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with Nitroalkane Precursors as the Initiator**

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Complete List of Authors:	Tsutsuba, Toyokazu; Gunma University, Division of Molecular Science, Faculty of Science and Technology Sogawa, Hiromitsu; RIKEN, Center of Sustainable Resource Science Takata, Toshikazu; Tokyo Institute of Technology, School of Materials and Chemical Technology, Tokyo Institute of Technology; JST, Core Research for Evolutional Science and Technology (CREST)



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Polyester Nitrile *N*-oxides for Click Reactions Synthesized with Nitroalkane Precursors as the Initiator

Toyokazu Tsutsuba^{a,c}, Hiromitsu Sogawa^{a,d} and Toshikazu Takata^{*a,b}

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Polyesters that have a nitrile *N*-oxide function at the initiation end were prepared and applied to a catalyst-free click reaction for star polymer synthesis. They were obtained by an initial living ring-opening polymerization of lactide and lactones with an alcohol-bearing nitroalkane as the initiator, followed by conversion of the nitroalkane to a nitrile *N*-oxide function. The resulting polymer and block copolymer nitrile *N*-oxides showed very high reactivity toward a hexakis(alkenyl) core to give the corresponding star polymers via complete conversion.

In light of the efficient introduction of polymer chains to various materials, end-functionalized polymers containing a clickable functional group^{1–5} have been receiving considerable attention as useful reagents for the construction of complex and sophisticated macromolecular architectures.^{6–16} The [3+2] cycloaddition of nitrile *N*-oxide¹⁷, which efficiently proceeds with various unsaturated bonds in the absence of any additives, is an exceptional reaction compared with other reactions classified as click chemistry^{18–20}. In particular, we synthesized kinetically stabilized nitrile *N*-oxides that suppressed some side reactions by introducing bulky substituents and leveraged them for efficient polymer modification, interlocked molecule synthesis, click polymerization, and crosslinking reactions of polyolefins.^{21–33} Among them, polymer nitrile *N*-oxide, which contains a nitrile *N*-oxide group at the polymer terminal, is a powerful clickable tool for creating a variety of polymers. For example, polymethacrylate and polyethylene glycol-based nitrile *N*-oxides^{31–33} have been successfully prepared via the post-modification of the polymer chain end and applied for the preparation of block, star, and grafted copolymers thus far.

However, the introduction of the nitrile *N*-oxide group via the post-modification approach has structural limitations because it demands a highly reactive group and excess reagents, leading to some side reactions.

In contrast, living polymerizations that involve an initiator with a functional group, are good methods for the synthesis of end-functionalized polymers. Among them, living ring-opening polymerization (ROP) allows polymerization of lactide and lactone derivatives to produce the corresponding aliphatic polyesters with a highly controlled molecular weight and polydispersity index (PDI).^{34–37} These polyesters exhibit excellent physical and chemical properties and are an important class of synthetic polymers as useful building blocks. In this paper, we report the synthesis of reactive polyesters that have nitrile *N*-oxide at the initiation ends. The polymer nitrile *N*-oxides were prepared via ROP of a lactide and lactones using an initiator containing nitroalkane, which is able to be dehydrated to the nitrile *N*-oxide function quantitatively, along with subsequent conversion of the nitroalkane. In addition, using the obtained polymer nitrile *N*-oxides, catalyst- and solvent-free preparation of star polymers with high molecular weights are also demonstrated.

Prior to the preparation of polymer nitrile *N*-oxide, alcohol-containing nitroalkane initiator **1** was synthesized via the conjugate addition of an excess amount of 1,6-hexanediol to diphenylnitroethene (see scheme S1). Waymouth and Hedrick reported the ROP of lactide using organic base catalysts, such as DMAP,³⁸ NHC,³⁹ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in detail.⁴⁰ They mentioned that only a small amount of DBU is sufficient to finish ROP with a few minutes. Based on these reports, DBU-catalyzed ROP of l-lactide (LLA) was carried out using **1** at a [LLA]₀/[**1**]₀/[DBU] ratio of 20/1/0.1. The reaction proceeded homogeneously, and after precipitation into a hexane/ethanol mixture to remove the DBU, further acetylation of the propagation chain end using acetic anhydride and diphenyl phosphate (DPP) was performed to avoid decomposition of the main chain to provide poly(LLA) having nitroalkane terminal, **PLLA**₂₀-NA, in a 98% yield. Although the direct acylation should proceed with the use of DBU, DPP was used to prevent the side reaction of nitroalkane.

^a Address: Department of Chemical Science and Engineering, Tokyo Institute of Technology 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan. E-mail: takata.t.ab@m.titech.ac.jp.

^b JST-CREST.

^c Present address: Division of Molecular Science, Faculty of Science and Technology, Gunma University, 1-5-1 Tenjin, Kiryu, Gunma 376-8515, Japan

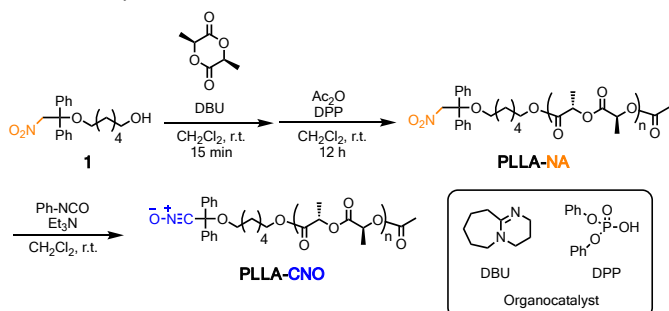
^d Present address: Biomacromolecules Research Team, RIKEN Center for Sustainable Resource Science, 2-1, Hirasawa, Wako-shi, Saitama, 351-0198, Japan

†Electronic Supplementary Information (ESI) available: Experimental procedures, ¹H, ¹³C NMR, FT-IR, MALDI-TOF MS spectra, SEC profiles, and DSC and TGA traces are contained in ESI. See DOI: 10.1039/x0xx00000x

Subsequently, efficient dehydration of the nitroalkane to the nitrile *N*-oxide function using phenylisocyanate with Et₃N afforded the PLLA-based nitrile *N*-oxide, **PLLA₂₀-CNO**, in a 88% overall yield ($M_{n(\text{NMR})}$; 3300 g/mol, $M_{n(\text{SEC})}$; 4000 g/mol, PDI; 1.12, run 1 in Table 1).

The chemical structures of **PLLA₂₀-NA** and **PLLA₂₀-CNO**

Table 1. Synthesis of **PLLA-CNO**



Sample	[M]/[I] ^a	$M_{n(\text{NMR})}^{\text{b}}$ (g/mol)	DP_n^{b}	PDI^{c}	Overall yield ^d (%)
PLLA₂₀-CNO	20	3300	20	1.12	88
PLLA₅₁-CNO	50	7700	51	1.09	91
PLLA₉₈-CNO	100	14500	98	1.08	92

a) Polymerization conditions for **PLLA-NA**: [M] = 0.1 M for 10 min. b) Determined by ¹H NMR. c) Determined by SEC (CHCl₃, PS standard). d) Isolated yield.

were characterized by ¹H NMR, IR, SEC, and MALDI-TOF MS spectra (see ESI). The partial ¹H NMR spectra of **PLLA₂₀-NA** and **PLLA₂₀-CNO** are shown in Fig 1(a). In the ¹H NMR spectrum of **PLLA₂₀-NA**, the main chain peaks of PLLA and the initiating end peaks of **1** were observed. $M_{n(\text{NMR})}$ was calculated from these integral values and was coincident with the identical value based on the feeding ratio, indicating that the formed PLLA was successfully initiated from **1**. Additionally, the methylene peak neighboring the nitro group (5.30 ppm) was maintained after the ROP in the presence of DBU, indicating the nitroalkane moiety was stable under these basic polymerization conditions. This peak completely disappeared after the dehydration of the nitroalkane to form the nitrile *N*-oxide group. Moreover, for **PLLA₂₀-CNO**, the FT-IR spectra gave direct evidence of the generation of the nitrile *N*-oxide group via the characteristic absorption observed at around 2275 cm⁻¹ (see Fig. S7). The SEC traces exhibited unimodal peaks with a narrow PDI, suggesting successful living polymerization and dehydration without any side reactions (see Fig. S10). To determine the functionalized ratio of the nitrile *N*-oxide moiety in detail, the catalyst-free 1,3-dipolar cycloaddition reaction of **PLLA₂₀-CNO** with allyltrimethylsilane was performed to give **PLLA₂₀-Iso** (see Scheme S4). The ¹H NMR spectrum of **PLLA₂₀-Iso** is also shown in Fig. 1 (a) as a comparison with **PLLA₂₀-CNO**. Quantitative conversion was determined based on the integral ratio of the initiator and isoxazoline moieties in **PLLA₂₀-Iso**. This cycloaddition regioselectively proceeded to form the 1,4-substituted

isoxazoline, which was supported by previous studies.^{28,33} Fig. 1 (b) shows the MALDI-TOF MS spectra of **PLLA₂₀-CNO** and **PLLA₂₀-Iso**. One series of peaks for the lactide repeating unit was observed, and the m/z values of the peaks were fully shifted to corresponding values for each terminal structure. M_n of **PLLA-CNO** was highly controlled by changing the molar ratio of the monomer, initiator, and catalyst. The polymerization of monomer and conversion of nitroalkane were fully confirmed by ¹H NMR and IR spectra. A $M_{n(\text{NMR})}$ of 14500 g/mol (98-mer, run 3 in Table 1) was readily achieved at the highest molecular weight while maintaining the narrow PDI. These results clearly indicate that the quantitative introduction of the nitrile *N*-oxide moiety into the PLLA terminal was achieved via ROP using the nitroalkane-containing initiator and subsequent facile chain end conversion.

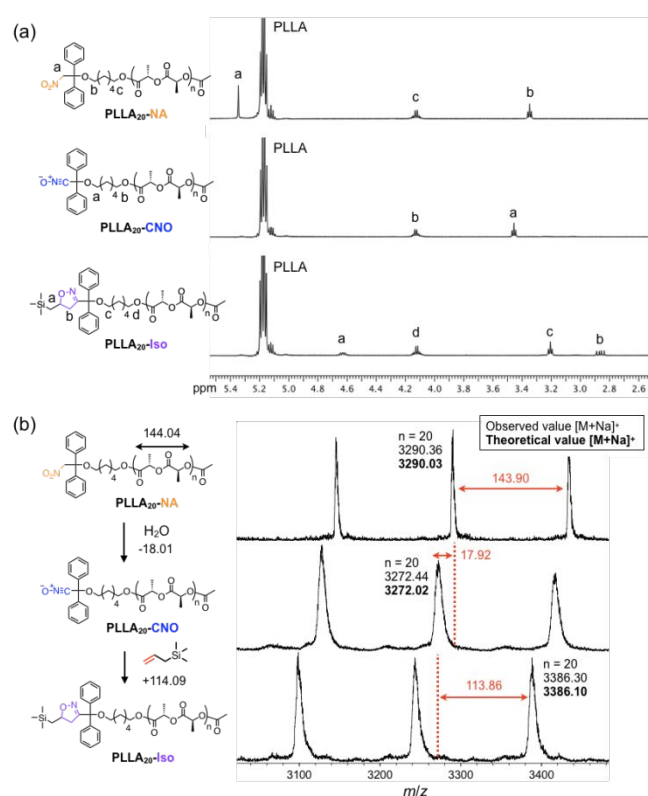
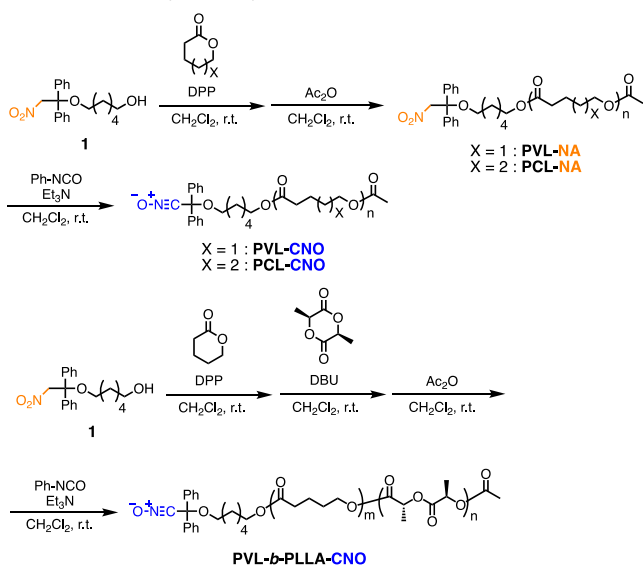


Fig 1. (a) Partial ¹H NMR spectra of **PLLA₂₀-NA**, **PLLA₂₀-CNO**, and **PLLA₂₀-Iso** (500 MHz, 298 K, CDCl₃) and (b) MALDI-TOF MS spectra of **PLLA₂₀-NA**, **PLLA₂₀-CNO**, and **PLLA₂₀-Iso** (matrix: dithranol, linear mode)

Based on this protocol, synthesis of the poly(lactone)-based nitrile *N*-oxide was also achieved using the same initiator. Note that DPP catalytic system, which is able to polymerize the lactone derivatives under mild conditions, was applied to prevent some side reactions of nitroalkane.^{41–43} When the ROP of δ -valerolactone (VL) using **1** with the DPP catalyst was conducted, the nitroalkane moiety was maintained during the polymerization, and the obtained nitroalkane was smoothly converted to nitrile *N*-oxide to produce **PVL₄₂-CNO** (run 1 in Table 2). Additionally, the DPP-catalyzed ROP of ϵ -caprolactone (CL) was also performed to afford the

corresponding polymer nitrile *N*-oxide, **PCL₄₁-CNO** (run 2 in Table 2). Remarkably, the block copolymer-based nitrile *N*-oxide could be synthesized by the combination of DPP- and DBU-catalyzed ROP systems (run 3 in Table 2). First, VL was polymerized using **1** in the presence of DPP. After isolation of the resulting PVL by precipitation, ROP of LLA was also performed as the second polymerization to afford **PVL₂₁-b-PLLA₁₈-CNO**. The structures of the polylactone-based nitrile *N*-oxides were fully confirmed by ¹H NMR, IR, SEC, and MALDI-TOF MS measurements and model cycloaddition with allyltrimethylsilane. The detailed experimental procedure and structural characterization are described in the ESI.⁴⁴ The combined protocol of the organocatalyzed-ROP and conversion of the nitroalkane also provided the polylactone-based nitrile *N*-oxide as well as the polylactide-based nitrile *N*-oxide in reasonable yield.

Table 2. Synthesis of the polyester-based and polyester block nitrile *N*-oxides (**PX-CNO**)



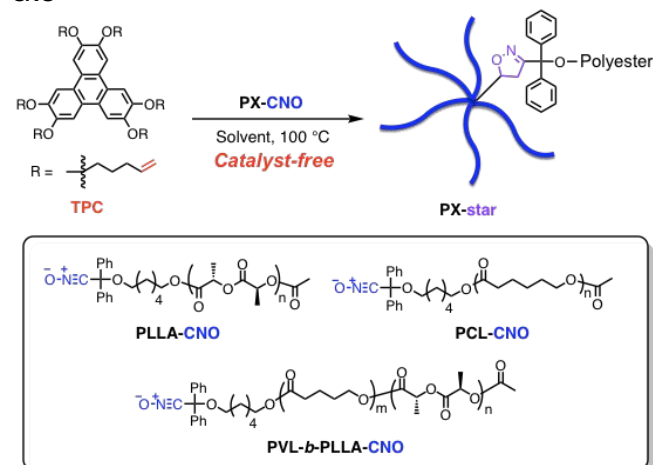
PX-CNO	$M_n(\text{NMR})^c$ (g/mol)	DP_n^c	PDI ^d	Overall Yield ^e (%)
PVL₄₂-CNO^{a)}	4600	42	1.21	63
PCL₄₁-CNO^{a)}	5100	41	1.10	69
PVL₂₁-<i>b</i>-PLLA₁₈-CNO^{b)}	5100	21 (PVL) 18 (PLLA)	1.14	40

a) Polymerization conditions for **PVL-NA** and **PCL-NA**: [monomer]₀/[1]₀/[DPP] = 50/1/1, [M] = 0.1 M. b) Copolymerization conditions for **PVL-*b*-PLLA-NA**: [VL]₀/[1]₀/[DPP] = 20/1/1, [LLA]₀/[1st polymer]₀/[DBU] = 20/1/0.2. c) Determined by ¹H NMR. d) Determined by SEC (CHCl₃, PS standard). e) Isolated yield.

To demonstrate the potential usefulness of polyester-based nitrile *N*-oxides for constructing unique macromolecular architectures, synthesis of 6-arm star polymers was performed via the arm-first method using the triphenylene alkene core unit (**TPC**). A mixture of polymer nitrile *N*-oxides and **TPC** in anisole was heated for 12 h under catalyst-free conditions (Table 3). The ¹H NMR showed the disappearance of the

alkenyl group of **TPC**, suggesting the quantitative connection of polymers to give the corresponding 6-arm star polymers, **PLLA-star**, **PCL-star**, and **PVL-*b*-PLLA-star**.⁴⁵ Fig 2 shows the SEC charts of **PLLA₉₈-CNO**, crude **PLLA₉₈-star** and purified **PLLA₉₈-star** (run 3 in Table 2). In crude sample, the peak corresponded to formed star polymer appeared at higher molecular weight region compared with that of reactant polymer without widening the PDI. When the peak separation of this chart was performed, it was mainly assigned to two peaks, that are **PLLA₉₈-CNO** and 6-arm star polymer, with very good fitting quality⁴⁶. These results indicated the selective formation of 6-arm star polymer, being the same as other star polyester synthesis (Fig S46 and S47). In particular, **PLLA₉₈-star** showed a very high M_n with a narrow PDI ($M_n(\text{SEC})$; 99600 PDI; 1.05). These results proved that the resulting polyester-based nitrile *N*-oxides have considerable reactivity as clickable polymer reagents. In previous studies, star polylactides have been synthesized via the core-first method using a multi-functionalized initiator.^{47–49} To our knowledge, this is the highest M_n star-shaped polylactide having 6-arm PLLA chains prepared via the arm-first method.⁵⁰ The thermal properties of the obtained star polymers were evaluated by DSC and TGA (see Table S1). The melting temperatures (T_m) appeared in the lower region owing to their branched structures, whereas the

Table 3. Catalyst- and solvent-free synthesis of **PX-star** using **PX-CNO**



Run ^{a)}	PX-CNO	PX-star	Time (h)	Conv. ^{b)} (%)	Yield ^{d)} (%)
1	PLLA₂₀-CNO	PLLA₂₀-star	12	>99	61
2	PLLA₅₁-CNO	PLLA₅₁-star	12	>99	65
3	PLLA₉₈-CNO	PLLA₉₈-star	12	>99	60
4	PCL₄₁-CNO	PCL₄₁-star	12	>99	70
5	PCL₄₁-CNO	PCL₄₁-star	1	45	- ^{e)}
6 ^{d)}	PCL₄₁-CNO	PCL₄₁-star	1	>99	- ^{e)}
7	PVL₂₁-<i>b</i>- PLLA₁₈-CNO	PVL₂₁-<i>b</i>- PLLA₁₈-star	12	>99	54

a) Reaction conditions: the catalyst-free reaction was carried out in anisole, [TPC] = 1.0 mM, [PX-CNO] = 1.7 eq. b) Determined by ¹H NMR. c) Isolated yield after purification using preparative GPC. d) The solvent-free reaction was carried out without any solvent. e) Not isolated.

thermal weight loss temperature (T_{d5}) remained almost unchanged compared with the corresponding polymer nitrile *N*-oxides. Finally, the preparation of **PCL₄₁-star** was also carried out under solvent-free conditions. Because the T_m of **PCL₄₁-CNO** (52 °C) is lower than the reaction temperature (100 °C), the reaction proceeded under melting conditions. Under the solvent-free condition, the reaction was rapidly completed in 1 h to form **PCL₄₁-star** (run 6), whereas the solution reaction was not completed in the same reaction time (run 5, 45% conv.). Significant acceleration of the click reaction was observed. Of note, our method should be perceived as a sustainable star polymer synthesis because it does not require

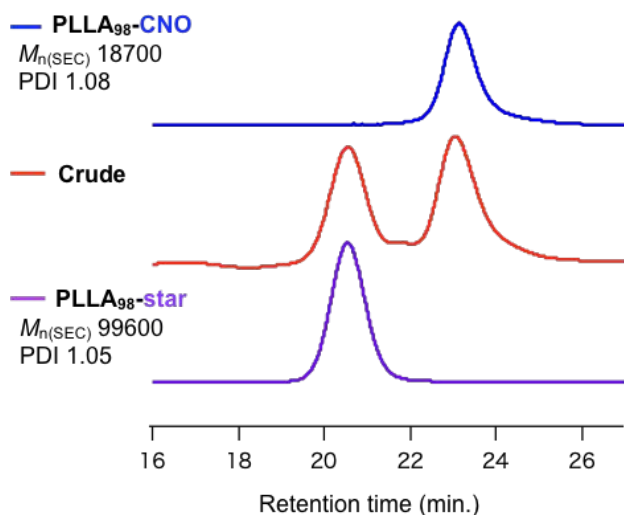


Fig. 2 SEC Charts of **PLLA₉₈-CNO**, crude **PLLA₉₈-star** and purified **PLLA₉₈-star** (PS standards; eluent, CHCl₃; flow rate, 0.85 mL min⁻¹; detected by RI)

the catalyst or solvent.

Conclusions

We found that ROP with an initiator that has a nitroalkane and its dehydration successfully provided polyesters with the nitrile *N*-oxide group in the polymer terminal. Importantly, the nitroalkane at the initiation end was stably maintained during the ROP with acid and base organocatalysts and quantitatively converted to the nitrile *N*-oxide group despite the polymer terminal. This procedure is applicable to lactide and lactone monomers for the preparation of polymer nitrile *N*-oxide, resulting in the expansion of its backbone structures. Thus, the nitroalkane can be regarded as an excellent precursor of nitrile *N*-oxide in the synthesis of well-defined polymer nitrile *N*-oxide. In addition, efficient formation of 6-arm star polymers demonstrated the high reactivity and usability of the obtained polymer nitrile *N*-oxides. These findings contribute to further construction of complex and sophisticated macromolecular architectures. Using the nitroalkane precursor, studies on further expansion of polymer nitrile *N*-oxide and its efficient click reaction are in progress.

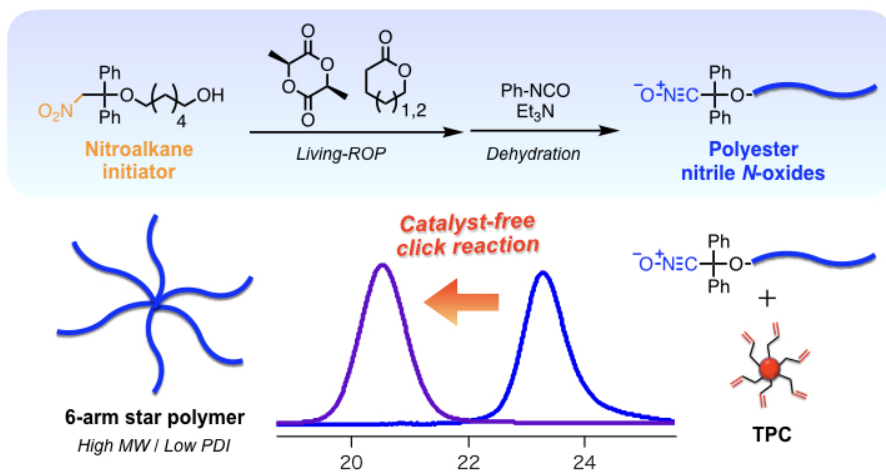
Acknowledgments

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- 43 R. Tanaka, K. Watanabe, T. Yamamoto, K. Tajima, T. Isono and T. Satoh, *Polym. Chem.*, 2017, **8**, 3647.
- 44 The overall yield of polyester-based and polyester block nitrile *N*-oxides was decreased by the precipitation to remove some reaction reagents. DPP-catalyzed ROP proceeded with over 80 % conversion, and nitrile *N*-oxide was formed with quantitative conversion consistently in Table 2.
- 45 In order to characterize the molecular weight and thermal properties of **PX-star**, these polymers were isolated absolutely by using preparative GPC. Therefore, these yields were not so high in spite of quantitative reaction conversion in Table 3.
- 46 In all crude samples, the minor peaks were also detected between two main peaks in peak separation. This minor peak was estimated to be the self-dimerized polyester-based nitrile *N*-oxide, which were often observed with the use of excess amount of polymer-based nitrile *N*-oxides to the substrate. This dimer formation was unavoidable especially for the polymer-polymer reaction because it usually requires the harsh reaction condition. Although side reaction peaks were very small (>14%), to remove the side product and reactant polymer, the yield of isolated star polymers were lost in purification using preparative GPC.
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