Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

for

Characterization and isolation of a 18-crown-6 complex of potassium hydroxyde prepared by milling: application to mechanochemical organic synthesis

by

Leonarda Vugrin,[a] Ivan Halasz,*,[a] Hervé Geneste*,[b]

[a]Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička c. 54, 10000 Zagreb, Croatia.

[b]AbbVie Deutschland GmbH & Co. KG, Neuroscience Research, D-67008 Ludwigshafen, Germany

E-mail: ivan.halasz@irb.hr; herve.geneste@abbvie.com

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1.0. General information

Experimental section

Materials and methods

The 18-crown-6 ether (CAS: 17455-13-9), potassium hydroxide pellets (CAS: 1310-58-3), and dibenzo-18-crown-6 ether (CAS: 14187-32-7) were purchased from Sigma-Aldrich. Potassium iodide (CAS: 7681-11-0), potassium bromide (CAS: 7758-02-3) and potassium chloride (CAS: 7440-09-7) were purchased from Kemika. 2-nitrobenzaldehyde (CAS: 552-89-6) was purchashed from Merck. 4-fluorobenzophenone (CAS: 97345-83-5) was purchased from Thermo Fisher Scientific. The chemicals used in this study were not further purified.

The experiments were performed at room temperature using an IST500 mixer mill operating at 30 Hz. Reactions were conducted in 14 mL polymethyl methacrylate (PMMA) transparent jars that allowed in situ Raman monitoring or stainless steel jars. Two stainless steel (SS, mass 1.4 g) and one (mass 3.4 g) or two (mass 1.6 g) zirconium oxide (ZrO_2) milling balls were used. For better reaction monitoring, aluminum oxide or silica gel was used as a milling auxiliary. The weighing of starting materials and the preparation for analysis were performed in a controlled nitrogen atmosphere in a glove box (Figure S1).

The 1D NMR spectra were recorded on a Bruker Avance III HD 300 or 600 MHz Avance spectrometer. Chemical shifts are reported in ppm and referenced to the residual solvent signals ($CDCl_3$). Infrared measurements were performed using a PerkinElmer Spectrum Two instrument (FTIR/ ATR). Thermal TGA/DTA was performed in a nitrogen-controlled atmosphere at a heating rate of 5 °C/min and a maximum temperature of 150 °C.

Powder X-ray diffraction data for the crystal structure solution were collected on a Panalytical Aeris desktop laboratory powder X-ray diffractometer equipped with a copper X-ray tube operating at 40 kV and 7.5 mA, in Bragg-Brentano geometry, with the sample prepared in a thin layer on a zero-background silicon holder. The synthesized complexes were covered with Kapton foil before performing the measurements because of their hygroscopic properties (Figure S2).[1] The crystallographic dataset for the structures is available from the Cambridge Structural Database and was used for structure refinement. Visualization of the structures was performed using Mercury. Crystal structure solution was carried out from laboratory diffraction data using rigid body description for the molecular fragments. Rietveld analysis and crystal structure solution were carried out using the computer program Topas. The crystal structure model for [18c6K]Cl(H_2O) is deposited with the Cambridge Crystallographic Data Centre under the deposition number CCDC 2232519.

Raman experiments were performed using a portable Raman system with a PD-LD (Necsel) BlueBox laser source with an excitation wavelength of 785 nm, equipped with a B&WTek fiber optic Raman BAC102 probe, and coupled to an OceanOptics Maya2000Pro spectrometer. Time-resolved in situ Raman spectra were automatically collected where monitoring was performed after the jar and background subtraction.[2] Experimental data were analyzed in Matlab.

Figure S1. Sample preparation in a glove box: weighing of starting materials, loading into the milling jars, and preparation for PXRD analysis.

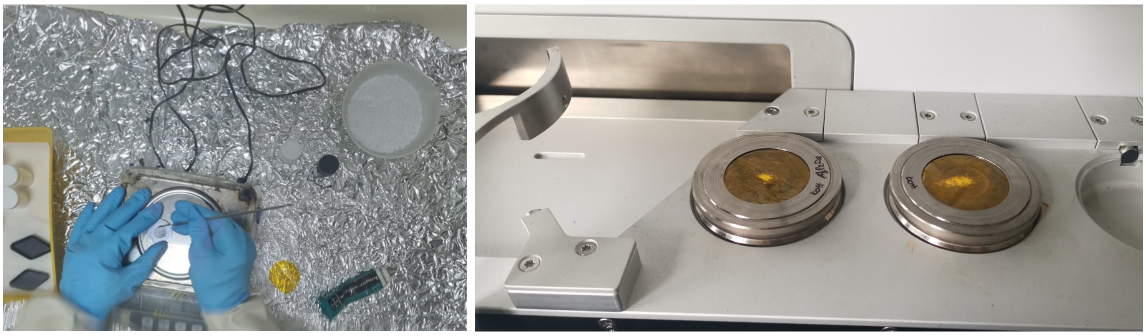
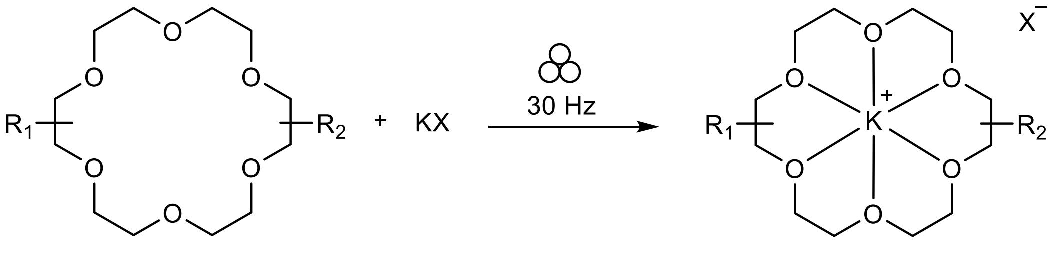


Figure S2. Preparation of samples for PXRD analysis in a glove box: the samples were covered with a Kapton foil, which was glued to the sides of the sample holder.

2.0. Milling synthesis details

2.1. Crown ether complexes

General procedure for the mechanochemical complexation of crown ethers

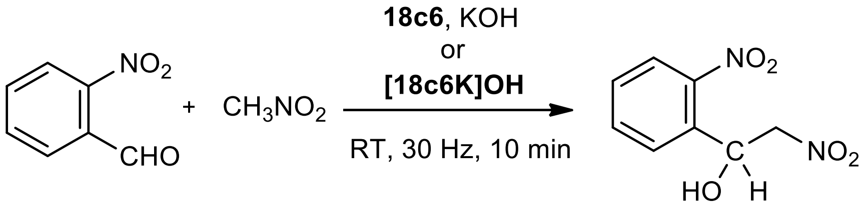


R_1, R_2 - H
R_1, R_2 - Ar

X - Cl^-,Br^-,I^-

Equimolar amounts of **18c6** ether or **db18c6** ether, and potassium salts were transferred to milling jars made of PMMA or SS with two milling balls made of SS or ZrO_2 inside the glove box. If it was necessary to record better Raman spectra in a real time, the filler (aluminum oxide or silica gel) was added to prevent gluing of the starting materials to the jar walls and to improve mixing. Milling was performed at 30 Hz, and after the milling was halted, the crude mixture was sent for PXRD and IR analysis. Complex formation was achieved after ca. 10 min of milling, which was confirmed by in situ experiments.

2.2. Henry reaction

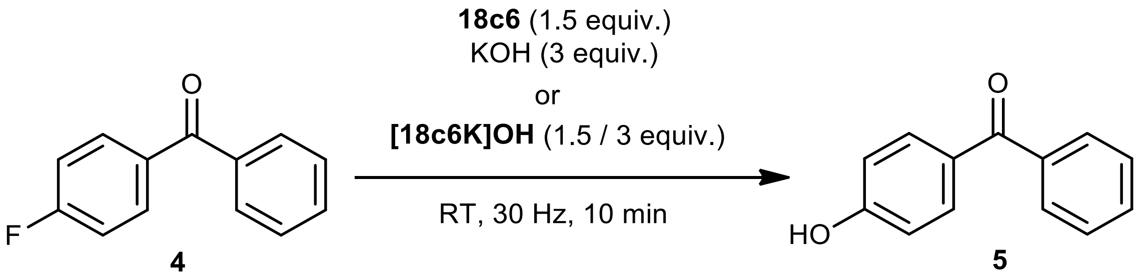


1 **2** **3**

The literature method was followed to synthesize the desired product (**3**).[3,4] 2-nitrobenzaldehye (**1**) (0.5 mmol, 75.56 mg), nitromethane (**2**) (2.5 equiv.), **18c6** ether (20 mol. %, 26.41 mg), and KOH (20 mol. %, 5.61 mg) were milled in an SS jar with two SS balls, mass 1.4 g for 1 h at RT. The reaction was monitored by TLC (hexane/EtOAc 8/2), where it was determined that the reaction was completed within 10 min. After milling, the mixture was added to water and extracted with tert-butyl methyl ether (3x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under a vacuum. A viscous yellow liquid was used for ^1H NMR analysis.

The reaction was also performed in the presence of a previously formed complex, **[18c6K]OH** (20 mol%), as well as in the absence of a catalyst under the same experimental conditions. Grinding without a catalyst was not efficient, and the desired product was not formed.

2.3. Hydroxylation reaction



4

5

4-fluorobenzophenone (**5**) (0.15 mmol), **18c6** ether (1.5 equiv.), and potassium hydroxide (3 equiv.) were added to the SS Jar with 2 SS balls, mass 1.4 g. After 1 h of reaction at 30 Hz, the mixture was purified by extraction (EtOAc/ H_2O), dried over Na_2SO_4, and evaporated using a rotary evaporator.[5] The white crude sample was sent to ^1H NMR analysis. The ^1H NMR yield was determined according to the signals of the trimethoxybenzene standard. The reaction was also performed without catalyst addition and with a previously mechanically formed complex **[18c6K]OH** (1.5 and 3 equiv.) under identical experimental conditions. The white product was analyzed using ^1H NMR and FTIR spectroscopy.

Real-time in situ Raman monitoring of the 4-fluorobenzophenone hydroxylation was performed.

3.0. Raman monitoring

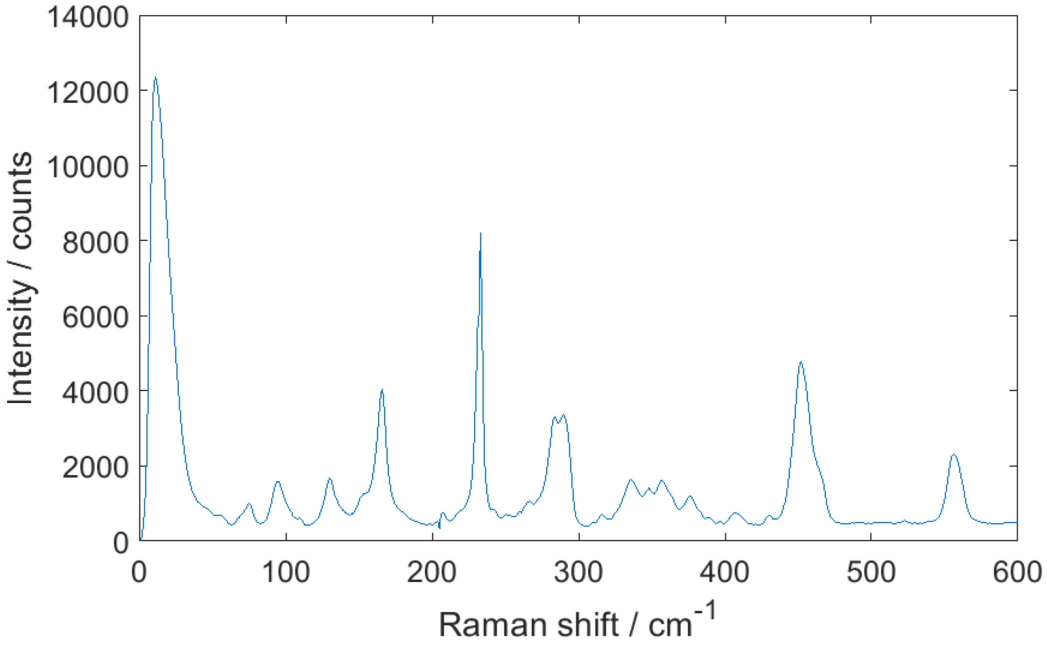


Figure 3. Extracted Raman spectra of starting material, **18c6** ether.

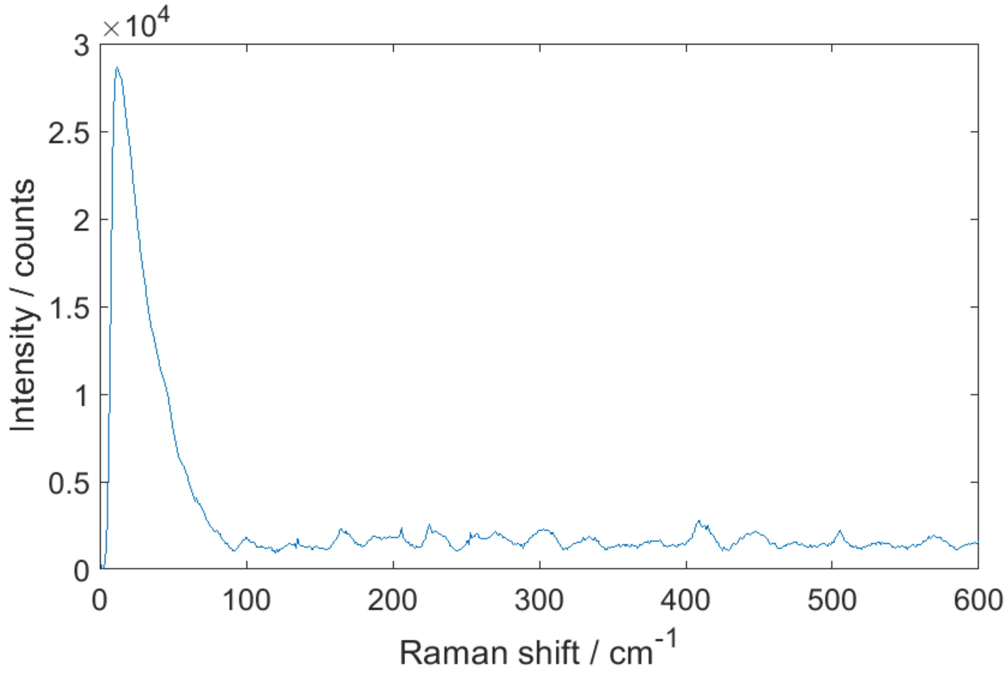


Figure 4. Extracted Raman spectra of starting material, **db18c6** ether.

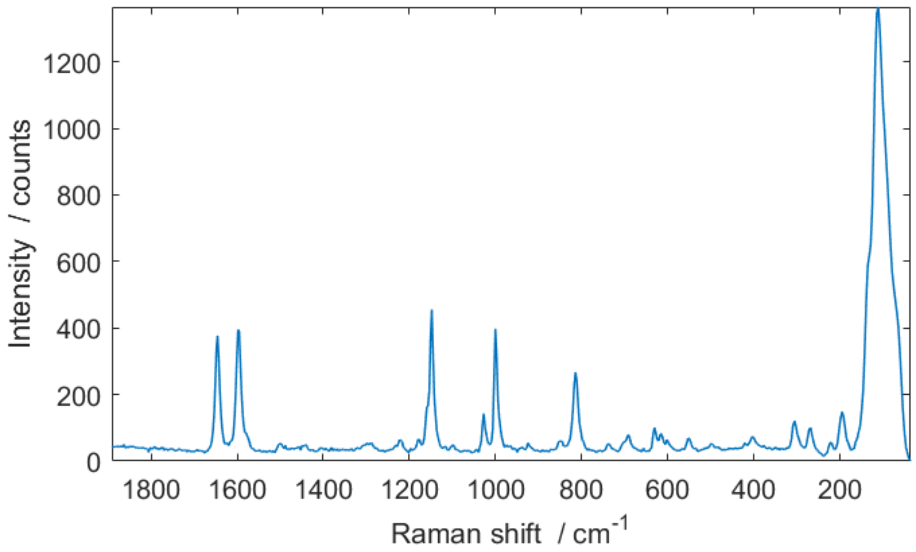


Figure 5. Extracted Raman spectra of the starting material, (**4**).

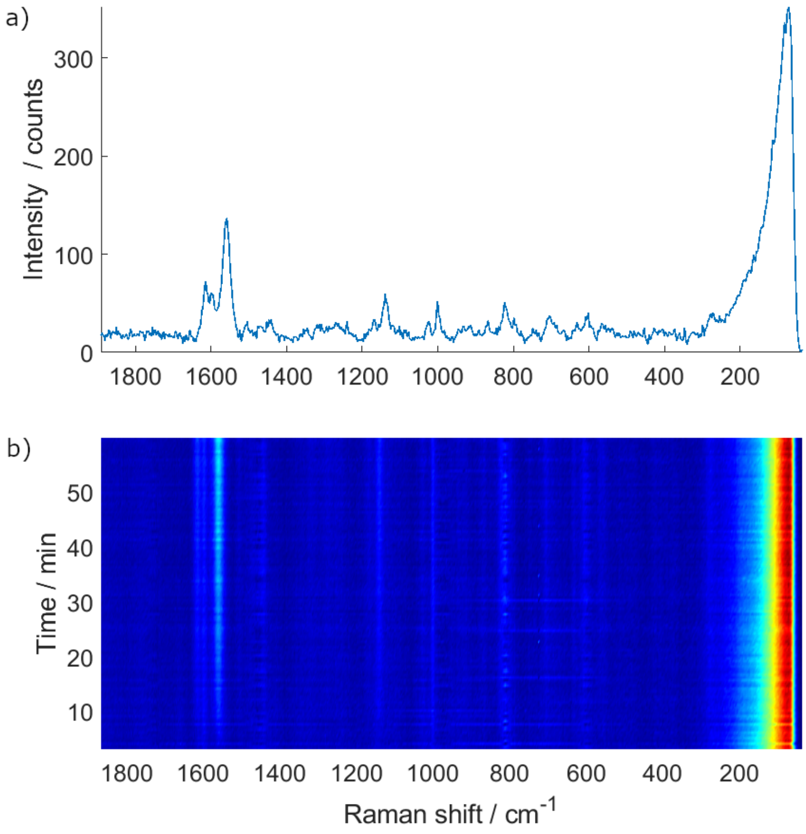


Figure 6. a) Extracted Raman plot corresponding to the spectrum collected in the 60th minute of recording the reaction between (**4**) and KOH catalyzed by **18c6** ether. b) 2D Raman plot of the formation of (**5**) via catalysis with **18c6** ether.

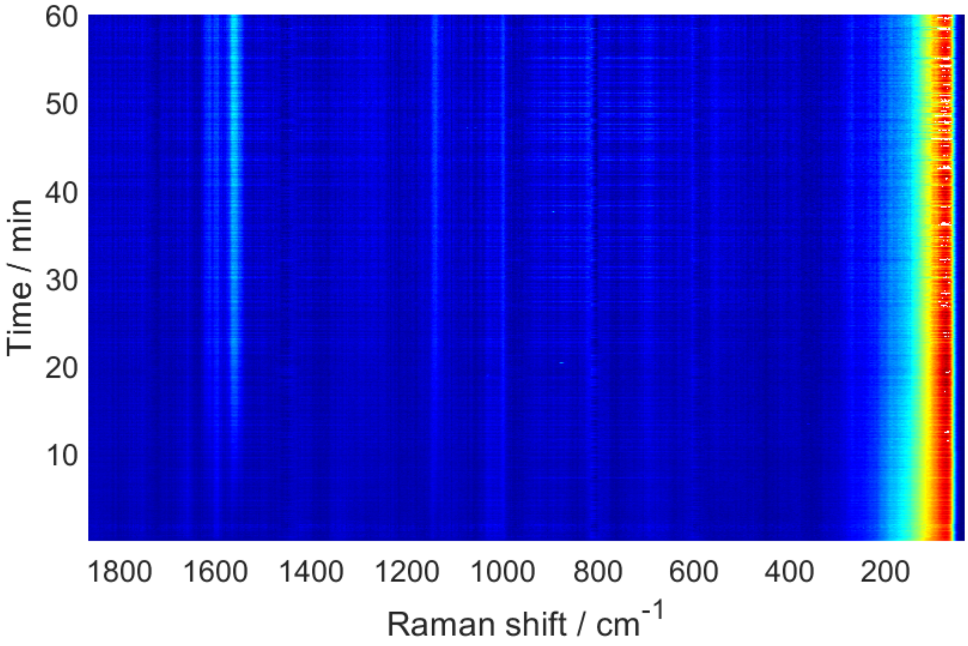


Figure 7. 2D Raman plot of the formation of (**5**) via catalysis with the **[18c6K]OH** complex.

4.0. Powder X-Ray Diffraction

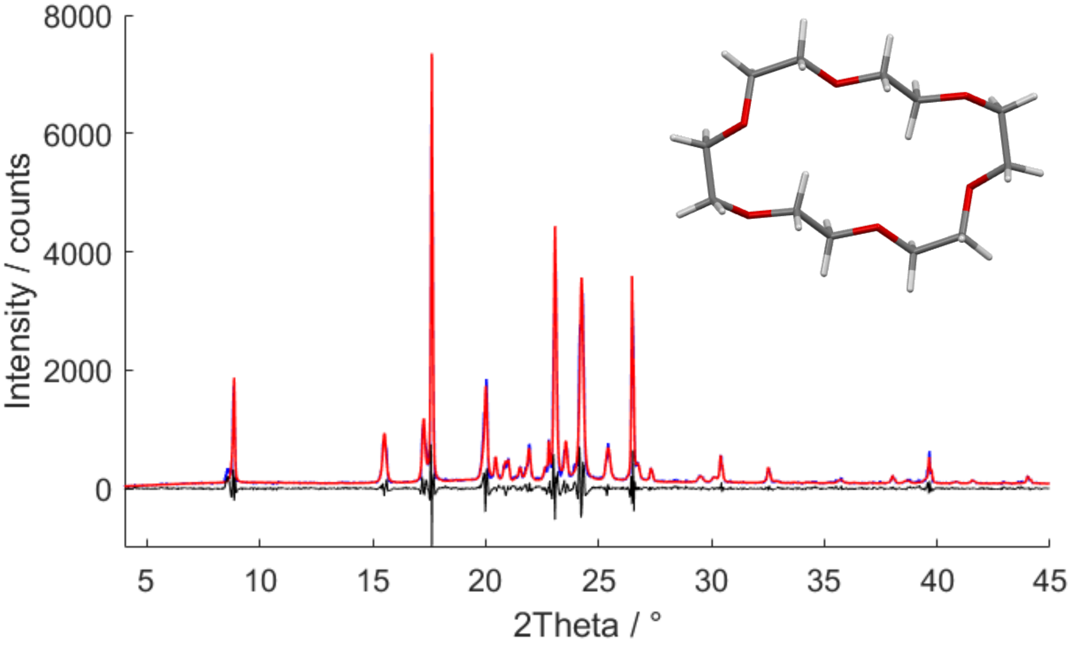


Figure S8. Rietveld plot for the starting material, **18c6** ether (refcode: HOXOCD).[6] Colour legend: blue – measured, red – calculated, black - difference.

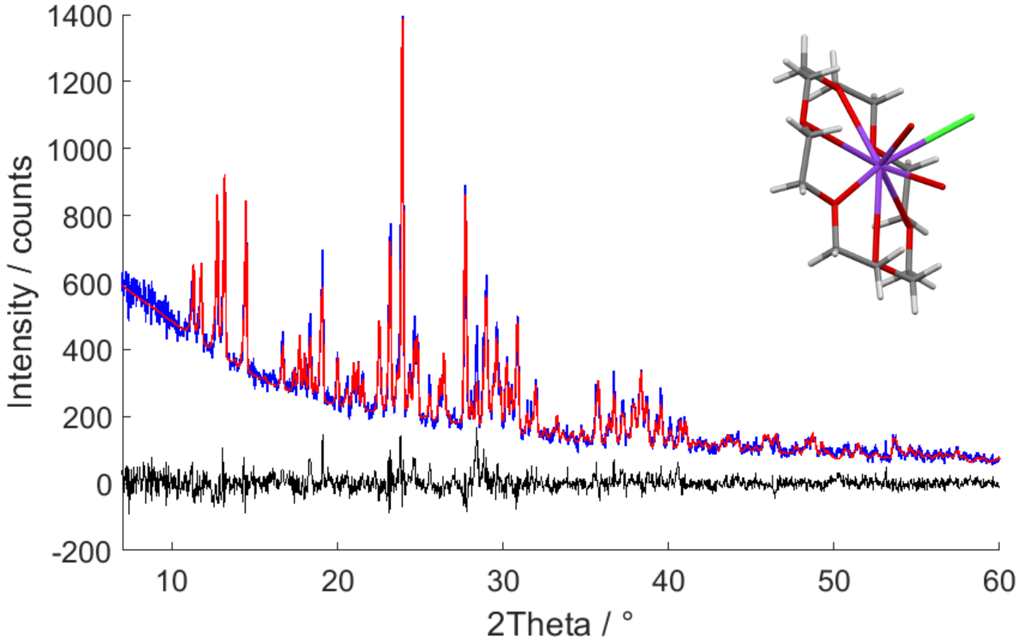


Figure S9. Rietveld plot for the sample prepared by milling **18c6** ether and **KCl** analyzed after a few days of standing in an air atmosphere (CSD refcode: GEBCOH).[7] The primary anhydrous complex absorbed two water molecules upon staying in an Eppendorf tube. Colour legend: blue – measured, red – calculated, black - difference.

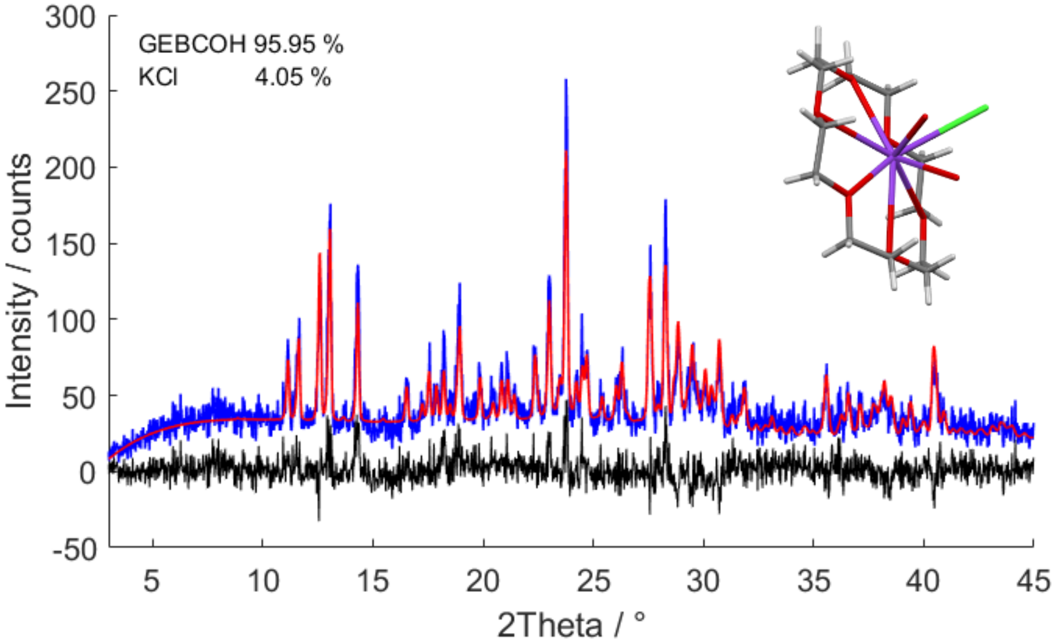


Figure S10. Rietveld plot for the sample prepared by milling **18c6** ether, **KCl**, and filler, Al_2O_3 added in order to improve the quality of Raman spectra during the monitoring of the complexation reaction. The diffractogram corresponds to the crystal structure of the dihydrate complex (refcode: GEBCOH). Colour legend: blue – measured, red – calculated, black - difference.

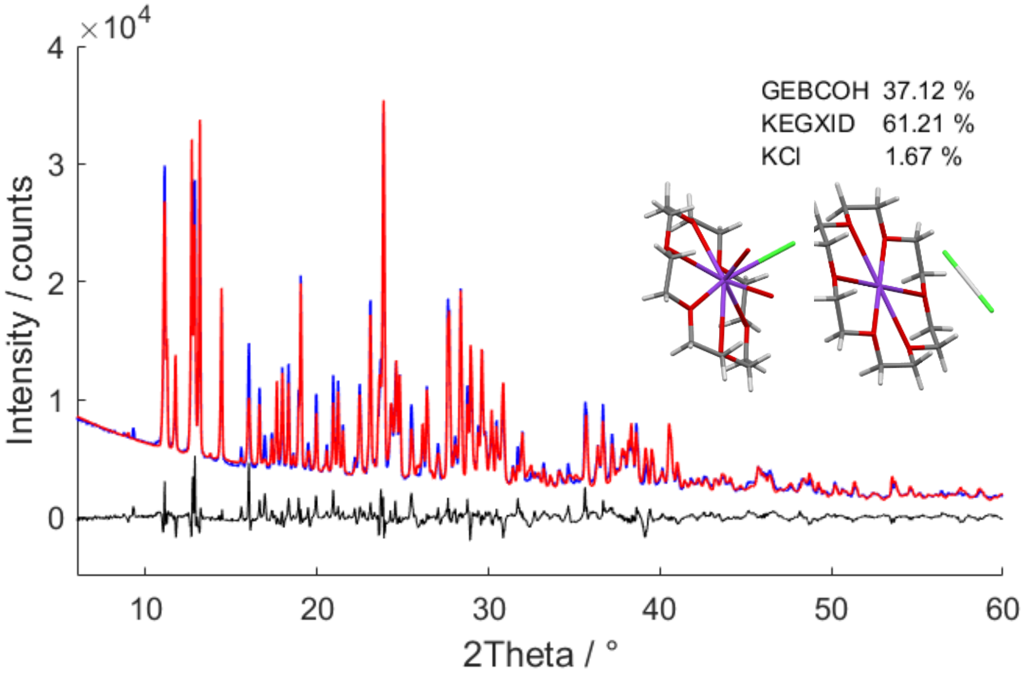


Figure S11. Rietveld plot for the sample collected after in situ Raman monitoring of the reaction between **18c6** ether and **KCl** with aluminum oxide as a filler. The sample was initially not prepared in the glove box, and after milling, it was sent for PXRD anaylsis without prior purification (refcode: GEBCOH and KEGXID).[8] Colour legend: blue – measured, red – calculated, black - difference.

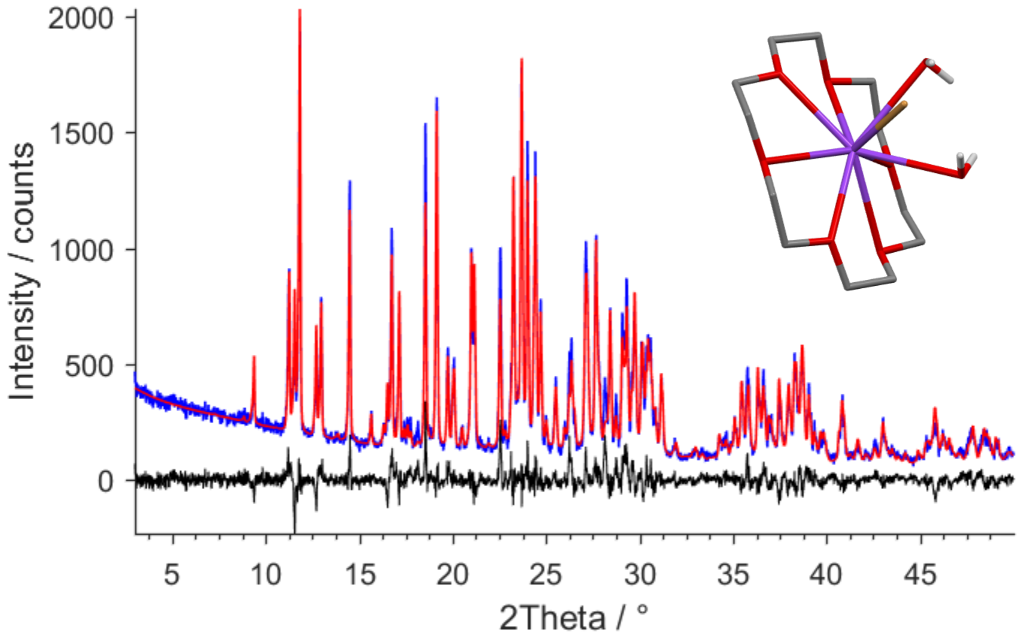


Figure S12. Rietveld plot for the complex [**18c6K]Br** (refcode: XATXUM).[9] Colour legend: blue – measured, red – calculated, black - difference.

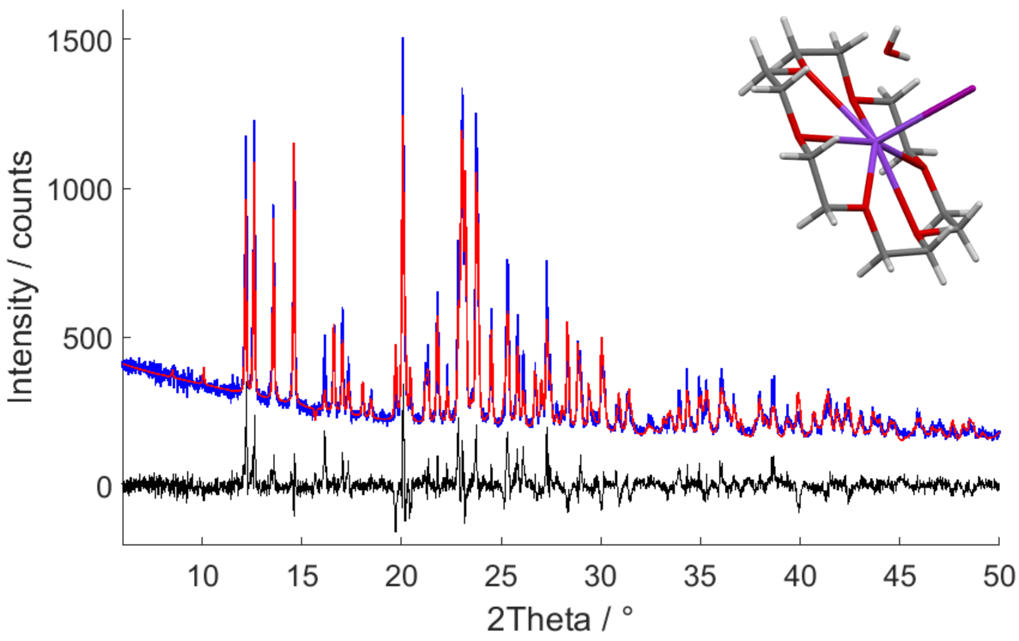


Figure S13. Rietveld plot for the complex between **18c6** ether and **KI** (refcode: NEBBEC01).[10] Colour legend: blue – measured, red – calculated, black - difference.

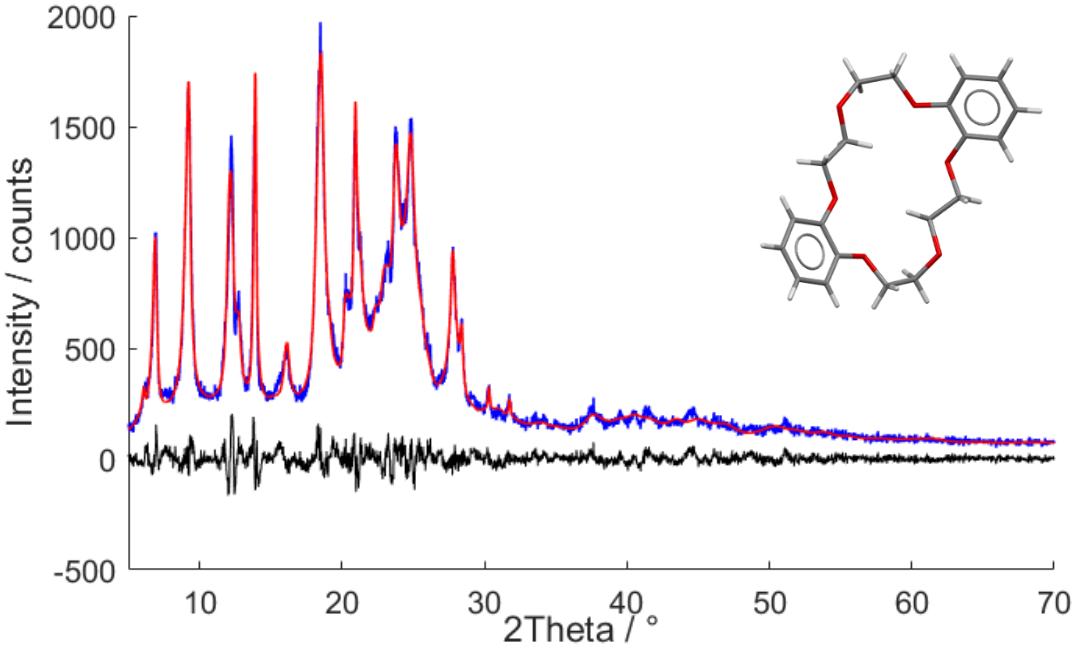


Figure S14. Rietveld plot for the starting material, **db18c6** ether (refcode: ROFYIV).[11] Colour legend: blue – measured, red – calculated, black - difference.

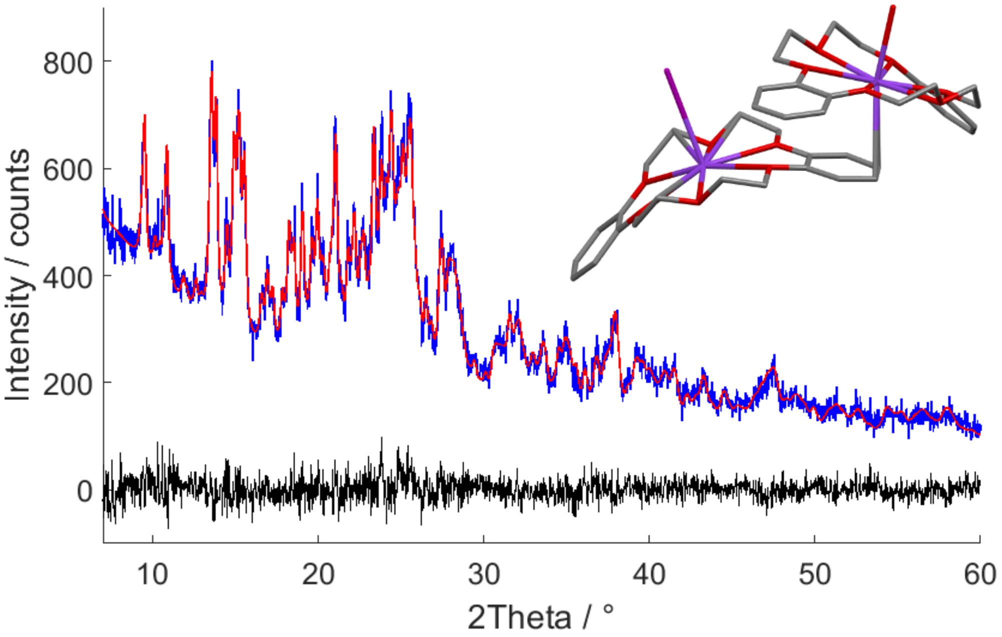


Figure S15. Rietveld plot for the complex [**db18c6K]I** (refcode: HOODKI01).[12] The same diffraction pattern was obtained when the milling was conducted using H_2O (1 equiv.) as an additive. Colour legend: blue – measured, red – calculated, black - difference.

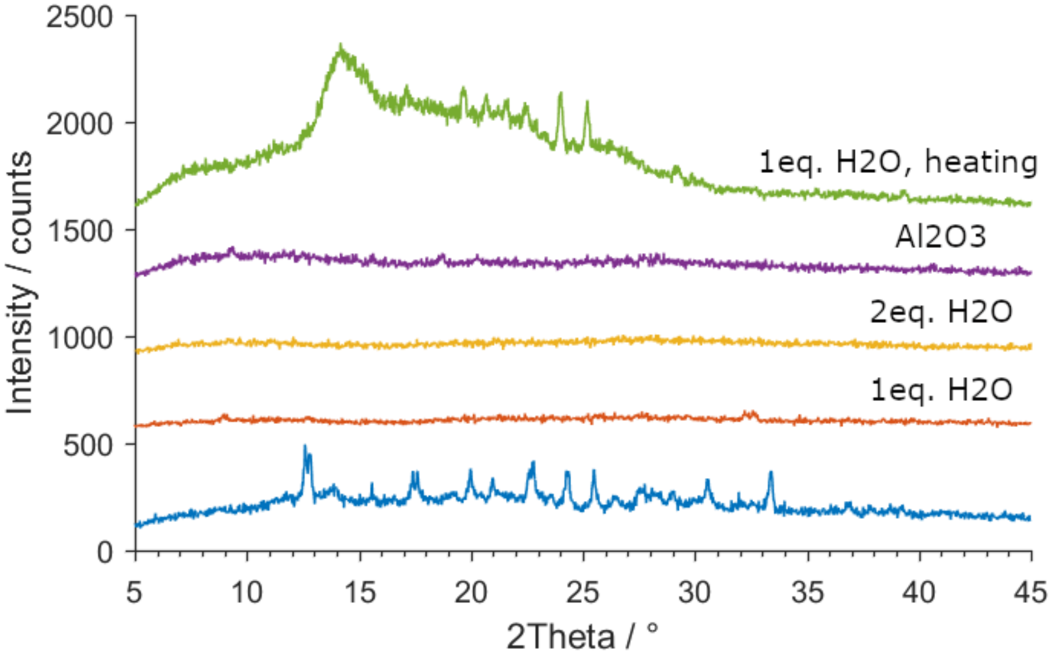


Figure S16. Diffractograms of complex between **18c6** and **KOH** prepared in different ways to improve its crystallinity by heating, solvent evaporation, water, or filler addition.

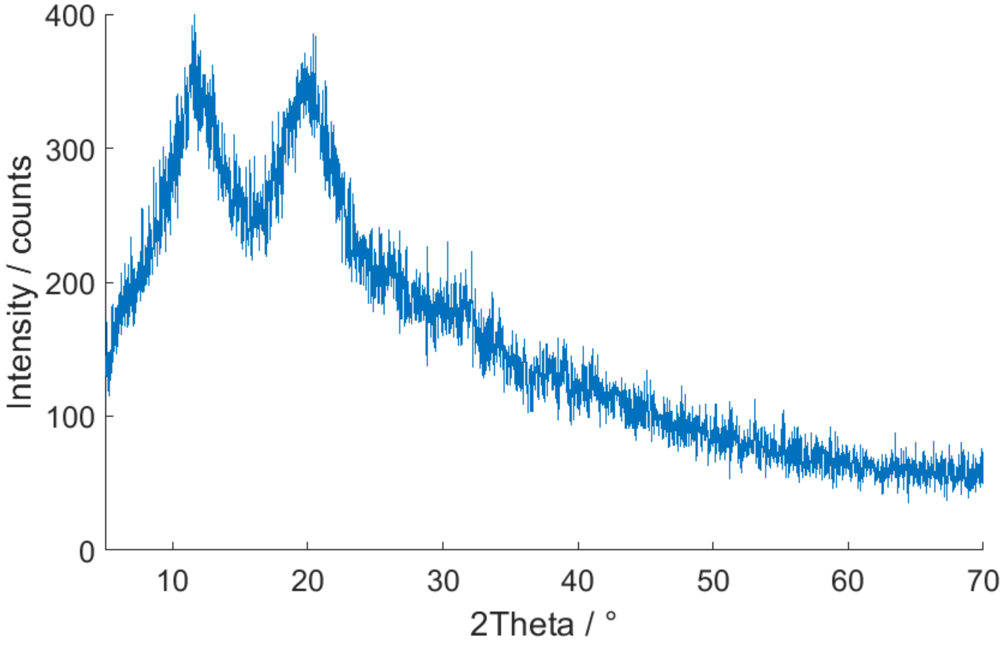
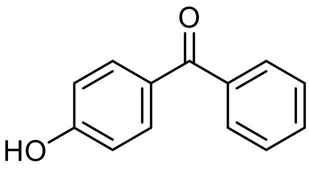


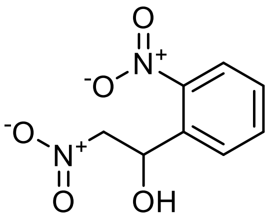
Figure S17. The diffraction pattern of a sample prepared by weighing the initial materials, **18c6** ether, and **KOH** in an inert atmosphere, milling and heating in a vacuum dryer at 80 °C. The sample was covered with capton foil for water protection during PXRD measurements.

5.0. ^{1}H NMR analysis



(4-hydroxyphenyl)(phenyl)methanone, (**65**) (white solid)

^{1}H NMR (600 MHz, CDCl$_3$), δ/ ppm = 7.82 – 7.77 (m, 2H), 7.78 – 7.73 (m, 2H), 7.64 – 7.53 (m, 1H), 7.52 – 7.41 (m, 2H), 6.96 – 6.87 (m, 2H), 5.75 (s, 1H).



2-nitro-1-(2-nitrophenyl)ethanol, (**3**) (orange visqous liquid)

^{1}H NMR (600 MHz, CDCl$_3$), δ/ ppm = 8.10 (d, *J* = 10.6 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.81 – 7.68 (m, 1H), 7.62 – 7.49 (m, 1H), 6.06 (d, *J* = 9.1 Hz, 1H), 4.93 – 4.81 (m, 1H), 4.64 – 4.52 (m, 1H), 3.31 – 3.18 (m, 1H).

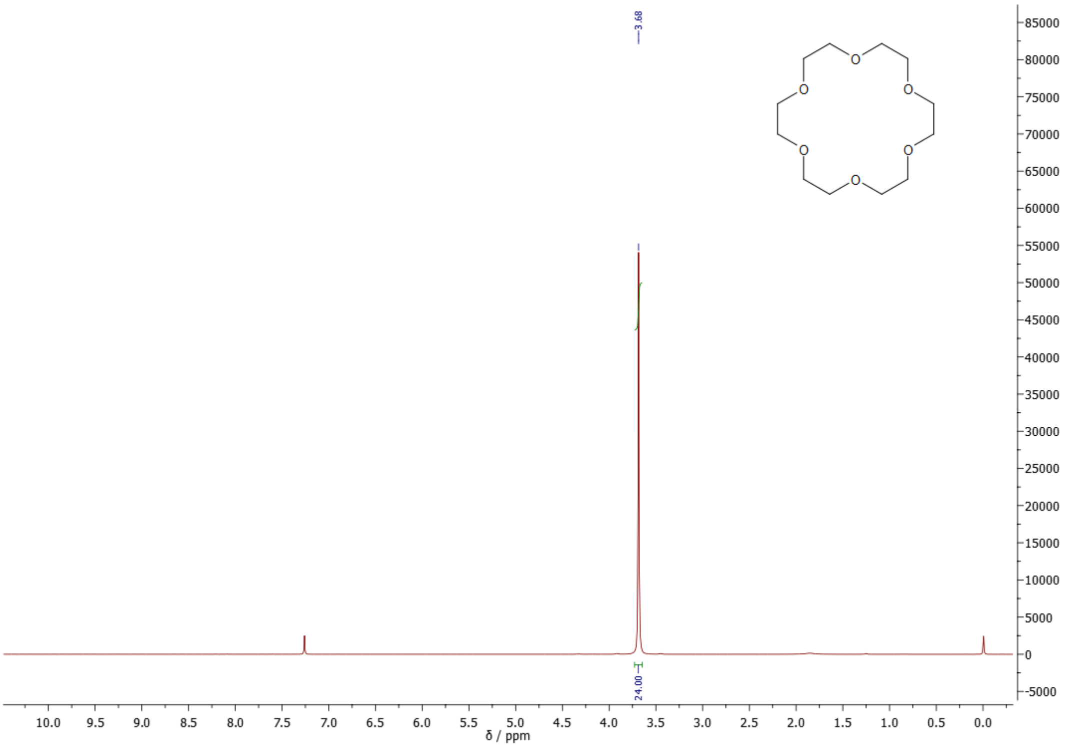


Figure S18. ^{1}H NMR spectrum of **18c6** ether ($CDCl_3$).

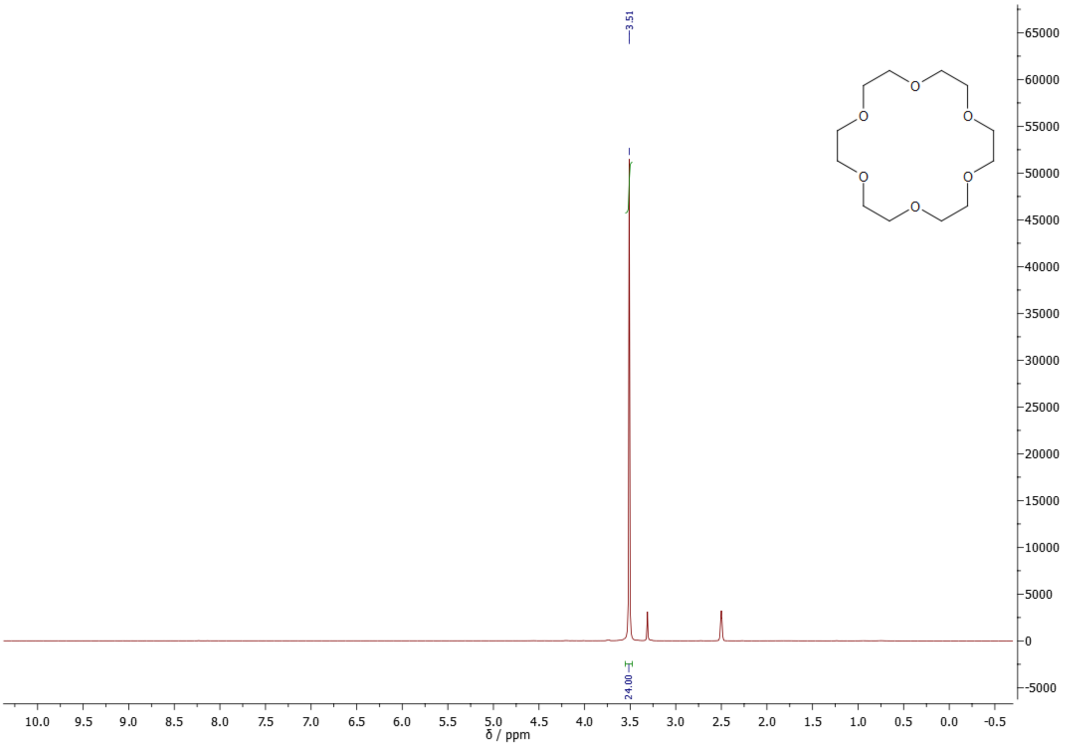


Figure S19. ^{1}H NMR spectrum of **18c6** ether after milling (DMSO).

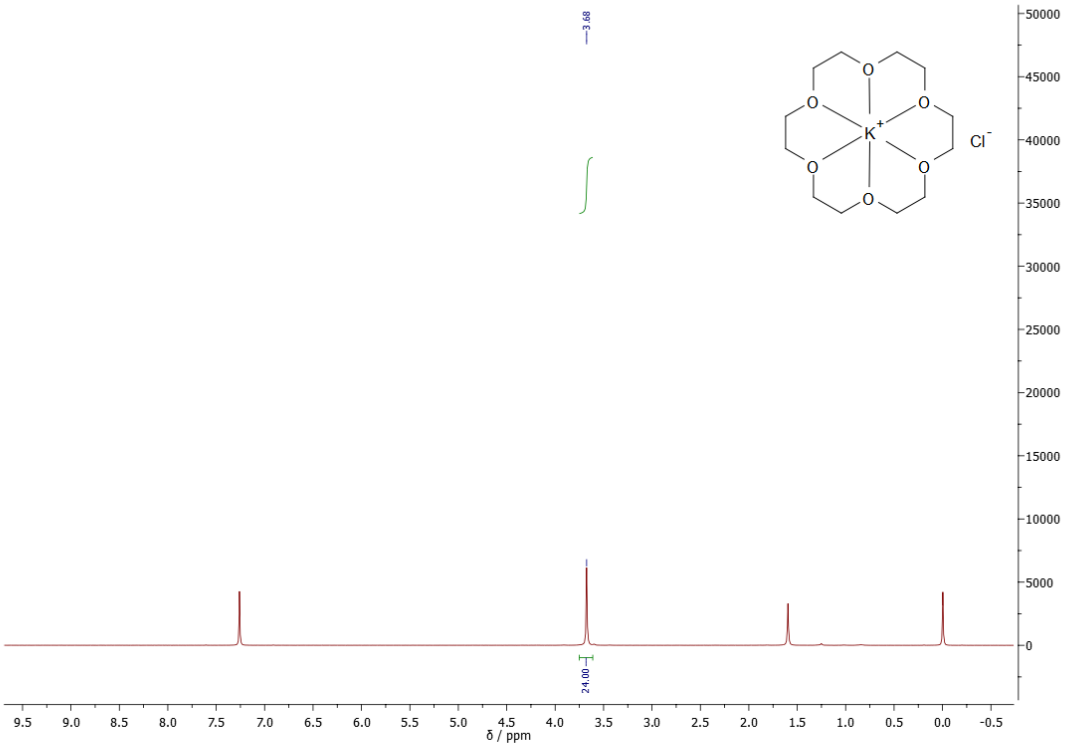


Figure S20. ^{1}H NMR spectrum of **[18c6K]Cl** ($CDCl_3$).

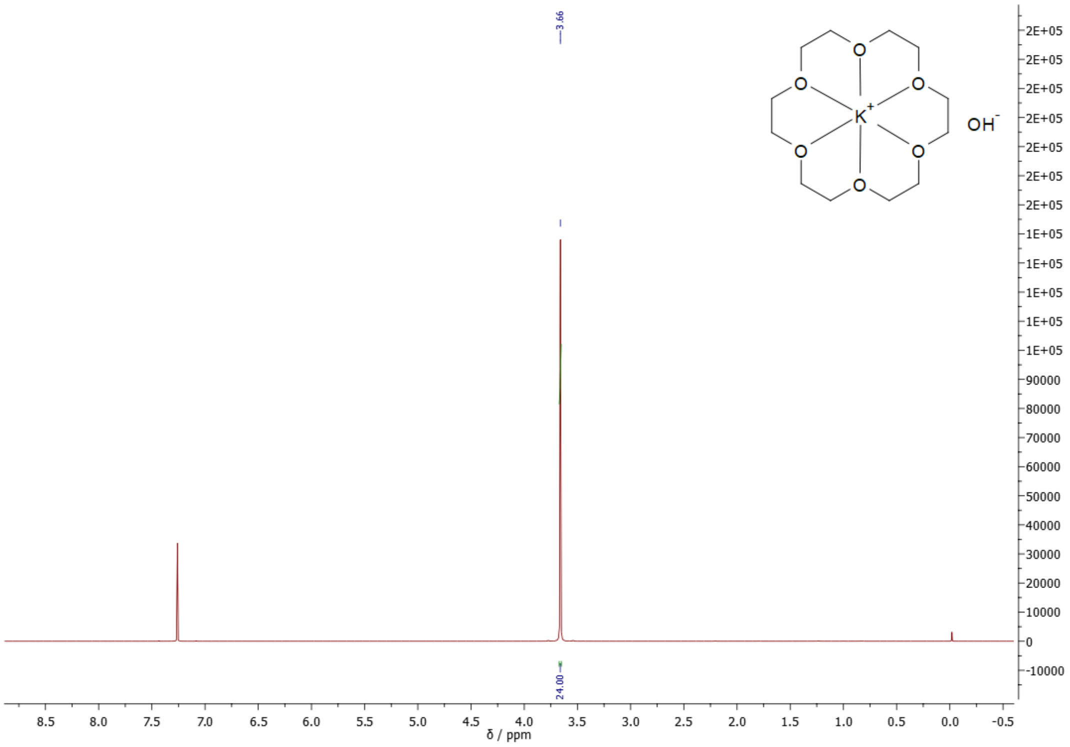


Figure S21. ^{1}H NMR spectrum of **[18c6K]OH** ($CDCl_3$).

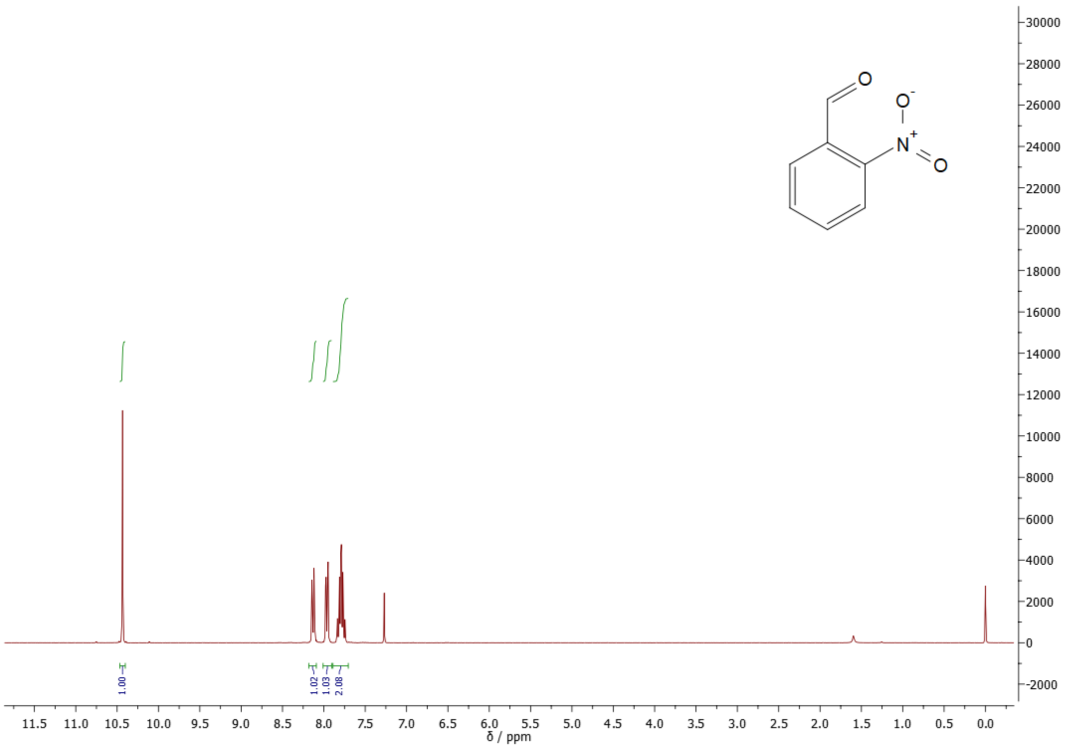


Figure S22. ^{1}H NMR spectrum the starting material of (**1**) for a Henry reaction ($CDCl_3$).

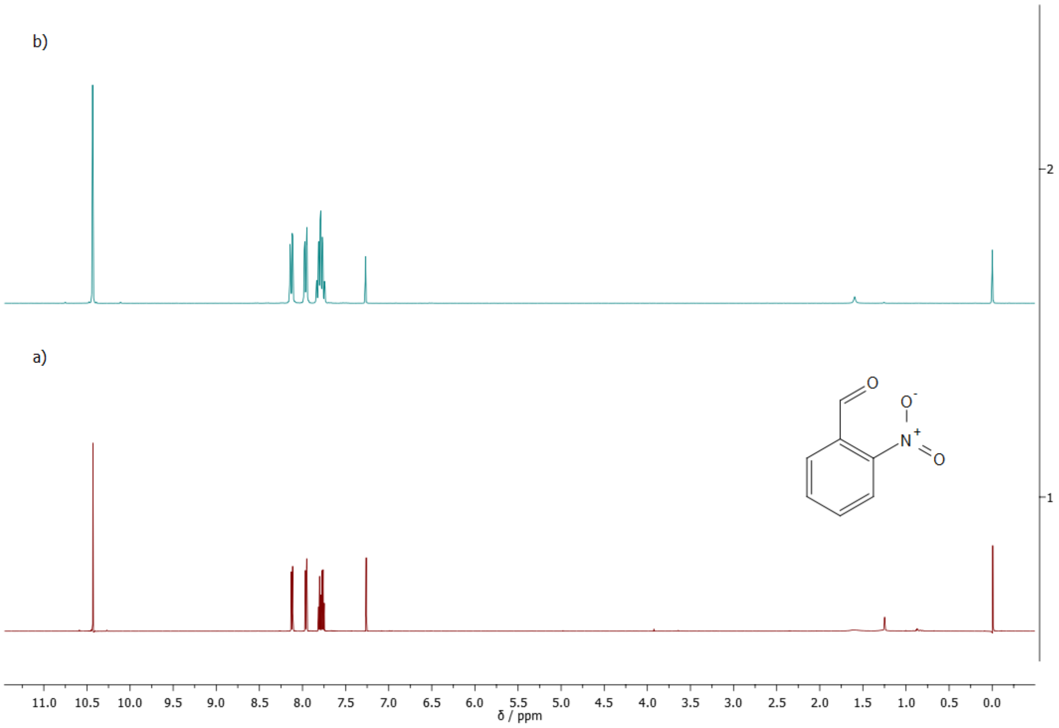


Figure S23. ^{1}H NMR spectrum ($CDCl_3$) of: a) starting material (**1**), b) sample prepared by milling (**1**) and (**2**) with KOH in the absence of a catalyst. No formation of the desired product was observed.

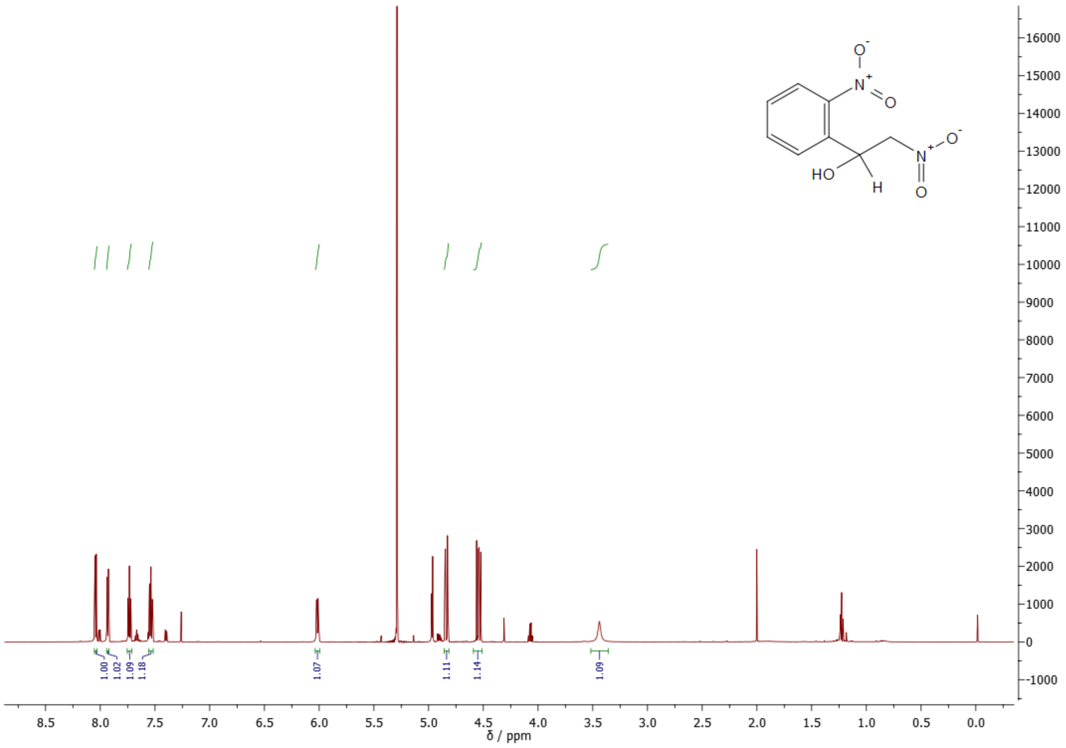


Figure S24. ^{1}H NMR spectrum of the reaction mixture prepared by grinding (**1**) and (**2**) with **18c6** ether and KOH ($CDCl_3$). The intense signal at 5.30 ppm corresponds to dichloromethane, which was added to transfer the sample after purification to an Eppendorf tube for 1D NMR analysis.

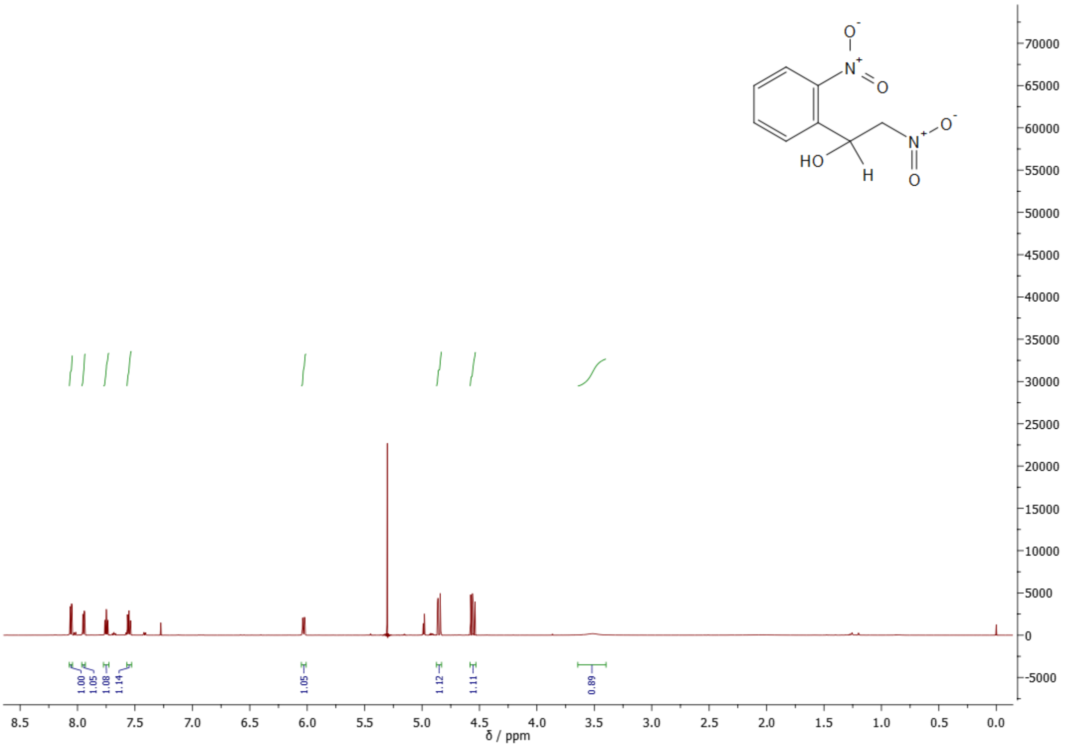


Figure S25. ^{1}H NMR spectrum of the reaction mixture prepared by grinding (**1**) and (**2**) with complex **[18c6K]OH** ($CDCl_3$). The intense signal at 5.30 ppm corresponds to dichloromethane, which was added to transfer the sample after purification to an Eppendorf tube for 1D NMR analysis.

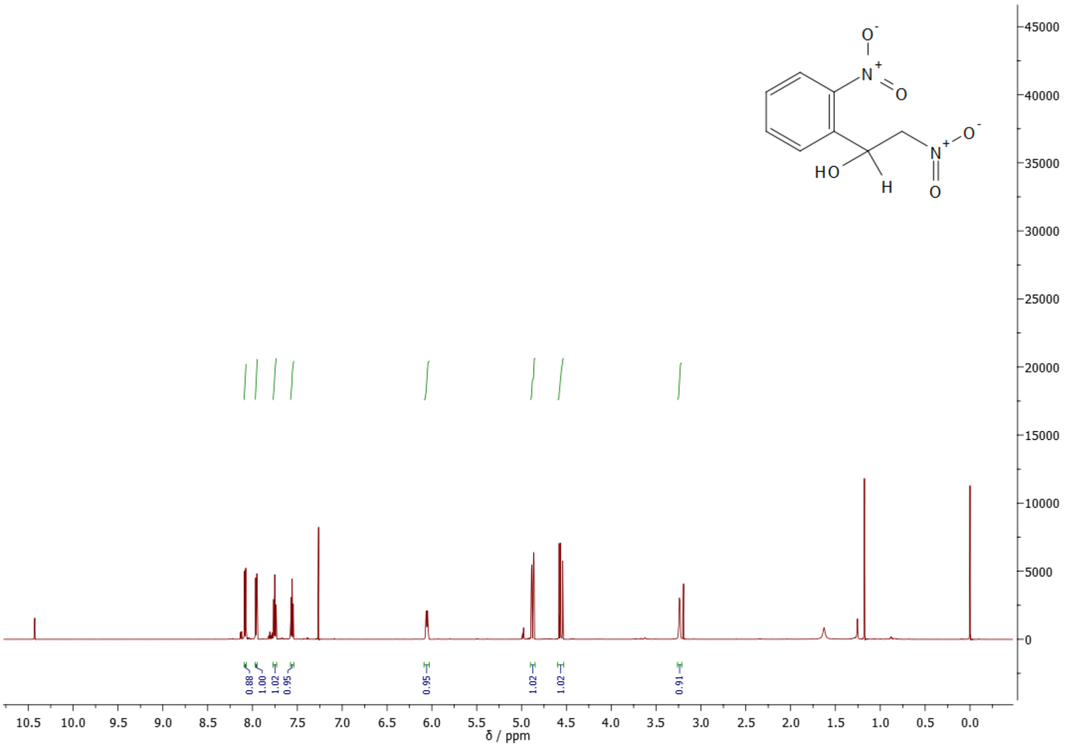


Figure S26. ^{1}H NMR spectrum of (**3**) obtained after 20 min of milling (**1**) and (**2**) with **[18c6K]OH**. NMR yield is 93%.

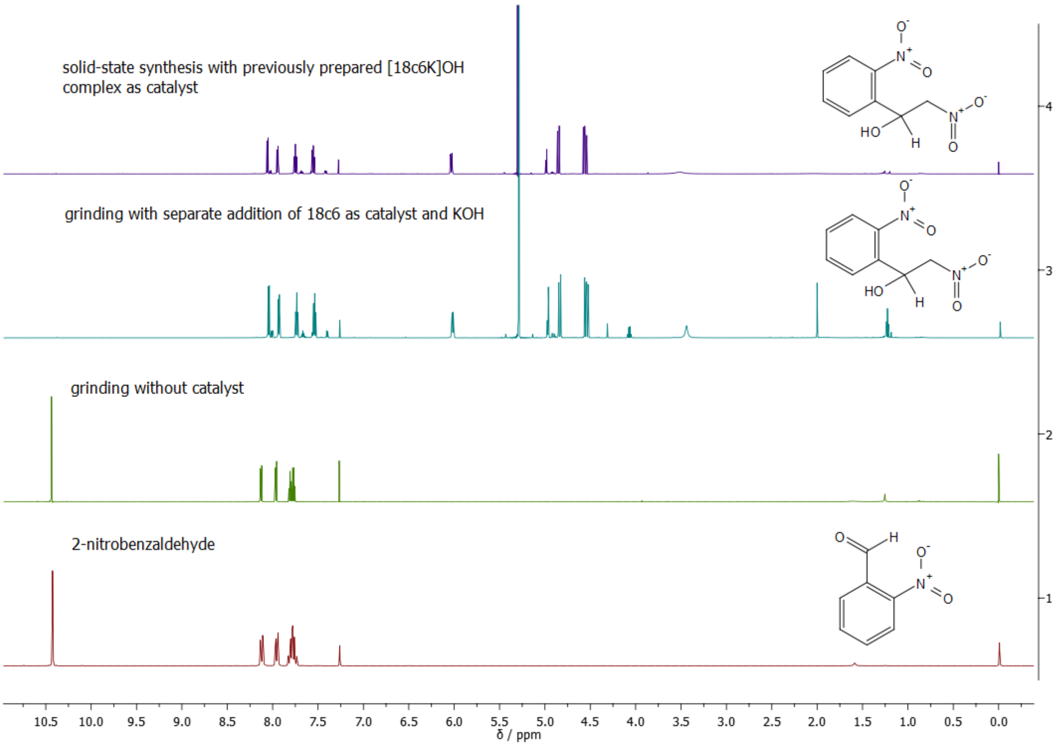


Figure S27. ^{1}H NMR spectrum comparison of mechanosynthesis of (**3**) after grinding starting materials (**1**) and (**2**) with **18c6** and **[18c6K]OH** as catalysts.

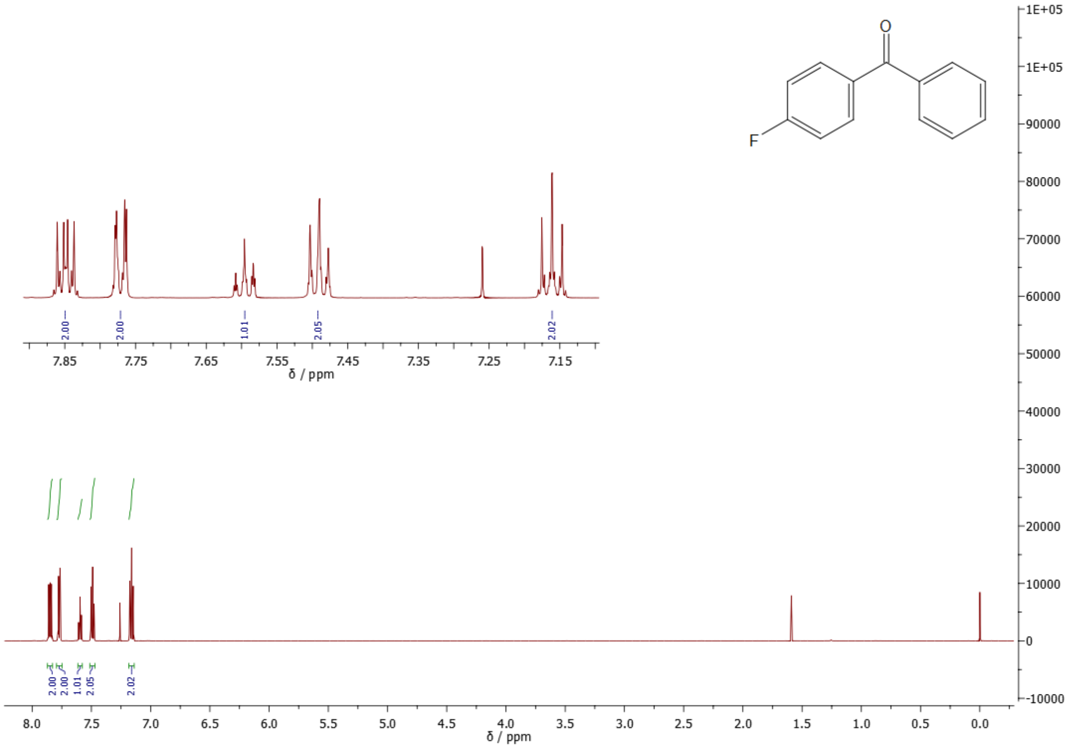


Figure S28. ^{1}H NMR spectrum of (**4**) ($CDCl_3$), NMR yield is 94%.

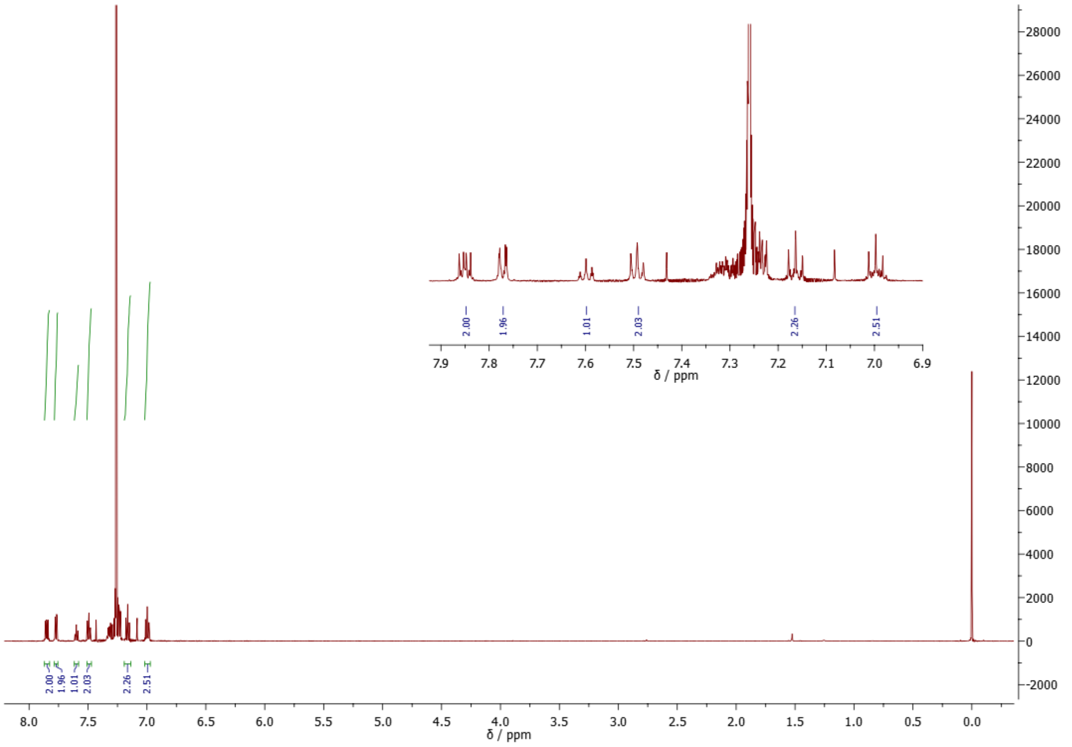


Figure S29. ^{1}H NMR spectrum of the sample (**4**) obtained after hydroxylation without catalyst addition ($CDCl_3$).

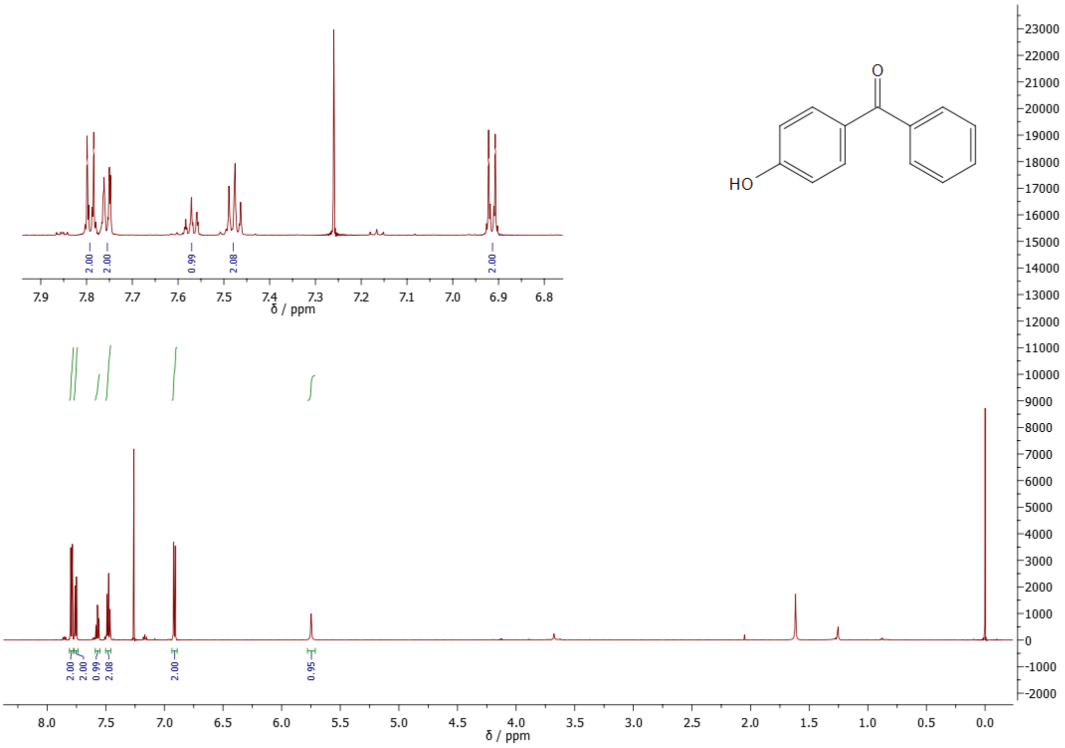


Figure S30. ^{1}H NMR spectrum ($CDCl_3$) of (**5**) prepared via catalysis with **18c6** ether (1.5 equiv.). NMR yield is 50%.

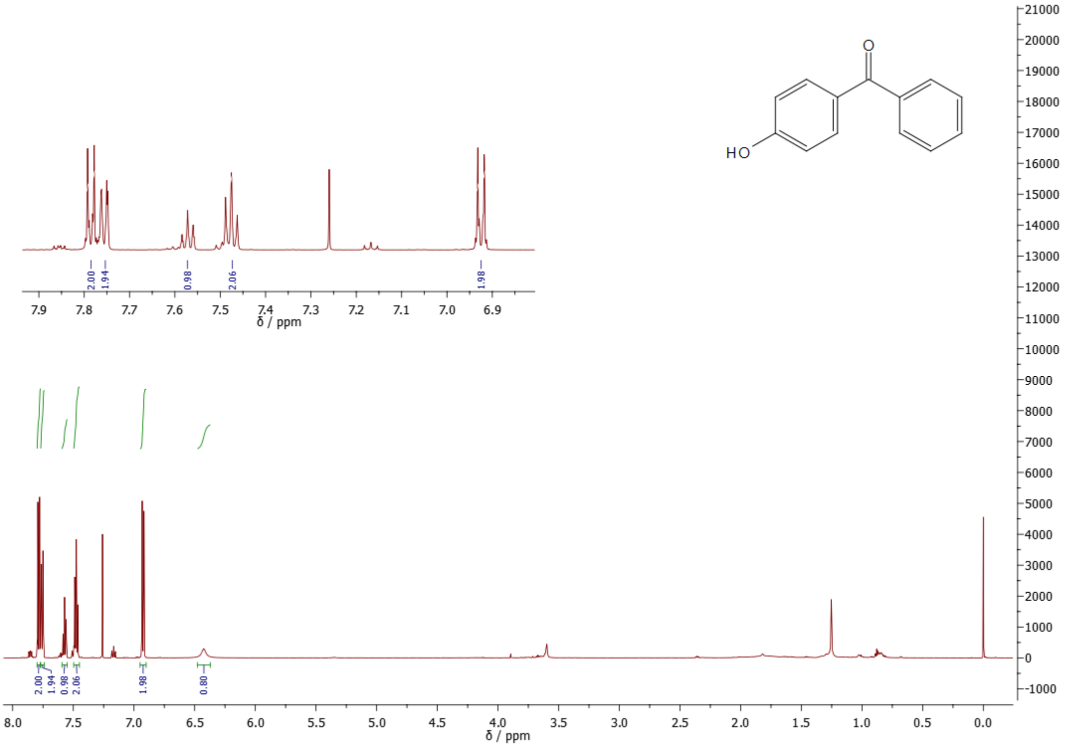


Figure S31. ^{1}H NMR spectrum ($CDCl_3$) of (**5**) prepared by catalysis with the **[18c6K]OH** complex (3 equiv.). NMR yield is 92%.

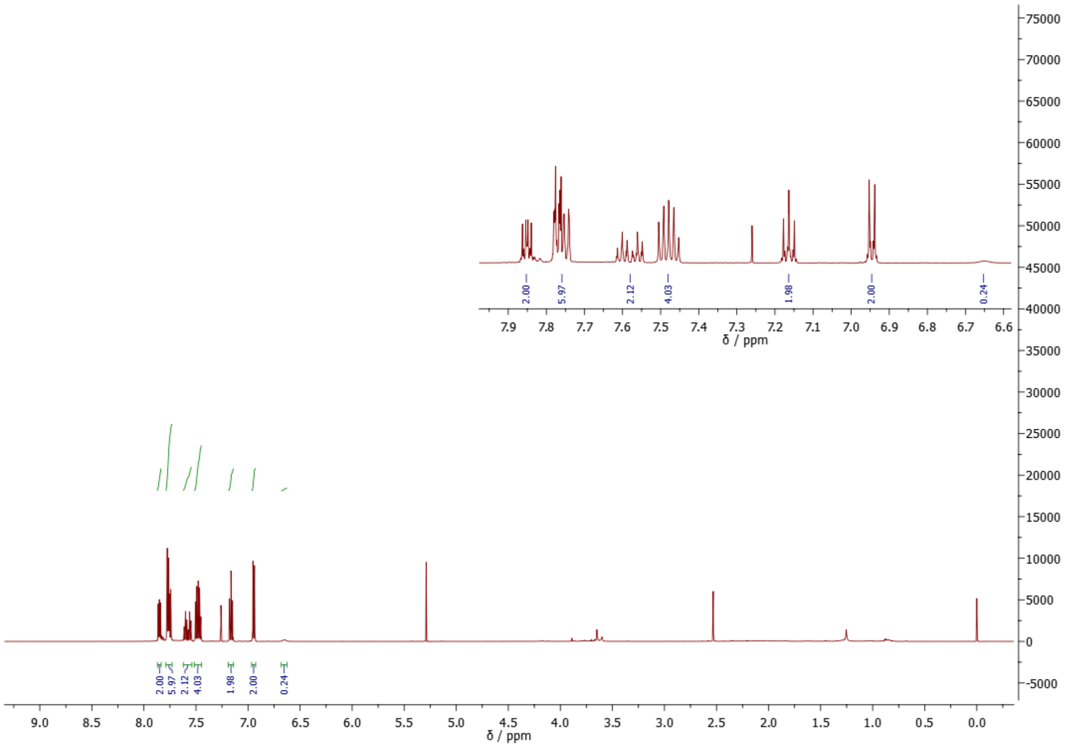


Figure S32. ^{1}H NMR spectrum ($CDCl_3$) of (**5**) prepared by catalysis with the **[18c6K]OH** complex (1.5 equiv.).

6.0. IR spectroscopy

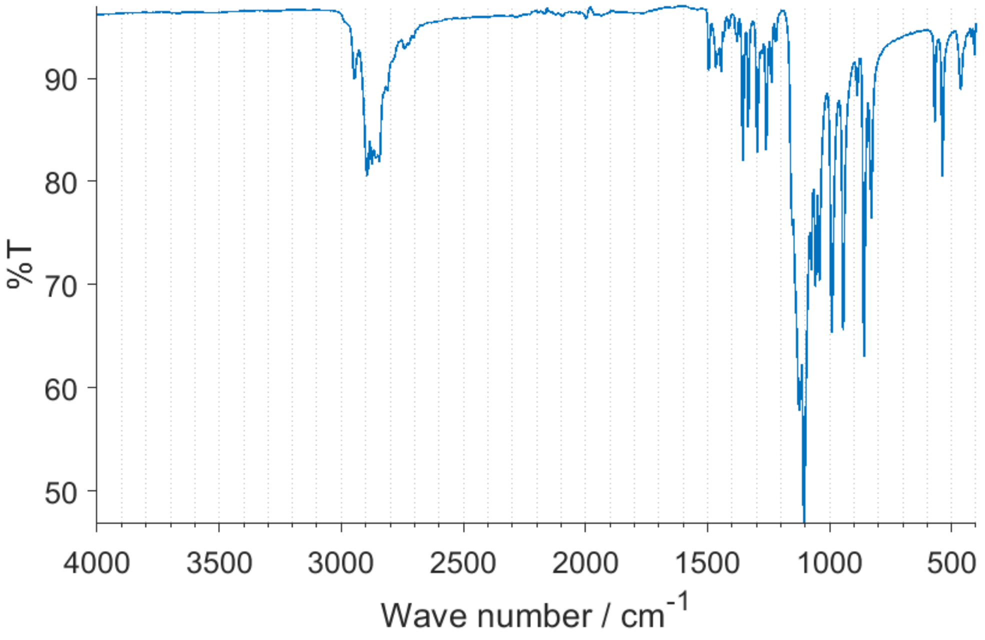


Figure S33. IR spectrum of **18c6** ether.

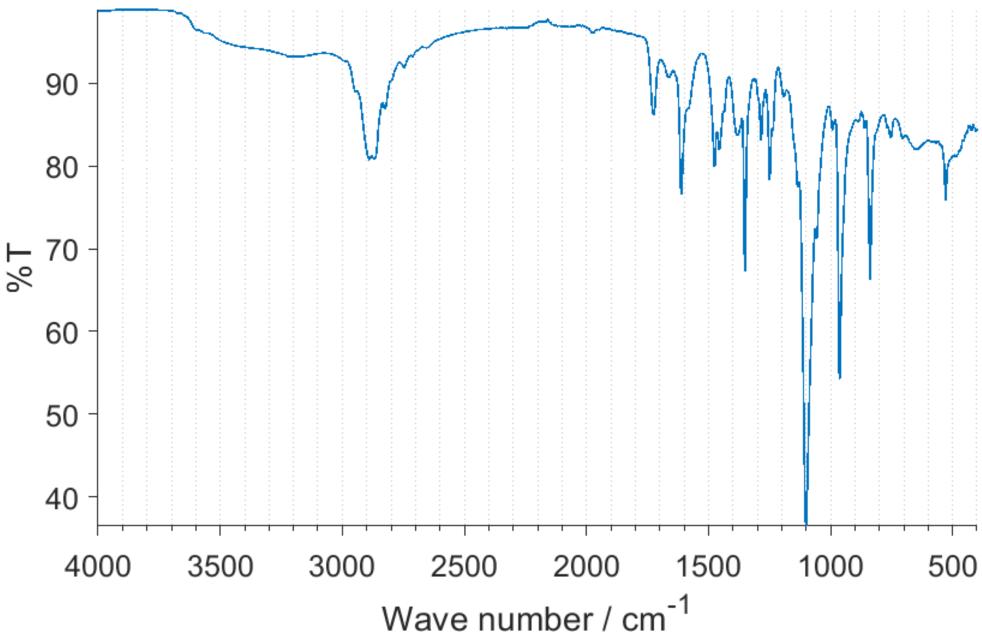


Figure S34. IR spectrum of **[18c6K]OH**.

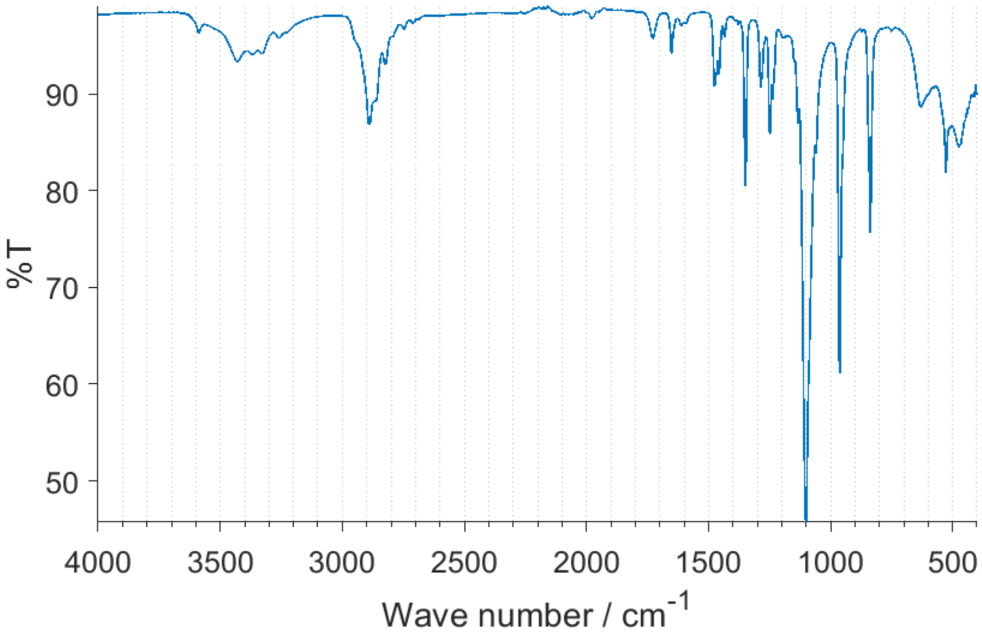


Figure S35. IR spectrum of **[18c6K]Cl**.

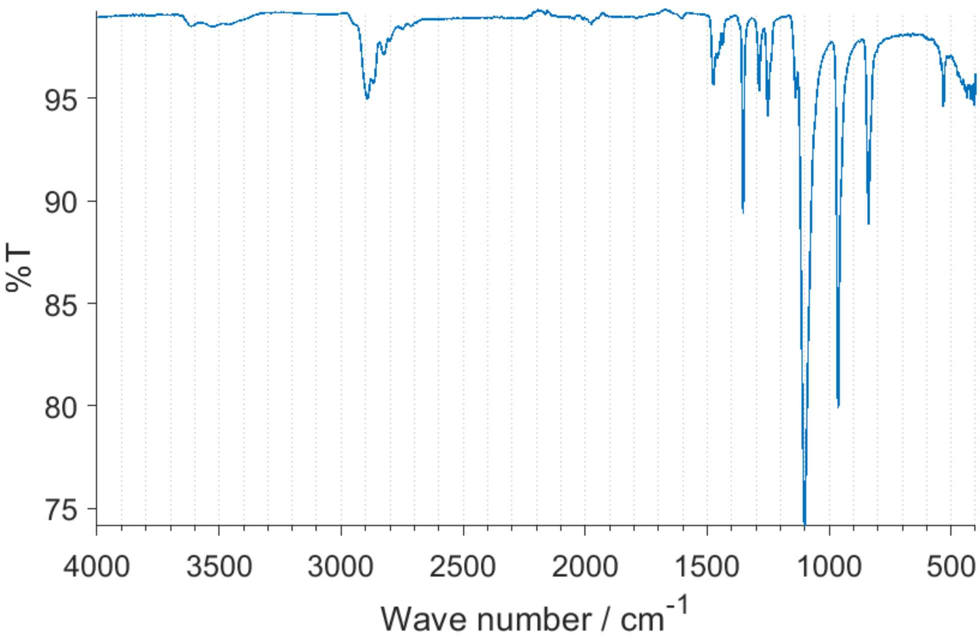


Figure S36. IR spectrum of **[18c6K]I**.

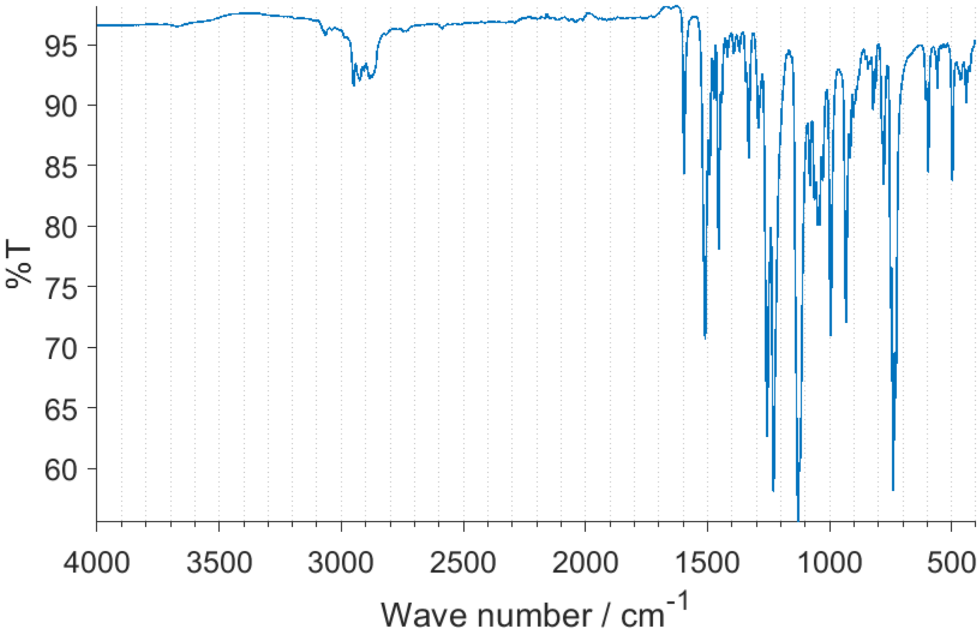


Figure S37. IR spectrum **db18c6** ether.

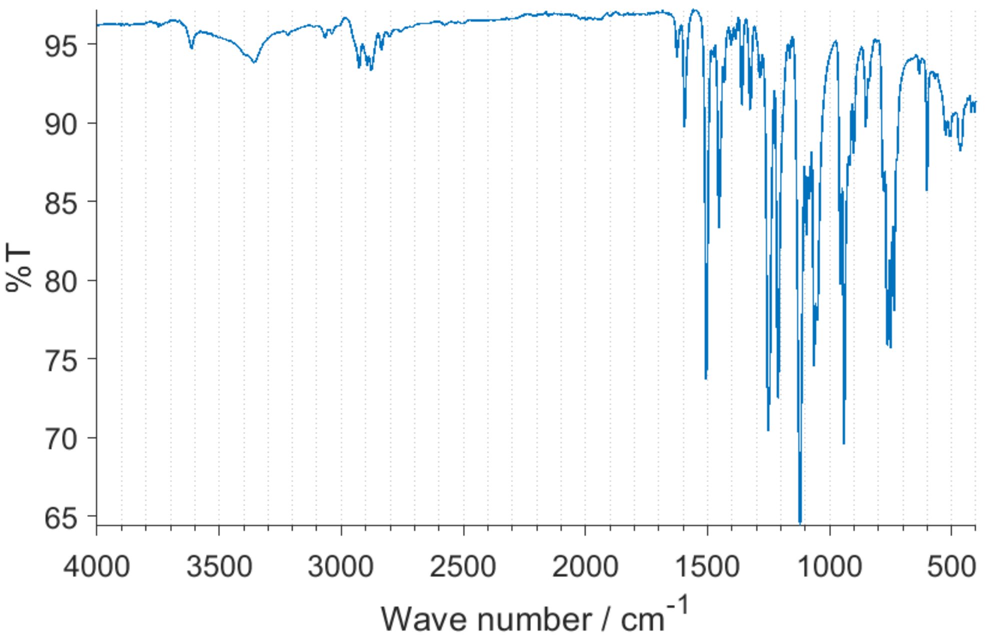


Figure S38. IR spectrum of **[db18c6K]I**.

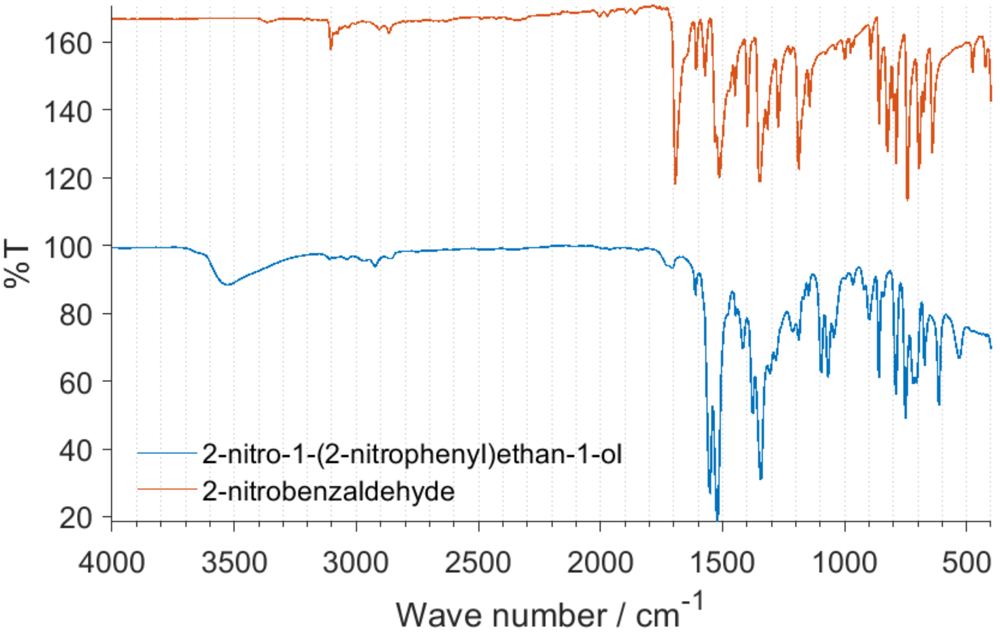


Figure S39. IR spectra comparison of the starting material (**1**) and reaction product (**3**).

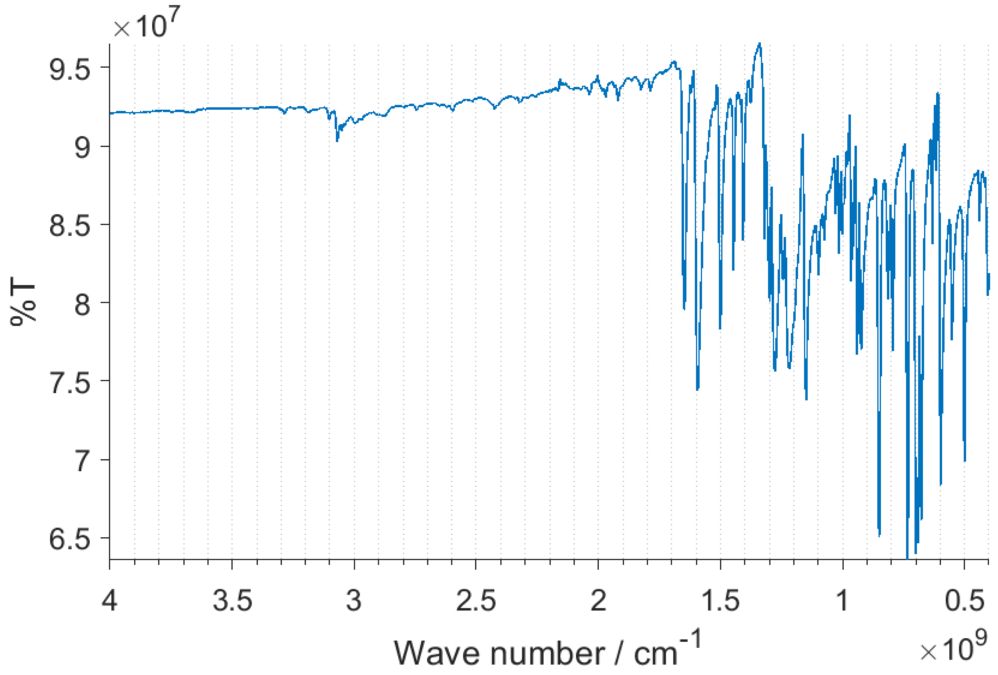


Figure S40. IR spectra of (**4**).

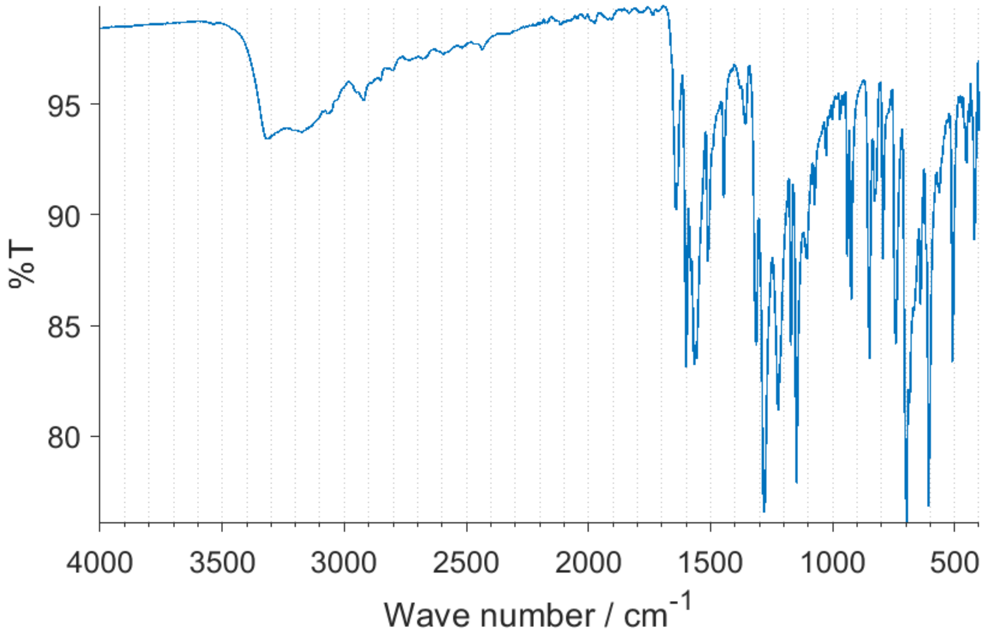


Figure S41. IR spectra of (**5**).

7.0. Thermal analysis

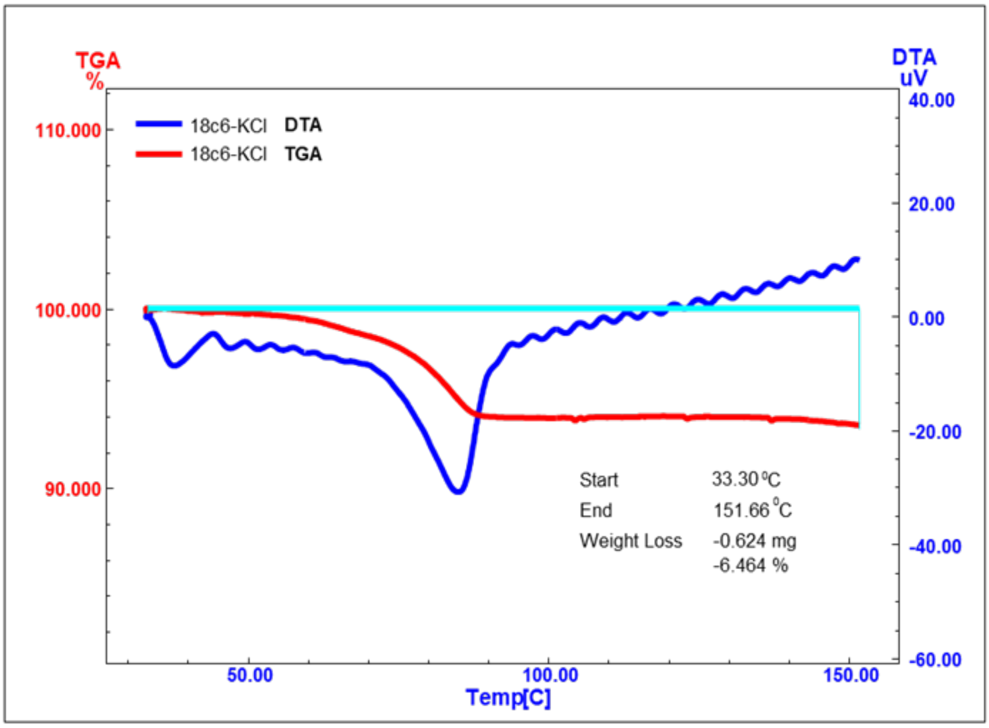


Figure 42. The TGA/DTA thermograms of the **[18c6K]Cl** sample show an endothermic decomposition process. A weight loss of 6.5 % corresponds to one water molecule per formula unit of the complex (the theoretical water weight fraction was 5.05 %).

8.0. References

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