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Orthogonal Click Postfunctionalization of Alternating Copolymers Prepared by Nitroxide Mediated Polymerization

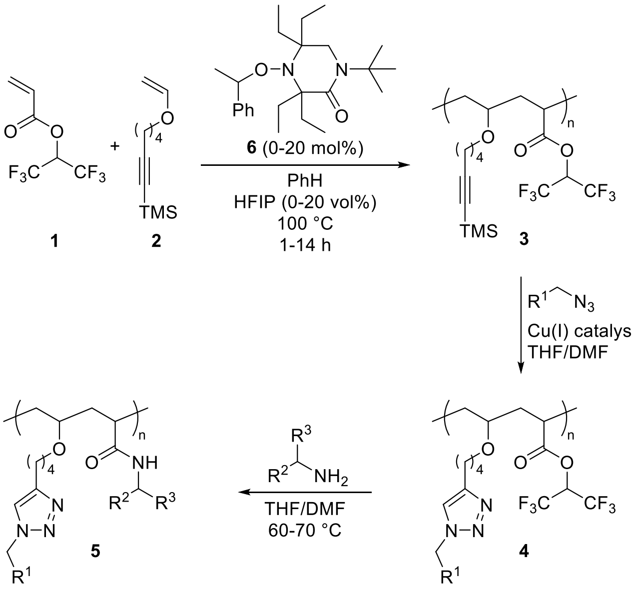
Matthias Tesch, Sergej Kudruk, Matthias Letzel, and Armido Studer*[a]

Abstract: Nitroxide Mediated Polymerization (NMP) was applied to prepare alternating copolymers using 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) **1** and ((6-trimethylsilyl)-hex-5-yn-1-yl)vinyl ether (THVE) **2** as monomers. The alternating sequence of the resulting poly(HFIPA-*alt*-THVE) **3** was proved *via* tandem mass spectrometry (MS/MS) and further supported by ^{1}H NMR spectroscopy. Alternating alkyne and activated ester moieties of copolymer **3** were further functionalized with organic azides and amines using sequential Cu-catalyzed azide-alkyne click (CuAAC) and amidation reactions, providing dually functionalized poly(acrylamide-*alt*-triazole) polymers **5**. Water-soluble alternating poly(acrylic acid-*alt*-triazole) copolymers **9** were obtained by saponification of HFIP esters. ^{1}H and ^{19}F NMR spectroscopy, IR spectroscopy as well as gel permeation chromatography (GPC) were used to characterize the polymers before and after functionalization.

The control over monomer sequence in polymer chemistry has gained a lot of attention in recent years. It has even been identified as “the next holy grail in polymer science”.[1,2] It is obvious that synthetic polymers, as compared to biopolymers such as proteins or nucleic acids, have much less complex primary structures due to the lack of appropriate synthetic methods, which would allow for accurate control over the sequence of a large number of monomers. It is known that the primary structure of natural polymers plays a key role for self-replication, self-assembly and molecular recognition.[3] Therefore, it is reasonable to assume that synthetic polymers with defined monomer sequence will set the stage for the generation of highly organized materials and man-made polymers with complex functions. Recently, valuable advances have been made in the field of sequence-controlled polymerization. Iterative multi-step approaches provide excellent sequence-fidelity but are tedious to conduct and therefore limited to oligomers and smaller polymeric chains.[4–17] Template-based strategies,[18–21] polymerizations based on multicomponent reactions,[22–25] and the polymerization of sequence-controlled precursors[26,27] allow for higher molecular weights but are limited to relatively simple repetitive patterns. Also pinpoint functionalization of polymer chains has been achieved by time-resolved addition of comonomers.[28] Although very rare, there are examples of complex molecular machines which mimic the translation process of ribosomes to yield sequence-defined polypeptides.[29]

Alternating radical polymerization has been achieved with nearly perfect sequence control.[30–41] Along these lines, we have recently introduced alternating NMP[42,43] of 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) **1** and (7-octenyl)vinyl ether (OVE). The resulting poly(HFIPA-*alt*-OVE) was orthogonally postfunctionalized *via* radical thiol-ene click reaction and subsequent amidation.[38,44] It is well known that the properties of polymers can be altered significantly by chemical postfunctionalization and numerous recent reports deal with the modification of polymers by thiol click chemistry,[16,45–49] Cu-catalyzed alkyne-azide click reaction (CuAAC),[34,49–57] amidation reactions,[46,47,58–60] and many others,[53,61–64] including combinations thereof. Our conceptual approach introduced allowed for preparation of a small library of alternating copolymers using a single type of parent copolymer and diversifying subsequent orthogonal postmodification.

We herein extend that valuable concept and present the alternating copolymerization of HFIPA **1** and ((6-trimethylsilyl)-hex-5-yn-1-yl)vinyl ether (THVE) **2** using alkoxyamine **6** as NMP initiator as well as the highly efficient orthogonal postfunctionalization of the resulting copolymers **3** (Scheme 1). To our knowledge, this is the first example describing orthogonal CuAAC/amidation postfunctionalization of alternating copolymers THVE **2** was readily prepared from commercially available hex-5-yn-1-ol in a two-step procedure on a multi-gram scale in 56 % overall yield (see supporting information, SI).



Scheme 1. Nitroxide mediated copolymerization of **1** and **2** and subsequent dual click functionalization *via* CuAAC and amidation.

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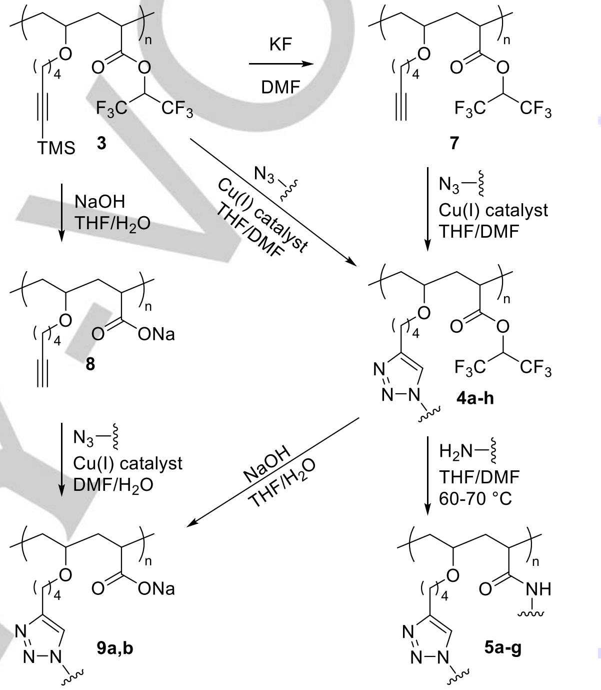
Copolymerization of **2** with HFIPA **1** was systematically investigated. To this end, copolymerizations at different monomer feed ratios *f* were performed using initiator **6** (2 mol%) in benzene at 100 °C and reactions were stopped at low conversion (≤ 35%). Ratio of incorporated monomers *F* was plotted against *f* in a *Mayo-Lewis* plot (Figure 1a).[65] Using a monomer feed of 1:1 ($f = 0.50$) resulted in preferential HFIPA incorporation over THVE with a ratio of $F = 0.58$. At $f = 0.20$ both monomers were incorporated in equal amounts, suggesting an alternating sequence of the copolymer, which was proved by tandem mass spectrometry (see SI). A further increase in vinyl ether concentration ($f = 0.11$) did not lead to a higher incorporation of **2** over **1** ($F = 0.50$) due to the inability of vinyl ethers to form homopolymeric sequences under conventional radical polymerization conditions. In contrast, a large excess of **1** ($f = 0.90$) resulted in HFIPA-enriched copolymers (69:31).

Reactivity ratios $r_1 = 0.21$ and $r_2 = 0.00$ were then obtained by fitting the data points to the *Mayo-Lewis* copolymerization equation using the method of least squares (see SI). These values reflect the tendency of the HFIPA/THVE monomer pair to copolymerize in an alternating mode. It should be noted that acrylate **1** tends to undergo homopolymerization to some extent ($r_1 = 0.21$) whereas vinyl ether **2** does not undergo any homopolymerization ($r_2 = 0.00$). From figure 1a one can extract that good alternating sequence control can be achieved using a fourfold excess of vinyl ether **2** which is unfortunately the more expensive monomer in the mixture. We therefore tried to lower the **2**-loading keeping alternating sequence control and found that upon addition of a small amount of HFIP (3 vol% compared to benzene) good control is achieved with just a twofold excess of **2**. We attribute this effect to the efficient coordination of HFIP to the acrylate monomer, decreasing its electron density and enhancing cross-propagation. Under these conditions, $M_{n,exp}$ was varied from 5 300 to 11 100 g/mol using **6** (0.5-20 mol%). The incorporation ratio (HFIPA/THVE) varied from 50/50 to 52/48 (details can be found in the SI). Notably, NMP-regulator **6** can be replaced by commercially available 4-cyano-4-(phenylcarbonothioylthio)-pentanoic acid as a RAFT reagent (2 mol%) and AIBN as radical initiator, providing poly(HFIPA-*alt*-THVE) with a 50:50 incorporation of both monomers ($M_{n,exp}$ = 8 200 g/mol and PDI = 1.19) showing that this process is, as expected, not restricted to NMP.

Figure 1b shows the monomer conversion of HFIPA and polydispersity index (PDI) plotted against reaction time (HFIPA (1 equiv.), THVE (2 equiv.), and alkoxyamine **6** (2 mol%) in benzene/HFIP (97/3) at 100 °C for 3-45 min). The plot of the average molecular weight $M_{n,exp}$ against HFIPA conversion is depicted in figure 1c. Both plots show the typical linear behavior for a controlled/living radical polymerization (PDI between 1.11 and 1.20).

After the in-depth investigation of the copolymerization of **1** and **2** we turned our attention to the post-polymerization functionalization of poly(HFIPA-*alt*-THVE) **3** (Scheme 2).



Scheme 2. Chemical postmodification of poly(HFIPA-alt-THVE) **3**. Results are summarized in Table 1 and substituents for the postmodified copolymers **5a-g** and **9a,b** are specified in Table 1.

These studies were conducted using poly(HFIPA-*alt*-THVE) with a DP of 16 monomer units each ($M_{n,exp}$ = 7 900 g/mol; PDI 1.26). The trimethylsilyl group in **3** could be quantitatively removed with KF in DMF at room temperature to give **7**. Copolymer **3** was readily transferred into the corresponding alternating acrylic acid

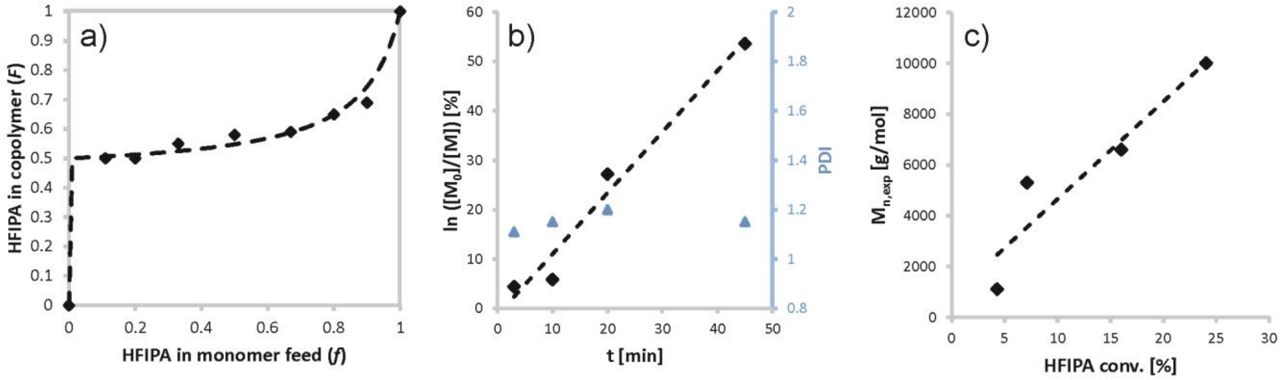


Figure 1. a) *Mayo-Lewis* plot of the copolymerization of **1** and **2**. Reactivity ratios ($r_1 = 0.21$, $r_2 = 0.00$) were obtained by fitting the data points to the *Mayo-Lewis* equation; b) monomer conversion and PDI plotted *vs*. time; c) $M_{n,exp}$ plotted vs. HFIPA conversion.

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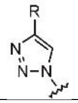
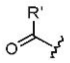
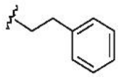
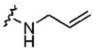
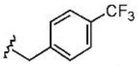
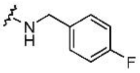
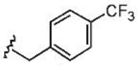
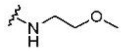
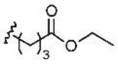
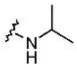
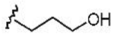
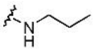
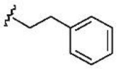
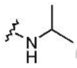
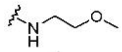
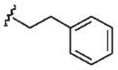
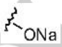
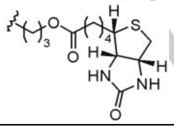
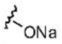
Na-salt **8** by saponification using NaOH in THF/H_2O. Under these conditions the TMS group was also removed.

Next we attempted CuAAC of the alkyne functionality in the copolymer and found that in most cases silyl deprotection prior to the CuAAC is not necessary, since desilylation occurred under the conditions of the click reaction.[66,67] Hence, reaction of **3** with homobenzyl azide (1.0 equiv.) was achieved in THF/DMF (1:1) at ambient temperature in the presence of $CuSO_4$ as a catalyst precursor and sodium ascorbate as a reducing reagent (Table 1, entry 1). After extraction of the Cu catalyst using aqueous EDTA solution and subsequent concentration *in vacuo*, the monofunctionalized poly(HFIPA-*alt*-triazole) **4a** obtained was analyzed by ^{1}H NMR spectroscopy (see SI for spectra). The signal at 2.1 ppm, assigned to the propargylic CH_2 group in **3** completely vanished, whereas a new signal for the corresponding methylene group at the triazole ring appeared at 2.6 ppm, indicating quantitative cycloaddition. Moreover, appearance of new benzylic and homobenzylic as well as the expected aromatic signals further confirmed successful CuAAC. Importantly, both ^{1}H NMR and IR spectroscopy showed that the HFIP ester was stable under the applied CuAAC conditions.

Table 1. Dual functionalization of alternating copolymers **3**, **7** and **8** using various organic azides and amines. Functionalization degrees were ≥95 % in all cases for both transformations.

Entry (**No.**)			$M_{n,exp}$ [g/mol]^a	PDI^a	yield^b [%]
1 (**5a**)			4 900	1.12	82
2 (**5b**)			6 100	1.31	53
3 (**5c**)			5 800	1.23	89
4 (**5d**)			2 400	1.37	69
5 (**5e**)			-^{c}	-^{c}	36
6 (**5f**)			2 800	1.41	38
7 (**5g**)			3 800	1.18	86
8 (**9a**)			-^{c}	-^{c}	82
9 (**9b**)			-^{c}	-^{c}	16

^{a} Obtained by GPC in THF against PMMA standards; ^{b} Isolated yield over 2 functionalization steps; functionalization degree ≥95 % in all cases; ^{c} GPC data could not be obtained due to poor solubility.

Analysis of polymer **4a** by GPC revealed an average molecular weight of $M_{n,exp}$ = 9 000 g/mol with a PDI of 1.26. For the second postmodification, **4a** was converted into the alternating acrylamide **5a** with allylamine (5.0 equiv.) at 70 °C in THF/DMF (1:1) for 72 h in 82% overall yield. Completion of the reaction was confirmed by IR spectroscopy: the C=O stretching frequency of HFIPA at 1778 cm^{-1} completely disappeared and a new prominent amide C=O band at 1653 cm^{-1} emerged (see SI for spectra). In addition, a broad peak at 3300 cm^{-1} corresponding to the N-H stretching frequency of the amide is visible. In the ^{1}H NMR spectrum the HFIPA ester signal at 5.6 ppm disappeared and alkene signals of the allylamide moiety appeared. GPC revealed an $M_{n,exp}$ of 4 900 g/mol and a PDI of 1.12. The underestimation of $M_{n,exp}$ is likely due to the different coiling behavior and the resulting hydrodynamic volume of the poly(acrylamide-*alt*-triazole) copolymer **5a** as compared to the PMMA calibration standard.

To further prove the high efficiency of both post-polymerization processes, we followed a sequence by ^{19}F NMR (Table 1, entry 2). To this end, 4-(trifluoromethyl)benzyl azide was reacted with **3** using CuBr and *N*,*N*,*N′*,*N″*,*N″*-pentamethyldiethylenetriamine (PMDETA) as a catalyst. In addition to the HFIP fluorine signals at around -74 ppm (see Figure 2a), a second fluorine signal from the aromatic CF_3 group appeared at -63 ppm (Figure 2b).

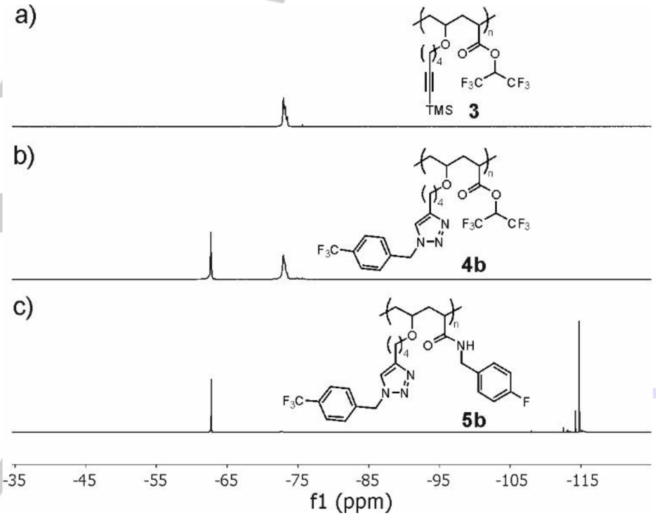


Figure 2. ^{19}F NMR spectra of a) poly(HFIPA-*alt*-THVE) **3**, b) poly(HFIPA-*alt*-triazole) **4b** and c) poly(acrylamide-*alt*-triazole) **5b**.

Copolymer **4b** was subsequently treated with 4-fluorobenzylamine at 60 °C for 72 h. The excess amine was removed by extraction with HCl and polymer **5b** was isolated after precipitation into pentane (53%). The ^{19}F NMR spectrum unambiguously showed high consumption of the HFIP esters as only traces of the F-signals at around -74 ppm were visible (Figure 2c). Moreover, new signals at around -115 ppm proved successful amidation with the fluorinated benzyl amine.

The sequential postmodification strategy was then successfully applied to prepare copolymers **5c**-**g**. Ester, alcohol and aliphatic residues were introduced *via* the CuAAC (see Table 1, entries 4,5,7) and the subsequent amidation worked efficiently with various primary amines (Table 1, entries 3-7). It is of note that amidation with isopropylamine (Table 1, entries 4 and 6) delivers alternating copolymers of poly(*N*-isopropylacrylamide) (PNIPAM).[68] We could also show that CuAAC can be conducted with the polyelectrolyte **8** as a substrate. This was documented by the successful preparation of alternating poly(acrylic acid-*alt*-triazole) **9a** (Table 1, entry 8). The biotin-conjugated congener **9b**

(Table 1, entry 9) was prepared from biotinylated copolymer **4h** by saponification of the HFIP groups. In the latter case, the isolated yield dropped to 16% over two functionalization steps due to problems during workup. All other dually functionalized copolymers were isolated in moderate to excellent overall yields (36-89%). The functionalization degrees for both transformations were ≥95% in all cases and alternating copolymers were characterized using ^{1}H NMR and IR spectroscopy as well as GPC (see SI for details).

In summary, alternating copolymerization of HFIPA **1** and THVE **2** was achieved *via* NMP. The copolymerization could also be conducted using a commercially available RAFT reagent under otherwise identical conditions, demonstrating the robustness of this approach. Dual postfunctionalization of **3** with azides and amines was achieved *via* CuAAC and subsequent amidation. The degree of functionalization for all of those transformations was ≥95%. The postmodification sequence was carefully analyzed by ^{1}H and ^{19}F NMR, IR, and GPC. To our knowledge, this is the first example of orthogonal CuAAC/amidation postfunctionalization of alternating copolymers, which should open up new pathways for the preparation of functional polymeric materials. Notably, sequence control in functionalized polymers is a challenging task and the concept presented herein is highly valuable along those lines.

Experimental Section

Typical procedure for the copolymerization of 1 and 2 (GP 1): A heat gun-dried *Schlenk* tube was charged with initiator **6** (1.8 mg, 4.6 µmol, 2 mol%), **2** (88 mg, 0.45 mmol, 2.0 equiv.), **1** (50 mg, 0.23 mmol, 1.0 equiv.), benzene (0.50 mL) and HFIP (15 µL, 3 vol%). The tube was subjected to three freeze-thaw cycles and then sealed. The copolymerization was carried out at 100 °C for 14 h. After the mixture was cooled to room temperature it was transferred to a 10 mL round bottom flak (washing with CH_2Cl_2). Residual monomers and solvent were removed under reduced pressure and the polymer was dried *in vacuo* and obtained as a clear colorless gel. Conversion was determined gravimetrically, monomer incorporation was determined using ^{1}H NMR, and $M_{n,exp}$ as well as PDI were determined by GPC in THF against PMMA standards.

Typical procedure for the postmodification of 3 *via* CuAAC (GP 2): A heat gun-dried *Schlenk* tube was charged with $CuSO_4$ pentahydrate (2.4 mg, 9.6 µmol, 20 mol%) and sodium ascorbate (2.8 mg, 14 µmol, 30 mol%). Copolymer **3** (20 mg, 0.048 mmol, 1.0 equiv.) and an azide (0.057 mmol, 1.0 equiv.) were dissolved in THF (0.5 mL) and transferred to the *Schlenk* tube using a syringe and the mixture was diluted with DMF (0.5 mL). The mixture was stirred at room temperature for 24 h and aqueous 5% EDTA solution (3 mL) was added. The mixture was stirred at room temperature overnight, after which the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The functionalized polymer **4** was dried *in vacuo* and obtained as a viscous gel. Functionalization degree was determined using ^{1}H NMR, $M_{n,exp}$ and PDI were determined by GPC.

Typical procedure for the postmodification of 4 *via* amidation (GP 3): In a heat gun-dried *Schlenk* tube, polymer **4** (0.044 mmol, 1.0 equiv.) was dissolved in THF (0.5 mL) and an amine (5.0 equiv.) as well as DMF (0.5 mL) were added. The mixture was stirred at 70 °C for 72 h, after which completion of the reaction was confirmed by IR. The volatiles were removed under reduced pressure. The crude polymer was dissolved in THF (0.2 mL), precipitated into pentane (5 mL) and the supernatant was decanted. The dually functionalized target polymer **5** was isolated as a viscous gel or solid. Functionalization degree was determined by using ^{1}H NMR spectroscopy, $M_{n,exp}$ and PDI were determined by GPC.

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Keywords: Alternating Copolymerization • NMP • Postfunctionalization • CuAAC • Amidation

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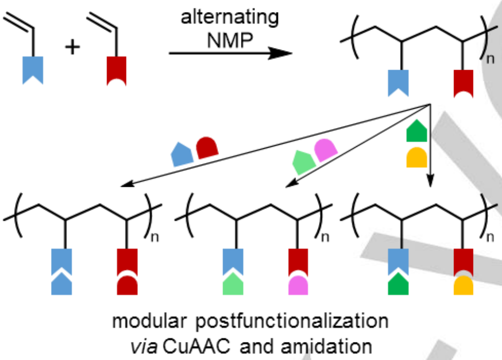
[68] Unfortunately, due to insolubility of copolymers **5d** and **5f** in water, their LCST behavior could not be determined.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

A protocol for alternating copolymerization of an activated ester (HFIPA) and an alkyne-terminated vinyl ether (THVE) is presented. Sequential postfunctionalization with azides and amines *via* CuAAC and subsequent amidation provides access to various alternating copolymers in a modular approach.



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Orthogonal Click Postfunctionalization of Alternating Copolymers Prepared by Nitroxide Mediated Polymerization