

# Highly Crosslinked and Clickable Poly(divinylbenzene) Microspheres by Type II Photoinitiated Precipitation Polymerisation

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(This paper is dedicated to the memory of Prof. Niyazi Bicak)

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CuAAC, click chemistry)

## Abstract

A new method for the synthesis of highly crosslinked and in-situ alkyne functionalised microspheres, by combining type II photoinitiation with precipitation polymerisation, is reported. **Using a benzophenone-tertiary amine initiation system**, the method allows the preparation of functional microspheres at room temperature by UV irradiation in the absence of stabilisers or surfactants of any kind. To demonstrate the presence and accessibility of the alkyne moiety on the polymer particles, fluorescent pyrene groups are attached to the microspheres by copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click reaction, using 1-azidomethyl pyrene (Py-N<sub>3</sub>) as a model compound. FTIR, fluorescence spectroscopy, fluorescence microscopy, and scanning electron microscopy (SEM) are used for characterisation of the particles and to monitor the click reaction.

## 1. Introduction

Highly crosslinked polymer microspheres have been extensively investigated due to their great potential in materials science.<sup>[1-6]</sup> Among various preparation methods for obtaining such particles, precipitation polymerisation (PP) is arguably the most popular due to its easy operation, and highly crosslinked microspheres with clean surfaces can routinely be prepared in the absence of a surfactant or stabiliser by this method.<sup>[7]</sup> So far, distillation precipitation polymerisation,<sup>[8]</sup> and photoinitiated precipitation polymerisation,<sup>[9-12]</sup> which are based on the conventional free radical polymerisation mechanism, have been developed for the preparation of uniform and cross-linked spherical polymer particles. More recently, reversible-deactivation radical polymerisations, including atom transfer radical polymerisation (ATRP),<sup>[13, 14]</sup> reversible addition-fragmentation chain transfer (RAFT),<sup>[15]</sup> and iniferter polymerisation<sup>[16]</sup> are successfully combined with precipitation polymerisation for the synthesis of highly crosslinked and micron-size polymer microspheres with “living” chain ends on their surfaces.

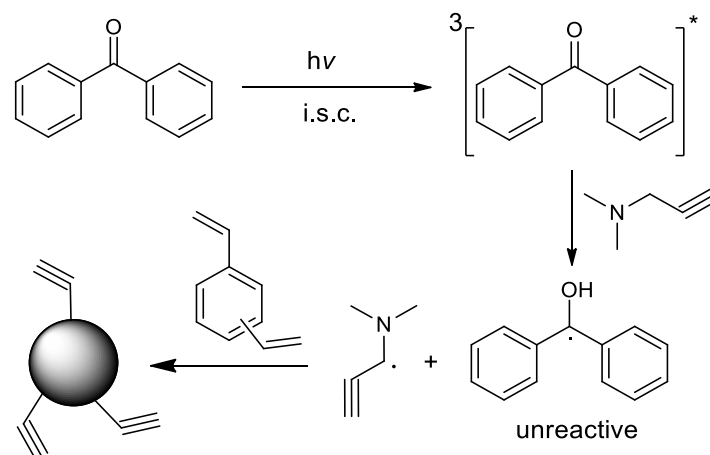
Photopolymerisations have some unique advantages such as spatial and temporal control simply by switching on and off the light source. Moreover, they generally require less energy compared to their thermal initiated analogues, due to being conducted at room temperature. Depending on their radical generation mechanism, photoinitiators can be classified as Type I and Type II, where Type I photoinitiators are unimolecular photoinitiators that undergo a homolytic bond cleavage upon absorption of light. Type II initiators are on the other hand, two component systems where the singlet excited state of a photoinitiator undergoes intersystem crossing to form triplet states upon irradiation and abstract hydrogen from co-initiators, such as amines, thiols, carbazoles, alcohols and ethers, to form radicals that initiate polymerisation.<sup>[17-22]</sup> **In principle, various commercially available alcohols, tertiary amines and thiols can be used as hydrogen donors in type II photoinitiation.**

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Functionalisation of polymer particles is of great importance for their application, and polyDVB microspheres prepared by precipitation polymerisation have unreacted double bonds on their surface allowing their post functionalisation.<sup>[23]</sup> Hydrobromination and hydroboration/oxidation followed by esterification reactions have been employed for the modification of residual double bonds on the microspheres with ATRP initiator, allowing their surface modification by “grafting from” approach via surface initiated ATRP.<sup>[24, 25]</sup> Unreacted vinyl groups on the particle surface also allow the synthesis of microspheres with core-shell structures by two stage precipitation polymerisation.<sup>[26-28]</sup> Use of a RAFT agent in precipitation polymerisation allows the synthesis of microspheres with RAFT groups at the chain ends that enable their further functionalisation by hetero Diels-Alder chemistry.<sup>[29]</sup> The click reactions, particularly Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC), have attracted great interest due to their high specificity and nearly quantitative yields in the presence of other functional groups.<sup>[30, 31]</sup> CuAAC reaction has been widely employed for functionalisation of polymers as well as the functionalisation of microspheres.<sup>[32-35]</sup> For instance, residual double bonds on the polymer microspheres are brominated by hydrobromination reaction. Azide functionality is then introduced to the microspheres by azidation of bromine end groups prior to their click modification with alkyne functional pyrene to yield fluorescent particles.<sup>[36]</sup> In another report, 1- azido-undecane-11-thiol was reacted with residual double bonds on the microspheres via the thiol-ene reaction, for the introduction of azide functionality to the microspheres prior to their coupling with an alkyne terminated polymer via CuAAC click chemistry.<sup>[37]</sup> CuAAC clickable macroporous microspheres are also prepared by sequential HBr addition and by bromo-azide substitution, or Br<sub>2</sub> addition followed by double elimination.<sup>[38]</sup> The above examples illustrate the necessity of polymer modification prior to their functionalisation with CuAAC click chemistry.

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Herein, a simple one pot and one step synthetic strategy is reported for the preparation of highly crosslinked microspheres with click functionality. In this approach, a tertiary amine with acetylene functionality, namely 3-dimethylamino-1-propyne (DAP), is used in combination with benzophenone as a bimolecular photoinitiation system. Py-N<sub>3</sub> is then attached onto polymer particles by “Click Chemistry” to show the presence and accessibility of the alkyne groups on the polymer microspheres. **The reaction operates at room temperature and it benefits from the inherent characteristic of precipitation polymerisation, in that there is no need for a stabiliser or surfactant of any type.** To the best of our knowledge, this is the first report combining type II photoinitiation with precipitation polymerisation for the synthesis of highly crosslinked microspheres.

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Type-II photoinitiation is employed to precipitation polymerisation by simply replacing conventional one component initiator with bimolecular initiator system using DPA and benzophenone as hydrogen donor and photoinitiator, respectively. **Inspired by the successful use of photoinitiation in precipitation polymerisation, DVB is deliberately chosen as the crosslinker since the UV absorption of DVB in acetonitrile does not overlap with the wavelength of UV irradiation (350 nm).<sup>[9]</sup> Tertiary amine/benzophenone type II photoinitiation system proceeds via electron transfer upon electron excitation of benzophenone with a subsequent proton transfer.** When irradiated, benzophenone undergoes intersystem crossing to form excited triplet states. Radicals are then formed by hydrogen abstraction of excited benzophenone from DPA, followed by free radical polymerisation that is analogous to conventional precipitation polymerisation. Highly crosslinked and narrow disperse microspheres with alkyne functional groups are synthesised in the absence of any stabilisers or surfactants at room temperature by this method. The overall mechanism of particle formation is illustrated in **Scheme 1**.

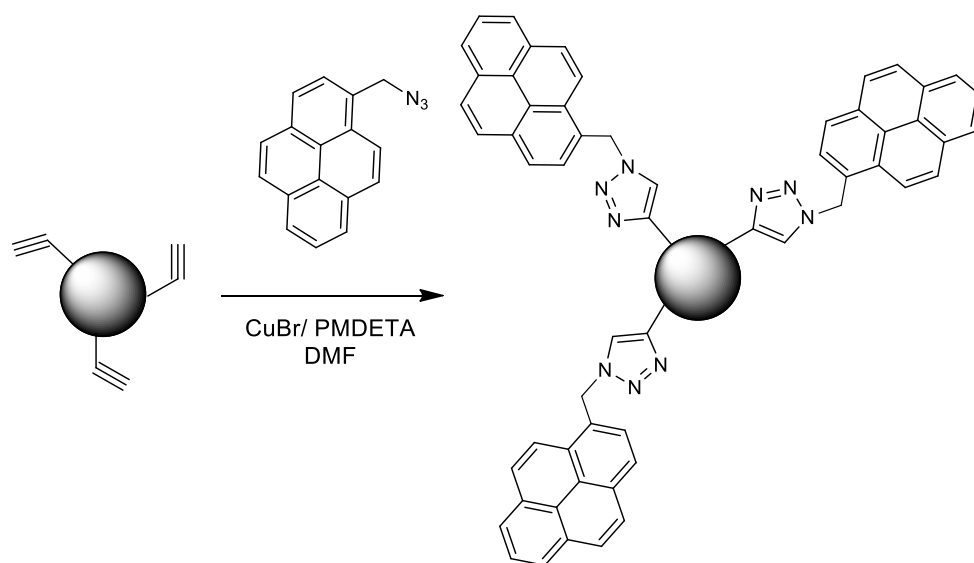


**Scheme 1.** Synthesis of clickable polyDVB microspheres by type-II photoinitiated free radical precipitation polymerisation.

The co-initiator component of the bimolecular initiation system is deliberately used in excess with respect to benzophenone (10:1 by mole) for increasing the amount of the incorporated alkyne functionality to the microspheres by increasing the possibility of radical formation from different DAP molecules. Initial experiments were carried out at 2% monomer concentration (vol% wrt total volume of reaction medium), which is typical for precipitation polymerisation and the overall reaction yield was low (8%). Photoinitiated precipitation polymerisation allows the preparation of uniform particles at higher monomer concentrations, therefore the following experiments were carried out at around 4% monomer concentration to increase the amount of isolated material.<sup>[9]</sup> As in other precipitation polymerisation systems, the reaction medium was homogenous in the beginning and it became heterogeneous as the reaction proceeds, due to the formation of insoluble oligomers. The monomer to particle conversion was almost linear during 48 hours of reaction (2%, 6% and 11% for 8 h, 24 h, and 48 h, respectively), which is in parallel with the results obtained by one component photoinitiated precipitation polymerisation. When the polymerisation is further continued, a decrease in the rate of conversion was observed (18% and 19% for 72 h and 96 h, respectively) which might be attributed to the inefficient irradiation of reaction mixture due to the formation of milky suspension. The kinetic of the overall reaction

is relatively slow compared to thermally and redox initiated polymerisation, which might also be attributed to the formation of milky suspension as the reaction proceeds. Once the oligomers start to form and precipitate out from the solution, only the molecules closer to the surface of the reaction tube absorbs light efficiently, while other molecules at the inner part of the reaction vessel cannot be irradiated efficiently due to the blocking effect.

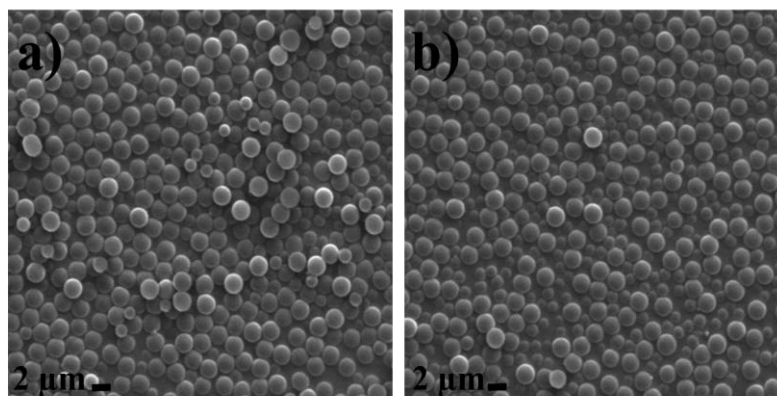
Py-N<sub>3</sub> is deliberately selected as the other click component for the functionalisation of the microspheres since it enables the efficient characterisation of crosslinked particles through its fluorescent properties. Thus, 1-(bromomethyl)pyrene is converted to Py-N<sub>3</sub> simply by azidation processes. Then, CuAAC reaction between propargyl moieties of the microspheres and Py-N<sub>3</sub> is conducted in DMF using copper(I)bromide (CuBr) and N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA) to attach fluorescent pyrene groups onto the microspheres (**Scheme 2**).



**Scheme 2.** Synthesis of pyrene-functionalised PDVB microspheres via click chemistry.

SEM images of the particles reveal that the microspheres obtained by this method are coagulum free and have number-average diameter of 1.81  $\mu\text{m}$  (weight-average diameter: 1.89  $\mu\text{m}$  and polydispersity index: 1.044) (**Figure 1a**). The size of the particles is slightly bigger than those

prepared by conventional one component photoinitiation method under similar conditions.<sup>[9]</sup> This might be attributed to the use of co-initiator component of the type II photoinitiation system in slightly higher amounts compared to the conventional photopolymerisation. Initiator concentration is known to have an impact on the particle size and reaction yield in conventional precipitation polymerisation and the size of the particles generally increase as the initiator concentration increases.<sup>[39]</sup> Smaller particles having diameters around 1  $\mu\text{m}$  are also observed, which can be explained by secondary nucleation of the particle growth during photopolymerisation. Particle size remained same after functionalisation with pyrene units, likely due to using a relatively small molecule for functionalisation (**Figure 1b**). Covalent attachment of bigger molecules such as polymers onto the polymer microspheres results in an increase in particle size.<sup>[13]</sup>

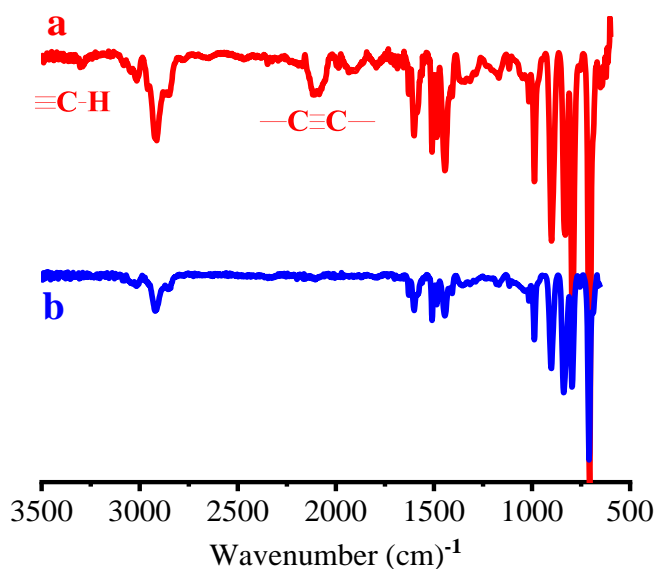


**Figure 1.** SEM images of the clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub>.

FT-IR analysis is used to confirm the presence of alkyne groups in the polymer microspheres (**Figure 2**). The alkyne group on the polymer microspheres is proven by the presence of the characteristic stretching vibration bands appearing at 3277 and 2121  $\text{cm}^{-1}$ , which refer to C-H single bond and C $\equiv$ C triple bond, respectively (**Figure 2a**). The clear observation of these peaks in the spectrum of the microspheres can be attributed to the use of alkyne functional initiator in relatively high amounts, which further confirms the bimolecular initiation mechanism for the

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polymer synthesis (The mole ratio of [DVB-80]:[DPA] = [10]:[1]). As is seen in **Figure 2b**, these peaks disappear completely after CuAAC reaction, confirming the success of functionalisation of microspheres by click chemistry. It is important to note that the use of a functional monomer possessing a vinyl group in conventional precipitation polymerization results in a decrease in crosslinking density of the particles, whereas in the current approach, crosslinking density of the particles doesn't change since functionalisation is introduced by the initiator used.

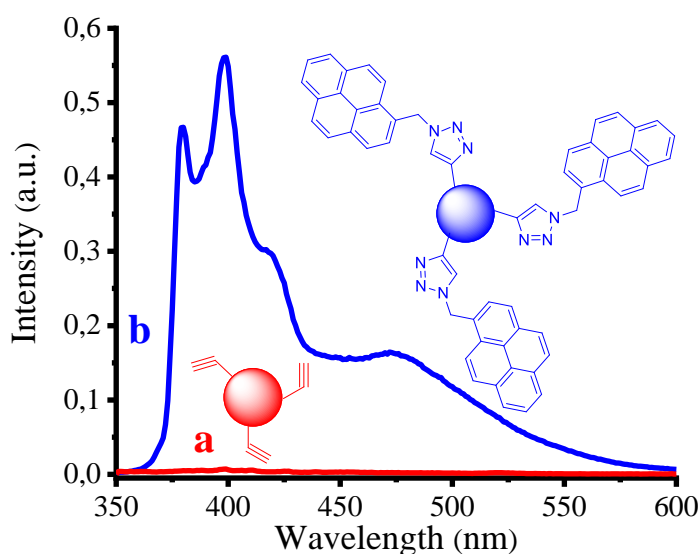


**Figure 2.** FT-IR spectra of clickable PDVB microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub>.

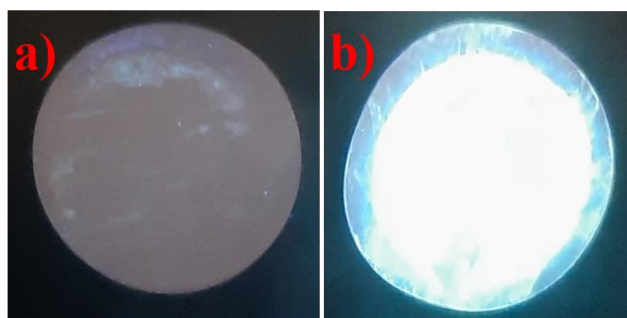
The fluorescence properties of the microspheres were also studied to further confirm the presence and accessibility of the alkyne functionality on the particles. **Figure 3** shows the fluorescence emission spectra of the microspheres before and after click reaction recorded in CHCl<sub>3</sub>. As can be seen, particles show no fluorescence emission before functionalisation with Py-N<sub>3</sub> (**Figure 3a**). Peaks appearing at 379 nm and 400 nm correspond to characteristic monomer fluorescence emission of the pyrene, confirming the presence of pyrene group



(Figure 3b). A broader emission band observed at 472 nm corresponds to the excimer fluorescence of the pyrene, indicating the spatial proximity of fluorophores on the polymer network.<sup>[40, 41]</sup> Figure 4 shows a physical observation of the fluorescence properties of clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> under UV irradiation using a 366 nm lamp. It can clearly be seen that particles become highly fluorescent after the incorporation of pyrene moiety via click reaction.

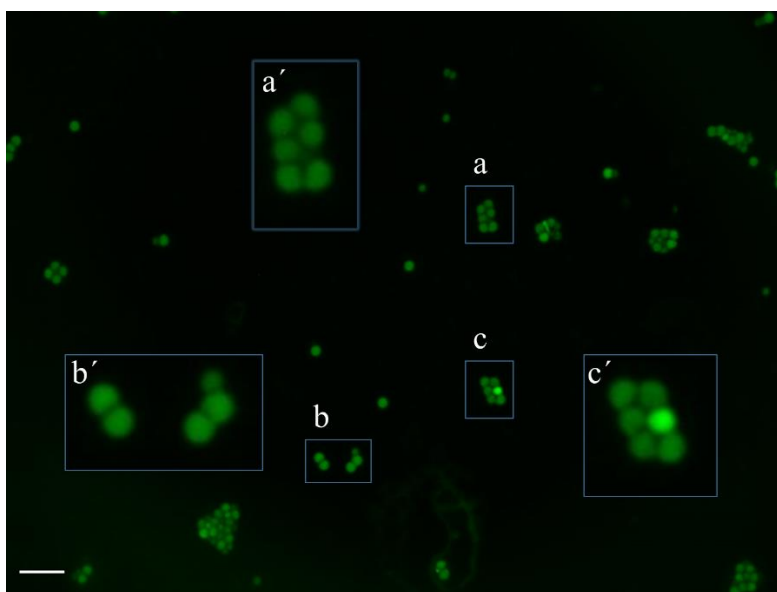


**Figure 3.** Fluorescence spectra of clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> in CHCl<sub>3</sub> at room temperature.



**Figure 4.** Photographs of clickable polyDVB microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> under irradiation with a 366-nm UV lamp.

1 Attachment of the pyrene group onto the polymer microspheres is further supported by  
2 fluorescence microscopy. **Figure 5** shows the fluorescence microscope images of the particles  
3 after functionalisation of the particles by CuAAC reaction. As can be seen, microspheres  
4 become fluorescent after the attachment of pyrene groups and their fluorescence intensities are  
5 similar, suggesting the uniform distribution of alkyne moieties on the precursor individual  
6 polymer particles.  
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35 **Figure 5.** Fluorescence images of the microspheres after functionalisation with pyrene group  
36 (a, b, c) and their corresponding 3X magnified images (a', b', c'). The scale bar corresponds  
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38 to 10 microns.  
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## 44 2. Conclusion

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47 Type II photoinitiation is employed to precipitation polymerisation for the first time to yield  
48 highly cross-linked and spherical polyDVB particles with click functionality. The method  
49 offers a one-step method for the preparation of alkyne functionalised microspheres. In addition,  
50 crosslinking density of the particles doesn't change since functionalisation is introduced by the  
51 initiator used. It is important to note that Type II photoinitiating systems include but are not  
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1 limited to benzophenone and tertiary amine system. By simply replacing the co-initiator with  
2 different hydrogen donors, various alcohols, thiols and other tertiary amine derivatives can be  
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4 incorporated into the polymer matrix in one step. Further studies in this line as well as the  
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6 detailed investigation on the type II photoinitiated precipitation polymerisation kinetics are now  
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8 in progress.  
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### 10 11 12 3. Experimental Section/Methods

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14 *Materials:* Divinylbenzene (DVB-80, technical grade, Aldrich) consisting of 80%  
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16 divinylbenzene isomers was purified by passing through a basic alumina column to remove  
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18 inhibitor. 3-Dimethylamino-1-propyne (DAP, 97%, Aldrich), 1-(bromomethyl)pyrene (98%,  
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20 Aldrich), sodium azide ( $\text{NaN}_3 \geq 99.5\%$ , Aldrich), copper(I) bromide (CuBr, Aldrich, 99%),  
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22 benzophenone ( $\geq 99\%$ , Aldrich), acetonitrile (ACN, 99%, Aldrich), N, N-dimethylformamide  
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24 (DMF, 99.8%, Aldrich), N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA, 99%,  
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26 Aldrich), acetone (99%, Aldrich), were used as received.  
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33 *Methods:* Photopolymerisations were carried out at room temperature using a photoreactor  
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35 equipped with 6 lamps (General Electric T5 F8W blacklight) emitting light from 320 nm to 400  
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37 nm with an average wavelength of 365 nm and with a light intensity of  $3.0 \text{ mW cm}^{-2}$ .  
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39 Fluorescence spectra was recorded using Varian Cary eclipse fluorescence spectrophotometer  
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41 (Mulgrave, Australia). Polymer particles were suspended in chloroform ( $5 \mu\text{g/ml}$ ) and were  
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43 irradiated ( $\lambda_{\text{ex}} = 320 \text{ nm}$ ) in quartz cuvette. FT-IR spectra were recorded on a 4500 Series  
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45 Agilent ATR FT-IR spectrometer performing 64 scans for each sample, operating in the range  
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47  $4700\text{--}650 \text{ cm}^{-1}$ , with a resolution of  $2 \text{ cm}^{-1}$  and the number of scans set to 4. The fluorescence  
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49 image was acquired with an upright Nikon Eclipse LV100 microscope with a  $50\times$  ( $\text{NA} = 0.55$ )  
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51 ELWD objective and a CoolSNAP HQ monochrome camera. A false green color was then  
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53 applied to the image using ImageJ software. SEM analyses were performed on a Cambridge  
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Instruments Stereoscan 90 scanning electron microscope. Samples were sputter-coated with gold using a Polaron SC500A Sputter Coater for 4 minutes under argon. Image analyses of the SEM micrographs were performed using Image J47 software, on a population of 100 microspheres. The following equations were used to determine the particle sizing characteristics:

$$U = \frac{D_w}{D_n}; D_n = \sum_{i=1}^k (n_i D_i) / \sum_{i=1}^k (n_i); D_w = \sum_{i=1}^k (n_i D_i^4) / \sum_{i=1}^k (n_i D_i^3)$$

where U is the polydispersity index,  $D_n$  is the number-average diameter,  $D_w$  is the weight-average diameter, N is the total number of the measured particles, and  $D_i$  is the particle diameters of the microspheres.

*Synthesis of Clickable Microspheres:* To a borosilicate Kimax tube was added DVB-80 (976 mg, 1068 mL, 7.5 mmol), benzophenone (14 mg, 75  $\mu$ mol), DAP (62 mg, 0.75 mmol), and MeCN (24 mL), and the mixture was ultrasonicated for two minutes until a clear solution was obtained. Then, the mixture is purged with nitrogen gas for 10 minutes prior to sealing of the reaction vessel. The sealed tube was then placed into a low profile roller operating at 60 rpm and irradiated from a photoreactor equipped with 6 lamps that emits light at 365 nm, with a light intensity of 3.0 mW  $\text{cm}^{-2}$  for 72 hours. The polymer microspheres were isolated from the reaction media by vacuum filtration on a 0.45  $\mu$ m nylon membrane filter, and washed sequentially with MeCN (50 mL) and acetone (50 mL). Finally, the product was dried overnight in a vacuum oven (60  $^{\circ}$ C, 50 mbar) to constant mass (yield: 18%).

*Synthesis of 1-azidomethyl pyrene (Py-N<sub>3</sub>):* The synthesis of Py-N<sub>3</sub> is adapted from the literature.<sup>[42]</sup> 1-(Bromomethyl)pyrene (118 mg, 0.4 mmol) and (78 mg, 1.2 mmol) was dissolved in 8 mL DMF under a nitrogen atmosphere and the reaction mixture was stirred for 2 days at 65  $^{\circ}$ C. After extraction of the product with  $\text{CH}_2\text{Cl}_2$ /water, the organic layer was dried with anhydrous  $\text{MgSO}_4$  and solvent was evaporated with a rotary evaporator. The oily yellow

product was dried under vacuum (yield: 48%). (H NMR: (300 MHz, CDCl<sub>3</sub>): δH 4.97 (s, 2H);  
7.80–8.22 (m, 9H)).

*Modification of the Microspheres by CuAAC Click Reaction:* In a typical click reaction, alkyne functional microspheres (20 mg), CuBr (14 mg, 0.1 mmol), PMDETA (17 μL, 0.1 mmol), 1-(azidomethyl)pyrene (26 mg, 0.1 mmol) and 5 mL of DMF were placed in a Schlenk tube. The reaction mixture was degassed by three freeze–pump–thaw cycles and stirred at 40 °C for 24 hours. After the click reaction, the polymer microspheres were isolated from the reaction media by vacuum filtration on a 0.45 μm nylon membrane filter, and washed sequentially with water (100 mL) and acetone (100 mL). Finally, the product was dried overnight in a vacuum oven (60 °C, 50 mbar) to constant mass.

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## Highly Crosslinked and Clickable Poly(divinylbenzene) Microspheres by Type II Photoinitiated Precipitation Polymerization

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(This paper is dedicated to the memory of Prof. Niyazi Bicak)

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### Abstract

A new method for the synthesis of highly crosslinked and in-situ alkyne functionalized microspheres, by combining type II photoinitiation with precipitation polymerization, is reported. Using a cheap and readily available benzophenone-tertiary amine initiation system, the method allows the preparation of functional microspheres at room temperature by UV irradiation in the absence of stabilizers or surfactants of any kind. To demonstrate the presence and accessibility of the alkyne moiety on the polymer particles, fluorescent pyrene groups are attached to the microspheres by copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click reaction, using 1-azidomethyl pyrene (Py-N<sub>3</sub>) as a model compound. FTIR, fluorescence spectroscopy, fluorescence microscopy, and scanning electron microscopy (SEM) are used for characterization of the particles and to monitor the click reaction.

## 1. Introduction

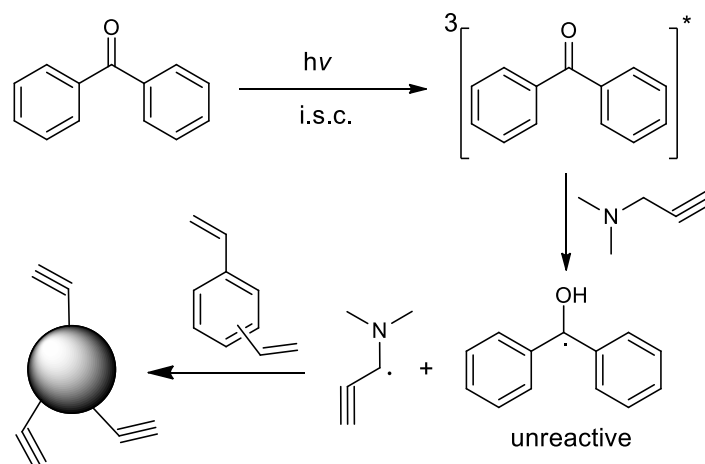
Highly crosslinked polymer microspheres have been extensively investigated due to their great potential in materials science.<sup>[1-5]</sup> Among various preparation methods for obtaining such particles, precipitation polymerization (PP) is arguably the most popular due to its easy operation, and highly crosslinked microspheres with clean surfaces can routinely be prepared in the absence of a surfactant or stabilizer by this method.<sup>[6]</sup> So far, distillation precipitation polymerization,<sup>[7]</sup> and photoinitiated precipitation polymerization,<sup>[8, 9]</sup> which are based on the conventional free radical polymerization mechanism, have been developed for the preparation of uniform and cross-linked spherical polymer particles. More recently, reversible-deactivation radical polymerizations, including atom transfer radical polymerization (ATRP),<sup>[10, 11]</sup> reversible addition-fragmentation chain transfer (RAFT),<sup>[12]</sup> and iniferter polymerization<sup>[13]</sup> are successfully combined with precipitation polymerization for the synthesis of highly crosslinked and micron-size polymer microspheres with “living” chain ends on their surfaces.

Photopolymerizations have some unique advantages such as spatial and temporal control simply by switching on and off the light source. Moreover, they generally require less energy compared to their thermal initiated analogues, due to being conducted at room temperature. Depending on their radical generation mechanism, photoinitiators can be classified as Type I and Type II, where Type I photoinitiators are unimolecular photoinitiators that undergo a homolytic bond cleavage upon absorption of light. Type II initiators are on the other hand, two component systems where the singlet excited state of a photoinitiator undergoes intersystem crossing to form triplet states upon irradiation and abstract hydrogen from co-initiators, such as amines, thiols, carbazoles, alcohols and ethers, to form radicals that initiate polymerization.<sup>[14-19]</sup> Compared to conventional Type I photoinitiators, Type II photoinitiators have unique advantages such as being cheap, commercially available and safer to handle.

Functionalization of polymer particles is of great importance for their application, and polyDVB microspheres prepared by precipitation polymerization have unreacted double bonds on their surface allowing their post functionalization.<sup>[20]</sup> Hydrobromination and hydroboration/oxidation followed by esterification reactions have been employed for the modification of residual double bonds on the microspheres with ATRP initiator, allowing their surface modification by “grafting from” approach via surface initiated ATRP.<sup>[21, 22]</sup> Unreacted vinyl groups on the particle surface also allows the synthesis of microspheres with core-shell structures by two stage precipitation polymerization.<sup>[23-25]</sup> Use of a RAFT agent in precipitation polymerization allows the synthesis of microspheres with RAFT groups at the chain ends that enable their further functionalization by hetero Diels-Alder chemistry.<sup>[26]</sup> The click reactions, particularly Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC), have attracted great interest due to their high specificity and nearly quantitative yields in the presence of other functional groups.<sup>[27, 28]</sup> CuAAC reaction has been widely employed for functionalization of polymers as well as the functionalization of microspheres.<sup>[29-32]</sup> For instance, residual double bonds on the polymer microspheres are brominated by hydrobromination reaction. Azide functionality is then introduced to the microspheres by azidation of bromine end groups prior to their click modification with alkyne functional pyrene to yield fluorescent particles.<sup>[33]</sup> In another report, 1- azido-undecane-11-thiol was reacted with residual double bonds on the microspheres via the thiol-ene reaction, for the introduction of azide functionality to the microspheres prior to their coupling with an alkyne terminated polymer via CuAAC click chemistry.<sup>[34]</sup> CuAAC clickable macroporous microspheres are also prepared by sequential HBr addition and by bromo-azide substitution, or Br<sub>2</sub> addition followed by double elimination.<sup>[35]</sup> The above examples illustrate the necessity of polymer modification prior to their functionalization with CuAAC click chemistry.

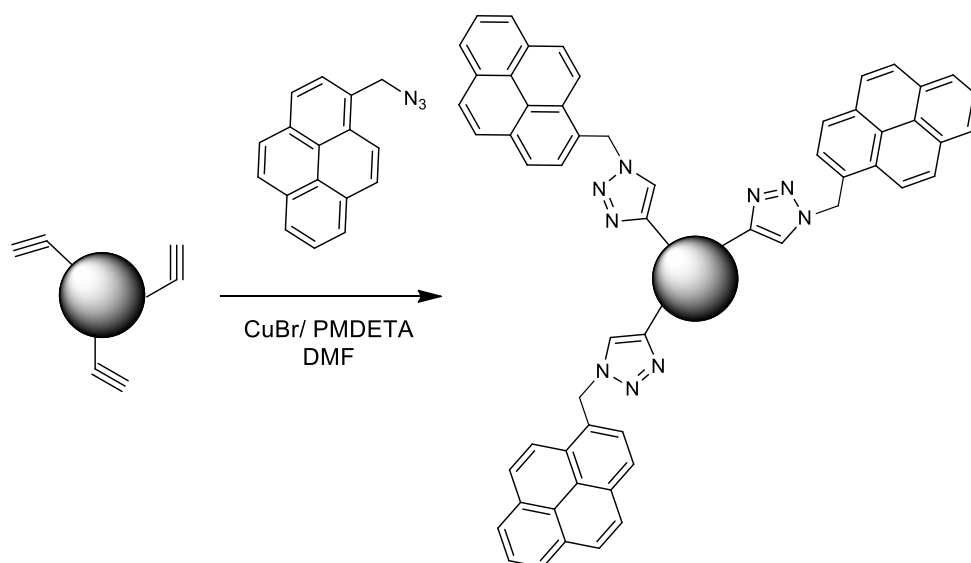
Herein, a simple one pot and one step synthetic strategy is reported for the preparation of highly crosslinked microspheres with click functionality. In this approach, a tertiary amine with acetylene functionality, namely 3-dimethylamino-1-propyne (DAP), is used in combination with benzophenone as a bimolecular photoinitiation system. Py-N<sub>3</sub> is then attached onto polymer particles by “Click Chemistry” to show the presence and accessibility of the alkyne groups on the polymer microspheres. The reaction operates at room temperature without the need for a stabilizer or surfactant of any type. To the best of our knowledge, this is the first report combining type II photoinitiation with precipitation polymerization for the synthesis of highly crosslinked microspheres.

Type-II photoinitiation is employed to precipitation polymerization by simply replacing conventional one component initiator with bimolecular initiator system using DPA and benzophenone as hydrogen donor and photoinitiator, respectively. DVB is deliberately chosen as the crosslinker since the UV absorption of DVB in acetonitrile does not overlap with the wavelength of UV irradiation (350 nm).<sup>[8]</sup> When irradiated, benzophenone undergoes intersystem crossing to form excited triplet states. Radicals are then formed by hydrogen abstraction of excited benzophenone from DPA, followed by free radical polymerization that is analogous to conventional precipitation polymerization. Highly crosslinked and narrow disperse microspheres with alkyne functional groups are synthesized in the absence of any stabilizers or surfactants at room temperature by this method. The overall mechanism of particle formation is illustrated in **Scheme 1**.



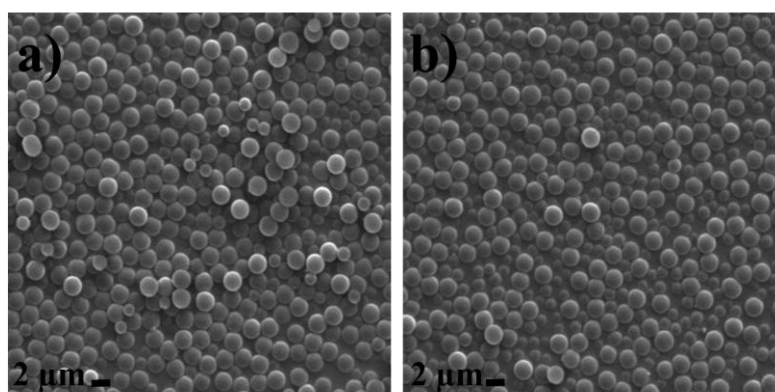
**Scheme 1.** Synthesis of clickable polyDVB microspheres by type-II photoinitiated free radical precipitation polymerization.

Py-N<sub>3</sub> is deliberately selected as the other click component for the functionalization of the microspheres since it enables the efficient characterization of crosslinked particles through its fluorescent properties. Thus, 1-(bromomethyl)pyrene is converted to Py-N<sub>3</sub> simply by azidation processes. Then, CuAAC reaction between propargyl moieties of the microspheres and Py-N<sub>3</sub> is conducted in DMF using copper(I)bromide (CuBr) and N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA) to attach fluorescent pyrene groups onto the microspheres (**Scheme 2**).



**Scheme 2.** Synthesis of pyrene-functionalized PDVB microspheres via click chemistry.

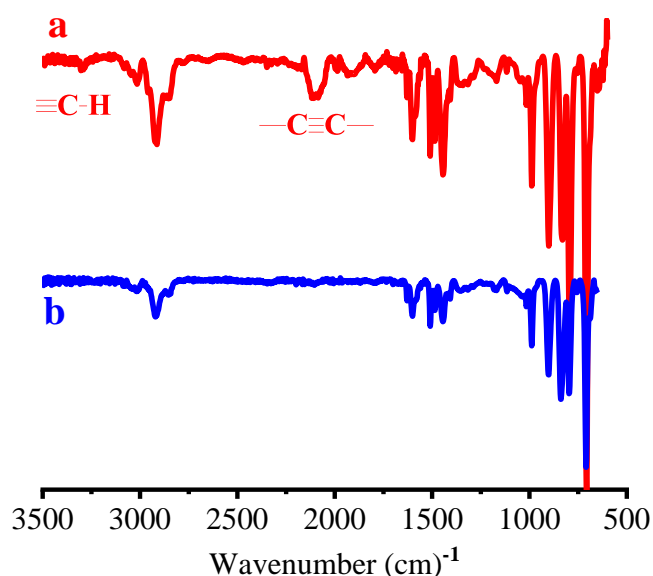
SEM images of the particles reveal that the microspheres obtained by this method are coagulum free and have an average diameter of 1.8  $\mu\text{m}$  (**Figure 1a**). The size of the particles is slightly bigger than those prepared by conventional one component photoinitiation method under similar conditions.<sup>[8]</sup> This might be attributed to the use of co-initiator component of the type II photoinitiation system in slightly higher amounts compared to the conventional photopolymerization. Initiator concentration is known to have an impact on the particle size and reaction yield in conventional precipitation polymerization and the size of the particles generally increase as the initiator concentration increases.<sup>[36]</sup> Particles having diameters around 1  $\mu\text{m}$  is also observed, which can be explained by secondary nucleation of the particle growth during photopolymerization. Particle size remained same after functionalization with pyrene units, likely due to using a relatively small molecule for functionalization (**Figure 1b**). Covalent attachment of bigger molecules such as polymers onto the polymer microspheres results in an increase in particle size.<sup>[10]</sup>



**Figure 1.** SEM images of the clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub>.

FT-IR analysis is used to confirm the presence of alkyne groups in the polymer microspheres (**Figure 2**). The alkyne group on the polymer microspheres is proven by the presence of the characteristic stretching vibration bands appearing at 3277 and 2121  $\text{cm}^{-1}$ , which refer to C-H

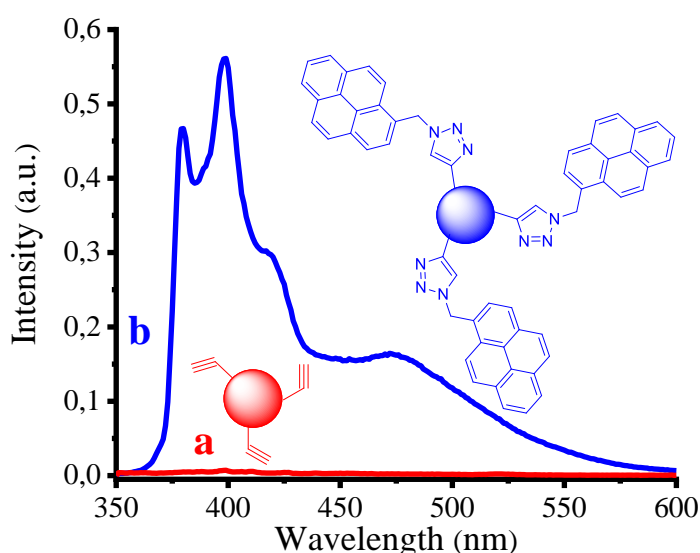
single bond and C $\equiv$ C triple bond, respectively (**Figure 2a**). The clear observation of these peaks in the spectrum of the microspheres can be attributed to the use of alkyne functional initiator in relatively high amounts, which further confirms the bimolecular initiation mechanism for the polymer synthesis (The mole ratio of [DVB-80]:[DPA] = [10]:[1]). As is seen in **Figure 2b**, these peaks disappear completely after CuAAC reaction, confirming the success of functionalization of microspheres by click chemistry. It is important to note that the use of a functional monomer possessing a vinyl group results in a decrease in crosslinking density of the particles, whereas in the current approach, crosslinking density of the particles doesn't change since functionalization is introduced by the initiator used.



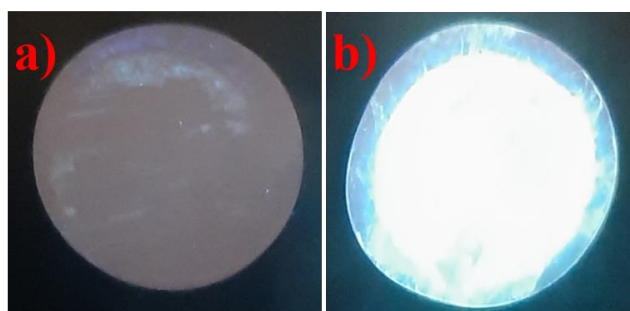
**Figure 2.** FT-IR spectra of clickable PDVB microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub>.

The fluorescence properties of the microspheres were also studied to further confirm the presence and accessibility of the alkyne functionality on the particles. **Figure 3** shows the fluorescence emission spectra of the microspheres before and after click reaction recorded in CHCl<sub>3</sub>. As can be seen, particles show no fluorescence emission before functionalization with

Py-N<sub>3</sub> (**Figure 3a**). Peaks appearing at 379 nm and 400 nm correspond to characteristic monomer fluorescence emission of the pyrene, confirming the presence of pyrene group (**Figure 3b**). A broader emission band observed at 472 nm corresponds to the excimer fluorescence of the pyrene, indicating the spatial proximity of fluorophores on the polymer network.<sup>[37, 38]</sup> **Figure 4** shows a physical observation of the fluorescence properties of clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> under UV irradiation using a 366 nm lamp. It can clearly be seen that particles become highly fluorescent after the incorporation of pyrene moiety via click reaction.



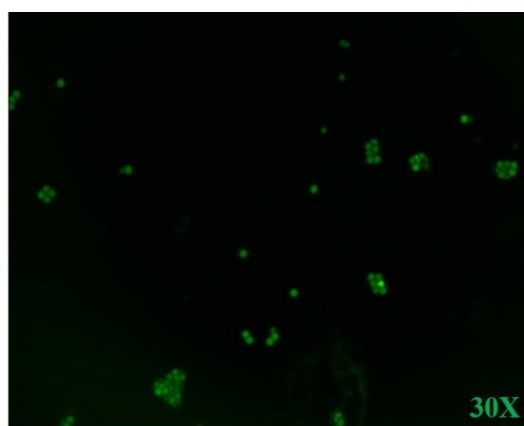
**Figure 3.** Fluorescence spectra of clickable microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> in CHCl<sub>3</sub> at room temperature.





**Figure 4.** Photographs of clickable polyDVB microspheres before (a) and after (b) click reaction with Py-N<sub>3</sub> under irradiation with a 366-nm UV lamp.

Attachment of the pyrene group onto the polymer microspheres is further supported by fluorescence microscopy. **Figure 5** shows the fluorescence microscope images of the particles after functionalization of the particles by CuAAC reaction. As can be seen, microspheres become fluorescent after the attachment of pyrene groups and their fluorescence intensities are similar, suggesting the uniform distribution of alkyne moieties on the precursor individual polymer particles.



**Figure 5.** Fluorescence image of the microspheres after functionalization with pyrene group at 30X magnification.

## 2. Conclusion

Type II photoinitiation is employed to precipitation polymerization for the first time to yield highly cross-linked and spherical polyDVB particles with click functionality. The method offers a one step method for the preparation of alkyne functionalized microspheres. In addition, crosslinking density of the particles doesn't change since functionalization is introduced by the initiator used. It is important to note that Type II photoinitiating systems include but are not limited to benzophenone and tertiary amine system. By simply replacing the co-initiator with

different hydrogen donors, various alcohols, thiols and other tertiary amine derivatives can be incorporated into the polymer matrix in one step. Further studies in this line are now in progress.

### 3. Experimental Section/Methods

*Materials:* Divinylbenzene (DVB-80, technical grade, Aldrich) consisting of 80% divinylbenzene isomers was purified by passing through a basic alumina column to remove inhibitor. 3-Dimethylamino-1-propyne (DAP, 97%, Aldrich), 1-(bromomethyl)pyrene (98%, Aldrich), sodium azide ( $\text{NaN}_3 \geq 99.5\%$ , Aldrich), copper(I) bromide (CuBr, Aldrich, 99%), benzophenone ( $\geq 99\%$ , Aldrich), acetonitrile (ACN, 99%, Aldrich), N, N-dimethylformamide (DMF, 99.8%, Aldrich), N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), acetone (99%, Aldrich), were used as received.

*Synthesis of Clickable Microspheres:* To a borosilicate Kimax tube was added DVB-80 (976 mg, 1068 mL, 7.5 mmol), benzophenone (14 mg, 75  $\mu\text{mol}$ ), DAP (54 mg, 0.5 mmol), and MeCN (22 mL), and the mixture was ultrasonicated for two minutes until a clear solution was obtained. Then, the mixture is purged with nitrogen gas for 10 minutes prior to sealing of the reaction vessel. The sealed tube was then placed into a low profile roller operating at 60 rpm and irradiated from a photoreactor equipped with 6 lamps that emits light at 350 nm, with a light intensity of 3.0  $\text{mW cm}^{-2}$  for 72 h. The polymer microspheres were isolated from the reaction media by vacuum filtration on a 0.45  $\mu\text{m}$  nylon membrane filter, and washed sequentially with MeCN (50 mL) and acetone (50 mL). Finally, the product was dried overnight in a vacuum oven (60  $^\circ\text{C}$ , 50 mbar) to constant mass (yield: 18%).

*Synthesis of 1-azidomethyl pyrene (Py-N<sub>3</sub>):* The synthesis of Py-N<sub>3</sub> is adapted from the literature.<sup>[39]</sup> 1-(Bromomethyl)pyrene (118 mg, 0.4 mmol) and (78 mg, 1.2 mmol) was dissolved in 8 mL DMF under a nitrogen atmosphere and the reaction mixture was stirred for 2 days at 65  $^\circ\text{C}$ . After extraction of the product with  $\text{CH}_2\text{Cl}_2$ /water, the organic layer was dried

with anhydrous  $\text{MgSO}_4$  and solvent was evaporated with a rotary evaporator. The oily yellow product was dried under vacuum. ( $^1\text{H NMR}$ : (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.97 (s, 2H); 7.80–8.22 (m, 9H)).

*Modification of the Microspheres by CuAAC Click Reaction:* In a typical click reaction, alkyne functional microspheres (20 mg), CuBr (14 mg, 0.1 mmol), PMDETA (17  $\mu\text{L}$ , 0.1 mmol), 1-(azidomethyl)pyrene (26 mg, 0.1 mmol) and 5 mL of DMF were placed in a Schlenk tube. The reaction mixture was degassed by three freeze–pump–thaw cycles and stirred at 40 °C for 24 h. After the click reaction, the polymer microspheres were isolated from the reaction media by vacuum filtration on a 0.45  $\mu\text{m}$  nylon membrane filter, and washed sequentially with water (100 mL) and acetone (100 mL). Finally, the product was dried overnight in a vacuum oven (60 °C, 50 mbar) to constant mass.

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