5

The Role of Click Chemistry in Polymer Synthesis

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5.1 Introduction

The expected increased demand for novel nanomaterials is directly accompanied by a need for efficient routes to prepare such materials. The realm of macromolecular science has always been intimately entwined with studies in the nanosciences, and a great deal of attention has been recently devoted to increase the diversity of available polymeric materials. Despite the enormous progress made over the last few decades, synthetic macromolecules generally remain rather undefined in comparison to many biopolymers, such as proteins or nucleic acids. Such limitations of polymer chemistry may seem surprising to many nonspecialists since modern organic synthesis provides a plethora of solutions for the preparation of chemo-, regio- and stereo-controlled low-molecular-weight compounds.[1] However, these chemical tools are not always readily transferable to the macromolecular scale. While the last 50 years has resulted in the development of a multitude of new synthetic polymerization and polymer modification strategies, many of these methods were plagued by their complexity and narrow focus. Ironically, it is often the case that the more complex a macromolecular structure is, the more important it is to have a simple pathway for its preparation. Whether the goal is to ensure complete consumption of a plurality of reactive functionalities or to specifically functionalize a single site on a polymer chain, efficient and/or orthogonal synthetic strategies are crucial.

While Nature has optimized its chemistry through evolution to select robust chemical tools perfectly adapted to Earth's environmental conditions, the discovery and selection of simpler and more universal synthetic methods is essential for advancement in polymer

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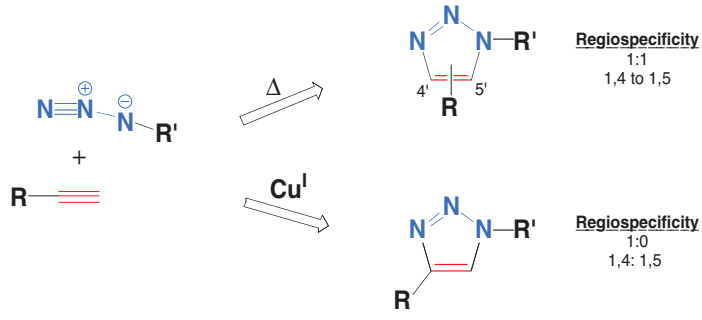


Scheme 5.1 *Thermal and copper-catalyzed cycloaddition of azides and alkynes.*

science. Selection of the most versatile chemical tools is the essence of click chemistry, an appealing concept proposed by Sharpless and coworkers.[2] Click chemistry is not a scientific discipline, but rather a synthetic philosophy focused on *function* and inspired by the simplicity and efficiency of the chemistry utilized by Nature. Highly complex biological systems rely on a modest library of monomers joined by only a few efficient reactions. Similarly, the objective of click chemistry is to establish an ideal set of straightforward and highly selective reactions in synthetic chemistry. For instance, the archetypal example of click chemistry is undoubtedly the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes.[3–6] In the absence of an appropriate catalyst, this reaction is generally slow and lacks regiospecificity, but in the presence of copper(I), which binds to terminal alkynes to form intermediate copper acetylides, this cycloaddition reaction is dramatically accelerated, regioselective and highly efficient (Scheme 5.1). Moreover, the copper-catalyzed azide–alkyne cycloaddition (CuAAC) can be performed in a variety of solvents (including water) and in the presence of numerous other functional groups.[5,6]

Although click chemistry was initially postulated as a general concept for organic synthesis, this strategy also has enormous potential in materials science.[1,7] The first example to illustrate this point was reported by the groups of Hawker, Fokin and Sharpless.[8] Afterwards, the visibility of click chemistry within the materials community grew.[7–26] The goal of this chapter is not to be a comprehensive review of the application of click chemistry in materials science, as many of these topics will inevitably be covered in other chapters of this volume. Rather, by highlighting some specific examples, many of which represent the first instances of click chemistry being employed in macromolecular synthesis and functionalization, we hope to give context to the click concept and its particular utility in polymer science.

5.2 Polymerization via CuAAC

High conversion is fundamental requirement for obtaining high molecular weight polymer by step-growth polymerization mechanisms. Therefore, it is logical that many of the first applications of the click concept in polymer synthesis involved the polymerization of azide- (or nitrile-) and alkyne-containing monomers to form linear polymers, dendrimers

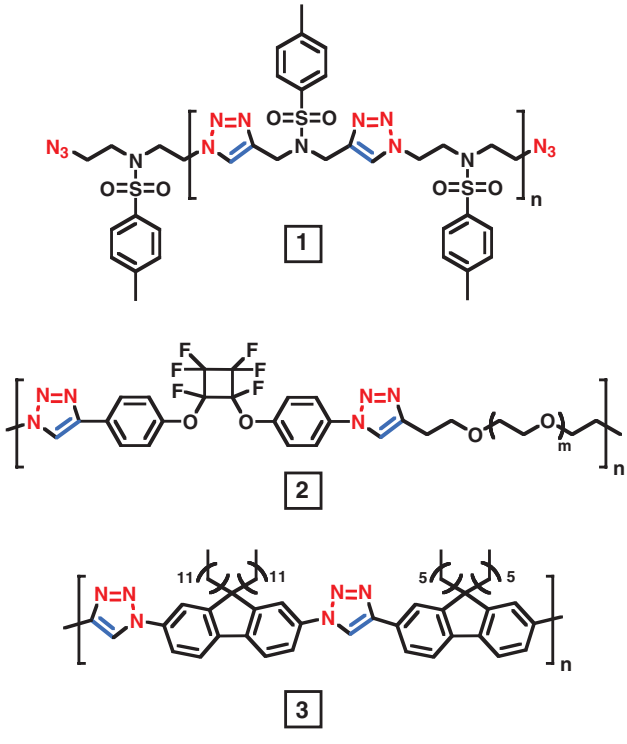


Figure 5.1 *Examples of CuAAC being employed to prepare linear polymer structures by polymerization of azide and alkyne functional monomers.*[9,27,29] *Reprinted with permission from J.-F. Lutz, (2007), 1,3 Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science,* Angew. Chem. Int. Ed., ***46*** *(7), 1018–1025. Copyright 2007 Wiley-VCH.*

and rotaxanes.[8,9,12,20,27–29] In these cases, the resulting structures contain multiple triazole or tetrazole repeating units and constitute a novel class of macromolecules with potentially interesting properties. Hawker, Fokin and Sharpless first reported CuAAC for the convergent synthesis of dendrimers.[8] The application of click strategies for the preparation of dendrimers proved highly beneficial, as there is perhaps no other area of polymer synthesis that relies so heavily on near-quantitative reaction conversions. This method proved to be a straightforward strategy for large-scale synthesis of near-perfect triazole-containing dendrimers. Shortly thereafter, Finn *et al*. extended CuAAC to prepare linear polymer chains (Figure 5.1, **1**) and macromolecular networks.[9] Both cases resulted in a prominent presence of triazole functionalities within the polymer structure, and the latter proved to be remarkable copper–copper adhesives as a result of the ability of these triazole rings to coordinate to miniscule amounts of copper(I) inevitably present on the surface of copper metal.

Fleury and coworkers recently conducted in-depth investigations regarding the polymerization of difunctional azide and alkyne monomers.[30] 1,6-Diazidohexane and a,w-bis(*O*-propargyl)diethylene glycol were polymerized with a $Cu(PPh_3)_3Br$ catalyst to yield triazole-containing copolymers. Kinetic studies were conducted, and polymerizations

at various temperatures allowed the activation energy for the polyaddition process to be calculated as $E_a = 45 \pm 5$ kJ/mol. Poly(alkyl aryl) ethers containing 1,2,3-triazolyl and perfluorocyclobutyl units (Figure 5.1, **2**) were prepared by Qing *et al*. via click poly(cycloaddition).[29] These novel macromolecules exhibited a rather interesting thermal stability and melting fluidity. On the other hand, polymers containing tetrazole units were found to be significantly less thermally stable. Polymers containing multiple tetrazole side-groups can be prepared by reacting well-defined polyacrylonitrile precursors with sodium azide, leading to tetrazole-functionalized polymers that decompose at temperature as low as 120 °C.[31] In addition to polymerization of low molecular weight azides and alkynes, Matyjaszewski and coworkers demonstrated that linear polymers with alkynyl and/or azido end groups could be further polymerized, with the chain extension leading to high molecular weight homopolymers[32] or multiblock copolymers.[33]

Because of the aromaticity of the resulting triazoles, CuAAC has also proven efficient for the synthesis of conjugated polymers. Both Reek *et al*. (Figure 5.1, **3**) and Bunz *et al*. reported the preparation of poly(fluorenylene-triazolene) via the reaction of diazido-fluorene monomers with various diynes.[27,34] Without relying on a copper catalyst, Bunz and coworkers also reported that these polymers could be prepared by local heating with an AFM tip.[34]

Overall, Huisgen cycloadditions seem to be straightforward and efficient reactions for building novel polymer structures. However, so far the prime focus of the aforementioned works has been on synthesis. Further studies are needed to assess comprehensively the physical behavior of these novel triazole- or tetrazole-containing polymers. Nonetheless, some of these early works already suggested some interesting properties (e.g. solubility, swelling, metal adhesion).

5.3 Post-polymerization Modification via Click Chemistry

Macromolecular engineering involves the synthesis of complex macromolecular structures with defined composition, microstructure, functionality and architecture (e.g. telechelic polymers, block copolymers, macromolecular brushes, stars, networks), using covalent chemistry approaches.[35] In addition to versatile polymerization chemistry, the synthesis of such complex macromolecules often requires the use of efficient and specific post-polymerization modification techniques to incorporate functionality potentially incompatible with the polymerization, characterization, or processing conditions.[36] Click reactions are especially suited for such advanced macromolecular design. Indeed, modification of multiple points on a polymer chain requires a highly efficient reaction mechanism, since the unreacted byproducts cannot be simply separated, as is the case is most small molecule reactions. Click strategies have served as a complementary tools for most of the major synthetic polymerization techniques, such as cationic or anionic ring opening polymerization (ROP),[37–40] ring opening metathesis polymerization (ROMP),[41] polycondensation,[42] conventional free-radical polymerization,[10,43] nitroxide-mediated polymerization (NMP),[11,14] reversible addition-fragmentation transfer polymerization (RAFT)[44–49] and atom transfer radical polymerization (ATRP).[19,31,32,50–65] The latter method has been coupled with CuAAC more than any of the others, and the reader is directed to a review specifically highlighting the combination of ATRP and click chemistry.[66] ATRP is a facile and versatile

polymerization technique and one of the most employed tools in modern polymer chemistry.[35,67] Despite its inherent versatility, the range of macromolecular structures available by ATRP can be further broadened by click strategies (Figure 5.2).

A first important application of CuAAC in polymer chemistry is undeniably the synthesis of functional polymers (either end-functional or pendant-functional). Telechelic polymers (i.e. polymers with functional end groups) can be efficiently prepared via a straightforward ATRP/CuAAC combination. The halogen end groups of polymers prepared using ATRP can be easily transformed into azide moieties[68–70] and subsequently involved in CuAAC with functional alkynes (Figure 5.2).[32,51,53,63,64] Alternatively, azide- or alkyne-functional initiators can be also utilized, though in the latter case protection of the alkyne moiety is often required to prevent its consumption during polymerization.[32,54,55] Functional telechelic polymers can also be prepared by RAFT polymerization, as first demonstrated by the groups of Barner-Kowollik and Stenzel[46] and Sumerlin *et al*.[45] In this case, the azide or alkyne moiety is typically incorporated in the chain transfer agent (CTA) structure prior to polymerization.

Polymers with multiple functional side chains have been prepared by CuAAC using precursors built with alkyne-functional monomers.[10,14,37,40,42] For example, Fréchet and coworkers constructed dendronized polymers (i.e. linear polymer chains with bulky side dendrons) via side-chains cycloadditions (Scheme 5.2).[10] Hawker and coworkers exploited this concept even further via cascade side-chain functionalization of macromolecules (Scheme 5.3).[14] Mantovani and Haddleton recently demonstrated that glycopolymers could be prepared in a one pot-process by simultaneous ATRP of an alkynyl monomer and CuAAC with azido-functionalized sugars.[71] The relative rates of polymerization and click functionalization were conveniently tunable by varying the catalyst concentration, solvent and temperature.

Azide-containing monomers and related polymer precursors have been also studied for preparing macromolecules with functional side-groups.[38,41,43,56] For example, after preparing homopolymers and block copolymers of 3-azidopropyl methacrylate (AzPMA), Sumerlin *et al*. functionalized the resulting azido-functionalized polymer (PAzPMA) by coupling with a variety of low molecular weight alkynyl species (Scheme 5.4).[56] Interestingly, the rate of azide–alkyne coupling of this polymer was observed to be significantly higher than that for the corresponding monomer, an effect attributed to autoacceleration by anchimeric assistance. Previous reports had demonstrated polytriazoles to be excellent ligands for copper(I).[72] Thus, during functionalization of PAzPMA in the absence of additional ligand, triazoles formed along the polyAzPMA backbone were believed to complex the catalyst, leading to a higher local copper(I) concentration in the immediate vicinity of neighboring unreacted azido groups. Similar autocatalytic results were reported by Fokin and Finn.[73]

Although efficient, such strategies are potentially experimentally risky (like any approach involving molecules with a high density of azide groups) due to the potentially explosive character of organic azides and should be investigated with extreme care.[74,75] However, an alternative route was reported by Matyjaszewski *et al*. in which poly(glycidyl methacrylate) (PGMA) copolymers were prepared by ATRP, and subsequent ring opening of the pendant epoxide with NaN_3 led to efficient incorporation of azide groups on each PGMA repeat unit (Scheme 5.5).[76] The resulting 1-hydroxy-2-azido copolymers were reacted with alkyne-terminated poly(ethylene oxide) (PEO) to yield graft copolymers.

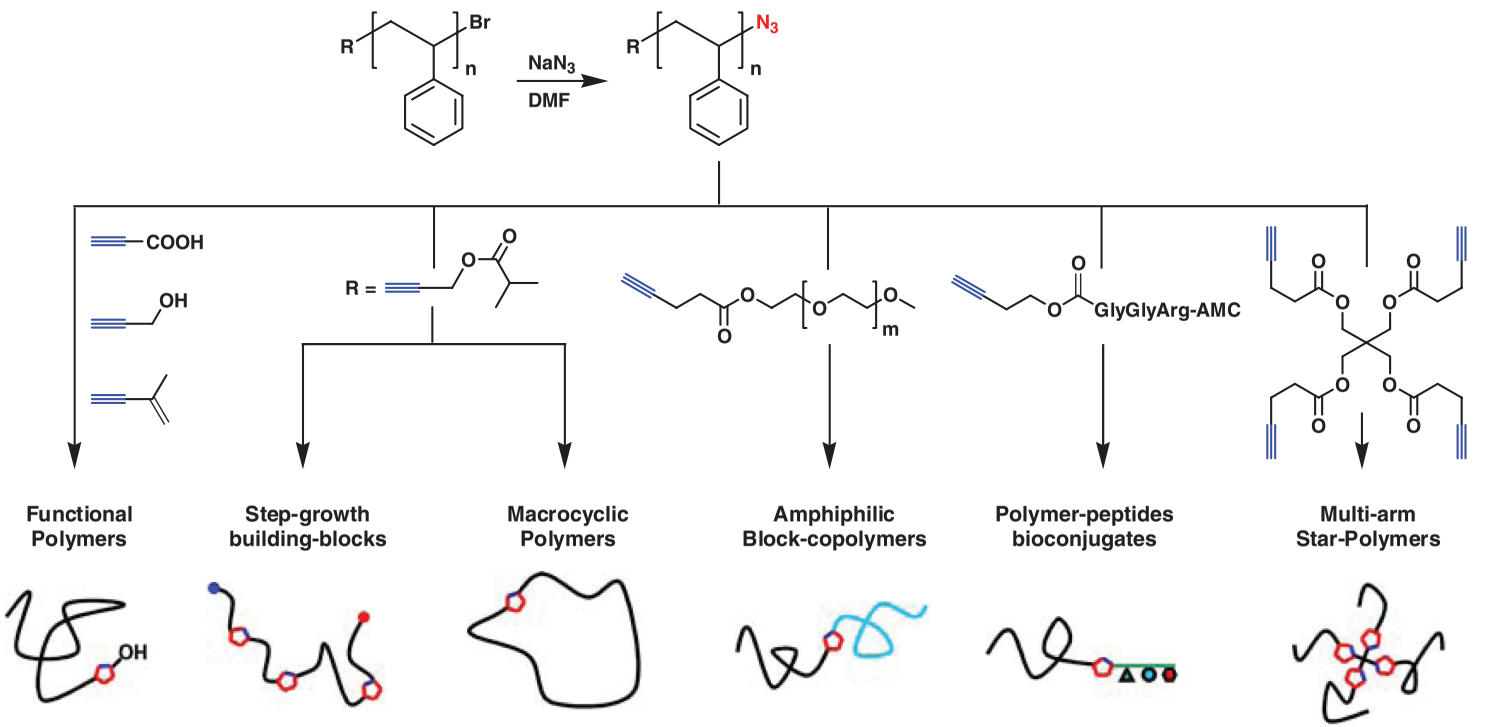
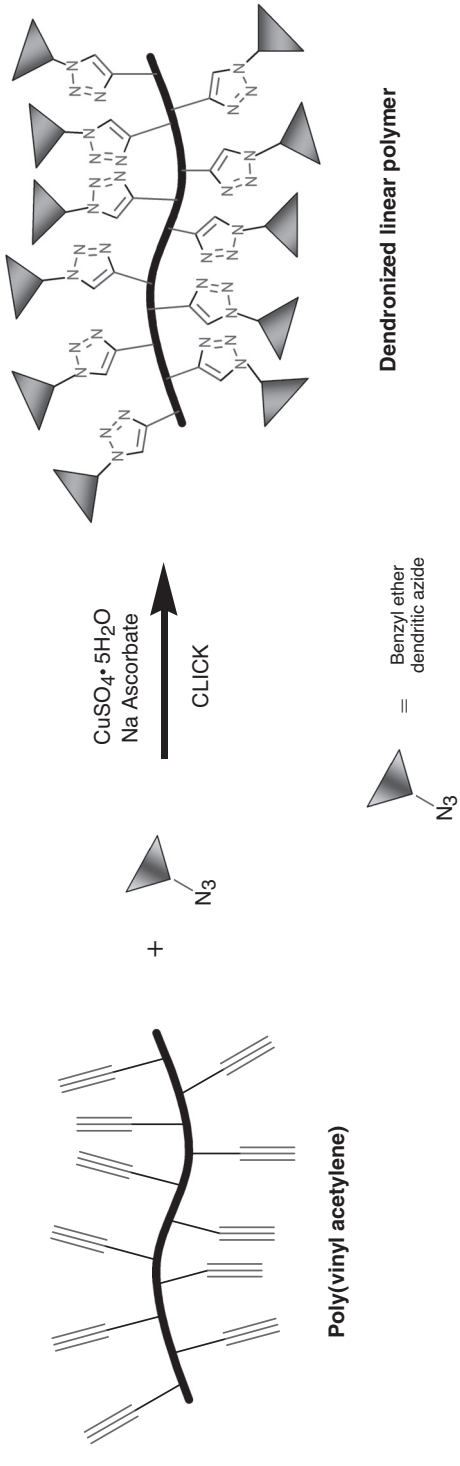
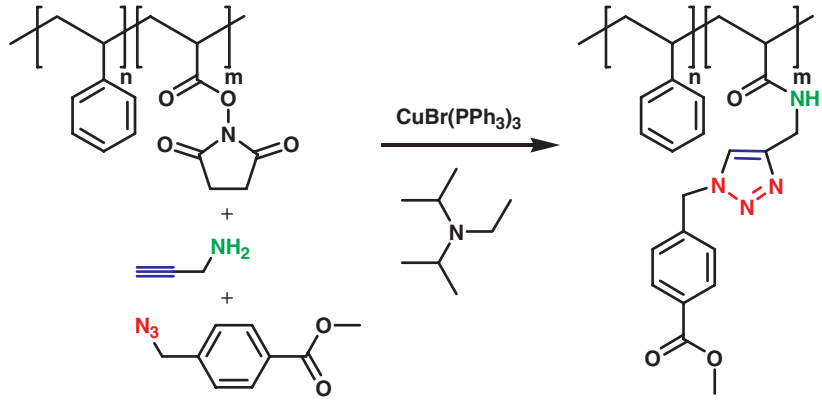


Figure 5.2 *Example macromolecular architectures accessible via the click modification of well-defined polystyrene prepared by ATRP.*[32,50,53,55,58,61] *Reprinted with permission from J.-F. Lutz, (2007), 1,3 Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science,* Angew. Chem. Int. Ed., ***46*** *(7), 1018–1025. Copyright 2007 Wiley-VCH.*



Scheme 5.2 *Synthesis of dendronized linear polymers by grafting-to via CuAAC.*[10]



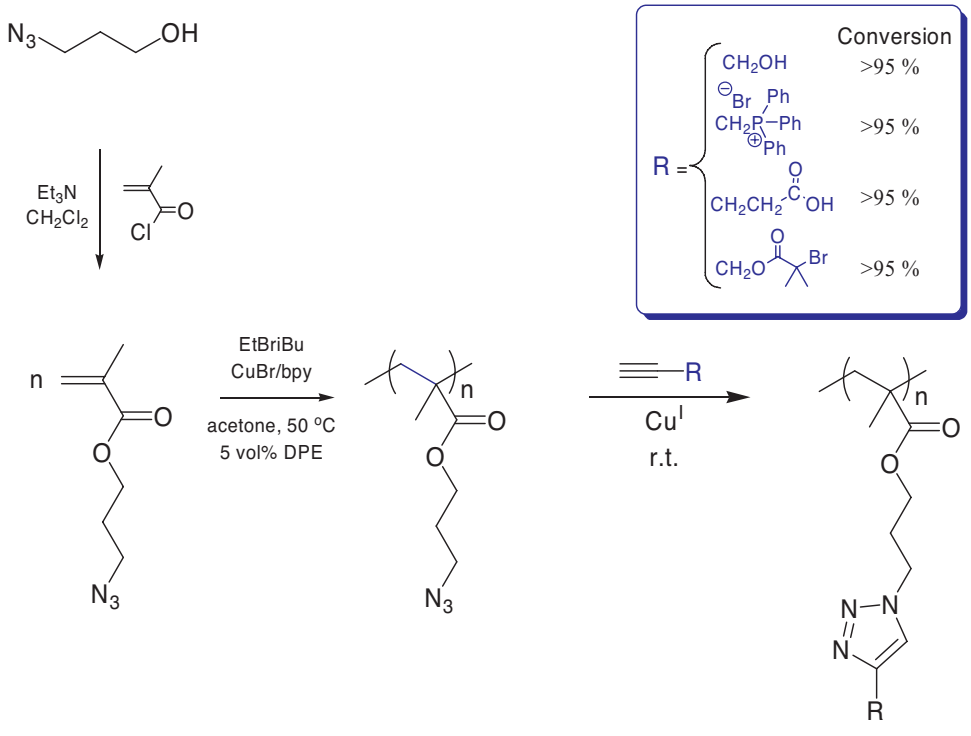
Scheme 5.3 *Example of cascade functionalization (i.e. amide formation and cycloaddition) of synthetic macromolecules.[14] Reprinted with permission from J.-F. Lutz, (2007), 1,3 Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science,* Angew. Chem. Int. Ed., ***46*** *(7), 1018–1025. Copyright 2007 Wiley-VCH.*

In addition to proving useful for the synthesis of pendant functional and telechelic macromolecules, click strategies have also been employed to build polymers with complex architectures. One of the first examples of architectural control using was reported by the team of Van Hest, which synthesized amphiphilic block copolymers by coupling azide- and alkyne- functional homopolymers (Figure 5.1).[55] Such ligation strategy has been shown to be quite efficient for linking segments of various natures. Barner-Kowollik and Stenzel later used a similar approach to couple azido- and alkyne-terminated polymers prepared by RAFT.[46] Self-ligation of a-alkyne-w-azido-telechelic polymers has proven to be an elegant strategy for preparing macrocycles, an often difficult synthetic challenge (Figure 5.1).[32,61,77] Additionally, other nonlinear architectures such as stars,[39,58] miktoarm stars,[57,65,78] graft copolymers,[64,79] networks[15,19] and hyperbranches[80] were constructed using click chemistry. All of these reports relied on CuAAC, with the exception of the approach reported by Yagci and coworkers for preparing graft copolymers by Diels–Alder chemistry.[79]

As mentioned previously, CuAAC has been used to prepare triazole-containing dendrimers. Alternatively, CuAAC can be used to functionalize the outer-shells of dendrimers or for linking preformed dendrons (e.g. polyamidoamine or polyester-based dendrons).[13,17,81,82] The latter is an interesting route for preparing unsymmetrical dendrimers with distinct hemispheres.[17]

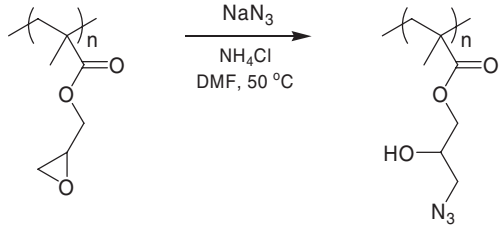
5.4 Polymer–Biomacromolecule Conjugation

The combination of macromolecules of both natural and synthetic origin is an appealing strategy to prepare hybrid materials that combine the advantages of standard synthetic polymers with advanced biological functions (e.g. molecular recognition, programmed self-organization, biological targeting, enzymatic activity).[83] Fortunately, the high degree of selectivity of click reactions makes them particularly attractive for modifying biomolecules



Scheme 5.4 *Click functionalization of azido-pendant polymers with various functional alkynes.*[56]

that often contain a wide range of reactive functionalities. CuAAC was reported to be an excellent method to modify biological polymers such as nucleic acids or polysaccharides (the strategies for functionalizing biopolymers are conceptually similar to those described above for synthetic polymers).[84–86] More specifically, CuAAC is a highly versatile tool for covalently functionalizing biological molecules with synthetic polymers.[87] For instance, several reports indicated that sequence-defined oligopeptides can be linked to synthetic macromolecules using click ligation.[37,50,63,88,89] In particular, Nolte *et al*. described the



Scheme 5.5 *Alternative strategy for preparing azido-pendant polymers by ring opening of epoxy functionalities in PGMA.*[76]

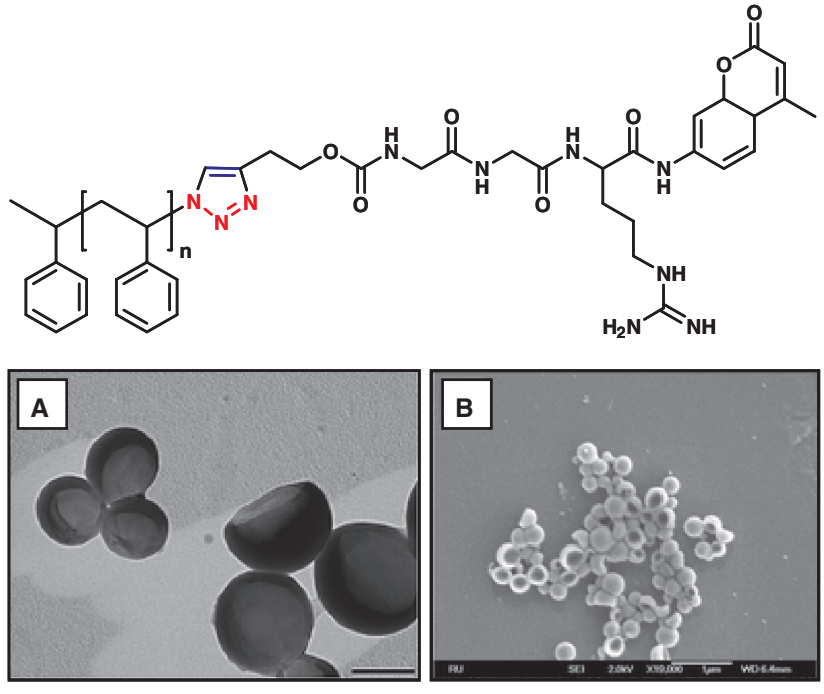


Figure 5.3 *Molecular structure of an amphiphilic polymer bioconjugate polystyrene-b-oligopeptide synthesized partly by click chemistry (top) and visualization by electron microscopy of its aggregates in water [bottom: TEM (A) and SEM (B)]. Reprinted with permission from A. J. Dirks* et al.*, (2005),* Chem. Commun.*, **33**, 4172–4174. Copyright 2005 The Royal Society of Chemistry.*

synthesis and self-assembly in aqueous medium of bio-hybrid amphiphiles composed of a hydrophobic polystyrene segment coupled to a hydrophilic oligopeptide (Figure 5.3). Lutz and coworkers studied the click cycloaddition of short peptides with well-defined synthetic polymers synthesized by ATRP (Figure 5.4).[63,89] Typically, the ω-bromine chain-ends of ATRP polymers were transformed into azides by nucleophilic substitution and subsequently reacted with alkyne-functionalized peptides. This allowed azido-terminated polystyrene to be coupled with an alkyne-labeled protein transduction domain, specifically the short arginine-rich sequence GRKKRRQRRR that is known for enhancing the intracellular delivery of low molecular weight drugs, proteins, oligonucleotides, and DNA plasmids (Figure 5.4).[89] A similar approach resulted in conjugation of poly[oligo(ethylene glycol) acrylate] to oligopeptides containing the particularly useful arginine–glycine–aspartic acid (RGD) sequence.[63] In these studies, the protecting side-groups of the amino acids were not cleaved after solid-phase synthesis to allow sufficient solubility of the peptide segment to facilitate size exclusion chromatography in organic eluents (Figure 5.4).

This precaution was not necessary for efficient synthesis since CuAAC is a highly chemoselective reaction. Indeed, unprotected peptides can be directly employed in click reactions.[37,50,88] Nevertheless, oligopeptides may also be deprotected after performing a

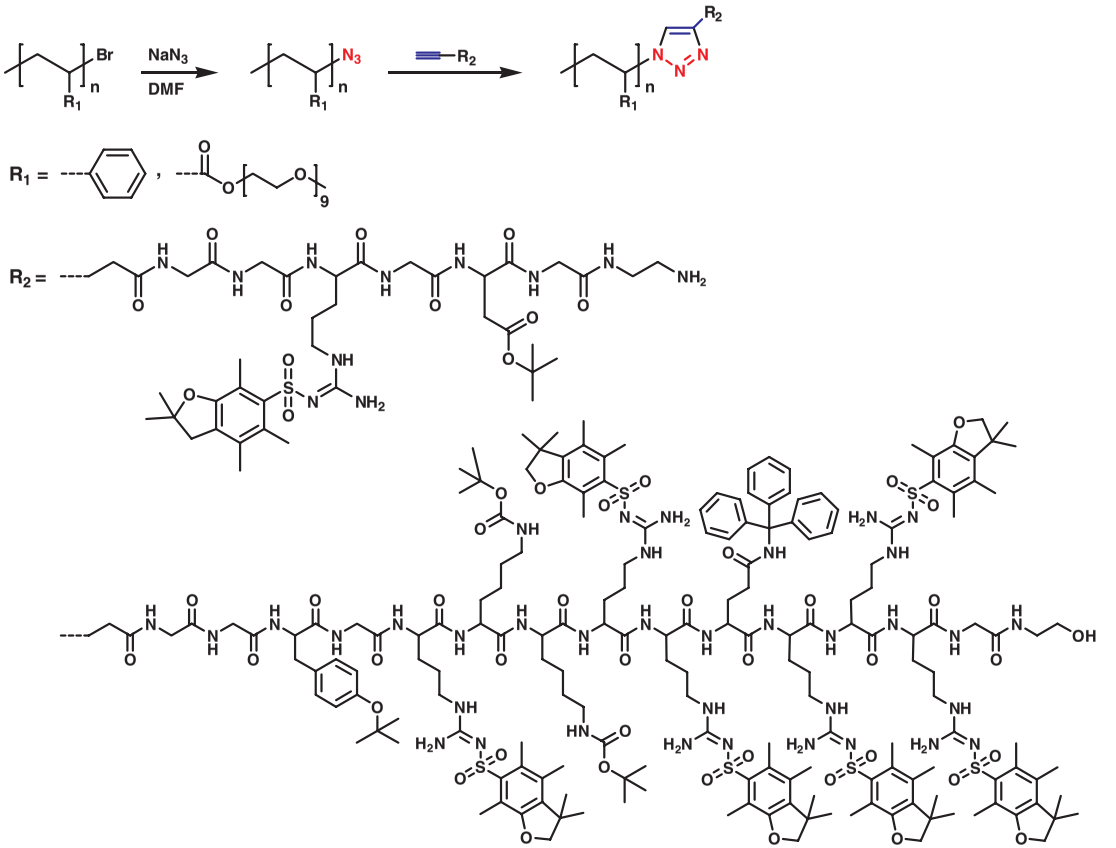
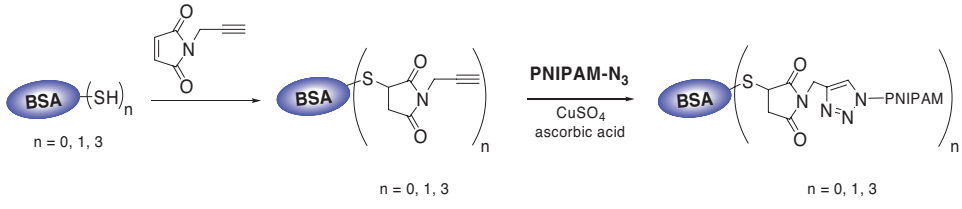


Figure 5.4 *Examples of click bioconjugation of synthetic polymers prepared by ATRP with sequence-defined oligopeptides.*[63,89] *Reprinted with permission from J.-F. Lutz, H. G. Börner, (2008), Modern trends in polymer bioconjugates design,* Progr. Polym. Sci., ***33*** *(1), 1–39. Copyright 2008 Elsevier.*

CuAAC as triazole rings are generally not damaged in concentrated trifluoroacetic acid.[16,20] Besides peptide bioconjugation, CuAAC has also been employed to functionalize linear or dendritic synthetic macromolecules with carbohydrates (e.g. mannose, galactose, fucose or lactose moieties)[17,60,90] or cancer-targeting folate ligands.[91,92]

More complex biological entities such as proteins, enzymes, viruses, bacteria or cells may also be functionalized by azide–alkyne chemistry.[93–98] For example, Finn and coworkers efficiently modified the surface of the cowpea mosaic virus using CuAAC.[96] Such reactions can be performed with experimental conditions compatible with biological environments (e.g. aqueous medium and room temperature). However, such chemical modifications of biological assemblies should be cautiously characterized since many reactants or catalysts may induce denaturation or disassembly.[96] Additionally, the team of Nolte reported interesting examples of protein conjugation [either transport proteins such as bovine serum albumin (BSA) or enzymes such as lipases] using CuAAC to couple polymers prepared by ATRP.[50,99] Sumerlin and coworkers later employed a similar concept by labeling BSA with an alkyne by reaction of its lone free cysteine with propargyl maleimide.[100] The resulting activated protein was coupled with azido-terminated PNIPAM, prepared by RAFT, to yield well-defined polymer–protein bioconjugates capable of temperature-responsive self-assembly (Scheme 5.6). Alternatively, Cornelissen and Nolte combined click chemistry and a cofactor reconstitution approach for building polymer-protein bioconjugates. Well-defined diblock copolymers PEG-*b*-PS were linked to the heme cofactor via azide–alkyne cycloaddition and subsequently reconstituted with either myoglobin or horse radish peroxidase (Figure 5.5).[101] This site-specific cofactor strategy was more versatile than the direct click coupling approach since various proteins can be functionalized with the same cofactor and there was no requirement for the transition metal catalysts in the presence of the proteins. Depending on the nature of the protein and the length of the polymer segment, a wide diversity of solution aggregate morphologies were accessible, including rods, vesicles, toroids, figure eight structures, stars and lamellar spheres.[101]

Many of the first reports detailing protein functionalization by CuAAC were by the teams of Schultz and Tirrell.[93,94,98,102] Their modification approaches relied on the use of nonnatural amino acids containing azido moieties (e.g. *para*-azidophenylalanine, azidohomoalanine, azidonorvaline or azidonorleucine), which were incorporated into



Scheme 5.6 *Polymer–protein bioconjugates prepared by CuAAC of alkyne-functionalized bovine serum albumin and azido-terminated PNIPAM.[100] Reprinted with permission from M. Li* et al.*, (2008), Responsive Polymer–Protein Bioconjugates Prepared by RAFT Polymerization and Copper-Catalyzed Azide–Alkyne Click Chemistry,* Macromol. Rapid Commun.*, **29**, 12–13, 1172–1176. Copyright 2008 Wiley-VCH.*

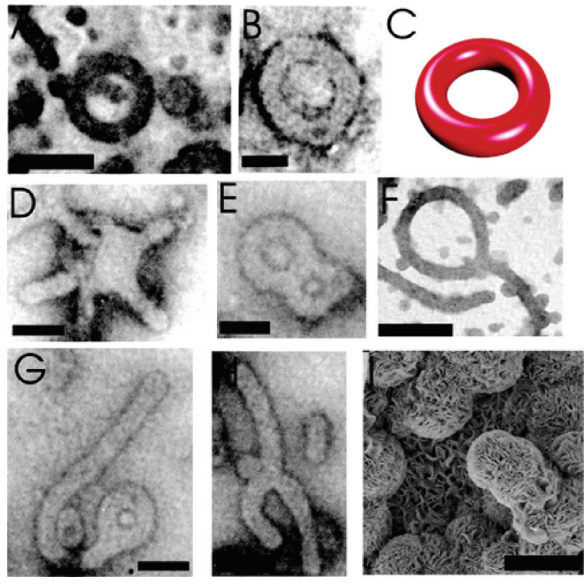


Figure 5.5 *Transmission electron microscopy images of solution aggregates composed of myoglobin conjugated with a* PS_{144}-b-PEG_{113} *block copolymer. (A, B) toroids, (C) schematic figure of a toroid, (D) octopi, (E) figure eights, and (F, G and H) micellar aggregates. (I) Scanning electron microscopy images of spherical aggregates consisting of lamellae. Bars represent 100 nm for A–H and 500 nm for I. Reprinted with permission from I. C. Reynhout,* et al.*, (2007), Self-assembled architectures from Biohybrid Triblock Copolymers,* J. Am. Chem. Soc.*,* ***129*** *(8), 2327–2332. Copyright 2007 American Chemical Society.*

mutant proteins by either genetic engineering or the metabolic replacement of a natural amino acid by a noncanonical substitute.[93,103] The resulting azido-functional proteins were subsequently reacted with various functional alkynes. Such ligations were also directly performed on cell surfaces after mutation of membrane proteins.[94,98] The click strategy of Tirrell *et al*. was also applied to distinguish recent proteins from old proteins in mammalian cells.[104] In this approach, only the newly synthesized proteins contained azidohomoalanine and were therefore selectively labeled by an alkyne affinity tag.

5.5 Functional Nanomaterials

In addition to proving highly relevant in the fields of polymer synthesis and polymer-modified biological materials, highly efficient and selective click reactions have made an enormous impact in nanoscience. As compared with macromolecular products prepared by covalent means, modern nanomaterials often rely on fragile supramolecular construction, and are therefore not easily purified or isolated. In this context, straightforward *in situ* reactions are invaluable in materials science. Thus, the versatility of CuAAC that allows it to be performed at room temperature, in multiple solvents, with stoichiometric amounts of

reactants and in the presence of other functional materials has led to it being an attractive tool for nanomaterial synthesis and modification.

CuAAC has proven to be a versatile tool for functionalizing or crosslinking colloidal objects such as polymer, lipid or inorganic nanoparticles.[11,105–109] Wooley *et al*. obtained shell-crosslinked polymeric micelles by reacting alkyne moieties present in the hydrophilic outer-shell of the micelles with azide-functional first generation dendrimers.[11] Schuber and Kros *et al*. reported elegant pathways for efficiently functionalizing lipid vesicles, employing alkyne-functional surfactants that were incorporated in the lipid bilayers and further reacted with azide-containing molecules.[105,107] The mild conditions used in the reaction allowed the lipid membranes to not be damaged during the functionalization process, and only the outer surfaces of the vesicles were modified. Additionally, a few routes were reported for the click functionalization of inorganic nanoparticles with polymers.[108,109] In particular, Turro and coworkers coated the surface of maghemite particles with either azide- or alkyne functional ligands, which were evidenced to be highly versatile platforms for further functionalization.[109] Besides spherical particles, anisotropic objects such as nanotubes were also modified by click chemistry. Adronov *et al*. reported an efficient route to functionalize single-walled carbon nanotubes with polymers to promote their colloidal dispersion in organic solvents (Figure 5.6).[52]

The azide–alkyne ligation has also been employed to prepare various types of bulk materials.[15,16,18,21,110] The teams of Hawker and Hilborn synthesized poly(ethylene glycol) or poly(vinyl alcohol) hydrogels that were crosslinked by triazoles.[15,110] Similar chemistry was used for attaching ligands onto gel bead surfaces to be utilized in affinity chromatography or electrophoresis.[16,21]

In addition to nanoparticles and nanotubes, CuAAC has proven to be an excellent tool for functionalizing flat surfaces. Collman and Chidsey were pioneers in this area and reported several important examples of self-assembled monolayers (SAMs) functionalized by triazole linkages.[111–114] Their work primarily focused on gold surfaces but was extended by other groups to different types of substrates such as silicon wafers or glass slides.[115,116]

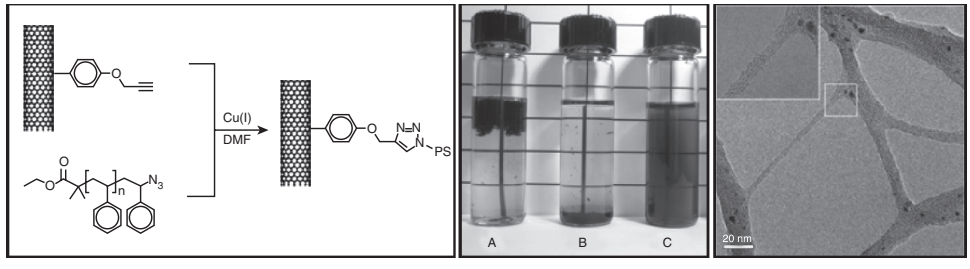


Figure 5.6 *Preparation of polystyrene-modified single walled-carbon nanotubes using click chemistry (left). The middle image shows THF solutions of either pristine (A), alkyne-functional (B) or polymer modified (C) carbon nanotubes. The right image shows transmission electron micrographs of the polymer-nanotubes organic/inorganic hybrid structures. Reprinted with permission from the H. Li,* et al.*, (2005), Functionalization of Single-Walled Carbon Nanotubes with Well-Defined Polystyrene by Click Coupling,* J. Am. Chem. Soc.*, **127** (41), 14518–14524. Copyright 2005 American Chemical Society.*

Overall, a very wide variety of functional molecules (synthetic or biological) have been already attached to SAMs using an azide–alkyne strategy, thus opening a wide range of opportunities for applications such as molecular electronic, catalysis or bio-sensors.[111,112,115–118] Besides the functionalization of SAMs, the Huisgen cycloaddition of alkynes and azides was also utilized for constructing polymer modified surfaces. For example, Caruso and coworkers described a click layer-by-layer approach using alternating layers of alkyne- and azide-functional polymers to construct defined polymer films on gold, silicon, and quartz surfaces.[44]

In addition to the traditional CuAAC conditions being employed for surface functionalization, Lahann *et al*. described the spatial control of click cycloadditions on flat surfaces using microcontact printing.[119,120] Defined biotin functional surface patterns were prepared using a poly(dimethylsiloxane) (PDMS) stamp that was inked with a solution of copper sulfate. The stamp was used to locally catalyze the cycloaddition of an adsorbed alkyne polymer and biotin azide.[119] Alternatively, Reinhoudt and coworkers used an alkyne-inked PDMS stamp for creating a variety of functional patterns on azido SAMs (Figure 5.7).[120] Interestingly, this approach did not necessitate a metal catalyst. Because of the high local concentration of reactants in the confined regions between the stamp and the substrate, the azide–alkyne cycloaddition occurred spontaneously within a short period of time.

5.6 Summary and Outlook

Since the renaissance of Huisgen's azide–alkyne cycloaddition was initiated by Meldal and Sharpless, CuAAC has become one of favorite ligation tools of polymer and materials scientists, proving particularly useful in areas as diverse as polymer synthesis, molecular biology and nanoelectronics. While not all of the examples above employ conditions that truly meet the criteria of click chemistry (especially the requirement for equal reactant stoichiometry), it is clear that CuAAC in particular has provided a versatile polymerization/functionalization procedure that is widely applicable, exceedingly efficient and highly orthogonal. Perhaps in no other area of the chemical sciences are these aspects as important as in polymer science. It may be true that the lasting legacy of the click concept in this area is that it has refocused the community to encourage the use of only the most efficient routes available to prepare complex macromolecular structures.

Nevertheless, there are still limitations of the CuAAC reaction that must be considered before considering its use. While perhaps mostly a problem of perception, the use of a copper-based catalyst could pose problems in some sensitive and highly regulated applications. Thus, the further development and enhanced applicability of optimized catalytic methods[59] or metal-free reactions are important issues in this field.[121–124] Similarly, while the majority of reports of click chemistry being used in polymer science have certainly involved the CuAAC reaction, many other reactions offer the efficiency and selectivity necessary to enhance synthetic capabilities. Thus, the search for and further development of alternative versatile reactions are necessary to provide a more complete toolbox of click reactions for the future.

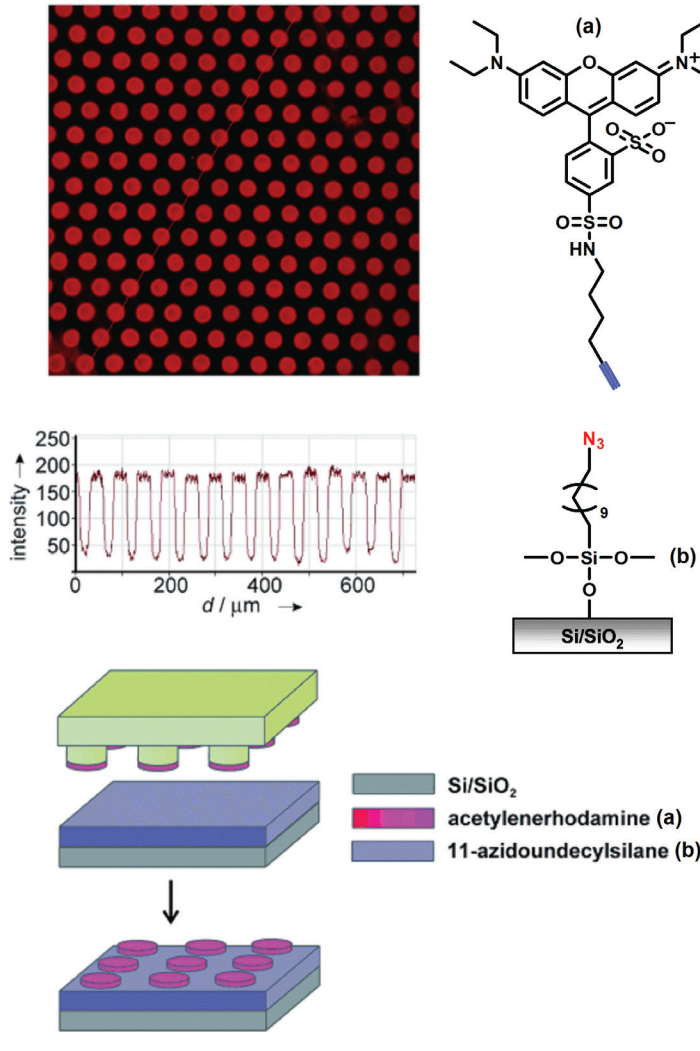


Figure 5.7 *Microcontact click printing in the absence of a copper catalyst. The image on top left shows the visualization of the surface pattern by fluorescence microscopy (image width is 700 mm). Reprinted with permission from D. I. Rozkiewicz,* et al.*, (2006), Click Chemistry by Microcontact Printing,* Angew. Chem.*, **45** (32), 5292–5296. Copyright 2006 Wiley-VCH.*

References

(1) Hawker, C. J., Wooley, K. L., (2005), *Science*, **309**, 1200.
(2) Kolb, H. C., Finn, M. G., Sharpless, K. B., (2001), *Angew. Chem. Int. Ed.*, **40**, 2004.
(3) Huisgen, R., (1963), *Angew. Chem. Int. Ed. Engl.*, **2**, 565.
(4) Huisgen, R., (1963), *Angew. Chem. Int. Ed. Engl.*, **2**, 633.

(5) Rostovtsev, V. V., Green, L. G., Fokin, V. V., Sharpless, K. B., (2002), *Angew. Chem. Int. Ed.*, **41**, 2596.
(6) Tornoe, C. W., Christensen, C., Meldal, M., (2002), *J. Org. Chem.*, **67**, 3057.
(7) Binder, W. H., Kluger, C., (2006), *Curr. Org. Chem.*, **10**, 1791.
(8) Wu, P., Feldman, A. K., Nugent, A. K., Hawker, C. J., Scheel, A., Voit, B., Pyun, J., Frechet, J. M. J., Sharpless, K. B., Fokin, V. V., (2004), *Angew. Chem. Int. Ed.*, **43**, 3928.
(9) Díaz, D. D., Punna, S., Holzer, P., McPherson, A. K., Sharpless, K. B., Fokin, V. V., Finn, M. G., (2004), *J. Polym. Sci. Part A: Polym. Chem.*, **42**, 4392.
(10) Helms, B., Mynar, J. L., Hawker, C. J., Frechet, J. M. J., (2004), *J. Am. Chem. Soc.*, **126**, 15020.
(11) Joralemon, M. J., O'Reilly, R. K., Hawker, C. J., Wooley, K. L., (2005), *J. Am. Chem. Soc.*, **127**, 16892.
(12) Joralemon, M. J., O'Reilly, R. K., Matson, J. B., Nugent, A. K., Hawker, C. J., Wooley, K. L., (2005), *Macromolecules*, **38**, 5436.
(13) Malkoch, M., Schleicher, K., Drockenmuller, E., Hawker, C. J., Russell, T. P., Wu, P., Fokin, V. V., (2005), *Macromolecules*, **38**, 3663.
(14) Malkoch, M., Thibault, R. J., Drockenmuller, E., Messerschmidt, M., Voit, B., Russell, T. P., Hawker, C. J., (2005), *J. Am. Chem. Soc.*, **127**, 14942.
(15) Malkoch, M., Vestberg, R., Gupta, N., Mespouille, L., Dubois, P., Mason, A. F., Hedrick, J. L., Liao, Q., Frank, C. W., Kingsbury, K., Hawker, C. J., (2005), *Chem. Commun.*, 2774.
(16) Punna, S., Kaltgrad, E., Finn, M. G., (2005), *Bioconjugate Chem.*, **16**, 1536.
(17) Wu, P., Malkoch, M., Hunt, J. N., Vestberg, R., Kaltgrad, E., Finn, M. G., Fokin, V. V., Sharpless, K. B., Hawker, C. J., (2005), *Chem. Commun.*, 5775.
(18) Diaz, D. D., Rajagopal, K., Strable, E., Schneider, J., Finn, M. G., (2006), *J. Am. Chem. Soc.*, **128**, 6056.
(19) Johnson, J. A., Lewis, D. R., Diaz, D. D., Finn, M. G., Koberstein, J. T., Turro, N. J., (2006), *J. Am. Chem. Soc.*, **128**, 6564.
(20) Li, C., Finn, M. G., (2006), *J. Polym. Sci. Part A: Polym. Chem.*, **44**, 5513.
(21) Slater, M., Snauko, M., Svec, F., Frechet, J. M. J., (2006), *Anal. Chem.*, **78**, 4969.
(22) Thibault, R. J., Takizawa, K., Lowenheilm, P., Helms, B., Mynar, J. L., Frechet, J. M. J., Hawker, C. J., (2006), *J. Am. Chem. Soc.*, **128**, 12084.
(23) Binder, W. H., Sachsenhofer, R., (2007), *Macromol. Rapid Commun.*, **28**, 15.
(24) Evans, R. A., (2007), *Aust. J. Chem.*, **60**, 384.
(25) Lutz, J.-F., (2007), *Angew. Chem. Int. Ed.*, **46**, 1018.
(26) Lutz, J.-F., Schlaad, H., (2008), *Polymer*, **49**, 817.
(27) van Steenis, D. J. V. C., David, O. R. P., van Strijdonck, G. P. F., van Maarseveen, J. H., Reek, J. N. H., (2005), *Chem. Commun.*, 4333.
(28) Dichtel, W. R., Miljanic, O. S., Spruell, J. M., Heath, J. R., Stoddart, J. F., (2006), *J. Am. Chem. Soc.*, **128**, 10388.
(29) Zhu, Y., Huang, Y., Meng, W.-D., Li, H., Qing, F.-L., (2006), *Polymer*, **47**, 6272.
(30) Binauld, S., Boisson, F., Hamaide, T., Jean-Pierre Pascault, Drockenmuller, E., Fleury, E., (2008), *J. Polym. Sci. Part A: Polym. Chem.*, **46**, 5506.
(31) Tsarevsky, N. V., Bernaerts, K. V., Dufour, B., Du Prez, F. E., Matyjaszewski, K., (2004), *Macromolecules*, **37**, 9308.
(32) Tsarevsky, N. V., Sumerlin, B. S., Matyjaszewski, K., (2005), *Macromolecules*, **38**, 3558.
(33) Golas, P. L., Tsarevsky, N. V., Sumerlin, B. S., Matyjaszewski, K., (2007), *Aust. J. Chem.*, 60.
(34) Bakbak, S., Leech, P. J., Carson, B. E., Saxena, S., King, W. P., Bunz, U. H. F., (2006), *Macromolecules*, **39**, 6793.
(35) Matyjaszewski, K., (2005), *Prog. Polym. Sci.*, **30**, 858.
(36) Sumerlin, B. S., Tsarevsky, N. V., Gao, H., Golas, P., Louche, G., Lee, R. Y., Matyjaszewski, K., (2006), Click functionalization of well-defined copolymers prepared by atom transfer radical polymerization. In *Controlled/Living Radical Polymerization: From Synthesis to Materials*, ACS: Washington, DC, Vol. 944.
(37) Parrish, B., Breitenkamp, R., Emrick, T., (2005), *J. Am. Chem. Soc.*, **127**, 7404.

(38) Riva, R., Schmeits, S., Stoffelbach, F., Jerome, C., Jerome, R., Lecomte, P., (2005), *Chem. Commun.*, 5334.
(39) Hoogenboom, R., Moore, B. C., Schubert, U. S., (2006), *Chem. Commun.*, 4010.
(40) Luxenhofer, R., Jordan, R., (2006), *Macromolecules*, **39**, 3509.
(41) Binder, W. H., Kluger, C., (2004), *Macromolecules*, **37**, 9321.
(42) Englert, B. C., Bakbak, S., Bunz, U. H. F., (2005), *Macromolecules*, **38**, 5868.
(43) Wang, X.-Y., Kimyonok, A., Weck, M., (2006), *Chem. Commun.*, 3933.
(44) Such, G. K., Quinn, J. F., Quinn, A., Tjipto, E., Caruso, F., (2006), *J. Am. Chem. Soc.*, **128**, 9318.
(45) Gondi, S. R., Vogt, A. P., Sumerlin, B. S., (2007), *Macromolecules*, **40**, 474.
(46) Quémener, D., Davis, T. P., Barner-Kowollik, C., Stenzel, M. H., (2006), *Chem. Commun.*, 5051.
(47) O'Reilly, R. K., Joralemon, M. J., Hawker, C. J., Wooley, K. L., (2006), *Chem. Eur. J.*, **12**, 6776.
(48) O'Reilly, R. K., Joralemon, M. J., Hawker, C. J., Wooley, K. L., (2006), *J. Polym. Sci. Part A: Polym. Chem.*, **44**, 5203.
(49) Li, M., De, P., Gondi, S. R., Sumerlin, B. S., (2008), *J. Polym. Sci. Part A: Polym. Chem.*, **46**, 5093.
(50) Dirks, A. J., vanBerkel, S. S., Hatzakis, N. S., Opsten, J. A., vanDelft, F. L., Cornellissen, J. J. L. M., Rowan, A. E., vanHest, J. C. M., Rutjes, F. P. J. T., Nolte, R. J. M., (2005), *Chem. Commun.*, **333**, 4172.
(51) Gao, H., Louche, G., Sumerlin, B. S., Jahed, N., Golas, P., Matyjaszewski, K., (2005), *Macromolecules*, **38**, 8979.
(52) Li, H., Cheng, F., Duft, A. M., Adronov, A., (2005), *J. Am. Chem. Soc.*, **127**, 14518.
(53) Lutz, J.-F., Börner, H. G., Weichenhan, K., (2005), *Macromol. Rapid Commun.*, **26**, 514.
(54) Mantovani, G., Ladmiral, V., Tao, L., Haddleton, D. M., (2005), *Chem. Commun.*, 2089.
(55) Opsteen, J. A., van Hest, J. C. M., (2005), *Chem. Commun.*, 57.
(56) Sumerlin, B. S., Tsarevsky, N. V., Louche, G., Lee, R. Y., Matyjaszewski, K., (2005), *Macromolecules*, **38**, 7540.
(57) Altintas, O., Hizal, G., Tunca, U., (2006), *J. Polym. Sci. Part A: Polym. Chem.*, **44**, 5699.
(58) Gao, H., Matyjaszewski, K., (2006), *Macromolecules*, **39**, 4960.
(59) Golas, P., Tsarevsky, N. V., Sumerlin, B. S., Matyjaszewski, K., (2006), *Macromolecules*, **39**, 6451.
(60) Ladmiral, V., Mantovani, G., Clarkson, G. J., Cauet, S., Irwin, J. L., Haddleton, D. M., (2006), *J. Am. Chem. Soc.*, **128**, 4823.
(61) Laurent, B. A., Grayson, S. M., (2006), *J. Am. Chem. Soc.*, **128**, 4238.
(62) Liu, Q., Chen, Y., (2006), *J. Polym. Sci. Part A: Polym. Chem.*, **44**, 6103.
(63) Lutz, J.-F., Börner, H. G., Weichenhan, K., (2006), *Macromolecules*, **39**, 6376.
(64) Vogt, A. P., Sumerlin, B. S., (2006), *Macromolecules*, **39**, 5286.
(65) Whittaker, M. R., Urbani, C. N., Monteiro, M. J., (2006), *J. Am. Chem. Soc.*, **128**, 11360.
(66) Golas, P. L., Matyjaszewski, K., (2007), *QSAR Comb. Sci.*, **26**, 1116.
(67) Matyjaszewski, K., Xia, J., (2001), *Chem. Rev.*, **101**, 2921.
(68) Coessens, V., Matyjaszewski, K., (1999), *J. Macromol. Sci., Pure Appl. Chem.*, **A36**, 667.
(69) Coessens, V., Nakagawa, Y., Matyjaszewski, K., (1998), *Polym. Bull.*, **40**, 135.
(70) Coessens, V., Pintauer, T., Matyjaszewski, K., (2001), *Prog. Polym. Sci.*, **26**, 337.
(71) Geng, J., Lindqvist, J., Mantovani, G., Haddleton, D. M., (2008), *Angew. Chem. Int. Ed.*, **47**, 4180.
(72) Chan, T. R., Hilgraf, R., Sharpless, K. B., Fokin, V. V., (2004), *Org. Lett.*, **6**, 2853.
(73) Rodionov, V. O., Fokin, V. V., Finn, M. G., (2005), *Angew. Chem. Int. Ed.*, **44**, 2210.
(74) Hassner, A., Stern, M., *Angew. Chem. Int. Ed. Engl.* (1986), **25**, 478.
(75) Bräse, S., Gil, C., Knepper, K., Zimmermann, V., (2005), *Angew. Chem. Int. Ed.*, **44**, 5188.
(76) Tsarevsky, N. V., Bencherif, S. A., Matyjaszewski, K., (2007), *Macromolecules*, **40**, 4439.
(77) Goldmann, A. S., Quemener, D., Millard, P.-E., Davis, T. P., Stenzel, M. H., Barner-Kowollik, C., Mueller, A. H. E., (2008), *Polymer*, **49**, 2274.
(78) Rao, J., Zhang, Y., Zhang, J., Liu, S., (2008), *Biomacromolecules*, **9**, 10.1021/bm800462q.

(79) Gacal, B., Durmaz, H., Tasdelen, M. A., Hizal, G., Tunca, U., Yagci, Y., Demirel, A. L., (2006), *Macromolecules*, **39**, 5330.
(80) Vogt, A. P., Gondi, S. R., Sumerlin, B. S., (2007), *Aust. J. Chem.*, **60**, 396.
(81) Lee, J. W., Kim, J. H., Kim, B.-K., (2005), *Tetrahedron Lett.*, **47**, 2683.
(82) Lee, J. W., Kim, J. H., Kim, B.-K., Kim, J. H., Shin, W. S., Jin, S.-H., (2006), *Tetrahedron*, **62**, 9193.
(83) Lutz, J.-F., Börner, H. G., (2008), *Prog. Polym. Sci.*, **33**, 1.
(84) Seo, T. S., Li, Z., Ruparel, H., Ju, J., (2003), *J. Org. Chem.*, **68**, 609.
(85) Burley, G. A., Gierlich, J., Mofid, M. R., Nir, H., Tal, S., Eichen, Y., Carell, T., (2006), *J. Am. Chem. Soc.*, **128**, 1398.
(86) Liebert, T., Hänsch, C., Heinze, T., (2006), *Macromol. Rapid Commun.*, **27**, 208.
(87) Droumaguet, B. L., Velonia, K., (2008), *Macromol. Rapid Commun.*, **29**, 1073–1089.
(88) Rijkers, D. T. S., van Esse, G. W., Merkx, R., Brouwer, A. J., Jacobs, H. J. F., Pieters, R. J., Liskamp, R. M. J., (2005), *Chem. Commun.*, 581.
(89) Lutz, J.-F., Börner, H. G., Weichenhan, K., (2007), *Aust. J. Chem.*, **60**, 410.
(90) Fernandez-Megia, E., Correa, J., Rodriguez-Meizoso, I., Riguera, R., (2006), *Macromolecules*, **39**, 2113.
(91) McCormick, C. L., Sumerlin, B. S., Lokitz, B. S., Stempka, J. E., (2008), *Soft Matter*, DOI: 10.1039/b719577j.
(92) De, P., Gondi, S. R., Sumerlin, B. S., (2008), *Biomacromolecules*, **9**, 1064.
(93) Deiters, A., Cropp, T. A., Mukherji, M., Chin, J. W., Anderson, J. C., Schultz, P. G., (2003), *J. Am. Chem. Soc.*, **125**, 11782.
(94) Link, A. J., Tirrell, D. A., (2003), *J. Am. Chem. Soc.*, **125**, 11164.
(95) Speers, A. E., Adam, G. C., Cravatt, B. F., (2003), *J. Am. Chem. Soc.*, **125**, 4686.
(96) Wang, Q., Chan, T. R., Hilgraf, R., Fokin, V. V., Sharpless, K. B., Finn, M. G., (2003), *J. Am. Chem. Soc.*, **125**, 3192.
(97) Agard, N. J., Prescher, J. A., Bertozzi, C. R., (2004), *J. Am. Chem. Soc.*, **126**, 15046.
(98) Link, A. J., Vink, M. K. S., Tirrell, D. A., (2004), *J. Am. Chem. Soc.*, **126**, 10598.
(99) Brennan, J. L., Hatzakis, N. S., Tshikhudo, T. R., Dirvianskyite, N., Razumas, V., Patkar, S., Vind, J., Svendsen, A., Nolte, R. J. M., Rowan, A. E., Brust, M., (2006), *Bioconjugate Chem.*, **17**, 1373.
(100) Li, M., De, P., Gondi, S. R., Sumerlin, B. S., (2008), *Macromol. Rapid Commun.*, **29**, 1172.
(101) Reynhout, I. C., Cornelissen, J. J. L. M., Nolte, R. J. M., (2007), *J. Am. Chem. Soc.*, **129**, 2327.
(102) Deiters, A., Cropp, T. A., Summerer, D., Mukherji, M., Schultz, P. G., (2004), *Bioorg. Med. Chem. Lett.*, **14**, 5743.
(103) Kiick, K. L., Saxon, E., Tirrell, D. A., Bertozzi, C. R., (2002), *Proc. Natl Aacad. Sci. USA*, **99**, 19.
(104) Dieterich, D. C., Link, A. J., Graumann, J., Tirrell, D. A., Schuman, E. M., (2006), *Proc. Natl Aacad. Sci. USA*, **103**, 9482.
(105) Cavalli, S., Tipton, A. R., Overhand, M., Kros, A., (2006), *Chem. Commun.*, 3193.
(106) O'Reilly, R. K., Joralemon, M. J., Hawker, C. J., Wooley, K. L., (2006), *Chem. Eur. J.*, **12**, 6776.
(107) Said Hassane, F., Frisch, B., Schuber, F., (2006), *Bioconjugate Chem.*, **17**, 849.
(108) Sun, E. Y., Josephson, L., Weissleder, R., (2006), *Molecular Im.*, **5**, 122.
(109) White, M. A., Johnson, J. A., Koberstein, J. T., Turro, N. J., (2006), *J. Am. Chem. Soc.*, **128**, 11356.
(110) Ossipov, D. A., Hilborn, J., (2006), *Macromolecules*, **39**, 1709.
(111) Collman, J. P., Devaraj, N. K., Chidsey, C. E. D., (2004), *Langmuir*, **20**, 1051.
(112) Devaraj, N. K., Miller, G. P., Ebina, W., Kakaradov, B., Collman, J. P., Kool, E. T., Chidsey, C. E. D., (2005), *J. Am. Chem. Soc.*, **127**, 8600.
(113) Collman, J. P., Devaraj, N. K., Eberspacher, T. P. A., Chidsey, C. E. D., (2006), *Langmuir*, **22**, 2457.
(114) Devaraj, N. K., Decreau, R. A., Ebina, W., Collman, J. P., Chidsey, C. E. D., (2006), *J. Phys. Chem. B.*, **110**, 15955.
(115) Lummerstorfer, T., Hoffmann, H., (2004), *J. Phys. Chem. B.*, **108**, 3963.

(116) Sun, X.-L., Stabler, C. L., Cazalis, C. S., Chaikof, E. L., (2006), *Bioconjugate Chem.*, **17**, 52.
(117) Lee, J. K., Chi, Y. S., Choi, I. S., (2004), *Langmuir*, **20**, 3844.
(118) Zhang, Y., Luo, S., Tang, Y., Yu, L., Hou, K.-Y., Cheng, J.-P., Zeng, X., Wang, P. G., (2006), *Anal. Chem.*, **78**, 2001.
(119) Nandivada, H., Chen, H.-Y., Bondarenko, L., Lahann, J., (2006), *Angew. Chem. Int. Ed.*, **45**, 3360.
(120) Rozkiewicz, D. I., Janacuteczewski, D., Verboom, W., Ravoo, B. J., Reinhoudt, D. N., (2006), *Angew. Chem. Int. Ed.*, **45**, 5292.
(121) Baskin, J. M., Prescher, J. A., Laughlin, S. T., Agard, N. J., Chang, P. V., Miller, I. A., Lo, A., Codelli, J. A., Bertozzi, C. R., (2007), *Proc. Natl Acad. Sci. USA*, **104**, 16793.
(122) Baskin, J. M., Bertozzi, C. R., (2007), *QSAR Comb. Sci.*, **26**, 1211.
(123) Sletten, E. M., Bertozzi, C. R., (2008), *Org. Lett.*, **10**, 3097.
(124) Johnson, J. A., Baskin, J. M., Bertozzi, C. R., Koberstein, J. T., Turro, N. J., (2008), *Chem. Commun.*, 3064.