SUPPORTING INFORMATION

Phase transfer of metal cations by induced dynamic carrier agents: biphasic extraction based on dynamic covalent chemistry

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1 Materials and Methods

All solvent and reagents were purchased from commercial supplier (Sigma-Aldrich, TCI, Acros, Alfa Aesar or Fluorochem). 2-pyridinecarboxaldehyde was distillated using a Kugelrohr apparatus before use. Acetichydrazide and octanoic hydrazide were recrystalized in ethanol. Others chemicals were used without further purification. Deuterated solvents were purchased from Euriso-TOP and Sigma-Aldrich and deuterated chloroform was filtered on basic alumina before use. Deionised water was obtained using arium® advance EDI pure water systems from Sartorius and was used in all experiments where deuterated solvent was not needed. pH was determined by Seven Compact pH meter S220. We gratefully thanks Cyril Antheaume, Dr. Jean-Louis Schmitt for NMR and HR-MS analyses and method development. We thank Dr. Bruno Vincent for NMR analyses. AC thanks Dr. Karmazin Lydia (University de Strasbourg) and Corinne Bailly (University de Strasbourg) for the single crystal structures determinations as well as Dr. Anne Boos, Ilsah El Masoudi and Pascale Ronot for ICP-AES analyses.

1.1 Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded on a Bruker Avance III 400 (400.14 MHz for ^{1}H and 100.62 MHz for ^{13}C), Bruker Avance III HD 400 (400.34 MHz for ^{1}H and 100.67 MHz for ^{13}C) and Bruker Avance Ascend Spectroscope Avance Neo-500 MHz (500 MHz for ^{1}H and 125 MHz for ^{13}C). All the collected spectra were referenced on residual solvent signal according to Nudelman et al[1]. The quantitative ^{1}H NMR was measured by using HMDSO (hexamethyldisiloxane) as internal standard in chloroform and TMSPA (tetramethylsilyl propanoic acid) as internal standard in water. The stock solution of components and constituents were prepared in D_2O or $CDCl_3$ and added to the set of the experiments. In all of the cases, the sum of the % for each component in the different entities present in the DCL is equal to 100%, the maximum any constituent can reach. The error in ^{1}H-NMR integration amounts to about 5%.

1.2 High-resolution mass spectrometry (HR-MS)

High resolution mass spectra were recorded on a ThermoFisher Orbitrap Exactive Plus EMR mass spectrometer. Liquid-chromatography coupled with high-resolution mass spectrometry was used in positive mode to determine the composition of the system. The column used for the LC is an Accucore Phenyl-Hexyl 150X2.mm purchased from ThermoFischer and the eluent is acidified acetonitrile HPLC grade (0.1% formic acid). Direct injection high-resolution mass spectrometry was used in negative mode to quantify the amount of nitrate anion. The eluent is methanol HPLC grade. The method was also used in positive mode to quantify the amount of Cu(II) derivative in the system. The quantitative study was developed by Cyril Antheaume and Dr. Jean-Louis Schmitt. We gratefully thank them for their expertise about the HR-MS technique.

1.3 UV/Vis spectrophotometry

Absorption spectra were recorded with a Jasco V-670 spectrophotometer equipped with a peltier thermostated cell holder at 25 °C using analytical grade solvents and a 1 cm quartz cell. All the spectra were recorded in water, chloroform and methanol (and mixtures of the three solvents) from 200 to 800 nm.

1.4 Single crystal diffraction

The crystals were placed in oil, and a single crystal was selected, mounted on a glass fiber and placed in a low-temperature N_2 stream.
For complex type 1 [Cu(II)(**HA1B1**)$_2$](NO_3)$_2$, X-Ray diffraction data collection was carried out on a Bruker APEX II DUO Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å). The crystal-detector distance was 38mm. The cell parameters were determined (APEX3 software)[2] from reflections taken from three sets of 12 frames, each at 10s exposure. The structure was solved using the program SHELXT-2014[3]. The refinement and all further calculations were carried out using SHELXL-2014[4]. The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. A semi-empirical absorption correction was applied using SADABS in APEX3[2]; transmission factors: T_{min}/T_{max} = 0.6969/0.7456. The SQUEEZE instruction in PLATON[5] was applied. The residual electron density was assigned to a molecule of the acetonitrile solvent.

For complex type 2 [Cu(II)(**HA1B1**)(**A1B1**)](NO_3), X-ray diffraction data collection was carried out on a Bruker PHOTON III DUO CPAD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å). The crystal-detector distance was 37mm. The cell parameters were determined (APEX3 software)[2] from reflections taken from 1 set of 180 frames at 1s exposure. The structure was solved using the program SHELXT-2014[3]. The refinement and all further calculations were carried out using SHELXL-2014[4]. The hydrogen atom of the NH group was located from Fourier difference. The other H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. A semi-empirical absorption correction was applied using SADABS in APEX3[2]; transmission factors: T_{min}/T_{max} = 0.6637/0.7458.

For the complex type 3 [Cu(II)(**A1B1**)$_2$], single crystals of 'Cu compound' were grown in acetonitrile/chloroform. The crystals were placed in oil, and a red needle single crystal of dimensions 0.35 x 0.12 x 0.10 mm was selected, mounted on a glass fiber and placed in a low-temperature N_2 stream.
X-Ray diffraction data collection was carried out on a Bruker APEX II DUO Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Cu-Kα radiation (λ = 1.54178 Å). The crystal-detector distance was 40mm. The cell parameters were determined (APEX3 software)[2] from reflections taken from three sets of 20 frames, each at 10s exposure. The structure was solved by Direct methods using the program SHELXT-2014[3]. The refinement and all further calculations were carried out using SHELXL-2014[4]. The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. A semi-empirical absorption correction was applied using SADABS in APEX2[2]; transmission factors: T_{min}/T_{max} = 0.5666/0.7528.

1.5 Ionization Coupling Plasma – Optical Emission Spectrometry (IPC-OES)

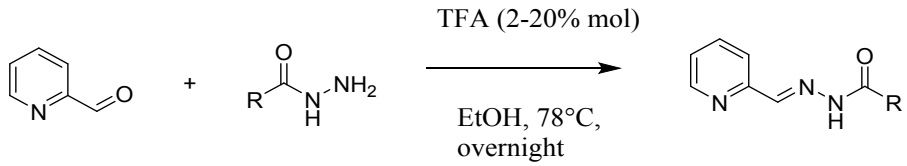
Metals content determination of initial and extracted solutions was realized using ICP-AES with a Varian 720 ES instrument at 324.754 nm for Cu. Quantification was done with a calibration curve established with standards (0, 0.025, 0.1, 0.5, 2, 10 mg/L) prepared using certified standards (1000 $mg.L^{-1}$; CPI International) after dilution of the samples.

2 Synthetic Procedures and Characterization for Newly Prepared Compounds

The newly synthesized compounds are **HA1B2**, **HA1B3**, **HA1B4**, **HA2B4**, **HA3B1**, **Me-A1B1**, **Me-A1B2**, **Me-A1B4**.

Chemical shifts are given in ppm. Residual solvent peaks were taken as reference (eg: $CHCl_3$: 7.26 ppm). The coupling constants *J* are given in Hertz. Peaks are described as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd) and multiplet (m). The assigned proton (X) is written as H^x.

2.1 General procedure for the preparation of acylhydrazones



Scheme S1. General procedure for the preparation of acylhydrazones

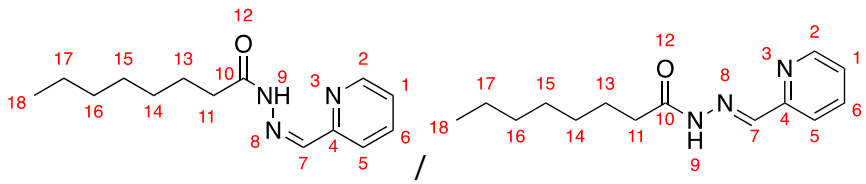
Equimolar quantities of hydrazide and aldehyde were solubilized in ethanol (5 volumes). Trifluoroacetic acid (for 5 to 20% mol) was added. The mixture was stirred overnight at reflux. After the completion of the reaction, the ethanol was evaporated under vacuum and the mixture was solubilized in two volumes of chloroform. The organic phase was washed with $NaHCO_3$ (sat) and then with HCl 1 M solution. The aqueous phase was washed with brine. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered-off. Solvent was evaporated on the rotavapor. Recrystallization of the residue from cold ethanol (or hexane or diethyl ether) afforded between 60 to 90% yield. Most of synthetized compounds are solid at room temperature.
The washing step is not always needed as several compounds started to crystalize directly after solvent removal.

Synthesis of (HA1B1) - N'-(pyridin-2-ylmethylene)acetohydrazide - CAS N° 101259-13-6

See reference [6]

Synthesis of (HA1B2) - N'-(pyridin-2-ylmethylene)octanehydrazide - CAS N° 392721-11-8

Octanoic hydrazide (1 eq., 1.85 g, 9.34 mmol) and 2-pyridine carboxaldehyde (1 eq., 1 g, 0.892 mL, 9.34 mmol), were solubilized in ethanol (200 mL). Trifluoroacetic acid (20 %, 0.213 g, 0.139 mL, 1.87 mmol) was added slowly. The mixture was heated overnight at 78 °C. After this time, the ethanol is evaporated under vacuum and the mixture is solubilized in 2 volumes of chloroform. The organic phase was washed with $NaHCO_3$ (sat) and then with HCl 1 M solution. The aqueous phase was washed with brine. The combined organic phases were dried over anhydrous Na_2SO_4, which was filtered-off. Solvent was evaporated on the rotavapor. Recrystallization of the residue from hexane afforded N'-(pyridin-2-ylmethylene)octanehydrazide (1.53 g, 6.186 mmol, 66%) as pale yellow solid.



^{1}H NMR (500 MHz, $CDCl_3$, 298K)
Isomer cis: δ 8.76 (s, 1H, H^9), 8.61 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H, H^2), 7.94 (d, *J* = 8.0 Hz, 1H, H^5), 7.82 (s, 1H, H^7), 7.74 (td, *J* = 7.8, 1.8 Hz, 1H, H^1), 7.29 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H^6), 2.76 (t, 1.8H, H^{11}), 1.73 (p, 2H, H^{13}), 1.56 – 1.14 (m, 1H, $H^{14+15+16+17}$), 0.88 (t, *J* = 13.9, 7.0 Hz, 3H, H^{18}).
Isomer trans: δ 8.76 (s, 1H, H^9), 8.61 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H, H^2), 8.15 (s, 1H, H^7 + d, 1H, H^5), 7.74 (td, *J* = 7.8, 1.8 Hz, 1H, H^1), 7.29 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H^6), 2.40 – 2.33 – 2.20 (t, *J* = 15.8, 8.1 Hz - t, *J* = 7.6 Hz - m, 1H, H^{11}), 1.73 (p, 2H, H^{13}), 1.56 – 1.14 (m, 1H, $H^{14+15+16+17}$), 0.88 (t, *J* = 13.9, 7.0 Hz, 3H, H^{18}).

^{13}C NMR (101 MHz, $CDCl_3$, 298K) δ 175.72 (C^{10}), 153,11 (C^4), 149.57 (C^2), 143.22 (C^7), 136.50 (C^1), 124.11(C^6), 120.22 (C^5), 32.72 (C^{11}), 24.59 (C^{13}), 31.72 - 29.34 - 29.07 - 22.65 ($C^{14+15+16+17}$), 14.10 (C^{18}).

ESI-MS: calculated for $[C_{14}H_{21}N_3O+H]^+$ 248.17574, found, 248.17509.

Elemental analysis calculated (%) for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99; found: C, 67.9; H, 8.57; N, 16.98.

Melting point: 65.4 - 68.6°C

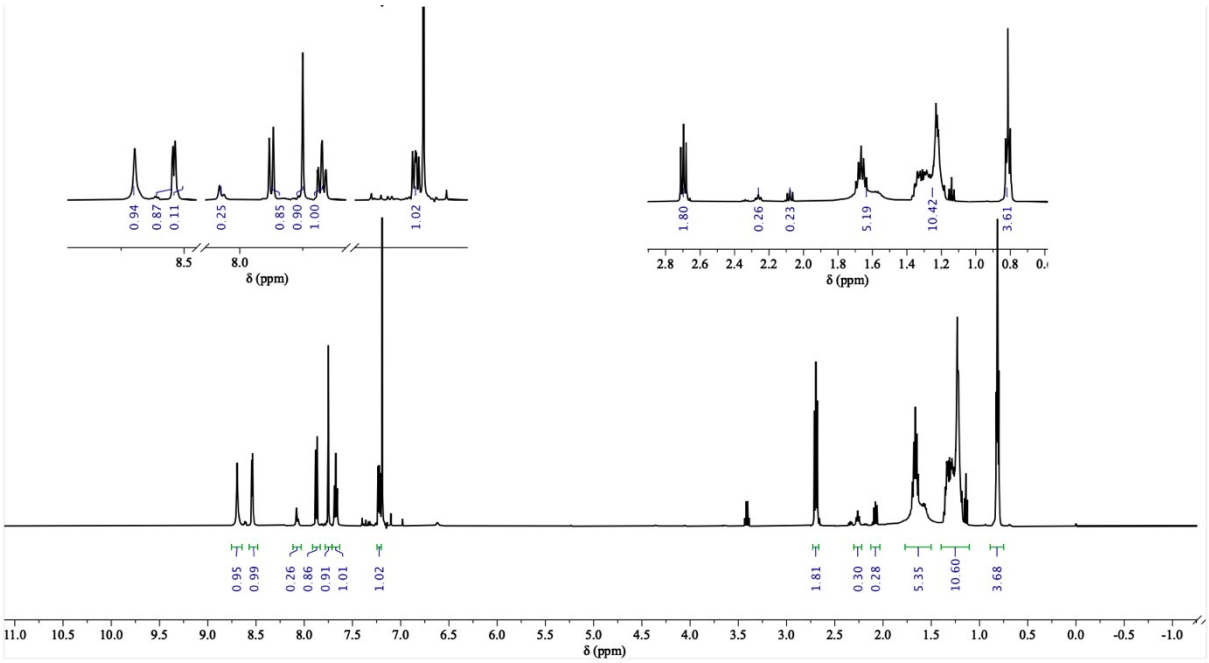


*Figure S1. 1H NMR spectrum (500 MHz, CDCl3, 298 K) of **HA1B2***

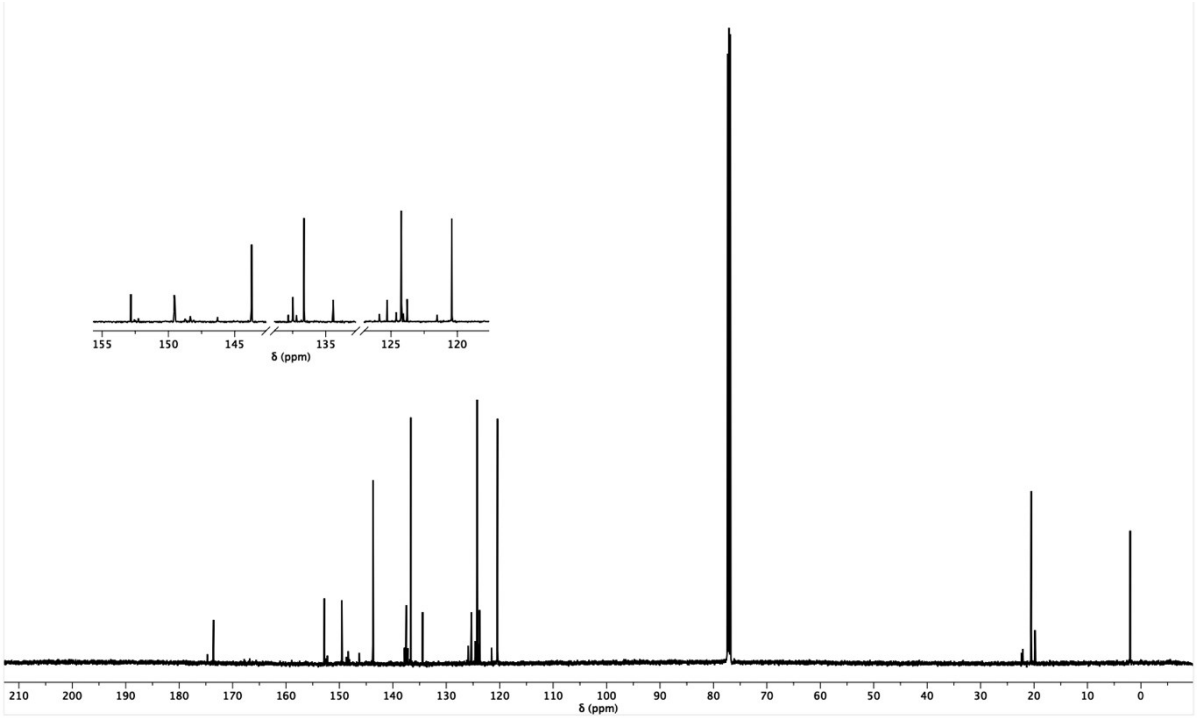
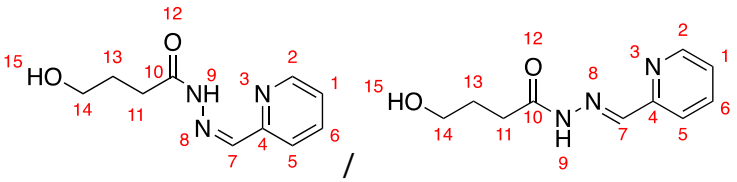


Figure S2. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) of **HA1B2**

Synthesis of (HA1B3) - 4-hydroxy-N'-(pyridin-2-ylmethylene)butanehydrazide

4-hydroxybutanehydrazide (1 eq., 1 g, 8.3 mmol) and 2-pyridine carboxaldehyde (1 eq., 0.90 g, 0.798 mL, 8.3 mmol), were solubilized in ethanol (20 mL). The mixture was heated overnight at 78°C. The mixture is concentrated under vacuum and the obtained oil crystalized. The crystals are washed with cyclohexane and recrystallized in cold ethanol. 4-hydroxy-N'-(pyridin-2-ylmethylene)butanehydrazide is obtained (1.47 g, 7.10 mmol, 86%).



^{1}H NMR (400 MHz, DMSO, 298K)
Isomer cis: δ 11.41 (s, 1H, H^{9}), 8.58 (d, *J* = 9.6 Hz, 1H, H^{2}), 8.02 (s, 1H, H^{7}), 7.87 (m, 2H, H^{1+5}),) 7.38 (ddt, *J* = 6.5, 4.8, 2.3 Hz, 1H, H^{6}), 3.51 – 3.37 (m, 1H, H^{14}), 2.68 (t, *J* = 7.5 Hz, 1H, H^{11}), 1.73 (p, *J* = 7.0 Hz, 2H, H^{13}).
Isomer trans: δ 11.55 (s, 1H, H^{9}), 8.58 (d, *J* = 9.6 Hz, 1H, H^{2}), 8.17 (s, 1H, H^{7}), 7.87 (m, 2H, H^{1+5})) 7.38 (ddt, *J* = 6.5, 4.8, 2.3 Hz, 1H, H^{6}), 4.52 – 4.49 (t, *J* = 5.1 Hz, t, *J* = 5.3 Hz, 2H, H^{14}), 2.27 (t, *J* = 7.5 Hz, 2H, H^{11}), 1.73 (p, *J* = 7.0 Hz, 2H, H^{13}).

^{13}C NMR (101 MHz, DMSO, 298K)
Isomer cis: δ 175.12 (C^{10}), 153.67 (C^{4}), 149.91(C^{2}), 143.33 (C^{7}), 137.27 (C^{1}), 124.52(C^{6}), 119.87(C^{5}), 60.74 (C^{14}), 29.13 (C^{11}), 27.97 (C^{13}).
Isomer trans: δ 169.45 (C^{10}), 153.80 (C^{4}), 149.91(C^{2}), 146.42 (C^{7}), 137.27 (C^{1}), 124.70 (C^{6}), 120.18(C^{5}), 60.54 (C^{14}), 31.42 (C^{11}), 28.66 (C^{13}).

ESI-MS: calculated for $[C_{10}H_{13}N_3O_2+H]^+$ 208.1081, found, 208.1082

Elemental analysis calculated (%) for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28; found: C, 57.72; H, 6.40; N, 20.44.

Melting point: 104.2 - 105°C

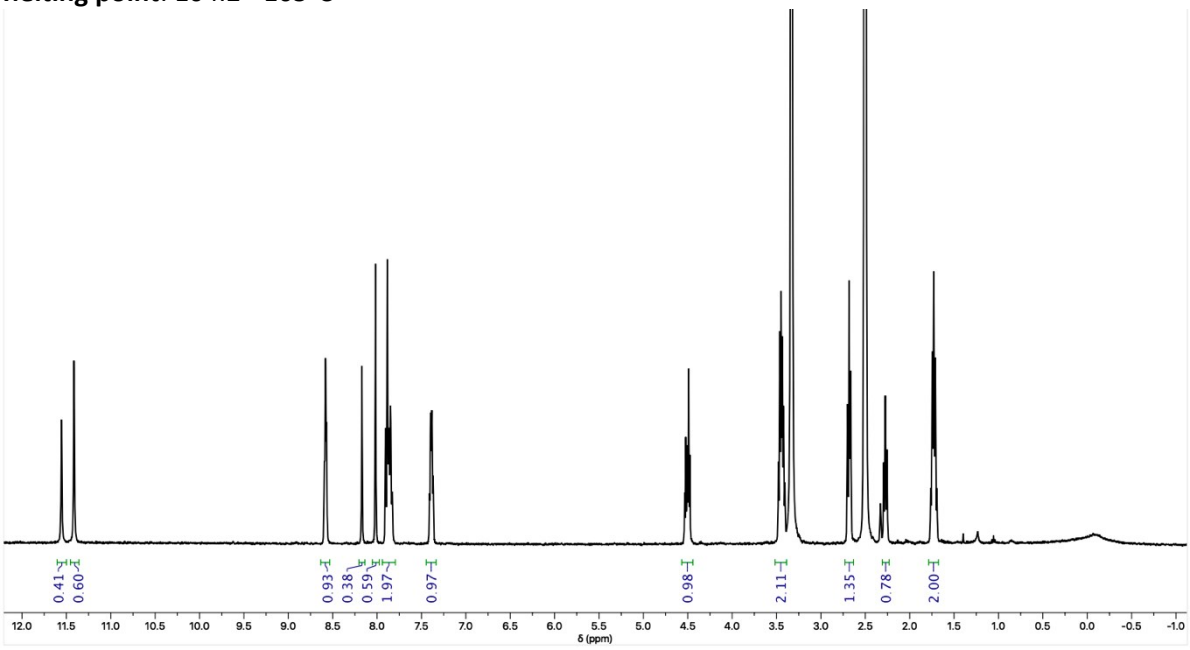


Figure S3. ^{1}H NMR (400 MHz, DMSO, 298 K) of **HA1B3**

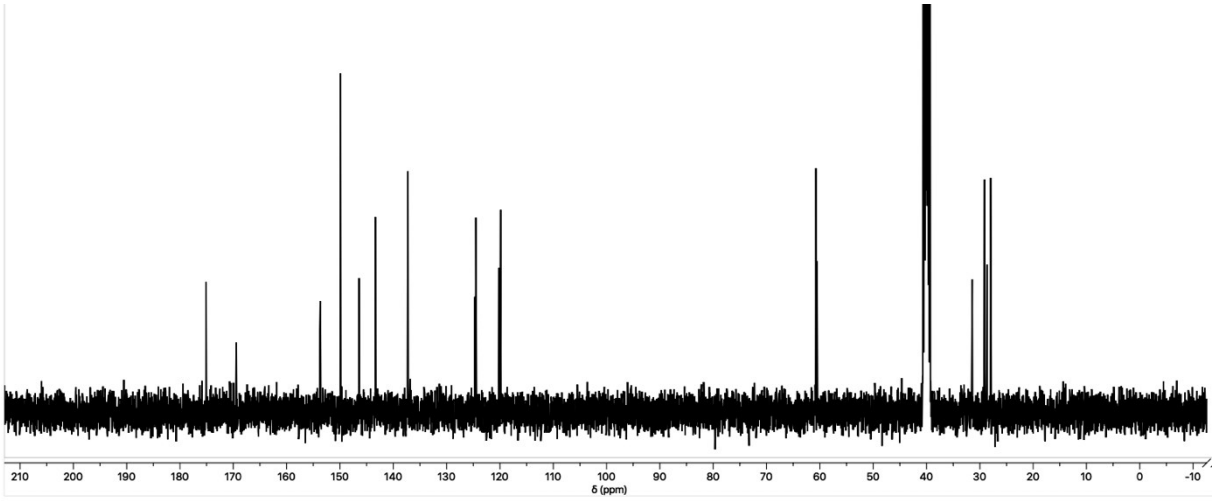
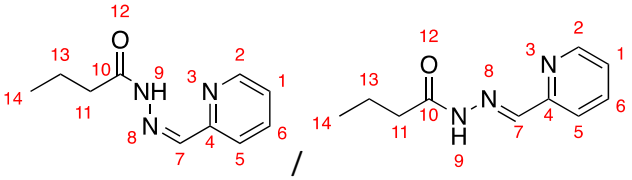


Figure S4. ^{13}C NMR (101 MHz, DMSO, 298 K) of **HA1B3**

Synthesis of (HA1B4) - N'-(pyridin-2-ylmethylene)butyrohydrazide

Butanoic hydrazide (1 eq., 1 g, 9.79 mmol) and 2-pyridine carboxaldehyde (1.05 eq., 1.1 g, 0.98 mL, 10.3 mmol) were solubilized in ethanol (20 mL). The mixture was heated for overnight at 78 °C. After this time, the ethanol is evaporated under vacuum and the mixture is solubilized in 2 volumes of chloroform. 2 volumes of water are added and the middle is placed in a separation funnel. Classical liquid-liquid extraction is performed. The organic phase was washed with $NaHCO_3$ (sat) and HCl 1 M solution. The aqueous phase was washed with brine. The aqueous phase was washed with brine. The combined organic phases were dried over anhydrous $MgSO_4$ and filtered-off. Solvent was evaporated and attempts of recrystallization in hexane did not succeed. Flash chromatography was performed with Petroleum Ether/Ethyl Acetate gradient. Pure N'-(pyridin-2-ylmethylene)butyrohydrazide is obtained (0.68 g, 3.56 mmol, 36%) as yellow solid.



There are 4 isomers of **HA1B4** (cis/trans forms and keto/enol forms). Unfortunately, the peak separation is not good enough (peaks overlap) and we did not focus on this aspect as our final goal is the evaluation of extraction of paramagnetic copper (II).

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ 9.36 (s, broad, 1H, H^9), 8.61 (d, *J* = 5.0 Hz, 1H, H^2), 7.94 (d, *J* = 8.0 Hz, 1H, H^5), 7.88 (s, 1H, H^7), 7.73 (td, *J* = 7.8, 1.8 Hz, 1H, H^1), 7.28 (dd, *J* = 7.4, 5.0 Hz, 1H, H^6), 2.76 – 2.25 (t, *J* = 7.5 Hz - t, *J* = 7.5 Hz, 2H, H^{11}), 1.83 – 1.67 (m, 3H, H^{13}), 1.00 (dt, *J* = 35.4, 7.4 Hz, 3H, H^{14}).
^{13}C NMR (126 MHz, $CDCl_3$, 296K) δ 176.01 - 170.20(C^{10}), 153.20 (C^4), 149.69 (C^2), 143.63 (C^7), 136.62 (C^1), 124.20 (C^6), 120.38 (C^5), 36.12 - 34.69 (C^{11}), 19.02 - 18.17 (C^{13}), 14.10 - 13.81(C^{14}).

ESI-MS: calculated for $[C_{10}H_{13}N_3O+H]^+$ 192.11314, found, 192.11272.

Elemental analysis calculated (%) for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97; found: C, 61.94; H, 7.516; N, 21.27.

Melting point: 92.8 - 94.8°C

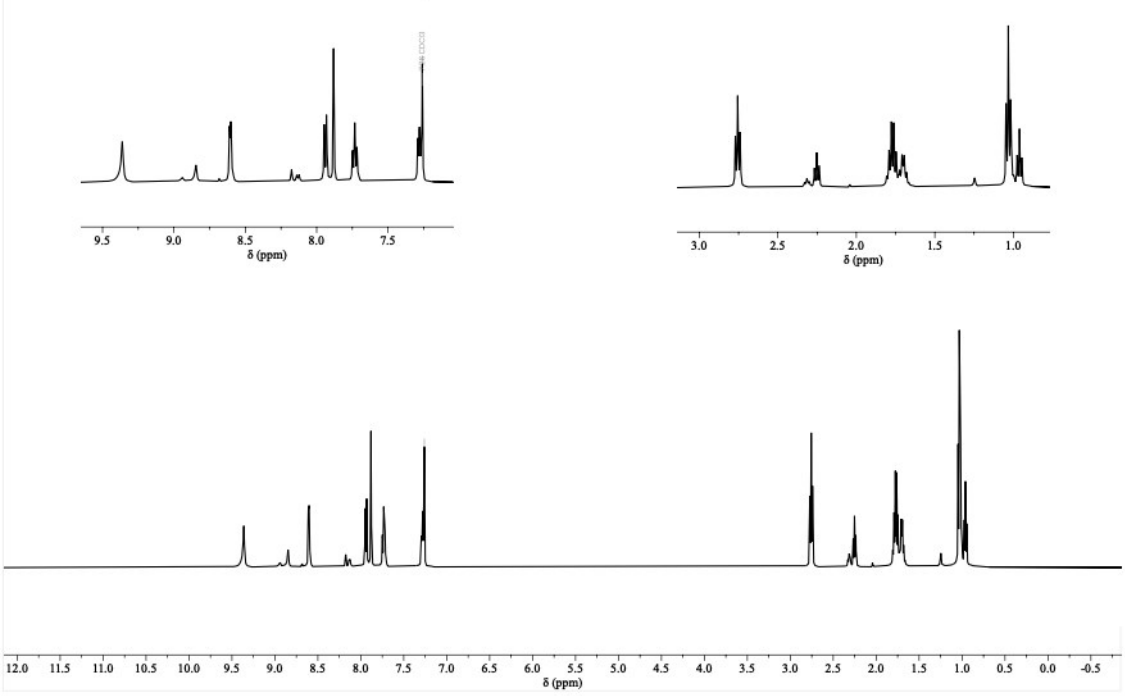


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$, 298K) of **HA1B4**

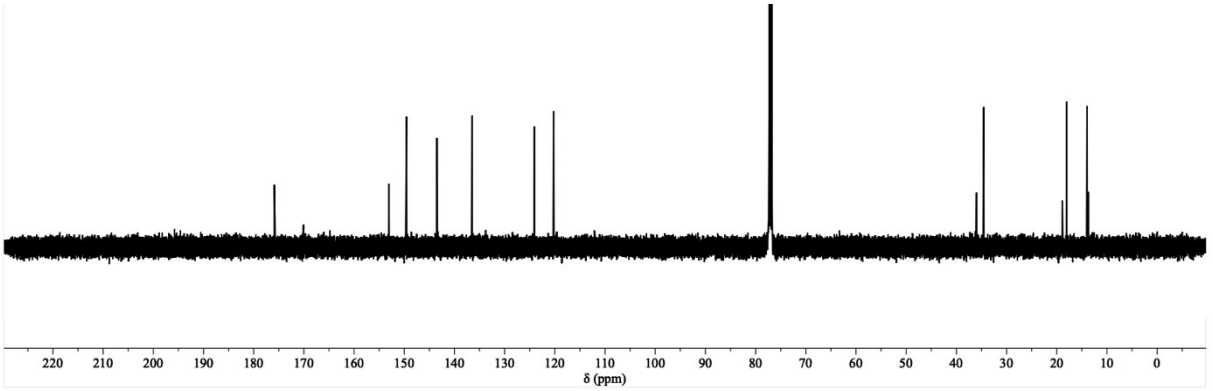
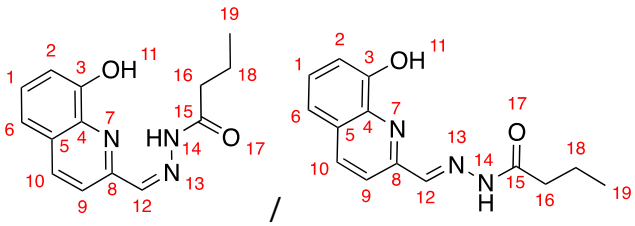


Figure S6. ^{13}C NMR (101 MHz, $CDCl_3$, 298K) of **HA1B4**

Synthesis of (HA2B1) - *N*'-((8-hydroxyquinolin-2-yl)methylene)acetohydrazide – CAS N° 1621711-91-8

See reference [7]

Synthesis of (HA2B4) - *N*'-((8-hydroxyquinolin-2-yl)methylene)butyrohydrazide
Butanoic hydrazide (1 eq., 0.8 g, 7.83 mmol), and 8-hydroxy-2quinolinecarboxaldehyde (1.1 eq., 1.49 g, 8.61 mmol), were solubilized in ethanol (50 mL). Trifluoroacetic acid (5%, 0.05 eq., 39.1 mg, 29.1 µL, 0.39 mmol) was added slowly. The addition makes the mixture turns green. The mixture was heated overnight at 78 °C. After this time, the reaction is red and a white solid precipitate. The middle is filtered on Buchner and the solid is the wished compound. The filtrate is concentrated and Et2O is added to precipitate the residual product. *N*'-((8-hydroxyquinolin-2-yl)methylene)butyrohydrazide is obtained (1.81 g, 7.03 mmol, 90%).



^{1}H NMR (500 MHz, DMSO, 298K)
Enol form: δ 11.71 (s, 1H, H^{14}), 9.81 (s, 1H, H^{11}), 8.36 (s, 1H, H^{12}), 8.32-8.29 (dd, *J* = 8.7, 3.6 Hz, 1H, H^6), 8.02 (d, *J* = 8.6 Hz, 1H, H^9), 7.49 – 7.34 (m, 2H, H^{1+10}), 7.11 (t, *J* = 7.0 Hz, 1H, H^2), 2.25 (t, *J* = 7.3 Hz) (2H, H^{16}), 1.06 (h, *J* = 13.2, 10.4 Hz) (2H, H^{18}), 0.95 (dt, *J* = 18.4, 7.4 Hz, 3H, H^{19}).

Keto form: δ 11.66 (s, 1H, H^{14}), 9.84 (keto) (s, 1H, H^{11}), 8.20 (s, 1H, H^{12}), 8.32-8.29 (dd, *J* = 8.7, 3.6 Hz, 1H, H^6), 8.02 (d, *J* = 8.6 Hz, 1H, H^9), 7.49 – 7.34 (m, 2H, H^{1+10}), 7.11 (t, *J* = 7.0 Hz, 1H, H^2), 2.70 (t, *J* = 7.4 Hz) (2H, H^{16}), 1.64 (hept, *J* = 7.3 Hz) (2H, H^{18}), 0.95 (dt, *J* = 18.4, 7.4 Hz, 3H, H^{19}).

^{13}C NMR (126 MHz, DMSO, 298K)
Enol form: δ 169.40 (C^{15}), 153.84 (C^3), 152.25 (C^8), 146.39 (C^{12}), 138.53 (C^4), 137.02 (C^{10}), 129.23 (C^5), 128.69 (C^1), 118.05 (C^6), 117.74 (C^9), 112.59 (C^2), 36.65 (C^{16}), 18.84 (C^{18}), 14.12 (C^{19}).

Keto form: δ 175.10 (C^{15}), 153.87 (C^3), 152.05 (keto) (C^8), 143.41 (C^{12}), 138.54 (C^4), 137.03 (C^{10}), 129.18 (C^5), 128.59 (C^1); 118.27 (C^6); 117.74 (C^9), 112.68 (C^2), 34.2 (C^{16}), 18.06 (C^{18}), 14.32 (C^{19}).

ESI-MS: calculated for $[C_{14}H_{15}N_3O_2+H]^+$ 258.1237, found, 258.1239.

Elemental analysis calculated (%) for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33; found: C, 65.01; H, 5.94; N, 16.12.

Melting point: 190.4 – 190.8°C

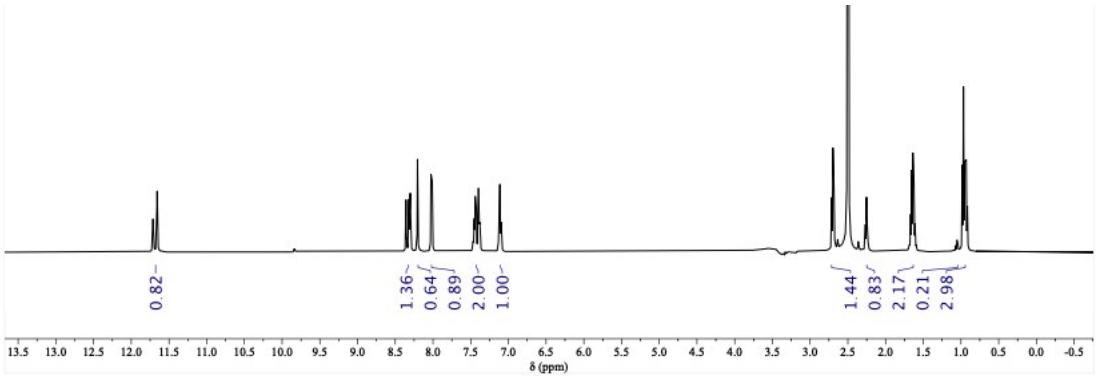


Figure S7. ^{1}H NMR (400 MHz, DMSO, 298K) of **HA2B4**

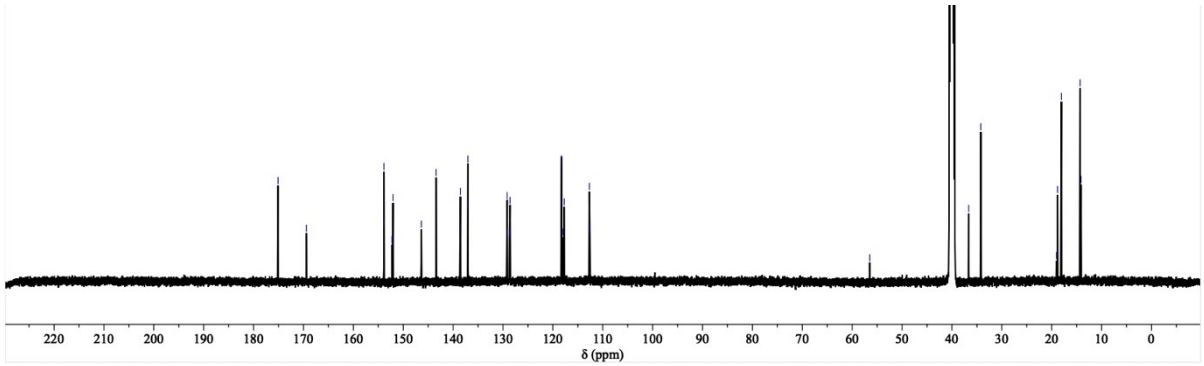
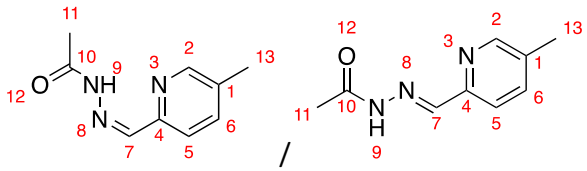


Figure S8. ^{13}C NMR spectrum (126 MHz, DMSO, 298K) of **HA2B4**

Synthesis of (HA3B1) - N'-[(5-methylpyridin-2-yl)methylidene]acetohydrazide – CAS N° 1865862-31-2

5-methylpyridine-2-carbaldehyde (1 eq., 1.64 g, 13.5 mmol) and then acethydrazide (1 g, 13.5 mmol) are introduced in a flask without any solvent. The solids are heated until they melt and the neat reaction proceed for 8h at 80°C. After 8h, a yellow solid is obtained and solubilized in chloroform. The solution is washed with brine and dried on anhydrous Na_2SO_4. The N'-[(5-methylpyridin-2-yl)methylidene]acetohydrazide is obainted (1.07 g, 6.075 mmol, 49%).



/

^{1}H NMR (400 MHz, $CDCl_3$, 298K)
Isomer cis: δ 8.98 (s, 1H, H^9), 8.43 (d, J = 2.1 Hz, 1H, H^2), 7.83 (t, J = 4.0 Hz, 2H, H^{5+7}), 7.54 (dd, J = 8.2, 2.2 Hz, 1H, H^6), 2.39 (s, 3H, H^{13}), 2.37 (s, 3H, H^{11}).

Isomer trans: δ 8.83 (s, 1H, H^9), 8.43 (d, J = 2.1 Hz, 1H, H^2), 8.11 (s, 1H, H^7), 8.04 (d, J = 8.3 Hz, 1H, H^5), 7.54 (dd, J = 8.2, 2.2 Hz, 1H, H^6), 2.39 (s, 3H, H^{13}), 2.15 (s, 1H, H^{11}).

^{13}C NMR (126 MHz, $CDCl_3$, 296K) δ 173.73 (C^{10}), 150.49 (C^4), 150.06 (C^2), 144.15 (C^7), 137.22 (C^6), 134.27 (C^1), 120.04 (C^5), 20.53 (C^{11}), 18.62 (C^{13}).

ESI-MS: calculated for $[C_9H_{11}N_3O+H]^+$ 178.0975, found, 178.0978.

Elemental analysis calculated (%) for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71; found: C, 60.66; H, 6.33; N, 23.99.

Melting point: 152 – 153.1°C

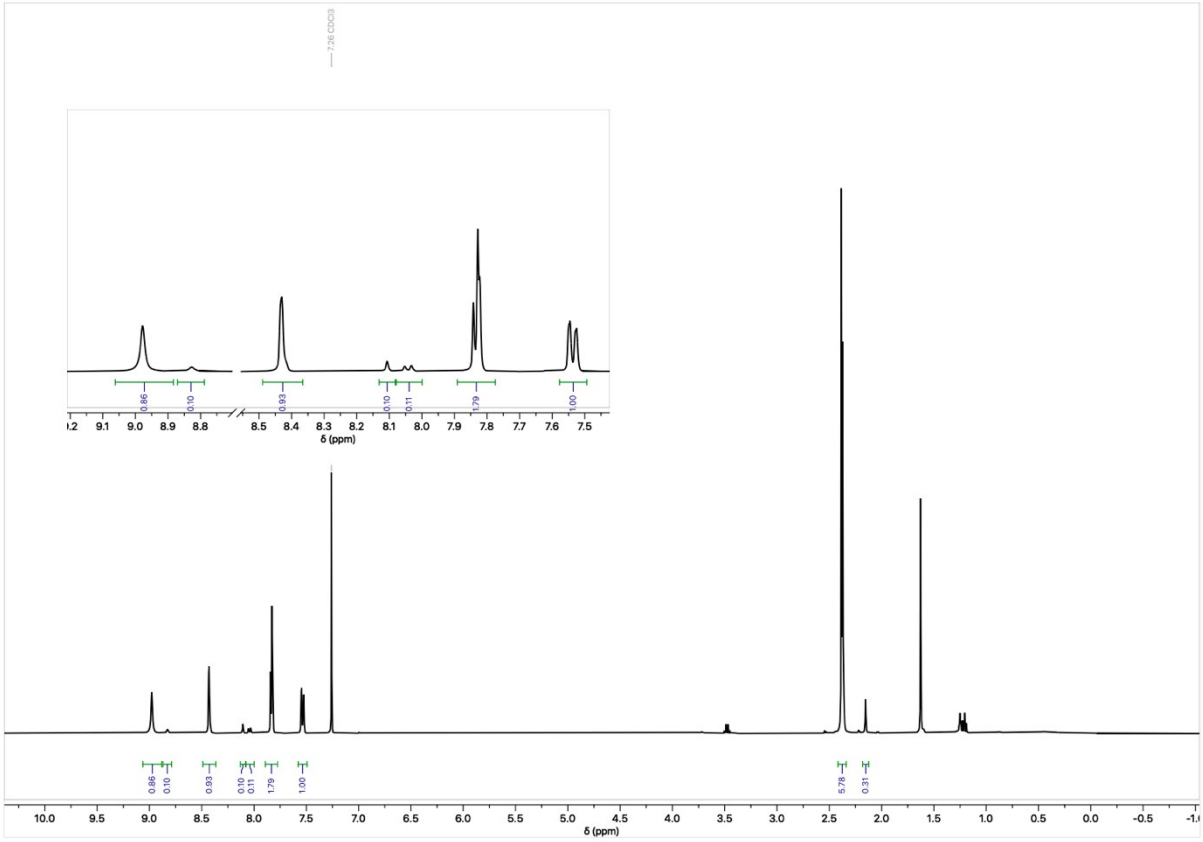


Figure S9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of **HA3B1**

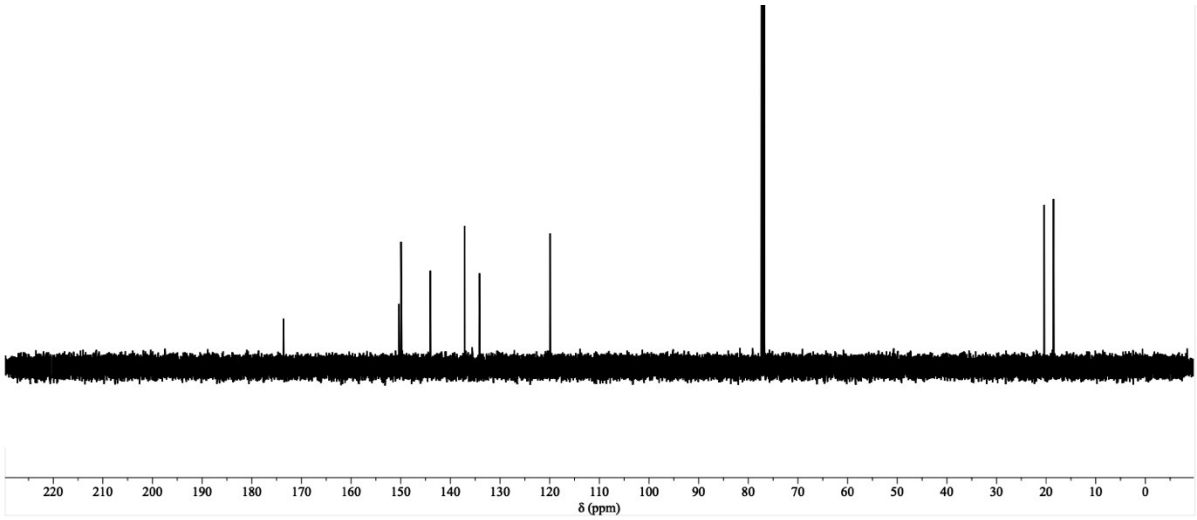
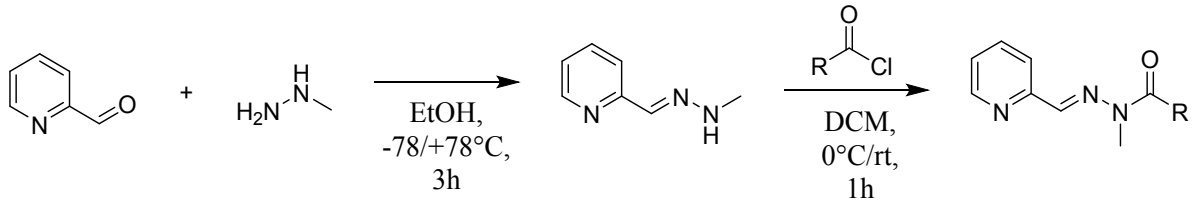


Figure S10. ^{13}C NMR spectrum (126 MHz, CDCl3, 296K) of **HA3B1**

2.2 General procedure for the preparation of the methylated acylhydrazones

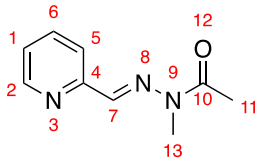


Scheme S2. General procedure for the preparation of the methylated acylhydrazones

Step 1. 2-pyridine carboxaldehyde (1 eq., 1 g, 6.512 mL, 68.15 mmol) and methylhydrazine (1 eq., 1 g, 3.651 mL, 68.15 mmol) were mixed at solid stated at -78°C. The reaction was left warm-up to room temperature and ethanol (50 mL) was added. The reaction was heated to 78°C for 3 hours. The final mixture was evaporated and then purified by distillation by a Kugelrhor apparatus. 2-((2-methylhydrazineylidene)methyl)pyridine is obtained and will be used in the second step.
Step 2. To 1 equivalent of 2-((2-methylhydrazineylidene)methyl)pyridine solubilized in dichloromethane and cooled down to 0°C, 1.1 equivalent of acyl chloride is added dropwise. The reaction is left to warm-up to room temperature for few hours.

Synthesis of (Me-A1B1) - *N*-methyl-*N*'-(pyridin-2-ylmethylene)acetohydrazide

Step 2. A solution of 2-((2-methylhydrazineylidene)methyl)pyridine (1 eq., 1.36 g, 10.1 mmol) in dichloromethane (60 mL) was cooled down to 0 °C in an ice bath followed by the dropwise addition of acetyl chloride (1.1 eq., 0.869 g, 0.79 mL, 11.1 mmol). The reaction mixture was left to warm-up to room temperature for 1 hour.
After this time, the reaction mixture was diluted with dichloromethane (100 mL) and organic phase was washed with $NaHCO_3$ (sat). Then, it was washed with HCl 1M. The aqueous phase was basified with Na_2CO_3 (sat) and the product was extracted with dichloromethane. Organic phase was dried over anhydrous Na_2SO_4, which was filtered-off. Solvent was evaporated on the rotavapor. The solid obtained is recrystallized in cold ethanol. *N*-methyl-*N*'-(pyridin-2-ylmethylene)acetohydrazide is obtained in a quantitative yield.



^{1}H NMR (400 MHz, $CDCl_3$, 298K) δ 8.62 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, H^2), 7.98 (dt, *J* = 8.0, 1.1 Hz, 1H, H^5), 7.82 (s, 1H, H^7), 7.76 (td, *J* = 7.8, 1.8 Hz, 1H, H^6), 7.35 – 7.28 (m, 1H, H^1, overlapping residual $CDCl_3$), 3.40 (s, 3H, H^{13}), 2.50 (s, 3H, H^{11}).
^{13}C NMR (126 MHz, $CDCl_3$, 298K) δ 172.91 (C^{10}), 153.98 (C^4), 149.43 (C^2), 139.65 (C^7), 136.55 (C^1), 123.76 (C^6), 119.70 (C^5), 27.80 (C^{13}), 21.59 (C^{11}).

ESI-MS: calculated for $[C_9H_{11}N_3O+H]^+$ 178.09749, found, 178.09709.

Elemental analysis calculated (%) for $C_9H_{11}N_3O$: C, 61; H, 6.26; N, 23.71; found: C, 61.13; H, 6.25; N, 23.79.

Melting point: 77.3 - 78.3°C

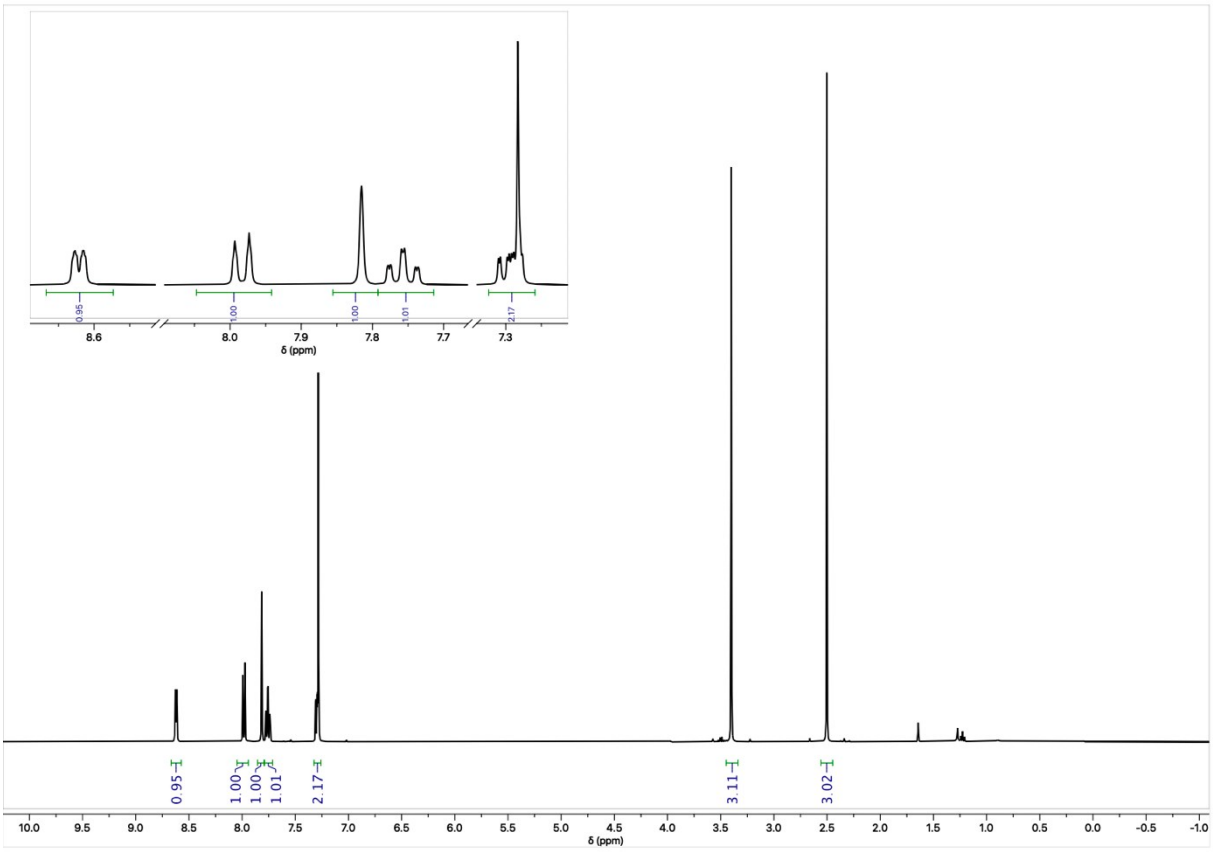


Figure S11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of **Me-A1B1**

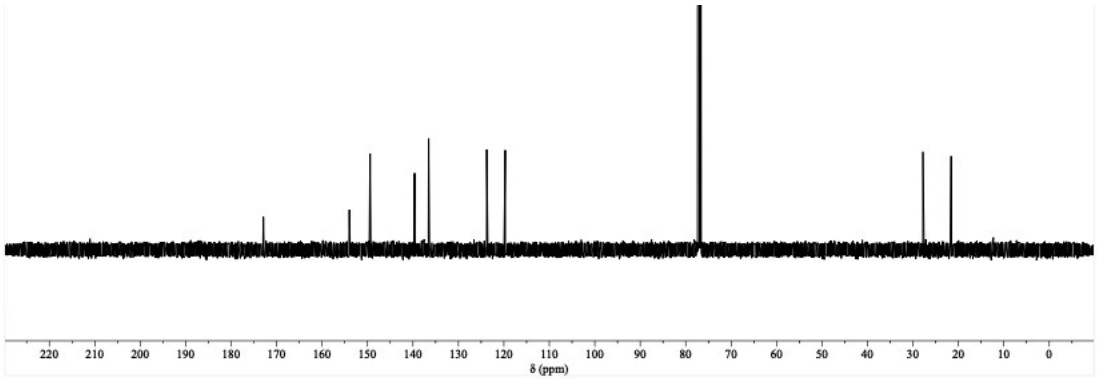
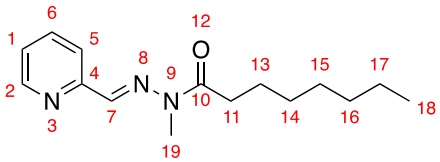


Figure S12. ^{13}C NMR spectrum (126 MHz, CDCl3, 298K) of **Me-A1B1**

Synthesis of (Me-A1B2) - N-methyl-N'(pyridin-2-ylmethylene)octanehydrazide

Step 2. 2-((2-methylhydrazineylidene)methyl)pyridine (1 eq., 1 g, 7.4 mmol) is solubilized in dichloromethane (25 mL). Triethylamine (3 eq., 2.25 g, 3.09 mL, 22.2mmol) is added slowly. The mixture is cooled down to 0 °C in an ice bath. The octanoyl chloride (1.05 eq., 1.26 g, 1.34 mL, 7.77 mmol) in solution in 25 mL of dichloromethane is added dropwise. The reaction is let to warm-up overnight. Dichloromethane and water are added and the organic phase is washed with $NaHCO_3$ (sat) and HCL 1M solution. The organic phase is washed with brine, dried on anhydrous Na_2SO_4, filtered and concentrated. The recrystallization affords N-methyl-N'(pyridin-2-ylmethylene)octanehydrazide (1.28 g, 4.9 mmol, 84%).



^{1}H NMR (400 MHz, $CDCl_3$, 298K) δ 8.62 (dt, *J* = 4.9, 1.4 Hz, 1H, H^{2}), 7.97 (dt, *J* = 8.0, 1.2 Hz, 1H, H^{5}), 7.82 (s, 1H, H^{7}), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H, H^{1}), 7.32 – 7.27 (m, 1H, H^{6}, overlapping residual $CDCl_3$), 3.40 (s, 3H, H^{19}), 2.90 (t, 2H, H^{11}), 1.74 (p, *J* = 7.5 Hz, 2H, H^{13}), 1.50 – 1.08 (m, 8H, $H^{14+15+16+17}$), 0.89 (t, 3H, H^{18}).

^{13}C NMR (126 MHz, $CDCl_3$, 296K) δ 175.46 (C^{10}), 154.15 (C^{4}), 149.41 (C^{2}), 139.28 (C^{7}), 136.53 (C^{1}), 123.67 (C^{6}), 119.61 (C^{5}), 33.62 (C^{11}), 27.95 (C^{19}), 25.31 (C^{13}), 31.75, 29.50, 29.15, 22.66 ($C^{14+15+16+17}$), 14.10 (C^{18}).

ESI-MS: calculated for $[C_{15}H_{23}N_3O+H]^+$ 262.1914, found, 262.1915.

Elemental analysis calculated (%) for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08; found: C, 69.05; H, 8.96; N, 16.19.

Melting point: 52.8 - 53.8°C

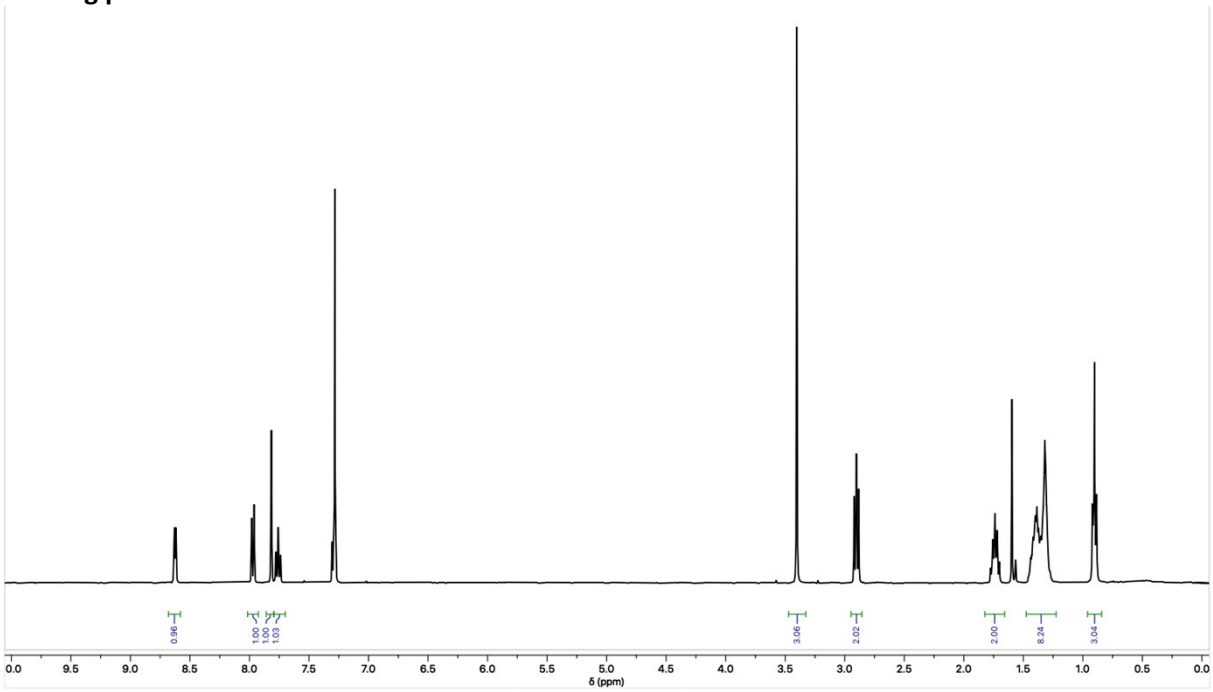


Figure S13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of **Me-A1B2**

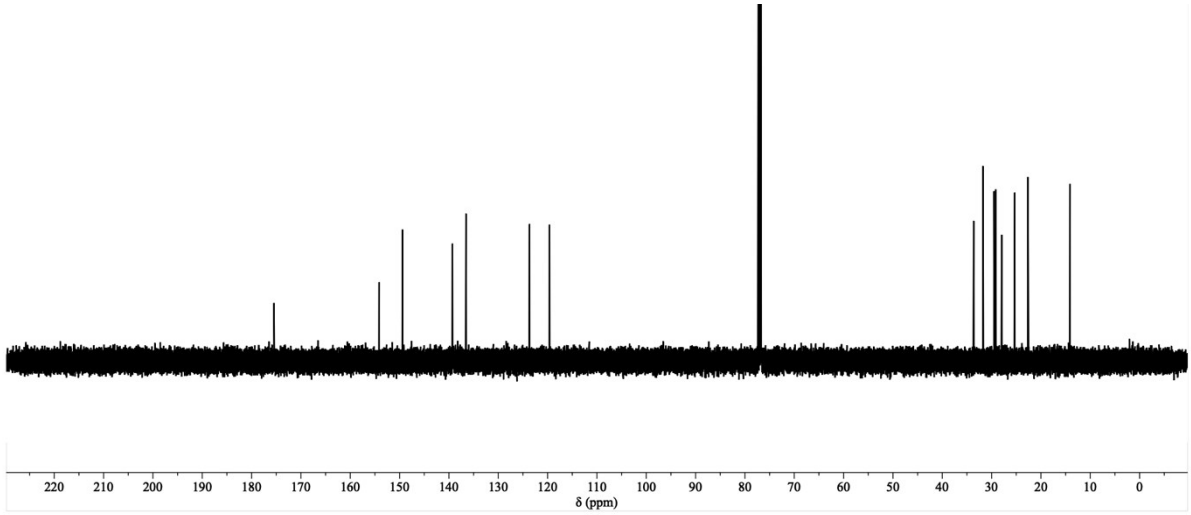
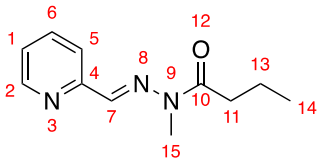


Figure S14. ^{13}C NMR spectrum (126 MHz, CDCl3, 296K) of **Me-A1B2**

Synthesis of (Me–A1B4) - N-methyl-N'(pyridin-2-ylmethylene)butyrohydrazide

Step 2. 2-((2-methylhydrazineylidene)methyl)pyridine (1 eq., 1 g, 7.4 mmol) is solubilized in dichloromethane (25 mL). Triethylamine (3 eq., 2.25 g, 3.09 mL, 22.2mmol) is added slowly. The mixture is cooled down to 0 °C in an ice bath. The butyryl chloride (1.1 eq., 0.83 g, 0.85 mL, 7.83 mmol) in solution in 25 mL of dichloromethane is added dropwise. After the addition, the temperature was left to warm-up to room temperature. After 2h, the reaction mixture was diluted with dichloromethane (20 mL) and organic phase was washed with HCl 1M. The aqueous phase was then neutralized with Na_2CO_3 (sat) and the product was extracted with dichloromethane. Organic phase was dried over anhydrous $MgSO_4$, which was filtered-off. Solvent was evaporated on the rotavapor. The solid obtained is recrystallized in cold hexane. The product N-methyl-N'(pyridin-2-ylmethylene)butyrohydrazide is afforded with a 94% yield (1.44 g, 7.01 mmol, 94%).



^{1}H NMR (400 MHz, $CDCl_3$, 298K) δ 8.59 (dt, *J* = 5.0, 1.4 Hz, 1H, H^2), 7.95 (dd, *J* = 8.0, 1.4 Hz, 1H, H^5), 7.79 (s, 1H, H^7), 7.73 (td, *J* = 7.7, 1.7 Hz, 1H, H^6), 7.42 – 7.14 (m, 1H, H^1, overlapping residual $CDCl_3$), 3.38 (s, 3H, H^{15}), 2.86 (t, *J* = 7.5 Hz, 2H, H^{11}), 1.75 (h, *J* = 7.4 Hz, 2H, H^{13}), 1.01 (t, *J* = 7.4 Hz, 3H, H^{14}).

^{13}C NMR (101 MHz, $CDCl_3$, 298K) δ 175.25 (C^{10}), 154.12 (C^4), 149.38 (C^2), 139.25 (C^7), 136.58 (C^6), 123.68 (C^1), 119.64 (C^5), 35.51 (C^{15}), 27.94 (C^{11}), 18.67 (C^{13}), 14.08 (C^{14}).

ESI-MS: calculated for $[C_{11}H_{15}N_3O+H]^+$ 206.12879, found, 206.12830.

Elemental analysis calculated (%) for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47; found: C, 63.71; H, 7.37; N, 20.40.

Melting point: liquid at room temperature

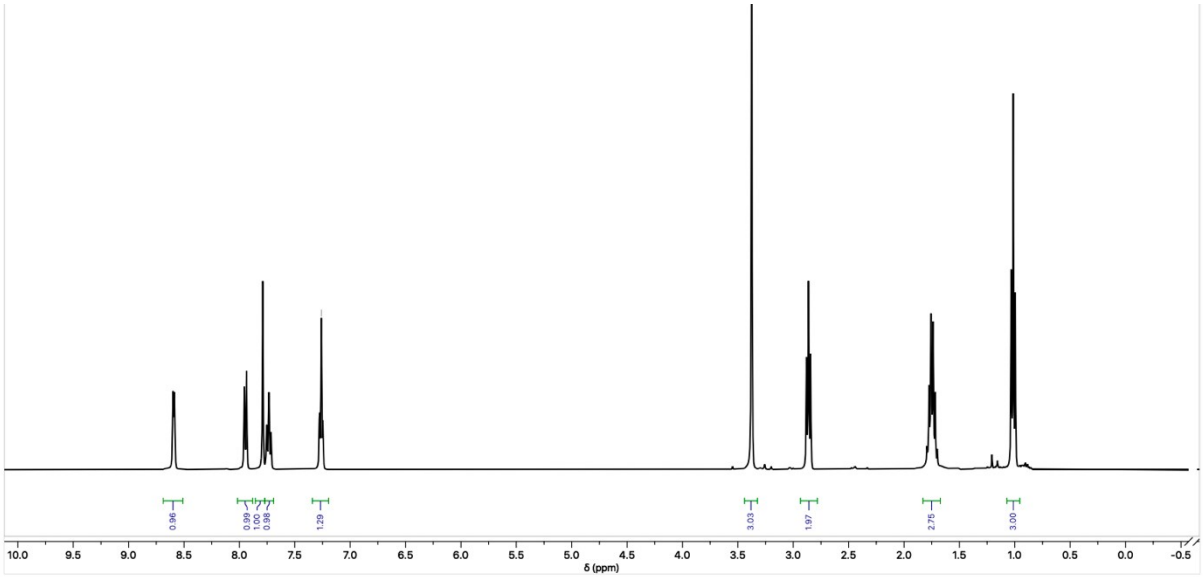


Figure S15. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of **Me-A1B4**

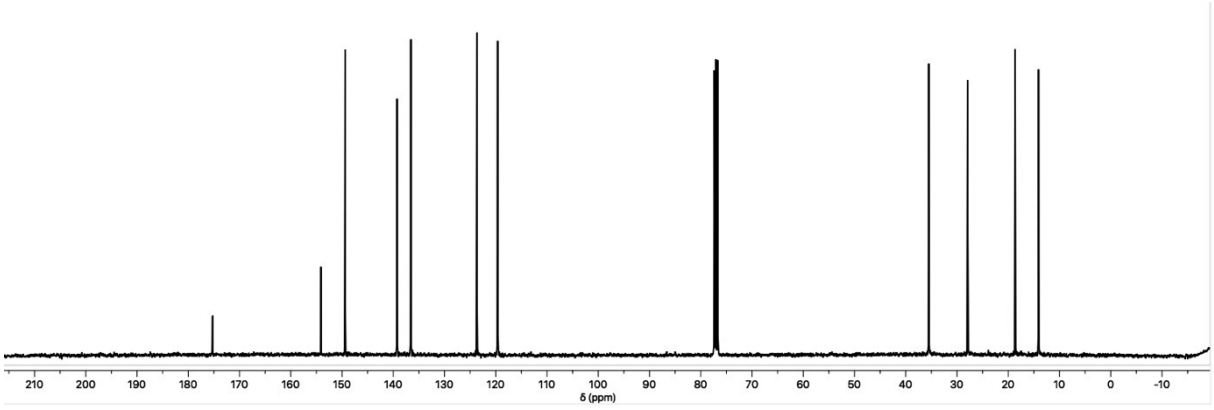


Figure S16. ^{13}C NMR spectrum (101 MHz, $CDCl_3$, 298K) of **Me-A1B4**

2.3 General procedure for the preparation of relevant metal complexes

2 equivalents of ligand are solubilized in 1 volume of acetonitrile. In another flask, 1 equivalent of the metal salt is solubilized in 1 volume of acetonitrile. The ligand solution is stirred and the metal solution is slowly added. Let the complex precipitates and wash the solid with cold ethanol then with diethyl ether. The solid is dried under vacuum at 40°C.

To get deprotonated ligand, add the corresponding equivalent of diisopropylethylamine in the ligand solution before the addition of the metal salt.

Synthesis of [Cu(II)(**HA1B1**)$_2$] $(NO_3)_2$: N'-(pyridin-2-ylmethylene)acethydrazide (2 eq., 0.3 g, 1.84 mmol) is solubilized in 5 mL of acetonitrile. Copper nitrate trihydrate (1 eq., 0,222 g, 0.92 mmol) is solubilized in 5 mL of acetonitrile. The copper solution is slowly added to the ligand solution and the solution turns green. After 10 minutes of stirring, the complex starts to precipitate. After 2h of stirring, the precipitate is filtered and wash with cold ethanol and diethyl ether. The solid is dried under vacuum. The complex is obtained in a quantitative yield.

Synthesis of [Cu(II)(**HA1B1**)(**A1B1**)] (NO_3): The same procedure is made to synthesize the monodeprotonated complex. After the ligand solubilization, 1 equivalent of diisopropylethylamine (1. eq., 118.9 mg, 152 µL, 0.92 mmol) is added to the solution.

Synthesis of [Cu(II)(**A1B1**)$_2$]: The same procedure is made to synthesize the dideprotonated complex. After the ligand solubilization, 2.5 equivalent of diisopropylethylamine (2.5 eq., 297.2 mg, 380 µL, 2.3 mmol) is added to the solution.

3 Choice of the library

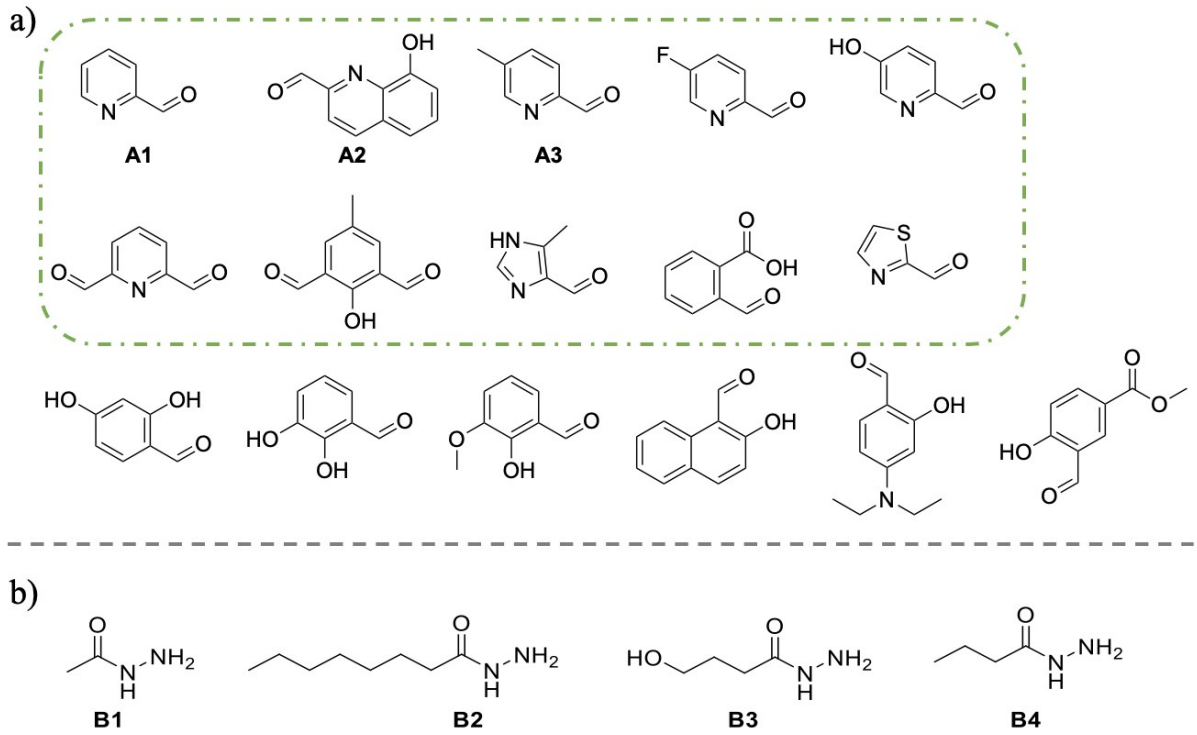


Figure S17. a) Aldehydes selected to be components of the library: the group surrounded by a green circle reacts with B2 to form acylhydrazone quantitatively at room temperature within 4h – b) Selected hydrazides

4 Preliminary study of extraction properties

4.1 Extraction properties of selected ligands evaluated by direct observation

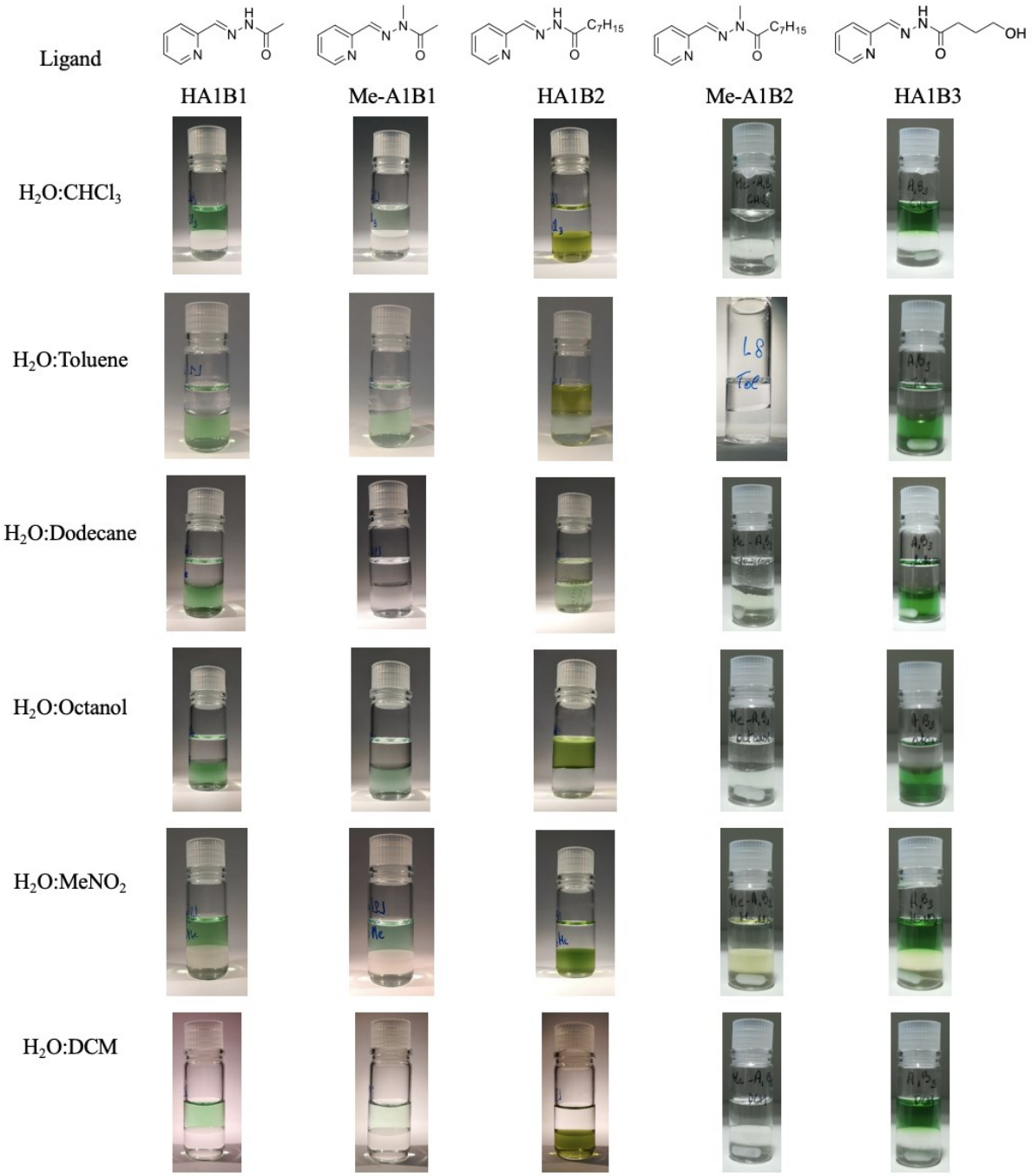


Figure S18. Extraction tests of **HA1B1**, **Me–A1B1**, **HA1B2**, **Me–A1B2**, **HA1B3**

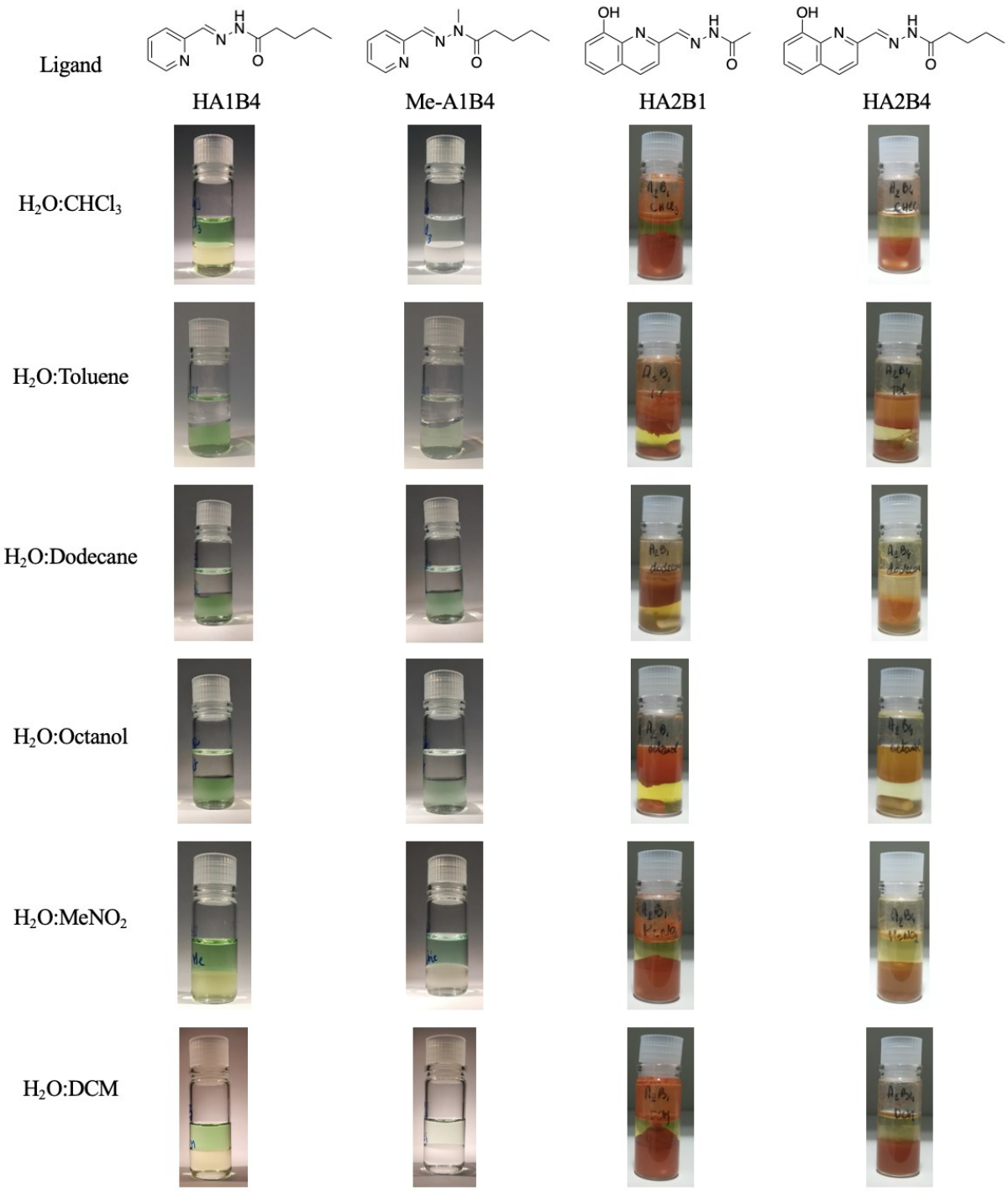


Figure S19. Extraction tests of **HA1B4**, **Me–A1B4**, **HA2B1**, **HA2B4**

4.2 Evaluation of pKa

Simulation of predominance diagram of **HA1B1** and **HAB2** along pH scale done with MarvinSketch software from ChemAxon.

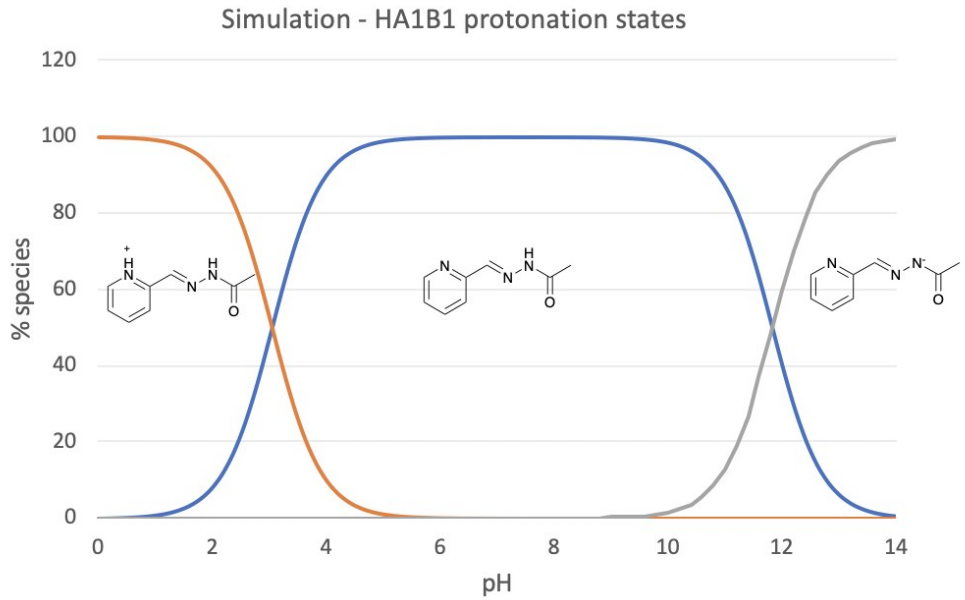


Figure S20. Predominance diagram of **HA1B1** protonated/deprotonated forms

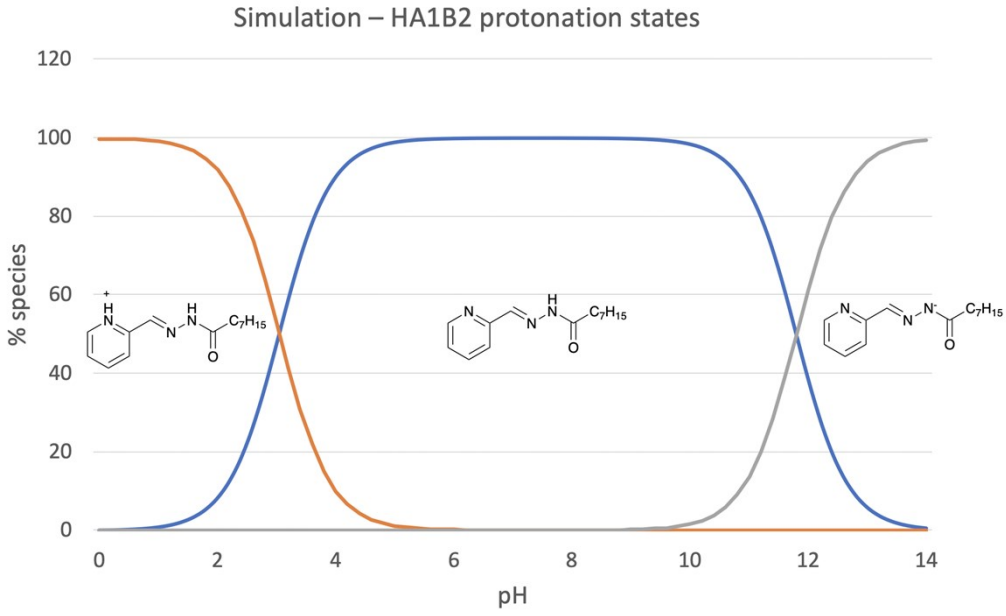


Figure S21. Predominance diagram of **HA1B1** protonated/deprotonated forms

Titration curves of Cu(**HA1B1**)$_2$ and Cu(**HA1B2**)$_2$ by NaOH (0.5 M)

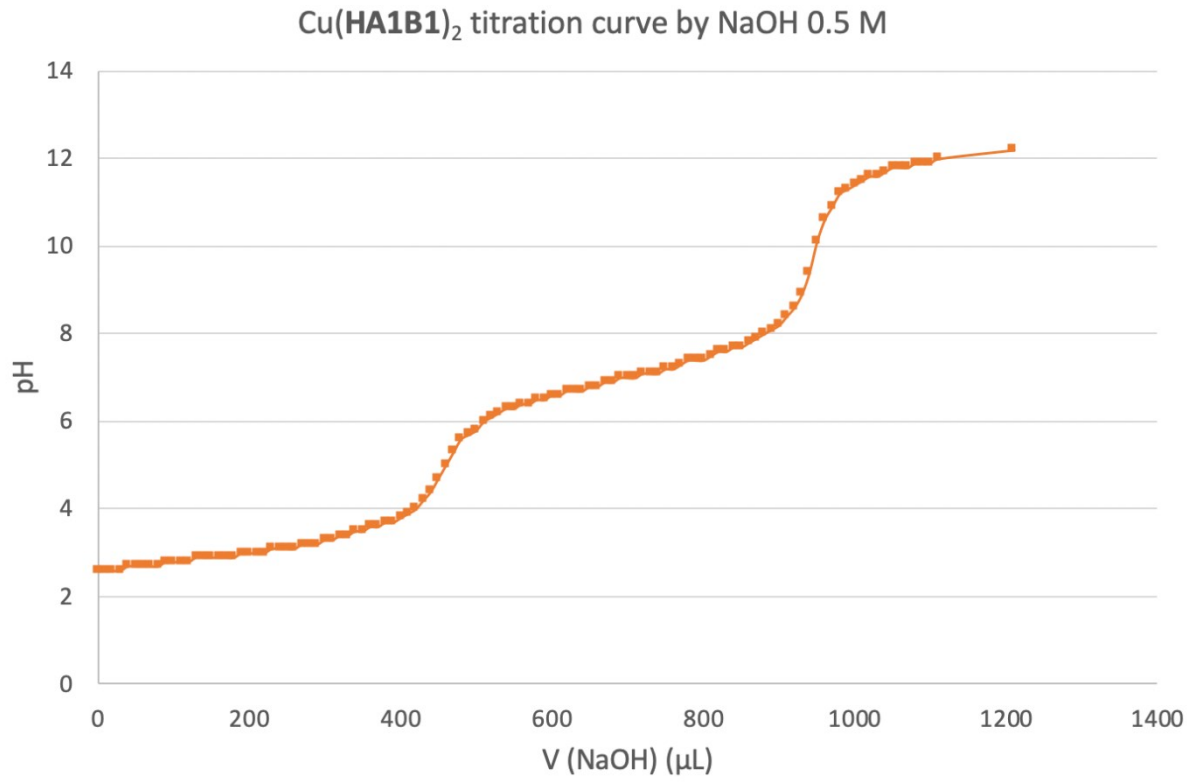


Figure S22. Titration of Cu(**HA1B1**)$_2$ by NaOH (0.5 M)

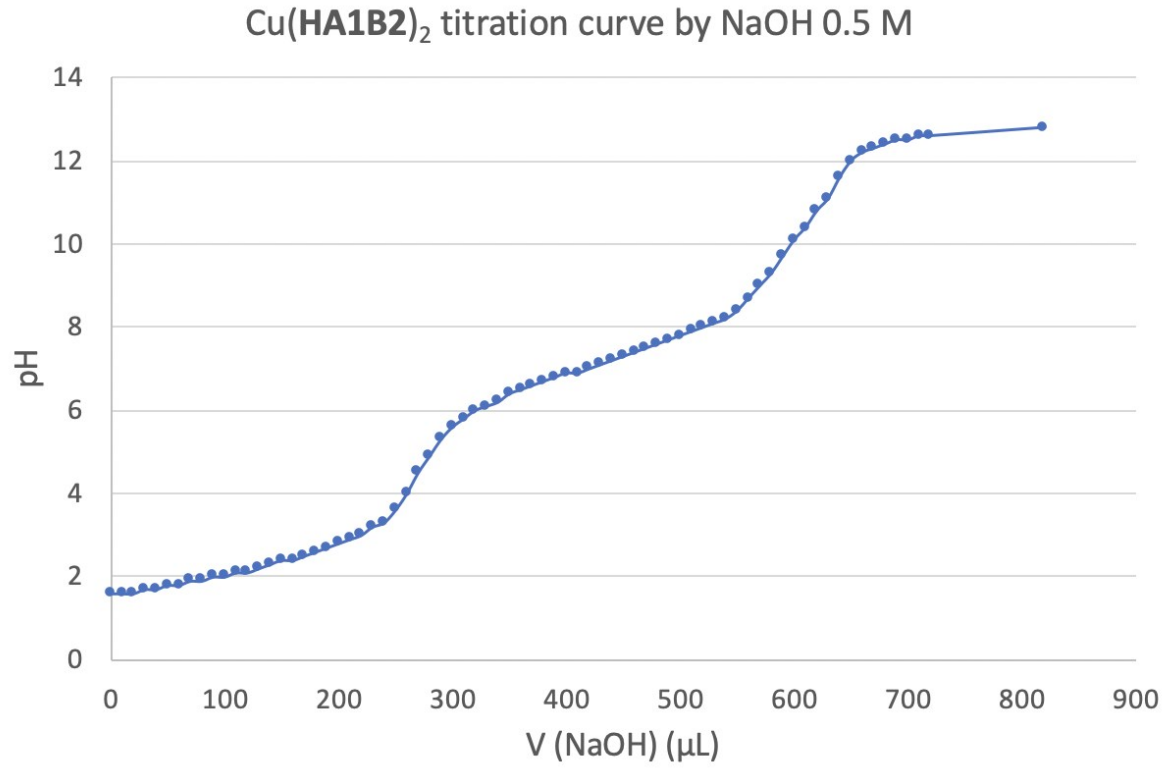


Figure S23. Titration of Cu(**HA1B2**)$_2$ by NaOH (0.5 M)

4.3 Standard procedure for extraction properties evaluation by UV-visible spectrophotometry

Fresh stock solution of copper (II) nitrate is prepared at 500 mM in deionized water. Fresh stock solutions of ligands are prepared at 500 mM in chloroform or water according to the solubility of the ligand.
In a vial, 960 µL of water and 40 µL of copper stock solution are introduced. Then 920 µL of chloroform and 80 µL of ligand stock solution are added. The system, composed of 1 mL of water and 1 mL of chloroform is stirred for 1 hour. Then the vial is centrifuged for 1 minute at 2000 rpm. 3 mL of each phase are placed in a 1 cm long quartz cuvette and analyzed by UV-visible spectrophotometry.

4.4 Extraction properties of selected ligands evaluated by UV-visible spectrophotometry

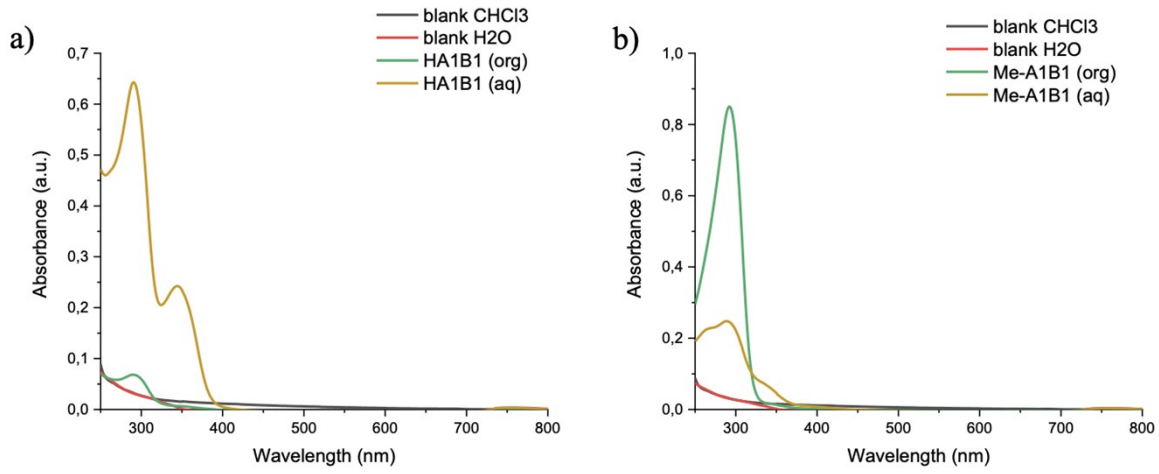


Figure S24. Extraction test – a) **HA1B1** – b) **Me–A1B1** in water: chloroform (1:1) with 0.5 equiv. of $Cu(NO_3)_2$

With **HA1B1**, a peak at λ_{max} = 344 nm is present in the water phase only and demonstrate the formation of the complex between [Cu(II)(**HA1B1**)$_2$]. With **Me–A1B1**, there is no peak in the visible part of the spectra and the majority of **Me–A1B1** is free in the chloroform phase.

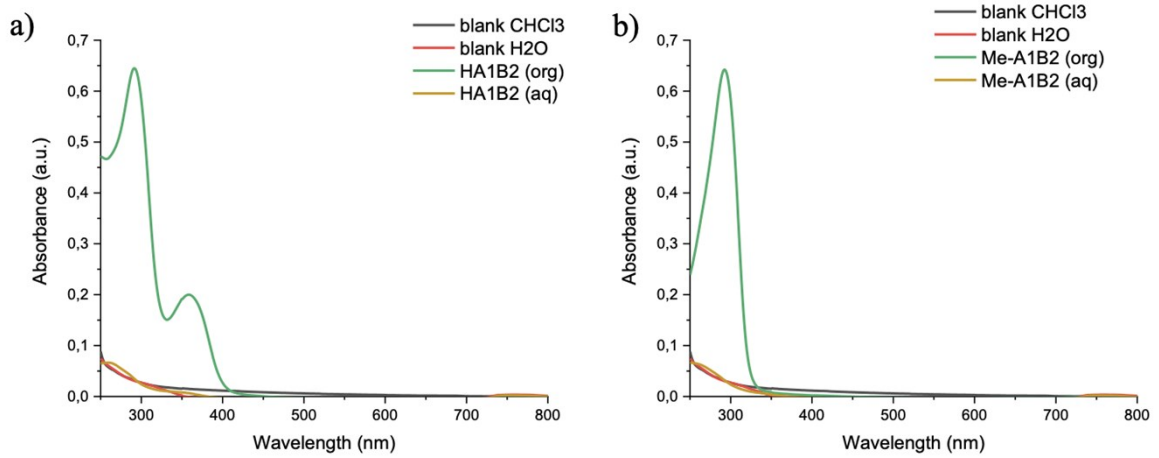


Figure S25. Extraction test – a) **HA1B2** – b) **Me–A1B2** in water: chloroform (1:1) with 0.5 equiv. of $Cu(NO_3)_2$

With **HA1B2**, a colorful peak at λ_{max} = 358 nm is present in the chloroform phase only and proves the transfer of copper in the organic phase by a coordination phenomenon with **HA1B2**. With **Me–A1B2**, there is no peak in the visible part of the spectra and the majority of **Me–A1B2** is free in the chloroform phase.

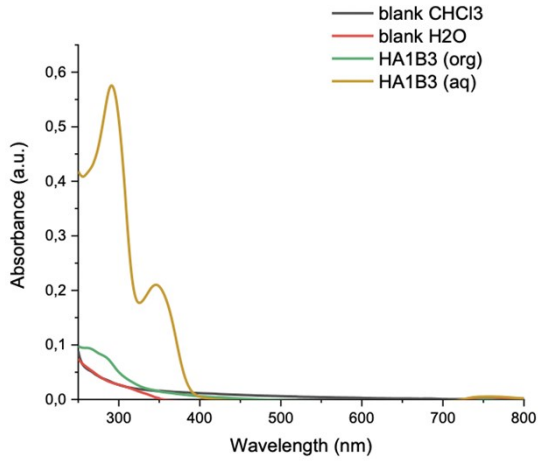


Figure S26. Extraction test – **HA1B3** in water: chloroform (1:1) with 0.5 equiv. of $Cu(NO_3)_2$

A colorful peak at λ_{max} = 346 nm is present in the water phase only and demonstrate the formation of the complex between [Cu(II)(**HA1B3**)$_2$]

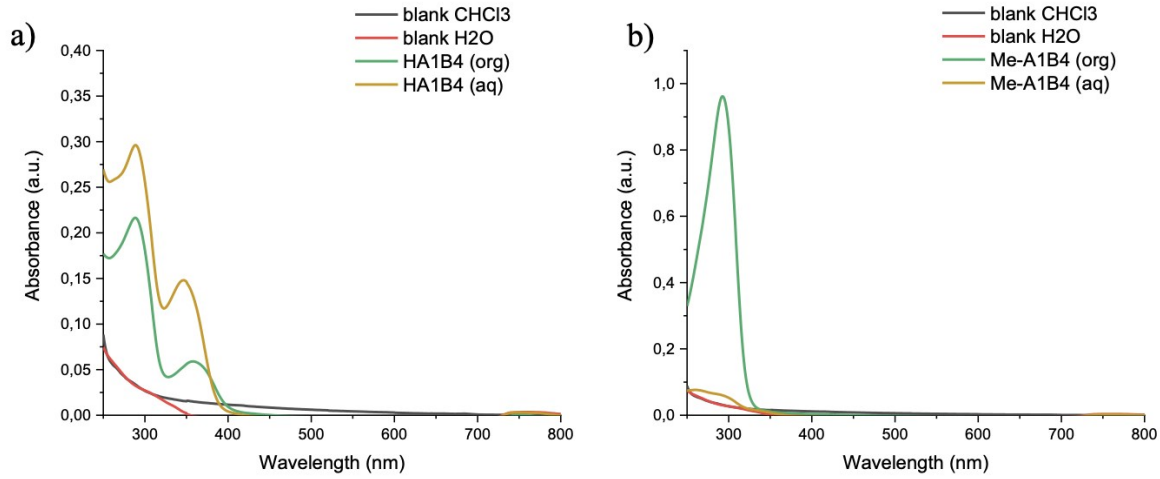


Figure S27. Extraction test – a) **HA1B4** – b) **Me–A1B4** in water: chloroform (1:1) with 0.5 equiv. of $Cu(NO_3)_2$

With **HA1B4**, the formation of coordination complex is clear and the formed specie distributes into both phases. The peak in the chloroform phase is at λ_{max} = 358 nm whereas the one in the water is at λ_{max} = 346 nm. The distribution is about 25:75 (chloroform: water). With **Me–A1B4**, there is no peak in the visible part of the spectra and the majority of **Me–A1B4** is not coordinated and in the chloroform phase.

5 Dynamic Covalent Library - Kinetic and thermodynamic behaviors

5.1 Standard procedure in single phase system

All the reactions are followed by ^{1}H NMR at 296K and performed at 20mM in NMR tubes. Stock solutions at 500 mM of reactants and references were prepared except metal complexes. For the study of metal complexes exchanges, the complexes are formed in situ by introduction of the ligand (2 equiv.) and then the metal salt (1 equiv.). An initial NMR spectrum is performed to verify the complete formation of the complex.
Internal standards were used in both middles: trimethylsilylpropanoic acid in D_2O (signal integrate for 9H) and hexamethylsiloxane in $CDCl_3$ (signal integrate for 18H).

In an NMR tube, 450 µL of deuterated solvent, 10 µL of the internal standard (500 mM) and 20 µL of the first reactant (500 mM) are introduced. Then the pD is adjusted by addition of NaOD or DCl in the tube. The first spectrum is recorded when the tube contains only one reactant. Then, the addition of 20 µL of the second reactant (500 mM) is made. The tube is vigorously agitated and the spectrum is registered as fast as possible. The variation of volume (addition of 20 µL on a total amount of 500 µL) is considered as negligible. Then the kinetic study is followed over a determined period of time (maximum 3 days) and the time interval between two spectra is adjusted along the studies.
After phase and baseline corrections, spectra are integrated in MestreNova 12.0.1 using the Data analysis tool. The integration values are corrected to correspond to one single proton.

5.2 Single phase – Formation of acylhydrazones

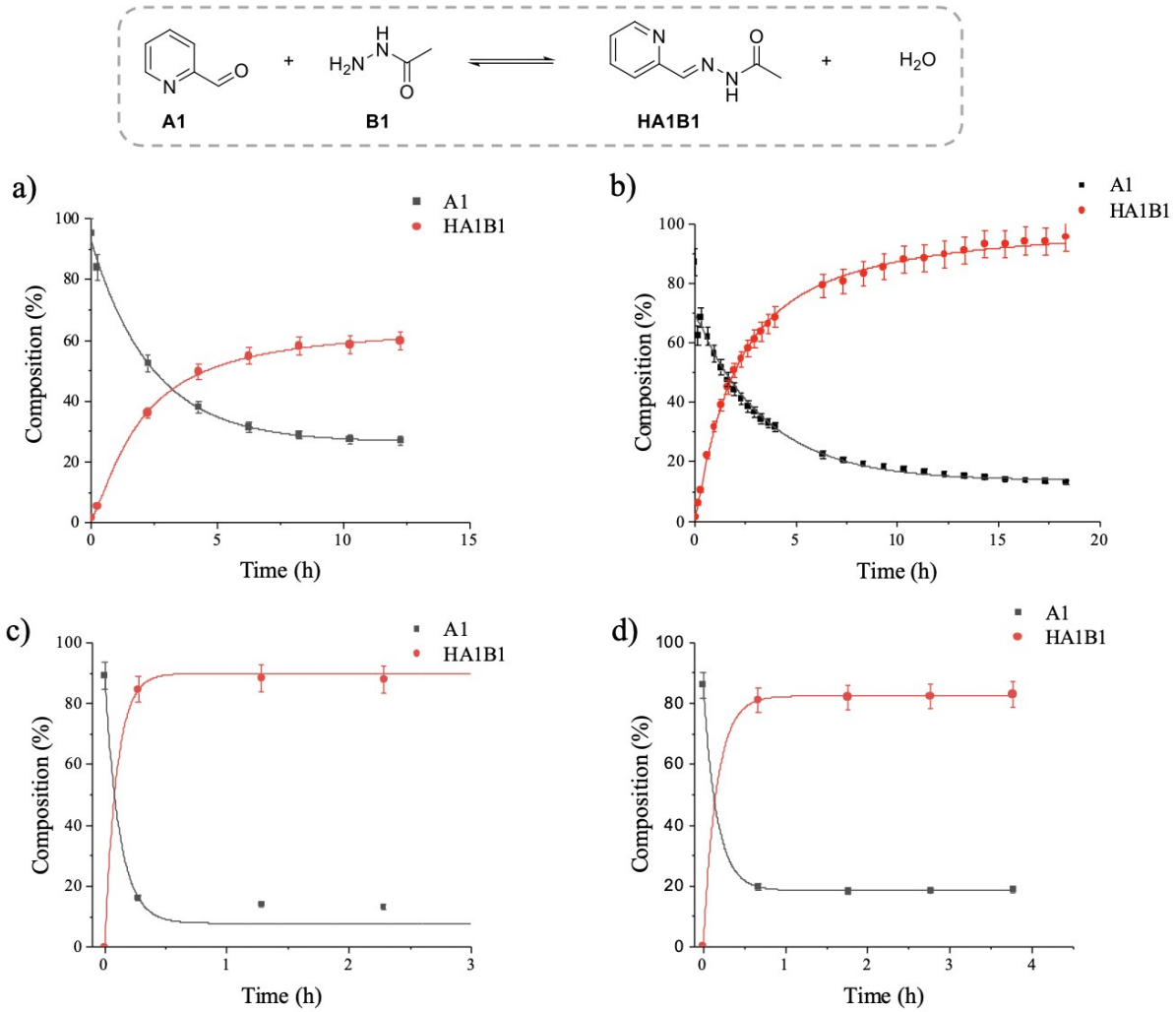


Figure S28. Formation of **HA1B1** – 296K – 20 mM in a) $CDCl_3$ – D_2O at pD = b) 7.3 – c) 5.0 – d) 2.5

5.3 Single phase – Exchanges of components/constituents

Exchange 1.

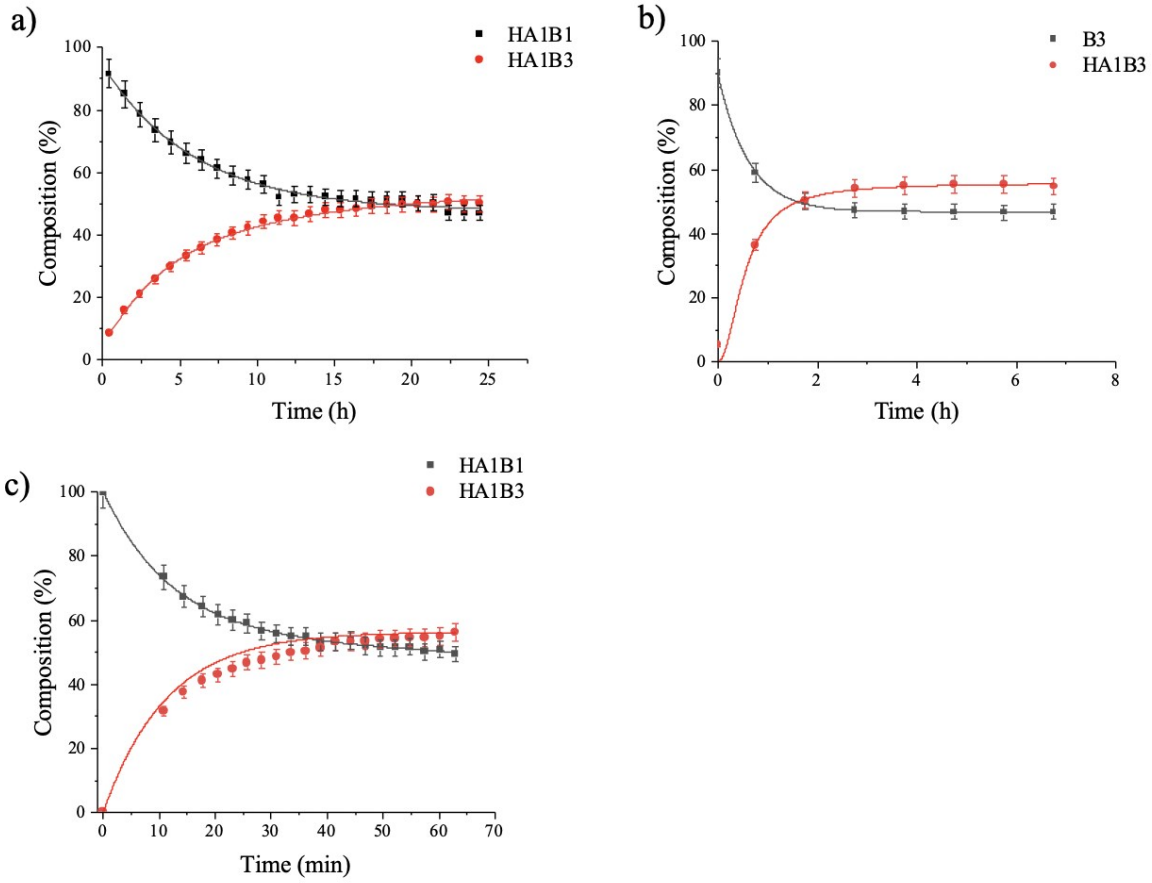


Figure S29. Exchange 1 – **B3** + **HA1B1** – 296K – 20 mM in D2O at pD = a) 7.4 – b) 4.7 – c) 2.3

Exchange 2.

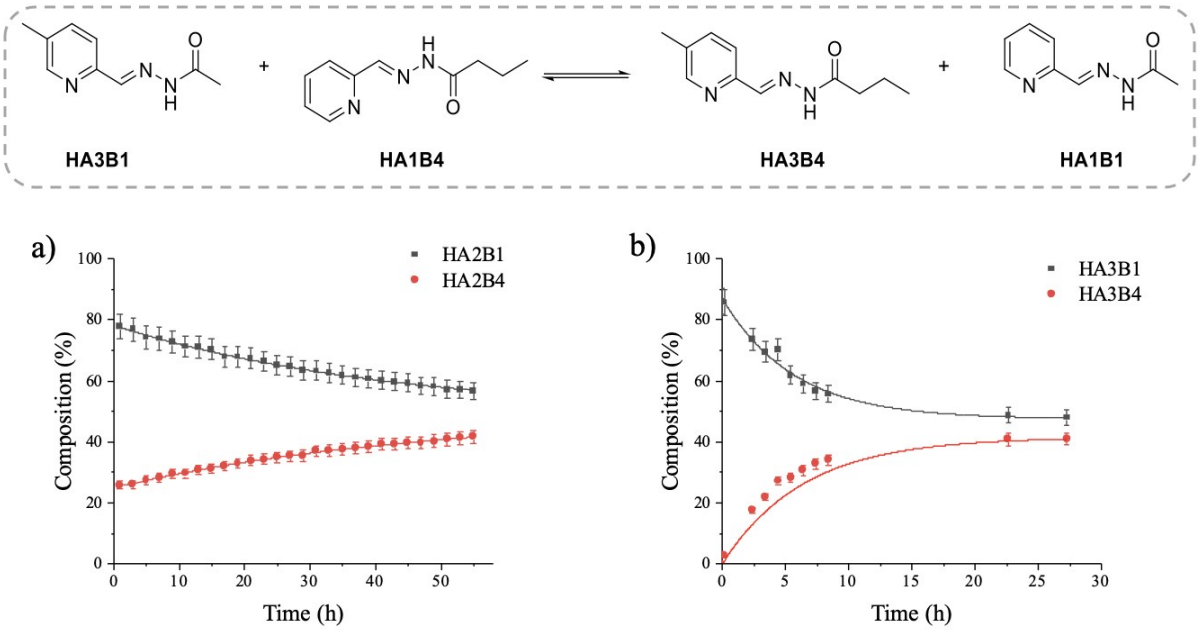
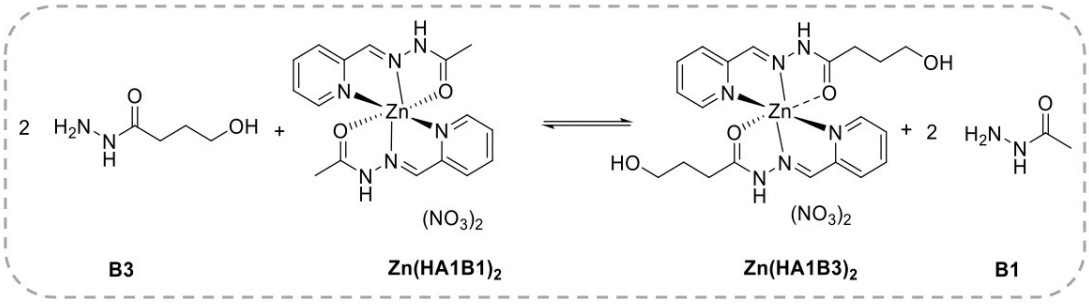


Figure S30. *E*xchange 2 – **HA3B1** + **HA1B4** – 296K – 20 mM in D_2O at pD = a) 5.0 – b) 2.0

Exchange 3.



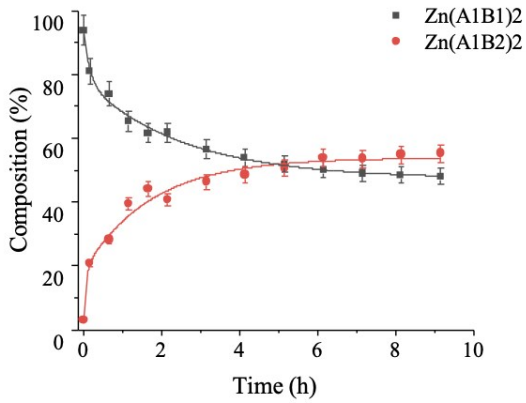


Figure S31. Exchange 3 – **B3** + [Zn(II)(**HA1B1**)$_2$] $(NO_3)_2$ – 296K - 20 mM in D_2O at pD = 4.9

5.4 Standard procedure in biphasic system

All the reactions are followed by ^{1}H NMR at 296K and performed at 20 mM on a total volume of 4mL. In the vial, 80 µL of stock solution at 500 mM of each reactant are introduced. The solvents are added in the amount corresponding to a final volume of 2 mL of D_2O and 2 mL of $CDCl_3$. The pD is adjust by addition of NaOD or TFA in the vial. The reaction is started and as we assume the kinetic is slow, the first spectra is performed one day later. To analyze the reaction, 500 µL of each phase are taken, analyzed as fast as possible with a quantitative NMR method and put back into the vial. The study lasts on 3 weeks and we did our best to avoid loss and evaporation in the vial.
As in the monophasic study, MestreNova software is used to integrate all the spectra. After correction and rationalization, the evolutions of the systems are plot in the charts presented below.

To ensure that acid is not extracted in chloroform after pD adjustment, the acidity of the chloroform phase was determined by reverse extraction.

5.5 Biphasic system – Formation of acylhydrazone

For the biphasic studies, the initial distributions of the components and constituents between D_2O and $CDCl_3$ were determined at pD = 6 with an error of ± 2%.

Table S1. Half-reaction time of formation and equilibration times of exchange reactions in monophasic system

Component	**A1**	**A2**	**A3**	**B1**	**B2**	**B3**	**B4**
Water (%)	5	< d.l.*	< d.l.*	> 99	< d.l.*	> 99	85
Chloroform (%)	95	> 99	> 99	< d.l.*	> 99	< d.l.*	15
Constituent	**HA1B1**	**Me-A1B1**	**HA1B2**	**Me-A1B2**	**HA1B3**	**HA1B4**	**Me-A1B4**
Water (%)	40	5	< d.l.*	< d.l.*	> 99	13	< d.l.*
Chloroform (%)	60	95	> 99	> 99	< d.l.*	87	> 99
Footnote of the table: *d.l. denotes detection limit, experimental error is ± 2%							

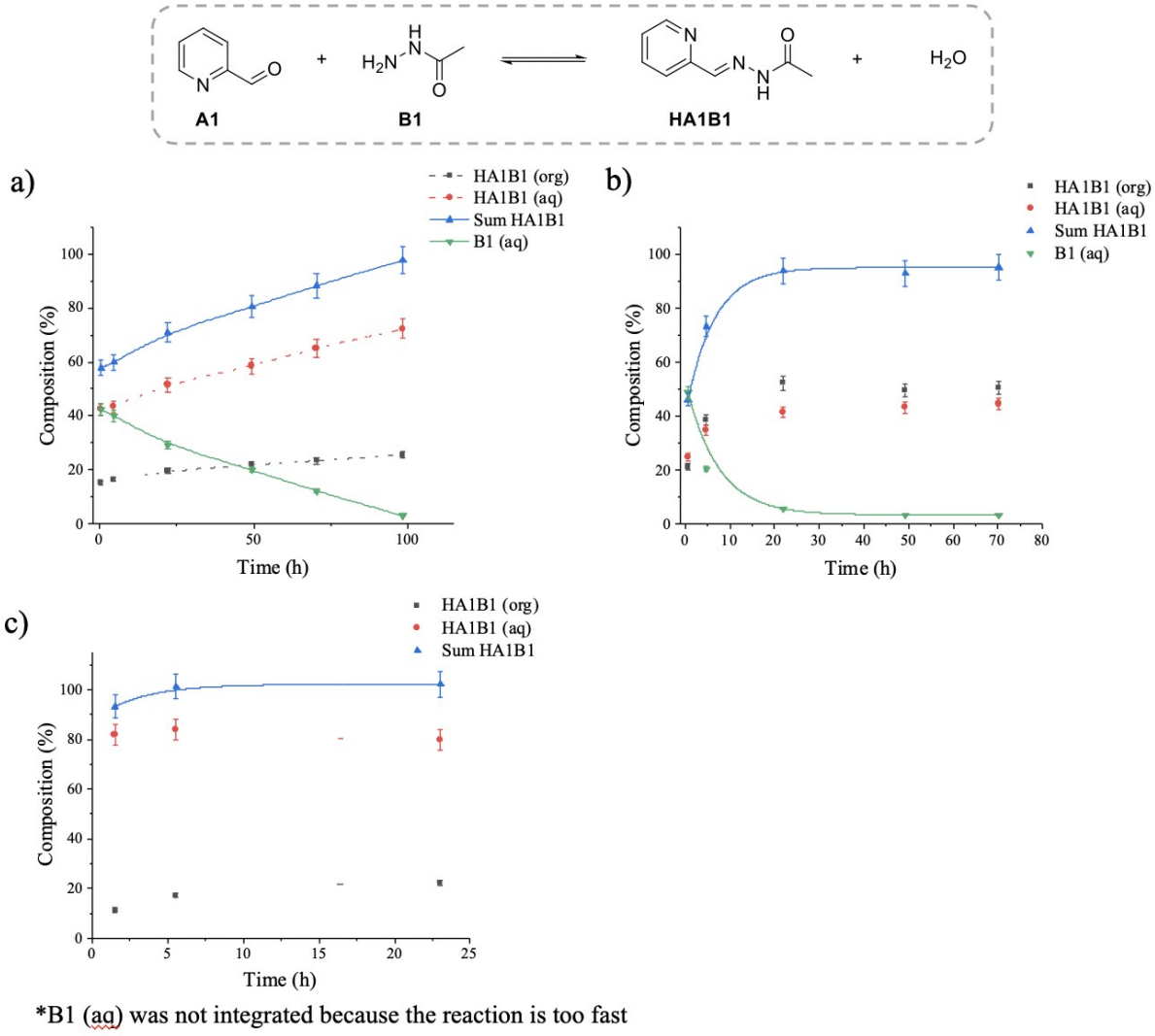
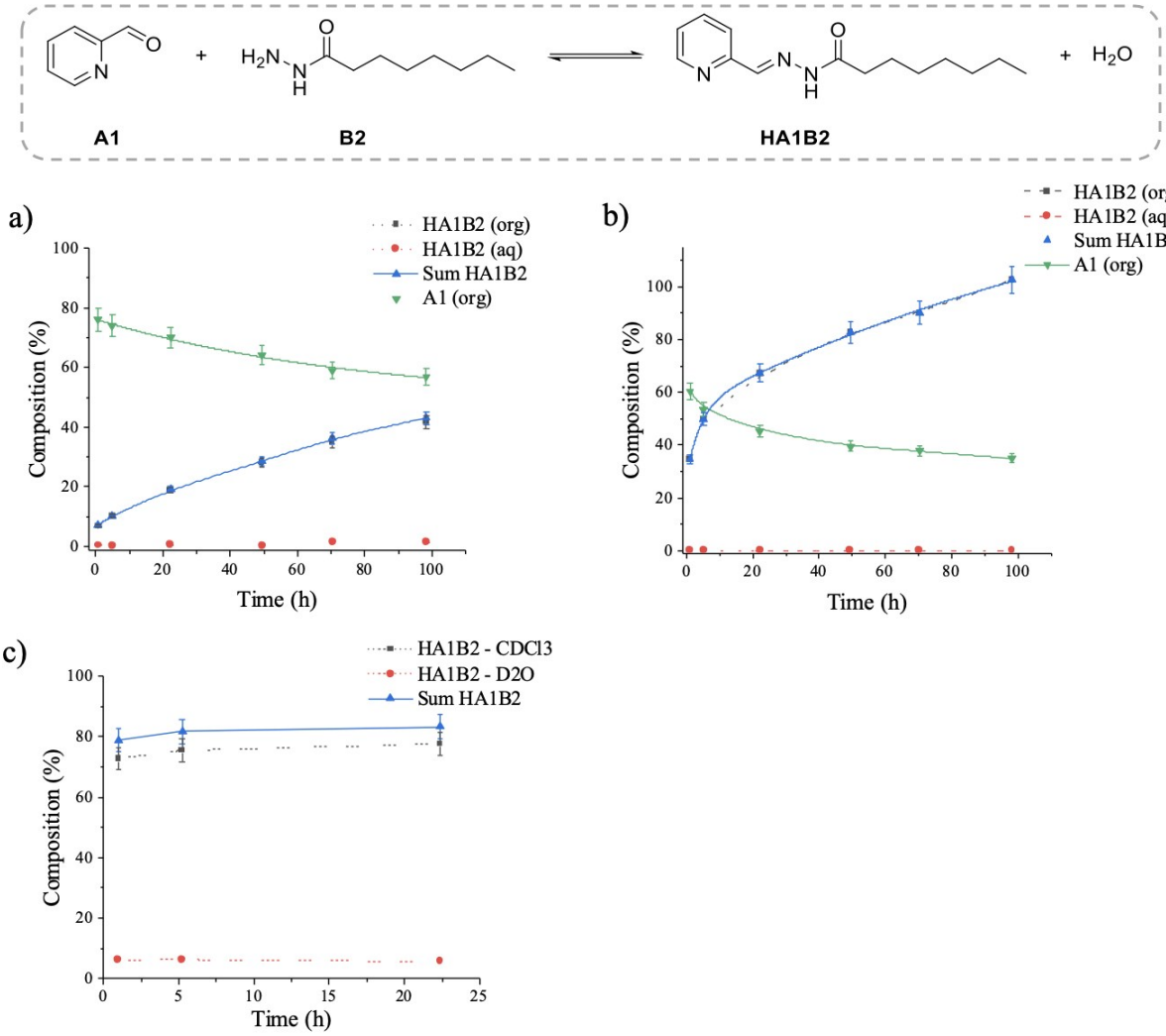


Figure S32. Formation of **HA1B1** – 296K - 20 mM in D_2O:$CDCl_3$ at pD = a) 8 – b) 5 – c) 2.6



*B1 (aq) was not integrated because the reaction is too fast

Figure S33. Formation of **HA1B2** – 296K – 20 mM in D_2O:$CDCl_3$ at pD = a) 7.7 – b) 5.8 – c) 2.5

5.6 Biphasic system – Exchange between a hydrazide and an acylhydrazone

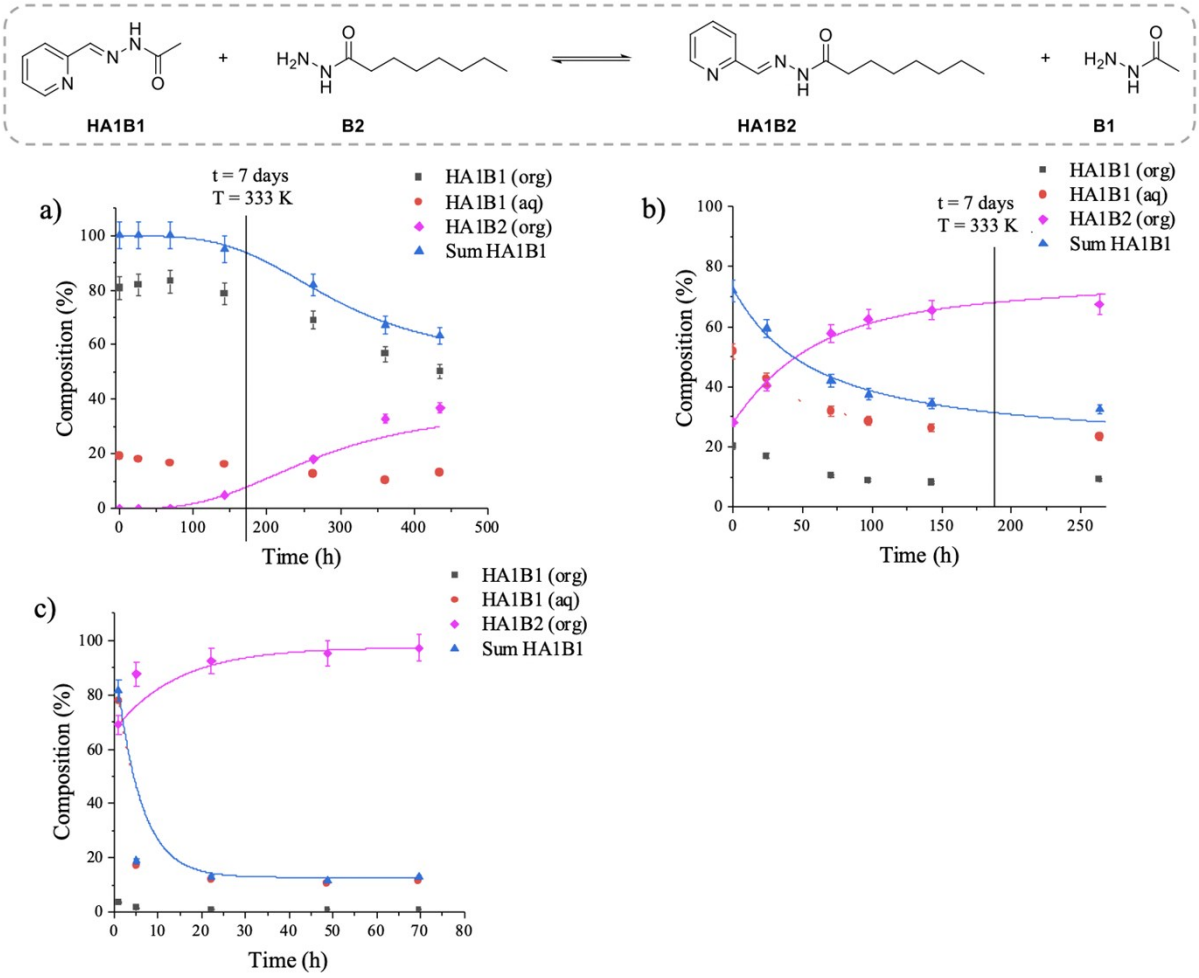


Figure S34. **HA1B1** + **B2** exchange – 20 mM in D_2O:$CDCl_3$ at pD = a) 8 – b) 6.3 – c) 2.6

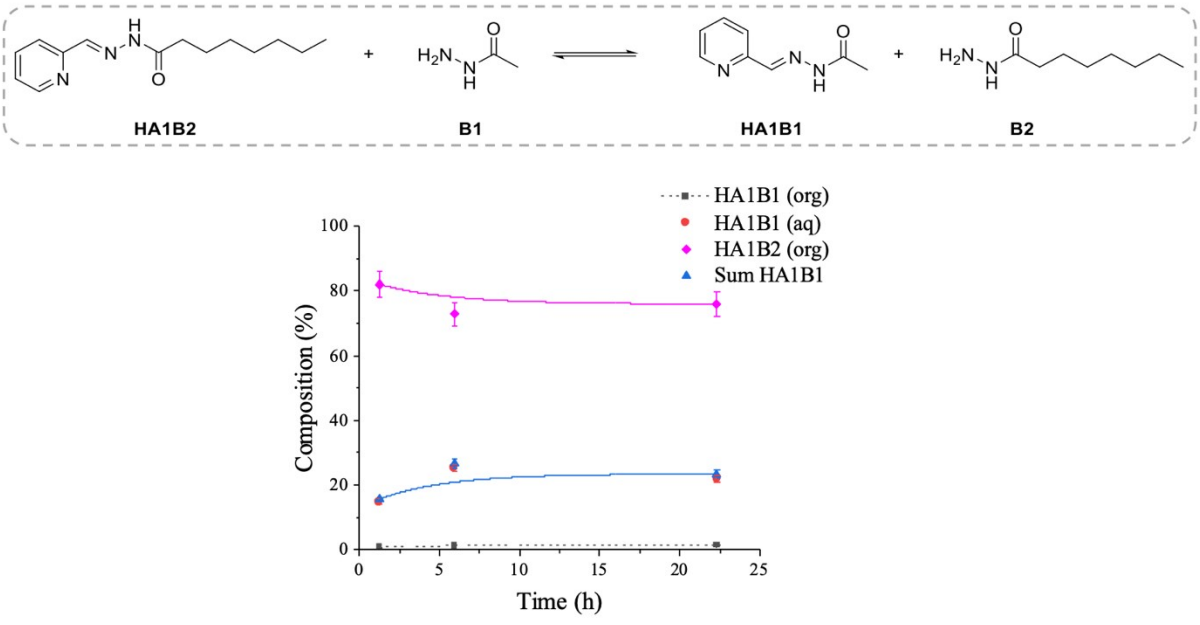


Figure S35. **HA1B2** + **B1** exchange – 296K - 20 mM in D_2O:$CDCl_3$ at pD = 2.6

5.7 Biphasic system – Behavior of a three membered library

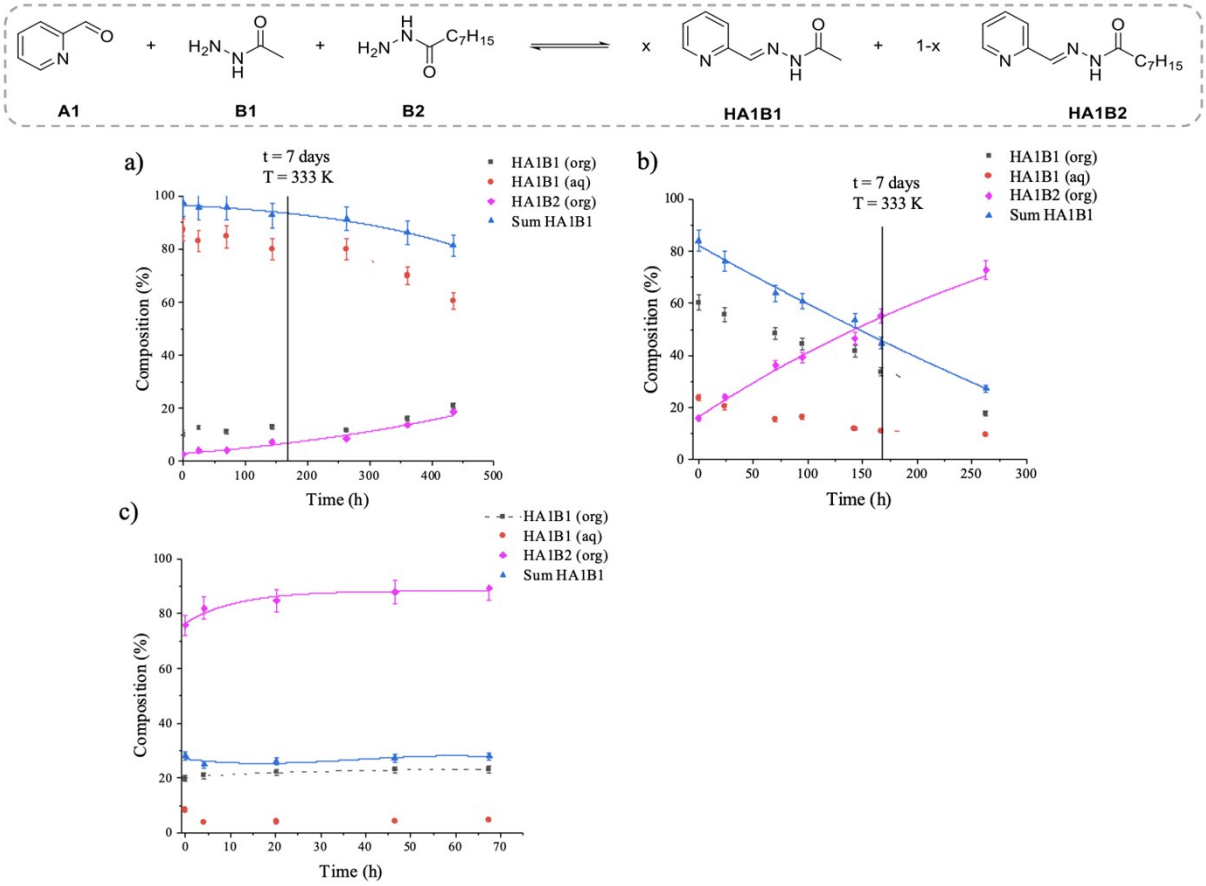


Figure S36. [**A1** + **B1** + **B2**] – 20 mM in D_2O:$CDCl_3$ at pD = a) 8.1 – b) 6 – c) 2.5

6 Single Crystal Diffraction

Table S2. Crystal data and structure refinement of structures type 1 and 2

Type	1		2	
Compound	$Cu(HA1B1)_2(NO_3)_2$		$Cu(HA1B1)\ (A1B1)(NO_3)$	
Empirical Formula	C16 H18 Cu N8 O8		C16 H17 Cu N7 O5	
Formula weight ($g.mol^{-1}$)	513.92		450.90	
Temperature (K)	173		120	
Wavelength (Å)	0.71073		0.71073	
Crystal system	Triclinic		Monoclinic	
Space group	P -1		P 21/c	
Unit cell dimensions (Å)/ Angle (deg.)	**a** = 7.8003	**α** = 70.989	**a** = 8.4150	**α** = 90
	b = 10.8755	**β** = 88.162	**b** = 13.2916	**β =** 100.322
	c = 15.0688	**γ** = 70.8860	**c** = 16.6694	**γ** = 90
Volume ($Å^3$)	1137.98		1834.28	
Z	2		4	
Calculated density (mg/m^3)	1.500		1.633	
Absorption coefficient (mm^{-1})	1.018		1.237	
F(*000*)	526		924	
Crystal size (mm^3)	0.220 x 0.180 x 0.120		0.100 x 0.080 x 0.060	
Θ range for data collection (deg.)	2.102 to 28.036		1.972 to 29.025	
Reflections collected	59670		28986	
Independent reflections	5494 [R(int) = 0.0446]		4897 [R(int) = 0.0458]	
Completeness to Θ = 25.242	100.0 %		100.0 %	
Absorption correction	Semi-empirical from equivalents		Semi-empirical from equivalents	
Max. and min. transmission	0.7456 / 0.6969		0.7458 / 0.6637	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	5494 / 0 / 300		4897 / 0 / 268	
Goodness-of-fit on F^2	1.057		1.034	
Final R indices [I>2σ (I)]	R_1 = 0.0455, wR_2 = 0.1150		R_1 = 0.0294, wR_2 = 0.0665	
R indices (all data)	R_1 = 0.0584, wR_2 = 0.1216		R_1 = 0.0413, wR_2 = 0.0725	
Largest diff. peak and hole (e. $Å^{-3}$)	1.071 and -0.607		0.449 and -0.472	

Table S3. Crystal data and structure refinement of structure type 3

Type	3	
Compound	Cu(**A1B1**)$_2$	
Empirical Formula	C16 H16 Cl Cu2 N6 O2	
Formula weight (g.mol^{-1})	486.88	
Temperature (K)	173(2)	
Wavelength (Å)	1.54178	
Crystal system	Monoclinic	
Space group	P 2/c	
Unit cell dimensions (Å)/ Angle (deg.)	**a** = 9.3690	**α** = 90
	b = 8.7013	**β** = 112.512
	c = 12.195	**γ** = 90
Volume (Å^3)	918.42	
Z	2	
Calculated density (mg/m^3)	1.761	
Absorption coefficient (mm^{-1})	4.415	
F(*000*)	490	
Crystal size (mm^3)	0.350 x 0.120 x 0.100	
Θ range for data collection (deg.)	5.083 to 66.646	
Reflections collected / unique	9027	
Independent reflections	1622 [R(int) = 0.0941]	
Completeness to Θ = 66.646	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 / 0.5666	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1622 / 0 / 125	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ (I)]	R_1 = 0.0526, wR_2 = 0.1344	
R indices (all data)	R_1 = 0.0795, wR_2 = 0.1498	
Largest diff. peak and hole (e. Å^{-3})	0.541 and -0.759	

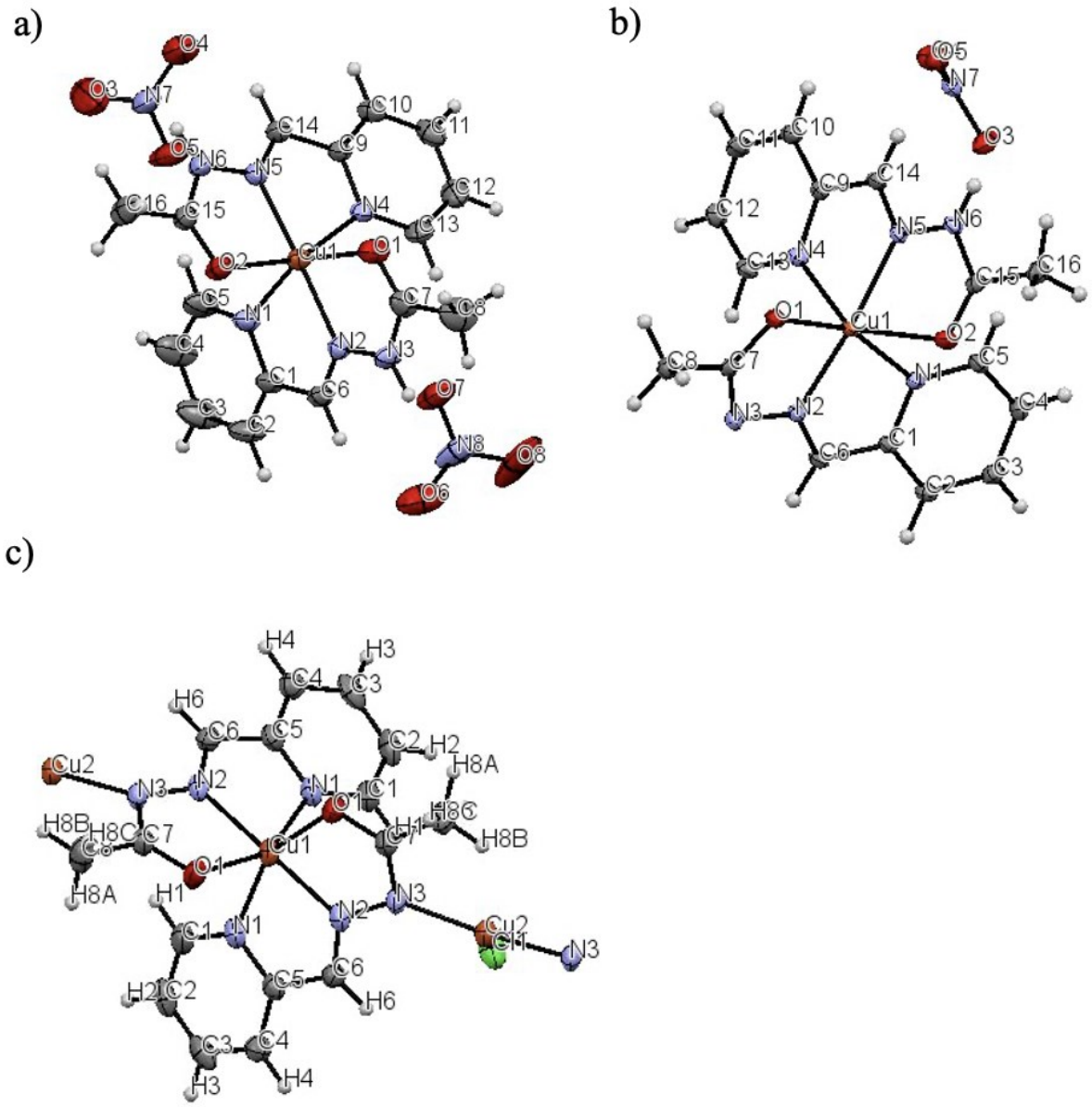


Figure S37. Single crystal structure of a) complex type 1– b) complex type 2 – c) complex type 3

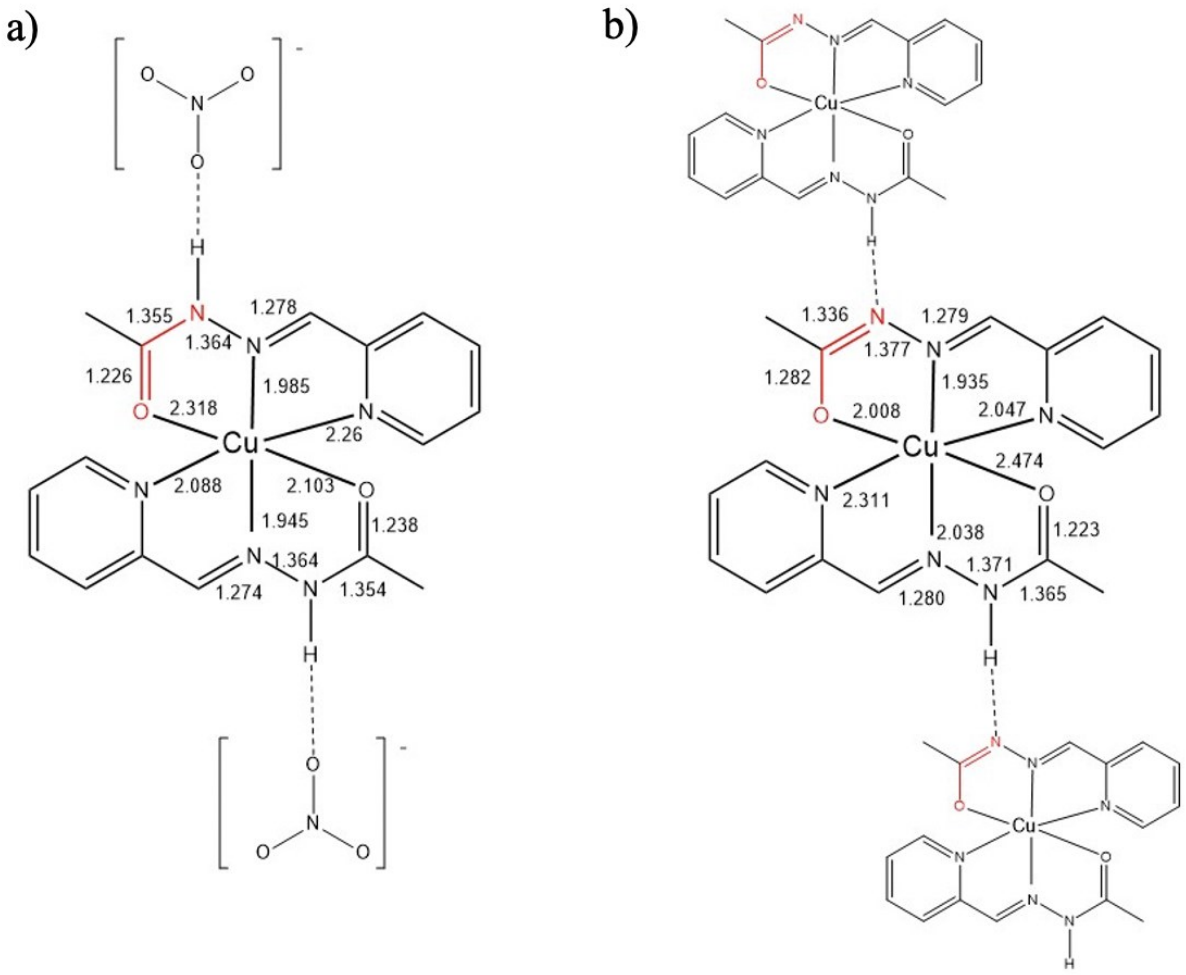


Figure S38. a) keto-amine form of type 1 complex and b) enol-imine form for type 2 complex

Table S4. Single Crystals - Bonds lengths and Angles

	Atom A	Atom B	Atom C	A-B-C (deg)	A-B (Å)	B-C (Å)	C-A (Å)
Complex Type 1	N5	Cu1	N2	177.5548	1.9447	1.9846	3.9285
	N5	Cu1	N4	78.8304	1.9447	2.0882	2.5631
	N5	Cu1	O2	77.8998	1.9447	2.1033	2.5478
	N5	Cu1	N1	102.5984	1.9447	2.2597	3.2871
	N5	Cu1	O1	107.3010	1.9447	2.3177	3.4402
	N2	Cu1	N4	103.2530	1.9846	2.0882	3.1937
	N2	Cu1	O2	100.0893	1.9846	2.1033	3.1345
	N2	Cu1	N1	75.9902	1.9846	2.2597	2.6217
	N2	Cu1	O1	74.0263	1.9846	2.3177	2.6036
	N4	Cu1	O2	156.4888	2.0882	2.1033	4.1036
	N4	Cu1	N1	96.3153	2.0882	2.2597	3.2411
	N4	Cu1	O1	92.2380	2.0882	2.3177	3.1797
	O2	Cu1	N1	91.9775	2.1033	2.2597	3.1398
	O2	Cu1	O1	91.4730	2.1033	2.3177	3.1696
	N1	Cu1	O1	149.9616	2.2597	2.3177	4.4210
Complex Type 2	N2	Cu1	O1	78.5161	1.9350	2.0076	2.4956
	N2	Cu1	N5	174.3260	1.9350	2.0383	3.9685
	N2	Cu1	N1	80.1854	1.9350	2.0475	2.5663
	N2	Cu1	N4	99.6650	1.9350	2.3108	3.2536
	N2	Cu1	O2	114.5154	1.9350	2.4737	3.7197
	O1	Cu1	N5	99.3553	2.0076	2.0383	3.0847
	O1	Cu1	N1	156.6838	2.0076	2.0475	3.9714
	O1	Cu1	N4	96.0403	2.0076	2.3108	3.2166
	O1	Cu1	O2	94.4249	2.0076	2.4737	3.3039
	N5	Cu1	N1	102.7039	2.0383	2.0475	3.1910
	N5	Cu1	N4	75.2371	2.0383	2.3108	2.6635
	N5	Cu1	O2	70.7659	2.0383	2.4737	2.6367
	N1	Cu1	N4	96.7787	2.0475	2.3108	3.2633
	N1	Cu1	O2	85.8422	2.0475	2.4737	3.0947
	N4	Cu1	O2	145.6071	2.3108	2.4737	4.5709

7 Extraction of copper(II) nitrate

7.1 Extraction properties of components and constituents

To evaluate the extraction properties of the selected components and constituents, the procedure "Standard procedure for extraction properties evaluation by UV-visible spectrophotometry" described above is used. Then the contents of copper are determined by photometric titration and ICP-OES measurements.

7.1.1 General procedure for the photometric titration of copper(II)

Ethylene diamine (ED) is a bidentate chelating ligand which forms complex with copper (II) salts. For the photometric titration, ED is used as color indicator. It forms strong purple-colored complex with copper(II) and give us the possibility to titrate the copper in both phases by forming $[Cu(II)(ED)_2(H_2O)_2]^{2+}$. Stock solutions of $Cu(NO_3)_2 \cdot 3H_2O$ at 500 mM in water and of ethylene diamine at 100 mM in methanol are prepared.

Determination of the ideal concentration of Cu to get a UV-visible spectrum

Different copper concentrations were studied in order to determine the ideal quantity that we should have in our final aliquots during the real experiments. The concentration values tested are: 100 mM – 10 mM – 1 mM. The titration is done with a large excess of ED toward copper: 9:1 molar equivalent.
300 µL of the copper stock solution is introduced in the quartz cuvette. Then 2.7 mL of ED solution are added. The excess of ED is measured by the ratio ED:Cu equal to 9:1. The color change is instantaneous after a vigorous shake and the UV-visible spectrum is recorded.
For the components and constituents experiments, the 300 µL of copper stock solution are replaced by 300 µL of the studied phase and the procedure is exactly the same.

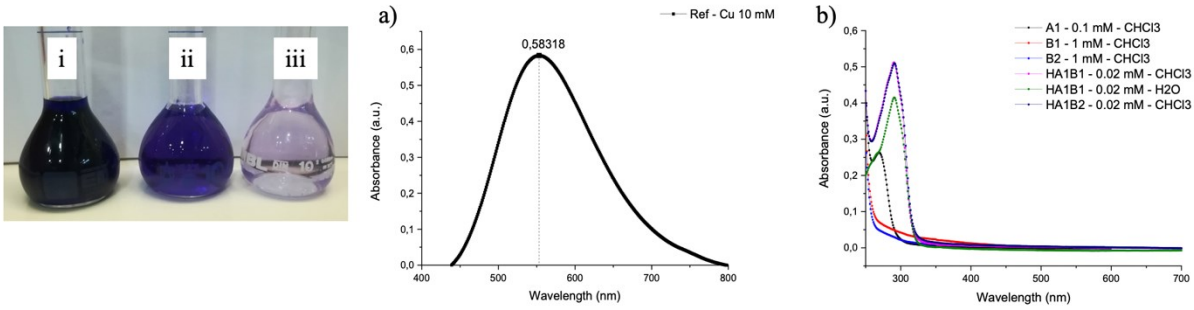


Figure S39. Titration of copper with ethylene diamine at i. 100 mM – ii. 10 mM – iii. 1mM in MeOH - a) UV-visible absorption spectrum of $Cu(NO_3)_2$ at 10 mM with 9 equivalents of ED – b) UV-visible spectra of components and constituents

The best concentration range of $Cu(NO_3)_2 \cdot 3H_2O$ to get readable analyses with UV-visible titration technique is 10 mM (fig.39). The maximum absorbance wavelength (λmax) of the complex of Cu(II) with ED is 553 nm (fig.40). The spectra of components and constituents of interest had been recorded and do not present any peak in the 550 nm region (figure S39).
A1 at 0.1 mM, **B1** at 1mM, **B2** at 1mM, **HA1B1** at 0.02 mM and **HA1B2** at 0.02 mM in chloroform and water.

7.1.2 General procedure for the determination of copper(II) contents by ICP-OES

For ICP-OES samples, only water phases are analysed. The analyses are made on the same experiment that the one done for the photometric determination of Cu(II). 10 µL of the studied phase are introduced in 990 µL of deionised water. Then, 10 µL of fuming nitric acid are added. The sample are sent to another laboratory of Strasbourg university to be analysed.

Extraction yield of **A1**, **B1**, **B2**, **HA1B1** and **HA1B2** at pH 4.4, initial pH of the $Cu(NO_3)_2$ solution, and M:L ratio is 1:1 and extraction yield of **B2** and **HA1B2** at 2.7 < pH < 3.6 at ligand concentration = 100 mM and the amount of Cu(II) changes.

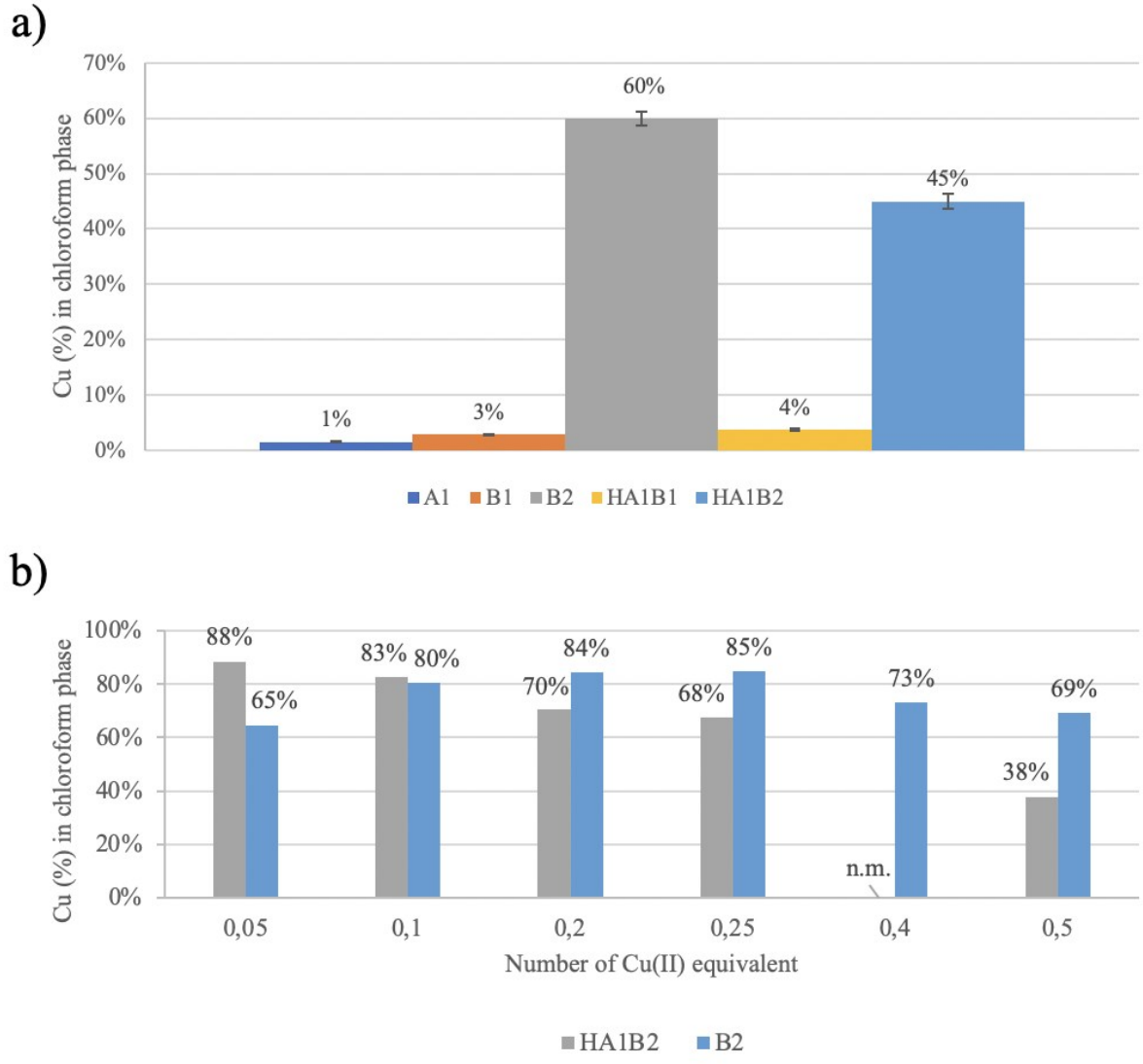


Figure S40. a) ICP-OES analyses - Extraction yield of each member of the reference library at pH 4.4 – b) Comparison of **B2** and **HA1B2** extraction yield – Analyzed by ICP-OES (n.m. = not measured)

7.2 Compound A1, 2-pyridinecarboxaldehyde

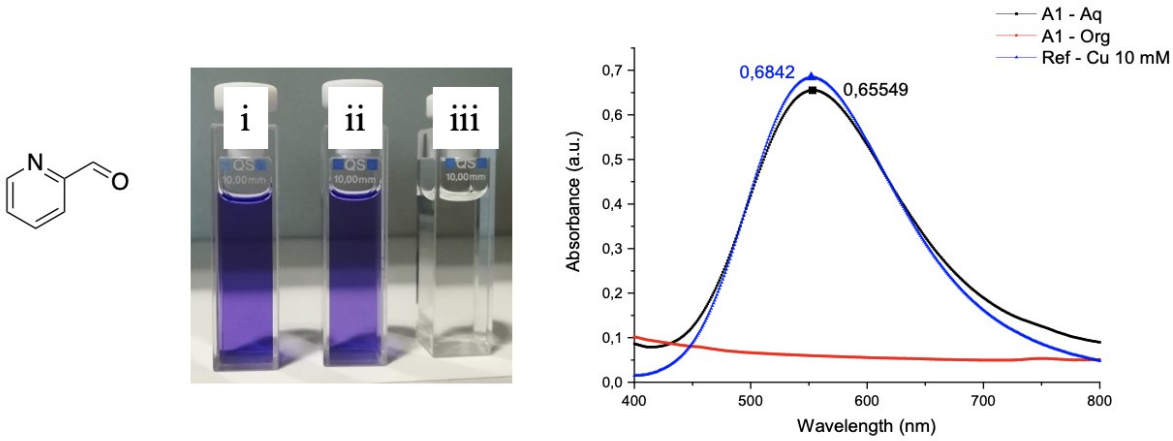


Figure S41. UV-visible solutions of **A1** experiment after ED addition: i. Cu reference – ii. aqueous phase – iii. organic phase & UV-visible spectra of **A1** experiment

a. Compound B1, Acetic hydrazide

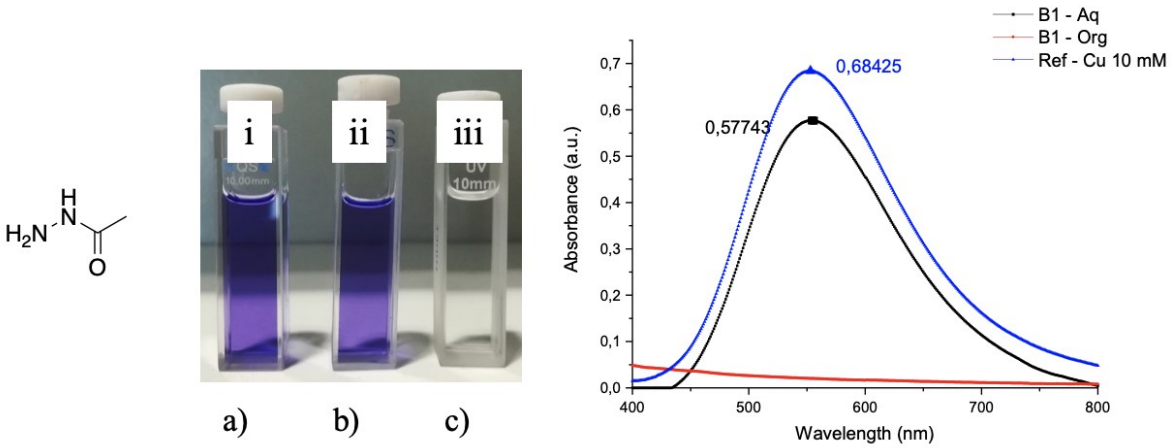


Figure S42. UV-visible solutions of **B1** experiment after ED addition: i. Cu reference – ii. aqueous phase – iii. organic phase & UV-visible spectra of **B1** experiment

7.3 Compound B2, Octanoic hydrazide

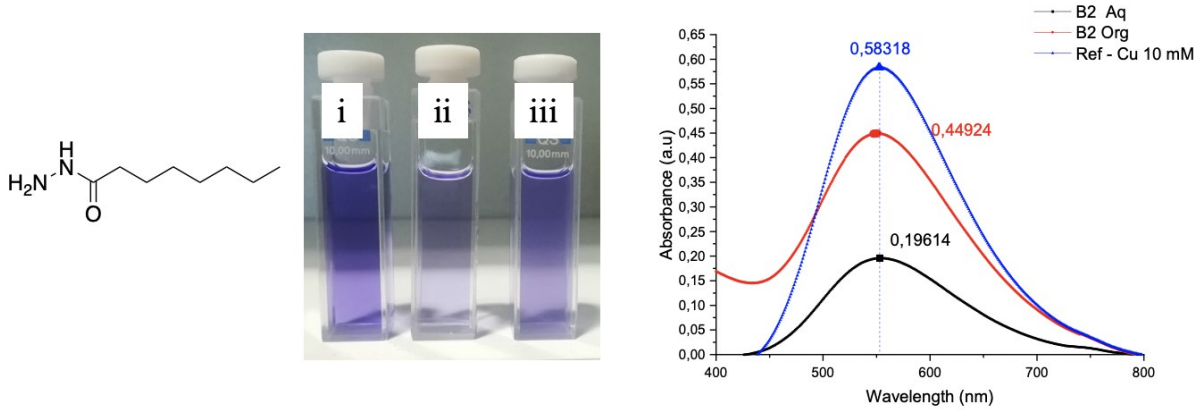


Figure S43. UV-visible solutions of **B2** experiment after ED addition: i. Cu reference – ii. aqueous phase – iii. organic phase & UV-visible spectra of **B2** experiment

B2 shows extraction properties for copper(II). There is more copper in the organic phase than in the aqueous phase.
For the pH experiments, we measured and adjusted the pH value of the aqueous phase charged with copper before contacting the two phases. The results reported in the tables are obtained by ICP-OES analyses. If not the variable, the (M:L) ratio is (1:2) and the stirring time is c.a. one hour. The intrinsic pH of the copper solution is 4.4.

Table S5.**B2** extraction properties evolution with pH change

pH	Extraction yield
2	63%
3	62%
4	60%
5	60%

Table S6. **B2** extraction properties evolution with (M:L) ratio change

Equivalent of Cu	M:L ratio	Extraction yield
0,05	1:20	58%
0,1	1:10	68%
0,2	1:5	72%
0,25	1:4	71%
0,5	1:2	63%

Table S7. **B2** extraction properties evolution with stirring time change

Time (min)	Extraction yield
5	59%
10	58%
20	58%
900	54%

7.4 Compound HA1B1, (E)-N'-(pyridin-2-ylmethylene)acetohydrazide

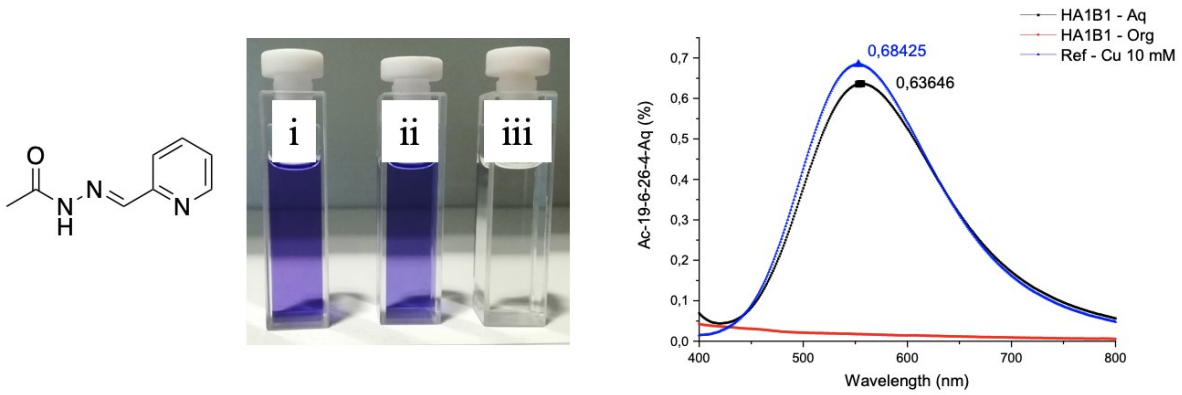
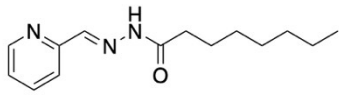
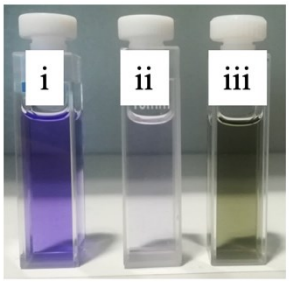


Figure S44. UV-visible solutions of **HA1B1** experiment after ED addition: i. Cu reference – ii. aqueous phase – iii. organic phase & UV-visible spectra of **HA1B1** experiment

7.5 Compound HA1B2, N'-(pyridin-2-ylmethylene)octanhydrazide





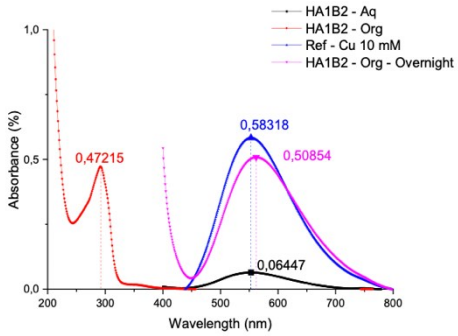


Figure S45. UV-visible solutions of **HA1B2** experiment after ED addition: i. Cu reference – ii. aqueous phase – iii? organic phase & UV-visible spectra of **HA1B2** experiment

The titration of copper by ED in the case of the extraction by **HA1B2** is different from those we studied before. The color change is not instantaneous and right after the addition of ED, the coloration of the cuvette is not violet but greenish. If we wait overnight, the reaction occurs and the solution in the cuvette finally turns violet. The right spectra on the figure 10 shows the extraction is finally efficient. Here, we figure out that the overnight system shows a better yield of extraction of copper than what can be reached with ICP-OES. We think about the involvement of ethylene diamine in the extraction process and we prefer to rely on the ICP-OES analyses.
The tables report the results obtained by ICP-OES analyses. If not the variable, the (M:L) ratio is 1:2 and the stirring time is c.a. one hour.

Table S8. **HA1B2** extraction properties evolution with pH change

pH	Extraction yield
2	55%
3	48%
4	47
5	45%

Table S9. **HA1B2** extraction properties evolution with (M:L) ratio change

Equivalent of Cu	M:L ratio	Extraction yield
0,05	1:20	88%
0,1	1:10	83%
0,2	1:5	70%
0,25	1:4	68%
0,5	1:2	38%

Table S10. **HA1B2** extraction properties evolution with stirring time change

Time (min)	Extraction yield
5	23%
10	25%
20	24%
900	43%

8 Dynamic extraction

8.1 General procedure for the dynamic extraction experiments

The system is constituted of 2mL of water, 2 mL of chloroform placed in a closed vial. In the first step, the components/constituents are introduced at 100 mM which represent 1.0 equivalent. The system is stirred for one hour at room temperature. The second step is the addition of 0.4 equivalent of the metal salt, $Cu(NO_3)_2{\cdot}3H_2O$. The second step is stirred for one hour at room temperature and then the introduction of 1.0 equivalent of additional components/constituents is considered as the third step. In Extraction III, there is no third step.

When the copper is absent from the system, ^1H NMR is used as the preferential analysis method. ICP-OES analysis and UV-visible photometric titration with ethylenediamine are used to determine the amount of copper in each phase. UV-visible spectroscopy is used to characterized the species but cannot differentiate all of them because of the similarity of the molecules. Liquid-chromatography coupled with high-resolution mass spectrometry is used in a quantitative way to determine the concentration of each organic species (**A1**, **B1**, **B2**, **HA1B1**, **HA1B2**). Direct injection high-resolution mass spectrometry method is used both in negative and positive modes to quantify nitrate anion and copper complex species in the system. For all the mass spectrometry analyses, calibration curves have been triplicated.

8.2 Liquid-chromatography coupled with high-resolution mass spectrometry

All the species quantified in this study have been characterized by HR-MS. Sodium, potassium, methanol and formic acid adducts are also present and taken into account in the quantification. The list of the main peaks is presented in the table 15.

Table S11. Species present in the complex HR-MS spectra

Species	M/z	Molecular formula	Experimental mass	Theorical mass	Error (ppm)
$\mathbf{B_1+H^+}$	1	$C_2H_7N_2O$	75,0564	75,0553	14,3575
$\mathbf{A_1+H^+}$	1	C_6H_6NO	108,045	108,0444	5,4631
$\mathbf{B_2+H^+}$	1	$C_8H1_9N_2O$	159,1494	159,1492	1,5858
$\mathbf{A_1B_1+H^+}$	1	$C_8H_{10}N_3O$	164,0818	164,0818	0,6
$\mathbf{A_1B_2+H^+}$	1	$C_{14}H_{22}N_3O$	248,1753	248,1757	1,325
$\mathbf{Cu(B1)_2^+}$	1	$C_4H_{11}CuN_4O_2$	210,017	210,0173	1,5094
$\mathbf{Cu(B2)_2^+}$	1	$C_{16}H_{35}CuN_4O_2$	378,2042	378,2051	1,623
$\mathbf{Cu(HA1B1)_2^+}$	1	$C_{16}H_{17}CuN_6O_2$	388,0691	388,0703	3,3057
$\mathbf{Cu(HA1B1)(A1B2)^+}$	1	$C_{22}H_{29}CuN_6O_2$	472,1635	472,1643	0,142
$\mathbf{Cu(HA1B2)_2^+}$	1	$C_{28}H_{41}CuN_6O_2$	556,2567	556,2582	2,6242

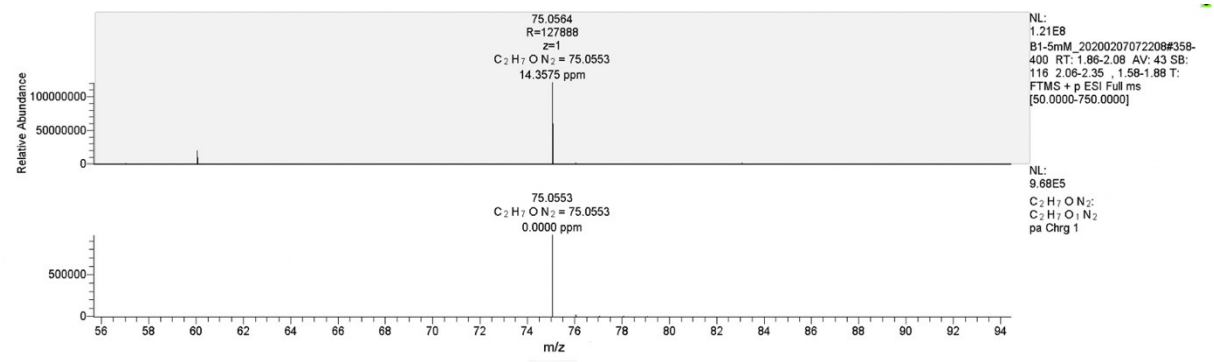


Figure S46. Mass spectrum of compound **B1** [M+H$^+$]

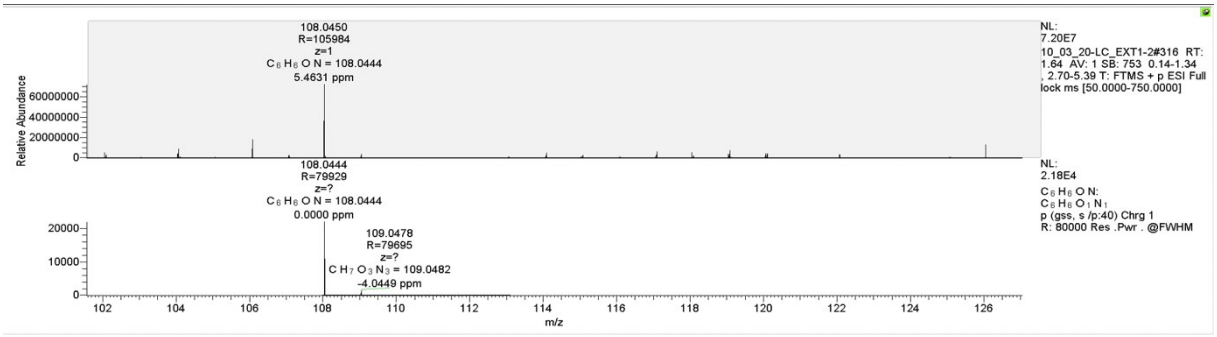


Figure S47. Mass spectrum of compound **A1** [M+H$^+$]

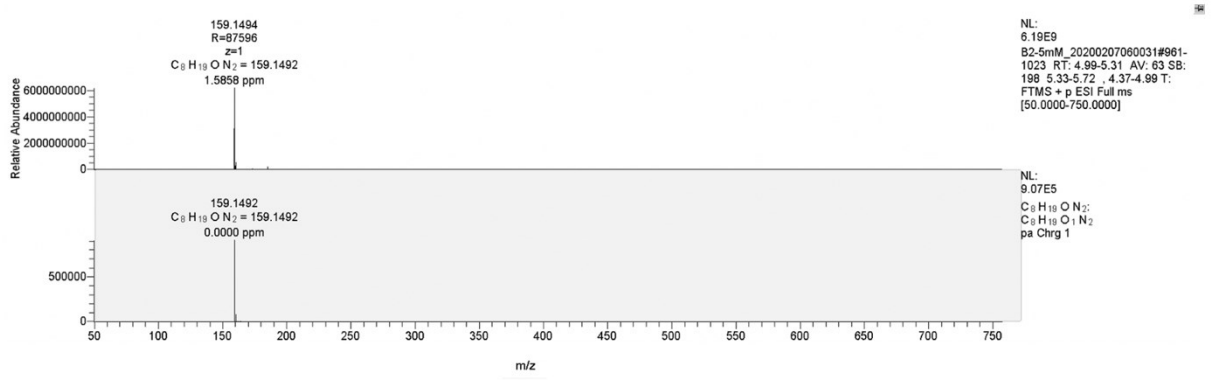


Figure 48 . Mass spectrum of compound **B2** [M+H$^+$]

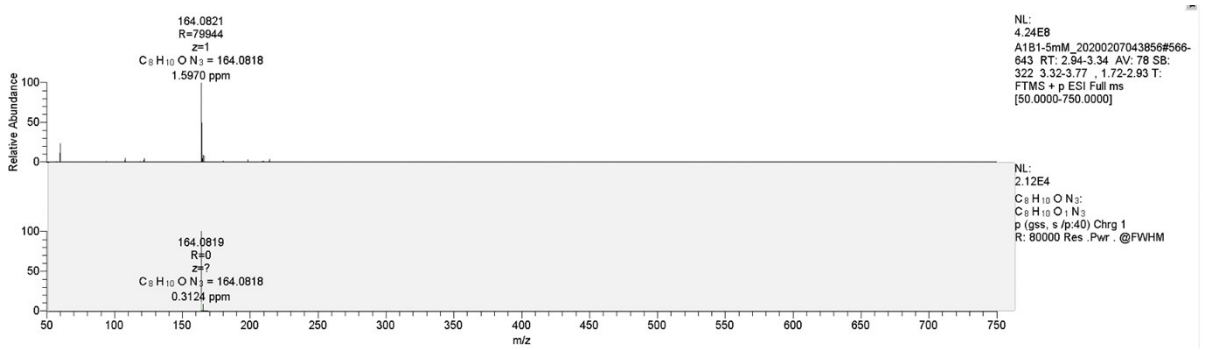


Figure S49. Mass spectrum of compound **A1B1** [M+H$^+$]

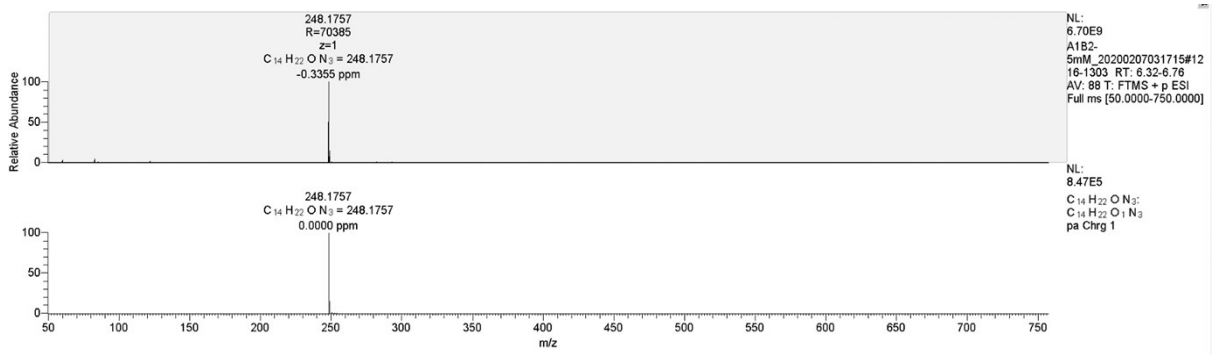


Figure S50. Mass spectrum of compound **A1B2** [M+H$^+$]

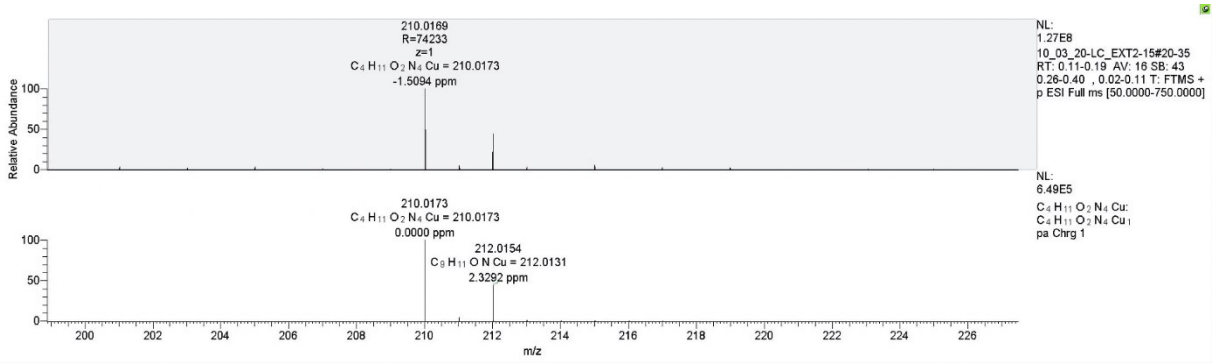


Figure S51. Mass spectrum of compound **[Cu(B1)$_2$]** [M$^+$]

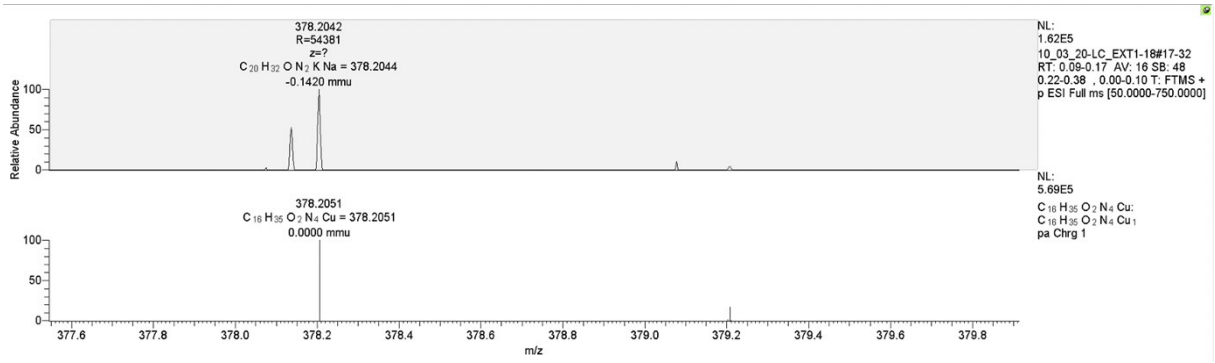


Figure S52. Mass spectrum of compound [Cu(**B2**)$_2$] [M$^+$]

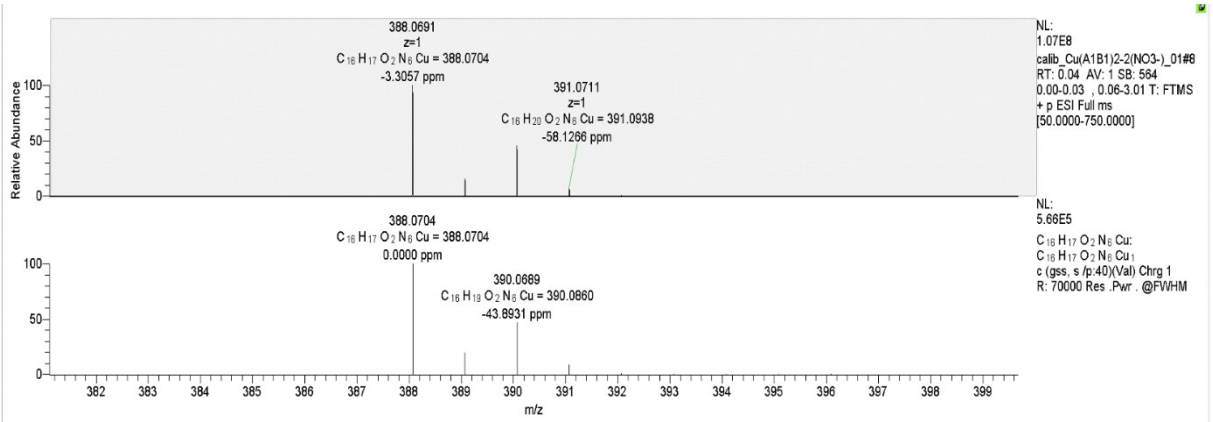


Figure 53 Mass spectrum of compound [Cu(**HA1B1**)$_2$] [M$^+$]

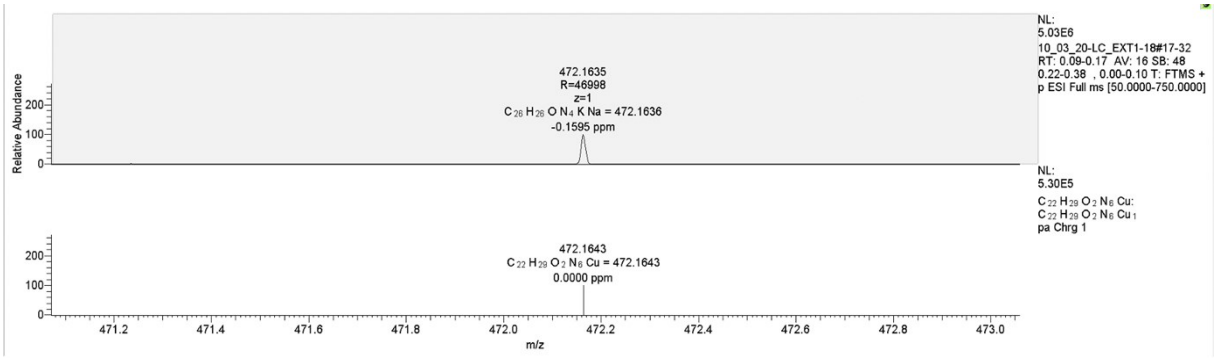


Figure S54. Mass spectrum of compound [Cu(**HA1B1**)(**HA1B2**)] [M^+]

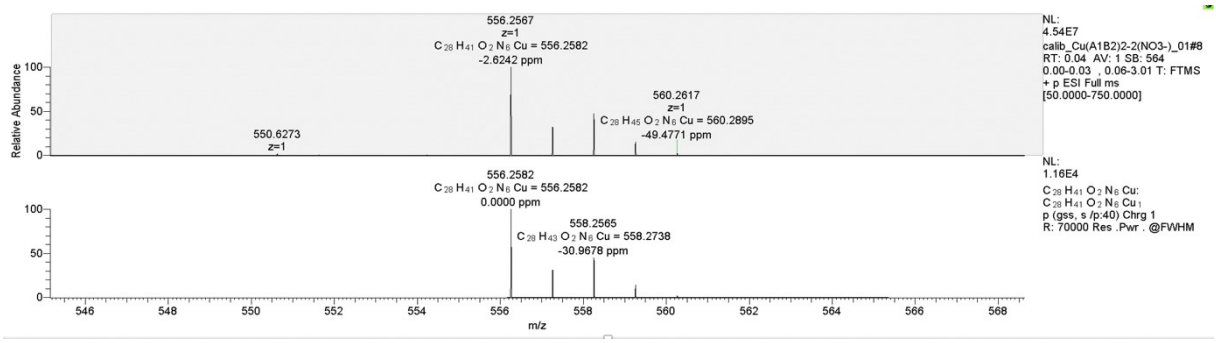
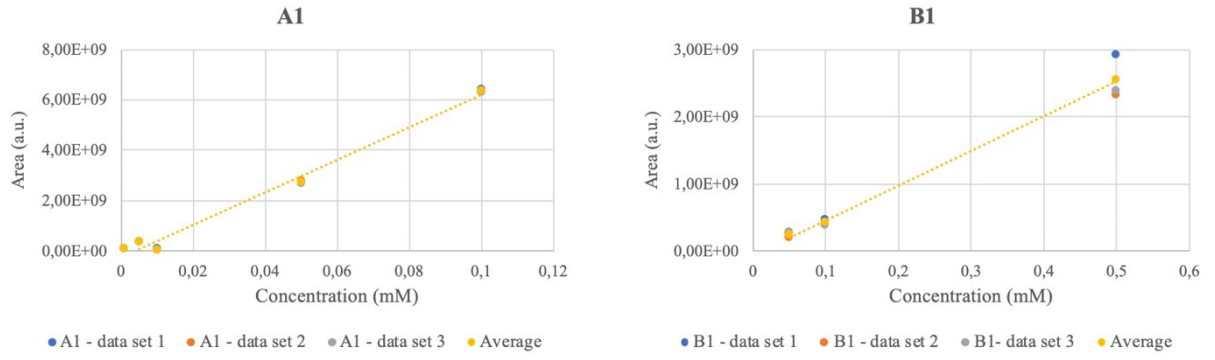


Figure S55 Mass spectrum of compound [Cu(**HA1B2**)$_2$] [M^+]

Solutions at 5mM of **A1**, **B1**, **B2**, **A1B1** and **A1B2** were prepared in methanol. Then dilutions from the stock solutions were done to get standards at 0.5, 0.1, 0.01, 0,005 and 0.001 mM. The LC-MS profiles were recorded and the calibration curves were plotted. Three replicates of calibration curves were done in order to determine as accurately as possible the concentration of the organic species in the system.

To analyze the experiments, 10 µL of the studied phase are dilute in 990 µL of methanol. Then the LC-MS profile is recorded and the equation of the calibration curve average is used to determine the concentration of the organic species.



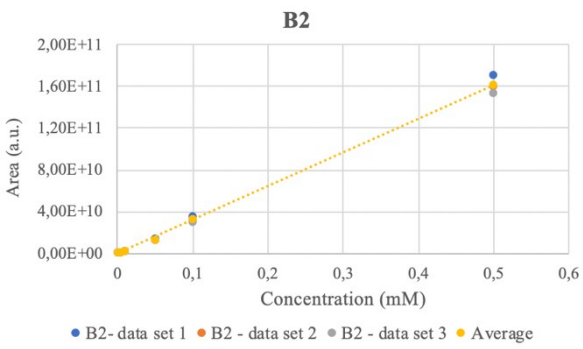
$$y = 6\times10^{10}\,x - 2\times10^{8}$$

$$R^2 = 0{,}9886$$

$$y = 5\times10^{9}\,x - 6\times10^{7}$$

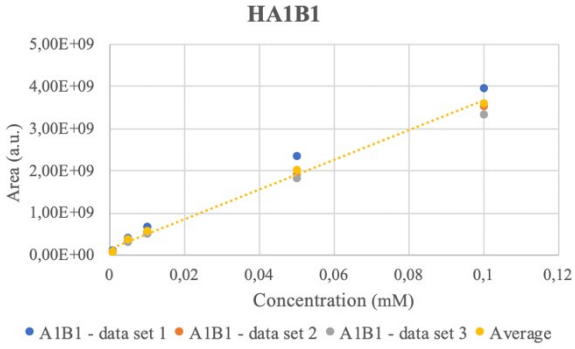
$$R^2 = 0{,}9989$$

Figure S56. **A1** and **B1** calibration curves in LC-MS



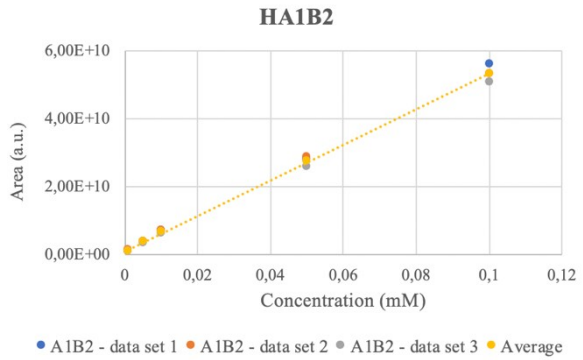
$$y = 3{\times}10^{11}\,x - 7{\times}10^{8}$$

$$R^2 = 0{,}9996$$



$$y = 3{\times}10^{10}\,x + 2{\times}10^{8}$$

$$R^2 = 0{,}9963$$



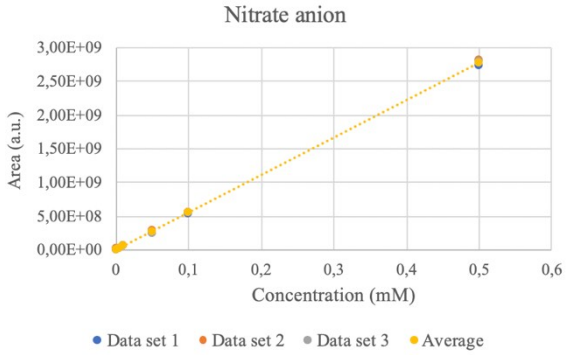
$$y = 5{\times}10^{11}\,x + 9{\times}10^{8}$$

$$R^2 = 0{,}9997$$

Figure S57. **B2, HA1B1** and **HA1B2** calibration curves in LC-MS

8.3 Direct injection high-resolution mass spectrometry

For the quantification of nitrate anion, direct injection method is used. The current of nitrate anion is extracted from the TIC (total ion current) of the negative mode of detection. Standards solution of tetramethylammonium nitrate were prepared at 0.5, 0.1, 0.05, 0.01, 0.005, 0.001 mM in methanol. Different injection volumes (0.1, 0.2 and 0.5 µL) were tested and 0.5 µL was chosen as it gave the best linear regression factor (R^2). To analyses the sample, 10 µL of the phase is diluted in 990 µL of methanol and 0.5 µL are injected in the mass spectrometer. The calibration curve obtained are presented below.



$$y = 6{\times}10^{9}\,x - 3{\times}10^{6}$$

$$R^2 = 1$$

Figure S58. (NO_3^-) Calibration curve – Direct injection HR-MS

The quantification of copper complex species is realized with the same technique and the same king of calibration curves (0.5, 0.1, 0.05, 0.01, 0.005, 0.001 mM in methanol).

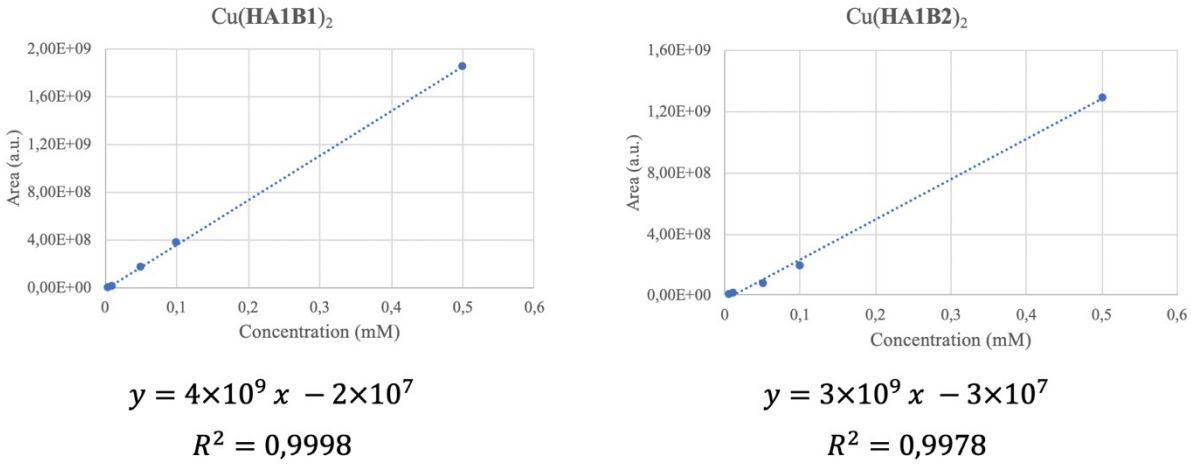


Figure S59.[Cu(II)(**HA1B1**)$_2$] and [Cu(II)(**HA1B2**)$_2$] Calibration curve – Direct injection HR-MS

8.4 Results of HR-MS analyses

In the tables below, the amount of species is done in percent where only organic species and complex species have been considered. The amount of total copper is calculated only with Cu(II) complex species and the amount of nitrate is calculated alone. These different quantities are expressed in percent to get the comparison possible.

Table S12. Extraction I – LC-MS results

Composition (%)	**A1**	**HA1B1**	**HA1B2**	**B1**	**B2**
Step1-Aq	0,5	42,8	0,0	0,0	0,0
Step2-Aq	0,2	19,5	0,0	0,0	0,0
Step3-Aq-2h	0,1	9,6	0,3	2,7	0,1
Step3-Aq-5h	0,1	8,2	0,1	4,8	0,4
Step3-Aq-22h	0,1	5,1	0,0	9,0	0,3
Step3-Aq-70h	0,2	2,6	0,0	12,3	0,3
Step1-Org	0,6	56,0	0,0	0,0	0,0
Step2-Org	0,2	0,1	0,0	0,0	0,0
Step3-Org-2h	0,1	2,0	1,3	1,5	2,3
Step3-Org-5h	0,1	1,7	1,8	0,9	1,8
Step3-Org-22h	0,1	0,8	3,3	0,0	1,0
Step3-Org-70h	0,2	0,1	4,1	0,0	0,3

Table S13. Extraction I – Infusion-MS results

Composition (%)	Cu(**HA1B1**)$_2$	Cu(**HA1B2**)$_2$	Cu(**HA1B1**)(**HA1B2**)	Cu(**B1**)$_2$	Cu(**B2**)$_2$	Nitrate
Step1-Aq	0,0	0,0	0,0	0,0	0,0	0 ,0
Step2-Aq	77,5	0,0	0,0	1,6	0,4	98,3
Step3-Aq-2h	29,8	4,1	4,7	2,7	1,2	52,0
Step3-Aq-5h	34,9	2,3	3,1	2,6	0,8	60,3
Step3-Aq-22h	32,0	1,1	2,0	10,9	1,1	72,5
Step3-Aq-70h	19,2	0,7	1,4	25,2	0,4	76,8
Step1-Org	0,0	0,0	0,0	0,0	0,0	0,0
Step2-Org	0,3	0,0	0,0	0,1	0,0	1,7
Step3-Org-2h	15,6	14,1	3,9	3,9	0,0	48,0
Step3-Org-5h	8,3	18,9	5,1	0,9	3,1	39,7
Step3-Org-22h	3,9	24,3	2,3	0,8	1,7	27,5
Step3-Org-70h	1,2	28,3	1,5	1,1	1,0	23,1

Table S14. Extraction II – LC-MS results

Composition (%)	**A1**	**HA1B1**	**HA1B2**	**B1**	**B2**
Step1-Aq	0,9	24,0	0,0	5,2	0,0
Step2-Aq	1,2	9,6	0,0	2,4	0,0
Step3-Aq-2h	0,3	3,9	0,1	2,4	0,2
Step3-Aq-21h	0,3	0,8	0,0	3,6	0,6
Step3-Aq-38h	0,1	0,4	0,0	7,8	0,5
Step3-Aq-62h	0,3	0,4	0,0	7,7	0,5
Step1-Org	10,1	48,3	0,0	11,5	0,0
Step2-Org	1,3	4,1	0,0	1,5	0,0
Step3-Org-2h	0,1	6,0	2,2	3,0	1,8
Step3-Org-21h	0,2	2,8	5,7	4,5	1,5
Step3-Org-38h	0,2	1,2	4,9	4,1	0,8
Step3-Org-62h	0,2	1,0	4,8	4,3	0,9

Table S15. Extraction II – Infusion-MS results

Composition (%)	Cu(**HA1B1**)$_2$	Cu(**HA1B2**)$_2$	Cu(**HA1B1**)(**HA1B2**)	Cu(**B1**)$_2$	Cu(**B2**)$_2$	Nitrate
Step1-Aq	0,0	0,0	0,0	0,0	0,0	0,0
Step2-Aq	76,7	0,0	0,0	1,6	0,0	97,6
Step3-Aq-2h	25,0	4,1	13,3	13,5	1,3	62,4
Step3-Aq-21h	10,8	1,8	8,8	23,2	1,3	82,7
Step3-Aq-38h	8,4	1,4	6,9	28,4	1,1	78,5
Step3-Aq-62h	8,2	1,3	6,7	29,5	0,5	82,5
Step1-Org	0,0	0,0	0,0	0,0	0,0	0,0
Step2-Org	1,7	0,0	0,0	0,0	0,0	2,4
Step3-Org-2h	2,3	14,9	3,5	0,6	1,5	37,6
Step3-Org-21h	0,8	30,0	1,8	0,6	0,7	17,3
Step3-Org-38h	0,7	30,4	1,5	0,6	0,6	21,5
Step3-Org-62h	0,8	29,8	2,0	0,6	0,6	17,5

Table S16. Extraction III – LC-MS results

Composition (%)	**A1**	**HA1B1**	**HA1B2**	**B1**	**B2**
Step1-Aq	1,1	9,2	0,0	17,8	2,0
Step2-Aq-1h	0,2	3,2	0,0	3,2	0,8
Step2-Aq-3h	0,2	2,4	0,0	3,6	0,6
Step2-Aq-22h	0,2	1,1	0,0	6,4	0,5
Step2-Aq-39h	0,2	1,0	0,0	5,2	0,5
Step2-Aq-63h	0,2	1,2	0,0	5,8	0,3
Step1-Org	1,5	31,4	13,8	12,9	10,3
Step2-Org-1h	0,4	4,2	3,2	3,3	1,4
Step2-Org-3h	0,1	4,9	3,7	3,0	1,4
Step2-Org-22h	0,2	2,3	5,0	3,6	0,7
Step2-Org-39h	0,2	2,2	5,5	4,5	0,8
Step2-Org-63h	0,2	3,8	3,8	4,5	0,2

Table S17. Extraction III – Infusion-MS results

Composition (%)	Cu(**HA1B1**)$_2$	Cu(**HA1B2**)$_2$	Cu(**HA1B1**)(**HA1B2**)	Cu(**B1**)$_2$	Cu(**B2**)$_2$	Nitrate
Step1-Aq	0,0	0,0	0,0	0,0	0,0	0,0
Step2-Aq	24,0	3,2	1,3	19,7	1,5	69,0
Step3-Aq-2h	22,1	3,4	1,1	22,0	1,2	69,4
Step3-Aq-21h	13,1	2,0	0,9	26,0	0,8	81,6
Step3-Aq-38h	11,7	2,2	1,0	21,4	0,9	63,6
Step3-Aq-62h	13,3	2,0	0,9	28,2	0,8	75,6
Step1-Org	2,0	23,9	2,9	0,5	1,0	0,0
Step2-Org	1,8	24,4	2,6	0,4	0,9	31,0
Step3-Org-2h	1,5	33,9	1,3	0,0	0,4	30,6
Step3-Org-21h	1,7	38,9	1,4	0,5	0,5	18,4
Step3-Org-38h	1,4	31,0	1,2	0,4	0,8	36,4
Step3-Org-62h	24,0	3,2	1,3	19,7	1,5	24,4

Table S18. Molar ratio of Cu:NO_3 in chloroform phase

Extraction I		Extraction II		Extraction III	
Step	ratio	Step	ratio	Step	ratio
Step2-Org	n.c.	Step2-Org	n.c.	Step2-Org-1h	0,8
Step3-Org-2H	0,6	Step3-Org-2h	0,7	Step2-Org-3h	0,8
Step3-Org-5h	0,5	Step3-Org-21h	1,0	Step2-Org-22h	1,2
Step3-Org-22H	0,7	Step3-Org-38h	1,1	Step2-Org-39h	1,0
Step3-Org-70H	0,8	Step3-Org-62h	1,1	Step2-Org-63h	1,2

8.5 ICP-OES analysis – Determination of Copper content

Table S19. Extraction I, II and III – ICP-OES results – Cu tenors

Extraction I			Extraction II			Extraction III		
% Cu	Aq	Org	%Cu	Aq	Org	%Cu	Aq	Org
Step2	99%	1%	Step2	98%	2%	Step2-1h	52%	48%
Step3-2h	53%	47%	Step3-2h	51%	49%	Step2-3h	56%	44%
Step3-5h	55%	45%	Step3-21h	64%	36%	Step2-22h	56%	44%
Step3-22h	59%	41%	Step3-38h	62%	38%	Step2-39h	56%	44%
Step3-70h	59%	41%	Step3-62h	62%	38%	Step2-63h	57%	43%

Table S20. Extraction reverse order – ICP-OES results – Cu tenors

%Cu	Aq	Org
Step2	14%	86%
Step3-2h	61%	39%
Step3-14h	66%	34%
Step3-21h	66%	34%
Step3-38h	68%	32%
Step3-46h	70%	30%
Step3-62h	68%	32%

8.6 Extraction I (full characterization)

8.6.1.1 Step 1

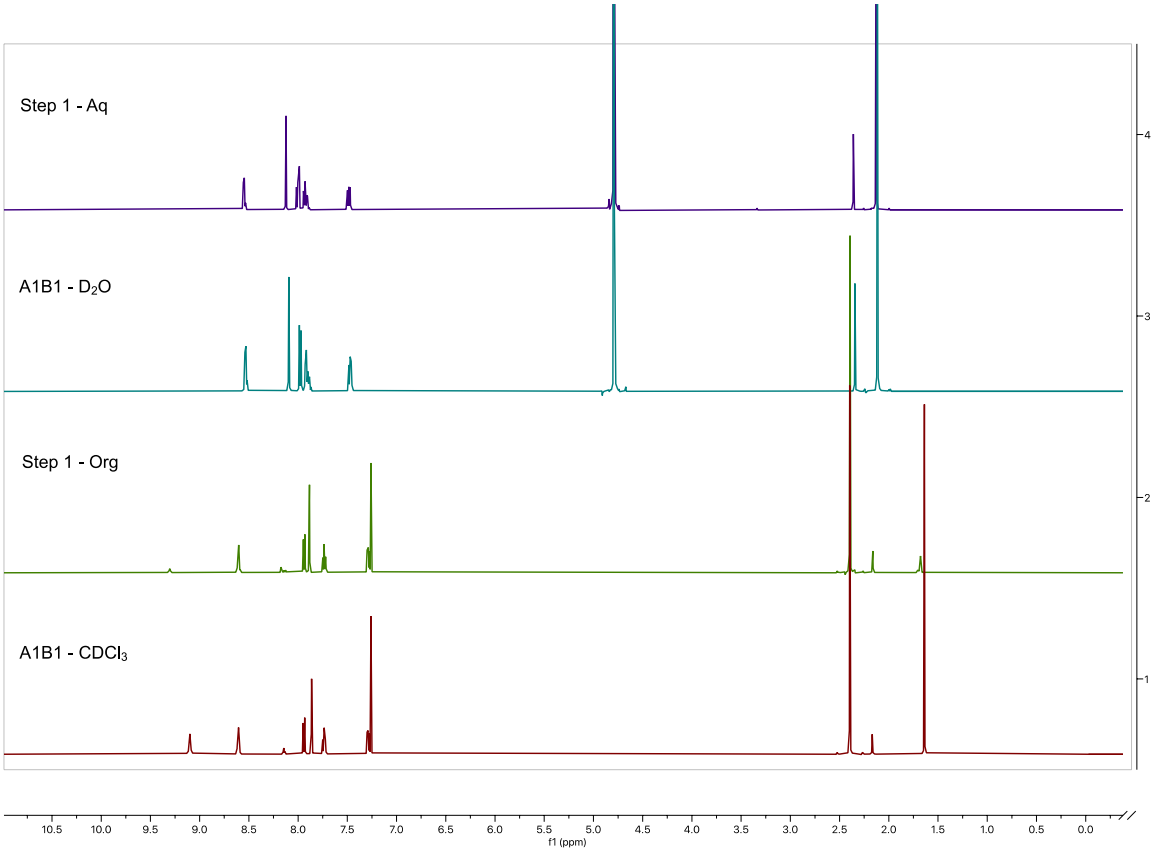


Figure S60. ^{1}H NMR spectra of step 1 with references – $D_2O/CDCl_3$ – 296 K

8.6.1.2 Step 2

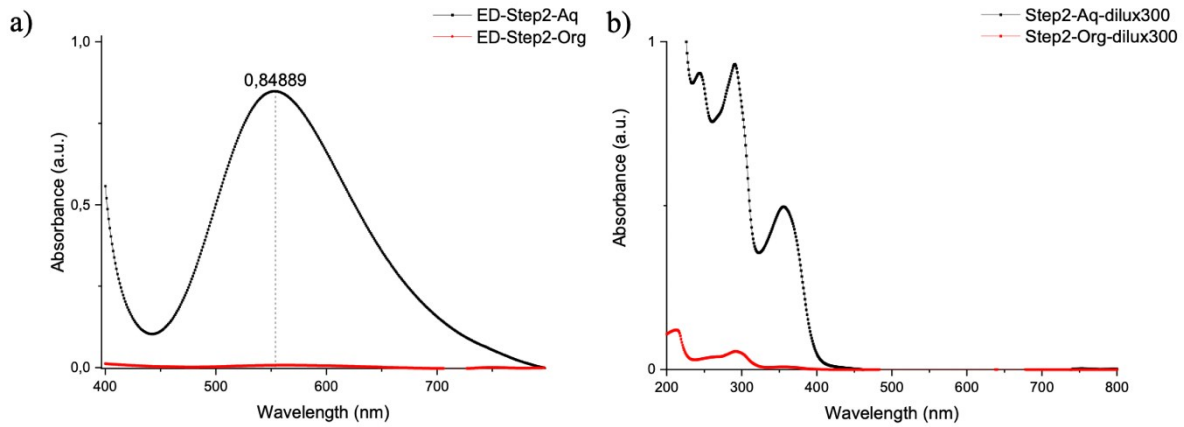


Figure S61. a) UV-visible photometric titration of Cu(II) in step 2 – b) UV-visible spectra of aqueous and organic phase of step 2

λ = 244 nm: CHCl3 λ = 268 nm: (**A1**) λ = 291 nm: (**HA1B1**) λ = 356 nm: [Cu(II)(**HA1B1**)$_2$]

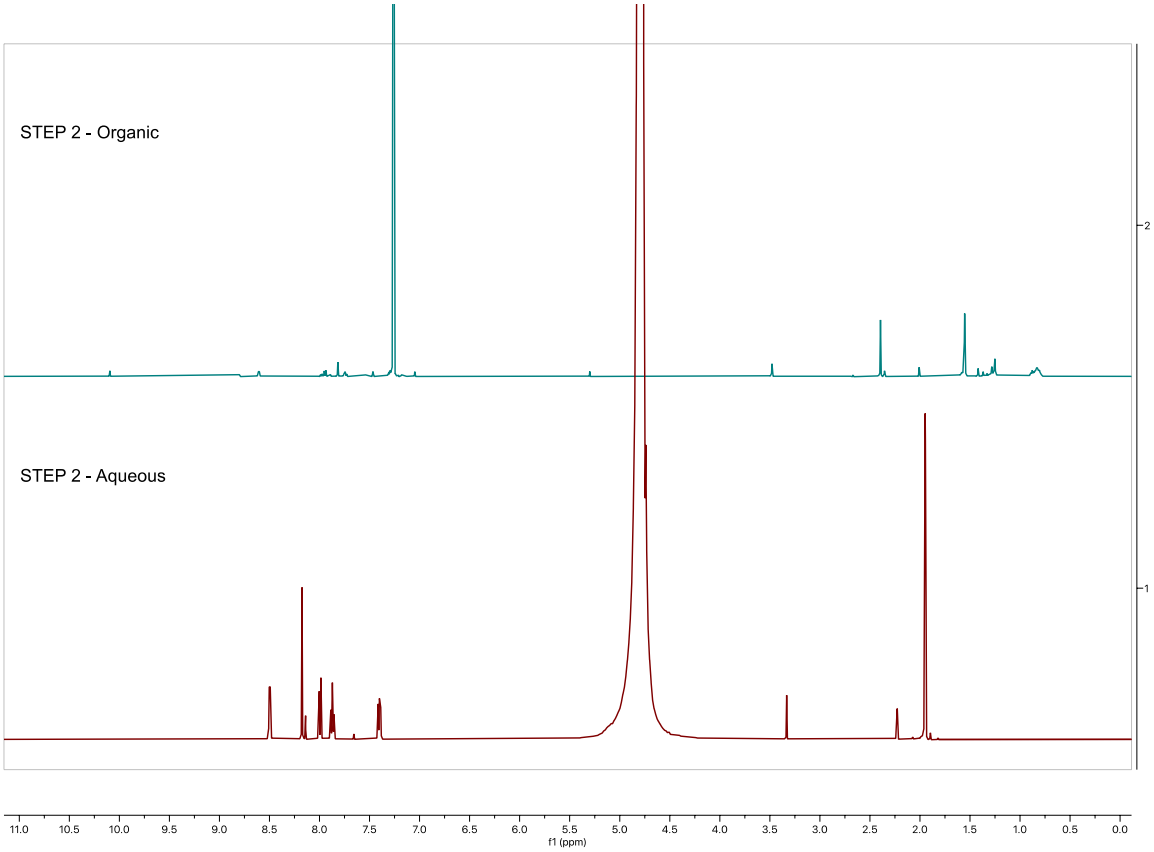


Figure S62. ^{1}H NMR spectra of step 2 – Comparison – $D_2O/CDCl_3$ – 296 K

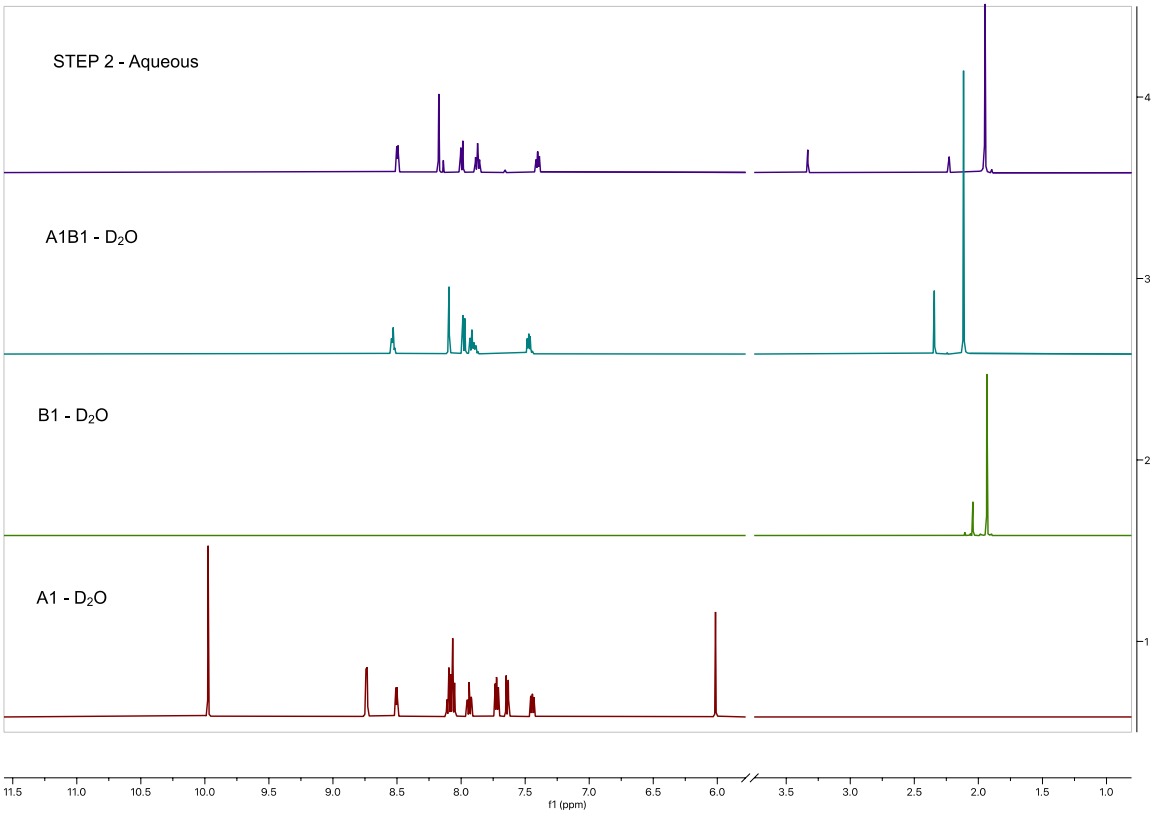


Figure S63. ^{1}H NMR spectra of step 2 – Aqueous phase with references – D_2O– 296 K

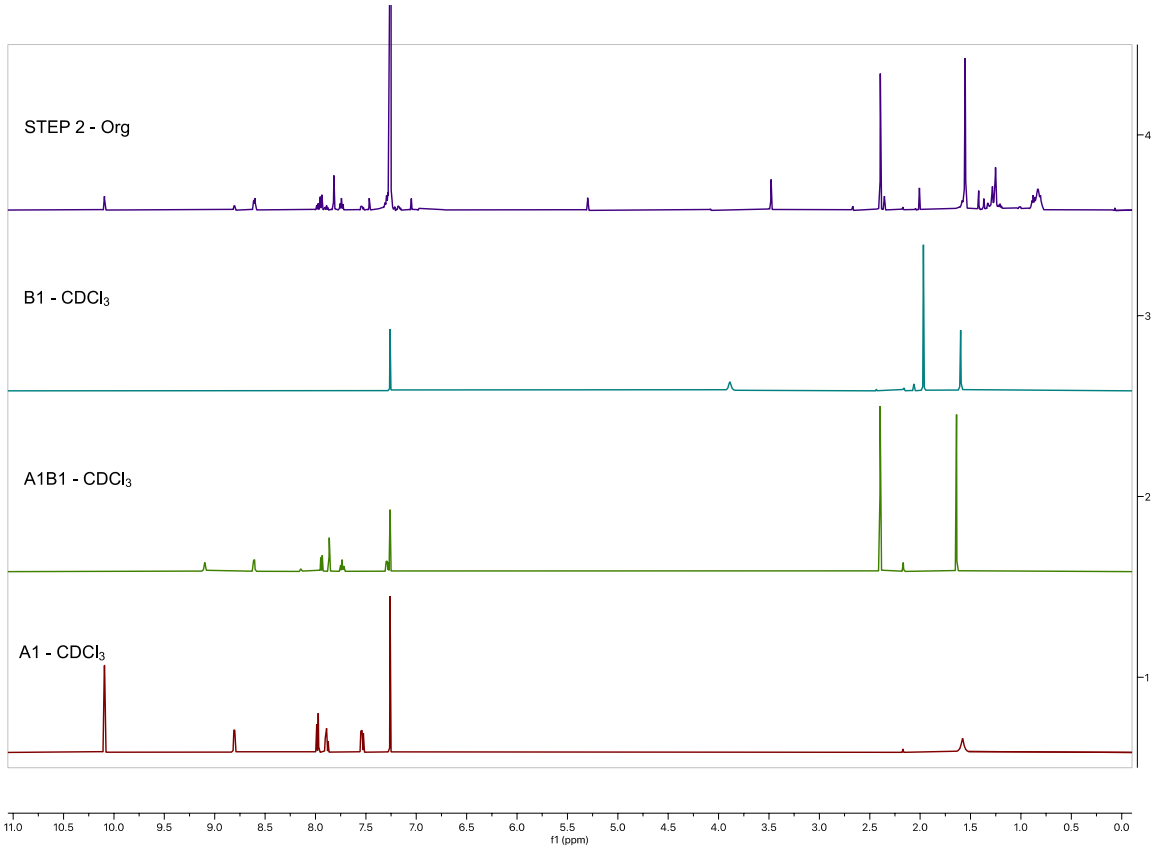


Figure S64. ^{1}H NMR spectra of step 2 – Organic phase with references - $CDCl_3$ – 296 K

8.6.1.3 Step 3

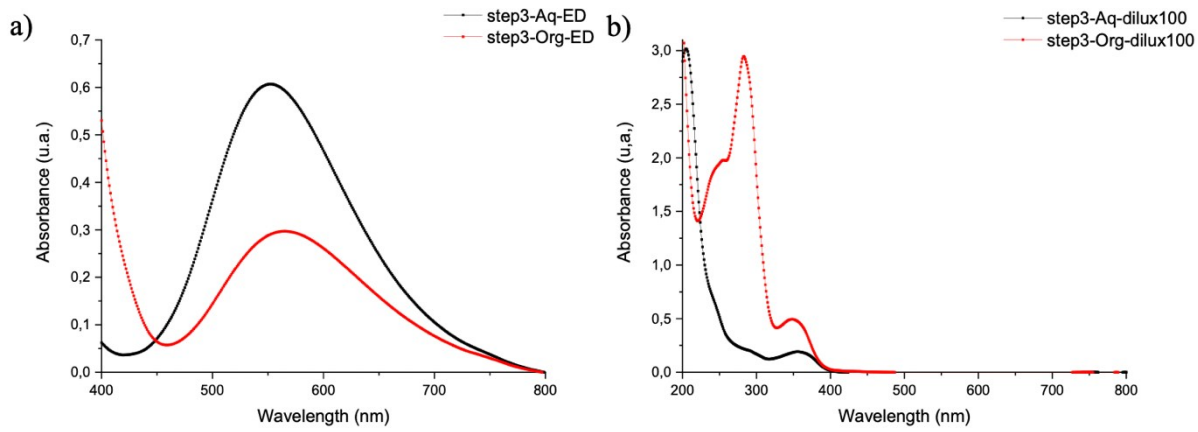


Figure S65. a) UV-visible photometric titration of copper in step 3 – b) UV-visible spectra of aqueous and organic phase of step 3

λ = 244 nm: $CHCl_3$ λ = 267 nm: (**A1**) λ = 293 nm: (**HA1B1**) + (**HA1B2**)
λ = 355 nm: [Cu(II)(**HA1B1**)$_2$] λ = 358 nm: [Cu(II)(**HA1B2**)$_2$]

For ^{1}H NMR analysis, Cu(II) is precipitated with an excess of $Na_2S{\cdot}9H_2O$ (50 ·µL at 1M).

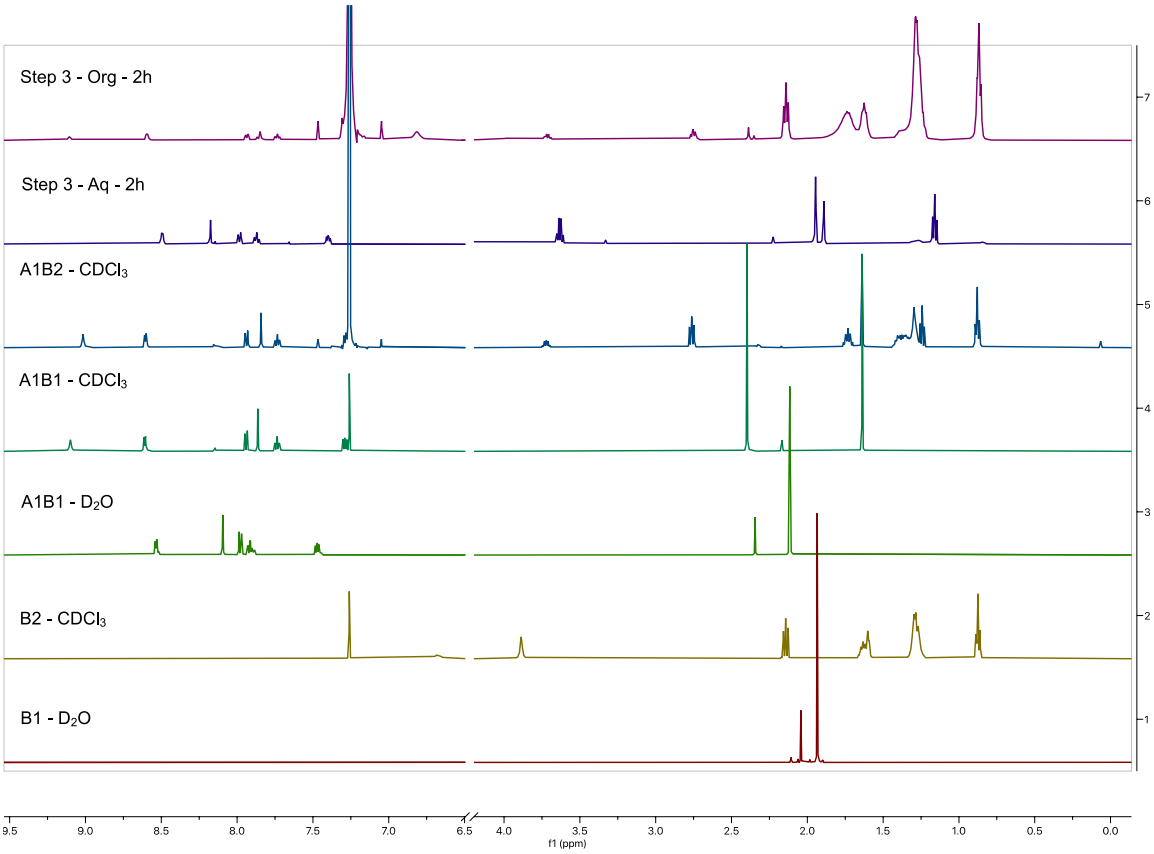


Figure S66. ^{1}H NMR spectra of step 3 – 2 hours after **B2** addition – Aqueous and organic phases with references

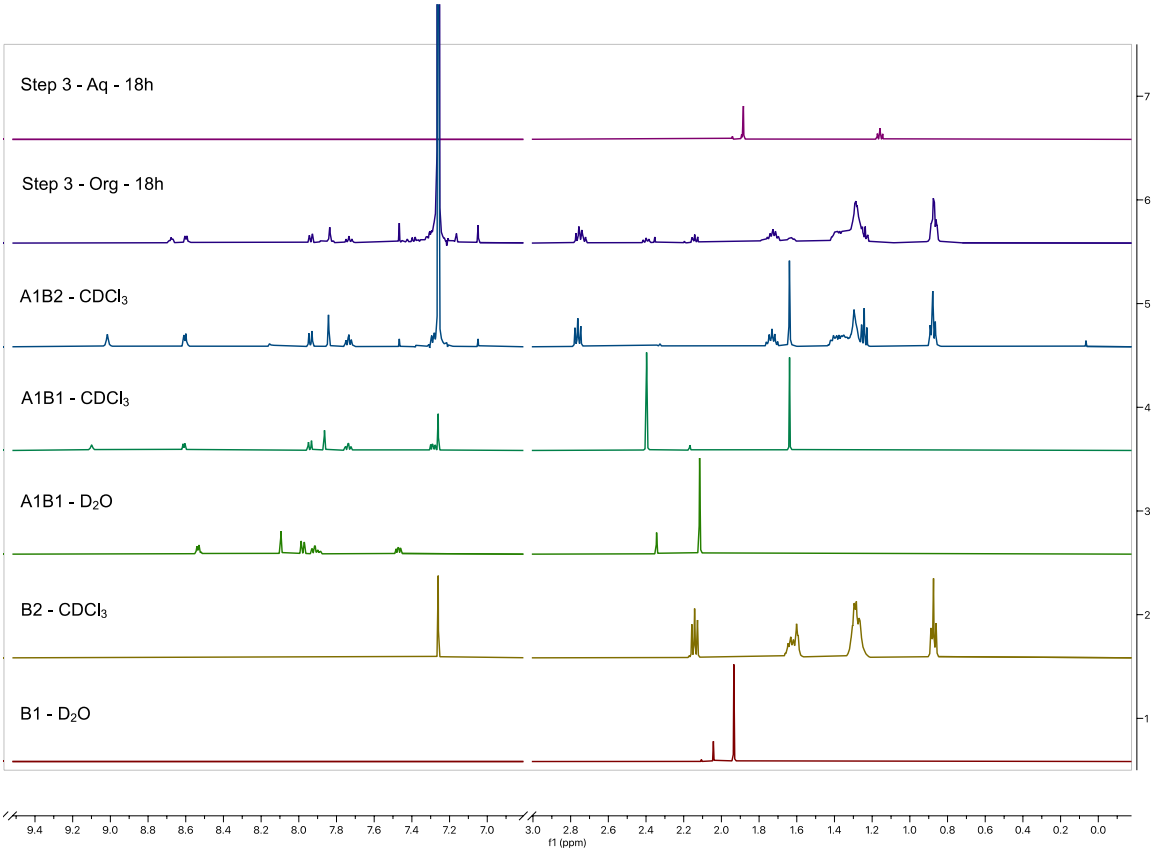


Figure S67. ^{1}H NMR spectra of step 3 –18 hours after **B2** addition – Aqueous and organic phases – $D_2O/CDCl_3$ 296K

8.7 Extraction mechanism scheme

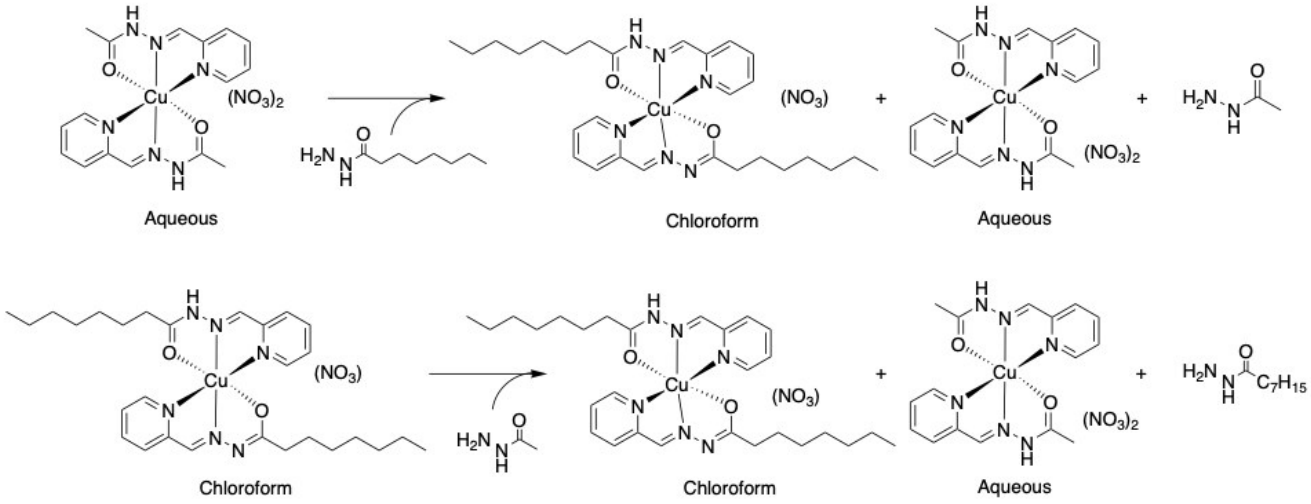


Figure S68. Phase transfer of copper(II) by adaptive dynamic covalent chemistry

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The three single crystals structures have been deposited on the CCDC base with the registration number: CCDC-2014872-2014874.