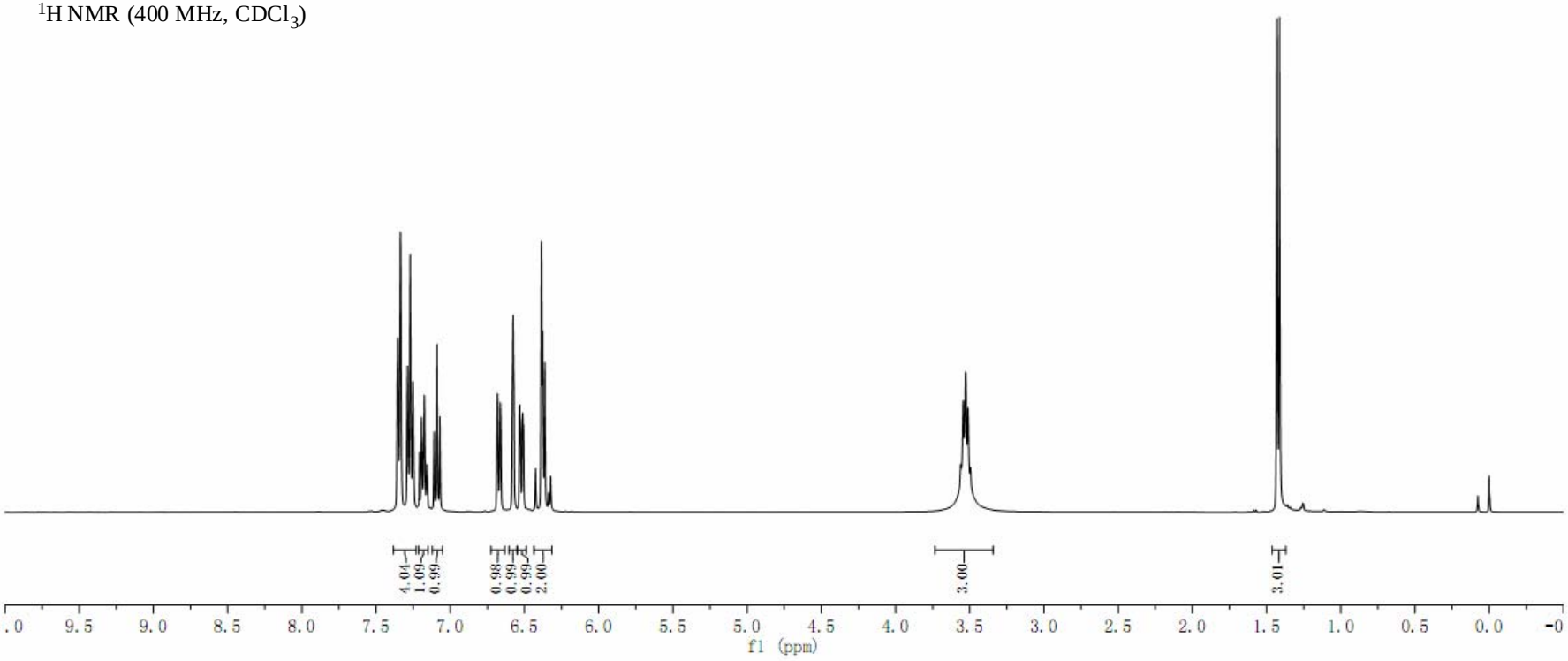
^{1}H NMR (400 MHz, $CDCl_3$)

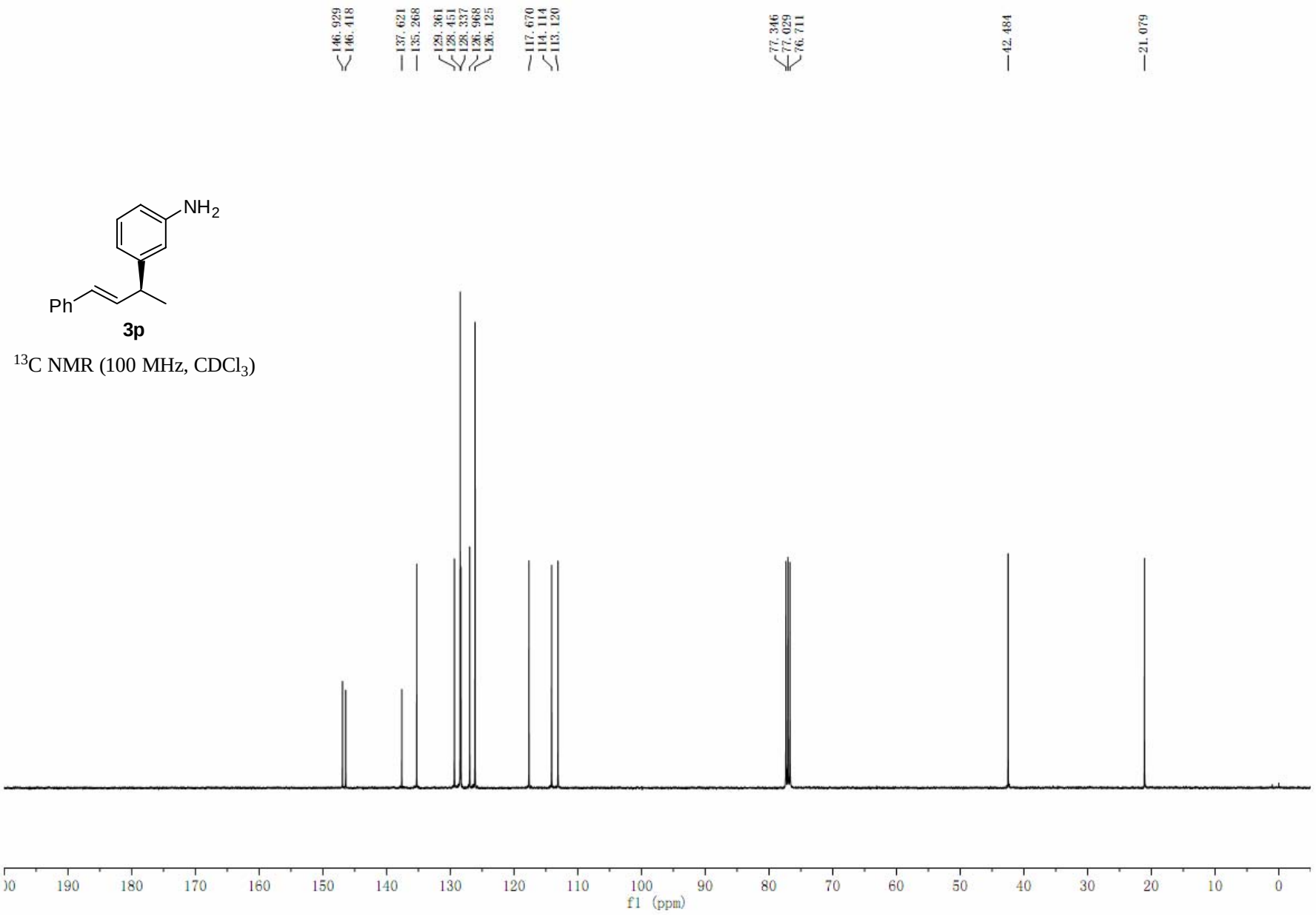

167.046
150.996
137.282
134.155
129.875
129.242
128.529
128.226
127.346
127.253
126.176
77.340
77.023
76.706
51.989
42.618
21.048
CO2Me
Ph
Me
3o
13C NMR (100 MHz, CDCl3)
f1 (ppm)



3p

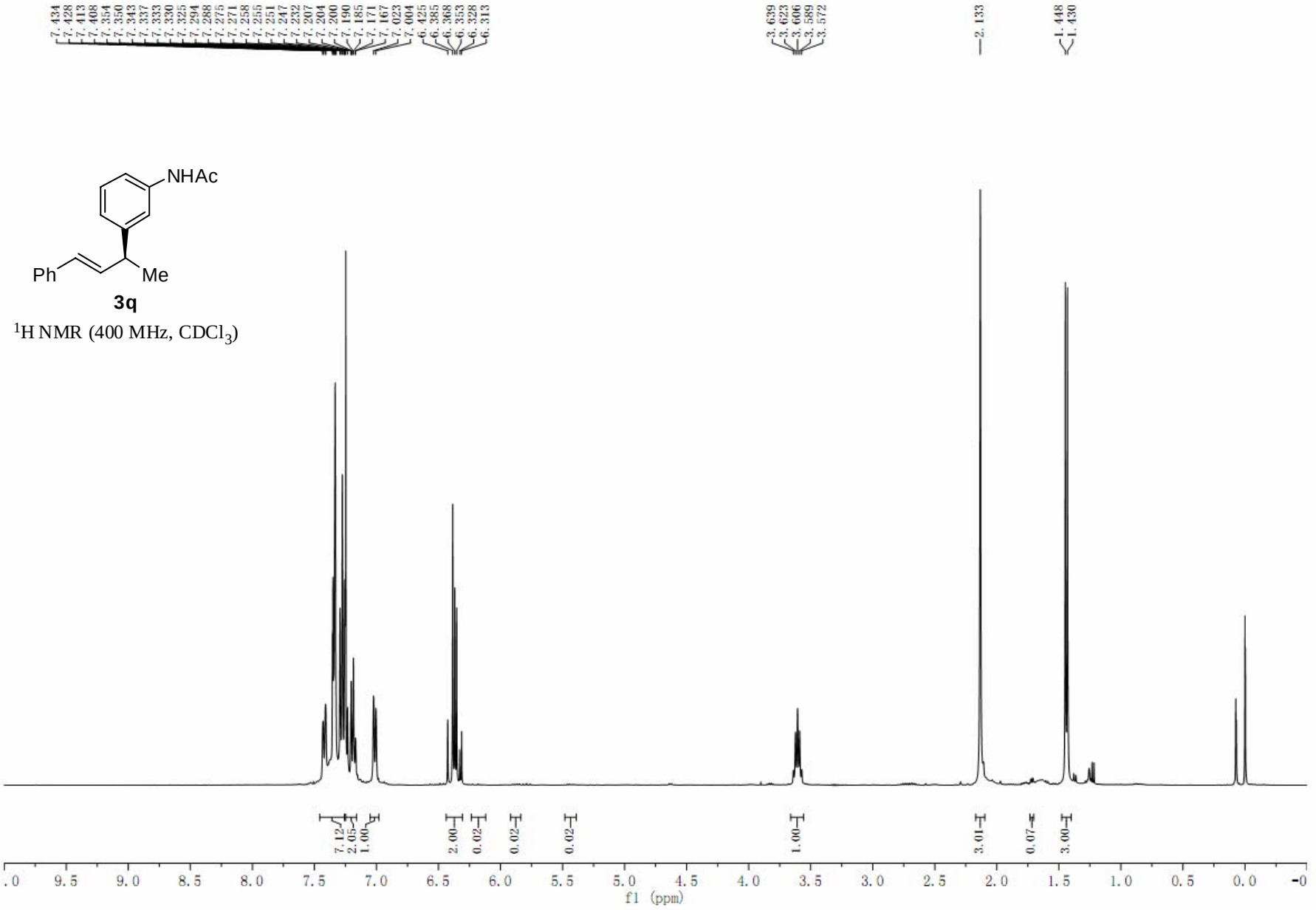
^{1}H NMR (400 MHz, $CDCl_3$)

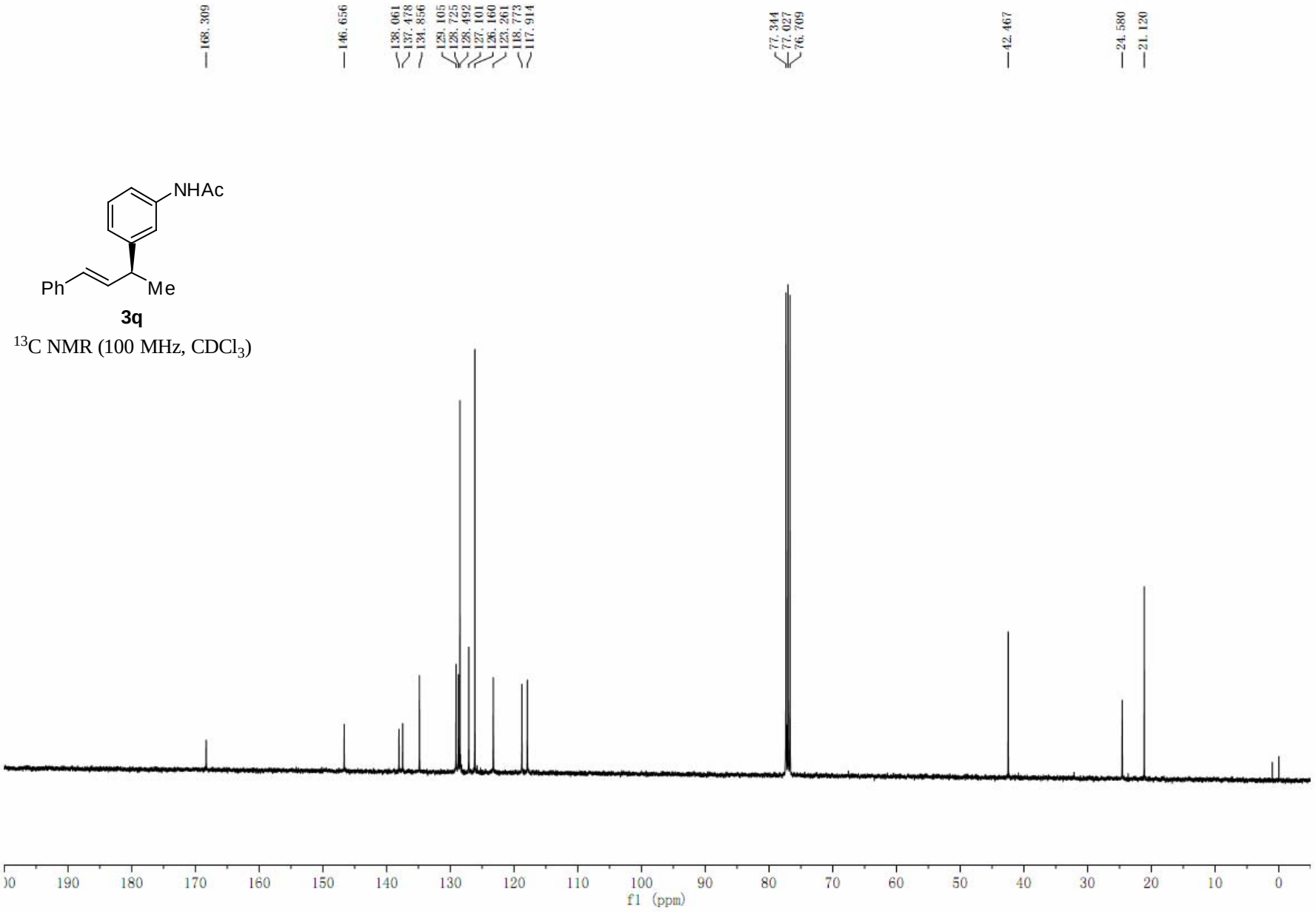




3p

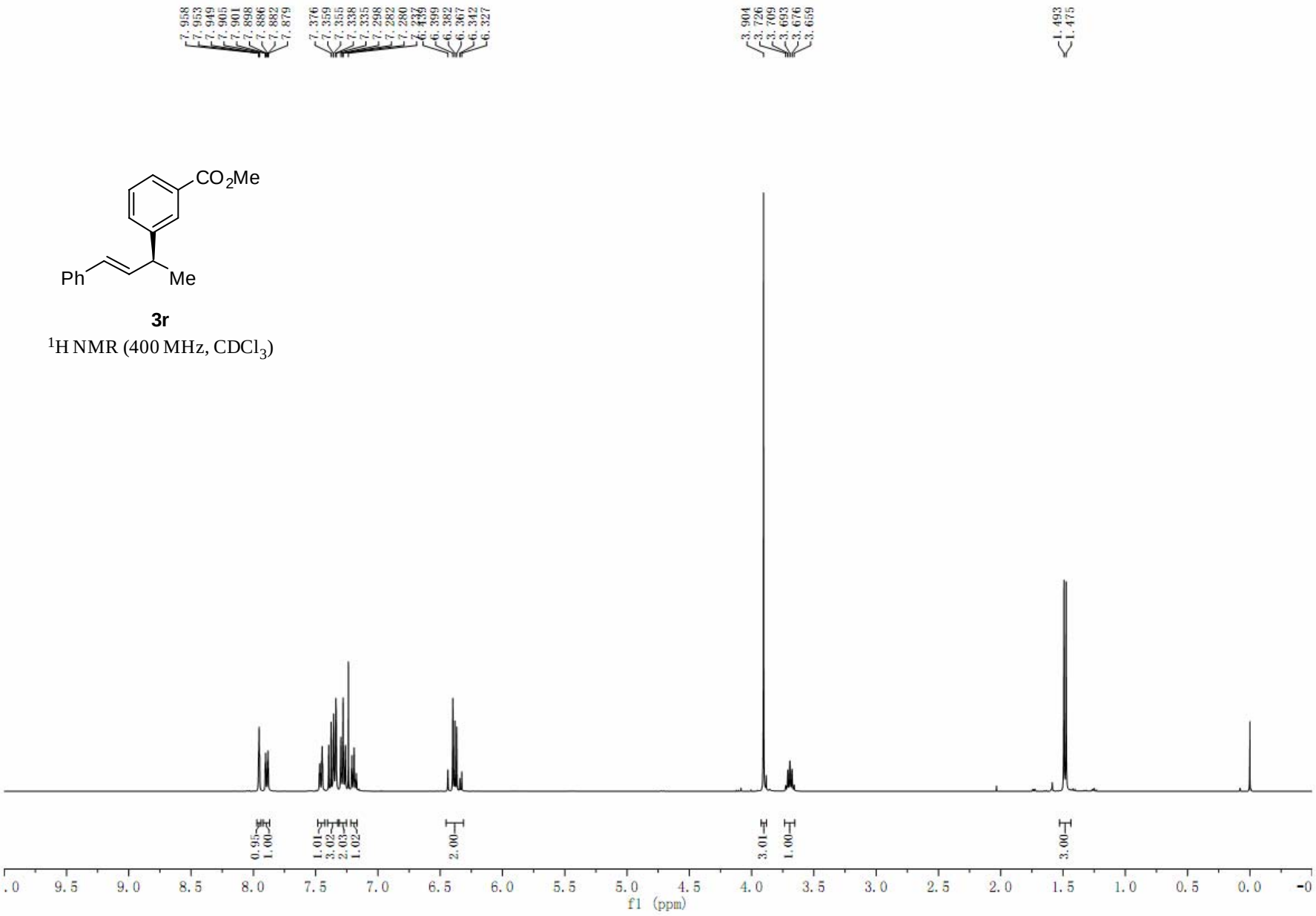
^{13}C NMR (100 MHz, $CDCl_3$)


7.434
7.428
7.413
7.408
7.354
7.350
7.343
7.337
7.333
7.330
7.325
7.294
7.288
7.275
7.271
7.258
7.255
7.251
7.247
7.232
7.207
7.204
7.200
7.190
7.185
7.171
7.167
7.023
7.004
6.425
6.385
6.368
6.353
6.328
6.313
3.639
3.623
3.606
3.589
3.572
2.133
1.448
1.430
NHAc
Ph
Me
3q
^{1}H NMR (400 MHz, $CDCl_3$)
7.12
2.05
1.00
2.00
0.02
0.02
0.02
1.00
3.01
0.07
3.00
f1 (ppm)



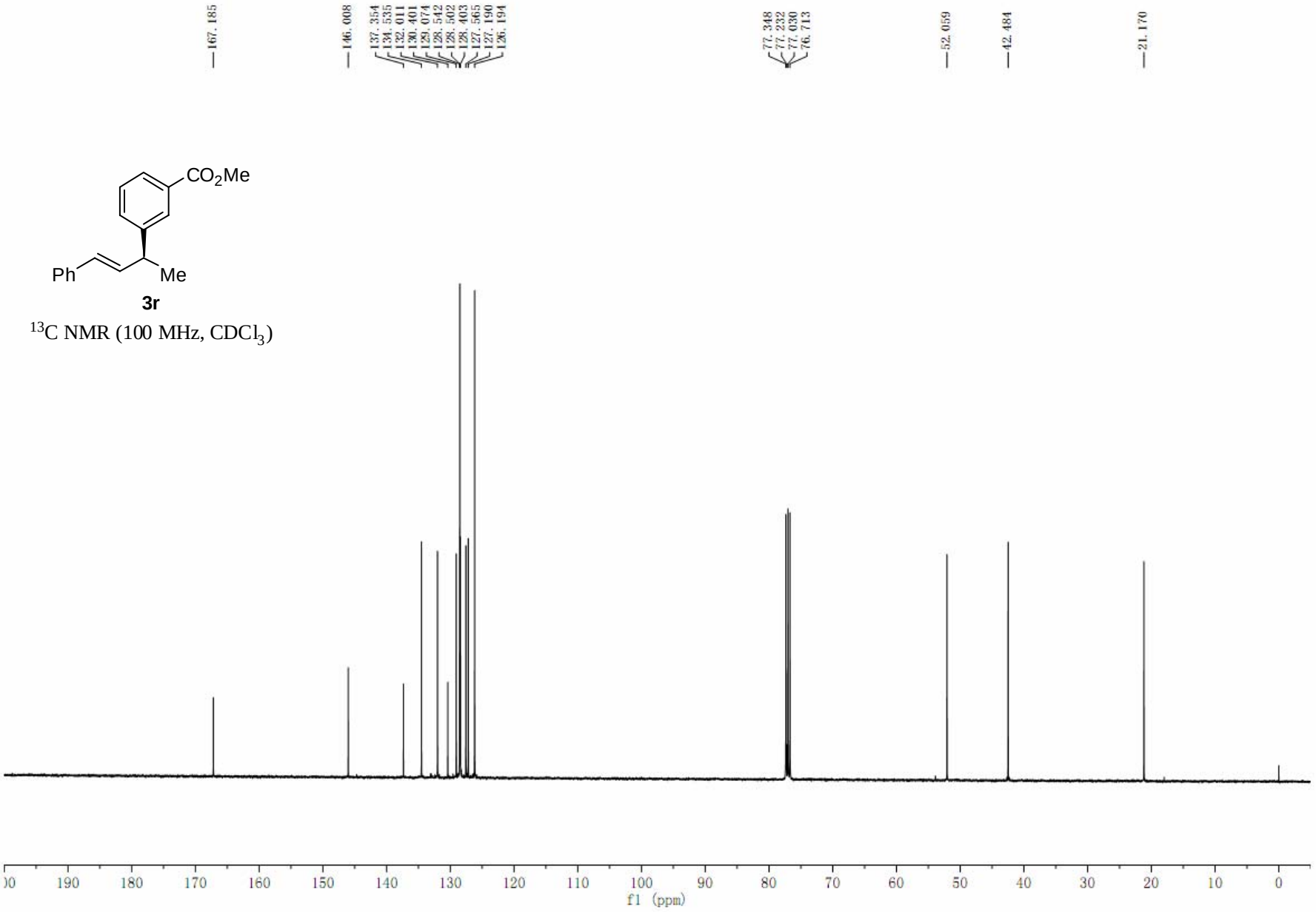
3q

^{13}C NMR (100 MHz, $CDCl_3$)



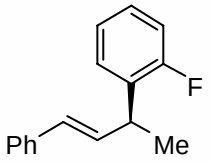
3r

^{1}H NMR (400 MHz, $CDCl_3$)



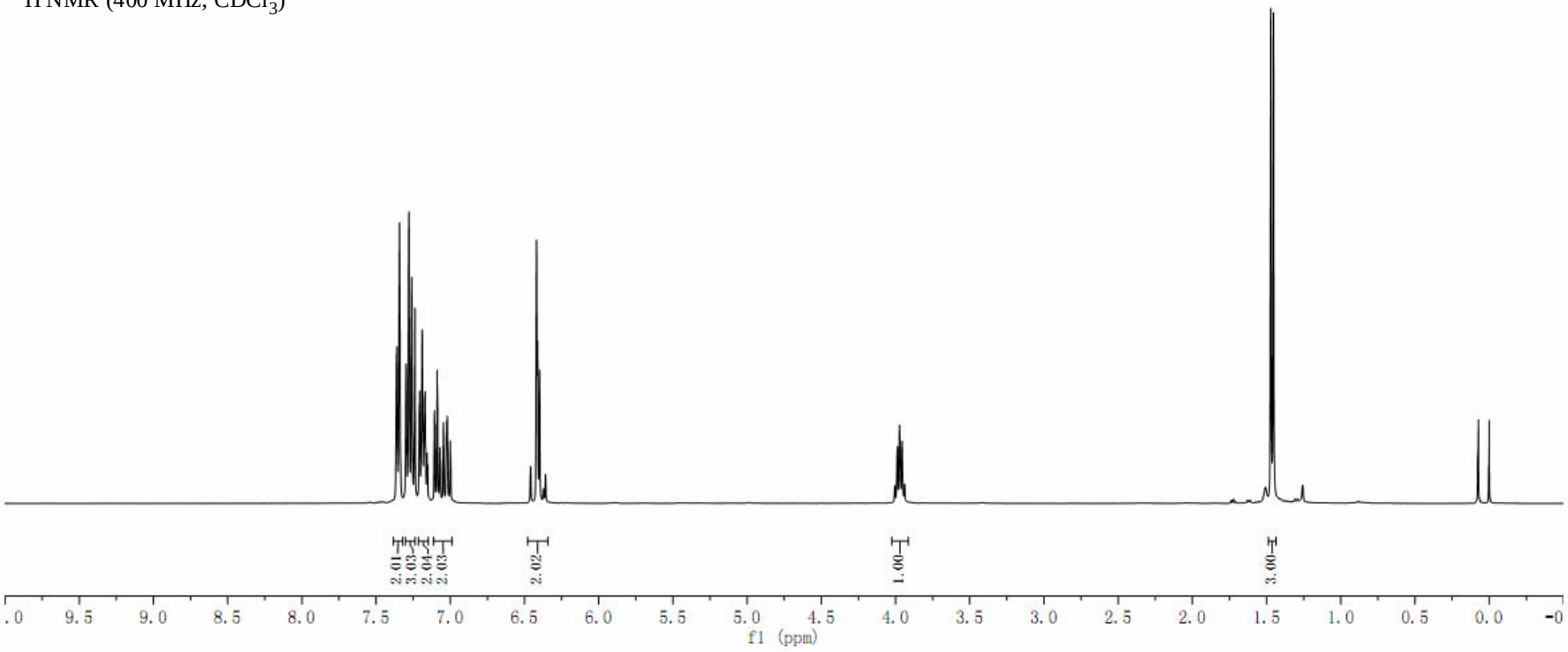
3r

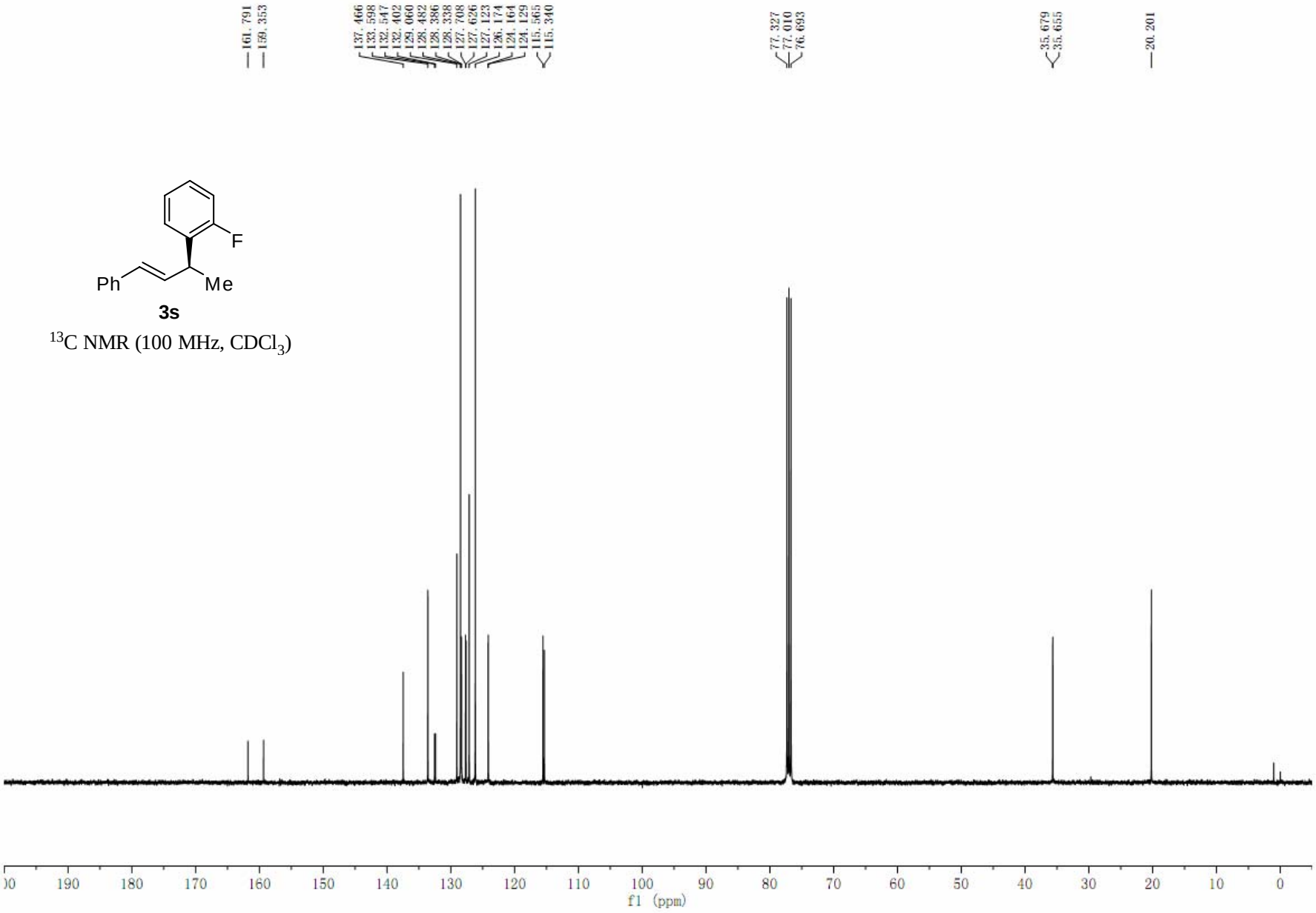
^{13}C NMR (100 MHz, $CDCl_3$)



3s

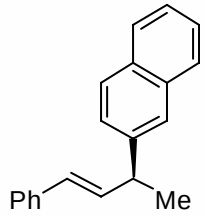
^{1}H NMR (400 MHz, $CDCl_3$)





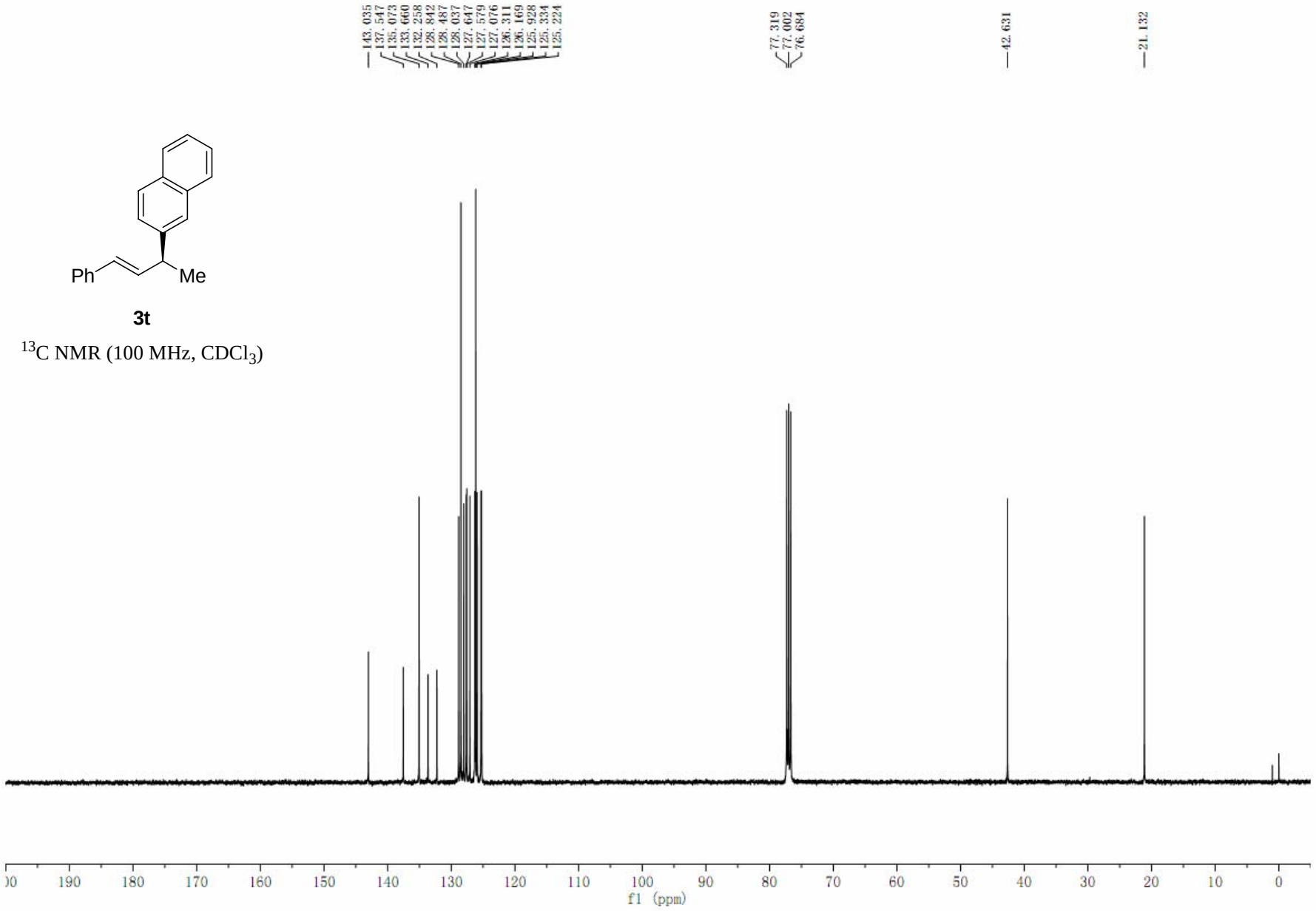
3s

^{13}C NMR (100 MHz, $CDCl_3$)



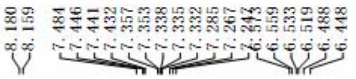
3t

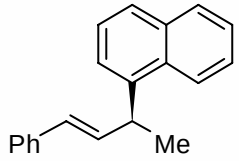
^{1}H NMR (400 MHz, $CDCl_3$)



3t

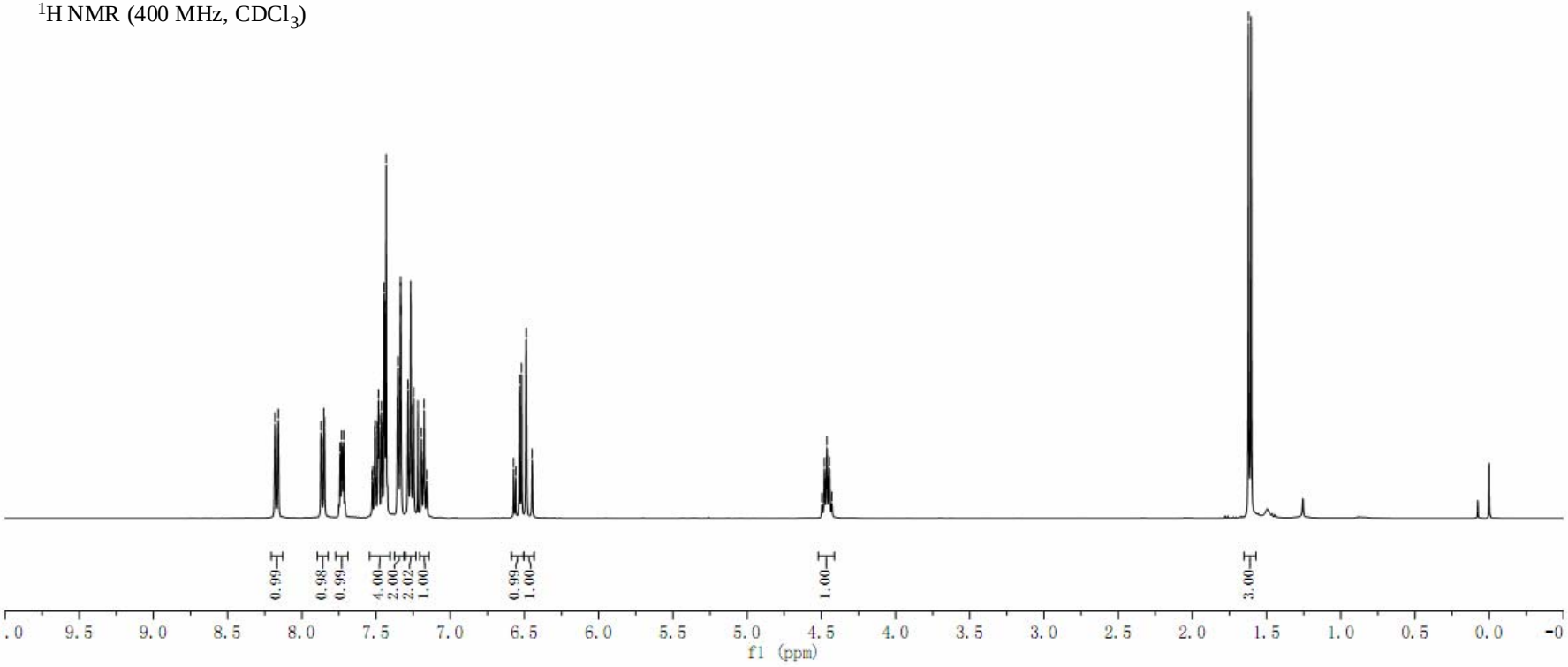
^{13}C NMR (100 MHz, $CDCl_3$)

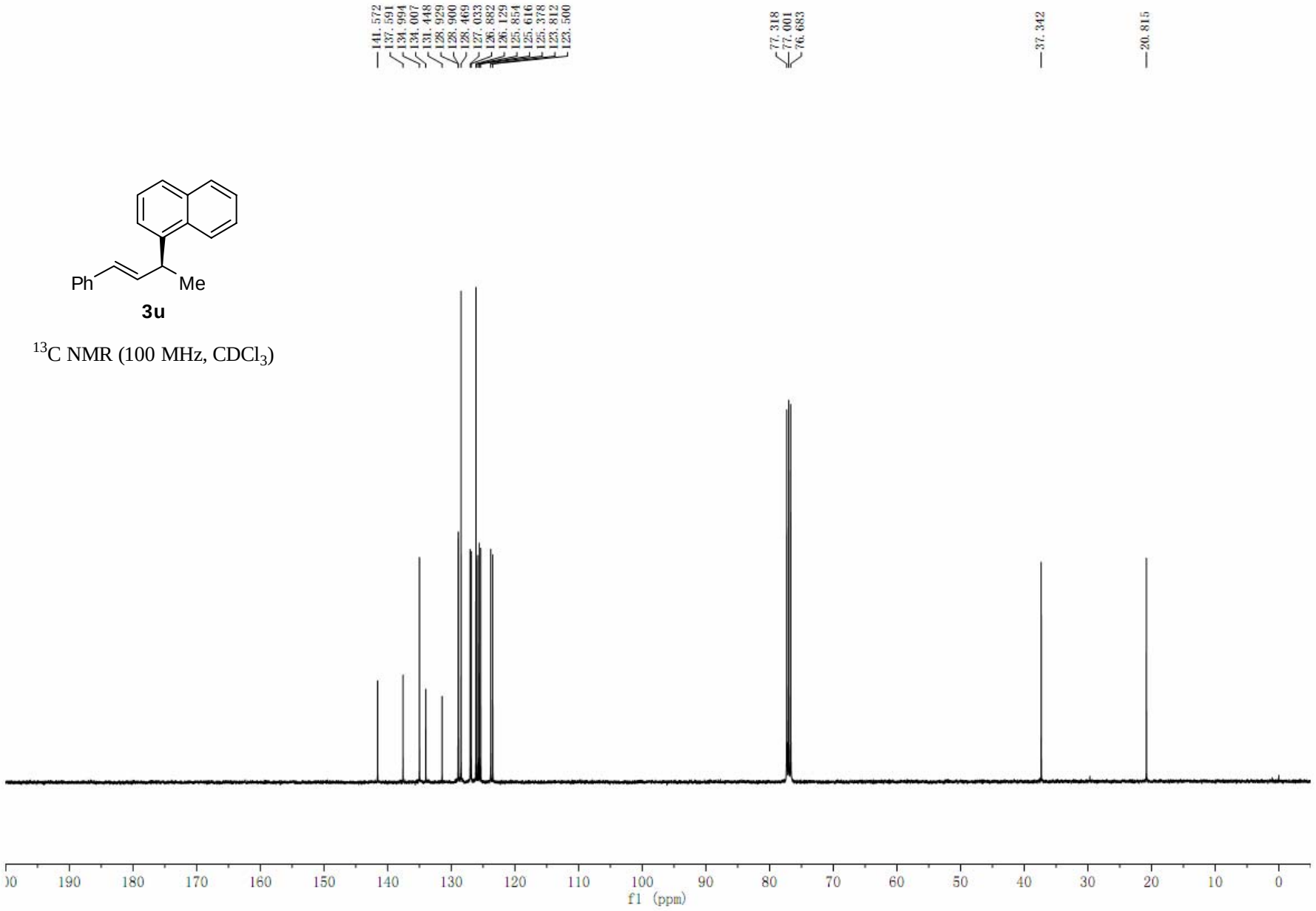


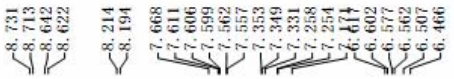


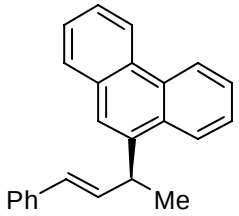
3u

^{1}H NMR (400 MHz, $CDCl_3$)



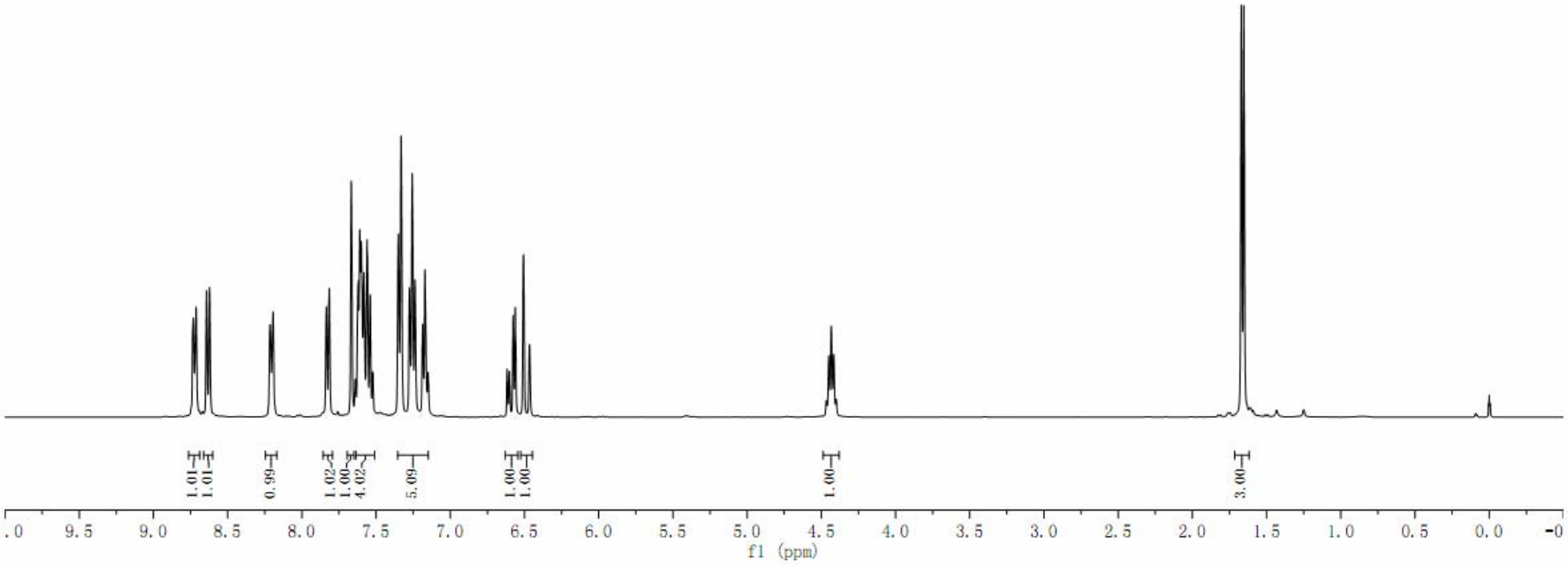


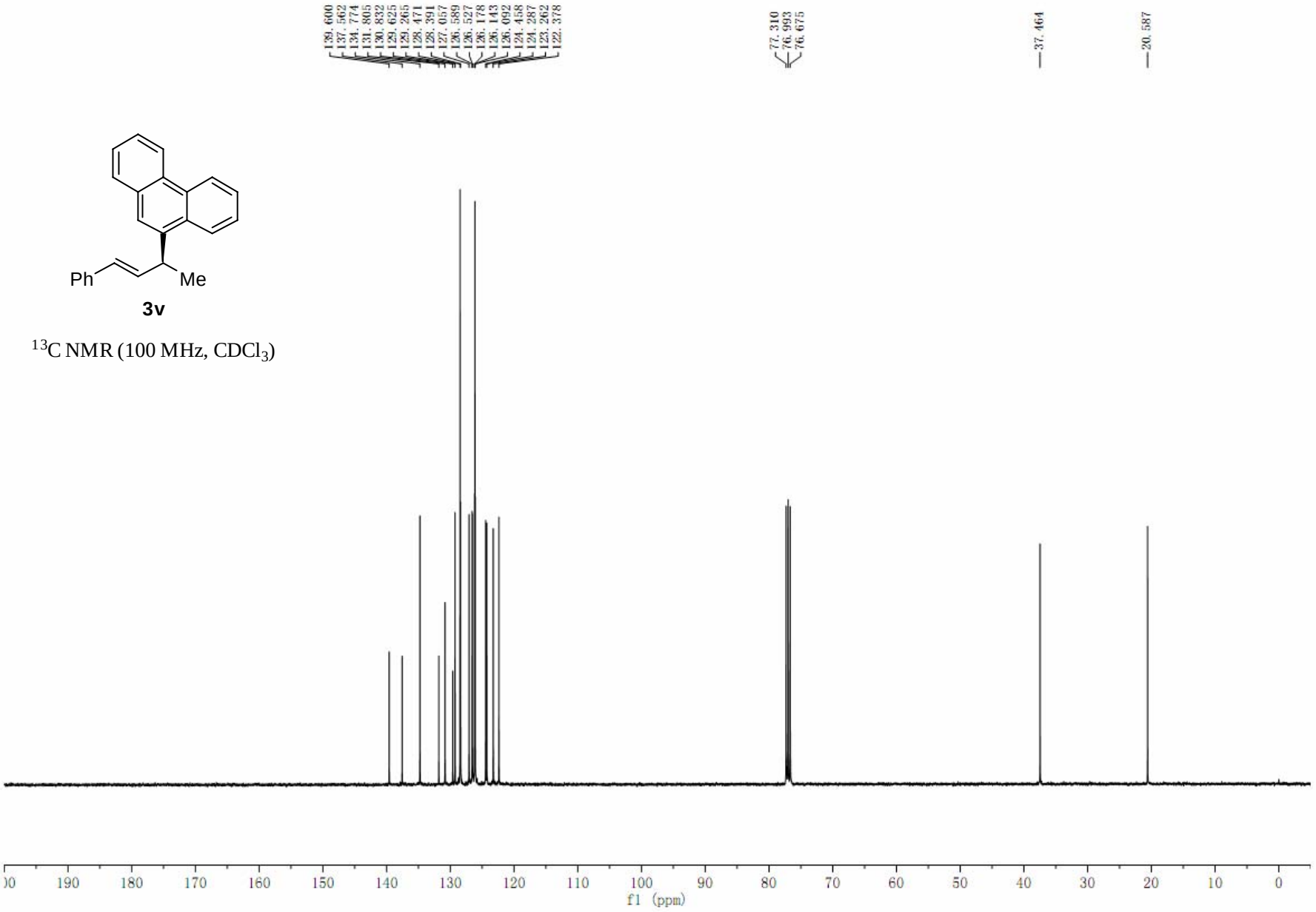




3v

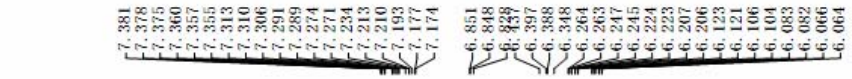
^{1}H NMR (400 MHz, $CDCl_3$)

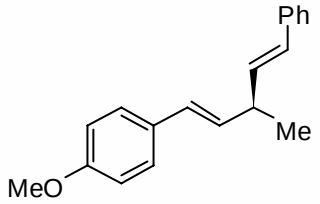




3v

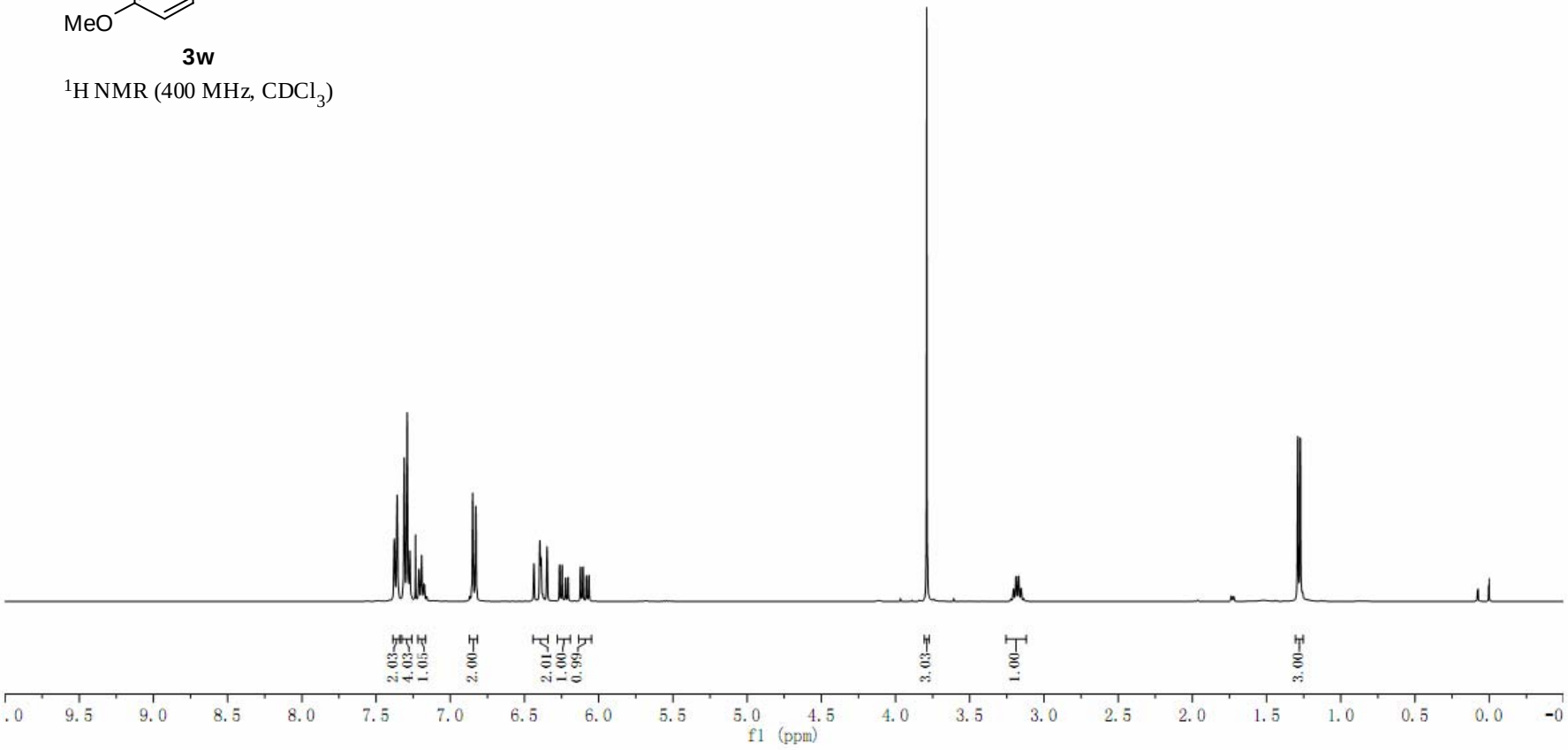
^{13}C NMR (100 MHz, $CDCl_3$)

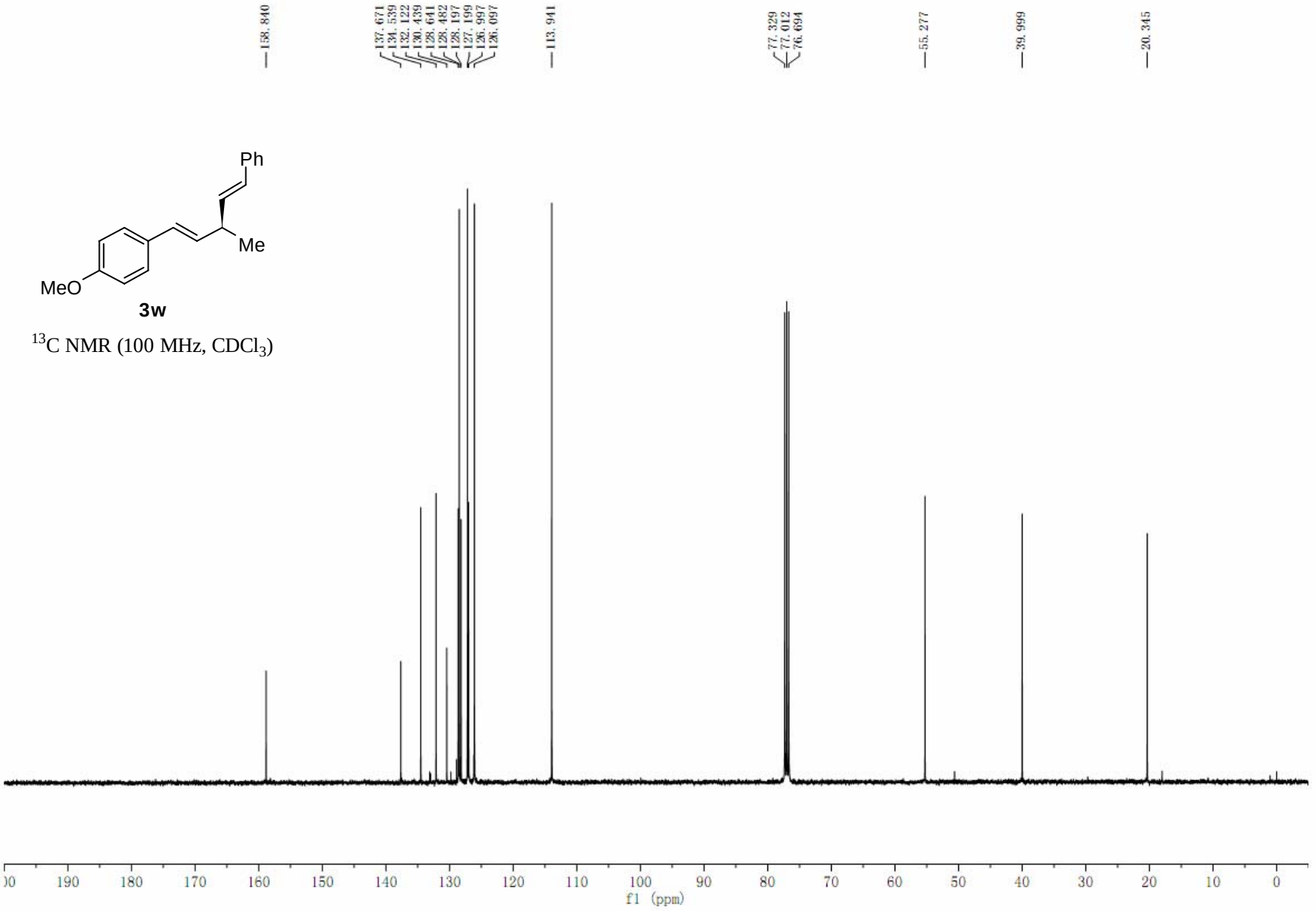


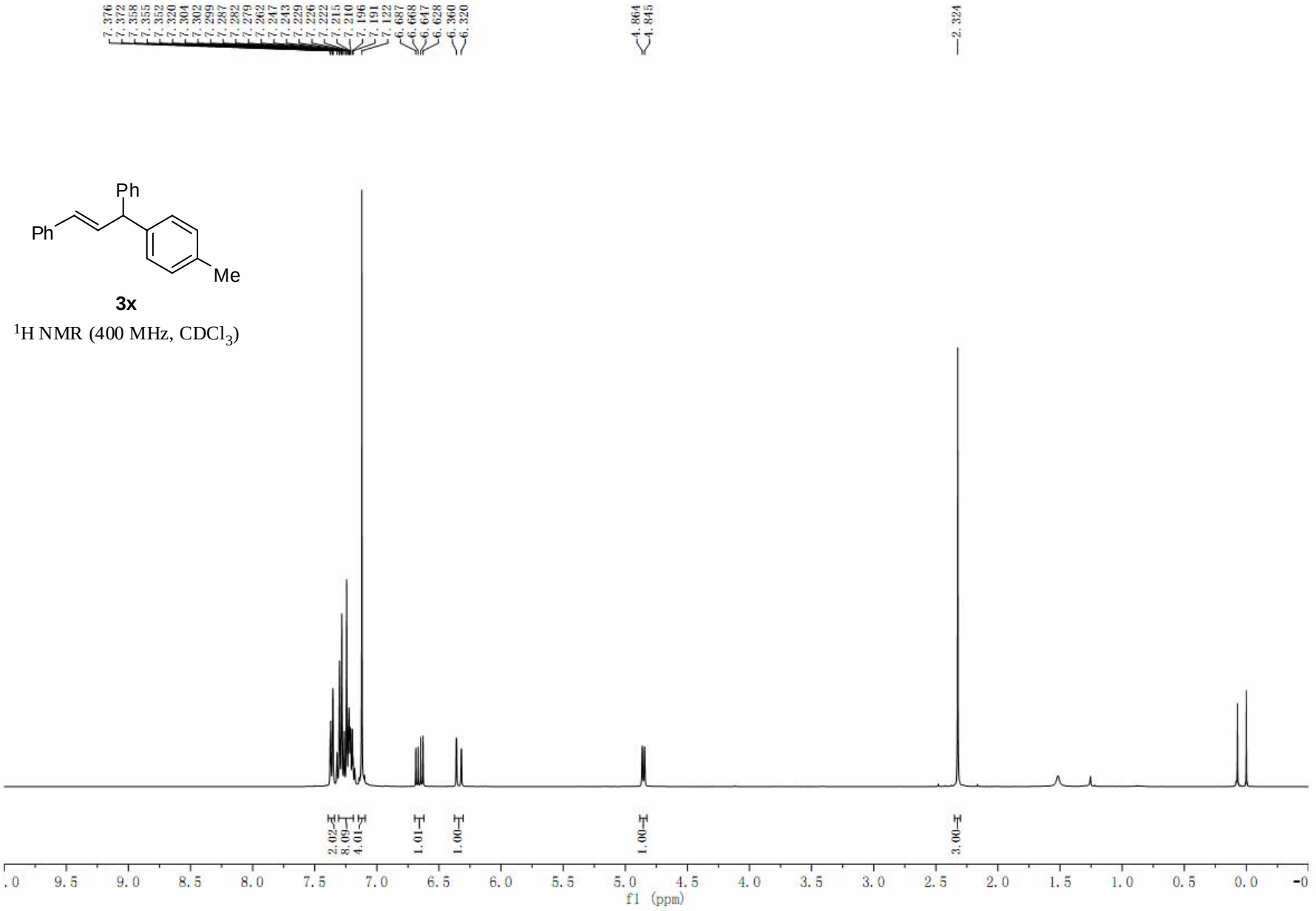


3w

^{1}H NMR (400 MHz, $CDCl_3$)

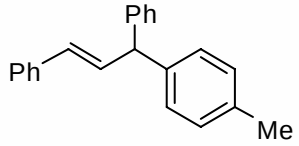



158.840
137.671
134.539
132.122
130.439
128.641
128.482
128.197
127.199
126.997
126.697
113.941
77.329
77.012
76.694
55.277
39.999
20.345
Ph
Me
MeO
3w
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)



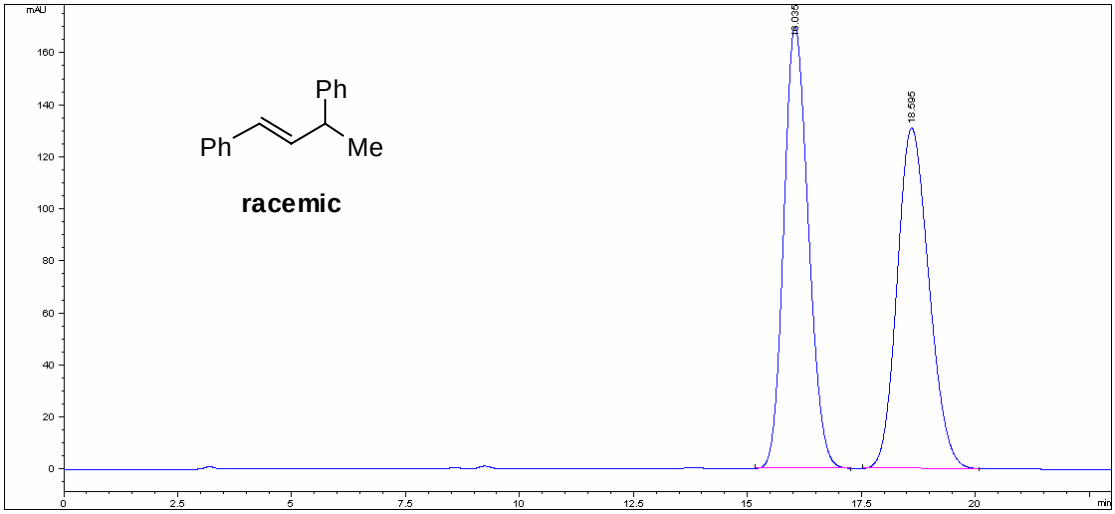
3x

^{1}H NMR (400 MHz, $CDCl_3$)

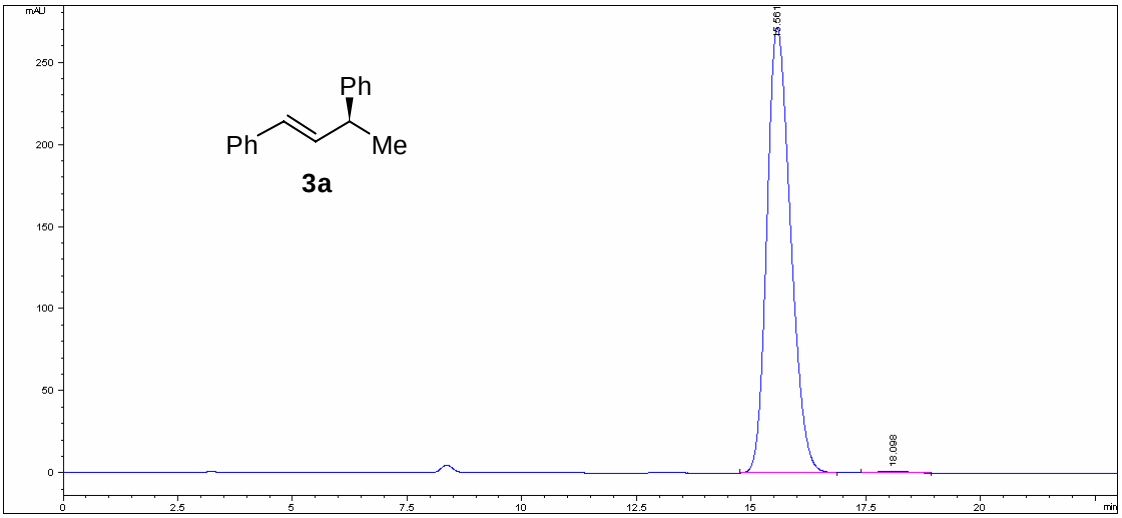


3x

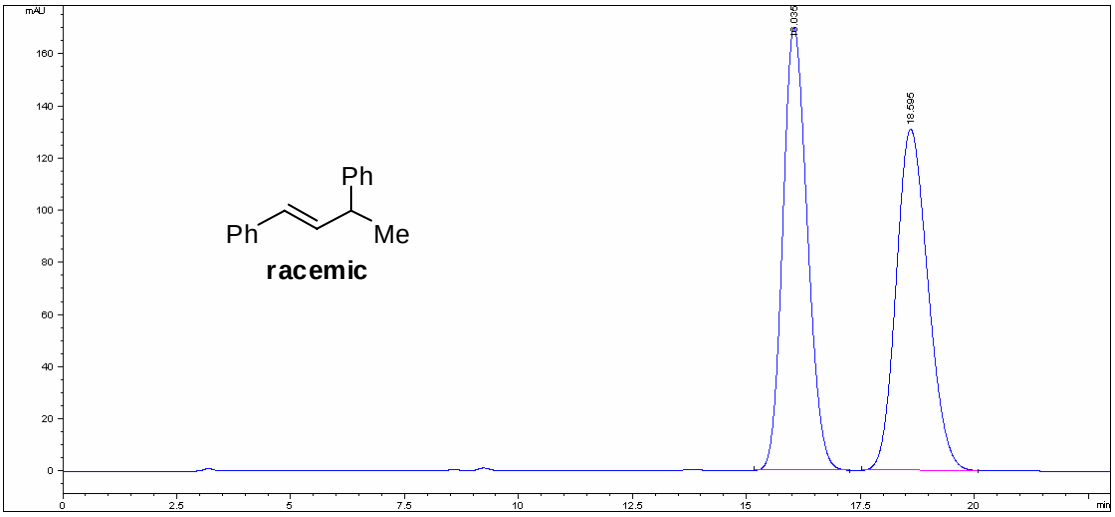
^{13}C NMR (100 MHz, $CDCl_3$)



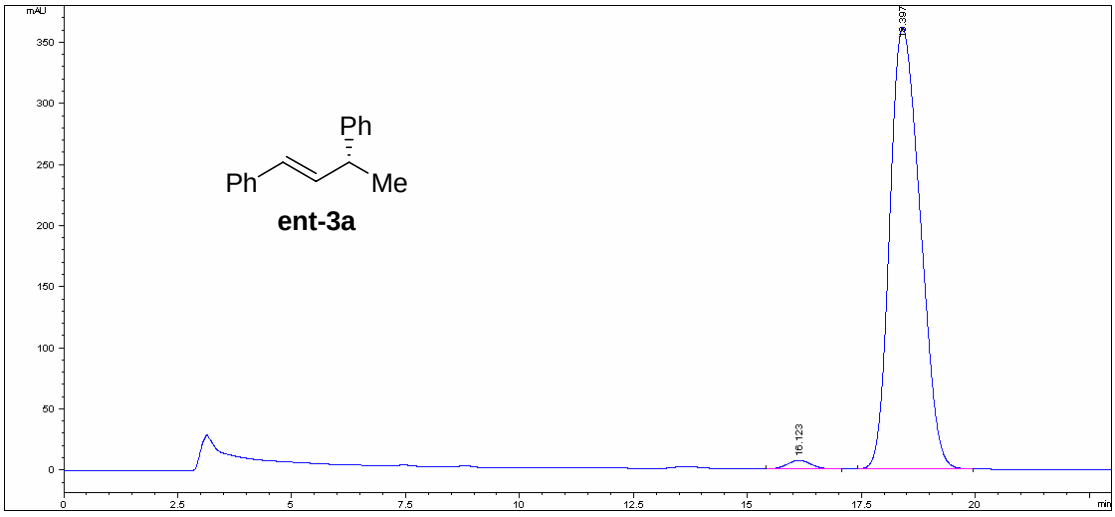
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.035	6368.6	169.9	0.5844	0.799	50.047
2	18.595	6356.6	131	0.7541	0.802	49.953



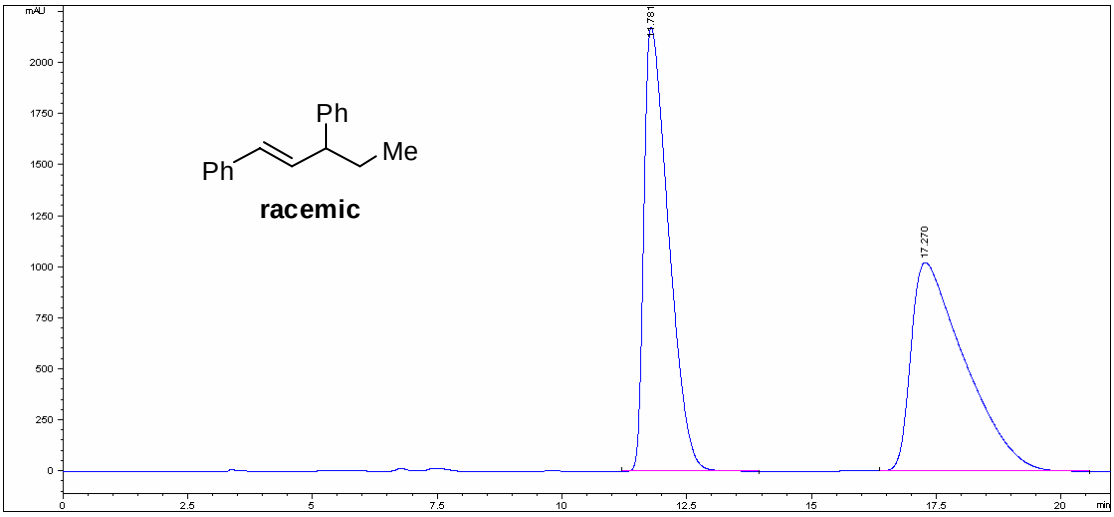
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	15.561	9720.2	271	0.5567	0.733	99.412
2	18.098	57.4	1.3	0.7523	0.939	0.588



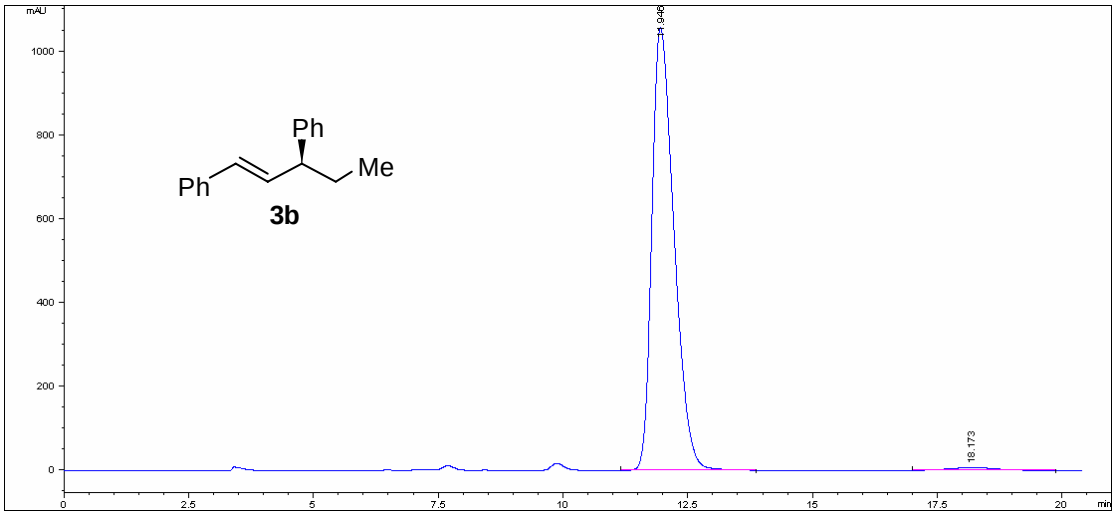
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.035	6368.6	169.9	0.5844	0.799	50.047
2	18.595	6356.6	131	0.7541	0.802	49.953



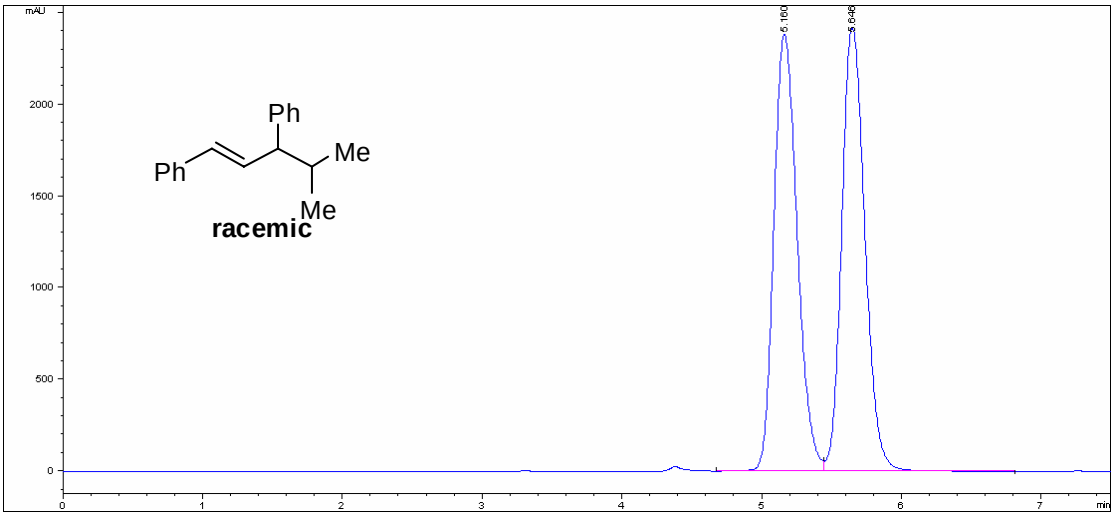
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.123	245.8	6.9	0.5544	0.925	1.452
2	18.397	16682.9	361.2	0.7384	0.702	98.548



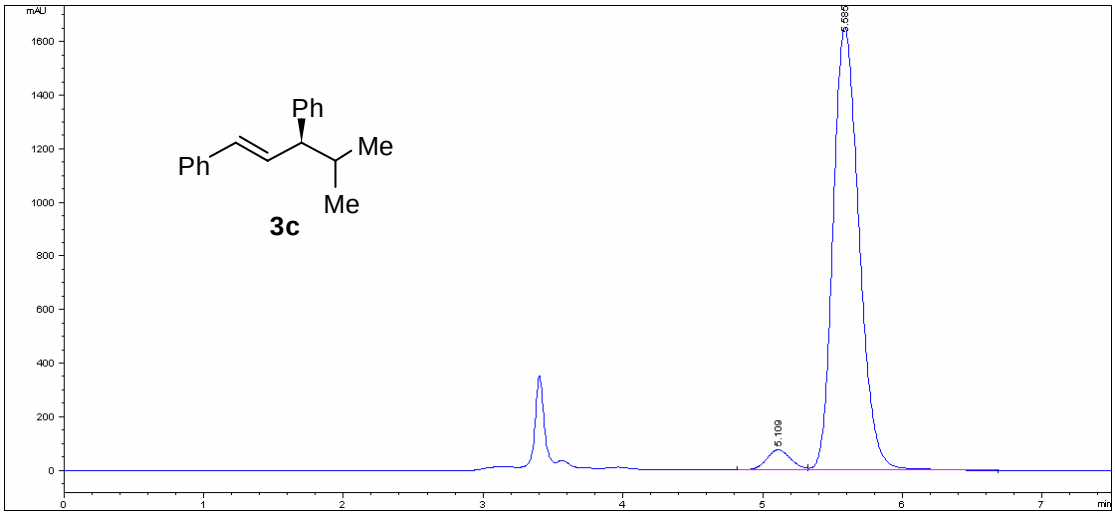
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.781	74641.2	2173.7	0.5273	0.396	49.335
2	17.27	76652.3	1022.2	1.07	0.336	50.665



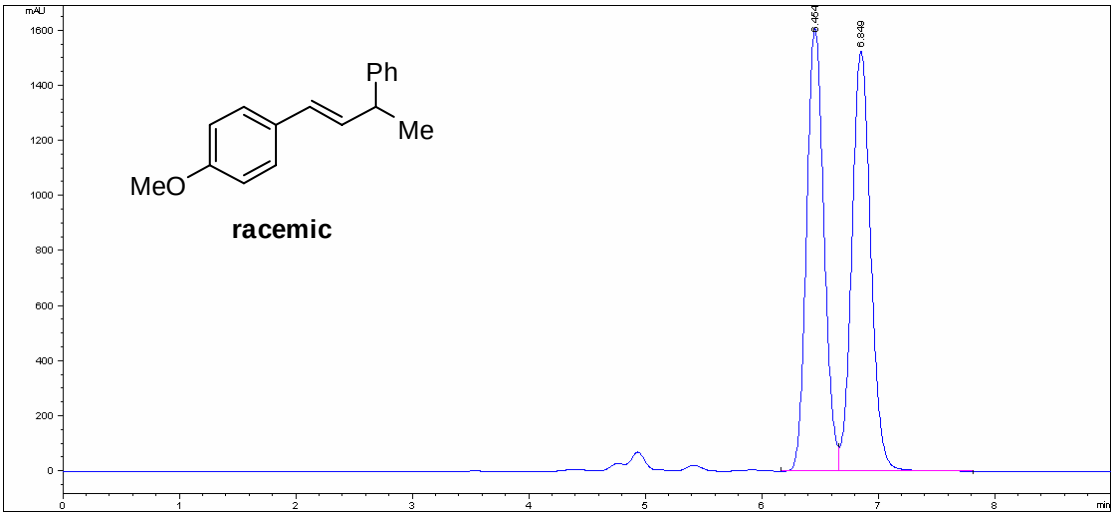
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.946	34542.3	1057.2	0.4727	0.601	98.737
2	18.173	416.2	6.4	0.8688	0.896	1.263



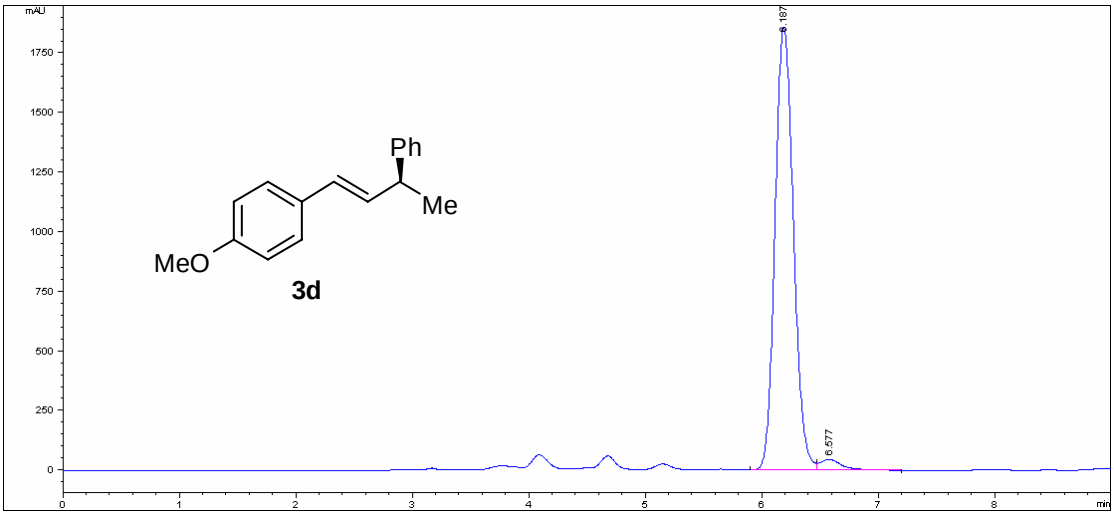
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.16	27629.6	2384.3	0.1818	0.774	49.813
2	5.646	27837.5	2419.2	0.1794	0.785	50.187



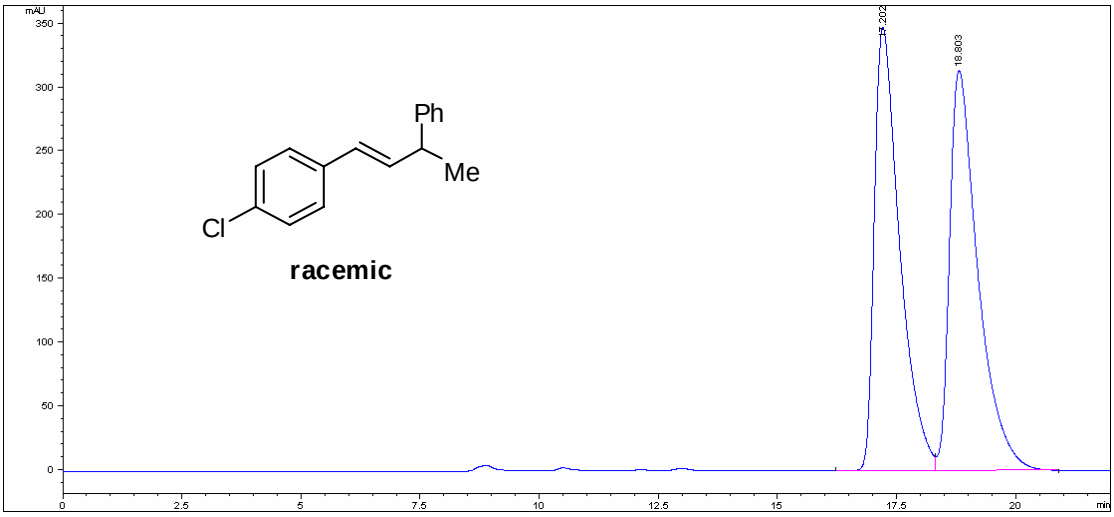
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.109	956.2	76.3	0.1928	0.925	4.284
2	5.585	21363.5	1653.2	0.2017	0.76	95.716



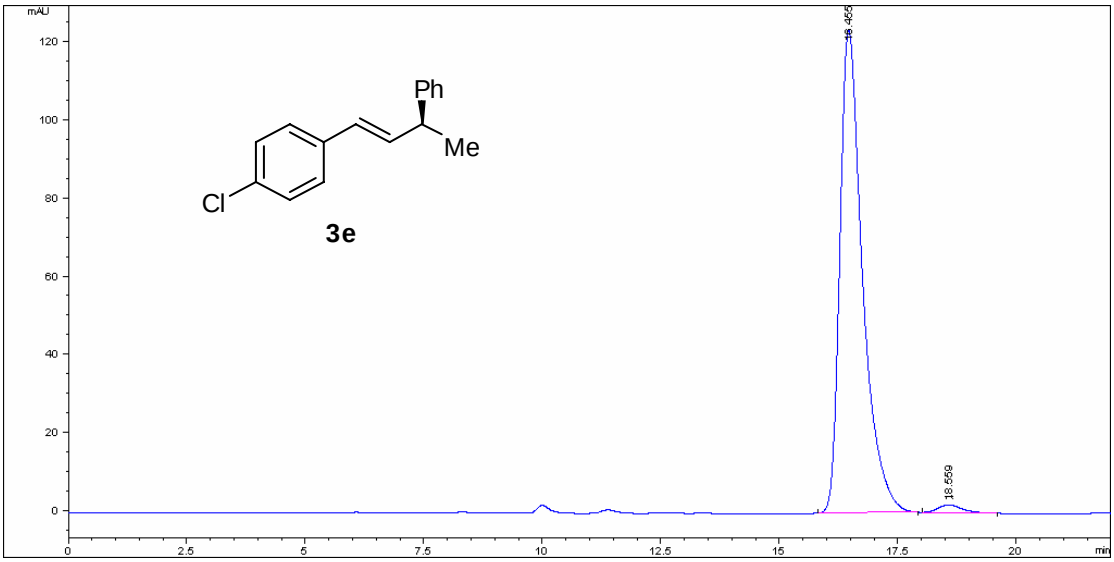
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	6.454	16706.1	1610.5	0.1618	0.869	49.354
2	6.849	17143.7	1525.7	0.1748	0.866	50.646



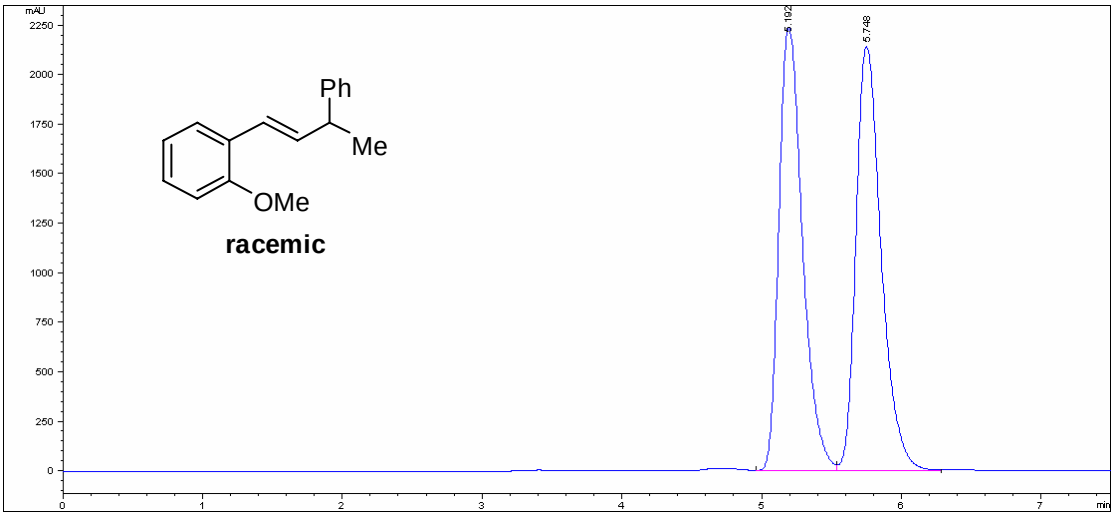
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	6.187	20440.7	1857.1	0.1735	0.854	97.216
2	6.577	585.4	45.2	0.1905	0.63	2.784



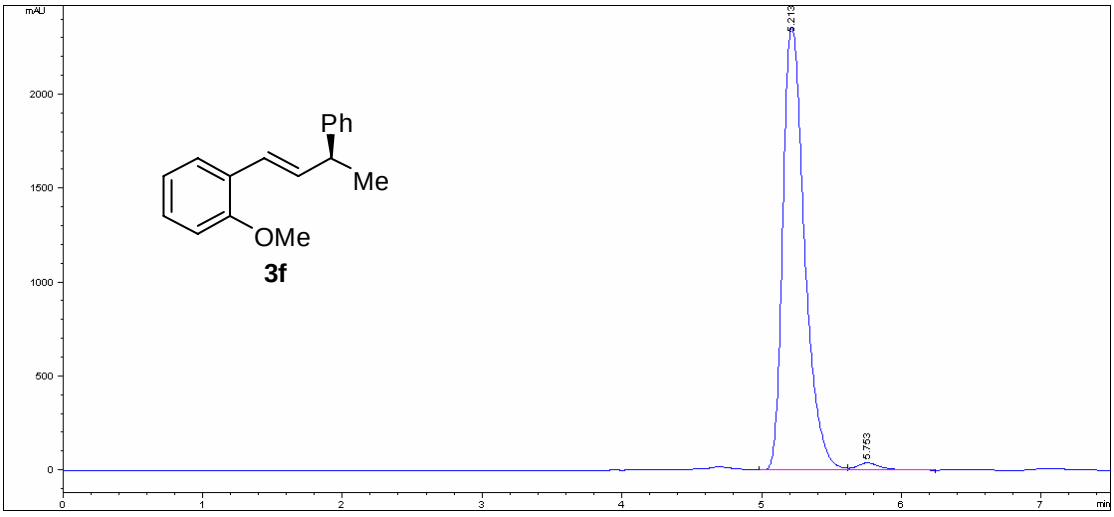
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	17.202	12917.2	347.5	0.5559	0.466	49.802
2	18.803	13020	313.8	0.6166	0.465	50.198



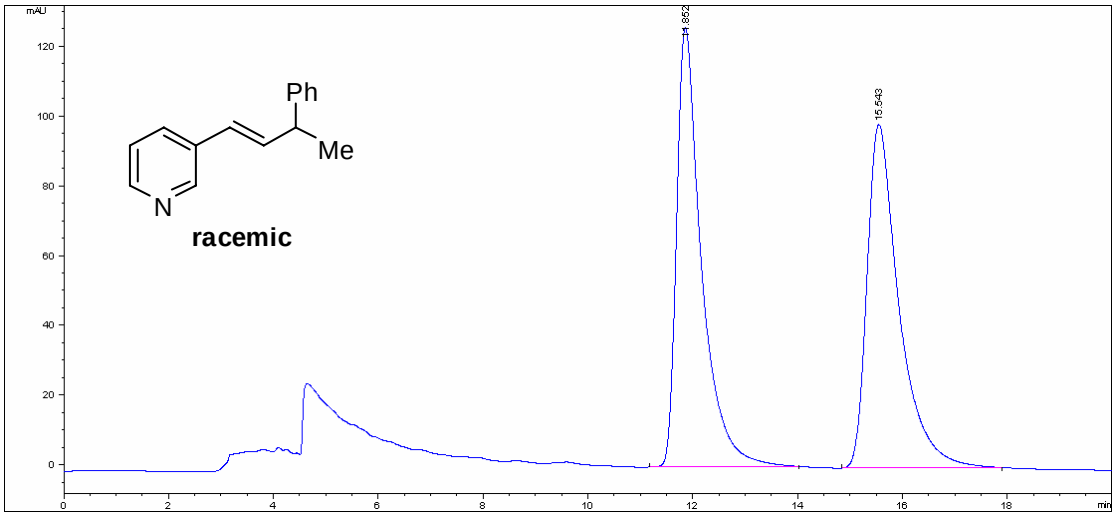
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.455	4107.7	123.8	0.4977	0.583	98.142
2	18.559	77.8	2.1	0.6151	0.729	1.858



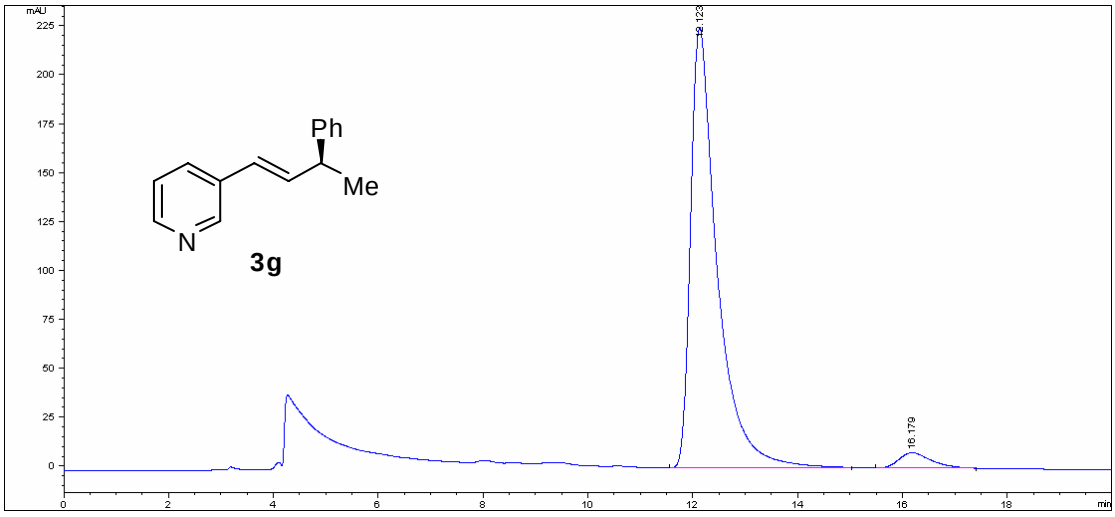
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.192	26340.8	2239.9	0.1823	0.672	49.330
2	5.748	27056	2146	0.1937	0.672	50.670



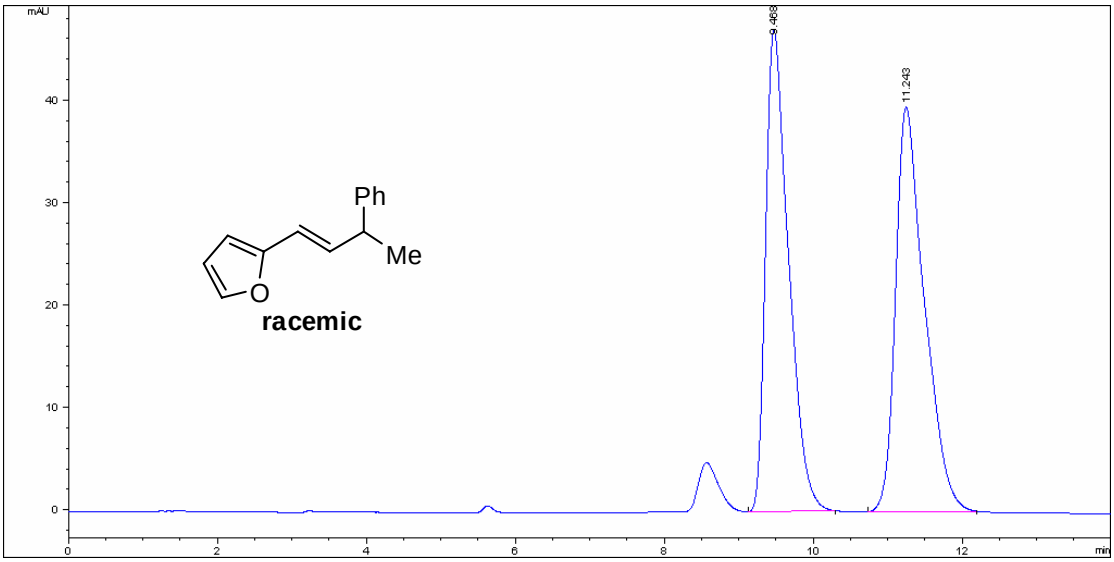
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.213	25577.6	2357.5	0.1673	0.651	98.065
2	5.753	504.7	39.8	0.1831	0.644	1.935



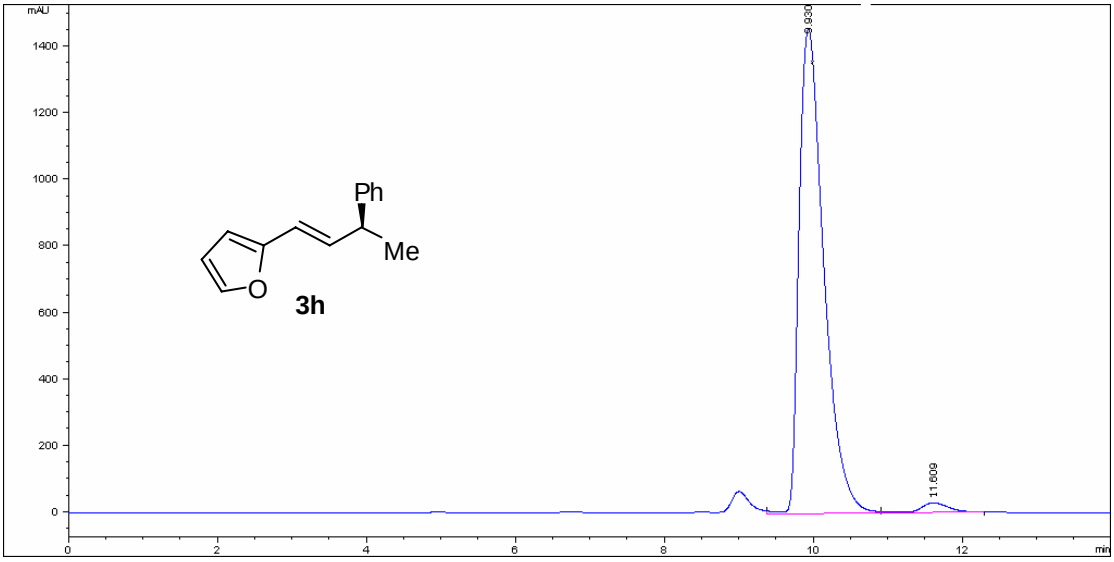
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.852	4167.2	126	0.4833	0.496	49.928
2	15.543	4179.2	98.5	0.6261	0.535	50.072



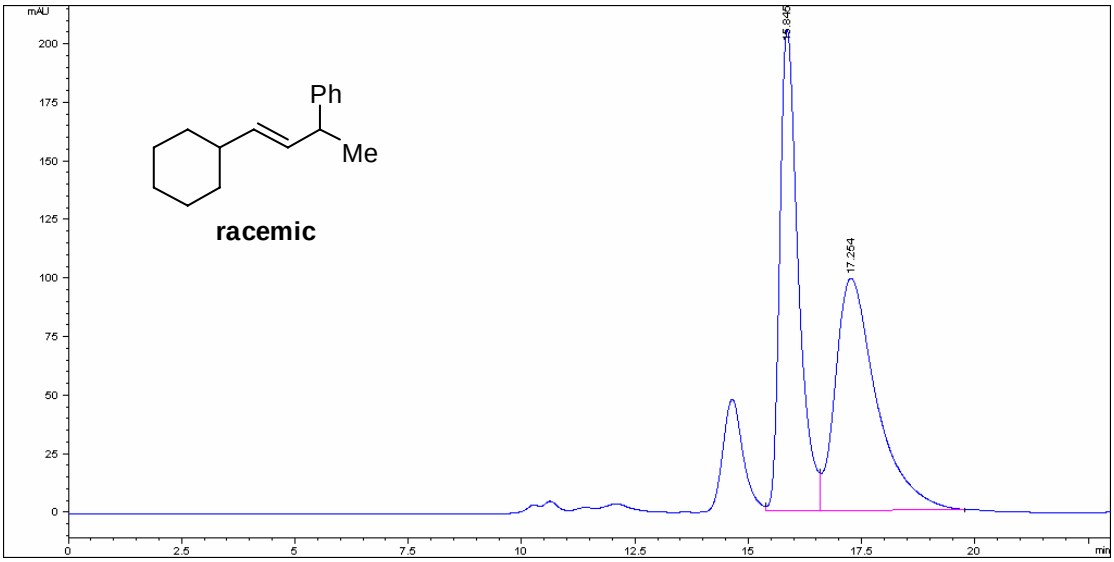
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	12.123	7930.8	225	0.5132	0.464	95.870
2	16.179	341.7	7.9	0.6386	0.647	4.130



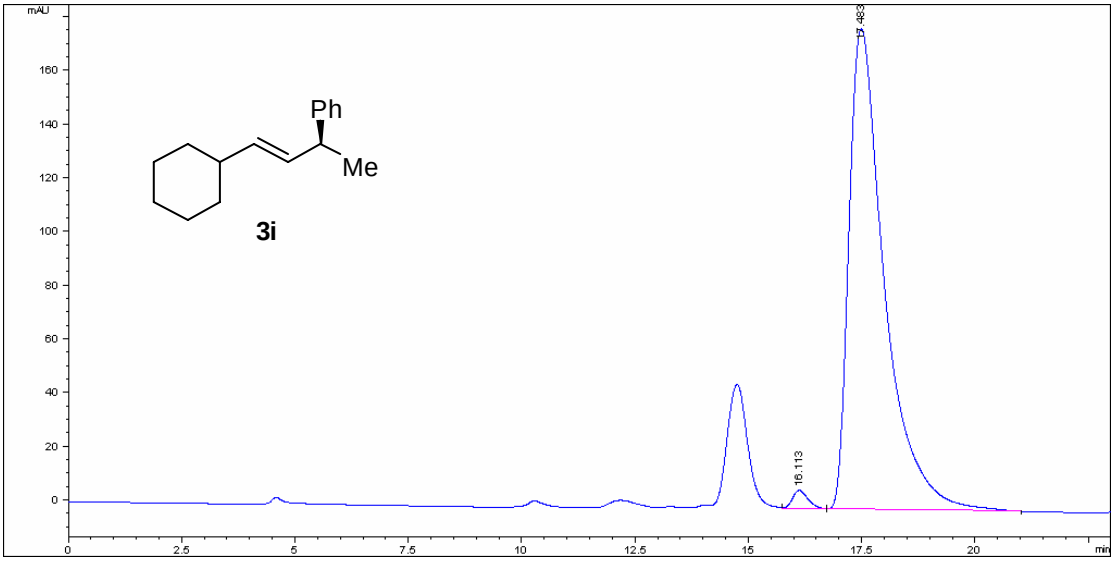
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	9.468	1003.7	47.1	0.3114	0.537	48.589
2	11.243	1062	39.5	0.3892	0.511	51.411



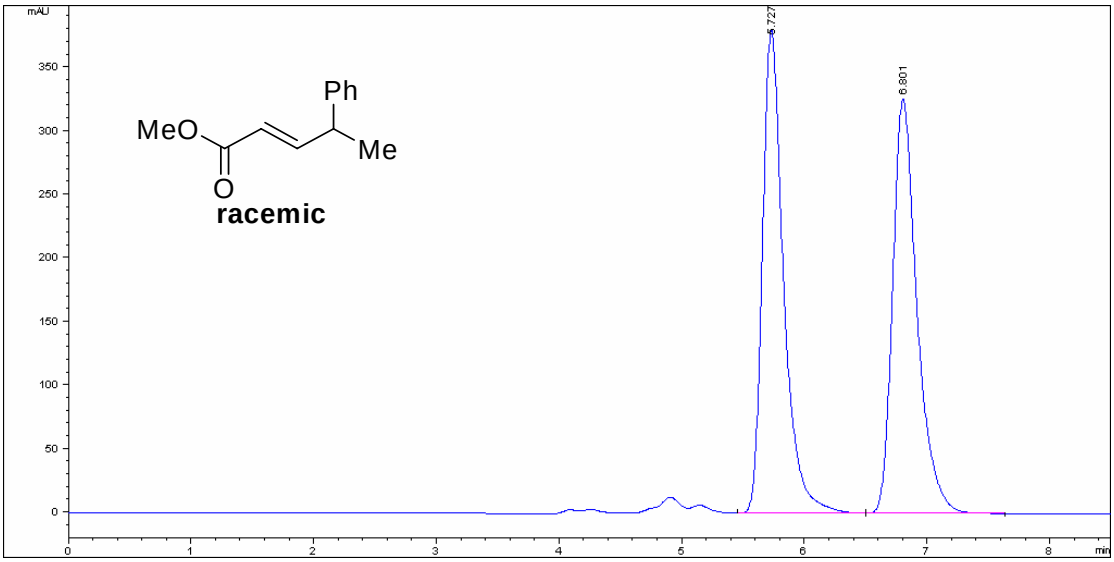
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	9.93	33715.8	1459.1	0.3851	0.577	97.564
2	11.609	841.8	30.2	0.4646	0.587	2.436



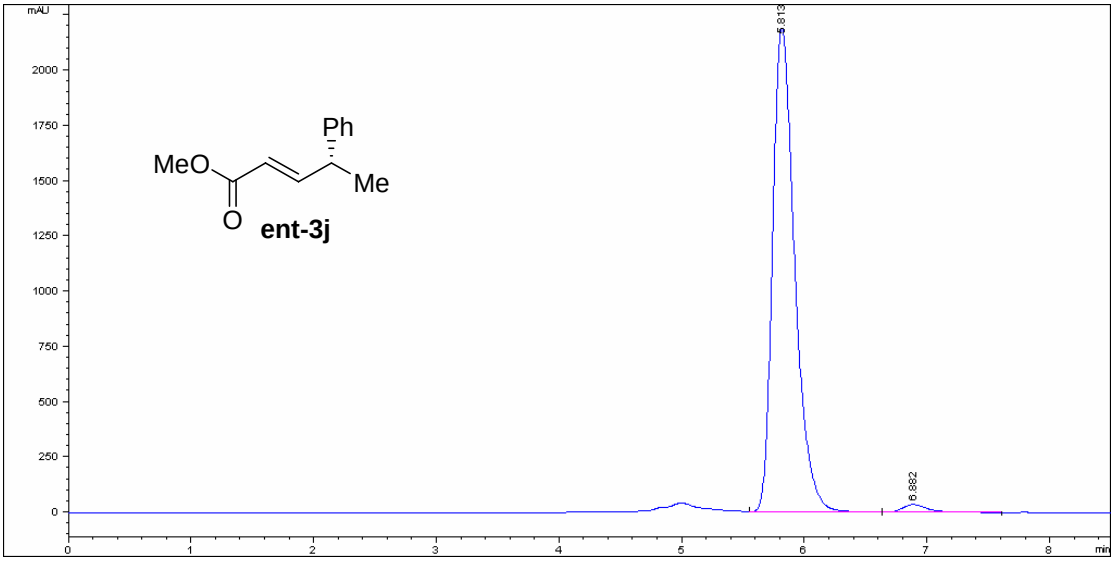
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	15.845	5874.6	205.7	0.4293	0.597	48.492
2	17.254	6240.1	99.2	0.9331	0.56	51.508



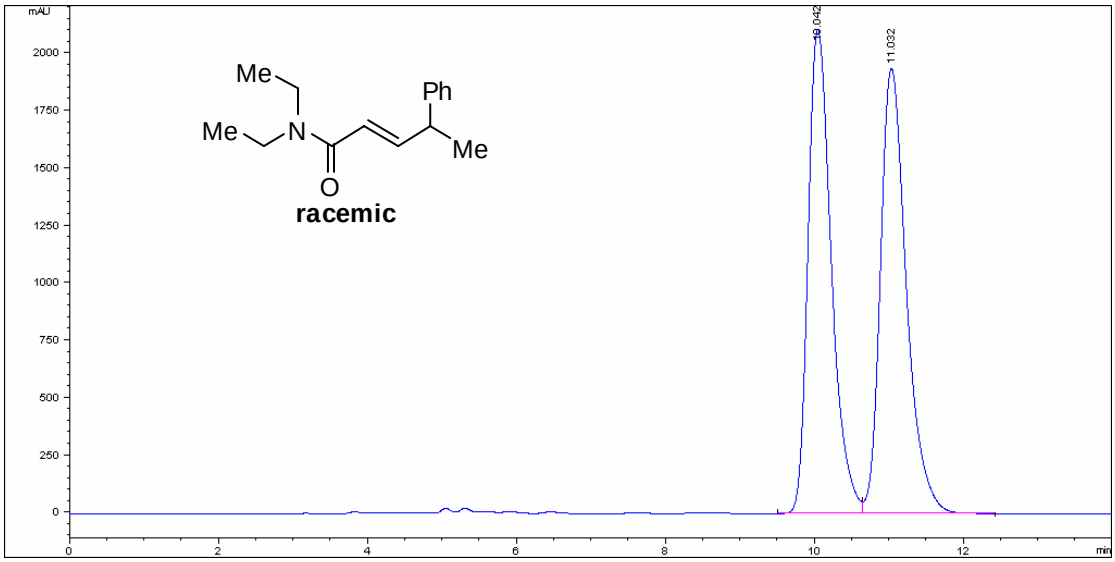
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	16.113	168.7	6.9	0.3722	0.708	1.692
2	17.483	9802.4	179.1	0.8161	0.484	98.308



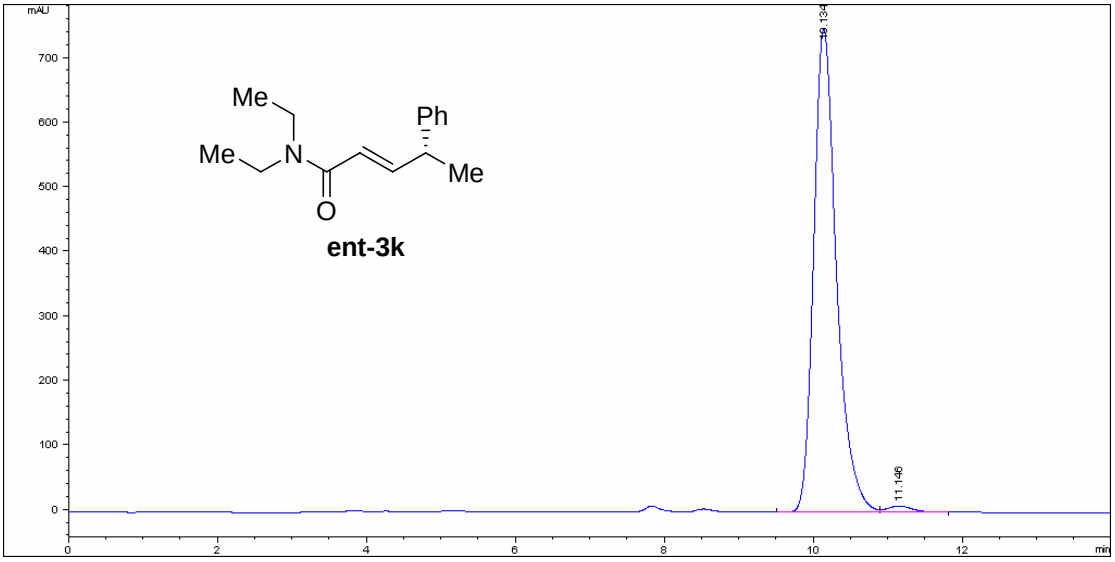
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.727	4572.9	380.4	0.181	0.652	50.451
2	6.801	4491.2	326	0.2073	0.685	49.549



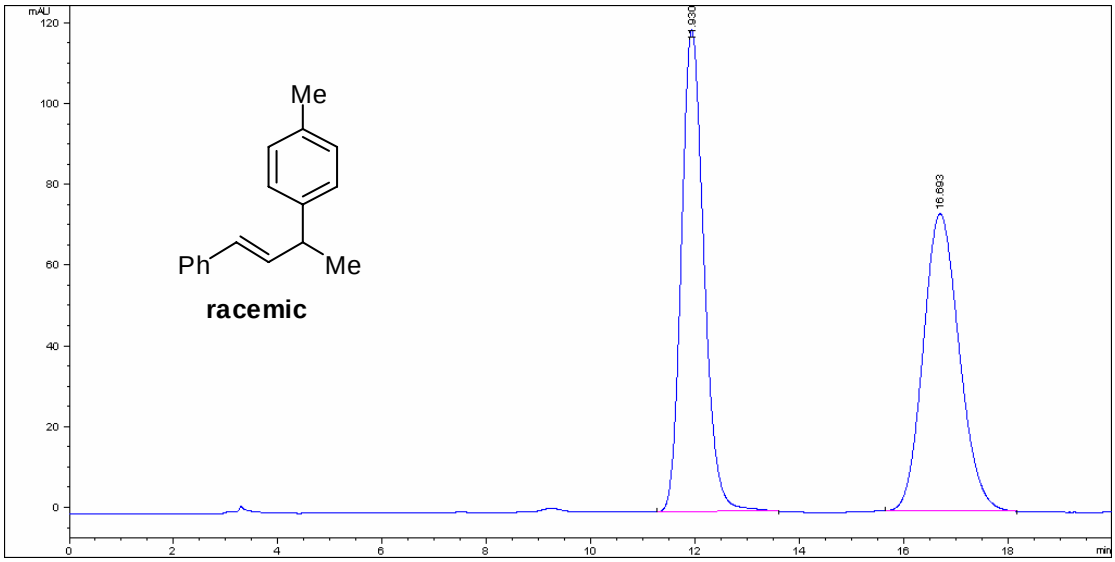
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	5.813	27612.2	2189.8	0.1922	0.666	97.995
2	6.882	565	36.3	0.2281	0.611	2.005



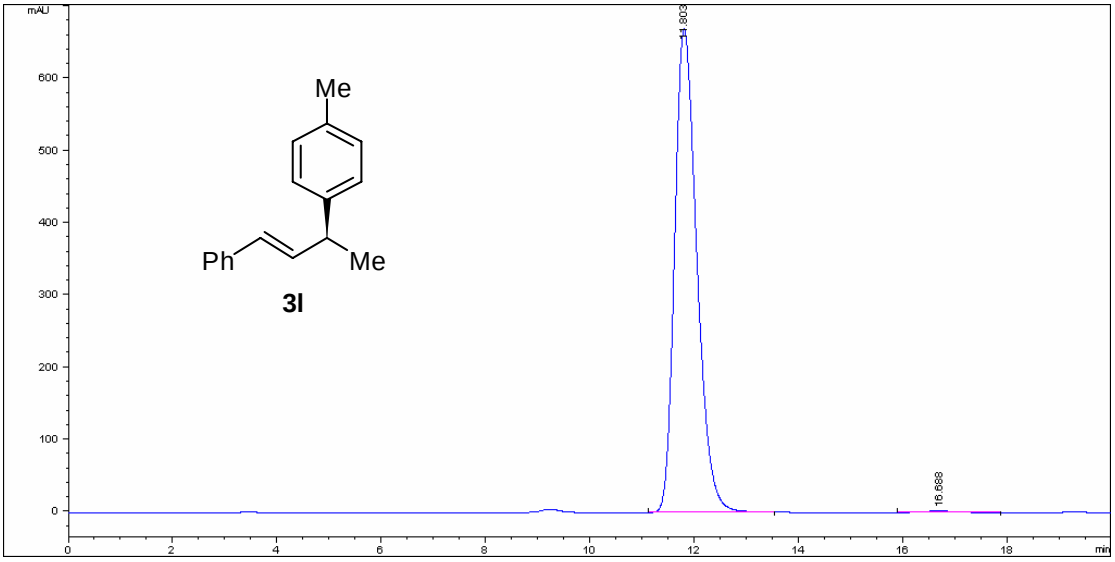
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	10.042	45871.4	2106	0.3327	0.668	49.529
2	11.032	46743.5	1936.9	0.3689	0.685	50.471



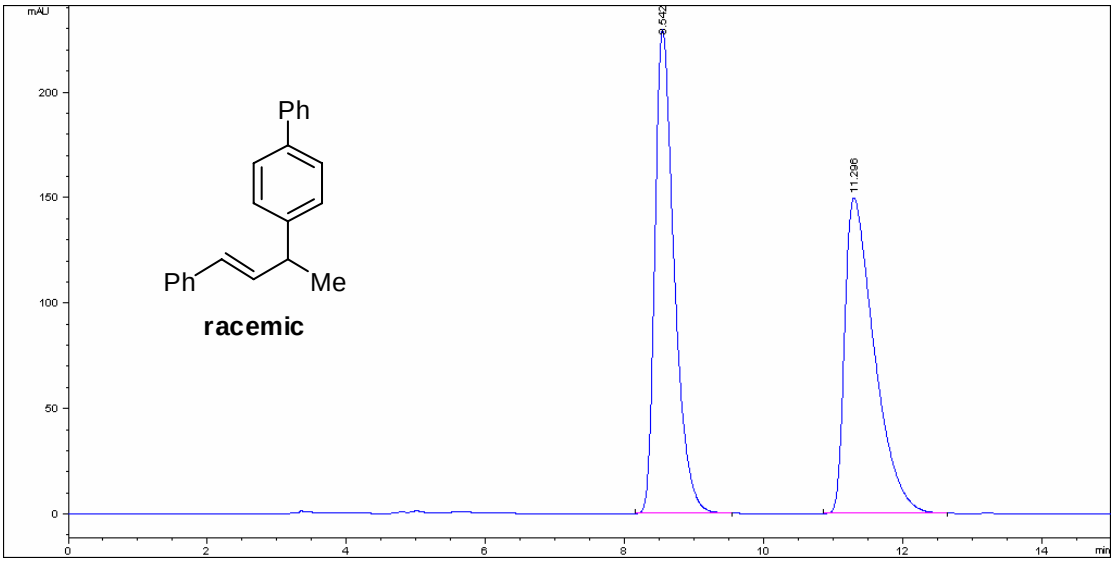
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	10.134	16039	749.1	0.3255	0.714	98.598
2	11.146	228	9.9	0.3264	0.811	1.402



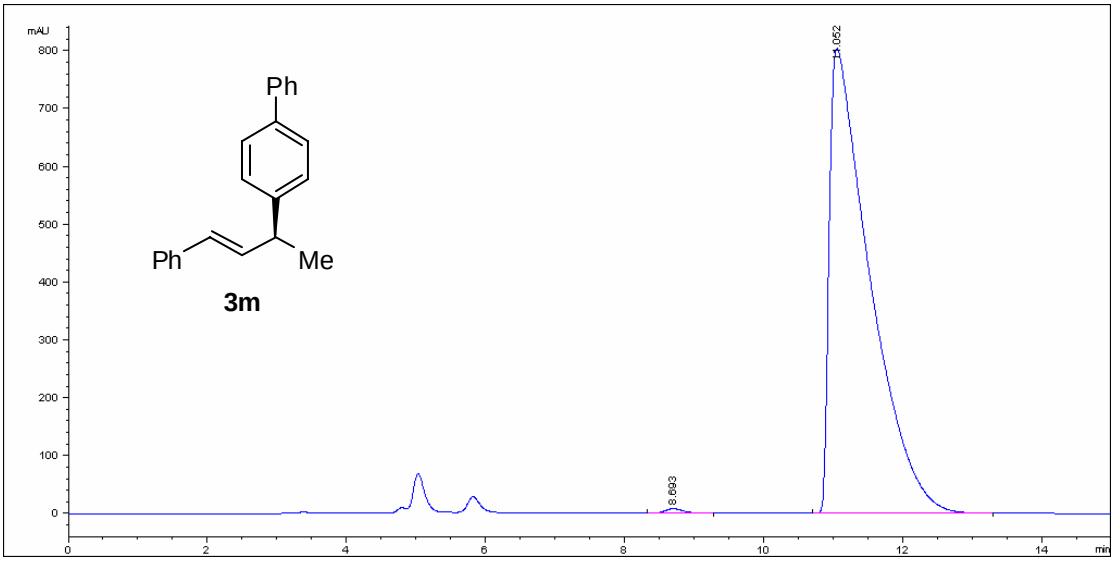
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.93	3583.9	119.4	0.4638	0.791	50.325
2	16.693	3537.6	73.7	0.7451	0.843	49.675



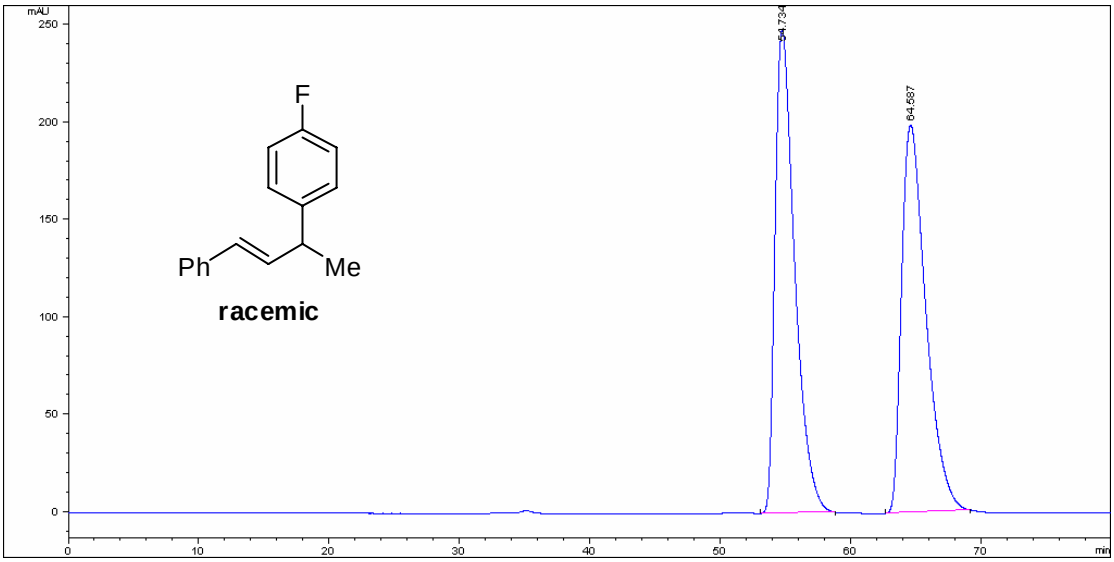
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.803	19801.9	670.1	0.4569	0.702	99.483
2	16.688	103	2.2	0.5993	0.932	0.517



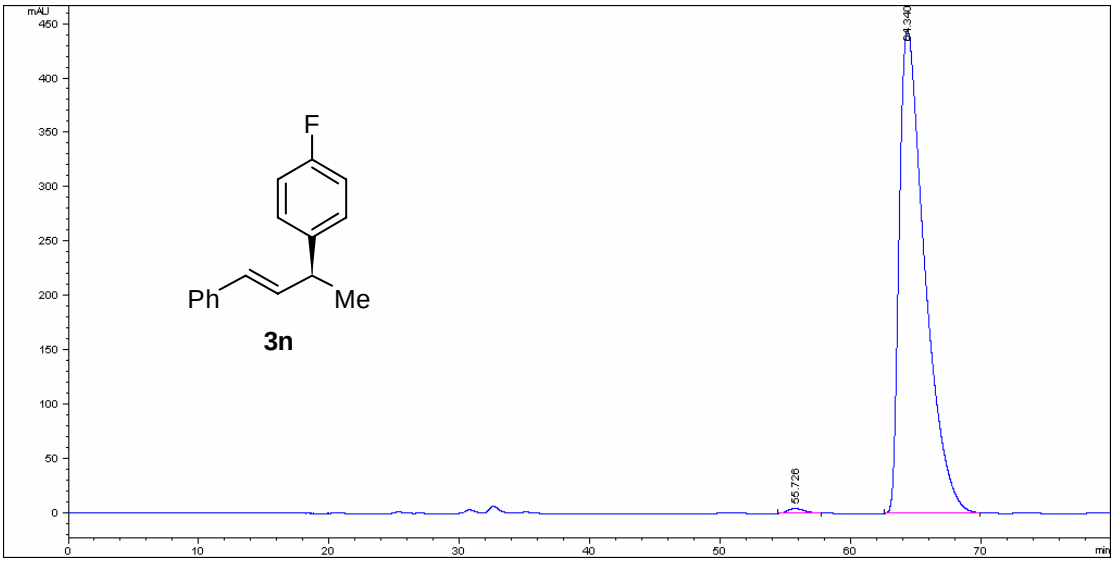
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.542	4430.3	229.3	0.2923	0.608	50.031
2	11.296	4424.8	149.7	0.4482	0.421	49.969



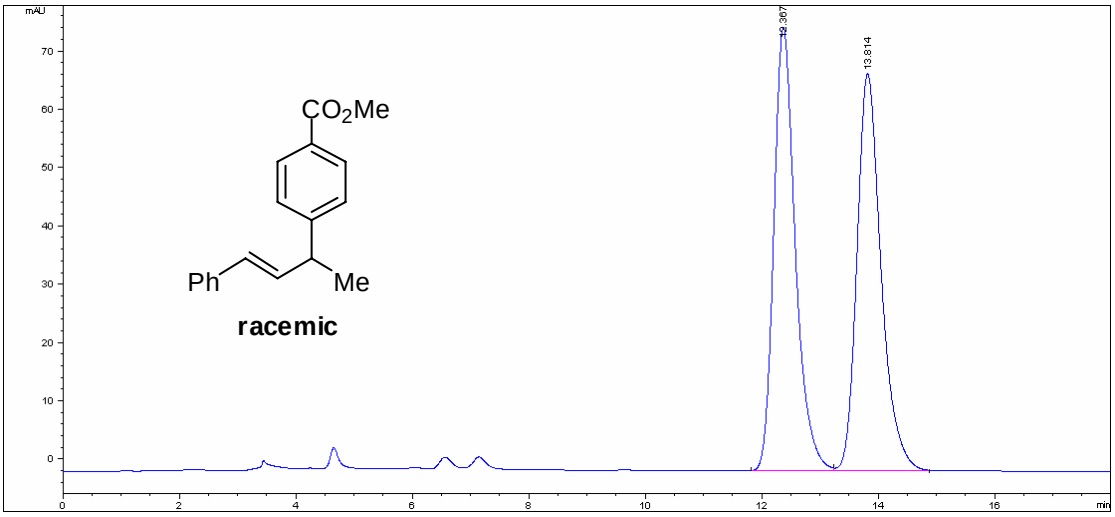
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.693	147.5	7.9	0.2846	0.73	0.452
2	11.052	32508.4	803.7	0.5767	0.214	99.548



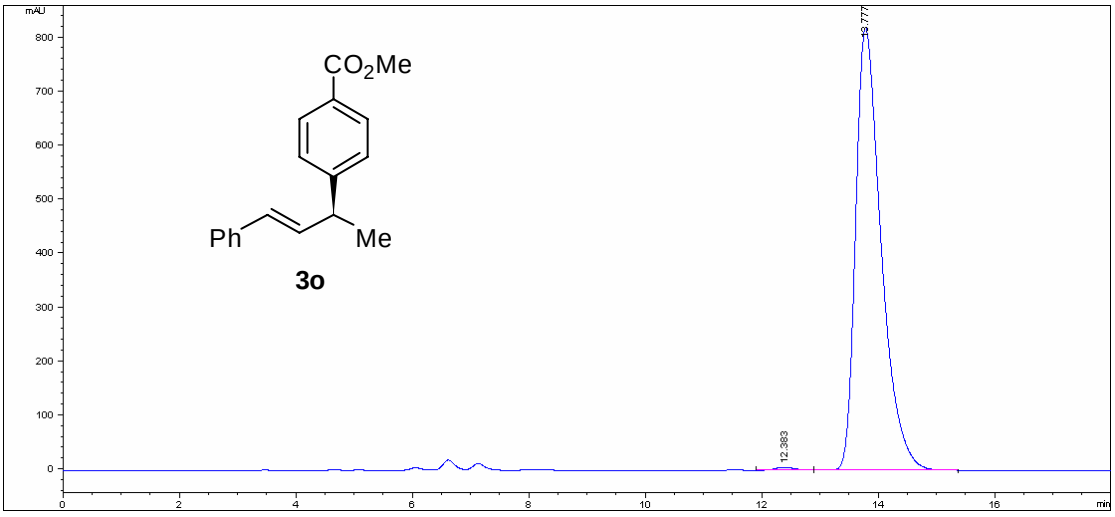
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	54.734	26022.7	248.1	1.5762	0.526	50.237
2	64.587	25776.8	198.9	1.9458	0.548	49.763



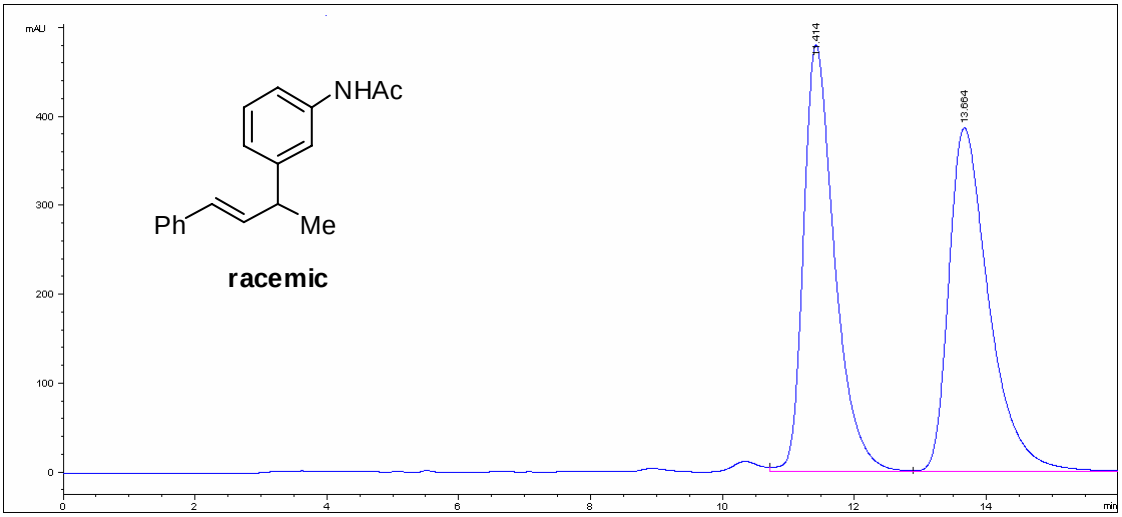
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	55.726	378.6	4.4	1.1089	0.776	0.624
2	64.34	60302.7	445.3	2.0151	0.431	99.376



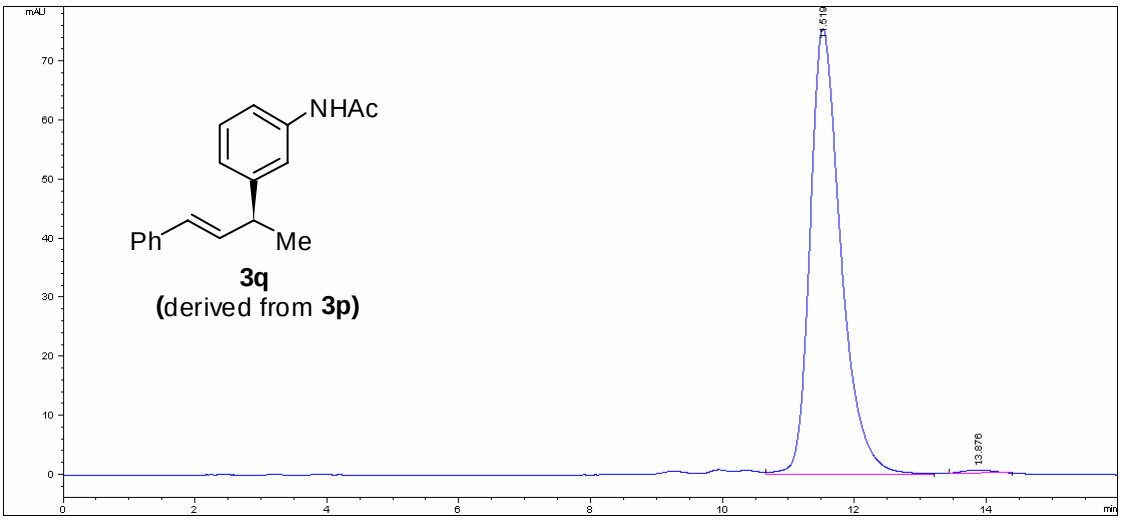
Number	Time （min）	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	12.367	1951.2	76	0.3883	0.742	49.911
2	13.814	1958.2	68.1	0.4361	0.743	50.089



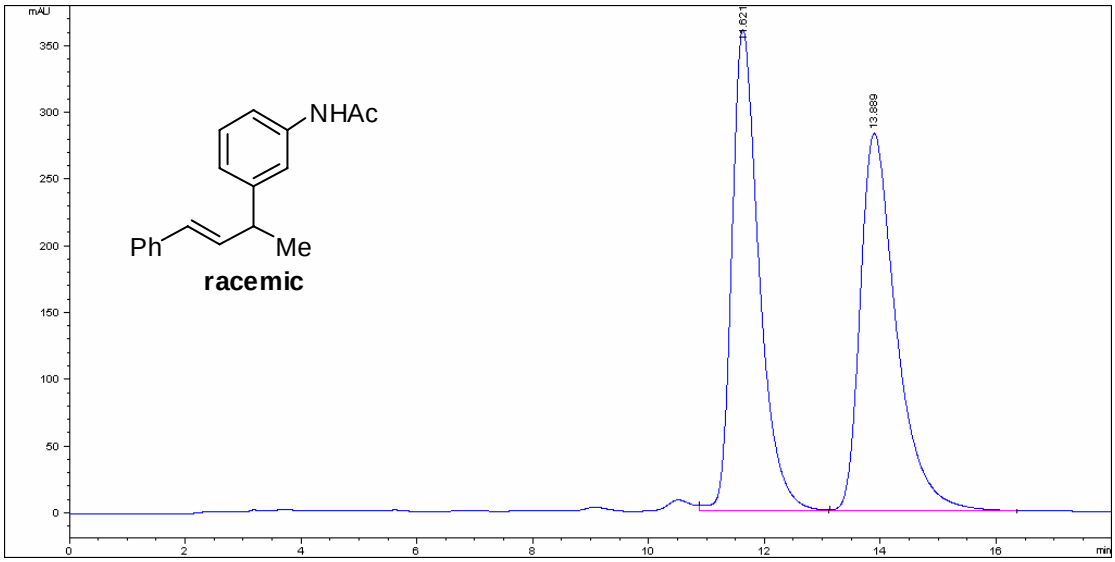
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	12.383	136.9	5.5	0.383	0.766	0.545
2	13.777	24982.7	820	0.4617	0.591	99.455



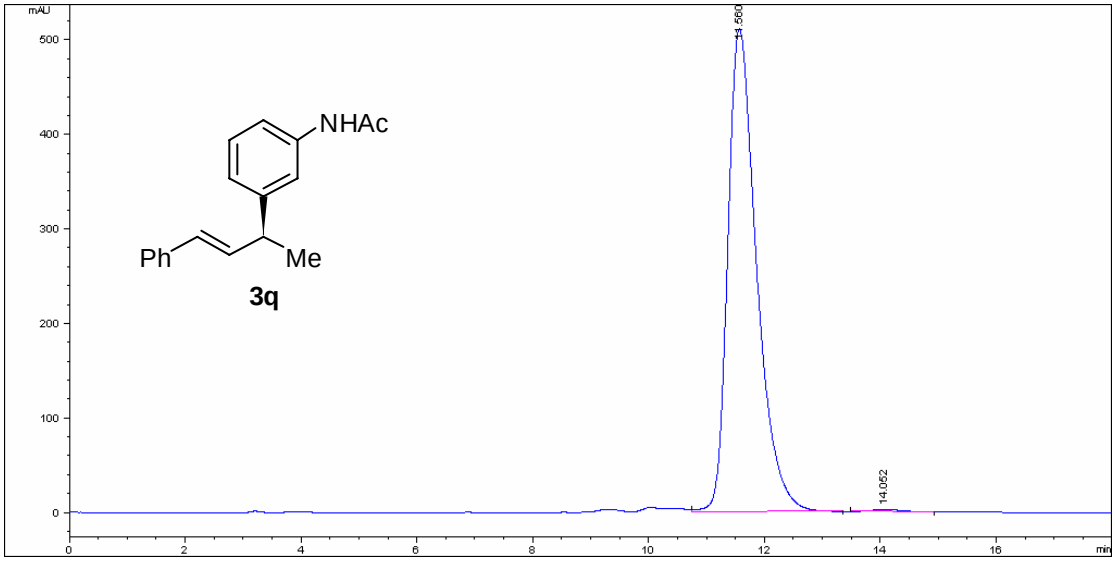
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.414	1582.9	480.3	0.498	0.633	49.153
2	13.664	16373.5	387.1	0.705	0.608	50.847



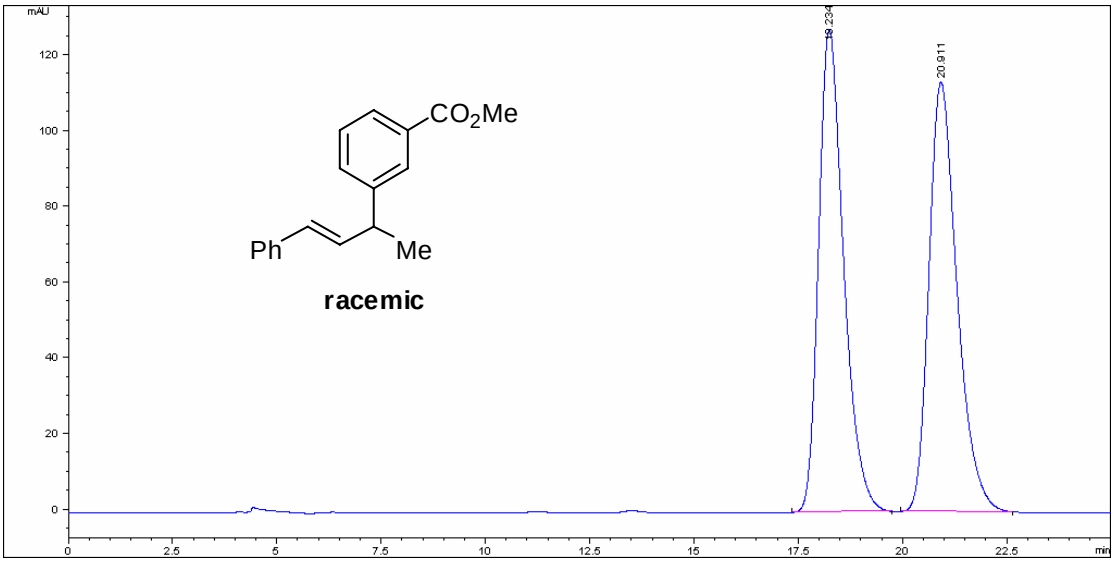
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.519	2469.2	75.5	0.495	0.673	99.273
2	13.876	18.1	5.5E-1	0.5447	0.945	0.727



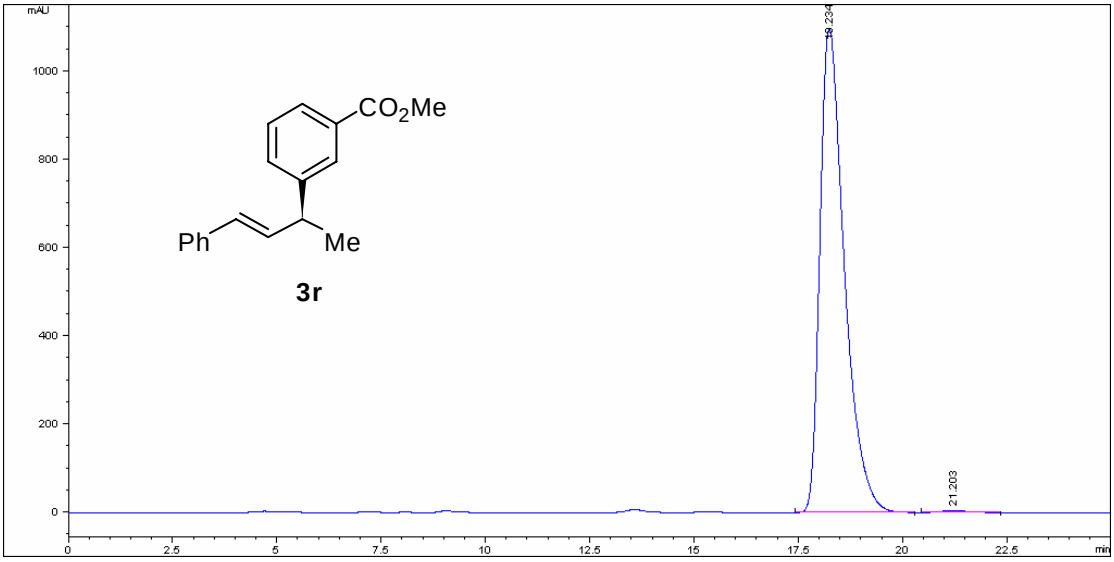
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.621	11869.4	360.9	0.4958	0.642	49.213
2	13.889	12249.1	283	0.6506	0.592	50.787



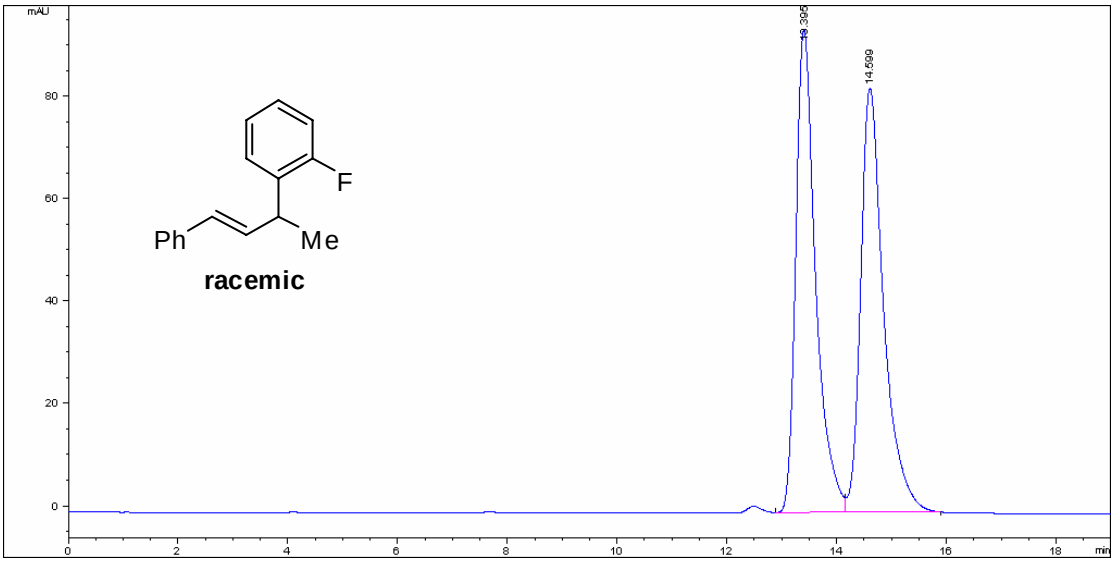
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	11.56	17660.4	511.3	0.5238	0.629	99.518
2	14.052	85.6	2.3	0.5463	0.713	0.482



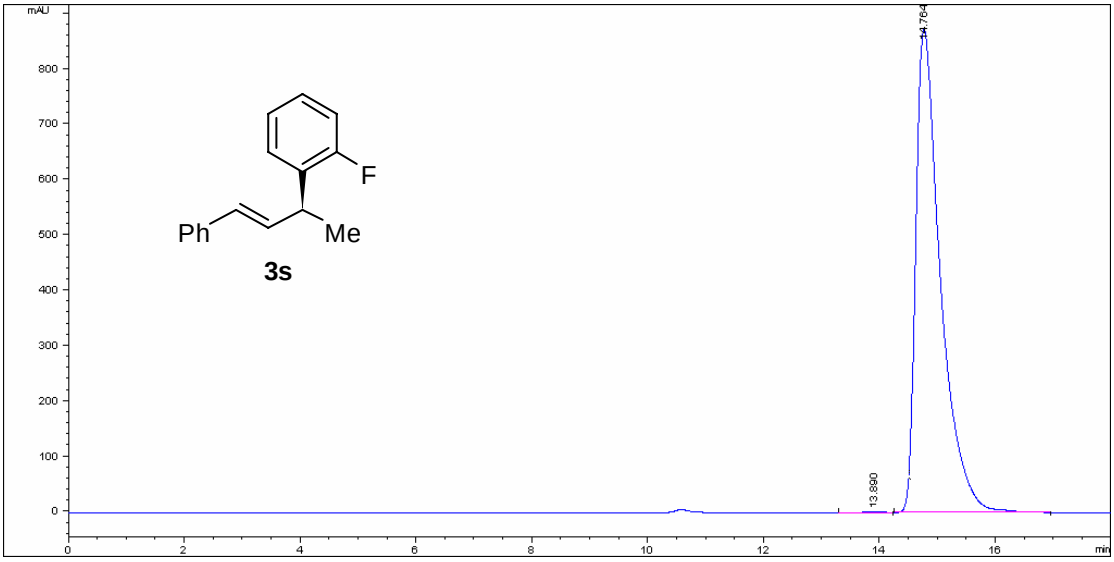
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.234	5325.4	127.4	0.6391	0.69	49.988
2	20.911	5328	113.5	0.7124	0.698	50.012



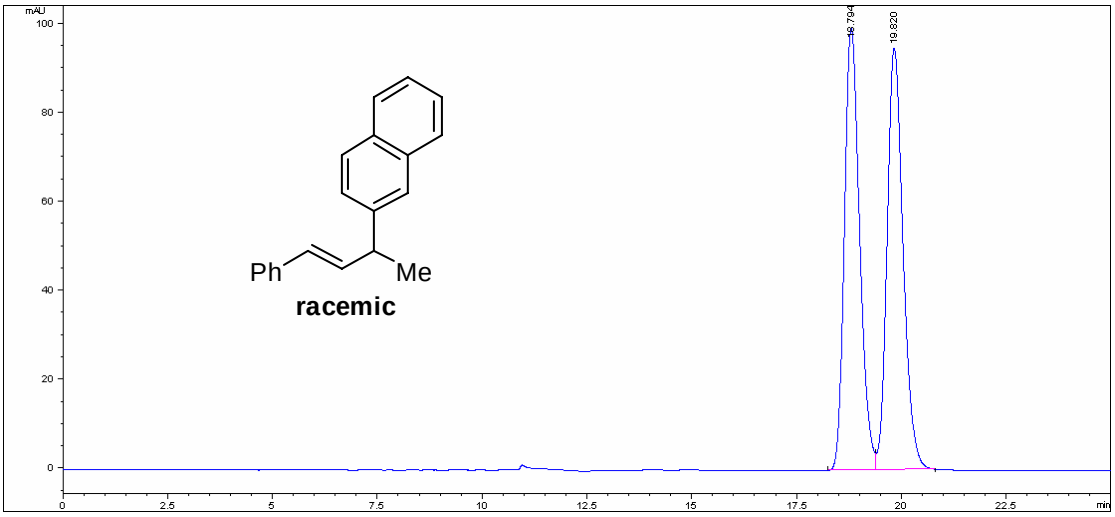
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.234	44743.5	1096.6	0.6187	0.57	99.551
2	21.203	201.6	4.6	0.6369	0.75	0.449



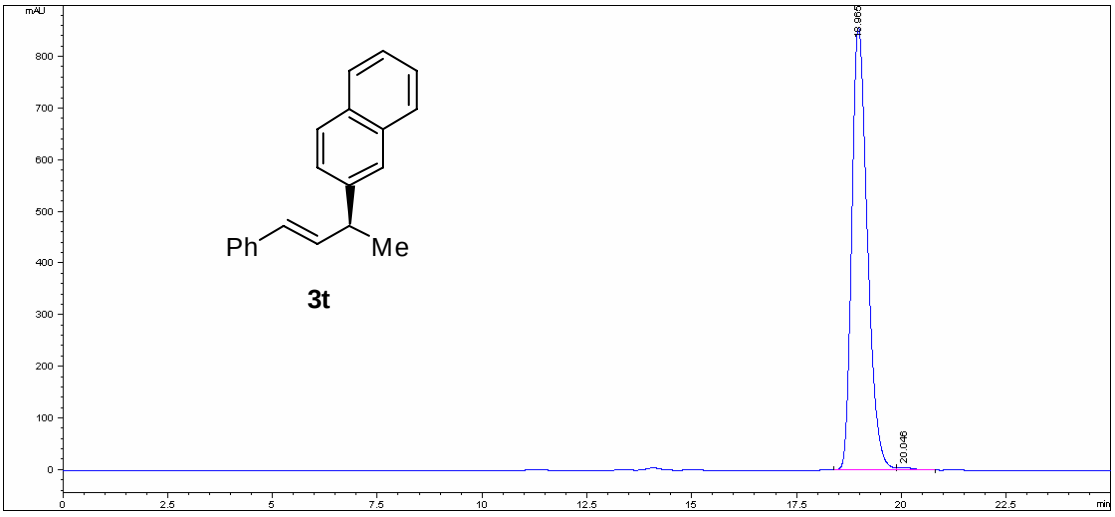
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.395	2380.1	94.4	0.3772	0.632	49.623
2	14.599	2416.2	82.9	0.4332	0.625	50.377



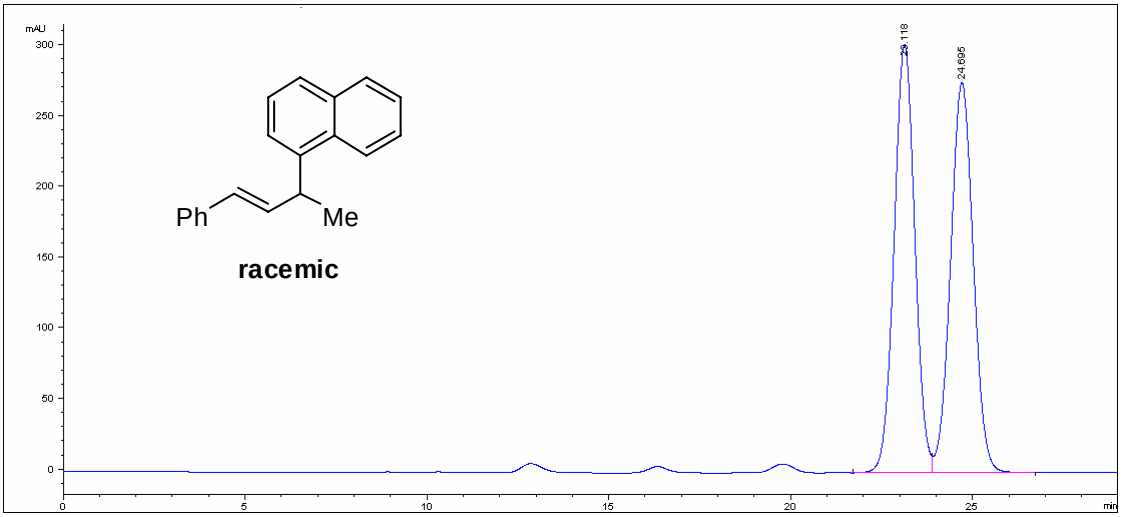
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	13.89	151.2	3.4	0.7307	1.408	0.581
2	14.764	25871.6	874.1	0.4371	0.456	99.419



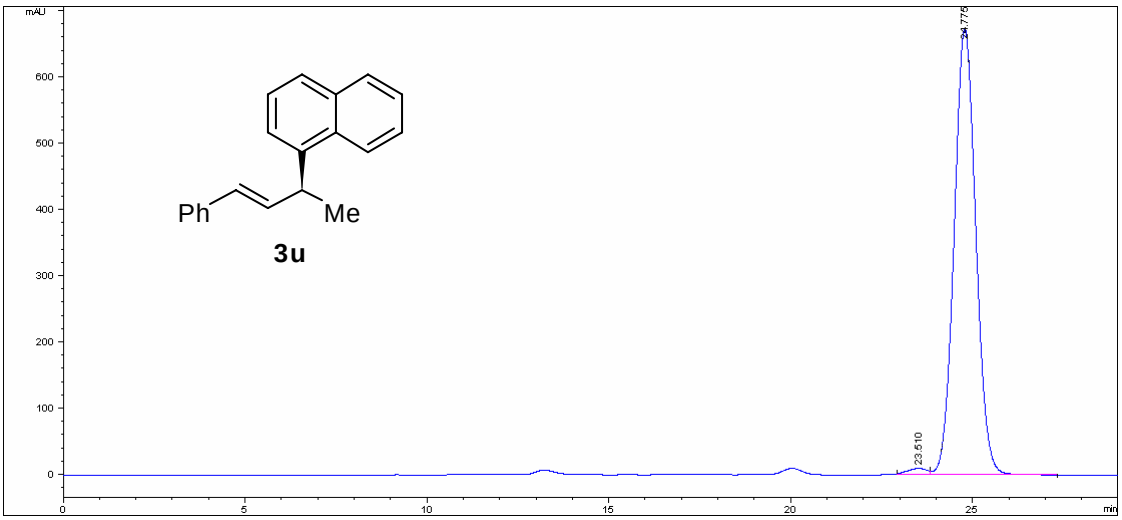
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.794	2509	99.5	0.3874	0.763	49.876
2	19.82	2521.5	94.8	0.4079	0.766	50.124



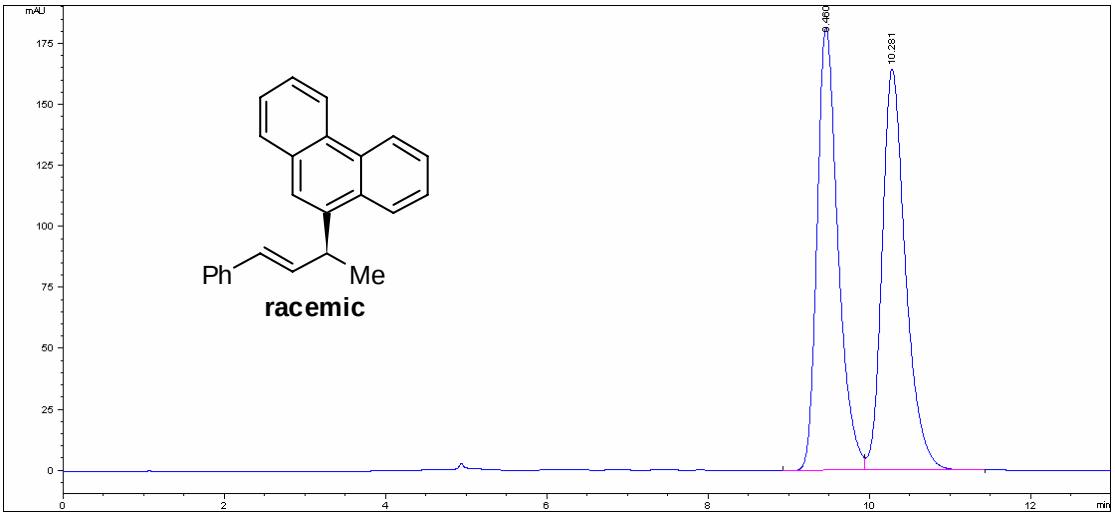
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	18.965	22249.7	857.1	0.399	0.692	99.381
2	20.046	138.6	5.1	0.4003	0.499	0.619



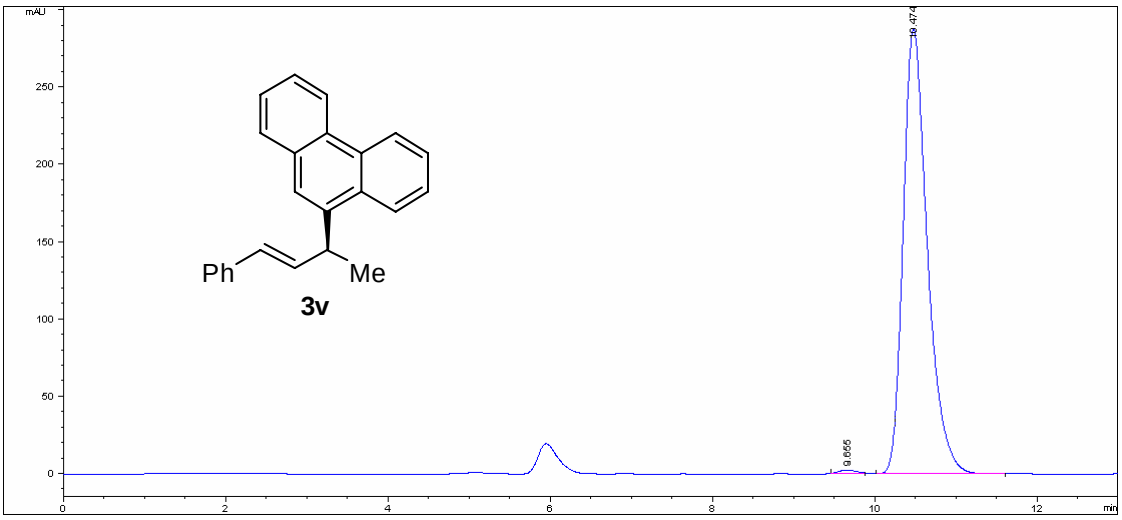
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	23.118	12013.9	302.5	0.6163	0.982	50.097
2	24.695	11967.5	275.7	0..6739	0.955	49.903



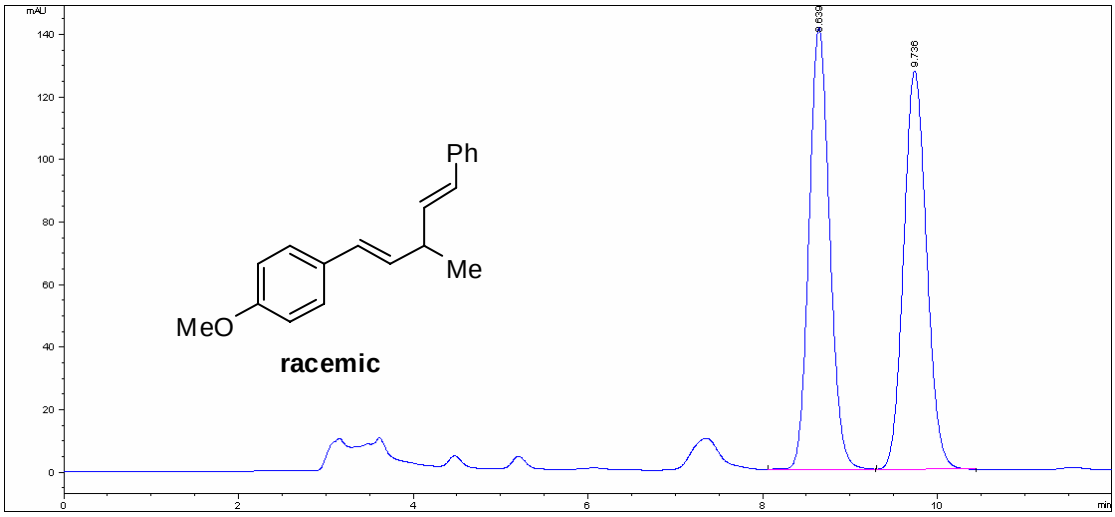
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	23.51	328.1	8.9	0.6115	1.336	1.166
2	24.775	27809.6	672.7	0..689	0.93	98.834



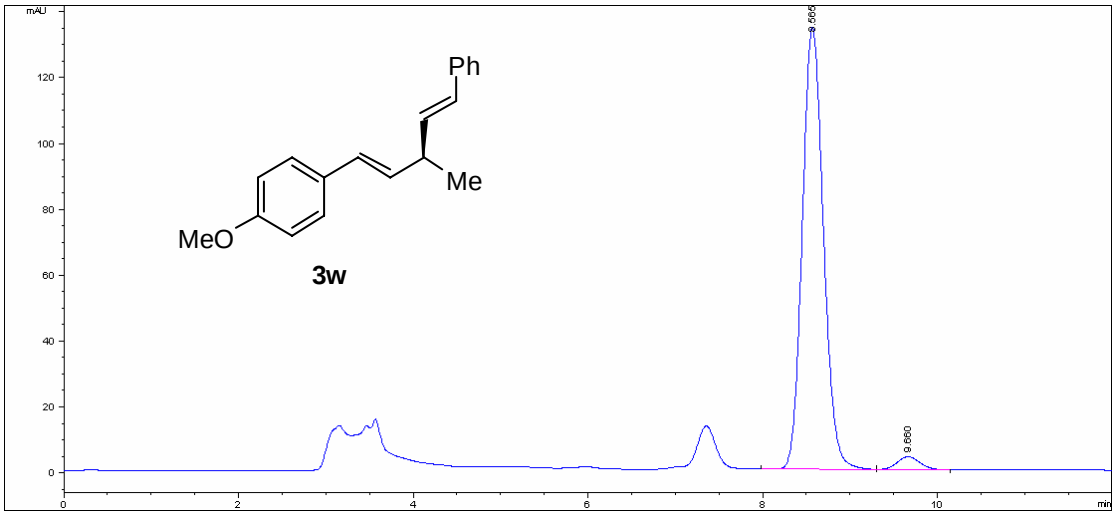
Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	9.46	3282.7	181.6	0.2735	0.696	49.597
2	10.281	3336	164.5	0.3064	0.701	50.403



Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	9.655	37.1	2.3	0.2642	0.861	0.617
2	10.474	5978.1	288.1	0.3149	0.692	99.383



Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.639	2322.6	141.4	0.2542	0.872	49.868
2	9.736	2335	127.4	0.2851	0.885	50.132



Number	Time (min)	Area (mAU.s)	Height (mAU)	Width (min)	Symmetry factor	Area (%)
1	8.565	2260.6	134.2	0.262	0.856	96.872
2	9.66	73	4	0.2868	0.903	3.128