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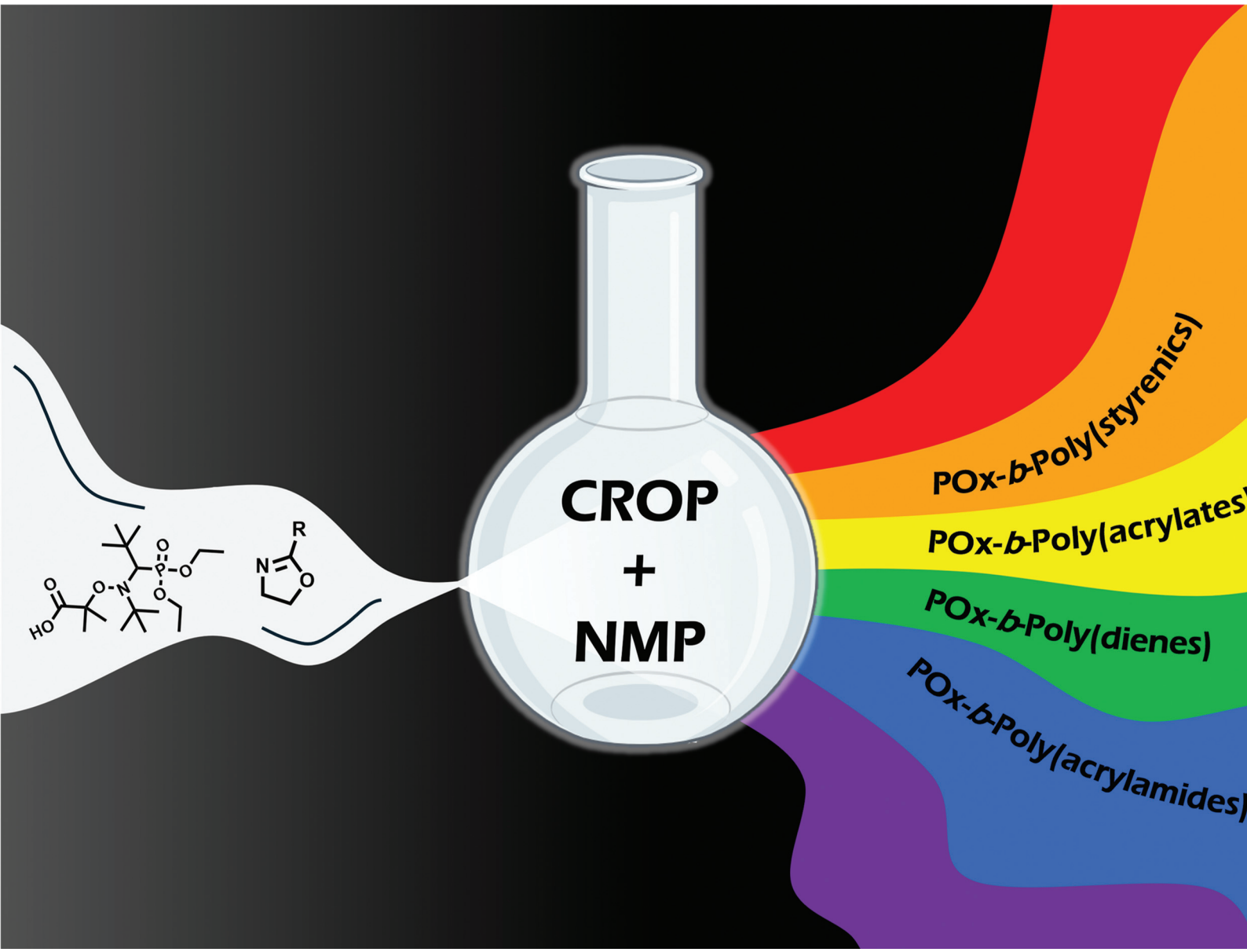

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Expanding the poly(2-oxazoline) block copolymer possibilities through nitroxide mediated polymerisation†

James Lefley and C. Remzi Becer *

In recent years, poly(2-oxazoline)s (POx) have become a sought-after biomaterial to replace PEG. However, access to POx based block copolymers is rather limited and their combination with controlled radical polymerization (CRP) techniques is required. Herein, we report the combination of cationic ring opening polymerization (CROP) and nitroxide mediated radical polymerization (NMP) to enable block copolymerization of poly(2-oxazoline)s with styrenics, acrylics, 1,3-dienes, and acrylamides as the second block. A well-defined poly(2-ethyl-2-oxazoline) macroinitiator has been prepared *via* CROP and *in situ* termination *via* the carboxylic acid functional group of BlocBuilder alkoxyamine has been achieved with a functionalization efficiency of 78%. Four different monomers in each class have been copolymerized *via* NMP and gel permeation chromatography analysis allowed us to identify the suitable set of comonomers to be utilized in block copolymerization with POx in an efficient, facile, metal- and sulfur-free polymerization environment.

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Introduction

Poly(2-oxazoline)s and their block copolymers are increasingly gaining interest as a major class of polymeric materials. They exhibit excellent water solubility,[1] biocompatibility,[2] and *in vivo* stealth properties,[3–5] thus, making them highly suitable for biomedical applications. Additional features such as thermoresponsive behavior[6,7] and the ability to form self-assembled nanostructures from amphiphilic copolymers[8–10] further enhance their appeal. Their facile synthesis *via* CROP and extensive customizability has established POx as a versatile platform for block copolymer synthesis, allowing numerous combinations in block composition and order to fine tune properties for specific applications.[11] Consequently, combining POx with other polymer classes can create novel block copolymers with potentially unique physical and chemical properties for further study.

As a result, the combination of CROP with other CRP techniques has garnered significant attention in the past few years. We have recently published a review on the synthetic methods for conjugating POx with vinyl polymers by highlighting the reported combinations of CROP with CRP techniques, such as RAFT and ATRP.[12] Of the main synthetic methods used, the macroinitiator route is one of the most common pathways for synthesizing POx-*b*-vinyl copolymers. In this method, a vinyl polymer is propagated from a POx-based macroinitiator synthesized *via* CROP and terminated with a compatible CRP initiator. Examples include terminating POx with functional CTAs or using a heterofunctional initiator for chain extension *via* RAFT.[3,13–18] Similarly, terminating POx with a carboxylic acid-functionalized ATRP initiator or using a heterofunctional initiator allows chain extension *via* ATRP.[19–21]

Nitroxide mediated polymerization (NMP) is another type of CRP that traditionally offers excellent control over the polymerization of styrenic type monomers. Briefly, thermolysis of a unimolecular initiator yields the initiating radical species and a stable nitroxide radical. Reversible capping and uncapping of the nitroxide radical onto the propagating species affords very good control of the polymerization by limiting irreversible bimolecular termination of the propagating radicals. Seen as one of the first examples of a CRP technique,[22] NMP is tolerant to a variety of functionalities, encompasses a broad range of monomers, and requires no metal catalysts or thio-containing CTAs,[23] making it a powerful synthetic technique in polymer chemistry.

However, examples of combining CROP and NMP seldom exist in the literature. In 1997, Sogah and coworkers used heterofunctional initiators with NMP, CROP, and AROP initiating functionalities for consecutive polymerizations to synthesize comb polymers.[24] A year later, they reported another hetero-

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK.
E-mail: Remzi.Becer@warwick.ac.uk

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functional NMP and CROP initiator for simultaneous controlled polymerizations, producing poly(styrene) (PS) and poly (2-phenyl-2-oxazoline) (PPhOx) block copolymers with high molecular weights (33.5 kDa) with moderate dispersities ($Đ$ = 1.40).[25] Nearly a decade later, Wang and Brittain adapted this procedure to create binary mixed homopolymer brushes *via* simultaneous polymerization of styrene (S) and 2-phenyl-2-oxazoline (PhOx).[26] In 2009, the first POx-based NMP macroinitiator was reported by Ibrahim and Voit.[27] They used an alkoxyamine chloride (TIPNO-Cl) initiator to synthesize poly(2-methyl-2-oxazoline) (PMeOx) *via* CROP, followed by chain extension with S *via* NMP, yielding PMeOx-*b*-PS diblock copolymers. However, TIPNO-Cl initiation resulted in poor control and broad dispersities for CROP ($Đ$ = 2.1). To address this, Amiel and coworkers synthesized TIPNO-functionalized PMeOx macroinitiators using a more reactive alkoxyamine iodide initiator (TIPNO-I) or by terminating with TIPNO-amine.[28] The termination strategy proved to be most successful, producing well-defined PMeOx-*b*-PS diblock copolymers with narrow molecular weight distributions ($Đ$ = 1.2), though the maximum PS conversion was 23%.

BlocBuilder MA (also known as MAMA-SG1) was developed by Tordo and coworkers around the same time as the TIPNO alkoxyamine and offers similar monomer compatibility.[29] The highly labile SG1-based alkoxyamine provides excellent control over styrenic and acrylate monomers with good control over diene[30,31] and acrylamide[32,33] monomers too. Additionally, BlocBuilder MA has been commercially available and produced on an industrial scale by Arkema since 2005.[34] Therefore, its near-universal compatibility, commercial availability, and simple post-polymerization purification process makes NMP with BlocBuilder MA an ideal synthetic technique. Hence, the integration of CROP and NMP polymerization techniques through BlocBuilder MA presents a powerful avenue for the copolymerization of POx with a diverse array of vinylic monomers. This strategy holds promise for producing unique copolymer combinations, particularly by merging the stimuli-responsive properties of various vinyl polymers with the biocompatibility of POx for advanced drug delivery or gene therapy applications. Furthermore, in a biomedical context, utilizing a metal- and sulfur-free polymerization environment for the synthesis of such copolymers presents a significant advantage of using this system compared to other CRP techniques.

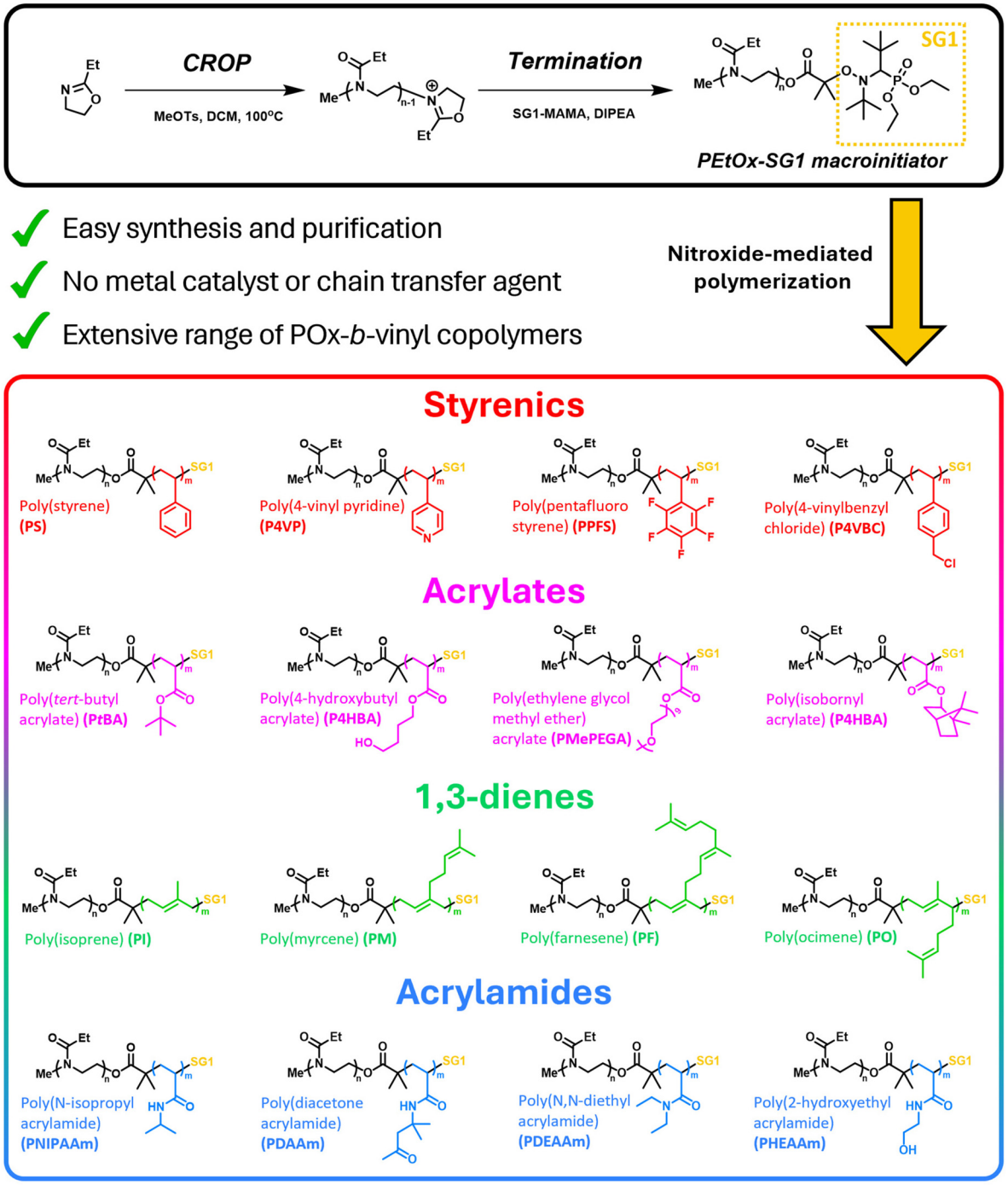
Herein, we report the synthesis of a well-defined, SG1-functionalized PEtOx macroinitiator *via* CROP. Termination of the living POx chain with the carboxylic acid moiety of BlocBuilder MA affords the SG1-terminated PEtOx macroinitiator and was characterized by nucelar magnetic resonance (NMR) and gel permeation chromatography (GPC) analysis. To demonstrate the versatility of the macroinitiator, various styrenic, acrylate, diene, and acrylamide monomers were chain extended using PEtOx-SG1 using fixed reaction conditions for every reaction unless stated otherwise (THF, 2.5M, 110 °C, 24 hours). All diblock copolymers were characterized by NMR and GPC analysis and their purification methods are outlined. The extensive copolymer library produced from a single macroinitiator represents one of the most comprehensive POx macroinitiators for conjugation with vinyl polymers ever reported.

Results and discussion

Synthesis of the PEtOx-SG1 macroinitiator is outlined in Scheme 1. It proceeds *via* CROP of EtOx followed by termination of the living chain with excess BlocBuilder MA. Optimizing the reaction conditions was crucial to ensure high functionalization efficiency with the alkoxyamine. Initial syntheses were conducted in acetonitrile and chlorobenzene, two solvents known to be effective for CROP of 2-oxazolines.[35,36] However, due to the poor solubility of BlocBuilder MA in these solvents, termination efficiencies were low. Therefore, CROP of EtOx was performed in DCM at a lower temperature of 100 °C in a sealed microwave vial. Fig. 1A shows full conversion of EtOx ([M] : [I] = 19) in 90 minutes. Then, 4 equivalents of SG1-MAMA and DIPEA were added to terminate the polymerization and functionalize the ω-chain with the alkoxyamine. GPC analysis of PEtOx-SG1 shows a monomodal distribution with a narrow dispersity of 1.12 (Fig. 1B). The theoretical and obtained molecular weights for PEtOx-SG1 are in very good agreement with each other ($M_{n,\,theor}$ = 2178.67 Da *vs.* $M_{n,\,GPC}$ = 2200 Da) thus confirming DCM to be a suitable solvent for CROP of EtOx. ^{1}H NMR spectroscopic analysis revealed a functionalization efficiency of 78% by comparing the integrals of the methyl –CH_3 protons of the α-chain end and the ethoxy –CH_3 protons of SG1 end group (Fig. 1A). The steric hinderance of the bulky terminating agent is ascribed to non-complete functionalization of the PEtOx chain. MALDI-ToF MS analysis was conducted to determine end group fidelity of PEtOx-SG1 but unfortunately none of the multiple distributions could be assigned due to the spontaneous dissociation of the nitroxide end group in mass spectrometry.[37–39]

Due to the versatility of BlocBuilder MA, a wide range of monomers can be polymerized in a controlled manner. Therefore, to demonstrate the compatibility of PEtOx-SG1, we selected four monomers from styrenic, acrylate, diene, and acrylamide monomer classes producing a 16-copolymer library. The conjugation of poly(2-oxazoline)s with styrenics, acrylates, and acrylamides have been previously reported. However, to the best of our knowledge, conjugation with dienes has not been documented and offers a unique new type of block copolymer combination, potentially opening the field to POxylated rubbers for medical implants or devices.

All polymerizations targeted a 100 : 1 monomer-to-macroinitiator ratio, producing block copolymers with large vinyl polymer mass fractions to simplify purification *via* precipitation into a non-solvent. For block copolymers where precipitation was unfeasible, dialysis or liquid–liquid extraction was utilized. To promptly screen suitable monomers, all polymerizations were conducted in THF at 110 °C for 24 hours with a 2.5M monomer concentration unless stated otherwise. Optimizing reaction conditions was beyond the scope of this study and will



Scheme 1 Synthesis of the PEtOx-SG1 macroinitiator and the diblock copolymers formed *via* nitroxide mediated polymerization with a variety of styrenic, acrylate, diene and acrylamide monomers.

be addressed in future work in individual copolymer studies. Full characterization data of the copolymer library can be found in Table 1. GPC traces are shown in Fig. 2 and ^{1}H NMR analysis of all copolymers can be found in the ESI (Fig. S1–S4†).

NMP is highly suitable for controlled polymerization of styrenic monomers, offering narrow dispersities and precise molecular weight control. Chain extension of PEtOx-SG1 with S, 4VP, and PFS resulted in narrow dispersities ($Đ$ = 1.09–1.18) for **PS**, **P4VP** and **PPFS** (Fig. 2A1–3). Previous reports on POx-*b*-PS copolymers include Becer *et al.* who used a heterofunctional CROP/ATRP initiator for PEtOx and PS conjugation, yielding diblock copolymers with $Đ$ = 1.27.[21] Our approach using PEtOx-based NMP macroinitiators achieved better control, producing diblock copolymers with a narrower disper-

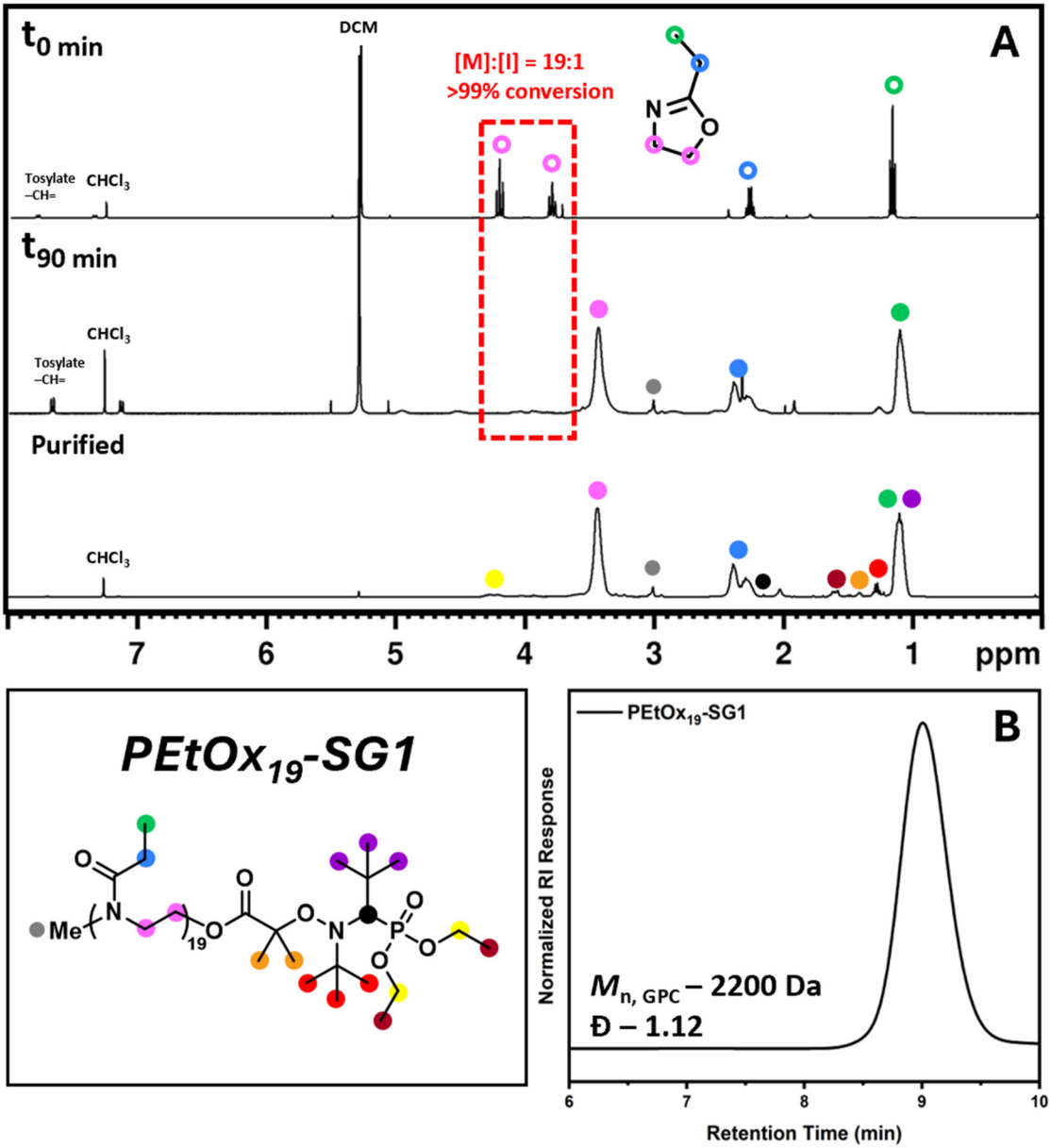


Fig. 1 (A) ^{1}H NMR spectra of the reaction mixture before polymerization ($t_{0\ min}$), at 90 minutes showing full conversion of EtOx ($t_{90\ min}$) and the purified SG1-functionalized macroinitiator (purified). (B) GPC trace of the purified PEtOx-SG1. Measurement performed using THF (2% TEA and 0.01% BHT) as the eluent. PMMA standards were used for the calibration.

sity ($Đ$ = 1.18). These findings align with other POx-*b*-PS systems synthesized *via* termination and chain extension using functional CRP initiators such as RAFT[13] and NMP.[28] Recently, de Menezes and Felisberti synthesized PEtOx-*b*-P4VP block copolymers *via* ATRP using a PEtOx macroinitiator. Despite achieving average termination efficiencies (38–54%), narrowly disperse block copolymers were synthesized ($Đ$ = 1.20).[19] In this study, the PEtOx-SG1 synthesis achieved a higher functionalization efficiency (78%), producing a PEtOx-*b*-P4VP diblock copolymer with superior dispersity ($Đ$ = 1.09) and, consequently, less unfunctionalized PEtOx homopolymer remaining post polymerization. Although, a high molecular weight shoulder can be seen in the GPC trace of **P4VP** (Fig. 2A2), indicating some chain coupling reactions. A broader dispersity ($Đ$ = 1.72) was observed for **P4VBC** (Fig. 2A4) indicating a loss of control of the polymerization. Under the set conditions, NMP of PFS with PEtOx-SG1 showed the highest monomer conversion (91%) among the four styrenic monomers. S and 4VP also achieved high conversions (79% and 86% respectively), while 4VBC had the lowest conversion (73%) after 24 hours. The large mass fraction of the styrenic block in these copolymers allows for easy removal of the unfunctionalized PEtOx homopolymer *via* precipitation into cold methanol or acetonitrile (Table S1†).

Table 1 List of PEtOx-based diblock copolymers synthesized *via* NMP

Polymer	Conc. [M]	[M] : [PEtOx-SG1][a]	Conv.[a] (%)	DP_{theo} [b]	DP_{NMR} [a]	$M_{n,\,theo}$ [c] (kDa)	$M_{n,\,GPC}$ (kDa)	$Đ$
PS	2.5	102	86	112	142	13.9	15.6[d]	1.18[d]
P4VP	2.5	110	79	112	84	14.0	21.7[e]	1.09[e]
PPFS	2.5	106	91	123	—	26.0	18.2[d]	1.14[d]
P4VBC	2.5	110	73	103	140	17.9	17.0[d]	1.72[d]
P*t*BA	2.5	113	77	112	92	16.5	6.6[d]	1.31[d]
PIBOA	2.0	114	98	144	99	32.0	21.2[d]	1.22[d]
PMePEGA	1.0	50	70	45	33	23.8	7.4[d]	1.35[d]
P4HBA	2.0	185	95	225	244	34.6	21.5[e]	1.94[e]
PI	2.5	70	99	88	7	8.2	3.4[d]	1.22[d]
PM	2.5	97	75	94	65	15.0	11.1[d]	1.21[d]
PO	2.5	[f]	[f]	[f]	[f]	[f]	2.9[d]	1.28[d]
PF	2.5	[f]	[f]	[f]	[f]	[f]	2.8[d]	1.31[d]
PNIPAAm	2.5	111	28%	40	38	6.7	5.5[d]	1.30[d]
PDAAm	2.5	97	>99%	124	[f]	23.1	14.9[d]	2.41[d]
PDEAAm	2.5	116	92%	137	[f]	19.6	9.6[d]	1.32[d]
PHEAAm	1.5M	107	>99%	137	[f]	18.0	12.4[e]	1.69[e]

[a] Determined by ^{1}H NMR. [b] Assuming 78% functionalization efficiency – calculated by ([M] : [PEtOx-SG1] × Conversion)/0.78. [c] Calculated using DP_{theor}. [d] Determined by THF GPC (2% TEA + 0.01% BHT). [e] Determined by DMF GPC (5 mM NH_4BF_4). [f] Unable to determine due to peak overlap in NMR.

The development of the SG1 alkoxyamine in the early 2000s enabled controlled polymerization of acrylic monomers *via* NMP.[29] Chain extension of PEtOx-SG1 with *t*BA, IBOA, and MePEGA yielded block copolymers **P*t*BA**, **PIBOA**, and **PMePEGA** with fairly narrow dispersities ($Đ$ = 1.22–1.35) (Fig. 2B1–3). Chain extension of *t*BA *via* NMP using PEtOx-SG1 showed poorer control compared to RAFT using a trithiocarbonate functionalized PEtOx macroinitiator ($Đ$ = 1.31 *vs.* $Đ$ = 1.19) reported by Krieg *et al.*[13] However, **PMePEGA** synthesized *via* NMP using PEtOx-SG1 had similar dispersities to PEtOx-*b*-PeTEGA copolymers synthesized *via* RAFT[14] ($Đ$ = 1.35 *vs.* $Đ$ = 1.30), indicating comparable control for polymerizing oligo/polyethylene glycol acrylic monomers using RAFT and NMP functional POx macroinitiators. A high molecular weight shoulder observed for **PIBOA** (Fig. 2B2) indicates the presence of some chain coupling reactions. NMP of 4HBA produced **P4HBA** diblock copolymer with a broad dispersity ($Đ$ = 1.94), indicating poor control and loss of polymerization livingness (Fig. 2B4). Like styrenic monomers, the propagation rates for acrylates using PEtOx-SG1 are generally fast, with high conversions (70–98%) achieved after 24 hours at 110 °C.

The versatility of the SG1 alkoxyamine is further demonstrated by its control over the polymerization of diene monomers. NMP of isoprene and β-myrcene with the PEtOx-SG1 macroinitiator produced narrowly disperse diblock copolymers **PI** and **PM**, with dispersity values $Đ$ = 1.22 and $Đ$ = 1.21 respectively. However, **PI** showed a significant discrepancy between theoretical DP (DP = 88) and NMR DP (DP = 7) (Table 1), likely due to the low boiling point of isoprene (34 °C) causing monomer loss during N_2 purging and/or condensation of the monomer during the reaction. The GPC chromatogram of **PI** (Fig. 2C1) shows a small molecular weight shift, suggesting a low DP for the poly(isoprene) block. While **PM** (Fig. 2C2) shows a clear shift, indicating successful chain extension with high conversion (75%). The large poly(myrcene) block allowed easy purification *via* precipitation into acetonitrile (Table S1†). A key feature of poly(dienes) is the stereochemistry of the polymer backbone, yielding 1,4-, 3,4-, and 1,2-products. For radical polymerization, the 1,4-addition is predominantly favoured. Analysis of Fig. S5B† reveals **PM** consists of 92% of the 1,4-product, 6% of the 3,4-product, and 2% of the 1,2-product, which corroborates nicely with similar CRP studies of β-myrcene.[40–42] The presence of a small percentage of pendant alkenyl groups in **PM** holds potential for further functionalization *via* thiol–ene click chemistry. Ocimene, an isomer of β-myrcene, was also polymerized with the PEtOx-SG1 macroinitiator but showed less successful propagation compared to β-myrcene (Fig. 2C3). The GPC chromatogram of the **PO** diblock copolymer closely matches the PEtOx-SG1 macroinitiator with a slight high molecular weight shoulder, suggesting that partial chain extension to oligomeric lengths was achieved within 24 hours. This slow propagation is likely attributed to the stability of the propagating radical. Ocimene produces a more stable secondary radical compared to the primary radical of β-myrcene, resulting in much slower propagation rates (Fig. S6†). The final diene monomer, farnesene, exhibited similar reactivity to ocimene. The GPC chromatogram of **PF** (Fig. 2C4) shows minimal peak shift, with only a small high molecular weight shoulder after 24 hours, indicating very poor conversion. This low conversion is likely due to the monomer's composition, which includes a mixture of farnesene isomers. Only β-farnesene, the primary propagating species, participates in the radical polymerization, while the other isomers do not or do so incredibly slowly. Further optimization of the reaction conditions would be necessary to achieve successful polymerization of isoprene, ocimene and farnesene.

Lastly, to showcase the extensive compatibility of the PEtOx-SG1 macroinitiator with a variety of monomers classes, acrylamides NIPAAm, DAAm, DEAAm, and HEAAm were polymer-

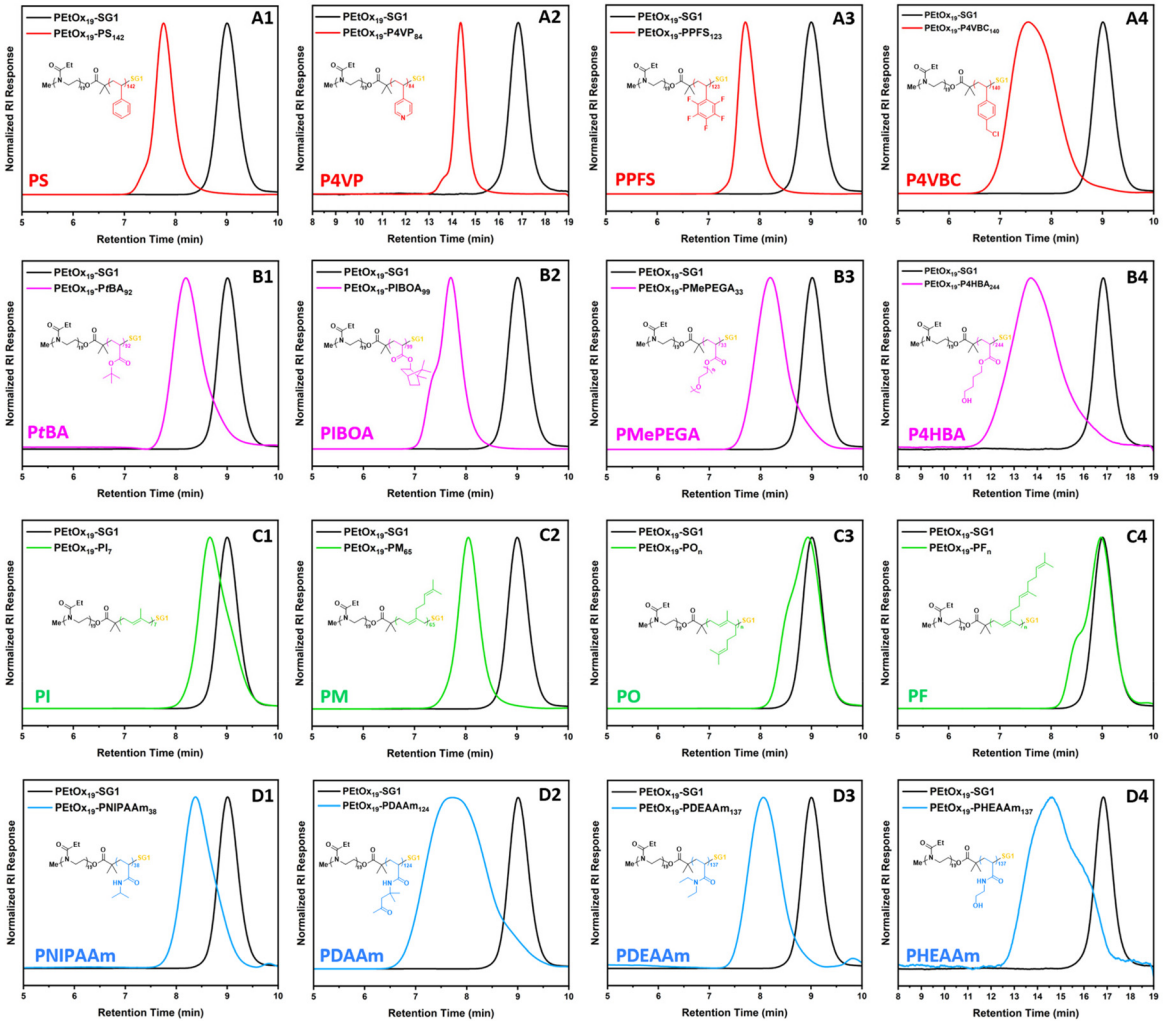
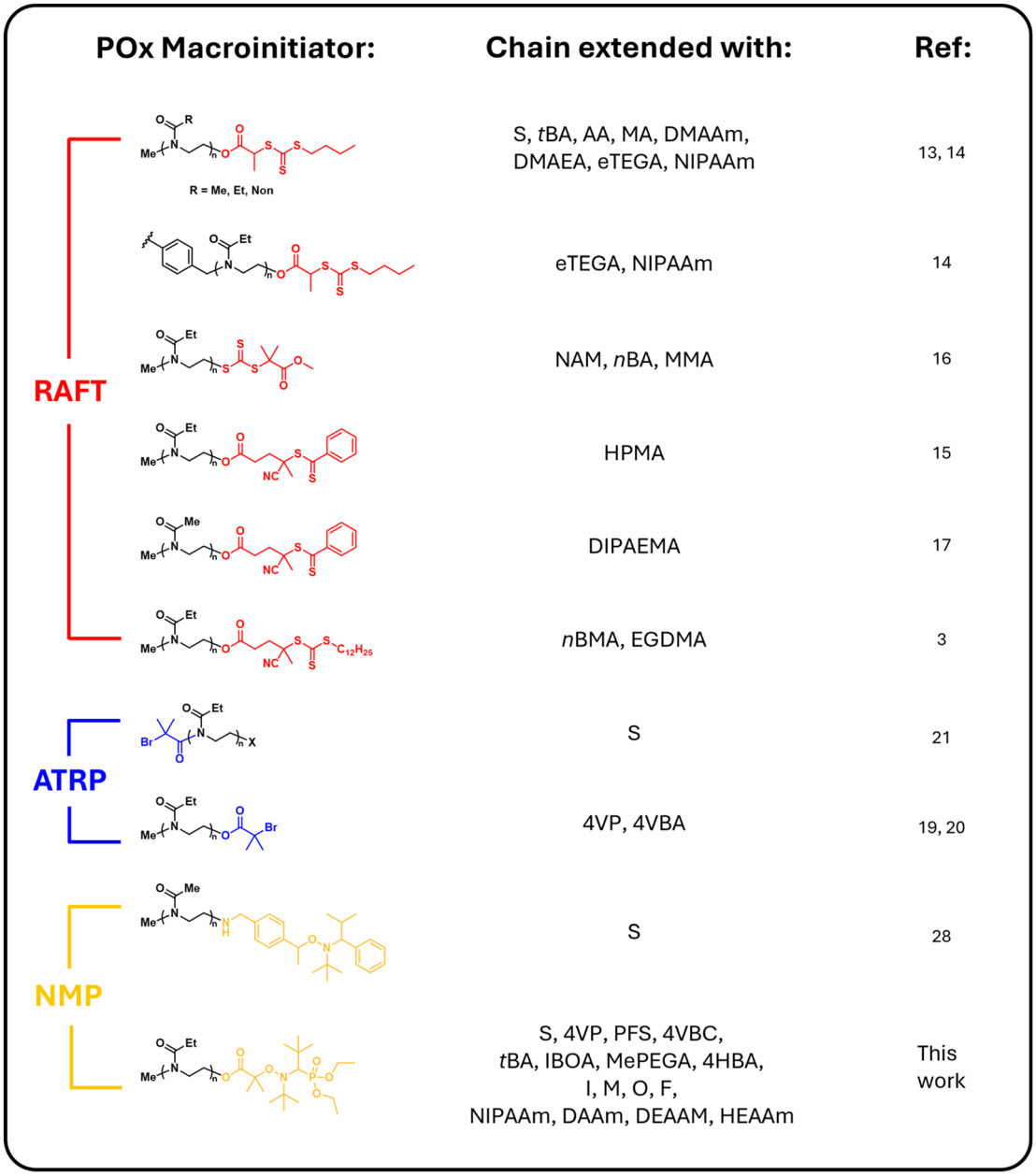


Fig. 2 GPC traces of PEtOx-styrenic diblock copolymers (A1–A4), PEtOx-acrylate diblock copolymers (B1–B4), PEtOx-diene diblock copolymers (C1–C4) and PEtOx-acrylamide diblock copolymers (D1–D4) synthesized *via* NMP. All samples ran using THF (2% TEA, 0.01% BHT) as the eluent apart from P4VP (A2), P4HBA (B4) and PHEAAm (D4) which were ran using DMF (5 mM NH_4BF_4) as the eluent. PMMA standards were used for the calibration.

ized *via* NMP. These block copolymer combinations could form the basis of a further study into their potentially interesting thermoresponsive solution behaviours. Chain extension of PEtOx-SG1 with these acrylamide monomers yielded varied results in overall control. Fig. 2D1 and D3 show that **PNIPAAm** and **PDEAAm** produced monomodal molecular weight distributions with moderate dispersities ($Đ$ = 1.30 and $Đ$ = 1.32, respectively). Although the polymerization was relatively controlled, NIPAAm conversion was surprisingly low (28%) after 24 hours, compared to the near-complete conversion for DEAAm (Table 1). Historically, it has been challenging to synthesize NIPAAm copolymers *via* NMP, often yielding broad molecular weight dispersities.[43,44] Zetterlund *et al.* found that NMP of NIPAAm in DMF was hindered by chain transfer to solvent, limiting molar mass.[45] The low NIPAAm conversion here may be due to chain transfer to THF. In contrast, using a RAFT functionalized PEtOx macroinitiator achieves greater control over the polymerization of NIPAAm.[14] With very narrow dispersities ($Đ$ < 1.10) obtained for PEtOx-*b*-PNIPAAm copolymers synthesized *via* RAFT, compared to NMP ($Đ$ = 1.30). NMP of DAAm using the PEtOx-SG1 macroinitiator yielded **PDAAm** with a very broad dispersity ($Đ$ = 2.41) (Fig. 2D2), indicating poor control over the polymerization. Despite this, full conversion was achieved within 24 hours, indicating a faster propagation rate compared to NIPAAm and DEAAm. Similarly, NMP of HEAAm showed a substantial lack of control, yielding a **PHEAAm** diblock copolymer with a broad dispersity ($Đ$ = 1.69) but complete monomer conversion within 24 hours (Fig. 2D4). Due to the double hydrophilic nature of **PNIPAAm**, **PDEAAm**, and **PHEAAm**, dialysis was used to remove residual PEtOx homopolymer as their different solubilities could not be exploited. In contrast, **PDAAm** was sufficiently hydrophobic enough to be purified *via* DCM/H_2O extraction (Table S1†).

Scheme 2 summarizes the current literature on POx-based macroinitiators functionalized with a CRP initiator. While the combination of CROP with RAFT remains the most extensively



Scheme 2 Overview of current POx-based macroinitiators used for combining CROP with CRP techniques such as RAFT, ATRP, and NMP.

studied pairing of CROP with a CRP technique, we aim to demonstrate that combining CROP with NMP, using an SG1-functionalized POx macroinitiator, can offer a similarly versatile platform. This approach is compatible with a wide range of monomer types and has the added advantage of being carried out in a metal- and sulfur-free polymerization environment.

Conclusion

In conclusion, we have synthesized a well-defined PEtOx-based macroinitiator bearing an SG1 functional group for nitroxide-mediated polymerization. Chain extension with various styrenic, acrylate, diene, and acrylamide monomers demonstrated the versatility of this macroinitiator for metal catalyst-free and CTA-free CRP. Styrenic and acrylate monomers showed the highest compatibility with PEtOx-SG1, characterized by low dispersities and high conversions. Unique combinations of **PPFS**, **PM**, and **PDEAAm** with PEtOx yielded well-defined copolymers with narrow dispersities, offering the potential for novel future studies. This work may pave the way for future in-depth studies into new POx-*b*-vinyl diblock copolymers, with a focus on optimizing their synthesis and investigating their unique properties.

Author contributions

JL performed all experimental work. CRB has supervised the work and supported the writing and editing.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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