Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

Additive-free selective methylation of amines with formic acid over a Pd/In_2O_3 catalyst

Caroline Genre*[a], Idir Benaissa[a], Timothé Godou[a], Mathieu Pinault[a], and Thibault Cantat*[a]

[a] *Université Paris-Saclay, CEA, CNRS, NIMBE, 91191 Gif-sur-Yvette (France)*

caroline.genre@cea.fr

General considerations

Commercially available products (Sigma-Aldrich or Alfa Aesar or Acros Organics) were used without further purification.

Gas chromatography data were acquired with a Shimadzu GC2010 gas chromatograph; column: Carboxen 1010 PLOT fused silica capillary (30 m* 0.53 mm * 30 µm); injection temperature: 230°C; column temperature: 100°C; flow: 5mL/min; purge : 2mL/min; carrier gas: Ar; detector: TCD 203°C, 30 mA. .

GC-MS data were collected on a Shimadzu GCMS-QP2010 Plus gas chromatograph equipped with a Supelco SLB^{TM}-ms fused silica capillary column (30 m*0.25 mm*0.25 µm) using He as a carrier gas.

NMR spectra were obtained on a Bruker Avance NEO 400 MHz spectrometer. Chemical shifts for the products were referenced to solvent impurities.

Catalyst preparation

In_2O_3 was obtained from Acros Organics. M/In_2O_3 (10 wt%. M, M = Pd, Pt, Ru) catalysts were prepared by an impregnation method using the nitrate salts. For the preparation of Pd/In_2O_3 as an example, 400mg $Pd(NO_3)_2.3H_2O$ were dissolved in 50 mL distilled water at room temperature. 1.4 g In_2O_3 were then added and the suspension was stirred for 3h. The suspension was then evaporated to dryness and the solid was let to dry overnight at 80°C. It was then annealed in air at 400°C for 3h.

Catalytic reactions

In a typical experiment, a 25 mL stainless steel autoclave equipped with a stirring bar was charged with 5 mmol of substrate, 10 mL of solvent, 60 mmol (2,23 mL) of formic acid and the required amount of catalyst. The autoclave was sealed and heated to 200°C for 18h. It was then let to cool down to room temperature and depressurized, and the reaction medium was centrifuged. Conversions and yields were determined by GCMS with isooctane as an internal standard. The GCMS sensibility was calibrated using the commercial or the isolated products.

Purification of the methylated amines

To obtain the isolated products, the reaction mixture was cooled to room temperature and the catalyst was removed by centrifugation. The solvent was evaporated and the desired products were isolated by column chromatography over silica gel with petroleum ether/ethyl acetate/trimethylamine (89:10:1 for **1b**; 94:5:1 for **2b**; 87:10:3 for **3b**, **5b**, **7b**; 77:17:6 for **8b**) or dichloromethane (**4b**, **6b**, **10b**).

Catalyst recycling experiments

After each run, the catalyst was separated by centrifugation, washed with 10 mL of acetone 3 times, dried in air and annealed at 400°C for 3 hours, then used directly for the next run.

Products identification

^{1}H NMR and ^{13}C NMR spectra of the following products were compared with commercial samples purchased from Aldrich: **1b**, **2b, 5b**, **6b**, **8b**, **9b**, **14b**.

^{1}H NMR and ^{13}C NMR spectra of the following products are identical to reported data: **3b**[1], **4b**[2], **7b**[2], **10b**[3].

12b, **13b**, **15b** were identified by GC/MS chromatography and by ^{1}H NMR and ^{13}C NMR from the crude mixture.

GC analysis

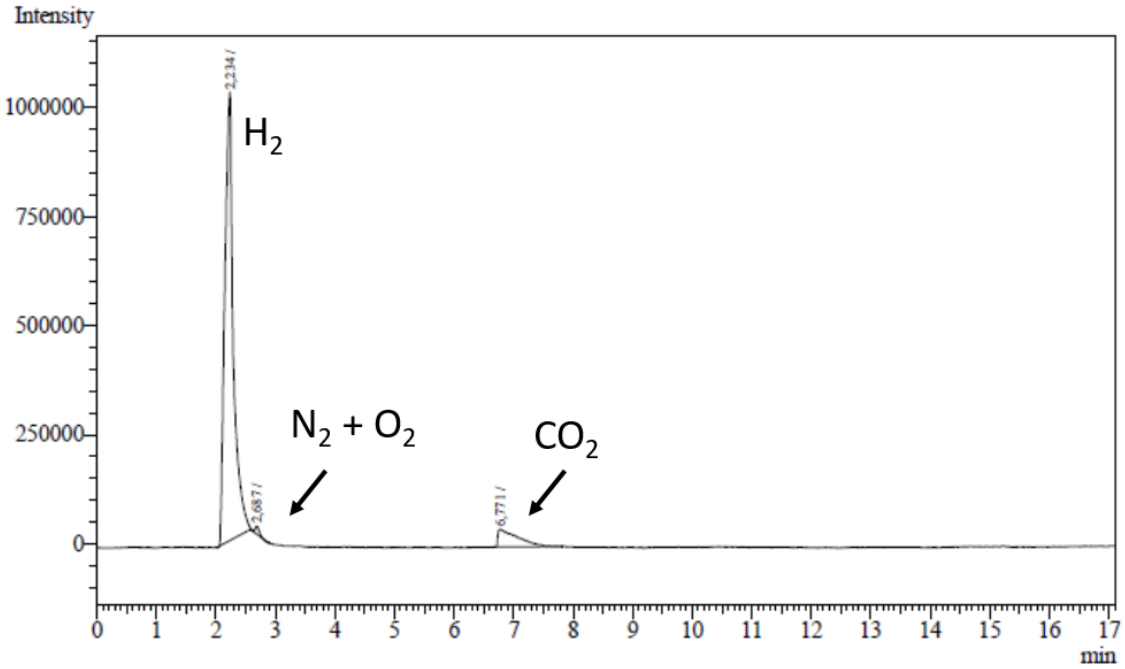


***Fig S1**: GC trace of the volatiles produced by the catalytic methylation of p-fluoro-N-methylaniline in DME in a sealed autoclave (catalyst Pd/In2O3, 200°C, 18h).*

Optimization of the reaction conditions

***Table S1**: Optimization of the reaction conditions for the Pd/In_2O_3 catalyzed methylation of 4-fluoro-N-methylaniline with FA.*

Entry	Equiv. FA	Solv.	Temp. (°C)	Time (h)	Conv. (%)	Yield (%) **1b**	**1c**
1	12	DME	200	12	100	85	13
2	12	DME	150	12	100	22	78
3	12	Hexane	200	12	95	22	72
4	12	THF	200	12	100	79	13
5	12	DME	200	18	100	94	4
6	12	DME	200	60	80	63	9
7	8	DME	200	18	93	23	56
8	4	DME	200	18	73	16	52
9	2	DME	200	18	58	6	48

[a] Reaction conditions: **1a** (5 mmol), Pd/In_2O_3 80 mg, formic acid (*n* equiv.), solvent (10 mL). Yields determined by GC/MS using isooctane as an internal standard, after calibration. [b] Yield determined by NMR

Catalyst characterization

SEM-EDX

Scanning Electron Microscopy (SEM) was performed on a SEM-FEG Zeiss Ultra 55 model to study the morphology of the catalysts. The spatial distribution of the metals can be monitored by mean of an EDX chemical analyzing system (BRUCKER SDD detector) interfaced with the ESPRIT software.

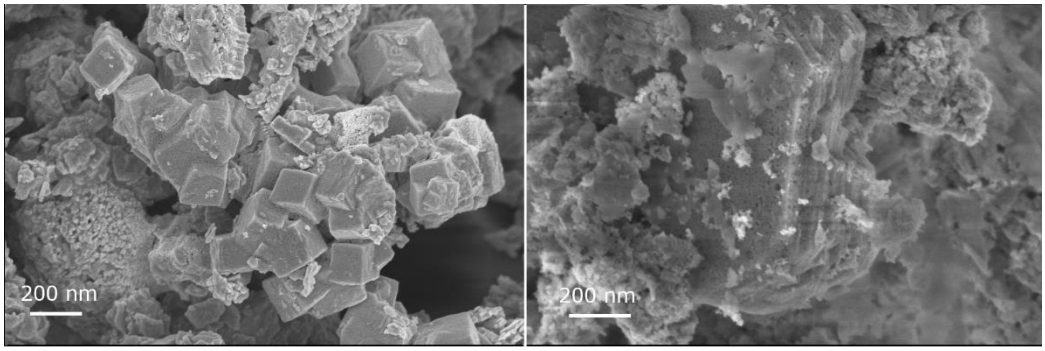


***Fig. S2**: SEM images of a sample of Pd/In_2O_3 (10 wt%) before (left) and after (right) reaction*

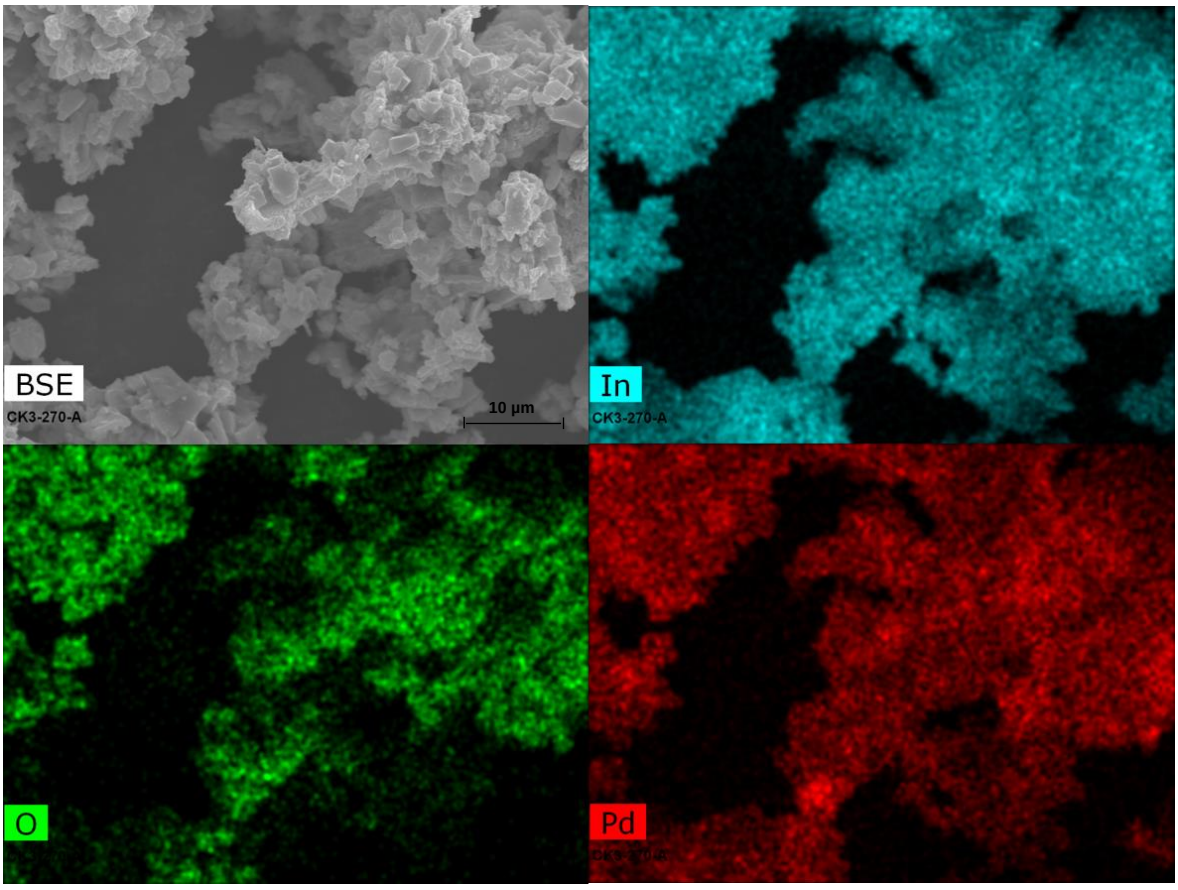


***Fig. S3**: EDX mapping for In, O, and Pd in a sample of Pd/In_2O_3 (10 wt.%) synthesized by wet impregnation followed by calcination.*

XPS analysis of the Pd/In_2O_3 catalyst

XPS was carried out using a Kratos Axis Ultra DLD spectrometer with a monochromatic Al Kα (1486.7eV) X-ray source and charge compensation system. Spectra were collected using a pass energy of 160 eV for the survey and 40 eV for core levels. The binding energy scale was calibrated using the position of the C1s peak at 284.8 eV.

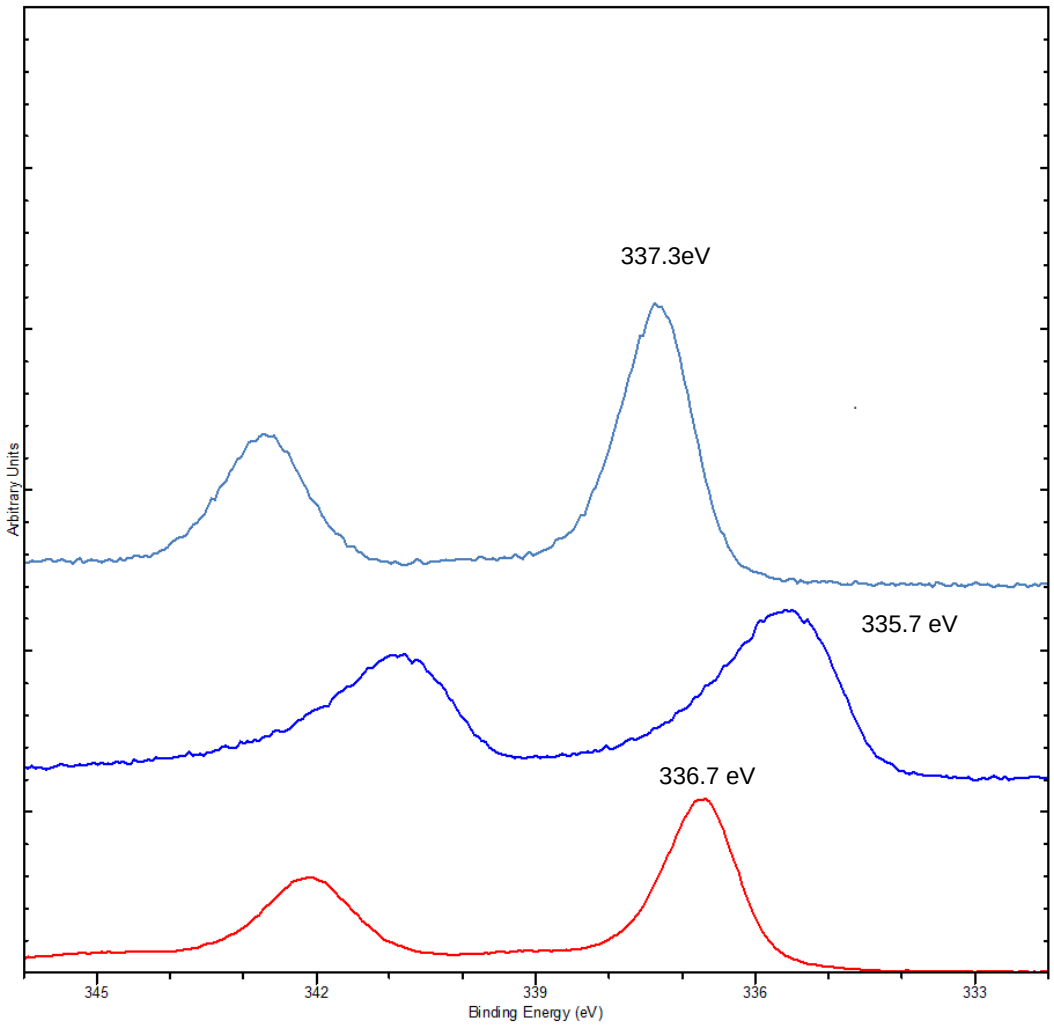


***Fig. S4**: Pd 3d XPS spectra of fresh (bottom), reacted (middle) and recycled (top) catalyst Pd/In_2O_3 (10 wt%).*

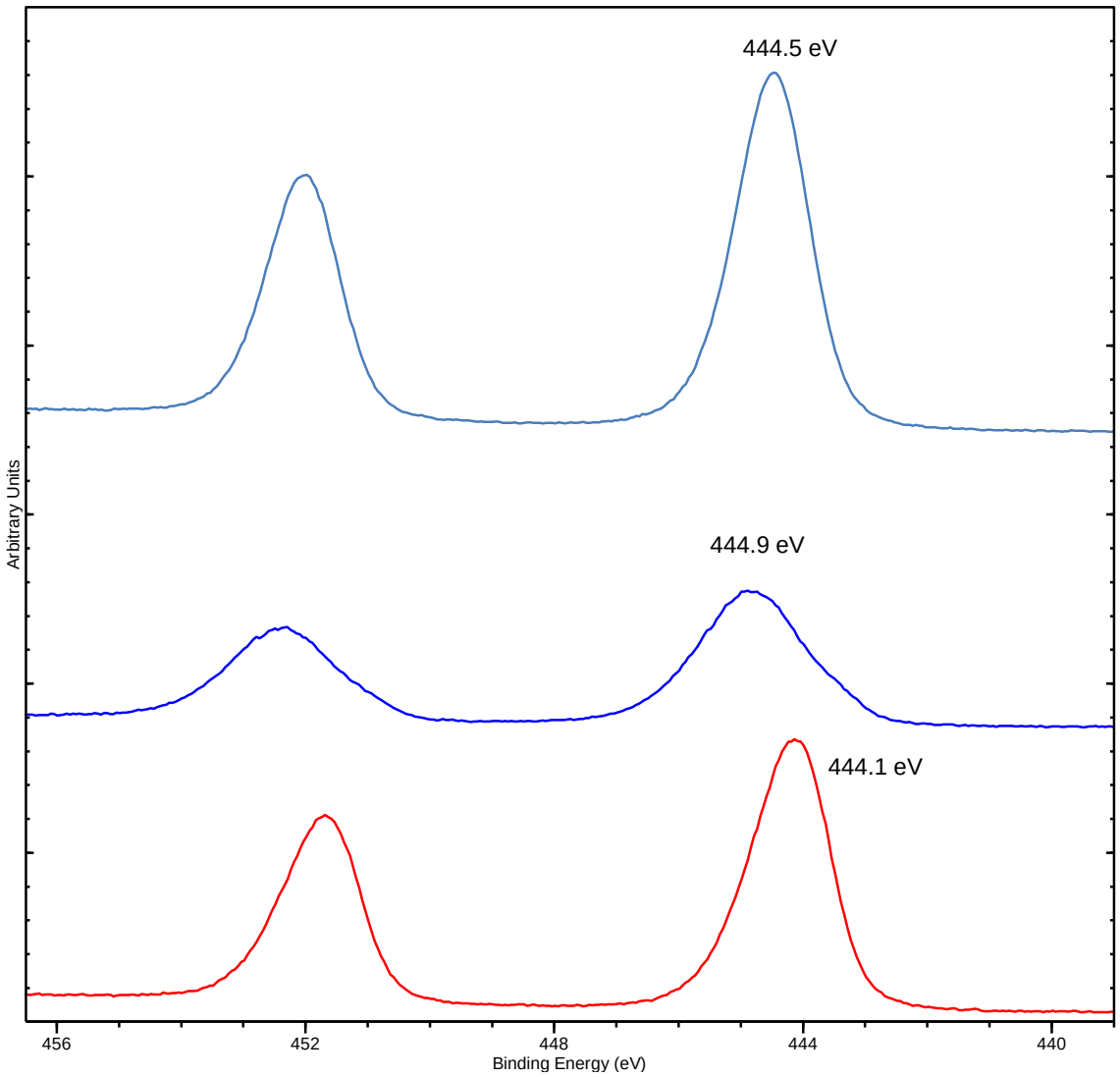


***Fig. S5**: In 3d XPS spectra of fresh (bottom), reacted (middle) and recycled (top) catalyst Pd/In_2O_3 (10 wt%).*

Table S2: Pd, In, O, C atomic concentrations in the catalyst before and after reaction (18h, 200°C) obtained from the high-resolution spectra with cross sections calculated by J. H. Scofield (1973).

Conc. % at.	Before reaction	After reaction	After recycling
In	17,7	10,1	19,4
Pd	16,7	4,1	4,2
O	22,3	43,8	47,4
C	43,3	42	29

HR-TEM and EDX measurements

Transmission Electron Microscopy (TEM) imaging was performed on a ThermoFisher Scientific™ G3 Titan Themis 300 transmission electron microscope (C-Twin objective lens: Cs = 2.7 mm, Cc = 2.7 mm, Focal length = 3.5 mm) operating at 300 kV accelerating voltage. Prior to the observation samples were deposited on a glow discharged 3 mm diameter copper grid covered with a thin carbon film. To analyze morphological and structural characteristics of the samples, HR-TEM observations were performed at 200.000x and 840.000x magnifications at extended scherzer focus (-90 nm) using low dose mode on a ThermoFisher Scientific™ Falcon3 EC 4k/4k Direct Detection Electron (DDE) camera. For HR-TEM imaging, to best preserve samples from electron beam irradiation during image acquisition, a total electron dose of 25 $e^{-}/Å^{2}$ was used for a limited exposure time of 1 sec. Energy-dispersive X-ray spectroscopy (EDX) was performed with an Oxford Instruments™ X-Max 80T spectrometer at 840.000x magnification on pre-selected areas. To confirm elements composition, spectra were recorded with Oxford Instrument™ AZtec v3.3 software in "Analyser" mode for a specimen tilt of 25 deg at highest electron dose condition for acquisition times from 15 to 25 sec.

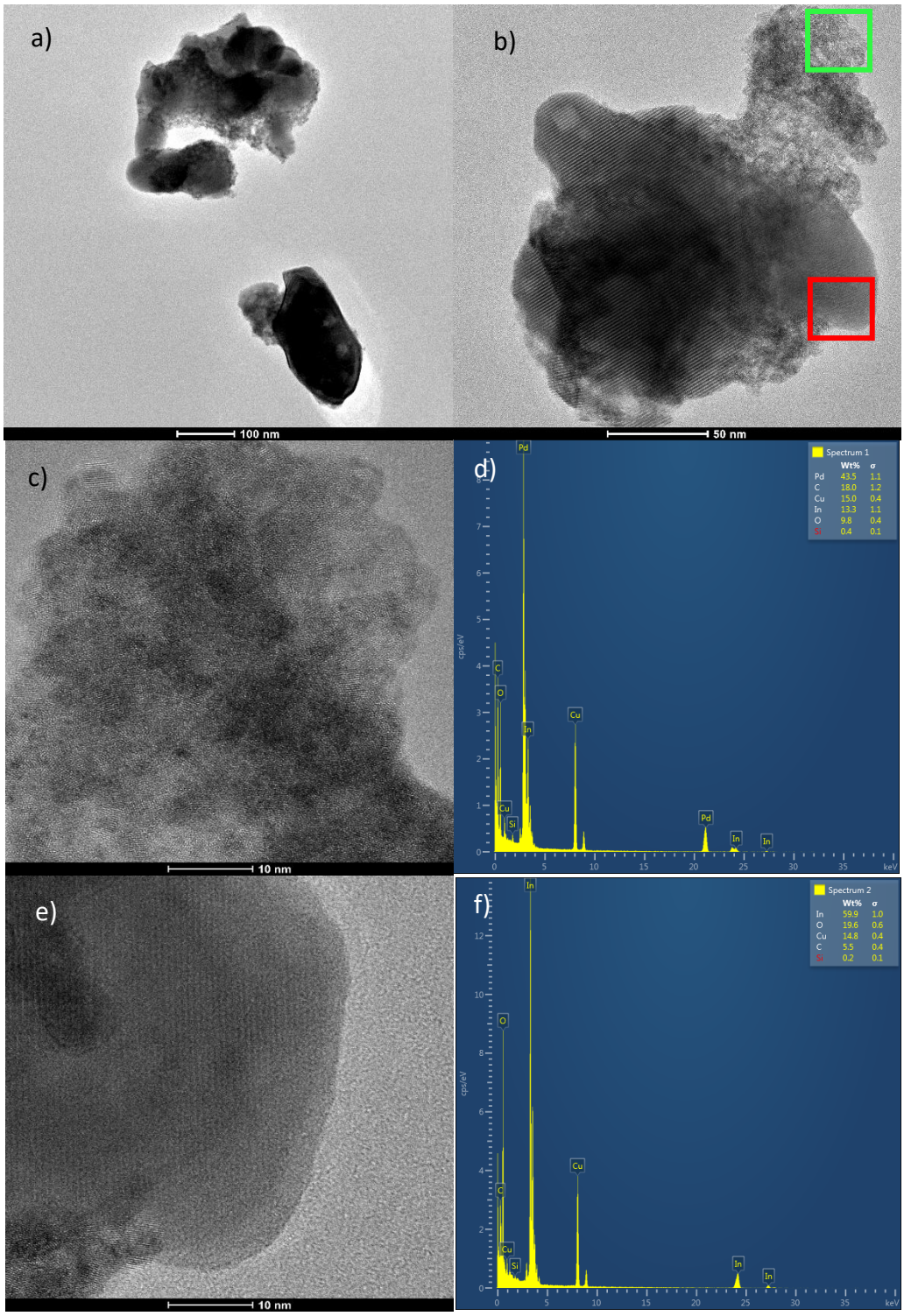


***Fig. S6**: TEM micrographs of a fresh sample of catalyst Pd/In_2O_3 a) Two particles of Pd/In_2O_3 displaying two types of material; b) a particle of catalyst that was selected for HR-TEM and EDX studies. The green square indicates zone1 and the red square indicates zone 2; c) HR-TEM image of zone 1; d) EDX spectrum of zone 1; e) HR-TEM image of zone 2; f) EDX spectrum of zone 2.*

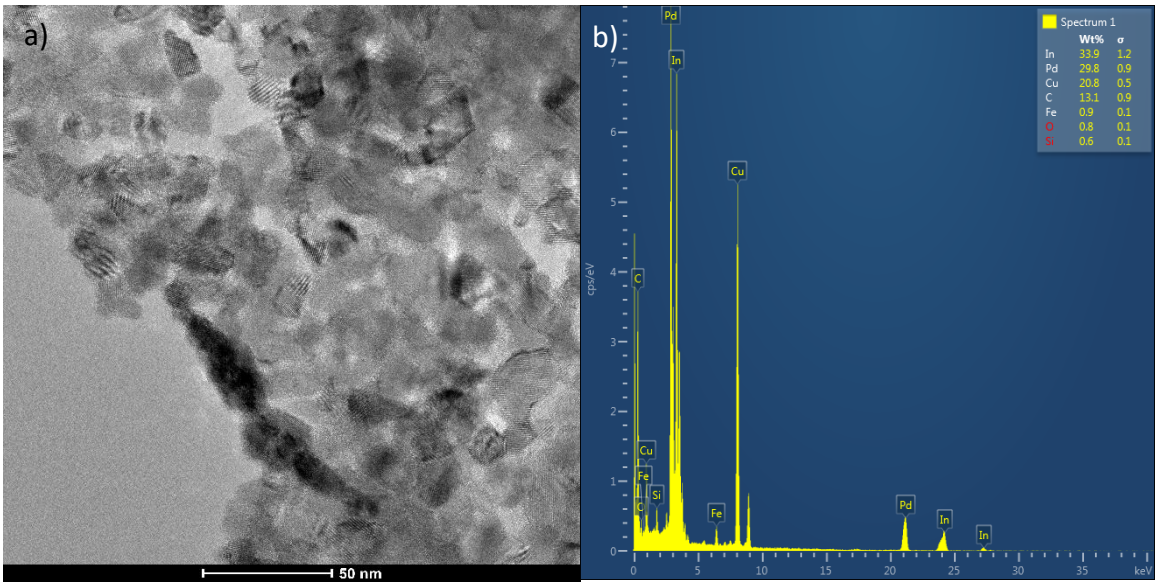


***Fig. S7**: a) TEM micrograph of a reacted sample of catalyst Pd/In_2O_3. b) Example of an EDX spectrum recorded on one spot of the material.*

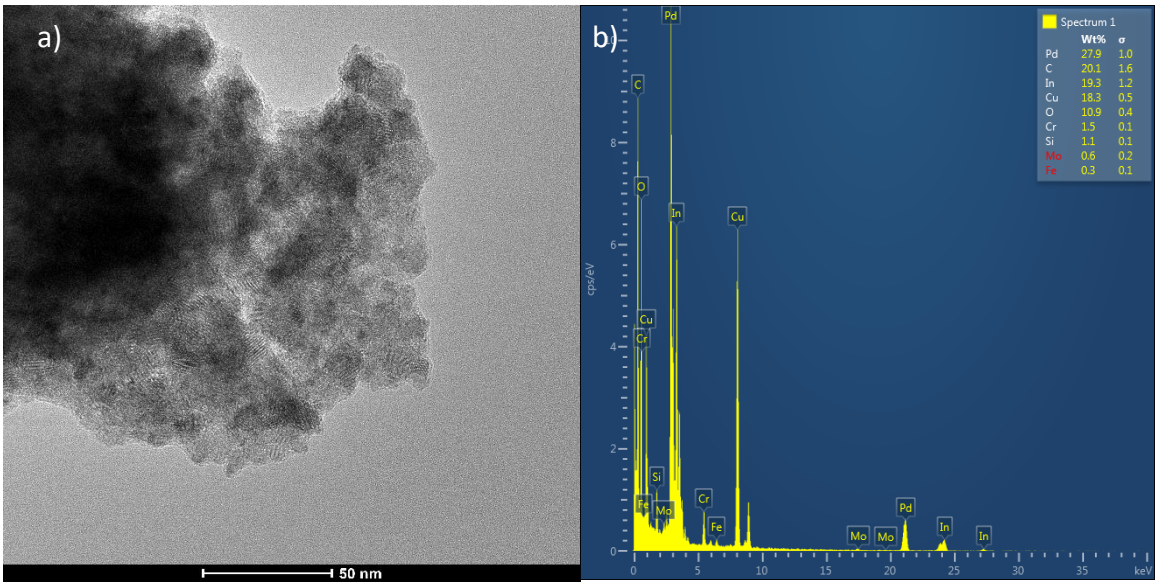
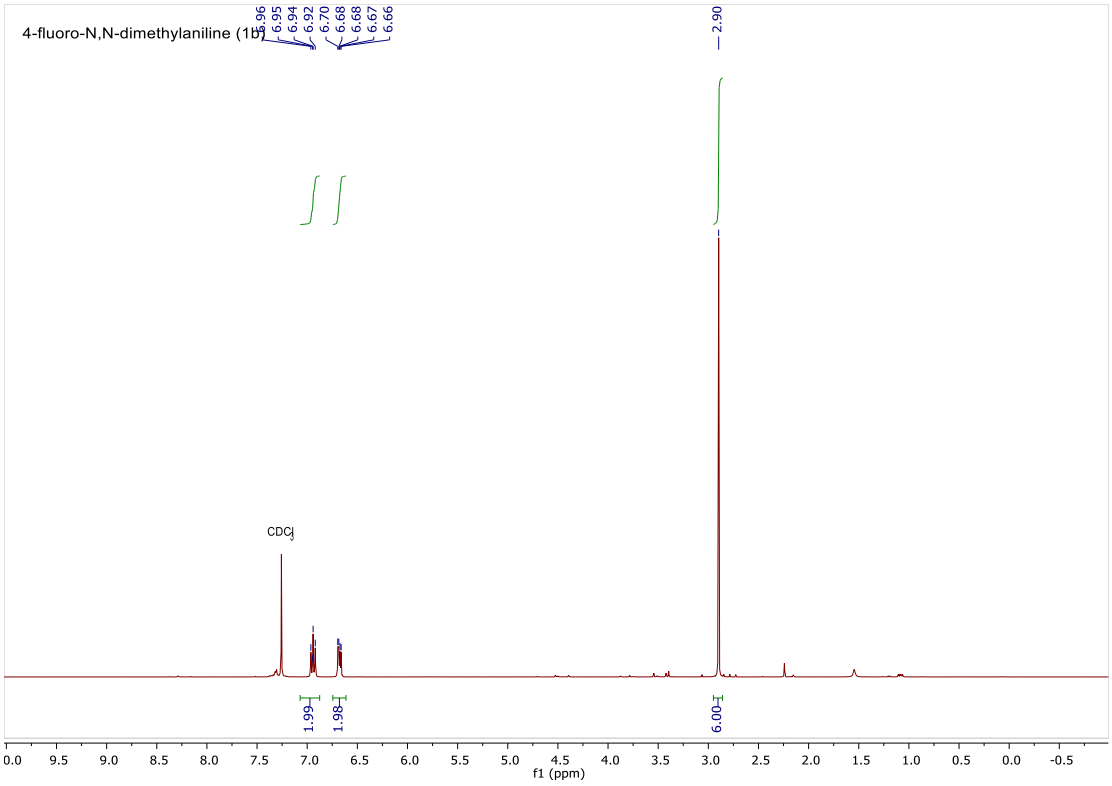


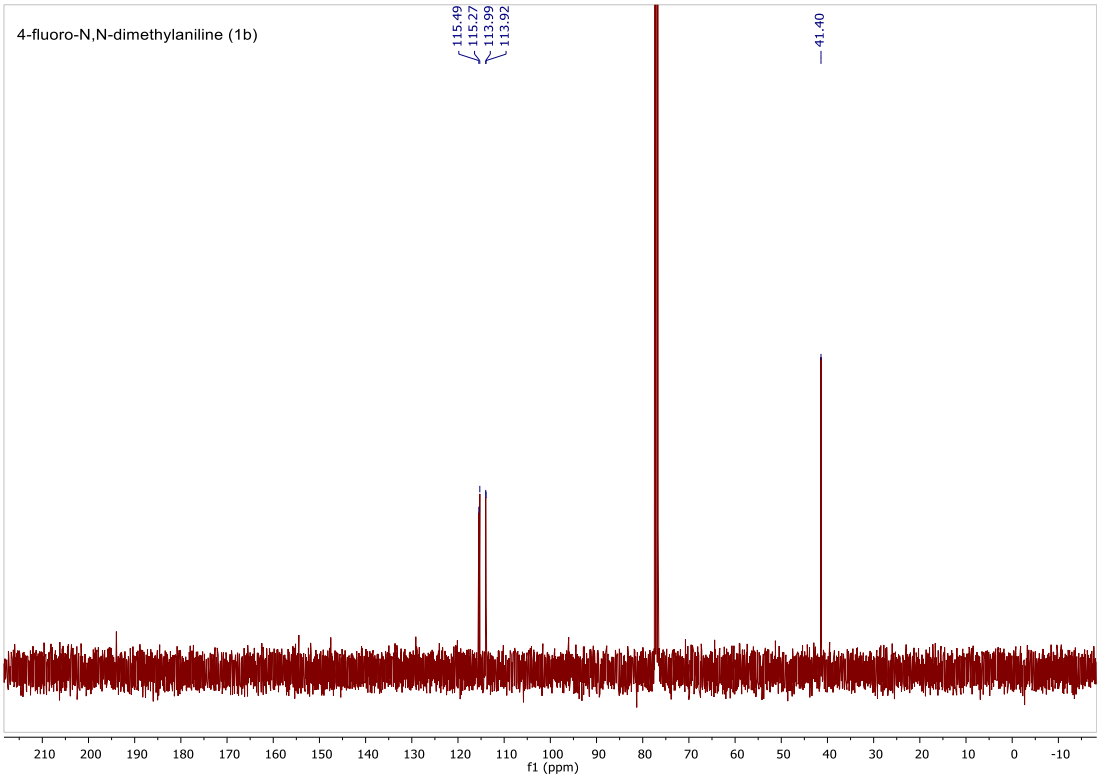
***Fig. S8**: a) TEM micrograph of a recycled sample of catalyst Pd/In_2O_3. b) Example of an EDX spectrum recorded on one spot of the material.*

Spectral data

4-fluoro-N,N-dimethylaniline (1b)

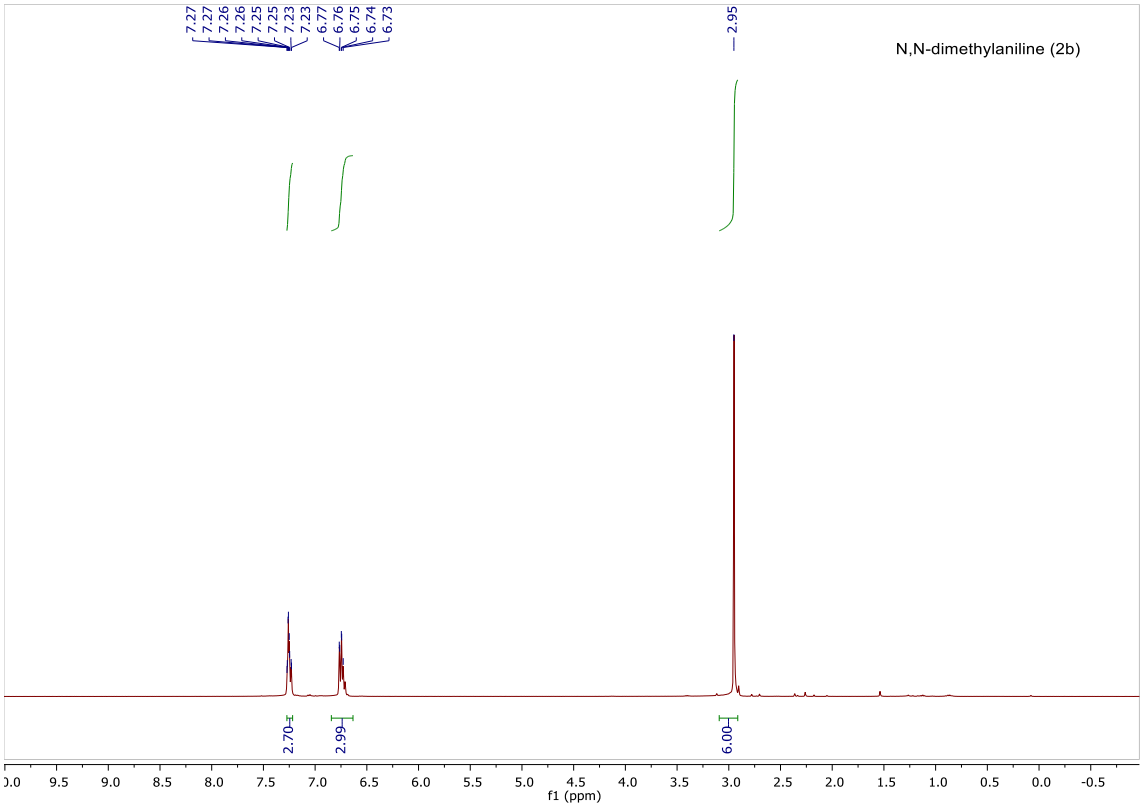
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.90 (s, 6H), 6.66-6.70 (m, 2H), 6.92-6.96 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 41.40, 113.92, 113.99, 115.27, 115.49

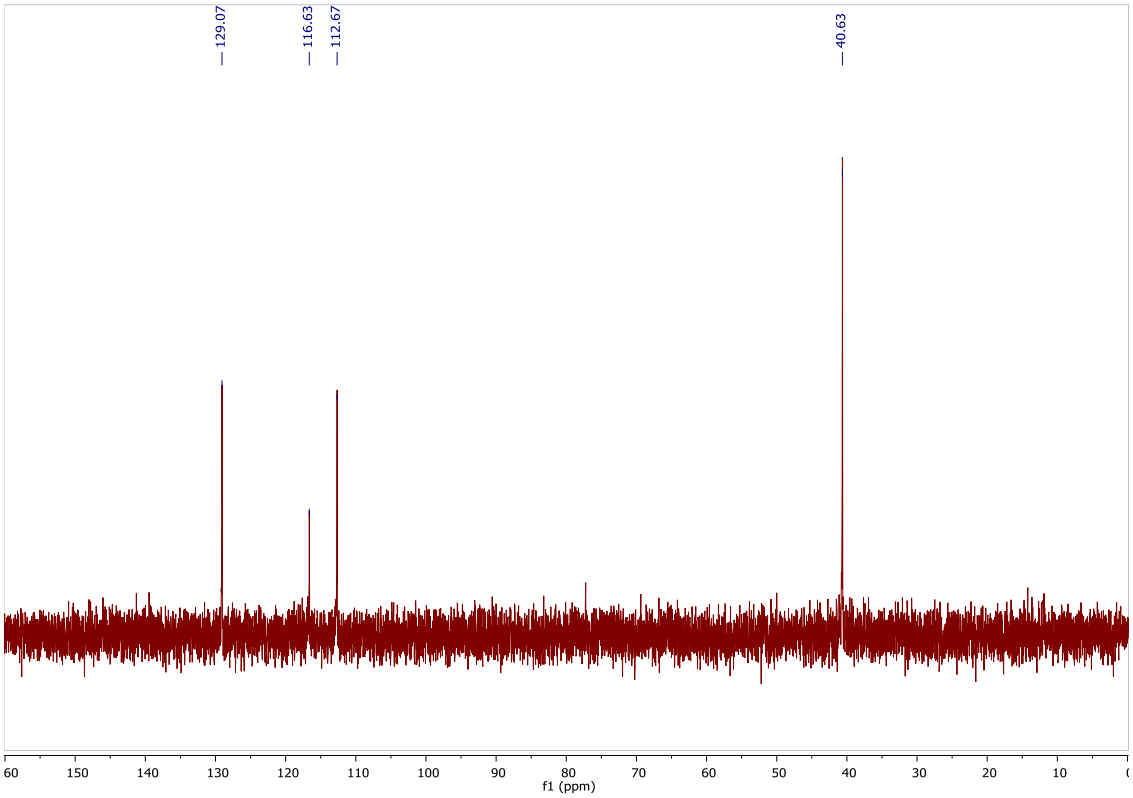




N,N-dimethylaniline (2b)

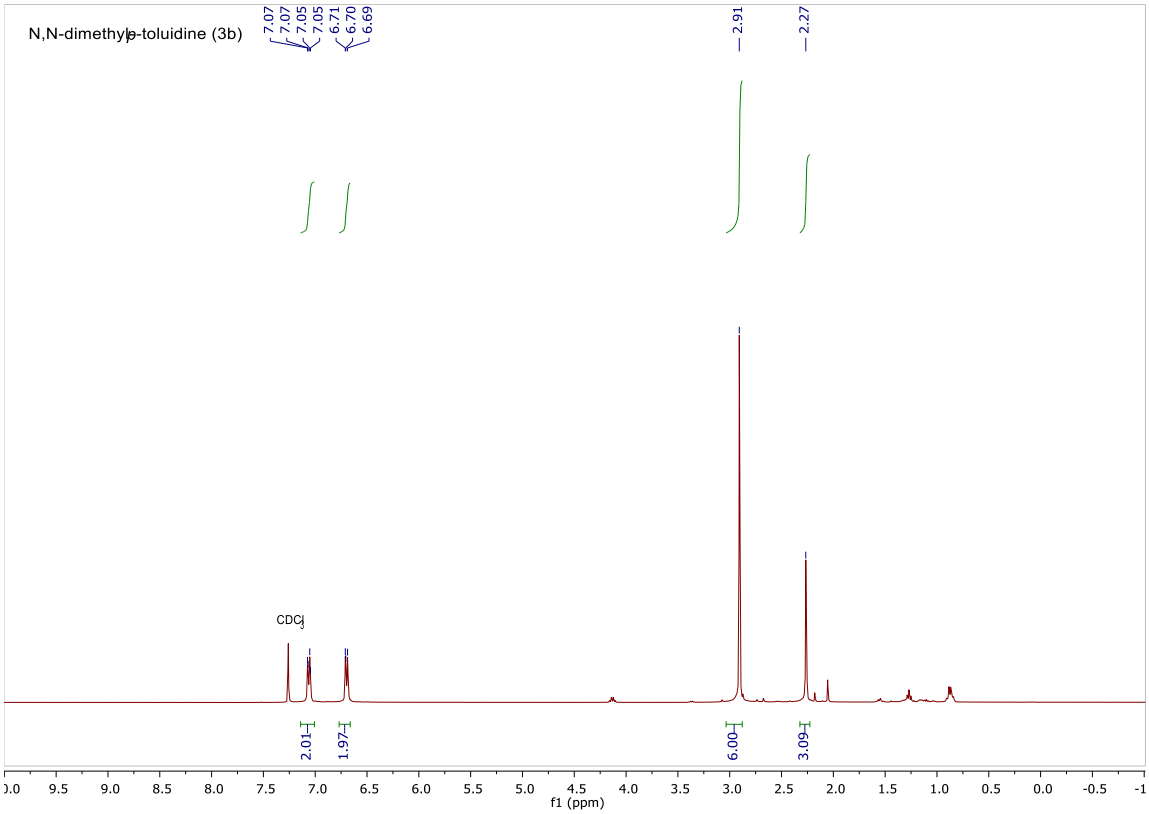
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.95 (s, 6H), 6.73-6.77 (m, 3 H), 7.23-7.27 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 40.63, 112.67, 116.63, 129.07

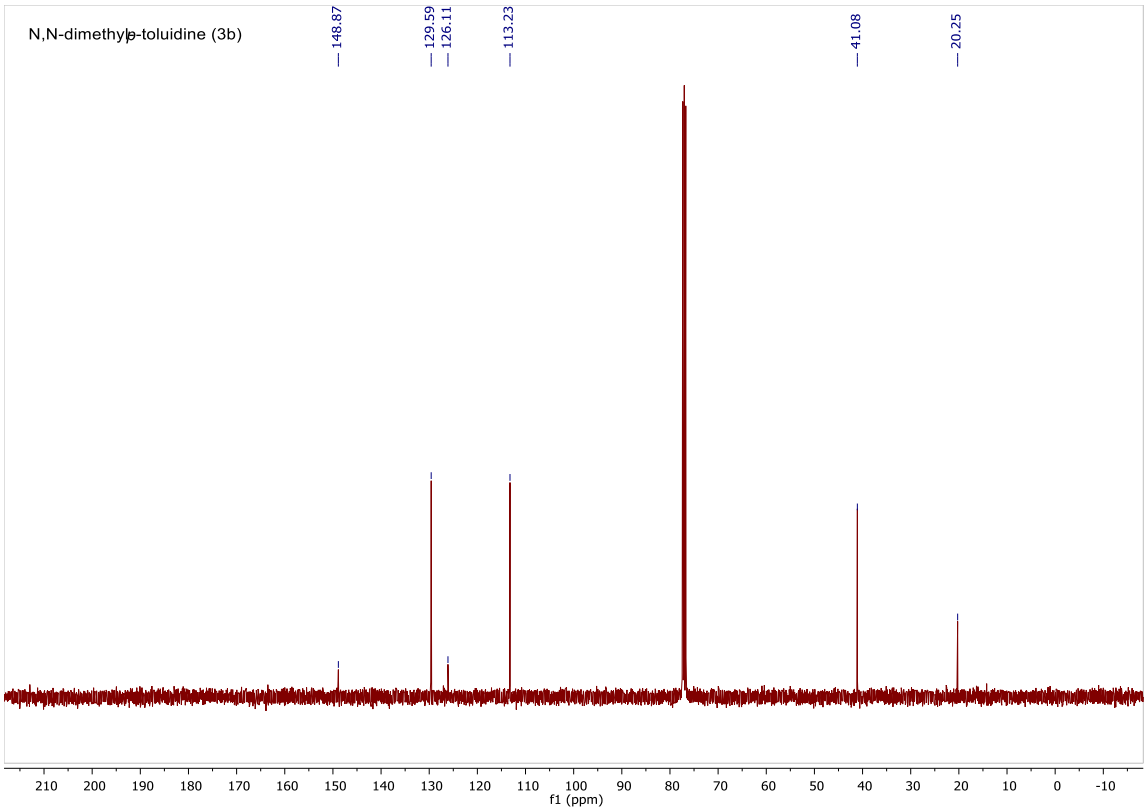




N,N-dimethyl-p-toluidine (3b)

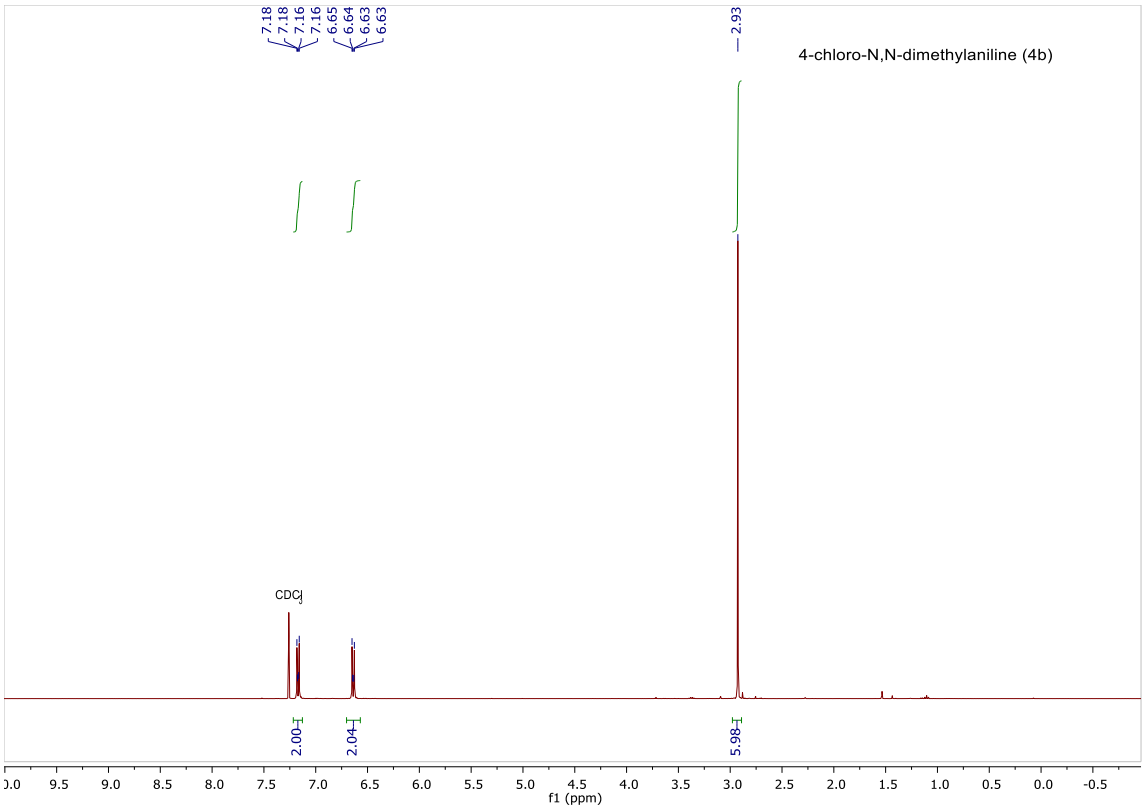
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.27 (s, 3H), 2.91 (s, 6H), 6.69-6.71 (m, 2H), 7.05-7.07 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 20.25, 41.08, 113.23, 126.11, 129.59, 148.87

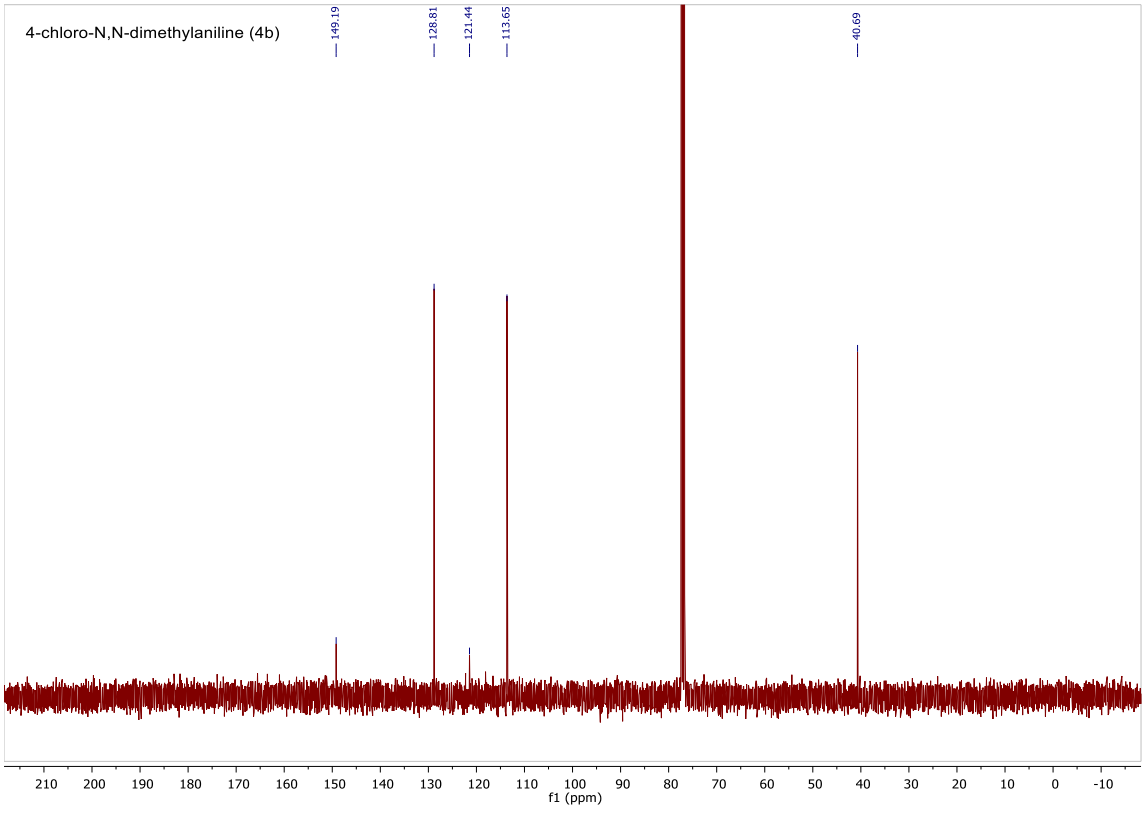




4-chloro-N,N-dimethylaniline (4b)

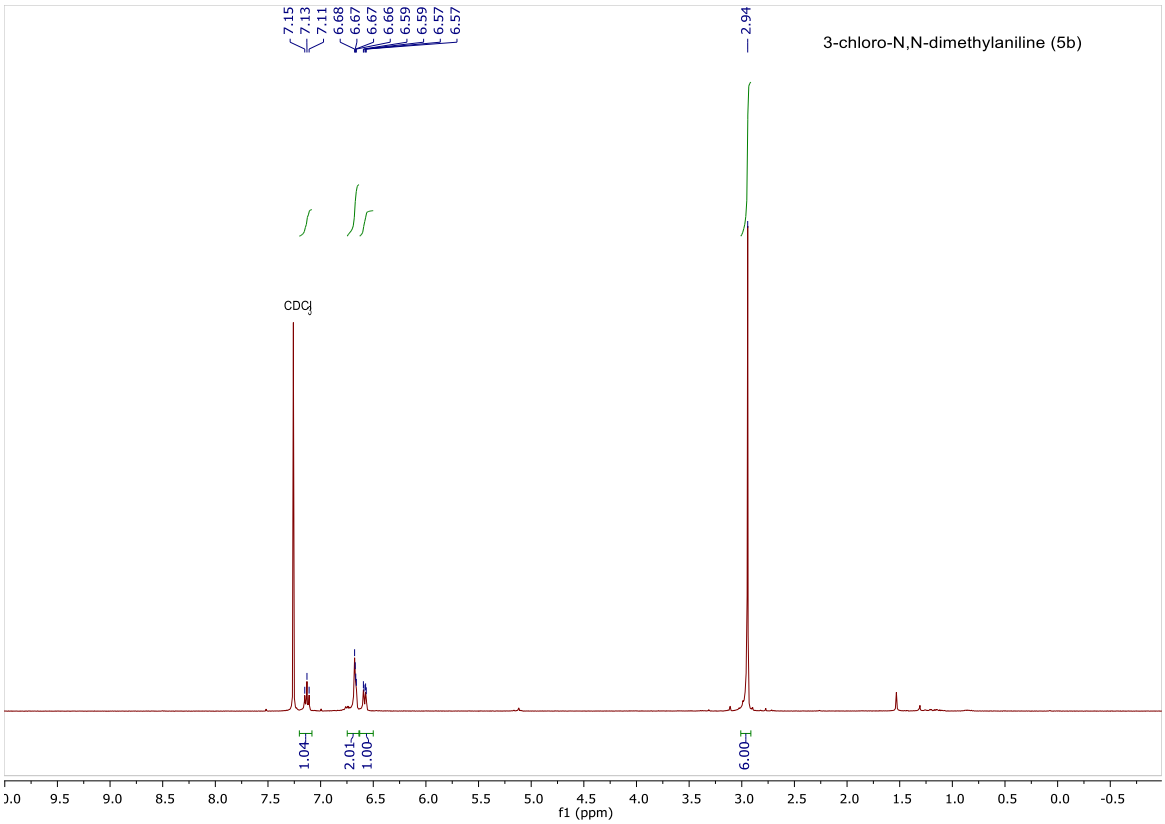
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.93 (s, 6H), 6.63-6.65 (m, 2H), 7.16-7.18 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 40.69, 113.65, 121.44, 128.81, 149.19

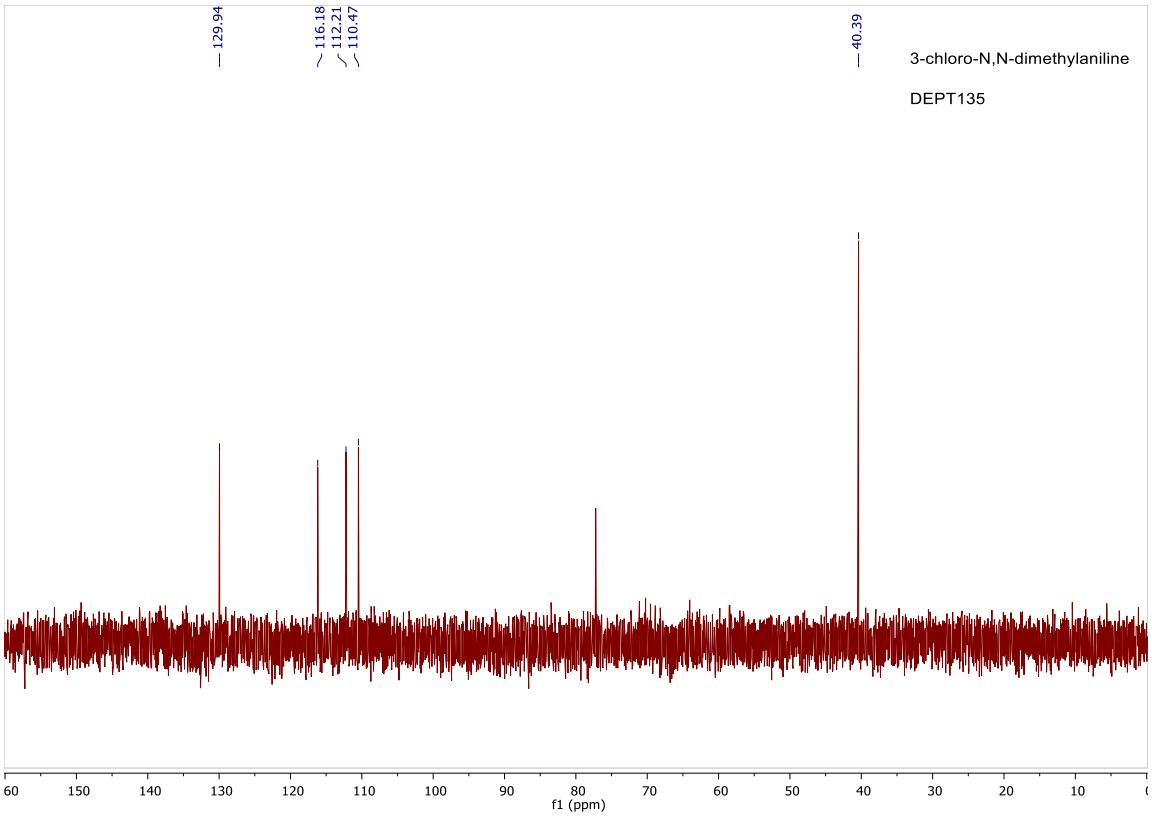




3-chloro-N,N-dimethylaniline (5b)

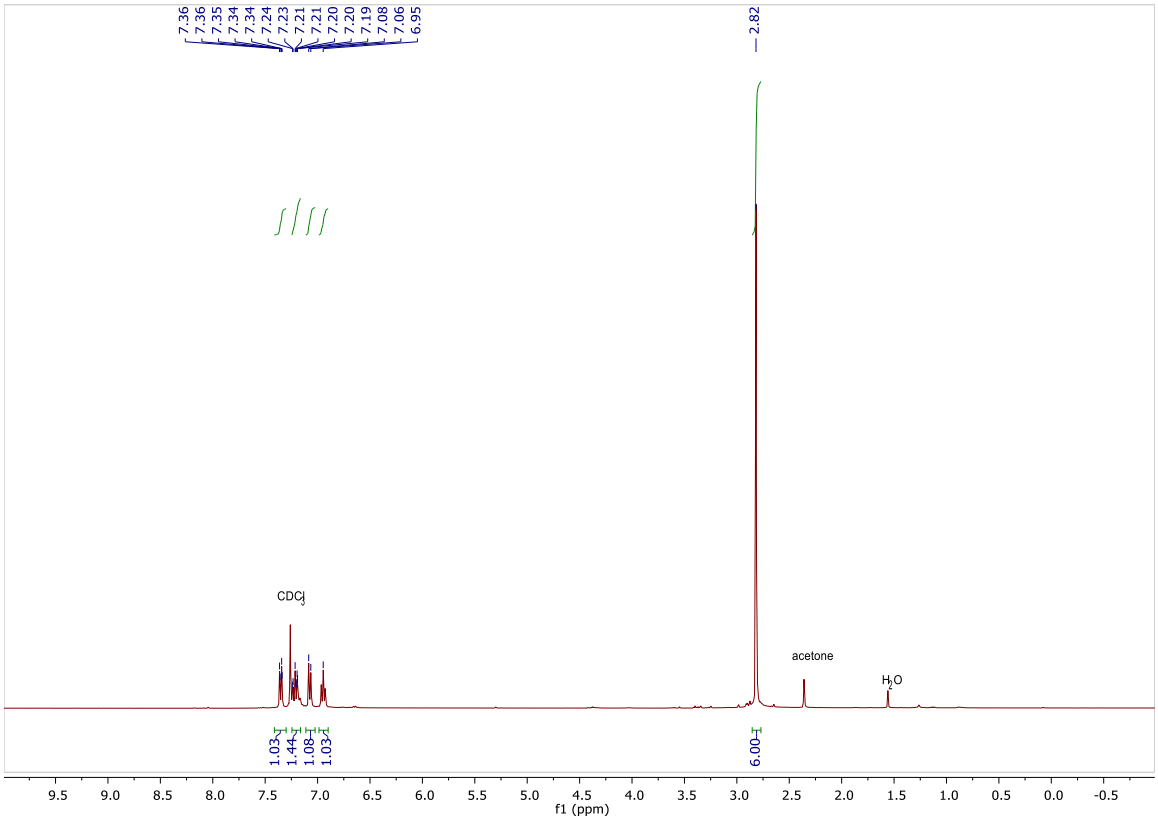
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.94 (s, 6 H), 6.57-6.59 (m, 1 H), 6.67-6.68 (m, 2H), 7.11-7.15 (m, 1 H); ^{13}C NMR (100.63 MHz, $CDCl_3$, DEPT135): δ (ppm) = 40.39, 110.47, 112.21, 116.18, 129.94

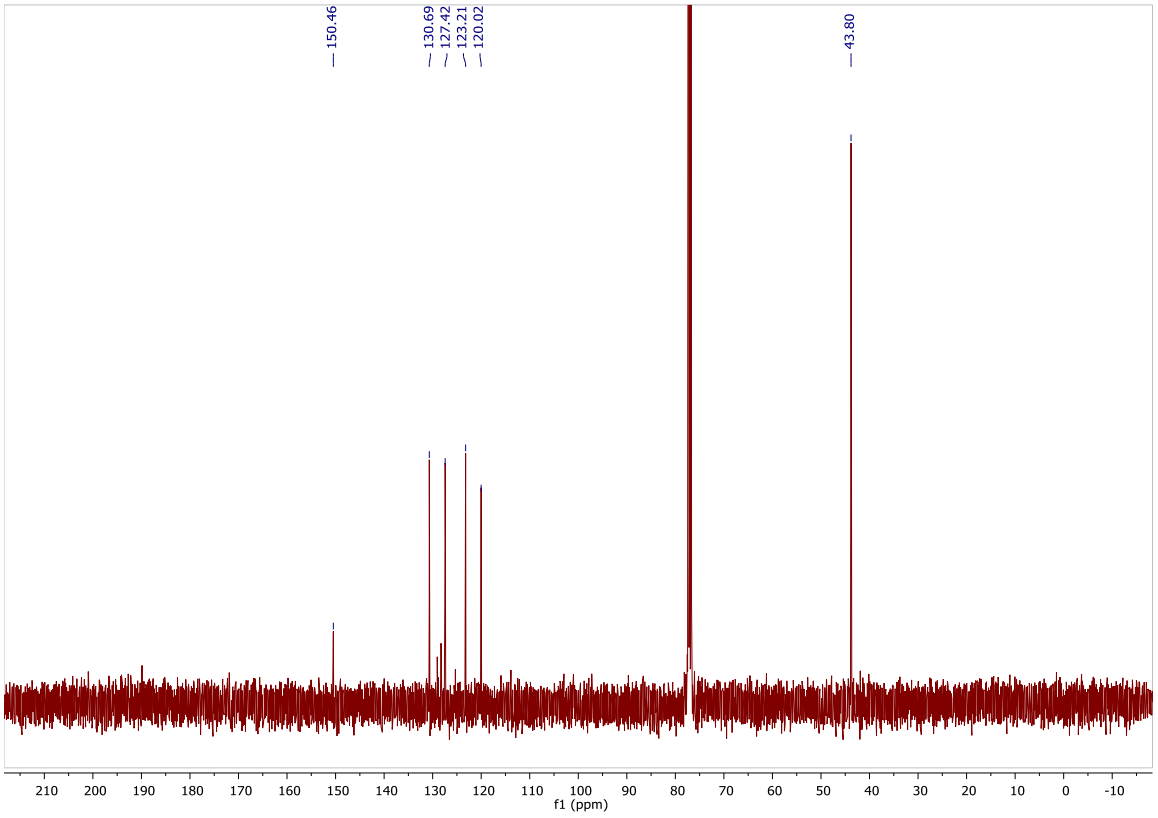




2-chloro-N,N-dimethylaniline (6b)

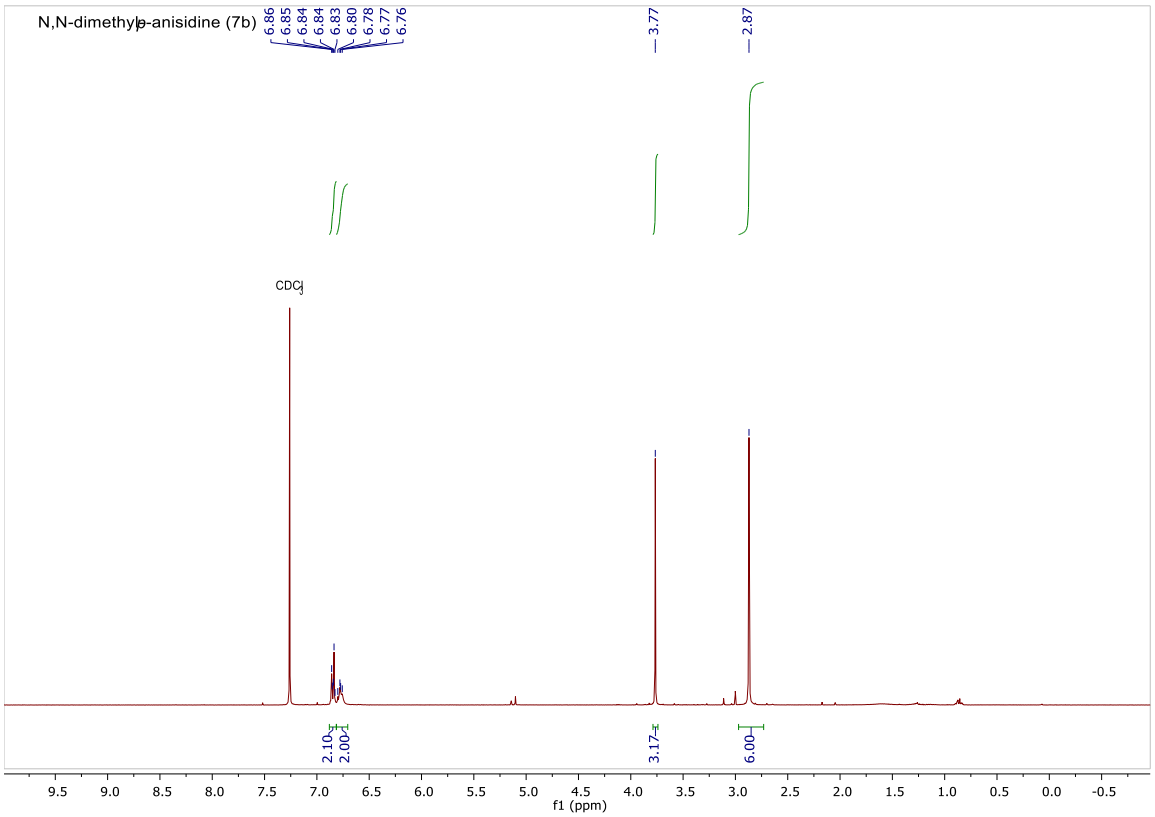
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.82 (s, 6 H), 6.93-6.97 (m, 1 H), 7.06-7.08 (m, 1H), 7.19-7.24 (m, 1 H), 7.34-7.36 (m, 1H)f; ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 43.80, 120.02, 123.21, 127.42, 130.69, 150.46

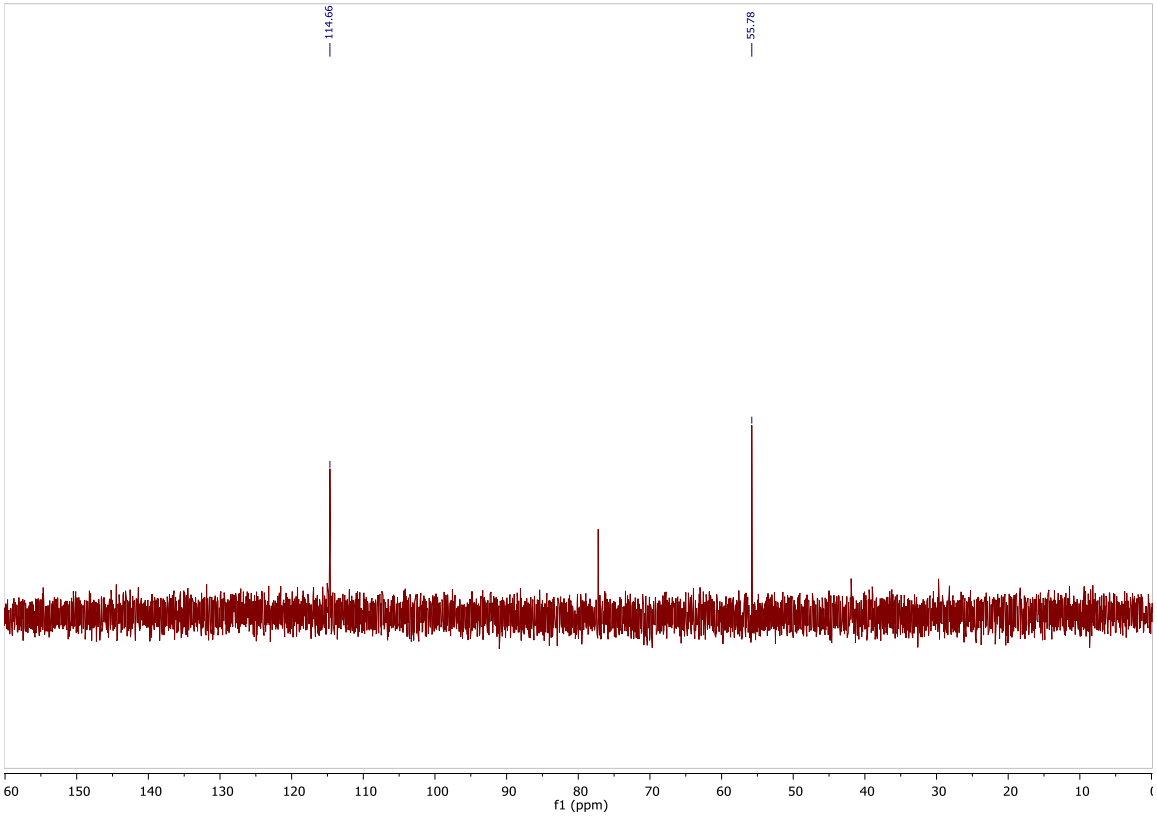




N,N-dimethyl-p-anisidine (7b)

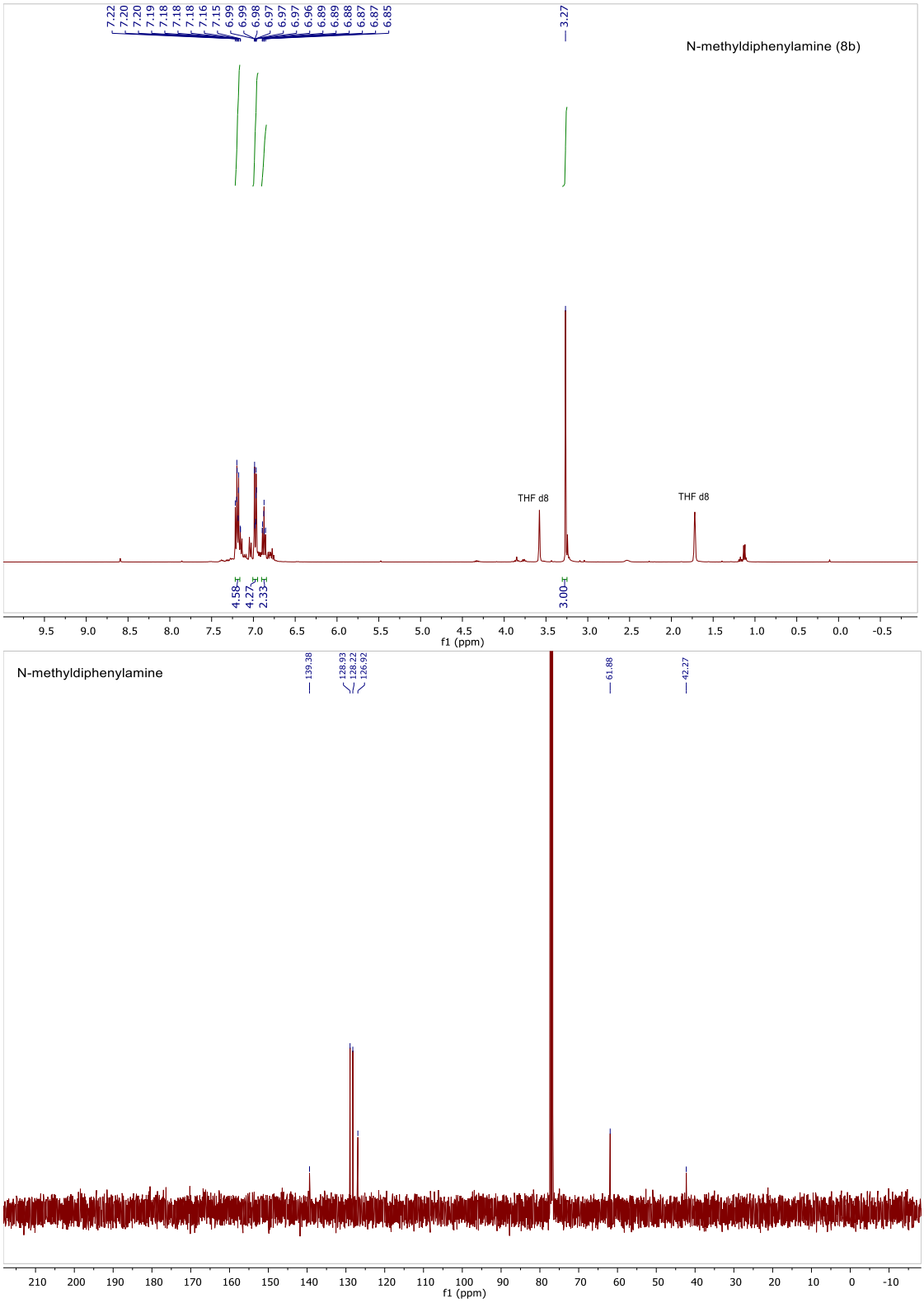
^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 2.87 (s, 6H), 3.77 (s, 3H), 6.76-6.80 (m, 2H), 6.80-6.86 (m, 2H), 6.84-6.86 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$, DEPT135): δ (ppm) = 55.78, 114.66





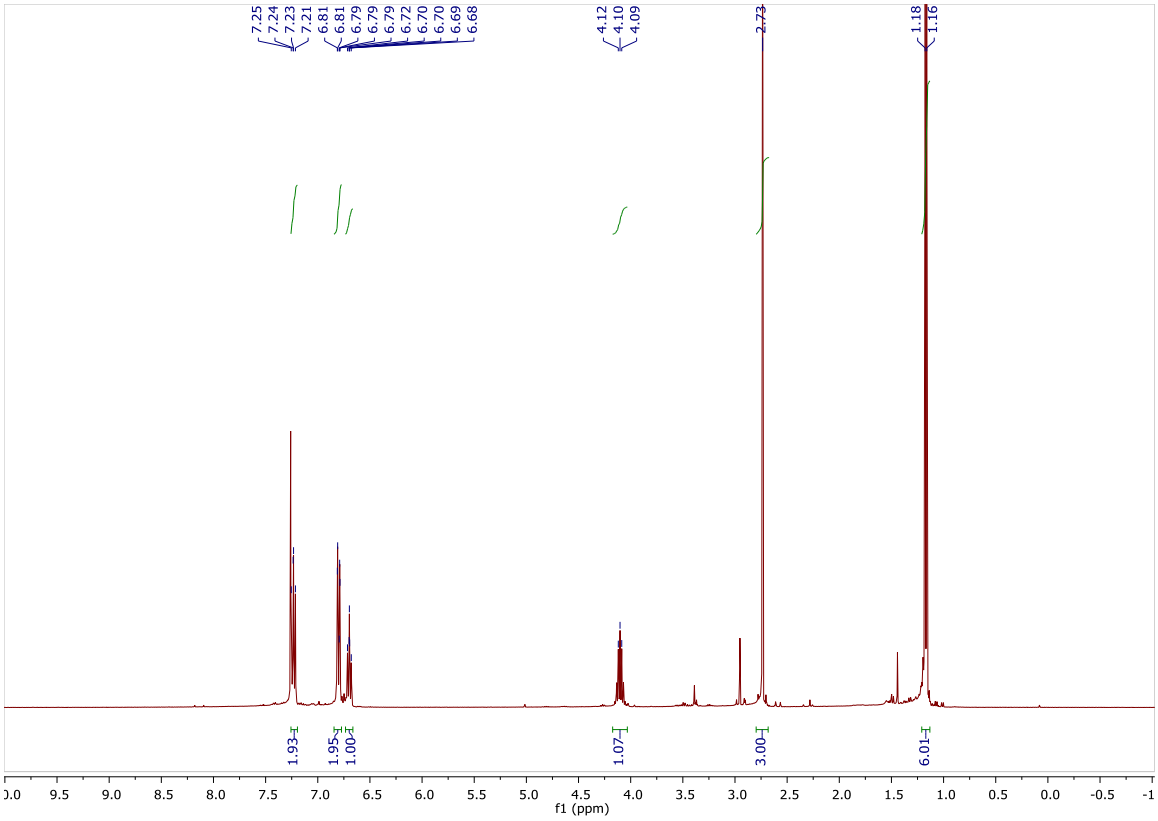
N-methyldiphenylamine (8b)

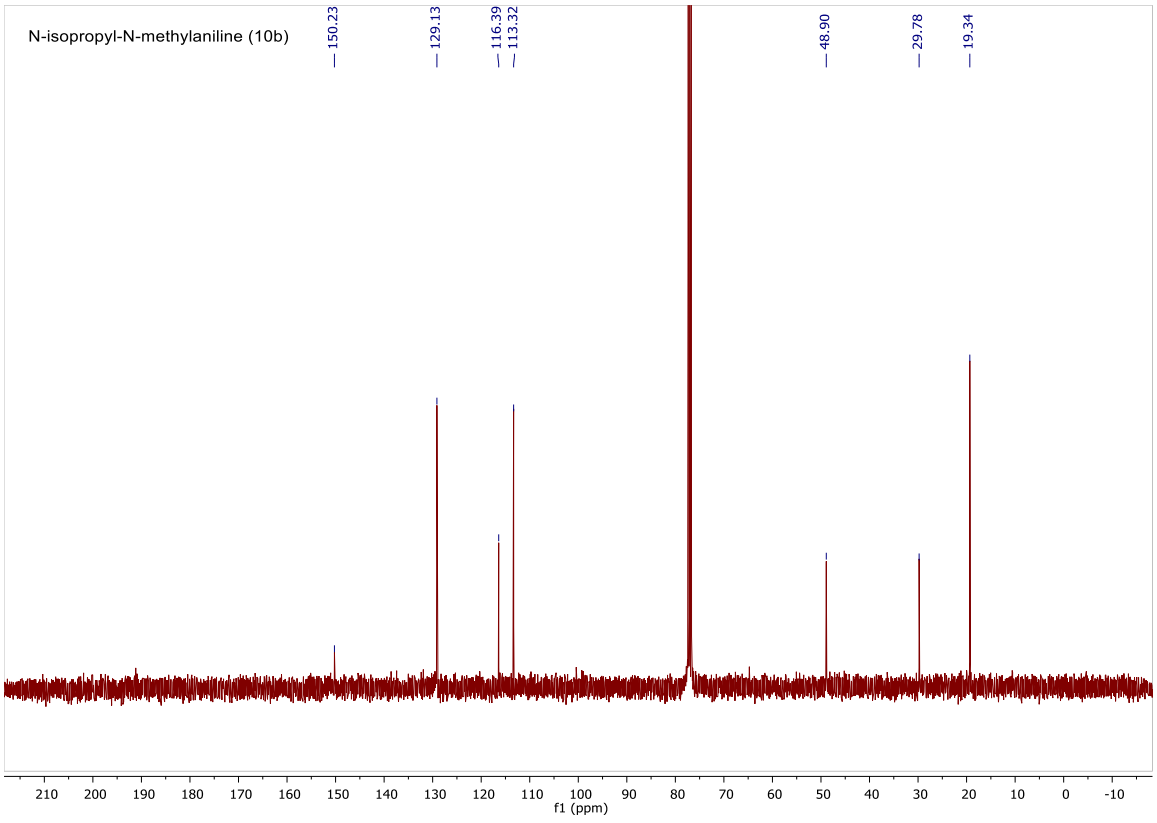
^{1}H-NMR (400.132 MHz, THF d8): δ (ppm) = 3.26 (s, 3H), 6.87 (m, 2H), 6.98 (m, 4H), 7.19 (m, 4H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 42.27, 61.88, 126.92, 128.22, 128.93, 139.38



N-isopropyl-N-methylaniline (10b)

^{1}H-NMR (400.132 MHz, $CDCl_3$): δ (ppm) = 1.17 (d, 6H), 2.73 (s, 3H), 4.10 (t, 1H), 6.68-6.72 (m, 1H)-6.79-6.81 (m, 2H), 7.21-7.25 (m, 2H); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ (ppm) = 19.34, 29.78, 48.90, 113.32, 116.39, 129.13, 150.23





1. R. J. Lundgren, A. Sappong-Kumankumah and M. Stradiotto, *Chemistry – A European Journal*, 2010, **16**, 1983-1991.
2. L. Huang, X. Zhang and Y. Zhang, *Org. Lett.*, 2009, **11**, 3730-3733.
3. D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 57-68.