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Exclusive One-Way Cycle Sequence Control in Cationic Terpolymerization of General-Purpose Monomers via Concurrent Vinyl-Addition, Ring-Opening, and Carbonyl-Addition Mechanisms

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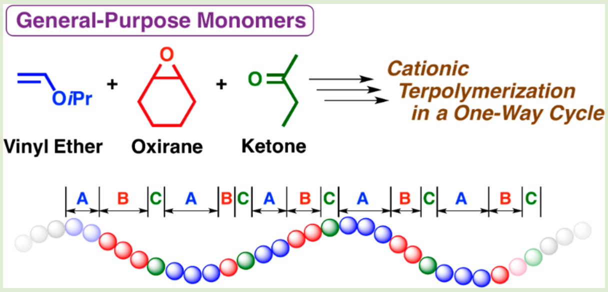
Supporting Information

ABSTRACT: Cationic terpolymerization of vinyl ether (VE), oxirane, and ketone successfully proceeded via unprecedented concurrent vinyl-addition, ring-opening, and carbonyl-addition mechanisms. In particular, the use of cyclohexene oxide as an oxirane resulted in terpolymerization via an exclusive one-way cycle, i.e., the reactions occurred only in the VE → oxirane, oxirane → ketone, and ketone → VE directions. Terpolymers that have repeating units of $(\text{VE}_{\sim 2}\text{–oxirane}_{\sim 2}\text{–ketone})_n$ were obtained under appropriate conditions. In addition, no two-monomer combination achieved efficient copolymerization, which suggests that three specific types of crossover reactions are required for successful terpolymerization. The presence of a ketone, a compound that has rarely been employed as a monomer, is indispensable for a one-way cycle: terpolymerization also proceeded with an aliphatic aldehyde but resulted in two-way crossover reactions at the aldehyde-derived propagating ends.



Precise control over sequences of synthetic polymer chains has attracted considerable interest in various fields of chemistry because polymers with properties similar to those of naturally occurring polymers, such as proteins and DNA, can be precisely designed.[1,2] The iterative methods such as the synthesis of polypeptides using the Merrifield Resin have been developed for the synthesis of sequence-regulated polymers (Scheme 1A).[3−7] However, complete sequence control has never been accomplished in chain-reaction-type polymerizations such as addition or ring-opening polymerizations, which are widely used for industrial purposes, because stepwise propagation in chain polymerization is extremely difficult to achieve. Although the iterative methods (Scheme 1A) have been applied to the synthesis using vinyl monomers,[8−12] only oligomers composed of several monomer units were obtained, mainly due to the need of time-consuming purification in each step. One other method for the synthesis of sequence-regulated polymers is the polymerization of monomers containing or concealing specific sequences of two or more vinyl monomer units or template monomers (Scheme 1B).[13−25]

Sequence control via direct chain copolymerization of several monomers, such as terpolymerization, is the simplest approach (Scheme 1C) but has been a considerable challenge because of the difficulty associated with inducing the specific single crossover reaction for the propagating species from a given monomer. The previously reported direct ABC-type alternating terpolymerizations include only the following two examples: the reactions of ethylene oxide, maleic anhydride, and tetrahydrofuran via the ring-opening mechanism[26] and the reactions of ethylene phenylphosphonite, a vinyl monomer with an electron-withdrawing substituent, and carbon dioxide via the zwitterionic mechanism.[27] Moreover, terpolymerization via a one-way cycle or polymerization in which the specific crossover reaction occurs from each propagating end has rarely been achieved, as previously mentioned.

To broaden the choice of monomers for sequence-controlled copolymerization, the polymer sequence should be governed by certain reaction conditions, including temperature, solvent, and/or additive. This control may be more feasible in a copolymerization reaction of different types of monomers that polymerize via different mechanisms. The specific direction of the crossover reaction was promoted by the addition of a weak Lewis base, such as an ester and an ether, in the concurrent cationic copolymerization of vinyl ethers (VEs) and oxiranes through the vinyl-addition and ring-opening mechanisms.[28−30] In this reaction, the crossover from the oxirane-derived oxonium ion to a VE monomer requires the generation of an open-form carbocation from the ring-opening reaction of the oxonium ion.[29] Thus, oxiranes that generate relatively unstable secondary carbocations via ring opening did not efficiently copolymerize with VEs because the unstable carbocations were rarely generated. However, the use of weak Lewis bases increased the frequency of crossover reactions from the oxirane-derived propagating end to VE.[30] Weak Lewis bases possibly promoted the ring-opening reaction via nucleophilic

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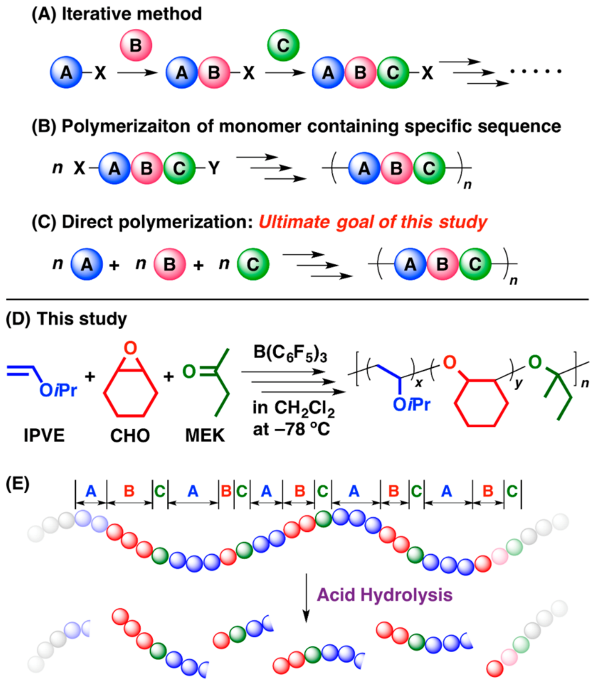
Scheme 1. (A–C) Schematic Illustration for the Synthesis of Sequence-Regulated Polymers (Reactions That Use Three Monomer Units Are Shown As Examples), (D) Terpolymerization Conducted in This Study, and (E) an Illustration of Terpolymer Obtained under Appropriate Conditions and Acid Hydrolysis of the Terpolymer



attack on the carbon atom adjacent to the oxygen atom of the propagating oxonium ion.

The use of a monomer that undergoes an addition reaction but not homopolymerization is expected to facilitate precise sequence control, thus providing a one-way cycle terpolymerization. Thus, a compound that nucleophilically attacks the oxonium ion in a similar manner but is polymerizable can be terpolymerized with VE and oxirane. Ketone, a weak base, would induce the ring-opening reaction of the oxonium ion via nucleophilic attack to generate a carbocation with a structure similar to that of the VE-derived carbocation with an adjacent alkoxy group. However, cationic copolymerization using a ketone via carbonyl-addition mechanisms has rarely been reported,[31,32] possibly because of the instability of the resulting ketal structure.[33] In this study, we report the unprecedented cationic terpolymerization of VE, oxirane, and ketone via the vinyl-addition, ring-opening and carbonyl-addition mechanisms (Scheme 1D). The instabilities of particular propagating species and sequences were utilized for the selective generation of specific crossover reactions. In particular, an oxirane that does not efficiently copolymerize with VE in the absence of a ketone was found to be suitable for the terpolymerization via a one-way cycle.

Cationic terpolymerization of isopropyl VE (IPVE), cyclohexene oxide (CHO), and methyl ethyl ketone (MEK) was conducted using $B(C_6F_5)_3$, a Lewis acid that generates a weakly coordinating counteranion,[28] as a catalyst in dichloromethane at −78 °C (Scheme 1D). The monomer concentrations were settled on the basis of the reactivities of monomers (e.g., a smaller amount of CHO than IPVE was employed because CHO has higher reactivity than IPVE). The initiation reaction possibly occurred from a proton derived from adventitious water and/or the coordination of $B(C_6F_5)_3$ to CHO or MEK. The polymerization proceeded smoothly to give a product with a unimodal molecular weight (MW) distribution and M_n of 8.6 × 10^3 (Figure 1A). The MW was lower than homopolymers obtained under similar conditions (entries 7 and 8 in Table 1). Chain transfer reactions are responsible for the lower MW, but the detail has not been elucidated. The ^{1}H NMR spectrum of the product (Figure 2) exhibited the peak associated with the acetal structure, which was generated through the crossover reaction from a VE-derived propagating end to a CHO monomer. The ^{1}H NMR spectrum also contained the peak of the methyl proton of the MEK units. These results indicate that the three components were successfully incorporated into the polymer chain (see Figures S1–S4 for ^{13}C and 2D NMR spectra). In addition, acid hydrolysis (Figure 1E) gave a product (Figure 1A, purple curve) with a MW substantially lower than that of the original copolymer, indicating the frequent occurrence of the IPVE-to-CHO crossover reactions that generated acid-labile acetal moieties.

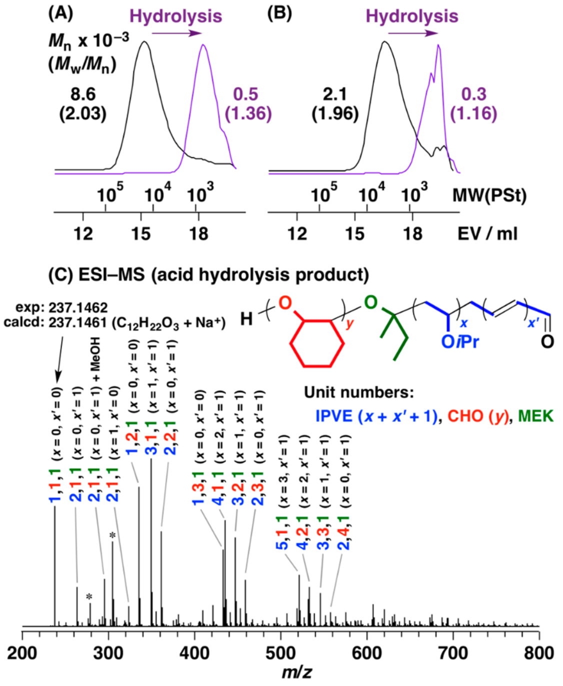


Figure 1. (A, B) MW distribution curves of the IPVE-CHO-MEK terpolymers (black) and their hydrolysis products (purple) [(A) entries 1 and (B) 3 in Table 1], and (C) ESI–MS spectrum of the hydrolysis product of the terpolymer (entry 3 in Table 1, the purple curve in (B); the numbers represent the possible VE, CHO, and MEK unit numbers that constitute the structures whose mass values agree with the *m*/*z* values of the peaks; * contamination, see also Figure S6 for the assignments of minor peaks).

Interestingly, the terpolymerization reaction was demonstrated to proceed via a one-way cycle; that is, the reactions proceeded only through the IPVE → CHO, CHO → MEK, and MEK → IPVE sequences in addition to homosequences of IPVE and CHO (Scheme 2). This finding was evidenced by experimental results that indicated that no efficient copolymerization of any two of the three monomers occurred and that the incorporated amounts of the acetal moieties and the MEK units were equivalent. In particular, the crossover reactions from CHO to IPVE negligibly occurred in the copolymerization of IPVE and CHO in the absence of MEK (entry 4; Figure

Table 1. Cationic Terpolymerizations Using IPVE, Oxirane, and Carbonyl Compounds[a]

entry	IPVE (M)	oxirane (M)		carbonyl compound (M)		time	GC conv[b] (%) VE	Oxr	Car	$M_n \times 10^{-3}$ [$M_n \times 10^{-3}$ (hydrolyzed)][c]	M_w/M_n[c]	monomer units per acetal[d] VE	Oxr	Car
1	0.80	CHO	0.20	MEK	1.2	30 min	19	69	10	8.6 [0.5]	2.03	4.1	3.7	1.0
2	0.80		0.20		5.0	49 h	42	92	5	3.6 [0.3]	2.25	3.3	1.8	1.0
3[e]	0.80		0.20		5.0	19 h	27	83	4	2.1 [0.3]	1.96	2.3	2.1	0.96
4	0.80		0.20		–	10 s	18	94	–	12.7 [6.3]	2.21	44	63	–
5	–		0.20		1.2	3 h	–	51	0	0.5	1.54	–	–	–
6	0.41		–		1.2	22 h	97	–	0	38.2 [38.2]	6.50	–	–	–
7	0.75		–		–	3 min	93	–	–	37.4	3.18	–	–	–
8	–		0.20		–	5 s	–	100	–	17.2	1.93	–	–	–
9	–		–		1.2	78 h	–	–	0	–	–	–	–	–
10	0.40	IBO	0.60	MEK	0.60	5 h	60	21	19	4.0 [0.4]	1.83	6.8	1.6	0.79
11	1.2	CHO	0.40	CHA	0.40	1.5 h	3	59	6	9.2 [0.7]	2.05	0.49 (1.1)	7.3 (16)	1.1 (2.4)
12	–		0.40		0.40	1 min	–	85	19	7.8 [0.6]	2.09	–	6.3	1.0

[a] $[B(C_6F_5)_3]_0$ = 1.0 (entries 1, 2, 4–8, and 10–12) or 3.0 (entries 3 and 9) mM, in dichloromethane at −78 °C. Oxr: oxirane, Car: carbonyl compounds. [b] Determined by gas chromatography. [c] Determined by GPC (polystyrene standards). The values in parentheses are M_n after acid hydrolysis. [d] Estimated by ^{1}H NMR (see page S3 in the Supporting Information for the details). The values in parentheses are units per VE-derived acetal moieties. [e] In hexane/dichloromethane (8/2 v/v).

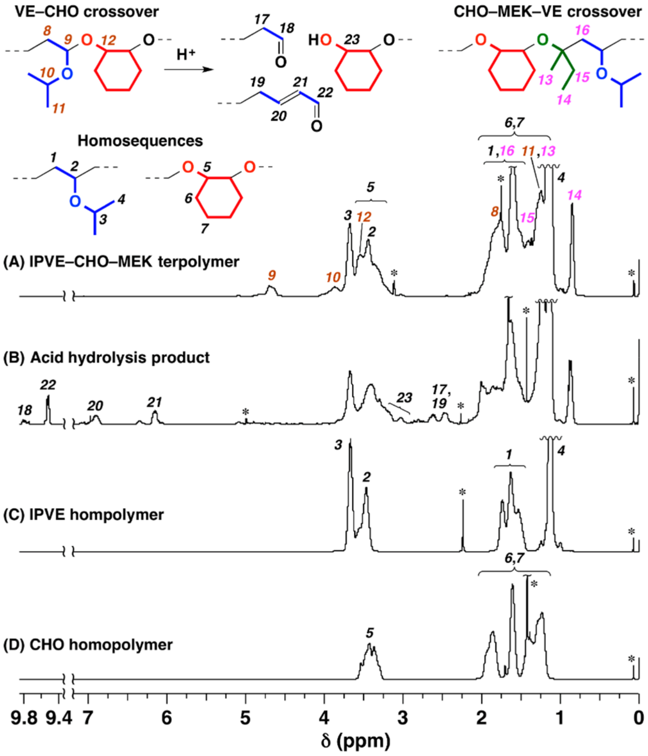


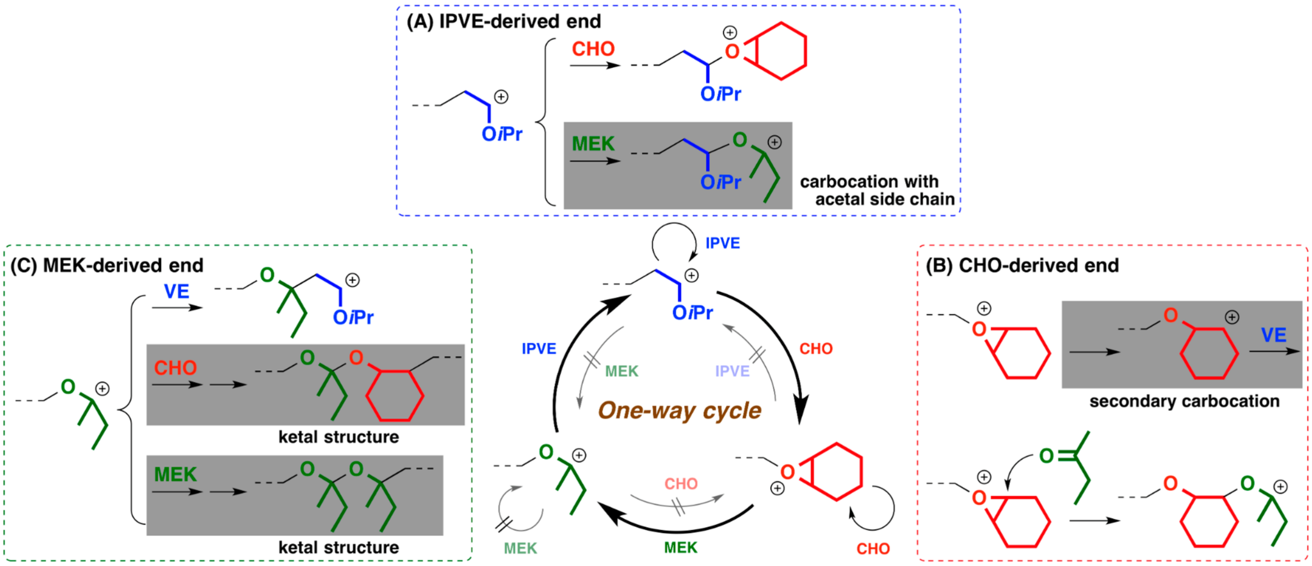
Figure 2. ^{1}H NMR spectra of (A) the IPVE–CHO–MEK terpolymer (entry 1 in Table 1), (B) its hydrolysis product, (C) IPVE homopolymer (entry 7), and (D) CHO homopolymer (entry 8); in $CDCl_3$ at 30 °C (*grease, solvent, water, monomer, or stabilizer).

S5 for ^{1}H NMR),[34] which indicates that MEK is indispensable for efficient crossover reactions. In addition, neither IPVE nor CHO copolymerized with MEK in the absence of one of the three monomers (entries 5 and 6), indicating that the terpolymerization proceeded through the $CHO_y \rightarrow MEK_1 \rightarrow IPVE_x$ sequences.

The stabilities of both the propagating species and the generating sequences may be responsible for the unique terpolymerization that proceeded via a one-way cycle. Possible crossover reactions that occur during terpolymerization are shown in Scheme 2. The propagating species generated via the reaction of the VE-derived propagating end with an MEK monomer is a carbocation with an adjacent acetal structure at the side chain (Scheme 2A, lower). The copolymerization of IPVE and MEK did not proceed (entry 6), revealing that the formation of this type of carbocation did not occur due to its instability. The generation of a carbocationic species is required for the crossover to a VE monomer; most likely, however, this species is rarely generated via the ring-opening reaction of the CHO-derived oxonium ion because of the instability of the secondary carbocation (Scheme 2B, upper).[29] Thus, the crossover reactions from CHO to IPVE do not occur because of the virtual absence of this carbocationic species. The crossover reaction from the CHO-derived oxonium ion occurs exclusively via the nucleophilic attack of an MEK monomer, which generates a carbocation with a structure similar to that of the VE-derived carbocation with an adjacent alkoxy group (Scheme 2B, lower). Subsequently, the MEK-derived carbocation reacts only with VE, not with MEK or CHO (Scheme 2C), because the structures that result from the homopropagation of MEK and the crossover reaction from MEK to CHO are unstable ketal structures[33] and are not produced (entries 5 and 9).

The frequency of crossover reactions was significantly dependent on the experimental conditions, including the feed monomer ratios and solvent polarity. The numbers of IPVE, CHO, and MEK units of the obtained terpolymers were estimated on the basis of the ^{1}H NMR spectrum to be 4.1, 3.7, and 1.0 per acetal moiety, respectively. Increasing the concentration of MEK from 1.2 to 5.0 M generated a terpolymer with sequences resulting from more frequent crossover reactions (entry 2 in Table 1; IPVE, CHO, and MEK units: 3.3, 1.8, and 1.0, respectively). In addition, the decrease of solvent polarity increased the frequency of the crossover reactions because the crossover from the VE-derived end to the oxirane was promoted[30] (entry 3, Figure 1B; IPVE, CHO, and MEK units: 2.3, 2.1, and 0.96, respectively). The ESI–MS spectrum of the hydrolysis product of the terpolymer (Figure 1C) exhibited peaks with values that agreed with the

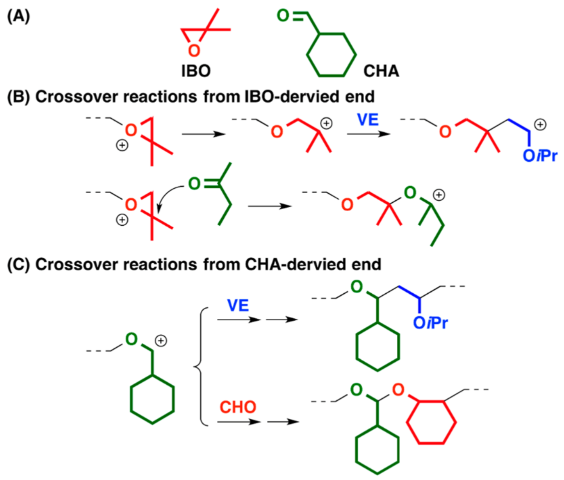
Scheme 2. Crossover Reactions That Generate from (A) IPVE-, (B) CHO-, and (C) MEK-Derived Propagating Species (Reactions with Gray Shadow Negligibly Occur)



mass values of sequences composed of several units of monomers (see also Figure S7 for the MALDI–TOF–MS spectrum). In particular, all the values agreed with the mass values of structures composed of a few or several IPVE and CHO units and a single MEK unit. These results suggest that the terpolymerization in a one-way cycle successfully proceeded via highly frequent crossover reactions. An ABC-type alternating terpolymer would be produced when the homopropagation reactions of IPVE and CHO are completely suppressed through the elaborate design of the reaction conditions.

The terpolymerization using isobutylene oxide (IBO, Scheme 3A) instead of CHO efficiently proceeded through crossover reactions, although the polymerization did not occur in a one-way cycle (entry 10 in Table 1). The ^{1}H and ^{13}C NMR spectra (Figures S8 and S9; see Figures S10–S12 for the 2D NMR spectra) showed small peaks that were assigned to the structures derived from the IBO–IPVE crossover reactions.

Scheme 3. (A) Structures of IBO and CHA and Crossover Reactions That Proceed from (B) IBO- and (C) CHA-Derived Propagating Species



The ratios of the crossover reactions from the IBO-derived propagating end to the MEK/IPVE monomers were estimated to be 0.79/0.21. The crossover reaction from IBO to IPVE occurred because the tertiary carbocation, which is more stable than a secondary carbocation, was generated via the ring-opening reaction of the IBO-derived oxonium ion (Scheme 3B), similar to the copolymerization of IBO and IPVE.[28]

An aliphatic aldehyde was used as a carbonyl compound instead of MEK, which resulted in nonselective crossover reactions at the aldehyde-derived propagating end. The terpolymerization of IPVE, CHO, and cyclohexanecarbaldehyde (CHA, Scheme 3A) proceeded, yielding a product with a unimodal MW distribution (entry 11 in Table 1). In contrast to the ketone reaction, which does not generate the crossover reaction to an oxirane because of the resulting unstable ketal structure, the crossover reaction from the CHA-derived propagating end to CHO occurred to generate an acetal structure (Scheme 3C, lower). The ^{1}H NMR spectrum of the product (Figure S13) showed peaks of two types of acetal structures at 4.7 and 4.4 ppm. The peak at 4.4 ppm was assigned to acetal moieties derived from the crossover reactions from the CHA-derived propagating species to CHO. Furthermore, because these crossover reactions were feasible, the copolymerization of CHO and CHA also proceeded through crossover reactions to yield a copolymer (entry 12; cf. entry 5). The product copolymer containing acid-labile acetal moieties in the main chain was degraded into a lower-MW compound under acidic conditions.

In conclusion, the cationic terpolymerization of VE, oxirane, and ketone via a one-way cycle was successfully achieved through the concurrent vinyl-addition, ring-opening, and carbonyl-addition mechanisms. Appropriate monomers selected on the basis of the stability of the propagating species and the generating sequences were indispensable for the selective crossover reactions. In particular, an oxirane monomer that rarely generates a carbocationic species via the ring-opening reaction of the oxonium ion was required for the selective generation of the oxirane–ketone–VE sequence. The results in this study will lead to the synthesis of sequence-regulated polymers from a variety of commercially available, general-purpose monomers through the sophisticated design of crossover reactions among different types of monomers.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section and additional data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00365.

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Notes

The authors declare no competing financial interest.

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