A Facile Method for the Preparation of MOM-Protected Carbamates

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Experimental Procedures, Analytical Instrumentation and Data. ^{1}H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublets of doublets, m=multiplet, br=broad), coupling constant(s), integration and peak assignment. ^{13}C NMR spectra were recorded on a Bruker AMX-400 (100 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. Mass spectra were acquired on a Joel JMS-SX-102 spectrometer. HPLC analyses were carried out on Hewlett-Packard system model 1100. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, New Jersey.

Solvents and reagents were used as purchased. Protected phenethylamine derivatives were prepared by reaction of phenethylamine with the suitable reagent in dichloromethane.

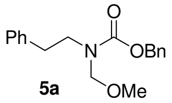
Benzyl *N*-methoxymethyl(phenethyl)carbamate (5a)

A flask was charged with *N*-benzyloxycarbonyl phenethylamine[1] (**4a**, 1 g, 3.9 mmol), paraformaldehyde (0.18 g, 6 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. TMSCl (1.28 g, 11.7 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 2 hours, at which point HPLC analysis indicated that the reaction was complete. To the flask was charged 3 ml of MeOH, and the reaction was stirred for 1 hr.

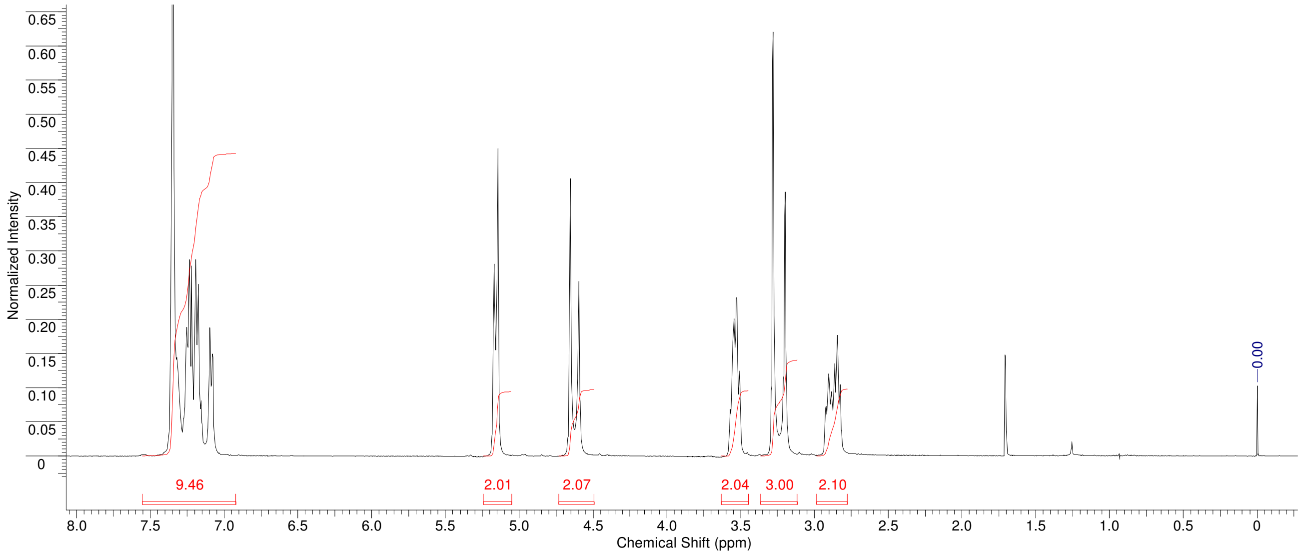
The reaction mixture was quenched into 15 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 10 ml of CH_2Cl_2 and the combined organic phases were washed with 10 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 1.03 g (88 % yield) of benzyl *N*-methoxymethyl(phenethyl)carbamate **5a**.

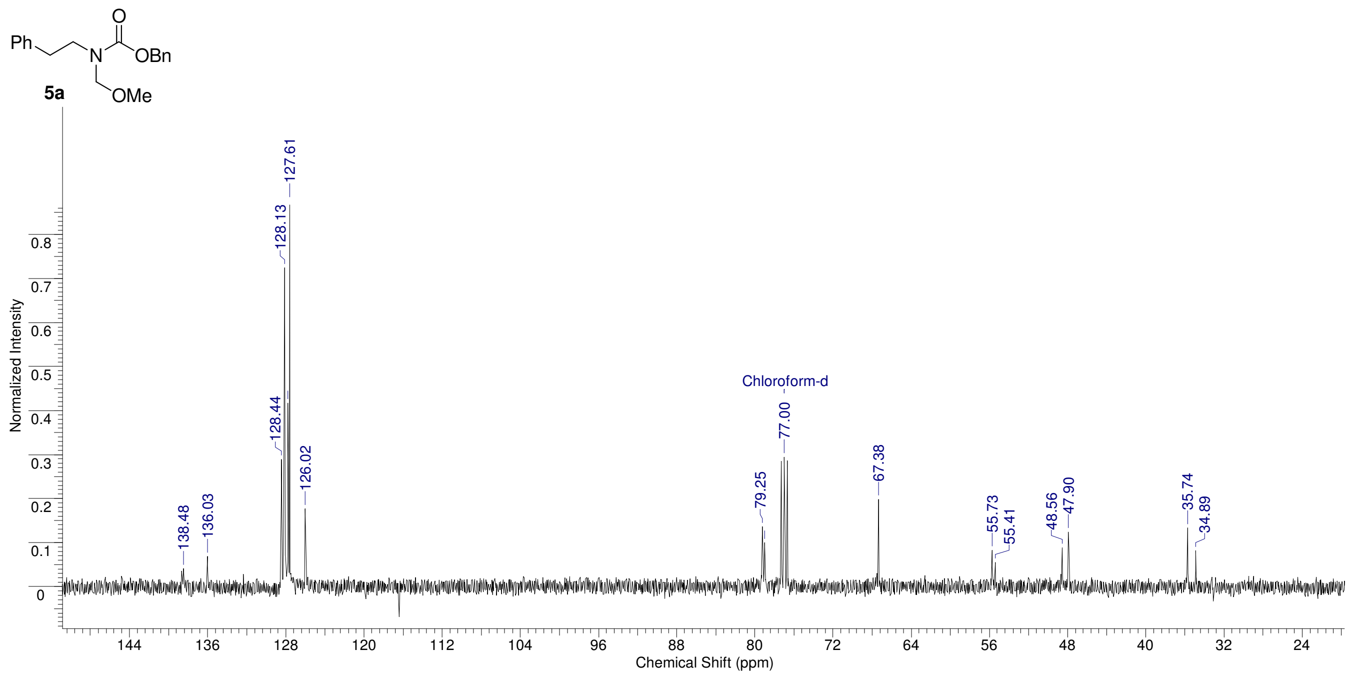
^{1}H NMR ($CDCl_3$) δ 2.87 (m, 2H), 3.24 (d, 3H), 3.53 (m, 2H), 4.63 (d, 2H), 5.16 (d, 2H), 7.09 (d, 1H), 7.22 (m, 4H), 7.35 (br, 5H). ^{13}C NMR ($CDCl_3$) δ 34.9, 35.7, 47.9, 48.6, 55.4, 55.7, 67.4, 79.0, 79.2, 126.0, 127.6, 127.8, 128.1, 128.2, 128.4, 136.0, 138.5. IR: 1706 cm^{-1}.

MS: 322.14226 (M+Na). Anal calcd for $C_{18}H_{21}NO_3$: C, 72.22%; H, 7.07%; N, 4.68%. Found: C, 72.30%; H, 7.32%; N, 4.70%.



5a





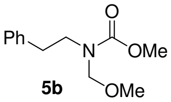
Methyl *N*-methoxymethyl(phenethyl)carbamate (5b)

A flask was charged with *N*-methoxycarbonyl phenethylamine[2] (**4b**, 1 g, 5.6 mmol), paraformaldehyde (0.25 g, 8.3 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. TMSCl (1.82 g, 16.7 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 2 hours, at which point HPLC analysis indicated that the reaction was complete. To the flask was charged 3 ml of MeOH, and the reaction was stirred for 1 hr.

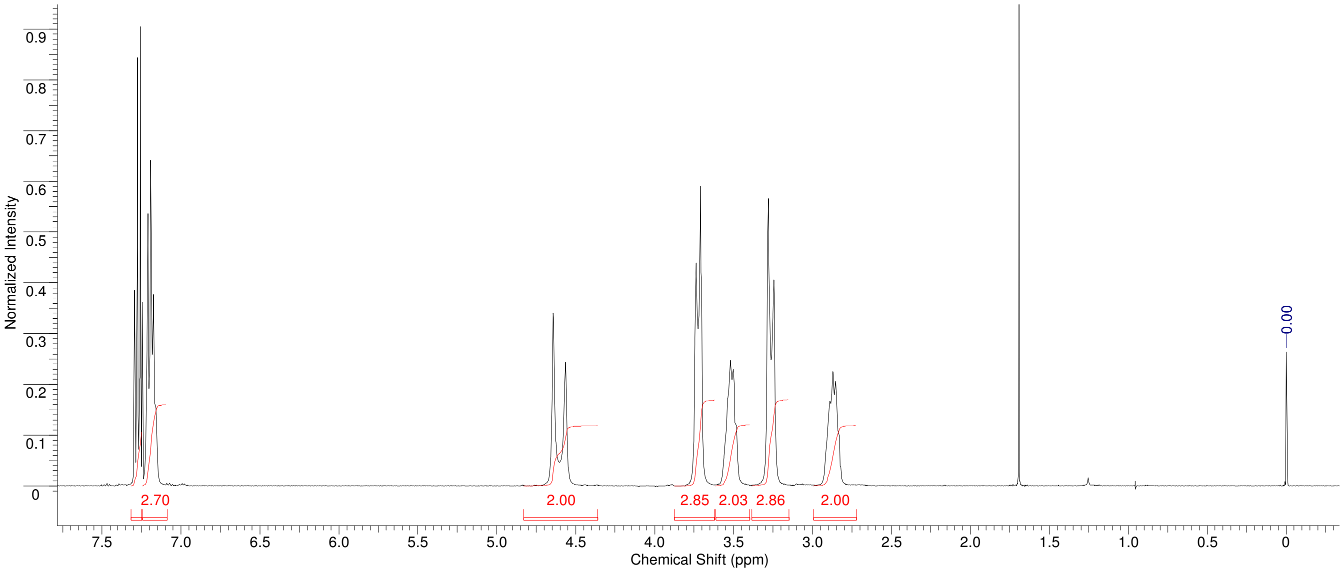
The reaction mixture was quenched into 20 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 10 ml of CH_2Cl_2 and the combined organic phases were washed with 10 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 1 g (80 % yield) of *N*-methoxycarbonyl-*N*-methoxymethyl phenethylamine **5b**.

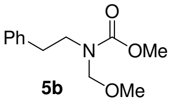
^{1}H NMR ($CDCl_3$) δ 2.87 (m, 2H), 3.26 (d, 3H), 3.52 (m, 2H), 3.72 (d, 3H), 4.60 (d, 2H), 7.19 (m, 3H), 7.27 (t, 2H). ^{13}C NMR ($CDCl_3$) δ 35.0, 35.7, 47.8, 48.7, 52.9, 55.4, 55.7, 79.2, 126.0, 128.1, 128.5, 138.6. IR: 1708 cm^{-1}.

HRMS: 224.12888 (M+H). Anal calcd for $C_{12}H_{17}NO_3$: C, 64.55%; H, 7.67%; N, 6.27%. Found: C, 64.30%; H, 7.87%; N, 6.29%.

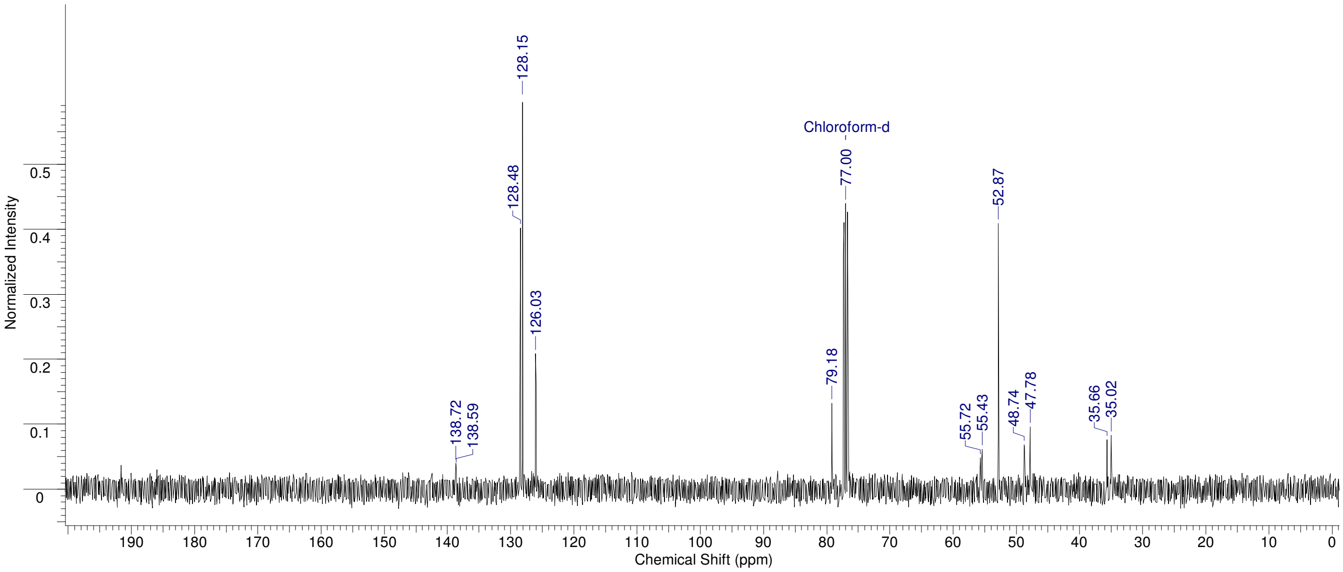


5b





5b



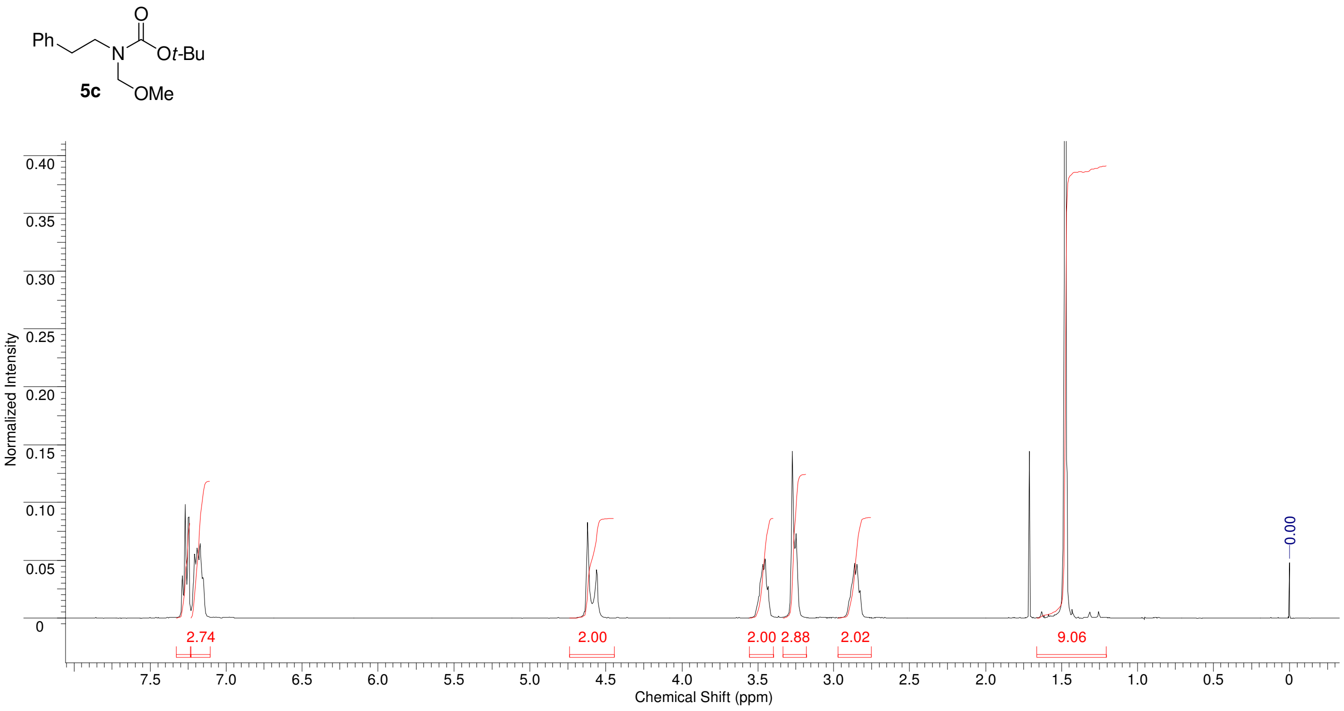
tert-Butyl methoxymethyl(phenethyl)carbamate (5c)

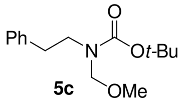
A flask was charged with *tert*-butyl phenethylcarbamate[3] (**4c**, 1 g, 4.5 mmol), paraformaldehyde (0.2 g, 6.7 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. The mixture was cooled to 2 ºC, TMSCl (1.45 g, 13.3 mmol, 3 equiv) was charged, and the reaction was stirred for 4 hours. To the flask was charged 3 ml of 9:1 MeOH:Et_3N, and the reaction was stirred for an additional hour.

The reaction mixture was quenched into 15 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 10 ml of CH_2Cl_2 and the combined organic phases were washed with 10 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 0.87 g (74 % yield) of *tert*-butyl methoxymethyl(phenethyl)carbamate **5c** as an oil.

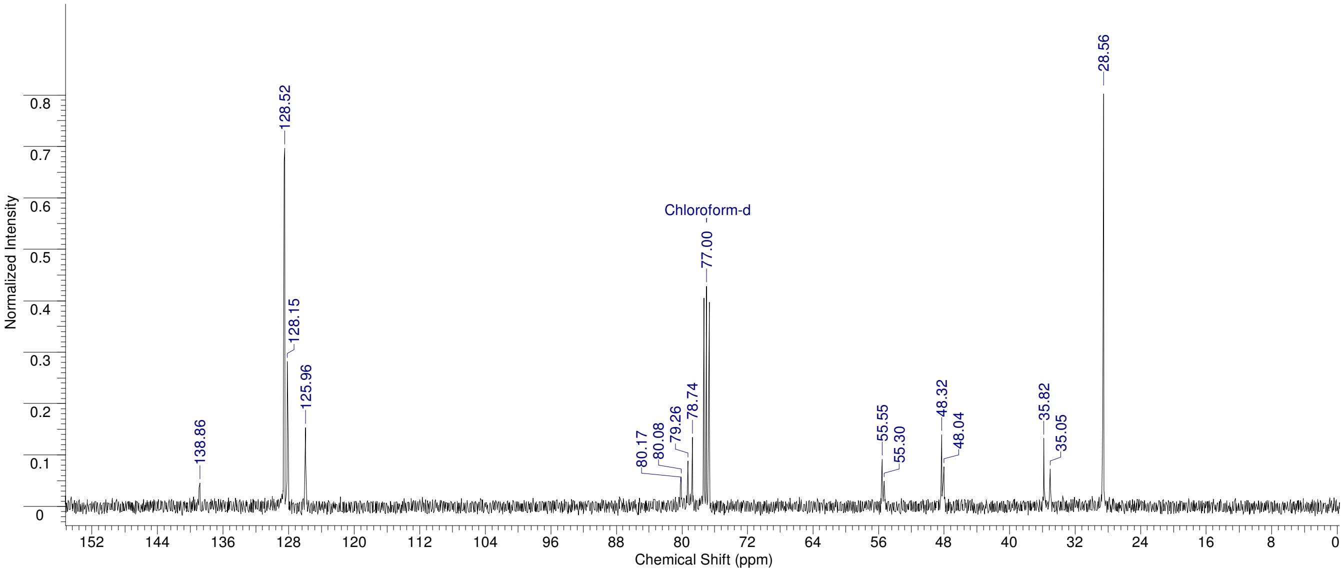
^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.86 (m, 2H), 3.26 (d, 3H), 3.45 (m, 2H), 4.59 (d, 2H), 7.18 (m, 3H), 7.27 (t, 2H). ^{13}C NMR ($CDCl_3$) δ 28.6, 35.0, 35.8, 48.0, 48.3, 55.3, 55.5, 78.7, 79.3, 80.2, 126.0, 128.1, 128.5, 138.9. IR: 1701 cm^{-1}.

HRMS: 288.15705 (M+Na). Anal calcd for $C_{15}H_{23}NO_3$: C, 67.90%; H, 8.74%; N, 5.28%. Found: C, 67.66%; H, 9.11%; N, 5.28%.





5c

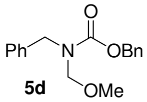


***N*-Methoxymethyl benzylamine, benzyl carbamate** (**5d**).

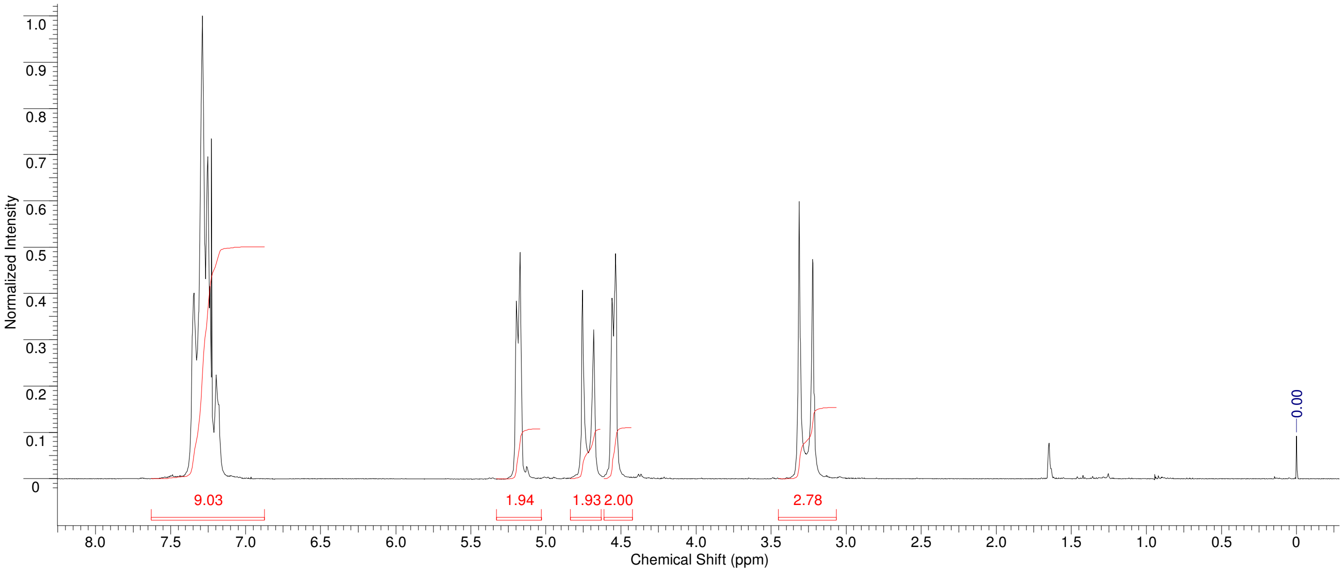
A flask was charged with *N*-benzyl benzylcarbamate[4] (**4d**, 2.41 g, 10 mmol), paraformaldehyde (0.48 g, 16 mmol, 1.6 equiv) and 40 mL of CH_2Cl_2. TMS-Cl (3.8 mL, 30 mmol, 3 equiv) was added, and the reaction was stirred at room temperature for 1 hour. The reaction was quenched with 10 mL of MeOH and stirred for 1.5 h, then quenched into 70 mL of 10% aqueous $NaHCO_3$. After separation, the aqueous layer was extracted with 20 mL CH_2Cl_2. The combined organic phases were washed with 40 mL of 20% aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to afford 2.81 g (98% yield) of *N*-methoxymethyl benzylamine, benzyl carbamate (**5d**) as an oil.

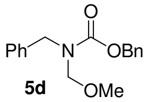
^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ ppm 3.24, 3.33 (3 H) 4.56, 4.58 (2 H) 4.71, 4.78 (2 H) 5.19, 5.22 (2 H) 6.97 - 7.58 (m, 10 H). ^{13}C (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm 48.8, 55.6, 55.9, 67.6, 77.4, 78.3, 127.0, 127.1, 127.3, 127.6, 127.8, 127.9, 128.2. IR 1708, 1422 cm^{-1}.

Anal calcd for $C_{17}H_{19}NO_3$: C, 71.56%; H, 6.71%; N, 4.91%. Found: C, 71.24%; H, 6.68%; N, 4.97%.

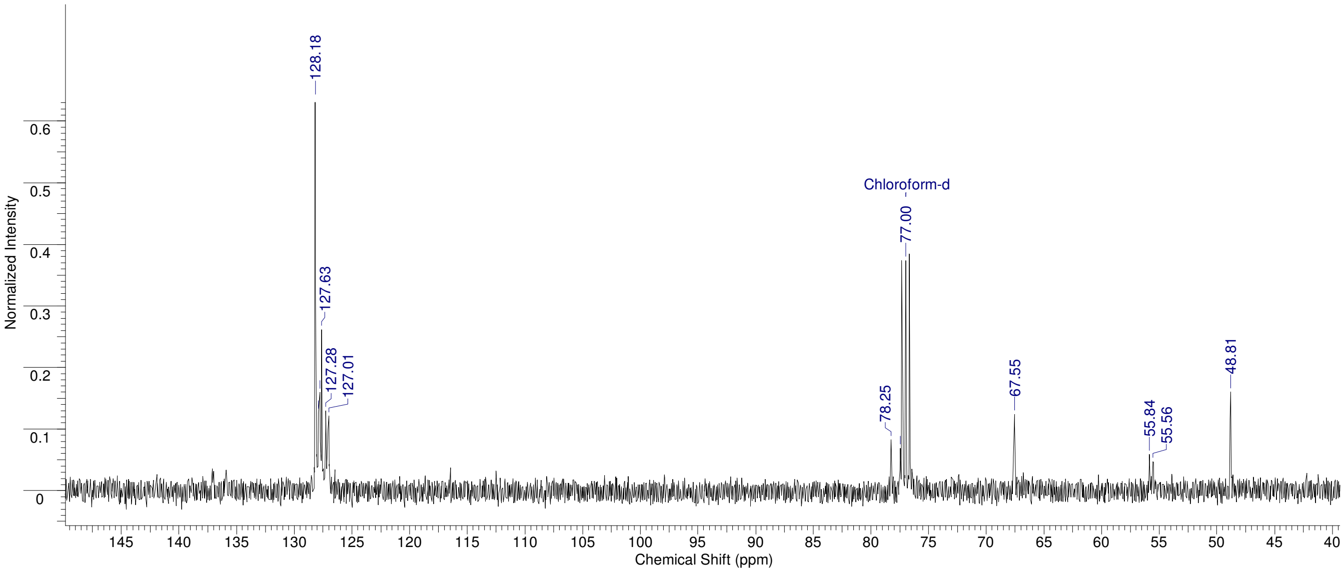


5d





5d

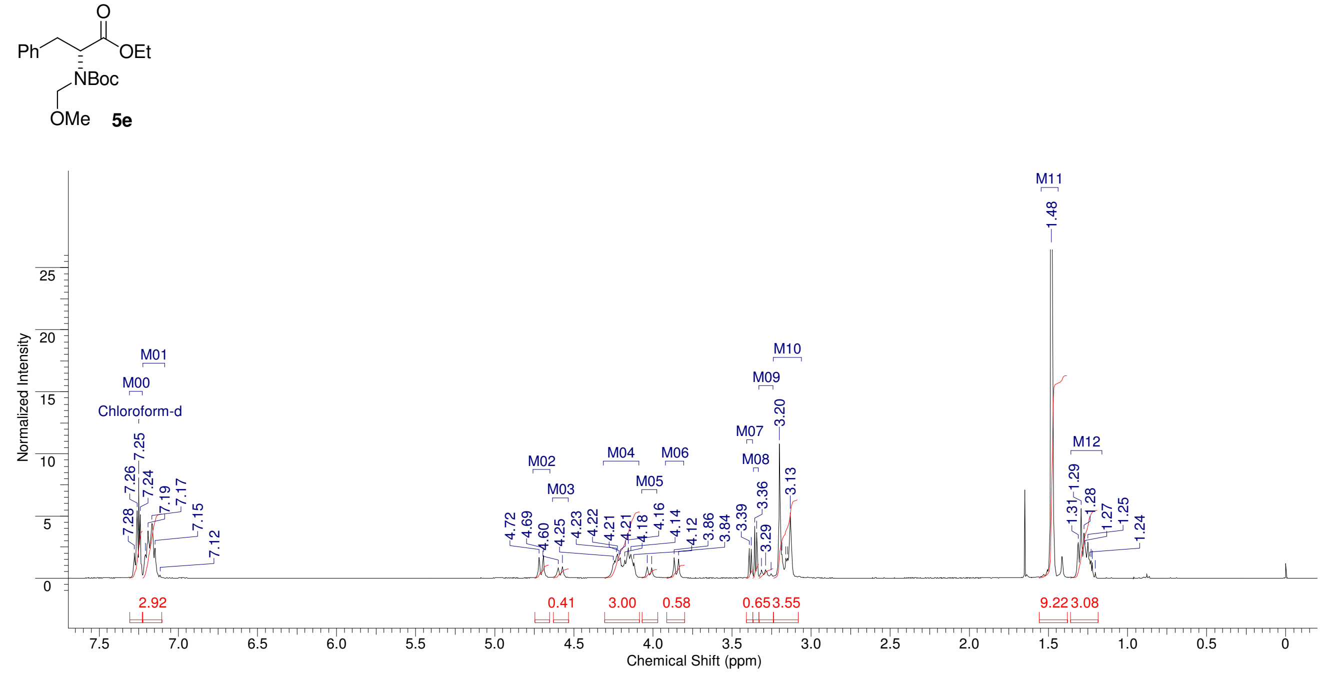


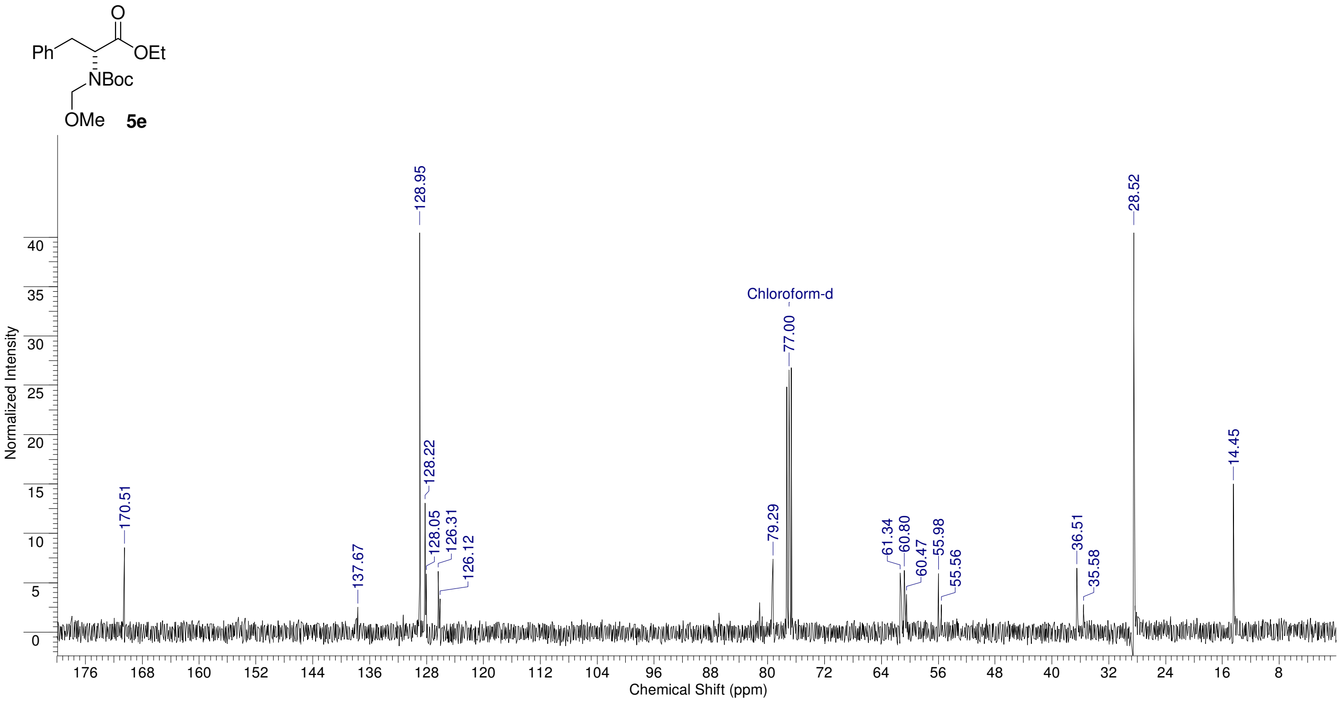
(*R*)-Ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-3-phenylpropanoate (**5e**).

A flask was charged with (*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (**4e**, 3.3 g, 11.3 mmol), paraformaldehyde (0.48 g, 16 mmol, 1.4 equiv) and 40 mL of CH_2Cl_2 and cooled in an ice/water bath. TMS-Cl (3.8 mL, 30 mmol, 2.7 equiv) was added, and the reaction was stirred at 0 °C for 4.5 hour. The reaction was quenched into 50 mL of chilled 9:1 MeOH:Et_3N and stirred for 30 min. The reaction mixture was washed with 100 mL of water (backwashed with 2x30 mL CH_2Cl_2) then the combined organic layers were washed with 50 mL of 10% aqueous $NaHCO_3$, then 100 mL of 10% aqueous NaCl. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered and concentrated. Chromatographic purification (SiO_2, EtOAc/heptane) afforded 3.13 g (82% yield) of (*R*)-ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-3-phenylpropanoate (**5e**) as an oil.

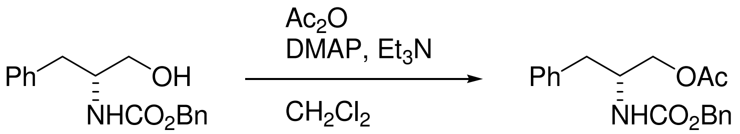
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 - 1.36 (m, 3 H) 1.48 (s, 9 H) 3.06 - 3.24 (m, 3 H) 3.24 - 3.33 (m, 1 H) 3.35 (d, *J*=5.21 Hz, 1 H) 3.38 (d, *J*=5.21 Hz, 1 H) 3.85 (d, *J*=10.70 Hz, 1 H) 4.02 (d, *J*=11.11 Hz, 1 H) 4.09 - 4.31 (m, 3 H) 4.59 (d, *J*=11.25 Hz, 1 H) 4.71 (d, *J*=10.84 Hz, 1 H) 7.09 - 7.22 (m, 3 H) 7.23 - 7.31 (m, 2 H). ^{13}C (100 MHz, $CDCl_3$) δ ppm 14.5, 28.5, 35.6, 36.5, 55.6, 56.0, 60.5, 60.8, 61.2, 61.3, 79.3, 126.1, 126.3, 128.1, 128.2, 129.0, 137.7, 170.5. IR 1742, 1708, 1429 cm^{-1}.

Anal calcd for $C_{18}H_{27}NO_5$: C, 64.07%; H, 8.07%; N, 4.15%. Found: C, 64.29%; H, 8.24%; N, 4.11%.





(*R*)-2-Benzyloxycarbonylamino-3-phenylpropyl acetate (4f).

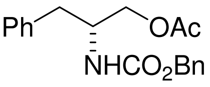


4f

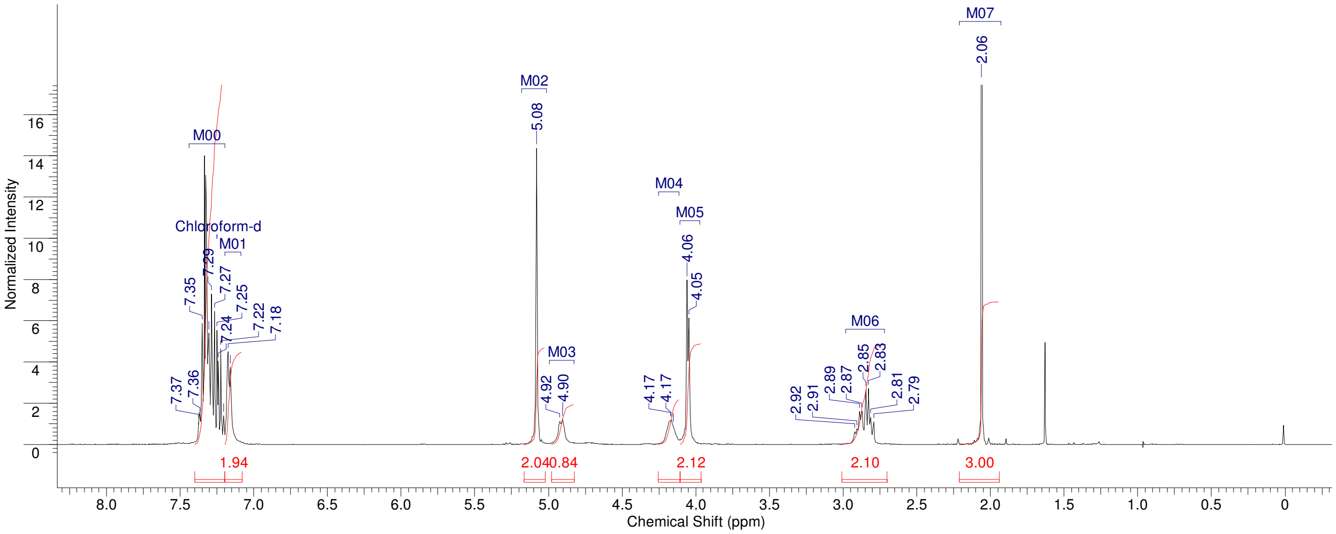
A flask was charged with (*R*)-benzyl 1-hydroxy-3-phenylpropan-2-ylcarbamate (2.85 g, 10 mmol) and DMAP (0.12 g, 1 mmol, 0.1 equiv). 30 mL of CH_2Cl_2 and Et_3N (2.1 mL, 15 mmol, 1.5 equiv) were added followed by Ac_2O (1.1 mL, 12 mmol, 1.2 equiv). After 30 min., HPLC analysis indicated that the reaction was complete. 1 mL of MeOH was added, and after stirring 30 min., the reaction was extracted with 50 mL of 0.5 N HCl, then with 50 mL of 10% aqueous $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated. The product was crystallized from 25 mL of heptane to afford 3.1 g (95% yield) of (*R*)-2-benzyloxycarbonylamino-3-phenylpropyl acetate (**4f**) as a white solid.

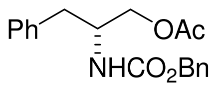
Mp = 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.06 (s, 3 H) 2.72 - 2.98 (m, 2 H) 4.05 (d, *J*=4.39 Hz, 2 H) 4.11 - 4.25 (m, 1 H) 4.91 (d, *J*=7.55 Hz, 1 H) 5.08 (s, 2 H) 7.17 (d, *J*=7.00 Hz, 2 H) 7.20 - 7.44 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.3, 155.2, 136.5, 128.9, 128.3, 128.2, 127.9, 127.8, 126.6, 66.8, 64.9, 51.4, 38.0, 21.1.

LC-MS (ESI+) M+H = 328. Anal calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 68.72; H, 6.55; N, 4.22.

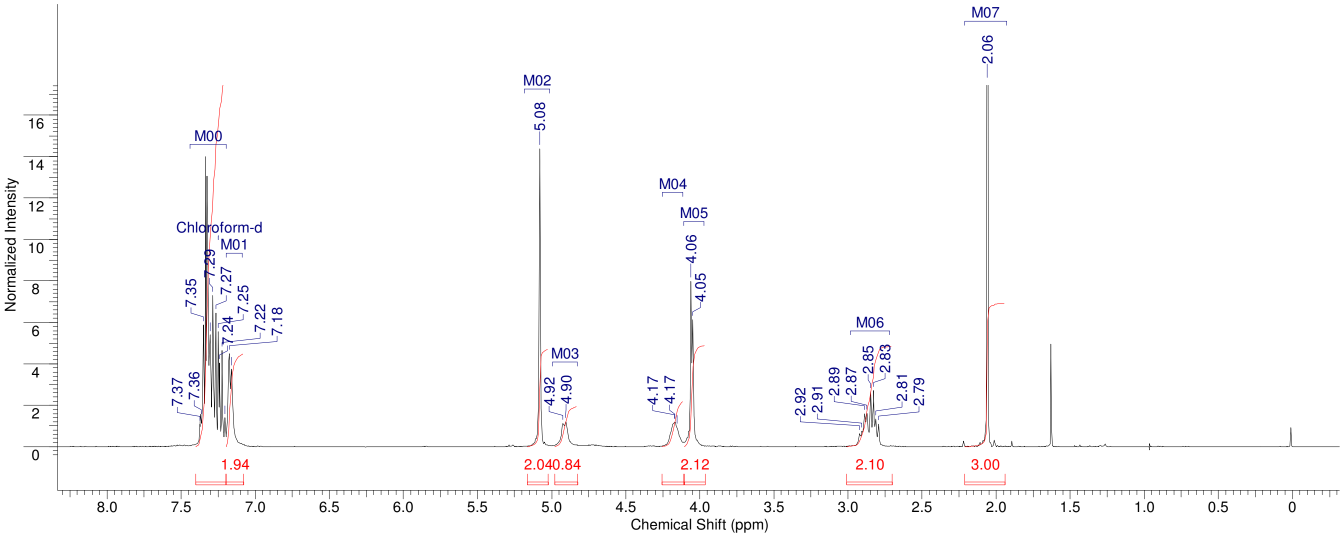


4f





4f

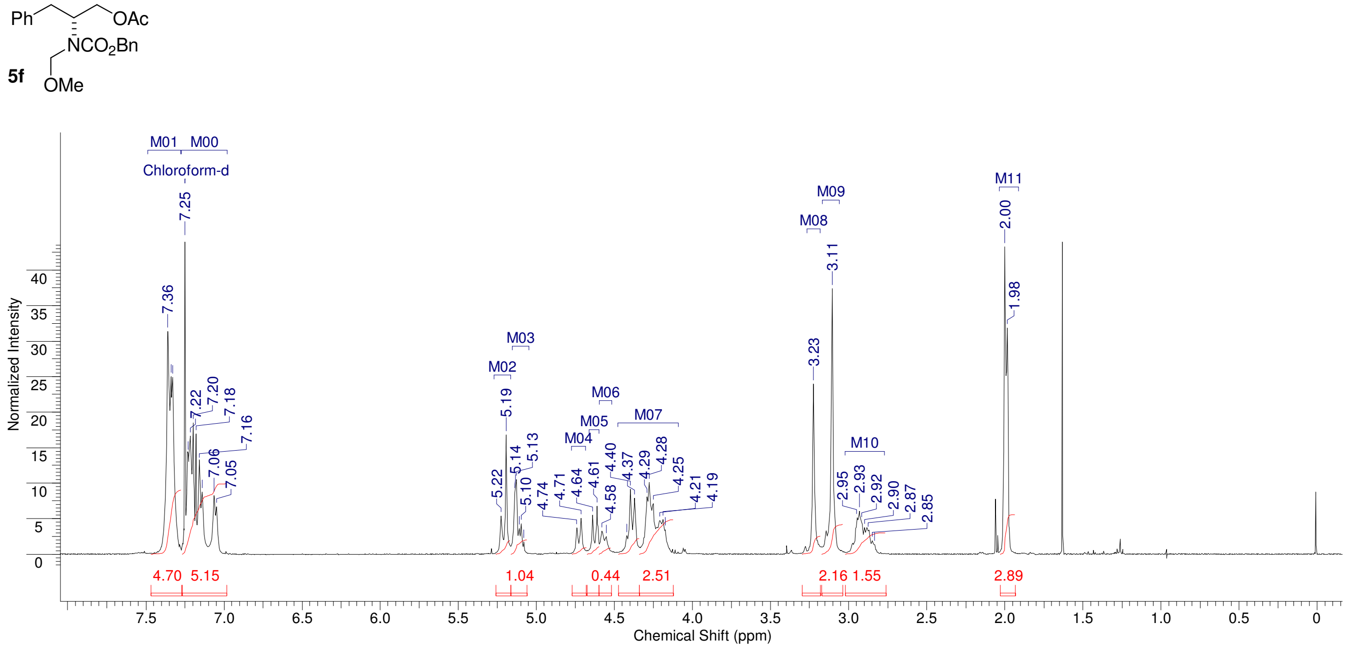


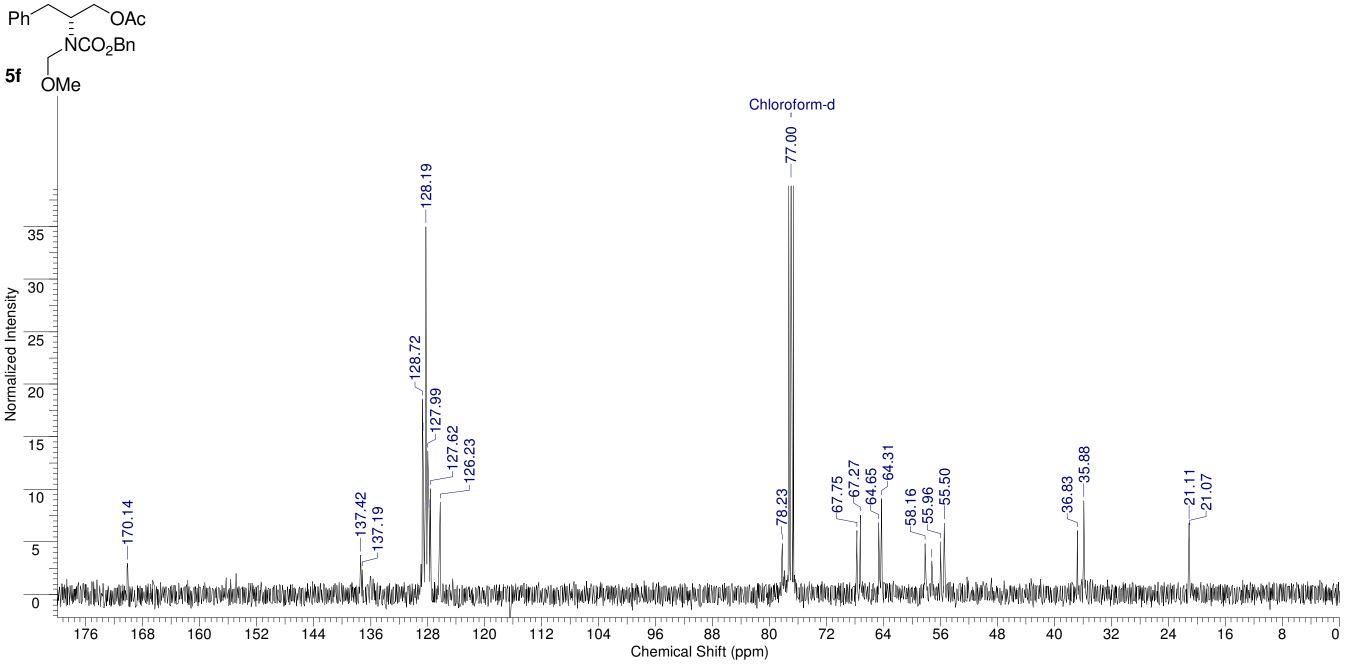
(*R*)-2-((Benzyloxycarbonyl)(methoxymethyl)amino)-3-phenylpropyl acetate (5f).

A flask was charged with (*R*)-2-benzyloxycarbonylamino-3-phenylpropyl acetate (**4f**, 1.14 g, 3.5 mmol), paraformaldehyde (0.17 g, 5.7 mmol, 1.6 equiv) and 14 mL of CH_2Cl_2. TMS-Cl (1.3 mL, 10.5 mmol, 3 equiv) was added, and the reaction was stirred at room temperature overnight. The reaction was quenched into 20 mL of 9:1 MeOH:Et_3N and stirred for 1 hour. The reaction mixture was washed with 100 mL of water (backwashed with 2x30 mL CH_2Cl_2) then the combined organic layers were washed with 50 mL of 10% aqueous $NaHCO_3$, then 50 mL of 20% aqueous NaCl. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered and concentrated. Chromatographic purification (ISCO Combiflash Companion, SiO_2, dichloromethane/EtOAc) afforded 1.21 g (93% yield) of (*R*)-2-((benzyloxycarbonyl)(methoxymethyl)amino)-3-phenylpropyl acetate (**5f**) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.99 (d, *J*=6.31 Hz, 3 H) 2.77 - 3.02 (m, 2 H) 3.11 (s, 2 H) 3.23 (s, 1 H) 4.09 - 4.48 (m, 4 H) 4.57 (d, *J*=11.25 Hz, 1 H) 4.62 (d, *J*=10.98 Hz, 1 H) 4.73 (d, *J*=11.80 Hz, 1 H) 5.05 - 5.15 (m, 1 H) 5.21 (d, *J*=11.90 Hz, 1 H) 6.98 - 7.27 (m, 5 H) 7.27 - 7.49 (m, 5 H). ^{13}C (100 MHz, $CDCl_3$, mixture of rotamers) δ ppm 21.07, 21.11, 35.9, 36.8, 55.5, 56.0, 57.2, 58.2, 64.3, 64.7, 67.3, 67.8, 78.2, 126.2, 126.3, 127.6, 127.8, 128.0, 128.2, 128.3, 128.6, 128.7, 137.2, 137.4, 170.1. IR 1742, 1707, 1455 cm^{-1}.

Anal calcd for $C_{21}H_{25}NO_5$: C, 67.91%; H, 6.78%; N, 3.77%. Found: C, 67.97%; H, 6.97%; N, 3.76%.





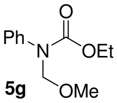
N-(Methoxymethyl)aniline, ethyl carbamate (5g).

A flask was charged with *N*-phenyl ethylcarbamate (**4g**, 1.65 g, 10 mmol), paraformaldehyde (0.48 g, 16 mmol, 1.6 equiv) and 40 mL of CH_2Cl_2. TMS-Cl (3.8 mL, 30 mmol, 3 equiv) was added, and the reaction was stirred at room temperature for 16 hours. The reaction was quenched with 10 mL of

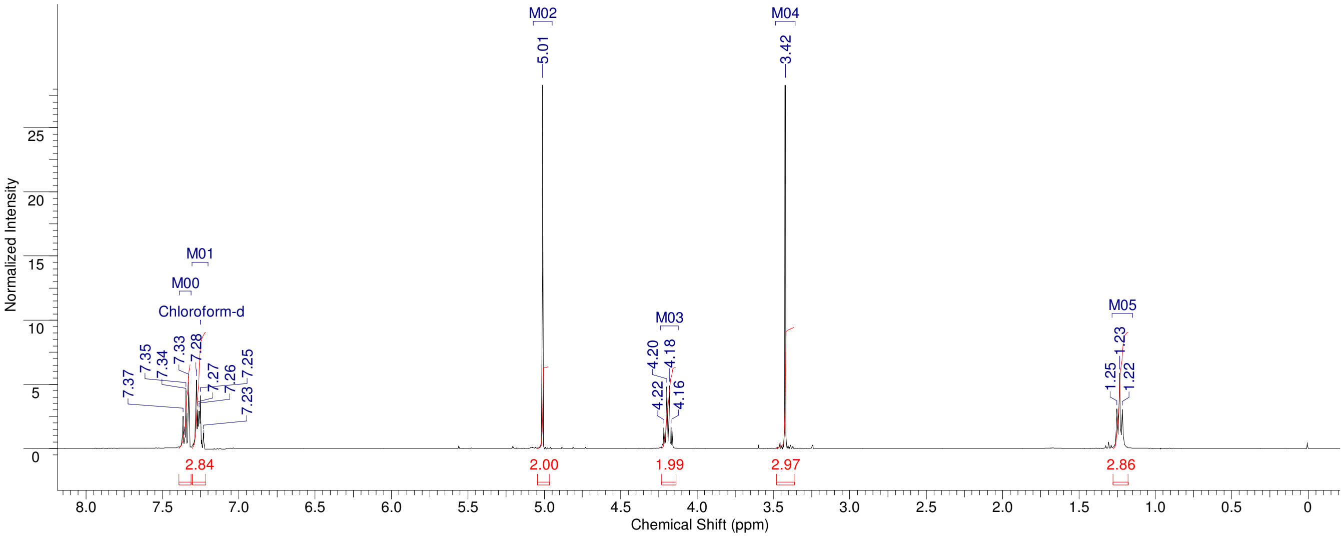
MeOH and stirred for 45 min, then quenched into 50 mL of 10% aqueous $NaHCO_3$. After separation, the aqueous layer was extracted with 20 mL CH_2Cl_2. The combined organic phases were washed with 50 mL of 20% aqueous NaCl, dried over $MgSO_4$, filtered and concentrated to afford 2.01 g (96% yield) of *N*-(methoxymethyl)aniline, ethyl carbamate (**5g**) as an oil.

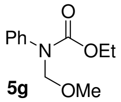
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=7.07 Hz, 3 H) 3.42 (s, 3 H) 4.19 (q, *J*=7.00 Hz, 2 H) 5.01 (s, 2 H) 7.20 - 7.31 (m, 3 H) 7.31 - 7.39 (m, 2 H). ^{13}C (100 MHz, $CDCl_3$) δ ppm 14.8, 56.1, 62.1, 81.2, 126.5, 126.6, 128.5, 141.1, 155.4. IR 1712, 1599, 1497 cm^{-1}.

LCMS (ESI+) 178 (M - OMe). Anal calcd for $C_{11}H_{15}NO_3$: C, 63.14%; H, 7.23%; N, 6.69%. Found: C, 62.54%; H, 6.95%; N, 6.70%.

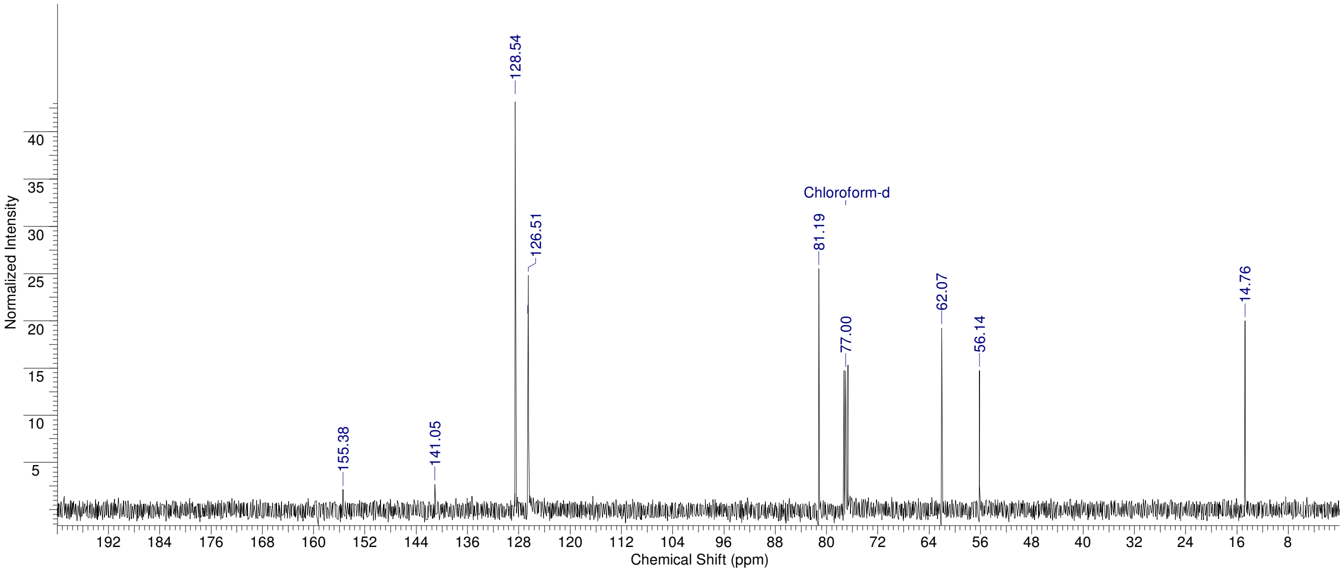


5g





5g



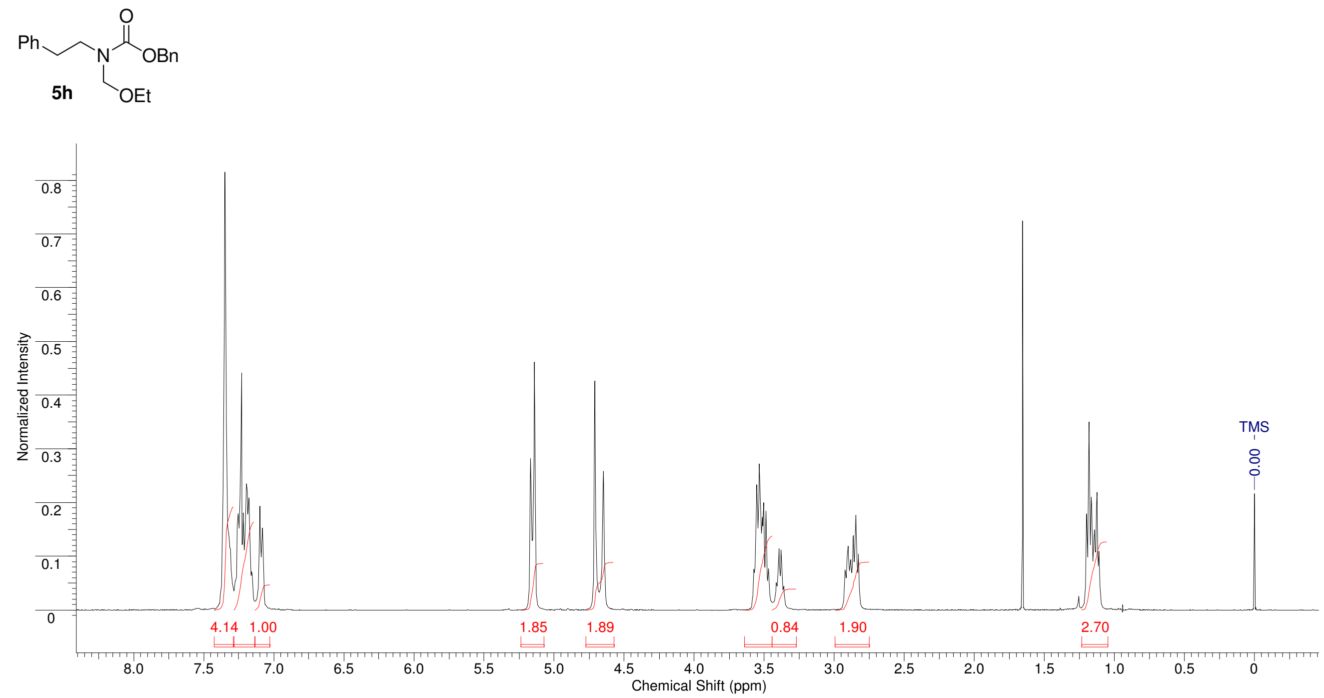
Benzyl ethoxymethyl(phenethyl)carbamate (5h)

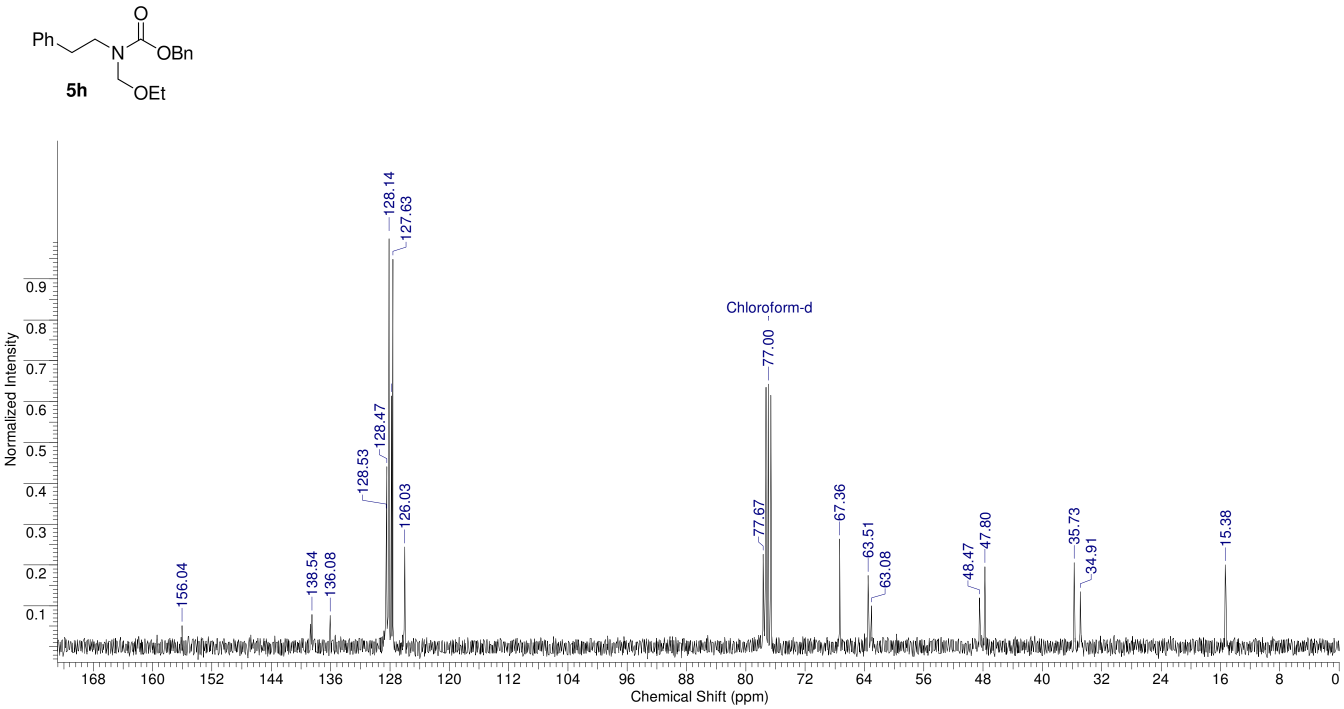
A flask was charged with *N*-benzyloxycarbonyl phenethylamine (**4a**, 1 g, 3.9 mmol), paraformaldehyde (0.18 g, 6.0 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. TMSCl (1.28 g, 11.7 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 1.5 hours. To the flask was charged 3 ml of EtOH, and the reaction was stirred for 1 hr.

The reaction mixture was quenched into 15 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 10 ml of CH_2Cl_2 and the combined organic phases were washed with 10 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 1.09 g (93 % yield) of benzyl ethoxymethyl(phenethyl)carbamate **5h**.

^{1}H NMR ($CDCl_3$) δ ppm 1.17 (tt, 3H), 2.87 (tt, 2H), 3.39 (q, 1H), 3.52 (m, 3H), 4.68 (d, 2H), 5.16 (d, 2H), 7.09 (d, 1H), 7.22 (m, 4H), 7.35 (br, 5H). ^{13}C NMR ($CDCl_3$) δ ppm 15.4, 34.9, 35.7, 47.8, 48.5, 63.1, 63.5, 67.4, 126.0, 127.6, 127.8, 128.13, 128.19, 128.46, 128.52, 136.1, 138.5, 156.0. IR: 1706 cm^{-1}.

HRMS: 314.17549 (M+H). Anal calcd for $C_{19}H_{23}NO_3$: C, 72.82%; H, 7.40%; N, 4.47%. Found: C, 72.33%; H, 7.76%; N, 4.46%.





Benzyl benzyloxymethyl(phenethyl)carbamate (5i)

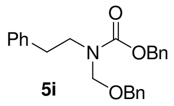
A flask was charged with *N*-benzyloxycarbonyl phenethylamine (**4a**, 2.55 g, 10 mmol), paraformaldehyde (0.48 g, 16 mmol, 1.6 equiv) and 40 ml of CH_2Cl_2. TMSCl (3.8 mL, 30 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 1.5 hours. The reaction was quenched into a flask containing benzyl alcohol (5.2 mL, 50 mmol, 5 equiv) and diisopropylethylamine

(5.2 mL, 30 mmol, 3 equiv) in 20 mL CH_2Cl_2 in an ice-water bath, such that the internal temperature was kept below 15 ^{o}C.

The reaction mixture was washed twice with 50 mL of water, then with 50 mL of 10% NaCl. The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield 3.41 g (91%) of the product as an oil.

^{1}H NMR ($CDCl_3$, mixture of rotamers) δ ppm {2.86 (t, *J*=7.5 Hz) 2.93 (t, *J*=7.4 Hz), 2H}, 3.47 - 3.66 (m, 2 H), {4.41, 4.52 (2H)}, {4.73, 4.81 (2H)}, {5.17, 5.19 (2H)}, 7.08 (d, *J*=7.1 Hz, 1H), 7.14-7.30 (m, 7H), 7.30-7.44 (m, 7H). ^{13}C NMR ($CDCl_3$) δ ppm 34.9, 35.8, 47.9, 48.6, 67.5, 69.7, 70.3, 77.7, 126.1, 127.4, 127.9, 128.1, 128.2, 128.3, 128.5, 136.0. IR: 3029, 1706, 1421, 1067, 698 cm^{-1}.

Anal calcd for $C_{24}H_{25}NO_3$: C, 76.77%; H, 6.71%; N, 3.73%. Found: C, 76.57%; H, 6.82%; N, 3.80%.



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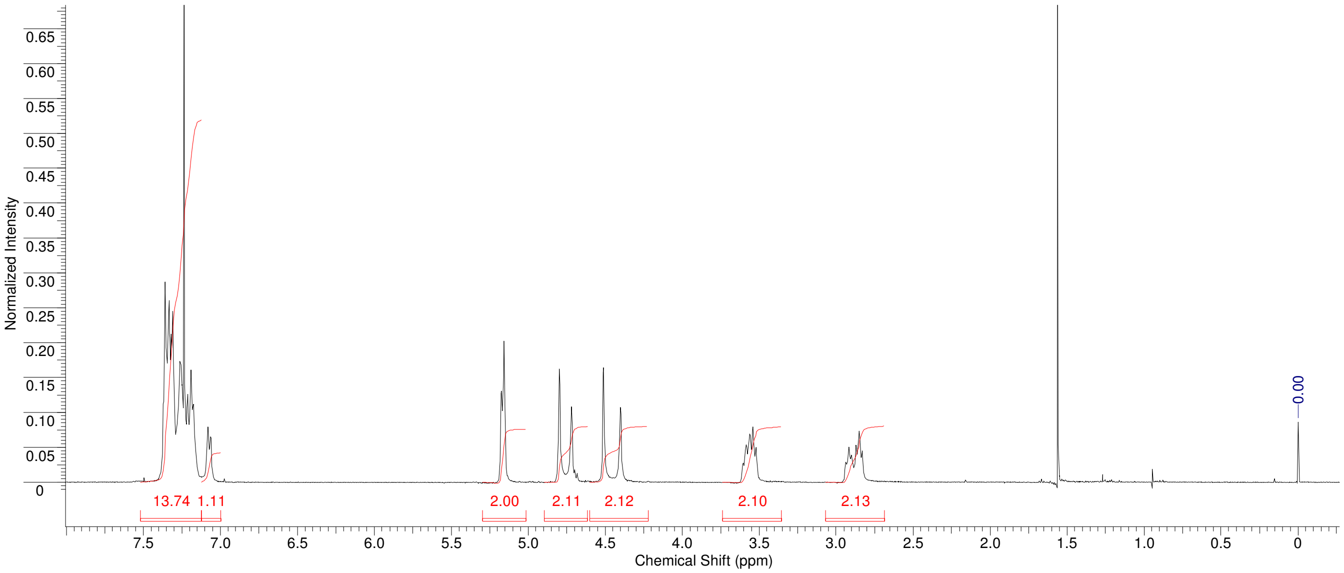

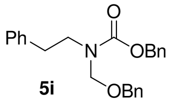

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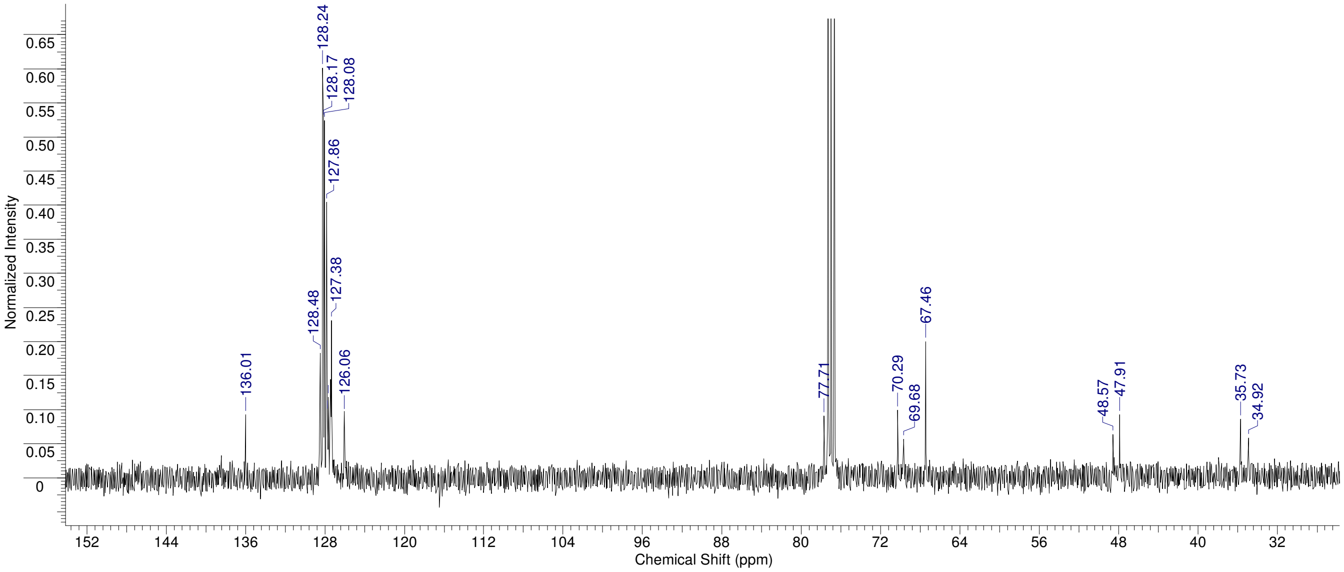
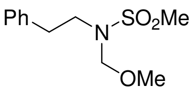


N-(methoxymethyl)-*N*-phenethylmethanesulfonamide (**7**)

A flask was charged with *N*-phenethylmethanesulfonamide (1.05 g, 5.3 mmol), paraformaldehyde (0.27 g, 8.6 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. TMSCl (1.7 g, 15.9 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 15 hours. The mixture was poured into a solution of 4 ml triethylamine and 10 ml methanol and stirred for 1 hr. The reaction mixture was quenched into 50 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 25 ml of CH_2Cl_2 and the combined organic phases were washed with 50 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 0.85 g (66 % yield) of *N*-(methoxymethyl)-*N*-phenethylmethanesulfonamide (**7**).

^{1}H NMR ($CDCl_3$) δ ppm 2.82 (s, 3H), 2.94 (dd, 2H), 3.29 (s, 3H), 3.52 (dd, 2H), 4.23 (s, 2H), 7.19-7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ ppm 36.0, 40.5, 48.7, 55.7, 79.7, 126.3, 128.2, 128.5, 137.9. IR: 1336 cm^{-1}.

Anal calcd for $C_{11}H_{17}NO_3S$: C, 54.30%; H, 7.04%; N, 5.76%. Found: C, 54.11%; H, 7.38%; N, 5.66%.



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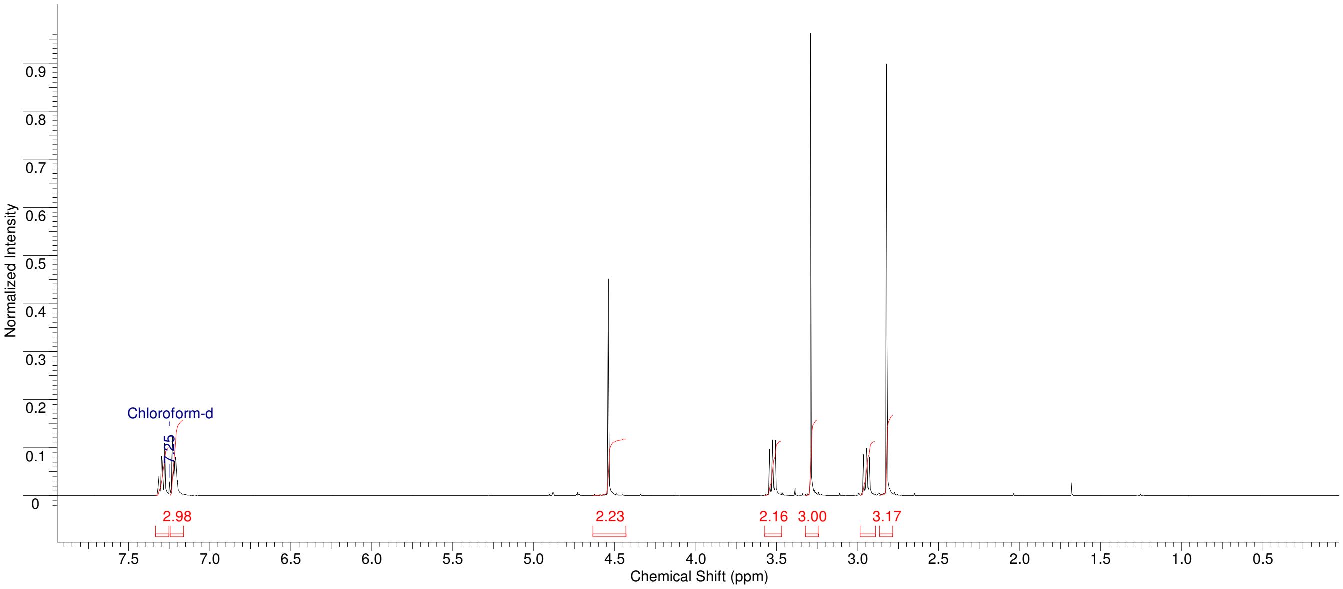

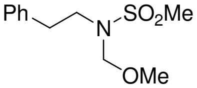

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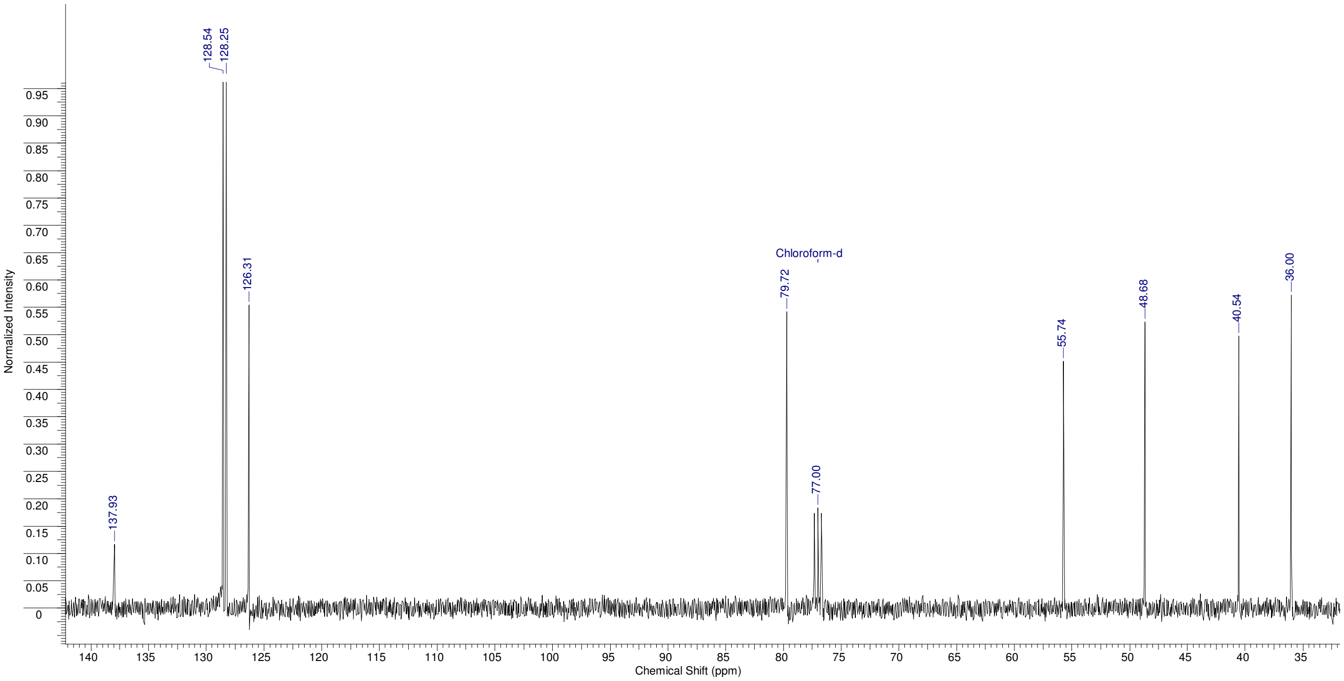
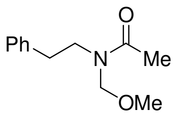


N-(methoxymethyl)-*N*-phenethylacetamide (8)

A flask was charged with *N*-phenethylacetamide (0.93 g, 5.7 mmol), paraformaldehyde (0.27 g, 8.6 mmol, 1.5 equiv) and 10 ml of CH_2Cl_2. TMSCl (1.7 g, 15.9 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 15 hours. The mixture was poured into a solution of 4 ml triethylamine and 10 ml methanol and stirred for 1 hr. HPLC of the reaction mixture indicated 75% conversion (PA% at 210 nm). The reaction mixture was quenched into 50 ml of saturated aqueous $NaHCO_3$ solution, mixed and separated. The aqueous phase was extracted with 25 ml of CH_2Cl_2 and the combined organic phases were washed with 50 ml of brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography afforded 0.54 g (46% yield) of *N*-(methoxymethyl)-*N*-phenethylacetamide (**8**).

^{1}H NMR ($CDCl_3$) δ ppm 2.09 (d, 3H), 2.90 (m, 2H), 3.29 (d, 3H), 3.59 (m, 2H), 4.60 (d, 2H), 7.19-7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ ppm 21.8, 34.8, 48.7, 55.3, 75.9, 81.3, 126.0, 128.2, 128.5, 170.75. IR: 1661 cm^{-1}.

Anal calcd for $C_{12}H_{17}NO_2$: C, 69.54%; H, 8.27%; N, 6.76%. Found: C, 68.34%; H, 8.20%; N, 6.63%.



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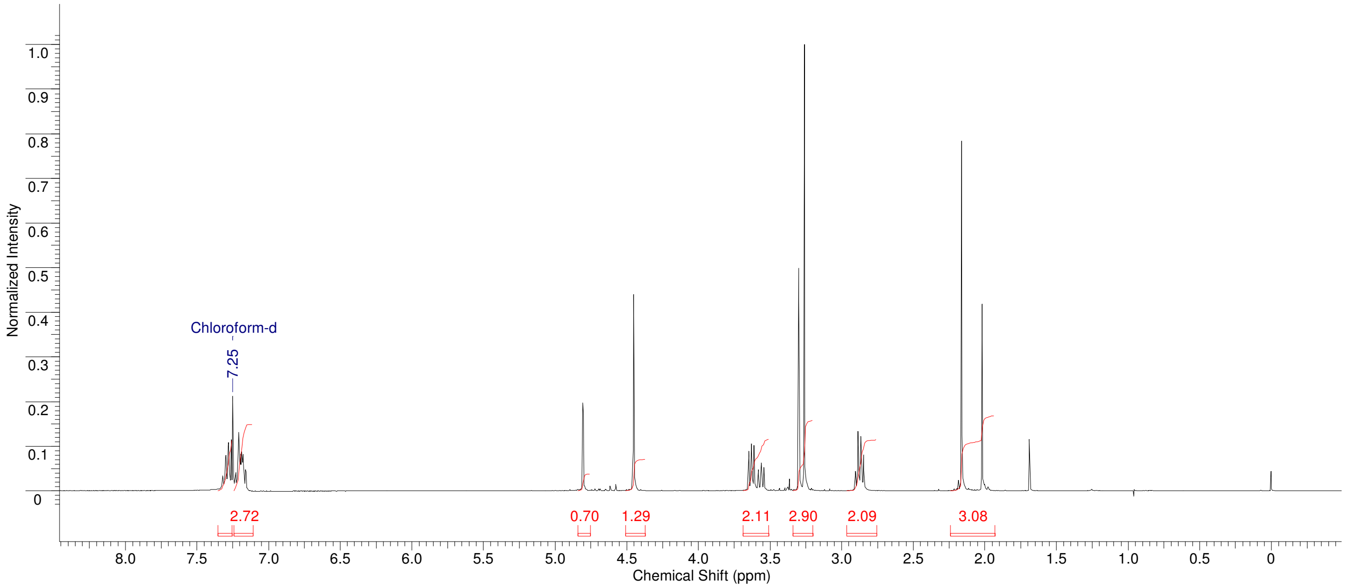

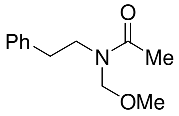

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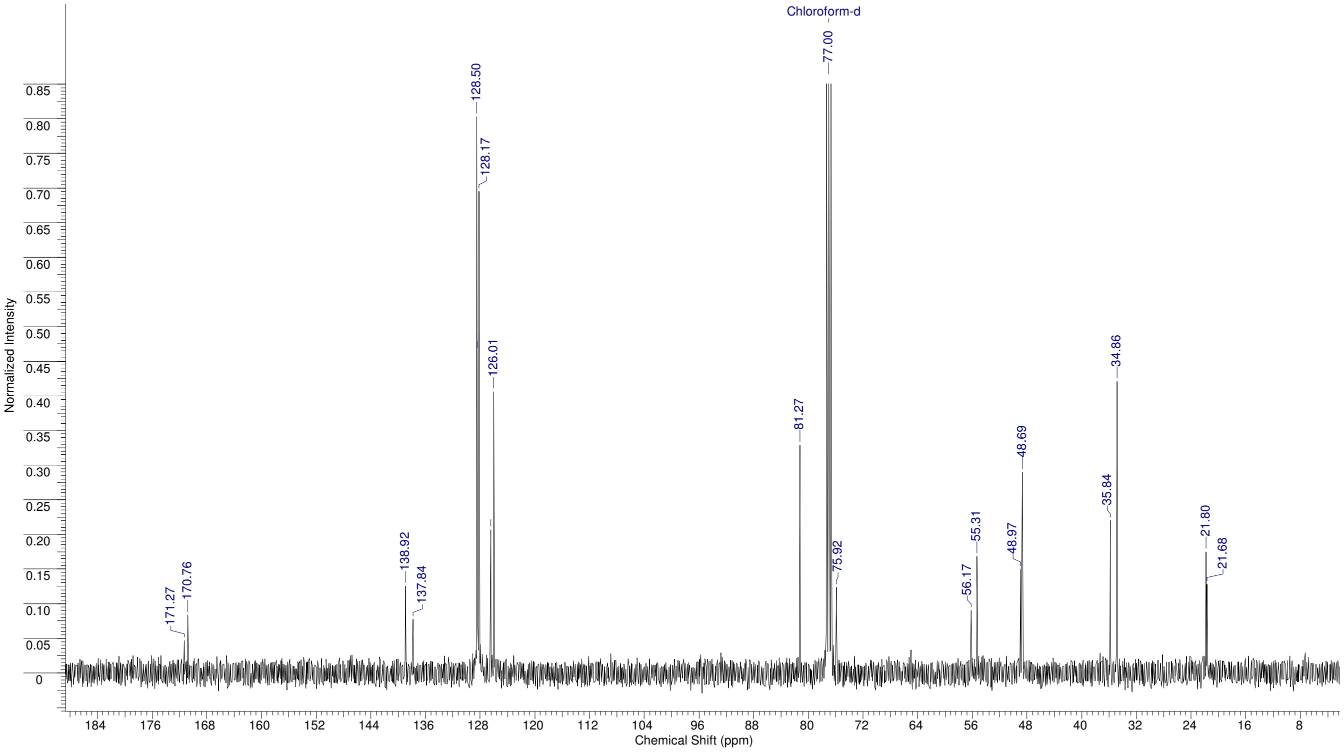
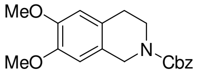


Benzyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (10).[5]

A flask was charged with benzyl 3,4-dimethoxyphenethylcarbamate[6] (**9**, 1.0 g, 3.2 mmol), paraformaldehyde (0.15 g, 5 mmol, 1.6 equiv) and 12 mL of CH_2Cl_2. TMS-Cl (1.2 mL, 9.6 mmol, 3 equiv) was added, and the reaction was stirred at room temperature for 1 hour. The reaction was quenched with 20 mL of 10% aqueous $NaHCO_3$, and extracted with 2x25 mL CH_2Cl_2. The combined organic phases were washed with 50 mL of 10% aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography afforded 1.01 g (96% yield) of benzyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (**10**) as an oil.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.77 (s, 2 H) 3.71 (s, 2 H) 3.84 (s, 3 H) 3.85 (s, 3 H) 4.57 (s, 2 H) 5.17 (s, 2 H) 6.56 (s, 1 H) 6.61 (s, 1 H) 7.27 - 7.44 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.0, 147.3, 147.2, 136.4, 128.2, 127.7, 111.3, 108.9, 108.8, 67.2, 56.04, 56.02 (CH3), 45.6, 41.9, 41.6, 28.7, 28.5.

LC-MS (ESI+) M+H = 328. Anal calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.33; H, 6.57; N, 4.23.



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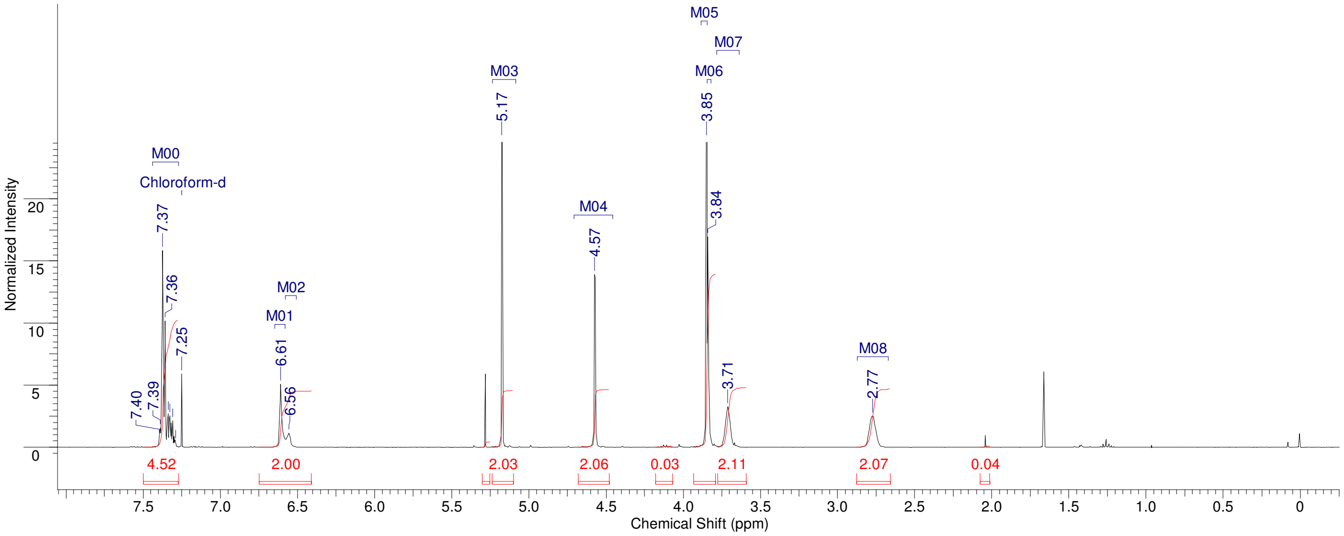

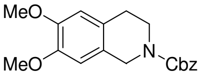

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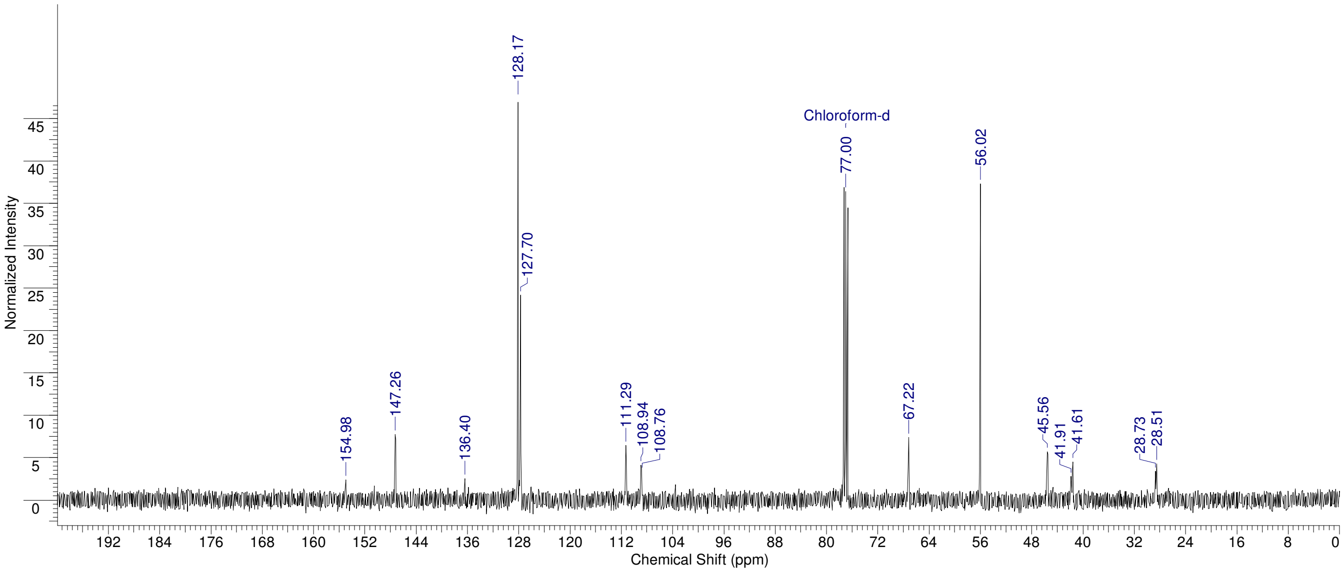


Deprotection of benzyl *N*-methoxymethyl(benzyl)carbamate (5d)

To a solution of benzyl *N*-methoxymethyl(phenethyl)carbamate (**5d**, 500 mg, 1.75 mmol) in 18 mL MeCN was added sodium toluenesulfinate (623 mg, 3.5 mmol, 2 equiv), and 2N HCl (2.2 mL, 4.4

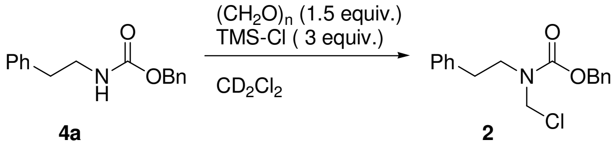
mmol, 2.5 equiv) and the biphasic reaction mixture was stirred at ambient temperature for 27 hours. The reaction mixture was diluted with EtOAc, and then washed with 1 molal $NaHCO_3$ (backwashed). The combined EtOAc layers were washed with 20% NaCl solution, dried over $MgSO_4$, and concentrated. Chromatography (60 mL SiO_2, 4% EtOAc/CH_2Cl_2), afforded 390 mg (92%) of *N*-benzyloxycarbonyl benzylamine (**4d**) as a crystalline solid.

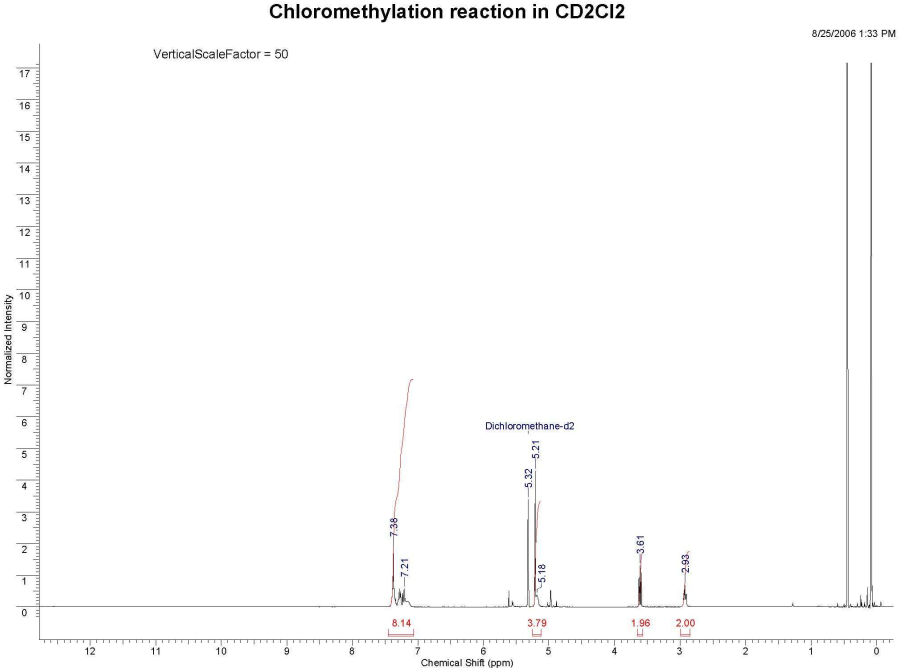
Deprotection of (*R*)-ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-3-phenylpropanoate (5e).

To a solution of (*R*)-ethyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-3-phenylpropanoate (**5e**, 372 mg, 1.1 mmol) in 11 mL MeCN was added sodium toluenesulfinate (392 mg, 2.2 mmol, 2 equiv), and 2N HCl (1.3 mL, 2.6 mmol, 2.4 equiv) and the biphasic reaction mixture was stirred at ambient temperature for 27 hours. The reaction mixture was quenched with 1 molal $NaHCO_3$ and extracted twice with EtOAc. The combined EtOAc layers were washed with 20% NaCl solution, dried over $MgSO_4$, and concentrated. Chromatography (60 mL SiO_2, 5% EtOAc/CH_2Cl_2), afforded 247 mg (76%) of *N*-(*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (**4e**) as an oil.

In situ NMR characterization of the *N*-chloromethyl intermediate 2.

A reaction run in CD_2Cl_2 was diluted with additional CD_2Cl_2 after 2.5 hours, and analyzed by NMR.





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