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Blocks, Stars and Combs: Complex Macromolecular Architecture Polymers via Click Chemistry

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6.1 Introduction

The formation of complex macromolecular architectures, such as blocks, stars and combs,* has been a constant theme in synthetic polymer chemistry over the last few decades. In the past, anionic polymerization was the method of choice for the synthesis of well-defined complex (co)polymer architectures, yet under relatively demanding reaction conditions.¹ More recently, the development of living/controlled radical polymerization protocols have made complex macromolecular construction a far less demanding feat. Amongst the most prominent living/controlled radical polymerization methods are the reversible addition-fragmentation transfer (RAFT) process,²⁻⁵ nitroxide-mediated polymerization (NMP)⁶ as well as atom transfer radical polymerization (ATRP).⁷ RAFT and ATRP are the most employed techniques, with RAFT arguably being the most versatile in terms of monomer range and functionality tolerance.

All of the above three control methodologies on their own can not only be employed to construct linear block copolymers, but also more complicated macromolecular architectures such as stars and comb-shaped entities.^{6,8,9} Typically, multifunctional molecular scaffolds are employed for this purpose, carrying bromine endgroups (for ATRP), nitroxides (for NMP)

* The term *comb* is taken to mean a polymer which consists of a main chain and a plurality of long side chains.

or thiocarbonyl thio entities (for RAFT). Theoretically, it should be possible to generate any combination of block copolymers via these techniques. Unfortunately, the process of generating block structures and star polymers via such approaches has its limits and not all desired structures can be obtained. The reasons for the limitations in block copolymer formation are multipronged: (i) the reactivity and type of the monomers from which the polymeric building blocks are synthesized may be very different. In using one of the forms of living/controlled radical polymerization, for example, the reactivities of two monomers must be comparable in order to achieve block structures through chain extension. The consequences of vastly different monomer reactivities can be illustrated by the example of the preparation of a (hypothetical) block copolymer made from vinyl acetate and styrene. The combination of the highly reactive vinyl acetate derived radical and the relatively unreactive styrene derived radical precludes the use of a single controlling agent or initiating system to achieve a well-defined block structure. To date, the most convenient method to polymerize vinyl acetate in a controlled fashion is by the RAFT process, using a xanthate controlling agent.¹⁰ However, this methodology is not appropriate for polymerizing most other monomers. Additionally, in order to synthesize polymer conjugates from different classes of monomers (e.g. vinylic monomers and lactones), polymerization initiators/controlling agents must be specifically designed to perform different techniques of polymerization, e.g. an NMP initiator equipped with a hydroxyl moiety to perform ring-opening polymerization (ROP).¹¹ (ii) It is often desirable to generate block copolymers that are amphiphilic, i.e. featuring a hydrophobic and a hydrophilic component. Such amphiphilic block copolymers can be assembled in solution into micellar structures or vesicles, which in turn can serve as containers for the target delivery of pharmaceuticals.^{12–19} Alternatively, these hydrophobic/hydrophilic structures may be self-assembled in the solid state. However, due to the bipolar nature of amphiphilic block copolymers, their preparation is often limited by the identification of a common solvent in which the block copolymer synthesis can be carried out. (iii) The formation of nonlinear block copolymers (i.e. block-stars or combs) is not only beset with the above two listed problems but also with additional complications, depending upon the method employed for their construction. While in ATRP and NMP processes, radical propagation (i.e. chain growths) always occurs from the multifunctional core (and thus can lead to core-core coupling and other undesirable termination reactions), the RAFT process allows (via its so-called Z-group approach) arm growths without the interference of coupling processes. Both approaches (radical core vs RAFT Z-group approach) have disadvantages. When the core itself carries the radical functionalities, conversions have to be limited as otherwise termination products contribute significantly to the product distribution. While the RAFT-Z group approach yields multiarm polymers free from terminated impurities, the molecular weights that may be reached are limited in many cases due to the growing inaccessibility of the thiocarbonyl thio functions located at the core.

The separate preparation of the individual building blocks and their subsequent coupling to achieve the desired complex polymer structure provides an elegant solution to problems (i) and (iii). However, such an approach of post-polymerization coupling requires chemical transformations of high efficiency as well as the tolerance against a variety of functional groups and reaction conditions. These requirements are perfectly facilitated by the characteristics of click chemistry. In fact, although the concept of click chemistry was initially conceived for use in low molecular weight organic synthesis in 2001,²⁰ it has seen a great increase of application in polymer science since its first appearance there in 2004.^{21–23} In particular, the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has been proven

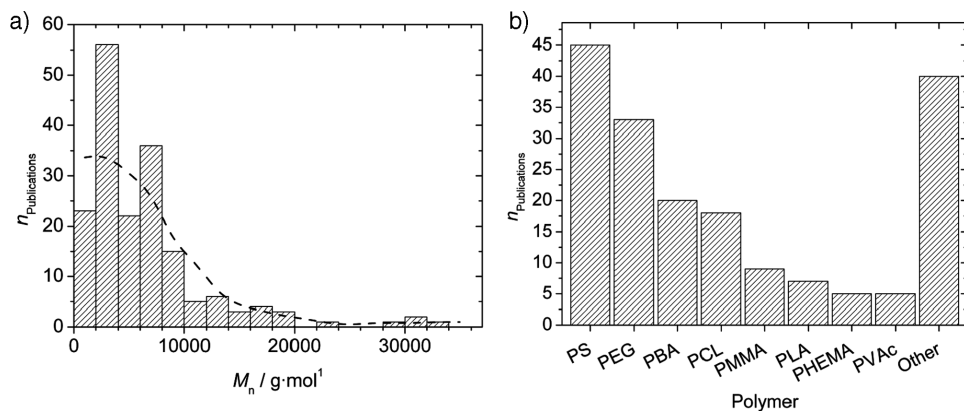


Figure 6.1 Frequency with which particular molecular weights (a) and polymers (b) have been utilized in the literature to prepare complex architectures via click methodologies.

as an ideal candidate to fulfill the click criteria²⁰ and was therefore the reaction of choice in the vast majority of publications. However, Diels–Alder cycloadditions, nucleophilic substitution chemistry of strained rings and additions to carbon–carbon multiple bonds (thiol–ene reaction) have also been shown as efficient orthogonal synthetic strategies and have been used alternatively to or in combination with the CuAAC.

Considering the above-mentioned potential of click chemistry in polymer science, one would expect a great versatility to have emerged in the synthesis of complex macromolecular architectures. It is therefore an interesting exercise to inspect the literature and to statistically explore two aspects of click chemistry for the construction of complex polymer structures. Firstly, it is instructive to establish what molecular weight ranges have thus far been utilized as building blocks in the generation of larger and more complicated structures. Figure 6.1(a) shows the number of studies that have used click chemistry to achieve block, star and comb structures and the molecular weights of the building blocks used. The figure includes the use of all types of pericyclic click reactions; however, the main preparation method has been the CuAAC. Secondly, it is interesting to take note of the types of polymers that have been employed in click reactions. As such, Figure 6.1(b) depicts the frequency in which particular polymers have been utilized in the literature to prepare complex architectures via click methodologies. By a close inspection of Figure 6.1(a and b), it is observed that the vast majority of studies concern themselves with the use of polystyrene (PS) and poly(ethylene glycol) (PEG) polymers with molecular weights below 10 000 g mol^{-1} . This may suggest that the vast majority of publications are concerned with proving the concept rather than expanding the number of available materials. In the following, we will highlight and summarize the most modern approaches that are employed to generate complex macromolecular architectures via orthogonal, selective and rapid cycloadditions.

6.2 Block Copolymers

It seems apt to start our foray into the construction of complex macromolecular architectures with block copolymers, as it was in this area where the first steps using click chemistry for the

construction of complex polymers were made. Early in the introduction of click chemistry to polymer science, the synthesis of the most simple of complex architectures, blocks, was a convenient avenue towards proving the concept that click chemistry may have the potential to be useful in the construction of more complicated architectures. Furthermore, block copolymer structures and, in particular, amphiphilic block copolymers are of high interest in polymer science for their self assembly properties, (both in solution and in the solid state) as well as for their potential application in the construction of nano containers that may be of benefit in fields such as organic synthesis and targeted drug delivery.

As mentioned in the introduction, block copolymers may be synthesized through direct polymerization via chain extension in controlled radical polymerization or by the use of multifunctional initiators, in which two separate polymerization reactions occur from a single initiator. The difficulties in this strategy center around the lack of freedom in the choice of monomers that may be used. For example, monomers of significantly different reactivity cannot be used in a chain extension approach. An alternative strategy is to use highly efficient conjugation reactions (click chemistry) to link two or more polymer chains together in a post-polymerization approach.

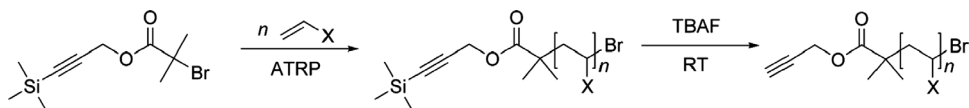
The greatest advantage of constructing complex macromolecular architectures via click conjugations is that it allows for the complete segregation of synthetic techniques by which individual building blocks are generated. In the field of creating block structures in polymeric systems, such efficient conjugation techniques have been proven to be an invaluable addition to the collection of tools, which has been at the disposal of the organic chemist. Since one of the earliest reports on the synthesis of block structures by click reactions by van Hest *et al.*,²⁴ the use of click chemistry has opened an entirely new playing field in which a much wider variety of such structures may be synthesized with unprecedented ease. For example, it enables the creation of polymer blocks from monomers of very disparate reactivities such as vinyl acetate and styrene.²⁵ In the following, we explore how the click concept has been applied to the construction of a wide variety of block copolymer structures that have been otherwise very difficult, if not impossible, to achieve.

6.2.1 Polymer Preparation for Click Conjugations

The first step in generating block structures is to equip the individual building blocks with the complementary functional groups, which react together to establish a linkage. There are essentially two ways in which this may be performed: (i) functionalization of the initiator by which the polymer chain is generated; or (ii) post-polymerization functionalization of a polymer end-group.

Pre-polymerization Functionalization

The use of clickable initiators warrants consideration of the compatibility of the click moiety with the polymerization process. Looking at the most widely used form of click chemistry, the CuAAC, one's attention is immediately drawn to the alkyne moiety. The triple bond is susceptible to addition reactions, under conditions of polymerization reactions. For example, in anionic polymerizations, the acidic proton of terminal alkynes interferes with the highly nucleophilic initiators used for the polymerization of styrene derivatives.²⁶ The predominant method of generating alkyne terminated linear polymers, via pre-polymerization functionalization, has been the use of ATRP.^{24,27–30} The catalyst system by which ATRP



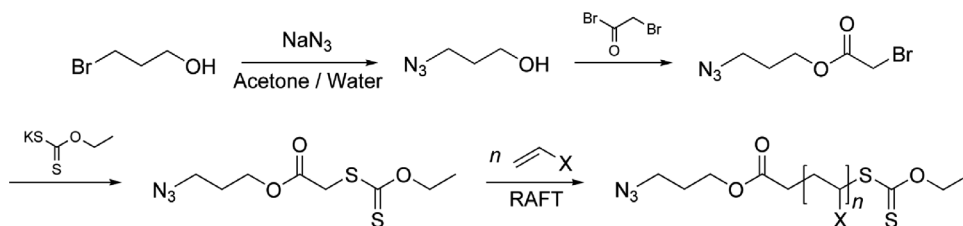
Scheme 6.1 Pre-polymerization strategy for equipping polymer chains with alkyne moieties.

is performed is very similar and in many instances identical to that, which is used in the CuAAC. The mechanism by which the latter proceeds involves complexation of the alkyne moiety with the copper(I) catalyst, thus the same may occur during ATRP with an alkyne equipped initiator. Therefore, it would appear necessary to introduce some form of protective chemistry to the alkyne moiety. Such protection of the alkyne moiety has mostly been achieved through the use of a trimethylsilyl (TMS) group, which can readily be removed post-polymerization, e.g. by treatment with tetrabutylammonium fluoride (TBAF) (1–10 equivalents) at room temperature (Scheme 6.1).^{24,25,29} Where higher-order linear blocks, such as triblocks, are synthesized by α -azido- ω -alkyne-functionalized polymers, completely protected alkynes is essential. However, van Hest *et al.* has reported that, during an ATRP using a protected alkyne initiator, 70% of the TMS groups were removed when using the conventional copper(I) bromide–*N,N,N',N''*-pentamethyldiethylenetriamine (PMDETA) catalyst system.²⁹ The nucleophilic attack of one of the nitrogen atoms of the PMDETA on the silyl-group was postulated as a possible side-reaction. In an attempt to circumvent this problem, the less nucleophilic copper(I) bromide–2,2'-bipyridyl (BPY) ATRP catalyst system was trialed, which showed an improvement in that only 10% of the protective groups were removed. In another attempt to circumvent this problem, the TMS group was replaced by a triisopropyl silane group. This variant proved not to be affected by the ATRP process and, consequently, continued to protect the alkyne group.

Chain transfer agents used in RAFT polymerizations have also been equipped with alkyne groups in much the same way as ATRP initiators in the generation of linear block structures.^{25,31} Here, the TMS group was also used as the protective group and was removed after the polymerization in the same manner as mentioned previously.

Whilst most authors claim the necessity of using protective chemistry in their alkyne-functionalized initiators, there have been some reports on the use of nonprotected initiators/chain transfer agents. The use of a nonprotected alkyne ATRP initiator was reported by Matyjaszewski *et al.* in the synthesis of α,ω -bifunctional polystyrene.³² Here, a ¹H-NMR spectrum is provided that clearly shows the presence of the alkyne α -protons in the polymer chain; however, a quantitative analysis is not provided. Furthermore, Nasrullah *et al.*³³ and Ranjan and Brittain³⁴ report the use of RAFT agents equipped with nonprotected alkyne moieties. The resulting polymers were shown to bear the alkyne moiety and were successfully used in subsequent CuAAC reactions. It is also possible to use alkyne based initiators for ROP. Here, propargyl alcohol is a convenient choice and no protective chemistry is required.^{35,36}

One of the hallmark features of the CuAAC is the benign characteristic of the azide group in that it may be incorporated into a polymerization initiator or chain transfer agent without it reacting during any process except for the click reaction itself. Thus, there have been many occurrences in the literature of a pre-polymerization functionalization strategy being used to generate polymers bearing an azide moiety.^{25,27,31,35} A selected example of such



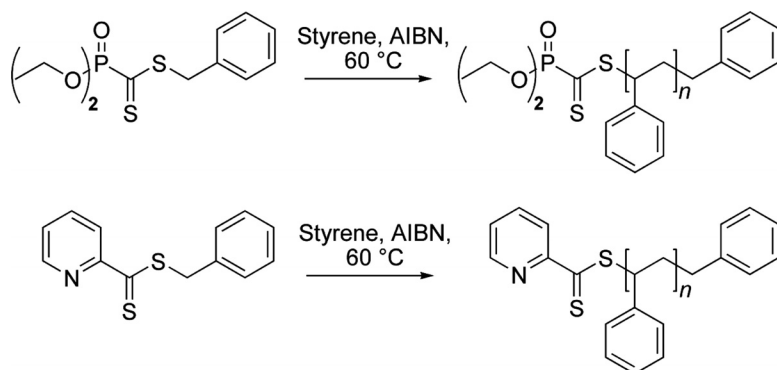
Scheme 6.2 Pre-polymerization strategy for equipping polymer chains with azide moieties via the use of an azide functionalized RAFT (xanthate) agent.

strategy for the preparation of an azide functionalized RAFT (xanthate) agent is presented in Scheme 6.2.²⁵

However, there have been instances in the literature in which a decrease in the azide content has been observed during the polymerization process.^{37–39} Most recently, Perrier *et al.* showed in a series of on-line nuclear magnetic resonance (NMR) experiments that the azide moiety can undergo a 1,3-cycloaddition with the double bond of various monomers.⁴⁰ The electron-withdrawing character of the monomers used was identified as key in determining the extent to which the loss of azide occurred. Under the conditions applied (60 °C, 20 h), the reaction of an azide with methyl acrylate yielded a 95% conversion of the azide whereas reaction with the more stable styrene achieved only 5% conversion. Therefore, when considering using an azide equipped radical polymerization initiator, the monomer that is to be used must also be considered and, as recommended by Perrier *et al.*, the limiting of these side reactions of the azide may be achieved by using short reaction times and low temperatures.⁴⁰ However, by utilizing a post-polymerization strategy, as has been the case in the vast majority of reports,^{24,28,29,33,41,42} this problem has not been more widely reported.

Although the CuAAC has clearly been dominating the realm of click chemistry, other methodologies have been employed that have proven to be equally efficient and useful. The Diels–Alder cycloaddition between anthracene- and maleimide-functionalized polymers has successfully been used to generate numerous block structures.^{41,42} In the pre-polymerization approach to equip linear polymer chains with these functional groups, 9-anthracene methanol is a useful anthracene derivative. Although behaving as a reactive diene in the Diels–Alder cycloaddition, anthracene derivatives are stable against radical attack, thus no protective chemistry is required under such conditions. Maleimides, on the other hand, require protection if they are to be incorporated pre-polymerization. Maleimide functional groups have been protected as the Diels–Alder adduct with furan and, unlike the protective chemistry used with alkynes, the deprotection of the maleimide occurs through an *in situ* retro-Diels–Alder reaction during the click conjugation step, which will be elaborated upon in a subsequent section.

Most recently, the RAFT–hetero Diels–Alder (HDA) concept has efficiently demonstrated the pre-polymerization functionalization strategy in that the RAFT agents used in the synthesis of the precursor, linear polymer chains require no additional functional groups to perform the conjugation reaction.^{43,44} The dithioester end-group that is inherent of the RAFT process is sequentially used for the controlled polymerization process and as the reactive heterodienophile in a HDA reaction. The RAFT agents that have been successfully utilized in this context are shown in Scheme 6.3. The principal criterion for a RAFT



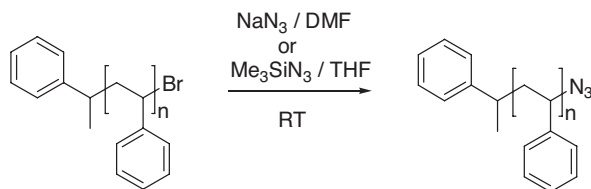
Scheme 6.3 Appropriate RAFT agents for use in the RAFT-HDA concept.

agent to be useful in the RAFT-HDA concept is an electron-withdrawing Z group. The complementary moiety with which the RAFT end-group reacts to form a linkage is a diene. For the purposes of the RAFT-HDA concept, *trans,trans*-2,4-hexadien-1-ol has been used successfully as an initiator for the ROP of CL to produce diene terminated PCL.⁴⁴

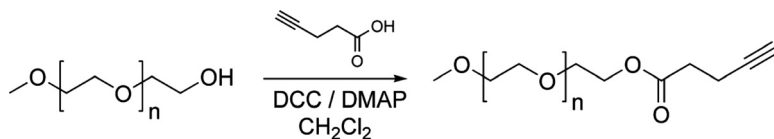
Post-polymerization Functionalization

The second method by which linear polymer chains may be equipped with the functionalities required to perform a click conjugation is by modifying the polymer chain, typically through some form of substitution chemistry. By inspection of the literature, the most widely used form of post polymerization functionalization in the context of click chemistry has been the nucleophilic substitution of the terminal bromide of a polymer that has been prepared via ATRP, typically with sodium azide in *N,N*-dimethylformamide (DMF) or azido-trimethylsilane in tetrahydrofuran (THF) in an overnight, room-temperature reaction (Scheme 6.4).^{24,28–30,33,36,42,45,46} This methodology circumvents any potential side reaction of the azide during the polymerization process and its only downfall is the fact that, for higher degrees of polymerization, the number of polymer chains bearing the bromide end-group decreases, thus limiting the number of polymer chains that can potentially be transformed into a ‘clickable’ species.

The major advantage of the post-polymerization alkyne functionalization is that it circumvents the issues with protective chemistry of the alkyne moiety. The incorporation of



Scheme 6.4 Post-polymerization bromide substitution to prepare azide terminated polymers.



Scheme 6.5 Functionalization of a polymer chain with an alkyne moiety.

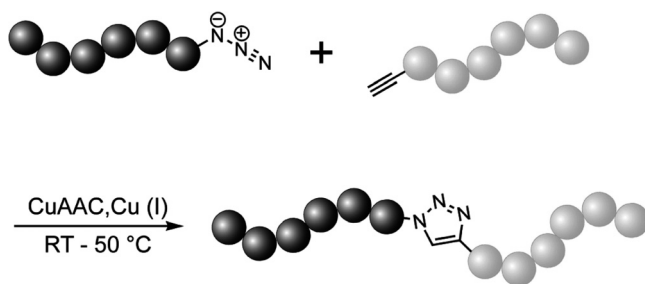
an alkyne moiety onto the end of a polymer chain has mostly been achieved through a simple *N,N'*-dicyclohexylcarbodiimide (DCC) coupling of low molecular weight derivatives such as 4-pentynoic acid to the target polymer (Scheme 6.5).^{42,46–48} Other methodologies include the use of Grignard chemistry⁴⁹ or substitution chemistry.⁵⁰

The anthracene–maleimide route also lends itself easily to the post-polymerization functionalization strategy in that the maleimide functionality can be incorporated into a commercially available PEG chain through simple DCC couplings.^{41,42}

6.2.2 The Click Reaction: Methodologies and Isolation

There are a variety of ways in which the CuAAC may be performed to create a linkage between two polymer blocks. The fundamental components are the azide-functionalized block, the alkyne-functionalized block, a source of copper(I) and an appropriate ligand to solubilize the copper source if necessary. The most widely used catalyst system has been the combination of copper(I) bromide and PMDETA in either THF or DMF solvent.^{27–30,33,35,36,42,45,51} Other catalyst systems that have been reported include the combination of copper(I) iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),^{24,25} as well as copper(I) bromide with BPy.^{46,47} For polymeric systems that are sensitive to strong bases, such as those containing imide groups, the catalyzing copper complex tris(triphenylphosphine)copper(I) bromide in DMF may also be used.^{48,49} Surprisingly, catalyst systems containing copper(II) sulfate–sodium ascorbate, which allows for the *in situ* formation of a copper(I) source, have not been utilized in the synthesis of block copolymer structures.

Scheme 6.6 illustrates the use of the CuAAC for the construction of polymeric blocks. The CuAAC is typically performed in an overnight reaction at a temperature ranging from ambient to 50 °C. Exceptions to this are observed when performing a one-pot conjugation



Scheme 6.6 Construction of block copolymers via the CuAAC.

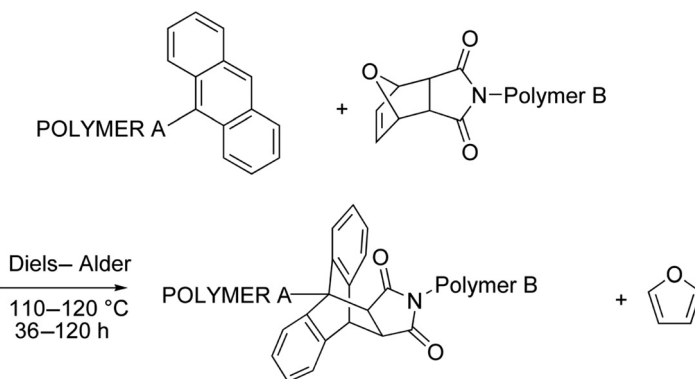
that utilizes two different forms of click coupling. For example, Tunca *et al.* synthesized various triblock copolymers of PEG, PS, poly(methyl methacrylate) (PMMA) and poly(ϵ -caprolactone) (PCL) by a one-pot combination of the CuAAC and the anthrance–maleimide Diels–Alder cycloaddition.⁴² Here, as will be seen shortly, the Diels–Alder reaction requires high temperatures (110–120 °C); hence the one-pot reaction was also performed at this temperature. As another example Huang *et al.* achieved a series of triblocks from PEG, poly(*tert*-utyl acrylate) (PtBA), PS and PCL from a 90 °C, one-pot reaction involving the CuAAC and an atom transfer nitroxide radical coupling.²⁸

While there have been some occurrences of authors using a 1:1 ratio of azide-functionalized polymer to alkyne-functionalized polymer in the CuAAC,^{25,33} most reports of block formation have involved using an excess of either the azide or the alkyne.^{24,27–30,35,36,42,47–50} The vast majority of polymers investigated in the construction of block structures have been prepared by some variety of controlled free radical polymerization technique. As such, despite obtaining narrowly disperse molecular weight distributions, there still remains the inevitable presence of polymer chains that do not bear a reactive end-group that would lend itself to being used in a conjugation reaction. It is for this reason that several authors have utilized an excess of one reagent to drive the click reactions to completion. The disadvantage here is that it is often necessary to remove the excess reagent in some additional purification strategy.

The nature of the purification strategy is dependent upon the nature of the polymers in the system. For example, the coupling of alkyne-functionalized PEG with azide-functionalized PS or PMMA may be driven to completion by using an excess of the PEG segment, which can then be removed by a washing stage with methanol.²⁴ Alternatively, if the CuAAC product may be precipitated into methanol, an excess of the PEG chain would remain in solution.⁴¹ Another example of a simple purification technique was performed by Du Prez *et al.*³⁰ Here, an excess alkyne-functionalized poly(1-ethoxyethyl acrylate) (PEEA) was removed from the click product with poly(isobornyl acrylate) by selective precipitation in cold methanol.

However, there have been some reports on the use of more elaborate purification strategies to remove excess reagent. In the synthesis of PS-*b*-PMMA, van Hest *et al.* used an excess of the alkyne-functionalized PMMA, which was removed by passing the crude product mixture through a column of azidomethyl polystyrene resin.²⁴ Yet another more complicated strategy involves removal of an excess of azide by first converting the excess to amines by reaction with triphenylphosphine followed by column chromatography.²⁹ Of course, in situations where a simple precipitation cannot be performed, these above-mentioned more complicated strategies still produce good results.

Whilst on the topic of purification, the use of the CuAAC bears the requirement of the removal of the copper catalyst. This may be achieved by passing the click reaction solution over through a column of basic or neutral alumina.^{28,42,47} Despite this simplicity, it is still a technique that is really only feasible in the laboratory and not on an industrial scale. In the context of block formation, there have been two reported examples, however, of the removal of the copper catalyst without the use of a column. The catalyst, under the right circumstances, may be removed by a series of precipitations. For water-insoluble polymers, it is possible to precipitate the polymer and isolate by filtration, thus separating the polymer from the copper salt.³⁵ Furthermore, purification of the polymer product by dialysis against water may also achieve an effective removal of the copper catalyst.³¹



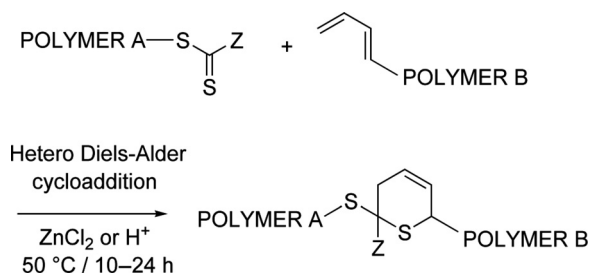
Scheme 6.7 Construction of block copolymers via the Diels–Alder cycloaddition of anthracene and maleimide.

The Diels–Alder cycloaddition of anthracene and maleimide has the distinct advantage that no catalyst is required. Where the efficiency of the CuAAC, whilst dependent upon the system in which it is used, can range from 80% to close to quantitative, the said Diels–Alder approach has proven to be just as efficient (97%).⁴¹ The anthracene–maleimide conjugation can be performed by simply heating a solution of the two functionalized blocks in a high-boiling solvent, such as toluene. The concept is illustrated in Scheme 6.7.

In a similar fashion to the CuAAC, the maleimide moiety requires protective chemistry for the stages leading to the final click reaction. However, whereas the protection used for the alkyne moiety in the CuAAC requires a separate deprotection step, the furan-protected maleimide undergoes an *in situ* retro Diels–Alder reaction during the coupling step.^{41,42} Furthermore, this Diels–Alder click chemistry requires no catalyst, thus isolation of the formed block copolymers is a simple matter of precipitation. Although, in these two areas, the anthracene–maleimide Diels–Alder cycloaddition appears to be more convenient than the CuAAC, high temperatures (110–120 °C) and long reaction times (36–120 h) are the drawback.

Being one of the most recent forms of efficient conjugation chemistries, the RAFT–HDA concept is an atom-economical approach to block copolymer synthesis (Scheme 6.8). The entire concept is based upon the electron-withdrawing dithioester end-group that is inherent in polymers prepared with specially chosen controlling agents in RAFT polymerization. Unlike the CuAAC and the anthracene–maleimide Diels–Alder approach, the RAFT agent used does not require additional functionalities to be used in the post-polymerization conjugation step. The reaction is quite simply performed by keeping a solution of the dithioester-terminated polymer, diene-functionalized polymer and catalyst at 50 °C for between 10 and 24 h, depending upon the nature of the dithioester end-group.⁴⁴

The reaction is catalyzed by the addition of zinc chloride in the case of the diethoxyphosphoryl dithioester end-group or a simple Brønsted acid such as trifluoroacetic acid in the case of the pyridinyl dithioester end-group. The role of these catalysts is to coordinate with specific atoms on the dithioester end-group in order to enhance the electron withdrawing effect on the thiocarbonyl bond. This serves to lower the energy of the lowest unoccupied molecular orbital of the thiocarbonyl so as to enhance its reactivity towards a



Scheme 6.8 The construction of block copolymers via the RAFT–HDA approach.

hetero Diels–Alder cycloaddition with a diene. This technique has been proven to be just as efficient as the CuAAC and anthracene–maleimide Diels–Alder cycloaddition.^{43,44} It circumvents the requirement of using a copper catalyst and also circumvents the requirement of high temperatures.

6.2.3 Polymer Characterization

As polymeric architectures become more and more complex, the use of a wide variety of characterization techniques is necessary. As such, amongst the most important and useful techniques that have been used to characterize complex macromolecules include gel permeation chromatography (GPC), NMR, Fourier transform infrared (FT-IR), UV–vis as well as mass spectrometry (MS) methods.

GPC is convenient in that the molecular weight distributions of the individual blocks may be compared with that of the coupled product. In many respects, useful qualitative information concerning the success of the click reaction may be elucidated by a quick inspection of the product chromatogram. For example, the presence of shoulders or a bimodal distribution can indicate the presence of unreacted starting material. Figure 6.2 displays three GPC analyses of block formation via the CuAAC, the anthracene–maleimide Diels–Alder (DA) reaction and the RAFT–HDA concept. It may be observed that each effectively showed a complete shift of the molecular weight distribution (either to lower retention times or higher molecular weight) from the individual building blocks to the final coupled product. It is important to note, however, that the molecular weight of the block structure, as determined by GPC measurements, may not necessarily be in agreement with the arithmetic sum of the building blocks. Although not being widely used in this context in the surveyed literature, more advanced techniques such as GPC with triple detection may allow better insights into the molecular weight of the obtained species.

When analyzing more complicated structures via GPC, such as stars or combs, one must also take into consideration two important factors. Firstly, the relatively compact structure of such architectures leads to an under-estimation of M_n as determined by GPC measurements. As such, increases in the observed molecular weight become less pronounced with increasing arm number. Secondly, the determination of M_n by this technique takes into consideration any remaining linear precursor material as well as any material that has not completely been converted, which tends to skew the observed M_n to lower values and leads to broader polydispersity index (PDI) values. This is particularly noticeable in

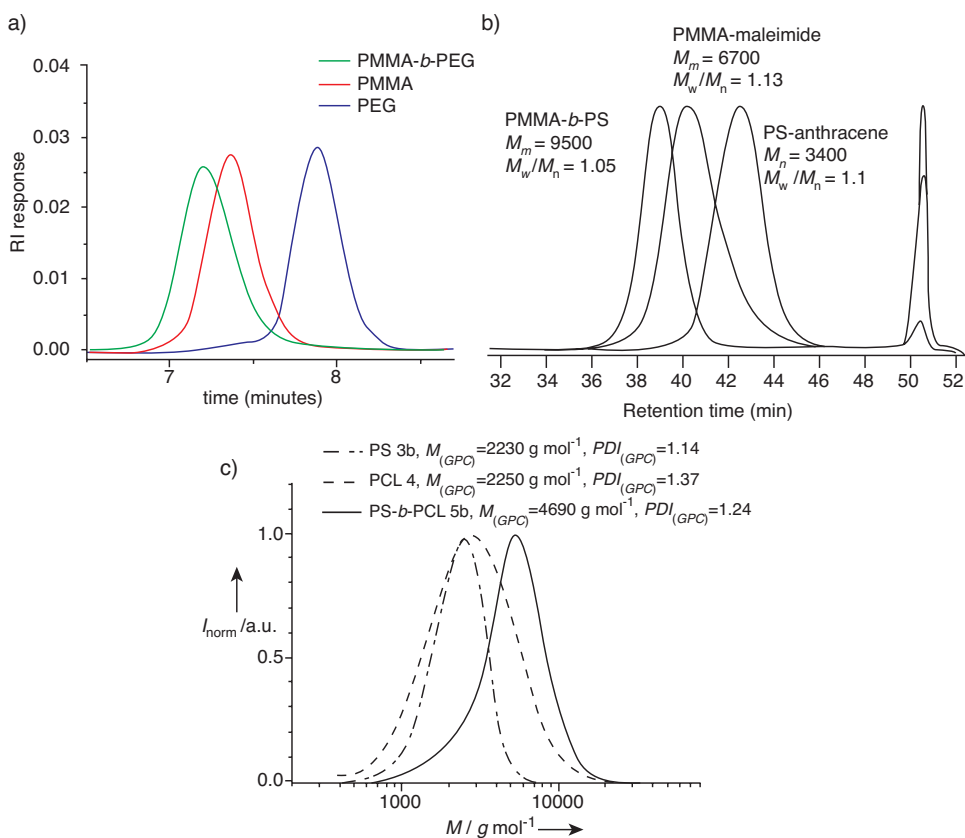


Figure 6.2 GPC spectra for block copolymer formation via (a) CuAAC (Reprinted with permission from ref.²⁴. Copyright 2005 Royal Society of Chemistry), (b) anthracene-maleimide Diels-Alder cycloaddition (Reprinted with permission from ref.⁴¹. Copyright 2006 Wiley-VCH) and (c) RAFT-HDA concept (Reprinted with permission from ref.⁴⁴. Copyright 2008 Royal Society of Chemistry).

starpolymers synthesized by click approaches.^{43,51} In order to extract more useful data out of size-exclusion chromatography measurements, it is possible to deconvolute the data via peak splitting and arrive at corrected M_n and PDI values as well as the relative ratios of different products in the sample.^{43,51,52} Interestingly, in two reported examples of the synthesis of graft copolymer structures, a reduction in molecular weight of the graft product with respect to the linear precursors was observed.^{53,54} These examples nicely show the difficulties that can occur through the above-mentioned effects.

One characteristic that all click reactions share is that the transformations from the separate reactive functional groups to the final adduct may be verified by a number of different spectroscopic techniques, depending upon the nature of each reaction.

NMR spectroscopy has been widely used across all forms of click chemistry in determining the success of the conjugation reaction. For example, the CuAAC may be monitored by the shift of the azido methylene protons as well as the terminal alkyne protons to higher ppm values after the triazole formation.^{28,30,32,35,47} Furthermore, the conversion of anthracene and

maleimide into the Diels–Alder adduct^{41,42} as well as the conversion of dithioesters and dienes into the HDA adduct^{43,44,55} may also be monitored via NMR spectroscopy.

FT-IR spectroscopy is a particularly useful technique for the monitoring of the CuAAC in that the disappearance of the azide signal ($\sim 2100\text{ cm}^{-1}$) can be used as an indicator of the success of the conversion.^{24,25,34,36,56} UV-vis spectroscopy has also been conveniently utilized in determining the progress of click reactions. The appearance of an absorbance signal of the 1,2,3-triazole ring ($\lambda_{\text{max}} = 258\text{ nm}$) clearly displays the success of the CuAAC.⁵⁶ In the anthracene–maleimide DA approach, the characteristic absorption pattern of the anthracene ($\lambda_{\text{max}} = 366\text{ nm}$) completely disappears after conversion to the conjugation adduct.^{41,42} Furthermore, the transformation of the chromophoric RAFT thiocarbonyl group into the colourless 3,6-dihydro-2*H*-thiopyran ring in the RAFT–HDA concept can also be conveniently followed by UV–vis spectroscopy.⁴³

Mass spectrometry has also been used to determine the success of click reactions between polymers and low molecular weight species. However, mass spectrometry of block structures can lead to spectra that are complex to the point of being devoid of any useful information. Nevertheless, click-functionalized polymers have been converted with low-molecular-weight species bearing the required complimentary click moiety and the relatively small shift in the mass spectrum peaks that results, very convincingly reveal the success and efficiency of the click reaction.^{29,44}

6.3 Star Polymers

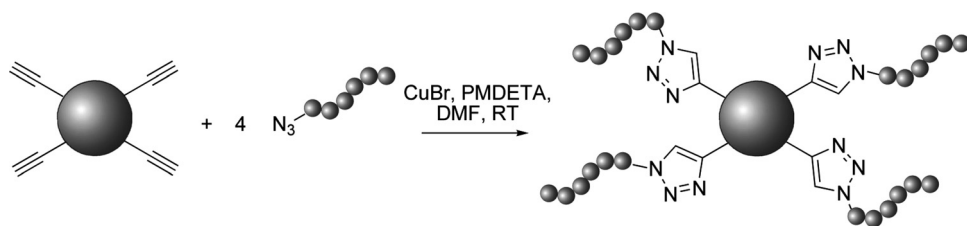
Star polymers can be subdivided into conventional star polymers with arms of similar chemical nature, miktoarm star polymers with three or more different arms and dendrimer-type star polymers with additional branching in each arm. While the CuAAC is predominant in all these approaches, other pathways have been explored additionally. The RAFT–HDA concept, which employs directly the thiocarbonyl group of the RAFT agent in combination with a diene, was as successfully employed as the maleimide-anthracene Diels–Alder approach.

6.3.1 Star polymers A_n

The simplest case of a spherical structure is a star polymer with several chemically identical arms.

CuAAC Chemistry Routes

For star polymer formation via CuAAC, a linear polymer chain, which carries either an alkyne or azide functionality, is coupled onto a core with multiple opposite functionalities. The core can theoretically be based upon either group. In reality, practical considerations play a role such as the type of reaction that has been used to generate the arm. An azide group can be generated at a chain end by the simple replacement of bromide groups – which are present in ATRP generated structures. Polymers bearing hydroxyl functionality such as PEG can be converted in a similar, facile approach via the tosylate and then into azides. It is therefore not surprising to find more reports using alkyne containing cores, which are then reacted with azide end-functional polymer chains (Scheme 6.9).

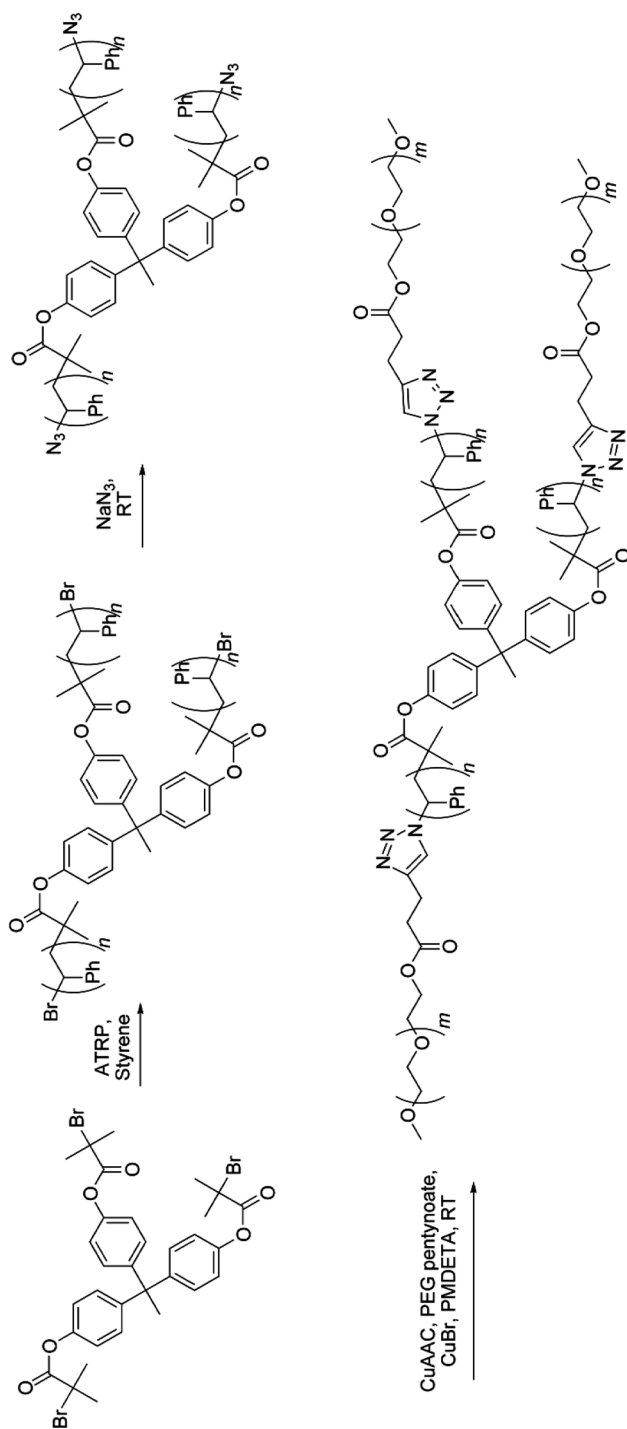


Scheme 6.9 The synthesis of an A_4 star polymer via the CuAAC approach using typical reaction conditions.

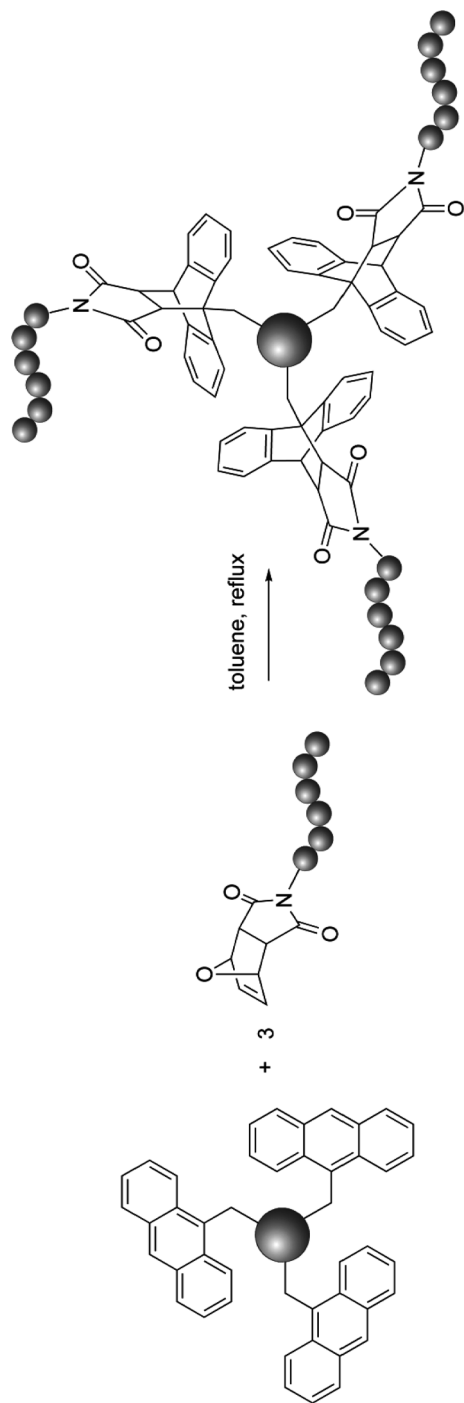
The success of a click reaction is expected to be a function of not only the length of the coupled polymer chain, but also the functionality of the core. A detailed study using ATRP-generated and azide-functionalized PS chains with molecular weights of 1400, 6800 and 18 100 g mol^{-1} confirmed that the yield is highly dependent upon the chain length of each arm. Di-, tri- and tetrafunctional alkyne containing cores were employed; the results that were obtained showed the yield drops from 90% (difunctional core) to 83% (tetrafunctional core) already with low molecular weight polystyrene (1400 g mol^{-1}). As expected, a more dramatic effect was observed when using higher molecular weight branches. A maximum yield of 80% was obtained when attempting to attach PS chains with a molecular weight of 18 100 g mol^{-1} to a difunctional core.⁵¹ Similar results were obtained when coupling other polymers such as azide-functionalized PEG ($M_n = 2600 \text{ g mol}^{-1}$) or PtBA ($M_n = 6700 \text{ g mol}^{-1}$) to a trifunctional core. Conversions of not more than 87% were obtained, resulting in stars with an average number of arms of fewer than three.⁵⁷ An excess of the functionality belonging to the arm can sometimes enhance the completeness of the reaction. One such example has been observed in the case of the CuAAC between alkyne-functionalized PCL ($M_n = 2200 \text{ g mol}^{-1}$) and azide-functionalized β -cyclodextrin. The formation of the seven-arm star was reported to be quantitative after using a 9-fold excess of the reactive linear precursor.⁵⁸ However, in another example, an excess of the linear precursor could not ensure the quantitative conversion in the synthesis of a three-arm star block copolymer (see Scheme 6.10).⁵⁹ Various ratios between PEG-azide (arm, $M_n = 2000 \text{ g mol}^{-1}$) and alkyne (core) were tested showing that the maximum conversion of 85% could not be improved upon using alkyne-azide ratios of up to 4.5:1. In an alternative attempt reported by Monteiro *et al.*, the conversion of the binding sites could be improved (from 75 to 78%) by slowly feeding a solution of the core to the arm reaction mixture.⁶⁰

The obtained star polymers described above required the use of a purification step to remove the copper catalyst, which was in most cases coordinated by PMDETA as the ligand. Synthetic strategies, which do not require the use of copper catalysts are therefore of potential interest. The predominant candidates as discussed below involve the Diels-Alder cycloaddition of anthracenes and maleimides as well as the RAFT-HDA concept.

The Diels-Alder reaction between maleimide and anthracene derivatives (Scheme 6.11) is carried out under the absence of any type of catalyst, but requires an extended reaction period at high temperatures.⁵² Interestingly, this approach was observed to gain high conversions even for high molecular weight arms (PMMA, $M_n = 8450 \text{ g mol}^{-1}$, 89%; PtBA, $M_n = 10\,600 \text{ g mol}^{-1}$, 93%).



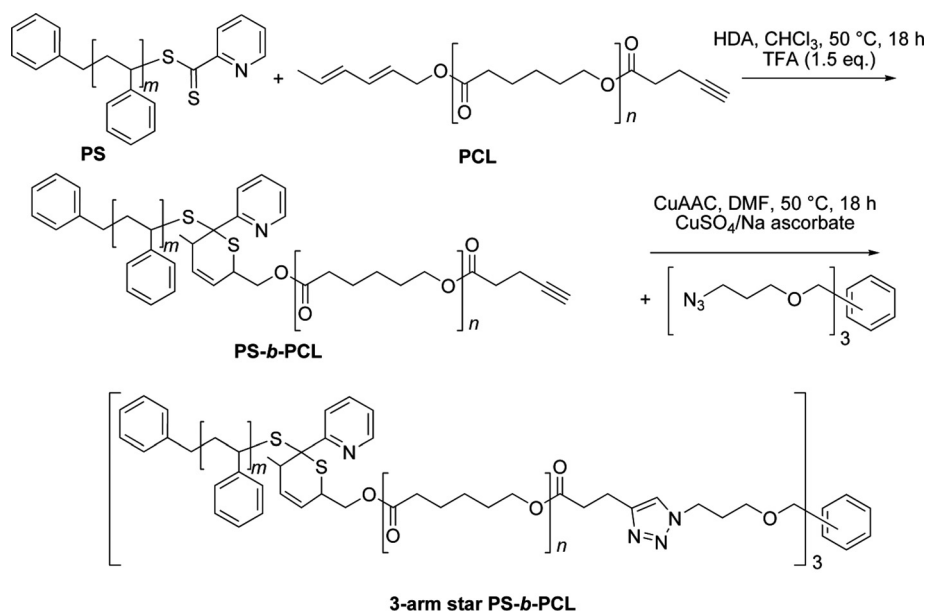
Scheme 6.10 Synthesis of PS-b-PEG 3-arm star block copolymers by combination of core-first and coupling onto methods. For detailed reaction conditions please refer to Gao et al.⁵⁹



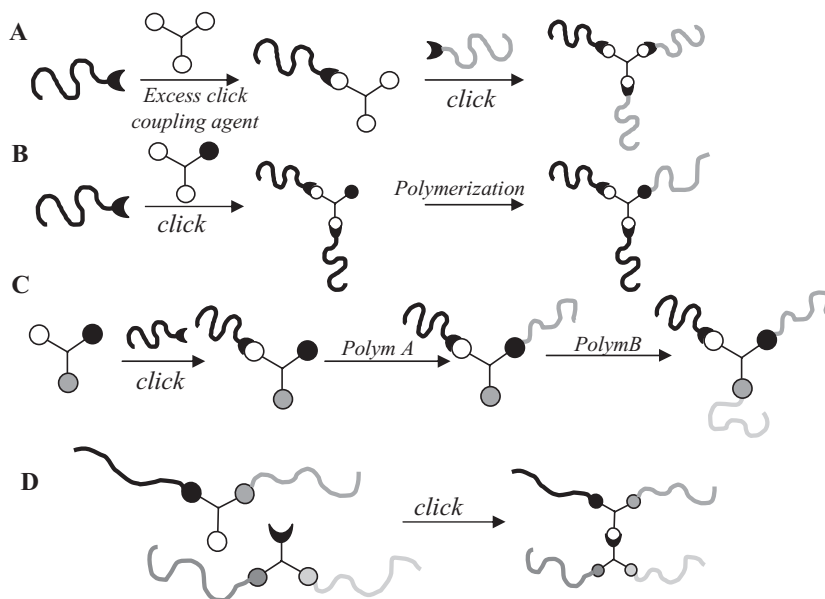
Scheme 6.11 Synthesis of star polymers via a Diels–Alder reaction between furan-protected maleimide end-functionalized polymer and trianthracene core.

The direct reaction between the RAFT groups and dienes, as described previously, can also be employed in the synthesis of star polymers by coupling RAFT-generated polymers onto multifunctional cores, which carry a multitude of diene functionalities. Similar to the CuAAC, the conversion between both functional groups was dependent upon the functionality of the coupling agent. While the reaction between PS ($M_n = 3600 \text{ g mol}^{-1}$) synthesized using benzylpyridin-2-ylthioformate as RAFT agent and bis-diene functional core yielded 91% conversion, the tri- and tetrafunctional core resulting permitted a maximum conversion between arms and core of 86 and 81%, respectively. Interestingly, the type of the RAFT agent employed to generate the PS arms was found to have a pronounced influence on the reactivity, thus influencing the average number of arms. Replacing the pyridyl-Z-group of RAFT agent by diethoxyphosphoryl group to prepare a PS arm of similar molecular weight led to PS arms of lower HDA activity. As a result, the maximum conversion was reduced by more than 10% with conversions of 81, 77 and 65%.⁴³ In terms of efficiency, the RAFT HDA concept is therefore comparable to the CuAAC strategy. Importantly, both methods can be applied in a combined approach, which lends itself to independent control of two different binding sites.⁵⁵ The generation of three-arm stars with block structures in each arm by this technique is shown in Scheme 6.12.

A range of concepts were explored in the generation of star polymers with heteroarm structure (Scheme 6.13). These approaches typically involve the combination of a click reaction with other techniques such as RAFT,⁶¹ ATRP,⁶⁰⁻⁶⁴ NMP^{62,65} or ROP.^{63,65} Apart from one exception,⁶⁶ the CuAAC was the reaction of choice so far to synthesize these



Scheme 6.12 Arm-first strategy for the preparation of three-arm star PS-b-PCL via a consecutive combination of CuAAC and HDA chemistry. For detailed reaction conditions please refer to Barner-Kowollik et al.⁵⁵



Scheme 6.13 Concepts to generate heteroarm star polymers: (A) AB_2 ; (B) AB_2 ; (C) ABC 3-miktoarm; (D) ABCD 4-miktoarm.

structures. A complete click approach to heteroarm star polymers was achieved by reacting the reactive polymer chain (azide-functionalized) with an excess of trialkyne-functionalized core. In a subsequent step, the remaining binding sites were coupled with further reactive polymer chains, resulting in AB_2 stars. A range of these stars with various combinations of PS, PMMA, PtBA and poly(methyl acrylate) (PMA) have been prepared using polymers with molecular weights of around $5000\text{--}7000\text{ g mol}^{-1}$ each.⁶⁰

Most approaches to heteroarm stars, however, involve the synthesis of a multifunctional initiators that can undergo click reactions, while acting as initiators for a range of living polymerizations [Scheme 6.13(B, C)]. The click reaction was either carried out as an initial step^{61,63,64} or as the final step after other arms had already been generated by the various polymerization techniques.⁶²

An elegant approach is the use of a simultaneous click reaction with ROP and NMP. A multifunctional click-ROP-NMP compound was heated for 48 h at $125\text{ }^\circ\text{C}$ in the presence of styrene, ϵ -caprolactone, azide-terminated PMMA (or PEG) and copper(I) bromide-PMDETA.⁶⁵

Similar concepts were explored in the synthesis of ABCD 4-miktoarm star polymers. Two different trifunctional initiators were prepared – one carrying an azide group, the other containing an alkyne group.^{66,67} Prior to the click reaction, various polymerizations were carried out, creating AB block copolymers carrying an azide group and CD block copolymers with an alkyne group between the two blocks. The two components were then combined – usually with a 10–30% excess of one block copolymer and an extended reaction

period of 2 days. NMR studies were usually employed to calculate the conversion of the reaction, which was typically around 90%.

6.3.2 Dendritic Star Polymers

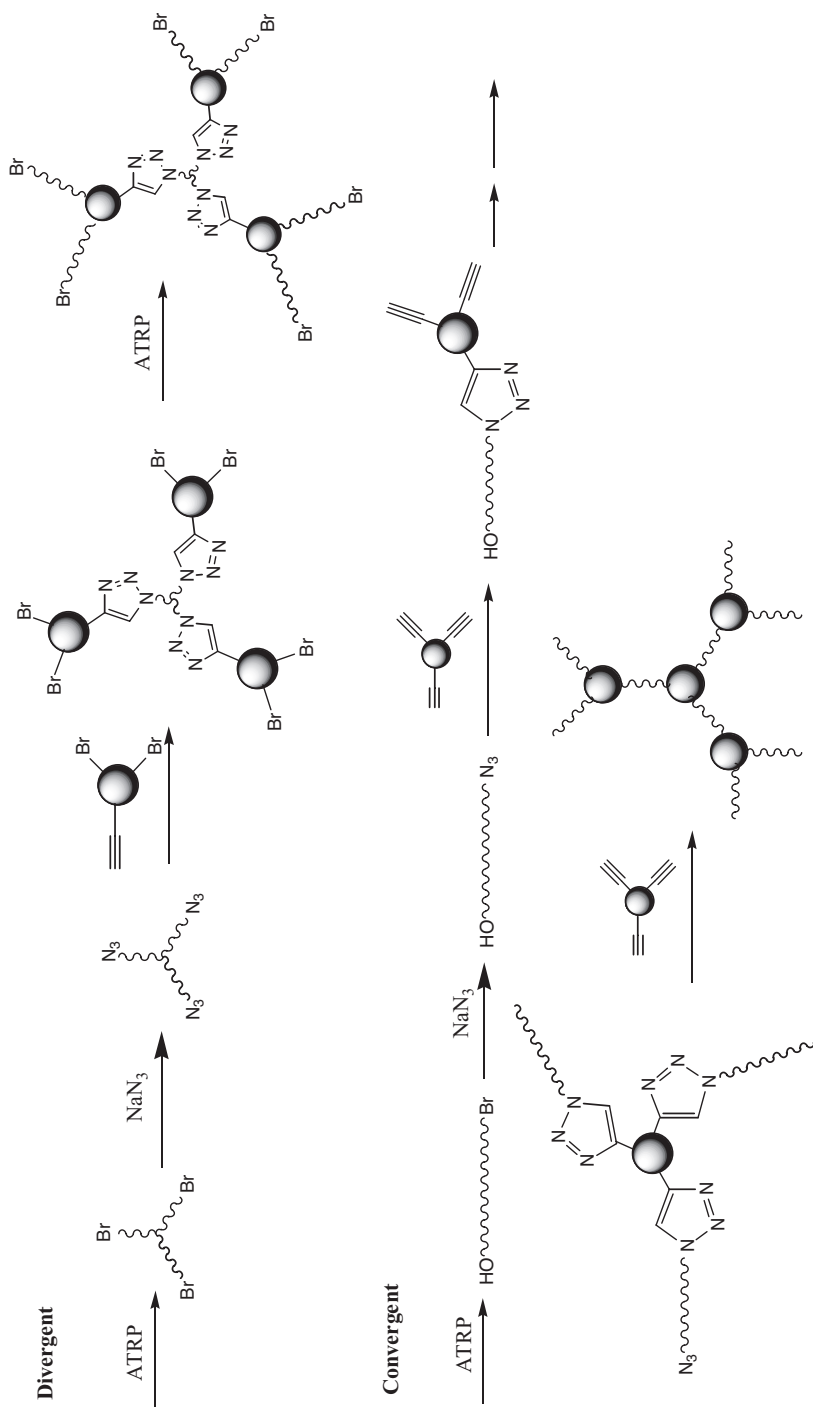
Star polymers with well-defined, branched arms were prepared using alternating ATRP and click reactions with an intermediate step replacing bromide with azide.^{60,68,69} Divergent⁶⁸ and convergent⁶⁹ synthetic pathways were explored (Scheme 6.14). While the divergent approach involved only click reactions between polymers and a low-molecular-weight coupling agent, the convergent approach attempted in the final step to couple three-branched polymer chains to a trifunctional core. Not surprisingly, the reaction was reported to be sluggish, but fractionation allowed for the isolation of well-defined G₂ dendrimers.⁶⁹

6.4 Graft Copolymers

Of the various macromolecular architectures, graft copolymers attract special interest owing to their unique material properties. Depending upon the chemical nature of the backbone and side chains, such structures are of potential application in tissue engineering, polymer-based biomaterials, nanotechnology and drug delivery vectors.

In principle, graft copolymers can be synthesized by three different routes: ‘grafting from’, ‘grafting through’ and ‘grafting onto’. In particular, the efficiency of the ‘grafting onto’ methodology is often limited due to the steric repulsion of the reactive side chains. Grafting densities are therefore usually low and unreacted side chains are often left behind and have to be removed by further fractionation steps. To overcome these difficulties, highly efficient coupling strategies such as click reactions are of potential benefit. It is therefore not surprising that the first report about a CuAAC ‘grafting onto’ approach appeared already in 2005 soon after the first applications of click chemistry in polymer science, in which Emrick *et al.* grafted PEG chains and oligopeptides onto aliphatic polyesters.⁷⁰ Since then, a number of publications have appeared reporting the use of click strategies for the ‘grafting onto’ approach, a summary of which is presented in the following.

The two principal designs for the construction of graft copolymers via CuAAC ‘grafting onto’ chemistry are depicted in Figure 6.3. Either the macromolecular scaffold is equipped with azide functions (Table 6.1), which are converted with polymers carrying the alkyne moiety or alkyne-functionalized polymeric backbones (Table 6.2) are combined with azido-terminated polymers. The question of which linking strategy should be followed mostly depends upon which monomer family and which polymerization technique are chosen for the construction of the according building blocks. Finally, the use of protective group chemistry or post-polymerization functionalization allows for the synthesis of macromolecular scaffolds of varying chemical structure. Although there are a number of reports in the literature in which the CuAAC is used to graft low molecular weight reactants onto polymer backbones, the following section highlights the examples describing the construction of a variety of graft/brush copolymers. Reactive polymer chains, as counterparts in the ‘grafting onto’ methodology, are thoroughly discussed in the blocks section (see Section 6.2.1) and are therefore only briefly mentioned here.



Scheme 6.14 Divergent and convergent synthesis approach to dendritic star polymers by a combined ATRP/click approach.

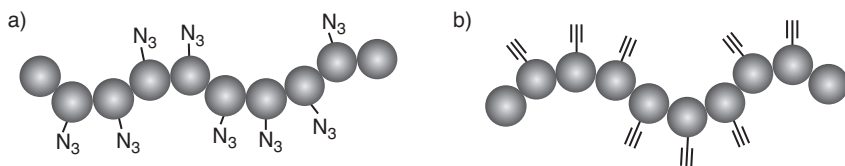


Figure 6.3 Azide- (a) and alkyne (b)-functionalized polymer chains as the two principal macromolecular scaffolds for the construction of graft copolymers via CuAAC chemistry.

6.4.1 ‘Grafting-to’ Azide Main Chains

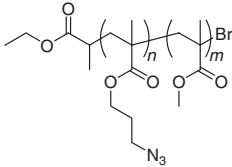
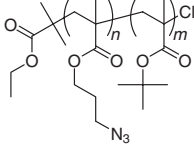
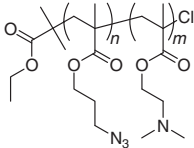
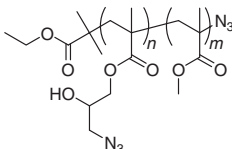
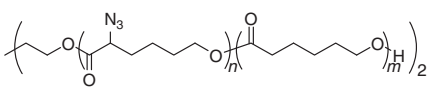
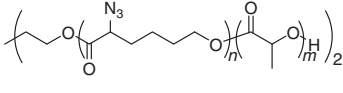
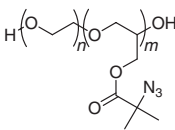
The main advantage of the use of azido polymer backbones is the nonrequirement of protective group chemistry in the case of radical polymerizations of vinylic azido monomers.

However, a recent study by Perrier *et al.* revealed that under typical radical polymerization conditions, electron-deficient monomers can undergo side reactions in the presence of organic azides, which result in a significant loss of orthogonality.⁴⁰ Nevertheless, short reaction times and low polymerization temperatures minimize the occurrence of this side reaction and well-defined materials are obtained. One such example was reported by Du Prez and coworkers, in which methyl methacrylate was copolymerized with 3-azidopropyl methacrylate via ATRP.³⁰ Subsequently, PEEA chains obtained after ATRP with an alkyne-containing initiator were attached to the macromolecular precursor using a copper(I) bromide–PMDETA system. GPC analysis revealed the successful coupling reaction. However, excessive PEEA needed to be removed via preparative GPC. Similar results were found by Liu *et al.*, who copolymerized 3-azidopropyl methacrylate with both *tert*-butyl methacrylate and 2-(dimethylamino)ethyl methacrylate.⁷¹ Successive CuAAC ‘grafting-to’ reactions with poly(*N*-isopropyl acrylamide) (PNIPAM) carrying an alkyne end-group were performed with copper(I) bromide under ligand-free conditions. Complete conversions of the alkynyl residues were achieved by using alkyne to azide ratios of <0.5:1.

The versatility of click strategies for the construction of graft copolymers was further shown by Matyjaszewski *et al.*, who used a combination of two consecutive click reactions for the synthesis of polymeric brushes with PEG side chains.⁷² An epoxide ring containing copolymer of glycidyl methacrylate and methyl methacrylate was converted with sodium azide to obtain the corresponding 1-hydroxy-2-azido compound, which was further converted in a CuAAC reaction in the presence of PEG pentynoate and copper(I) bromide in a ligand-free or PMDETA environment. With an alkyne:azide ratio of 1:1 a maximum conversion of the reactive alkyne side chains of 75% was reached within 1 h, which could not be further increased after longer reaction times or a higher catalyst loading.

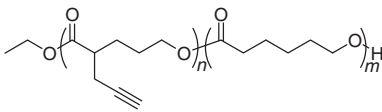
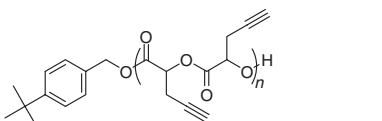
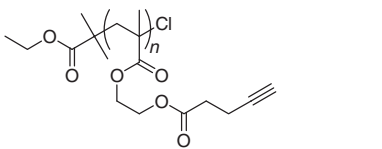
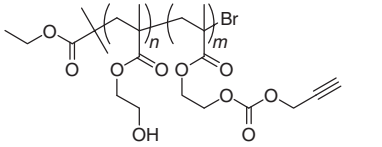
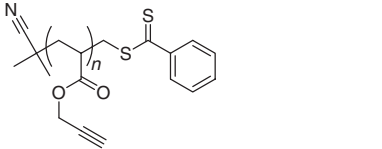
The use of ROP techniques for the preparation of aliphatic polyesters carrying azide substituents was reported by Jerome and coworkers.⁷³ Copolymers of α -chloro- ϵ -caprolactone and ϵ -caprolactone (CL) or lactide (LA) were transformed into the corresponding azide containing copolymer by substitution of the chloride. After the CuAAC with an alkyne-functionalized PEG using copper(I) iodide–triethylamine–THF, an amphiphilic graft copolymer with a grafting density of \sim 25% was obtained. In a more recent work, the same authors improved the synthesis protocol and prepared a polyester PEG graft copolymer with a grafting density of 40%.⁷⁴ Finally, this synthesis protocol led to the formation of tadpole-shaped PCL with two PEG grafted tails and eight-shaped PCL-g-PEG with

Table 6.1 Azide-functionalized macromolecular scaffolds

Polymer structure ^a	Polymer synthesis	Reference
	ATRP	30
	ATRP	71
	ATRP	71
	ATRP + 1 post-polymerization step	72
	ROP + 1 post-polymerization step	74
	ROP + 1 post-polymerization step	73
	ROP + 3 consecutive post-polymerization steps	53

^aAll copolymer structures represent random copolymers.

Table 6.2 Alkyne-functionalized macromolecular scaffolds

Polymer structure ^a	Polymer synthesis	Reference
	ROP	70
	ROP	76
	ATRP + 1 post-polymerization step	77
	ATRP + 1 post-polymerization step	78
	RAFT + 1 post-polymerization step	56

^aAll copolymer structures represent random copolymers.

potentially novel macroscopic and self-assembly properties.^{54,75} The reverse strategy – a PEG-based main chain carrying azide groups – was presented by Huang and coworkers.⁵³ The polymer backbone was prepared via ROP and three consecutive post-polymerization modifications. CuAAC reactions between the main chain and alkyne-functionalized miktoarm star-shaped side chains were carried out in the presence of copper(I) bromide–PMDETA with a graft-efficiency of 63% (determined by NMR spectroscopy).

6.4.2 ‘Grafting-to’ Alkyne Main Chains

Alternatively to the azide-functionalized main chains, polymer backbones carrying alkyne residues have been used for the construction of graft copolymers via CuAAC ‘grafting onto’ chemistry. ROP as well as controlled radical polymerization methods have been used for the synthesis of the macromolecular scaffolds; a summary is presented in Table 6.2.

In this case, the ROP provides an easy access to the desired alkyne main chains whereby routes via radical polymerization methods require the use of protective groups or

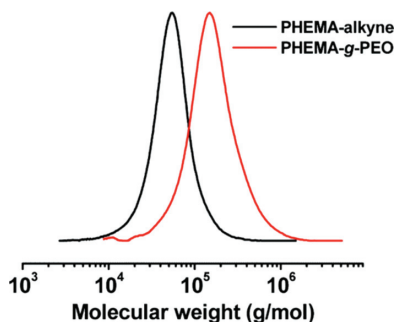


Figure 6.4 GPC traces of PHEMA-g-PEG grafted copolymers synthesized by the ‘grafting onto’ method. For detailed reaction conditions please refer to Gao and Matyjaszewski.⁷⁷ Reprinted with permission from Gao, H. F., Matyjaszewski, K., (2007), *Synthesis of molecular brushes by ‘grafting onto’ method: combination of ATRP and click reactions*, *J. Am. Chem. Soc.*, **129**, 6633–6639. Copyright 2007 American Chemical Society.

post-polymerization functionalization. Emrick and coworkers homo- and copolymerized α -propargyl- γ -valerolactone to obtain aliphatic polyesters with different degrees of alkyne content.⁷⁰ The obtained (co)polymers were subsequently used for the grafting of PEG and oligopeptide moieties. Interestingly, CuAAC reactions were performed in aqueous dispersion of the polyester, which solubilized in the aqueous environment as the reaction proceeded. The amphiphilic graft copolymers, with grafting densities of >80%, were shown to be biocompatible. A similar approach was performed by Smith, Baker and coworkers who used a lactide-based monomer with two alkyne functions for the ring-opening (co)polymerization, resulting in polyglycolide homo and copolymers with pendant alkyne groups.⁷⁶ CuAAC reactions with an azide terminated PEG were performed with copper(II) sulfate in the presence of sodium ascorbate. The synthesis of polymer backbones via radical polymerization and their successive functionalization with alkyne groups was shown by Gao and Matyjaszewski.⁷⁷ The polymerization of 2-hydroxyethyl methacrylate (HEMA) via ATRP, followed by an esterification of the hydroxyl groups with 4-pentynoic acid yielded polymer main chains with high alkyne functionality. CuAAC reactions with different azide end-capped polymers, namely PEG (Figure 6.4), PS, poly(butyl acrylate) (PBA) and PBA-*b*-PS, were complete within 3 h and yielded the according graft copolymers with moderate graft densities (<50%) for the bulkier polymers like PBA and PBA-*b*-PS and high densities (up to 88%) for the PEG side chains.

The use of poly(2-hydroxyethyl methacrylate) (PHEMA) as precursor for the alkyne functionalization was also reported by Hennink and coworkers.⁷⁸ In this case, propargyl alcohol was linked via a carbonate function onto the polymer backbone, which allowed for the hydrolytic degradation of the polymeric brushes obtained after CuAAC with PDMAEMA. A combination of RAFT polymerization and protective group chemistry was used by Stenzel, Barner-Kowollik and coworkers.⁵⁶ The polymerization of trimethylsilylpropargyl methacrylate and the successive deprotection of the obtained polymers led to well-defined polymers carrying alkyne groups on each monomer unit. CuAAC reactions with poly(vinyl acetate) (PVAc) chains obtained after RAFT polymerizations using an azide-functionalized RAFT agent led to PVAc brushes.

6.4.3 Non-CuAAC Routes

Besides the number of publications using CuAAC chemistry for the ‘grafting-to’ approach, there are two examples in which alternative synthetic routes were used. The Diels–Alder cycloaddition of anthracenes attached to a polymer backbone with maleimide-functionalized PEG as reactive polymer side chains was successfully used in the construction of graft copolymers.⁷⁹ The other example involved substitution reactions on poly(pentafluorostyrene) using amide-functionalized polymers as synthetic handles.⁸⁰

6.5 Concluding Remarks

In summary, the construction of complex macromolecular architecture polymers via facile, rapid and orthogonal conjugation chemistries is one of the key driving forces in modern polymer science. The current chapter has highlighted, in detail, access routes to block, star and comb (co)polymers via several click reactions including the CuAAC as well as Diels–Alder conjugation protocols in combination with living/controlled polymerization (including RAFT, NMP, ATRP and ROP) methodologies. The focus lies on synthetic advances that have opened novel and efficient approaches to these architectures as well as the monomer classes that have been employed. The chapter also provides selection guidelines in terms of the molecular scaffolds and end-group structures to arrive at specific complex polymers.

Many authors have described click chemistry as a technique that attempts to widen the synthetic toolbox that is made available to the organic chemist in the generation of such complex structures. However, from the way in which click chemistry has been used, it more or less is akin to a universal tool that may be used to great avail in a wide variety of circumstances in polymer science. It thus has functioned to narrow down the synthetic tool box to a few select reactions, which attempt to vastly improve the efficiency with which one may achieve complex macromolecular architectures.

In the introduction to this chapter, an analysis of the molecular weight ranges and types of polymers that have been used in click conjugation methodologies is provided. However, upon inspection of these figures, one may observe that there is a lack of the versatility that click chemistry is claimed to be able to offer polymer science. The time has come for the combination of click chemistry and polymer science to be taken to the next step to take advantage of its potential versatility and drive forward the development of well-defined complex macromolecular architectures in the pursuit of new, functional materials.

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