In Situ Xanthate Deprotection to Generate Thiol Chain Transfer Agents for Conventional Free Radical Linear and Branched Vinyl Polymerisation

Sean Flynn, Simon D. Dale, Andrew B. Dwyer, Pierre Chambon and Steve P. Rannard*

Department of Chemistry, University of Liverpool, Crown Street, L69 7ZD, UK

Correspondence to: Steve P. Rannard (Email srannard@liverpool.ac.uk)

KEYWORDS: Branched vinyl polymerisation, gel permeation chromatography, chain transfer

Branched polymers have received considerable interest over recent decades due to their unique properties including complex architectures, low viscosities, good solubility and high numbers of potentially diverse terminal functional groups. [1-3] The preparation of branched polymers by conventional free radical polymerization (FRP) of mixtures of mono-vinyl and multi-vinyl monomers is somewhat limited due to the onset of gelation following excessive crosslinking, which may readily occur at low monomer conversion. [4] Nonetheless, a number of branched polymer architectures have been reported using various strategies including the chain transfer monomer approach,[5-8] homopolymerisation of multi-functional monomers; [9-12] gelation is prevented in the latter case through excessive dilution, employing solvents exhibiting high transfer constants or by utilising excessive amounts of initiator at high temperature. Another approach, commonly referred to as the Strathclyde methodology, involves the copolymerization of mono- and bi-functional monomers in the presence of a chain transfer agent (CTA). [13-15] The resulting branched polymers contain a large number of conjoined primary chains that are chemically near-identical to linear polymers generated in the absence of the bi-functional monomer; consequently, the statistical nature of the branching generates broad molecular weight distributions and a range of species with varying numbers of chain-ends. The Strathclyde methodology has received significant attention in the literature with the majority of publications relying on the use of thiol-based CTAs. [16-20]

Whilst thiols have been extensively studied as CTAs in the FRP of a wide range of monomers, they have considerable malodour, may exhibit acute toxicity and readily undergo oxidation under atmospheric conditions, [21] which generates handling problems during industrial scale processing. [22] The synthesis of thiol based CTAs containing bespoke structures remains a difficult task and as a result the range of CTA structures studied is generally heavily dependent upon commercial availability thiols, thereby limiting the diversity of research scope. Routes that allow ready synthesis of a diverse range of thiols, or synthetic equivalents of thiols, for use in FRP would offer access to new chain end functionality *via* readily scale-able syntheses.

Dithiocarbonates (xanthates) offer an efficient protecting group chemistry for thiols, they can be synthesized without difficulty and readily undergo deprotection in the presence of primary amines under ambient conditions. [23] We have recently reported the use of xanthates as thiol protecting groups for the synthesis and surface group modification of low generation thiol-functional dendrimers, linear-dendritic hybrids and hyper-branched polydendrons, using a one-pot deprotection / functionalisation strategy. [24-26] Thiocarbonyl containing compounds including xanthates, dithiobenzoates, dithiocarbamates and trithiocarbonates are commonly used to provide control within reversible addition/ fragmentation chain transfer (RAFT or MADIX) polymerisation. [27-29] Their roles involve limiting the concentration of active radicals during polymerization, limiting termination reactions

and maintaining control over polymer chain lengths. Here we employ an approach in which a xanthate plays an alternative role within the polymerisation. In this approach, the synthesis of xanthates from alkyl/aryl halides offers access to a wide range of thiols with varying structure; deprotection within the polymerization reaction vessel allows the avoidance of thiol handling issues; and the presence of thiol within a free radical polymerization after deprotection leads to a conventional chain transfer mechanism. The approach is demonstrated in linear polymerisations and its versatility has been extended to more complex architectures through the production of branched vinyl polymers by FRP *via* a modified Strathclyde methodology, using a one-pot, two-step procedure. A comparative study between linear and branched vinyl polymerization is also presented using conventional thiol CTA analogues.

In this study benzyl mercaptan (BzSH) was selected as a comparative, conventional thiol CTA as it exhibits a high chain transfer constant in the FRP of methacrylate monomers. [30] *S*-benzyl *O*-ethyl carbonodithioate (BzXan) offers the xanthate protected analogue which generates BzSH following deprotection in the presence of primary amines. BzXan used in this study was synthesized as previously reported (Supporting Information (SI), Figures S1-S3). [31] To investigate the formation of BzSH *via* xanthate deprotection a model study was conducted by treating BzXan with 1.2 equivalents of *n*-butyl amine in toluene. The product, BzSH, was isolated in high yield and characterized by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) and chemical ionisation mass spectroscopy (SI, Figures S4-S5). The Strathclyde methodology requires stringent stoichiometric control between the bi-functional branching co-monomer and CTA at the start of polymerisation (brancher/thiol ratio; $[B]_0/[S]_0$) in order to suppress gelation. It is therefore essential that xanthate deprotection occurs rapidly and with high efficiency. Xanthate deprotection was studied using UV-Vis spectroscopy and ^{1}H NMR to investigate the influence of concentration upon the rate and efficiency of xanthate deprotection. Deprotection kinetic studies were conducted at concentrations varying from 25 - 400 mg mL^{-1} of BzXan in toluene. (Figure 1, SI Figures S6-S7, Tables S1-S3). Good agreement was observed between UV-Vis spectroscopy and ^{1}H NMR and the results demonstrate that the rate of deprotection is highly dependent upon xanthate concentration. Although xanthate deprotection conducted at 25 mg mL^{-1} achieved >98% conversion within 3h (SI Figure S8, Table S1), the data shows that in order to achieve *in situ* thiol CTA formation within a timescale commensurate with the setup of the polymerization reaction, essential to ensuring rigid control over the concentration of thiol present within a linear and branched polymerisation, the deprotection reaction was best conducted at high concentration (for example, 400 mg mL^{-1} in toluene).

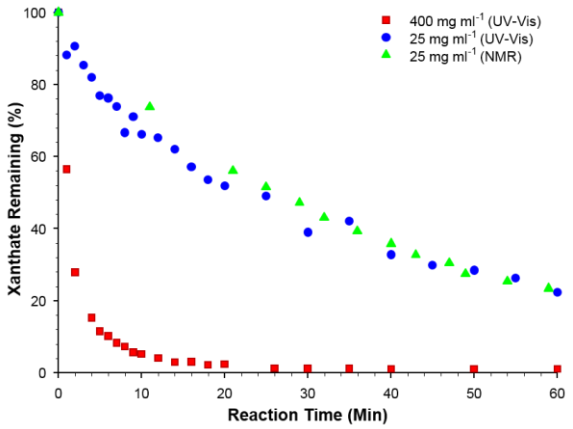
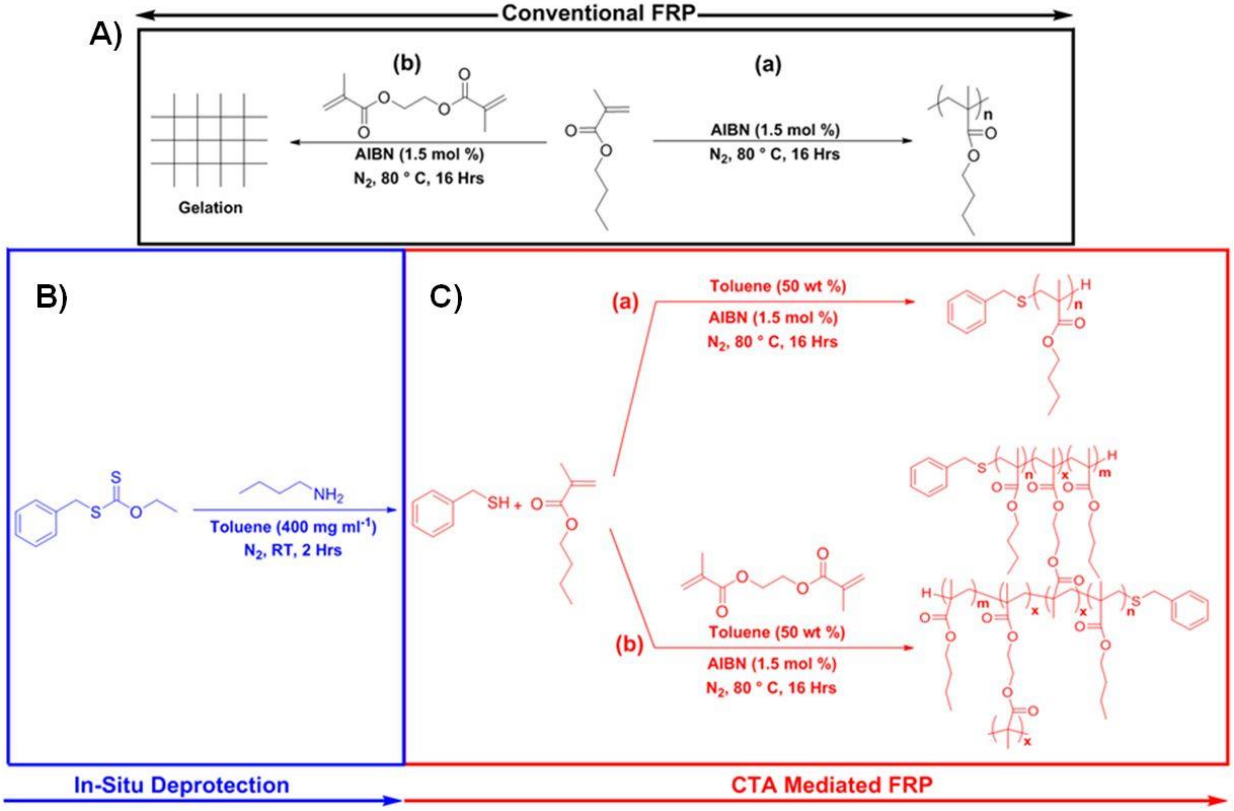


FIGURE 1 Analysis of xanthate deprotection kinetics by UV-Vis spectroscopy and ^{1}H NMR. Deprotection *via* aminolysis of BzXan with *n*-butyl amine at various concentrations in toluene at ambient temperature.

A series of three conventional free radical polymerisations of *n*-butyl methacrylate (BMA) free compared under varying conditions as outlined in Scheme 1. This included: 1) azo-initiated FRP conducted in the absence of a CTA (Scheme 1Aa); 2) azo-initiated FRP mediated by a CTA generated *via* an *in situ* xanthate deprotection (BzXan; Scheme 1Ba); and 3) conventional CTA (BzSH) mediated azo-initiated FRP (Scheme 1Ca). Polymerisations were

conducted in toluene (50 wt %) at 80 °C, using azobisisobutyronitrile (AIBN) as the radical initiator (1.5 mol % w.r.t. vinyl groups). All polymerisations achieved high monomer conversion (≥ 99 %) and were characterized using triple detection size exclusion chromatography (SEC) and ^{1}H NMR (Table 1, SI Figures S9-S12). P(BMA) produced by FRP in the absence of a CTA (Scheme 1Aa) contained high molecular weight material (M_w = 62 000 g mol^{-1}, M_n = 30 800 g mol^{-1}) and a dispersity matching theoretical values for such reactions conducted without controlling agents (Đ = 2.01), see Table 1, despite the potential for chain transfer when using this solvent. As expected a dramatic decrease in molecular weight was observed on addition of BzSH (Scheme 1 Ca) at various monomer to CTA thiol ratios ($[M]_0/[S]_0$ = 6-142) into the polymerisation of BMA under identical conditions (Table 1, SI; Figure S13, Table S4). The molecular weights of the purified polymers obtained varied from M_n = 1100 - 16,500 g mol^{-1} and M_w = 1300 – 24,300 g mol^{-1}.



Scheme 1 Three comparative free radical polymerisation strategies used in the production of P(BMA); A) Conventional FRP conducted in the absence of CTA (black), B) FRP mediated by a CTA generated by *in situ* xanthate deprotection (blue), and C) FRP mediated by a conventional thiol based CTA (red). These approaches have been used to make linear polymers (a routes) and branched vinyl polymers (b routes).

P(BMA) produced using the *in situ* xanthate deprotection approach (Scheme 1 Ba) also contained molecular weights significantly lower than that obtained by conventional FRP which were comparable to that produced using the conventional CTA approach (Table 1, Figure 2a; Figure S14, Table S5). This decrease in molecular weights, characteristic of CTA-medicated FRP, is attributed to the capping of growing polymer chains through a chain transfer reaction with BzSH during polymerisation, which is also evident by the appearance of chemical shifts within the aromatic region of the ^{1}H NMR spectra obtained for purified polymers (Figure S15). The reduced dispersity values (<2.00) for both comparative reactions are potentially due to fractionation of the samples during

purification; especially probable at these low molecular weights.

Branched polymer synthesis, using a modified Strathclyde methodology, was also studied using a copolymerization of BMA with ethylene glycol dimethacrylate (EGDMA) using each strategy.

Polymer	^{1}H NMR			TD-SEC[c]			
	$[M]_0/[S]_0$[a]	$[B]_0/[S]_0$[a]	DP_n[b]	M_w	M_n	Đ	α
FRP							
P(BMA)	-	-	-	62 000	30 800	2.01	0.697
Conventional CTA							
$P(BMA)_6$	6	-	-	1 300	1 100	1.18	0.472
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.93	9	152 000	3 100	49.03	0.356
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.89	8	65 800	3 700	17.78	0.366
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.76	7	35 000	5 000	7.00	0.372
In Situ Deprotection							
$P(BMA)_6$	6	-	-	1 800	1 300	1.38	0.472
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.93	-	Gelation Observed			
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.88	8	223 000	8 300	26.87	0.397
$P(BMA_6$-*co*-$EGDMA_{0.93})$	6	0.76	9	49 100	5 600	8.77	0.367

Table 1 Characterisation of recovered P(BMA) linear and branched polymers produced by; conventional FRP, FRP mediated by a conventional CTA and FRP mediated by a CTA generated by in-situ xanthate deprotection.

[a] Obtained by ^{1}H NMR of reaction mixture at t=0. [b] Obtained by ^{1}H NMR of purified polymers. [c] Obtained by triple detection SEC (THF/TEA (98/2 volume %) calibrated using narrow and broad poly(styrene) standards. $[M]_0$ = initial monomer concentration; $[S]_0$ = initial thiol or thiol equivalent concentration; $[B]_0$ = initial divinyl brancher concentration.

The presence of EGDMA had a considerable impact on each of the reaction conditions studied. As expected, all copolymerisations conducted in the absence of CTA (Scheme 1Ab) formed insoluble gel networks within 60 minutes due to cross-linking of primary chains. Copolymerisations in the presence of BzSH (Scheme 1Cb), conducted using the same $[M]_0$ / $[S]_0$ ratios studied for linear polymer synthesis, led to soluble branched copolymers; when BzXan was deprotected *in situ* prior to polymerization, similar soluble branched copolymers were also formed. High molecular weights polymers with broad molecular weight distributions were observed by SEC, a characteristic of materials produced using the Strathclyde methodology (Table 1, Figure 2b-c).

Further evidence of the formation of branched architectures is demonstrated by decreased α values obtained from the Mark Houwink-Sakurada plots for each polymer (Table 1). In order to increase the degree of branching, polymerisations were conducted using various brancher to thiol ($[B]_0/[S]_0$) ratios. Branched polymers were produced using the conventional Strathclyde approach using BzSH as CTA at $[B]_0/[S]_0$ ratios varying from 0.76-0.93. In all cases gelation was avoided and soluble branched polymers were obtained.

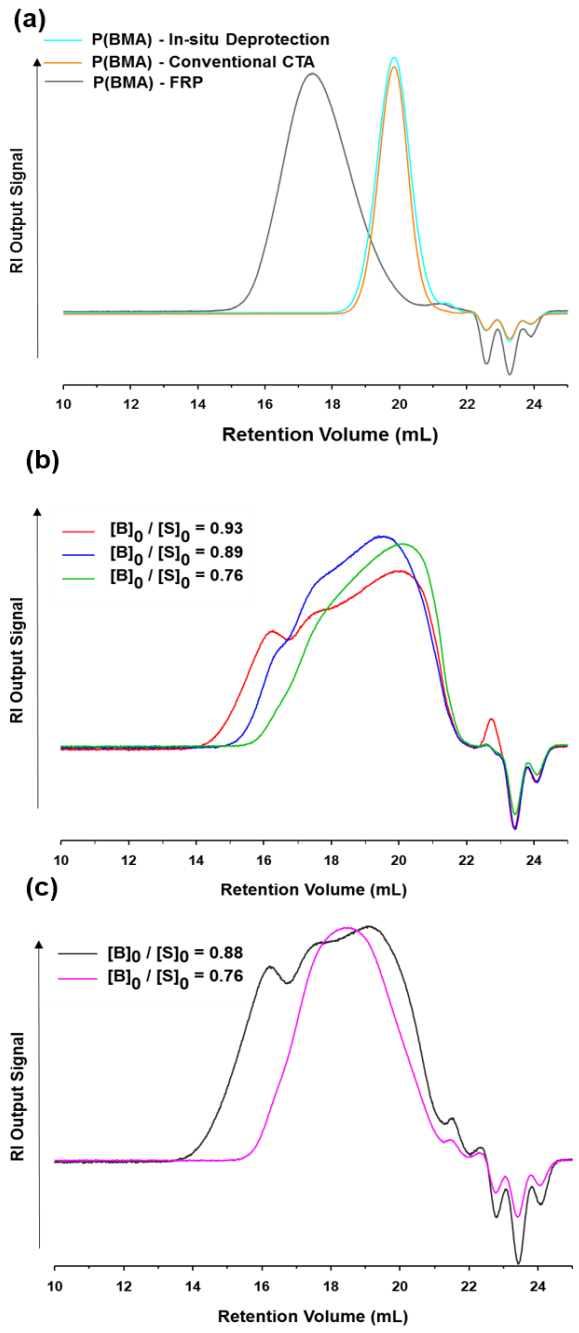


FIGURE 2 SEC analysis (RI chromatograms) of polymers formed by conventional FRP, CTA-mediated FRP and FRP mediated after *in situ* formation of CTA. (a) linear polymers; (b) branched copolymerisations using BzSH; and (c) branched copolymerisations using *in situ* deprotection of BzXan.

The weight average molecular weights and dispersities increased with $[B]_0/[S]_0$ ratios due to an increased fraction of primary chains containing a branching co-monomer that can partake in branching reactions. Branching copolymerisations were also conducted using the addition of BzXan and *in situ* deprotection, maintaining the same $[B]_0/[S]_0$ ratios used for the Strathclyde approach employing the conventional CTA. Again, molecular weights and polymer dispersities increased with increasing $[B]_0/[S]_0$ ratios as seen when BzSH was present. Comparison between the branched polymers show that those produced using the *in situ* deprotection approach contained higher but comparable molecular weight distributions.

A clear difference between polymers obtained using these two approaches was observed in the branching copolymerisations conducted at a nominal $[B]_0/[S]_0$ ratio of 0.93, where a soluble branched polymer was obtained when using a conventional CTA and an insoluble gelled network was formed using the *in situ* deprotection approach (Figure S16). This observation can be explained by a lower than expected xanthate deprotection efficiency leading to higher $[B]_0/[S]_0$ ratios than targeted or trapping of radicals by thiocarbonyl based deprotection side products. The linear polymerizations do suggest a relatively efficient deprotection of BzXan but deviation of the polymerisations utilizing *in situ* CTA formation was observed from analogous polymerisations using BzSH conducted using similar $[M]_0$ / $[S]_0$ ratios (Table 1; Table S4 – S5, Figure S17) and targeting longer chain lengths. Slight increases in actual $[B]_0/[S]_0$ ratios achieved using the *in situ* deprotection would lead to higher than expected molecular weights and the polymerization conditions approaching stoichiometries that would eventually lead to gelation.

In conclusion, in their role as protected thiols, xanthates offer the potential to open routes to diverse CTA structures for conventional free radical polymerization chemistries. Ready formation of xanthates from the facile reaction of alkyl and benzyl halides with the commercially available and inexpensive potassium ethyl xanthogenate, renders this chemistry very

approachable for a wide range of researchers, especially as it avoids the use of CS_2. The comparison of polymerisations using BzSH and the *in situ* formation of BzSH from BzXan presented here, suggests that through a series of relatively straightforward optimization experiments, tuning of outcomes and targeting of desired molecular weights is highly possible; although the actual mechanistic pathways leading to a diversion from the outcomes using commercial thiols requires further study, high conversions were obtained in all cases suggesting that the complications are only minor. We have also demonstrated that complex branched polymer architectures may be synthesized using the "Strathclyde" methodology after initial reaction of the xanthate with a primary amine and direct free radical polymerization without purification. This suggests that the approach may have wide and direct applicability across a range of polymer syntheses, including monomers other than our selected model of BMA and various solvents, offering a rapid and efficient route to generate thiols whilst preserving close stoichiometric control over reactants. This work continues beyond the scope of this communication with the production of xanthates containing a variety of functionalities targeting functionalised branched polymers under industrially relevant conditions.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support from the University of Liverpool and the Engineering and Physical Sciences Research Council for a PhD studentship (SF) and grant funding (EP/L02635X/1, EP/I038721/1) that underpinned the research. SF is also highly grateful for a Liverpool John Lennon Scholarship. Dr Konstantin Luzyanin and Dr Sean Higgins (Centre for Materials Discovery) at the University of Liverpool are also acknowledged for assistance with aspects of the analytical studies.

REFERENCES AND NOTES

1. R. M. England and S. Rimmer, *Polymer Chemistry*, 2010, **1**, 1533-1544.
2. H. Chen and J. Kong, *Polymer Chemistry*, 2016, **7**, 3643-3663.
3. D. Konkolewicz, M. J. Monteiro and S. Perrier, *Macromolecules*, 2011, **44**, 7067-7087.
4. O. Wichterle and D. Lim, *Nature*, 1960, **185**, 117-118.
5. J. Liu, Y. Wang, Q. Fu, X. Zhu and W. Shi, *Journal of Polymer Science Part A: Polymer Chemistry*, 2008, **46**, 1449-1459.
6. L. Jiang, W. Huang, X. Xue, H. Yang, B. Jiang, D. Zhang, J. Fang, J. Chen, Y. Yang, G. Zhai, L. Kong and S. Wang, *Macromolecules*, 2012, **45**, 4092-4100.
7. Q. Jiang, W. Huang, H. Yang, X. Xue, B. Jiang, D. Zhang, J. Fang, J. Chen, Y. Yang, G. Zhai, L. Kong and J. Guo, *Polymer Chemistry*, 2014, **5**, 1863-1873.
8. W. Huang, C. Liu, H. Yang, X. Xue, B. Jiang, D. Zhang, L. Kong, Y. Zhang and S. Komarneni, *Polymer Chemistry*, 2014, **5**, 3326-3334.
9. R. Hu, J. W. Y. Lam, Y. Yu, H. H. Y. Sung, I. D. Williams, M. M. F. Yuen and B. Z. Tang, *Polymer Chemistry*, 2013, **4**, 95-105.
10. Y. Liu, J. C. Haley, K. Deng, W. Lau and M. A. Winnik, *Macromolecules*, 2008, **41**, 4220-4225.
11. J. D. Campbell, F. Teymour and M. Morbidelli, *Macromolecules*, 2005, **38**, 752-760.
12. T. Sato, Y. Arima, M. Seno and T. Hirano, *Macromolecules*, 2005, **38**, 1627-1632.
13. N. O'Brien, A. McKee, D. C. Sherrington, A. T. Slark and A. Titterton, *Polymer*, 2000, **41**, 6027-6031.
14. F. Isaure, P. A. G. Cormack and D. C. Sherrington, *Journal of Materials Chemistry*, 2003, **13**, 2701-2710.
15. G. Saunders, P. A. G. Cormack, S. Graham and D. C. Sherrington, *Macromolecules*, 2005, **38**, 6418-6422.
16. P. Chambon, L. Chen, S. Furzeland, D. Atkins, J. V. M. Weaver and D. J. Adams, *Polymer Chemistry*, 2011, **2**, 941-949.
17. S. Graham, S. P. Rannard, P. A. G. Cormack and D. C. Sherrington, *Journal of Materials Chemistry*, 2007, **17**, 545-552.
18. U. Wais, A. W. Jackson, Y. Zuo, Y. Xiang, T. He and H. Zhang, *Journal of Controlled Release*, 2016, **222**, 141-150.

19. J. V. M. Weaver, R. T. Williams, B. J. L. Royles, P. H. Findlay, A. I. Cooper and S. P. Rannard, *Soft Matter*, 2008, **4**, 985-992.
20. R. T. Woodward, R. A. Slater, S. Higgins, S. P. Rannard, A. I. Cooper, B. J. L. Royles, P. H. Findlay and J. V. M. Weaver, *Chemical Communications*, 2009, DOI: 10.1039/B904320A, 3554-3556.
21. R. Munday, *Free Radical Biology and Medicine*, 1989, **7**, 659-673.
22. G. A. Bagiyan, I. K. Koroleva, N. V. Soroka and A. V. Ufimtsev, *Russian Chemical Bulletin*, 2003, **52**, 1135-1141.
23. M. Le Neindre, B. Magny and R. Nicolay, *Polymer Chemistry*, 2013, **4**, 5577-5584.
24. S. E. R. Auty, O. Andren, M. Malkoch and S. P. Rannard, *Chemical Communications*, 2014, **50**, 6574-6577.
25. S. E. R. Auty, O. C. J. Andren, F. Y. Hern, M. Malkoch and S. P. Rannard, *Polymer Chemistry*, 2015, **6**, 573-582.
26. F. Y. Hern, S. E. R. Auty, O. C. J. Andren, M. Malkoch and S. P. Rannard, *Polymer Chemistry*, 2017, **8**, 1644-1653.
27. G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2006, **59**, 669-692.
28. D. J. Keddie, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 2012, **45**, 5321-5342.
29. S. Perrier and P. Takolpuckdee, *Journal of Polymer Science Part A: Polymer Chemistry*, 2005, **43**, 5347-5393.
30. J. L. O'Brien and F. Gornick, *Journal of the American Chemical Society*, 1955, **77**, 4757-4763.
31. S. Kakaei, N. Chen and J. Xu, *Tetrahedron*, 2013, **69**, 302-309.

GRAPHICAL ABSTRACT

Sean Flynn, Simon D. Dale, Andrew B. Dwyer, Pierre Chambon and Steve P. Rannard*

In Situ Xanthate Deprotection to Generate Thiol Chain Transfer Agents for Conventional Free Radical Linear and Branched Vinyl Polymerisation

Xanthates are used to mediate controlled polymerizations, but here we demonstrate xanthate deprotection as a route to readily form thiol chain transfer agents *in situ* and prior to conventional free radical polymerization. This decreases the hazards of thiol manipulation and allows a range of polymer architectures to be synthesized under simplified conditions. The ease of xanthate synthesis also opens the potential to access tailored chain transfer agent structures which are not available commercially.