

Review

# Advances in Phototriggered Synthesis of Single-Chain Polymer Nanoparticles

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**Abstract:** Clean use of photons from light to activate chemical reactions offer many possibilities in different fields, from chemistry and biology to materials science and medicine. This review article describes the advances carried out in last decades toward the phototriggered synthesis of single-chain polymer nanoparticles (SCNPs) as soft nanomaterials with promising applications in enzyme-mimicking catalysis and nanomedicine, among other different uses. First, we summarize different strategies developed to synthesize SCNPs based on photoactivated intrachain homocoupling, phototriggered intrachain heterocoupling and photogenerated collapse induced by external cross-linker. Next, we comprehensively review the emergent topic of photoactivated multifolding applied to SCNP construction. Finally, we conclude by summarizing recent strategies towards phototriggered disassembly of SCNPs.

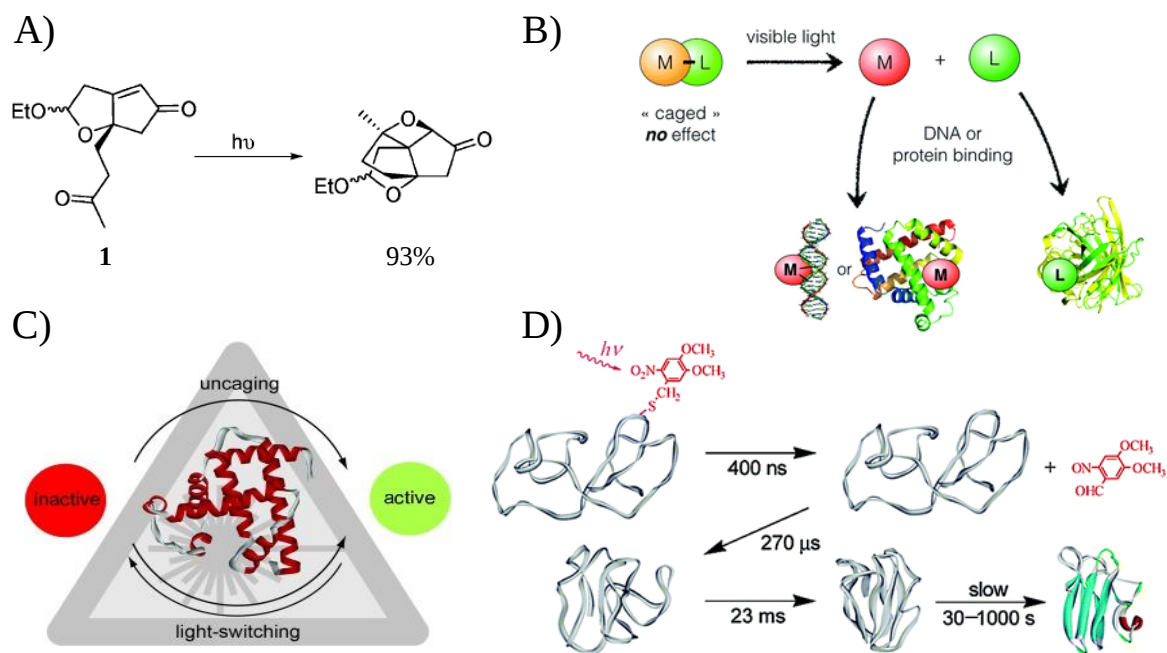
**Keywords:** Photochemistry, photofolding, single-chain nanoparticles

## 1. Introduction

Light from the sun is one of the most cheap and available energy sources in the Earth. Moreover, photons from sunlight can activate many chemical reactions. As early as 1908, photochemistry pioneer Giacomo Ciamician recognized the milder reaction conditions of photoactivated reactions when compared to thermal procedures [1,2]. At these early dates, Ciamician was able to envision photochemistry as an artificial way to put solar energy into practical uses [3].

In general, the energy of photons in the ultraviolet (UV) and visible regions of the electromagnetic spectrum is enough to promote molecules to excited electronic states [4]. Upon photoactivation, often challenging transformations result under very mild conditions without the use of high temperatures or aggressive reagents. Some uses of photochemistry include phototriggered oxidations [5], isomerizations [6], cross-couplings [7], deprotections [8] and cycloadditions [9]. As an example, Figure 1A illustrates the power of photochemical [2 + 2] cyclizations for constructing complex tetracyclic rings as found in some natural compounds. Hence, a simple intramolecular [2 + 2] Paternò-Büchi photoaddition from keto-enone **1** (see structure in Figure 1A) produces in high yield [10] the central oxetane ring of Merrilactone A, a potent neurotrophic compound isolated from the pericarps of *Illicium merrillianum* plant.

Concerning biochemistry, Engels [11] and Kaplan [12] in the late 1970s pioneered the UV-induced deprotection of “photocaged” nucleotides, such as cyclic adenosine monophosphate (cAMP) and adenosine triphosphate (ATP). Hence, through protection of the phosphate group of cAMP and ATP with a photocleavable nitrobenzyl group they were able to show that the biological function of these molecules recovered after cleavage *via* UV irradiation. Morrison in the late 1980s pioneered the idea of photoactivation in inorganic chemistry by introducing the compound Rh(phen)<sub>2</sub>Cl<sub>2</sub><sup>+</sup> which upon UV irradiation was able to bind DNA irreversibly [13]. Modern photoactivated chemo-



**Figure 1.** A) Illustration of the use of photochemistry for easy construction of the complex tetracyclic ring of Merrilactone A, a potent neurotrophic compound isolated from the pericarps of *Illicium merrillianum* plant, starting from compound 1. B) Principle of photoactivated chemotherapy using a non-toxic metal-ligand (M-L) compound: upon photocleavage of the M-L bond, either the fragment M or L, or both, display toxicity to cancer cells. C) The use of photoresponsive structural cross-linkers allows phototriggering to be employed as a useful method to investigate protein conformational changes. D) Introduction of photolabile motifs enables the investigation of initial protein folding dynamics. Reprinted from [10], [14], [15] and [16] with permission.

therapeutic (PACT) compounds follow this concept: the non-irradiated form of the metal-ligand (M-L) compound has no biological activity and low toxicity, while the irradiated form has high toxicity to cancer cells by interacting with DNA, lipids, or proteins (see Figure 1B) [14]. In biology, the fundamental principles that govern protein folding, misfolding and aggregation have often been explored by the introduction of photoresponsive structural cross-linkers (Figure 1C) [15] and photolabile motifs (Figure 1D) [16].

Concerning polymer chemistry, photochemical reactions facilitate precision polymer design allowing easy end-group and polymer functionalization, as well as surface modification and cross-linking [17]. As ultra-fine cross-linked nano-objects, single-chain polymer nanoparticles (SCNPs) obtained *via* folding/collapse of individual linear polymer chains have attracted significant interest in recent years due to their favorable prospects for catalysis, drug delivery and sensing applications [18]. The interest in the use of photochemistry to synthesize SCNPs has also grown in parallel. In fact, the advantages of photoactivated synthesis of SCNPs include: i) relatively mild reaction conditions, ii) possibility to investigate the complex SCNP formation process *via* phototriggered multifolding, and iii) in the case of some photocoupling reactions, to endow the SCNPs with fluorescence properties.

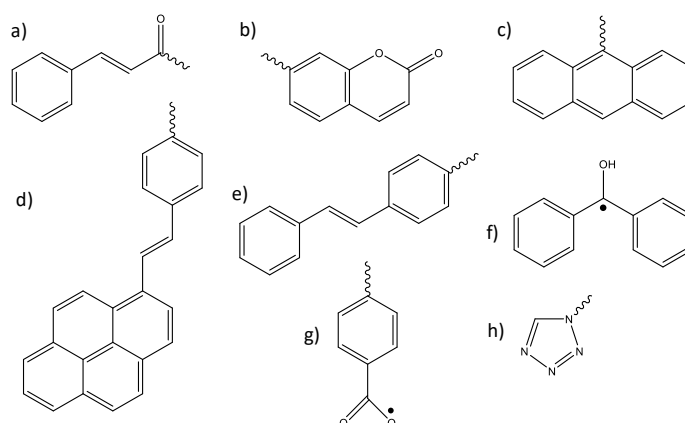
In this review article, we describe the different strategies developed to synthesize SCNPs based on photochemical reactions, including methods such as: i) photoactivated intrachain homocoupling, ii) phototriggered intrachain heterocoupling, and iii) photogenerated collapse induced by external cross-linkers. Additionally, we comprehensively review the emergent branch of photoactivated multifolding applied to SCNP construction. To conclude, we cover recent strategies towards phototriggered disassembly of SCNPs.

## 2. Synthesis of single-chain polymer nanoparticles *via* photoactivated intrachain homocoupling

In a broad sense, photoactivated intrachain homocoupling refers to the folding/collapse process induced by photons to an isolated polymer chain through the involvement of a single type of photoresponsive functional groups. Nowadays, the different strategies developed to synthesize SCNPs based on photoactivated intrachain homocoupling include: i) photodimerization, ii) photocyclization, iii) photoisomerization, iv) photogeneration of reactive species, and iv) self-assembly induced by photodeprotection.

### 2.1. Photodimerization

Figure 2 shows the main functional groups used in photodimerization for SCN formation *via* photoactivated intrachain homocoupling.



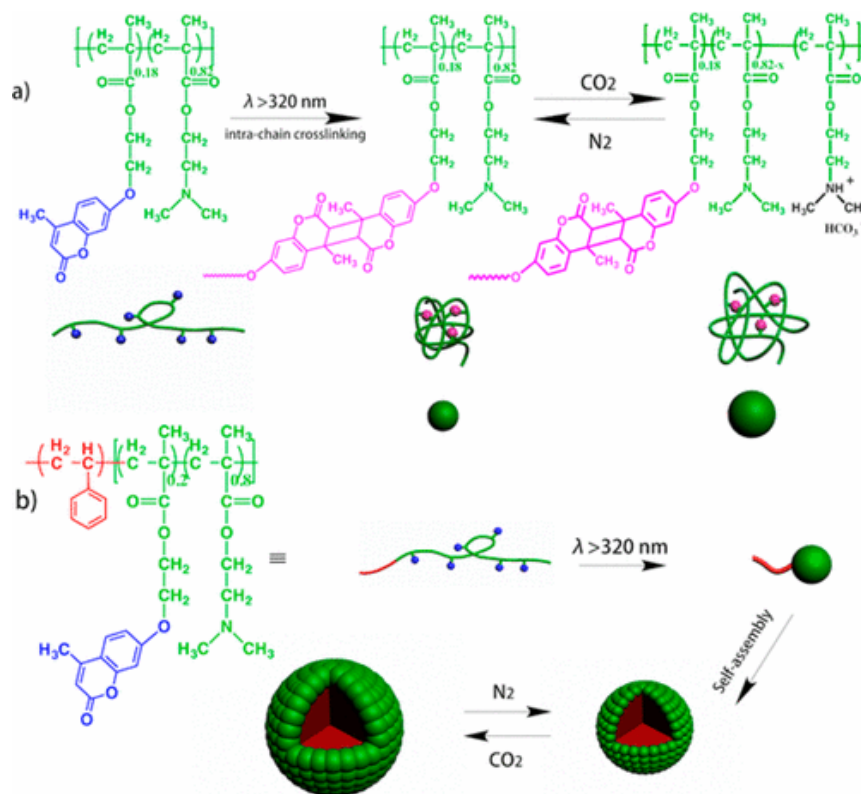
**Figure 2.** Functional groups employed for SCN formation *via* intrachain photodimerization: a) cinnamoyl, b) coumarin, c) anthracene, d) styrylpyrene, e) stilbene, f) ketyl radical, g) carboxyl radical, and h) nitrile imine (for details see text below).

#### 2.1.1. Cinnamoyl functional groups

Photodimerization of cinnamoyl units (see Figure 2a) was one of the earliest photochemical reactions adopted to produce SCNPs. Hence, Tao and Liu in the late 1990s pioneered the UV-induced formation of tadpole-shaped SCNPs using diblock copolymers in which one of the blocks contained photodimerizable cinnamoyl moieties and the other contained inert styrene repeat units [19]. UV irradiation of unimer chains of the precursor diblock copolymer produced tadpole-shaped SCNPs *via* intrachain cinnamoyl dimerization, as confirmed by combining UV absorbance analysis, size exclusion chromatography (SEC), static light scattering (SLS) and nuclear magnetic resonance (NMR) spectroscopy measurements. In a further work by this group, the photochemical technique was refined to obtain essentially pure tadpole-shaped SCNPs at high final polymer concentration [20]. Imprinted tadpole-shaped SCNPs of 7.4 nm in diameter with exceptionally high binding capacity and high selectivity for L-phenylalanine anilide were fabricated by means of this improved photoactivated synthesis technique [21]. Very recently, cinnamoyl dimerization has been used by He and coworkers [22] to investigate the self-assembly of amphiphilic diblock copolymers with the photocross-linkable units placed either in the hydrophobic or the hydrophilic blocks. When compared to the unreacted diblock copolymers, significant differences were found for the resulting tadpole-shaped SCNPs. Hence, photoinduced collapse of the hydrophobic block induced a morphological transition from branched cylindrical micelles to completely spherical micelles at a cinnamoyl dimerization degree of *ca.* 63%. When photocross-linking was performed in the hydrophilic block, the sizes of the micelles showed a dramatic increase due to a shift of the hydrophobic/hydrophilic balance. Interestingly, at a dimerization degree > 60% the tadpole-shaped SCNPs assembled into non-conventional aggregates with a non-smooth surface.

### 2.1.2. Coumarin functional groups

Zhao and coworkers reported in 2011 the preparation of neat SCNPs using the intramolecular photodimerization of coumarin moieties (Figure 2b) upon  $\lambda > 310$  nm UV irradiation in a dilute solution of coumarin-containing copolymers (7 or 13 mol% of coumarin units) [23]. The dimerization degree was *ca.* 75% after 1 h irradiation, as determined by UV absorbance analysis. The resulting SCNPs were characterized by SEC, solution viscosity, differential scanning calorimetry (DSC) and  $^1\text{H}$  NMR spin-spin relaxation time measurements. These SCNPs were further used as useful nanoreactors to synthesize gold nanoparticles (AuNPs). Remarkably, the rate of AuNP formation was found to depend on the dimerization degree of the coumarin moieties, which significantly determined the SCNPs compaction degree and presumably also the intrachain mobility. Attempts to disassemble the SCNPs *via* photocleavage of the coumarin dimers under UV irradiation at  $\lambda < 260$  nm were unsuccessful, as revealed by SEC experiments. In fact, after 2 h of irradiation the dimerization degree remained as high as 38 %. In a further work by this group [24],  $\text{CO}_2$ -responsive SCNPs as well as micelles self-assembled from amphiphilic tadpole-shaped Janus SCNPs were prepared relying on the intramolecular photodimerization of coumarin units from diblock copolymers (see Figure 3). Both



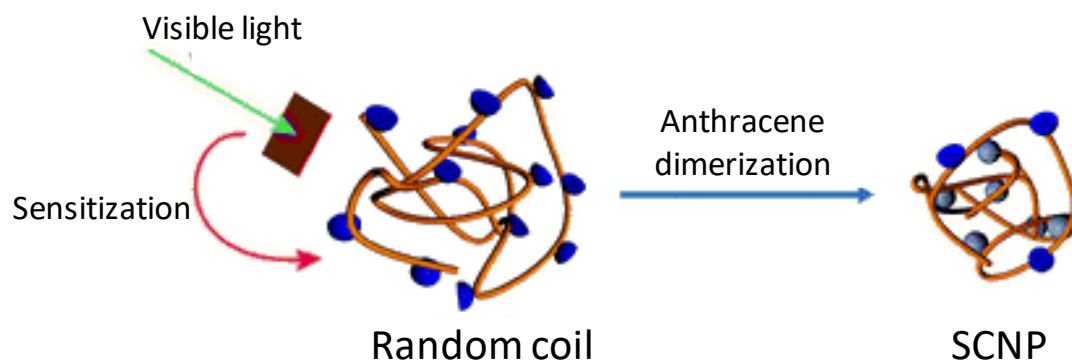
**Figure 3.** Schematic illustration of the synthesis *via* intrachain coumarin dimerization of: a) CO<sub>2</sub>-responsive SCNPs, and b) CO<sub>2</sub>-responsive micelles self-assembled from amphiphilic tadpole-shaped Janus SCNPs. Reprinted from [24] with permission.

the dimensions of the SCNPs and that of self-assembled micelles from tadpole-shaped Janus SCNPs were found to undergo reversible swelling / shrinking in response to CO<sub>2</sub> / N<sub>2</sub> bubbling. Hence, CO<sub>2</sub> / N<sub>2</sub> stimulation was investigated by these authors to develop gas-tunable nanoreactors for synthesizing AuNPs, in which both the kinetics of AuNP formation and the AuNP size can be finely controlled. Subsequently, Zhao and coworkers reported photoresponsive liquid crystalline single chain nanoparticles (LC-SCNPs) prepared *via* intramolecular photodimerization of coumarin using a side-chain liquid crystalline polymer containing coumarin moieties and azobenzene mesogens [25]. Interestingly, the resulting LC-SCNPs exhibited several interesting properties: i) when dispersed in chloroform (poor solvent), they displayed fluorescent emission that was dependent on the *cis/trans*

ratio of azobenzene mesogens, ii) when exposed to linearly polarized irradiation, they undergo photoinduced deformation that was dependent on the excitation wavelength, and iii) when dispersed in a poly(methyl methacrylate) (PMMA) matrix to form a nanocomposite film that was stretched at 113 °C to 400% strain followed by cooling to room temperature, the stretched film displayed strong parallel dichroism as a consequence of the stretching-induced orientation of the azobenzene moieties confined in the SCNPs.

### 2.1.3. Anthracene functional groups

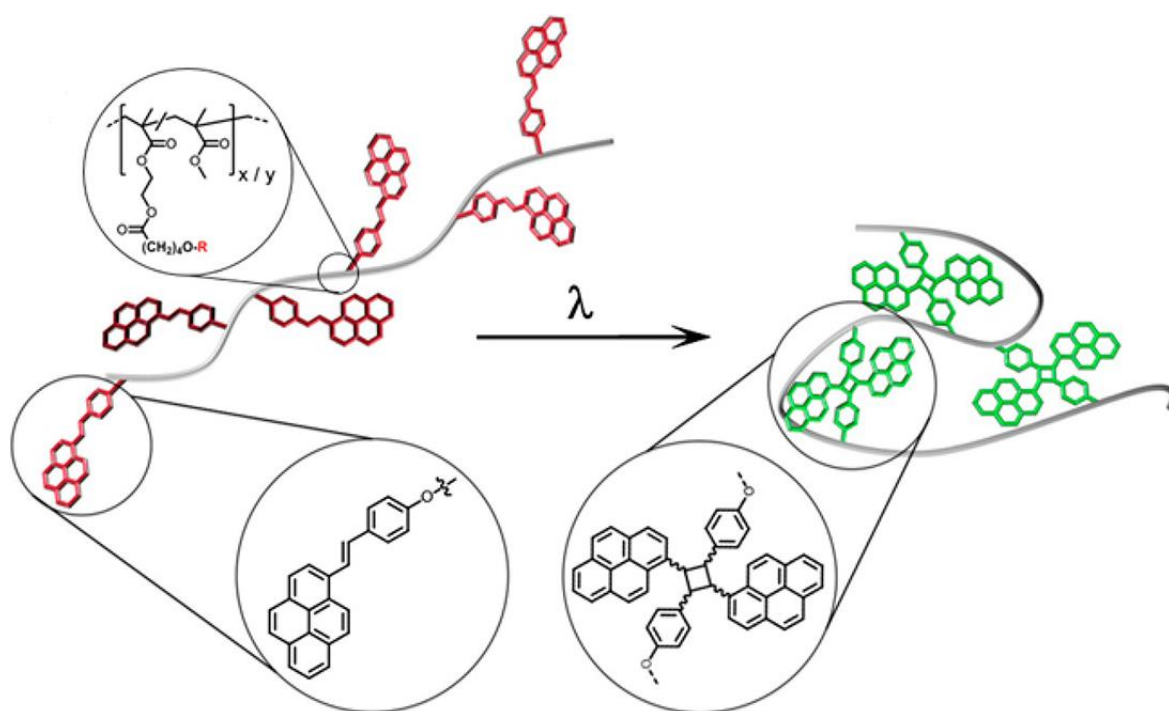
Berda and coworkers in 2013 pioneered the intrachain photodimerization of pendant anthracene units (Figure 2c) as an efficient route to SCNP fabrication [26]. As precursors, these authors used PMMA-based copolymers containing 10, 20 and 46 mol% of anthracene photodimerizable units. The [4 + 4] cycloaddition of pendant anthracene groups was carried out by irradiating a diluted solution of the precursor (0.1 mg/mL) with 350 nm centered UV light. The dimerization degree was determined through UV-visible spectroscopy by monitoring the disappearance of the characteristic  $\pi-\pi^*$  absorption peak at *ca.* 360 nm from the anthracene groups. Depending on the anthracene content, different reaction times were required to ensure SCNP formation: 11.5, 22.5 and 60 min for precursors containing 10, 20 and 46 mol% of anthracene units, giving to a photodimerization degree of 85, 86 and 88%, respectively. SEC with triple (UV, SLS and viscosimetric) detection confirmed successful SCNP formation although the SLS detector traces revealed the presence of a small amount of inter-chain cross-linking. The morphology of isolated SCNPs was visualized by transmission electron microscopy (TEM). In a further work by this group [27], intrachain anthracene photodimerization was used to prepare porphyrin-cored polymer nanoparticles as macromolecular models for heme iron coordination. In this case, a porphyrin core functionalized with 4 arms of identical polymers containing *ca.* 25 mol% of anthracene groups each was selected as SCNP precursor. Remarkably, the resulting nanoparticles exhibited redox and ligand-binding reactivity similar to that of native heme proteins. Subsequently, the strategy of intrachain photodimerization of pendant anthracene units was adopted by Zhao *et al.* to construct amphiphilic Janus twin SCNPs [28] as well as biohybrid vesicles by coassembly of proteins and tadpole-shaped SCNPs [29], and by Temel and coworkers [30] to develop SCNPs as carbon nanotube catchers. On the other hand, Simon and coworkers [31] pioneered the use of visible light ( $\lambda = 532$  nm) in the presence of a sensitizer (platinum octaethylporphyrin) as the driving force for SCNP formation through dimerization of pendant anthracene groups *via* photochemical upconversion (see Figure 4). Conventional anthracene dimerization was selected by Barner-Kowollik *et al.* [32] for photoactivated SCNP formation under UV irradiation at  $\lambda = 330$  nm, before the photoactivated ligation of the formed SCNP with a second polymer chain using blue light ( $\lambda = 455$  nm).



**Figure 4.** Schematic illustration of the synthesis of SCNPs through photochemical upconversion (also referred to as triplet-triplet annihilation upconversion) *via* intrachain dimerization of pendant anthracene groups under visible light irradiation ( $\lambda = 532$  nm) in the presence of platinum octaethylporphyrin as a sensitizer. Reprinted from [31] with permission.

#### 2.1.4 Styrylpyrene functional groups

Recently, Barner-Kowollik and coworkers [33] have shown in an elegant work the significant advances offered by performing the photodimerization of styrylpyrene units (Figure 2d) in a confined macromolecular environment, such as that offered by a SCNP precursor, when compared to a control styrylpyrene [2 + 2] photocycloaddition carried out in free solution with a low-molecular-weight photoreactive compound at exactly the same absolute concentration. Hence, the enhanced reactivity of confined styrylpyrene moieties within single polymer chains allowed photoactivated SCNP formation at  $\lambda = 445$  nm LED-irradiation within 15 min, or using ambient light within 24 h (see Figure 5). Critically, the advantages of photochemistry in such confined environments were a drastically increased photoreactivity toward longer wavelengths as well as quantum yield, when compared to a (reference) free solution environment.



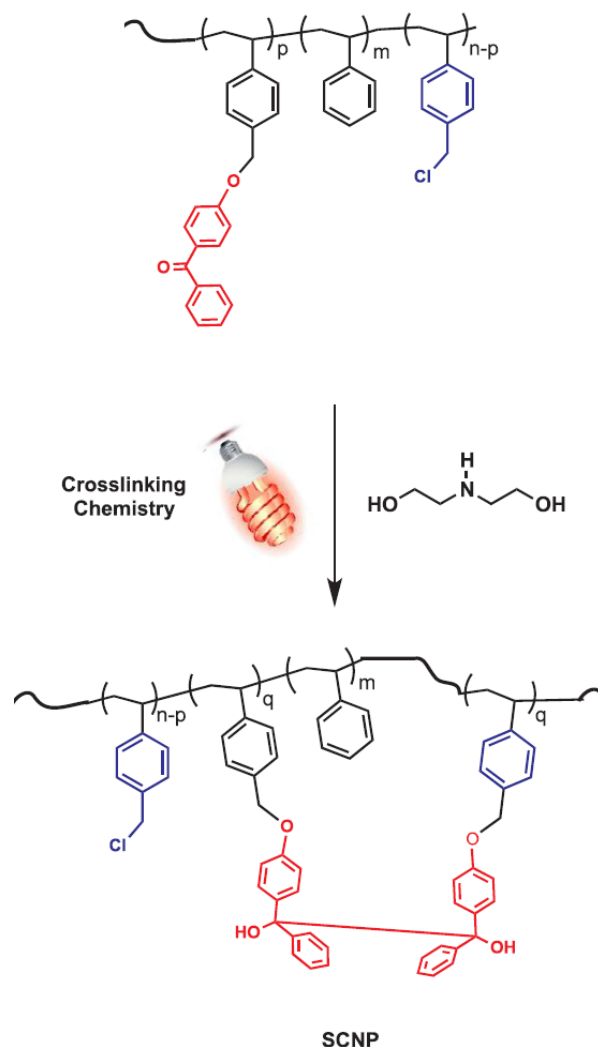
**Figure 5.** Schematic illustration of the enhanced reactivity of confined styrylpyrene moieties (shown in red color) within single polymer chains allowing photoactivated SCNP formation at  $\lambda = 445$  nm LED-irradiation within only 15 min. *via* single chain folding induced by formation of styrylpyrene dimers (shown in green color). Reprinted from [33] with permission.

#### 2.1.5. Stilbene functional groups

Photodimerization of stilbene units (Figure 2e) was selected by Chen and coworkers [34] to investigate the self-assembly behavior of Janus SCNPs endowed with tunable liquid crystalline properties. These Janus SCNPs were prepared *via* intrachain photocross-linking of stilbene-containing amphiphilic block copolymers. In this system, the size and liquid crystalline properties of the SCNPs were tuned by varying the UV irradiation time. Remarkably, upon changing the UV irradiation time and the block copolymer composition a morphology transition from nonspherical assemblies (irregular clusters, tubular vesicles, doughnut-like assemblies and saddle-shaped lamellae) to spherical nanoparticles was observed. This transition was attributed to a significant decrease in internal liquid crystalline ordering upon increasing the UV irradiation time, as observed by small-angle X-ray scattering (SAXS) and polarized optical microscopy.

### 2.1.6. Ketyl radical functional groups

An innovative photoactivated route toward SCNPs has been recently developed by Temel and coworkers [35] relying on radical coupling of photogenerated ketyl radicals (see Figure 2f) from benzophenone units to give benzopinacol units after coupling. Ketyl radicals were formed through  $\lambda = 350$  nm UV irradiation of copolymers containing benzophenone pendants at high dilution conditions ( $c = 0.2$  mg/mL) in acetone as solvent and in the presence of a hydrogen donor co-initiator (diethanolamine or isopropyl alcohol) (Figure 6). Successful SCNPs formation after 5 h of UV irradiation was determined by means of a combination of characterization techniques involving SEC, DSC, UV and NMR spectroscopy as well as TEM and atomic force microscopy (AFM) measurements.

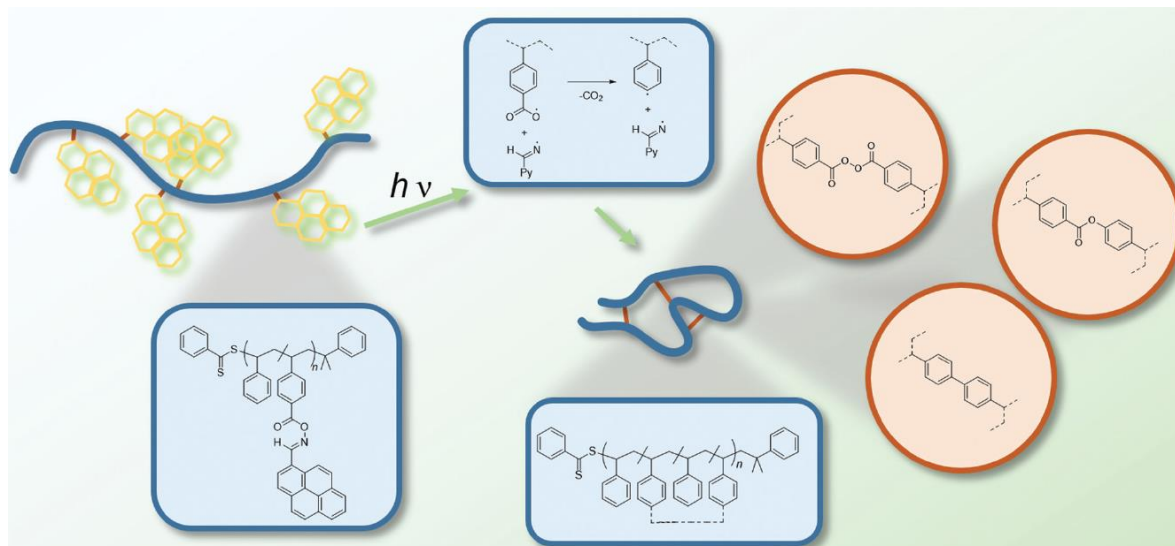


**Figure 6.** Schematic illustration of the synthesis of SCNPs through intrachain coupling of ketyl radicals from benzophenone units to give benzopinacol moieties under UV irradiation ( $\lambda = 350$  nm) in the presence diethanolamine as a hydrogen donor co-initiator. Reprinted from [35] with permission.

### 2.1.7. Carboxyl radical functional groups

Recently, Barner-Kowollik and coworkers [36] have introduced a facile photoinduced self-reporting methodology for the compaction of polymer chains in highly diluted solution based on intrachain radical coupling of carboxyl radicals (Figure 2g). The carboxyl radicals were generated *via* light-induced fragmentation of pyrene-substituted oxime ester moieties along a polymer chain. CO<sub>2</sub> release from the carboxyl radicals leads to highly reactive phenyl radicals as an additional secondary species for chain compaction *via* homo- and hetero-radical coupling (see Figure 7). Interestingly, LED

light irradiation ( $\lambda = 430\text{--}435\text{ nm}$ ) for 2.5 h of a highly diluted solution of the SCNP precursor containing oxime ester pendants was enough to produce SCNPs. Concomitantly, release of pyrene units after light-induced fragmentation of the oxime ester moieties allowed to “switch on” the fluorescence of the initially non-fluorescent solution under UV irradiation at  $\lambda_{\text{exc}} = 366\text{ nm}$ . The resulting SCNPs were in-depth characterized *via* SEC, UV and NMR spectroscopy measurements.



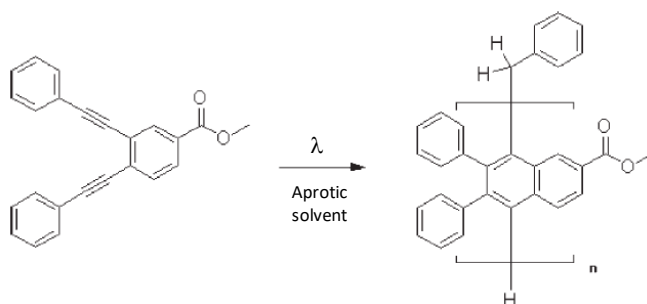
**Figure 7.** Schematic illustration of the synthesis at high dilution of self-reporting SCNPs through intrachain coupling of radicals generated from pyrene-substituted oxime ester moieties under LED light irradiation ( $\lambda = 430\text{--}435\text{ nm}$ ). Chain folding was accompanied by release of pyrene units inducing fluorescence in the initially non-fluorescent solution. Reprinted from [36] with permission.

#### 2.1.8. Nitrile imine functional groups

Visible light-induced nitrile imine (Figure 2h) self-dimerization has been recently employed by Barner-Kowollik *et al.* [37] to produce SCNPs showing fluorescent properties. Polystyrene-based polymers functionalized with pyrene-tetrazole pendants (12 mol %) were used as precursors. SCNPs were prepared upon irradiation a highly diluted solution of the precursor in dichloromethane (hydrodynamic size = 10.6 nm) with LED light ( $\lambda = 410\text{--}420\text{ nm}$ ) for 1.5 h. Upon nitrile imine self-dimerization, the resulting SCNPs exhibited fluorescence with an emission maximum at 475 nm and a hydrodynamic size of 5.0 nm.

#### 2.2. Photocyclization

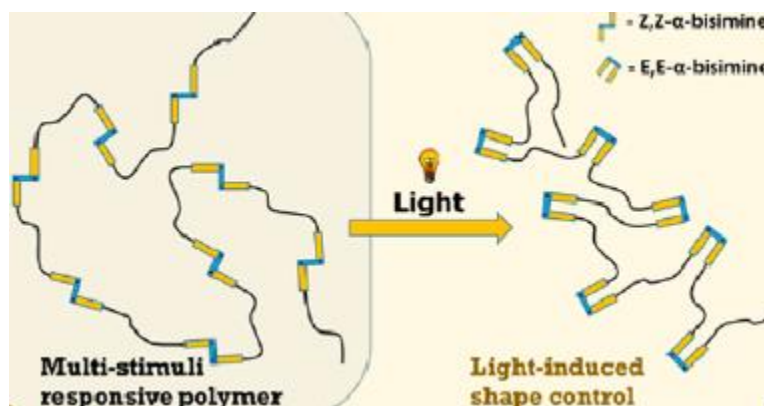
Photo-Bergman cyclization was introduced by Hu and coworkers [38] as a novel yet efficient strategy to synthesize SCNPs *via* Bergman cyclization without the requirement of harsh thermal conditions ( $>200\text{ }^{\circ}\text{C}$ ). Figure 8 illustrates the chemical structure of the enediyne compound employed by these authors to give oligomeric products upon photoirradiation in aprotic solvents. Upon UV irradiation of the enediyne compound for 6 h, the presence of oligomeric products containing the naphthalene motif was revealed by NMR, Raman scattering and fluorescence spectroscopy measurements. Subsequently, SCNPs were obtained through UV irradiation for 6 h of a precursor containing photoreactive enediyne pendants at high dilution in toluene. The resulting SCNPs were characterized by Raman scattering, NMR as well as fluorescence spectroscopy, SEC and AFM measurements.



**Figure 8.** Illustration of the structure of photo-Bergman cyclization products obtained after UV irradiation of an enediyne compound in an aprotic solvent. Reprinted from [38] with permission.

### 2.3 Photoisomerization

The groups of Barner-Kowollik and Lehn [39] introduced in 2015 the use of photoresponsive *N*-alkyl  $\alpha$ -bisimines as main-chain functional groups in acyclic diene metathesis (ADMET)-polymers for the controlled switching of the polymeric particle shape with light *via* photoisomerization (Figure 9). Upon irradiation with light of 254 nm of the (*Z/Z*)-parent precursor (hydrodynamic size = 5.1 nm), *Z/E*-photoisomerization of the C=N bond was found to give an almost pure (*E/E*)-chain (hydrodynamic size = 3.3 nm). The photoisomerization process was found to be completely reversible *via* a subsequent thermal back reaction (15 h, room temperature) or, alternatively, by irradiation with light of 365 nm. Remarkably, SCNP formation (hydrodynamic size = 4.3 nm) was also carried out using the same precursors *via* bisimine-Pd(II) complexation, conferring dual responsiveness for the controlled switching of size/shape with light and metal ions.



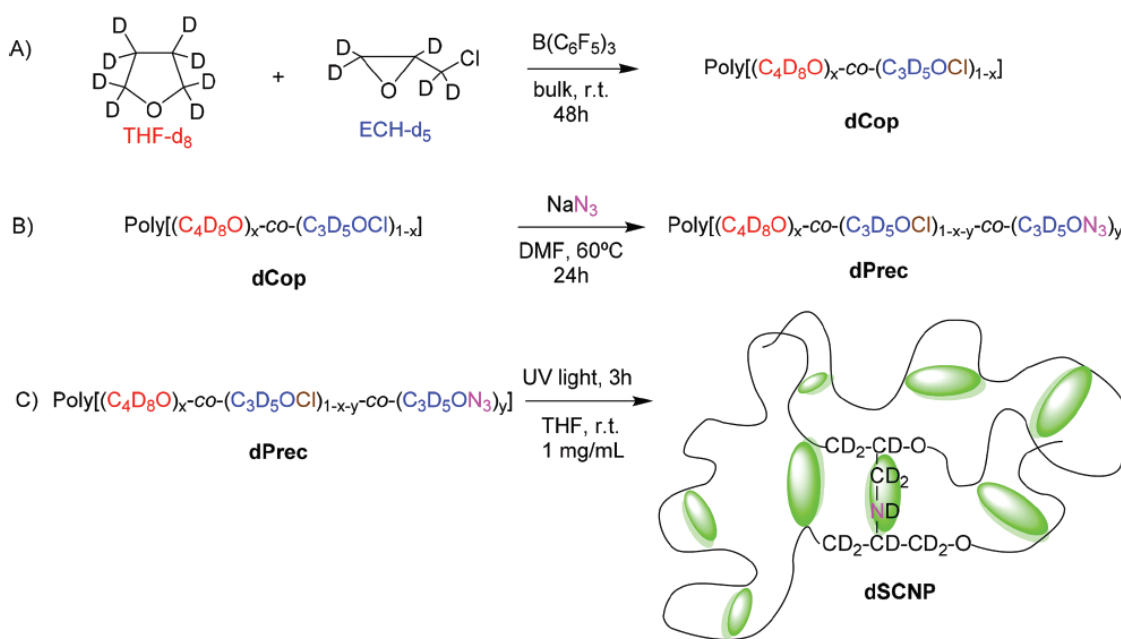
**Figure 9.** Schematic illustration of the controlled switching of size/shape with light *via* photoisomerization of an ADMET-polymer containing main-chain *N*-alkyl  $\alpha$ -bisimine units. Reprinted from [39] with permission.

### 2.4. Photogeneration of reactive species

#### 2.4.1. Nitrenes

Bai and coworkers [40] reported in 2014 a facile strategy for the preparation of SCNPs *via* intramolecular photocross-linking of azide polymers. Hence, copolymers of styrene and 4-vinylbenzyl azide containing 2.5, 5.2 and 9.6 mol% of azide groups were prepared as photoreactive SCNP precursors. Upon UV irradiation ( $\lambda = 365$  nm) of the precursors at high dilution in chloroform (1 mg/mL), highly reactive nitrene species formed from photodecomposition of the azide groups after release of  $N_2$ . The folding of the linear copolymer chains to SCNPs was attributed to fast intrachain nitrene C-H insertion events. In fact, the complete disappearance of the azide moieties as followed by

FTIR spectroscopy took place in only 2, 4.5 and 8 min for the copolymers containing 2.5, 5.2 and 9.6 mol% of azide groups, respectively. SEC, DLS and TEM measurements confirmed the successful formation of SCNPs. Subsequently, Pomposo and coworkers [41] adopted the technique of photogeneration of nitrene species to fabricate *completely* deuterated SCNPs, paving the way to deploy the full possibilities of neutron scattering techniques for investigating these soft nanomaterials. The precursors were synthesized from available perdeuterated cyclic ether monomers by a simple bulk ring-opening copolymerization process (see Figure 10A) followed by a facile post-polymerization functionalization reaction with sodium azide as reagent (Figure 10B). UV irradiation ( $\lambda = 300\text{--}400\text{ nm}$ ) of the precursor at high dilution for 3 h produced completely deuterated SCNPs *via* insertion reactions upon azide decomposition (Figure 10C).



**Figure 10.** Schematic illustration of the different steps during the synthesis of completely deuterated SCNPs: A) Bulk ring-opening copolymerization of available perdeuterated cyclic ether monomers. B) Post-polymerization functionalization reaction with sodium azide as reagent. C) SCNPs formation *via* photogeneration of nitrene species followed by intrachain nitrene C-H insertion events. Reprinted from [41] with permission.

#### 2.4.2. Carbenes

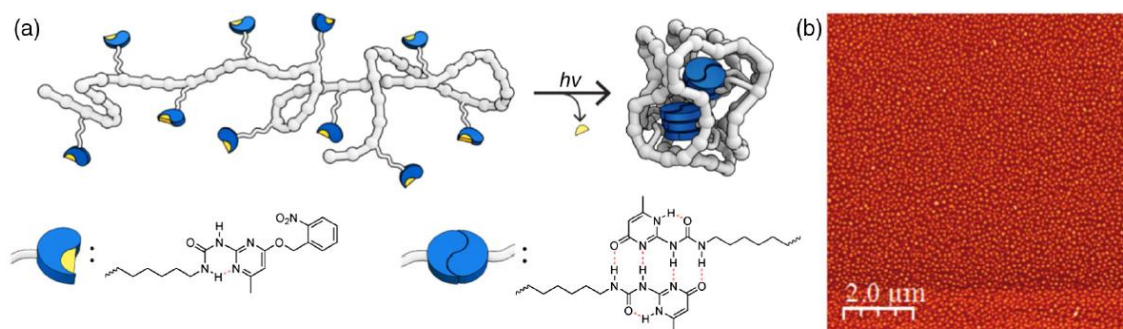
More recently, De La Cuesta and Pomposo [42] have produced SCNPs *via* photogeneration of highly reactive carbene species from copolymers containing photoreactive  $\alpha$ -diazo- $\beta$ -ketoester pendants. The efficiency of carbene generation was as high as 90.4% as determined from elemental analysis data. SEC measurements confirmed successful SCNPs formation *via* intrachain carbene insertion events.

#### 2.5. Self-assembly induced by photodeprotection

##### 2.5.1. Hydrogen-bonded dimers

Meijer and coworkers in 2009 pioneered the synthesis of reversible, non-covalent bonded SCNPs *via* photodeprotection of *o*-nitrobenzyl-substituted 2-ureido-pyrimidinone (UPy) moieties [43, 44]. Polymers decorated with *o*-nitrobenzyl-protected UPy pendants were selected as precursors since the bulky protecting group prevented UPy dimerization *via* quadruple hydrogen bonding interactions and, hence, SCNPs formation. UV irradiation ( $\lambda = 350\text{ nm}$ ) of a highly diluted solution of the precursors

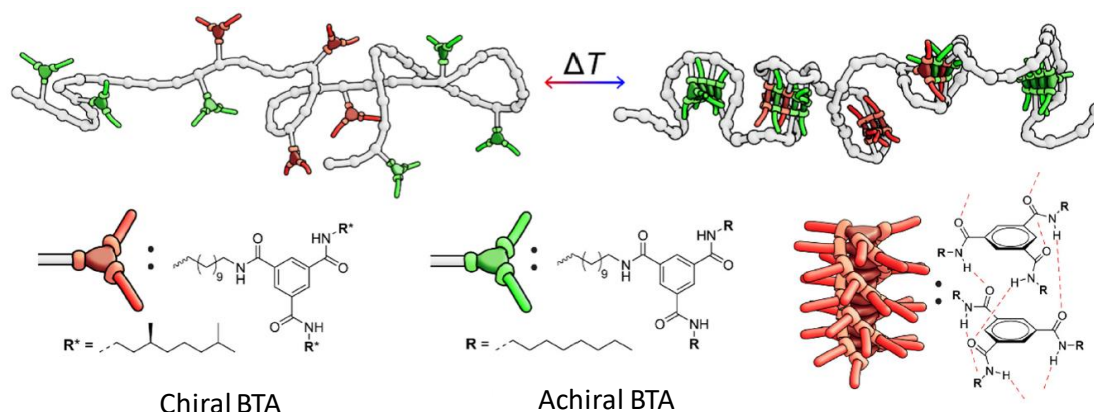
in chloroform resulted in removal of the protecting groups and SCNP formation, as determined by SEC and AFM measurements (Figure 11). The reversible nature of the SCNPs was revealed by adding formic acid to the SCNP solution that disrupted the hydrogen bonding interactions leading to a hydrodynamic size of the chains similar to that of the initial precursor. This Group further used the strategy of dimerization induced by photodeprotection to establish useful structure-function relationships in non-covalent bonded SCNPs, as summarized in a recent review paper [44].



**Figure 11.** Schematic illustration of the synthesis of reversible, non-covalent bonded SCNPs *via* photodeprotection of *o*-nitrobenzyl-substituted 2-ureido-pyrimidinone (UPy) moieties followed by UPy dimerization *via* quadruple hydrogen bonding interactions (a) and AFM picture of the resulting SCNPs (b). Reprinted from [44] with permission.

### 2.5.2. Hydrogen-bonded helical stacks

Subsequently, Palmans, Meijer and coworkers in 2011 were the first to investigate the preparation of reversible, non-covalent bonded SCNPs *via* helical stacking induced by photodeprotection [45]. As photoprotected functional groups they selected *o*-nitrobenzyl-substituted benzene-1,3,5-tricarboxamide (BTA) moieties which were attached to linear poly(isobornyl methacrylate) chains by means of a postfunctionalization approach. The presence of the bulky *o*-nitrobenzyl-protecting group prevented the BTAs of the precursor to self-assemble into helical stacks stabilized by 3-fold hydrogen-bonding and, hence, SCNP formation. Interestingly, step-wise photodeprotection of the *o*-nitrobenzyl-substituted BTAs (UV light,  $\lambda = 350$  nm) induced the folding of the precursor in a step-wise manner. Circular dichroism (CD) spectroscopy revealed that the BTAs did still self-assemble into helical stacks in the SCNPs. Several different supramolecular SCNPs based on helical stacking (see Figure 12) are the subject of a recent review paper by this Group [44].



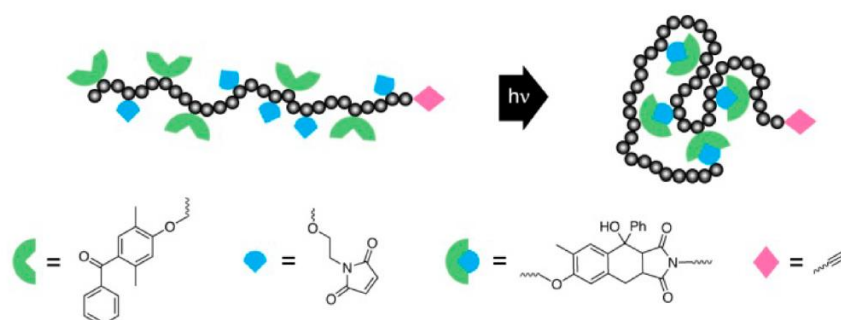
**Figure 12.** Synthesis of reversible, non-covalent bonded SCNPs *via* helical stacking using a precursor containing both chiral (in orange color) and achiral (in red color) benzene-1,3,5-tricarboxamide (BTA) units showing the formation of multiple, segregated BTA stacks instead of a single chiral BTA stack. Reprinted from [44] with permission.

### 3. Synthesis of single-chain polymer nanoparticles *via* phototriggered intrachain heterocoupling

Phototriggered intrachain heterocoupling refers to the folding/collapse process induced by photons to an isolated polymer chain containing complementary (hetero)functional groups (*i.e.*, A-type, B-type) that react between them, upon photoactivation, in a pairwise manner (*i.e.*, A + B).

#### 3.1. Photoinduced Diels-Alder (DA) reaction

Barner-Kowollik and coworkers introduced in 2013 the UV-light-triggered DA ligation as a mild and efficient approach to produce functional SCNPs [46]. Precursors were prepared based on polystyrene copolymers containing 2,5-dimethyl benzophenone (DMBP) as well as *N*-maleimide (Mal) pendants and an alkyne functional group as chain-end. Upon UV irradiation ( $\lambda = 320$  nm) for 30 min of a diluted solution of the precursor (0.017 mg/mL) the photoactivated DMBP groups were found to react intramolecularly with the Mal units *via* DA ligation resulting in the formation of SCNPs through intrachain heterocoupling (Figure 13). The resulting functional SCNPs were characterized

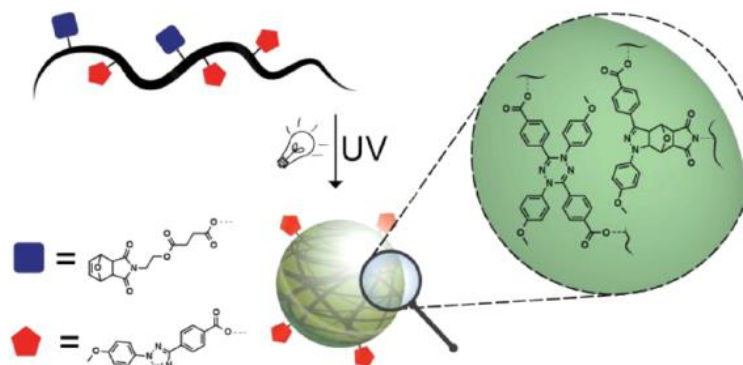


**Figure 13.** Functional SCNP formation *via* photoinduced DA ligation using a precursor having 2,5-dimethyl benzophenone (in green color) as well as *N*-maleimide pendants (in blue color) and an alkyne functional group as chain-end (in pink color). Reprinted from [46] with permission.

by SEC, NMR, DLS and AFM measurements. In a further work, a functionalized polythiophene containing DMBP and Mal groups was used to produce  $\pi$ -conjugated SCNPs *via* photoinduced DA reaction [47].

#### 3.2. Photoinduced nitrile imine mediated tetrazole-ene cycloaddition (NITEC)

In another contribution by the Barner-Kowollik group [48], the phototriggered intrachain heterocoupling for SCNP formation relied on photoinduced nitrile imine mediated tetrazole-ene cycloaddition (NITEC) by using polymers containing protected maleimide (PG-Mal) as well as tetrazole (Tet) moieties (Figure 14). Remarkably, the resulting SCNPs were endowed with fluorescent



**Figure 14.** SCNP formation *via* photoinduced NITEC using polymers containing protected maleimide (in blue color) as well as tetrazole (in red color) moieties. In addition to the NITEC heterocoupling reaction, also the nitrile imine self-dimerization from tetrazole units (homocoupling reaction) takes place as a secondary reaction. Reprinted from [48] with permission.

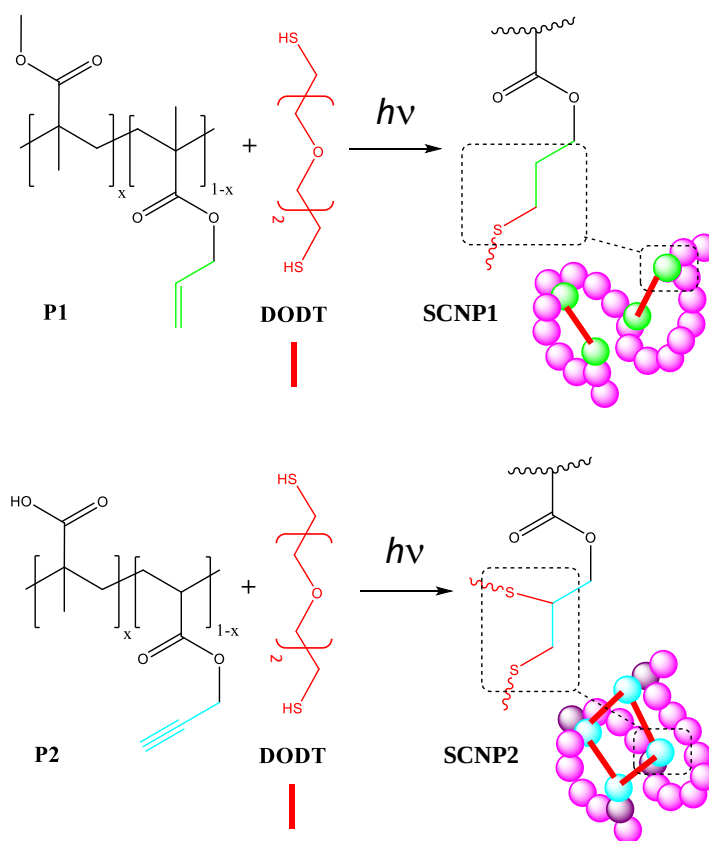
properties due to the fluorescence of the pyrazoline cycloadducts formed upon NITEC. Hence, a broad fluorescence band centered at 558 nm was observed upon excitation of the SCNPs at  $\lambda_{\text{exc}} = 415$  nm. Fluorescence was also observed in the case of SCNPs obtained *via* photoinduced NITEC using polybutadiene [49] and glycopolymer [50] precursors both decorated with PG-Mal as well as Tet units.

### 3.3. Photoinduced nitrile imine-carboxylic acid ligation (NICAL)

Similar to the case of photoinduced NITEC, appropriate copolymers containing Tet as well as carboxylic acid moieties were collapsed with success to SCNPs by Barner-Kowollik and coworkers *via* photoinduced intrachain nitrile imine-carboxylic acid ligation (NICAL) [51].

## 4. Synthesis of single-chain polymer nanoparticles *via* photogenerated collapse induced by external cross-linkers

Pomposo and coworkers reported in 2014 the room temperature synthesis of SCNPs *via* photoactivated radical-mediated thiol-ene/thiol-yne coupling by using 3,6-dioxa-1,8-octane-dithiol (DODT) as homobifunctional cross-linker [52]. As precursors, copolymers decorated with alkene or alkyne pendants synthesized *via* redox-initiated RAFT polymerization were used (see Figure 15). Remarka-



**Figure 15.** Synthesis of SCNPs *via* photoactivated radical-mediated thiol-ene/thiol-yne coupling using 3,6-dioxa-1,8-octane-dithiol (DODT) as homobifunctional cross-linker and copolymers P1 and P2 as precursors decorated with alkene (in red color) and alkyne (in blue color) pendants, respectively. Reprinted from [52] with permission.

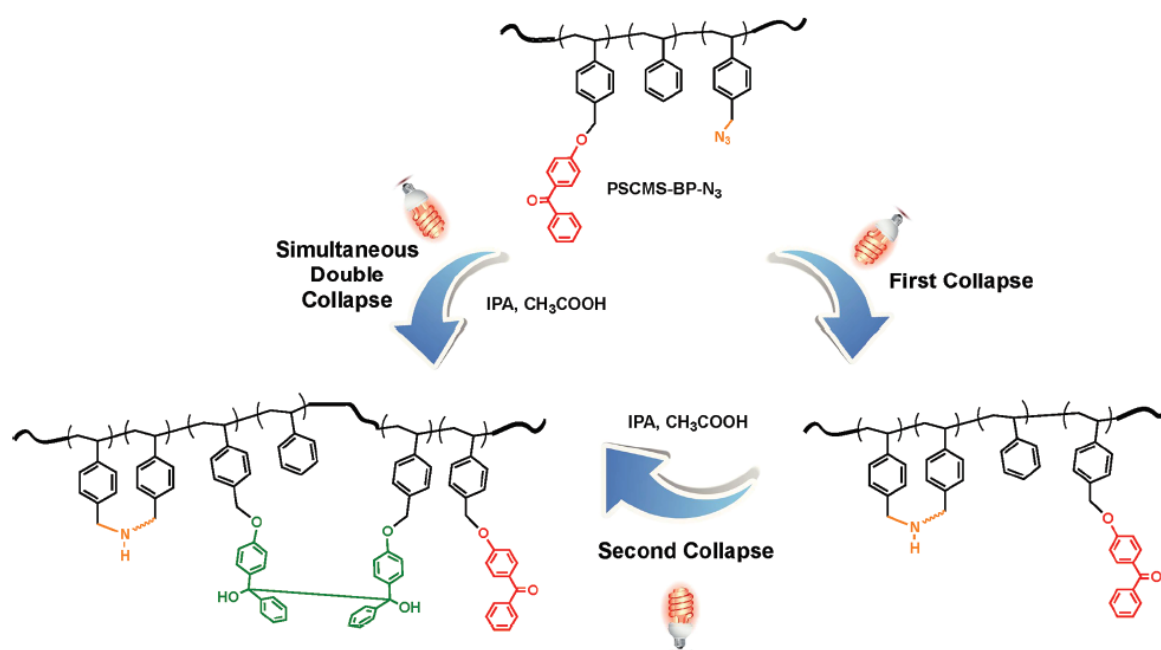
bly, higher chain compaction was observed in the case of SCNPs prepared *via* photoactivated radical-mediated thiol-yne coupling as observed by SAXS measurements and supported by molecular dynamics (MD) simulations. In a subsequent work [53], the merging of zwitterionic ring opening polymerization (ZROP) and photoactivated radical-mediated thiol-yne coupling allowed, for the first

time, the synthesis of elusive polyether SCNPs, broadening the scope of photoactivated radical-mediated thiol-yne coupling for SCNPs formation. Additionally, photogenerated collapse induced by UV irradiation of external bis-azide-containing aggregation induced emission (AIE) cross-linkers has been employed by De La Cuesta and Pomposo [42] as a fast and efficient method to produce highly fluorescent SCNPs. Recently, SCNPs have been additionally prepared through photogenerated collapse using external cross-linkers *via* photoinduced NICAL [37] and *via* photoinduced nitroxide radical- $\alpha$ -hydroxyalkyl phenyl ketone coupling [54].

## 5. Synthesis of single-chain polymer nanoparticles *via* photoactivated multi-folding

### 5.1. Simultaneous photoactivated multi-folding

Barner-Kowollik and coworkers reported the simultaneous photoactivated multi-folding *via* photoinduced NITEC and nitrile imine self-dimerization in copolymers containing protected maleimide as well as tetrazole units [48, 51]. This Group also pioneered the use of simultaneous photoactivated NITEC and NICAL to induce the folding of amphiphilic precursors to fluorescent SCNPs in pure water [50]. More recently, Temel and coworkers [55] have introduced a straightforward method to produce SCNPs by simultaneous photoactivated (UV light,  $\lambda = 350$  nm) double folding of single linear chains containing both pendant azide and benzophenone motifs (see Figure 16-left). Interestingly, these authors performed a clear comparison between SCNPs prepared through simultaneous *vs.* sequential photoactivated double folding (see next section).



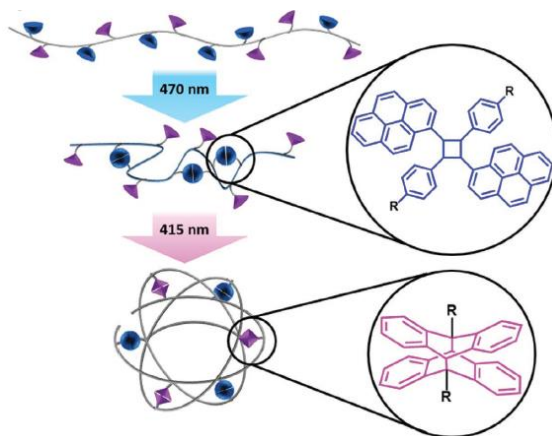
**Figure 16.** Illustration of SCNP formation *via* simultaneous (left) or sequential (right) photoactivated double folding/collapse. IPA = isopropyl alcohol. Reprinted from [55] with permission.

### 5.2. Sequential photoactivated multi-folding

#### 5.2.1. Without external cross-linkers

Figure 16-right shows SCNP fabrication using the sequential photoactivated double folding of a precursor containing azide and benzophenone moieties, as recently reported by Temel and coworkers [55]. Intrachain nitrene C-H insertion upon azide decomposition was selected as the first folding process. The second folding process relayed on intramolecular benzopinacol formation in the presence of isopropyl alcohol (IPA) as a hydrogen donor. A comparison of SCNPs prepared by these authors *via* simultaneous *versus* sequential photoactivated double folding revealed similar values of

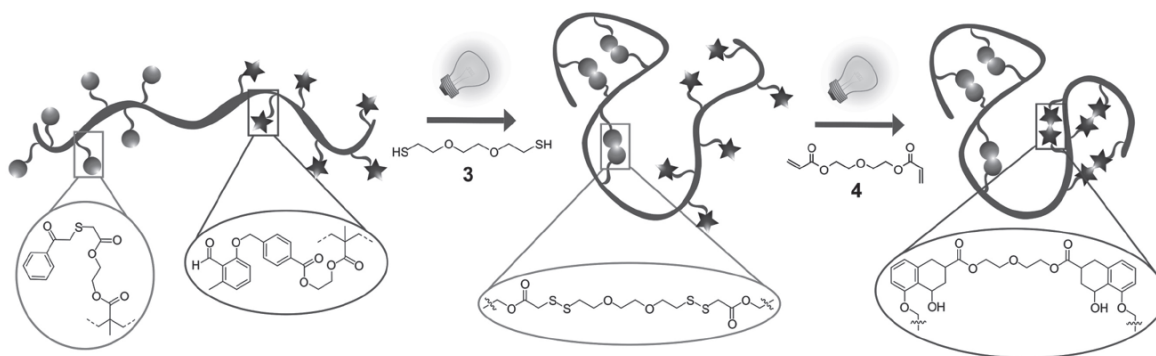
apparent molecular weight (5630 *vs.* 5400 g/mol), hydrodynamic radius (6.6 *vs.* 6.9 nm) and glass transition temperature (151 *vs.* 150°C). Subsequently, Barner-Kowollik *et al.* [56] reported the wavelength-selective folding of single polymer chains decorated with styrylpyrene as well as anthracene groups with different colors of visible light. In a first step, irradiation with blue light ( $\lambda = 470$  nm) triggered the [2 + 2] photocycloaddition of styrylpyrene units whereas violet light ( $\lambda = 415$  nm) induced the [4 + 4] photocycloaddition of anthracene groups in a subsequent step (see Figure 17).



**Figure 17.** Schematic illustration of wavelength-selective folding of single polymer chains decorated with styrylpyrene as well as anthracene groups with different colors of visible light: irradiation with blue light ( $\lambda = 470$  nm) triggered the [2 + 2] photocycloaddition of styrylpyrene units in a first step whereas violet light ( $\lambda = 415$  nm) induced the [4 + 4] photocycloaddition of anthracene groups in a second step. Reprinted from [56] with permission.

### 5.2.2. With external cross-linkers

Pioneering work by Perrier, Delaittre, Barner-Kowollik and coworkers [57] showed the stepwise light-induced dual compaction of single polymer precursors to SCNPs assisted by the use of external cross-linkers in each folding step (Figure 18). As precursors, block copolymers containing phenacyl



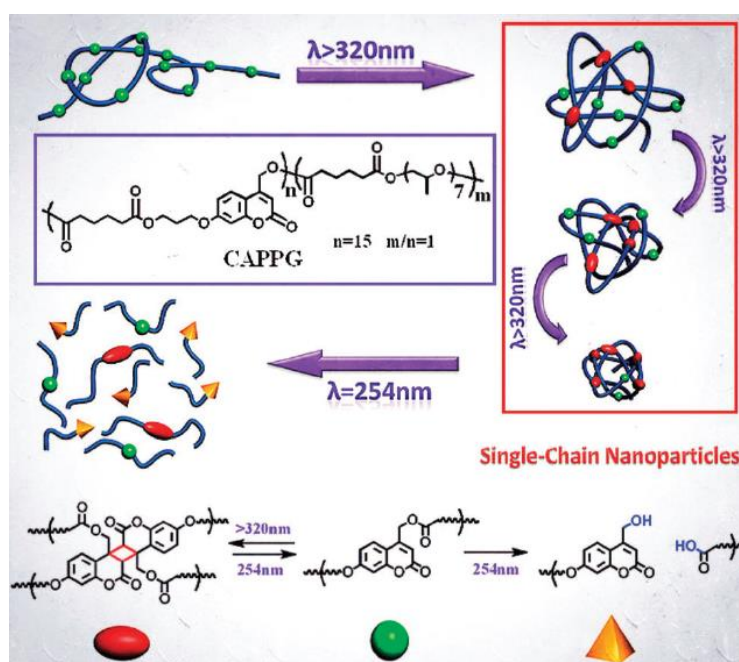
**Figure 18.** Schematic illustration of the sequential photoactivated multi-folding of a precursor containing phenacyl sulfide and protected  $\alpha$ -methylbenzaldehyde units with a dithiol cross-linker ( $\lambda = 355$  nm, 30 min) and a diacrylate cross-linker ( $\lambda = 320$  nm, 30 min), respectively. Reprinted from [57] with permission.

sulfide and protected  $\alpha$ -methylbenzaldehyde pendants were selected. The first folding step was activated with irradiation at 355 nm in the presence of a free dithiol cross-linker for 30 min. The second folding process was performed by irradiation at 320 nm for 30 min using a flexible diacrylate cross-linker. At least for this system, SEC and DLS showed a significantly higher degree of chain compaction in the first step than in the second one.

## 6. Phototriggered disassembly of single-chain polymer nanoparticles

### 6.1. Main-chain disassembly

In a pioneering work, Zhao and coworkers [58] reported the preparation of size-tunable and photodegradable SCNPs using a polyester precursor (hydrodynamic radius = 5.2 nm) bearing coumarin moieties in the main chain (see Figure 19). Hence, SCNPs resulted upon UV irradiation at

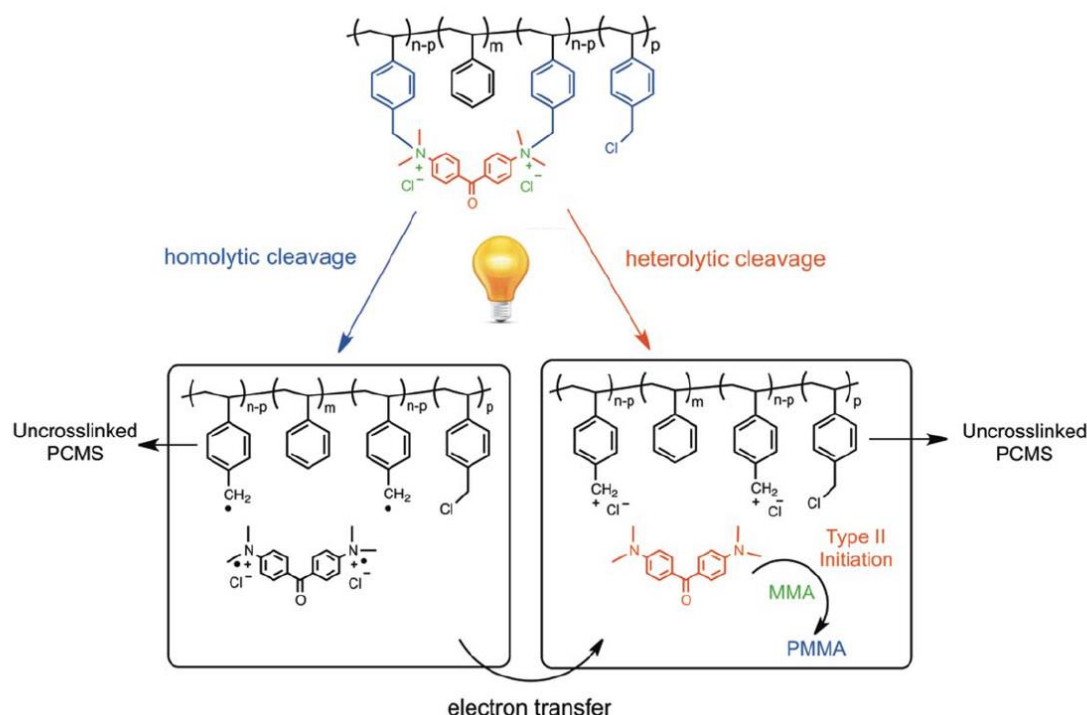


**Figure 19.** Schematic illustration of the formation of size-tunable SCNPs from a polyester precursor bearing coumarin moieties in the main chain (in green color) *via* UV-irradiation ( $\lambda > 320\text{ nm}$ ) at high dilution to give coumarin dimers (in red color) and subsequent main-chain disassembly through UV-irradiation at  $\lambda > 254\text{ nm}$  leading to coumarin photocleaved fragments (in yellow color). Reprinted from [58] with permission.

$\lambda > 320\text{ nm}$  of this precursor under high dilution conditions. SEC and DLS measurements revealed that SCNP size decreases upon increasing UV irradiation time. The degree of coumarin dimerization was found to reach a maximum level of 87 % after 2 h of UV irradiation at  $\lambda > 320\text{ nm}$  (SCNP hydrodynamic radius = 3.0 nm). Remarkably, photo-triggered disassembly of the SCNPs was observed upon progressive UV-irradiation at  $\lambda > 254\text{ nm}$  (up to a limiting time of 3 h) as determined by SEC and DLS measurements. SCNP disassembly was attributed to photocleavage of the coumarin chromophores under such conditions.

### 6.2. External cross-linker disassembly

Recently, Temel and coworkers [59] have reported the unfolding of SCNPs *via* phototriggered external cross-linker disassembly (Figure 20). First, SCNPs were synthesized at high dilution *via* Menshutkin chemistry from a polystyrene copolymer containing  $-\text{CH}_2\text{-Cl}$  functional groups using Michler's ketone (4,4'-bis(dimethylamino)benzophenone) as external cross-linker. Successful SCNP formation was certified by means of a combination of techniques including SEC, DLS, FTIR, DSC and TEM. Remarkably, it was found that the Michler's ketone parts of the SCNPs were highly reactive under photoexcitation so UV irradiated SCNPs ( $\lambda = 350\text{ nm}$ , 2 h, air atmosphere) were able to initiate methyl methacrylate (MMA) polymerization without the need of an external initiator. Concurrently to the release of Michler's ketone upon UV irradiation, unfolding of the SCNPs was observed through SEC and DLS measurements.



**Figure 20.** General mechanism of unfolding of SCNPs *via* phototriggered external cross-linker disassembly for SCNPs prepared from a polystyrene copolymer containing  $-\text{CH}_2\text{-Cl}$  pendants (PCMS) using Michler's ketone as external cross-linker and concurrent photopolymerization of MMA by the released Michler's ketone units. Reprinted from [59] with permission.

## 7. Conclusions

Clean use of photons from light to activate chemical reactions offer many possibilities for the phototriggered synthesis of SCNPs as soft nanomaterials with promising applications in enzyme-mimicking catalysis and nanomedicine, among other different uses. As illustrated in this review article, the energy of photons in the ultraviolet (UV) and visible regions of the electromagnetic spectrum is enough to promote a large variety of photoreactive moieties to excited electronic states. Hence, activation of phototriggerable functional groups in a SCNPs precursor copolymer under highly diluted conditions to drive subsequent intrachain reactions opens the door to facile SCNPs fabrication under very mild photochemical conditions, without the use of high temperatures or aggressive reagents. Nowadays, the different strategies developed for the phototriggered synthesis of SCNPs are: i) photoactivated intrachain homocoupling, with a variety of photodimerizable moieties available such as cinnamoyl, coumarin, anthracene, styrylpyrene, stilbene, ketyl radical, carboxyl radical, nitrile imine functional groups, ii) phototriggered intrachain heterocoupling, and iii) photogenerated collapse induced by external cross-linkers. Current research interest is shifting towards visible-light photoactivated multifolding applied to SCNPs construction as well as innovative strategies for phototriggered disassembly of SCNPs. A bright activity in these new topics is expected in next years.

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