ChemComm

Chemical Communications

Conversion (%)

Cu^0 wire with added Cu^{II}
Cu^0 wire
Pre-treated Cu^0 wire

Time (min)

k_{deact}

k_{act0} Cu^{I}X/L k_{act1}

k_{comp} k_{disp}

P_n-P_n

k_t

P_n-X   Cu^0 +   Cu^{II}X$_2$/L   P$_n$+M k_p

ROYAL SOCIETY
OF CHEMISTRY
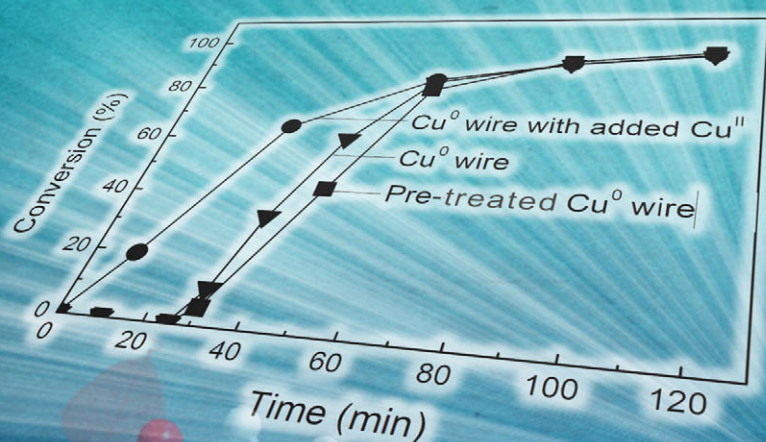
COMMUNICATION
Wenxin Wang *et al.*
Insights into relevant mechanistic aspects about the induction period of
Cu^0/Me$_6$TREN-mediated reversible-deactivation radical polymerization

ChemComm

Insights into relevant mechanistic aspects about the induction period of Cu⁰/Me₆TREN-mediated reversible-deactivation radical polymerization†

Yongsheng Gao,[a] Tianyu Zhao,[a] Dezhong Zhou,[a] Udo Greiser[a] and Wenxin Wang*[ab]

There is a controversial debate about the mechanism of the Cu⁰-catalyzed radical polymerization. Herein, a comparative analysis of a series of reactions catalyzed by different valent copper shows that the induction period and the subsequent autoaccelerated polymerization of a Cu⁰/Me₆TREN-catalyzed system originate from the accumulation of soluble copper species, and Cu^I is still a powerful activator under its disproportionation favored conditions.
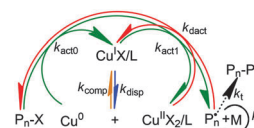
Atom transfer radical polymerization (ATRP) is one of the most commonly used reversible-deactivation radical polymerization (RDRP) techniques for designing and synthesizing polymers with well-defined composition, functionalities, and architecture.[1–3] The key step is to establish activation–deactivation equilibrium between a lower oxidized transition metal/ligand complex (Cu^{I}X/L, X typically stands for Br or Cl) and an alkyl halide to generate a growth radical and a higher oxidized transition metal/ligand complex (Cu^{II}X₂/L). Due to the existence of the persistent radical effect (PRE)[4] in traditional ATRP, resulting in the loss of chain end functionalities and accumulation of copper, several alternative techniques have been developed recently, including activators regenerated by electron transfer (ARGET) ATRP,[5] initiators for continuous activator regeneration (ICAR) ATRP,[6] electrochemically mediated ATRP,[7] and photochemically mediated ATRP.[8]

Another technique, developed by Percec *et al.*,[9] employs the metallic copper (Cu⁰) as an activator in the presence of appropriate solvents and ligands, which was termed single electron transfer living radical polymerization (SET-LRP). The detailed mechanism of SET-LRP has been the subject of controversial debate with disagreement over the pathway of the Cu^I species generated in the activation steps and the extent of the subsequent disproportionation. Originally, proposed by Percec *et al.*, the activation of the dormant

species by Cu⁰ species occurs through an outer-sphere electron-transfer (OSET) process. The generated Cu^{I}X/L complexes disproportionate 'spontaneously' into highly reactive 'nascent' Cu⁰ and Cu^{II}X₂/L species. The formation of deactivators does not involve bimolecular termination or PRE as reported in classical ATRP. However, another interpretation, reported by Matyjaszewski *et al.*, is that the metallic copper acts as a supplemental activator and a reducing agent (SARA), and Cu^{I}X/L complexes, instead of Cu⁰, activate the dormant species *via* the inner-sphere electron-transfer (ISET) process. Cu⁰ mainly acts as a reducer of the comproportionation with Cu^{II}. Activation by Cu⁰ occurs at a slow rate and disproportionation of Cu^I is negligible.[10,11] All of the possible reactions are outlined in Scheme 1.

Continued efforts have been made to identify at which end of the spectrum the 'truth' lies. Unlike those two incompatible interpretations, some intermediate explanations have also been proposed. Harrisson *et al.*[12–14] concluded that both Cu^{I}X/L and Cu⁰ act as activators and both disproportionation and comproportionation coexist with the overall effect of disproportionation and comproportionation depending on the equilibrium constant and the concentrations of Cu^{I}X/L and Cu^{II}X₂/L in nonpolar and polar solvents. Wang *et al.*[15] proposed that the mechanism behind Cu⁰/PMDETA-mediated RDRP with added CuBr₂ lies between the competition and equilibrium results of SET-LRP and SARA ATRP.

Remarkably, understanding the detailed process of the activation and disproportionation of the copper species in the initial stage of the Cu⁰-mediated RDRP is of great interest and crucial to distinguish the mechanism.[12,14] One of the unique features in this stage is that an apparent period of slow reaction rate with low monomer conversion (similar to induction period) is observed

[a] *Charles Institute of Dermatology, School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4, Ireland.*
  E-mail: wenxin.wang@ucd.ie
[b] *School of Materials Science and Engineering, Tianjin University, Tianjin, China*

Scheme 1 Possible reactions in Cu⁰-mediated RDRP.

in the early stage of various Cu^0-mediated RDRP systems.[16–22] For the extensively studied system: Cu^0(wire)/Me_6TREN in DMSO, Haddleton et al.,[17] Percec et al.,[21,23–25] Whittaker et al.[22] and Guliashvili et al.[16] independently reported the presence of the induction period (30–50 min) at the initial stage of the polymerization of MA with even a rigorous deoxygenation process. Similar results are also observed in other solvents.[26,27] Initially, Haddleton et al.[17] observed that the induction period was followed by an exothermic reaction due to the inefficient heat transfer, resulting in a rapid raise in temperature and a significant quick polymerization rate. Moreover, both the induction time and the exothermic effect were dependent on the surface area of the copper wire. Specifically, bigger surface area of the copper wire leads to a shorter induction period and generation of a larger amount of heat. An alternative explanation for the induction time, proposed by Percec et al.,[24,25] is the existence of the passivating layer (e.g., Cu_2O) from the surface of a commercial metallic copper wire, which, thereby, can be eliminated by activating the commercial Cu^0 wire. The absence of initial induction period was reported by activating the copper wires with hydrazine hydrate[24] or acids.[25]

Despite the fact that the copper oxide layer hindrance explanation is now widely accepted, it still cannot account for all experimental phenomena. For instance, the induction period can be diminished by using larger surface area of the copper wire[17] or adding a small quantity of deactivators.[16,17,22] This leads us to ask what else occurs during the initial stage beyond the slow dissolution of the copper oxide layer. To address this question, all of the relevant processes (including the activation, deactivation, disproportionation, comproportionation, propagation and termination) need to be studied and considered in a real polymerization situation, as the SET-LRP has been ascribed as a complex system where no one component can be truly viewed on its own, but only in the context of its effect on other parts of the system.[28] Herein, we investigated the observed induction time by conducting a series of Cu^0-mediated RDRP of MA in DMSO at 25 °C with different valent coppers and tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as the ligand. This work aims to evoke the attention to this problem beyond the current explanation and tries to shed light on the underlying mechanism involved in the Cu^0-mediated RDRP.

Followed by the copper oxide layer hindrance explanation, we tried to activate the commercial copper wire by pre-equilibration. Specifically, the commercial copper wire was exposed to a degassed polymerization solution (the ratio of MA/EBriB/Me_6TREN is 100 : 1 : 0.18 in DMSO) for 30 min (the length of the induction period in DMSO). After a brief rinse with DMSO, the 'activated' copper wire was transferred to another freshly degassed reaction solution. Upon sampling the reaction at the designed time points and determining the molecular weight and conversion by SEC and NMR, we noticed the identical reaction kinetics obtained using the untreated and pre-treated copper wires and the length of the induction period was still 30 min (Fig. 1). This result was unexpected, however, it was consistent with the previous study of the activation of a copper wire in MeCN.[12] One may argue that this unexpected result originated from the failure of the strict experimental operation, which initially was also one of our concerns, as the induction periods in the 'activated' copper wire catalysed
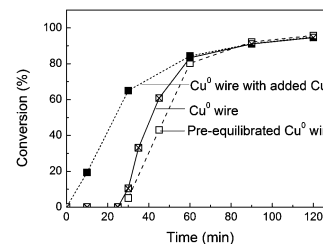

Fig. 1 Kinetic plots of polymerization using an untreated Cu^0 wire with and without additional Cu^{II}, and a pre-equilibrated Cu^0 wire.

systems were still observed (Fig. S1 and Table S1, ESI†). However, under the identical reaction conditions except the addition of a small quantity of $CuBr_2$ (0.05 equiv. relative to the initiator) at the beginning of the reaction, the absence of the induction period was observed (Fig. 1) indicating that the observed induction period stems from the internal reaction system instead of the external operation conditions.

These perplexing results drove us to reconsider all the possible reactions involved in this initial stage as outlined in Scheme 1. Considering that it is about the auto-acceleration after an induction period, our attention was therefore drawn to the mutual conversion of the catalysts (Cu^0, Cu^I and Cu^{II}) and their resulting relative concentrations. It should be noted that, under real polymerization conditions, two equilibriums – activation/deactivation equilibrium and disproportionation/comproportionation equilibrium – coexisted. Thereby, even if the solvent and ligand thermodynamically favour disproportionation over comproportionation ($k_{disp} \gg 1$, Scheme 1), the relative concentrations of Cu^I and Cu^{II} species may not approach the disproportionation equilibrium ratio ($[Cu^{II}]/[Cu^I]^2 = k_{disp}$), since this ratio may be far from that in the activation/deactivation equilibrium.[12,16] Although DMSO and Me_6TREN are commonly used as solvent and ligand favouring activation with Cu^0 and disproportionation (with a relatively high k_{act0} and k_{disp}), the preferred activator (Cu^0 or Cu^I species) and the extent of the disproportionation depend on both the relevant reaction rate constants and the relative concentrations of the copper species during polymerization. The synergistic effect of the two equilibriums makes the mechanism more complicated and we cannot isolate them from each other as they are in a complex system.

We start the investigation from the polymerization of MA using an acid treated copper wire wrapped around the stirring bar, EBriB, Me_6TREN, and DMSO as a catalyst, initiator, ligand and solvent, respectively, with a [MA] : [EBriB] : [Me_6TREN] feed ratio of 100 : 1 : 0.18 (entries 1–6 in Table S2, ESI†). The polymerization is well controlled. Specifically, the recorded kinetic plot (Fig. 2a) was first order with respect to monomer conversion, demonstrating a living polymerization, and k_p^{app} was found to be 0.03 min^{-1}. 93% monomer conversion is reached within 2 h. The evolution of the number average molecular weight (M_n) and polydispersity ($Đ$) with respect to theoretical molar mass is depicted in Fig. 2b. Fig. 2c displays the SEC traces of the polymerization process with a narrow molecular weight distribution ($Đ < 1.1$). However, the presence of a 30 min induction period was observed. Harrisson et al.[12] attributed the initial slow rate of reaction and the subsequent auto-acceleration to autocatalysis through studying the conversion of initiators.
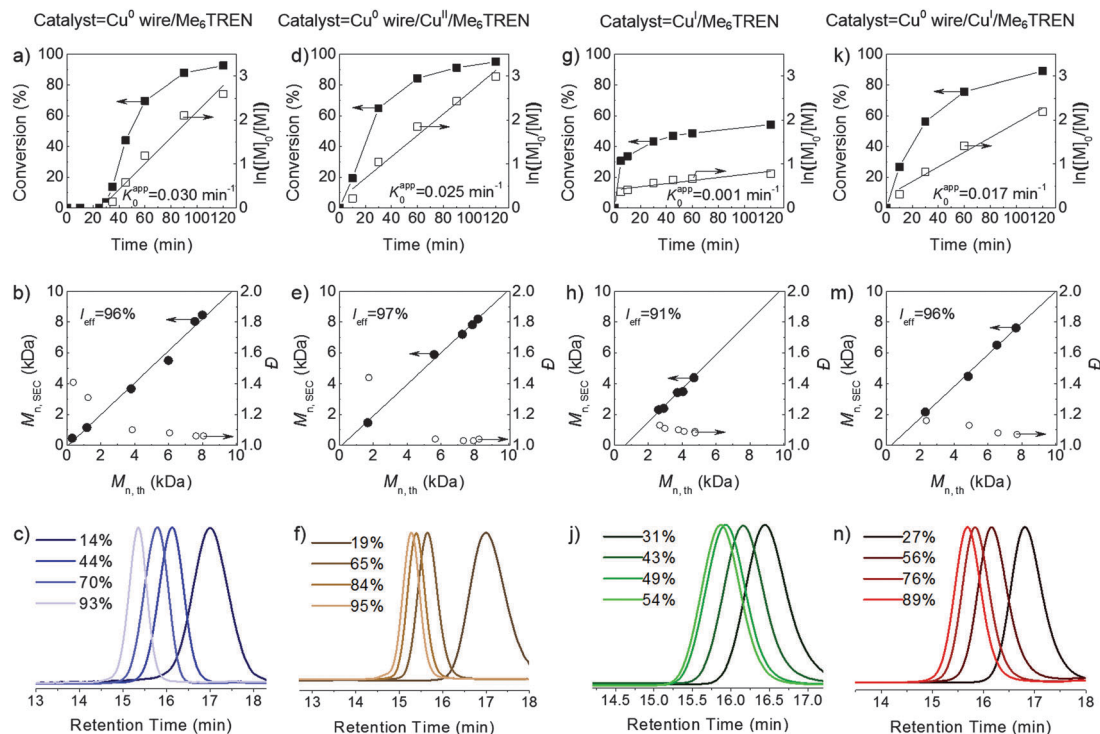
Fig. 2 Kinetic plots of conversion and ln([M]$_0$/[M]) *versus* time (a, d, g and k), plots of number-average molecular weights ($M_{n,SEC}$) and polydispersity ($Đ$) *versus* theoretical number-average molecular weights ($M_{n,th}$) (b, e, h and m), and the evolution of molecular weight monitored by SEC (c, f, j and n) for polymerization of MA catalyzed by the Cu^0 wire (a, b and c), Cu^0 wire/Cu^{II} (d, e and f), Cu^I (g, h and j) and Cu^0 wire/Cu^I (k, m and n) with Me$_6$TREN as a ligand in DMSO at 25 °C.

This conclusion cannot be applied directly here, since the reaction conditions are different and the conversion of monomers instead of initiators was monitored here, but it is helpful to understand the reason for the induction period.

It is obvious that the reaction must start from the activation of initiators by Cu^0 species since there is no other mechanism available to activate the initiators and produce the Cu^I species under these reaction conditions without the additional Cu^{II} species. Once other copper species form, it is crucial to the reaction process how these different copper species are converted and which species are accumulated. In principle, accumulation of all of the three kinds of copper species (Cu^0, Cu^I and Cu^{II}) produced during the reaction may have the auto-catalytic effect. Specifically, accumulation of Cu^I might accelerate the polymerization *via* the reaction with alkyl halide. Similarly, accumulation of Cu^{II} may result in the comproportionation with metallic copper to form 2 equiv. of Cu^I which activate the reaction subsequently. Alternatively, highly reactive 'nascent' Cu^0 may also be 'accumulated' by the 'instantaneous' disproportionation of Cu^I to accelerate the reaction. But, accumulation of Cu^0 is a pseudo-concept, since the highly reactive 'nascent' Cu^0 has been assumed either to be oxidized or precipitated as soon as it is formed.[29] Considering the slow rate of polymerization occurred during the initial stage, it is reasonable to assume that the relative concentrations of different copper species are far from the polymerization equilibrium (activation/ deactivation) ratio. So we hypothesized that disproportionation equilibrium dominates the mutual conversion of the different valent copper species and the dissolved copper species is

accumulated in the initial stage, and once the [Cu^I]/[Cu^{II}] ratio approaches the polymerization equilibrium ratio, the polymerization would be accelerated.

We started the investigation of this hypothesis from the addition of different copper species. Firstly, a small quantity of CuBr$_2$ (0.05 equiv. relative to EBriB) was added in the previously mentioned Cu^0-mediated RDRP. The polymerization is still well controlled (entries 7–11 in Table S2, ESI,† and Fig. 2d–f). The living polymerization nature was demonstrated from the first order kinetic plot with respect to monomer conversion (Fig. 2d), and k_p^{app} was found to be 0.025 min^{-1}. 95% monomer conversion is reached within 2 h. The evolution of the number average molecular weight (M_n) and $Đ$ with respect to theoretical molar mass is depicted in Fig. 2e. The SEC traces of the polymerization process with a narrow molecular weight distribution ($Đ < 1.1$) are shown in Fig. 2f. Most importantly, as previously observed, the polymerization was started at the very beginning of the reaction and the induction period was absent. The most likely reason is that the added Cu^{II} species participate in the mutual conversion of different valent copper species at the beginning of the reaction either through the comproportionation with copper metal or deactivation. However, the latter pathway should in principle slow down the polymerization rate instead of accelerating it, since the polymerization rate is proportional to radical concentration which is decreased due to the deactivation. Therefore, the comproportionation dominates in this case. It needs to be mentioned that in a real system, the preferred equilibrium direction depends not only on the absolute rate constants, but also on the relative concentrations

of the different copper species. In this case, the excess Cu^{II}, ligand and copper metal shifted the disproportionation equilibrium towards the Cu^{I} species, in other words, the comproportionation was kinetically favoured in the initial stage and contributed positively to the build-up of polymerization equilibrium. It should be noted that the comproportionation of Cu^{II} with copper metal will form 2 equiv. of Cu^{I}, resulting in accumulation of the dissolved copper species. Therefore, it can be deduced that the disappearance of induction period is because of the instant accumulation of dissolved copper species (Cu^{I} and Cu^{II} species). But the details on the 'actual' activator and the extent of the disproportionation of Cu^{I} in this unsteady initial stage still remain unclear.

Most studies devoted to clarify these details based on model experiments,[30] which, to some extent, are not able to faithfully mimic the true polymerization conditions due to the nature of the complex system, and the results are conflicting. In order to further understand these unclear mechanisms based on the true polymerization conditions, the polymerization of MA initiated with EBriB in DMSO at 25 °C using Cu^{I}/Me_6TREN in the absence and presence of a Cu^0 wire was conducted. In both cases, the initial induction period disappeared (entries 12–21 in Table S2, ESI,† and Fig. 2g–n) as expected, because of the increase of dissolved copper species. However, the kinetic profiles are significantly different. For the MA polymerization catalysed by Cu^{I}/Me_6TREN in the absence of Cu^0, the monomer conversion is *ca.* 30% within 5 min but stops with the final conversion less than 60%. Addition of fresh Cu^{I}/Me_6TREN solution, however, allows the polymerization to proceed towards conversion as high as 86% (Fig. S2, ESI†), which is in agreement with the previous study,[16] using added Cu^0 to further increase the monomer conversion. This result indicates that the polymerization stops due to the accumulation of Cu^{II} species by the disproportionation of Cu^{I} species instead of the radical termination, *e.g.* PRE, since the polymerization can be restarted. In contrast, for the MA polymerization catalysed by Cu^{I}/Me_6TREN in the presence of Cu^0, the recorded kinetic plot (Fig. 2k) was first order with respect to monomer conversion with k_p^{app} of 0.017 min^{-1}, and 89% monomer conversion was achieved within 2 h. The higher monomer conversion obtained in the Cu^{I}/Me_6TREN catalysed system with additional Cu^0 further demonstrates that the excessive accumulation of Cu^{II} is avoided due to the comproportionation with Cu^0. In other words, in the Cu^{I}/Me_6TREN catalysed polymerization of MA, the disproportionation effect (equilibrium shifted to Cu^{II}) on the time scale of the reaction contributes negatively to the build-up of polymerization equilibrium, but this negative effect can be avoided by adding Cu^0 to shift the equilibrium back to Cu^{I}. Thereby, Cu^{I} is still a powerful activator even under its disproportionation favoured reaction conditions (in the presence of Me_6TREN as a ligand and DMSO as a solvent) according to our investigation, indicating that both SET-LRP and SARA ATRP mechanisms coexisted.

In summary, the current agreed hindrance of a passivating layer (Cu_2O) on commercial copper wires cannot account for the elimination of the observed induction period in the Cu^0/Me_6TREN-mediated RDRP of MA by addition of Cu^{II}. The current study proves that the induction period and the subsequent autoaccelerated polymerization originate from the accumulation of dissolved copper species (Cu^{I} and Cu^{II}) to approach the activation/deactivation equilibrium. Cu^{I} is verified as also a powerful activator even under its disproportionation favored conditions.

Notes and references

1 M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721–1723.
2 J. S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614–5615.
3 Y. Li, H. Yu, Y. Qian, J. Hu and S. Liu, *Adv. Mater.*, 2014, **26**, 6734–6741.
4 H. Fischer, *Chem. Rev.*, 2001, **101**, 3581–6610.
5 W. Jakubowski and K. Matyjaszewski, *Angew. Chem., Int. Ed.*, 2006, **45**, 4482–4486.
6 K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker and N. V Tsarevsky, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 15309–15314.
7 A. J. D. Magenau, N. C. Strandwitz, A. Gennaro and K. Matyjaszewski, *Science*, 2011, **332**, 81–84.
8 N. J. Treat, H. Sprafke, J. W. Kramer, P. G. Clark, B. E. Barton, J. Read de Alaniz, B. P. Fors and C. J. Hawker, *J. Am. Chem. Soc.*, 2014, **136**, 16096–16101.
9 V. Percec, T. Guliashvili, J. S. Ladislaw, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *J. Am. Chem. Soc.*, 2006, **128**, 14156–14165.
10 D. Konkolewicz, Y. Wang, M. Zhong, P. Krys, A. a. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 8749–8772.
11 D. Konkolewicz, Y. Wang, P. Krys, M. Zhong, A. a. Isse, A. Gennaro and K. Matyjaszewski, *Polym. Chem.*, 2014, **5**, 4409.
12 S. Harrisson, P. Couvreur and J. Nicolas, *Macromolecules*, 2012, **45**, 7388–7396.
13 J. Tom, B. Hornby, A. West, S. Harrisson and S. Perrier, *Polym. Chem.*, 2010, **1**, 420.
14 A. G. West, B. Hornby, J. Tom, V. Ladmiral, S. Harrisson and S. Perrier, *Macromolecules*, 2011, **44**, 8034–8041.
15 Y. Gao, T. Zhao and W. Wang, *RSC Adv.*, 2014, **4**, 61687–61690.
16 T. Guliashvili, P. V. Mendonça, A. C. Serra, A. V. Popov and J. F. J. Coelho, *Chem. – Eur. J.*, 2012, **18**, 4607–4612.
17 M. E. Levere, I. Willoughby, S. O'Donohue, A. de Cuendias, A. J. Grice, C. Fidge, C. R. Becer and D. M. Haddleton, *Polym. Chem.*, 2010, **1**, 1086.
18 S. Harrisson and J. Nicolas, *ACS Macro Lett.*, 2014, **3**, 643–647.
19 G. Lligadas and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 3174–3181.
20 B. M. Rosen, G. Lligadas, C. Hahn and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 3940–3948.
21 N. H. Nguyen, X. Leng and V. Percec, *Polym. Chem.*, 2013, **4**, 2760.
22 F. Nyström, A. H. Soeriyadi, C. Boyer, P. B. Zetterlund and M. R. Whittaker, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 5313–5321.
23 N. H. Nguyen, B. M. Rosen, G. Lligadas and V. Percec, *Macromolecules*, 2009, **42**, 2379–2386.
24 N. Nguyen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 5109–5119.
25 N. H. Nguyen and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 4241–4252.
26 N. H. Nguyen, B. M. Rosen, X. Jiang, S. Fleischmann and V. Percec, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 5577–5590.
27 M. E. Levere, I. Willoughby, S. O'Donohue, P. M. Wright, A. J. Grice, C. Fidge, C. Remzi Becer and D. M. Haddleton, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 1753–1763.
28 B. M. Rosen and V. Percec, *Chem. Rev.*, 2009, **109**, 5069–5119.
29 N. H. Nguyen, H.-J. Sun, M. E. Levere, S. Fleischmann and V. Percec, *Polym. Chem.*, 2013, **4**, 1328.
30 Y. Wang, M. Zhong, W. Zhu, C.-H. Peng, Y. Zhang, D. Konkolewicz, N. Bortolamei, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3793–3802.