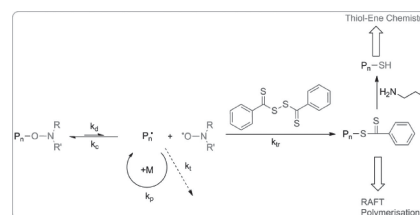


# From NMP to RAFT and Thiol-Ene Chemistry by In Situ Functionalization of Nitroxide Chain Ends

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A straightforward, novel strategy based on the in situ functionalization of polymers prepared by nitroxide-mediated polymerization (NMP), for the use as an extension toward block copolymers and post-polymerization modifications, has been investigated. The nitroxide end group is exchanged for a thiocarbonylthio end group by a rapid transfer reaction with bis(thiobenzoyl) disulfide to generate in situ reversible addition–fragmentation chain transfer (RAFT) macroinitiators. Moreover, not only have these macroinitiators been used in chain extension and block copolymerization experiments by the RAFT process but also a thiol-terminated polymer is synthesized by aminolysis of the RAFT end group and subsequently reacted with dodecyl vinyl ether by thiol-ene chemistry.



Nitroxide-mediated polymerization (NMP) was discovered more than 20 years ago<sup>[1,2]</sup> and has been recognized since then as a straightforward method for the controlled radical polymerization of various monomers including styrenics,<sup>[2]</sup> acrylates,<sup>[3]</sup> methacrylates (under specific conditions),<sup>[4–7]</sup> acrylamides,<sup>[8]</sup> acrylonitrile,<sup>[9]</sup> and even 1,3-dienes.<sup>[10–12]</sup> Furthermore, NMP allows for the design of complex macromolecular architectures such as block, graft, and star copolymers.<sup>[9,13,14]</sup> The technique is based on reversible termination of the propagating chains in the presence of a nitroxide.<sup>[15]</sup> For a polymerization to be controlled, the equilibrium must be shifted toward dormant species to minimize termination. Also, the exchange between active and dormant species must be several orders of magnitude faster than the propagation itself to ensure that all

chains statistically grow at the same time.<sup>[16]</sup> Thus, one of the main features of NMP is that the nitroxide end group is retained onto the polymer chain end after the polymerization. This can be an advantage for the synthesis of block copolymers as the polymerization can be reinitiated in presence of a second monomer.<sup>[9]</sup> However, there is an interest in removing the nitroxide end group, for example, to improve thermal stability<sup>[17]</sup> or introduce functional groups.<sup>[1,18,19]</sup> Furthermore, there is a growing trend for combining different polymerization methods for the synthesis of new copolymers, which cannot be obtained by one technique only.<sup>[20–22]</sup>

Another controlled radical polymerization method of interest is reversible addition–fragmentation chain transfer (RAFT) polymerization.<sup>[23]</sup> Its concept relies on the use of a thiocarbonylthio compound as a chain transfer agent (CTA) to create a living free-radical polymerization system as first described in 1998.<sup>[24]</sup> The CTA satisfied the criteria for living polymerization since the products obtained exhibited narrow polydispersity indexes, linear evolution of the number average molar mass ( $\overline{M}_n$ ) with conversion, and an agreement with theoretical  $\overline{M}_n$ . In

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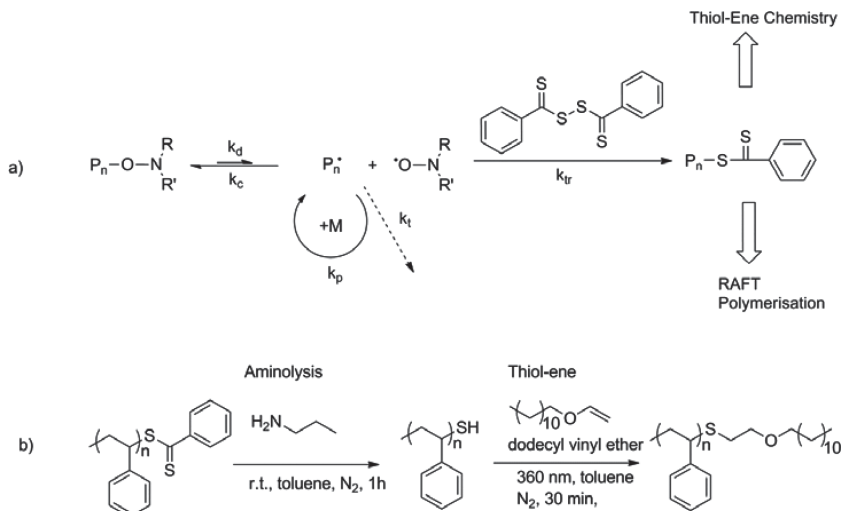
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addition, the end groups of the polymer chains retain the CTA, thus allowing further chain growth or block extension to occur upon subsequent monomer addition.<sup>[25]</sup> The thiocarbonylthio end-group fidelity is not only an illustration of the living character of the RAFT polymerization but also an important feature for further post-polymerization experiments. For example, thiol end groups can easily be generated from the CTA<sup>[26]</sup> and used to introduce different functionalities through thiol-ene chemistry.<sup>[27,28]</sup>

RAFT polymerization provides the ability to control polymerization of the most employed monomers such as acrylics, methacrylics, styrenics, dienes, and other vinyl monomers.<sup>[23]</sup> It is tolerant to unprotected functionalities (e.g., OH, NR<sub>2</sub>, CO<sub>2</sub>H, SO<sub>3</sub>H, CONR<sub>2</sub>) in monomer, solvent, and initiating system;<sup>[29]</sup> it is also compatible with a wide range of reaction conditions<sup>[23,30]</sup> (e.g., bulk, organic or aqueous solution, emulsion, mini-emulsion, suspension). In addition, it is simple to implement for both research and industrial purposes.<sup>[31]</sup> The well-defined complex macromolecules made by RAFT have been proven to be efficient to build nanostructures such as micelles, vesicles, and nanoparticles of either synthetic or synthetic polymers combined with biomolecules or inorganic nanoparticles.<sup>[23]</sup>

We recently reported a technique for the one-pot removal of nitroxide during NMP with the use of highly active transfer agents such as thiols, radical initiators, and CBr<sub>4</sub> to obtain thermally stable polymers.<sup>[32]</sup> Furthermore, the use of the latter allowed for the in situ bromination of the polymer chain ends. Consequently, this bromine-terminated precursor was successfully used in chain extension experiments by atom transfer radical polymerization. This motivated us to investigate the possibility to switch from NMP to RAFT polymerization in a one-pot approach through in situ functionalization and to provide at the same time an extension toward thiol-ene chemistry.

As reported in the literature, disulfides are well known as CTAs in free radical polymerization.<sup>[33]</sup> For example, cyclic and linear disulfides were used by Tobolsky and Baysal<sup>[34]</sup> to be incorporated into polystyrene (PS), yielding polymers with variable sulphur content. Murthy et al.<sup>[35]</sup> showed that poly(styrene disulfide) was an efficient CTA in the conventional radical polymerization of styrene (S), with transfer constants in the order of 6 to 9 × 10<sup>-2</sup>. Otsu et al.<sup>[36]</sup> determined the chain transfer constants of substituted diphenyl disulfides in radical bulk polymerization of methyl methacrylate (MMA) and observed that the



**Scheme 1.** a) One-pot nitroxide removal and route toward RAFT polymerization and thiol-ene chemistry. b) Functionalization of PS (entry 1, Table 1): aminolysis and UV assisted radical thiol-ene reaction.

substituent on the phenyl rings had noticeable effects on the reactivity of the disulfide toward the PMMA radical. Beyou et al.<sup>[37]</sup> functionalized polymers bearing nitroxide end groups in presence of thiuram disulfides in a two-steps process. More recently, Rizzardo and co-workers<sup>[38]</sup> studied the effect of diphenyl and dibenzoyl disulfides as CTA in the polymerization of the cyclic monomer 7-methylene-2-methyl-1,5-dithiacyclooctane (MDTO), and they observed that diphenyl disulfide presented a higher chain transfer constant, presumably as a result of an increase of the resonance stabilization of the resulting radical.

As all these studies clearly show the suitability of disulfides as chain transfer agents, the controlled addition of bis(thiobenzoyl) disulfide during NMP was investigated in this research (Scheme 1a). Bis(thiobenzoyl) disulfide is readily available but can also easily be synthesized in the laboratory.<sup>[39]</sup> The end-group modification of the NMP synthesized polymers with this compound is not only expected to remove the dormant nitroxide moiety but also to provide, in one-pot, a thiobenzoylthio polymer chain-end. The resulting polymer can subsequently be used as a RAFT precursor, which can be employed for chain extension experiments. Furthermore, the RAFT end group can be reduced to a thiol by aminolysis in a post-polymerization reaction, followed by functionalization through thiol-ene chemistry (Scheme 1b).

The effectiveness of bis(thiobenzoyl) disulfide as CTA in NMP was tested in three model experiments (Table 1). NMP of styrene—with bimolecular (entry 1) or unimolecular (entry 2) initiator systems—and isobornyl acrylate (entry 3) was performed in bulk in the presence of *N*-tert-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (SG1). Bis(thiobenzoyl) disulfide, dissolved in a minimal

■ Table 1. Experiments for one-pot removal of nitroxides from NMP polymers with bis(thiobenzoyl) disulfide.<sup>a)</sup>

Entry	M <sup>b)</sup>	Initiation <sup>c)</sup>	DP <sup>d)</sup>	Disulfide Eq. <sup>e)</sup>	t <sub>i</sub> -t <sub>f</sub> <sup>f)</sup> (min)	$\overline{M}_{n,i}$ - $\overline{M}_{n,f}$ <sup>g)</sup> [g mol <sup>-1</sup> ]	PDI <sub>i</sub> -PDI <sub>f</sub> <sup>h)</sup>	End-group fidelity <sup>i)</sup> [%]
1	S	AIBN/SG1 (1/3)	139	0.7	240–250	4200–4300	1.12–1.10	99.9 <sup>j)</sup>
2	S	BlocBuilder MA	71	1.9	120–130	4500–4500	1.11–1.12	99.9 <sup>k)</sup>
3	iBA	AIBN/SG1 (1/2)	100	1	360–370	5800–5900	1.14–1.14	50.6

<sup>a)</sup>Temperature: 120 °C; further details on the polymerization conditions can be found in the Supporting Information; <sup>b)</sup>M = monomer; <sup>c)</sup>Initiator/Nitroxide molar ratio is given between brackets for bimolecular systems; <sup>d)</sup>Theoretical degree of polymerization at 100% conversion; <sup>e)</sup>Bis(thiobenzoyl) disulfide equivalents compared to the nitroxide; <sup>f)</sup>t<sub>i</sub> = bis(thiobenzoyl) disulfide injection time; t<sub>f</sub> = final reaction time; <sup>g)</sup> $\overline{M}_{n,i}$  = molar mass just before bis(thiobenzoyl) disulfide injection;  $\overline{M}_{n,f}$  = molar mass at the end of the reaction; <sup>h)</sup>PDI<sub>i</sub> = PDI just before bis(thiobenzoyl) disulfide injection; PDI<sub>f</sub> = PDI at the end of the reaction; <sup>i)</sup>CTA end-group fidelity determined by elemental analysis; <sup>j,k)</sup>The measured values of resp. 113 and 108%, as a result of experimental error, have been rounded to 99.9%.

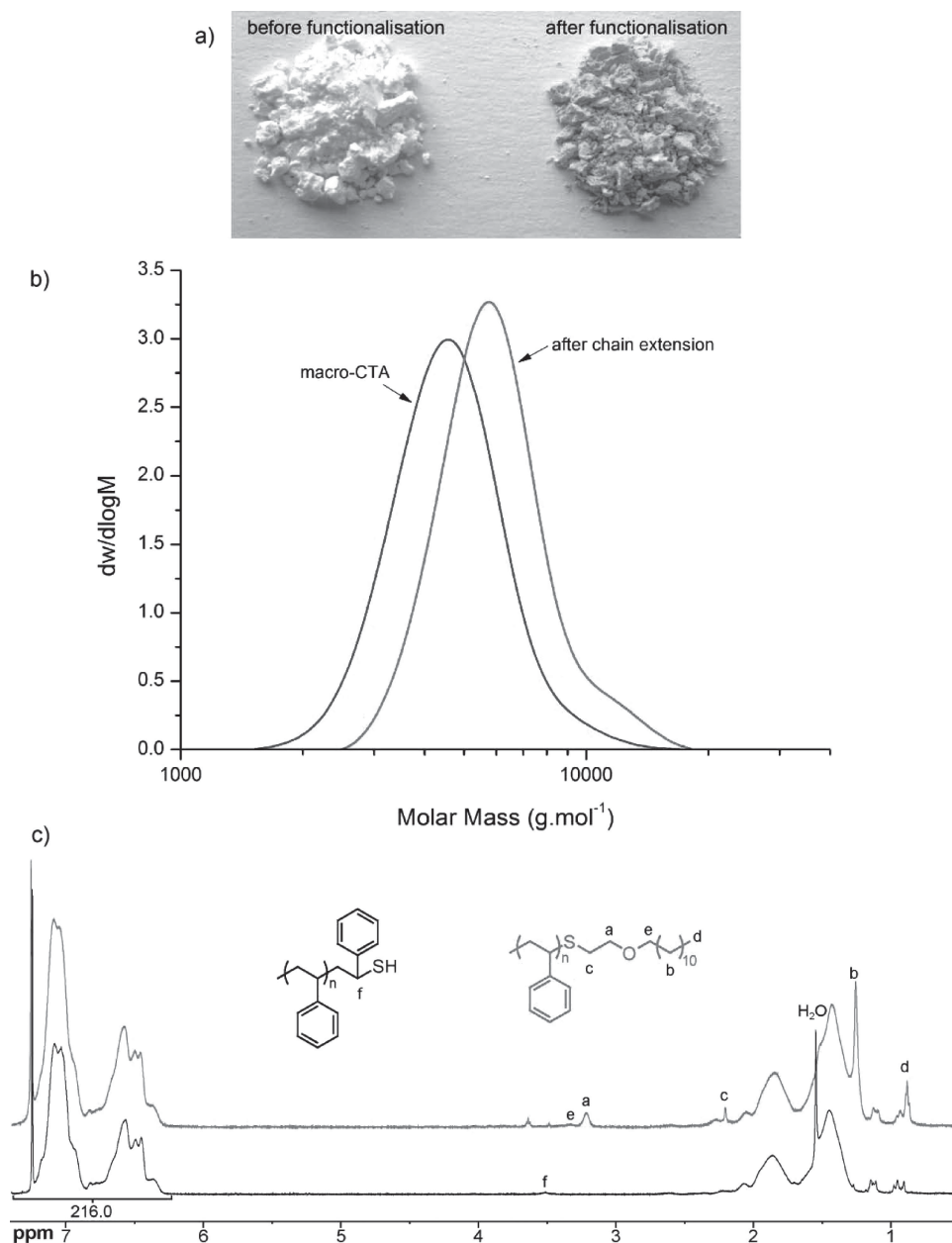
amount of solvent, was added to the crude reaction mixture after a predetermined reaction time (see the Supporting Information for more information on experimental conditions). The influence of the concentration of the bis(thiobenzoyl) disulfide compound, ranging from 0.7 to almost 2 equivalents compared to SG1, has been studied. From the values in Table 1, it can be clearly noticed that, after addition of the CTA, the polymerization was stopped as no molar mass increase was observed and polydispersity index values (PDIs) remained the same, both for styrene (S) and isobornyl acrylate (iBA). Figure 1a shows photographs of the purified PS sample (entry 1) before and after addition of bis(thiobenzoyl) disulfide. While the polymer samples were purified by repeated precipitations in a 10-fold excess of a non-solvent, the resulting thiobenzoylthio-terminated PS and poly(isobornyl acrylate) (PiBA) show the characteristic pink color after in situ functionalization, which constitutes an additional proof for the effectiveness of the method employed.

The end-group fidelity was determined by elemental analysis (Table 1) after the functionalization reaction on samples purified by repeated precipitations. Remarkably, the thiobenzoylthio functionalization was quantitative for PS (entries 1,2, Table 1), only 10 min after addition of bis(thiobenzoyl) disulfide. On the other hand, the end group functionalization in the case of PiBA (entry 3, Table 1) was much lower, which might be explained by the bulkiness of the isobornyl group that is known to reduce the segmental mobility of the growing chains in free radical polymerization relative to other acrylic monomers.<sup>[40]</sup> The outcome might be a slower transfer to the disulfide during NMP, which results in this incomplete functionalization.

The successful functionalization of PS with bis(thiobenzoyl) disulfide during NMP was used to perform a chain extension of the PS macro-CTA with styrene (entry 4, Table 2). From literature, it is expected that this type of macro-CTA based on dithiobenzoate CTA's will be efficient for the RAFT polymerization of, at least, styrenic and acrylic based monomers.<sup>[25]</sup> In a typical procedure,

an overall ratio of 300/1/0.2 between styrene, macro-CTA and AIBN was employed (see the Supporting Information for further details). An initial monomer solution (25 vol%) in toluene was employed and the monomer was added step-wise every 2 h to have a better control over the polymerization.

Figure 1b shows the SEC chromatograph obtained for the chain extension experiment. A noticeable shift can be observed after 8 h of reaction at 90 °C, which is a clear evidence for the ability of the macro-CTA to polymerize styrene by the RAFT process and thus for the suitability of the functionalization procedure. In addition, no shoulder at low molar masses is observed, indicating that the chain extension proceeded in a controlled fashion. The polymerization was found to be relatively slow due to the occurrence of retardation, which is a well-known phenomenon for RAFT polymerization with dithiobenzoate CTA's.<sup>[41]</sup> As expected, when performing a RAFT polymerization experiment under the same conditions with the PiBA-sample (entry 3), a much higher polydispersity index was observed because of the uncomplete end group functionalization (entry 5, Table 2). The thiocarbonylthio functional group on the polymer chain end can easily be transformed into a thiol functionality in one step under mild conditions.<sup>[42]</sup> Subsequently, this thiol can be used for various post-modification reactions.<sup>[26]</sup> Here, we investigated the possibility to perform thiol-ene click chemistry after transforming a PS macro-CTA (entry 1, Table 1) into a thiol-terminated polymer through aminolysis (Scheme 1b). More specifically, the mercapto-functionalized PS was obtained by propylamine-induced aminolysis, following a slightly modified version of the procedure reported earlier by our group<sup>[28]</sup> (see the Supporting Information for more details). The reaction proceeds with a 20 molar equivalents of amine per mol of thiocarbonylthio group, generating the desired thiol-terminated polymer in the presence of tributyl phosphine as a reducing agent to avoid disulfide coupling. Both the UV spectra of the parent and modified PS (Figure S5, Supporting Information) as well as the SEC traces of the polymer before and after aminolysis



**Figure 1.** a) Photographs of PS synthesized by NMP (entry 1, Table 1) before (left) and after (right) bis(thiobenzoyl) disulfide addition. b) Molar mass distribution before (left) and after (right) chain extension of a PS macro-CTA (entry 2, Table 1) by RAFT polymerization (entry 4, Table 2). c) <sup>1</sup>H-NMR 500 MHz (CDCl<sub>3</sub>) spectrum of thiol-containing PS before (bottom) and after thiol-ene functionalization (top) with dodecyl vinyl ether (Scheme 1b).

**Table 2.** Chain extension and block copolymerization by RAFT polymerization from macro-CTA.<sup>a)</sup>

Entry	Ma-CTA <sup>b)</sup>	t [min]	$\overline{M}_{n,i}$ <sup>c)</sup> [g mol <sup>-1</sup> ]	PDI <sup>c)</sup>	$\overline{M}_{n,f}$ <sup>d)</sup> [g mol <sup>-1</sup> ]	PDI <sup>d)</sup>
4	PS-CTA (entry 2)	480	4500	1.11	5600	1.10
5	PiBA-CTA (entry 3)	120	5900	1.14	12 600	1.59

<sup>a)</sup> Monomer: styrene;  $[M]_0/[Ma-CTA]/[AIBN] = 300/1/0.2$ ; temperature: 90 °C (Further details on the polymerization conditions can be found in the Supporting Information); <sup>b)</sup> Ma-CTA = macroinitiator; <sup>c)</sup> Molar mass and PDI of the macroinitiator; <sup>d)</sup> Molar mass and PDI after chain extension.



were recorded (Figure S6, Supporting Information). These experiments confirmed the completeness of the reaction, without observation of disulfide formation. Consequently, the thiol-containing PS was subjected to thiol-ene reaction with dodecyl vinyl ether, in the presence of 2,2-dimethoxy-2-phenylacetophenone as UV cleavable photoinitiator, to afford PS with modified chain-end structure within 30 min (Scheme 1b). The thiol-ene chemistry allowed successful polymer modification under 360 nm irradiation, as evidenced by the appearance of new signals in the  $^1\text{H}$  NMR spectrum (Figure 1c), corresponding to both the methylene protons from the newly formed ether bond (peak a, 3.22 ppm) and to the protons of the alkyl chain of dodecyl vinyl ether (peak b, 1.27 ppm). Furthermore, a good agreement was found with NMR data previously reported for a similar thiol-ene reaction.<sup>[28]</sup>

In conclusion, by applying a one-pot procedure and in situ functionalization, it was possible to extend NMP toward RAFT and thiol-ene chemistry. Through the use of bis(thiobenzoyl) disulfide, polymer chains prepared by NMP were transformed into thiocarbonylthio-terminated polymers. These polymers were subsequently used as macro-CTA in RAFT polymerization. Copolymerization and chain extension experiments were performed. In addition, a PS macro-CTA was chemically modified by aminolysis as a post-polymerization process, yielding a thiol-terminated polymer that was subsequently employed for thiol-ene chemistry.

The straightforward strategy presented in this work offers to our knowledge for the first time an efficient transformation between two of the most employed controlled radical polymerization techniques, namely NMP and RAFT, and also provides a pathway from NMP to thiol-ene “click” chemistry.

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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