

Catalytically active N-heterocyclic carbene release from single-chain nanoparticles following a thermolysis-driven Unfolding Strategy

Garmendia, Sofiem; Lawrenson, Stefan; Arno, Maria Chiara; O'Reilly, Rachel; Taton, Daniel; Dove, Andrew

DOI:

[10.1002/marc.201900071](https://doi.org/10.1002/marc.201900071)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Garmendia, S, Lawrenson, S, Arno, MC, O'Reilly, R, Taton, D & Dove, A 2019, 'Catalytically active N-heterocyclic carbene release from single-chain nanoparticles following a thermolysis-driven Unfolding Strategy', *Macromolecular Rapid Communications*, vol. 40, no. 15, 1900071, pp. 1-8. <https://doi.org/10.1002/marc.201900071>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is the peer reviewed version of the following article: Garmendia, S, Lawrenson, S, Arno, MC, O'Reilly, R, Taton, D & Dove, A 2019, 'Catalytically active N-heterocyclic carbene release from single-chain nanoparticles following a thermolysis-driven Unfolding Strategy', *Macromolecular Rapid Communications*, vol. 40, no. 15, 1900071, pp. 1-8, which has been published in final form at <https://doi.org/10.1002/marc.201900071>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Catalytically Active *N*-Heterocyclic Carbene Release from Single-Chain Nanoparticles following a Thermolysis-driven Unfolding Strategy

Sofiem Garmendia,^{1,2,3} Stefan B. Lawrenson,³ Maria C. Arno,³ Rachel K. O'Reilly,³ Daniel Taton*,¹ and Andrew P. Dove*³*

¹*Laboratoire de Chimie des Polymères Organiques, Université de Bordeaux IPB-ENSCBP, F-33607 Pessac Cedex, France*

¹*Laboratoire de Chimie des Polymères Organiques Centre National de la Recherche Scientifique, 16 Avenue Pey-Berland, F-33607 Pessac Cedex, France*

²*Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK*

³*School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

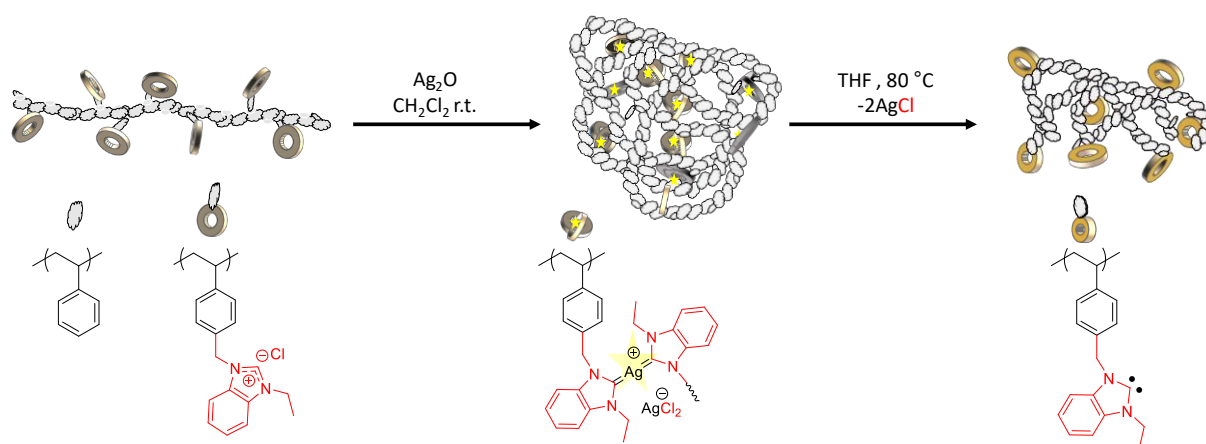
ABSTRACT: The need for efficient, tailor-made catalysts has inspired chemists to design synthetic macromolecular architectures for selective catalysis. To this purpose, we report herein the synthesis and in-depth characterization of Ag(I)-crosslinked single-chain nanoparticles (SCNPs) and demonstrate their application as catalysts. Specifically, a copolymer of styrenic benzimidazolium chloride was synthesized as a linear precursor *via* RAFT polymerisation. Metalation of the benzimidazolium moieties by Ag(I) resulted in the intramolecular cross-linking of single chains *via* the formation of Ag-NHC (silver-*N*-heterocyclic carbene) linkages under dilute conditions. The successful formation of well-defined, robust SCNPs was evidenced by size-exclusion chromatography, dynamic light scattering, nuclear magnetic resonance, and transmission electron microscopy. Finally, we demonstrate that our Ag-SCNPs can be used as NHC pre-catalysts, by firstly indirectly evidencing the formation of the corresponding unfolded NHC-CS₂ polybetaine and then organocatalysing a benzoin condensation reaction.

INTRODUCTION Stable *N*-heterocyclic carbenes (NHCs) have become an fascinating area of research since their discovery by Arduengo in 1991.[1] Specifically, their peculiar electronic and steric properties make them powerful ligands of transition metals,[2–6] while their inherent nucleophilicity[7] and Brønsted-basicity[8] account for their efficient performance as

organocatalysts for both molecular[9] and macromolecular transformations.[10–12] To overcome their air and moisture sensitivity, a variety of masked NHCs, including NHC-CO₂ adducts, NHC-2-alkoxy adducts or NHC-Ag have been developed.[11–17] Interestingly, silver complexes represent a versatile class of labile NHC metal complexes because of the relative weakness of the C₂-Ag bond.[18] The most popular route to obtain Ag(I)-NHC compounds uses Ag₂O, allowing the direct conversion of imidazolium salts (ionic liquids; ILs) into the corresponding metal complexes by transmetalation reaction. Thus, in comparison to the approaches used to produce Zn- and Sn-NHC complexes,[19] the free carbenes do not interfere with the synthesis of Ag(I)-NHC, allowing to achieve good yields using standard laboratory techniques.[6,11,13,20,21]

Moreover, thanks to the easy accessibility and high versatility of NHCs, several functionalized architectures can be achieved from Ag(I)-NHC complexes for different applications, such as antibacterial agents [18,22] or catalysis.[23–26] In particular, a promising synthetic strategy inspired by nature has emerged to prepare unimolecular versatile nano-objects referred to as single-chain nanoparticles (SCNPs).[27–31] Indeed, these folded/collapsed soft nanostructures have gained increasing attention for the development of functional materials in the fields of nanomedicine, protein mimicry, and catalysis.[30–34] In the catalysis field, the design of supported organometallic catalysts aims to emulate the unique features of (metallo)enzymes, such as structural complexity, compartmentalized functions, and site isolation.[33,35–39] Previous work in the area has typically focused on the formation of SCNPs by hydrogen or covalent bonding between supported orthogonal functions.[34] More recently, coordination chemistry, where metals act as cross-linkers inducing the single-chain particle formation, has been developed.[33,40–44,44] Surprisingly, the ability of Ag to trigger the single-chain folding of catalytically active SCNPs remains unexploited despite the potential of Ag(I)-NHC complexes to generate free NHCs and undergo transmetalation.[30]

Herein, we report for the first time the formation of Ag-SCNPs obtained by cross-linking benzimidazolium moieties using Ag(I) as metalation agent. Upon heating, the free carbene can be released from the Ag-NHC precursors, thus enabling free NHC to catalyse the benzoin condensation in THF. The generation of NHC-CS₂ betaine resulting from the reaction between Ag-SCNPs and CS₂ provided indirect evidence of free NHC formation upon thermal-triggered unfolding of SCNPs. Therefore, our Ag-SCNPs combine the unique properties of Ag-NHC complexes with the SCNPs technology to create versatile and functional nanoparticles for catalytic applications.



Scheme 1. Folding of a single-chain polymer into a nanoparticle structure *via* addition of a metal ion source (*i.e.* Ag_2O). These SCNPs are then employed as sources of free NHC upon thermal decomposition of the organometallic Ag-NHC bond in the nanoreactor to form an active catalyst species.

EXPERIMENTAL

Materials

Methanol, benzimidazole (>95%), 4-vinylbenzyl chloride (90%), ethyl bromide (99%), 2-cyano-2-propyl benzodithioate (>97%), potassium hydroxide (pellets), and benzyl chloride (97%) were obtained from Aldrich and used as received. Dichloromethane (99.7%), carbon disulfide (CS_2), 2-Cyano-2-propyl dodecyl trithiocarbonate and (CTA) lithium bis(trifluoromethane)sulfonylimide (LiTFSI) were obtained from Aldrich and used as received. Azobis(2-methylpropionitrile) (AIBN, 99%) was received from Aldrich and was purified by recrystallization (2x) from methanol. The synthesis of 4-vinylbenzylethylbenzimidazolium chloride (**1**) was performed as previously described.[45–48] The synthesis of 1,3-dibenzyl-1H-benzimidazol-3-ium chloride was performed as described elsewhere.[49,50] Tetrahydrofuran (THF) was distilled over Na/benzophenone. Styrene and benzaldehyde were dried over CaH_2 and distilled prior to use. All synthesized polymers were purified by dialysis against methanol using “Standard Grade Regenerated Cellulose Dialysis Membranes (Spectra/Por6) Pre-wetted RC tubing” (SpectrumLab) with a molecular weight cut off (MWCO) of 3.5 kDa. All polymers were azeotropically dried using previously distilled THF before performing catalysis. Polymerization, catalyst loadings, and catalysis experiments were carried out by the syringe technique under dry argon in baked glass tubes equipped with a two-way stopcock.

Characterisation

^1H , ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC-400 spectrometer in appropriate deuterated solvents. All ^{13}C measurements were performed at 298 K on a Bruker Avance III 400 spectrometer operating at 400, 376.5 and 100 MHz and equipped with a 5 mm Bruker multinuclear direct cryo-probe. Dimethyl formamide (10 mM ammonium tetrafluoroborate) soluble polymers were first solubilized in concentrations of 1 mg mL^{-1} , and their masses were determined by size exclusion chromatography (SEC) in DMF at 20 °C using refractometric (RI) detector (Varian) and polystyrene calibration as standards. Analyses were performed using a three-column set of TSK gel TOSOH (G4000, G3000, G2000 with pore sizes 20, 75, and 200 Å, respectively, connected in series). Hydrodynamic diameters (D_h) and size distributions of SCNPs were determined by dynamic light scattering (DLS) on a Malvern Zetasizer Nano ZS operating at 20 °C with a 4 Mw He-Ne 633 nm laser module. Samples were filtered through a 0.22 μm PTFE filter prior to measurement, and quartz cuvettes were used. Measurements were made at a detection angle of 173° (back scattering), and the data were analysed with Malvern DTS 6.20 software, using the multiple narrow modes setting. All measurements were performed in triplicate, with 10 runs per measurement. TEM analyses were performed on a JEOL 2011 (LaB₆) microscope operating at 200 KeV, equipped with a GATAN UltraScan 1000 digital camera. Conventional bright field conditions were lacey carbon-coated copper grids (Agar Scientific, 400 mesh, S116-4). SCNPs solutions were diluted to 1 mg mL^{-1} in MeOH before 4 μL of each sample were drop-deposited onto the graphene oxide coated grids and allowed to air dry. Subsequent staining was applied using uranyl acetate (1 mg mL^{-1} , 7 μL) to enhance the contrast.[51] Images were analyzed using Image J software, and 50 particles were measured to produce a mean and standard deviation for the particle size (D_{av}).

Synthesis

Additional experimental procedures for synthesis and characterization, including SEC traces and DLS are further detailed in the Electronic Supporting Information (ESI). All ^1H , ^{13}C , and ^{19}F NMR spectra are also included.

Synthesis of copolymeric linear precursor 2.

2-Cyano-2-propyl dodecyl trithiocarbonate (60 mg, 0.17 mmol), styrene (3.1 mL, 30 mmol) 4-vinylbenzylethylbenzimidazolium chloride **1** (1.57 g, 5.21 mmol), AIBN (27 mg, 0.17 mmol) were dissolved in dry methanol in a 10 mL glass tube. The solution was degassed by five successive freeze-pump cycles and stirred for 16 h at 80 °C. The as-obtained copolymer (**2**) was purified by dialysis against methanol (3.5 kDa MWCO) and obtained as a pink powder (yield:

51%, 2.05 g). ^1H NMR (400MHz; 298 K; DMSO- d_6): 10.7-10.1 (br, 1H, N-CH=N), 8.2-6.1 (br, 32.8H, Ar-*H*), 5.9-5.5 (br, 2H, Ar-CH₂-N), 4.6-4.4 (br, 2H, N-CH₂-CH₃), 2.1-0.9 (br, 27.5H, backbone: CH and CH₂, CH₂-CH₃) (**Fig. S1**); ^{13}C NMR (100.7 MHz; 298 K; DMSO- d_6): 146.7, 142.3, 132.9, 129.1-126.6, 114.1, 62.9, 50.8, 42.6, 14.3 (**Fig. S2**). SEC analysis: $M_n = 18,000 \text{ g mol}^{-1}$, $M_w = 21,600 \text{ g mol}^{-1}$, $D_M = 1.2$

Synthesis of SCNP 3

Linear copolymer **2** (350 mg; 0.44 mmol referred to benzimidazolium) was dissolved in 350 mL of dry dichloromethane at a concentration of 1 mg mL^{-1} in a 1 L round bottom flask. Then, Ag₂O (60 mg; 0.26 mmol) was added by previously preparing a dispersion in dichloromethane in order to ease the dropwise addition into the flask. Molecular sieves (4 Å) were added in order to trap the generated water, shifting the equilibrium towards the bis-NHC-Ag moiety. The red colored solution was stirred for 72 h, during which time the solution turned transparent, and filtered twice to remove the excess of Ag₂O. The solvent was finally removed under reduced pressure, and **3** was obtained as a viscous liquid (yield: 82%, 322.1 mg). ^1H NMR (400 MHz; 298 K; DMSO- d_6) = 8.2-6.0 (br, 34.1, Ar-*H*), 5.9-5.4 (br, 2H, Ar-CH₂-N), 4.6-4.3 (br, 2H, N-CH₂-CH₃), 2.2-0.9 (br, backbone: CH and CH₂, CH₂-CH₃) (**Fig. S3**); ^{13}C NMR (100.7 MHz; 298 K; DMSO- d_6): 188.8, 147.3, 134.0, 129.9-123.7, 113.5, 52.8, 47.7, 44.1, 17.9 (**Fig. S4**). SEC analysis: $M_n = 17,600 \text{ g mol}^{-1}$, $M_w = 21,100 \text{ g mol}^{-1}$, $D_M = 1.2$

Synthesis of SCNP 4

SCNP **3** (150 mg; 0.19 mmol) was solubilized in a glass flask containing 35 mL of methanol and 80 mg (0.29 mmol) of LiTFSI previously dissolved in 35 mL methanol. The solution was stirred at rt (room temperature) until SCNP **4** precipitated. The precipitate was then washed with methanol (5 mL x 2) (yield: 48%, 77.8 mg). ^1H NMR (400 MHz; 298 K; DMSO- d_6) = 8.3-6.0 (m, broad, Ar-*H*), 6.0-5.5 (s, broad, Ar-CH₂-N), 4.9-4.4 (d, broad, N-CH₂-CH₃), 2.3-0.9 (m, broad, backbone: CH and CH₂, CH₂-CH₃) (**Fig. S5**); ^{13}C NMR (100.7 MHz; 298 K; DMSO- d_6): 179.8, 145.5, 132.3, 129.9-123.7, 121.5, 119.1, 112.4, 51.9, 43.8, 41.2, 17.8 (**Fig. S6**); ^{19}F NMR (376.5 MHz; 298 K; DMSO- d_6): -79.9 (**Fig. S7**). SEC analysis: $M_n = 17,300 \text{ g mol}^{-1}$, $M_w = 20,700 \text{ g mol}^{-1}$, $D_M = 1.2$

Synthesis of copolymer **5**

SCNP **3** (30 mg; 0.04 mmol) was solubilized in dry THF (1 mL) in a glass tube and CS₂ (0.3 mL; 2.6 mmol) was added at rt under argon. The colorless solution was stirred at 80 °C for 24 h, during which time a color change to red was observed, indicative of NHC-CS₂ formation. After cooling, the excess of CS₂ and solvent were removed under reduced pressure, obtaining **5** as a viscous liquid (yield: >95%, 27.3 mg). ¹H NMR (400 MHz; 298 K; DMSO-*d*₆) = 8.2-6.1 (m, broad, Ar-*H*), 5.9-5.5 (s, broad, Ar-CH₂-N), 4.8-4.4 (d, broad, N-CH₂-CH₃), 2.5-0.9 (m, broad, backbone: CH and CH₂, CH₂-CH₃) (**Fig. S8**); ¹³C NMR (100.7 MHz; 298 K; DMSO-*d*₆): 219.9, 151.8, 145.4, 131.3-124.6, 112.8, 48.2, 43.2, 14.8 (**Fig. S9**).

General procedure for benzoin condensation reaction

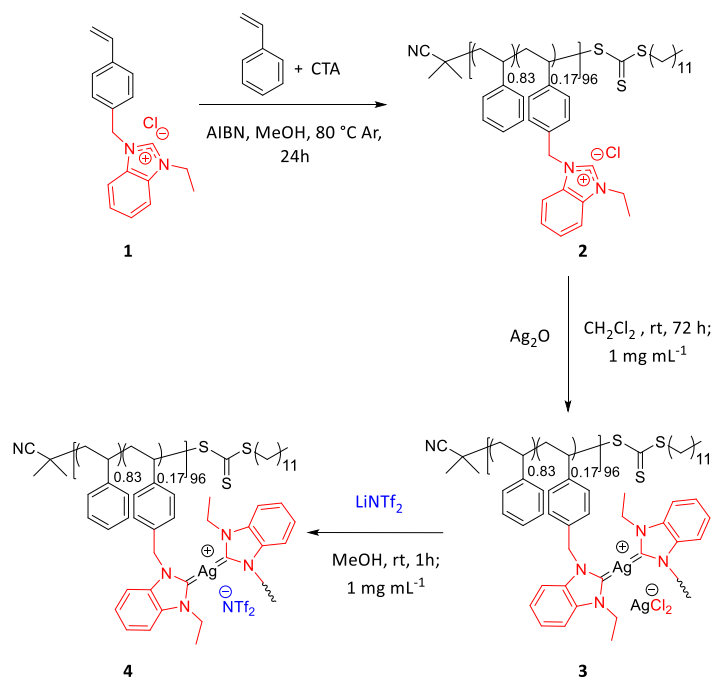
In a typical experiment, 10 mol% of catalyst (61 mg; 0.07 mmol) was suspended in dry THF (3 mL; catalyst concentration 20 mg mL⁻¹) in a 10 mL Schlenk tube, to which 0.07 mL of benzaldehyde (0.7 mmol) was added under argon. The reaction mixture was stirred for 24 h at 80 °C. The mixture was allowed to cool down to rt, and an aliquot was withdrawn for ¹H NMR spectroscopy characterization. Benzoin conversion was determined by ¹H NMR spectroscopy in DMSO-*d*₆ by comparing the integral value of the aldehyde signal of benzaldehyde (s, 1 H, 10 ppm) with the one of the –CH– benzoin signal (s, 1H, 6 ppm) (**Fig. S10**). For the experiments with variable quantity of catalyst, the volume of solvent and substrate were kept constant.

RESULTS AND DISCUSSION

Synthesis of Catalytically-Active SCNP

The 4-vinylbenzylethylbenzimidazolium chloride (**1**) ionic liquid monomer was prepared following a two-step synthesis (**Scheme 2**), as previously reported in the literature.[45–48] A random copolymer of monomer **1** and styrene units was then obtained *via* reversible addition-fragmentation chain-transfer (RAFT) polymerisation, using 2-cyano-2-propyl dodecyl trithiocarbonate as chain transfer agent (CTA) and azobisisobutyronitrile (AIBN) as radical source in methanol to yield copolymer **2**. The monomer conversion was quantified *via* ¹H NMR spectroscopy by following the disappearance of the C(H) signals of styrene and **1**, as well as the broadening of CH_{imi} in the polymer. Moreover, the consumption of styrene and **1** in similar ratio indicates that the imidazolium functional groups were homogeneously distributed throughout the chains. The final structure of **2** corresponded to a styrene/benzimidazolium ratio

of ~5, as confirmed by ^1H NMR spectroscopy (**Fig. S1**), which was selected to increase the solubility of **2** and its derivatives (*i.e.* **3**, **4** and **5**) in relatively apolar solvents, such as THF.



Scheme 2. Synthesis of copolymer **2** via RAFT polymerization of styrene and **1** in methanol. The subsequent addition of Ag_2O results in the formation of **3** as SCNPs. Further anion exchange was performed by inserting a non-coordinating anion (NTf_2^-) into **3** to confer less dynamic behavior (**4**).

In contrast to previous works where the preparation of imidazolium-based SCNPs involved harsh reaction conditions[45] and tedious purification steps,[52] our approach affords robust NHC-loaded SCNPs under relatively mild conditions. The controlled intramolecular formation of SCNPs (**4**) was achieved by simply adding Ag_2O to a solution of copolymer **3** (1 mg.mL⁻¹) in dichloromethane at rt. Trapping the produced H_2O with molecular sieves (4 Å) afforded a better yield of **3**.^[26] Interestingly, the insolubility of Ag_2O in dichloromethane provided a means of monitoring the reaction progress by observing its gradual disappearance, as a consequence of its incorporation in the copolymer structure. The folding of **2** was thus monitored through the disappearance of the C_2H signal corresponding to the benzimidazolium ($\delta = 10.2$ ppm), as well as the broadening of the *N*-ethyl signals ($\delta = 4.55$ ppm) by ^1H NMR spectroscopy (**Fig. 1A**). After 72 h, full conversion to the Ag-NHC moieties ($\delta = 10.7\text{--}10.1$) was also confirmed by ^{13}C NMR spectroscopy with the complete disappearance of the C_2H signal from benzimidazolium at $\delta = 146.7$ ppm, and the observation of a new signal at $\delta = 188.8$ ppm corresponding to C-Ag (**Fig. 2 and S4**). In addition, SEC characterization was used to further confirm the folding of **2** into well-defined SCNPs (**3**). Specifically, in comparison to **2**

($M_n = 18,000 \text{ g mol}^{-1}$, $D_M = 1.2$), the SEC trace of **3** shifted towards a smaller apparent molecular weight (**Fig. 1B**, $M_n = 17,600 \text{ g mol}^{-1}$, $D_M = 1.2$), which is indicative of the formation of a more compact structure with a smaller hydrodynamic radius, compared to the linear polymer. While the reduction in molecular weight is low, we note that rather than the 35% increase that would be expected by addition of the AgCl salts, a reduction of ~2.5% is instead observed. As a consequence of the poor solubility of **2** in THF (with added salt for SEC analysis), it was not possible to directly compare the apparent molecular weight in the same solvent as catalysis is performed. Finally, mean hydrodynamic diameters of $4.5 \pm 0.4 \text{ nm}$ (number-weighted size distribution) and $4.8 \pm 0.7 \text{ nm}$ (volume-weighted size distribution at a concentration of 1 mg mL^{-1} of polymer sample) were determined by DLS for **3** (**Fig. S11**), in excellent agreement with the size (*ca.* $5 \pm 1.5 \text{ nm}$) observed by transmission electron microscopy (TEM) (**Fig. 1C**). The change in hydrodynamic diameter is also observed with linear polymer **2** displaying $D_h = 9.2 \pm 2.1 \text{ nm}$. We note however that the same trend was not confirmed for the volume-weighted size distribution as a consequence of a significant contribution from aggregated species at *ca.* 100 nm (**Fig. S13**).

In order to confirm the thermolability of the Ag-NHC crosslinking bridges present in **3**, the variation in size distribution of the SCNPs with temperature was monitored by DLS analysis. Interestingly, while at 1 mg.mL^{-1} , a minimal change in size with temperature was observed, at 5 mg.mL^{-1} , the size of SCNPs **3** increased notably, from 15 nm to 70 nm , at $\sim 40^\circ\text{C}$ (**Fig.1D**), likely as a consequence of intermolecular rearrangements into larger aggregates after disassembly.[20] In fact, the silver-carbene bond, which is the weakest among the noble metals (*i.e.* gold > copper > silver), is subjected to dynamic exchange, especially when the steric hindrance is less pronounced.[6] Furthermore, in Ag-NHC complexes, both the nature of the azolium anion and the solvent also play an important role in the bond strength, as coordinating anions, such as halides (*e.g.* Cl^- , Br^- , I^-), form stronger hydrogen bonds compared to non-coordinating anions (*e.g.* BF_4^- , NTf_2^-).[53–55] However, halides usually facilitate the dynamic exchange in the resulting complexes *via* their reversible binding to the silver center, whereas non-coordinating anions prevent such dynamic behavior, which leads exclusively to the formation of cationic bis(NHC) complexes, *i.e.* crosslinked SCNPs.[6] Hence, such dynamic exchange behavior allows halide Ag-NHC complexes to generate free NHCs by thermolysis. Conversely, the enhanced stability of Ag-NHC complexes with non-coordinating anions prevents such dynamic process.[6,56]

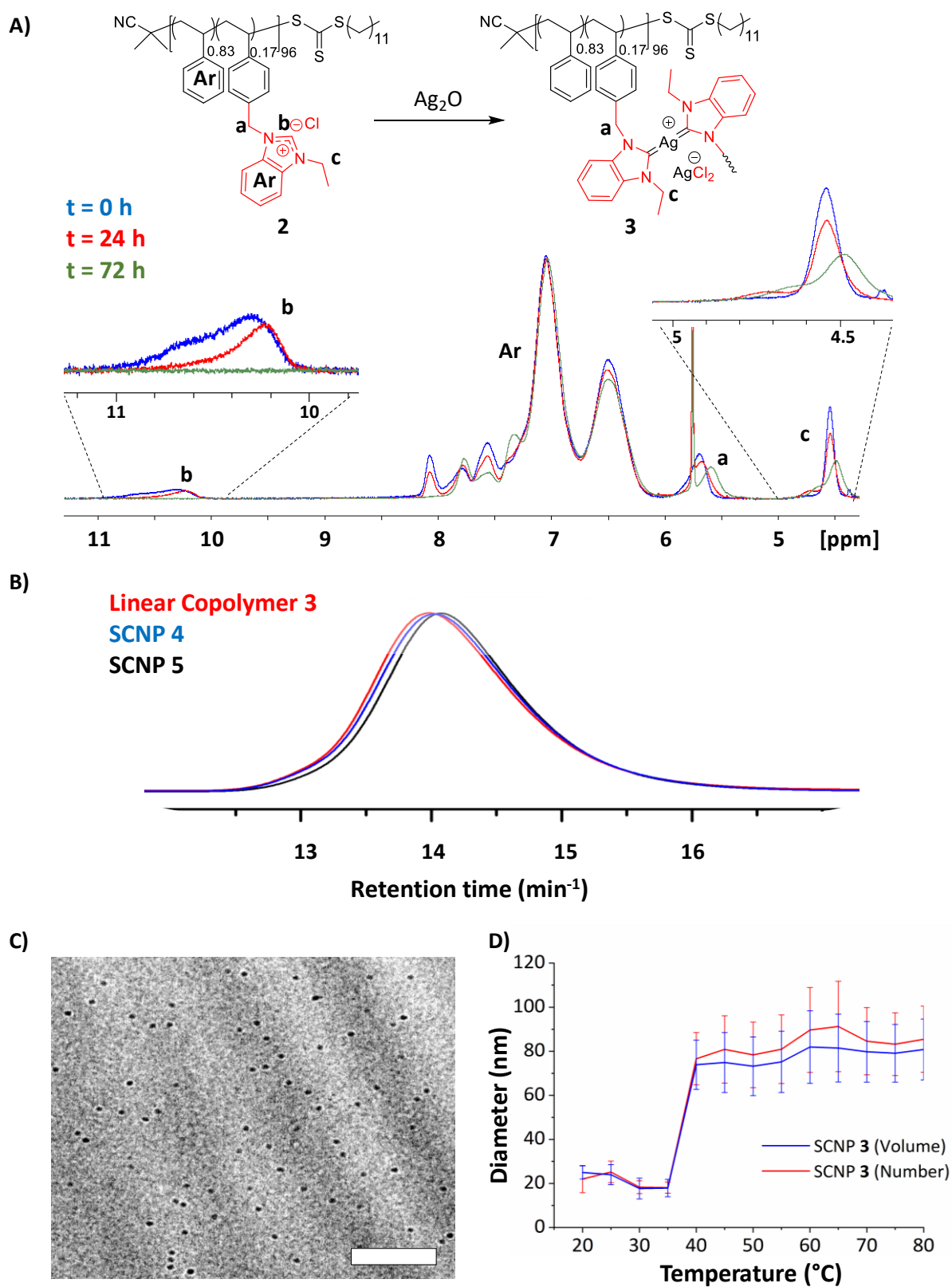


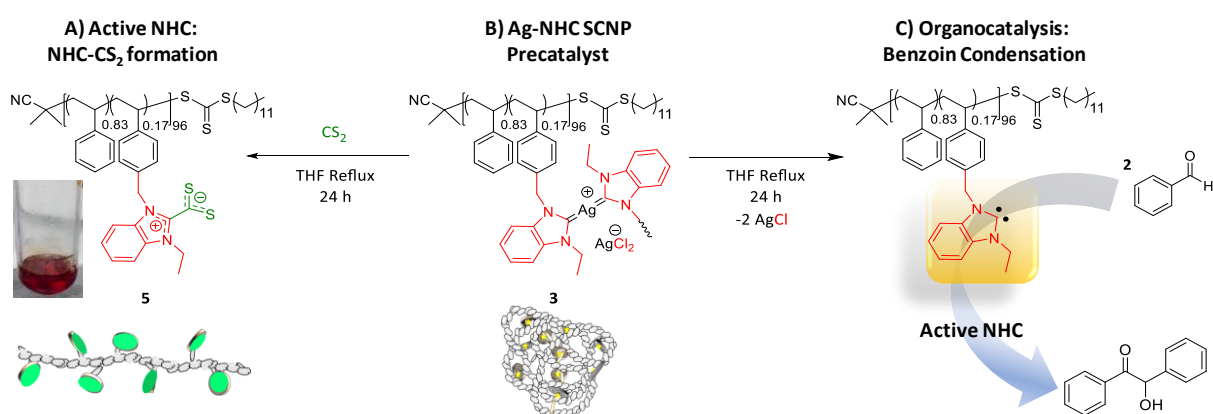
Figure 1. A) Ag-NHC complexation reaction monitored by ^1H NMR spectroscopy (400 MHz; 298 K; $\text{DMSO-}d_6$) at different time points (t_0 = blue line, 24 h = red line, 72 h = green line). B) SEC curves (in DMF with 10 mM NH_4BF_4) of **2** (red line), **3** (blue line) and **4** (black line) using RI detector polystyrene

standard. **C)** TEM micrograph of SCNPs **4** (scale bar = 50 nm). **D)** Hydrodynamic mean diameter of SCNPs **4** (blue line volume distribution; red line number distribution) using multi-temperature DLS analysis from 20 °C to 80 °C in THF (Conc. 5 mg mL⁻¹).

In addition to **3** which is stabilized by coordinating AgCl₂⁻ anions, the more stable Ag-NHC complex **4** bearing non-coordinating NTf₂⁻ anions, was prepared by applying a mild anion-exchange to **3** using an excess of LiNTf₂ salt that provided an efficient driving force to displace Cl⁻, precipitating AgCl as a byproduct. SEC analysis of the resulting polymer showed a decrease in apparent molecular weight (**Fig. 1B**, $M_n = 17,300 \text{ g mol}^{-1}$, $D_M = 1.2$) which is most likely a consequence of the strong preference of the NTf₂⁻ containing SCNPs to be retained as a dimeric NHC-Ag complex and hence presenting a more compact hydrodynamic volume during analysis.

NHC-mediated benzoin condensation reaction

Before investigating **3** as a catalyst for the carbene-mediated benzoin condensation reaction,[57,58] we first examined whether active carbene species could be generated upon thermal decomposition of the poly(bis-NHC)-silver complex in **3**. For that purpose, **3** was heated at 80 °C in THF in the presence of carbon disulfide (CS₂; **Scheme 3**). After 24 h, the solution turned red-brown, which was indicative of the formation of copolybetaine **5**, as it was further confirmed by ¹³C NMR spectroscopy ($\delta = 151.8$ and 219.9 ppm corresponding to C_{2(im)} and CS₂⁻ respectively; **Fig. 2**).[20,21]



Scheme 3. Application of SCNPs **3** as a catalytic platform (**B**) for the benzoin condensation reaction by exposing active NHC upon heating (**C**) Indirect evidence of the formation of active NHC intermediate (**A**).

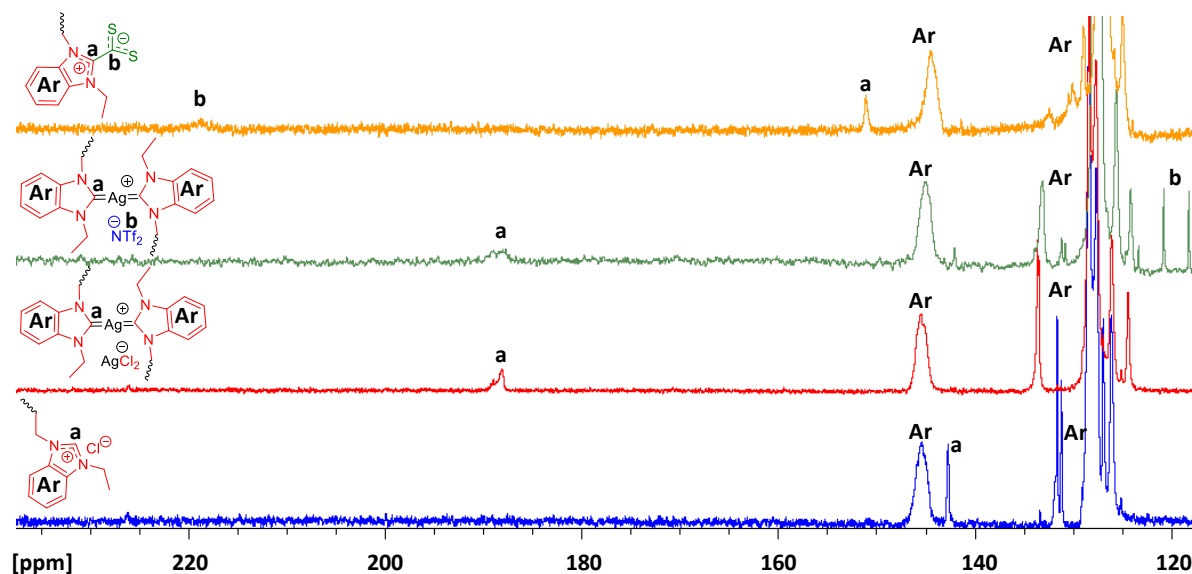


Figure 2. ^{13}C NMR spectra (100.7 MHz; 298 K; $\text{DMSO-}d_6$) of **2** (blue), SCNP **3** (red), SCNP **4** (green), and copolybetaine **5** (yellow).

Since the benzoin condensation is specifically catalyzed by carbenes,[57,58] **3** was evaluated as pre-catalyst for this reaction (**Scheme 3**). Firstly, we tested the catalyst system at ambient temperature which displayed no activity and hence confirms that no NHC catalyst (SCNP **3**) was delivered at room temperature (Run 1; **Table 1**). Therefore, although the thermolysis of Ag-bis(NHC) complexes can occur at temperatures as low as 40 °C,[20] the temperature was set at 80 °C to increase the release of free NHCs. As summarized in **Table 1**, the conversion increased from 13 to 32% by increasing the catalyst loading from 1 to 10 mol%, under otherwise identical conditions (*i.e.* THF at 80 °C for 24 h; Runs 2-4). However, increasing the reaction time up to 48 h (Run 5) did not afford any improvement, suggesting the likely decomposition of the catalyst at this temperature for longer than 24 h, as previously reported.[6] This premature deactivation also prevented the recycling of SCNP **3**, as no catalytic activity was observed in the subsequent run (6).

In order to introduce a control system, a small molecule model with benzylic *N*-substituents on the NHC moieties, **6**, (see ESI) was used to catalyze the benzoin condensation reaction under similar conditions (Runs 7-9). This experiment showed higher catalytic activity, reaching up to 51% conversion of benzaldehyde after 24 h, probably because of the easier access to the catalytic site (Run 7). Similarly, no further increase in conversion was observed after 48 h (Run 8), while the non-recyclability of the molecular model became further evident in the subsequent run (9). It has to be acknowledged however, that both Ag-(bis)NHC based molecular and

macromolecular systems show lower catalytic performance for this reaction compared to our previously reported masked-NHC based SCNPs.[47,52]

Finally, in good agreement with our initial hypothesis, the presence of non-coordinating counteranions (*i.e.* NTf₂⁻) in **4** hindered the formation of active carbenes, precluding the formation of active catalytic species and thus preventing the synthesis of benzoin (Run 10). Hence, the nature of the counteranion significantly influences the robustness and thermolability of Ag-SCNPs to deliver catalytically active NHC in a suitable environment, hence highlighting the potential to employ the anion exchange reaction as a successful strategy to switch on and off the catalytic activity of this system.

Table 1. Condensation reaction of benzaldehyde under different conditions using Ag-NHC SCNPs and a small molecule model as catalysts.

Run	Catalyst	Loading mol (%) ^a	Cycle	Solvent	Temperature (°C)	Time (h)	Conv (%) ^b
1	SCNP 3	10	1	THF ^c	80	24	0
2	SCNP 3	1	1	THF	80	24	13
3	SCNP 3	5	1	THF	80	24	21
4	SCNP 3	10 ^d	1	THF	80	24	32
5	SCNP 3	10	1	THF	80	48	32
6	SCNP 3	10	2 ^e	THF	80	24	0
7	6^f	10	1	THF	80	24	51
8	6	10	1	THF	80	48	51
9	6	10	2 ^g	THF	80	24	0
10	SCNP 4	10	1	THF	80	24	0

^a Mol% calculated relative to the benzimidazolium moieties; ^b conversion was calculated by ¹H NMR spectroscopy (**Fig. S10**); ^c THF was dried over Na/Benzophenone before distillation; ^d a 20 mg mL⁻¹ concentration of catalyst was used as reference; ^e **3** purified by dialysis against MeOH; ^f synthesis and characterization of the molecular model used in this reaction is included in the ESI. ; ^g molecular catalyst was recovered by precipitation into cold MeOH.

CONCLUSIONS

The formation of SCNPs crosslinked by Ag-NHC bridges has been achieved for the first time. Ag was used as metalation agent to trigger the folding of a linear styrene-benzimidazolium

copolymer into 5 nm SCNPs under relatively mild conditions. These nanoreactors were able to respond to external increase in temperature and unfold to release free NHC, which was then able to catalyse the benzoin condensation reaction in the same pot, although in modest yield. Furthermore, by simply changing the counterion, the catalytic activity can be switched off. In conclusion, Ag-NHC SCNPs can be envisaged as a valuable nanoplatform for transmetalation reactions.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures for synthesis and characterization including DLS and $^1\text{H}/^{13}\text{C}/^{19}\text{F}$ NMR spectra.

AUTHOR INFORMATION

Corresponding Author

* E-mail: a.dove@bham.ac.uk, r.oreilly@bham.ac.uk, taton@enscbp.fr

ACKNOWLEDGMENT

The authors gratefully thank the European Union for funding through project SUSPOL-EJD 642671.

REFERENCES

- [1] A.J. Arduengo III, R.L. Harlow, M. Kline, A stable crystalline carbene, *Journal of the American Chemical Society*. 113 (1991) 361–363.
- [2] D. Bourissou, O. Guerret, F.P. Gabba, G. Bertrand, Stable Carbenes, *Chemical Reviews*. 100 (2000) 39–92. doi:10.1021/cr940472u.
- [3] M.N. Hopkinson, C. Richter, M. Schedler, F. Glorius, An overview of N-heterocyclic carbenes, *Nature*. 510 (2014) 485–496. doi:10.1038/nature13384.
- [4] P. de Frémont, N. Marion, S.P. Nolan, Carbenes: Synthesis, properties, and organometallic chemistry, *Coordination Chemistry Reviews*. 253 (2009) 862–892. doi:10.1016/j.ccr.2008.05.018.
- [5] S. Díez-González, N. Marion, S.P. Nolan, N-Heterocyclic Carbenes in Late Transition Metal Catalysis, *Chemical Reviews*. 109 (2009) 3612–3676. doi:10.1021/cr900074m.
- [6] Han Vinh Huynh, *The Organometallic Chemistry of N-heterocyclic Carbenes*, John Wiley & Sons Ltd., 2017.
- [7] B. Maji, M. Breugst, H. Mayr, N-Heterocyclic Carbenes: Organocatalysts with Moderate Nucleophilicity but Extraordinarily High Lewis Basicity, *Angewandte Chemie International Edition*. 50 (2011) 6915–6919. doi:10.1002/anie.201102435.
- [8] E.M. Higgins, J.A. Sherwood, A.G. Lindsay, J. Armstrong, R.S. Massey, R.W. Alder, A.C. O'Donoghue, pK_a s of the conjugate acids of N-heterocyclic carbenes in water, *Chem. Commun.* 47 (2011) 1559–1561. doi:10.1039/C0CC03367G.
- [9] D.M. Flanigan, F. Romanov-Michailidis, N.A. White, T. Rovis, Organocatalytic reactions enabled by N-heterocyclic carbenes, *Chem. Rev.* 115 (2015) 9307–9387.

- [10] S. Naumann, A.P. Dove, N-Heterocyclic carbenes as organocatalysts for polymerizations: trends and frontiers, *Polym. Chem.* 6 (2015) 3185–3200. doi:10.1039/C5PY00145E.
- [11] M. Fevre, J. Pinaud, Y. Gnanou, J. Vignolle, D. Taton, N-Heterocyclic carbenes (NHCs) as organocatalysts and structural components in metal-free polymer synthesis, *Chemical Society Reviews*. 42 (2013) 2142. doi:10.1039/c2cs35383k.
- [12] W.N. Ottou, H. Sardon, D. Mecerreyes, J. Vignolle, D. Taton, Update and challenges in organo-mediated polymerization reactions, *Progress in Polymer Science*. 56 (2016) 64–115. doi:10.1016/j.progpolymsci.2015.12.001.
- [13] S. Naumann, M.R. Buchmeiser, Liberation of N-heterocyclic carbenes (NHCs) from thermally labile progenitors: protected NHCs as versatile tools in organo- and polymerization catalysis, *Catalysis Science & Technology*. 4 (2014) 2466. doi:10.1039/c4cy00344f.
- [14] Y. An, J. Yu, Y. Han, Recent Advances in the Chemistry of *N*-Heterocyclic-Carbene-Functionalized Metal-Nanoparticles and Their Applications, *Chinese Journal of Chemistry*. 37 (2019) 76–87. doi:10.1002/cjoc.201800450.
- [15] A. Melaie, Z. Sun, K. Hindi, A. Milsted, D. Ely, D.H. Reneker, C.A. Tessier, W.J. Youngs, Silver(I)–Imidazole Cyclophane *gem*-Diol Complexes Encapsulated by Electrospun Tecophilic Nanofibers: Formation of Nanosilver Particles and Antimicrobial Activity, *Journal of the American Chemical Society*. 127 (2005) 2285–2291. doi:10.1021/ja040226s.
- [16] C.K. Lee, C.S. Vasam, T.W. Huang, H.M.J. Wang, R.Y. Yang, C.S. Lee, I.J.B. Lin, Silver(I) N-Heterocyclic Carbenes with Long N-Alkyl Chains, *Organometallics*. 25 (2006) 3768–3775. doi:10.1021/om060198h.
- [17] D. Yu, M.X. Tan, Y. Zhang, Carboxylation of Terminal Alkynes with Carbon Dioxide Catalyzed by Poly(N-Heterocyclic Carbene)-Supported Silver Nanoparticles, *Advanced Synthesis & Catalysis*. 354 (2012) 969–974. doi:10.1002/adsc.201100934.
- [18] A. Kascatan-Nebioglu, M.J. Panzner, C.A. Tessier, C.L. Cannon, W.J. Youngs, N-Heterocyclic carbene–silver complexes: A new class of antibiotics, *Coordination Chemistry Reviews*. 251 (2007) 884–895. doi:10.1016/j.ccr.2006.08.019.
- [19] V. Nesterov, D. Reiter, P. Bag, P. Frisch, R. Holzner, A. Porzelt, S. Inoue, NHCs in Main Group Chemistry, *Chemical Reviews*. 118 (2018) 9678–9842. doi:10.1021/acs.chemrev.8b00079.
- [20] A.C. Sentman, S. Csihony, R.M. Waymouth, J.L. Hedrick, Silver(I)–Carbene Complexes/Ionic Liquids: Novel *N*-Heterocyclic Carbene Delivery Agents for Organocatalytic Transformations, *The Journal of Organic Chemistry*. 70 (2005) 2391–2393. doi:10.1021/jo048555q.
- [21] P. Coupillaud, J. Vignolle, D. Mecerreyes, D. Taton, Post-polymerization modification and organocatalysis using reactive statistical poly(ionic liquid)-based copolymers, *Polymer*. 55 (2014) 3404–3414. doi:10.1016/j.polymer.2014.02.043.
- [22] N.A. Johnson, M.R. Southerland, W.J. Youngs, Recent Developments in the Medicinal Applications of Silver-NHC Complexes and Imidazolium Salts, *Molecules*. 22 (2017) 1263. doi:10.3390/molecules22081263.
- [23] I.J.B. Lin, C.S. Vasam, SILVER(I) N-HETEROCYCLIC CARBENES, *Comments on Inorganic Chemistry*. 25 (2004) 75–129. doi:10.1080/02603590490883652.
- [24] H.M. Wang, I.J. Lin, Facile synthesis of silver (I)- carbene complexes. Useful carbene transfer agents, *Organometallics*. 17 (1998) 972–975.
- [25] C.A. Citadelle, E.L. Nouy, F. Bisaro, A.M.Z. Slawin, C.S.J. Cazin, Simple and versatile synthesis of copper and silver N-heterocyclic carbene complexes in water or organic solvents, *Dalton Transactions*. 39 (2010) 4489. doi:10.1039/c0dt00128g.

- [26] A.A. Tulloch, A.A. Danopoulos, S. Winston, S. Kleinhenz, G. Eastham, N-Functionalised heterocyclic carbene complexes of silver, *Journal of the Chemical Society, Dalton Transactions*. (2000) 4499–4506.
- [27] M. Gonzalez-Burgos, A. Latorre-Sanchez, J.A. Pomposo, Advances in single chain technology, *Chem. Soc. Rev.* 44 (2015) 6122–6142. doi:10.1039/C5CS00209E.
- [28] O. Altintas, C. Barner-Kowollik, Single-Chain Folding of Synthetic Polymers: A Critical Update, *Macromolecular Rapid Communications*. 37 (2016) 29–46. doi:10.1002/marc.201500547.
- [29] M. Ouchi, N. Badi, J.-F. Lutz, M. Sawamoto, Single-chain technology using discrete synthetic macromolecules, *Nature Chemistry*. 3 (2011) 917–924. doi:10.1038/nchem.1175.
- [30] A.M. Hanlon, C.K. Lyon, E.B. Berda, What Is Next in Single-Chain Nanoparticles?, *Macromolecules*. 49 (2016) 2–14. doi:10.1021/acs.macromol.5b01456.
- [31] S. Mavila, O. Eivgi, I. Berkovich, N.G. Lemcoff, Intramolecular Cross-Linking Methodologies for the Synthesis of Polymer Nanoparticles, *Chemical Reviews*. 116 (2016) 878–961. doi:10.1021/acs.chemrev.5b00290.
- [32] J. Rubio-Cervilla, E. González, J. Pomposo, Advances in Single-Chain Nanoparticles for Catalysis Applications, *Nanomaterials*. 7 (2017) 341. doi:10.3390/nano7100341.
- [33] H. Rothfuss, N.D. Knöfel, P.W. Roesky, C. Barner-Kowollik, Single-Chain Nanoparticles as Catalytic Nanoreactors, *Journal of the American Chemical Society*. (2018). doi:10.1021/jacs.8b02135.
- [34] O. Altintas, T.S. Fischer, C. Barner-Kowollik, Synthetic Methods Toward Single-Chain Polymer Nanoparticles, in: J.A. Pomposo (Ed.), *Single-Chain Polymer Nanoparticles*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2017: pp. 1–45. doi:10.1002/9783527806386.ch1.
- [35] A. Sanchez-Sanchez, A. Arbe, J. Colmenero, J.A. Pomposo, Metallo-Folded Single-Chain Nanoparticles with Catalytic Selectivity, *ACS Macro Letters*. 3 (2014) 439–443. doi:10.1021/mz5001477.
- [36] S. Thanneeru, S.S. Duay, L. Jin, Y. Fu, A.M. Angeles-Boza, J. He, Single Chain Polymeric Nanoparticles to Promote Selective Hydroxylation Reactions of Phenol Catalyzed by Copper, *ACS Macro Letters*. (2017) 652–656. doi:10.1021/acsmacrolett.7b00300.
- [37] S. Mavila, C.E. Diesendruck, S. Linde, L. Amir, R. Shikler, N.G. Lemcoff, Polycyclooctadiene Complexes of Rhodium(I): Direct Access to Organometallic Nanoparticles, *Angewandte Chemie International Edition*. 52 (2013) 5767–5770. doi:10.1002/anie.201300362.
- [38] Y. Bai, X. Feng, H. Xing, Y. Xu, B.K. Kim, N. Baig, T. Zhou, A.A. Gewirth, Y. Lu, E. Oldfield, S.C. Zimmerman, A Highly Efficient Single-Chain Metal–Organic Nanoparticle Catalyst for Alkyne–Azide “Click” Reactions in Water and in Cells, *Journal of the American Chemical Society*. 138 (2016) 11077–11080. doi:10.1021/jacs.6b04477.
- [39] J. Chen, J. Wang, Y. Bai, K. Li, E.S. Garcia, A.L. Ferguson, S.C. Zimmerman, Enzyme-like Click Catalysis by a Copper-Containing Single-Chain Nanoparticle, *Journal of the American Chemical Society*. 140 (2018) 13695–13702. doi:10.1021/jacs.8b06875.
- [40] Y. Azuma, T. Terashima, M. Sawamoto, Self-Folding Polymer Iron Catalysts for Living Radical Polymerization, *ACS Macro Letters*. 6 (2017) 830–835. doi:10.1021/acsmacrolett.7b00498.
- [41] N.D. Knöfel, H. Rothfuss, J. Willenbacher, C. Barner-Kowollik, P.W. Roesky, Platinum(II)-Crosslinked Single-Chain Nanoparticles: An Approach towards Recyclable

- Homogeneous Catalysts, *Angewandte Chemie International Edition*. 56 (2017) 4950–4954. doi:10.1002/anie.201700718.
- [42] S. Mavila, I. Rozenberg, N.G. Lemcoff, A general approach to mono-and bimetallic organometallic nanoparticles, *Chemical Science*. 5 (2014) 4196–4203.
- [43] I. Berkovich, V. Kobernik, S. Guidone, N.G. Lemcoff, Metal Containing Single-Chain Nanoparticles, in: J.A. Pomposo (Ed.), *Single-Chain Polymer Nanoparticles*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2017: pp. 217–257. doi:10.1002/9783527806386.ch6.
- [44] K. Freytag, S. Säfken, K. Wolter, J.C. Namyslo, E.G. Hübner, Hybrid single-chain nanoparticles *via* the metal induced crosslinking of N-donor functionalized polymer chains, *Polymer Chemistry*. 8 (2017) 7546–7558. doi:10.1039/C7PY01487B.
- [45] R. Lambert, A.-L. Wirotius, S. Garmendia, P. Berto, J. Vignolle, D. Taton, Pd(II)–NHC coordination-driven formation of water-soluble catalytically active single chain nanoparticles, *Polymer Chemistry*. 9 (2018) 3199–3204. doi:10.1039/C8PY00326B.
- [46] S. Garmendia, R. Lambert, A.-L. Wirotius, J. Vignolle, A.P. Dove, R.K. O'Reilly, D. Taton, Facile synthesis of reversibly crosslinked poly(ionic liquid)-type gels: Recyclable supports for organocatalysis by N-heterocyclic carbenes, *European Polymer Journal*. 107 (2018) 82–88. doi:10.1016/j.eurpolymj.2018.07.031.
- [47] S. Garmendia, A.P. Dove, D. Taton, R.K. O'Reilly, Reversible ionically-crosslinked single chain nanoparticles as bioinspired and recyclable nanoreactors for N-heterocyclic carbene organocatalysis, *Polymer Chemistry*. 9 (2018) 5286–5294. doi:10.1039/C8PY01293H.
- [48] R. Lambert, A.-L. Wirotius, J. Vignolle, D. Taton, C–C couplings in water by micellar catalysis at low loadings from a recyclable polymer-supported Pd(II)–NHC nanocatalyst, *Polymer Chemistry*. 10 (2019) 460–466. doi:10.1039/C8PY01509K.
- [49] H.M. Lima, C.J. Lovely, Synthesis of 2-Imidazolones and 2-Iminoimidazoles, *Organic Letters*. 13 (2011) 5736–5739. doi:10.1021/ol2022438.
- [50] P.O. Asekunowo, R.A. Haque, Mohd.R. Razali, S.W. Avicor, M.F.F. Wajidi, Dose-, time- and lipophilicity-dependent silver(I)-N-heterocyclic carbene complexes: Synthesis, characterization and interaction with plasmid and *Aedes albopictus* DNA: Ag–NHC complexes as potential anti-dengue agents, *Applied Organometallic Chemistry*. 31 (2017) e3655. doi:10.1002/aoc.3655.
- [51] M.W.P. van de Put, J.P. Patterson, P.H.H. Bomans, N.R. Wilson, H. Friedrich, R.A.T.M. van Benthem, G. de With, R.K. O'Reilly, N.A.J.M. Sommerdijk, Graphene oxide single sheets as substrates for high resolution cryoTEM, *Soft Matter*. 11 (2015) 1265–1270. doi:10.1039/C4SM02587C.
- [52] R. Lambert, A.-L. Wirotius, D. Taton, Intramolecular Quaternization as Folding Strategy for the Synthesis of Catalytically Active Imidazolium-Based Single Chain Nanoparticles, *ACS Macro Letters*. 6 (2017) 489–494. doi:10.1021/acsmacrolett.7b00161.
- [53] S. Kuwata, F.E. Hahn, Complexes Bearing Protic N-Heterocyclic Carbene Ligands, *Chemical Reviews*. 118 (2018) 9642–9677. doi:10.1021/acs.chemrev.8b00176.
- [54] M.-M. Gan, J.-Q. Liu, L. Zhang, Y.-Y. Wang, F.E. Hahn, Y.-F. Han, Preparation and Post-Assembly Modification of Metallosupramolecular Assemblies from Poly(N-Heterocyclic Carbene) Ligands, *Chemical Reviews*. 118 (2018) 9587–9641. doi:10.1021/acs.chemrev.8b00119.
- [55] Á. Vivancos, C. Segarra, M. Albrecht, Mesoionic and Related Less Heteroatom-Stabilized N-Heterocyclic Carbene Complexes: Synthesis, Catalysis, and Other Applications, *Chemical Reviews*. 118 (2018) 9493–9586. doi:10.1021/acs.chemrev.8b00148.

- [56] H.-L. Su, L.M. Pérez, S.-J. Lee, J.H. Reibenspies, H.S. Bazzi, D.E. Bergbreiter, Studies of Ligand Exchange in N-Heterocyclic Carbene Silver(I) Complexes, *Organometallics*. 31 (2012) 4063–4071. doi:10.1021/om300340w.
- [57] R.S. Menon, A.T. Biju, V. Nair, Recent advances in N-heterocyclic carbene (NHC)-catalysed benzoin reactions, *Beilstein Journal of Organic Chemistry*. 12 (2016) 444–461. doi:10.3762/bjoc.12.47.
- [58] M. Alrayyani, O.Š. Miljanić, Benzoin and cyclobenzoin in supramolecular and polymer chemistry, *Chemical Communications*. 54 (2018) 11989–11997. doi:10.1039/C8CC07407K.

Graphical Abstract

