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Synthesis of a bulky nitroxide and its application in the nitroxide-mediated radical polymerization

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ABSTRACT

The synthesis of a sterically highly hindered morpholine-based nitroxide is described. Trapping of an α-ester radical with this novel nitroxide leads to an alkoxyamine which is used as an efficient initiator/regulator in the controlled nitroxide-mediated radical polymerization (NMP) of *n*-butyl acrylate and styrene. Controlled polymerization of *n*-butyl acrylate can be conducted at very low temperature (50 °C) convincingly documenting the efficiency of this nitroxide for acrylate polymerization.

1. Introduction

The controlled/living radical polymerization (CLRP) that emerged from the early 1980s has initiated a new research branch in polymer science focusing on the synthesis of tailored polymers with excellent control over their molecular architecture. Guided by the pioneering work in the field, various CLPR technologies have been established since then.[1] Nitroxide-mediated polymerization (NMP) is historically the earliest applied CLPR technology, and is experimentally easy to conduct. Notably, NMP proceeds in the absence of any transition metal and colored compounds are not required. As a result, colorless polymers that are free of any transition metal impurities bearing nitroxyl functional groups at the terminus of the chains are obtained.

NMP is controlled by the persistent radical effect (PRE)[2] and is generally conducted with an alkoxyamine initiator under neat conditions at elevated temperature (>100 °C). NMP proceeds via reversible C–ON bond cleavage of a polymeric alkoxyamine generated during the polymerization process. Upon thermolysis of the C–ON bond in an alkoxyamine initiator at an appropriate temperature, a nitroxide and a transient C radical are generated. Addition of the latter species to the alkene group of a monomer and subsequent recombination with the nitroxide radical produces a polymeric alkoxyamine with extended chain, which undergoes renewed thermolysis to generate the nitroxide and a new polymeric radical (the C-radical generally adds to more than one monomer before being trapped by the nitroxide). Since the equilibrium between free nitroxide/polymeric radical and polymeric alkoxyamine lies far to the site of the closed shell polymeric alkoxyamine, the concentration of free radicals is kept low during the entire polymerization process, thereby suppressing termination reactions. Hence, control of the polymerization depends on the equilibrium constant *K* between the polymeric alkoxyamine and the macroradical/nitroxide. It is known that the equilibrium constant *K* is strongly affected by structural properties of the nitroxide such as internal H-bonding, steric, electronic and polar effects.[3] The structure of a nitroxide influences both the polymerization rate and polydispersity of the resulting macromolecules.

The pioneering works on NMP were conducted with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as the nitroxide component. However, application of TEMPO as a mediator in NMP is limited. It works well only for polymerization of styrene and its derivatives. Moreover, high temperature (125–145 °C) and a long reaction time (1–3 days) are often required.[1e,4] Considering these limitations, various nitroxides have been developed in order to achieve well-controlled polymerization of a broader range of monomers at lower temperature. For instance, the readily prepared acyclic nitroxides *N*-*tert*-butyl-*N*-(1-diethyl- phosphono-2,2-dimethyl) propylnitroxyl radical (SG1)[3h,i,5] and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-oxyl (TIPNO)[6] were shown to be highly efficient mediators for well-controlled acrylate NMP. We found the sterically hindered cyclic nitroxides **1**[7] and **2**[8] to be efficient regulators for polymerization of styrene and *n*-butyl acrylate (Fig. 1).

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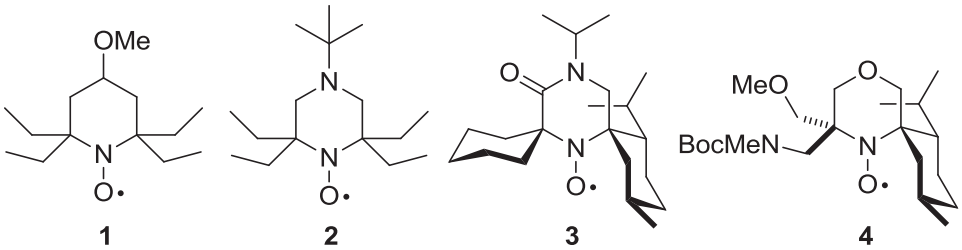


Fig. 1. Known efficient cyclic six-membered nitroxides **1**–**3** and the novel congener **4**.

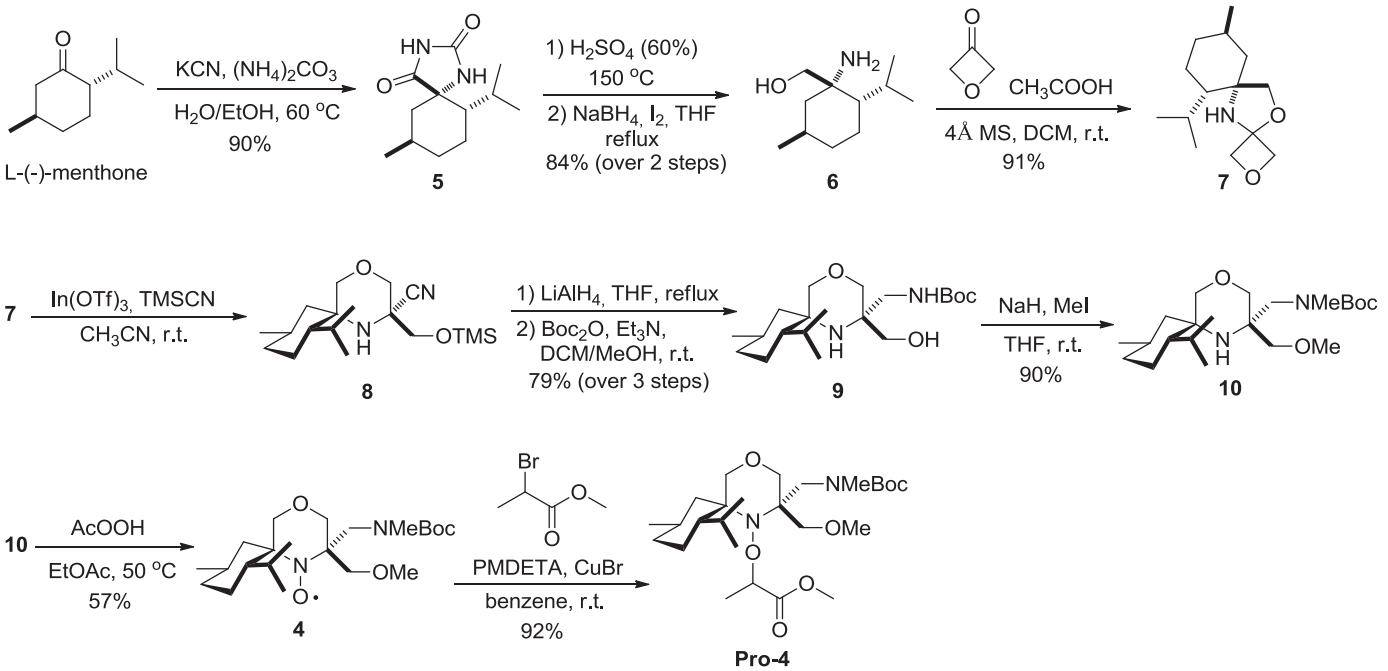
Although good results were obtained by using these nitroxides in the polymerizations of styrene and acrylates, temperatures above 90 °C are still required for well-controlled polymerizations within a reasonable time frame. Very recently, we developed a chiral bulky nitroxide **3** bearing a spiro-annellated six-membered ring in α-position of the nitroxyl functionality (Fig. 1).[9] The *iso*propyl and methyl groups at the cyclohexane ring are located in equatorial position fixing the six-membered ring in a sterically shielding chair conformation. Nitroxide **3** was found to be a highly efficient regulator for NMP of styrene and *n*-butyl acrylate, and these polymerizations could be conducted even at 50 °C.

Herein, we will present a straightforward synthesis of nitroxide **4** (Scheme 1). As compared to the highly efficient system **3**, the piperidinone core in **3** is replaced by a morpholine ring thereby altering electronic effects of the nitroxide. Preparation of an alkoxyamine derived from **4** is described and this alkoxyamine is applied as an initiator/regulator to NMP of *n*-butyl acrylate and styrene.

2. Results and discussions

2.1. Synthesis of nitroxide 4 and of alkoxyamine Pro-4

The synthesis commenced with the commercially available and cheap enantiopure L-(-)-menthone (Scheme 1). According to a previously reported procedure, L-(-)-menthone was diastereoselectively transformed to the corresponding hydantoin **5** in high yield by a *Bucherer* reaction.[10] After hydrolysis with 60% aqueous H_2SO_4 at 150 °C, the corresponding amino acid was obtained, which was directly reduced with $NaBH_4/I_2$ without any further purification to give the amino alcohol **6** (84% yield over two steps). Applying a method that was recently introduced by *Carreira* and co-workers,[11] the amino alcohol **6** was reacted with 3-oxetanone to form the N,O-ketal **7** in high yield. In the presence of TMSCN and a catalytic amount of $In(OTf)_3$, **7** further reacted via a *Strecker* reaction with subsequent ring expansion to afford morpholine **8** which was isolated as a single diastereoisomer. Nitrile reduction with $LiAlH_4$ went along with silyl ether cleavage. N-Bocylation by using Boc-anhydride provided bicycle **9**. Treatment of **9** with NaH and an excess of MeI led to protection of the primary alcohol as methyl ether and at the same time also Boc*N*H-methylation was achieved (see **10**). Finally, oxidation of the secondary amine with AcOOH afforded the targeted bulky spiro morpholine-based nitroxide **4**. The corresponding alkoxyamine **Pro-4** was prepared in 92% yield according to a known literature procedure[12] with methyl α-bromopropiolate. **Pro-4** was isolated as a mixture of the two diastereoisomers. Due to the signal overlap in the NMR spectra, the isomer ratio could not be unambiguously determined.



Scheme 1. Synthesis of nitroxide **4** and the corresponding alkoxyamine **Pro-4**.

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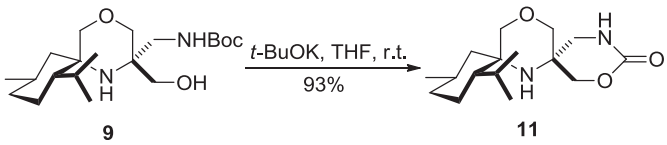
Unfortunately, nitroxide **4** and the alkoxyamine **Pro-4** were both isolated as oils and conformation analysis by X-ray structure studies was not possible. To proof the relative configuration of **4** and to get an idea on the conformation of the two six-membered rings we decided to prepare a crystalline derivative therefrom. Cyclization of the Boc-protected amino alcohol **9** under basic condition provided crystalline tricyclic carbamate **11** (Scheme 2).



Scheme 2. Synthesis of dispiro-annelated morpholine **11**.

X-ray structure analysis allowed for assignment of the relative configuration of the two fully substituted stereogenic centers in **11** (Fig. 2). The *iso*propyl group at the cyclohexane ring is located *cis* to the oxygen atom of the carbamate ring. In analogy to nitroxide **3**, the cyclohexane ring in **11** lies in a chair conformation with the *iso*propyl and methyl groups both oriented in equatorial positions. We assume that also in the nitroxide **4** the six-membered carbocycle will stay in the same fixed chair conformation that strongly shields the *N*-oxyl radical. As expected, the morpholine ring also lies in a chair conformation whereas the carbamate ring is distorted from a chair due to the different hybridization of the carbonyl C-atom and the two heteroatoms.

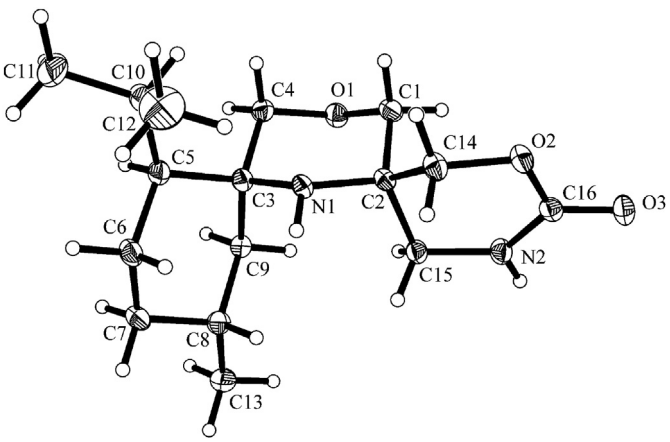


Fig. 2. Crystal structure of compound **11** (Thermals ellipsoids are shown with 50% probability.).

Cyclovoltammetry (CV) measurements confirmed a change of the electronic properties of **4** when compared to **3**. Both nitroxides show a distinct reversible oxidation as well as an irreversible reduction (for spectra, see Supplementary data). With E_{ox}=+0.1991 V versus ferrocene (Fc^+/Fc) as internal standard, the oxidation potential of **4** is significantly lower than the oxidation potential of **3** (E_{ox}=+0.3695 V, versus Fc^+/Fc), indicating that **4** is less electrophilic and more readily oxidized to the corresponding oxoammonium ion. The electron-withdrawing lactam moiety in the heterocycle of **3** shifts the oxidation potential to a higher value as compared to **4**. Notably, nitroxide **4** is even more readily oxidized than the TEMPO radical which has an oxidation potential of E_{ox}=+0.2287 V (versus Fc^+/Fc).

2.2. Polymerization studies

Polymerizations were conducted in sealed tubes in neat styrene or *n*-butyl acrylate using different initiator concentrations (0.25–1 mol %). Conversion of NMP was determined gravimetrically. Polydispersity index (PDI) and molecular weight ($M_{n,exp}$) of the resulting polymers were analyzed by using size exclusion chromatography (SEC).

Poly-*n*-butyl acrylate (PBA) synthesis was first investigated by using alkoxyamine **Pro-4** as initiator/regulator at 50–70 °C and results obtained are summarized in Table 1. All polymerizations were well controlled delivering PBA with small PDIs (<1.30). At 70 °C polymerizations proceeded rapidly and very high conversions (94–98%) were obtained within 15 h (Table 1, entries 1–3). For example, PBA with a molecular weight of 49,800 g/mol and small PDI (1.24) was isolated by using 0.25 mol % of initiator **Pro-4** (entry 3). As expected for a controlled living polymerization, at higher initiator loading (0.5 and 1 mol %, respectively) PBA with smaller molecular weight was formed. Reactions with **Pro-4** proceeded well also at 60 °C and 75–93% conversions were achieved after 26 h (Table 1, entries 4–6). PBA isolated in these experiments showed small PDIs and the molecular weight was controlled by the initiator concentration, clearly revealing that polymerization was well controlled at 60 °C. We then repeated BA-polymerizations at 50 °C (Table 1, entries 7–9). Pleasingly, polymerization was still occurring albeit reaction time had to be increased to 125 h in order to get conversions of 45–79%. PDI of the PBA isolated was small and molecular weight was controlled by the initiator concentration.

Table 1
NMP of *n*-butyl acrylate under different conditions using alkoxyamines **Pro-4**, **Mal-3** and **Pro-3**

Entry	Alkoxyamine (mol %)	Temperature (°C)	Time (h)	Conversion (%)	$M_{n,th}$ (g/mol)	$M_{n,exp}$ (g/mol)	PDI
1	**Pro-4** (1)	70	15	98	12,600	20,600	1.25
2	**Pro-4** (0.5)	70	15	97	25,000	33,600	1.21
3	**Pro-4** (0.25)	70	15	94	48,100	49,800	1.24
4	**Pro-4** (1)	60	26	93	12,000	23,500	1.29
5	**Pro-4** (0.5)	60	26	81	20,700	30,600	1.30
6	**Pro-4** (0.25)	60	26	75	38,500	48,900	1.24
7	**Pro-4** (1)	50	125	79	10,100	22,500	1.23
8	**Pro-4** (0.5)	50	125	61	15,700	23,700	1.15
9	**Pro-4** (0.25)	50	125	45	23,000	26,000	1.29
10[a]	**Mal-3** (1)	60	22	81	10,400	12,800	1.15
11[a]	**Mal-3** (0.5)	60	22	71	18,200	22,800	1.13
12[a]	**Mal-3** (0.25)	60	22	66	33,700	34,800	1.11
13[a]	**Pro-3** (1)	60	24	81	10,900	12,700	1.16
14[a]	**Pro-3** (0.5)	60	24	80	20,500	29,600	1.12
15[a]	**Pro-3** (0.25)	60	24	69	35,400	40,900	1.13

[a] Data taken from Ref. 9.

For comparison, results previously obtained[9] for BA-polymerization under identical conditions (neat, 60 °C with 0.25–1 mol % of initiator) with alkoxyamines **Pro-3** and **Mal-3** (Fig. 3), which are the most efficient cyclic NMP-initiators/regulators known to date, are included into Table 1 (entries 10–15). Compared to **Mal-3** and **Pro-3**, the novel alkoxyamine **Pro-4** is slightly more reactive (higher conversions) but delivers PBA with slightly larger PDIs.

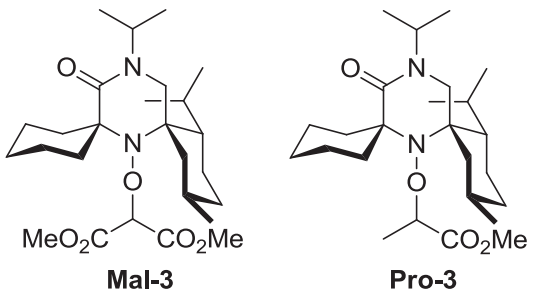


Fig. 3. Alkoxyamines **Mal-3** and **Pro-3** included into this study for comparison.

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Finally, styrene polymerizations were investigated by using **Pro-4** as an initiator/regulator at 70 and 60 °C and different initiator concentrations. Results obtained are depicted in Table 2. Polymerizations occurred smoothly at 70 °C (Table 2, entries 1–3) and 55–72% conversion was achieved after 18 h providing polystyrene (PS) with a narrow molecular weight distribution (PDIs=1.13–1.17). Decreasing the reaction temperature to 60 °C led to a significant reduction of the polymerization rate. Upon extending the reaction time to 47 h, acceptable conversions (55–79%) were obtained (Table 2, entries 4–6). Molecular weight was well-controlled based on the initiator loading. However, only very little conversion (<5%) was obtained at 50 °C after 48 h. Again styrene polymerization results obtained with **Pro-4** are compared with those previously obtained with initiator **Pro-3** (Table 2, entries 7–9). For styrene, we found a different reactivity trend. The novel nitroxide **4** is clearly less active (lower conversion) as compared to **3** and also slightly lower control over the molecular weight distribution (larger PDIs) was achieved.

Table 2
NMP of styrene under different conditions using alkoxyamine **Pro-4** and **Pro-3**

Entry	Alkoxyamine (mol %)	Temperature (°C)	Time (h)	Conversion (%)	$M_{n,th}$ (g/mol)	$M_{n,exp}$ (g/mol)	PDI
1	**Pro-4** (1)	70	18	72	7500	8500	1.17
2	**Pro-4** (0.5)	70	18	62	12,900	14,600	1.13
3	**Pro-4** (0.25)	70	18	55	23,000	25,500	1.14
4	**Pro-4** (1)	60	47	79	8200	8300	1.23
5	**Pro-4** (0.5)	60	47	64	13,000	12,800	1.16
6	**Pro-4** (0.25)	60	47	55	23,000	23,200	1.22
7[a]	**Pro-3** (1)	60	24	64	6600	7500	1.12
8[a]	**Pro-3** (0.5)	60	24	53	11,000	14,000	1.13
9[a]	**Pro-3** (0.25)	60	24	41	17,000	18,600	1.09

[a] Data obtained from Ref. 9.

The livingness of the **Pro-4**-mediated polymerization of styrene was proved by plotting $\ln(M_0/M)$ as a function of time as well as M_n as a function of conversion (Fig. 4). The data set shows the typical behavior for controlled radical polymerizations.

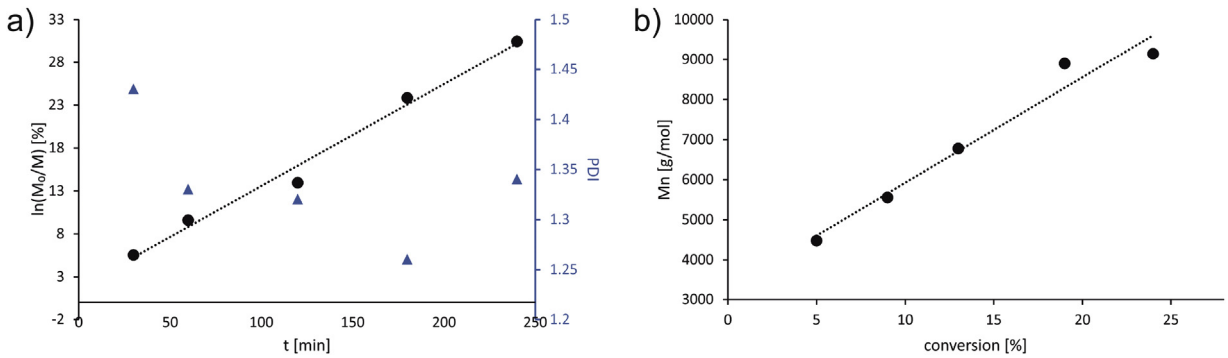

Fig. 4. a) Pseudo-first order kinetic plot for the **Pro-4** (0.5 mol %) mediated NMP of neat styrene at 70 °C and corresponding PDI values plotted as a function of time. b) Number average molecular weight M_n as a function of conversion.

3. Conclusions

We presented the synthesis of a novel sterically highly hindered nitroxide **4**. The developed multi-step approach allows preparing **4** in large amounts. The chiral nitroxide **4** carries a spiro anellated doubly substituted cyclohexane ring which is fixed in a highly shielding chair conformation. The corresponding alkoxyamine **Pro-4** was readily prepared in excellent yield and was found to be a highly efficient initiator/regulator for NMP of *n*-butyl acrylate. Although known nitroxide **3** as compared to **4** afforded slightly better results as initiator/regulator for styrene polymerization, it is important to note that the herein introduced **4** outperforms almost all existing known NMP regulators.

4. Experimental section

4.1. General

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in heat gun-dried glassware under an argon atmosphere and were performed using standard *Schlenk* techniques. All solvents for extraction and flash chromatography (FC) were distilled before use. Benzene was distilled from Na, THF was distilled from K, and CH_2Cl_2 was distilled from P_2O_5. All the other solvents and chemicals were used as received from the suppliers (Alfa, Acros, Aldrich, ABCR, Fluka). Styrene (Acros, 99%) and *n*-butyl acrylate (Acros, 99%) were distilled under reduced pressure from CaH_2 to remove stabilizer. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates; detection by UV or dipping into a solution of $KMnO_4$ (1.5 g), $NaHCO_3$ (5.0 g) in H_2O (400 mL), followed by heating. Flash chromatography (FC) was carried out on Merck or Fluka silica gel 60 (40–63 μm) at about 1.4 bar. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 (^1H: 300 MHz; ^{13}C: 75 MHz), a Varian Inova 500 (^1H: 500 MHz; ^{13}C: 125 MHz), or a Varian Unity plus 600 (^1H: 600 MHz; ^{13}C: 150 MHz). Chemical shifts δ in ppm are referenced to the solvent residual peak. IR spectra were recorded on a Varian 3100 FT-IR equipped with an MKII Golden Gate Single Reflection ATR unit. ESI-MS (*m/z*) and HRMS (*m/z*) were performed using a Bruker MicroTof and a Waters-Micromass Quattro LCZ (ESI-MS). Cyclovoltammetry (CV) was conducted in a non-separated micro cell (6 mL, Metrohm) using a Ag/AgCl reference electrode (0.1 M *n*-$BuBF_4$ in MeCN: +0.21 V versus SHE), a glassy carbon counter electrode and a round Pt electrode (d=3 mm) used as working electrode. A PG-STAT 20 in combination with a VA 663 (Metrohm) was used as power source. The data were collected with GPES 4.6 (Eco-Chemie B.V.) software and analyzed with Origin Pro 2015. Ferrocene was used as internal standard. Size exclusion chromatography (SEC) was carried out with degassed THF as eluent at a flow rate of 1.0 mL/min at rt on a system consisting of a L6200A Intelligent Pump (Merck Hitachi), a set of two PLgel 5 μm MIXED-C columns (300×7.5 mm, Polymer Laboratories), and a Knauer RI differential refractometer detector. Data were analyzed with PSS WinGPC Compact V.7.20 software (Polymer Standards Service) based on calibration curves built upon polystyrene and poly(methyl

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methacrylate) standards (Polymer Laboratories Polystyrene Medium MW Calibration Kit S-M-10 to determine the molecular weight of styrene and Poly(methyl methacrylate) Medium MW Calibration Kit M-M-10 to determine the molecular weight of poly(n-butyl acrylate)) with peak molecular weights ranging from 1660 to 1,000,000 g/mol.

4.2. Synthesis of nitroxide 4 and alkoxyamine Pro-4

*4.2.1. (5S,6S,9R)-6-Isopropyl-9-methyl-1,3-diazaspiro[4.5] decane-2,4-dione (**5**).*[10b] According to literature protocols reported by *Munday*[10a] and *Edwards*,[10c] L-(-)-menthone (17.3 mL, 100 mmol, 1.0 equiv) was added to a suspension of KCN (7.16 g, 110 mmol, 1.1 equiv) and $(NH_4)_2CO_3$ (46.12 g, 480 mmol, 4.8 equiv) in EtOH/H_2O (1:1, 310 mL). The mixture was stirred at 60 °C for 17 h and was then cooled to 0 °C. The white precipitate formed was filtered and rinsed with H_2O to afford the crude product, which was further purified by recrystallization from 200 mL hot EtOH. The pure product **5** was obtained as colorless needles as a single diastereoisomer (20.3 g, 90.7 mmol, 90% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54–10.35 (br s, 1H, NH), 8.29 (s, 1H, NH), 1.76–1.41 (m, 6H, 3×CH_2), 1.31 (m, 2H, 2×CH), 0.99–0.77 (m, 10H, 3×CH_3, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.42 (CO), 156.50 (CO), 67.00 (C_q), 45.65 (CH), 44.24 (CH_2), 34.02 (CH_2), 27.80 (CH), 27.24 (CH), 23.16 (CH_3), 21.82 (CH_3), 21.38 (CH_2), 18.19 (CH_3).

*4.2.2. ((1S,2S,5R)-1-Amino-2-isopropyl-5-methylcyclohexyl) methanol (**6**).*[13] According to a modified protocol of *Munday*,[10a] the hydantoin **5** (20.3 g, 90.7 mmol, 1.0 equiv) was added to an aqueous H_2SO_4 solution (60%, 240 mL). The reaction mixture was stirred for 2 days at 150 °C. Then the dark solution was cooled to room temperature, filtered and washed with H_2O. After neutralization of the filtrate with NaOH, the water in the solution was removed by freeze-drying technology. Methanol was added to the resulting white solid to extract the product (amino acid). The suspension was stirred at 40 °C for 30 min and then filtered. After repeating this procedure three times, the combined filtrate was concentrated. The crude amino acid was obtained by removal of methanol, and was used without any further purification. The crude amino acid (16 g) and $NaBH_4$ (10.7 g, 284 mmol, 3.5 equiv) were suspended in THF (250 mL) under argon. A solution of I_2 (24.7 g, 97.2 mmol, 1.2 equiv) in THF (80 mL) was added dropwise to the reaction mixture. After ceasing of gas formation, the reaction mixture was heated to reflux. After refluxing for 18 h, the reaction mixture was cooled to rt and treated with methanol. The mixture was concentrated under vacuum and then redissolved with an aqueous KOH solution (20%, 260 mL). The resulting solution was refluxed for 3 h and then cooled to rt. After extraction with CH_2Cl_2, the collected organic phase was dried over $MgSO_4$ and concentrated under vacuum. Upon bulb to bulb distillation under reduced pressure, the pure amino alcohol **6** was obtained as a colorless oil (12.6 g, 68 mmol, 84% yield over two steps), which slowly crystallized at 0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 (d, J=10.5 Hz, 1H, CHH), 3.32 (d, J=10.5 Hz, 1H, CHH), 2.06 (pd, J=6.9, 1.9 Hz, 1H), 1.85 (br s, 3H, NH_2, OH), 1.76 (dq, J=12.7, 3.2 Hz, 1H), 1.61–1.50 (m, 3H), 1.35 (qd, J=12.9, 3.5 Hz, 1H), 1.17 (ddd, J=12.7, 3.4, 1.9 Hz, 1H), 1.04–0.93 (m, 1H), 0.93–0.76 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.80 (CH_2), 56.30 (C_q), 47.84 (CH), 46.45 (CH_2), 35.41 (CH_2), 28.00 (CH), 25.92 (CH), 24.60 (CH_3), 22.65(CH_3), 21.39 (CH_2), 18.81 (CH_3).

*4.2.3. (6S,7S,10R)-7-Isopropyl-10-methyl-2,13-dioxa-5-aza- dispiro [3.1.5^6.2^4]tridecane (**7**).* According to a modified procedure developed by *Carreira* et al.,[11] the amino alcohol **6** (1.85 g, 10.0 mmol, 1.0 equiv) was added to a solution of 3-oxetanone (792 mg, 11.0 mmol, 1.1 equiv), acetic acid (58 μL, 0.10 mmol, 10 mol %) and 4 Å MS (1.0 g) in CH_2Cl_2 (20 mL). After being stirred at rt for 4 days, the reaction mixture was concentrated under reduced pressure. Subsequent purification by FC (pentane: Et_2O, 3:1) afforded the pure product **7** as a colorless oil (2.18 g, 9.1 mmol, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (dd, J=7.0, 1.0 Hz, 1H), 4.75–4.66 (m, 2H), 4.57 (d, J=6.4 Hz, 1H), 3.84 (d, J=8.3 Hz, 1H), 3.37 (d, J=8.3 Hz, 1H), 2.10 (br s, 1H, NH), 1.90 (pd, J=6.9, 1.5 Hz, 1H), 1.82–1.62 (m, 2H), 1.58 (dq, J=13.2, 3.4 Hz, 1H), 1.45–1.26 (m, 2H), 1.11 (ddd, J=12.7, 3.5, 1.6 Hz, 1H), 1.03–0.81 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.62 (C_q), 86.74 (CH_2), 83.51 (CH_2), 75.75 (CH_2), 65.44 (C_q), 48.06 (CH_2), 47.89 (CH), 35.22 (CH_2), 29.41 (CH), 25.89 (CH), 24.84 (CH_3), 23.24 (CH_2), 22.40 (CH_3), 18.90 (CH_3). IR (neat): 3334, 2948, 2928, 2866, 1454, 1356, 1212, 1041, 976, 838 cm^{-1}. HRMS (ESI): calculated for $C_{14}H_{25}NO_2Na$ $[M+Na]^+$ m/z 262.1778, found 262.1773.

*4.2.4. tert-Butyl (((2R,6S,7S,10R)-2-(hydroxymethyl)-7-isopropyl-10-methyl-4-oxa-1-aza-spiro[5.5]undecan-2-yl)methyl)carbamate (**9**).* According to a modified procedure developed by *Carreira* et al.,[11] TMSCN (507 μL, 4.05 mmol, 1.5 equiv) was added to a solution of the compound **7** (647 mg, 2.70 mmol, 1.0 equiv) and $In(OTf)_3$ (30 mg, 54 μmol, 2 mol %) in CH_3CN (6 mL). The reaction mixture was stirred at rt overnight. An aqueous $NaHCO_3$ (sat.) was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic phase was then dried over $MgSO_4$ and concentrated under vacuum to afford the crude product **8** (915 mg), which was used without further purification. Under argon, LAH (512 mg, 13.5 mmol, 5.0 equiv) was slowly added to a solution of crude **8** in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was then stirred for further 30 min. Next, the reaction mixture was heated under reflux overnight. After cooling to 0 °C, H_2O (0.5 mL), aqueous NaOH (15%, 0.5 mL) and H_2O (1.5 mL) were added successively. The resulting suspension was filtered through Celite and washed with EtOAc. After concentration of the filtrate under vacuum, the crude amino alcohol (730 mg) was obtained. The crude amino alcohol and NEt_3 (565 μL, 4.00 mmol, 1.5 equiv) were dissolved in a mixture of CH_2Cl_2/MeOH (1:4, 20 mL). A solution of Boc_2O (766 mg, 3.50 mmol, 1.3 equiv) in MeOH (4.0 mL) was then added and the reaction mixture was stirred at rt overnight. After removal of the solvent under reduced pressure, the crude product was purified by FC (CH_2Cl_2: Et_2O, 6:1) to afford **9** as a colorless oil (790 mg, 2.13 mmol, 79% yield over three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 (t, J=6.7 Hz, 1H), 3.62 (t, J=10.7 Hz, 2H), 3.38–3.18 (m, 5H), 3.08 (d, J=11.3 Hz, 1H), 2.22–1.99 (m, 2H), 1.75 (dp, J=12.8, 3.2 Hz, 1H), 1.55–1.36 (m, 12H), 1.36–1.23 (m, 1H), 0.92–0.71 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.50, 80.27, 76.02, 71.21, 66.07, 54.88, 53.94, 48.28, 47.23, 44.40, 35.39, 28.46, 28.17, 26.02, 24.84, 22.60, 21.45, 19.43. IR (neat): 3372, 2953, 2868, 1691, 1504, 1458, 1367, 1252, 1171, 1115, 1086, 1047, 666 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{38}N_2O_4H$ $[M+H]^+$ m/z 371.2904, found 371.2901.

*4.2.5. tert-Butyl (((2R,6S,7S,10R)-7-isopropyl-2-(methoxy methyl)-10-methyl-4-oxa-1-aza-spiro[5.5]undecan-2-yl)methyl) (methyl)carbamate (**10**).* NaH (690 mg, 17.3 mmol, 5.0 equiv) was added to a solution of compound **9** (1.28 g, 3.45 mmol, 1.0 equiv) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature and then MeI (1.08 mL, 17.3 mmol, 5.0 equiv) was added dropwise. The resulting solution was allowed to warm to rt and stirring was continued overnight. H_2O was added and the resulting mixture was extracted with EtOAc (three times). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum. Purification by FC (pentane: Et_2O, 3:1) afforded the product **10** as a colorless oil (1.19 g, 3.10 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94–3.79 (m, 1H), 3.74 (d, J=11.4 Hz, 1H), 3.60–3.51 (m, 1H), 3.33–3.24 (m, 4H), 3.20–3.08 (m, 2H), 3.04–2.98 (m, 1H), 2.93–2.80 (m, 4H), 2.26 (dt, J=13.9, 2.7 Hz, 1H), 2.12–1.97 (m, 1H), 1.72–1.63 (m, 2H), 1.49–1.35 (m, 12H), 0.92–0.81 (m, 11H), 0.75–0.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.73,

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77.23, 75.75, 59.06, 53.78, 53.39, 48.73, 47.01, 36.99, 35.69, 28.54, 27.26, 25.85, 25.02, 22.53, 21.14, 18.97. IR (neat): 2952, 2869, 1697, 1457, 1389, 1255, 1161, 1108, 876, 773 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{42}N_2O_4H$ $[M+H]^+$ *m/z* 399.3217, found 399.3221.

*4.2.6. tert-Butyl (((2R,6S,7S,10R)-7-isopropyl-2-(methoxy methyl)-10-methyl-4-oxa-1-aza-spiro[5.5]undecan-2-yl)methyl) (methyl)carbamate-1-oxyl (**4**).* Peroxoacetic acid (39% in AcOH, 1.1 mL, 6.3 mmol, 2.5 equiv) was slowly added to a solution of compound **10** (1.0 g, 2.5 mmol, 1.0 equiv) in EtOAc (25 mL). The resulting mixture was then stirred at 50 °C for 2 days. H_2O was added to hydrolyze the excess oxidant, and the aqueous phase was extracted by EtOAc (three times). The combined organic layer was washed with aqueous sat. $NaHCO_3$, and dried over $MgSO_4$. After filtration and concentration under vacuum, purification by FC (CH_2Cl_2: Et_2O, 6:1) provided the nitroxide **4** as an orange oil (592 mg, 1.40 mmol, 57%). IR (neat): 2952, 2925, 2870, 1698, 1455, 1389, 1367, 1312, 1254, 1155, 1121, 1096, 876, 774 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{41}N_2O_5Na$ $[M+Na]+$ *m/z* 436.2908, found 436.2911.

*4.2.7. Methyl 2-(((2R,6S,7S,10R)-2-(((tert-butoxycarbonyl) (methyl) amino)methyl)-7-isopro-pyl-2-(methoxymethyl)-10-methyl-4-oxa-1-azaspiro[5.5]undecan-1-yl)oxy)propanoate (**Pro-4**).* Following a modified procedure reported by *Matyjaszewski*[12a] and *Kiriy*,[12b] pentamethyl-diethylenetriamine (PMDETA, 336 μL, 1.60 mmol, 2.0 equiv) was slowly added to a suspension of methyl 2-bromopropanoate (267 mg, 1.60 mmol, 2.0 equiv), CuBr (230 mg, 1.60 mmol, 2.0 equiv) and the nitroxide **4** (331 mg, 800 μmol, 1.0 equiv) in benzene under argon. After stirring at rt for 1 h, the product was isolated by FC (pentane: Et_2O, 3:1). The solvent after the column was rapidly removed at 10 °C under vacuum to provide the alkoxyamine **Pro-4** as a colorless oil as a mixture of the two diastereoisomers (367 mg, 730 μmol, 92% yield). The ratio of the two isomers could not be determined due to signal overlap in the ^1H NMR spectrum. ^1H NMR (300 MHz, $CDCl_3$): one isomer: δ 4.67–4.46 (m, 1H), 4.09–3.86 (m, 2H), 3.85–3.47 (m, 7H), 3.33–3.19 (m, 4H), 3.15–2.87 (m, 4H), 2.59–2.41 (m, 1H), 2.30–2.04 (m, 2H), 1.79–1.68 (m, 1H), 1.60–1.23 (m, 15H), 0.99–0.90 (m, 6H), 0.87–0.70 (m, 5H); the other isomer: δ 4.62 (q, *J*=6.9 Hz, 1H), 4.18 (d, *J*=14.6 Hz, 1H), 3.95 (dd, *J*=11.8, 2.2 Hz, 1H), 3.87–3.65 (m, 4H), 3.59 (d, *J*=11.3 Hz, 1H), 3.42–3.23 (m, 3H), 3.20 (s, 3H), 3.03 (d, *J*=10.0 Hz, 1H), 2.91 (s, 3H), 2.54 (d, *J*=14.8 Hz, 1H), 2.28–2.01 (m, 2H), 1.80 (d, *J*=13.1 Hz, 1H), 1.72–1.53 (m, 3H), 1.52–1.35 (m, 12H), 1.02–0.92 (m, 6H), 0.89–0.72 (m, 5H). The ^{13}C NMR of the two isomers of **Pro-4** couldn't be assigned due to the complexity of the spectrum. IR (neat): one isomer: 2954, 2871, 1755, 1696, 1454, 1391, 1159, 1105, 973, 878, 774 cm^{-1}; the other isomer: 2953, 2870, 1749, 1694, 1453, 1390, 1367, 1158, 1104, 973, 877, 731 cm^{-1}. HRMS (ESI) calculated for $C_{26}H_{48}N_2O_7Na$ $[M+Na]^+$ *m/z* 523.3354, found one isomer: 523.3361; the other isomer: 523.3365.

*4.2.7. (6S,8S,9S,12R)-9-Isopropyl-12-methyl-2,15-dioxa-4,7-diazadispiro[5.1.5^8.3^6]hexa-decan-3-one (**11**).* The Boc-protected amino alcohol **9** (503 mg, 1.36 mmol, 1.0 equiv) was dissolved in THF (10 mL) and the reaction mixture was cooled to 0 °C. Potassium *tert*-butoxide (229 mg, 2.04 mmol, 1.5 equiv) was then added slowly and the reaction mixture was allowed to warm to rt. After stirring overnight, aqueous NH_4Cl (sat.) was added. The resulting mixture was extracted with EtOAc (three times) and the combined organic phase was dried over $MgSO_4$ and concentrated. The pure carbamate **11** was obtained by FC (CH_2Cl_2: Et_2O, 1:2) as a white solid (374, 1.26 mmol, 93%). ^1H NMR (600 MHz, $CDCl_3$): δ 6.10 (br s, 1H), 4.01 (d, *J*=11.5 Hz, 1H), 3.90–3.77 (m, 3H), 3.70 (d, *J*=11.0 Hz, 1H), 3.39 (d, *J*=11.0 Hz, 1H), 3.31 (d, *J*=11.6 Hz, 1H), 3.23–3.09 (m, 1H), 2.13–1.98 (m, 2H), 1.78–1.69 (m, 1H), 1.57–1.48 (m, 1H), 1.48–1.37 (m, 1H), 1.29–1.08 (m, 2H), 0.95–0.78 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 153.81, 76.26, 74.09, 71.67, 54.43, 49.91, 48.03, 46.47, 46.45, 35.23, 29.82, 28.05, 26.02, 24.61, 22.45, 20.93, 19.19. IR (neat): 3324, 3248, 2953, 2869, 1700, 1491, 1283, 1119, 1090, 1036, 736, 706 cm^{-1}. HRMS (ESI): calculated for $C_{16}H_{28}N_2O_3Na$ $[M+Na]^+$ *m/z* 319.1992, found 319.1997.

4.3. Nitroxide mediated polymerization

4.3.1. General procedure for the polymerization of n-butyl acrylate. Under argon atmosphere, the alkoxyamine **Pro-4** and *n*-butyl acrylate (0.50 mL, 3.5 mmol) were added into a heat gun dried *Schlenk* tube. The reaction mixture was subjected to freeze-thaw cycles for three times and was then heated to the given temperature (see Table 1, 50–70 °C) for a specified time. The reaction mixture was cooled to room temperature, dissolved in CH_2Cl_2, and transferred into a vial. Solvent was evaporated under reduced pressure and the polymer was obtained after removing the unreacted monomer in a vacuum-drying cabinet at 60 °C overnight. The conversion of the polymerization was determined gravimetrically, and molecular weight and polydispersity index (PDI) were determined by GPC.

4.3.2. General procedure or the polymerization of styrene. Under argon, the alkoxyamine **Pro-4** and styrene (0.50 mL, 4.4 mmol) were added into a heat gun dried *Schlenk* tube. The reaction mixture was subjected to freeze-thaw cycles for three times, and was then heated to given temperature (see Table 2, 60 or 70 °C) for a specified time. The reaction mixture was cooled to room temperature, dissolved in CH_2Cl_2, and transferred into a vial. Solvent was evaporated under reduced pressure and the polymer was obtained after removing the unreacted monomer in a vacuum-drying cabinet at 60 °C overnight. The conversion of the polymerization was determined gravimetrically, and molecular weight and PDI were determined by GPC.

4.4. X-ray diffraction

Data sets for the compound **11** were collected with a D8 Venture Dual Source 100 CMOS diffractometer. Programs used: data collection: APEX2 V2014.5–0;[14] cell refinement: SAINT V8.34A (Bruker AXS Inc., 2013); data reduction: SAINT V8.34A (Bruker AXS Inc., 2013); absorption correction, SADABS V2014/2 (Bruker AXS Inc., 2014); structure solution SHELXT-2014;[15] structure refinement SHELXL-2014.[15] *R*-values are given for observed reflections, and wR^2 values are given for all reflections. Thermals ellipsoids are shown with 50% probability. *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

X-ray crystal structure analysis of 11: A colorless plate-like specimen of $C_{16}H_{28}N_2O_3 \cdot CH_4O$, approximate dimensions 0.084 mm×0.090 mm×0.254 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1078 frames were collected. The total exposure time was 19.01 h. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 10,240 reflections to a maximum θ angle of 68.46° (0.83 Å resolution), of which 3268 were independent (average redundancy 3.133, completeness=98.3%, R_{int}=2.60%, R_{sig}=2.69%) and 3125 (95.62%) were greater than $2\sigma(F^2)$. The final cell constants of a=8.3182(2) Å, b=9.6473(2) Å, c=11.6026(3) Å, β=99.9790(10)°, volume=917.00(4) Å^3, are based upon the refinement of the XYZ-centroids of 7487 reflections above 20 σ(I) with 7.736°<2θ<136.9°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.915. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8470 and 0.9450. The final anisotropic full-matrix

least-squares refinement on F^2 with 227 variables converged at $R1$=2.70%, for the observed data and w$R2$=6.70% for all data. The goodness-of-fit was 1.032. The largest peak in the final difference electron density synthesis was 0.157 $e^-/Å^3$ and the largest hole was −0.121 $e^-/Å^3$ with an rms deviation of 0.030 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.190 g/cm^3 and F(000), 360 e^-.

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Supplementary data

Supplementary data (Crystallographic data (excluding structure factors) for compound **11** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC1445405. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk.)) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.008.

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