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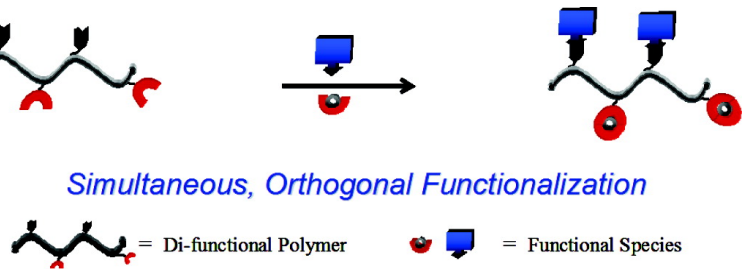

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Orthogonal Approaches to the Simultaneous and Cascade Functionalization of Macromolecules Using Click Chemistry

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Abstract: The development of selective chemistries that are orthogonal to the diverse array of functional groups present in many polymeric systems is becoming an important tool for the synthesis and use of macromolecules in fields ranging from biomedical devices to nanotechnology. By combining copper-catalyzed cycloaddition chemistry with other synthetic transformations such as esterification, amidation, etc., highly efficient and modular simultaneous and cascade functionalization strategies have been developed. These single-step strategies for preparing multifunctional macromolecules represent a significant advance as compared to traditional multistep approaches, and the utility of these concepts is demonstrated by selective preparation of a diverse range of orthogonally functionalized vinyl polymers.

Introduction

The ability to perform multiple reactions on a single substrate in a complex chemical environment is a grand challenge in many different aspects of chemistry and materials science.[1] In addressing this fundamental issue, nature provides inspiration because biological systems can orthogonally perform a multitude of different reactions with excellent fidelity and regio/stereospecificity in the presence of many other reactive molecules under mild conditions.[2,3] In the organic chemistry community, numerous groups have tried to mimic nature's guiding principles to develop orthogonal chemistry in vitro, and these systems fall into two main categories, either cascade or simultaneous reactions. For cascade reactions, several sequential reactions occur from a single functional group resulting in a significant increase in complexity of the original functional group, while simultaneous reactions involve separate and distinct chemistry occurring at different functional groups at the same time and in the same reaction mixture. Several inspiring examples of these orthogonal or multiple-component condensation reactions have been demonstrated, most notably the convergent assembly of β-peptide analogues,[4] or the natural product *Daphniphyllum*, a complex polycyclic alkaloid whose total synthesis involved 12 sequential steps occurring in one pot.[5]

For polymer chemistry and materials science, application of similar concepts is still in its infancy due to the inherent difficulties in working with polyfunctional macromolecules.[6] The unique features of macromolecules when compared to small molecules (number of functional groups, purification techniques, etc.) make the elucidation of orthogonal chemistries that proceed with fidelity, high levels of control, and functional group compatibility a challenge. In this work, the development of cascade or simultaneous strategies for the orthogonal functionalization of macromolecules through utilization of the concept of Click chemistry is explored.[7−9] The selection of a Click reaction, specifically the copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes, is based on its near quantitative yield, regiospecific conversion, and compatibility with a broad range of functional groups and reaction conditions. As a result, Click chemistry has been used as the growth step in the preparation of dendrimers,[10,11] block copolymers,[12] cross-linked adhesives,[13] and for the coupling of telechelic polymers prepared

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(1) Langer, R.; Tirrell, D. A. *Nature* **2004**, *428*, 487−493. Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200.
(2) Klok, H.-A. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1−14.
(3) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2004**, *126*, 15046−15047.
(4) Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc.* **2004**, *126*, 13606−13607.
(5) Wallace, G. A.; Heathcock, C. H. *J. Org. Chem.* **2001**, *66*, 450−454.
(6) Becker, M. L.; Liu, J. Q.; Wooley, K. L. *Biomacromolecules* **2005**, *6*, 220−228.
(7) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.
(8) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897−3899.
(9) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *4*, 2331−2336.
(10) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928−3932.
(11) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436−5443.
(12) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, 57−59.
(13) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem*. **2004**, *42*, 4392−4399.

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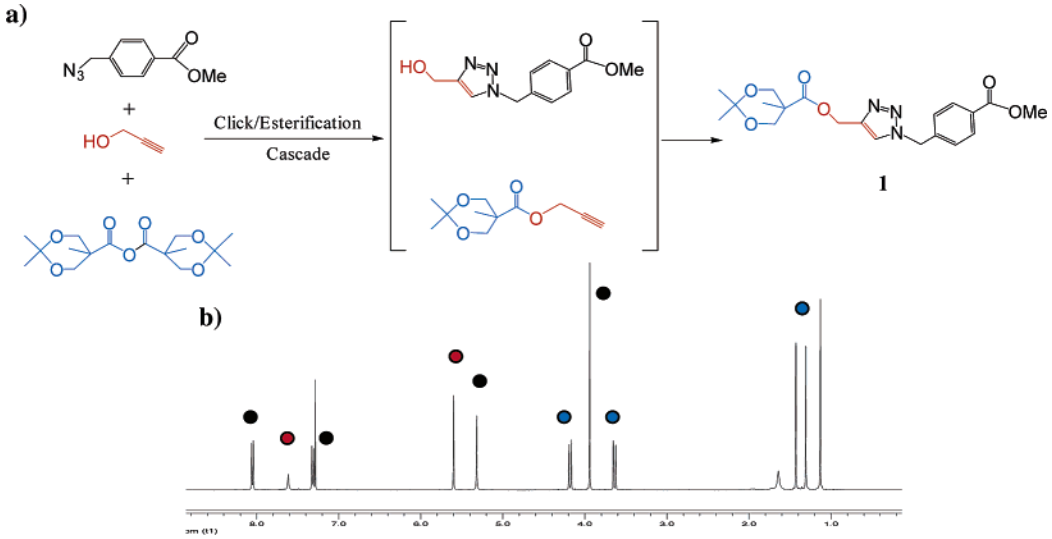
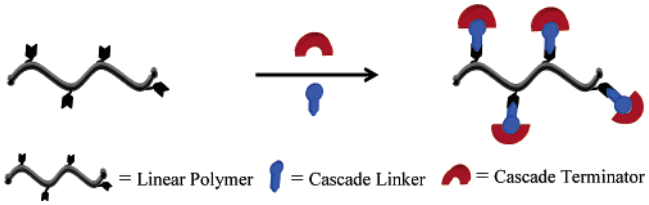
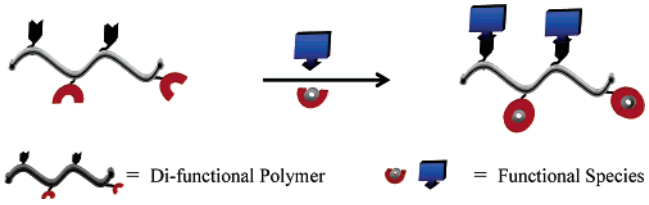


Figure 1. Model Click chemistry/esterification cascade system using DIPEA and $CuBr(PPh_3)_3$: (a) Reaction scheme for coupling of the acetonide-protected bis-MPA, methyl 4-(azidomethyl)benzoate, and propargyl alcohol to give **1**; (b) crude ^1H NMR spectrum of the reaction mixture after washing with water; resonances for the product, **1**, are depicted with colored circles, and color choice is based on the three different starting materials.

Scheme 1. Schematic Illustration of a One-Pot Cascade Approach to Polymer Functionalization



Scheme 2. Schematic Illustration of a Simultaneous Approach to Polyfunctionalization of Multifunctional Macromolecules



by atom transfer radical polymerization.[14] These accomplishments have been matched in the area of polymer functionalization where the efficiency of this reaction has been exploited for the quantitative derivatization of linear polymer backbones,[15−18] chains ends,[19,20] and dendrimers.[21] The success of these efforts allows for the first time the application of orthogonal functionalization concepts derived from nature to the preparation of polymeric materials, permitting polymer chemistry to go beyond traditional single or mono-functionalization strategies to more sophisticated and powerful simultaneous and cascade functionalization approaches.

Results and Discussion

The general concept of orthogonal functionalization occurring either in a cascade fashion or simultaneously for a polymeric substrate is shown in Schemes 1 and 2, respectively. For a sequential, cascade-type reaction, a linear polymer functionalized with a single type of reactive group along the backbone is allowed to undergo reaction with two molecules, denoted linker and terminator (Scheme 1). The nature of the reactive groups is chosen so that there is a definite sequence of coupling reactions; the terminator molecule will only react with the linker molecule, which in turn can react with both the terminator and the linear backbone functionalities. If the reactions occur with high fidelity and selectivity, a simple backbone functional group can be elaborated into a complex moiety through multiple reaction steps at the same time.

In contrast, the simultaneous strategy involves a polymeric material having multiple copies of different functional groups along the backbone undergoing distinct and independent reactions to give, in a single step, a new polyfunctional macromolecule (Scheme 2). For the two strategies described above to be

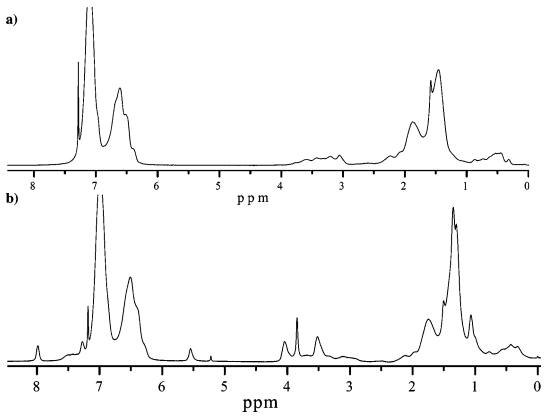


Figure 2. ^1H NMR spectra of (a) the starting random copolymer, **10**, containing acetylenic and hydroxyl groups and (b) the functionalized polymer, **11**, after simultaneous Click and esterification reactions.

(14) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558−3561.
(15) Parrish, B.; Breitenkamp, R. B.; Emrick, T. *J. Am. Chem. Soc.* **2005**, *127*, 7404−7410.
(16) Tsarevsky, N. V.; Bernaerts, K. V.; Dufour, B.; Du Prez, F. E.; Matyjaszewski, K. *Macromolecules* **2004**, *37*, 9308−9313.
(17) Englert, B. C.; Bakbak, S.; Bunz, U. H. F. *Macromolecules* **2005**, *38*, 5868−5877.
(18) Helms, B.; Mynar, J. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020−15021.
(19) Mantovani, G.; Ladmiral, V.; Tao, L.; Haddleton, D. M. *Chem. Commun.* **2005**, 2089−2091.
(20) Lutz, J. F.; Borner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514−518.
(21) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663−3678.

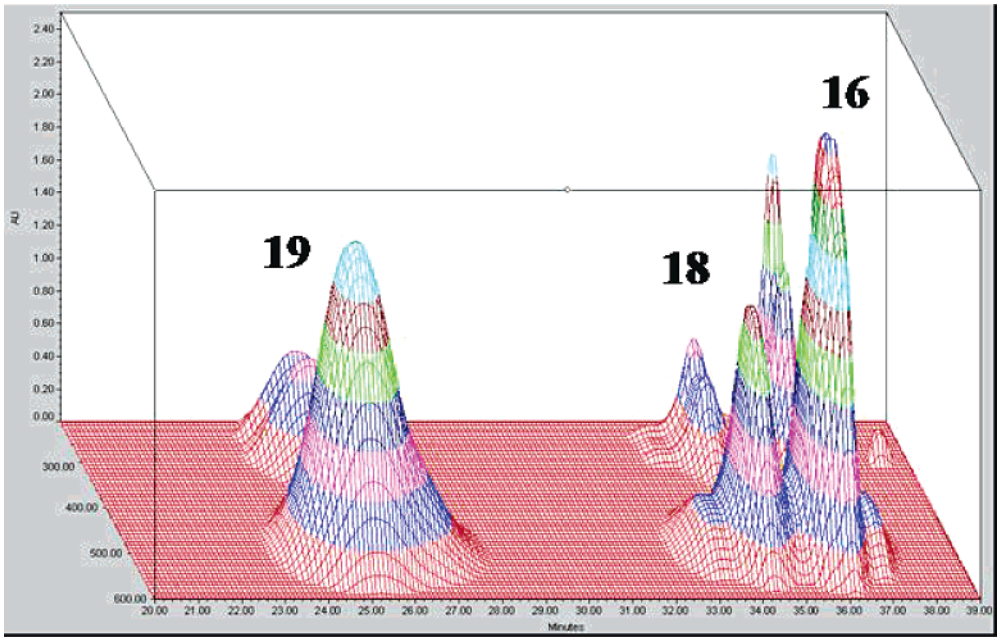
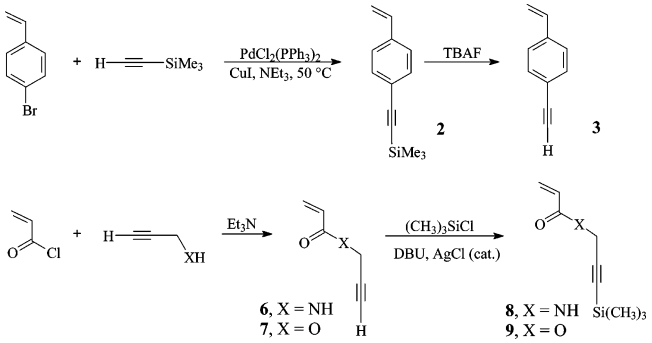


Figure 3. Three-dimensional GPC−UV−vis traces after 6 h of reaction between **14**, propargylamine, **15**, and the azide derivative of Disperse Red **16**. The three sets of peaks correspond to materials containing the Disperse Red chromophore, unreacted starting material **16**, the initial triazole-based Click product, **18**, and the desired cascade product, **19**.

Scheme 3. Synthesis of Acetylene Functionalized Vinyl Monomers, **2**, **3**, and **6**−**9**

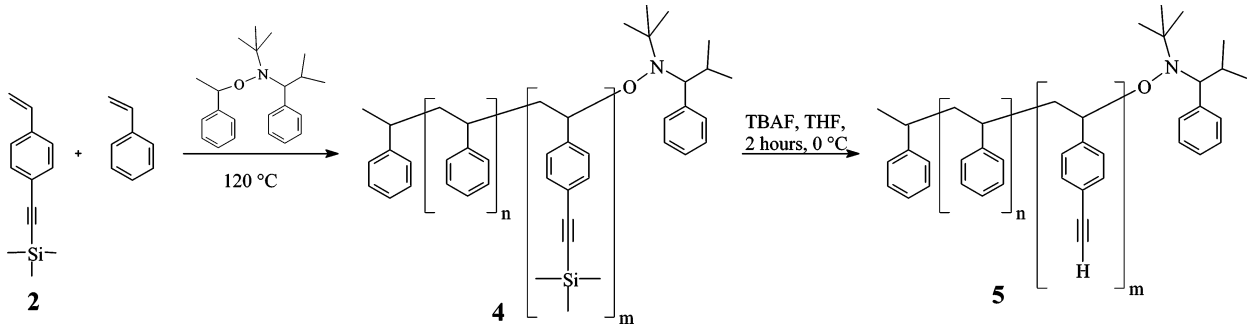


successful, a key feature is that at least one of the reactions employed must be highly tolerant and compatible with a variety of functional groups and reaction conditions. Many of these attributes are present for Click chemistry,[13] and this versatile methodology is used in combination with a variety of other chemical reactions as test vehicles to prove the versatility and highly modular nature of orthogonal reactions in polymer chemistry. To demonstrate this, simultaneous and cascade reactions will be examined with both hydrophobic and hydrophilic scaffolds and in combination with both nucleophilic and electrophilic reactions.

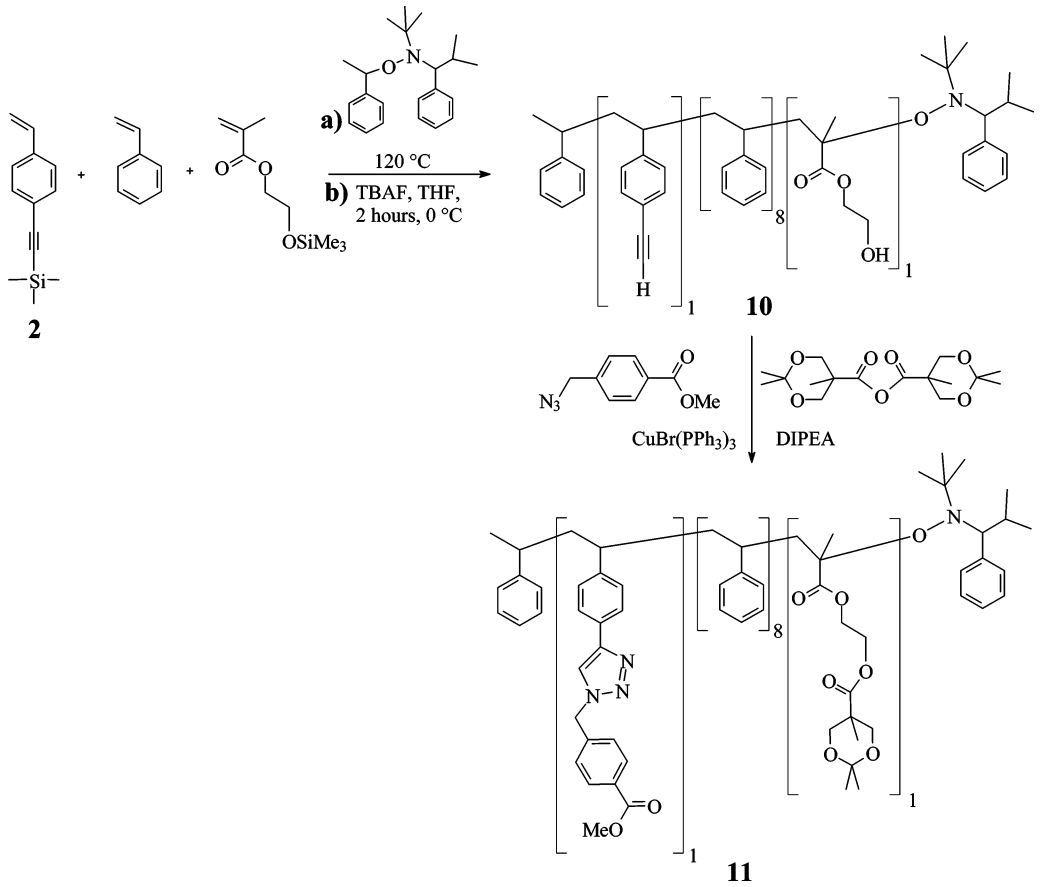
Model Reactions. Initially, the viability of both the cascade and the simultaneous strategies was examined with the aid of a model system involving the combination of Click chemistry with an anhydride-based esterification reaction. To this end, a tetrahydrofuran (THF) solution of equimolar amounts of methyl 4-(azidomethyl)benzoate, propargyl alcohol, and acetonide-protected 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) was stirred at 50 °C in the presence of catalytic amounts of diisopropylethylamine (DIPEA) and $CuBr(PPh_3)_3$ (Figure 3a). Notably, DIPEA serves as both the base for the Click chemistry as well as the catalyst for the esterification reaction. Chromatographic analysis (HPLC) of the reaction system at regular intervals revealed that both reactions proceeded simultaneously to give the cascade product, **1**, in over 98% yield. Further confirmation of the efficiency and fidelity of this process can be obtained from the crude ^{1}H NMR spectrum in Figure 1b, which shows the emergence of the triazole proton (∼7.6 ppm) and the downfield shift of the 4-azidomethyl resonances (∼5.5 ppm) coupled with the concomitant disappearance of resonances for the starting materials (CH_2N_3 at 4.6 ppm and CH_2OH at 3.9 ppm).

After establishing the potential of the cascade and simultaneous concepts for small molecule systems, extension to polyfunctional macromolecular scaffolds was attempted. A key

Scheme 4. Synthesis of Acetylene Functionalized Random Copolymer, **5**, by Nitroxide Mediated Living Free Radical Procedure

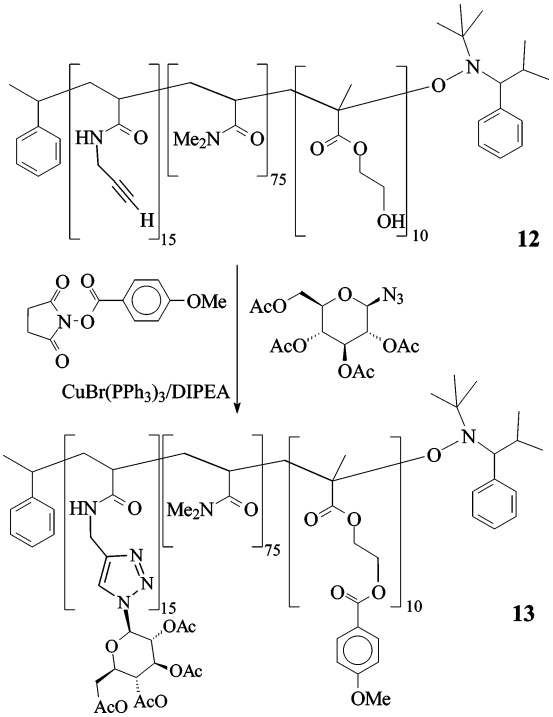


Scheme 5. Synthesis and Simultaneous Functionalization of Terpolymer, **10**



component of these studies are polymeric systems having acetylenic functional groups, and due to the scarcity of such systems in the literature[22] the preparation of acetylene-based monomers and their subsequent polymerization was investigated. The styrenic derivative, **3**, was prepared from 4-bromostyrene by initial Pd-catalyzed coupling with (trimethylsilyl)acetylene followed by deprotection of **2** with tetrabutylammonium fluoride (Scheme 3). Polymerization of **3** by traditional and living free radical[23] processes was, however, complicated by coupling reactions, which led to cross-linking at high conversions and/or high monomer loadings of **3**. Presumably this chain−chain coupling is due to minor amounts of unwanted radical addition reactions occurring at the terminal acetylenic triple bond, and to overcome this difficulty the copolymerization of the protected derivative, **2**, was investigated. Under standard nitroxide mediated LFRP procedures, the copolymerization of **2** and styrene proved to be a facile process leading to well-defined copolymers, **4**, of controlled molecular weight and polydispersity (PDI = 1.10−1.20), which could be quantitatively deprotected to give the pendant acetylene functionalized copolymer, **5** (Scheme 4). For the acrylamide- and acrylate-based monomers, **6** and **7**,

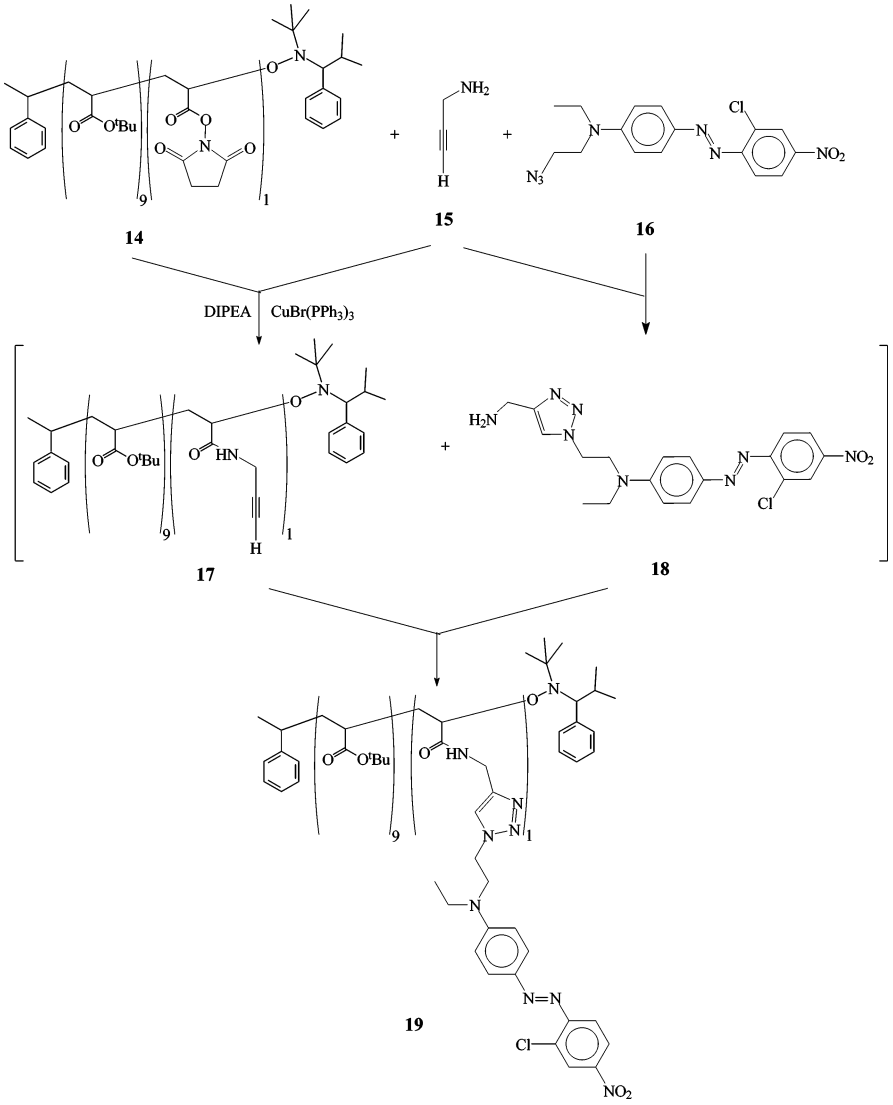
Scheme 6. Simultaneous Functionalization of Water-Soluble Terpolymer, **12**



silylation of the propargyl derivatives, **8** and **9**,[24] was accomplished by reaction with trimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of a catalytic amount of silver chloride (Scheme 3).

(22) Sessions, L. B.; Miinea, L. A.; Ericson, K. D.; Glueck, D. S.; Grubbs, R. B. *Macromolecules* **2005**, *38*, 2116−2121.
(23) Huang, J.; Pintauer, T.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 3285−3292. Percec, V.; Popov, A. V.; Ramirez-Castillo, E.; Weichold, O. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 6364−6374. Zhang, H.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4882−4894. Szablan, Z.; Toy, A. A.; Davis, T. P.; Hao, X.; Stenzel, M. H.; Barner-Kowollik, C. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 2432−2443. Drockenmuller, E.; Li, L. Y. T.; Ryu, D. Y.; Harth, E.; Russell, T. P.; Kim, H. C.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1028−1037.

Scheme 7. Cascade Functionalization of the Active Ester Functionalized Polyacrylate, **14**

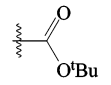
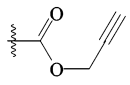
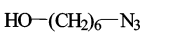
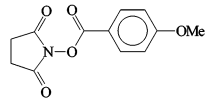
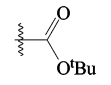
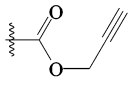
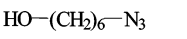
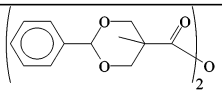
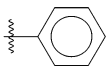
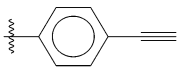
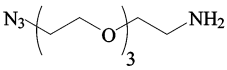
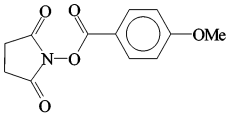
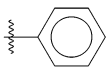
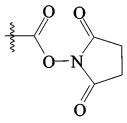
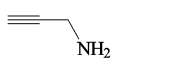
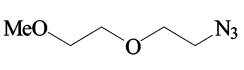
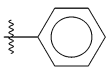
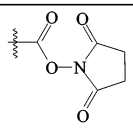
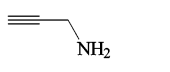
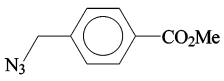
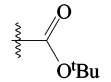
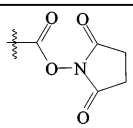
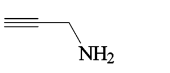
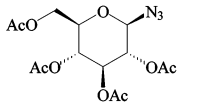
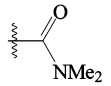
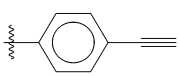
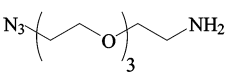
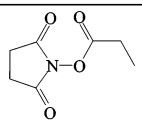
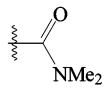
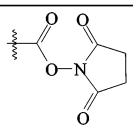
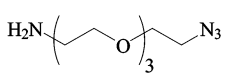
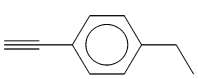


Simultaneous Strategy. Building on these results, a terpolymer of 8:1:1 styrene, *p*-(trimethylsilylacetylene)styrene **2**, and 2-(trimethylsiloxyethyl)methacrylate was prepared using LFRP, and deprotection of both protecting groups with tetrabutylammonium fluoride (TBAF) gave the desired difunctional macromolecule, **10** (M_n = 31 900 amu; PDI = 1.16). In a fashion similar to the small molecule example, the acetylene and hydroxyl functionalities present in **10** afford sites capable of simultaneous reaction with both methyl 4-(azidomethyl)benzoate and the acetonide-protected bis-MPA anhydride in the presence of Cu(I) and DIPEA. The orthogonally functionalized macromolecule, **11** (M_n = 39 900 amu; PDI = 1.19), was therefore obtained in which the terminal acetylene group has been elaborated into a methyl benzoate substituted triazole groups and the hydroxyl group has been esterified with a first generation protected bis-MPA dendron (Scheme 5).[25] As evidenced by the ^{1}H NMR spectra in Figure 2, conversion of the acetylene and hydroxyl groups to the triazole ring and dendron ester, respectively, results in the appearance of resonances at 8.00, 5.55, 4.05, 3.85, and 3.50 ppm, which correspond to the introduction of the desired functional groups. Evaluation of the extent of these reactions by quantitative ^{13}C NMR and IR spectroscopy showed no detectable acetylene and hydroxyl groups and greater than 95% functionalization of both functionalities. The fidelity of these orthogonal reactions was also examined by performing the simultaneous reactions under the same conditions as defined above except in the absence of methyl 4-(azidomethyl)benzoate, Cu(I), or the acetonide-protected bis-MPA anhydride. In each case, only a single functionalization event occurred, and both ^{1}H NMR and IR analysis showed that the other functional group was still present and did not undergo any unwanted side reactions.

The additional power of this concept is in its modular nature, which allows a wide range of different backbones and functional groups to be investigated. To demonstrate this diversity, the water-soluble, (*N*,*N*-dimethyl)acrylamide-based terpolymer, **12**, was prepared, which contains both a propagyl-substituted acrylamide for Click modification as well as a hydroxy group for nucleophilic attack (Scheme 6). In this case, reaction with 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate and succinimidyloxy 4-methoxybenzoate was again shown to proceed to

(24) MacInnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077−82.
(25) Vestberg, R.; Nilsson, C.; Lopes, C.; Lind, P.; Eliasson, B.; Malmström, E. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1177−1187.

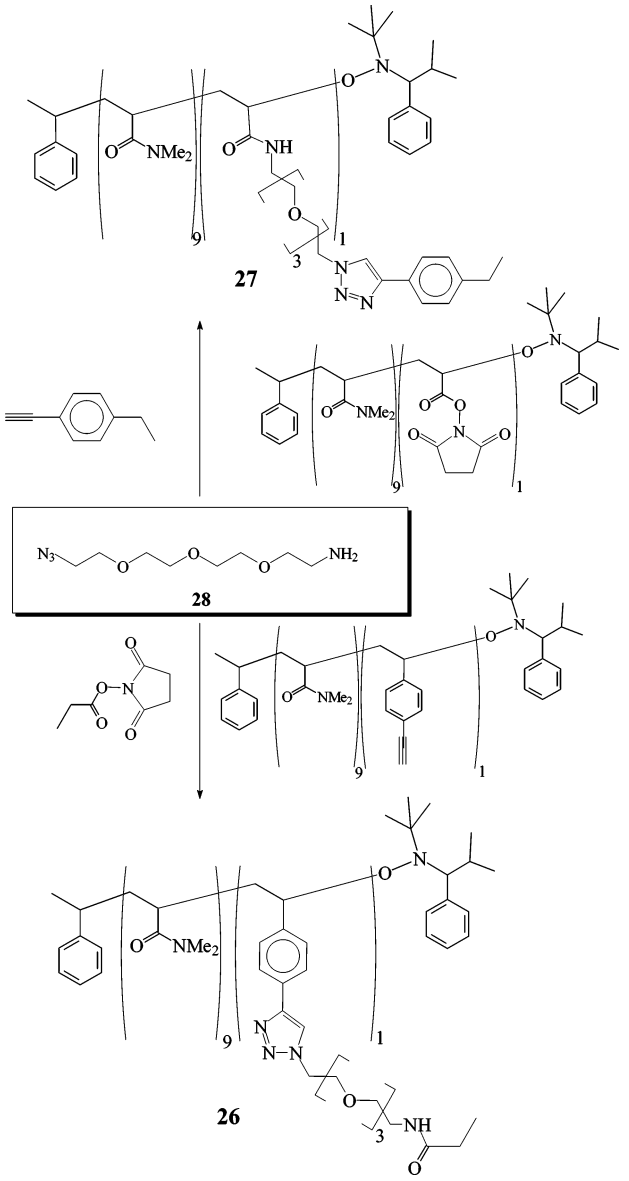
Table 1. Structure of Comonomer, Functional Monomer, **X**, Linker Group, **Y**, and Terminal Group, **Z**, Employed in the Cascade Functionalization of Linear Polymers

Comonomer Unit	Functional Monomer **X**	Linker Group **Y**	Terminal Group **Z**	Prod. No.
				**20**
				**21**
				**22**
				**23**
				**24**
				**25**
				**26**
				**27**

completion with quantitative and simultaneous functionalization of both the acetylene and the hydroxyl groups observed.

Cascade Strategy. Having demonstrated the synthesis of complex random terpolymers by a simultaneous approach to polymer functionalization, the development of a cascade strategy to the functionalization of macromolecules was investigated. In this approach, functional groups along the backbone are elaborated in a multistep fashion in the same reaction mixture and at the same time. As a result, a single type of backbone functional group, **X**, reacts with molecules **Y** and **Z** to give the cascade functionality **X**−**Y**−**Z**. The cascade approach to polymer functionalization was first demonstrated using a 9:1 random copolymer of *tert*-butyl acrylate and *N*-acryloyloxy succinimide, **14** (Scheme 7). To a solution of this copolymer in THF were added propargylamine, **15**, and 2-[4-(2′-chloro-4′-nitrophenylazo)-*N*-ethylphenylamino]ethyl azide (Disperse Red 13), **16**. In this case, the Cu(I) acts as a catalyst for the Click reaction between **15** and **16** or the intermediate coupling product, **17**, with **16**, while the DIPEA catalyzes the amidation reaction of **14** with either **15** or the intermediary Click product **18**. This sequence of reactions was monitored by GPC/HPLC and ^{1}H NMR, which showed that all reactions reached completion after 16 h at 50 °C and that the amidation chemistry and Click reactions were occurring at approximately the same rate. As shown in Figure 3, the three-dimensional GPC/UV−vis profile for the reaction mixture allows the distribution of the Disperse Red 13 chromophore among the possible products to be accurately identified and quantified. After 6 h of reaction, the characteristic absorbance for Disperse Red 13 at 503 nm is visible at 25.5, 34.5, and 36.0 min for three peaks in the GPC trace. This correlates with the starting azido derivative, **16**, the initially formed intermediary Click product, **18**, and the final cascade functionalized polyacrylate, **19**, in a ca. 4:2:3 ratio. Similar data were obtained from HPLC and ^{1}H NMR experi-

Scheme 8. Modular Synthesis of Different Cascade Products, **26** and **27**, from the Same Starting Linker, 1-Amino-11-azido-3,6,9-trioxoundecane, **28**



ments, which showed the disappearance of peaks for **14**−**16**, the appearance and subsequent disappearance of the intermediates, **17**−**18**, and the concomitant appearance of the final product **19**.

One of the unique attributes of the Cu-catalyzed [3+2π] coupling reaction of terminal acetylenes with azide derivatives is its compatibility with a wide range of substrates and reagents. This allows significant diversity and modularity in the nature of the functional polymer, linker, and terminal groups, and this modularity and diversity was investigated by the synthesis of a variety of polymeric backbones bearing either acetylene or active ester groups. In addition, the structure of the linker and terminating groups was varied to demonstrate that the sequence of reactions could be changed with little or no effect on the effectiveness of this strategy. Random copolymers containing styrenic-, acrylic-, and acrylamide-based backbones were prepared to reflect the versatility of this approach, while the presence of either a "clickable" terminal acetylene or an active ester functionality along the backbone demonstrates the modularity of this strategy (Table 1). An interesting feature of the cascade reactions shown in Table 1 is the ability to occur regardless of the chemical arrangement of the functional groups or the sequence of the reactions. The modular nature is also exemplified by the schematic representation of these cascade reactions as shown in Scheme 8, where a copolymer backbone with functional group, **X**, undergoes reaction with a linker group, **Y**, and a terminal group, **Z**.

An excellent example of this involves the two acrylamide-based products, **26** and **27**. In both cases, 1-amino-11-azido-3,6,9-trioxoundecane, **28**, was used as the linker group; however, the sequence of reactions is reversed. For **26**, the acetylene functionalized backbone leads to the formation of a phenyl-triazole group directly attached to the backbone and a propionamide terminal group, while in the case of **27**, the acryloyl backbone undergoes amidation to give a propionamide derivative and subsequent Click reaction with 4-ethylphenyl acetylene yields the same phenyl-triazole group at the end of the side chain. As a result, both reactions lead to the same side chain with the point of attachment to the polymer backbone being reversed (triazole in **26** vs amide in **27**) (Scheme 8).

Characterization of the cascade products depicted in Table 1 by a combination of spectroscopic and chromatographic techniques demonstrated the high efficiency of this approach. The yield of ca. 98+% for each functionalization step, which was confirmed by a combination of NMR, IR, and UV techniques, can be further appreciated in the ^{1}H NMR spectrum of the purified copolymer **24** where no detectable resonances are observed for unreacted acetylene groups or active ester groups that would result from incomplete cascade functionalization of the polymeric backbone. Unique resonances for the triazole ring and *o*-aryl protons from the benzoate ring (7.95 ppm), benzyl group (5.35 ppm), and methyl ester group (3.85 ppm) could be identified (Figure 4), and the absence of small molecule impurities (GPC) clearly demonstrates that the active ester functionality of the starting copolymer has been elaborated by reaction with both propargylamine and methyl 4-(azidomethyl)-benzoate. Control experiments in which the linker molecule was not present in the reaction mixture showed no detectable reaction, and the starting materials were recovered in essentially quantitative yield.

In the case of **27**, incomplete Click functionalization would lead to a polymer bearing small amounts of azide groups attached to the backbone. To confirm the complete consumption of azide groups and the absence of this intermediate in the final product, a highly sensitive ninhydrin test, developed for the detection of resin-bound azides,[26] was employed. This analytical method is more sensitive than IR spectroscopy, and in none of the above cases were any azide groups detected.

Conclusion

In conclusion, we have demonstrated the unique opportunities that afford polymer synthesis through performing multiple, independent functionalization reactions orthogonally. By combining Click chemistry with other synthetic transformations, highly efficient, versatile, and modular simultaneous and cascade strategies were developed for the one-pot preparation of polyfunctional macromolecules. These strategies were shown

(26) Punna, S.; Finn, M. G. *Synlett* **2004**, 99−100.

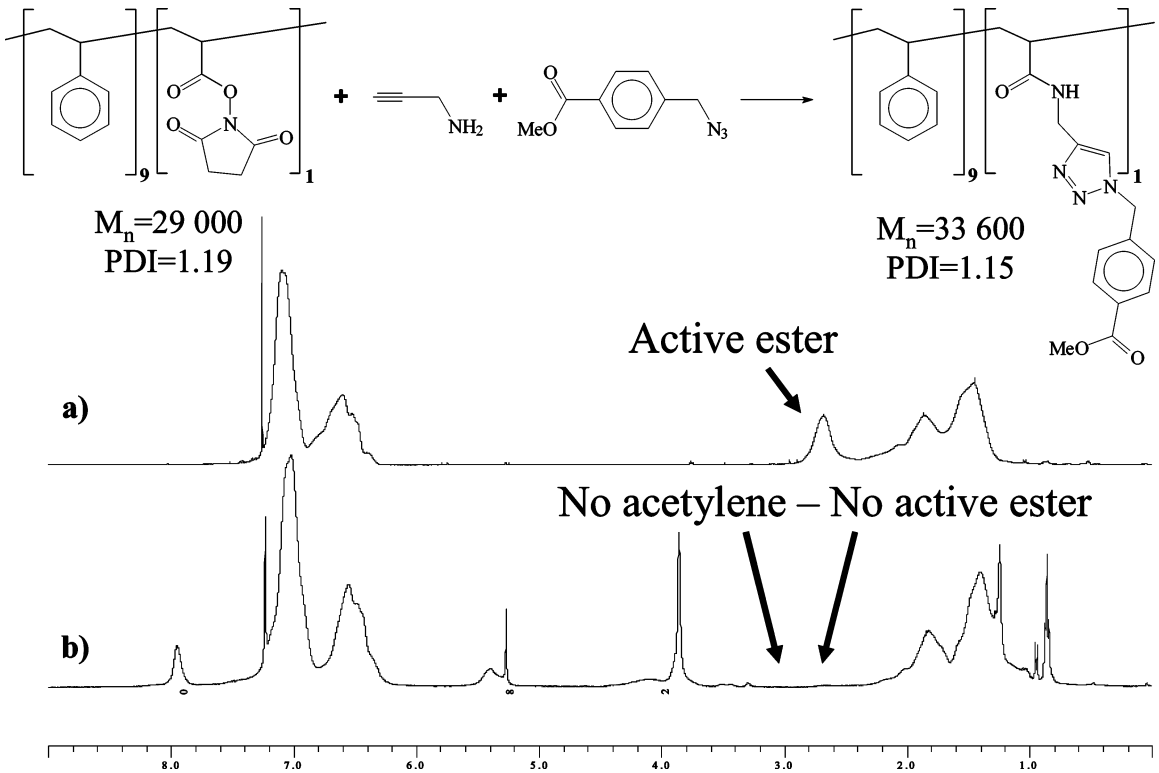


Figure 4. (a) ^{1}H NMR spectrum of starting active ester copolymer and (b) ^{1}H NMR spectrum of the cascade product, **24**, obtained after reaction with propargylamine and methyl 4-(azidomethyl)benzoate.

to be highly effective and proceed with absolute fidelity and essentially quantitative yields under mild conditions on multiple polymeric scaffolds. This unprecedented ability to routinely prepare multifunctional macromolecules in a single step represents a significant advance as compared to traditional multistep approaches and is further evidence of the power of the Click concept in materials chemistry.[27]

Acknowledgment. Financial support from the MRSEC Program DMR-0080034 (MRL-UCSB), the NSF Chemistry Program (CHE-0514031), the NSF-Europe Collaborative program DMR-0301833, the DAAD, the Foundation BLANCEFLOR Boncompagni-Ludovisi, nee Bildt, and the IBM Corp. is gratefully acknowledged.

Supporting Information Available: Experimental methods and characterization data for monomer/polymer synthesis and all functionalization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) Parent, M.; Mongin, O.; Kamada, K.; Katan, C.; Blanchard-Desce, M. *Chem. Commun.* **2005**, 2029−2031.

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