Macromolecules

Article

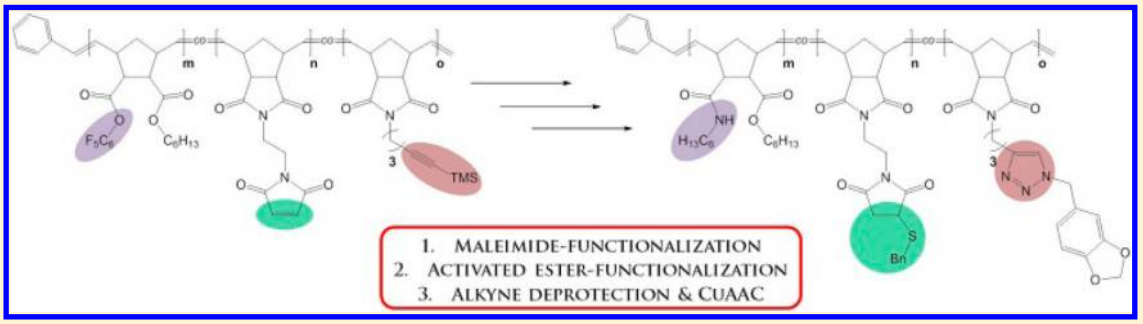
pubs.acs.org/Macromolecules

ROMP Copolymers for Orthogonal Click Functionalizations

Mark Schaefer, Nils Hanik, and Andreas F. M. Kilbinger*

Department of Chemistry, University of Fribourg, Chemin du Musée 9, CH-1700 Fribourg, Switzerland

Supporting Information



ABSTRACT: The ring-opening metathesis polymerization using ruthenium carbene initiators developed by Grubbs et al. is one of the most functional group tolerant living polymerization methods known. One of the most used postpolymerization functionalization methods used today is the copper-catalyzed 1,3-dipolar cycloaddition between alkynes and organic azides. Organic azides are, however, not tolerated by ruthenium carbene initiators, and nonprotected alkynes have been shown to slow down the propagation reaction or react with the propagating species leading to broad molecular weight distributions. Here we report the copolymer synthesis of three orthogonally functionalizable monomers: one carrying an activated pentafluorophenyl ester, one a maleimide unit, and a third one a trialkylsilyl-protected alkyne. From these monomers, statistical terpolymers as well as diblock copolymers were synthesized with different molecular weights and monomer compositions or block ratios, respectively. Excellent control over molecular weight and molecular weight distribution could be achieved using Grubbs' first-generation ruthenium carbene initiator. Herein we present the synthesis and orthogonal triple postpolymerization functionalization of these copolymers.

1. INTRODUCTION

Since the term "click chemistry" was coined by Sharpless in 2001,[1] the interest in modular, widely applicable, and high yielding reactions has virtually exploded. In polymer chemistry in particular, high yielding reactions have always been the foundation of all step-growth processes and postpolymerization modifications of polymer side- and end-groups. Focusing on chemoselectivity and orthogonality, postpolymerization modifications offer a synthetic pathway leading to functional polymers with defined molecular weight, composition, and architecture. This method can therefore facilitate the establishment of structure−property relationships in e.g. combinatorial material discovery due to the synthesis of a broad variety of functional polymers based on one single polymer precursor. With the advancements of living radical polymerization techniques, well-defined polymers capable of undergoing high yielding postpolymerization functionalization have received increased attention. Theato and Klok recently reviewed the areas of active ester-functionalized polymers[2] and postpolymerization functionalization of polymers in general.[3,4] The group of Binder reviewed the azide−alkyne click reaction in the context of polymer and material science.[5,6] In fact, most of the examples reported on postpolymerization modifications were prepared by living radical polymerizations,[7−10] whereas the number of living ring-opening metathesis polymers (ROMP) carrying highly functional groups fulfilling the Sharpless criteria of a click reaction (activated esters, alkynes, maleimides, etc.) for postpolymerization modification is comparatively few.[11−20]

Our group has previously been reporting the synthesis of functional ROMP polymers in particular those with functional end-groups[21−27] or end-groups capable of alkyne azide click modification.[28]

ROMP polymers carrying azide and alkyne moieties were prepared by Kluger et al. as well as Weck et al. in a two-step process from an imide or alkyl bromide functionalized polymer.[12,20] In contrast, we utilized a complementary approach starting from a trimethylsilyl-protected alkyne in order to avoid side reactions of the intermediate alkyl bromide. It was reported that the Grubbs' first-generation ruthenium initiator did not tolerate the alkyl azide side group[29] in the monomer repeat unit and propagation was slowed down significantly, and the molecular weight distribution broadened by an unprotected alkyne.[12,30,31] The group of Tew recently showed a synthetic approach to protect the alkyne moiety in a norbornene derivative using $Co_2(CO)_6$. There the complexed norbornene carrying alkyne could be polymerized in a ring-

Received: May 24, 2012
Revised: August 3, 2012

   dx.doi.org/10.1021/ma301061z | Macromolecules XXXX, XXX, XXX−XXX

opening metathesis polymerization using Grubbs' third-generation initiator.[32] Krovi et al. could show that a trimethylsilyl-protected alkyne connected to the norbornene moiety via an oligoethylene glycol spacer could be polymerized using Grubbs' first-generation initiator.[33] Because of presence of a variety of different functional groups, we chose the more stable Grubbs' first-generation initiator in particular as its third generation analogue led to very similar molecular weights and polydispersities. Here we present the synthesis of statistical terpolymers as well as diblock copolymers via living ROMP that carry a combination of alkyne−azide click, activated ester−amine click, and maleimide−thiol click functionalizable repeat units for orthogonal postpolymerization derivatization.

2. EXPERIMENTAL SECTION

2.1. Materials. Ammonium hydroxide solution, benzyl mercaptan, benzylidene−bis(tricyclohexylphosphine)dichlororuthenium (Grubbs' first-generation catalyst), chlorotriisopropylsilane, chlorotrimethylsilane, 1-dodecylamine, ethyl vinyl ether, 1-hexanol, 1-hexylamine, maleic anhydride, phosphorus pentoxide, piperonyl alcohol, propargyl bromide solution, sodium L-ascorbate, sodium azide, tetrabromomethane, tetrabutylammonium fluoride solution (1 M in THF), *p*-toluenesulfonyl chloride, 5-(trimethylsilyl)-4-pentyn-1-ol, and triphenylphosphine were purchased from Sigma-Aldrich and used without further purification. Acetic anhydride, *n*-butyllithium solution, oxalyl chloride, pentafluorophenol, potassium carbonate, and copper(II) sulfate hydrate were purchased from Acros, ABCR, Merck, or Reactolab and used without further purification. Triethylamine (Acros) and ethylenediamine (Sigma) were freshly distilled before usage, and *endo*-carbic anhydride (Acros) was heated to 180 °C for 2 h and recrystallized from benzene to obtain pure *exo*-carbic anhydride.

2.2. Characterization. Standard nuclear magnetic resonance spectra as well as two-dimensional spectra were recorded at 300 MHz (^{1}H NMR)/75 MHz (^{13}C NMR)/282 MHz (^{19}F NMR) on a Bruker Avance III 300 or at 400 MHz (^{1}H NMR)/100 MHz (^{13}C NMR)/377 MHz (^{19}F NMR) on a Bruker DPX 400 spectrometer. All NMR signals were referenced internally to residual solvent signals or trifluoroacetic acid in the case of fluorine NMR. Relative molecular weights and molecular weight distributions were measured by gel permeation chromatography (GPC) equipped with a Viscotek GPCmax VE2001 GPC Solvent/Sample Module, a Viscotek UV-Detector 2600, a Viscotek VE3580 RI-Detector, and two Viscotek T6000 M columns (7.8 × 300 mm, 10^3−10^7 Da each). All measurements were carried out at room temperature using THF as the eluent with a flow rate of 1 mL/min. The system was calibrated with polystyrene standards in a range from 10^3 to 3 × 10^6 Da. Field desorption mass spectra were measured on a Finnigan MAT 95 and electrospray ionization mass spectra on a Bruker Esquire HCT.

2.3. Synthesis of the Reactive Ester-Containing Monomer. *exo-3-[(Hexyloxy)carbonyl]norbornene-2-carboxylic Acid (**1**).* To a solution of *exo*-carbic anhydride (15.0 g, 91.4 mmol, 1 equiv) in dichloromethane (300 mL) and a catalytic amount of triethylamine, 1-hexanol (9.34 g, 91.4 mmol, 1 equiv) was added dropwise at room temperature before heating to reflux overnight. After removal of the solvent the product was recrystallized from petroleum ether. Yield: 20.17 g, 75.7 mmol, 83%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.23 (s, 2H, C=C**H**); 4.11−3.98 (m, 2H, O−C**H**$_2$); 3.12 (s, 2H, =CH−C**H**); 2.65 (s, 2H, CO−C**H**); 2.13−2.11 (d, 1H, ^2J = 9.6 Hz, C**H**$_2$-bridge); 1.64−1.57 (quint, 2H, ^3J = 7.0 Hz, O−CH$_2$−C**H**$_2$); 1.51−1.49 (d, 1H, ^2J = 9.6 Hz, C**H**$_2$-bridge); 1.37−1.24 (m, 6H, hexyl-chain); 0.91−0.88 (m, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 179.99 (**C**OOH); 173.39 (**C**OO−C); 138.10 and 137.79 (**C**=**C**); 65.01 (O−**C**H$_2$); 47.56 (**C**^{3}); 47.30 (**C**^{4}); 45.72 (**C**^{2}); 45.45 (**C**^{1}); 45.34 (**C**H$_2$-bridge); 31.41, 28.39, 25.57, 22.49 (**C**H$_2$-chain); 13.99 (**C**H$_3$). FD-MS: 265.4, 266.4, 267.4, 268.4, 269.4 *m*/*z* (266.2 calcd).

*exo-2-Hexyl-3-(pentafluorophenyl)norbornene-2,3-dicarboxylate (**2**).* Compound **1** (19.95 g, 74.9 mmol, 1 equiv) was dissolved in an excess of oxalyl chloride (1.2 equiv) and stirred at room temperature for 1 h before removal of residual chlorination agent. After addition of triethylamine (25 mL), pentafluorophenol (13.79 g, 74.9 mmol, 1 equiv) in triethylamine (5 mL) was added dropwise within 30 min. After stirring for 3 h at room temperature the solvent was evaporated and the product purified via column chromatography with chloroform as eluent. Yield: 29.52 g, 68.3 mmol, 91%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.32−6.28 (m, 2H, C=C**H**); 4.19−4.10 (m, 2H, O−C**H**$_2$); 3.27 (s, 1H, C^{1}C**H**); 3.20 (s, 1H, C^{4}C**H**); 2.97−2.94 (dd, 1H, $^3J_1$ = 9.6 Hz, $^3J_2$ = 1.7 Hz, C^{3}C**H**); 2.78−2.77 (d, 1H, ^3J = 3.5 Hz, C^{2}C**H**); 2.12−2.09 (d, 1H, ^2J = 9.6 Hz, C**H**$_2$-bridge); 1.58−1.56 (m, 1H, C**H**$_2$-bridge); 1.41−1.26 (m, 6H, hexyl-chain); 0.91−0.86 (m, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 173.68 (**C**O−OAl); 169.58 (**C**O−OAr); 142.92, 139.53, 137.91, 136.42 (**Ar**); 138.53, 137.44 (**C**=**C**); 65.39 (O−**C**H$_2$); 47.83 (**C**^{2}); 47.35 (**C**H$_2$-bridge); 46.69 (**C**^{1}); 46.59 (**C**^{3}); 46.20 (**C**^{4}); 31.38, 28.55, 25.49, 22.45 (**C**H$_2$-chain); 13.93 (**C**H$_3$). ^{19}F NMR (377 MHz, $CDCl_3$), δ (ppm): (−154.89)−(−155.01) (ortho C−**F**); (−160.69)−(−160.99) (para C−**F**); (−165.07)−(−165.33) (meta C−**F**). FD-MS: 432.3, 433.3, 434.3 *m*/*z* (432.1 calcd).

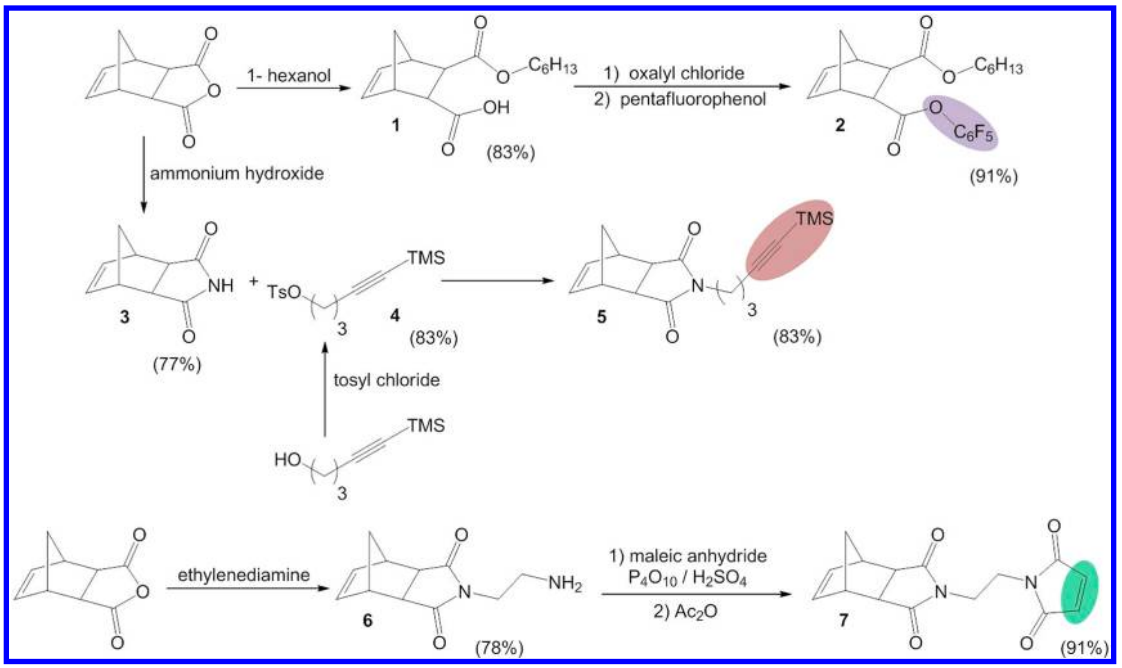
2.4. Synthesis of the Protected Alkyne Monomer. *exo-Norbornene-2,3-dicarboximide (**3**).* *exo*-Carbic anhydride (15.03 g, 91.37 mmol, 1 equiv) and aqueous ammonia (25%) (100 mL) were combined in a round-bottom flask equipped with reflux condenser and drying tube before heating to reflux for 48 h. Crystallization occurred overnight, and the colorless powder was filtered and washed with hexane. Yield: 11.52 g, 70.60 mmol, 77%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.66 (brs, 1H, N**H**); 6.28 (s, 2H, C=C**H**); 3.29 (s, 2H, =CH−C**H**); 2.73 (s, 2H, CO−C**H**); 1.59−1.56 (d, 1H, ^2J = 9.99 Hz, C**H**$_2$-bridge); 1.47−1.44 (d, 1H, ^2J = 9.99 Hz, C**H**$_2$-bridge). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 178.42 (**C**O); 137.72 (**C**=**C**); 49.14 (CO-**C**H); 45.10 (=CH−**C**H); 42.88 (**C**H$_2$-bridge). ESI-MS: 186.0, 187.0, 188.0 *m*/*z* (163.1 calcd + sodium).

*exo-N-[5-(Trimethylsilyl)pent-4-yn-1-yl]-5-norborene-2,3-dicarboximide (**5**).* Anhydrous potassium carbonate (1.09 g, 7.9 mmol, 1.3 equiv), compound **3** (1.09 g, 6.7 mmol, 1.1 equiv), and dry acetone (15 mL) were combined in a Schlenk flask and stirred for 10 min at 55 °C before compound **4** (1.84 g, 6.1 mmol, 1.0 equiv) dissolved in dry acetone (10 mL) was added dropwise via a syringe. After 48 h at 55 °C, the mixture was filtered and the organic solvent removed. The crude product was purified via column chromatography with dichloromethane as eluent. Yield: 1.52 g, 5.0 mmol, 83%. ^{1}H NMR (300 MHz, CDCl3), δ (ppm): 6.28 (t, 2H, ^3J = 1.70 Hz, C=C**H**); 3.57−3.52 (m, 2H, N−C**H**$_2$); 3.27 (t, ^3J = 1.70 Hz, 2H, =CH−C**H**); 2.67 (d, ^3J = 1.32 Hz, 2H, CO−C**H**); 2.22−2.27 (t, 2H, ^3J = 1.80 Hz, ≡C−C**H**$_2$); 1.83−1.74 (q, 2H, ^3J = 7.36 Hz, N−CH$_2$−C**H**$_2$); 1.54−1.49 (dt, 1H, ^2J = 9.82 Hz, ^3J = 1.51 Hz, C**H**$_2$-bridge); 1.29−1.26 (d, 1H, ^2J = 10.01 Hz, C**H**$_2$-bridge); 0.14 (s, 9H, C**H**$_3$). ^{13}C NMR (75 MHz, CDCl3), δ (ppm): 177.86 (**C**O); 137.77 (**C**=**C**); 105.40 (CH$_2$−**C**≡); 85.41 (Si−**C**≡); 47.77 (CO−**C**H); 45.11 (=CH−**C**H); 42.77 (**C**H$_2$-bridge); 37.86 (N−**C**H$_2$); 26.71 (N−CH$_2$−**C**H$_2$); 17.71 (≡C−**C**H$_2$); 0.03 (**C**H$_3$). ESI-MS: 324.1, 325.1 *m*/*z* (301.1 calcd + sodium).

2.5. Synthesis of the Maleimide-Containing Monomer. *exo-N-(2-Aminoethyl)-5-norbornene-2,3-dicarboximide (**6**).* To freshly distilled ethylenediamine (50 mL, 0.75 mol, 8.2 equiv) a solution of *exo*-carbic anhydride (15.0 g, 91.4 mmol, 1 equiv) in toluene (300 mL) was added dropwise over 1.5 h under mechanical stirring. The mixture was held under Dean−Stark conditions overnight before the solvent as well as residual ethylenediamine were removed via distillation. Purification was achieved by column chromatography with chloroform: methanol (1%→10%) as eluent. Yield: 14.67 g, 71.1 mmol, 78%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 6.23 (t, 2H, ^3J = 1.70 Hz, C=C**H**); 3.48 (t, 2H, ^3J = 6.42 Hz, CO−N−C**H**$_2$); 3.21 (t, 2H, ^3J = 1.70 Hz, =CH−C**H**); 2.83 (t, 2H, ^3J = 6.42 Hz, C**H**$_2$−NH$_2$); 2.64 (d, 2H, ^3J = 1.32 Hz, CO−C**H**); 1.47−1.43 (dt, 1H, ^2J = 9.82 Hz, ^3J = 1.32 Hz, C**H**$_2$-bridge); 1.31−1.28 (d, 1H, ^2J = 9.82 Hz, C**H**$_2$-bridge). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 178.15 (**C**O); 137.63 (**C**=**C**); 47.68 (CO−**C**H); 45.02 (=CH−**C**H); 42.65 (**C**H$_2$-bridge); 41.28 (CO−N−**C**H$_2$); 39.77 (**C**H$_2$−NH$_2$).

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of "Clickable" ROMP Monomers That Can Be Functionalized Independently of Each Other



exo-N-[2-(1H-Pyrrole-2,5-dione)ethyl]-5-norbornene-2,3-dicarboximide (7). Compound **6** (10.66 g, 43.1 mmol, 1 equiv) and maleic anhydride (5.07 g, 51.7 mmol, 1.2 equiv) were dissolved in DMF (12.8 mL) and cooled to 0 °C. A solution of phosphorus pentoxide (1.76 g, 4.6 mmol, 0.1 equiv) in DMF (6.4 mL) and sulfuric acid (1.01 g) was added dropwise, and the ice bath was removed upon complete addition. The solution was heated to 70 °C for 2 h, poured on iced water, and extracted with chloroform. Upon removal of the solvent the crude product was dissolved in acetic anhydride (50 mL), sodium acetate was added, and the solution was heated to 100 °C for 2 h. Upon extraction with chloroform the product was purified by column chromatography with chloroform:methanol (5%) as eluent. Yield: 11.28 g, 39.4 mmol, 91%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 6.68 (s, 2H, CO−C**H**=); 6.25 (t, 2H, ^3J = 1.70 Hz, =C**H**−CH⟨); 3.75−3.67 (m, 4H, N−C**H**$_2$); 3.22 (t, 2H, ^3J = 1.70 Hz, =CH−C**H**); 2.65 (d, 2H, ^3J = 1.32 Hz, CO−C**H**⟨); 1.52−1.51 (dt, 1H, ^2J = 10.01 Hz, ^3J = 1.51 Hz, C**H**$_2$-bridge); 1.26−1.23 (d, 1H, ^2J = 9.82 Hz, C**H**$_2$-bridge). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 177.97 (⟩CH−**C**O); 170.57 (=CH−**C**O); 137.74 (=**C**H−CH⟨); 134.16 (=**C**H−CO); 47.89 (CO−**C**H); 44.92 (=CH−**C**H); 42.90 (**C**H$_2$-bridge); 37.30 (⟩CH−CO−N−**C**H$_2$); 36.17 (**C**H$_2$−N−CO−CH=). ESI-MS: 309.1, 310.1 *m*/*z* (286.1 calcd + sodium).

2.6. NMR Studies for Orthogonal Functionalization. *Functionalization with Mercaptans.* A mixture of compounds **2** (12 mg, 0.03 mmol, 1 equiv) and **7** (8 mg, 0.03 mmol, 1 equiv) in 0.6 mL of $CDCl_3$ was filled into a NMR tube, and ^{1}H NMR has been measured. Benzyl mercaptan (7 mg, 0.06 mmol, 2 equiv) was added, the NMR tube inverted once, and ^{1}H as well as ^{19}F NMR spectra recorded every 5 min for 1 h. The same procedure was performed for the subsequent addition of triethylamine (10 mg, 0.10 mmol, 3.3 equiv).

Functionalization with Amines. A mixture of compounds **2** (10 mg, 0.02 mmol, 1 equiv) and **7** (7 mg, 0.02 mmol, 1.1 equiv) in 0.6 mL of $CDCl_3$ was filled into a NMR tube, and ^{1}H NMR has been measured. Benzylamine (7 mg, 0.06 mmol, 3 equiv) was added, the NMR tube inverted once, and ^{1}H as well as ^{19}F NMR spectra were recorded every 5 min for 1 h.

Alkyne Deprotection with TBAF. A mixture of compounds **2** (12 mg, 0.03 mmol, 0.9 equiv), **5** (9 mg, 0.03 mmol, 1 equiv), and **7** (8 mg, 0.03 mmol, 0.9 equiv) in 0.6 mL of THF-d_8 was filled into a NMR tube, and ^{1}H as well as ^{19}F NMR has been measured. TBAF ([1 M] in THF-d_8, 0.05 mL, 0.05 mmol, 1.7 equiv) was added, the NMR tube was inverted once, and ^{1}H as well as ^{19}F NMR spectra were recorded every 5 min for 1 h.

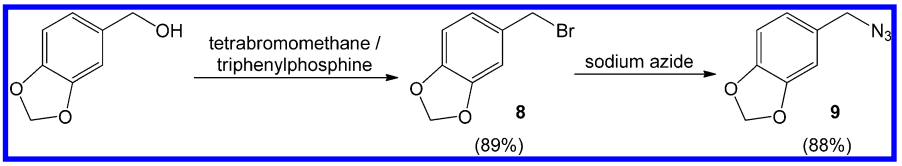
2.7. Copolymerization and Functionalization. *General Procedure for the Synthesis of Statistical Copolymers.* A sealed Schlenk-flask containing compounds **2**, **5** and **7** (Scheme 1) was evacuated and charged with argon gas repeatedly before degassed dichloromethane (ca. 5 mL/g of monomer) was added via syringe. The polymerization was initiated by quickly adding a solution of the appropriate amount of Grubbs' first generation catalyst in degassed dichloromethane (ca. 1 mL per 100 mg). The reaction times depended on the desired molecular weight of the individual copolymers. Upon complete monomer conversion the polymerization was terminated with ethyl vinyl ether (1 mL) before the polymer was precipitated in ice-cold methanol and dried in a vacuum oven yielding 80−90% of a brownish solid. Yield: 222 mg, 83%

General Procedure for the Synthesis of Block Copolymers. A sealed Schlenk flask containing compound **2** (Scheme 1) was evacuated and charged with argon gas repeatedly before degassed dichloromethane (ca. 5 mL per gram of monomer) was added via syringe. The polymerization was initiated by quickly adding a solution of the appropriate amount of Grubbs' first-generation catalyst in degassed dichloromethane (ca. 1 mL per 100 mg). The reaction times depended on the desired molecular weight of the individual block (60 min for 5000 g mol^{-1}, 90 min for 10 000 g mol^{-1}, and 120 min for 20 000 g mol^{-1}, all at room temperature). Upon complete monomer conversion a solution of compound **SI2** in dichloromethane (ca. 2 mL per gram of monomer) was added via syringe, and the mixture was stirred until no residual monomer was left (determined via GPC). The polymerization was terminated with ethyl vinyl ether (1 mL) before the product was either precipitated in ice-cold methanol and/or purified via column chromatography with dichloromethane as eluent. The block copolymer was dried in a vacuum oven yielding 70−90% of a brownish solid. Yield: **SI3a** 203 mg, 73% (after column chromatography and precipitation); **SI3b** 371 mg, 86% (after column chromatography and precipitation)

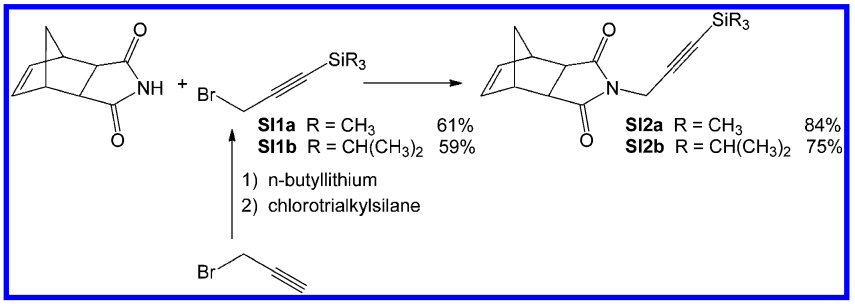
Functionalization with Benzyl Mercaptan. A sealed Schlenk flask containing the precursor polymer was evacuated and charged with argon gas repeatedly before dissolving in degassed dichloromethane (ca. 3 mL per 100 mg of polymer). A solution of benzyl mercaptan (150 mg per 100 mg of polymer) and freshly distilled triethylamine (1 mL per 150 mg of benzyl mercaptan) was added via syringe, and the

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of Piperonyl Azide for the Attachment to Polymeric Alkynes via CuAAC



Scheme 3. Synthesis of Alkyne-Containing Monomers with a Short Spacer SI2a,b



mixture was stirred for 3 h at room temperature before precipitating in a 10-fold excess of ice-cold methanol. Yield: 127 mg, 91%.

Functionalization with Alkylamines. A sealed Schlenk flask containing the precursor polymer was evacuated and charged with argon gas repeatedly before dissolving in degassed dichloromethane (ca. 3 mL per 100 mg of polymer). A solution of the corresponding *n*-alkylamine (150 mg per 100 mg of polymer) in freshly distilled triethylamine (1 mL per 150 mg of alkylamine) was added via syringe, and the mixture was stirred overnight at room temperature before precipitating in a 10-fold excess of ice-cold methanol. The yield, depending on the polymer, was around 90%. Yield: **12** 84 mg, 88%; **SI4a** 92 mg, 90%; **SI4b** 134 mg, 87%.

Functionalization via CuAAC. (a) Deprotection of the Alkyne. Procedure 1: The statistical copolymer was dissolved in tetrahydrofuran containing 5% water (5 mL per 100 mg) under an inert atmosphere, and tetrabutylammonium fluoride solution (1 M in THF, 0.5 mL per 100 mg polymer) was added. The mixture was stirred for 24 h at room temperature, and the polymer precipitated in a 10-fold excess of ice-cold methanol. Yield: **13** 69 mg, 92%.

Procedure 2: The block copolymer was dissolved in a mixture of chloroform and methanol (10:1, 15 mL per 200 mg of polymer) under an inert atmosphere, anhydrous potassium carbonate (same amount as polymer) was added, and the mixture was stirred for 72 h at 50 °C. After filtration and removal of the solvents, the polymer was redissolved in a small amount of dichloromethane and precipitated in a 10-fold excess of ice-cold methanol. Yield: **SI5a** 45 mg, 56% (after reprecipitating 3 times); **SI5b** 66 mg, 47% (after reprecipitating 3 times).

(b) CuAAC Reaction: The cycloaddition was carried out in a biphasic mixture of dichloromethane and water (1:1). The polymer and compound **9** (1.25 equiv with respect to the content of alkyne included in the polymer) were dissolved in the organic solvent (2 mL per 50 mg of piperonyl azide), whereas copper(II) sulfate hydrate (0.04 equiv) and sodium L-ascorbate (0.22 equiv) were dissolved in the same amount of water. The combined solutions were stirred at room temperature overnight before the phases were separated, and the aqueous phase was extracted twice with dichloromethane. Precipitation in a 10-fold excess of ice-cold methanol or column chromatography with dichloromethane as eluent was utilized to separate the polymer from residual azide. Yield: **14** 50 mg, 83% (after precipitation); **SI6a** 20 mg, 33% (after column chromatography and precipitation); **SI6b** 60 mg, 75% (after precipitation).

3. RESULTS AND DISCUSSION

A norbornene carrying a hexyl ester in addition to an activated pentafluorophenyl ester (**2**, Scheme 1) could easily be synthesized in high yield (76% overall) in a two-step reaction. The reaction of *exo*-carbic anhydride with 1-hexanol (**1**) was followed by the *in situ* synthesis of the carboxylic acid chloride using oxalyl chloride and its subsequent treatment with pentafluorophenol yielding compound **2** (91%). During the formation of this amine-selective ester a side reaction occurred, converting the before pure *exo* compound **1** into an *endo*/*exo* mixture of **2** via a ketene intermediate as shown by ^{1}H NMR spectroscopy (see Supporting Information, Figure SI1). Field desorption mass spectrometry confirmed the formation of the desired product. The reactive pentafluorophenyl ester can easily and selectively be reacted with alkylamines. Functional groups such as dyes, binding sites for biomolecules, and nanoparticles or other functional groups can thus be introduced readily via this type of high yielding "click" reaction.

The trimethylsilyl-protected alkyne **5** was synthesized via the corresponding tosylate **4** (Scheme 1),[34] whereas alkynes **SI2a,b** (Scheme 3) were synthesized according to reported syntheses of their non-silyl-protected analogues.[35] First, propargyl bromide was deprotonated with *n*-butyllithium before reacting it with the corresponding chlorotrialkylsilane (**a**: trimethylsilyl chloride (61%); **b**: triisopropylsilyl chloride (59%)). Norbornenimide **3** was prepared and N-alkylated using **4** and **SI1a,b** to give monomers **5** (83%) and **SI2a,b** (84% and 75%) according to a literature procedure.[36] All monomers were fully characterized via ^{1}H and ^{13}C NMR spectroscopy as well as electrospray ionization mass spectrometry.

In order to have a substrate to evaluate the alkyne−azide click reaction within the polymers we prepared from monomers **5** and **SI2a,b**, we synthesized azide **9** (Scheme 2) (78% overall).[37] Piperonyl azide was synthesized in a two-step reaction starting from 5-(methanol)-1,3-benzodioxole (Scheme 2, left) via Appel bromination using tetrabromomethane and triphenylphosphine (**8**) (89%), followed by nucleophilic substitution with sodium azide to give **9** (88%).

The conversion from 5-(methanol)-1,3-benzodioxole via the intermediate **8** to the final product **9** could be followed by ^{1}H NMR spectroscopy (see Supporting Information, Figure SI3) where the chemical shift of the benzylic CH_2 protons changed from a doublet at 4.58−4.56 ppm (5-(methanol)-1,3-benzodioxole) via a singlet at 4.47 ppm (**8**) to a singlet at 4.24 ppm (**9**).

First attempts of combining ring-opening metathesis polymerization and the well-established copper-catalyzed

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX−XXX

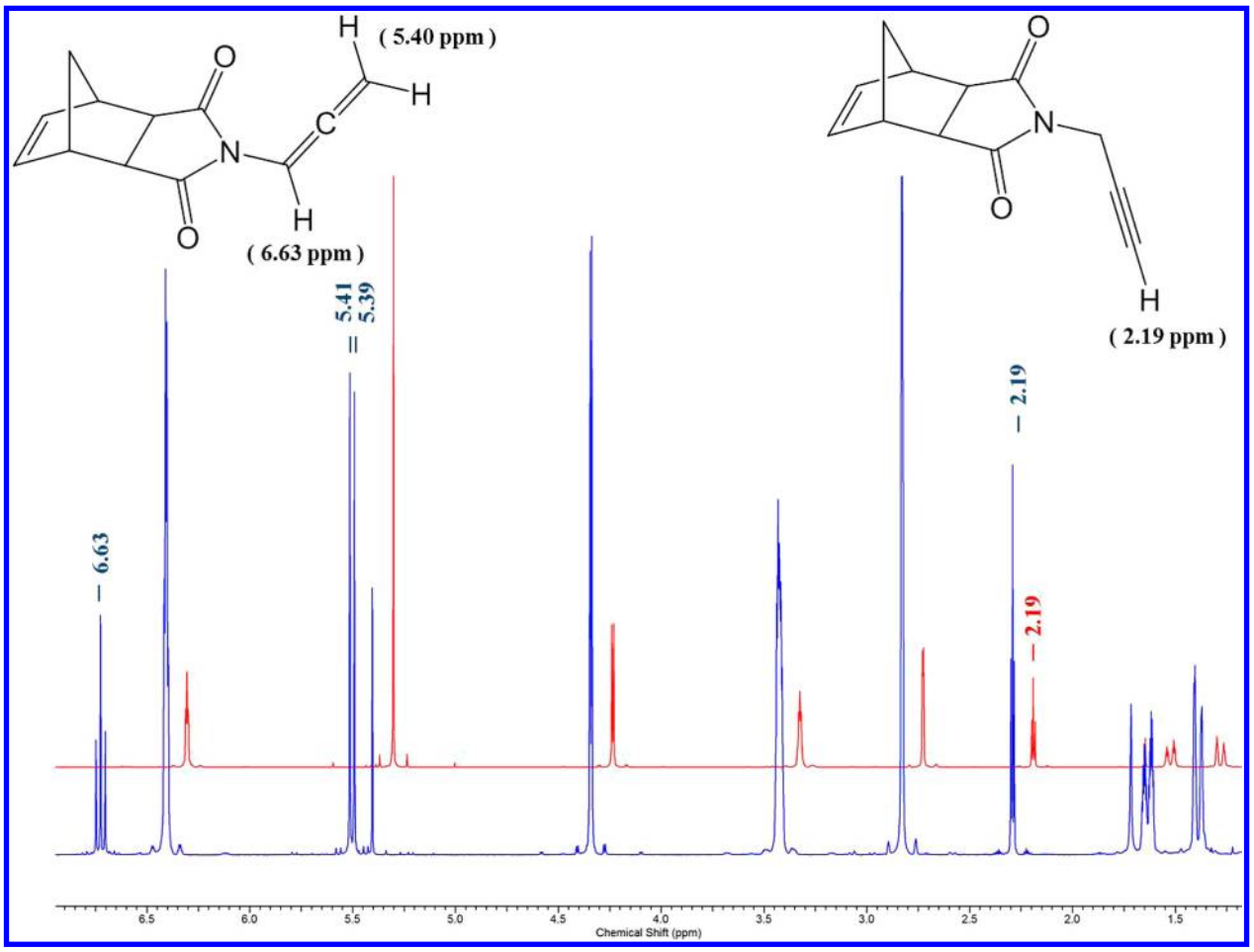


Figure 1. Deprotection of monomer **SI2** with TBAF in THF (red, only alkyne at 2.19 ppm) and DMF (blue, allene at 5.40 and 6.63 ppm as well as alkyne at 2.19 ppm). Blue spectrum with offset of 0.1 ppm.

alkyne–azide cycloaddition were studied on two easy-to-synthesize monomers **SI2a,b**.

The resulting homo- and block copolymers indicated high molecular weight polymers and low polydispersities, but nevertheless, during the deprotection step, the homopolymers became insoluble in various solvents such as chloroform, tetrahydrofuran, methanol, and dimethyl sulfoxide. Independent of the deprotection conditions, TBAF in tetrahydrofuran or potassium carbonate in methanol/chloroform, gelation occurred, and the resulting product could not be analyzed further. To shed light on the occurring side reaction, both monomers were exposed to tetrabutylammonium fluoride in tetrahydrofuran as well as dimethylformamide. Figure 1 shows that during this treatment the protecting group was cleaved off quantitatively in THF (red, with alkyne at 2.19 ppm), whereas in DMF a mixture of the desired alkyne and the corresponding allene was formed (blue, with alkyne at 2.19 ppm and allene at 5.40 and 6.63 ppm). This led us to the conclusion that the precursor polymer got insoluble in THF upon formation of a large number of terminal alkynes and that the allenes formed under the same conditions in DMF, which led to cross-linking of the polymer, also rendering it insoluble.

To overcome this limitation, a modified monomer (**5**) was synthesized, bearing a longer spacer between the norbornene and the alkyne moiety. The larger number of CH_2 units was on one hand introduced to increase the flexibility of the side chain and hence the solubility of the resulting polymer in tetrahydrofuran and on the other hand to prevent allene formation due to spatial separation of the highly electronegative nitrogen atom and the alkyne moiety. To verify this assumption, monomer **5** was deprotected with tetrabutylammonium fluoride in the same solvents used before and only formation of the expected alkyne was observed. Having this new monomer at hand, the same studies were carried out utilizing the corresponding polymer leading to a fully deprotected and organo-soluble product.

In order to evaluate the chemical stability of each functionalizable group contained in monomers **2**, **5**, and **7** toward the reaction conditions of the three different postpolymerization treatments, trial experiments were carried out in separate NMR tubes to follow potential product degradation or formation of byproducts.

First, the potential Michael addition of amines to the maleimide function was investigated, and as can be seen in Figure 3, the integral corresponding to its double bond decreased with time (Scheme 4, **A**, red). This indicated slow addition and hence chemical instability toward further nucleophiles present in the reaction mixture. Upon addition of tetrabutylammonium fluoride to a separate mixture of monomers **2**, **5**, and **7** the spectrum did not indicate any sign of reaction or degradation of the maleimide function (Scheme 4, **B**, product not shown because unreactive toward TBAF).

Second, the stability of the activated ester was investigated by exposing it to a mercaptan or to tetrabutylammonium fluoride

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX–XXX

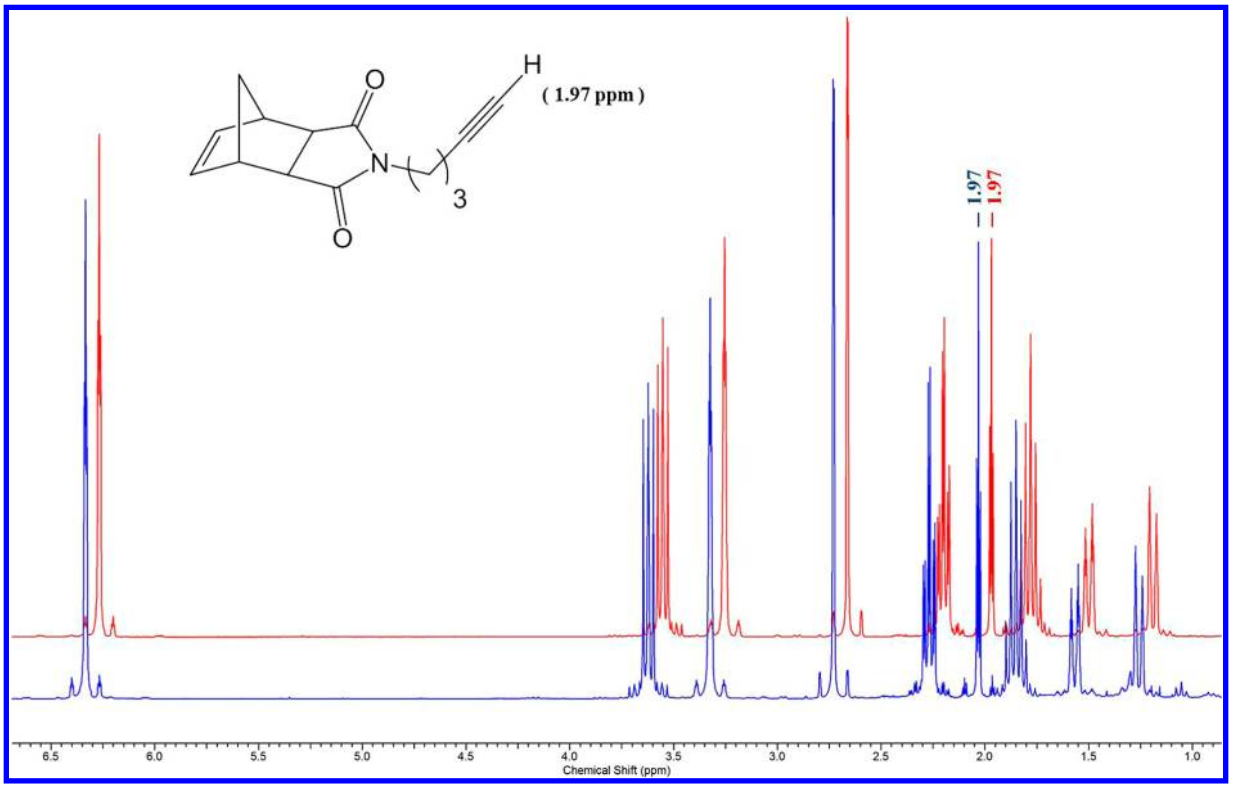


Figure 2. Deprotection of monomer **5** with TBAF in THF (red) and DMF (blue), both leading to pure alkyne at 1.97 ppm and absence of corresponding allene. Blue spectrum with offset of 0.1 ppm.

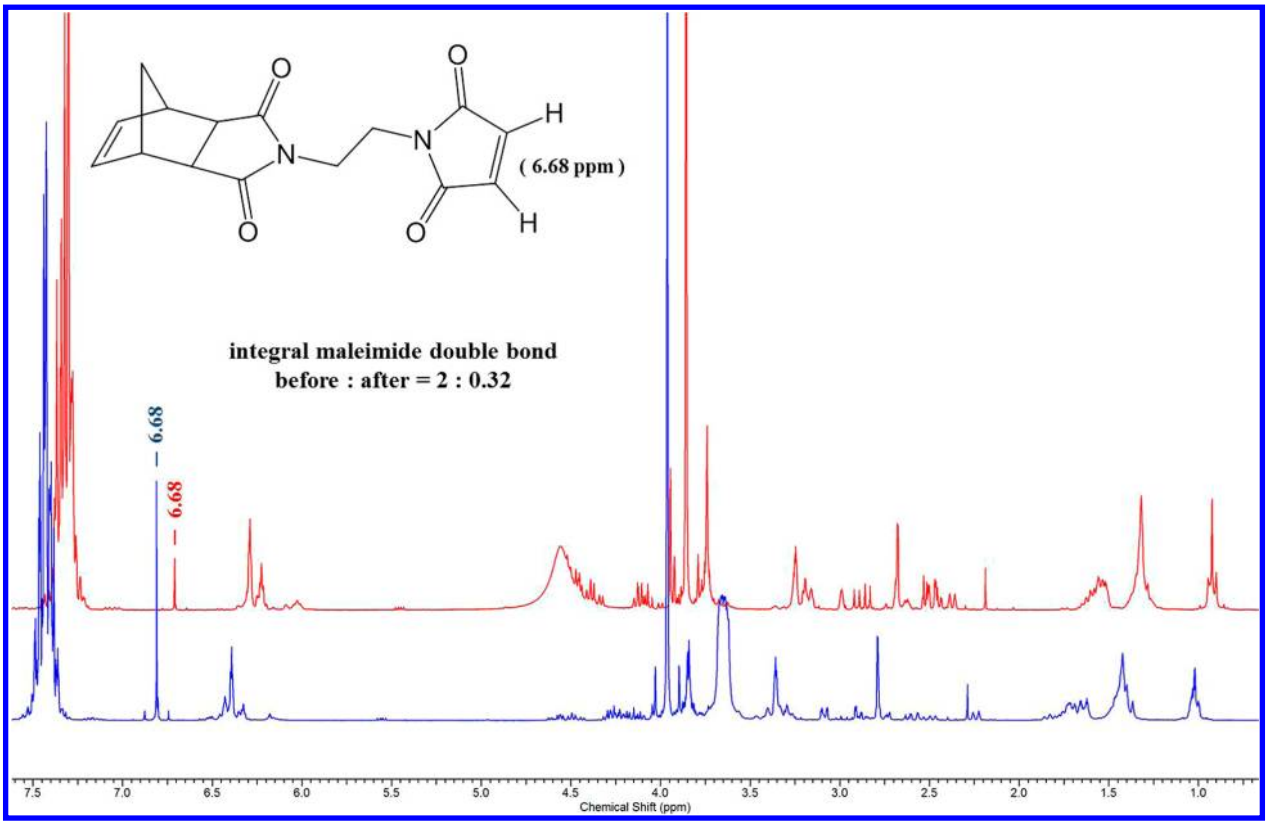
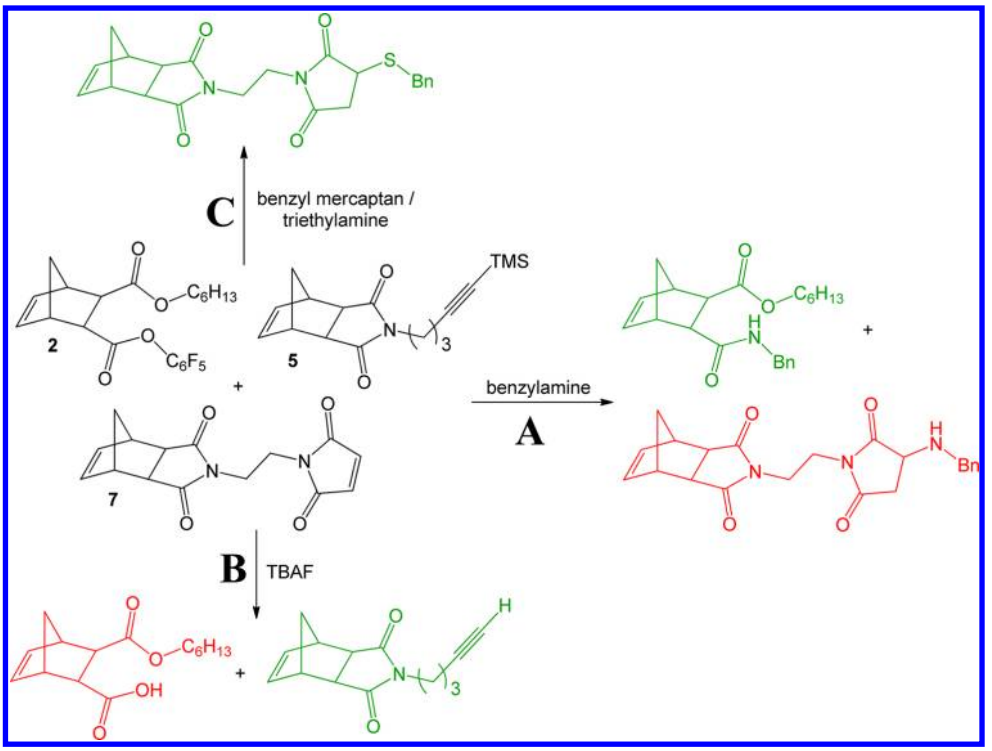


Figure 3. ^{1}H NMR spectra of a mixture of compounds **2**, **5**, and **7** before (blue) and 120 min after addition of benzylamine (red). Decreasing signal intensity corresponding to the maleimide double bond at 6.68 ppm. Blue spectrum with offset of 0.1 ppm.

(Figure 4). In the fluorine NMR spectra it can easily be seen that upon addition of benzyl mercaptan (green) the pentafluorophenol ester remains intact whereas degradation occurs via addition of TBAF (red), and the free alcohol is set

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX–XXX

Scheme 4. Summary of Products (Green) and Byproducts (Red) Occurring during Postpolymerization Treatment[a]



[a]Monomers that were unreactive under the respective conditions are not shown on the product side of the chemical equations.

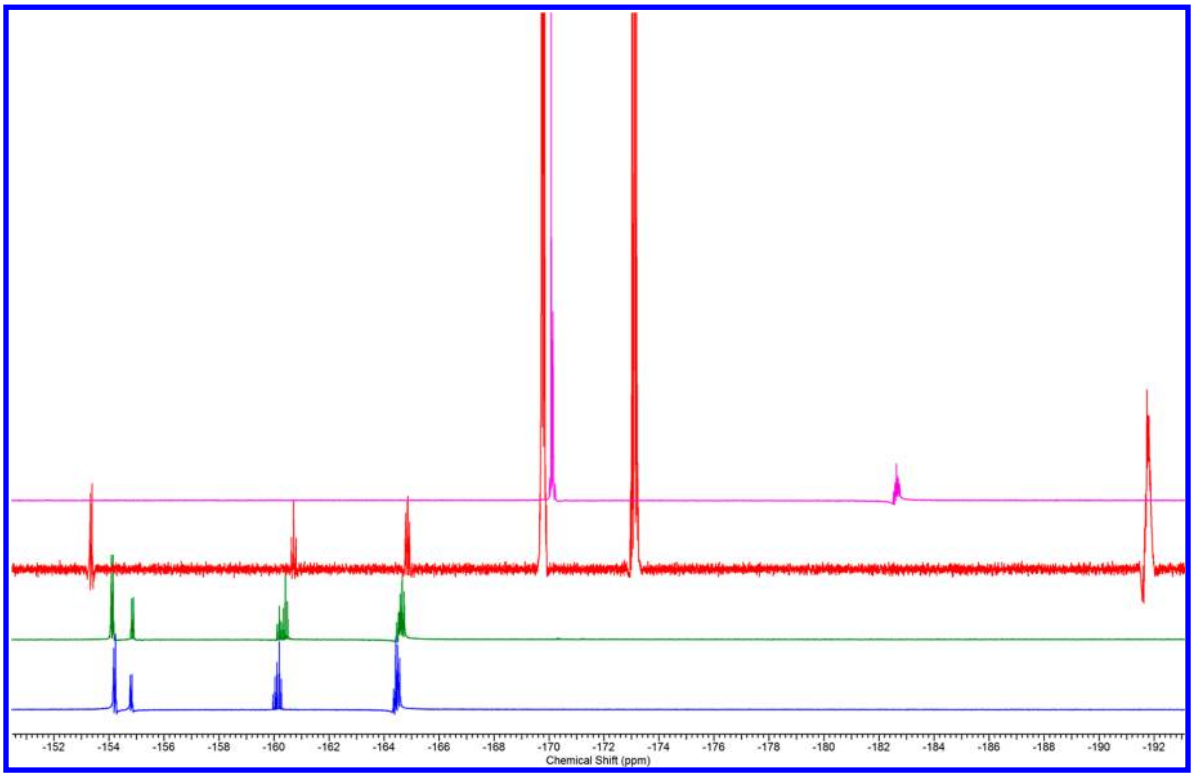


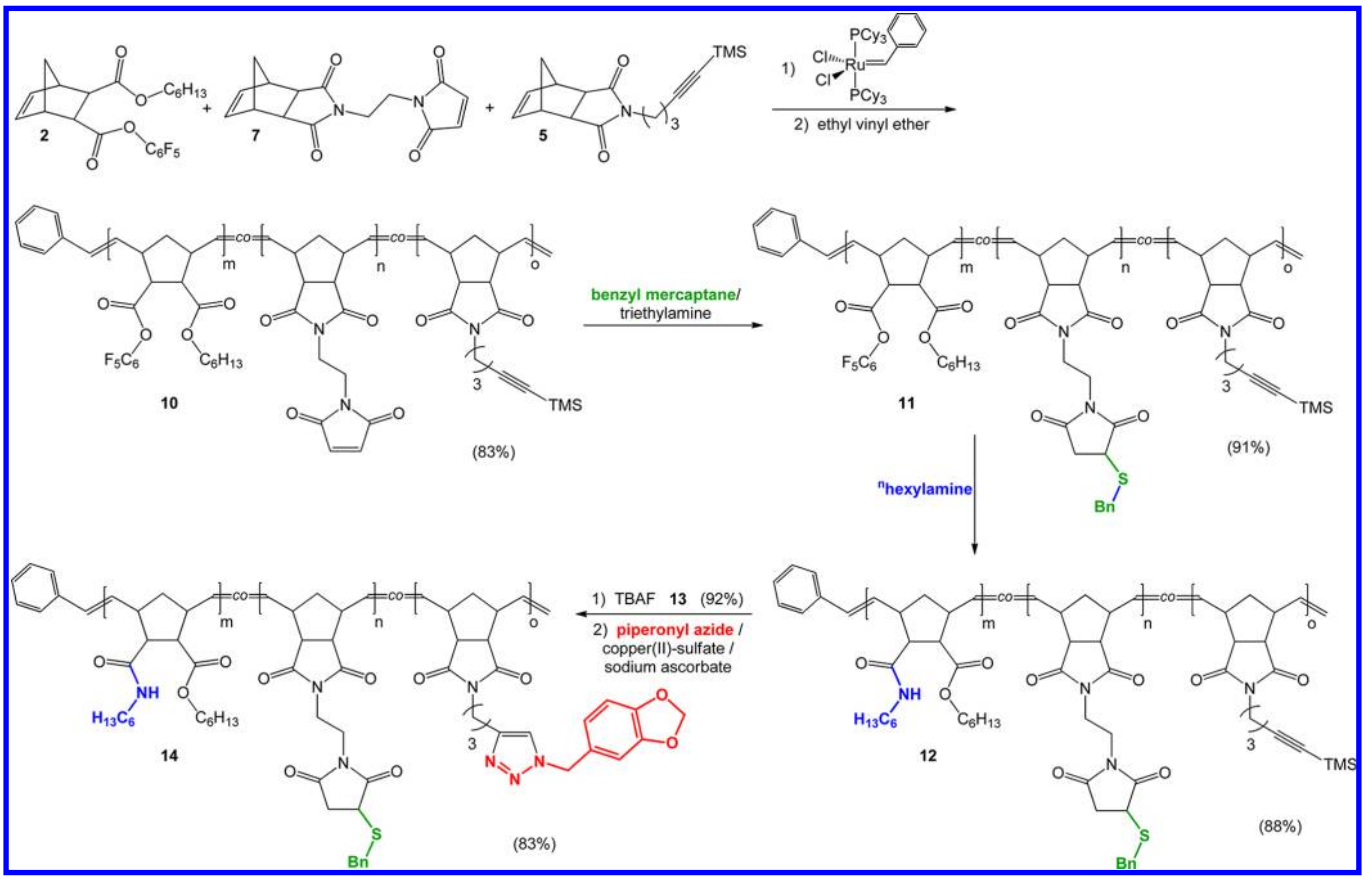
Figure 4. ^{19}F NMR spectra of a mixture of compounds **2**, **5**, and **7** (blue), 120 min after addition of benzyl mercaptan/triethylamine (green), 14 h after addition of TBAF (red), and 60 min after the addition of benzylamine (pink). Spectra without offset in the *x*-direction.

free if it is exposed to an amine (pink). Additionally, the deprotection of the alkyne was performed utilizing potassium carbonate which also lead to degradation of the activated ester (Figure SI12).

According to these results, a procedure to orthogonally functionalize the precursor polymers could be established. First it needs to be treated with a mercaptan to prevent Michael addition of the amine to the maleimide function, followed by

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX–XXX

Scheme 5. Synthetic Scheme Visualizing Statistical Copolymerization Leading to Multifunctional Precursor Polymers and Their Orthogonal "Triple-Click" Reaction



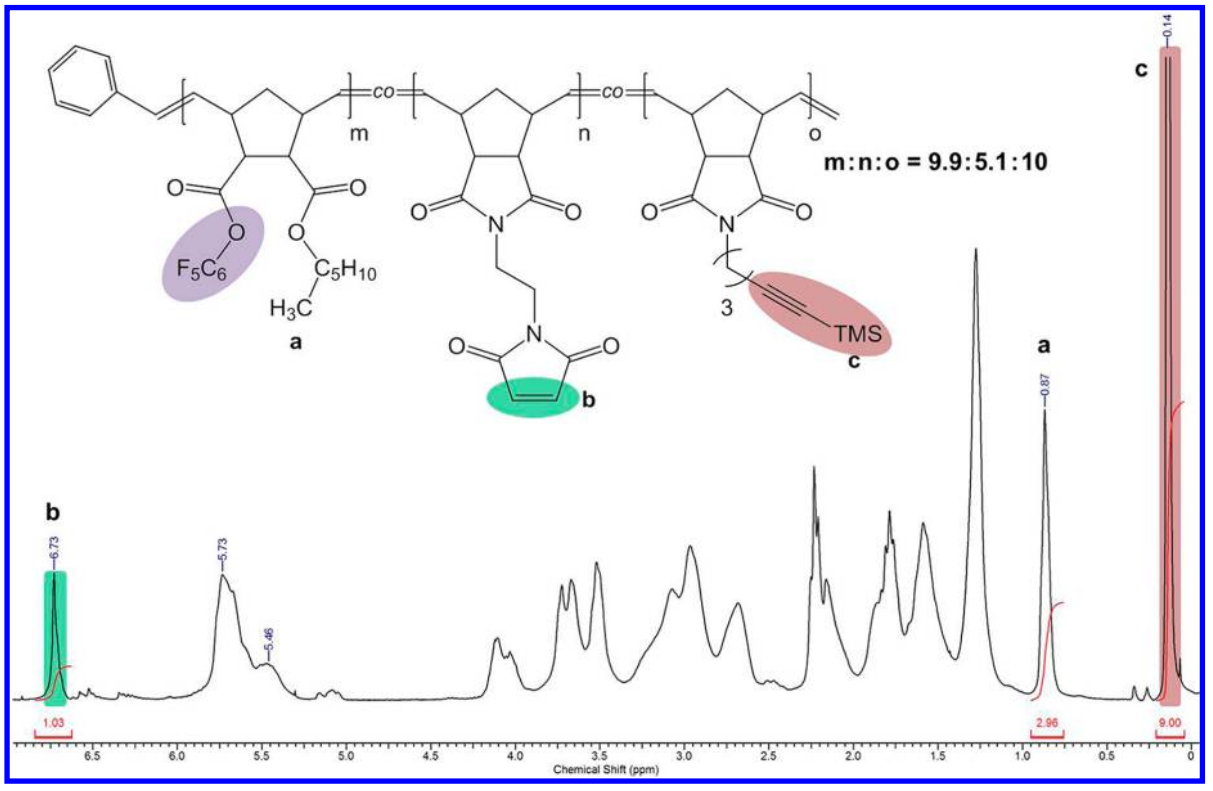


Figure 5. [1]H NMR spectrum of precursor polymer **10**. No signals for potential enyne-metathesis products can be observed.

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX–XXX

addition of an amine that selectively reacts with the activated ester. Finally, the alkyne deprotection can be carried out with tetrabutylammonium fluoride in order to rule out degradation of the pentafluorophenol ester under these reaction conditions. Copper-catalyzed azide−alkyne cycloaddition between the polymeric alkyne and compound **9** led to the fully functionalized polymer **14**.

With monomers **2**, **5**, and **7** in hand, we carried out a statistical copolymerization using Grubbs' first-generation ruthenium carbene initiator (benzylidene−bis(tricyclohexylphosphine)dichlororuthenium) according to Scheme 5. Polymer samples were taken every 30 min in order to confirm complete monomer conversion. The synthesis of terpolymers gave good control over molecular weight according to the chosen monomer/catalyst ratio based on the living character of this polymerization technique. Polymer **10** with the intended composition *m*:*n*:*o* = 10:5:10 (see Scheme 5) was synthesized and analyzed by ^{1}H NMR spectroscopy (Figure 5) as well as gel permeation chromatography (Table 1).

Table 1. Results of GPC Traces for Precursor Polymer 10 and Intermediates 11, 12, and 13 as Well as "Triple-Clicked" Polymer 14

	calculated	RI detector			
sample	M_n [g/mol]	M_n [g/mol]	M_w [g/mol]	PDI	elution time at peak maximum [min]
10	8800	9700	14 400	1.48	22.46
11	9400	9800	13 800	1.38	22.42
12	8600	10 600	13 700	1.29	22.29
13	7900	11 100	16 200	1.47	22.34
14	9700	10 800	15 100	1.41	22.46

Comparing the integral of the terminal methyl group (Figure 5, **a**) at 0.87 ppm versus the integral of the maleimide double bond (Figure 5, **b**) at 6.73 ppm and the TMS-protecting group (Figure 5, **c**) at 0.14 ppm allowed us to calculate the content of the three functional monomers (**2** vs **5** vs **7**). For polymer **10** a ratio of *m*:*n*:*o* = 9.9:5.1:10.0 was found, which agreed well with the aimed at values. Furthermore, it could be shown that introducing a covalently bound protecting group renders the alkyne sterically hindered and prevents enyne metathesis and the formation of previously proposed resting states that slow down propagation.[12] Indicators for the absence of such side reactions are the narrow molecular weight distribution (lack of cross-linking) and the formation of the target molecular weight as shown in Table 1.

According to the procedure described above, the first click-functionalization needs to be the Michael addition of benzyl mercaptan, as a model compound, to the maleimide double bond. In the ^{1}H NMR spectrum, the aromatic protons can be integrated with respect to the terminal methyl group and the alkyne-protecting group in order to calculate the degree of functionalization. The composition of polymer **11** (Scheme 5) was found to be *m*:*n*:*o* = 9.6:4.9:10.5, which in combination with the disappearance of the peak corresponding to the maleimide double bond at 6.73 ppm suggested complete conversion of this click reaction. Subsequently, the functionalization of the amine selective ester was performed utilizing *n*-hexylamine, which also only served as a model reagent. This resulted in the formation of polymer **12**. In future investigations this model amine could be substituted for a broad variety of functional moieties bearing amino groups. The advantage of this primary *n*-alkylamine is the fact that the terminal methyl groups can easily be integrated and used to determine the degree of functionalization as already described above. Here,

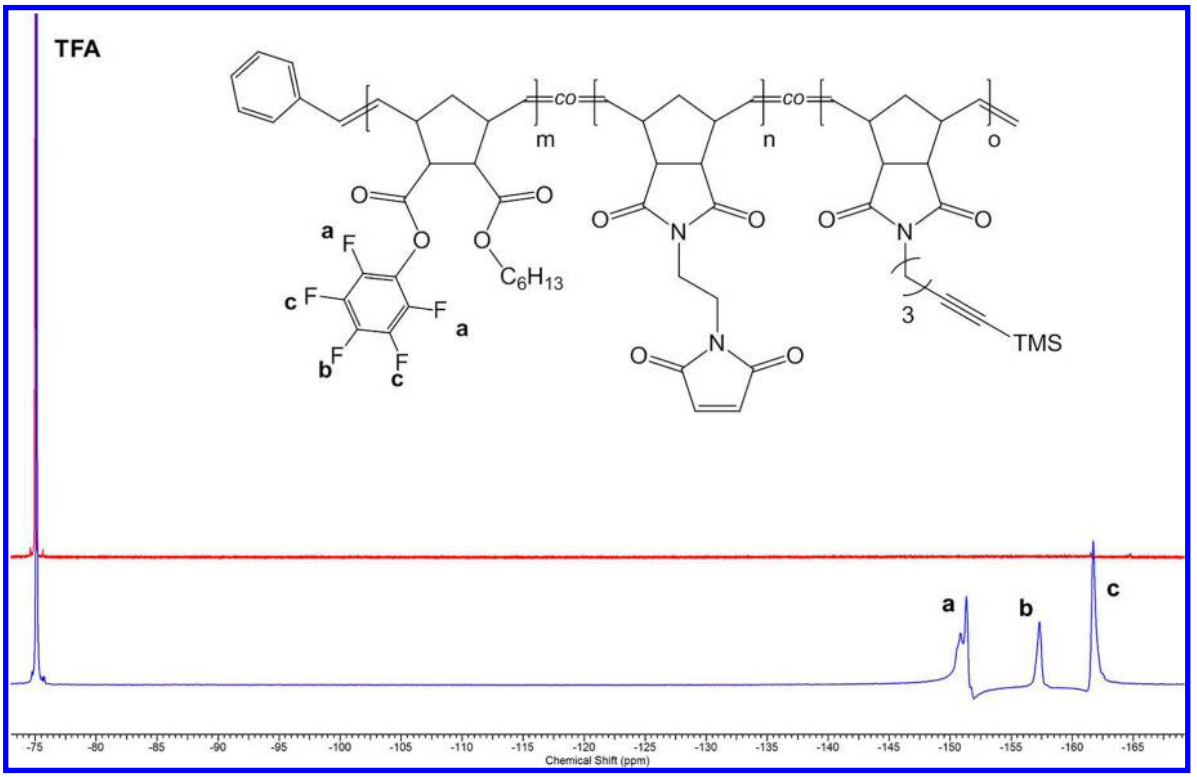


Figure 6. ^{19}F NMR spectra of nonfunctionalized polymer **10** (blue) and functionalized polymer **12** (red). Complete conversion indicated by disappearance of peaks a, b, and c.

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX−XXX

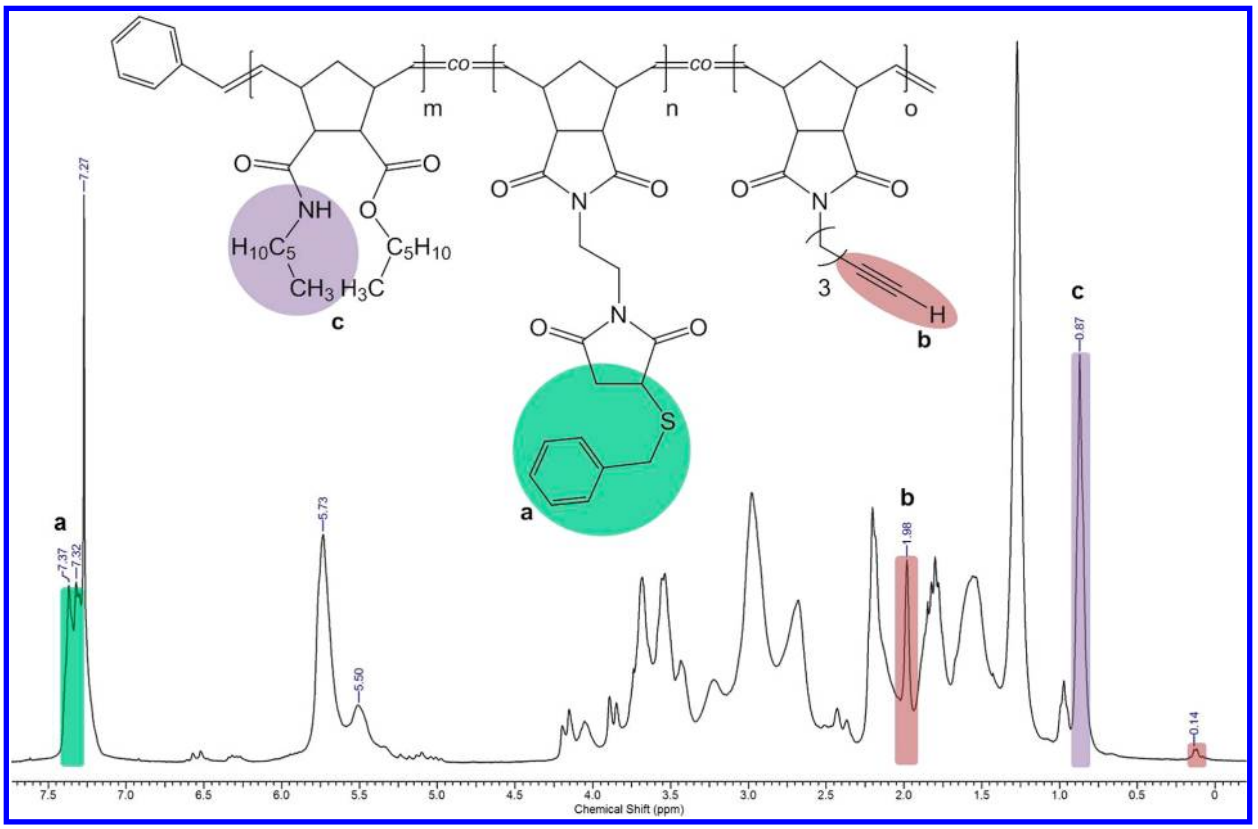


Figure 7. [1]H NMR spectrum of polymer **13** showing complete liberation of the terminal alkyne by vanishing signal of the TMS protecting group at 0.14 ppm as well as appearance of the terminal methyne **b** at 1.98 ppm.

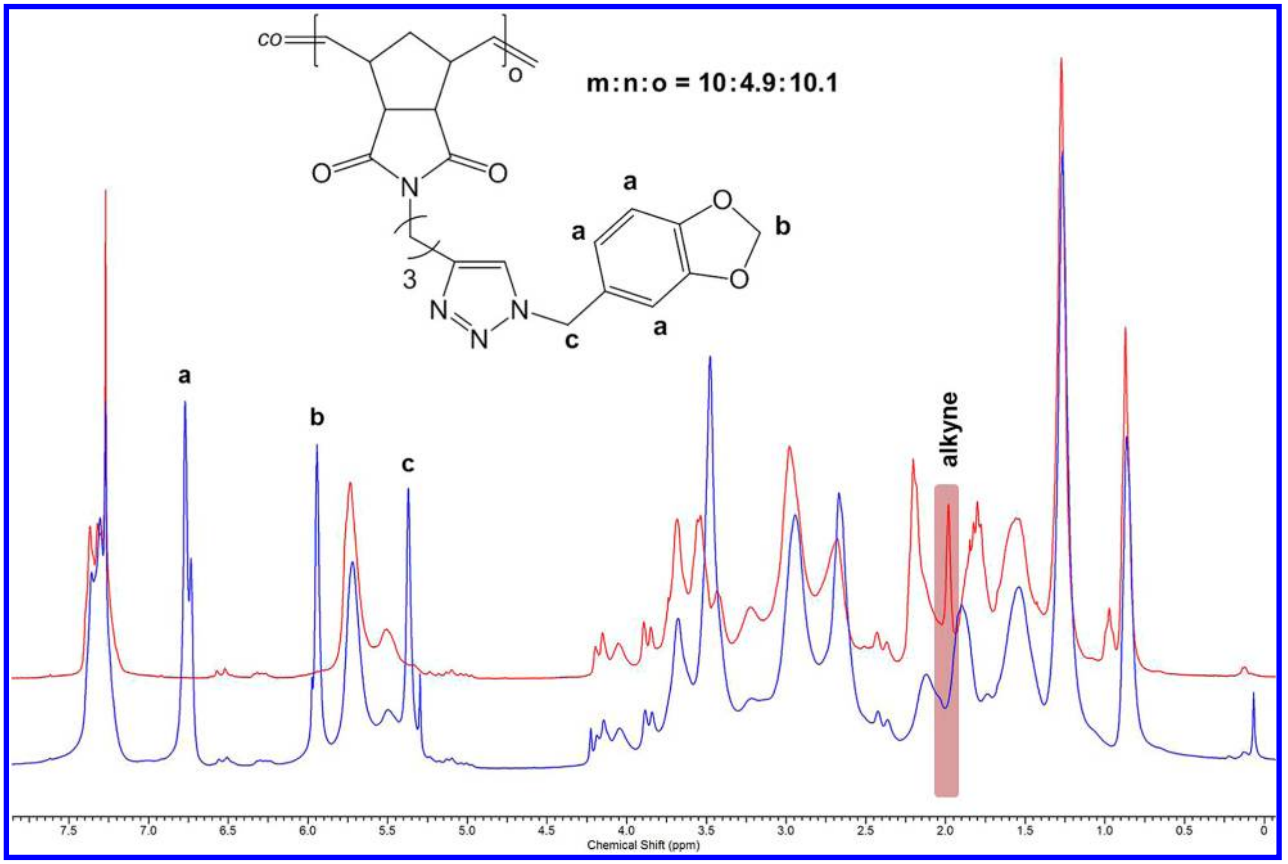


Figure 8. [1]H NMR spectra before and after the third click reaction (CuAAC). Occurrence of multiple signals corresponding to the protected catechol but the triazole proton overlaps with these of the aromatic mercaptan.

dx.doi.org/10.1021/ma301061z | *Macromolecules* XXXX, XXX, XXX–XXX

these calculations showed the following composition for polymer **12** *m*:*n*:*o* = 9.8:4.7:10.5. Complete conversion could also be proven in the ^{19}F NMR spectrum due to complete disappearance of the signals corresponding to the pentafluorophenol ester (Figure 6).

For the alkyne to be suitable for CuAAC (copper-catalyzed azide−alkyne cycloaddition), the silyl protective group had to be cleaved quantitatively in order to ensure complete conversion to the corresponding triazole. Utilizing the newly synthesized alkyne-containing monomer **5** (Scheme 1), standard deprotecting conditions using a tetrabutylammonium fluoride (TBAF) solution in THF led to quantitative cleavage of the TMS protective groups under mild conditions whereas polymers containing monomers **SI2a,b** needed to be exposed to potassium carbonate in methanol for 72 h at 50 °C. The quantitative removal of the trialkylsilyl group can be shown by ^{1}H NMR (Figure 7), but due to the peak overlap of the terminal methyne proton at 1.98 ppm with signals of the polymer backbone, it could not be integrated properly to estimate the degree of functionalization.

Cu-catalyzed reaction of the terminal alkynes in polymer **13** with compound **9** (Scheme 2) yielded the corresponding 1,2,3-triazoles. The copper(I) species were synthesized *in situ* by reduction of catalytic amounts of copper(II) sulfate with an excess of sodium L-ascorbate. The formation of the triazole can clearly be shown by investigating the ^{1}H NMR spectra of the final, fully functionalized polymer due to the occurrence of the aromatic (Figure 8, **a**) and benzylic (Figure 8, **c**) protons as well as the protons corresponding to the acetal (Figure 8, **b**). Because of overlap of the triazole proton and the aromatic protons of the benzyl mercaptan, the aromatic signal of the former azide (Figure 8,**a**) will be used to estimate the degree of functionalization *m*:*n*:*o* = 10.0:4.9:10.1.

According to the corresponding GPC traces (data in Table 1), the addition of a mercaptan as well as the substitution reaction by an amine led to an increase of molecular weight. For the latter this is believed to be due to the formation of a strongly solvated amide, hence increasing the hydrodynamic volume of polymer **12**. The same effect occurred after the alkyne-deprotection step where the nonpolar trimethylsilyl group was cleaved off, revealing a C−H acidic alkyne. Also contrary to our expectations, the apparent molecular weight of polymer **14** was smaller after the functionalization. This collapse is believed to be caused by aromatic interactions between the side chains and due to poorer solvation of the protected aromatic catechol groups leading to a decrease in hydrodynamic volume.

The azide (**9**) used in this investigation served as a model organic azide and can readily be replaced by other functional organic azides. However, cleavage of the acetal protective group contained in **9** can lead to a catechol group, which will be exploited in the binding to metal oxide surfaces or nanoparticles. This is currently under investigation in our group.

4. CONCLUSION

New orthogonally functionalizable statistical terpolymers as well as diblock copolymers have been reported employing living ring-opening metathesis polymerization (ROMP). The statistical terpolymers carried pentafluorophenol esters, maleimides, and protected alkynes whereas the diblock copolymers carried amine-selective esters in one block and protected alkynes in the other. First, these different functional groups were tested for their chemical stability toward all functionalization conditions used in order to elaborate a procedure leading to an orthogonal triple-functionalization of a precursor polymer. The maleimide functions could be reacted quantitatively with a model mercaptan and the active esters (PFP-esters) with a model primary amine. Following the silyl deprotection of the polymeric alkyne, a Cu-catalyzed alkyne−azide click reaction could be carried out in high yields using a model azide reagent. Protecting the reactive and strongly coordinating alkynes with silyl protective groups yields monomer structures that can easily be polymerized using commercial ruthenium carbene initiators. In combination with the high functional group tolerance of the olefin metathesis reaction, we believe that the ROMP process has great potential for the synthesis of highly reactive postpolymerizable copolymers.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedure of compounds **SI1a,b** and **SI2a,b** as well as **8** and **9**; NMR spectra of monomers **2**, **5**, and **7** as well as additional NMR analysis of various intermediates; synthetic scheme of block copolymer synthesis and postpolymerization functionalization including NMR analysis as well as corresponding GPC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail andreas.kilbinger@unifr.ch; Tel +41 (0)26 300 8713; Fax +41 (0)26 300 9738.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research project is funded by the Swiss National Science Foundation (SNF). The authors thank Christof Storz for valuable discussions regarding the synthesis of piperonyl azide **9** and its polymer analogous click reaction.

■ REFERENCES

(1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.
(2) Theato, P. *J. Polym. Sci., Polym. Chem.* **2008**, *46*, 6677−6687.
(3) Gauthier, M. A.; Gibson, M. I.; Klok, H. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 48−58.
(4) Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620−5686.
(5) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15−54.
(6) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791−1815.
(7) Spruell, J. M.; Wolffs, M.; Leibfarth, F. A.; Stahl, B. C.; Heo, J.; Connal, L. A.; Hu, J.; Hawker, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 16698−16706.
(8) Giuntini, F.; Dumoulin, F.; Daly, R.; Ahsen, V.; Scanlan, E. M.; Lavado, A. S. P.; Aylott, J. W.; Rosser, G. A.; Beeby, A.; Boyle, R. W. *Nanoscale* **2012**, *4*, 2034−2045.
(9) Nilles, K.; Theato, P. *J. Polym. Sci., Polym. Chem.* **2010**, *48*, 3683−3692.
(10) Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 14942−14949.
(11) Vogel, N.; Theato, P. *Macromol. Symp.* **2007**, *249−250*, 383−391.
(12) Binder, W. H.; Kluger, C. *Macromolecules* **2004**, *37*, 9321−9330.

(13) Strong, L. E.; Kiessling, L. L. *J. Am. Chem. Soc.* **1999**, *121*, 6193−9196.
(14) Yang, S. K.; Weck, M. *Macromolecules* **2008**, *41*, 346−351.
(15) Allen, M. J.; Wangkanont, K.; Raines, R. T.; Kiessling, L. L. *Macromolecules* **2009**, *42*, 4023−4027.
(16) Liaw, D. J.; Huang, C. C.; Fu, C. W. *J. Polym. Sci., Polym. Chem.* **2006**, *44*, 4428−4434.
(17) Owen, R. M.; Gestwicki, J. E.; Young, T.; Kiessling, L. L. *Org. Lett.* **2002**, *4*, 2293−2296.
(18) Roberts, K. S.; Sampson, N. S. *Org. Lett.* **2004**, *6*, 3253−3255.
(19) Carrillo, A.; Yanjarappa, M. J.; Gujraty, K. V.; Kane, R. S. *J. Polym. Sci., Polym. Chem.* **2006**, *44*, 928−939.
(20) Yang, S. K.; Weck, M. *Soft Matter* **2008**, *5*, 582−585.
(21) Hilf, S.; Kilbinger, A. F. M. *Nat. Chem.* **2009**, *1*, 537−546.
(22) Hilf, S.; Grubbs, R. H.; Kilbinger, A. F. M. *Macromolecules* **2008**, *41*, 6006−6011.
(23) Hilf, S.; Kilbinger, A. F. M. *Macromolecules* **2009**, *42*, 1099−1106.
(24) Hilf, S.; Kilbinger, A. F. M. *Macromolecules* **2009**, *42*, 4127−4133.
(25) Hilf, S.; Kilbinger, A. F. M. *Macromolecules* **2010**, *43*, 208−212.
(26) Hilf, S.; Berger-Nicoletti, E.; Grubbs, R. H.; Kilbinger, A. F. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 8045−8048.
(27) Hilf, S.; Grubbs, R. H.; Kilbinger, A. F. M. *J. Am. Chem. Soc.* **2008**, *130*, 11040−11048.
(28) Hilf, S.; Hanik, N.; Kilbinger, A. F. M. *J. Polym. Sci., Part A* **2008**, *46*, 2913−2921.
(29) Xia, Y.; Verduzco, R.; Grubbs, R. H.; Kornfield, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 1735−1740.
(30) Kluger, C.; Binder, W. H. *J. Polym. Sci., Polym. Chem.* **2007**, *45*, 485−499.
(31) Binder, W. H.; Kluger, C.; Josipovic, M.; Straif, C. J.; Friedbacher, G. *Macromolecules* **2006**, *39*, 8092−8101.
(32) Al-Badri, Z. M.; Tew, G. N. *Macromolecules* **2008**, *41*, 4173−4179.
(33) Krovi, S. A.; Smith, D.; Nguyen, S. T. *Chem. Commun.* **2010**, *46*, 5277−5279.
(34) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601−11624.
(35) Valverde, I. E.; Delmas, A. F.; Aucagne, V. *Tetrahedron* **2009**, *65*, 7597−7602.
(36) Ishizumi, K.; Kojima, A.; Antoku, F. *Chem. Pharm. Bull.* **1991**, *39*, 2288−2300.
(37) Glacera Contour, M.-O.; Sidhu, A.; Roubert, P.; Thurieau, C. US Patent US 2005/154039 A1, 2005.