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Perspective

Resolving the incompatibility between SET-LRP and non-disproportionating solvents

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Cu(0)-catalyzed single-electron transfer-living radical polymerization (SET-LRP) has shown great potential for applications in which well-defined chain end-functionalized polymers are demanded as final products or as intermediates. However, the use of polar reaction media favoring the disproportionation of Cu(I)X species into Cu(0) and Cu(II)X_2 was considered a limiting factor specially in the synthesis of complex hydrophobic polymers with functional chain ends. "Self-generated" biphasic systems, in which the polymer phase-separates from the homogeneous reaction mixture above a certain molecular weight, together with fundamental studies on the role of solvent, including catalytic solvent effect, and methodological developments such us the "mixed-ligand" concept served as inspiration, although sometimes in an unknown way, to solve this problem. Today, SET-LRP of both acrylic and methacrylic vinyl monomers is already feasible in both polar and non-polar non-disproportionating solvents using their corresponding bi(multi)phasic "programmed" mixtures with water. Under these conditions, SET-LRP is an interfacial process in which disproportionation and activation events occur independently in the aqueous and organic compartments, and the "self-controlled" reversible deactivation takes place at the interface. Consequently, this design entirely defeats the limiting requirement to exclusively use disproportionating solvents. After a brief discussion of the historical evolution of the field of LRP, starting with the landmark work of Otsu from 1950th, this feature article will describe the elaboration of "programmed" bi(multi)phasic SET-LRP systems starting from initial inspiration to development in laboratory large-scale experiments.

1 Introduction

Many years after the concept of living radical polymerization (LRP) was conceived under the name INIFERTER (INItiator transFER TERminator) by Otsu [1], great success on the development of complex functional macromolecular systems was

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achieved by this synthetic methodology. In 1950th Professor Takayuki Otsu of Osaka City University pioneered the field of LRP by formulating the landmark concept named INIFERTER that contains the steps involved in most of the successful contemporary LRP methodologies. We strongly recommend that all practitioners of this field, juniors, seniors, as well as those interested to join LRP as a new topic of research, read the highlight invited by one of us (VP) when he was editing the Journal of Polymer Science: Part A: Polymer Chemistry. This benchmark publication will help everybody understand all current LRP developments and provide inspiration for new ideas in this field [1]. Early examples of halogen atom transfer, of one electron transfer, of degenerative chain transfer of numerous examples of reversible deactivation, of metal catalyzed activation-deactivation that paved the way to the current ATRP and other metal-catalyzed LRPs [2–6] including SET-LRP and SET-DTLRP [7–10] as well as various degenerative LRPs [11,12], and RAFT [13,14] were all elaborated and blended in the word INIFERTER by Otsu. The nitroxide [15], the disproportionating solvent part of SET-LRP [9], TERminator Multifunctional INItiator, TERMINI concept [16–20], and the catalytic part of the catalytic chain transfer [21–23] were the only concepts not elaborated by Otsu in his INIFERTER landmark work concept. While we recommend all publications from the highlight of Otsu to be consulted, we specially stress the following forgotten paper to be inspected by everybody working or interested in this field [24].

Before starting the discussion of the topic from the title of this perspective, we would like to mention few words on different nomenclatures employed during the discussion of this topic. Synthetic polymers represent the last chapter from most textbooks of undergraduate organic chemistry. Therefore, polymer chemistry is a subfield of organic chemistry as it was pioneered by Staudinger and Carothers [25]. In the field of organic chemistry there are historical or common names and several generations of IUPAC or systematic names. We must state that IUPAC nomenclature, although recommended, is not frequently used. We would like to mention a classic example when the IUPAC name of a dendrimer takes about one page of published manuscript and the name does not convey the structure of the dendrimer to the reader [26]. This problem was discussed in more details in a book [27]. When absolutely required, Chemical Abstracts provides the IUPAC name for any organic molecule or macromolecule, at no cost. One of us (VP), was long ago a member of the IUPAC nomenclature committee but he resigned after a series of inefficient meetings. Therefore, while sometimes is helpful, many times the IUPAC nomenclature does not help, especially since there are several editions/versions and their number continues to increase. Briefly, our laboratories, in respect for its inventor [28], prefers to use the name living radical polymerization. The definition of living was relaxed by the inventor in an elegant highlight describing how he discovered the field of living anionic polymerization by single electron transfer [29]. On pages xiii bottom of right column and xiv, top of left column of reference [29] Michael Szwarc, the inventor of the concept living, states. "Anionic polymerization is not unique in its ability to produce living polymers. *Let us reconsider the definition of living polymers. "Ideally, living polymers propagate while their termination or chain transfer are rigorously prevented*." This is an ideal concept, like the ideal gas or ideal solution. We strive to achieve this goal, but it will never be reached. Nothing lives forever. Even the stars in heaven or elementary particles eventually die. In fact, a very slow termination of the anionic polymerization of living polystyryl, due to the formation of sodium hydride, was reported as early in 1962. *Hence, the following provides a more plausible definition of living polymers. "These are the polymers that retain their ability to propagate for a long time and grow to a desired maximum size while their degree of termination or chain transfer is still negligible*." Such behavior has now been observed not only in anionic polymerization, but in many other polymerization systems based on cationic, metathesis, and radical reactions as well." After the submission of this paper Michael Szwarc called my office and insisted that this definition should not be changed at the recommendation of reviewers. Therefore, in respect for these two great scientists, Otsu and Szwarc, I see no reason to add anything to the historical name of living radical polymerization, even on behalf of IUPAC [30]. Most probably, the IUPAC Committee on Nomenclature was not aware of the revised version of the definition of living polymerization by its inventor Michael Szwarc and of the definition of Otsu and therefore, provided a "new definition" that relies on mechanism as Otsu INIFERTER name does rather than on the life-time of the propagating growing species as living polymerization definition outlines. The positive recommendation of the IUPA was to discourage the use of the name "*controlled*" which created a lot of confusion in the field since many new entry practitioners did not know the difference between living and controlled. Changing the name of an already classic organic reaction does not bring a new reaction but instead, produces a lot of confusion between its practitioners, especially when they are junior or are interested to enter the field. Also, we consider that name or historical names of various reactions should not be pushed by senior practitioners to be changed since mechanisms are debated for decades and even centuries and debated mechanisms should not be used to change the historical name of a certain reaction or of a name reaction. What we recommend instead is that senior scientists encourage all other practitioners to pursue perfection by working hard and invent new ways to rigorously decrease or even prevent termination and chain transfer reactions up to the limit of detection by the analytical methods available at a certain time. This will be one of the goals of this perspective.

Single electron transfer living radical polymerization (SET-LRP), an outer-sphere single electron transfer reaction mediated by Cu(0) which is a heterogeneous process rather than a homogeneous inner-sphere Cu(I)X reaction, is extremely attractive when fast reaction rates and outstanding control over end-group functionality are demanded at room temperature under conditions that tolerate oxygen from air [7,9,10,31–34]. Although first reported in 2002 [7], the origins of SET-LRP trace back to mid 1980s, with some fundamental studies on the application of metal-catalyzed SET-reactions to radical step condensation and living radical polymerization [6,29,35–43]. A perspective article from our laboratories disclosed most relevant aspects of the SET-LRP mechanism and technique and how it evolved from those pioneering studies [32]. Relevant for the

discussion presented here is the fact that the mechanistic pathway proposed for SET-LRP is sustained by the self-regulated generation of an extremely reactive Cu(0) activator and a Cu(II)X_2/ligand deactivator *via* the solvent-ligand mediated disproportionation of Cu(I)X species, which are produced after activation of dormant species (R-X) [9,10,31,33]. Whereas disproportionation of cuprous ions is near quantitative in water (equilibrium constant for disproportionation, $K_{disp} = 0.89 \times 10^6$-$5.8 \times 10^7$) [44,45], it is much more subtle in most of polar organic solvents [46]. However, this special type of SET reaction is dramatically enhanced by the presence of tris(2-dimethylaminoethyl)amine (Me_6-TREN), tris(2-aminoethyl)amine (TREN), branched poly(ethylenimine) (PEI), or by some of their mixtures known as the mixed-ligand concept [47,48], because these N-ligands destabilize Cu(I)X *via* preferentially binding to Cu(II)X_2 [46,49,50]. For instance, K_{dis} of the Cu(I)Br/Me_6-TREN complex in a polar solvent such as DMSO can be 1-3 orders of magnitude higher than that determined in the absence of this ligand [49]. Conversely, Cu(I)X species are insoluble and when soluble are stable in both non-polar and polar Cu(I)-stabilizing solvents such as acetonitrile (MeCN) [51], and do not disproportionate even in the presence of such ligands [46,49]. Disproportionation was previously demonstrated to be essential for the discovery of metal-catalyzed SET-degenerative transfer living radical polymerization (SET-DTLRP) [7,8], which is still the best method to conduct the LRP of the challenging vinyl chloride (VC) monomer [52]. Similarly, the livingness of SET-LRP is also inherently at the expense of proper reaction conditions favoring disproportionation. The catalytic effect of DMSO that stabilizes Cu(0) atoms and their aggregated nanoparticles obtained during disproportionation [53] must also be taken into account since it provides highly active catalytic Cu(0) species that overcome the lower extent of disproportionation through a higher rate constant of activation. One aspect that we must permanently have in mind when reading this paper and thinking about SET-LRP and ATRP is that the first process is heterogeneous while the second is homogeneous [10,31–33]. The activity of Cu(0) species used at the beginning of SET-LRP is much lower than of the Cu(0) generated by disproportionation during the polymerization. At the same time the activity of Cu(I)X and Cu(II)X_2 species is unchanged throughout the polymerization process with the condition that they are soluble in the reaction mixture. Cu(0) species generated during disproportionation are atomic species with extremely high but unknown activity. Therefore, it is not the extent of disproportionation but the extent of disproportionation combined with the ability of the solvent or of the reaction mixture to stabilize Cu(0) atomic species, that otherwise aggregate and form Cu(0) nanoparticles and crystals with specific activity for each crystal site, that determines the overall activity of the Cu(0) catalytic species. Different Cu(0) particle size activate with different rate constants and therefore, both the concentration and the activity of Cu(0) species determine the overall activity of the Cu(0) catalytic species. Since SET-LRP is a heterogeneous process the polymer and initiator must be first adsorbed on the surface of the Cu(0) species before activation can occur and while adsorbed, the reactivity of radicals towards bimolecular termination decreases dramatically [10,31–33]. None of these events occur during the ATRP homogeneous process. This perspective article aims to highlight the importance of this redox reaction in the practice of SET-LRP and disclose recently elaborated methodologies to resolve the incompatibility between this synthetic methodology and non-disproportionating solvents.

2 Disproportionation as a crucial step to protect SET-LRP livingness

2.1 DMSO and water are top solvents to practice SET-LRP

Perfect polymer chain end functionality is crucial for the synthesis of well-defined polymers with complex topologies and architectures. Nowadays, Cu(0)-catalyzed SET-LRP in disproportionating media state including in water [54–57], DMSO [58–61], alcohols [60,61] and other polar solvents [62,63,64] or mixtures of solvents [65,66] offers exciting opportunities in the current and ongoing applications of polymeric materials. Under these conditions, the self-regulated regeneration of the atomic and extremely reactive Cu(0) activator [67] and Cu(II)X_2/N-ligands deactivator *via* disproportionation eliminates the need for bimolecular termination to accumulate Cu(II)X_2 *via* the persistent radical effect [68]. Hence, the proper selection of the solvent component is of outmost importance because its role goes further than merely dissolving monomer and polymer because is responsible to ensure the high chain end fidelity [9,10,31–33]. In this context, the solvent and monomer scope of this appealing technique was supposed to be limited to polar disproportionating solvents and relatively polar polymers due to solubility issues not only for monomer and polymer but also for Cu(I)X and Cu(II)X_2 species.

Solvent effects were rigorously investigated by our laboratories and others using heterogeneous Cu(0) powder of different particle sizes and both activated and non-activated Cu(0) wire [46,49,69–75]. Experimental results systematically supported the statement that DMSO is the best organic solvent to conduct SET-LRP in homogeneous state because it provides fast polymerization rates, good solubility for Cu(I)X and Cu(II)X_2 without compromising control over molecular weight, molecular weight distribution and polymer chain ends [46,49,69–72,76]. Recently it has been shown that DMSO overcomes a low equilibrium constant of disproportionation by its catalytic effect derived from its extraordinary ability to stabilize highly active Cu(0) nanoparticles, a feature that no other known solvent has [53]. These appealing features are related to the high polarity of DMSO, which encourages extensive disproportionation of the Cu(I)Br/N-ligand or mixed-ligand complexes [47,48], and the unexpected ability of this solvent to stabilize the Cu(0) nanoparticles activating species [49,77–79], generated *via* disproportionation (see Fig. 1). The complex dynamics of Cu(0) formation, nucleation and growth on the existing Cu(0) surface (i.e. Cu(0) wire) and activation of dormant species finally determines catalyst consumption during polymerization [80].

Representative examples of the potential of this solvent when combined with Me_6-TREN or Me_6-TREN /TREN mixed-ligand in Cu(0)-catalyzed SET-LRP is the preparation of ultrahigh molar mass polymers [81], block copolymers [82,83], dendritic macromolecules [16–20,84,85], and perfectly telechelic polymers [86–89], based on all acrylate monomers. Outstanding levels of chain end functionality even enabled recently the

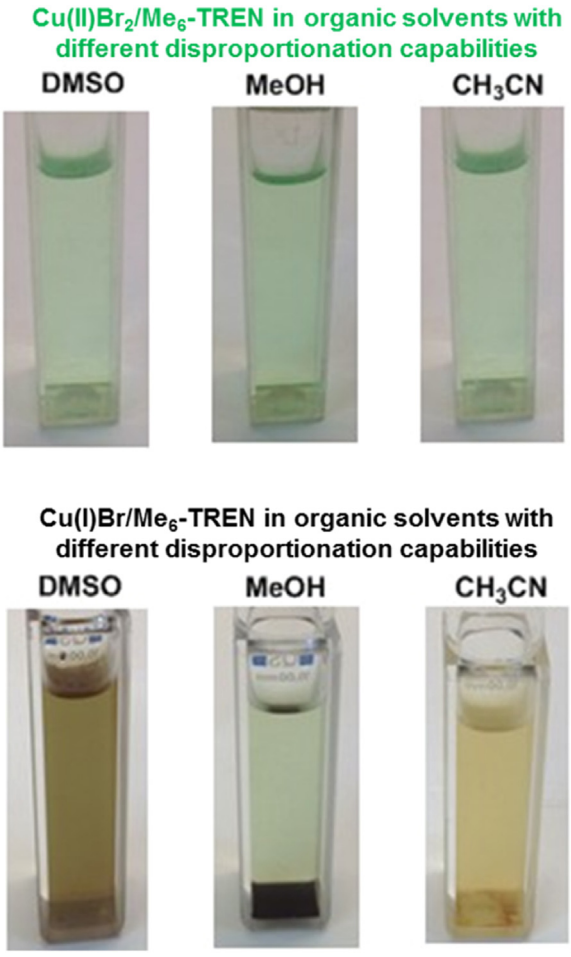

Fig. 1

Visual observation of the disproportionation of Cu(I)Br in DMSO, MeOH, and MeCN in the presence of Me_6-TREN after 60 min (lower images). Conditions: [Cu(I)Br] = 13 mM, solvent = 2.5 mL, $[Cu(I)Br]_0/[Me_6\text{-TREN}]_0$ = 1/0.5. Controls of $Cu(II)Br_2$ dissolved in the same solvent are also shown (upper images). Conditions: $[Cu(II)Br_2]$ = 6.5 mM, solvent = 2.5 mL, $[Cu(II)Br_2]_0/[Me_6\text{-TREN}]_0$ = 1/1. Stabilization of Cu(0) nanoparticles are observed in the DMSO/Cu(I)Br/Me_6-TREN experiment. Adapted with permission [134]. Copyright 2017, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

preparation of multi-block copolymers from telechelic α,ω-dibromo homopolymers *via* a step-growth thio-bromo "click" polymerization using dithiols as coupling agent [60,85,90]. Methacrylate monomers could also be polymerized by SET-LRP in DMSO [7,91,92], but avoiding the use of sulfonyl halide-type initiators [6,35–43], because they undergo side reactions with this solvent [93]. Cu(0) wire-catalyzed SET-LRP was also successfully adapted to continuous-flow operation, which is a fundamental step for the preparation of large quantities of product in commercial applications [94–100].

Similarly, SET-LRP mediated by TREN and Me_6-TREN/TREN mixed-ligand in DMSO also retained all the LRP characteristics because this N-ligand also mediates the disproportionation of Cu(I)X/N-ligand complexes in polar media [46,101]. In fact, the use of TREN in combination with DMSO solvent was

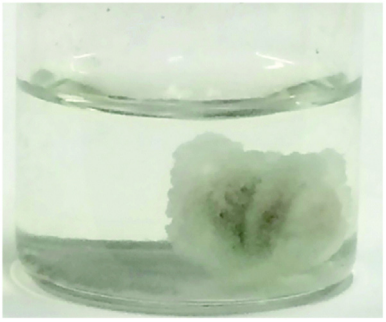

Fig. 2

Insoluble polymer gel generated during Cu(0) wire-catalyzed SET-LRP of HEA in water at 25 °C. Reproduced with permission [117]. Copyright 2015, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fundamental to eliminate the DT component of SET-DTLRP and perform SET-LRP of VC using bromo-containing initiators such as bromoform [9,102,103,104]. Note that this is the only method available to synthesize poly(vinyl chloride) (PVC) with intact gem-chlorobromo chain ends, and therefore, becomes attractive for the construction of complex PVC-based architectures [105–110].

Cu(0) wire-catalyzed SET-LRP in aqueous media also allowed the synthesis of well-defined hydrophilic homopolymers from biorelevant water-soluble monomers such as 2-hydroxyethyl acrylate (HEA) [65,111,112,113], oligo(ethylene oxide) methyl ether acrylate (OEOMEA) [114], oligo(ethylene oxide) methyl ether methacrylate [115], 2-aminoethyl methacrylamide hydrochloride [65], and N-(2-hydroxypropyl) methacrylamide [116]. Interestingly, the polymer gel formation on the Cu(0) wire surface observed during some of these experiments supports the heterogeneous nature of the Cu(0)-mediated SET activation process proposed for SET-LRP (Fig. 2) [111,112,117]. *N*-Isopropyl acrylamide (NIPAM), acrylamide and zwitterionic carboxybetaines could also be grafted from hemicelluloses in aqueous media using Cu(0) wire catalyst to prepare hybrid copolymers showing thermoresponsive properties [118] and self-assembled nanoparticules [119]. Importantly, it was demonstrated that oligo(ethylene oxide)-derived monomers and initiators might form micellar supramolecular structures in water, thus resulting in long induction periods at the beginning of the Cu(0)-catalyzed SET-LRP due to physical inaccessibility between catalyst and hydrophobic reactive centers of monomer and initiator [115].

The quantitative disproportionation of Cu(I)Br in water and water-rich binary mixtures of solvents also inspired the development of an original SET-LRP methodology in which Cu(0) and $Cu(II)/(Me_6\text{-TREN})Br_2$ are generated *"in situ"* from Cu(I)Br/Me_6-TREN *via* disproportionation before the addition of a deoxygenated aqueous solution of monomer and initiator (Fig. 3) [89,117,120–125]. The rate of polymerization for the aqueous SET-LRP of certain hydrophilic monomers applying this approach showed an unexpected dependence on temperature [117]. Higher polymerization rates for OEOMEA and HEA at 0 °C than at 25 °C were explained by the lower particle size of the Cu(0) catalyst prepared *"in situ"* by disproportionation of Cu(I)Br at 0 °C in water. However, perhaps one of the most significant achievements

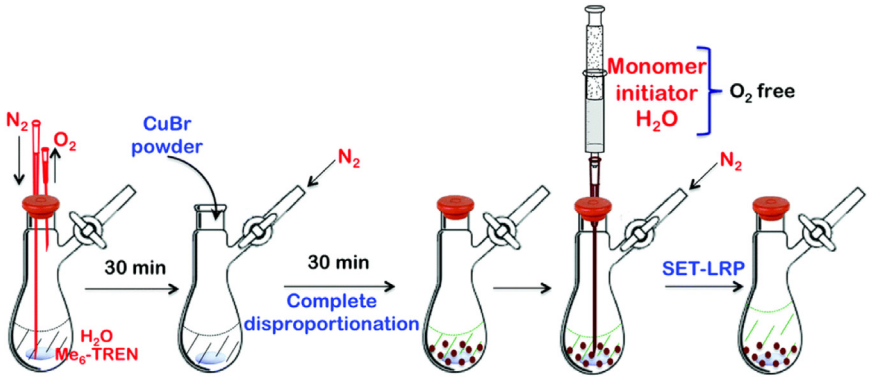

Fig. 3

Schematic representation of the general SET-LRP methodology in which Cu(0) catalyst is generated "*in situ*" *via* disproportionation. Reproduced with permission [117]. Copyright 2015, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

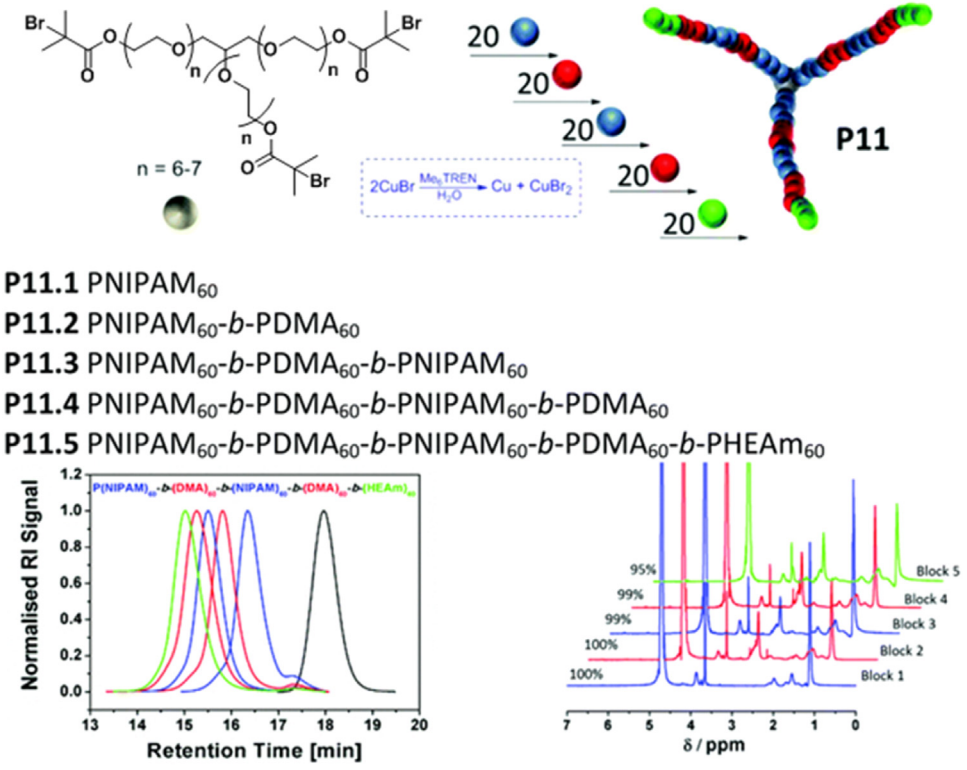

Fig. 4

Representative scheme for the synthesis of pentablock star copolymer from NIPAM, DMA and HEAm *via* aqueous SET-LRP using $[M]_0/[I]_0/[Cu(I)Br]_0/[Me_6\text{-}TREN]_0 = 60/1/1.8/1.2$ at 0 °C (top), obtained molecular weight distributions of each block (bottom left) and ^{1}H NMR spectra displaying full conversion for each block (bottom right). Reproduced with permission [124]. Copyright 2015, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of this methodological protocol, that was also applied in a range of international alcoholic beverages [126] and blood serum [127], is that enabled the accelerated synthesis of sequence-controlled linear [128] and star-shaped [124] multi-block copolymers based on a myriad of acrylamide monomers including NIPAM, N,N,-dimethyl acrylamide (DMA) and N-hydroxyethyl acrylamide (HEAm) while maintaining excellent control over the molecular weight distribution (Fig. 4).

2.2 Recommended and non-recommended solvent alternatives

Aside from top solvents, Cu(0)-catalyzed SET-LRP has been also demonstrated to be effective in other polar solvents. Alcohols such as methanol (MeOH) [112,120,129–131], ethanol (EtOH) [132], isopropanol [129], dimethyl lactamide [133], ethyl lactate [132,134], and fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) [60,135–140] and 2,2,3,3-tetrafluoroethanol (TFP) [136,139,141], are a competitive

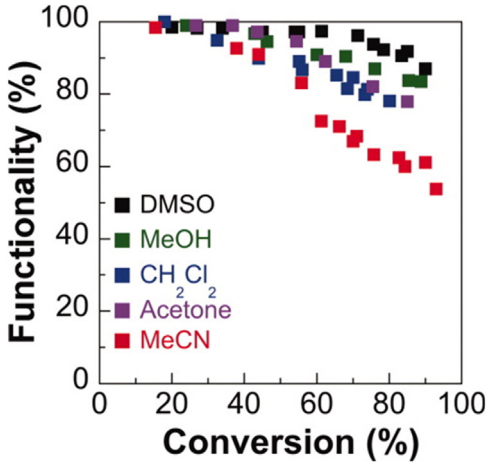

Fig. 5

Evolution of the polymer bromine chain-end functionality with conversion during the SET-LRP of MA initiated with methyl 2-bromopropionate (MBP), and catalyzed with activated Cu(0) wire in solvents mediating different degrees of disproportionation at 25 °C. Reaction conditions: MA = 1 mL, solvent = 0.5 mL, $[MA]_0/[MBP]_0/[Me_6\text{-TREN}]_0 = 222/1/0.1$. Cu(0) wire = 12.5 cm of 20 gauge wire. Reproduced with permission [69]. Copyright 2011, Wiley Periodicals, Inc. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

alternative with low environmental impact. In fact, isopropanol was used to establish universal conditions to perform the LRP of acrylates, methacrylates, and styrene under SET-LRP reaction conditions [142]. Indeed, other dipolar aprotic solvents such as dimethyl formamide (DMF) [143,144] and dimethyl acetamide (DMAc) [143] have also been used successfully [145,146]. However, as illustrated in Fig. 1, alcohols and other polar solvents are not able to stabilize colloidal Cu(0) nanoparticles generated *via* disproportionation in SET-LRP [46].

Homogeneous binary mixtures of such solvents with water [112,132,143,147] and also bicomponent mixtures of two organic solvents [148–152] became also viable alternatives to create ideal reaction conditions. Other polar solvents such as ethylene carbonate (EC), propylene carbonate (PC) [143], polyethyleneglycol [153], polypropyleneglycol [153], and ionic liquids [9,154] can also favor, although to a lower extent, the disproportionation of cuprous ions and consequently still might result in efficient polymerizations. However, getting away from the recommended options can outcome in penalties such as decreased reaction rates, low monomer conversion and undesired changes in chain end fidelity [46,49,69–72]. The evolution of the polymer bromine chain end functionality with conversion during the Cu(0) wire-catalyzed SET-LRP of methyl acrylate (MA) initiated with MBP in the presence of solvents mediating different degrees of disproportionation showcases this claim (Fig. 5). Experimental data clearly supported that loss of chain end functionality during SET-LRP is more pronounced when solvents with poor disproportionating capabilities such as acetone and dichloromethane (CH_2Cl_2) are used [69]. However, the livingness of the polymerization is worryingly compromised when polar Cu(I)X-stabilizing solvents such as MeCN and hexafluroroisopropanol [70]. The non-disproportionating character of MeCN is illustrated by digital images shown in Fig. 1. Under these unfavorable conditions, SET-LRP shows non-first-order kinetic plots suggesting the occurrence of bimolecular termination events that consume active species and accumulates $Cu(II)X_2$ (Fig. 6). Obviously, the use of classical hydrocarbon non-polar solvents such as hexanes, toluene and anisole is also non-recommended because not only they are not disproportionating solvents but also are not good solvents for Cu(I)X and $Cu(II)X_2$ [71,72]. Fig. 7 shows the MALDI-TOF spectrum of a low molecular weight poly(methyl acrylate) (PMA) sample prepared by Cu(0)-mediated polymerization in toluene at room temperature after thio-bromo "click" thioetherification reaction with thiophenol [85,90].

The structural analysis clearly evidences the presence of noticeable amount of dead polymer chains generated by bimolecular termination due to the lack of disproportionation under these conditions and also lack of proper solubility of Cu(I)X and $Cu(II)X_2$ species [46]. Overall, these results demonstrate that the absence of disproportionation effectively leads to the lack of first-order kinetics, broad molecular weight distributions, significant loss of bromide chain end functionality, and therefore, the absence of a living polymerization reaction. Thus, the elaboration of innovative approaches to expand the table of solvents available for SET-LRP was desirable after the early steps of this technique.

3 Sources of inspiration to expand the table of solvents for SET-LRP

The development of "programmed" bi(multi)phasic SET-LRP systems expanded the solvent scope of this LRP technique to almost any organic solvent regardless of its ability to mediate or not disproportionation of Cu(I)X/ligand [155–165]. As will be disclosed later in this perspective article, these systems are based on the use of binary aqueous-organic solvent mixtures. In this section, we will discuss previous studies that inspired this significant step forward in this field.

3.1 SET-LRP in homogeneous aqueous-organic solution

The use of aqueous-organic solvent mixtures as a reaction media in SET-LRP was already considered during the early developments of this technique [129]. However, in most of the cases, special attention was paid to retain the reaction in homogeneous state thus limiting further developments. Symptoms of faster SET-LRP reaction rates in reaction mixtures containing small amounts of water (5%) were already noted during the polymerization of MA in various alcohols using Cu(0) powder catalyst [129]. As the hydrophobic character of the alcohol increased, the apparent rate constant of the polymerization (k_p^{app}) decreased. In this series of experiments, the addition of water served to significantly increase the k_p^{app} of the reaction without compromising molecular weight control. For example, the k_p^{app} for the polymerization of MA using a difunctional initiator ($[MA]_0/[initiator]_0 = 222$) increased from 0.0749 min^{-1} to 0.0109 min^{-1} after the addition of 5% water to EtOH. However, the sparse solubility of PMA in aqueous alcoholic mixtures limited the amount of water that could be added in the system. Fundamental reports from our laboratory investigated later the Cu(0) wire-catalyzed SET-LRP of MA in a

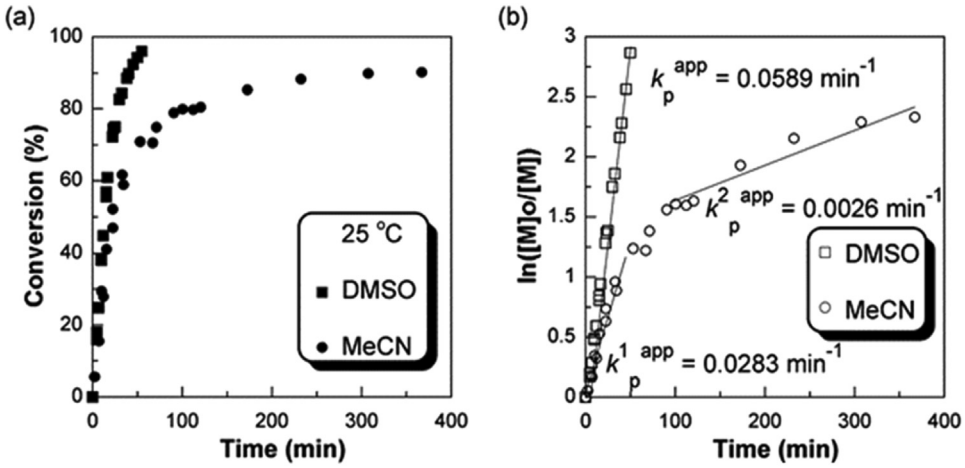

Fig. 6

The kinetic plots for the Cu(0)-catalyzed SET-LRP of MA initiated with MBP at 25 °C in DMSO and MeCN are astonishingly dissimilar. Polymerization conditions: MA = 1 mL, solvent = 0.5 mL, $[MA]_0 = 7.4$ mol/L, $[MA]_0/[MBP]_0/[Cu(0)]_0/[Me_6\text{-TREN}]_0 = 222/1/0.1/0.1$, and Cu(0) < 75 mm. Adapted with permission [70]. Copyright 2008, American Chemical Society.

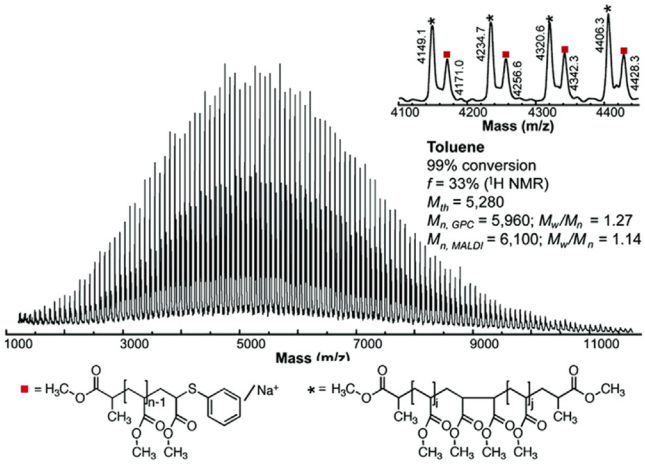

Fig. 7

MALDI-TOF spectra of PMA obtained at 99% conversion from Cu(0)-catalyzed polymerization of MA in toluene after thio–bromo "click" modification with thiophenol. Polymerization conditions: $[MA]_0/[MBP]_0/[Cu(0)]_0/[Me_6\text{-TREN}]_0/[TEMPO]_0 = 60/1/1/1/0.05$, Cu(0) 75 μm. Reproduced with permission [71]. Copyright 2012, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

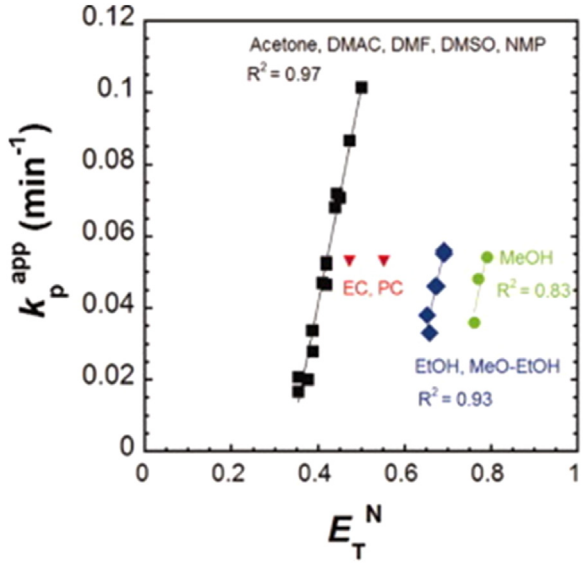

Fig. 8

k_p^{app} (left) *vs* E_T^N for the SET-LRP of MA initiated by MBP in various solvents, aqueous-organic mixtures, and binary mixtures of organic solvents. Reaction conditions: MA = 1.0 mL, solvent 0.5 mL, $[MA]_0 = 7.4$ mol/L, $[MA]_0/[MBP]_0/[Me_6\text{-TREN}]_0 = 222/1/0.1$, Cu(0) = 12.5 cm of 20 gauge wire. Adapted with permission [143]. Copyright 2009, Wiley Periodicals, Inc. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

myriad of aqueous mixtures of other solvents including DMSO, DMF, acetone and PC with up to 10% water content [143]. It was demonstrated that this acceleration effect correlated linearly or log-linearly in non-alcoholic reaction mixtures with the Dimroth-Reichardt solvent polarity parameter (E_T^N) in agreement with the proposed SET-LRP mechanism involving a polar transition state between the Cu(0) electron donor and the alkyl halide electron acceptor (Fig. 8).

Indeed, in most cases, a modest improvement on molecular weight control was also detected. The same trend was demonstrated previously when a good organic disproportionation solvents (e.g. DMSO) was added to a SET-LRP reaction mixture with moderate/poor disproportionating capabilities [70,149,150]. Both effects have been attributed to the enhanced disproportionation efficiency as well as to the ability of more polar solvent mixtures that stabilize the polar transition state between the Cu(0) electron donor and the alkyl halide electron acceptor [10,33]. Later on, it was also demonstrated that upon addition of a small amount of water (10%) to TFE or TFP, the k_p^{app} for the polymerization of methacrylates such as methyl methacrylate (MMA) and butyl methacrylate (BMA) using sulfonyl halide-type

initiators was almost doubled [137]. Recently, the addition of water to ethyl lactate also served to accelerate and improve the livingness during the SET-LRP of biobased monomer ethyl lactate acrylate [132]. Interestingly, targeting water-soluble monomers such as HEA and DMA allowed even larger rate acceleration effects by using aqueous-organic mixtures with higher water-contents [112,121].

3.2 SET-LRP in "self-generated" biphasic systems: the first-generation of biphasic SET-LRP systems

The first signs that SET-LRP may tolerate heterogeneous reaction mixtures dates back to 2002, when we were pursuing the LRP of VC in a mixture of THF/water [7]. PMA gel formation in the organic phase was also observed later during the Cu(0) powder-catalyzed SET-LRP of MA in DMSO but only when ultrahigh molar mass polymers were targeted [9]. Phase separation was also observed later during the polymerization of n-butyl acrylate (BA) in the same solvent [86]. Such changes in the nature of the reaction mixture were thought to be unimportant at the time they were first detected, because the focus was on pushing the limits of homogeneous systems. A decade later, Haddleton and Whittaker laboratories re-observed the biphasic system emerging during the Cu(0) wire-catalyzed SET-LRP of BA in DMSO and named it, for the first time, "self-generated" biphasic system [155–166]. It is remarkable that this interfacial system allowed the successful "*in situ*" chain extension of poly(butyl acrylate) (PBA) several times with BA to high conversion without intermediate purifications steps (Fig. 9). At the same time, the same phenomenon was detected again in our laboratory during the polymerization of 2-ethyhexyl acrylate in TFE [135]. In "self-generated" systems, polymer phase separates from the homogeneous disproportionating reaction mixture above a certain molecular weight to form a solvent swollen polymer-rich layer with very low copper content and a second organic solvent-rich layer containing residual monomer, ligand, and soluble Cu(II)X_2 species [166]. "Self-generating" biphasic reaction mixtures emerged also during the polymerization of other hydrophobic monomers such as lauryl acrylate or menthyl acrylate in polar solvents such as TFE [139], 2-propanol [152], ethyl lactate [134] and dimethyl lactamide [133]. It is noteworthy that phase separation did not affect the success of the polymerization reaction in terms of control and livingness.

Hence, this approach represents a convenient procedure to target hydrophobic polymers and can be considered the first-generation of biphasic SET-LRP systems. However, it is important to point out that those systems still requires the use of a polar disproportionating solvent because disproportionation of Cu(I)X into Cu(0) and Cu(II)X_2 is mediated by the organic solvent. The use of such interfacial systems was demonstrated to be beneficial during the synthesis of star polymers by one-pot core-first method, because it minimizes bimolecular termination events, particularly at high molecular weight and high conversion [167]. However, one of the main benefits of self-generated SET-LRP systems is that they allow efficient separation and removal of almost all copper residues from the polymer product without the need of using complex purification procedures (Fig. 9**c**). For example, the level of copper in poly(lauryl acrylate) prepared in a "self-generated"

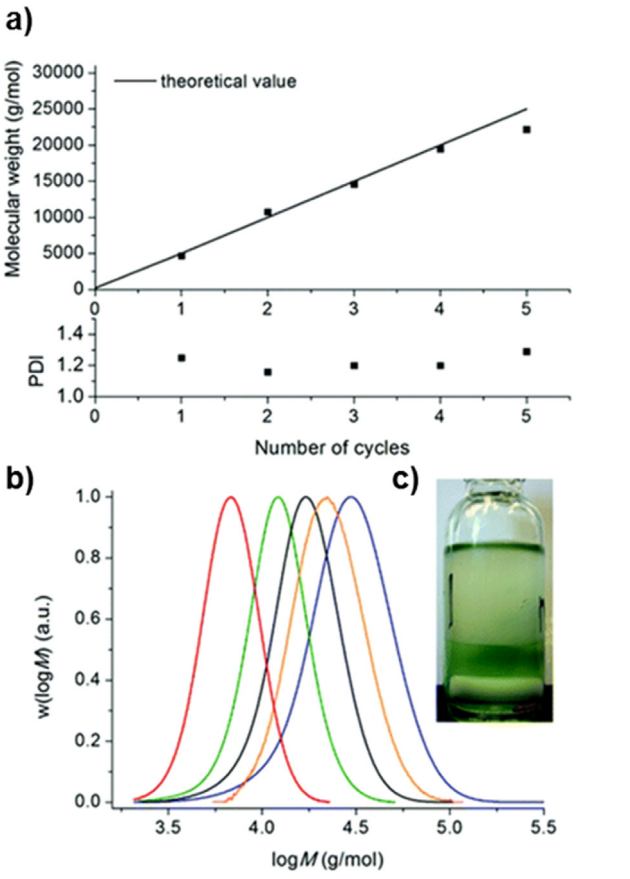

Fig. 9

(a) Number-average molecular weight and molecular weight distribution values, (b) GPC traces for five successive chain extensions of PBA at >99% conversion, and (c) digital image of a "self-generated" biphasic reaction mixture of PBA in DMSO. Adapted with permission [166]. Copyright 2013, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

system using isopropanol was determined by ICP-MS analysis to be as low as 38 ppm [152].

3.3 SET-LRP catalyzed by Cu(0) generated "in situ" by the reduction of Cu(II)Br_2 with $NaBH_4$

The current practice of SET-LRP covers the use of a broad range of Cu(0) catalyst forms. Thus, for example, Cu(0) powder particles of a wide range of sizes [77] including nanopowder [67] allowed the LRP of a myriad of vinyl monomers. Furthermore, Cu(0) in the form of coin [168], tube [94], bar [169], and specially wire (non-activated) [170,171], activated by external procedures [172–174], or self-activated [136,175] has been demonstrated to provide excellent results in both homogeneous organic and aqueous reaction media even in the presence of air and radical inhibitors [115,130,176,177]. Among the various available options, the use Cu(0) wire is perhaps the most popular option as it provides the best balance between control over polymerization rate, molecular weight and chain ends, and at the same time almost unlimited catalyst recyclability [170]. Moreover, Cu(0) wire-catalyzed SET-LRP was demonstrated to be not only living but also highly robust and immortal after numerous interruptions of the polymerization

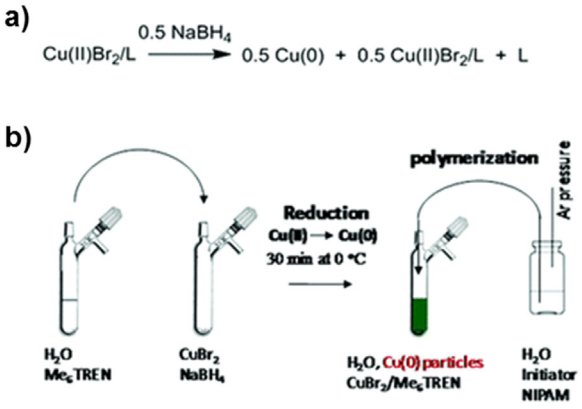

Fig. 10

(a) Partial reduction of Cu(II)Br_2/*N*-ligand complex to Cu(0) using strong reducing agent $NaBH_4$ in water. (b) General procedure for the aqueous SET-LRP catalyzed by Cu(0) generated "*in situ*" by the reduction of Cu(II)X_2 with $NaBH_4$. Adapted with permission [182]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

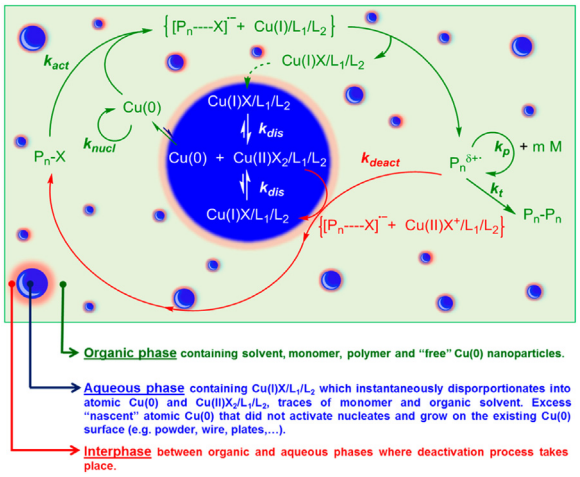

Fig. 11

Schematic representation of Cu(0)-catalyzed SET-LRP in organic-water "programmed" biphasic reaction mixtures. Color code: organic phase, green; aqueous phase, blue; interphase, red. Reproduced with permission [47]. Copyright 2019, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of MA by exposing the reaction mixture to air [171]. Together with the exponential development of aqueous SET-LRP systems, the previously discussed use of Cu(0) nanopowder generated "*in situ*" by complete disproportionation of Cu(I)Br in water but also in aqueous-organic mixtures has been demonstrated an efficient methodology [35,121–125]. Nanopowder prepared by disproportionation in water can also be isolated and used as well as the commercial nanopowder product is employed [67,114]. However, the most singular and reliable methodology to generate Cu(0) "*in situ*" in the reaction mixture is the use of an air-stable Cu(II) salt (e.g. Cu(II)Br_2 or Cu(II)SO_4) as a copper source in combination with a reducing agents such as hydrazine hydrate [178], ascorbic acid [179], and Zn(0) [180]. In fact, this approach is routinely used in the preparation of Cu(0) nanoparticles [181]. Recently, the multi-component SET-LRP catalytic system based of Cu(II)Br_2, Me_6-TREN, and $NaBH_4$ as a reducing agent facilitated the SET-LRP of water-soluble monomers such as NIPAM [54,182]. Interestingly, the "prereduction approach" in which partial reduction of Cu(II)Br_2/Me_6-TREN to Cu(0) allowed the generation of predetermined ratios of Cu(0) activator and Cu(II)Br_2 deactivator in the reaction mixture allowed the synthesis of PNIPAM with controlled and narrow molecular weight distributions within minutes (Fig. 10). Indeed, the "*in situ*" azidation in aqueous media enabled outstanding preservation of PNIPAM end-group functionality [54].

4 Second-generation of biphasic SET-LRP systems: "programmed" Bi(multi)phasic reaction mixtures

The above-described experiments inspired and facilitated the elaboration of a second-generation of interfacial SET-LRP systems. These systems, named by us "programmed" bi(multi)phasic SET-LRP systems, are based on binary mixtures of organic solvents and water. In these systems, polymerization takes place in the organic phase and both Cu(I)X and Cu(II)X_2 are partitioned from the organic into the water phase where a fast and quantitative disproportionation occurs. This is possible due to the unexpected immiscibility of water containing Cu(II)X_2 and ligand with water miscible organic solvents containing monomer and polymer (Fig. 11) [33].

This design can be considered universal as has been successfully applied to a large library of organic solvents. However, of particular interest biphasic systems based on aqueous mixtures of both polar and/or non-polar non-disproportionating solvents because have the dreamed capability to expand widely the table of solvents available for SET-LRP. Although these interfacial "programmed" systems were initially developed applying the above described complex multi-component methodology developed by Monteiro and co-workers (i.e. Cu(0) is generated "*in situ*" *via* reduction of Cu(II)Br_2 with $NaBH_4$) [182], most of them have already been successfully reinvestigated applying the simpler Cu(0) wire methodology. In this subsection, a more detailed overview of these interfacial SET-LRP systems is presented.

4.1 SET-LRP of acrylates in "programmed" Bi(multi)phasic systems catalyzed with Cu(II)Br_2/Me_6-TREN/$NaBH_4$

As mentioned above, the SET-LRP of alkyl acrylates in alcoholic-water mixtures only tolerated small amounts of water in homogeneous state [129,143]. However, recently investigations on the SET-LRP of the same monomers in mixtures with much higher amounts of water (up to 50%) served as a starting point for the development of the second generation of bi(multi)phasic SET-LRP systems [159]. The reduction of Cu(II)Br_2 into Cu(0) is instantaneous upon addition of $NaBH_4$ in water, but also in alcohol-water mixtures containing monomer and ligand (Fig. 12) [159]. Taking advantage of this reaction, in these studies SET-LRP was conducted inside inexpensive test tubes under a blanket of nitrogen generating the Cu(0) catalyst "*in situ*" in the reaction mixture from Cu(II)Br_2, in the presence of monomer, initiator, ligand, organic solvent, and water (Fig. 13).

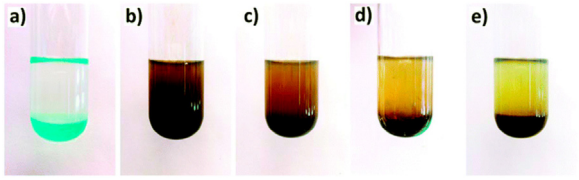

Fig. 12

Visualization of the reduction of Cu(II)Br_2 (11.28 mg) with $NaBH_4$ (1.91 mg) in a solution of MeOH/water (7/3, v/v) (2 mL) in the presence of BA (4 mL) and Me_6-TREN (13.50 μL). Photos were taken before (a) and 15 s (b), 30 s (c), 45 s (d), and 60 s (e) after the addition of reducing agent. Reproduced with permission [159]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A myriad of different aqueous mixtures based on alcohols with a broad range of polarities including MeOH, EtOH, *n*-propanol, isopropanol and 2-ethylhexanol were investigated [159]. It is important to mention that, depending on the monomer, selected alcohol and water content in the reaction mixture, the SET-LRP proceeded in homogeneous state (Fig. 14**a**), started homogeneous but transitioned to biphasic above certain monomer conversion (Fig. 14**b**), or remained biphasic during the entire reaction course (Fig. 14**c**).

In biphasic reaction mixtures, the upper green-blue phase contains mostly Cu(II)Br_2 and ligand in water, whereas the bottom phase consists of alcohol, soluble polymer and residual monomer. However, under certain conditions, the biphasic system evolved at high conversion into a more complex triphasic mixture consisting of an insoluble gel-like polymer as the first phase, solvent and residual monomer as the second phase, and water containing Cu(II)Br_2 and ligand in the third phase. This phenomenon occurred for example during the polymerization of MA in a methanol-water mixture (7/3, v/v) (Fig. 14**d**). Representative first-order kinetic plots resulting from the SET-LRP of BA in various "programmed" alcohol-water mixtures demonstrates that SET-LRP also retains the living features under interfacial reaction conditions (Fig. 15). In agreement with previous experiments with much lower water loadings [129,143], the k_p^{app} also increased in this case with the increase of the amount of water in the

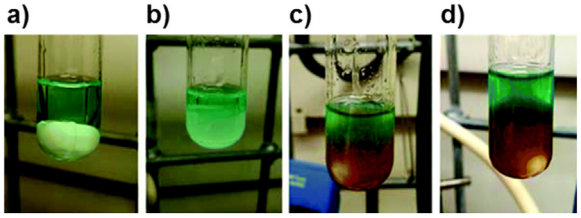

Fig. 14

Visualization of the reaction mixture after SET-LRP of MA or BA (4 mL) in various alcohol/water mixtures (2 mL) initiated with MBP and catalyzed by Cu(0) prepared *via "in situ"* reduction of Cu(II)Br_2 with $NaBH_4$ at 25 °C. Stirring was stopped before taking the photos. (a) SET-LRP of MA in methanol/water (9/1, v/v) showing one phase at the end, (b) SET-LRP of MA in methanol/water (7/3, v/v) showing two phases at the end generated during the reaction, (c) tert-butanol/water (7/3, v/v) two phases at the end observed from the beginning of the reaction, and (d) SET-LRP of MA in methanol/water (7/3, v/v) showing three phases at the end. Adapted with permission [159]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

multiphasic reaction mixture. For example, with the transition from MeOH/water ratio 9/1 to 6/4, v/v in the SET-LRP of BA, the k_p^{app} increases by a factor of ~11.

This series of experiments represent the origin of the elaboration of the second generation of SET-LRP bi(multi)phasic SET-LRP systems after the above described "self-generated" systems [133–135,139,152,166]. In a back to back publication, it was demonstrated that the simple addition of at least 10 % hexanes to the EtOH-water mixture transforms the triphasic reaction mixtures previously observed during the SET-LRP of BA in aqueous mixtures of EtOH (7/3, v/v) into more technological attractive biphasic system [158]. Even more interestingly is that the resulting biphasic system showed a synergistic effect on k_p^{app} with the increase of the volume fraction of hexane (ϕ_{Hex}) (Fig. 16**)**. Increasing the concentration of hexanes up to $\phi_{Hex} = 0.4$ provided a continuous increase of k_p^{app} from 0.093 min^{-1} to 0.0166 min^{-1} with no detrimental effect on the molecular weight distribution of the resulting PBA. However, higher concentrations of hexanes started to penalize both k_p^{app} and M_w/M_n. Also promising for future technological developments was that other non-polar non-

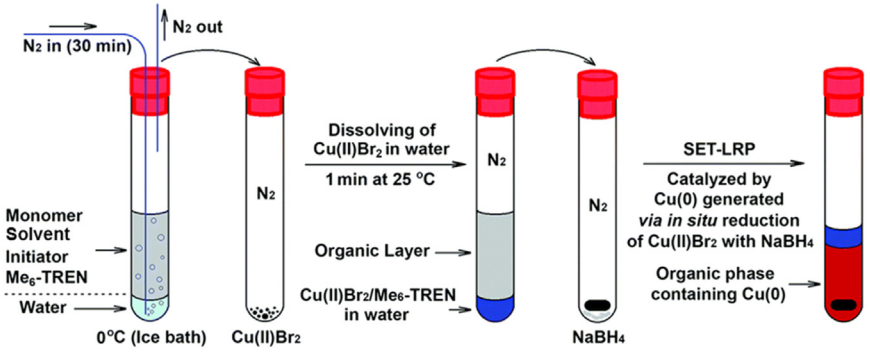

Fig. 13

General schematic procedure to conduct the SET-LRP of acrylic monomer generating Cu(0) *"in situ"* in the reaction mixture *via* reduction of Cu(II)Br_2 with $NaBH_4$ in an aqueous-organic mixture. Adapted with permission [155]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

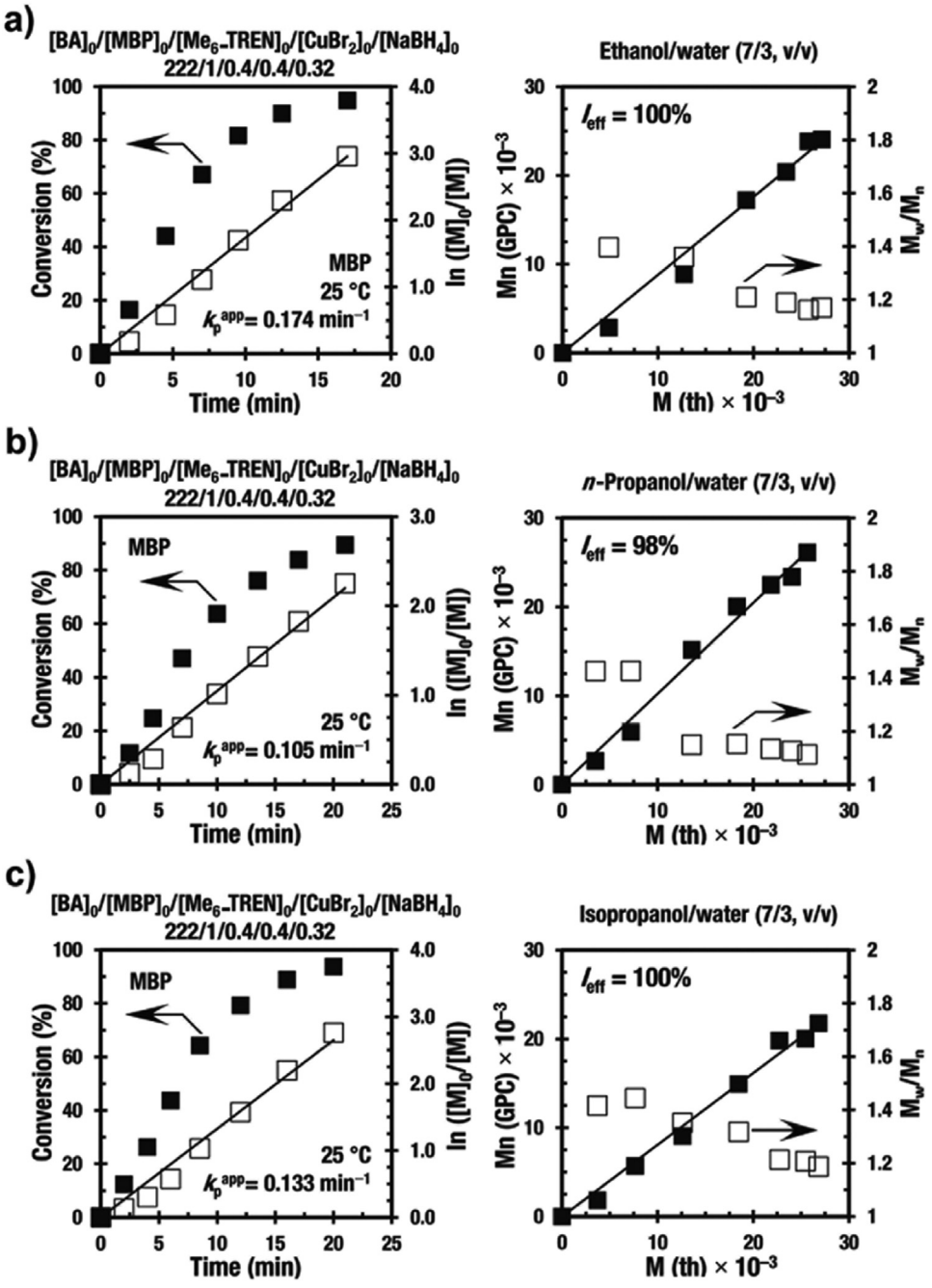

Fig. 15

Representative kinetic plots, molecular weight and polydispersity evolution for the SET-LRP of BA (4 mL) in various alcohol/water mixtures (2 mL) initiated with MBP and catalyzed by Cu(0) prepared "*in situ*" *via* reduction of $Cu(II)Br_2$ with $NaBH_4$ at 25 °C. (a) EtOH/water (7/3, v/v); (b) n-propanol/water (7/3, v/v) and (c) isopropanol/water (7/3, v/v). Reproduced with permission [159]. Copyright 2016, The Royal Society of Chemistry.

disproportionating solvents such as ethyl acetate, toluene, anisole and cyclohexane could also be used instead of hexanes.

The table of solvents suitable for "programmed" bi(multi)phasic SET-LRP systems was later successfully expanded, applying the same methodology, to aqueous mixtures of other disproportionating solvents with excellent to moderate disproportionating properties such as dipolar aprotic solvents (e.g. DMSO, sulfolane, and DMF), carbonates (e.g. EC and PC), and cyclic ethers (e.g. THF and dioxane) [160]. However, the most attractive feature of this design is the possibility to use aqueous mixtures of organic solvents with poor disproportionating capability. Delightfully, this approach facilitated the use of acetone, one of the most common and least expensive solvents with limited use in SET-LRP due to its low equilibrium constant for the disproportionation of Cu(I)X into Cu(0) and $Cu(II)X_2$ but also due to its potential side reactions [143,157]. However, following the proper protocol, the use of biphasic aqueous mixtures of acetone containing 10-40% water enabled the ultrafast SET-LRP

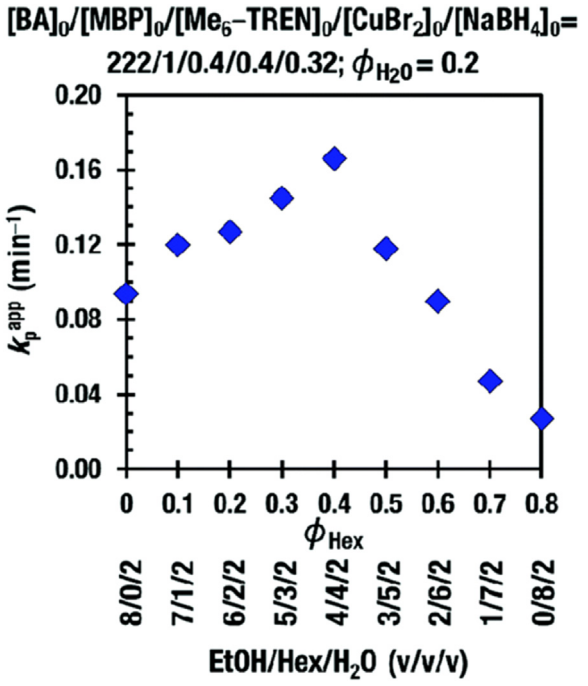

Fig. 16

Dependence of k_p^{app} to the ϕ_{Hex} in ethanol-hexanes-water experiments maintaining ϕ_{H2O} constant at 0.2. Reaction conditions: BA = 4 mL, EtOH + hexanes + water = 2 mL, $[BA]_0/[MBP]_0/[Me_6\text{-}TREN]_0/[CuBr_2]_0/[NaBH_4]_0$ = 222/1/0.4/0.4/0.32. Adapted with permission [158]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

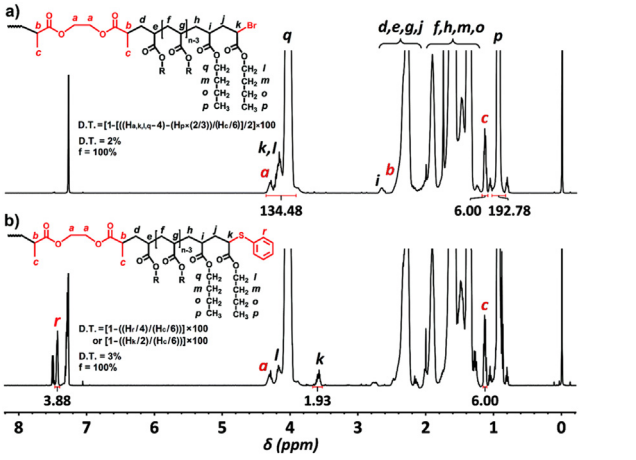

Fig. 17

500 MHz ^{1}H NMR spectra of PBA, isolated at 97% conversion, obtained by SET-LRP of BA (4 mL) initiated with BPE in a "programmed" acetonitrile-water biphasic system (2 mL) before (a) and after (b) thio-bromo "click" reaction. Reaction conditions: $[BA]_0/[BPE]_0/[Me_6\text{-}TREN]_0/[Cu(II)Br_2]_0/[NaBH_4]_0$ = 65/1/0.4/0.4/0.32. Reproduced with permission [155]. Copyright 2016, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of MA and BA to polyacrylates with near quantitative chain end functionality at room temperature [157].

Finally, the potential of this concept was demonstrated putting in the spotlight MeCN-water mixtures [155]. As mentioned above, MeCN is a classic polar non-disproportionating solvent that provides non-linear first-order SET-LRP kinetics with incomplete monomer conversions and poor retention of the bromine chain end functionality in classic homogeneous systems [69–72]. In previous reports, binary mixtures of MeCN and DMSO were successfully to transition from non-living to living polymerizations for the SET-LRP of MA in homogeneous state [70]. With the same goal in mind, the use of a "programmed" biphasic system based on MeCN-water mixtures showed living features and furnished well-defined polyacrylates (i.e. PMA and PBA) at almost quantitative conversion (Fig. 17) [155].

4.2 SET-LRP of acrylates in "programmed" Bi(multi)phasic systems catalyzed with Cu(0) wire

As discussed above, the "*in situ*" generation of Cu(0) *via* reduction of $Cu(II)Br_2$ with $NaBH_4$ is an efficient approach to conduct SET-LRP in interfacial bi(multi)phasic systems. However, this methodology requires high level of expertise and is not appealing for technological and industrial applications mainly because $NaBH_4$ requires carefully handling and storage conditions. Hence, a series of screening experiments were designed to explore the use of non-activated Cu(0) wire catalysis in these previously elaborated systems. The use of Cu(0) wire air-stable catalyst in combination with Me_6-TREN in mixtures of dipolar aprotic solvents such as dipolar aprotic (e.g. DMSO and DMF) [160], cyclic ethers (e.g. THF and dioxane) [160], carbonates (PC and EC) [160], acetone [157], and fluorinated alcohols [162,165] (e.g. TFE, TFP, and hexafluoroisopropanol) containing up to 30% water enabled the successful preparation of well-defined polyacrylates. A systematic chain end analysis of selected samples combining ^{1}H NMR analysis and MALDI-TOF demonstrated that the use of Cu(0) wire catalyst does not compromise the livingness of resulting polymers. MALDI-TOF analyses shown in Fig. 18, prove the high chain end functionality of the synthesized polymers even in aqueous mixtures of a non-disproportionating solvents such as hexafluoroisopropanol [46,165]. These results offer new opportunities to dual control molecular weight and tacticity under SET-LRP conditions [183–185]. In another series of experiments, the replacement of Me_6-TREN by TREN, which is 80 times less expensive, was investigated [161,162,165]. Importantly, the external addition of $Cu(II)Br_2$ deactivator to the water phase was a requirement to produce well-defined polyacrylates when switching from Me_6-TREN to TREN. However, the performance of a wide library of both water soluble and water insoluble solvents including THF, dioxane, EtOH, TFE, acetone, acetonitrile and toluene and anisole was evaluated positively in the presence of TREN and $Cu(II)Br_2$ [161,162,165].

Fig. 19 illustrates how the external addition of $Cu(II)Br_2$ deactivator is mandatory to reach control in the SET-LRP of MA under these interfacial conditions. However, it is important to highlight that 0.025 mol% deactivator (relative to the initiator) was sufficient to ensure a living process (Fig. 19**b**). Nevertheless, it is noteworthy that all the tested compositions were biphasic as can be seen from the representative digital images captured after

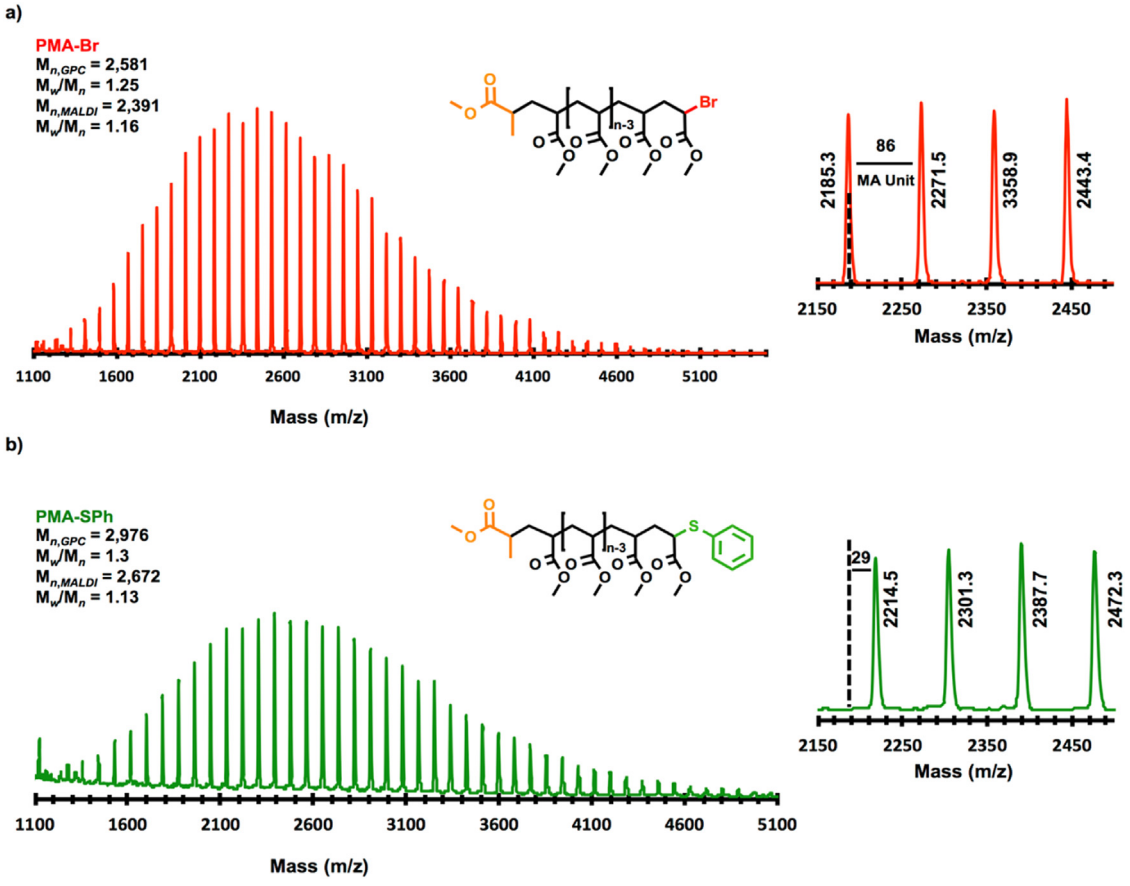

Fig. 18

MALDI-TOF of PMA-Br isolated at 90% conversion from biphasic Cu(0) wire/Me6-TREN catalyzed SET-LRP of MA in a hexafluoroisopropanol-water (8/2, v/v) initiated with MBP at 25 °C before (a) and after the thio-bromo "click" reaction with thiophenol (b). Reproduced with permission [165]. Copyright 2018, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the interfacial SET-LRP process in aqueous mixtures of TFE and TFP containing 10, 20 and 30% water (Fig. 20). Although better dispersion of the water phase containing Cu(II)Br_2 and TREN in the organic phase was noted, high water loadings resulted in reaction mixtures showing bluish water droplets which are not miscible with the organic phase containing polymer and residual monomer.

4.3 SET-LRP of methacrylates in "programmed" Bi(multi)phasic systems catalyzed with Cu(0) wire/Me_6-TREN

Pursuing to expand the monomers scope for "programmed" interfacial reaction mixture, the polymerization of methacrylate monomers was recently investigated in various environmentally friendly aqueous alcoholic mixtures using Cu(0) wire catalyst and Me_6-TREN ligand at 50 °C [186]. According to previous results, sulfonyl halide-type initiators were used to initiate the SET-LRP [6,35–43,137,138],and *p*-toluenesulfonyl chloride (Ts-Cl) as initiator. The effect of water on the nature of the reaction mixture during the SET-LRP process, reaction rate, and control of the polymerization showed similar trends than those observed previously during the polymerization of acrylates. The transition from a homogeneous to a biphasic system was also accompanied by important variations on the rate of polymerization. For instance, the addition of 10% water to isopropanol increased the rate constant of the SET-LRP of BMA from k_p^{app} = 0.0056 to 0.0101 min^{-1}. However, k_p^{app} value did not increase in this case further at higher water loadings, although it remained in all cases above the control value in pure alcohol (Fig. 21**a**). Note that regardless of the transition from a mono to biphasic system, the living behavior of this series of experiments was in all cases supported by the linear evolution of $ln([M]_0/[M])$ vs time. GPC analysis revealed only a small penalty on molecular weight distribution as the water content increased. Importantly, alcohol-water mixtures allowed the accelerated preparation of PBMA up to 75,000 $g.mol^{-1}$ with a high conversion and a narrow molecular weight distribution targeting degrees of polymerization (DP) from 100 to 600 (Fig. 21**b**). The control retained under these heterogeneous reaction conditions was further proved using "*in situ*" chain extension re-initiation experiments at high conversion. Fig. 21**c,d** illustrates the successful "*in situ*" block copolymerization of MMA and ethyl lactate methacrylate (EtLMA) with tetrahydrofurfuryl methacrylate (THFMA) and isosorbide 2-methacrylate-5-laurate (IMAL), respectively. These results support the potential technological applications of SET-LRP in "programmed" bi(multi)phasic reaction mixtures.

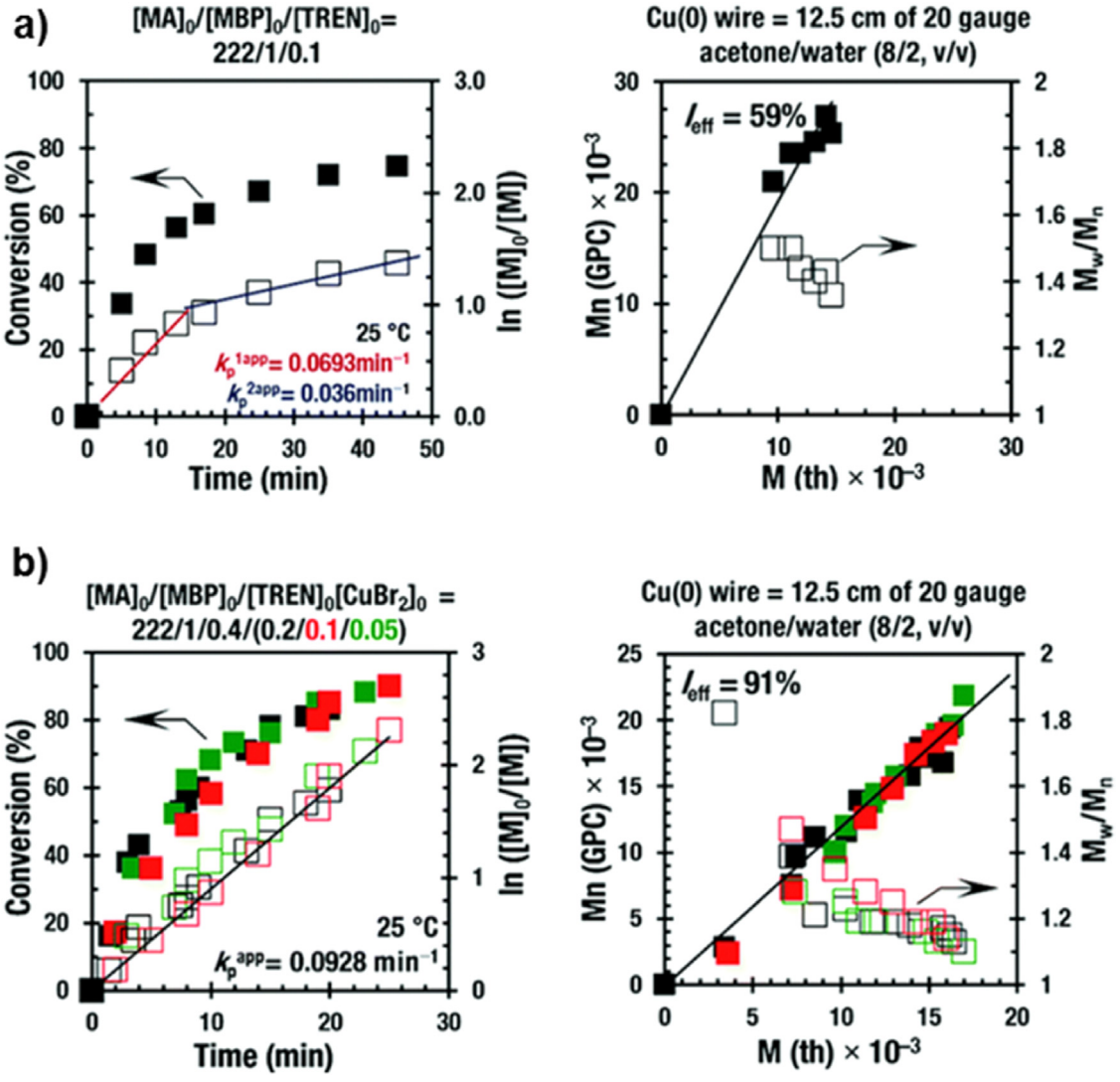

Fig. 19

Kinetic plots, molecular weight and dispersity evolution for the Cu(0) wire-catalyzed SET-LRP of MA (1 mL) in an acetone/water mixture (8/2, v/v) (0.5 mL) at 25 °C in the presence of TREN (a) and TREN + different amounts of externally added $Cu(II)Br_2$ deactivator. Experimental data in different colors were obtained from different kinetics experiments. Adapted with permission [161]. Copyright 2017, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.4 The stirring rate provides a dramatic acceleration of "programmed" Bi(multi)phasic systems catalyzed with $Cu(II)Br_2/Me_6$-TREN/$NaBH_4$

An unexpected influence of the stirring rate on the SET-LRP of MA and BA in acetonitrile-water mixtures was observed when Cu(0) catalyst was generated by the reduction of $Cu(II)Br_2$ with $NaBH_4$. Although symptoms of the influence of the stirring rate were obtained using the above described "*in situ*" methodology, the highest rate increase mediated by the stirring rate was observed when adopting the "prereduction" procedure developed by Monteiro and co-workers for the aqueous SET-LRP of NIPAM (see Fig. 10) [182] In this case, the reduction of $Cu(II)Br_2$ was carried out before the addition of other reagents to produce a sponge-like Cu(0) catalyst of low density [156]. Under these conditions, kinetic experiments showed two linear kinetic domains with a linear increase of polymer molar mass. However, reactions performed at various stirring rates revealed that this parameter provides a dramatic acceleration of the first kinetic domain ($k^1{}_p{}^{app}$) observed for the interfacial SET-LRP in biphasic acetonitrile-water mixtures (Fig. 22).

This singular and interesting feature was attributed to the destruction of the sponge-like Cu(0) catalyst that generates the smallest nanoparticles of Cu(0) at higher stirring rates. No effect on the second linear domain ($k^2{}_p{}^{app}$) was suggested to be due the stabilization of Cu(0) nanoparticles by PBA chains generated during the polymerization. Note that this effect was never reported before for Cu(0) wire-catalyzed polymerizations proceeding under homogeneous reaction conditions.

4.5 The importance of the order of reagents mixing

The proper mixing order of reagents is important to avoid side reactions in the current practice of SET-LRP, in both homogeneous

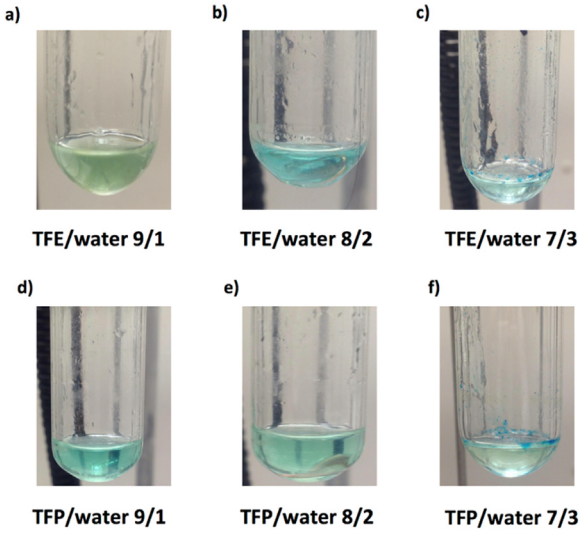

Fig. 20

Visualization of the reaction mixture after SET-LRP of MA (1 mL) initiated with MBP and catalyzed by non-activated Cu(0) wire at 25 °C in various fluorinated alcohol-water mixtures (0.5 mL). Reaction conditions: $[MA]_0/[MBP]_0/[TREN]_0/[Cu(II)Br_2]_0 = 222/1/0.2/0.1$. Adapted with permission [162]. Copyright 2018, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and interfacial reaction mixtures [187,188]. For example, control experiments established that $Cu(II)Br_2$ has a limited solubility in acetone but reacts with it at 25 °C very fast furnishing a mixture of bromoacetone, diacetone alcohol, and mesityl oxide (Fig. 23**a-c**) [188]. At longer reaction times, the formation of 4-bromo-4-methylpentan-2-one was also detected (Fig. 23**d**). The formation of bromoacetone in the reaction mixture is especially undesirable because it can act as an N-alkylating agent toward amino groups under mild conditions, and also as an extra initiator. On the other hand, it was also observed that $Cu(II)Br_2$ also brominates MA and BA in MeCN at room temperature leading to the corresponding dibromoderivative that spontaneously produce highly reactive α-bromoacrylate compounds *via* E2 elimination in the presence of Me_6-TREN or TREN (Fig. 24). α-Bromoacrylates are known to undergo radical polymerization [189]. Hence, the formation of even trace amounts of these products is not desirable in most of conventional applications of SET-LRP because would produce hyperbranched/crosslinked polymers [190]. Noteworthy, both undesired reactions were demonstrated to be eliminated in the presence of an N-ligand such as Me_6-TREN. Thus, special emphasis must be placed to not mix acrylate monomers and/or acetone with $Cu(II)Br_2$ in absence of N-ligand during the reaction set-up in order to perform a clean SET-LRP under both homogeneous and heterogeneous reaction conditions.

4.6 Exploiting the high chain end functionality of polyacrylates synthesized by SET-LRP in a biphasic acetone-water mixture

Among the LRP techniques, SET-LRP in homogeneous state was until recently the first choice when demanding outstanding chain end functionality [7,9,10,31–35]. On account of the high bromine chain end functionality of PMA and PBA prepared in "programmed" bi(multi)phasic mixtures, the functionalization of polymer chain ends with acrylate groups was investigated *via* direct nucleophilic substitution with potassium acrylate [163,164] First, the α-bromoester end groups of mono and difunctional PMAs, synthesized by Cu(0) wire-catalyzed SET-LRP in a biphasic acetone-water mixture using TREN as ligand, could be quantitatively reacted with potassium acrylate in MeCN or acetone to yield the corresponding macromonomer (PMA-A) and telechelic (A-PMA-A) with α- and α,ω-acrylate chain ends, respectively (Fig. 25). This reaction is similar to the thio-bromo click elaborated earlier in our laboratory and discussed in great details in a recent perspective and therefore, it can be considered a new click reaction to be named carboxylate-bromo click reaction [191,192].

Potassium acrylate is not soluble in acetone or in acetonitrile. Thus, it is important to point out that both SET-LRP reaction and esterification occurred under heterogeneous reaction conditions. The efficient interfacial nucleophilic substitution at the chain end of SET-LRP polymers could be monitored by ^{1}H NMR by the disappearance of the signal *k* characteristic of polyacrylate bromine chain ends, and the appearance of signal *k''* at 5.1 ppm, and vinylic signals of the acrylate moieties (Fig. 26). Complete functionalization of a monofunctional PMA of $M_n \sim 4500$ g mol^{-1} required approximately 30 h in acetone at 50 °C. However, functionalization reactions were much faster when conducted in acetonitrile at 75 °C (Fig. 27, purple columns). In another study, the aforementioned combination of biphasic SET-LRP and biphasic esterification was applied to PBA in order to expand the methodology to more hydrophobic polymers [164]. Unfortunately, the transition from PMA to PBA was not so successful due to the higher hydrophobicity and steric hindrance of PBA chain ends.

For instance, a degree of functionalization of approximately 45% was determined by ^{1}H NMR after 30 h of reaction using MeCN as solvent at 75 °C. However, the "*in situ*" chain extension of PBA with few units of MA dramatically changed the reactivity of PBA chain ends and allowed the complete functionalization of PBA with acrylate end groups using potassium acrylate as a reagent (Fig. 27, orange columns). Overall, these results open new avenues in the preparation of complex macromolecular architectures based on hydrophobic polymers prepared by SET-LRP in "programmed" bi(multi)phasic reaction mixtures.

5 Summary and prospects

Cu(0)-catalyzed SET-LRP is a versatile polymerization technique that has attracted considerable interest, since it appeared to be effective at preparing tailored end-functional polymers at room temperature. The choice of solvent is a variable of outmost importance for SET-LRP as it can either encourage or disfavor the disproportionation of Cu(I)X into Cu(0) and $Cu(II)X_2$, which is critical in the mechanistic pathway. Hence, the solvent-dependent nature of this LRP technique limited its scope due to the inability to proceed with living features in non-disproportionating solvents. In this context, a myriad of polar solvents such as water, dipolar aprotic (i.e. DMSO and DMF), and fluorinated/hydrogenated alcohols (i.e. MeOH, EtOH, and TFE) and mixtures therefrom have allowed to

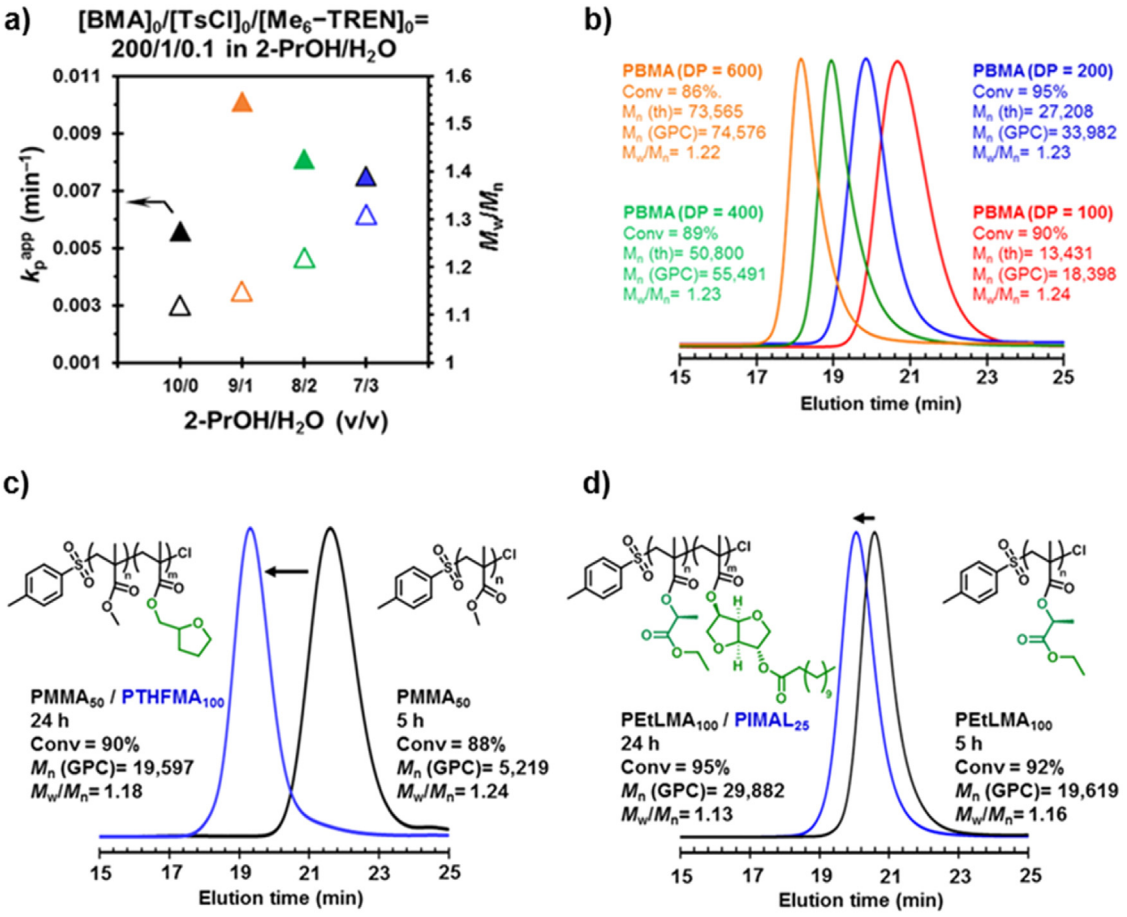

Fig. 21

(a) Dependence of k_p^{app} and M_w/M_n with the percentage of water (% H_2O) for the SET-LRP of BMA in isopropanol/H_2O. Color/shape color: filled symbols refer to k_p^{app} *y*-axis (left) and empty symbols refer to M_w/M_n *y*-axis (right), (b) GPC traces of PBMA with different targeted DPs obtained by SET-LRP of BMA initiated with tosyl chloride and catalyzed by Cu(0) wire at 50 °C in isopropanol/water (9/1, v/v). (c) GPC traces of polymer before and after "*in situ*" block copolymerization of PMMA with PTHFMA. Initial conditions for block copolymerization: $[MMA]_0/[Ts\text{-}Cl]_0/[Me_6\text{-}TREN] = 50/1/0.1$ in isopropanol/water 9/1, v/v (MMA/solvent = 2/1, v/v). Block copolymerization achieved by the addition of THFMA (100 equiv) and Me_6-TREN (0.1 equiv) in isopropanol/water 9/1, v/v (THFMA/solvent = 2/1, v/v). (d) GPC traces of polymer before and after "*in situ*" block copolymerization of PEtMA with PIMAL. Initial conditions for block copolymerization: $[EtMA]_0/[Ts\text{-}Cl]_0/[Me_6\text{-}TREN] = 100/1/0.1$ in TFE/water 9/1, v/v (MMA/solvent = 2/1, v/v). Block copolymerization achieved by the addition of IMAL (25 equiv) and Me_6-TREN (0.1 equiv) in TFE/water 9/1, v/v (IMAL/solvent = 2/1, v/v). Reproduced with permission [186] Copyright 2019, American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

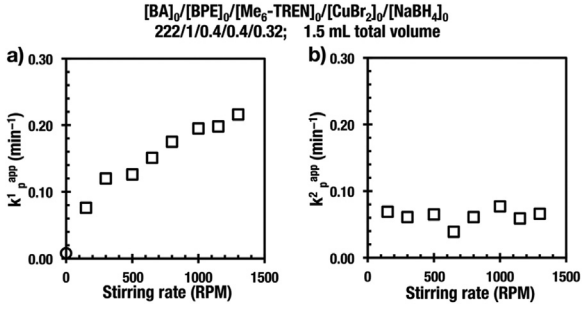

Fig. 22

$k^1{}_p^{app}$ and $k^2{}_p^{app}$ rate constants as a function of the stirring rate for SET-LRP of BA by the "prereduction method" (prereduction time = 2 s) in acetonitrile/water (7/3, v/v) initiated with BPE and catalyzed by Cu(0) generated by reduction of 2.82 mg $Cu(II)Br_2$ with 0.39 mg $NaBH_4$ at 25 °C. Reproduced with permission [156]. Copyright 2017, The Royal Society of Chemistry.

enjoy most of the advantages of this LRP technique under homogeneous reaction conditions. However, the use of poor disproportionation solvents such as acetonitrile, THF and dioxane or non-polar solvents in which Cu(I)X does not dissolve even in the presence of N-ligands such as toluene and acetone have been banned for a long time since their use compromise monomer conversion and more importantly the functionality of the resulting polymers. This perspective article aims to comprehensively present recent developments to overcome this intrinsic limitation. The discussion of a series of experimental results illustrates how "programmed" bi(multi)phasic libraries of aqueous-organic solvent mixtures enables efficient SET-LRP reactions in non-disproportionating solvents. Under these conditions, SET-LRP is an interfacial reaction in which disproportionation and activation events occur independently in the aqueous and organic compartments, and the "self-controlled" reversible deactivation takes place at

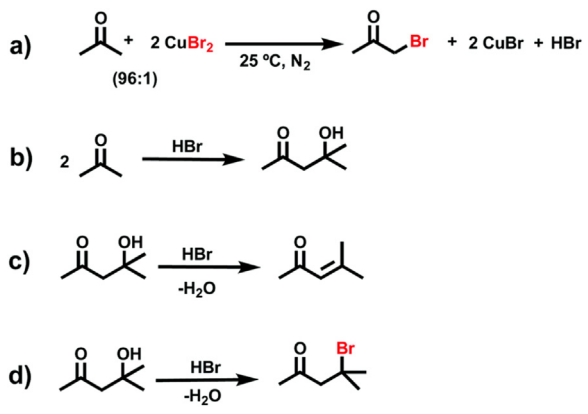

Fig. 23

(a) Non-stoichiometric Cu(II)Br_2-mediated bromination of acetone, (b) HBr-catalyzed aldol condensation of acetone, (c) HBr-mediated dehydration of DAA, and (d) HBr-mediated bromination of DAA. All reactions were observed to occur at room temperature. Adapted with permission [187]. Copyright 2018, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

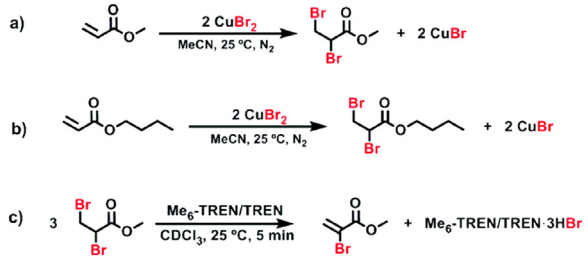

Fig. 24

(a,b) Cu(II)Br_2-mediated dibromination of MA and BA and (c) dehydrobromination of methyl 2,3-dibromopropionate mediated by Me_6-TREN or TREN in acetonitrile at 25 °C. Adapted with permission [188]. Copyright 2018, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the interface. This design is also compatible with good SET-LRP solvents when accelerated rates are demanded without compromising the livingness of polymerization. The interfacial SET-LRP concept disclosed in this perspective article can be applied in recyclable test tubes using inert gas sparging rather than in Schlenk flasks applying tedious and time-consuming free-pump-thaw deoxygenating protocols. Moreover, although it was developed using a complex multicomponent catalytic system, it showed later a remarkable compatibility with the use of Cu(0) wire catalyst. Thus, inherent characteristics of Cu(0) wire-catalyzed SET-LRP in homogeneous mixtures including high tolerance to oxygen-containing environments and commercial grade monomers will also apply to bi(multi)phasic systems [61,115,130,171,176,177]. Indeed, we expect that the system could be simplified to the point of completely removing the requirement of deoxygenating procedure because Cu(0) catalyst consumes by itself the oxygen from the reaction mixture. We envision that the results discussed here will facilitate in the near future the preparation of functional non-polar self-assembling dendritic polymers that so far were most successfully accessible *via* free-radical [192–199], living cationic [200–202], metathesis polymerizations [203,204,197], and cationic ring-opening polymerization of oxazolines [205–210] but were difficult or impossible by SET-LRP in homogeneous state or were expected to be inaccessible to SET-LRP [211–215]. Additional hydrophobic building blocks should also be employed in new SET-LRP developments to construct complex architectures [216–221]. So far only DMSO [9,53] and ionic liquids [222] are known to stabilize Cu(0) nanoparticles during disproportionation and provide the very important catalytic effect of solvent in SET-LRP [53]. Additional solvents and/or mixtures of solvents providing the solvent catalytic effect most probably *via* the cooperative and synergistic effect already observed but not explained [149] will be of great importance for the future development of this field. SET-LRP to complete conversion with zero termination [76], additional experiments on surface mediated activation and bimolecular termination [117], no reduction of $CuBr_2$ during SET-LRP [79], alternative solvents and mixture of solvents that exhibit the catalytic effect observed for DMSO [53,149] and the mixed-ligand effects [47,48] are problem that require additional investigations. Of course, that the highest rate constant of radical species is for bimolecular termination. This is well know to all of us. However, the challenge is rather than arguing that this is the case and claiming that nothing can be done about it, the alternative is to search and discover ways to retard the bimolecular termination

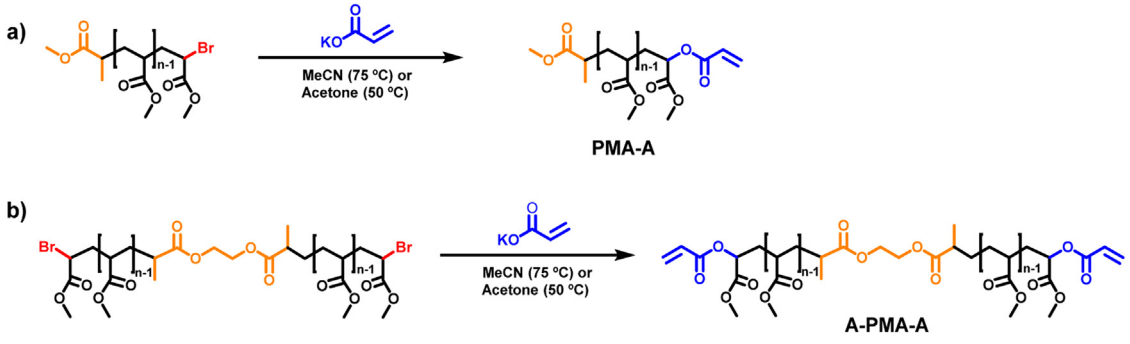

Fig. 25

Functionalization of polymer chain ends of mono and bifunctional PMA with potassium acrylate yielding PMA-A macromonomer (a) and A-PMA-A telechelic diacrylate (b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

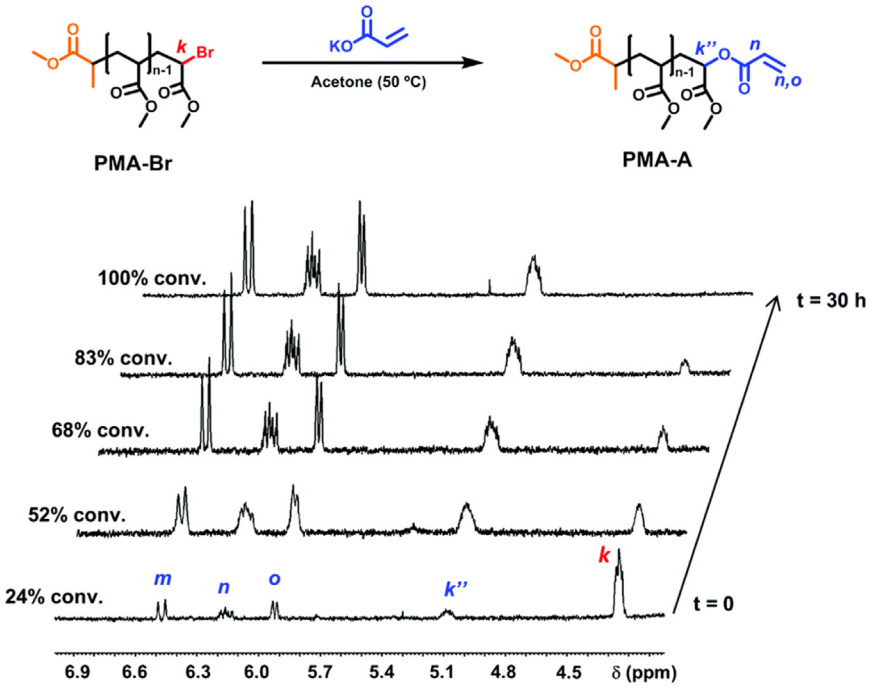

Fig. 26

^{1}H-NMR evolution traces for the functionalization of PMA (M_n = 4,596 g mol^{-1}) with potassium acrylate in acetonitrile at 50 °C to produce a PMA-A macromonomer. Degree of functionalization is shown at the left side of ^{1}H NMR traces. Reproduced with permission [163]. Copyright 2018, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

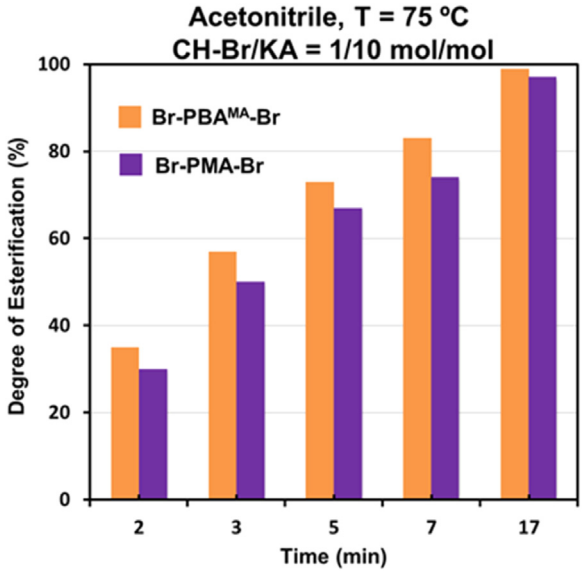

Fig. 27

Evolution for the degree of esterification *vs* time of difunctional PMA (Br-PMA-Br) and difunctional PBA chain extended with few units of MA (Br-PBA^{MA}-Br) using potassium acrylate in MeCN at 75 °C. Code color: orange (Br-PBA^{MA}-Br of M_n^{GPC} = 6,680 g/mol) and purple (Br-PMA-Br of M_n^{GPC} = 3,675 g/mol). Reproduced with permission [164]. Copyright 2018, The Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

reaction as already demonstrated that it is possible [76,117]. The same was in the case for living anionic polymerization. Free-anions are extremely reactive species and cannot produce living polymerizations due to their side-reactions. However, equilibria between free-anions and ion-pair aggregates led to the discovery of the living anionic polymerization [28,29]. We are certain that the above recommended experiments will perfect the current SET-LRP technologies and generate even more efficient polymerization processes than the current one [223,224].

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Acknowledgements

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