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SG1-based alkoxyamine bearing a *N*-succinimidyl ester: A versatile tool for advanced polymer synthesis

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ABSTRACT

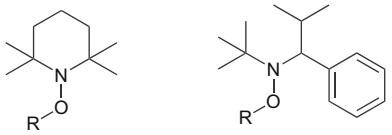
This paper reports the preparation of a MAMA-SG1 (BlocBuilder™) derived alkoxyamine bearing a *N*-succinimidyl (NHS) ester group **1**, valuable for functional and advanced polymer synthesis. This alkoxyamine was exploited following two strategies: (i) a *post-functionalization* approach based on the transformation of α-NHS chain ends of polymers previously obtained by nitroxide mediated polymerization (NMP) from **1** (path A) and (ii) a *pre-functionalization* approach based on the functionalization of alkoxyamine **1** prior to NMP (path B). Path A was demonstrated by derivatization of α-NHS functionalized polystyrenes with ethanolamine, yielding hydroxyl-functionalized polystyrenes. Path B was illustrated by two examples: first, a OH functional alkoxyamine initiator, prepared by reaction of **1** with ethanolamine, was used for the synthesis of polystyrene-*b*-poly(D,L-lactide) by combining NMP and ring-opening polymerization. Secondly, a poly(propylene oxide)–SG1 macroalkoxyamine, obtained from reaction of **1** with NH_2-functionalized poly(propylene oxide), was used as a macroinitiator for NMP of styrene to obtain a PS-*b*-PPO block copolymer.

1. Introduction

Nitroxide mediated polymerization (NMP) is a controlled radical polymerization (CRP) technique, which already offers the ability to prepare a wide variety of well-defined polymer architectures [1]. However, emerging technologies such as optics, microelectronics, and biomaterials are driving for new materials exhibiting continuously more sophisticated properties and performance [2]. Despite the significant improvements brought to CRP techniques such as NMP, atom transfer radical polymerization (ATRP) or reversible addition fragmentation chain transfer (RAFT), the preparation of complex architectures by CRP is restricted by the exclusion of monomer systems that are polymerized by fundamentally different mechanisms, like lactides, ethylene/propylene oxide. The most promising approaches to extend the range of polymer compositions are based on the use of heterofunctional initiators [3] allowing the combination of mechanistically distinct polymerization reactions without the need for intermediate transformation and protection steps.

In the field of NMP, the development of multifunctional initiators was focused on TEMPO and TIPNO based alkoxyamine derivatives (Fig. 1) and the combination of either ring-opening polymerization (ROP), ring-opening metathesis polymerization (ROMP) or ATRP techniques with NMP [4].

However, these alkoxyamines exhibit several drawbacks such as the restriction to styrenic monomers when using TEMPO and the multi-step synthesis required to prepare TIPNO derivative alkoxyamines [5]. To overcome these drawbacks the aim of this work was to develop an initiator based on the commercially available BlocBuilder™ alkoxyamine also called in this paper MAMA-SG1 bearing a succinimidyl activated ester moiety, **1**, Scheme 1. As already reported for ATRP [6] and RAFT [7] techniques but, from the best of our knowledge, not yet for NMP, such NHS-activated ester CRP precursors are indeed particularly convenient for the functionalization of polymer chain ends.



TEMPO-R TIPNO-R

Fig. 1. TEMPO and TIPNO based alkoxyamines.

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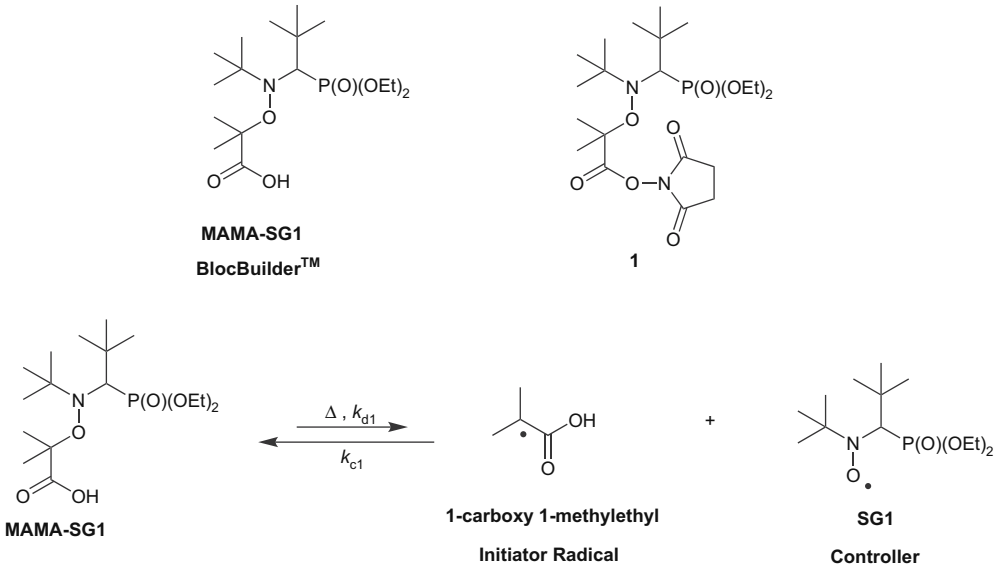


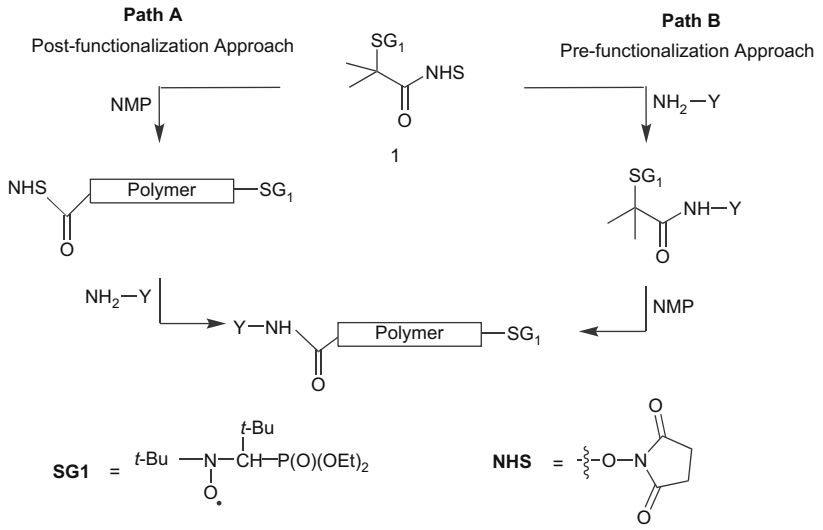
Scheme 1. MAMA-SG1 structure (and dissociation scheme) and derived NHS-ester alkoxyamine analog **1**.

MAMA-SG1 has been developed in our group in collaboration with Arkema company [8]. Thanks to a particularly high dissociation rate constant value k_{d1}, up to now this alkoxyamine has proved to be one of the most potent alkoxyamines reported in the field of NMP [9–11].

Another potential advantage of MAMA-SG1 is the presence of the terminal carboxylic acid group, which could be further transformed to offer new possibilities for complex macromolecular architecture synthesis. However, attempts to transform by esterification (using allyl alcohol for example) or amidification (using allyl amine or aminoethanol) this carboxylic acid group, in presence of either *N*,*N*′-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-dimethylaminopyridine (DMAP) or via reaction with thionyl chloride, were unsuccessful. Indeed in each case the reactions lead to a complex reaction mixture difficult to work up. These results could be explained by the combination of several reasons, like steric hindrance, decomposition reaction during the synthesis due to the formation of highly labile intermediates or undesired side reactions. In order to partially overcome these drawbacks, we then decided to focus our attention on the preparation of an isolable SG1-based alkoxyamine bearing an activated ester which can be further easily transformed.

Due to the high homolysis rate constant of SG1-alkoxyamine derivatives bearing a stabilized tertiary alkyl moiety, it was necessary to develop a strategy where the synthesis and reaction of the corresponding activated ester could be performed rapidly and at room temperature or lower. Among a number of possibilities [12], the introduction of a *N*-succinimidyl ester was chosen because of the easy preparation of such esters and for their high reactivity towards nucleophiles and particularly amines [13]. Many examples in the literature show the formation of bulky amides by this mean in a short reaction time at room temperature [14]. Such reactivity can thus be used for the preparation of a large range of heterofunctional initiators and advanced polymers.

According to specific experimental requirements, this strategy enables the synthesis of α-functional (Y group in Scheme 2) polymers, either by chemical transformation of the α-NHS chain ends of **1**-derived NMP polymers (path A, so-called *post-functionalization approach*) or by functionalization of alkoxyamine **1** prior to NMP (path B, *so-called pre-functionalization approach*).



Scheme 2. The two synthetic approaches based on the alkoxyamine **1** leading to functional polymers.

Depending on the nature of the Y group (functional molecule, biomolecule or macromolecule) specific properties can be easily introduced in the polymer and preparation of block copolymers that would be difficult to obtain by other methods becomes accessible.

In this article, the synthesis of **1** and its use as an efficient initiator for NMP of styrene and *n*-butyl acrylate are described. In addition, several examples are given to illustrate the potential and versatility of this novel alkoxyamine for the preparation, following path A and path B, of α-functional polymers (NHS-, OH-polystyrenes), and advanced polymer architectures (polystyrene-*b*-polylactide, PS-*b*-PLA, and polypropylene oxide-*b*-polystyrene, PPO-*b*-PS, block copolymers).

2. Experimental section

2.1. Materials

BlocBuilder™ (MAMA-SG1) was kindly provided by Arkema (France). Styrene, *n*-butyl acrylate, ethanolamine polypropylene oxide, dicyclohexylcarbodiimide, *N*-hydroxysuccinimide and tin(II)-2-ethylhexanoate ($Sn(Oct)_2$) were purchased from Aldrich and used as-received. D,L-Lactide was purchased under vacuum from Purac Biochem (The Netherlands).

2.2. Analytical techniques

^{13}C, ^{31}P, ^{1}H NMR analyses were performed on a Bruker Advance 300 spectrometer in $CDCl_3$ or DMSO-d_6. Mass analyses were performed using a mass spectrometer 3200 QTRAP (Applied Biosystems SCIEX) equipped with a pneumatically assisted atmospheric pressure ionization. The sample was dissolved in methanol then diluted (dilution factor 1/1000) in a methanolic solution of ammonium acetate (3 mmol L^{-1}). The sample solution was infused in the ionization source at a 5 mL min^{-1} flow rate. Ionization is performed in positive mode electrospray under the following conditions: electrospray voltage (ISV): 5500 V; orifice voltage (OR): 20 V; nebulizing gas flow pressure (air): 20 psi. The mass spectrum was obtained using a quadrupole mass analyzer.

Polymer molecular weights and polydispersities were determined by gel permeation chromatography (GPC) on a system comprising of a Waters 515 HPLC pump equipped with three "Styragel" columns used in series (HR 3 (4.6 mm × 300 mm, separation between 500 and 30 000 g mol^{-1}), HR 4 (4.6 mm × 300 mm, separation between 5000 and 600 000 g mol^{-1}), and HR 5 (4.6 mm × 300 mm, separation between 2000 and 4.10^6 g mol^{-1})) or alternatively one single PSS GRAM column (8 mm × 300 mm, 10 μm particle size, 1000 Å pore size), and two detectors: UV/visible (Waters 486) and RI (Waters 2414). THF was the mobile phase, with a flow rate of 1 mL min^{-1}. Calibration was based on polystyrene standards. Poly(*n*-butyl acrylate) molecular weights were determined using the Mark–Houwink parameters. Liquid chromatography under critical conditions (LC-CC) was performed on a PL-GP120 high temperature chromatograph using DMF as eluent. The following columns were used: Macherey & Nagel 250 mm × 4.6 mm NucleodurC_{18} Gravity, pore diameter 110 Å, particle size 3 μm and Macherey & Nagel 250 mm × 4.6 mm NucleodurC_{18} Gravity, pore diameter 110 Å particle size 5 μm. PS critical conditions were obtained at 78.3 °C.

2.3. Alkoxyamine synthesis

2.3.1. 2-Methyl-2-[N-tert-butyl-N-(1-diethoxyphosphoryl-2,2-dimethylpropyl)aminoxy]-N-propionyloxysuccinimide (**1**)

MAMA-SG1 (5 g, 13.1 mmol) and *N*-hydroxysuccinimide (1.81 g, 15.7 mmol) were dissolved in THF (20 mL) and deoxygenated by nitrogen bubbling for 15 min. Then, a degassed solution of *N*,*N*′-dicyclohexylcarbodiimide (3 g, 14.4 mmol) in THF (5 mL) was added. After stirring at 0 °C for 1.5 h, the precipitated *N*,*N*′-dicyclohexylurea (DCU) was removed by filtration and the filtrate volume was reduced under vacuum to one third and placed at −20 °C for 2 h in order to precipitate the residual DCU. After filtration, the solution was concentrated under reduced pressure and precipitation was performed in pentane. The obtained solid was further washed with water to remove *N*-hydroxysuccinimide. After drying under vacuum, alkoxyamine **1** was obtained as a white powder. Yield: 72% (9.43 mmol, 4.5 g). mp: 97–100 °C.

^{31}P NMR (121.59 MHz, $CDCl_3$, δ, ppm): 25.84.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.17–1.33 (m, 24H), 1.82 (s, 3H), 1.88 (s, 3H), 2.82 (s, 4H), 3.31 (d, $J_{(H,P)} = 27$ Hz, 1H), 3.95–4.35 (m, 4H).

^{13}C NMR (75.48 MHz, $CDCl_3$, δ, ppm): 16.12 (d, $J_{(C,P)} = 6.7$ Hz, $POCH_2CH_3$), 16.51 (d, $J_{(C,P)} = 5.7$ Hz, $POCH_2CH_3$), 21.83 (s, CH_3CO), 25.53 (s, $(CH_2)_2C(O)N$), 28.09 (s, $(CH_3)_3CN$), 29.25 (s, CH_3CO), 30.01 (d, $J = 6.0$ Hz, $CHC(CH_3)_3$), 29.63 (s, $(CH_3)_3CN$), 35.96 (d, $J_{(C,P)} = 6.4$ Hz, $(CH_3)_3$–C–CHP), 58.71 (d, $J_{(C,P)} = 7.6$ Hz, $POCH_2CH_3$), 61.80 (d, $J_{(C,P)} = 6.0$ Hz, $POCH_2CH_3$), 62.55 (s, N–$C(CH_3)_3$), 69.81 (d, $J_{(C,P)} = 137.3$ Hz, CHP), 83.58 (s, NO–$C(CH_3)_2$–), 168.76 (s, C(O)–N–C(O)), 170.17 (s, $(CH_3)_2C$–C(O)O).

ESI (MS): *m*/*z* ($C_{21}H_{39}N_2O_8P$, $M = 478$ g mol^{-1}); $[M+H]^+ = 479.3$; $[M+Na]^+ = 501.3$; $[M+K]^+ = 517.3$.

2.3.2. 2-Methyl-2-[N-tert-butyl-N-(1-diethoxyphosphoryl-2,2-dimethylpropyl)aminoxy]-N-hydroxyethyl propionamide (**2a**)

Ethanolamine (160 μL, 2.65 mmol) was added through a syringe to a solution of **1** (1 g, 2.08 mmol) in dichloromethane (40 mL) at 0 °C under inert atmosphere. After 1 h under stirring, the precipitated *N*-hydroxysuccinimide was removed by filtration. The filtrate was then concentrated under reduced pressure to about 2 mL volume and added in pentane (50 mL). The precipitated product was filtrated off and the filtrate placed at −20 °C for recrystallization. Yield: 60%. mp: 92–96 °C.

^{31}P NMR (121.59 MHz, $CDCl_3$, δ, ppm): 27.76.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.09 (s, 9H), 1.24 (s, 9H), 1.31 (t, $J = 8$ Hz, 3H), 1.37 (t, $J_{(H,H)} = 8$ Hz, 3H), 1.55 (s, 3H), 1.76 (s, 3H), 3.38 (d, $J_{(H,P)} = 28$ Hz, 1H), 3.30–3.55 (m, 2H), 3.71–3.80 (m, 2H), 3.95–4.35 (m, 4H).

^{13}C NMR (75.48 MHz, $CDCl_3$, δ, ppm): 16.16 (d, $J_{(C,P)} = 6.8$ Hz, $POCH_2CH_3$), 16.54 (d, $J_{(C,P)} = 5.9$ Hz, $POCH_2CH_3$), 22.78 (s, CH_3CO), 29.20 (s, CH_3CO), 29.57 (d, $J_{(C,P)} = 6.5$ Hz, $CHC(CH_3)_3$), 29.63 (s, $(CH_3)_3CN$), 36.42 (d, $J_{(C,P)} = 8.1$ Hz, $(CH_3)_3$–C–CHP), 43.6 (s, CONH–CH_2–), 60.18 (d, $J_{(C,P)} = 8.0$ Hz, $POCH_2CH_3$), 62.03 (s, CH_2CH_2OH), 62.14 (d, $J_{(C,P)} = 6.0$ Hz, $POCH_2CH_3$), 62.79 (s, N–$C(CH_3)$), 70.08 (d, $J_{(C,P)} = 133.5$ Hz, CHP), 86.28 (s, NO–$C(CH_3)_2$–), 177.01 (s, $(CH_3)_2C$–C(O)NH).

Anal. Calcd for $C_{19}H_{41}N_2O_6P$: C, 53.76; H, 9.73; N, 6.60. Found: C, 53.43; H, 9.99; N, 6.55.

2.3.3. Macroalkoxyamine PPO–SG1 (**2b**)

Alkoxyamine **1** (3 g, 6.27 mmol) was added to a solution of poly(propylene glycol)-bis(2-aminopropyl ether) (PPO-di-NH_2) $M_n = 2000$ g mol^{-1} (25.2 g, 12.6 mmol) in THF (100 mL) at 0 °C under inert atmosphere. The reaction mixture was then stirred for 2 h. After elimination of the precipitated *N*-hydroxysuccinimide by filtration, THF was removed under reduced pressure to lead to the macroalkoxyamine PPO–SG1 as a mixture of two diastereoisomers and remaining PPO-di-NH_2. Yield: 82%. ^{31}P NMR (121.59 MHz, $CDCl_3$, δ, ppm): 26.59 (s), 26.36 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.09 (m, CH3 (PPO) + 2 *t*-Bu (SG1 moiety)), 1.28–1.38 (m, $POCH_2CH_3$), 1.88, 1.97 (2bs, $(CH_3)_2CO$), 3.41–4.07 (m CH_2 + CH (PPO) + $POCH_2CH_3$ (SG1 moiety)).

2.4. Polymerizations

2.4.1. General procedure for styrene or n-butyl acrylate polymerization

Styrene or *n*-butyl acrylate and alkoxyamine were introduced in a 250 mL two neck round-bottom flasks, fitted with septum, condenser, and degassed for 20 min by nitrogen bubbling. The mixture was then heated to 120 °C (styrene) or 115 °C (*n*-butyl acrylate) under N_2 with vigorous stirring. After polymerization, the final polymer mixture was either stripped under vacuum (*n*-butyl acrylate) or dissolved in a minimum THF and precipitated in cold ethanol, followed by drying under vacuum at 30 °C (styrene).

2.4.2. Functionalization of NHS-terminated PS with ethanolamine

PS–NHS (1 g, 0.147 mmol, $M_n = 6800\ g\ mol^{-1}$) was dissolved in 20 mL dichloromethane. Ethanolamine (14 μL, 0.232 mmol) was then added through a syringe, and the solution was stirred for 1 h at 4 °C. The product was purified by precipitation in methanol, in which NHS and excess ethanolamine were soluble.

2.4.3. Synthesis of PS-b-PLA

First, OH-terminated PS was obtained by polymerization of styrene (15 g, 0.144 mol) in the presence of alkoxyamine **2a** (0.32 g, 0.75 mmol, targeted molecular weight of 20 000 g mol^{-1}) in bulk at 120 °C. After precipitation in methanol, the latter was used as a macroinitiator for the ring-opening polymerization (ROP) of D,L-lactide in the presence of $Sn(Oct)_2$ as a catalyst. A reaction flask containing a stir bar was fitted with a septum, flamed under vacuum, and placed into a glove box, where the D,L-lactide (0.675 g, 4.69 mmol), PS–OH (0.4 g, 0.0454 mmol, 8800 g mol^{-1}, PDI = 1.11) and $Sn(Oct)_2$ (9 mg, 0.022 mmol) were filled (targeted $DP_{PLA} = 100$). Then dry toluene (5 mL) was added under argon atmosphere. The reaction mixture was then stirred at 105 °C for 6 h. The obtained mixture was dissolved in few milliliters of non-distilled THF, followed by precipitation in cold methanol and drying at 30 °C under vacuum.

2.4.4. Synthesis of PPO-b-PS

The non-purified macroalkoxyamine **2b** (PPO–SG1 + PPO-di-NH_2, 4.47 g, 0.832 mmol of PPO–SG1) was used as initiator for the polymerization of styrene (33.3 g, 0.320 mol, targeted PS molecular weight of 40 000 g mol^{-1}). The reaction was performed in bulk, at 120 °C under nitrogen. After removal of styrene under vacuum, the block copolymer has been characterized by GPC without further purification. The copolymer was finally purified by precipitation in methanol and dried under vacuum at 30 °C.

3. Results and discussion

3.1. Synthesis and characterization of alkoxyamine *1*

Alkoxyamine **1** was obtained after a simple one step procedure in 72% yield. Typically, **1** was prepared upon the reaction of MAMA-SG1 with NHS in the presence of DCC for 1.5 h at 0 °C in THF (Scheme 3). Alkoxyamine was isolated as a white powder easy to store and handle after precipitation in pentane.

Dissociation rate constant of **1** was measured by ESR following a described procedure [15] in *tert*-butyl benzene at 120 °C and the activation energy E_a was estimated using the average frequency factor $2.4 \times 10^{14}\ s^{-1}$ [16]. Under these conditions k_{d1} for **1** was found equal to 5 s^{-1} ($E_a = 103\ kJ\ mol^{-1}$). It should be noted that the k_{d1} value for **1** is 15 times higher than the k_{d1} measured for MAMA-SG1 under the same experimental conditions ($k_{d1} = 0.32\ s^{-1}$, $E_a = 112\ kJ\ mol^{-1}$). As previously described for the SG1-propionate type alkoxyamines (SG1-CHMeCOOY) the increase in k_{d1} can be ascribed to a long-range polar effect [17] due to the presence of NHS moiety.

The interest of **1** relies on the versatility of both SG1 as control agent for a large range of monomer and NHS-activated ester for the coupling of specific molecule or macromolecule. This coupling reaction can be conducted in mild conditions before (path B, Scheme 2) or after (path A,) the NMP process and is generally characterized by high yields.

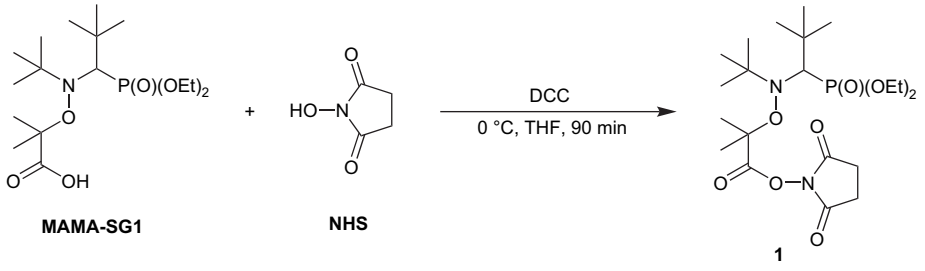
3.2. Post-functionalization approach (path A, Scheme 2)

3.2.1. Preparation of NHS-functional polystyrene and poly(n-butyl acrylate) from alkoxyamine *1*

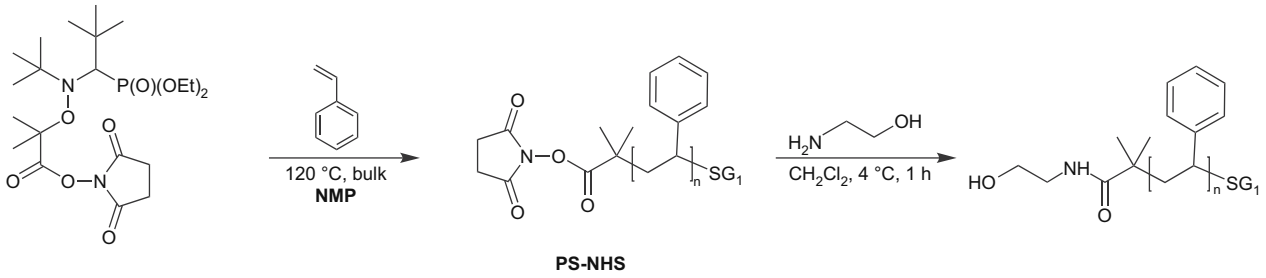
In order to evaluate its efficiency in NMP, **1** was used to perform styrene polymerizations in bulk at 120 °C and targeting a M_n of 40 000 g mol^{-1} (Scheme 4, first step).

The polymerization kinetics was followed by ^1H NMR spectroscopy and a linear plot of $\ln([M]_0/[M])$ *vs* time (Fig. 2a) was observed. As already stated, this result suggests a mechanism not based on the persistent radical effect [18] but on a reversible scavenging process similar to a polymerization carried out in the presence of initial free nitroxide [9]. Indeed, due to its high dissociation rate constant at 120 °C, **1** affords quickly enough the excess of SG1 required for control, as if nitroxide had been added separately.

The linear evolution of the average molecular weight *vs* conversion and low PDI value (~1.2 at 60% conversion) (Fig. 2b) fulfills the criteria of a controlled polymerization [19] process. Moreover the good agreement observed between experimental and theoretical M_n values highlights initiator efficiency close to 1 for alkoxyamine **1**. Similar results were obtained for lower targeted molecular weights (10 000 g mol^{-1}). It is interesting to note that both the kinetic evolution of $\ln([M]_0/[M])$ *vs* time and M_n evolution *vs* conversion obtained with **1** are similar to those observed in the presence of MAMA-SG1 (Fig. 1a and b). These results suggest that the replacement of OH group by a NHS moiety has no significant effect on both the efficiency of the initiator and the quality of the controlled character. NMP of *n*-butyl acrylate with alkoxyamine **1** (targeted M_n: 40 000 g mol^{-1}) was controlled as well, as shown by the linear evolutions of the curves corresponding to $\ln([M]_0/[M])$ *vs* time (Fig. 3a) and M_n *vs* conversion (with M_n values close to that expected), together with low polydispersities (b).



Scheme 3. Synthesis of *N*-hydroxysuccinimide MAMA-SG1 derivative, **1**.



Scheme 4. NMP of styrene with **1** as alkoxyamine initiator and post-functionalization (path A) with ethanolamine.

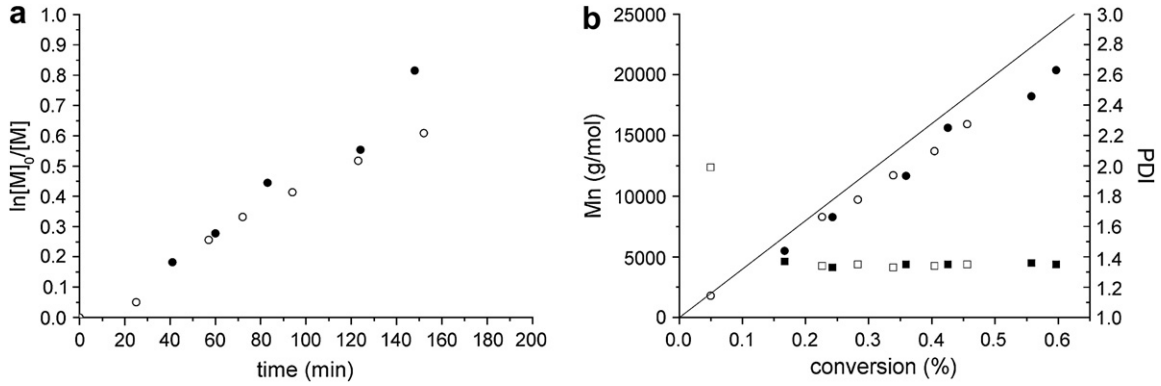


Fig. 2. Nitroxide mediated polymerization of styrene at 120 °C with alkoxyamine **1** (in black) and MAMA-SG1 (in white). (a) ln([M_0]/[M]) *vs* time; (b) M_n (rounds) and PDI (squares) *vs* conversion (line is theoretical curve).

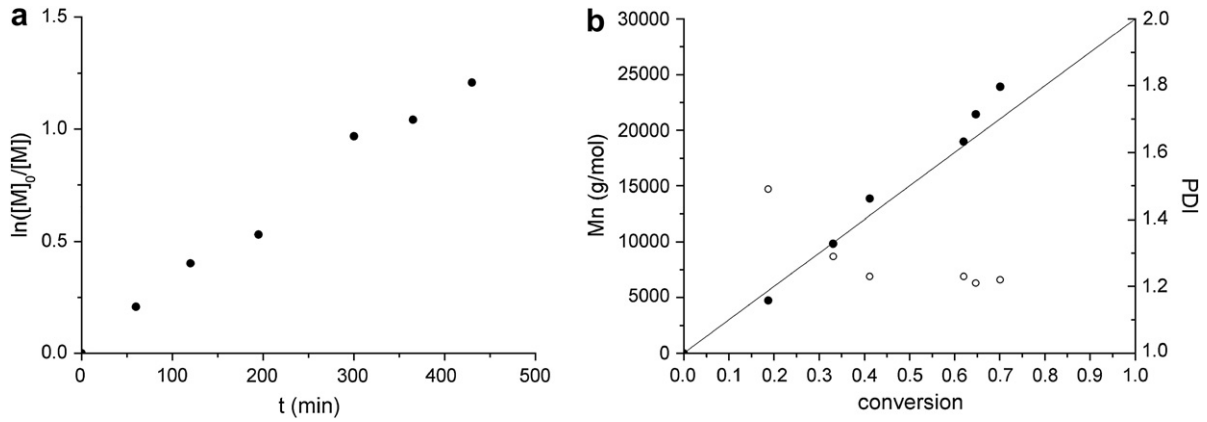


Fig. 3. Nitroxide mediated polymerization of *n*-butyl acrylate at 115 °C with alkoxyamine **1**. (a) ln([M_0]/[M]) *vs* time; (b) M_n (black rounds) and PDI (white rounds) *vs* conversion (line is theoretical curve).

The NHS-terminated PS (6800 g mol^{-1}, PDI = 1.19) obtained with **1** was further characterized by liquid chromatography under critical conditions (LC-CC) that enables the separation of polymers only depending on their functional groups [20,21]. In our case, the critical conditions for PS were found at 78.3 °C using DMF as eluent with apolar C_{18} columns (see Section 2). As shown in Fig. 4a (black line), the chromatogram of NHS-functionalized PS revealed one major peak corresponding to the expected chains bearing a NHS α-chain end originating from **1** and a SG1 ω-chain end (NHS–PS–SG1). Two other minor peaks at lower retention times were also observed. Because during NMP process termination reactions are never totally suppressed [22] these minor peaks could correspond to the disproportionation and combination termination reaction products of PS macroradicals initiated by alkoxyamine **1**.

As a comparison, the chromatogram of a PS (6900 g mol^{-1}, PDI = 1.12) initiated by MAMA-SG1 is plotted on Fig. 4a (grey line). For this polymer, the major peak corresponding to COOH–PS–SG1 species was eluted at higher retention times than NHS–PS–SG1, which can be attributed to a probable higher polarity of the NHS ester compared to COOH group.

3.2.2. Derivatization of the NHS-functional polystyrene after polymerization

To illustrate the possibilities of derivatization of NHS-functionalized polymers, a model compound (ethanolamine) was coupled to the NHS-terminated PS via an amidification reaction. This leads to OH-functionalized PS, that can be used as macroinitiators for ROP of lactones, as described later in this paper.

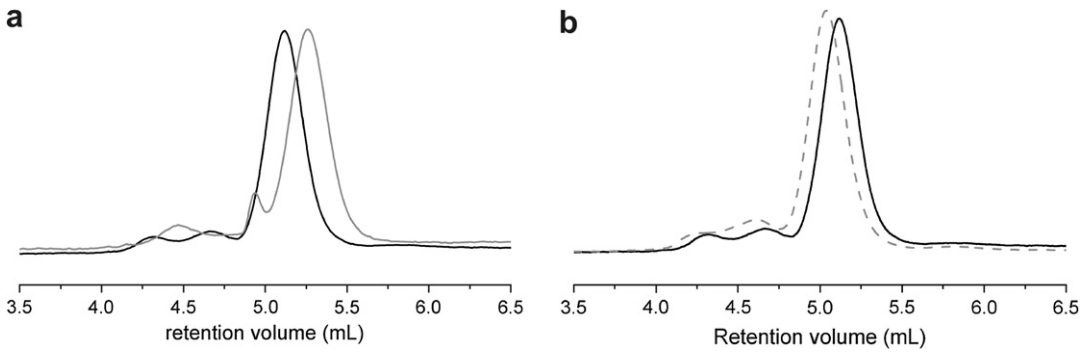


Fig. 4. LC-CC chromatograms obtained for (a) NHS-functionalized PS (black curve) and COOH-functionalized PS (polymerization with the MAMA-SG1, grey curve) under PS critical conditions; (b) NHS-functionalized PS (black curve) and OH-functionalized PS (grey curve) under PS critical conditions.

The reaction was performed with 1.5 equiv of ethanolamine per PS–NHS chain for 1 h at 4 °C (Scheme 4, second step). Fig. 5 represents the ^{1}H NMR of the NHS-terminated PS before coupling (a) and ^{1}H NMR of the OH-terminated PS (precipitated in methanol) obtained after ethanolamine coupling (b). It clearly shows a nearly total disappearance of the NHS proton peaks after coupling, together with the appearance of the CH_2 proton arising from ethanolamine (3.05 and 3.45 ppm). Calculation of the M_n of PS via integration of these CH_2 peaks and the aromatic protons gave a value of 6800 g mol^{-1} very close to that expected (7000 g mol^{-1}) and found by GPC (6800 g mol^{-1}), indicating a functionalization yield close to 100%.

Interestingly, the shape of the LC-CC chromatogram of this OH-functionalized PS was similar to that of NHS-functionalized PS, but translated to slightly lower retention times (Fig. 4b). This result can be explained by the substitution of NHS by polar amide and alcohol end-groups on the PS chain end. No residual shoulder corresponding to unreacted NHS-functional PS was observed, suggesting a quantitative functionalization by ethanolamine and thus confirming the ^{1}H NMR results.

NMP performed with alkoxyamine **1** thus proved to give very well-defined α-NHS functional PS and PBA. Thanks to the versatility of the SG1 nitroxide for NMP, **1** is expected to control the polymerization of a large range of other vinylic monomers. Moreover, the resulting well-defined NHS-functional polymers could be used as useful intermediates for the preparation of a wide array of α-functional polymers, as illustrated by the introduction of ethanolamine chosen as model compound.

3.3. Pre-functionalized MAMA-SG1 derivatives as NMP initiators (path B, Scheme 2)

After proving the efficiency of alkoxyamine **1** as initiator for NMP to provide functional polymers, we aimed at showing its suitability for the preparation of various functional initiators to provide advanced macromolecular architectures involving

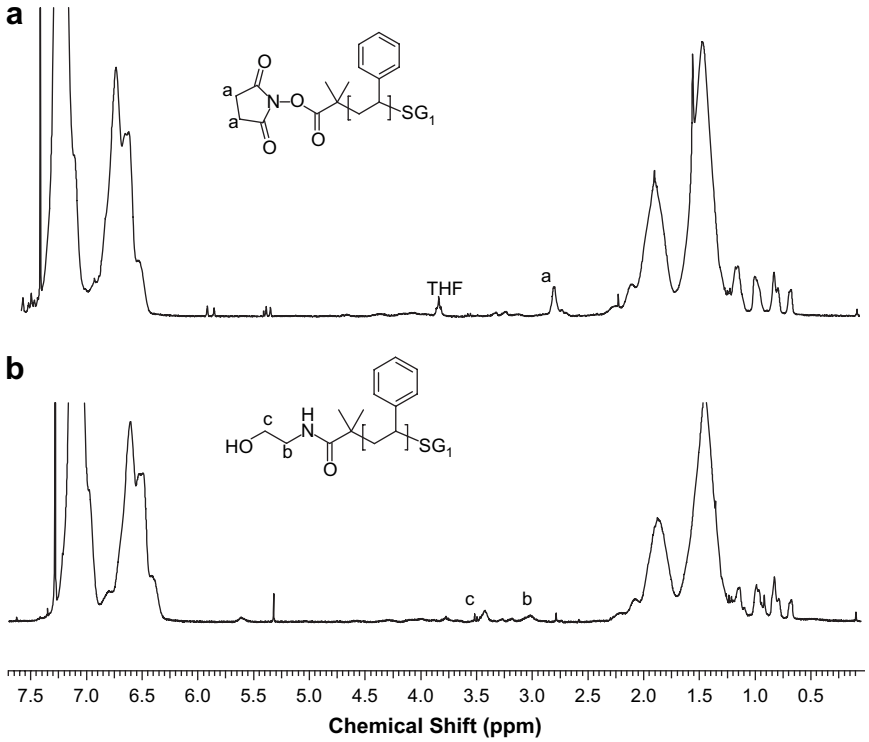


Fig. 5. ^{1}H NMR (in $CDCl_3$) of (a) NHS-terminated PS and (b) OH-terminated PS obtained after reaction with ethanolamine.

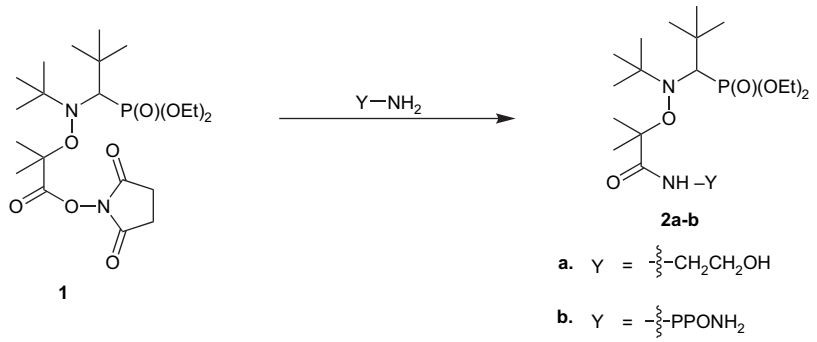
non-vinylic monomers, namely PS-*b*-PLA and PS-*b*-PPO block copolymers (Scheme 5).

3.3.1. Combined NMP–ROP techniques: PS-b-PLA copolymer synthesis

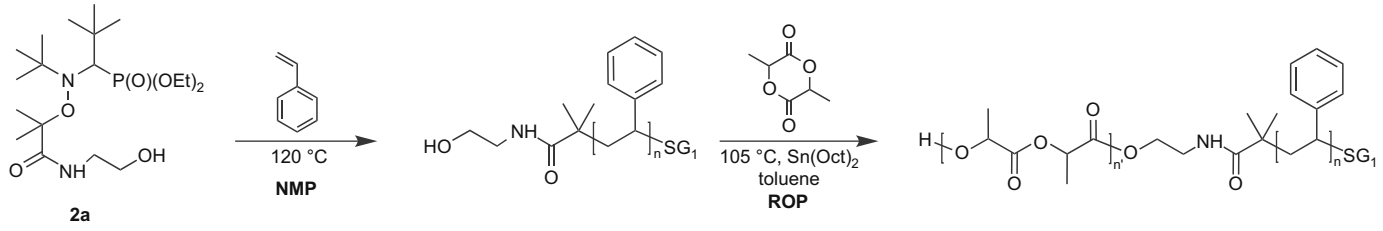
The OH-functional alkoxyamine initiator **2a** has been prepared from the reaction of **1** with ethanolamine to combine ROP and NMP techniques (Scheme 6). One interesting issue is the production of block copolymers in which the ROP-derived block is biodegradable (polylactide/lactone). Such copolymers have recently received high attention, particularly as precursors for the fabrication of nanoporous materials [23,24]. The initiator **2a** was prepared by the reaction of alkoxyamine **1** with a slight excess of ethanolamine (1.27 equiv/alkox.) in dichloromethane at 0 °C. After 1 h, the reaction was quantitative as shown by the total disappearance of the ^{31}P signal of **1** at 25.8 ppm and the presence of one single peak at 27.8 ppm corresponding to **2a**. This dual initiator was then used to prepare a diblock copolymer PS-*b*-PLA by successive NMP and ROP steps. The tertiary stabilized moiety of alkoxyamine **2a** acts as an efficient initiator for the NMP while the primary alcohol is used in combination with a metal catalyst such as $Sn(Oct)_2$ to initiate the living ROP of the D,L-lactide (Scheme 6).

In the first step, styrene polymerization was performed in bulk at 120 °C under nitrogen and in the presence of alkoxyamine **2a** (targeted M_n of 20 000 g mol^{-1}). The linear evolution of the molecular weight *vs* conversion (close to the theoretical curve) and the decreasing polydispersity index down to 1.1 are the characteristics of a controlled NMP process (Fig. 6a).

At 35% conversion, the polymer (PS–OH) was purified by precipitation in cold methanol (M_n 8800 g mol^{-1} determined by GPC) and further used as an alcohol macroinitiator for the ROP of D,L-lactide. The polymerization was performed in toluene at 105 °C, in the presence of $Sn(Oct)_2$ as a catalyst (0.5 equiv/PS–OH) targeting a degree of polymerization ([D,L-lactide]/[PS–OH]) of 100 ($M_{n,PLA}$ = 14 400 g mol^{-1}). The ROP of the D,L-lactide was controlled as shown by the linear curve of M_n *vs* conversion and low polydispersities (Fig. 6b). At 30% conversion in lactide, the block copolymer was precipitated in methanol and characterized by ^{1}H



Scheme 5. Alkoxyamine precursors developed in this work: **2a** for ROP-NMP combined polymerizations; **2b** for PPO based diblock polymers.



Scheme 6. Preparation of a PS-*b*-PLA diblock copolymer from the alkoxyamine **2a** by NMP/ROP combined polymerizations.

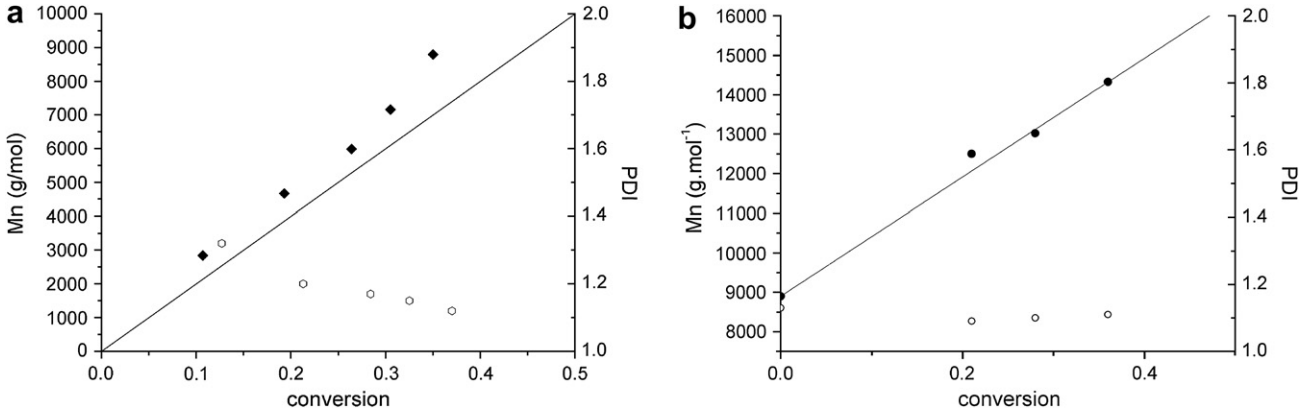


Fig. 6. (a) M_n and PDI as a function of conversion for NMP of styrene with alkoxyamine **2a**; (b) M_n and PDI as a function of conversion for D,L-lactide ROP from PS–OH (line is theoretical curve).

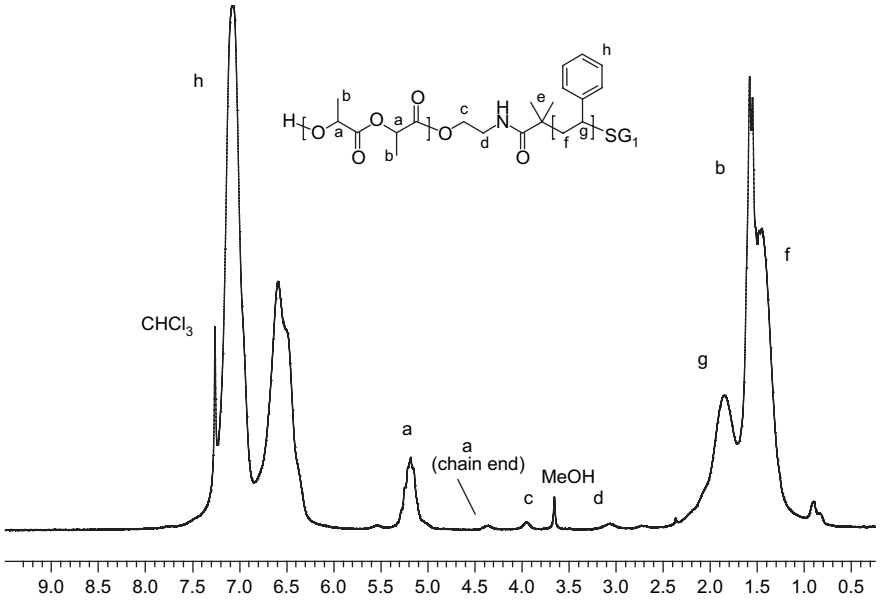


Fig. 7. ^{1}H NMR spectrum (in $CDCl_3$) of the block copolymer PS-*b*-PLA after precipitation in methanol.

NMR (Fig. 7). One can clearly observe the shift of the CH_2 proton peak (c) in α-position of oxygen present at the chain end of PS from 3.45 to 3.96 ppm, showing that the alcohol chain end of PS was transformed into ester function and thus acted as an effective initiator for the D,L-lactide ROP. Finally, Fig. 8 shows the shift towards higher molecular weight observed for the GPC traces of PS-*b*-PLA compared to the PS–OH macroinitiator. No shoulder corresponding to unreacted PS–OH was observed on the PS-*b*-PLA chromatogram, suggesting a very efficient initiation of ROP of the lactide. The M_n of the block copolymer given by GPC (13 050 g mol^{-1}) was close to that found by ^{1}H NMR (M_n = 12 500 g mol^{-1}).

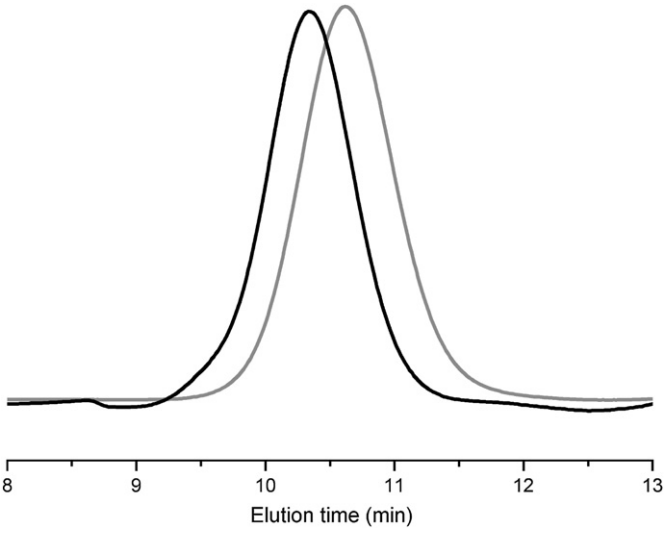


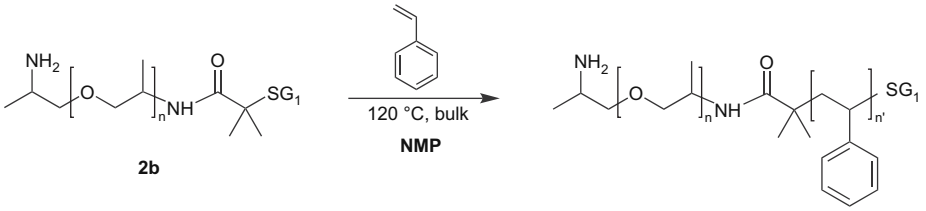
Fig. 8. GPC traces of the PS–PLA (black line) and PS-OH macroinitiator (grey line).

In conclusion the dual initiator **2a** approach provides an easy access to very well-defined block copolymers through the combination of ROP and NMP. Moreover, this initiator illustrates the potency of path B depicted in Scheme 2 as an alternative to path A to obtain the OH-functionalized polymers.

3.3.2. *PS*-b-*PPO diblock copolymer synthesis*

The interest of **1** was also illustrated by the preparation of PS-*b*-PPO diblock copolymers following the path B (Scheme 2). In this example we demonstrated the direct coupling of a polymer chain on **1** to afford first a macroalkoxyamine and then a diblock copolymer after a NMP process. In the first step a PPO macroalkoxyamine **2b**, Scheme 5, was prepared by amidification reaction between PPO-di-NH_2 (2000 g mol^{-1}) and alkoxyamine **1**. The reaction was performed at 0 °C in THF over 2 h and with a fourfold excess of amine function per SG1 in order to avoid formation of difunctional macroalkoxyamine (Scheme 5). After evaporation of THF under vacuum the polymer material was characterized by ^{31}P and ^{1}H NMR. According to the ^{1}H NMR spectrum the yield of the reaction was 82% by comparing the integration value of the multiplet at 3.5 ppm corresponding to the ($CH + CH_2$) of PPO with that of singlets of the methyl groups in β position of the carbonyl function, arising from **1** (1.88 and 1.97 ppm).

In the second step, macroalkoxyamine **2b** was used without further purification as initiator for the NMP of styrene. Polymerization was carried out, in bulk, at 120 °C and targeting an average molecular weight of 40 000 g mol^{-1}, Scheme 7.



Scheme 7. Preparation of a PS-*b*-PPO from the PPO–SG1 macroalkoxyamine **2b**.

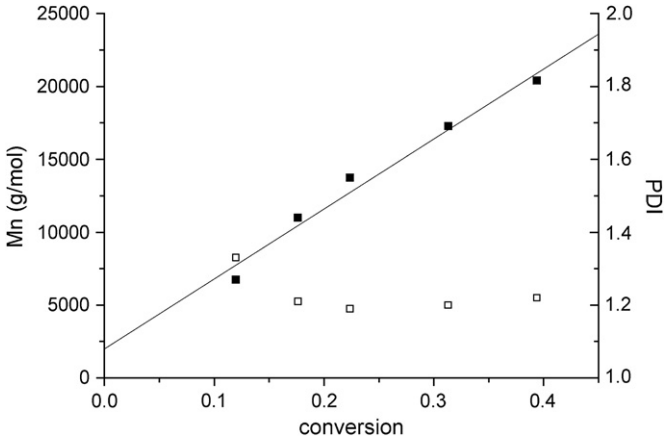


Fig. 9. Molecular weight and polydispersity index as a function of conversion for styrene NMP with macroalkoxyamine PPO–SG1 **2b** (line is theoretical curve).

A linear increase in molecular weight (determined by GPC) *vs* conversion was observed indicating that the styrene polymerization proceeds in a controlled manner and PPO macroalkoxyamine is able to produce a block copolymer (Fig. 9).

Molecular weight of the PS block was estimated by ^{1}H NMR analysis on PS-*b*-PPO sample obtained at 39% conversion after precipitation in methanol. Use of methanol allowed the removal of free PPO chains. In these conditions, M_n of the PS block was found to be 14 200 g mol^{-1} by comparing the integral values corresponding to the PPO peaks (multiplet at 3.5 ppm) with the one corresponding to the aromatic protons of the PS chains (multiplet at 7 ppm). This value is in good agreement with the expected one (theoretical $M_n = 15\,600$ g mol^{-1}) showing a high initiator efficiency for the macroinitiator PPO–SG1.

4. Conclusion

After the synthesis of the NHS-activated ester alkoxyamine **1**, several examples were used to demonstrate its potential and versatility using both paths A and B, Scheme 2.

First of all, we showed that **1** was an efficient alkoxyamine for NMP of styrene and *n*-butyl acrylate and for achieving well-defined α-NHS functional polymers (NHS–PS–SG1). Then the post-functionalization approach (path A) was illustrated by derivatization of the NHS–PS–SG1 with ethanolamine chosen as a model compound. The pre-functionalization approach (path B) was demonstrated by the preparation of an OH-functionalized alkoxyamine and a PPO macroalkoxyamine that were, respectively, used for the preparation of polystyrene-*b*-polylactide (PS-*b*-PLA) diblock copolymers (by combining NMP and ROP techniques) and poly(propylene oxide)-*b*-polystyrene (PPO-*b*-PS) diblock copolymers.

This set of experiments thus demonstrates that the novel alkoxyamine **1** is a very efficient precursor for the preparation of functional polymers and complex macromolecular architectures that can find very useful applications across many fields of research. The preparation of PS-*b*-PLA copolymers not only demonstrates the ability to combine two mechanistically different polymerization procedures but is also very interesting due to the biodegradability properties of the polyester block. The preparation of PS-*b*-PPO shows the possibility to covalently bind SG1-based NMP initiators onto polymers to form macroalkoxyamines in order to synthesize original block copolymers difficult to obtain by other ways. Furthermore, our strategy is promising regarding possibilities to attach covalently NHS-functionalized alkoxyamine and polymers on biomolecules or nano-objects for bio-related and nanotechnology applications.

References

[1] Hawker CJ, Bosman AW, Harth E. Chem Rev 2001;101:3661.
[2] Braunecker WA, Matyjaszewski K. Prog Polym Sci 2007;32:93.
[3] Bernaerts KV, Du Prez FE. Prog Polym Sci 2006;31:671.
[4] (a) Mecerreyes D, Moineau G, Dubois P, Jérôme R, Hedrick JL, Hawker CJ, et al. Angew Chem Int Ed 1998;37:1274;
(b) Shanmugananda Murthy K, Ma Q, Clark C, Remsen E, Wooley K. Chem Commun 2001:773;
(c) Tunca U, Karliga B, Ertekin S, Ugur AL, Sirkecioglu O, Hizal G. Polymer 2001; 42:8489;
(d) Tunca U, Erdogan T, Hizal G. J Polym Sci Part A Polym Chem 2002;40:2025;
(e) Celik C, Hizal G, Tunca U. J Polym Sci Part A Polym Chem 2003;41:2542;
(f) He T, Li D, Sheng X, Zhao B. Macromolecules 2004;37:3128;
(g) Altintas O, Yilmaz I, Hizal G, Tunca U. J Polym Sci Part A Polym Chem 2006; 44:3242;
(h) Erdogan T, Gungor E, Durmaz H, Hizal G, Tunca U. J Polym Sci Part A Polym Chem 2006;44:1396;
(i) Durmaz H, Karatas F, Tunca U, Hizal G. J Polym Sci Part A Polym Chem 2006; 44:3947;
(j) Altintas O, Hizal G, Tunca U. J Polym Sci Part A Polym Chem 2006;44:5699;
(k) Fleischmann S, Komber H, Appelhans D, Voit BI. Macromol Chem Phys 2007;208:1050.
[5] Van As BAC, Thomassen P, Kalra B, Gross RA, Meijer EW, Palmas ARA, et al. Macromolecules 2004;37:8973.
[6] Lecolley F, Tao L, Mantovani G, Durkin I, Lautru S, Haddleton DM. Chem Commun 2004:2026.
[7] Bathfield M, D'Agosto F, Spitz R, Charreyre MT, Delair T. J Am Chem Soc 2006; 128:2546.
[8] Gigmes D, Bertin D, Guerret O, Marque SRA, Tordo P, Chauvin F, et al. PCT WO 2004/014926, 13 February 2004.
[9] Chauvin F, Dufils PE, Gigmes D, Guillaneuf Y, Marque SRA, Tordo P, et al. Macromolecules 2006;39:5238.
[10] Nicolas J, Charleux B, Guerret O, Magnet S. Angew Chem Int Ed 2004;43:6186.
[11] Dufils PE, Chagneux N, Gigmes D, Trimaille T, Marque SRA, Bertin D, et al. Polymer 2007;48:5219.
[12] Montalbetti CAGN, Falque V. Tetrahedron 2005;46:10827.
[13] Anderson GW. J Am Chem Soc 1964;86:1839.
[14] Nicolas J, Mantovani G, Haddleton DM. Macromol Rapid Commun 2007;28: 1083.
[15] Marque S, Le Mercier C, Tordo P, Fischer H. Macromolecules 2000;33:4403.
[16] Marque S, Fischer H, Baier E, Studer A. J Org Chem 2001;66:1146.
[17] Ananchenko G, Beaudoin E, Bertin D, Gigmes D, Lagarde P, Marque SRA. J Phys Org Chem 2006;19:269.
[18] Kothe T, Marque S, Martschke R, Popov M, Fischer H. J Chem Soc Perkin Trans 2 1998:1553.
[19] Souaille M, Fischer H. Macromolecules 1997;33:7378.
[20] Skvortsov A, Gorbunov A. Polym Sci USSR 1980;22:2893.
[21] Petit C, Luneau B, Beaudoin E, Gigmes D, Bertin D. J Chromatogr A 2007;1163: 128.
[22] Chevalier C, Guerret O, Gnanou Y. Advances in controlled/living radical polymerization. In: Matyjaszewski, editor. ACS Symposium Series, vol. 854. Washington, DC; 2002. p. 424–37.
[23] Zalusky AS, Olayo-Valles R, Wolf JH, Hillmyer MA. J Am Chem Soc 2002;124: 12761.
[24] Leiston-Belanger JM, Russell TP, Drockenmuller E, Hawker CJ. Macromolecules 2005;38:7676.