Atom transfer radical addition and polymerization reactions catalyzed by ppm amounts of copper complexes

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Over the past decade, copper-catalyzed atom transfer radical polymerization (ATRP) has had a tremendous impact on the synthesis of polymeric materials with well defined compositions, architectures and functionalities. Apart from synthetic aspects of ATRP, considerable effort has also been devoted to structural and mechanistic understanding of copper complexes involved in ATRP, as well as development of methodologies to decrease the amount of catalyst needed in these systems. This *tutorial review* reports on recent advances in the area of catalyst regeneration in ATRP and mechanistically similar atom transfer radical addition (ATRA) using environmentally benign reducing agents. The outlined processes termed ARGET (activators regenerated by electron transfer) and ICAR (initiators for continuous activator regeneration) ATRP enable the synthesis of well-defined (co)polymers and single addition adducts using very low concentrations of copper catalysts (1–100 ppm). Recent developments in this area could have profound industrial implications on the synthesis of well-defined polymeric materials and small organic molecules.

1 Introduction and background

Fundamentals of atom transfer radical addition (ATRA)

The addition of halogenated compounds to alkenes or alkynes through a radical process is one of the fundamental reactions in organic chemistry.[1–3] It was first reported in the 1940s in which halogenated methanes were directly added to olefinic bonds in the presence of radical initiators or light.[4,5] Today, this reaction is known as the Kharasch addition or atom transfer radical addition (ATRA),[3] and it is accepted to occur *via* a free-radical mechanism as illustrated in Scheme 1. The early work in this area mostly involved ATRA of CCl_4 and CBr_4 to simple olefins in the presence of radical initiators such as 2,2′-azobis(2-methylpropionitrile) (AIBN). Very high yields of the monoadduct were obtained in the addition of CBr_4 to α-olefins (1-hexene, 1-octene and 1-decene), but were significantly decreased for more reactive monomers such as styrene and methyl acrylate. The principal reason for decreased yield of the monoadduct was radical–radical coupling and repeating radical addition to alkene to generate oligomers. Although radical–radical coupling reactions could be suppressed by decreasing radical concentration, telomerization reactions

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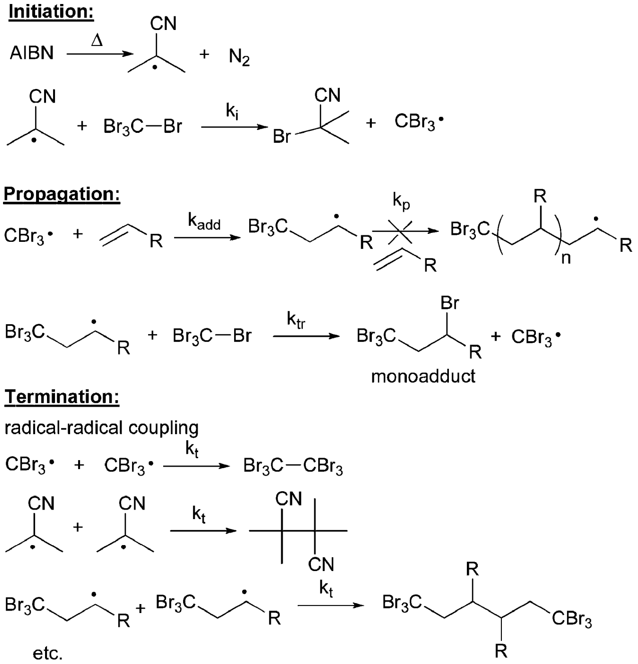
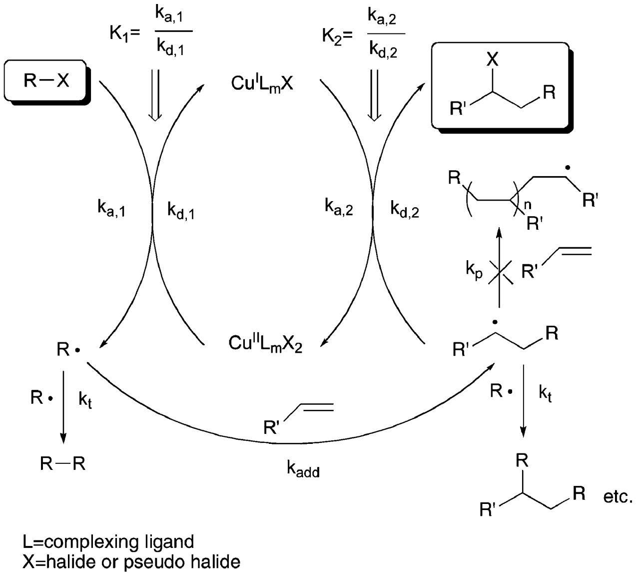


Scheme 1 Kharasch addition of CBr_4 to alkenes.



Scheme 2 Proposed mechanism for copper catalyzed ATRA.

could not be avoided due to the low chain transfer constant (k_{tr}/k_p, Scheme 1). The research was thus shifted in a direction of finding means to selectively control the product distribution.

In 1960s, several groups began to investigate the use of transition metal complexes to catalyze ATRA. The basic idea to increase chemoselectivity of the monoadduct was to increase chain transfer constant (k_{tr}/k_p, Scheme 1), by recognizing that transition-metal complexes are more effective halogen transfer agents than alkyl halides. Complexes of Cu, Fe, Ru and Ni were found to be particularly active catalysts for ATRA.[6–10] Great progress has been made in not only controlling the product selectivity, but also in utilizing a variety of halogenated compounds (alkyl and aryl halides, *N*-chloroamines, alkylsulfonyl halides and polyhalogenated compounds). Furthermore, it was also demonstrated that a variety of alkenes (styrene, alkyl acrylates and acrylonitrile) could be used as the source of reactive unsaturation. Therefore, transition-metal catalyzed (TMC) ATRA became broadly applicable synthetic tool.

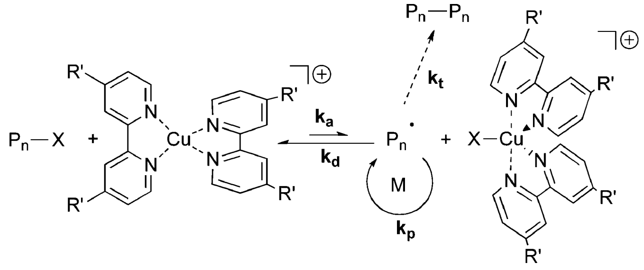
Based on chemo-, regio- and stereoselectivity, it is generally accepted that the mechanism of copper-catalyzed ATRA involves free-radical intermediates (Scheme 2).[10,11] Typically, copper(I) halide complexed by a suitable ligand undergoes an inner-sphere electron transfer through abstraction of a halogen atom from an alkyl halide. This reaction generates a corresponding copper(II) complex and an organic radical. The radical may terminate or add to an alkene in an inter- or intramolecular fashion. It can also abstract the halogen atom from the copper(II) complex and return back to the original dormant alkyl halide species, or if the abstraction of the halogen occurs after the addition to alkene, the desired monoadduct will be formed. Abstraction of the halogen atom from copper(II) complex generates the corresponding copper(I) complex, completing the catalytic cycle. The key to increase chemoselectivity of the monoadduct in copper-mediated ATRA lies in radical generating step. In order to achieve high selectivity, the following general guidelines need to be met:

1. Radical concentration must be low in order to suppress radical termination reactions; rate constant of activation ($k_{a,1}$ and $k_{a,2}$) $\ll$ rate constant of deactivation ($k_{d,1}$ and $k_{d,2}$).
2. Further activation of the monoadduct should be avoided, $k_{a,1} \gg k_{a,2}$.
3. The formation of oligomers/polymers should be suppressed; rate of deactivation ($k_{d,2}[Cu^{II}L_mX]$) $\gg$ rate of propagation (k_p[alkene]).

Substrates for copper-catalyzed ATRA are typically chosen such that if addition occurs, then the newly formed radical is much less stabilized than the initial radical and will essentially react irreversibly with the copper(II) complex to form an inactive monoadduct. Therefore, in copper-mediated ATRA, usually only one addition step occurs.

Fundamentals of atom transfer radical polymerization (ATRP)

In 1995, a new class of controlled/"living" radical polymerization method was reported independently by the groups of Matyjszewski[12] and Sawamoto.[13] This new process named atom transfer radical polymerization (ATRP),[12] has had a tremendous impact on the synthesis of macromolecules with well-defined compositions, architectures and functionalities.[14–16] ATRP has been successfully mediated by a variety of metals, including those from groups 4 (Ti), 6 (Mo), 7 (Re), 8 (Fe, Ru, Os), 9 (Rh, Co), 10 (Ni, Pd) and 11 (Cu).[14,17] Complexes of copper have been found to be the most efficient catalysts in the ATRP of a broad range of monomers in diverse media. ATRP is mechanistically similar to ATRA with the exception that the reaction conditions are modified in such a way that more than one addition step occurs. Thus, if the radical species in Scheme 2, both before and after addition of the unsaturated substrate (monomer) possess comparable reactivity, then the activation–addition–deactivation cycle will repeat until all of the monomer present is consumed. This process results in a chain-growth polymerization (Scheme 3).



Scheme 3 Proposed mechanism for copper/2,2′-bipyridine mediated ATRP.

Similarly to ATRA, a copper(I) complex is responsible for a homolytic cleavage of an alkyl halide bond (RX) to generate a corresponding copper(II) complex and an organic radical. The generated radical can then propagate with vinyl monomer (k_p), terminate by either coupling or disproportionation (k_t), or be reversibly deactivated (k_d) by the copper(II) complex to generate halide-capped dormant polymer chain and copper(I) complex. Radical concentration is diminished in ATRP due to persistent radical effect (PRE),[18] and the ATRP equilibrium ($K_{ATRP} = k_a/k_d$) is strongly shifted towards dormant species ($k_a \ll k_d$). As a result, polymers with predictable molecular weights, narrow molecular weight distribution and high functionalities have been synthesized.[14,16,19]

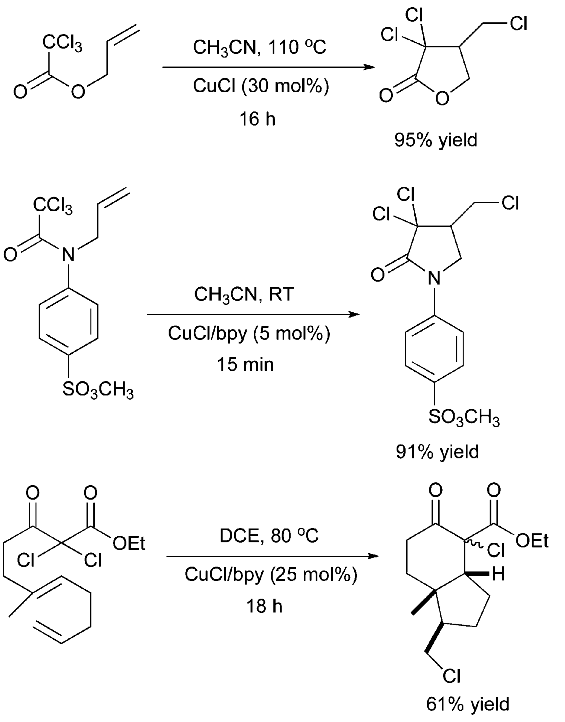
2 ATRA in organic synthesis

Radical chemistry in organic synthesis has advanced tremendously since the discovery of triphenylmethyl radical in 1900 by Gomberg. The early work started with the discovery of Kharasch addition reaction in which halogenated methanes were directly added to olefinic bonds (in an anti-Markownikoff fashion) in the presence of radical initiators and later transition metal complexes.[4,5] However, it was not until early 1980s that the full potential of radical chemistry as a tool for complex molecule and natural product synthesis was realized due to the pioneering work of Giese (tin hydride mediated radical addition to olefins),[20] Barton (radical decarboxylation and deoxygenation)[21] and Curran (iodine atom transfer radical reactions).[22] The first successful examples included the synthesis of natural products prostalglandin, alkaloid and triquinane, followed by many others. Radical chemistry in organic synthesis, like most current methodologies, employs stepwise formation of individual bonds in a target molecule using radical means. Increasingly common methodology also includes domino or tandem reactions which enable the synthesis of multiple carbon–carbon bonds in a single step.[23] Since the 1980s, radical chemistry in organic synthesis has come a long way due to its predictability, generality and variability. In other words, radical reactions can be conducted under mild conditions, are tolerant to many functional groups and solvents, and can be very stereoselective. As a result, radical carbon–carbon bond forming reactions are today routinely considered in strategic planning of complex molecules.[24–27]

Transition-metal catalyzed ATRA, despite being discovered nearly 40 years before tin mediated radical addition to olefins and iodine atom transfer radical addition, is still not fully utilized as a technique in organic synthesis. The principal reason for small participation of ATRA in complex molecule and natural product syntheses is a large amount of transition metal complexes needed to achieve high selectivity (typically 10–30 mol% relative to alkene). This obstacle causes serious problems in product separation and catalyst regeneration, making the process environmentally unfriendly and expensive.

Intramolecular transition-metal catalyzed ATRA or atom transfer radical cyclization (ATRC) is a very attractive tool because it enables the synthesis of functionalized ring systems that can be used as starting materials for the preparation of complex molecules. Furthermore, the halide functionality in the resulting product can be very beneficial because it can be easily reduced, eliminated, displaced, converted to a Grignard reagent, or can serve as a further radical precursor. The use of copper-mediated ATRC in organic synthesis has been reviewed recently, however, we will concentrate on a couple of elegant examples that have appeared in literature over the past two decades (Scheme 4) in order to demonstrate its potential.[9]

The first successful example of a copper-mediated ATRC reaction included the synthesis of trichlorinated γ-lactones from readily accessible alkenyl trichloroacetates.[28] The reaction was highly selective, but required elevated temperatures (110–130 °C) and large amounts of copper catalyst (20–30 mol% relative to substrate). Some improvements have been achieved utilizing tetradentate nitrogen based ligands such as tris(2-pyridylmethyl)amine (TPMA) and tris[2-(*N*,*N*-dimethylamino)ethyl]amine (Me_6TREN) (Scheme 6), which were first successfully applied in copper-mediated ATRP, resulting in a decrease in the amount of required catalyst (3–10 mol% relative to substrate) and reaction temperature (80 °C).[29] Copper-mediated ATRC reactions have also been used to synthesize γ-lactams and similarly required relatively large



Scheme 4 Successful examples of copper-mediated ATRC reactions.

amounts of copper catalysts (10–30 mol%).[9] Very recently, copper(I) chloride, in conjunction with bipyridine or bis(oxazoline) ligand, was found to efficiently catalyze ATRC reactions of unsaturated α-chloro β-keto esters under mild reaction conditions, which was the first example of successful cascade or domino transition-metal mediated ATRC.[30]

It is evident from the examples provided in Scheme 4, and many others in the literature,[9] that copper-catalyzed ATRC reactions can be utilized in the synthesis of various substrates that can be used as building blocks for the construction of complex molecules and natural products. This tutorial review article focuses on recent advances in copper-meditated ATRA and ATRP from the point of view of development of novel methodologies that can be used to drastically reduce the amount of copper catalysts.

3 ATRP in polymer synthesis

Similarly to conventional free-radical polymerization, ATRP is applicable to a large number of monomers with carbon–carbon double bonds and it is tolerant towards many solvents, functional groups, and impurities.[14,16,19] One of the main advantages of ATRP is that it is a controlled radical polymerization, which resembles a living process. This is achieved by utilizing dynamic equilibrium between propagating radicals and dormant species, which is strongly shifted towards its left hand side (Scheme 3). As a result, radical termination reactions are suppressed, and well-defined polymers with predetermined molecular weights, narrow molecular weight distributions and precisely controlled architectures can be synthesized. The basic strategies for producing polymeric structures by ATRP with controlled topologies, compositions and functionalities (illustrated in Fig. 1) are summarized below. Other, more comprehensive reviews cover structures prepared by ATRP in greater detail.[16,19,31–33]

Topology

ATRP is well suited for preparation of (co)polymers with controlled topologies, including star- and comb-like polymers as well as branched, hyperbranched, dendritic, network, and cyclic type structures. Star-like polymers have been synthesized using four different approaches: (1) a core-first approach which employs multifunctional initiators from which several arms are grown simultaneously, (2) an arm-first approach which involves attachment of chains to a functional core, (3) crosslinking of the arms in the presence of divinyl compounds, and (4) further chain extension of the crosslinked arms (3) to generate mikto-arms of different lengths or different monomers.[31]

Comb-like polymers can be prepared by three different techniques corresponding to grafting from, onto and through. In grafting from approach, chains are grown (*via* ATRP) from a polymer backbone. Click chemistry can be applied between azide functionalized chains and an acetylene functionalized core to efficiently attach side chains to a backbone in grafting onto approach.[34] In grafting through, vinyl terminal macromonomers are utilized as comonomers together with a low molecular weight monomer. Variations in grafting density enable the synthesis of combs of different shapes, as well as gradient brushes. An interesting combination of a star-brush system is shown in an AFM image (Fig. 1) of a four-arm star molecular brush with a degree of polymerization for each poly(methacrylate) arm $DP_n = 300$ and each poly(*n*-butyl acrylate) side chain $DP_n = 37$. The inset shows the magnification at higher resolution in which the individual chains are resolved on mica surface by tapping mode AFM.[31]

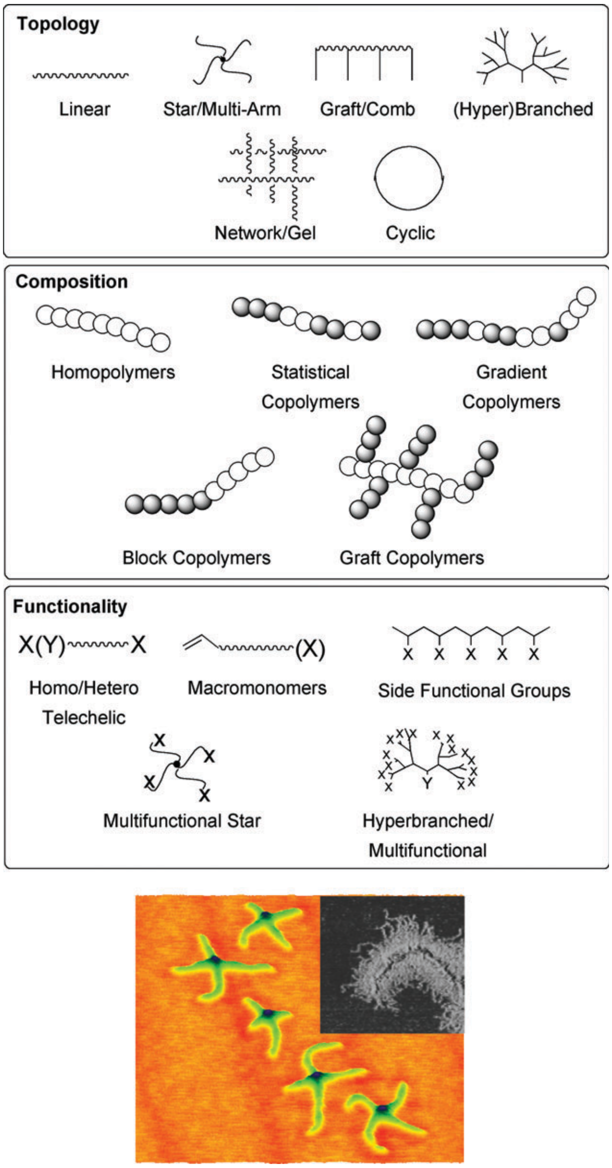


Fig. 1 Schematic representation of polymers with controlled topology, composition and functionality and AFM image of four star brush synthesized using copper-mediated ATRP. Reproduced with permission from ref. 33. Copyright 2007, Wiley-VCH.

ATRP can also be used to prepare hyperbranched polymers with either monomers that serve as initiators or divinyl monomers that are used in small relative concentrations or are copolymerized to relatively low conversions. While these hyperbranched structures are irregular, the degree of branching is controlled by the degree of polymerization.[33]

ATRP can significantly improve network uniformity over structures prepared using free-radical polymerization. This is achieved by utilizing well-defined polymers with crosslinkable pendant moieties. Degradable gels can also be prepared with disulfide linkages, and crosslinkers can be reversible cleaved to lead to the formation of reversible gels.[35]

Although cationic and/or anionic polymerizations are much more suited for the preparation of cyclic polymers, ATRP has been used in conjunction with "click" coupling to yield cyclic polymers.[31,36]

Composition

ATRP is very tolerant towards functional groups,[16] which allows for the synthesis of a large number of statistical, segmented (blocks and graft), periodic (mostly alternating), and gradient copolymers.[19,33] ATRP can be used to prepare ABC and ABCBA segments using sequential polymerization techniques. Graft copolymers, on the other hand, have been synthesized using techniques similar to those applied in the preparation of comb polymers. Molecular hybrids can be generated by covalently attaching synthetic polymers to inorganic materials and natural products. Functional groups (NH_2 or OH^-) can be converted to ATRP initiators (bromoamides and bromoesters) and polymerization sequences conducted. Also, on the other hand, polymer chains prepared using ATRP containing NH_2 and OH^- functionalities can be used to grow peptides or DNA.

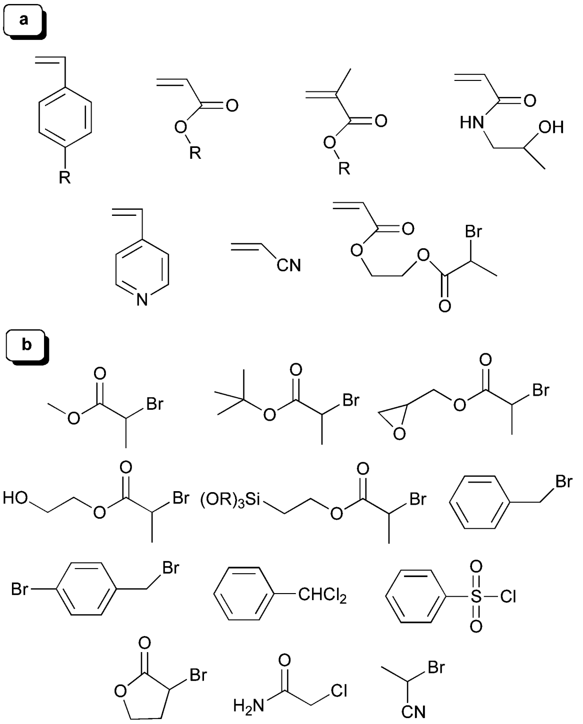
Functionality

Because of its radical nature, ATRP is tolerant to many functionalities present in monomers, leading to polymers with functionalities along the chains.[16] Moreover, the initiator used determines the end groups of the polymers. By using a functional initiator, functionalities such as vinyl, hydroxyl, epoxide, cyano and other groups have been incorporated at one chain end, while the other chain end remains as an alkyl halide. The polymers synthesized using ATRP can be dehalogenated in a one-pot process or the halogen group can be transformed to other functionalities using nucleophilic substitution or electrophilic addition reactions.[16]

4 Highly efficient ATRP in the presence of catalytic amounts of copper

Basic components of copper-catalyzed ATRP

In order to understand factors that led to the development of novel methodologies that can be used to drastically reduce the amount of copper-catalysts in ATRA/ATRP, it is necessary to carefully define and examine the components and characteristics of both systems. Copper-catalyzed ATRP is a multicomponent system, composed of a monomer, an initiator with a transferable (pseudo)halogen, and a copper complex (comprised of a copper(I) (pseudo)halide and nitrogen-based complexing ligand). Sometimes an additive is used. For a successful ATRP, other factors, such as solvent and temperature, must also be taken into consideration. Typical monomers that are used in ATRP include styrenes, (meth)acrylates), meth(acrylamides), acrylonitrile and (meth)acrylic acids (Scheme 5). Initiators, on the other hands, are commonly halogenated alkanes, benzylic halides, α-haloketones, α-halonitriles and sulfonyl halides (Scheme 5). Copper complex is perhaps the most important component of the catalytic system because it regulates dynamic equilibrium between the dormant and propagating species. This is typically achieved utilizing nitrogen based complexing ligands which range from bidentate, tridentate and tetradentate as depicted in Scheme 6.



Scheme 5 Examples of vinyl monomers (a) and various initiators (b) that are used in copper-catalyzed ATRP.

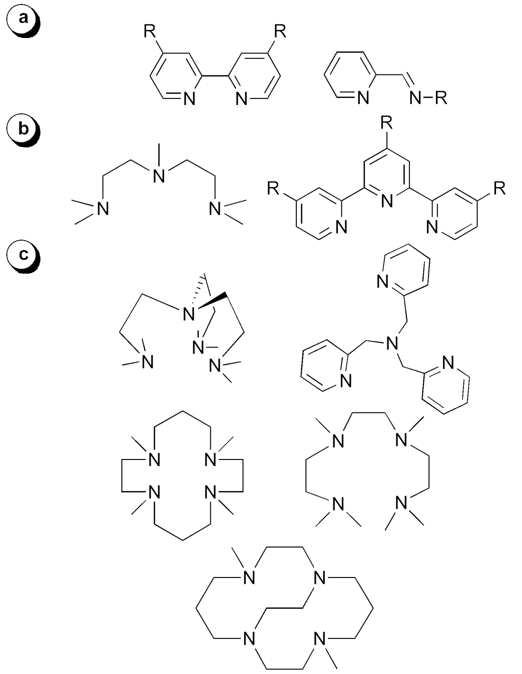
Kinetics of copper-catalyzed ATRP

A successful ATRP process should meet several requirements. Firstly, initiator should be consumed in the early stages of polymerization and generate propagating chains leading to polymers with degrees of polymerization (DP) predetermined by the ratio of concentrations of converted monomer (M) to the introduced initiator (I), DP = $\Delta[M]/[I]_0$. Secondly, the number of monomer molecules added during one activation step should be small, resulting in polymers with low polydispersity index (PDI = M_w/M_n). Finally, the contribution of chain-breaking reactions, such as transfer and termination, should be negligible, enabling the synthesis of polymers with high degrees of end functionality.

According to Scheme 3, neglecting termination reactions due to persistent radical effect and using a fast equilibrium approximation, the rate law for ATRP can be derived as follows:

$$\frac{-\mathrm{d}[M]}{\mathrm{d}t} = k_p[M][P^\bullet] = \frac{k_p K_{ATRP}[M][PX][Cu^I]}{[X{-}Cu^{II}]} \qquad (1)$$

where $K_{ATRP} = k_a/k_d$. According to eqn (1), polymerization rate in ATRP depends on the equilibrium constant for ATRP (K_{ATRP}), concentrations of dormant species (PX) and monomer (M), propagation rate constant of monomer (k_p), and the ratio of concentrations of activator (Cu^I) and deactivator



Scheme 6 Structures of bidentate (a), tridentate (b) and tetradentate (c) nitrogen-based ligands commonly used in copper-catalyzed ATRP and ATRA.

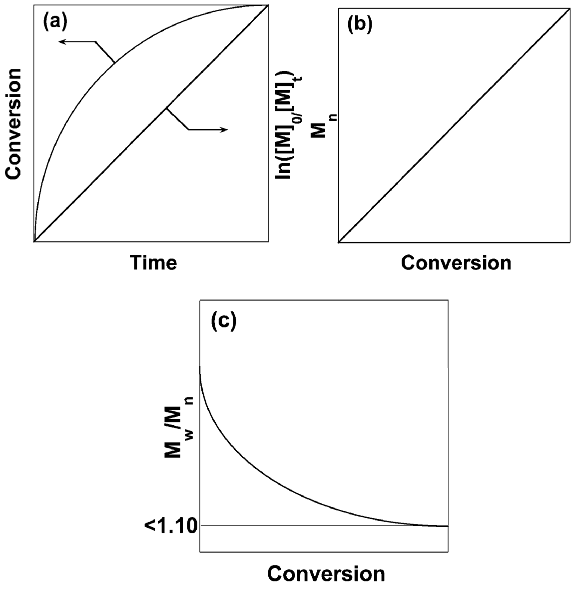


Fig. 2 Typical kinetic features of copper-mediated ATRP.

($X–Cu^{II}$). On the other hand, molecular weight distribution or polydispersity index (PDI = M_w/M_n) in ATRP depends on the propagation rate constant (k_p), deactivation rate constant (k_d), monomer conversion (p), and concentrations of dormant species, monomer and deactivator ($X–Cu^{II}$) according to eqn (2):

$$\frac{M_w}{M_n} = 1 + \left(\frac{[PX]k_p}{k_d[X–Cu^{II}]}\right)\left(\frac{2}{p} - 1\right) \qquad (2)$$

Fig. 2(a) shows a typical linear variation of conversion with time in semilogarithmic coordinates observed in metal mediated ATRP. The plot indicates that there is a constant concentration of active species in the polymerization and first-order kinetics with respect to monomer. Furthermore, a plot of polymer molecular weight *vs.* conversion is linear, indicating a constant number of polymer chains (Fig. 2(b)). Also, on the other hand, the molecular weight distribution (M_w/M_n) or polydispersity index (PDI) typically decreases with conversion and in a well controlled process approaches a value that is usually less than 1.10 (Fig. 2(c)).[14]

Towards lowering the concentration of copper-catalyst in ATRP

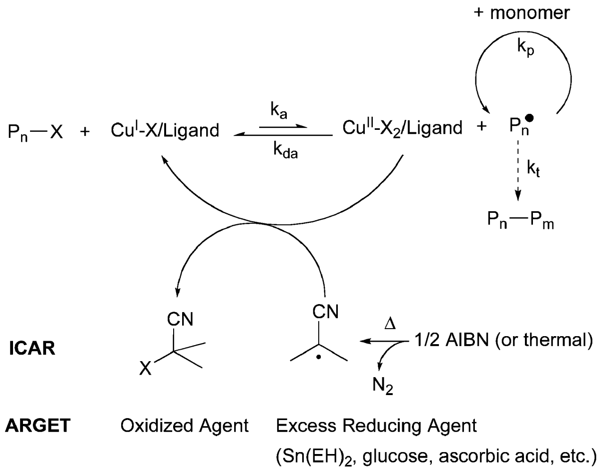
Over the past decade, copper-mediated ATRP has had a tremendous impact on the synthesis of polymeric materials with well defined compositions, architectures and functionalities.[16,19,31–33] Apart from the synthetic aspects of ATRP, considerable effort has also been devoted to structural and mechanistic understanding of copper complexes involved in ATRP, as well as development of methodologies to decrease the amount of catalyst needed in these systems.[17,31,35,37–40] Such movement towards "greening" of copper-mediated ATRP was needed to overcome the drawback of traditional ATRP, which required relatively large amounts of copper-catalyst (typically on the order of 0.1–1 mol% relative to the monomer). Various methodologies have been developed and they include: (a) simple removal of the catalyst using ion-exchange resins, extractions with water or polymer precipitation, (b) the use of biphasic systems such as fluorous solvents, (c) solid supported catalysts, (d) development of highly active catalysts based on the ligand design and (e) the use of reducing agents for catalyst regeneration.[35] The following paragraphs will outline the principles of catalyst regeneration in ATRA/ATRP processes using environmentally benign reducing agents.

AGET ATRP

The limitation of normal and simultaneous reverse initiation in copper-mediated ATRP is evident in the inability of these techniques to produce clean block copolymers. In AGET (activators generated by electron transfer) ATRP, stoichiometric amounts of reducing agents are added to the reaction mixture containing alkyl halide, monomer and the air-stable deactivator ($X–Cu^{II}$), to regenerate the activator (Cu^I). After regeneration of the activator (Cu^I), the polymerization kinetics resemble the kinetics of conventional ATRP. AGET ATRP utilizes reducing agents that are unable to initiate new polymer chains such as zero-valent copper, tin(II) 2-ethylhexanoate, ascorbic acid or triethylamine. This technique has been shown to be particularly useful in aqueous and miniemulsion systems.[41–44]

ARGET ATRP

An ATRP catalyst that is sufficiently stable and active can be used at very low concentrations. However, it is very important to mention that a catalyst in the lower oxidation state (Cu^I complex in the case of copper-mediated ATRP) is constantly being converted to a complex in the higher oxidation state ($X–Cu^{II}$), as a result of unavoidable radical termination reactions. Therefore, the deactivator ($X–Cu^{II}$) will accumulate in the system as the reaction proceeds. The amount of lost Cu^I



Scheme 7 Proposed mechanism for regeneration of copper(I) complex in ARGET and ICAR ATRP.

complex due to termination is equal to the amount of terminated chains, as shown by eqn (3).

$$\Delta[\mathrm{Cu^IL}_m] = \Delta[\mathrm{X–Cu^{II}L}_m] = \Delta[P_{\mathrm{dead}}] = k_t[\mathrm{P^\bullet}]^2 t \qquad (3)$$

Furthermore, accumulation of the deactivator (X–Cu^{II}) results in slowing down of the polymerization rate, which in turn limits high monomer conversions.

ARGET (activators regenerated by electron transfer) ATRP is similar to AGET ATRP, with the exception that it utilizes much smaller concentrations of the activator (Cu^I) and consequently a large excess of the reducing agent.[45–47] As a result, copper(II) that accumulates as a persistent radical during ATRP is continuously reduced to the corresponding copper(I) complex. Copper(I) complex is needed to homolytically cleave the alkyl halide bond (R–X). As indicated in eqn (1), rate of monomer consumption in ATRP depends on the absolute ratio of the concentrations of activator (Cu^I) and deactivator (X–Cu^{II}). Therefore, the absolute amount of copper-catalyst in ATRP can be decreased under normal ATRP conditions without affecting the rate of polymerization. In ARGET ATRP, the presence of large excess of the reducing agent enables polymerization to be conducted using very small amounts of copper catalysts (Scheme 7). Table 1 summarizes experimental conditions and properties of poly(*n*-butyl acrylate) and poly(methyl methacrylate) prepared by copper-mediated ARGET ATRP.[45] The polymerization of *n*-butyl acrylate was initiated by ethyl 2-bromoisobutyrate (EtBrIB) and a final molecular weight of M_n = 20 000 g mol^{-1} was targeted. A constant amount (10 mol% *vs.* initiator or 0.07 mol% *vs.* monomer) of tin(II) 2-ethylhexanoate (Sn(EH)$_2$) and variable concentrations of the copper based catalyst with tris[2-(dimethylamino)ethyl]amine (Me$_6$TREN) and tris[(2-pyridyl)methyl]amine (TPMA) ligands were employed. Very good control over the polymerization was obtained using as little as 10 ppm of copper. Furthermore, slightly better results were obtained with TPMA ligand, which, although less active than Me$_6$TREN, has stronger binding constant to copper (entry 2 *vs.* entry 4, Table 1). ARGET ATRP of *n*-butyl acrylate was also performed using glucose as a reducing agent.[45] Under conditions similar to those presented in Table 1, entry 5, poly(*n*-butyl acrylate) was formed in 48% yield with M_n = 10 500 g mol^{-1} and M_w/M_n = 1.47 ($M_{n,\mathrm{theor}}$ = 9600 g mol^{-1}). Similarly to *n*-butyl acrylate, ARGET ATRP of methyl methacrylate initiated by ethyl α-bromophenylacetate (EtBPA) in the presence of Sn(EH)$_2$ was successfully conducted using between 2 and 50 ppm of copper catalyst.

Table 1 Experimental conditions and properties of poly(*n*-butyl acrylate) and poly(methyl methacrylate) synthesized using ARGET ATRP

Entry	Cu^a /ppm	t /min	Conv. (%)	$M_{n,\mathrm{theor}}$^{b} /g mol^{-1}	$M_{n,\mathrm{GPC}}$ /g mol^{-1}	M_w/M_n
n-Butyl acrylate^c						
1	50	370	91	18 100	19 400	1.26
2	10	360	90	17 900	19 100	1.40
3	50	1320	71	14 300	15 100	1.16
4^d	10	1320	84	16 800	19 300	1.33
Methyl methacrylate^e						
5	50	360	70	14 000	19 300	1.16
6	10	370	61	12 200	15 900	1.34
7	2	335	66	13 300	15 300	1.36

[a] Molar ratio *vs.* monomer. [b] $M_{n,\mathrm{theor}}$ = ([M]$_0$/[I]$_0$) × conv. × M_{monomer}. [c] Ratio of reactants: [*n*BA]$_0$: [EBrIB]$_0$: [Me$_6$TREN]$_0$: [Sn(EH)$_2$]$_0$ = 160 : 1 : 0.1 : 0.1. [d] TPMA (0.03 equiv.) was used as ligand instead of Me$_6$TREN. [e] Ratio of reactants: [MA]$_0$: [EtBPA]$_0$: [TPMA]$_0$: [Sn(EH)$_2$]$_0$ = 200 : 1 : 0.03 : 0.1.

Copper-catalyzed ARGET ATRP was also very successful in controlled polymerization of styrene.[46] As indicated in Fig. 3, ARGET ATRP of styrene initiated by ethyl 2-bromoisobutyrate (EBrIB) and catalyzed by CuCl/Me$_6$TREN complex in the presence of Sn(EH)$_2$ was very well controlled in the presence of only 15 ppm of copper.

ARGET ATRP was also successfully applied in the synthesis of block copolymers, poly(*n*-butyl acrylate)-*b*-poly(styrene) and poly(styrene)-*b*-poly(*n*-butyl acrylate).[46] Initially, poly(*n*-butyl acrylate) was prepared using ARGET ATRP of *n*-butyl acrylate with 50 ppm of copper complex ($M_{n,\mathrm{GPC}}$ = 19 400 g mol^{-1} and $M_{n,\mathrm{theor}}$ = 18 100 g mol^{-1}), and it was then used as a macroinitiator. Chain extension of poly(*n*-butyl acrylate) macroinitiator with styrene by ARGET ATRP with 15 ppm of copper-catalyst yielded block copolymer ($M_{n,\mathrm{GPC}}$ = 34 900 g mol^{-1}, $M_{n,\mathrm{theor}}$ = 37 000 g mol^{-1} and M_w/M_n = 1.18).

Apart from Sn(EH)$_2$ and glucose, ascorbic acid was also successfully used as a reducing agent in ARGET ATRP of methyl acrylate, *n*-butyl acrylate, methyl methacrylate and styrene.[47] Furthermore, excess reducing agent can also be used to consume oxygen and other inhibitors from the reaction mixture and eliminate deoxygenation step. This process has also been applied to grafting from various surfaces.[48]

ICAR ATRP

As discussed earlier, under typical ATRP conditions, radical termination reactions lead to irreversible accumulation of persistent radical or deactivator (X–Cu^{II} complex). In other words, if the initial catalyst concentration is too low, all of the

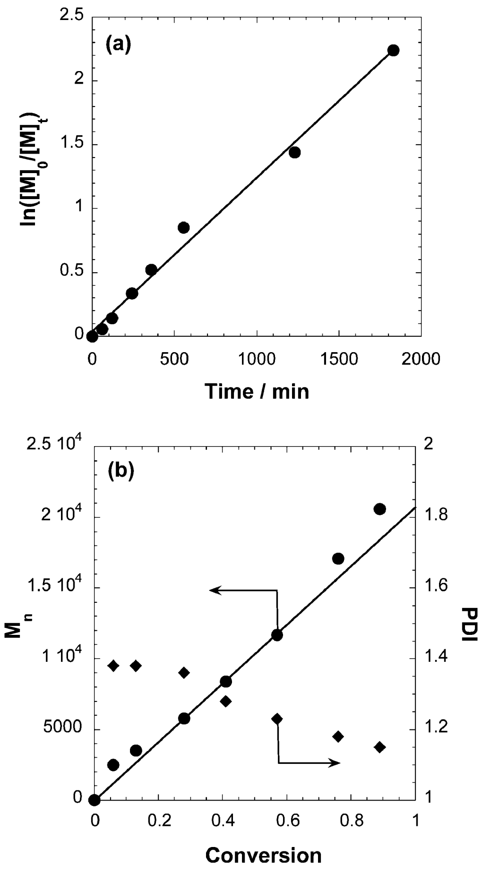


Fig. 3 Kinetic plots for ARGET ATRP of styrene with 15 ppm of copper (a) and polystyrene molecular weight and polydispersity as a function of conversion (b). $[Sty]_0 : [EtBrIB]_0 : [Cu^{II}]_0 : [Me_6TREN]_0 : [Sn(EH)_2]_0 = 200 : 1 : 0.003 : 0.1 : 0.1$, $[Sty]_0 = 5.82$ M, $T = 110$ °C, in anisole (0.5 vol equiv. *vs.* monomer). Reproduced with permission from ref. 43. Copyright 2006, American Chemical Society.

activator will eventually be consumed as a persistent radical and polymerization will only reach limited conversions. A new technique known as initiators for continuous activator regeneration (ICAR) in ATRP can be used to both scavenge oxidants and also decrease the amount of catalyst.[49] In ICAR ATRP, free radicals are slowly and continuously generated by conventional radical initiators (*e.g.* AIBN) throughout the polymerization, to constantly reduce the copper(II) complex that accumulates as a persistent radical (Scheme 7). The potential of ICAR ATRP has been demonstrated in recent studies utilizing four ATRP catalysts with a broad range of K_{ATRP} values.[49] These included $CuCl_2$ complexes with tris[2-(dimethylamino)ethyl]amine (Me_6TREN), tris[(2-pyridyl)-methyl]amine (TPMA), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) and 4,4′-di-(5-nonyl)-2,2′-bipyridine (dNbpy) (Scheme 6). Rates of the polymerization in ICAR ATRP of styrene at 60 °C in the presence of AIBN (0.1 equiv. *vs.* ethyl 2-bromoisobutyrate (EBrIB) initiator) and 50 ppm of $CuCl_2$ were found to be relatively independent on the complexing ligand (Table 2). These results indicated that the polymerization rate and radical concentration in ICAR ATRP are controlled by the rate of free-radical initiator decomposition. The polymerization of styrene mediated by $CuCl_2/Me_6TREN$ and $CuCl_2$/TPMA complexes was very well controlled in terms of molecular weight and polydispersity (M_w/M_n). For $CuCl_2$/PMDETA and $CuCl_2$/dNbpy complexes, molecular weight was controlled, however, polydispersities (M_w/M_n) were significantly higher. These results are not surprising, because the latter two complexes have the lowest K_{ATRP} values.

At higher temperatures (110 °C), where the complexes are more prone to dissociate, excess of ligand was used (between 10 and 500 equiv. relative to copper). Reactions were also conducted in the absence of AIBN because the radicals were generated from thermal initiation of styrene. Polymerization mediated by $CuCl_2$/TPMA was better controlled (in terms of M_w/M_n) under these conditions. Decreasing the copper concentration from 50 to 1 ppm resulted in the increase of M_n values relative to $M_{n,theor}$ accompanied by broader molecular weight distributions ($M_n/M_w = 1.13$ (50 ppm), 1.38 (10 ppm) and 1.72 (1 ppm). However, quite impressively, just 1 ppm of copper in the presence of an excess of TPMA was ultimately sufficient to control molecular weights in this ATRP system.

ICAR ATRP of methyl methacrylate (MMA) also proved very efficient when mediated by 50 ppm of $CuCl_2$: TPMA (1 : 1 molar ratio) and initiated by ethyl α-bromophenylacetate (EtBrPA).[49] Linear first-order kinetics were observed, molecular weights agreed well with theoretical values, and polydispersities were low ($M_w/M_n \approx 1.2$). Similarly, good control over molecular weights and acceptable M_w/M_n in the

Table 2 ICAR ATRP of styrene[a]

Ligand[b] $T = 60$ °C	Cu/L /ppm	t /min	Conv. (%)	$M_{n,theor}$[b] /g mol^{-1}	$M_{n,GPC}$ /g mol^{-1}	M_w/M_n
Me_6TREN	50 (1 : 1)[c]	2760	44	8700	7900	1.12
TPMA	50 (1 : 1)	2880	39	7800	6800	1.09
PMDETA	50 (1 : 1)	2880	29	5600	4500	1.62
dNbpy	50 (1 : 1)	2940	36	7200	5600	1.68
$T = 110$ °C						
Me_6TREN	50 (1 : 10)	1775	65	12 900	11 000	1.25
TPMA	50 (1 : 10)	1930	49	9800	9600	1.13
TPMA	10 (1 : 50)	1720	42	8400	7600	1.38
TPMA	1 (1 : 500)	1700	55	11 000	8400	1.72

[a] Ratio of reactants: $[Sty]_0 : [EtBrIB]_0 : [AIBN]_0 = 200 : 1 : 0.1$ at 60 °C and $200 : 1 : 0$ at 110 °C, $[Sty]_0 = 5.82$ M; 50% anisole by volume. [b] $M_{n,theor} = ([M]_0/[EtBrIB]_0) \times \text{conv.} \times M_{monomer}$. [c] Copper/ligand ratio.

polymerization of *n*-butyl acrylate (BA) initiated by EtBrIB was obtained with 50 ppm of $CuCl_2$/TPMA, illustrating the broad application of ICAR ATRP.

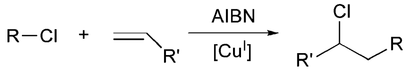
Similarly to ARGET ATRP, the development of ICAR ATRP has profound industrial implications because it lowers the amount of necessary copper-catalyst from several thousand ppm, under normal reaction conditions, to <50 ppm, while still allowing excellent control over molecular weight and molecular weight distribution.

4 Highly efficient ATRA in the presence of catalytic amounts of copper complexes

Transition-metal catalyzed atom transfer radical addition (TMC ATRA) is a very useful reaction for the synthesis of carbon–carbon bonds through a radical process.[1–3] It can be applied to a variety of halogenated substrates and alkenes in both intermolecular and intramolecular fashion.[9] However, until recently, the principal drawback of this useful synthetic tool remained the large amount of metal catalyst required to achieve high selectivity towards the desired monoadduct. Similarly to ATRP, various methodologies have been developed to overcome these drawbacks and they include: (a) design of solid supported catalysts, (b) use of biphasic systems such as fluorous solvents, and (c) use of highly active copper(I) complexes based on ligand design.[9]

As discussed in the previous section, the most significant solution to the problem of catalyst recycling and regeneration has been found for ATRP, which originated from ATRA. These new processes termed ARGET and ICAR ATRP utilize copper(II) complexes, which are continuously reduced to copper(I) complexes in the presence of phenols, glucose, ascorbic acid, hydrazine, tin(II) 2-ethylhexanoate and radical initiators.[45–47,49] This technique for catalyst regeneration has recently been utilized with great success in ATRA reactions catalyzed by $[Cp^*Ru^{III}Cl_2(PPh_3)]$[50] and $[Cu^{II}(TPMA)X][X]$ (X = Br^- and Cl^-)[51,52] complexes. In the case of copper-catalyzed ATRA, tetradentate nitrogen-based ligand TPMA was chosen for the study because its complexation to Cu^IX or $Cu^{II}X_2$ (X = Br or Cl) results in a formation of one of the most active catalysts in copper-mediated ATRP.[31] Table 3 shows the results for ATRA of polychlorinated compounds to alkenes catalyzed by Cu^I(TPMA)Cl in the presence of AIBN.

Table 3 ATRA of polychlorinated compounds to alkenes catalyzed by Cu^I(TPMA)Cl in the presence of AIBN[a]



Entry	Alkene	RCl	$[Alk]_0 : [Cu^I]_0$	Yield (%)	TON
1	1-Hexene	CCl_4	10 000 : 1	72	7200
2			5000 : 1	98	4900
3	1-Octene	CCl_4	10 000 : 1	67	6700
4			5000 : 1	87	4350
5	Styrene	CCl_4	250 : 1	85	212
6	Methyl acrylate	CCl_4	1000 : 1	60	600
7	1-Hexene	$CHCl_3$	1000 : 1	56	560
8	1-Octene	$CHCl_3$	500 : 1	49	245
9	Styrene	$CHCl_3$	1000 : 1	58	580
10	Methyl acrylate	$CHCl_3$	1000 : 1	63	630

[a] All reactions were performed in toluene at 60 °C for 24 h with $[R\text{–}Cl]_0 : [alkene]_0 = 4.0$. The yield is based on the formation of monoadduct and was determined by ^1H NMR using toluene as internal standard or column chromatography. The conversion of alkene for all substrates was in the range 85–100%.

For simple alkenes (1-hexene and 1-octene), excellent yields of the monoadduct were obtained with olefin to catalyst ratios as low as 10 000 : 1 (entry 1–4, Table 3) (Fig. 4). The TONs in these experiments ranged between 4900–7200 (1-hexene) and 4350–6700 (1-octene). Previously reported TONs for copper-mediated ATRA ranged between 0.1 and 10.[9] Experiments conducted starting with the air-stable $[Cu^{II}(TPMA)Cl][Cl]$ complex yielded similar results, indicating that AIBN is capable of efficiently regenerating copper(I) complex, which is needed to homolytically cleave the R–Cl bond.

As indicated in Table 3, the methodology for copper(I) regeneration was quite successful for other alkenes and alkyl halides. Relatively high yields of monoadduct were obtained in ATRA of CCl_4 to styrene (entry 5, Table 3) and methyl acrylate (entry 6, Table 3), but with much higher catalyst loadings. For Cu^ICl/TPMA to styrene ratio of 1 : 250 (entry 5, Table 3), complete conversion of styrene was observed after 24 h and monoadduct was obtained in 85% yield. Further increase in the ratio of styrene to Cu^ICl/TPMA still resulted in quantitative conversion of styrene, however, a more pronounced decrease in the yield of monoadduct was observed. Decrease in the yield of monoadduct was mostly due to the formation of oligomers/polymers. Similar results were also obtained for methyl acrylate. The experiments with less active $CHCl_3$ substrate also worked reasonably well. Relatively high yields were obtained for all alkenes investigated at $[alkene]_0 : [Cu^I]_0$ ratios between 500 and 1000 (entry 7–10, Table 3).

Encouraged by the results, additional experiments were performed in the presence of $[Cu^{II}(TPMA)Br][Br]$ complex and polybrominated compounds.[52] This selection of the catalyst and alkyl halide should result in a significant improvement in the catalytic performance because Cu–Br and C–Br bonds are much weaker than the corresponding chloride analogues. Indeed, truly remarkable results were obtained. Table 4 shows the results for ATRA of polybrominated compounds to

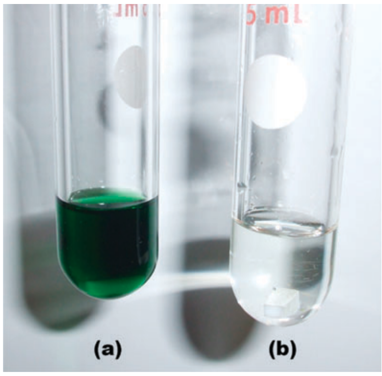
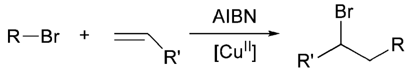


Fig. 4 Standard ATRA of (a) 1-hexene ($[Cu^I]_0 : [1\text{-hex}]_0 = 1 : 3$) and (b) ATRA of 1-hexene in the presence of AIBN ($[Cu^I]_0 : [1\text{-hex}]_0 = 1 : 10\,000$).

Table 4 ATRA of polybrominated compounds to alkenes catalyzed by [Cu^{II}(TPMA)Br][Br] in the presence of AIBN[a]



Entry	Alkene	RBr	[Alk]$_0$: [Cu^I]$_0$	Yield[b] (%)	TON
1	Methyl acrylate[c]	CBr_4	—	32	—
2			200 000 : 1	81 (76) [d]	1.6×10^5
3			100 000 : 1	94	9.4×10^4
4	Styrene[c]	CBr_4	—	72	—
5			200 000 : 1	95 (86) [d]	1.9×10^5
6			100 000 : 1	99	9.9×10^4
7	Methyl acrylate	$CHBr_3$	1000 : 1	57	5.7×10^2
8			500 : 1	66	3.3×10^2
9	Styrene	$CHBr_3$	10 000 : 1	70	7.0×10^3
10			5000 : 1	77	3.9×10^3
11			1000 : 1	92	9.2×10^2
12	1-Hexene	$CHBr_3$	10 000 : 1	61 (59)[d]	6.1×10^3
13	1-Octene	$CHBr_3$	10 000 : 1	69 (54)[d]	6.9×10^3
14	1-Decene	$CHBr_3$	10 000 : 1	63 (64)[d]	6.3×10^3

[a] All reactions were performed in bulk at 60 °C for 24 h with [R–Br]$_0$: [alkene]$_0$: [AIBN]$_0$ = 4 : 1 : 0.05, except reactions for entries 1–6 which were performed in CH_3CN. The conversion of alkene for all substrates was quantitative, except for substrates 12–14 (65–75%). [b] The yield is based on the formation of monoadduct and was determined by ^{1}H NMR using anisole or toluene as internal standard. [c] Reactions were performed without copper(II) complex. [d] Isolated yield after column chromatography.

alkenes catalyzed by [Cu^{II}(TPMA)Br][Br] complex in the presence of reducing agent AIBN. For methyl acrylate, a significant improvement in the yield of the monoadduct was achieved using [Cu^{II}(TPMA)Br][Br] to methyl acrylate ratios of 1 : 200 000 (81%, entry 2, Table 4) and 1 : 100 000 (94%, entry 3, Table 4). Furthermore, using identical reaction conditions, the complete conversion of styrene was also achieved with the main product being the desired monoadduct (95%, entry 5 and 99%, entry 6, Table 4). In the absence of catalyst, but in the presence of AIBN, moderate to high yields of the mono adduct were obtained for both monomers (32%, entry 1 and 72%, entry 4, respectively) due to the fact that CBr_4 is a highly efficient chain transfer agent.

As indicated in Table 4, the methodology for copper(I) regeneration in ATRA in the presence of reducing agent AIBN worked very well for less active bromoform. Relatively high yields of monoadduct were obtained in ATRA of $CHBr_3$ to methyl acrylate (entry 7 and 8, Table 4) and styrene (entry 9–11, Table 4), but with much higher catalyst loadings. Further decrease in the amount of catalyst for both monomers resulted in a decrease in the yield of the monoadduct. The decrease in the yield of monoadduct was mostly due to the formation of oligomers/polymers, which was explained by (a) insufficient trapping of radicals generated from AIBN by the copper(II) complex and (b) further activation of the monoadduct by the copper(I) complex (more pronounced in the case of methyl acrylate). In the ATRA of $CHBr_3$ to 1-hexene (entry 12, Table 4), 1-octene (entry 13, Table 4) and 1-decene (entry 14, Table 4), moderate yields of the monoadduct were attributed to incomplete alkene conversions. Furthermore, conversions of alkene for entries 12–14 (Table 4) were relatively independent on the alkene : copper(II) ratios between 500 : 1 and 10 000 : 1, indicating that the rate of addition of $CHBr_2^{\bullet}$ radicals to alkenes was slow.

The activity of the [Cu^{II}(TPMA)Br][Br] complex in ATRA of polybrominated compounds to alkenes in the presence of AIBN, based on catalyst loading, conversion of alkene and the yield of monoadduct, was approximately 10 times higher than the activity of previously reported [Cu^{II}(TPMA)Cl]Cl] in the ATRA of polychlorinated compounds to alkenes. Also, for comparable monomers and alkyl halides, its activity was very close to the activity of the [Cp*Ru^{III}Cl$_2$(PPh$_3$)] complex.[50] [Cu^{II}(TPMA)Br][Br], in conjunction with AIBN, effectively catalyzed ATRA reactions of polybrominated compounds to alkenes with concentrations between 5 and 100 ppm, which is by far the lowest number achieved in copper-mediated ATRA.

6 Conclusions

Recent advances in the area of catalyst regeneration in ATRP and mechanistically similar ATRA using environmentally benign reducing agents were reported. The outlined processes termed ARGET (activators regenerated by electron transfer) and ICAR (initiators for continuous activator regeneration) ATRP enable the synthesis of well defined (co)polymers using very low concentrations of the copper catalysts (1–100 ppm). Both processes utilize copper(II) complexes which are continuously reduced to copper(I) complexes in the presence of phenols, glucose, ascorbic acid, hydrazine and tin(II) 2-ethylhexanoate in the case of ARGET, and radical initiators in the case of ICAR ATRP. These techniques for catalyst regeneration have also been applied with great success in ATRA reactions catalyzed by copper and ruthenium, achieving one of the highest TONs for any metal-mediated ATRA process. It is envisioned that the recent developments in this area could have profound implications for the large-scale industrial synthesis of well-defined polymeric materials and small organic molecules.

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