Supplementary Material (ESI) for Chemical Communications

Supplementary Data

Title: Asymmetric S_NAr Reaction using the Molecular Chirality in Crystal

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Experimental

General. NMR spectra were recorded on $CDCl_3$ solutions on a BRUKER 300 operating 300 MHz, respectively, for ^{1}H- and ^{13}C-NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standards. IR spectra were recorded on a JASCO FT/IR-230 spectrometers.

General procedure for the preparation of naphthamides 1a and 1b. Both naphthamides **1a-1b** were provided from the corresponding 2-alkoxy-1-naphthoic acids and corresponding amines. The synthesis of **1a** was exemplified as follows. To a THF solution containing 1.11 g (5.5 mmol) of 2-methoxy-1-naphthoic acid and triethylamine 0.67g (6.6 mmol) was added 0.79 g (6.6 mmol) of thionyl chloride at 0°C. The reaction mixture was stirred for 0.5 h, and then a THF solution containing 1.09 g of pyrrolidine (13.0 mmol) was added dropwise. After the reaction mixture was stirred for 2 h, water and ethyl acetate were added, and the organic layer was extracted in the usual manner. After the organic solvent was evaporated in *vacuo*, the residual mixture was subjected to chromatography on silica gel and the naphthamide **1a** was separated. The structures of **1a** and **1b** were determined on the basis of spectral data, mass spectroscopy, and unequivocally X-ray single crystallographic analyses.

***N*-(2-Methoxy-1-naphthoyl)piperidine 1a** was obtained as colorless prismatic crystals from hexane-chloroform: m.p.103-105°C; IR (cm^{-1}, KBr) 1621; ^{1}H-NMR: ($CDCl_3$) δ 1.72-1.93 (m, 2H), 1.95-2.04 (m, 2H), 2.94-3.02 (m, 1H), 3.16-3.25 (m, 1H), 3.71-3.88 (m, 2H), 3.95 (s, 3H), 7.28 (d, *J*=8.1 Hz), 7.32-7.38 (m, 1H), 7.41-7.49 (m, 1H), 7.67 (d, *J*=8.7 Hz, 1H), 7.79 (d, *J*=7.0 Hz, 1H), 7.85 (d, *J*=9.1 Hz, 1H), ^{13}C-NMR

($CDCl_3$) δ 25.16, 26.21, 45.78, 47.64, 56.93, 113.52, 121.71, 124.17, 124.43, 127.85, 128.44, 129.28, 130.76, 130.99, 152.85, 167.46; EI-MS *m/z* (rel intensity): 255 (M^+, 20); HRMS (FABMAS) *m/z* calcd for $C_{16}H_{18}NO_2$ 256.1338, found 256.1344.

***N*-(2-Methoxy-1-naphthoyl)pyrrolidine 1b** was obtained as colorless prismatic crystals from hexane-chloroform: m.p. 111-112°C; IR (cm^{-1}, KBr) 1618; ^{1}H-NMR: ($CDCl_3$) δ 1.31-1.40 (m, 1H), 1.42-1.52 (m, 1H), 1.61-1.70 (m, 2H), 1.71-1.84 (m, 2H) 3.12-3.16 (m, 2H), 3.75-3.83 (m, 1H), 3.95 (s, 3H), 3.96-4.04 (m, 1H), 7.27 (d, *J*=9.1 Hz, 1H), 7.32-7.38 (m, 1H), 7.43-7.49 (m, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=9.1 Hz, 1H), ^{13}C-NMR ($CDCl_3$) δ 25.1, 26.3, 27.0, 42.8, 48.1, 56.8, 113.3, 120.5, 124.4, 124.4, 127.7, 128.4, 129.3, 130.6, 131.3, 152.9, 167.2; EI-MS *m/z* (rel intensity): 269 (M^+, 27); HRMS (FAB-MS) *m/z* calcd for $C_{17}H_{20}NO_2$ 270.1494, found 270.1474.

X-Ray single crystal analyses of 1a and 1b.[5]

Crystal data of **1a** (recrystallized from a mixture of $CHCl_3$ and hexane); $C_{16}H_{17}NO_2$, *Mr* = 255.31, Orthorhombic space group $P2_12_12_1$, a = 7.6281(15) Å, b = 11.856(2) Å, c = 14.408(3) Å, V = 1303.0(4) Å^3, Z = 4, ρ= 1.301 Mg/m^3, in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0339, *wR*2 = 0.0937, and GOF = 0.735 for 2991 reflections (CCDC 638448). The absolute structure of **1a** was not determined, and the ORTEP drawing shows the tentative absolute structure (Fig. S1).

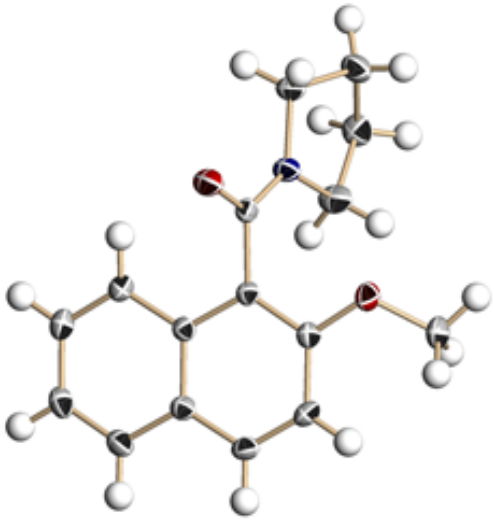

Fig. S1. Ortep view of **1a** showing the atoms and thermal ellipsoids at 50% probability.

Kinetic studies for racemization of 1a and 1b

Cryostat apparatus was used for measuring CD spectra at low temperature. The powdered crystals of **1** were dissolved into cooled THF in a cryostat apparatus and the CD spectra were monitored. The rate for enantiomerization was determined on the basis of the attenuation of the CD spectra. The activation parameters were obtained from the Eyring equation and Arrhenius plot. When a single crystal of **1b** selected randomly was dissolved in THF at 5°C using a cryostat apparatus, a strong Cotton effect was observed at below 350 nm (Figure S2). One showed a positive Cotton effect (Figure S2-(a)), and the other showed a negative Cotton effect at the same wavelengths (Figure S2-(b)). Furthermore, the Cotton effect gradually decreased with racemization as a result of the rotation about the naphthalene-C(=O) bond. The half-life was 11.8 minutes when the crystals were dissolved in THF at 15°C, and the value increased upon. The rate of racemization was measured at other temperature and $\Delta H^{\neq}$, $\Delta S^{\neq}$ was calculated on the basis of Arrenium parameters (Table S1).

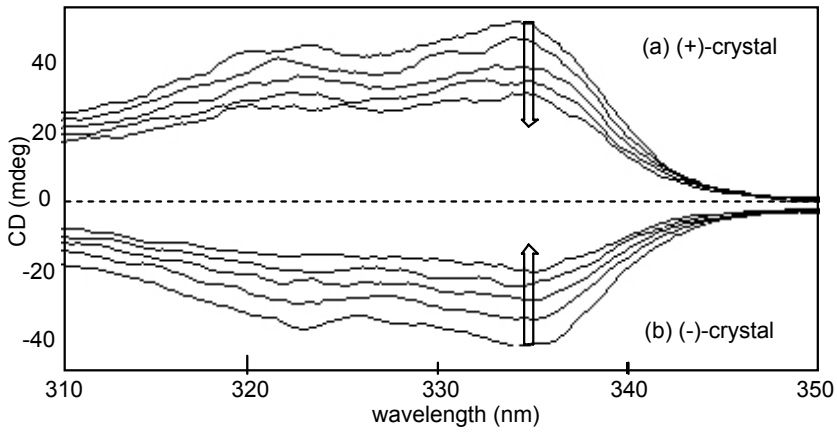

Fig. S2. CD spectra in THF solution provided by dissolving each enantiomorphic crystal of **1b** to THF at 5°C using cryostat apparatus. (a) CD spectra of a solution of (+)-crystal measured every 10 min. (b) CD spectra of a solution of (-)-crystal measured every 12 min.

Table S1. Kinetic parameters for racemization of amides **1a** and **1b** in THF.

amide	temp (°C)	$t_{1/2}$ (sec)	$\Delta G^{\neq}$ (kcal mol^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})	$k \times 10^{-4}$ (s^{-1})
1a	5	2445	21.14	14.12	-25.23	1.418
	10	1546	21.27	14.11	-25.29	2.241
	15	973	21.39	14.10	-25.30	3.563
1b	5	2199	21.08	17.53	-12.77	1.576
	10	1163	21.11	17.52	-12.69	2.979
	15	707	21.21	17.51	-12.84	4.902

Arrhenius parameter E value was 14.68 and 18.08 kcal mol^{-1} for **1a** and **1b**, respectively.

General procedure for S_NAr reaction of naphthamides 1 with *n*-butyllithium or *t*-butyllithium

The S_NAr reaction of **1a** with *t*-butyllithium was exemplified. To a cooled 5.0 mL of toluene solution containing *n*-pentane solution of 3.0 eq. of *t*-butyllithium were added powdered crystals of **1a** (0.5 mmol) at once, and the reaction mixture was stirred at the same temperature for 1h under argon atmosphere. Toluene and saturated aqueous ammonium chloride were added and the organic layer was separated. After organic layer was washed with burin and dried with magnesium sulfate, toluene was evaporated off in *vacuo*, and the residual mixture was subjected to chromatography on silica gel. *Ees* of **2a-b** and **3a-b** were determined by HPLC using CHRALCEL-IA column (eluant: hexane : EtOH = 10 : 1).

Kinetic studies for racemization of 2a, 2b, 3a, and 3b.

The rate for enantiomerization was determined on the basis of the attenuation of the $[\alpha]_D$ value. When a partially resolved **2a** by HPLC using CHRALCEL-IA column (eluant: hexane : EtOH = 10 : 1) was diluted in $CDCl_3$ at 40°C, the $[\alpha]_D$ value was gradually decreased with racemization as a result of the rotation along the naphthalene-C(=O) bond. The racemization of **2a** was measured in the range from 35°C to 45°C. Those of **2b** were measured from 30 to 40°C. Activation parameters for **3a** and **3b** were high; then the rate for racemization were measured in the range of 100-120°C and 90-110°C, for **3a** and **3b**, respectively. The activation parameters were obtained from the Eyring equation and Arrhenius plot. The values of $\Delta H^{\neq}$, $\Delta S^{\neq}$ was calculated on the basis of Arrhenius parameters (Table S2).

Table S2. Kinetic parameters for racemization of amides, 2 and 3, in *n*-nonane[a]

Amide	Temp. (°C)	$t_{1/2}$ (sec.)	$\Delta G^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal/mol deg)	$k \times 10^{-4}$
2a	35	10996	24.41	21.73	-8.68	0.316
	40	5585	24.39	21.72	-8.53	0.621
	45	3497	24.49	21.71	-8.75	0.991
2b	30	3155	23.25	20.03	-10.62	1.099
	35	1744	23.28	20.02	-10.58	1.988
	40	1057	23.35	20.01	-10.69	3.280
3a	100	11184	29.71	28.91	-2.13	0.310
	110	3845	29.71	28.89	-2.14	0.901
	120	1463	29.75	28.87	-2.24	2.369
3b	90	7042	28.56	24.36	-11.57	0.492
	100	3182	28.78	24.34	-11.90	1.089
	110	1145	28.79	24.32	-11.68	3.027

[a] Arrhenius parameter *E* value was 22.34, 20.63, 29.65, and 25.08 kcal mol^{-1}, for **2a, 2b**, **3a**, and **3b**, respectively.

_N_-(2-_n_-butyl-1-naphthoyl)pyrrolidine 2a

IR (cm^{-1}, KBr) 1627; ^{1}H-NMR: ($CDCl_3$) δ 0.94 (t, _J_=7.3 Hz, 3H), 1.35-1.47 (m, 2H), 1.60-1.70 (m, 2H), 1.71-1.87 (m, 2H), 1.97-2.06 (m, 2H), 2.63-2.79 (m, 2H), 2.91-3.05 (m, 2H), 3.74-3.92 (m, 2H), 7.38 (d, _J_=8.5 Hz, 1H), 7.41-7.50 (m, 2H), 7.67 (d, _J_=7.6 Hz, 1H), 7.77-7.83 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 14.4, 23.3, 25.1, 26.3, 33.4, 33.7, 45.7, 48.1, 124.8, 125.8, 127.3, 127.8, 128.5, 128.8, 129.7, 132.3, 134.3, 136.4, 169.5; EI-MS _m/z_ (rel intensity): 281 (M^+, 40); HRMS (FAB-MS) _m/z_ calcd for $C_{19}H_{24}NO$ 282.1858, found 282.1856.

_N_-(2-_n_-butyl-1-naphthoyl)piperidine 2b

IR (cm^{-1}, KBr) 1630; ^{1}H-NMR: ($CDCl_3$) δ 0.95 (t, _J_=7.3 Hz, 3H), 1.35-1.48 (m, 4H), 1.58-1.75 (m, 6H), 2.71 (t, _J_=8.0 Hz, 2H), 3.05-3.09 (m, 2H), 3.78-4.07 (m, 2H), 7.37 (d, _J_=8.5, 1H), 7.43-7.47 (m, 2H), 7.69 (d, _J_=7.3 Hz, 1H), 7.71-7.82 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 14.4, 23.4, 25.0, 26.3, 27.0, 33.5, 33.7, 42.6, 48.1, 125.1, 125.9, 127.1, 127.6, 128.4, 128.7, 130.2, 132.2, 133.1, 136.7, 169.2; EI-MS _m/z_ (rel intensity): 295 (M^+, 30); HRMS (FAB-MS) _m/z_ calcd for $C_{20}H_{26}NO$ 296.2014, found 296.1999.

_N_-(2-_tert_-butyl-1-naphthoyl)pyrrolidine 3a

IR (cm^{-1}, KBr) 1620; ^{1}H-NMR: ($CDCl_3$) δ 1.48 (s, 9H), 1.77-1.84 (m, 2H), 1.94-2.01 (m, 2H), 2.86-2.92 (m, 1H), 3.05-3.11 (m, 1H), 3.63-3.69 (m, 1H), 3.85-3.91 (m, 1H), 7.40-7.48 (m, 2H), 7.60-7.69 (m, 2H), 7.75 (s, 1H), 7.78 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 25.0, 26.1, 31.9, 37.2, 45.8, 48.5, 124.8, 126.0, 126.6, 127.3, 128.1, 128.7, 130.3, 132.2, 132.4, 143.2, 170.9; EI-MS _m/z_ (rel intensity): 281 (M^+, 11); HRMS (FAB-MS) _m/z_ calcd for $C_{19}H_{24}NO$ 282.1858, found 282.1877.

_N_-(2-_tert_-butyl-1-naphthoyl)piperidine 3b

IR (cm^{-1}, KBr) 1627; ^{1}H-NMR: ($CDCl_3$) δ 1.23-1.58 (m, 12H), 1.68-1.80 (m, 3H), 2.90-3.11 (m, 2H), 3.33-3.42 (m, 1H), 4.31-4.39 (m, 1H), 7.40-7.49 (m, 2H), 7.61 (d, _J_=8.97 Hz, 1H), 7.74-7.79 (m, 3H); ^{13}C-NMR ($CDCl_3$)δ24.9, 25.7, 26.1, 32.1, 37.3, 42.3, 48.5, 125.5, 126.1, 126.6, 127.0, 128.0, 128.5, 130.7, 131.3, 132.1, 143.5, 170.9; EI-MS _m/z_ (rel intensity): 295 (M^+, 20); HRMS (FAB-MS) _m/z_ calcd for $C_{20}H_{26}NO$ 296.2014, found 296.1999.

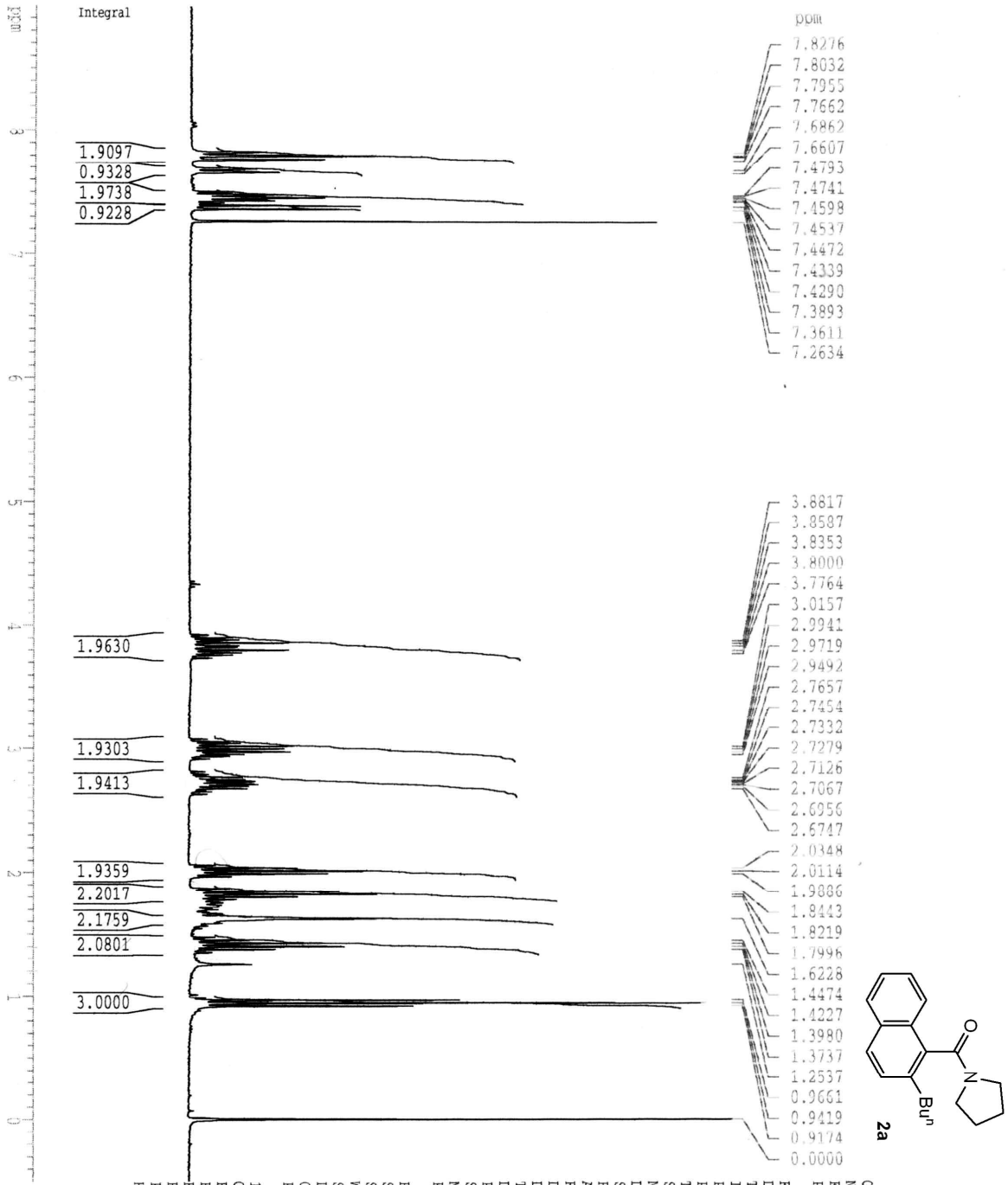

Fig. S3. ^{1}H NMR spectrum of **2a**

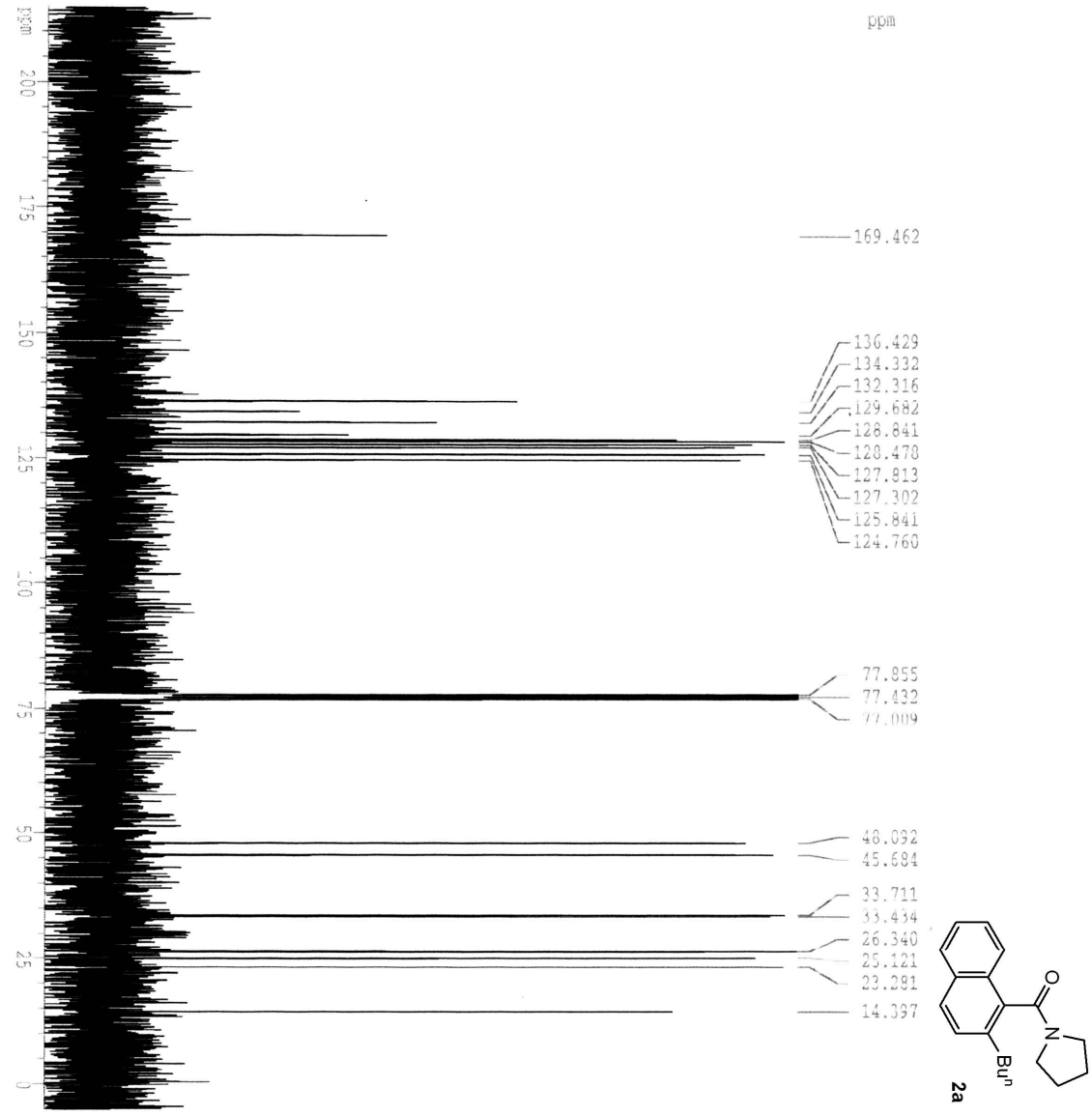

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Fig. S4. ^{13}C-NMR spectrum of **2a**

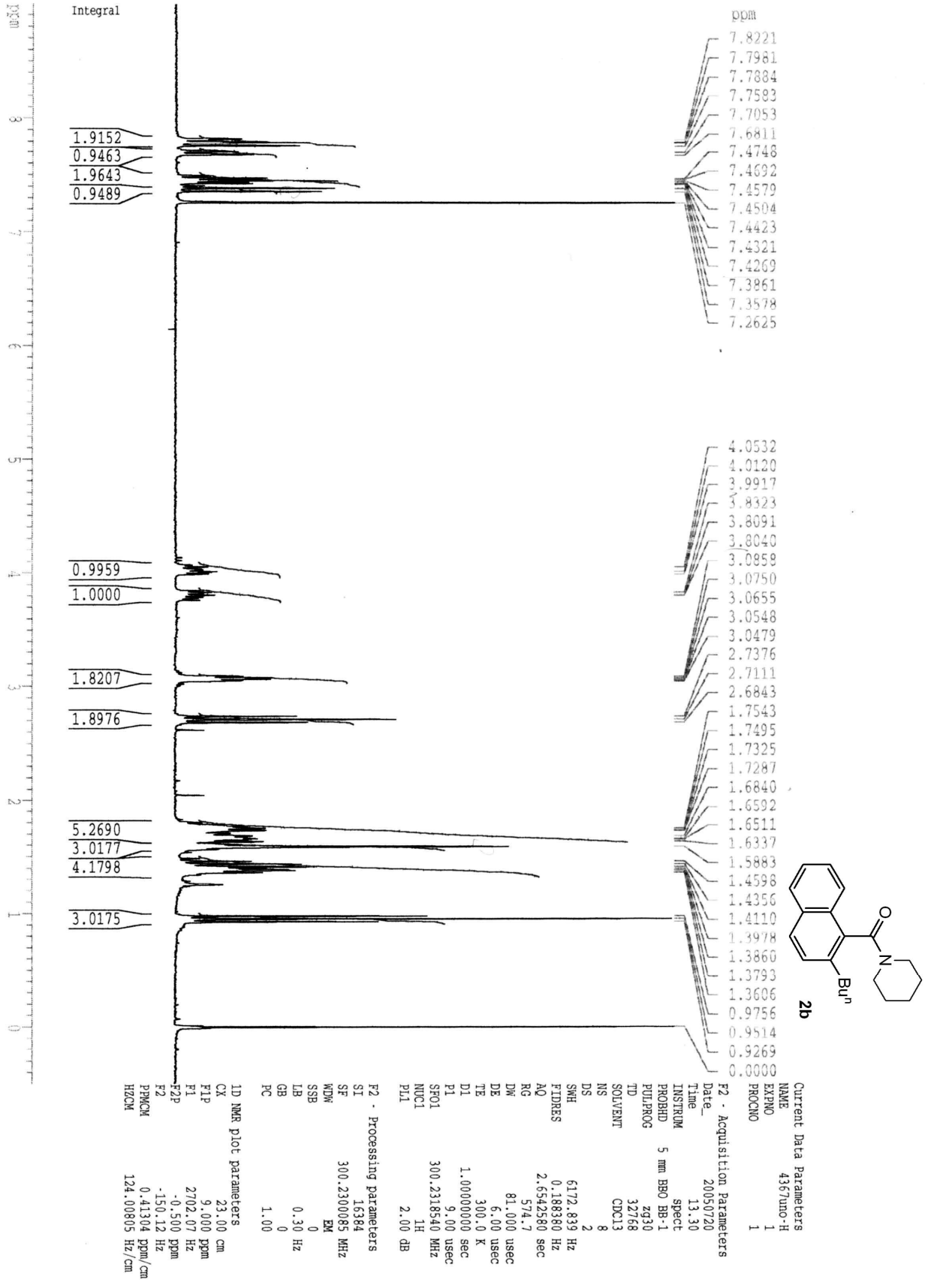

Fig. S5. ^{1}H NMR spectrum of **2b**

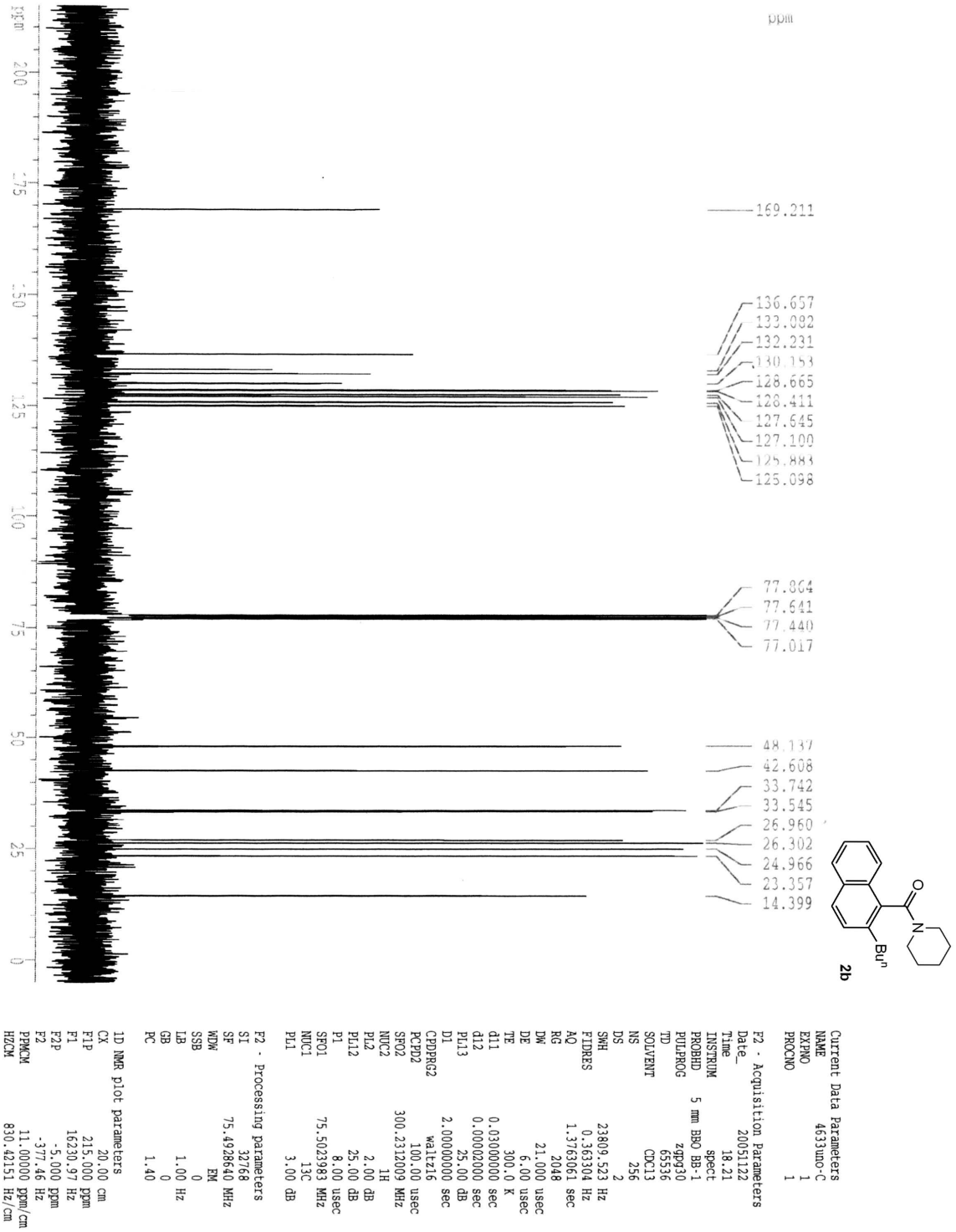

Fig. S6. ^{13}C-NMR spectrum of **2b.**

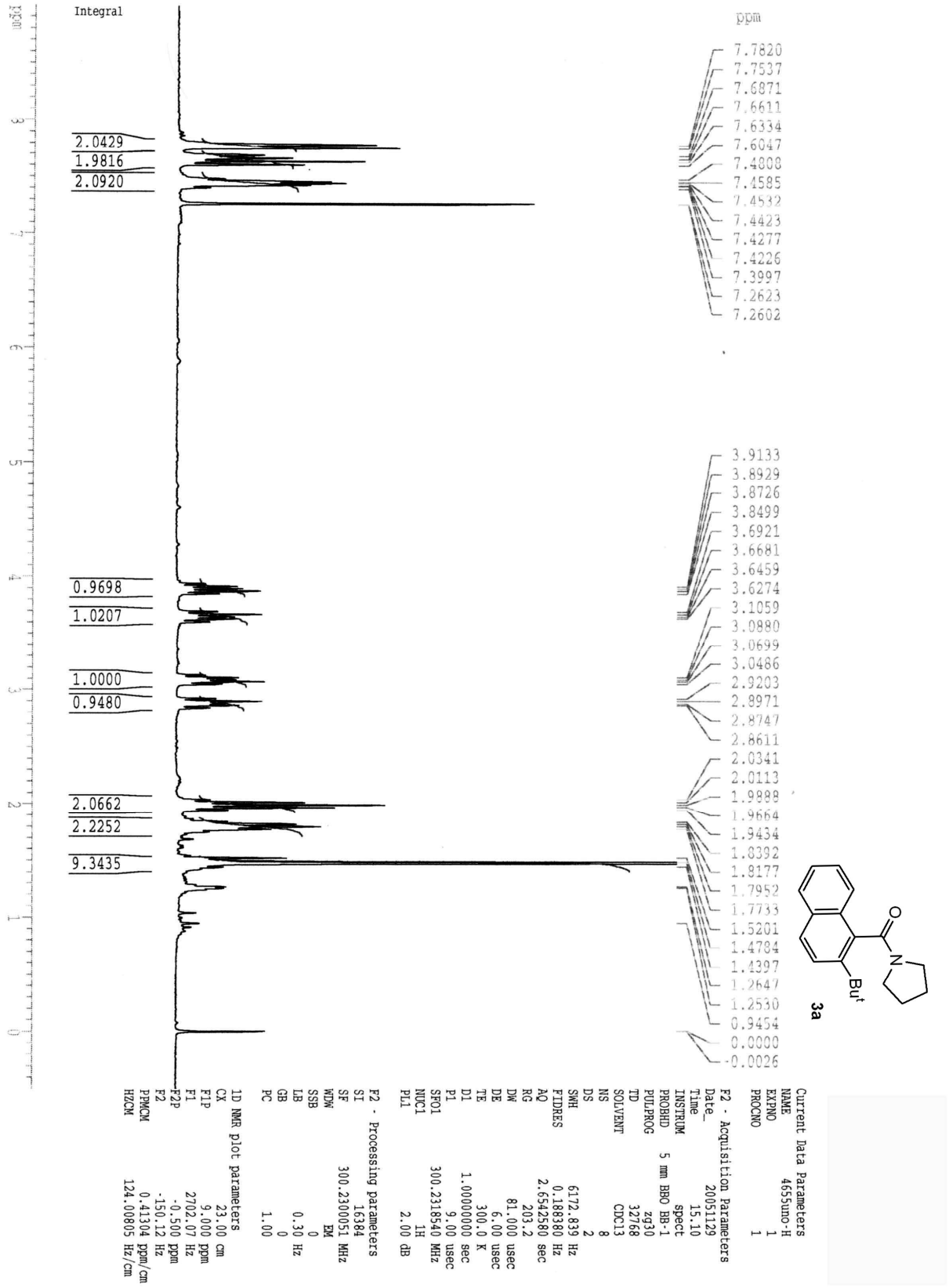

Fig. S7. ^{1}H NMR spectrum of **3a**

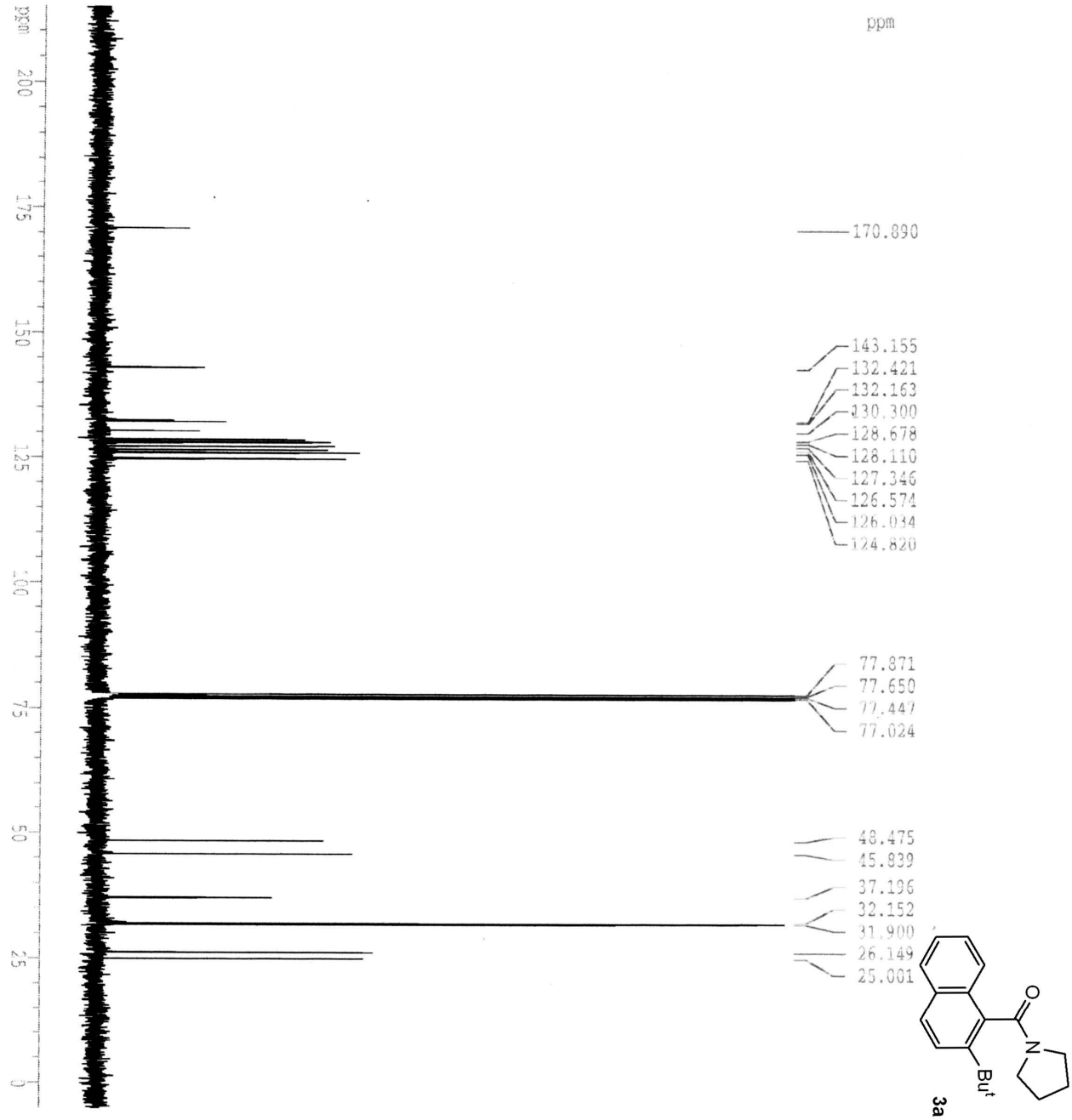

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Fig. S8. ^{13}C-NMR spectrum of **3a**

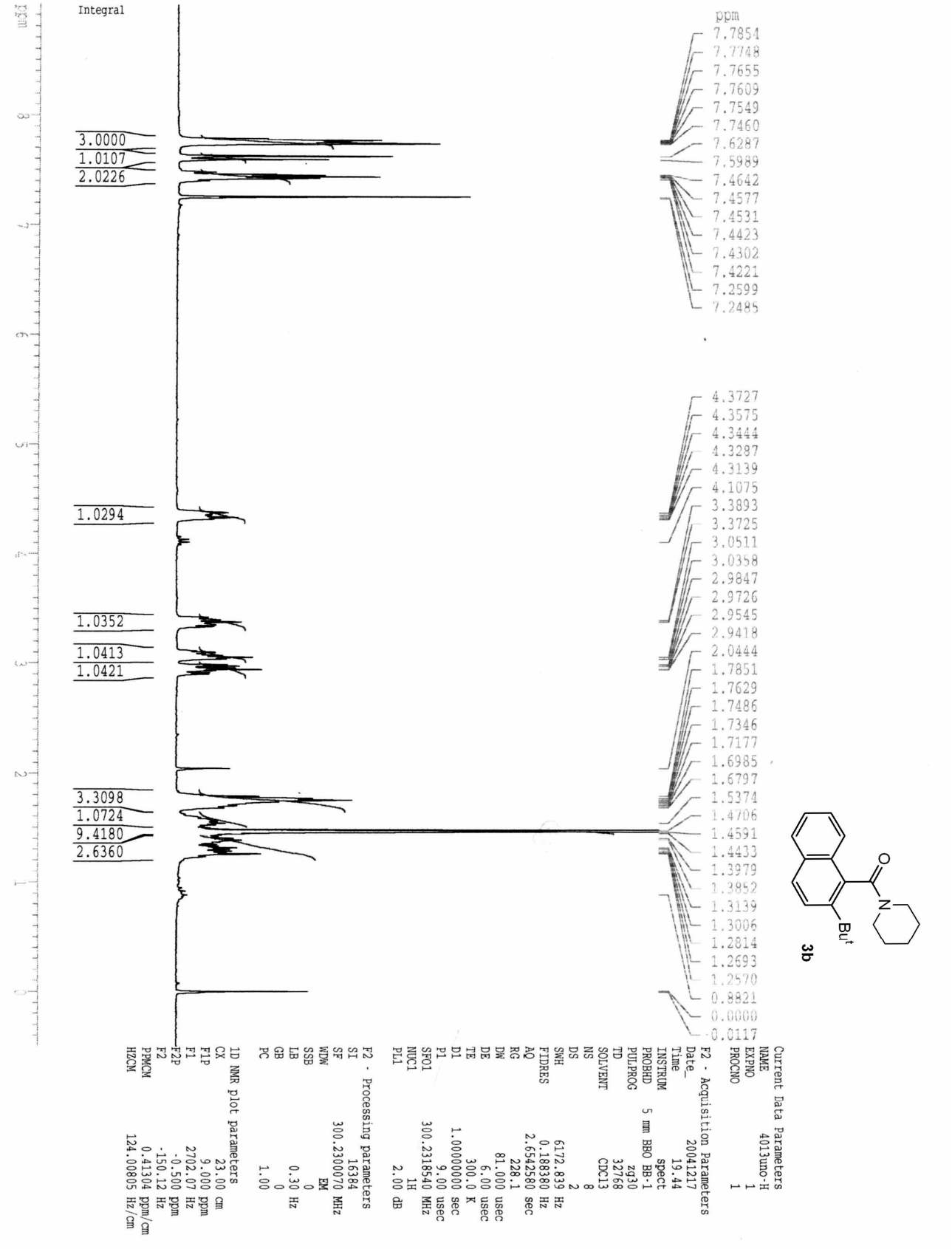

Fig. S9. ^{1}H NMR spectrum of **3b**

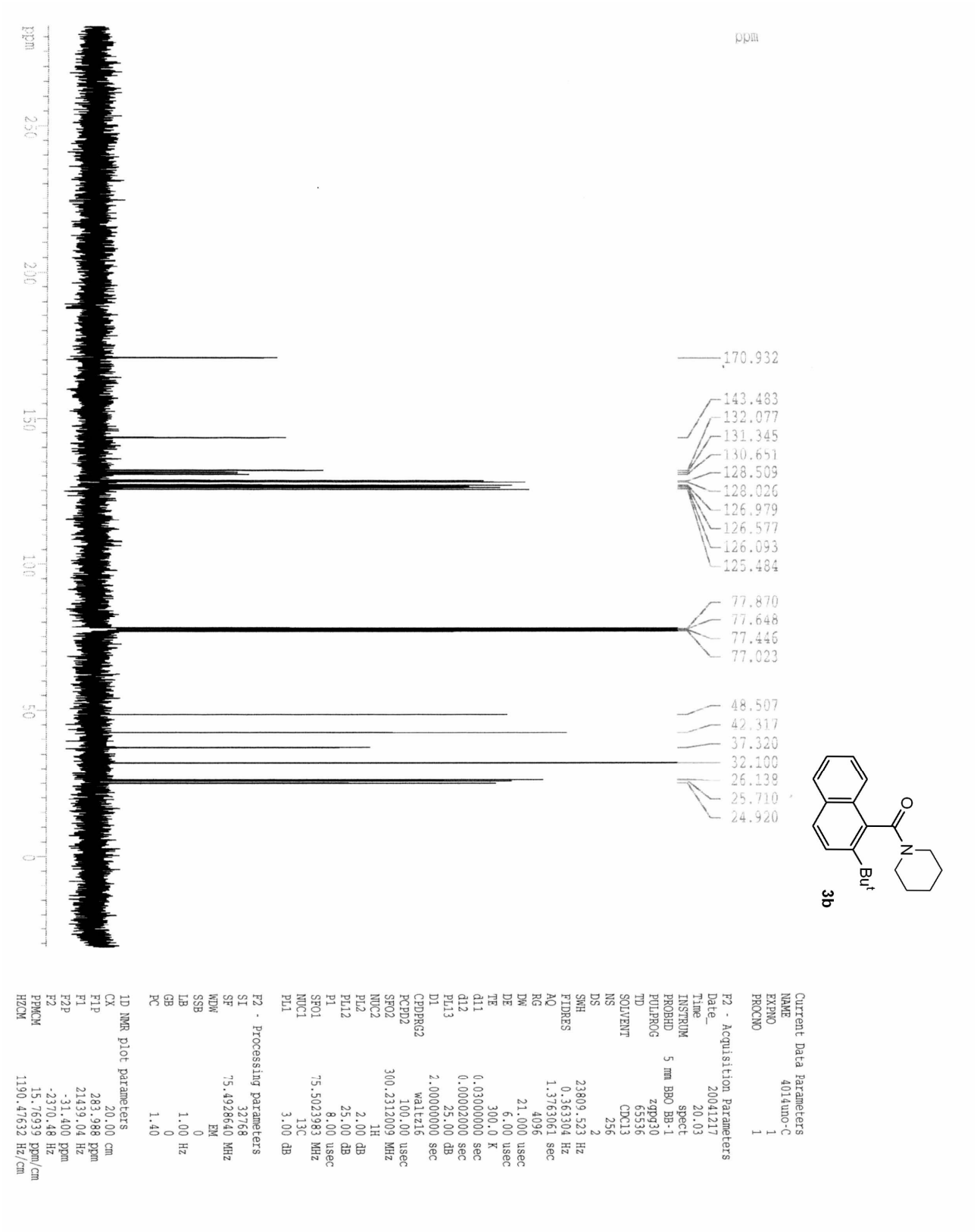

Fig. S10 ^{13}C-NMR spectrum of **3b**