

# Spin capturing with nitrones: radical coupling reactions with concurrent introduction of mid-chain functionality†

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**Nitrones are demonstrated to efficiently mediate radical coupling reactions on the example of the conjugation of ATRP-made polymers, yielding macromolecules with distinct functional alkoxyamine centres in mid-chain locations of the chains.**

Nitrones are widely recognized as a highly effective class of radical spin traps for electron spin resonance spectroscopy.<sup>1</sup> Although nitrones are also widely known to participate in dipolar cycloaddition reactions,<sup>2</sup> thus leading to useful applications in synthetic chemistry, utilisation of nitrones as a synthetic tool in other areas such as synthetic radical chemistry, is somewhat rare.<sup>3</sup> Only a few procedures are known that make use of the ability of nitrones to efficiently capture radicals to form nitroxide radicals with subsequent coupling with another radical, even though such reactions can be advantageously applied for synthetic purposes.<sup>4</sup> Recently, a few groups have successfully used nitrones as synthetic precursors for the generation of alkoxyamines<sup>4</sup> as well as their direct employment as molecular weight control agents for controlled radical polymerization reactions, *i.e.* enhanced spin capturing polymerization.<sup>5–7</sup> Based on these studies, it is worthwhile to further explore the synthetic potential of nitrones, for instance as a convenient starting material for alkoxyamine synthesis. Macromolecules are good candidates for studying such reactions due to the availability of (macromolecular) radical sources, the relative ease of analyzing the coupling efficiency without tedious preparative chromatographic product separation and also because they are good examples to demonstrate the synthetic potential of such reactions. Additionally, only a few examples of radical polymer coupling reactions exist so far.<sup>8–10</sup>

The successful combination of controlled polymerization techniques<sup>11</sup> and orthogonal conjugation reactions<sup>12</sup> has allowed the generation of various macromolecular architectures with exactly controllable compositions. Pericyclic reactions are among the most efficient methods employed in

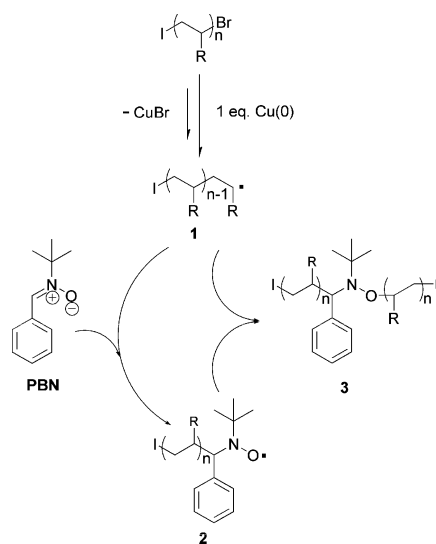
the synthesis of such materials. Radical–radical coupling reactions are more scarce. There are two reasons for this: (i) radicals have a high propensity to undergo undesirable side reactions (disproportionation, transfer) thus leading to partly non-selective coupling reactions; (ii) the coupling reaction is not orthogonal; if radicals of a different type are coupled, product mixtures are obtained, thus access to non-symmetric block polymers is not granted. Nonetheless, as mentioned above, there are a few examples for which efficient radical coupling reactions have been reported such as: (i) the atom transfer radical coupling (ATRC)<sup>8</sup> reactions for the conjugation of two halogenated polymer chains to make telechelic polymers; (ii) the atom transfer nitroxide radical coupling<sup>9</sup> strategy which involves trapping chains with a persistent nitroxide radical; and (iii) the isoprene-assisted radical coupling<sup>10</sup> method whereby isoprene molecules act as linkages between two polymer chains preformed by cobalt-mediated radical polymerization. Each of the above techniques have their own advantages and limitations. However, they all have in common that they are restricted to certain systems.

Herein, we report an efficient and versatile radical–radical conjugation method for the conjugation of polymer chains prepared by atom transfer radical polymerization, ATRP,<sup>11</sup> employing a nitron as a coupling agent. Thereby the formation of nitroxides upon reaction of a radical with the nitron is utilized to enforce the combination with a second macroradical. Even in systems where radical disproportionation must usually be expected, only combination products will be found.<sup>7</sup> As a unique structural feature the conjugated polymer displays an embedded alkoxyamine mid-chain functionality that originates from the nitron coupling agent (see Scheme 1). Concomitantly, the nitron, *i.e.* the formed alkoxyamine, will be located in the middle of the polymer chain and can thus serve to introduce secondary functionalities, which is another feature that the current existing techniques cannot as easily fulfil. Both the nitroxide formation and spin coupling reaction are tolerant towards a large number of functional groups and the nitron can thus be employed to introduce linkages such as alkynes or hydroxyl groups for subsequent polymer conjugation reactions. Another potential of such mid-chain alkoxyamines is that the formed product can be used in further polymerization reactions, *e.g.* nitroxide-mediated polymerization, which then gives access to triblock copolymer structures.

Fig. 1 depicts the molecular weight distributions of ATRP-made polymer (polystyrene, PS I, and polyisobornyl acrylate, PiBoA I, IV). This polymer was then reacted in the absence of

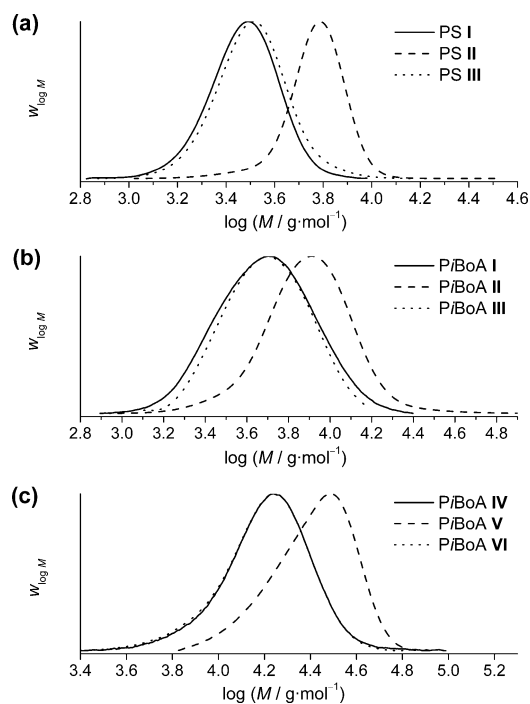
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**Scheme 1** Reaction mechanism for the nitrone-mediated radical coupling reaction yielding the narrow polydispersity mid-chain functional alkoxyamine **3** (I represents the polymer end group resulting from the initiator employed in the ATRP reaction).

monomer with Cu(0)/PMDETA at 60 °C for 3 h to generate macroradicals that subsequently undergo addition to *N-tert* butyl- $\alpha$ -phenylnitrone, PBN, followed by termination with another macroradical as depicted in Scheme 1. After the reaction, the molecular weight of the polymer increases as a consequence of the coupling. Table 1 gives the  $M_n$  of the individual traces. Within experimental accuracy, a doubling of the molecular weight is seen, demonstrating the success of the radical coupling. To support the experimental observations made *via* SEC analysis, Fig. 2 depicts the NMR spectra for the end group region of the samples PS I and PS II (for full spectra, the reader is referred to the ESI†). The peak corresponding to the proton in an  $\alpha$  position to the bromine in the starting material (b, 4.3–4.5 ppm) disappears entirely and only the end group originating from the ATRP-initiator used in the first reaction step (a, 3.3–3.5 ppm) remains. Thus, it can safely be concluded that all bromine functions are removed (and hence macroradicals freed) over the course of the reaction. The origin of the peaks marked as ‘impurities’ is uncertain, but these are also observed for similar ATRP systems in the literature.<sup>11</sup> In the case of the PS sample, a clear shift of the molecular weight distribution (MWD) towards higher molecular weights is observed and the  $M_n$  of the obtained coupling product is almost exactly twice the average weight of the original ATRP polymer. Only a small shoulder can be identified on the low-molecular weight side. With the two *PiBoA* samples, a qualitatively similar result is observed. The shift in  $M_n$  is slightly smaller than expected, which however is not due to an inefficiency of the nitrone coupling reaction but due to imperfect functionalization of the bromine-functional ATRP polymer. NMR analysis analogous to Fig. 2 reveals that in sample *PiBoA* I only 90% of the chains carried a bromine function and in *PiBoA* IV even only 80% of all chains (see ESI†). The lower functionality of the starting material thus may explain the slightly more pronounced shoulder visible in the SEC trace of *PiBoA* V.



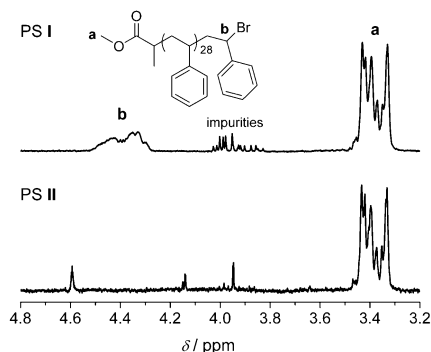
**Fig. 1** Molecular weight distributions of polymer before nitrone coupling (I, IV), after coupling (II, V) and after quenching of the alkoxyamine bond (III, VI) for polystyrene (a) and polyisobornyl acrylate (b, c).

The successful coupling by itself, however does not prove that the coupling proceeded *via* the proposed mechanism, as direct radical annihilation (*via* ATRC) would lead to similar traces if all direct termination events between two macroradicals occur *via* combination rather than disproportionation. Therefore, the coupled product was quenched by heating the sample in the presence of a radical scavenger (in this case tributyltin hydride). If the nitrone is truly incorporated in a mid-chain position, the two former chains are bridged by an alkoxyamine which undergoes cleavage at higher temperatures (>100 °C). Hence, by the action of the scavenger, polymer chains with a molecular weight of the original ATRP polymer should be obtained again and the full distribution should be transformed back into its original shape. Indeed, inspection of Fig. 1 and Table 1 shows that this is indeed the case. For all three systems, the molecular weight is reduced to its original  $M_n$  (and overall peak shape) and it may thus be concluded that all chains have been efficiently functionalized during the radical coupling reaction and that the shoulder visible in the conjugated product is due to starting material rather than side-products during the coupling reaction.

Another aspect of the nitrone-mediated coupling reaction is the efficiency of the reaction in terms of molar amounts of reactants required. Fig. 1(a) and (b) depict cases where a 5-fold excess of PBN compared to polymer concentration was employed. In the case of styrene, such an excess of spin trap is required as the nitrone trapping reaction is in competition with bimolecular termination of macroradicals. Thus, if PS is reacted with lower amounts of nitrone, no complete introduction of functionality is achieved (however, the coupling is yet successful due to direct ATRC).

**Table 1** Average and peak molecular weight data for the distributions shown in Fig. 1

Entry	Polymers prepared by ATRP			Conjugated polymers			Quenched polymers					
	Polymer	$M_p/g\ mol^{-1}$	$M_n/g\ mol^{-1}$	$M_w/M_n$	Polymer	$M_p/g\ mol^{-1}$	$M_n/g\ mol^{-1}$	$M_w/M_n$	Polymer	$M_p/g\ mol^{-1}$	$M_n/g\ mol^{-1}$	$M_w/M_n$
a	PS I	3000	2800	1.11	PS II	6100	5600	1.08	PS III	3200	3000	1.13
b	PiBoA I	4800	4400	1.29	PiBoA II	8100	7000	1.26	PiBoA III	4700	4600	1.22
c	PiBoA IV	17900	14300	1.19	PiBoA V	31700	23200	1.18	PiBoA VI	17800	14100	1.21

**Fig. 2** NMR spectra for the end group-specific shift region for the PS samples I and II given in Fig. 1.

With PiBoA (or in principle, all acrylates), lower amounts of PBN may be used. Fig. 1(c) depicts the traces from coupling of a PiBoA sample with a slightly higher molecular weight employing 0.5 eq. of PBN (every nitron binds two macroradicals, thus this amount is the stoichiometric equivalent). The reduction in spin trap concentration is possible because acrylates add about two orders of magnitude faster to nitrones than polystyryl radicals.<sup>6</sup> (Note that with the low-molecular weight sample used in Fig. 1(b), similar efficiencies are observed when equimolar amounts of PBN are used). A detailed kinetic simulation of the competition between formation of unfunctionalized combination product and formation of the desired alkoxyamine functional polymer can be found in the ESI.† Ultimately, the concentration of radicals and thus the release rate of macroradicals from the ATRP polymer determines which product is predominantly formed. Thus, for PS I, conditions could in principle be tuned to obtain well functionalized material even when only 0.5 eq. PBN are employed by decreasing the radical production. Such a radical release rate reduction can be achieved by using less effective ligand systems or a copper catalyst with a less active surface.

In conclusion, the shift of molecular weight distributions in Fig. 1 in conjunction with the ability to reverse the coupling reaction *via* quenching of the alkoxyamine bond proves that the coupling of macroradicals following the mechanism in Scheme 1 was successful. The slight shoulders in the product distributions can be traced back to incomplete functionalization of the starting material as the quenching action completely restores the original peak shape, thus allowing the conclusion that no material is formed during the coupling that did not carry an alkoxyamine bond in the middle of its chain. In addition—at least for radical types that exhibit fast addition rates to nitrones—the reaction can be carried out efficiently with stoichiometric amounts of the reaction partners. Overall,

the nitron-mediated polymer coupling reaction allows the facile generation of functionalized polymer chains that carry an alkoxyamine bond in a mid-chain location.

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## Notes and references

- 1 T. J. Kemp, *Prog. React. Kinet. Mech.*, 1999, **24**, 287–358.
- 2 (a) N. Singh and S. Mohan, *Chem. Commun.*, 1968, 787–788; (b) K. V. Gothelf and K. A. Jorgensen, *Chem. Commun.*, 2000, 1449–1458.
- 3 I. A. Grigor'ev, in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, ed. H. Feuer, Wiley & Sons, 2008.
- 4 (a) M.-O. Zink, A. Kramer and P. Nesvadba, *Macromolecules*, 2000, **33**, 8106–8108; (b) V. Sciannamea, R. Jerome and C. Detrembleur, *Chem. Rev.*, 2008, **108**, 1104–1126; (c) Q. Xia and R. B. Grubbs, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 5128–5136; (d) E. V. Kolyakina and D. F. Grishin, *Russ. Chem. Rev.*, 2009, **78**, 535–568.
- 5 E. H. H. Wong, T. Junkers and C. Barner-Kowollik, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 7273–7279.
- 6 E. H. H. Wong, M. H. Stenzel, T. Junkers and C. Barner-Kowollik, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 1098–1107.
- 7 T. Junkers, E. H. H. Wong, M. H. Stenzel and C. Barner-Kowollik, *Macromolecules*, 2009, **42**, 5027–5035.
- 8 (a) T. Sarbu, K.-Y. Lin, J. Ell, D. J. Siegwart, J. Spanswick and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 3120–3127; (b) T. Sarbu, K.-Y. Lin, J. Spanswick, R. R. Gil, D. J. Siegwart and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9694–9700; (c) B. Otazaghine, C. Boyer, J.-J. Robin and B. Boutevin, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 2377–2394.
- 9 (a) C. Liu, M. Pan, Y. Zhang and J. Huang, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 6754–6761; (b) Q. Fu, G. Wang, W. Lin and J. Huang, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 986–990; (c) J. Kulis, C. A. Bell, A. S. Micallef, Z. Jia and M. Monteiro, *Macromolecules*, 2009, **42**, 8218–8227.
- 10 A. Debuigne, C. Jerome and C. Detrembleur, *Angew. Chem., Int. Ed.*, 2009, **48**, 1422–1424.
- 11 (a) W. A. Braunecker and K. Matyjaszewski, *Prog. Polym. Sci.*, 2007, **32**, 93–146; (b) C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661–3688; (c) G. Moad and C. Barner-Kowollik, in *Handbook of RAFT Polymerization*, ed. C. Barner-Kowollik, Wiley-VCH, Weinheim, 2008, ch. 2, pp. 51–60; (d) K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921–2990.
- 12 (a) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (b) C. Barner-Kowollik and A. J. Inglis, *Macromol. Chem. Phys.*, 2009, **210**, 987–992; (c) B. Gacal, H. Durmaz, M. A. Tasdelen, G. Hizal, U. Tunca, Y. Yagci and A. L. Demirel, *Macromolecules*, 2006, **39**, 5330–5336; (d) J. F. Lutz and H. G. Börner, *Prog. Polym. Sci.*, 2008, **33**, 1–39; (e) H. F. Gao and K. Matyjaszewski, *Macromolecules*, 2006, **39**, 4960–4965.