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Macromolecular Engineering through Click Chemistry and Other Efficient Transformations

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ABSTRACT: Precision synthesis of advanced polymeric materials requires efficient, robust, and facile chemical reactions. Paradoxically, the synthesis of increasingly intricate macromolecular structures generally benefits from exploitation of the simplest reactions available. This idea, combined with requirements of high efficiency, orthogonality, and simplified purification procedures, has led to the rapid adoption of "click chemistry" strategies in the field of macromolecular engineering. This Perspective provides context as to why these newly developed or recently reinvigorated reactions have been so readily embraced for the preparation of polymers with advanced macromolecular topologies, increased functionality, and unique properties. By highlighting important examples that rely on click chemistry techniques, including copper(I)-catalyzed and strain-promoted azide−alkyne cycloadditions, Diels−Alder cycloadditions, and thiol−ene reactions, among others, we hope to provide a succinct overview of the current state of the art and future impact these strategies will have on polymer chemistry and macromolecular engineering.

Introduction

More tools than ever are readily available to engineer well-defined macromolecules with increasing complexity and functionality. Recent advances in living/controlled polymerization techniques have facilitated access to (co)polymers with controlled molecular weights, complex architectures, and precisely positioned functional groups. However, even the most robust polymerization methods are not sufficient for the synthesis of many interesting macromolecules. Postpolymerization modification is still an essential method of incorporating functionality not compatible with polymerization, characterization, or processing conditions. Polymer−polymer conjugation is often the only viable means to prepare complex chain topologies or copolymers that contain monomer units not polymerizable by the same methods. However, transformations on polymers are often inefficient and may lead to side reactions with other groups within the polymer. Therefore, efficient and specific reactions are needed to ensure successful postpolymerization modification.

Structure and function are intimately related in the field of polymer chemistry. Subtle manipulation of functional groups and chain architecture gives rise to new materials with dramatically different properties. While a plethora of synthetic strategies exists for the preparation of new organic molecules, not all of these are easily applied to polymers in a well-controlled and facile manner. Many of the most precise chemistries are limited by scarcity of starting materials, experimental complexity, or a lack of specificity. Since structure begets properties, a primary goal during polymer synthesis and functionalization should be to arrive at the necessary structure by the simplest, cleanest, and most efficient means possible. What is needed is not an ever-expanding library of synthetic strategies that can be employed in each specific instance; rather, it is advantageous to have a group of a few select reactions that, when strategically chosen, can facilitate access to nearly any polymeric structure. This idea of *facilitation*—the act of making easy—is the essence of the "click chemistry" concept introduced by Sharpless and colleagues in 2001.[1] One of the central tenants of the click philosophy is the deliberate avoidance of sophisticated synthetic techniques in favor of methods that are modular, reliable, and easy to implement.[2] Click reactions are highly efficient and specific reactions capable of being conducted in a range of environments under relatively mild conditions. Any byproducts should be benign, and the reactions should be fast, tolerant to functional groups, wide in scope, and applicable in a modular manner. Only the very best reactions meet these criteria.

Since their development, click chemistry strategies have been rapidly integrated into the field of macromolecular engineering. It could be argued that the marriage of click chemistry with polymer science is a tenuous one, a temporary movement relying on revisiting and rebranding well-known reactions to capitalize on a fashionable concept. Such an assessment ignores the more philosophical aspect of click chemistry as a call to refocus on simplified and efficient techniques, without which the synthesis of many new materials might be significantly slowed or unnecessarily complicated.[3]

The purpose of this Perspective is not to comprehensively summarize all of the work to date on the application of click chemistry in polymer science, as there are several excellent reviews on this topic.[3−22] Rather, it is our goal to provide context as to why the philosophy and methods of these newly developed or recently reinvigorated reactions have been so readily adopted within the field of macromolecular engineering. While simplicity lies at the core of the click concept, likely the advantages of enhanced efficiency and specificity have allowed the click methods to so vibrantly flourish. The discussion that follows will describe how these two specific benefits relate to macromolecular engineering and then overview the most common click reactions with several examples of how each facilitates access to well-known polymers or allows the preparation of previously inaccessible materials.

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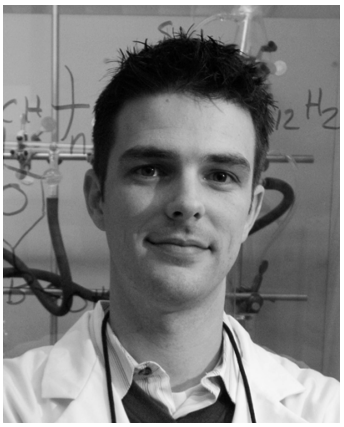

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Andrew P. Vogt received his Ph.D. in Chemistry from Southern Methodist University in Dallas, TX, under the direction of Prof. Brent S. Sumerlin. His dissertation research focused on combining controlled radical polymerization and click chemistry techniques for the creation of well-defined polymeric materials. Dr. Vogt received his B.S. in Chemistry from Texas Lutheran University in Seguin, TX, under the guidance of Prof. John V. McClusky while investigating montmorillonite/polyurethane composites. Currently, he is a postdoctoral research fellow in the Centre for Nanoscale Science and Technology in the School of Chemistry and Physics at Flinders University in Adelaide, Australia. His current research involves carbon nanotube/polymer nanocomposite fabrication and analysis.

Enhanced Efficiency

Enhancing the efficiency of chemical transformations is arguably more important in reactions of polymers than those of small molecules. In many cases, the distinctive features of macromolecules (e.g., high molecular weight, multiplicity of functional groups, etc.) complicate the direct application of standard organic chemistry techniques to polymer synthesis.[23] Inefficient small molecule reactions require separation of product from unreacted starting materials, generally by chromatography, crystallization, precipitation, etc. However, if the functionalization reaction is intended to take place at multiple sites within a single macromolecule, inefficiency leads to a final product in which reacted units are covalently linked to unreacted units. Therefore, no simple method of separation leads to a pure product. In this case, the only method to ensure product purity is to achieve quantitative transformations.

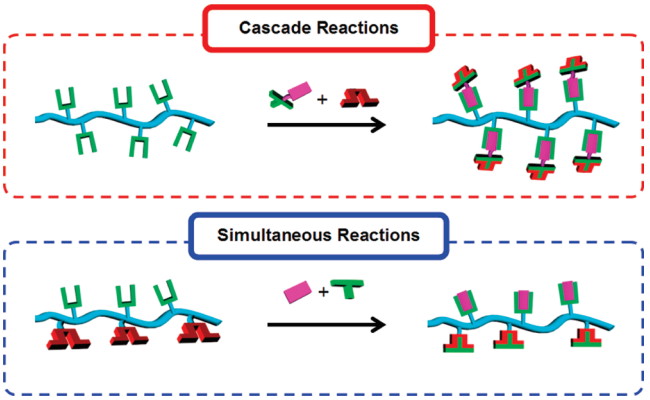


Figure 1. Complex macromolecules typically requiring several reactions steps can be prepared by cascade or simultaneous reactions with one-pot procedures because of the orthogonality of many click reactions.

Efficiency is also important in polymer functionalization even when only a single site of transformation is desired. For instance, a significant portion of the literature describing the use of click chemistry to functionalize polymers involves the modification of polymer end groups. High efficiency is especially important in this case, as kinetic limitations can lead to low yields because of the low concentration and reactivity of end groups present in linear high molecular weight chains. In this case, purification can again be complicated since there are currently no viable large-scale methods that can successfully separate macromolecules based solely on a difference in end-group identity (reacted versus unreacted).

Enhanced Specificity/Orthogonality

Even in small molecule organic chemistry, reaction specificity is an important concern. Because the functional groups present in a molecule generally affect its potential applications, it is important to carefully incorporate or preserve such moieties as needed. Many reactions in nature are inherently specific, but this level of orthogonality is difficult to reproduce in synthetic systems. Copolymers with multiple types of monomer units having widely varying functionality must be reacted carefully to avoid nonspecific functionalization. If multiple transformations on a single polymer are desired, an ideal click functionalization procedure would allow simultaneous parallel or cascade reactions to occur in one-pot with little or no cross-functionalization or interference (Figure 1).[10,24−28] The capability to prepare complex macromolecular structures in fewer individual reaction/purification steps holds significant promise for increased synthetic productivity. Additionally, specificity is especially important in reactions that involve at least one biological component. A diverse selection of functional groups is present in proteins, peptides, etc., and strategies for the modification of such biological molecules with polymers should proceed with high fidelity to limit side reactions.

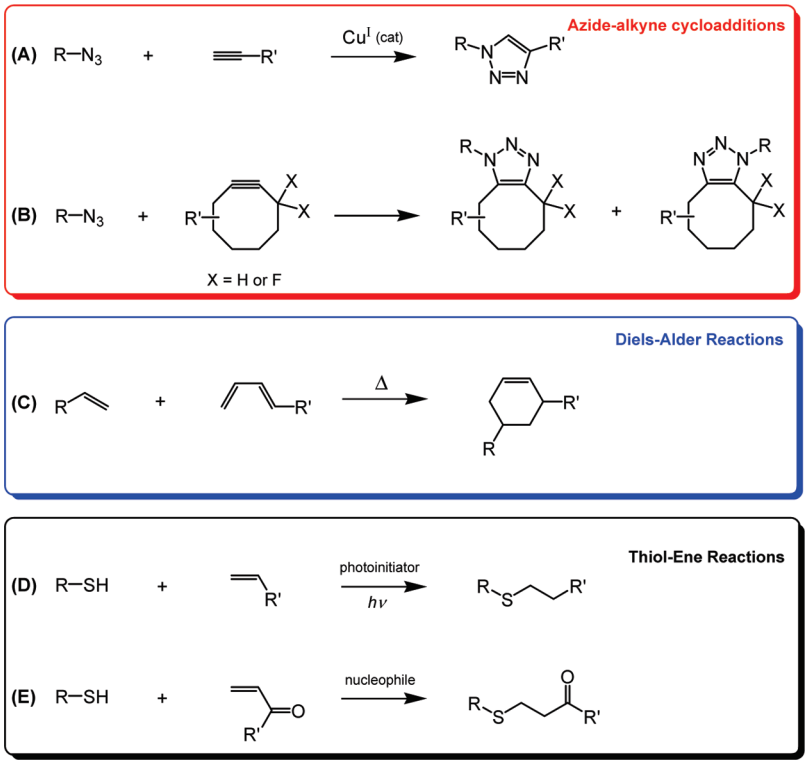


Figure 2. Examples of click reactions commonly employed in polymer synthesis and functionalization.

Common Click Reactions Employed in Polymer Science

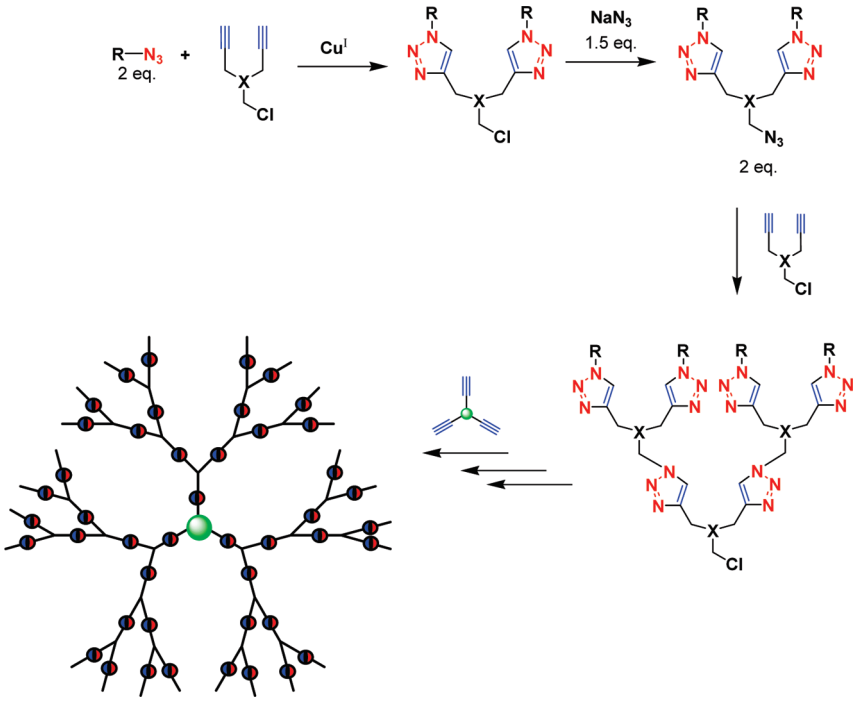
In 2002, the groups of Meldal[29] and Sharpless[30] independently reported the use of a copper(I) catalyst to allow azide−alkyne cycloadditions to be conducted at low temperatures with high rates, efficiency, and (regio)specificity (Figure 2A). This coupling process reaches near-quantitative conversion in both aqueous and organic media with little or no side reactions being observed. While the large majority of reports to date have relied on CuAAC to enhance macromolecular engineering capabilities, several other highly efficient reactions also meet the click criteria.[31] Additional cycloaddition reactions such as strain-promoted azide−alkyne coupling[32] (SPAAC) (Figure 2B) and Diels−Alder reactions[33] (Figure 2C) have allowed many new polymers to be efficiently prepared or functionalized. Thiol−ene reactions (radical- or nucleophile-mediated) have proven particularly useful for polymer synthesis under extremely mild conditions, often with no solvent and little-to-no product cleanup (Figure 2D,E).[18] These reactions are not the only examples of click chemistry applied to polymeric systems, and brief discussions below will highlight other methods used to lesser extents.

Copper-Catalyzed Azide−Alkyne Cycloadditions. Since its initial development, CuAAC has served as the quintessential example of a click reaction. More than any of the other methods, its impact has been enormous in the field of macromolecular engineering. It is no coincidence that Hawker, Sharpless, and Fokin et al. employed this reaction during convergent dendrimer preparation (Scheme 1),[34] and it was likely this approach that originally brought click chemistry to the attention of the polymer community. Dendrimer synthesis often requires high monomer concentrations and tedious chromatographic separations, while simultaneously generating considerable waste. Thus, the possibility of high efficiency and simple purification with only stoichiometric amounts of reagents make CuAAC particularly attractive for the synthesis of dendrimers. Employing monomer structures containing azide and alkyne moieties and constructing each generation by CuAAC, the authors were able to prepare well-defined dendrimers in a straightforward and high yielding manner. Hawker and Wooley later extended the reaction to prepare dendrimers in a divergent fashion.[35] The high efficiency of CuAAC was particularly beneficial in this case since defects in uniform functionality are especially problematic during iterative procedures, as the impact of a missing functional group early in the pathway is amplified in subsequent steps. Many other groups have similarly capitalized on the efficiency and specificity of CuAAC to prepare dendrimers or hyperbranches,[34,36−41] and thorough reviews on this topic were recently published by Voit[42] and Malkoch et al.[43]

Many of the first examples of click reactions being employed in materials synthesis involved polymers being prepared by step-growth click-type polymerizations.[13] Polymers synthesized by step-growth polymerizations require significant degrees of monomer conversion to achieve high molecular weights; therefore, click polymerizations that proceed by linking monomer units via near-quantitative reactions should encourage growth to high molecular weight polymer under moderate conditions. However, despite the promise of polymerizations that proceed by click-type processes, the area in which the click concept has demonstrated the most impact is the functionalization of preexisting polymers. Indeed, a large variety of polymeric, network, or multilayer materials have been functionalized by CuAAC reactions.[44−58]

Perhaps the promise of click chemistry for macromolecular engineering has been most thoroughly realized by combination with controlled/living polymerization techniques. For example, the combination of atom transfer radical polymerization (ATRP) and CuAAC has been extensively exploited to prepare a range of end-functional polymers with interesting reactive, surface, or topological properties.[59] While the azide or alkyne moieties can be incorporated at either the α or ω chain end of the polymers, the facility with

Scheme 1. General Method for Convergent Dendrimer Synthesis via CuAAC, As Initially Reported by Hawker, Sharpless, and Fokin et al.[34]



which the ω-halogen end groups inherent to ATRP can be substituted to contain azide groups[60,61] has led to well-defined polymers being functionalized with, or immobilized to, a variety of substrates. Lutz et al. first reported the functionalization of ATRP-prepared polymers by substitution with NaN_3 and subsequent CuAAC with low molecular weight alkynes.[62] Since that time, systematic studies have shown the rate of CuAAC reactions with the ω-end of ATRP polymers is strongly dependent on end-group structure[63] and catalyst.[64] Haddleton and co-workers reported an alternative method for clicking ATRP-generated macromolecules by polymerizing with an azide-functionalized initiator.[25] These initial reports led to rapid proliferation of other methods describing the combination of ATRP and CuAAC to facilitate synthesis of functional telechelics,[65] macro monomers,[66,67] chain-extended homopolymers or multiblock copolymers,[68−71] macrocyclics,[68,72−75] stars,[41,64,76−82] networks,[49,83] bioconjugates,[14,16,84−86] bionanoparticles,[87] and functional surfaces.[88,89] CuAAC has also been effectively combined with other controlled polymerization methods, including reversible addition−fragmentation chain transfer (RAFT) polymerization,[38,39,89−101] nitroxide-mediated polymerization (NMP),[98,102−105] cationic polymerization,[96,106−109] anionic polymerization,[110−114] and ring-opening metathesis polymerization.[24,115,116]

The efficiency afforded by CuAAC has influenced the field of macromolecular engineering in many ways. For example, block copolymer synthesis commonly relies on living/controlled polymerization methods to grow one block from another; however, many click reactions have proven capable of coupling preexisting homopolymers to prepare block copolymers in a modular and highly efficient manner (Figure 3). Several benefits arise from employing a modular method of this type. Each block can be individually characterized prior to coupling, and block copolymers can be prepared from monomers that do not polymerize by a common mechanism. However, any reaction used in this capacity must be highly efficient, since the concentration of complementary reactive moieties is necessarily low and because significant steric hindrance must be overcome. Moreover, purification can be challenging when trying to remove unreacted high molecular weight starting materials from the block copolymer product, especially if there is no appreciable difference in solubility. Opsteen and van Hest first demonstrated it was possible to prepare a library of AB[117] or ABC[118] block copolymers by coupling various combinations of azido- or alkyne-terminated polymers by CuAAC. Barner-Kowollik and Stenzel et al.[95] successfully coupled RAFT-generated polymers by a similar approach. Macromolecular architectures of greater intricacy have been prepared in an analogous manner, with CuAAC facilitating efficient preparation of various types of graft[119−121] and star[76,78,102,122] copolymers via modular grafting-to approaches (Figure 3).

Much of the original work exploring the potential of CuAAC involved functionalization of biological substrates such as virus particles[123] or enzymes[124] with small molecules. Thus, it is no surprise this method has been extended to the immobilization of polymers to various biological macromolecules, as described in a recent review by Velonia.[12] Schultz and co-workers coupled alkyne-terminated polymer to an azido-functionalized protein,[125] and Cornelissen and Rutjes et al. conjugated azido-terminated polystyrene to alkyne-functionalized proteins and peptides to form giant amphiphiles that self-assembled in water (Figure 4).[126] Our group employed a similar synthetic approach to prepare "smart" bioconjugates.[127] Poly(*N*-isopropylacrylamide) (PNIPAM) prepared by RAFT with a novel azido chain transfer agent[90] was coupled to alkyne-functionalized bovine serum albumin to yield temperature-responsive conjugates capable of forming reversible polymer−protein nanoaggregates when heated in aqueous solution.

Although many new materials have been successfully prepared by CuAAC, one often overlooked aspect is the nature and role of the resulting 1,2,3-triazole moieties on the resulting material properties. In addition to having many of the spatial and electronic characteristics of *trans*-peptide bonds, these aromatic rings often lend interesting properties

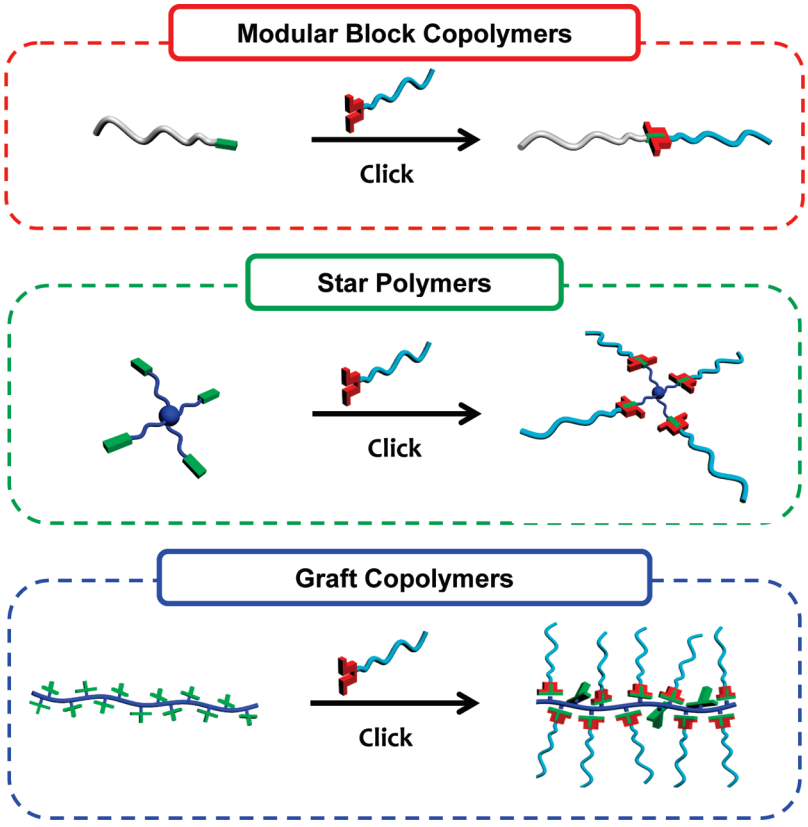


Figure 3. Modular approach of synthesizing block copolymers,[117,118] stars,[76,78,102,122] and graft copolymers[119] by click chemistry. The nature of many click reactions allows efficient ligation of high molecular weight chains even with low concentrations of reactive groups and/or significant steric hindrance. Despite increased efficiency when compared to more conventional methods, quantitative conversion is difficult to achieve in the case of densely grafted copolymers.

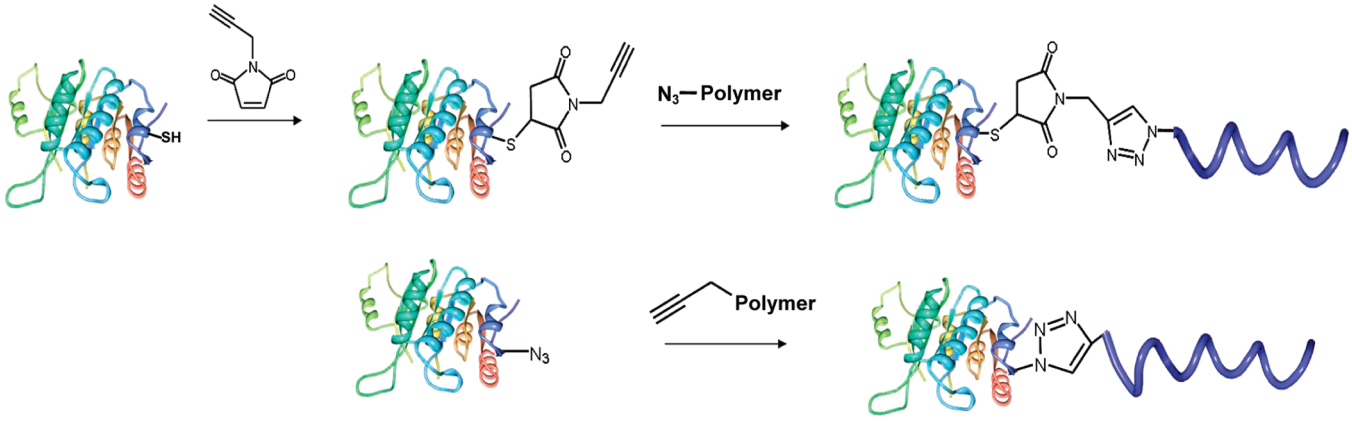


Figure 4. Polymer−protein conjugates prepared by copper-catalyzed azide−alkyne cycloaddition of alkyne- or azide-labeled proteins with polymers bearing the complementary functionality.[125−127] The azide-functionalized protein was prepared by site-specific incorporation of *p*-azidophenylalanine into proteins in yeast. Reproduced with permission from ref 12. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA.

to the molecules in which they reside.[128] For instance, the triazole π-system provides aromatic character beneficial for use in monomers,[129,130] RAFT agents,[131] conjugated polymers,[50,132] and fluorescent probes.[133−135] Triazoles can serve as ligands for Cu(I) ions, resulting in autocatalytic behavior for many reactions.[136,137] This effect can be especially important for macromolecules containing multiple closely spaced triazole rings. Matyjaszewski et al. showed that polymers with azide moieties on each monomer unit reacted much faster with model alkynes than low molecular weight, nonlinked azides.[138] It was hypothesized that the triazoles formed along the backbone complexed copper in the immediate vicinity of unreacted azides. Fokin and Finn et al. originally demonstrated that monomers containing azide and alkyne groups could be polymerized between two copper surfaces to form polymers with excellent adhesion properties, a result attributed in part to multivalent surface interactions of the polymer-bound triazoles.[139,140] In this case, no external catalyst was required since the low concentration of native Cu(I) ions on the surfaces of the metal was sufficient.

The simplicity with which relatively complex polymers can be synthesized or functionalized via CuAAC has led to its extensive employment in the field of macromolecular

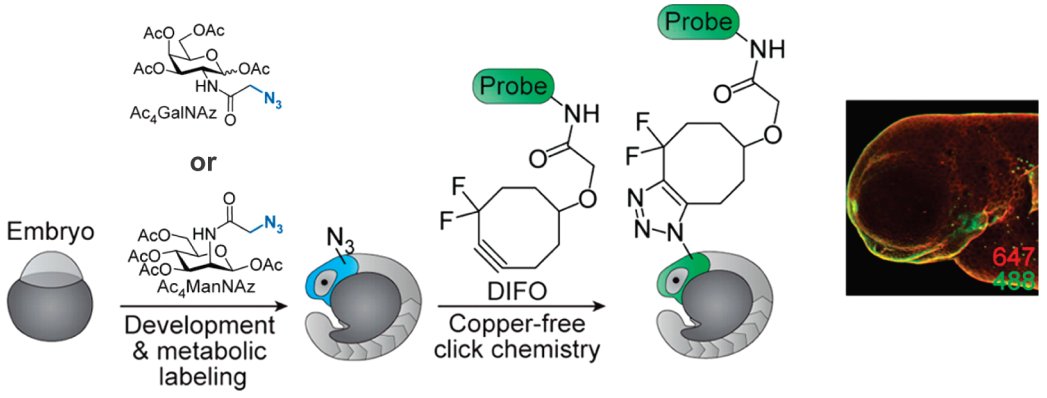


Figure 5. Noninvasive copper-free click in live developing organisms. Bioorthogonal strain-promoted azide−alkyne cycloaddition allowed imaging of metabolically incorporated glycans in developing zebrafish embryos by in vivo reaction with a cyclooctyne−fluorophore. Reproduced with permission from ref 147. Copyright 2009 National Academy of Sciences, U.S.A.

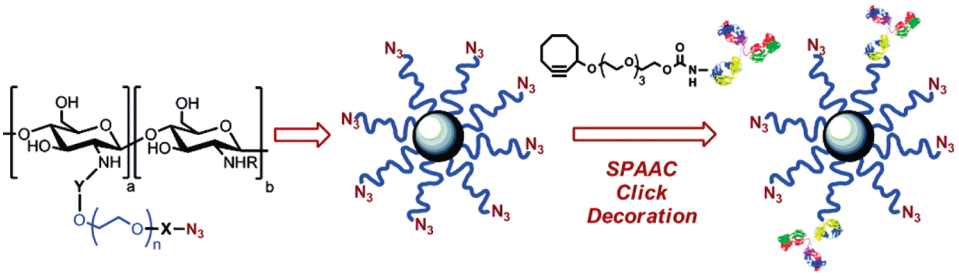


Figure 6. Preparation of immunonanoparticles by strain-promoted azide−alkyne cycloaddition. Azide-decorated chitosan-*graft*-poly(ethylene glycol) nanostructures were coupled with cyclooctyne-functionalized immunoglobulin G under physiological conditions. Adapted with permission from ref 149.

engineering. However, during the preparation of biological materials, the potentially undesirable reliance on copper has generated interest in new metal-free azide−alkyne cycloaddition reactions.

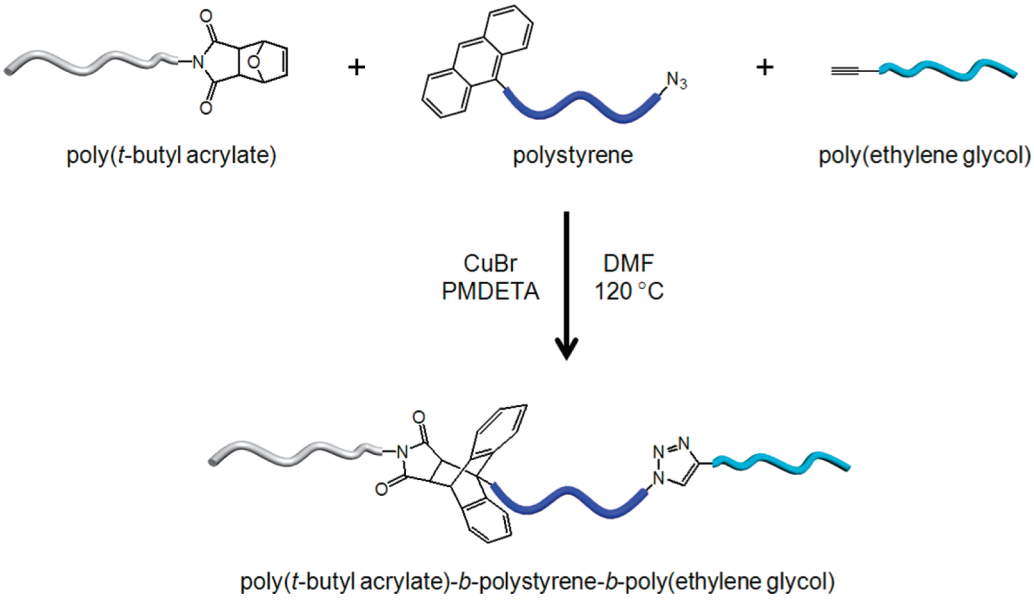
Strain-Promoted Azide−Alkyne Coupling. Though the reduced yields and demanding reaction conditions characteristic of traditional uncatalyzed Huisgen 1,3-dipolar azide−alkyne cycloaddition prevents its inclusion into the suite of click chemistry methods, coupling of azides with strained cycloalkynes is relatively fast and proceeds to high conversion under mild conditions (Figure 2B). In addition to being highly efficient and robust, strain-promoted azide−alkyne cycloaddition (SPAAC) does not rely on a copper catalyst, thereby making it an attractive alternative for conducting click reactions in situations where biocompatibility is a concern. Bertozzi et al.[32,48,141−145] developed and extensively studied the bioorthogonality[146] of SPAAC for labeling various molecules in living cells and other biological environments. Nonactivated cyclooctynes react somewhat slowly with azides, but incorporating electron-withdrawing groups on the ring results in dramatically accelerated rates more typical of click reactions.[32] For instance, the presence of a *gem*-difluoro group adjacent to the strained alkyne led to reactions with azides that were 30−60 times faster than those with non-fluorinated cyclooctynes. This rate acceleration allowed efficient click coupling of fluorophores to biological molecules in ∼1 min.

In a comparative study, CuAAC, SPAAC, and Staudinger ligations were employed to label azides on biomolecules in complex lysates and on live cell surfaces.[141] While the CuAAC process proved to be the most efficient labeling method, the latter two were beneficial in that they did not suffer from toxicity issues. An example of this reaction being employed in a living system was demonstrated by the in vivo labeling of glycans in zebrafish embryos.[143,147] The embryos were exposed to azido-functionalized sugars during their development, which resulted in metabolic labeling of glycans with azides. Glycans produced at various points during development were imaged by microscopic investigation after exposing the embryos to activated cyclooctyne−fluorophores (Figure 5).

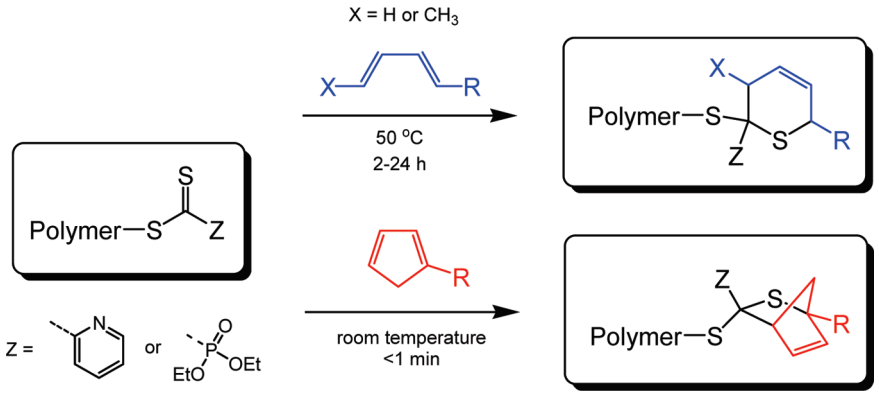
The intriguing bioorthogonal nature of the SPAAC reaction has led to its increasing use for functionalizing biomolecules in their native environments. Alkyne- or cyclooctyne-functionalized phosphatidic acid derivatives have been incorporated into mammalian cell membranes and subsequently labeled by reacting with an azido-functionalized coumarin derivative by either CuAAC or SPAAC.[148] CuAAC again proved to be problematic due to toxicity issues, but SPAAC was an efficient and biocompatible method to label the membrane lipids. Polysaccharide nanoparticles have also been functionalized by SPAAC under physiological conditions (Figure 6). Azide-decorated chitosan-*graft*-poly(ethylene glycol) (PEG) nanostructures were coupled with cyclooctyne-functionalized immunoglobulin G to obtain immunonanoparticles.[149] In addition to strain-promoted reactions, other copper-free azide−alkyne cycloadditions have shown promise of high efficiency and fidelity. Generally these involve coupling reactions of electron-deficient[150−152] or metal-activated alkynes.[153]

Diels−Alder Reactions. Being specific, atom-economical, and highly efficient, many Diels−Alder reactions possess characteristics of click techniques. First reported in 1928, this reaction has been employed in organic chemistry for many years, but the emergence of click chemistry concepts has led to its increased use in the area of materials synthesis. As opposed to the majority of click reactions that create new carbon−heteroatom bonds, traditional

Scheme 2. Orthogonal One-Pot Synthesis of ABC Triblock Copolymers by Simultaneous Diels−Alder and Copper-Catalyzed Azide−Alkyne Cycloaddition[164]



Scheme 3. Hetero-Diels−Alder Reactions of Dienes and Thiocarbonylthio-Terminated Polymers Prepared by Reversible Addition−Fragmentation Chain Transfer Polymerization[170−174]



Diels−Alder reactions rely on carbon−carbon bond formation between dienes and electron-deficient dienophiles (Figure 2C).

Owing to efficiency and facile work-up, Diels−Alder reactions have been extensively considered for the synthesis of dendrimers,[42,154−158] stars,[26,159−162] graft copolymers,[163] and other highly congested macromolecular architectures. Hizal, Tunca, and co-workers have reported many of these examples, demonstrating that a variety of structures can be synthesized with diene and dieneophile-functionalized polymers. For example, maleimide-terminated polymers were reacted with trianthracene cores to yield PEG, poly(methyl methacrylate), or poly(*tert*-butyl acrylate) (PtBA) stars with 82−93% coupling efficiency.[159] Miktoarm stars with PEG, polystyrene, and PtBA chains were prepared by Diels−Alder coupling of maleimide-terminated PEG to an anthracene-functionalized small molecule capable of initiating both ATRP and NMP.[162] The orthogonality of Diels−Alder and CuAAC reactions was demonstrated by preparing modular ABC triblock copolymers from maleimide-terminated PtBA, alkyne-terminated PEG, and α-anthracene-ω-azide-terminated polystyrene (Scheme 2).[164] By conducting the reaction at high temperatures in the presence of a Cu^{I} catalyst, both reactions took place simultaneously, and the triblock copolymer was obtained with high coupling efficiencies. A similar one-pot "double-click" approach was employed to prepare three-arm stars[26] and H-shaped ABCDE quintopolymers.[165] Other applications of traditional Diels−Alder reactions in materials synthesis include immobilization of unsaturated DNA strands onto maleimide-coated Au nanoparticles,[166] surface attachment of proteins and cell-adhesion ligands,[167,168] and the synthesis of macrophotoinitiators.[169]

Barner-Kowollik, Stenzel, and co-workers recently reported a unique functionalization procedure that relies on hetero-Diels−Alder reactions of dienes with terminal thiocarbonylthio groups on RAFT-generated polymers (Scheme 3).[170] Chain transfer agents with electron-withdrawing Z groups result in polymers capable of highly efficient cycloaddition reactions to yield modular block copolymers,[170,171] polymer-functionalized microspheres,[172] and star block copolymers.[173,174] Reactions with linear dienes proceed to high conversion in a few hours at 50 °C, but cyclopentadienes react near-instantaneously at room temperature.[171] Provided sufficient availability of chain transfer agents with electron-withdrawing Z groups, this RAFT−hetero-Diels−Alder approach has similar potential to that of the ATRP−CuAAC combination for the synthesis of well-defined end-functional polymers.

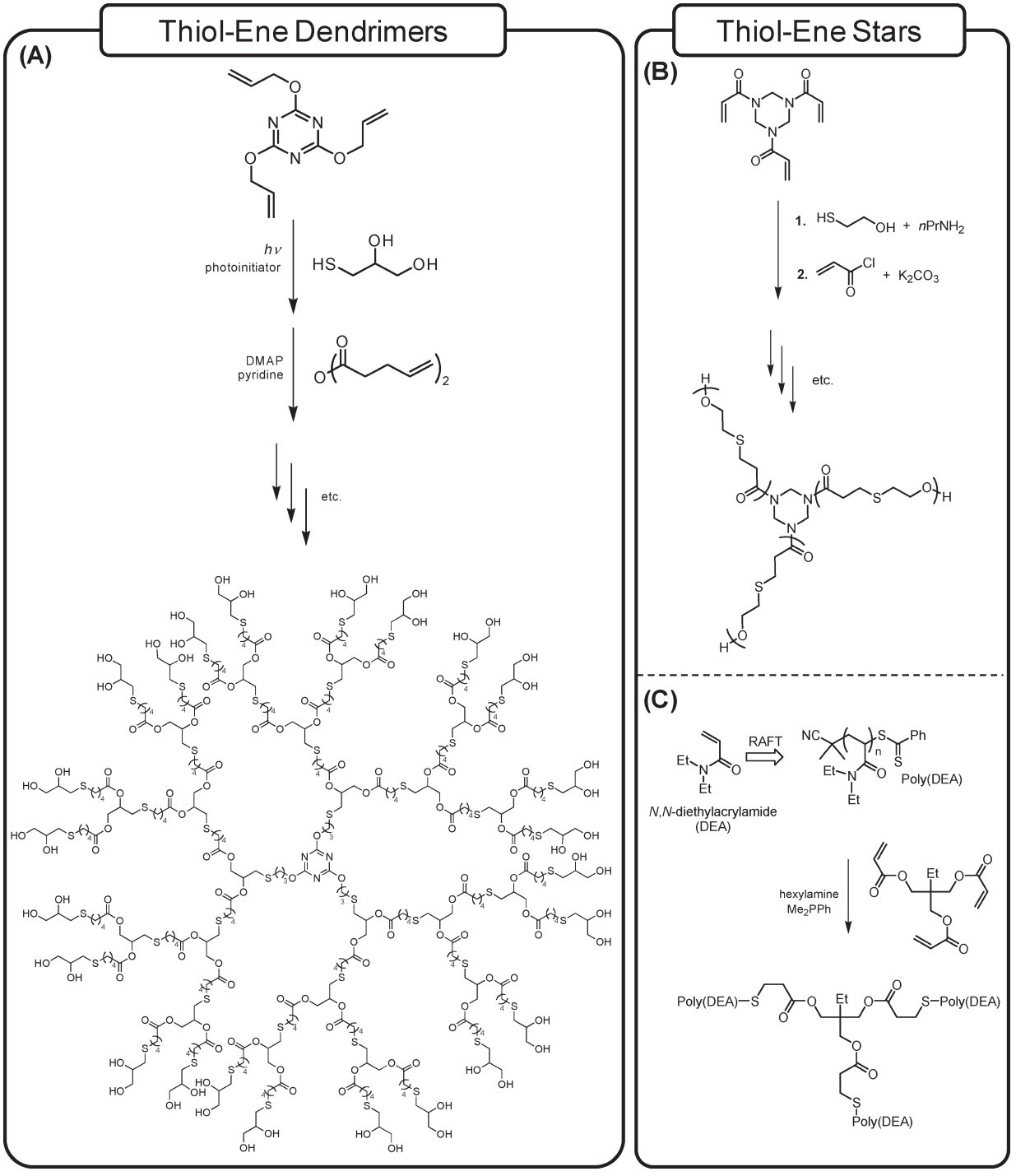


Figure 7. Synthesis of (A) dendrimers by esterification and photochemical thiol−ene reactions,[184] (B) oligomeric stars by esterification and nucleophilic thiol−ene reactions,[186] and (C) polymeric stars[189] by reversible addition−fragmentation chain transfer (RAFT) polymerization and nucleophilic thiol−ene reactions.

Thiol−Ene Reactions. Hydrothiolation of virtually any alkene C=C bond occurs by either radical or nucleophilic mechanisms (Figure 2D,E).[175−178] While such broad applicability could be a drawback in terms of specificity, the high efficiency and robust nature of thiol−ene chemistry is attractive for materials synthesis. Indeed, a great deal of work employing these concepts in the field of polymer chemistry[179] was reported prior to the advent of the click concept. In addition to thiols being present in biological systems, which may facilitate bioconjugations,[180] sulfhydryl and alkenyl groups are easily incorporated into polymer or monomer structures to enable subsequent postpolymerization modification.

Schlaad and co-workers coined the term "thio-click" to describe reactions of thiols with unsaturated side chains of polyacrylates or polyoxazolines[107,181] and later extended the process to the functionalization of 1,2-polybutadiene.[182,183] In situ formation of radicals by irradiating with UV or sunlight at room temperature allowed highly efficient functionalization in a relatively short period. Thiol−ene radical reactions can also be initiated thermally. Hawker and coworkers compared the thermal and photochemical initiation

methods in model reactions and found the photoinitiated radical process proceeded with greater efficiency, requiring shorter reaction times for high conversion, and displayed better functional group tolerance.[27] The orthogonality of the nucleophilic process was demonstrated by the successful one-pot reaction of α-alkene ω-azide functional polystyrene by consecutive thiol−ene and CuAAC reactions.

Similar to many of the other click methods, the ability to reach near-quantitative conversions under moderate conditions has led to thiol−ene reactions being employed for the synthesis of dendrimers and other sterically hindered architectures. For instance, Hawker and co-workers reported that photochemical thiol−ene reactions allowed efficient synthesis of dendrimers in a divergent manner (Figure 7A).[184] As opposed to the CuAAC methods, the combination of thiol−ene chemistry with traditional esterification reactions allowed efficient synthesis without a metal catalyst and under solvent-free conditions. Son et al. demonstrated that three-armed oligomeric stars could be prepared in a similar manner[185,186] (Figure 7B) and separately reported the synthesis of branched[187] and dendritic[188] organosilanes by photochemical thiol−ene reactions. Interestingly, virtually all reports of polymer synthesis via radical thiol−ene reactions have involved at least one low molecular weight compound (i.e., either the thiol or the ene). The versatility of this approach for coupling two or more macromolecular components remains largely unexplored.

The facility with which thiol or alkene end groups can be incorporated into polymers has allowed the synthesis of a variety of end-functional macromolecules. One particularly straightforward manner of obtaining thiol-terminated polymers is by reduction of thiocarbonylthio end groups that result from the RAFT process. Indeed, the fact that sulfur containing end groups are inherent to RAFT has given rise to a variety of applications that capitalize on the versatile chemical reactivity of sulfhydryl groups.[190−193] Moreover, the orthogonal nature of reductive aminolysis and thiol−ene reactions allows the two processes to be conducted in one pot.[190,194,195] This is especially useful, since it avoids the need to isolate the oxidatively unstable thiol-terminated polymers and because the amine used for aminolysis can also facilitate addition of the thiol to the activated alkene by a nucleophilic mechanism.[196,197] The groups of Hoyle and Lowe recently demonstrated that the one-pot method could be used to efficiently prepare three-armed stars from RAFT-generated polymers (Figure 7C). Employing a similar approach, Nelson and co-workers efficiently functionalized the end groups of RAFT polymers by reacting thiol-terminated chains with a variety of low and high molecular weight acrylate species. Thiol-terminated RAFT polymers have also been immobilized to ene-decorated microspheres.[198] On the basis of the success already demonstrated in this area and the abundance of commercially available activated alkene substrates susceptible to nucleophilic addition (e.g., acrylates and maleimides), it is likely that the RAFT/thiol−ene combination will continue to be a valuable macromolecular synthesis strategy.

Other Emerging Click Reactions. A variety of other click-type reactions has recently been employed to prepare polymeric materials. In addition to adding to alkenes, thiols can efficiently add to alkynes by a radical-based "thiol−yne" process. For example, Lowe and co-workers employed a combination of thiol−ene and thiol−yne chemistries to prepare end-functional PNIPAM.[199] Thiol-terminated chains were reacted with the double bond of propargyl acrylate by a phosphine-mediated nucleophilic process, and the resulting alkyne-terminated chains were photochemically reacted with thiols to prepare polymers with end groups of varying hydrophobicity. Patton and co-workers prepared multicomponent surfaces by photochemically reacting various thiols with surface-immobilized poly(propargyl methacrylate).[200] Percec and co-workers recently described base-mediated thioetherification of α-bromoesters with thiols.[201,202] This "thio−bromo click" reaction successfully allowed efficient divergent dendrimer synthesis. Hoogenboom and Schubert et al. observed that nucleophilic substitution of *para*-fluorine substituents of polymer-bound pentafluorophenyl groups with primary amines and thiols has many of the characteristics of a click reaction and used the process to prepare graft copolymers[203] and glycopolymers.[204] While certainly not a new reaction, recent expansion of traditional thiol−maleimide Michael addition, a process that adheres to much of the click criteria, has allowed our group and others to prepare modular block copolymers,[205] stars,[206] bioconjugates,[84,85,191,207,208] and other functional telechelics.[205,206,209]

Oxime bond formation by the reaction of *O*-hydroxylamines with aldehydes and ketones is another excellent example of a click reaction.[210−214] Maynard and co-workers prepared aminooxy-terminated poly(methacrylates), PNIPAM, and polystyrene by ATRP or RAFT with functional initiators or CTAs.[213−215] These polymers were capable of rapid and efficient ligation with aldehyde-functionalized small molecules, heparin, and fluorescent nanospheres and also with ketone-modified proteins. Oxime bond formations hold particular promise for biological applications, as no metal catalyst is required, no byproduct is formed, and modification of proteins, polysaccharides, etc., with aminooxy, aldehyde, or ketone moieties is relatively straightforward.[215,216]

Outlook and Challenges

Many of the materials made by click chemistry could in principle be prepared by conventional reactions commonly employed prior to the advent of the click chemistry concept. However, while effective, many of these conventional approaches rely on complicated synthetic routes or extensive and tedious purification. For example, the synthesis of near-monodisperse dendritic macromolecules was possible prior to Hawker, Sharpless, and Fokin et al. reporting the use of CuAAC to prepare such structures. Similarly, preparation of block copolymers by end-to-end coupling of two homopolymers has been known for many years. However, achieving these transformations with the typical set of available reactions often led to low yields only alleviated by employing excess reagents, enhanced purification procedures, and/or extended reaction times. The enhanced specificity of click chemistry has also contributed to its rapid adoption within the polymer field. While many reactions other than those described here can be used to prepare, for example, macromonomers, cyclic polymers, or functional telechelics, many times these techniques are less inefficient or limited in scope, only being applicable to polymers without specific functional groups that could interfere with the ligation, cyclization, or functionalization processes. Click methods provide a simplified toolbox of available reactions that are wide in scope and require less individual consideration for their employment. Interestingly, the field has reached a level of maturity in which various click methodologies are being effectively combined to prepare a diverse range of polymeric materials. A combination of this sort is particularly enabling since the click reactions are, by definition, orthogonal and can often be carried out via one-pot simultaneous or cascade processes.

There is no doubt the careful application of click strategies will continue to facilitate the synthesis of increasingly functional macromolecules with unprecedented structural control.

However, a few points warrant consideration. Each of the reactions mentioned above has limitations, and previous reports demonstrate it is sometimes necessary to employ excess reagents, higher than catalytic amounts of copper, etc. To meet the criteria of the click philosophy, reasonable efforts should be made to employ aqueous or solvent-free conditions and to use reactions that are atom-economical or yield only inoffensive byproducts. Additionally, it is counterproductive to resort to overly complex synthetic routes to starting materials that contain the functionality necessary for click reactions. If the synthesis of a particular precursor containing azido, alkynyl, thio, or alkenyl moieties is a tedious and inefficient process, a significant portion of the benefit provided by clicking in later steps is lost. Therefore, new methods are needed to facilitate the incorporation of functionality necessary for subsequent click transformations. An example of such an advance was reported by Matyjaszewski and co-workers.[217] While side-chain functionalization via CuAAC traditionally requires synthesis and polymerization of monomers containing azide or alkyne groups, NaN_3 was used to ring open the epoxide units in glycidyl methacrylate copolymers to yield azido monomer units. In addition to being straightforward and proceeding to high conversion (ring-opening of epoxides is, after all, another click reaction), this method circumvents problems associated with synthesis and handling of potentially unstable low molecular weight azides. Goldmann and co-workers also used click methods to incorporate functionality needed for a second separate click reaction.[198] Reacting 1-azidoundecane-11-thiol with vinyl groups on the surface of microspheres allowed the resulting azido-decorated particles to be functionalized with alkyne-terminated polymer. Other reactions could benefit from simplified routes to starting materials as well. Although the toxicity of low level copper is debatable, biological applications are likely to benefit from many of the copper-free techniques, and the elegant and promising SPAAC reactions would undoubtedly be even more appealing if simplified routes to the cyclooctyne precursors are devised.

Additional insight regarding the limits of the click methods is also needed. For example, many azides are photosensitive, and recent reports by Perrier[218] and Benicewicz[99] indicate that with long reaction times and/or high temperatures azides can undergo cycloaddition reactions with electron-deficient alkene monomers during polymerization. Additionally, alkynes can undergo side reactions during radical polymerization, and alkyne−alkyne Glaser coupling can be a potential complication during materials synthesis by CuAAC.[138,219−221] Without proper precautions, reactions involving thiols may be limited by undesirable nucleophilicity, incompatibility with competing radical processes, or the tendency to form disulfides. Many of the other click methods have important limitations as well, and it is important to gain more information in this respect.

Finally, further advancements in macromolecular engineering will benefit from additions to the click repertoire. Continued developments in promising chemistries such as the reaction of *N*-heterocyclic carbenes with azides (1,3-disubstituted triazene formation)[222,223] and pentafluorophenyl groups with thiols or amines,[203,204] among others, should facilitate the preparation of increasingly complex macromolecules from a few simple reactions.

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