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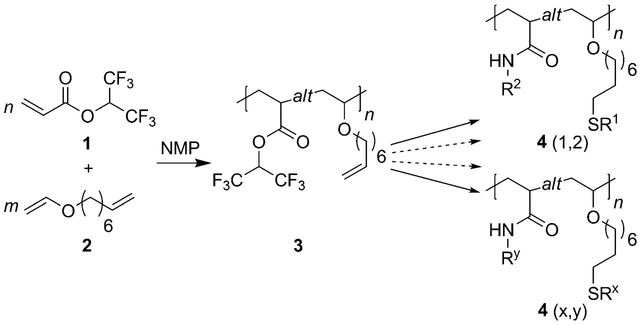
Alternating Copolymerization by Nitroxide-Mediated Polymerization and Subsequent Orthogonal Functionalization**

*Matthias Tesch, Johannes A. M. Hepperle, Henning Klaasen, Matthias Letzel, and Armido Studer**

Abstract: *A novel method for the preparation of functionalized alternating copolymers is presented. Nitroxide-mediated polymerization of hexafluoroisopropyl acrylate with 7-octenyl vinyl ether provides the corresponding alternating polymer, which can be chemically modified using two orthogonal polymer-analogous reactions. A thiol–ene click reaction followed by amidation provides dual-functionalized alternating copolymers. The potential of this method is illustrated by the preparation of a small library (15 examples) of functionalized alternating copolymers.*

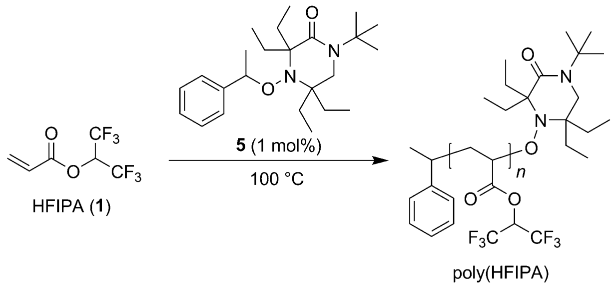
Natural polymers such as proteins show broad and defined structural and biological properties owing to the sequence-controlled incorporation of various functional monomers. Compared to their natural counterparts, the properties of synthetic polymers are far less diverse and less specific because they are generally composed of fewer monomer building blocks, and sequence-defined incorporation cannot be achieved. Sequence control is therefore one of the greatest challenges in modern polymer science. Recently, great advances have been achieved in the field of radical polymerization along these lines.[1,2] Over the past decade, controlled living radical polymerization (CLRP) has been intensively studied, and several new methods have been developed.[3] Proper tuning of the electronic properties of two different monomer units allows the formation of an alternating copolymer. However, controlled alternating copolymerization using CLRP is still not well established, and only a few examples have been reported. Successfully used monomer pairs are styrene/maleic anhydride,[4] styrene/methacrylates,[5] and vinyl ethers/methacrylates.[6] It is obvious that these approaches currently lack generality in terms of the preparation of larger series of alternating polymeric materials.

We herein present a conceptually novel approach that comprises alternating nitroxide-mediated radical polymerization (NMP) of two electronically distinct monomers **1** and **2** followed by two polymer-analogous reactions. The monomers bear functional groups in their side chains that are chemically orthogonal.[7] Hence, a single type of alternating copolymer **3** with defined molecular weight and a narrow polydispersity index (PDI) can selectively react by sequential orthogonal polymer-analogous reactions, such as amidation[8] and thiol–ene click reactions,[9] to give various alternating polymers **4** (x,y) bearing different functionalities, which should show distinct properties (Scheme 1).



Scheme 1. Synthesis of various alternating polymers by sequence-controlled NMP and subsequent orthogonal polymer functionalization.

As the active ester component we chose hexafluoroisopropyl ester, which is known to be readily amidated.[10] Importantly, the corresponding monomer, 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA, **1**), is commercially available, but to our surprise, HFIPA has not been used in CLRP thus far. Therefore, we started our investigations by studying the NMP of **1** using the sterically hindered alkoxyamine **5** as the initiator/regulator (Scheme 2).[11] Controlled polymerizations performed in sealed tubes at 100 °C delivered poly(HFIPA) with a narrow PDI. For example, a conversion of



Scheme 2. NMP of HFIPA (**1**) with the highly hindered alkoxyamine **5** as the initiator/regulator.

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[*] M. Tesch, J. A. M. Hepperle, H. Klaasen, M. Letzel, Prof. Dr. A. Studer
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de

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75 % was achieved within 20 hours at 100 °C in neat HFIPA with 1 mol % of **5** (16 200 g mol^{-1}, PDI 1.1; see the Supporting Information).

Moreover, poly(HFIPA) prepared by NMP (M_n = 20 500 g mol^{-1}, PDI 1.1) was successfully used as a macroinitiator for the polymerization of styrene (neat styrene at 100 °C, 24 h) to provide the corresponding block copolymer poly(HFIPA-*b*-styrene) (85 000 g mol^{-1}, PDI 1.04), indicating a high degree of livingness for the initial NMP of **1** (see the Supporting Information). The living character was further confirmed by ESI mass spectrometry of a low-molecular-weight poly(HFIPA) sample (see the Supporting Information).[12]

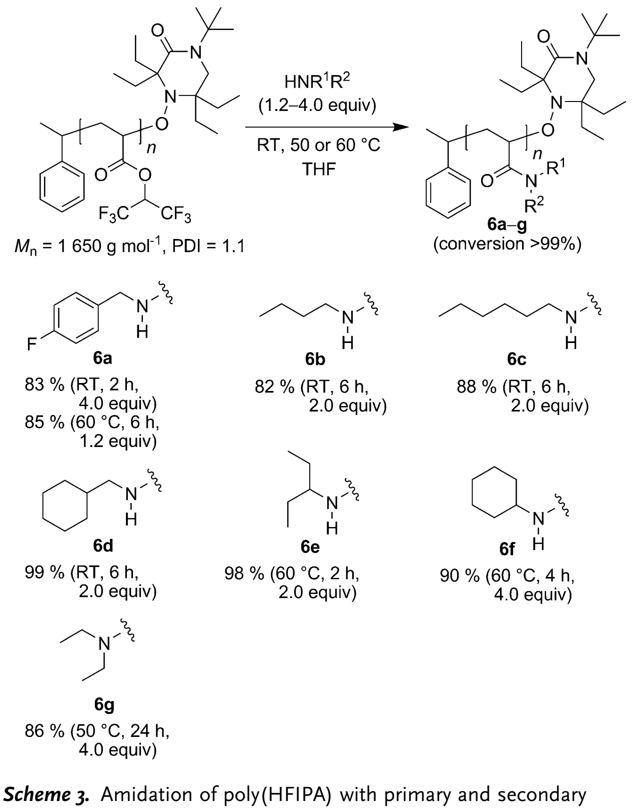
We then investigated the postfunctionalization of poly(HFIPA); the amidation of poly(HFIPA) (M_n = 10 600 g mol^{-1}, PDI 1.1, 1.0 equiv) with *para*-fluorobenzylamine (4.0 equiv) in THF at room temperature for two hours was chosen as the model reaction. After extraction of excess amine with aqueous HCl, polyacrylamide **6a** was isolated in 83 % yield (Scheme 3). The degree of postfunctionalization was readily determined by ^{19}F NMR spectroscopy, which showed that amidation occurred quantitatively (the CF_3 signals of the hexafluoroisopropyl groups at ca. −74 ppm completely vanished, and new signals for the *para*-fluorine atom of the benzyl group appeared at ca. −117 ppm; for the spectra, see the Supporting Information).

Gel permeation chromatography (GPC) showed that the PDI (1.2) slightly increased while the molecular weight (9000 g mol^{-1}) decreased. The change in M_n is due to the different GPC properties of poly(HFIPA) and **6a**.

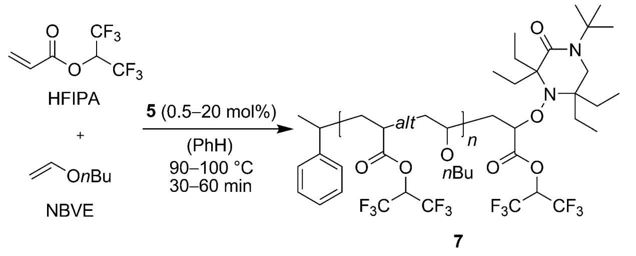
We also tested whether the amine concentration can be further reduced to obey the rules of a polymer-analogous click reaction.[13] Decreasing the amine concentration to 1.2 equivalents resulted in 80 % conversion under otherwise identical conditions (determined by ^{19}F NMR spectroscopy). However, upon increasing the temperature to 60 °C, amidation occurred with complete conversion.

To study the substrate scope, we systematically varied the amine component and used a low-molecular-weight poly(HFIPA) sample (M_n = 1650 g mol^{-1}, PDI 1.1, 1.0 equiv) as the substrate, which allows for determining the degree of amidation by ^{1}H NMR spectroscopy (see the Supporting Information). Importantly, in the amidation with *para*-fluorobenzylamine, we did not see any difference in reactivity upon switching from poly(HFIPA) with M_n = 10 600 g mol^{-1} to the polymer with M_n = 1650 g mol^{-1}. Therefore, we regard the results that were obtained with the smaller poly(HFIPA) as representative. Under the conditions specified in Scheme 3, complete conversion was achieved for all tested amines, and the yields given correspond to the isolated material after aqueous workup. Amidation was quantitative with linear aliphatic primary amines (see **6b**, **6c**), and α-branched as well as β-branched aliphatic primary amines also turned out to be good nucleophiles (**6d–f**). As expected, diethylamine is less reactive for steric reasons, and a longer reaction time was necessary for complete conversion (**6g**).

Having identified poly(HFIPA) as a valuable polymer for polymer-analogous amidations, we addressed the alternating polymerization of HFIPA using *n*-butyl vinyl ether (NBVE) as the second monomer (Scheme 4).



Scheme 3. Amidation of poly(HFIPA) with primary and secondary amines.



Scheme 4. Copolymerization of HFIPA (**1**) and NBVE with initiator **5**.

Polymerizations were performed in sealed tubes (90–100 °C, 5–240 min) with HFIPA (1.0 equiv) and various amounts of NBVE (0.13–8.0 equiv) in the presence of alkoxyamine **5** (0.5–20 mol %) under argon atmosphere (Table 1). It is important to note that vinyl ethers do not undergo homopolymerization under these conditions owing to the electronic mismatch between the nucleophilic radical at the chain end and the electron-rich character of the vinyl ether double bond. Unreacted monomers were removed under reduced pressure, and the resulting copolymers **7** were analyzed by ^{1}H NMR spectroscopy, GPC, and ESI mass spectrometry (see the Supporting Information).

At a 1:1 monomer feed ratio, we obtained a copolymer with an HFIPA/NBVE incorporation ratio of 55:45 and

Table 1: Copolymerization of HFIPA (**1**) with NBVE and OVE (**2**). Unless stated otherwise, reactions were carried out at 90 °C.

Entry	**5** [mol %]	Vinyl ether	HFIPA/vinyl ether monomer ratio	Solvent	*t* [min]	Conv. HFIPA [%]	HFIPA/vinyl ether incorporation ratio[a]	Calc. DP_{HFIPA}	M_n [g mol^{-1}][b]	PDI[b]
1	2	NBVE	1:1	PhH	60	15	55:45	30	9200	1.4
2	2	NBVE	1:2	PhH	60	9	52:48	38	12 000	1.2
3	2	NBVE	1:4	PhH	60	12	50:50	52	16 700	1.2
4	2	NBVE	1:8	PhH	60	12	50:50	57	18 200	1.2
5	0.5	NBVE	1:8	–	60	39	50:50	82	26 500	1.4
6	1	NBVE	1:8	–	60	51	50:50	66	21 300	1.3
7	5	NBVE	1:8	–	60	68	50:50	30	9500	1.4
8	10	NBVE	1:8	–	60	77	50:50	21	6600	1.4
9	20	NBVE	1:8	–	60	94	50:50	18	5700	1.3
10	–[c]	NBVE	1:8	–	20	96	50:50	470	152 000	1.5
11[d]	2	NBVE	1:8	–	30	75	50:50	144	46 200	1.3
12	2	NBVE	8:1	PhH	60	11	65:35	84	25 500	1.4
13	2	NBVE	1:8	PhH/HFIP (89:11)	60	18	45:55	61	25 100	1.2
14	2	OVE	1:8	PhH	60	16	63:37	38	12 000	1.5
15	2	OVE	1:8	PhH/HFIP (89:11)	60	63	50:50	73	27 600	1.4

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by GPC at 25 °C using dichloromethane as the eluent against PMMA standards. [c] AIBN (1 mol %) was used as the initiator; the experiment was conducted at 80 °C. [d] The experiment was conducted at 100 °C.

a HFIPA conversion of 15 % after one hour at 90 °C in benzene (Table 1, entry 1). The incorporation ratio was determined by ^{1}H NMR spectroscopy, and the higher amount of HFIPA compared to NBVE in the copolymer was corroborated by ESI mass spectrometry. Upon doubling the amount of NBVE in the monomer feed, we observed an increase in NBVE incorporation (entry 2). For a HFIPA/NBVE feed ratio of 1:4, we obtained a copolymer with a monomer incorporation ratio of 50:50 (entry 3). As NBVE does not undergo homopolymerization under these conditions, a further increase in the amount of NBVE in the monomer feed did not lead to a preferential incorporation of NBVE in the polymer chain (entry 4). Attempts to systematically adjust the average molecular weight by variation of the reaction time were not successful. However, performing alternating polymerization in neat monomers and varying the concentration of the alkoxyamine initiator from 0.5 to 20 mol % allowed for good control over the molecular weight, which ranged from $M_n = 5700$ to 26 500 g mol^{-1} with PDIs between 1.3 and 1.4 and HFIPA conversions of 39–94 % (entries 5–9). Polymerization of HFIPA/NBVE (1:8) with 2 mol % of alkoxyamine **5** at 100 °C for 30 minutes provided poly(HFIPA-*alt*-NBVE) with $M_n = 46\,200$ g mol^{-1} and a PDI of 1.3 (entry 11). When AIBN was used as the initiator, gelation occurred after 20 minutes (entry 10). The isolated highly viscous polymer also exhibited a 50:50 monomer incorporation ratio. However, the average molecular weight of 152 000 g mol^{-1} as well as the increased PDI of 1.5 indicate low control over the polymerization and cross-linking of the material. By using HFIPA in large excess with respect to NBVE (8:1) in benzene, a copolymer with a HFIPA/NBVE ratio of 65:35 was formed (entry 12).

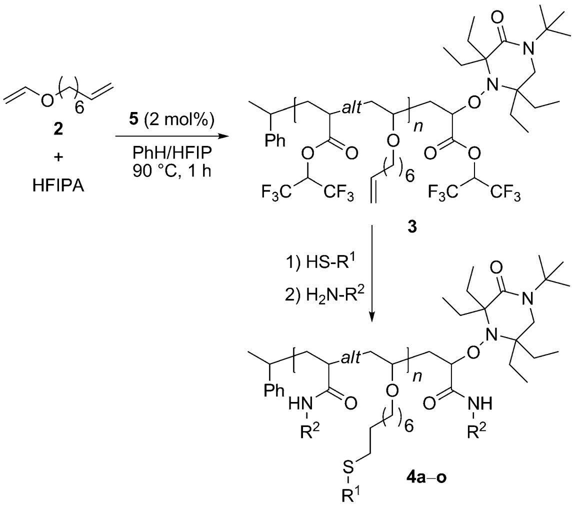
We also determined the reactivity ratios for the copolymerization of HFIPA and NBVE mediated by **5**. To this end, we carried out copolymerization reactions with different monomer feed ratios in benzene, and the reactions were stopped at low conversion. The HFIPA content of the copolymer was then plotted against the initial monomer feed ratio, and the data were fitted to the Mayo–Lewis copolymerization equation using the least-squares method (see the Supporting Information),[14] providing reactivity ratios $r_1 = 0.12$ and $r_2 = 0.028$. These values are close to zero, which illustrates that the copolymerization occurs in an alternating fashion.

We further analyzed copolymer **7** by ^{13}C NMR spectroscopy and compared the chemical shifts of the methylene carbon atoms of poly(HFIPA-*alt*-NBVE) **7** with those of the homopolymer [poly(HFIPA), see the Supporting Information]. All signals of poly(HFIPA-*alt*-NVBE) **7** were unambiguously assigned, and signals at 41–42 ppm, which would be expected if sequences of homo-HFIPA were present in the copolymer, were not observed.

Careful MS analysis of a low-molecular-weight poly(HFIPA-*alt*-NBVE) sample (5200 g mol^{-1}, PDI 1.2) revealed that all polymer chains contained a styryl moiety as the initiating unit as well as a nitroxide moiety as the terminating unit (see structure **7** in Scheme 4). ESI mass spectrometry further showed that for the major peak series the number of HFIPA moieties exceeded the number of NBVE moieties by one (for spectra see the Supporting Information). Considering that no homo-HFIPA was formed (within the error limit of ^{13}C NMR analysis), we can conclude that HFIPA must be the initiating as well as the terminating monomer. MS-MS studies further supported the structure of **7** (see the Supporting Information). Although monomer incorporation ratios of 50:50 had been determined for these polymers within the error limit of ^{1}H NMR spectroscopy, ESI MS spectra also showed a small peak series of polymer chains where the number of HFIPA exceeded the number of NBVE by two. This can only be explained with one single sequence error along the chain where two HFIPA moieties were incorporated sequentially.

To demonstrate the living character of the copolymerization we showed that amidated polymers of type **7** can be used as macroinitiators for the preparation of block copolymers (see the Supporting Information). This further indicates that the ultimate monomer unit in the majority of polymer chains is a HFIPA moiety, as the C–O bond dissociation energy in α-alkoxy-alkoxyamines is too large for the bond to be homolytically cleaved at 100 °C.[15] Despite the living nature of the vast majority of polymer chains, ESI MS spectra also showed a minor peak series where the numbers of incorporated HFIPA and NBVE monomers are the same. In these cases, the chain is terminated by NBVE, and the C–O bond of the corresponding alkoxyamine cannot be cleaved thermally (see the Supporting Information).[16] From these results, we conclude that the copolymerization of HFIPA and NBVE is to a large extent alternating and living.

For the preparation of alternating copolymers bearing two reactive orthogonal functionalities, we replaced NBVE with the electronically similar oct-7-enyl vinyl ether (OVE, **2**) bearing a terminal alkene, which can be chemically addressed by thiol–ene reactions.[9] Copolymerization was performed with OVE (8.0 equiv) and HFIPA (1.0 equiv) in benzene using alkoxyamine **5** (2 mol% with respect to HFIPA) as the initiator/regulator at 90 °C for one hour (Scheme 5; Table 1, entry 14). Residual monomers and solvent were removed under reduced pressure.[17]



Scheme 5. Alternating NMP of HFIPA with OVE (**2**) and sequential orthogonal chemical functionalization.

Disappointingly, ^{1}H NMR analysis revealed that HFIPA was incorporated to a larger extent (HFIPA/OVE ratio = 63:37), and further increasing the amount of OVE with respect to HFIPA did not change the ratio. Obviously, the terminal alkene unit alters the kinetics of the polymerization. The reactivity ratios determined for the HFIPA/OVE system were $r_1 = 0.37$ and $r_2 = 0.0011$, indicating a higher tendency for HFIPA incorporation compared to the HFIPA/NBVE system. In fact, copolymerization of *n*-octyl vinyl ether (NOVE), which lacks the alkene moiety, and HFIPA under the same conditions delivered an alternating copolymer containing equal amounts of the two monomers ($r_1 = 0.11$, $r_2 = 0.0030$; see the Supporting Information). The same outcome was also observed for the copolymerization of hex-5-enyl vinyl ether (HVE) with HFIPA, which did not provide an alternating copolymer (HFIPA/HVE ratio = 60:40; $r_1 = 0.54$, $r_2 = 0.0020$). Again, copolymerization of HFIPA with the corresponding saturated *n*-hexyl vinyl ether (NHVE) occurred well controlled, and the monomers were incorporated in equal amounts (in a ratio of 50:50 according to NMR analysis; $r_1 = 0.12$, $r_2 = 0.0026$; see the Supporting Information).[18]

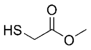
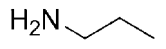
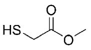
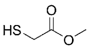
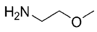
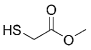
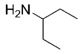
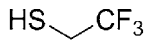
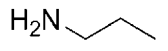
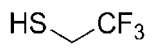
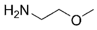
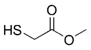
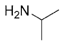
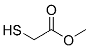
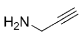
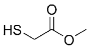
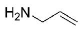
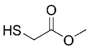
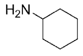
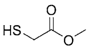
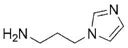
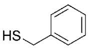
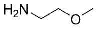
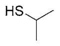
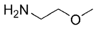
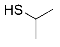
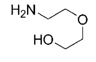
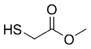
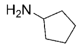
We therefore studied the effect of additives on the alternating polymerization of HFIPA/OVE and found lithium salts to alter the ratio of the incorporated monomers. However, results were not reproducible. We then switched to hexafluoroisopropanol (HFIP) as an additive and noted a dependence of the HFIPA/OVE ratio in the resulting copolymer on the amount of HFIP.[19] Experiments were conducted with OVE (**2**; 8.0 equiv), HFIPA (1.0 equiv), and HFIP as the additive in benzene with alkoxyamine **5** (2 mol%) at 90 °C for one hour. With 3.4 vol% HFIP with respect to benzene, the HFIPA/OVE ratio in the polymer dropped from 63:37 to 55:45. A further stepwise increase of the HFIP concentration to 11 vol% led to a HFIPA/OVE ratio of 50:50 in the polymer (Table 1, entry 15; see the Supporting Information). A similar influence of the HFIP additive was also observed for the copolymerization of HVE with HFIPA, which could be well controlled when using 11 vol% of HFIP with respect to benzene (HFIPA/HVE ratio in the copolymer: 52:48; see the Supporting Information). With the HFIPA/NBVE system, we were able to obtain NBVE-enriched copolymers with a HFIPA/NBVE ratio of 45:55 (Table 1, entry 13), demonstrating the significance of HFIP as an additive as the NBVE-enriched copolymers could not be prepared under the standard conditions.

Having identified suitable conditions for the preparation of an alternating poly(HFIPA-*alt*-OVE) copolymer of type **3** with a narrow PDI (1.4) and a molecular weight of $M_n = 27\,600\ \text{g mol}^{-1}$, we studied its sequential orthogonal functionalization using various thiols and amines (Table 2).

The thiol–ene reaction of the terminal alkene was conducted under UV light irradiation (365 nm) of poly(HFIPA-*alt*-OVE) **3** (1.0 equiv) in the presence of a thiol (5.0 equiv) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 0.2 equiv) as the photoinitiator at ambient temperature in THF for three hours. Under these conditions, functionalization degrees of > 95% were achieved for all tested thiols, as determined by ^{1}H NMR spectroscopy and ESI mass spectrometry (see the Supporting Information). In the second step, the resulting polymeric thioethers were amidated. To this end, the monofunctionalized poly(HFIPA-*alt*-OVE-SR) copolymer and the corresponding amine (5.0–10 equiv) were heated in THF or DMF at 75 °C for 24–72 hours, and the resulting dual-functionalized alternating polymers **4a–o** were analyzed by ^{1}H NMR spectroscopy and GPC. For a poly(HFIPA-*alt*-OVE) sample, the stepwise postmodification was also confirmed by ESI mass spectrometry (see the Supporting Information). All relevant signals were assigned to fully functionalized oligomers, and signals of partially unfunctionalized oligomers could not be identified.

This two-step postmodification of **3** was successfully conducted with various thiols and amines. Considering the scope of the thiol–click process, the reaction worked well for

Table 2: Orthogonal functionalization of **3** using various thiols and amines to give copolymers of type **4**. The degrees of functionalization were >95% for both postmodification reactions.

Entry	HSR^1	H_2NR^2	$M_{n,exp}$[a] [g mol^{-1}]	PDI	Yield[b] [%] (Product)
1			15600	1.3	68 (**4a**)
2			18600	1.3	65 (**4b**)
3			19500	1.3	80 (**4c**)
4			11600	1.2	78 (**4d**)
5			34900	1.4	86 (**4e**)
6			30200	1.5	66 (**4f**)
7			22400	1.3	48 (**4g**)
8			16000	1.5	36 (**4h**)
9			16900	1.5	64 (**4i**)
10			34500	1.4	92 (**4j**)
11			–[c]	–[c]	35 (**4k**)
12			17700	1.5	57 (**4l**)
13			16800	1.3	60 (**4m**)
14			15000	1.3	51 (**4n**)
15			25600	1.4	94 (**4o**)

[a] At 25 °C in THF against PMMA standards. [b] Yield of isolated product over two steps after extraction and precipitation. [c] No GPC data obtained owing to poor solubility.

thiols bearing ester groups, which were also inert to the following amidation of the HFIPA moieties (Table 2, entries 1–4, 7–11, and 15). Furthermore, fluorinated thiols (entries 5 and 6), alkyl thiols (entries 13 and 14), and a phenyl-substituted thiol (entry 12) were readily introduced. Subsequent amidation with primary amines occurred with >95% conversion, and polymers **4a–o** were isolated in 35–94% yield over two steps after extraction and precipitation.

As shown in Table 2, various amines can be readily introduced by this approach. Hydroxy groups, which can be used for subsequent crosslinking of the resulting polymer **4n**, were readily incorporated by amide bond formation (entry 14). Notably, alternating copolymers of poly(*N*-isopropyl acrylamide) (PNIPAM) were readily obtained by reacting HFIPA moieties with isopropylamine (entry 7). Linear (entries 1, 2, and 5), and α-branched (entries 4, 7, 10, and 15) amines were introduced as well as amines bearing methyl ether (entries 3, 6, 12, and 13) or imidazole (entry 11) entities. Allyl and propargyl groups (entries 8 and 9), which are amenable to further functionalization, could also be incorporated into the polymer, documenting the potential of our novel approach.

In summary, we have developed a novel method for the preparation of various alternating copolymers. NMP of two electronically distinct monomers, namely HFIPA (**1**) and NBVE, delivered alternating poly(HFIPA-*alt*-NBVE) **7**. Careful MS and NMR analyses were conducted to characterize the polymers. Replacing NBVE with OVE (**2**) enabled the synthesis of alternating poly(HFIPA-*alt*-OVE) **3** using a slightly modified procedure. We showed that the monomer incorporation can be adjusted with hexafluoroisopropanol (HFIP) as an additive during NMP. Subsequent sequential orthogonal functionalization of poly(HFIPA-*alt*-OVE) **3** with thiols and amines provided alternating dual-functionalized copolymers of type **4**. The potential of the approach was demonstrated by the successful synthesis of a small library of 15 dual-functionalized alternating polymers **4a–o**, which were obtained from a single precursor, polymer **3**.

Keywords: active esters · alternating polymerization · nitroxide-mediated polymerization · orthogonal functionalization · thiol–ene reactions

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[16] As ESI MS can only visualize the low-molecular region, a sample of larger poly(HFIPA-*alt*-NBVE) with a higher average molecular weight ($M_n = 8200\,\mathrm{g\,mol^{-1}}$, PDI 1.4) clearly showed a peak series of NBVE-terminated polymer chains (see the Supporting Information). Therefore, for larger polymers, the dead NBVE-terminated chains are enriched in the MS-visible low-molecular region.

[17] In some cases, when the polymerization was run without or with less benzene as the solvent, we observed gelation after 15–30 minutes, and the material obtained was hardly soluble in any organic solvent, likely because of cross-linking. We attribute this cross-linking behavior to the participation of the terminal alkene, which can undergo intramolecular radical cyclization at the chain end as well as chain transfer to the monomer. However, when the reaction was run in an adequate amount of benzene, we did not find any indication for the participation of the terminal alkene in the polymerization.

[18] The reason for the difference in the kinetic properties of the saturated and unsaturated systems could not be elucidated thus far. We hypothesize that it might be caused by a change in the monomer aggregation state. This is known for acrylate monomers, but has not be reported for vinyl ethers; see: A. P. Haehnel, M. Schneider-Baumann, L. Arens, A. M. Misske, F. Fleischhaker, C. Barner-Kowollik, *Macromolecules* **2014**, *47*, 3483 – 3496.

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