

# Living Polymerization of 2-Ethylthio-2-oxazoline and Postpolymerization Diversification

You-Chi Mason Wu<sup>1b</sup> and Timothy M. Swager<sup>\*1b</sup>

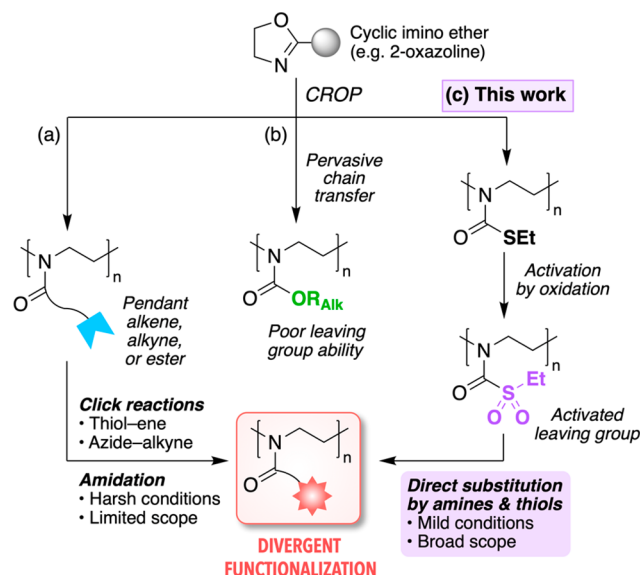
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

**S** Supporting Information

**ABSTRACT:** The postpolymerization modification of polymers produced by living polymerization is an attractive method to create precision nanomaterials. We describe the living cationic ring-opening polymerization of a 2-alkylthio-2-oxazoline to furnish a polythiocarbamate. The polythiocarbamate is activated toward substitution by *N*- and *S*-nucleophiles via oxidation of the *S* to an  $\text{SO}_2$ . Mild substitution conditions provide broad functional group tolerance, constituting a versatile postpolymerization modification platform with access to a diversity of polyureas and polythiocarbamates. We further demonstrate the utility of this strategy by synthesizing and functionalizing block copolymers.

The ability to tailor chemical functionalities of polymers dictates their practical applications. The development of new functional polymers is often limited by the polymerization reaction, and small changes in monomers can compromise access to controllable compositions and molecular weights.<sup>1,2</sup> Postpolymerization modification (PPM) can address these challenges, wherein functional groups that would be incompatible with a polymerization can be used for the diversification of polymer structures.<sup>1,2</sup> Furthermore, *in situ* PPM within complex systems can confer stimuli-responsive properties, with implications in sensing, drug delivery, and dynamic materials.<sup>3–6</sup>

PPM platforms ideally utilize modification chemistries that are mild and specific, such as click chemistry or nucleophilic substitution of activated leaving groups.<sup>1,7–10</sup> PPM methods often employ polymers created by radical polymerization, whereas compatibility with cationic polymerizations constrains the available platforms for PPM.<sup>2</sup> Among the most extensively investigated monomers for cationic ring-opening polymerization (CROP) are cyclic imino ethers, such as oxazolines.<sup>11,12</sup> The living character of oxazoline polymerization enables controlled molecular weight and dispersity, as well as access to complex architectures such as block and graft copolymers.<sup>13</sup> Polyoxazolines have wide utility in biomedical and materials applications as a result of their desirable features including robust polymerization, biocompatibility, and chemical versatility.<sup>14–16</sup> Critical to these applications is the incorporation of functional groups that tailor the chemical, biological, thermomechanical, and other properties of the polymers (Figure 1). To this end, polyoxazolines with pendant alkenes and alkynes have been reported, allowing functionalization via click chemistries such as thiol–ene addition and azide–alkyne cycloaddition (Figure 1a).<sup>5,17,18</sup> Direct substitution by nucleophiles is often a more straightfor-



**Figure 1.** PPM strategies based on CROP of oxazoline derivatives. (a) Elaboration of polyoxazolines with pendant alkenes and alkynes by click chemistries, or with pendant esters by amidation (refs 17–22). (b) Polymerization of 2-alkoxy-2-oxazolines (ref 25). (c) This work: Living CROP of 2-ethylthio-2-oxazoline and postpolymerization functionalization.

ward and versatile PPM method. Methyl ester-containing polyoxazolines undergo amidation with primary amines, but this method has limited scope, and to avoid harsh conditions additional manipulations were undertaken to convert the methyl ester to an activated ester (Figure 1a).<sup>19–22</sup> As such, the development of more general, versatile, and robust PPM strategies warrants further attention.

Investigations of oxazolines beyond those with C-based substituents at the 2-position are limited. Miyamoto et al. disclosed the polymerization of cyclic amine-substituted oxazolines (i.e., pseudoureas), but the polymerization was hindered by substituents larger than pyrrolidinyl, and living character was not demonstrated.<sup>23,24</sup> The same group investigated the polymerization of 2-alkoxy-2-oxazolines (i.e., cyclic iminocarbonates) and found that pervasive chain transfer occurred as a result of nucleophilic attack of the monomer on the alkoxy group of the active chain end (Figure 1b), unless the monomer contained a bulky neopentoxy group.<sup>25</sup>

Received: June 5, 2019

Published: July 31, 2019

We were encouraged to explore the polymerization of novel oxazolines by reports of nucleophilic diversification of carbamates by displacement of the *O*-substituent.<sup>26–28</sup> Nonetheless, the substitution is particularly challenging for *N,N*-disubstituted carbamates and requires a highly activated leaving group (e.g., 4-nitrophenolate) or activation by a Lewis acid (e.g.,  $\text{AlMe}_3$ ).<sup>26,28</sup> In these cases, however, the corresponding cyclic imino ether monomers are synthetically difficult to access and polymerize, and substitution conditions are harsh.

Our approach to create oxazolines for PPM was inspired by biological studies showing that thiocarbamate-based pesticides are oxidized to the sulfinyl or sulfonyl species in cells, upon which they act as potent *S*-carbamoylating agents.<sup>29–33</sup> As a result, we set out to create similar structures by the CROP of a 2-alkylthio-2-oxazoline (Figure 1c). We hypothesized that the alkylthio side chain would suppress chain transfer processes relative to the alkoxy side chain owing to the diminished driving force of the ensuing  $\text{C}=\text{S}$  vs  $\text{C}=\text{O}$  bond formation. Subsequently, postpolymerization activation of the thiocarbamates by oxidation would enable substitution by moderate nucleophiles. This scheme constitutes a versatile and atom-economical platform to access 2-substituted polyoxazolines—alternatively viewed as *N,N*-linked polyureas and polythiocarbamates—with broad functional group tolerance (Figure 1c).

The 2-ethylthio-2-oxazoline monomer (**1**) was synthesized in two steps from ethanolamine<sup>34,35</sup> and purified by distillation from  $\text{CaH}_2$  under reduced pressure. Monomer **1** was polymerized at 90 °C in PhCN using MeOTs as the initiator to yield polythiocarbamate **P1** (Figure 2a). The polymerization was terminated at 8 h using *N*-phenylpiperazine, and  $^1\text{H}$  NMR end group analysis supports successful end-capping (Figure S3). We note that, based on the kinetics data in Figure 2e, monomer conversion is near completion (97%) at 8 h; when the

terminating agent was added at 16 h instead of 8 h, end groups were not observed by  $^1\text{H}$  NMR, suggesting that chain-terminating side reactions do occur after prolonged heating at high monomer conversions. The structure of **P1** was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, FT-IR, and MALDI-TOF MS analyses (Figures S12, S13, and S71 of the Supporting Information and 2b).

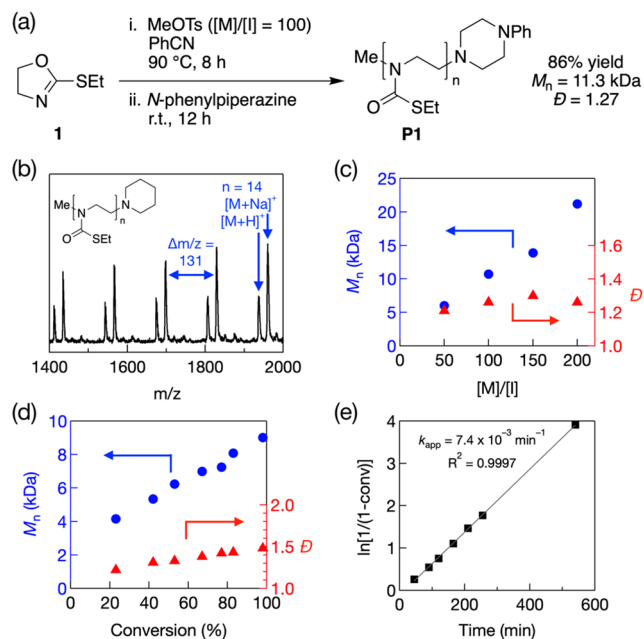
Paralleling the well-known CROP of 2-alkyl-2-oxazolines, the polymerization of **1** is living. To demonstrate this behavior, we polymerized **1** at various monomer-to-initiator ratios ( $[\text{M}]/[\text{I}]$ ). The size exclusion chromatography (SEC) traces are monomodal and narrow (Figure S4), and  $M_n$  increased linearly with  $[\text{M}]/[\text{I}]$  while  $\bar{D}$  remained low ( $\leq 1.3$ ) and largely insensitive to  $M_n$  (Figure 2c). A single polymerization reaction monitored at various monomer conversion values displayed linear  $M_n$  vs conversion (Figure 2d). Additionally, the consumption of the monomer exhibited first-order kinetics (Figure 2e). These observations are consistent with a low incidence of chain transfer, which was anticipated with the alkylthio substituent.

The activation and substitution steps for PPM were developed using a small-molecule analog of polymer **P1**, wherein we found that the sulfoxide and sulfone are neatly generated with the respective addition of 1 or 2 equiv of *m*-CPBA (Scheme S1).<sup>31</sup> The substitution step was probed by reacting the sulfone with benzylamine as the nucleophile. Reaction with the sulfone at room temperature gave the corresponding urea in 97% isolated yield, whereas the sulfoxide required mild heating to 35 °C to reach full conversion within the same reaction time (Scheme S2). Notably, we found that the thiocarbamate sulfoxide and sulfone groups are hydrolytically stable, which allowed all reactions to be performed in wet solvents under open flask conditions.

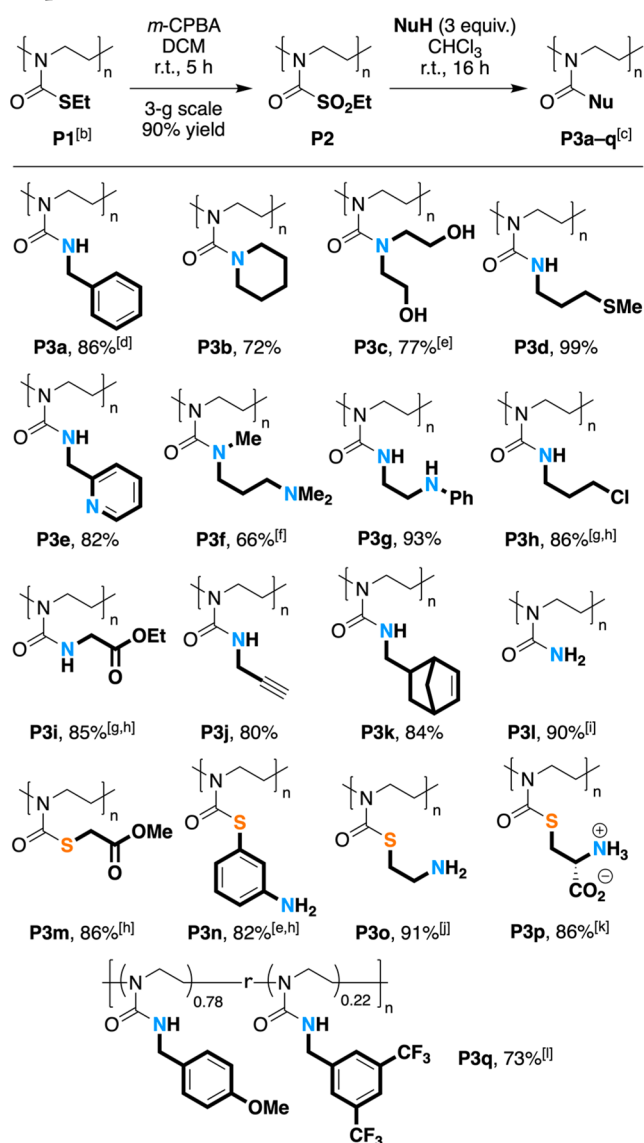
Polythiocarbamate **P1** is converted by *m*-CPBA to sulfonyl polymer **P2**, which enables substitution by various *N*- and *S*-nucleophiles (Scheme 1). We first assessed the substitution with benzylamine, a primary alkylamine, to provide polyurea **P3a**.  $^1\text{H}$  NMR spectra of **P1**, **P2**, and **P3a**, shown in Figure 3, confirm the high efficiencies of both the oxidation and substitution reactions. SEC traces of the polymers remained monomodal and narrow and retention times remained mostly unchanged (Figures S6 and S7), which indicates that polymer degradation or cross-linking does not occur.

The scope of the explored functionalization is reported in Scheme 1. Substitution proceeded smoothly and selectively with secondary alkylamines (**P3b**, **c**) in addition to primary alkylamines, with no observed cross-reactivity with nucleophilic alcohols (**P3c**), thioethers (**P3d**), pyridines (**P3e**), and tertiary amines (**P3f**). Arylamines were unreactive under these conditions (**P3g**, **n**). Electrophilic groups such as alkyl chlorides (**P3h**) and esters (**P3i**, **m**) were tolerated as well. The installation of alkynyl (**P3j**) and norbornenyl (**P3k**) groups provides opportunities for further functionalization via azide-alkyne cycloaddition or ring-opening metathesis, respectively. Substitution by ammonia produced an intriguing polyurea (**P3l**), which is only soluble in fluorinated alcohols (TFE and HFIP). High isolated yields and full conversion of the sulfonyl groups were achieved in all cases, and products were purified by precipitation, dialysis, or preparative SEC, depending on solubility and scale.

Aliphatic (**P3m**) and aryl (**P3n**) thiols proved to be competent substitution partners with the addition of an amine base such as DIPEA (Scheme 1). Following this observation, we evaluated the competitive reactivity of thiol vs amine groups. Treatment of **P2** with cysteamine resulted in exclusive reactivity at the thiol to give



**Figure 2.** (a) CROP of **1** to give **P1**. (b) MALDI-TOF MS of a low-molecular weight, piperidine-terminated sample of **P1**. (c)  $M_n$  and  $\bar{D}$  of **P1** at various  $[\text{M}]/[\text{I}]$ . (d) Monitoring of  $M_n$  and  $\bar{D}$  of **P1** at increasing monomer conversion. (e) First-order kinetic analysis of the polymerization of **1**.  $M_n$  and  $\bar{D}$  determined by SEC with polystyrene standards; monomer conversion determined by NMR.

Scheme 1. Activation of P1 by Oxidation and Substitution Scope of P2<sup>a</sup>

<sup>a</sup>Isolated yields reported. Full conversion observed in all cases. <sup>b</sup> $M_n = 21.2$  kDa,  $D = 1.26$ . See SI for full SEC characterization. <sup>c</sup>0.1 mmol scale. <sup>d</sup>0.9 g, 5 mmol scale. <sup>e</sup>DMF used as solvent. <sup>f</sup>2 equiv of DBU added. <sup>g</sup>Amine added as HCl salt. <sup>h</sup>3 equiv of DIPEA ( $N(\text{Et})(i\text{-Pr})_2$ ) added. <sup>i</sup> $\text{NH}_3(\text{aq})$  (5 equiv), TFE. <sup>j</sup>DMF/MeOH used as solvent. <sup>k</sup>L-Cysteine methyl ester HCl (3 equiv),  $\text{Et}_3\text{N}$  (3 equiv), DMF/MeOH; then LiOH/ $\text{H}_2\text{O}$ , 2 h. <sup>l</sup>1.5 equiv of each amine was used. Substitution ratio determined by <sup>1</sup>H NMR.

polythiocarbamate **P3o**, while the amine remained unaffected. The S-selectivity was corroborated by NMR analysis of model compound reactions as well as FT-IR characterization of the polymer (Figures S1 and S2) and is consistent with literature reports in aqueous systems at pH 8.<sup>31</sup> Lastly, substitution by L-cysteine methyl ester, followed by one-pot hydrolysis with the addition of LiOH/ $\text{H}_2\text{O}$ , provided zwitterionic poly(amino acid) **P3p**.

In addition to homopolymers, random copolymers were produced by substitution of **P2** with multiple nucleophiles in one pot. A mixture of an electron-rich and an electron-poor benzylamine was used (Scheme 1, **P3q**). Unsurprisingly, the nucleophilicities of the amines influenced their relative

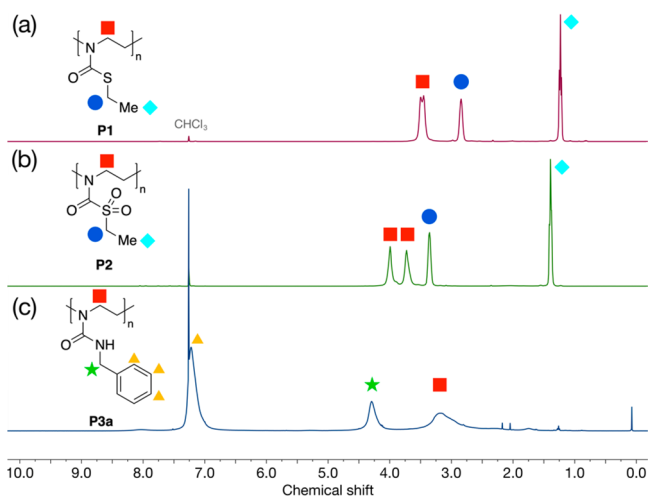
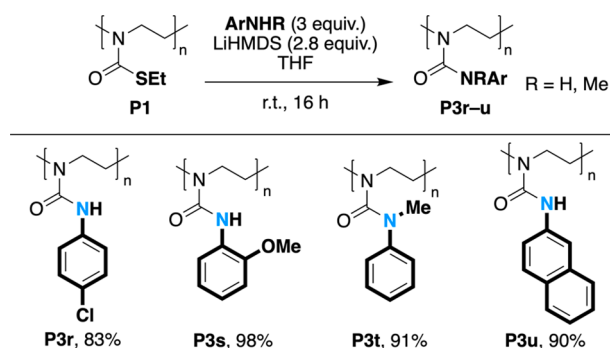


Figure 3. <sup>1</sup>H NMR spectra of (a) **P1**, (b) **P2**, and (c) **P3a**.

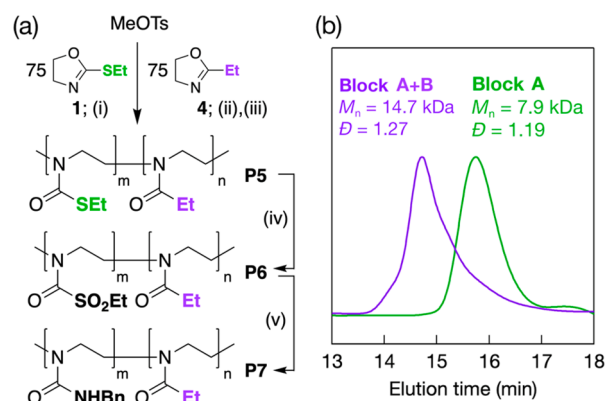
substitution rates and thus the final composition of the copolymer. This heterofunctionalization strategy opens the door to multifunctional polymers with tunable compositions.

Although arylamines were unreactive toward substitution under the aforementioned conditions, we hypothesized that the addition of a strong, hindered base would generate highly nucleophilic anilides by deprotonation. In this case, direct substitution of the relatively inert polythiocarbamate **P1** should be possible, obviating the need for the oxidative activation step. Gratifyingly, with the use of LiHDMS as the base in THF, the substitution of **P1** proceeded smoothly with arylamines containing an electron-withdrawing chloro substituent (**P3r**) or an electron-donating methoxy substituent (**P3s**), as well as with a secondary alkylarylamine (**P3t**) and a polycyclic arylamine (**P3u**) (Scheme 2). In addition to expanding the scope to encompass arylamines, these results highlight the range of reactions achievable with this polymer system.

Scheme 2. Substitution of P1 by Arylamines<sup>a</sup>

<sup>a</sup>Isolated yields reported. Full conversion observed in all cases.

In order to further demonstrate the utility of the living CROP and mild functionalization conditions, we synthesized a block copolymer **P5** from monomers **1** and 2-ethyl-2-oxazoline (**4**) via sequential monomer addition (Figure 4a). Samples taken after the first and second block formation were each analyzed by SEC, which showed a clear shift in retention time after the addition and reaction of **4**, while  $D$  remained low (<1.3) (Figure 4b). The small high-molecular weight shoulder and low-molecular weight tail in the SEC trace of the diblock copolymer (Figure 4b, purple) are likely due to chain coupling and transfer processes known to



**Figure 4.** (a) Polymerization, activation, and substitution of block copolymer. (i) PhCN, 90 °C, 4 h. (ii) 90 °C, 12 h. (iii) Piperidine, 1 h, 74% yield. (iv) *m*-CPBA, DCM, rt, 5 h. 96% yield. (v) BnNH<sub>2</sub>, CHCl<sub>3</sub>, rt, 16 h. 95% yield. (b) SEC traces of block copolymer **P5** sampled after step (i) (green) and (iii) (purple).

occur in the polymerization of 2-ethyl-2-oxazoline.<sup>36</sup> Subsequently, the same procedure was employed for the activation of the thiocarbamate groups in the block polymer (**P6**), followed by substitution with benzylamine (**P7**, Figure 4a). Using this mild method, the amide groups were unaffected while additional functionalities were installed, as confirmed by NMR (Figures S57–S62).

In conclusion, we have demonstrated an efficient, general procedure to access diverse polyureas and polythiocarbamates via CROP of 2-ethylthio-2-oxazoline. The living polymerization enables the construction of precise, complex polymer architectures. The mild conditions and broad functional group tolerance of postpolymerization substitution provide a platform for the divergent synthesis of functional polymers.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06009.

Experimental details, model compound studies, and characterization data (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*tswager@mit.edu

### ORCID

You-Chi Mason Wu: 0000-0002-6585-7908

Timothy M. Swager: 0000-0002-3577-0510

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the U.S. Army Research Laboratory (ARL) and the U.S. Army Research Office through the Institute for Soldier Nanotechnologies (ISN), under Cooperative Agreement number W911-NF-18-2-0048.

## ■ REFERENCES

- Blasco, E.; Sims, M. B.; Goldmann, A. S.; Sumerlin, B. S.; Barner-Kowollik, C. *Macromolecules* **2017**, *50*, 5215–5252.
- Gauthier, M. A.; Gibson, M. I.; Klok, H.-A. *Angew. Chem., Int. Ed.* **2009**, *48*, 48–58.

- Zeininger, L.; Nagelberg, S.; Harvey, K. S.; Savagatrup, S.; Herbert, M. B.; Yoshinaga, K.; Capobianco, J. A.; Kolle, M.; Swager, T. M. *ACS Cent. Sci.* **2019**, DOI: 10.1021/acscentsci.9b00059.

- Yu, J.; Zhang, Y.; Ye, Y.; DiSanto, R.; Sun, W.; Ranson, D.; Ligler, F. S.; Buse, J. B.; Gu, Z. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 8260–8265.

- Estabrook, D. A.; Ennis, A. F.; Day, R. A.; Sletten, E. M. *Chem. Sci.* **2019**, *10*, 3994–4003.

- Wei, M.; Gao, Y.; Li, X.; Serpe, M. *Polym. Chem.* **2017**, *8*, 127–143.

- Larsen, M. B.; Herzog, S. E.; Quilter, H. C.; Hillmyer, M. A. *ACS Macro Lett.* **2018**, *7*, 122–126.

- Larsen, M. B.; Wang, S.-J.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2018**, *140*, 11911–11915.

- Kubo, T.; Swartz, J. L.; Scheutz, G. M.; Sumerlin, B. S. *Macromol. Rapid Commun.* **2019**, *40*, 1800590.

- Agar, S.; Baysak, E.; Hizal, G.; Tunca, U.; Durmaz, H. *J. Polym. Sci., Part A: Polym. Chem.* **2018**, *56*, 1181–1198.

- Kobayashi, S.; Uyama, H. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 192–209.

- Bloksma, M. M.; Schubert, U. S.; Hoogenboom, R. *Macromol. Rapid Commun.* **2011**, *32*, 1419–1441.

- Verbraeken, B.; Monnery, B. D.; Lava, K.; Hoogenboom, R. *Eur. Polym. J.* **2017**, *88*, 451–469.

- Lorson, T.; Lübtow, M. M.; Wegener, E.; Haider, M. S.; Borova, S.; Nahm, D.; Jordan, R.; Sokolski-Papkov, M.; Kabanov, A. V.; Luxenhofer, R. *Biomaterials* **2018**, *178*, 204–280.

- Nam, S.; Seo, J.; Woo, S.; Kim, W. H.; Kim, H.; Bradley, D. D. C.; Kim, Y. *Nat. Commun.* **2015**, *6*, DOI: 10.1038/ncomms9929.

- Glassner, M.; Vergaelen, M.; Hoogenboom, R. *Polym. Int.* **2018**, *67*, 32–45.

- Luxenhofer, R.; Jordan, R. *Macromolecules* **2006**, *39*, 3509–3516.

- Gress, A.; Völkel, A.; Schlaad, H. *Macromolecules* **2007**, *40*, 7928–7933.

- Mees, M. A.; Hoogenboom, R. *Macromolecules* **2015**, *48*, 3531–3538.

- Vancoillie, G.; Brooks, W. L. A.; Mees, M. A.; Sumerlin, B. S.; Hoogenboom, R. *Polym. Chem.* **2016**, *7*, 6725–6734.

- Van Guyse, J. F. R.; Mees, M. A.; Vergaelen, M.; Baert, M.; Verbraeken, B.; Martens, P. J.; Hoogenboom, R. *Polym. Chem.* **2019**, *10*, 954–962.

- Glassner, M.; Verbraeken, B.; Jerca, V. V.; Van Hecke, K.; Tsanaktisidis, J.; Hoogenboom, R. *Polym. Chem.* **2018**, *9*, 4840–4847.

- Miyamoto, M.; Aoi, K.; Yamaga, S.; Saegusa, T. *Macromolecules* **1992**, *25*, 5111–5114.

- Miyamoto, M.; Shimakura, M.; Tsutsui, K.; Hasegawa, K.; Aoi, K.; Yamaga, S.; Saegusa, T. *Macromolecules* **1993**, *26*, 7116–7124.

- Miyamoto, M.; Aoi, K.; Morimoto, M.; Chujo, Y.; Saegusa, T. *Macromolecules* **1992**, *25*, 5878–5885.

- Bridgeman, E.; Tomkinson, N. C. *Synlett* **2006**, No. 2, 243–246.

- Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. J. *Org. Chem.* **2005**, *70*, 6960–6963.

- Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. *Tetrahedron* **2004**, *60*, 3439–3443.

- Casida, J. E.; Gray, R. A.; Tilles, H. *Science* **1974**, *184*, 573–574.

- Zimmerman, L. J.; Valentine, H. L.; Valentine, W. M. *Chem. Res. Toxicol.* **2004**, *17*, 258–267.

- Erve, J. C. L.; Jensen, O. N.; Valentine, H. S.; Amarnath, V.; Valentine, W. M. *Chem. Res. Toxicol.* **2000**, *13*, 237–244.

- Melnyk, O.; Ollivier, N.; Besret, S.; Melnyk, P. *Bioconjugate Chem.* **2014**, *25*, 629–639.

- Hwang, Y.; Thompson, P. R.; Wang, L.; Jiang, L.; Kelleher, N. L.; Cole, P. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7621–7624.

- Long, L.; Clapp, R. C.; Bissett, F. H.; Hasselstrom, T. *J. Org. Chem.* **1961**, *26*, 85–88.

- Perez, C.; Monserrat, J.-P.; Chen, Y.; Cohen, S. M. *Chem. Commun.* **2015**, *51*, 7116–7119.

- Monnery, B. D.; Jerca, V. V.; Sedlacek, O.; Verbraeken, B.; Cavill, R.; Hoogenboom, R. *Angew. Chem., Int. Ed.* **2018**, *57*, 15400–15404.