Construction of Linear Polymers, Dendrimers, Networks, and Other Polymeric Architectures by Copper-Catalyzed Azide-Alkyne Cycloaddition “Click” Chemistry

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The enrichment of materials synthesis with the diverse chemical building blocks and functional groups of small molecule organic chemistry has been greatly accelerated in recent years by the introduction of the copper-catalyzed azide-alkyne cycloaddition (CuAAC). The efficiency and modular nature of this unique reaction enables materials chemists to prepare novel functional materials of unprecedented complexity. This review summarizes the application of CuAAC to the field of materials construction, defined here as the preparation of materials with architectural integrity dependent upon the triazole linkage. Recent examples, including linear polymers, dendrimers, polymer networks, polymeric nanoparticles, and other polymeric architectures, are described.

Introduction

Every chemistry student learns the second law of thermodynamics: the entropy of the universe is always observed to increase. A glance at the recent explosion of papers describing the use of click chemistry may leave one with a similar sense of increasing disorder. However, as a referee pointed out to us, the terms of thermodynamics provide a more apt analogy: the field of click chemistry is an open system in constant exchange with its environment (other disciplines). As in living systems, entropy may also decrease locally when certain forces intersect, and click chemistry certainly has helped to give life to the realization of long-held goals in materials science, as we discuss in several examples below. The timeline of the development and evolution of this enabling philosophy and technology is instructive.
Sharpless and coworkers introduced the click chemistry concept in 2001, explicitly attempting to bring the chemical sensibility of polymer chemistry to the world of organic chemists.\textsuperscript{[1]} Of course all chemists prize reactions of high efficiency, and the click reactions introduced in that original paper were mostly already known. Sharpless and coworkers focused their attention, however, on the enabling conviction that all branches of chemical science could benefit from the same abiding focus on function, and the same acceptance of a relatively limited but extraordinarily powerful palette of bond-forming reactions that has always characterized the field of polymer and materials synthesis. The subsequent few years brought a resounding affirmation of that expectation, with an explosion of papers worldwide applying the tenets of click chemistry to a range of applications which could arguably not be approached by any other means.

“Click chemistry” focuses on the extraordinary power of a very few reactions which form desired bonds under diverse reaction conditions, with highly diverse building blocks, in high yields and with no (or conveniently separated) byproducts.\textsuperscript{[2]} For materials chemists, an appreciation of the value of such processes is decidedly not new. The reactions that modern click chemistry has created, and one process in particular, have thereby brought new capabilities to a field better prepared than any other to take advantage of them. That process is the popular copper-catalyzed azide-alkyne cycloaddition (CuAAC), which is the subject of this review (Scheme 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Scheme 1: Copper-catalyzed azide-alkyne cycloaddition (CuAAC).}
\end{figure}
The CuAAC reaction was first reported in 2002 by the laboratories of Meldal and Sharpless, in the latter case as a direct result of an appreciation of the potential for such a reaction in the context of the click chemistry concept.\[3,4\] The mechanistic and procedural details of this reaction are largely beyond the scope of this review and we direct the reader to several references from the primary\[5–8\] and review\[9\] literature on these topics. Recent reports of new classes of accelerating copper-binding ligands,\[10\] the isolation of a copper(I)triazolide click intermediate,\[11\] and a novel way to remove all traces of copper from click reaction mixtures are particularly relevant.\[12\] We will focus on the application of CuAAC to the construction of interesting materials in the rest of this review. A number of excellent review articles in the past year have summarized the use of CuAAC in polymer and materials synthesis,\[13–23\] but new reports appear quite frequently in this fast-moving field. We therefore endeavor to bring the reader the most recent advances available, but also to set them in context with older examples when appropriate.

Materials Modification versus Construction

There are two fundamentally different ways to use any reaction in materials synthesis: to construct materials or to modify them (Scheme 2). Modification (“decoration” or “functionalization”), pertains to the attachment or removal of functionality to or from an already existing material thereby imbuing it with new properties. Scheme 2 illustrates two potential means by which materials can be modified - route \(a\) in which new modifier building blocks are added to the material, and route \(b\) in which one or more existing blocks are chemically altered. Perhaps the most important requirements of route \(a\) modification reactions are chemoselectivity (to ensure functionalization at the desired site) and high yield (to ensure complete functionalization), challenges that the CuAAC reaction is well equipped to meet. The vast majority of applications of CuAAC reactions to materials synthesis therefore involve the modification of polymers, surfaces, dendrimers, nanoparticles, viruses, networks, and other structures via route \(a\). Furthermore, thanks to the orthogonal reactivity of CuAAC, route \(b\) schemes can be used in conjunction with CuAAC functionalization to yield chemically diverse macromolecular structures [for example, constructing and modifying materials derived from poly(tert-butyl acrylate) (PtBA) enables the orthogonal route \(b\) conversion of hydrophobic PtBA to hydrophilic poly(acrylic acid) (PAA) via acid hydrolysis].

Material construction pertains to building an architecture and the reactions thus employed provide the mortar with which the building blocks of macroscopic architectures are connected (Scheme 2). For materials synthesis applications, high yields and chemoselectivity are necessary, and the concept of modularity is crucial. Furthermore, the more easily the required functional groups can be introduced into potential building blocks, the more structurally and chemically diverse the material that can be synthesized. Because azides and alkynes are readily attached to molecular scaffolds via a variety of simple techniques, and are stable toward a wide variety of solvents and reaction conditions, CuAAC allows the user to bring almost any necessary building block to the problem at hand without worrying about the connection reaction.

We focus here on the efforts of our laboratories and others to employ the CuAAC reaction for the construction of materials, but references are also provided for a number of recent materials modification applications which utilize
CuAAC. In many cases, a reaction can be seen as both a modification and a construction reaction. For example, the attachment of alkyne end-functionalized polymers to azide side-chain derivatized polymers to yield graft copolymers can be considered both the modification of the azide derivatized polymer and the construction of a graft copolymer. Due to space limitations, such cases are considered modification reactions and only limited examples are given.

A triazole-containing material will be defined as resulting from CuAAC “construction” if at least one triazole within the structure can be traced in every direction along the structure to another triazole. For the graft copolymer example given above, every triazole in the structure is the result of a modification reaction because it can be traced directly to the end of the alkyne end-functionalized polymer. Due to space limitations, such cases are considered modification reactions and only limited examples are given.

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Linear “Click” Polymers and Oligomers
(From Small Molecule Precursors)

If materials construction is viewed as progressing from simpler to more complex structures (Scheme 3), then it should come as no surprise that CuAAC was first applied to materials synthesis in the construction of linear polymers and oligomers and has since been employed in a variety of unique ways for the synthesis of such materials (Scheme 4). The earliest example, from 2004, was reported by Finn and coworkers as a control reaction in their discovery of metal adhesives. The authors showed that a bis-azide and bis-alkyne formed a soluble linear polymer thus confirming their hypothesis that CuAAC could be used for addition polymerizations (Scheme 5, 24) [24]

Further details of this work, along with a recent article by Ravelo and coworkers describing linear CuAAC polymers incorporated into networks (Scheme 5, 25) [25] will be discussed later in the section on network synthesis.

In 2005, Angelo and coworkers reported using an iterative diazo-transer/CuAAC process to construct peptidomimetic oligomers that possessed a “zigzag” secondary structure resulting from the large dipole moment of the triazole CuAAC product (Scheme 5, 26) [26] In this work, the triazoles of 26 were viewed as replacements for the traditional amide peptide bond, while the R groups mimicked amino-acid side chains. The authors suggested that this strategy could lead to peptide mimics with enhanced stability in in vivo applications. Around the same time, Reek and coworkers reported the construction of novel conjugated polymers derived from A,A and B,B diazide and dialkyne fluorene monomers (Scheme 5, 27) [27] Introduction of bipyridine-type functionalities into these polymers opened a route to novel metal-coordinated conjugated polymers.

Meudtner and Hecht recently reported an example of a triazole polymer which possessed secondary structure and metal-binding pyridine units. Step-growth polymerization of 2,6-dithynylpyridines with a bifunctional aromatic azide yielded linear polymers with 2,6-bis(1,2,3-triazol-4-yl)pyridine units on the backbone which are known to adopt an anti–anti conformation thus giving rise to helical polymers (Scheme 5, 28) [28] Circular dichroism spectroscopy confirmed the existence of chiral helices and when a
variety of metal salts (Zn$^{2+}$, Fe$^{2+}$, Eu$^{3+}$) were added to dilute solutions of 28 cross-linking occurred yielding supramolecular metallogels which have potential as novel magnetic and/or emissive materials.

In 2006, an interesting one-pot synthesis of triazole oligomers was reported by Aucagne and Leigh (Scheme 6). The authors utilized a trimethylsilyl-protected acetylene (TMS-alkyne) - azide A,B type monomer which was reacted with an alkyne under CuAAC conditions. Upon completion of this reaction, a silver(I) salt was added along with a second azide to the same reaction mixture facilitating deprotection of the TMS-alkyne and subsequent CuAAC with the newly added azide. This methodology has the potential to be useful in a range of applications including the one-pot synthesis of ABC block copolymers.

Burgess and coworkers later reported an iterative construction of oligomers derived from the CuAAC connection of triethylene glycol (TEG) subunits (Scheme 5, 30). By utilizing TEG fragments possessing an alkyne on one end and a tosylate on the other, the authors were able to repeatedly perform CuAAC followed by nucleophilic displacement of the tosylate with sodium azide to grow oligomers which then could be end-functionalized with any desired moiety via a final CuAAC step (R and R$^*$ in 30 could be varied). The water-solubility of these materials makes them attractive linkers for bioconjugation applications. Finally, Qing and coworkers prepared addition polymers by CuAAC which possessed perfluoro-cyclobutyl (PFCB) groups along the main chain (Scheme 5, 31). The resulting polymers were thermally stable up to $\approx 400^\circ$C and were soluble in organic solvents making them attractive candidates for low dielectric and other high performance coating applications.

### Linear “Click” Polymers and Oligomers (from Polymeric Precursors)

All of the aforementioned examples utilize CuAAC to couple small molecules together to construct polymers or oligomers. Because azides and alkynes have such a narrow spectrum of reactivity, they can also be incorporated into polymerization initiators to make end-functionalized macromonomers. The use of such building blocks to yield high molecular weight block copolymers has been described by several laboratories. We also include the formation of circular polymers, derived from end-functionalized linear macromolecules, in this section.

In 2005, Opsteen and van Hest reported the construction of a variety of polystyrene (PS), poly(methyl methacrylate) (PMMA), and poly(ethylene glycol) (PEG) block copolymers by a click chemistry strategy. Atom transfer radical polymerization (ATRP) of the selected monomers followed by end-group transformation of the terminal bromine to an azide using sodium azide yielded polymers which were coupled with other ATRP-derived polymers grown from an alkyne initiator. The same authors recently reported an extension of this technique using triisopropylsilyl-alkyne (TIPS-alkyne) ATRP initiators to prepare $\sigma,\omega$-heterobifunctional polymers possessing TIPS-alkyne on one end and azides on the other. CuAAC followed by deprotection and subsequent CuAAC with another azide-terminated polymer yielded ABC triblock copolymers (Scheme 7, 33). Notably, the authors mention that ATRP using a TMS-alkyne initiator resulted in a significant degree of TMS loss during the ATRP process. The TIPS group, on the other hand, was found to be completely stable during ATRP. It would perhaps be interesting to see if these polymers could be used in conjunction with
Leigh’s method described above (CuAAC followed by Ag(I) deprotection and CuAAC again) to prepare ABC triblocks in a one-pot procedure.

Matyjaszewski and coworkers reported the synthesis of an α,ω-heterobifunctional-PS which was prepared by ATRP from an alkyne initiator followed by nucleophilic substitution of the bromine end group with sodium azide.[34] Polymerization of these macromonomers (MACs) by CuAAC gave high molecular polymer products as well as a small amount of cyclic material (Scheme 7, 34). The authors mentioned an attempt to perform a one-pot end-group exchange/CuAAC coupling without success.

The next year, Laurent and Grayson reported the synthesis of macrocyclic polymers (Scheme 7, 35) derived from the same polymers reported by Matyjaszewski and coworkers above, but under different CuAAC conditions (i.e., higher dilution to favor the cyclization reaction).[35] In 2007, Tunca and coworkers elegantly achieved a one-pot click construction of an ABC triblock polymer by utilizing tandem CuAAC and Diels-Alder reactions to yield PMMA-PS-PEG triblocks (Scheme 7, 36).[36]

Another example of a CuAAC constructed linear polymer was reported in 2007 by Wang and coworkers.[37] The authors coupled alkyne-telechelic PEGs with 2,2-bis(azidomethyl)propane-1,3-diol by CuAAC to yield higher molecular weight PEG polymers with pendant functionalities (R groups, Scheme 7, 37) including an alendronate-PEG for potential bone-targeted drug delivery. The high yield of CuAAC was demonstrated by the production of hydrogels if no monofunctional PEG was added to the polymerization mixture (indicating extremely high molecular weight).

Brown and coworkers have recently described the fascinating and potentially very useful synthesis of a circular DNA catenane.[38] The authors prepared a single-stranded DNA with a 5’-alkyne and a 3’-azide. CuAAC coupling under dilute conditions yielded a macrocyclic DNA. When the complementary DNA strand, also possessing alkyne and azide termini, was allowed to anneal to the closed DNA loop and treated with Cu(i), a double-stranded DNA catenane resulted, connected with two stable triazole units (Scheme 8).

Network/Branched Architectures

Dendrimers

A number of groups have recently utilized CuAAC in elegant ways to modify the surfaces of discrete molecular objects like dendrimers.[39–41] In this review we only mention the use of CuAAC to construct dendritic architectures (Scheme 9) and direct the reader to the aforementioned reviews to find a wealth of examples of CuAAC for dendrimer modification.

Scheme 7. Representative structures of linear polymers prepared by CuAAC connection of polymeric building blocks. Triazole units, the product of CuAAC are shown in blue. The corresponding numbers refer to the reference from which the structure was taken.

Scheme 8. Synthesis of a double-stranded DNA catenane by Brown and coworkers.[38] CuAAC circularization of a single DNA strand (shown in red) followed by annealing of the complementary strand (shown in blue) and CuAAC gave the desired structure (triazoles represented by blue pentagons).

Scheme 9. Schematic of dendrimer modification versus construction. In this review we only describe dendrimers constructed using CuAAC. These dendrimers possess triazoles at branching points within the dendrimer structure rather than only at the surface.
The synthesis of dendritic molecules requires extremely efficient reactions for each iterative step to ensure quantitative conversion of the geometrically increasing number of functionalities as the dendrimer grows. For this purpose, chemists in the field of dendrimer synthesis had been utilizing click-type reactions for years\[^{42-44}\] but it was Fokin, Hawker, and coworkers who first brought the CuAAC reaction to the field in 2004.\[^{45}\] Soon thereafter, the Wooley laboratory reported a complementary divergent synthesis of triazole dendrimers.\[^{46}\] Hawker and coworkers then highlighted the chemoselectivity and efficiency of the CuAAC reaction in this context by making multivalent, bifunctional dendrimers that one would be hard-pressed to prepare so easily by conventional means (Scheme 10).\[^{47}\]

The final structure featured 16 surface-active mannose groups and two fluorescent coumarin units derived from two dendrons, each made with triazole linkages and then subsequently joined by a CuAAC reaction. The resulting dendrimer was shown to be 240 times more potent than monomeric mannose in a standard hemagglutination assay thereby providing a nice demonstration of the polyvalent effect of highly functionalized macromolecular scaffolds.

CuAAC has repeatedly been shown to be an efficient way to functionalize solid supports.\[^{48-54}\] For example, Santoyo-Gonzalez and coworkers convergently prepared glyco-dendrimers with a silica core and demonstrated their effectiveness as materials for affinity chromatography separation of proteins (Scheme 11).\[^{55}\]

A particularly interesting combination of CuAAC and ATRP for the synthesis of polymeric dendrimers was introduced by Monteiro and coworkers.\[^{56}\] In an approach similar to that of Opsteen\[^{33}\] and Matyjaszewski,\[^{34}\] ATRP of styrene using a bifunctional initiator provided azidoo telechelic PS. CuAAC capping of each end of this polymer

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**Scheme 10.** Hawker's multivalent, bifunctional dendrimer bearing protein-binding mannose units and fluorescent coumarin moieties.
with tripropargylamine provided tetra-alkyne terminated PS, which was then addressed with an azido-terminated PAA. The result was a polymeric dendrimer possessing a hydrophobic PS core with a hydrophilic PAA shell. The same authors recently expanded this approach by using degradable branching units to yield higher generation polymeric dendrimers with a cleavable periphery (Scheme 12). These amphiphilic dendrimers self-assembled into micelles in aqueous environments, and degradation was achieved via basic hydrolysis of ester groups built into the structure at the branching points. This work provides a nice example of the compatibility of ATRP and CuAAC by offering a straightforward route to complicated polymeric dendrimers.

Dendrimer synthesis typically involves iterative activation-functionalization steps requiring two synthetic steps per generation. Recently, Malkoch and coworkers reported a beautifully streamlined scheme for the preparation of 2,2-bis(methylol)propionic acid (bis-MPA)-triazole and benzyl ether (Frechet type)-triazole dendrimers. Because neither azides nor alkynes require protection during etherification or esterification, and because azide-alkyne ligation can take place in the presence of the unprotected nucleophiles and electrophiles required for etherification or esterification, every step in the synthetic sequence was used to grow the polymer. Fourth generation dendrimers possessing 24 surface hydroxyls were prepared in only four steps, thereby greatly reducing the time required to make such structures and increasing their commercial viability (Scheme 13).

Astruc and coworkers have pioneered the use of the metal binding properties of triazole dendrimers in the field of catalysis. Recently, they reported the catalysis of a number of carbon-carbon bond forming reactions using triazole dendrimer-bound palladium metal. These third generation dendrimers, with 81 surface ferrocene units, were prepared by iterative hydrosilylation-CuAAC reactions and represent novel nanoreactors (Scheme 14).

During the preparation of this manuscript, Liu and coworkers reported a novel synthesis of triazole dendrons which possessed azobenzene chromophores at each branching unit. Structures with as many as 15 azobenzene moieties were prepared by iterative CuAAC/ $S_N2$ reactions (Scheme 15), taking advantage of the special anchimeric assistance reactivity of $\beta$-haloamine electrophiles with azide. It was shown that, despite the steric hindrance within the dendrimer structure, all of the azobenzene groups could quantitatively be converted between cis and trans isomers reversibly using UV and visible light, respectively. The authors mention the potential of these dendrimers as fast, nanoscale, photoactive switches.
Other Discreet Polymeric Structures (Hyperbranched, Brush, and Star Polymers).

Hyperbranched polymers possess properties similar to dendrimers and are typically easier to make at the expense of being polydisperse. The only example of soluble hyperbranched polymer synthesis performed with the aid of the CuAAC reaction to have appeared so far is found in a 2007 report by Sumerlin and coworkers.[63] Here, the click reaction was used to conveniently combine the sensitive acryloyl and trithiocarbonate groups into an initiator for reversible addition-fragmentation chain transfer (RAFT) polymerization. This initiator then provided hyperbranched triazole-based polymers upon reaction with styrene or isopropylacrylamide under standard RAFT conditions.

In recent years CuAAC has been utilized by a number of groups for modular ligation of linear polymers with other molecules to give novel graft/brush polymers,[64–74] star polymers,[75–83] and other architectures.[84,85] Since these can be considered as modification rather than construction applications of CuAAC (see Scheme 2), we only highlight a few interesting examples in this review, with apologies to those omitted because of space considerations. First, Lecomte and coworkers have presented novel tadpole-shaped (Scheme 16)[84] and eight-shaped[85] polymers using a cyclic tin(IV) dialkoxide initiator for controlled ring-opening polymerization of ε-caprolactones (CL) including an α-chlorinated monomer. Conversion of the chlorine groups to azides and subsequent CuAAC with alkyne-PEG yielded complicated structures with potentially novel properties including unexplored modes of self-assembly.

Tunca and coworkers have recently presented an elegant CuAAC-dependent synthesis of star polymers possessing four chemically different arms (ABCD stars, Scheme 17).[76] The authors utilized two novel hetero-trifunctional molecules, the first of which possessed a nitroxide for...
nitroxide-mediated radical polymerization (NMRP), an alcohol for tin(IV)-mediated ring-opening polymerization, and a bromine for later conversion to an azide for CuAAC. The second molecule contained an alkyne for CuAAC, an ATRP initiator, and an alcohol. Ring-opening polymerization of CL from the hydroxyl group of the first molecule, NMRP of styrene from the nitroxide group, and conversion of the bromine to an azide yielded a PS-PCL diblock possessing a single azide at the center. ATRP of methyl acrylate or tert-BA, and carbodiimide coupling of PEG to the second molecule yielded both PtBA-PEG and PMMA-PEG diblock copolymers possessing a single alkyne at the center. CuAAC proved to be an efficient means to couple the PS-PCL-N3 block to the PtBA-PEG-alkyne or PMMA-PEG-alkyne block to yield ABCD star polymers with potentially novel properties.

Scheme 14. Ferrocene-terminated triazole dendrimers used by Astruc and coworkers to bind palladium. The resulting metallo-dendrimers were useful nanoreactors for the catalysis of a number of carbon-carbon bond forming reactions.

or the hydrophobic PS block (for shell and core crosslinking, respectively). These polymers formed micelles in aqueous solution and were subsequently CuAAC crosslinked with bifunctional azides and multifunctional dendritic azides to form polymeric nanoparticles which were further functionalized with fluorescent moieties (Scheme 18). Liu and coworkers recently pursued a similar approach by preparing core crosslinked nanoparticles comprised of poly(N,N-dimethylacrylamide) (PDMA) and poly(N-isopropylacrylamide-co-azidopropylacrylamide).[110]

Caruso and coworkers reported a fascinating synthesis of ultrathin microcapsules by a unique layer-by-layer (LBL)/CuAAC approach.[111] The authors started by making use of electrostatic and hydrogen bonding interactions between PAA and silica to deposit a thin layer of PAA, which had a fraction of its carboxylic acid units converted to azides (PAA-N3), onto the silica particle. A layer of PAA displaying alkynes (PAA-alkyne) was then coated and coupled to the previous layer via CuAAC. This process was repeated for the desired number of iterations yielding covalently crosslinked PAA of controllable thickness on the silica surface (Scheme 19). Fluorescent rhodamine moieties were attached to the remaining alkynes for imaging of the particles. Degradation of the silica interior with hydrofluoric acid produced covalently linked capsules which were shown to swell and deswell reversibly with changing pH.

Hennink and coworkers recently described the synthesis of biodegradable microcapsules using CuAAC between azide- and alkyne-modified dextrans (Scheme 20).[112] The clickable functional groups were linked to dextran precursors via hydrolyzable carbonates which were shown to break down under physiological conditions to release their components at controlled rates. These materials show promise in drug delivery applications where controlled delivery of a bioactive moiety is often necessary.

CuAAC for the Synthesis of Macroscopic “Infinite” Networks

Much of our own work on the materials applications of the CuAAC reaction has been related to the synthesis of infinite networks (materials of macroscopic dimensions) from small molecule and/or polymeric precursors. Such materials require efficient reactions for their preparation as there is a necessary critical conversion percentage of functional groups (depending on the branching functionality) which must be achieved before an infinite network (or gelation) is reached.[114,115] In this vein, CuAAC provides a route to diversely functional crosslinked networks for the same reasons that make it so useful throughout materials synthesis: ease of functional group introduction, chemoselectivity, and high yield. In recent years, CuAAC has

Nanoscale Objects Constructed by CuAAC

A number of groups have recently utilized CuAAC for the decoration of biological,[86–95] polymeric,[96–98] inorganic,[99–106] and carbon[107] nanoscale objects, but only a few examples exist wherein CuAAC was employed for the direct construction of such materials. Wooley and coworkers have demonstrated the synthesis of both shell[108] and core[109] crosslinked polymeric nanoparticles derived from amphiphilic PS–PAA diblock copolymers possessing alkynes on a fraction of either the hydrophilic PAA block

or the hydrophobic PS block (for shell and core crosslinking, respectively). These polymers formed micelles in aqueous solution and were subsequently CuAAC crosslinked with bifunctional azides and multifunctional dendritic azides to form polymeric nanoparticles which were further functionalized with fluorescent moieties (Scheme 18). Liu and coworkers recently pursued a similar approach by preparing core crosslinked nanoparticles comprised of poly(N,N-dimethylacrylamide) (PDMA) and poly(N-isopropylacrylamide-co-azidopropylacrylamide).[110]

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been employed for the construction and functionalization of a range of macroscopic networks which have vast potential in applications ranging from tissue engineering and drug delivery to adhesives and microelectronics. This section is divided into three major categories which summarize the major classes of infinite networks which have been prepared by CuAAC: small molecule covalently linked networks, small molecule supramolecular networks, and crosslinked polymer networks.

Small Molecule Covalently Linked Networks

The first example of CuAAC for network synthesis was reported by Finn and coworkers in 2004 and was recently updated with new results. Taking advantage of the anticipated affinity of triazoles for metal surfaces, an array of multifunctional azides and alkynes were prepared.

**Scheme 15.** Azobenzene dendrons prepared by Liu and coworkers via CuAAC.

**Scheme 16.** Tadpole-shaped polymers prepared by Lecomte and coworkers.

**Scheme 17.** ABCD star polymer prepared by CuAAC coupling of two different block copolymers.
which were polymerized between copper, brass, aluminum, and zinc plates yielding adhesives (Scheme 21). The addition of copper catalyst was not required for adhesive formation on metallic copper and brass plates, indicating that a sufficient amount of Cu(I) is present on the surface to catalyze the CuAAC reaction. The addition of copper salts did accelerate the reaction, however, as did performing the crosslinking at elevated temperatures (although the final adhesive strength did not depend strongly on temperature). In the cases where no catalyst was added, the final crosslinked products contained between 2 and 5 wt.% of copper indicating that the triazole products efficiently leach copper ions from the surface. This study identified a tetrafunctional alkyne and trifunctional azide combination that yielded adhesives which were twice as strong as commercially available metal adhesives in peel tests. Several crosslinked polymers analogous to the adhesive materials were made in bulk and characterized by standard techniques. Interestingly, the glass transition temperatures of these materials were found to be as much as 80 °C higher than the curing temperatures employed indicating a high degree of crosslinking even in the diffusion-restricted glassy state. Potential contributing factors include the high mobility of catalytic Cu(I) centers through a developing matrix of triazoles, the great efficiency of the CuAAC coupling reaction, and the great amount of energy that it releases (approximately 50 kcal mol⁻¹). Recently, Katritzky et al. reported a similar study wherein a library of multifunctional azides and alkynes were polymerized in solution and characterized by standard techniques.

Finn and coworkers also utilized two of their previously studied adhesive molecules, tripropargyl amine with 1,6-diazidohexane, in a solution phase CuAAC reaction to yield a highly crosslinked polymer which was observed to reversibly swell and deswell when treated with trifluoroacetic acid due to the amine functionalities within the material (Scheme 22). The authors suggest that the polarity, stability, and π-stacking properties of the triazole products can potentially be exploited for a range of applications, a notion that has been abundantly confirmed by reports that have appeared in the past few years.

Small Molecule Supramolecular Networks

The first example of small molecule supramolecular hydrogelators prepared by CuAAC was presented by Kim and coworkers in 2003. The authors appended a...
variety of groups to the C5 position of 2'-deoxyuridines via the click reaction. They then showed that these molecules formed lamellar or fibrous hydrogen-bonded gels in water depending on the nature of the C5 substituent. Gallardo

and coworkers have utilized CuAAC to prepare chiral\textsuperscript{124,125} and nonlinear diaryl\textsuperscript{126} triazole compounds which were shown to possess liquid crystalline properties thus warranting their categorization as supramolecular infinite networks. The authors note the simplicity of CuAAC for preparing these compounds and indicate they are screening a library of triazole structures in a search for novel properties.

The CuAAC process was used to "stabilize" organogels by Finn and coworkers in\textsuperscript{127} The authors reasoned that the introduction of azides and alkynes onto the termini of the alkyl chains of the undecylamide of trans-1,2-diaminocyclohexane, a molecule known to self-assemble into supramolecular networks via hydrogen bonding, would not disrupt gelation but perhaps provide a way to strengthen the gel products (Scheme 23). Indeed, self-assembly followed by CuAAC provided a simple and novel means to alter the properties (glass transition temperature and rigidity) of these materials without sacrificing the thermoreversibility of gelation which is unique to supramolecular gels.

An interesting example of CuAAC for the synthesis of metal-organic frameworks (MOFs) was recently reported by Ferey and coworkers\textsuperscript{128} This work explored the isoreticular principle—the concept that the size of pores...
in MOFs can be tuned solely by altering the length of a rigid organic linker connecting the inorganic metal portions. The authors exploited the synthetic convenience provided by the CuAAC to test the principle by installing small flexible units at the ends of rigid organic core molecules. The resulting materials lacked permanent microporosity as a result of contraction facilitated by the small flexible organic components, thereby confirming that the isoreticular principle is limited to completely rigid organic linkers.

Ding and coworkers recently described an example of a different type of supramolecular small molecule network enabled by CuAAC. The authors prepared meso-tetraaryl zinc(II) porphyrins decorated with anion-binding β-cyclodextrin (β-CD) or permethyl-β-CD units by CuAAC attachment of the tetra-alkyne porphyrin to CD azides. Addition of tetraphenylporphyrin tetrasulfonate (TPP-TS) to these compounds resulted in either networks with tetrafunctional branching points (as observed for the permethylated CD derivative, Scheme 24) or one-dimensional nanorods (as observed for the standard CD derivative). The difference in network structure was proposed to depend on the orientations of the cup-shaped CDs: either “expansive” (all four cups facing outward) or “contractive” (only two cups facing outward). The expansive state was observed for the permethyl derivative, allowing each sulfonate group of TPP-TS to be bound by a CD host, resulting in a tetrafunctional branched network. In contrast, the standard CD derivative was found to be locked in the contracted state, resulting in the formation of linear networks via binding of only two TPP-TS moieties in a *trans* fashion.

**Scheme 24.** Supramolecular networks prepared by interaction between TPP-TS and tetra-functional CDs. Different structures (2-D network vs. linear) were observed depending on which CD derivative (R) was employed for the crosslinking. CuAAC was utilized to construct the self-assembling building blocks by attachment of CDs to a zinc porphyrin.

Crosslinked Polymer Networks

CuAAC has proven useful for the synthesis of a range of crosslinked polymeric materials. In 2006, Ossipov and Hilborn presented the first example of CuAAC for the synthesis of polymeric hydrogels. By modifying poly(vinyl alcohol) (PVA) with a fraction of either azide or alkyne functionalities, the authors showed that...
hydrogel materials with tunable mechanical properties could be prepared by CuAAC crosslinking with either bifunctional crosslinkers bearing the antagonist azide or alkyne functionality, or by crosslinking of the azide-PVA with alkyne-PVA (Scheme 25, 130).

Soon after this work, Hawker and coworkers reported the first application of CuAAC to the synthesis of end-linked polymeric “model network” hydrogels. Bifunctional alkyne-PEGs were crosslinked with tetrafunctional azide-PEGs (Scheme 25, 131),[131] to produce materials with mechanical strengths about ten times greater than conventional photo-crosslinked PEG materials. Any remaining azide and alkyne groups could be functionalized by CuAAC post-gelation to “decorate” the gel with imaging moieties. Importantly, gels crosslinked by CuAAC in the presence of additives such as a radical scavenger, carbon black, and TiO₂ still possessed excellent mechanical properties. In contrast, photocrosslinking under these conditions would be inefficient due to adsorption of light and quenching of excited state radicals by the additives. Lastly, PEGs containing ester linkages were shown to yield hydrolytically degradable materials whereas ether linked gels were completely stable to changes in pH.

A recent article by Lamanna and coworkers describes the CuAAC synthesis of novel hyaluronan hydrogels from azide and alkyne-modified polymers (Scheme 25, 132)[132] Crosslinking in the presence of the drug molecules benzidamine and doxorubicin yielded loaded gels which released the drugs at rates dependent on the degree of crosslinking. Furthermore, CuAAC crosslinking in the presence of yeast cells provided porous materials with homogeneously distributed live cells. This report contradicts the conventional wisdom that the copper AAC catalyst is toxic to in vivo applications of the reaction. While this expectation is certainly reasonable and is undoubtedly true in some circumstances, it has yet to be conclusively tested, especially in the presence of Cu-binding ligands. Furthermore, one can certainly expect many cells to survive exposure to Cu-containing media, since copper is a common element and cells possess effective means to regulate Cu trafficking. Thus, work by Lamanna, and other reports in nonmaterials areas,[133–135] suggest that CuAAC in the presence of live cells is a promising approach to biocompatible scaffolds for tissue engineering, among other biomaterials applications.

Recently, Lecomte and coworkers utilized ring-opening polymerization of an α-chloro caprolactone followed by conversion of the halides to azides to obtain azide-functionalized PCL. These materials were then subjected to CuAAC crosslinking in one pot with a PEG dialkyne and
N,N-dimethyl propargylamine to yield amphiphilic materials with grafted amine functionalities (Scheme 25, 136). The authors demonstrated the pH-dependent swelling of the final materials as well as the pH-dependent release of a model dye cargo. This work provides another example of the tailoring of physical properties of networks such as hydrogels by the use of alternately functionalized click components (alkynylamines in this case) in the CuAAC step.

A very recent publication by Baker and coworkers described an interesting synthesis of biodegradable propargyl glycolide polymers (Scheme 25, 137). By CuAAC grafting of different ratios of decyl and PEG chains to the glycolide backbone, polymer brushes that displayed lower critical solution temperature (LCST) behavior were produced. LCST occurs when polymers form a supramolecular crosslinked gel driven by the expulsion of water as temperature is lowered. The cloud point of these materials was found to vary between 25 and 70 °C in direct proportion to the percentage of PEG chains (from 55 to 90%, respectively) employed, and the authors suggest that expanding these boundaries may be possible. Such materials provide novel, biodegradable, and thermoresponsive hydrogels which may be useful for a range of biomedical applications.

Anseth and coworkers have reported the synthesis of PEG-peptide model hydrogels derived from tetraazido-terminated PEG star polymers coupled with linear alkyne-telechelic peptides. The peptide domains featured photo-reactive alloxyycarboxyl (Alloc) groups which were coupled to fluorescent, cysteine-containing peptides via transparency-based photolithography to yield internally patterned materials and gradient-functionalized hydrogel networks. The latter are of biological importance, as cell migration can often be controlled using chemical gradients. Although we do not describe it in this review, our laboratories are pursuing an alternate pathway to model networks having chemical and mechanical gradients by photolithography of materials possessing selectively photodegradable units.

The above examples all describe hydrogel networks, however, a number of groups have reported examples of other polymeric crosslinked networks prepared from click chemistry. Turro and coworkers have utilized CuAAC to prepare novel degradable end-linked PtBA model networks (139). ATRP polymerization of PtBA from a bifunctional initiator containing an internal double bond, and subsequent end-group transformation with sodium azide yielded ozone-cleavable $\alpha,\omega$-azido-PtBA macromonomers. CuAAC crosslinking with tri- and tetra-functional alkynes yielded end-linked model networks that possessed pore sizes related to the molecular weight of the starting macromonomer. Ozonolysis of these materials yielded star polymer products of defined molecular weight, as determined by SEC analysis, depending on which crosslinker was used. The same authors later reported an extension of this work wherein the ozonizable double bond was replaced with a photocleavable nitrobenzyloxycarbonyl linkage to yield photodegradable materials of defined structure. In this article, they also demonstrated the first tandem CuAAC/ATRP reaction for the assembly of clickable four-armed structures. In this case, the resulting tetra-azido-terminated photodegradable star polymers were crosslinked with a bifunctional alkyne to give photodegradable materials in a route complementary to that based on linear polymers described above (Scheme 26).

In 2007, a paper by Yagci and coworkers highlighted the ability of CuAAC to introduce orthogonal functionality for post-polymerization processing in a convenient fashion, in this case for the production of thermally curable PS. First, a PS-co-poly(chloromethylstyrene) random copolymer was prepared by NMRP. The $p$-chloromethyl groups were exchanged with azides by nucleophilic substitution which was followed by CuAAC to attach alkyne-functionalized benzoxazine moieties. Benzoxazines are known to polymerize under thermal conditions and the resulting crosslinked networks (Scheme 27) obtained upon heating of the benzoxazine-functionalized PS showed stronger mechanical properties than networks prepared by typical copolymerization with divinyl monomers.
Ravelo and coworkers recently utilized diazide and dialkyne organogelators to prepare novel organogels.[25] In this case, however, the CuAAC reaction was performed prior to gelation yielding linear polymers which were then shown to form thermoreversible gels by hydrogen bonding in dimethylsulfoxide (DMSO) and other DMSO-organic solvent mixtures. Interestingly, two unexpected requirements of gel formation were the presence of an SO2 group on the backbone of the polymers and the presence of some residual copper from the CuAAC reaction. The presumed interaction of Cu2+ with the triazole products of CuAAC modification is thought to facilitate gelation, allowing these materials to be considered as “metallogels”.

Grubbs and coworkers recently reported the synthesis of liquid crystal gel networks which were shown to be reversible electro-optic switches which converted between a “scattering polydomain state” and a “transmissive monodomain state” in the presence of an electric field.[141] These gels were prepared by CuAAC crosslinking of azido-telechelic poly(cyclooctene) polymers which possessed a mesogenic cyano-biphenyl group on each repeat unit (Scheme 28). As the authors note, the modularity of the synthetic method makes it possible to study the effects of polymer chain length and structure on the electro-optical properties of liquid crystals.

**Crosslinked Polymer Surfaces and Thin Films**

Thin polymer films are important in a range of applications including sensors, electronics, displays, and gas separation. An obvious approach would be covalent LBL construction, but relatively few examples exist due to a lack of orthogonal, high-yielding reactions capable of producing such materials. As a result, most LBL surfaces rely on noncovalent interactions such as hydrogen bonding or electrostatic attraction between polymers, and so their mechanical properties and chemical diversity may be limited for certain applications. Recently, CuAAC has provided a unique route to covalently linked thin films and has effectively opened the field of LBL synthesis to nearly any polymeric precursors.

The first example of CuAAC for LBL construction of thin films was reported by Caruso and coworkers in 2006.[142] The authors utilized PAA-N3 and PAA-alkyne to iteratively CuAAC-couple PAA layers onto a variety of macroscopically flat surfaces. UV-Vis and FTIR measurements confirmed the increase in film thickness with each subsequent CuAAC reaction as well as the high yield of the CuAAC process. This methodology was later used for the synthesis of ultrathin spherical capsules[111] as mentioned above (Scheme 19).

Polyethylene (PE) is well known to be resistant to LBL modification, but Chance and coworkers recently incorporated CuAAC into such a scheme.[143] Oxidation of PE with CrO3/H2SO4 and functionalization of the resulting carboxylic acids with alkynes provided a substrate that could be addressed with water-soluble azide and alkyne-functionalized poly(alkylacrylamides) (PAM) in an LBL fashion. The resulting PAM-coated PE materials were further derivatized with small molecules in a final CuAAC step. As is frequently the case, the CuAAC chemistry here was performed in water, a reaction medium of increasing interest in materials processing because of its perceived environmental benefits.

Hawker and coworkers recently reported LBL film synthesis using dendritic alkynes and azides (Scheme 29).[144] The authors hypothesized that the monodispersity and high degree of functionality of dendrimers should provide for stable films with greater control over the thickness growth with each layer. Indeed,
by ellipsometry measurements the authors confirmed that the film thickness increase with each layer was dependent on the generation of dendrimer used and was a constant for each new layer. Interestingly, the fifth generation bis-MPA dendrimers give a drastic increase in thickness due to the “dendritic” effect, in which steric hindrance causes the structure to avoid compression and remain spherical. As expected, linear polymeric azide and alkyne analogs gave much larger and more variable increases in thickness for each LBL step.

Crosslinked Structures Derived from Nanosized Building Blocks

Covalent crosslinking of nanoscale objects is a blossoming field which promises to give rise to novel materials possessing potentially unprecedented properties. Rao and coworkers have recently studied the structural diversity of CuAAC covalently crosslinked nanorods, nanoparticles, and nanotubes. An interesting example was provided by their observation that thioazide- and thioalkyne-capped gold nanorods formed chain-like structures (Figure 1) whereas spherical gold particles formed an organized network. The authors suggested that the rods form chain structures because the thiol linkers prefer to bind to the ends of the gold rods where the (1,1,1) face of gold is available. These results hint at the diversity of phenomena to be uncovered in the exciting field of covalent nanostructure assembly. These investigators have also provided exciting TEM images of CuAAC crosslinked CdSe nanocrystals showing the formation of periodic arrays as well as the marriage of alkyne-
functionalized gold nanoparticles with azide-functionalized carbon nanotubes to yield novel nanoscopic hybrid structures.

**Conclusion**

The CuAAC reaction has proven effective for a broad range of materials construction applications. From small molecules to linear polymers to branched polymers to organogels, the CuAAC process has been successfully applied to building blocks of every scale and chemical functionality. Furthermore, structure–property relationships of many complicated materials (for example the electro-optic properties of liquid crystals as a function of polymer chain length) can now be studied in great depth, as the synthesis of the required polymeric precursors is made reliable by CuAAC. Lastly, the process is user friendly: many first-time attempts are successful, with off-the-shelf and inexpensive catalyst components.

These features place even greater emphasis on the function of the materials that can be envisioned, rather than on the potential problems of their construction. We are excited to see the continued use of CuAAC for an increasingly creative and diverse array of materials applications.

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