Modular Covalent Multifunctionalization of Copolymers

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ABSTRACT: Poly(norbornene)-based random copolymers possessing either azide, aldehyde, or ketone functionalities on each repeating unit were synthesized using ring-opening metathesis polymerization. The orthogonal functionalization of the resulting copolymers using 1,3-dipolar cycloadditions and hydrazone formations was investigated. While the azide- and aldehyde-containing copolymers were insoluble in organic solvents, the azide- and ketone-functionalized copolymers were fully soluble in common solvents such as CH_2Cl_2, THF, and DMF and can be quantitatively functionalized with a library of small organic and biological molecules in a stepwise fashion. The orthogonal functionalization of the ketone/azide copolymers was characterized by NMR and IR spectroscopies and gel-permeation chromatography. A one-pot dual functionalization strategy is also presented that allows for the quantitative dual functionalization of copolymers. This one-pot strategy introduced herein for the preparation of multifunctional macromolecules provides a modular platform for potential applications ranging from electronic materials to polymer-mediated drug delivery.

Introduction

The synthesis of highly functionalized polymers has been widely investigated since such polymers are potential materials for a variety of applications ranging from electronic devices to biological materials.[1−4] For example, in the context of biological applications, orthogonal multifunctionalization of polymers plays an important role in the fabrication of biomaterials for drug delivery,[2] sensors,[3] and therapeutics.[4] In nature, biological systems can undergo bioorthogonal chemical reactions in which the coupling partners react selectively without interference between the diverse biological functionalities.[5] Examples of these orthogonal approaches include enzyme−substrate, antibody−antigen, or neuroreceptor−neurotransmitter interactions.[6] Nature's principles have been an inspiration for the development of new synthetic functionalization strategies to produce multifunctional polymeric materials. These strategies fall into two main categories, either noncovalent or covalent functionalization.[7] We and others have employed noncovalent interactions such as hydrogen bonding and metal coordination to functionalize polymers.[7−13] While highly desirable due to their simple and fast functionalization steps as well as reversibility,[12,13] noncovalent functionalization strategies have often limited stabilities. In contrast, covalent approaches[14,15] have increased stability and might allow, for example, for stable polymer−drug conjugates which can be delivered to a target site without any unwanted loss. However, covalent functionalization methods are often cumbersome, time-consuming, and, in general, not quantitative, resulting in the formation of ill-defined polymeric materials.[13] These challenges can be overcome by employing highly selective covalent reactions which proceed in quantitative yields without byproducts under mild reaction conditions, often referred to as click reactions.[16] An excellent example is the copper-catalyzed 1,3-dipolar cycloaddition between an azide and an alkyne.[17] In addition, chemoselective ligation reactions between aldehydes or ketones and hydrazide or aminooxy groups to form hydrazones and oximes, respectively, fulfill these criteria.[18] Both classes of reactions are compatible with a broad range of functional groups and reaction conditions. Herein, we report a methodology for the orthogonal functionalizations of random copolymers in quantitative yields under mild reaction conditions via covalent functionalization strategies using click chemistry. The combination of control over polymer properties such as molecular weights and polydispersities, functional group tolerance, and modular multifunctionalization in quantitative yields is unprecedented in the literature.

Figure 1. Schematic representation of the one-pot covalent multifunctionalization of random copolymers.

Research Design. Our research design follows two important design requirements: (1) a well-controlled polymer scaffold and (2) distinct and independent functional groups which undergo highly selective and quantitative covalent reactions in an orthogonal fashion (Figure 1).

Our well-defined polymeric scaffold is based on norbornenes as the polymerizable unit. Ring-opening metathesis polymerization (ROMP) was employed using a ruthenium-based initiator.[19] Ruthenium-catalyzed ROMP is highly tolerant of functional groups, often living, and provides for highly controlled and tailored polymer backbones such as poly(norbornene)s.[10−13,19−22] We have recently demonstrated that poly(norbornene)-based random as well as block copolymers can be formed using norbornene−precursors with an *exo* stereochemistry.[10d] Furthermore, poly(norbornene)s have been employed as materials in a variety of biological applications. For example, poly(norbornene)s have been utilized recently as mechanistic probes of receptor clustering in cell signaling by Kiessling and coworkers, who demonstrated that the poly(norbornene)-based multivalent ligands can activate immune responses in vivo.[21] In addition, they have employed poly(norbornene)s as polymeric scaffolds to create biologically active multivalent arrays.[22]

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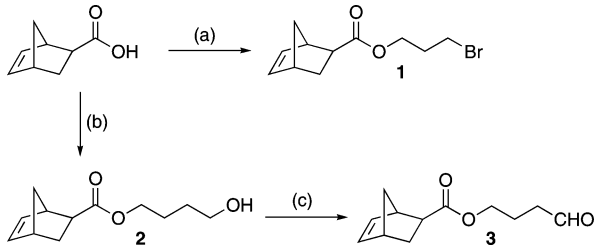
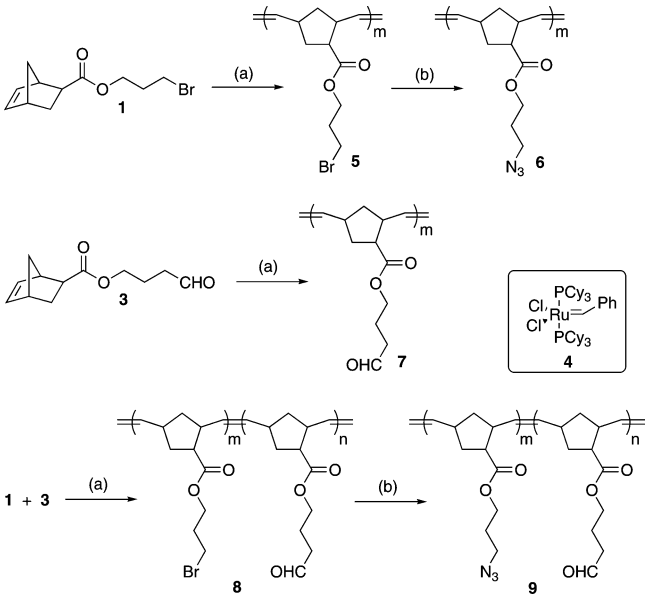
Scheme 1. Synthesis of Monomers 1 and 3[a]



[a] Reagents and conditions: (a) $Br(CH_2)_3OH$, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 96%; (b) $HO(CH_2)_4OH$, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 77%; (c) PCC, CH_2Cl_2, 25 °C, 2 h, 80%.

Scheme 2. Synthesis of Random Copolymer 9[a]



[a] Reagents and conditions: (a) **4**, CH_2Cl_2, 25 °C, 2 h, 97−98%; (b) NaN_3, DMF, 25 °C, 3 h, 96−97%.

The second requirement was fulfilled by using two different transformations: (i) 1,3-dipolar cycloadditions[17] and (ii) hydrazone formation starting with polymer-supported aldehydes and ketones. By appropriate design of these polymers, we present a library of modular functionalizations of the resultant copolymers that involves (a) a single orthogonal functionalization via either 1,3-dipolar cycloaddition or hydrazone formation and (b) a one-pot multifunctionalization using both transformations in a single step.

Results and Discussion

Aldehyde-Based System. Monomers **1** and **3** were prepared starting from isomerically pure *exo*-norbornene acid[23] (Scheme 1). *exo*-Norbornene acid was esterified with 3-bromo-1-propanol or 1,4-butanediol using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to afford **1** and **2**, respectively. Monomer **3** was then synthesized by the oxidation of **2** using pyridinium chlorochromate (PCC).

To investigate the polymerization behaviors, monomers **1** and **3** were homopolymerized in dichloromethane using Grubbs' first-generation initiator **4**[24] (Scheme 2).

In both cases, monomer-to-initiator ratios ([M]:[I]) of 25:1 were employed, and complete conversions were observed within 10 min at room temperature. We also conducted a series of homopolymerizations with [M]:[I] ranging from 25:1 to 125:1 to investigate the control of the polymerization of **1** and **3**. A linear relationship between M_n and [M]:[I] (Figure 2) was found

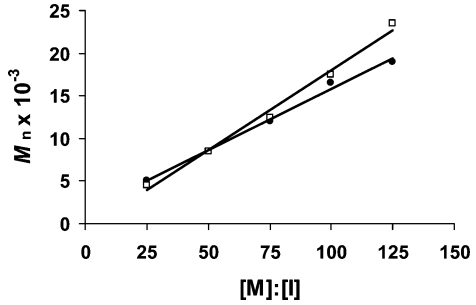


Figure 2. Plot of M_n vs monomer/initiator ratios for polymers **5** (□) and **14** (●). Molecular weights are reported vs poly(styrene).

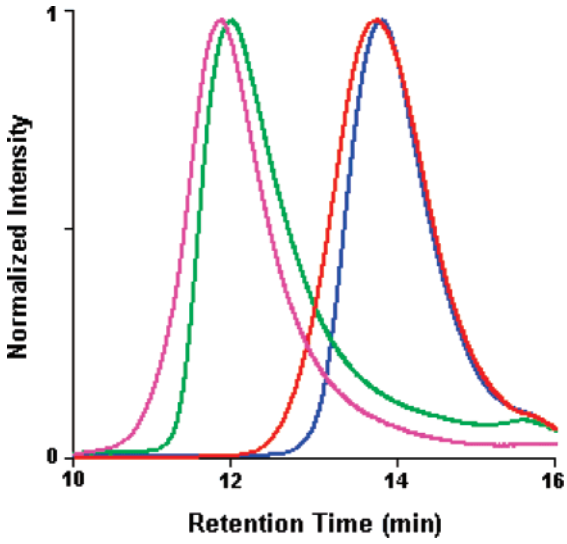


Figure 3. GPC traces of the homoblock copolymers prepared using monomers **1** and **13**. Blue trace: polymer **5** after complete conversion ([M]:[I] = 25:1, M_w = 7500, M_n = 5000, PDI = 1.54). Green trace: polymer **5** after the addition of 375 equiv of additional monomer **1** ([M]:[I] = 400:1, M_w = 68 000, M_n = 38 500, PDI = 1.78). Red trace: polymer **14** after complete conversion ([M]:[I] = 25:1, M_w = 8000, M_n = 4500, PDI = 1.77). Pink trace: polymer **14** after the addition of 375 equiv of additional monomer **13** ([M]:[I] = 400:1, M_w = 101 500, M_n = 55 500, PDI = 1.82). All molecular weights are reported vs poly(styrene).

for homopolymer **5**, indicating the controlled nature of the polymerization for **1**.

However, the controlled polymerization of **3** could not be fully determined due to the insolubility of the isolated homopolymer **7** in common organic solvents. Nevertheless, full initiations were observed for both homopolymerizations as indicated by complete shifts of the carbene signals of **4** in the ^1H NMR spectra from 20.0 ppm before the addition of **1** or **3** to 18.8 ppm after complete initiations. While no signal corresponding to uninitiated **4** was observed, the integration of the former signal at 20.0 ppm and the "initiated" carbene species at 18.8 ppm were identical, suggesting the absence of significant side reactions.

To further characterize the living nature of **1**, we carried out a homoblock copolymerization experiment. First, a 25:1 [M]:[I] ratio of **1**:**4** was polymerized to completion. Subsequently, 375 equiv of additional **1** was added to the reaction mixture. The gel-permeation chromatography (GPC) trace of the homoblock copolymer after the addition of the 375 equiv of **1** showed a complete shift to high molecular weight without traces of terminated low molecular weight polymer (Figure 3). This result in conjunction with the linear relationship between M_n and [M]:[I] clearly proves the living nature of the ROMP of **1** using **4**.

Initially, the synthesis of a norbornene azide monomer was attempted via the azidation of **1**. However, the azide functionality reacted with the highly strained norbornene double bond, resulting in inactive monomers. In order to circumvent this problem, a postpolymerization strategy to introduce the azide onto the polymer was developed. We converted **5** to **6** in quantitative yields as confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **6** showed the complete loss of the bromomethyl resonance at 3.43 ppm and the appearance of a new signal at 3.35 ppm corresponding to the azidomethyl group.

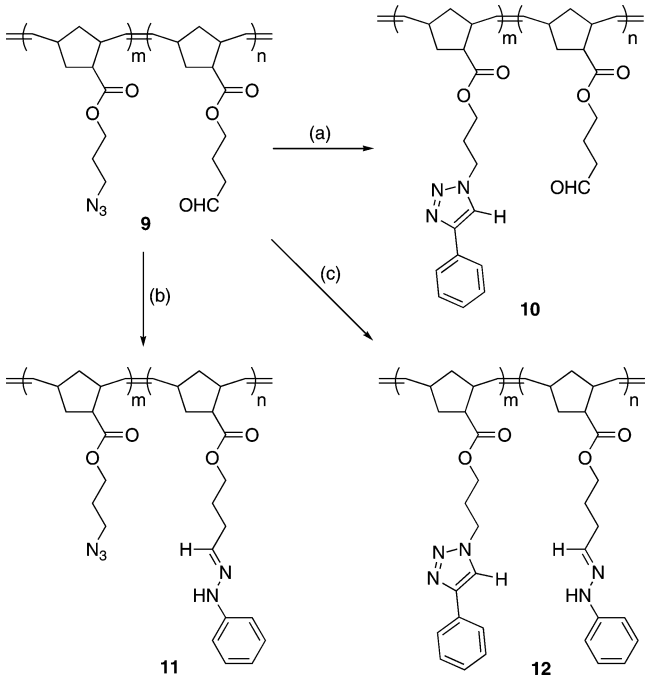
The synthesis of random copolymer **9** was straightforward and is shown in Scheme 2. Monomers **1** and **3** were copolymerized quantitatively at a 1:1 ratio using 4 mol % of **4**. We have previously reported that the copolymerization of *exo*-norbornenes proceeds in a random fashion, suggesting the formation of random copolymers in the described systems.[10d] Polymer **8** was isolated by precipitation into methanol and reacted with sodium azide to yield target polymer **9** in 96% yield. Unfortunately, isolated **9** was not soluble in common organic solvents. The insolubility of **9** can be attributed to the aldehyde group along the polymer side-chains, which was supported by the insolubility of the aldehyde homopolymer **7**. Aldehydes along polymer backbones have a tendency to take part in inter- and intramolecular hydrogen bonding, dipole−dipole interaction, and/or cross-linking, resulting in insoluble material. A similar phenomenon has been reported recently by Maynard and co-workers,[14] who demonstrated that polymers containing aldehyde side-chains have to be generated in situ and used directly without isolation due to the insolubility of the aldehyde polymer.

We investigated whether the desired difunctional polymer **9**, which was generated in situ without isolation, was able to undergo distinct and independent reactions with functional moieties. To achieve this goal, several requirements must be realized, including reactions with near-quantitative yields, high fidelities and selectivities, and no interference of the two functional handles, the azide and the aldehyde, with each other during the functionalization steps. As described above, 1,3-dipolar cycloaddition and hydrazone formation fulfill these requirements and were employed in the orthogonal functionalizations of **9**.

Scheme 3 shows the orthogonal functionalization strategy of **9**. Functionalization of **9** via 1,3-dipolar cycloaddition was accomplished using phenylacetylene as substrate under typical 1,3-dipolar cycloaddition conditions: $CuSO_4 \cdot 5H_2O$ as the catalyst, sodium ascorbate as the ligand, and THF as the solvent. The conversion was confirmed by the ^{1}H NMR spectrum of **10**, which showed the emergence of the triazole proton at 7.82 ppm and a diagnostic downfield shift of the azidomethyl signal from 3.36 to 4.44 ppm. Furthermore, no change of the signal for the aldehyde was observed, indicating the stability of the aldehyde groups to the 1,3-dipolar cycloaddition conditions. Copolymer **9** was also treated with phenylhydrazine in THF to obtain **11**. The hydrazone formation was verified by the ^{1}H NMR spectrum of **11**, which showed upfield shifts from 9.78 ppm ($-CH_2CHO$) to 7.43 ppm ($-CH_2CH{=}N-$) and 2.50 ppm ($-CH_2CHO$) to 2.32 ppm ($-CH_2CH{=}N-$). The ^{1}H NMR also showed that the azide group was unchanged during the hydrazone formation, indicating the absence of any unwanted side reactions. These results demonstrated that (a) both reactions can be carried out on the poly(norbornene) backbone and (b) the two functional handles are orthogonal to each other.

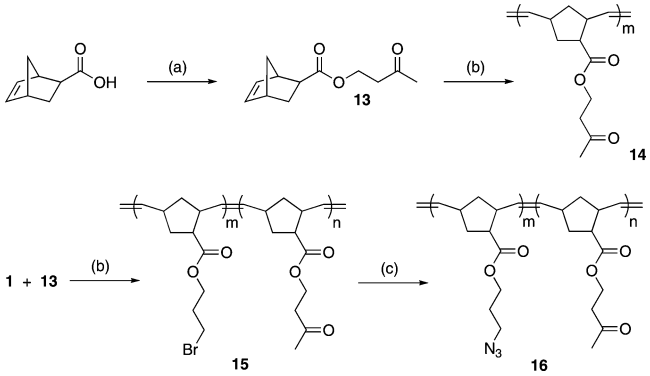
Finally, we performed the one-pot 1,3-dipolar cycloaddition and hydrazone formation of **9** using phenylacetylene and phenylhydrazine. The ^{1}H NMR spectrum of **12** showed the characteristic shifts for both transformations. Unfortunately, after precipitation and isolation, pure polymers **10**, **11**, and **12** were not soluble in common solvents precluding characterization.

Scheme 3. Functionalization Strategies of 9[a]



[a] Reagents and conditions: (a) phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 5 h; (b) phenylhydrazine, THF, 65 °C, 2 h; (c) phenylacetylene, phenylhydrazine, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 5 h.

Scheme 4. Synthesis of Random Copolymer 16[a]

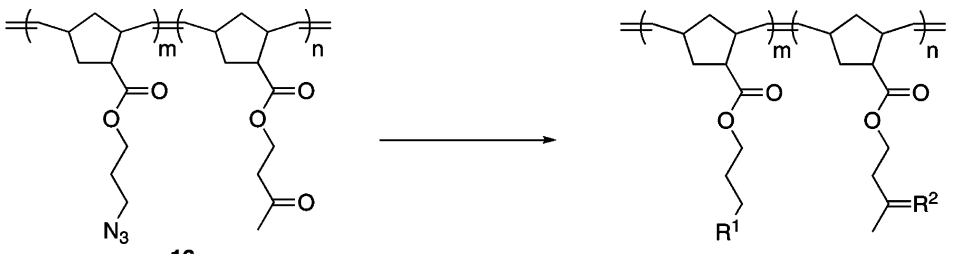


[a] Reagents and conditions: (a) 4-hydroxy-2-butanone, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 76%; (b) **4**, CH_2Cl_2, 25 °C, 2 h, 98−99%; (c) NaN_3, DMF, 25 °C, 3 h, 96%.

Ketone-Based System. In order to overcome the insolubility of the aldehyde-functionalized polymers, we employed a ketone group for the hydrazone formation instead of the more reactive aldehyde. It is well-known that ketones can also undergo hydrazone formation with hydrazide in high yields.[18] The synthesis of the azide- and ketone-functionalized polymer **16** is outlined in Scheme 4. Ketone monomer **13** was synthesized by the DCC-mediated esterification of *exo*-norbornene acid with 4-hydroxy-2-butanone.

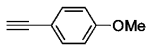
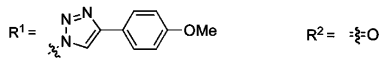
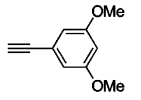
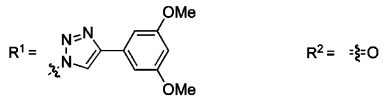
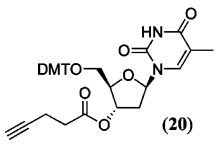
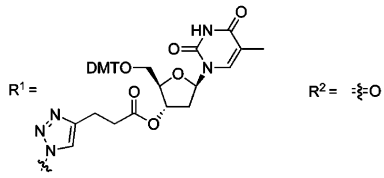
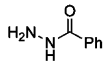
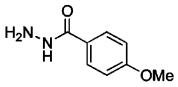
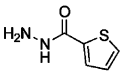
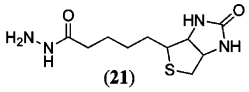
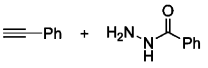
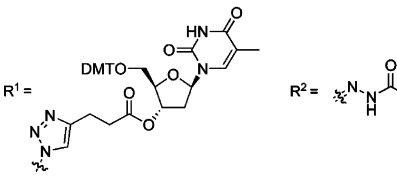
We investigated the homopolymerization of monomer **13**. Complete polymerization of **13** in CH_2Cl_2 with 4 mol % of Grubbs' first-generation initiator **4** was observed. Monomer **13** was also found to polymerize in a living fashion. A linear relationship between M_n and [M]:[I] was established for **13**

Table 1. Functionalization of Copolymer 16



16

17: 1,3-Dipolar cycloaddition functionalized copolymer
18: Hydrazone functionalized copolymer
19: One-pot 1,3-dipolar cycloaddition & hydrazone functionalized copolymer

Entry	Reagent	Reaction conditions[a]	Product	Isolated yield, %
17a		(a)		99
17b		(a)		98
17c		(a)		97
17d	 **(20)**	(a)		99
18a		(b)		99
18b		(b)		97
18c		(b)		98
18d	 **(21)**	(c)		98
19a		(d)		97
19b	**(20)** + **(21)**	(e)		96

[a] Reaction conditions: (a) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 5 h; (b) DMF, 25 °C, 2 h; (c) DMSO, 25 °C, 24 h; (d) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF, 25 °C, 2 h; (e) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMSO, 25 °C, 24 h.

(Figure 2). Furthermore, full initiation was observed by a complete shift of the carbene signal of **4** in the ^{1}H NMR spectrum from 20.0 to 18.8 ppm after complete initiation. No signal corresponding to the uninitiated ruthenium complex was observed, and the integration of the signal before (20.0 pmm) and after the addition of monomer (18.8 ppm) was identical. Finally, a homoblock copolymerization experiment of **13** was performed. A 25:1 [M]:[I] ratio of **13** was polymerized to completion. Subsequently, 375 equiv of additional **13** was added. The GPC analysis showed a complete and dramatic shift to high

molecular weight without traces of terminated low molecular weight polymer (Figure 3). These results in conjunction with the linear relationship between M_n and [M]:[I] clearly prove the living nature of the ROMP of **13**.

With monomers **1** and **13** in hand that both polymerize in a living fashion and therefore allow for full control over molecular weights and degree of polymerization, we investigated the copolymerization of **1** and **13**. The random copolymerization of **1** and **13** at a 1:1 ratio using 4 mol % of **4** gave copolymers in 98% isolated yield. Since the kinetics of the homopolymerizations of monomers **1** and **13** are approximately the same within experimental errors (monomer-to-initiator ratios of 25:1 polymerize in 10 min for both monomers), the copolymerization of **1** and **13** proceeds in a random fashion. The azide-functionalized polymer **16** was synthesized in close analogy to **9** using NaN_3 in DMF in 96% yield. GPC analyses of **15** and **16** were carried out, and molecular weights and polydispersity indices (PDIs) were measured (M_n = 12 500, PDI = 1.62 for **15** and M_n = 16 500, PDI = 1.62 for **16**, all versus poly(styrene) standards). The unchanged PDIs indicate that the postpolymerization functionalization step does not change basic polymer properties. Both isolated copolymers **15** and **16** containing ketones along the side-chains were fully soluble in common solvents such as CH_2Cl_2, THF, DMF, and DMSO. Thus, we were able to overcome the insolubility problem observed for the aldehyde polymers by using the ketone-based system.

Both 1,3-dipolar cycloaddition and hydrazone formation are compatible with a wide range of substrates and reagents allowing for modularity and diversity in the nature of the functional polymer. We investigated the modularity and diversity of our orthogonal functionalization strategies of **16** by reacting a library of compounds with **16** via 1,3-dipolar cycloaddition and hydrazone formation, as outlined in Table 1. The one-pot dual functionalization of **16** was also examined.

The 1,3-dipolar cycloaddition transformations were carried out between **16** and phenylacetylene, 4-ethynylanisole, and 4-ethynyl-3,5-dimethoxybenzene under the typical 1,3-dipolar cycloaddition conditions described above (Table 1, entries **17a**−**c**). In all cases, we observed quantitative conversions of the azide to the corresponding triazole products as indicated by NMR and IR spectroscopies and gel-permeation chromatography. The isolated yields of all azide-functionalized copolymers ranged from 97 to 99%. The ^{1}H NMR spectra of **17a**−**c** showed the emergence of the triazole protons at 7.73−7.81 ppm and the diagnostic downfield shifts of the azidomethyl signals from 3.35 to 4.42−4.46 ppm, depending upon the acetylene groups. Complete disappearance of the azide band of **16** at 2099 cm^{-1} was observed in the IR spectra of **17a**−**c**. GPC data of **17a**−**c** revealed M_n ranging from 14 000 to 15 000 and PDIs ranging from 1.82 to 1.88.

To obtain the hydrazone products **18a**−**c**, **16** was coupled to benzhydrazide, 4-methoxybenzhydrazide, and 2-thiophenecarboxylic acid hydrazide in DMF (Table 1, entries **18a**−**c**). Quantitative formations in all cases were verified by the characteristic upfield shifts in the ^{1}H NMR spectra from 2.16 ppm [−C(C*H*$_3$)═O] to 1.98−2.04 [−C(C*H*$_3$)═N−], depending upon the hydrazide groups employed and the disappearance of the ketone carbonyl signal at 205.1 ppm in the ^{13}C NMR spectra. Isolated yields of **18a**−**c** ranged from 97 to 99%. GPC data of **18a**−**c** showed M_n ranging from 10 500 to 13 500 and PDIs ranging from 1.53 to 2.29.

One-pot dual functionalization of **16** to **19a** was performed using phenylacetylene and benzhydrazide (Table 1, entry **19a**). Complete conversion to the bifunctionalized product **19a** was observed as characterized by NMR and IR spectroscopies and gel-permeation chromatography. The ^{1}H NMR spectrum of **19a** showed a combination of the characteristic shifts observed for both the **17a** and **18a**. The ^{13}C NMR and IR spectra of **19a** revealed a complete loss of the ketone and azide groups, respectively. The M_n and PDI of **19a** were 10 000 and 1.78, respectively.

As a proof of principle to demonstrate that our functionalization strategy can be employed to yield biological relevant materials and that substrates containing a variety of functionalities that do not interfere with the click chemistry can be utilized, we functionalized **16** with two biologically significant molecules: the alkyne-functionalized nucleoside **20**[25] and the biotin hydrazide **21**. Polymer **16** was quantitatively converted to the nucleoside-functionalized polymer **17d** using **20** and 1,3-dipolar cycloaddition as characterized by the appearance of the triazole proton at 7.40 ppm and the diagnostic downfield shift of azidomethyl signal from 3.35 to 4.37 ppm in the ^{1}H NMR spectrum as well as complete disappearance of the azide band at 2099 cm^{-1} in the IR spectrum. Furthermore, polymer **16** was treated with **21** in DMSO to obtain the biotin-functionalized polymer **18d**. The quantitative conversion was confirmed by the characteristic shift in the ^{1}H NMR spectrum from 2.08 ppm [−C(C*H*$_3$)═O] to 1.80 [−C(C*H*$_3$)═N−] in DMSO-d_6 and the complete loss of the ketone carbonyl signal at 205.1 ppm in the ^{13}C NMR spectra. Finally, the one-pot dual functionalization of **16** was carried out using both **20** and **21**. Complete conversions to **19b** were verified by a combination of the characteristic shifts observed for **17d** and **18d** as well as the complete loss of the ketone and azide groups in the ^{13}C NMR and IR spectra of **19b**, respectively. GPC analyses of **17d** and **19b** were carried out (M_n = 17 000, PDI = 1.65 for **17d** and M_n = 15 000, PDI = 1.67 for **19b**; molecular weights are reported vs poly(styrene) standards). In the case of **18d**, GPC analysis could not be performed because of the insolubility of **18d** in CH_2Cl_2, THF, and DMF.

During all monofunctionalizations of **16** via 1,3-dipolar cycloaddition (Table 1, **17a**−**d**) or hydrazone formation (Table 1, **18a**−**d**), only single products were obtained, and no other part or functional group of the polymer or substrates underwent any side reactions. These results clearly demonstrate that both functionalization methods of **16** are independent of each other and can be addressed in an orthogonal fashion. Furthermore, all functionalizations proceed in quantitative yields and all resulting fully functionalized copolymers were soluble in common solvents, demonstrating the synthetic potential of our methodology.

Conclusion

We have presented a novel methodology for the quantitative covalent functionalization of copolymers based on highly efficient, versatile, and modular covalent synthetic strategies. Modular functionalization of the azide- and ketone-functionalized random copolymer was accomplished with small organic and biological molecules containing alkyne or hydrazide groups via a single orthogonal functionalization using either 1,3-dipolar cycloaddition or hydrazone formation and a one-pot multifunctionalization by combining both reactions simultaneously. All investigated functionalization transformations proceed quantitatively in an orthogonal manner with high fidelity and absolute selectivity under mild reaction conditions. Our study demonstrates the potential for the employment of such a single-step functionalization strategy in polymeric materials.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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