Kinetic Resolution of Amines via Dual-Catalysis: Remarkable Dependence of Selectivity on the Achiral Cocatalyst

Nisha Mittal, Diana X. Sun, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854.

Supporting Information

General Information: Reagents and solvents were purchased from commercial sources and were used as received. Toluene was freshly distilled from sodium under nitrogen prior to use. Reactions were run under a nitrogen atmosphere. Purification of reaction products was carried out by flash chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light and anisaldehyde stain, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, m = multiplet, comp = complex, integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Nucleophilic catalysts **6b–i** ,[1] **6j**,[2] **6k**,[3] **7**,[4] **8**,[5] **9**,[6] **10a–d**,[7] **14**,[8] .and benzylic amines **1c**, **1d**, **1f**, were prepared according to literature procedures.[9] Catalysts **6a**, **11**, **12**, **13**, **15**, *ent*-**15** and benzylic amines **1a**, **1b**, **1e**, **1g**, **1h** and **1i** were purchased from commercial sources and recrystallized or distilled prior to use. Products **2a**, **2b**, and **2e–i** were reported previously and their published characterization data matched our own in all respects.[10]

Conversions and s-factors were calculated in accord with standard procedures.[11]

General Procedure for Kinetic Resolutions:

A flame dried round bottom flask was charged with benzoic anhydride (28 mg, 0.125 mmol, 0.5 equiv.) and 4Å MS (100 mg), followed by addition of toluene (18 mL). Nucleophilic catalyst (0.0125 mmol, 0.05 equiv.) in 1 mL of toluene was added. The resulting solution was stirred at room temperature for 5 min and then cooled to –78 ºC over 15 min. A solution of HB catalyst

(7.82 mg, 0.0125 mmol, 0.05 equiv.) in 4 mL of toluene was added. After 15 min, a solution of amine (0.25 mmol) in 2 mL of toluene was added and the reaction mixture was stirred at –78 ºC for 2 hours. The reaction was quenched by adding 3 M MeMgCl in THF (0.5 mmol, 0.167 mL) at –78 ºC. The reaction mixture was then stirred for another 10 minutes. Excess Grignard reagent was quenched with 1M aqueous HCl (5 mL) solution. The reaction mixture was allowed to warm to room temperature and was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 5 mL of 1 M HCl, then brine. The combined organic extracts were then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography.

The unreacted amine was isolated by basifying the aqueous layer with 15% NaOH (pH 10) and subsequent extraction with diethyl ether (5 x 50 mL). The combined organic layers were washed with brine, and then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure. The crude material was benzoylated following a standard procedure.

The second runs were conducted using the general procedure without any modifications.

The conversion, $\boldsymbol{C_{HPLC}}$, for each catalytic reaction was calculated using the following equation:

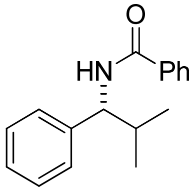
$\boldsymbol{C_{HPLC}} = \frac{\boldsymbol{ee_{SM}}}{\boldsymbol{ee_P + ee_{SM}}}$, where $\boldsymbol{ee_p}$ is the enantiomeric excess of the amide product and $\boldsymbol{ee_{SM}}$ is the enantiomeric excess of the recovered benzoylated amine.

The s-factor was calculated using the calculated conversion and enantiomeric excess from either the product, $\boldsymbol{ee_p}$, or recovered starting material, $\boldsymbol{ee_{SM}}$, following the equation:

$$\boldsymbol{s} = \frac{\boldsymbol{ln\big((1 - C_{HPLC})(1 - ee_P)\big)}}{\boldsymbol{ln\big((1 - C_{HPLC})(1 + ee_P)\big)}}$$

$$\boldsymbol{s} = \frac{\boldsymbol{ln\big((1 - C_{HPLC})(1 - ee_{SM})\big)}}{\boldsymbol{ln\big((1 - C_{HPLC})(1 + ee_{SM})\big)}}$$

Characterization Data of Products

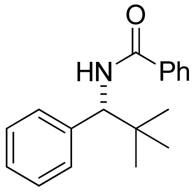


(*R*)-*N*-(2-Methyl-1-phenylpropyl)benzamide (2c): Following the general procedure, compound **8a** was obtained as a white solid in 49% yield (31 mg). mp = 105–107 ºC; R_f 0.21 (Hexanes/EtOAc 8:2 v/v); $[\alpha]_D^{20}$ +18.2 (c 1.0, $CHCl_3$, 91.6% *ee*); IR (KBr) cm^{-1} 3279, 3065, 2955, 1632, 1579, 1491, 700. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.66 (comp, 2H), 7.48–7.38 (m, 1H), 7.37–7.32 (comp, 2H), 7.31–7.21 (comp, 4H), 7.20–7.15 (m, 1H), 6.38 (app d, *J* = 8.1 Hz, 1H), 4.90 (app t, *J* = 8.3 Hz, 1H), 2.17–2.03 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 141.5, 134.8, 131.4, 128.6, 128.5, 127.2, 127.0, 126.9, 59.4, 33.6, 19.8, 18.9.; *m/z* (ESI-MS) 254.2 $[M+H]^+$;HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R =7.3 min (major) and t_R = 9.0 min.

The recovered starting material was benzoylated and the *ee* was determined by HPLC (88.9% *ee*, *S*-enantiomer). Calculated conversion = 49; **s = 68**.

Second run: conversion = 49; **s = 66** (benzoylated product: 31 mg, 49% yield, 91.5% *ee*; benzoylated starting material: 88.2% *ee*, *S*-enantiomer).

The absolute configuration of **2c** ($[\alpha]_D^{20}$ +16 (c 0.6, $CHCl_3$, 91.6% *ee*) was assigned by comparison with the amine reported in literature[12] ($[\alpha]_D^{20}$ +6.4 (c 0.6, $CHCl_3$, 88.0% *ee).*



(*R*)-*N*-(2,2-Dimethyl-1-phenylpropyl)benzamide (2d): Following the general procedure, compound **8a** was obtained as a white solid in 34% yield (23 mg). mp = 124–126 ºC; R_f 0.31 (Hexanes/EtOAc 8:2 v/v); $[\alpha]_D^{20}$ –25 (c 1.0, $CHCl_3$, 86.8% *ee*); IR (KBr) cm^{-1} 3411, 3056, 2959, 1640, 1521, 1488, 702. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.73 (comp, 2H), 7.54–7.47 (m, 1H), 7.46–7.40 (comp, 2H), 7.37–7.21 (comp, 5H), 6.75 (app d, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 9.3 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 140.0, 135.0, 131.3, 128.6, 128.0, 127.8, 127.1, 126.8, 61.9, 35.1, 26.1; *m/z* (ESI-MS) 268.3 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 254 nm, t_R = 26.0 min (major) and t_R = 28.7 min.

The recovered starting material was benzoylated and the *ee* was determined by HPLC (43.2% *ee*, *S*-enantiomer). Calculated conversion = 33; **s = 22**.

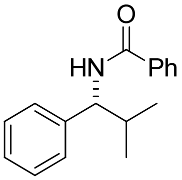
Second run: conversion = 31; **s = 21** (benzoylated product: 22 mg, 33% yield, 86.5% *ee*; benzoylated starting material: 38.5% *ee*, *S*-enantiomer).

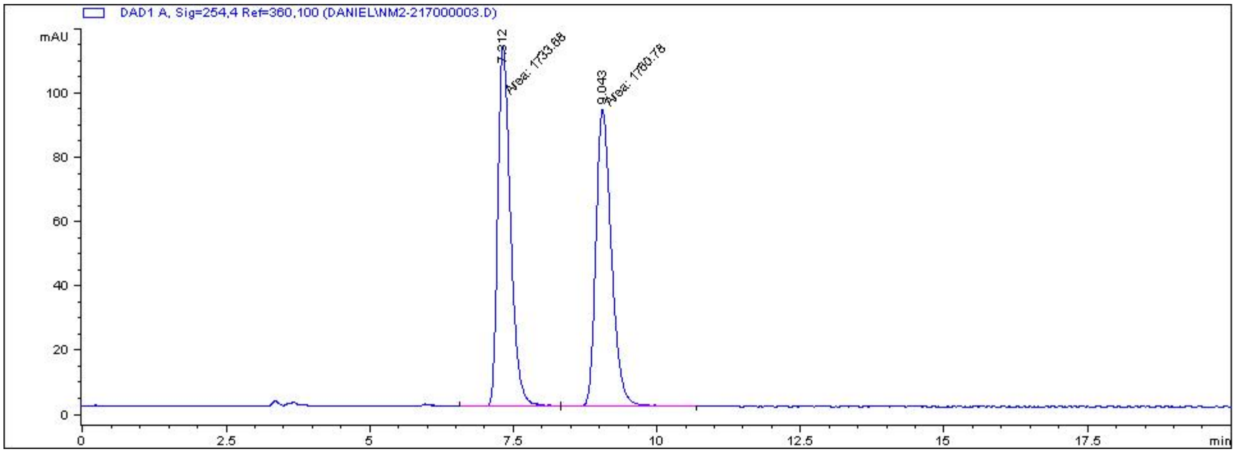
The absolute configuration of **2d** was assigned by analogy.

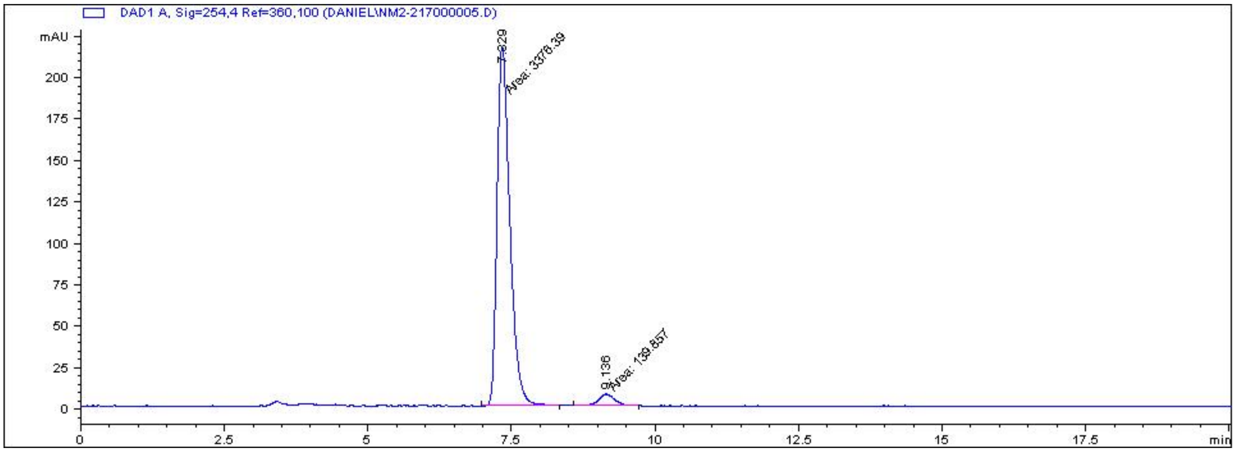
References:

(1) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.
(2) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515.
(3) Jaspers, D.; Doye, S. *Synlett* **2011**, *2011*, 1444.
(4) Narayan, S.; Seelhammer, T.; Gawley, R. E. *Tetrahedron Lett.* **2004**, *45*, 757.
(5) Conejo-García, A.; Pisani, L.; del Carmen Núñez, M.; Catto, M.; Nicolotti, O.; Leonetti, F.; Campos, J. M.; Gallo, M. A.; Espinosa, A.; Carotti, A. *J. Med. Chem.* **2011**, *54*, 2627.
(6) Wong, K.-T.; Ku, S.-Y.; Yen, F.-W. *Tetrahedron Lett.* **2007**, *48*, 5051.
(7) Rycke, N. D.; Berionni, G.; Couty, F.; Mayr, H.; Goumont, R.; David, O. R. P. *Org. Lett.* **2010**, *13*, 530.
(8) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.
(9) Ho, B.; Michael Crider, A.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265.
(10) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060.
(11) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
(12) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484.

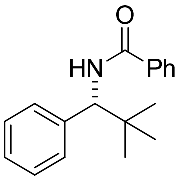
HPLC profile of 2c

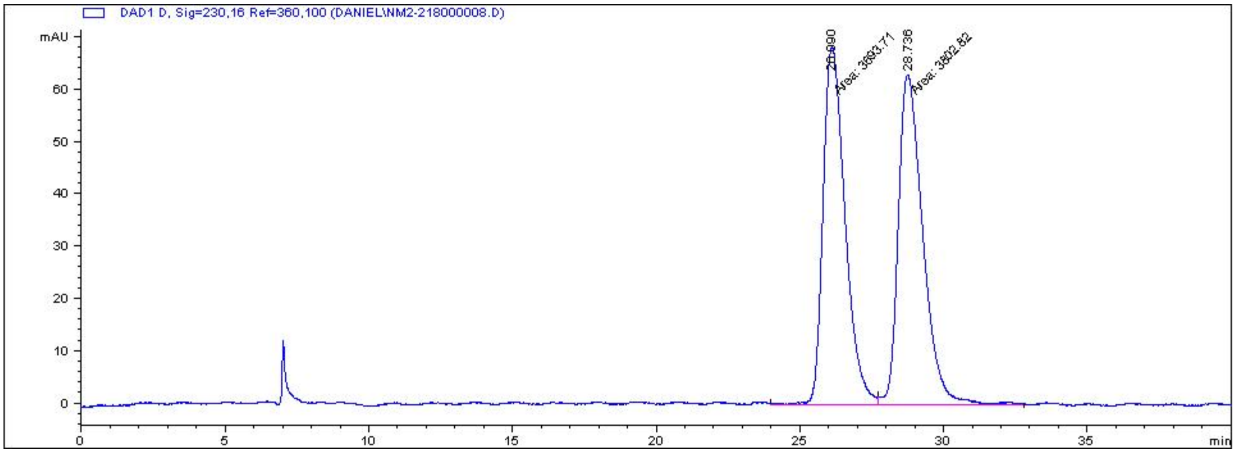


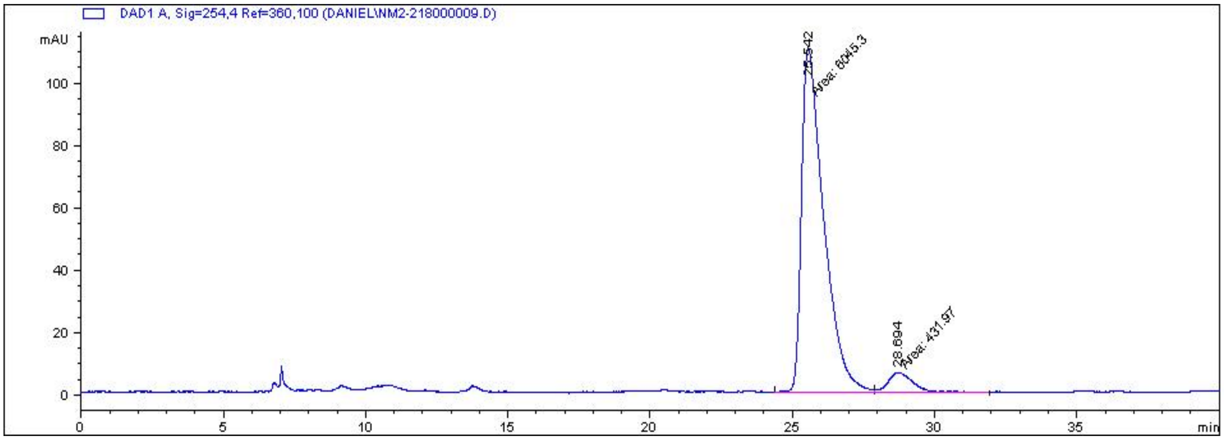




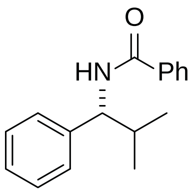
HPLC profile of 2d

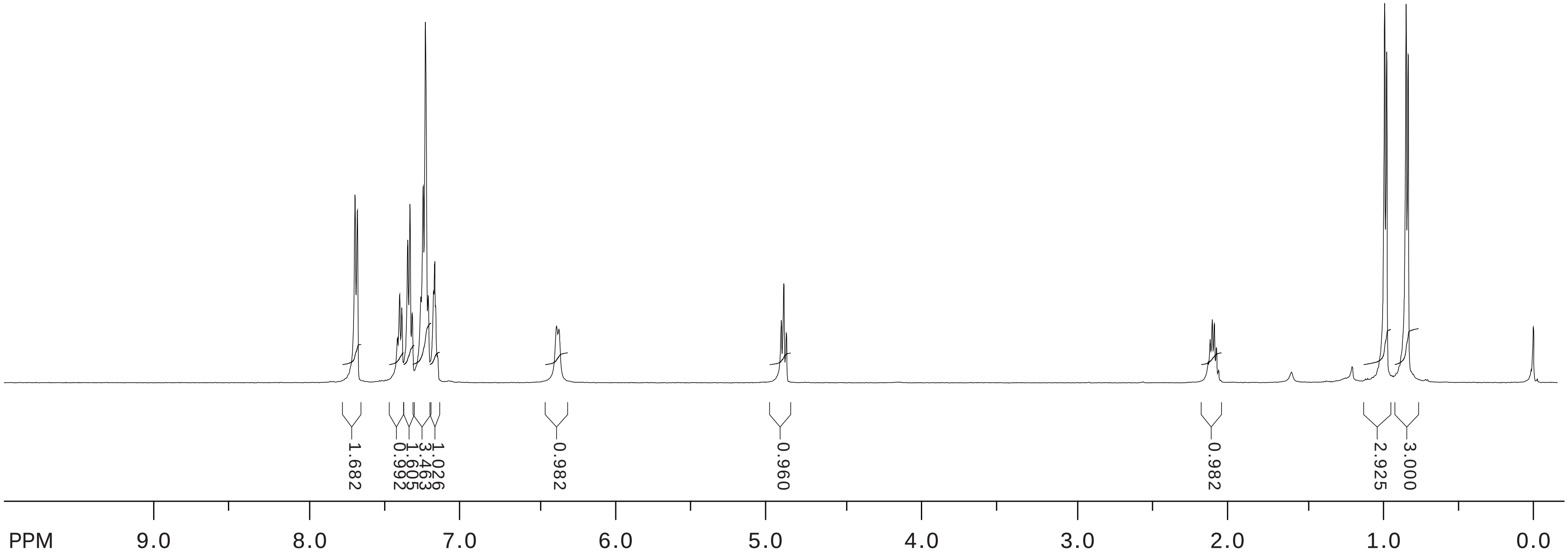




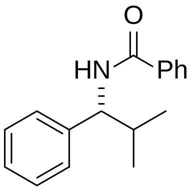


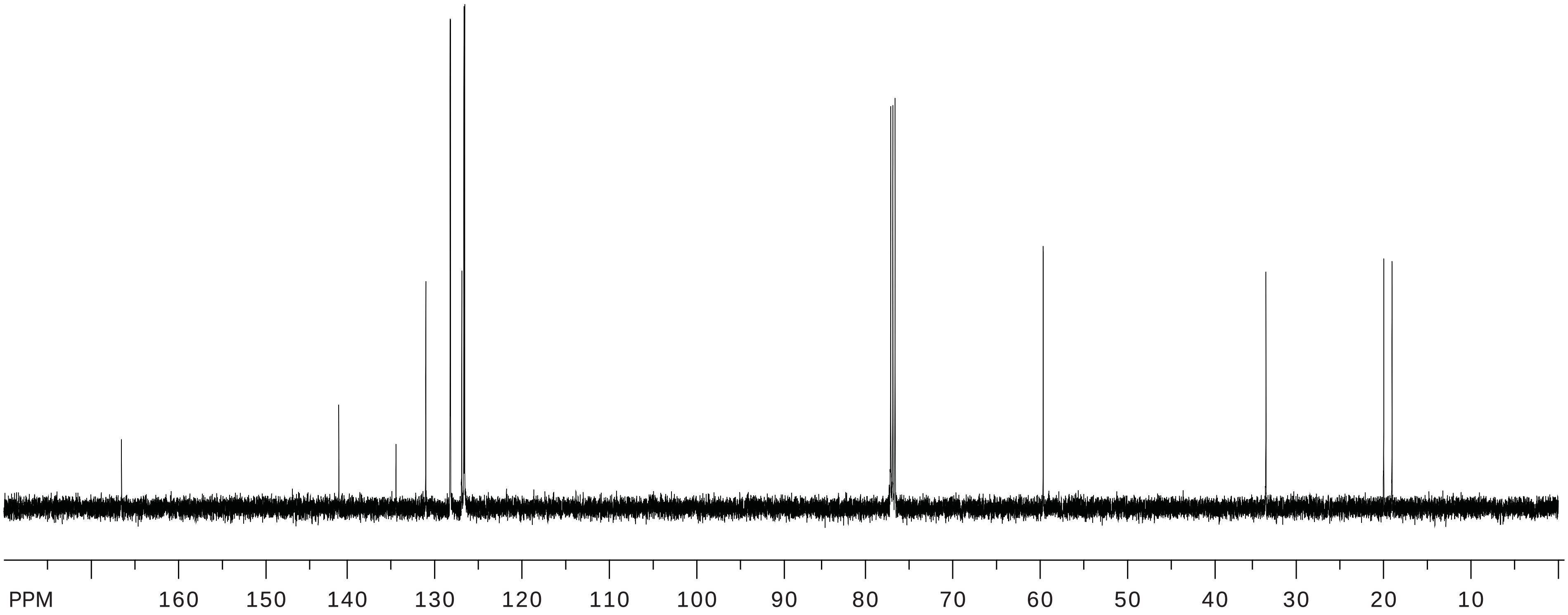
^{1}H NMR of **2c** in $CDCl_3$



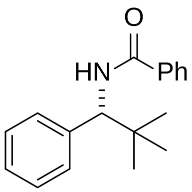


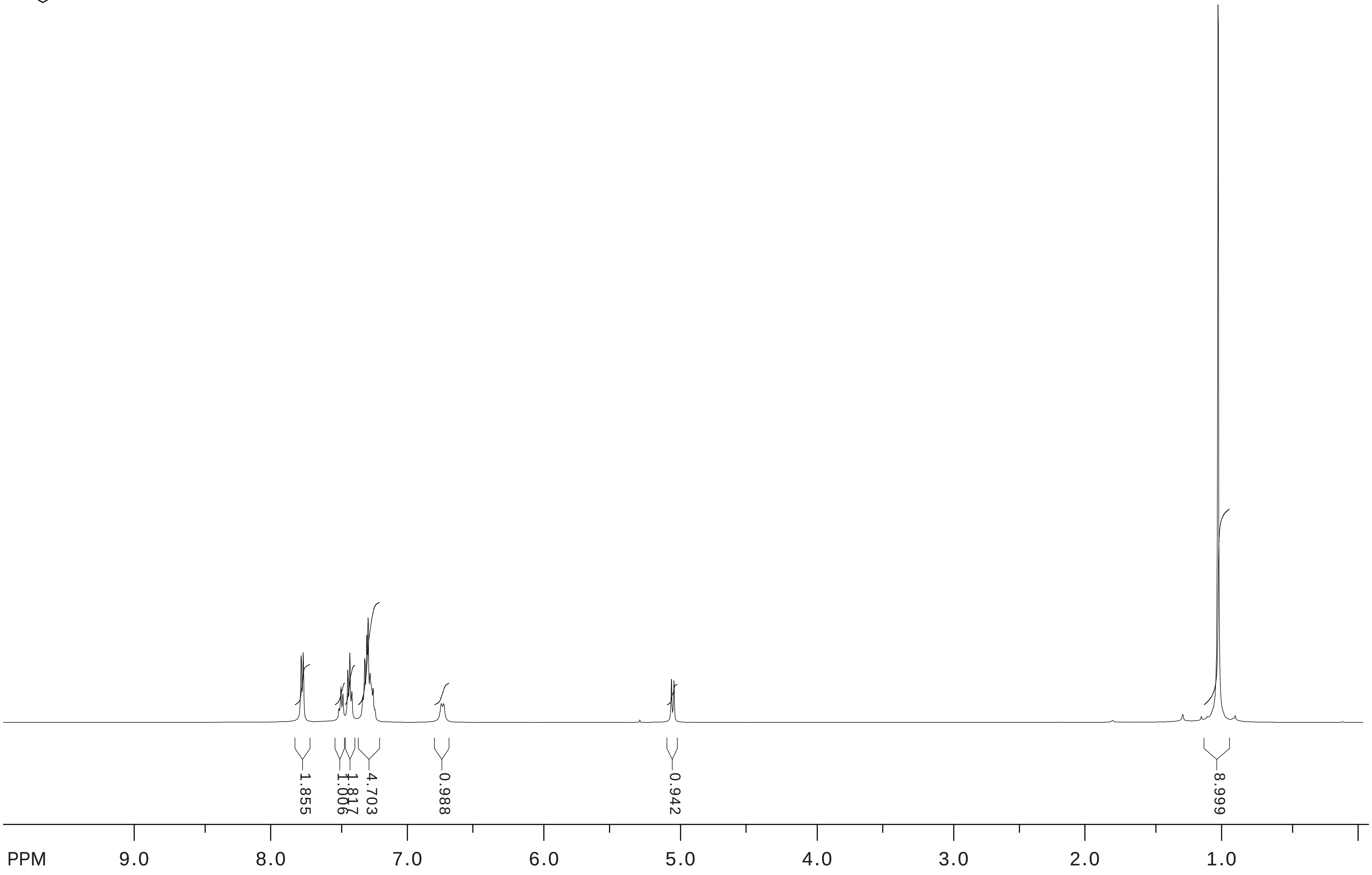
^{13}C NMR of **2c** in $CDCl_3$





^{1}H NMR of **2d** in $CDCl_3$





^{13}C NMR of **2d** in $CDCl_3$