Modular Synthesis of ABC Type Block Copolymers by "Click" Chemistry

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ABSTRACT: Heterotelechelic polystyrene (PS), poly(tert-butyl acrylate) (PtBA), and poly(methyl acrylate) (PMA), containing both azide and triisopropylsilyl (TIPS) protected acetylene end groups, were prepared in good control ($M_w/M_n < 1.24$) by atom transfer radical polymerization (ATRP). The end groups were independently applied in two successive ‘‘click’’ reactions, that is: first the azide termini were functionalized and, after deprotection, the acetylene moieties were utilized for a second conjugation step. As a proof of concept, PS was consecutively functionalized with propargyl alcohol and azidoacetic acid, as confirmed by MALDI-ToF MS. In addition, the same methodology was employed to modularly build up an ABC type triblock terpolymer. Size exclusion chromatography measurements demonstrated first coupling of PtBA to PS and, after the deprotection of the acetylene functionality on PS, connection of PMA, yielding a PMA-b-PS-b-PtBA triblock terpolymer. The reactions were driven to completion using a slight excess of azide functionalized polymers. Reduction of the residual azide groups into amines allowed easy removal of this excess of polymer by column chromatography.

Keywords: atom transfer radical polymerization (ATRP); block copolymers; functionalization of polymers

INTRODUCTION

‘‘Click’’ chemistry, a term proposed by Sharpless and coworkers,1 is defined as a reaction process that intrinsically is modular, wide in scope and high yielding, which, furthermore, is based on easily applicable reaction conditions and facile purification methods. The most pronounced example of a ‘‘click’’ reaction is the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between azides and terminal acetylenes, which leads to the formation of 1,4-disubstituted 1,2,3-triazole rings.2 Due to the functional group tolerance of this reaction, ‘‘click’’ chemistry has become a powerful tool for, among other things, bioconjugation.3–8

Over the last year, ‘‘click’’ chemistry has taken a tremendous flight in polymer chemistry to prepare main-chain triazole polymers,9,10 dendrimers,11–14 dendronized linear polymers,15,16 hydrogels,17,18 block copolymers,19 graft copolymers,20,21 star polymers,22–25 and new classes of functionalized monomers.26 It has also been used to functionalize both end groups27–29 and side chains30–33 of polymers. As a result of the efficiency of the reaction, we have previously proven it to be possible to connect polymer fragments via their end groups, thus modularly synthesizing diblock copolymers.19 The polymer modules were prepared by atom transfer radical polymerization (ATRP),34,35 allowing the introduction of azide and acetylene end groups, via the use of func-
tional initiators\textsuperscript{36–38} and postpolymerization end group modification procedures.\textsuperscript{39,40}

By employing both functionalization methods, an azide as well as an acetylene end group can be introduced into one single macromolecule. These heterotelechelic polymers have been used to linearly extend polymer chains\textsuperscript{41,42} and for the synthesis of cyclic polymers using “click” chemistry.\textsuperscript{43}

Here we report the modular synthesis of ABC type block copolymers by “click” chemistry utilizing such heterotelechelic polymeric building blocks. In this way, block copolymers can be prepared in a controlled fashion, which, otherwise, can be a difficult synthetic task by means of consecutive polymerization of distinct monomers. By exploiting polymers bearing protected acetylene moieties and azides, first “click” reactions can be performed using the azide functionalities, and, after deprotection of the acetylene groups, a second polymer block can be coupled to the other terminus, yielding ABC type block copolymers. In this way, poly(\textit{N},\textit{N}-dimethyl acrylate)-block-polystyrene-block-poly(\textit{t}-butyl acrylate) (PMA-b-PS-b-PrBA) has been synthesized in a modular and controlled manner. Very recently, Hizal, Tunca, and co-workers showed the synthesis of ABC type block copolymers by simultaneous attachment of two polymer chains to a core B-block by performing both a Diels–Alder and a “click” reaction.\textsuperscript{44} The advantage of this methodology is that the trilobate terpolymer synthesis can be executed in one pot. However, the method here described of utilizing solely “click” chemistry can be performed at lower temperatures, thereby reducing the likelihood of side-reactions. Furthermore, the complete “click” chemistry approach is versatile and can be used for the asymmetric functionalization of polymer chains with a myriad of distinct moieties, for example, biomolecules.

**EXPERIMENTAL**

**Materials**

Chlorotriisopropylsilane (TIPS-Cl) (Acros, 97%), ethylmagnesium bromide (Aldrich, 3.0 M solution in Et\textsubscript{2}O), propargyl alcohol (Acros, 99%), 2-bromoisoobutyryl bromide (Aldrich, 98%), tetrabutylammonium fluoride (TBAF) (Janssen Chimica, 1 M solution in tetrahydrofuran (THF)), N,N,N′,N″,N‴-pentamethyldiethylenetriamine (PMDETA) (Aldrich, 99%), 2,2′-bipyridine (bpy) (Aldrich, >99%), sodium azide (NaN\textsubscript{3}) (Acros, 99%), tris(2-aminoethyl)amine (Aldrich, 96%), and silver trifluoromethanesulfonate (AgOTf) (Aldrich, >99%), 3-indoleacrylic acid (IAA) (Aldrich, ≥99%) were used as received. Copper(I)-bromide (CuBr) was purified by washing with glacial acetic acid three times and twice with diethyl ether.\textsuperscript{45} Triphenylphosphine (PPh\textsubscript{3}) was recrystallized from isopropanol. Triethylamine (Et\textsubscript{3}N) was distilled under nitrogen from potassium hydride. Dimethylformamide (DMF) was dried with magnesium sulfate and distilled under reduced pressure.

**Instruments**

Proton and carbon-13 nuclear magnetic resonance (\textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR) spectra were recorded on a Bruker DPX300 spectrometer. Chemical shifts are expressed in parts per million (δ scale) relative to the internal standard tetramethylsilane (δ = 0.00 ppm) for \textsuperscript{1}H-NMR spectra and relative to CDCl\textsubscript{3} (δ = 77.16 ppm) for \textsuperscript{13}C-NMR spectra. Infrared (IR) spectra were obtained using an ATI Matson Genesis Series FTIR spectrophotometer fitted with an ATR cell. Data are presented as the frequency of absorption (cm\textsuperscript{-1}).

Molecular weight distributions were measured using size exclusion chromatography (SEC) on a system equipped with a guard column and a PL gel 5\textmu m mixed D column (Polymer Laboratories) with differential refractive index (RI) and UV (254 nm) detection, using THF as an eluent at 1 mL/min and T = 35 °C. Polystyrene (PS) standards in the range of 162–6,035,000 g/mol were used to calibrate the SEC.

Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates (layer thickness 0.25 mm). Compounds were visualized by UV, permanganate, or ninhydrin reagent.

Column chromatography (CC) was performed using silica gel, Acros (0.035–0.070 mm, pore diameter ~6 nm), unless otherwise stated.

Gas chromatography (GC) measurements were conducted on a Hewlett–Packard 5890 Series II gas chromatograph equipped with a capillary column (HP1701, 25 m × 0.32 mm × 0.25 \textmu m), using flame ionization detection.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF MS) mass spectra were measured on a Bruker Biflex III machine. IAA was used as the matrix. If necessary, AgOTf was added as an ionizing agent. Samples were prepared by mixing 10 μL of a 20 mg/mL IAA solution, 10 μL of a 1 mg/mL polymer solution, and 1 μL of a 5 mg/mL AgOTf solution. From this mixture 1 μL was spotted on a MALDI plate.

Synthesis of 3-(1,1,1-Triisopropylsilyl)-2-propyn-1-ol [2]

A solution of propargyl alcohol (1.13 g, 20.2 mmol) in THF (20 mL) was added dropwise at room temperature to a 3.0 M solution of ethylmagnesium bromide (20.0 mL, 60.0 mmol), which was diluted with THF (50 mL). After complete addition, the reaction mixture was refluxed for 18 h. The reaction mixture was allowed to cool to room temperature to a 3.0 M solution of ethylmagnesium bromide (1040 cm⁻¹) 2863, 2172 (C=C), 1463, 1385, 1359, 1247, 1096, 1040 cm⁻¹.

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Polymerization Procedures

Schlenk flasks fitted with stoppers were loaded with CuBr, evacuated and back-filled with argon. This procedure was repeated three times. After these evacuating cycles, the stoppers were replaced by septa. Subsequently, monomers, solvents (if necessary), internal standards, and PMDETA were added and the reaction mixtures were stirred for 15 min to allow catalyst formation. Before adding 3-(1,1,1-triisopropylsilyl)-2-propynyl 2-bromo-2-methylpropanoate [3], the reaction mixtures were cooled in an ice bath. Afterwards, the reaction mixtures were purged with argon for 5 min and placed in an oil bath at the desired temperature. Samples were taken periodically for conversion analysis by $^1$H-NMR or GC. To quench the polymerizations, the reaction mixtures were cooled and diluted with CHCl$_3$. To remove the catalysts, the reaction mixtures were purified using a basic alumina column. The reaction mixtures were concentrated in vacuo and the polymers were precipitated in MeOH (for PS), MeOH/H$_2$O (1:1) (for P$_t$BA), and n-heptane (for poly(methyl acrylate) (PMA)). The polymers were dried in a vacuum oven at 60 °C.

The temperatures and concentrations used for the polymerization reactions are included in Scheme 3 and in the caption of Figure 1, respectively. The polydispersity indices (PDI’s) are rendered in Table 1.

General Procedure for the Synthesis of Azide End-Functionalized Polymers

Polymers containing bromide end groups were dissolved in DMF (0.01 M solution). Subsequently, NaN$_3$ (10 equiv.) was added and the reaction mixtures were stirred for 20 h at room temperature. Afterwards, the reaction mixtures were diluted with CH$_2$Cl$_2$ and washed four times with distilled water. The reaction mixtures were concentrated in vacuo and the polymers precipitated in MeOH (for PS and block copolymers), MeOH/H$_2$O (1:1) (for P$_t$BA), and n-heptane (for PMA). The polymers were dried in a vacuum oven.

Table 1. SEC Data from Polymeric Building Blocks and Formed Block Copolymers by “Click” Chemistry

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$M_n$ (kg/mol)</th>
<th>$M_w/M_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPS−PS−Br</td>
<td>[4a]</td>
<td>5.82</td>
</tr>
<tr>
<td>TIPS−PS−Br</td>
<td>[5a]</td>
<td>5.82</td>
</tr>
<tr>
<td>TIPS−PS−N$_3$</td>
<td>[5b]</td>
<td>6.98</td>
</tr>
<tr>
<td>TIPS−PS−N$_3$</td>
<td>[5b]</td>
<td>6.98</td>
</tr>
<tr>
<td>TIPS−$t$BA−Br</td>
<td>[6]</td>
<td>3.58</td>
</tr>
<tr>
<td>H−$t$BA−Br</td>
<td>[7]</td>
<td>3.56</td>
</tr>
<tr>
<td>TIPS−PMA−Br</td>
<td>[8]</td>
<td>7.17</td>
</tr>
<tr>
<td>TIPS−PMA−N$_3$</td>
<td>[9]</td>
<td>7.15</td>
</tr>
<tr>
<td>TIPS−PS−OH</td>
<td>TIPS−[5b]−OH</td>
<td>7.31</td>
</tr>
<tr>
<td>HOOC−PS−OH</td>
<td>HOOC−[5b]−OH</td>
<td>7.45</td>
</tr>
<tr>
<td>TIPS−PS−$t$BA−Br</td>
<td>TIPS−[5a]−block-[7]−Br</td>
<td>8.30</td>
</tr>
<tr>
<td>TIPS−PMA-6-PS-6-$t$BA−Br</td>
<td>TIPS−[9]−block-[5a]−block-[7]−Br</td>
<td>15.29</td>
</tr>
</tbody>
</table>
oven at 60 °C. Successful introduction of the azide moieties was determined by the appearance of azide signals in the FTIR spectra, along with the presence of the correct end groups analyzed with MALDI-ToF MS.

**General Procedure for the Deprotection of Acetylene Moieties Present in Polymers**

Polymers bearing TIPS protected acetylene end groups were dissolved in THF (0.01 M solution). After complete dissolution, a solution of TBAF (10 equiv.) in THF (1.0 M) was added and the reaction mixture was stirred for 17 h at room temperature. The reaction mixture was concentrated in vacuo and the polymers were precipitated in MeOH and isolated as a white solid, which was dried under vacuum. Yield: 194.3 mg (93%); TLC: \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH}) = 0.12; \ R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 95:5) = 0.96. \)

\(^1\)H-NMR (300 MHz, CDCl₃) \( \delta 7.60 \) (br. s, triazole \( H \)), 7.41–6.25 (br. m, arom. \( H \)), 5.08 (br. m, \( \text{CH}_2\text{C}(\text{Ph})\text{N}^- \)), 4.66 (br. m, \( \text{CH}_2\text{OH}^- \)), 4.08 (br. m, \( \equiv \text{CH}_2 \)), 2.33–1.12 (br. m, backbone \( \text{CH}_2 \)), 1.12–0.78 (br. m, \( \text{O}_2\text{C}^-\text{C}(\text{CH}_3)_2\text{CH}_2 \)). FTIR–ATR: 3084, 3054, 3023, 2920, 2846, 1943, 1865, 1796, 1731, 1601, 1493, 1450, 1359, 1260, 1178, 1027 cm\(^{-1}\); SEC: \( M_n = 7.31 \) kg/mol; \( M_w/M_n = 1.16 \); MALDI-ToF MS: \( m/z = 7247 \pm 104.06 \) (65 repeating units + end groups + Ag\(^+\)).

**Synthesis of \( \alpha \)-(Carboxylic acid)-\( \omega \)-hydroxy-PS (HOOC—[5b]—OH): Test Reaction for Performing Two Consecutive “Click” Reactions**

**Coupling of Propargyl Alcohol**

Heterotelechelic PS [5b] (206 mg, 0.047 mol) was placed in a Schlenk tube fitted with a stopper, evacuated, and back-filled with argon. This evacuating cycle was repeated three times and, afterwards, the stopper was replaced by a septum. THF (5 mL) and propargyl alcohol (27.3, 0.49 mmol) were added. Subsequently, 0.2 mL of a stock solution containing CuBr (0.45 M) and PMDETA (0.45 M) in THF, which was prepared under Schlenk conditions, was added. The reaction mixture was stirred for 18 h at room temperature. Completion of the reaction was determined by disappearance of the azide signal with FTIR–ATR and TLC (CH₂Cl₂). CH₂Cl₂ (4 mL) was added and the reaction mixture was washed three times with a 0.055 M aqueous EDTA solution and twice with distilled H₂O. The organic layer was dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. The formed hydroxyl functionalized PS (TIPS—[5b]—OH) was precipitated in MeOH and isolated as a white solid, which was dried under vacuum. Yield: 51.0 mg (95%); TLC: \( R_f (\text{CH}_2\text{Cl}_2) = 0.09 \).

\(^1\)H-NMR (300 MHz, CDCl₃) \( \delta 7.41–6.24 \) (br. m, arom. \( H \)), 5.08 (br. m, \( \text{CH}_2\text{C}(\text{Ph})\text{N}^- \)), 4.65 (br. m, \( \equiv \text{CH}_2 \)), 4.06 (br. m, \( \equiv \text{CH}_2 \)), 2.33–1.12 (br. m, backbone \( \text{CH}_2 \)), 1.07–0.92 (br. m, \( \text{O}_2\text{C}^-\text{C}(\text{CH}_3)_2\text{CH}_2 \)); SEC: \( M_n = 7.28 \) kg/mol; \( M_w/M_n = 1.16 \).

**“Click” Reaction with Azidoacetic Acid**

A Schlenk tube fitted with a stopper was loaded with deprotected hydroxyl functionalized PS (H—[5b]—OH) (47.0 mg, 0.011 mmol) and azidoacetic acid (11.2 mg, 0.11 mmol). The Schlenk tube was evacuated and back-filled with argon. After repeating this procedure three times, the stopper was replaced by a septum and THF (1 mL) was added. Subsequently, 0.1 mL of a stock solution containing CuBr (0.11 M) and PMDETA (0.11 M) in THF, which was prepared under Schlenk conditions, was added. The reaction mixture was stirred for 18 h at room temperature. Completion of the reaction was determined by TLC (CH₂Cl₂/MeOH 95:5). CH₂Cl₂ (5 mL) was added and the reaction mixture was washed three times with a 0.055 M aqueous EDTA solution and twice with distilled H₂O. The organic layer was dried using anhydrous magnesium sulfate and...
concentrated in vacuo. \( \alpha \)-(Carboxylic acid)-ω-hydroxy-PS (HOOC-[5b]-OH) was precipitated in MeOH and isolated as a white solid which was dried under vacuum. Yield: 39.6 mg (82%); TLC: \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 95:5) = 0.04 \).

1H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.41–6.24 (br. m, arom. \( H \)), 5.20–4.92 (br. m, HOOC-CH\(_2\)-N, CH\(_2\)-CH(Ph) -N, N(=C)-CH\(_2\)-O\(_2\)C), 4.67 (br. m, CH\(_2\)-OH), 2.33–1.12 (br. m, backbone CH\(_2\), CH), 1.07–0.92 (br. m, O\(_2\)C-C(CH\(_3\)_2)-CH\(_2\)); FTIR-ATR 3084, 3054, 3023, 2920, 2846, 1943, 1865, 1796, 1731, 1728, 1601, 1493, 1450, 1359, 1260, 1178, 1083, 1078, 1027 cm\(^{-1}\); SEC: \( M_n = 7.45 \text{ kg/mol} \); \( M_w/M_n = 1.16 \); MALDI-ToF MS: \( m/z \) 7192, 1H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.43–6.24 (br. m, CH\(_2\), ((C\(_3\)_2)\(_3\)O\(_2\)C), 4.78 (br. m, CH\(_2\)-CH(Ph) -N, CH\(_2\)-CH(CO\(_2\)Me) -N), 4.20–3.57 (br. m, \( \equiv -CH\(_2\)-O\(_2\)C, CH\(_2\)-CH(CO\(_2\)Bu) -Br), 3.99–3.28 (br. s, \( H_3\text{C}-O-C(=O) \)), 2.53–0.73 (br. m, CO\(_2\)-C(CH\(_3\)_3), O\(_2\)C-C(CH\(_3\)_2)-CH\(_2\), ((CH\(_3\)_2)CH\(_2\)Si- \( \equiv \)), backbone CH\(_2\), CH); SEC: \( M_n = 15.29 \text{ kg/mol} \); \( M_w/M_n = 1.20 \).

**RESULTS AND DISCUSSION**

To modularly synthesize ABC type triblock terpolymers, two successive “click” reactions have to be enforced on the central polymer chain (B block). To accomplish this, polymers bearing both azide and acetylene end groups have to be used and, moreover, one of the termini has to be protected to circumvent linear chain extension and the formation of cyclic products. The most straightforward methodology is to protect the terminal acetylene moieties and to utilize the azide termini for the first “click” coupling. Next, the acetylene functionalities have to be deprotected to be available for a subsequent “click” reaction. Therefore,

**Synthesis of PS-b-PfBA Diblock Copolymer (TIPS-[5a]-block-[7]-Br) via “Click” Chemistry**

Heterotelechelic PS [5a] (533.1 mg, 0.085 mmol) and acetylene-functional PBA[7] (435.8 mg, 0.075 mmol) were placed in a Schlenk tube. The Schlenk tube was evacuated and back-filled with argon three times and, subsequently, DMF (4 mL) was added. After complete dissolution of the polymers, 0.1 mL of a stock solution containing CuBr (0.075 mmol) was added. The reaction mixture was stirred for 20 h and purified by rotary evaporation and purified by CC (CH\(_2\)Cl\(_2\)/MeOH 95:5) by the disappearance of azide functionalized PBA and the presence of a ninhydrin positive spot at the baseline. The reaction mixture was concentrated by rotary evaporation and purified by CC (CH\(_2\)Cl\(_2\)/MeOH 95:5). Subsequently, the polymer was precipitated in MeOH and isolated as a white solid which was dried under vacuum. Yield: 53.8 mg (72%); TLC: \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 95:5) = 0.96 \).

1H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.48–6.17 (br. m, arom. \( H \)), 5.09–4.98 (br. m, N(=C)-CH\(_3\)-CH\(_2\)-O\(_2\)C), 4.83–4.69 (br. m, CH\(_2\)-CH(Ph) -N, CH\(_2\)-CH(CO\(_2\)Me) -N), 4.20–3.57 (br. m, \( \equiv -CH\(_2\)-O\(_2\)C, CH\(_2\)-CH(CO\(_2\)Bu) -Br), 3.99–3.28 (br. s, \( H_3\text{C}-O-C(=O) \)), 2.53–0.73 (br. m, CO\(_2\)-C(CH\(_3\)_3), O\(_2\)C-C(CH\(_3\)_2)-CH\(_2\), ((CH\(_3\)_2)CH\(_2\)Si- \( \equiv \)), backbone CH\(_2\), CH); SEC: \( M_n = 15.29 \text{ kg/mol} \); \( M_w/M_n = 1.20 \).
the first step was to prepare polymeric building blocks containing azide as well as protected acetylene end groups.

**Synthesis of α-(Protected acetylene)-ω-azide Functionalized polymers**

The most appropriate method to introduce terminal acetylene functionality in polymers is to use functionalized initiators. In previous research,\(^1\) trimethylsilyl (TMS)-protected ATRP initiator [1] (Scheme 1) was utilized. After close examination of the obtained polymers by \(^1\)H-NMR, however, it was found that 70% of the TMS groups were lost when using CuBr/PMDETA as the ATRP catalyst complex, although the polymerization proceeded in a controlled fashion (Scheme 1). In previous research, this side reaction did not give problems since deprotected acetylene functionalized polymers were used anyhow in the subsequent coupling reactions. However, for the synthesis of well-defined ABC type block copolymers, fully protected acetylene functionalized polymers are essential. A conceivable side reaction is nucleophilic attack of one of the nitrogen atoms of PMDETA on the TMS group. Therefore, instead of PMDETA, the less nucleophilic CuBr/bpy complex was tested as ATRP catalyst system, which indeed suppressed the deprotection reaction substantially; yet 10% of the TMS groups was still removed.

As a next step in eliminating this undesirable side reaction, the TMS protecting group was replaced by the more stable TIPS group. TIPS-protected acetylene-functionalized ATRP initiator [3] was synthesized from commercially available propargyl alcohol by first protecting the acetylene moiety and, subsequently, reacting the hydroxyl...
functionality with 2-bromoisobutyryl bromide, as depicted in Scheme 2.

Next, styrene, tert-butyl acrylate, and methyl acrylate were polymerized under ATRP conditions utilizing TIPS-protected acetylene-bearing initiator \[3\] (Scheme 3). As can be seen in Figure 1, the polymerization reactions of styrene and tert-butyl acrylate proceeded via first order kinetics, except for a little jump during the initiation stage in case of tert-butyl acrylate, which indicates control over the polymerization process and, accordingly, the polydispersity indices (PDI’s) are reasonably low \(M_w/M_n < 1.24\). The ATRP of methyl acrylate deviated slightly from first order behavior, nevertheless the PDI was low \(M_w/M_n = 1.18\). Furthermore, in this case \(^1\)H-NMR and MALDI-ToF MS measurements displayed no loss of the TIPS protecting group, owing to the significantly increased stability compared with TMS as a result of its bulky character. It has to be noted that the polymerizations were stopped at around 50% conversion to circumvent loss of bromide functionality because of termination processes, which eventually can lead to incomplete introduction of azide groups.

After ATRP polymerization, the bromide end groups present in the polymers could be exploited to introduce azide moieties by nucleophilic substi-

**Scheme 3.** Synthesis of trisopropyl silyl (TIPS) protected acetylene functionalized polymers by ATRP, and either the subsequent substitution of the bromide end groups yielding \(\alpha\)-(TIPS—acetylene)-\(\omega\)-azide terminated polymers \([5a], [5b], and [9]\), or deprotection of the acetylene moiety \([7]\).

**Scheme 4.** Test reaction for the heterotelechelic functionalization of polystyrene prepared by ATRP using “click” chemistry.
tution. As can be seen in Scheme 3, this methodology was applied using sodium azide in DMF, yielding $\omega$-(TIPS-acetylene)$_x$-azide functionalized PS [5a] and [5b], and PMA [9]. Presence of azide functionality was determined by appearance of azide signals in FTIR spectra (2090 cm$^{-1}$) and a complete upfield shift of the methine protons adjacent to the end groups in $^1$H-NMR spectra. The acetylene terminus of PtBA [6] was deprotected quantitatively according to $^1$H-NMR measurements by a straightforward protocol using TBAF, as depicted in Scheme 3. This yielded a handle to conjugate this polymeric building block to the azide functionalized polymers.

Test Reaction for Conducting Two Successive “Click” Reactions

To examine the possibility of functionalizing both end groups of polymers with two distinct substrates, first propargyl alcohol was coupled to the azide terminus of heterotelechelic PS [5b] (Table 1, Scheme 4). Subsequently, the acetylene moiety was deprotected by treatment with TBAF prior to a second “click” reaction using azidoacetic acid. Both “click” reactions were conducted applying CuBr/PMDETA as a catalyst.Formation of hydroxy functionalized PS (TIPS—[5b]—OH) and $\omega$-(carboxylic acid)$_x$-hydroxy functionalized PS (HOOC—[5b]—OH) was visualized by TLC, along with the appearance of extra signals in the $^1$H-NMR spectra originating from the functionalized end groups. Moreover, as can be seen in Table 1, no molecular weight increase was observed in the SEC traces after the performed “click” reactions, implying no linear chain extension of PS occurred, which means that the TIPS protecting group fully prevented reaction of the acetylene moiety under “click” conditions.

Additionally, as can be seen in Figure 2, MALDI-ToF MS spectra display the formation of the desired products. The difference in mass exactly corresponds to the loss of the TIPS protecting group and the addition of azidoacetic acid. The presence of a second distribution in the spectrum of HOOC—[5b]—OH is caused by complexation of potassium ions instead of silver ions, which were added as ionizing agents during sample preparation. The mass spectrum of TIPS—[5b]—OH display traces of terminated PS by expelling hydrogen bromide, especially at lower molecular weights. This loss of minute amounts of bromide end groups is inherent to the ATRP process. However, these impurities could not be detected by TLC or $^1$H-NMR, which implies that only a little trace was present.

Modular Formation of ABC Type Triblock Terpolymers by “Click” Chemistry

The abovementioned experiments proved the concept of conducting two consecutive “click” reactions onto one single polymer chain. Therefore, this paved the way to modularly synthesize ABC triblock terpolymers using the TIPS protected acetylene strategy. As a first step, heterotelechelic PS [5a] and unprotected acetylene functionalized PtBA [7] were “clicked” together by applying CuBr/PMDETA as a catalyst. According to SEC measurements, completion of this “click” reaction, however, could not be obtained using either THF or DMF as a solvent. Additionally, heating of the

Figure 2. MALDI-ToF mass spectra of mono-(TIPS—[5b]—OH) and difunctionalized (HOOC—[5b]—OH) polystyrene.
reaction mixtures even up to reflux temperatures had not the desired effect as well and, hence, 
CuBr/Me₆TREN was employed as a catalyst sys-
tem, as depicted in Scheme 5.

To drive the reaction to completion, a slight excess of PS [5a] (1.13 equivalents) was used. Af-
after 18 h of reaction, residual azide groups were 
reduced via a Staudinger reduction by addition 
of PPh₃ (Scheme 5) and the thus formed amine 
terminated PS could easily be removed by 
employing CC (CH₂Cl₂/MeOH 95:5). The 
Rf value of the block copolymer was 0.98, whereas 
the amine functionalized PS did not elute at all. 
Formation of PS-b-PtBA diblock copolymer 
(TIPS-[5a]-block-[7]—Br) was determined by a 
complete shift in the SEC trace towards higher 
molecular weight, as can be seen in Figure 3. 
Additionally, no increase of the PDI was 
observed for the formed diblock copolymer, indicating successful removal of the excess of PS 
[5a] and the absence of linear chain extended 
polymers (Table 1).

Subsequently, the acetylene end group of the 
diblock copolymer was made available for a next 
coupling reaction by removal of the TIPS group in 
the same manner as for PtBA [7], namely by 
TBAF addition (Scheme 5). Completion of this 
reaction was determined by the disappearance of 
the TIPS signals in the ¹H-NMR spectrum.

As the final step in preparing an ABC type 
triblock terpolymer, azide terminated PMA [9] (1.5 
equivalent) was coupled to the free acetylene end 
functionality of the PS-b-PtBA (H-[5a]-block-
[7]—Br) diblock copolymer (Scheme 5). The 
same methodology was applied as for the synthe-
sis of the diblock copolymer, that is, the “click” 
reaction was conducted with DMF as a solvent 
and CuBr/Me₆TREN as the copper(I) source. In 
this case, however, the reaction did not go to

**Scheme 5.** Modular formation of an ABC-type triblock terpolymer from heterotele-
chelic precursors using “click” chemistry.
completion over night as determined by the presence of residual diblock copolymer in the SEC trace of the reaction mixture. Subsequently, the reaction was performed at 50 °C, which resulted in complete disappearance of the diblock copolymer, and hence the formation of the PMA-b-PS-b-PtBA triblock terpolymer. The excess of azide functionalized PMA [7] was again removed by a reduction of the azide moieties and purification of the triblock terpolymer using CC (CH$_2$Cl$_2$/MeOH 95:5). As illustrated in Figure 4, once more a complete shift of the distribution towards higher molecular weight was observed indicating formation of the triblock terpolymer. Additionally, the PDI did not increase upon triblock terpolymer formation (Table 1), which leads to the conclusion that no or minute amounts of residual starting material or linearly extended polymers were present.

CONCLUSIONS

A method was developed to functionalize polymer end groups with two different substrates by “click” chemistry. In addition, this allowed the modular synthesis of ABC type triblock terpolymers by performing two successive “click” couplings of polymeric building blocks onto a central block (B).

Certainly, a prerequisite for these used heterotelechelic polymers are fully protected acetylene end groups. It was shown that a trimethylsilyl (TMS) group is susceptible to side reactions, especially when CuBr/PMDETA was used as an ATRP catalyst. Nevertheless, side reactions were completely excluded by application of the more stable TIPS protecting group, which afterwards could be quantitatively removed by subjection to TBAF.

To test the possibility of sequentially functionalizing both polymer end groups, propargyl alcohol was conjugated to the azide terminus of PS using CuBr/PMDETA as a catalyst and, after deprotection, azidoacetic acid was coupled to the acetylene end group.

To synthesize an ABC type triblock terpolymer by connection of polymer end groups, first PS, containing both a TIPS protected acetylene and an azide end group, was successfully coupled to PtBA functionalized with an unprotected acetylene end group using CuBr/Me$_6$TREN as a catalyst. After deprotection of the acetylene functionality, PMA with an azide end group was attached as the third block, using a similar protocol as for the synthesis of the diblock copolymer, apart from the fact that this reaction was performed at 50 °C. Once more, SEC measurements displayed successful formation of the PMA-b-PS-b-PtBA triblock terpolymer.

The synthetic methodology described in this article is very promising with respect to the asymmetric functionalization of polymers prepared by ATRP, also due to the efficiency and orthogonality of the utilized “click” coupling.

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REFERENCES AND NOTES

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