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Supporting Information

Tailoring the Chemical Structure of Nitrogen-Doped Carbon Dots for Nano-Aminocatalysis in Aqueous Media

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List of abbreviations

^{1}H-NMR Proton Nuclear Magnetic Resonance

^{19}F-NMR Fluorine Nuclear Magnetic Resonance

AFM Atomic force microscopy

Arg L-Arginine

BCA Bicinchonininc acid

ATR-IR Attenuated Total Reflectance - Infrared spectroscopy

BDA 1,4-Diaminobutane**.**

NCDs Nitrogen Carbon Nanodots

EDA 1,2-Diaminoethane

HDA 1,6-Diaminohexane

KT Kaiser Test

Lys L-Lysine

QY Quantum yield

r.T. Room Temperature

TGA Thermogravimetric analysis

UV-Vis Ultraviolet-visible spectroscopy

A.1. GENERAL INFORMATION

The microwave synthesis was performed on a CEM Discover-SP instrument. UV-Vis measurements were carried out on Cary 5000 UV-Vis-NIR. All the spectra were recorded at room temperature using 10 mm path-length quartz cuvettes. Emission spectra and absolute Quantum Yield (QY) have been recorded utilizing FS5 Spectrofluorometer provided by Edinburgh Instruments Ltd equipped with a SC-30 Integrating Sphere. AFM images were obtained with a Nanoscope IIIa, VEECO Instruments. As a general procedure to perform AFM analyses, tapping mode with a HQ:NSC19/ALBS probe (80kHz; 0.6 N/m) (MikroMasch) from drop cast of samples in an aqueous or MeOH solutions (concentration in the order of µg/mL) on a mica substrate was performed. The AFM raw data were analyzed using S3 Gwyddion 2.35. TGA was performed with a TGA Q500 (TA instruments), under a flow of N_2 (25 mL/min), following a temperature program consisting in the equilibration of the sample at 100°C for 10 minutes followed by a ramp at 5°C/min up to 800°C. The sample aliquot ranged from 1 to 2 mg, exactly weighed. ATR-IR measurements were performed using a Spectrum 2000 FT-IR Instrument (Perkin Elmer). The NMR spectra were recorded on Varian 400 spectrometer (^{1}H: 400 MHz; ^{19}F-NMR: 376.0 MHz ^{13}C: 101.0 MHz).

General procedures. All organocatalytic reactions were set up in glass vials, unless otherwise stated. Chromatographic purification of products was accomplished using flash chromatography on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were employed, using UV light as the visualizing agent (254 nm), basic aqueous potassium permanganate ($KMnO_4$) stain solution or iodine, and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. Dialysis tubes Float-A-Lyzer® with molecular weight cutoff 0.5-1 Kda were bought from Spectrum Labs and used as stated by the manufacturer. The power supply for electrophoresis was bought from Consort (Model E844). Ultrapure fresh water obtained from a Millipore water purification system (>18 MΩ Milli-Q, Millipore) was used in all experiments.

Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich, Fluka, Alfa Aesar, Fluorochem and VWR. They were used as received, without further purification, unless otherwise stated. Synthesis grade and anhydrous solvents were used as purchased. The preparation of starting materials **2l**, **4a-d** is detailed in Section C.1.

B.1. GENERAL PROCEDURES FOR THE SYNTHESIS OF NCDs 1-5

For the synthesis of NCDs **1-5**, the following experimental procedures have been followed, as previously reported in the literature.[1,2]

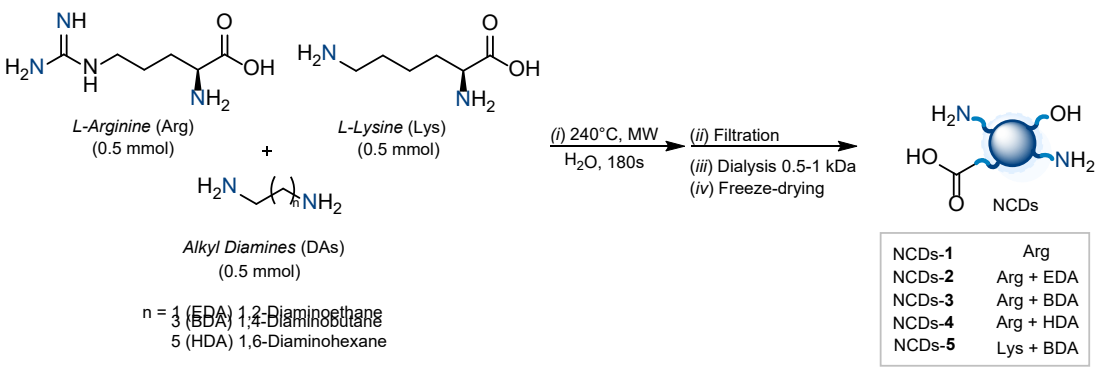


Figure S1. General synthetic scheme for the preparation of NCDs.

Mono-component synthesis: Arg (87.0 mg, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were added into a sealable microwave reaction vessel and subsequently heated in a microwave reactor (200 W) at 240°C, 26 bar for 180 seconds.

Bi-component synthesis: Arg (87.0 mg, 0.5 mmol, 1 equiv.) or Lys (73.1 mg, 0.5 mmol, 1 equiv.), Milli-Q water (100.0 µL), along with one of the alkyl diamines selected for this experimental work (Figure S1), namely EDA or BDA or HDA (0.5 mmol, 1 equiv.) were added into a sealable microwave reaction vessel and subsequently heated in a microwave reactor (200 W) at 240°C for 180 seconds.

The solution of the starting materials changes color from transparent to brown because of the formation of CDs. The solution was then diluted with water and filtered through a 0.1 µm PTFE microporous membrane. The crude so obtained was dialyzed against Milli-Q water through a dialysis membrane (0.5-1 kDa Cut-Off) Float-A-Lyzer® for 48 hours. The resulting aqueous solution of CDs was lyophilized resulting in an orange-to-yellow fluffy solid. The solid was collected and its weight was measured. To prevent the absorption of moisture the samples have been kept in a desiccator.

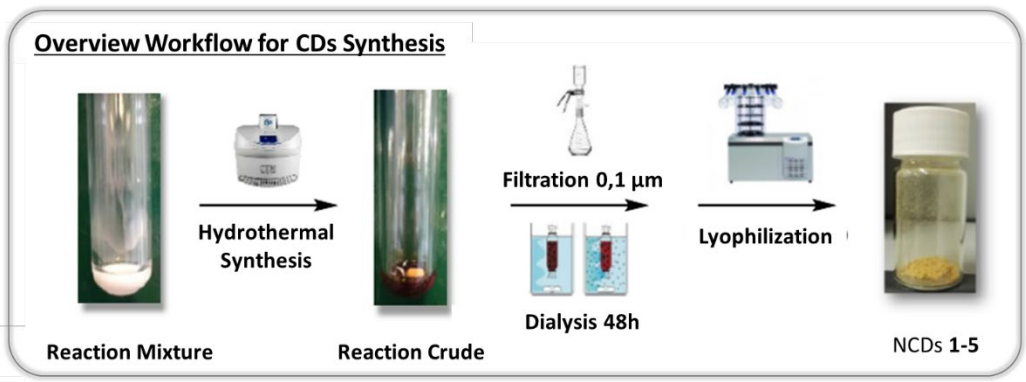


Figure S2. Summary of NCDs **1-5** preparation in the herein work.

NCDs-**1**. L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were heated in a microwave reactor (200 W) at 240°C for 180 seconds. The aqueous solution of NCDs-8 was lyophilized giving a yellow solid (NCDs-**1**: 43.0 mg, 49% mass yield).

NCDs-**2**. L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), 1,2-Diaminoethane (EDA) (33.0 µL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were heated in a microwave reactor (200 W) at 240°C for 180 seconds. The aqueous solution of NCDs-8 was lyophilized yielding an orange solid (NCDs-**2**: 29.4 mg, 25% mass yield).

NCDs-**3**. L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), 1,4-Diaminobutane (BDA) (50.0 µL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were irradiated into a microwave reactor (200 W) at 240°C for 180 seconds. The aqueous solution of CDs-3 was lyophilized resulting in a yellow solid (NCDs-**3**: 15.6 mg, 17% mass yield).

NCDs-**4**. L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), 1,6-diaminohexane (HAD) (69.0 µL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were irradiated into a microwave reactor (200 W) at 240°C for 180 seconds. The aqueous solution of CDs-3 was lyophilized resulting in a yellow solid (NCDs-**4**: 14.5 mg, 10% mass yield).

NCDs-**5**. L-Lysine (73.1 mg, 0.5 mmol, 1 equiv.), 1,4-Diaminobutane (BDA) (50.0 µL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 µL) were heated in a microwave reactor (200 W) at 240°C for 180 seconds. The aqueous solution of CDs-7 was lyophilized giving a yellow solid (NCDs-**5**: 14.0 mg, 12% mass yield).

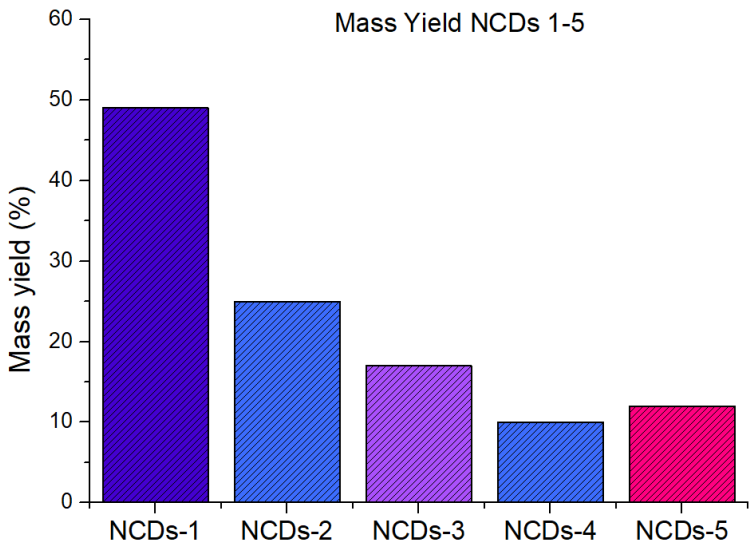


Figure S3. Mass yield for NCDs **1-5**.

B.2. PHYSICO-CHEMICAL CHARACTERIZATION OF NCDs 1-5

B.2.1. PHOTOPHYSICAL CHARACTERIZATION

UV-vis absorption and fluorescence spectra were recorded at a concentration of 0.1 mg/mL in Milli-Q water using a standard quartz cuvette with an optical path length of 1 cm.

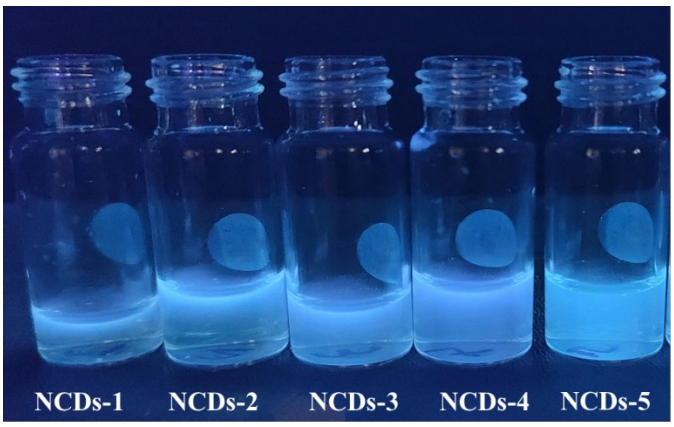


Figure S4. NCDs-**1-5** solutions in water under 365 nm light irradiation.

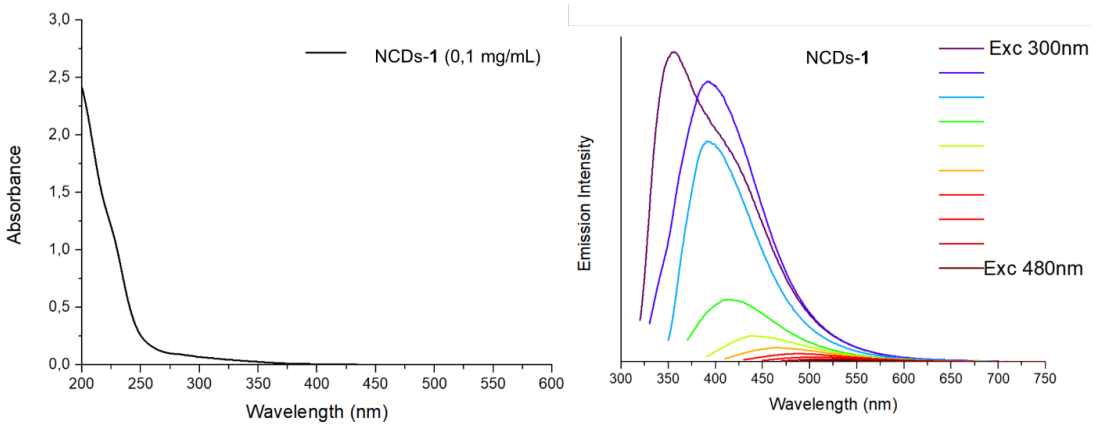


Figure S5. UV-vis and Emission spectra of NCDs-**1**.

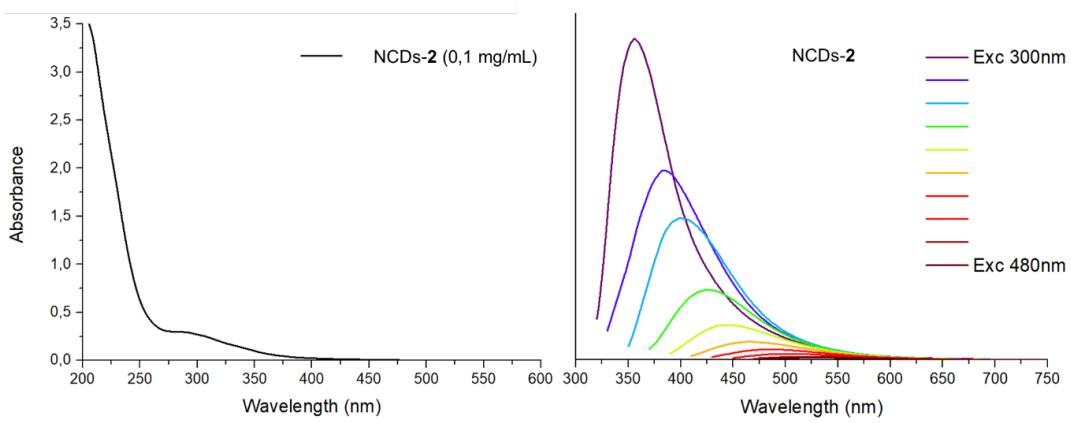


Figure S6. UV-vis and Emission spectra of NCDs-**2**.

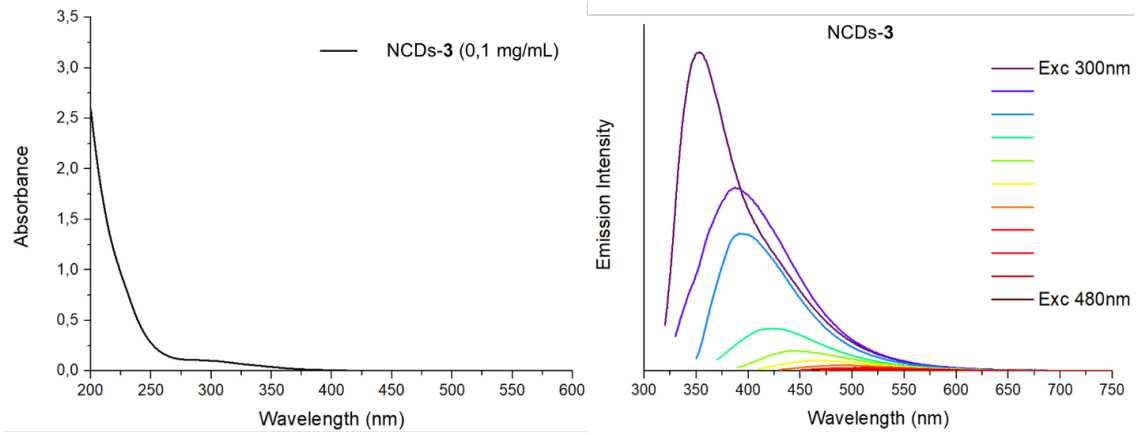


Figure S7. UV-vis and Emission spectra of NCDs-**3**.

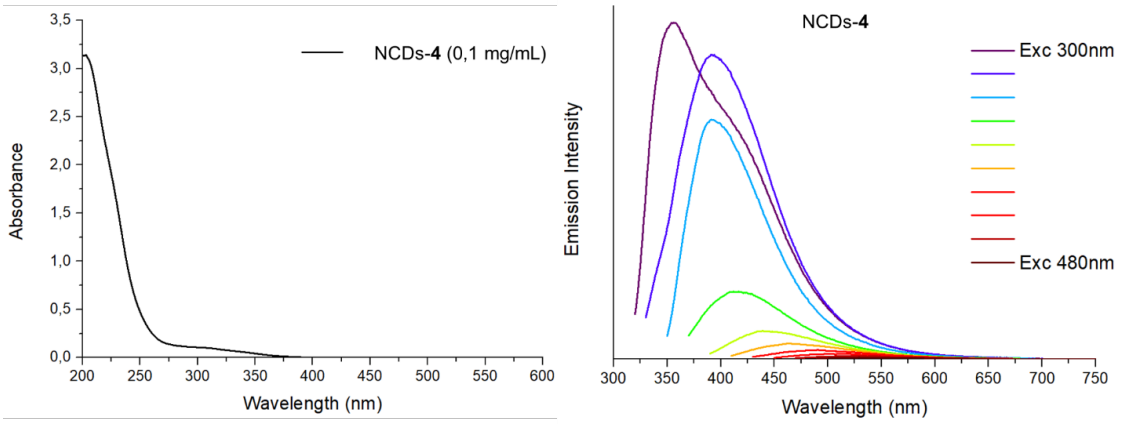


Figure S8. UV-vis and Emission spectra of NCDs-**4**.

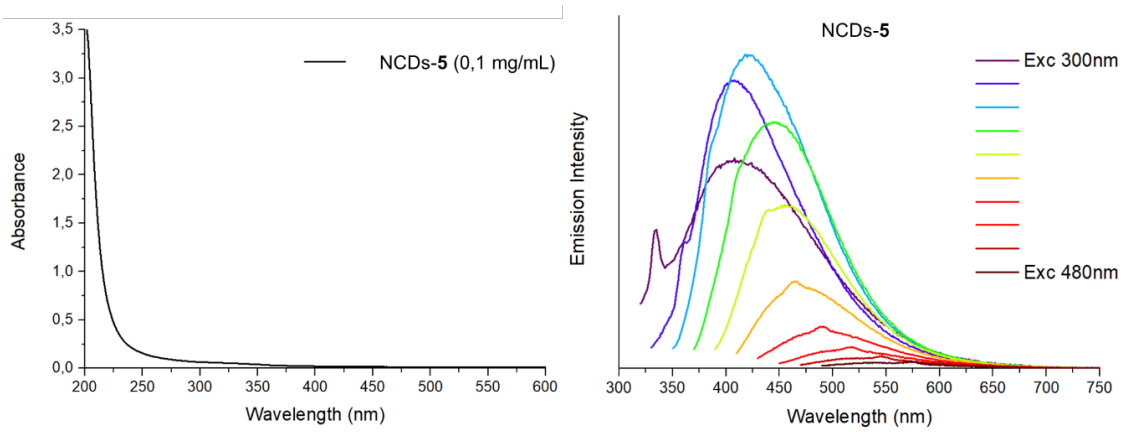


Figure S9. UV-vis and Emission spectra of NCDs-**5**.

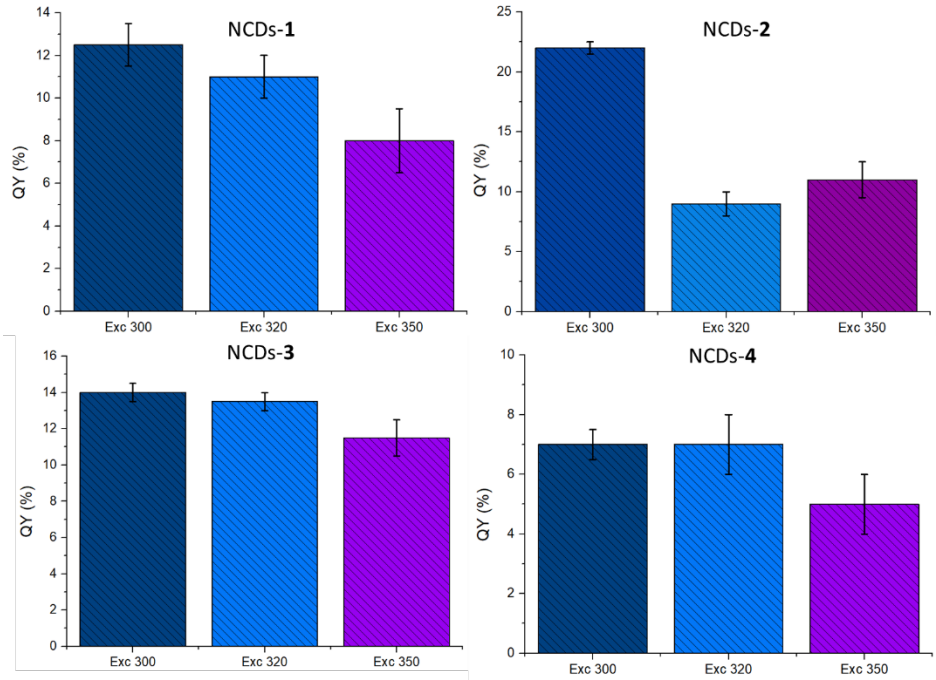


Figure S10. Absolute quantum yield (QY, %) of L-Arginine derived NCDs **1-4**.

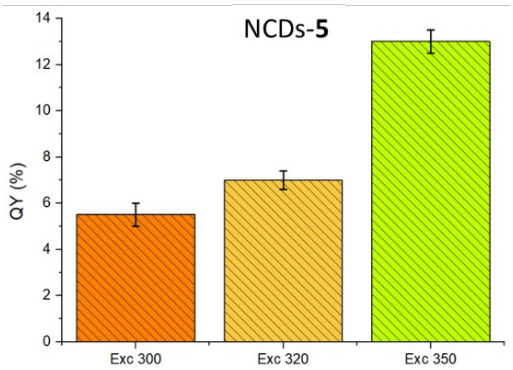


Figure S11. Absolute quantum yield (QY, %) for NCDs-**5**.

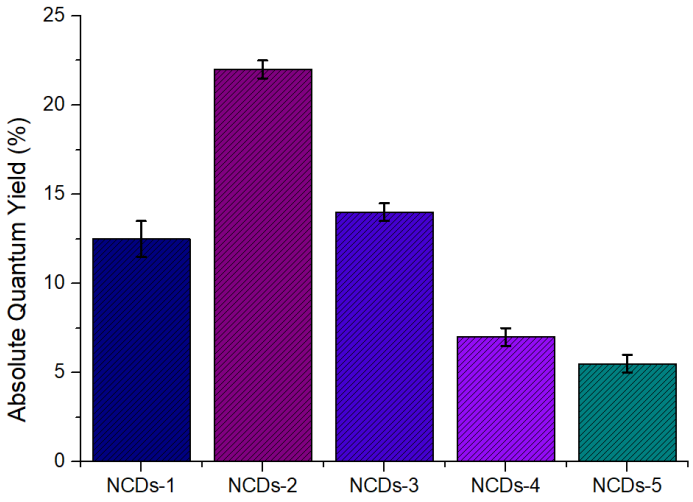


Figure S12. Comparison of absolute QY (%) at 300 nm for NCDs **1-5**.

B.2.2. ^{1}H-NMR CHARACTERIZATION

The ^{1}H-NMR spectra were recorded by dissolving 7 mg of NCDs **1-5** into 700 µL of D_2O.

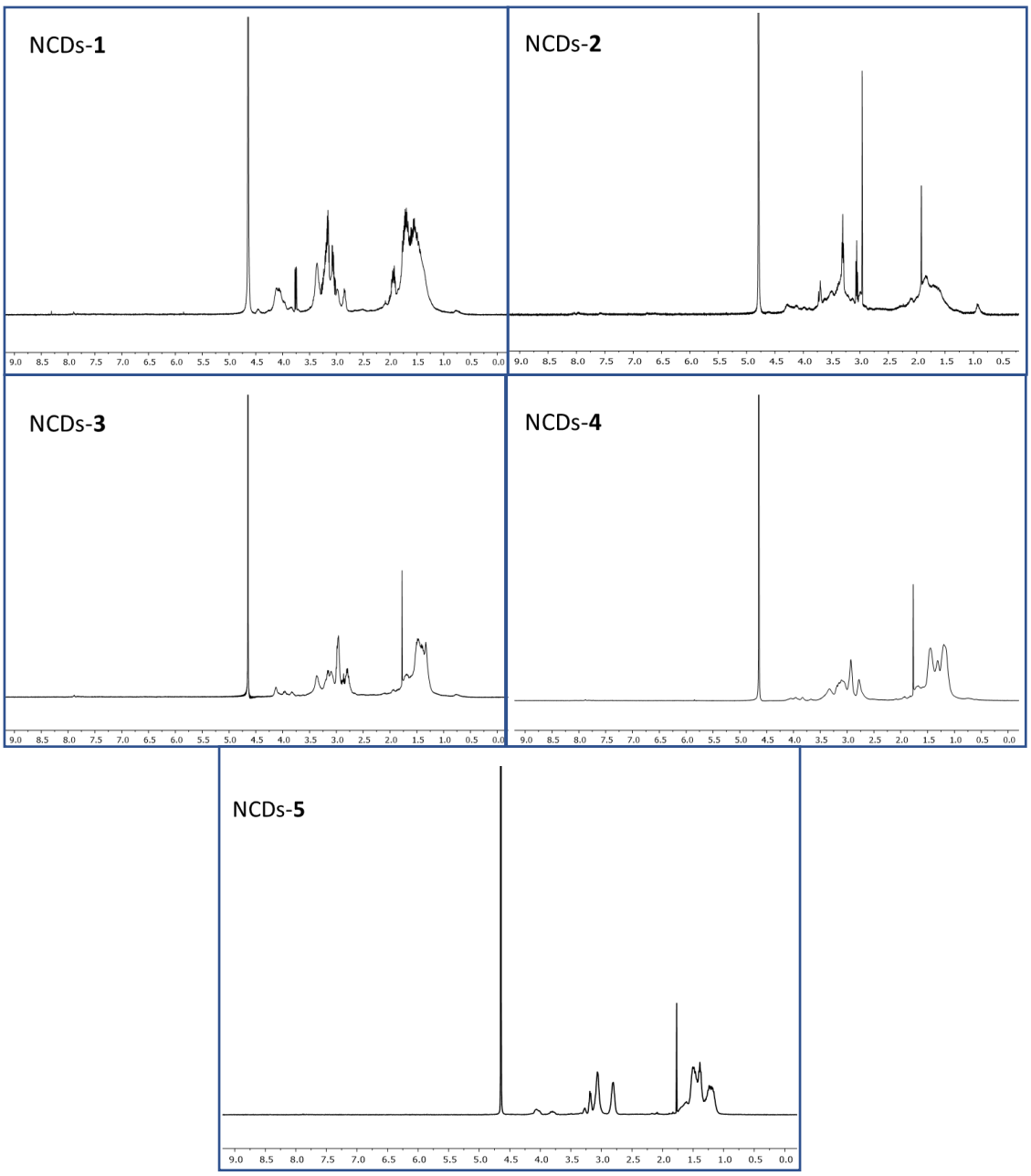


Figure S13. ^{1}H-NMR of NCDs **1-5**.

B.2.3. SURFACE CHARACTERIZATION

Kaiser test procedure. Kaiser tests (KTs) were performed according to a modified protocol by employing a commercially available kit provided by Merck.[3] Typically, about 1 mg of NCDs was placed in a test tube. Then, 75 µL of a phenolic solution in ethanol (Sol A), 100 µL of a KCN solution in pyridine/water (Sol B), and 75 µL of a ninhydrin solution in ethanol (Sol C) were added. The tube was sealed and the so obtained mixture was heated at 120°C for 10 minutes. The resulting solution was diluted with ethanol in water (60% v/v, 1:18 dilution) and its absorption spectrum was recorded. A blank solution was also run to be used as reference. For each sample, at least three independent analyses were performed. Primary amines on the carbon dots surface were thus quantified from the absorbance value recorded at 570 nm, considering a molar absorption coefficient for the ninhydrin derivative of 15000 M^{-1} cm^{-1} (Ruhemann's purple). Equation 1 was used to determine the KT value.

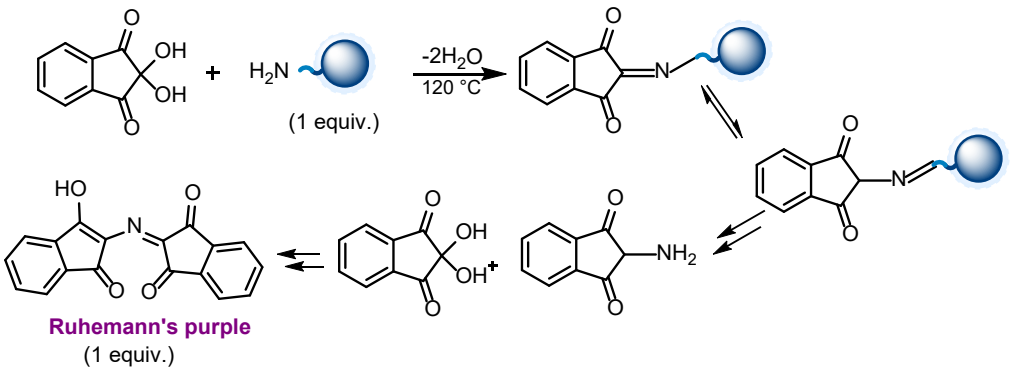


Figure S14. Schematization of Kaiser test molecular mechanism.

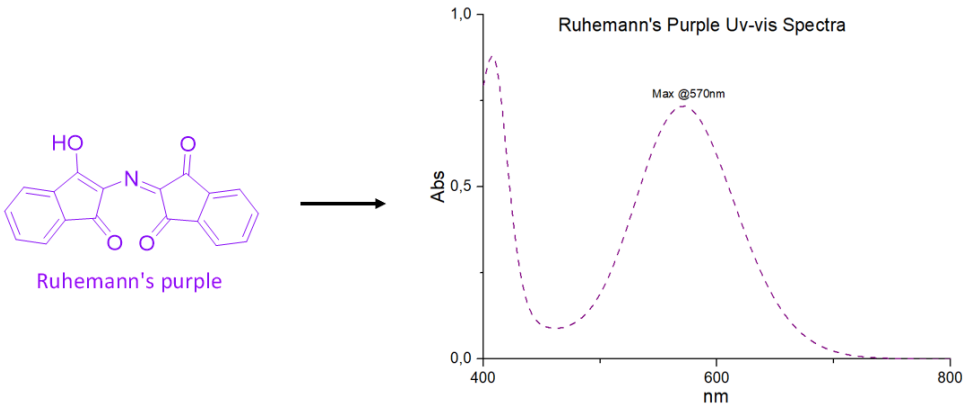


Figure S15. Visible spectra of Ruhemann's purple dye.

$$KT\ (^{\mu mol}/_{g}) = \frac{[Abs@570nm \times dil \times 10^6]}{\varepsilon \times Weight\ (mg)}$$

Equation 1. Calculation of primary amines on NCDs **1-5**.

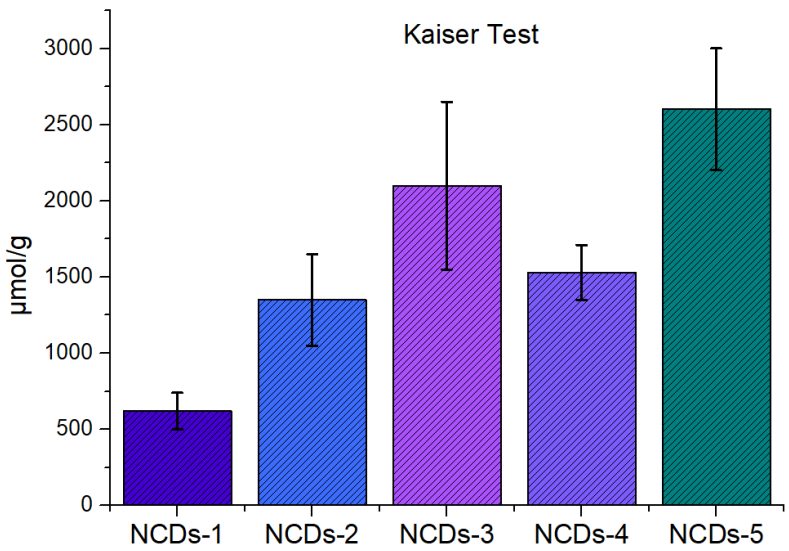


Figure S16. Results of Kaiser test performed at 120°C on NCDs **1-5**.

Room Temperature Kaiser Test. In the accessibility experiments, the analyzed solution was kept at room temperature (r.t., 25°C) throughout the experiment. Therefore, to a known amount of NCDs (about 1 mg), the Kaiser test solutions (Sol A, B and C) were added as previously described. At a

certain time, an aliquot (20 µL) was collected, diluted, and analyzed. The experiment was repeated in triplicate for each NCDs material. Equation 2 was used to determine the accessibility value.

$$Accessibility\ (\%) = \frac{KT\ (r.t)}{KT\ (120\ °C)} \times\ dil\ \times\ 100$$

Equation 2. Determination of the accessibility of the examined amines into the corresponding ninhydrin derivative.

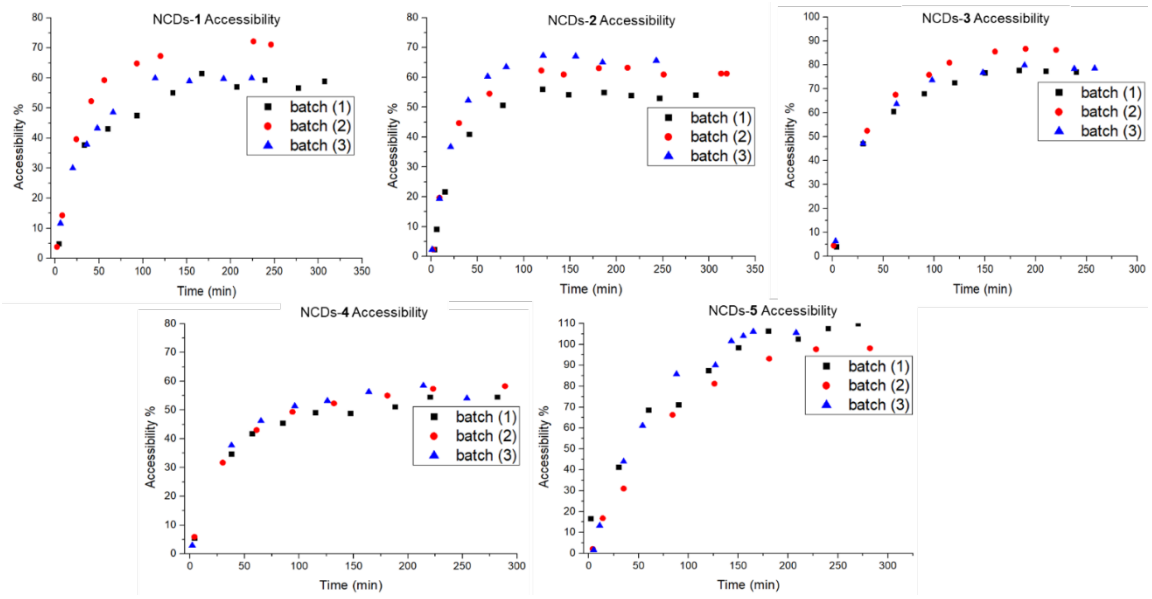


Figure S17. Time-dependent Kaiser test performed at 25°C for NCDs **1-5**.

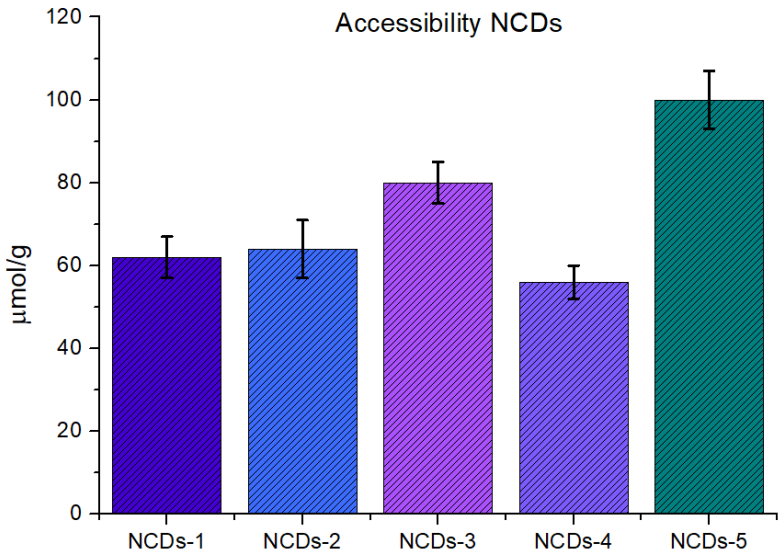


Figure S18. Comparison between the Kaiser test values obtained at 25°C after 250 minutes for NCDs **1-5**.

Acid/base back titration. A known amount of NCDs (about 10 mg) was solubilized in 4 mL of milli-Q-water. Subsequently, 1 mL of NaOH 0.5 M (Titripur ®, Merck) was added and then the resulting solution was titrated with a 0.1 N or 1.0 N solution of HCl (Titripur ®, Merck).
For the quantification of acid/base sites, a Gran Plot analysis was performed.[4] By plotting the µmol of H^+ and OH- *vs*. the µmol of titrant), two linear regions were individuated. The resulting amounts of titrant at the equivalent point (μmol_{eq1} and μmol_{eq2}) were extrapolated through a linear fitting. Finally, the total number of acid/base active sites were calculated by subtracting μmol_{eq2} from μmol_{eq1} and dividing the resulting number by the amount of carbon dots analysed.[1] Back titrations

and Gran plot analysis were repeated in triplicate. A sample titration curve and the corresponding linearized plots for each NCDs are shown below (Figure S19-S23). The intrinsic pH turned out to be 9.0 for NCDs-**1**, 9.2 for NCDs-**2**, 9.5 for NCDs-**3**, 9.8 for NCDs-**4**, and 9.5 for NCDs-**5**, respectively.

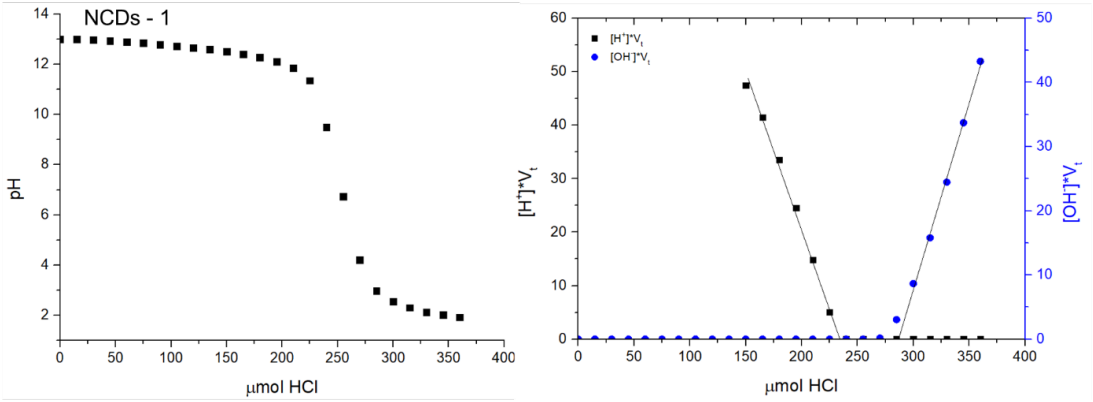


Figure S19. Back titration of NCDs-**1** (left) and Gran plot linearization (right).

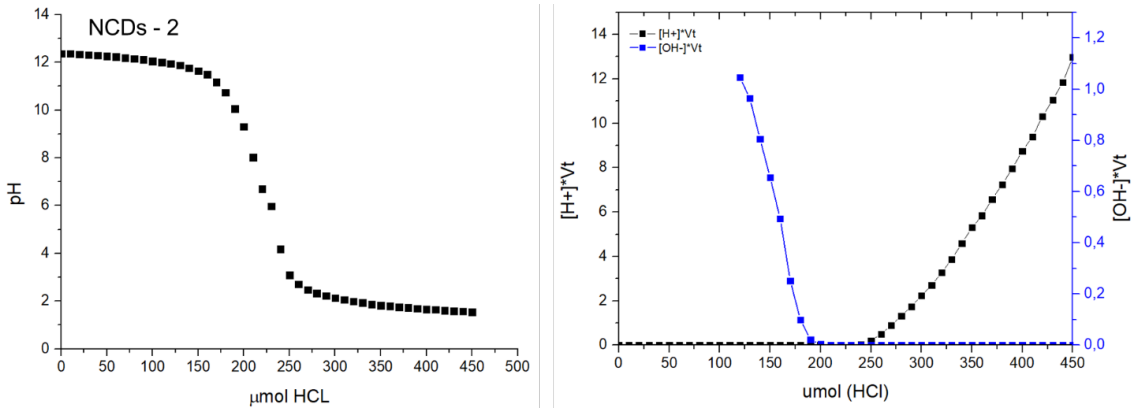


Figure S20. Back titration of NCDs-**2** (left) and Gran plot linearization (right).

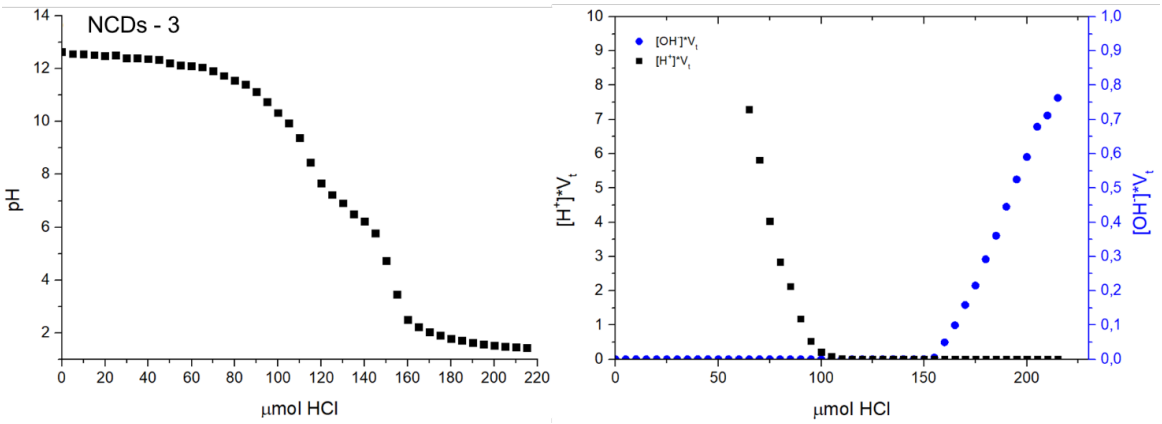


Figure S21. Back titration of NCDs-**3** (left) and Gran plot linearization (right).

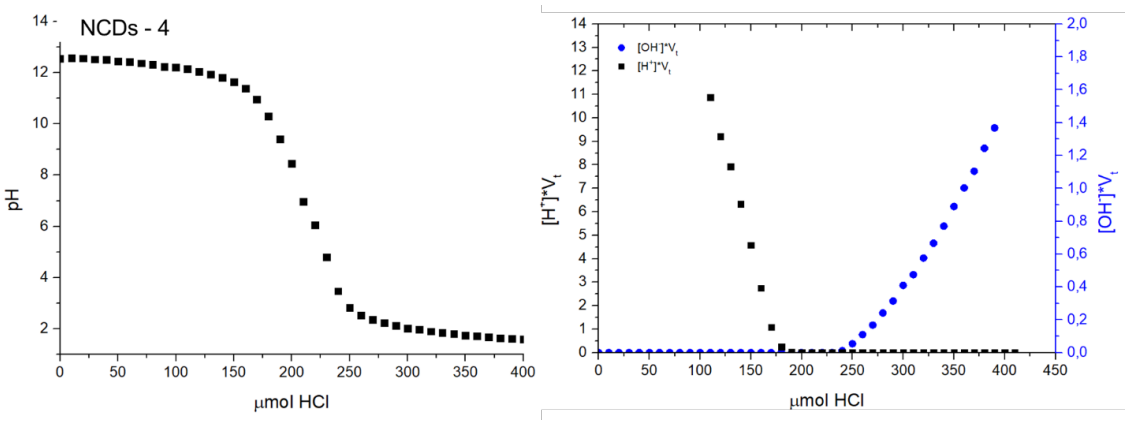


Figure S22. Back titration of NCDs-**4** (left) and Gran plot linearization (right).

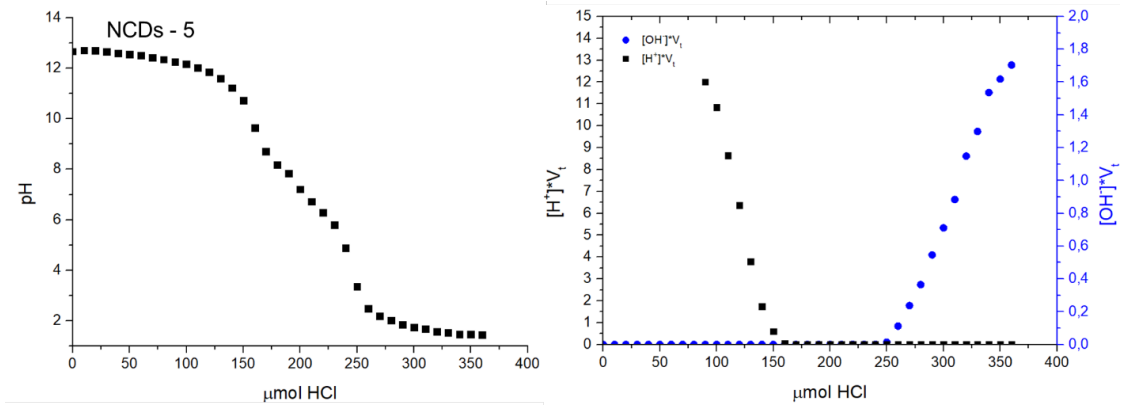


Figure S23. Back titration of NCDs-**5** (left) and Gran plot linearization (right).

ATR-FTIR analysis. NCDs **1-5** were analyzed by infrared spectroscopy.

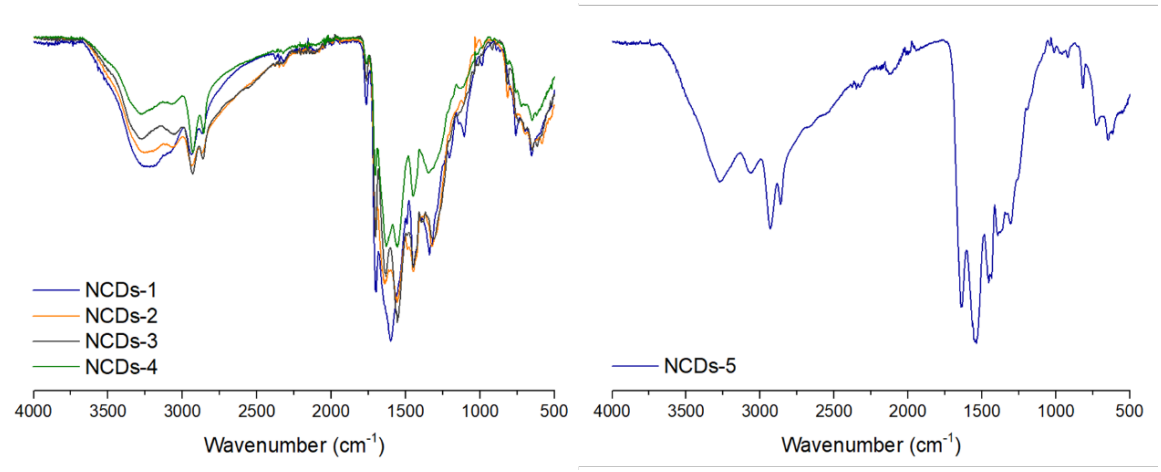


Figure S24. ATR-FTIR spectra of NCDs **1-4** (left) and NCDs-**5** (right).

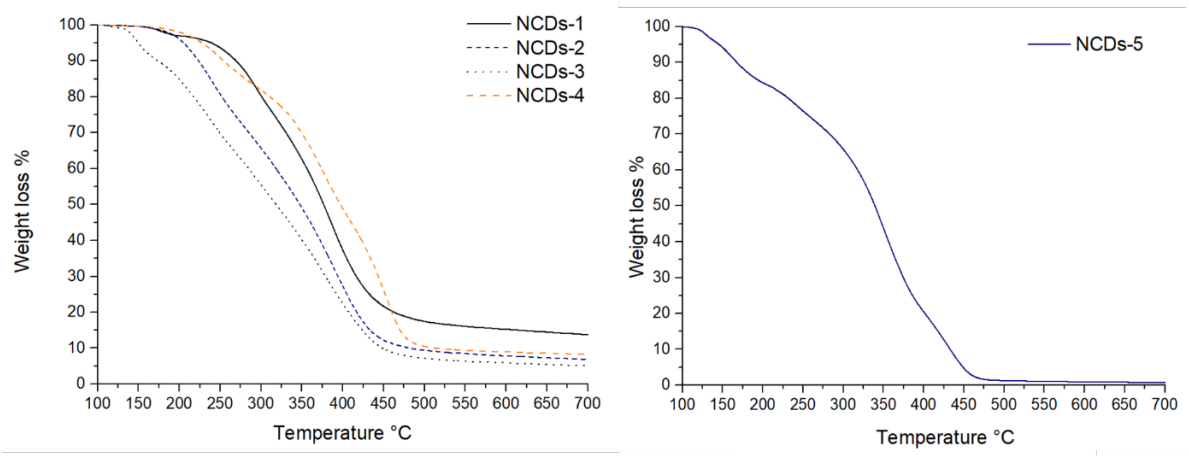


Figure S25. Thermogravimetric analysis under nitrogen of NCDs-**1-4** (left) and NCDs-**5 (**right).

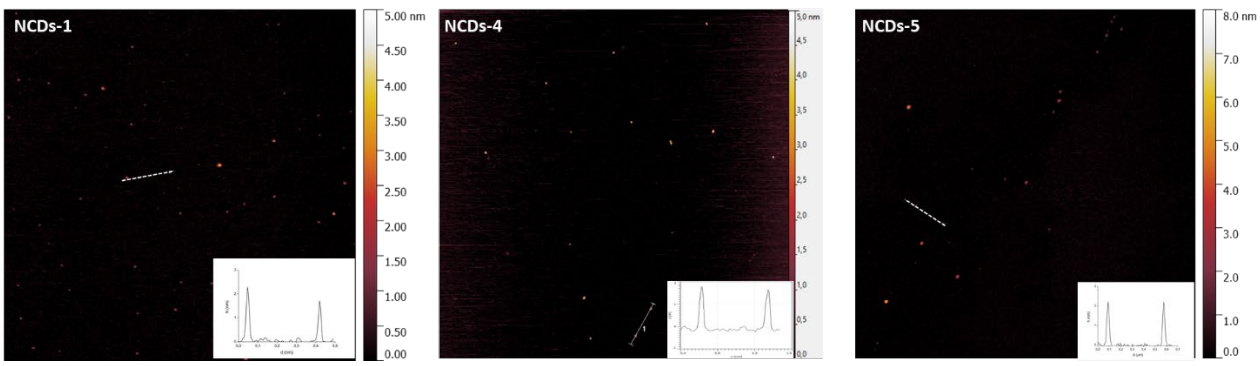


Figure S26. Tapping mode AFM from drop-cast on a mica substrate of NCDs-**1**, NCDs -**4** and NCDs -**5**. NCDs **1** and NCDs-**5** were drop-casted from an aqueous solution. NCDs-**4** were drop-casted from methanol.

Biuret assay. To demonstrate the actual presence of amide groups on NCDs, Biuret test was performed. This assay is based on the ability of peptide bond to reduce Cu(II) ions to Cu(I) in alkaline aqueous solution. In alkaline solutions containing sodium potassium tartrate, Cu(I) ions complex with the peptide bonds of proteins forming a light blue to purple colored complex.[5] The process is schematized in Figure S27.

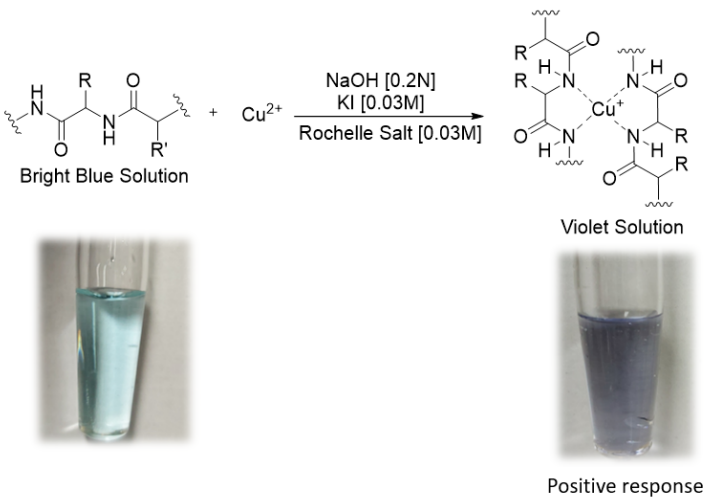


Figure S27. General schematization for Biuret assay.

Subsequently, a reagent solution was prepared by mixing 0.9% w/w sodium potassium tartrate (Rochelle salt), 0.5 %w/w copper sulphate pentahydrate and 0.5% w/w potassium iodide in a 0.2 N sodium hydroxide solution.

To run the text, 2.5 mL of the reagent solution were transferred into a test tube along with 200 µL of 2 mg/mL NCDs solution in Milli-Q water. The test tube was subsequently sealed with a silicon lid and incubated at 37°C for 30 minutes. After the incubation time the NCDs produced from L-Lysine (NCDs-**5**) tested positive affording the characteristic violet colored copper complex, whereas no violet coloration was observed for the NCDs produced from L-Arginine (NCDs **1-4**). Figure S28 shows the UV-Vis afforded by a positive response to the biuret test. As known, L-Arginine can interfere with standard Biuret test,[6] therefore bicinchoninic acid (BCA) assay was performed to detect and quantify the superficial amide functionalities on NCDs **1-5**.

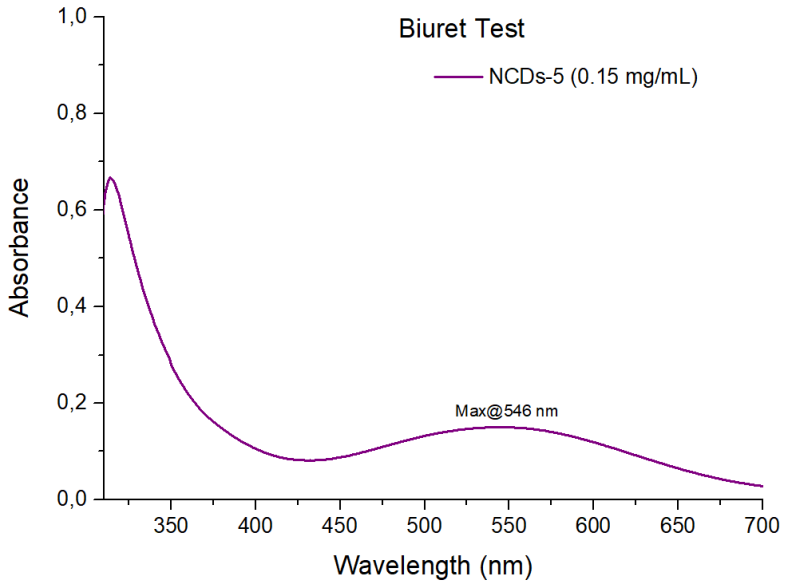


Figure S28. UV-Vis spectra recorded on NCDs-**5** after Biuret assay (0.15 mg/mL in water).

Bicinchoninic acid (BCA) assay. BCA assay is a biochemical assay routinely applied to determine the total concentration of protein in an aqueous media. After the reduction of copper Cu(II) ions to Cu(I) in a basic aqueous buffer (pH: 11.25), the Cu(I) ion produced is chelated by two molecules of BCA^{2-} to form a colored copper complex with a characteristic maximum of absorption at 562 nm that can be easily detected by UV-Vis spectroscopy.[7,8]

Initially the BCA Buffer solution was prepared (Sol A) accordingly with a well-established procedure.[7] To Milli-Q water it has been added 1 %w/w BCA-Na_2 • H_2O, 2% w/w Na_2CO_3, 0.4% w/w NaOH and 0.95% w/w $NaHCO_3$. The buffer solution was adjusted to a pH = 11.25 dropwise with a NaOH 50% w/w solution. Moreover, a 4% w/w $CuSO_4$ • $5H_2O$ solution was prepared in Milli-Q water (Sol B). Finally, the working solution (WR-S) was obtained by mixing Sol A and Sol B in a 50:1 ratio.

To run the test, 1000 µL of the WR-S solution was added to an Eppendorf tube followed by 40 µL of NCDs-**1-4** derived from L-Arginine and 80 µL of NCDs-**5** derived from L-Lysine. All NCDs solutions were at 2 mg/mL concentration. The Eppendorf tube was closed and incubated through a thermostatic water bath at 37°C for 30 minutes. Then, an aliquot (900 µL) of the sample was taken and diluted with an alkaline buffer solution adjusted at pH = 11.25 containing 2% Na_2CO_3, 0.4% NaOH and 0.95% $NaHCO_3$. UV-Vis spectra were recorded within 10 minutes (Figure S29).

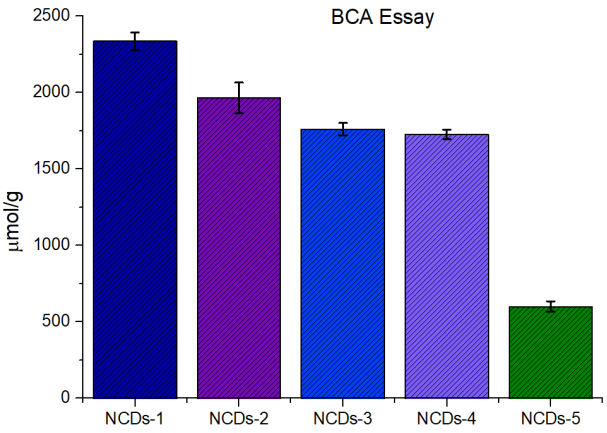


Figure S29. BCA assay results for NCDs-**1-5**.

To measure the molar extinction coefficient of the $[Cu\ (BCA)_2]^{3-}$ complex in the buffer solution, $Na_2BCA \cdot H_2O$ (23.30 mg, $6x10^{-5}$ mol) was added to a 20 mL volumetric flask along with $CuSO_4 \cdot 5H_2O$ (5.00 mg, $6x10^{-5}$ mol). Finally, ascorbic acid (5.30 mg, $3x10^{-5}$ mol) was introduced as reducing agent and the volume was finalized at 20 mL with the alkaline buffer.

The flask was incubated at 37°C for 30 minutes and subsequently aliquots were collected and diluted opportunely to a known concentration. UV-Vis spectra has been recorded. The plotted data and the corresponding linear fitting are shown in Figure S30. The molar extinction coefficient of the $[Cu(BCA)_2]^{3-}$ complex was calculated at [6.800 x 10^3 L (mol Cu $\cdot$ cm)$^{-1}$]. The value fits with what reported in literature.[8]

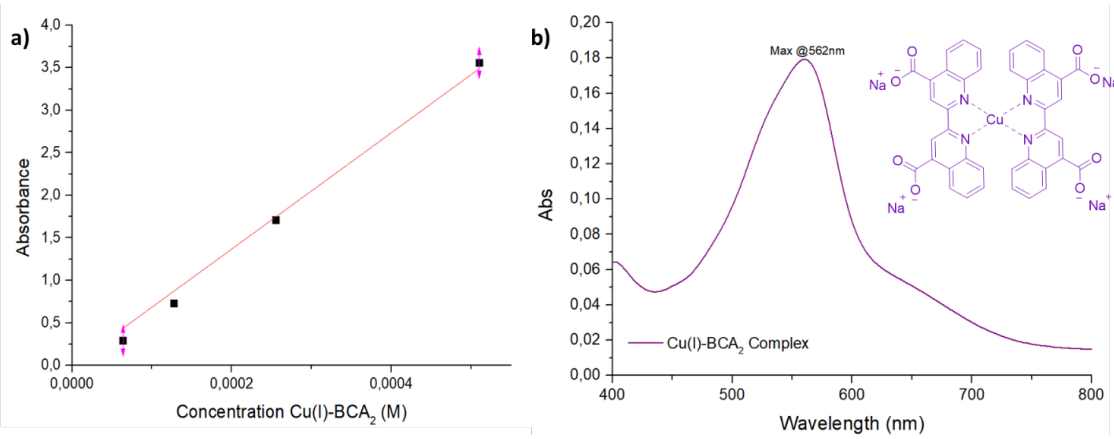


Figure S30. a) Linear fitting for molar extinction coefficient b) UV-Vis spectra and structure of $[Cu\ (BCA)_2]^{3-}$complex

Gel electrophoresis. For the electrophoresis studies, an agarose gel was prepared in a pH = 4 citrate buffer. The buffer was obtained by dissolving citric acid and trisodium citrate in milli-Q-water ($C_6H_8O_7$ 0.0330 M and $Na_3C_6H_5O_7$ 0.0170 M), providing a final pH equal to 4.0. The gel precursors employed for each electrophoresis experiment, were freshly obtained mixing agarose along with the buffer solution (2 wt%) and heated up at 100°C for 10 min. Therefore, the so-formed gel was allowed to cool into the electrophoresis chamber. NCDs **1-5** solutions (total volume = 200 µL, concentration = 50 mg/mL) were prepared in the citrate buffer.

In a typical electrophoresis experiment, 20 µL of NCDs solution were placed in the loading well of the gel and the chamber was filled with the buffer solution. Then, an electric current of 250 mA was applied recording a voltage of 60 V. UV light irradiation at 365 nm was used to visualize the fluorescent NCDs after the electrophoretic experiment (Figure S31).

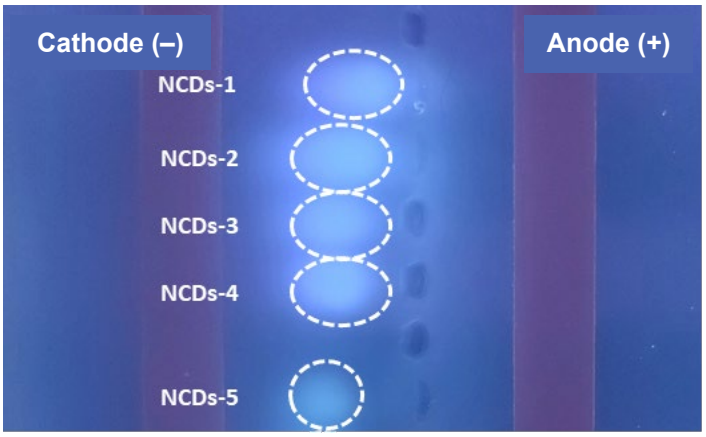


Figure S31. Post-electrophoresis photograph taken under UV light (365 nm) of the gel at pH 4 for NCDs **1-5**.

Coomassie Brilliant Blue staining for gel electrophoresis.

To prepare the staining solution 250 mg of Coomassie Brilliant Blue dye were solubilized in a mixture of 50 mL of glacial acetic acid, 250 mL of methanol and 200 mL of Milli-Q water affording a final dye concentration of 5.80 x 10^{-4} M The agarose gel containing the CDs particles was placed in the dye mixture for 45 min. Subsequently, the gel was removed from the coloring solution and rinsed three times with a washing solution composed by 30% methanol, 10% acetic acid and 60% Milli-Q water. The gel was then placed overnight in the washing solution. The following morning, the picture reported in Figure S32 was acquired.

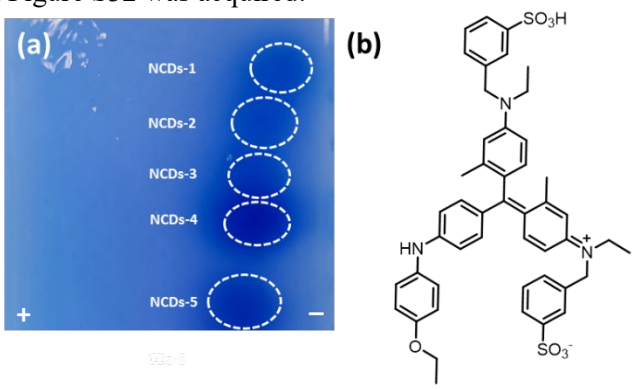
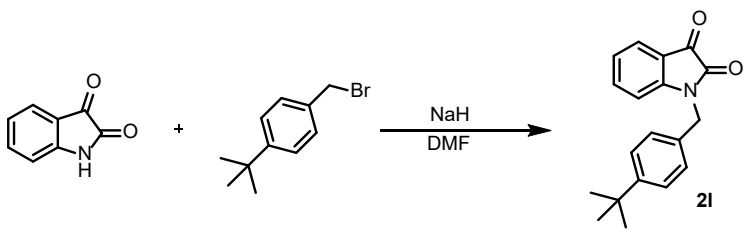


Figure S32. (a) Post-electrophoresis photograph taken after Coomassie brilliant blue staining. The symbols "+" and "–" indicate the anode and the cathode, respectively. (b) Structure of Coomassie blue dye.

C.1. GENERAL PROCEDURES FOR THE SYNTHESIS OF STARTING MATERIALS

C.1.1. PREPARATION OF N-FUNCTIONALISED ISATIN (2l)



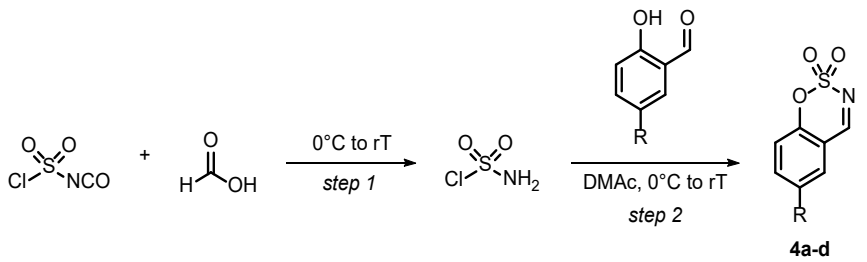
Prepared according to a modified literature procedure.[9] Isatin (1.0 mmol, 1.0 equiv., 165 mg) was dissolved in anhydrous DMF (2 mL, 0.5 M) at 0°C before the addition of sodium hydride (60% dispersion in mineral oil, 1.3 mmol, 1.3 equiv., 91 mg). The resulting mixture was stirred for 30 minutes at 0°C. 4-*tert*-butylbenzyl bromide (1.2 mmol, 1.2 equiv., 221 µL) was then added and the reaction was stirred for 5 hours at room temperature. At the end, the reaction was quenched with

saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water and brine, then dried over anhydrous sodium sulfate. The residue was purified by flash chromatography (Hex/EtOAc) to afford the corresponding product **2l** as red solid (125 mg, 43%).

Characterization Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.49 (td, *J* = 7.8, 1.3 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.28 (dd, *J* = 7.7, 5.7 Hz, 2H), 7.08 (td, *J* = 7.6, 0.7 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.89 (s, *J* = 12.3 Hz, 2H), 1.29 (s, *J* = 3.3 Hz, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 183.46, 158.34, 151.30, 150.97, 138.41, 131.57, 127.37, 126.04, 125.44, 123.87, 117.77, 111.15, 43.81, 34.67, 31.38. The characterization data matched with the reported one.[10]

C.1.2. PREPARATION OF CYCLIC IMINES (4a-4d)

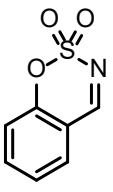


STEP 1, according to a modified literature procedure.[11] Anhydrous formic acid (10.0 mmol, 1 equiv., 377 µL) was added dropwise to neat chlorosulfonyl isocyanate (10.0 mmol, 1 equiv., 868 µL) at 0°C with rapid stirring. Strong gas evolution was observed during the addition process. The resulting suspension was stirred at room temperature for 2 hours. The resulting white solid was immediately used in the following step.

STEP 2, according to a modified literature procedure.[11] To a solution of the appropriate salicylaldehyde (3.75 mmol, 1 equiv.) in *N,N*-dimethylacetamide (DMAc, 25 mL, 0.15 M) at 0 °C was carefully added the freshly prepared sulfamoyl chloride (10.0 mmol, 2.67 equiv., 1.16 g) in small portions, and the resulting solution was stirred for 18 hours at room temperature. The reaction was quenched carefully with ice-cold water (50 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), then dried over anhydrous sodium sulfate. The residue was purified by flash chromatography (Hex/EtOAc) to afford the corresponding cyclic imines **4a-4d** as solids.

Characterization Data

Benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (4a)

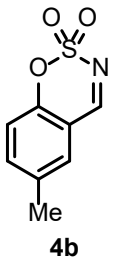


4a

4a was synthesized according to the general procedure **A.1** from salicylaldehyde (398 µL, 3.75 mmol). The cyclic imine **4a** was obtained as a pale-yellow solid (652 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.80 – 7.68 (m, 2H), 7.43 (td, *J* = 7.6, 1.0 Hz, 1H), 7.30 – 7.24 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.96, 154.21, 137.81, 131.03, 126.36, 118.60, 115.38. The characterization data matched with the reported one.[12]

6-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (4b)

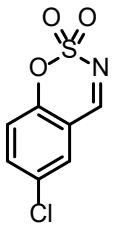


4b

4b was synthesized according to the general procedure **A.1** from 2-hydroxy-5-methylbenzaldehyde (511 mg, 3.75 mmol). The cyclic imine **4b** was obtained as a pale-yellow solid (587 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.63 – 7.51 (m, 1H), 7.46 (d, *J* = 1.5 Hz, 1H), 7.26 (s, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 2.44 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.91, 152.33, 138.54, 136.51, 130.75, 118.42, 115.25, 20.77. The characterization data matched with the reported one.[13]

6-chlorobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (4c)

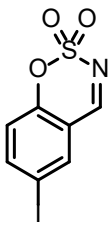


4c

4c was synthesized according to the general procedure **A.1** from 5-chloro-2-hydroxybenzaldehyde (511 µL, 3.75 mmol). The cyclic imine **4c** was obtained as a pale-yellow solid (434 mg, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.55 (m, 1H), 7.77 – 7.62 (m, 2H), 7.31 – 7.19 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.50, 152.76, 137.48, 131.80, 130.07, 120.39, 116.22. The characterization data matched with the reported one.[14]

6-iodobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (4d)

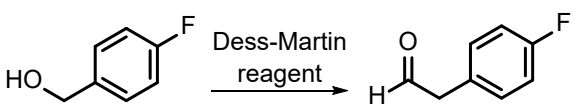


4d

4d was synthesized according to the general procedure **A.1** from 2-hydroxy-5-iodobenzaldehyde (930 mg, 3.75 mmol). The cyclic imine **4d** was obtained as a pale-yellow solid (583 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.04 – 7.97 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.27, 154.07, 146.09, 139.07, 120.68, 117.05, 88.73. The characterization data matched with the reported one.[12]

C.1.3. PREPARATION OF 4-PHENYLACETALDEHYDE



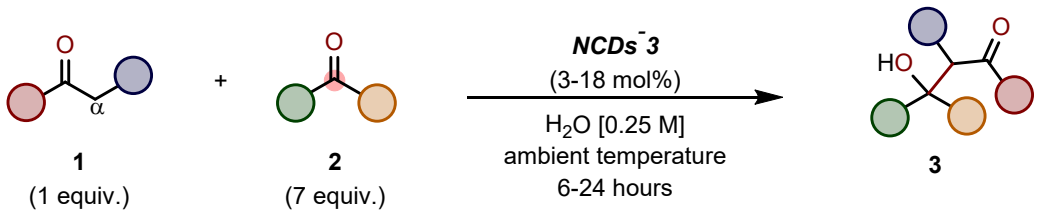
Prepared according to a modified literature procedure.[15] To a solution of the (4-fluorophenyl)methanol (1.0 mmol, 1 equiv., 125 µL) in dichloromethane (4 mL, 0.25 M) at 0°C was carefully added the Dess-martin reagent (1.2 mmol, 1.2 equiv., 509 mg), and the resulting solution was stirred for 2 hours at room temperature. The reaction was filtered on celite. The residue was purified by flash chromatography (Hex/EtOAc) to afford the product as colorless liquid (33 mg, 24% yield).

Characterization Data

^{1}H NMR (400 MHz, DMSO) δ 9.68 (t, *J* = 1.7 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 3.78 (d, *J* = 1.2 Hz, 2H). **^{19}F NMR (376 MHz, DMSO)** δ -116.19. The characterization data matched with the reported one.[15]

D.1. GENERAL PROCEDURES FOR THE USE OF NCDs-3 AS NANO-ORGANOCATALYSTS

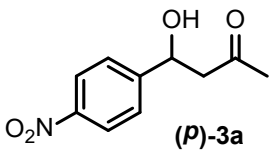
D.1.1. AMINOCATALYTIC ALDOL REACTIONS (3a-3l)



A 4 mL glass vial was charged with the appropriate nucleophile **2** (0.7 mmol, 7 equiv.), NCDs-**3** (3-18 mol%, 2.8-11 mg), the appropriate electrophile **1** (0.1 mmol, 1 equiv.) and water (final concentration: 0.25 M). The resulting mixture was stirred for the indicated time (generally 24 hours) at ambient temperature. The reaction crude was then extracted with EtOAc and the organic phase was filtered through sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: Hex/EtOAc) to give the corresponding β-hydroxy carbonyl compounds **3**.

Characterization Data

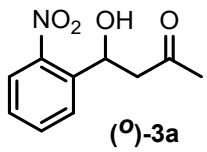
4-hydroxy-4-(4-nitrophenyl)butan-2-one ((*p*)-3a)



Prepared according to the general procedure **D.1.1.** using 4-nitrobenzaldehyde **2a** (0.1 mmol, 10 µL) and acetone **1a** (0.7 mmol, 50 µL). The product **(*p*)-3a** was obtained as yellowish solid (11 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.11 (m, 2H), 7.63 – 7.42 (m, 2H), 5.26 (dd, *J* = 7.4, 4.5 Hz, 1H), 3.58 (s, 1H), 2.92 – 2.82 (m, 2H), 2.22 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.62, 150.05, 126.55, 123.91, 69.06, 51.63, 30.85. **HRMS** calculated for $C_{13}H_{15}NO_4$ (M-Na): 232.0550, found: 232.0580. The characterization of the compound matches with the data reported in the literature.[16]

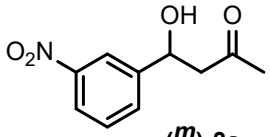
4-hydroxy-4-(2-nitrophenyl)butan-2-one ((*o*)-3a)



Prepared according to the general procedure **D.1.1.** using 2-nitrobenzaldehyde **2b** (0.1 mmol, 10 µL) and acetone **1a** (0.7 mmol, 50 µL). The product **(*o*)-3a** was obtained as yellowish solid (12 mg, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.67 (m, 1H), 7.48 – 7.40 (m, 1H), 5.68 (dd, *J* = 9.4, 1.9 Hz, 1H), 3.72 (s, 1H), 3.14 (dd, *J* = 17.8, 2.1 Hz, 1H), 2.72 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.24 (s, 3H). **HRMS** calculated for $C_{13}H_{15}NO_4$ (M-Na): 232.0583, found: 232.0580. The characterization of the compound matches with the data reported in the literature.[17]

4-hydroxy-4-(3-nitrophenyl)butan-2-one ((*m*)-3a)

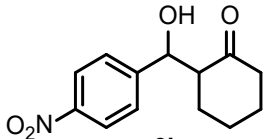


(*m*)-3a

Prepared according to the general procedure **D.1.1.** using 3-nitrobenzaldehyde **2c** (0.1 mmol, 10 µL) and acetone **1a** (0.7 mmol, 50 µL). The product **(*m*)-3a** was obtained as yellowish solid (15 mg, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (t, *J* = 1.9 Hz, 1H), 8.13 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.75 – 7.61 (m, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 5.30 – 5.22 (m, 1H), 3.60 (d, *J* = 3.2 Hz, 1H), 2.92 – 2.85 (m, 2H), 2.23 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.73, 148.52, 144.93, 131.94, 129.65, 122.73, 120.86, 68.93, 51.64, 30.85. **HRMS** calculated for $C_{13}H_{15}NO_4$ (M-Na): 232.0581, found: 232.0580. The characterization of the compound matches with the data reported in the literature.[18]

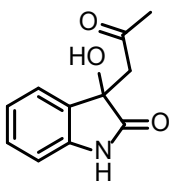
2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (3b) Prepared according to the general procedure **D.1.1.** using 4-nitrobenzaldehyde **2a** (0.1 mmol, 10 µL) and 2-cyclohexen-1-one **1b** (0.7 mmol, 29 µL). The product **3b** was obtained as yellowish solid (16 mg, 65% yield).



3b

^{1}H-NMR (400 MHz, CD_3OD) δ 8.22 – 8.15 (m, 2H), 7.63 – 7.56 (m, 2H), 5.35-5.10 (m, 1H), 2.76 (tdd, *J* = 11.8, 8.6, 4.9 Hz, 1H), 2.45 – 2.33 (m, 2H), 2.01 (tdd, *J* = 10.6, 6.7, 3.5 Hz, 1H), 1.91 – 1.57 (m, 5H), 1.36 – 1.24 (m, 1H). **^{13}C NMR (101 MHz, CD_3OD)** δ 212.51, 211.64, 151.69, 150.14, 147.26, 146.69, 127.78, 126.93, 122.79, 122.69, 71.75, 69.48, 57.26, 56.73, 41.61, 41.58, 30.21, 27.68, 26.93, 26.12, 24.03, 23.84. **HRMS** calculated for $C_{13}H_{15}NO_4$ (M-Na): 272.0892, found: 272.0893. The characterization of the compound matches with the data reported in the literature.[19]

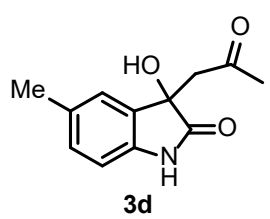
3-hydroxy-3-(2-oxopropyl)indolin-2-one (3c). Prepared according to the general procedure **D.1.1.** using isatin **2d** (0.1 mmol, 15 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3c** was obtained as brownish solid (18 mg, 90% yield).



3c

^{1}H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 7.23 (dd, *J* = 7.3, 0.5 Hz, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.00 (s, 1H), 3.27 (d, *J* = 16.6 Hz, 1H), 3.00 (d, *J* = 16.6 Hz, 1H), 1.99 (s, *J* = 4.5 Hz, 3H). **^{13}C NMR (101 MHz, DMSO)** δ 205.38, 178.31, 142.60, 131.58, 129.13, 123.79, 121.42, 109.59, 72.78, 50.35, 30.67. **HRMS** calculated for $C_{11}H_{11}NO_3$ (M-Na): 228.0567, found: 228.0631. The characterization of the compound matches with the data reported in the literature.[20]

3-hydroxy-5-methyl-3-(2-oxopropyl)indolin-2-one (3d)

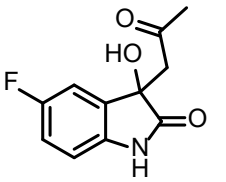


3d

Prepared according to the general procedure **D.1.1.** using 5-methylisatin **2e** (0.1 mmol, 17 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3d** was obtained as brownish solid (17 mg, 78% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.16 – 7.12 (m, 1H), 7.05 (ddd, *J* = 7.9, 1.7, 0.8 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 3.39 – 3.28 (m, 1H), 3.14 (d, *J* = 16.6 Hz, 1H), 2.29 (s, 3H), 2.07 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD)** δ 207.45, 181.16, 141.01, 133.09, 132.29, 130.90, 125.49, 110.99, 74.87, 51.11, 30.69, 21.08. **HRMS** calculated for $C_{12}H_{13}NO_3$ (M-Na): 242.0786, found: 242.0788. The characterization of the compound matches with the data reported in the literature.[20]

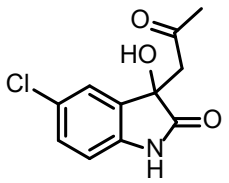
5-fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3e). Prepared according to the general procedure **D.1.1.** using 5-fluoroisatin **2f** (0.1 mmol, 17 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3e** was obtained as brownish solid (18 mg, 81% yield).



3e

^{1}H-NMR (400 MHz, CD_3OD) δ 7.11 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.97 (ddd, *J* = 9.4, 8.5, 2.7 Hz, 1H), 6.84 (dd, *J* = 8.5, 4.2 Hz, 1H), 3.37 (d, *J* = 18.7 Hz, 1H), 3.18 (d, *J* = 17.2 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD)** δ 205.80, 179.67, 160.21, 157.83, 132.75, 132.67, 115.31, 115.08, 111.42, 111.17, 110.51, 110.43, 109.99, 73.50, 49.54, 29.11. **^{19}F NMR (376 MHz, CD_3OD)** δ -123.21 (ddd, *J* = 9.4, 8.1, 4.3 Hz). **HRMS** calculated for $C_{11}H_{12}FNO_3$ (M-Na): 246.0534, found: 246.0534. The characterization of the compound matches with the data reported in the literature.[20]

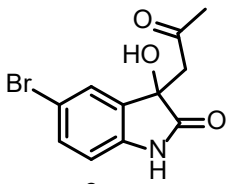
5-chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3f). Prepared according to the general procedure **D.1.1.** using 5-chloroisatin **2g** (0.1 mmol, 18 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3f** was obtained as white solid (21 mg, 89% yield).



3f

^{1}H-NMR (400 MHz, CD_3OD) δ 7.32 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 3.39 (d, *J* = 17.2 Hz, 1H), 3.19 (d, *J* = 17.2 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD)** δ 205.81, 179.36, 141.03, 132.96, 128.98, 127.11, 123.86, 110.92, 73.24, 49.55, 29.04. **HRMS** calculated for $C_{11}H_{10}ClNO_3$ (M-Na): 262.0239, found: 262.0241. The characterization of the compound matches with the data reported in the literature.[21]

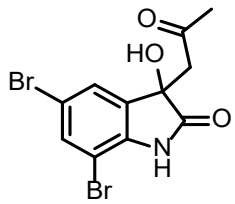
5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3g). Prepared according to the general procedure **D.1.1.** using 5-bromoisatin **2h** (0.1 mmol, 18 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3g** was obtained as as brownish solid (19 mg, 67% yield).



3g

^{1}H-NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 1.8 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.82 – 6.79 (m, 1H), 3.39 (d, *J* = 17.0 Hz, 1H), 3.19 (d, *J* = 17.2 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD)** δ 207.53, 180.93, 143.23, 135.07, 133.67, 128.39, 115.93, 113.13, 74.90, 51.28, 49.30, 30.75. **HRMS** calculated for $C_{11}H_{10}BrNO_3$ (M-Na): 305.9737, found: 305.9736. The characterization of the compound matches with the data reported in the literature.[20]

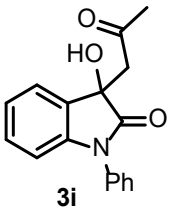
5,7-dibromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (3h). Prepared according to the general procedure **D.1.1.** using 5,7-dibromoisatin **2i** (0.1 mmol, 30 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3h** was obtained as yellowish solid (15 mg, 41% yield).



3h

^{1}H NMR (500 MHz, DMSO) δ 10.70 (s, 1H), 7.68 – 7.56 (m, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 6.27 (s, 1H), 3.13 (d, *J* = 17.8 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 205.67, 177.76, 141.86, 135.53, 133.52, 125.88, 113.56, 102.64, 73.45, 50.08, 30.19. **HRMS** calculated for $C_{11}H_9Br_2NO_3$ (M-Na): 383.8843, found: 383.8841. The characterization of the compound matches with the data reported in the literature.[20]

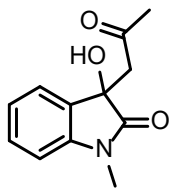
3-hydroxy-3-(2-oxopropyl)-1-phenylindolin-2-one (3i). Prepared according to the general procedure **D.1.1.** using 1-phenylisatin **2j** (0.1 mmol, 22 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3i** was obtained as brownish solid (24 mg, 85% yield).



3i

^{1}H-NMR (400 MHz, CD_3OD) δ 7.61 – 7.53 (m, 2H), 7.49 – 7.39 (m, 4H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 – 6.67 (m, 1H), 3.62 – 3.51 (m, 1H), 3.37 (s, 1H), 2.07 (s, 3H). **^{13}C NMR (101 MHz, CD_3OD)** δ 205.91, 177.41, 144.47, 134.56, 130.16, 129.31, 129.27, 128.05, 126.65, 123.27, 122.94, 109.14, 72.92, 50.38, 28.97. **HRMS** calculated for $C_{17}H_{15}NO_3$ (M-Na): 304.0943, found: 304.0944. The characterization of the compound matches with the data reported in the literature.[22]

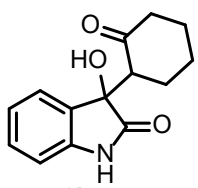
3-hydroxy-1-methyl-3-(2-oxopropyl)indolin-2-one (3j). Prepared according to the general procedure **D.1.1.** using 1-methylisatin **2k** (0.1 mmol, 17 mg) and acetone **1a** (0.7 mmol, 50 µL). The product **3j** was obtained as brownish solid (8 mg, 37% yield).



3j

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.32 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.18 (m, 4H), 2.94 (d, *J* = 17.0 Hz, 1H), 2.17 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.68, 176.02, 143.50, 130.03, 129.70, 123.85, 123.13, 108.58, 74.22, 48.62, 29.68, 28.74, 26.28. **HRMS** calculated for $C_{12}H_{13}NO_3$ (M-Na): 242.0788, found: 242.0788. The characterization of the compound matches with the data reported in the literature.[22]

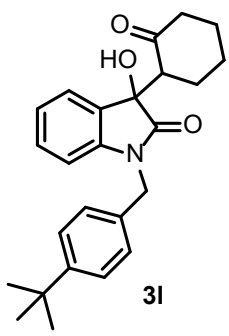
3-hydroxy-3-(2-oxocyclohexyl)indolin-2-one (3k). Prepared according to the general procedure **D.1.1.** using isatin **2d** (0.1 mmol, 15 mg) and cyclohexanone **1b** (0.7 mmol, 73 µL). The product **3k** was obtained as brownish solid (15 mg, 62% yield, d.r. 13:1, major diastereoisomer: *syn*).



3k

^{1}H-NMR (400 MHz, CD_3CN) δ 7.34 – 7.30 (m, 1H), 7.26 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.92 – 6.88 (m, 1H), 4.30 (s, 1H), 3.12 (ddd, *J* = 13.1, 5.3, 1.2 Hz, 1H), 2.46 – 2.29 (m, 2H), 2.26 – 2.20 (m, 1H), 2.08 – 1.99 (m, 1H), 1.88 – 1.47 (m, 4H). **^{13}C NMR (101 MHz, CD_3CN)** δ 211.63, 179.15, 143.71, 131.00, 130.29, 125.81, 122.71, 118.26, 110.59, 76.35, 57.47, 42.56, 27.92, 27.37, 25.32. **HRMS** calculated for $C_{14}H_{15}NO_3$ (M-Na): 268.0946, found: 268.0944. The characterization of the compound matches with the data reported in the literature.[23]

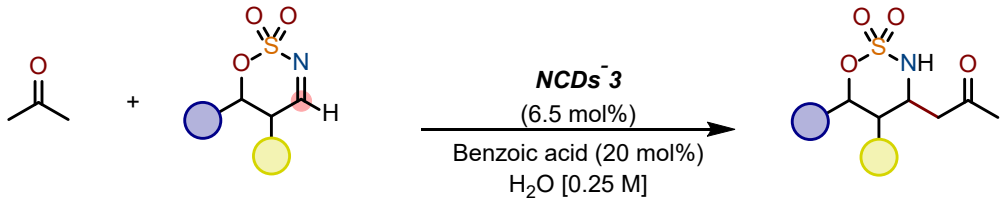
1-(4-(tert-butyl)benzyl)-3-hydroxy-3-(2-oxocyclohexyl)indolin-2-one (3l). Prepared according to the general procedure **D.1.1.** using 1-para-tertbutilphenylisatin **2l** (0.1 mmol, 29 mg) and cyclohexanone **1b** (0.7 mmol, 73 µL). The product **3l** was obtained as red solid (19 mg, 67% yield, d.r. >20:1, major diastereoisomer: *syn*).



3l

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (dt, *J* = 8.4, 2.0 Hz, 3H), 7.30 – 7.25 (m, 2H), 7.21 (td, *J* = 7.8, 1.2 Hz, 1H), 7.02 (td, *J* = 7.6, 0.9 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 4.96 (dd, *J* = 34.2, 18.5 Hz, 1H), 4.78 (d, *J* = 15.7 Hz, 1H), 3.03 (dd, *J* = 12.1, 5.4 Hz, 1H), 2.48 (dd, *J* = 8.9, 6.2 Hz, 1H), 2.39 – 2.26 (m, 1H), 1.87 (t, *J* = 9.1 Hz, 1H), 1.73 – 1.53 (m, 3H), 1.31 – 1.24 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 211.94, 176.90, 150.62, 143.87, 132.70, 129.94, 129.04, 127.18, 125.79, 124.08, 123.00, 109.66, 77.23, 55.46, 43.71, 42.23, 34.63, 31.44, 27.34, 26.14, 24.62. **HRMS** calculated for $C_{25}H_{29}NO_3$ (M-Na): 414.2014, found: 414.2040.

D.1.2. AMINOCATALYTIC MANNICH REACTIONS (5a-5d)

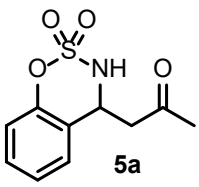


1a (15 equiv.) **4** (1 equiv.) **5**

A 4 mL glass vial was charged with the appropriate cyclic imine **4** (0.1 mmol, 1 equiv.), NCDs-**3** (3.3% mol, 2 mg), acetone **1a** (1.5 mmol, 15 equiv.), benzoic acid (0.02 mmol, 0.2 equiv.) and water (final concentration: 0.25 M). The resulting mixture was stirred for the indicated time (24 hours) at ambient temperature. The reaction crude was then extracted with EtOAc and the organic phase was filtered through sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: dicloromethane) to give the corresponding product **5**.

Characterization Data

1-(2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)propan-2-one (5a).

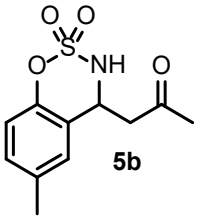


5a

Prepared according to the general procedure **D.1.2.** using benzo[e][1,2,3]oxathiazine 2,2-dioxide **4a** (0.1 mmol, 19 mg), benzoic acid (0.02 mmol, 2.5 mg) and acetone **1a** (1.5 mmol, 110 µL). The product **5a** was obtained as white solid (22 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dddd, *J* = 8.1, 7.5, 1.7, 0.7 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.04 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.17 (dd, *J* = 7.3, 4.0 Hz, 1H), 3.63 (dd, *J* = 18.2, 7.3 Hz, 1H), 2.97 (dd, *J* = 18.2, 4.0 Hz, 1H), 2.24 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.80, 151.31, 129.83, 125.88, 125.61, 121.46, 119.33, 53.55, 46.43, 31.20. **HRMS** calculated for $C_{10}H_{11}NO_4S$(M-Na): 264.0307, found: 264.0301. The characterization of the compound matches with the data reported in the literature.[24]

1-(6-methyl-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)propan-2-one (5b)

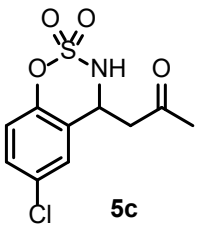


5b

Prepared according to the general procedure **D.1.2.** using 6-methylbenzo[e][1,2,3]oxathiazine 2,2-dioxide **4b** (0.1 mmol, 20 mg), benzoic acid (0.02 mmol, 2.5 mg) and acetone **1a** (1.5 mmol, 110 µL). The product **5b** was obtained as white solid (13 mg, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 1H), 6.95 – 6.86 (m, 2H), 5.62 (d, *J* = 7.8 Hz, 1H), 5.13 (td, *J* = 7.7, 3.9 Hz, 1H), 3.61 (dd, *J* = 18.1, 7.6 Hz, 1H), 2.95 (dd, *J* = 18.2, 3.9 Hz, 1H), 2.31 (s, 3H), 2.24 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.80, 149.17, 135.40, 130.40, 126.19, 121.01, 119.01, 53.50, 46.71, 31.17, 20.98. **HRMS** calculated for $C_{11}H_{13}NO_4S$(M-Na): 278.0455, found: 278.0457.

1-(6-chloro-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)propan-2-one (5c)

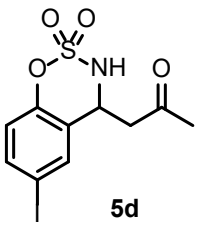


5c

Prepared according to the general procedure **D.1.2.** using 6-chlorobenzo[e][1,2,3]oxathiazine 2,2-dioxide **4c** (0.1 mmol, 22 mg), benzoic acid (0.02 mmol, 2.5 mg) and acetone **1a** (1.5 mmol, 110 µL). The product **5c** was obtained as white solid (8 mg, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 1H), 7.09 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 5.71 (s, 1H), 5.12 (m, 1H), 3.60 (dd, *J* = 18.4, 7.1 Hz, 1H), 2.99 (dd, *J* = 18.4, 4.0 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.46, 149.82, 130.85, 129.91, 125.85, 123.07, 120.71, 53.25, 46.23, 31.11. **HRMS** calculated for $C_{10}H_{10}ClNO_4S$(M-Na): 297.9910, found: 297.9911.

1-(6-iodo-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)propan-2-one (5d).

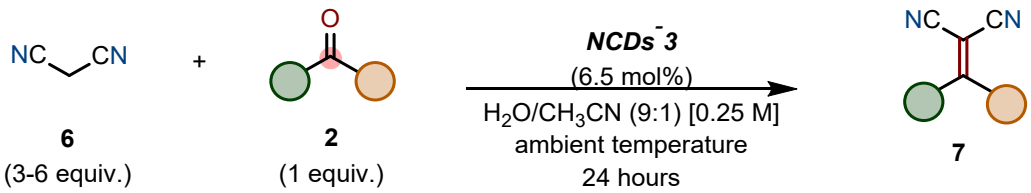


5d

Prepared according to the general procedure **D.1.2.** using 6-iodobenzo[e][1,2,3]oxathiazine 2,2-dioxide **4d** (0.1 mmol, 31 mg), benzoic acid (0.02 mmol, 2.5 mg) and acetone **1a** (1.5 mmol, 110 µL). The product **5d** was obtained as white solid (16 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (ddd, *J* = 8.7, 2.1, 0.6 Hz, 1H), 7.42 (dd, *J* = 2.0, 0.8 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.75 (s, 1H), 5.13 (s, 1H), 3.60 (dd, *J* = 18.3, 7.3 Hz, 1H), 2.97 (dd, *J* = 18.3, 3.9 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.47, 151.24, 138.73, 134.75, 123.81, 121.25, 88.71, 52.92, 46.34, 31.14. HRMS calculated for $C_{10}H_{10}INO_4S$(M-Na): 389.9268, found: 389.9267.

D.1.3. AMINOCATALYTIC KNOEVENAGEL REACTIONS (7a-7d)



6
(3-6 equiv.)

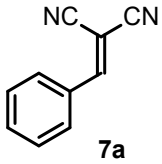
2
(1 equiv.)

7

A 4 mL glass vial was charged with malononitrile **6** (0.3-0.6 mmol, 3-6 equiv.), NCDs-**3** (6.5% mol, 3.7 mg), the appropriate electrophiles **2** (0.1 mmol, 1 equiv.), and water/acetonitrile (9:1) (final concentration: 0.25 M). The resulting mixture was stirred for the indicated time (24 hours) at ambient temperature. The reaction crude was then extracted with EtOAc and the organic phase was filtered through sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: Hex/EtOAc) to give the corresponding product **7**.

Characterization Data

2-benzylidenemalononitrile (7a).



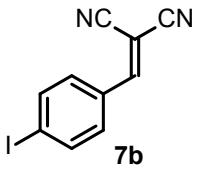
7a

Prepared according to the general procedure **D.1.3.** using malononitrile **6** (0.6 mmol, 6 equiv.), and benzaldehyde **2m** (0.1 mmol, 1 equiv.). The product **7a** was obtained as white solid (9 mg, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.85 (m, 2H), 7.78 (s, 1H), 7.70 – 7.61 (m, 1H), 7.58 – 7.47 (m, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.05, 134.76, 131.07,

130.86, 129.77, 113.83, 112.66, 83.06. It was not possible to measure the HRMS (ESI-MS) of compound **7a** due to its poor tendency to ionize. The characterization of the compound matches with the data reported in the literature.[25]

2-(4-iodobenzylidene)malononitrile (7b).

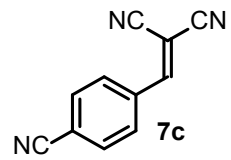


7b

Prepared according to the general procedure **D.1.3.** using malononitrile **6** (0.6 mmol, 6 equiv.), and 4-iodobenzaldehyde **2n** (0.1 mmol, 1 equiv.). The product **7b** was obtained as white solid (13 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.69 (s, 1H), 7.63 – 7.57 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.79, 139.21, 131.65, 130.28, 113.60, 112.47, 102.97, 83.73. It was not possible to measure the HRMS (ESI-MS) of compound **7b** due to its poor tendency to ionize. The characterization of the compound matches with the data reported in the literature.[26]

2-(4-cyanobenzylidene)malononitrile (7c).

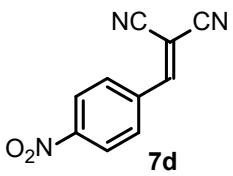


7c

Prepared according to the general procedure **D.1.3.** using malononitrile **6** (0.6 mmol, 6 equiv.), and 4-cyanobenzaldehyde **2o** (0.1 mmol, 1 equiv.). The product **7c** was obtained as white solid (8 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.86 – 7.75 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.79, 139.21, 131.65, 130.28, 113.60, 112.47, 102.97, 83.73. It was not possible to measure the HRMS (ESI-MS) of compound **7c** due to its poor tendency to ionize. The characterization of the compound matches with the data reported in the literature.[26]

2-(4-nitrobenzylidene)malononitrile (7d).

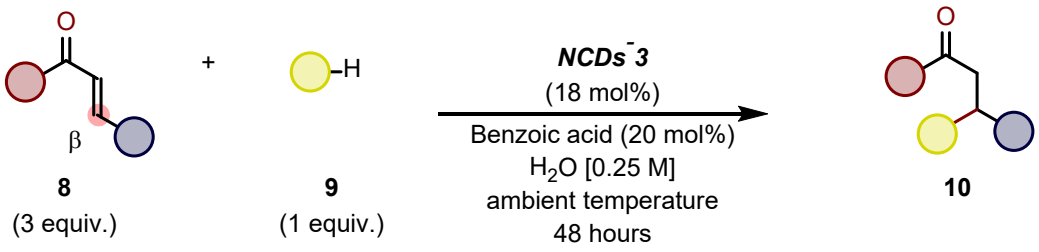


7d

Prepared according to the general procedure **D.1.3.** using malononitrile **6** (0.3 mmol, 3 equiv.), and 4-nitrobenzaldehyde **2a** (0.1 mmol, 1 equiv.). The product **7d** was obtained as yellow solid (13 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.35 (m, 2H), 8.11 – 8.03 (m, 2H), 7.88 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.97, 135.92, 131.45, 124.79, 112.75, 111.73, 87.71. It was not possible to measure the HRMS (ESI-MS) of compound **7d** due to its poor tendency to ionize. The characterization of the compound matches with the data reported in the literature.[26]

D.1.4. AMINOCATALYTIC MICHAEL ADDITIONS (10a-10l)



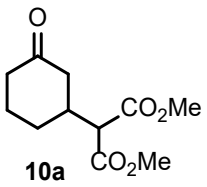
8 (3 equiv.) **9** (1 equiv.) **10**

A 4 mL glass vial was charged with the appropriate α,β-unsatured carbonyl compound **8** (0.3 mmol, 3 equiv.), NCDs-**3** (18 mol%, 11 mg), the appropriate nucleophile **9** (0.1 mmol, 1 equiv.), benzoic acid (0.02 mmol, 0.2 equiv.) and water (final concentration: 0.25 M). The resulting mixture was

stirred for the indicated time (48 hours) at ambient temperature. The reaction crude was then extracted with EtOAc and the organic phase was filtered through sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: Hex/EtOAc) to give the corresponding β-sostituited carbonyl compound **10**.

Characterization Data

Dimethyl 2-(3-oxocyclohexyl)malonate (10a).

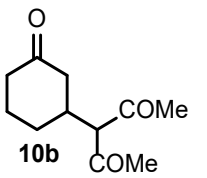


10a

Prepared according to the general procedure **D.1.4.** using dimethyl malonate **9a** (0.1 mmol, 11 µL) and 2-cyclohexen-1-one **8a** (0.3 mmol, 29 µL). The product **10a** was obtained as yellowish oil (9 mg, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (d, *J* = 3.5 Hz, 6H), 3.34 (d, *J* = 8.0 Hz, 1H), 2.54 (dddd, *J* = 15.5, 11.4, 7.7, 3.7 Hz, 1H), 2.47 – 2.35 (m, 2H), 2.26 (m, 2H), 2.14 – 2.02 (m, 1H), 2.00 – 1.88 (m, 1H), 1.78 – 1.61 (m, 1H), 1.56 – 1.43 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 209.62, 168.40, 168.31, 56.77, 52.74, 45.23, 41.13, 38.26, 28.94, 24.66. HRMS calculated for $C_{11}H_{16}O_3$ (M-Na): 251.0892, found: 251.0890. The characterization of the compound matches with the data reported in the literature.[27]

3-(3-oxocyclohexyl)pentane-2,4-dione (10b).

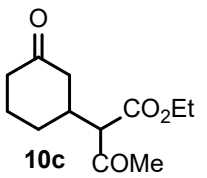


10b

Prepared according to the general procedure **D.1.4.** using acetylacetone **9b** (0.1 mmol, 10 µL) and 2-cyclohexen-1-one **8a** (0.3 mmol, 29 µL). The product **10b** was obtained as yellowish oil (12 mg, 59% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.63 (d, *J* = 10.2 Hz, 1H), 2.76 – 2.60 (m, 1H), 2.45 – 2.35 (m, 1H), 2.34 – 2.20 (m, 2H), 2.17 (d, *J* = 9.4 Hz, 6H), 2.10 – 1.98 (m, 2H), 1.89 – 1.63 (m, 2H), 1.44 – 1.30 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 209.04, 202.88, 202.70, 74.91, 45.22, 41.06, 38.39, 29.75, 29.58, 28.81, 24.45. **HRMS** calculated for $C_{11}H_{16}O_3$ (M-Na): 219.0993, found: 219.0992. The characterization of the compound matches with the data reported in the literature.[28]

Ethyl 3-oxo-2-(3-oxocyclohexyl)butanoate (10c).

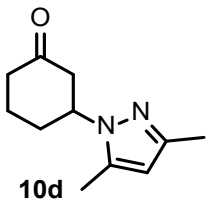


10c

Prepared according to the general procedure **D.1.4.** using ethyl acetoacetate **9c** (0.1 mmol, 13 µL) and 2-cyclohexen-1-one **8a** (0.3 mmol, 29 µL). The product **10c** was obtained as yellowish oil (14 mg, 60% yield, d.r. 1:1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.14 (m, 2H), 3.38 (dd, *J* = 8.7, 7.5 Hz, 1H), 2.66 – 2.50 (m, 1H), 2.46 – 2.32 (m, 2H), 2.30 – 2.19 (m, 3H), 2.19 – 2.12 (m, 1H), 2.11 – 1.99 (m, 1H), 1.96 – 1.81 (m, 1H), 1.77 – 1.62 (m, 1H), 1.61 – 1.49 (m, 1H), 1.32 – 1.23 (m, 4H). **^{13}C NMR (101 MHz, CDCl3)** δ 209.68, 209.59, 201.77, 201.65, 168.42, 168.22, 65.33, 64.91, 61.83, 61.76, 45.55, 45.17, 41.25, 41.19, 37.90, 29.66, 29.64, 29.18, 28.72, 24.69, 14.28, 14.25. **HRMS** calculated for $C_{12}H_{18}O_6$ (M-Na): 249.1096, found: 249.1097. The characterization of the compound matches with the data reported in the literature.[29]

3-(3,5-dimethyl-1H-pyrazol-1-yl)cyclohexan-1-one (10d).

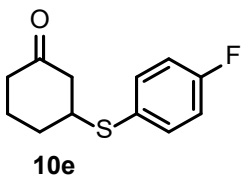


10d

Prepared according to the general procedure **D.1.4.** using 3,5-dimethyl-pyrazol **9d** (0.1 mmol, 10 mg) and 2-cyclohexen-1-one **8a** (0.3 mmol, 28 µL). The product **10d** was obtained as yellowish oil (17 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.35 – 4.17 (m, 1H), 3.09 (dd, *J* = 14.3, 11.5 Hz, 1H), 2.74 – 2.52 (m, 1H), 2.48 – 2.38 (m, 2H), 2.37 – 2.23 (m, 1H), 2.22 – 2.18 (m, 6H), 2.17 – 2.09 (m, 1H), 2.09 – 1.99 (m, 1H), 1.87 (s, 1H), 1.74 – 1.58 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.95, 147.82, 137.92, 105.16, 55.80, 48.12, 40.70, 31.50, 22.32, 13.71, 10.95. **HRMS** calculated for $C_{11}H_{16}N_2O$ (M-Na): 215.1157, found: 215.1155.

3-((4-fluorophenyl)thio)cyclohexan-1-one (10e).

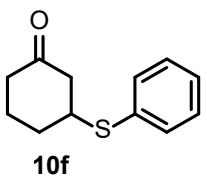


10e

Prepared according to the general procedure **D.1.4.** using 4-fluorophenylthiol **9e** (0.1 mmol, 11 µL) and 2-cyclohexen-1-one **8a** (0.3 mmol, 28 µL). The product **10e** was obtained with 97% yield (22 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.09 – 6.96 (m, 2H), 3.40 – 3.24 (m, 1H), 2.64 (ddt, *J* = 14.3, 4.5, 1.6 Hz, 1H), 2.42 – 2.19 (m, 3H), 2.19 – 2.06 (m, 2H), 1.80 – 1.55 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.07. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.55, δ 162.81 (d, J = 248.7 Hz), 136.16 (d, J = 8.2 Hz), 116.18 (d, J = 21.8 Hz), 47.66, 46.85, 40.82, 31.17, 23.96. **HRMS** calculated for $C_{12}H_{13}FOS$ (M-Na): 247.0564, found: 247.0563. The characterization of the compound matches with the data reported in the literature.[30]

3-((4-fluorophenyl)thio)cyclohexan-1-one (10f).

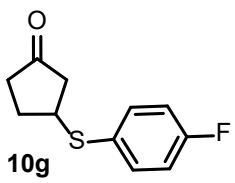


10f

Prepared according to the general procedure **D.1.4.** using thiophenol **9f** (0.1 mmol, 10 µL) and 2-cyclohexen-1-one **8a** (0.3 mmol, 28 µL). The product **10f** was obtained as yellowish oil (15 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.36 – 7.27 (m, 3H), 3.43 (ddd, *J* = 14.1, 10.1, 4.2 Hz, 1H), 2.69 (dd, *J* = 14.3, 4.4 Hz, 1H), 2.43 – 2.23 (m, 3H), 2.22 – 2.06 (m, 2H), 1.88 – 1.63 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.71, 133.23, 132.98, 129.05, 127.78, 47.77, 46.12, 40.87, 31.26, 24.04. **HRMS** calculated for $C_{12}H_{14}OS$ (M-Na): 229.0657, found: 229.0658. The characterization of the compound matches with the data reported in the literature.[31]

3-((4-fluorophenyl)thio)cyclopentan-1-one (10g).

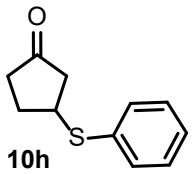


10g

Prepared according to the general procedure **D.1.4.** using 4-fluorophenylthiol **9e** (0.1 mmol, 11 µL) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10g** was obtained as yellowish oil (17 mg, 82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.08 – 6.97 (m, 2H), 3.84 – 3.71 (m, 1H), 2.64 – 2.39 (m, 1H), 2.37 – 2.14 (m, 3H), 2.04 – 1.91 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.99 – -120.35 (m). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 216.29, 162.76 (d, *J* = 248.5 Hz), 135.25 (d, *J* = 8.2 Hz), 129.07 (d, *J* = 3.4 Hz), 116.41 (d, *J* = 22.0 Hz), 45.23, 44.49, 36.87, 29.42. **HRMS** calculated for $C_{11}H_{11}FOS$ (M-Na): 233.0406, found: 233.0407.

3-(phenylthio)cyclopentan-1-one (10h).

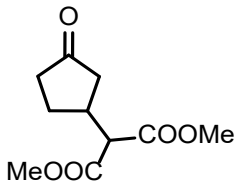


10h

Prepared according to the general procedure **D.1.4.** using thiophenol **9f** (0.1 mmol, 10 µL) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10h** was obtained as yellowish oil (10 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 1H), 7.36 – 7.24 (m, 2H), 3.95 – 3.82 (m, 1H), 2.61 (dd, *J* = 18.7, 7.2 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.41 – 2.17 (m, 2H), 2.09 – 1.96 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 216.54, 134.31, 132.16, 129.25, 127.58, 45.38, 43.55, 36.93, 29.49. **HRMS** calculated for $C_{11}H_{12}OS$ (M-Na): 215.0502, found: 215.0501. The characterization of the compound matches with the data reported in the literature.[31]

Dimethyl 2-(3-oxocyclopentyl)malonate (10i).

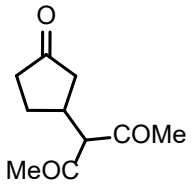


10i

Prepared according to the general procedure **D.1.4.** using dimethyl malonate **9a** (0.1 mmol, 11 µL) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10i** was obtained as yellowish oil (14 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.74 (s, *J* = 1.6 Hz, 3H), 3.37 (d, *J* = 9.4 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.50 (dd, *J* = 18.4, 7.6 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.29 – 2.13 (m, 2H), 2.00 (ddd, *J* = 18.4, 11.0, 1.4 Hz, 1H), 1.75 – 1.54 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 217.04, 168.65, 168.57, 56.24, 52.79, 52.78, 43.01, 38.31, 36.53, 27.62. **HRMS** calculated for $C_{10}H_{14}O_5$ (M-Na): 237.0733, found: 237.0733. The characterization of the compound matches with the data reported in the literature.[27]

3-(3-oxocyclopentyl)pentane-2,4-dione (10j).

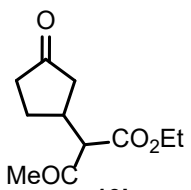


10j

Prepared according to the general procedure **D.1.4.** using acetylacetone **9b** (0.1 mmol, 10 µL) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10j** was obtained as yellowish oil (10 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (d, *J* = 10.5 Hz, 1H), 2.95 (qdd, *J* = 10.4, 7.1, 5.5 Hz, 1H), 2.47 – 2.27 (m, 2H), 2.24 – 2.21 (m, 3H), 2.21 – 2.09 (m, 5H), 1.78 (ddd, *J* = 18.2, 11.0, 1.3 Hz, 1H), 1.54 – 1.44 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 216.55, 202.85, 202.63, 75.10, 42.81, 38.07, 36.36, 29.70, 29.45, 27.67. The characterization of the compound matches with the data reported in the literature.[32]

3-(3-oxocyclohexyl)pentane-2,4-dione(10k).

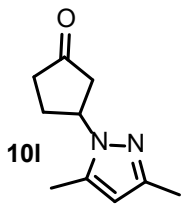


10k

Prepared according to the general procedure **D.1.4.** using ethyl acetoacetate **9c** (0.1 mmol, 13 µL) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10k** was obtained as yellowish oil (18 mg, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.09 (m, 1H), 3.41 (dd, J = 9.8, 6.3 Hz, 1H), 2.95 – 2.79 (m, 1H), 2.45 (ddd, J = 12.1, 7.1, 3.2 Hz, 1H), 2.36 – 2.10 (m, 6H), 1.88 (dddd, J = 53.0, 18.3, 11.0, 1.4 Hz, 1H), 1.69 – 1.41 (m, 1H), 1.36 – 1.18 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 217.03, 216.99, 201.54, 201.38, 168.37, 168.29, 64.81, 64.60, 61.70, 61.68, 42.94, 42.69, 38.15, 38.00, 35.83, 35.74, 29.44, 29.21, 27.61, 27.33, 14.10, 14.07. **HRMS** calculated for $C_{11}H_{16}O_4$ (M-Na): 235.0943, found: 235.0941. The characterization of the compound matches with the data reported in the literature.[29]

3-(3,5-dimethyl-1H-pyrazol-1-yl)cyclopentan-1-one (10l).

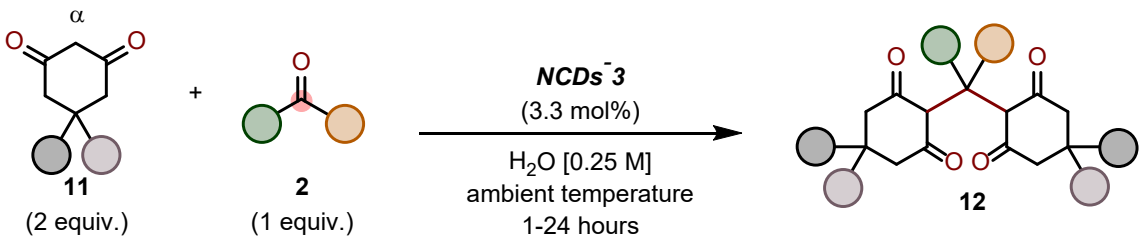


10l

Prepared according to the general procedure **D.1.4.** using 3,5-dimethyl-pyrazol **9d** (0.1 mmol, 10 mg) and 2-cyclopenten-1-one **8b** (0.3 mmol, 25 µL). The product **10l** was obtained as yellowish oil (16 mg, 88% yield).

^{1}H NMR (499 MHz, $CDCl_3$) δ 5.79 (s, 1H), 4.77 (p, *J* = 7.2 Hz, 1H), 2.94 – 2.82 (m, 1H), 2.64 (dddd, *J* = 30.4, 21.7, 11.8, 4.6 Hz, 2H), 2.48 – 2.32 (m, 2H), 2.31 – 2.21 (m, 4H), 2.19 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 215.59, 147.58, 138.27, 105.29, 77.27, 77.01, 76.76, 54.41, 44.35, 37.16, 29.86, 13.58, 10.93. **HRMS** calculated for $C_{10}H_{14}N_2O$ (M-Na): 201.0997, found: 201.0998.

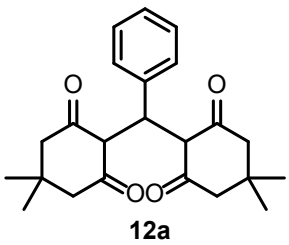
D.1.5. AMINOCATALYTIC TANDEM KNOEVENAGEL-MICHAEL REACTIONS (12a-12h)



A 4 mL glass vial was charged with the appropriate diketone **11** (0.2 mmol, 2 equiv.), NCDs-**3** (3.3% mol, 2 mg), the appropriate electrophiles **2** (0.1 mmol, 1 equiv.) and water (final concentration: 0.25 M). The resulting mixture was stirred for the indicated time (1-24 hours) at ambient temperature. The reaction crude was then extracted with EtOAc and the organic phase was filtered through sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: Hex/EtOAc) to give the corresponding β-sostituited carbonyl compound **12**.

Characterization Data

2,2'-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione) (12a).

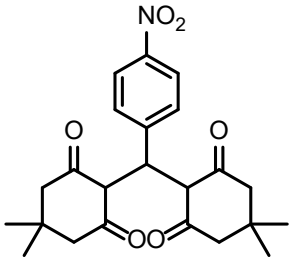


12a

Prepared according to the general procedure **D.1.5.** using cyclohexane-1,3-dione (0.2 mmol, 28 mg) and benzaldehyde (0.1 mmol, 10 µL) for 1 hour. The product **12a** was obtained as white solid (35 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H), 7.30 – 7.22 (m, 2H), 7.21 – 7.14 (m, 1H), 7.12 – 7.06 (m, 2H), 5.54 (s, 1H), 2.57 – 2.21 (m, 8H), 1.24 (s, *J* = 8.0 Hz, 7H), 1.10 (s, *J* = 20.1 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.59, 189.52, 138.20, 128.34, 126.91, 125.97, 115.73, 47.21, 46.60, 32.89, 31.56, 29.80, 27.55. **HRMS** calculated for $C_{23}H_{28}O_4$ (M-Na): 369.2063, found: 369.2060. The characterization of the compound matches with the data reported in the literature.[33]

2,2'-((4-nitrophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione)(12b).

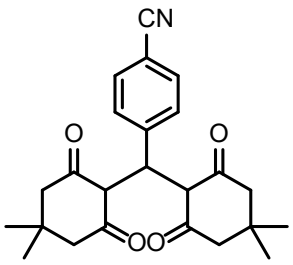


12b

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and 4-nitrobenzaldehyde (0.1 mmol, 15 μL) for 2 hours. The product **12b** was obtained as white solid (37 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 8.27 – 8.00 (m, 2H), 7.33 – 7.14 (m, 2H), 5.54 (s, 1H), 2.40 (dq, *J* = 27.6, 17.6 Hz, 8H), 1.23 (s, *J* = 7.4 Hz, 6H), 1.11 (s, *J* = 22.8 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 191.09, 189.70, 146.67, 146.24, 127.77, 123.64, 115.04, 47.13, 46.56, 33.38, 31.61, 29.67, 27.59. **HRMS** calculated for $C_{23}H_{27}NO_6$ (M-Na): 414.1917, found: 414.1919. The characterization of the compound matches with the data reported in the literature.[34]

4-(bis(4,4-dimethyl-2,6-dioxocyclohexyl)methyl)benzonitrile (12c).

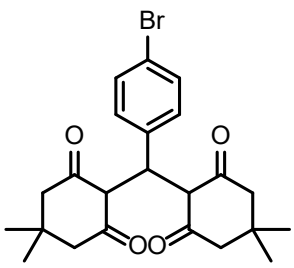


12c

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and 4-formylbenzonitrile (0.1 mmol, 14 μL) for 2 hours. The product **12c** was obtained as white solid (36 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 7.62 – 7.46 (m, 2H), 7.19 (dd, *J* = 8.6, 1.0 Hz, 2H), 5.52 (s, 1H), 2.55 – 2.29 (m, 8H), 1.22 (s, 6H), 1.11 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 191.06, 189.65, 144.47, 132.21, 127.74, 119.05, 114.96, 109.89, 47.14, 46.56, 33.38, 31.60, 29.69, 27.60. **HRMS** calculated for $C_{24}H_{27}NO_4$ (M-Na):394.2017, found: 394.2013. The characterization of the compound matches with the data reported in the literature.[35]

2,2'-((4-bromophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione) (12d).

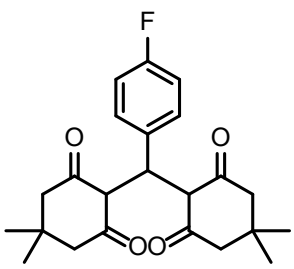


12d

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and 4-bromobenzaldehyde (0.1 mmol, 11 μL) for 2 hours. The product **12d** was obtained as white solid (39 mg, 92% yield).

^{1}H NMR (499 MHz, $CDCl_3$) δ 12.32 (s, 1H), 12.07 (s, 1H), 7.40 – 7.34 (m, 2H), 7.00 – 6.95 (m, 2H), 5.38 (s, 1H), 2.61 (ddt, *J* = 32.7, 17.8, 3.7 Hz, 4H), 2.51 – 2.33 (m, 4H), 2.11 – 1.96 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.42, 191.03, 137.22, 131.36, 128.50, 119.79, 116.26, 33.63, 33.13, 32.78, 20.21. **HRMS** calculated for $C_{23}H_{27}BrO_6$ (M-Na): 469.0986, found: 469.0985. The characterization of the compound matches with the data reported in the literature.[34]

2,2'-((4-fluorophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione) (12e).



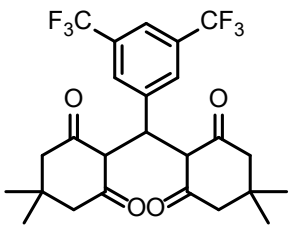
12e

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and 4-fluorobenzaldehyde (0.1 mmol, 11 μL) for 2 hours. The product **12e** was obtained as white solid (36 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (s, 1H), 7.08 – 7.00 (m, 2H), 6.99 – 6.89 (m, 2H), 5.48 (s, 1H), 2.38 (dq, *J* = 26.2, 17.7 Hz, 8H), 1.22 (s, *J* = 22.7 Hz, 6H), 1.10 (s, *J* = 19.4 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.79. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.67, 189.51, 162.36, 159.93, 133.76, 133.72, 128.42, 128.34, 115.67, 115.24, 115.03, 47.19, 46.56, 32.36, 31.54, 29.74,

27.53. **HRMS** calculated for $C_{23}H_{27}FO_4$ (M-Na): 387.1965, found: 387.1966. The characterization of the compound matches with the data reported in the literature.[34]

2,2'-((3,5-bis(trifluoromethyl)phenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione)(12f).

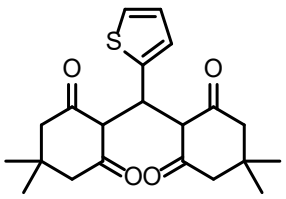


12f

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and 3,5-bis(trifluoromethyl)benzaldehyde (0.1 mmol, 17 μL) for 2 hours. The product **12f** was obtained as white solid (42 mg, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 7.69 (s, 1H), 7.54 (s, 2H), 5.54 (s, 1H), 2.64 – 2.23 (m, 8H), 1.23 (s, 6H), 1.12 (s, 6H).^{19}F NMR (376 MHz, $CDCl_3$) δ -63.04. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 191.31, 189.74, 141.37, 132.07, 131.75, 131.42, 131.09, 127.27, 124.89, 122.18, 120.17, 114.60, 47.09, 46.53, 33.11, 31.48, 29.92, 27.01. **HRMS** calculated for $C_{25}H_{26}F_6O_4$ (M-Na): 505.1807, found: 505.1808.

2,2'-(thiophen-2-ylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione) (12 g).

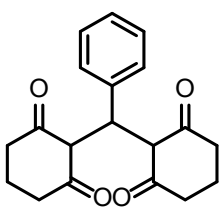


12g

Prepared according to the general procedure **D.1.5.** using 5,5-dimethylcyclohexane-1,3-dione (0.2 mmol, 28 mg) and thiophene-2-carbaldehyde (0.1 mmol, 9 μL) for 24 hours. The product **12g** was obtained as white solid (40 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (s, 1H), 7.10 (d, J = 5.1 Hz, 1H), 6.87 (dd, J = 5.1, 3.6 Hz, 1H), 6.66 – 6.59 (m, 1H), 5.63 (s, 1H), 2.44 – 2.21 (m, 9H), 1.21 (s, J = 15.8 Hz, 6H), 1.10 (s, J = 19.4 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.11, 189.63, 143.85, 126.48, 124.66, 123.60, 116.11, 47.15, 46.41, 31.31, 30.51, 30.09, 26.90. **HRMS** calculated for $C_{21}H_{26}O_4S$ (M-Na): 397.1444, found: 397.1444. The characterization of the compound matches with the data reported in the literature.[34]

2,2'-(phenylmethylene)bis(cyclohexane-1,3-dione) (12h).



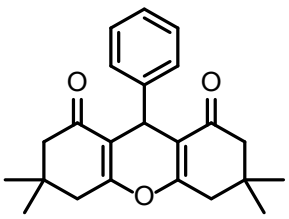
12h

Prepared according to the general procedure **D.1.5.** using cyclohexane-1,3-dione (0.2 mmol, 23 mg) and benzaldehyde (0.1 mmol, 11 μL) for 2 hours. The product **12h** was obtained as white solid (23 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 1H), 7.29 – 7.23 (m, 1H), 7.17 (ddd, J = 7.9, 3.8, 1.1 Hz, 1H), 7.13 – 7.08 (m, 1H), 2.61 (dd, J = 22.2, 18.1 Hz, 4H), 2.42 (m, 4H), 2.10 – 1.97 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 192.23, 191.01, 137.99, 128.30, 126.62, 125.99, 116.58, 33.66, 33.15, 33.06, 20.27. **HRMS** calculated for $C_{19}H_{20}O_4$ (M-Na): 335.1299, found: 335.1254. The characterization of the compound matches with the data reported in the literature.[33]

D.1.5.1. MANIPULATION OF COMPOUND 12a (13a-13b)

3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (13a)

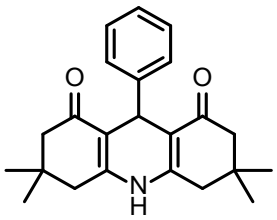


13a

A 4 mL glass vial was charged with the compound **12a** (0.5 mmol, 1 equiv.), acetic acid (2 mL). The resulting mixture was stirred for 18 hours at ambient temperature. The reaction crude was purified by crystallization from ethanol/water (8:2) to give the corresponding product **13a** (121 mg, 71% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 3.1, 1.7 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.12 – 7.06 (m, 1H), 4.75 (s, 1H), 2.46 (s, 4H), 2.20 (q, *J* = 16.3 Hz, 4H), 1.10 (s, 6H), 0.99 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.50, 162.36, 144.22, 128.51, 128.18, 126.50, 115.82, 50.89, 41.03, 32.35, 31.98, 29.42, 27.48. **HRMS** calculated for $C_{23}H_{27}O_3$ (M-Na): 373.1773, found: 373.1774. The characterization of the compound matches with the data reported in the literature.[36]

3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (13b).



13b

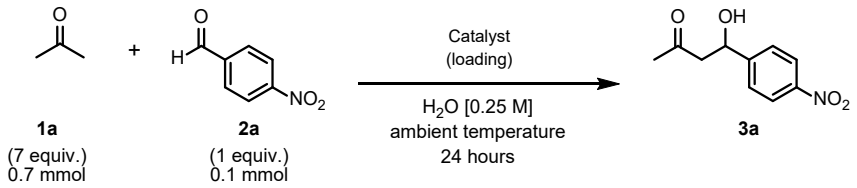
A 4 mL glass vial was charged with the compound **12a** (0.5 mmol, 1 equiv.), ammonium acetate (2.5 mmol, 5 equiv.), and water (2 mL). The resulting mixture was stirred for the indicated time (16 hours) at ambient temperature. The reaction crude was purified by crystallization from ethanol/water (8:2) to give the corresponding product **13b** (98 mg, 57% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 5.08 (s, 1H), 2.44 – 2.11 (m, 8H), 1.08 (s, 6H), 0.96 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.04, 149.31, 146.75, 128.14, 128.08, 126.10, 113.36, 51.02, 40.80, 33.76, 32.74, 29.69, 27.23. **HRMS** calculated for $C_{23}H_{27}NO_2$ (M-Na): 350.2113, found: 350.2115. The characterization of the compound matches with the data reported in the literature.[36]

E.1. COMPARATIVE STUDIES WITH FREE MOLECULAR AMINES

We also compared the catalytic performance of NCDs-**3** with some simple molecular amines (entries 1-3) and readily available amine-bearing polymers (entries 4-5, Table 1). NCDs-**3** significantly outperformed all the amines and polyamines tested.

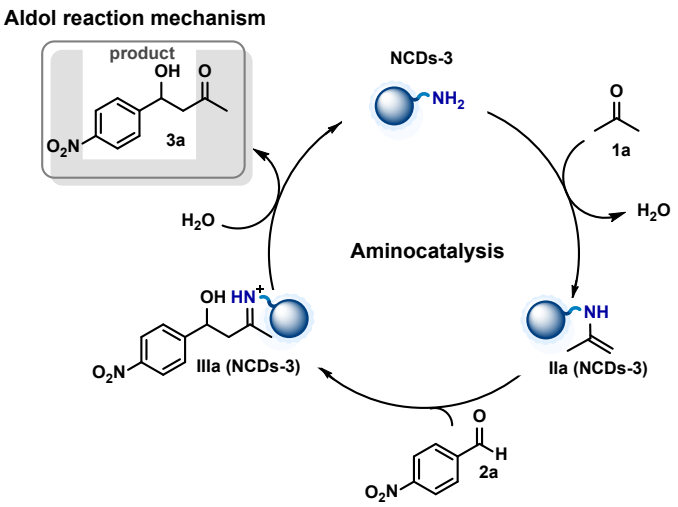
Table 1. Comparative study on different free molecular amines and NCDs-**3** in the aldol addition reaction between acetone **1a** and *p*-nitrobenzaldehyde **2a**. The general procedure of this reaction is described in Section D.1.1.



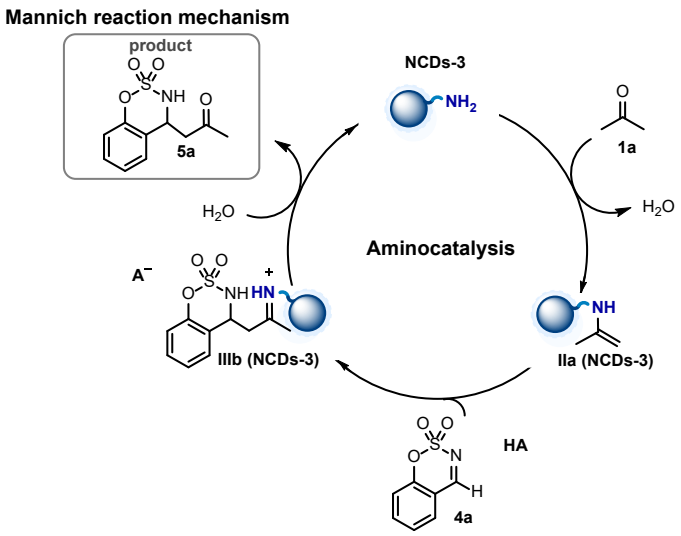
Entry	Catalyst	Loading (mol%)	Yield (%)[c]
1	Benzylamine	83[a]	7±3
2	Pyrrolidine	83	0
3	Aniline	83	0
4	Polyethyleneimine	18[b]	24±4
5	PAMAM 1.0 dendrimer	18	14±2
6	NCDs-**3**	18	75±3

[a] Catalytic loading calculated based on acid/base backtitration on NCDs-**3**. [b] Catalytic loading calculated on the basis of Kaiser Test at 25°C on NCDs-**3**. [c] Yield determined by ^{1}H-NMR spectroscopy using 1,1,2-trichloroethene as the internal standard over five independent experiments.

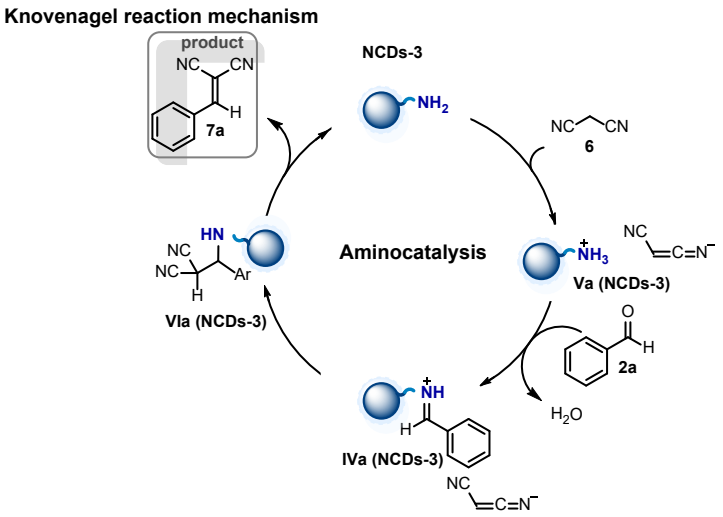
F.1. PROPOSED REACTION MECHANISMS



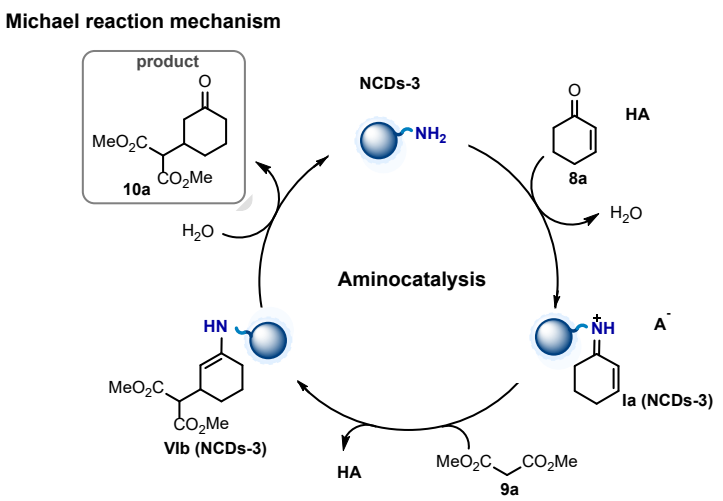
Scheme 1. Proposed mechanism of the aminocatalytic aldol reaction between **1a** and **2a** using NCDs-**3.**



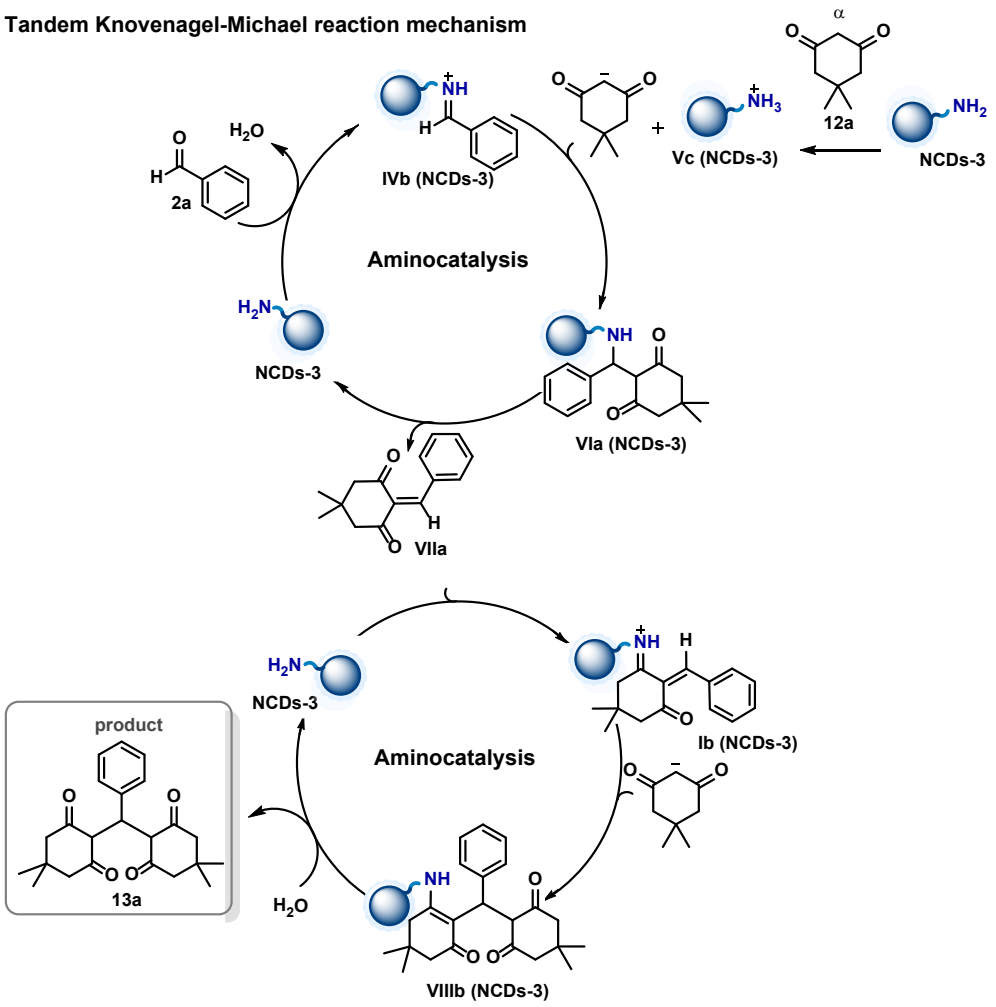
Scheme 2. Proposed mechanism for the aminocatalytic Mannich reaction between **1a** and **4a** using NCDs-**3.**



Scheme 3. Proposed mechanism for the aminocatalytic Knoevenagel reaction between **6** and **2a** using NCDs-**3.**



Scheme 4. Proposed mechanism for the aminocatalytic Michael reaction between **8a** and **9a** using NCDs-**3.**



Scheme 5. Proposed mechanism for the aminocatalytic tandem Knoevenagel-Michael reaction between **2a** and **11a** using NCDs-**3.**

G.1. ^{19}F-NMR STUDIES

First, we studied the formation and stability of the imines and enamines derived from different representative amines, namely butylamine (**14a**), aniline (**14b)**, benzyl amine (**14c**) with 4-fluorobenzaldehyde. Then, the corresponding derivatives obtained from benzyl amine (**14c**) and pyrrolidine (**14d**) with 4-fluorophenylacetaldehyde, in DMSO-d_6. ^{19}F-NMR (Figure S33-41) and ^{1}H-NMR (Figure S42-55) spectra have been used to characterize the so-formed imine and enamine derivatives.

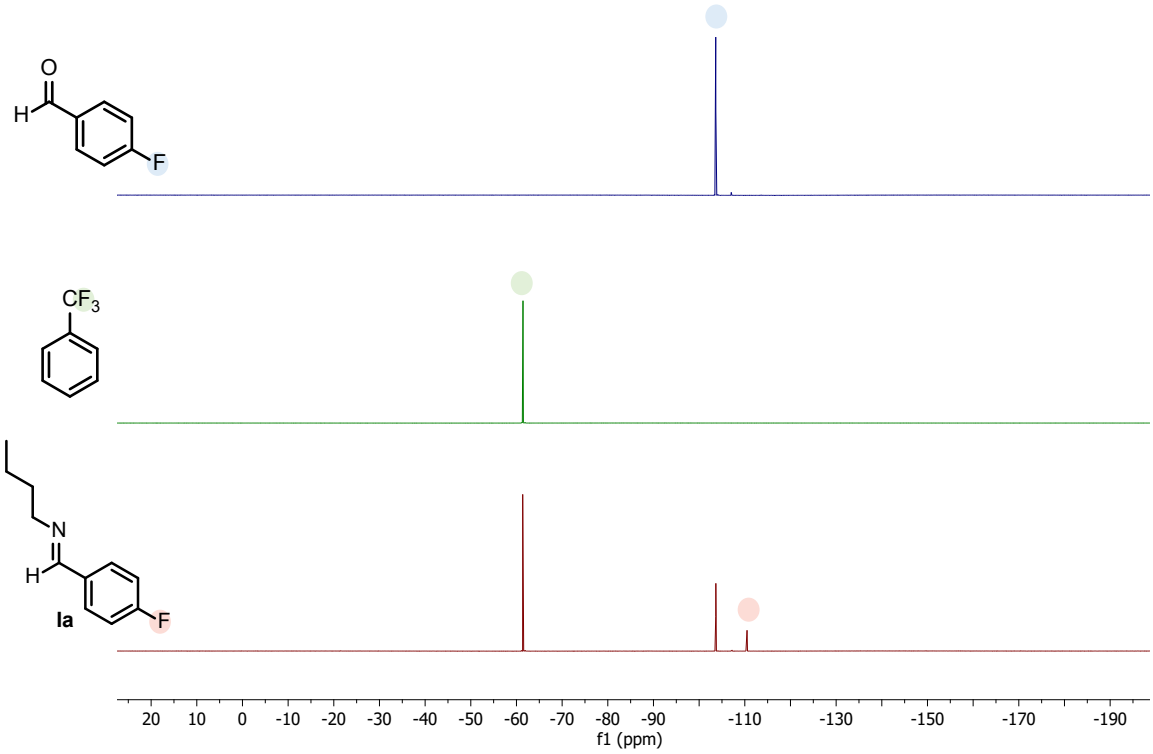


Figure S33. ^{19}F NMR spectra of the in-situ formation of the imine derived from 4-fluorobenzaldehyde and butylamine **14a** in DMSO-*d*$_6$. Comparison between ^{19}F NMR spectra of 4-fluorobenzaldehyde (blue), trifluorotoluene as internal standard (green) and (*E*)-N-butyl-1-(4-fluorophenyl)methanimine **Ia** (red).

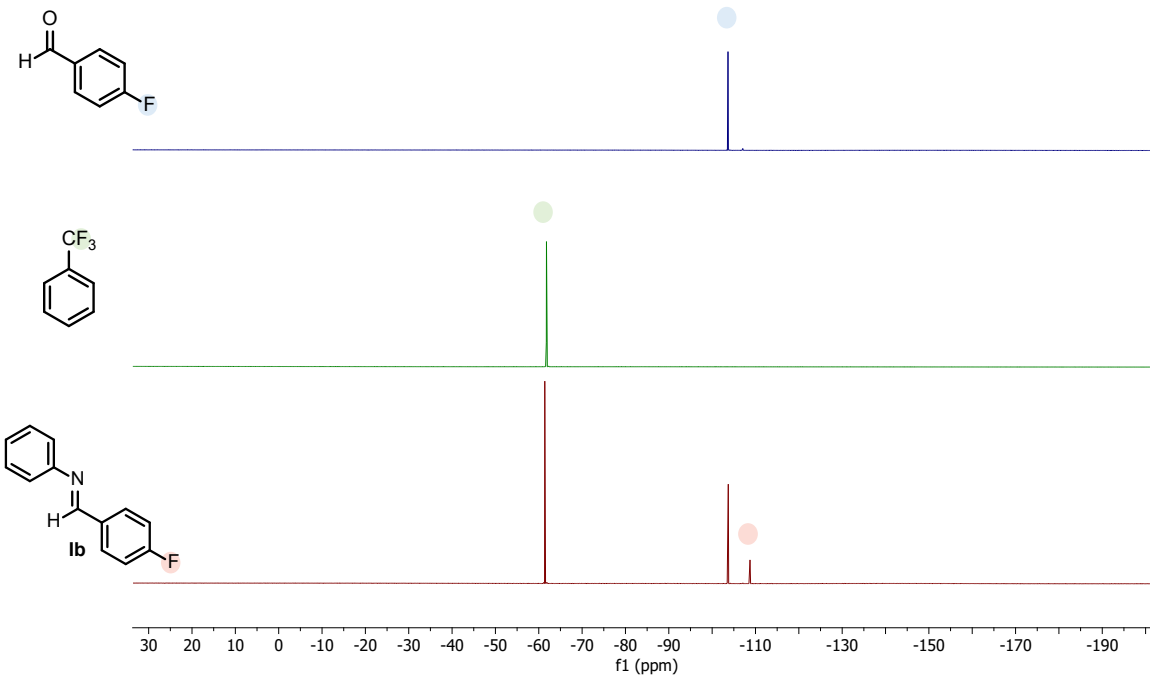


Figure S34. ^{19}F NMR spectra of the in-situ formation of the imine derived from 4-fluorobenzaldehyde and aniline **14b** in DMSO-*d*$_6$. Comparison between ^{19}F NMR spectra of 4-fluorobenzaldehyde (blue), trifluorotoluene as internal standard (green) and N-phenyl-1-(4-fluorophenyl)methanimine **Ib** (red).

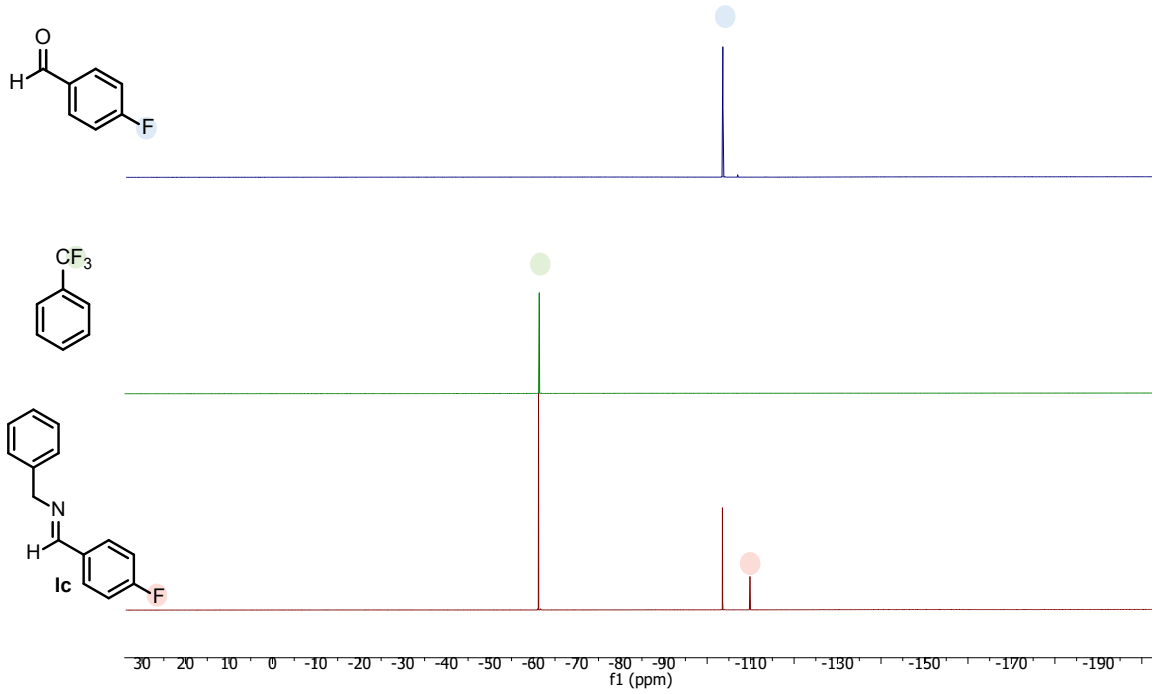


Figure S35. ^{19}F NMR spectra of the in-situ formation of the imine derived from 4-fluorobenzaldehyde and benzylamine **14c** in DMSO-d_6. Comparison between ^{19}F NMR spectra of p-fluorobenzaldehyde (blue), trifluorotoluene as internal standard (green) and N-benzyl-1-(4-fluorophenyl)methanimine **Ic** (red).

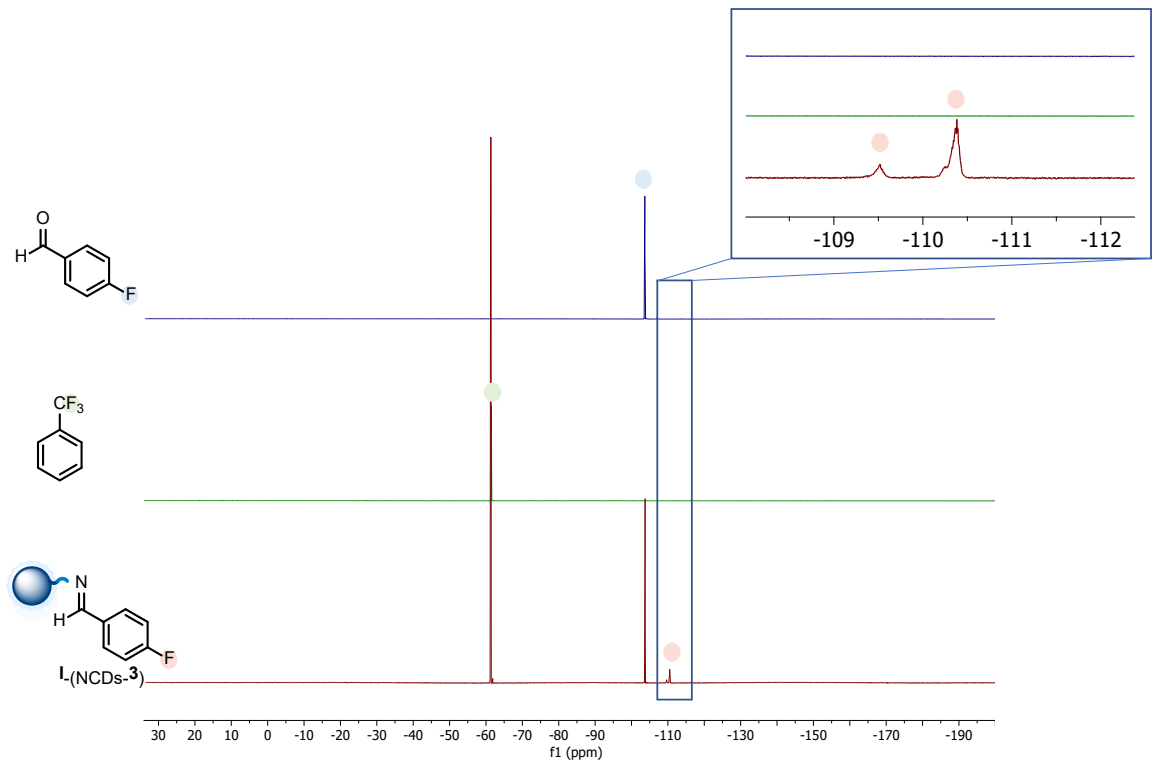


Figure S36. ^{19}F NMR spectra of the in-situ formation of the imine derived from 4-fluorobenzaldehyde and NCDs-**3** in DMSO-d_6. Comparison between ^{19}F NMR spectra of 4-fluorobenzaldehyde (blue), trifluorotoluene as internal standard (green) and **I**-(NCDs-**3**) (red). The ^{19}F NMR expansion between -109 and -112 ppm shows the broad fluorine signal of **I**-(NCDs-**3**) that experience different chemical environments.

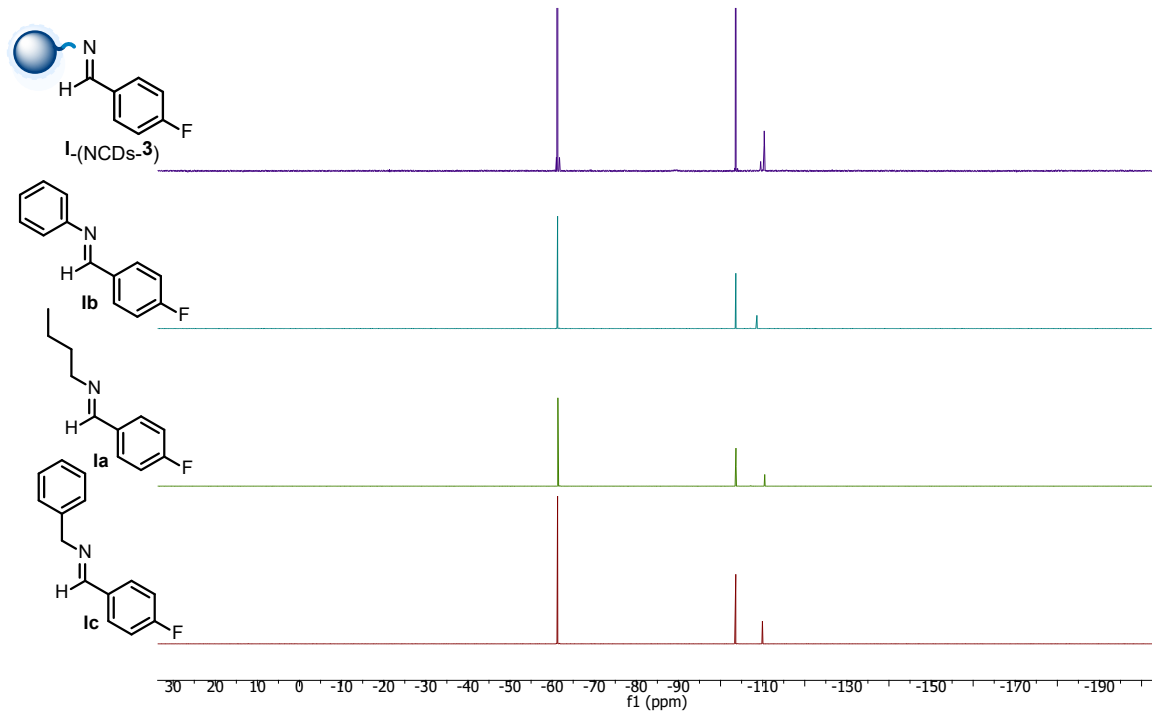


Figure S37. Comparison between ^{19}F NMR spectra of imine **I**-(NCDs-**3**) (blue), **Ib** (light blue), **Ia** (green) and **Ic** (red).

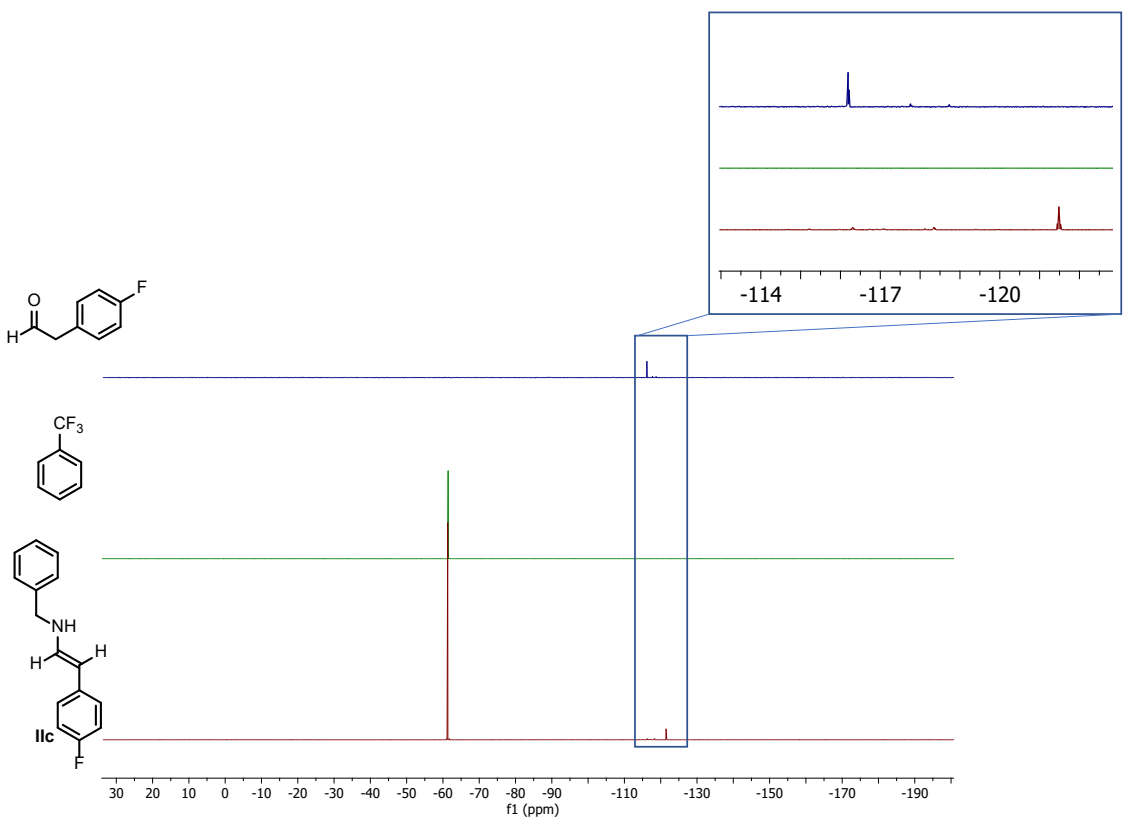


Figure S38. ^{19}F NMR spectra of the in-situ formation of the enamine derived from 4-fluorophenylacetaldehyde and **14c** in DMSO-d_6. Comparison between ^{19}F NMR spectra of 4-fluorophenylacetaldehyde (blue), trifluorotoluene as internal standard (green) and **IIc** (red). The ^{19}F NMR expansion between -114 and -120 ppm shows the fluorine signal of **IIc.**

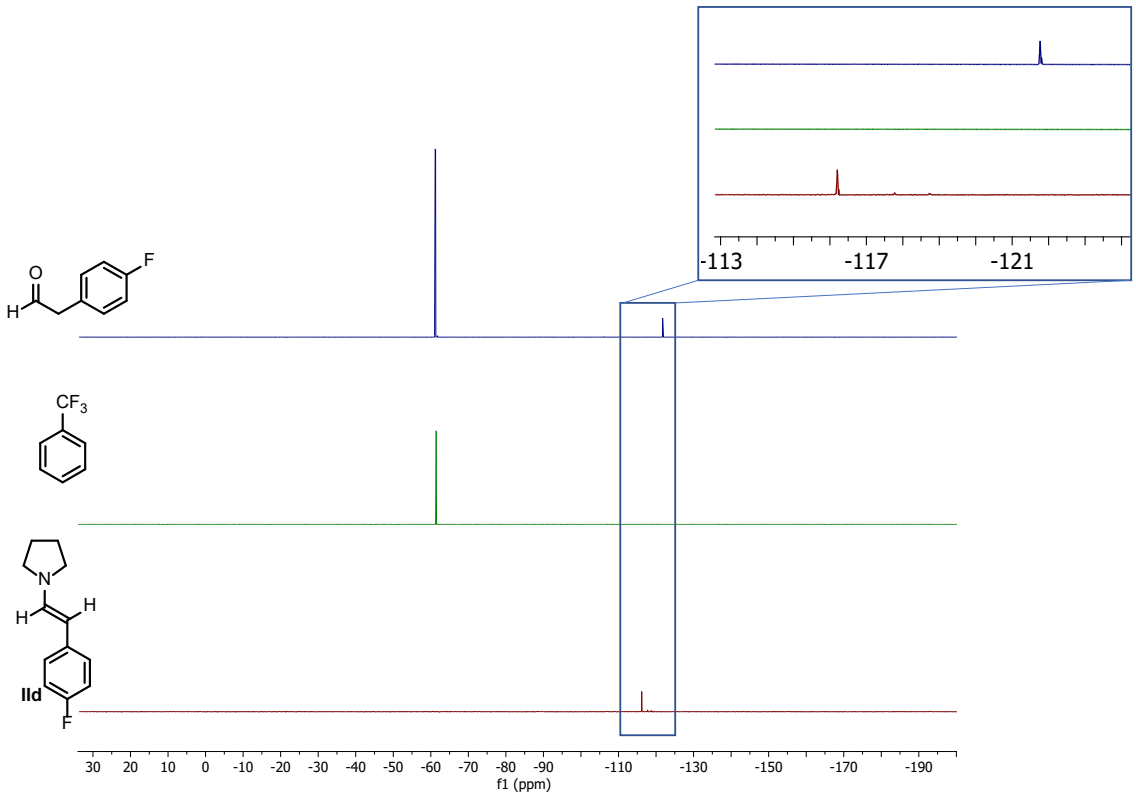


Figure S39. ^{19}F NMR spectra of the in-situ formation of the enamine derived from 4-fluorophenylacetaldehyde and **14d** in DMSO-d_6. Comparison between ^{19}F NMR spectra of 4-fluorophenylacetaldehyde (blue), trifluorotoluene as internal standard (green) and **IId** (red). The ^{19}F NMR expansion between -113 and -121 ppm shows the fluorine signal of **IId.**

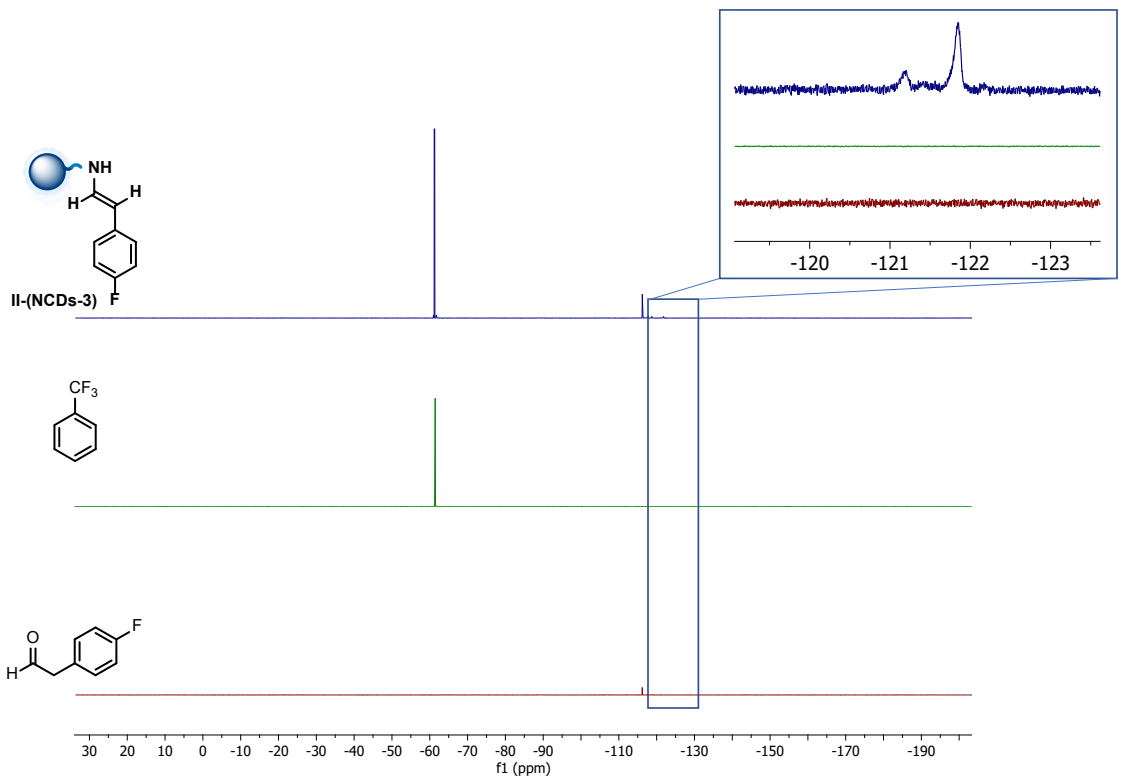


Figure S40. ^{19}F NMR spectra of the in-situ formation of the enamine derived from 4-fluorophenylacetaldehyde and NCDs-**3** in DMSO-d_6. Comparison between ^{19}F NMR spectra of 4-fluorophenylacetaldehyde (blue), trifluorotoluene as internal standard (green) and **II**-(NCDs-**3**) (red). The ^{19}F NMR expansion between -120 and -123 ppm shows the broad fluorine signal of **II**-(NCDs-**3**) that experience different chemical environments.

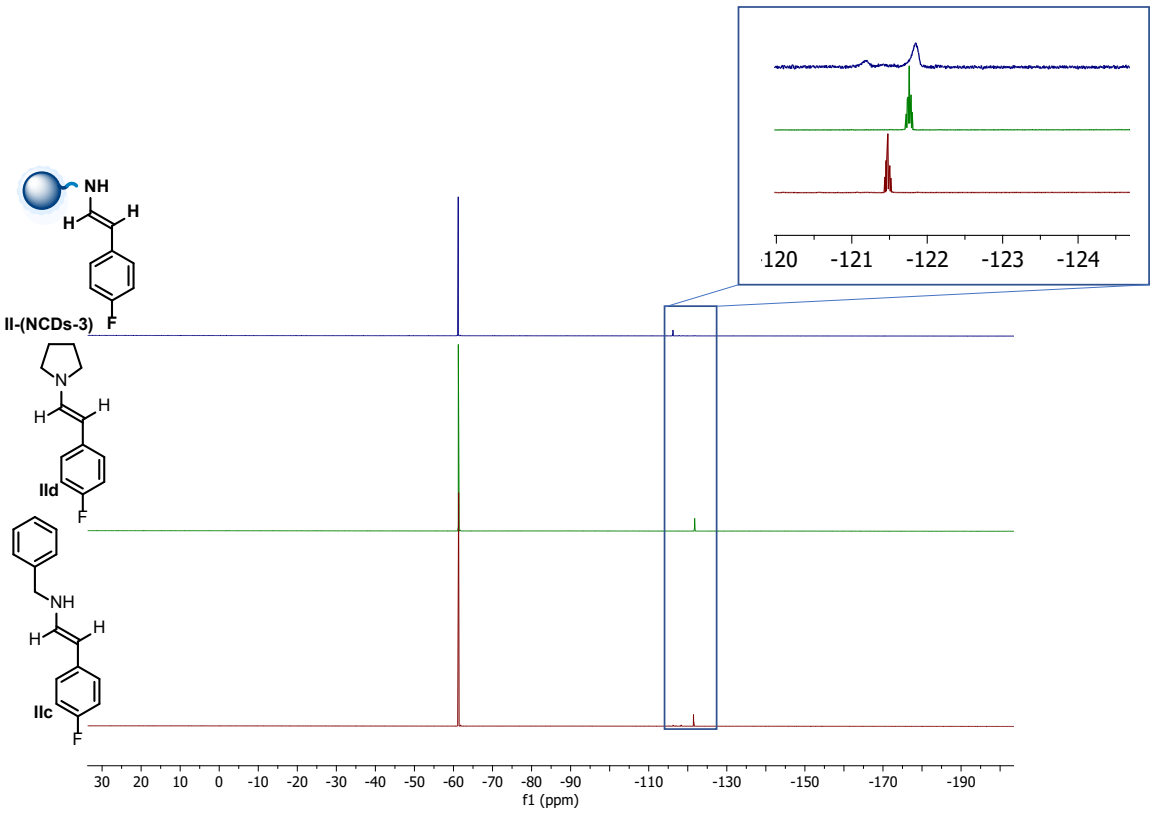


Figure S41. Comparison between ^{19}F NMR spectra of enamine **II**-(NCDs-**3**) (blue), **IId** (green) and **IIc** (red).

G.2. ^{1}H-NMR STUDIES

In this Section, the formation of imines and enamines derivatives are demonstrated by ^{1}H-NMR spectroscopy.

Firstly, ^{1}H-NMR spectra of the formation of imine **Ia** are shown, starting from butylamine **14a** and 4-fluorobenzaldehyde. The corresponding imine presents the diagnostic proton at around 8.3 ppm.

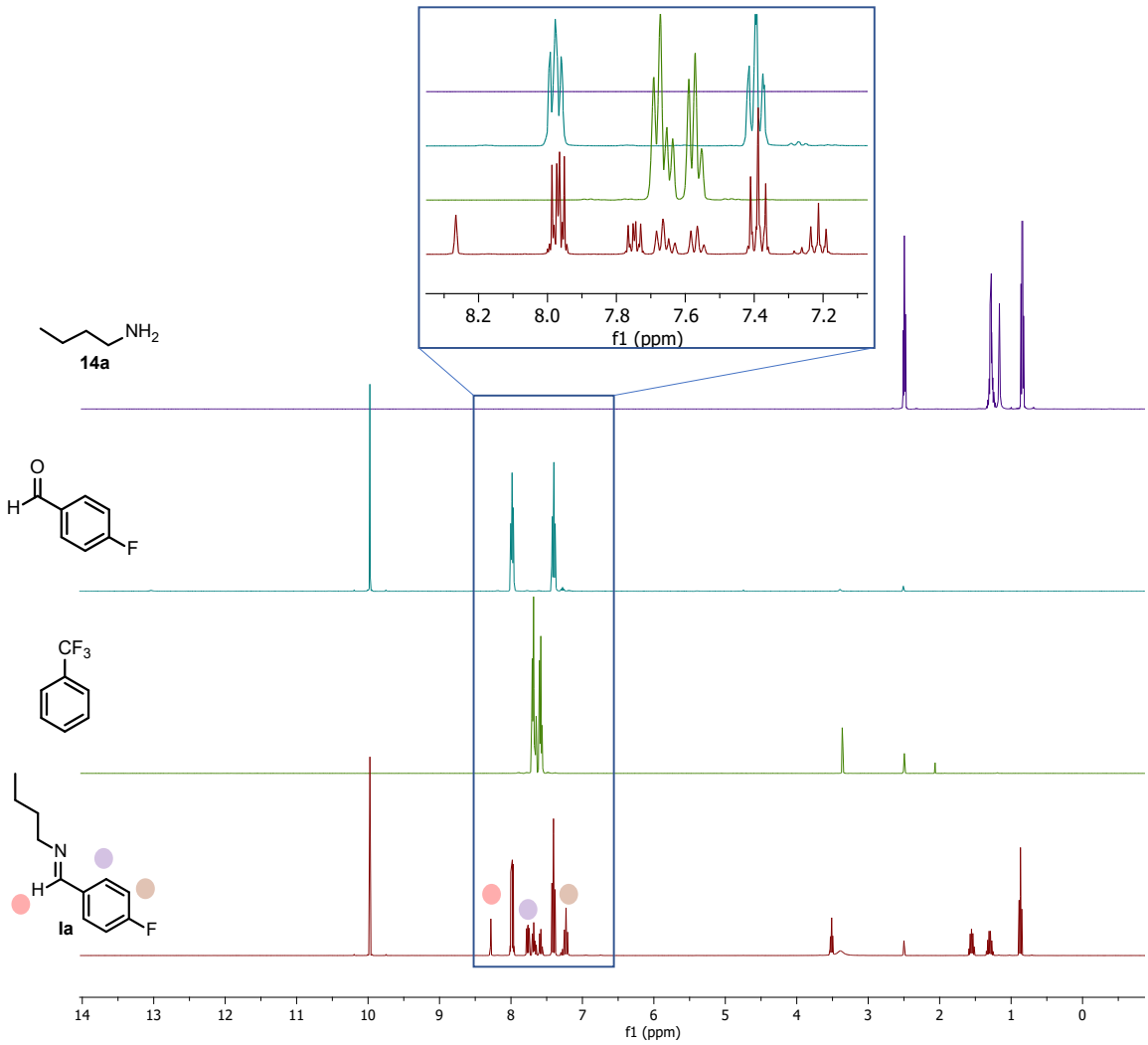


Figure S42. ^{1}H NMR of the in-situ formed imine **Ia** in DMSO-d_6. Comparison between ^{1}H NMR spectra of aniline **14a** (blue), 4-fluorobenzaldehyde (light blue), trifluorotoluene as internal standard (green) and N-butyl-1-(4-fluorophenyl)methanimine **Ia** (red). The ^{1}H NMR expansion between 7.1 and 8.3 ppm shows the signals in the aromatic region.

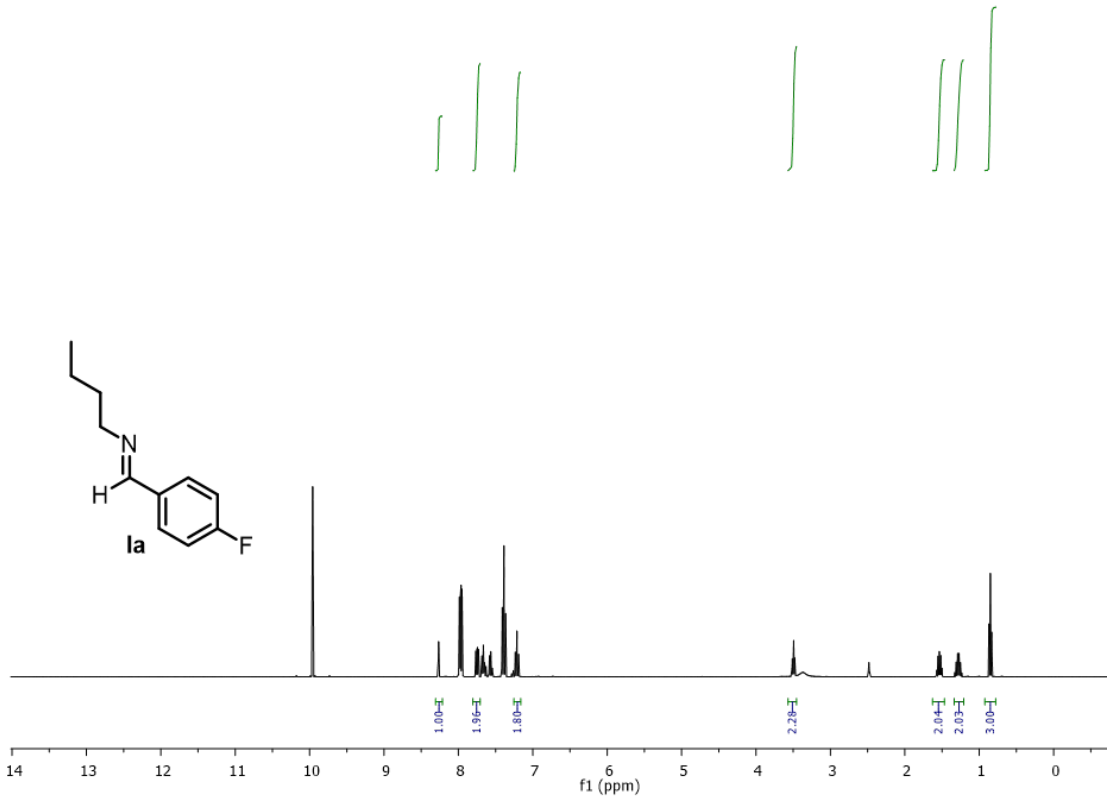


Figure S43. ^{1}H NMR of the in-situ formed imine **Ia** in DMSO-d_6.

^{1}H NMR spectra of the formation of imine **Ib** starting from aniline **14b** and 4-fluorobenzaldehyde are reported in Figure S44-45. The corresponding imine presents the diagnostic proton at around 8.6 ppm.

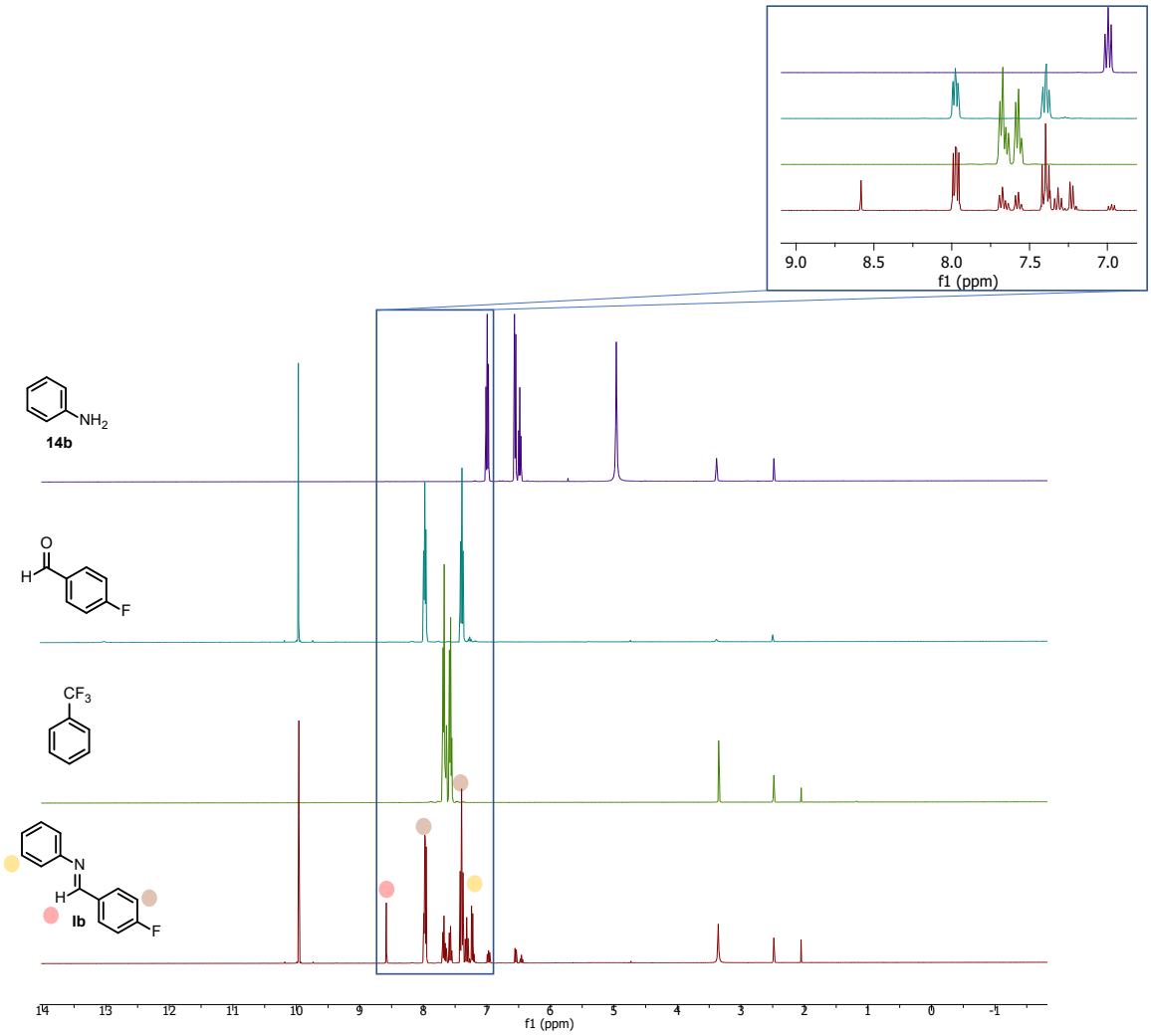


Figure S44. ^{1}H NMR of the in-situ formed imine **Ib** in DMSO-d_6. Comparison between ^{1}H NMR spectra of aniline **14b** (blue), p-fluorobenzaldehyde (light blue), trifluorotoluene as internal standard (green) and N-phenyl-1-(4-fluorophenyl)methanimine **Ib** (red). The ^{1}H NMR expansion between 7.0 and 9.0 ppm shows the signals in the aromatic region.

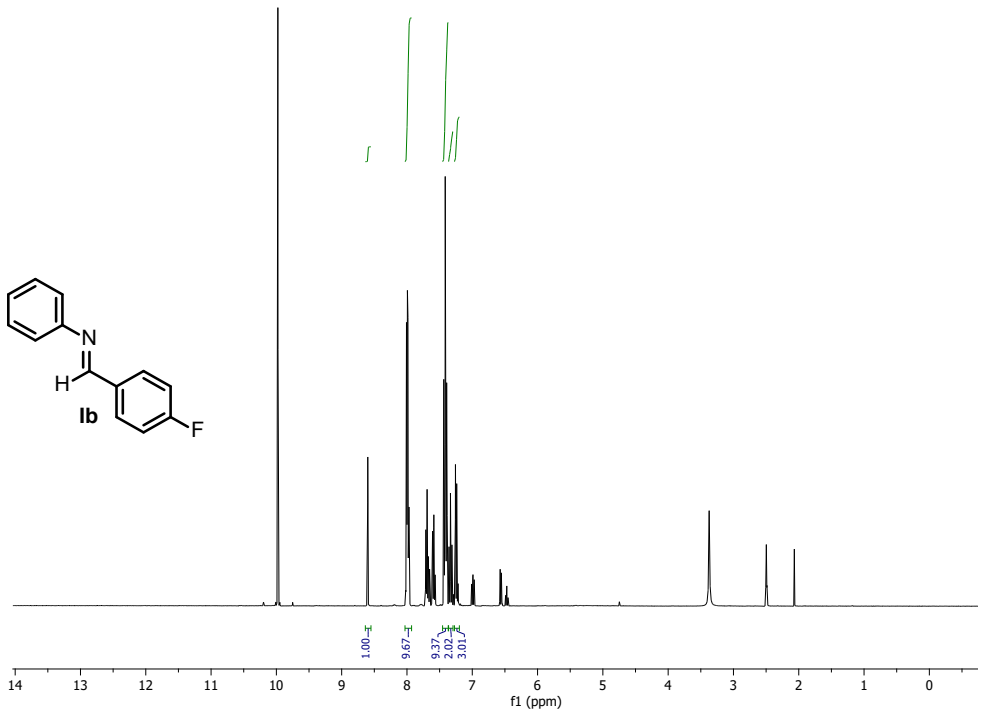


Figure S45. ^{1}H NMR of the in-situ formed imine **Ib** in DMSO-d_6. The signals at 7.4 and 8.0 ppm correspond to the overlapped protons of 4-fluorobenzaldehyde and imine **Ib**.

^{1}H NMR spectra of the formation of imine **Ic** starting from benzylammine **14c** and 4-fluorobenzaldehyde are reported in Figure S46-47. The corresponding imine presents the diagnostic proton at around 8.5 ppm.

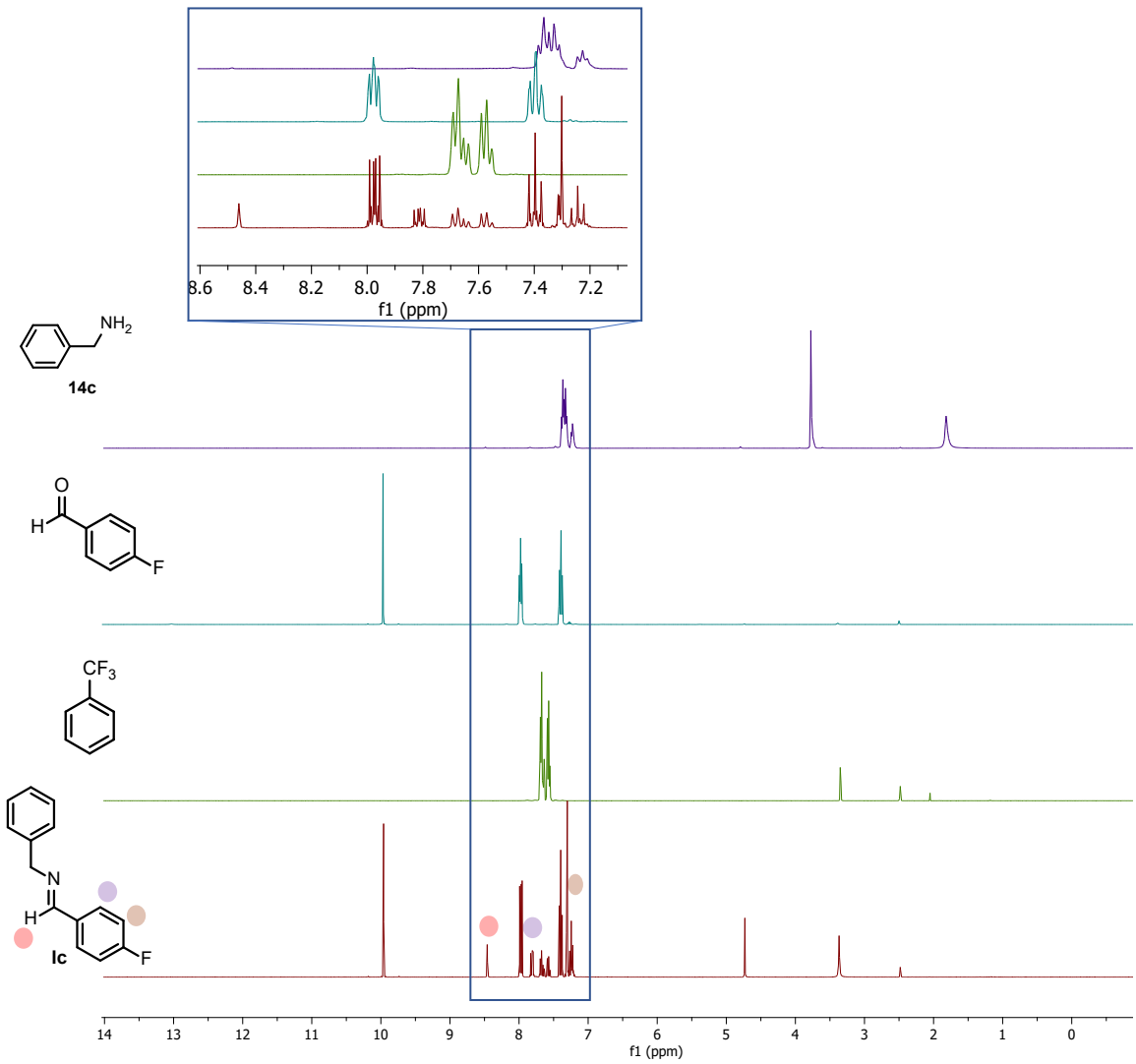


Figure S46. ^{1}H NMR of the in-situ formed imine **Ic** in DMSO-d_6. Comparison between ^{1}H NMR spectra of aniline **14c** (blue), p-fluorobenzaldehyde (light blue), trifluorotoluene as internal standard (green) and N-phenyl-1-(4-fluorophenyl)methanimine **Ic** (red). The ^{1}H NMR expansion between 7.2 and 8.6 ppm shows the signals in the aromatic region.

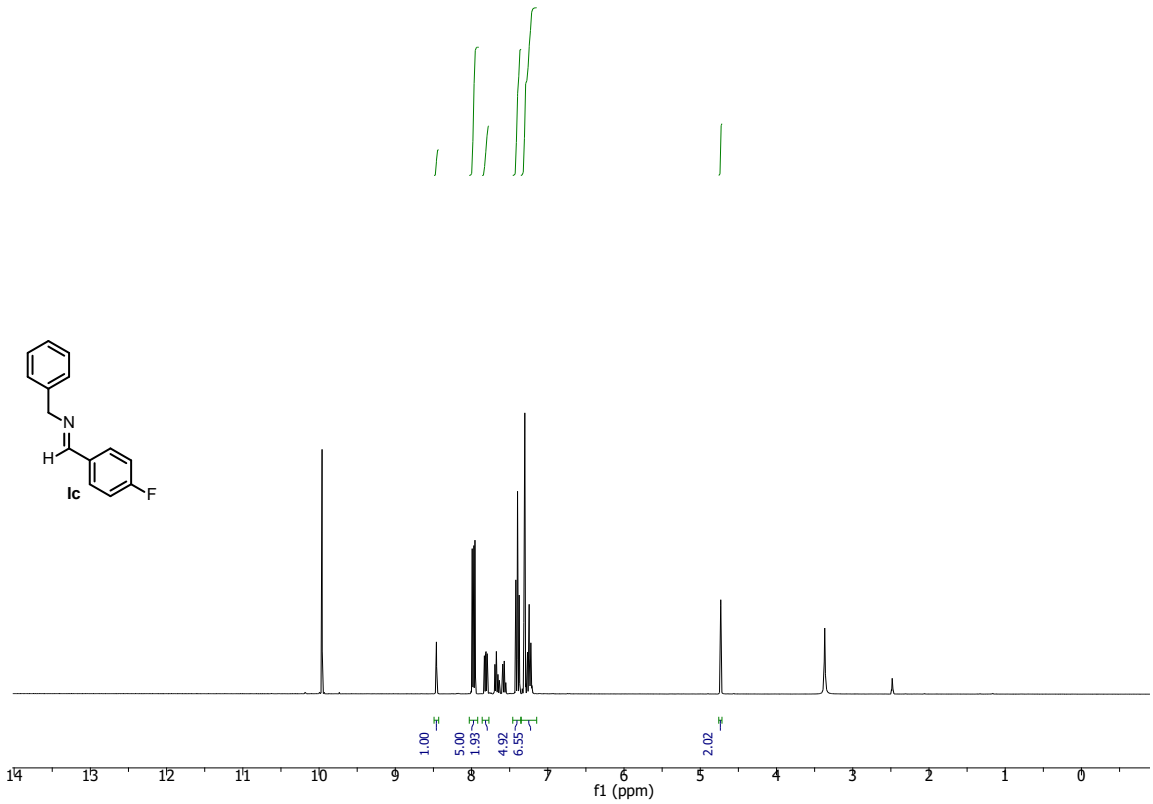


Figure S47. ^{1}H NMR of the in-situ formed imine **Ic** in DMSO-d_6. The signals at 7.4 and 8.0 ppm correspond to the overlapped protons of 4-fluorobenzaldehyde and imine **Ic**.

^{1}H NMR spectra of the formation of imine **I**-(NCDs-**3**) starting from NCDs-**3** and 4-fluorobenzaldehyde are reported in Figure S48-49. The corresponding imine **I**-(NCDs-**3**) presents the diagnostic broad signal at around 8.3 ppm.

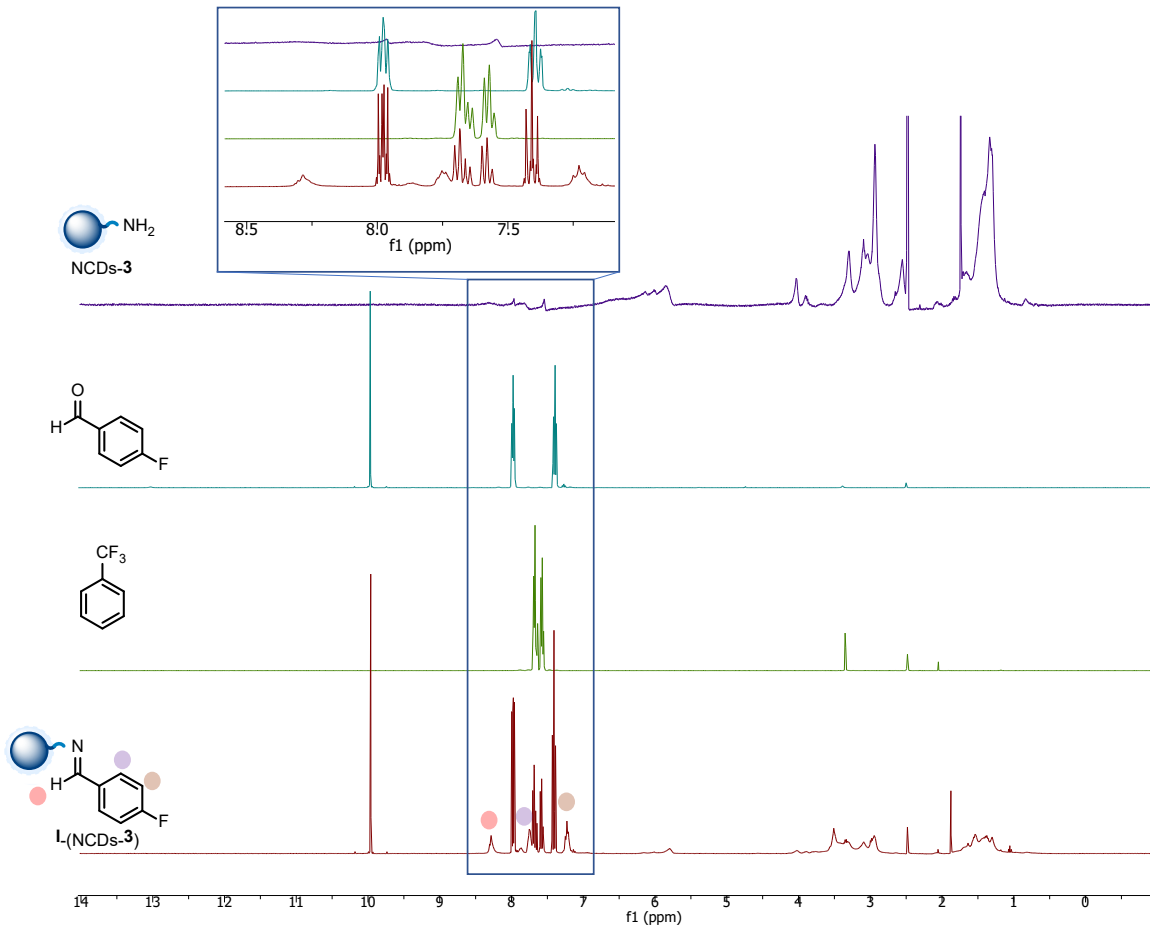


Figure S48. ^{1}H NMR of the in-situ formed imine **I**-(NCDs-**3**) in DMSO-d_6. Comparison between ^{1}H NMR spectra of aniline NCDs-**3** (blue), p-fluorobenzaldehyde (light blue), trifluorotoluene as internal standard (green) and **I**-(NCDs-**3**) (red). The ^{1}H NMR expansion between 7.0 and 8.5 ppm shows the signals in the aromatic region.

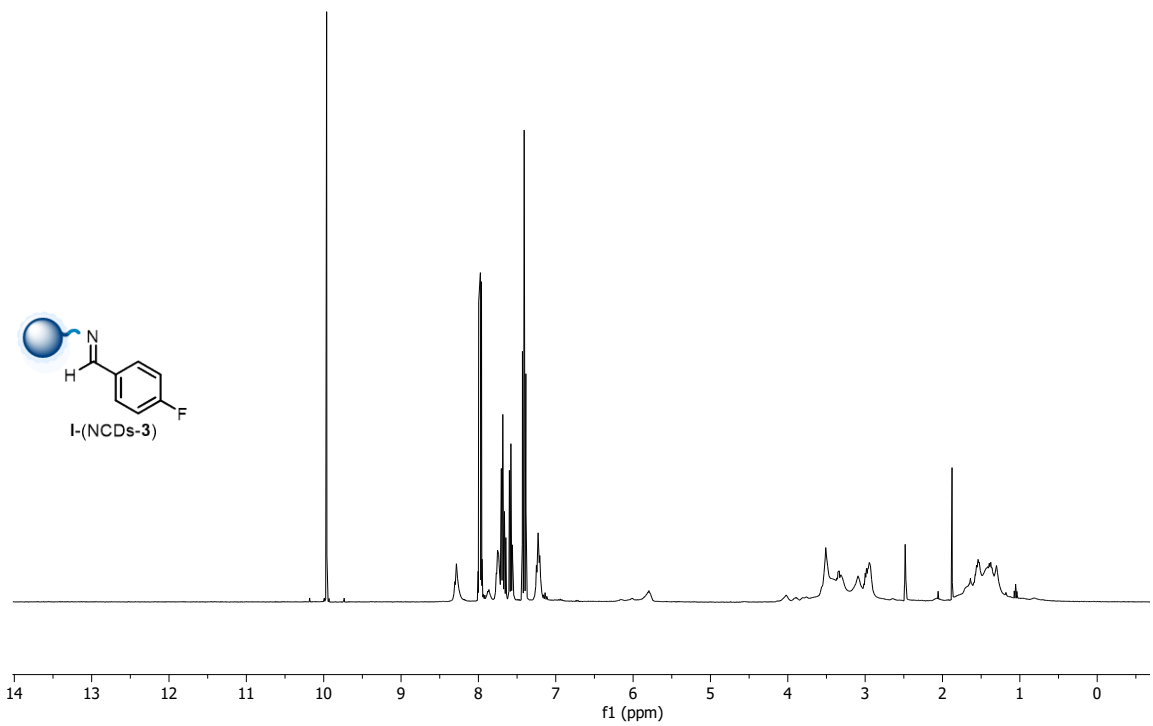


Figure S49. ^{1}H NMR of the in-situ formed imine **I**-(NCDs-**3**) in DMSO-d_6.

^{1}H NMR spectra of the formation of enamine **IId** starting from 14d and 4-phenylacetaldehyde are reported in Figure S50-51. The corresponding imine **IId** presents the diagnostic broad signal at around 5.0 ppm.

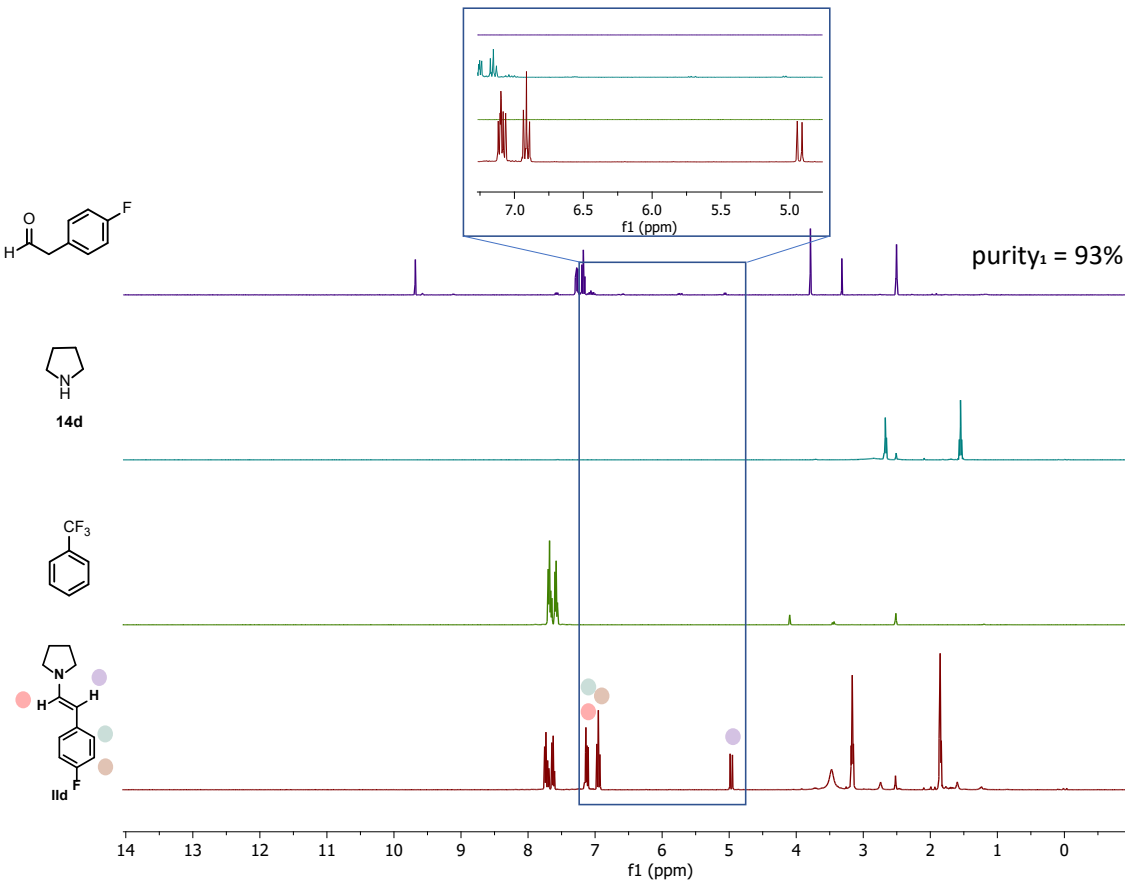


Figure S50. ^{1}H NMR of the in-situ formed enamine **IId** in DMSO-d_6. Comparison between ^{1}H NMR spectra of 4-fluorophenylacetaldehyde (blue), pyrrolidine (light blue), trifluorotoluene as internal standard (green) and **IId** (red). The ^{1}H NMR expansion between 4.9 and 7.3 ppm shows the signals in the aromatic region.

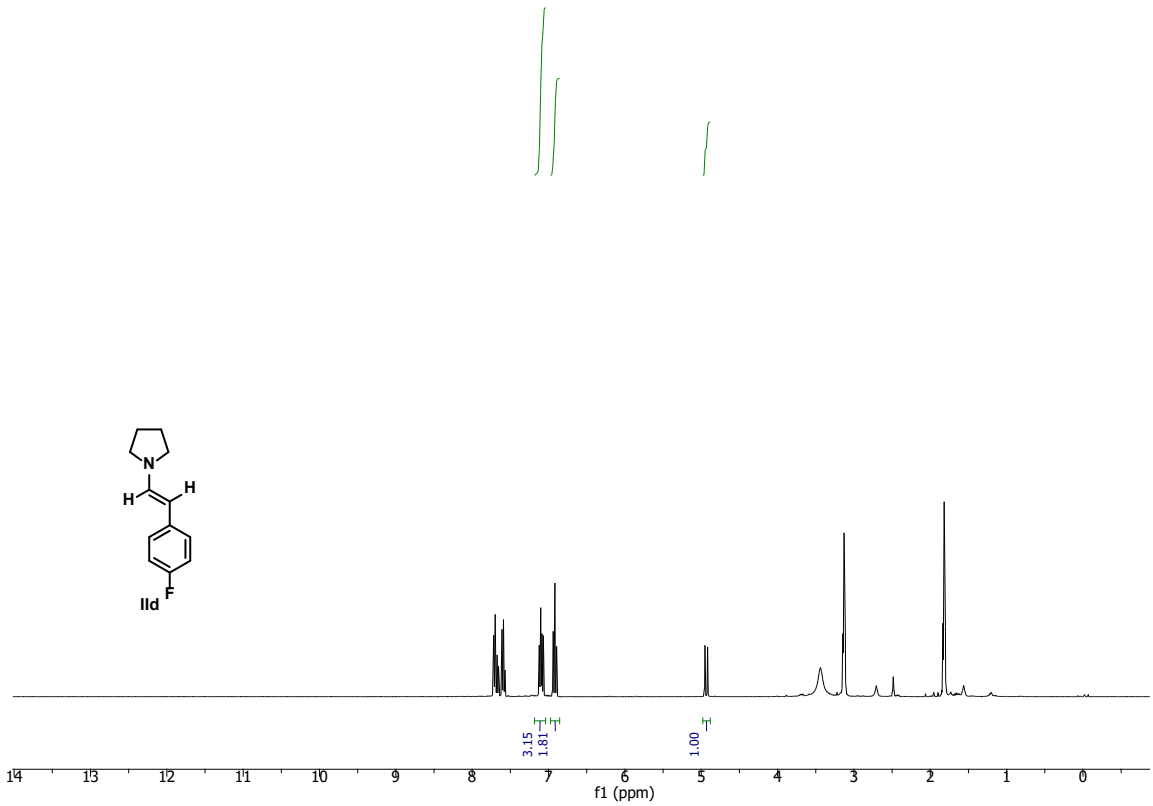


Figure S51. ^{1}H NMR of the in-situ formed enamine **IId** in DMSO-d_6. The signal at 7.1 ppm shows the protons of enamine **IId** overlapped with the corresponding aromatic signals.

^{1}H NMR spectra of the formation of enamine **IIc** starting from 14c and 4-phenylacetaldehyde are reported in Figure S50-51. The corresponding imine **IIc** presents the diagnostic broad signal at around 5.2 ppm.

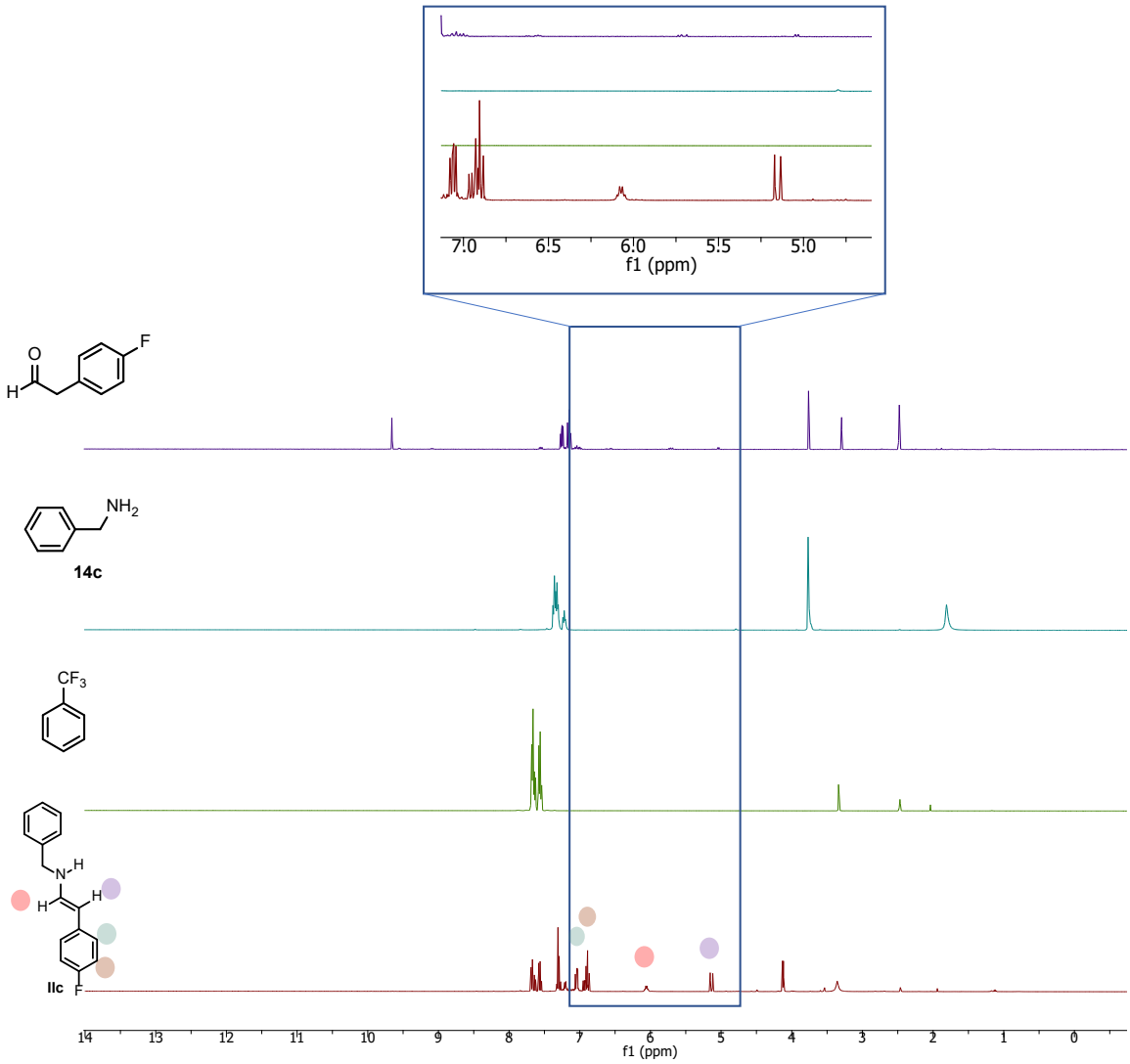


Figure S52. ^{1}H NMR of the in-situ formed enamine **IIc** in DMSO-d_6. Comparison between ^{1}H NMR spectra of 4-fluorophenylacetaldehyde (blue), pyrrolidine (light blue), trifluorotoluene as internal standard (green) and **IIc** (red). The ^{1}H NMR expansion between 4.5 and 7.5 ppm shows the signals in the aromatic region.

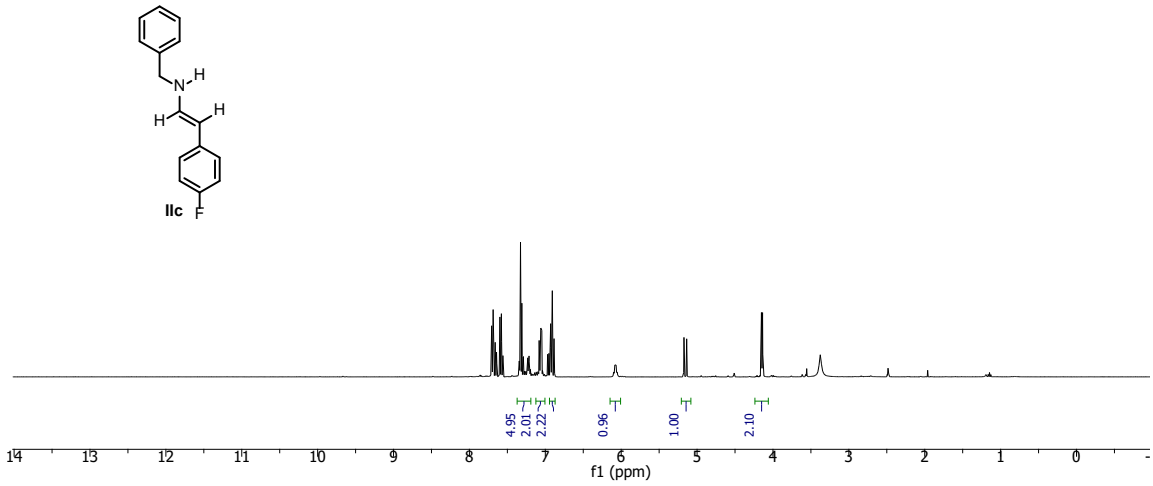


Figure S53. ^{1}H NMR of the in-situ formed enamine **IIc** in DMSO-d_6. The signal at 7.1 ppm shows the protons of enamine **IIc** overlapped with the corresponding aromatic signals.

^{1}H NMR spectra of the formation of enamine **II-(NCDs-3)** starting from NCDS-**3** and 4-phenylacetaldehyde are reported in Figure S54-55. The corresponding imine **II-(NCDs-3)** presents the diagnostic broad signal at around 5.5 ppm.

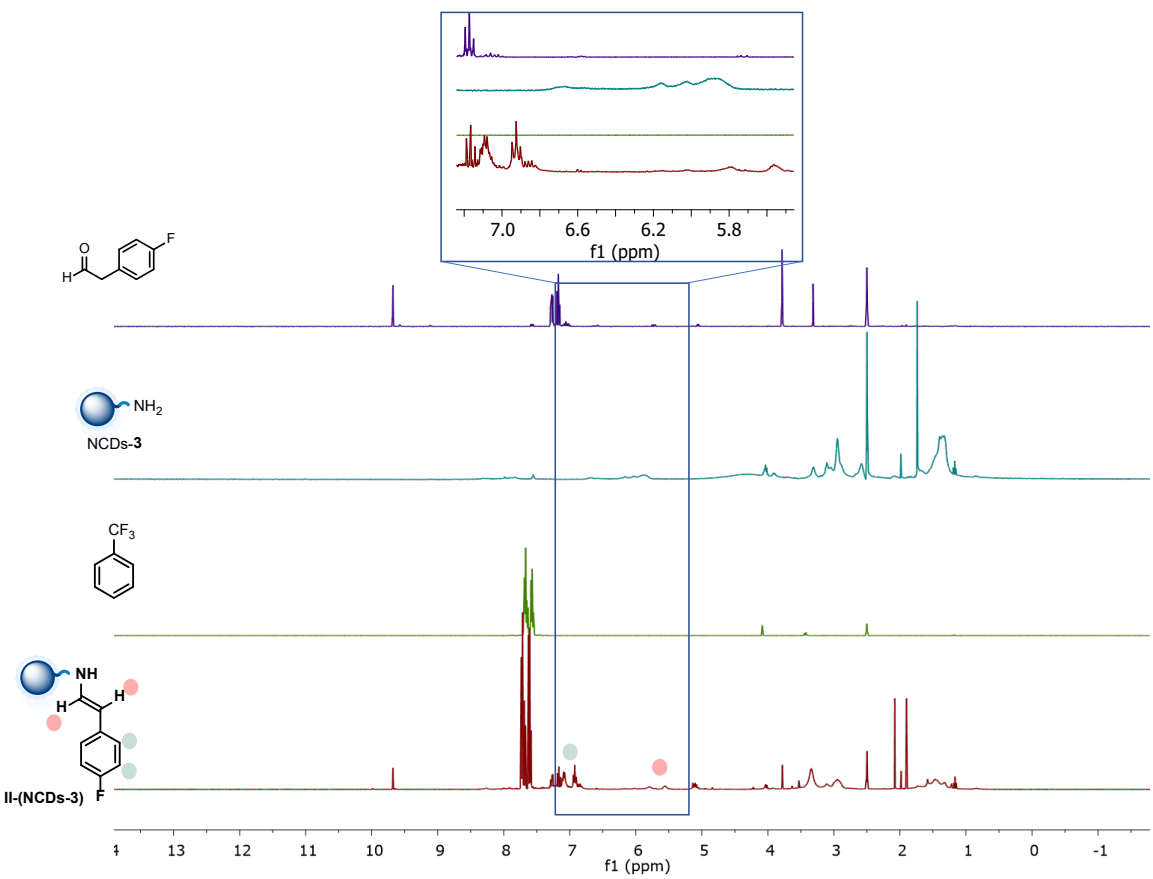


Figure S54. ^{1}H NMR of the in-situ formed enamine **II-(NCDs-3)** in DMSO-d_6. Comparison between ^{1}H NMR spectra of 4-fluorophenylacetaldehyde (blue), pyrrolidine (light blue), trifluorotoluene as internal standard (green) and **II-(NCDs-3)** (red). The ^{1}H NMR expansion between 5.5 and 7.3 ppm shows the signals in the aromatic region.

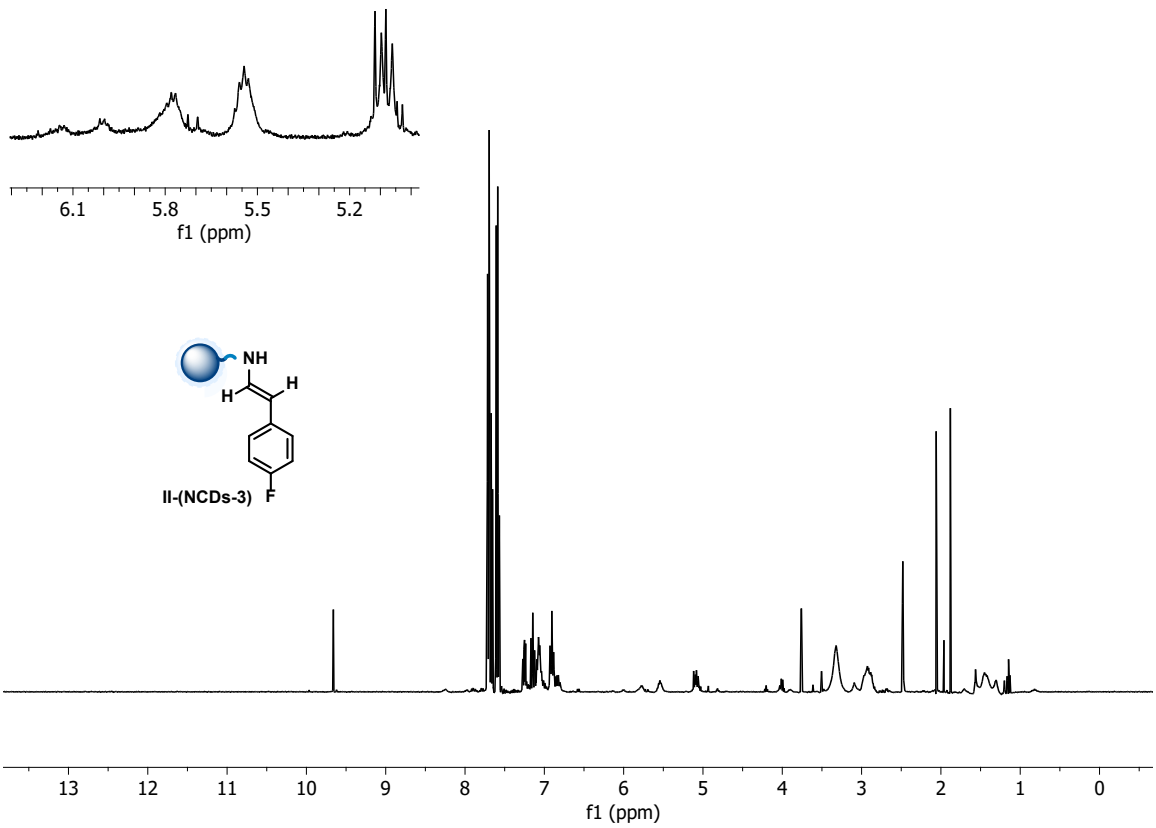
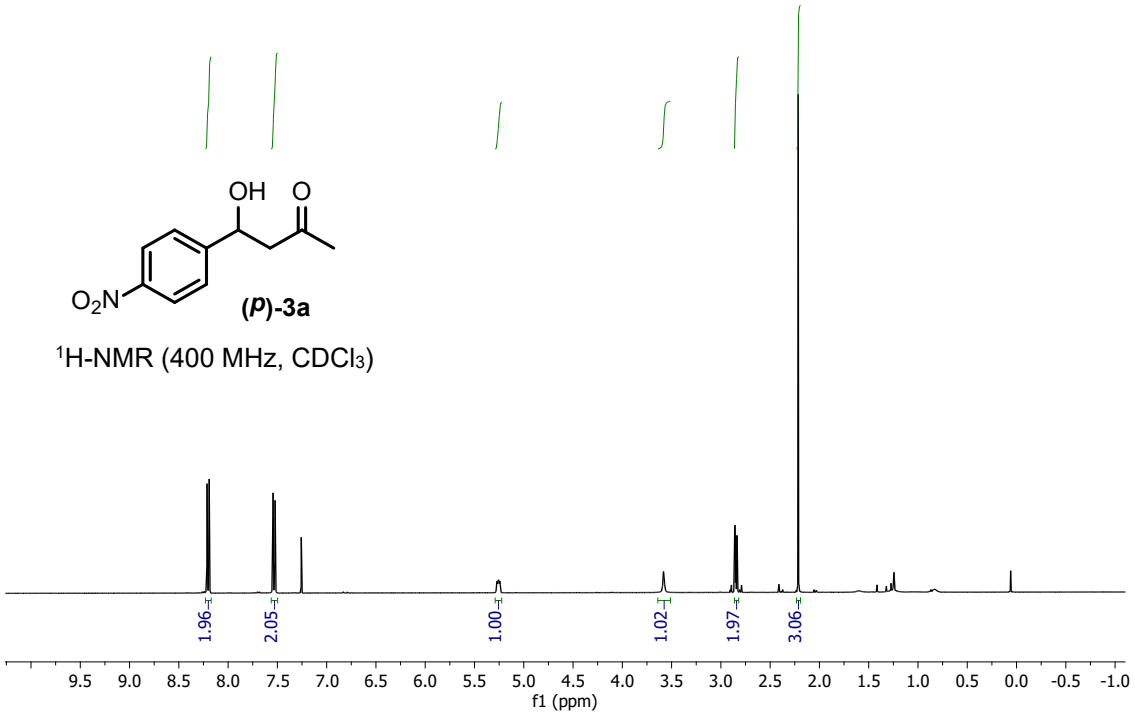
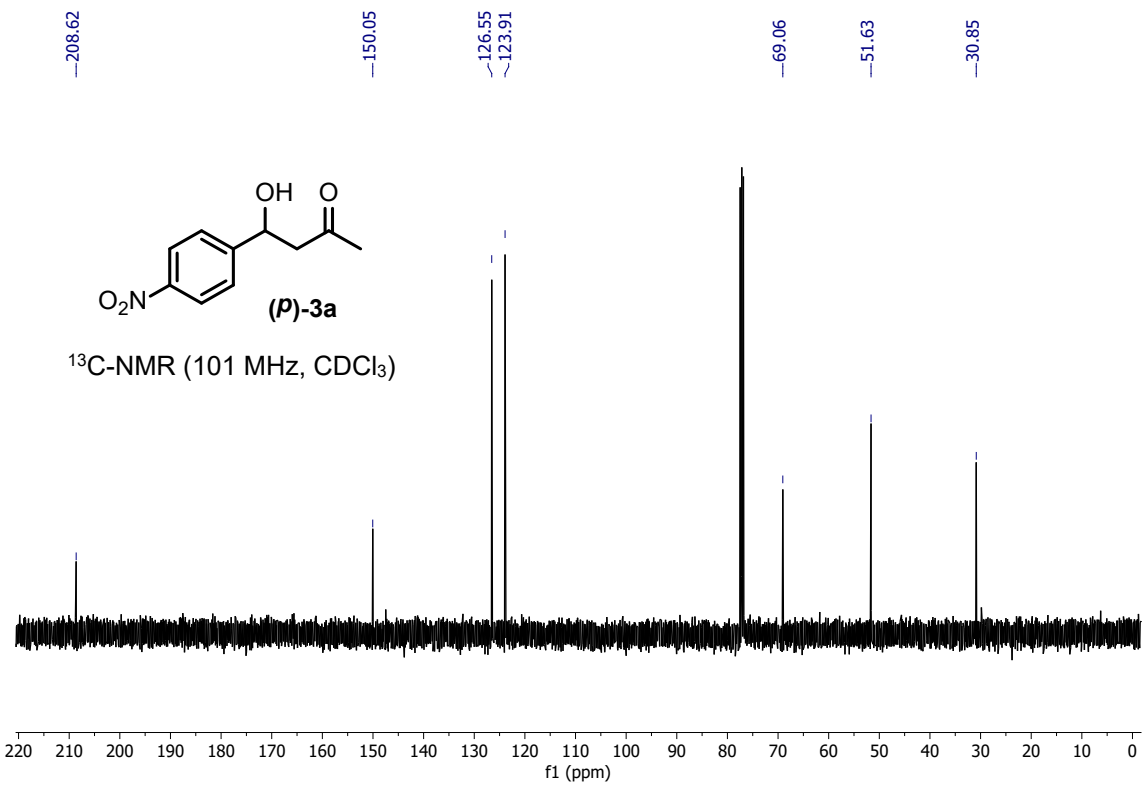
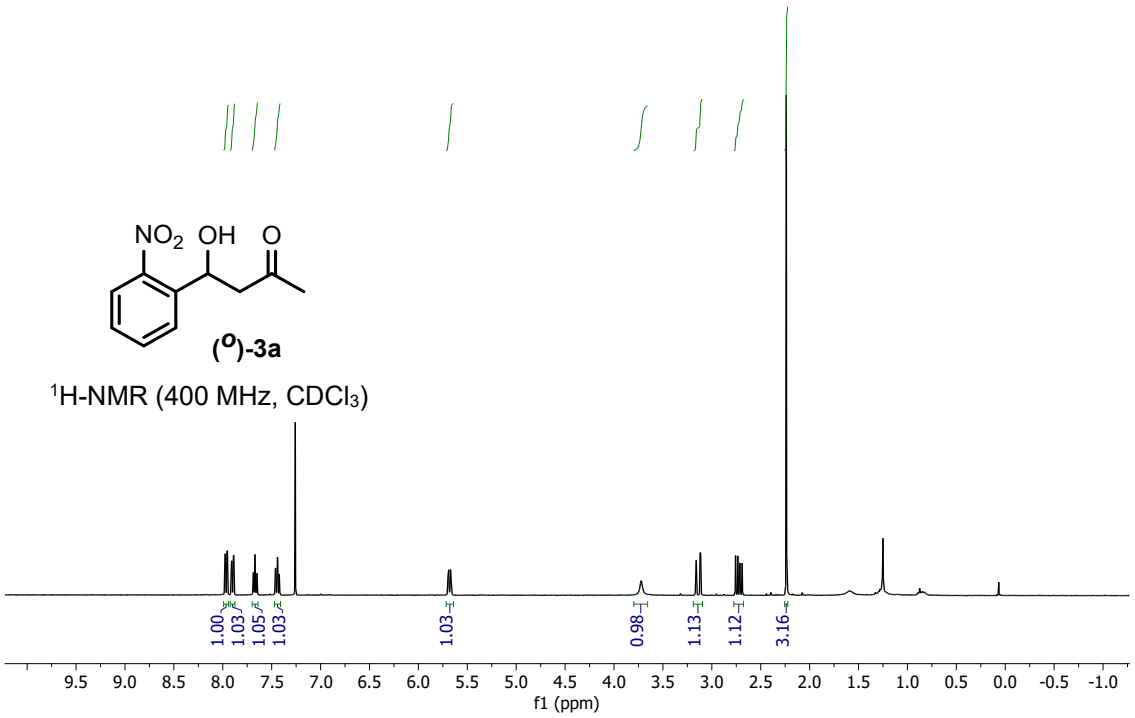


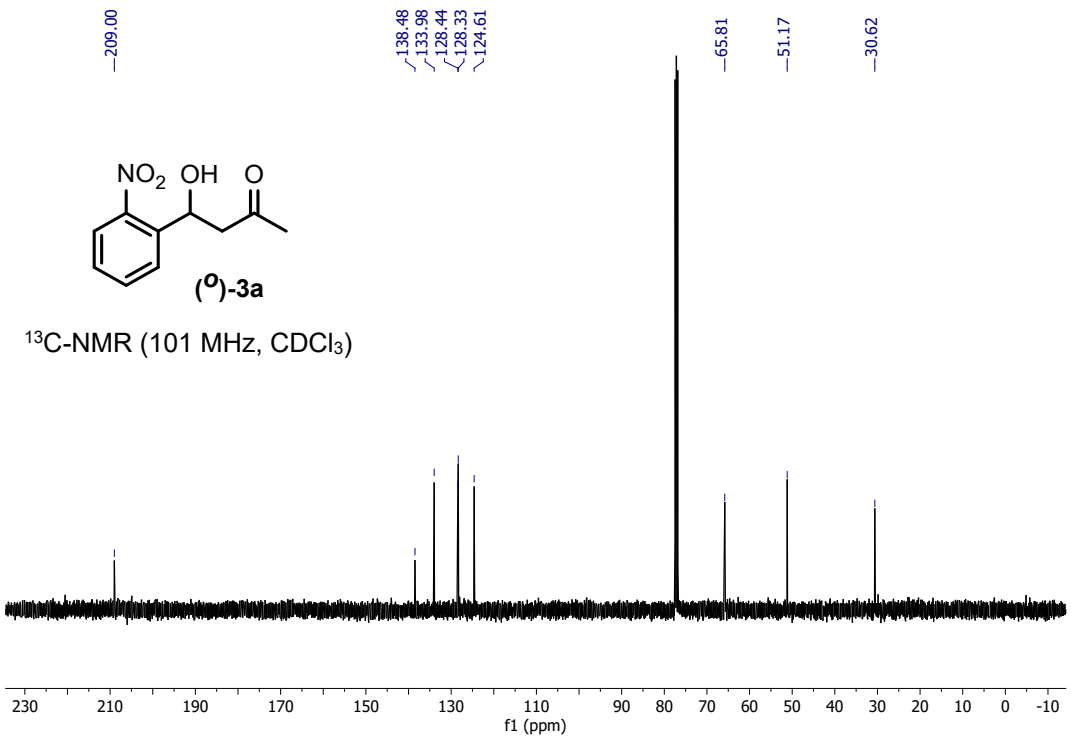
Figure S55. ^{1}H NMR of the in-situ formed enamine **II-(NCDs-3)** in DMSO-d_6.

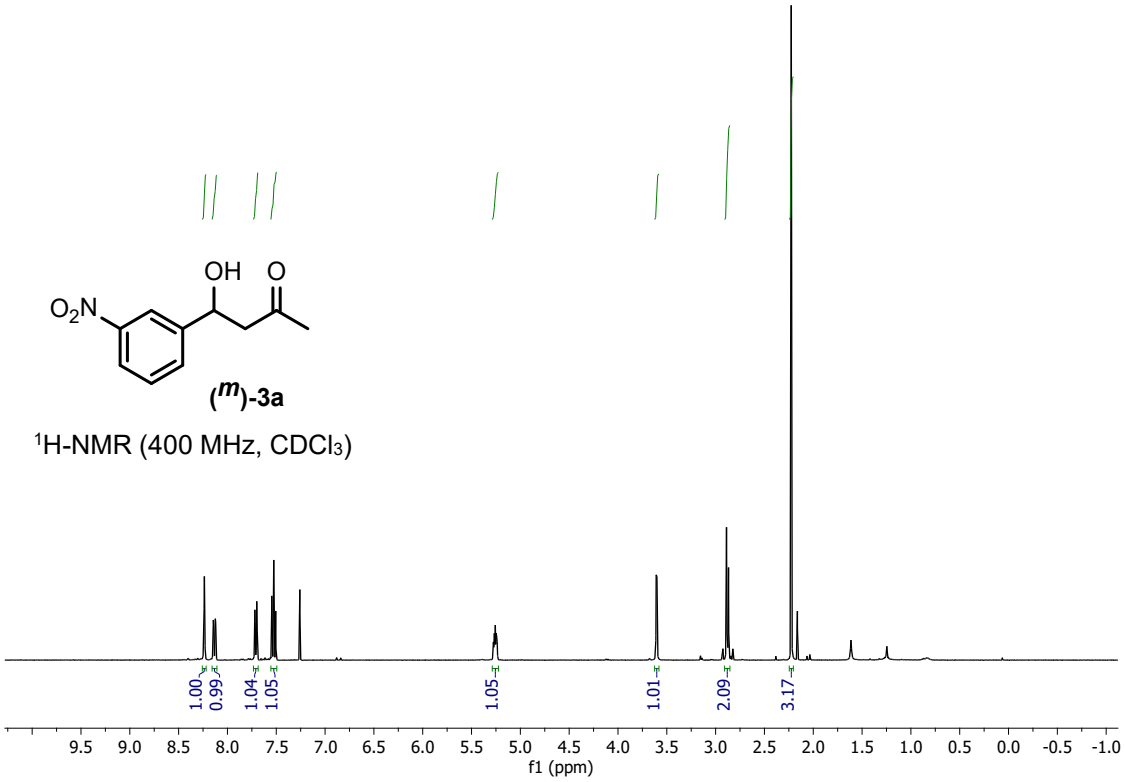
G.3. NMR SPECTRA

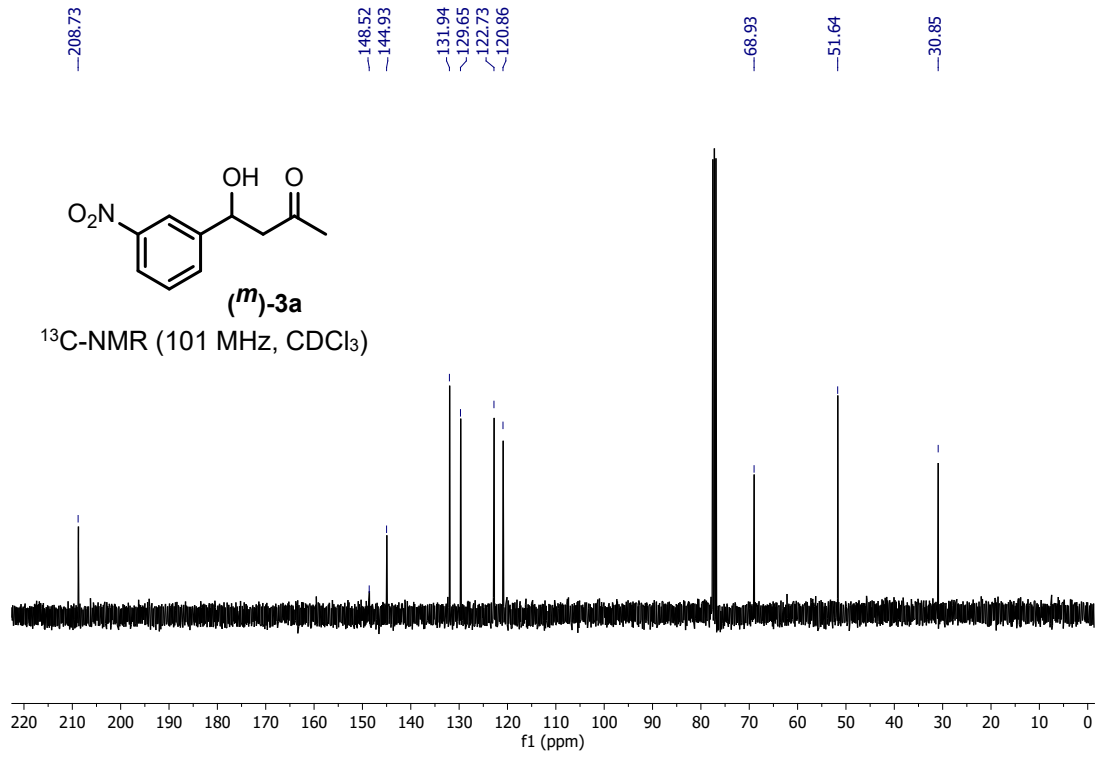


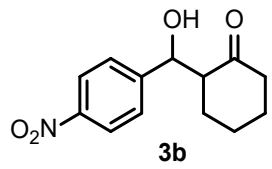



NO2 OH O
(O)-3a
1H-NMR (400 MHz, CDCl3)
1.00
1.03
1.05
1.03
1.03
0.98
1.13
1.12
3.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


209.00
138.48
133.98
128.44
128.33
124.61
65.81
51.17
30.62
NO2 OH O
(O)-3a
13C-NMR (101 MHz, CDCl3)
230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

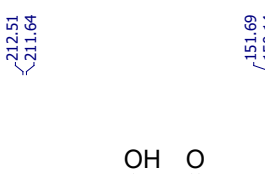

OH
O
O_2N
(*m*)-3a
^{1}H-NMR (400 MHz, $CDCl_3$)
1.00
0.99
1.04
1.05
1.05
1.01
2.09
3.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


208.73
148.52
144.93
131.94
129.65
122.73
120.86
68.93
51.64
30.85
OH
O
O_2N
(*m*)-3a
^{13}C-NMR (101 MHz, $CDCl_3$)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



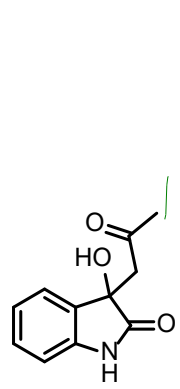
3b

^{1}H-NMR (400 MHz, CD_3OD)



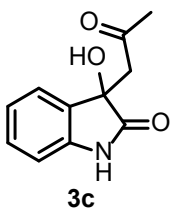
3b

^{13}C-NMR (101 MHz, CD_3OD)



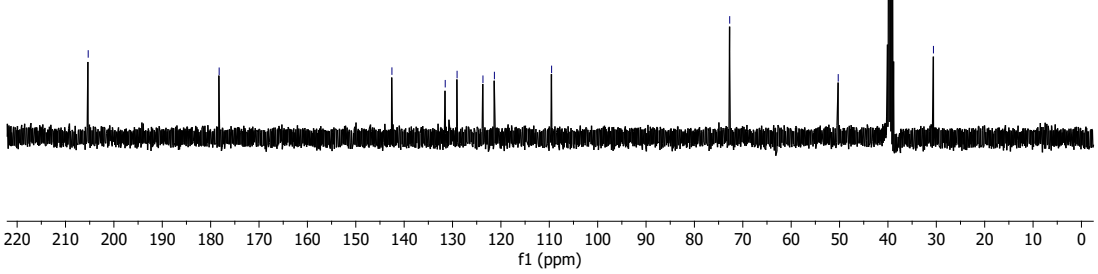
3c

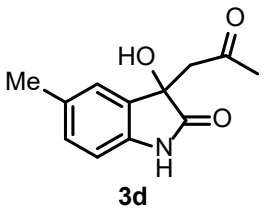
^{1}H-NMR (400 MHz, DMSO-d_6)



3c

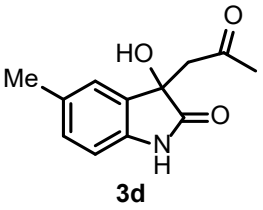
^{13}C-NMR (101 MHz, DMSO-d_6)





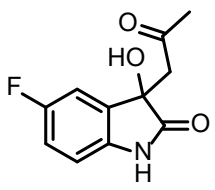
3d

^{1}H-NMR (400 MHz, CD_3OD)



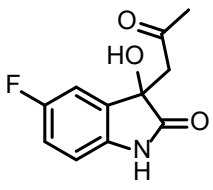
3d

^{13}C-NMR (101 MHz, CD_3OD)



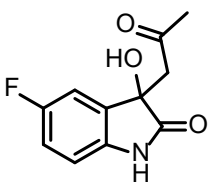
3e

^{1}H-NMR (400 MHz, CD_3OD)



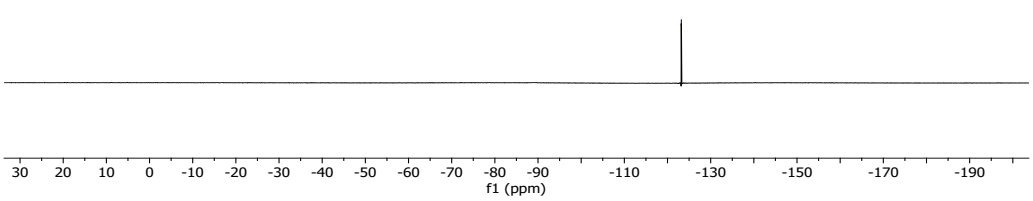
3e

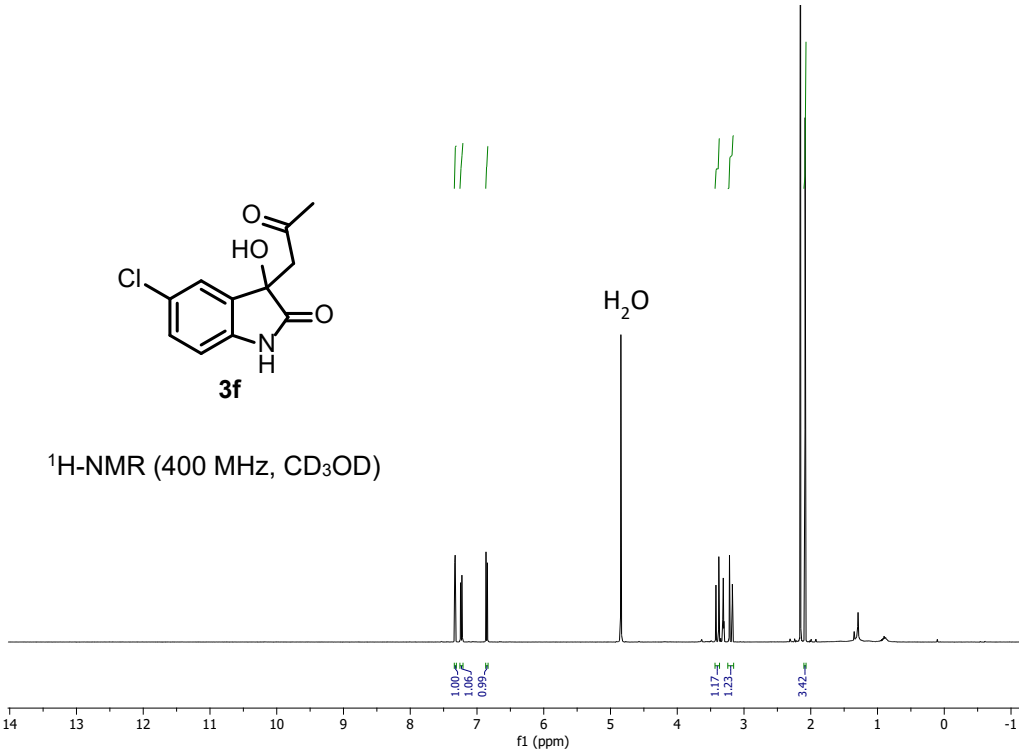
^{13}C-NMR (101 MHz, CD_3OD)



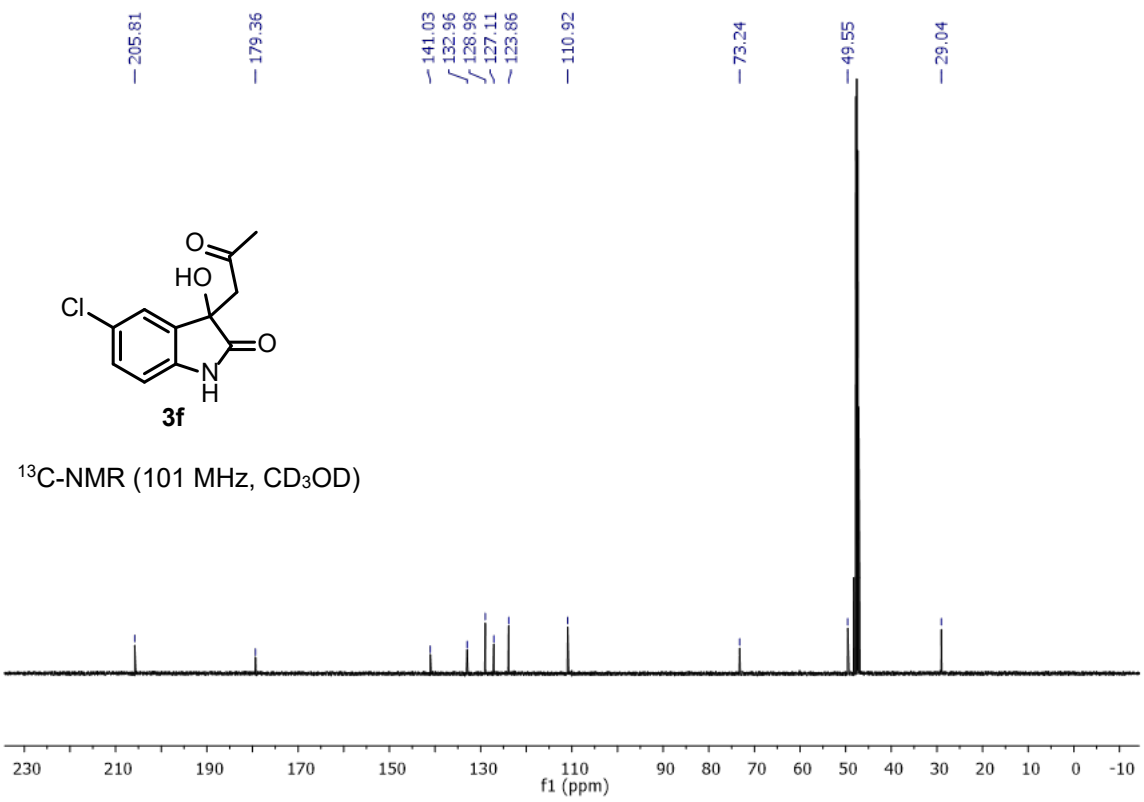
3e

^{19}F-NMR (376 MHz, CD_3OD)

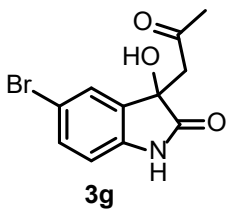




^{1}H-NMR (400 MHz, CD_3OD)

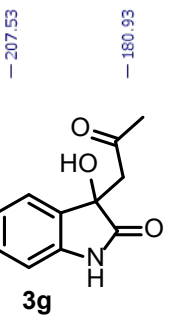


^{13}C-NMR (101 MHz, CD_3OD)



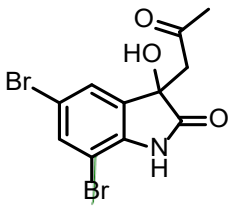
3g

^{1}H-NMR (400 MHz, CD_3OD)



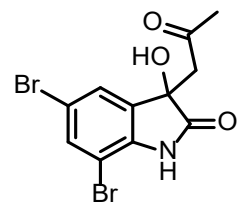
3g

^{13}C-NMR (101 MHz, CD_3OD)



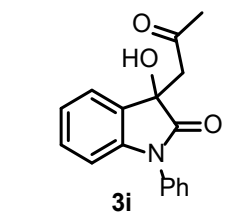
3h

^{1}H-NMR (400 MHz, DMSO-*d*$_6$)



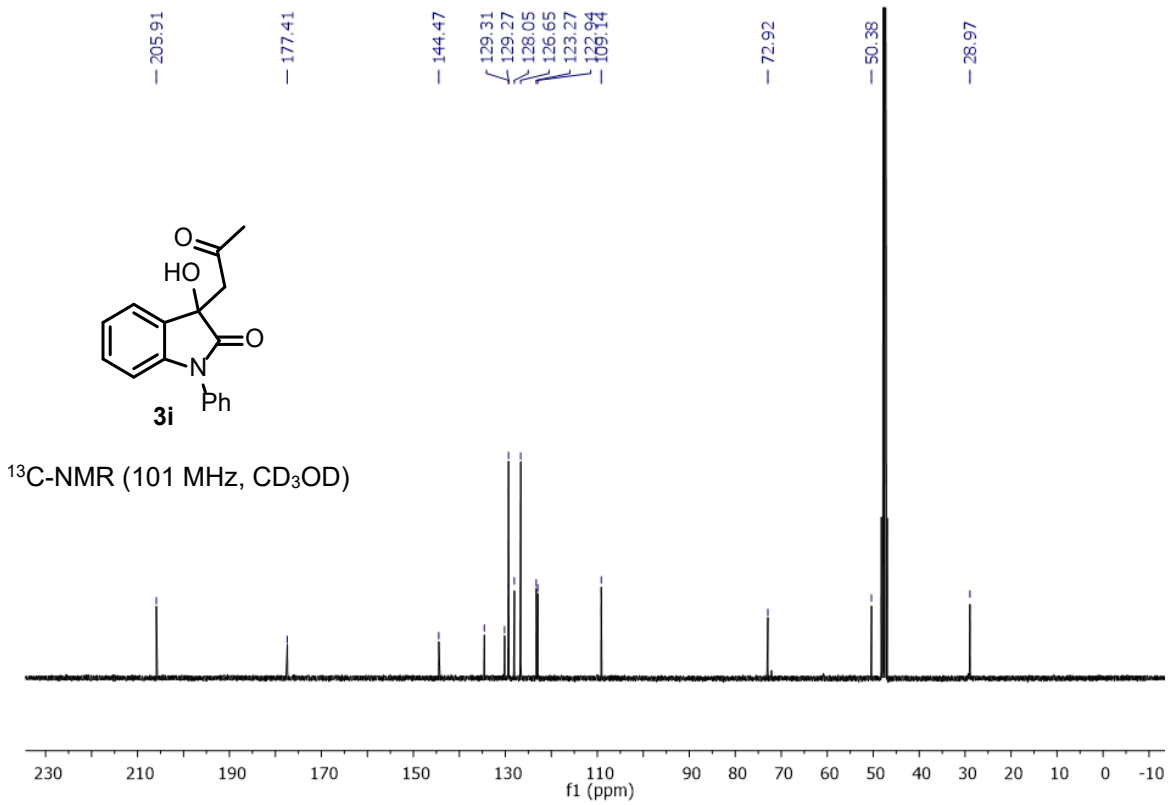
3h

^{13}C-NMR (101 MHz, DMSO-*d*$_6$)



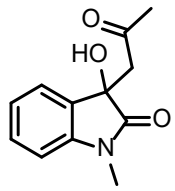
3i

^{1}H-NMR (400 MHz, CD_3OD)



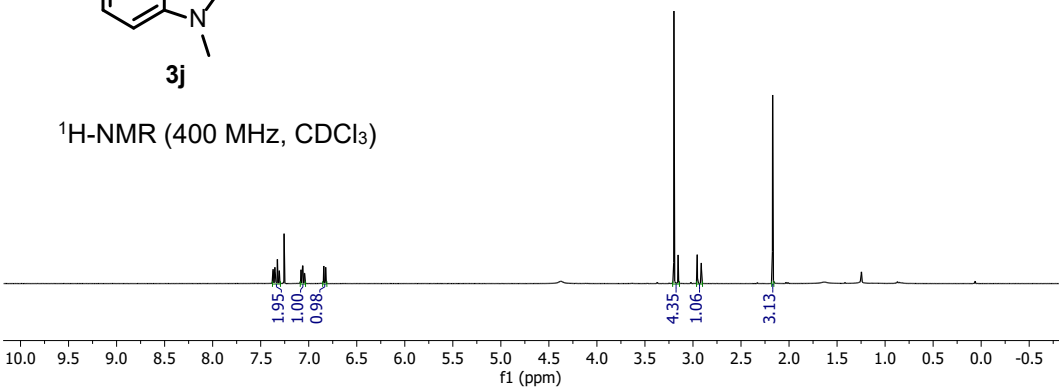
3i

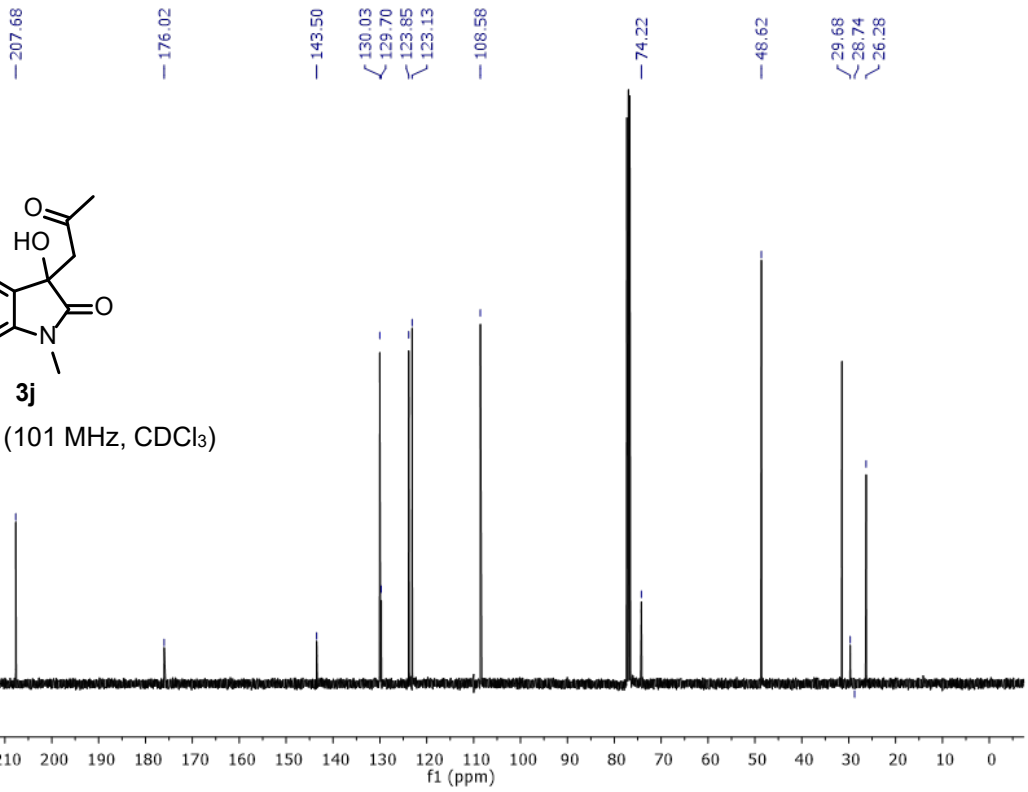
^{13}C-NMR (101 MHz, CD_3OD)



3j

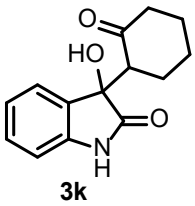
^{1}H-NMR (400 MHz, $CDCl_3$)





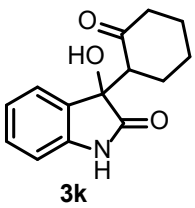
3j

^{13}C-NMR (101 MHz, $CDCl_3$)



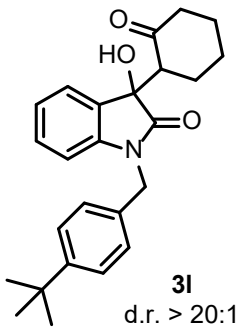
3k

^{1}H-NMR (400 MHz, CD_3CN)



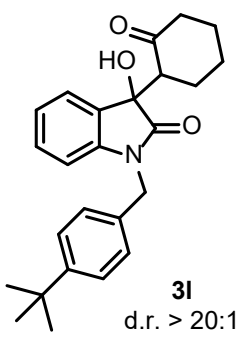
3k

^{13}C-NMR (101 MHz, CD_3CN)



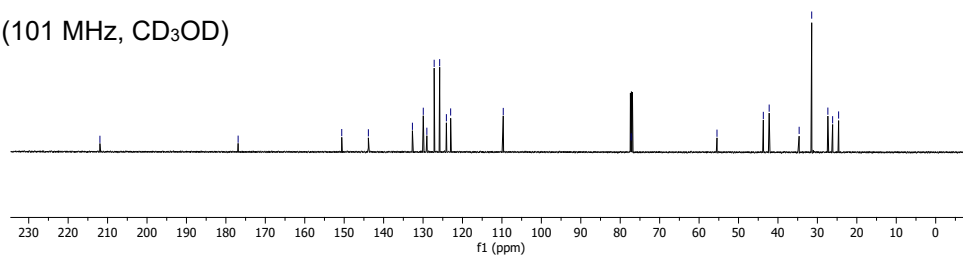
3l
d.r. > 20:1

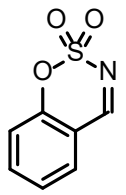
^{1}H-NMR (400 MHz, CD_3OD)



3l
d.r. > 20:1

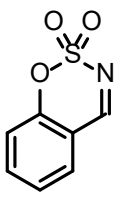
^{13}C-NMR (101 MHz, CD_3OD)





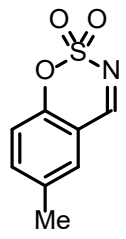
4a

^{1}H-NMR (400 MHz, $CDCl_3$)



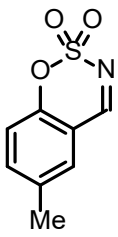
4a

^{13}C-NMR (101 MHz, $CDCl_3$)



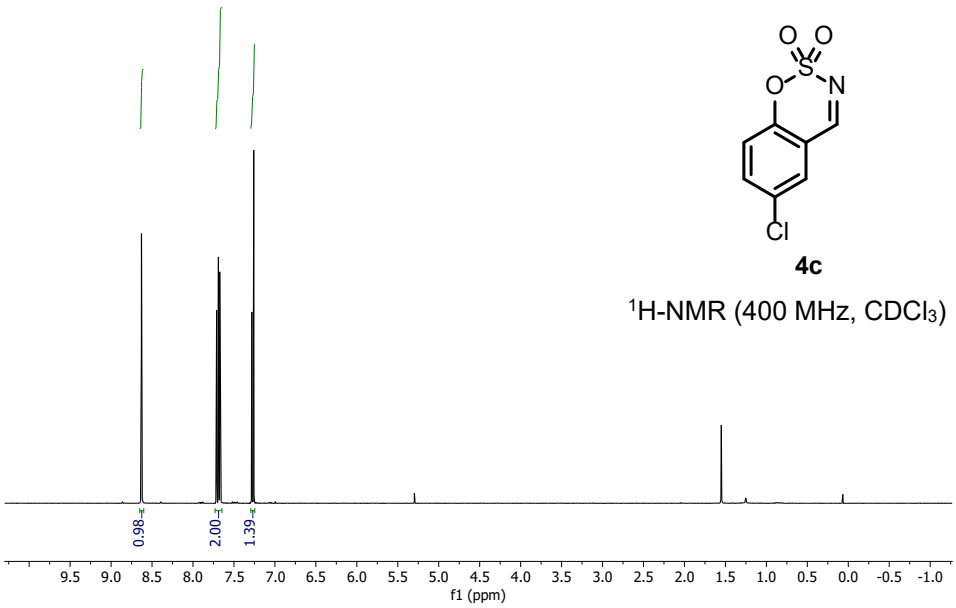
4b

^{1}H-NMR (400 MHz, $CDCl_3$)



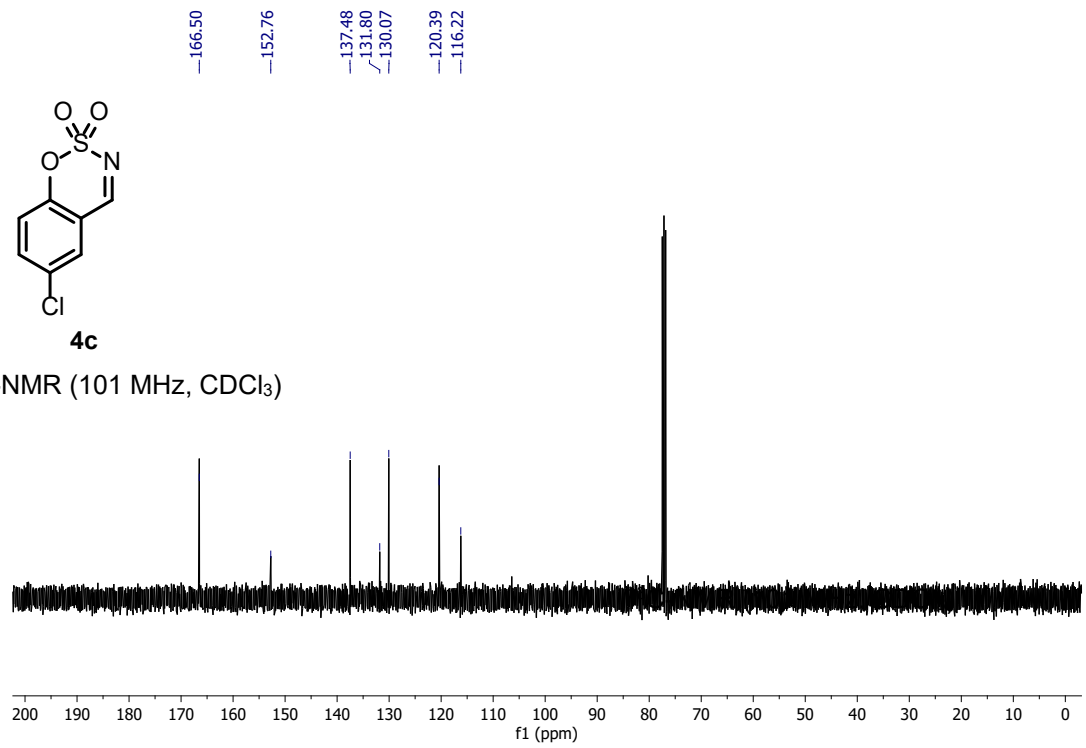
4b

^{13}C-NMR (101 MHz, $CDCl_3$)



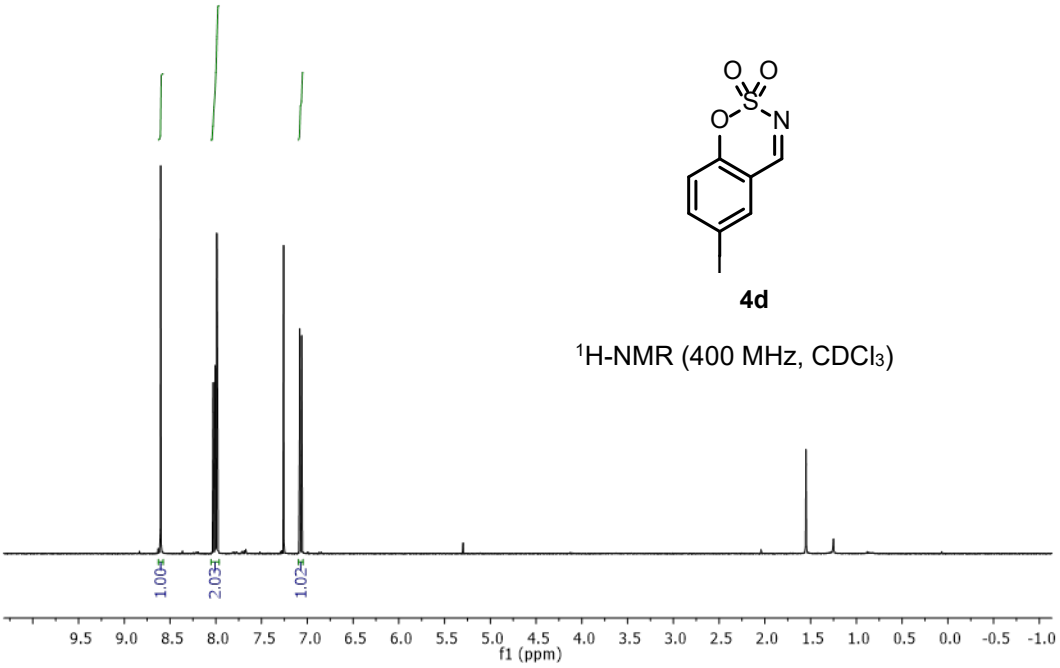
4c

^{1}H-NMR (400 MHz, $CDCl_3$)



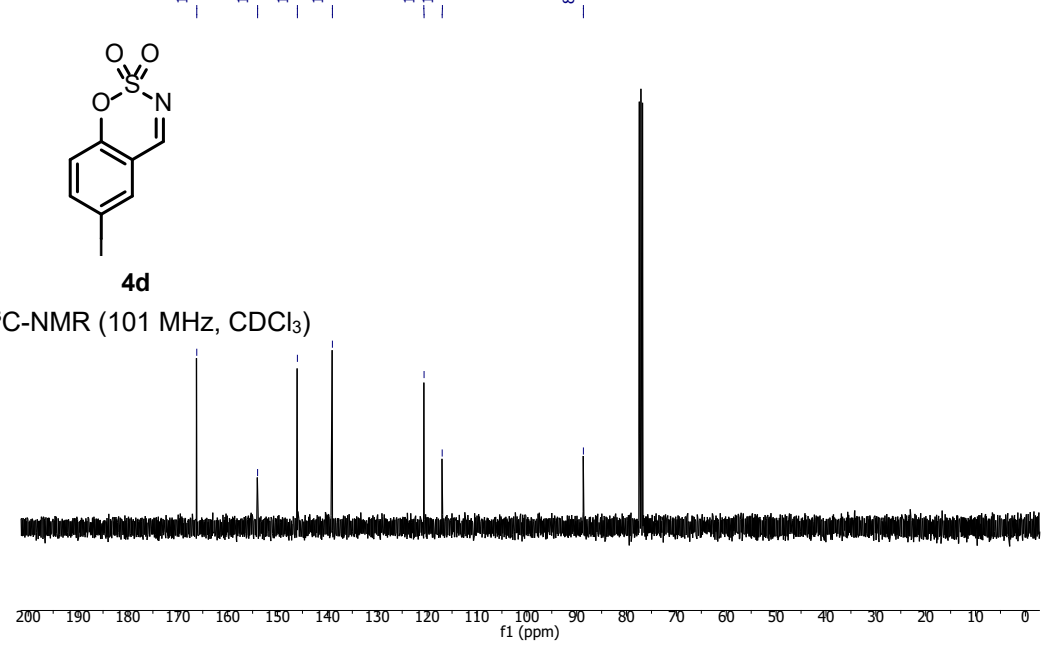
4c

^{13}C-NMR (101 MHz, $CDCl_3$)



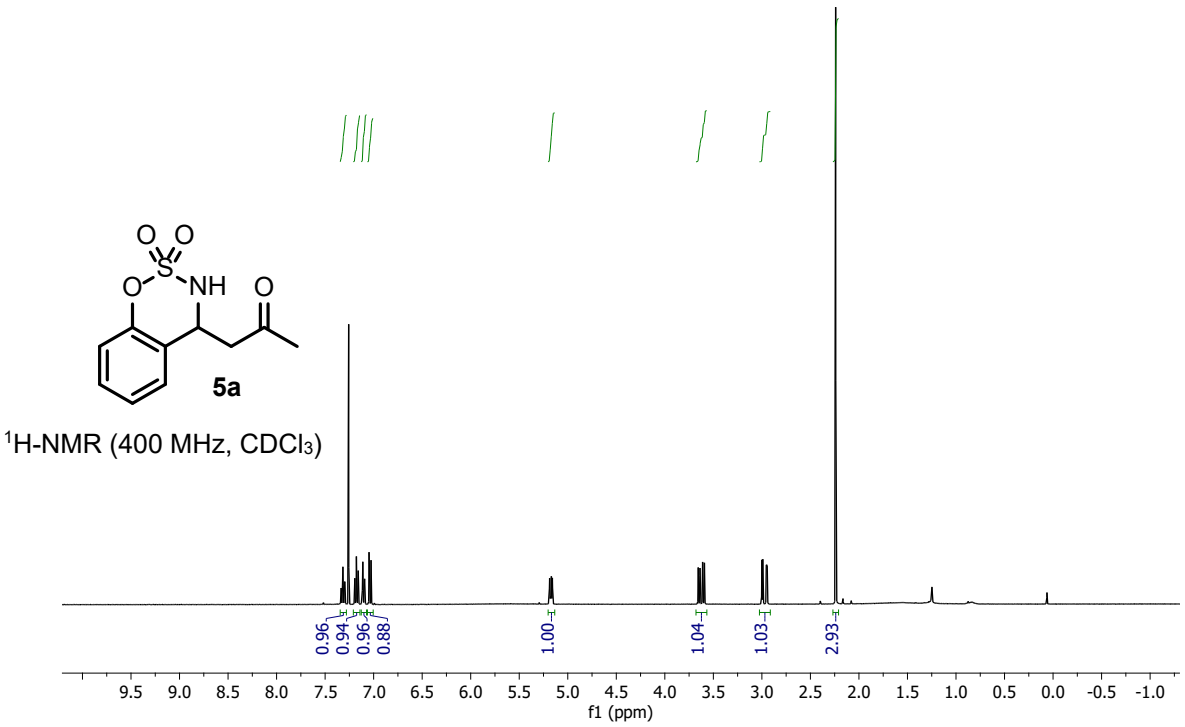
4d

^{1}H-NMR (400 MHz, $CDCl_3$)

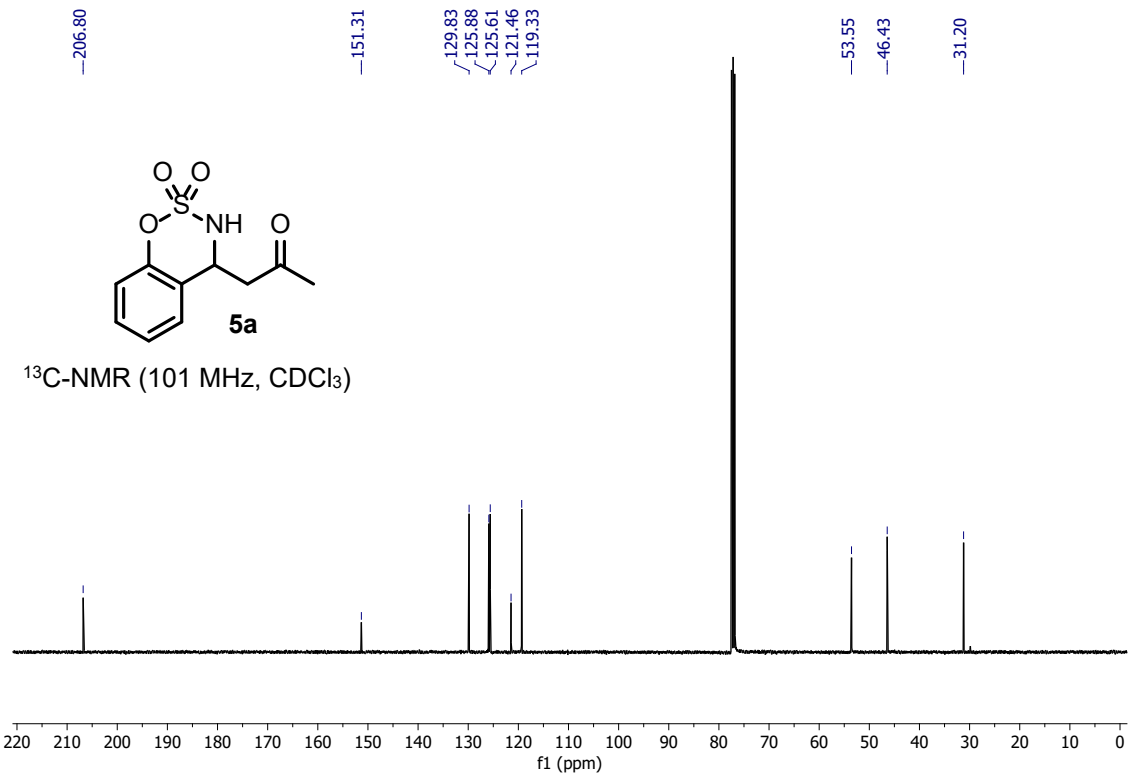


4d

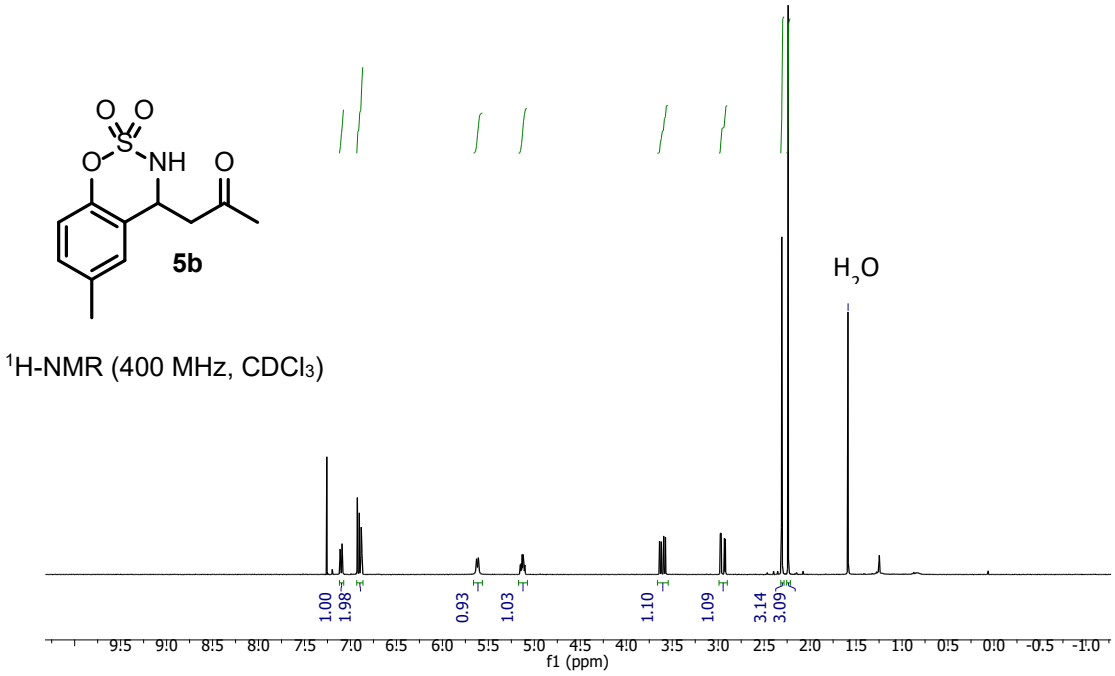
^{13}C-NMR (101 MHz, $CDCl_3$)



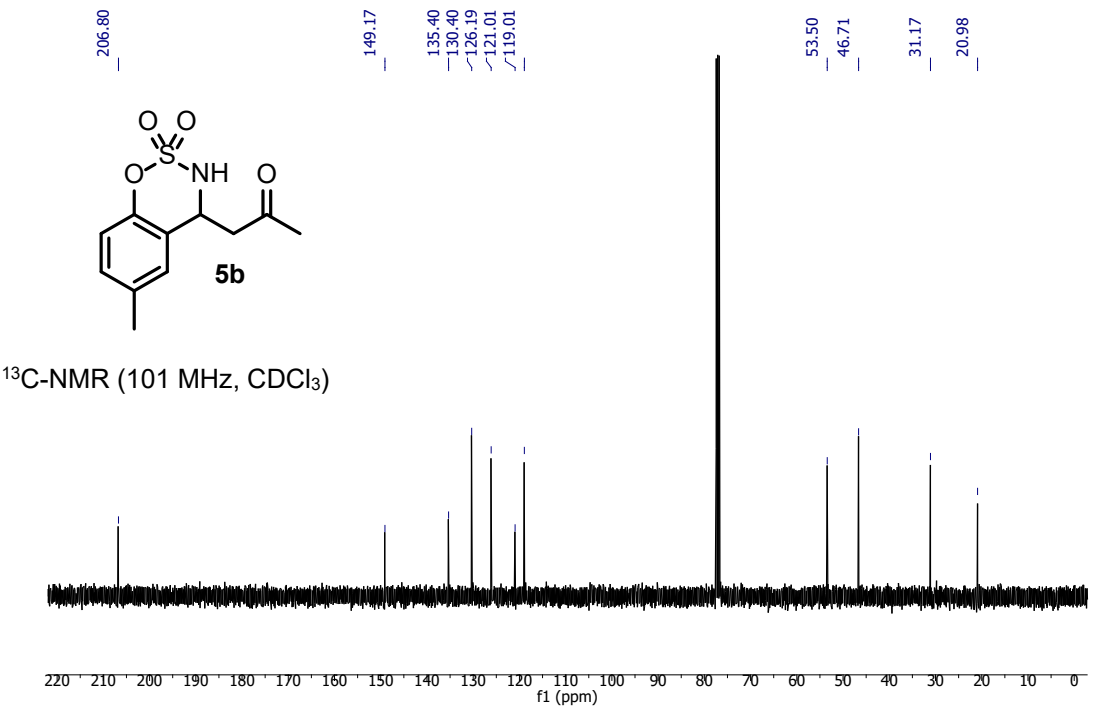
^{1}H-NMR (400 MHz, $CDCl_3$)



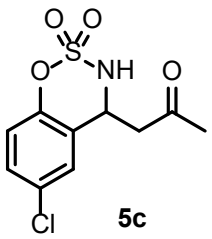
^{13}C-NMR (101 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$)

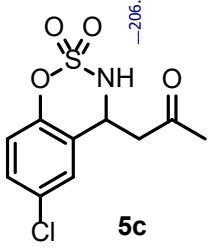


^{13}C-NMR (101 MHz, $CDCl_3$)



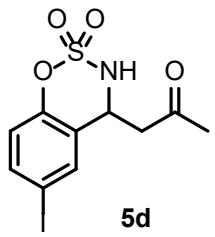
5c

^{1}H-NMR (400 MHz, $CDCl_3$)



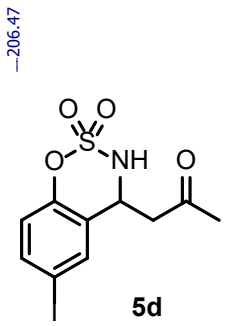
5c

^{13}C-NMR (101 MHz, $CDCl_3$)



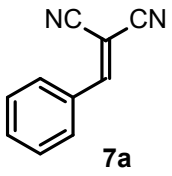
5d

^{1}H-NMR (400 MHz, $CDCl_3$)



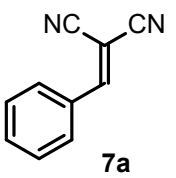
5d

^{13}C-NMR (101 MHz, $CDCl_3$)



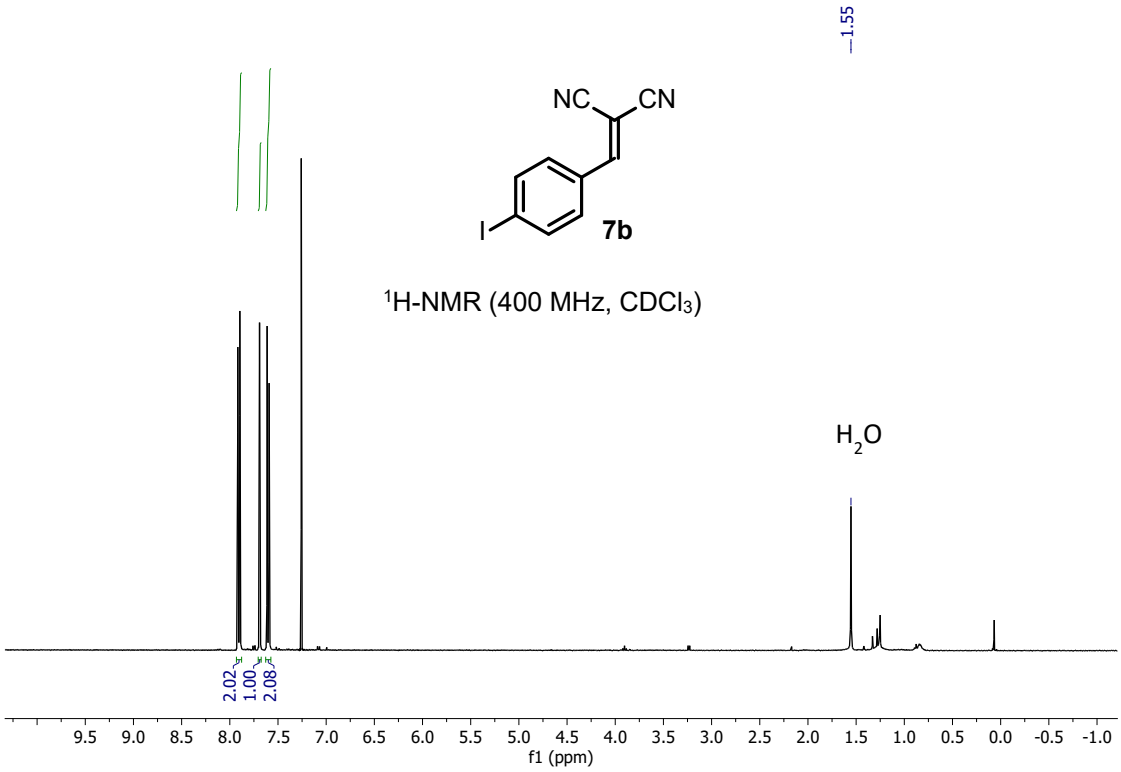
7a

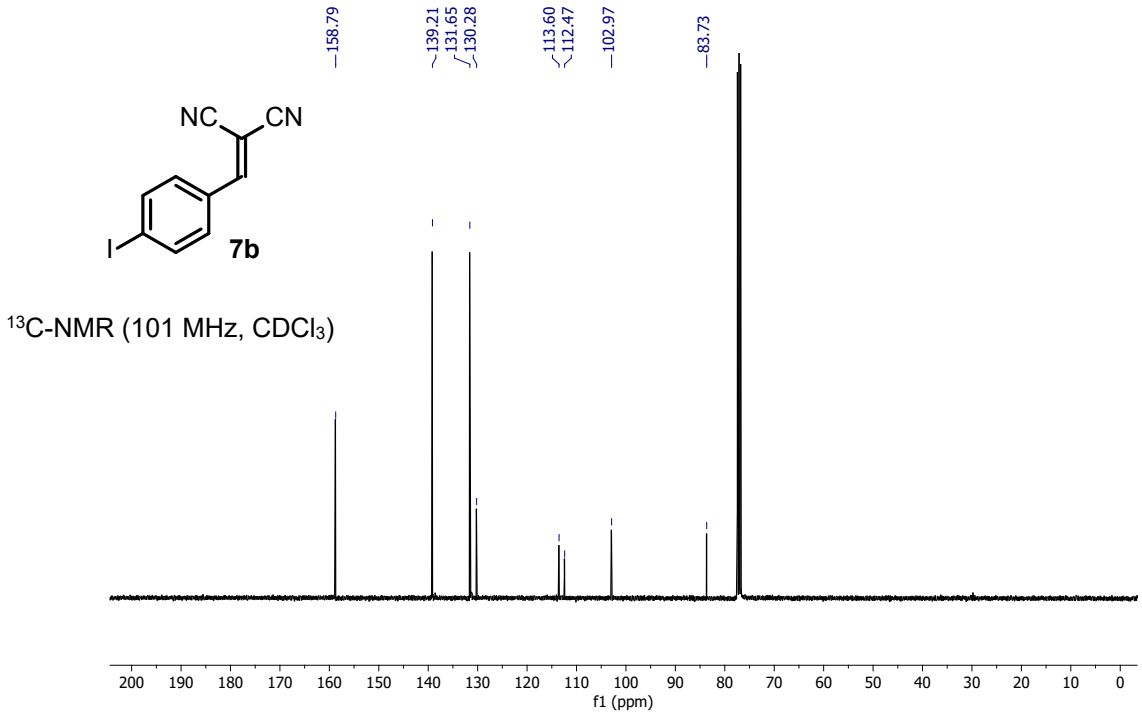
^{1}H-NMR (400 MHz, $CDCl_3$)

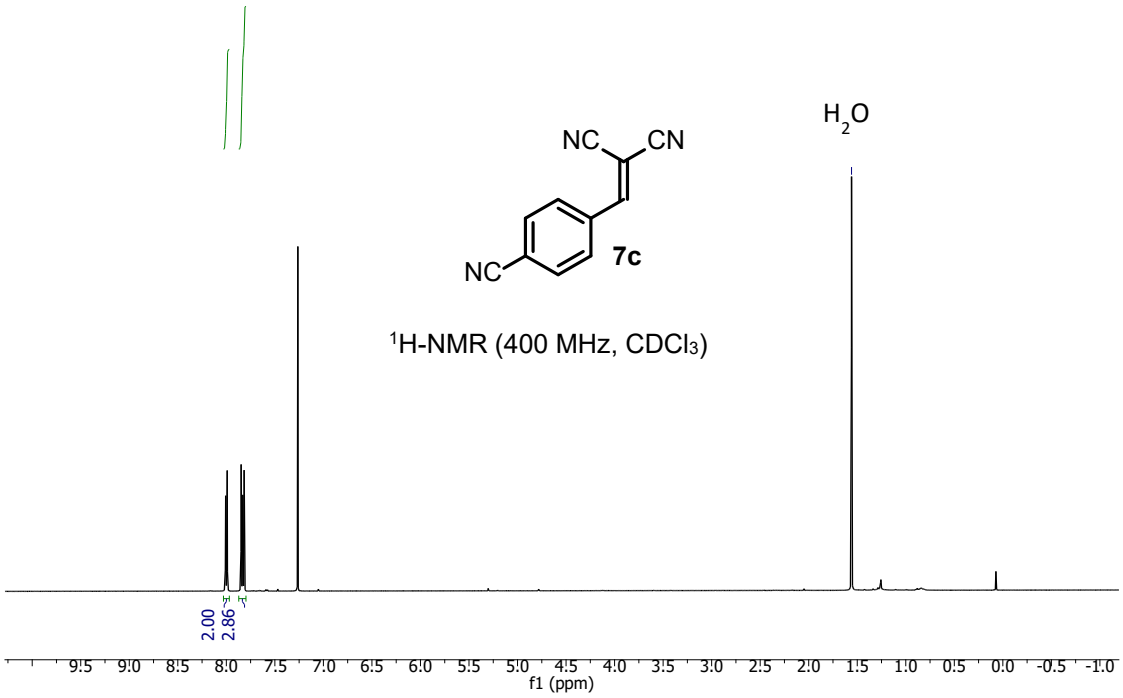


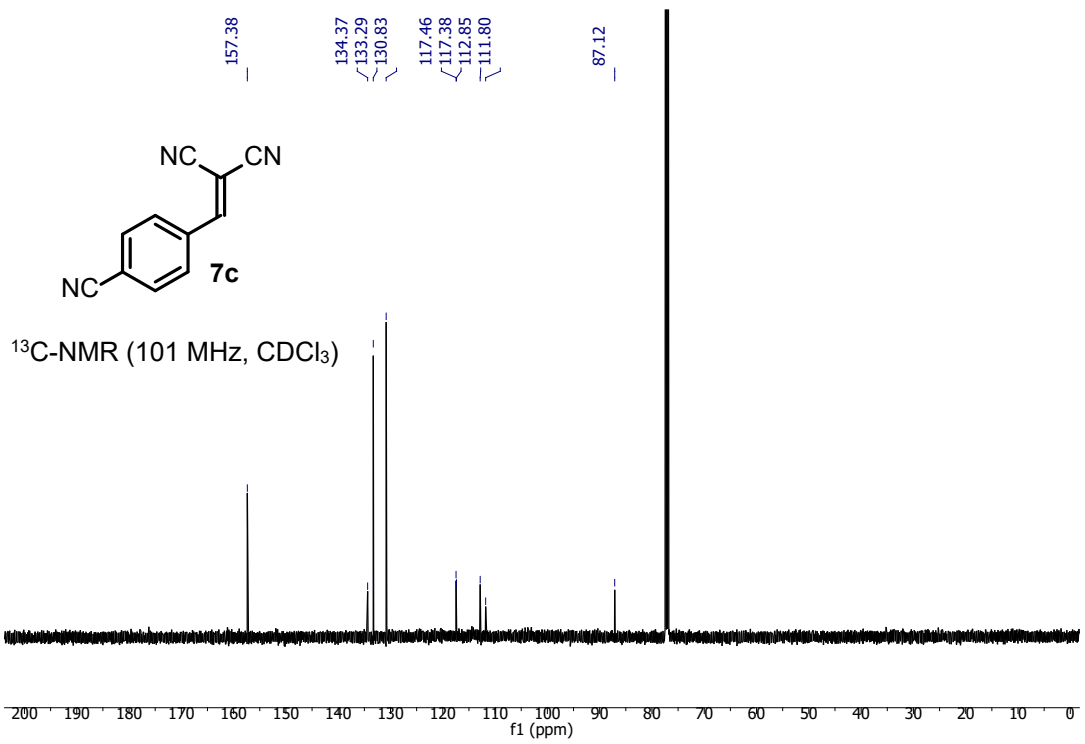
7a

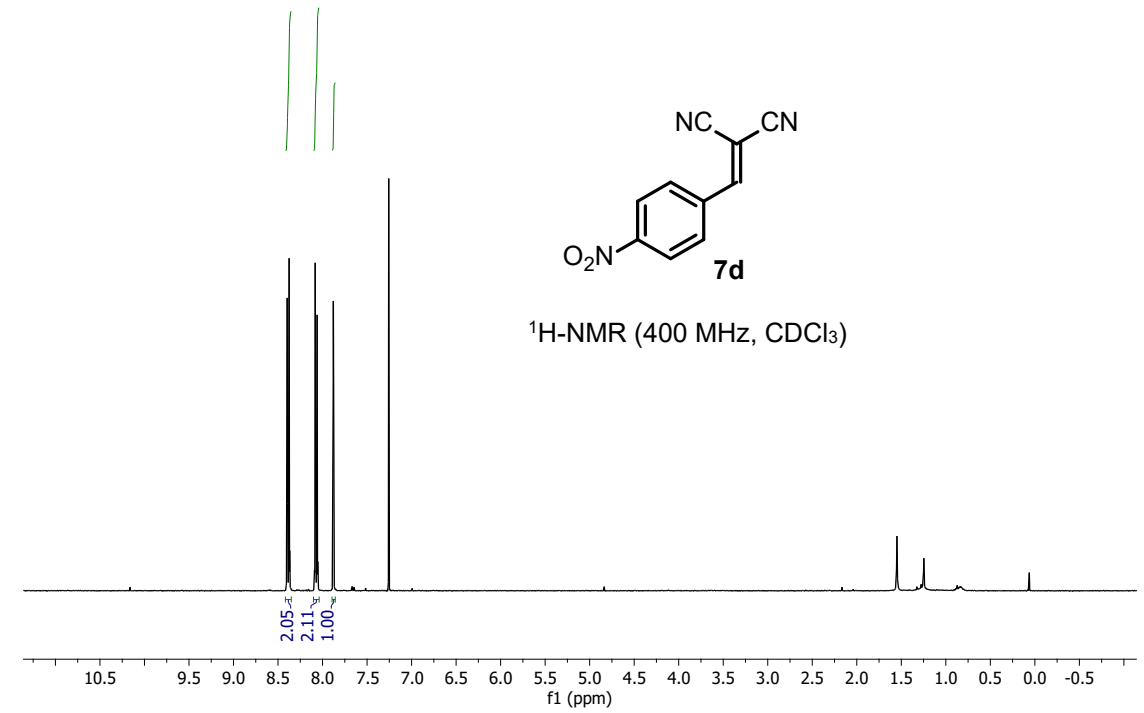
^{13}C-NMR (101 MHz, $CDCl_3$)

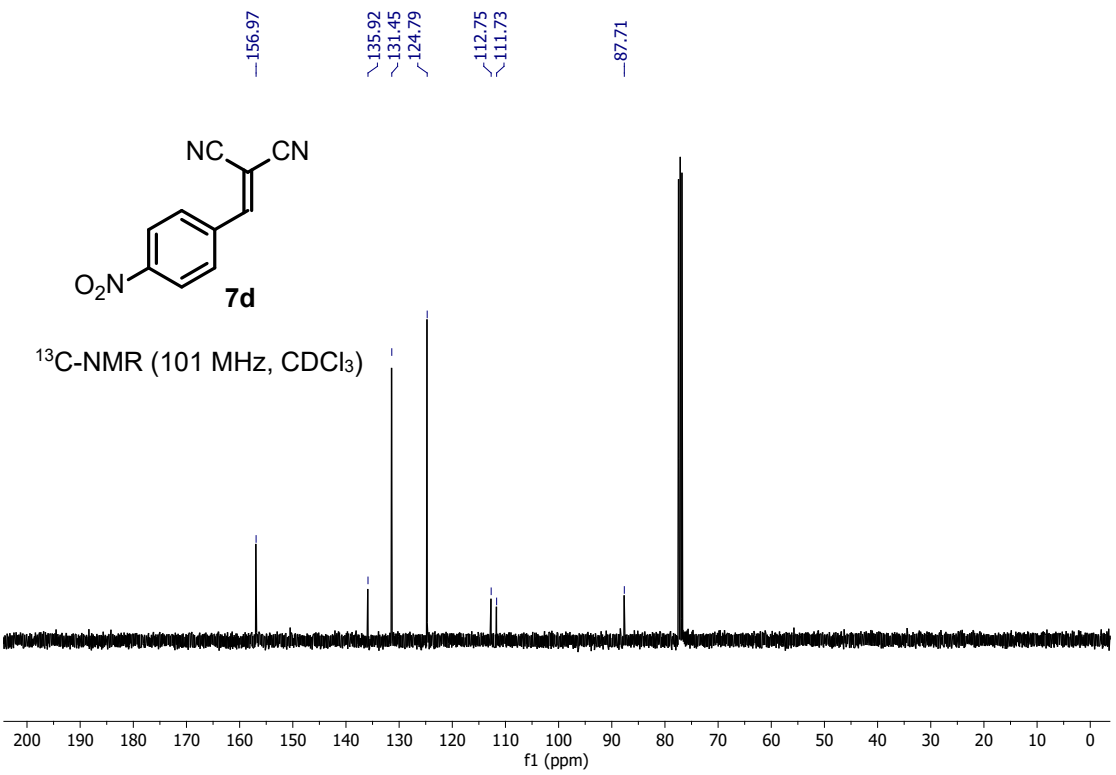

1.55
NC
CN
I
7b
^{1}H-NMR (400 MHz, $CDCl_3$)
H_2O
2.02
1.00
2.08
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

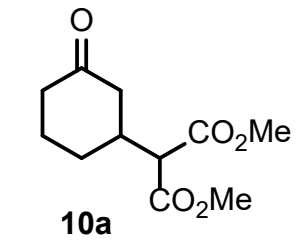

158.79
139.21
131.65
130.28
113.60
112.47
102.97
83.73
NC
CN
I
7b
^{13}C-NMR (101 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NC
CN
NC
7c
H2O
1H-NMR (400 MHz, CDCl3)
2.00
2.86
f1 (ppm)


157.38
134.37
133.29
130.83
117.46
117.38
112.85
111.80
87.12
NC
CN
NC
7c
13C-NMR (101 MHz, CDCl3)
f1 (ppm)

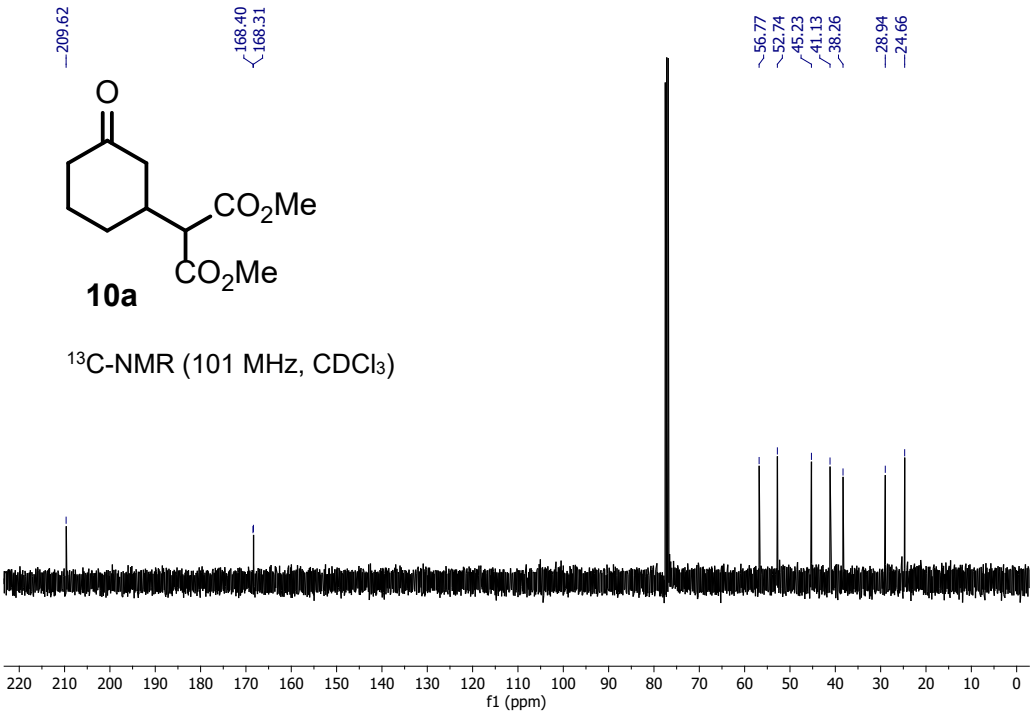

NC
CN
O2N
7d
1H-NMR (400 MHz, CDCl3)
2.05
2.11
1.00
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


156.97
135.92
131.45
124.79
112.75
111.73
87.71
NC
CN
O2N
7d
13C-NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



10a

^{1}H-NMR (400 MHz, $CDCl_3$)

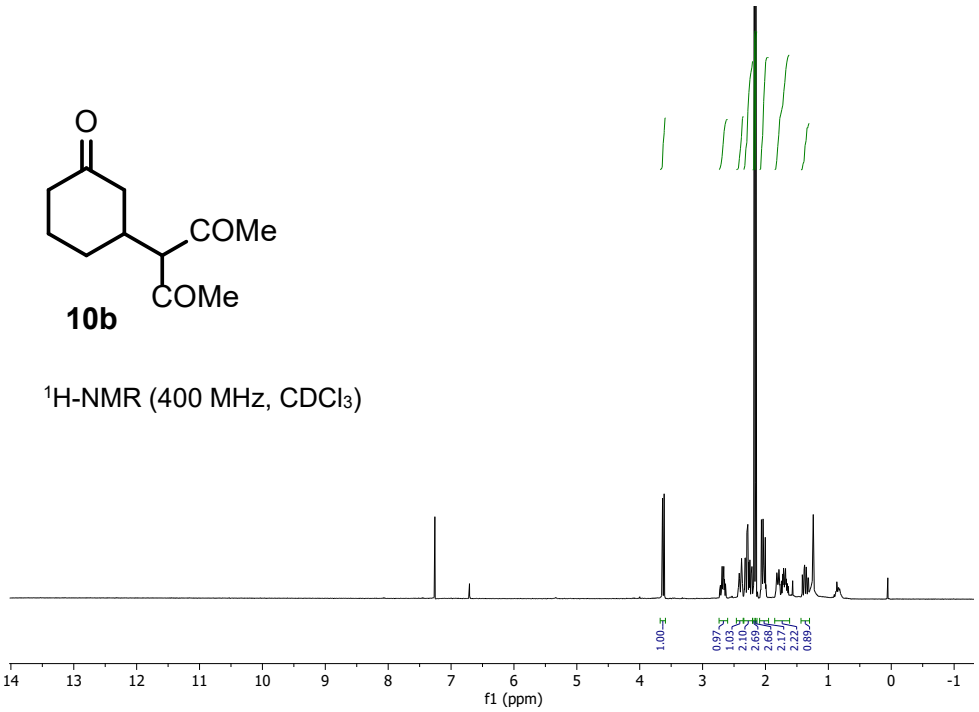


10a

^{13}C-NMR (101 MHz, $CDCl_3$)

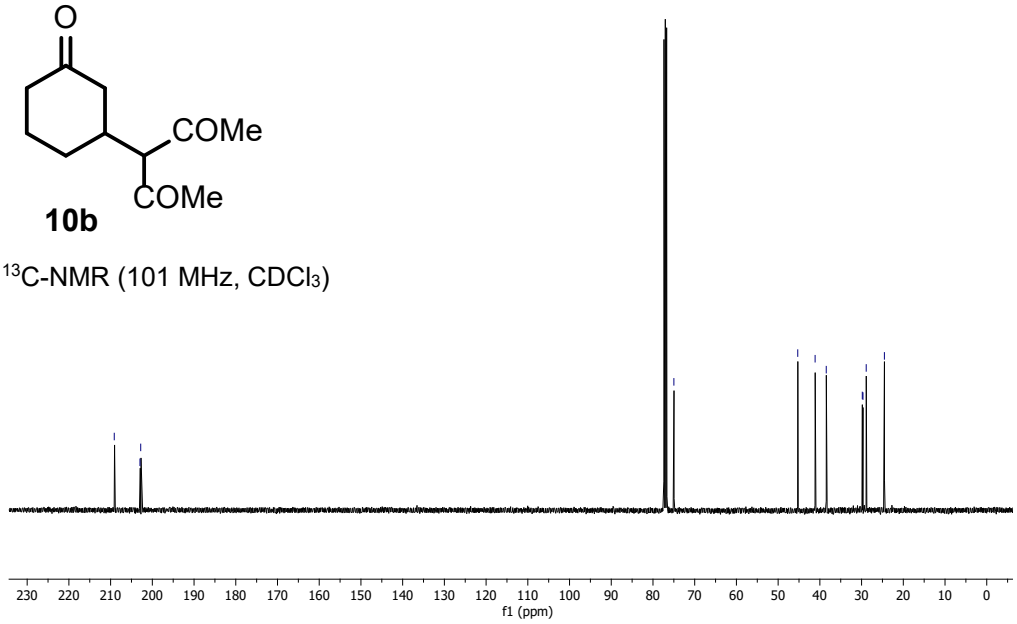
10b

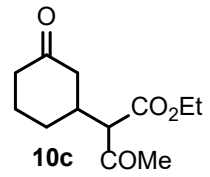
^{1}H-NMR (400 MHz, $CDCl_3$)



10b

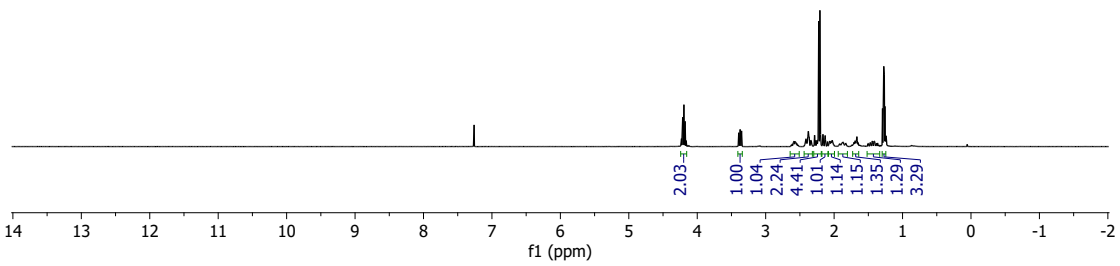
^{13}C-NMR (101 MHz, $CDCl_3$)

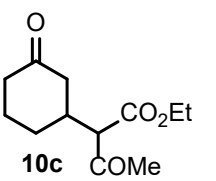




10c

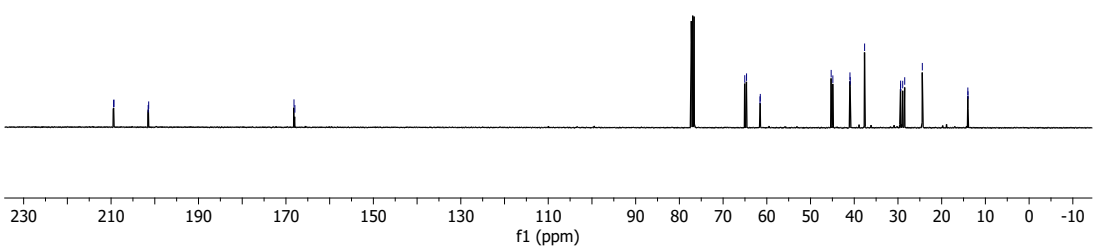
^{1}H-NMR (400 MHz, $CDCl_3$)

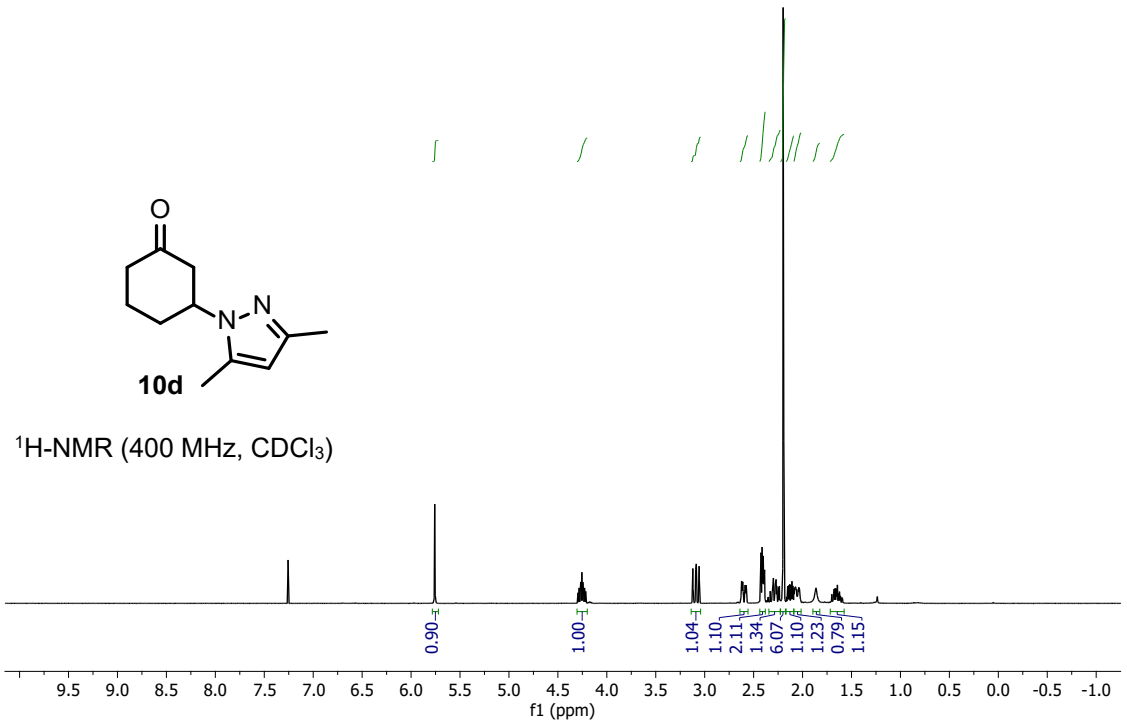




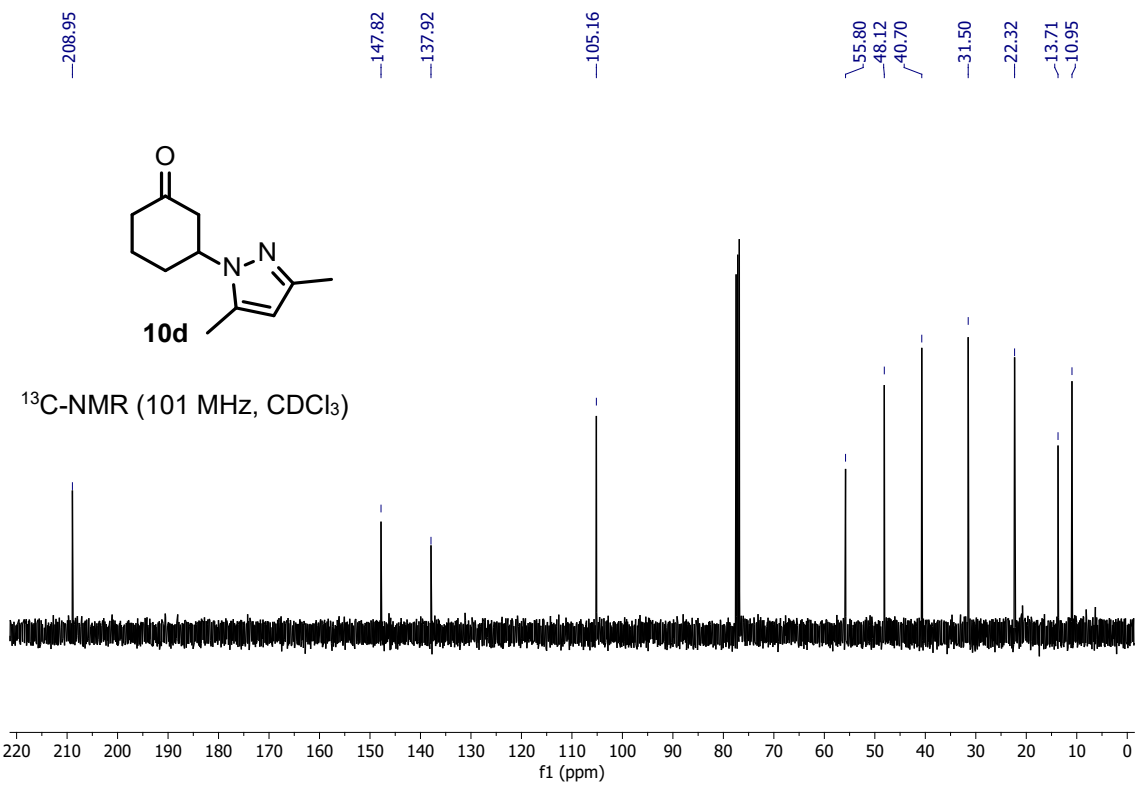
10c

^{13}C-NMR (101 MHz, $CDCl_3$)

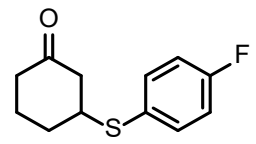




^{1}H-NMR (400 MHz, $CDCl_3$)

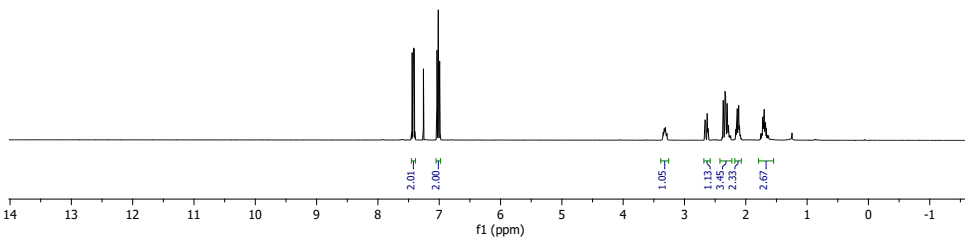


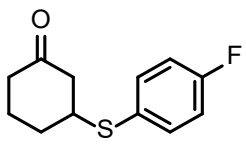
^{13}C-NMR (101 MHz, $CDCl_3$)



10e

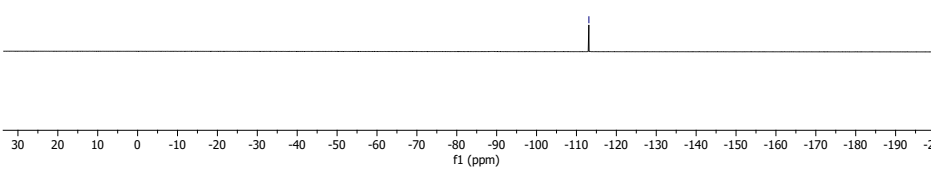
^{1}H-NMR (400 MHz, $CDCl_3$)

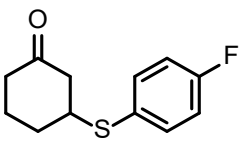




10e

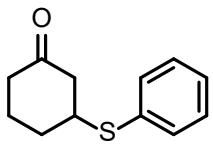
^{19}F-NMR (376 MHz, $CDCl_3$)





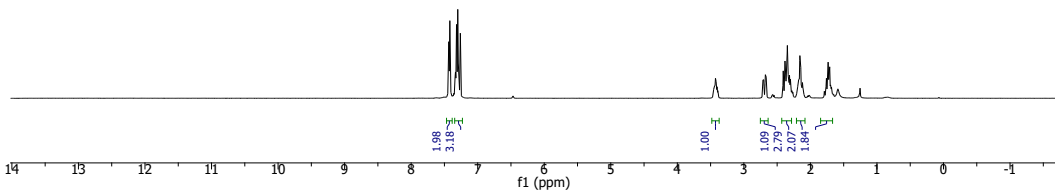
10e

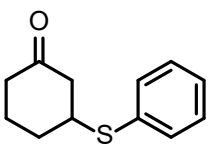
^{13}C-NMR (101 MHz, $CDCl_3$)



10f

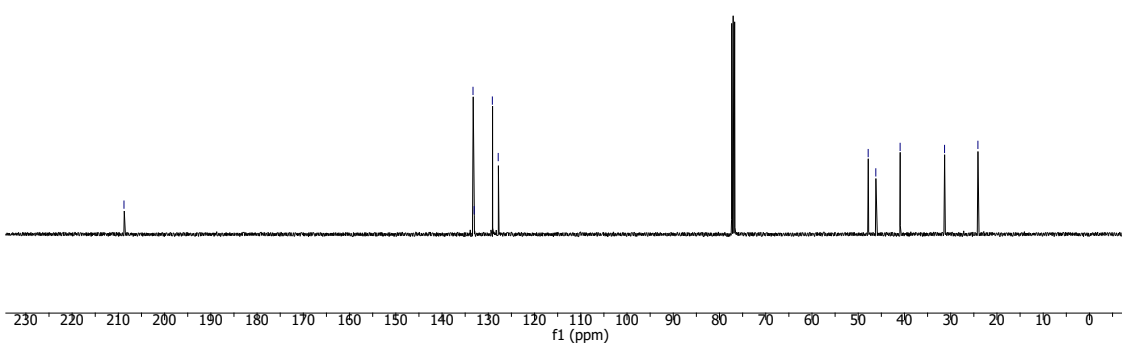
^{1}H-NMR (400 MHz, $CDCl_3$)

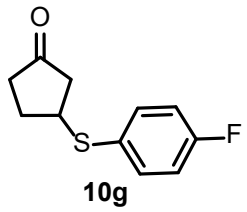




10f

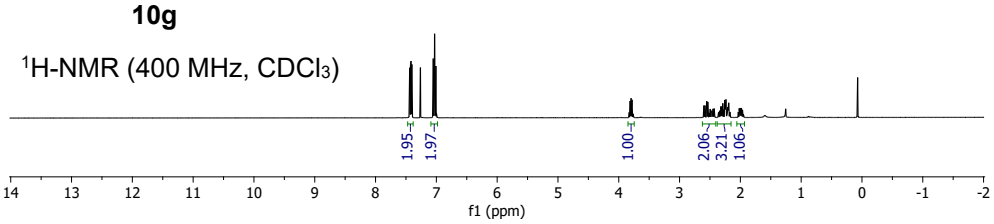
^{13}C-NMR (101 MHz, $CDCl_3$)

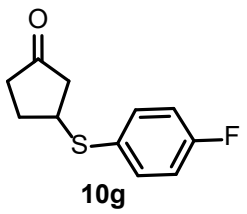




10g

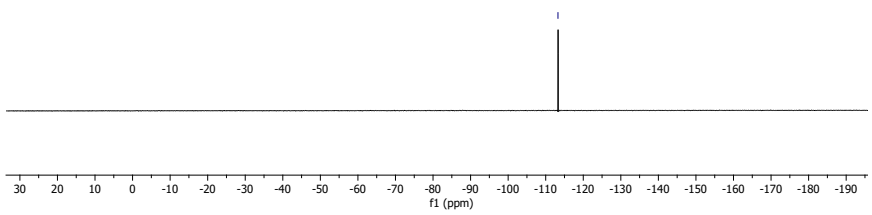
^{1}H-NMR (400 MHz, $CDCl_3$)

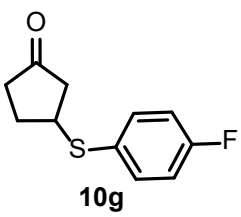




10g

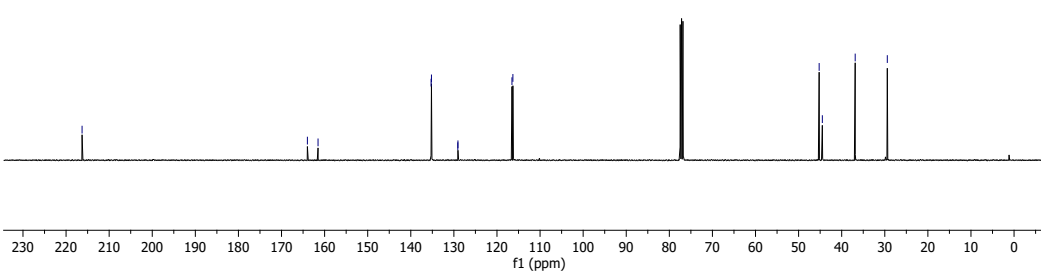
^{19}F-NMR (376 MHz, $CDCl_3$)

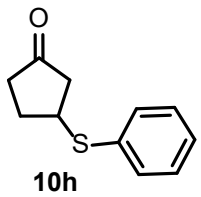




10g

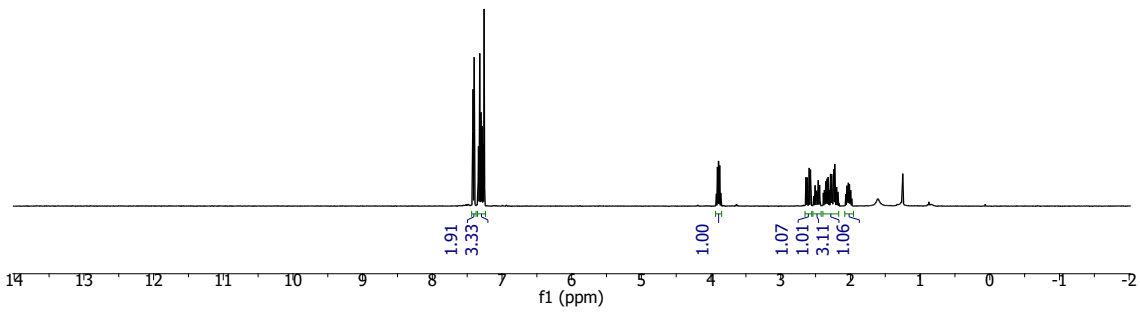
^{13}C-NMR (101 MHz, $CDCl_3$)

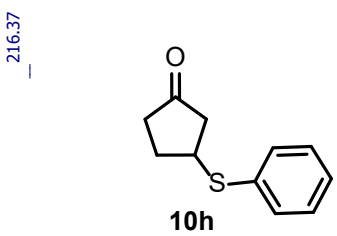




10h

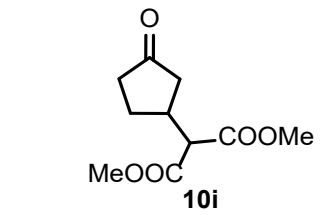
^{1}H-NMR (400 MHz, $CDCl_3$)





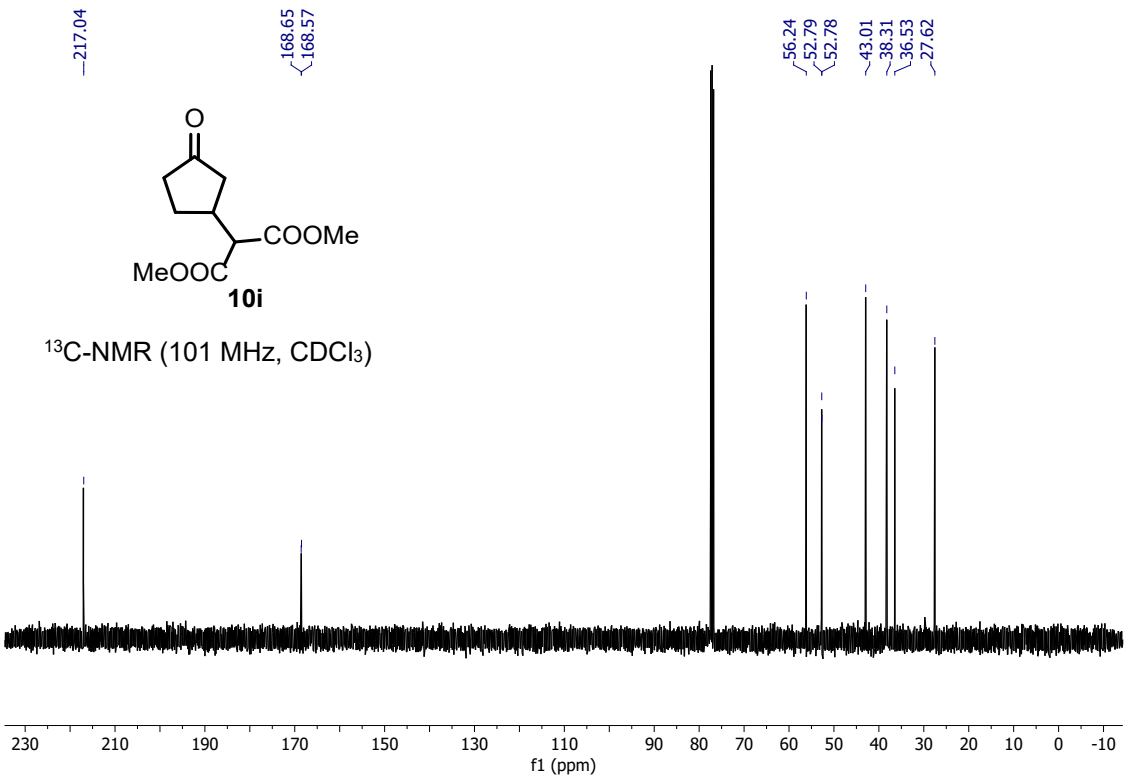
10h

^{13}C-NMR (101 MHz, $CDCl_3$)



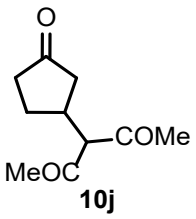
10i

^{1}H-NMR (400 MHz, $CDCl_3$)



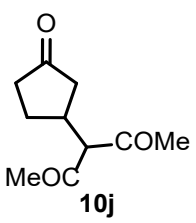
10i

^{13}C-NMR (101 MHz, $CDCl_3$)



10j

^{1}H-NMR (400 MHz, $CDCl_3$)



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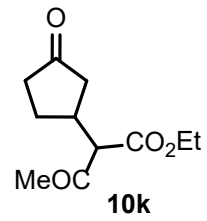
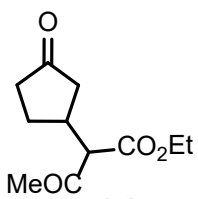


10k

^{1}H-NMR (400 MHz, $CDCl_3$)



10k

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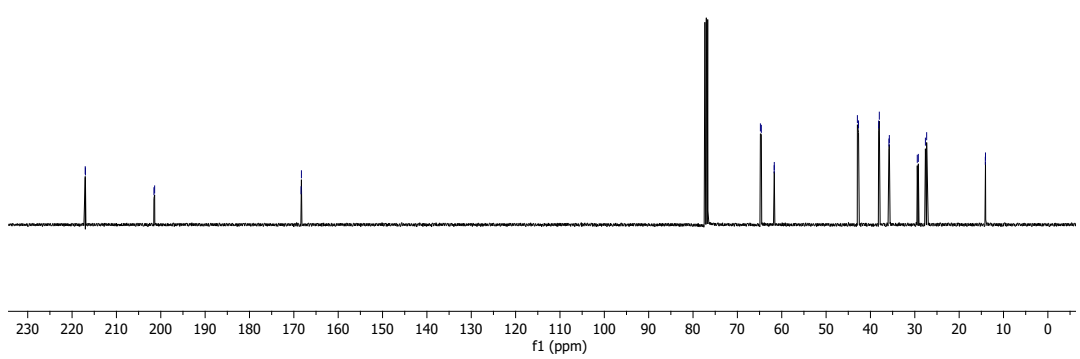
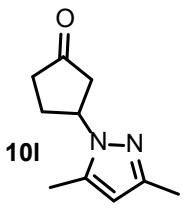
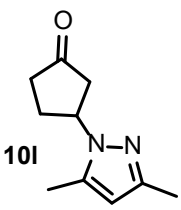




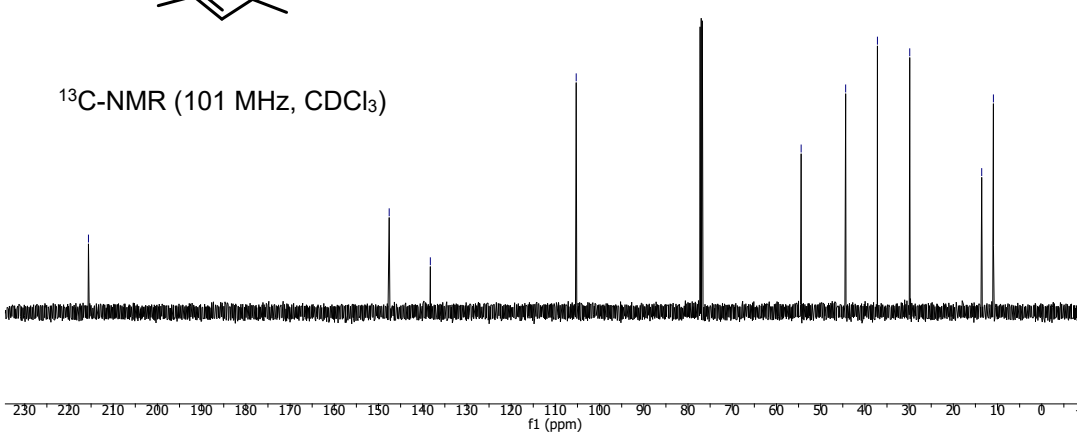
10l

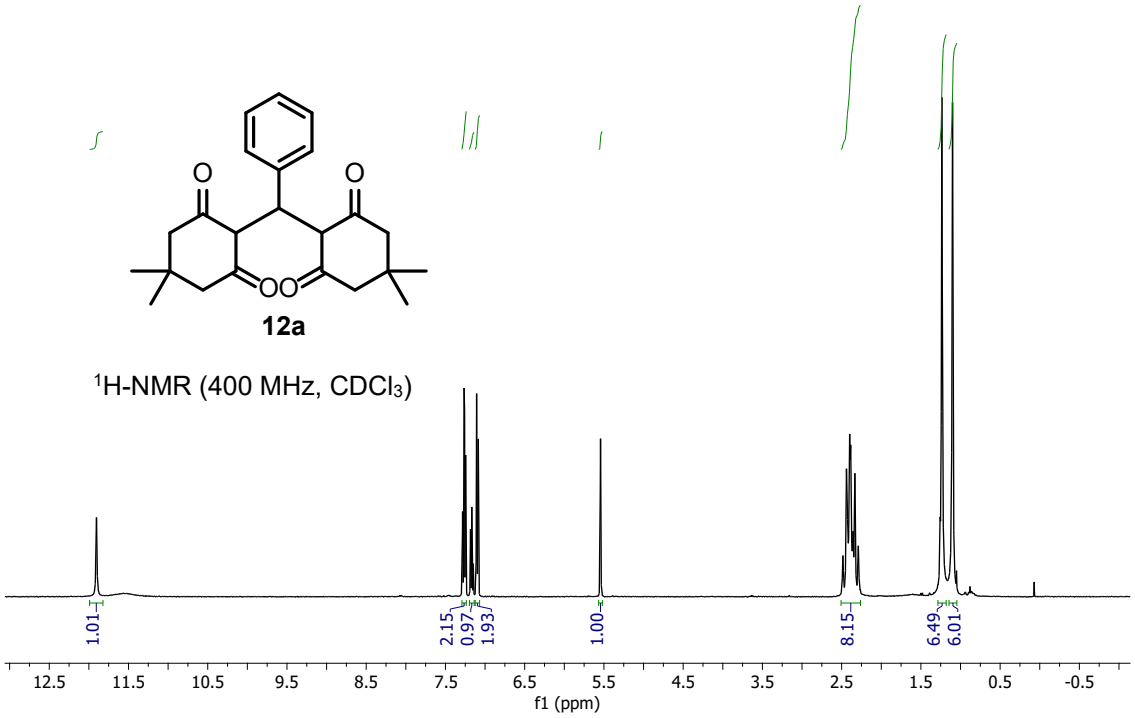
^{1}H-NMR (400 MHz, $CDCl_3$)

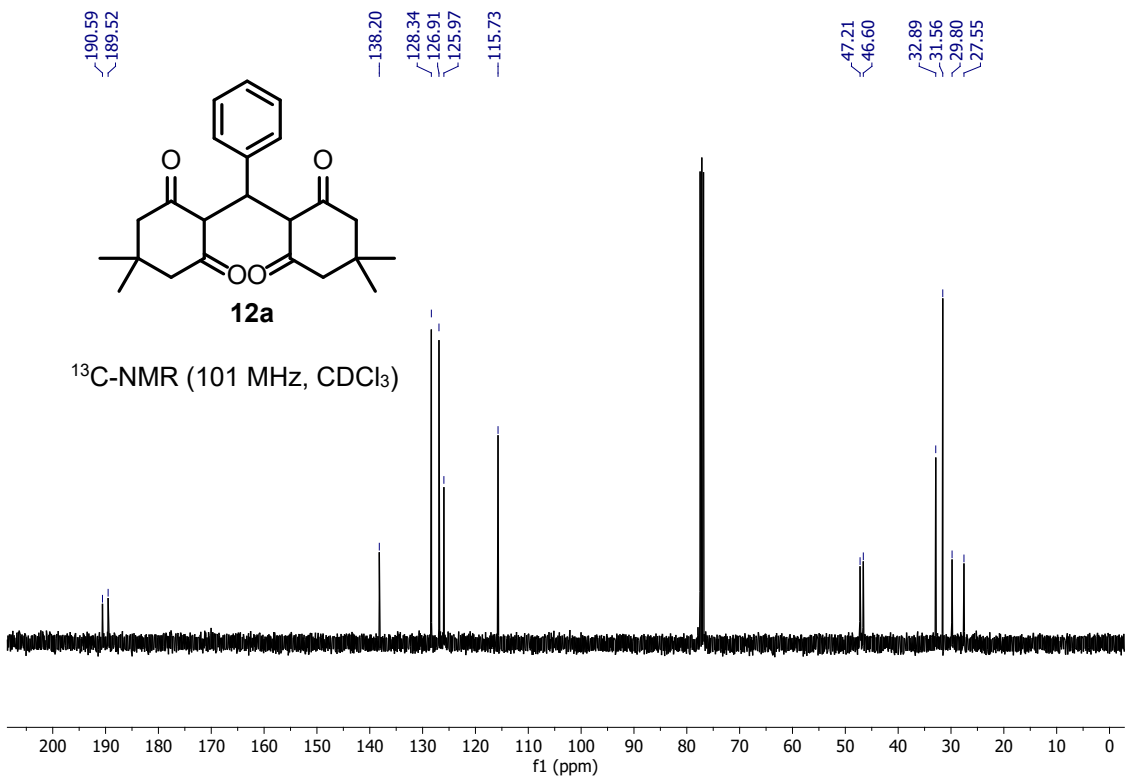


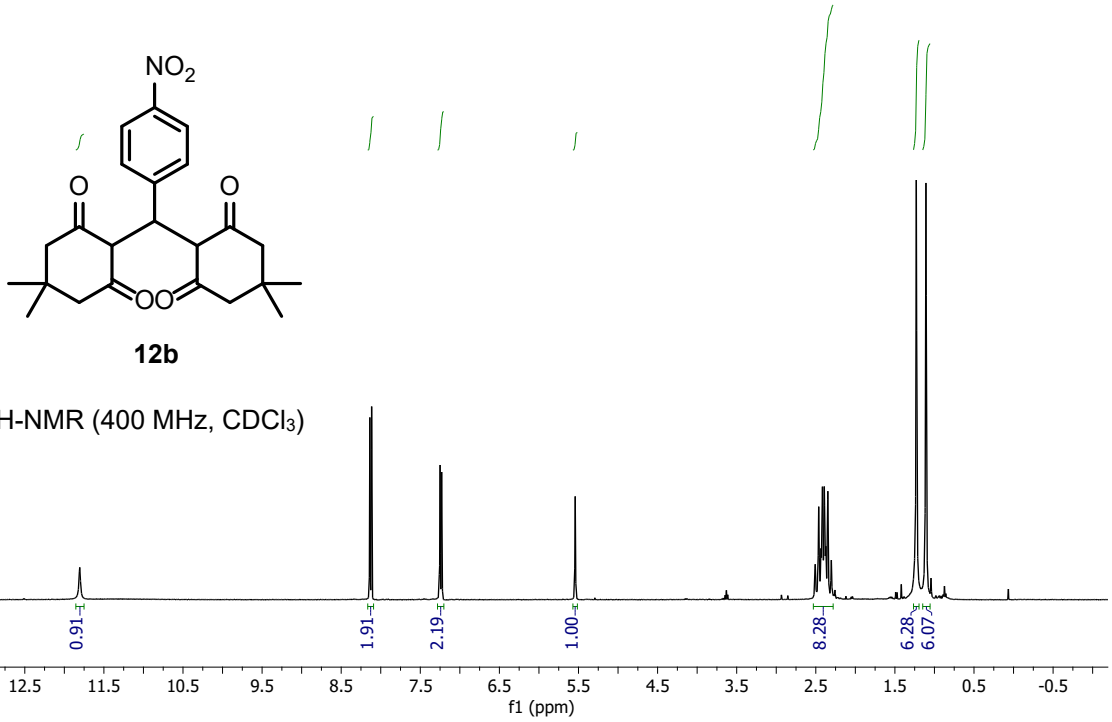
10l

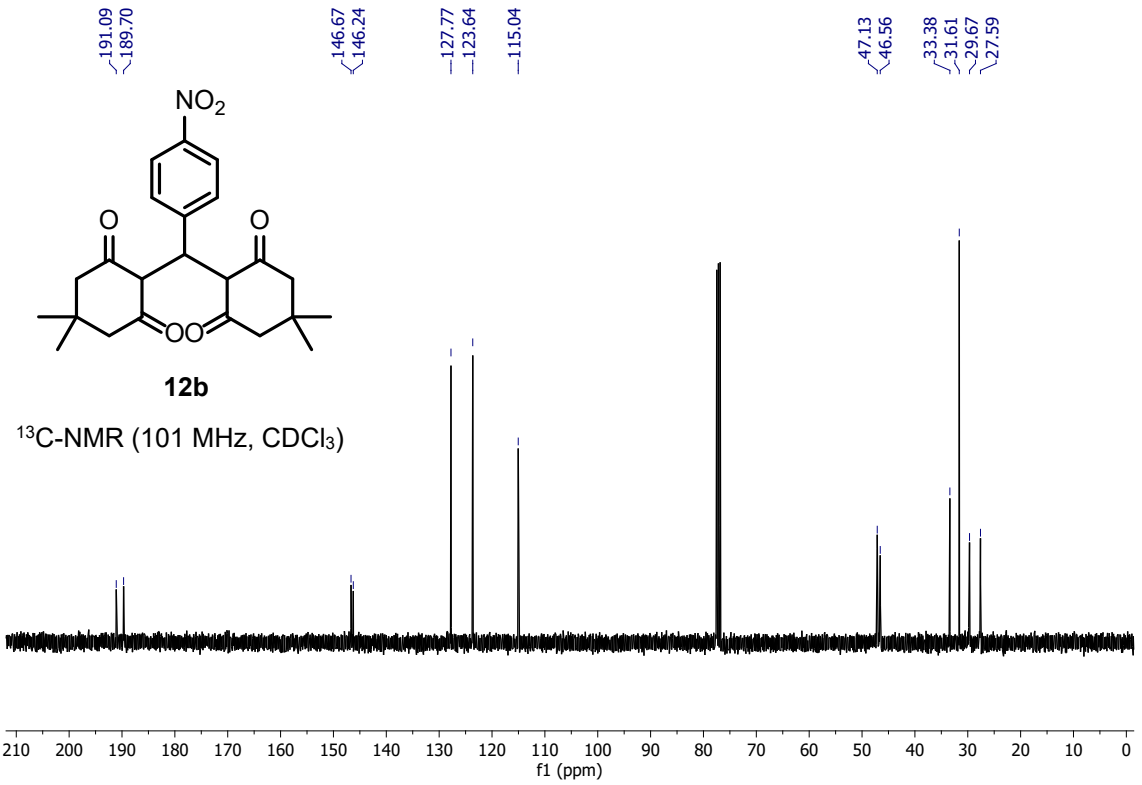
^{13}C-NMR (101 MHz, $CDCl_3$)

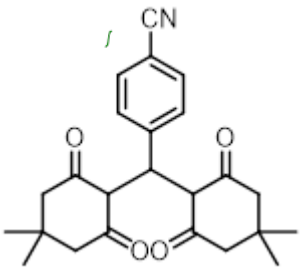



12a
1H-NMR (400 MHz, CDCl3)
1.01
2.15
0.97
1.93
1.00
8.15
6.49
6.01
12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5
f1 (ppm)


190.59
189.52
138.20
128.34
126.91
125.97
115.73
47.21
46.60
32.89
31.56
29.80
27.55
12a
13C-NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

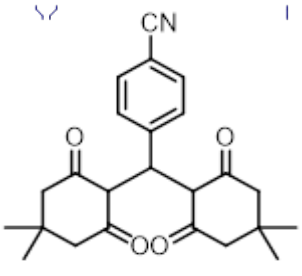

NO2
O
O
O
O
12b
1H-NMR (400 MHz, CDCl3)
0.91
1.91
2.19
1.00
8.28
6.28
6.07
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


191.09
189.70
146.67
146.24
127.77
123.64
115.04
47.13
46.56
33.38
31.61
29.67
27.59
NO2
O
O
O
O
12b
13C-NMR (101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



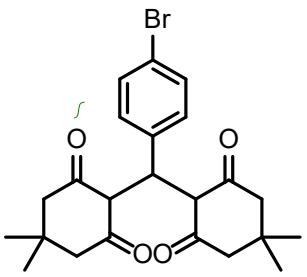
12c

^{1}H-NMR (400 MHz, $CDCl_3$)



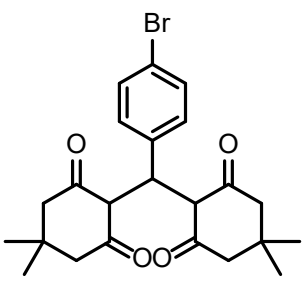
12c

^{13}C-NMR (101 MHz, $CDCl_3$)



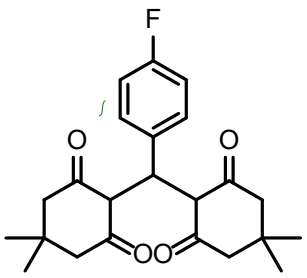
12d

^{1}H-NMR (400 MHz, $CDCl_3$)



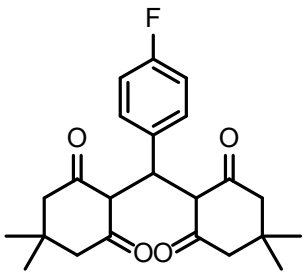
12d

^{13}C-NMR (101 MHz, $CDCl_3$)



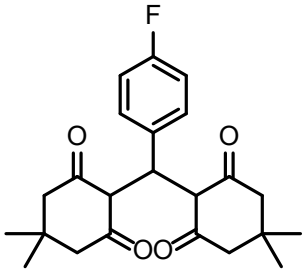
12e

^{1}H-NMR (400 MHz, $CDCl_3$)



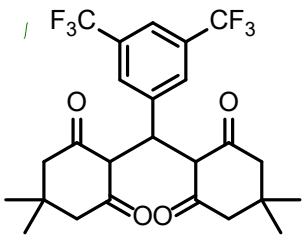
12e

^{19}F-NMR (376 MHz, $CDCl_3$)



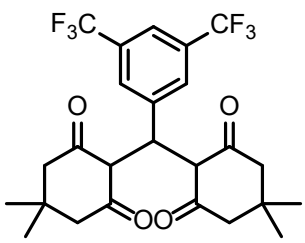
12e

^{13}C-NMR (101 MHz, $CDCl_3$)



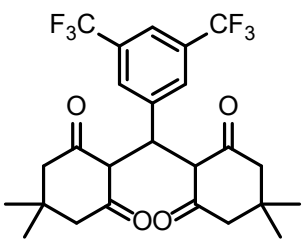
12f

^{1}H-NMR (400 MHz, $CDCl_3$)



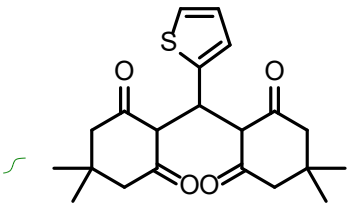
12f

^{19}F-NMR (376 MHz, $CDCl_3$)



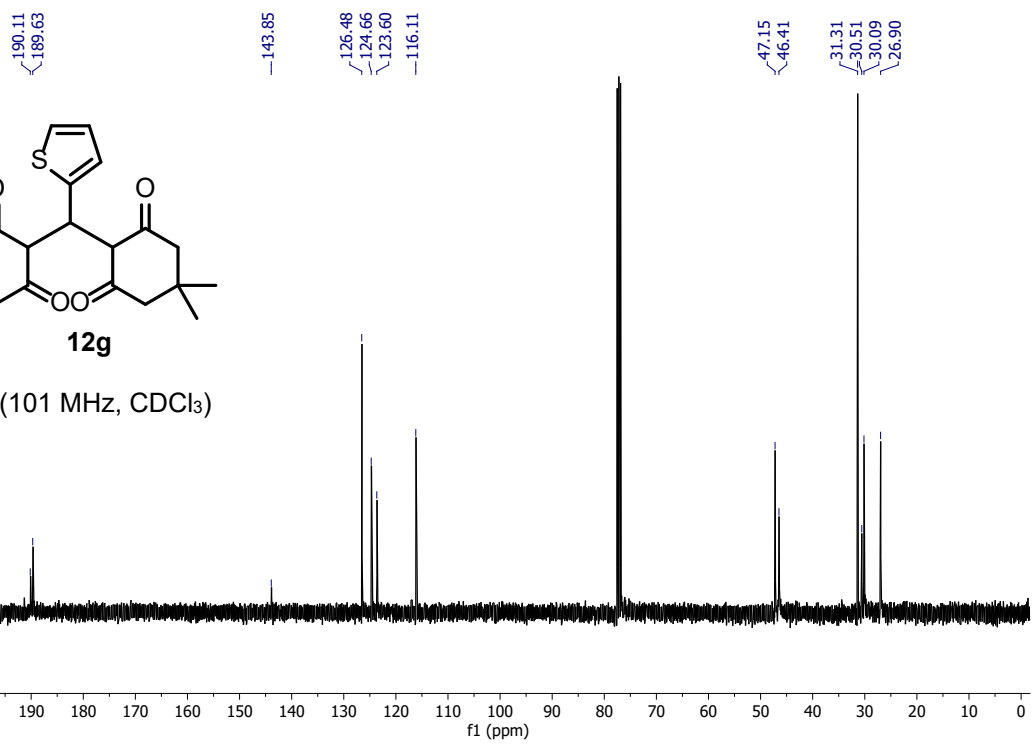
12f

^{13}C-NMR (101 MHz, $CDCl_3$)



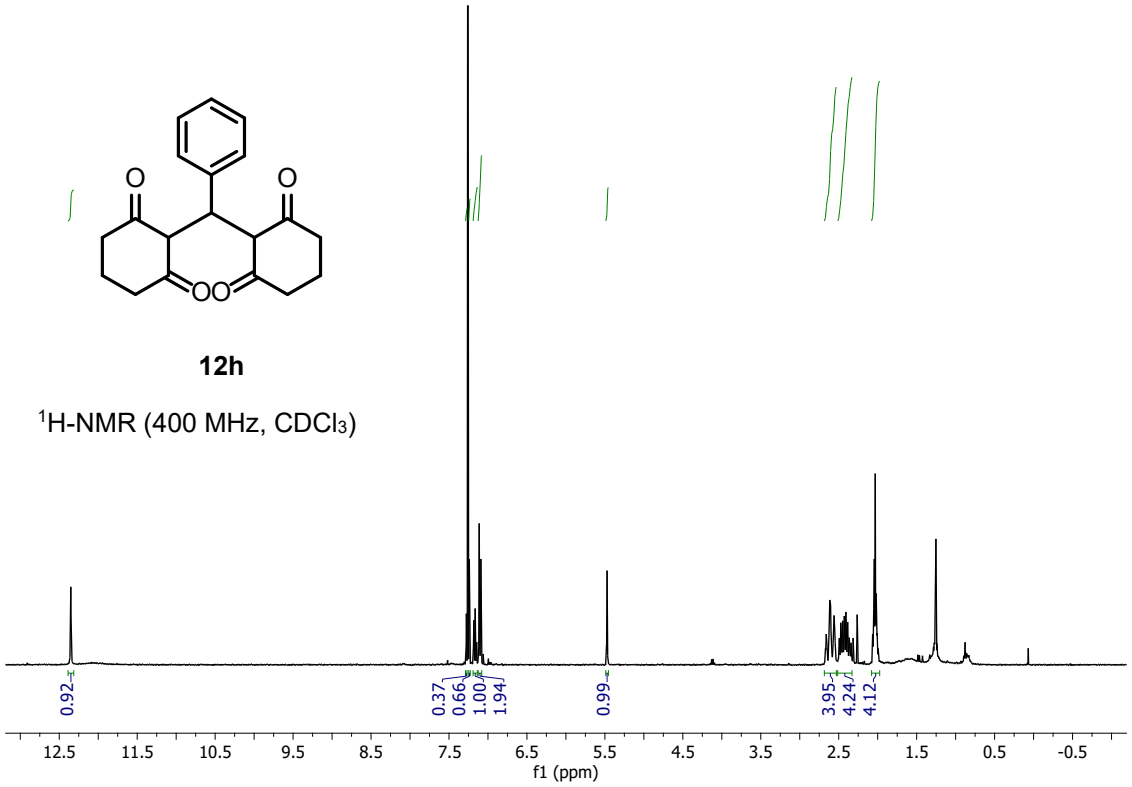
12g

^{1}H-NMR (400 MHz, $CDCl_3$)



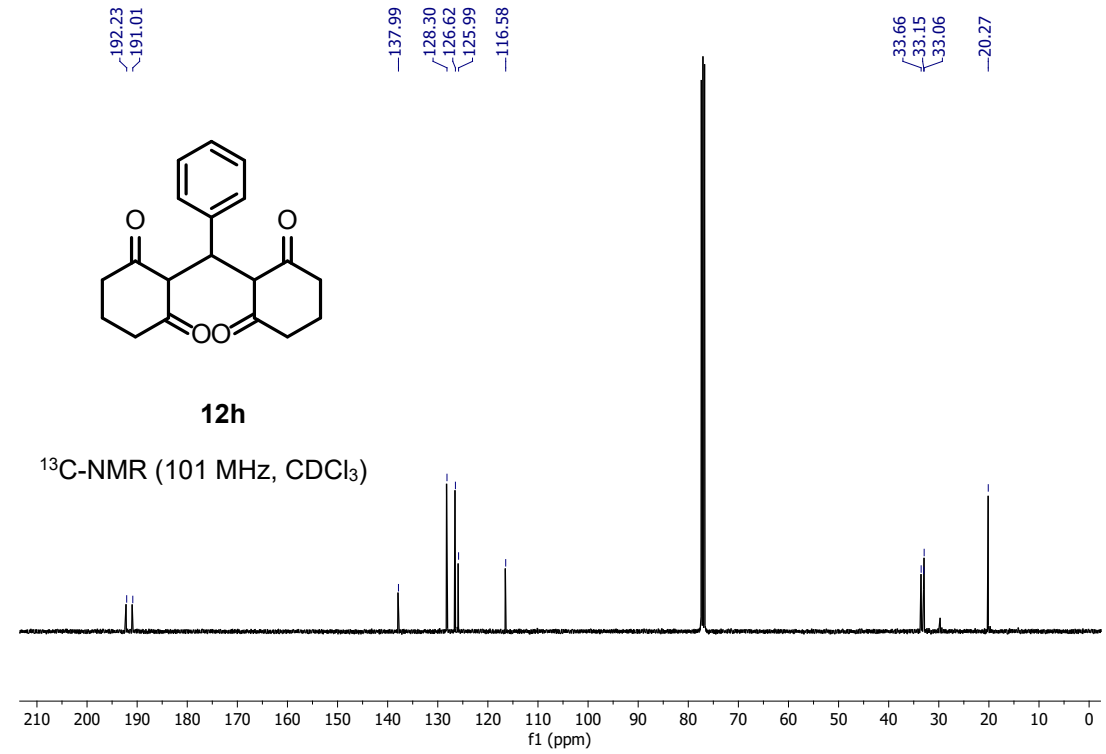
12g

^{13}C-NMR (101 MHz, $CDCl_3$)



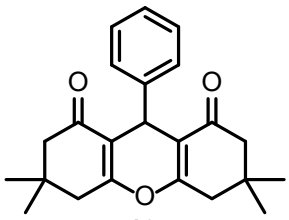
12h

^{1}H-NMR (400 MHz, $CDCl_3$)



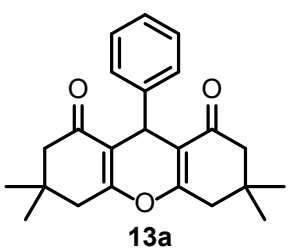
12h

^{13}C-NMR (101 MHz, $CDCl_3$)



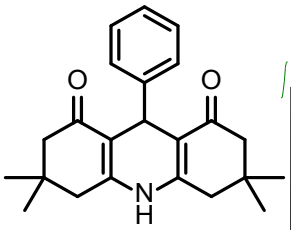
13a

^{1}H-NMR (400 MHz, $CDCl_3$)



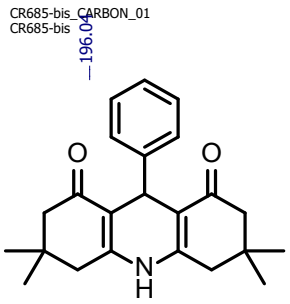
13a

^{13}C-NMR (101 MHz, $CDCl_3$)



13b

^{1}H-NMR (400 MHz, $CDCl_3$)



13b

^{13}C-NMR (101 MHz, $CDCl_3$)

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