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## Synthetic approaches for multiblock copolymers

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Multiblock copolymers (MBCs) are an emerging class of synthetic polymers that exhibit different macromolecular architectures and behaviours to those of homopolymers or di/triblock copolymers. Owing to the rapidly expanding field of synthetic methodologies applied in the field of polymer chemistry, sequenced controlled MBCs are becoming the new functional materials of this decade. MBCs can now be synthesised with precision and control unlike before and yet some of the synthetic limitations remain a challenge. In this review article, we summarise the various synthetic methodologies that have been reported to date with recent advances in different polymerisation techniques and applications.

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### Introduction

There is a desire amongst synthetic polymer scientists to mimic nature in terms of well-defined and sophisticated macromolecules. The precision of DNA sequences leads to a flawless translation into proteins, which then self-assemble into highly complex 3D macromolecular architectures encompassing a myriad of biological functions. However, the sequential accuracy of biopolymers is yet to be achieved in synthetic polymers. MBCs, which we will define in this review as poly-

mers containing four or more blocks, are emerging as promising materials to achieve similar unique properties for a wide range of applications.<sup>1,2</sup> Stepwise synthesis on solid<sup>3</sup> or liquid<sup>4</sup> supports comprise the main approaches towards sequence definition but synthetic challenges in terms of yield and purification limit the resulting materials to oligomers in small quantities.

The discovery and optimisation of novel polymerisation techniques, combined with highly efficient coupling methodologies allow the synthesis of a seemingly endless array of macromolecular architectures ranging from block and cyclic, to graft polymers.<sup>5–9</sup> The opportunity of designing well-defined MBC chains comprised of several segments, which differ in their physical or chemical properties, opens avenues towards tuneable nanoscale-domain geometry, packing symmetry and chemical composition.<sup>10</sup> The first examples of MBCs were

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predominantly derived from step-growth polymerisations of different polymer segments yielding high molecular weight polycondensation products.<sup>11,12</sup>

The coining of living anionic polymerisation by Szwarc more than 60 years ago marked a milestone for the synthesis of well-defined block copolymers and is to date one of the best available techniques for polymeric materials with very low molecular weight distributions (MWD) and therefore achieving a high degree of control.<sup>13,14</sup> In most of the developed systems, unwanted side or termination reactions are suppressed through the introduction of modified initiators or other reagents and catalysts, allowing propagation to be the main reaction step. Therefore, the terms controlled polymerisation or reversible deactivation radical polymerisation (RDRP), which is recommended by IUPAC, are the more fitting descriptors for polymerisation techniques with living features.<sup>15</sup>

In the last 25 years, tremendous progress has been achieved in the field of RDRP, enabling scientists to produce sophisticated macromolecular architectures with an infinite degree of freedom in terms of monomer choice and polymer structure. The most applied and versatile examples for RDRP are: reversible addition-fragmentation chain-transfer polymerisation (RAFT)<sup>16</sup> and nitroxide-mediated polymerisation (NMP),<sup>17</sup> Cu-mediated RDRP.<sup>18–20</sup> The copper-mediated polymerisation systems of supplemental activator and reducing agent atom-transfer radical polymerisation (SARA ATRP)<sup>18,21,22</sup> and single-electron transfer living radical polymerisation (SET-LRP)<sup>20,23–25</sup> continue to gain increasing attention due to their growing compatibility with a variety of monomers. Although debate still surrounds the “true” mechanism of Cu-mediated RDRP, in practice the two models use the same components and comprise the same reactions, but with different contributions to the overall polymerisation.<sup>26–29</sup> The

field of MBC synthesis was revolutionised through RDRP techniques, allowing multiple chain extension experiments by retaining a high end-group fidelity of the obtained polymers. Therefore, sequential monomer addition without inter-mediated purifications steps is enabled. It is also imperative to remember that chain-growth polymerisations are a statistical process and therefore an ideal living reaction will obey a Poisson distribution with no side reactions.<sup>30</sup> Also, the inevitable occurrence of side- and termination reactions combined with the addition of multiple monomers per activation/deactivation cycle causes further deviations from this distribution. Fortunately, there are numerous examples in nature, such as structural proteins, which are less precisely controlled while displaying fascinating properties as can be found in mucins and collagens.<sup>31</sup>

Polymerisation techniques are improving rapidly and one can only imagine what will be possible in the near future. To date, LRP are powerful enough to enable the synthesis of highly complex architectures, which are sufficiently controlled to show unique properties such as self-assembly into flower-like micelles<sup>32</sup> or stress-stiffening gels.<sup>33</sup> Furthermore, the imperfection in terms of dispersity of macromolecules allows novel self-assembly behaviour, expanding the scope of chain-growth polymers even further.<sup>34–38</sup>

In this review, we summarise important examples of MBC synthesis *via* different living polymerisation techniques, post-polymerisation functionalisation, coupling reactions and their combinations. With the expanding scope of polymerisation, and the recent demonstrations in highly commendable MBC synthesis by various groups, the question still remains unanswered as to whether MBCs is a panacea or simply a demonstration of an impressive synthetic work.

## Anionic and cationic polymerisation techniques

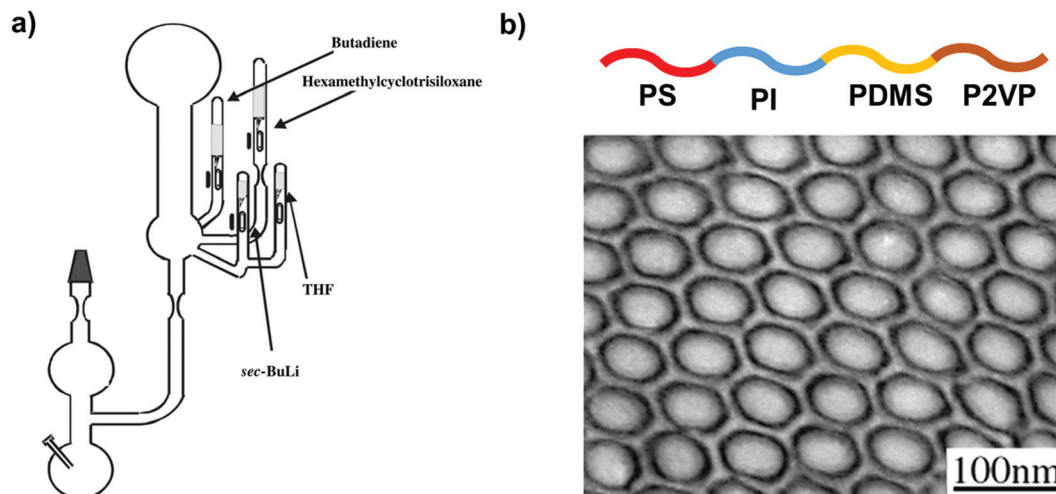
The discovery of carbanionic polymerisation more than 60 years ago marked the leap into a new era of polymer chemistry. The emerging possibilities of synthesising extremely well-defined macromolecules and even block copolymers still shape the polymer synthesis field.<sup>13,14</sup> Whilst polymerisation methods have improved steadily over the decades, anionic polymerisation yields polymers with the lowest polydispersities. Despite the extremely tedious reaction set up, including: absolute exclusion of humidity, ultra-high vacuum and tailor-made glassware, anionic polymerisation is extensively used to date (Scheme 1a). The restrictions on using this technique can be attributed to the lack of compatibility with many functional monomers and the limitations of combining monomers with different reactivity. Nevertheless, anionic polymerisation has been demonstrated as a versatile tool for the synthesis of a plethora of triblock-, multi-arm star- and hyperbranched polymers (Table 1).<sup>39,40</sup>



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**Scheme 1** a) Schematic reaction setup for the synthesis of a diblock copolymer *via* anionic polymerisation and (b) electron micrograph of annealed tetrablock polymer from polystyrene (PS), polyisoprene (PI), polydimethylsiloxane (PDMS) and poly-2-vinylpyridine (P2VP) stained with  $\text{OsO}_4$ . (Reproduced from ref. 54 and 55 with permission from Springer and ACS, 2015.)

**Table 1** Summary of MBCs prepared by anionic or cationic polymerisation techniques

Monomers	Block number	Block structure	Solvent	$T$ ( $^{\circ}\text{C}$ )	PDI	Ref.
CHD, S, I, B	4	ABCD	Benzene	5–25	1.03	40
S, I, 2VP, <i>t</i> -BMA, EO	5	ABCDE	THF	–78	1.32	41
H, I, S	5	ABCBA	THF	–78	$\leq 1.5$	42
C, E, P	12	(ABABA) <sub>2</sub> C	CH	40	1.09	43
I, 4MS	10	(AB) <sub>5</sub>	CH	30	$\leq 1.25$	44
MMA, S	10	(AB) <sub>5</sub>	THF	–78	1.06	45
EO, S, B	4	ABCA	CH	40	1.21	46
S, I, DMS, 2VP	4	ABCD	Ben	40	$\leq 1.07$	47
dcPA, <i>n</i> BA, EHA, EA, MA, cHA	6	ABCDEF	Tol	25	1.05	48
THFMA, DEAEMA, EMA, MEGMA, DMAEMA	15	(ABCDE) <sub>3</sub>	THF	25	$\leq 1.3$	49
MeOx, EtOx, PhOx, NonOx	4	ABCD	MeCN	140	1.33	50 and 51
EO, TsMAz	5	ABABA	THF/DMSO	60	$\leq 1.30$	52

Monomers were abbreviated as follows: cyclohexadiene (CHD), styrene (S), isoprene (I), butadiene (B), 2-vinylpyridine (2VP), *tert*-butyl methacrylate (*t*-BuMA), ethylene oxide (EO), *n*-hexyl isocyanate (H), ethylene (E), cyclohexylethylene (C), ethylene-*alt*-propylene (P), 4-methyl styrene (4MS), methyl methacrylate (MMA), dimethyl siloxane (DMS), ethyl methacrylate (EtMA), (dimethylamino)ethyl methacrylate (DMAEMA), 2-(diethylamino)ethyl methacrylate (DEAEMA), tetrahydrofurfuryl methacrylate (THFMA) and ethylene glycol methyl ether methacrylate (MEGMA), 2-methyl-2-oxazoline (MeOx), 2-ethyl-2-oxazoline (EtOx), 2-phenyl-2-oxazoline (PhOx), 2-phenyl-2-oxazoline (NonOx), 2-methyl-*N*-tosylaziridine (TsMAz).

Furthermore, the compatibility with sequential monomer addition was demonstrated by the synthesis of tetrablock quarterpolymers from styrene, isoprene, butadiene and cyclohexadiene. MBCs were obtained with PDI values below 1.10 and up to 28 kDa in molecular weight by utilising *N,N,N,N*-tetramethylethylenediamine (TMEDA) or 1,4-diazobicyclo[2.2.2]octane (DABCO) as additives.<sup>41</sup> In a similar fashion, very well-defined pentablock quinterpolymers of ethylene oxide with styrene, isoprene, 2-vinyl pyridine, *t*-butyl methacrylate were shown to be accessible by anionic polymerisation.<sup>42</sup> The same group synthesised pentablock terpolymers from *n*-hexyl isocyanate, styrene and isoprene. The polymerisation, which was

carried out in a high vacuum setup at  $-98$   $^{\circ}\text{C}$  using a sodium naphthalene/sodium tetraphenylborate initiating system yielded the pentablock block polymer with a PDI value of 1.32 and a high molecular weight of 128 kDa.<sup>53</sup>

The power of carbanionic polymerisation is further underpinned by numerous examples for the synthesis of MBCs with rubbery, glassy and semicrystalline segments. The obtained MBCs and blends thereof have been exhaustively investigated on their mechanical properties, phase behaviour and morphology. The key features of the polymer synthesis are the use of monomers with similar reactivity followed by a post-polymerisation hydrogenation reaction to transform styrene moi-

eties into cyclohexyl (glassy), 1,4-butadiene into polyethylene (semicrystalline) and isoprene or 1,2-butadiene into ethylene-*alt*-propylene (rubbery) moieties.<sup>43,44,56–63</sup>

Recently, the disparate reactivity of isoprene (fast reaction rate) and 4-methylstyrene or styrene (slow reaction rate) was exploited to synthesise tapered alternating MBCs by sequential addition of monomer mixtures. The obtained polymers contained up to 10 blocks, molecular weights ranging from 80–400 kDa and very low polydispersity values (1.06–1.28). In addition, thermomechanical properties and nanophase separation behaviour of the tapered multiblock polymers was analysed thoroughly.<sup>45,64,65</sup>

In order to circumvent the challenge of copolymerising monomers of different reactivity, different linking strategies for carbanionically polymerised polymers were developed. The endcapping of *sec*-butyllithium (sBuLi) initiated polymers with the heterofunctional linking agent chloromethylphenylethynyl dimethylchlorosilane (CMPDMS) yielded a well-defined triblock polymer of styrene, isoprene and dimethylsiloxane (DMS) containing a linker moiety at the chain end. Efficient coupling of the linker group with a second sBuLi-initiated polymer of 2-vinylpyridine resulted in a defined tetrablock polymer with four-phase triple coaxial cylindrical microdomain morphology (Scheme 1b).<sup>47,55</sup> Utilising similar methodologies, (AB)<sub>*n*</sub> (*n* = 2, 3, 4, 5) polymers from methyl methacrylate and styrene as well as multiblock polymers from DMS, 2-vinyl pyridine, methyl methacrylate and polystyrene were successfully synthesised (Scheme 2).<sup>66,67</sup> Furthermore, a synthetic route starting from a protected initiator in combination with diphenylmethyl potassium (DPMK) as the base activator for ethylene oxide polymerisation was shown as a suitable approach towards tetrablock terpolymers of styrene, butadiene and flanking asymmetric segments of ethylene oxide.<sup>46</sup>

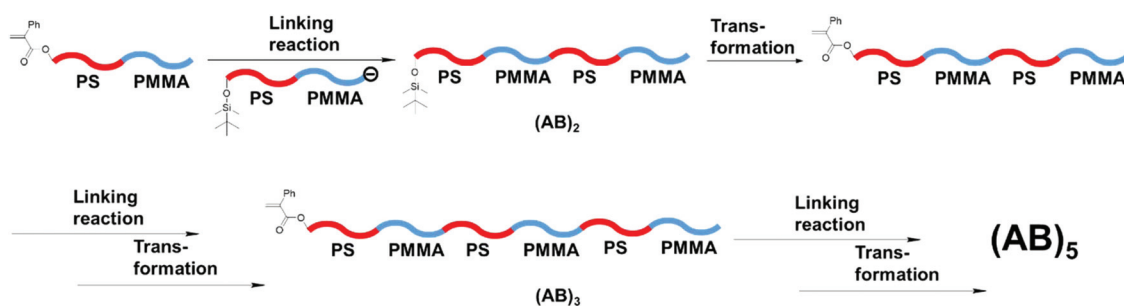
In a reaction sequence comprising 5 steps, the synthesis of telechelic diblock polymers with azide and alkyne chain ends were reported. Copper(i)-catalysed alkyne–azide cycloaddition (CuAAC) yielded cyclic or step growth MBCs depending on the concentration of the reaction solution. The step growth process generated polymer species containing up to 57 PS-*b*-PI diblock units.<sup>68</sup>

More recently, the synthesis of a triblock terpolymer of styrene, butadiene, and diphenylethylene was demonstrated through anionic polymerisation. Due to the stark contrast in

reactivity ratios between three monomers, a block structure was achieved with the most reactive monomer, butadiene, polymerising first; a method dubbed as the “fire and forget” process.<sup>69</sup> Though this was only a triblock, which by the scope of this review does not count as a MBC, this process has the potential application for further copolymerisation.

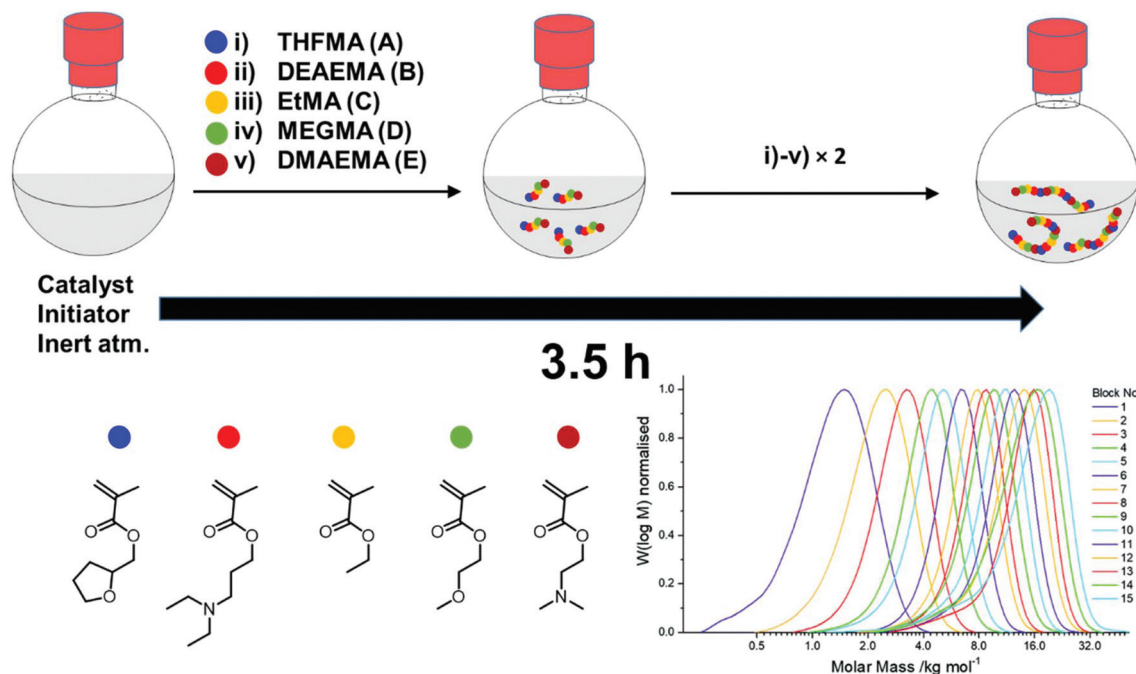
Nowadays, group-transfer polymerisation (GTP) is believed to function *via* a dissociative anionic process and hence will also be discussed in this section.<sup>70</sup> GTP was discovered more than four decades ago, likewise opening avenues towards multiblock architectures. Starting from a silyl ketene acetal initiator, the polymerisation of predominantly (meth)acrylates commences smoothly, allowing chain extension towards block polymer chains.<sup>71–73</sup> It should be pointed out that GTP is not compatible with water or monomers with acidic or active hydrogen functional groups.<sup>74</sup> Nevertheless, GTP enables the synthesis of various polymer architecture including MBCs. For example, up to hexablock bipolymers from 2-(dimethylamino) ethyl methacrylate and methyl methacrylate, undergoing self-assembly in aqueous solution, were readily synthesised.<sup>75</sup> The scope of GTP was further expanded by utilising organocatalysis to allow the synthesis of di-, hexa or dodeca-block copolymers from a wide range of acrylate monomers.<sup>76</sup> Pushing the limits, the synthesis of pentadecablock quinquaterpolymers from methacrylates in under 210 minutes was demonstrated, yielding a final dispersity of  $\bar{D} < 1.30$  (Scheme 3).<sup>49</sup> The same group utilised GTP to synthesise a library of thermoresponsive tetrablock polymers and further investigated self-assembly behaviour and gelling properties.<sup>77</sup>

Examples of cationic and anionic ring-opening polymerisations are predominantly comprising triblock polymers. There are only few examples for the synthesis of MBCs by sequential monomer addition due to chain transfer and/or chain termination events. Nevertheless, tetrablock quaterpolymers from four 2-oxazolines, namely 2-methyl-2-oxazoline (MeOx), 2-ethyl-2-oxazoline (EtOx), 2-phenyl-2-oxazoline (PhOx) and 2-phenyl-2-oxazoline (NonOx) were successfully synthesised utilising microwave-assisted cationic ring-opening polymerisation, comprising polar and nonpolar segments.<sup>50,51</sup> The obtained tetrablock polymers were investigated on surface energy and revealed that the block order impacts the surface behaviour of the polymers (Scheme 4).



**Scheme 2** Schematic synthesis of alternating (AB)<sub>5</sub> MBC of styrene and methyl methacrylate utilising a combination of anionic polymerisation, transformation and coupling reaction. (Reproduced from ref. 66 with permission from ACS, 2010.)





**Scheme 3** Schematic representation of the facile GTP, resulting in the synthesis of a pentadecablock polymer from ethyl methacrylate (EtMA), (di-methylamino)ethyl methacrylate (DMAEMA), 2-(diethylamino)ethyl methacrylate (DEAEMA), tetrahydrofurfuryl methacrylate (THFMA) and ethylene glycol methyl ether methacrylate (MEGMA) with SEC traces of the chain extensions. (Reproduced from ref. 49 with permission from RSC, 2018.)

Furthermore, activated sulphonamide-substituted aziridines were copolymerised with epoxides in a one-pot, one step or two step fashion, yielding amphiphilic multiblock polymers.<sup>78</sup> However, the obtained materials show excellent livingness and yield very well-defined polymers.

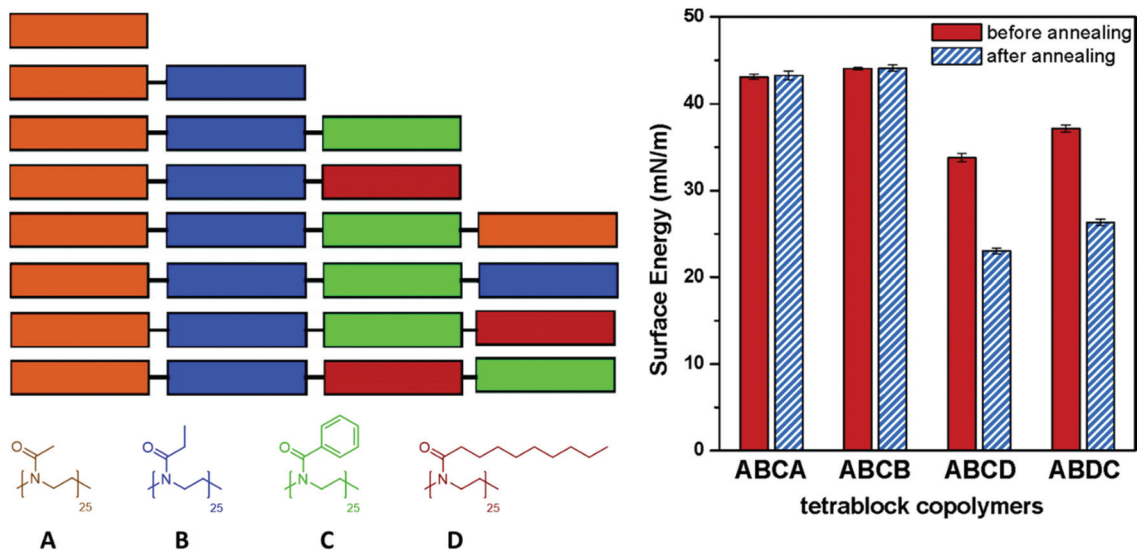
Experimentally speaking, ionic and especially carbanionic polymerisation might pose many difficulties and drawbacks in terms of compatibility with functional groups and reaction setups. However, sophisticated reaction apparatuses and progress in ultrahigh vacuum techniques allow the larger scale synthesis of the most defined polymers among most chain-growth polymerisations. Furthermore, monomers such as isoprenes, butadienes or cyclohexadienes are deployable with anionic polymerisation. The discovery of novel linking strategies and the combination with other polymerisation techniques make well-defined polymers for example 4-miktoarm star quartpolymers<sup>79</sup> and polyolefin-polystyrene MBCs<sup>80</sup> accessible. In order to complement this exciting polymerisation technique, researchers discovered an arsenal of other approaches, opening avenues towards MBCs with a broader scope of monomers while also retaining good and sufficient living characteristics.

## Ring opening metathesis polymerisation

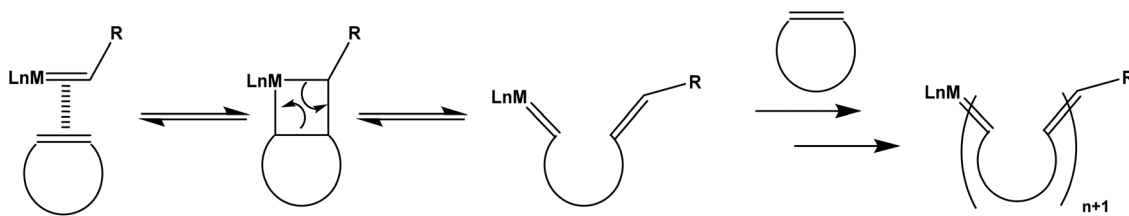
Ring Opening Metathesis Polymerisation (ROMP), a derivative of olefin metathesis, uses strained cyclic olefins to form linear

polymers that contain olefinic bonds in the backbone, offering a distinct architecture different to that of polymers formed from other methods (Scheme 5). Although the first demonstration of ROMP in 1955 used  $\text{TiCl}_4/\text{EtMgBr}$  as a catalyst for polymerisation,<sup>81</sup> it has been more common in recent years to use a catalyst, such as Schrock or Grubbs for better defined polymers, with a plethora of literature reporting polymers formed from Rh/Mo based catalysts.<sup>82–84</sup>

The main driving force of ROMP is the release of ring strain (negative enthalpy change) and is an equilibrium controlled reaction.<sup>85</sup> The majority of the polymerisation reaction involves the ring opening of norbornene derivatives because it has great ring strain, driving the equilibrium to the product side (Table 2). Although the reaction can be terminated by either complete consumption of monomer or by quenching the reaction, it can also undergo inter/intramolecular chain transfer reactions, which can broaden the polydispersity of the polymer.<sup>86</sup> Therefore, sequential addition of blocks through ROMP to form MBCs can be a synthetically challenging and laborious procedure because with the addition of each new monomer the livingness of the chain decreases with some being terminated by trace impurities.<sup>87</sup> Furthermore, because of the double bonds present in the polymer backbone, the polymer can undergo secondary metathesis. Consequently, the sequence of blocks is pre-determined by the bulkiness of the monomer; usually the bulky monomer, with a slower rate of polymerisation, being polymerised first in order to minimise secondary metathesis.<sup>88</sup> This results in a limited number of reports on block



**Scheme 4** Schematic representation of the tetrablock quarterpolymer sequences synthesised by sequential addition of MeOx, EtOx, PhOx, NonOx and the surface energy according to the block sequence. (Reproduced from ref. 51 with permission from ACS, 2007.)



**Scheme 5** General mechanism for ring opening metathesis polymerisation (ROMP).

**Table 2** Examples of MBCs prepared by ROMP

Monomers	Block number	Block structure	Block DP	Solvent	Time/block (h)	$T$ ( $^{\circ}\text{C}$ )	Ref.
N	4	ABCD	50 : 5 : 10 : 5	Tol	0.5	RT	89
Nb	5	ABABA	44 : 35 : 44 : 35 : 44	DCM	1	RT	90
Nb	4	ABAB	15 : 10 : 10 : 10	$\text{CHCl}_3$	2 : 19 : 4 : 24	RT	91
Co, MO	4	ABAB	50 : 5 : 10 : 5	Tol	0.5	RT	92

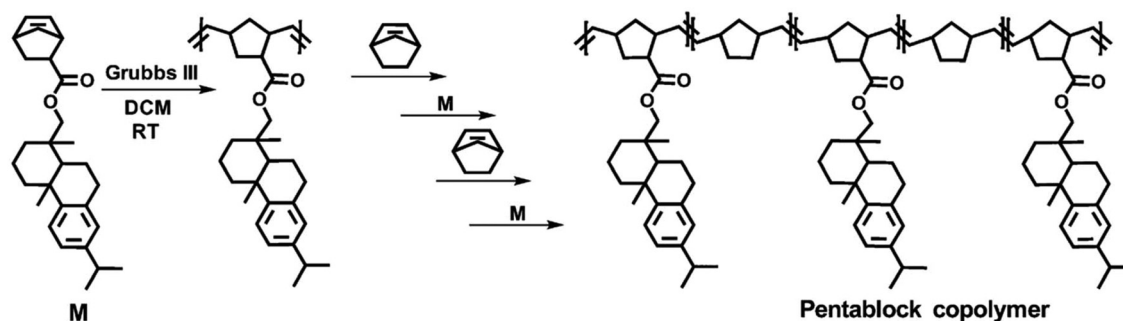
Monomers were abbreviated as follows: norbornediol (N), norbornene (Nb), polyhydroxyoctenamer (PHO), cyclooctaone (Co), macrocyclic olefin (MO), dichloromethane (DCM), not determined (ND), toluene (Tol).

copolymers *via* sequential addition of monomers compared to other polymerisation methods. However, ROMP has been incorporated with other polymerisation and coupling techniques to form unique MBC architectures.

Early demonstration of MBCs using solely ROMP can be dated to 1995 where a tetrablock quarterpolymer of norbornediol derivatives were synthesised using Schrock's catalyst.<sup>89</sup> Low polydispersity MBCs were obtained by controlling the monomer to catalyst ratio and keeping the subsequent block lengths between 5–10 monomer units. Well-defined tetrablock bispolymer of blocks containing on average 10 monomer units

was synthesised also by sequential addition with a Ru-based catalyst. The norbornene units contained sugar units, desirable for biomedical purposes, and were synthesised with near-full conversion and with good polydispersity.<sup>91,92</sup>

Recently, research has been done on bioplastics derived from rosin based polymers. Pentablock copolymers were synthesised by sequential addition *via* ROMP using Grubbs III catalyst (Scheme 6). It was also noted in this particular case that the synthetic procedure was cumbersome due to the fast reaction time each monomer had to be added very quickly.<sup>90</sup> However, it was definitive from the research that MBCs had



**Scheme 6** Sequential addition of dehydroabietic acid-derived norbornene and norbonene by ROMP. (Reproduced from ref. 90 with permission from ACS, 2017.)

superior toughness compared to homo and triblock copolymers in this case, highlighting the application and importance of MBCs.

With synthetic challenges remaining, coupling pre-formed polymer blocks through ROMP has been utilised in order to maintain unique features and architectures of the ring opened polymers whilst bypassing the difficulties of the sequential addition procedure. This can be done by synthesising  $\alpha,\omega$ -telechelic polymers through ROMP and coupling together by methods such as “click” chemistry<sup>93</sup> and Wittig coupling.<sup>94</sup> In addition, the apparently boundless array of MBCs is complemented by the synthesis of polyolefins *via* insertion polymerisation utilising rare earth metal catalysts,<sup>95,96</sup> the ring-opening of nitroxide-containing cyclic peptides<sup>97</sup> and organo-catalysed polymerisation of acrylates.<sup>98,99</sup> For more examples of MBC synthesis, the reader is instructed to refer to the recent review article covering the state of the art in olefin metathesis of MBCs.<sup>87</sup>

In general, olefin metathesis in polymerisation provides a synthetic pathway for polymers much different to that of polymers formed from radical polymerisation, the highlight being olefin bonds present in the backbone, which is seldom seen in other polymerisation techniques. However, it simultaneously hinders the type of monomer that can be used with this procedure, the other polymerisation methods accommodate for a larger variety of monomer types. Also, sequential addition to form MBCs with this technique is challenging; as mentioned previously, it is prone to secondary metathesis and chain transfer reactions. In lieu of this, ROMP can be used in combination of various coupling strategies to form MBCs, relieving the complications associated with the synthetic procedure.

## Reversible-addition fragmentation chain transfer: RAFT

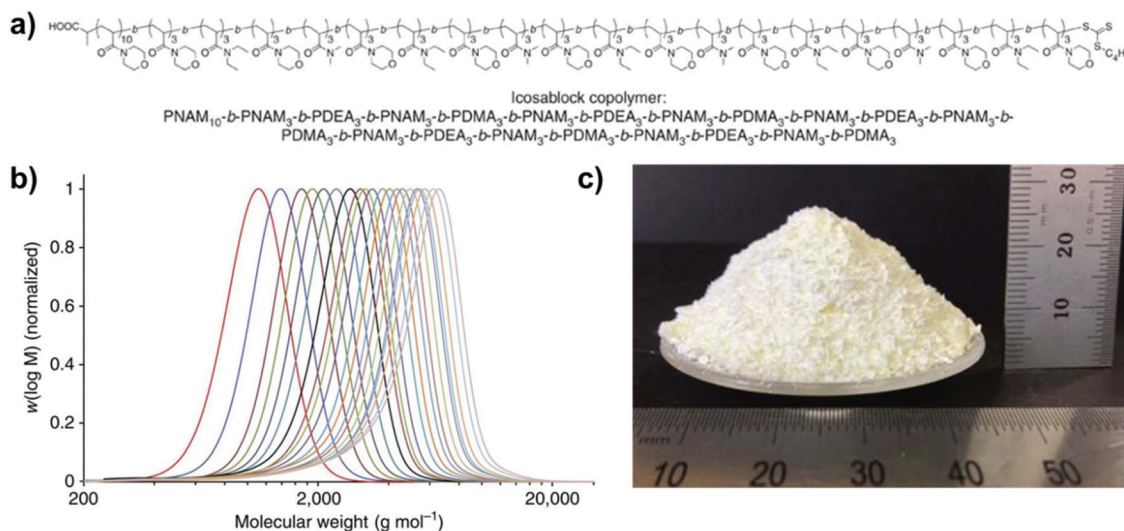
RAFT polymerisation was first reported in 1998<sup>100</sup> and since its discovery, tremendous progress in terms of chain-transfer agent (CTA) design and reaction condition optimisation have propelled RAFT polymerisation to become one of the most utilised techniques for the synthesis of macromolecules. The liv-

ingness of RAFT polymerisation is achieved by addition of radicals to the chain-transfer agent (CTA), which most frequently comprise of dithioesters, trithiocarbonates, dithiobenzoates, and xanthates. The rate of the formed addition–fragmentation equilibrium is much higher than the propagation and therefore, the degree of polymerisation (DP) is similar among all growing species. For a more detailed view on the mechanism and kinetics of RAFT polymerisation, the reader is referred to recent exhaustive reviews on this topic.<sup>101–109</sup> In particular, RAFT polymerisation is extensively utilised for the synthesis of block copolymers due to the availability of a wide range of different CTAs and the possibility of sequential monomer addition, allowing the polymerisation of styrenics, (meth)acrylates and acrylamides.<sup>110</sup> Furthermore, simulations have been carried out showing that after ten chain extensions, the fraction of living chains still remain very high at 93%.<sup>111</sup>

In 2013, the remarkable synthesis of MBCs with a high number of blocks *via* the RAFT process was first reported. The utilisation of a trithiocarbonate CTA and free radical initiator 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044) yielded well-defined acrylamide polymers with up to 20 blocks and full monomer conversion for all reaction steps in a one-pot reaction (Scheme 7). The use of water/dioxane mixtures allowed the polymerisation to proceed within 2 hours per segment. It has to be noted, that the degrees of polymerisation (DP) for the 20-block polymer were kept very low (DP = 3) and that monomers with very similar properties were copolymerised (Table 3).<sup>112</sup> The livingness of this RAFT process was further optimised by exploiting the degenerative transfer mechanism, enabling the synthesis of alternating decablock copolymers. The chain end fidelity was increased to 97% to yield well defined acrylamide MBCs.<sup>114</sup>

The same group further improved this approach to obtain well-defined dodecablock polymers, incorporating four different acrylamides with a DP of 10 in two hours per segment. Additionally, higher molecular weight pentablock copolymers with 3 different acrylamides and a DP of 100 for each segment were synthesised successfully, reaching full monomer conversion with 2 hours reaction time per block.<sup>113</sup>

By increasing the reaction temperature to 100 °C, alternating pentablock (DP = 10) copolymers of acrylamides were syn-



**Scheme 7** Synthesis of alternating icosablock polymer from acrylamides: (a) chemical structure of obtained MBC; (b) SEC traces of chain extension steps and (c) scale of obtained polymer after purification. (Reproduced from ref. 112 with permission from Springer, 2013.)

**Table 3** Examples of MBCs synthesised by RAFT polymerisation

Monomer	Block number	Block structure	Block DP	Solvent	Time/block (h)	$T$ (°C)	Ref.
Am	20	(AB) <sub>10</sub>	3	H <sub>2</sub> O	2–24	65–70	112
Am	12	(ABABAC) <sub>2</sub>	10	H <sub>2</sub> O/Dio	2	70	113
Am	10	(A) <sub>10</sub>	10	H <sub>2</sub> O	24	65–70	114
Am	5	(AB) <sub>n</sub>	50–100	H <sub>2</sub> O/Dio	2	70	115
Am	5	ABACA	25	H <sub>2</sub> O	0.05	100	116
Am/(M)Ac	10	(AB) <sub>n</sub>	50	PBS	1	30	117
Ac	6	ABCDEF	≤10	<i>n</i> -But	0.6	100	118
MAc	21	(AB) <sub>11</sub>	≤50	H <sub>2</sub> O	3	85	119
MAc	8	ABCABCAB	25	H <sub>2</sub> O	2	80	120
MAc	10	ABCDEF	100	H <sub>2</sub> O	0.5	80	121
(M)Ac, S	5–9	ABCDE	100–150	H <sub>2</sub> O	3	75	122

Monomers were abbreviated as follows: acrylamide (Am), acrylate (Ac), methacrylate (MAc), styrene (S), dioxane (Dio), *n*-butanol (*n*-But).

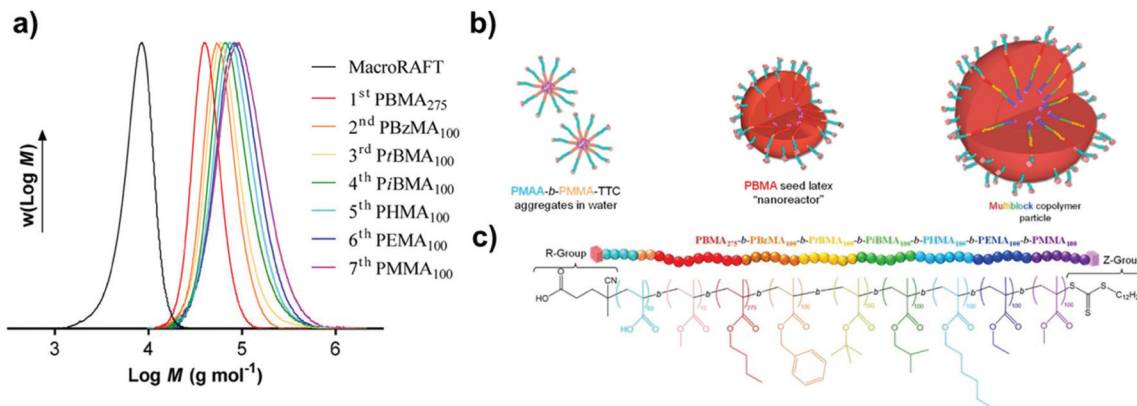
thesised in an ultrafast RAFT process with only a 3 minutes reaction time per polymer segment. Furthermore, the polymerisations showed perfect tolerance towards the presence of air, facilitating the reaction setup enormously.<sup>116</sup> The versatility and robustness of this RAFT polymerisation method was also underpinned by the ultrafast synthesis of multiblock polymers in microliter reaction volumes without deoxygenation.<sup>123</sup> Despite the short reaction times, well-defined end products and full monomer conversions, it has to be noted that the applied conditions are only suitable for fast propagating and water soluble monomers, limiting the scope of this approach. Nevertheless, aqueous RAFT polymerisation is a powerful tool for the synthesis of multiblock polymers and even more sophisticated architectures such as complex multi-segmented bottle brush polymers.<sup>115</sup> Additionally, scaling up of the MBC synthesis was shown to be feasible by using different looped flow RAFT processes.<sup>118,124</sup> Achieving high DPs for polymer blocks is restricted by the initiator concen-

tration, which can only partially be compensated by the resulting shorter reaction time. High target degree of polymerisation also results in a reduction of living chains due to smaller amounts of RAFT agent. Therefore, the polymerisation of low  $k_p$  monomers such as methacrylates is particularly difficult.

The challenge of multiblock methacrylate polymerisation via a RAFT process was elegantly resolved by utilising an emulsion polymerisation methodology, allowing the synthesis of high molecular weight (>100 000 Da) multiblock polymers, and moreover, a heptablock polymer consisting of 7 different DP = 100 blocks. The macro-CTA approach in an emulsion polymerisation leads to a monomer swollen state, resulting in very high polymerisation rates.

The described method yields MBCs with short reaction times, low RAFT agent concentration, no purification steps and good colloidal stability, fulfilling all requirements for and industrial scale synthesis (Scheme 8).<sup>121</sup>





**Scheme 8** One pot nanoreactor emulsion RAFT polymerisation of high DP MBCs from a wide range of methacrylates; (a) SEC analysis of obtained polymers after each polymerisation cycle and (b) schematic representation of *in situ* nanoreactor formation accompanied by chemical structure of final nonablock polymer. (Reproduced from ref. 121 with permission from ACS, 2019.)

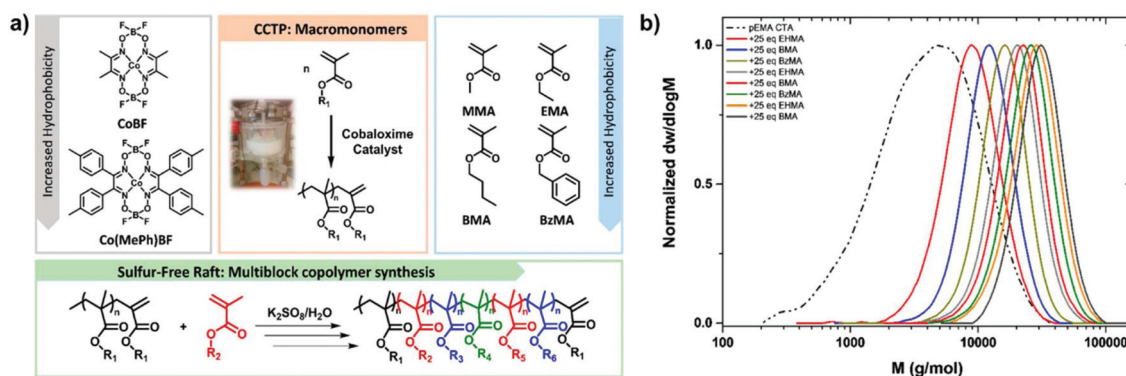
The “nanoreactor” concept was further harnessed to produce styrene-methacrylate and styrene-acrylate MBCs in aqueous media with high molecular weights and low PDI values. It has to be noted that styrene-butyl acrylate block copolymers were only accessible when butyl acrylate blocks were copolymerised in the presence of 10% styrene.<sup>122</sup>

In addition, methacrylate MBCs were synthesised *via* a sulphur-free RAFT emulsion polymerisation utilising a vinyl-terminated polymer as macro-CTA. High conversions and low polydispersities were achieved by feeding monomers slowly into the emulsion polymerisation reactor, allowing the synthesis of macromolecules with 20 consecutive chain extensions and undecablock polymers with alternating monomer block sequences in aqueous reaction media.<sup>119</sup> The scope of this reaction was further expanded by using different macro chain transfer agents and synthesising multiblock methacrylate copolymers with up to 50 monomer units per block and PDI values <1.20. The reaction setup is insensitive towards monomer sequence, proceeds with high reaction rates and does not use malodorous or coloured substances (Scheme 9).<sup>120</sup>

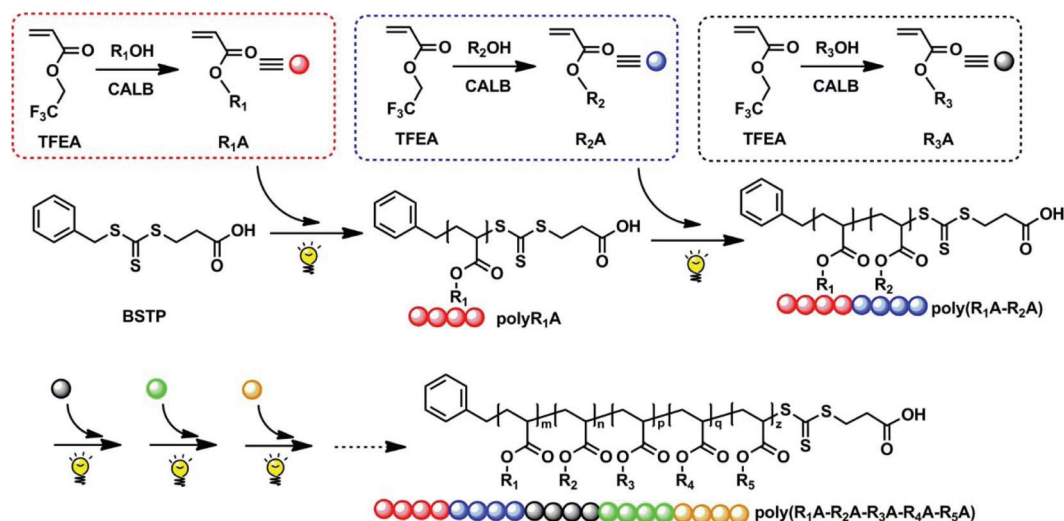
Despite the high potential for a diverse range of application of these MBCs, only a few results are published to date. MBCs from methyl acrylate, maleic anhydride and styrene were investigated on their performance as asphalt additives. The incorporation of functional monomers resulted in an increased chemical interaction with the asphalt polar fraction and therefore improved viscosity, elasticity and storage stability.<sup>120</sup>

In an impressive fashion, thermally-induced RAFT polymerisation was shown to be a powerful tool for the synthesis of well-defined MBCs. Complementarily, photoinduced electron transfer-reversible addition-fragmentation chain transfer (PET-RAFT) polymerisation was demonstrated as a suitable technique for MBC synthesis. Well-defined pentablock copolymers consisting of up to 5 different acrylate blocks with DPs up to 50 were successfully synthesised utilising an iridium catalyst and visible light irradiation. In addition, enzymatic monomer transformation allowed the generation of acrylates with tuneable functionalities, for example protected alkynes (Scheme 10).<sup>125</sup>

The same research group demonstrated the use of zinc porphyrins for PET-RAFT towards block copolymers at a wide



**Scheme 9** Cobalt-catalysed chain-transfer polymerisation of different methacrylic monomers: (a) schematic representation of polymerisation reaction with monomers, catalyst and sequential monomer addition; (b) SEC traces of chain extension experiments. (Reproduced from ref. 120 with permission from ACS, 2018.)

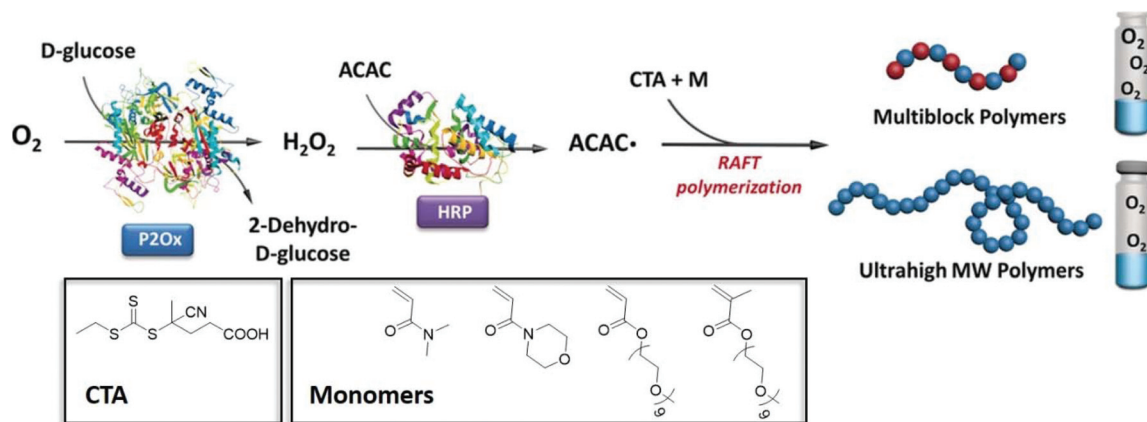


**Scheme 10** Schematic representation of PET-RAFT process for the sequential synthesis of MBCs utilising monomers capable of enzymatic transformation with alcohols. (Reproduced from ref. 125 with permission from ACS, 2014.)

range of wavelengths (435–655 nm) consisting of methacrylates, methacrylamides and/or styrene. However, multiple chain extension utilising the oxygen tolerant system was only shown for a pseudo pentablock polymer of methyl acrylate blocks (DP = 5). Similar results were obtained when using trithiocarbonyl compounds with a  $n \rightarrow \pi^*$  transition in the visible light area ( $\sim 460$  nm) without using any external catalyst or initiator. Due to quantitative monomer conversions, the polymers were obtained in their purest form. The method was shown to be suitable for one pot chain extension polymerisations and it has to be noted that reaction times are fairly long, reaching from 16–24 hours. Furthermore, multiple chain extension experiments were only carried out with methyl acrylate, yielding a pseudo hexablock polymer with a degree of polymerisation of 100 for each polymerisation cycle.<sup>125</sup> The limits of PET-RAFT were further pushed forward by applying a high-throughput reaction set up in 96-well

plates. The technique was shown to be suitable for up to 6 chain extensions with 120–240 min per DP = 25 block *N*-acryloyl morpholine at extremely low reaction volumes.<sup>126</sup> The same group further demonstrated the use of the photo-induced RAFT process to tailor a wide range of polymeric materials with tuneable antimicrobial properties. Varying block compositions, multiblock polymers with up to 6 blocks made from *tert*-butyl-(2-acrylamidoethyl)-carbamate, 2-phenylethyl acrylamide and 2-hydroxyethyl acrylamide have been synthesised, retaining livingness for 70–90% of the chains.<sup>127</sup> Additionally, a green, enzymatic cascade catalysis coupled with the RAFT process was utilised to produce well defined alternating decablock copolymers from acrylamides with remarkable oxygen tolerance of the polymerisation process (Scheme 11).<sup>117</sup>

RAFT polymerisation emerged to become a leading technique to synthesise well-defined macromolecules not only in a



**Scheme 11** Schematic representation for the enzyme-cascade mediated RAFT polymerisation of acrylamides and water-soluble (meth)acrylates towards MBCs in aqueous media. (Reproduced from ref. 117 with permission from Wiley, 2017.)

laboratory scale but also in multi ton quantities. Due to being a simply modified free radical polymerisation process, RAFT became a powerful tool for the synthesis of sophisticated polymer architectures, crossing over from the metier of trained polymer chemists to engineers and biologists. The optimisation of reaction conditions in terms of initiator choice and chain-transfer agent enable the synthesis of incredible polymers from a wide range of styrenics, (meth)acrylates and acrylamides, joining the entourage of polymerisation techniques capable of producing MBCs.

## Cu-mediated living radical polymerisation

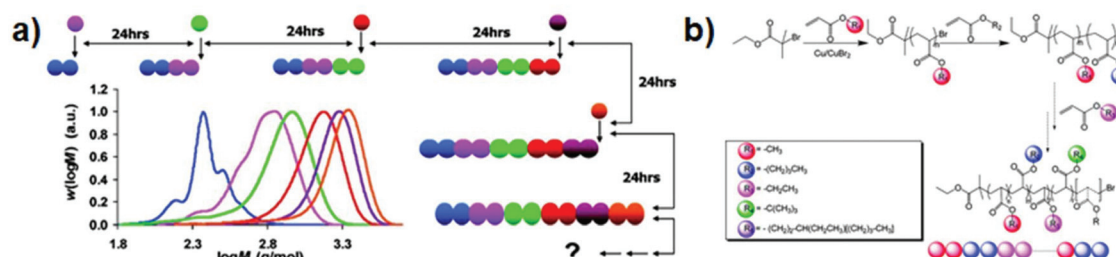
MBCs from Cu-mediated reversible deactivation radical polymerisation (Cu-RDRP) was demonstrated as early as 2001, by Dadmun and Eastwood, with the synthesis of a pentablock copolymer (consisting of two different monomers) of methyl methacrylate and styrene in an AB alternating fashion.<sup>128</sup> Since then, a plethora of MBCs of varying functionalities have been shown from both Cu(0) and Cu(I) mediated polymerisation. Though there is an ongoing debate regarding the mechanism and the role of the Cu complex in the polymerisation,<sup>23,129,130</sup> this section of the review will focus on the synthetic outcome of this method rather than the mechanistic details of the reactions.

Similar to other controlled radical polymerisation techniques, Cu-mediated RDRP can reach full/near full monomer conversion whilst still maintaining its living features. It is often the case that controlled radical polymerisation requires purification after each block to remove unreacted monomers thus resulting in loss of 'livingness'. This is a significant deterrent for high order MBCs and therefore makes well defined high molecular weight MBC synthesis a challenge. Since 2011, a multitude of Cu-mediated MBC synthesis has been demonstrated, starting from a hexablock quarter polymer consisting of two monomer units per block (Scheme 12) by Whittaker *et al.* By using solvents which promote disproportionation, in this case DMSO, and ensuring full/near full-conversion by keeping the block lengths short (on average two monomer units per block), a MBC of acrylates was synthesised.<sup>131</sup> This sequence-controlled, well-defined MBC of various acrylates still maintained high end-group fidelity, which yielded MBCs

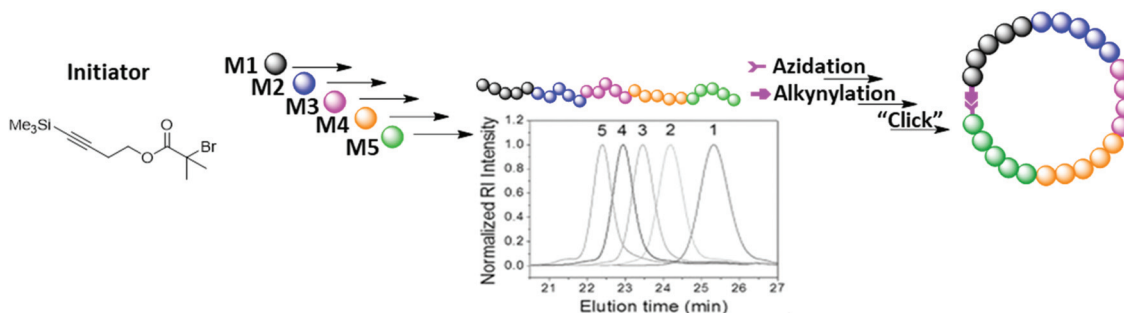
with three possible end group functionalisations (nucleophilic substitution of sodium methanethiolsulfonate, benzyl mercaptan, and atom transfer radical coupling in the presence of nitroxide). However, it must be noted that the molecular weight distribution gradually increases with the increasing block numbers. Continuing on from this, other MBCs were synthesised *via* Cu-mediated polymerisation, once again using similar conditions in terms of good disproportionation promoting solvent and short block lengths.<sup>132</sup> With these initial outcomes, a criteria was established in forming sequence controlled MBCs in that the synthesis must have: no intermediate purification steps to ease the experimental procedure, subsequently meaning a full/near monomer conversion of each block, whilst still maintaining a narrow molecular weight distribution per block.<sup>131,133,134</sup>

Higher molecular weight MBCs were later achieved by using the same procedure;<sup>135</sup> developing on from the low molecular weight MBCs, blocks of up to 100 monomer units was achieved by tuning the amount of Cu(II) and ligand which hinders side reactions that cause termination reactions. In early examples of Cu-mediated living radical polymerisation was achieved by sequential addition of similar monomers (*e.g.* all acrylates) with similar reactivity rates, but with the desire to mimic the precise nature of sequences of varying functionalities that are present in biomolecules, the synthetic procedure was optimised to accommodate various monomers types. Glycopolymers were also synthesised *via* this approach by forming a multiblock of poly(glycidyl acrylate)-*co*-(acrylic acid 3-trimethylsilylprop-2-ynylester) (poly(GA)-*co*-(TMSPA)) and then using thiol-halogen or thiol-epoxy reactions as post modifications to form a glycopolymers.<sup>136</sup>

Expanding from the linear approach, other architecture such as star shaped MBCs have been formed.<sup>137,138</sup> It was also recently demonstrated that cyclic MBCs can be formed *via* SET-LRP and CuAAC ring closure (Scheme 13).<sup>139</sup> As with other multiblock formations using this approach, the first acrylate block was synthesised and the subsequent monomers were added in a sequential manner to form the multiblock with an average brush length of 10 repeating units. The polymer was then modified by azidation and deprotection of the alkyne end, allowing cyclisation of the end groups through click chemistry. Though an application for cyclic MBCs is yet to be reported, the desirable properties of cyclic polymers including better



**Scheme 12** An early example of Cu-mediated RDRP MBC synthesis. (Reproduced from ref. 131 and 132 with permission from RSC and ACS, 2011.)



**Scheme 13** Cyclisation of  $\alpha,\omega$ -telechelic pentablock copolymer through Click chemistry. (Reproduced from ref. 139 with permission from Wiley, 2017.)

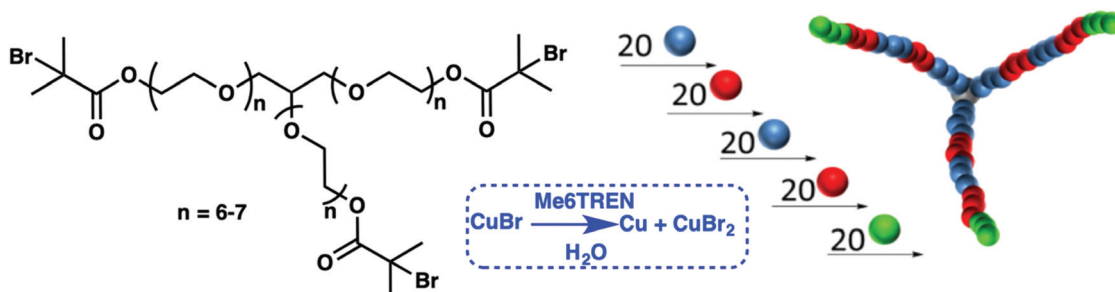
thermal stability, lower melt viscosity, shows that it is a promising area of research.

Cu-Mediated polymerisation was also shown to give well defined MBCs in aqueous media, which has the advantage of having a faster rate of reaction than in organic media; the key component being the full disproportionation of the metal-ligand complex before the addition of monomer and initiator.<sup>140</sup> The versatility of aqueous Cu-mediated polymerisation was demonstrated as a facile synthetic pathway for hydrophilic/thermo-responsive containing MBCs in just two hours.<sup>141</sup> This rapid synthetic protocol has an advantage over other polymerisation methods, such as RAFT, in that it can be conducted at ambient temperatures or lower, which means that thermo-responsive blocks can be incorporated into the polymers. Heptablock copolymers of ten units per block was also achieved in aqueous media whilst still maintaining excellent control over polydispersity by allowing Cu-ligand disproportionation prior to the addition of monomer and initiator. In addition, the reaction was carried out at low temperature, 0 °C, to minimise competing side reactions, allowing the chain extension without compromising the integrity of the MBC.<sup>142</sup> Additionally, because it is conducted in water, it can be classed as safer and cheaper in comparison to Cu-mediated polymerisation in organic media. Multiblock star polymers have been synthesised in less than 90 minutes through this approach, which used acrylamide to form a pentablock three arm star polymer (Scheme 14).<sup>143</sup> By monitoring the monomer conversion closely, loss of end group functionality and

unnecessary reaction was reduced, allowing for rapid chain extension. This demonstration of aqueous Cu-mediated polymerisation showed potential for biomedical and drug delivery applications.

More recently, amphiphilic nonablock copolymers of PEG and PNIPAM were synthesised rapidly in aqueous media to form well defined linear MBCs.<sup>144</sup> These then underwent self-assembly to form polymeric vesicles, also called polymersomes, which were biocompatible. Polymersomes are of great interest from a bionanotechnology perspective and in this case, addition of small blocks of PNIPAM in a sequential fashion allowed for polymersomes of permeability which could be fabricated by controlling the chain length, which can be easily done by altering the number of PNIPAM blocks.

Photoinduced Cu-mediated living radical polymerisation has also been shown to produce well defined MBCs in a one-pot reaction. Compared to Cu(0) or Cu(I) initiated systems, light mediated polymerisation is conducted at ambient temperatures and requires lower amounts of copper, which can be desirable in a polymerisation system for its economic benefits (for scale up reactions) and lower toxicity. In addition, milder reaction conditions can lead to more well defined polymers as it diminishes side reactions and thus provide a better control over the polymerisation. With photo-induced Cu-mediated polymerisation, there is an added benefit that control over the reaction can be improved as the reaction can be stopped when the light is switched off, and can proceed when the light is on



**Scheme 14** Pentablock star polymer in aqueous media synthesised in under 90 min. (Reproduced from ref. 143 with permission from RSC, 2016.)



**Table 4** Examples of MBCs prepared by Cu mediated RDRP

Monomer	Block number	Block sequence	Block DP	Solvent	Time/block (h)	<i>T</i> (°C)	Ref.
Ac	6	ABCDCB	2	DMSO	24	25	131
Ac	10	(ABCC) <sub>2</sub> AB	2	DMSO	24	25	132
Ac	<5	ABCD	<5	DMSO	24	25	137
Ac	5	(A) <sub>5</sub>	100	DMSO	24–28	25	148
Ac	11	ABCDBCBCDB	3	DMSO	2–24	25	145
Ac	6	ABABAB	8, 4	DMSO	6–14	25	136
Ac	23	(BDBCADACDCB) <sub>2</sub> A	<100	DMSO	10–24	15	149
Ac	4	ABCD	23	DMSO	6–24	25	138
Ac	5	ABCDE	10	DMF	2–22	25	139
Ac	5	ABCDE	25	TFE	10–18	25	150
Ac, MAc	10	ABACABADBD	5	DMSO	2–7	25	147
Am	6	ABCACB	10	H <sub>2</sub> O	<1 s	0	142
Am	7	ABCDCEA	10	H <sub>2</sub> O	0.3	0	141
Am	5	ABABC	20	H <sub>2</sub> O	0.3	25	143

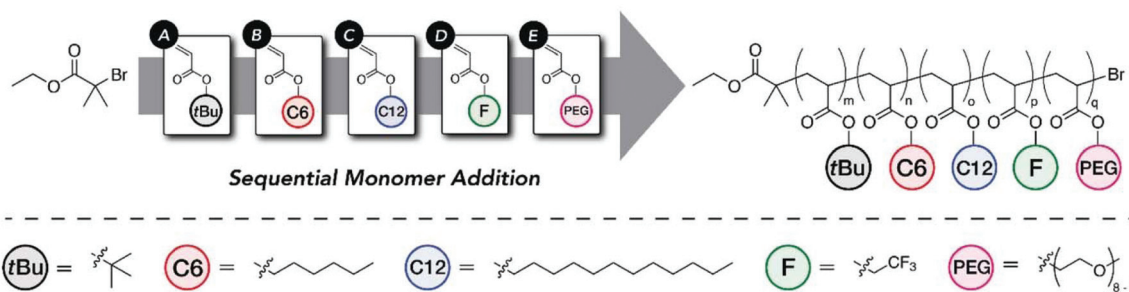
Monomers were abbreviated as follows: acrylate (Ac), acrylamides (Am), methacrylates (MAc).

again. This elegant approach to MBC synthesis was demonstrated in 2012 with a dodecablock quarterpolymer.<sup>145</sup> By addition of ligand and Cu(II) in every three iterations, well defined high molecular weight (up to ten units per block) MBCs were achieved. In a similar fashion, higher order MBC synthesis was demonstrated by the same research group, achieving copolymers with 3–13 units per block. In addition to being  $\alpha,\omega$ -telechelic, through the use of a bisinitiator, they showed that the degree of control in photoinduced polymerisation can be increased by employing a disulphide bond containing bisinitiator. Upon reductive cleavage, the polymer was exactly half the molecular weight of the original MBC, showing the true symmetrical nature of the original polymer.<sup>133</sup> Furthermore, photoinduced polymerisation at ambient conditions allows for straightforward synthesis of MBCs with biological applications. It should be noted that one of the drawbacks of photoinitiation is increased loss of chain end functionality (bromine in most cases), which is essential for chain extension in multiblock synthesis, and coupling reactions. This is attributed to the decrease in monomer concentration as the reaction proceeds leading to radical interchange between the active and dormant species.<sup>146,147</sup> However, in order to form the MBC without any purification steps in

between block formation, a near full conversion is ideal (around 95%) (Table 4).<sup>147</sup>

Cu-mediated polymerisation of MBCs have shown numerous interesting application potentials in recent years. With most CRP methods, a challenge remains in that it is difficult to polymerise monomers that are vastly different in reactivity and the difficulty is only compounded for MBCs. Choice of solvent is also important for well-defined polymers and TFE, a commercially available solvent, was shown to dissolve monomers of varying functionalities. Through the use of TFE in a light-Cu-mediated process, pentablock copolymers were synthesised that contained hydrophobic, hydrophilic, and semi-fluorinated blocks (Scheme 15).<sup>150</sup> The use of a bisfunctional initiator enabled the synthesis of symmetric nonablock copolymers.

As shown with the above highlighted examples, Cu-mediated RDRP has vastly improved the scope of MBC synthesis, with an impressive display of synthetic methodology allowing high order multiblocks to be formed. It is a powerful and versatile synthetic tool, which can be utilised in both organic and aqueous media, can be photoinitiated, and also be carried out at ambient temperatures or 0 °C. Recent reports introducing “universal conditions” for copper-mediated poly-



**Scheme 15** Light mediated Cu-RDRP combining hydrophobic, hydrophilic and semi-fluorinated blocks using TFE as solvent. (Reproduced from ref. 150 with permission from Wiley, 2017.)

merisation allow the utilisation of methacrylates and styrenics.<sup>151</sup> However, MBCs from methacrylates or styrenics *via* Cu-RDRP have not been realised to date.

## Coupling strategies

The sheer perpetual scope of MBC synthesis can be further expanded by combining living polymerisation techniques with high-yielding chemical reactions, for example “click” chemistry. Moreover, the high end-group fidelity of living polymers allows the installation of reactive linker groups to chain termini, opening avenues towards the combination of polymers, which are derived from different polymerisation techniques (Table 5).<sup>152</sup>

For instance, anionically polymerised bishydroxy terminated polystyrene and polybutadiene building blocks were readily coupled in an urethane-based polycondensation reaction to yield high molecular weight alternating or random MBCs.<sup>153</sup> Furthermore, bisalkyne-terminated ABA triblock polymers from polyethylene oxide (PEO) and polypropylene oxide (PPO) were reacted with their bisazide-terminated counterparts to result in the step-growth polymerisation *via* CuAAC. The click reaction was shown to be driven by self-assembly of the polymer building blocks in aqueous media.<sup>171</sup> In a similar fashion, norbornene-terminated PS, PEO and PDMS were coupled by a thiol-ene reaction with bisfunctional thiol compounds to yield thermally stable MBCs showing microphase separation behaviour (Scheme 16).<sup>154</sup> Additionally, the synthesis of poly(urethane-tetramethylene oxide) diblock polymers with alkoxyamine initiating sites

have been reported. The nitroxide-mediated polymerisation of styrene allowed the synthesis of multiblock polymers in a controlled fashion.<sup>155</sup>

In another example, a peptide-containing bisfunctional CTA was utilised to polymerise *N*-(2-hydroxypropyl)methacrylamide (HPMA). The subsequent aminolysis yielded bithiol-terminated polymer chains, which were reacted with a PEG-derived bismaleimide to yield enzymatically degradable MBCs.<sup>156</sup> The same research group developed a bisalkyne containing RAFT agent, showing living features for the polymerisation of HPMA. The CuAAC click reaction with a bisazide-terminated peptide resulted in the formation of an enzyme degradable periodic multiblock step-growth polymer (Scheme 17).<sup>157</sup> Furthermore, heterotelechelic HPMA-peptide conjugates were synthesised bearing an azide and an alkyne functionality at the opposite chain-ends. The CuAAC reaction led to intermolecular step-growth polymerisation, yielding a biodegradable peptide-acrylamide MBC.<sup>158</sup> Furthermore, bisfunctional RAFT agents were also utilised for the synthesis of PNIPAM and poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA). In a single aminolysis-oxidation step, disulphide linked, oxidation and temperature responsive random MBCs were synthesised.<sup>159,160</sup>

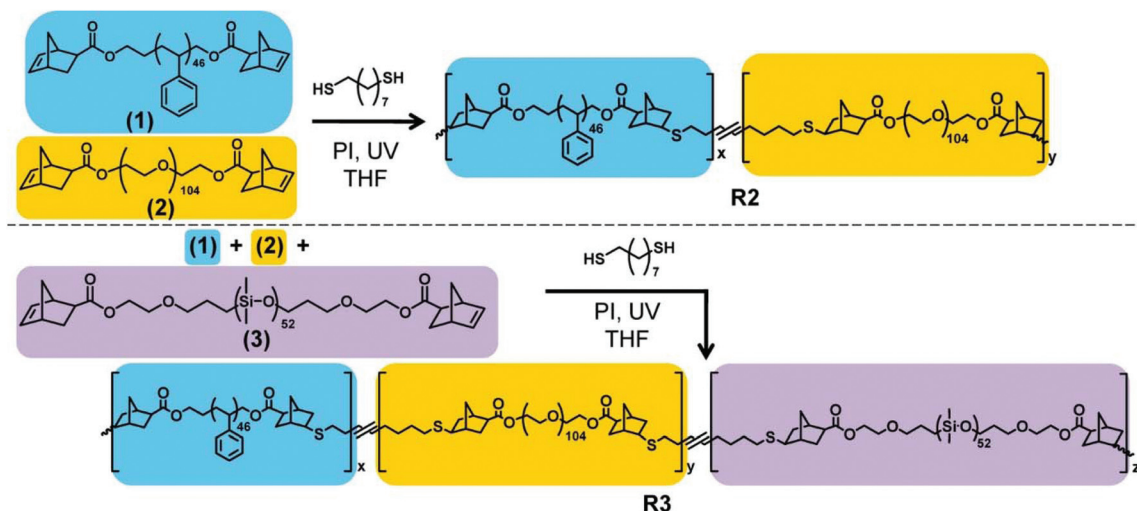
Perrier *et al.* have demonstrated this approach earlier by utilising a bisfunctional CTA in the synthesis of a poly(*n*-butyl acrylate)-*b*-(methyl methacrylate) (PBA-*b*-PMMA-*b*-PBA) triblock copolymer. The subsequent aminolysis and oxidation produced a redox responsive MBC.<sup>161</sup>

In a less controlled reaction sequence, a RAFT agent was functionalised with a  $\alpha$ -double bromoester group. The alkyl-bromide functionalities were shown to be retained after the

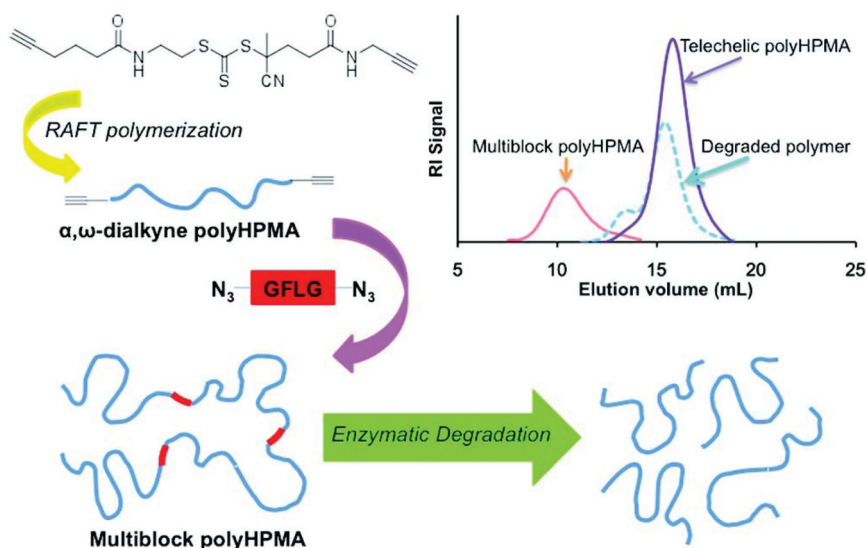
**Table 5** Summary of multiblock synthesis strategies combining living RDRP and coupling reactions

Monomer <sup>a</sup>	Coupling reaction <sup>b</sup>	Block number	Block sequence	$M_n$ (kDa)	Ref.
S, butadiene	AP, NCO-coupling	7–25	(AB) <sub>n</sub>	90–321	153
S, EO, DMS	Thiol-norbornene	4–5	(ABC) <sub>n</sub>	~40	154
TMO, S	NMRP	~13	(AB) <sub>n</sub> ( <i>alt</i> )	~30	155
HPMA, peptide, EO	RAFT, thiol ene	~8	(ABC) <sub>n</sub>	~200	156
HPMA, peptide	RAFT, CuAAC	~7	(ABA) <sub>n</sub>	~290	157
HPMA, peptide	RAFT, CuAAC	~9	(AB) <sub>n</sub>	~290	158
AA, S, DMAEMA	RAFT, aminolysis, oxidation	7–13	(A) <sub>n</sub>	20–40	159
NIPAM, DMAEMA	RAFT, aminolysis, oxidation	7–20	(AB) <sub>n</sub> <i>ran</i>	70–180	160
BA, MMA	RAFT, aminolysis, oxidation	~8	(BAAB) <sub>n</sub>	17	161
MA	RAFT, thiol-bromo	~10	A <sub>n</sub>	~70	162
S	Cu-RDRP, CuAAC	6–8	A <sub>n</sub>	15–22	163
BA, MMA	Cu-RDRP, CuAAC	5–7	(BAAB) <sub>n</sub>	~60	164
OEGA, EHA	Cu-RDRP, thiol-bromo	6–7	(BAAB) <sub>n</sub>	~70	165
S	Cu-RDRP, disulphide bridging	n.d.	A <sub>n</sub>	n.d.	166
S, PO	Cu-RDRP, ATRC	4–5	(AB) <sub>n</sub>	25–50	167
iP, MMA, S	Cu-RDRP, ATRC	3–5	(BAB) <sub>n</sub>	~40	168
EO, MMA, CL, S, BMA	Cu-RDRP, DA, CuAAC	5	ABCDE	40	169
S, CL, <i>t</i> BA, EO	Cu-RDRP, CuAAC, NRC, DA	4	ABCD	12	170

<sup>a</sup> Monomers were abbreviated as follows: styrene (S), ethylene oxide (EO), dimethyl siloxane (DMS), tetramethylene oxide (TMO), *N*-(2-hydroxypropyl)methacrylamide (HPMA), acrylic acid (AA), (dimethylamino)ethyl methacrylate (DMAEMA), *N*-isopropyl acrylamide (NIPAM), butyl acrylate (BA), methyl methacrylate (MMA), oligoethylene glycol methyl ether acrylate (OEGA), 2-ethylhexyl acrylate (EHA), phenylene oxide (PO), isotactic propylene (iP),  $\epsilon$ -caprolactone (CPL), butyl methacrylate (BMA), *tert*-butyl methacrylate. <sup>b</sup> Reaction names were abbreviated as follows: anionic polymerisation (AP), nitroxide-mediated radical polymerisation (NMRP), reversible-addition fragmentation chain transfer (RAFT), Cu-mediated reversible deactivation radical polymerisation (Cu-RDRP), copper-catalysed azide alkyne cycloaddition (CuAAC), Diels–Alder reaction (DA).



**Scheme 16** MBC synthesis by thiol-addition across norbornene. (Reproduced from ref. 154 with permission from ACS, 2014.)

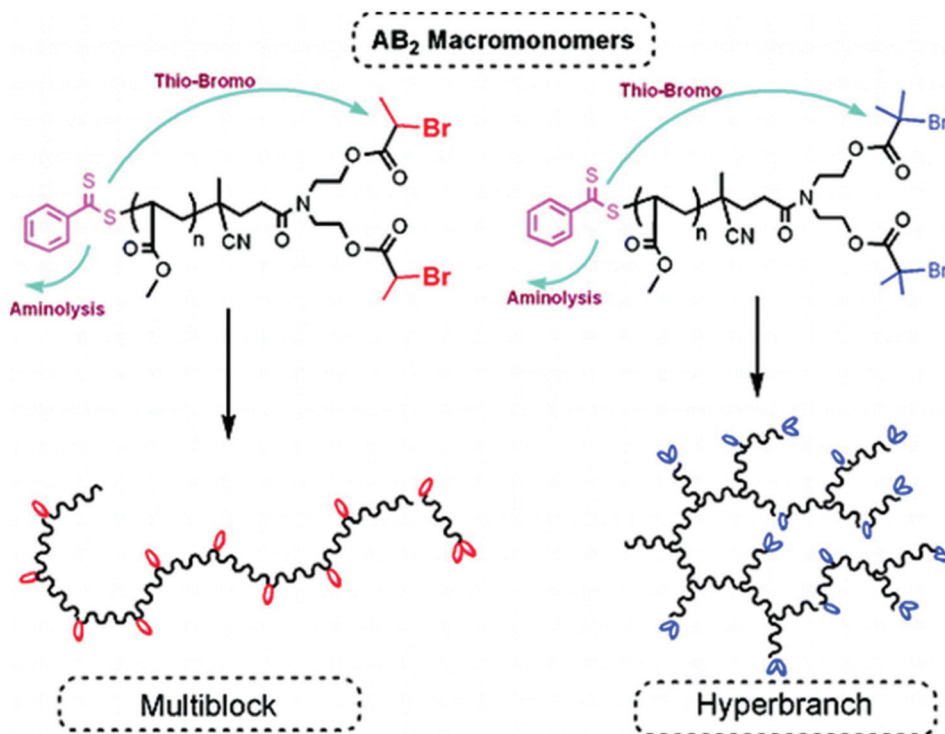


**Scheme 17** Synthesis of biodegradable HPMA-peptide MBCs via RAFT polymerisation and CuAAC. (Reproduced from ref. 157 with permission from ACS, 2011.)

RAFT polymerisation of methyl acrylate. After the aminolysis of the dithiobenzoate, the polymers underwent instant intermolecular thiol-bromo reaction to form multiblock/lightly branched or hyperbranched polymers. The architecture of the obtained product was controlled by the nature of the alkyl bromide moiety. The use of the more reactive secondary species resulted in a network formation whereas the tertiary alkyl bromide reacted to form mostly linear polymer chains (Scheme 18).<sup>162</sup>

Harnessing the high end group fidelity of living polymerisations, copper-mediated RDRP techniques were demonstrated to be suitable for applying coupling chemistry towards MBCs. First examples include the transformation of the telechelic

living bromine chain ends of bisinitiated vinyl polymers into azide moieties. The obtained difunctional azides were then further reacted with propargyl ether *via* CuAAC to induce a step-growth polymerisation, coupling an average of 10 polystyrene chains. Similar coupling efficiency was obtained by utilising a  $\alpha$ -acetylene- $\omega$ -azido-terminated polystyrene, which readily underwent intermolecular CuAAC reaction to form a MBC.<sup>163</sup> The reaction conditions for the CuAAC click reaction were further optimised by investigating ligand and metal effects.<sup>164</sup> Subsequently, the scope of this step-growth click reaction was expanded by coupling ATRP-derived alternating tri- and pentablock polymers from MMA and *n*-butyl methacrylate to form multiblock architectures with an average of 5–7



**Scheme 18** Synthesis of multiblock or hyperbranched polymers by the combination of RAFT polymerisation and thiol-bromo reaction. (Reproduced from ref. 162 with permission from ACS, 2010.)

linked polymer segments.<sup>172</sup> The obtained multi-segmented macromolecules behave like an elastic material, while the precursors show viscoelastic properties.

Becer *et al.* exploited the high bromine end group fidelity of Cu(0)-mediated RDRP. Eliminating the required post-polymerisation modifications allowed the rapid step growth reaction with difunctional thiol compounds in a one-pot fashion. The obtained amphiphilic, periodic MBCs from oligo(ethylene glycol methyl ether) acrylate (PEGA480) and 2-ethylhexyl acrylate (EHA) underwent further degradation upon oxidation, methylation and thermolysis reactions (Scheme 19).<sup>165</sup> This report demonstrates both the synthesis and degradation of MBCs.

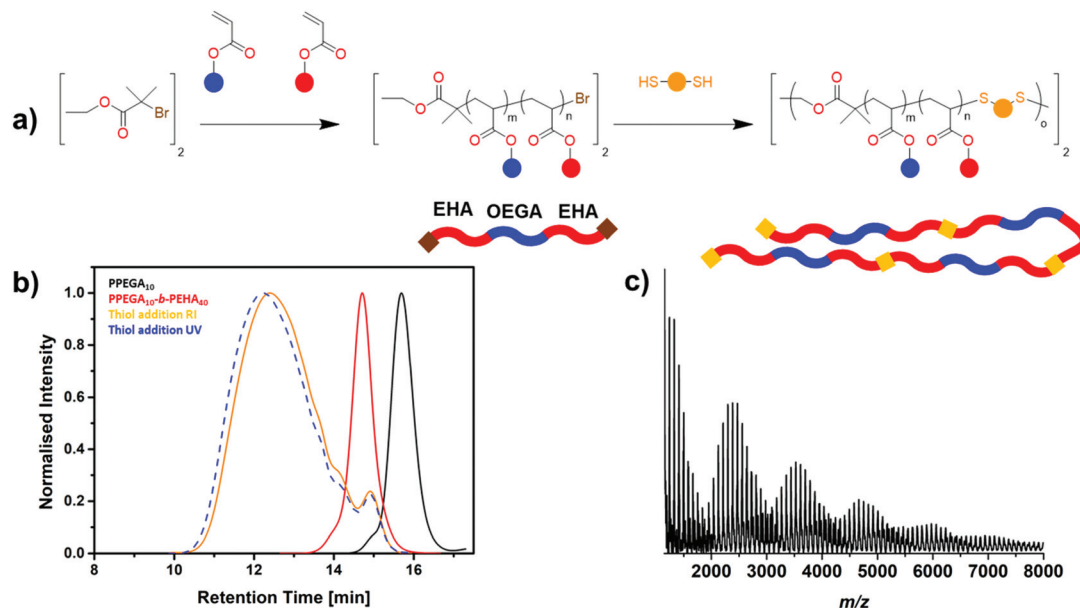
In a similar fashion, thiol-bromo reaction induced step-growth of  $\alpha,\omega$ -bromo terminated polystyrene with a disulphide-initiator yielded a periodic block copolymer upon reductive cleavage of the disulphide bridge to the respective thiols.<sup>166</sup> Alternatively, atom transfer radical coupling (ATRC) was shown to be applicable in the synthesis of MBCs. The combination of ATRC with atom transfer radical polymerisation (ATRP) or atom transfer radical addition (ATRA) allowed the synthesis of periodic block copolymers comprised of poly(styrene-*b*-bisphenol  $\alpha$ -carbonate),<sup>167</sup> poly(styrene-*b*-isotactic polypropylene(iPP)-*b*-styrene) and poly(MMA-*b*-iPP-*b*-MMA)<sup>168</sup> or styrene-MMA-MMA-styrene building blocks.<sup>173</sup>

The availability of a seemingly infinite number of approaches is further underpinned by the successful synthesis of amphiphilic MBCs *via* the combination of acyclic diene

metathesis (ADMET), ATRP and CuAAC.<sup>174</sup> Additionally, Diels-Alder- and CuAAC were utilised in a sequential double or quadruple polymer click sequence to obtain ABCDE-type quinpolymer<sup>169</sup> and graft-blockpolymers<sup>175</sup> or cysteine-terminated linear MBCs,<sup>170</sup> respectively. In addition, segmented copolymers have been demonstrated to be accessible *via* the combination of Diels-Alder reaction and RAFT chemistry.<sup>176</sup> Accessing MBC compositions, olefin metathesis was demonstrated to be compatible with a wide range of other polymerisation methods and coupling reactions, such as NMP,<sup>177</sup> Wittig-type coupling,<sup>94</sup> CuAAC<sup>93</sup> and ATRP.<sup>174</sup> The synthesis of  $\alpha,\omega$ -hydroxy terminated multi-segmented polymers was demonstrated by utilising a ruthenium/quinaldic acid catalyst to from polycondensation products from bishydroxy precursors.<sup>178</sup> Ring-opening polymerisations of cyclic esters, ethers, anhydrides and carbonates are predominantly carried out to produce di- and triblock polymers.<sup>82</sup> However, several macromonomer approaches were utilised to synthesise polycondensation MBCs by either (self-)condensation or *via* coupling strategies.<sup>179-185</sup>

Sophisticated living polymerisation techniques combined with powerful chemical coupling reactions equip chemists with a vast number of possibilities to synthesise MBCs from a wide range of different precursors. By carefully designing reaction pathways and utilising contemporary tools from organic, inorganic and polymer chemistry, the synthesis of any polymer architecture and composition is realisable. However, the majority of examples for the combination of coupling reac-





**Scheme 19** a) Schematic representation of the amphiphilic MBC synthesis from oligoethylene glycol methyl ether acrylate (OEGA) and 2-ethylhexyl acrylate (EHA) via bis-initiated Cu-mediated RDRP followed by *in situ* thiol-bromo reaction induced step growth polymerisation; (b) SEC traces of chain extension and thiol-bromo induced step growth with RI and UV detector response; (c) MALDI-ToF spectra showing the periodic nature of an methyl acrylate polymer (bottom). (Reproduced from ref. 165 with permission from RSC, 2019.)

tions with polymers require additional modification steps, resulting in reduced yields and the loss of end group fidelity.

## Conclusion

The rapid and vast expansion of polymerisation techniques, especially RDRPs, has flooded the polymer chemistry field with respectable feats in pushing the limit of the different synthetic methods. Due to the relatively straightforward reaction methodologies, MBCs are gaining growing attention beyond the classical boundaries of polymer science. Despite tremendous efforts, however, a universal condition for RDRP techniques regarding monomer compatibility is yet to be achieved. Furthermore, absolute position of a monomer in controlled chain polymerisations remains a challenge for the actual segmented nature of a polymer. According to literature reports, the uncertainty of monomer location in a polymer chain increases in proportion to the square root of the chain length.<sup>31</sup>

Therefore, the sequential quality of MBCs is likely to be poor for very small blocks and increases in proportion to the block length, resulting in a growing number of chains bearing the targeted number of blocks. In the near future, sequential perfection of MBCs, which are derived from controlled chain growth polymerisations, is highly unlikely to be achieved. Fortunately, nature provides us with various inspirational examples for less defined biomolecules with outstanding physiochemical properties, which should be the focal point for the design of MBCs.

In addition, the theoretical understanding for the phase behaviour of block copolymers is established for triblock bis-polymers (ABA) but lacks for triblock terpolymers (ABC).<sup>10</sup> Consequently, the synthetic abundance for MBCs is outgrowing actual understanding for the produced materials, leading towards over-engineering of macromolecules and competition over the fanciest polymer architecture.

Undoubtedly, the development and optimisation of chain growth polymerisations opened avenues towards the realisation of sophisticated macromolecular designs. The achievements accomplished to date provide a glimpse of the bright future of MBCs and other polymer architectures.

## Conflicts of interest

There are no conflicts to declare.

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