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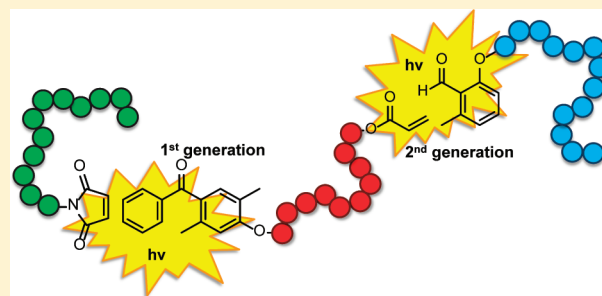
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## Highly Orthogonal Functionalization of ADMET Polymers via Photo-Induced Diels–Alder Reactions

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## S Supporting Information

**ABSTRACT:** Within the current contribution, we introduce two strategies for the catalyst-free, modular, ambient temperature synthesis of ABC triblock copolymers via photoinduced Diels–Alder reactions. On the one hand, the 2-formyl-3-methylphenoxy (FMP) moiety (a second generation photoenol precursor) was employed for orthogonal polymer–polymer conjugations using terminal acrylates of diblock copolymers synthesized via acyclic-diene-metathesis (ADMET) polymerizations to directly prepare triblock copolymers. On the other hand, the disparate reactivity of 2,5-dimethylbenzophenone (first generation photoenol) and the FMP moiety was exploited to selectively synthesize complex triblock copolymers ( $6.5 \text{ kDa} \leq M_n \leq 11.5 \text{ kDa}$ ,  $1.16 \leq \text{PDI} \leq 1.30$ ) via a sequential one pot approach utilizing the extraordinary orthogonality of the photoinduced Diels–Alder reaction. Polymers functionalized with a photoenol (second generation) moiety were employed for conjugation reactions with polymers featuring an acrylate terminus, while polymers having a photoenol (first generation) end group were employed for selective conjugations of maleimide functional polymers. In this context, the selective head-to-tail ADMET polymerization was employed as a straightforward methodology for the preparation of bifunctional polymers having a terminal acrylate and a photoenol end-group.



## ■ INTRODUCTION

One of the main objectives of polymer chemistry is the interdisciplinary bridging between synthesis and material science to promote the preparation of functional materials for potential high-value applications, such as biomedicine (e.g., drug delivery, bone tissue engineering or cell regeneration). To meet the complex challenges that are imposed on such functional materials, it is necessary to prepare well-defined polymers with tailored properties.<sup>1</sup> Specific properties can be achieved by controlling, e.g., the polymer topology, composition, molecular weight and/or the polydispersity.<sup>2</sup> An important class of materials, which has achieved considerable attention due to their unique and specific properties, are block copolymers. Because of their characteristic micro- and nanophase morphologies, they can have unique properties that are difficult to achieve by common homopolymers or polymer blends.<sup>3–5</sup> Classically, well-defined block copolymers are prepared by controlled/living polymerization of one monomer and subsequent chain extension. Of special interest is the incorporation of functional groups during the block copolymer synthesis, because they increase the application possibilities of polymers and allow for a more advanced material design depending on specific structure–property relationships.<sup>6</sup> However, various designed macromolecular materials are

often not accessible by the classic chain extension approach due to the incompatibility of the desired functionalities with the polymerization technique.<sup>7</sup> In order to accelerate the investigation and preparation of new polymeric materials, the introduction of the *click* chemistry concept has possibly led to a paradigm shift toward the modular construction of macromolecular materials.<sup>8</sup> Additionally, modern conjugation protocols enable the (reversible) linkage of biological molecules to functional polymers.<sup>9</sup> The most frequently employed conjugation method in polymer chemistry is the 1,3-dipolar Huisgen cycloaddition, which often meets the extended criteria for highly efficient modular macromolecular synthesis.<sup>10</sup> However, also selected Diels–Alder reactions were classified as *click*-type reactions as outlined by Sharpless and co-workers when introducing the *click* chemistry concept.<sup>11</sup> Diene/dienophile functionalities employed in Diels–Alder polymer–polymer conjugation reactions are furan/maleimide, anthracene/maleimide, and butadiene or cyclopentadiene/electron-deficient dithioesters.<sup>12</sup> We recently introduced a highly efficient photoinduced Diels–Alder conjugation approach,

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which is based on the photoisomerization of *o*-methylphenyl ketones or aldehydes and the resulting *in situ* formation of hydroxy-*o*-quinodimethanes (photoenols) that are suitable for modular polymer–polymer conjugations.<sup>13</sup> Moreover, Meador and co-workers demonstrated the usability and versatility of such a photoinduced [4 + 2] cycloaddition as a polymerization technique for bifunctional molecules to generate polyimides or photocured polymer films.<sup>14,15</sup> Most significantly, however, the light triggered conjugation of photoenol functional polymers has highly attractive features, including nondemanding reaction conditions (e.g., no required catalyst, ambient temperature). Moreover, in contrast to thermally induced Diels–Alder reactions, the phototriggered [4 + 2] cycloaddition is irreversible; this fact should result in thermally more stable polymers that are not susceptible to retro-Diels–Alder reactions. Additionally, we reported the 2-formyl-3-methylphenoxy (FMP) moiety a (second generation photoenol) as a significantly more reactive photoenol precursor compared to the 2,5-dimethylbenzophenone (first generation photoenol) due to the stabilization of the *in situ* formed photoenol intermediate by hydrogen bond formation.<sup>16</sup> However, so far only very reactive dienophiles (e.g., maleimides or electron-deficient dithioesters) have been used for polymer–polymer conjugations via thermally or photoinduced Diels–Alder reactions, whereas relatively unreactive dienophiles such as acrylates have not yet been employed for polymer–polymer conjugations via this method. In a recent publication, we presented a strategy for the postpolymerization modification of polymers having a terminal acrylate. The introduced ADMET–Heck protocol was employed for the selective synthesis of di- and triblock copolymers having an unsaturated backbone.<sup>17</sup> Heck coupling reactions of acrylate terminated polymers with aryl iodide functional polymers were performed at mild temperatures under Jeffery's conditions.<sup>18</sup> As an orthogonal and catalyst-free alternative to the above-noted Heck coupling approach, we introduce herein a photoinduced Diels–Alder modular ligation method, entailing the very efficient conjugation of acrylate terminated polymers with FMP-capped polymers via photoinduced Diels–Alder reaction at ambient temperature. Importantly, the disparate reactivity of the two photoenol (first and second generation) moieties was exploited for the synthesis of triblock copolymers by a sequential one-pot approach, demonstrating the extraordinary orthogonality of these phototriggered *click* reactions.

## ■ EXPERIMENTAL SECTION

**Materials.** Chloroform, dichloromethane and triethylamine were distilled over CaH<sub>2</sub>. *ε*-Caprolactone (*ε*-CL) was distilled from CaH<sub>2</sub> and stored over molecular sieves (4 Å) in a glovebox. Dioxane was distilled over sodium pieces. Benzoic acid (99.5%, Sigma-Aldrich), 10-undecen-1-ol (98%, Aldrich), hexyl acrylate (99%, Aldrich), butyl acrylate (98%, Sigma-Aldrich) *N,N'*-dicyclohexylcarbodiimide (DCC, 99%, Acros), 4-(dimethylamino)pyridine (DMAP, 99% Acros), succinic anhydride (≥99%, Sigma-Aldrich), 2-bromoethanol (95%, Sigma-Aldrich), toluene (extra dry, water <30 ppm, Acros Organics), poly(ethylene glycol) methyl ether (*M<sub>n</sub>* = 2000 g·mol<sup>−1</sup>, Sigma-Aldrich), poly(ethylene glycol) methyl ether methacrylate (PEG-MMA, *M<sub>n</sub>* = 950 Da, Sigma-Aldrich), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 99%, Sigma-Aldrich), acryloyl chloride (97%, Sigma-Aldrich), ethyl vinyl ether (99%, Sigma-Aldrich) were used as received. Monomer 3,<sup>19</sup> model compound 6,<sup>17</sup> 4-hydroxyethoxy-2,5-dimethylbenzophenone, FMP functional poly(*ε*-caprolactone) (P3) and maleimide functional PEG (P14) were synthesized according to published procedures.<sup>13,16</sup>

**Characterization.** FAB (fast atom bombardment) mass spectra and high resolution mass spectra (HRMS) FAB were measured on a Finnigan MAT 95.

<sup>1</sup>H NMR measurements were performed on a Bruker Avance spectrometer operating at 300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C. All samples were dissolved in CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub> and the chemical shifts  $\delta$  are reported in ppm relative to TMS.

Determinations of molecular weights were performed on a Polymer Laboratories PL-SEC 50 Plus system having an auto injector, a guard column (PLgel Mixed C, 50 × 7.5 mm) followed by three linear columns (PLgel Mixed C, 300 × 7.5 mm, 5  $\mu$ m bead-size) and a differential refractive index detector, operating in THF at 40 °C, with a flow rate of 1 mL × min<sup>−1</sup>. The GPC system was calibrated with poly(methyl methacrylate) standards (Polymer Standards Service (PSS), Mainz, Germany) ranging from 700 to 2 × 10<sup>6</sup> Da. The molecular weight distributions were determined relative to PMMA.<sup>20</sup>

SEC/ESI-MS spectra were recorded on a LXQ mass spectrometer (Thermo Fisher Scientific, San Jose, CA) equipped with an atmospheric pressure ionization source operating in the nebulizer-assisted electrospray mode. The instrument was calibrated in the *m/z* range 195–1822 using a standard containing caffeine, Met-Arg-Phe-Ala acetate (MRFA), and a mixture of fluorinated phosphazenes (Ultramark 1621) (all from Aldrich). A constant spray voltage of 4.5 kV, a dimensionless sweep gas flow rate of 2, and a dimensionless sheath gas flow rate of 12 were applied. The capillary voltage, the tube lens offset voltage, and the capillary temperature were set to 60 V, 110 V, and 275 °C, respectively. The LXQ was coupled to a Series 1200 HPLC-system (Agilent, Santa Clara, CA) consisting of a solvent degasser (G1322A), a binary pump (G1312A), and a high-performance autosampler (G1367B), followed by a thermostated column compartment (G1316A). Separation was performed on two mixed bed size exclusion chromatography columns (Polymer Laboratories, Mesopore 2504.6 mm, particle diameter 3  $\mu$ m) with precolumn (Mesopore 50–4.6 mm) operating at 30 °C. THF at a flow rate of 0.30 mL × min<sup>−1</sup> was used as eluent. The mass spectrometer was coupled to the column in parallel to an RI-detector (G1362A with SS420x A/D) in the setup described previously, 0.27 mL × min<sup>−1</sup> of the eluent was directed through the RI detector, and 30  $\mu$ L × min<sup>−1</sup> was infused into the electrospray source after post column addition of a 100  $\mu$ M solution of sodium iodide in methanol at 20  $\mu$ L × min<sup>−1</sup> by a micro flow HPLC syringe pump (Teledyne ISCO, Model 100DM). A 20  $\mu$ L aliquot of a polymer solution with a concentration of ~3 mg mL<sup>−1</sup> was injected onto the HPLC system (the description was taken from a recent publication).<sup>20</sup>

**Synthesis of PEG–Acrylate (P5).** Poly(ethylene glycol) methyl ether acrylate (1.35 g, 0.675 mmol) was weighed into a round-bottom flask and set under argon atmosphere. CHCl<sub>3</sub> (20 mL) was added and the reaction mixture was stirred for 5 min. Subsequently, acryloyl chloride (0.122 g, 1.35 mmol) and, after further 5 min of stirring, Et<sub>3</sub>N (0.171 g, 1.69 mmol) was added. The mixture was stirred for 16 h at ambient temperature. The solvent was removed under reduced pressure and the residue was rapidly filtered through a short column (silica gel, ethyl acetate) to remove the ammonium salts. After concentration of the solution the polymer was precipitated in cold diethyl ether (*M<sub>n,SEC</sub>* = 2.8 kDa, PDI = 1.03).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz),  $\delta$ /ppm: 6.42 (dd, *J* = 17.4, 1.5 Hz, 1H, –CH=CH<sub>2</sub>), 6.14 (dd, *J* = 17.4, 10.3 Hz, 1H, –CH=CH<sub>2</sub>), 5.83 (dd, *J* = 10.3, 1.5 Hz, 1H, –CH=CH<sub>2</sub>), 4.32–4.29 (m, 2H, –O–CH<sub>2</sub>–CH<sub>2</sub>–OCO–), 3.75–3.71 (m, 2H, –O–CH<sub>2</sub>–CH<sub>2</sub>–OCO–), 3.67–3.59 (m, PEG backbone), 3.36 (s, 3H, –OCH<sub>3</sub>).

**Synthesis of Photoenol Precursor (First Generation) (2-(4'-Benzoyl-2',5'-dimethylphenoxy)ethyl Acrylate) (5).** 4-Hydroxyethoxy-2,5-dimethylbenzophenone (1.08 g, 4.00 mmol) was dissolved in CHCl<sub>3</sub> (40 mL). Subsequently, acryloyl chloride (0.72 g, 8.0 mmol) and, after 5 min of additional stirring, Et<sub>3</sub>N (1.01 g, 10.0 mmol) was added. The mixture was stirred for 16 h at ambient temperature. The solvent was then removed under reduced pressure and the residue was rapidly filtered through a short column (silica gel, ethyl acetate) to remove the ammonium salts. After concentration of the solution the crude product was purified by flash chromatography (silica gel,

hexane:ethyl acetate, 2:1). The product was obtained as a highly viscous yellowish oil (1.22 g, 94%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz),  $\delta/\text{ppm}$ : 7.81 (d,  $J = 7.0$  Hz, 2H, ArH), 7.58 (t,  $J = 7.4$  Hz, 1H, ArH), 7.45 (t,  $J = 7.5$  Hz, 2H, ArH), 7.21 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.65 (dd,  $J = 17.3, 1.3$  Hz, 1H,  $-\text{CH}=\text{CH}_2$ ), 6.37 (dd,  $J = 17.3, 10.4$  Hz, 1H,  $-\text{CH}=\text{CH}_2$ ), 6.05 (dd,  $J = 10.4, 1.3$  Hz, 1H,  $-\text{CH}=\text{CH}_2$ ), 2.32 (s, 3H, Ar- $\text{CH}_3$ ), 2.20 (s, 3H, Ar- $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz),  $\delta/\text{ppm}$ : 197.95 (Ar-C(O)-Ar'), 166.08 ( $-\text{OC}(\text{O})-\text{CH}=\text{CH}_2$ ), 158.33 ( $-\text{C}_{\text{Ar}}-\text{O}-$ ), 138.85 ( $\text{C}_{\text{Ar}}$ ), 137.69 ( $\text{C}_{\text{Ar}}$ ), 132.58 ( $\text{C}_{\text{Ar}}$ ), 131.39 ( $-\text{OC}(\text{O})-\text{CH}=\text{CH}_2$ ), 130.77 ( $\text{C}_{\text{Ar}}$ ), 130.07 ( $\text{C}_{\text{Ar}}$ ), 128.37 ( $2 \times \text{C}_{\text{Ar}}$ ), 128.17 ( $-\text{OC}(\text{O})-\text{CH}=\text{CH}_2$ ), 123.70 ( $\text{C}_{\text{Ar}}$ ), 113.76 ( $\text{C}_{\text{Ar}}$ ), 66.18 ( $-\text{CH}_2-\text{CH}_2-\text{OC}(\text{O})-$ ), 62.81 ( $-\text{CH}_2-\text{CH}_2-\text{OC}(\text{O})-$ ), 20.61 ( $-\text{C}_{\text{Ar}}-\text{CH}_3$ ), 15.69 ( $-\text{C}_{\text{Ar}}-\text{CH}_3$ ).

HRMS (FAB) of  $\text{C}_{20}\text{H}_{20}\text{O}_4$ ,  $[\text{M} + \text{H}]^+$ : calcd, 325.1439; found, 325.1440.

**General Procedure for ADMET Polymerizations.** Monomer 3 and the selected chain-stopper (4, 5, P5) were weighed into a Supelco conical vial. DCM (0.3 mL) was subsequently added and the vial was closed with a screw cap comprising a rubber septum. After 5 min of stirring at a temperature of 40 °C, the required amount of ruthenium-catalyst (Hoveyda–Grubbs second generation) (1.0 mol % to 3) in DCM (150  $\mu\text{L}$ ) was added and a needle was inserted into the rubber septum. After 24 h the reaction was quenched by adding ethyl-vinyl ether (9 eq. to catalyst) to the cooled reaction mixture and THF (ca. 2 mL) was added. The ADMET polymers were isolated by precipitation in cold pentane. Yields ranged from 85 to 95%. The molecular weights were determined by SEC analysis (see Table 1).

**Table 1. Analytical Data (SEC) of Homopolymers and Diblock Copolymers Prepared via Head-to-Tail ADMET Polymerization with Selective Chain-Stoppers**

| monomer | chain-stopper | ratio [3]:<br>[CS] | copolymer | $M_{n,\text{SEC}} /$<br>[kDa] | PDI  |
|---------|---------------|--------------------|-----------|-------------------------------|------|
| 3       | 4             | 10:1               | P6        | 3.9                           | 1.34 |
| 3       | 5             | 20:1               | P8        | 7.2                           | 1.76 |
| 3       | 5             | 15:1               | P9        | 5.1                           | 1.63 |
| 3       | 5             | 10:1               | P10       | 3.5                           | 1.42 |
| 3       | 5             | 20:1               | P11       | 7.1                           | 1.77 |
| 3       | P5            | 10:1               | P7        | 5.6                           | 1.30 |

**General Procedure for Photoinduced Diels–Alder Reactions.** The dienophile (1 equiv) and the photoactive *o*-methylphenyl ketone or aldehyde (1 equiv) were weighed in a vial (Pyrex, diameter 20 mm). A mixture of DCM/MeCN (1:2, 2 mL) was added and the vial was sealed with a rubber septum. Argon was then percolated through the solution for 15 min. The solution was irradiated for selected times (3 or 24 h) with a 36 W compact low-pressure UV-A

lamp (Arimed B6, Cosmedico GmbH, Stuttgart, Germany) emitting at 320 nm ( $\pm 30$  nm) at a distance of 40–50 mm in a custom-built photoreactor. After evaporation of the solvent, the polymers were dried under vacuum without any further purification.

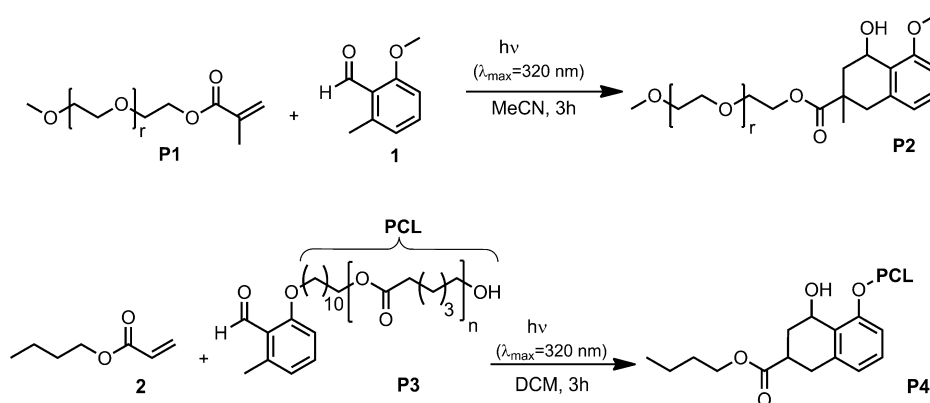
## RESULTS AND DISCUSSION

Initially, the suitability of the 2-formyl-3-methylphenoxy (second generation photoenol) moiety as photoenol precursor for the photoinduced conjugation of terminal acrylates via Diels–Alder reactions was explored. Thus, two acrylates (P1, 2) and the FMP precursor (1) or FMP functional polymer P3 were employed in photoinduced Diels–Alder reactions (Scheme 1).

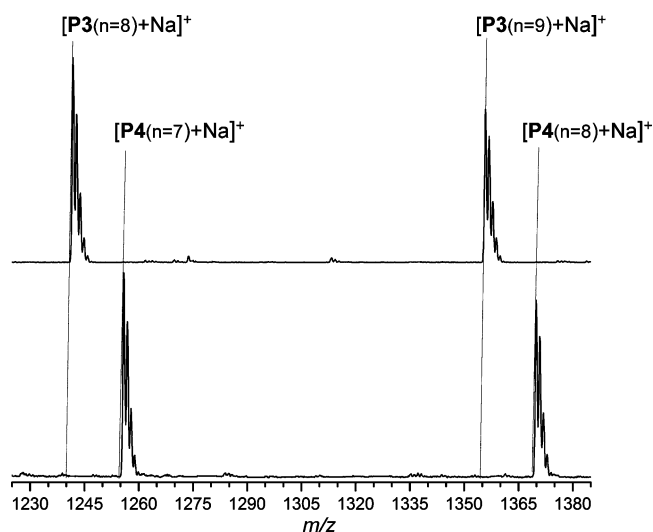
Initially, the FMP precursor (1) was reacted with poly-(ethylene glycol) methyl ether methacrylate (PEG-MMA,  $M_n = 950$  Da, P1), and butyl acrylate (2) with FMP functional PCL (P3). The photoinduced Diels–Alder reactions were performed using a 1:1 molar ratio between the reactants and either acetonitrile or dichloromethane as solvent. Congruent with the *click* criteria defined for macromolecular chemistry,<sup>10</sup> the SEC-ESI/MS analysis of the crude reaction mixtures showed quantitative conversion of the polymer end-groups after 3 h of irradiation with UV-light (320 nm) (Figure 1, mass assignments (Tables S1 and S2) and additional SEC-ESI/MS spectrum (Figure S1); see also Supporting Information).

These promising model reactions demonstrated the utility of the FMP moiety as a suitable photoenol precursor for polymer–polymer conjugations with (meth)acrylate functional polymers. Moreover, PEG with a methacrylate end-group as a sterically more demanding dienophile (compared to an acrylate) was successfully employed in the photoinduced conjugation with the FMP moiety. However, we wanted to focus on acrylate terminated polymers in order to facilitate polymer–polymer conjugations. Such polymers are prepared in a straightforward fashion by, e.g., acrylation of hydroxyl terminated polymers or directly via acyclic diene metathesis (ADMET) polymerization of unsymmetrical  $\alpha,\omega$ -dienes.<sup>21</sup> We recently introduced the concept of a selective head-to-tail ADMET polymerization using a monomer containing both a terminal double bond and an acrylate. Such monomers polymerize with high cross-metathesis selectivity, opening access to different polymer architectures, such as diblock or star-shaped polymers, if a selective and irreversible chain-transfer agent (mono- or multifunctional acrylate) is added.<sup>19</sup> Such a chain-transfer agent allows controlling the molecular

**Scheme 1. Model Reactions of the FMP Photoenol Precursor (1) or FMP Functional Poly( $\epsilon$ -caprolactone) (FMP–PCL, P3,  $M_{n,\text{SEC}} = 2.2$  kDa, PDI = 1.06)**



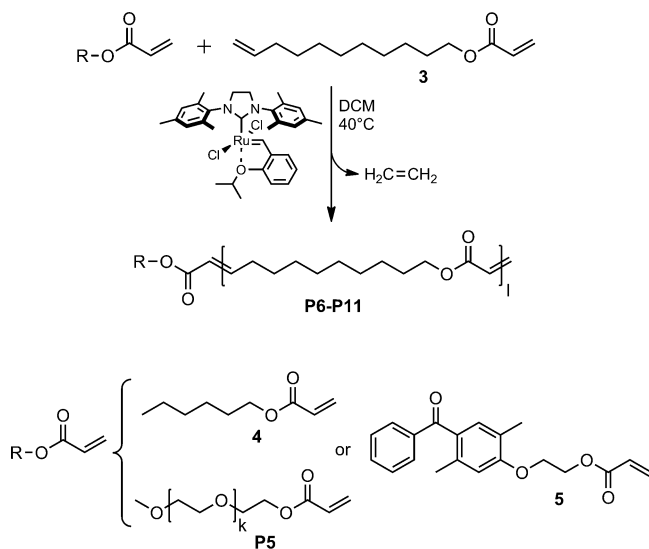




**Figure 1.** Expanded ESI-MS spectrum ( $m/z = 1230\text{--}1380$ ) of the photoinduced  $[4 + 2]$  cycloaddition of **P3** (top) and **2** to afford **P4** (bottom).

weight and direct functionalization of the ADMET polymer by reacting selectively with one of the end groups (terminal double bond). On the basis of this principle, diverse homopolymers and (amphiphilic) diblock copolymers were synthesized (Scheme 2) for the current work using undec-10-enyl acrylate

**Scheme 2.** Head-to-Tail ADMET Polymerization of Monomer (**3**) in Presence of a Selective Chain-Stopper (**4**, **5**, or **P5**) at  $40^\circ\text{C}$  Using the Hoveyda–Grubbs Second Generation Catalyst (1–2 mol % to **3**)



(**3**) as monomer, and either hexyl acrylate, acrylated PEG, or an acrylated photoenol moiety (first generation) as chain-stoppers (for analytical SEC data, see Table 1).

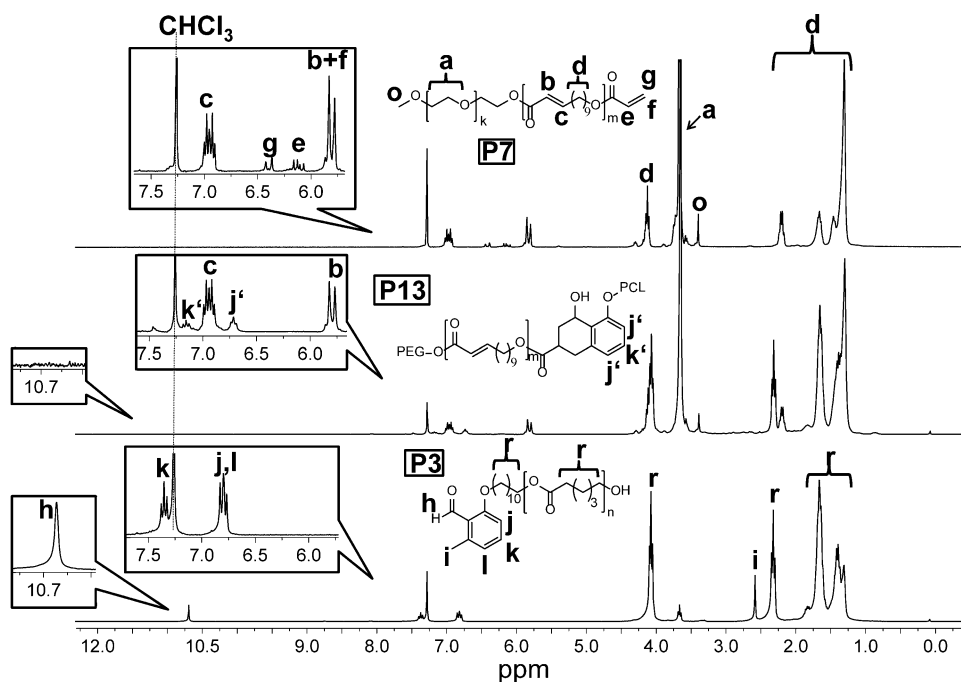
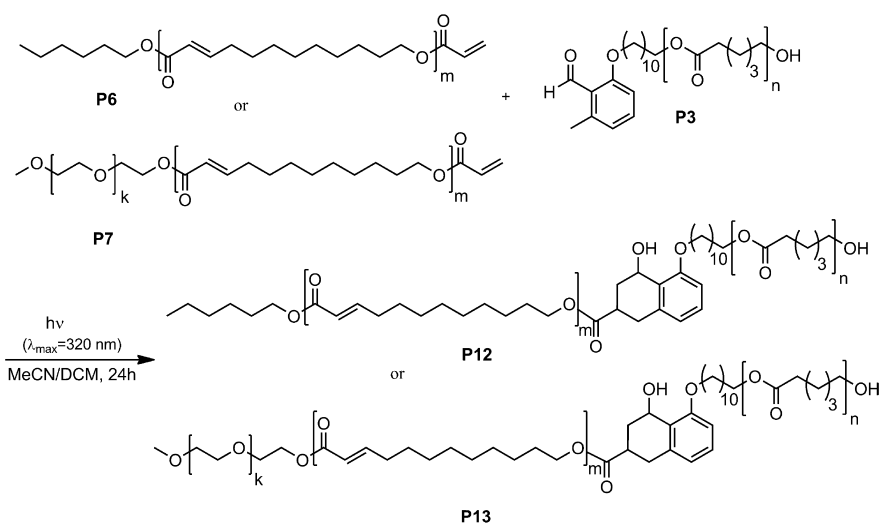
The generated ADMET polymers contain internal  $\alpha,\beta$ -unsaturated ester functions and acrylate end-moieties, allowing for their postpolymerization functionalization. In order to determine the selectivity of the photoinduced Diels–Alder reaction between the acrylate end group and the internal  $\alpha,\beta$ -unsaturated esters, several test reactions were carried out using a model compound (**6** having both an acrylate and an internal

$\alpha,\beta$ -unsaturated ester function). These model studies should be representative for possible conjugation reactions of the ADMET polymers (see Supporting Information for details of these experiments, in Scheme S1 and Figures S2 and S3).  $^1\text{H}$  NMR analysis demonstrated that it is possible to achieve orthogonal conjugation of the terminal acrylic double bond without reaction of the internal  $\alpha,\beta$ -unsaturated ester after 2 h of irradiation with UV-light (320 nm) using the FMP functional polymer (**P3**) in these photoinduced Diels–Alder reactions at ambient temperature. Therefore, in subsequent reactions, the terminal acrylate of the ADMET polymers was employed for selective polymer–polymer conjugations via photoinduced Diels–Alder reactions. Initially, polymer–polymer conjugations were centered on the light triggered reaction of ADMET homopolymers or diblock copolymers synthesized with hexyl acrylate (**4**) or acrylated PEG (**P5**) chain stopper and the FMP functional PCL (**P3**) (Scheme 3). It should be noted that, in principle, two regio-isomers can be formed during the photoinduced Diels–Alder reaction, which is predominantly determined by secondary orbital interactions.<sup>22</sup> However, for a successful polymer–polymer conjugation it is not important which regio-isomer will be formed. Therefore, all schemes within this manuscript only depict one of the possible regio-isomers.

Generally, the same conditions were used as for the model studies except for the reaction time, which was extended to 24 h in order to ensure a full end-group conversion. In addition, the photoinduced conjugation was performed with a 1:1 molar ratio of the polymers. The successful polymer–polymer conjugation of the ADMET polymer (**P7**) and the photoenol-capped PCL (PCL-FMP, **P3**) was shown via  $^1\text{H}$  NMR analysis. The NMR spectrum of the crude reaction mixture (after 24 h of irradiation with UV-light) showed complete conversion of the photoenol (**h**, **i**) and acrylate (**e**, **f**, **g**) end group signals, and the presence of the characteristic signals (**j'**, **k'**) of the expected block copolymer in the expected integrals' ratio (2:1) (Figure 2). Furthermore, the internal  $\alpha,\beta$ -unsaturated ester functions remained unaltered. The SEC analysis of the crude product displayed a clear shift to higher molecular weights, if compared to the starting polymers (Figure 3 and Table 2), which is further proof for the successful polymer–polymer conjugation.

So far, it was shown that polymers with an FMP moiety can be successfully employed in efficient polymer–polymer conjugations with acrylate terminated polymers, while at the same time the 2,5 dimethylbenzophenone moiety (first generation photoenol precursor) has emerged as a very efficient photoenol precursor for polymer–polymer conjugations with maleimide functional polymers.<sup>13</sup> Therefore, we intended to prepare functionalized ADMET polymers having an additional terminal photoenol moiety. Such polymers are readily accessible via an acrylated photoenol precursor as a chain-transfer agent in ADMET polymerizations of monomer (**3**), which leads directly to end-group functionalized ADMET polymers (refer to Scheme 2). In this context, the acrylated photoenol precursor (first generation) appears to be particularly well suited as selective chain-transfer agent, because—in contrast to the aldehyde functional photoenol (second generation)—no compatibility problems with the metathesis catalyst were observed. With regard to the end-groups, the ADMET polymers are telechelic, having one photoenol and one acrylate moiety. To assess their selectivity in photoinduced Diels–Alder reactions, a blank test of the ADMET polymer

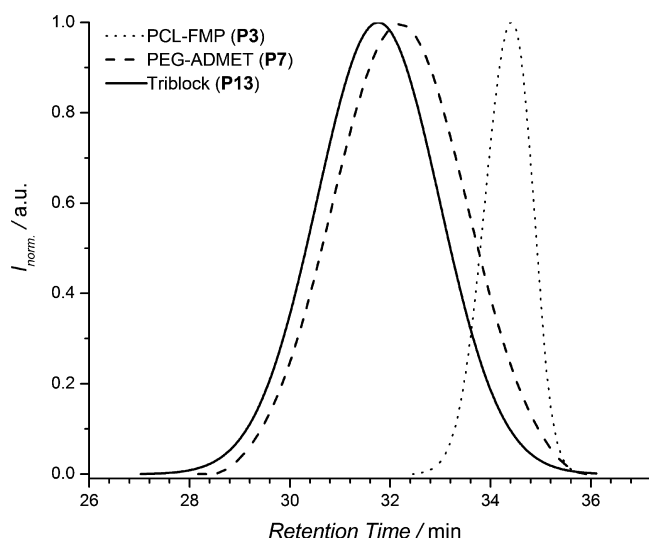
**Scheme 3.** Synthesis of Diblock and Triblock Copolymers by Photo-Induced Diels–Alder Reaction of the ADMET Polymers (P6, P7) and the FMP Functional PCL (P3)



**Figure 2.** Full scale and expansion of the  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) spectra of the photoenol (second generation) functionalized poly( $\epsilon$ -caprolactone) ( $M_{n,\text{SEC}} = 2.2$  kDa, PDI = 1.06, P3, bottom), the ADMET diblock copolymer P7 (top), and the Diels–Alder product P13 (middle).

(P8) equipped with a terminal acrylate ( $\omega$ -chain end) and a photoenol moiety (first generation,  $\alpha$ -chain end) was carried out. In the absence of any further dienophile, inter- or intramolecular reactions of this bifunctional ADMET polymer were not observed, since  $^1\text{H}$  NMR and SEC analysis showed no difference before and after this blank test. Thus, the photoenol moiety (first generation) shows different reactivity compared to the photoenol moiety (second generation), because it does not react with the terminal acrylate (for details see Supporting Information, Figures S1 and S7). After this successful study, the generated bifunctional ADMET polymers were employed for the synthesis of diblock copolymers using a maleimide functional PEG (P14) as dienophilic substrate, which should further demonstrate the applicability of the photoenol capped ADMET polymer for selective photoinduced polymer–

polymer conjugations (see Supporting Information, Figures S8 and S9). In order to prove the high orthogonality that photoinduced Diels–Alder *click* reactions can display, we employed both photoenol precursors (first and second generation) in polymer–polymer conjugations with different dienophiles using a sequential one pot procedure. Thus, the photoenol moiety (first generation) was employed for selective polymer–polymer conjugation with maleimide functional PEG, and on the other hand, the photoenol moiety (second generation) functioned in polymer–polymer conjugations of macromolecules having a terminal acrylate, as already demonstrated in synthesis of triblock copolymers described above. We developed a strategy for the synthesis of triblock copolymers from the already prepared bifunctional ADMET polymers P9–P11 including the primary photoinduced



**Figure 3.** SEC analysis of the polymer conjugation of the FMP functional poly( $\epsilon$ -caprolactone) ( $M_{n,SEC} = 2.2$  kDa, PDI = 1.06, **P3**) and the ADMET diblock copolymer ( $M_{n,SEC} = 5.6$  kDa, PDI = 1.30, **P7**) and thereof derived triblock copolymer ( $M_{n,SEC} = 7.5$  kDa, PDI = 1.28, **P13**). The photoinduced Diels–Alder reaction was performed at ambient temperature  $c(\text{P7}) = 5 \text{ g} \times \text{L}^{-1}$ , for 24 h under irradiation with UV light ( $\lambda_{\text{max}} = 320 \text{ nm}$ ).

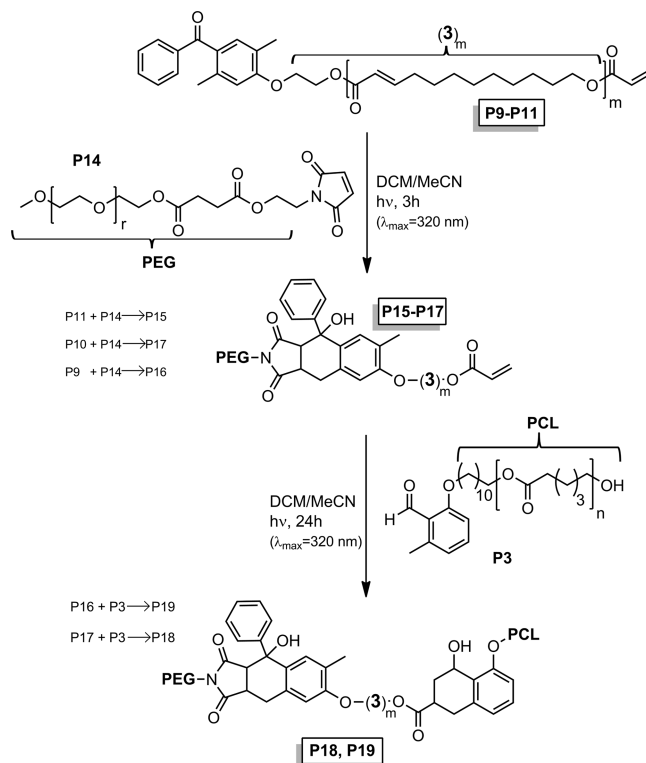
reaction of the photoenol end-group moiety (first generation) with a maleimide functional PEG (**P14**) and the subsequent phototriggered reaction of the terminal acrylate with a photoenol (second generation) capped PCL (**P3**) (Scheme 4).

The ABC-triblock copolymer synthesis was carried out as a sequential one-pot procedure, taking a control sample for  $^1\text{H}$  NMR/SEC analysis after the first conjugation of **P9** or **P10** with **P14** to test for full conversion of the end-groups and formation of the corresponding AB-diblock copolymer **P16** or **P17**. After the subsequent photoinduced Diels–Alder reaction of the diblock copolymers (**P16** and **P17**) with **P3**, the final ABC-triblock copolymers (**P18** and **P19**) were analyzed via  $^1\text{H}$  NMR and SEC analysis (see also Supporting Information, Figures S10–S13).

Comparison of the NMR spectra of the diblock copolymer **P17**, photoenol (second generation) capped PCL **P3** and the product **P18** showed complete conversion of the end-group signals (**h–l**) and display the expected signals of the conjugated polymer (**a–e**, **o'–q'**) (Figure 4).

The SEC analysis of the crude product **P18** displayed a clear shift to higher molecular weights relatively to the starting polymers **P10**, **P14**, and **P3** (Figure 5, Table 3) and the temporary diblock copolymer **P17**, which is a further proof for the successful polymer–polymer conjugation to afford the triblock copolymer.

**Scheme 4.** Sequential One Pot Approach for the Synthesis of Triblock Copolymers Employing the Bifunctional ADMET Polymer (**P9**, **P10**) as Middle Block



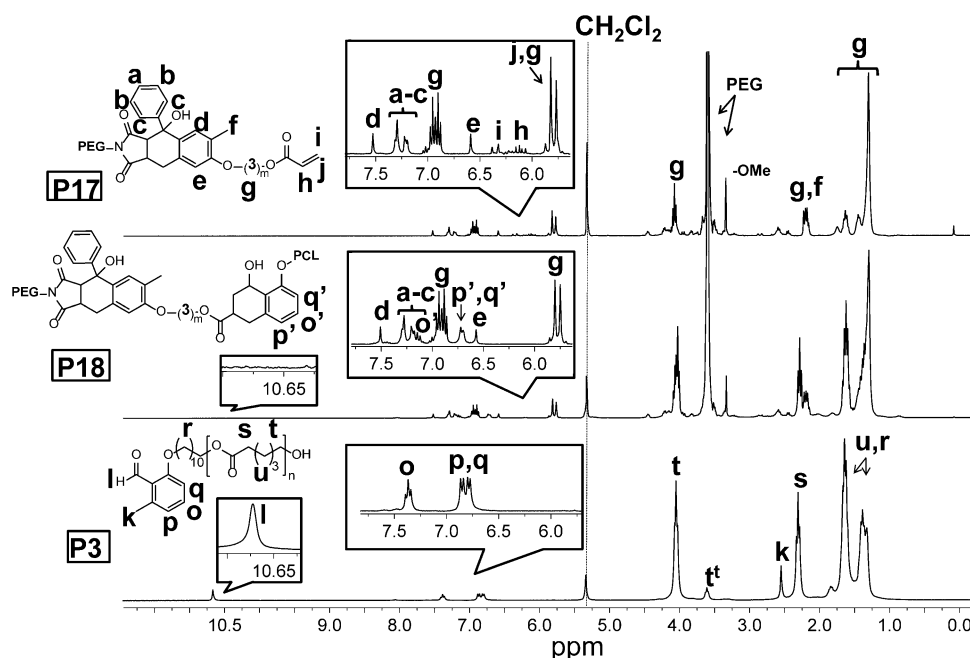
## CONCLUSIONS

Photoinduced Diels–Alder reactions are introduced as a highly orthogonal polymer–polymer conjugation methodology for polymers having a terminal acrylate and a photoenol precursor moiety. Herein, the photoenol moiety (second generation) proved to be a powerful diene for the remarkably selective conjugation of acrylate terminated polymers (as dienophilic substrates) having unsaturated entities in their backbone. Notably, such a modular ligation of acrylate functional polymers via Diels–Alder chemistry was thus demonstrated for the first time, offering new opportunities in bioconjugation, macromolecular synthesis and preparation of novel advanced materials. In order to achieve additional orthogonality of the photoinduced Diels–Alder reaction, we evidenced that both *click* functionalities (photoenol first and second generation) can be employed for highly orthogonal polymer–polymer conjugation reactions with selected dienophiles. Thus, the selectivity of the photoenol functional groups toward different dienophiles was employed for the synthesis of complex triblock copolymers by performing two orthogonal Diels–Alder reactions on the same telechelic polymers in a stepwise, one-pot fashion. Here, the ADMET polymerization technique confirmed its efficiency in preparing sophisticated end-group

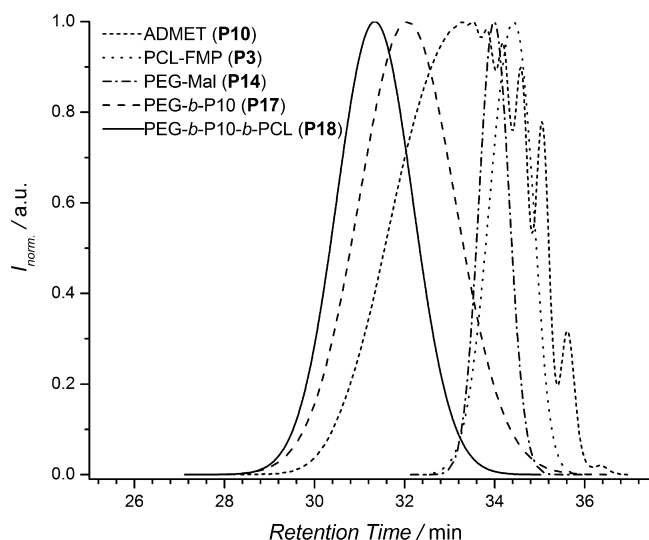
**Table 2.** SEC Data of Diblock and Triblock Copolymers Prepared *via* Photo-Induced Diels–Alder Reaction of ADMET Polymers and FMP-Terminated Polymer **P3** (Scheme 3)

| acrylate polymer | $M_{n,SEC}$ (PDI) <sup>a</sup> [kDa] | photoenol polymer | $M_{n,SEC}$ (PDI) <sup>a</sup> [kDa] | copolymer  | $M_{n,SEC}$ (PDI) <sup>a</sup> [kDa] |
|------------------|--------------------------------------|-------------------|--------------------------------------|------------|--------------------------------------|
| <b>P6</b>        | 3.9 (1.34)                           | <b>P3</b>         | 2.2 (1.06)                           | <b>P12</b> | 6.9 (1.16)                           |
| <b>P7</b>        | 5.6 (1.30)                           | <b>P3</b>         | 2.2 (1.06)                           | <b>P13</b> | 7.5 (1.28)                           |

<sup>a</sup>Relative to linear PMMA Standards.



**Figure 4.** Full scale and expansion of the  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 300 MHz) spectra of the photoinduced Diels–Alder reaction of diblock copolymer **P17** (top) and FMP functional PCL **P3** (bottom) to afford the triblock copolymer **P18** (middle).



**Figure 5.** SEC analysis of the polymer–polymer conjugation of the bifunctional ADMET polymer **P10** ( $M_{n,\text{SEC}} = 3.5$  kDa, PDI = 1.42), maleimide functional PEG **P14** ( $M_{n,\text{SEC}} = 2.6$  kDa, PDI = 1.03), FMP functional PCL **P3** ( $M_{n,\text{SEC}} = 2.2$  kDa, PDI = 1.06), temporary diblock copolymer PEG-*b*-P10 **P17** ( $M_{n,\text{SEC}} = 6.5$  kDa, PDI = 1.33) and the final triblock copolymer PEG-*b*-P10-*b*-PCL **P18** ( $M_{n,\text{SEC}} = 9.4$  kDa, PDI = 1.20).

**Table 3.** Analytical Data (SEC) of the Triblock Copolymer **P18** and Its Components *via* a Sequential One-Pot Procedure (Scheme 4)

|  | $M_{n,\text{SEC}} / [\text{kDa}]$ | PDI  |
|--|-----------------------------------|------|
| PCL–FMP ( <b>P3</b> )                            | 2.2                               | 1.06 |
| ADMET ( <b>P10</b> )                             | 3.5                               | 1.42 |
| PEG–Mal ( <b>P14</b> )                           | 2.6                               | 1.03 |
| PEG- <i>b</i> -P10 ( <b>P17</b> )                | 7.9                               | 1.21 |
| PEG- <i>b</i> -P10- <i>b</i> -PCL ( <b>P18</b> ) | 9.4                               | 1.20 |

functionalized polymers in a straightforward fashion. Finally, the additional selectivity of the photoinduced Diels–Alder *click* reaction through the choice of the photoenol and dienophile end group functionality is a unique attribute, which cannot readily be achieved by any other *click* methodology, allowing advanced macromolecular material design. Moreover, the one pot procedure for the straightforward preparation of such sophisticated triblock copolymers illustrates the versatility, simplicity, and efficiency of the highly orthogonal photo-triggered Diels–Alder *click* reaction for modular polymer–polymer conjugations.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Additional NMR spectra, SEC analyses, and ESI–MS spectra/analyses related to the present investigation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Liu, F.; Urban, M. W. *Prog. Polym. Sci.* **2010**, *35* (1–2), 3–23.



- (2) Roy, D.; Cambre, J. N.; Sumerlin, B. S. *Prog. Polym. Sci.* **2010**, *35* (1–2), 278–301.
- (3) Katz, J. S.; Zhong, S.; Ricart, B. G.; Pochan, D. J.; Hammer, D. A.; Burdick, J. A. *J. Am. Chem. Soc.* **2010**, *132* (11), 3654–3655.
- (4) Kim, J. K.; Yang, S. Y.; Lee, Y.; Kim, Y. *Prog. Polym. Sci.* **2010**, *35* (11), 1325–1349.
- (5) Gohy, J.-F.; Abetz, V., *Adv. Polym. Sci.: Block Copolymers II*, Ed. Springer: Berlin and Heidelberg, Germany, 2005; Vol. 190, pp 65–136.
- (6) Frechet, J. *Science* **1994**, *263* (5154), 1710–1715.
- (7) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2009**, *43* (1), 1–13.
- (8) Barner-Kowollik, C.; Inglis, A. J. *Macromol. Chem. Phys.* **2009**, *210* (12), 987–992.
- (9) Chmielewski, M. K. *Org. Lett.* **2009**, *11* (16), 3742–3745.
- (10) Barner-Kowollik, C.; Du Prez, F. E.; Espeel, P.; Hawker, C. J.; Junkers, T.; Schlaad, H.; Van Camp, W. *Angew. Chem., Int. Ed.* **2011**, *50* (1), 60–62.
- (11) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40* (11), 2004–2021.
- (12) Tasdelen, M. A. *Polym. Chem.* **2011**, *2* (10), 2133–2145.
- (13) Gruending, T.; Oehlenschlaeger, K. K.; Frick, E.; Glassner, M.; Schmid, C.; Barner-Kowollik, C. *Macromol. Rapid Commun.* **2011**, *32* (11), 807–812.
- (14) Meador, M. A. B.; Meador, M. A.; Williams, L. L.; Scheiman, D. A. *Macromolecules* **1996**, *29* (27), 8983–8986.
- (15) Tyson, D. S.; Ilhan, F.; Meador, M. A. B.; Smith, D. D.; Scheiman, D. A.; Meador, M. A. *Macromolecules* **2005**, *38* (9), 3638–3646.
- (16) Pauloehr, T.; Delaittre, G.; Winkler, V.; Welle, A.; Bruns, M.; Börner, H. G.; Greiner, A. M.; Bastmeyer, M.; Barner-Kowollik, C. *Angew. Chem., Int. Ed.* **2012**, *51* (4), 1071–1074.
- (17) Winkler, M.; Montero de Espinosa, L.; Barner-Kowollik, C.; Meier, M. A. R. *Chem. Sci.* **2012**, DOI: 10.1039/C2SC20402A.
- (18) Jeffery, T. J. *Chem. Soc., Chem. Commun.* **1984**, *19*, 1287–1289.
- (19) Montero de Espinosa, L.; Meier, M. A. R. *Chem. Commun.* **2011**, *47* (6), 1908–1910.
- (20) Glassner, M.; Oehlenschlaeger, K. K.; Gruending, T.; Barner-Kowollik, C. *Macromolecules* **2011**, *44* (12), 4681–4689.
- (21) Mutlu, H.; de Espinosa, L. M.; Meier, M. A. R. *Chem. Soc. Rev.* **2011**, *40* (3), 1404–1445.
- (22) Alston, P. V.; Ottenbrite, R. M.; Cohen, T. J. *Org. Chem.* **1978**, *43* (10), 1864–1867.