Nitroxide radical coupling reaction: a powerful tool in polymer and material synthesis

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The aim of this review is to summarize and highlight the rapidly expanding area of nitroxide radical coupling reactions, including atom transfer nitroxide radical and single electron transfer nitroxide radical coupling reactions, in polymer and material synthesis. Initial discussion is focused on the influencing factors, e.g., temperature, solvent, catalyst and the structure of reactant, on the reaction rate and efficiency. In addition, this review attempts to demonstrate the broad applications of nitroxide radical coupling reactions on the terminal functionalization of polymers, the synthesis of polymers with complex and well-defined architecture, and the preparation of organic–inorganic composites. Finally, the current challenges and future directions of nitroxide radical coupling reactions are also discussed.

1 Introduction

There are many interesting and attractive phenomena in nature. For example, highly complex biological systems with various functionalities are often constructed via only a few reactions, but with a high efficiency, selectivity and simplicity, among certain building units.† Inspired by this fact, researchers have been putting considerable effort into exploiting robust and efficient approaches to prepare soft materials with desired functionalities. In 2001, Sharpless et al. firstly highlighted a Cu(i)-mediated Huisgen reaction between an alkyne and an azide, and proposed this reaction as a ‘click’ reaction due to its amazing features, including high yield (often above 95%), high tolerance of functional groups and insensitivity to solvents.2 Besides these amazing features, Barner-Kowollik et al. mentioned that a true ‘click’ reaction in polymer synthesis should possess some other characteristics, such as equimolarity for building blocks of polymers, large scale of purification, reasonable reaction time and no tedious fine-tuning of reaction conditions.3

The Cu(i)-mediated Huisgen reaction has been recognized as an efficient strategy, not only in traditional organic chemistry, but also in polymer and material chemistry.4–6 This ‘click’ reaction has been utilized to construct a wide range of materials, such as functional polymers, organic–inorganic composites and self-assembled materials.4,5

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reaction showed broad applications in the synthesis of complex and functional polymers, surface and interface modification and the functionalization of biological systems. However, the azide compound used in the Cu(0) catalyzed azide–alkyne cycloaddition (CuAAC) reaction is inconvenient to be used and stored, due to its poor photo, thermal and shock stability. It is highly desirable to develop other types of ‘click’ reactions and evaluate their potential applications. Recently, thiol–ene and thiol–alkene reactions, (hetero)Diels–Alder reaction, nitroxide radical coupling (NRC) reactions, including the atom transfer nitroxide radical coupling (ATNRC) reaction and the single electron transfer nitroxide radical coupling (SET-NRC) reaction, the nitrene mediated radical coupling reaction, and the cobalt mediated radical coupling reaction (CMRC), which display the essential characteristics of a ‘click’ reaction, have attracted increasing attention.

Enlightened by the atom transfer radical addition (ATRA) reaction, in 1998 Matyjaszewski et al. synthesized a series of alkoxamines with a high efficiency (up to 95%) and selectivity through a radical–radical coupling reaction, where radicals generated via an ATRA process from bromine containing compounds were trapped by nitroxide radicals. In 2008, this reaction was developed to synthesize polymers. In this reaction, macroradicals, generated from polymers with a halogen terminal group in the presence of CuBr/N,N,N’,N’-pentamethyldiethylenetriamine (PMDETA) as an activating agent, was immediately captured by a polymer with a stable nitroxide radical terminal group. This new coupling reaction was termed an atom transfer nitroxide radical coupling (ATNRC) reaction, because the reaction of activating halogen terminated polymers by Cu(0)/ligand complexes to generate macroradicals is believed to occur via an atom transfer radical addition mechanism, involving a ‘homolytic’ inner sphere electron transfer (ISET) process (Fig. 1).

The rate of the coupling reaction between a carbon-centered radical and a stable nitroxide radical was close to diffusion controlled \( (k_c \sim 10^8 \text{ L mol}^{-1} \text{ s}^{-1}) \), and the kinetic simulation results showed that the total reaction rate was mainly limited by the formation rate of the carbon-centered radical. Enlightened by the single electron transfer-living radical polymerization (SET-LRP), postulated by Percec et al., the ATNRC reaction was optimized by using a suitable Cu(0)-based catalyst, which could significantly accelerate the rate of radical formation. Thus, the coupling reaction could be finished within several minutes, with a high yield and selectivity, and little or no byproduct, even in the presence of functional groups. This developed coupling reaction was denoted as a single electron transfer nitroxide radical coupling (SET-NRC) reaction. As shown in Fig. 1, the reaction of activating a halogen terminated polymer by a Cu(0)/ligand to generate radicals is assumed to occur via both outer sphere electron transfer (OSET) and ISET mechanisms depending on the interactions between the donor, Cu(0), and the acceptor.

In this review, the term, ‘nitroxide radical coupling’ (NRC), will be used to define the coupling reaction between a nitroxide radical and a macroradical or radical regardless of the generation mechanism (activation by Cu(0) or Cu(0)). A NRC reaction possesses several attractive features. Firstly, any polymer prepared by ATRP or SET-LRP could be directly used as a building unit without further modification. Since the ATRP and SET-LRP reactions have shown great ability in the preparation of polymers with different functional groups and topologies, providing a new strategy to construct polymers with complex and well-defined architectures via a NRC reaction. Secondly, a NRC reaction is highly tolerant with a diverse range of functional groups, e.g. glycidyl ether, styryl, acrylate, alkene, alkyne, active esters and fluorophores. Thirdly, the reaction rate of a NRC reaction is highly dependent on the reaction mechanism, and could be modulated in a time range from several minutes to several days by varying the reaction temperature, the solvent or the catalyst. Finally, a NRC reaction may be reversible at elevated temperatures (≤100 °C) according to the properties of the utilized nitroxide and radical species. The reversibility can be used for further functionalization of the polymer with a nitroxide chain end through competitively exchanging with other functional nitroxides.

This review aims to summarize and highlight the recent advances of NRC reactions in polymer and material synthesis. Some other interpolymer radical coupling reactions, such as
ATRC, silane radical atom abstraction (SRAA), cobalt mediated radical coupling reaction, and nitrene mediated radical coupling reaction, are not well covered in this review. For further insight into these reactions, readers are directed towards some excellent reviews on these subjects.

The factors influencing the rate and efficiency of a NRC reaction, as well as the applications of the NRC reaction in highly efficient functionalization of the terminal groups of polymers, the synthesis of polymers with complex and well-defined architecture and preparation of inorganic–organic composites will be discussed in detail. A particular emphasis will be given to the reaction’s applications in the design and preparation of complex and highly functional macromolecules with the combination of living polymerizations, including living ionic polymerization, atom transfer radical polymerization (ATRP), single electron transfer–living radical polymerization (SET-LRP), reversible addition–fragmentation chain transfer (RAFT) polymerization, ring opening polymerization (ROP), and ring opening metathesis polymerization (ROMP).

2 Influencing factors

A NRC reaction relies on the generation of a carbon-centered radical by a mechanism of atom transfer or single electron transfer, because then the catalyst, Cu(i), could be transferred into highly active Cu(0), this process is highly dependent on the solvent, catalyst and ligand. Monteiro et al. have reported a kinetic study on a NRC reaction between linear polystyrene (PS) with a bromine terminal group prepared by ATRP and trinitrrobenzene-1,3,5-tricarboxylate, using CuBr/PMDETA or CuBr/tris(2-(dimethylamino)ethyl)-amine (Me6TREN) as the catalyst, in benzene-1,3,5-tricarboxylate, using CuBr/PMDETA or CuBr/Me6TREN as the catalyst, where the activation proceeded via an atom transfer radical mechanism. In the case of using Me6TREN as a ligand instead of PMDETA, after reaction at 70 °C for 10 min, the yields were 65%, 98% and 98% in solvents of toluene, toluene–DMSO (50 : 50, v/v), and toluene–DMSO (20 : 80, v/v), respectively. In addition, the reaction rate decreased very slightly at 25 °C and could reach a high yield (>95%) after 10 min for all the cases using DMSO as a cosolvent. These phenomena suggested that the reaction was consistent with a single electron transfer (SET) mechanism. The reaction rate increased with the increase of the volume ratio of DMSO, since both DMSO and Me6TREN could facilitate the disproportionation of Cu(i) to generate highly active Cu(0) for the SET process. Furthermore, it was remarkable that the simulation results showed that the radical–radical termination between the macroradicals was extremely low, indicating that the probability of atom transfer radical coupling (ATRC) or single transfer radical coupling (SETRC) could be excluded during the NRC process.

Recently, Monteiro et al. reported the synthesis of branched polymers through modulating the copper-catalytic activity by choosing different solvents and ligands (Fig. 3). This was based on the fact that Cu(i) possesses the ability to catalyze both CuAAC and NRC reactions, and the reaction rates with different solvents and ligands were very different. They exemplified this methodology through the one-pot preparation of G2 by coupling together 2-propynyloxy)silane (1), 2-(3,5-bis(azido-methyl)-phenoxy)ethyl-2-bromopropanoate (2) and tris(4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxy)-benzene-1,3,5-tricarboxylate (3), using CuBr with PMDETA or Me6TREN as the catalyst and reacting at 70 °C for 10 min, the yields were 67%, 82% and 95% in solvents of toluene, toluene–DMSO (50 : 50, v/v) and toluene–DMSO (20 : 80, v/v), respectively. Decreasing the reaction temperature to 50 °C only resulted in a slight decrease of the yields. However, as the temperature was decreased further to 25 °C, the reactions became much slower. These results indicated that both the solvent (composition) and the reaction temperature influenced the reaction rate while using Cu(i)/PMDETA as the catalyst, where the activation proceeded via an atom transfer radical mechanism. In the case of using Me6TREN as a ligand instead of PMDETA, after reaction at 70 °C for 10 min, the yields were 65%, 98% and 98% in solvents of toluene, toluene–DMSO (50 : 50, v/v), and toluene–DMSO (20 : 80, v/v), respectively. In addition, the reaction rate decreased very slightly at 25 °C and could reach a high yield (>95%) after 10 min for all the cases using DMSO as a cosolvent. These phenomena suggested that the reaction was consistent with a single electron transfer (SET) mechanism. The reaction rate increased with the increase of the volume ratio of DMSO, since both DMSO and Me6TREN could facilitate the disproportionation of Cu(i) to generate highly active Cu(0) for the SET process. Furthermore, it was remarkable that the simulation results showed that the radical–radical termination between the macroradicals was extremely low, indicating that the probability of atom transfer radical coupling (ATRC) or single transfer radical coupling (SETRC) could be excluded during the NRC process.

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catalyst and DMSO or toluene as the solvent. While using DMSO as the solvent and CuBr/Me₆TREN as the catalytic system, the disproportionation of Cu(I) to Cu(0) is facile, which could convert 2 to its radical via a SET process. Thus, 5 was predominantly formed through the NRC reaction, and then the final product 6 was formed via a CuAAC reaction between 5 and 1. In the situation of using toluene as the solvent and CuBr/PMDETA as the catalyst, which is favorable for the atom transfer radical mechanism, the CuAAC reaction between 1 and 2 could be conducted to give 4, and then 4 coupled with 3 via a NRC reaction to give 6. Subsequently, the same group synthesized a series of highly branched polymers using PS, poly(tert-butyl acrylate) (PtBA), poly(ethylene oxide) (PEO) and poly(N-isopropylacrylamide) (PNIPAM) as building units via the combination of SETNRC and CuAAC. All these results suggested that the solvent and catalyst were critical to the reaction rate of CuAAC and NRC.

Besides the solvent, temperature and catalyst, the structure of the starting polymer is also an important influencing factor to the coupling efficiency of an NRC reaction. Huang et al. from Fudan University examined the NRC reaction between 2,2,6,6-tetramethylpiperidinyl-1-oxy-containing poly(c-caprolactone) (PCL-TEMPO) and linear polymers (PS, PtBA, and poly(methyl methacrylate) (PMMA) with a bromine terminal group), using CuBr/Cu(0)/PMDETA as the catalytic system (Fig. 4). It was found that the reaction temperature had a slight influence on the coupling efficiency of the NRC reaction between PS-Br and PCL-TEMPO, and a high efficiency (>90%) was observed in the temperature range from 90 °C to 25 °C. For the reaction between PtBA-Br and PCL-TEMPO, a high efficiency (>85%) was also found in the temperature range from 75 °C to 25 °C. However, when the reaction was conducted at 90 °C, the coupling efficiency decreased to 76%. The authors suspected that the higher temperature facilitated the cleavage of the alkoxylamine bond, leading to the decrease of coupling efficiency. For the reaction between PMMA-Br and PCL-TEMPO, the efficiency decreased with the increase of the reaction temperature. In the temperature range from 90 °C to 45 °C, the coupling efficiency was lower than 30%. Only at a lower temperature, such as 25 °C, could a high coupling efficiency (91%) be obtained. The low coupling efficiency for PMMA might mainly result from the side reaction, the α-H transfer of the macroradical, at high temperature. The α-H of the methyl in the PMMA backbone is rather reactive and can be captured by nitroxide radical to form a double bond terminal via the disproportionation of the radical at the end. The higher the temperature was, the easier the β-H of methyl in PMMA backbone was captured.

3 The preparation of terminal functional polymers

A terminal functional polymer, containing one or more functional groups at the chain end, is essential to construct macromonomers, polymers with complex architecture, bioconjugates, functional surfaces and organic–inorganic composites. Although a wide variety of terminal functional polymers could be prepared through ATRP, SET-LRP, RAFT polymerization, nitrooxide-mediated stable free-radical polymerization (NMP) and ROMP strategies, some certain reactive functional groups are incompatible with the polymerization methods mentioned above. For example, a carboxyl group would poison the catalyst for ATRP, and an amino group would aminolyze (reduce) the chain transfer agent for RAFT. Chemical modification of the terminal group of polymers prepared by ATRP, SET-LRP, RAFT, NMP and ROMP is an another efficient and versatile pathway to introduce chemical moieties to the chain end of the polymer. For example, the RAFT end group can be used for hetero-Diels–Alder chemistry or transforming into a thiol group via an aminolysis reaction for the subsequent thiol–ene reaction to introduce functional moieties. The most commonly used approach for terminal functionalization of the polymers prepared by ATRP or SET-LRP is the replacement of the terminal halogen group with an azide group, which makes the subsequent introduction of functional groups by CuAAC reaction facile. However, the azide group is difficult to preserve, due to its poor photo and thermal stability. For polymers prepared by ATRP and SET-LRP, the NRC reaction provides another strategy for the preparation of terminal functionalized polymers. In 2011, Monteiro et al. reported a rapid and highly efficient strategy to functionalize polymers with a bromide terminal group by NRC (SETNRC), as
shown in Fig. 5. They first prepared PS-Br and PtBA-Br by conventional ATRP, and then a variety of functionalities were introduced to the terminal ends of the polymers through SETNRC reaction between TEMPO-based functional compounds and PS-Br or PtBA-Br, which was conducted in DMSO–toluene (1/1, v/v) using CuBr/Me₆TREN as a catalyst at 25 °C for 10 min with a high degree of functionalization above 88.0%. Furthermore, there was only negligible radical polymerization of the macromonomers despite the experimental condition being suitable for a radical polymerization. These results indicated that the NRC reaction was highly selective and nitroxide radicals had a remarkable trapping activity for radicals.

In another work, Monteiro et al. also reported the functionalization of PS terminal groups with TEMPO derivatives containing alkenes, alcohols, carboxylic acids, ketones and amines under the same reaction conditions. Furthermore, they demonstrated the reversibility of alkoxyamine to regenerate nitroxide radicals and carbon-centered radicals at elevated temperature. Utilizing this interesting feature the terminal group of the polymer could be exchanged with nitroxides containing a different functionality. For example, the functional group at the terminal end of PS alkoxyamine was transformed into an alkyne at 120 °C for 5 h, with a high efficiency in 30-fold excess of TEMPO-alkyne (Fig. 6). A huge excess of nitroxides was used to kinetically eliminate side reactions from decoupling and consequent bimolecular termination.

Barner-Kowollik and Junkers et al. reported an efficient method to insert a specific functionality into the middle of a polymer on the basis of NRC (Fig. 7). The ATRP prepared PS-Br was reacted at 60 °C for 3 h using Cu(0)/PMDETA as the catalyst to generate PS macroradicals. Then, N-tert-butyl-α-phenyl-nitrone (PBN) was added and coupled with a PS macroradical to form a PS macro-nitroxide, which would be terminated by another PS macroradical. Taking advantage of the reversibility of the alkoxyamines at elevated temperature, the coupled products could be decoupled in the presence of a radical scavenger (tributyltin hydride) at 100 °C. The GPC trace of the decoupled product overlapped with that of the original PS, indicating that the coupling reaction proceeded via a nitroxide radical coupling mechanism, rather than an atom transfer radical coupling. These results suggested that PBN had a significantly high reactivity with macroradicals to form macro-nitroxides, which could immediately be captured by other macroradicals. Given the tolerance of this coupling reaction towards a large number of functionalities, this approach provided an efficient and attractive pathway to introduce functional groups into the middle of the polymer chain, which cannot be easily obtained by other current existing techniques.

Following this work, in 2011, Barner-Kowollik and Junkers et al. expanded the application of the nitrobase nitroxide coupling reaction to embed multiple site-specific functionalities into polymer chains by combination of NRC and step growth polymerization (Fig. 8). Bifunctional poly(isobornyl acrylate)s (PiBoA) containing α,ω-bromo terminals were prepared by ATRP using dimethyl 2,6-dibromohexanediolate as the initiator. Then, PiBoA and different amounts of PBN (0, 1, 2, 5 equivalent based on the amount of Br) were dissolved in toluene for step growth polymerization at 60 °C for 4 h using Cu(0)/PMDETA as the catalyst. 1H NMR spectra of the resultant polymers showed that all the microradicals were entirely released from the dormant state. In addition, the GPC results showed that the molecular weight of the resultant polymers
increased as the amount of PBN increased, which violated Carothers equation for step growth polymerization, suggesting that the increase of PBN amount was favorable to the reactions between macroradicals, and minimized the side reactions, such as the disproportionation and electron transfer reaction. GPC trace of the decoupled product was almost overlapped with that of the starting PiBoA, regardless of the amounts of PBN, which further proved that all the coupled polymers were efficiently functionalized on the polymer backbone. Based on this result, alkylamine-functionalized PiBoA was prepared by the reaction of bifunctional PiBoA containing α,ω-bromo terminals with 5 equivalents of 2-((trimethylsilyl)prop-2-ynyloxy)-N-tert-butyl nitrore. Then, the alkyl-functionalized PiBoA was used for a UV-induced thiol-yne reaction with an excess of 3-mercaptopropanionic acid. $^1$H NMR spectrum confirmed the formation of the thiol-functionalized product.

It is vital to maintain adequate halogen terminal groups in the starting polymers for the subsequent functionalization via NRC. A high level of halogen terminals could be obtained by terminating the reaction at a low conversion and adding a certain amount of Cu(II) during the ATRP process, which could prevent the accumulation of dead polymers without halogen. SET-LRP might be an excellent choice, Percec et al. have reported that an exceptionally high level of halogen terminals could be reserved by Cu(0)-mediated SET-LRP even at a high conversion (>90%).$^{26,27}$ Inspired by this result, Whittaker et al. synthesized a high-order multi-block copolymer via SET-LRP by sequentially adding different monomers after the last reaction reached a full conversion.$^{29}$ One important advantage of this method is that the initially added Cu(II) could significantly exclude the side reactions, such as bimolecular termination.

4 The preparation of polymers with well-defined architecture

Functional soft materials have showed great increasing potential in the fields of electronics, sensors, nanomedicine, catalysis, and so on. The chain architecture of a polymer is one of the most important factors to influence its properties. With the tremendous development of the polymerization techniques, such as ATRP, SET-LRP, RAFT, NMP and ROMP, a wide range of novel polymers with different chain architectures, e.g. linear, gradient, star, graft, cyclic, hyperbranched and dendritic, have been prepared.$^{26-30,40-46}$ However, it is still highly required to find an easier and more efficient way to prepare polymers with well-defined architecture. Due to the high specificity, high yield and reversibility of an NRC reaction, it has emerged as a powerful tool for construction of polymers with well-defined architecture.

4.1 The preparation of linear polymers

Block copolymers, composed of two or more homopolymers linked by covalent or non-covalent bonds, have attracted considerable attention, since they are important building units for functional soft materials. Controllable polymerization techniques have been widely employed to synthesize block copolymers through macrorinitiator strategy or the sequential addition of monomers approach. Some nice reviews on anionic polymerization, ATRP, SET-LRP, RAFT, NMP and ROMP for the preparation of block copolymers have been documented.$^{27,30,40-45}$ However, the incompatibility of some certain functional groups with the polymerization strategies mentioned above is often a synthetic challenge. Connecting different functional homopolymers through one or more robust, efficient and orthogonal reactions is becoming an attractive alternative.

In 2008, Huang et al. from Fudan University first developed an ATNR reaction to synthesize an ABC type of triblock copolymers, poly(tert-butyl acrylate)-b-polystyrene-b-poly(ethylene oxide) [P(nBA-PEO) and poly(tert-butyl acrylate)-b-polystyrene-b-poly(ε-caprolactone)] (PiBa-PS-PCL).$^{31}$ The CuAAC and NRC reactions between alkyne-PeBr, azide-PeBA and PEO-TEMPO or PCL-TEMPO were performed as one-pot reactions in $N,N$-dimethylformamide at 90 °C using CuBr/PMDETA as the catalytic system. $^1$H NMR spectra of the products showed that the characteristic peak of $CH\equiv C-CH\equiv C$ disappeared, and a new signal relating to triazole appeared, which indicated the occurrence of the CuAAC reaction. Similarly, the disappearance of the characteristic peak of $-CH(Ph)Br$ also proved the occurrence of the NRC reaction. The coupling efficiencies of NRC and CuAAC obtained by calculating the ratio of PS to PiBa, PeO and PCL in the triblock copolymers were in the range from 80.1% to 89.6%. Subsequently, Huang et al. from Fudan University reported the synthesis of block copolymers by using Cu(0)/PMDETA as a catalyst at ambient temperature (25 ± 5 °C).$^{41}$ They prepared a series of PS, PeBa, poly(methyl acrylate) (PMA) and poly(methyl methacrylate) (PMMA) with a Br terminal group by ATRP or SET-LRP, and PEO and PCL with a TEMPO terminal group by ROMP. Then, the coupling reactions were conducted between Br terminal polymers and TEMPO terminal polymers to give diblock copolymers, PS-b-PeA, PiBa-b-POE, PMa-b-POE, PMMA-b-POE, PS-b-PCL, PiBa-b-PCL, PMA-b-PCL and PMMA-b-PCL, with a high coupling efficiency (89.9% to 94.8%). The high coupling efficiency resulted from the fact that the low reaction temperature (room temperature) inhibited the side reactions, such as thermal cross-linking, chain transfer and $\alpha$-$H$ transfer of PMMA macroradical which usually occur at a higher temperature. Expanding on this work, the same group reported the synthesis of ABC triblock copolymers including poly(isoprene)(Pi)-b-PS-b-PeO, Pi-b-PiBa-b-PeO, and Pi-b-PiBa-b-POE by the combination of anionic polymerization, ATRP and NRC.$^{62}$

The Tunca group reported an attractive strategy that employed triple ‘click’ reactions, NRC, CuAAC and Diels–Alder in a one-pot method, to synthesize linear tetrablock quaterpolymers (Fig. 9).$^{63}$ A maleimide-terminated PEO (male-PEO) was prepared via the esterification between hydroxyl of PEO and 4-[(3-acetyl-7-oxabicyclo[2.2.1]hept-5-yl-2-yl)(carbonyl)amino]ethoxy)-4-oxobutanoic acid. $\alpha$-Alkyn-ω-Br-terminated-PeB (alkyne-PeBA-Br) and poly(n-butyl acrylate) (alkyne-PnBA-Br) were synthesized via ATRP using prop-2-ynyl 2-bromo-2-methylpropanoate as an initiator and CuBr/PMDETA as the catalytic system. TEMPO-terminated PCL was prepared using HTEMPO as the initiator and Sn(Oct)$_2$ as the catalyst by ROMP.
such as crystallinity, mechanical and viscoelastic behaviors, compared with its linear counterpart.\textsuperscript{72} In 2009, Huang et al. from Fudan University prepared 3-miktoarm star terpolymers via CuAAC and NRC reactions.\textsuperscript{73} They prepared PS containing both alkyne and Br terminals (alkyne-PS-Br) by anionic polymerization and successive chain terminal modification, TEMPO terminated PEO by ROM using HTEMPO as an initiator and PtBA-N\textsubscript{3} by ATRP and sequential substitution reaction with sodium azide. The CuAAC reaction between the azide of PtBA-N\textsubscript{3} and alkyne of alkyne-PS-Br, and an NRC reaction between TEMPO and Br were achieved in a one-pot synthesis in the presence of CuBr/Cu(0)/PMDETA, to give a miktoarm star terpolymer (PtBA-PS-PtEO) with a yield of over 90%. There were two T\textsubscript{g}s for the miktoarm terpolymer of PtBA-PS-PtEO at 27 °C for PtBA segment and 90 °C for PS segment, and a melting transition at 51 °C for PEO segment. On the contrary, three T\textsubscript{g}s were observed for its linear corresponding counterpart at −51 °C, 38 °C and 70 °C for PEO, PtBA and PS segments, respectively. These results indicated that the arrangement of the polymer chains played a key role in the interactions among different segments.

In 2012, the Tunca group reported the synthesis of a miktoarm star terpolymer by triple ‘click’ reactions: Diels–Alder, CuAAC and NRC.\textsuperscript{74} They prepared anthracen-9-ylmethyl 2-(2-bromo-2-methylpropanoyloxy)-methyl)-2-methyl-3-oxo-3-(prop-2-ynyloxy)propyl succinate, containing anthracene, active bromine and alkyne groups, and used it as a central point for the construction of miktoarm star terpolymers. Then, it was clicked with PEO with a maleimide terminal group through a Diels–Alder reaction in toluene at 110 °C for 24 h, to give alkyne and Br-terminated PEO. This precursor was subsequently coupled with PCL-TEMPO and PS-N\textsubscript{3} in a one-pot reaction using Cu(0)/CuBr/PMDETA as a catalyst in DMF at room temperature, to give the miktoarm star terpolymer PEO-PCL-PS. They also prepared azide-terminated poly(N-butyl oxanorbornene imide) (PONB-N\textsubscript{3}) via ROM of N-butyl oxanorbornene imide (ONB) using the Grubbs’ 1st generation catalyst, followed by quenching the reaction with (Z)-but-2-ene-1,4-diy bis(2-bromopropanoate) and subsequent substitution reaction with sodium azide. Miktoarm star terpolymer PEO-PCL-PONB was obtained by using PONB-N\textsubscript{3} instead of PS-N\textsubscript{3} in the one-pot coupling reaction. Later on, the same group prepared a series of miktoarm star terpolymers through ROMP and NRC reaction.\textsuperscript{75}

Recently, Barner-Kowollik et al. developed an easier pathway to construct miktoarm star polymers, as shown in Fig. 10.\textsuperscript{76} First, poly(isobornyl acrylate) (PiBoA) was prepared by ATRP of iBoA using CuBr/PMDETA as a catalyst in butyl acetate at 75 °C for 30 min with a conversion of around 35%. Then, the obtained PiBoA was subjected to an NRC reaction in the presence of a 2-fold excess of (Z)-4-(3-(trimethylsilyl)prop-2-ynyloxy)-N-tert-butyl nitrone, using Cu(0)/PMDETA as a catalyst at 60 °C for 3 h. The macroradical of PiBoA generated by an atom transfer process in the presence of Cu(0)/PMDETA was captured by a nitrone to form the macronitroxide of PiBoA in situ, which was quenched by another macroradical of PiBoA through an NRC process. As a result, two PiBoA chains were coupled together and an alkyne group was introduced into the middle of the coupled PiBoA. \textsuperscript{1}H NMR analysis showed that the coupling efficiency was about

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**4.2 The preparation of non-linear polymers**

Non-linear polymers with cyclic, graft, star, hyperbranched and dendritic architectures possess some unusual properties compared to their linear counterparts with the same building units.\textsuperscript{60,64-72} For example, cyclic PNIPAM has a lower LCST and melt viscosity than their linear counterparts.\textsuperscript{71} It is necessary to synthesize non-linear polymers with desired topology, functionality and molecular weight, for deep insight into the relationship between the topologies of polymers and their properties, which is essential to exploit novel functional soft materials. The advancement of living polymerization and the click reaction make it possible to synthesize polymers with predetermined topologies and functionalities. The NRC reaction undoubtedly affords a robust and efficient alternative.

A miktoarm star copolymer contains two or more arms with different chemical composition or molecular weight, and these arms spread outwards from a central junction. The asymmetric structure of a miktoarm copolymer leads to different properties, such as crystallinity, mechanical and viscoelastic behaviors, compared with its linear counterpart.\textsuperscript{72} In 2009, Huang et al. from Fudan University prepared 3-miktoarm star terpolymers via CuAAC and NRC reactions.\textsuperscript{73} They prepared PS containing both alkyne and Br terminals (alkyne-PS-Br) by anionic polymerization and successive chain terminal modification, TEMPO terminated PEO by ROM using HTEMPO as an initiator and PtBA-N\textsubscript{3} by ATRP and sequential substitution reaction with sodium azide. The CuAAC reaction between the azide of PtBA-N\textsubscript{3} and alkyne of alkyne-PS-Br, and an NRC reaction between TEMPO and Br were achieved in a one-pot synthesis in the presence of CuBr/Cu(0)/PMDETA, to give a miktoarm star terpolymer (PtBA-PS-PtEO) with a yield of over 90%. There were two T\textsubscript{g}s for the miktoarm terpolymer of PtBA-PS-PtEO at 27 °C for PtBA segment and 90 °C for PS segment, and a melting transition at 51 °C for PEO segment. On the contrary, three T\textsubscript{g}s were observed for its linear corresponding counterpart at −51 °C, 38 °C and 70 °C for PEO, PtBA and PS segments, respectively. These results indicated that the arrangement of the polymer chains played a key role in the interactions among different segments.

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90%. After removal of the TMS group by tetrabutylammonium fluoride trihydride, an alkyne group was obtained. Then, the PS chain was connected to the middle of the coupled PiBoA through the CuAAC reaction between the alkyne group and the azide group of PS, to give the miktoarm star copolymer. Although the conventional GPC techniques could demonstrate the formation of the miktoarm star copolymers, it was difficult to evaluate the purity of the copolymers, since the retention time of the polymer is also dependent on its composition and functionality, not just the molecular weight. Two-dimensional liquid absorption chromatography with a critical conditions-size exclusion chromatography (LACCC-SEC) technique was employed to investigate the purity of the product. In LACCC-SEC, the miktoarm star copolymers were firstly separated according to their chemical composition in the HPLC dimension, and then the respective eluents were further examined according to their hydrodynamic volumes in the SEC dimension. The results from LACCC-SEC also confirmed the successful formation of the miktoarm star copolymers. In addition, this synthetic method was further employed for the synthesis of third generation dendrimers and amphiphilic star and H-shape copolymers.77,78

Enlightened by this work, Huang et al. prepared a H-shaped PEO3-PS-PEO3 copolymer by a combination of NRC and an in situ generation of nitroxide strategy.79 First, three armed PEO with a potential hydroxyl group was prepared by anionic polymerization using 1-[bis(2-hydroxyethyl)amino]-3-(1-ethoxy-ethoxy)propan-2-ol as an initiator, followed by termination of the reaction with an excess of benzyl bromide. After deprotection of the potential hydroxyl group to form a hydroxyl group, it was esterified with 2-bromoisobutyl bromide to give bromide terminated PEO3–Br. Then, the bromide terminated PEO3–Br was used as an initiator for the ATRP of St to afford A3B star shape copolymer PEO3–(PS–Br), which was employed as the precursor to prepare the H-shaped copolymer PEO3–PS–PEO3 in the presence of CuBr/Me6TREN and 2-methyl-2-nitropropane (MNP) in the mixture of DMSO–THF. Under these conditions, the macroradicals of PEO3–PS generated by a single electron transfer process were reacted with MNP to form macronitroxide radicals, which were further coupled with PEO3–PS macroradicals to form H-shaped PEO3–PS–PEO3.

Another kind of interesting non-linear copolymer are the graft copolymers, which contain a great quantity of side chains chemically attached onto a linear backbone. A graft copolymer is endowed with fascinating properties, including wormlike conformation, compact molecular dimension and notable chain terminal effects, due to its confined and compact structure, in comparison with its corresponding linear counterparts with similar molecular weight.80 Huang et al. from the Shanghai Institute of Organic Chemistry (SIOC) reported the synthesis of poly(acrylic)g-poly(propylene oxide) (PAA-g-PPO) and PBA-g-PPO via a combination of RAFT, NRC and graft-onto strategy (Fig. 11).81 A bromide-containing backbone was prepared firstly by RAFT of tert-butyl-(2-bromopropanoyloxy)acrylate (rBBPMA). NRC reaction between the backbone with TEMPO terminated PPO was conducted using CuBr/PMDETA or Cu(0)/PMDETA as a catalyst in toluene to give PBA-g-PPO. The graft densities of PPO chains were in the range from 19.5% to 65.4% according to the feed ratio of TEMPO-PPO to the bromide group on the backbone. After hydrolysis in the presence of trifluoroacetic acid in dichloromethane, PAA-g-PPO was obtained. Diverse morphologies of the self-assembled PAA-g-PPO in water were observed, including spheres, branched short rods, nanofibers and vesicles, for the graft copolymers with different contents of PPO segments. The same group further synthesized star-like graft copolymers by combination of RAFT and NRC.82 They firstly prepared four armed PiBBPMA via RAFT polymerization of βBBPMA using a tetrafunctional chain transfer agent, which was subsequently reacted with TEMPO-terminated PPO in the presence of Cu(0)/PMDETA in toluene at 25 °C for 2 days, to give a star-like graft copolymer PBA-g-PPO. Similarly, after the hydrolysis of PiBA segment of the copolymer, amphiphilic star-like graft copolymer, PAA-g-PPO, was obtained. This strategy was also employed to prepare PAA-g-PPO and star-like PAA-g-PEO.83,84

![Fig. 10](image-url) Construction of miktoarm star polymers via nitronate-based NRC and CuAAC.

![Fig. 11](image-url) Synthesis of amphiphilic graft copolymers of PAA-g-PPO via RAFT and NRC.
The application of the NRC reaction, combined with living polymerization and ‘click’ reactions, is a rapidly expanding area for constructing complex and functionalized polymers. On the basis of the selected examples highlighted here, there are two major pathways to employ NRC in the preparation process. First, TEMPO and its derivatives were used as radical coupling reagents, functional groups or polymers were connected to the TEMPO, followed by NRC reaction with other polymers with active halogen. Generally, the side reactions, including chain transfer and coupling termination, could be excluded under certain conditions during the NRC process. Second, the strategy of \textit{in situ} formation of nitroxide radical by some certain nitrones or their derivatives was employed. Although, this is an efficient way to introduce functionalities into the mid-chain of a polymer and form nitroxide radicals, a side reaction of radical coupling termination often occurs, which would decrease the functionalization efficiency and bring out another issue of purification. Thus, more attention should be paid to design and to preparing highly efficient radical capturing reagents to prevent the side reactions.

5 The preparation of organic–inorganic composites

The surface modification of metal/inorganic materials, such as carbon nanotubes, fullerence, graphene, silica and metal oxide and quantum dots, is a fascinating research area. The lack of reactive groups on the surface of these materials results in their low solubility or dispersibility in most organic solvents, water and polymer matrices, which is a key factor in hindering their development in biomedical, electronic and optical applications. Therefore, functionalization of the surface of these metal/inorganic materials is an essential prerequisite to exploit their potential applications. Given the properties of the NRC reaction it might be an excellent candidate.

In 2009, Sui \textit{et al.} modified multi walled carbon nanotubes (MWNTs) with PS via an NRC reaction. Pristine MWNTs were treated with a mixture of nitric acid and sulfuric acid to attach carboxylic acid groups onto the surface of MWNTs (MWNTs–COOH), which was further functionalized with HTEMPO via an esterification reaction to give MWNTs with TEMPO groups on the surface (MWNTs–TEMPO). Then, PS was grafted onto the surface of MWNTs via NRC reaction between MWNTs–TEMPO and PS–Br using CuBr/PMDETA as a catalyst in toluene at 90 °C for 24 h. The polymer content of MWNTs–PS measured by TGA was about 46.7%, much higher than Fan’s work (30.7%), in which PS chains were introduced onto the surface of MWNTs via NMP of styrene using TEMPO containing MWNTs as the mediator, and Lou’s report (30%), in which poly(2-vinyl pyridine) (P2VP) was attached to the surface of pristine MWNTs by heating TEMPO terminated P2VP with pristine MWNTs directly. This result indicated that NRC might be a more efficient approach for the preparation of polymer modified MWNTs. Recently, Huang \textit{et al.} from SIOC provided an excellent example for the modification of graphene sheets with polymer via an NRC reaction (Fig. 12). The graphene oxide (GO) was prepared according to a modified Hummers method. Then, GO was reacted with thionyl chloride, followed by HTEMPO to attach the TEMPO groups onto the surface of GO to give GO–TEMPO. Then, PNIPAM prepared by SET-LRP with a chloride terminal group was coupled with GO–TEMPO to obtain PNIPAM functionalized GO (GOPNIPAM) via an NRC reaction using CuBr/PMDETA as a catalyst in the mixture of DMF–H$_2$O (1/1, v/v) at 25 °C for 4 days. The elemental analysis, thermogravimetric analysis (TGA) and X-ray photoelectron spectroscopy (XPS) results indicated that the weight content of PNIPAM was around 26.9%, and the coupling efficiency of PNIPAM onto GO-TEMPO was around 17.4%. Due to the thermo-responsive behavior of PNIPAM with a lower critical solution temperature (LCST) at around 33 °C in water, GO–PNIPAM formed a stable suspension in water at ambient temperature, but readily precipitated when the temperature was higher than the LCST of the nanocomposites at around 37.4 °C, which was determined by DSC. The applications of NRC for the modification of MWNTs and graphene sheets implies that the NRC reaction may become a useful tool in the preparation of organic–inorganic composites, considering its high selectivity, efficiency and tolerance of a wide range of reactive groups.

6 Conclusions and outlook

Since the development of the NRC reaction, it has emerged as a robust, efficient and orthogonal ‘click’ reaction in polymer terminal functionalization, the synthesis of polymers with well-defined and complex architecture and the preparation of functional organic–inorganic composites. However, side reactions, such as chain transfer and termination, should be minimized as much as possible by considerably optimizing the conditions for conducting these reactions. The polymers prepared by NRC reaction contain an alkoxyamine bond, which could be broken at an elevated temperature, and this process is highly dependent on the structure of the alkoxyamine group. This property has been widely used to confirm the formation of an alkoxyamine group in the NRC reaction. Given that the ring size and steric bulk of the nitroxide group has a great influence on the cleavability of the alkoxyamine bond, the temperature of
the bond broken could be tuned through designing the structure of the nitroxide group. Therefore, the potential usage of NRC for the preparation of thermally responsive and degradable soft materials looks promising and prosperous.

To date, most of the NRC reactions were conducted by using Cu-based catalysts with more than a stoichiometric amount of copper, which is very toxic. This will significantly hamper its application in industrial systems and drug delivery. Previous results have already showed that Fe-based catalysts and trace amounts of Cu-based catalysts are also efficient for ATRP, activators regenerated by electron transfer (ARGET) ATRP and initiators for continuous activator regeneration (ICAR) ATRP.96–97 Thus, exploring non-toxic or less toxic catalytic systems for the NRC reaction will be an attractive research direction in this field.

Acknowledgements

The authors thank the financial support from the National Natural Science Foundation of China (50873029, 20974117, 51073042 and 51103026), the Shanghai Natural Science Funds (11ZR1403100), the Shanghai Scientific and Technological Innovation Project (11JC140600 and 1043190300), the Shanghai Rising Star Program (12QB1402900) and the Specialized Research Fund for the Doctoral Program of Higher Education (20110071120006).

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