Supplemental Information

Core-Shell Palladium/MOF Platforms
as Diffusion-Controlled Nanoreactors
in Living Cells and Tissue Models

Raquel Martínez, Carolina Carrillo-Carrión, Paolo Destito, Aitor Alvarez, María Tomás-Gamasa, Beatriz Pelaz, Fernando Lopez, José L. Mascareñas, and Pablo del Pino
Supplemental Experimental Procedures

Synthesis and characterization of the probes and palladium complexes

General procedures: The compounds propargyl-protected coumarin 1, propargyl-protected 2-(2'-hydroxyphenyl)benzothiazole 3, and bis-propargyl carbamate-protected cresyl violet 5 are known compounds and were synthesized according to those previously reported procedures. Compounds 2, 4 and 6 are commercially available and were purchased from Sigma-Aldrich.

Palladium complexes (Pd-1 = [Pd(allyl)Cl]₂⁴ Pd-2 = [(PPh₃)Pd(allyl)Cl] Pd-3 = [(PdCl₂(TFP)₂]⁶) have been previously described and were synthesized from the corresponding ligands and palladium precursors following reported procedures. Their ¹H, ¹³C and ³¹P NMR data were in complete agreement with the reported values. Precursors [Pd(allyl)Cl]₂ and [PdCl₂(CH₃CN)₂] are commercially available and were purchased from Sigma-Aldrich and Strem Chemicals, respectively. Ligands triphenylphosphine and tris(2-furyl)phosphine (TFP) were acquired from Sigma-Aldrich.

Reactions were conducted in dry solvents under nitrogen atmosphere using vacuum-line and standard Schlenk techniques unless otherwise stated. Dry solvents were freshly distilled under argon from an appropriate drying agent before use. The removal of solvents under reduced pressure was carried out on a rotary evaporator. Water was deionized and purified on a Millipore Milli-Q Integral system. The abbreviation “r.t.” refers to reactions carried out approximately at 23 °C (room temperature). Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Reaction temperatures were maintained using Thermo watch-controlled silicone oil baths. Thin-layer chromatography (TLC) was performed on silica gel plates (Merck 60 silica gel F 254) and components were visualized by observation under UV light, and/or by treating the plates with p-anisaldehyde followed by heating. Flash chromatography was carried out in silica gel (Merck Geduran Si 60, 40 – 63 m silica gel, normal phase) unless otherwise stated. Dryings were performed with anhydrous Na₂SO₄ or MgSO₄. Concentration refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator followed by residual solvent removal under high vacuum.

Mass spectra were acquired using IT-MS Bruker AmaZon SL at CiQUS and also using electrospray ionization (ESI) and were recorded at the CACTUS facility of the University of Santiago de Compostela. UV and fluorescence spectra were acquired using Jasco V-670 spectrometer and Varian Cary Eclipse fluorescence spectrofluorometer.

Synthesis of 4-methyl-7-(prop-2-yn-1-yloxy)-2H-chromen-2-one (1)

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{Br} & \quad \text{Na}_2\text{CO}_3 \\
\text{acetone, reflux,} & \quad 24 \text{ h} \\
\text{50%} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

4-Methylumbelliferone (2, 0.300 g, 1.702 mmol, 1 eq.) was dissolved in acetone (15 mL) followed by addition of Na₂CO₃ (0.361 g, 3.411 mmol, 2 eq.). The reaction mixture was stirred at r.t. for 10 min. Further, 3-bromopropyne (0.380 g, 2.552 mmol, 1.5 eq.) was added to the reaction and the resulting mixture was heated at reflux under nitrogen for 24 h. Upon completion, the reaction mixture was cooled to r.t., adsorbed onto silica and purified by silica gel column chromatography EtOAc (20% → 50% v/v)-hexane to give the corresponding product as a white solid. (1, 0.182 g, 50%).
Synthesis of 3-(benzo[d]thiazol-2-yl)-5-methyl-2-(prop-2-yn-1-yloxy)benzaldehyde (3)

4 (0.250 g, 0.928 mmol, 1 eq.) was dissolved in DMF (5 mL) followed by addition of K₂CO₃ (0.256 g, 1.864 mmol, 2 eq.). The reaction mixture was stirred at r.t. for 10 min. Further, 3-bromopropyne (0.207 g, 1.392 mmol, 1.5 eq.) was added to the reaction mixture, and heated at 50 ºC under nitrogen and stirring for 24 h. Upon completion, the reaction mixture was cooled to r.t., concentrated under vacuum, the crude dissolved in CH₂Cl₂ (15 mL), adsorbed onto silica, and purified by silica gel column chromatography EtOAc (10% → 30% v/v)-hexane to give the corresponding product as a white solid. (3, 0.120 g, 42%).

Synthesis of prop-2-yn-1-yl (Z)-(9-(((prop-2-yn-1-yloxy)carbonyl)amino)-5H-benzo[a]phenoxazin-5-ylidene)carbamate (5)

Procedure adapted from Bradley et al.3 1H and 13C NMR data of 5 are in agreement with the reported values.3 Cresyl violet acetate (0.150 g, 0.467 mmol, 1 eq.) was dissolved in anhydrous DMF (5 mL) and cooled to 0 ºC followed by addition of Et₃N (0.142 g, 1.403 mmol, 3 eq.). Propargyl chloroformate (5 eq, 2.33 mmol, 0.237 mL in anhydrous DMF (1 mL) was added dropwise to the solution. The reaction mixture was stirred at r.t. for 24 h and followed by RP-HPLC-MS. After that, it was concentrated under vacuum, dissolved in MeOH (15 mL), adsorbed onto silica, and purified by silica gel column chromatography EtOAc (5% → 40% v/v)-hexane to give the corresponding product as a red solid (5, 0.044 g, 22%).

Synthesis of [(PPh₃)Pd(allyl)Cl] (Pd-2)

Procedure adapted from Mascareñas et al.5 1H, 13C and 31P NMR data of Pd-2 are in agreement with the reported values.5
Triphenylphosphine (0.035 mg, 0.133 mmol, 2 eq.) was dissolved in THF (3.3 mL) followed by addition of
\([\text{Pd(allyl)}\text{Cl}_2]\) (Pd-1, 0.024 mg, 0.066 mmol, 1 eq.). The solution was stirred at r.t. under nitrogen for 3 h. After that, it was concentrated under vacuum. The crude was dissolved in AcOEt (ca. 4 mL). Hexane was added (ca. 15 mL) and a pale yellow solid precipitated. After removal of the solvent by decantation, the solid was washed with hexane (3 x 10 mL) and dried under vacuum. The palladium complex (Pd-2) was isolated as a pale yellow solid and stored under nitrogen (0.019 g, 65%).

**Synthesis of \([\text{PdCl}_2(\text{TFP})_2]\) (Pd-3)**

![Image](image_url)

Procedure adapted from Weissleder et al.\(^6\)

\(^1\text{H}, \ ^{13}\text{C} \) and \(^{31}\text{P} \) NMR data of Pd-3 are in agreement with the reported values.\(^6\)

[\text{PdCl}_2(\text{CH}_3\text{CN})_2]\ (0.025 mg, 0.098 mmol, 1 eq.) was dissolved in dry MeCN (3.75 mL) followed by addition of a solution of tris(2-furyl)phosphine (TFP) (0.045 mg, 0.196 mmol, 2 eq.) in MeCN (0.5 mL). The reaction mixture was stirred at r.t. overnight and a bright yellow precipitated. The crude product was collected and washed twice with water (2 x 10 mL), dissolved in dried methanol and stored at -30 °C. The palladium complex (Pd-3) was isolated as a yellow microcrystalline powder and stored under nitrogen (0.031 mg, 50%).
UV and Fluorescence spectra:

4-methyl-7-(prop-2-yn-1-yl)oxy-2H-chromen-2-one (1)

Figure S1. UV spectra (left) of 1 (30 µM, 1:1 v/v mixture of DMSO:Tris buffer 200 mM, pH = 7.5) and fluorescence spectra (10 µM, 7:3 v/v mixture of DMSO:H₂O) λ<sub>ex</sub> 323 nm, λ<sub>em</sub> 380 nm, λ<sub>cut</sub> 330 nm (right).

7-hydroxy-4-methyl-2H-chromen-2-one (2)

Figure S2. UV spectra (left) of 2 (30 µM, 1:1 v/v mixture of DMSO:Tris buffer 200 mM, pH = 7.5) and fluorescence spectra (10 µM, 7:3 v/v mixture of DMSO:H₂O) λ<sub>ex</sub> 323 nm, λ<sub>em</sub> 452 nm, λ<sub>cut</sub> 330 nm (right).

Figure S3. Calibration curve of 2 (9:1 v/v H₂O:MeOH), λ<sub>ex</sub> 323 nm, λ<sub>em</sub> 452 nm. Dashed red line: linear regression fitting I (counts) = 1+188·c(µM); coefficient of determination R² = 0.999.
3-(benzo[d]thiazol-2-yl)-5-methyl-2-(prop-2-yn-1-ylxy)benzaldehyde (3)

Figure S4. UV spectra (left) of 3 (20 µM, 7:3 v/v DMSO:H₂O) and fluorescence spectra (5 µM, 7:3 v/v DMSO:H₂O) λ_ex 335 nm, λ_em 377 nm, λ_cut 340 nm (middle), λ_ex 368 nm, λ_em 412 nm, λ_cut 380 nm (right).

3-(benzo[d]thiazol-2-yl)-2-hydroxy-5-methylbenzaldehyde (4)

Figure S5. UV spectra (left) of 4 (20 µM, DMSO:H₂O 7:3), and fluorescence spectra (5 µM, 7:3 v/v mixture of DMSO:H₂O) at different wavelengths (λ_ex 368 nm, λ_em 558 nm, λ_cut 380 nm and λ_ex 460 nm, λ_em 535 nm, λ_cut 465 nm (right).

Figure S6. Calibration curve of 4 (7:3 v/v DMSO:H₂O), λ_ex 460 nm, λ_em 535 nm, λ_cut 470 nm. Dashed red line: linear regression fitting I (counts) = 81 + 108·c(µM); coefficient of determination R² = 0.990.
prop-2-yn-1-yl(Z)-(9-(((prop-2-yn-1-yloxy)carbonyl)amino)-5H-benzo[a]phenoxazin-5-ylidene)carbamate (5)

Figure S7. UV spectra (left) of 5 (10 µM, 8:2 PBS:MeOH), and fluorescence spectra (1 µM, 8:2 PBS:MeOH) under excitation at $\lambda_{ex}=540$ nm; maximum emission at $\lambda_{em}=610$ nm (right).

9-Amino-5-imino-5H-benzo[a]phenoxazine (6)

Figure S8. UV spectra (left) of 6 (10 µM, 8:2 PBS:MeOH), and fluorescence spectra (1 µM, 8:2 PBS:MeOH) under excitation at $\lambda_{ex}=540$ nm; maximum emission at $\lambda_{em}=624$ nm (right).

Figure S9. Calibration curve of 6 (8:2 PBS:MeOH), $\lambda_{ex}=540$ nm, $\lambda_{em}=624$ nm. Dashed red line: linear regression fitting $I \times 10^5$ (counts) = 0.006 + 8.504 · c(µM); coefficient of determination $R^2 = 0.998$. 
Synthesis of PMA-modified Pd/ZIF-8 nanocomposites (NRs)

Chemicals: All the reagents including potassium tetrachloropalladium (II) (K₂PdCl₄; Sigma Aldrich #205796), L-ascorbic acid (AA; Sigma Aldrich #A5960), zinc nitrate hexahydrate (Zn(NO₃)₂·6H₂O; Sigma Aldrich #96482), 2-methylimidazole (MeIm; Sigma Aldrich #M50850), and hexadecyltrimethylammonium bromide (CTAB; Sigma Aldrich #H5882) were used as purchased without any purification. The PMA-based amphiphilic polymer (i.e., poly[isobutylene–alt–maleic anhydride]–graft–dodecyl) was synthesized as described previously.⁷

Synthesis of Pd nanocubes: CTAB-coated Pd nanocubes enclosed by {100} facets were synthesized according to a previously reported protocol,⁸ using K₂PdCl₄ as precursor, L-ascorbic acid (AA) as reducing agent, and hexadecyltrimethylammonium bromide as capping agent and stabilizer. In a typical synthesis, 0.5 mL of 0.1 M CTAB, 21.25 mL of deionized water and 2.5 mL of 0.01 M K₂PdCl₄ were placed in a 50 mL glass vial, and then 0.75 mL of 0.1 M AA was added while magnetic stirring. The mixture is stirred at room temperature for some minutes (~5 min) observing during this time that the solution turns into black color, which indicates the formation of the Pd nanocubes (in the following referred to as Pd-NPs). Next, the black product was collected by centrifugation (7200 RCF, 10 min), washed twice with MilliQ water to remove the excess of CTAB (Figure S10), and finally the purified Pd-NPs were redispersed in 1.4×10⁻³ M CTAB.

Synthesis of Pd/ZIF-8: These particles were synthesized according to a previously reported protocol with slight modifications.⁹ The Pd-NPs were used as seeds onto which a shell of ZIF-8 was grown, in the presence of CTAB as size-controlling and structural-directing agent, obtaining in this way the core-shell nanocomposite. Briefly, an aqueous solution of zinc nitrate (1 mL, 0.025 M) was added to an aqueous solution of 2-methylimidazole (1 mL, 1.3 M) under magnetic stirring (350 rpm) at r.t., and immediately after, a solution containing the Pd-NPs (1mL, 2 nM of nanoparticles dispersed in 1.4×10⁻³ M of CTAB) was added. After 2 min, the stirring was stopped, and the mixture was left undisturbed for 3 h at r.t. The gradual appearance of brownish turbidity indicated the formation of the Pd/ZIF-8 particles. Finally, the particles were collected by centrifugation (7000 RCF, 5 min), washed twice with methanol (MeOH) and redispersed in 1 mL of MeOH. The concentration of particles in this solution was assumed to be ~2 nM, considering that one Pd/ZIF-8 particle was formed per Pd-NP (seed). Note that under optimized conditions virtually all the ZIF-8 particles contained a Pd-NP as core (Figure S11).

Post-functionalization of Pd/ZIF-8 with PMA polymer: The as-prepared Pd/ZIF-8 particles were functionalized with a PMA-based amphiphilic polymer (i.e., poly[isobutylene–alt–maleic anhydride]–graft–dodecyl) by following a recently described protocol.⁹ Briefly, the Pd/ZIF-8 particles dispersed in methanol were mixed with the solution of the polymer in chloroform in an optimized proportion; specifically, 150 monomers of polymer per nm² of Pd/ZIF-8 particle, assuming a spherical particle with diameter of 250 nm; and the mixture was placed in a rotary evaporator. After complete evaporation of the solvent (3:1 MeOH:CHCl₃) the dried product was resuspended by addition of sodium borate buffer (0.1 M, pH 9) and aided by sonication (1-2 min). The resulting PMA-modified Pd/ZIF-8 nanocomposites (in the following referred to as NRs) were collected and purified by centrifugation (7000 RCF, 10 min), washing twice with water, and finally redispersed in water.
Morphological/structural characterization of NRs

**Scanning Electron Microscopy (SEM):** The size and morphology of Pd-NPs and NRs were investigated with SEM (Figures S10 and S11). SEM images were acquired with a FESEM Zeiss Ultra Plus operated at 3 kV or 20 kV.

![SEM image and histogram](image)

**Figure S10.** (A) Representative SEM image (scale bar corresponds to 100 nm); and (B) the corresponding histogram of the number distribution $N$ of the side length $L$ of the Pd-NPs (200 particles measured) as determined from SEM images, $L = (23.9 \pm 2.0)$ nm.
Figure S11. Representative SEM images of the NRs acquired with different detectors and different voltages: (A) Everhart-Thornley detector (SE2, secondary electrons) at 3 kV, (B) InLens detector (SE1, secondary electrons) at 20 kV, and (C) AsB detector (backscattered electrons) at 20 kV. Scale bars correspond to 200 nm. (D) Histogram of the number distribution N of the diameter (i.e., vertex-to-vertex distance) $d_{NR}$ of the NRs (idealized as spherical particles; 100 particles measured); regions of interest (ROIs, outlines) were drawn in the SEM images to estimate the size of the NRs, i.e., $d_{NR} = (253 \pm 12) \text{ nm}$. 
**Powder x-ray diffraction (PXRD):** An x-ray diffractometer Philips was used to study the crystallinity of the Pd/ZIF-8 nanocomposites. Sample was examined in the range of 2θ between 2° and 75° with a passage of 0.02° and a time by step of 2s. Table S1 shows the major diffraction peaks identified by PXRD (cf., Figure S12).

![PXRD spectrum of Pd/ZIF-8 nanocomposites](image.png)

**Figure S12:** PXRD spectrum of Pd/ZIF-8 nanocomposites. For comparison, simulations of ZIF-8 (black, COD - Crystallography Open Database: 7111970) and Pd-fcc (red; COD: 9008478) are added. $I_{\text{norm}}$ is the normalized intensity.

**Table S1:** Major peaks (relative intensity > 6%) identified in the Pd/ZIF-8 diffractogram.

| Pos. ($^\circ$2θ) | Height (cts) | FWHM Left ($^\circ$2θ) | d-spacing (Å) | Rel. Int. (%) |
|-------------------|--------------|------------------------|---------------|---------------|
| 7.37              | 447          | 0.16                   | 11.977        | 100.0         |
| 10.44             | 95           | 0.16                   | 8.470         | 21.2          |
| 12.79             | 209          | 0.15                   | 6.918         | 46.6          |
| 14.75             | 33           | 0.16                   | 5.999         | 7.5           |
| 16.52             | 49           | 0.17                   | 5.363         | 11.0          |
| 18.09             | 93           | 0.15                   | 4.899         | 20.7          |
| 24.52             | 30           | 0.16                   | 3.627         | 6.6           |
| 26.68             | 33           | 0.22                   | 3.339         | 7.4           |
| 40.13             | 46           | 0.34                   | 2.245         | 10.3          |
**Dynamic light scattering (DLS) and Zeta-Potential (ζ)**: The hydrodynamic diameter (dₜ) and polydispersity index (PDI) of the nanocomposites were determined by DLS using a Malvern Zetasizer Nano ZSP equipped with a 10 mW He–Ne laser operating at a wavelength of 633 nm and fixed scattering angle of 173°. DLS spectra of the NRs dispersed in water freshly prepared, as well as measured over time up to one week are presented in Figure S13, and the corresponding dₜ values of the NRs both in water, cell medium (supplemented with 10% fetal bovine serum - FBS) and artificial lysosomal fluid (ALF, 10% FBS or without supplements) over time, are summarized in Table S2.

**Figure S13.** DLS spectra, given as intensity, volume and number distributions, of NRs dispersed in water (A) freshly prepared, and (B) measured at different time points up to one week.
Table S2. Hydrodynamic diameters $d_h$ (mean value ± SD) as derived from DLS measurements of the NRs and Pd-NPs dispersed in water, cell culture medium (DMEM supplemented with 10% FBS), artificial lysosomal fluid (ALF), or ALF supplemented with 10% FBS at different time points. SD values correspond to the standard deviation of the diameter mean value as obtained from several repetitions ($n=3$) of the measurement. The polydispersity index (PDI) values are also given.

| Time | NRs | Water | Cell Medium | ALF | ALF (10% FBS) |
|------|-----|-------|-------------|-----|---------------|
|      |     | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI |
| 0 h  |     | 252 ± 2 | 0.18 | 299 ± 8 | 0.22 | 268 ± 3 | 0.14 | 289 ± 6 | 0.12 |
| 1 h  |     | 249 ± 3 | 0.21 | 291 ± 9 | 0.24 | 273 ± 4 | 0.15 | 300 ± 7 | 0.21 |
| 5 h  |     | 251 ± 2 | 0.22 | 289 ± 11 | 0.24 | 278 ± 4 | 0.20 | 295 ± 7 | 0.20 |
| 24 h |     | 252 ± 2 | 0.20 | 294 ± 10 | 0.30 | 292 ± 2 | 0.11 | 293 ± 9 | 0.19 |
| 7 days |   | 250 ± 4 | 0.22 | 301 ± 10 | 0.35 | 296 ± 3 | 0.19 | 294 ± 8 | 0.22 |

| Time | Pd-NP | Water | Cell Medium | ALF* | ALF (10% FBS) |
|------|-------|-------|-------------|------|---------------|
|      |       | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI | $d_{hn}$ (nm) | PDI |
| 0 h  |     | 25 ± 1 | 0.16 | 50 ± 3 | 0.19 | 376 ± 15 | 0.23 | 58 ± 2 | 0.15 |
| 1 h  |     | 68 ± 2 | 0.20 | 53 ± 3 | 0.20 | -       |    | 61 ± 3 | 0.21 |
| 5 h  |     | 113 ± 3 | 0.24 | 51 ± 3 | 0.20 | -       |    | 61 ± 4 | 0.20 |
| 24 h |     | 171 ± 10 | 0.27 | 49 ± 4 | 0.21 | -       |    | 56 ± 3 | 0.19 |
| 48 h |     | 362 ± 24 | 0.39 | 50 ± 3 | 0.22 | -       |    | 54 ± 3 | 0.19 |
| 7 days |   | 480 ± 25 | 0.41 | 49 ± 4 | 0.19 | -       |    | 53 ± 4 | 0.20 |

*Pd-NPs aggregated immediately in ALF, leading to irreversible precipitation.
Quantification of Pd by inductively coupled plasma mass spectrometry (ICP-MS) and estimation of potentially active Pd

**Quantification of Pd by ICP-MS:** ICP-MS measurements were performed on an Agilent 7700x inductively coupled plasma mass spectrometer after acidic digestion of the particles sample with aqua regia. To this end 300 µL of fresh aqua regia (i.e. HCl 35 wt % and HNO3 67 wt % in 3:1 volume ratio) was added to 50 L of sample solution (solutions of NRs or Pd nanoparticles as control; both at the same concentration), and then the samples were left for digestion overnight. Afterwards 4.65 mL of HCl solution (2 wt % HCl) was added prior to their injection into ICP-MS, being thus the total dilution sample of 100. External calibration was applied to quantify the amount of elemental Pd and Zn. External standards were prepared by diluting ICP-MS standards of all the ions in the same background solution (2 wt % HCl) as the samples, measured by triplicate and used for obtaining the external calibration curves.

Results revealed that the total amount of Pd atoms used per reaction were: 8.9 µg (RSD = 1.0 %) for NRs and 9.1 µg (RSD = 1.4 %) for Pd-NPs (Table S3). This clearly indicates that when we are carrying out equivalent reactions with NRs and Pd-NPs (for comparison), we are using the same amount of Pd.

The amount of Pd per NR was determined from ICP-MS data; and considering that the empirical formula of ZIF-8 is C₈H₁₀N₄Zn, which means that 1 mol of ZIF-8 contains 1 mol of Zn. Therefore, the Pd amount in NR (i.e. Pd/ZIF-8) could be determined by the following equation:

\[
\% \text{Pd} = \frac{m_{\text{Pd}}}{M_{\text{ZIF-8}}} \times \frac{M_{\text{Zn}}}{m_{\text{Zn}}} \times 100
\]

where,

- \(m_{\text{Pd}}\) = Amount of \(^{105}\text{Pd}\) obtained by ICP-MS
- \(m_{\text{Zn}}\) = Amount of \(^{65}\text{Zn}\) obtained by ICP-MS
- \(M_{\text{Zn}}\) = Atomic mass of Zn (65.38 g/mol)
- \(M_{\text{ZIF-8}}\) = Molecular mass of ZIF-8 (227.58 g/mol)

Applying this equation, we obtained that the percentage of total Pd in the NR is 3.8 wt%. It was also determined by ICP-MS that this wt% of Pd in the NR is the same after performing the reaction, which is a clear indication of the stability of the NRs during the catalytic reaction.

**Table S3** Amount of Pd per reaction as derived from ICP-MS measurements.

| Catalyst | V_{cat} (µL) | C_{particles} (nM) | V_{react} (µL) | c_{Zn} (µg/µL)* | c_{Pd} (µg/µL)* | m_{Zn} (µg) | m_{Pd,total} (µg) | Pd total (wt %) |
|----------|--------------|-------------------|----------------|-----------------|-----------------|-------------|------------------|------------------|
| Pd-NPs   | 50           | 2                 | 400            | –               | 0.183           | –           | 9.1              | 100              |
| NRs      | 50           | 2                 | 400            | 1.296           | 0.179           | 64.8        | 8.9              | 3.8              |

*RRelative standard deviation (RSD) < 1.5%*
Estimation of the Pd potentially active for catalysis: Whereas ICP-MS measurements give us the total amount of Pd contained in the NR, it is important to note that only the Pd atoms on the surface of the Pd-NP (located in the center of the NR) will be able to catalyze the reactions and therefore, only this fraction of Pd (hereinafter referred to as surface-Pd) is potentially active. We can estimate this surface-Pd as follows (cf., Table S4).

1) First, we calculate the number of Pd atoms contained in a Pd-NP:

The volume of a Pd-NP ($V_{NP}$) with a side length of 23.9 nm as determined from SEM images:

$$V_{NP} = L^3 = (23.9 \text{ nm})^3 = 1.36 \times 10^4 \text{ nm}^3$$

The structure is face-centered-cubic (fcc structure) with a lattice constant of 0.389 nm, being the volume of a unit cell ($V_{fcc\ cell}$):

$$V_{fcc\ cell} = (0.389 \text{ nm})^3 = 0.059 \text{ nm}^3$$

Knowing that each unit cell contains 4 Pd atoms, the total number of Pd atoms in a single Pd-NP is:

$$N_{Pd,\ cell} = \frac{(1.56 \times 10^4 \text{ nm}^3)}{(0.059 \text{ nm}^3)} \times 4 = 9.26 \times 10^5$$

2) Next, we calculate the number of Pd atoms on the surface of a Pd-NP:

A Pd-NP is enclosed by 6 {100} facets, so the total surface area of a Pd-NP ($A_{nanocube}$) can be calculated as:

$$A_{nanocube} = 6 \times L^2 = 6 \times (23.9 \text{ nm})^2 = 3.43 \times 10^3 \text{ nm}^2$$

The lattice constant of the fcc unit cell is 0.389 nm, and each two-dimensional unit cell on the {100} facets contains two Pd atoms. Therefore, the total number of Pd atoms on the surface of a single nanocube ($N_{Pd,\ surface}$) can be calculated as:

$$A_{fcc\ cell} = (0.389 \text{ nm})^2 = 0.151 \text{ nm}^2$$

$$N_{Pd,\ surface} = \frac{(3.43 \times 10^3 \text{ nm}^2)}{(0.151 \text{ nm}^2)} \times 2 = 4.54 \times 10^4$$

3) Knowing the number of NRs used for the catalytic reaction we calculate the amount of surface-Pd per reaction:

The total amount of Pd used per reaction is 8.94 × 10^{-6} g as determined by ICP-MS. Thus, the total number of Pd atoms in the catalytic reaction is:

$$N_{Pd} = \frac{(8.94 \times 10^{-6} \text{ g})}{(106.42 \text{ g/mol}) \times (6.02 \times 10^{23} \text{ mol}^{-1})} = 5.06 \times 10^{16}$$

The number of Pd-NPs involved in the catalytic reaction is (note that one nanocube contains 9.26 × 10^5 Pd atoms as calculated above):

$$N_{nanocube} = \frac{(5.06 \times 10^{16})}{(9.26 \times 10^5)} = 5.46 \times 10^{10}$$

Note here that owing to the architecture of the nanocomposite particle (one Pd-NP in the center of one NR), the number of NRs involved in the reaction is the same as the number of Pd-NPs.

Thus, the actual concentration of NRs used per reaction (total volume 400 µL) is:

$$n_{NR} = \frac{(5.46 \times 10^{10})}{(6.022 \times 10^{23})} = 9.07 \times 10^{-14} \text{ mol of NR}$$

$$C_{NR} = \frac{(9.07 \times 10^{-14})}{(4 \times 10^4)} = 2.3 \times 10^{-10} \text{ M} = 0.23 \text{ nM}$$

Regarding the fraction of Pd potentially active, the total number of Pd atoms on the surface of Pd-NPs used in the catalytic reaction is:
\[ N_{\text{total surface-Pd}} = (4.77 \times 10^{10}) \times (4.96 \times 10^4) = 2.71 \times 10^{15} \]

\[ n_{\text{total surface-Pd}} = (2.71 \times 10^{15}) / (6.022 \times 10^{23}) = 4.5 \times 10^{-9} \text{ mol of surface-Pd} \]

As the total volume of the reaction is 400 µL, the concentration of surface Pd in the reaction is \(~10 \mu\text{M}\).

**Table S4.** Amounts of Pd (total and surface) per reaction as derived from ICP-MS measurements.

| Catalyst | \(V_{NP}\) (nm\(^3\)) | \(V_{\text{fcc.cell}}\) (nm\(^3\)) | \(N_{Pd,\text{cell}}^*\) | \(A_{NP}\) (nm\(^2\)) | \(A_{\text{fcc.cell}}\) (nm\(^2\)) | \(N_{Pd,\text{surface}}^#\) | \(m_{Pd,\text{total}}\) (µg) | \(m_{\text{Surface-Pd}}\) (µg) | \(C_{\text{Surface-Pd}}\) (µM) |
|----------|--------------------------|-------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Pd NPs   | 1.36 \times 10^4         | 0.059                               | 9.26 \times 10^5         | 3.43 \times 10^3         | 0.151                    | 4.54 \times 10^4         | 9.14                     | 3.78 \times 10^{-5}      | 10.1                     |
| NRs      | 1.36 \times 10^4         | 0.059                               | 9.26 \times 10^5         | 3.43 \times 10^3         | 0.151                    | 4.54 \times 10^4         | 8.94                     | 3.69 \times 10^{-5}      | 9.8                      |

*Each unit cell with fcc structure contains 4 Pd atoms

*Each two-dimensional unit cell on the \{100\} facets contains 2 Pd atoms
Evaluation of porous accessibility/porosity of NRs

The porosity and possibility of diffusion-controlled flow of molecules through the porous of the ZIF-8 shell in the NRs was evaluated using model fluorescent probes. To this end, NRs were incubated with two fluorescent probes: TAMRA (tetramethylrhodamine 5-(and-6)-carboxamide cadaverine) and DOX (doxorubicin); and the amount loaded probes was quantified by fluorescence. NRs as dispersed in water (100 µL, 1 nM) were mixed with a solution of fluorescent probes in MeOH (10 µL, 1.5 mM), having thus $1.5 \times 10^5$ probe/NC during the incubation, and the mixture was incubated for 4 h at r.t. Afterwards, the NRs were quickly collected by centrifugation (1 min, 10,000 RCF), and the loaded fluorescent molecules were determined after digestion/destruction of the NRs in order to avoid errors in the quantification associated to potential fluorescence quenching and/or scattering/turbidity interference. For the digestion, the pellet of NR containing the fluorescent molecules were treated with 40 µL of 2% HCl solution for 15 min. Then, 10 µL of 2 M NaOH solution was added to neutralize the medium, plus 250 µL of water, and fluorescence measurement of this mixture was performed. The concentration of TAMRA or DOX loaded was determined by interpolation of the measured fluorescence intensity (I) to a previously constructed analytical calibration curve (Figure S14). This led to a value (mean ± standard deviation, n=2) of $4.24 \times 10^4 \pm 8.29 \times 10^2$ TAMRA per NR and $7.58 \times 10^4 \pm 6.25 \times 10^2$ DOXO per NR (Table S5).

![Figure S14](image)

**Table S5.** Determination of loading percentage of two fluorescent probes into the NRs after 4 h of incubation.

| probe | $N_{\text{probe/NR}}$ (incubated) | $N_{\text{probe/NR}}$ (loaded) | % loading |
|-------|----------------------------------|--------------------------------|-----------|
| TAMRA | $1.5 \times 10^5$                | $4.24 \times 10^4 \pm 8.29 \times 10^2$ | 28.3 ± 0.8 |
| DOX   | $1.5 \times 10^5$                | $7.58 \times 10^4 \pm 6.25 \times 10^2$ | 50.5 ± 0.6 |

**Figure S14.** Calibration curves of TAMRA (A) and DOX (B) in water obtained from fluorescence measurements: for TAMRA $\lambda_{\text{exc}}/\lambda_{\text{em}}=550/580$ nm and for DOXO $\lambda_{\text{exc}}/\lambda_{\text{em}}=480/588$ nm. Fluorescence intensity (I) at the maximum emission peak as a function of HOE concentration c is plotted and calibration equation is obtained by fitting a linear regression line to the collected data; $R^2$ is the coefficient of determination.
General procedures of the depropargylation reactions

**Depropargylation of substrates 1 and 3 promoted by NR or Pd-NPs:** 1 or 3 (8 µL, 0.5 mM stock solution in MeOH) was added to a H₂O:MeOH 9:1 solution (342 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of Pd-NPs or NRs (50 µL, 2 nM; this corresponds to 10 µM of surface-Pd). The influence of the catalyst concentration was also evaluated by varying the amount of the aqueous solution of Pd-NPs or NRs added. The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. After overnight (15 h), NRs were collected by centrifugation (7000 RCF, 10 min), and the supernatant was separated. The precipitate was washed once with 400 µL of a 9:1 H₂O:MeOH solution, centrifuged again (7000 RCF, 10 min), and the supernatant was separated and mixed with the first supernatant. Finally, this supernatant was analyzed by fluorescence to quantify the obtained amount of 2 or 4 respectively (Table S6, Figure S15), cf. calibration curves in Figure S3.

**Depropargylation of substrate 5 promoted by NR:** 5 (8 µL, 0.5 mM stock solution in MeOH) was added to a PBS:MeOH 8:2 solution (342 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of NRs (50 µL, 2 nM; this is the concentration of NRs). The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. After overnight (15 h), the NRs were collected by centrifugation (7000 RCF, 10 min), and the supernatant was separated. The precipitate was washed once with 400 µL of a 8:2 PBS:MeOH solution, centrifuged again (7000 RCF, 10 min), and the supernatant was separated and mixed with the first supernatant. Finally, this supernatant was analyzed by fluorescence to quantify the amount of 6 obtained (Table S6, Figure S15), cf. calibration curve in Figure S6.

**Depropargylation of substrate 1 in the presence of 3 promoted by NR:** 1 (8 µL, 0.5 mM stock solution in MeOH) and 3 (8 µL, 0.5 mM stock solution in MeOH) were added to a H₂O:MeOH 9:1 solution (334 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of NRs (50 µL, 2 nM; this is the concentration of NRs). The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. After overnight (15 h), the NRs were collected by centrifugation (7000 RCF, 10 min), and the supernatant was separated. The precipitate was washed once with 400 µL of a 9:1 H₂O:MeOH solution, centrifuged again (7000 RCF, 10 min), and the supernatant was separated and joined with the first supernatant. Finally, this supernatant was analyzed by fluorescence to quantify the obtained amount of 2 and 4 (Table S6), cf. calibration curve in Figure S9.
Table S6 Reaction conditions and yields of the depropargylation of several substrates promoted by NRs or Pd-NPs; as control, we also used ZIF-8 nanoparticles without the Pd core.

| Catalyst type | Surface Pd (µM) | Conditions | Substrate | [Substrate] (µM) | Product | [Product] (µM) | Yield (%) |
|---------------|-----------------|------------|-----------|-----------------|---------|----------------|-----------|
| NRs 1         | 1               | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 3.70 ± 0.08    | 37.0 ± 1.2 |
| NRs 5         | 5               | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 8.92 ± 0.14    | 89.2 ± 1.4 |
| NRs 10        | 10              | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 9.70 ± 0.13    | 97.0 ± 1.3 |
| NRs 15        | 15              | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 9.85 ± 0.15    | 98.5 ± 1.5 |
| NRs 10        | 10              | PBS:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 9.20 ± 0.14    | 92.0 ± 1.4 |
| Pd-NPs 10     | 10              | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 10              | 2       | 1.90 ± 0.45    | 19.0 ± 4.5 |
| ZIF-8#         | 0               | H₂O:MeOH 9:1, 37 ºC, 15h | 1         | 0               | n.r.*   | n.r.*          | n.r.*     |
| NRs 10        | 10              | H₂O:MeOH 9:1, 37 ºC, 15h | 3         | 10              | n.r.*   | n.r.*          | n.r.*     |
| Pd-NPs 10     | 10              | H₂O:MeOH 9:1, 37 ºC, 15h | 3         | 10              | 4       | 1.54 ± 0.18    | 15.4 ± 1.8 |
| NRs 10        | 10              | H₂O:MeOH 9:1, 37 ºC, 15h | 1+3       | 10+10           | 2       | 5.40 ± 0.37    | 54.0 ± 3.7 |
| NRs 10        | 10              | PBS:MeOH 8:2, 37 ºC, 15h | 5         | 10              | 6       | 8.23 ± 0.10    | 82.3 ± 1.0 |

*n.r. : no reaction; *ZIF-8 nanoparticles equivalent to NRs, but without the Pd core.
**Figure S15.** (A) Photographs under visible and UV light of the reaction mixture for the depropargylation reaction of 1 (A1) or 5 (A2) promoted by NRs taken before and after the reaction. (B) Photographs under visible light of the reaction mixture for the depropargylation reaction of 1 promoted by Pd NPs taken before and after the reaction, where aggregation of Pd-NPs is observed. Scale bars correspond to 100 nm.

**Calculation of turnover number (TON):** As it was calculated in a previous section, the concentration of the catalyst (surface-Pd) used in the reaction under the optimized conditions was 10 µM. Knowing that the total volume of the reaction is 400 µL, this corresponds to $4 \times 10^{-9}$ mol of catalyst per reaction. The calculation of the yield of the reactions, and therefore, the amount of substrate converted to the desired product, allows us to calculate the TON by using the following equation:

$$\text{TON} = \frac{\text{moles of desired product formed}}{\text{moles of catalyst}}$$

We determined the TON values as function of the amount of catalyst used and maintaining constant the amount of substrate (see Table S7).
Table S7. TON values of the reaction for the depropargylation reaction of 1 and 5 by using different amounts of NRs. In all cases the reactions were carried out overnight at 37 °C, except in one case where the reaction was performed for 7 days.

| [Catalyst] (µM surface Pd) | Substrate | [Substrate] (µM) | Conditions | Yield (%) | [Product] (µM) | TON |
|---------------------------|-----------|------------------|------------|-----------|---------------|-----|
| 15                        | 1         | 10               | 37 °C, 15 h| 98.5 ± 1.5| 9.85 ± 0.15   | 0.66 ± 0.01|
| 10                        | 1         | 10               | 37 °C, 15 h| 97.0 ± 1.3| 9.70 ± 0.13   | 0.97 ± 0.01|
| 5                         | 1         | 10               | 37 °C, 15 h| 89.2 ± 1.4| 8.92 ± 0.14   | 1.78 ± 0.04|
| 1                         | 1         | 10               | 37 °C, 15 h| 37.0 ± 1.2| 3.70 ± 0.08   | 3.70 ± 0.11|
| 1                         | 1         | 10               | 37 °C, 7 d | 99.6 ± 1.1| 9.96 ± 0.11   | 9.96 ± 0.15|
| 15                        | 5         | 10               | 37 °C, 15 h| 90.8 ± 1.5| 9.08 ± 0.15   | 0.60 ± 0.01|
| 10                        | 5         | 10               | 37 °C, 15 h| 82.3 ± 1.0| 8.23 ± 0.10   | 0.82 ± 0.01|
| 5                         | 5         | 10               | 37 °C, 15 h| 65.6 ± 1.2| 6.56 ± 0.12   | 1.31 ± 0.03|
| 1                         | 5         | 10               | 37 °C, 15 h| 26.6 ± 0.9| 2.66 ± 0.09   | 2.66 ± 0.13|

Influence of the washing step after reaction: In order to minimize the number of steps in the general procedure for the determination of the product generated, the influence of the washing step after the reaction was evaluated. As described above, the general procedure consisted of separating the NRs by centrifugation after the reaction, washing them once with the same medium used for carrying out the reaction, and finally determining the amount of product formed by measuring the fluorescence in the total supernatant. The need of this washing step was evaluated by performing the procedure with and without this additional washing step. The obtained data are presented in Table S8 in which it is clear that depending on the substrate (1 or 5), and thus of the retention of the generated product within the pores of the ZIF-8 structure (i.e., hydrophobicity/hydrophilicity, polarity, and so on), this step of washing is important for achieving a quantitative determination or not.

Table S8. Effect of washing step on the quantitative yield determination of the depropargylation of two different substrates promoted by NRs.

| Catalyst type | Surface Pd (µM) | Substrate | Substrate (µM) | Product | Yield (%) |
|---------------|-----------------|-----------|----------------|---------|-----------|
|               |                 |           |                |         | without washing | with washing |
| NCs           | 10              | 1         | 10             | 2       | 93.0 ± 3.8   | 97.0 ± 1.3 |
| NCs           | 10              | 5         | 10             | 6       | 60.0 ± 6.1   | 85.7 ± 2.8 |
Leaking of Pd during the depropargylation of substrate 1: The stability of the Pd-NPs inside the ZIF-8 structure was studied by evaluating the potential leaking of Pd from the NRs during the reaction. To this end, the reaction was performed under the optimized conditions described above (used during the reaction of 1 as model) and the amount of Pd released to the supernatant after the reaction was quantified by ICP-MS. For comparison the same was done with the CTAB-protected Pd-NPs. Data presented in Table S9 are expressed in ppm (i.e., mg/L), showing that the amount of Pd released was much higher in the case of working with Pd-NPs while the leaching in the case of NRs was negligible. As we know the amount of total Pd in both Pd-NPs and NRs, the amount of released Pd was also expressed as percentage of the total Pd. These results clearly indicate that the Pd-NPs are well protected inside the ZIF-8 structure, avoiding not only their potential passivation by biomolecules as demonstrated above, but also their surface damage leading to the irreversible leaching of Pd from the catalyst.

Table S9 Leaking of Pd (ppm of Pd released) during the depropargylation reaction of 1 depending on the catalyst used as derived from ICP-MS analysis.

| Catalyst type | Surface Pd (µM) | Pd released (ppm) | % Pd released |
|---------------|-----------------|-------------------|---------------|
| NRs 10        | 0.146 ± 0.011   | 0.081 ± 0.008     |               |
| Pd-NPs 10     | 30.4 ± 2.0      | 16.6 ± 1.1        |               |

Reusability of NRs: In order to investigate the potential reuse of the NRs, after the reaction the NRs were collected by centrifugation, washed twice with water to remove potential remaining substrate/products, and redispersed in a fresh aqueous solution containing the substrate for a new run. The supernatants from each use were measured by fluorescence to quantify the amount of generated product. Using the substrate 1 the same procedure was carried out with Pd-NPs in order to compare the stability of NRs with that of Pd-NPs. Data presented in Table S10 clearly shows that the loss of efficiency of the NRs for promoting the depropargylation reaction was negligible after four runs.

Table S10 Yields of the depropargylation of two different substrates promoted by NRs or Pd-NPs after successive runs of the catalyst.

| Catalyst type | Surface Pd (µM) | Substrate [Substrate] (µM) | Product | Yield (%) / Run number |
|---------------|-----------------|---------------------------|---------|------------------------|
| NRs 10        | 1 10            | 2                         | 97.0 ± 3.1 96.1 ± 2.5 98.0 ± 2.1 95.4 ± 3.4 |
| Pd-NPs 10     | 1 10            | 2                         | 19.0 ± 1.5 9.2 ± 2.1 5.0 ± 2.8 2.1 ± 2.7 |
| NRs 10        | 5 10            | 6                         | 80.3 ± 2.9 81.1 ± 3.2 77.9 ± 4.7 71.0 ± 6.1 |
Kinetic of the depropargylation reaction $1 \rightarrow 2$: To study the kinetic of the reaction of the substrate 1, the reaction was evaluated as a function of time. Several reactions were carried out in parallel under identical conditions and each one was stopped at different time points. To this end, 1 (8 µL, 0.5 mM stock solution in MeOH) were added to a H$_2$O:MeOH 9:1 solution (342 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of NRs (50 µL, 2 nM; this is the concentration of NRs). The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. After different times, the reaction was stopped and the NRs were collected by centrifugation (7000 RCF, 10 min), and washed once with 400 µL of a H$_2$O:MeOH 9:1 solution. All the supernatants were collected and the fluorescence from product 2 was measured. The fluorescence intensity of 2 was plotted versus the time (see Figure S16) to obtain the kinetic curve. Moreover, the kinetic of the reaction of substrate 1 was evaluated also in the presence of 3 as interference, knowing that the depropargylation of substrate 3 is not promoted by the NRs. In this case 10 µM of 3 (8 µL, 0.5 mM stock solution in MeOH) was added together with 10 µM of 1 (8 µL, 0.5 mM stock solution in MeOH) to the reaction mixture.

![Figure S16](image.png)

**Figure S16.** Kinetics of the depropargylation of substrate 1, either by mixing NR with 1 in the absence (green) or presence of 1 eq. of 3 (light green). Dashed lines correspond to logistic fitting curves obtained with Originlab; $R^2 >0.99$.

In order to figure out a potential reason of the fact that the substrate 3 is not catalyzed by NRs, and additionally not only slow down the kinetic reaction of 1 but also it seems that a change of the slope in the kinetic curve takes place from 10 h, we carried out studies of the NRs after reaction by DLS and Z-Potential. As shown in Table S11, after the reaction of NRs with substrate 3 the hydrodynamic size of the NRs increased, and a decrease of the negative charge was also observed. This could be attributed to a binding of some molecules of substrate 3 on the surface of NRs, avowing their diffusion into the NR core, and also partially blocking the diffusion of substrate 1. In contrast, the substrate 1 did not cause any significant change in the NRs.
Table S11. Hydrodynamic diameters \(d_h\) (mean value ± SD) as derived from DLS measurements of the NRs dispersed the reaction mixture before reaction and after reaction with substrate 1 or 3 in H\(_2\)O/MeOH 9:1. SD values correspond to the standard deviation of the diameter mean value as obtained from several repetitions (n=3) of the measurement. The polydispersity index (PDI) and \(\zeta\)-potential values are also given.

| Parameter | before reaction | After reaction with 1 | After reaction with 3 |
|-----------|----------------|----------------------|---------------------|
| \(d_h\) (nm) | 249 ± 3 | 252 ± 4 | 306 ± 3 |
| PDI | 0.10 | 0.12 | 0.11 |
| \(\zeta\) (mV) | -34.5 ± 0.5 | -34.4 ± 0.8 | -26.5 ± 0.7 |

Performance of the NRs as “continuous” nanoreactors: The performance of the NRs for promoting the depopargylation reaction of 5 by in three successive steps was studied as follows: for 1 cycle, 5 (8 µL, 0.5 mM stock solution in MeOH) was added to a PBS:MeOH 8:2 solution (342 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of NRs (50 µL, 2 nM; this is the concentration of NRs). The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. After 18 h, the NRs were collected by centrifugation (7000 RCF, 10 min), and the supernatant was separated. The precipitate was washed once with 400 µL of a 8:2 PBS:MeOH solution, centrifuged again (7000 RCF, 10 min), and the supernatant was separated and mixed with the first supernatant. The generated product in the supernatant was measured by fluorescence. For 2 successive cycles, the reaction was carried out in identical conditions and after 18 h, instead of purified the product, another shot of 5 (8 µL, 0.5 mM stock solution in MeOH) was added to the reaction mixture. The mixture was left to react 18 h, with stirring and at 37 ºC, and afterwards the total generated product was separated and quantify as described in first cycle. The same was repeated with one more addition for 3 cycles. Results are presented in Table S12.

Table S12 Cumulative yield of the depopargylation of 5 promoted by NRs after successive reuses of the catalyst.

| Catalyst type | surface-Pd (µM) | Cycles Number | [Substrate] (µM) | Product | Cumulative Yield (%) |
|---------------|-----------------|---------------|------------------|---------|---------------------|
| NRs           | 10              | 1             | 10               | 2       | 94.6 ± 5.3          |
| NRs           | 10              | 2             | 10 + 10          | 2       | 178.4 ± 6.8         |
| NRs           | 10              | 3             | 10 + 10 + 10    | 2       | 250.6 ± 8.1         |
Reverse phase high-performance liquid chromatography-diode array detector/mass spectrometry (RP-HPLC-DAD/MS) characterization of the NR-promoted depropargylation of the cresyl violet 5: The depropargylation reaction of substrate 5 promoted by NR was carried out in slightly different conditions as described above in the general procedures section, in order to obtain the product 6 concentrated enough for their posterior analysis. Specifically, the substrate solution (8 µL, 0.5 mM stock solution in MeOH) was added to a PBS:MeOH 1:1 solution (342 µL) in a 1.5 mL HPLC vial (containing a stirring bar) followed by addition of an aqueous solution of NRs (50 µL, 2 nM; this is the concentration of NRs). The vial was sealed with a screw cap and the reaction mixture was stirred (400 rpm) at 37 ºC. This was performed in parallel in 5 vials. After overnight (15 h), the NRs were collected by centrifugation (7000 RCF, 10 min), and the supernatants were separated. The precipitates were washed once with 400 µL of MeOH solution, centrifuged again (7000 RCF, 10 min), and all the supernatants from the different vials were mixed. This supernatant was preconcentrated by evaporation of the MeOH solvent, and 100 µL of DMSO was added to avoid the precipitation of the product and unreacted substrate. Finally, this supernatant was analyzed by RP-HPLC-DAD/MS, and as controls the pure substrate and product were also analyzed (Figure S17).

Figure S17. RP-HPLC-DAD chromatogram (left) and ESI-MS spectra (right) of compound 5, RP-HPLC-DAD chromatogram (left) and ESI-MS spectra (right) of compound 6, and RP-HPLC-DAD chromatogram (left) of the obtained reaction mixture promoted by NRs.
Performance of the reactions in the presence of bio-additives

**Reaction of substrate 1 in the presence of additives:** The reaction was carried out as described in the previous section, but adding the following additives (Table S13): (i) different amounts of BSA (for a final concentration in the total volume of 40 µM, 80 µM, or 150 µM); (ii) DMEM (supplemented with 10 % FBS), and in this case the reaction was studied after 15 h and 72 h; (iii) 5 mg/mL of cell lysate.

**Reaction of substrate 5 in the presence of additives:** The reaction was carried out as described in the previous section, but adding the following additives (Table S13): (i) different amounts of BSA (for a final concentration in the total volume of 40 µM, 80 µM, or 150 µM); (ii) 5 mg/mL of cell lysate.

**Cell Lysate preparation:** For the preparation of the HeLa cells lysates, 3x10⁶ exponentially growing HeLa cells were washed twice with PBS, scrapped with a rubber policeman in 0.5 mL of PBS, and sonicated intensely for 2 rounds of 1 min with a 30 second cooling period in between. The protein concentration of the lysates was quantified by DCTM Protein Assay (BioRad) and equalised to 10 mg/mL for reproducibility among experiments.

Table S13. Reaction yields of the depropargylation of two substrates promoted by NRs or Pd-NPs in the presence of different bioadditives.

| Catalyst type | surface-Pd (µM) | Additive          | Substrate | [Substrate] (µM) | Product | Yield (%) |
|---------------|-----------------|-------------------|-----------|-----------------|---------|-----------|
| NRs           | 10              | -                 | 1         | 10              | 2       | 97.0 ± 1.3 |
| NRs           | 10              | BSA, 40 µM        | 1         | 10              | 2       | 55.0 ± 3.0 |
| NRs           | 10              | BSA, 80 µM        | 1         | 10              | 2       | 53.0 ± 2.9 |
| NRs           | 10              | BSA, 150 µM       | 1         | 10              | 2       | 33.0 ± 3.5 |
| Pd-NPs        | 10              | -                 | 1         | 10              | 2       | 19.0 ± 1.5 |
| Pd-NPs        | 10              | BSA, 40 µM        | 1         | 10              | 2       | 9.0 ± 1.6  |
| Pd-NPs        | 10              | BSA, 80 µM        | 1         | 10              | 2       | 7.0 ± 2.0  |
| Pd-NPs        | 10              | BSA, 150 µM       | 1         | 10              | 2       | 7.0 ± 2.1  |
| NRs           | 10              | DMEM, 10%, 15h    | 1         | 10              | 2       | 22.0 ± 3.2 |
| NRs           | 10              | DMEM, 10%, 72h    | 1         | 10              | 2       | 47.0 ± 3.7 |
| NRs           | 10              | Lysate, 5 mg/mL   | 1         | 10              | 2       | 19.0 ± 2.8 |
| NRs           | 10              | -                 | 5         | 10              | 6       | 84.8 ± 2.5 |
| NRs           | 10              | BSA, 20 µM        | 5         | 10              | 6       | 62.8 ± 2.3 |
| NRs           | 10              | BSA, 40 µM        | 5         | 10              | 6       | 54.1 ± 2.9 |
| NRs           | 10              | BSA, 8 µM         | 5         | 10              | 6       | 23.8 ± 3.9 |
| NRs           | 10              | Lysate, 5 mg/mL   | 5         | 10              | 6       | 22.5 ± 4.1 |
Cell studies

Cell culture: HeLa (cervical cancer cell line) were cultured in Dulbecco’s Modified Eagle’s Medium with phenol red, 4.5 g/L D-glucose, L-glutamine and pyruvate (DMEM, 1X, Gibco, #41966-029) supplemented with 10% Fetal Bovine Serum (Gibco, #10270-106) and 1% Penicillin Streptomycin (P/S, Corning, 100X, #30-002-CI). Cells were maintained under humid conditions at 37 °C and 5% of CO₂. Cells were passaged after cleaning Dulbecco’s Phosphate Buffered Saline (DPBS, 1X, Gibco, #14190-094) with 0.25% Trypsin-EDTA (1X, Gibco, 25200-056) when the culture reached confluency.

Cell Viability: In order to study number of viable cells after the exposure to the substrates, Pd-NPs and/or NRs, we carried resazurin assays (Figure S18). HeLa cells were seeded in 96-well plates (NEST Scientific, #701001), 7.5·10³ cells per well in 100 µL of cell growth medium (0.3 cm² per well) 24 h before the exposition. Then media was removed and 100 L of cell culture growth medium with the desired concentration of the substrates, Pd-NPs and/or NRs were added. The cells were incubated with the samples the time of interest at 37 °C and 5% CO₂. After that, we rinsed each well three times with PBS and added 100 µL of freshly prepared solution with 90% of media and 10% of resazurin (resazurin sodium salt in water 0.2 mg/mL filtered; Resazurin Sodium Salt, Sigma Aldrich, #199303-1G). Cells were incubated at 37 °C and 5% CO₂ under dark conditions.

Non-fluorescent resazurin (Alamar blue) is oxidized by living cells into its fluorescent product resorufin (excitation at 579 nm and emission at 584 nm). In this way, the fluorescence intensity of each well is proportional to the number of living cells there. After the incubation time, plates were measured with a plate reader (Infinite® 200 PRO, Tecan, Switzerland) under 560±20 nm excitation and collecting fluorescence with a 610±20 nm filter. The fluorescence value of each well provided by the instrument is an average of nine consecutive measures in the same well. Final intensity value for control cells (Ic), the ones that were not treated, is an average of, at least, nine different well values. Final intensity values for samples (Is) are a mean of three independent well values. So, we can calculate the final cell viability values as:

\[
\text{cell viability (\%)} = \frac{I_s}{I_c} \cdot 100
\]

Pd content per cell. ICP-MS was used to quantify the average Pd content per cell, which we used to estimate the number of Pd-NPs or NRs per cell (Table S14); see calculations in Section IV “Quantification of Pd by inductively coupled plasma mass spectrometry (ICP-MS) and estimation of Pd potentially active”. Note that to estimate the number of particles per cell, we assume that the particles (Pd-NPs or NRs) retain their original Pd content; however, in contrast to the Pd-NPs, such assumption seems valid for the NRs according to the stability data (Table S2). HeLa cells (~6.4·10⁶ cell per experiment) were cultured as previously discussed, supplemented with Pd-NPs or NRs (50 pM – 2 µM in surface Pd, equivalent to ~5.7·10³ particles per cell), and incubated overnight. Extracellular Pd (either free, Pd-NP or NRs) were washed out, and the Pd-loaded cells were digested with aqua regia (see detailed procedures in previous work10).

Table S14. Amounts of Pd per cell and particle uptake % (measured-to-added) as derived from ICP-MS measurements.

| Particle | Pd per particle (µg)* | Cells (No.) | Particles per cell (added) | ICP-MS |
|----------|-----------------------|-------------|---------------------------|--------|
|          |                       |             |                           | Pd per | Particle per | % particle |
|          |                       |             |                           | cell (µg) | cell (No.) | internalization* |
| Pd-NPs   | 1.7·10¹⁰             | 6.5·10⁵     | 5.6·10¹                   | 1.2·10⁸ ± 8.9·10⁻¹¹ | 71 ± 1 | 0.5       |
| NRs      | 1.7·10¹⁰             | 6.3·10⁵     | 5.8·10¹                   | 2.0·10⁸ ± 2.5·10⁻¹⁰ | 120 ± 1 | 0.8       |

*See section S4.

*Assuming particles retain their Pd original content inside cells.
Confocal imaging: In order to perform all the confocal imaging experiments with living cells, 20·10^3 HeLa cells (200 µL) were seeded on µ-Slide 8 well-ibiTreat chambers (1 cm² per well, Ibidi, Germany, #80826) at least 12 h before NR/substrate exposure. Organelle staining with LysoTracker Blue (#L7525), MitoTracker Green (#M 7514) and CellMask Deep Red (#H32721) was performed following provider (Thermo Fisher Scientific) instructions. Confocal images of living cells were captured on an Andor Dragonfly spinning disk confocal system mounted on a Nikon TiE microscope equipped with a Zyla 4.2 PLUS camera (Andor, Oxford Instruments) and an OKO-lab incubator to keep cells at 37 °C during all the experiment. Images were taken with different magnification objectives (60x, 100x). All the images were processed with ImageJ.

Confocal microscopy images of the NR system in which PMA was fluorescently labeled (covalently) with a rhodamine (tetramethylrhodamine 5-(and-6)-carboxamide cadaverine), are shown in Figure S19, aiming to illustrate the efficient cell internalization (HeLa cells) of the proposed NRs (50 pM) and colocalization with lysosomes. Note that we used equivalent particle (NR or Pd-NP) incubation conditions in all the cell studies.

Excitation/Emission wavelengths used for confocal imaging of the rhodamine-labeled NRs/product 6 are 561/620(60).

Depropargylation reactions inside cells. Different concentrations of the substrate 5 (Figure S20-21) were added to cells pretreated with NRs or Pd-NPs (50 pM, overnight). The productions of 6 was inspected by checking the intracellular fluorescence after the time of interest (1-24 h).

For the study of the depropargylation of 5 over time (Figure S21-24), we preload the cells with the NR (50 pM) overnight and, after three washing steps with PBS to remove the excess of NR non-associated with cells, substrate 5 (10 µM) was added with fresh medium. We incubated the substrate 5 during 1, 3, 6 and 24 h. Washing steps to remove extracellular excess of 5 and or 6 were not required before confocal inspection.

Controls were carried with the same concentrations of 5 but with Pd-free cells (Figure S25).

We also confirmed that Pd-NPs (50 pM  2 µM in surface Pd, overnight) without the MOF shell, or a series of discrete Pd complexes (Pd-1, Pd-2 and Pd-3; 2 µM Pd, overnight), promote the intracellular depropargylation of the substrate 5 (Figure S26), although with much less efficiency than the NRs (Figure S21-24).

Intracellular recycling. In order to study the reusability of our cell-nanoreactor for the depropargylation of 5, we stopped the incubation of the substrates with NR-preloaded cells after the time of interest (substrate 5: 20 µM, 3 h). Then, the intracellular production of 6 was inspected under the microscope; notice that washing to remove extracellular substrates/products step was not required for visualizing the depropargylation of 5.

Next, before adding a second shot of 5 (10 µM, 3 h), we cleaned with PBS, added fresh complete DMEM and waited for the cells to “wash away” 6 (~ 3 h, cleansing). We repeated these steps to complete up to four cycles (Figure S27).

As controls for the recycling experiments, we also performed similar studies for the depropargylation of 5 (two runs) but using Pd-NPs (50 pM  2 µM in surface Pd, overnight) or the discrete Pd complexes (Pd-1, Pd-2 or Pd-3; 2 µM Pd, overnight). However, such alternative Pd catalysts were unable to achieve a second depropargylation cycle, at least to any degree observable by the intracellular fluorescence of 6 (Figure S26).

Depropargylation and recycling in 3D NR-preloaded HeLa spheroids. Spheroids of HeLa cells were cultured in 96 well plates previously treated with agarose as follows: a 1% agarose solution in filtered PBS was heated until
100 °C; the tips and the 96-well plate was pre-warmed in the incubator for ~1 h, and 40 µL of the agarose solution were added to each well; the agarose filled wells were led to cool down during, at least, 30 minutes in sterile conditions. Then, we confirmed a homogeneous agarose gelation without bubbles by inspection under the microscope. Once agarose was solidified, 100 µL of cells (NR-preloaded or “empty”) solution at different concentrations were added slowly. Cells were led to attach to each other during 24 hours before checking the spheroids formation. After 24 h, the sizes of spheroids were between 0.4 and 1 µm when varying total cells amounts from ~1·10^4 to 3·10^4 cells per spheroid (Figure S28). Media of the wells containing the spheroids were changed daily.

For spheroids imaging, spheroids formed as previously discussed were placed onto a µ-plate angiogenesis 96 well (0.125 cm² per well, Ibidi, Germany #89646) using a pipette with a sterile cut tip to facilitate the spheroid’s manipulation. Using an Andor Dragonfly spinning disk confocal system with the 20x objective, spheroids were observed in the brightfield channel (Figure S28) and in the Cy3 channel (wavelengths: excitation 561 nm; emission 620(60) nm) where the fluorescence from TAMRA (Figure S29) or from the depropargylation of 5 (Figure S30) were collected. For the bigger ones (~1 µm in diameter), 4 different images in the plane XY were required. Z-scans were made with ~300 different stack images in the Z axis. 3D reconstructions were done with ~300 stack images (total thickness ~150 µm; step thickness ~0.5 µm). Scale bars correspond to 100 µm (20x). In order to treat the 2D images as well as to crop or stitch 4x4 images, ImageJ was used. Deconvolution of the z-scans were done with Fusion software and finally, for 3D reconstructions, Imaris software (Oxford Instruments) was used.

In order to form spheroids with catalytic properties, 2·10^4 cells per well were seeded on 6 well plates. After 24 hours of cell attachment, cells were treated with the NRs (50 pM, overnight) as previously discussed. Notice that non-treated cells were always seeded and maintained as control, to form control non-catalytic spheroids. Once the NR were internalized, extracellular NRs were washed three times with fresh PBS. Cells were trypsinized with 200 µL of trypsin and neutralized with 2 mL of DMEM (10% FBS). After that, dilutions were made to obtain the desired number of cells in 100 µL. After one day of spheroids formation, the medium was removed and fresh medium containing 5 (20 µM) was added to both NR-loaded spheroids and control spheroids without NRs (Figure S30). After 24 hours, spheroids were checked under the confocal microscope. Media was removed and the spheroids were thoroughly washed (3x) with PBS to remove extracellular substrates and/or products and fresh medium was added, which facilitated the cleansing of 6 during 24 h. After cleansing, a second addition of 5 (24 hours, 20 µM) were added to confirm that the spheroids were still catalytic and confirm reusability.
Figure S18. Cell viability using the resazurin assay of HeLa cells exposed to increasing concentrations of reactant(s) and/or NRs and/or Pd-NPs. Half-maximal responses (EC50 values) were estimated by fitting (Dose Response function in OriginLab). a) Pd-NPs (50 pM), 24 h incubation; b) NRs (50 pM), 24 h incubation; c) 5, 24 h incubation; d) 6, 24 h incubation; e) 5, 24 h incubation with Pd-NPs (50 pM)-preloaded cells; f) 5, 24 h incubation with NR (50 pM)-preloaded cells; g) 5, 3 h incubation with NR (50 pM)-preloaded cells; h) 5, 6 h incubation with NR (50 pM)-preloaded cells; i) 5, 9 h incubation with NR (50 pM)-preloaded cells; j) comparison between the incubation (24 h) of 6 with Pd-free cells and 5 with NR (50 pM)-preloaded cells.
Figure S19. Collage of confocal microscopy images. a1,a2,a3) Rhodamine-labelled NRs (pink); b1,b2,b3: Rhodamine-labelled NRs (pink) + LysoTracker® Blue (cyan); c1,c2,c3) Display of colocalization of NR and
LysoTracker® Blue (Pearson correlation coefficient: 0.42 ± 0.05, n=5); d1,d2,d3) LysoTracker® Blue + MytoTracker® Green + CellMaskTM Deep Red; e1,e2,e3: d1,d2,d3 + rhodamine-labelled NRs (pink); f1,f2,f3: Display of colocalization of NR and MitoTracker® Green (Pearson correlation coefficient: -0.23 ± 0.04, n=5). Scale bars correspond to 40 µm. Colocalization analysis in fluorescence was performed with ImageJ (Coloc 2 Fiji’s plugin for colocalization analysis).

**Figure S20.** Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; 60x) for the production of 6 after 6 h incubation with NR-preloaded cells (using 2.5 µM of 5); a1-a2) controls without NRs; b1-b2) two examples using NR-preloaded cells as previously discussed. Scale bars correspond to 40 µm.
Figure S21. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; 60x) for the production of 6 after 1 h incubation with NR-preloaded cells (using 10 µM of 5); a1-a2) controls without NRs (a1: 60x; a2: 100x); b1-c1) two examples using NR-preloaded cells as previously discussed (60x); b2-c2) two examples using NR-preloaded cells as previously discussed (60x). Scale bars correspond to 20 µm (100x) or 40 µm (60x).
Figure S22. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; 60x) for the production of 6 after 3 h incubation with NR-preloaded cells (using 10 µM of 5); a1-a2) controls without NRs (a1: 60x; a2: 100x); b1-c1) two examples using NR-preloaded cells as previously discussed (60x); b2-c2) two examples using NR-preloaded cells as previously discussed (60x). Scale bars correspond to 20 µm (100x) or 40 µm (60x).
Figure S23. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; 60x) for the production of 6 after 6 h incubation with NR-preloaded cells (using 10 µM of 5); a1-a2) controls without NRs (a1: 60x; a2: 100x); b1-c1) two examples using NR-preloaded cells as previously discussed (60x); b2-c2) two examples using NR-preloaded cells as previously discussed (60x). Scale bars correspond to 20 µm (100x) or 40 µm (60x).
Figure S24. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; 60x) for the production of 6 after 24 h incubation with NR-preloaded cells (using 10 µM of 5); a1-a2) controls without NRs (a1: 60x; a2: 100x); b1-c1) two examples using NR-preloaded cells as previously discussed (60x); b2-c2) two examples using NR-preloaded cells as previously discussed (60x). Scale bars correspond to 20 µm (100x) or 40 µm (60x).

Figure S25. Collage of confocal microscopy images (left: fluorescence channel; right: merged fluorescence + bright field; 60x and 100x) for the incubation of 6 with Pd-free cells; cells were incubated with 6 (0.2 µM) for ~1 h. Before microscope inspection, cells were washed to remove extracellular probes. Scale bars correspond to 20 µm (100x) or 40 µm (60x).
Figure S26. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field; top: first generation run; bottom: second generation run using the same catalyst-preloaded cells) for the production of 6, using cells preloaded with (a) NR (50 pM 2 µM in surface Pd, overnight), (b) Pd-NP (50 pM 2 µM in surface Pd, overnight), of discrete Pd complexes (c) Pd-1, (d) Pd-2, or (e) Pd-3, which were incubated with 5 (10 µM) for ~6 h before microscope inspection. f) Control experiments using “empty” cells (Pd “free” cells). Scale bars correspond to 20 µm. All these experiments were carried out using exactly the same experimental conditions.
Figure S27. Collage of confocal microscopy images (left: pink channel; right: merged pink + bright-field). a) Control without NRs and the addition of substrate 5 (20 µM). b-g) First, second and third generation runs using the same NR-preloaded cells and recorded by confocal microscopy; b,d,f) generation of 6 after 3 h incubation of 5 (20 M); c,e,g) 3 h cleansing. h) fourth reaction cycle. Scale bars correspond to 20 µm.
Figure S28. Collage of brightfield images of 3D HeLa (Pd “free” spheroids). a) HeLa spheroid with diameter ~ 0.4 µm (1 image per stack); b) Three different stacks of the spheroid shown in a. c) HeLa spheroid with diameter ~ 1 µm (4 images in each plane); d) Three different stacks of the spheroid shown in c. e) 3D reconstruction (top-view) of a spheroid with diameter ~ 0.4 µm. Scale bars correspond to 100 µm.
Figure S29. Collage of confocal images of 3D spheroids of HeLa cells loaded with TAMRA-labeled NRs. a) Three different views of a 3D reconstruction of a NR-loaded spheroid with diameter ~ 1 µm. b) Different stacks of the spheroid shown in a. Scale bars correspond to 100 µm
Figure S30. 3D reconstructions of spheroids of NR-preloaded HeLa cells treated with the substrate 5. a) First generation of 6 after 24 h incubation of 5 (20 µM). b) 24 h cleansing. c) Second generation of 6 after 24 h incubation of 5 (20 µM). d) Control experiment of “empty” (Pd “free”) spheroids incubated during 24 h with substrate 5 (20 µM). All these experiments were carried out using exactly the same experimental conditions and acquisition settings.
Supplemental References

1. Wang, J., Zheng, S., Liu, Y., Zhang, Z., Lin, Z., Li, J., Zhang, G., Wang, X., Li, J., Chen, P. R. (2016). Palladium-Triggered Chemical Rescue of Intracellular Proteins via Genetically Encoded Allene-Caged Tyrosine. J. Am. Chem. Soc. 138, 15118-15121.

2. Chen, T., Wei, T., Zhang, Z., Chen, Y., Qiang, J., Wang, F., Chen, X. (2017). Highly sensitive and selective ESIPT-based fluorescent probes for detection of Pd2+ with large Stocks shifts. Dyes Pigm. 140, 392-398.

3. Clavadetscher, J., Indrigo, E., Chankeshwara, S. V., Lilienkampf, A., Bradley, M. (2017). In-Cell Dual Drug Synthesis by Cancer-Targeting Palladium Catalysts. Angew. Chem. Int. Ed. 56, 6864-6868.

4. Li, J., Yu, J., Zhao, J., Wang, J., Zheng, S., Lin, S., Chen, L., Yang, M., Jia, S., Zhang, X. et al. (2014). Palladium-triggered deprotection chemistry for protein activation in living cells. Nat. Chem. 6, 352.

5. Martínez-Calvo, M., Couceiro, J. R., Destito, P., Rodríguez, J., Mosquera, J., Mascareñas, J. L. (2018). Intracellular Deprotection Reactions Mediated by Palladium Complexes Equipped with Designed Phosphine Ligands. ACS Catal. 8, 6055-6061.

6. Miller, M. A., Askevold, B., Mikula, H., Kohler, R. H., Pirovich, D., Weissleder, R. (2017). Nano-palladium is a cellular catalyst for in vivo chemistry. Nat. Commun. 8, 15906.

7. Hühn, J., Carrillo-Carrion, C., Soliman, M. G., Pfeiffer, C., Valdeperez, D., Masood, A., Chakraborty, I., Zhu, L., Gallego, M., Yue, Z. et al. (2017). Selected Standard Protocols for the Synthesis, Phase Transfer, and Characterization of Inorganic Colloidal Nanoparticles. Chem. Mater. 29, 399-461.

8. Xie, X., Gao, G., Pan, Z., Wang, T., Meng, X., Cai, L. (2015). Large-Scale Synthesis of Palladium Concave Nanocubes with High-Index Facets for Sustainable Enhanced Catalytic Performance. Sci. Rep. 5, 8515.

9. Carrillo-Carrion, C., Martinez, R., Navarro Poupard, M. F., Pelaz, B., Polo, E., Arenas-Vivo, A., Olgiati, A., Taboada, P., Soliman, M. G., Catalan, U. et al. (2019). Aqueous Stable Gold Nanostar/ZIF-8 Nanocomposites for Light-Triggered Release of Active Cargo Inside Living Cells. Angew. Chem. Int. Ed. Engl. 58, 7078-7082.

10. del Pino, P., Yang, F., Pelaz, B., Zhang, Q., Kantner, K., Hartmann, R., Martinez de Baroja, N., Gallego, M., Möller, M., Manshian, B. B. et al. (2016). Basic Physicochemical Properties of Polyethylene Glycol Coated Gold Nanoparticles that Determine Their Interaction with Cells. Angew. Chem. Int. Ed. 55, 5483-5487.

11. Weiswald, L.-B., Bellet, D., Dangles-Marie, V. (2015). Spherical Cancer Models in Tumor Biology. Neoplasia 17, 1-15.