

REVIEW

Playing construction with the monomer toy box for the synthesis of multi-stimuli responsive copolymers by reversible deactivation radical polymerization protocols

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Abstract

In this review article, we survey the 2016–June 2021 scientific literature on the synthesis of multi-stimuli responsive (MSR) polymers, the main focus being on reversible deactivation radical polymerization techniques (RDRPs, also known as controlled radical polymerizations). In fact, along more than 40 years of extensive research, RDRPs have boosted the synthesis of stimuli-responsive polymers. RDRPs are now robust, versatile, relatively user-friendly and even interconvertible, thus allowing control over composition, sequence, and topology of polymers. Such control can afford materials with well-defined responses to physical, chemical, and biological external stimuli. Furthermore, “click” reactions are used to combine macromolecular precursors or to introduce specific functional groups in the target structure. As a result, MSR polymers are obtained from diverse combinations of commercial or specially synthesized building blocks arranged at will into desired sequences and architectures.

Abbreviations: AA, acrylic acid; AAm, acrylamide; AN, acrylonitrile; AmBC, amphiphilic block copolymers; ADPS, 3-([3-aminopropyl] dimethylammonio)propane-1-sulfonateacrylamide; ARGET, activators regenerated by electron transfer; ATRP, atom transfer radical polymerization; *t*BA, *tert*-butyl acrylate; *t*BAMA, *tert*-butoxycarbonylaminomethyl acrylate; BnMA, benzyl methacrylate; BMA, 2-hydroxy-4-(methacryloyloxy) benzophenone; *t*BMA, *tert*-butyl methacrylate; BuA, butyl acrylate; BuMA, butyl methacrylate; BnAAm, benzylacrylamide; CA, controlling agent; CTA, chain transfer agent; CuAAC, copper-catalyzed alkyne-azide cycloaddition; DEA, 2-(diethylamino)ethyl methacrylate; DEAEMA, N,N-diethylaminoethyl methacrylate; DMAEMA, N,N-dimethylaminoethyl methacrylate; DPA, 2-diisopropylaminoethyl methacrylate; EDOT, 3,4-ethylenedioxythiophene; EG, ethylene glycol; EMA, ethyl methacrylate; EO, ethylene oxide; FAISA, facial amphiphilicity-induced self-assembly; FMA, 2,2,2-trifluoroethyl methacrylate; GA, glycolic acid; GMA, glycidyl methacrylate; LAM, less activated monomer; LCST, lower critical solution temperature; LMA, lauryl methacrylate; MAA, methacrylic acid; MAF-TBE, *t*-butyl trifluoromethacrylate; MAM, more activated monomer; 4MBA, 4-methacryloyloxy benzoic acid; MEO₂MA, 2-(2-methoxyethoxy)ethyl methacrylate; 5MPA, 5-methacryloyloxy pentatonic acid; MPMA, *p*-methoxyphenacyl methacrylate; MSR, multi-stimuli responsive; NBA, *o*-nitrobenzylacrylate; NIPAAm, N-isopropylacrylamide; NIPMAM, N-isopropylamino methacrylamide; NMP, nitroxide-mediated polymerization; OEGMA, oligo(ethylene glycol) methacrylate; ODA, octadecyl acrylate; PISA, polymerization-induced self-assembly; ProDOT, 3,4-propylenedioxythiophene; St, styrene; RAFT, reversible addition-fragmentation chain-transfer; RDRP, reversible deactivation radical polymerization; RIM, restriction of intramolecular motion; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl; Tfa, 2,2,2-trifluoroethylacrylamide; TPE, tetraphenylethene; TPEMA, (2-hydroxyethyl methacrylate tetraphenylethene ether) or 4-(1,2,2-triphenylvinyl)phenyl methacrylate; TAD, 1,2,4-triazoline-3,5-dione; UCST, upper critical solution temperature; UPy, ureidopyrimidinone; VA, vinyl acetate; 4VP, 4-vinylpyridine.

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Thanks to this versatility, self-assembling polymeric structures are designed either to respond to triggers and perform specific applicative tasks, or to investigate the influence of structural variables on the responsivity of polymers. The “green” trend emerging in the field of responsive polymers and RDRPs is also briefly discussed.

KEYWORDS

block copolymers, controlled radical polymerization, functional polymers, green polymers, reversible deactivation radical polymerization, self-assembling, stimuli-responsive polymers

1 | INTRODUCTION

Ever since the first implementation of reversible deactivation radical polymerizations (RDRPs, also known as CRPs: controlled radical polymerizations), polymers of well-defined composition, length, dispersity, and topology have become increasingly accessible.¹ This opportunity has had a tremendous impact on research focusing on polymers that respond to one or more external physical or chemical changes. The key feature in multi-stimuli responsive polymers (MSR) polymers is the presence of covalently linked multiple copies of stimuli-responsive functional groups or segments, which enables cumulative and cooperative interactions within, without, and around polymer chains. As a result, an amplification of the triggered response and, sometimes, an interdependence of one response with another can be observed. Such is the case, for instance, of dual light- and temperature-responsive polymers that change their transition temperatures as a consequence of irradiation.^{2–4} This is fundamentally different from the working principle of molecular machines, which respond by individual motions to external stimuli.

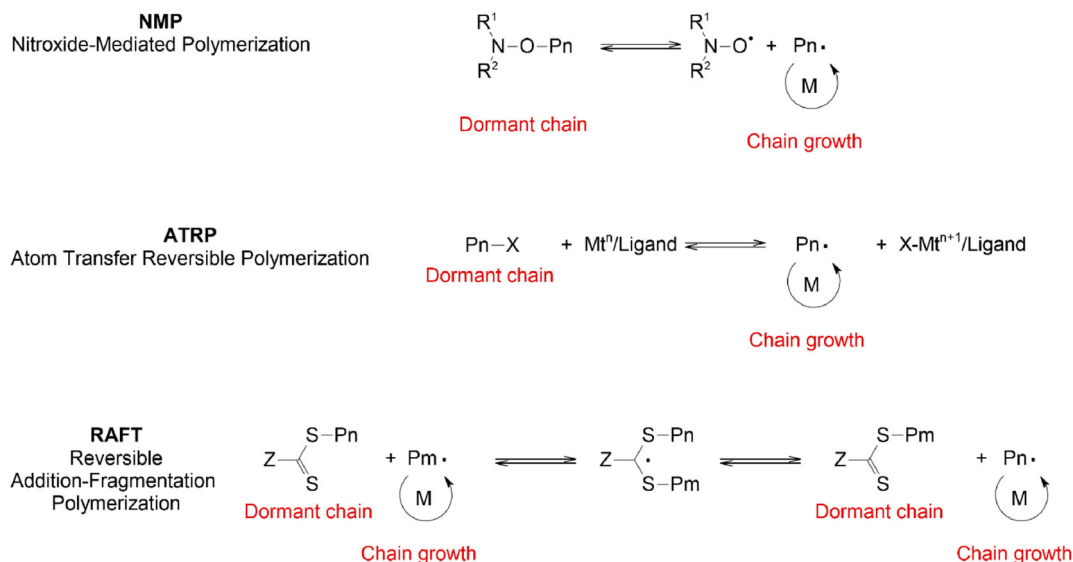
With drug delivery as the main driving force for research in the stimuli-responsive polymers field,^{5–7} the vast majority of papers deals with hydrophilic and amphiphilic copolymers that are also capable of spontaneously or forcibly assemble into nano-aggregates. Often in these cases, investigations focus on the response of the nano-object as a consequence of the triggered modification of the chemistry of the material (photoisomerizations, bond cleavage, ionization, etc.) or of its intramolecular and solvent interactions (usually prompted by temperature). However, the potential or actual fields of application for multi-responsive polymers are extremely numerous, thanks to the inherent versatility of these structures.^{8,9}

This review article attempts to provide, from the synthesis point of view, a narrative of the recent strategies adopted by polymer scientists in the 2016–2021 time range toward building MSR copolymers by means of RDRP protocols. Any attempt at being exhaustive in examining recent research articles and reviews on stimuli-responsive

polymers would be frustrated by their overwhelming number, so we limit ourselves to providing examples to sketch an overall picture. Free radical polymerization and RDRP fundamentals are described elsewhere and will not be dealt with here.^{1,10,11} Other polymerization techniques are also mentioned when used in combination with RDRPs. The main focus is on block copolymers, with some insight into different sequences and topologies. In some cases, we report accomplished syntheses of MSR materials. In other cases, we refer to singly triggered polymers that are relevant toward obtaining multi-responsive structures. Because structures and syntheses are our main focus, we deliberately overlook the applicative side of the story, lest the thread of the tale be lost.

RDRPs are grouped into three major categories, namely nitroxide-mediated polymerization (NMP), atom-transfer radical polymerization (ATRP), and reversible addition-fragmentation radical polymerizations (RAFT) (Scheme 1).

Extensive research into different reaction conditions, initiators and reactants has been giving rise to many variations (and acronyms) of these three broad categories. Of course, traditional living (ionic) polymerizations, in which termination and transfer are not accessible to chain ends, also afford structural control. As long as chain ends are not quenched by moisture or impurities, chain elongation with different monomers can be performed to obtain block copolymers. However, purity requirements are stringent and the living character of chains is difficult to preserve over time. Metathesis polymerization (ROMP and MCP) and metal-catalyzed ring-opening polymerizations are also suited for the synthesis of polymers of controlled structure.^{12–17} The synthesis of hyperbranched structures heavily relies on sequential Michael addition reactions.^{18,19} However, RDRPs are of wide scope and relatively user-friendly, and have therefore become a fundamental tool in the field of stimuli-responsive materials. One of the aims of research focused on RDRPs is to assess the scope of different protocols for the reliable polymerization of different kinds of vinyl monomers.^{20–26} At the next level of complexity,



SCHEME 1 Main equilibria involved in the reversible deactivation of radical-terminated polymer chains in the three major RDRP categories: NMP, ATRP, RAFT. ATRP, atom transfer radical polymerization; NMP, nitroxide-mediated polymerization; RAFT, reversible addition-fragmentation chain-transfer; RDRP, reversible deactivation radical polymerization technique

conditions are sought to ensure a good balance of reactivity of different monomers in order to obtain truly random copolymers.^{27–33} This is a particularly sensitive issue since random copolymers are widely used to modulate the properties of block copolymers (Section 4). Linear block copolymers and more complex architectures, for example star, miktoarm, hyperbranched, dendritic, and so on, are obtained by either a convergent approach, where preformed blocks are joined through stable or labile bonds, or by chain elongation of macromolecular precursors. In some cases, a combination of both approaches is used. In this context, the control of reactive polymer chain ends and the introduction of specific functional groups for post-polymerization modifications are the key to creativity in playing construction (Sections 2 and 3).³⁴ The versatility of radical polymerization combined with polymerization control allows the conceptual switch from “assessing the properties of polymers” to “designing a responsive polymer”.³⁵ In fact, the polymer scientist is now in a position to apply a study-through-synthesis approach, that is, to play with the composition and topology of copolymers not only to obtain materials with desired properties,³⁶ but also to seek answers to specific questions regarding the physical chemistry and the dynamics of aggregation^{37–40} (Section 5). The next problem to be tackled is to process the wealth of data provided by the overwhelming combination of various controlled polymerization techniques, numerous monomers, and diverse architectures⁴¹ with the purpose of reverse engineering the synthesis of new materials, that is, to “uncover the optimal recipes satisfying predetermined

targets” and to “crack the interrelationship between recipe-architecture-property”.⁴² These concepts were introduced by Matyjaszewski and coworkers,⁴² who envisage intelligent machine learning for tailor making of macromolecules. It is worth noting, however, that the behavior of stimuli-responsive materials can also be manipulated through the environment in which the stimulus is delivered. For example, the lower critical solution temperature/upper critical solution temperature (LCST/UCST) behavior of polymer solutions is modulated by the presence of other solution components that affect polymer–polymer and polymer–solvent interactions.⁴³

The basic toy box, which contains readily available commercial monomers of reasonable cost, is quite diverse to begin with. The complexity of properties and responsiveness that is achieved with well-designed copolymers of “conventional” monomers (Section 6) ensues creativity in their assembly. However, as advanced applications that require subtle responses demand innovative materials and promise large added values, creativity may also be addressed toward obtaining monomers endowed with elaborate properties (Section 7) that will be reflected in the behavior of the resulting macromolecule. Last but not least, research on stimuli-responsive copolymers should aim at environmental sustainability of monomers, polymerization processes, and final products. This translates into obtaining monomers from renewable sources (Section 8),⁴⁴ applying the principles of green chemistry to RDRPs,^{45–49} ensure sustainable scalability of polymerization processes and addressing the biodegradation of target polymers.^{50,51}

2 | BACKGROUND: MATCHING BUILDING BLOCK STUDS FOR SPECIFIC COMPOSITIONS, ARCHITECTURES, AND FUNCTIONS

The controlled construction of random, random-block, gradient, sequence-specific copolymers, and complex topologies requires a good match between monomers and RDRP techniques. To obtain a truly random copolymer in a batch copolymerization, the ratio of the rates of incorporation of the two monomers should be the same as the concentration ratio. When this is not the case, monomer addition to the growing chain, at any given reaction stage is biased by the relative reactivity of monomers and it eventually results in specific chemical composition distributions and/or spontaneous gradients along the chain, entailing consequences in the physico-chemical properties of the material.^{37,52,53} The synthesis of block copolymers from macromolecular precursors

requires the appropriate chain terminal for chain elongation, whereas gradient and sequence-specific copolymers require subtle strategies, given the inherent limitations of radical polymerization toward sequence control.^{54–59}

The choice of controlling agents (CAs) in RDRPs is largely dictated by the nature of the monomer, along with desirable reaction conditions (temperature, solvent, concentration) and method of initiation (thermal, photochemical, redox). RDRP options are extremely numerous, so that a good match between the target structure and a suitable polymerization technique is most likely to be found.⁶⁰ Ad hoc initiators and CAs are also synthesized in order to obtain specific chain ends and polymer architectures. Some examples discussed herein are also illustrated in Figure 1.

It is also possible to switch between living polymerization types through suitable chemical transformations⁴⁹ or to resort to dual- or even triple-function initiators and CAs. The latter combine in a single molecule the

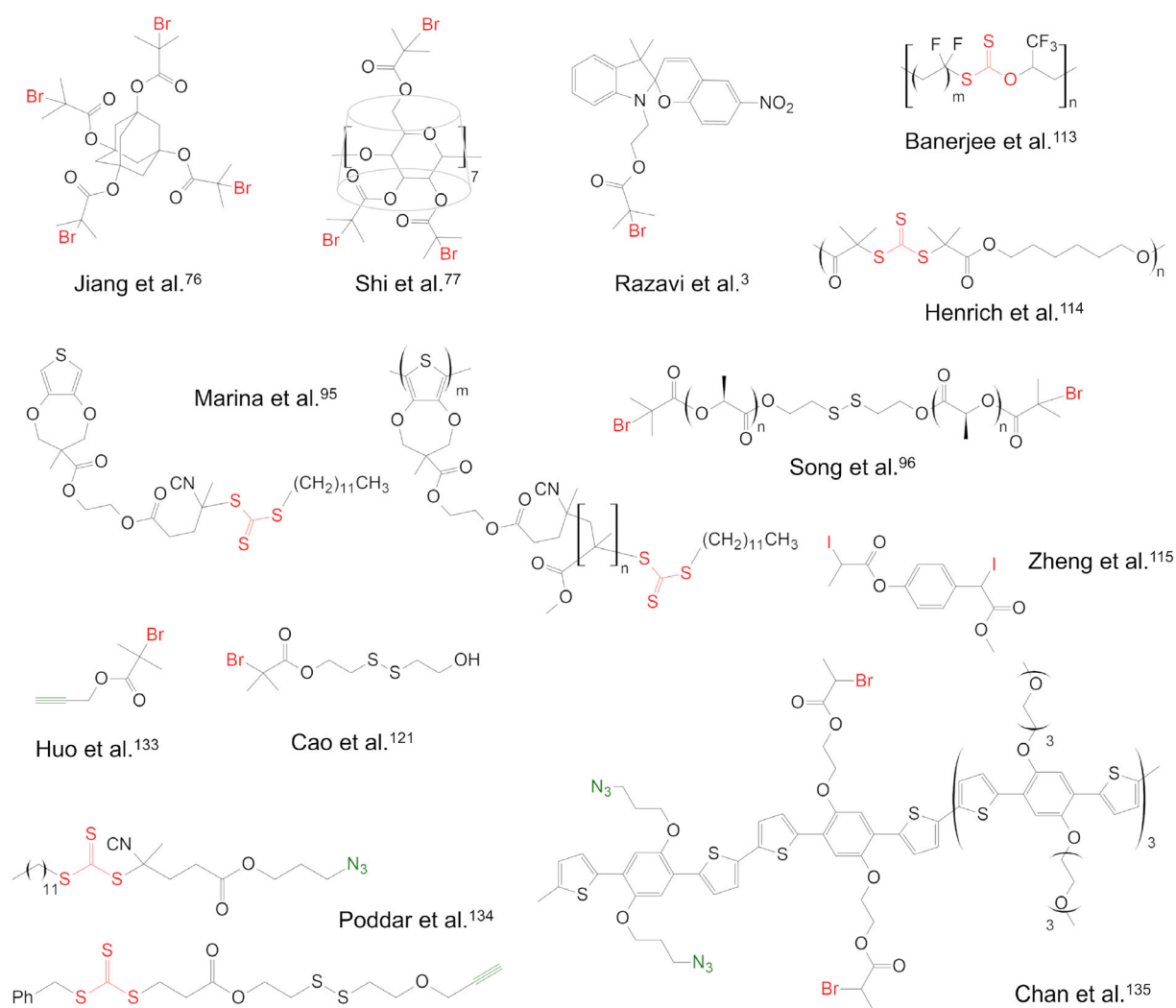


FIGURE 1 Some of the initiators and controlling agents discussed in this review

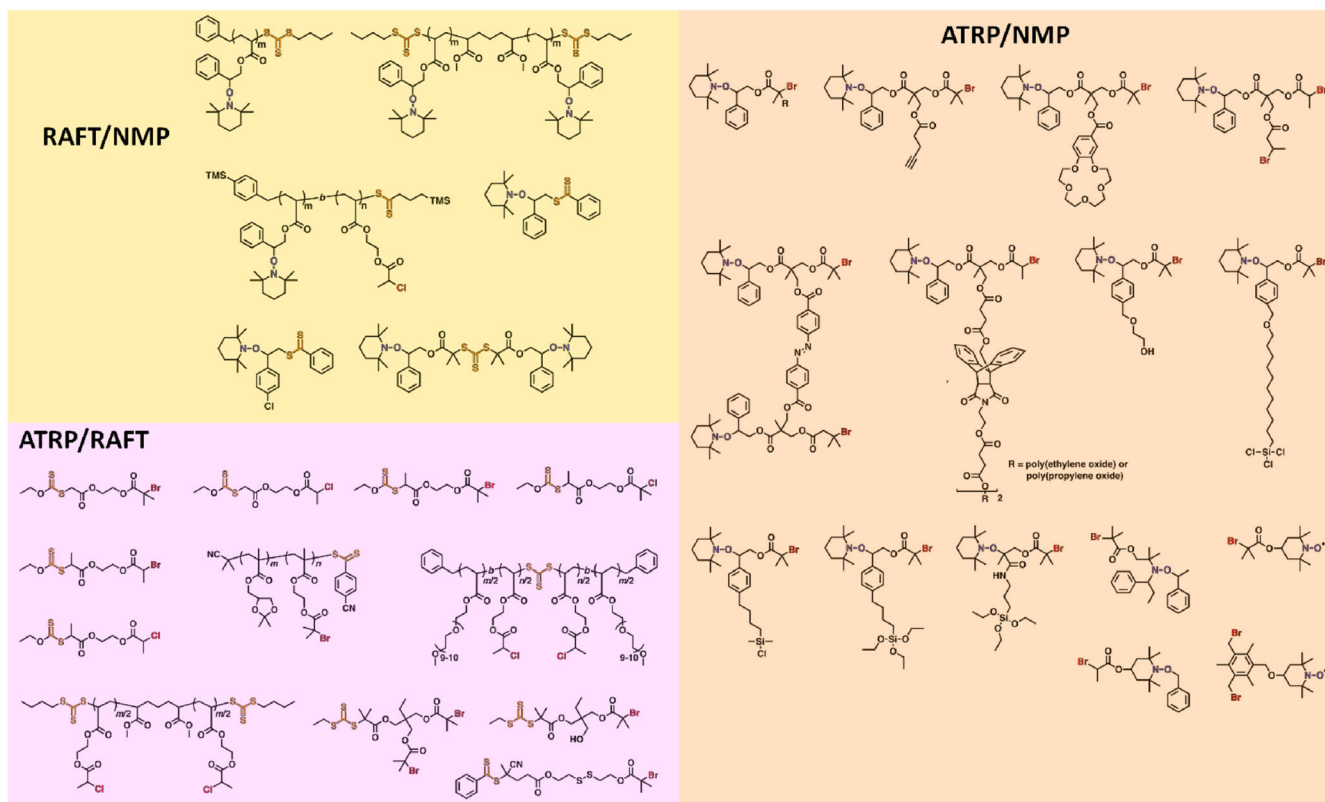
necessary functionalities to perform different RDRP techniques, as reviewed by Pearson et al.⁶¹ (Scheme 2).

NMP is the first RDRP technique to have been studied, as it can be traced back to the 60s and has been applied to polymer synthesis since the late 70s.⁶² It suffers from several limitations, due to the high temperatures that may be required to reactivate the radical dormant species, especially when it is unconjugated. Still, these limitations have been dealt with through several variants of NMP.^{63,64} Furthermore, when seeking block copolymer synthesis, nitroxide chain end can be exchanged with a halogen atom for ATRP chain elongation or with a dithiobenzoate to form a RAFT macro-chain transfer agent (CTA) (Scheme 3).⁶⁵

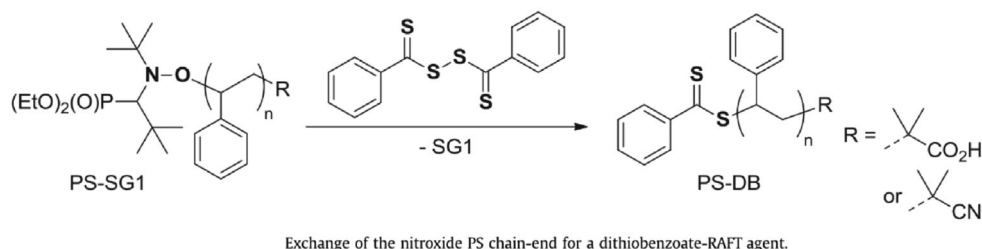
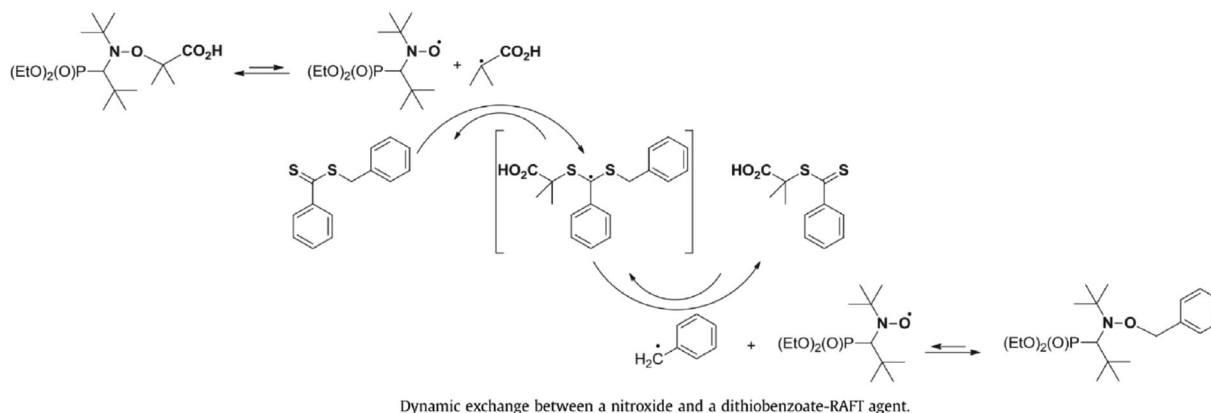
As a result, NMP is still a viable technique also when dealing with non-styrenic monomers.⁶⁶ Rabyk et al.⁶⁷ relied on the difference in reactivity of St and DMAEA to obtain a block-gradient copolymer that is responsive to temperature and pH. Wang et al.⁶⁸ turned the stability of the C—O bond resulting from the NMP of St with a 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) derivative to their advantage. (Scheme 4) Their TEMPO derivative comprises an aromatic ring for azo-coupling with an aniline-functionalized PEG reagent. They thus obtained a self-assembling amphiphilic block copolymer (AmBC)

with the nitroxide as the integral part of its structure (Scheme 4). The polymer is also enzyme-responsive through disassembly of nanoaggregates upon reduction of the diazo moiety.

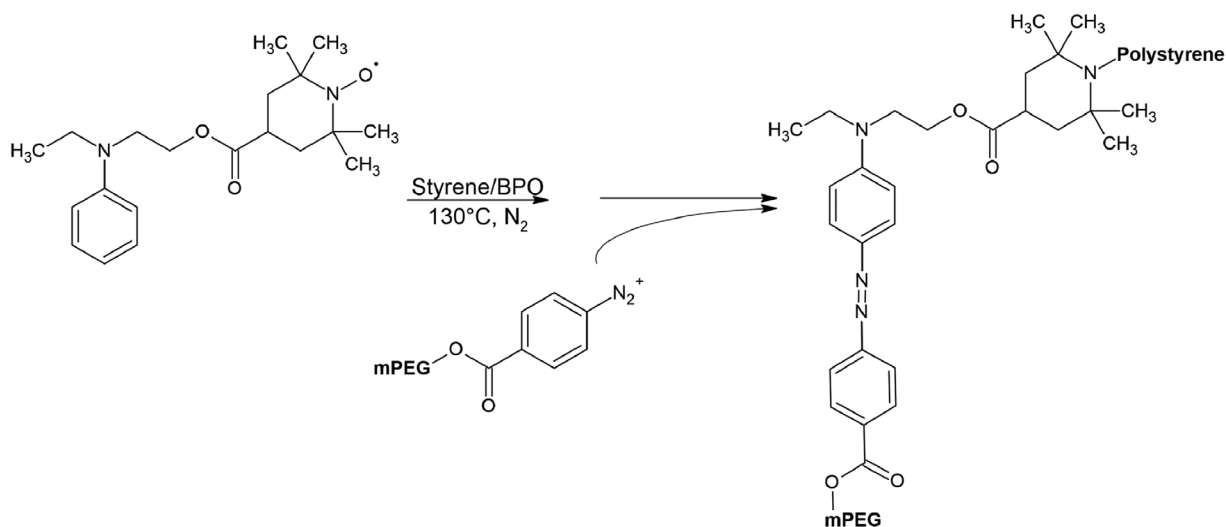
ATRP is an RDRP process based on a ligated metal complex, the majority of systems using copper, to mediate the reversible halogenation of propagating radical species and to provide control of the polymerization. It is robust, applicable to diverse vinyl monomers and has been contributing immensely to the development of functional materials since its discovery in the 1990s.^{1,69} Since recovery of metal complex catalysts has been a concern with ATRP, research has been directed toward different ATRP variants that allow to minimize the concentration of metal complex catalyst and to apply mild initiation conditions.^{48,49,70} Furthermore, recent investigations focus on the development of organic photocatalysts to be used in metal-free ATRP.⁷¹ The following examples confirm the functional group tolerance of ATRP and related polymerization protocols. ATRP was applied to the sequential polymerization of N-isopropylacrylamide (NIPAAm) and a phenylboronic monomer to obtain a temperature/reduction dual-sensitive material.⁷² A glycosylated acrylamide was copolymerized with NIPAAm in water by



SCHEME 2 Dual controlling agents combining RAFT, ATRP, and NMP functionalities. Reproduced with permission.⁶¹ Copyright the Royal Society of Chemistry 2017. ATRP, atom transfer radical polymerization; NMP, nitroxide-mediated polymerization; RAFT, reversible addition-fragmentation chain-transfer



SCHEME 3 Exchange reactions between nitroxides and RAFT agents. Reproduced with permission.⁶⁵ Copyright Elsevier 2016. RAFT, reversible addition-fragmentation chain-transfer



SCHEME 4 Amphiphilic mPEG-*b*-Pst with a diazo-TEMPO block connection. The copolymer is self-assembling and the resulting nanoaggregates are enzyme-sensitive thanks to enzymatic reduction of the diazo moiety.⁶⁸ TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl

Cu(0)-RDRP to yield a temperature/pH responsive star copolymer.⁷³ ARGET ATRP polymerization of a disulfide-containing co-monomer with a vinyl ether initiator was employed to obtain a temperature/pH/reduction responsive copolymer.⁷⁴ The ATRP-challenging monomer *tert*-butoxycarbonylaminoethyl acrylate (*t*BAMA), which forms copper complexes, was copolymerized with a careful optimization of reaction conditions, yielding a

precursor to pH- and Cu- sensitive self-assembling double hydrophilic block copolymer.⁷⁵ Since ATRP initiators consist of aliphatic halides, various architectures for stimuli-responsive materials become accessible through the structure of ATRP initiators. A tetrabrominated adamantane initiator (Figure 1) was used to perform ARGET ATRP of EMA, *t*BMA, and oligo(ethylene glycol)methacrylate (OEGMA) to obtain star-shaped, self-assembling, pH-

sensitive block copolymers.⁷⁶ Functionalization of β -cyclodextrin with three bromo-isobutyryl units per sugar (Figure 1) afforded 20 active sites on each macroinitiator for sequential polymerization with a disulfide-linked methacrylic prodrug and OEGMA, resulting in a self-assembling starburst reduction-sensitive prodrug.⁷⁷

Other metal-catalyzed polymerization reactions besides ATRP can prove convenient in the field of stimuli-responsive polymers. When di- or tri-block polymers are sought, starting from monomers that do not share a common mechanism for polymerization, one would build the blocks separately with complementary chain ends, or elaborate the chain end of a first block to promote chain elongation with a second monomer. For instance, in the case of poly(3-hexylthiophene) blocks, convergent synthesis or chain elongation can be inefficient, laborious and problematic in terms of purification. Yu et al.⁷⁸ sequentially carried out the living polymerization of an allene and a chloromagnesium thiophene in a one-pot reaction with *p*-allylnickel(II) as single catalyst. The resulting triblock copolymer, comprising a conjugated segment, exhibits helicity and is responsive to pH and temperature. Chen et al.⁷⁹ obtained complex polymeric micelles that are H₂O₂- and pH-responsive through one-pot sequential polymerization with a Pd(II) complex catalysis. The composition of this tri-block copolymer is highly specific for the targeted biomedical application and it comprises oxidation and pH responsive functionalities and a NIR-sensitive group for induced hyperthermia. This structure is obtained thanks to the simultaneous growth of two blocks by two distinct mechanisms and then sequential growing of the third block.

Polymerization control in the RAFT process is based on the degenerate addition-fragmentation equilibria involving a CTA (dithioester, xanthate, trithiocarbonate, or dithiocarbamate) and the chain-propagating radical.^{80–82} Recent literature confirms the significant impact of RAFT in the field of MSR polymers with a wealth of diverse monomers processed. With a careful choice of CTA,⁵³ a wide variety of unsaturated monomers can be polymerized, from more activated monomers (MAMs; conjugated double bonds such as methacrylates or styrenics) to less activated monomers (LAMs; the double bond is unconjugated or substituted with a heteroatom, e.g., allylamines, vinyl acetate). “Universal” RAFT agents can be used to polymerize LAMs and then the resulting macroCTA is easily switched by treatment with a Lewis acid for sequential chain extension with a MAM to obtain a block copolymer.⁸³ Initiation is not only thermal, but also redox-, light-, or even sound induced.^{84,85} Reaction media range from organic to aqueous to bulk. In recent reports, thermally initiated and photo-RAFT were carried out in “hard confinement” conditions at (or close to) room temperature, also with ionic liquid monomers.^{86,87}

Thiocarbonylthio end group susceptibility to aminolysis, hydrolysis or reduction, however, should always be taken into account for monomer compatibility. Thus, aminoacid-containing methacrylates can be polymerized by RAFT, provided the amino group is protected. This strategy afforded, for example, an aminoacid-based CO₂-responsive polymethacrylate after N-BOC deprotection.⁸⁸ Notwithstanding this limitation, monomers bearing diverse functional groups have been RAFT-polymerized, including metallo-monomers such as the recently reported metallo-salphen methacrylate⁸⁹ or mannosylated methacrylamides.⁹⁰ RAFT polymerization allowed the three-step synthesis of a triblock copolymer, where PAA-CTA was polymerized with a poly(diazobenzene derivative methacrylate), and the resulting di-block-CTA was polymerized with NIPAAm.⁹¹ The resulting linear polymer is triple-responsive to pH, light, and temperature. The three steps, however, were carried out in three different solvents, so the procedure was not one-pot. UCST-type responsive copolymers were obtained by RAFT polymerization of monomers functionalized with bile acid,⁹² zwitterionic sulfobetaines, nitrile, diacetone acrylamide.⁹³ Multiple hydrogen bond forming monomers were polymerized using a PEG-based CTA to obtain double hydrophilic block copolymers affording core-stabilized, thermoresponsive micelles.⁹⁴ RAFT and ATRP both offer the opportunity to cap the α -end of the polymer with a functional moiety through CA design. Razavi et al.³ obtained a triple-responsive (light, pH, temperature) PDMAEMA-*b*-PMMA with a spiropyran ester as ATRP initiator (Figure 1). The photo-induced switch from hydrophobic spiropyran to hydrophilic merocyanin chain-end resulted in a 7°C LCST increase in water. Marina et al.,⁹⁵ obtained PMMA, PNIPAAm, POEGMA using a novel RAFT agent having propylenedioxythiophene (ProDOT) in the fragmenting (R) group (Figure 1). The resulting α -ProDOT polymethacrylates/polyacrylamide was then elongated at the α -end with PEDOT by chemical oxidative polymerization, to yield a new family of multi-responsive electroactive block copolymers. As an alternative, the α -end group in α -ProDOT-PMMA was polymerized oxidatively, resulting in a branched copolymer with multiple CTA Z-groups in the side chains. A temperature and reduction-sensitive ABA triblock was obtained by Song et al.⁹⁶ by using ROP to obtain a symmetrical disulfide-containing PLA with free OH groups at both ends. These were esterified, resulting in a double ATRP initiator that was used to construct the two lateral B blocks with OEGMA (Figure 1). In fact, ROP involving, for instance, 2-oxazolines, lactide and caprolactam derivatives, is often used in conjunction with RDRPs to obtain complex polymer compositions or architectures. Lin et al.⁹⁷ joined a hydrophilic block obtained from a caprolactam derivative and an SH-terminated PNIPAAm

through a disulfide bond, thus obtaining a linear block copolymer that is responsive to temperature, ultrasound and redox stimuli. O'Reilly's group provided an elegant example of a combination between RAFT and ROP.⁹⁸ Here, HEMA acts as a bifunctional unit for ROP (through the —OH residue) and RAFT (with the conjugated double bond) and hyperbranched polymers that are responsive to temperature and reduction were thus obtained without the need for a specially designed RAFT agent. Tang et al.⁹⁹ designed a polyfunctional initiator to obtain a PNIPAAm with a ω -end dithiobenzoate, a α -end alkyl bromide and a hydroxyl handle for subsequent ROP (Scheme 5). The ω -thiol group revealed by aminolysis undergoes thiol-bromo click with the α -end, yielding a multisegmented PNIPAAm ready for ROP of CL at each segment. The final product is a dual-responsive (thermal and redox) graft copolymer of exact architecture.

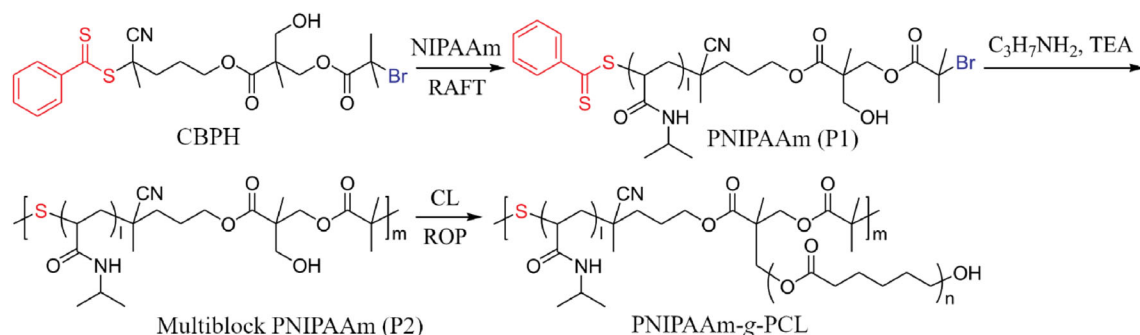
Chain growth condensation polymerization (CGCP)¹⁰⁰ by S_NAr with a —NO₂ leaving group on a rigid diazoaryl monomer was utilized by Kim, S.Y. and co-workers in combination with ATRP of MEO₂MA and OEGMA to obtain amphiphilic rod-coil copolymers¹⁰¹ and dual-responsive micelles (light and temperature) thereof.

Aiming to access the peculiar self-assembling and stimuli-responsivity of amphiphilic gradient copolymers, control over gradient distribution of monomers is becoming increasingly desirable.^{59,102} To this end, in semi-batch polymerizations, monomers are fed into the reaction mixture at programmed speed through syringe pumps. Sequence specific copolymers, such as multiblocks and strictly alternating AB copolymers, are also believed to have a high potential in the field of MSR polymers.¹⁰³ The latter are more conveniently obtained through ring-opening and step-growth polymerizations.^{104–108} However, Ameduri and co-workers¹⁰⁹ optimized a RAFT protocol that affords an alternating copolymer of *t*-butyl-2-trifluoromethacrylate and VA in a one-pot reaction, owing to the inability of MAF-TBA radical to self-propagate. This alternating copolymer was elongated with NIPAAm to yield an amphiphilic block copolymer. After hydrolysis of the ester groups, the final product was a

fluorinated double-hydrophilic block copolymer that is responsive to pH and temperature.¹¹⁰ The synthesis of well-defined multiblocks has been recently reviewed as an emerging field of research and RAFT polymerization is reported as successful in obtaining up to icosablock copolymers.¹¹¹ Besides conventional and switchable RAFT agents,⁸³ polymeric multi-trithiocarbonyl,¹¹² or xanthate¹¹³ RAFT agents (Figure 1) can be used to obtain multiblock copolymers. A polytrithiocarbonate RAFT agent was used by Vana and co-workers¹¹⁴ to obtain a multiblock copolymer of *N*-acryloyl-L-phenylalanine and acrylic acid (AA). This material was designed as silk-mimic and exhibited self-healing and enhanced mechanical properties. It would be interesting to assess its response to pH changes, thanks to the presence of AA repeats. Goto and co-workers¹¹⁵ obtained a CABC tetrablock, where A is hydrophobic, B is hydrophilic and C is thermally responsive. The polymerization was carried out with a dual organocatalyst as initiator (Figure 1) in which one initiator site is activated at a lower temperature than the other. This way, the AB blocks were first built sequentially at the lowest temperature, then the di-block was C-capped on both sides at the highest temperature. The polymers are self-assembling thanks to their amphiphilicity and the LCST induces the transition between a star- and a flowerlike morphology instead of precipitation or aggregate disruption. Therefore, temperature change can be used to release a hydrophobic cargo without releasing free polymer molecules. Furthermore, when the B block is a poly(glycerol monomethacrylate), temperature can be used to expose this segment and thus induce micelle reactivity toward boronic acids.

3 | CLICK AND OTHER REACTIONS FOR POST-POLYMERIZATION ASSEMBLY AND MODIFICATIONS

“Click” reactions are widely employed in multistep polymer syntheses,¹¹⁶ to graft polymers, including MSR ones,



SCHEME 5 PNIPAAm-g-PCL by successive RAFT process, thio-bromo click reaction and ROP. Reproduced with permission.⁹⁹ Copyright Elsevier 2018. RAFT, reversible addition-fragmentation chain-transfer

onto diverse platforms, or to obtain polymer-biomolecule conjugates. The subject is vast, so we limit ourselves to highlighting a few representative examples in the context of MSR polymers obtained by RDRP (Table 1). It should be noted that the question of a meaningful definition of “click chemistry” in connection with polymer synthesis and post-polymerization modifications deserves caution.¹³⁴ In polymer chemistry, the list of available “click” reactions is far longer than that in Table 1 and it comprises Diels-Alder, Alder-ene, thio-bromo, 1,2,4-triazoline-3,5-dione, amino-yne, and boronic acid-based chemistry.^{135–137} Our feeling, then, is that the potential of “click” reactions in the field of MSR polymers, granted by the orthogonality of these reactions, is not fully deployed to-date.

Huo et al.¹²⁹ set the stage for copper-catalyzed alkyne-azide cycloaddition (CuAAC) coupling of an *alkynyl*-PNIPAAm, and an *azido*-block copolymer of PEG and a nitrobenzene methacrylate through the synthesis of an ad hoc ATRP initiator (Figure 1). The resulting copolymer is an ABC miktoarm star structure that is responsive to temperature and light. Similarly, Poddar et al.¹³⁰ built CuAAC complementarity in two trithiocarbonate RAFT agents (Figure 1) to build two different blocks (a P[NIPAAm-co-OEGMA] and a novel pH-labile homopolymer) to be finally joined through the 1,2,3-triazole linkage, leaving the trithiocarbonate functions embedded in the product structure. Because one of the RAFT agents also contains a disulfide linkage, the resulting block copolymer is triple-responsive (temperature, pH, and redox). In Travas-Sejdic's group,¹³¹ POEGMA was grafted from a polythiophene core possessing side chains with ATRP initiating sites, azide groups and tri-ethylene glycol for water solubility (Figure 1). Propargyl functionalized poly(2-*n*-propyl-2-oxazoline) was then grafted to the core through CuAAC for thermal responsivity. CuAAC post-polymerization modification was performed by Xia et al.¹³³ to graft azide-functionalized diazo and tertiary amine pendent chains to the propargyl-equipped repeat units of a block copolymer obtained by PEG-initiated ROP. The resulting material was

light- and temperature sensitive. Tian et al.¹³² performed azidation of GMA repeat units on a PGA that had been obtained by RAFT polymerization, as part of a synthetic scheme aimed at linking porphyrins through CuAAC chemistry in a Janus macromolecular brush structure. Upon azidation of the glycidyl rings, free OH groups are revealed, so that each repeat unit could be converted to a RAFT CA through esterification and then sequentially polymerized with DPA to yield a pH and light-responsive Janus brush copolymer for enhanced chemotherapy. De Santis et al.¹³⁸ prepared a pH and thermosensitive linear L,D-octapeptide-PDMAEMA conjugate self-assembling into nanotubes through CuAAC coupling of the alkynyl peptide and the azido end-functionalized PDMAEMA.

Cao et al.¹¹⁷ used an ATRP initiator having a disulfide linkage and a hydroxyl group to implement two post-polymerization modifications (Figure 1). One uses the hydroxyl group for conjugation with RhodamineB, whereas the other is an intra- and interchain crosslinking through quaternization of part of the N,N-dimethylaminoethyl methacrylate (DMAEMA) repeat units with a photocleavable dibromide to form a nanogel. The system was designed for pH/temperature/light/redox-triggered release of dual cargoes, a hydrophilic and a hydrophobic one.

Quaternization is a straightforward strategy for post-polymerization modifications. The partial quaternization of the pendent amino groups of PDMAEMA with spiropyran chloride endows the modified polymer with photo-responsivity in addition to pH and temperature.¹¹⁸ The reader may find it interesting to compare the behavior of this system, which bears randomly distributed stable positive charges and multiple spiropyran pendent chains, with that of the neutral and intrinsically amphiphilic spiropyran-capped PDMAEMA-*b*-PMMA described in Section 2.³ Quaternization of random copolymers of DMAEMA and a diazobenzene methacrylate with various alkyl and benzyl halides, followed by anion metathesis with FeCl₃, is a straightforward strategy to obtain a polymer with a triple response to magnetism, pH and temperature.¹¹⁹

Sulfur chemistry, namely disulfide exchange and thiol-ene/yne reaction, is widely used in engineering polymeric structures.^{139–143} The fact that RAFT terminals can be viewed as latent thiols is a strong incentive toward using sulfur chemistry for post-polymerization modifications.¹⁴⁴ In a recent example of a multi-responsive polymer, a random polymethacrylate obtained by RAFT from OEGMA and a methacrylate with pyridyl disulfide pendent chain was subjected to post-polymerization modification by sulfide exchange with *o*-nitrobenzyl thiol to yield a photo- and reduction responsive linear random copolymer.¹²⁰ Zhao et al.¹²¹ included tandem amine-thiol-ene coupling in a complex synthetic scheme also

TABLE 1 Examples of “click” chemistry reported in this work

Chemistry for post-polymerization modifications	Reference
Quaternization of DMAEMA repeat units	117–119
Sulfur chemistry (disulfide exchange, thiol-ene, thiol-yne)	120,121
Perfluoroaryl chemistry (phenol ester displacement, perfluorobenzyl chemistry)	122–128
CuAAC	129–133

Abbreviations: CuAAC, copper-catalyzed alkyne-azide cycloaddition; DMAEMA, N,N-dimethylaminoethyl methacrylate.

comprising RAFT, ROP and ATRP to obtain a multicomponent miktoarm star copolymer that is responsive to pH, CO₂, O₂, temperature, and redox stimuli. Their synthetic strategy was that of “core first” polymerization followed by the coupling reaction.

Post-polymerization modifications through the chemistry of fluorinated polymers have been recently reviewed.¹²³ They are based on displacement of pentafluorophenol from ester pendent chains, or on *p*-substitution of perfluorobenzyl ester. O'Reilly's group has recently obtained redox-responsive polymeric micelles through postpolymerization modification of PEG-*b*-P(pentafluorophenyl methacrylate) with a reductant-sensitive diamine.¹²⁸ Hoven's group^{122,124} obtained pH- or redox-responsive polymeric nano-aggregates by nucleophilic displacement of poly(pentafluorophenyl acrylate) with 1-amino-2-propanol for hydrophilicity, sequentially followed by displacement of the residual pentafluorophenyl groups by the amino group of 1-(3-aminopropyl)imidazole for pH responsiveness. Roth, P.J. has demonstrated the versatility of the pentafluorobenzyl pendent chain in (meth)acrylic copolymers for post-polymerization modifications through substitution with thiols or azide.^{125,126} In a recent work, the azide group was present directly in the *p*-position of 1,2,4,5-tetrafluorobenzyl methacrylate for direct RAFT polymerization of this novel monomer. The authors then explored the post-polymerization chemistry (Scheme 6) that can be performed on both the free polymers and their nanoaggregates obtained in polymerization-induced self-assembly (PISA) conditions.¹²⁷ Although the subject of MSR materials is not tackled in this work, such a versatile system can easily be expected to have a significant impact on this field of research.

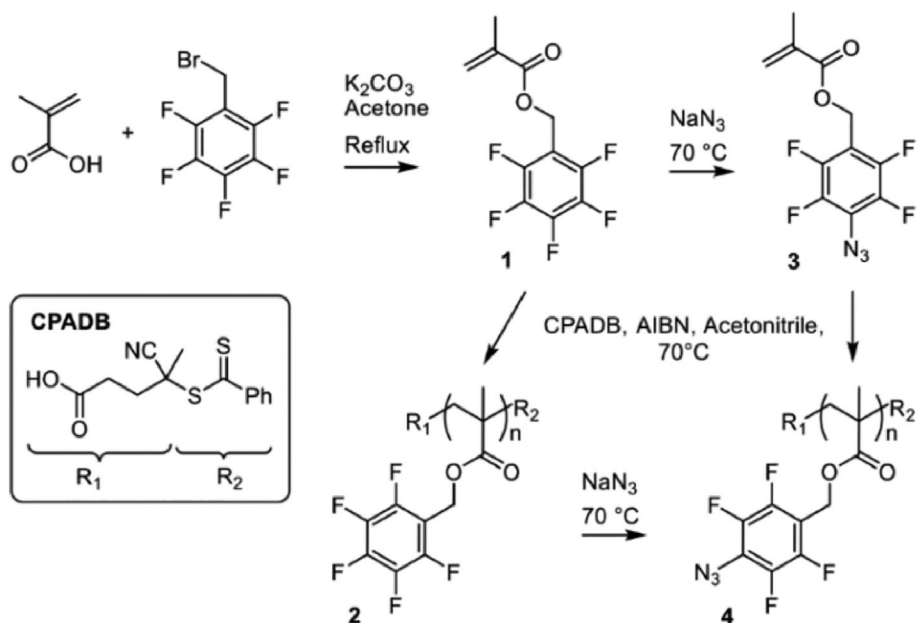
4 | RANDOM-, BLOCK-, AND RANDOM-BLOCK COPOLYMERS

Block copolymers are important constituents of MSR materials. In some instances, one block is responsible for thermal responsivity through miscibility gaps (cloud points, LCST, UCST), whereas the second block may be responsive to other stimuli.^{145–149} For instance, PEG-linked CAs provide the advantage of directly incorporating a hydrophilic and thermoresponsive block into the polymeric structure.^{59,94,147,149} Random copolymers offer the opportunity to modulate a property of interest in the resulting material. When a random copolymer constitutes one of the segments in a block copolymer, this modulation is reflected in the properties of the final product. Modulation of T_{CP} (LCST) in copolymers of OEGMAs with different lengths of the PEO chains has become a classic example since Lutz's investigation of the phase behavior of these copolymers.^{39,40,150,151} PNIPAAm is

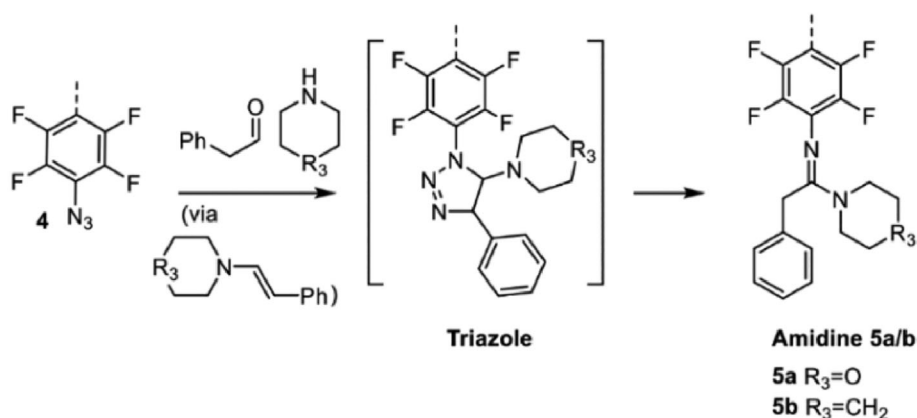
considered the “gold standard” due to the value of its LCST in water (32°C) and to the fact that this value is only slightly affected by other environmental parameters. Its T_{CP} increases with decreasing molecular weight for low-polydispersity polymers¹⁵² and can be easily tuned by copolymerization with hydrophilic or hydrophobic monomers, the former being useful to obtain thermosensitivity close to body temperature.^{153,154} PDMAEMA is another important example of LCST-polymer. Its cloud point can be adjusted from 25 to 80°C in pure water by changing molecular weight and pH.^{155–157} UCST-type copolymers are sparse in the scientific literature. They can be ionic, for example, when a sulfobetaine is present in the structure, or nonionic. In the latter case, intra-chain hydrogen bonds are disrupted upon temperature increase and interactions with solvent molecules take over in the solubilization process. In a recent communication,¹⁵⁸ a systematic investigation of the UCST of P(AAm-co-AN) copolymers is described, that may stimulate the design of multi-stimuli-responsive block copolymers with UCST behavior given by P(AAm-co-AN) blocks. PAAm may also be considered as a component in UCST-type copolymers, although it suffers from limitations such as amide hydrolysis at high temperature.¹⁵⁹ Amphiphilic block copolymers (AmBCs) are widely employed to form micellar nanoaggregates owing to segregation of solvophobic segments. The size and morphology of nanoaggregates depend on the interplay between polymer composition and architecture, relative volume fractions of blocks and the method used to induce an orderly assembly.¹⁶⁰ Furthermore, for a given composition, nanoaggregates formed by block copolymers may exhibit very different properties with respect to other distributions of the same repeat units along the polymeric chain. For, instance, block copolymers of acrylic acid and butyl acrylate yield kinetically frozen micelles, whereas a gradient-like distribution of the same monomers along the chain undergo reversible changes in size and morphology in response to changes in pH.¹⁶¹ Micellar or vesicular aggregates formed by stimuli-responsive block copolymers may respond to local environment changes by undergoing disruption, shrinkage or a switch to different morphologies. Smith et al.¹⁶² achieved higher order morphologies and electric field-responsive (electrophoretic) nano-objects by including a cationic monomer in the shell copolymer. Hydrophilic random copolymers exhibiting light-sensitive cloud points^{2,163} may be used as block constituents in more complex architectures. On the other hand, when a light-sensitive moiety is located in the hydrophobic micellar core, the nanoaggregate can be photo-stimulated to disassemble or modify its LCST. This is the case, for example, of photoacid generators, such as *o*-nitro benzylacrylate,^{8,146,164} or *N*-hydroxyphthalimide methacrylate,¹⁶⁵ which are

SCHEME 6 Synthesis and postpolymerization modifications on perfluorobenzyl methacrylate. Reproduced from ref. 127 with permission. Copyright American Chemical Society 2021

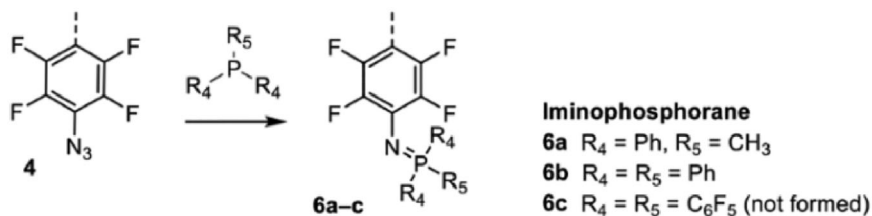
A. Synthesis of azide-functional polymer



B. Azide-aldehyde-amine multicomponent reaction



C. Azide-phosphine Staudinger Reaction



photocleaved to yield hydrophilic and pH-sensitive free acrylate groups. Coumarin moieties are incorporated in the design of functional polymers that can be used in electro-optical studies, photoreversible systems, chiral stationary phases for HPLC, fluorescent tags and fluorophores.¹⁶⁶ Block

copolymers containing a PMPMA sequence and a hydrophilic block can self-assemble in water to form micelles with a PMPMA core. Photolysis of the *p*-methoxyphenacyl methacrylate (MPMA) units can be used to induce the disruption of the micelles.^{167,168} In other instances, the response to a

stimulus rather affects local properties without necessarily entailing any dramatic effects on the morphology. Such can be the case when the environmental stimulus triggers a switch from amphiphilic to double-hydrophilic micelles. An example is provided by the dual-responsive nanoaggregates obtained by Kafetzi and Pispas¹⁵⁷ with di-block copolymers having a hydrophilic and thermoresponsive homopolymer (POEGMA) block and a P(DMAEMA-co-LMA) block. The latter is endowed with the permanently hydrophobic character of lauryl methacrylate (LMA) units and the hydrophobic/hydrophilic mixed character of DMAEMA segments, which is regulated by the pH and temperature. Furthermore, full quaternization of the amine groups yields a self-assembling polyelectrolyte exhibiting ionic strength-sensitive aggregation in addition to retaining temperature responsivity. The same authors also studied the effect of different types and extents of quaternization of DMAEMA units in POEGMA-*b*-PDMAEMA.¹⁴⁵

AmBCs are also useful in the preparation of adaptive and stimuli-responsive polymersomes. We refer the reader to previous reviews on this topic.^{169,170} Polymersomes are, in general, less permeable than liposomes, which may be a good feature for drug delivery systems, whereas it is definitely a drawback in their applications as nanoreactors. Response to environmental stimuli is one of the strategies to manipulate the permeability of polymersomes. However, by inspection of the scientific literature, it appears that the polymeric materials used for the construction of polymersomes mostly allow for single-trigger responses, whereas MSR random block copolymers are not as represented in polymersomes relative to other types of nano-objects.^{171,172} In a recent example, light-responsivity of polymersomes obtained from pH-responsive PEG-*b*-PDEAEMA was obtained through encapsulation of NIR-sensitive gold nanorods.¹⁷³

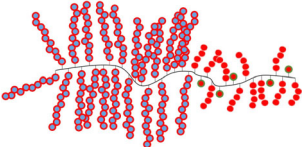
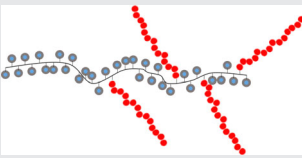
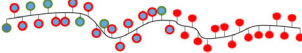
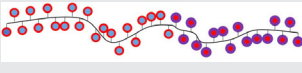
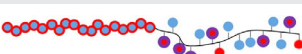
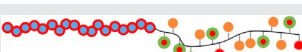



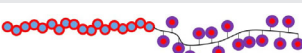

Gas-sensitive amphiphilic block copolymers may respond by outright aggregation disruption or through a modification in size and/or morphology of the aggregates.¹⁷⁴ CO₂ is the most widely investigated gas trigger.¹⁷⁵ However, O₂, NO, H₂S, and SO₂ have also been proposed. Theato's group has investigated O₂-interactive temperature-responsive copolymers comprising a PEG block and a hydrophobic random acrylamide terpolymer block with trifluoroethyl, benzylacrylamide, and sulfobetaine pendent chains.¹⁴⁷ The interaction between the fluorinated residues and O₂ grants a gas-triggered change in the inherent UCST of sulfobetaine acrylamide statistical copolymers. "Breathing" block copolymers have been recently obtained by combining CO₂-sensitive DMAEMA and O₂-interacting 2,2,2-trifluoroethyl methacrylate in a random terpolymer linked to a PEG block.¹⁴⁸ The response of this system to gas levels consists in changes in size and morphology of polymeric vesicles. In another recent example, a CO₂-responsive

polyacrylate is obtained by NMP, in which the hydrophilic block is simple PAA and the hydrophobic block is a random copolymer of AA and octadecyl acrylate (ODA).¹⁷⁶ In this case, the response is a transition from amorphous large compound micelles to semi-crystalline, bigger aggregates. Zhang et al.¹⁴⁹ combined CO₂ sensitivity with AIE fluorescence by using random copolymers of DMAEMA and (2-hydroxyethyl methacrylate tetraphenylethene ether) (TPEMA) as hydrophobic blocks coupled to a PEG block. CO₂ responsivity of DMAEMA induces the reversible transition from vesicles to micelles, whereas the effect on AIE is limited. It should be noted that, although the vast majority of investigations focus on nanoaggregation in water, complex thermally induced behavior at the nanoscale is also exhibited by block copolymers in other media. Armes et al.¹⁷⁷ obtained P(stearyl methacrylate)-*b*-PBnMA by RAFT-PISA, exhibiting temperature-induced vesicle-to-worm-to-sphere transition in mineral oil. The same research group demonstrated that the temperature for the vesicle-to-worm temperature transition can be modulated by randomly copolymerizing butyl methacrylate (BuMA) and benzyl methacrylate (BnMA) in the corresponding block.¹⁷⁸ PISA is an increasingly popular strategy that is being applied to virtually any RDRP technique. It exploits the spontaneous segregation of the growing solvophobic chain to directly obtain different nano-object morphologies, such as nanospheres, worms, and vesicles, through a careful choice of polymerization conditions and target degree of polymerization.^{179–181} PISA is advantageous over traditional self-assembly techniques in terms of time- and solvent-economy, allowing for easier scale-up and more sustainable protocols. In most of the recent examples of PISA-focused research, at least one of the copolymer blocks is a random copolymer that encompasses shell- or core-reactive functional groups.¹⁸² In a recent example, Nardi et al.¹⁸³ included suitable photoreactive groups in the solvophobic block to achieve stabilization of the obtained nanostructures via light-triggered nitrileimine carboxylic acid ligation. Sarkar et al.¹⁸⁴ exploited disulfide crosslinking to stabilize nanocapsules obtained by reversible complexation mediated polymerization in PISA conditions, thus allowing further chemical manipulation (hydrolysis and reduction) without disrupting the nanocapsule morphology. Shahrokhinia et al.¹⁸⁵ applied a photoATRP-PISA protocol using ppm levels of a copper catalyst at ambient temperature to obtain dual-responsive (pH and redox) crosslinkable nanoaggregates. (Table 2)

5 | STUDY-THROUGH-SYNTHESIS APPROACH IN MSR COPOLYMERS

RDRP techniques enable the polymer scientist to access copolymers that are rationally designed for physico-

TABLE 2 Schematic representation of cited block copolymers

Block architecture	Chemical and physical stimuli	Responsive units	Reference
	Temperature pH Ionic strength	DMAEMA, LMA, OEGMA DMAEMA, Quaternized DMAEMA, OEGMA	157 145
	Temperature O ₂ CO ₂	AA, ODA	176
	Temperature pH	NIPAAm, 5MPA, 4MBA	153
	Temperature pH Light	DMAEMA, NBA	8
	Temperature Light	PEG, NBA	146
	Temperature O ₂	PEG, ADPS, TFA	147
	Temperature O ₂ CO ₂	PEG, DMAEMA, FMA	148
	Temperature CO ₂ Light	DEAEMA, TPEMA	149
	Temperature Light	PEG, NBA	250
	Temperature non-covalent crosslinking	PEG, NIPAAm, UPy	94
	Temperature pH photocrosslinkable	PEG, NIPAAm, DEAEMA, BMA	172

Note: Color coding of repeat units: ● hydrophobic; ● hydrophilic; ● zwitterionic. Color coding of stimuli: ○ temperature; ○ light; ○ CO₂; ○ O₂; ○ pH. Abbreviations: AA, acrylic acid; ADPS, 3-([3-aminopropyl]dimethylammonio)propane-1-sulfonateacrylamide; BMA, 2-hydroxy-4-(methacryloyloxy) benzophenone; DMAEMA, N,N-dimethylaminoethyl methacrylate; FMA, 2,2,2-trifluoroethyl methacrylate; LMA, lauryl methacrylate; NBA, o-nitrobenzylacrylate; NIPAAm, N-isopropylacrylamide; ODA, octadecyl acrylate; OEGMA, oligo(ethylene glycol)methacrylate; TFA, 2,2,2-trifluoroethylacrylamide; TPEMA, (2-hydroxyethyl methacrylate tetraphenylethene ether)4-(1,2,2-triphenylvinyl)phenyl methacrylate; UPy, ureidopyrimidinone; 4MBA, 4-methacryloyloxy benzoic acid; 5MPA, 5-methacryloyloxy pentatonic acid.

chemical and biological studies. Kumbhakar et al.³⁹ focused on the dynamics of thermoresponsivity of random copolymers of MMA and POGMA. Stubbs et al.¹⁸⁶ were able to study systematically the dual pH and thermal responsivity of mPEG-*b*-PDMAEMA of different compositions and molecular weights. Radzevicius et al.¹⁸⁷ demonstrated that aggregation behavior and thermal responsivity of a pentablock containing PDMAEMA and PHEMA depend on the position of the blocks and content of HEMA units. Wright et al.¹⁸⁸ used RAFT to build a series of diblock copolymers with constant hydrophilic block made of PAA and variable hydrophobic components (ethyl or lauryl

acrylate or St). They carried out post-polymerization conjugation through amide bond with a thermolysin-labile peptide, then induced nanoaggregation through solvent switch. They studied, both experimentally and in silico, the molecular rearrangements underlying the equilibrium and nonequilibrium transitions occurring upon enzymatic cleavage of the peptide, finding core-dependent behavior ensuing the chemical modification of the corona.

Rahman et al.¹⁸⁹ synthesized random and block copolymers of OEGMA and bile acid methacrylic derivatives to explore the effect of hydrophobic interactions, charge density and monomers distribution on

aggregation induced by facial amphiphilicity-induced self-assembly (FAISA). The Authors also showed that the aggregates respond to temperature and ion screening.

Papadakis's group studied the temperature and salt-dependent “schizophrenic self-assembly” of block copolymers of PNIPMAM and a sulfobetaine methacrylate, respectively LCST- and UCST-type.¹⁹⁰ They endeavored to explore the predicted scenarios¹⁹¹ depicted in Figure 2 through a careful and systematic balance of polymer compositions.

Moghimi et al.¹⁹² combined synthesis, experiments and computer simulations to investigate self-assembly patterns of low-functionality telechelic star polymers (TSPs) in dilute solutions as a function of temperature and solvent quality, the main focus being the effect of the arm composition and length. Zhang et al.¹⁹³ compared the self-assembly and pH/oxidation responsivity of a linear and cyclic toothbrush copolymer.

In recent investigations, the in situ study of aggregation and morphological modifications is carried out by the incorporation of residues that exhibit AIE properties in the polymer structure.¹⁹⁴ AIEgens are molecules that are nonemissive in solution and become luminescent when their mobility is restricted. This phenomenon is the opposite of aggregation-induced Quenching. Peng et al.¹⁹⁵ suggested that the onset of AIE of (*Z*)- and (*E*)-TPE-OEG occurs even below the CMC in water, when the hydrophobic part of the molecules loosely interact with each other. This early onset allows the study of initial steps of self-assembly that cannot be detected by turbidimetry. The high sensitivity of AIEgens is exploited to study modifications in self-assembled states triggered by external stimuli. To this end, luminophore monomer TPMA was copolymerized by RAFT-PISA in the random sequence of a random-block copolymer and variation of its luminescence was correlated with real-time evolution of the morphology of aggregates during

polymerization progress and upon exposure to CO₂.¹⁹⁶ In a different example, the AIEgen was part of the RAFT CA, so that it was linked to the α -chain end of the polymers. Luminescence appears as a result of increased viscosity and restriction of intramolecular motion (RIM) so that polymerization progress can be monitored in situ.¹⁹⁷

An emerging field of interest for the controlled synthesis of copolymers is that of antimicrobial and antibiofilm macromolecular materials that are also able to deploy their properties on demand through response to physical or biological stimuli. A strong motivation for triggering the antimicrobial activity of polymers through external stimuli is to prevent the development of bacterial resistance to sub-lethal amounts of long-circulating macromolecules in the living system. Stimuli-responsive antimicrobial copolymers recently reviewed by Blackman et al.¹⁹⁸ include photodynamic polymer materials, materials that employ dynamic covalent chemistries or host-guest complexation, and materials with stimuli-responsive “on-demand” NO release. Judzewitsch et al.¹⁹⁹ prepared a library of multiblock all-polyacrylamide system by PET-RAFT, with different proportions and arrangements of hydrophilic, hydrophobic and cationic components and determined their activity against some bacteria. No direct involvement of responsivity to triggers is present in their work. However, this kind of investigation is essential to define the structural constraints, beyond amphiphilic balance, that should be taken into account in designing an effective antimicrobial multiblock that is also responsive to stimuli.

Another interesting family of thermoresponsive blocks that is amenable to a rich study-through-synthesis approach is provided by aminoacid-derived vinyl polymers. The RDRP synthesis of these polymers with sequence control is more convenient relative to solid-state synthesis of thermally responsive polypeptides. Higashi and Koga^{200,201} used a one-pot sequential

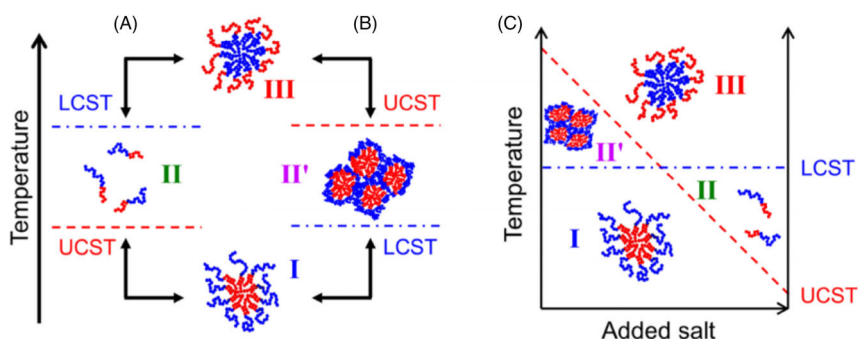


FIGURE 2 Possible thermoresponsive self-assembly of a diblock copolymer from a zwitterionic block exhibiting UCST behavior (red) and a nonionic block having LCST behavior (blue). (A) CPUCST < CPLCST, (B) CPUCST > CPLCST. (C) Schematic phase behavior for electrolyte-modulated “schizophrenic” self-assembly, uniting scenarios (A and B). Reproduced with permission.¹⁹⁰ Copyright American Chemical Society 2019. LCST, lower critical solution temperature; UCST, upper critical solution temperature

ultrafast RAFT technique to obtain several carefully designed sequences of two aminoacids of different hydrophilicity, that is, N-acryloyl-alanine-methyl ester, and N-acryloyl-glycine-methyl ester (Figure 3). Thereby, they were able to highlight how the order and length of the blocks affects thermoresponsivity in polyvinyls of this type. This is a rare example of an investigation where the number of sequences is variable, whereas the overall hydrophilic/hydrophobic balance is kept constant. A further recent example of copolymer synthesis with varied sequence and constant overall monomer composition is provided by the AA/BuA copolymers by Zhang et al.¹⁶¹ Interestingly, this series of pH-responsive copolymers self-assembled into different morphologies, depending on monomers distribution along the chain (Figure 3).

More frequently, the composition and sequential arrangement of different monomers are varied at the same time. Shieh et al.²⁰² compared the thermo-, pH, and CO₂ responsivity of P(NIPAAm-co-AA) copolymers with different ratios of the two monomers. One of the compositions was also obtained sequentially by RAFT as block copolymer and results were compared. Guo et al.⁵⁹

obtained statistical, gradient, and block copolymers from the same monomers at different cumulative compositions by adjusting the feed method (Figure 4).

6 | THE BASIC MONOMERS TOY BOX: PLENTY TO PLAY WITH

A great deal of research on MSR polymers is based on manipulating commercial monomers into specific combinations, architectures, and morphologies.⁹⁷ In a recent work, Skandalis and Pispas²⁰³ combined a limited number of simple components (DMAEMA, OEGMA, LMA, and a crosslinker) into miktoarm star or star-block architectures by arranging sequential polymerizations and crosslinking reaction in an “arms first” or “core first” sequence. Although their work does not deal with multiple responsivity, its fundamental logic should be taken into account toward obtaining diverse multi-stimuli-responsive structures through strategy rather than through complex synthons. In the recent examples herein, responses to external triggers and hydrophilic/hydrophobic balance are

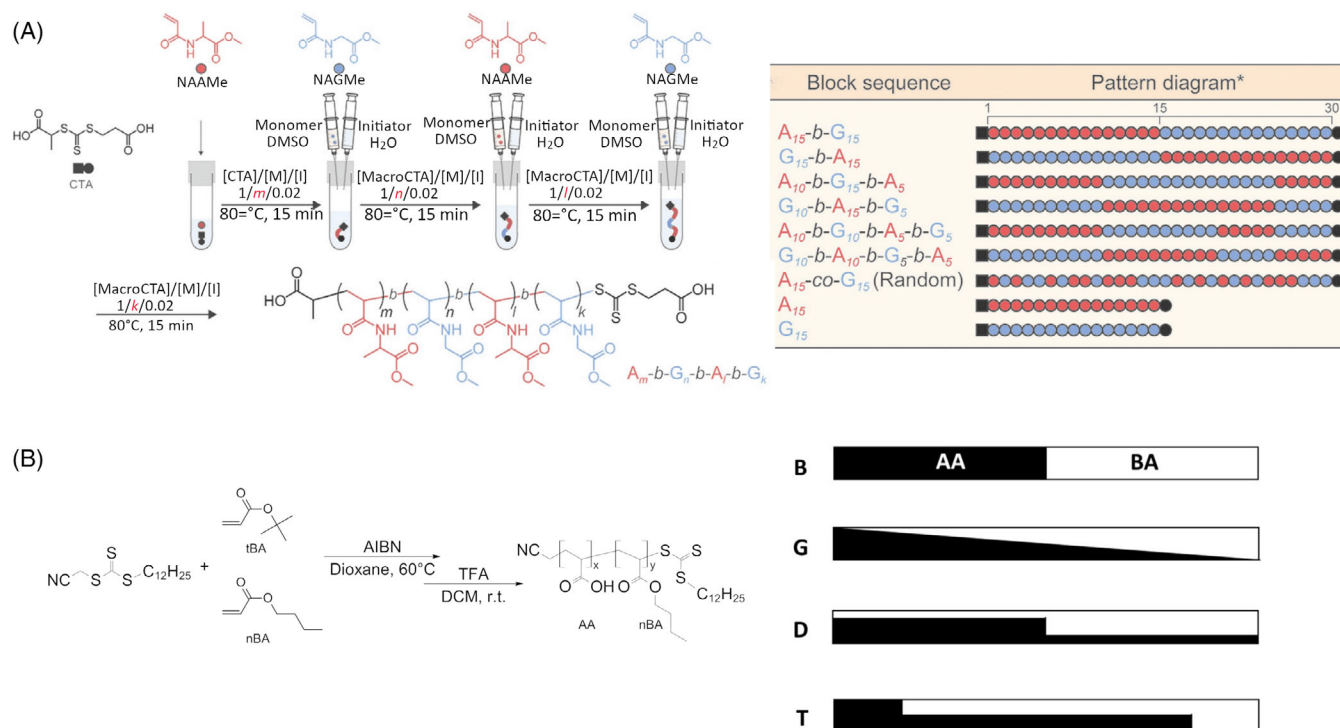


FIGURE 3 Synthesis of copolymers with same composition and different architectures through feed method. (a) Precise synthesis of sequence-controlled aminoacid-derived vinyl polymers; General synthetic scheme (left) and primary structure of the polymers (right). Reproduced with permission.²⁰⁰ Copyright John Wiley and Sons 2020. (b) Copolymers obtained by RAFT copolymerization of tBA/nBA = 1:1 (Mol/Mol) with different composition profiles, followed by deprotection: Block copolymers (B), linear gradient copolymers (G) and asymmetric diblock (D) and triblock (T) copolymers. Reproduced with permission.¹⁶¹ Copyright Wiley 2021. AA, acrylic acid; RAFT, reversible addition-fragmentation chain-transfer

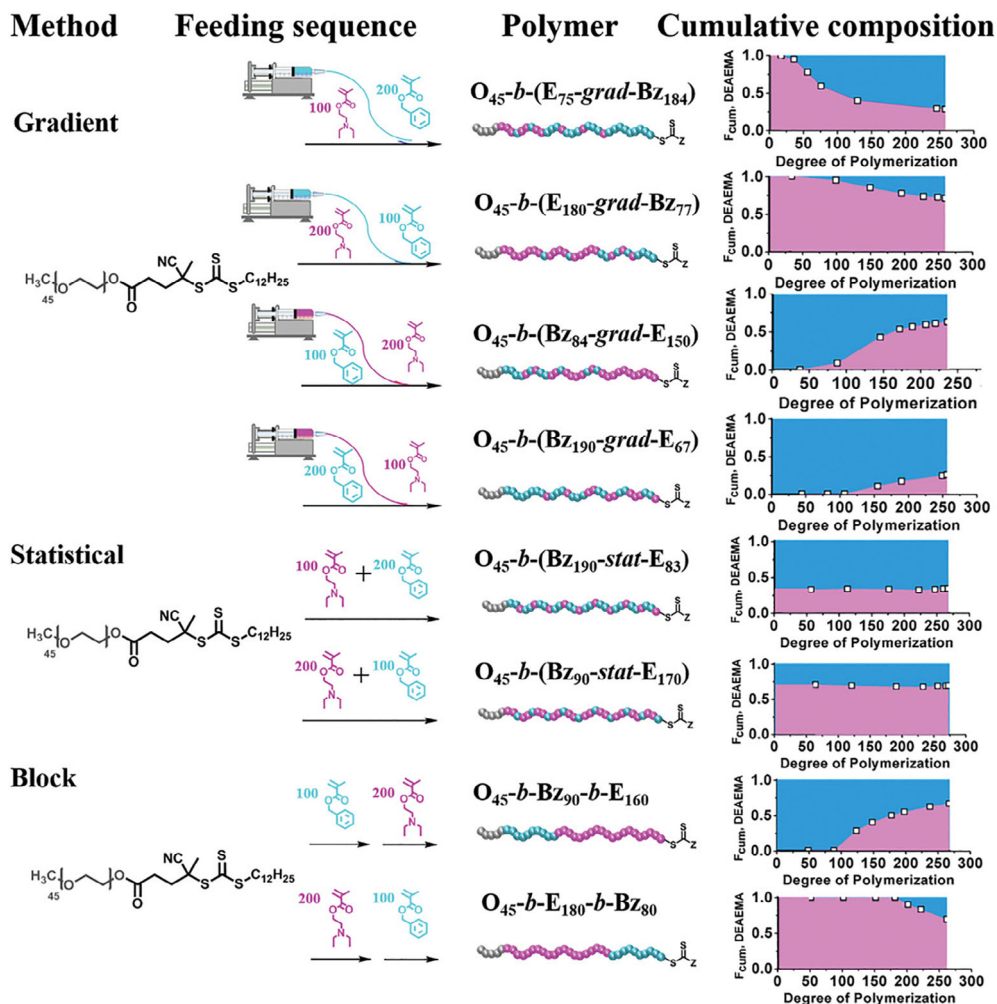


FIGURE 4 Adjusting copolymer composition and monomers sequence through feed method during a RAFT polymerization. Reproduced with permission.⁵⁹ Copyright Wiley 2021. RAFT, reversible addition-fragmentation chain-transfer

covered by materials that are solely based on “common” monomers, for example, OEGMA, HEMA, AA, AN, hydrophobic methacrylates, styryl monomers, NIPAAm, DMAEMA, PDEA, and so forth. PMMA-*b*-PDMAEMA with different DMAEMA block lengths exhibit dual and interrelated pH and thermal sensitivity and form aggregates of different morphologies.²⁰⁴ POEGMA-*b*-PBnMA-*b*-PDEA are self-assembling “breathing” terpolymers;²⁰⁵ miktoarm terpolymers *star*-(PEG-PSt-PDEA) forms interesting morphologies and is CO₂-responsive;²⁰⁶ POEGMA-*b*-PHPMA-*b*-PDMAEMA exhibits self-assembly and dual temperature/CO₂ responsivity.²⁰⁷ Harn et al.²⁰⁸ performed sequential ATRP polymerization on the 21 initiating sites established on β-cyclodextrin to obtain star-like triblock copolymers of 4VP, *t*BA and PMMA, PSt, or PEO as the third block. They, thus, established the experimental conditions for a good control of the sequential polymerization on the P4VP macroinitiator and to prevent cross-reaction between star-like units. Furthermore, they demonstrated the possibility to sequentially introduce diverse blocks on the cyclodextrin platform to achieve complex responsivity to triggers. Specifically, thermolysis of the *t*-butyl ester units

in the P4VP-*b*-P*t*BA star afforded a double-hydrophilic unimolecular micelle with a “biphasic” response to pH (Figure 5).²⁰⁸

Shin et al. obtained self-assembled giant polymer vesicles from double-hydrophilic diblock copolymers (PEO-*b*-PAA) that show significant disassembly in response to pH changes.²⁰⁹ Kafetzi and Pispas¹⁴⁵ obtained complex and tunable pH/temperature responses from straightforward random/block copolymers of conventional monomers. They first synthesized a simple double-hydrophilic di-block copolymer of DMAEMA and POEGMA, then they partially quaternized DMAEMA with C6 or C12 alkyl chains. One of the two blocks was thereby turned into a random copolymer with permanently charged and hydrophobic repeat units and free DMAEMA units granting pH-sensitivity. The result was a self-assembling, double-responsive system with tunable properties. UCST behavior is rarely observed under practically relevant conditions. However, relying on hydrogen bonding (HB-UCST) it has been possible to prepare MSR polymers based on the UCST copolymers P(AAm-*co*-AN).^{210,211}

Generally speaking, an apparently straightforward approach to multi-stimuli responsivity is to multiply the number of blocks. However, it should be noted that the phase behavior of multiblocks at the nanoscale exhibits a higher complexity with respect to diblocks and also depends on the exact sequence and composition of blocks.^{161,187,212,213}

7 | SPECIALLY DESIGNED MONOMERS FOR MSR COPOLYMERS

As an alternative to the creative assembling of readily available monomers to obtain copolymers endowed with multiple responsivity or to introducing specific functionalities by post-polymerization reactions, many research groups resort to the synthesis of monomers containing functional groups with specific tasks and then copolymerize them with readily available ones. In some cases, the novel monomer is responsive to more than one stimulus.^{2,214–221} This approach entails advantages and difficulties. The main advantage with respect to post-polymerization reactions is the control over the actual average number of functional groups per polymer chain. In fact, post-polymerization reactions may not be wholly quantitative and reproducible, leaving some uncertainty over non-reacted sites. The main concern is to achieve

good control on the polymerization reaction. In fact, the reactivity of a new monomer in a free radical copolymerization is not known a priori and it will influence the rate of the overall polymerization reaction and the sequence of incorporation in batch polymerizations. Other very important concerns are the purity of the synthesized monomer and the compatibility of the stimuli-responsive functional group with the polymerization conditions. Last but not least, the behavior of the response to stimuli by the copolymer cannot be fully extrapolated from that of the functional group embedded in the monomer, so that a great synthetic effort may be put into obtaining a material that, ultimately, behaves differently than expected or, worse, performs poorly. However, the ample possibilities that become accessible through the synthesis of “responsive monomers” make it worth to address the difficulties with the many weapons of RDRPs. Table 3 provides recent examples of specially synthesized monomers that have been (co)polymerized using the specified radical polymerization technique.

8 | TOWARD “GREENER” MSR POLYMERS

The need to eventually rid the production of synthetic polymers from petroleum-derived starting materials

FIGURE 5 (A) Size change of double hydrophilic star-like P4VP-*b*-PAA diblock copolymer at different pH values at 25°C, as measured by DLS. (B) Relation between average hydrodynamic diameter of P4VP-*b*-PAA diblock copolymer and pH value, summarized from DLS data in (A). (C) UV-vis transmittance of star-like P4VP-*b*-PAA diblock copolymers at 450 nm as a function of pH. The sample concentration is 1 mg/ml. (D) Proposed morphological changes of star-like P4VP-*b*-PAA under various pH environments. Reproduced with permission.²⁰⁸ Copyright American Chemical Society 2020

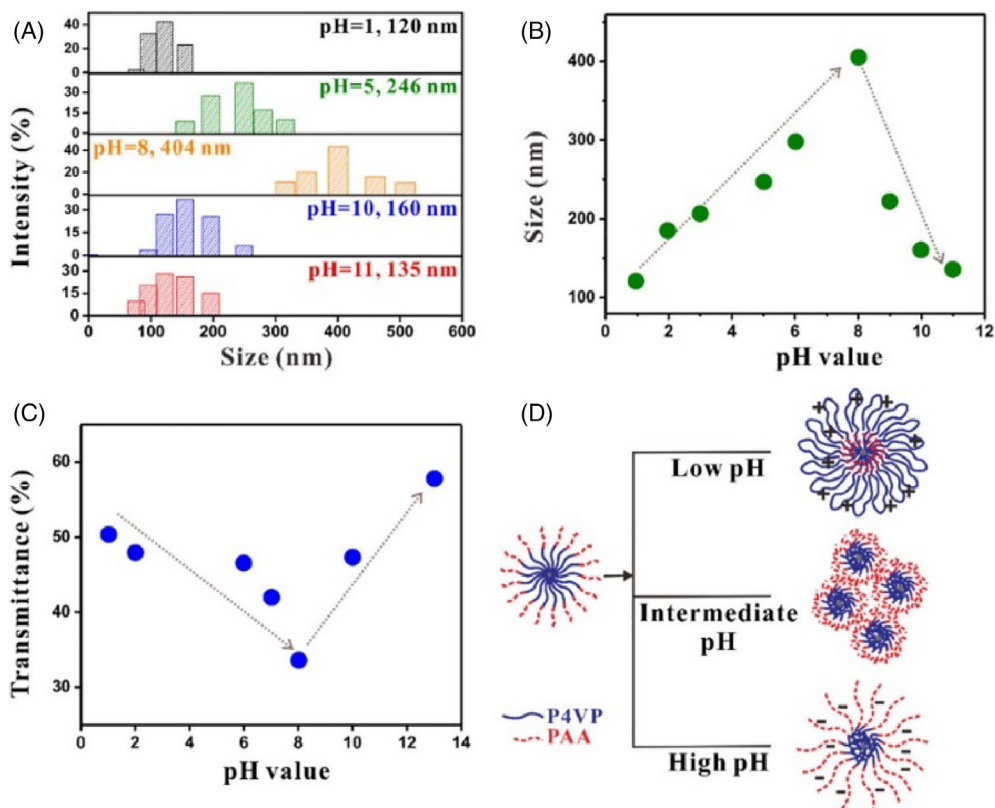


TABLE 3 Examples of functional monomers for RDRP synthesis of (multi)stimuli-responsive polymers

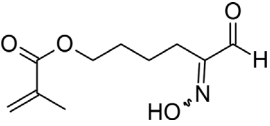
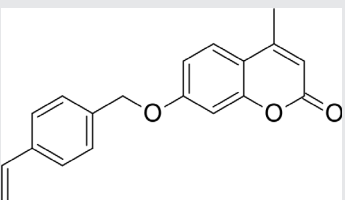
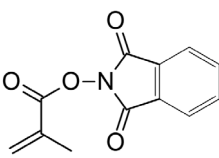
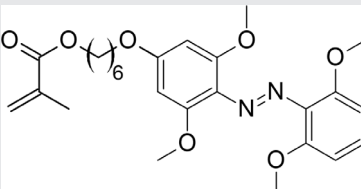
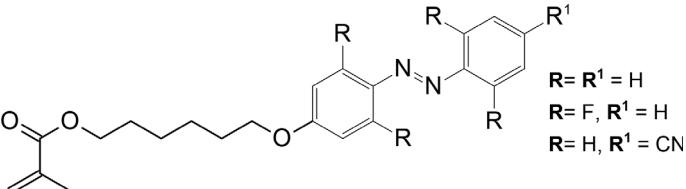
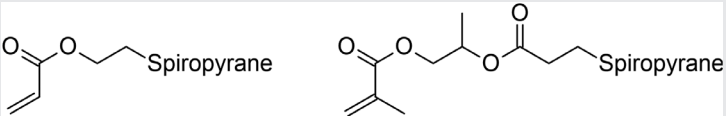
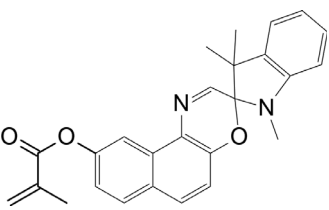
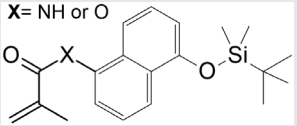
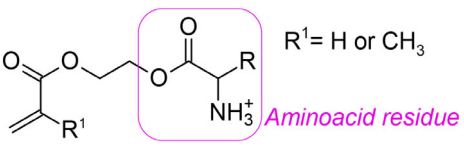
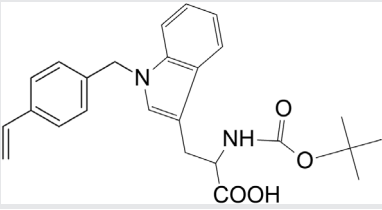
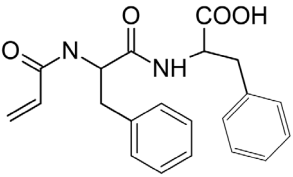
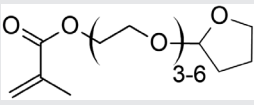
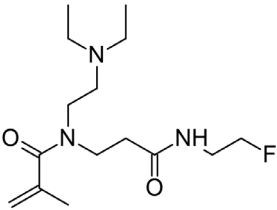
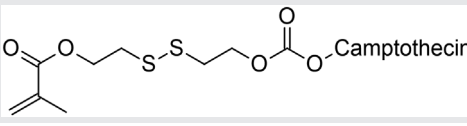
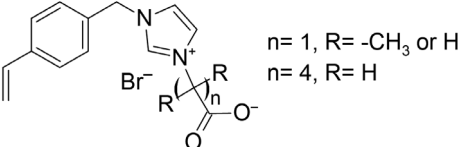
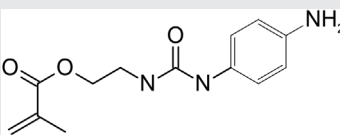
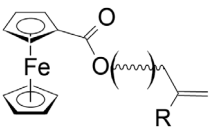
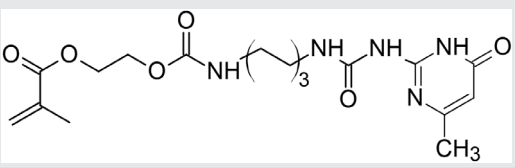
Monomer	RDRP technique	Stimuli and other features	Reference
	RAFT	pH (hydrophobic to hydrophilic with increasing pH) UV light: two orthogonal isomerizations ($\lambda = 278$ and 365 nm)	2,214
	RAFT FRP	pH UV light ($\lambda = 254$ and 365 nm)	215,216
	FRP	UV light	165
	RAFT	Visible light	222
 $R = R^1 = H$ $R = F, R^1 = H$ $R = H, R^1 = CN$	ATRP	Light (UV or vis) Reductant	217
	RAFT	UV light ($\lambda = 365$ nm)	223
	RAFT	UV light ($\lambda = 365$ nm)	224
 X = NH or O	RAFT	UV light ($\lambda = 365$ nm)	225
 R ¹ = H or CH ₃ Aminoacid residue	RAFT	pH	226,227

TABLE 3 (Continued)

Monomer	RDRP technique	Stimuli and other features	Reference
	RAFT	Temperature, pH	218
	RAFT	pH	228
	RAFT	Temperature pH	221
	RAFT	O ₂ , CO ₂ Ttemperature	229
	RAFT-PISA	Reduction-triggered release	230
	RAFT	Anion pH Temperature	219
	Ru-catalyzed RP	pH Transamination Metals	220
	ATRP, RAFT	Redox	231–234
	RAFT	Self-complementary quadruple hydrogen bonding	94

Abbreviations: ATRP, atom transfer radical polymerization; PISA, polymerization-induced self-assembly; RAFT, reversible addition-fragmentation chain-transfer.

stimulates research to find and manipulate monomers from renewable sources. To our knowledge, whereas self-assembling and single-stimulus responsive bio-based polymers are numerous, MSR examples are scarce.^{235–237} The use of monomers from renewable sources as (partial) substitutes for petroleum-derived vinyl monomers is gradually attracting attention and this is bound to infiltrate the field of MSR copolymers. Maric's group has been active in using NMP for the copolymerization of terpenes (myrcene, farnesene) with methacrylates and styrenes, achieving good control and defined sequences (from random to block and gradient).²³⁸ γ -Butyrolactones with exocyclic double bonds can be considered as methacrylates analogs from renewable sources and their potential in synthetic polymers has been recently reviewed.²³⁹ Itaconic acid derivatives are obtained from carbohydrates fermentation by fungi. Even though they react sluggishly in FRP conditions, ATRP and RAFT have been successful at obtaining copolymers containing itaconic acid derivatives.²⁴ For example, pH- and temperature-sensitive random copolymers of NIPAAm and itaconamic acid were obtained by RAFT in Rwei's group.^{240,241} RAFT polymerization of vinyl monomers derived from renewable sources, for example aminoacids, carbohydrates, lignin, plant oils, has been recently reviewed.²⁴²

Further progress in “greener” RDRPs should also tackle sustainability and scalability of production of MSR polymers. In fact, the source of raw materials is not the only concern in eco-friendly materials synthesis, since sustainability of transformation processes should always be kept in sight when moving away from oil-based thinking.⁴⁴ It is desirable, in RDRPs and stimuli-responsive polymers research, to avoid heavy metal catalysts, resort to greener and/or aqueous solvents and pursue solvent-economy, lower temperatures and light as a means of reaction activation and control. All of these features should be applicable to large-scale production. PISA achieves solvent-economy by definition, RDRPs can be carried out in alcoholic and aqueous solvents, and photopolymerization²⁴³ allows lower reaction temperatures. In this context, photoinitiation and photomodulation of RAFT is extensively researched.^{158,159,244–248} Another issue to be addressed is deoxygenation of the reaction mixture, which is normally achieved through inert atmosphere or freeze-pump-thaw cycles. Recent work by several research groups report enzymatic deoxygenation allowing open-air RDRPs. Tan's group²⁴⁹ provide an all-inclusive example with their visible light-RAFT-PISA synthesis of a CO₂-responsive copolymer in water in open vessels with glucose oxidase deoxygenation. Bibliography in Tan's work is a good source for insight into enzymatic

deoxygenation of polymerization media, which is beyond the scope of this review.

In short, preconditions for greener MSR polymers are already there and substantial progress in this direction is expected in the immediate future.

9 | SUMMARY AND OUTLOOK

MSR polymers are obtained through controlled polymerization of building blocks that respond to specific triggers. The modifications elicited by external stimuli should not be viewed as resulting simply from the parallel, albeit cooperative, response of each type of building block, as the sequence and architecture of a macromolecule are fundamental in determining the physico-chemical response. In this context, RDRPs have been extremely successful at providing the means to achieve control over the composition of copolymers, their molecular weight dispersion, the distribution of monomers along the chain, and the construction of desired architectures. In fact, RDRPs, also in combination with “click” reactions and other types of polymerization, provide a great variety of “studs” that allow the controlled connection of diverse building blocks and functionalities. As a result, research on the synthesis of MSR polymers has developed into an extremely creative and ingenious construction game that involves not only the assembly of building blocks with compatible connections, but also the design of new blocks and new connections. A further challenge is to play this game within “green” rules, that is, by resorting to renewable starting materials and applying the principles of green chemistry to RDRPs. In most cases, creativity in MSR polymers synthesis results in fine tuning of trigger-response combinations, temperature and pH being the most frequently explored, whereas new behaviors emerge in specific studies, as in the complex phase diagrams of schizophrenic copolymers or in the peculiar morphologies obtained through PISA of suitably designed polymers. As more and more structure-response relationship data become available and the relevance of sequence and architecture becomes increasingly clear, the main challenge in designing a material for a specific stimuli-dependent application, or developing an existing one, may be that of extrapolating relevant information from the scientific literature. On the other hand, there is plenty of room for increasing the complexity of response to environmental stimuli and for that the polymer chemist can rely largely on RDRPs.

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