# Click Assisted One-Pot Multi-Step Reactions in Polymer Science: Accelerated Synthetic Protocols

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Presently, the majority of reports deal with combining chemical reactions, in a stepwise fashion, to obtain well-defined polymers. In the future, chemists need to address new challenges such as increase in the range of available efficient reactions, developing libraries of compatible one-pot reactions, and the application of obtained materials in key industries. Indeed, the rising importance of the click concept has now devised robust synthetic approaches in various fields of research. The unique selectivity of the click reaction is today a new found toolbox for scientists to investigate one-pot multi-step systems. Several accelerated protocols have elegantly been reported to obtain a library of advanced polymers.
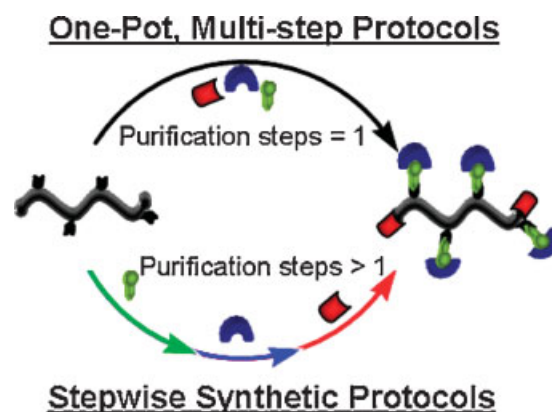
Introduction

Environmental and energy issues are rapidly emerging as grand challenges for the 21st century with the basic tenets of efficiency and economy being relevant to all aspects of science and engineering.[1] From a synthetic chemist's viewpoint, this newfound emphasis on environmental and energy issues is leading to an increased focus on developing accelerated/efficient strategies for the syn-

thesis of both traditional as well as novel compounds. For example, accelerated synthetic procedures can reduce the number of reactions and purification steps, therefore leading to more eco-friendly products. For inspiration, scientists have tried to mimic Nature's stunning ability to assemble small molecules, such as nucleotides, amino acids, and sugars to a myriad of macromolecules e.g., natural products, peptides, proteins, DNA, etc.[2] Indeed, these large macromolecules are constructed with unprecedented control including regio-/stereo-specificity in complex chemical environments using multi-step and one-pot strategies.[3] This efficiency and orthogonality allow Nature to develop the necessary toolbox for life.

This review will demonstrate the growing importance of robust, efficient, and orthogonal chemistries in synthesis by illustrating a number of elegant strategies from the field of organic chemistry and their migration to the field of polymer science. We will also present a definition for the classification of one-pot reactions in polymer science. Furthermore, a short review on published one-pot

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Pontus Lundberg was born in 1982 in Karlstad (Sweden). In 2006, he obtained his M.Sc degree in chemical engineering at Uppsala University (Uppsala, Sweden), whereby his undergraduate research was performed in the group of Professor Jöns Hilborn. He performed his degree project at IBM Almaden Research Center (San José, CA, USA) dealing with organo-catalysis, block-copolymer synthesis, and hydrogels under the supervision of Dr. James L. Hedrick. He is currently pursuing his Ph.D. in polymer chemistry at The Royal Institute of Technology (KTH) (Stockholm, Sweden) under the supervision of Professor Anders Hult and Assistant Professor Michael Malkoch. His research interests include synthesis of well-defined block-copolymer architectures and use of block co-polymers in antifouling coatings.

Craig J. Hawker is currently, Director of the Materials Research Laboratory and a Professor of Chemistry, Biochemistry and Materials at the University of California (Santa Barbara, USA). He received a B.Sc. (Hons) degree and University Medal in Chemistry from the University of Queensland in 1984 and a Ph.D. in bioorganic chemistry from the University of Cambridge in 1988 under the supervision of Professor Sir Alan Battersby. Jumping into the world of polymer chemistry, he undertook a postdoctoral fellowship with Professor Jean Fréchet at Cornell University from 1988 to 1990 and then returned to the University of Queensland as a Queen Elizabeth II Fellow from 1991 to 1993. From 1993 to 2004, he was a Research Staff Member and an investigator in the NSF Center for Polymer Interfaces and Macromolecular Assemblies at the IBM Almaden Research Center. He has been honoured by numerous awards including the 2005 ACS Award in Applied Polymer Science from the American Chemical Society, the 2005 Dutch Polymer Award, and the 2007 Hermann Mark Scholar Award. His research has focused on the interface between organic and polymer chemistry with emphasis on the design, synthesis, and application of well-defined macromolecular structures in biotechnology, microelectronics, and surface science.

Anders Hult received his master's degree in Chemical Engineering in 1978 and his Ph.D. in Polymer Technology in 1982 from the Swedish Royal Institute of Technology (Kungliga Tekniska högskolan, KTH). He joined the Department of Polymer Technology at KTH as a research associate (1984–1986) and an Associate Professor (1986). Shortly after in 1988, he attained a full professor status. Between 1999 and 2004, Dr. Hult served as the Dean of the School of Chemistry, Chemical Engineering, and Biotechnology at KTH. He was also a visiting Professor at Ecole Polytechnique Federale de Lausanne (EPFL) (Lausanne, Switzerland) in 1993 and University of Texas (Austin, USA) in 2004. He has published over 200 papers and has successfully filed nine patents. Professor Hult has a wide experience of synthesis of tailored polymer systems for thin film applications. The main field of expertise lies within advanced polymer synthesis and how to correlate relationships between molecular structure and architecture versus macroscopical user properties.

Michael Malkoch received his Ph.D. in Polymer Technology in 2003 from the Royal Institute of Technology (KTH) under the supervision of Professor Anders Hult. Between 2003 and 2005, Malkoch joined Professor Craig J. Hawker as a postdoctoral fellow at the Stanford University, IBM Almaden Research Center, and finally the Materials Research Laboratory in Santa Barbara (UCSB). Upon his return he was awarded the distinguish Assistant Professor fellowship in materials science from the Swedish Research Council and has now joined the Division of Coating Technology at KTH. Malkoch is also one of the founders of a materials research company, Polymer Factory, providing biocompatible dendritic materials. His main fields of interest are the construction of complex dendritic and other macromolecular architectures, living-controlled polymerizations, hydrogels, nano-particles, and coatings for a variety of industrial applications.

multi-step reactions using click chemistry as a key mechanism for the construction of advanced polymeric materials is presented. Finally, an outlook on future trends for the field of one-pot multi-step strategies and their application to the development of efficient strategies towards materials will be presented.

From Organic Chemistry to Polymer Science

The adaptation of synthetic methodologies used in organic chemistry to polymer chemistry is often difficult due to the additional constraints imposed by the macromolecular framework.[2a,4] In organic chemistry, the use of highly specific and efficient reactions can increase the yield of a specific product, however, when dealing with polyfunc-

tional macromolecules a highly specific and efficient reaction is of absolute necessity in order to obtain the desired macromolecules. For example, an organic reaction on a simple monofunctional molecule that reaches 90% conversion can lead to an isolated yield of approximately 90%, while the same reaction efficiency (conversion ca 90%) on a polymeric material with 25 functional groups leads to a very low yield of the desired, fully functionalized product i.e., 7.2% which in turn would be extremely difficult to obtain pure. In addition, sterical hindrance, random coil conformation, and large solubility changes are typical variables that affect the chemical reactions which further impacts the ability to obtain complete functionalization.

As a result, polymer chemists are on the lookout for the development of organic reactions that have efficiency and
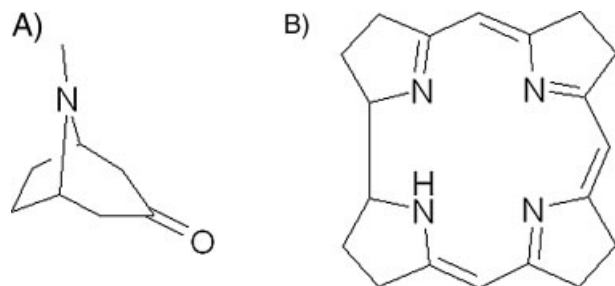
A)

B)

Figure 1. The structures synthesized by Robinson (A)[6] and Scott (B).[8]

versatility to be incorporated into the field of materials science. A new type of chemical reaction that comprises all necessary criteria to efficiently functionalize polymer species is the click reaction, introduced by Sharpless and coworkers.[5] The criteria and properties of the click reactions will be presented below.

Accelerated Protocols: One-Pot Multi-Step Reactions

Chemists have, since the early 20th century, devised and successfully accomplished one-pot multi-step strategies for the synthesis of both natural products as well as novel small molecules. In fact, in 1917 Sir Robert Robinson prepared tropinone (Figure 1A), a precursor to the potent drug atropine, from succindialdehyde, methylamine, and either acetone or a salt of acetonedicarboxylic acid, using an accelerated one-pot biomimetic strategy.[6] Since then, a great number of one-pot strategies have been developed and several reviews dealing with this topic have been published.[7] One of the most inspiring examples include

the one-pot synthesis of corrin (Figure 1B), a macrocyclic compound consisting of 4 pyrrol subunits, from 5-aminol-evulinic acid using 12 enzymes with a total number of 17 steps by Scott.[8] An interesting review by Heathcock describes several elegant examples on accelerated one-pot synthesis of a library of complex polycyclic *Daphniphyllum* alkaloids.[9]

Definitions

While examining the field of one-pot multi-step reactions, it soon becomes clear that the use of abbreviated definitions describing different types of reactions is often ambiguous. Efforts to clarify the proper use of these terms within organic chemistry have been made and one of the most complete terminologies can be found in a review by Fogg and dos Santos.[7d] However, this terminology is not always easily transferred into polymer science. With this in mind, we will present an adaptation of Fogg and dos Santos definitions, vide infra, which is more suitable to the field of polymer science.

One-pot multi-step reactions can be divided into two main categories:

- Non-tandem reactions (NTRs) – comprise the multi-catalytic and domino reaction strategies. Multi-catalytic reactions can be seen as one-pot processes where all necessary reagents and catalysts are added at different stages of the reaction (Scheme 1A). In the case of domino reactions, the reaction steps (≥2) are dependent on and occur after each other, where necessary materials are present from the start (Scheme 1B). NTRs that consist of at least three domino reactions are also defined as cascade reactions (≥3). The terminology cascade

A. One-pot (multicatalytic) reaction

B. Domino (cascade) reaction
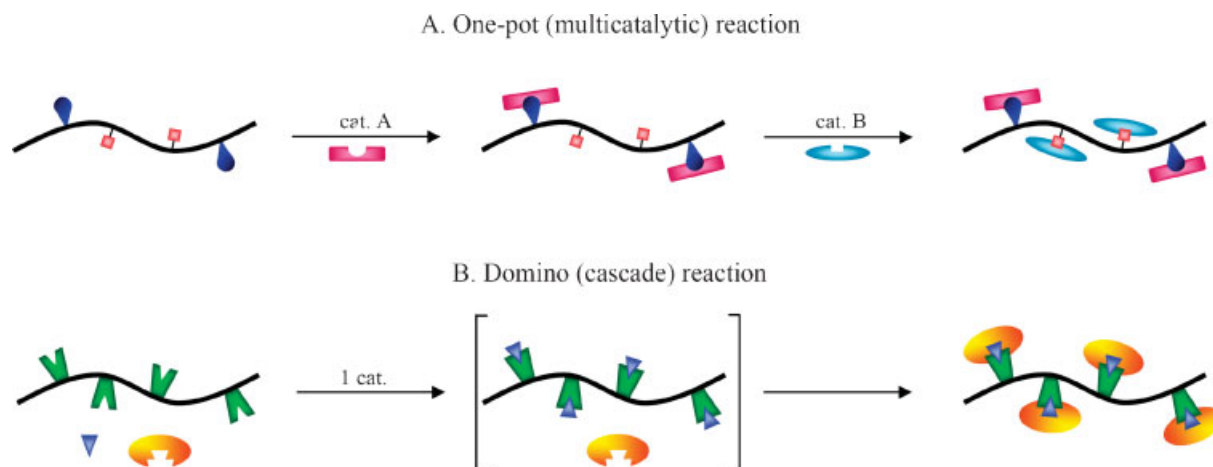
Scheme 1. General reaction schemes for NTRs; A. multi-catalytic reactions and B. domino reactions.

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reactions are often misinterpreted and need to be appropriately addressed by the scientific community. It is, however, important to note that reactions taking place in a domino or cascade fashion should occur as a consequence of the previous reaction.

- Tandem reactions (TRs) – three classes of TRs are identified and in all cases the catalysts are present from the start and two or more independent transformations are involved. These are: orthogonal tandem reactions (Scheme 2A), auto-tandem reactions (Scheme 2B), and assisted tandem reactions (Scheme 2C). Orthogonal tandem reactions have several catalysts and reagents present from the outset of the reactions. In auto-tandem reactions, a single catalyst catalyzes several reactions, either as single specie or after auto-transformation into another specie. The catalysis of the different reactions should also be able to coexist and the catalyst/reactants should be present from the outset of the reaction.

Finally, the assisted-tandem reaction strategy has one unique catalyst present that can be triggered to perform different catalytical reactions. By adding additional reagents, chemical triggers or triggering the reaction by other means (e.g., heat or UV), the catalyst performs different functions at different stages of the reactions. The different functions of the catalyst do not generally coexist.

Click Chemistry

The requirement for high efficiency and orthogonality for many tandem and non-tandem reaction sequences necessitates the development of new chemical reactions and strategies. A significant enabler is the concept of click
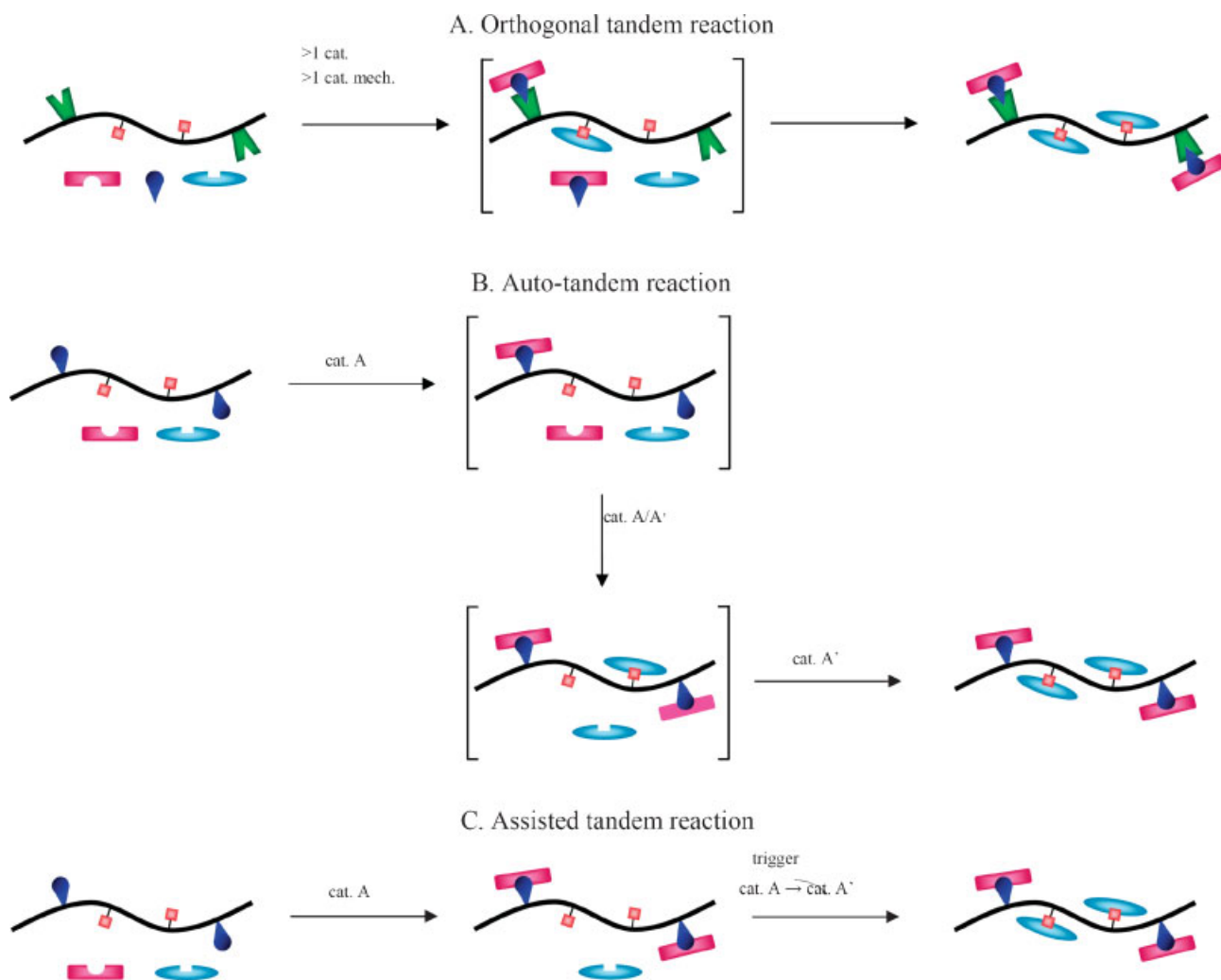
Scheme 2. General reaction schemes for TRs; (A) orthogonal tandem reactions and (B) auto-tandem reactions and C, assisted tandem reactions.

chemistry, originally introduced by Sharpless and cow-orkers in 2001[5] and identifies a family of chemical transformations that comply with a set of specific criteria including quantive yields, high regio-specificity, ortho-gonality, and generation of inoffensive by-products that can be removed by non-chromatographic methods. Further-more, the reaction conditions should be benign and straightforward, using readily available starting materials and reagents that can react in bulk, protic, or aprotic solvents. For many systems, the efficiency of click reac-tions is attributed to a high thermodynamic driving force, above 20 kcal·mol^{-1} for the reaction and the expanding list of click reactions can be divided into four categories:

- cycloadditions of unsaturated species such as the popular 1,3-dipolar cycloaddition reactions and Diels-Alder family of transformations;
- nucleophilic substitution chemistry, involving particu-larly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, and episulfonium ions;
- carbonyl chemistry of the nonaldol type such as formations of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides;
- additions of carbon–carbon multiple bonds such as epoxidations, dihydroxylation, aziridination, sulfenyl halide addition, and Michael additions of Nu-H reac-tants.

The classical example of a click reaction is the original Huisgen 1,3-dipolar cycloaddition between azides and acetylenes revisited by Sharpless and coworkers.[5] Due to high specificity, the reaction can be performed in biological conditions where both organic azides and alkynes are essentially inert, mimicking the reactions performed by Nature.[10] Based on the previous cycloaddition chemistry, the problem of poor regio-specificity, low yields, and harsh reaction conditions needed to be solved before the 1,3-dipolar cycloaddition reaction had an appropriate level of robustness and efficiency. This was achieved by the discovery of the copper(I) catalytic effect on cycloaddition reactions between azide and primary acetylenes and which further led to the definition of the click concept including the copper(I)-catalyzed azide-alkyne cycloaddi-tion (CuAAC).[10,11] The regioselectivity to form the 1,4-regioisomer exclusively and increasing the rate of reaction up to 10^7 times were pivotal.[12] It is today obvious that the CuAAC reaction can be performed under a variety of conditions and in the presence of a myriad of functional groups allowing it to assume a high level of popularity within the click family fulfilling all the criteria set for modern reaction efficiency as stated in other reviews, though it should be noted that the development and

identification of new click reactions is still an active and important area of research.[13]
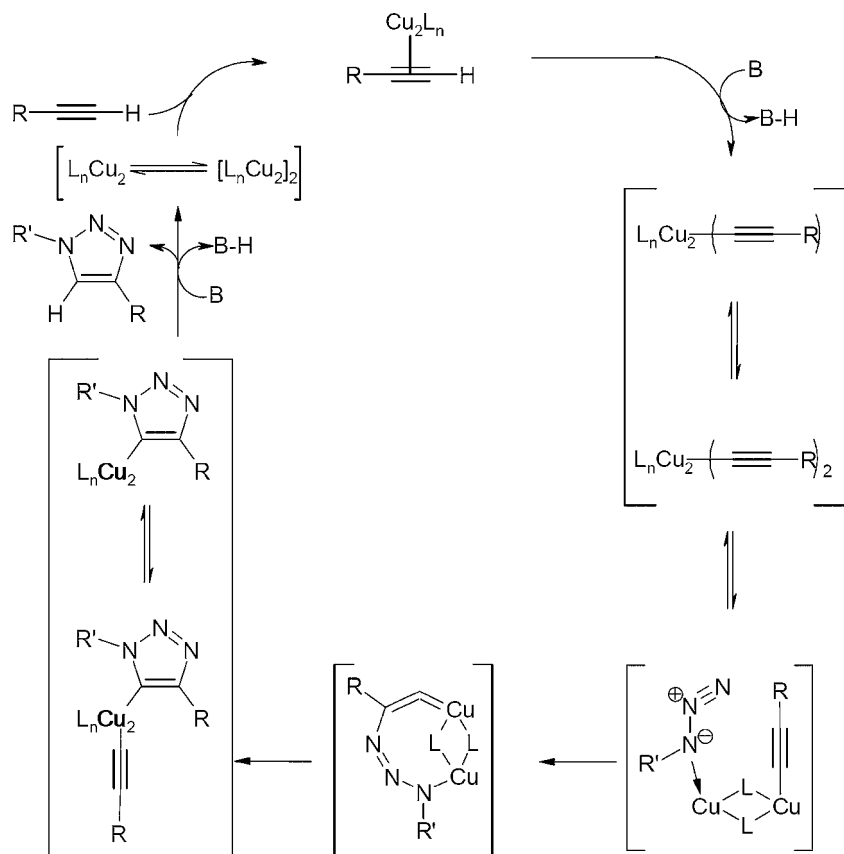
Bearing this in mind, this review will henceforth focus on the CuAAC reaction though many of the concepts and strategies can easily be applied to other systems. A mechanism of the CuAAC reaction cycle was first proposed by Meldal and coworkers[11] and Sharpless and co-workers[10d] reporting a multi-step mechanism via a Cu acetylide intermediate. Based on several observations, the proposed mechanism has recently been revised to include a binuclear reaction mechanism (Scheme 3).[13b] Apart from a range of different Cu(I) species as catalysts for the azide-alkyne cycloaddition, other metals (Ru, Ni, Pt, and Pd) have also been investigated.

Since the introduction of the click concept in 2001 the field has exploded and the original publication in Angewandte has already over 600 citations.[14] Originally used in organic chemistry and drug discovery, it was not until 2003 and through a collaborative effort between the Sharpless and Hawker [15] groups, the click reaction was introduced into the field of materials chemistry. This initial demonstration was powerful, demonstrating the effi-ciency of the click reaction in the construction of a library of monodisperse dendrimers. All dendrimers were obtained in high yields and synthesized under benign conditions with simple purification steps. Since then, CuAAC reaction has been further investigated for the synthesis of other dendritic structures, hyperbranched polymers, block-copolymers, cyclic polymers, star poly-mers, polymer gels and networks, end-functional poly-mers, and pendant group functioned materials.

As the author's intention is to give an overview of one-pot synthesis using click chemistry in polymer science, rather than to give a complete overview of the use of click chemistry in polymer science, the readers are strongly encouraged to read more general reviews on this subject by Lahann and coworkers,[13o] Schubert and coworkers,[13i] Evans,[13h] Binder and Sachsenhofer,[13f] Golas and Matyjaszewski[13k], and Lutz.[13q]

One-Pot Multi-Step Click Chemistry

The high fidelity of the Cu(I)-catalyzed cycloaddition reaction enables the use of click chemistry in combination with other reactions. Naturally, chemists have utilized this unique possibility to develop one-pot multi-step strate-gies. The most common type of one-pot reactions using CuAAC are the in situ generation of azides,[16] usually from a halide, which subsequently can react with primary acetylenes to afford triazoles. According to the previous definitions, these in situ reactions are considered as domino reactions (Scheme 1B). As organic molecules with high nitrogen content, e.g., $-N_3$ or NO_2 are documented

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Scheme 3. The mechanism of CuAAC reaction as presented by Maarseveen and coworkers.[13b]

by click functionalization.[18] If all materials are present at the outset of this reaction, it can also be classified as a domino reaction (Scheme 1B). Examples of multi step strategies include the incorporation of biologically active components. For instance, click chemistry have been combined with antibody complexation,[19] DNA-conjugation[20] as well as the functionalization of different sugars.[21]

While other examples can be found,[22] one of the most inspiring work includes the pioneering work of Ramachary and Barabas[23] who combined four different transformations in a multi-catalytic one-pot system: the Wittig olefination, the Knoevenagel condensation, the Diels-Alder cyclization, and the Cu^I-catalyzed alkyne with yields over >85% (Scheme 4). This work has also been further developed by Ramachary and Reddy,[24] in which a six-component multi-catalytic reaction using Knoevenagel condensation, hydrogenation, alkylation, and click chemistry was utilized to afford the product in a 90% yield (Scheme 5). These examples show that true efficient multi-step reactions can be developed.

explosives, it is obviously an advantage for chemists to use such an in situ approach, in which a generated azide-functional material undergoes further chemical transformation into a more stable triazole functional derivative. Assessment for explosive risks based on specific organic azides can be evaluated using the Smiths rule.[17]

Another frequently used one-pot multi-step reaction strategy is the deprotection of primary acetylenes followed

One-Pot Multi-Step Click Chemistry in Polymer Science

The synthetic protocols needed to successfully prepare sophisticated polymers in a mutli-step fashion require two or more highly efficient chemical reactions that can coexist and selectively perform the required functional group modifications. As mentioned earlier, the criteria to obtain
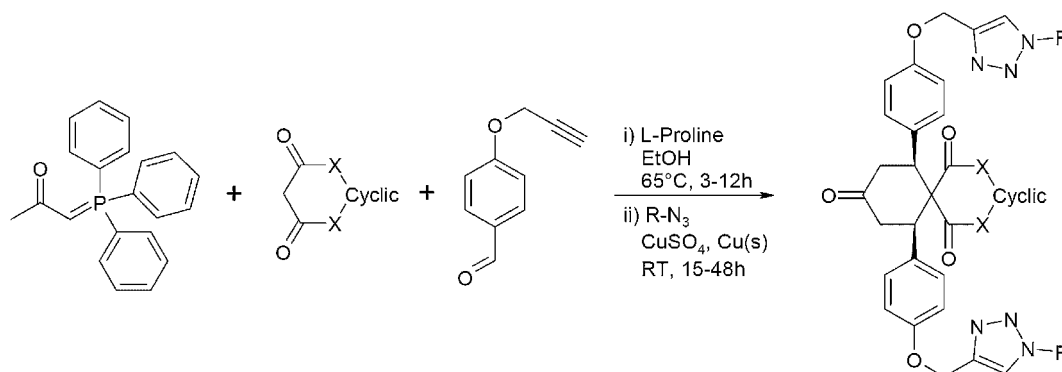
Scheme 4. Four component multi-catalytic one pot reaction, where $X = $ C, N or O.[23]
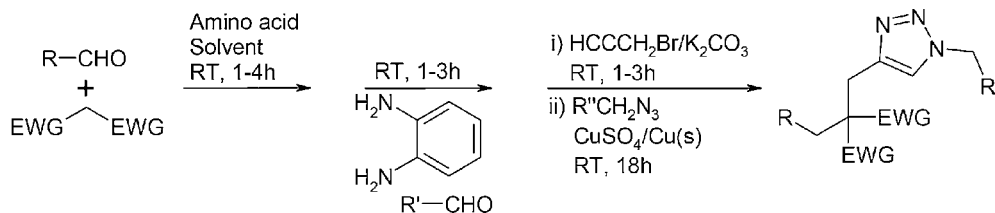
**Scheme 5.** Six component multi-catalytic one-pot reaction.[24]

small molecules via a one-pot multi-step approach is somewhat easier than for the construction of polymer derivatives. In polymer science, steric hindrance, random coil conformation and large solubility changes are typical variables that need to be addressed to obtain complete functionalization. Indeed, the unique selectivity and versatility of the CuAAC reaction has today been investigated for the use in multi-step strategies, either in combination with important polymer reactions including controlled radical polymerization (CRP), ring-opening polymerization, or for coupling reactions to polymer backbones. Below, we will highlight a selection of studies that elegantly execute accelerated one-pot multi-step strategies for the synthesis of sophisticated polymer architectures, Figure 2.

Figure 2. Overview of architectures synthesized using NTR and TR strategies with click chemistry in polymer science.

Non-Tandem Reactions (NTRs) in Polymer Science

The efficiency of click reactions in a multi-step one-pot NTR strategy was first reported by Hawker and coworkers.[25] The NTR strategy was applied to one of the most synthetically demanding polymers i.e., dendrimers and their derivatives, which due to their monodispersity are excellent test vehicles for evaluating synthetic procedures. The published work executed an elegant two-step multi-catalytical functionalization strategy using a fourth generation DAB dendrimer as a multifunctional macromolecular scaffold (Figure 2A, Scheme 6). In the first step, an amidation reaction between the amine end-groups and the dual functional activated ester of 4-pentynoic acid was conducted. An azido derivate of methoxy(diethylene glycol) was subsequently added together with a Cu(I)-catalyst to produce a click reaction. Using this one-pot strategy, the number of purification steps could be reduced by 50% since no isolation of the intermediate product was necessary. By precipitating the mixture in ethyl acetate and diethyl ether, the authors were able to isolate their product in a 77.5% yield, thus proving that dendrimer functionalization could be performed in an accelerated fashion.

Subsequently, Matyjaszewski and coworkers[26] reported a multi-catalytic three-step reaction strategy in which ATRP, in situ azidation, and CuAAC were combined for the synthesis of telechelic polystyrene derivative (Figure 2B, Scheme 7). 2-Propargyl bromoisobutyrate was used as the initiator during the polymerization which yielded the bromo end-functionalized polystyrene that was converted to an azide via in situ nucleophilic substitution reaction at low temperature. The ambient reac-
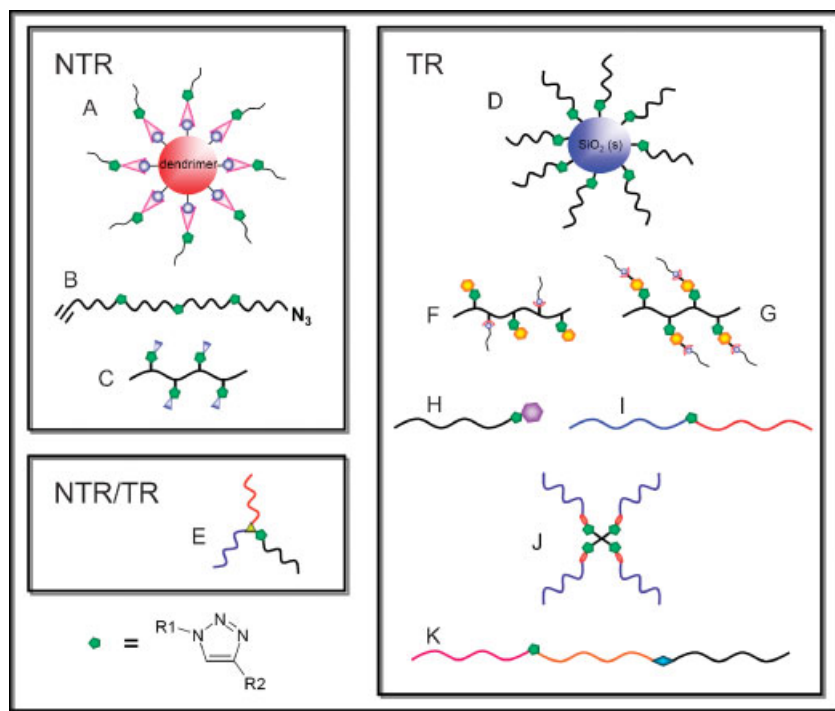
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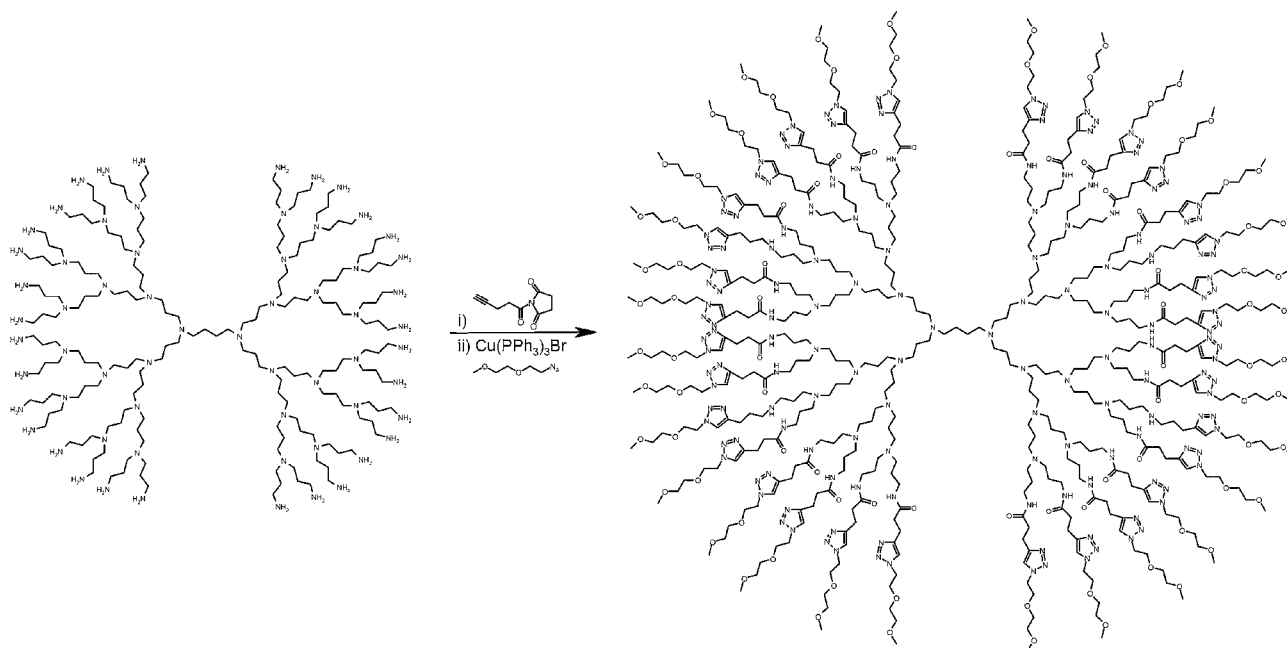
Scheme 6. One-pot multi-catalytic functionalization strategy for DAB dendrimers as reported by Hawker and coworkers.[25]

tion temperature was necessary to suppress any uncontrolled click reaction. Unfortunately, only limited success was achieved due to low efficiency of the click reaction that was attributed to a possible competing side reaction between the inorganic azide and acetylene groups, which would result in N-substituted triazoles, thus preventing further reaction. Other possible side reactions that could have contributed to the low efficiency include intramolecular cyclization or competing copolymerization of acetylene groups.

In overcoming this difficulty, Jérôme and coworkers[27] recently presented a domino NTR strategy combining an in situ azidation and subsequent click reaction of pendant groups along the polymer backbone (Figure 2C, Scheme 8). Initially, a random copolymer of α-chloro-ε-caprolactone and ε-caprolactone with 50% repeating units bearing chloro functionality was synthesized. These functionalities could subsequently be converted into azides using NaN$_3$ in DMF. The reaction was monitored with ^{1}H-NMR and was found to be quantitative after stirring overnight. A sub-

sequent domino click reaction with 3-(dimethylamino)-1-propyne was completed within 2 h at 35 °C and the mixture was precipitated in heptane to yield a polymer with a polydispersity of 1.2. Using traditional synthetic protocols the authors functionalized their copolymer with different alkynes to create a library of functionalized copolymers. Most of the alkynes which were attached were low molecular compounds, however a short hydrophilic polyethylene glycol chain ($\overline{M}_w = 750 \text{ g} \cdot \text{mol}^{-1}$) could also be used.

Tandem Reactions (TRs) in Polymer Science

One of the main differences between the TRs and the NTRs is the use of several catalysts or having a single catalyst perform different functions in the TRs. One such example was reported by Ranjan and Brittain[28] (Figure 2D, Scheme 9), combining CuAAC reaction with reversible addition-fragmentation chain transfer (RAFT)[29] polymer-
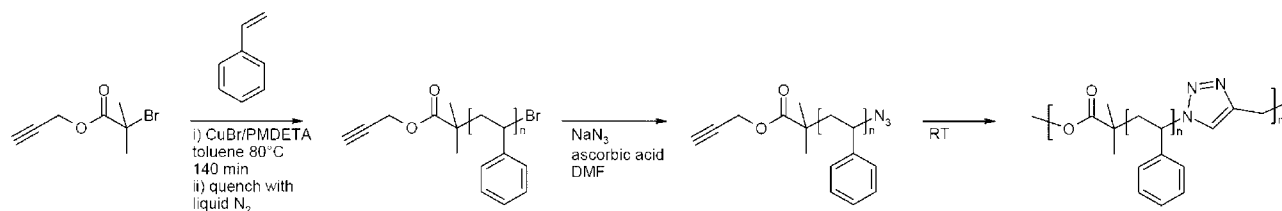
Scheme 7. Matyjaszewski and coworkers one-pot, multi-catalytical, three step strategy for the synthesis of telechelic polystyrene.[26]
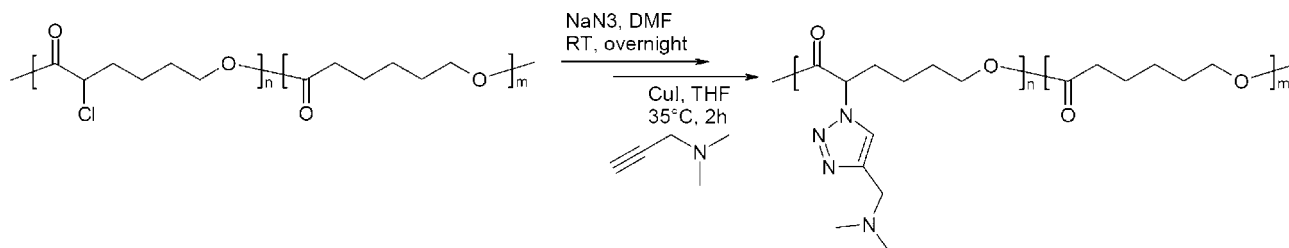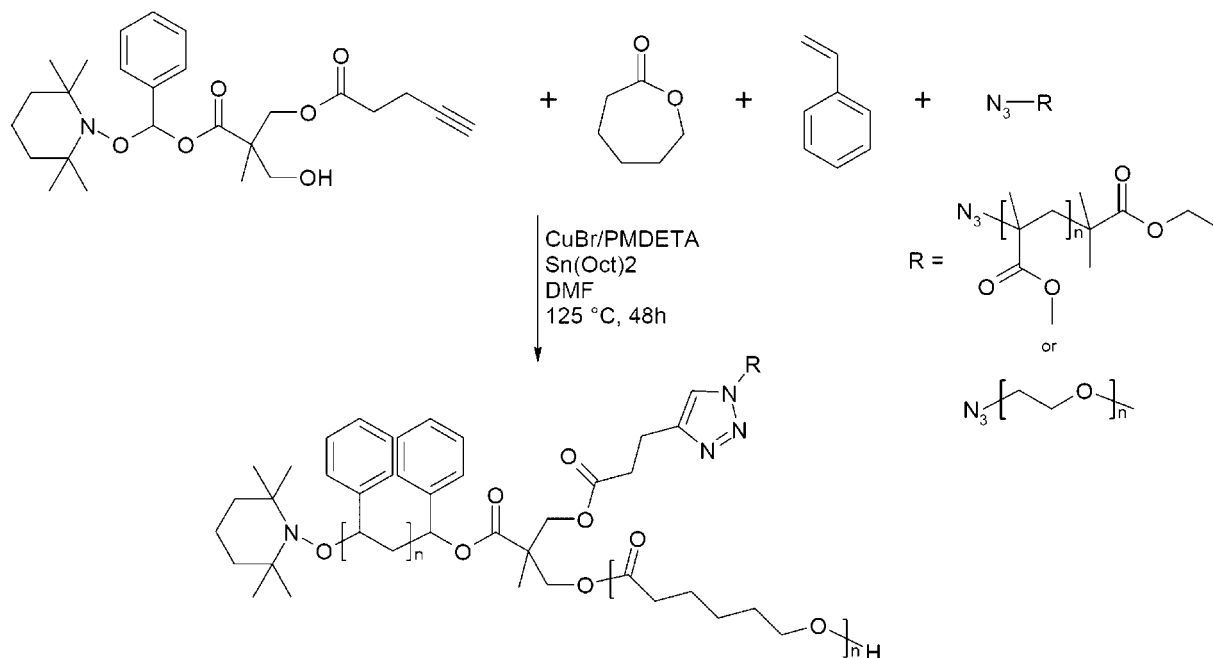
■ *Scheme 8*. Jérôme and coworkers domino strategy for the synthesis of dimethylamino functional PCL.[27]

ization. In this case, bromo-functional silanes were attached to silica nanoparticles and further converted into active azides. This enabled the attachment of a RAFT agent via click chemistry and the simultaneous polymerization of styrene in an orthogonal tandem fashion. The authors tested two different catalytic copper systems; copper sulfate/sodium ascorbate and copper bromide/PMDETA. The first system gave poor polymerization control, which was attributed to a possible radical scavenging effect of the formed ascorbic acid, however, the second system gave the desired control over the polymerization. The grafted material was characterized by TEM, TGA, FT-IR, and elemental analysis. NMR and GPC analysis of the sacrificial polystyrene in solution showed a defined polymer with a PDI 1.09. After grafting, the authors were able to obtain transparent suspensions of the particles in organic solvents indicating good dispersions. The authors also compared the tandem approach with traditional "grafting from" and "grafting to" techniques using the same system. The tandem approach was found to give a higher grafting density than "grafting to" but lower than "grafting from". Still, the orthogonal approach could be considered attractive due to its accelerated nature, reducing both time and the amount of solvents used.

The simplification of synthetic strategies for the preparation of complex polymer structures was further demonstrated by Tunca and coworkers[30] in which nitroxide mediated polymerization (NMP),[31] ring-opening polymerization (ROP), and click chemistry were combined in both a one-pot orthogonal tandem strategy as well as a two-step, multi-catalytic strategy (Figure 2E, Scheme 10). Their focus was to prepare a complex macromolecular structure from a trifunctional initiator that was designed with three active sites, each of which can undergo selective chemical transformations with high fidelity. As can be seen in Scheme 10, the hydroxyl group was utilized to initiate ROP of ε-CL monomer, the nitroxide group was the initiating species for styrene to afford PS, and PEG or PMMA segments were coupled to primary alkyne via the CuAAC reactions. Three armed mikto-star terpolymers with molecular weights ranging from about 13 000 to 16 000 g·mol^{-1} and PDIs around 1.2 were afforded. The authors also concluded that both TR and NTR strategies gave satisfactory results even though somewhat better control was obtained for systems using the two-step technique. The authors noted that radical combinations through star-to-star coupling appeared at high conversions and that low initiator concentration gave a poor click
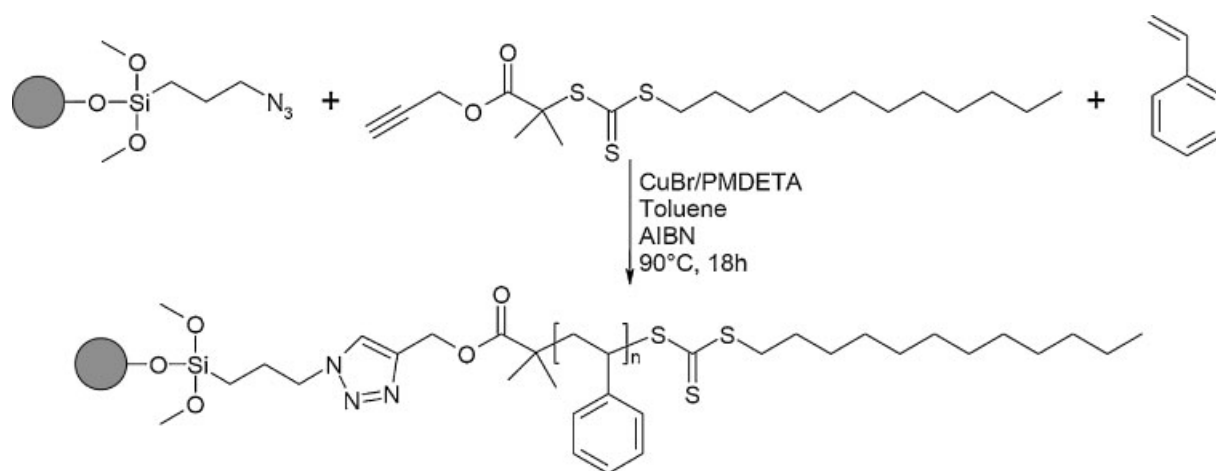
■ *Scheme 9*. Orthogonal tandem strategy using RAFT and the CuAAC reaction as reported by Ranjan and Brittain.[28]

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■ *Scheme 10*. The orthogonal tandem approach for the synthesis of miktoarm star terpolymers as presented by Tunca and coworkers.[30]

reaction efficiency. Nevertheless, it is obvious that the accelerated synthetic protocol provided an elevated scientific value in which three traditional polymers could be covalently bonded in a selective fashion without any purification requirements between every step, a significant increase in efficiency.

One of the most extensive work on NTR strategies was reported by Hawker and coworkers.[32] A comprehensive study demonstrated the powerful combination of esterification, amidation, and click chemistry in a one-pot fashion utilizing two different strategies on a wide variety of polymers, both hydrophilic as well as hydrophobic. In the first strategy, dual functional polymers such as the acetylene styrene and HEMA derivatives were synthesized and their post-functionalization was investigated in a simultaneous and orthogonal tandem fashion (Figure 2F, Scheme 11A). The pendant primary acetylenes and 4-(azidomethyl) benzoate underwent a CuAAC reaction simultaneously to the esterification reaction between the anhydride of acetonide-protected 2,2-dimethylolpropionic acid (bis-MPA) and the pendant hydroxyl group at the polymer backbone. The conversion of both the acetylenes to triazoles and the hydroxyl groups to esters was monitored by ^{1}H-NMR and found to reach completion within 12 h at 50 °C. Another example of a simultaneous one-pot strategy on dual functional polymers was reported (Figure 2F, Scheme 11B). In this case, a water-soluble random terpolymer with pendant alkyne and hydroxyl functionalities was reacted with 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate and succinimidyloxy 4-methoxybenzoate. The conver-

sion was followed with ^{1}H-NMR and the reaction was also found to reach completion within 12 h at 50 °C.

In the second, and equally efficient, approach Hawker and coworkers presented a cascade strategy (Figure 2G, Scheme 12, and Table 1). This accelerated one-pot strategy should however, be categorized as an orthogonal tandem reaction since all the reactions proposed can occur simultaneously and independently of one another. Compared with the first strategy, where dual functionality is located as pendant groups on the polymer backbone, the cascade strategy utilizes small molecules with dual functionality as molecular linkers. These linkers can undergo both a click reaction as well as orthogonal reactions such as esterification or amidation. The significant versatility and potential of this strategy is elucidated briefly in Scheme 12 and Table 1 where the two combined reactions afford a complex polymer with Dispersed Red 13 dye a as pendant group. A library of complex hydrophilic and hydrophobic polymers was obtained with a range of different pendant groups attached to the polymer backbone.

The versatility of the CuAAC reaction, in tandem with other coupling reactions, was further shown by Yang and Weck [33] who recently reported another example of orthogonal tandem functionalization from dual functional polymers. The authors synthesized random copolymer derivatives of exo-norbornene acid, with pendant bromo and aldehyde/ketone groups, using ring-opening metathesis polymerization (ROMP). The bromo groups were consequently converted into azides and the copolymers functionalized by tandem reactions, combining the CuAAC
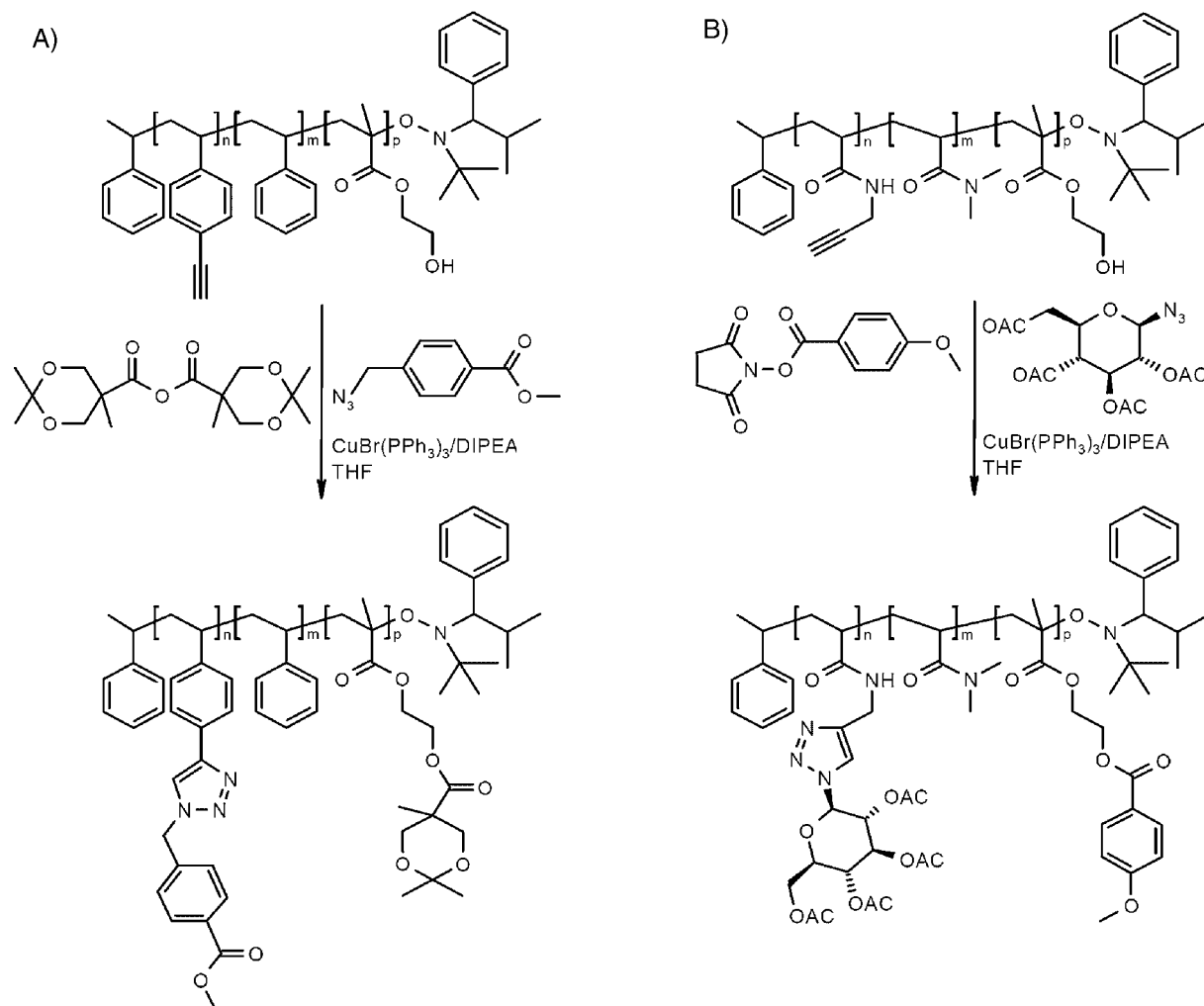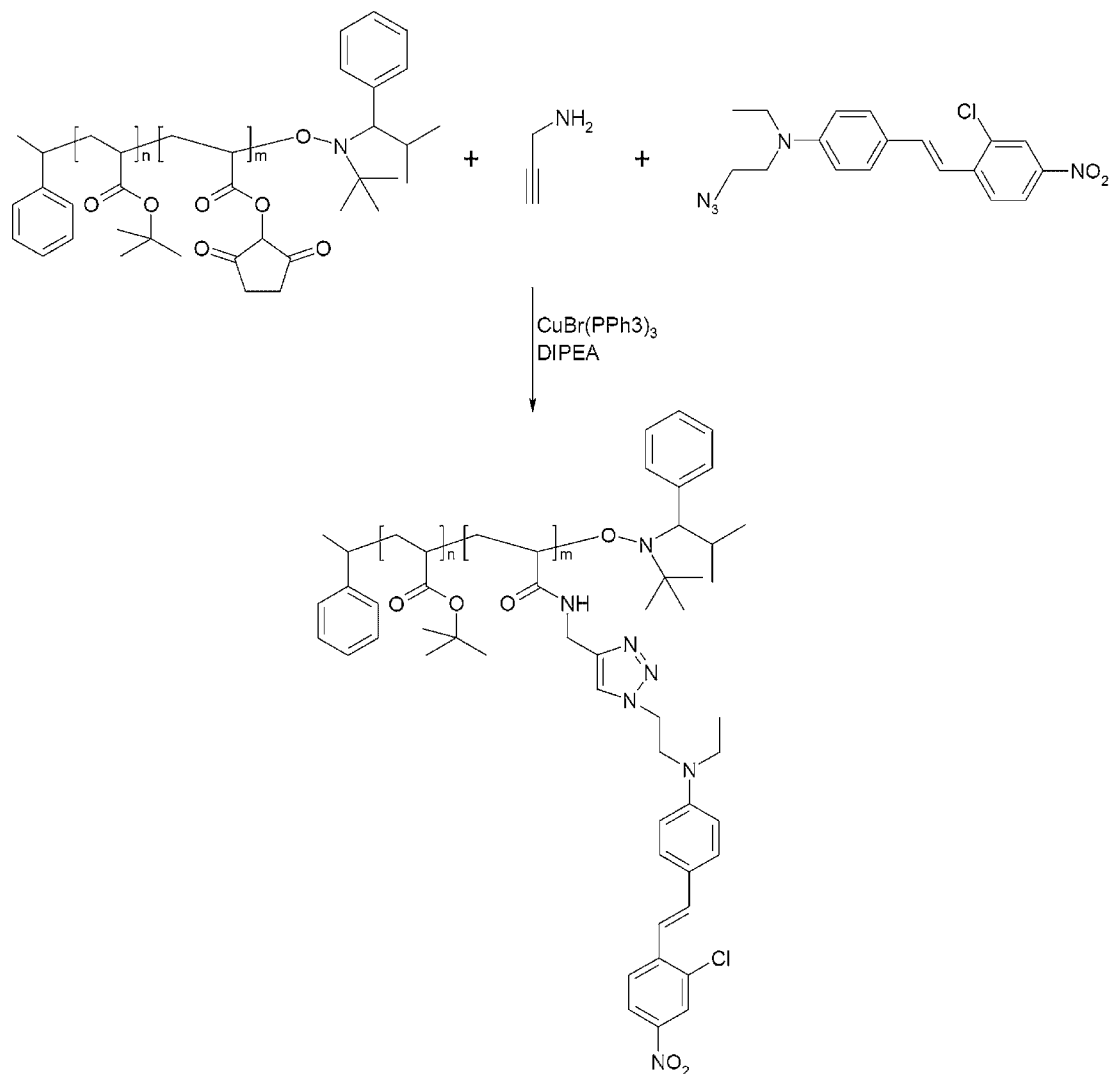
Scheme 11. Orthogonal tandem strategies for functionalization of polymer backbones using using CuAAC, esterification, and amidation reactions as reported by Hawker and coworkers.[32]

reaction with either aldehyde–hydrazine or ketone-hydrazine coupling. Initially, the authors performed accelerated functionalizations of the dual functional (azide/aldehyde) polynorbornene backbone with simple phenylacetylene and phenylhydrazine in a tandem fashion. A successful system that allowed complete functionalizations was reactions conducted in THF at 65 °C using CuSO$_4 \cdot$5H$_2$O/NaAsc as a Cu(I) source. The functionalization was found to reach completion within 5 h and was monitored by ^{1}H-NMR. In turn, the functionalization and subsequent characterization of the dual functional (azide/ketone) polynorbornene backbone was more successful. The functionalization protocols were performed in DMF or DMSO (Figure 2G, Scheme 13) using the CuAAC reaction in combination with ketone/hydrazide coupling reactions. An excellent example of the orthogonality of this process was the synthesis of complex and biologically active polymers with nucleoside and biotin attachments after complete conversion of both the azide and the ketone

groups which were confirmed by ^{1}H-NMR, ^{13}C-NMR, and IR.

The first example of a one-pot strategy combining CuAAC and atom transfer radical polymerization (ATRP)[34] was published by Haddleton and coworkers[35] (Figure 2H, Scheme 14). In the reported work, an accelerated tandem reaction approach was devised to investigate the construction of linear polymers with controlled end-functionalities. This strategy, which is in fact an assisted tandem strategy, was approached by first synthesizing a dual purpose molecule that will allow both controlled ATRP polymerization as well as efficient click coupling reactions. The construction of a difunctional linker, with both an initiating tertiary bromo specie for ATRP polymerization and an azido specie for click reaction was successful, starting from bromo-propanol ($n = 1$) or tosyl-hexanol ($n = 4$). These novel compounds were used as initiators for Cu catalyzed ATRP of methyl methacrylate and were allowed to proceed to 90% conversion before the

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■ *Scheme 12.* Orthogonal tandem strategy for functionalization using a linker as reported by Hawker and coworkers.[32]

addition of the alkyne. Initially, propargyl alcohol was used by the authors to evaluate the efficiency of the one-pot strategy in a range of solvents including toluene, anisole as well as polyethylene glycol ($\overline{M}_w = 400$). In all cases, the efficiency of the click reaction was excellent, independent of the type of solvent, and without the need of any additional copper. The authors also illustrated the efficiency of this one-pot strategy by introducing more complex end-functionalities e.g., diaza and coumarin dyes. Furthermore, their finding has shown the presence of a competing side reaction in which the azide moiety and the propagating site undergoes intramolecular cyclization.
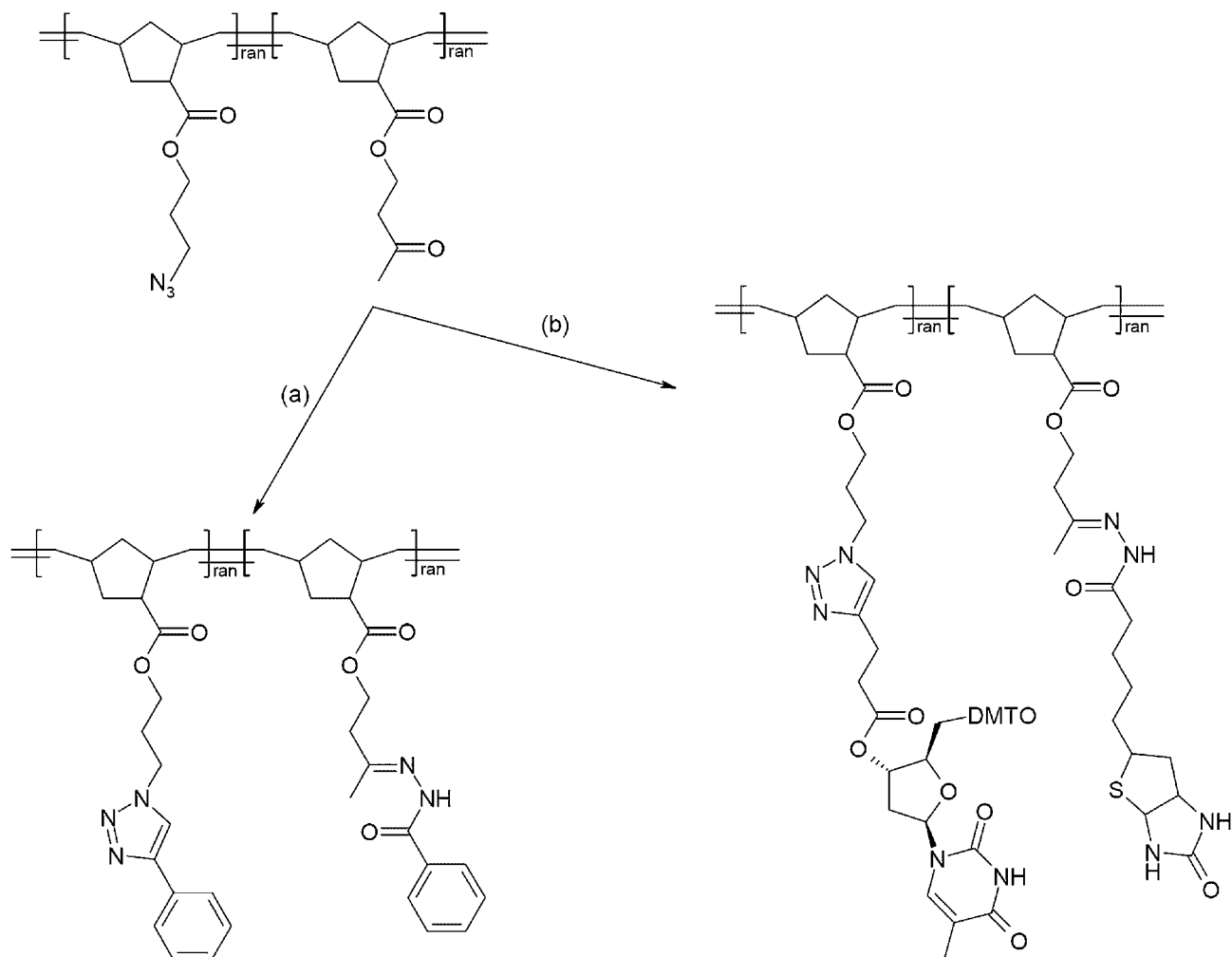
Dubois and coworkers[36] reported a similar example of an assisted tandem strategy, in which a dual purpose molecule is initially synthesized. This molecule allows both controlled ATRP polymerization as well as efficient click coupling reactions. In this case, alkyne terminal poly(caprolactone) (PCL) chains were reacted with 2-(2-

azidoethoxy)ethyl bromoisobutyrate, that also serves as an ATRP initiator, for polymerization of N,N-dimethylamino-2-ethyl methacrylate (DMAEMA) to form an amphiphilic and potentially thermo- and pH-responsive block-copolymer (Figure 2I, Scheme 15). The initial temperature of 25 °C allowed the click reaction to proceed and after 24 h the temperature was increased to 60 °C to promote polymerization of DMAEMA. The conversion of azides and alkynes into triazoles was virtually quantitative with monomer conversion of ca. 95%, yielding a block-copolymer with a molecular weight of 12 700 g · mol^{-1} and PDI of 1.3. The amphiphilic character of the block-copolymers was further demonstrated by surface tension measurements which allowed the critical micellization concentration to be determined.

Another recent example of an auto tandem reaction was published by Turro and coworkers[37] combining ATRP and CuAAC for the construction of a four-armed polymer star.

■ *Table 1.* Different functionalizations performed using an orthogonal tandem strategy by Hawker and coworkers.[32]

Comonomer	Functional monomer X	Linker group Y	Terminal group Z

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Scheme 13. Orthogonal tandem strategy for functionalization of dual functional polynoroborene acid derivatives, where as reported by Yang and Weck. (a) $CuSO_4 \cdot 5H_2O$/NaAsc, DMF, 25 °C, 2 h; (b) $CuSO_4 \cdot 5H_2O$/NaAsc, DMSO, 25 °C, 24 h.[33]
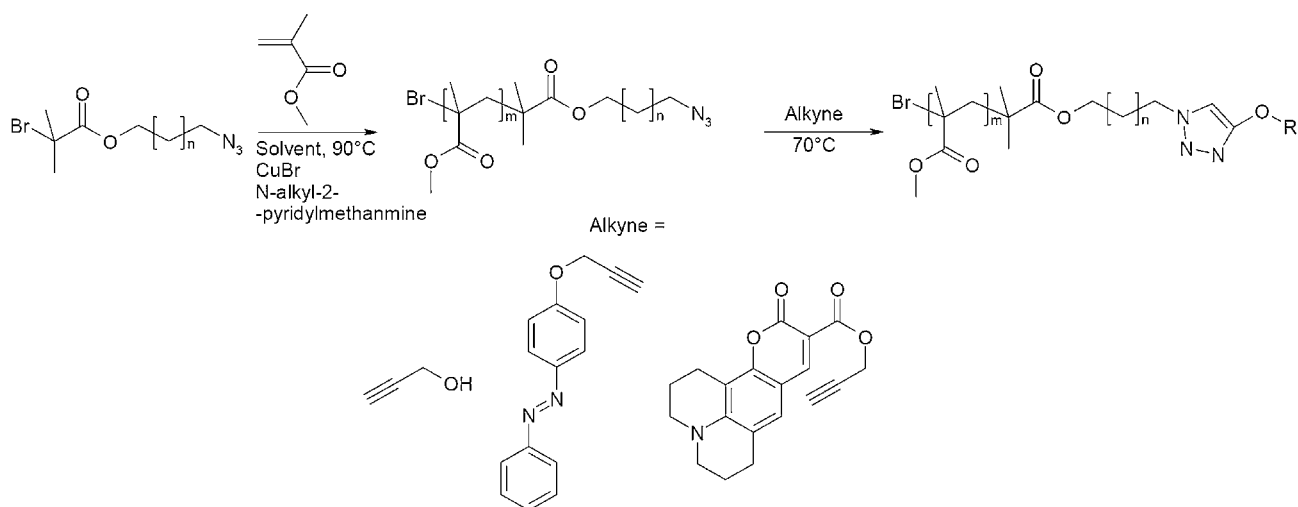
Scheme 14. Haddleton and coworkers assisted tandem strategy for the synthesis end-functionalized PMMA, where $n = 1$ or 4.[35]
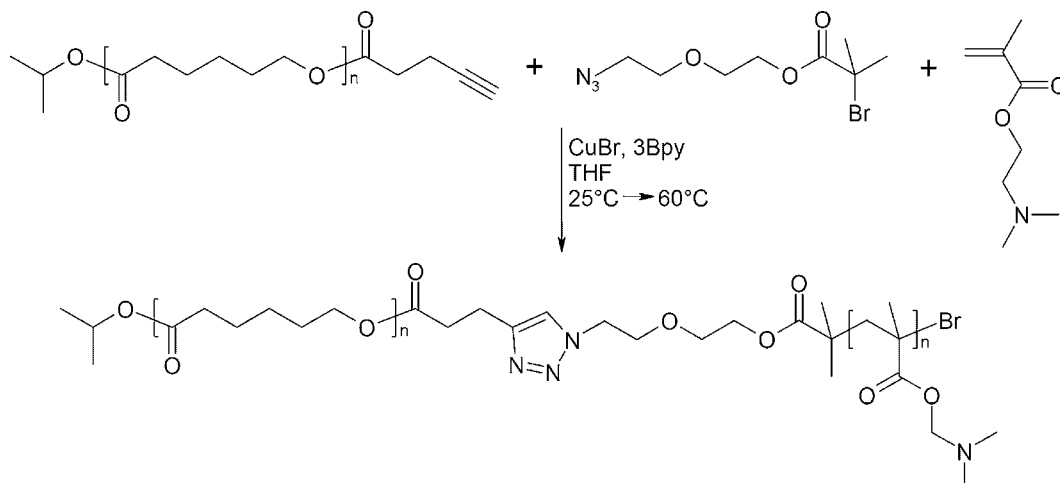
■ *Scheme 15.* The assisted-tandem strategy for the synthesis of PCL-DMAEMA block-copolymers presented by Dubois and coworkers.[36]
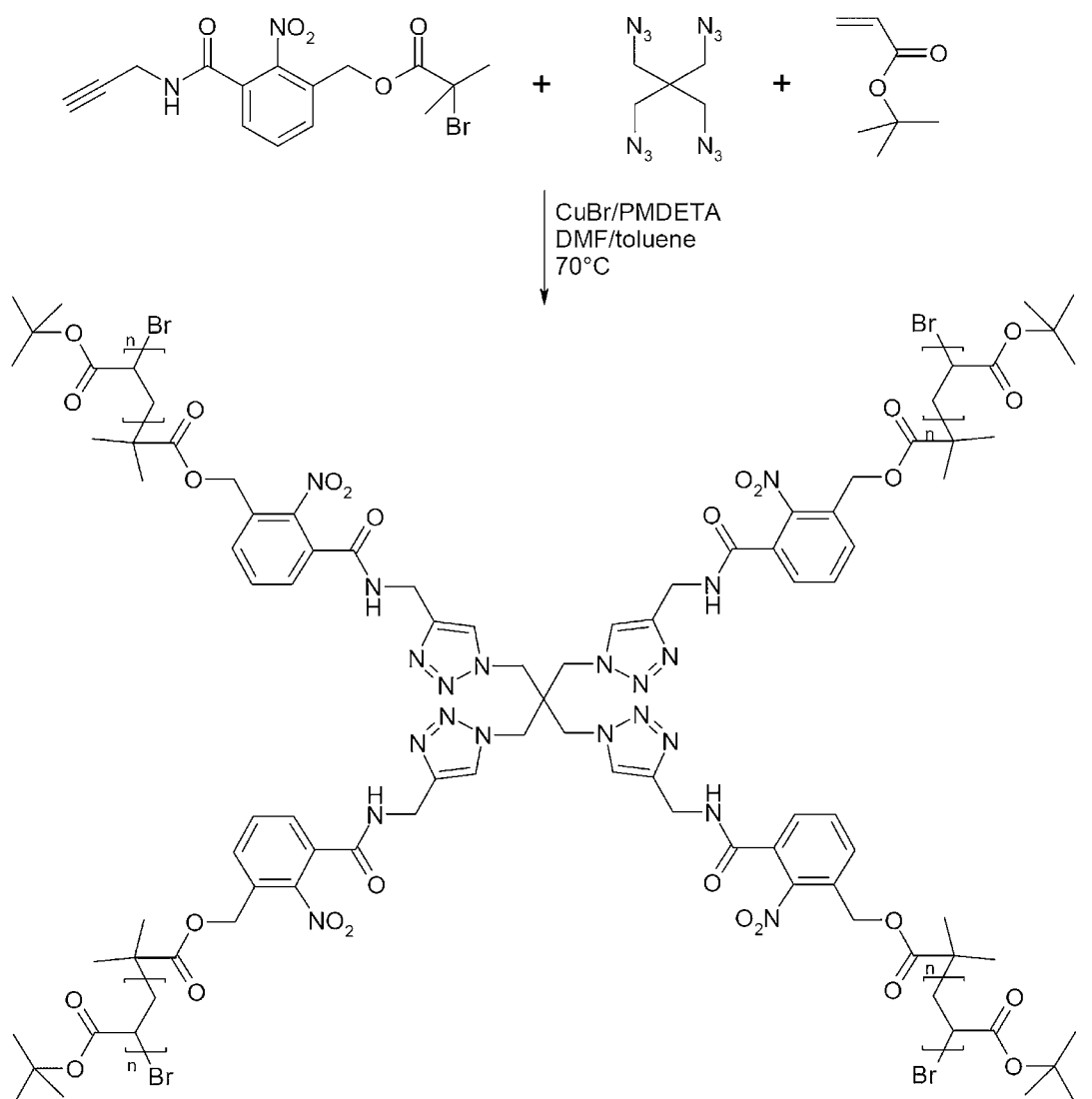

■ *Scheme 16.* Four armed star synthesized using an auto tandem strategy as reported by Turro and coworkers.[37]

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In developing a highly efficient and convergent synthetic approach, the authors allowed a potentially explosive compound, pentaerthrityl tetraazide, a low molecular ATRP initiator, and *tert*-butyl acrylate to react simultaneously (Figure 2J, Scheme 16). The click reaction and the ATRP polymerization were found to react with high fidelity and in tandem to elegantly form a four armed star. The formed polymer had a molecular weight of $37\,200\ \text{g} \cdot \text{mol}^{-1}$ and PDI as low as 1.1. The obtained tetrafunctional bromo polymer could subsequently be modified into azides which enabled further crosslinking of the system. These polymers were also shown to be photodegradable and might therefore be of interest in lithography or as a degradable plastic.

In all the cases above, the one-pot reaction strategies presented have taken advantage of the CuAAC efficiency in combination with traditional polymerization/chemical reactions. However, Tunca and coworkers[38] recently constructed a set of amphiphilic triblock-copolymers via a one-pot approach taking advantage of not one but two click reactions i.e., the CuAAC as well as the Diels-Alder reaction (Figure 2K, Scheme 17). This was enabled by the synthesis of a difunctional and dual purpose polystyrene block with an azide functionality at one end and an anthracene functionality at the other. These functionalities were subsequently reacted in an orthogonal tandem reaction with an alkyne functional PEG or PCL and a maleimide functional PMMA. This results in the triblock-copolymers, PMMA-PS-PEG and PMMA-PS-PCL with yields of 85 and 90%, respectively and molecular weights of $8\,200\ \text{g} \cdot \text{mol}^{-1}$ (PDI = 1.10), and $10\,450\ \text{g} \cdot \text{mol}^{-1}$ (PDI = 1.11), respectively.

Summary and Outlook

The goal of this review has been to highlight the critical importance of robust, efficient, and orthogonal chemical reactions in the synthesis of functionalized materials. The rising importance of the click chemistry concept with its flagship CuAAC reaction has illuminated the power and potential of efficient synthetic approaches in various fields of research. The unique opportunities afforded by the click concept have been fully embraced by materials scientists in particular and this can be traced to the inherent difficulty in synthesizing multifunctional materials with unique properties. The exceptional selectivity of the click reaction, expressing both environmental and reactive group independence, has given rise to a new trend for scientists to investigate one-pot multi-step systems for the development of complex macromolecules in accelerated fashion. As described above, several accelerated protocols that elegantly utilize various polymerization techniques and/or chemical reactions in combination with the click reaction have been developed and applied to the preparation of advanced material, including dendritic, hydrophilic, hydrophobic, amphiphilic, block-co-polymers, and Si particles-polymer hybrids. The outlook for accelerated synthetic protocols based on the expanding range of click reaction is undeniably promising and its impact on materials science will be felt in many areas. While the majority of reports currently deal with combining chemical reactions to obtain well-defined multi-functional polymers, in the future, chemists need to address new challenges, such as increasing the range of available click reactions that can be achieved without the need of metal
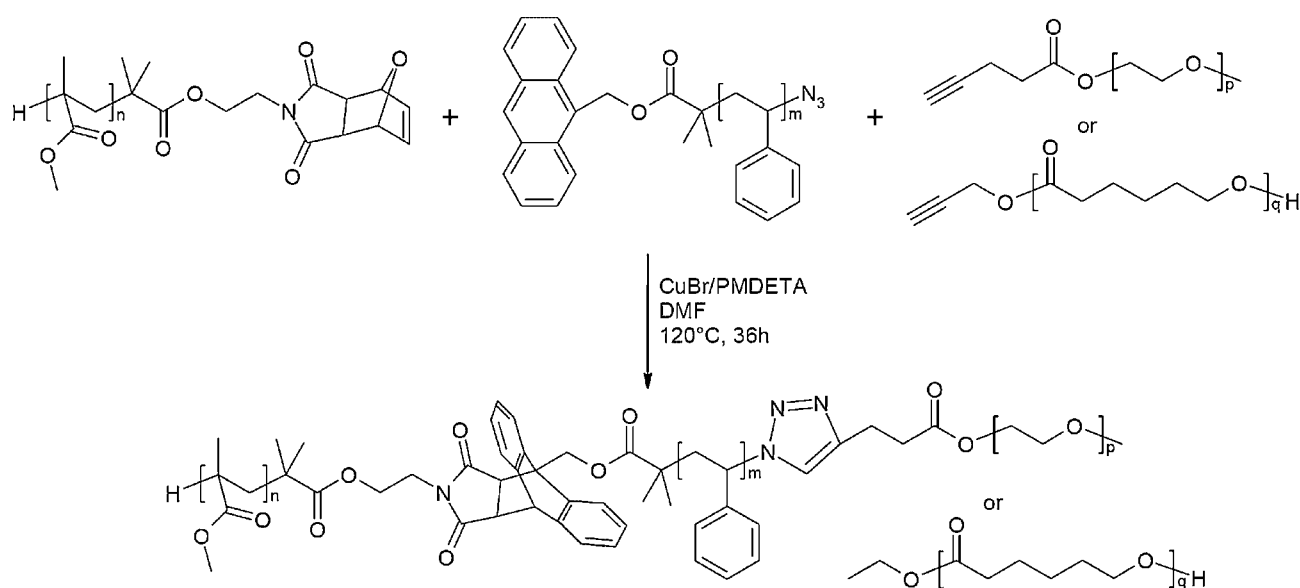
Scheme 17. Orthogonal tandem strategy combining the two-click reactions CuAAC and Diels-Alder for the synthesis of triblock-copolymers.

catalysts,[39] developing libraries of compatible reactions,[40] and the application of these systems for industrially relevant materials. In turn, the focus on the economical as well as environmental benefits of synthetic design will be a major educational opportunity for the next generation of scientists.

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