Supplementary Material (ESI) for Chemical Science

Palladium-Catalyzed Amination Reactions in Flow: Overcoming the Challenges of Clogging via Acoustic Irradiation**

Timothy Noël, John R. Naber, Ryan L. Hartman, Jonathan P. McMullen, Klavs F. Jensen* and Stephen L. Buchwald*

Supporting Information

1. General Reagent Information

All reactions were carried out using reagent grade solvents, and all solutions were prepared under argon atmosphere. Aryl halides, aryl triflates, amines, biphenyl and dioxane were purchased from Sigma-Aldrich chemical company and were used as received. BrettPhos **1**,[1] BrettPhos precatalyst **2**[1] and (2*R*, 4'*R*, 8'*R*)-*δ*-tocopheryltrifluoromethanesulfonate[2] were prepared according to literature procedures. Reaction solutions were prepared in screw-cap, oven-dried volumetric flasks. For the continuous flow experiments, three solutions were prepared. The first solution contained BrettPhos precatalyst **2** and THF. The second solution contained aryl halide or aryl triflate, aniline, internal standard (biphenyl) and THF. The third solution contained sodium *tert*-butoxide (2 M in THF) and THF. Reagents that were solids were added to the volumetric flasks that were then evacuated and refilled with argon. This process was repeated a total of 3 times. Liquid reagents were added by syringe and the solutions were made up to the desired volume with THF. These solutions were loaded into syringes and attached to syringe pumps. Sodium *tert*-butoxide was stored in a N_2-filled glove box. Small portions were taken outside the glove box in glass vials and weighed in air.

2. General Analytical Information

All compounds were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. Copies of the ^{1}H and ^{13}C spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. All ^{1}H NMR are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR are reported in ppm relative to deuterochloroform (77.23 ppm), unless otherwise stated, and all were obtained with 1H decoupling. All IR spectra were taken on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm ID). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

3. Experimental setup

The equipment configuration that was used for the palladium-catalyzed amination experiments is described in Figure 1. Two Harvard Apparatus PHD2000 syringe pumps were used to deliver reagents from Normject plastic syringes to the reactor. On one syringe pump, a 5 mL syringe with the catalyst and a 5 mL syringe with the reagents were mounted. On the second syringe pump, a 10 mL syringe containing the sodium *tert*-butoxide was placed. The reactor for the experiments in Table 1, 2 and 3 was made out of PFA capillary tubing (1/16″ OD x 1000 μm ID) and had a volume of 400 μL (0.5 m length). The reactor in Table 4 had a volume of 800 μL (1.0 m length). The tubing from the syringes to the reactor was made out of PFA capillary tubing (1/16″ OD x 500 μm ID) and all fluidic connections were made using either 1/4-28 flat bottemed flangeless fittings or 10-32 coned fittings (IDEX Health and Science). The reactor was submerged in a VWR ultrasonic bath (Model 50HT) and filled with deionized water. The bath temperature was monitored via a thermocouple and maintained with a Waage immersion heater controlled by a J-KEM Scientific Gemini PID controller. The reactor was connected at the end with a piece of PFA tubing with an inner diameter of 2000 μm and 12.7 cm length (400 μL volume). Upon exiting the reactor, the reaction stream was quenched by a stream of H_2O and EtOAc. For the experiments at 90°C (Table 4), we used *n*BuOAc instead. These two streams were delivered by two Chromtech P-1500 dual stainless steel piston HPLC pumps. The diluted reaction stream was then fed to a GILSON FC 204 fraction collector.

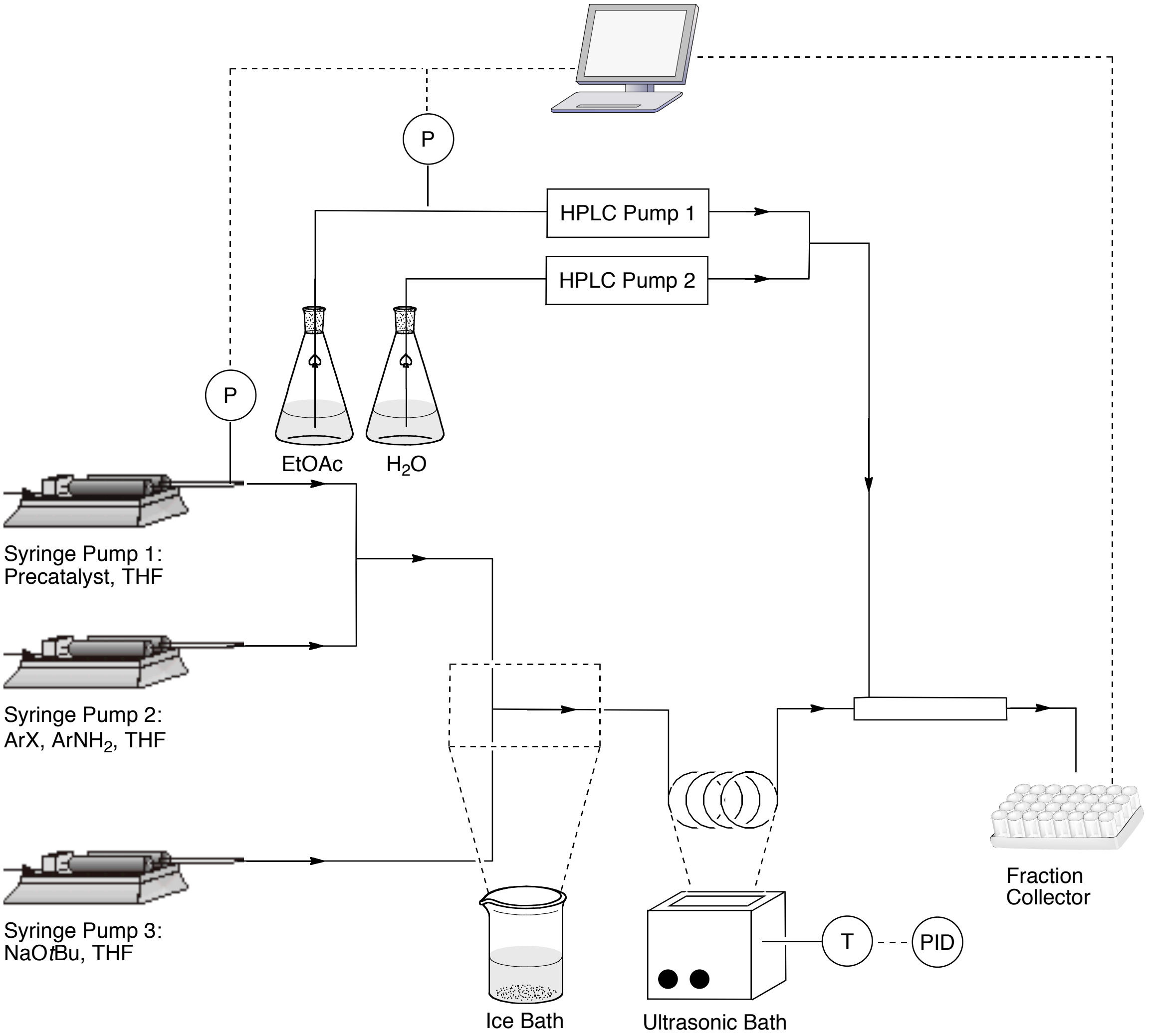


Figure 1. Experimental setup that can handle solids formed during the palladium-catalyzed amination reactions.

4. LabVIEW control:

Experimental conditions were controlled by a LabVIEW (National Instruments) program that contained Matlab scripts (Mathworks). A compact fieldpoint system (cFP, National Instruments) was used to interface the in-house LabVIEW software with experimental peripherals. Reaction fluid delivery was accomplished using Harvard Apparatus PHD2000 syringe pumps. The residence time of the reaction was adjusted by remotely controlling the flow rate of these syringe pumps with the developed LabVIEW program. Serial communications between the central computer and syringe pumps was made via standard RJ-45 cables. Delivery of the quench streams, ethyl acetate and water, was accomplished by using two dual-piston HPLC pumps (Chrome Tech, 1500 series). A 1,000 psi back pressure regulator (Idex) was incorporated downstream of each pump to achieve steady flow. The flow rates of these streams were also controlled remotely by varying the set point voltage supplied to these pumps using a cFP-AO-210 (National Instruments). Each pump was set to flow at twice the flow rate of the reaction stream. Reaction samples were collected using a Gilson FC-204 fraction collector.

The protocol for automated experiments developed for these investigations of palladium-catalyzed aminations are described in the following. Experimental conditions to be investigated were entered into a text file in matrix format. This file would contain the residence time and the stoichiometry for each experiment. The developed LabVIEW program imported this file and computed the corresponding flow rates of the syringe pumps to achieve these experimental conditions based upon the concentration of the reagent solutions loaded onto the syringe pumps. At the beginning of each experiment, the program would purge the system with a specified flush volume to ensure steady-state data collection. This flush volume corresponded to 5 reactor volumes. After this purge, seven samples of each 0.5 reactor volume were collected. Advancement of the fraction collector was achieved by activating a mechanical relay (National Instruments, cFP-RLY-425). Analysis of the reaction samples was performed off-line.

5. Workup and yields

Samples were collected in test tubes and were diluted with equal amounts of ethyl acetate and water and mixed vigorously. An aliquot of the organic phase was filtered through a short plug of silica gel and analyzed by GC. Yield and conversion were determined based on the peak area, relative to the internal standard. In certain cases, the phases were separated and the water phase was extracted in total 3 times with ethyl acetate. The organic phases were combined and concentrated in vacuo. The crude material was purified by column chromatography. Isolated yields were found to be in excellent agreement with the GC yields.

6. Typical procedure for GC Yield-Residence Time plots in a 400 μL reactor at 60°C.

An oven-dried screw-top volumetric flask (5.00 mL) that was fitted with a Teflon screw-cap, was charged with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and THF was added to make the solution up to 5 mL. A second oven-dried screw-top volumetric flask (5.00 mL) that was fitted with a Teflon screw-cap, was charged with biphenyl (308.4 mg, 2 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times). Next, the aryl halide or aryl triflate (10 mmol) and aryl amine (12 mmol) were added via syringe and THF was added to make the solution up to 5 mL. A third oven-dried screw-top volumetric flask (10.00 mL) that was fitted with a Teflon screw-cap, was evacuated and backfilled with argon (this process was repeated a total of 3 times). Sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) was added via syringe and THF was added to make the solution up to 10 mL. These three solutions were loaded into plastic syringes and fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor with the appropriate flow rates to give the different residence time (each experiment has 5 different residence times). When exiting the reactor the reactor was quenched with ethyl acetate and water. The flow rate of the ethyl acetate stream and the water stream are both two times the flow rate of the reaction stream. Software programs were developed to remotely control the pump flow rates and perform several experiments in a fully automated system. Typically, each experiment with a different residence time is preceded by a flush of 5 reactor volumes in order to ensure steady-state data collection. Next, 7 samples of each 0.5 reactor volume are collected. The samples were diluted with ethyl acetate and water, mixed vigorously, and an aliquot of the organic layer was filtered through a plug of silica eluting with ethyl acetate. The samples were analyzed by GC. Each data point in the plot is the average of 7 samples.

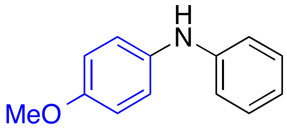
7. Typical procedure for GC Yield-Residence Time plots in a 800 μL reactor at 90°C.

An oven-dried screw-top volumetric flask (10.00 mL) that was fitted with a Teflon screw-cap, was charged with BrettPhos precatalyst **2** (11.7 mg, 14.2 μmol) and BrettPhos **1** (7.7 mg, 14.2 μmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and dioxane was added to make the solution up to 10 mL. A second oven-dried screw-top volumetric flask (10.00 mL) that was fitted with a Teflon screw-cap, was charged with biphenyl (440.7 mg, 2.86 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times). Next, the aryl chloride (14.3 mmol) and aryl amine (17.1 mmol) were added via syringe and dioxane was added to make the solution up to 10 mL. A third oven-dried screw-top volumetric flask (25.00 mL) that was fitted with a Teflon screw-cap, was charged with sodium *tert*-butoxide (2.64 g, 27.5 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and dioxane was added to make the solution up to 10 mL. These three solutions were loaded into plastic syringes and fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor with the appropriate flow rates to give the different residence time (each experiment has 5 different residence times). When exiting the reactor the reactor was quenched with *n*-butyl acetate and water. The flow rate of the *n*-butyl acetate stream and the water stream are both two times the flow rate of the reaction stream. Software programs were developed to remotely control the pump flow rates and perform several experiments in a fully automated system. Typically, each experiment with a different residence time is preceded by a flush of 5 reactor volumes in order to ensure steady-state data collection. Next, 7 samples of each 0.5 reactor volume are collected. The samples were diluted with ethyl acetate and water, mixed vigorously, and an aliquot of the organic layer was filtered through a plug of silica eluting with ethyl acetate. The samples were analyzed by GC. Each data point in the plot is the average of 7 samples.

8. Procedure to Obtain Isolated Yields

The different solutions with catalyst, reagents and base were prepared following the general procedure described above. The solutions were loaded into Normject plastic syringes and connected to the microfluidic system as shown in Figure 1. The solutions were injected with the flow rate that gave the highest conversion according to the GC Yield-Residence Time plot. The ultrasonic bath was filled with water and heated to 60°C or 90°C. While sonicating, the flow rates and pressures were allowed to stabilize to a steady-state (5 reactor volumes). Next, a sample was collected in order to obtain exactly 1 mmol of product. The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-20% ethylacetate).

9. Experimental Procedures for Examples Described in Table 1



4-methoxy-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 4-chloroanisole (1.22 mL, 10 mmol), aniline (1.09 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

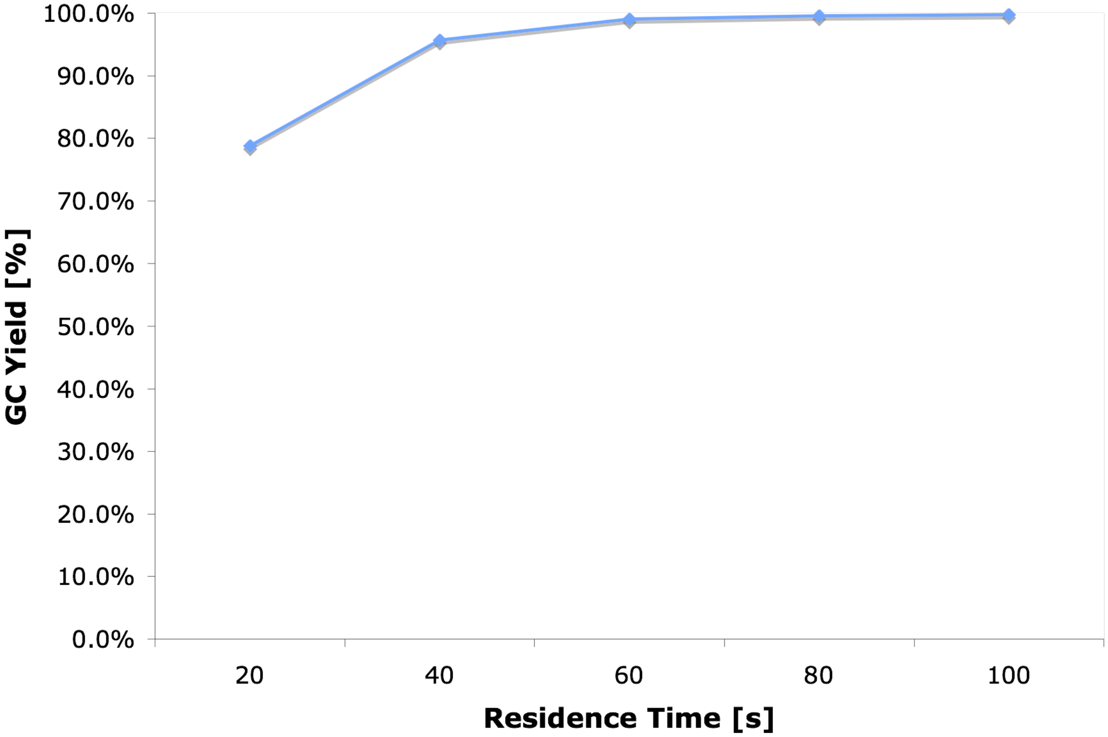
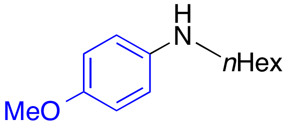


Figure 2. Yield of 4-methoxy-*N*-phenylaniline as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 60 minutes (12 mmol, 1 minute residence time, 400 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethylacetate) to give the title compound as an off-white solid (2.249 g, 94 %), mp = 104-106 °C (lit. 104-106 °C)[3]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.91-6.81 (m, 5H), 5.48 (br s, 1H), 3.79 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.4, 145.3, 135.8, 129.5, 122.4, 119.7, 115.8, 114.8, 55.7 ppm. IR (neat, cm^{-1}): 3388, 1596, 1513, 1502, 1317, 1298, 1249, 1237, 1033, 752. Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.26; H, 6.56.



***N*-hexyl-4-methoxyaniline.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (81.6 mg, 0.1 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 4-chloroanisole (1.22 mL, 10 mmol), *n*hexylamine (1.59 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

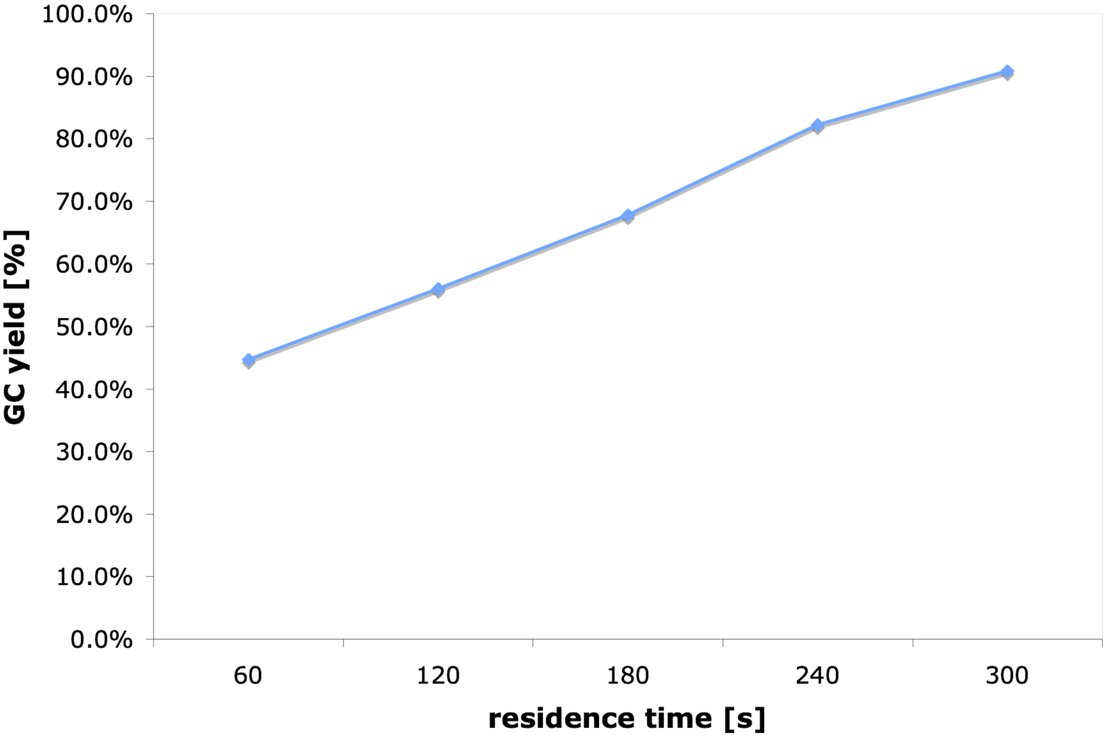
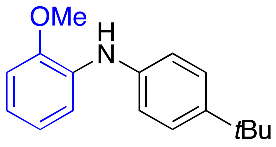


Figure 3. Yield of *N*-hexyl-4-methoxyaniline as a function of reaction time with 1.0 mol% catalyst at 60°C.

A sample was collected for 25 minutes (1 mmol, 5 minutes residence time, 80 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethylacetate) to give the title compound as a yellow oil (191.9 mg, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 3.28 (br s, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.58 (pentet, *J* = 7.2 Hz, 2H), 1.42-1.29 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 143.0, 115.0, 114.1, 55.9, 45.1, 31.8, 29.8, 27.0, 22.8, 14.2 ppm. IR (neat, cm^{-1}): 3394, 2928, 2856, 1514, 1465, 1294, 1236, 1179, 1040, 818. Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.47; H, 10.24.



***N*-(4-(*tert*-butyl)phenyl)-2-methoxyaniline.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 2-chloroanisole (1.27 mL, 10 mmol), 4-*tert*-butylaniline (1.90 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 µL) with the appropriate flow rates to give the different residence times.

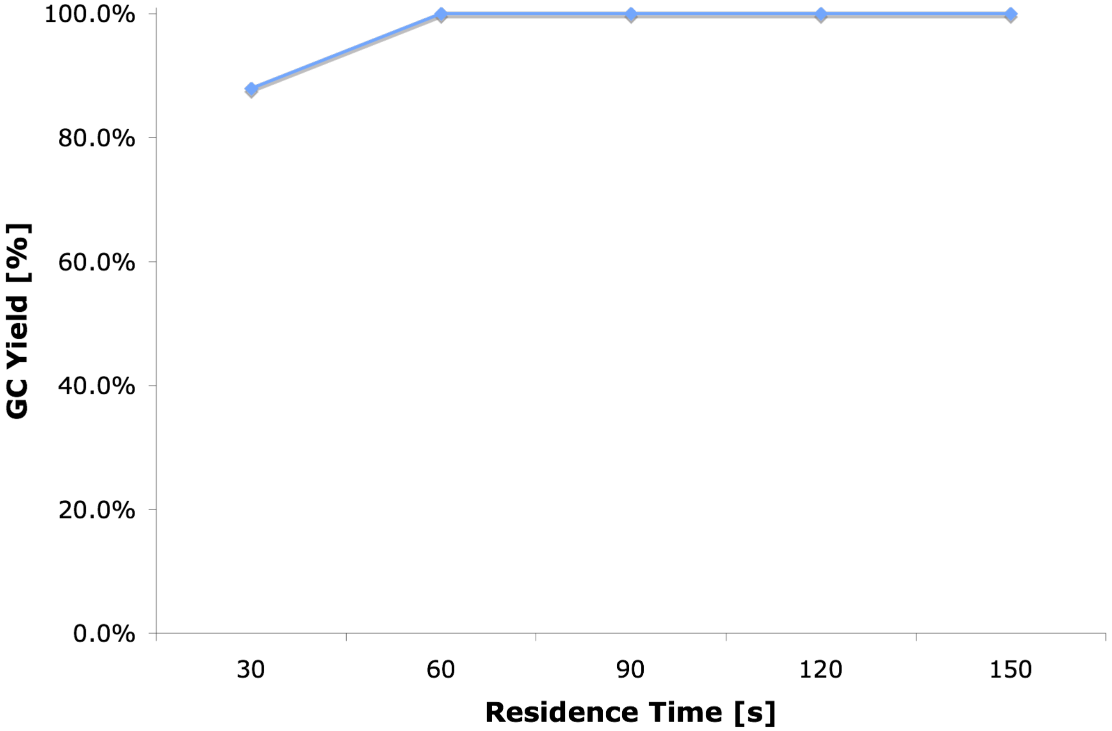
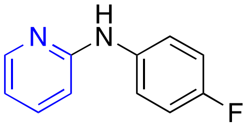


Figure 3. Yield of *N*-(4-(*tert*-butyl)phenyl)-2-methoxyaniline as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 5 minutes (1 mmol, 1 minutes residence time, 400 µL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-4% ether) to give the title compound as a orange solid (255.3 mg, 99.9 %), mp = 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.28 (m, 3H), 7.14-7.10 (m, 2H), 6.90-6.81 (m, 3H), 6.13 (br s, 1H), 3.89 (s, 3H), 1.34 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.1, 144.4, 140.1, 133.7, 126.2, 121.0, 119.4, 119.0, 114.1, 110.5, 55.7, 34.3, 31.6 ppm. IR (neat, cm^{-1}): 3411, 2960, 1599, 1518, 1457, 1298, 1238, 1109, 1028, 739. Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 79.90; H, 8.34.



***N*-(4-fluorophenyl)pyridin-2-amine.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 2-chloropyridine (0.95 mL, 10 mmol), 4-fluoroaniline (1.15 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

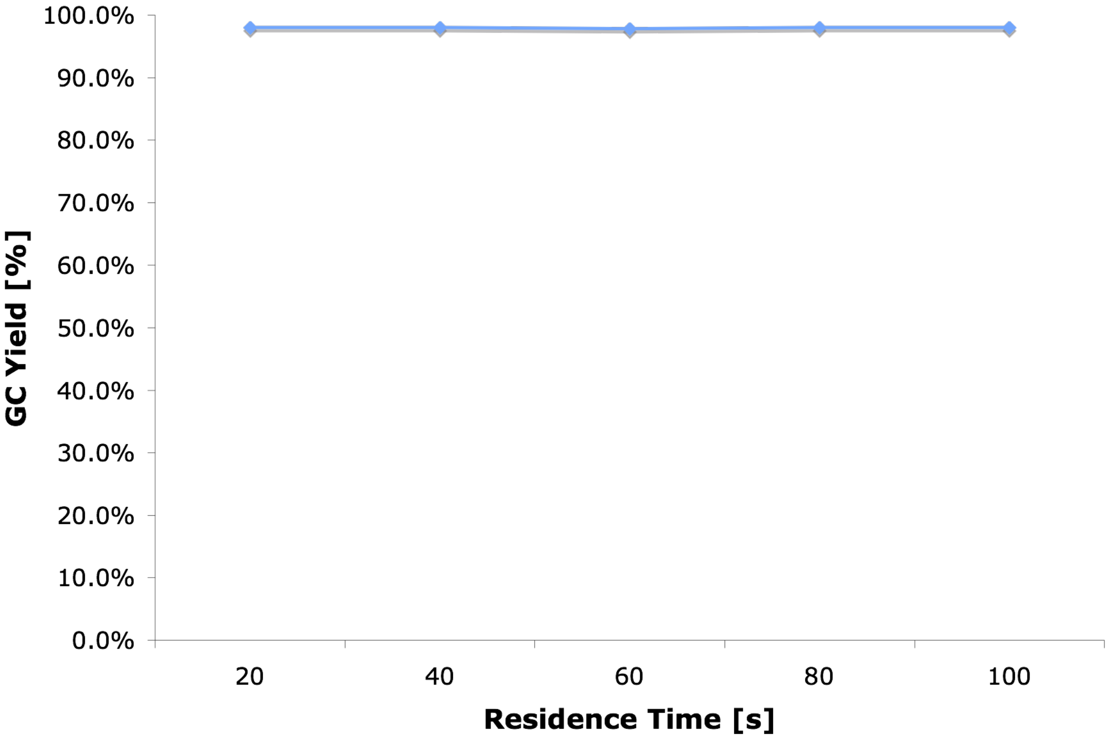
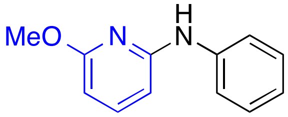


Figure 4. Yield of *N*-(4-fluorophenyl)pyridin-2-amine as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 100 seconds (1 mmol, 20 seconds residence time, 1200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5-10% ethyl acetate) to give the title compound as a light yellow solid (176.0 mg, 94 %), mp = 122-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.43 (m, 1H), 7.29-7.23 (m, 2H), 7.21 (br s, 1H), 7.00 (t, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.69-6.66 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 157.8, 156.8, 148.4, 137.9, 136.7, 136.7, 123.1, 123.0, 116.2, 115.9, 114.9, 107.9 ppm. IR (neat, cm^{-1}): 3229, 3025, 1605, 1581, 1505, 1458, 1441, 1333, 1213, 1156. Anal. Calcd. for $C_{11}H_9N_2F$: C, 70.20; H, 4.82. Found: C, 69.92; H, 4.80.



6-methoxy-*N*-phenylpyridin-2-amine. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 2-chloro-6-methoxypyridine (1.19 mL, 10 mmol), aniline (1.09 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 µL) with the appropriate flow rates to give the different residence times.

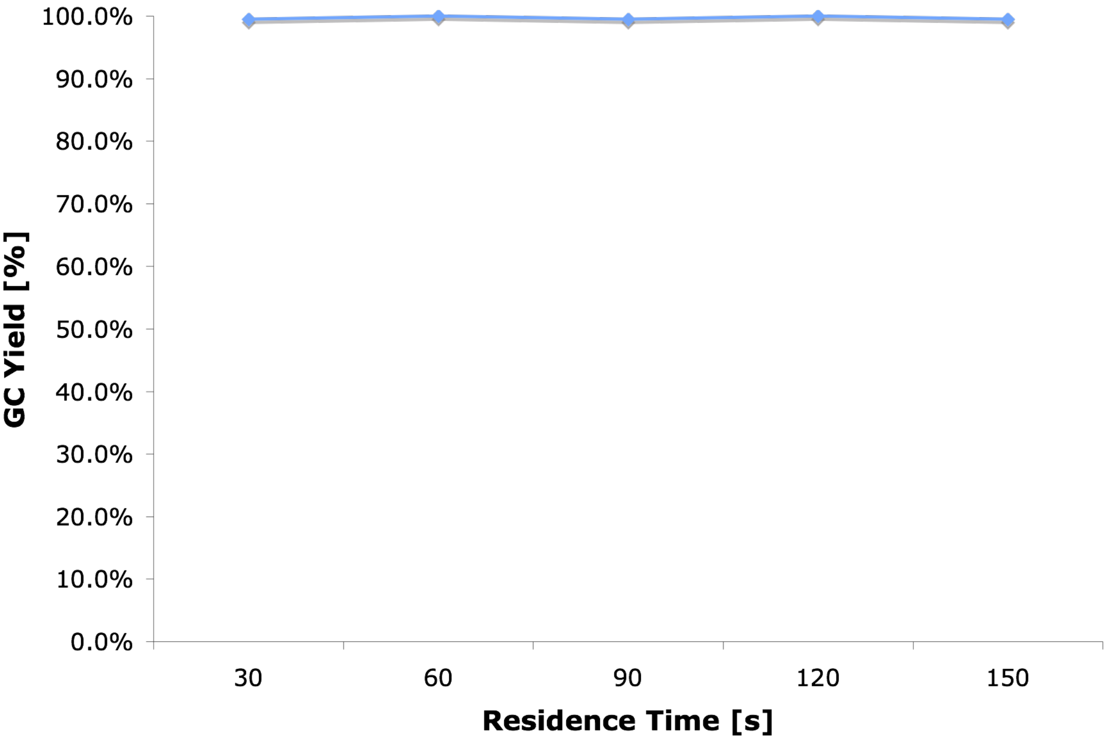
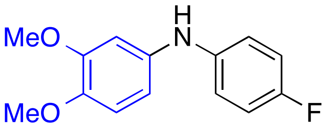


Figure 5. Yield of 6-methoxy-*N*-phenylpyridin-2-amine as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 150 seconds (1 mmol, 30 seconds residence time, 800 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as an orange oil (199.9 mg, 99.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.27 (m, 5H), 7.00 (tt, *J* = 1.2, 7.4 Hz, 1H), 6.40 (br s, 1H), 6.37 (dd, *J* = 0.5, 7.9 Hz, 1H), 6.19 (dd, *J* = 0.5, 7.9 Hz, 1H), 3.89 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 154.4, 140.8, 140.3, 129.3, 122.4, 119.9, 100.3, 99.8, 53.5 ppm. IR (neat, cm^{-1}): 3399, 2946, 1609, 1584, 1521, 1451, 1261, 1147, 1039, 782. Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 72.00; H, 6.06.

10. Experimental Procedures for Examples Described in Table 2



***N*-(4-fluorophenyl)-3,4-dimethoxyaniline.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 4-bromoveratrole (1.44 mL, 10 mmol), 4-fluoroaniline (1.15 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

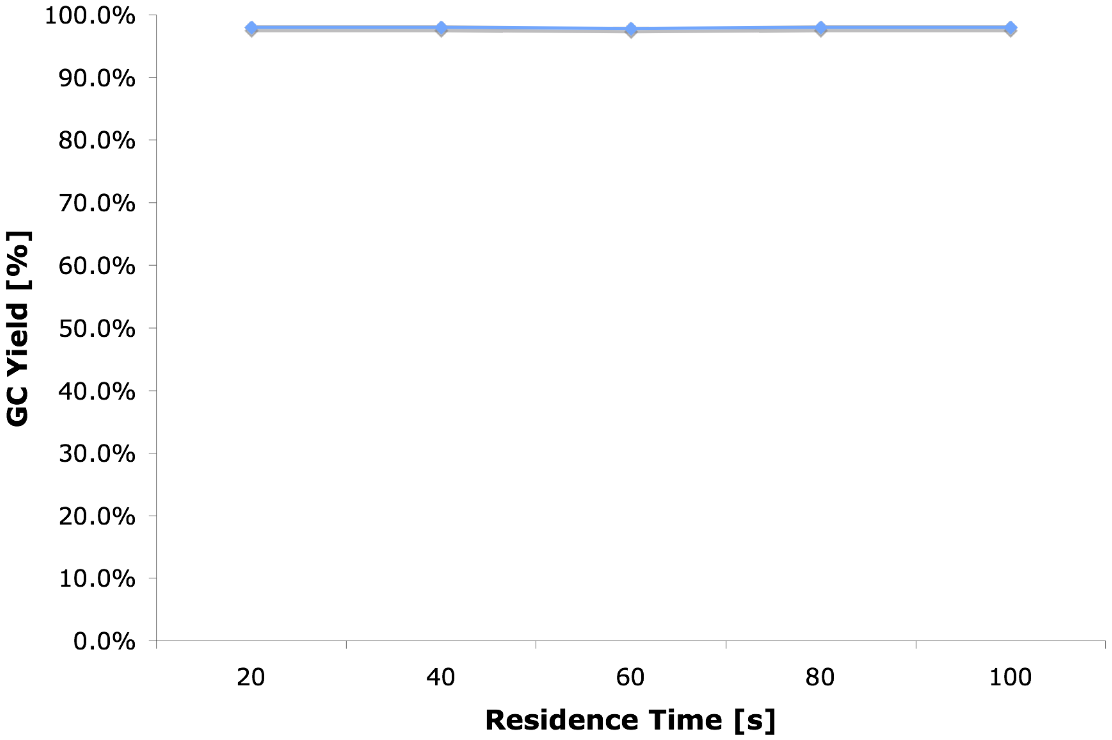
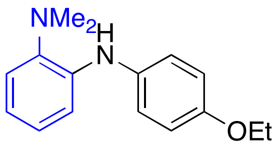


Figure 6. Yield of *N*-(4-fluorophenyl)-3,4-dimethoxyaniline as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 100 seconds (1 mmol, 20 seconds residence time, 1200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-15% ethyl acetate) to give the title compound as a brown oil (246.1 mg, 99.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94-6.86 (m, 4H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.56 (d, *J* = 2.5, 8.5 Hz, 1H), 5.40 (br s, 1H), 3.82 (s, 3H), 3.79 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.6, 156.2, 149.8, 144.5, 140.9, 140.9, 137.3, 118.5, 118.4, 116.1, 115.9, 112.4, 111.1, 104.5, 56.4, 56.0 ppm. IR (neat, cm^{-1}): 3355, 2978, 1596, 1512, 1477, 1455, 1291, 1241, 1046, 745. Anal. Calcd. for $C_{14}H_{14}FNO_2$: C, 68.00; H, 5.71. Found: C, 67.83; H, 5.71.



***N*'-(4-ethoxyphenyl)-*N*'',*N*''-dimethylbenzene-1,2-diamine.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 2-bromo-N,N-dimethylaniline (1.44 mL, 10 mmol), *p*-phenitidine (1.55 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 µL) with the appropriate flow rates to give the different residence times.

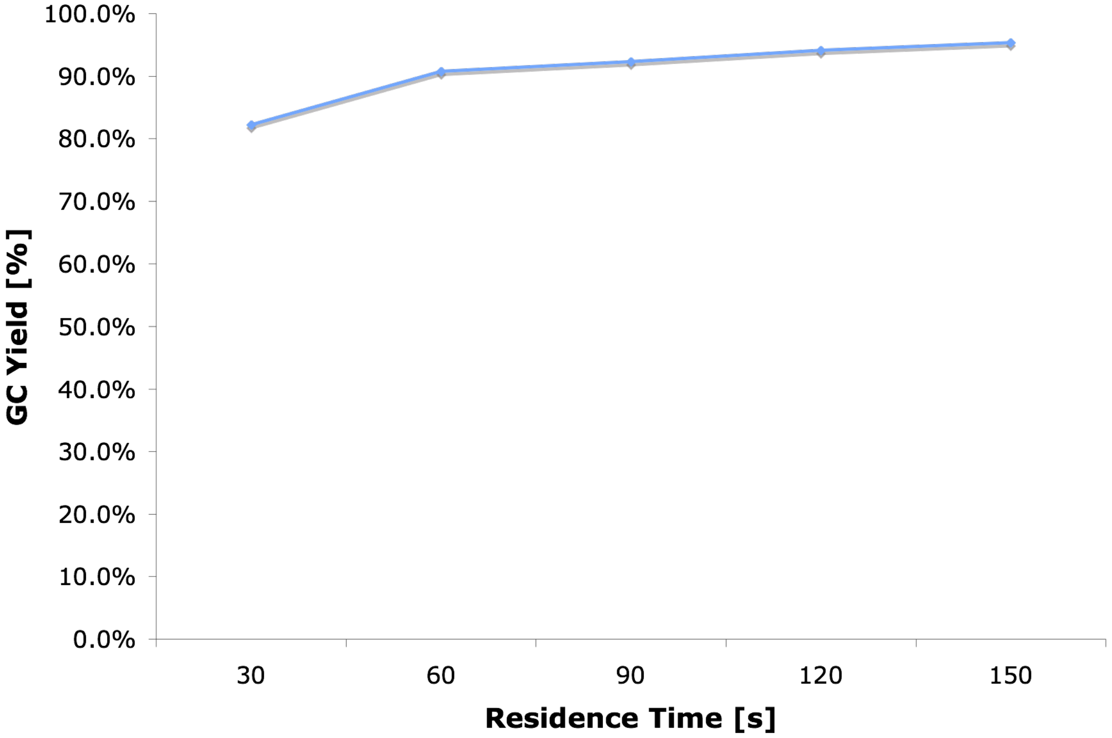
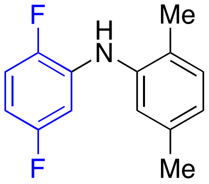


Figure 7. Yield of *N*'-(4-ethoxyphenyl)-*N*'',*N*''-dimethylbenzene-1,2-diamine as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 12.5 minutes (1 mmol, 150 seconds residence time, 160 µL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethyl acetate) to give the title compound as an orange oil (224.1 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12-7.07 (m, 4H), 6.94 (dt, *J* = 1.4, 7.5 Hz, 1H), 6.89-6.85 (m, 2H), 6.78 (dt, *J* = 1.4, 7.5 Hz, 1H), 6.43 (br s, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 2.69 (s, 6H), 1.41 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5, 141.5, 140.2, 136.0, 124.4, 122.4, 119.7, 118.8, 115.4, 112.6, 63.9, 44.3, 15.1 ppm. IR (neat, cm^{-1}): 3368, 2935, 1605, 1504, 1464, 1257, 1215, 1135, 1025, 827. Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86. Found: C, 74.86; H, 7.81.



***N*-(2,5-difluorophenyl)-2,5-dimethylaniline.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (81.3 mg, 0.1 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 1-bromo-2,5-difluorobenzene (1.13 mL, 10 mmol), 2,5-dimethylaniline (1.49 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

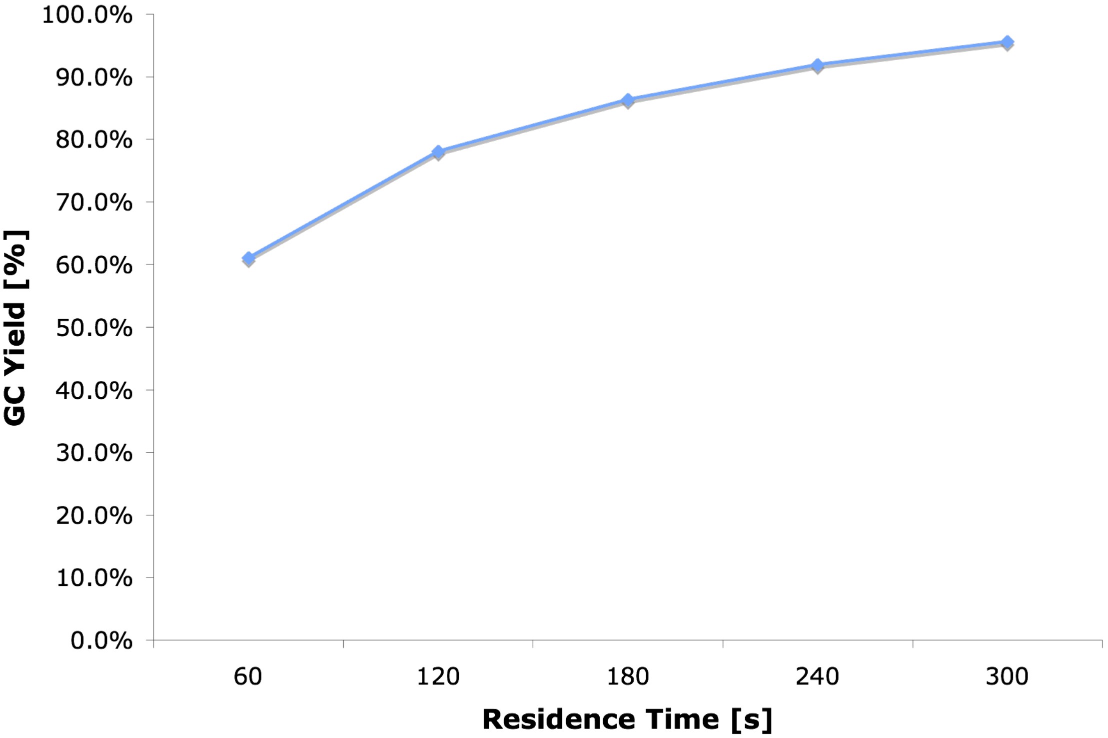
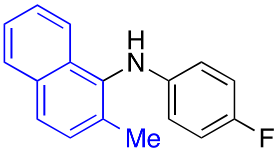


Figure 8. Yield of *N*-(2,5-difluorophenyl)-2,5-dimethylaniline as a function of reaction time with 1.0 mol% catalyst at 60°C.

A sample was collected for 25 minutes (1 mmol, 5 minutes residence time, 80 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-3% ethyl acetate) to give the title compound as an colorless oil (212.5 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, J = 7.7 Hz, 1H), 7.06 (s, 1H), 6.99-6.93 (m, 1H), 6.87 (d, J =

7.7 Hz, 1H), 6.60-6.55 (m, 1H), 6.41-6.35 (m, 1H), 5.53 (br s, 1H), 2.30 (s, 3H), 2.19 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ: 160.7, 160.7, 158.3, 158.3, 149.5, 149.5, 147.2, 147.2, 138.6, 136.9, 135.0, 134.8, 134.8, 134.7, 131.2, 128.4, 125.4, 123.0, 115.6, 115.5, 115.4, 115.4, 104.5, 104.4, 104.3, 104.2, 102.5, 102.5, 102.2, 102.2, 21.2, 17.4 ppm. IR (neat, cm^{-1}): 3433, 2924, 1633, 1578, 1523, 1504, 1445, 1179, 1163, 844. Anal. Calcd. for $C_{14}H_{13}F_2N$: C, 72.09; H, 5.62. Found: C, 72.23; H, 5.56.



***N*-(4-fluorophenyl)-2-methylnaphthalen-1-amine.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 1-bromo-2-methylnaphtalene (1.55 mL, 10 mmol), 4-fluoroaniline (1.15 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

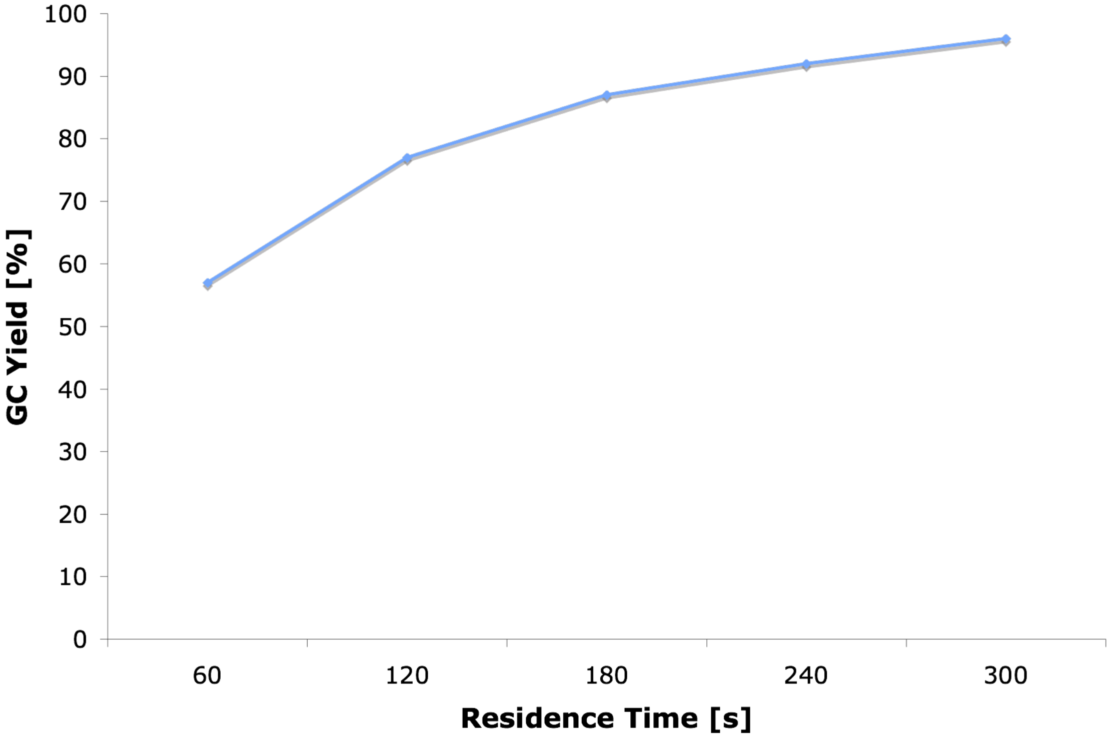
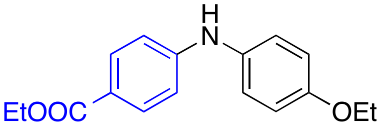


Figure 9. Yield of *N*-(4-fluorophenyl)-2-methylnaphthalen-1-amine as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 25 minutes (1 mmol, 5 minutes residence time, 80 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-5% ethyl acetate) to give the title compound as an off-white solid (227.7 mg, 91 %), mp = 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93-7.91 (m, 1H), 7.85-7.81 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.44-7.37 (m, 3H), 6.84-6.79 (m, 2H), 6.46-6.42 (m, 2H), 5.43 (br s, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 155.2, 143.4, 134.8, 133.5, 132.6, 131.6, 129.4, 128.4, 126.5, 126.2, 125.4, 123.3, 116.0, 115.8, 114.8, 114.7, 18.5 ppm. IR (neat, cm^{-1}): 3393, 1507, 1380, 1308, 1214, 1098, 816, 766, 745, 638.



Ethyl 4-((4-ethoxyphenyl)amino)benzoate. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (81.6 mg, 0.1 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with ethyl-4-bromobenzoate (1.63 mL, 10 mmol), *p*-phenitidine (1.55 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

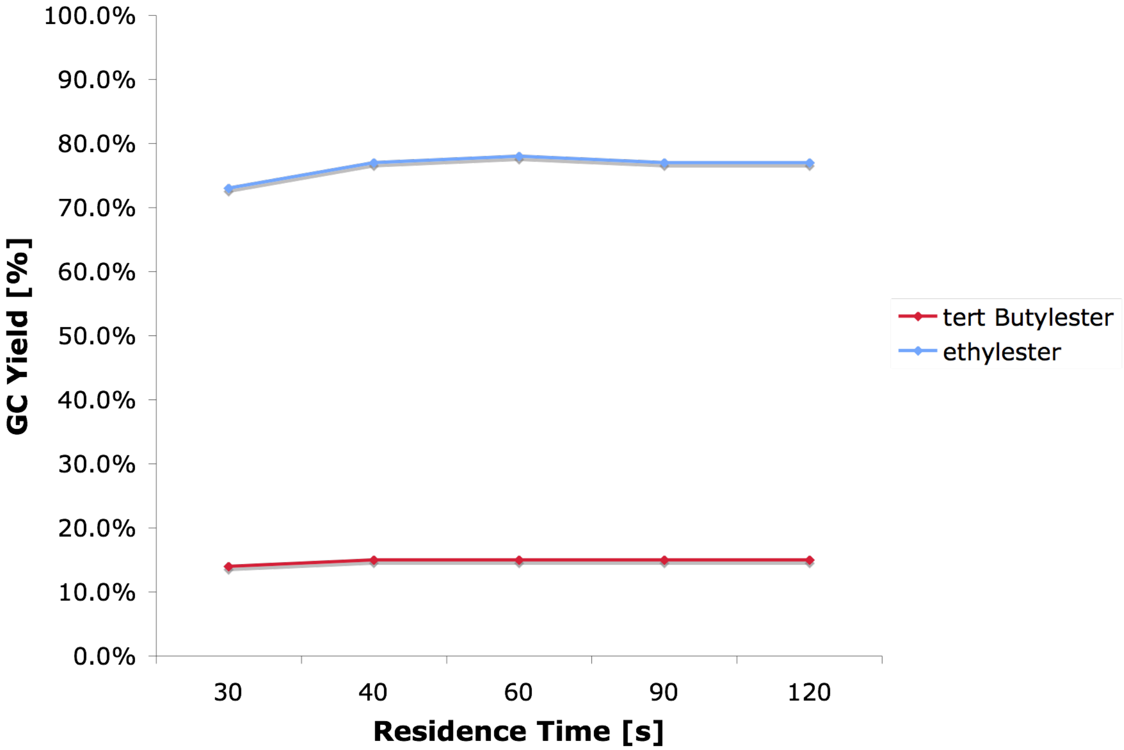
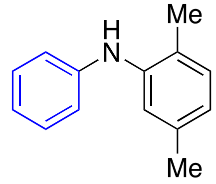


Figure 10. Yield of 4-((4-ethoxyphenyl)amino)benzoate and ethyl 4-((4-*t*-butoxyphenyl)amino)benzoate as a function of reaction time with 1.0 mol% catalyst at 40°C.

A sample was collected for 10 minutes (2 mmol, 1 minute residence time, 400 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethyl acetate) to give the title compound as an off-white solid (445.1 mg, 76 %), mp = 95-97 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.84 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.85 (br s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ: 166.8, 156.0, 149.9, 133.5, 131.6, 124.5, 120.5, 115.5, 113.3, 63.9, 60.5, 15.0, 14.6 ppm. IR (neat, cm^{-1}): 3343, 2978, 1678, 1598, 1528, 1511, 1281, 1243, 1173, 769. Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.79; H, 6.59.

Ethyl 4-((4-*t*-butoxyphenyl)amino)benzoate. The compound was obtained as a white solid (92.4 mg, 15 %), mp = 91-93 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.79 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.84 (br s, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 4.54 (s, 9H), 1.39 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 166.1, 155.8, 149.5, 133.7, 131.4, 124.2, 122.1, 115.5, 113.4, 80.2, 63.9, 28.5, 15.0 ppm. IR (neat, cm^{-1}): 3352, 2978, 1700, 1682, 1602, 1510, 1293, 1241, 1160, 1115. Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found: C, 73.09; H, 7.39.

11. Experimental Procedures for Examples Described in Table 3.



2,5-dimethyl-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with phenyltrifluoromethanesulfonate (1.62 mL, 10 mmol), 2,5-dimethylaniline (1.49 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

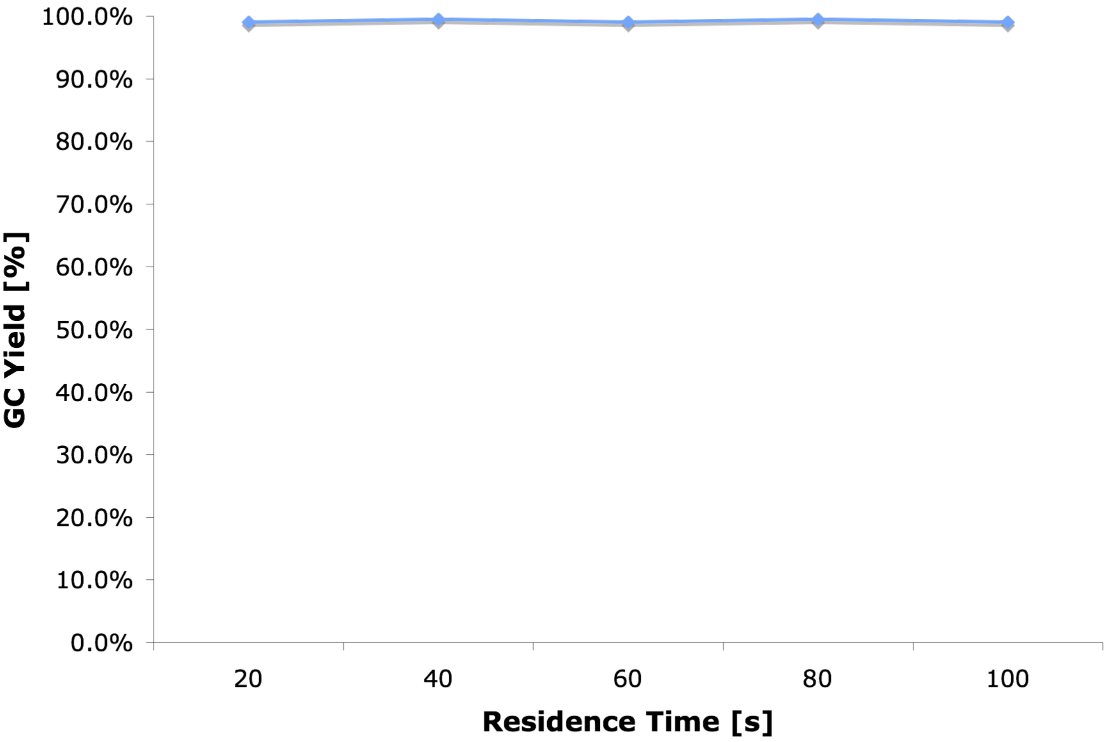
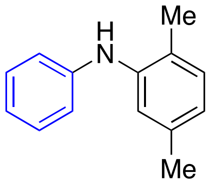


Figure 11. Yield of 2,5-dimethyl-*N*-phenylaniline as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 100 seconds (1 mmol, 20 seconds residence time, 1200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as a light yellow oil (189.2 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26-7.22 (m, 2H), 7.08-7.06 (m, 2H), 6.95-6.92 (m, 2H), 6.88 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.32 (br s, 1H), 2.26 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.2, 141.1, 136.6, 130.9, 129.4, 125.4, 122.9, 120.5, 119.6, 117.5, 21.3, 17.6 ppm. IR (neat, cm^{-1}): 3387, 2921, 1600, 1577, 1519, 1496, 1412, 1311, 747, 693. Anal. Calcd. for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 85.34; H, 7.72.



2,5-dimethyl-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (8.2 mg, 0.01 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with phenyltrifluoromethanesulfonate (1.62 mL, 10 mmol), 2,5-dimethylaniline (1.49 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

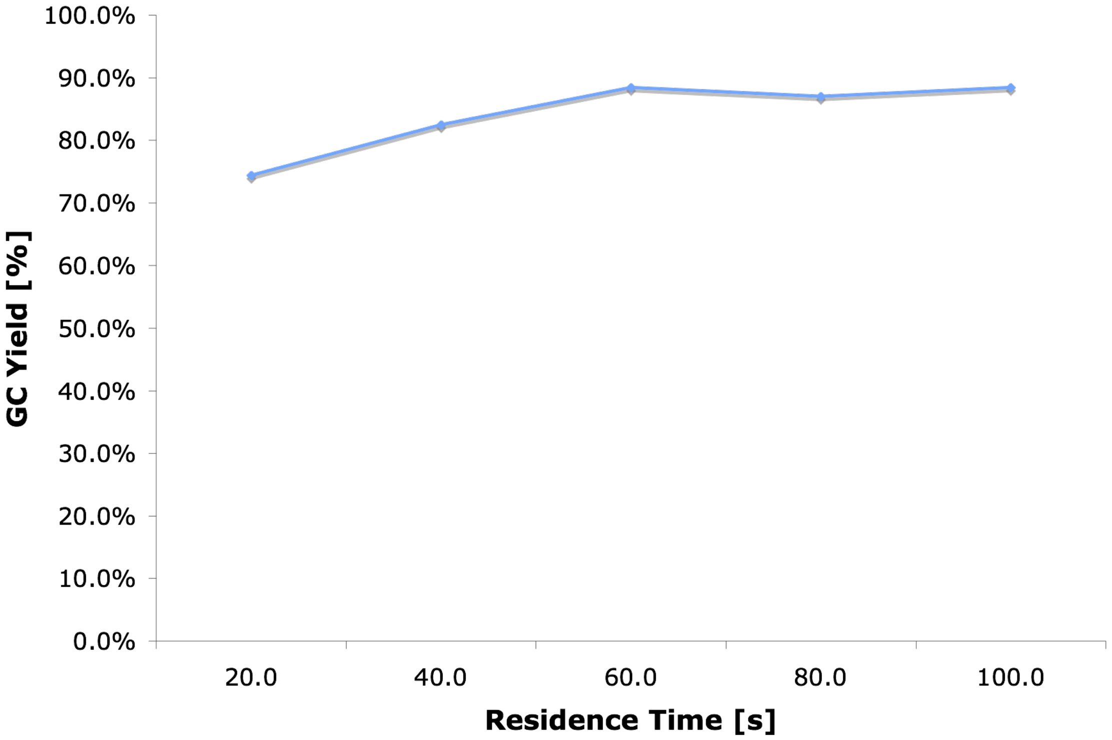
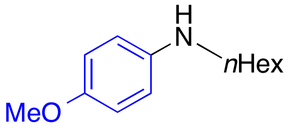


Figure 12. Yield of 2,5-dimethyl-*N*-phenylaniline as a function of reaction time with 0.1 mol% catalyst at 60°C.

A sample was collected for 300 seconds (1 mmol, 60 seconds residence time, 400 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as a light yellow oil (171.5 mg, 87 %).



***N*-hexyl-4-methoxyaniline.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 4-methoxyphenyltrifluoromethanesulfonate (1.8 mL, 10 mmol), *n*-hexylamine (1.59 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

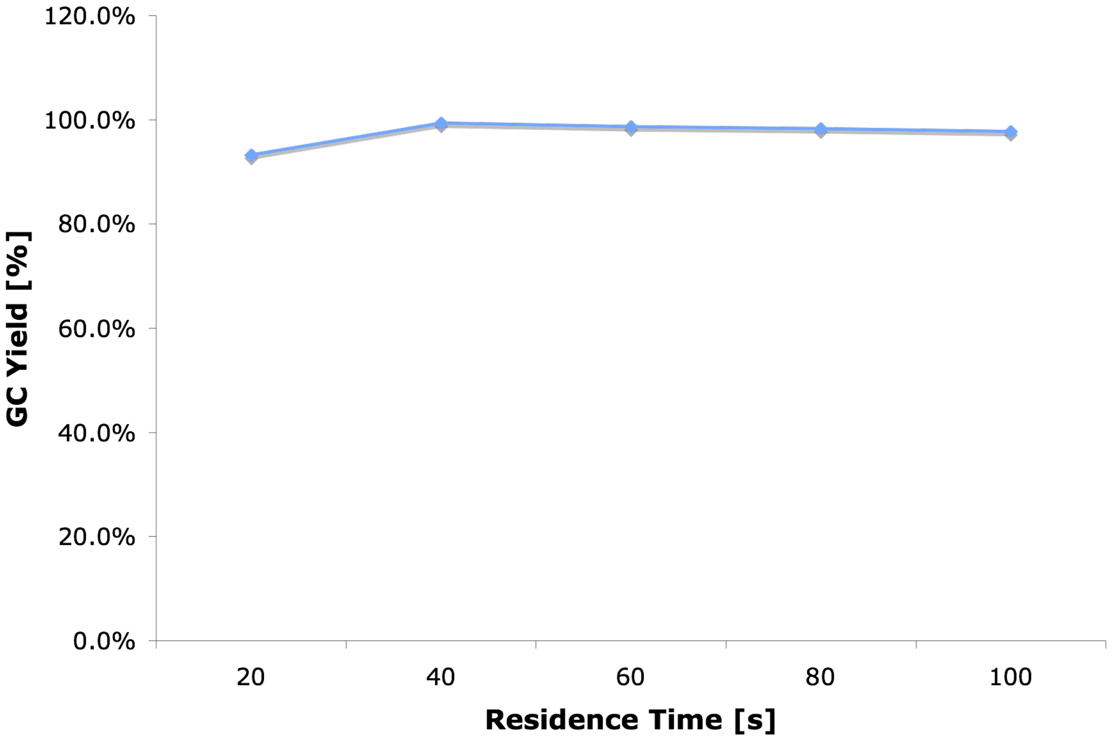
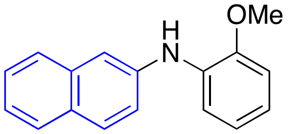


Figure 13. Yield of *N*-hexyl-4-methoxyaniline as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 200 seconds (1 mmol, 40 seconds residence time, 600 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethylacetate) to give the title compound as a yellow oil (195.6 mg, 95 %).



***N*-(2-methoxyphenyl)naphthalene-2-amine.** Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (40.8 mg, 0.05 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with 2-naphthyltrifluoromethanesulfonate (2.76 mL, 10 mmol), *o*-anisidine (1.35 mL, 12 mmol) and biphenyl (308.4 mg, 2 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 7 mL, 14 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (400 μL) with the appropriate flow rates to give the different residence times.

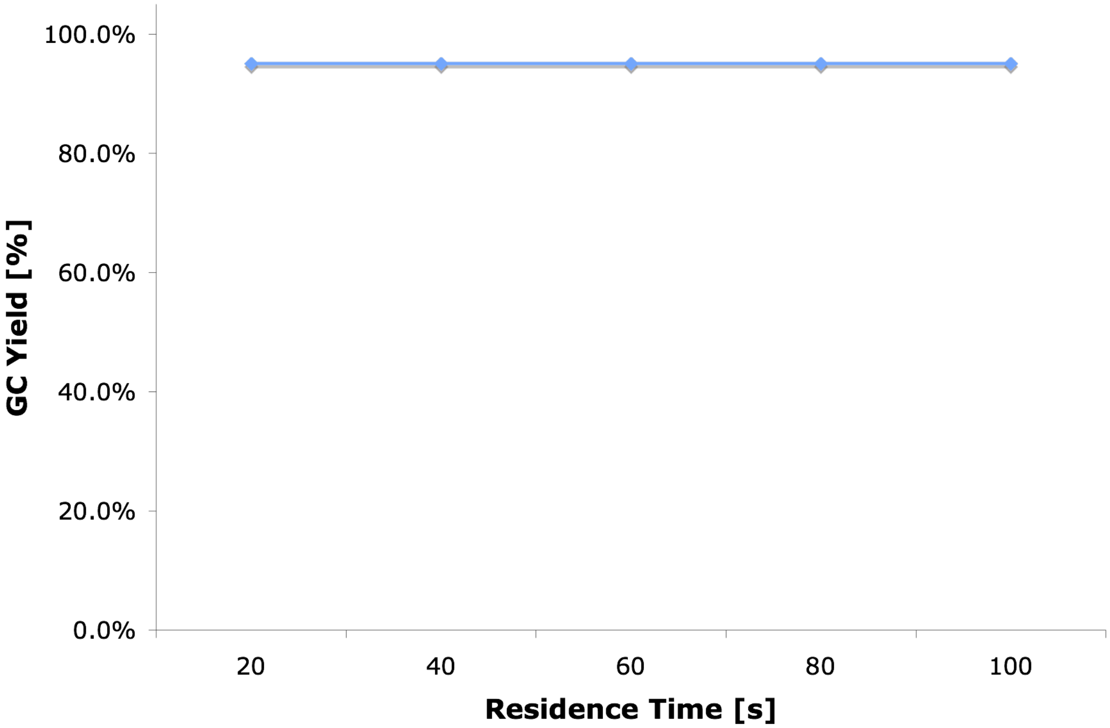
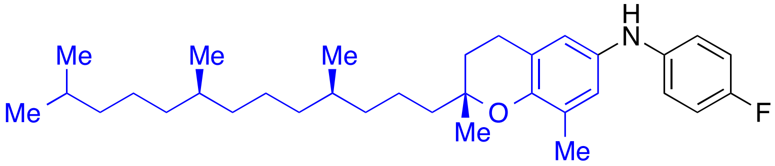


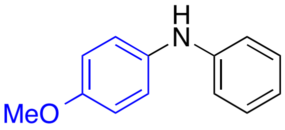
Figure 14. Yield of *N*-(2-methoxyphenyl)naphthalene-2-amine as a function of reaction time with 0.5 mol% catalyst at 60°C.

A sample was collected for 100 seconds (1 mmol, 20 seconds residence time, 1200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as a pink oil (233.8 mg, 94 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.77-7.75 (m, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.46-7.43 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.33-7.29 (m, 2H), 6.97-6.92 (m, 3H), 6.34 (br s, 1H), 3.91 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ: 148.6, 140.5, 134.8, 132.8, 129.4, 129.2, 127.8, 126.7, 126.5, 123.6, 121.0, 120.9, 120.5, 115.3, 112.3, 110.7, 55.8 ppm. IR (neat, cm^{-1}): 3407, 3049, 1631, 1595, 1526, 1506, 1462, 1246, 1223, 743. Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06. Found: C, 81.80; H, 6.05.



(2*R*, 4'*R*, 8'*R*)-*N*-(4-fluorophenyl)-δ-tocopheramine. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (5 mL solution) was loaded with BrettPhos precatalyst **2** (20.4 mg, 0.025 mmol) dissolved in THF. A second syringe (5 mL solution) was loaded with *δ*-tocopheryltrifluoromethanesulfonate (2.67 g, 5 mmol) and 4-fluoroaniline (0.575 mL, 6 mmol) dissolved in THF. A third syringe (10 mL solution) was loaded with sodium *tert*-butoxide solution (2 M in THF, 3.5 mL, 7 mmol) in THF. These syringes were fitted to syringe pumps as described in Figure 1. A sample was collected for 300 seconds (2 mmol, 30 seconds residence time, 800 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as a green oil (892.0 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90-6.80 (m, 4H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 5.23 (br s, 1H), 2.71-2.63 (m, 2H), 2.11 (s, 3H), 1.82-1.66 (m, 2H), 1.58-1.02 (m, 24 H), 0.85-0.81 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 155.8, 147.9, 141.9, 134.6, 127.4, 121.4, 121.4, 118.7, 117.5, 117.4, 115.9, 115.7, 76.0, 40.2, 39.5, 37.6, 37.6, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.6, 24.4, 22.9, 22.8, 22.7, 21.2, 19.9, 19.8, 16.3 ppm. IR (neat, cm^{-1}): 3393, 2926, 2867, 1608, 1509, 1480, 1378, 1215, 1152, 823. Anal. Calcd. for $C_{33}H_{50}FNO$: C, 79.95; H, 10.17. Found: C, 80.12; H, 10.22.

12. Experimental Procedures for Examples Described in Table 4.



4-methoxy-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (10 mL solution) was loaded with BrettPhos precatalyst **2** (23.3 mg, 28.6 μmol) and BrettPhos **1** (15.3 mg, 28.6 μmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with 4-chloroanisole (1.75 mL, 14.3 mmol), aniline (1.56 mL, 17.1 mmol) and biphenyl (440.7 mg, 2.86 mmol) dissolved in dioxane. A third syringe (20 mL solution) was loaded with sodium *tert*-butoxide (2.64 g, 22 mmol) in dioxane. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (800 μL) with the appropriate flow rates to give the different residence times.

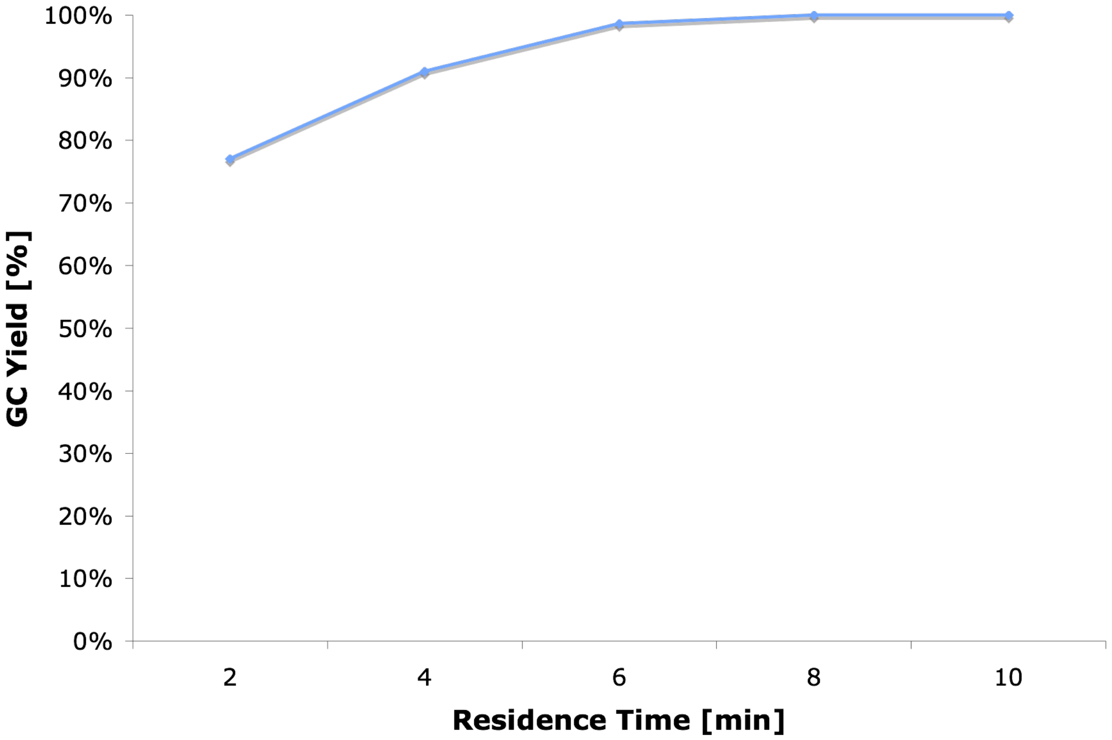
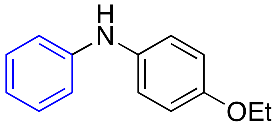


Figure 15. Yield of 4-methoxy-*N*-phenylaniline as a function of reaction time with 0.2 mol% catalyst at 90°C.

A sample was collected for 21 minutes (1 mmol, 6 minutes residence time, 133.33 µL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethylacetate) to give the title compound as an off-white solid (196.0 mg, 98 %).



4-ethoxy-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (10 mL solution) was loaded with BrettPhos precatalyst **2** (23.3 mg, 28.6 µmol) and BrettPhos **1** (15.3 mg, 28.6 µmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with chlorobenzene (1.45 mL, 14.3 mmol), *p*-phenitidine (2.21 mL, 17.1 mmol) and biphenyl (440.7 mg, 2.86 mmol) dissolved in dioxane. A third syringe (20 mL solution) was loaded with sodium *tert*-butoxide (2.64 g, 22 mmol) in dioxane. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (800 µL) with the appropriate flow rates to give the different residence times.

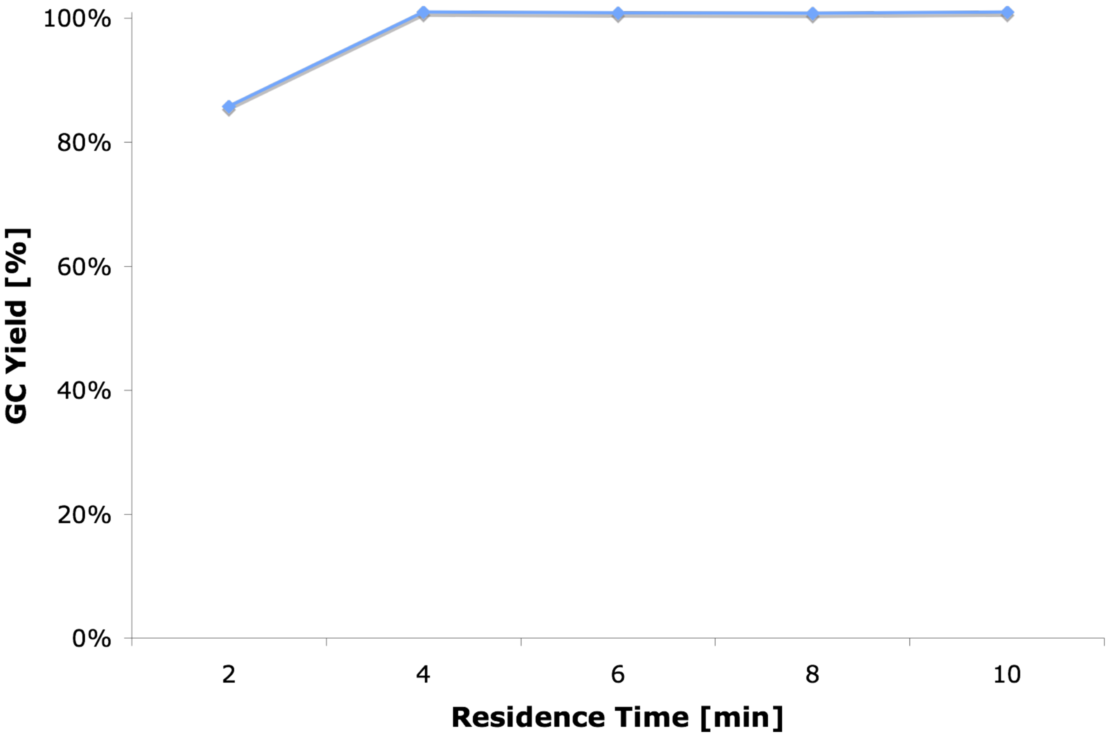
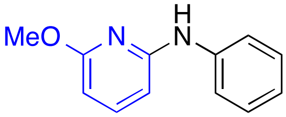


Figure 16. Yield of 4-ethoxy-*N*-phenylaniline as a function of reaction time with 0.2 mol% catalyst at 90°C.

A sample was collected for 14 minutes (1 mmol, 4 minutes residence time, 200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethylacetate) to give the title compound as an grey solid (210.6 mg, 99 %), mp = 70-72 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.22-7.18 (m, 2H), 7.06-7.04 (m, 2H), 6.90-6.80 (m, 5H), 5.48 (br s, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ: 154.7, 145.3, 135.7, 129.4, 122.3, 119.6, 115.7, 115.4, 63.9, 15.1 ppm. IR (neat, cm^{-1}): 3391, 2982, 1594, 1500, 1315, 1296, 1239, 1046, 810, 694. Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.59; H, 7.06.



6-methoxy-*N*-phenylpyridin-2-amine. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (10 mL solution) was loaded with BrettPhos precatalyst **2** (11.7 mg, 14.3 μmol) and BrettPhos **1** (7.7 mg, 14.3 μmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with 2-chloro-6-methoxypyridine (1.70 mL, 14.3 mmol), aniline (1.56 mL, 17.1 mmol) and biphenyl (440.7 mg, 2.86 mmol) dissolved in dioxane. A third syringe (20 mL solution) was loaded with sodium *tert*-butoxide (2.64 g, 22 mmol) in dioxane. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (800 μL) with the appropriate flow rates to give the different residence times.

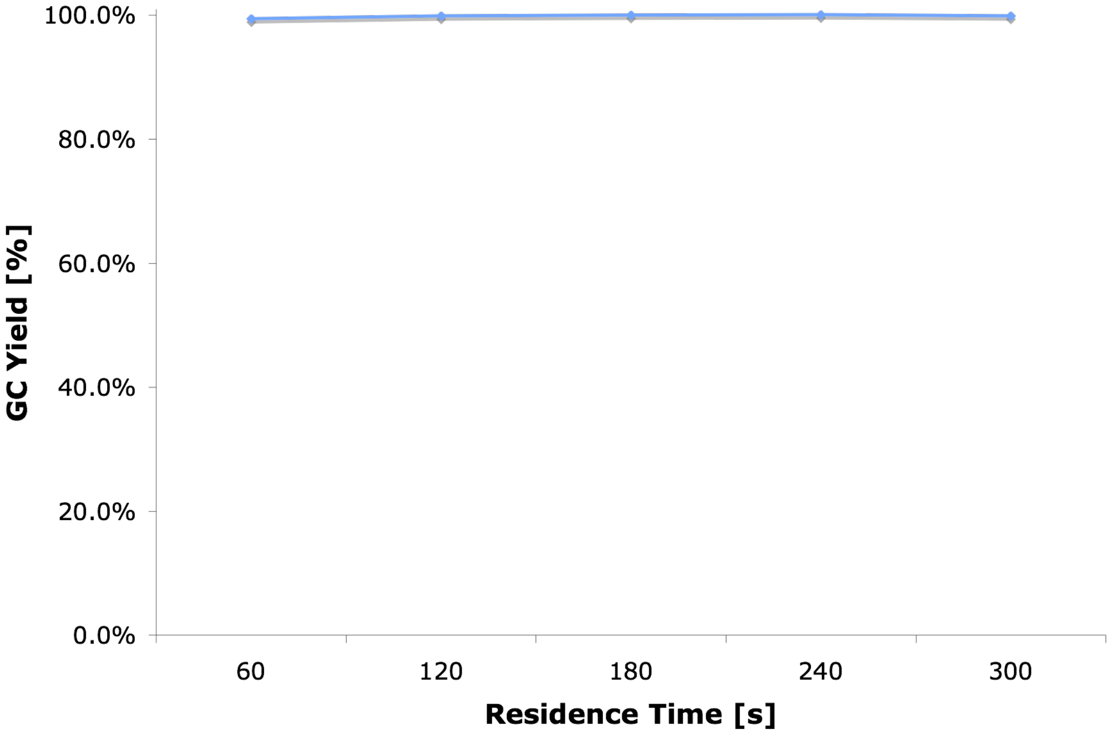
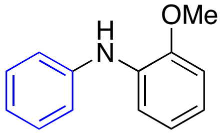


Figure 17. Yield of 6-methoxy-*N*-phenylpyridin-2-amine as a function of reaction time with 0.1 mol% catalyst at 90°C.

A sample was collected for 17.5 minutes (5 mmol, 1 minute residence time, 800 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5% ethyl acetate) to give the title compound as an orange oil (981.2 mg, 98 %).



2-methoxy-*N*-phenylaniline. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (10 mL solution) was loaded with BrettPhos precatalyst **2** (23.3 mg, 28.6 μmol) and BrettPhos **1** (15.3 mg, 28.6 μmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with chlorobenzene (1.45 mL, 14.3 mmol), *o*-anisidine (1.93 mL, 17.1 mmol) and biphenyl (440.7 mg, 2.86 mmol) dissolved in dioxane. A third syringe (20 mL solution) was loaded with sodium *tert*-butoxide (2.64 g, 22 mmol) in dioxane. These syringes were fitted to syringe pumps as described in Figure

1. The reagents were flowed through the reactor (800 μL) with the appropriate flow rates to give the different residence times.

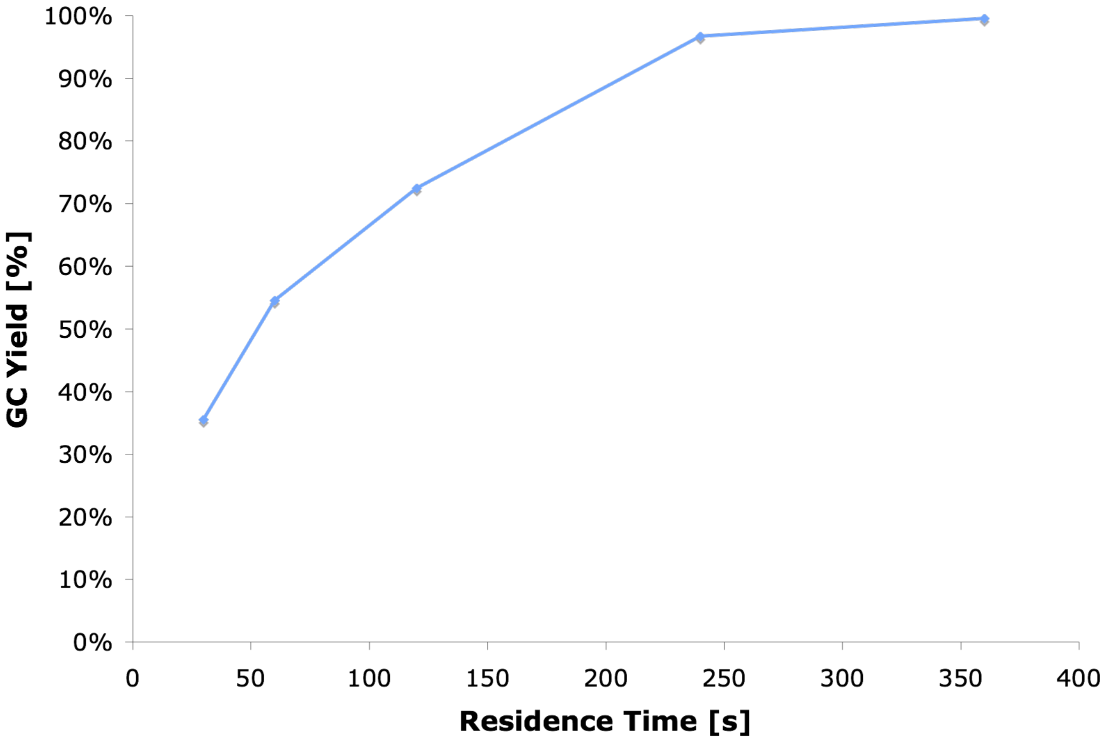
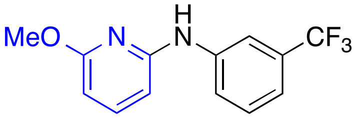


Figure 18. Yield of 2-methoxy-*N*-phenylaniline as a function of reaction time with 0.2 mol% catalyst at 90°C.

A sample was collected for 21 minutes (1 mmol, 6 minutes residence time, 133.33 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 0-5% ethylacetate) to give the title compound as an colorless oil (196.4 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.29 (m, 3H), 7.18 (dd, *J* = 1.0, 8.0 Hz, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.94-6.87 (m, 3H), 6.19 (br s, 1H), 3.92 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 142.9, 133.1, 129.4, 121.3, 121.0, 120.0, 118.7, 114.8, 110.7, 55.8 ppm. IR (neat, cm^{-1}): 3409, 1592, 1518, 1496, 1464, 1246, 1116, 1027, 741, 694. $C_{14}H_{15}NO$: C, 78.36; H, 6.58. Found: C, 78.26; H, 6.56.



6-methoxy-*N*-(3-(trifluoromethyl)phenyl)pyridin-2-amine. Following the typical procedure for GC Yields-Residence Time plots, a first syringe (10 mL solution) was loaded with BrettPhos precatalyst **2** (23.3 mg, 28.6 μmol) and BrettPhos **1** (15.3 mg, 28.6

μmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with 2-chloro-6-methoxypyridine (1.7 mL, 14.3 mmol), 3-(trifluoromethyl)aniline (2.10 mL, 17.1 mmol) and biphenyl (440.7 mg, 2.86 mmol) dissolved in dioxane. A third syringe (20 mL solution) was loaded with sodium *tert*-butoxide (2.64 g, 22 mmol) in dioxane. These syringes were fitted to syringe pumps as described in Figure 1. The reagents were flowed through the reactor (800 μL) with the appropriate flow rates to give the different residence times.

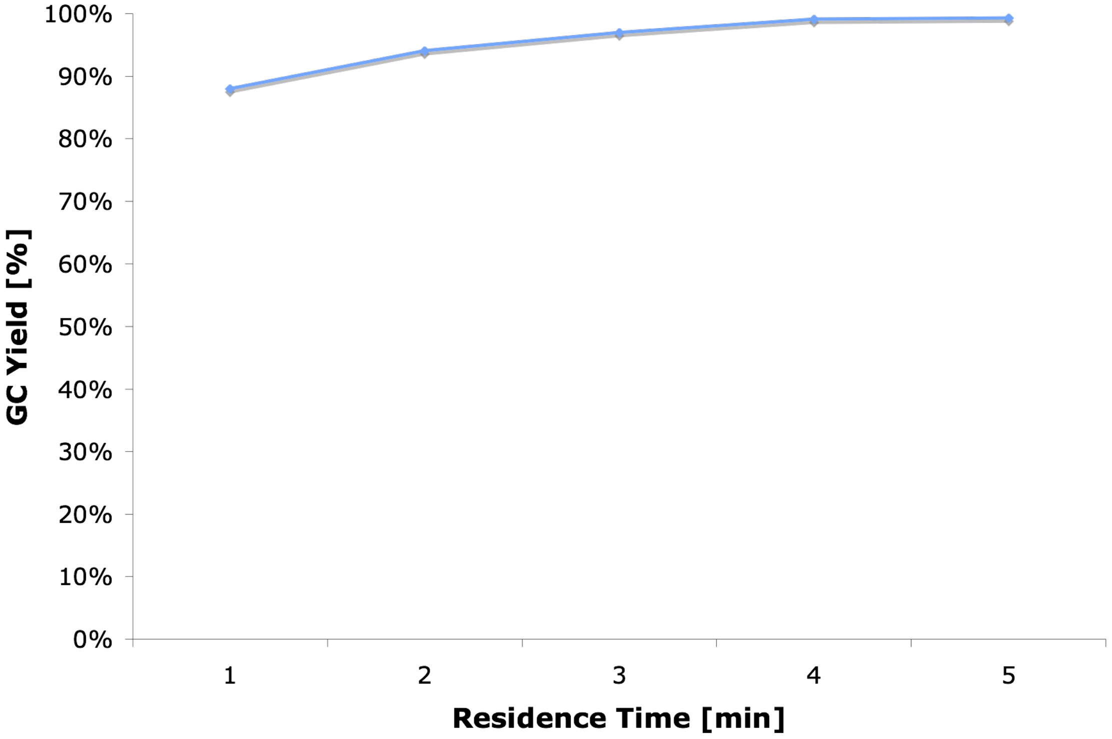


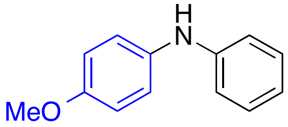
Figure 19. Yield of 6-methoxy-*N*-(3-(trifluoromethyl)phenyl)pyridin-2-amine as a function of reaction time with 0.2 mol% catalyst at 90°C.

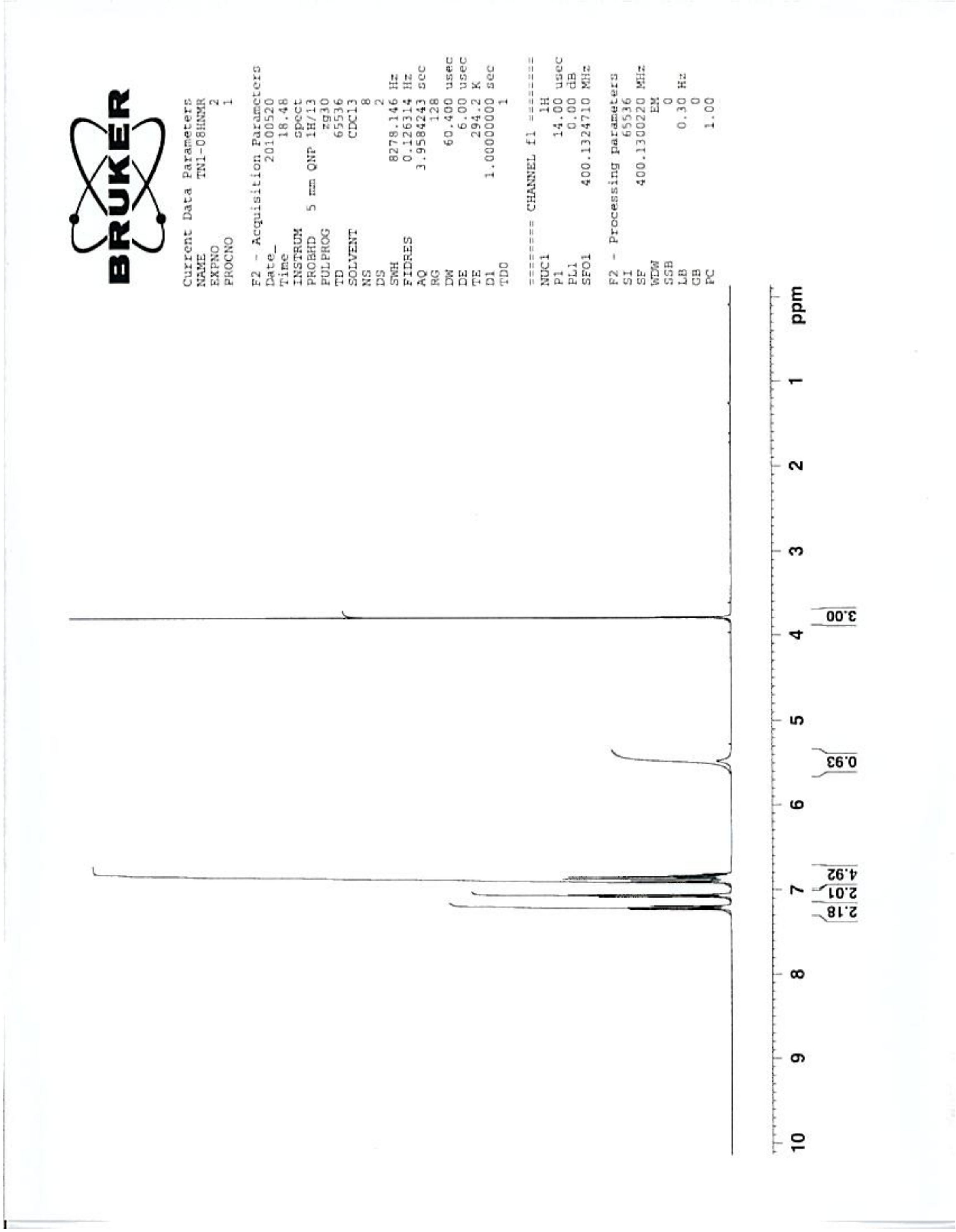
A sample was collected for 14 minutes (1 mmol, 4 minutes residence time, 200 μL/min total flow rate). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes and 5-10% ethylacetate) to give the title compound as an yellowish oil (261.8 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.47-7.37 (m, 3H), 7.22 (d, J = 7.5 Hz, 1H), 6.49 (br s, 1H), 6.31 (d, J = 7.9 Hz, 1H), 6.27 (d, J = 7.9 Hz, 1H), 3.94 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 153.6, 141.5, 140.4, 131.5 (q, J = 32.0 Hz), 129.6, 124.4 (q, J = 272.3 Hz), 121.8, 118.2 (q, J = 3.8 Hz), 115.6 (q, J = 4.0 Hz), 101.4, 101.0, 53.7 ppm. IR (neat, cm^{-1}): 3383, 1613, 1586, 1532, 1456, 1439, 1332, 1275, 1164, 1123. $C_{14}H_{15}NO$: C, 58.21; H, 4.13. Found: C, 58.46; H, 4.13.

13. References:

[1] B.P. Fors, D.A. Watson, M.R. Biscoe, S.L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554.
[2] F. Mazzini, T. Netscher, P. Salvadori, *Eur. J. Org. Chem.* **2009**, *2009*, 2063-2068.
[3] M.R. Biscoe, B.P, Fors, S.L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687.

14. ^{1}H NMR and ^{13}C NMR spectra:





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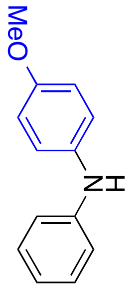

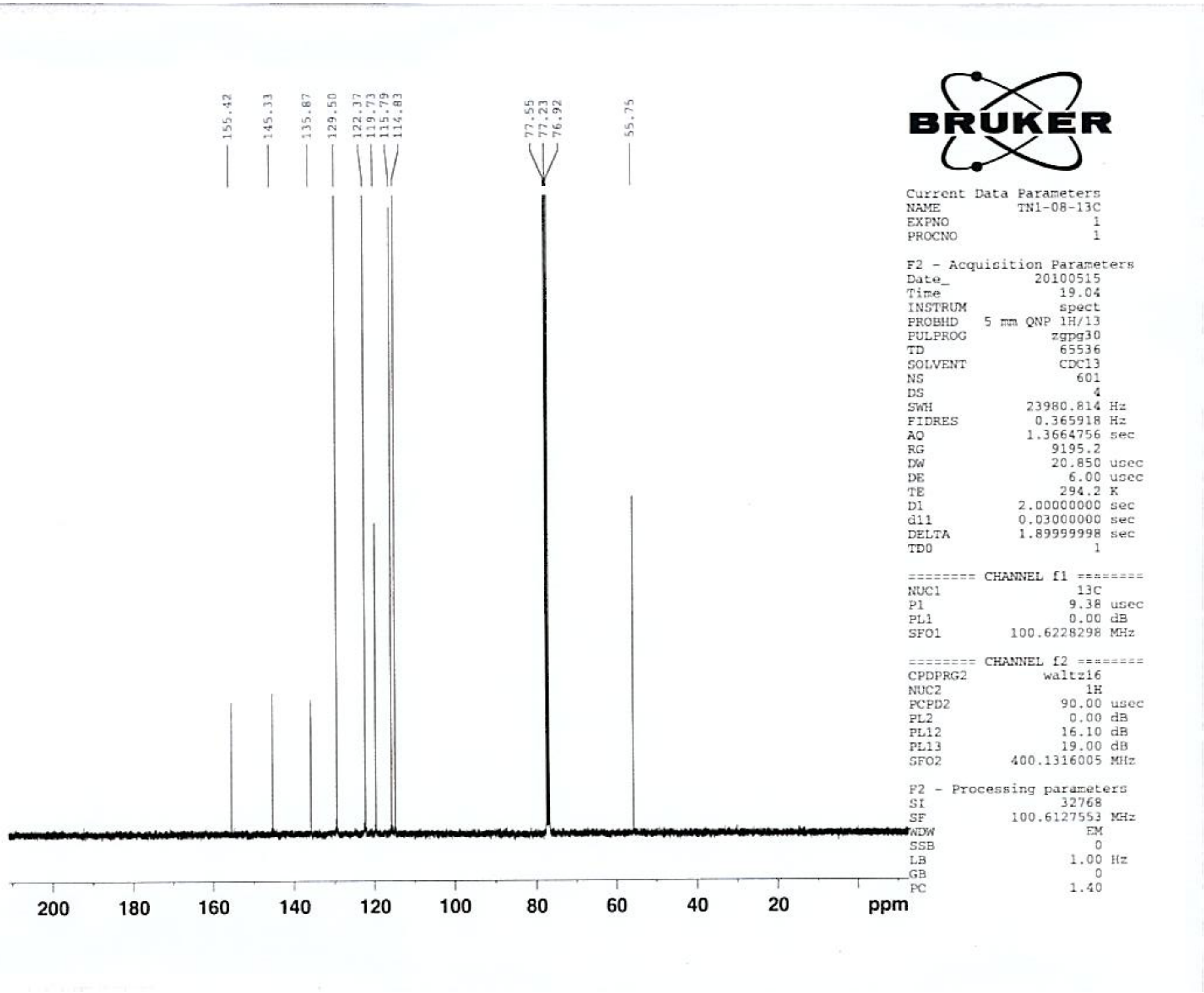

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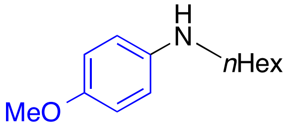

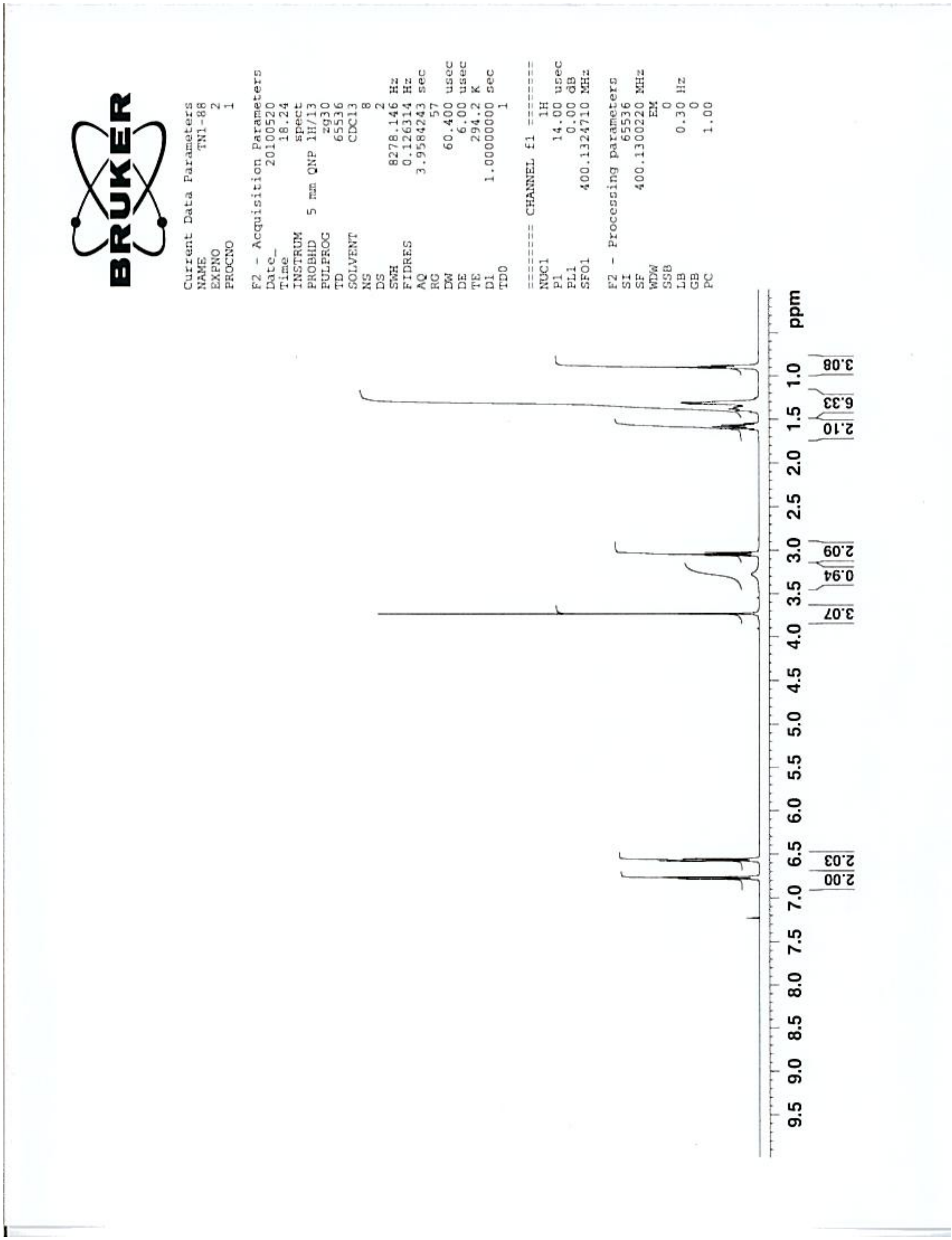

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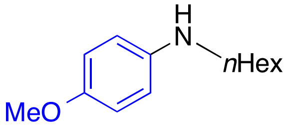

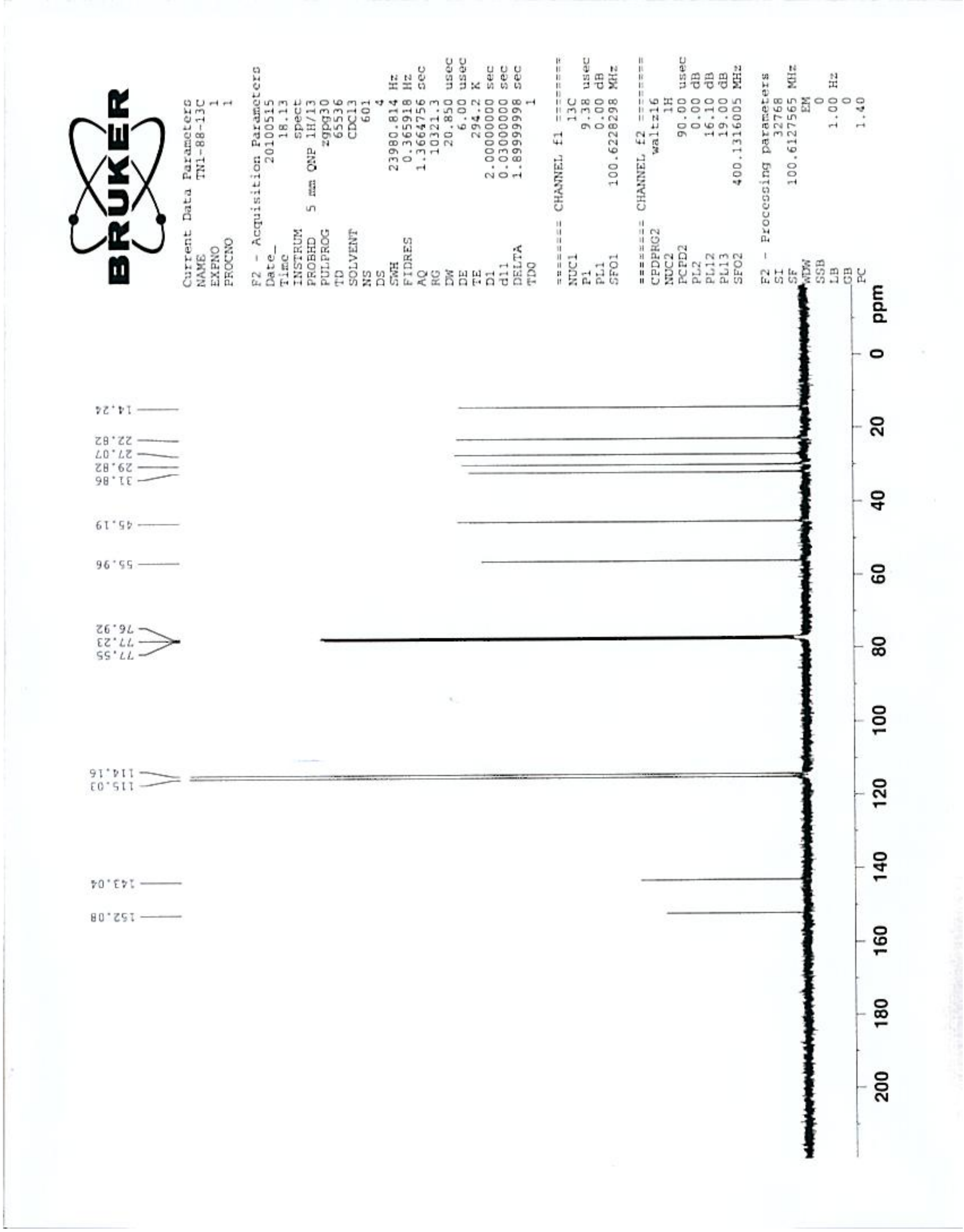

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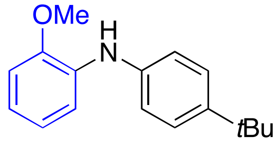

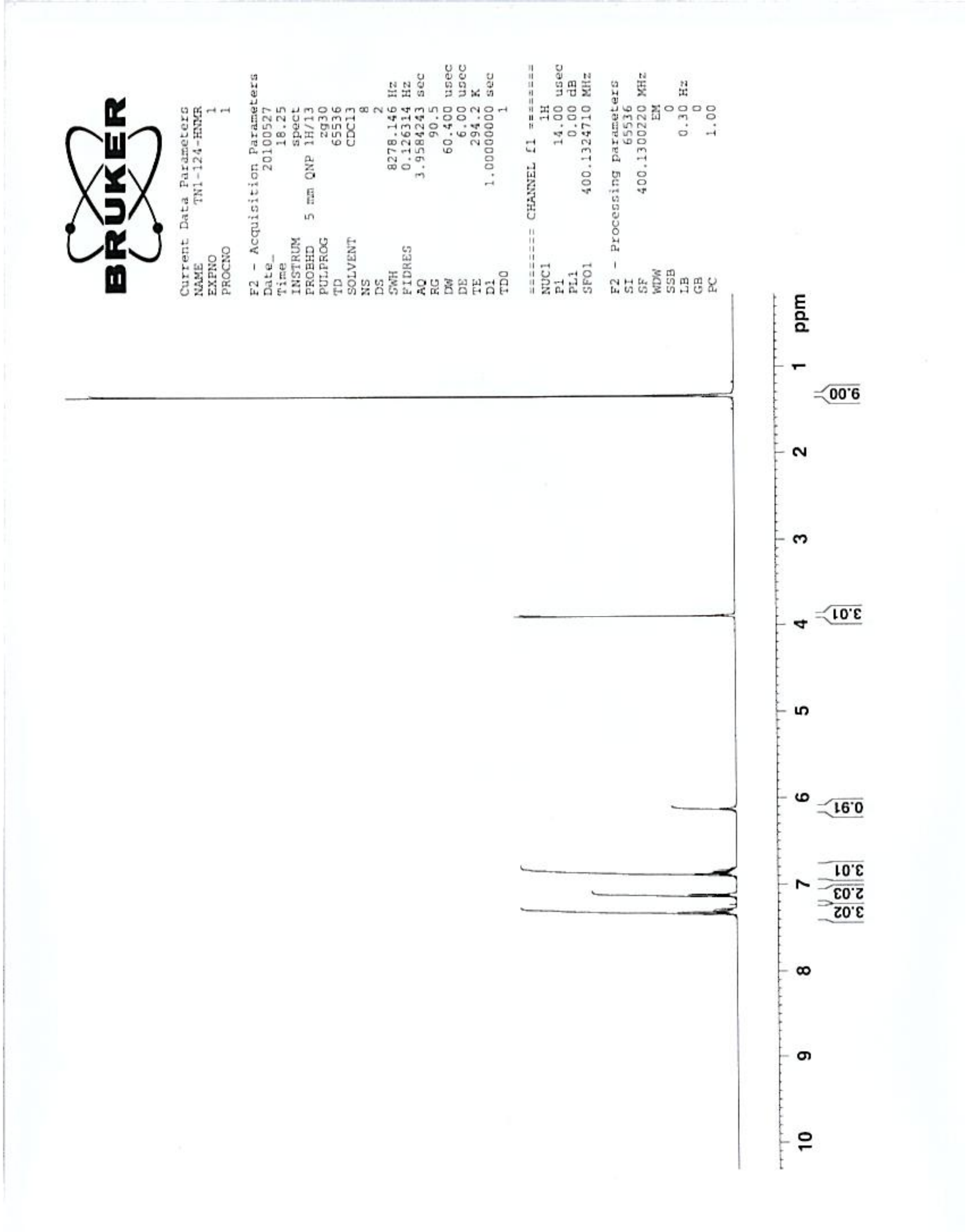

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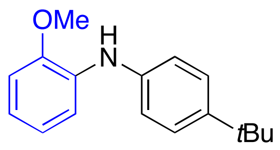

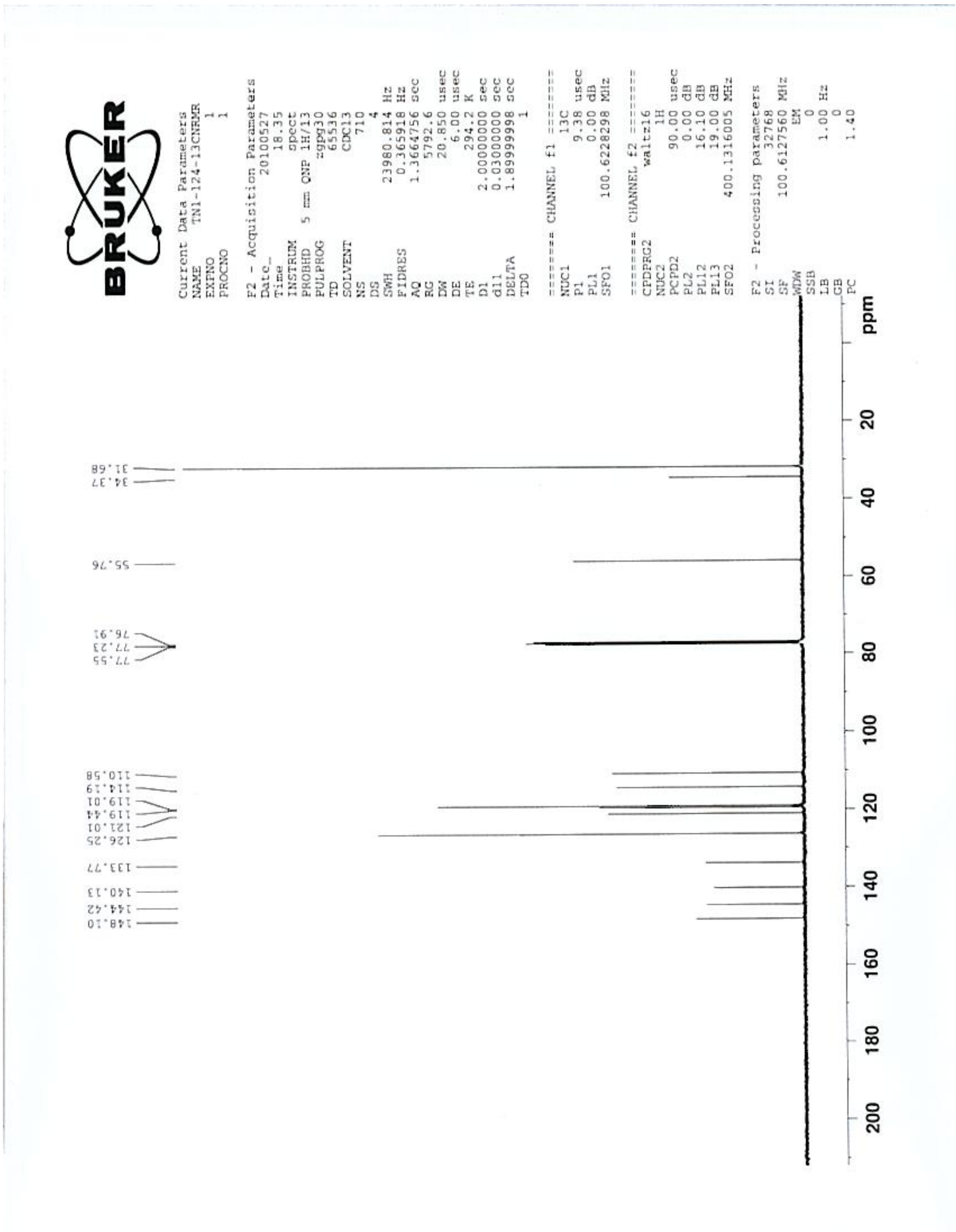

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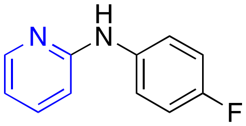
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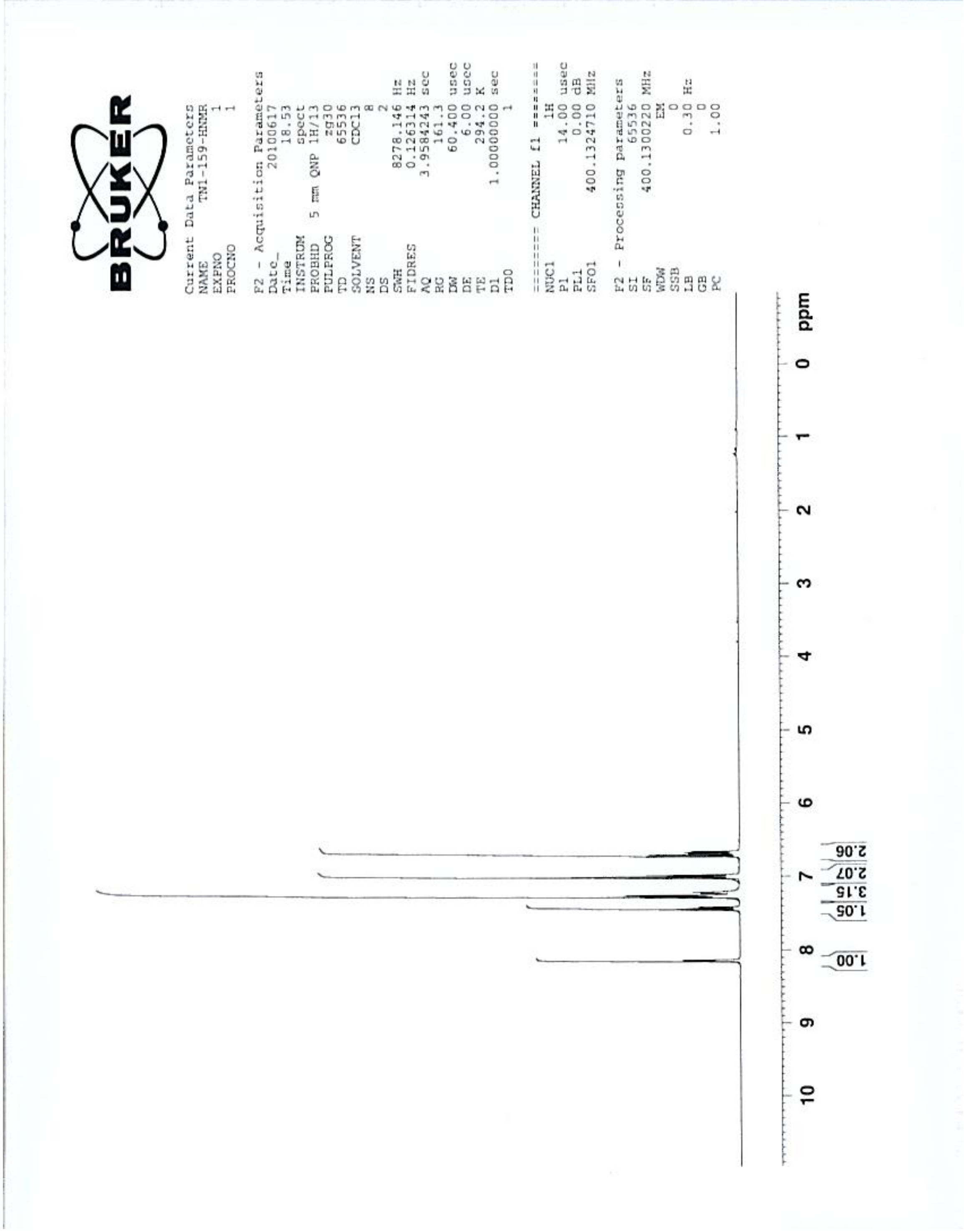
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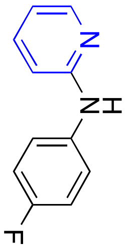

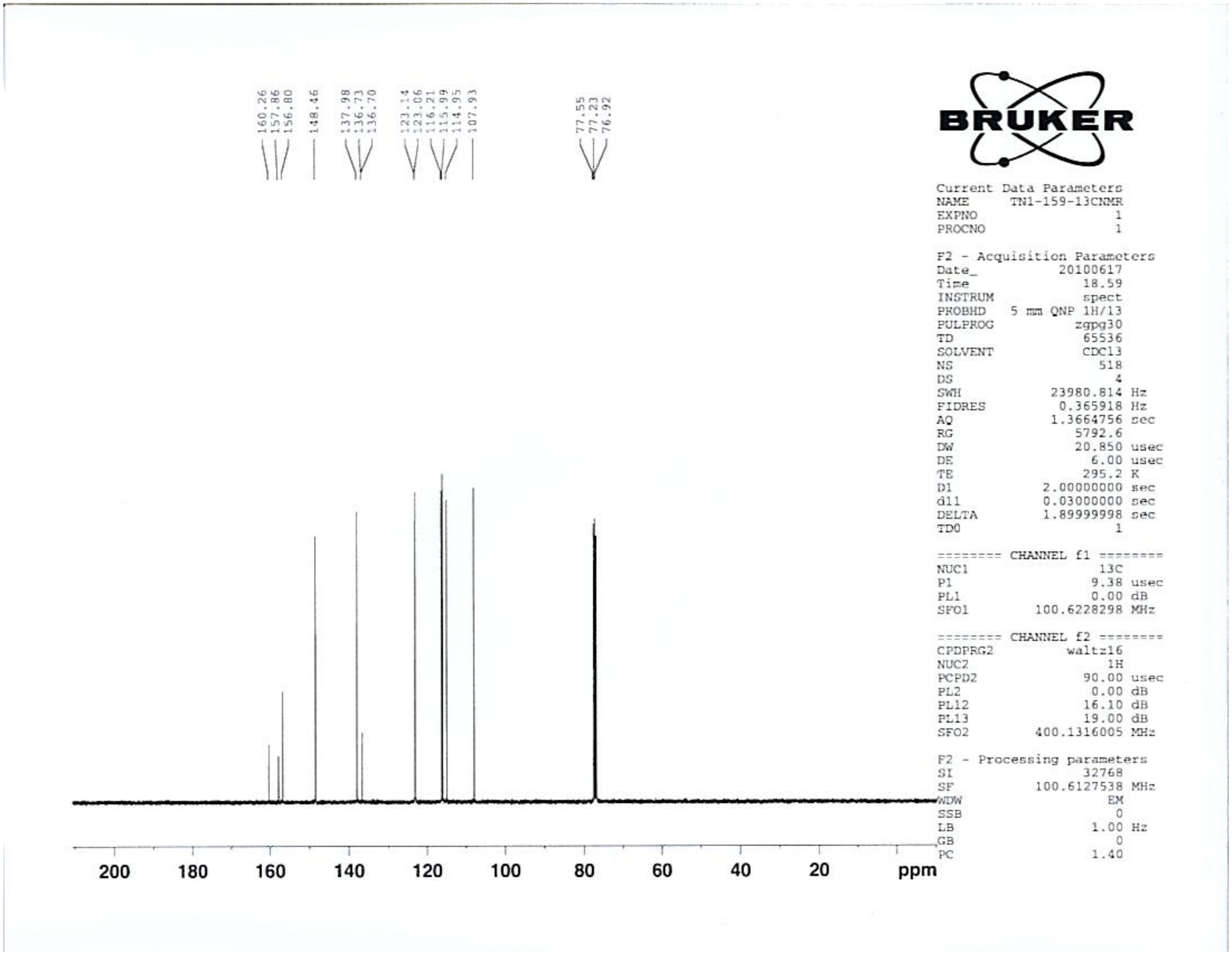

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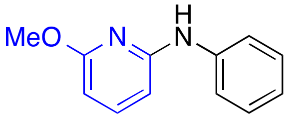
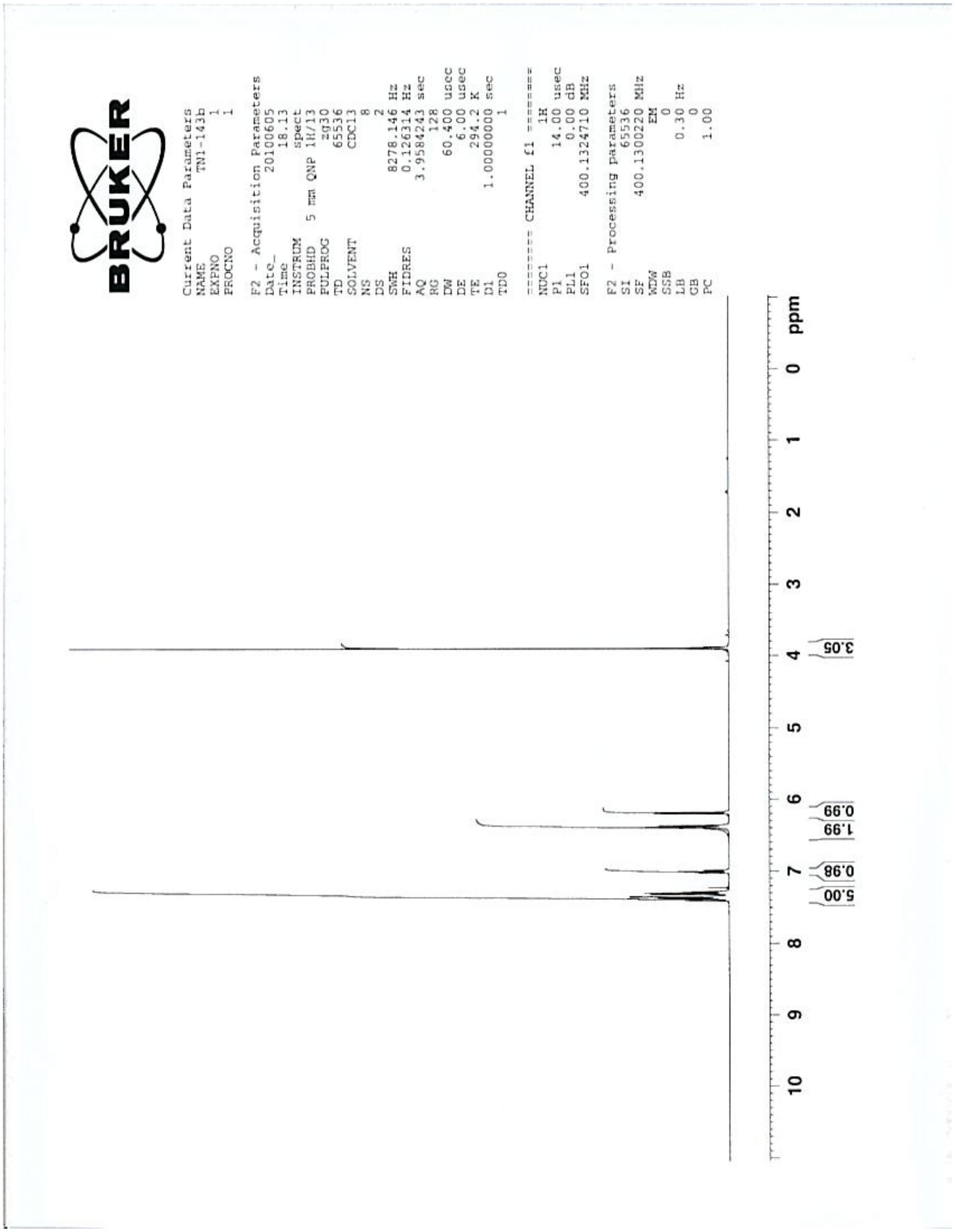
NUC2                 1H
PCPD2             90.00 usec
PL2                0.00 dB
PL12              16.10 dB
PL13              19.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127538 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



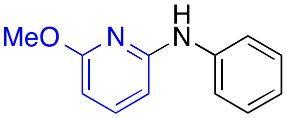


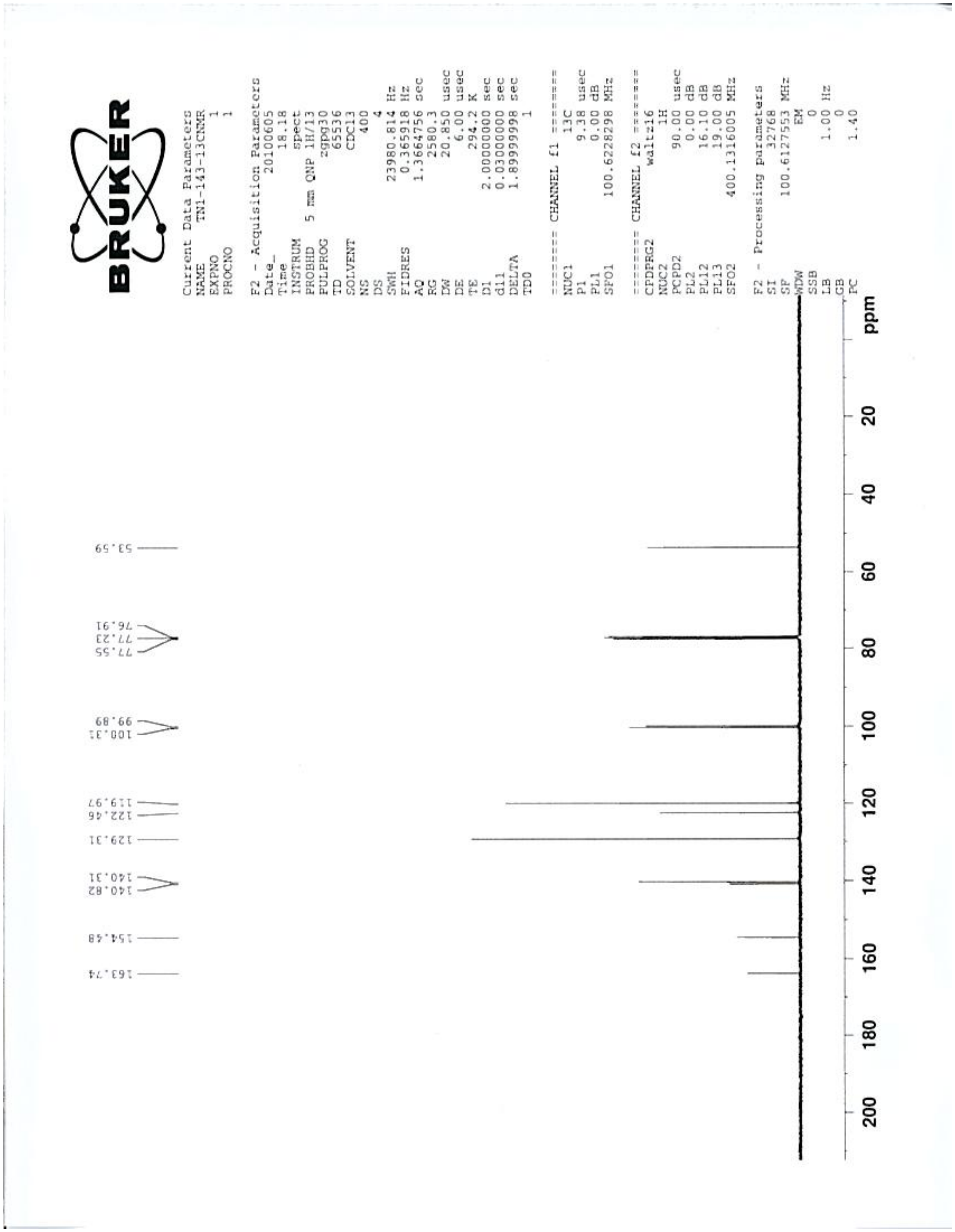
```
Current Data Parameters
NAME            TN1-143b
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100605
Time               18.13
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                   128
DW                60.400 usec
DE                  6.00 usec
TE                 294.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300220 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```





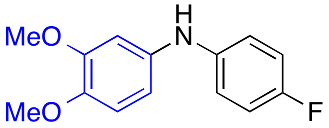
```
Current Data Parameters
NAME     TN1-143-13CNMR
EXPNO                 1
PROCNO                1

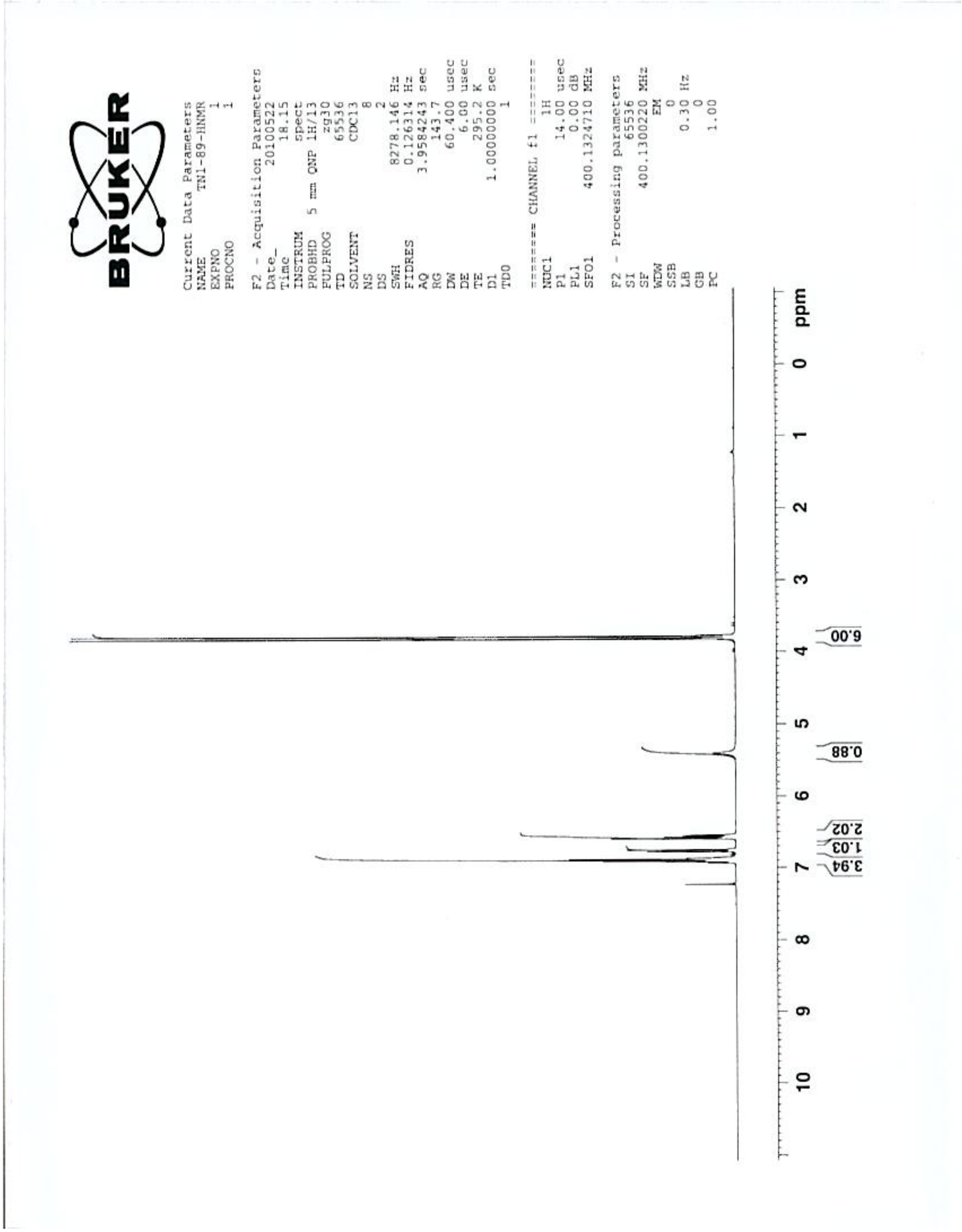
F2 - Acquisition Parameters
Date_          20100605
Time              18.18
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  400
DS                    4
SWH           23980.814 Hz
FIDRES         0.365918 Hz
AQ            1.3664756 sec
RG               2580.3
DW               20.850 usec
DE                 6.00 usec
TE                294.2 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.38 usec
PL1                0.00 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             90.00 usec
PL2                0.00 dB
PL12              16.10 dB
PL13              19.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127553 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



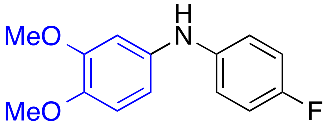


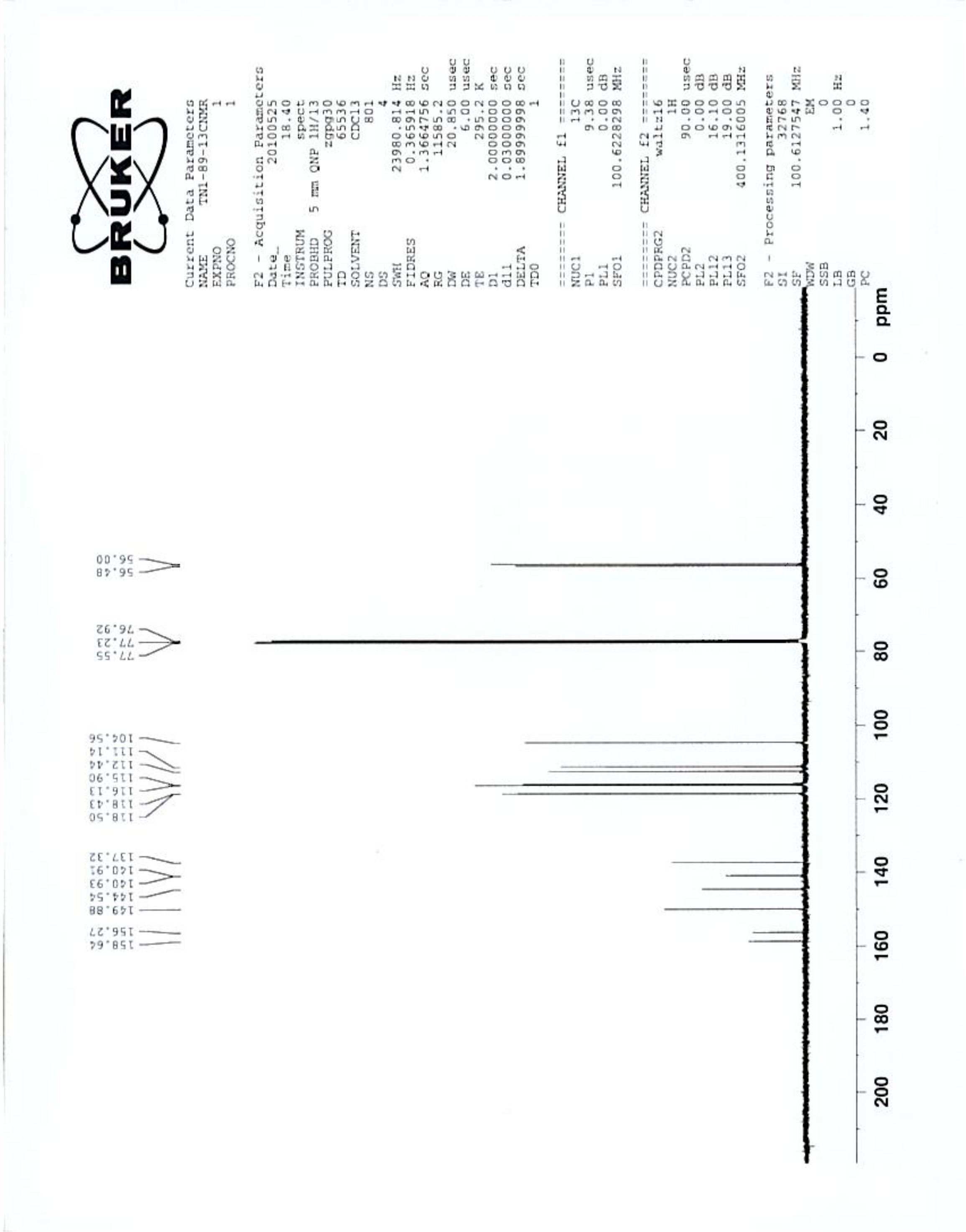
```
Current Data Parameters
NAME         TN1-89-HNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100522
Time               18.15
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                 143.7
DW                60.400 usec
DE                  6.00 usec
TE                 295.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300220 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```





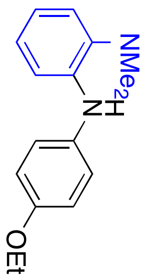
```
Current Data Parameters
NAME        TN1-89-13CNMR
EXPNO                   1
PROCNO                  1

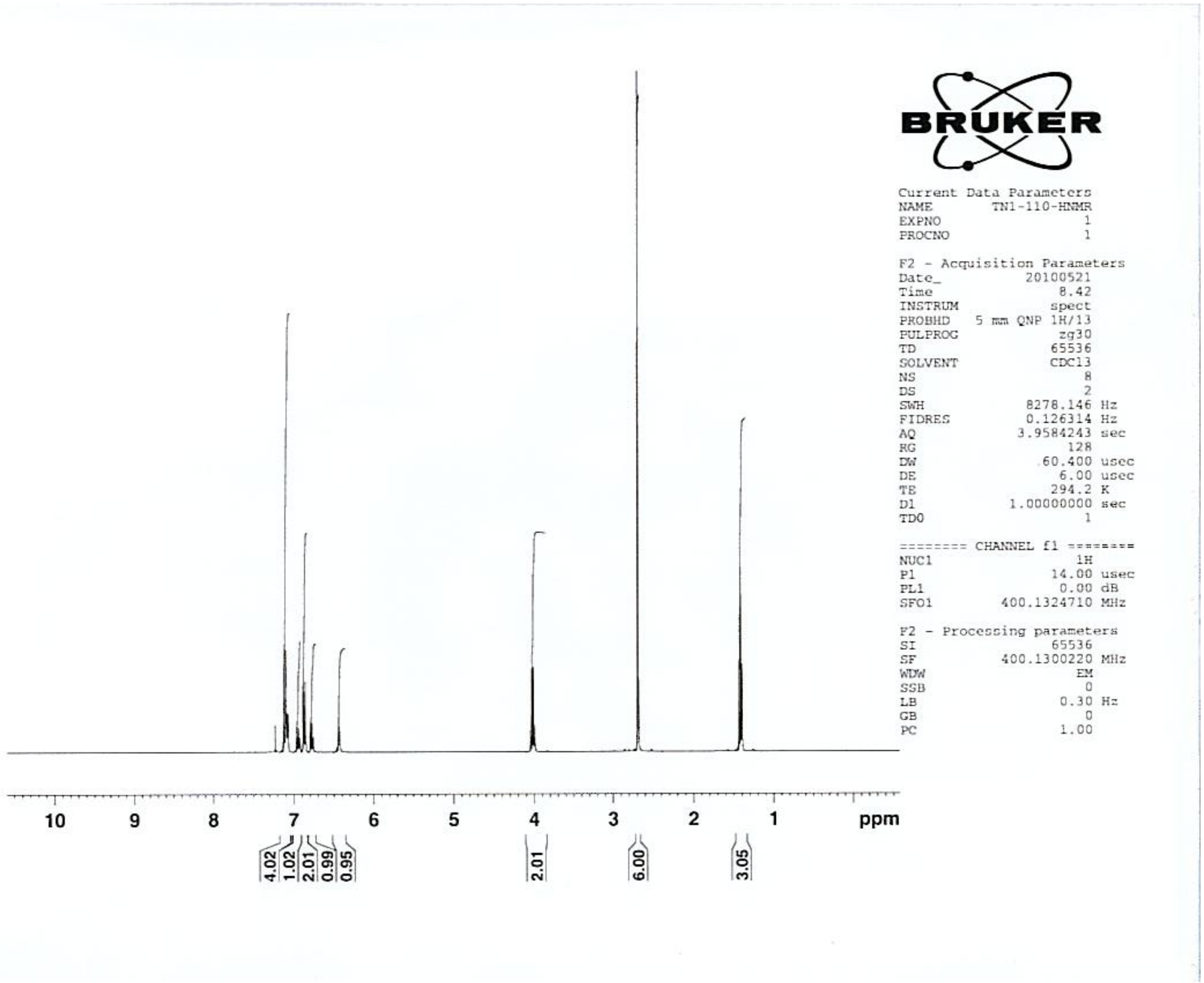
F2 - Acquisition Parameters
Date_            20100525
Time                18.40
INSTRUM             spect
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    801
DS                      4
SWH             23980.814 Hz
FIDRES           0.365918 Hz
AQ              1.3664756 sec
RG                11585.2
DW                 20.850 usec
DE                   6.00 usec
TE                  295.2 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.38 usec
PL1                  0.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               90.00 usec
PL2                  0.00 dB
PL12                16.10 dB
PL13                19.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127547 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



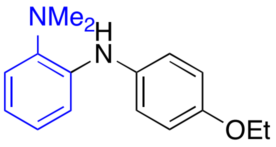


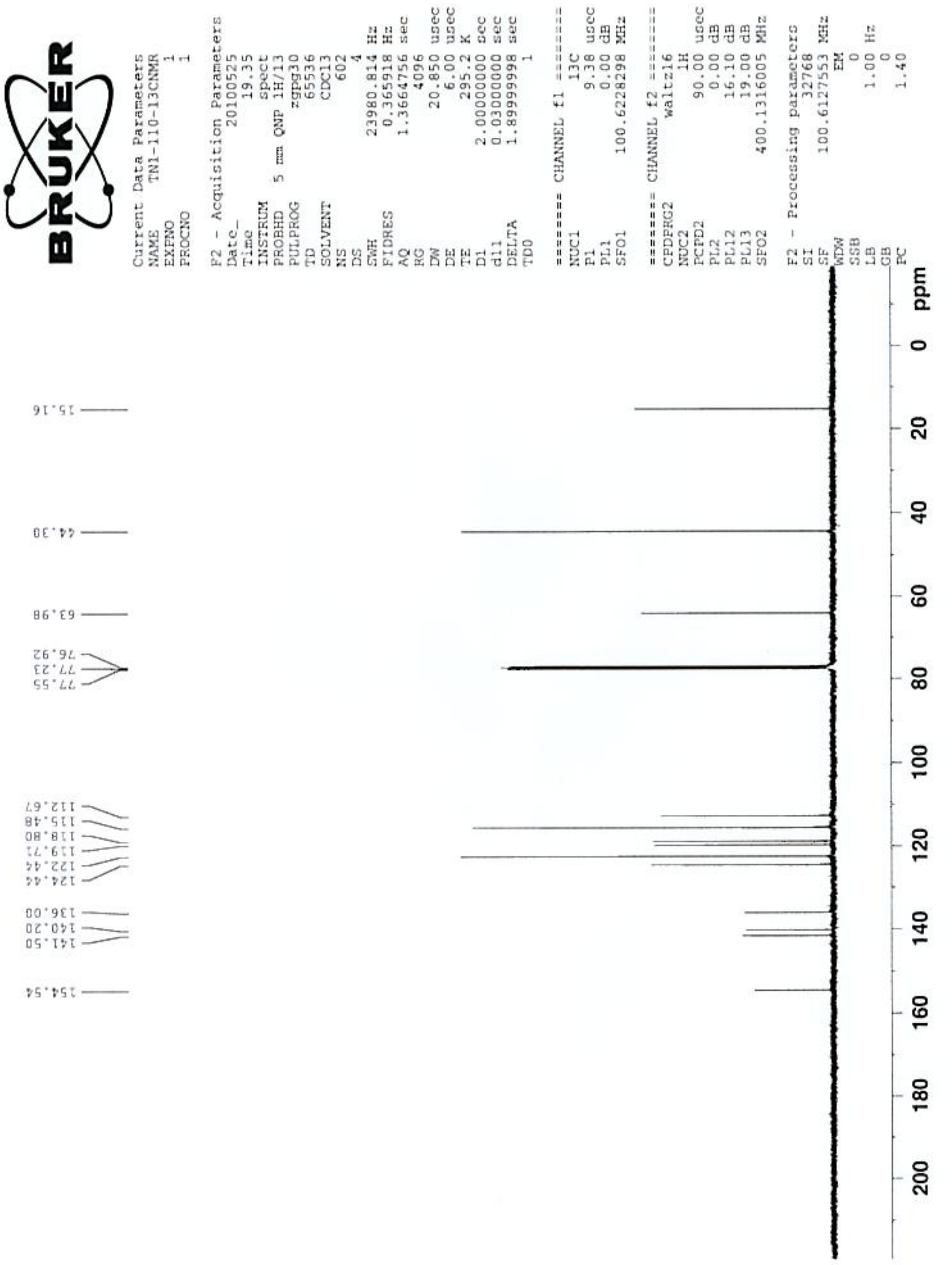
```
Current Data Parameters
NAME          TN1-110-HNMR
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100521
Time                  8.42
INSTRUM              spect
PROBHD   5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       8
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     128
DW                  60.400 usec
DE                    6.00 usec
TE                   294.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                   0.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   65536
SF             400.1300220 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





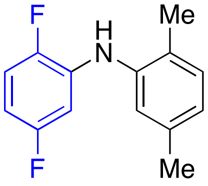
```
Current Data Parameters
NAME       TN1-110-13CNMR
EXPNO                   1
PROCNO                  1

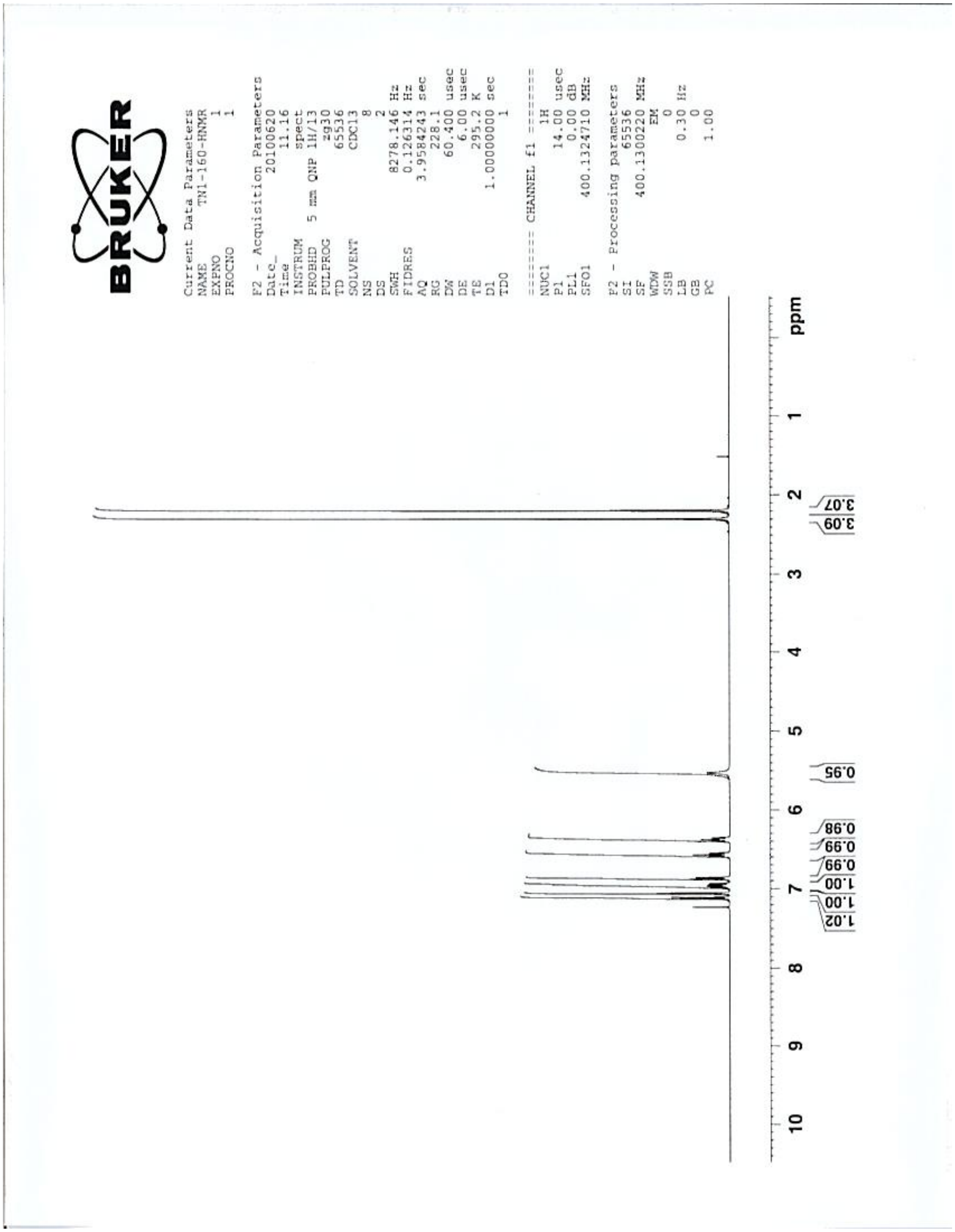
F2 - Acquisition Parameters
Date_            20100525
Time                19.35
INSTRUM             spect
PROBHD    5 mm QNP 1H/13
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    602
DS                      4
SWH             23980.814 Hz
FIDRES           0.365918 Hz
AQ              1.3664756 sec
RG                   4096
DW                 20.850 usec
DE                   6.00 usec
TE                  295.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.38 usec
PL1                  0.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               90.00 usec
PL2                  0.00 dB
PL12                16.10 dB
PL13                19.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127553 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



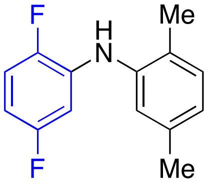


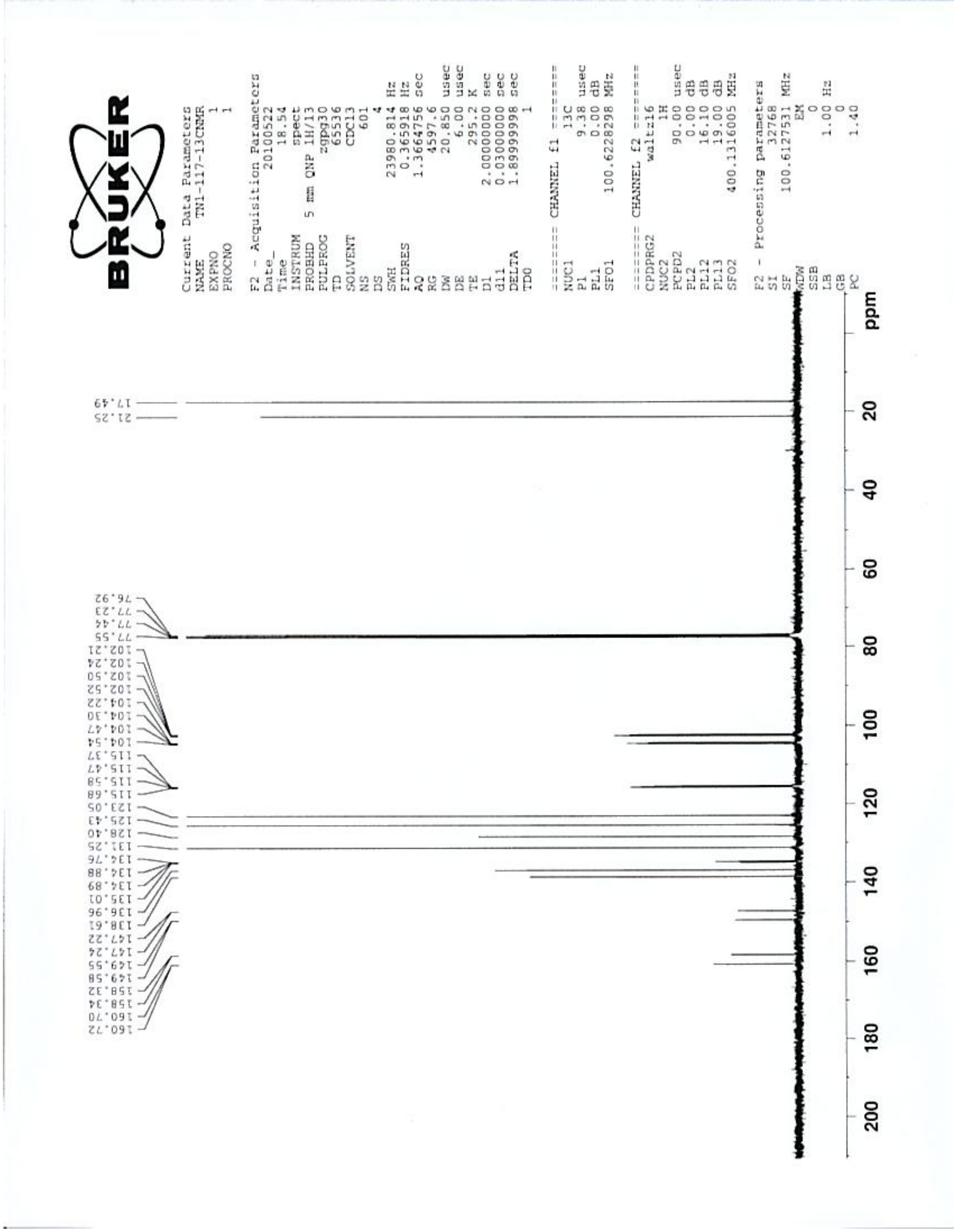
```
Current Data Parameters
NAME          TN1-160-HNMR
EXPNO                    1
PROCNO                   1

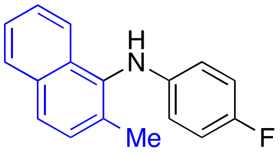
F2 - Acquisition Parameters
Date_             20100620
Time                 11.16
INSTRUM              spect
PROBHD     5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       8
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                   228.1
DW                  60.400 usec
DE                    6.00 usec
TE                   295.2 K
D1             1.00000000 sec
TD0                      1

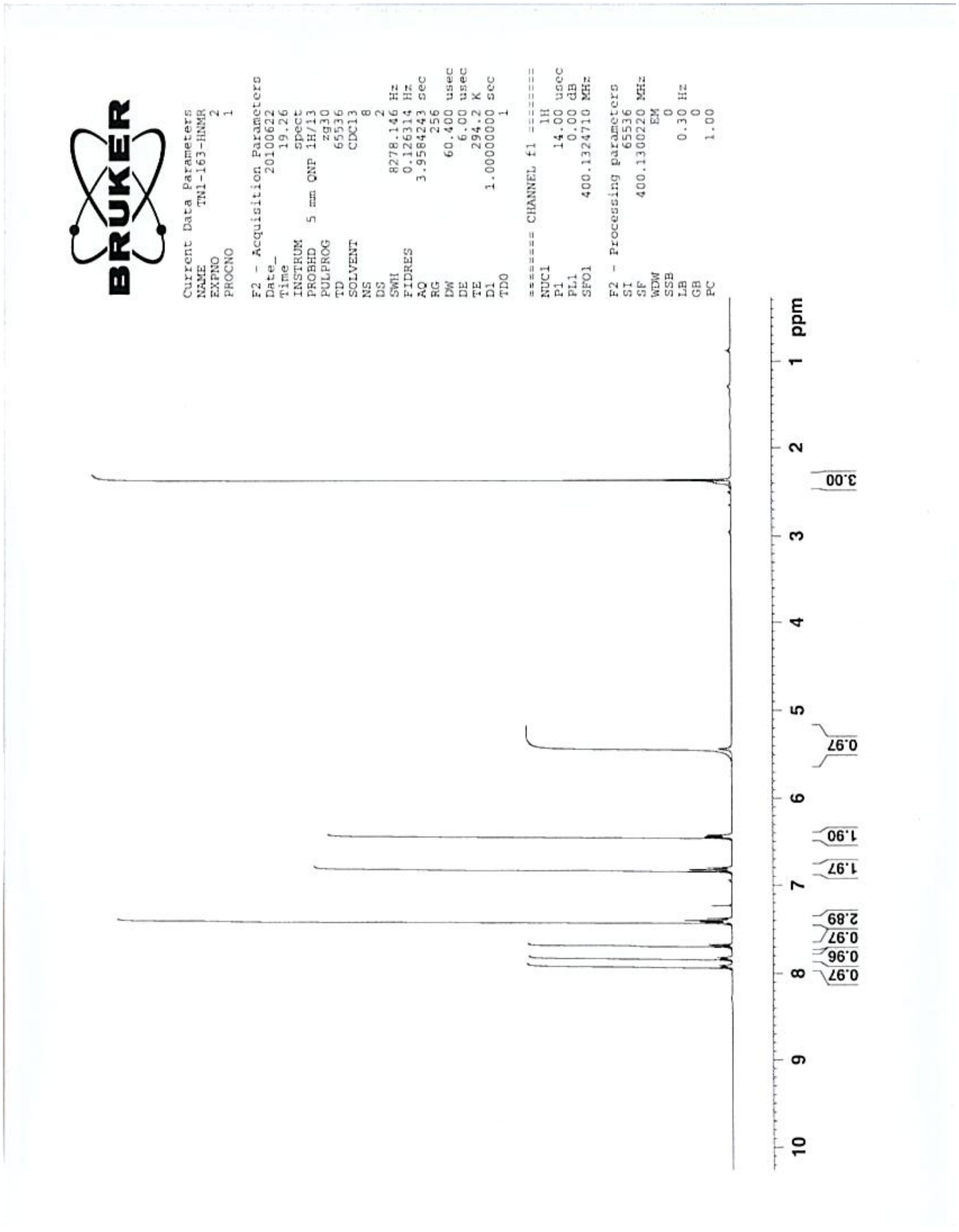
======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                   0.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   65536
SF             400.1300220 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```


F
H
N
Me
F
Me


BRUKER
Current Data Parameters
NAME TN1-117-13CNMR
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100522
Time 18.54
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 601
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 4597.6
DW 20.850 usec
DE 6.00 usec
TE 295.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.38 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 16.10 dB
PL13 19.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127531 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
17.49
21.25
76.92
77.23
77.44
77.55
102.21
102.24
102.50
102.52
104.22
104.30
104.47
104.54
115.37
115.47
115.58
115.68
123.05
125.43
128.40
131.25
134.76
134.88
134.89
135.01
136.96
138.61
147.22
147.24
149.55
149.58
158.32
158.34
160.70
160.72
ppm
20
40
60
80
100
120
140
160
180
200


H
N
Me
F


BRUKER
Current Data Parameters
NAME TN1-163-HNMR
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100622
Time 19.26
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
3.00
0.97
1.90
1.97
2.89
0.97
0.96
0.97
10
9
8
7
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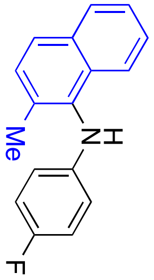
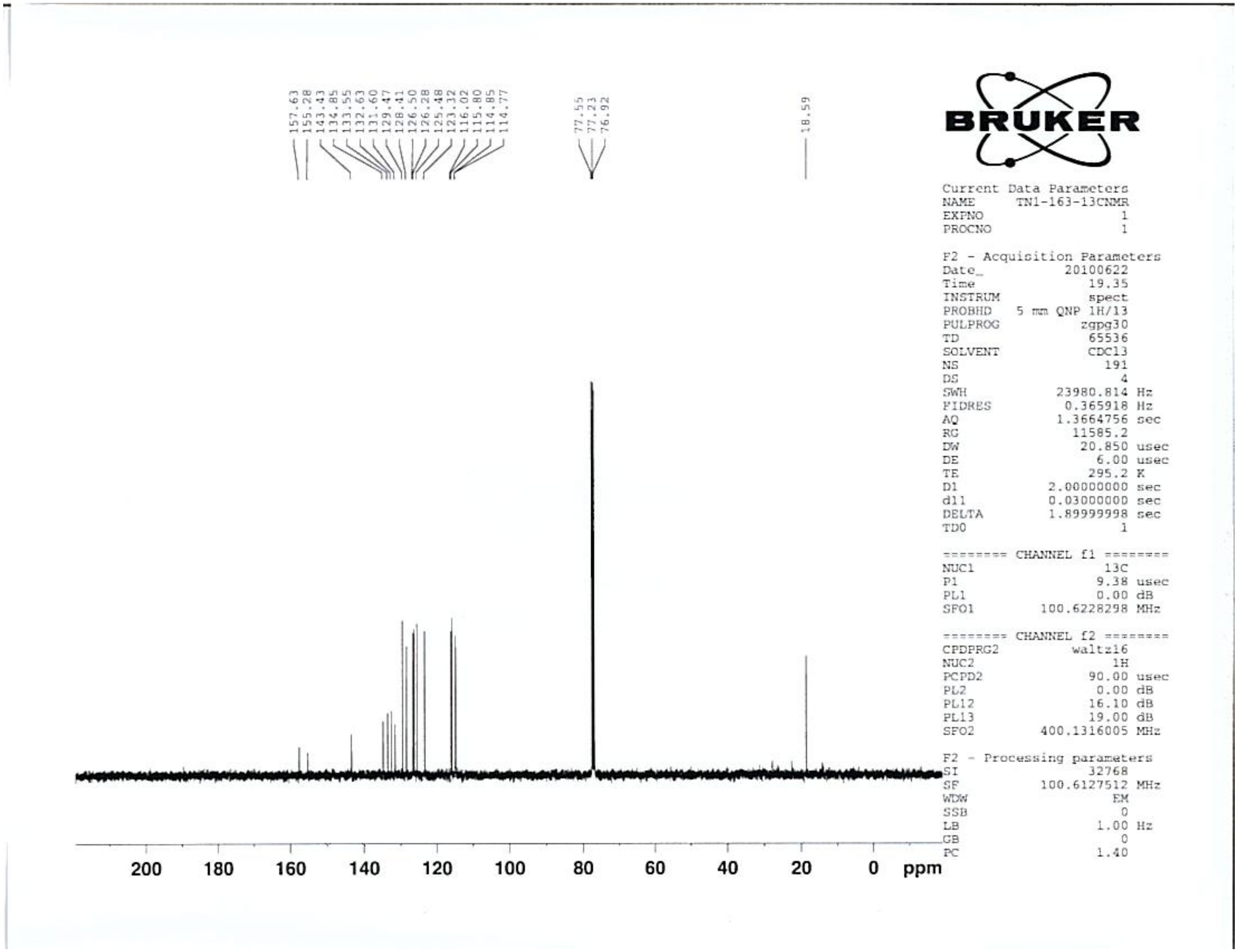
5
4
3
2
1
ppm





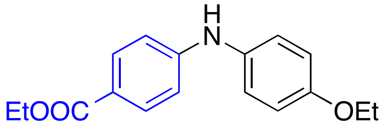
```
Current Data Parameters
NAME      TN1-163-13CNMR
EXPNO                  1
PROCNO                 1

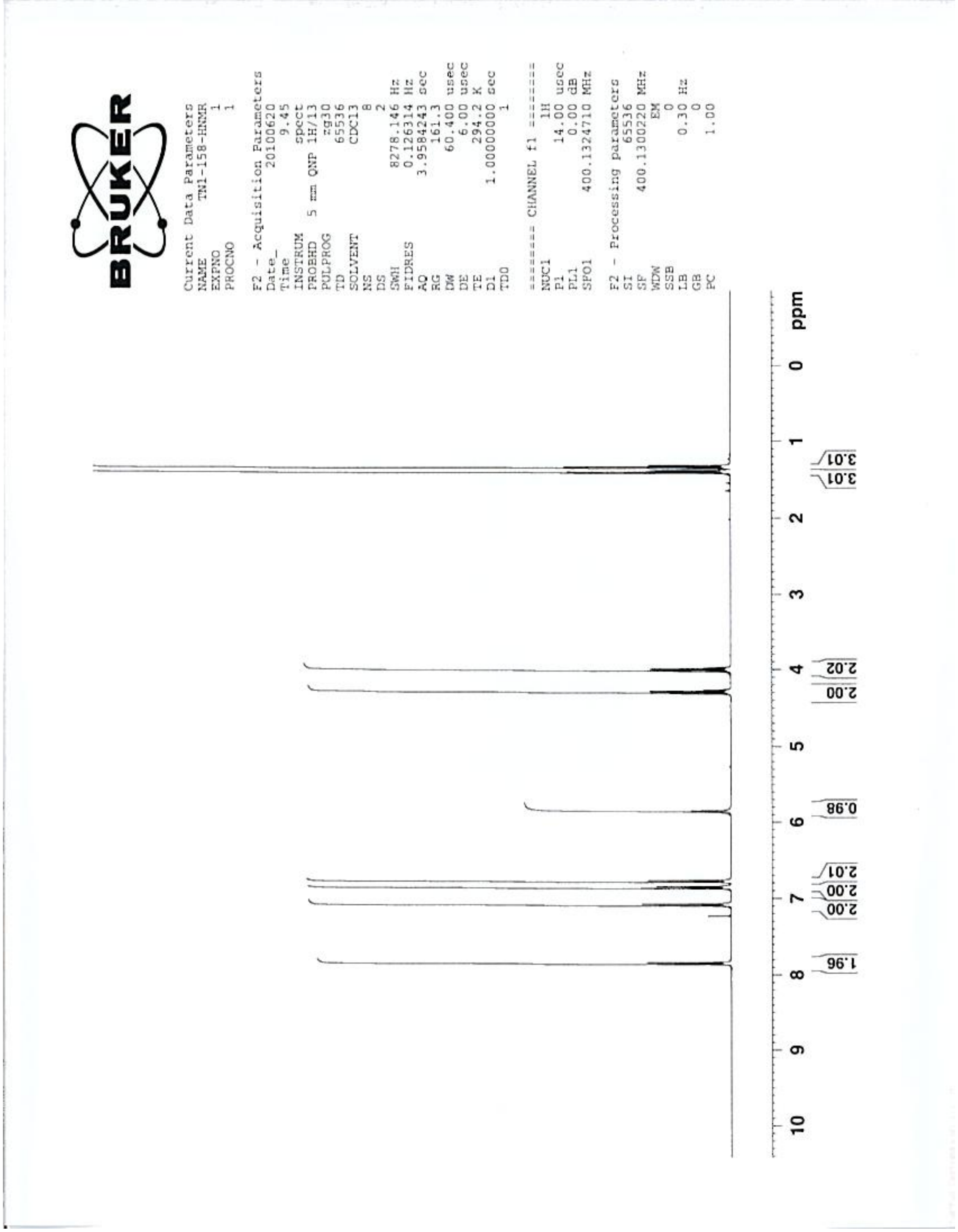
F2 - Acquisition Parameters
Date_           20100622
Time               19.35
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   191
DS                     4
SWH            23980.814 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG               11585.2
DW                20.850 usec
DE                  6.00 usec
TE                 295.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.38 usec
PL1                 0.00 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PL2                 0.00 dB
PL12               16.10 dB
PL13               19.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127512 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



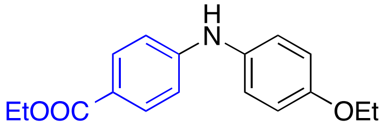


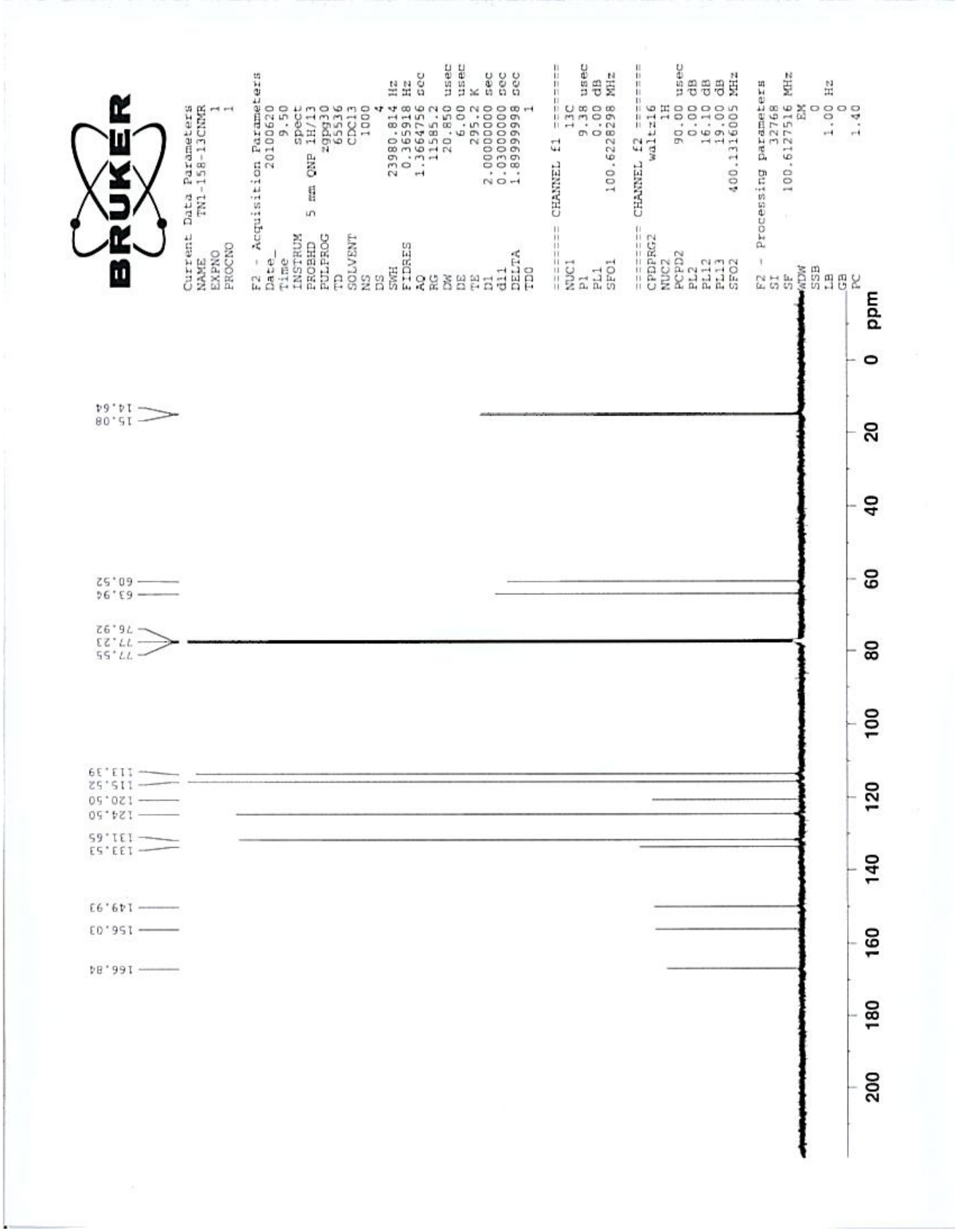
```
Current Data Parameters
NAME        TN1-158-HNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100620
Time                9.45
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                 161.3
DW                60.400 usec
DE                  6.00 usec
TE                 294.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300220 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



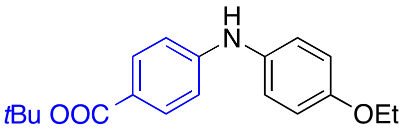

```
Current Data Parameters
NAME        TN1-158-13CNMR
EXPNO                    1
PROCNO                   1

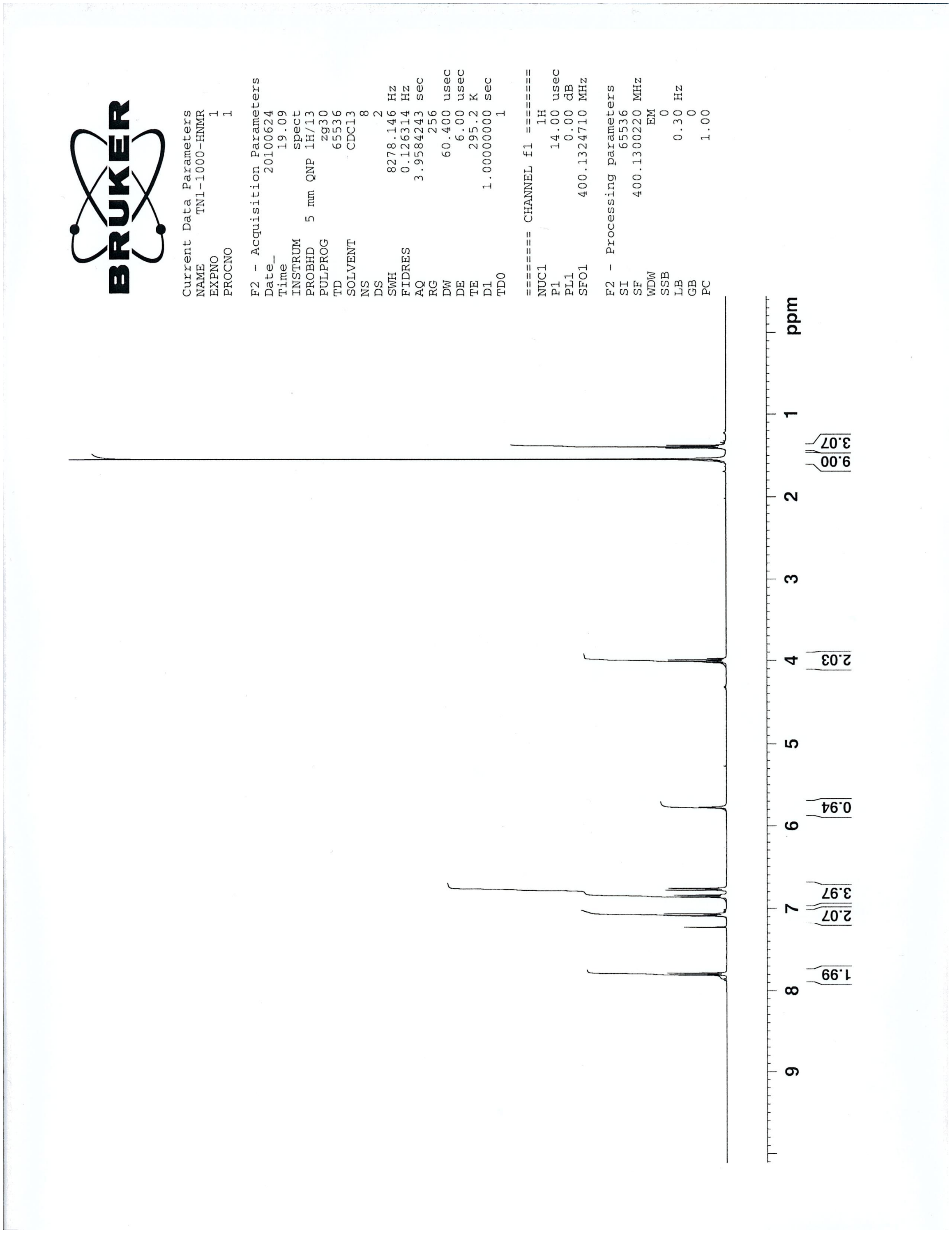
F2 - Acquisition Parameters
Date_             20100620
Time                  9.50
INSTRUM              spect
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1000
DS                       4
SWH          23980.814 Hz
FIDRES        0.365918 Hz
AQ          1.3664756 sec
RG                 11585.2
DW              20.850 usec
DE                6.00 usec
TE                 295.2 K
D1         2.00000000 sec
d11        0.03000000 sec
DELTA      1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                9.38 usec
PL1                0.00 dB
SFO1       100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2            90.00 usec
PL2                0.00 dB
PL12              16.10 dB
PL13              19.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF         100.6127516 MHz
WDW                     EM
SSB                      0
LB                 1.00 Hz
GB                       0
PC                    1.40
```



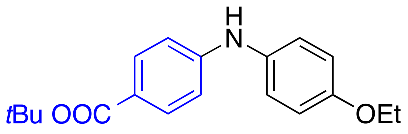


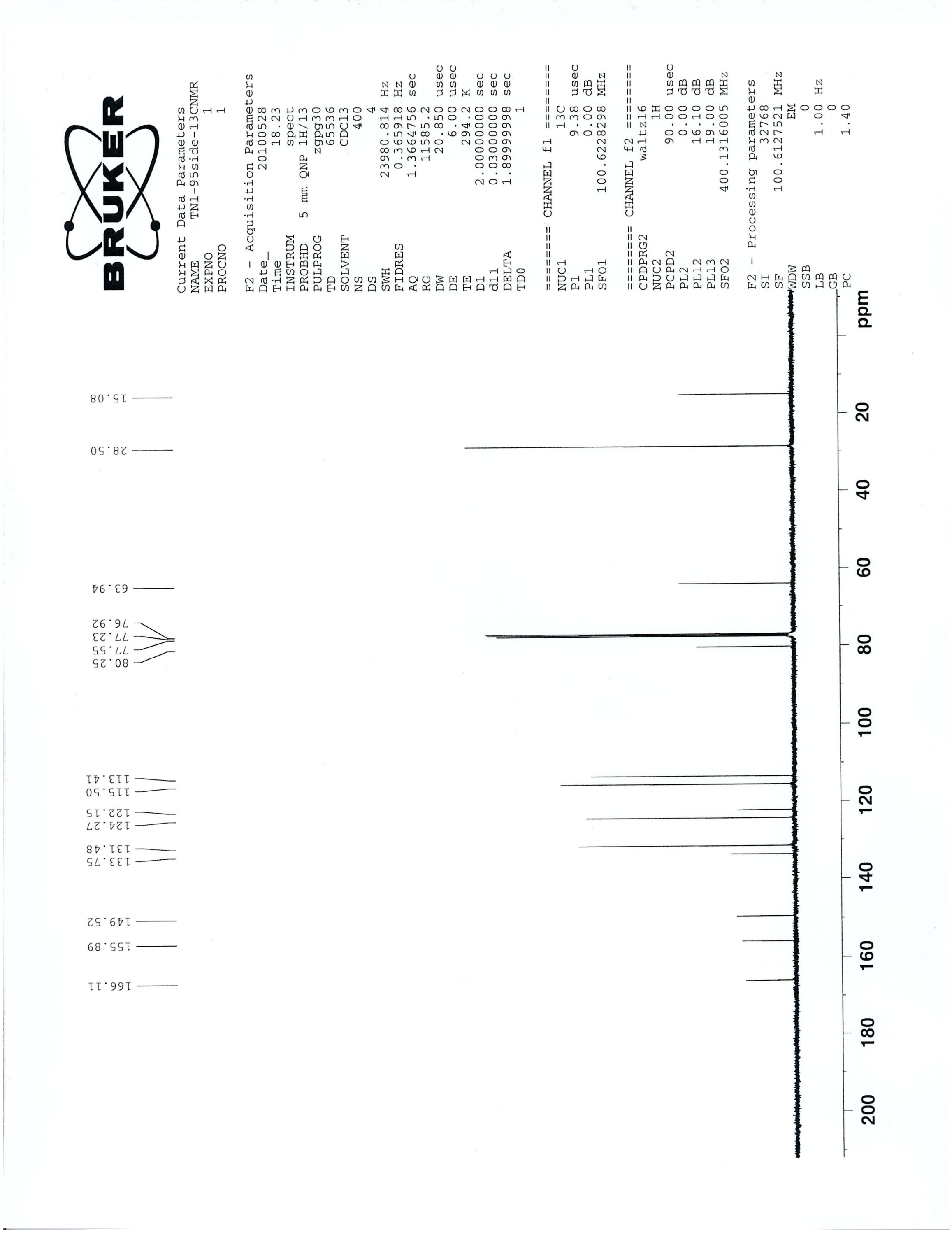
```
Current Data Parameters
NAME       TN1-1000-HNMR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100624
Time               19.09
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                   256
DW                60.400 usec
DE                  6.00 usec
TE                 295.2 K
D1            1.00000000 sec
TD0                    1

======= CHANNEL f1 =======
NUC1                  1H
P1                 14.00 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300220 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```





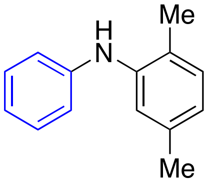
```
Current Data Parameters
NAME        TN1-95side-13CNMR
EXPNO                    1
PROCNO                   1

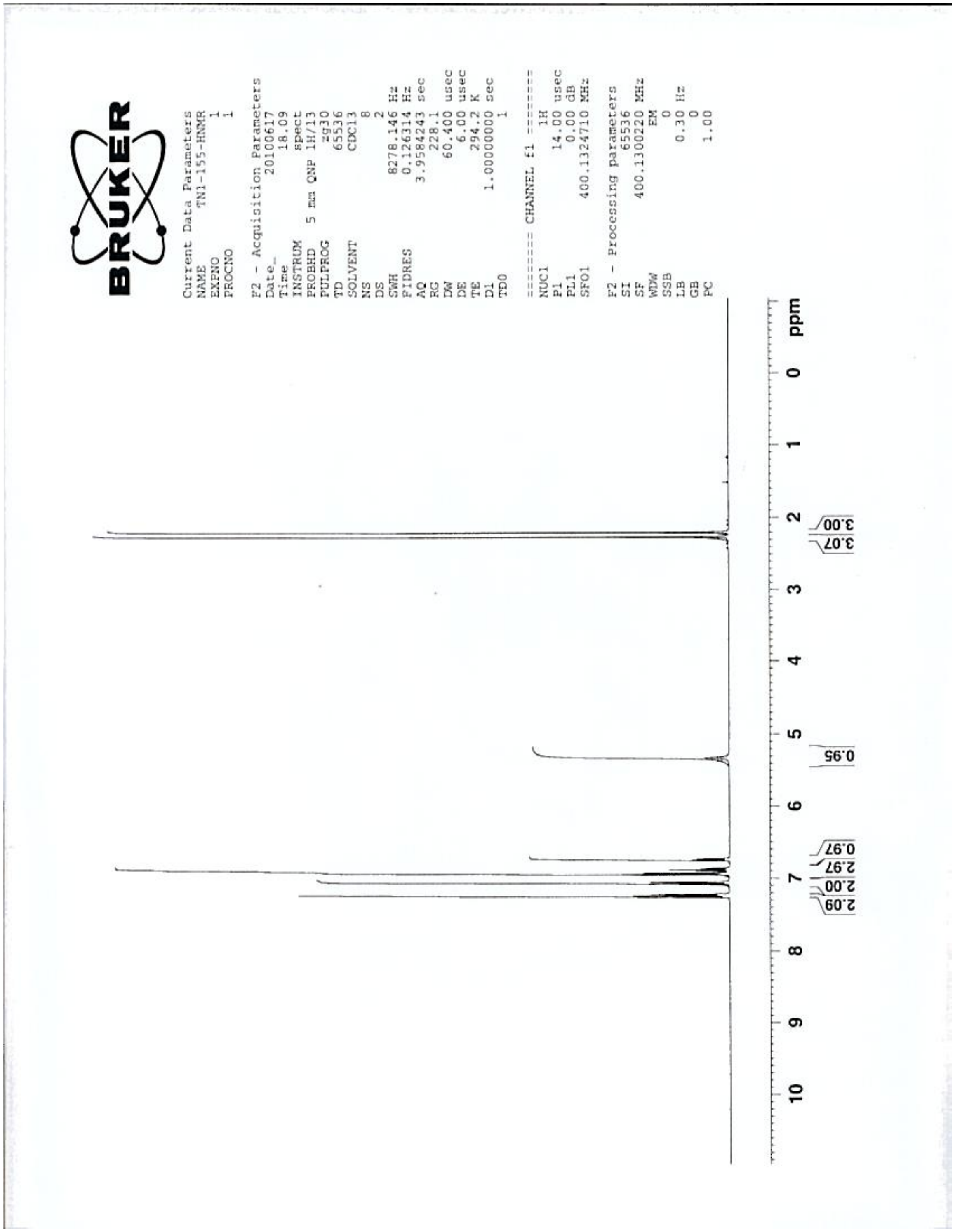
F2 - Acquisition Parameters
Date_             20100528
Time                 18.23
INSTRUM              spect
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     400
DS                       4
SWH            23980.814 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG                 11585.2
DW                  20.850 usec
DE                    6.00 usec
TE                   294.2 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.38 usec
PL1                   0.00 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                90.00 usec
PL2                   0.00 dB
PL12                 16.10 dB
PL13                 19.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF          100.6127521 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```



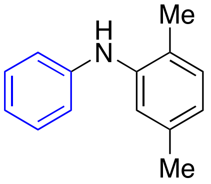


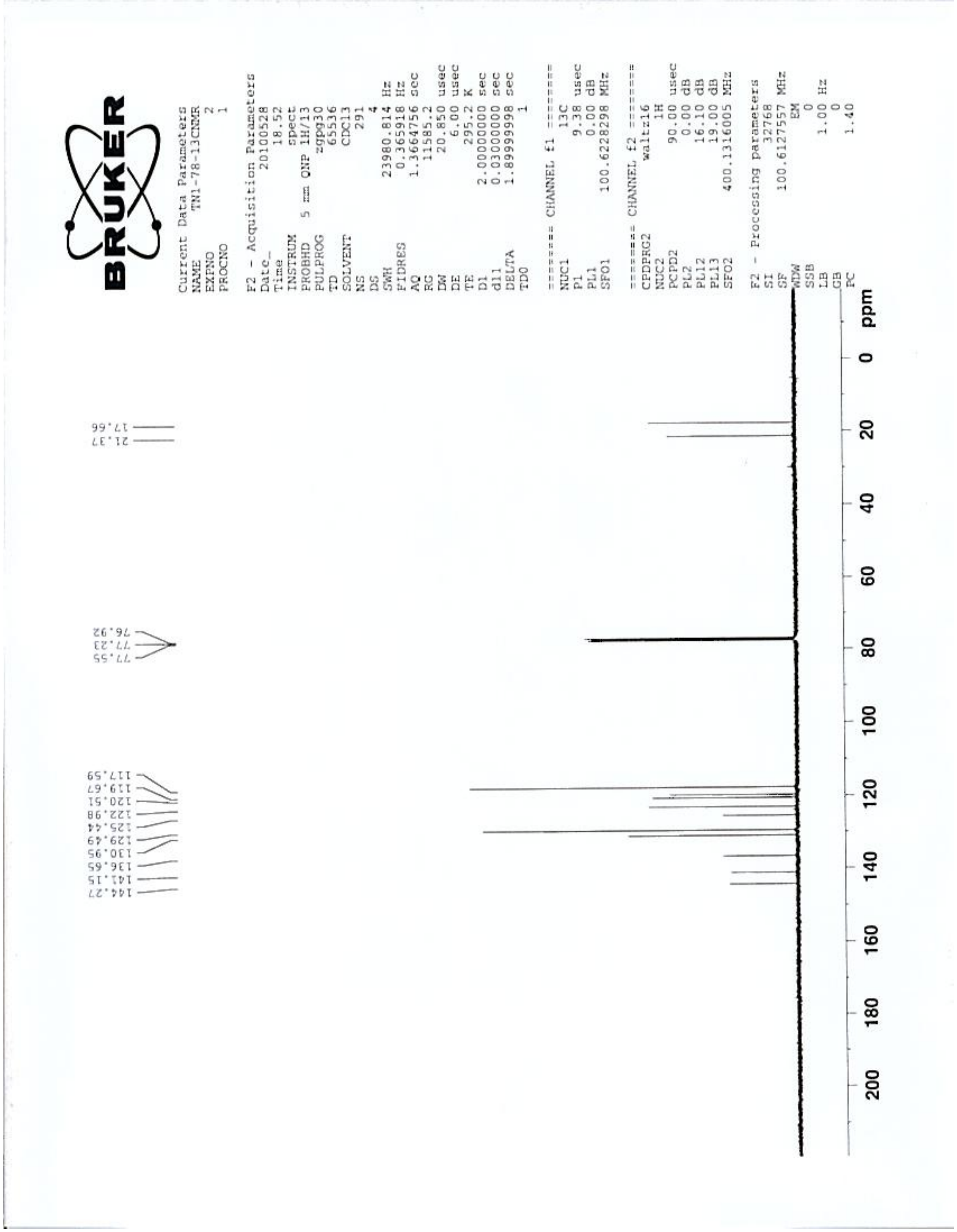
```
Current Data Parameters
NAME          TN1-155-HNMR
EXPNO                    1
PROCNO                   1

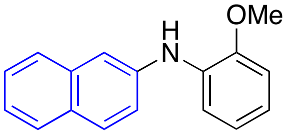
F2 - Acquisition Parameters
Date_             20100617
Time                 18.09
INSTRUM              spect
PROBHD   5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       8
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                   228.1
DW                  60.400 usec
DE                    6.00 usec
TE                   294.2 K
D1             1.00000000 sec
TD0                      1

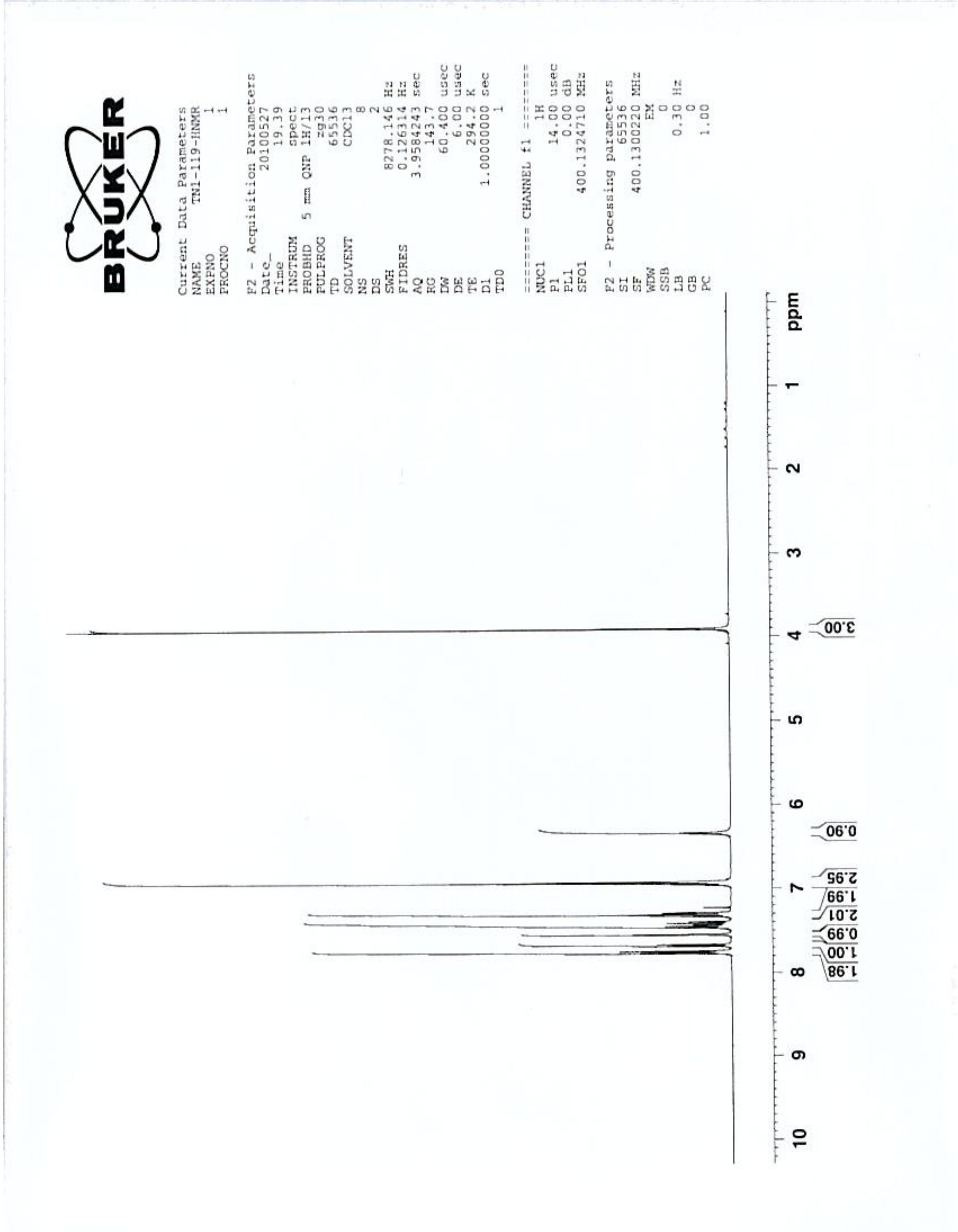
======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                   0.00 dB
SFO1           400.1324710 MHz

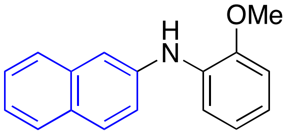
F2 - Processing parameters
SI                   65536
SF             400.1300220 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

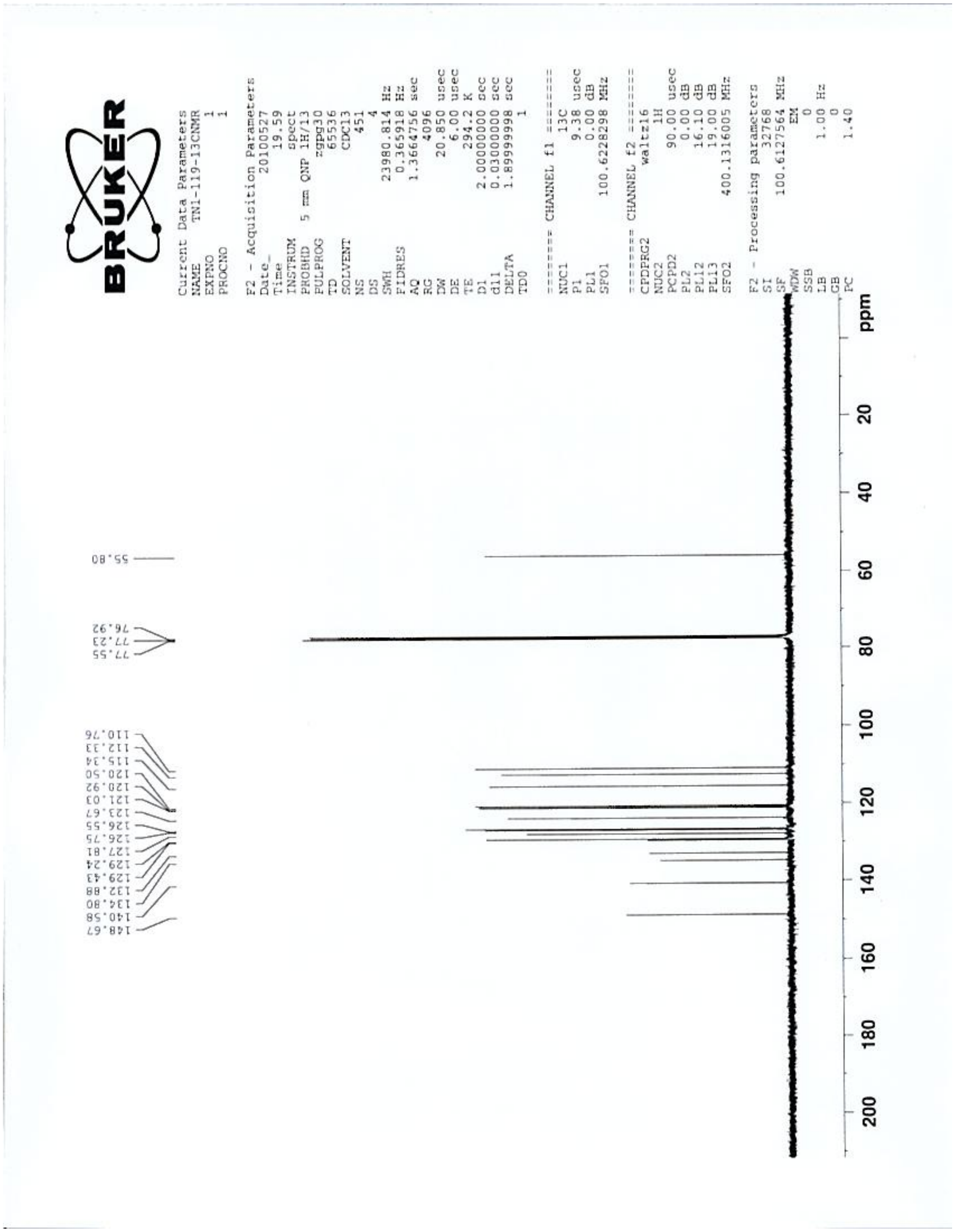

H
N
Me
Me


BRUKER
17.66
21.37
76.92
77.23
77.55
117.59
119.67
120.51
122.98
125.44
129.49
130.95
136.65
141.15
144.27
Current Data Parameters
NAME TN1-78-13CNMR
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100528
Time 18.52
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 291
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 11585.2
DW 20.850 usec
DE 6.00 usec
TE 295.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.38 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 16.10 dB
PL13 19.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127557 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
0
20
40
60
80
100
120
140
160
180
200


OMe
H
N


BRUKER
Current Data Parameters
NAME TN1-119-HNMR
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100527
Time 19.39
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 143.7
DW 60.400 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
3.00
0.90
2.95
1.99
2.01
0.99
1.00
1.98
ppm
1
2
3
4
5
6
7
8
9
10





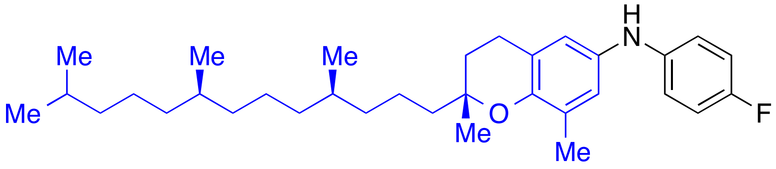
```
Current Data Parameters
NAME        TN1-119-13CNMR
EXPNO                    1
PROCNO                   1

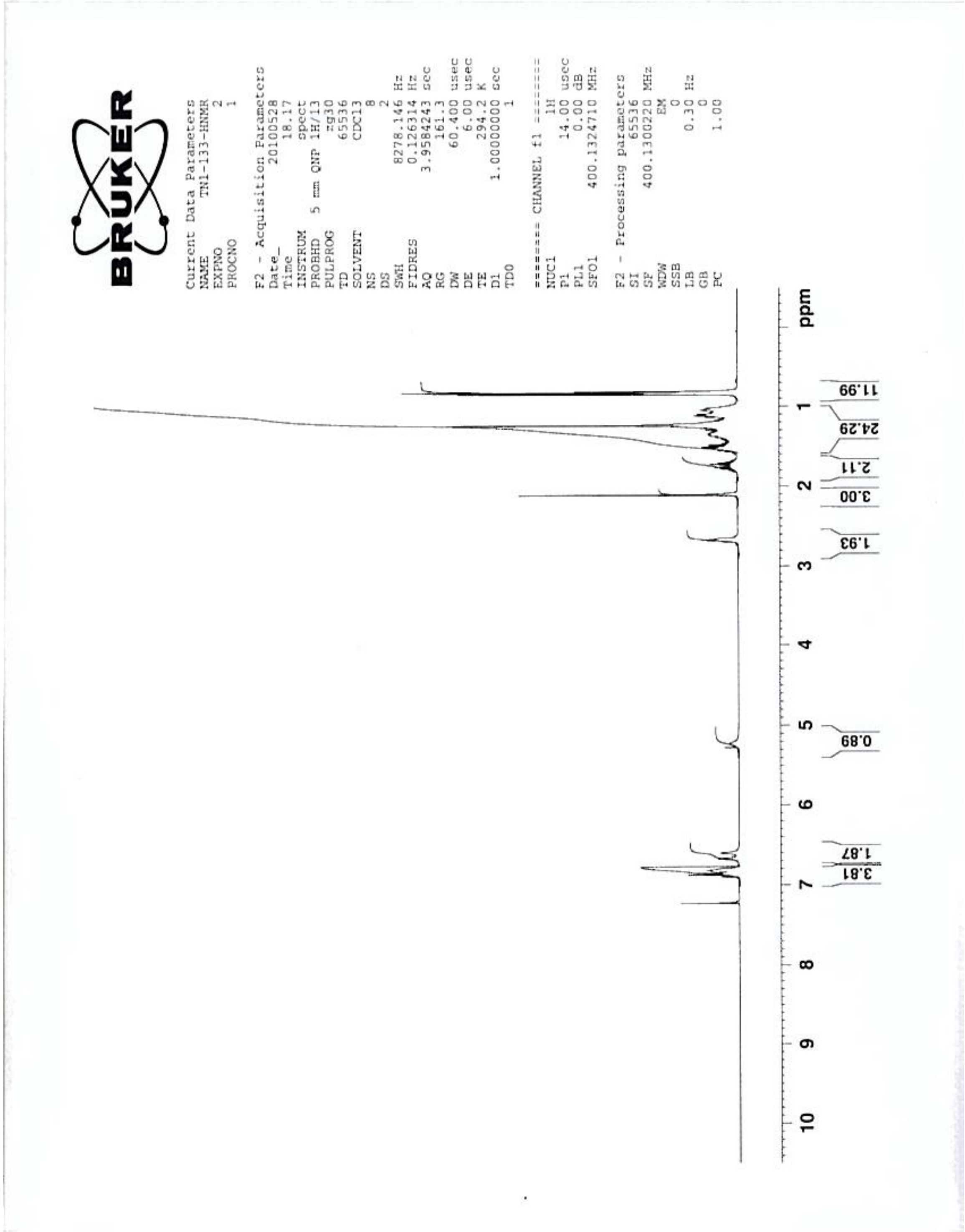
F2 - Acquisition Parameters
Date_             20100527
Time                 19.59
INSTRUM              spect
PROBHD   5 mm QNP 1H/13
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     451
DS                       4
SWH           23980.814 Hz
FIDRES         0.365918 Hz
AQ           1.3664756 sec
RG                    4096
DW              20.850 usec
DE                6.00 usec
TE                 294.2 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                9.38 usec
PL1                0.00 dB
SFO1       100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2            90.00 usec
PL2                0.00 dB
PL12              16.10 dB
PL13              19.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF         100.6127564 MHz
WDW                     EM
SSB                      0
LB                 1.00 Hz
GB                       0
PC                    1.40
```



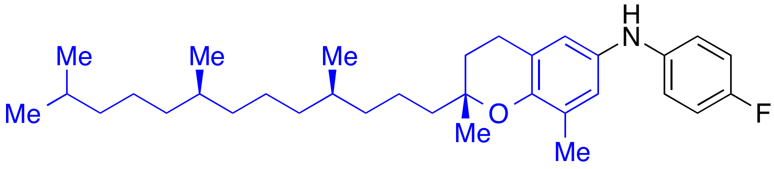


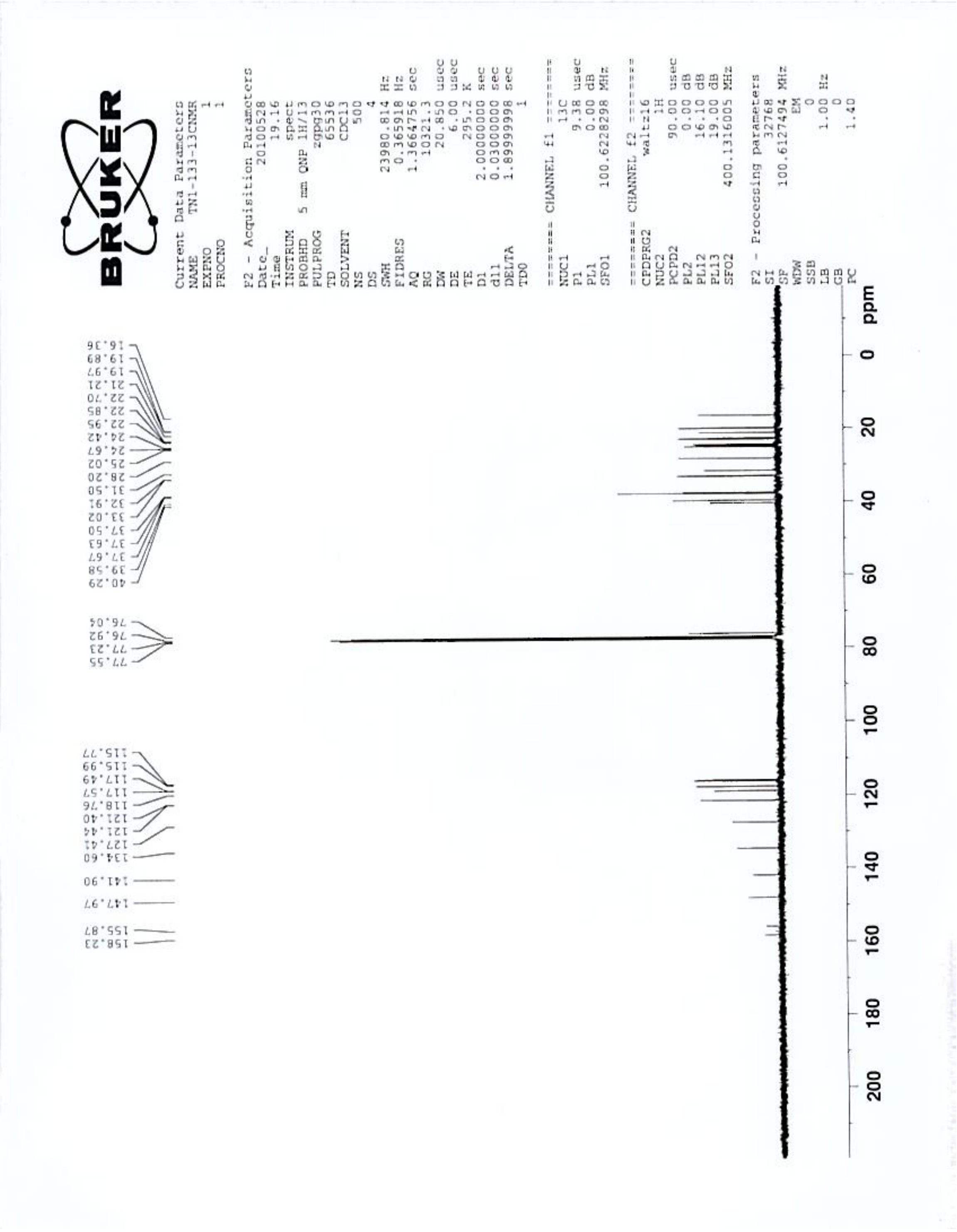
```
Current Data Parameters
NAME        TN1-133-HNMR
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100528
Time               18.17
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                 161.3
DW                60.400 usec
DE                  6.00 usec
TE                 294.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300220 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```





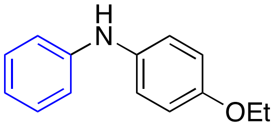
```
Current Data Parameters
NAME       TN1-133-13CNMR
EXPNO                   1
PROCNO                  1

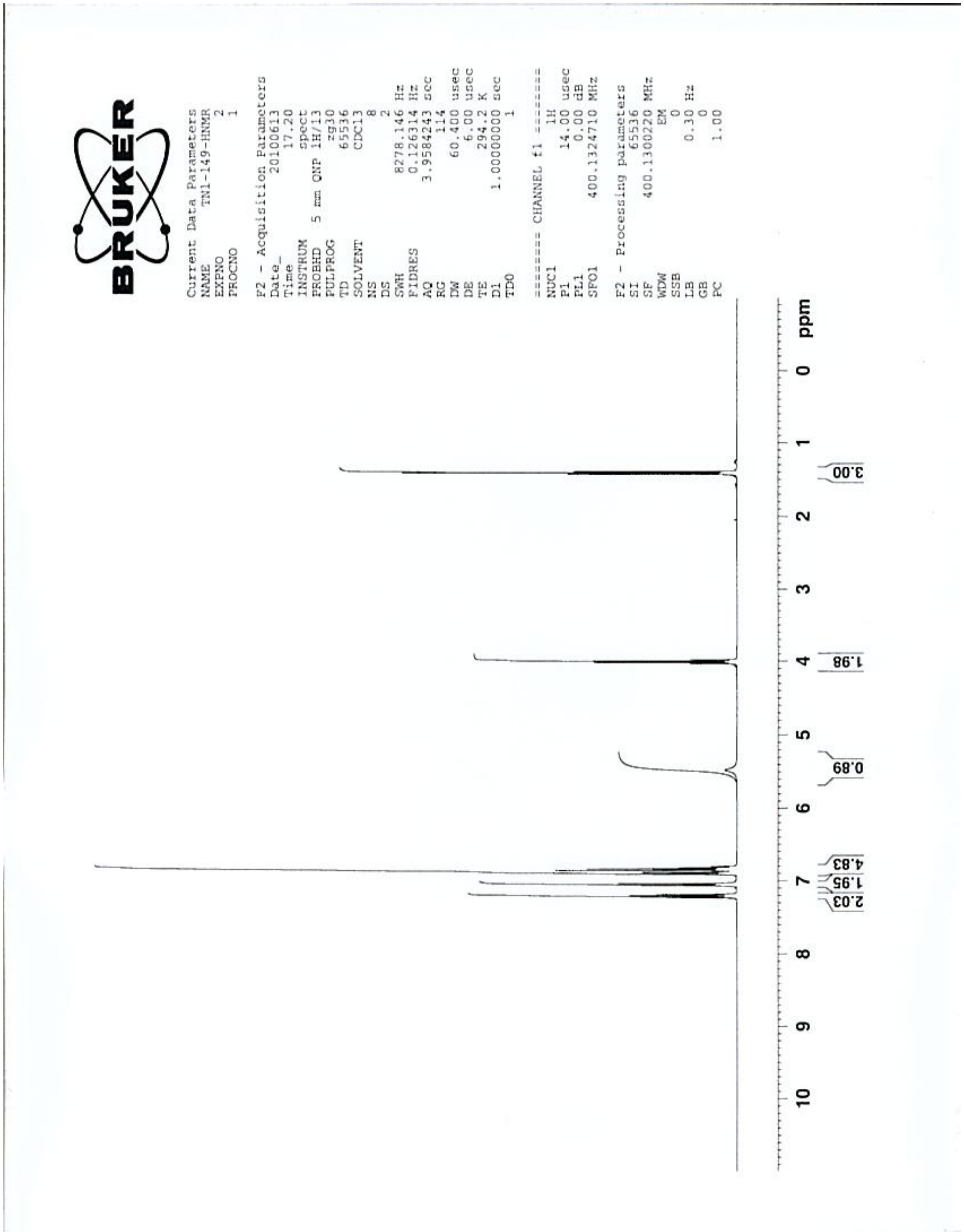
F2 - Acquisition Parameters
Date_            20100528
Time                19.16
INSTRUM             spect
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   500
DS                     4
SWH            23980.814 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG               10321.3
DW                20.850 usec
DE                  6.00 usec
TE                 295.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.38 usec
PL1                 0.00 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PL2                 0.00 dB
PL12               16.10 dB
PL13               19.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127494 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



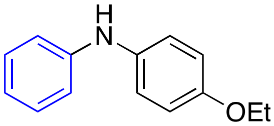


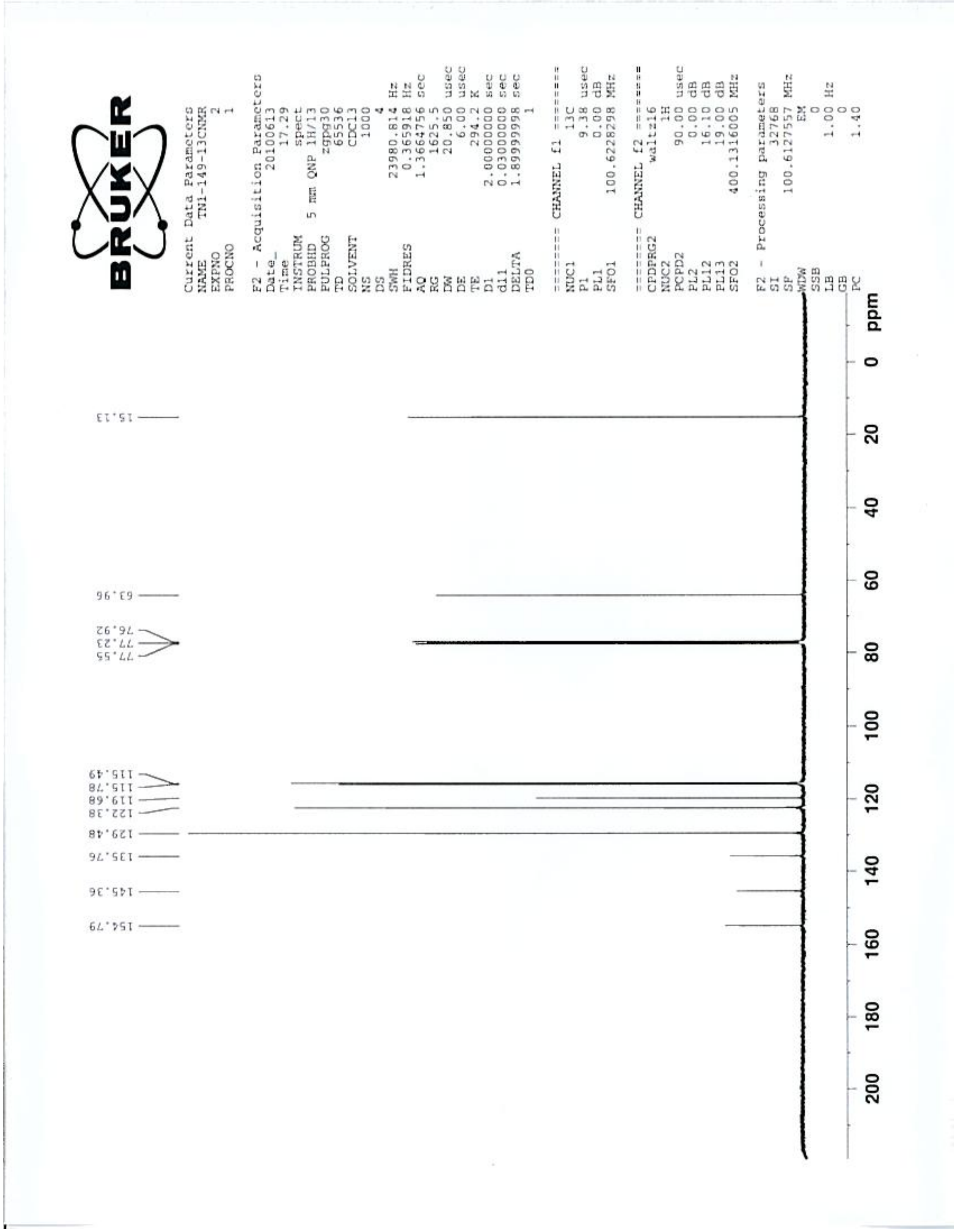
```
Current Data Parameters
NAME          TN1-149-HNMR
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100613
Time                 17.20
INSTRUM              spect
PROBHD    5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                       8
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     114
DW                  60.400 usec
DE                    6.00 usec
TE                   294.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                   0.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   65536
SF             400.1300220 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





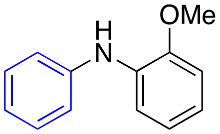
```
Current Data Parameters
NAME      TN1-149-13CNMR
EXPNO                  2
PROCNO                 1

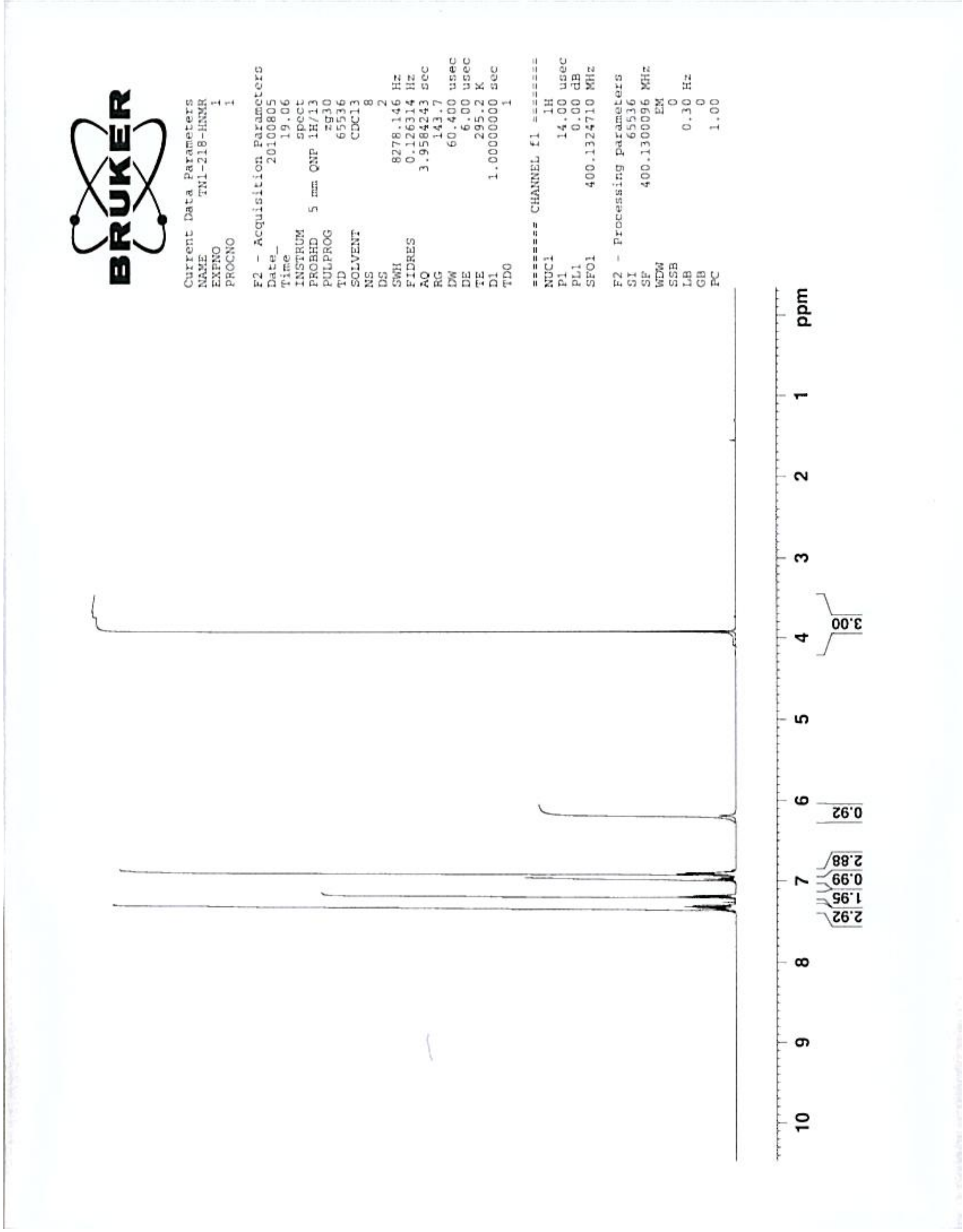
F2 - Acquisition Parameters
Date_           20100613
Time               17.29
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1000
DS                     4
SWH            23980.814 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG                1625.5
DW                20.850 usec
DE                  6.00 usec
TE                 294.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.38 usec
PL1                 0.00 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PL2                 0.00 dB
PL12               16.10 dB
PL13               19.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127557 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



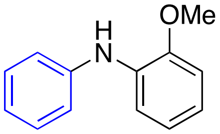


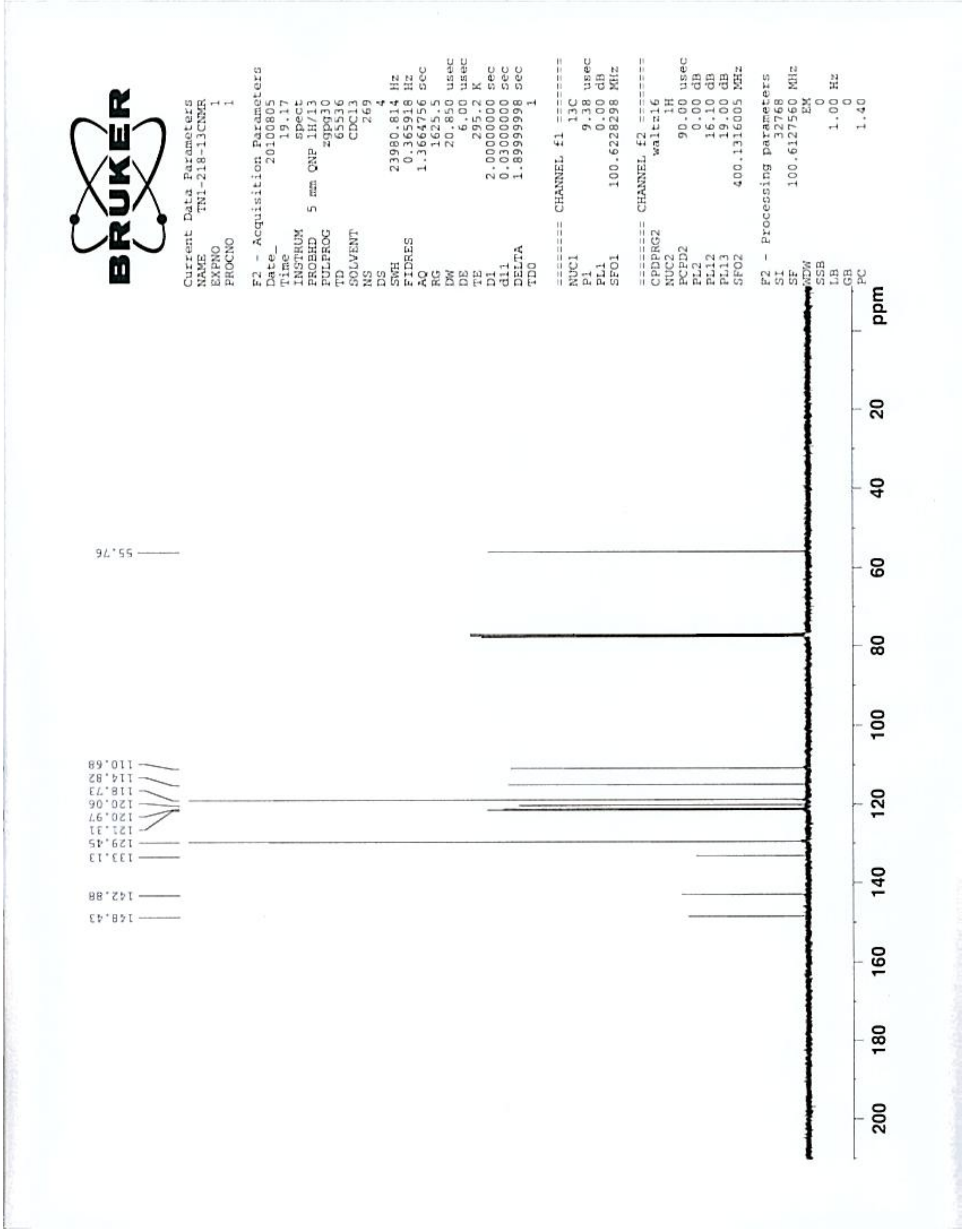
Current Data Parameters
NAME TN1-218-HNMR
EXPNO 1
PROCNO 1

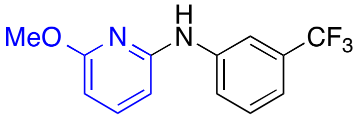
F2 - Acquisition Parameters
Date_ 20100805
Time 19.06
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 143.7
DW 60.400 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1

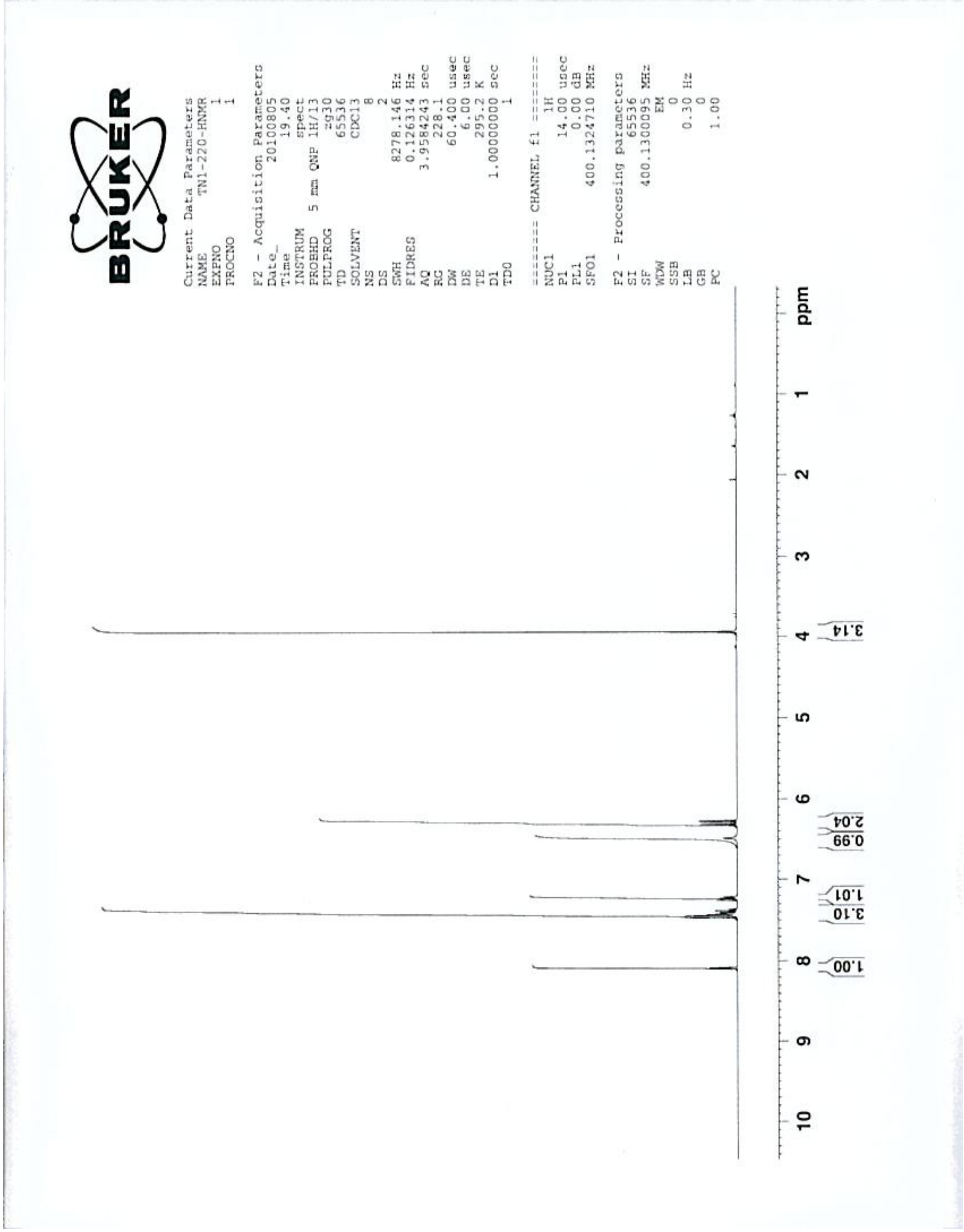
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300096 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


OMe
H
N


BRUKER
Current Data Parameters
NAME TN1-218-13CNMR
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100805
Time 19.17
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 269
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 1625.5
DW 20.850 usec
DE 6.00 usec
TE 295.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.38 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 16.10 dB
PL13 19.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127560 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
55.76
110.68
114.82
118.73
120.06
120.97
121.31
129.45
133.13
142.88
148.43
ppm
20
40
60
80
100
120
140
160
180
200



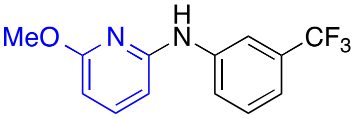


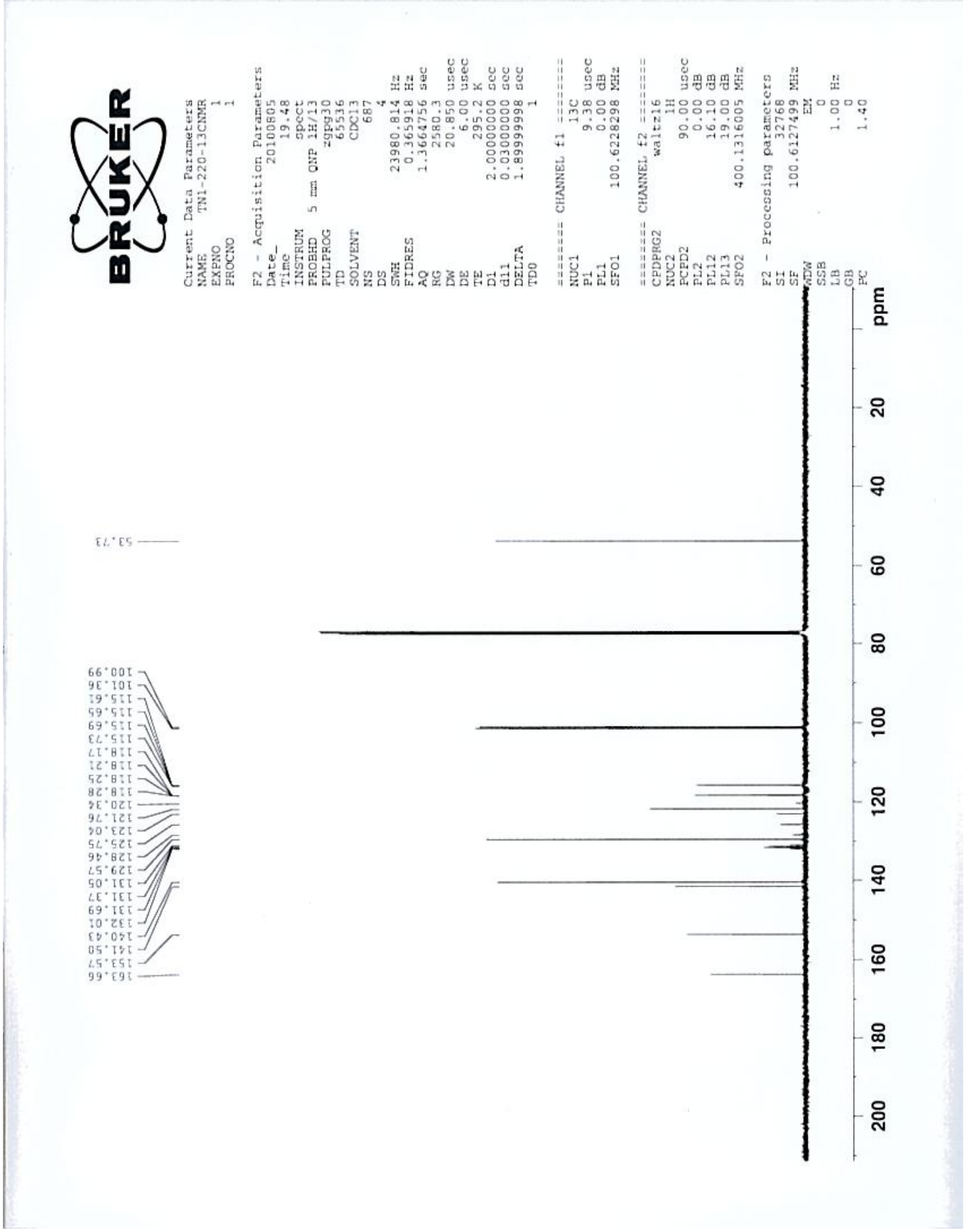
```
Current Data Parameters
NAME       TN1-220-HNMR
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20100805
Time              19.40
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                228.1
DW               60.400 usec
DE                 6.00 usec
TE                295.2 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                14.00 usec
PL1                0.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                65536
SF          400.1300095 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```


MeO
N
H
N
CF3


BRUKER
Current Data Parameters
NAME TN1-220-13CNMR
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100805
Time 19.48
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 687
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 2580.3
DW 20.850 usec
DE 6.00 usec
TE 295.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.38 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 16.10 dB
PL13 19.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127499 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
53.73
100.99
101.36
115.61
115.65
115.69
115.73
118.17
118.21
118.25
118.28
120.34
121.76
123.04
125.75
128.46
129.57
131.05
131.37
131.69
132.01
140.43
141.50
153.57
163.66
200
180
160
140
120
100
80
60
40
20
ppm