Clicking polymers: a straightforward approach to novel macromolecular architectures

David Fournier, Richard Hoogenboom and Ulrich S. Schubert*

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Living/controlled polymerization techniques have enabled the synthesis of a large variety of different well-defined (co)polymer structures. In addition, the use of click chemistry in polymer science is a quickly emerging field of research since it allows the fast and simple creation of well-defined and complex polymeric structures in yields that were previously unattainable. In this *critical review*, the application of the azide–alkyne 1,3-dipolar cycloaddition for the construction of well-defined polymer architectures will be discussed in detail, providing a comprehensive overview for all disciplines related to polymeric materials.

1 Introduction

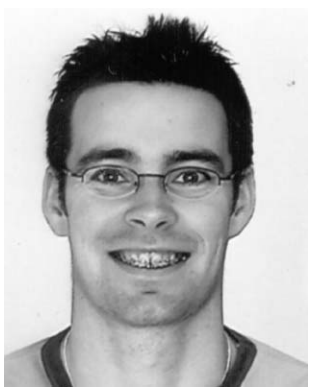
Over the past decades, chemists have continuously explored novel synthetic approaches for the preparation of functional polymers and materials with improved properties. Various well-known reactions in the field of organic chemistry have been transformed into polymer chemistry, which has led to the development of, for instance, atom transfer radical polymerizations[1] (ATRP) from the atom transfer radical addition reaction.[2] The development and the perfection of a variety of other living/controlled polymerization techniques has enabled the synthesis of a large variety of well-defined (co)polymer structures as depicted in Fig. 1.

Despite this major improvement made in the last 50 years[3] since the discovery of living polymerizations,[4] not all different polymer backbones can be easily combined into one single copolymer architecture due to incompatibilities between different polymerization methods. Nonetheless, the ever more demanding requirements for novel polymeric materials raise the necessity to be able to combine all kinds of polymers in an easy manner. To overcome this challenge, polymer chemists have explored a variety of approaches to combine different polymer chains including the use of heterofunctional initiators[5] and mechanistic transformations from one living/controlled polymerization method into another.[6] In addition, the combination of synthetic organic chemistry and polymer

Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology and Dutch Polymer Institute (DPI), PO Box 513, 5600 MB Eindhoven, The Netherlands. E-mail: u.s.schubert@tue.nl.; Fax: +31 40 247 4186

David Fournier

David Fournier was born in 1978 in Le Mans (France). In 2002, he received his Master degree in Chemistry and Physicochemistry of Polymers at the Université du Maine (Le Mans, France). In 2005, he obtained his PhD under the direction of Professor Laurent Fontaine and the supervision of Dr Sagrario Pascual as well as Dr Véronique Montembault (Unité de Chimie Organique Moléculaire et Macromoléculaire, Le Mans, France). The research topics were focused on the synthesis and the design of functionalized (co)polymers by controlled radical polymerizations in solution and onto polymeric supports and their applications in fields of scavenging and supported catalysts. He moved to the Laboratory of Macromolecular Chemistry and Nanoscience in Eindhoven as a postdoctoral fellow where he is working on the synthesis of well-defined thermosensitive copolymers via controlled radical polymerizations and living cationic ring-opening polymerization using high-throughput experimentation.



Richard Hoogenboom

Richard Hoogenboom was born in 1978 in Rotterdam (The Netherlands). In 2001 he obtained his MSc degree in chemical engineering at the Eindhoven University of Technology, whereby his undergraduate research was performed in the group of Bert Meijer (Eindhoven, The Netherlands). During the studies, he performed an internship within the group of Andrew Holmes (Cambridge, United Kingdom). In 2005, he obtained his PhD under supervision of Ulrich Schubert (Eindhoven, The Netherlands) focusing on supramolecular initiators for controlled polymerization techniques, automated parallel synthesis of well-defined polymers and microwave irradiation in polymer chemistry. Currently, he is working as project leader for the Dutch Polymer Institute (DPI). The major focus of his current research is related to the use of high-throughput experimentation and microwave irradiation for living/controlled polymerization techniques.

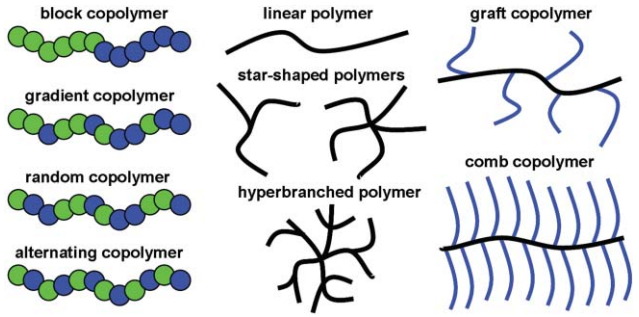


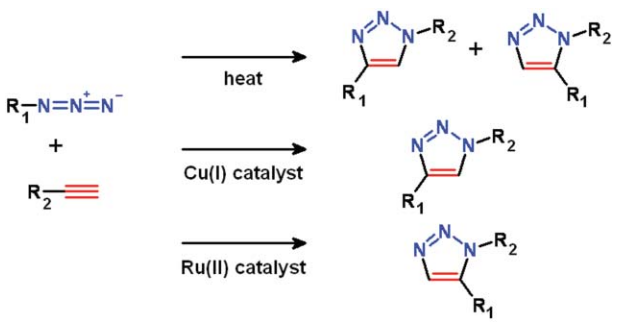
Fig. 1 Schematic overview of selected (co)polymer architectures.

chemistry is a very promising approach to build novel structures by coupling preformed polymers,[7] which allows the combination of the state-of-the-art in living/controlled polymer chemistry with the best known organic coupling procedures. In this respect, the concept of click chemistry that was introduced by Sharpless[8,9] seems to be the ideal method to couple preformed polymer structures. Click chemistry comprises a number of organic heteroatom coupling procedures that comply with the stringent criteria as defined by Sharpless:[8]

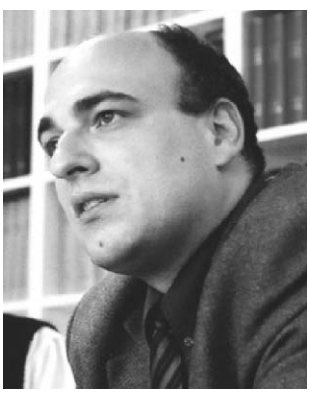
"The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification – if required – must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions."

These strict conditions can only be met when reagents with high energy content are involved including, *e.g.*, unsaturated C–C bonds or strained rings. Nowadays the most popular click reaction is the copper(I) catalyzed 1,3-dipolar azide–alkyne cycloaddition. Originally, the azide–alkyne (Huisgen) cycloaddition was performed at high temperatures resulting in the formation of both 1,4- and 1,5-substituted-1,2,3-triazoles conflicting with both the required simple reaction conditions and stereospecificity (Scheme 1).[10–12] Mock *et al.*[13,14] demonstrated that the azide–alkyne cycloaddition is catalyzed by encapsulation of amine functionalized reagents with cucurbituril yielding only the 1,4-substituted-1,2,3-triazole. This elegant procedure was also applied for the preparation of chain-extended polymers by Steinke and co-workers[15,16] using bisalkyne and bisazide monomers. However, the cucurbituril catalyzed cycloaddition requires amine containing reagents as driving force for the encapsulation and yields poly(rotaxane)s so limiting the versatility. The major drawbacks of the azide–alkyne cycloaddition were only successfully overcome in 2002, when two independent research teams led by Sharpless[17] and Meldal[18] reported the use of copper(I) catalysts for the 1,3-dipolar cycloaddition of azides and alkynes. The use of a copper(I) catalytic system results in the exclusive formation of the 1,4-substituted 1,2,3-triazole and it accelerates the reaction tremendously allowing room-temperature cycloadditions (Scheme 1).[19,20] In practice, the copper(I) catalyst can be generated *in situ* using copper(II) sulfate and sodium ascorbate as reducing agent or a copper(I) halide is used together with a stabilizing ligand. The mechanism of the copper-catalyzed azide–alkyne cycloaddition reaction has been studied in detail by Finn and co-workers.[21] In addition, Fokin, Jia and co-workers[22] demonstrated that using a ruthenium(II) catalyst for the azide–alkyne cycloaddition changes the stereospecificity leading to solely the 1,5-regioisomer of 1,2,3-triazole (Scheme 1).

The versatility and insensitivity, *i.e.* excellent functional group tolerance, that eliminates the need for protecting



Scheme 1 1,3-Dipolar cycloadditions between alkynes and azides resulting in the formation of a mixture of regioisomers [heat, no catalyst], the 1,4-regioisomer [copper(I) catalyst] or the 1,5- regioisomer [ruthenium(II) catalyst] of 1,2,3-triazole.



Ulrich S. Schubert

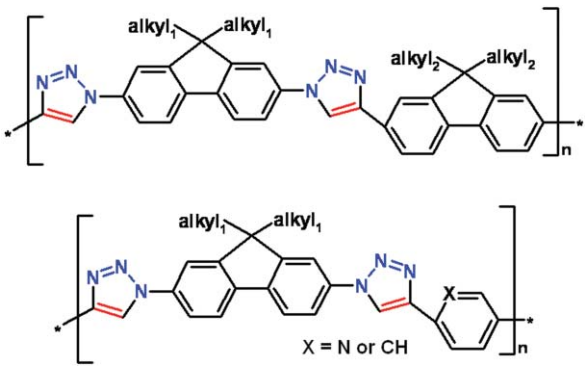
Ulrich S. Schubert was born in Tübingen in 1969. He studied chemistry at the Universities of Frankfurt and Bayreuth (both Germany) and the Virginia Commonwealth University, Richmond (USA). His PhD work was performed under the supervision of Professor Eisenbach (Bayreuth, Germany) and Professor Newkome (Florida, USA). In 1995 he obtained his doctorate with Prof. Eisenbach. After a postdoctoral training with Professor Lehn at the Université Strasbourg (France) he moved to the Technische Universität München (Germany) to obtain his habilitation in 1999 (with Professor Nuyken). From 1999 to spring 2000 he held a temporal position as a professor at the Center for NanoScience at the Universität München (Germany). Since Summer 2000 he is Full-Professor at the Eindhoven University of Technology (Chair for Macromolecular Chemistry and Nanoscience). His awards include the Bayerischen Habilitations-Förderpreis, the Habilitandenpreis of the GDCh (Makromolekulare Chemie), the Heisenberg-Stipendium of the DFG, the Dozenten-Stipendium of the Fonds der Chemischen Industrie and a VICI award of NWO. The major focus of his research interest relates to organic heterocyclic chemistry, supramolecular materials, combinatorial material research, nanoscience, inkjet printing functional materials and tailor-made macromolecules.

groups, of the copper(I) catalyzed 1,3-dipolar cycloaddition between azides and alkynes has led to its rapid evolution into a common tool in various research areas including, *e.g.*, organic synthesis,[8,23] biochemistry,[24–27] sugar derivatization[28,29] and drug discovery.[9] Additionally, the 1,3-dipolar cycloaddition has been used to tune the surface functionality of different polymeric or non-polymeric materials such as electrode surfaces,[30] gold,[31] magnetic metal oxides,[32] silica particles[33] and porous beads.[34,35] Moreover, microcontact printing[36,37] has been applied to modify azide- or alkyne-functionalized self-assembled monolayers (SAMs).

In recent years, polymer chemists also discovered the numerous advantages of using the copper(I) catalyzed 1,3-dipolar cycloadditions as an easy tool for the preparation of novel polymeric structures. Since the first report of click chemistry in polymer science by Hawker, Sharpless and co-workers,[38] the construction of well-defined and complex macromolecular architectures *via* click chemistry is a strongly growing field of research throughout the world. The current excitement of polymer chemists to adapt click chemistry, resulting in several new publications on this topic every week, demonstrates that click chemistry provides an easy solution to the longstanding challenge of quantitatively coupling polymers made by different living/controlled polymerization techniques. In this critical review, we will discuss recent applications of click chemistry in polymer science, whereby special attention will be given to the construction of novel well-defined macromolecular architectures. Related (mini)reviews have appeared in recent literature dealing with the convergence of synthetic organic and polymer chemistry,[7] azide–alkyne cycloadditions in material science and organic chemistry,[39] the use of azide–alkyne cycloadditions as a universal ligation tool in polymer and materials science[40] as well as click functionalization of polymers prepared *via* atom transfer radical polymerization.[41] Nonetheless, this review distinguishes from the others by its focus on the construction of well-defined macromolecular architectures, which became readily available by the elegant utilization of click chemistry.

2 Azide–alkyne click chemistry in polymer science

Only two years after the concept of click chemistry was introduced to polymer science by Hawker, Sharpless and co-workers,[38] click chemistry is a well-established method for the preparation of well-defined macromolecular architectures. For the preparation of such well-defined structures, click chemistry has to be combined with living/controlled polymerization methods that allow the preparation of well-defined polymeric building blocks functionalized with alkyne or azide groups. In contrast, the azide–alkyne cycloaddition of bifunctional alkyne and azide monomers can also be applied for step-growth polymerization[42] resulting in the formation of ill-defined polymeric structures with 1,2,3-triazoles in the main chain. Reek and co-workers used such a cycloaddition click polymerization for the preparation of conjugated polymers (Scheme 2) by the step-growth polymerization of diazido and diethynyl conjugated building blocks.[43] Similarly, step-growth click polymerizations can be performed using flexible polymeric building blocks resulting in chain-extended polymers as



Scheme 2 Examples of conjugated polymers made by step-growth click polymerization.[43]

was demonstrated by Matyjaszewski and co-workers using α-acetylene-ω-azido-functionalized polystyrene (PS)[44] as well as for the copolymerization of α,ω-diazido-functionalized PS with propargyl ether.[44,45] Qing and co-workers reported a similar approach for the synthesis of alternating copolymers starting from diazido-poly(ethylene oxide) (PEO) and 1,2-bis(4-ethynylphenoxy)perfluorocyclobutane.[46]

The use of click chemistry for step-growth click polymerizations provides a new platform for the efficient and mild preparation of chain-extended and alternating copolymers. Nevertheless, the use of click chemistry will have a much greater impact in the field of well-defined copolymers since ever more sophisticated methods and approaches are explored continuously to increase the complexity of the polymer structures without losing the control over the system. The use of azide–alkyne click chemistry for the preparation of well-defined polymers is discussed in the following sections.

2.1 End-functionalization of well-defined polymers

The preparation of well-defined polymeric building blocks with one or two azide and/or alkyne functionalities at the chain-end has received significant attention in the last several years, whereby especially the ATRP mechanism was often exploited for the synthesis of azide-functionalized polymers by exchange of the halogen chain ends using sodium azide (Fig. 2). The resulting well-defined azide functionalized polymers have been used for the quantitative preparation of polymers with otherwise difficultly accessible functional groups at the chain ends *via* click chemistry.

This approach was explored by Lutz *et al.*[47] for the end-functionalization of PS. The copper(I) catalyzed cycloaddition of several functional acetylenes with azido-PS allowed the quantitative formation of PS end-functionalized with a primary alcohol, a carboxylic acid or a vinylic group as depicted in Fig. 2. In addition, biocompatible azido-functionalized poly(oligo(ethylene oxide) acrylate) was used for the preparation of various functional biocompatible polymers as well as polymer bioconjugates using the copper(I) catalyzed azide–alkyne cycloaddition.[48] Cornelissen, Rutjes and co-workers[49] also used click chemistry to prepare amphiphilic PS bioconjugates that self-assembled into micellar structures in aqueous solutions. At this point, it should be noted that a major advantage of the copper(I) catalyzed cycloaddition is its

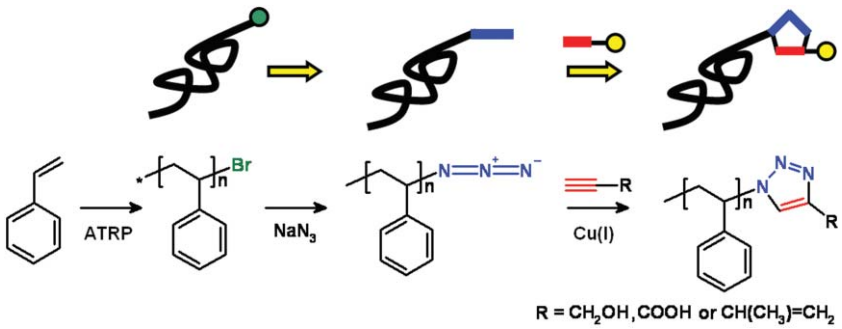


Fig. 2 Preparation of end-chain functionalized PS *via* a combination of ATRP and click chemistry.[47]

functional group tolerance that allows the preparation of bioconjugates without the commonly required functional group protection and deprotection steps.

A comparable strategy was applied by the groups of Chen[50] as well as Sumerlin[51] for the synthesis of well-defined macromonomers by clicking of propargyl methacrylate to azido-functionalized (block co)polymers that were prepared by ATRP. Subsequent free radical polymerization of these macromonomers resulted in the formation of ill-defined (amphiphilic) comb-like (co)polymers. Up to this point, the controlled polymerization of such macromonomers leading to well-defined comb polymers was not reported.

The preparation of end-functionalized polymers *via* click chemistry can be further expanded but the use of diazido-functionalized polymers that are also readily available through the ATRP mechanism by the use of bifunctional initiators. Matyjaszewski and co-workers[52] synthesized α,ω-diazido PS and investigated the copper(I) catalyzed click reaction of propargyl alcohol to this polymer in detail revealing that the second click reaction on the same polymer chain was about three times slower than the first.

2.2 Block copolymers

Well-defined block copolymers are of major interest in polymer science due to their demixing behavior in the bulk material (phase separation)[53] as well as in solution (self-assembly).[54] The concept of click chemistry appears to be ideally suited for the preparation of block copolymers that cannot simply be combined using one single or easily convertible polymerization methods. The main advantage of using a quantitative coupling method to couple end-functionalized polymers resides in the exclusion of, the often incomplete, reinitiation of the first block in order to grow the second block.

The copper(I) catalyzed 1,3-dipolar cycloaddition has been first explored for the preparation of block copolymers by Opsteen and Van Hest.[55] A variety of acetylene and azido functionalized polymers was prepared including azido and diazido PS, acetylene-functionalized poly(methyl methacrylate) (PMMA) as well as azide and acetylene functionalized PEO. These building blocks were combined using the copper(I) catalyzed 1,3-dipolar cycloaddition to prepare a series of amphiphilic diblock copolymers. In addition, the synthesis of a amphiphilic triblock copolymer based on PS and PEO was demonstrated as depicted in Fig. 3.

The one-pot synthesis of triblock copolymers by two simultaneous coupling procedures was reported by Hizal, Tunca and co-workers.[56] PMMA-*block*-PS-*block*-PEO and PMMA-*block*-PS-*block*-poly(ε-caprolactone) were prepared by a Diels–Alder coupling reaction to couple the PMMA and PS in combination with the copper(I) catalyzed azide–alkyne

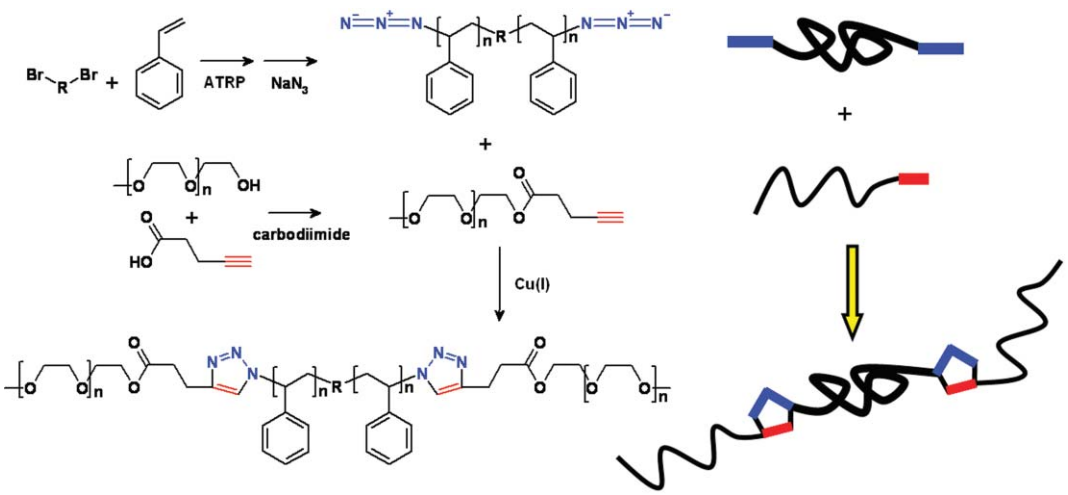


Fig. 3 Synthesis of a triblock copolymer *via* click chemistry. The diazido PS was prepared by ATRP utilizing a bifunctional initiator and the acetylene-functionalized PEO was prepared by a carbodiimide catalyzed esterification.

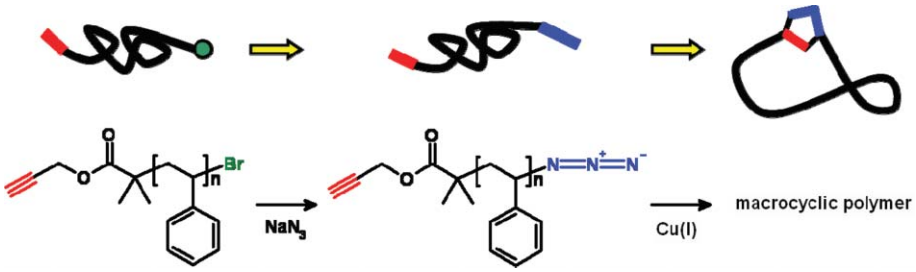


Fig. 4 Synthesis of macrocyclic polystyrene by clicking the ends of azide–alkyne functionalized polystyrene together.[59]

cycloaddition to couple the PS with the PEO or poly(ε-caprolactone) (PεCL). Although the reported procedure is a very elegant and promising approach for the synthesis of well-defined triblock copolymers, the required 36 h heating to 120 °C makes its classification as click chemistry questionable.

2.3 Cyclic polymers

The synthesis of cyclic polymers has been a goal for polymer chemists for a long time since such cyclic structures should offer interesting physical properties.[57] Although many ways have been explored to obtain macrocyclic polymers, they could only be prepared with very low yields.[58] To overcome this limitation, the 1,3-dipolar cycloaddition was explored for the preparation of cyclic polymers by Laurent and Grayson (Fig. 4).[59] An alkyne-functionalized initiator was employed for the ATRP of styrene to yield well-defined polystyrene bearing an alkyne moiety from the initiator on one chain end and a bromine atom that was converted into an azide functionality at the other chain-end. The subsequent macrocyclization *via* the click reaction was performed in a highly diluted medium while the azide–alkyne functionalized polymer was added continuously to the reaction mixture to avoid intermolecular reactions. In this way, the desired cyclic polymer could be obtained in 80% yield, which was previously unachievable with other coupling methods.

2.4 Side-chain functionalization

Tuning polymer properties in a predictable way for specific applications is a utopia in polymer science. The search for novel polymers often includes the synthesis and characterization of a large variety of different polymers. To accelerate this process, it would be highly desired to design a general polymer backbone with variable side-chain functionalities in order to tune the properties of the resulting copolymer. Nevertheless, the defined post-modification of polymer side-chains remains a challenge due to low conversions caused by sterical hindrance. Therefore, the quantitative copper(I) catalyzed azide–alkyne cycloaddition seems to be a promising alternative for the side-chain functionalization of polymeric materials and, thus, to tune the polymer properties.

In fact, one of the first reports of click chemistry in polymer science was dedicated to the cycloaddition of azide-functionalized dendritic wedges to poly(vinylacetylene).[60] After the click reaction, the size of the resulting polymers increased with increasing size of dendritic wedges up to generation 3 indicating their successful coupling while the generation 4 dendritic wedge could not be coupled at all, which was attributed to inaccessibility of the azide in the pseudo-aqueous environment. In related work, Binder and Kluger[61] have investigated the combination of ring-opening metathesis polymerization (ROMP) in combination with azide–alkyne click chemistry. Different 7-oxynorbornene monomers were prepared bearing acetylene side groups or alkyl-bromide side groups as precursor for the azido functionalized monomer. It was demonstrated that it was both possible to first perform the click reaction on the monomer followed by the ROMP as well as to first perform the ROMP followed by the click functionalization (Fig. 5). Various functional groups were clicked to the polymer backbones including alkyl chains, fluorinated chains[62] as well as thymine and the so-called Hamilton receptor[63] as hydrogen bonding moieties. The hydrogen bonding recognition units were used to bind nanoparticles onto polymeric films, whereby the hydrogen bonding receptor density was varied to study the effect on the binding. Surprisingly, the receptor density was varied by changing the copolymer structure (requiring the synthesis of a large number of copolymers) instead of changing the stoichiometry of the azide–alkyne click reaction.

Matyjaszewski and co-workers[64] explored the direct polymerization of acetylene and azido-functionalized monomers (*i.e.* propargyl methacrylate and 3-azidopropyl methacrylate) using ATRP to provide polymeric scaffolds for click chemistry. Only the polymerization of 3-azidopropyl methacrylate led to well-defined polymers and subsequent copper(I) catalyzed cycloaddition of acetylenes led to polymers with carboxylic acid, alcohol, triphenylphosphine or halogen functionalities in the side-chain. Haddleton and co-workers[65] overcame the ill-controlled polymerization of propargyl methacrylate by (co)polymerizing the protected 3-(trimethylsilyl)prop-2-ynyl methacrylate with either MMA or methoxy-(poly(ethylene glycol))$_{300}$ methacrylate using ATRP. After deprotection of the trimethylsilyl-alkyne, azidosugar derivatives were coupled to the polymers and the resulting glycopolymers could be used to efficiently bind appropriate lectins. Similarly, Weck and co-workers[66] synthesized copolymers of chloromethylstyrene and vinylcarbazole, whereby the chloromethyl group was utilized to incorporate azide groups in the side chain. These azide groups were used to click phosphorescent iridium(III) metal complexes as depicted in Fig. 6. The combination of this phosphorescent material with the hole-transporting poly(vinylcarbazole) are thought to improve the efficiencies of light emitting diodes, whereby the major advantage of the click chemistry is the easy

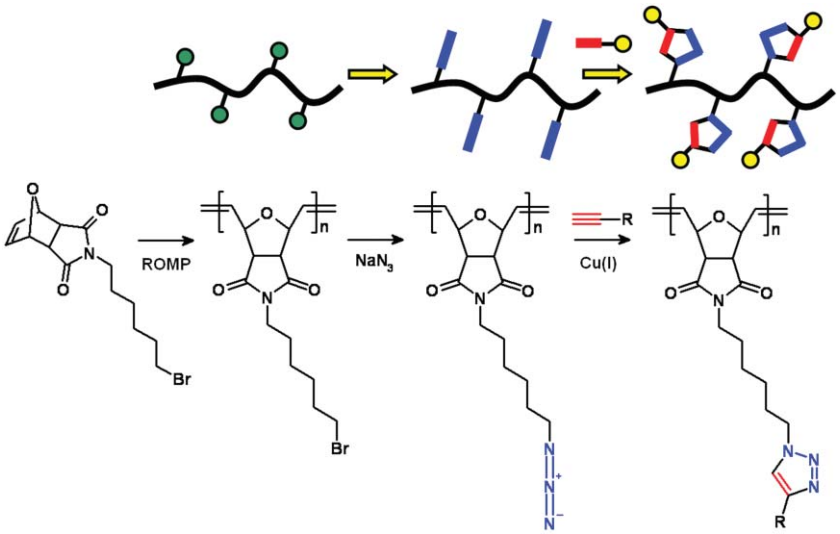


Fig. 5 ROMP of 7-oxynorbornene derivate and click reaction with the pendant chain functions.[61]

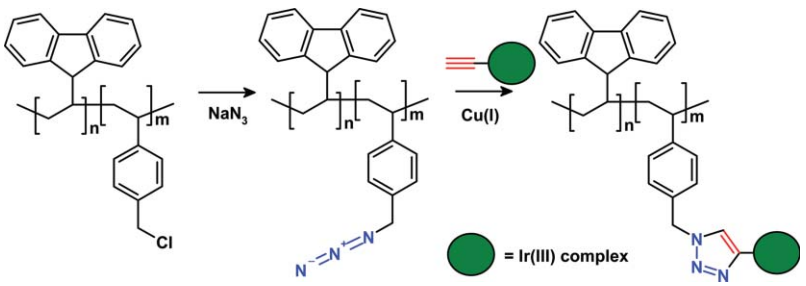


Fig. 6 Functionalization of copolymers with iridium(III) complexes using click chemistry.[66]

functionalization of the hole-transporting polymer with different or multiple phosphorescent groups.

The potential of the combination of azide–alkyne cycloaddition with other coupling procedures was fully explored and demonstrated by Hawker and co-workers.[67] Well-defined polymers bearing both alkyne and hydroxyl functional groups in the side chain were prepared *via* nitroxide mediated polymerization (NMP). Subsequent functionalization of the copolymers was successfully and quantitatively performed by simultaneous click chemistry and derivatization of the hydroxyl groups by anhydride esterification or coupling with a succinimidyl ester. The modularity of this approach was further demonstrated by using different hydrophilic and hydrophobic polymer backbones. In addition, well-defined polymers were prepared *via* NMP having alkyne or succinimidyl ester functionalities in the side chain. These copolymers were further functionalized in a one-pot cascade procedure that combined a click chemistry step and an esterification or amidation reaction, whereby the polymer functional group X reacts with a linker Y and a terminal group Z yielding the cascade product XYZ onto the polymer. By carefully choosing the functional group on the polymer (*e.g.* alkyne), the two functional groups of the linker (*e.g.* azide and amine) and the terminal group functionality (*e.g.* succinimiyl ester), the high fidelity of the cascade functionalization was achieved.

The click chemistry concept was also applied for the side-chain functionalization of biodegradable and biocompatible polymers. Luxenhofer and Jordan[68] prepared a 2-oxazoline monomer with a pendant alkyne function that could be successfully polymerized *via* a living cationic ring-opening polymerization mechanism without the need for protection. Poly(2-oxazoline)s with novel functional groups in the side chains were subsequently prepared *via* click chemistry resulting in novel biocompatible (co)polymers that can be used as polymeric therapeutics and to bind active recognition sites for drug delivery in cancer therapy.[69] Biodegradable aliphatic polyesters have been largely studied, whereby poly(ε-caprolactone) (PCL) and its derivates are the most studied class of polyesters. Jérôme and co-workers[70,71] reported the synthesis of poly(α-chloro-ε-caprolactone-*stat*-ε-caprolactone) by ring opening polymerization (ROP). The pendant chloride atom was subsequently substituted to an azide group using sodium azide in *N*,*N*-dimethylformamide at room temperature. Afterwards, the azido-functionalized copolymer was reacted with functional alkynes to provide biodegradable copolymers with functionalized side-chains. This click reaction had to be performed with CuI and triethylamine as catalytic system since the use of copper sulfate with sodium ascorbate led to partial degradation of the material.[70,71]

Besides the side-chain functionalization of flexible polymers, click chemistry was applied for the side-chain functionalization of rigid conjugated polymers. Bunz and co-workers[72] performed the synthesis of alkyne functionalized poly(*p*-phenyleneethynylene)s using protected alkyne building blocks. After

deprotection, click chemistry was applied for the attachment of, *e.g.*, alkyl chains, perfluoralkyl chains and crown ethers to the polymer.

In addition to the use of click chemistry for side-chain functionalization of preformed polymers, Hawker and co-workers[73] demonstrated that new classes of triazole based monomers can be prepared using click chemistry. The modularity of this approach provides easy access to novel functionalized monomers and polymers.

2.5 Hyperbranched and dendritic macromolecules

Hyperbranched polymers gain a lot of attention because of their advantageous properties compared to linear polymers, such as increased solubility, high functional group densities and low viscosity.[74] Nevertheless, the structure and architecture of hyperbranched polymers cannot be well-controlled.[75] Voit and co-workers[76] explored the synthesis of hyperbranched polymers by the 1,3-dipolar cycloaddition of monomers having one alkyne and two azides or two alkynes and one azide. The uncatalyzed polymerization of these monomers proceeded at ambient temperature yielding soluble hyperbranched polymers consisting of a mixture of both the 1,4- and 1,5-regioisomers of 1,2,3-triazole. Although the addition of a copper(I) catalyst to the polymerization mixture yielded only the 1,4-disubstitued 1,2,3-triazole rings, the resulting hyperbranched polymer was insoluble in common solvents.

The well-defined counterpart of hyperbranched polymers are dendrimers that combine the advantages of hyperbranched polymers with excellent control over size and polydispersity at the price of tedious synthetic preparation methods.[23,77–80] Dendritic macromolecules can be prepared by the repetition of organic coupling reactions using either divergent or convergent strategies.[81–83] The used organic coupling reactions include Michael reactions, reductions, Williamson etherifications and halogenations.[78,80] The efficient synthesis of these promising macromolecular scaffolds requires an organic coupling procedure that allows high yields, provides efficient isolation of the final products and offers a high tolerance toward functional groups. Therefore, azide–alkyne click chemistry seems to be the ideal method for the synthesis of dendrimers. Hawker, Sharpless and Fokin[38] were the first to explore the convergent synthesis of 1,2,3-triazole-based dendrimers using a variety of azide and acetylene precursors. Well-defined dendrimers could be obtained up to the fourth generation with quantitative yield as demonstrated by size exclusion chromatography. The followed approach is illustrated in Fig. 7 for the preparation of a first-generation dendron that was subsequently coupled to a trifunctional core molecule. The synthetic methodology to prepare the first-generation azide dendron could be repeated for the preparation of higher-generation dendrimers. Similarly, the divergent synthesis of 1,2,3-triazole dendrimers was also explored by Hawker, Wooley and co-workers.[84]

Besides the synthesis of the new class of 1,2,3-triazole based dendrimers, click chemistry was also explored for the derivatization of well-known dendrimers. Hawker and co-workers[85] nicely demonstrated the versatility of click chemistry for the peripheral functionalization of dendrimers and hyperbranched structures. A variety of different alkyne-functionalized dendrimers, including Fréchet-type,[86] bisMPA[87] and DAB dendrimers,[88] was prepared using commercially available propargyl derivatives. The subsequent functionalization with different azido-compounds *via* click chemistry yielded the functionalized dendrimers in high yields. Liskamp and co-workers[89] used a similar approach for the preparation of multivalent peptide dendrimers, in which the click chemistry allowed the use of unprotected peptide derivatives. Shabat and co-workers[90] used click chemistry for the PEO-conjugation of acetylene-functionalized dendritic prodrugs to increase their hydrophilicity and thus to decrease their aggregation in water solution. Riguera and co-workers[91] demonstrated a reversed approach using azido-functionalized dendrimers and

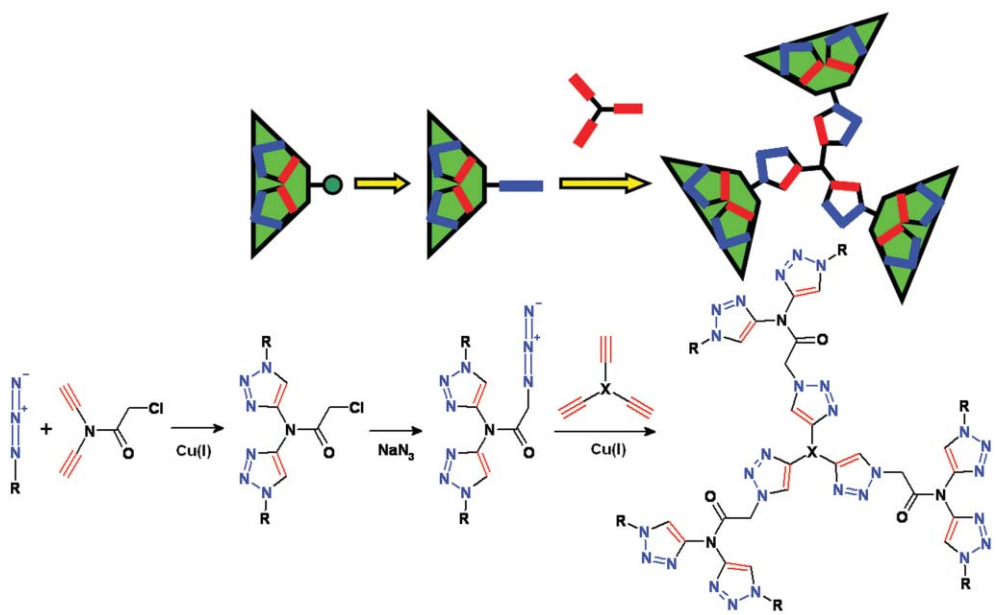


Fig. 7 Synthesis of a first-generation 1,2,3,-triazole-based dendritic wedge (G1) and subsequent coupling with a trifunctional core molecule.[38]

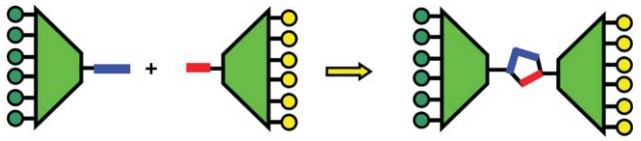


Fig. 8 Synthesis of asymmetrically functionalized bisMPA dendrimers *via* click chemistry.[93]

acetylene-functionalized sugar derivatives for the synthesis of glycodendrimers. Similarly, the same group reported the click functionalization of a PEO–dendritic block copolymer in which the periphery of the dendrimers was functionalized with azide functionalities.[92]

A third application of click chemistry in dendrimer synthesis is the coupling of traditional dendritic wedges in a convergent approach allowing the introduction of core-functionalities. The final assembly step in convergent dendrimer synthesis needs to be quantitative and without side-reaction to yield dendrimers with high purity. As such, the copper(I) catalyzed 1,3-dipolar cycloaddition was explored to stitch dendritic wedged together. In addition, click chemistry allows the preparation of asymmetrical dendrimers in high yields. Finn, Fokin, Sharpless and Hawker[93] demonstrated that click chemistry allowed the formation of bisMPA dendrimers bearing different functionalities on both sides by coupling an azido-functionalized dendritic wedge with an acetylene-functionalized dendritic wedge as schematically depicted in Fig. 8. In addition, click chemistry was applied for the further functionalization of the asymmetrical dendrimers with dyes and sugars.

Lee *et al*. used click chemistry to construct Fréchet-type dendrimers by coupling acetylene-functionalized dendritic wedges to a 1,3,5-(trisazido methyl)benzene core unit. Dendritic wedges of generation 1 to 4 were successfully clicked together in high yield as it was, *e.g.*, demonstrated by size exclusion chromatography (SEC). Besides these symmetric dendrimers, asymmetrical dendrimers consisting of two wedges from different generations were prepared by coupling azido-functionalized and acetylene-functionalized wedges. Moreover, the same group reported the convergent click synthesis of PAMAM dendrimers[94] by coupling azido-functionalized dendritic wedges to bifunctional[95] and tetrafunctional acetylene core molecules.[96] Similarly, acetylene-functionalized PAMAM dendritic wedges were prepared and coupled to bis(azido methyl)benzene.[97] The authors took full advantage of the click chemistry approach by first coupling only one dendritic wedge based on stoichiometry and subsequently coupling the second wedge yielding asymmetrical PAMAM dendrimers.

2.6 Star-shaped polymers

Star-shaped copolymers exhibit properties (*i.e.* low viscosity and good solubility) and application possibilities that are comparable to dendrimers, although the functional group density of star-shaped polymers is much lower.[58] However, the synthesis of well-defined star-shaped polymers is much easier than the multi-step synthesis of higher generation dendrimers. Star-shaped (co)polymers can be synthesized *via* two main strategies, namely starting a polymerization from a multifunctional initiator (“grafting from” method) or coupling chain-end functionalized (co)polymers with a multifunctional coupling agent (“grafting onto” method). The latter method suffers tremendously from sterical hindrance limiting the method to low molecular weight polymers, which might be overcome using click chemistry.

Gao and Matyjaszewski[98] explored the synthesis of star-shaped polystyrene *via* the copper(I) catalyzed coupling of azido-terminated polystyrene, synthesized by ATRP followed by reaction with sodium azide, with bis-, tris- or tetra-alkyne coupling agents in a 1 : 1 stoichiometry of azide to acetylene. Coupling of a low molecular weight polystyrene (number average molecular weight (M_n) = 1400 Da) to tris- or tetra-alkyne core molecules could be performed with 90 and 83% yield, respectively, while the coupling of a azido-polystyrene with M_n of 6800 Da to the trisalkyne yielded also 83% of the three-arm star-shaped copolymer, demonstrating the high efficiency of these polymer click reactions. Similarly, Tunca and co-workers[99] synthesized three-arm star-shaped PS, poly(*tert*-butylacrylate) (P*t*BA) and PEO in 82 to 97% yield by clicking the corresponding low molecular weight azido-functionalized PS (M_n = 3450 Da), P*t*BA (M_n = 6700 Da) and PEO (M_n = 2650 Da) to a trialkyne core molecule in a 1 : 1 ratio of azide to alkyne.

In principle, the yield of the star-formation might be further increased by using an excess of azido-polystyrene which then would complicate the purification due to the high similarity of the starting material and the product. Nonetheless, Schubert and co-workers[100] synthesized seven-arm star-shaped PεCL by reacting an excess of low molecular weight acetylene-PεCL (M_n = 2300 Da) to heptakis-azido-β-cyclodextrin (Fig. 9). The resulting seven-arm star-shaped PεCL was separated from the excess of alkyne-functional polymer using preparative SEC making the classification of this procedure as click chemistry debatable.

Besides star-shaped copolymers having all the same polymer arms, miktoarm star-shaped copolymers, consisting of different polymer arms, offer interesting properties and applications.[101,102] Monteiro and co-workers have used a click chemistry approach for the preparation of such miktoarm star-shaped copolymers.[103] Mono- or bis-azide-functionalized polymers were prepared by ATRP followed by replacement of the terminal bromide groups by azide groups. These polymers (M_n = 5000 to 7000 Da) were reacted with a large excess of tripropargylamine giving polymers with two-pendant alkyne groups at the chain end(s). Subsequent clicking of the resulting polymers bearing two or four alkyne groups with azide terminal polymers yielded well-defined 3-miktoarm star-shaped copolymers with 92% yield or first-generation dendritic polymers with >80% yield, respectively, indicating the high efficiency of the clicking methodology.

Crosslinked block copolymer micelles are another class of multi-armed star-shaped copolymers.[104] After aqueous self-assembly of the well-defined block copolymer, the structure can be stabilized by crosslinking either the core or the shell of the micelles. Wooley, Hawker and co-workers[105] have explored the use of click chemistry for both core- and shell-functionalization of aqueous block copolymer micelles before

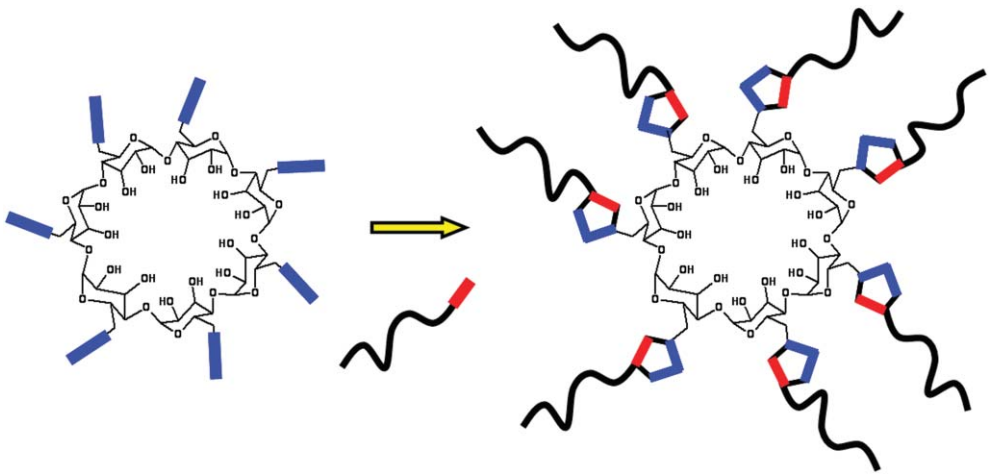


Fig. 9 Synthesis of star-shaped PεCL by copper(I) catalyzed azide–alkyne 1,3-dipolar cycloaddition.[100]

and after cross-linking. The success of the different functionalization approaches based on click chemistry demonstrates the versatility and tolerance of this method. In addition, the same groups also demonstrated that the actual crosslinking of the micelles can also be replaced by a click reaction.[106] When dendritic azide-functionalized crosslinkers were used in combination with acetylene functionalized block copolymers, the azide groups that not participated in the crosslinking process could be further exploited for functionalization of the crosslinked micelles.

2.7 Cross-linked polymeric networks

All previously discussed examples of click chemistry in polymer science were related to well-defined soluble polymeric materials. Nevertheless, there is an increasing scientific interest in tunable crosslinked materials for applications in, *e.g.*, drug delivery systems, cell-encapsulating materials or tissue engineering.[107–109] Click chemistry seems to be a promising method for the preparation of crosslinked materials under mild conditions, whereby the functional group tolerance might be advantageous for the incorporation of a wide variety of additives. For the preparation of crosslinked materials by the copper(I)-catalyzed 1,3-dipolar cycloaddition, two different methods could be envisioned: a one-step preparation method in which (polymeric) multifunctional acetylenes and azide precursors are reacted in the presence of copper(I) to form the crosslinked material or a two-step process in which polymers with pendant alkyne and azide groups are first mixed and possibly shaped followed by crosslinking upon addition of copper(I) ions. In both cases, the high yield of the click reaction should lead to high crosslinking efficiencies. These crosslinking approaches can be performed using a (polymeric) precursor with azide groups together with a (polymeric precursor) with alkyne groups (Fig. 10) or, alternatively, one (polymeric) precursor bearing both azide and alkyne functionalities could be used, whereby the occurrence of intramolecular coupling could interfere with the crosslinking process.

Ossipov and Hilborn[110] have investigated the formation of hydrogels based on poly(vinyl aclohol) (PVA) using click chemistry. Azide and alkyne-functionalized poly(vinyl alcohol) were prepared as well as diazido-PEO. Mixing the complementary alkyne-PVA and azido-PVA or alkyne-PVA with diazido-PEO in the presence of a copper(I) catalyst yielded the desired hydrogels. The properties of these hydrogels were studied in detail, including the swelling ratio as well as the storage and loss moduli, which were found to strongly depend on the stoichiometry of the reagents as well as the concentration. In addition, it was shown that the hydrogels prepared *via* the click reaction have better properties than the analogous structures with a common crosslinking agent. Hedrick, Hawker and co-workers[111] reported the preparation of well-defined hydrogel networks based on dialkyne-functionalized and tetraazide-functionalized PE) using copper sulfate and sodium ascorbate as catalyst. The efficiency of the crosslinking reaction was demonstrated by the addition of an alkyne-functionalized chromophore in the presence of a catalyst to the prepared hydrogel. UV and fluorescence spectroscopy revealed the presence of only 0.2% unreacted azide moieties in the hydrogel. Furthermore, it was demonstrated that the properties (*i.e.* swelling degree, stress and extension to break) of the hydrogels could be easily tuned by changing the preparation conditions.

Next to hydrogels, click chemistry was applied for the preparation of other functional crosslinked polymers. Finn, Koberstein, Turro and co-workers[112] have applied ATRP of

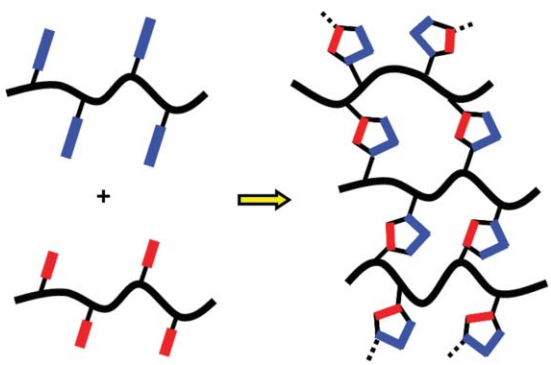


Fig. 10 Schematic representation of the preparation of crosslinked polymeric materials *via* the click chemistry process.

tert-butyl acrylate with a degradable bifunctional initiator for the preparation of a telechelic azido-functionalized polymer. The resulting diazido-P*t*BA was used for the preparation of polymer networks using tri- and tetra-acetylene crosslinkers and it was demonstrated that the formed crosslinked networks could be degraded by ozonization. Another potential application area of crosslinked polymer networks are adhesives. Fokin, Finn and co-workers[113] smartly used copper(I) catalyzed click chemistry to glue copper parts together: when a mixture of multifunctional alkyne and azide components is pressed in between two copper plates, the *in situ* generation of copper(I) from metallic copper, which was previously shown to be an effective copper(I) source,[17,114] results in a crosslinked adhesive coating. The maximum load of these adhesives could be effectively tuned by the mixture of azide and alkyne components demonstrating the flexibility of the click chemistry approach. In addition, the use of click chemistry for the synthesis of pH-responsive crosslinked networks was reported by Li and Finn.[115] The click reaction between a tertiary amine functionalized with three acetylenes together with a diazido compound resulted in a crosslinked network that reversibly swells upon protonation by trifluoroacetic acid.

3 Summary and outlook

Nowadays, the use of azide–alkyne click chemistry in polymer science is a rapidly growing field of research. The mild reaction conditions, functional group tolerance and quantitative yields allow the fast and simple creation of well-defined and complex polymeric structures that were previously unattainable. Since its introduction in polymer science in 2004, the copper(I) catalyzed azide–alkyne 1,3-dipolar cycloaddition has already been exploited for the synthesis of a variety of polymer architectures including end-functionalized polymers, block copolymers, cyclic polymers, graft copolymers, star-shaped copolymers, dendrimers and crosslinked materials.

Up to this moment, click chemistry has been mainly applied for the construction of novel polymeric structures, whereas one of the major opportunities of click chemistry is thought to be the easy tuning of polymer properties by (systematically) varying their structure. Therefore, it is expected that, after this first period of exploring the synthetic opportunities of click chemistry, future research of click chemistry in polymer science will be directed towards library preparation and screening to optimize selected polymer properties. As such, the impact of click chemistry is believed to grow beyond being a common tool in polymer chemistry and it will become an established tool for polymer science in general.

Nonetheless, the presence of copper(I) during the azide–alkyne click chemistry obstructs its use in future commercial applications in, *e.g.*, lithographic patterning, drug delivery or gene delivery and limits the biocompatibility of the resulting products indicating the need for other click reactions. Furthermore, the preparation of polymeric materials with a large number of triazole units is often limited by their low solubility. However, not many other coupling procedures exist that comply with all requirements of click chemistry, whereby especially the functional group tolerance and the readily availability of starting materials are not often met. Hence, future research should focus on the development of true click reactions that do not require a (toxic) metal catalyst as well.

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