JOC The Journal of Organic Chemistry

Article

Cite This: J. Org. Chem. 2018, 83, 2892−2897

pubs.acs.org/joc

Access to Bicyclo[4.2.0]octene Monomers To Explore the Scope of Alternating Ring-Opening Metathesis Polymerization

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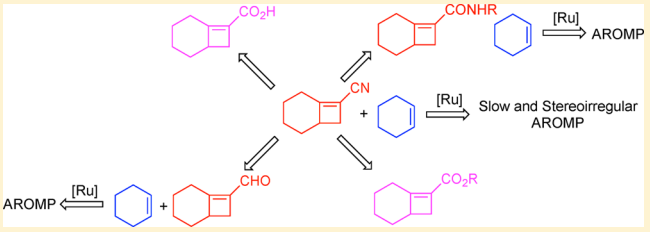
Supporting Information

ABSTRACT: Bicyclo[4.2.0]oct-1(8)-ene-8-carboxamides undergo alternating ring-opening metathesis polymerization (AROMP) with cyclohexene. Herein, a general method for the preparation of bicyclo[4.2.0]oct-(8)-ene-8-carboxy derivatives is described. The central 8-cyano intermediate provides entry to five different functional group substituents on the alkene. These monomers were tested as potential substrates for AROMP with cyclohexene. In addition to the carboxamide, the carboxynitrile and carboxaldehyde are also substrates for AROMP. In the case of the carboxaldehyde, the polymer is regioregular. However, the addition of carboxynitrile is stereoirregular and slow.

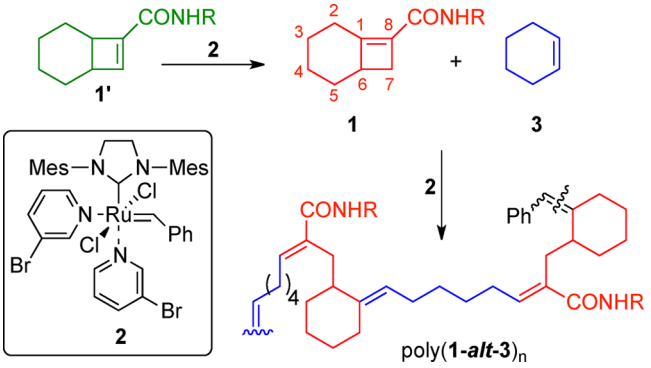


INTRODUCTION

Alternating copolymers are of interest for a multitude of applications ranging from the biological to nanoelectronics and catalysis.[1−8] Generally, alternating copolymers have been synthesized by radical polymerization[9−12] and metal-mediated routes, including CO_2/epoxide copolymerizations[13] and catalyst transfer polymerizations of heterocycles.[14] However, the introduction of functionality can be limited by reaction conditions. In addition, these polymerizations often provide broad molecular weight distributions. A more advanced method for the synthesis of alternating polymers is iterative chain extension,[15] but lengths are limited by yield and purification steps.

Recently, advances have yielded several approaches to polymer sequence control using metathesis and/or ring-opening methods.[16−25] We reported the rapid initiation and alternating propagation of bicyclo[4.2.0]oct-1(8)-ene-8-carboxamides with cyclohexene and ruthenium catalysis leads to very long alternating polymers of excellent dispersities (Scheme 1).[26] Monomers **1** were obtained by Ru-catalyzed (**2**) isomerization of bicyclo[4.2.0]oct-7-ene-7-carboxamides **1′** (Scheme 1). The isomerization and subsequent polymerization can be carried out in a single pot reaction. However, any loss of catalyst via decomposition during isomerization affected the ultimate molecular weight and molecular weight distribution of the polymer obtained. Moreover, the isomerization is sensitive to functionality in the amide side chain, and bulkier substituents led to incomplete isomerization. Thus, yields of monomers were affected by slow isomerization which necessitated isolating bicyclo[4.2.0]oct-1(8)-ene-8-carboxamide before isomerization was complete to prevent loss of carboxamide to ring-opening metathesis.[26] In addition, preparation of polymers of a specific molecular weight with narrow dispersities necessitated isolation and purification of monomer **1**, followed by initiation of polymerization with fresh catalyst **2**. As an additional consideration, preparation of the ester precursor to monomer **1′** requires an epoxidation step to separate regioisomers chromatographically that limits the scale of the reaction.[27]

Scheme 1. Original Route to Monomer 1, Which Is Used in AROMP with Cyclohexene 3

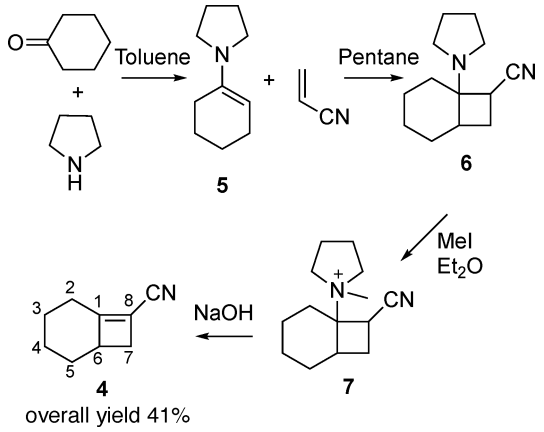


Therefore, we sought a simpler and more direct route to monomer **1** that would facilitate preparation of polymers with a greater diversity of substituents. Here, we describe the direct preparation of amide **1** from stable nitrile **4**, which can be easily prepared in multigram quantities from cyclohexanone and pyrrolidine (Scheme 2). A further advantage of the synthetic scheme is that the 1(8)-alkene in the bicyclo[4.2.0] scaffold is obtained through direct elimination. This approach provides entry to the nitrile **4**, aldehyde **10**, and ester-substituted bicyclo[4.2.0]oct-1(8)-ene **9** that have never been tested as monomers in AROMP (Scheme 3).

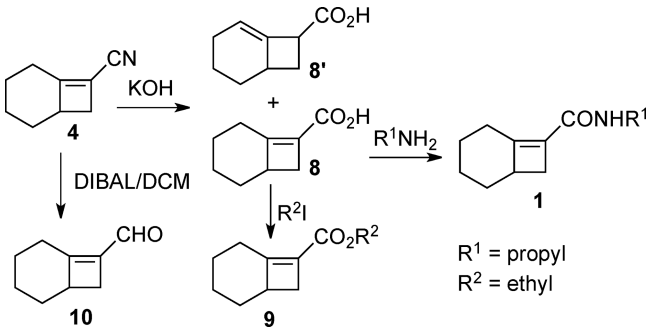
Received: January 8, 2018
Published: February 6, 2018

DOI: 10.1021/acs.joc.8b00054
J. Org. Chem. 2018, 83, 2892−2897

Scheme 2. Synthesis of Bicyclo[4.2.0]oct-8-ene-8-carbonitrile



Scheme 3. Synthesis of Potential AROMP Monomers from 4



RESULTS AND DISCUSSION

Synthesis of AROMP Monomers. The preparation of bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile **4** is based on Harley-Mason's approach.[28] Cyclohexanone and pyrrolidine are condensed to provide 1-*N*-pyrrolidinylcyclohexene **5**. A 2 + 2 cycloaddition with acrylonitrile yields carbonitrile **6**. Subsequent N-methylation and Hoffman elimination produces bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile **4** in 41% overall yield (Scheme 2). This synthetic route relies on isolation of solid intermediates that can be utilized without additional purification steps and a single chromatographic step to purify nitrile **4**. Thus, we routinely prepared **4** on a 5 g scale.

We envisioned nitrile **4** could be converted to a variety of potential AROMP monomers. First, we sought conversion of nitrile **4** to carboxylic acid **8** through hydrolysis of nitrile **4** without addition of metal catalyst and mild heating. Carboxylic acid **8** could then be coupled with an amine to provide the amide **1** or with an alcohol or alkyl iodide to yield ester **9**.

Initial attempts to hydrolyze nitrile **4** gave a very low yield of acid **8**. Moreover, during hydrolysis, isomerization of the alkene occurred to form bicyclo[4.2.0]oct1(2)-ene-8-carboxylic acid **8′** (Scheme 3 and Table 1). This alkene is approximately 1.5 kcal/mol more stable than **8**.[29] Therefore, we undertook optimization of this reaction to produce acid **8**.

The nitrile hydrolysis reaction was monitored by ^{1}H NMR spectroscopy to determine the degree of isomerization and conversion under a variety of conditions. The product distribution was assessed by comparing the ^{1}H NMR integration of the **8′** hydrogen with a resonance at 3.92 ppm to the **8** hydrogen with a resonance at 2.92 ppm (see, for example, Figure S1). Bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile

Table 1. Hydrolysis of Bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile 4 in H_2O

entry	time (d)	temp (°C)	% yield **8** + **8′**[a]	**8**:**8′**[b]	% remaining **4**[b]
1	1	110		1:1	0
2	1	55	17%	3.5:1	11%
3	1	60	12%	3:1	10%
4	2	60	25%	3:1	0
5	4	50	49%	4:1	0
6	9	50	52%	4:1	0
7	4	40			100%

[a]Isolated yield of carboxylic acids **8** and **8′**. [b]As assessed by ^{1}H NMR spectroscopy of the quenched reaction.

4 does not dissolve well in water, and the hydrolysis reaction is necessarily biphasic. Thus, we tested for possible cosolvents to improve the reaction yield and rate. Methanol, DMSO, DMF, THF, or ethylene glycol was mixed with 2 M NaOH (1:1, v:v), nitrile **4** was added, and the mixture was heated to 50 °C for 1 day. Although the solutions were homogeneous, none of the solvent mixtures improved selectivity or yield compared to the purely aqueous system.

Subsequently, temperature was studied (Table 1, entries 1, 2, 3, 4, 7). At 110 °C, the hydrolysis reaction proceeded rapidly, but selectivity for the desired alkene isomer was low. At 40 °C, the reaction did not proceed after 4 days. At 50 °C, the highest selectivity was obtained.

The intermediate amide was also obtained as an undesired side product. We investigated extension of reaction time to increase the yield of **8** (Table 1 entries 4, 5, 6, 7). Doubling the reaction time from 2 to 4 days increased the yield of acid **8** from 25% to 50% (Table 1, entries 4, 5). Although an extended reaction time of 9 days did not reduce selectivity, minimal improvements in yield were obtained.

With an inexpensive and simple synthesis of nitrile **4** and acid **8**, we prepared amide **1** and ester **9** by standard coupling methods (Scheme 3). In addition, reduction of nitrile **4** with DIBAL-H provides aldehyde **10** in 36% yield isolated as a solution to prevent self-condensation. Next, the propensity of the [4.2.0] derivatives to undergo alternating ring-opening metathesis polymerization (AROMP) was tested.

Investigation of [4.2.0] Derivative AROMP. Using ^{1}H NMR spectroscopy, we followed the alternating ring-opening metathesis polymerization (AROMP) of each type of monomer (**4**, **8**, **9**, and **10**) with cyclohexene **3**. The alkene region of the spectrum was monitored to determine whether ring-opened polymer was obtained and the degree of regio- and stereocontrol obtained (Figure 1). The AROMP of amide **1** previously reported to form poly(**1**-*alt*-**3**)$_n$[26] was used as a positive control.

Nitrile 4. Nitrile **4** underwent very slow initiation with catalyst **2**. The slow initiation of **4** may be due to the strong electron withdrawing cyano group. Upon addition of a 2-fold molar excess of cyclohexene **3**, only 30% of monomer **4** was consumed after 24 h (Table 2, entry 1). Therefore, we used a large molar excess (20-fold excess) of cyclohexene **3** to push the equilibrium toward ring-opening metathesis polymerization. One hour after cyclohexene **3** addition, no AROMP product was detected as evidenced by the lack of new alkene protons in the ^{1}H NMR spectrum of the reaction. After 24 h, all the nitrile **4** disappeared and AROMP product appeared (Figures 1 and S2; Table 2, entry 2).

DOI: 10.1021/acs.joc.8b00054
J. Org. Chem. 2018, 83, 2892−2897

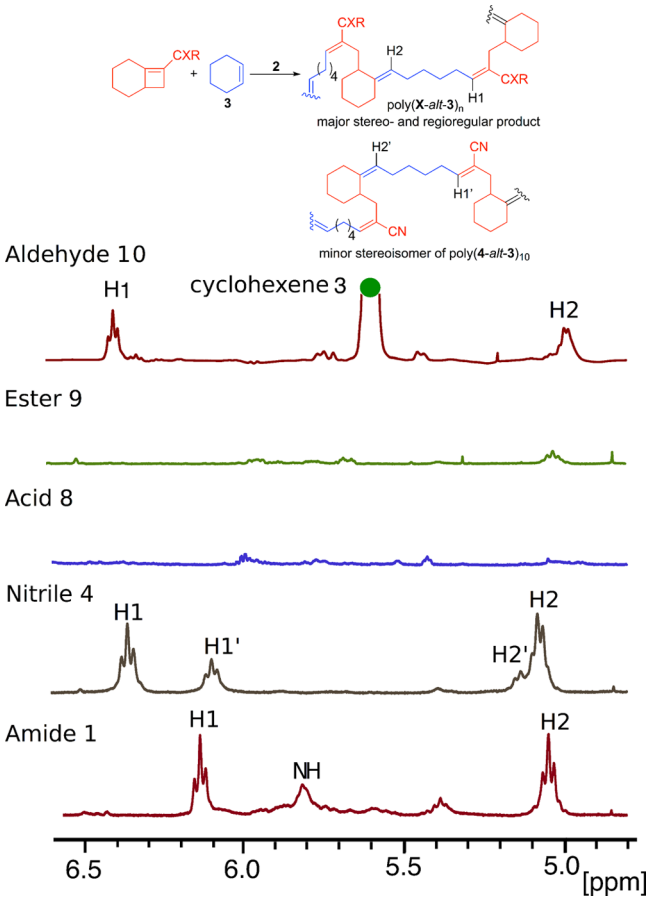


Figure 1. AROMP of **1**, **4**, **8**, **9**, **10** with cyclohexene **3**. The alkene region is shown in the figure. (Full spectra are included in the SI as Figures S2, S4–S6.) [4.2.0] Monomer **A** (0.25 M in $CDCl_3$,10 equiv for amide **1**, nitrile **4**, acid **8**, and ester **9**; 1.25 M in $CDCl_3$, 50 equiv for aldehyde **10**) was added to a solution of catalyst **2** (0.1 M in $CDCl_3$), and the reaction was initiated at 40 °C for 1 h. Then cyclohexene **3** (monomer **B**, 200 equiv) was added and the reaction was allowed to proceed for 1 h (amide **1** and aldehyde **10**) or 24 h (nitrile **4**, acid **8**, and ester **9**). For monomers **1**, **4**, **8**, and **9**, the reaction was quenched with excess ethyl vinyl ether, solvent was removed, and the crude product was redissolved in $CDCl_3$ and a ^{1}H NMR spectrum was acquired of the unpurified product(s).

Table 2. AROMP of [4.2.0] Monomers with Cyclohexene 3[a]

entry	A	[A]:[B[b]]:[2]	time (h)	conv
1	**4**	10:20:1	24	30%
2	**4**	10:200:1	24	100%
3	**9**	10:20:1	24	
4	**9**	10:200:1	24	
5	**8**	10:20:1	24	
6	**8**	10:200:1	24	
7	**10**	50:200:1	1	100%
8	**1**	100:200:1	1	89% isolated yield[26]
9	**1**	10:200:1	1	100%

[a]At 40 °C, [4.2.0] monomer is incubated with catalyst **2** in $CDCl_3$ for 1 h before addition of **3**, and the time of reaction after addition of **3** is measured. [b]Cyclohexene **3**.

Repeated attempts to purify the poly(**4**-*alt*-**3**)$_{10}$ polymer by silica column chromatography only yielded multiple decomposition products, which were not characterized further. Gel permeation chromatography analysis of the crude poly(**4**-*alt*-**3**)$_{10}$ polymer revealed that the expected molecular weight was obtained (M_n = 2300). However, the dispersity index was 1.7 (Figure S3), which is high in comparison to the narrower dispersity (1.1–1.2) poly(**1**-*alt*-**3**)$_n$ polymers obtained from amide **1**.[27] This high dispersity is consistent with the slow reaction times, suggesting that intermolecular chain transfer competes with AROMP of nitrile **4**.

Inspection of the alkene region of the ^{1}H NMR spectrum of poly(**4**-*alt*-**3**)$_{10}$ revealed that two isomers were formed during AROMP in approximately a 2:1 ratio (Figure 1). Previously, we established that the ^{1}H resonance of the *E*-alkene is shifted downfield compared to the *Z*-isomer.[30] Therefore, the major isomer of poly(**4**-*alt*-**3**)$_{10}$ formed is the *E*-alkene. The reduced selectivity for the *E*-alkene in the AROMP of nitrile **4** is consistent with reduced allylic 1,3 steric and electronic strain in the case of substitution of the alkene with the linear nitrile moiety. Thus, the carbonyl on the alkene amide substituent serves two functions. First, the amide increases the rate of AROMP compared to the nitrile, despite the strong nitrile dipole.[31] Second, the amide carbonyl is required to destabilize formation of the *Z*-alkene during metathesis of [4.2.0] monomer.

Ester 9. Surprisingly, bicyclo[4.2.0]oct-1(8)-ene-8-carboxylate ester **9** failed to react within 24 h under AROMP conditions, even with a large excess of cyclohexene **3** (Figures 1 and S4; Table 2, entries 3 and 4). It is unclear why ester **9** reacts more slowly than amide **1**. On the basis of ^{13}C chemical shifts, the electron density distribution on the alkene of ester **9** is similar to the alkene of amide **1** (124.1/163.9 vs 126.7/161.0 ppm). This low efficiency was unexpected considering that the isomeric methyl bicyclo[4.2.0]oct-7-ene-7-carboxylate readily undergoes AROMP with cyclohexene **3** and catalyst **2**, albeit at a slower rate than amide **1**.[27]

Acid 8. Similarly, acid **8** did not form a AROMP product with cyclohexene **3** (Table 2, entry 5). Even with an excess of cyclohexene **3**, after 24 h, no polymer was formed (Figures 1 and S5; Table 2, entry 6). Instead, the monomer decomposed under the reaction conditions, and further study was not pursued.

Aldehyde 10. Aldehyde **10** self-condenses if concentrated during distillation (bp ca. 70 °C); to prevent self-reaction, it was stored as a hexane solution (60% w/w in hexane). Despite these challenges, aldehyde **10** was subjected to AROMP conditions. The aldehyde monomer reacts rapidly within 1 h and undergoes regioselective AROMP reaction with cyclohexene **3** as evidenced by the appearance of alkene proton resonances at 5.0 and 6.4 ppm (Figures 1 and S6; Table 2, entry 7). The high reactivity of poly(**10**-*alt*-**3**)$_{50}$ precluded further characterization of the polymer molecular weight or molecular weight distribution by gel permeation chromatography.

■ CONCLUSION

In conclusion, we developed an efficient and scalable synthesis of bicyclo[4.2.0] acid **8** which provides ready and direct access to amide monomers for AROMP reactions. Additionally, this synthesis provided an opportunity to explore the scope of the AROMP reaction. Although the nitrile monomer **4** undergoes stereoirregular AROMP, the long reaction times led to a high dispersity. Therefore, the utility of this monomer is limited. The aldehyde monomer **10** is an interesting prospect for development based on its excellent kinetic performance in the cyclohexene **3** AROMP reaction. Although the resulting aldehyde polymer was very reactive and difficult to isolate for

DOI: 10.1021/acs.joc.8b00054
J. Org. Chem. 2018, 83, 2892–2897

full characterization, pre- or post-polymerization modification procedures will be pursued to introduce more complex functionality in the future. Our results suggest that the AROMP reaction is very sensitive to subtle shifts in carbonyl orientation and alkene substituent polarity. We conclude that a carbonyl on the alkene substituent is required for rapid, regio- and stereoregular AROMP between [4.2.0] monomers and cyclohexene **3**, but is not sufficient to ensure reaction.

EXPERIMENTAL SECTION

General Materials and Methods. Solvents, e.g., CH_2Cl_2 and THF, were purified with Pure Process Technology (PPT).[26] Deuterated solvents for all ring-opening reactions were degassed and filtered through basic alumina before use. Catalyst $Cl_2(H_2IMes)(PCy_3)Ru{=}CHPh$ and poly(styrene) standards were purchased from Aldrich. Freshly prepared catalyst $(3\text{-Br-Pyr})_2Cl_2(H_2IMes)Ru{=}CHPh$, **2**,[32] should be used to minimize oxidative degradation. Heteronuclear singular quantum correlation (HSQC) was used to establish atom connectivity and spatial relationships of acid **8**. Molecular weights (M_n and M_w) and polydispersity indices (M_w/M_n) were determined by gel permeation chromatography (GPC) using a Phenogel 5 μm 10E4A LC column (300 × 7.8 mm, 500 kDa exclusion limit, Phenomenex) with tetrahydrofuran as the mobile phase at 30 °C. Output was detected with a Brookhaven Instruments refractive index and light scattering detector using an eluent flow rate of 0.7 mL/min and a 200 μL injection loop.

Mallinckrodt silica gel 60 (230−400 mesh) was used for column chromatography. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates ($60F_{254}$), flash chromatography on silica gel-60 (230−400 mesh), and Combi-Flash chromatography on RediSep normal phase silica columns (silica gel-60, 230−400 mesh). R_f values reported are measured by TLC in the same solvent system used for column chromatography. Bruker Nanobay 400, Avance III 500, and Avance III 700 NMR instruments were used for analysis. Chemical shifts were calibrated from residual undeuterated solvents; they are denoted in ppm (δ). Functional groups for monomers and polymers were characterized using Fourier transform infrared spectroscopy (Nicolet iS 10 spectrophotometer Thermo Scientific, Inc.) and are expressed in cm^{-1}. GC/MS (Agilent LC-MSD, with a 1100 HPLC and G1956A mass spectrometer), was performed with an injection volume of 15 μL, column temperature = 26−35 °C, and MSD gas temperature = 300 °C.

Bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile, 4.[28] A 250 mL round-bottom flask containing 4 Å molecular sieves and cyclohexanone (19.1 g, 195 mmol) in toluene (100 mL) was fitted with a Dean−Stark trap with a reflux condenser and heating mantle. Pyrrolidine (30 mL, 365 mmol) was added to the above solution. The solution was heated to reflux for 18 h. The solvent was evaporated to yield crude 1-*N*-pyrrolidinylcyclohexene **5** as a yellow oil (29 g, 97% yield) with spectra identical to the literature.[33]

Crude **5** (crude, 5.5 mL, 70 mmol) in pentane (10 mL) was mixed with acrylonitrile (6.0 mL, 91 mmol) at 0 °C. The temperature was allowed to rise to rt (25 °C) over 1 h. The mixture was kept at 0 °C overnight and then cooled to −78 °C. The suspension was filtered to provide 1-*N*-pyrrolidinylbicyclo[4.2.0]octane-8-carbonitrile **6**[28] as a yellow waxy solid (13.4 g, 94% yield from **5**). The crude product was used immediately in the next reaction without further purification.

Crude **6** (crude, 1.0 g, 5 mmol) in dry diethyl ether (3 mL) was cooled to 0 °C. Methyl iodide (1.0 mL, 16 mmol) was added dropwise. The flask was stoppered and stored at rt for 7 days. Solvent was evaporated to give methyl iodide **7** as an amorphous solid. Crude methyl iodide **7** in water (5 mL) was mixed with 10% sodium hydroxide (4 mL); then the mixture was extracted with diethyl ether (20 mL × 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The residue was purified by silica column chromatography (EA/hexane = 1:100, R_f = 0.1) to provide bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile **4** as a yellow oil (0.54 g, 45% yield from **6**). The NMR, IR, and UV spectra were identical to the literature.[28]

Bicyclo[4.2.0]oct-8-ene-8-carboxylic acid, 8. Nitrile **4** (200 mg, 1.5 mmol) was mixed with 20% potassium hydroxide (20 mL) in a 25 mL flask. The reaction was heated to 50 °C for 4 days under an N_2 atmosphere. The cooled mixture was extracted with CH_2Cl_2 (20 mL × 3). The organic phase was dried over Na_2SO_4 to give bicyclo[4.2.0]-oct-1(8)-ene-8-carboxamide as a yellow amorphous solid (97 mg, 43% yield from **4**).[28] ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (s, 1H), 5.41 (s, 1H), 2.82 (dd, J = 3.8, 14.0 Hz, 1H), 2.72 (dt, J = 3.8, 12.1 Hz, 1H), 2.39 (m, 1H), 2.22 (ddd, J = 1.2, 3.0, 12.1 Hz, 1H), 2.17−2.05 (m, 2H), 1.98−1.92 (m, 1H), 1.80−1.74 (m, 1H), 1.37−1.31 (m, 2H), 1.19−1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 165.9, 163.0, 126.0, 37.9, 34.2 32.9, 27.4, 26.8, 24.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{14}NO$ 152.1075; Found 152.1072.

The aqueous phase was acidified to pH = 1 with HCl (2 M) and then extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The oily residue was purified by silica column chromatography (CH_2Cl_2, R_f = 0.8) to yield **8** as a 4:1 mixture with **8′**. The product was further purified by combined recrystallization (hexane) to give **8** as a white solid (87 mg, 38% yield from starting material **4**), mp 72−74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.75 (br, 1 H), 2.93 (dd, J = 3.2 Hz, 1H), 2.76 (dt, 1H), 2.41 (m, 1H), 2.28 (dd, J = 15.4 Hz, 1H), 2.17 (m, J = 2.3 Hz, 1H), 2.08 (m, J = 6.6 Hz, 1H), 1.98 (m, 1H), 1.76 (m, J = 2.2 Hz, 1H), 1.40−1.28 (m, J = 2.0, 2H), 1.20−1.11 (m, J = 11.24 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 171.4, 168.4, 123.4, 38.8, 34.2 33.1, 27.8, 26.9, 24.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}O_2$ 153.0916; Found 153.0911.

***N*-Propyl Bicyclo[4.2.0]oct-8-ene-8-carboxamide, 1.** Bicyclo-[4.2.0]oct-8-ene-8-carboxylic acid **8** (66.5 mg, 0.5 mmol) was dissolved in 0.8 mL of dry CH_2Cl_2 in a 4 mL vial. The solution was stirred and cooled to 0 °C for 30 min. Oxalyl dichloride (2.0 mmol, 175 μL) was added. The mixture was allowed to react for 1 h at rt, and the vial was evacuated for 30 min under high vacuum to evaporate solvent and residual oxalyl dichloride. *N*-Propylamine (57.5 μL, 0.7 mmol) and DIPEA (280 μL, 1.6 mmol) were dissolved in 0.5 mL of dry CH_2Cl_2. The solution was stirred at 0 °C for 1 h and then transferred to the vial containing acid chloride at 0 °C. The mixture was stirred for an additional 16 h. The reaction mixture was washed sequentially with 5% $NaHCO_3$ (3 × 20 mL), 1 N HCl (3 × 20 mL), and brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was filtered and removed by evaporation. The crude product was purified by silica column chromatography (CH_2Cl_2/Methanol = 10:1, R_f = 0.7) to give amide **1** as a white solid (82 mg, 85% yield). IR 3303, 2925, 2845, 1675, 1627, 1533, 1431 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were identical to those previously reported from the synthesis of **1** via a different route.[34]

Ethyl Bicyclo[4.2.0]oct-1(8)-ene-8-carboxylate, 9. Acid **8** (76 mg, 0.5 mmol) was dissolved in 1 mL of DMF. Potassium carbonate (84 mg, 0.6 mmol) and ethyl iodide (100 μL, 1.2 mmol) were added at rt (25 °C), and the solution was stirred for 24 h at rt. The solution was diluted with water (10 mL) and extracted with EtOAc (20 mL). The organic phase was washed with brine (3 × 20 mL) and dried over Na_2SO_4. The solvent was removed to give ester **9** as a clear oil (85 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (q, J = 5 Hz, 2H), 2.87 (dd, J = 3, 13.5 Hz, 1H), 2.75 (td, J = 3.5, 12.5 Hz, 1H), 2.34−2.41 (m, 1H), 2.24 (ddd, J = 1, 3, 12.5 Hz, 1H), 2.11−2.18 (m, 1H), 1.91−1.98 (m, 1H), 1.74−1.79 (m, 1H), 1.28−1.35 (m, 5H), 1.10−1.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 167.2, 163.9, 124.1, 59.6, 38.4, 34.4, 33.0, 27.5, 26.9, 24.6, 14.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}HO_2$ $[M + H]^+$ 181.1229; Found 181.1218.

Bicyclo[4.2.0]oct-1(8)-ene-8-carboxaldehyde, 10.[35,36] Nitrile **4** (132 mg, 1.0 mmol) in dry CH_2Cl_2 (0.9 mL) was cooled to −78 °C. DIBAL-H (1.05 mL, 1.05 mmol, 1.0 M in hexane) was added. The mixture was stirred for 30 min at −78 °C, and for 2 h at −40 °C until **4** was completely consumed as determined by GC/MS analysis. The system was cooled to −78 °C, and 0.5 mL of EtOAc was added over 10 min. After stirring for 30 min, the temperature was raised to rt and the reaction was stirred for another 30 min. The solution was diluted with 30 mL of Et_2O and was washed with 1 M HCl (3 × 20 mL) and dried over Na_2SO_4. The solvent was removed carefully by distillation

DOI: 10.1021/acs.joc.8b00054
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to give crude **10** as a clear oil (36% yield,60% in hexane w:w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 2.87 (td, J = 3.75, 10.67 Hz, 1H), 2.69−2.75 (td, J = 3.11, 1H), 2.43−2.48 (m, 1H), 2.04−2.35 (m, J = 0.99, 10.43 Hz, 3H), 2.11−2.18 (m, 1H), 1.93−2.03 (m, 1 J = 1.59 Hz, 1H), 1.71−1.78 (m, 2H), 1.29−1.38 (m, 2H), 1.07−1.28 (m, 3H), 0.81−0.98 (m, J = 6.91 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.3, 172.8, 134.2, 39.6, 33.2, 32.8, 27.2, 26.9, 22.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}O$ 137.0966; Found 137.0943.

General Procedure for NMR Scale AROMP Reactions. All experiments were performed under a N_2 atmosphere. A solution of [4.2.0] monomer **A** in 400 μL of $CDCl_3$ was added to the NMR tube; then catalyst **2** in 100 μL of $CDCl_3$ was added to the NMR tube. The NMR tube was heated in a water bath at 40 °C. Cyclohexene **3** (monomer **B**) was added after the catalyst was consumed as judged by the disappearance of the Ru alkylidene resonance at 19.1 ppm, or 1 h after the catalyst was added, whichever was shorter. After all monomer **A** was consumed as judged by the disappearance of the ^{1}H NMR peak around 2.9 ppm, or after 24 h, the reaction was quenched with excess ethyl vinyl ether for 30 min. The solvent was evaporated and the crude product was redissolved in $CDCl_3$ for NMR characterization.

*AROMP of N-Propyl Bicyclo[4.2.0]oct-8-ene-8-carboxamide **1**.* Amide **1** (19 mg, 0.1 mmol, 10 equiv) was dissolved in 400 μL of $CDCl_3$. Subsequently, a solution of catalyst **2** (8.9 mg, 0.01 mmol, 1 equiv) in 100 μL of $CDCl_3$ was added. After 1 h, 200 μL of **3** (200 equiv) was added. After 1 h, 50 μL of ethyl vinyl ether was added, and the reaction was stirred for 30 min. The solvent was evaporated and the reaction product was characterized in $CDCl_3$ by NMR spectroscopy, and regi- and stereoregular polymer product poly(**1**-*alt*-**3**)$_{10}$ was obtained. The ^{1}H NMR and ^{13}C NMR spectra were identical to those previously reported.[34] IR 3305, 2923, 2853, 1653, 1616 cm^{-1}.

*AROMP of Bicyclo[4.2.0]oct-8-ene-8-carboxylic acid **8**.* Acid **8** (15 mg, 0.1 mmol, 10 equiv) was dissolved in 400 μL of $CDCl_3$. Subsequently, a solution of catalyst **2** (8.9 mg, 0.01 mmol, 1 equiv) in 100 μL of $CDCl_3$ was added. After 1 h, 200 μL of **3** (200 equiv) was added. After 24 h, AROMP product was not observed in the ^{1}H NMR spectrum and 50 μL of ethyl vinyl ether was added, and the reaction was stirred for 30 min. The solvent was evaporated and the reaction product was characterized in $CDCl_3$ by NMR spectroscopy, and no polymer was obtained.

*AROMP of Bicyclo[4.2.0]oct-1(8)-ene-8-carbonitrile **4**.* Nitrile **4** (13 mg, 0.1 mmol, 10 equiv) was dissolved in 400 μL of $CDCl_3$. Subsequently, a solution of catalyst **2** (8.9 mg, 0.01 mmol, 1 equiv) in 100 μL of $CDCl_3$ was added. After 1 h, 200 μL of **3** (200 equiv) was added. After 24 h, 50 μL ethyl vinyl ether was added, and the reaction was stirred for 30 min. The solvent was evaporated, and the reaction product was characterized by NMR and IR spectroscopy. Stereoirregular polymer product poly(**4**-*alt*-**3**)$_{10}$ was obtained. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.37 (t, J = 14.28, 0.54 H), 6.11 (s, 0.33 H), 5.00−5.20 (m, J = 7.35, 1H), 2.41−2.62 (M, 2H), 2.36 (m, 2H), 1.96−2.27 (m, J = 6.65, 7H), 1.27−1.75 (m, J = 9.59, 7.14, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): 148.7, 140.5, 129.0, 120.3, 114.2, 42.9, 42.8, 42.7, 42.2, 37.0, 32.7, 31.4, 29.6, 29.4, 28.6, 28.3, 28.2, 28.1, 28.0, 27.8, 26.8, 26.7, 25.6, 23.6, 15.3. IR 2923, 2852, 2213, 1447, 1263 cm^{-1}. M_n^{GPC} = 2.3K. $Đ_M$ = 1.70.

*AROMP of Bicyclo[4.2.0]oct-1(8)-ene-8-carboxylate **9**.* Ester **9** (18 mg, 0.1 mmol, 10 equiv) was dissolved in 400 μL of $CDCl_3$. Subsequently, a solution of catalyst **2** (8.9 mg, 0.01 mmol, 1 equiv) in 100 μL of $CDCl_3$ was added. After 1 h, 200 μL of **3** (200 equiv) was added. After 24 h, AROMP product was not observed in the ^{1}H NMR spectrum and 50 μL of ethyl vinyl ether was added, and the reaction was stirred for 30 min. The solvent was evaporated and the reaction product was characterized in $CDCl_3$ by NMR spectroscopy, and no polymer was obtained.

*AROMP of Bicyclo[4.2.0]oct-1(8)-ene-8-carboxaldehyde **10**.* Aldehyde **10** (68.0 mg, 0.5 mmol, 50 equiv) was dissolved in 400 μL of $CDCl_3$. Subsequently, a solution of catalyst **2** (8.9 mg, 0.01 mmol, 1 equiv) in 100 μL of $CDCl_3$ was added to the NMR tube. After 1 h, the Ru alkylidene resonance at 19.1 ppm disappeared and 200 μL of **3** (200 equiv) was added. AROMP product poly(**10**-*alt*-**3**)$_{50}$ was the sole product observed in the ^{1}H NMR spectrum after 1 h. 50 μL of ethyl vinyl ether was added, and the reaction was stirred for 30 min. Repeated attempts to isolate the aldehyde polymer were unsuccessful. Crude material showed regions of interest via ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.29 (s, 1H), 6.41 (s, 1 H), 5.01 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00054.

Supplemental figures and spectra of compounds synthesized (PDF)

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Notes

The authors declare the following competing financial interest(s): Acid monomer 8 and nitrile monomer 4 are available for purchase through Kerafast to enable the chemical community to use the [4.2.0] AROMP method.

■ ACKNOWLEDGMENTS

We acknowledge funding from NSF CHE1609494 and NIH-NIGMS GM097971. We thank Guofang Li for help in initiating these experiments.

■ REFERENCES

(1) Chen, P. *Acc. Chem. Res.* **2016**, *49*, 1052.
(2) Parker, K. A.; Sampson, N. S. *Acc. Chem. Res.* **2016**, *49*, 408.
(3) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.
(4) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.
(5) Lutz, J.-F.; Ouchi, M.; Liu, D. R.; Sawamoto, M. *Science* **2013**, *341*, 1238149.
(6) Chang, A. B.; Miyake, G. M.; Grubbs, R. H. In *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties*; American Chemical Society: Washington, DC, 2014; Vol. *1170*, p 161.
(7) ten Brummelhuis, N.; Wieczorek, S.; Wilke, P.; Schwemmer, T.; Börner, H. G. In *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties*; American Chemical Society: Washington, DC, 2014; p 55.
(8) Li, J.; Washington, M. A.; Bell, K. L.; Weiss, R. M.; Rothstein, S. N.; Little, S. R.; Edenborn, H. M.; Meyer, T. Y. In *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties*; American Chemical Society: Washington, DC, 2014; Vol. *1170*, p 271.
(9) Shirota, Y.; Yoshimura, M.; Matsumoto, A.; Mikawa, H. *Macromolecules* **1974**, *7*, 4.
(10) Chen, G.-Q.; Wu, Z.-Q.; Wu, J.-R.; Li, Z.-C.; Li, F.-M. *Macromolecules* **2000**, *33*, 232.
(11) Lutz, J.-F.; Kirci, B.; Matyjaszewski, K. *Macromolecules* **2003**, *36*, 3136.
(12) Terashima, T.; Sawamoto, M. In *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties*; American Chemical Sociey: Washington, DC, 2014; Vol. *1170*, p 255.
(13) Trott, G.; Saini, P. K.; Williams, C. K. *Philos. Trans. R. Soc., A* **2016**, *374*, 20150085.
(14) Yokozawa, T.; Ohta, Y. *Chem. Rev.* **2016**, *116*, 1950.
(15) Norris, B.; Zhang, S.; Campbell, C.; Auletta, J.; Calvo-Marzal, P.; Hutchison, G.; Meyer, T. *Macromolecules* **2013**, *46*, 1384.
(16) Buchmeiser, M. R. *Polym. Rev.* **2017**, *57*, 15.
(17) Elling, B. R.; Xia, Y. *J. Am. Chem. Soc.* **2015**, *137*, 9922.

DOI: 10.1021/acs.joc.8b00054
J. Org. Chem. 2018, 83, 2892−2897

(18) Guillaume, S. M.; Kirillov, E.; Sarazin, Y.; Carpentier, J. F. *Chem. - Eur. J.* **2015**, *21*, 7988.
(19) Lee, H.-K.; Bang, K.-T.; Hess, A.; Grubbs, R. H.; Choi, T.-L. *J. Am. Chem. Soc.* **2015**, *137*, 9262.
(20) Lin, T.-P.; Chang, A. B.; Chen, H.-Y.; Liberman-Martin, A. L.; Bates, C. M.; Voegtle, M. J.; Bauer, C. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2017**, *139*, 3896.
(21) Moatsou, D.; Nagarkar, A.; Kilbinger, A. F.; O'Reilly, R. K. *J. Polym. Sci., Part A: Polym. Chem.* **2016**, *54*, 1236.
(22) Paul, S.; Zhu, Y.; Romain, C.; Brooks, R.; Saini, P. K.; Williams, C. K. *Chem. Commun.* **2015**, *51*, 6459.
(23) Tuba, R.; Al-Hashimi, M.; Bazzi, H. S.; Grubbs, R. H. *Macromolecules* **2014**, *47*, 8190.
(24) Jang, E. S.; John, J. M.; Schrock, R. R. *ACS Cent. Sci.* **2016**, *2*, 631.
(25) Jang, E. S.; John, J. M.; Schrock, R. R. *J. Am. Chem. Soc.* **2017**, *139*, 5043.
(26) Tan, L.; Li, G.; Parker, K. A.; Sampson, N. S. *Macromolecules* **2015**, *48*, 4793.
(27) Tan, L.; Parker, K. A.; Sampson, N. S. *Macromolecules* **2014**, *47*, 6572.
(28) Fleming, I.; Harley-Mason, J. *J. Chem. Soc.* **1964**, 2165.
(29) Curran, K.; Risse, W.; Hamill, M.; Saunders, P.; Muldoon, J.; Asensio de la Rosa, R.; Tritto, I. *Organometallics* **2012**, *31*, 882.
(30) Lee, J.; Parker, K. A.; Sampson, N. S. *J. Am. Chem. Soc.* **2006**, *128*, 4578.
(31) Song, A.; Lee, J. C.; Parker, K. A.; Sampson, N. S. *J. Am. Chem. Soc.* **2010**, *132*, 10513.
(32) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035.
(33) Naik, M.; Ghorpade, S.; Jena, L. K.; Gorai, G.; Narayan, A.; Guptha, S.; Sharma, S.; Dinesh, N.; Kaur, P.; Nandishaiah, R.; Bhat, J.; Balakrishnan, G.; Humnabadkar, V.; Ramachandran, V.; Naviri, L. K.; Khadtare, P.; Panda, M.; Iyer, P. S.; Chatterji, M. *ACS Med. Chem. Lett.* **2014**, *5*, 1005.
(34) Song, A.; Parker, K. A.; Sampson, N. S. *Org. Lett.* **2010**, *12*, 3729.
(35) Jansen, F.; Kwestro, M.; Schmitt, D.; Lugtenburg, J. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 552.
(36) Hirata, Y.; Tanaka, M.; Yada, A.; Nakao, Y.; Hiyama, T. *Tetrahedron* **2009**, *65*, 5037.

DOI: 10.1021/acs.joc.8b00054
J. Org. Chem. 2018, 83, 2892−2897