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Catalytic Y-tailed amphiphilic homopolymers – aqueous nanoreactors for high activity, low loading SCS pincer catalysts

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Abstract

A new amphiphilic homopolymer bearing an SCS pincer palladium complex has been synthesized by reversible addition fragmentation chain transfer polymerization. The amphiphile has been shown to form spherical and worm-like micelles in water by cryogenic transmission electron microscopy and small angle neutron scattering. Segregation of reactive components within the palladium containing core results in increased catalytic activity of the pincer compound compared to small molecule analogues. This allows carbon-carbon bond forming reactions to be performed in water with reduced catalyst loadings and enhanced activity.

Introduction

Palladium is one of the most widely used metals for catalysis of organic reactions and it is often employed in combination with different ligands for a variety of highly selective chemical transformations.¹ Like many other catalysts, it would be desirable to obtain a general protocol in order to perform reactions at low loadings with easy recovery, under ambient conditions (*i.e.* low temperatures, in air and/or water) and ideally at low catalyst loadings. In this direction, extensive research has been conducted on supported Pd using silica, polymers, carbon *etc.* to allow simple catalyst recovery and recyclability.²

Another approach for increasing catalyst efficiency is to perform reactions within self-assembled systems. This route has been investigated for both small molecule surfactants^{3–7} and amphiphilic polymers.^{8–11} Advantages of these self-assembled structures over non-supported systems include the segregation of reactive components in order to perform cascade reactions,^{12, 13} the ability to react hydrophobic substrates in water,⁸ increased local concentration of substrates^{14–18} and simple catalyst recovery.¹⁰ Recently, Uozumi and co-workers have shown that a nitrogen-carbon-nitrogen (NCN) pincer Pd-amphiphile was capable of self-assembling into vesicles and sequestering hydrophobic substrates into the catalytically active membrane. The substrates could then react within the membrane allowing the catalysis of non-water-soluble materials to take place in an overall aqueous medium.¹⁹ Unfortunately, neither recyclability nor increased activity (compared to reactions

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[†]Electronic Supplementary Information (ESI) available: Detailed experiment procedure for the synthesis of **1**, **2** and **3**. Details for characterization experiments of **1** and **2** by SANS and cryo-TEM. Synthetic procedure for catalysis experiments. See DOI: 10.1039/b000000x/

in organic solvents) was shown in this work. Herein we report the synthesis and self-assembly of a novel sulphur-carbon-sulphur (SCS) pincer Pd-nanoreactor in aqueous media, showing rate increases of > 100 times over small molecule non-self-assembled analogues, allowing for effective catalysis of a model cross-coupling reaction at significantly reduced catalyst loadings.

Experimental Section

Materials

All chemicals were used as received from Aldrich, Fluka, or Acros unless otherwise stated. *Tert*-butyl acrylate and styrene monomers were distilled over CaH₂ prior to use and stored at 5 °C. AIBN [azobisisobutyronitrile] was recrystallized twice from methanol and stored in the dark at 5 °C. DDMAT [S-dodecyl-S'-(α' , α' -dimethyl- α'' -acetic acid)] was synthesized as previously reported.²⁰ The SCS pincer ligand, **A** was synthesized using a modified literature preparation^{21–23} (see SI for full details).

Instrumentation

¹H NMR spectra were recorded on a Bruker DPX-400 spectrometer in CDCl₃. Chemical shifts are given in ppm downfield from tetramethylsilane (TMS). Size exclusion chromatography (SEC) measurements were conducted on a system comprised of a Varian 390-LC-Multi detector suite fitted with differential refractive index (DRI), light scattering (LS), and ultra-violet (UV) detectors and equipped with a guard column (Varian Polymer Laboratories PLGel 5 μ M, 50 $\times$ 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 μ M, 300 $\times$ 7.5 mm). The mobile phase was tetrahydrofuran with 5% triethylamine operating at a flow rate of 1.0 mL.min⁻¹, and samples were calibrated against Varian Polymer laboratories Easi-Vials linear poly(styrene) standards (162 - 2.4 $\times$ 10⁵ g.mol⁻¹) using Cirrus v3.3 software. Cryo-TEM samples (2 mg/mL in D₂O) were examined using a Jeol 2010F TEM operated at 200 kV and imaged using a GatanUltrascan 4000 camera. Images were captured using Digital Micrograph software (Gatan). A 3 μ L droplet the sample solution ambient temperature was added to a holey carbon-coated copper grid, and the grid was blotted to remove excess solution. Subsequently, the grid was plunged into liquid ethane to vitrify the sample. The temperature of the cryo stage was maintained below -170 °C, using liquid nitrogen, during imaging. Small Angle Neutron Scattering (SANS) experiments were conducted at ambient temperatures on the NG-7 30 m SANS instrument at the National Institute for Standards and Technology (NIST) Center for Neutron Research (NCNR) (Gaithersburg, MD, United States). Measurements were made using an incident neutron wavelength of 6.0 Å with a wavelength spread ($\Delta\lambda/\lambda$) of 0.12 and sample to detector distances of 1.0 m, 4.0 m, and 13.5 m. Additional low-q data were collected at a detector distance of 15.3 m using an incident neutron wavelength of 8.09 Å with $\Delta\lambda/\lambda = 0.12$ and focusing lenses. The total q-range used for these experiments was 0.001 Å⁻¹ < q < 0.6 Å⁻¹, where the scattering vector is defined as $q = 4\pi/\lambda \sin(\theta/2)$, and θ is the scattering angle. SANS data were reduced using the standard procedure provided by NIST. Samples were prepared at 2 mg/mL in D₂O.²⁴

SCS pincer chain transfer agent synthesis

S-dodecyl-S'-(α' , α' -dimethyl- α'' -acetic acid) (DDMAT) (0.580 g, 1.59 mmol) was dissolved in dichloromethane (*ca.* 20 mL) at 0 °C, under N₂. Then, *N*-(3-dimethyl-aminopropyl)-*N*-ethylcarbodiimide hydrochloride (0.308 g, 1.59 mmol) and 4-(dimethyl amino)pyridine (0.032 g, 0.27 mmol) were added, and the reaction mixture was stirred for 1 h. Next, **A** (0.712 g, 1.33 mmol) was added, and the reaction mixture was stirred at room temperature for 3 days. Finally, *N*-(3-dimethyl-aminopropyl)-*N*-ethylcarbodiimide hydrochloride (0.308 g, 1.59 mmol) and 4-(dimethyl amino)pyridine (0.032 g, 0.27 mmol)

were added to drive the reaction to completion, and the reaction mixtures stirred for an additional 2 days. The reaction mixture was extracted three times with a saturated brine solution, dried over magnesium sulphate, and filtered. The organic solution was removed *in vacuo*, and the crude product was purified *via* column chromatography using 40:1 petroleum ether:ethyl acetate. 1.17 g of **SCS Pincer CTA** (yellow solid) was recovered (78 % yield). ^1H NMR (CDCl_3): δ (ppm) 7.20 (s, 1H, Ar-*H*), 7.13 (s, 2H, Ar-*H*) 5.01 (s, 2H, Ar- CH_2O), 3.69 (s, 4H, $\text{SCH}_2\text{-Ar}$), 3.26 (t, $J = 7.6$ Hz, 2H, SCSCH_2), 2.40 (t, $J = 7.4$ Hz, 4H, SCH_2CH_2) 1.70 (s, 6H, $\text{C}(\text{CH}_3)_2$) 1.64 (tt, $J = 7.6, 7.2$ Hz, 2H, $\text{SCSCH}_2\text{CH}_2$), 1.50–1.60 (m, 4H, SCH_2CH_2), 1.35–1.18 (br m, 54H, $(\text{CH}_2)_9\text{CH}_3$), 0.88 (t, $J = 6.8$ Hz, 9H, CH_2CH_3). ^{13}C { ^1H } NMR (CDCl_3): δ (ppm) 221.2, 172.7, 139.2, 136.1, 129.1, 127.0, 67.4, 55.9, 37.0, 36.1, 32.0, 31.5, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 28.9, 27.9, 25.4, 22.7, 14.2. $\text{C}_{50}\text{H}_{90}\text{O}_2\text{S}_5$, Calc. C, 67.97; H, 10.27; O, 3.62; S, 18.15, Found C, 68.03; H, 10.39; O, 3.65; S, 17.93.

Polymerization of *tert*-butyl acrylate, **B**

SCS pincer CTA (0.094 g, 0.11 mmol), *t*-butyl acrylate (0.776 mL, 5.30 mmol), AIBN (1.7 mg, 0.011 mmol) and dioxane (0.776 mL) were added to a clean dry ampoule under N_2 (g). The solution was degassed *via* 3 freeze-pump-thaw cycles and heated to 65 °C for 2 hours under N_2 (g) with stirring. The viscous solution was dissolved in the minimum amount of THF, and the polymer was precipitated into 9:1 cold $\text{MeOH:H}_2\text{O}$. The $\text{MeOH:H}_2\text{O}$ solution was decanted, and the polymer was dissolved in THF. Then, the solution was dried over MgSO_4 and filtered, and the solvent removed *in vacuo*. 0.369 g of yellow polymer, **B** was recovered. $M_n^{\text{NMR}} = 6.9$ kDa, $M_n^{\text{SEC}} = 8.1$ kDa, $M_n/M_w^{\text{SEC}} = 1.07$. ^1H NMR (CDCl_3): δ (ppm) 7.20 (s, 1H, Ar-*H*), 7.14 (s, 2H, Ar-*H*), 5.05 (s, 2H, Ar- CH_2O), 3.68 (s, 4H, $\text{SCH}_2\text{-Ar}$), 3.33 (t, $J = 7.6$ Hz, 2H, SCSCH_2), 1.20–1.50 (br, $\text{C}(\text{CH}_3)_3$ polymer backbone), 1.30–2.30 (br, CH and CH_2 polymer backbone).

End group removal of poly(*tert*-butyl acrylate), **C**

Polymer **B** (0.36 g, 0.052 mmol), AIBN (0.003 g, 0.02 mmol), 1-ethylpiperidine hypophosphite (0.046 g, 0.26 mmol) and toluene (*ca* 5 mL) were added to a clean dry ampoule under N_2 (g). The reaction vessel was degassed *via* 5 freeze-pump-thaw cycles. The ampoule was filled with N_2 (g) and heated to *ca.* 100 °C for 12 hours. All volatiles were removed *in vacuo*, and the white solid was dissolved in a minimum volume of THF. The polymer was precipitated into $\text{MeOH:H}_2\text{O}$ 9:1 (*ca.* 100 mL). The solution was decanted from the solid polymer, and the polymer was re-dissolved in THF. Then, the solution was dried over MgSO_4 and filtered, and the solvent removed *in vacuo* to afford 0.26 g of a white polymer, **C**. ^1H NMR (CDCl_3): δ (ppm) 7.20 (s, 1H, Ar-*H*), 7.14 (s, 2H, Ar-*H*), 5.05 (s, 2H, Ar- CH_2O), 3.68 (s, 4H, $\text{SCH}_2\text{-Ar}$), 1.20–1.50 (br, $\text{C}(\text{CH}_3)_3$ polymer backbone), 1.30–2.30 (br, CH and CH_2 polymer backbone).

Complexation of poly(*tert*-butyl acrylate), **D**

Polymer **C** (0.250 g, 0.038 mmol), tetrakis(acetonitrile)palladium(II) tetrafluoroborate (50 mg, 0.11 mmol) and acetonitrile (*ca.* 15 mL) were added to a clean dry ampoule. The reaction vessel was degassed *via* 5 freeze-pump-thaw cycles. The ampoule was filled with N_2 (g) and stirred at room temperature for 2 days. The acetonitrile was removed *in vacuo*, and the polymer was re-dissolved in THF. After stirring for *ca.* 10 min, activated charcoal was added to remove the excess palladium. The solution was filtered, and the THF removed *in vacuo* affording a light orange solid, **D** that was used without further purification.

Deprotection of poly(*tert*-butyl acrylate) to form poly(acrylic acid), **1**

D (0.25 g, 0.038 mmol, mass used as estimate because previous product was used as crude) and trifluoroacetic acid (4.3 g, 37 mmol) were dissolved in CH₂Cl₂ (*ca.* 10 mL) at 0 °C. The solution was stirred at 0 °C for 60 mins then allowed to warm to room temperature overnight. All volatiles were removed under N₂ (g), and the remaining white solid was dissolved in THF:H₂O 1:1, transferred to a dialysis membrane tube (MWCO 1.0 kDa), and dialyzed against deionised water (3 L) with 7 water changes. Lyophilization resulted in 0.15 g of yellow solid, **1**. ¹H NMR (DMSO): δ (ppm) 12.50 (br, OH polymer backbone), 6.93 (s, 2H, Ar-*H*), 4.86 (br, 2H, Ar-CH₂O), 4.34 (br, 4H, SCH₂-Ar), 2.49-1.00 (br, CH and CH₂ polymer backbone).

Synthesis of poly(acrylic acid) polymer, **2**

Synthesis was repeated as for **1** but without the complexation step D. ¹H NMR (DMSO): δ (ppm) 12.50 (br, OH polymer backbone), 7.18 (s, 1H, Ar-*H*), 7.13 (s, 2H, Ar-*H*), 4.99 (s, 2H, Ar-CH₂O), 4.34 (br, 4H, SCH₂-Ar), 2.49-1.00 (br, CH and CH₂ polymer backbone).

Synthesis of alkyl pincer complex **3**

Dibromo-*m*-xylene (3.0 g, 11 mmol), 18-crown-6 (0.30, 1.4 g) and KOH (3.2 g, 57 mmol) were added to a Schlenk tube with THF (*ca.* 100 mL) at 0 °C under N₂ (g). Dodecanethiol (14 mL, 57 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 24 hours. The white precipitate that formed during the reaction was removed *via* filtration, and the reaction mixture was dried *in vacuo*. The product was dissolved in dichloromethane, and the organic solution was washed twice with sodium hydroxide (150 mL, 1M) and once with a saturated brine solution. The crude mixture was purified by column chromatography using 4:1 hexane:dichloromethane to afford 2.8 g of an off-white solid, **3a** (49% yield). ¹H NMR (CDCl₃): δ (ppm) 7.25-7.17 (m, 4H, Ar-*H*), 3.68 (s, 4H, SCH₂-Ar) 2.40 (t, 4H, J = 7.2 Hz, SCH₂CH₂) 1.55 (m, 4H, SCH₂CH₂) 1.25 (m, 36H, (CH₂)₉CH₃), 0.88 (t, 6H, J = 6.8 Hz, CH₂CH₃). ¹³C {¹H} NMR (CDCl₃): δ (ppm) 138.9, 129.3, 128.6, 127.4, 36.2, 31.9, 31.4, 29.7, 29.6, 29.6, 29.4, 29.3, 28.9, 22.7, 14.1. C₃₂H₅₈S₂ Calc. C, 75.82; H, 11.53; S, 12.65, Found C, 75.92; H, 11.49; S, 12.65.

3a (0.10 g, 0.20 mmol) and tetrakis(acetonitrile)palladium(II) tetrafluoroborate (0.105 g, 0.24 mmol) were dissolved in acetonitrile (*ca.* 10 mL). The stirred solution was purged with N₂ (g) for *ca.* 2 hours, sealed, and stirred for *ca.* 24 hours. Then, the solvent was removed *in vacuo* leaving a yellow precipitate. The solid was dissolved in the minimum amount of acetonitrile, to which ether was added dropwise forming a black precipitate. The solution was filtered, and the solvent removed *in vacuo*, affording 0.072 g of light brown flaky solid, **3** (50% yield). ¹H NMR (CDCl₃): δ (ppm) 7.04-6.94 (m, 3H, Ar-*H*), 4.22 (br, 4H, SCH₂-Ar) 3.13 (t, 4H, J = 7.2 Hz, SCH₂CH₂), 2.38 (s, br, 3H, PdNCCCH₃), 1.83 (tt, 4H, J = 7.6, 7.6 Hz, SCH₂CH₂), 1.25 (m, 36H, (CH₂)₉CH₃), 0.88, (6H, t, J = 6.8 Hz, CH₂CH₃). ¹³C {¹H} NMR (CDCl₃): δ (ppm) 149.1, 124.3, 122.3, 37.6, 30.9, 28.6, 28.6, 28.5, 28.3, 28.2, 27.6, 21.7, 13.1. C₃₂H₅₇PdS₂ HRMS: *m/z* 611.2945, [M-MeCN].²⁵

2 mol% catalyst loading using pincer compound **1**

3,4-Epoxy-1-butene (5.53 mg, 78.9 μmol), phenyl boronic acid (12.0 mg, 98.6 μmol) and caesium carbonate (55.7 mg, 157.8 μmol) were added to 0.7 mL of a D₂O stock solution of **1** (at a concentration of 10 mg/mL). Then, the solution was agitated at 25 °C. For kinetics experiments, samples were removed at predetermined times for analysis by ¹H NMR spectroscopy. Products were extracted twice with 1 mL CDCl₃ and analyzed by ¹H NMR spectroscopy (Fig. S6). Dimethyl formamide was used as an internal standard to determine

the reaction yield. For lower mol% experiments, the stock solutions of the assemblies were diluted accordingly.

2 mol% catalyst loading using pincer compound **3** in THF

3,4-Epoxy-1-butene (22.4 mg, 0.32 mmol), phenyl boronic acid (46.8 mg, 0.38 mmol) and caesium carbonate (226 mg, 0.64 mmol) were added to 0.66 mL of 10:1 THF:D₂O. Then, the solution was agitated at 25 °C. For kinetics experiments, samples were removed at predetermined times for analysis by ¹H NMR spectroscopy.

Results and Discussion

Preparation of SCS-pincer compounds

The structures of the SCS-pincer compounds are shown in Figure 1. A hydrophobic SCS-pincer functionalized reversible addition fragmentation chain transfer (RAFT) agent has been synthesized to afford amphiphilic homopolymers of hydrophobically end-functionalized poly(acrylic acid) (PAA) (**1** and **2**). The hydrophobicity of the SCS-pincer end group drives self-assembly and, at the same time, the pincer group is capable of complexation to Pd, making the polymer catalytically active. Upon self-assembly in water, polymer **1** will create confined catalytic hydrophobic pockets containing the active catalyst. Polymers **1** and **2** were synthesized by RAFT polymerization of *tert*-butyl acrylate followed by end group removal of the RAFT agent using 1-ethylpiperidine hypophosphite (EHP) and 2,2'-azo-*bis-iso*-butyronitrile (AIBN).²⁶ For polymer **1**, the end group removed *tert*-butyl acrylate polymer was complexed with Pd. Both the complexed and non-complexed *tert*-butyl acrylate polymers were then converted to poly(acrylic acid) polymer **1** and **2** respectively using established deprotection methods.^{22, 23, 27}

Analysis of self-assembled structure in water

Polymers **1** and **2** spontaneously self-assembled in water at 2 mg/mL as indicated by cryogenic-transmission electron microscopy (cryo-TEM) and Small Angle Neutron Scattering (SANS) (Fig. 2). The cryo-TEM images show the presence of both spherical and worm-like assemblies, both with a diameter of *ca.* 5 nm. In the cryo-TEM micrographs, it is likely that all contrast comes from the Pd-containing core, and the size-scale is consistent with the theoretical core diameter based on the volume of the aromatic ring and the alkyl chain length. The SANS data for **1** and **2** suggested both cylindrical micelles and aggregates of micelles. The modelling for both **1** and **2** suggested the cylinder radius and lengths were *ca.* 3–4 nm and 35–40 nm respectively with polydispersities consistent with the cryo-TEM images.

Catalytic activity of polymer **1** vs. small molecule **3**

The palladium catalyzed cross-coupling of boronic acids with unsaturated substitutes (Suzuki-Miyaura coupling) is an extremely important synthetic tool,²⁸ with specific examples of coupling to vinyl epoxides using Pd(II) having been previously reported.²⁹ To evaluate the effect of creating a catalytically active nanostructure, a small molecule analogue of **1** was also synthesized (**3**, Figure 1).^{28, 29} The catalytic activity of **1** and **3** were compared for the coupling reaction described in Scheme 1. Reagents were added simultaneously to the catalyst solution at 2 mol% and the mixture was agitated at 25 °C (note: for the micellar system was not necessary to pre-form the micelles in water and order of reagent addition did not effect the catalysis significantly). Samples from both reactions were removed at set times and analyzed by ¹H NMR spectroscopy in D₂O and CDCl₃ for **1** and **3** respectively in order to follow the reaction kinetics. The reaction rates of the benchmark catalyst **3** (at 2 mol %) in organic solvents were similar to previous literature (Fig. 3).^{29, 30} However, the self-

assembled structures of polymer **1** in water (also at 2 mol%) catalyzed the reaction approximately 100 times quicker than **3** in organic solvents (Fig. 3). For this reaction 100% conversion was reached in less than 20 minutes and facile separation of reactants and polymer supported catalyst was achieved by simple extraction with CDCl_3 (due to the poor solubility of PAA in this solvent). Under these conditions, isolated yields were quantitative and the products could be characterized after extraction without the need for further purification (see Figure S5 for crude ^1H NMR spectrum after extraction). Figure 3 shows that the ratio of product distribution remains constant throughout the reaction (6:7:1) (4:5*E*:5*Z*) for catalysis by **1**. As previously reported for similar systems, this selectivity shows a different product profile than the small molecule catalysts in organic solvents (typically 11:1:0.5),^{29, 30} which suggests that the product distribution is likely due to the reaction environment (aqueous vs. organic). The control reactions in water using **2** (a PAA-pincer amphiphile which self-assembled but without Pd complexation) or **3** (which was insoluble in water) under the same conditions showed no product formation after 24 hours. This result indicates that the nanostructures must be capable of sequestering the hydrophobic substrates and also have the active Pd-pincer complex to promote effective catalysis in water. The dramatic rate increase observed in our self-assembled system **1** compared to the small molecule reactions in organic solvents can be attributed to an increase in local concentration around the catalyst, driven by the hydrophobic concentrator effect.^{8, 14–16} This increase of rate compared to the previously reported nanoreactor vesicle system,³⁰ could be due to an increase in nanoreactor surface area (at a given polymer concentration) due to a reduced particle radius of spherical or cylindrical micelles compared to vesicles as well as the orientation in active site location. Since the active site is facing inward towards the hydrophobic membrane creates a more hydrophobic local environment.

Catalytic activity at different polymer concentrations (and Pd loadings)

The kinetics of the self-assembled catalytic system, **1**, were investigated as a function of catalyst loading by reducing the polymer concentration in solution (and hence micelle concentration). Figure 4 shows that even with 100 times less catalyst (0.02 mol %) the reaction is faster than **3** in organic solvents. However, under basic aqueous conditions the epoxide is prone to attack by hydroxide nucleophiles to form a diol, while Pd is known to catalyse this ring opening,³¹ the diol product was also observed in basic aqueous conditions in the absence of Pd (see SI). This side reaction is negligible for short reaction times but becomes significant at < 0.2 mol% catalysis. The side reaction can be monitored by NMR spectroscopy and the conversion adjusted accordingly, so that at < 0.2 mol% the reaction never reaches 100% (see Fig. 4 and SI). Despite the competing decomposition, turnover numbers (TON) of 872 (0.1 mol%) and 3500 (0.02 mol%) can be achieved (see SI). At 0.002 mol% (0.01 mg/mL of polymer) the reaction rate is significantly reduced because at this point the polymers do not form self-assembled structures, as confirmed by DOSY NMR spectroscopy (see SI),³² and hence are unable to sequester the hydrophobic starting materials. At polymer concentrations of 10, 1.0 and 0.5 mg/mL turn over frequencies (TOF) (at 30% conversion) of 7.2, 22.2 and 32.4 min^{-1} respectively were achieved. The later is *ca.* 1500 times greater than that of **3** (the small molecule catalyst) where the TOF (at 30%) was 0.022 min^{-1} . The increase of TOF with decreasing polymer concentration indicates that the initial rate of reaction is limited by the rate of substrate encapsulation into the core. For higher concentrations, there is an excess of active catalyst sites in the core with respect to substrates and therefore not all catalytic sites are continuously turning over substrates. At lower concentrations, there are less active sites, and therefore, each individual Pd center is working more efficiently.

Decoupling polymer concentration with Pd loading

In the previous section the catalyst loading (mol%) was reduced by decreasing the amount of polymer added to the reaction mixture. This changes two parameters for the catalytic system; the catalyst loading (mol%) and the concentration of micelles (mg/mL of polymer). In order to further reduce catalyst loadings while retaining high activity it would be desirable to decouple these two parameters i.e. to be able to reduce the mol% while retaining the same concentration of micelle forming polymer. In an attempt to decouple the micelle concentration from catalyst loading, reactions were performed with mixtures of **1** and **2**. It was hoped that by mixing these two polymers mixed micelles (micelles containing both **1** and **2**) would form. Using the same conditions as 0.1 mol% catalysis by **1**, the mass of **2** was added to give an equivalent polymer concentration to that in the 0.2 mol% experiment (i.e. the mass of each polymer added was roughly the same). Figure 5 shows kinetic data for reactions performed at 0.1 mol% by **1** and by **1** with unfunctionalized polymer **2**. The kinetics show that when polymer **2** is added to the reaction mixture the rate decreases. This could indicate that two discrete micellar aggregates are forming in solution; micelles made from **1** (catalytically active) and micelles made from **2** (not catalytically active). Both types of micelles are capable of sequestering starting material but only the micelles formed from **1** are able to promote catalysis. An analogous experiment performed with an excess of **2** compared to **1** (90% by weight) showed almost complete shutdown of catalysis, which is expected as they will be sequestering *ca.* 90% of the starting materials.

Recycling and degradation experiments

It is well known that these Pd-pincer complexes can leach out the Pd(II) species, forming highly catalytically active Pd(0). Weck^{33–35} and co-workers have studied this extensively and several reviews have been published on the subject.^{36, 37} Recently, Gebbink and van Koten³⁸ reported the first example of SCS-pincer Pd degradation under extremely mild reaction conditions, (e.g. low temperature, non-acidic, non-basic conditions) for the stannylation of cinnamyl chloride with hexamethylditin. This work suggests that the decomposition of such complexes is inherent to the catalytic cycle and not a result of harsh or inappropriate reaction conditions. Two common tests for evaluating the degree of leaching and its effect on the catalytic activity of the system are through the addition of Hg(0) or polyvinyl pyridine (PVP) to the reaction mixture. Both PVP and Hg(0) are known to selectively bind Pd(0), therefore removing it from the reaction mixture and preventing its involvement in catalysis.^{34, 35, 38, 39} Figure 6 shows that the addition of Hg(0) or PVP to the reaction mixture results in retardation of the reaction kinetics, for example at 0.2 mol% the reaction goes to completion after *ca.* 80 min, however with the addition of Hg(0) or PVP after an 80 min the reaction only proceeded to *ca.* 30% and 20% for Hg(0) and PVP respectively (see SI for full experimental details). Degradation of the Pd (II) site is supported by the decrease in activity upon recycling the catalyst by the addition of more starting materials after extraction of the products. Isothermal titration calorimetry (ITC) experiments confirmed this degradation and showed that *ca.* 40% of the catalyst has decomposed to Pd(0) following one cycle at 0.1 mol% (see SI).

Conclusions

The ability of palladium containing polymeric nanoreactors to sequester substrates due to the hydrophobic effect gives the opportunity to lower catalyst loadings while maintaining high catalytic activity. For this system, turnover numbers were increased significantly upon decrease in catalyst loading and this results in high efficiency reactions where TOFs of 32 min⁻¹ were achieved. Higher TON reactions were also achieved by further decreasing the catalyst concentration. It is possible that this is not the lower limit for catalytic loading; however, there are two limiting factors in this system: the ability to sequester hydrophobic

materials at low polymer concentrations and the degradation of the epoxide starting material in water. It has been confirmed that SCS-pincer ligands are not suitable for recycling experiments due to the formation of free Pd(0). However, if the incorporation of pincer ligands into hydrophobic nanopockets can be used to significantly reduce the loadings of otherwise relatively poor performing pincer catalysts, then recycling becomes much less important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Johansson Seechurn CC, Kitching MO, Colacot TJ, Snieckus V. *Angew. Chem. Int. Ed.* 2012; 51:5062–5085.
2. Molnar A. *Chem Rev.* 2011; 111:2251–2320. [PubMed: 21391571]
3. Dwars T, Paetzold E, Oehme G. *Angew. Chem. Int. Ed.* 2005; 44:7174–7199.
4. Trentin F, Scarso A, Strukul G. *Tetrahedron Lett.* 2011; 52:6978–6981.
5. Taşcıoğlu S. *Tetrahedron.* 1996; 52:11113–11152.
6. Manabe K, Iimura S, Sun X-M, Kobayashi S. *J. Am. Chem. Soc.* 2002; 124:11971–11978. [PubMed: 12358542]
7. Kunishima M, Kikuchi K, Kawai Y, Hioki K. *Angew. Chem. Int. Ed.* 2012; 51:2080–2083.
8. Cotanda P, Lu A, Patterson JP, Petzetakis N, O'Reilly RK. *Macromolecules.* 2012; 45:2377–2384.
9. Kim KT, Meeuwissen SA, Nolte RJ, van Hest JC. *Nanoscale.* 2010; 2:844–858. [PubMed: 20648280]
10. Liu Y, Wang Y, Wang Y, Lu J, Piñón V, Weck M. *J. Am. Chem. Soc.* 2011; 133:14260–14263. [PubMed: 21846087]
11. Bai Z, He Y, Young NP, Lodge TP. *Macromolecules.* 2008; 41:6615–6617.
12. Vriezema DM, Garcia PML, Sancho ON, Hatzakis NS, Kuiper SM, Nolte RJM, Rowan AE, van Hest JCM. *Angew. Chem. Int. Ed.* 2007; 46:7378–7382.
13. van Dongen SFM, Nallani M, Cornelissen JJLM, Nolte RJM, van Hest JCM. *Chem. Eur. J.* 2009; 15:1107–1114. [PubMed: 19072950]
14. Helms B, Liang CO, Hawker CJ, Fréchet JMJ. *Macromolecules.* 2005; 38:5411–5415.
15. Manabe K, Iimura S, Sun XM, Kobayashi S. *J. Am. Chem. Soc.* 2002; 124:11971–11978. [PubMed: 12358542]
16. Ievins AD, Wang XS, Moughton AO, Skey J, O'Reilly RK. *Macromolecules.* 2008; 41:2998–3006.
17. Lu A, Cotanda P, Patterson JP, Longbottom DA, O'Reilly RK. *Chem. Commun.* 2012; 48:9699–9701.
18. Cotanda P, O'Reilly RK. *Chem. Commun.* 2012; 48:10280–10282.

19. Hamasaka G, Muto T, Uozumi Y. *Dalton Trans.* 2011; 40:8859–8868. [PubMed: 21837316]
20. Skey J, O'Reilly RK. *Chem. Commun.* 2008;4183–4185.
21. Meijer MD, Mulder B, van Klink GPM, van Koten G. *Inorg. Chim. Acta.* 2003; 352:247–252.
22. Moughton AO, Stubenrauch K, O'Reilly RK. *Soft Matter.* 2009; 5:2361–2370.
23. Moughton AO, O'Reilly RK. *J. Am. Chem. Soc.* 2008; 130:8714–8725. [PubMed: 18549205]
24. Kline SR. *J. Appl. Crystallogr.* 2006; 39:895–900.
25. The expected mass for compound 3 minus the acetonitrile ligand.
26. Willcock H, O'Reilly RK. *Polym. Chem.* 2010; 1:149–157.
27. Ma QG, Wooley KL. *J. Polym. Sci., Part A: Polym. Chem.* 2000; 38:4805–4820.
28. Miyaura N, Suzuki A. *Chem. Rev.* 1995; 95:2457–2483.
29. Kjellgren J, Aydin J, Wallner OA, Saltanova IV, Szabó KJ. *Chem. Eur. J.* 2005; 11:5260–5268. [PubMed: 15991208]
30. Hamasaka G, Muto T, Uozumi Y. *Angew. Chem. Int. Ed.* 2011; 50:4876–4878.
31. Trost BM, McEachern EJ. *J. Am. Chem. Soc.* 1999; 121:8649–8650.
32. Bakkour Y, Darcos V, Li S, Coudane J. *Polym. Chem.* 2012; 3:2006–2010.
33. Sommer WJ, Yu K, Sears JS, Ji Y, Zheng X, Davis RJ, Sherrill CD, Jones CW, Weck M. *Organometallics.* 2005; 24:4351–4361.
34. Yu K, Sommer W, Richardson JM, Weck M, Jones CW. *Adv. Synth. Catal.* 2005; 347:161–171.
35. Yu K, Sommer W, Weck M, Jones CW. *J. Catal.* 2004; 226:101–110.
36. Weck M, Jones CW. *Inorg. Chem.* 2007; 46:1865–1875. [PubMed: 17348717]
37. Phan NTS, Van Der Sluys M, Jones CW. *Adv. Synth. Catal.* 2006; 348:609–679.
38. Pijnenburg NJM, Dijkstra HP, van Koten G, Gebbink RJMK. *Dalton Trans.* 2011; 40:8896–8905. [PubMed: 21731937]
39. Selander N, Szabo KJ. *Chem Rev.* 2011; 111:2048–2076. [PubMed: 21087012]

Figure 1. SCS pincer complexes, (1) amphiphilic Pd-pincer complex polymer, (2) non- complexed amphiphilic pincer polymer and (3) small molecule Pd-pincer complex.

Figure 2.
Cryo-TEM image (left) and SANS data with fit (right) of **1** in D₂O at 2 mg/mL.

Figure 3. Conversion vs. time data for catalysis by **1** (left) and **3** (right) at 2 mol%, showing the distribution of products and the total conversion.

Figure 4. Conversion against time data for catalysis by **1** (solid lines) at different loadings and **3** (dashed line) at 2 mol%, showing the total (4 + 5E + 5Z) conversion.

Figure 5.

Conversion vs. time data for catalysis by **1** and **1** with added polymer **2** at 0.1 mol% showing the total conversion. The data shows that when polymer **2** added to the reaction mixture the rate decreases.

Figure 6.

Conversion vs. time data for catalysis by **1** at 0.2 mol% showing the total conversion for the initial run, the recycled polymer and the Hg drop test.

Scheme 1.

SCS Pd-pincer catalyzed cross-coupling of vinyl epoxide with phenylboronic acid to afford branched (4) and linear (5) alcohols.