Supplementary Information

Erika Ghiglietti,[a] Sara Mecca,[a] Alice Fappani,[a] Annapia Fratepietro,[a] Sara Mattiello,*[a] Luca Beverina*[a]

[a] Department of Materials Science, University of Milano-Bicocca, Via R. Cozzi, 55, I-20125 Milan, Italy

Contents

1. Materials and methods

Starting materials were all commercially available. Reagents and solvents were purchased from Fluorochem, Sigma-Aldrich or Acros and used without any further purification. Ethylcellulose was purchased from Acros Organic, ethoxyl content 48% (300 cps). The surfactant Kolliphor EL (K-EL) is supplied by Sigma-Aldrich. The 2 wt% aqueous solution of industrial surfactant was prepared by dissolving 1.0 g of emulsifier in 49.0 g of deionized water and stored under air.

Filtration on silica gel is performed using Sigma-Aldrich high-purity grade silica gel (pore size 60 Å, 220-440 mesh, 35-75 µm particle size) for the flash column. The composition of eluents used in purification steps are indicated as volume/volume ratios. Thin-layer chromatography (TLC) is performed using Pre-coated TLC sheets Alugram Xtra SIL G/UV_{254} (Silica Gel 60, 0.20 mm thick).

Nuclear Magnetic Resonance (NMR) spectra are collected on a Bruker NMR Avance 400 NEO. $CDCl_3$, C_6D_6, and D_2O are used as NMR solvents. Differential Scanning Calorimetry (DSC) is recorded at 25-250 °C under nitrogen flow (80 mL/min) with a scanning rate of 10 °C/min using a DSC 1STARe system from MEttler Toledo in aluminium crucibles.[1,2] Calibration is performed with indium standard. Thermogravimetric Analysis (TGA) are carried out on TGA/DSC STARe System (MEttler TOLEDO). Method: 10 °C/min, N_2 flow 50 mL/min.[1] InfraRed spectra (IR) are collected with a Nicolet iS20 FT-IR spectrometer equipped with a Smart iTX accessory.[1,3,4] Melting grades are measured on a Buchi M-560 in a temperature range of 70-250 °C: 190 °C is taken as benchmark temperature. The instrument determines the melting grades of solid powders by evaluating optical changes in samples. Dynamic Light Scattering (DLS) experiments are performed on a Zetasizer Nano Series Analyzer from Malvern equipped with a laser (633 nm). Measurements are run in 1 cm disposable cuvettes at room temperature. Three consecutive measurements have been run on each sample and mediated to obtain the final distribution. Water is set as dispersant (refractive index=1.33 at room temperature) and the material selected for the refractive index is polystyrene latex. Samples are prepared by dispersing the fine powder (2 wt%) in the corresponding solvent under magnetic stirring. The Scanning Electron Microscopy (SEM) analysis is carried out using a Zeiss Gemini SEM 500 (equipped with a Bruker EDX). Transmission Electron Microscopy (TEM) characterization is performed on a JOEL JEM 2100 Plus operating at 200 kV. Ultracentrifugation is performed using a Sigma 3-16KL refrigerated benchtop centrifuge (temperature range from -10 °C to 40 °C) equipped with a fixed-angle rotor 12150 (max load 6 x 140 g, max rotation per minute 11000 rpm). An IKA EURO-STAR 60D S000 equipped with a dissolver impeller (R 1300, IKA) is used for mechanical stirring. Then, a high-shear turbo emulsifier homogenizer and an UP200St Hielscher high-power ultrasound probe are used to refine the emulsion. The high shear turbo emulsifier employed consists of a motor group IKA ULTRA-TURRAX 25 DIGITAL and a dispersing tool S25N-18G (immersion depth 40-165 mm, stator diameter 18 mm, rotor diameter 12.7 mm, fineness suspensions 10-50 µm, fineness emulsions 1-10 µm, max rotation 10k rpm, volume range 10-1500 mL). The UP200St Hielscher high-power ultrasound probe is composed of an ultrasonic transducer, a generator and a sonotrode S26d14 (technical specifications: working frequency 26 kHz, default amplitude 20-100%, pulse-duty cycle 10-100% as related to a second, in steps of 0.1 second).

All reactions are performed in a round-bottom test tube equipped with a cylindrical stirring bar PTFE-coated both under air and nitrogen atmosphere by means of a Schlenk-line. Reaction conversions are quantified by gas chromatography-mass spectroscopy (GC-MS). GC-MS chromatograms are collected on Clarus500 PerkinElmer coupled with Clarus560S mass spectrometer equipped with Elite-5MS 30.0 m x 250 µm. Helium is used as a carrier gas. The method used had the following parameters: solvent delay of 2 minutes, initial temperature of 100 °C, thermal ramp: 20 °C/min to 300 °C (hold for 5 minutes). GC-MS is calibrated for our model substrate as reported in the following section.

The samples concentration of palladium is detected using an Inductively coupled plasma - optical emission spectroscopy (ICP-OES OPTIMA 7000 DV Perkin Elmer). Each sample is digested in a multi-wave 5000 (Anton Paar) by adding nitric acid (HNO_3 65%) and hydrogen peroxide (H_2O_2 30%) 8:2 v/v. The system is programmed to reach power of 1000 W to ramp the detected temperature up to 220 °C. Then the vessel is kept at that temperature for 30 minutes. Digested samples are diluted with 10 mL of MQ water. After centrifuging and diluting 1:2, samples are analysed by ICP-OES. A certified standard reference material of Pd 1000 mg/L (Perkin Elmer) is used for calibration and quality control. The operating parameters of ICP-OES instrument are set up using emission line at 340,458 nm in Axial View and sample solutions are measured in triplicate. The detection limit for Pd is 0,01 mg/L.

Fig. S1 On the left photographs of a) the motor IKA EURO-STAR 60D S000 and b) the dissolver impeller R1300 IKA. On the centre c) the motor group IKA ULTRA-TURRAX 25 DIGITAL and d) the respective dispersing tool S25N-18G. On the right photographs of the e) generator of the UP200St Hielscher high-power ultrasonic processor and f) its ultrasonic transducer equipped with the sonotrode S26d14.

2. Synthetic process for ethylcellulose microcapsules (Mcs) and nanocapsules (Ncs)

2.1. General procedure

2.1.1. Synthesis of capsules

An organic phase is prepared in a beaker by dissolving ethylcellulose (EC, 5.00 wt/V%) in 200 mL of ethyl acetate (AcOEt). The mixture is mechanically stirred (700 rpm) for 24 hours until complete EC dissolution. When needed, trimethylpropane triglycidyl ether (TMPG 0.50 wt/V%) is also added at this stage. After 24 hours of stirring, the cargo (1:1 wt/wt to EC) is added. The mixture is allowed to stir for 30 minutes. In the meantime, a dispersing aqueous phase consisting of in polyvinyl alcohol (PVA 8-88, M_w 67000) 1 wt/V% in deionized water (600 mL) is prepared in a second beaker under mechanical stirring (700 rpm). Then, an oil-in-water emulsion (o/w) is formed by slowly adding the organic phase to the aqueous phase. The mixture is homogenized under mechanical stirring (700 rpm). In order to prepare microcapsules, the droplet size of the emulsion is then refined by using an IKA ULTRA-TURRAX 25 DIGITAL (14000 rpm). On the contrary, to make nanocapsules a high-power ultrasound probe is used (cycle 50%, amplitude 50%, 10 minutes). The organic solvent is thus distilled under reduced pressure from the emulsion produced. A dispersion of capsules in the solution of PVA in water is obtained.

Organic phase	
EC	10.0 g
TMPG (when needed)	1.0 g
Cargo (es. Vanillin)	10.0 g
AcOEt	200 mL

Aqueous phase	
PVA	6.0 g
Deionized water	600 mL

Samples prepared using EC only are labelled as EC Ncs/Mcs. Samples prepared using EC functionalized with TMPG are labelled as EC-TMPG Ncs/Mcs.

2.1.2. General procedure for the crosslinking process

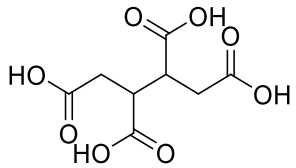
2.1.2.1. Crosslinking without previous isolation of the particles

The crosslinking agents (see following sections) are added directly in the water dispersing phase without previous isolation of the particles. The obtained dispersion is heated at 90 °C for 6 hours. After cooling down, the solid is recovered by filtration over a folding filter paper (for microcapsules) or by ultra-centrifugation at 11000 rpm for 30 minutes at 5 °C (x2 times, for nanocapsules). A white powder is obtained.

Two other methods were tested for the crosslinking procedure: dry crosslinking and wet crosslinking after particles isolation. The results are reported in section 6 along with the exact procedure. They were not prosecuted, as the dry crosslinking did not allow for single particles crosslinking, but it rather led to extensive inter-particles

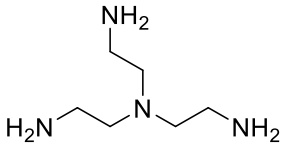
crosslinking/sintering, while the wet crosslinking performed after the isolation step led to results similar to those obtained when the isolation step was not performed.

The amount of crosslinking agent is reported in the following tables for each specific crosslinker.



1,2,3,4-butanetetracarboxylicacid (BTCA)

Component	Equivalent (eq.)	mmol	Mass (g)
EC	1.00	49.0	10.0
TMPG	0.067	3.3	1.0
BTCA	0.75	36.7	8.6
NaH_2PO_4	0.25	12.2	1.5



tris(2-aminoethyl)amine (TREN)

Component	Equivalent (eq.)	mmol	Mass (g)
EC	1.00	49.0	10.0
TMPG	0.10	3.3	1.0
TREN	0.12	4.0	0.6

2.1.2.2. Hardening with borax

After the first crosslinking step, the obtained micro- or nano- capsules can be further hardened using the following procedure. 10 g of particles are suspended in a solution of sodium tetraborate decahydrate (borax, $Na_2B_4O_7{\cdot}10H_2O$, 3.8 g, 10 mmol) in deionized water (500 mL). The mixture is sonicated by using a high-power ultrasound probe (cycle 50%, amplitude 50%, 10 minutes) and the dispersion is heated at 90 °C for 3 hours. After cooling, the obtained precipitate is isolated on a paper funnel and dried in the oven at 60 °C. A fine brown powder is recovered.

3. SEM images of samples prepared at different concentration of EC

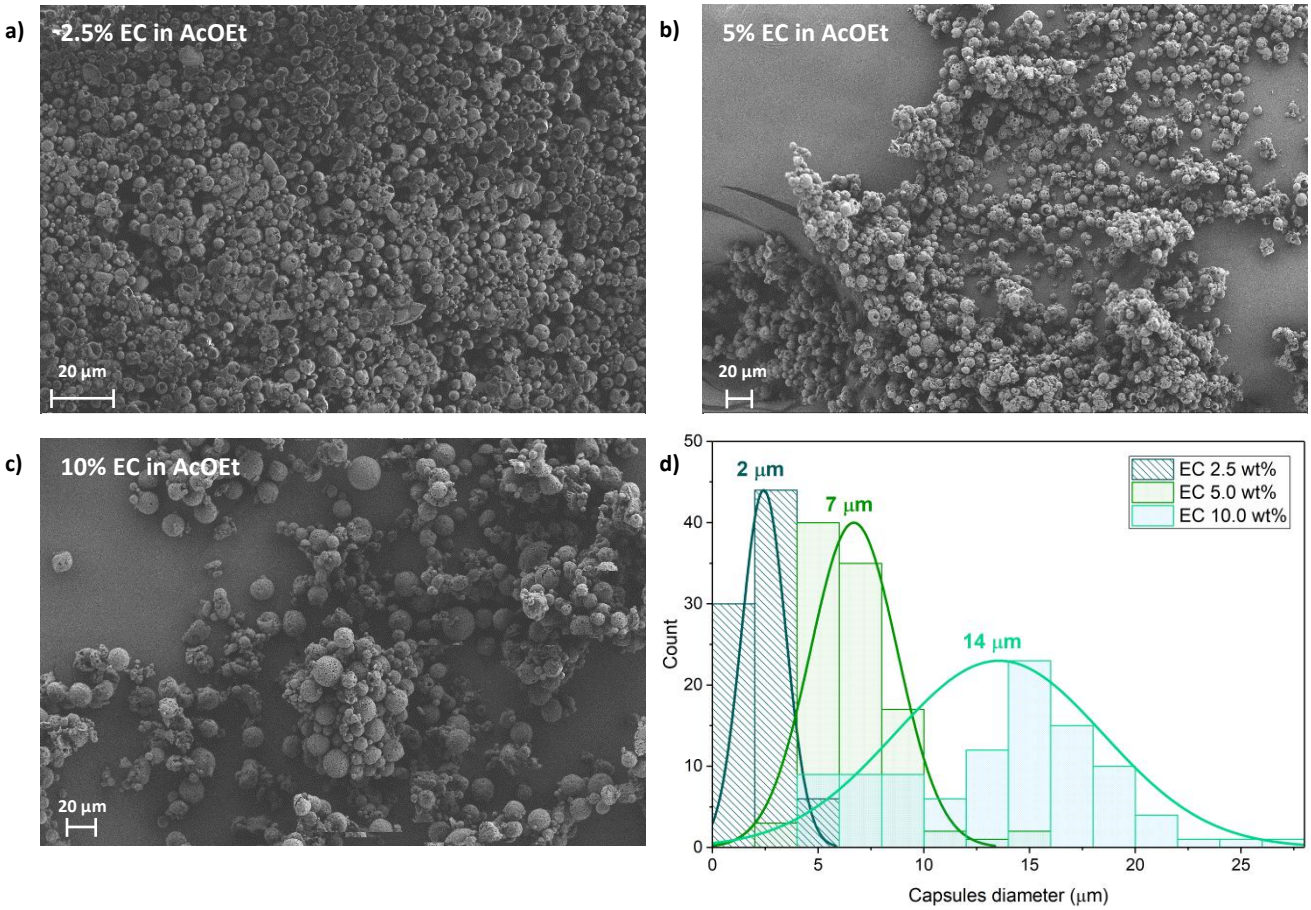


Fig. S2 SEM images of non-crosslinked microcapsules prepared according to the general procedure, using different initial concentrations of EC in the organic phase. a) 2.5 wt% of EC; b) 5.0 wt% of EC; c) 10 wt% of EC; d) distributions of the diameters of the particles, fitted with a gaussian curve: fwhm values are 2.5 µm (sample **a**), 4.8 µm (sample b), and 11.6 µm (sample c) respectively.

4. Kinetic study of the functionalization of ethylcellulose with TMPG

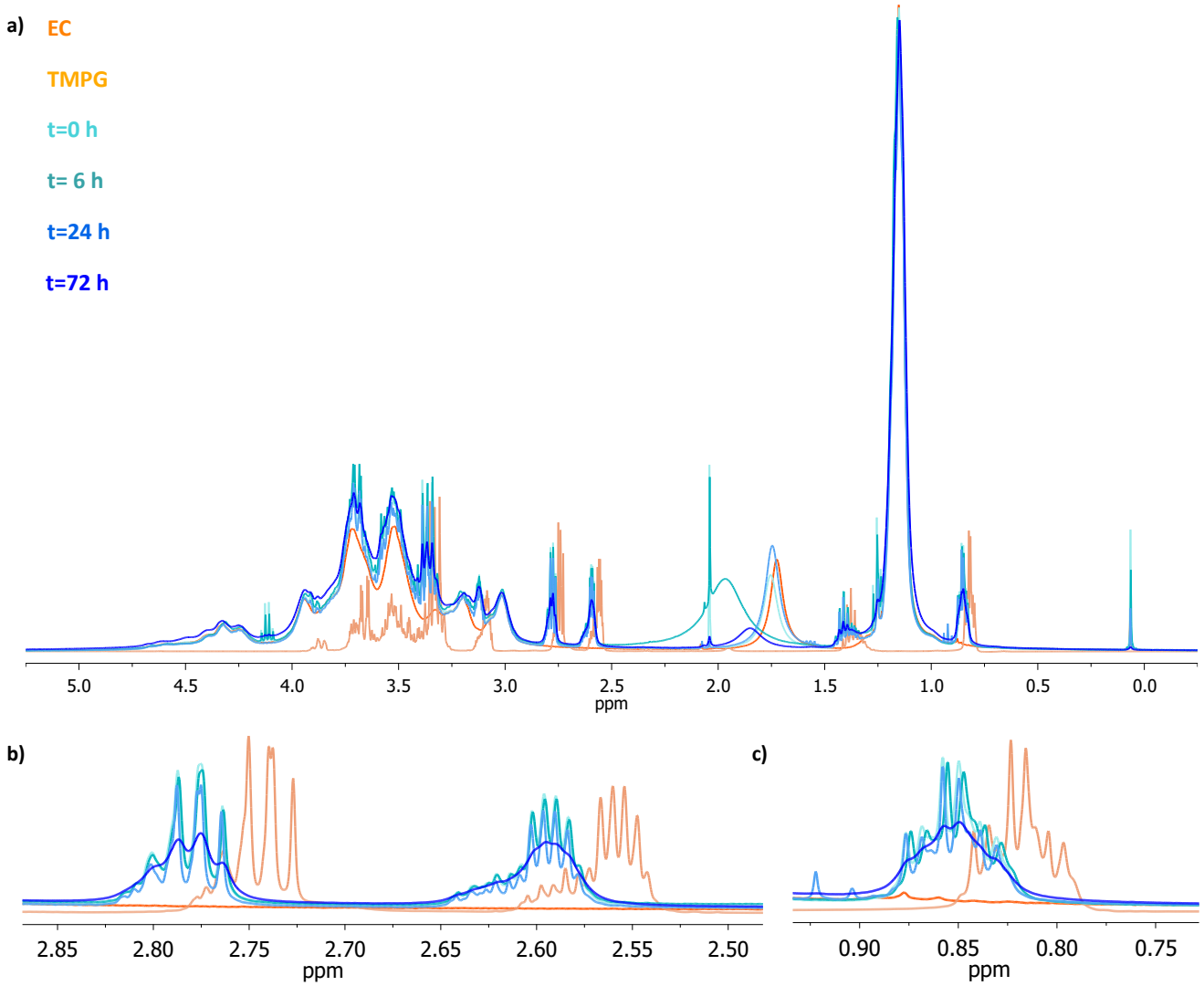


Fig. S3 ^{1}H NMR kinetic study of the functionalization of EC with TMPG in $CDCl_3$. a) Full spectrum; b/c) zoom in, showing the shift and the decrease of epoxide peaks.

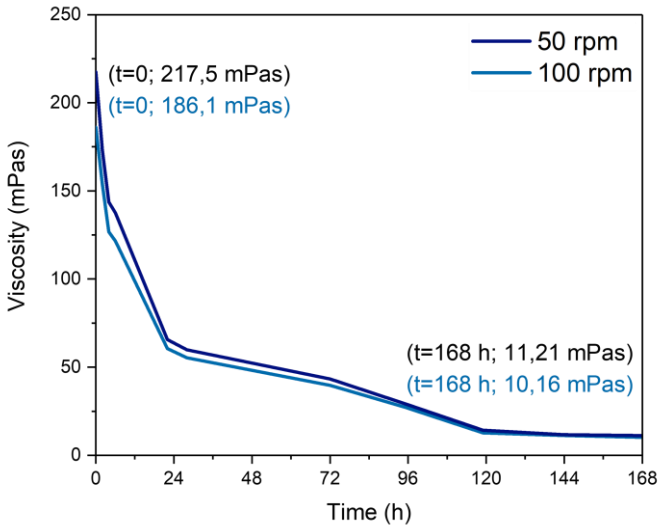


Fig. S4 Viscosity analysis of the solution of EC and TMPG in AcOEt over time at a speed of 50 rpm (blue line) and 100 rpm (light blue line). A viscosimeter VISCO/VISCO-895 is used.

5. Identification of all listed samples

To help the reader understanding how each sample of EC particles was prepared, we listed all the different samples we characterized in the following table, stating the type of particles (Mcs or Ncs), their cargo, the presence or absence of TMPG pre-functionalization, the crosslinking method (if performed) and the type of crosslinker. A reference to the section where the material is presented is also added in the last column.

Table S1. List of all capsules presented within the manuscript, with indication of their composition, and indications on where they are presented.

ID	Particles	Cargo	Prefunct.	Crosslinking	Listed in:
Sample 1	Mcs	-	-	-	Main text, Tab.1#1; S6
Sample 2	Mcs	-	-	-	Main text, Tab.1#2
Sample 3	Mcs	-	-	BTCA (alternative method A)	S6
Sample 4	Ncs	Vanillin	-	-	Main text, Tab.1#3; S6
Sample 5	Ncs	Vanillin	-	BTCA (alternative method B)	S6
Sample 6	Ncs	Vanillin	-	BTCA	Main text, Tab.1#4; S7.2
Sample 7	Ncs	Vanillin	TMPG	-	Main text, Tab.2#3; S7.2
Sample 8	Ncs	Vanillin	TMPG	BTCA	Main text, Tab.2#4; S7.2
Sample 9	Ncs	-	TMPG	BTCA	Main text, Tab.2#5; S8
Sample 10	Ncs	Vanillin	TMPG	TREN	Main text, Tab.2#6; S7.3
Sample 11	Ncs	Vanillin	TMPG	BTCA + borax	Main text, Tab.2#7; S7.4

6. Effect of crosslinking before or after isolation of the particles. Morphological and chemical analysis

During optimization of the procedure for the preparation and isolation of Ncs, we tested three different crosslinking procedures, here indicated as method A, B and C.

6.1. Method A: dry crosslinking after isolation of the particles

Capsules (freshly prepared as described in section 2.1.2) are recovered by filtration over a folding filter paper (microparticles) or by ultra-centrifugation (11000 rpm for 30 minutes at 5 °C, nanoparticles) and washed with water twice. The white solid obtained is then poured in 500 mL round-bottom flask and two different solutions previously prepared are added: 100 mL of a 1 wt% solution of crosslinker and 100 mL of a 1 wt% solution of base.[5] The mixture is stirred at ambient temperature for 30 minutes. The solid is then recovered by filtration. The dry powder recovered is poured in a 250 mL round-bottom flask equipped with a condenser and the solid is heated at 150 °C for 20 minutes. Collection of water as byproduct of the crosslinking process is observed on the top part of the round-bottom flask. After cooling down, a white powder is obtained.

Figure S5 shows the SEM images of Mcs before (sample 1) and after (sample 2) crosslinking using this method, as a comparison. Even if particles structure is recognizable, extensive sintering is observed.

6.2. Method B: wet crosslinking after isolation of the particles

Capsules (freshly prepared as described in section 2.1.2) are recovered by filtration over a folding filter paper (microparticles) or by ultra-centrifugation (11000 rpm for 30 minutes at 5 °C, nanoparticles) and washed with water twice. The white solid obtained is then redispersed in 500 mL of deionized water and the crosslinking agent (and in case also the base) is added. The mixture is heated at 90 °C for 6 hours. After cooling down, the solid is recovered by filtration over a folding filter paper (for microcapsules) or by ultra-centrifugation at 11000 rpm for 30 minutes at 5 °C (x2 times, for nanocapsules). A white powder is obtained.

Figure S6 shows the SEM images of Ncs before (sample 3) and after (sample 4) crosslinking using this method, as a comparison. Individual crosslinking in solution allows to perfectly preserve the Ncs, with their dimensions distribution remaining nearly identical.

6.3. Method C: crosslinking without previous isolation of the particles

This is the standard method described in section 2.1.2.3.

Figure S6 shows the SEM images of Ncs before (sample 3) and after (sample 5) crosslinking using this method, as a comparison. Individual crosslinking in solution allows to perfectly preserve the Ncs, with their average dimensions growing from 190 nm to 270 nm, possibly due to incorporation of both the crosslinker and the PVA.

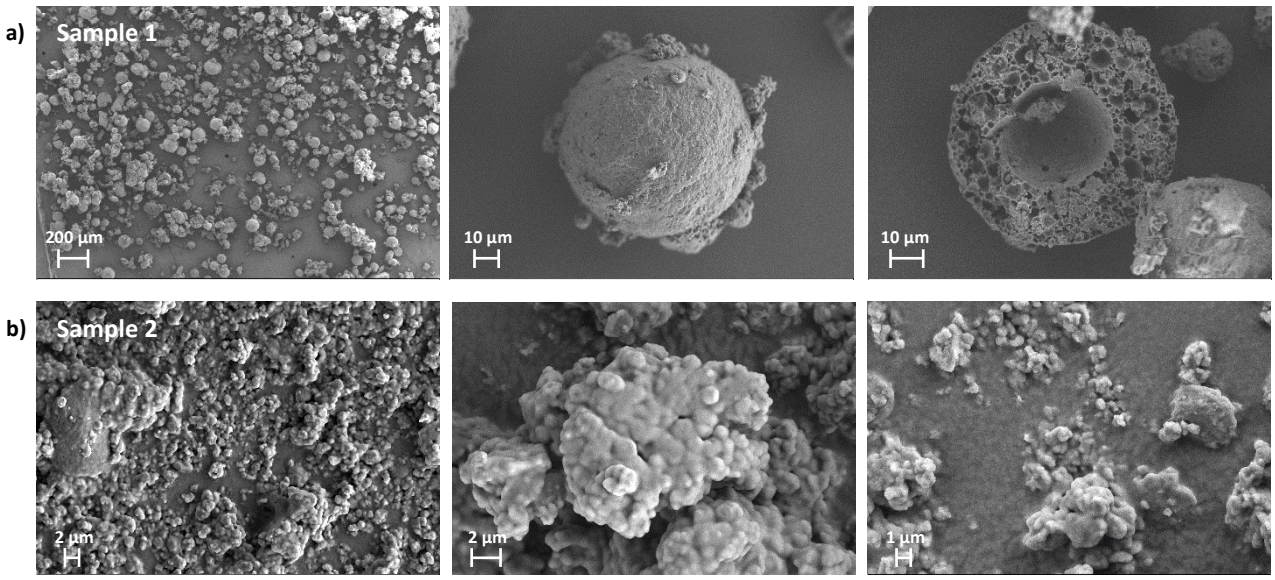


Fig. S5 SEM images of microcapsules prepared according to the general procedure with the following modification. a) Non-crosslinked microcapsules (sample **1**); b) microcapsules crosslinked according to method **A** (sample **4**).

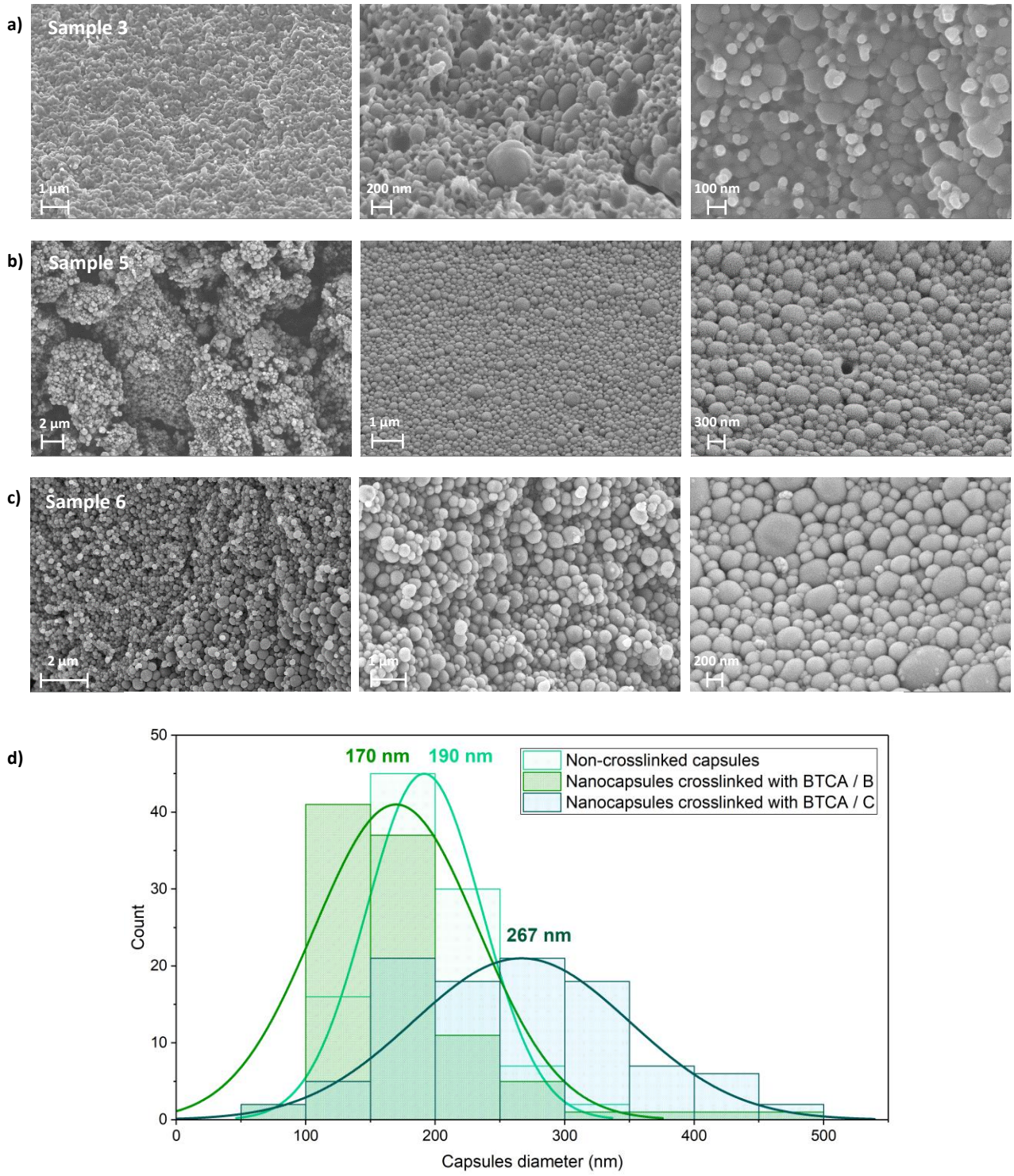


Figure S6. SEM-ZEISS images of nanocapsules prepared according to the general procedure with the following modification. a) Non-crosslinked nanocapsules (sample **3**); b) nanocapsules crosslinked according to method **B** (sample **5**); c) nanocapsules crosslinked with method **C** (sample **6**); d) distributions of the diameters of the particles, fitted with a gaussian curve: fwhm values are 125 nm (sample **3**), 170 nm (sample **5**), 197 nm (sample **6**)), respectively.

7. Crosslinking approach with different hardening agents

7.1. BTCA as crosslinker. Morphological, chemical and thermal characterization

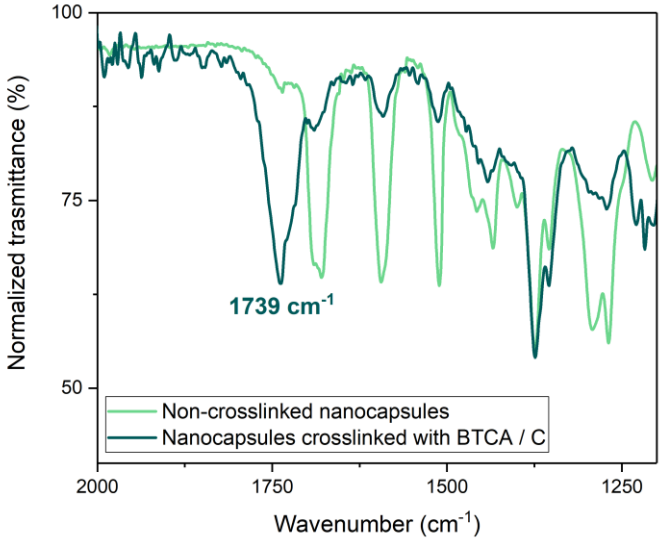


Fig. S7. Portion of FT-IR spectra between 2000 and 1200 cm^{-1} of both non-crosslinked (sample **3**) and crosslinked with BTCA (sample **6**, method **C**) nanocapsules: a peak at 1739 cm^{-1} is shown corresponding to C=O stretching.

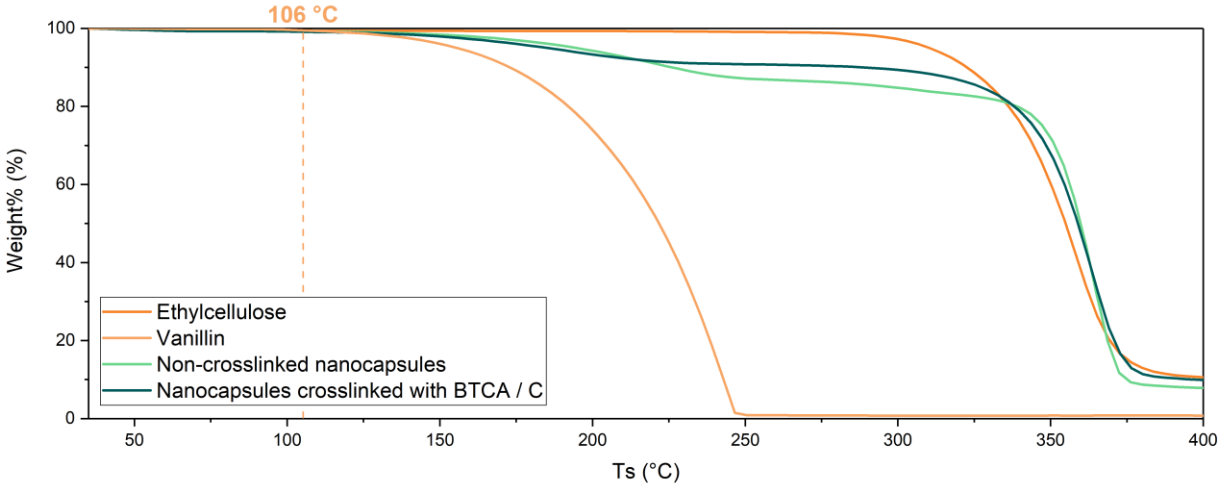


Fig. S8 TGA curve of ethylcellulose (weight loss at 277 °C), vanillin (weight loss at 106 °C), non-crosslinked nanocapsules functionalized with TMPG loaded with vanillin (weight loss at 137 and 297 °C) and nanocapsules loaded with vanillin and crosslinked with BTCA (sample **6**, weight loss at 137 and 300 °C).

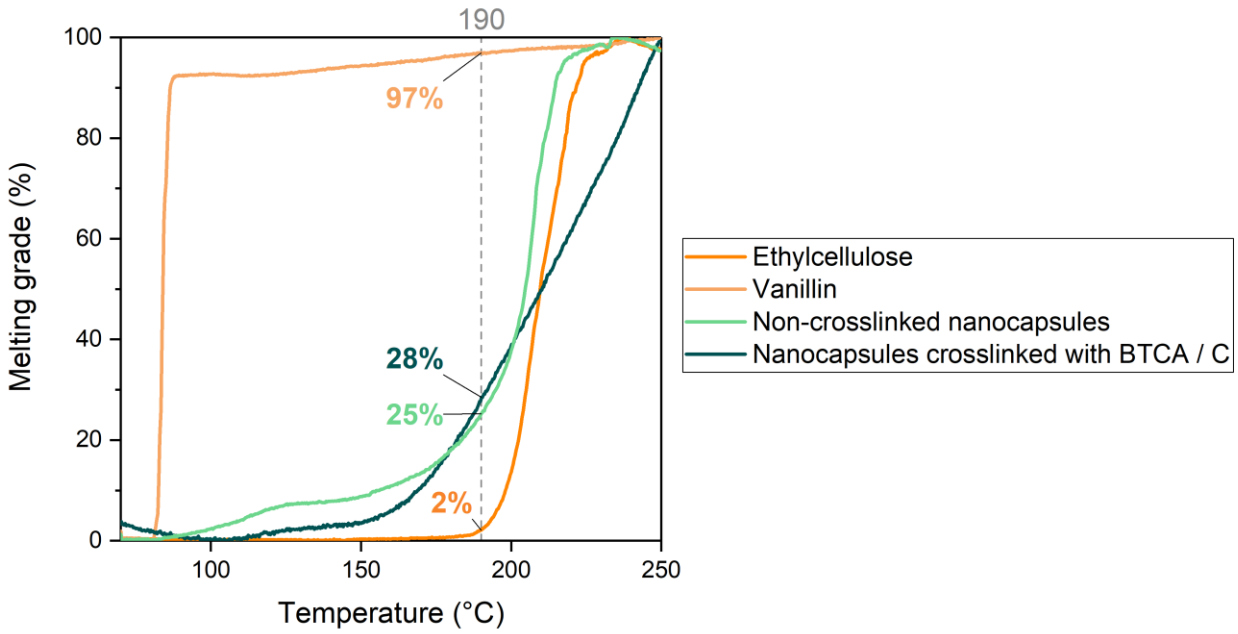


Fig. S9 Melting grade of ethylcellulose (melting grade 2%), vanillin (melting grade 97%), non-crosslinked nanocapsules (sample **3**, melting grade 25%); nanocapsules crosslinked with BTCA according to method **C** (sample **6**, melting grade 28%). T=190 °C is taken as the reference temperature.

7.1.3. Thermal stress

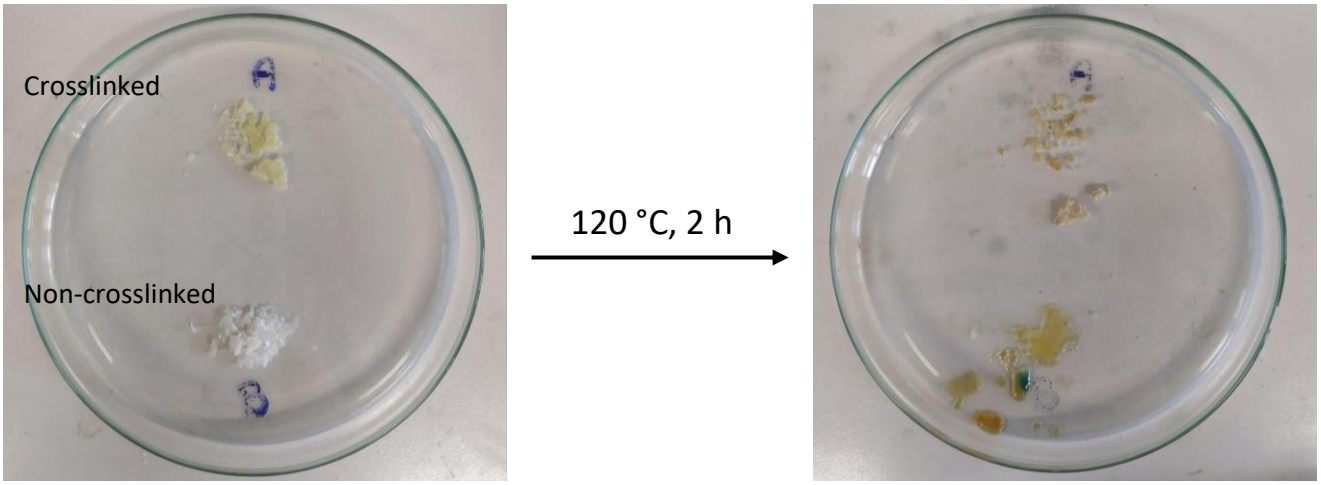


Fig. S10 Samples of crosslinked (a) and non-crosslinked (b) nanocapsules loaded with vanillin before and after thermal treatment of 2 h at 120 °C. The melting point of vanillin is 81-83 °C.

7.2. Control experiment: synergistic effect of crosslinking with both TMPG and BTCA. Morphological, chemical and thermal characterization

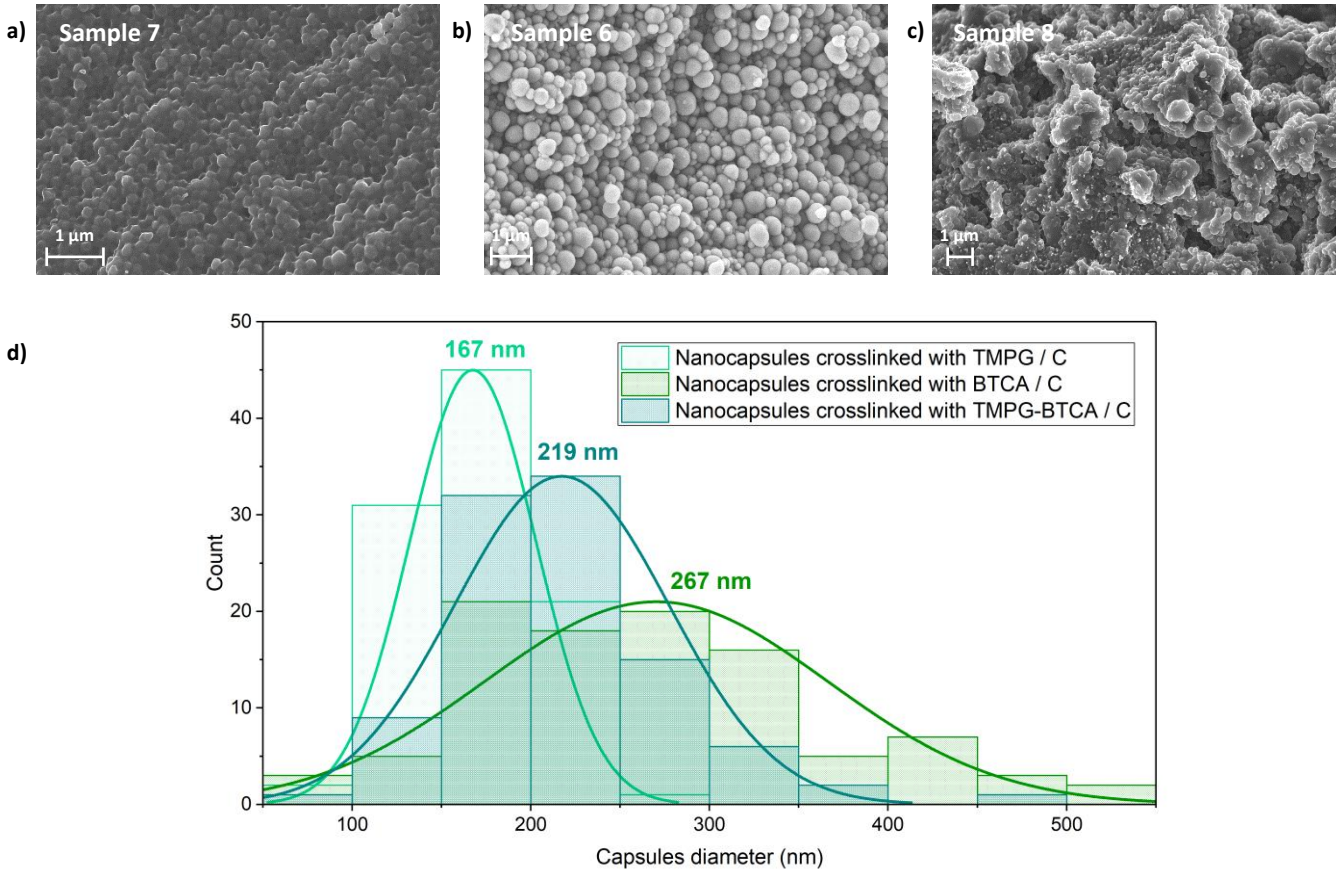


Fig. S11 SEM-ZEISS images of nanocapsules prepared according to the general procedure with crosslinking (method **c**) in the presence of a) just TMPG (sample **7**), b) just BTCA (sample **6**) and c) both TMPG and BTCA (sample **8**); d) distributions of the diameters of the particles, fitted with a gaussian curve: fwhm values are 84 nm (sample **7**), 197 nm (sample **6**), 143 nm (sample **8**)), respectively.

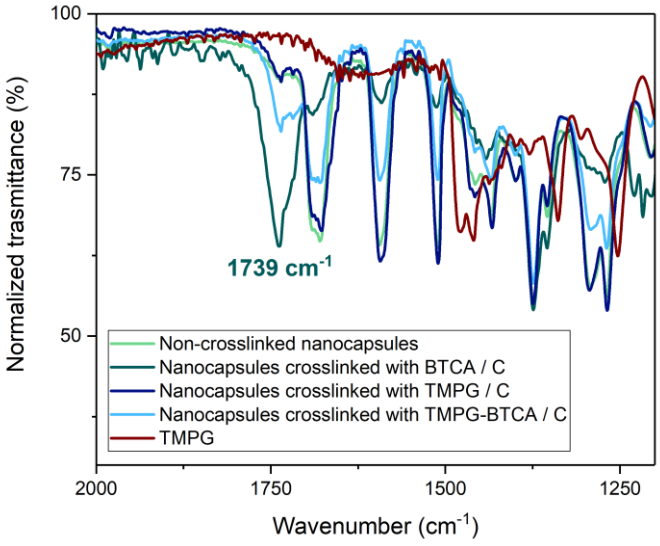


Fig. S12 Portion of FT-IR spectra between 2000 and 1200 cm^{-1} of non-crosslinked nanocapsules and crosslinked capsules with BTCA (sample **6**, method **C**), TMPG (sample **7**, method **C**) and both TMPG-BTCA (sample **8**, method **C**). As a reference the spectrum of the reagent TMPG (dark red line) is overlapped. A peak at 1739 cm^{-1} is shown corresponding to C=O stretching.

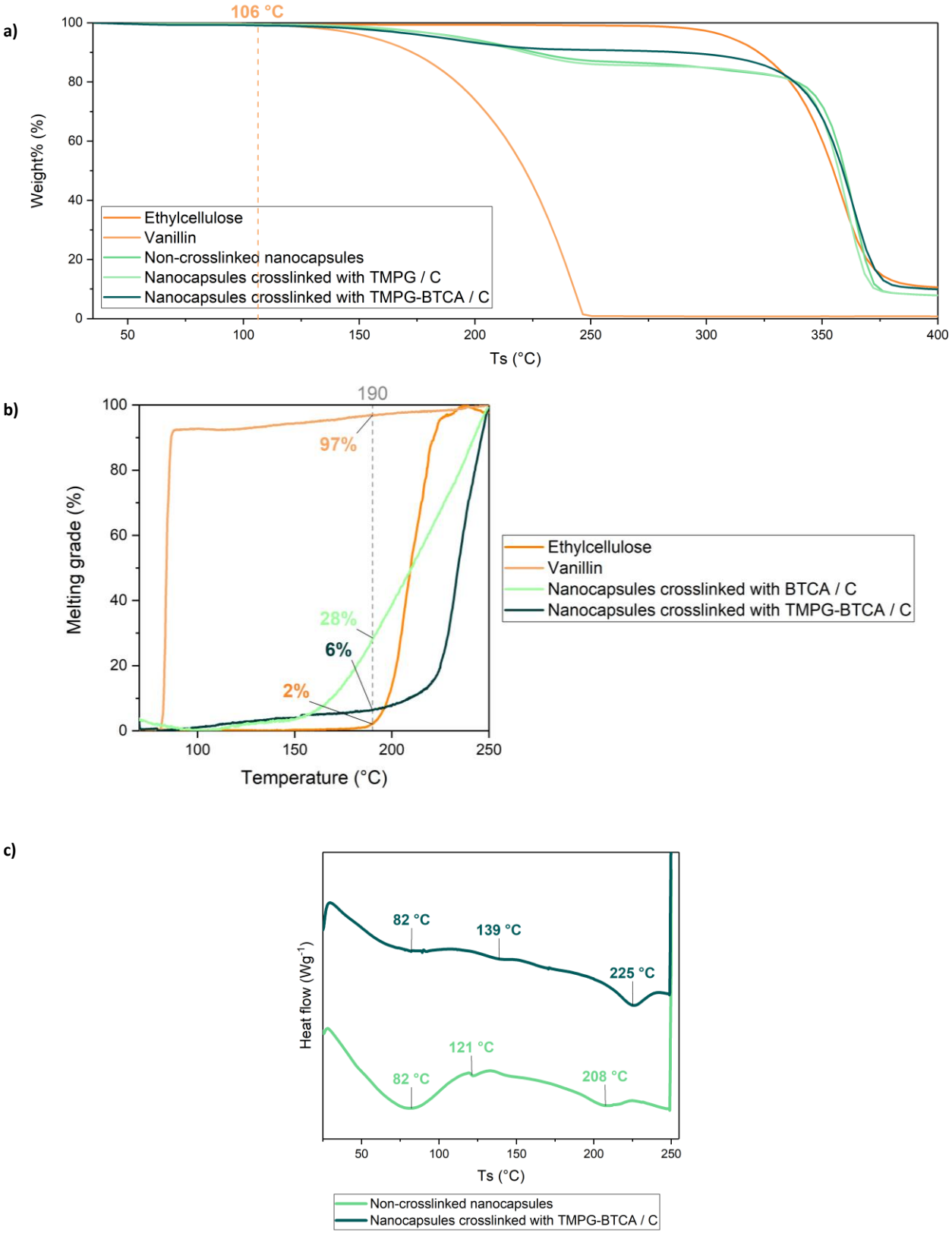


Fig. S13 a) TGA curves and b) melting grades of ethylcellulose (weight loss at 277 °C, melting grade 2%), vanillin (weight loss at 106 °C, melting grade 97%), non-crosslinked nanocapsules loaded with vanillin and functionalized with TMPG (weight loss at 137 and 303 °C), nanocapsules loaded with vanillin and crosslinked with TMPG (weight loss at 137 and 303 °C, melting grade 28%) and nanocapsules loaded with vanillin, functionalized with TMPG and crosslinked with BTCA (weight loss at 137 and 303 °C, melting grade 6%). For the melting grade analysis T=190 °C is taken as the reference temperature. c) DSC analysis of non-crosslinked and crosslinked with TMPG-BTCA (C) nanocapsules from 25 to 250 °C with scan rate of 10 °C/min.

7.3. TREN as crosslinker. Morphological and thermal characterization

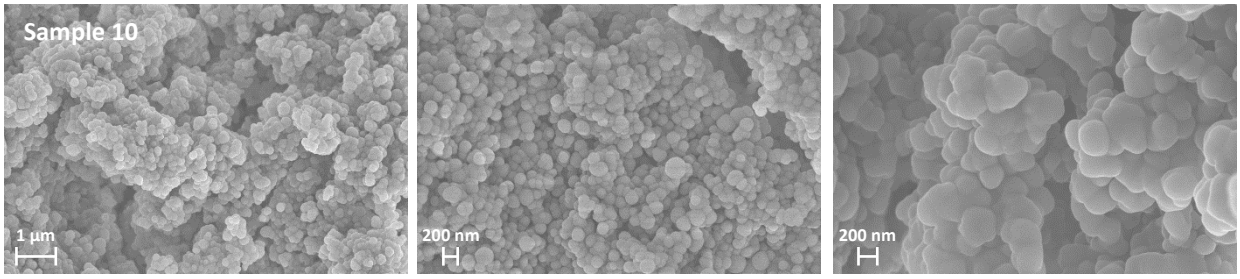


Fig. S14 SEM-ZEISS images of nanocapsules prepared according to the general procedure with crosslinking with method **C** by using TREN as a crosslinker (sample **10**).

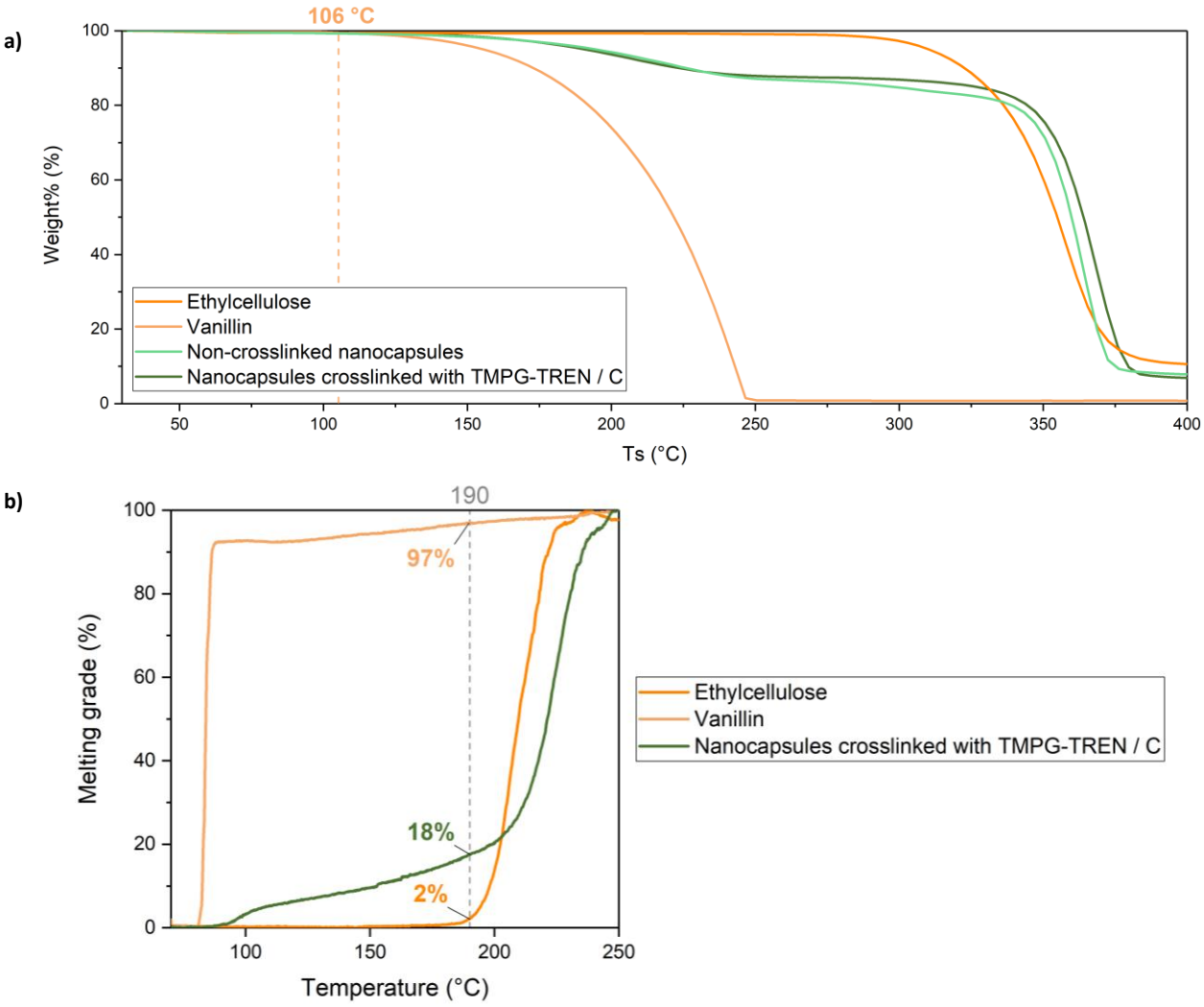
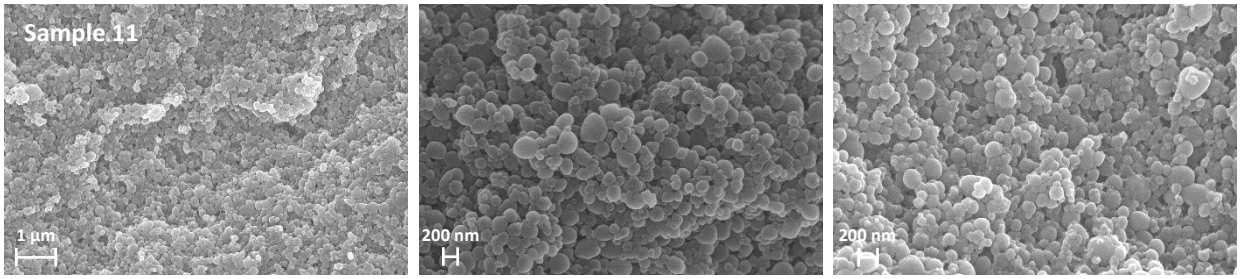


Fig. S15 a) TGA curves and b) melting grades of ethylcellulose (weight loss at 277 °C, melting grade 2%), vanillin (weight loss at 106 °C, melting grade 97%), non-crosslinked nanocapsules loaded with vanillin and functionalized with TMPG (weight loss at 137 and 284 °C) and nanocapsules loaded with vanillin, functionalized with TMPG and crosslinked with TREN (sample **10**, weight loss at 137 and 300 °C, melting grade 18%). For the melting grade analysis T=190 °C is taken as the reference temperature.

7.4. Further crosslinking: BTCA and borax. Morphological, chemical and thermal characterization

a)



b)

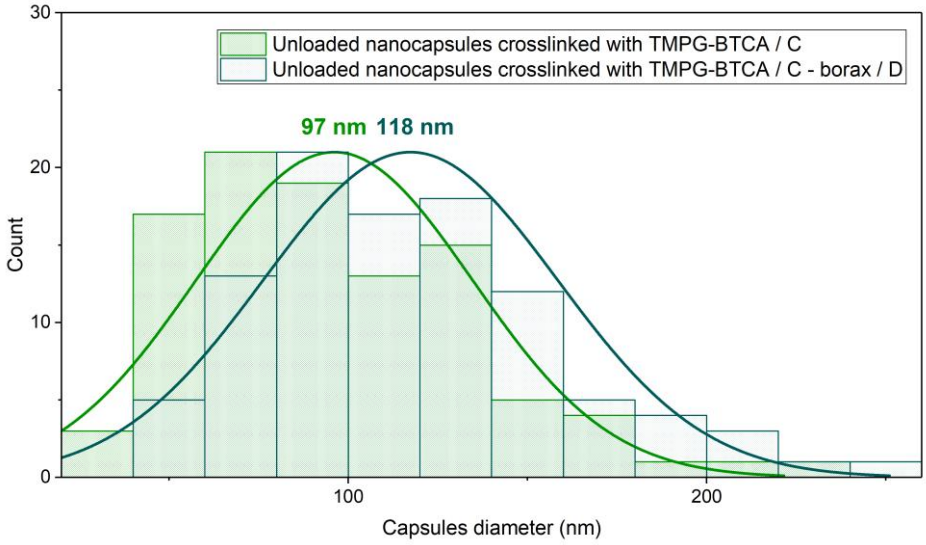


Fig. S16 a) SEM-ZEISS images of nanospheres prepared according to the general procedure with crosslinking with two crosslinking steps: first method **C** using BTCA (sample **9**) and then method **D** with borax (sample **11**); b) distributions of the diameters of the particles, fitted with a gaussian curve: fwhm values are 93,5 nm (sample **9**), nm (sample **11**)), respectively.

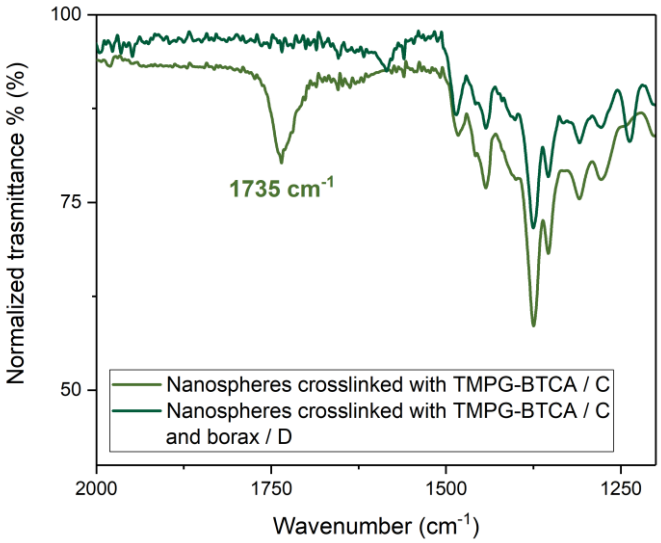


Fig. S17 Portion of FT-IR spectra between 2000 and 1200 cm^{-1} of crosslinked with TMPG-BTCA / C (green line, method **C**) and crosslinked with borax (dark green line, method **D**) nanocapsules: a peak at 1739 cm^{-1} is shown corresponding to C=O stretching.

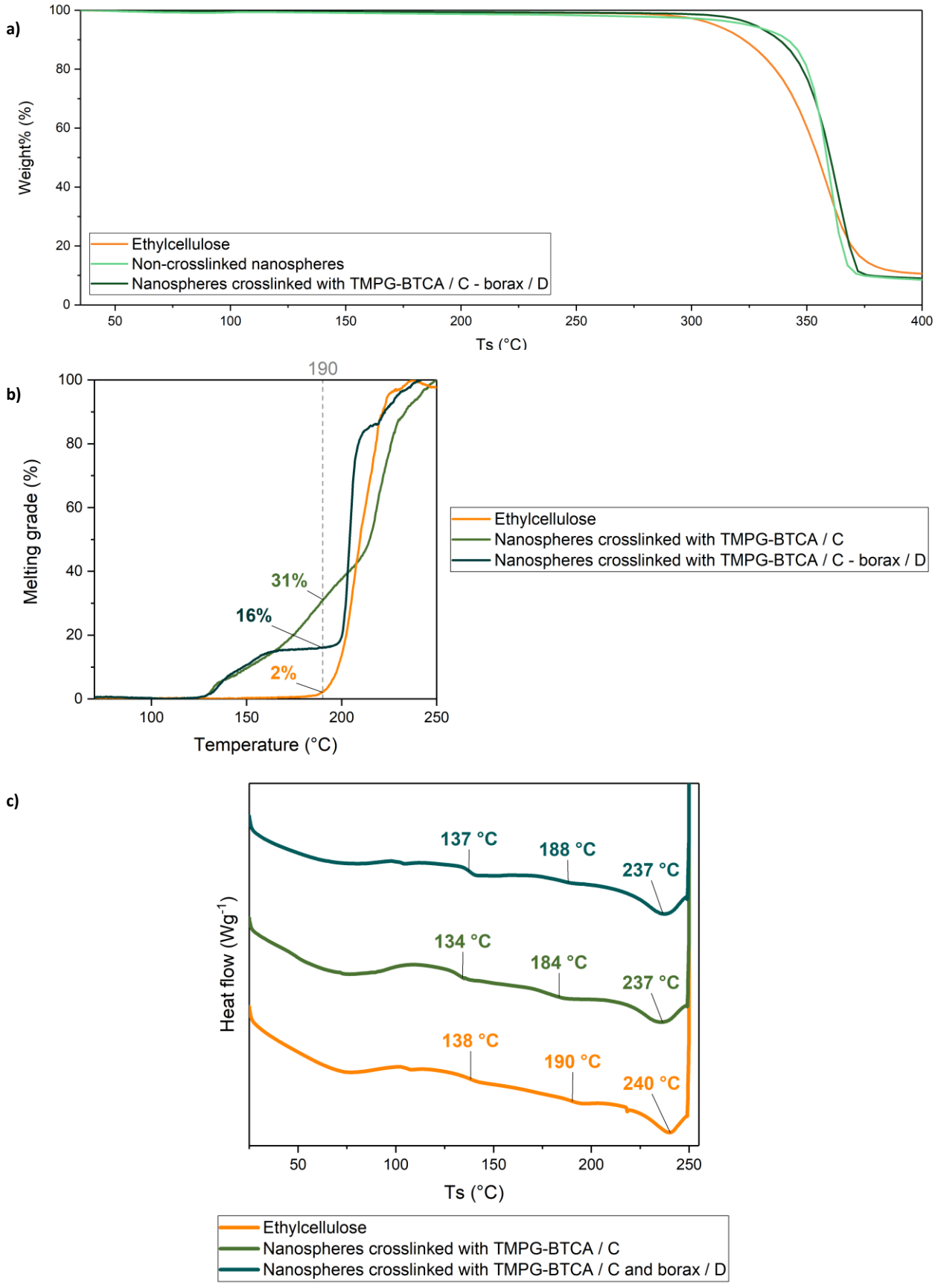


Fig. S18 a) TGA curves and b) melting grades of ethylcellulose (weight loss at 277 °C, melting grade 2%), non-crosslinked nanospheres functionalized with TMPG (weight loss at 300 °C), nanospheres functionalized with TMPG crosslinked with BTCA according to method **C** (melting grade 31%) and nanospheres functionalized with TMPG crosslinked with both BTCA (method **C**) and borax (method **D**) (weight loss at 300 °C, melting grade 16%). T=190 °C is taken as the reference temperature. c) DSC analysis of EC, nanospheres crosslinked with TMPG-BTCA (method **C**) and with borax (method **D**) from 25 to 250 °C with scan rate of 10 °C/min.

8. Nanospheres VS nanocapsules. Morphological and thermal characterization

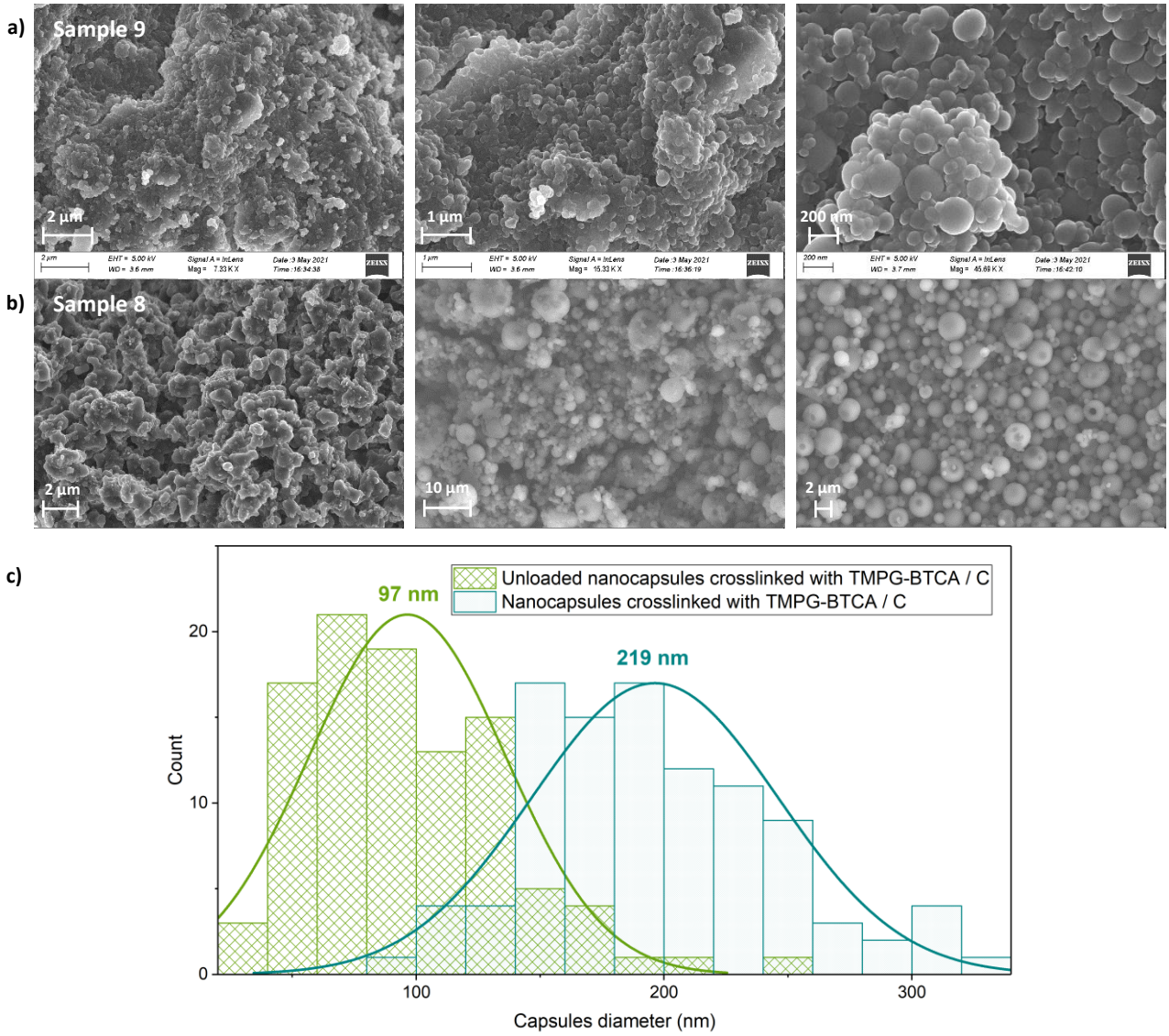


Fig. S19 SEM-ZEISS images of nanocapsules prepared according to the general procedure with the following modification. a) Crosslinked nanospheres (without any cargo, sample **9**); b) crosslinked nanocapsules loaded with vanillin (sample **8**); c) distributions of the diameters of the particles, fitted with a gaussian curve: fwhm values are 93.5 nm (sample **9**), 118.0 nm (sample **8**), respectively.

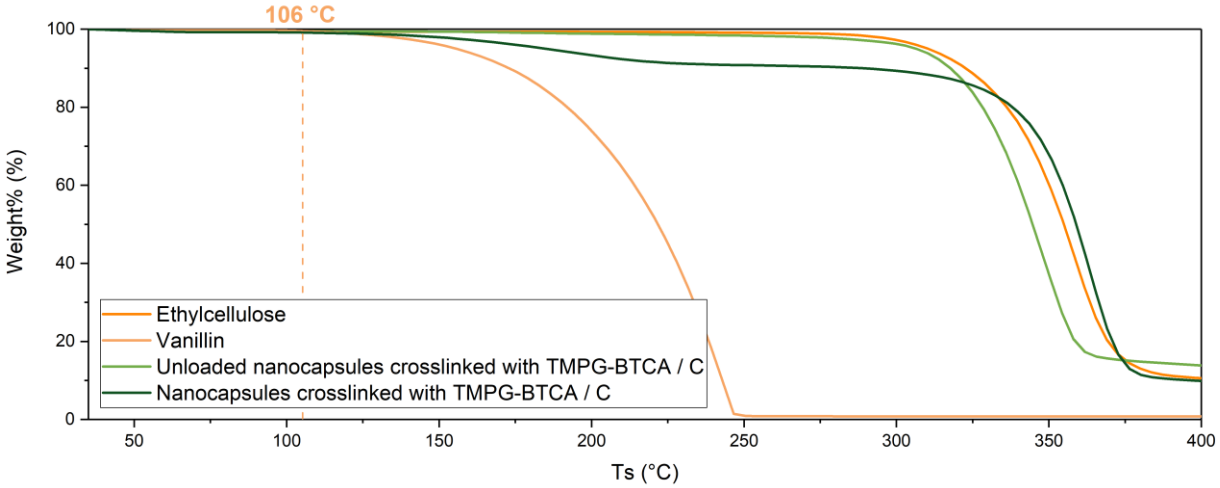


Fig. S20 TGA curve of ethylcellulose (weight loss at 277 °C), vanillin (weight loss at 106 °C, nanospheres functionalized with TMPG without cargo (sample **9**,weight loss at 278 °C) and nanocapsules functionalized with TMPG loaded with vanillin (sample **8**, weight loss at 137 and 300 °C).

9. Dynamic Light Scattering analysis

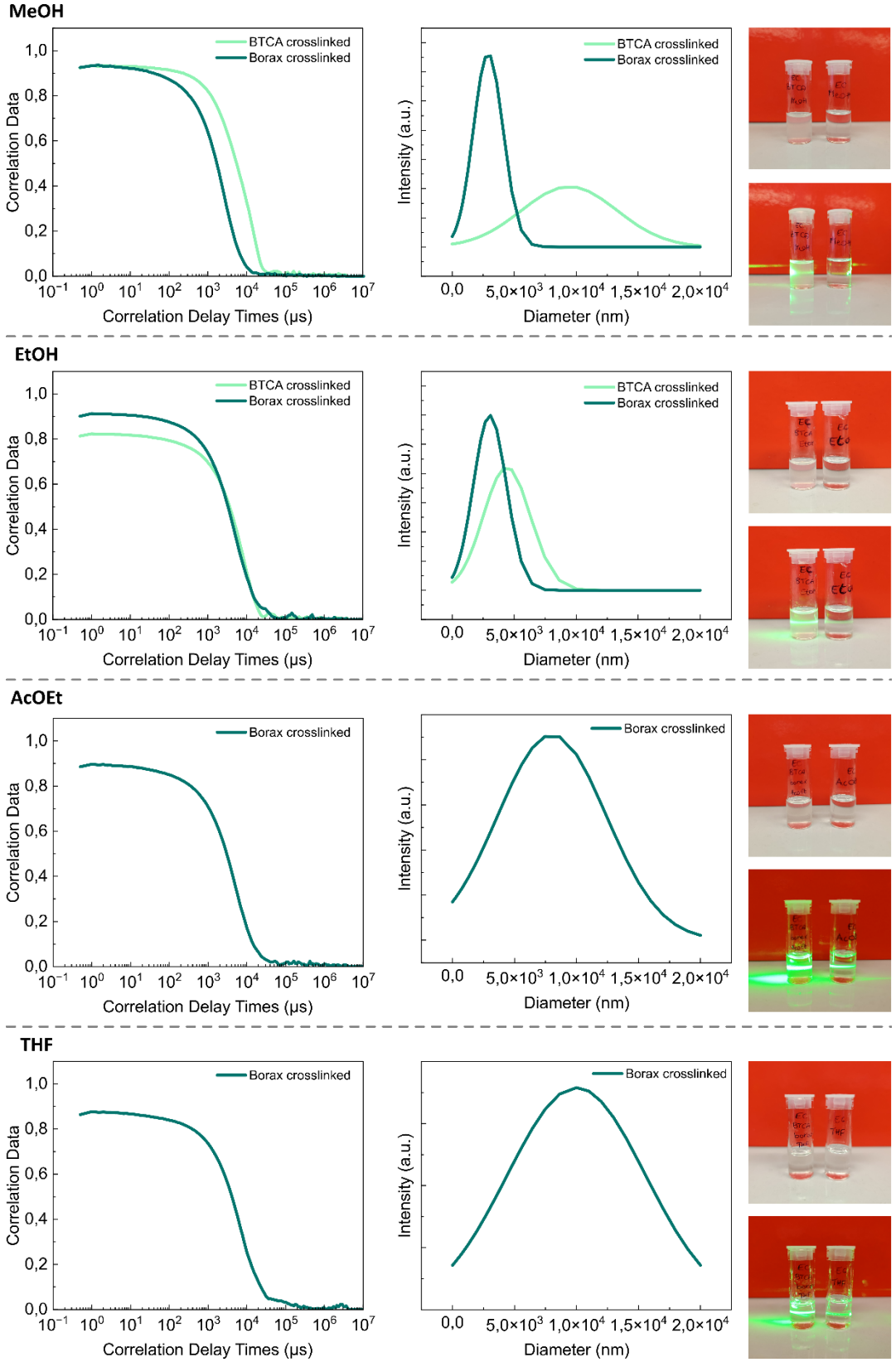


Fig. S21 DLS correlograms comparison of pristine ethylcellulose and crosslinked EC-nanospheres obtained using our modified-MESE approach. Samples are prepared dispersing materials (2 wt/V%) in polar protic solvents (MeOH, EtOH), and aprotic polar solvents (AcOEt, THF). On the right, photographs of pristine ethylcellulose and

10. Recovery of unreacted BTCA

After the synthesis and isolation of microcapsules crosslinked with BTCA, the unreacted hardening agent can be easily recovered applying the following work-up. The aqueous phase is collected and the solvent is distilled under reduced pressure. The obtained solid is then taken up with acetone and left stirring at ambient temperature for 30 minutes. The dispersion is filtered and washed with acetone. A white powder is obtained, corresponding to pure BTCA, as demonstrated by ^{1}H NMR in fig. S24 (mass recovery: 16%).

^{1}H NMR (BTCA, 400 MHz, D_2O): δ 3.23-3.20 (m, 2H), δ 2.72-2.65 (m, 2H), δ 2.57 (d, J = 4.1 Hz, 1H), δ 2.53 (d, J = 4.1 Hz, 1H) ppm.

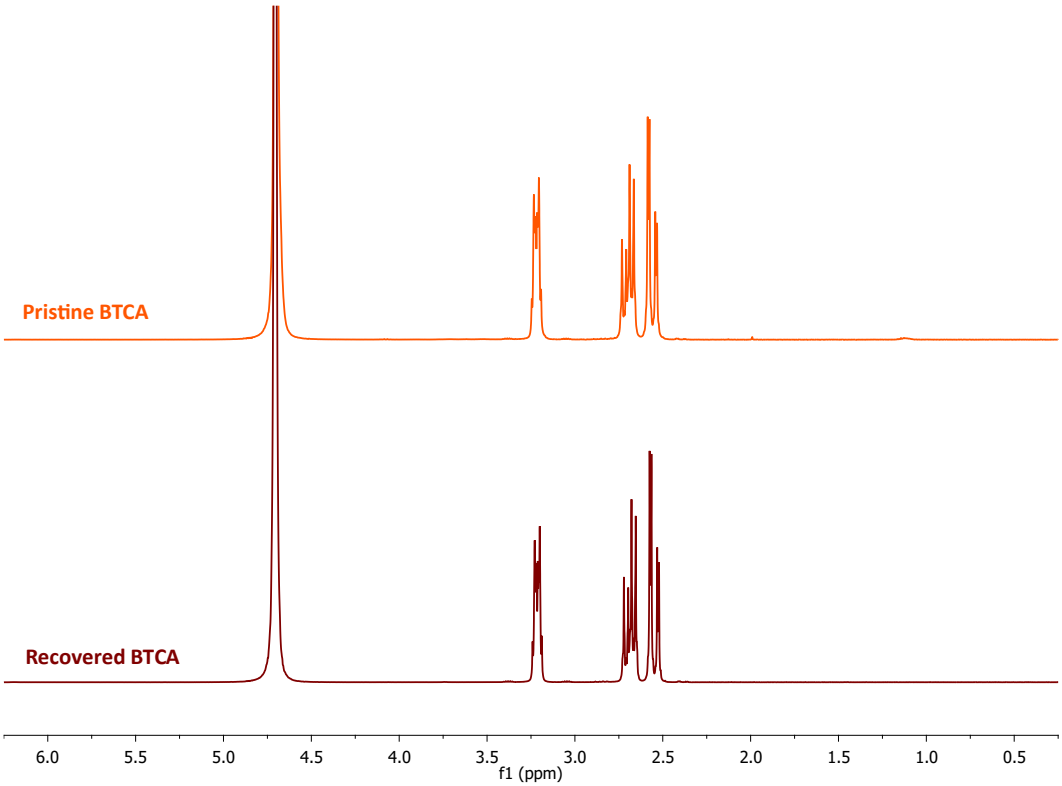


Fig. S22 ^{1}H NMR in D_2O of stacked spectra of pristine BTCA (orange line) and the white powder recovered (dark red line).

11. Scalability of the approach

Our methodology is tested on a 25 g scale. An organic phase is prepared in a beaker by dissolving ethylcellulose (EC, 5.00 wt/V%, 25.0 g) in 500 mL of AcOEt. The mixture is mechanically stirred (700 rpm) for 24 h until complete EC dissolution. Additionally, trimethylolpropane triglycidyl ether (TMPG 0.50% wt/V, 0.2 g) is introduced and the mixture is stirred for 24 h. Simultaneously, a dispersing aqueous phase consisting of PVA 1% wt/V in deionized water (1500 mL) is prepared in a second beaker under mechanical stirring (700 rpm). Then, an o/w emulsion is formed by slowly adding the organic phase into the aqueous phase. The mixture is homogenized under mechanical stirring (700 rpm). To prepare nanocapsules, a high-power ultrasound probe is used (cycle 50%, amplitude 50%, 10 minutes) is used. The organic solvent is thus removed by distillation under reduced pressure. A dispersion of capsules in the solution of PVA in water is obtained. Both BTCA (0.75 eq., 24.3 g) and NaH_2PO_4 (0.25 eq., 4.1 g) are added directly into the water dispersing phase without previous isolation of the particles. The obtained dispersion is heated at 90 °C for 6 hours. After cooling down, the solid is recovered by ultracentrifugation at 11000 rpm for 30 minutes at 5 °C (x2). A white powder is obtained (33 g, mass recovery efficiency 74%).

Fig. S23 Pictures of the organic phase in AcOEt (on the left), homogenization setup using a high-power ultrasound probe (on the centre) and crosslinking step with BTCA (on the right).

12. Greenness methodology evaluation

E-factor calculations:

$$Completed\ E_{factor} = \frac{mass_{waste}}{mass_{product}} = \frac{mass_{reag} + mass_{solv} - mass_{prod} - mass_{recycled}}{mass_{prod}}$$

$$E_{factor}(without\ water) = \frac{mass_{org\ waste}}{mass_{product}} = \frac{mass_{reag} - mass_{prod} - mass_{recycled}}{mass_{prod}}$$

Note:

- in the distillation step the organic solvent is fully recovered, thus it is not included in the E-factor calculation;
- as described in Section 10, 16% of the total amount of BTCA added in the crosslinking step is recovered and recycled.

Non-crosslinked capsules	
Material	Mass (g)
Ethylcellulose (EC)	4.0
AcOEt	72.2
Polyvinyl alcohol (PVA)	2.4
Water	240.0
Sum of waste	246.4
Recovery	1.3
Recovery efficiency	33%
E-factor	188.5
E-factor (without water)	3.9

Capsules crosslinked with BTCA (B)	
Material	Mass (g)
Ethylcellulose (EC)	1.3
AcOEt	22.6
Polyvinyl alcohol (PVA)	0.7
Water	75.0 + 50.0
BTCA	0.24 (waste 0.2)
NaH_2PO_4	0.04
Sum of waste	127.24
Recovery	0.2
Recovery efficiency	16%
E-factor	635.2
E-factor (without water)	260.2

Capsules crosslinked with BTCA (C)	
Material	Mass (g)
Ethylcellulose (EC)	6.0
AcOEt	108.2
Polyvinyl alcohol (PVA)	3.6
Water	360.0
BTCA	5.1 (waste 4.3)
NaH_2PO_4	0.9
Sum of waste	374.8
Recovery	4.5
Recovery efficiency	75%
E-factor	82.3
E-factor (without water)	2.3

Capsules crosslinked with BTCA (C) + borax	
Material	Mass (g)
Ethylcellulose (EC)	6.0
AcOEt	108.2
Polyvinyl alcohol (PVA)	3.6
Water	360.0 + 200.0
BTCA	5.1 (waste 4.3)
NaH_2PO_4	0.9
Borax	2.3
Sum of waste	577.1
Recovery	4.2
Recovery efficiency	71%
E-factor	135.4
E-factor (without water)	3.0

13. General procedure for the synthesis of Pd-loaded EC capsules

13.1. Synthesis of nanocapsules

An organic phase is prepared in a beaker by dissolving the encapsulating EC (4.50% wt/V) in 300 mL of DCM. The mixture is mechanically stirred (700 rpm) for 24 h until complete EC dissolution. Then, trimethylpropane triglycidyl ether (TMPG 0.45 wt/V%) is added. After 24 h of stirring, diphenylether (0.50% wt/V) and the catalytic species are added. The mixture is stirred for 30 min. In a second beaker, a dispersing aqueous phase consisting of polyvinyl alcohol (PVA 8-88, Mw 67000) 1% wt/V in deionized water (900 mL) is prepared under mechanical stirring (700 rpm). Then, the organic phase is slowly added to the water phase in order to form an oil-in-water emulsion (o/w). The mixture is homogenized under mechanical stirring (700 rpm). The droplet size of the emulsion is then refined by using a high-power ultrasound probe (cycle 50%, amplitude 50%, 10 min). The organic solvent is thus distilled under reduced pressure from the nanosized emulsion produced.

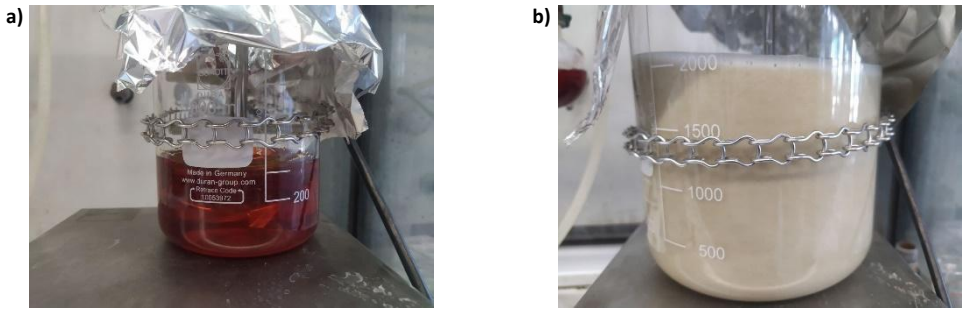


Fig. S24 Photographs of a) the organic phase composed of EC, TMPG, diphenylether and the catalytic species in DCM; b) emulsified mixture after the addition of the organic phase to the aqueous solution of PVA 8-88 1 wt/V%.

13.2. Crosslinking technology

1,2,3,4-Butanetetracarboxylic acid (0.75 eq.) and NaH_2PO_4 (sodium phosphate monobasic, 0.25 eq.) are added directly in the water dispersing phase without previous isolation of the particles. The dispersion is then heated at 90 °C for 6 hours. The mixture is ultra-centrifugated at 11000 rpm for 30 minutes at 5 °C (x2 times). The supernatant is removed and the obtained solid is dried in the oven at 60 °C under vacuum. The powder is characterized by FT-IR analysis.

To further crosslink the obtained nanocapsules, the solid is redispersed in water (500 mL) and sodium tetraborate decahydrate (borax, $Na_2B_4O_7 \cdot 10H_2O$, 0.20 eq.) is added. The mixture is sonicated by using a high-power ultrasound probe (cycle 50%, amplitude 50%, 10 minutes) to have complete homogenization of the powder in water. The dispersion is heated at 90 °C for three hours. After cooling, the obtained precipitate is isolated on a paper funnel and dried in the oven at 60 °C. A fine brown powder is recovered.

13.3. Details on single specific encapsulation process

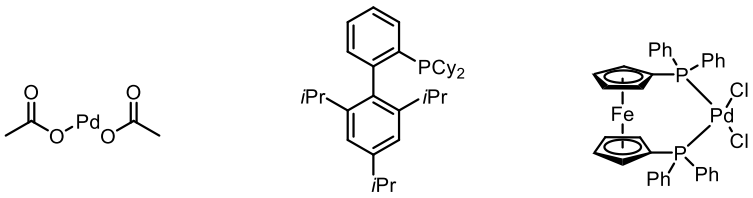


Fig. S25 Structures of the catalyst and combination of catalysts/phosphine ligands embedded within EC capsules.

Cargo	Pd wt%/EC	Acronyms
$Pd(OAc)_2$	0.90	a-Nc-$Pd(OAc)_2$
$Pd(OAc)_2$	4.50	Nc-$Pd(OAc)_2$
$Pd(OAc)_2$-XPhos	4.50	Nc-$Pd(OAc)_2$-XPhos
$Pd(OAc)_2$-XPhos	4.50	Mc-$Pd(OAc)_2$-XPhos
$Pd(dppf)Cl_2$	3.00	Nc-$Pd(dppf)Cl_2$

Tab. S1 List of all the samples produced with the corresponding acronyms.

13.3.1. a-Nc-$Pd(OAc)_2$

Nanocapsules with $Pd(OAc)_2$ 0.90 wt%/EC. The sample is obtained according to the general procedure with the amount of materials reported in the following table. Amount of Pd species actually loaded (measured with ICP-OES): 0.27 wt%.

Organic phase	
EC	13.50 g
TMPG	1.35 g
Diphenylether	1.50 g
$Pd(OAc)_2$	0.12 g
DCM	300 mL

13.3.2. Nc-$Pd(OAc)_2$

Nanocapsules with $Pd(OAc)_2$ 4.50 wt%/EC. The sample is obtained according to the general procedure with the amount of materials reported in the following table. Amount of Pd species actually loaded (measured with ICP-OES): 2.94 wt%.

Organic phase	
EC	13.50 g
TMPG	1.35 g
Diphenylether	1.50 g
$Pd(OAc)_2$	0.61 g
DCM	300 mL

This sample is the one used for the Sonogashira couplings reported in Tab. 3, entry 1-4 in the main text, as well as in Suzuki couplings reported in section 15 and 16.

13.3.3. Nc-Pd(OAc)$_2$-XPhos

Nanocapsules with Pd(OAc)$_2$ 4.50 wt%/EC + XPhos 23.90 wt%/EC. The sample is obtained according to the general procedure with the amount of materials reported in the following table. Both the palladium catalyst and the phosphine ligand are encapsulated. The phosphine ligand is added 2.5:1.0 mol/mol with respect to the palladium catalyst. Amount of Pd species actually loaded (measured with ICP-OES): 3.15 wt%.

Organic phase	
EC	13.50 g
TMPG	1.35 g
Diphenylether	1.50 g
Pd(OAc)$_2$	0.61 g
XPhos	3.23 g
DCM	300 mL

This sample is the one used for the Sonogashira couplings reported in Tab. 3, entry 5-12 in the main text.

13.3.4. Mc-Pd(OAc)$_2$-XPhos

Microcapsules with Pd(OAc)$_2$ 4.50 wt%/EC + XPhos 23.90 wt%/EC. The sample is obtained following the same procedure used for Nc-Pd(OAc)$_2$-XPhos, but using an IKA Ultra Turrax T25 dispersing apparatus (800 rpm for 10 minutes, impeller S 25N-25G) instead of the high-power ultrasound probe for the last mixing step. Both the palladium catalyst and the phosphine ligand are encapsulated. The phosphine ligand is added 2.5:1.0 mol/mol with respect to the palladium catalyst. Amount of Pd species actually loaded (measured with ICP-OES): 3.37 wt%.

Organic phase	
EC	13.50 g
TMPG	1.35 g
Diphenylether	1.50 g
Pd(OAc)$_2$	0.61 g
XPhos	3.23 g
DCM	300 mL

This sample is the one used for the Sonogashira couplings reported in Tab. 3, entry 13 in the main text, as well as for the synthesis of products reported in Scheme 3.

13.3.5. Nc-Pd(dppf)Cl$_2$

Nanocapsules with Pd(dppf)$_2$ 3.00 wt%/EC + XPhos 23.90 wt%/EC. The sample is obtained according to the general procedure with the following modification. Both the palladium catalyst and the phosphine ligand are encapsulated.

Organic phase	
EC	13.50 g
TMPG	1.35 g
Diphenylether	1.50 g
Pd(dppf)Cl$_2$	0.40 g
DCM	300 mL

This sample is tested in Suzuki couplings reported in section 15 and 16.

14. Characterizations of Pd-loaded EC capsules

14.1. Nc-Pd(OAc)$_2$

Thermal analysis

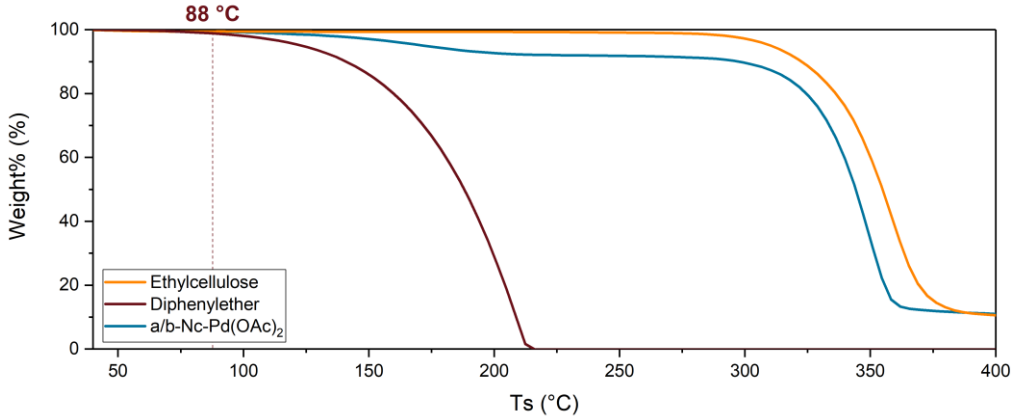


Fig. S26 TGA curve of Nc-Pd(OAc)$_2$ (weight loss at 88 and 272 °C). Temperature range: 40-400 °C. As references the TGA curves of diphenylether and pristine ethylcellulose are reported.

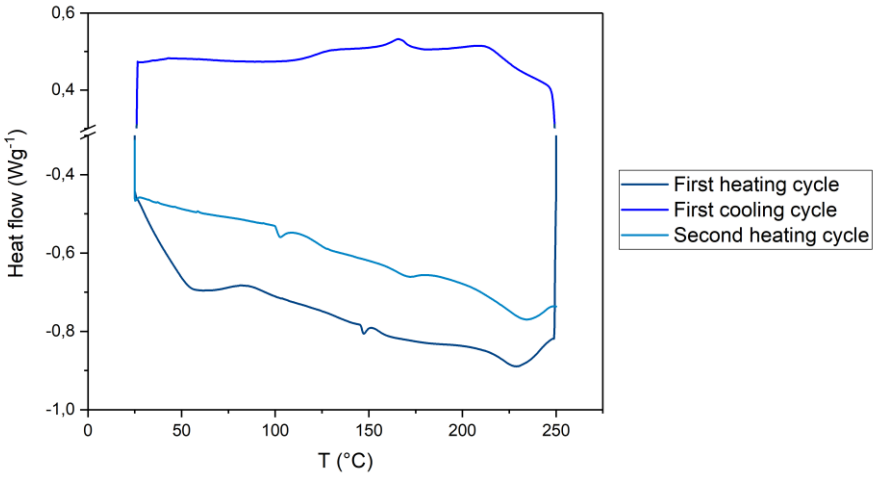


Fig. S27 DSC analysis of Nc-Pd(OAc)$_2$. Scan rate of 10 °C/min.

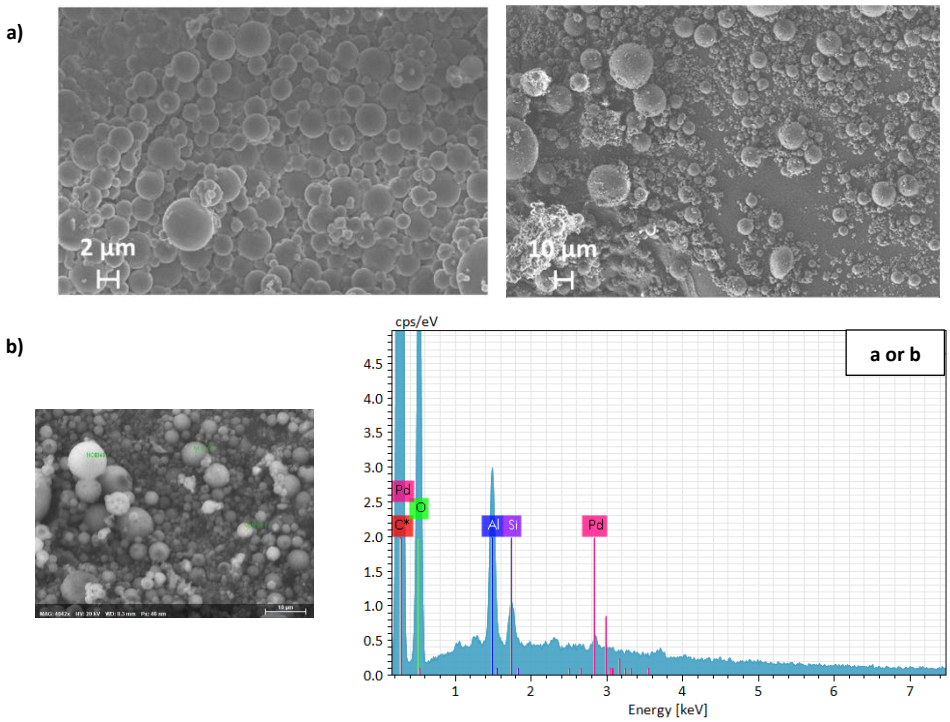


Fig. S28 a) SEM images and b) Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM-EDS) analysis of Nc-Pd(OAc)$_2$. EDS spectrum shows the presence of chemical elements Al, Si (from SEM sample stubs), C, O (mainly from ethylcellulose) and Pd (from Pd(OAc)$_2$).

13.1.1. Morphological and chemical analysis

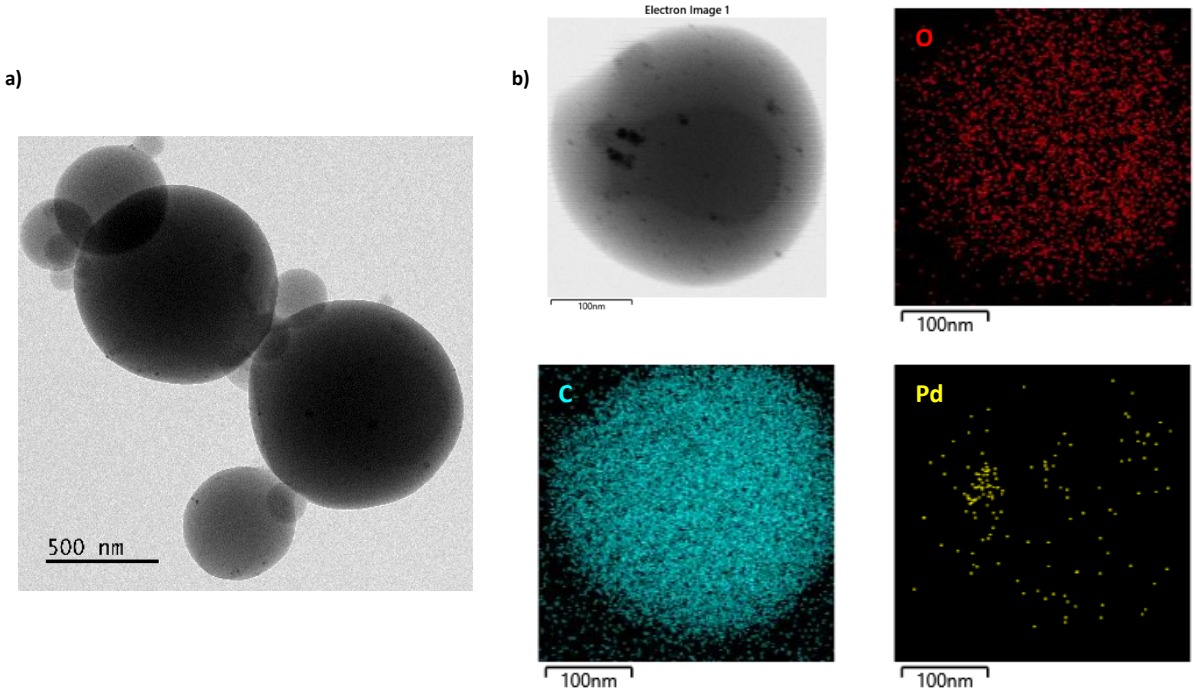


Fig. S29 a) High Resolution Transmission Electron Microscopy (HR-TEM) images of Nc-Pd(OAc)$_2$ and b) the corresponding mapping images: C, O and Pd are detected.

14.2. Nc-Pd(OAc)$_2$-XPhos

14.2.1. Thermal analysis

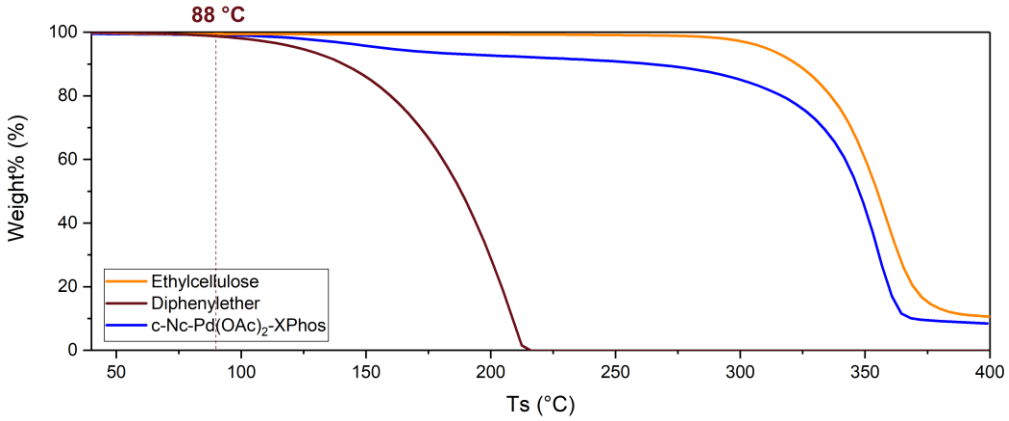


Fig. S28 TGA curve of Nc-Pd(OAc)$_2$-XPhos (weight loss at 88 and 272 °C). Temperature range: 40-400 °C. As references the TGA curves of diphenylether and pristine ethylcellulose are reported.

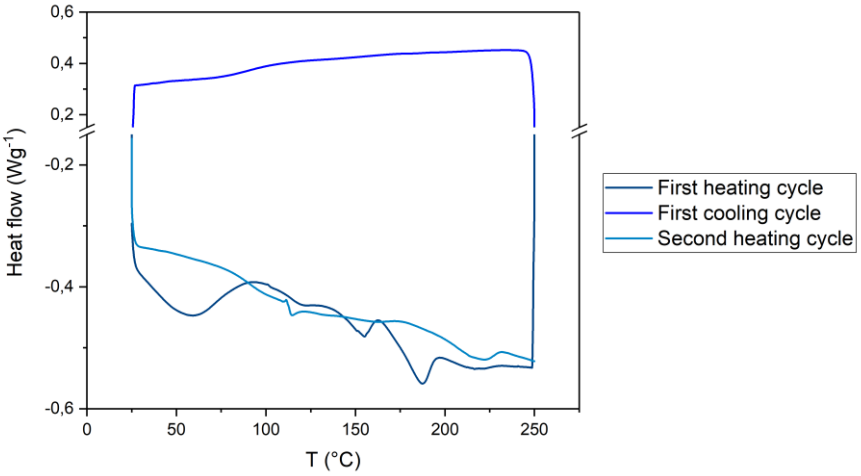


Fig. S29 DSC analysis of Nc-Pd(OAc)$_2$-XPhos. Scan rate of 10 °C/min.

14.2.2. Morphological and chemical analysis

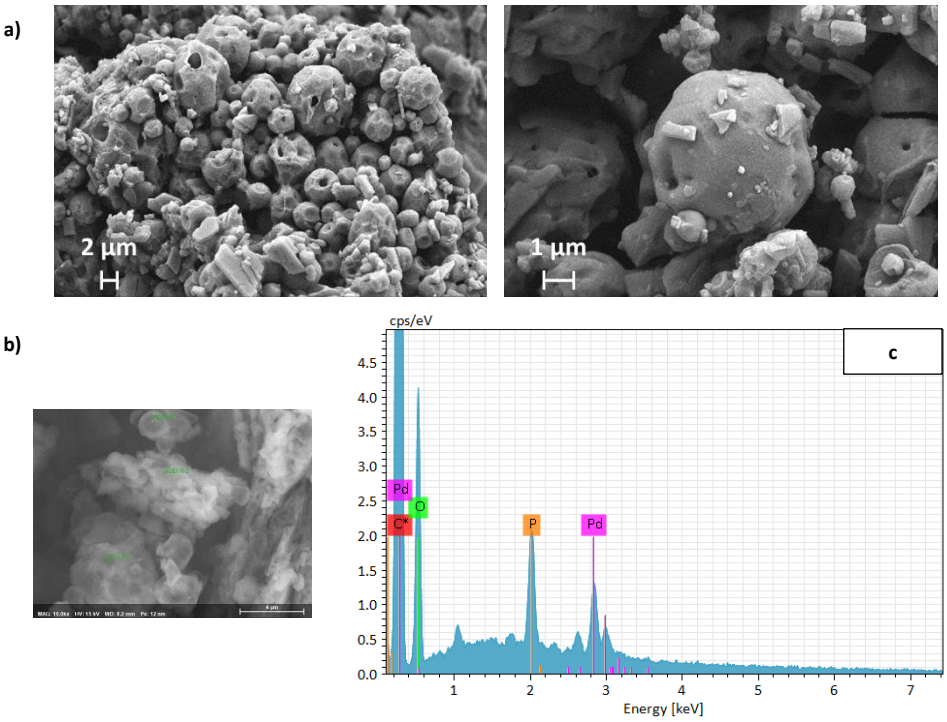


Fig. S30 a) SEM images and b) Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM-EDS) analysis of Nc-Pd(OAc)$_2$-XPhos. EDS spectrum shows the presence of chemical elements C, O (mainly from ethylcellulose), Pd (from Pd(OAc)$_2$ and P (from the phosphine ligand).

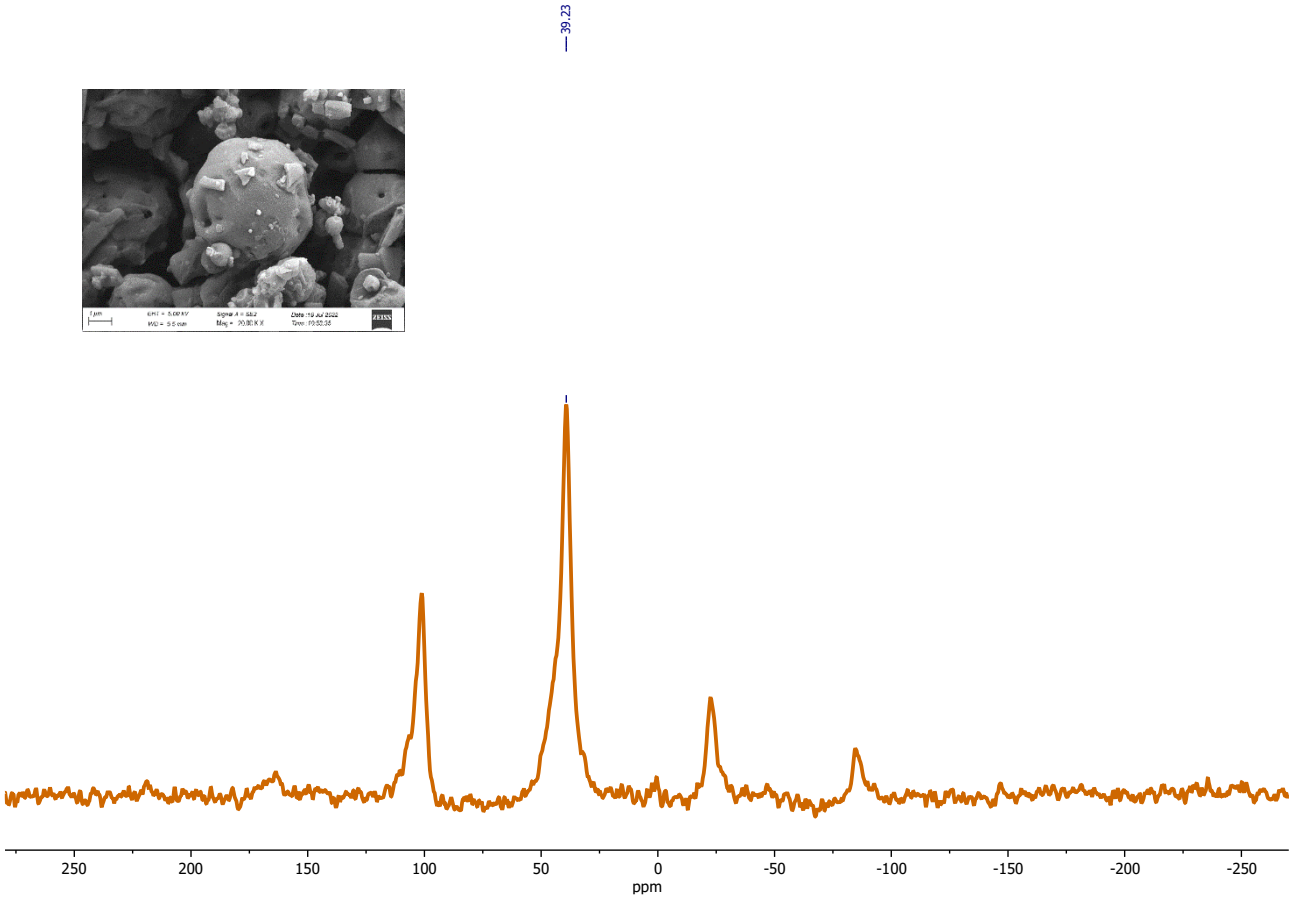


Fig. S31 ^{31}P Solid State NMR spectrum of Nc-Pd(OAc)$_2$-XPhos. The experiment is performed at a spinning speed of 10 kHz.

14.3. Mc-Pd(OAc)$_2$-XPhos

14.3.1. Thermal analysis

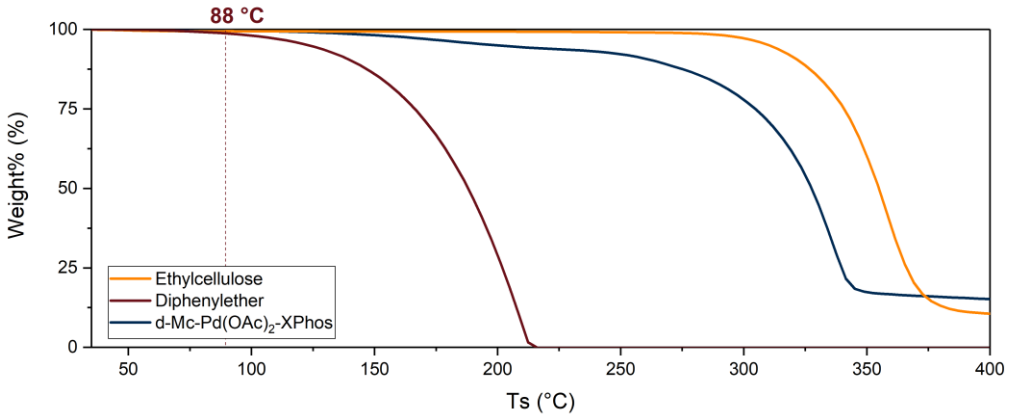


Fig. S32 TGA curve of Mc-Pd(OAc)$_2$-XPhos (weight loss at 88 and 250 °C). Temperature range: 40-400 °C. As references the TGA curves of diphenylether and pristine ethylcellulose are reported.

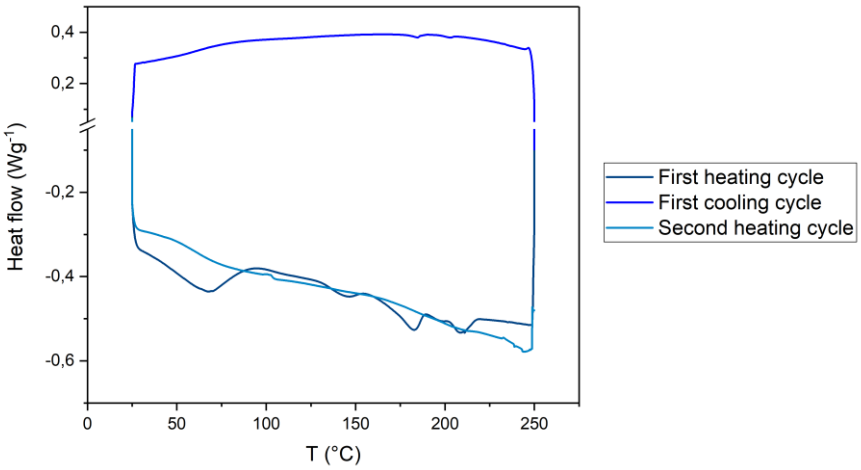


Fig. S33 DSC analysis of Mc-Pd(OAc)$_2$-XPhos. Scan rate of 10 °C/min.

14.3.2. Morphological and chemical analysis

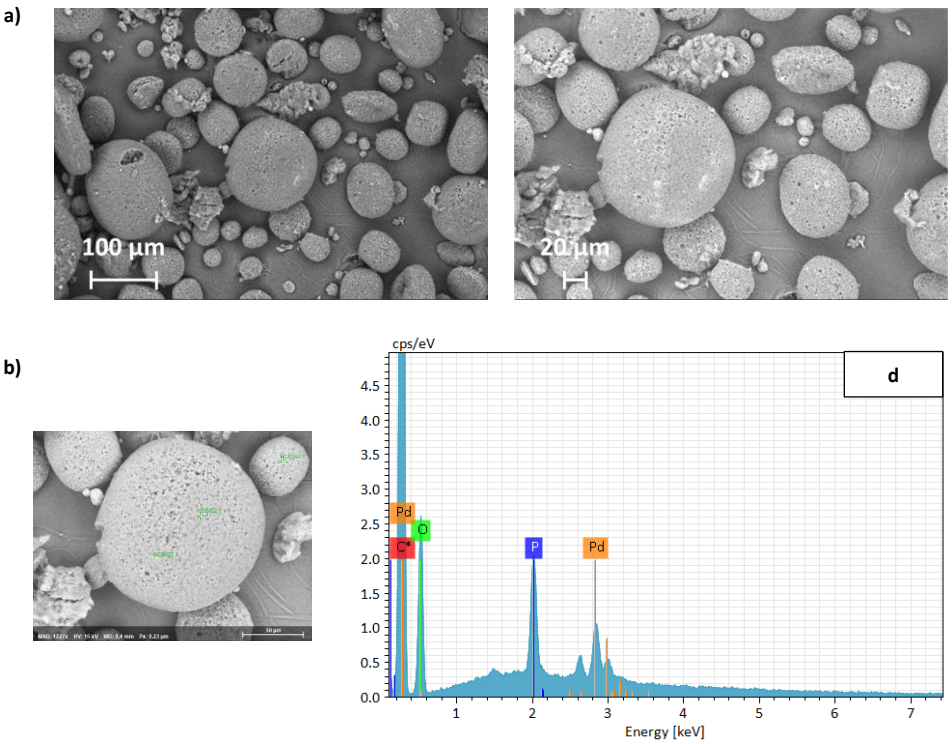


Fig. S34 a) SEM images and b) Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM-EDS) analysis of Mc-Pd(OAc)$_2$-XPhos. EDS spectrum shows the presence of chemical elements C, O (mainly from ethylcellulose), Pd (from Pd(OAc)$_2$ and P (from the phosphine ligand).

14.4. Nc-Pd(dppf)Cl$_2$

14.4.1. Thermal analysis

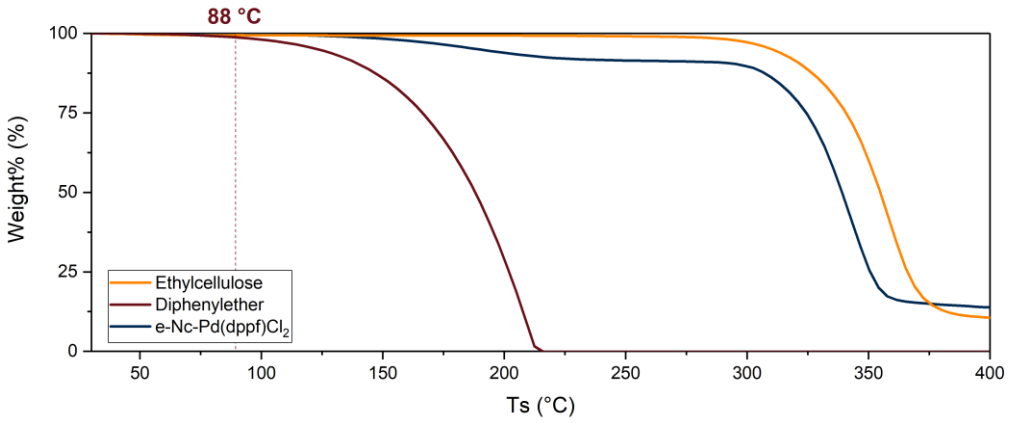


Fig. S35 TGA curve of Nc-Pd(dppf)Cl$_2$ (weight loss at 88 and 272 °C). Temperature range: 40-400 °C. As references the TGA curves of diphenylether and pristine ethylcellulose are reported.

14.4.2. Morphological and chemical analysis

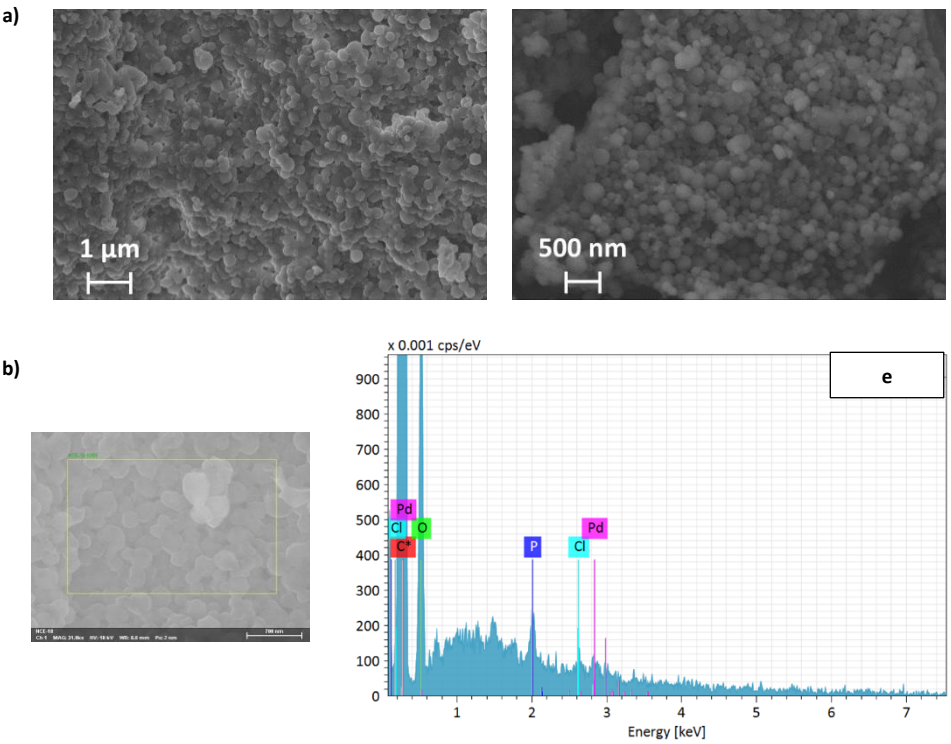


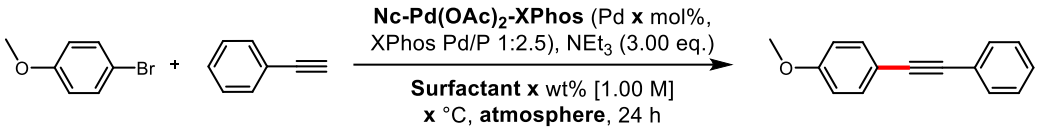
Fig. S38 a) SEM images and b) Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy (SEM-EDS) analysis of Nc-Pd(dppf)Cl_2. EDS spectrum shows the presence of chemical elements C, O (mainly from ethylcellulose), Pd and P (from Pd(dppf)Cl_2).

15. General procedures for cross-coupling reactions via heterogeneous catalysis

General procedure for the test Sonogashira reaction with EC capsules (main text, Tab. 3)

4-bromoanisole (4.00 mmol), phenylacetylene (4.00 mmol) are weighted in a round-bottom test tube, then catalyst loaded capsules are added. In the case of Nc-Pd(OAc)$_2$, fresh XPhos is also added. 4 mL of K-EL 2 wt% in water and 1.70 mL of NEt$_3$ (12.00 mmol) are added and the mixture is stirred at the chosen temperature for 24 hours. Reaction progress was monitored by TLC (Heptane/AcOEt 70:30) and GC-MS (see section 17).

In those cases when reaction reached completion, the mixture was diluted with water and the dispersion was centrifugated at 11000 rpm (10 min x2). The supernatant was removed and the dry solid was taken up with AcOEt and stirred for 1 hour at 80 °C. The resulting dispersion was centrifugated at 11000 rpm (30 min x3). The supernatant is collected and the organic solvent is removed under reduced pressure to afford the pure product. Light yellow powder, **98% yield (816.5 mg, 3.92 mmol)**. **R$_f$:** 0.6 (Heptane/AcOEt 70:30).



Scheme S1 General scheme for the Sonogashira optimization part using our synthetic catalyst.

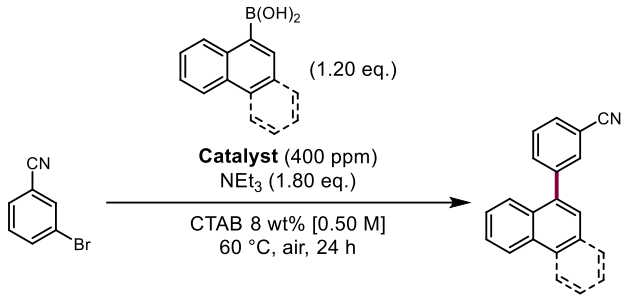
General procedure for other Sonogashira reactions with EC capsules (main text, Scheme 3)

In a typical procedure, the bromide (2.00 mmol) and the alkyne (2.00 mmol) are weighted in a round-bottom test tube, then Nc-Pd(OAc)$_2$-XPhos capsules (107 mg) are added. 2 mL of degassed K-EL 2 wt% in water and 0.84 mL of degassed NEt$_3$ (6.00 mmol) are added and the mixture is stirred at 45 °C for up to 24 hours. Reaction progress was monitored by TLC or GC-MS. After reaction reached completion, the mixture was diluted with water and the dispersion was centrifugated at 11000 rpm (10 min x2). The supernatant was removed and the dry solid was taken up with AcOEt and stirred for 1 hour at 80 °C. The resulting dispersion was centrifugated at 11000 rpm (30 min x3). The supernatant is collected and the organic solvent is removed under reduced pressure to collect the crude product.

Eventual further purification procedures are listed case by case (see section 22 for details).

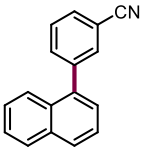
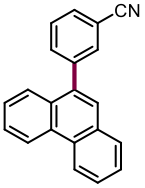
General procedure for Suzuki-Miyaura couplings with EC capsules

2-Bromobenzonitrile (5.00 mmol) and a boronic acid (6.00 mmol) are weighted in a round-bottom flask. Then nanocapsules loaded with various catalytic species are added (to have 400 ppm of Pd), followed by 10 mL of CTAB 8 wt% in water and 1.25 mL of triethylamine (9.00 mmol). The resulting dispersion is then heated at 60 °C for 24 h. Reaction progress can be monitored by TLC (Heptane/DCM 50:50). After completion of the reaction, the aqueous medium is evaporated under reduced pressure. The dry solid is then taken up with toluene. After 30 minutes stirring, the mixture is centrifugated at 11000 rpm (10 min x3) and the organic solvent is then removed from the supernatant. A light brown powder is obtained. Composition of the mixture is determined by GC-MS analysis.



Scheme S2 General scheme for the Suzuki part using our synthetic catalyst.

16. Suzuki trials

Entry	Catalyst	Product	GC-MS Conv. to product %*
1	Nc-Pd(OAc)$_2$		56
2	Nc-Pd(dppf)Cl$_2$		85
3	Nc-Pd(dppf)Cl$_2$		Quantitative

The attempts revealed some homogenization problems over time and affinity changes towards the reaction medium, suggesting the occurrence of certain side reactions involving the polymer shell. According to literature, this could potentially be attributed to interactions between boron and oxygen atoms on EC, that led to an undesirable condensation of EC with the reagent boronic acid. This competitive coupling could negatively affect the reaction outcomes, leading to decreased conversions. Additionally, it is worth noting that our polymer shell presented epoxide functionalities (derived from the functionalization with TMPG). The boronic acid could act as hydrogen bond donor to the epoxide-oxygen and promote the ring-opening via nucleophilic attack by alkoxide ions. Evidence is provided in the following Figure, where are reported the FT-IR overlapped spectra of nanocapsules before and after a basic treatment in the presence of phenylboronic acid. The typical peaks relative to the epoxide structure, located at 1481 and 1254 cm^{-1} [1], disappeared after the treatment, suggesting the opening of the epoxide-ring. Unfortunately, these in-situ transformations of the coating wall layer of our nanoreactors produced undesired alterations in the morphology and features of our structures, consequently affecting the catalytic activity and potentially promoting the release of the active agents previously embedded.

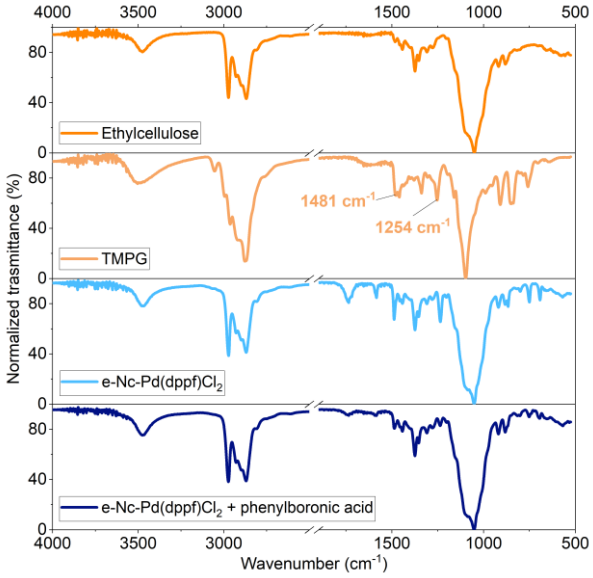


Fig. S39 Overlapped FT-IR spectra of EC, TMPG epoxide, Pd-loaded capsules before and after treatment with phenylboronic acid. Conditions: 500 mg of capsules (≈2.45 mmol) and phenylboronic acid (0.50 mmol) are added to a round-bottom flask, followed by 0.50 mmol of NaOH. Water is added and the mixture is stirred at 90 °C ovn.

17. GC-MS calibration: response factor method

The conversion of our model reaction between 4-bromoanisole and phenylacetylene is determined by ratio of integration of remaining aryl bromide and cross-coupling product signals by gas chromatography-mass spectroscopy (GC-MS). The composition of our mixture is then estimated through area normalization based on response factor method. For this aim, three standard solutions are prepared at known molar concentration (10^{-2}-10^{-3} M ca) of the pure species in dichloromethane as a solvent. Thus, each standard solution is analysed three times by GC-MS. Areas of each peak (A_x) are normalized by the weight of the corresponding compound (W_x). The following formula is used in order to obtain the response factors (s refers to the standard):

$$f_x = f_s \frac{A_s}{A_x} \frac{W_x}{W_s}$$

The 4-bromoanisole reagent is fixed as standard, thus:

$$f_s = f_{reag} = 1.0$$

The response factor of the cross-coupling product is calculated thanks to the previous equation:

$$f_{prod} = 1.1$$

f_{reag}	f_{prod}
1.0	1.1

Weight (wt%) and mole (mol%) percentage of each component are calculated with the following formula (MW refers to the molecular weight):

$$wt\%_x = \frac{f_x A_x^{sample}}{(f_{reag} A_{reag}^{sample} + f_{prod} A_{prod}^{sample})} \cdot 100$$

$$mol\%_x = \frac{wt\%_x / MW_x}{(wt\%_{reag}/MW_{reag} + wt\%_{prod}/MW_{prod})} \cdot 100$$

Here is reported a typical GC spectrum of the Sonogashira coupling between 4-bromoansiole and phenylacetylene.

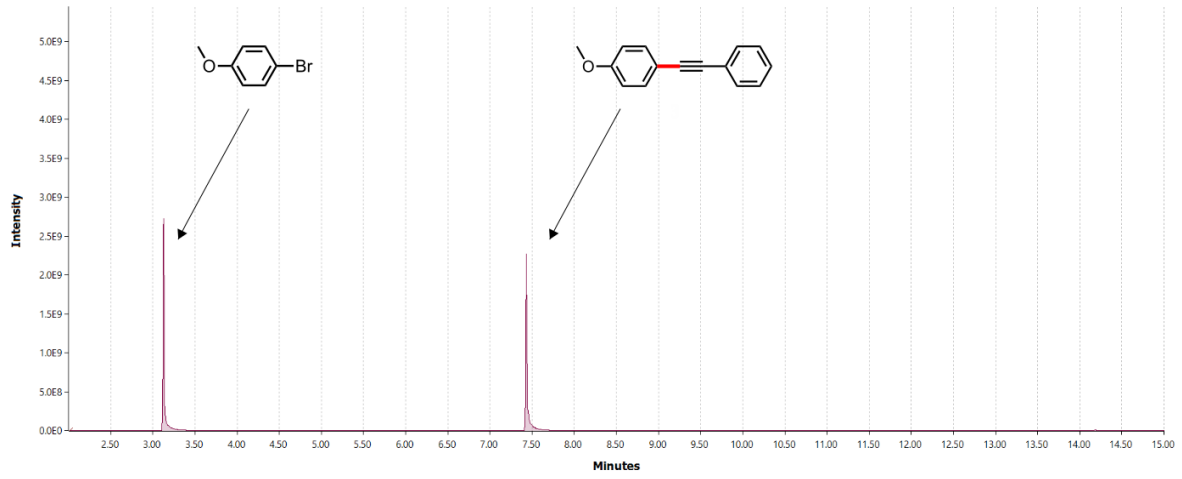
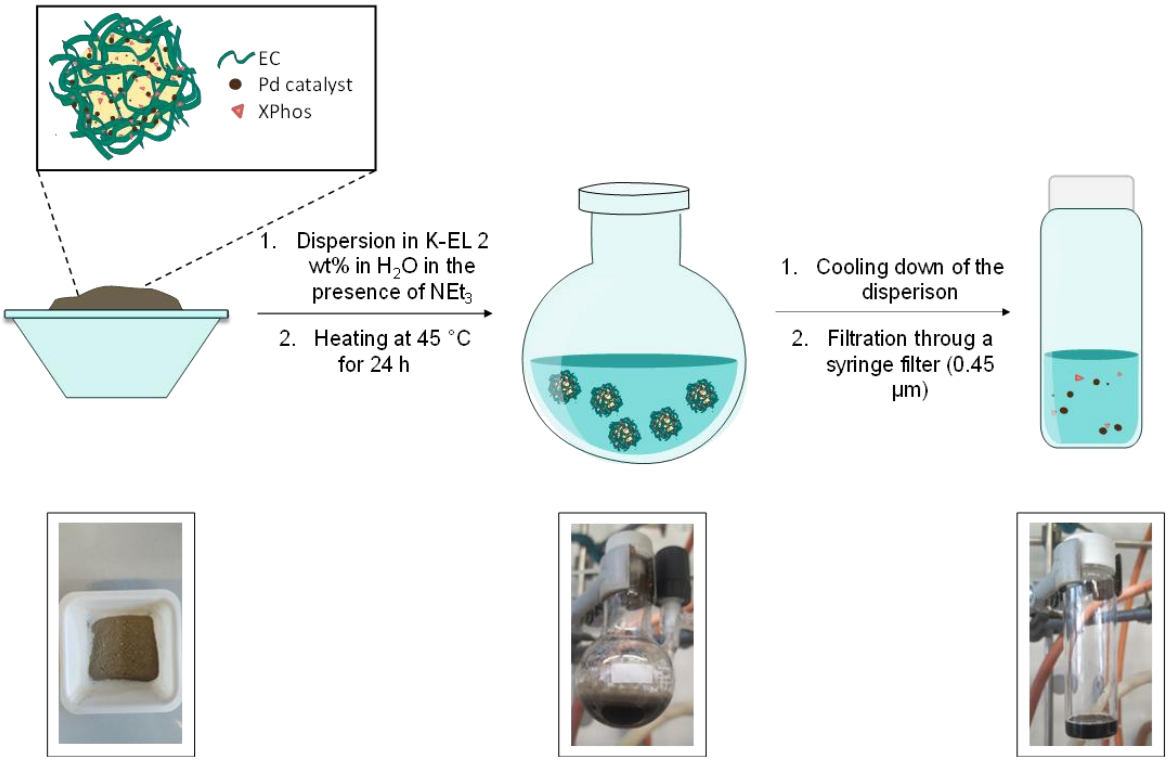


Fig. S36 Typical GC-MS spectrum of the Sonogashira coupling between 4-bromoanisole and phenylacetylene. 4-Bromoanisole retention time: 3.13 min; product retention time: 7.44 min.

18. Release test

For the release test, nanocapsules Nc-Pd-XPhos (53 mg, corresponding to 0.75 mmol% of $Pd(OAc)_2$) are weighted in a round-bottom under nitrogen atmosphere by mean of a Schlenk line. Then 1 mL of K-EL 2 wt% in water and 0.40 mL of NEt_3 (2.00 mmol) are added and the solution is stirred at 45 °C for 24 hours (reaction time). After cooling, the dispersion is filtered through a 0.45 µm size syringe filter. Water phase released is then used as medium in a Sonogashira coupling reaction with our model substrate. 4-bromoanisole (1.00 mmol), phenylacetylene (1.00 mmol) are weighted in another round-bottom test tube and the water phase collected from the release test is added. The mixture is stirred at 45 °C for 24 hours and the reaction progress is monitored by GC-MS analysis (**no reaction**).



19. Coupling product ICP-OES

A comparative experiment is conducted on our model Sonogashira reaction between 4-bromoanisole and phenylacetylene performed with both our synthetic heterogeneous catalytic systems and standard homogeneous catalysts with the aim of highlight the effective benefit of using our catalytic capsules. Therefore, we analysed by ICP-OES measurements the residual palladium in the products obtained with the just-mentioned approaches. The results indicated that the final product synthesized by using Ncs-$Pd(OAc)_2$-XPhos contained 2.7 times less palladium than that produced through common homogeneous methods.

	Homog. catalysis	**Heterog. catalysis**
wt% Pd/EC	0.36%	0.13%
mg Pd measured	3.56	1.30
mg EC measured	1000	1000
wt% $Pd(OAc)_2$	0.75%	0.27%
$\frac{\boldsymbol{wt\%\ Pd(OAc)_{2_{homog.\ released}}}}{\boldsymbol{wt\%\ Pd(OAc)_{2_{heterog.\ released}}}}$	**2.7**	

20. Recycling of Ncs in the Sonogashira coupling

Scaling up of reaction yielding product 4. The reaction was carried out under the optimized conditions and working with 4 mmol of phenylacetylene (406 mg), 4 mmol of 2-bromo-5-formylfurane (700 mg), 270 mg of Nc-Pd(OAc)$_2$-XPhos (0.03 mmol of Pd), 12 mmol of NEt_3 (1212 mg) in 4 mL of 2 wt% K-EL aqueous solution. After completion (18 h, as monitored by GC-MS analysis), the reaction mixture was centrifuged at 11000 rpm for 1 h. The solid was then taken up with AcOEt and centrifugated at 11000 rpm for 1 h.

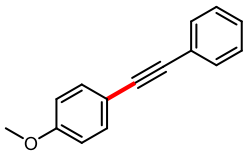
- The supernatant was collected and evaporated to dryness to give a yellow solid that was purified by vacuum sublimation to give the pure derivative **4** as light-yellow needles (660 mg, 3.28 mmol, 84% yield).
- The solid residue was taken up with 40 ml of MeOH, stirred for 4 h at 50 °C, cooled to rt and centrifuged at 11000 rpm for 1h. The supernatant was discarded and the solid residue (Ncs-Pd(OAc)$_2$-XPhos) was vacuum dried to constant weight and recycled (136 mg, recovery yield 52%).

Catalyst reuse. The standard procedure was performed using 1 mmol of phenylacetylene (102 mg), 2 mmol of 2-bromo-5-formylfurane (175 mg), 68 mg of recycled Nc-Pd(OAc)2-XPhos, 3 mmol of NEt3 (303 mg) in 1 ml of 2 wt% K-EL. After 24 h at 50 °C, all volatiles were removed at reduced pressure and residue was purified by column chromatography (SiO_2, Toluene) to give derivative **4** (131 mg, 0.66 mmol, 66% yield).

We did not attempt to further recycle the NC due to the still limited recovery yield. To overcome this shortcoming, we plan to tune our procedure to obtain bigger nanocapsules, likely improving on recovery capabilities.

21. Analytical data and spectra

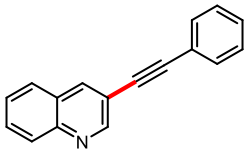
Product 1



Reaction performed on 748 mg of 4-bromoanisole and 410 mg of phenylacetylene. No further purification needed. Light brown powder, 817 mg (3.92 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.50 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.48 (d, *J* = 8.9, 2H), 7.34-7.32 (m, 3H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H) ppm.[6]

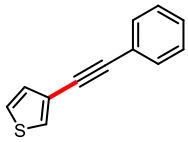
Product 2



Reaction performed on 423 mg of 3-bromoquinoline and 210 mg of phenylacetylene. No further purification needed. Off-white powder, 460 mg (2.01 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J=1.8 Hz, 1H), 8.35 (d, J=1.8 Hz, 1H), 8.15 (d, J=8.5 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.77-7.73 (m, 1H), 7.61-7.58 (m, 3H), 7.40-7.39 (m, 3H) ppm.[6]

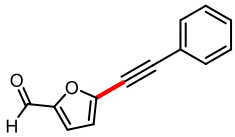
Product 3



Reaction performed on 326 mg of 3-bromothiophene and 204 mg of phenylacetylene. Product was further purified by sublimation. White powder, 328 mg (1.78 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.55 (m, 3H), 7.39-7.35 (m, 3H), 7.33-7.31 (dd, J=5.0, 3.0 Hz, 1H), 7.24 (dd, J=5.0, 1.0 Hz, 1H) ppm.[7]

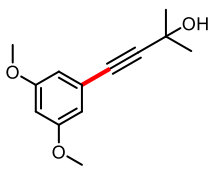
Product 4



Reaction performed on 204 mg of 2-bromofurancarboxyaldehyde and 350 mg of phenylacetylene. Product was further purified by sublimation. White powder, 295 mg (1.50 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.55-7.52 (m, 2H), 7.40-7.34 (m, 3H), 7.25 (d, J=3.7 Hz, 1H), 6.76 (d, J=3.7 Hz, 1H) ppm.[8]

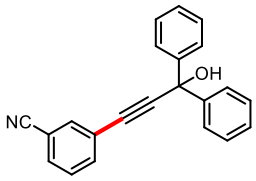
Product 5



Reaction performed on 204 mg of 2-bromofurancarboxyaldehyde and 84.1 mg of 2-methyl-3-butyn-2-ol. Product was further purified by filtration over silica using Heptane/AcOEt 8:2 as eluent. Off-white powder, 294 mg (1.33 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (d, J=2.3 Hz, 2H), 6.42 (t, J=2.3 Hz, 1H), 3.75 (s, 6H), 2.36 (b, 1H), 1.61 (s, 6H) ppm.[9]

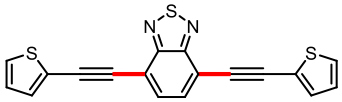
Product 6



Reaction performed on 368 mg of 3-bromobenzonitrile and 420 mg of 1,1-diphenyl-2-propyn-1-ol. Product was further purified by filtration over silica using toluene → toluene/Et_2O 5:1 as eluent. Light-yellow powder, 490 mg (1.58 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.66-7.64 (m, 4H), 7.61 (d, J=7.8 Hz, 1H), 7.45 (t, J=7.49, 1H), 7.39-7.36 (m, 4H), 7.33-7.29 (m, 2H), 2.98 (b, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.42, 135.82, 135.09, 131.88, 129.31, 128.45, 128.02, 126.01, 121.04, 117.93, 112.90, 94.25, 84.72, 74.81 ppm. Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C 85.13; H. 4.95; N, 4.50.

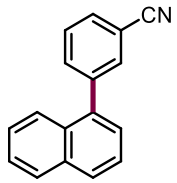
Product 7



Reaction performed on 296 mg of 4,7-dibromobenzo[c]-1,2,5-thiadiazole and 218 mg of 2-ethynylthiophene. Product was further purified by crystallization with acetic acid. Orange crystals, 250 mg (0.717 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 2H), 7.46 (d, J=3.7 Hz, 2H), 7.39 (d, J=5.2 Hz, 2H), 7.07 (dd, J=5.2, 3.7 Hz, 2H) ppm.[6]

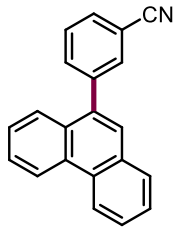
Products of Suzuki-Miyaura coupling



3-(Naphthalen-1-yl)benzonitrile: Compound is prepared according to the general Suzuki procedure. No further purifications are done. The product is collected as a light brown power (1066.15 mg, 93%).

Rf: 0.4 (Heptane/DCM 50:50).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7-95-7.91 (t, J = 7.7 Hz, 2H), 7.80 (t, J = 1.6 Hz, 1H), 7.76-7.72 (m, 3H), 7.63-7.59 (t, J = 7.7 Hz, 1H), 7.57-7.51 (m, 2H), 7-50-7.46 (td, J = 7.6, 1.5 Hz, 1H), 7.40-7.38 (dd, J = 7.1, 1.1 Hz, 1H) ppm.[10]



3-(Phenanthren-9-yl)benzonitrile: Compound is prepared according to the general Suzuki procedure. No further purifications are done. The product is collected as a light brown power (1270.95 mg, 91%).

Rf: 0.4 (Heptane/DCM 50:50).

1H NMR (400 MHz, CDCl3): δ 8.81-8.79 (dt, J = 8.3, 0.6 Hz, 1H), 8.75-8.73 (dd, J = 8.3, 0.6 Hz, 1H), 7.92-7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.85 (td, J = 1.7, 0.5 Hz, 1H), 7.80 (dt, J = 7.8, 1.5 Hz, 1H), 7.77-7.69 (m, 4H), 7.67-7.61 (m, 3H), 7.59-7.55 (ddd, J = 8.7, 6.9, 1.3 Hz, 1H) ppm.

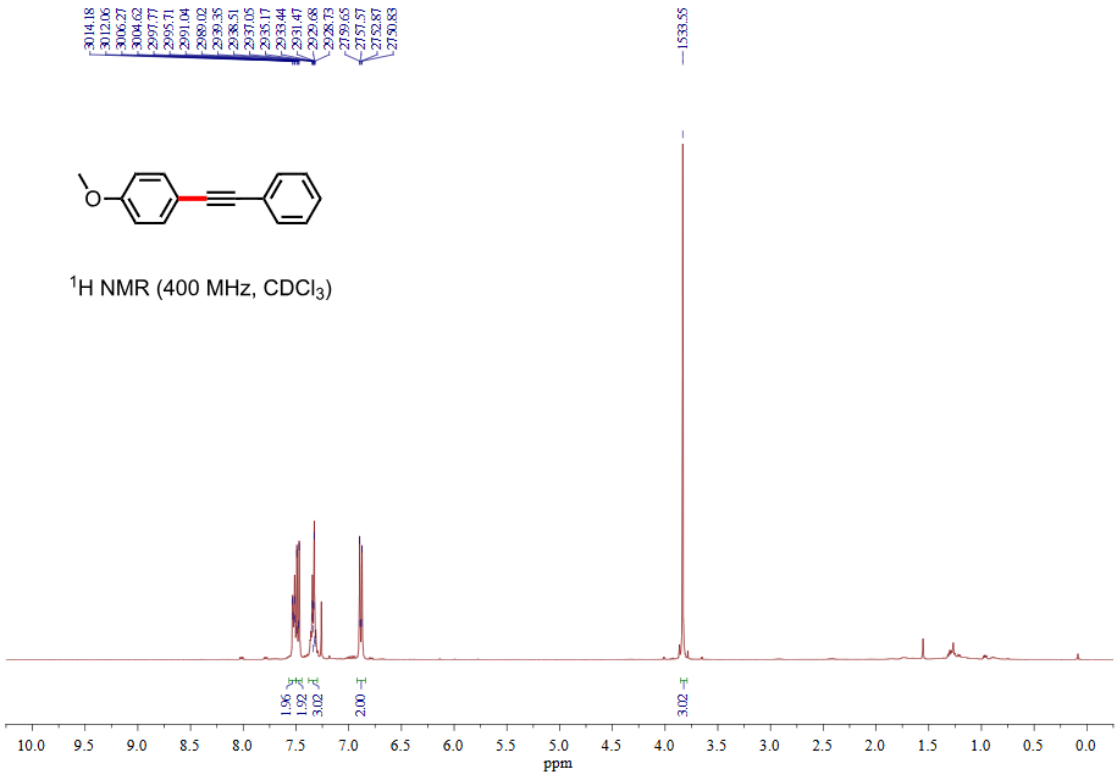


Fig. S37 ^{1}H NMR of Sonogashira product **1** in $CDCl_3$.

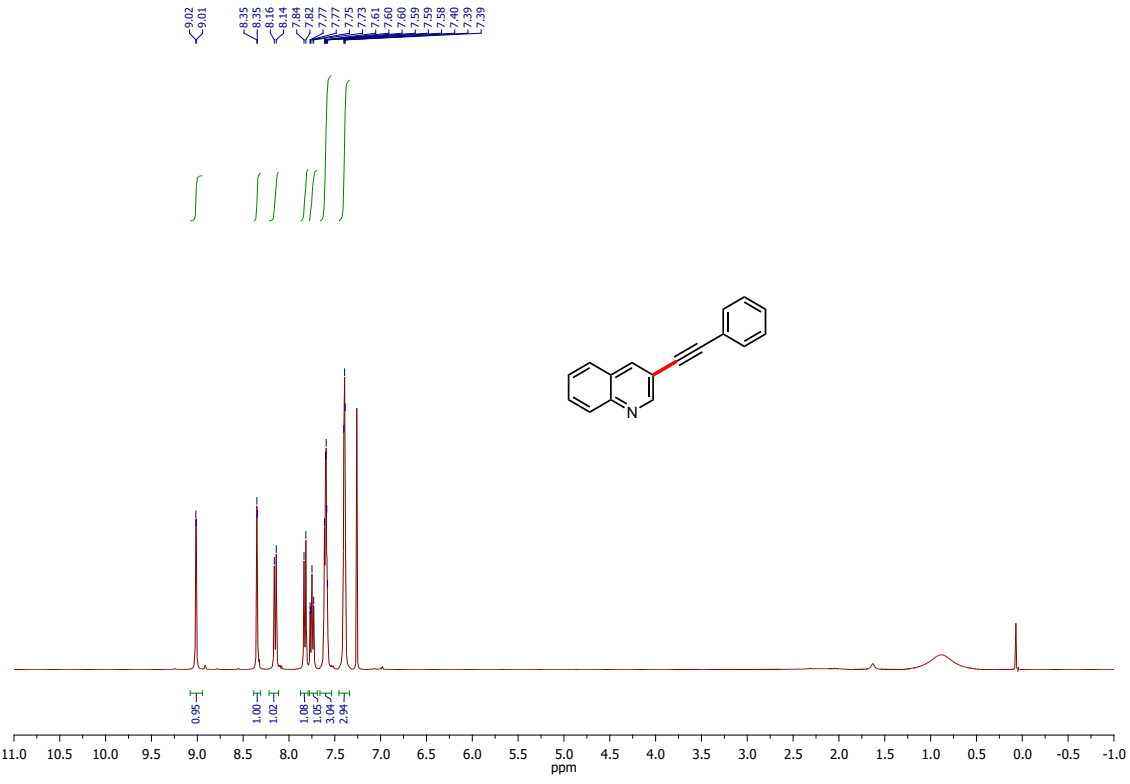


Fig. S38 ^{1}H NMR of Sonogashira product **2** in $CDCl_3$.

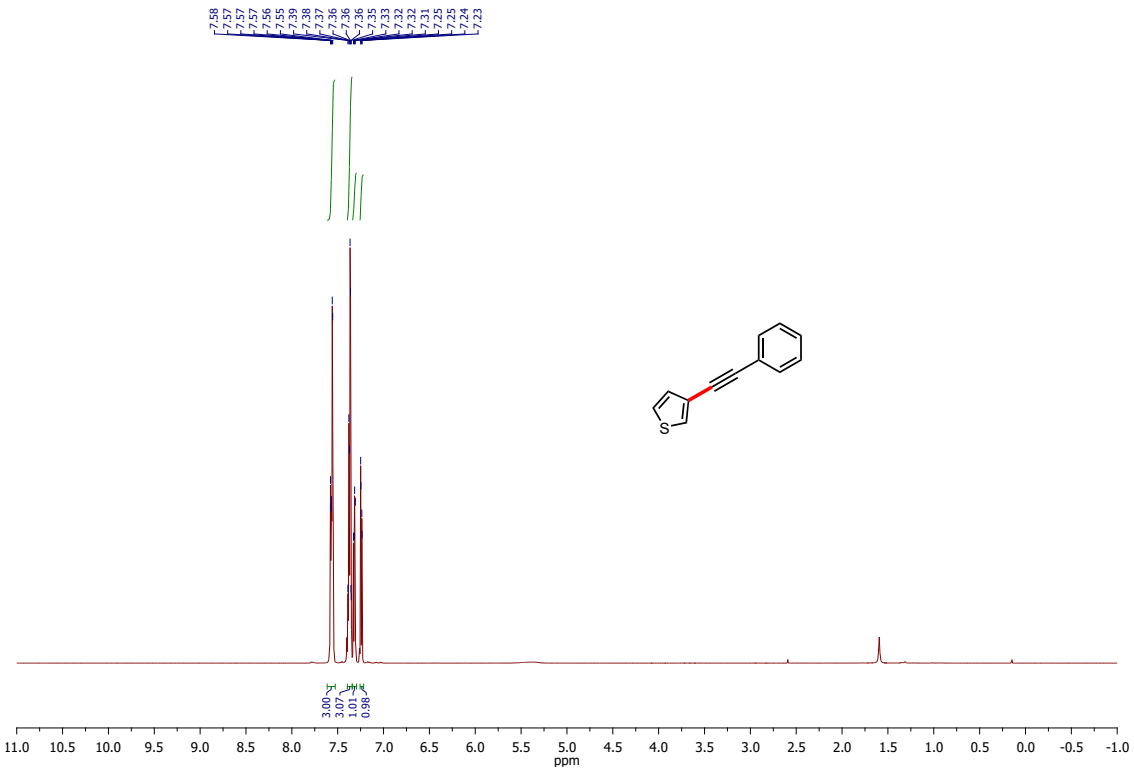


Fig. S40 ^{1}H NMR of Sonogashira product **3** in $CDCl_3$.

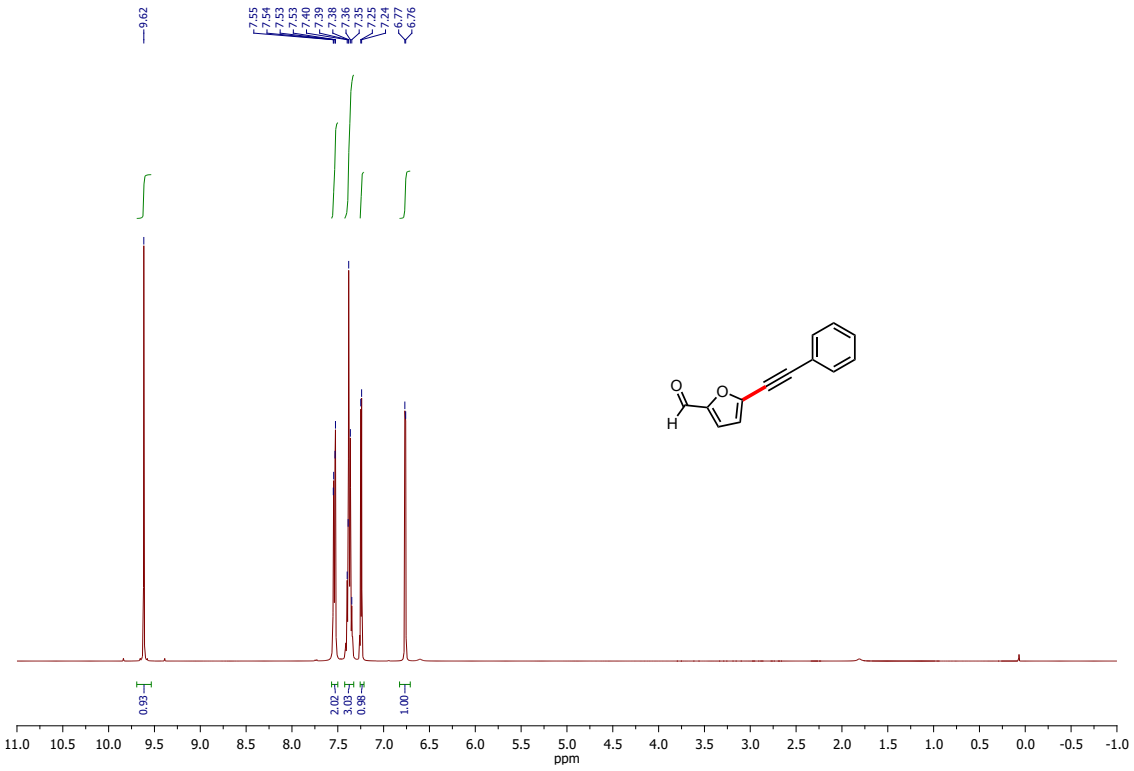


Fig. S39 ^{1}H NMR of Sonogashira product **4** in $CDCl_3$.

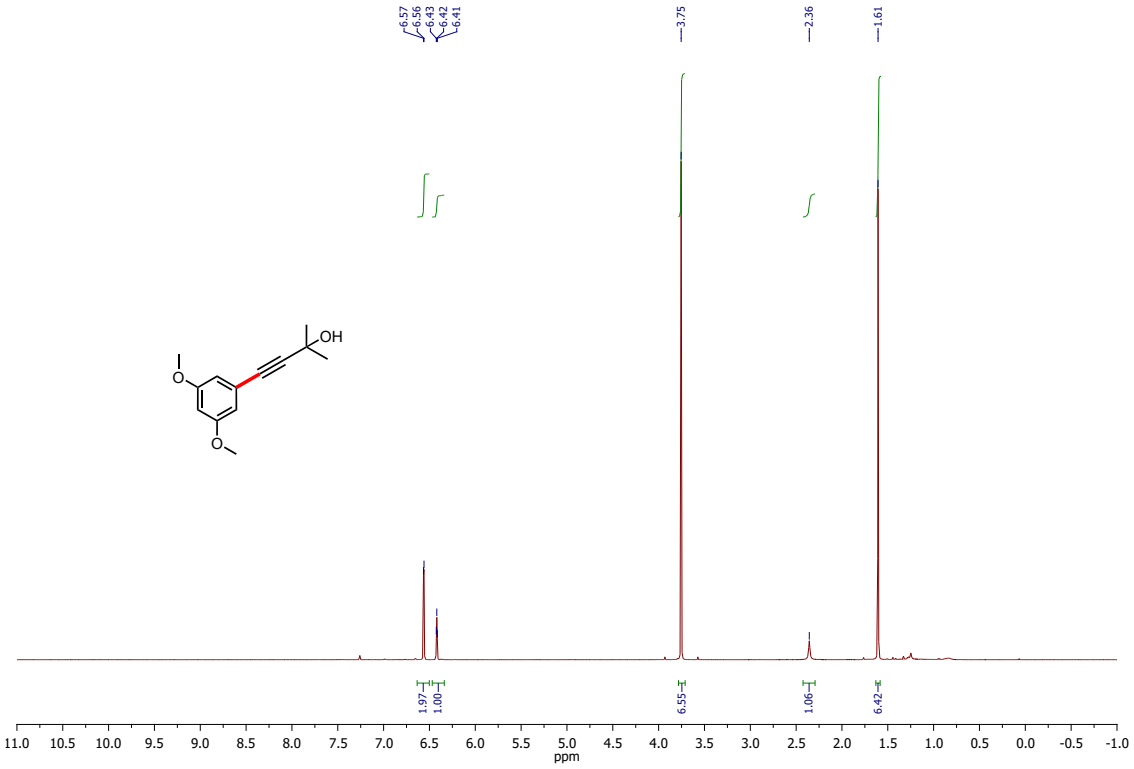


Fig. S42 ^{1}H NMR of Sonogashira product **5** in $CDCl_3$.

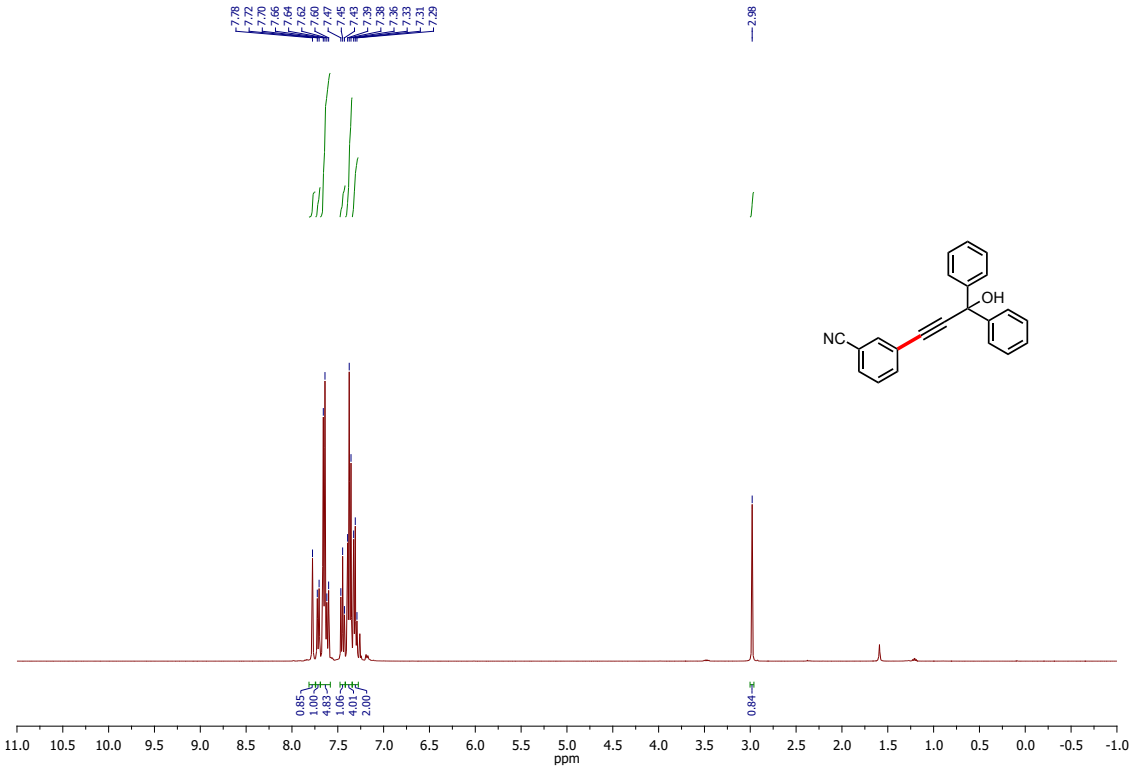


Fig. S41 ^{1}H NMR of Sonogashira product **6** in $CDCl_3$.

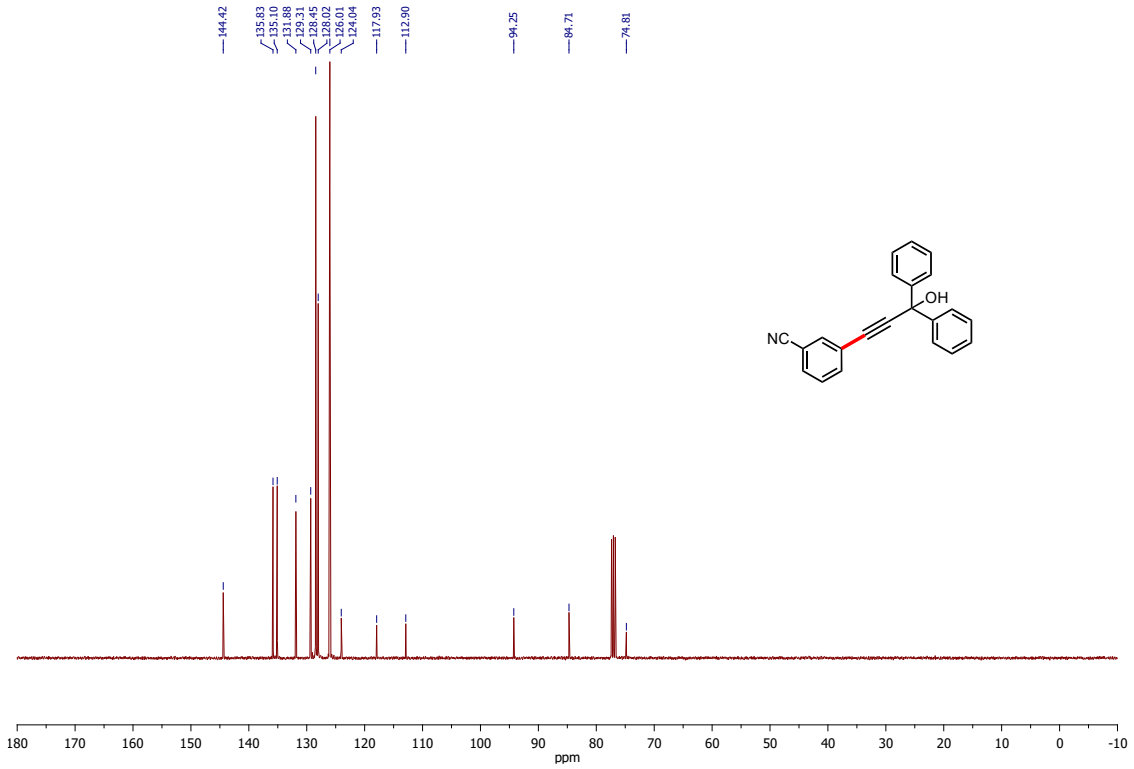


Fig. S43 ^{13}C NMR of Sonogashira product **6** in $CDCl_3$.

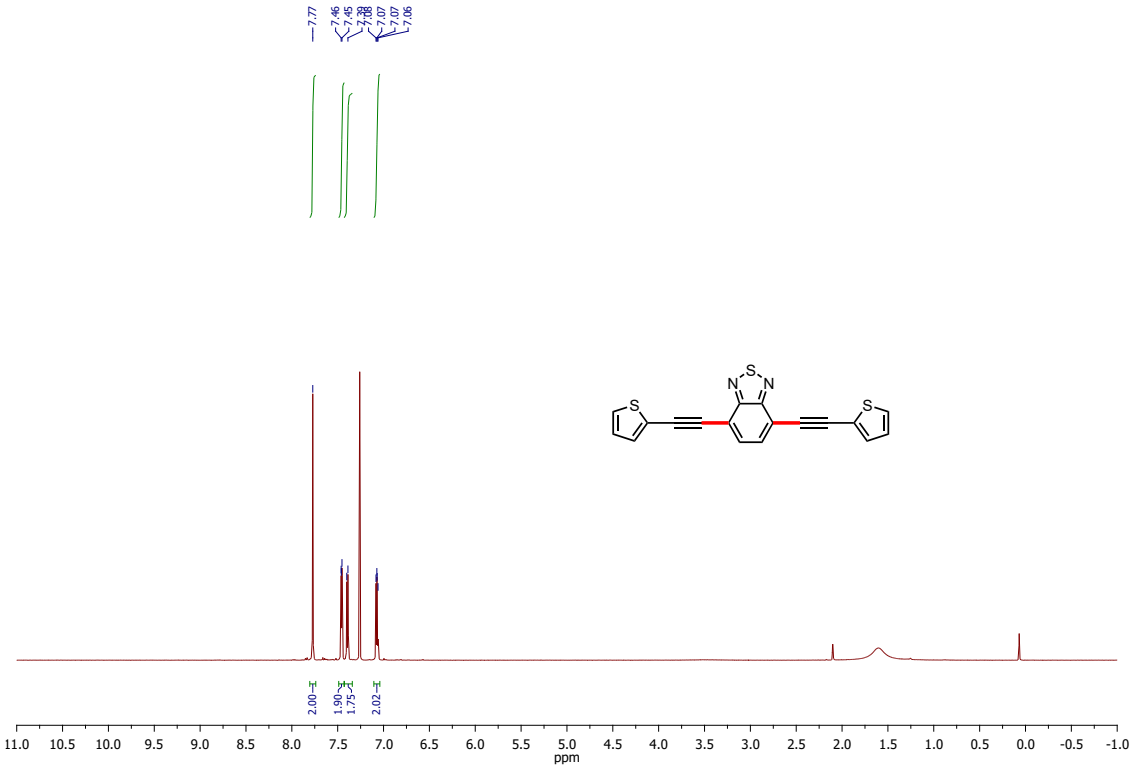


Fig. S50 ^{1}H NMR of Sonogashira product **7** in $CDCl_3$.

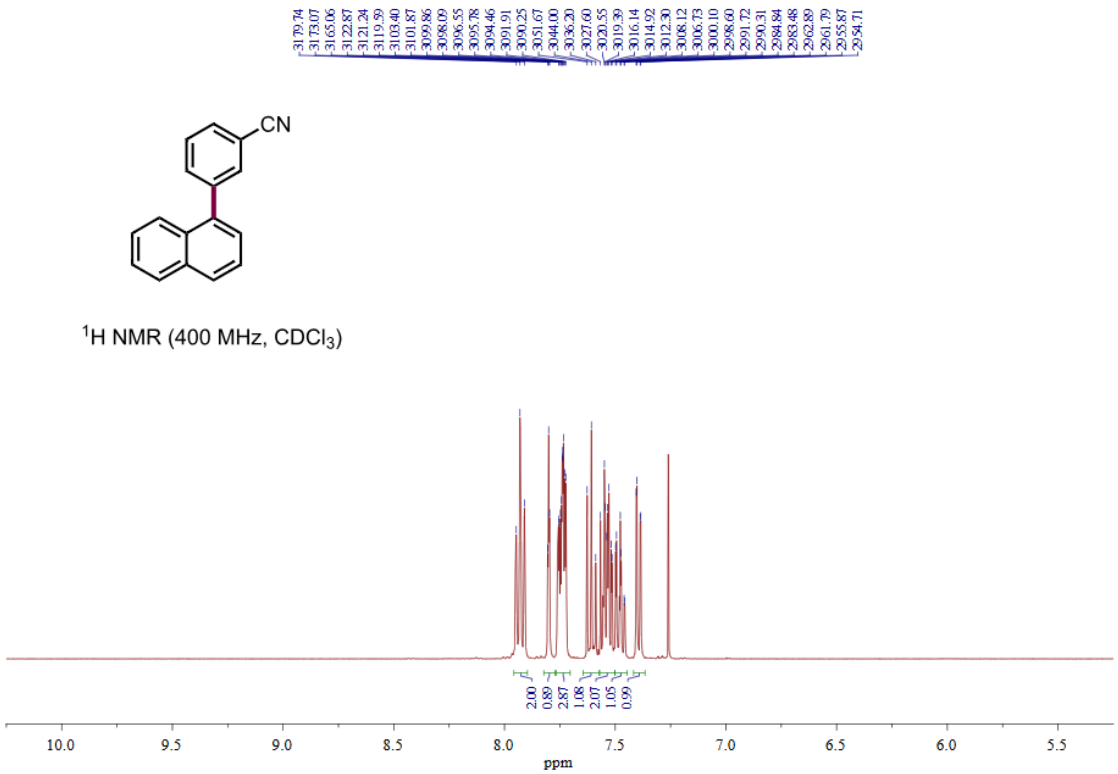


Fig. S44 ^{1}H NMR of 3-(naphthalen-1-yl)benzonitrile in $CDCl_3$.

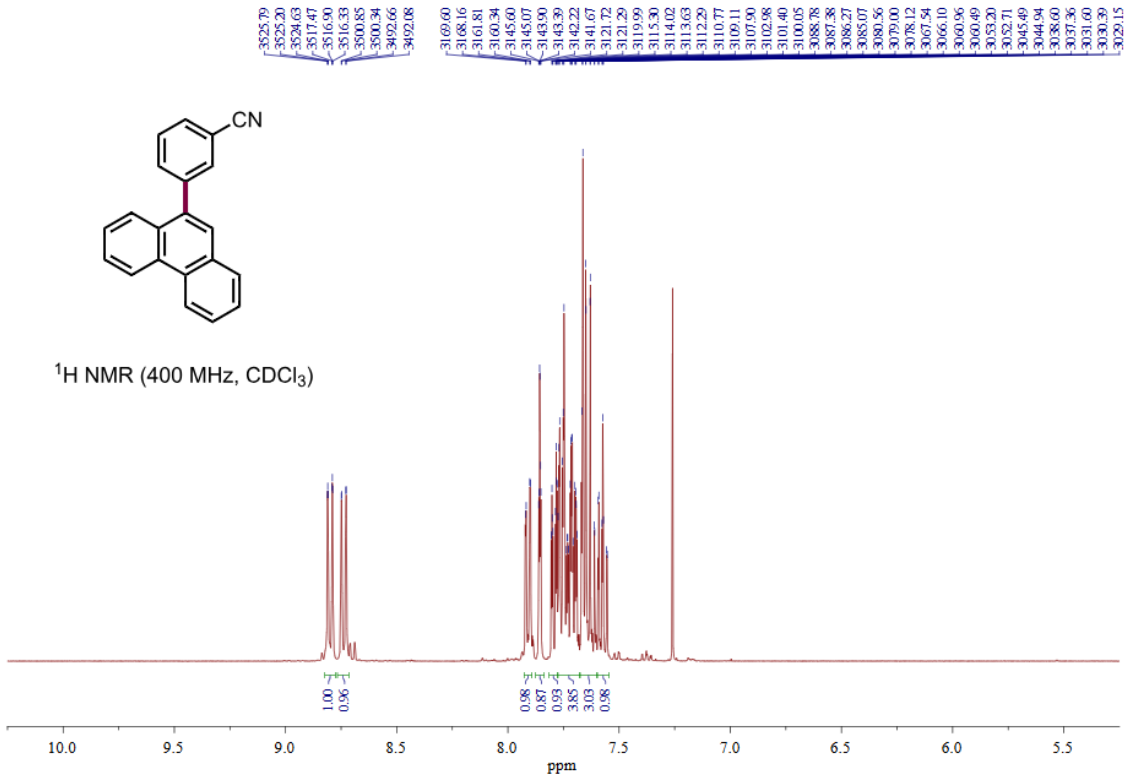


Fig. S45 ^{1}H NMR of 3-(phenanthren-9-yl)benzonitrile in $CDCl_3$.

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