



A versatile approach for the synthesis of degradable polymers via controlled ring-opening metathesis copolymerization

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Norbornene derivatives (NBEs) are common monomers for living ring-opening metathesis polymerization and yield polymers with low dispersities and diverse functionalities. However, the all-carbon backbone of poly-NBEs is non-degradable. Here we report a method to synthesize degradable polymers by copolymerizing 2,3-dihydrofuran with NBEs. 2,3-Dihydrofuran rapidly reacts with Grubbs catalyst to form a thermodynamically stable Ru Fischer carbene—the only detectable active Ru species during copolymerization—and the addition of NBEs becomes rate determining. This reactivity attenuates the NBE homoaddition and allows uniform incorporation of acid-degradable enol ether linkages throughout the copolymers, which enables complete polymer degradation while maintaining the favourable characteristics of living ring-opening metathesis polymerization. Copolymerization of 2,3-dihydrofuran with NBEs gives low dispersity polymers with tunable solubility, glass transition temperature and mechanical properties. These polymers can be fully degraded into small molecule or oligomeric species under mildly acidic conditions. This method can be readily adapted to traditional ring-opening metathesis polymerization of widely used NBEs to synthesize easily degradable polymers with tunable properties for various applications and for environmental sustainability.

Ring-opening metathesis polymerization (ROMP) is a widely used method to synthesize diverse functional polymers from cyclic olefins¹. In particular, living ROMP of norbornene derivatives (NBEs) readily produces low dispersity homopolymers and block copolymers with a wide range of properties, functionalities and architectures under mild conditions. Degradable polymers are highly desired for many technological and biomedical applications, as well as for environmental sustainability^{2–4}. But ROMP polymers typically consist of non-degradable all-hydrocarbon backbones, and the lack of backbone degradability has been a major limitation for ROMP chemistry. To this end, several special cyclic olefinic monomers that contain cleavable linkages were developed, but these monomers require multistep syntheses and often result in uncontrolled polymerizations^{5–9}. In addition, the special monomer designs limit accessible polymer structures and functionalities. Other approaches include the use of low-strain monomers with high equilibrium monomer concentrations^{10–12}.

Alternatively, a low-strain cyclic monomer (which often does not readily homopolymerize) that contains a cleavable linkage can be copolymerized with NBEs or other strained monomers to incorporate degradable linkages in the backbone^{13–19}. However, a remaining challenge for this copolymerization approach is that the homopropagation of NBEs is exceedingly fast compared to the addition of less-strained cyclic olefins that bear a degradable linkage^{13,15,16}. As a result, the produced copolymers contain large strands of NBE homopolymer that cannot be degraded. Additionally, the current copolymerization strategies often compromise the typical characteristics of living ROMP and produce copolymers with relatively high dispersity due to chain transfer on the unhindered backbone olefins during ROMP. Despite the recent progress²⁰, a simple and versatile approach for ROMP remains needed to access degradable polymers with controlled molecular weights (MWs), diverse properties and complete degradation. Ideally, this approach should retain the char-

acteristics of living ROMP, leverage the diverse structures of widely used NBEs and not require specially synthesized comonomers.

We recently reported the unexpected ROMP of 2,3-dihydrofuran (DHF), a commercially available cyclic enol ether, to form hydrolytically degradable poly-DHF²¹. Gutekunst and co-workers concurrently showed alternating cascade copolymerization of DHF with alkynes²². The efficacy of these polymerizations was particularly surprising due to the ubiquitous use of enol ethers to quench Grubbs catalysts via the generation of an electron-rich alkoxy-methylidene Fischer carbene, which is thermodynamically stable, but kinetically deactivated relative to typical Grubbs alkylidenes^{23–25}. Louie and Grubbs showed that the Fischer carbene exhibits metathesis activity for highly strained olefins, albeit substantially attenuated²⁴. Ozawa and co-workers and Liu and Rainier have likewise demonstrated ring-opening cross metathesis of (oxa)NBEs with the Grubbs Fischer carbenes^{26,27}. Intrigued by these observations, we hypothesized that DHF may be a particularly effective comonomer with NBEs to impart degradability and suppress the continuous homoaddition of NBEs that results in long segments of non-degradable poly-NBEs. Here we demonstrate that the addition of DHF to the ROMP of various NBEs is an easy and versatile method for the synthesis of degradable polymers with narrow dispersities, tunable properties and facile complete degradation under mildly acidic conditions.

Results and discussion

We explored copolymerization of DHF with several NBEs using a simple procedure typical of living ROMP. First, we examined copolymerization with *exo*-norbornene dimethyl ester **1** (Fig. 1). DHF and **1** were dissolved in THF (0.15 M for each monomer) at a 1:1 molar ratio, and the solution was initiated under inert atmosphere at room temperature by adding 0.02 equiv. third generation Grubbs catalyst (**G3**) to target a total degree of polymerization (DP) of 100.

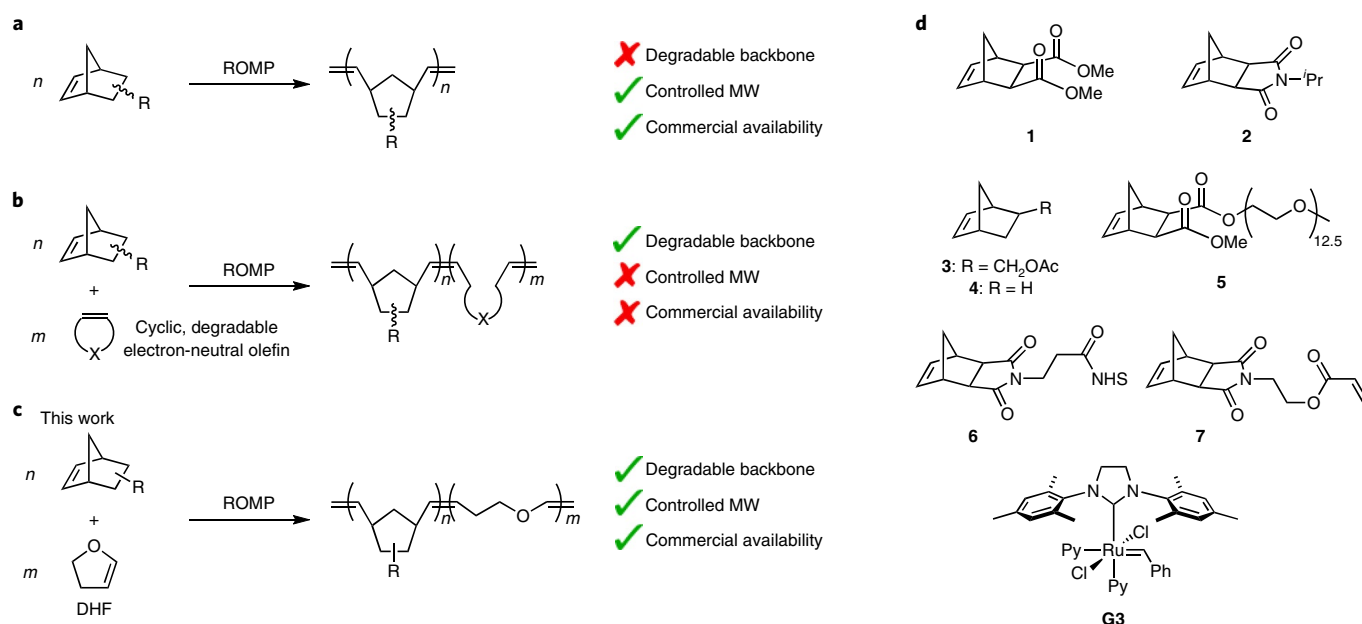


Fig. 1 | Different strategies and compound types for producing ROMP-based materials. **a.** The ROMP of typical NBE monomers results in polymers with non-degradable all-carbon backbones but well-controlled MWs. **b.** Copolymerization with cleavable electron-neutral cyclic olefins results in sporadic addition of cleavable linkages to the copolymer backbone and often broad MW distributions. **c.** Copolymerization with commercial DHF results in an even distribution of cleavable linkages along the backbone while maintaining good MW control. **d.** The structures of the NBE comonomers used in this work and the catalyst **G3**. NHS, *N*-hydroxysuccinimide.

Table 1 | ROMP copolymers of DHF with norbornenes^a

Polymer	NBE	DP	[NBE] ₀ : [DHF] ₀ [G3] ₀ ^b	Polymerization time (h)	Comonomer incorporation (NBE:DHF) ^c	Conversion (%) ^d	<i>M</i> _{n,MALLS} (kDa) ^e	<i>M</i> _{n,theoretical} (kDa) ^f	<i>Đ</i> ^g
P1a	1	100	50:50:1	2	100:75	94	13.4	13.3	1.05
P1b	1	200	100:100:1	2	100:78	94	23.7	26.5	1.09
P1c ^h	1	600	300:300:1	3	100:67	76	65.2	58.7	1.04
P2a	2	200	100:100:1	10	100:82	78	19.3	20.6	1.03
P2b	2	150	100:50:1	10	100:43	79	18.0	18.7	1.09
P2c	2	150	50:100:1	10	100:90	70	10.1	9.9	1.14
P2d	2	600	300:300:1	10	100:84	76	57.6	60.2	1.24
P3	3	200	100:100:1	0.75	100:45	>95	21.3	19.5	1.12
P4	4	200	100:100:1	0.75	100:41	>95	10.0	12.5	1.23
P5	5	200	100:100:1	2.75	100:96	95	83.6	89.0	1.07
P7	7	200	100:100:1	2	100:72	65	16.1	21.0	1.12

^aROMP was performed under an N₂ atmosphere at room temperature in THF with [NBE]₀ = 0.15 M. ^bInitial equivalents of NBE:DHF:Grubbs initiator. ^cRatio of monomers incorporated into copolymers, determined by ¹H NMR spectroscopy in CDCl₃. ^dConversion of NBE determined by ¹H NMR spectroscopy. ^eDetermined by GPC multiangle light scattering (MALLS) analysis in THF. ^fTheoretical *M*_n based on NBE conversion and composition determined by ¹H NMR spectroscopy. ^g*M*_w/*M*_n. ^hPolymerized with 5 equiv. 3-bromopyridine.

Owing to the reduced reactivity of the Fischer carbene generated in situ, the copolymerization was considerably slower than that typical of the ROMP of NBEs, which is often complete in minutes, but >90% conversion of **1** was still achieved within two hours. Excess ethyl vinyl ether was then added and the solution was stirred for 10 minutes to cleave the catalyst from the active chain end and terminate the polymerization. A white, rubbery polymer was isolated by precipitation into methanol. Although we previously showed that the addition of linear vinyl ether at the end of DHF homopolymerization resulted in a decreased polymer MW due to secondary enol

ether metathesis reactions²¹, no change in the MW or dispersity (*Đ*) of the NBE–DHF copolymer was observed after the addition of excess vinyl ether, even after 12 hours (Supplementary Fig. 1).

Gel permeation chromatography (GPC) analysis of the copolymer showed a peak with *Đ* < 1.1 and *M*_n = 13.4 kDa, which closely matched the theoretical value (Table 1 and Fig. 2a) and indicated a controlled polymerization with minimal chain transfer on the backbone olefins. ¹H NMR spectroscopy showed a composition of NBE:DHF = 100:78 for the isolated polymer (Supplementary Fig. 22). Only olefinic signals that corresponded to the *E*- and *Z*-isomers

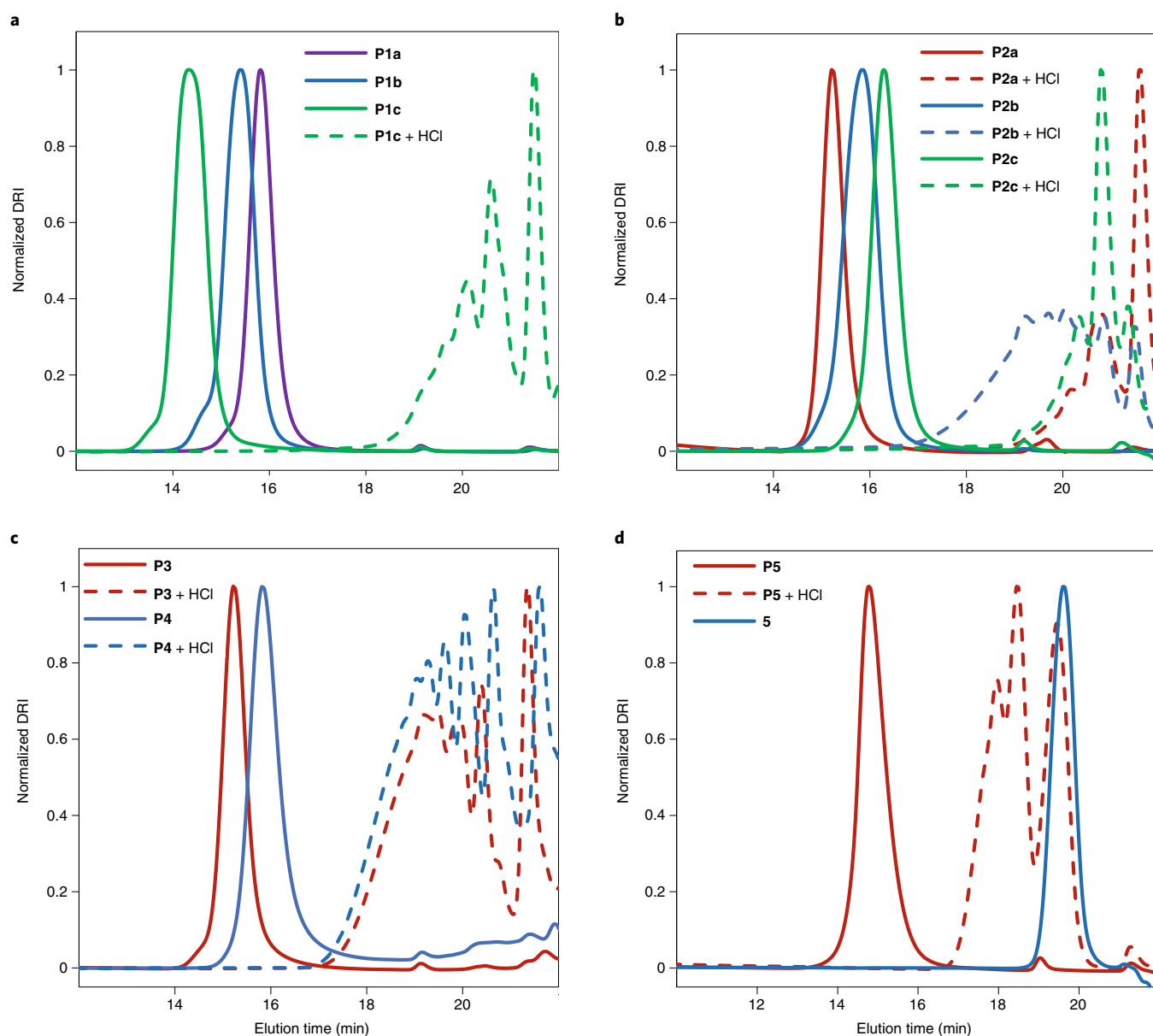


Fig. 2 | DHF-NBE copolymers and copolymer degradation products. **a–d**, GPC traces for copolymers of DHF with **1** (**a**), **2** (**b**), **3** and **4** (**c**) and **5** (**d**), and their respective acid-catalysed hydrolytic degradation products are shown by dashed lines. Degradable copolymers with well-controlled MWs can be readily synthesized with an array of NBE monomers. The size of the degradation products decreases with increasing copolymer DHF content. DRI, differential refractive index.

of the NBE–DHF heterodyads and NBE–NBE homodyads were observed in the ^{13}C NMR spectrum (Fig. 3). The absence of DHF–DHF homodyads and a high DHF content in the copolymer suggest that DHF units are incorporated throughout the copolymerization.

We then increased the targeted total DP while keeping the NBE:DHF feed ratio at 1:1. At a targeted DP of 200, the copolymer exhibited a similarly low dispersity and expected MW (Fig. 2a). However, when a high total DP of 600 was targeted, although >90% conversion was still achieved, a high MW shoulder in the GPC peak was observed (Supplementary Fig. 2). A labile ligand, 3-bromopyridine (5 equiv.), was added to the polymerization mixture prior to initiation to suppress chain coupling or other side reactions^{28,29}, and resulted in a controlled copolymer with $\bar{D}=1.04$ and M_n close to the theoretical value (Fig. 1a).

We next monitored the NBE conversion by ^1H NMR spectroscopy at $[1]_0=[\text{DHF}]_0=0.15\text{ M}$, and obtained a linear plot of $\ln[1]$

versus time (Supplementary Fig. 5), which suggests first-order kinetics for NBE. Interestingly, as $[\text{DHF}]_0$ was varied at 0.075, 0.15 or 0.3 M with fixed $[\text{NBE}]_0=0.15\text{ M}$, the polymerization rate remained unchanged, which indicates zero-order kinetics for DHF. These observations suggest that the addition of DHF to the propagating chain end is rapid, and the subsequent reaction of the Fischer carbene with NBE is the rate-limiting step. In addition, only ^1H NMR signals that correspond to the Fischer carbene were observed during the copolymerization (Supplementary Fig. 6), which indicates that the Fischer carbene is, indeed, the dominating Ru species. The reactivity ratios of the two monomers were measured to be $r_1=0.41$ and $r_{\text{DHF}}=0.088$ via the Meyer–Lowry method^{30,31}. The small product of the reactivity ratios ($r_1 \times r_{\text{DHF}} < 0.1$) suggests a moderate degree of monomer alternation in this copolymerization. The even incorporation of degradable DHF units throughout the polymer chain is highly desired to prevent the formation of long non-degradable

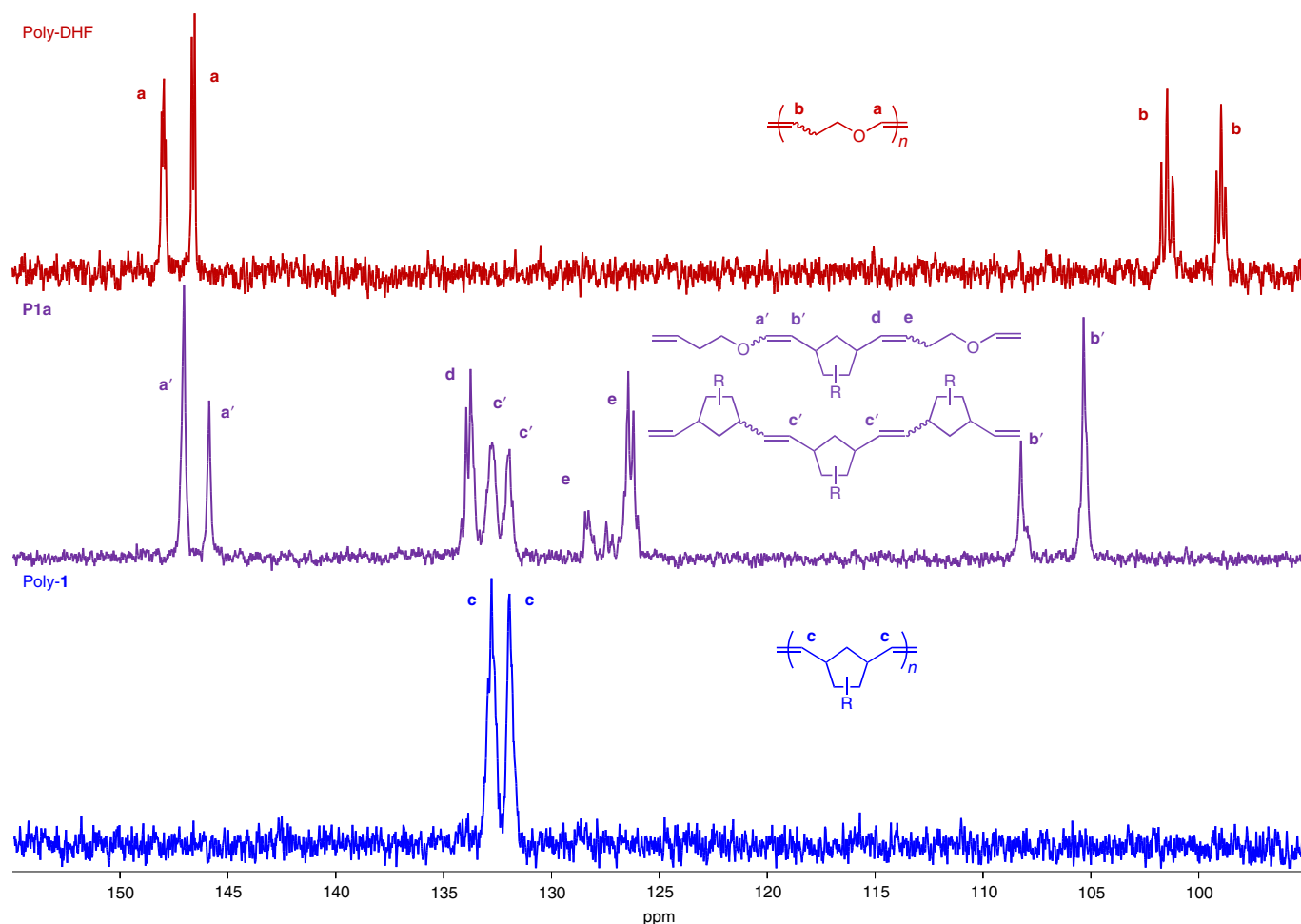


Fig. 3 | ^{13}C NMR spectroscopic analysis of dyads in **P1a.** Olefin region of ^{13}C NMR spectra of poly-DHF (top), **P1a** (middle) and poly-**1** (bottom). Representative repeat units in **P1a** are depicted. Although the spectrum of **P1a** includes NBE–NBE homodyads (c') and NBE–DHF heterodyads (a' , b' , d and e), DHF–DHF homodyad peaks are not observed. The absence of DHF–DHF homodyads indicates that DHF units are distributed throughout the copolymer backbone.

poly-NBE segments, and distinguishes this method from previous copolymerization approaches that use electron-neutral olefinic comonomers.

The isolated copolymers at different MWs, **P1a–P1c**, were rapidly degraded in THF solution with the addition of dilute HCl (~ 20 mM). GPC analysis of the crude degraded products showed a complete degradation of the polymers within 30 minutes into small-molecule species with no detectable residual polymers (Fig. 2a). The lack of polymeric degradation products also confirms the relatively uniform distribution of DHF units throughout the polymer chain. ^1H and ^{13}C NMR spectroscopy of the degradation products showed signals from the expected aldehyde and a small amount of (hemi)acetal, which resulted from enol ether hydrolysis (Supplementary Fig. 24).

We also explored NBE imide **2** for copolymerization with DHF. Under identical conditions and $[2]_0:[\text{DHF}]_0 = 100:100$, the copolymerization of **2** was slower than that of the disubstituted ester NBE **1**, and reached 78% conversion in ten hours for a total targeted DP of 200. The resulting polymer **P2a** exhibited $\bar{D} < 1.1$, a controlled M_n close to the theoretical value (Table 1 and Fig. 2b) and a composition of 2:DHF around 100:80. **P2a** exhibited a T_g of 69°C , higher than that of **P1b** ($T_g = 21^\circ\text{C}$), as a result of the more rigid NBE imide structure. **P2a** was also completely degraded into small molecules on hydrolysis with HCl in THF.

To examine the impact of the monomer feed ratio, the $[2]_0:[\text{DHF}]_0$ ratio was changed to 100:50. The rate of polymerization

did not change, consistent with our observation that the rate is zero order with respect to DHF. The resulting copolymer **P2b** remained narrow disperse and had a composition 2:DHF of about 100:45. The reduced composition of DHF in **P2b** resulted in a T_g of 86°C , higher than that of **P2a**. The reduced density of hydrolysable linkages in **P2b** gave some oligomers of **2** on degradation, but all initial polymeric species disappeared (Fig. 2b). For reference, a separately synthesized poly-**2** with an average DP of 10 eluted at 18 minutes in the GPC elution. When $[2]_0:[\text{DHF}]_0$ was changed to 50:100, the resulting copolymer had a close to equal composition to that of 2:DHF, at 100:90, and was completely degraded under acidic conditions. ^{13}C NMR spectroscopy of **P2c** again did not reveal signals that corresponded to DHF–DHF homodyads (Supplementary Fig. 32).

Monosubstituted NBEs should propagate faster than disubstituted NBEs. Indeed, copolymerization of DHF with a monosubstituted NBE, **3**, exhibited a faster polymerization than that with **1** under identical conditions, to give $>95\%$ NBE conversion in 45 minutes at a total targeted DP of 200. The resulting copolymer **P3** exhibited a low $\bar{D}$ of 1.12 and a M_n that matched the theoretical value (Table 1 and Fig. 2c). The high reactivity of **3** resulted in a higher incorporation of NBE in the copolymer than the feed ratio, and the copolymer had a composition of 3:DHF = 100:45. Despite the reduced incorporation of degradable units, the copolymer was still fully hydrolysed to give small molecule and oligomeric species (Fig. 2c). In comparison, the hydrolysis of a copolymer from the same NBE **3** and a silyl ether cyclic olefin was reported to result in

only a shift of the polymer GPC peak to a lower MW¹⁵. The high reactivity of DHF towards the Grubbs alkylidene attenuates the high reactivity of NBEs and effectively interrupts homopropagation, which offers a distinct advantage for its use in copolymerization. This attenuation of reactivity also allowed a relatively even incorporation of DHF units when copolymerizing with fast propagating, unsubstituted NBE **4**. The resulting copolymer **P4** was readily degraded into small molecules and oligomers (Fig. 2c).

We also synthesized a water-soluble NBE macromonomer **5** that bears an oligo(ethylene glycol) side chain of 550 Da (Fig. 1). The copolymerization at $[5]_0:[DHF]_0:[G3]_0=100:100:1$ reached 95% conversion of **5** in 2.75 hours, which resulted in a copolymer **P5** with $M_n=83.6$ kDa and $\bar{D}=1.07$ and an equal composition of **5** and DHF. **P5** was water soluble and exhibited no degradation in PBS buffer at physiological pH of 7.4. However, on the addition of 5% acetic acid, the copolymer slowly hydrolysed over several days (Supplementary Fig. 13). This controlled, acid-triggered hydrolysis is ideal for applications in which a material needs to be stable under physiological conditions but degrade after use or in acidic environments. GPC analysis of degraded **P5** showed only monomer and oligomeric species of the ring-opened NBE macromonomer (Fig. 2d).

To allow functionalization and crosslinking of the degradable copolymers, we synthesized NBEs with a pendent *N*-hydroxysuccinimide ester (**6**) or acrylate (**7**) (Fig. 1). Terpolymers of each of these functional monomers with DHF and another common NBE were readily synthesized with low dispersities and controlled MWs (Supplementary Table 1). Terpolymers of **1** and **6** and DHF at a monomer feed ratio of 90:10:100 can be functionalized with amines, such as dibenzyl amine, under basic conditions in the presence of 1.5 equiv. NaH (Supplementary Figs. 8 and 9). Interestingly, without added NaH for the functionalization, a slight degradation of the copolymer was observed in the GPC analysis (Supplementary Fig. 10), presumably due to the acidity of adventitious ammonium.

Acrylates, although a very useful functionality, are not compatible in typical living ROMP due to their selective cross metathesis with electron-neutral olefins^{32–35}. Surprisingly, copolymerization of DHF and NBE **7** with a pendent acrylate group gave a narrow-disperse copolymer with $\bar{D}=1.12$ and a controlled MW (Supplementary Fig. 4). The low reactivity of the Fischer carbene towards acrylates allows a straightforward incorporation of pendent acrylic groups, which provide a convenient means for postpolymerization crosslinking.

Mechanical properties are an important consideration for developing degradable polymers that can replace their non-degradable counterparts. **P1c**, with a composition of 1:DHF = 100:67, exhibited a low T_g of 21 °C, and behaved as a viscoelastic material with an elastic modulus (E) of 2.3 MPa, ultimate tensile strength (UTS) of 1.24 MPa, and strain at break over 500%. The addition of 3 mol% of **7** (relative to **1**) to the 1/DHF monomer mixture at a feed ratio of 1:7:DHF = 290:10:300 yielded a terpolymer that was readily crosslinked by curing with a radical initiator azobisisobutyronitrile at 70 °C. Crosslinked **P7ax** showed considerably enhanced mechanical properties compared with those of the analogous uncrosslinked polymer **P1c**, as it gave $E=600$ MPa, UTS=9.7 MPa and strain at a break of 230% (Fig. 4). These properties are similar to those of low-density polyethylene. The mechanical properties of the crosslinked copolymer can be further tuned by altering the crosslinking density. Increasing the loading of **7** to a monomer feed ratio of 1:7:DHF = 270:30:300 yielded a terpolymer which was similarly crosslinked to give a stronger material, **P7bx**, with $E=610$ MPa, UTS=25 MPa and strain at a break of 100% (Fig. 4), properties resembling high-density polyethylene, showing promise of these ROMP copolymers as degradable alternatives to common nondegradable polymers. These crosslinked polymers can still be degraded into fully soluble polymers and small molecules on treatment with HCl in THF (Supplementary Video 1 and Supplementary

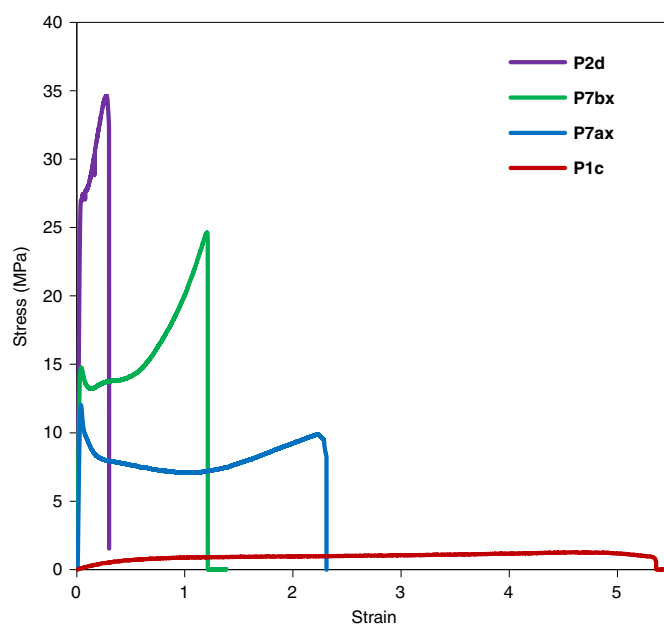


Fig. 4 | Tensile properties of NBE-DHF copolymers. Representative stress-strain curves of uncrosslinked and crosslinked NBE-DHF copolymers. The range of properties achievable with this copolymerization strategy demonstrates the mechanical tunability of these degradable copolymers.

Fig. 14). Stiffer and stronger polymers can also be generated using glassy copolymers of **2** with DHF. Copolymer **P2d** with an initial monomer loading of 2:DHF = 300:300 exhibited $E=1.04$ GPa, UTS = 34.9 MPa and strain at a break of 27%. The wide range of mechanical properties achievable from the crosslinked or uncrosslinked NBE-DHF copolymers demonstrates the versatility of this copolymerization strategy for developing degradable polymers.

For engineering and commercial applications of degradable plastics, it is highly desired that the materials be stable during storage and use, but degrade on-demand at the end of their life cycle. Thus, we evaluated the stability of NBE-DHF copolymers in the solid state under ambient conditions. After 14 days of storage under ambient conditions, crosslinked **P7bx** exhibited negligible changes in its mechanical properties, whereas linear **P1b** exhibited a slight shift of its GPC peak to a longer elution time (Supplementary Fig. 15). To prevent degradation, a weak base, such as K_2CO_3 , can be used as an additive to inhibit acid-catalysed enol ether hydrolysis. After precipitating into methanol that contained K_2CO_3 , **P1b** exhibited no change in its GPC trace after 45 days under ambient conditions (Supplementary Fig. 15). These observations suggest that the solid copolymers can be gradually composted under ambient conditions, but can also have extended shelf-life when a small amount of basic additive is used during storage. Likewise, although **P1b** slowly degraded in THF solution under air, the addition of a small amount of K_2CO_3 to the solution effectively stabilized the polymer (Supplementary Fig. 16).

Conclusions

We have demonstrated a simple yet powerful strategy to synthesize a range of easily degradable polymers via the ROMP of DHF with an array of NBEs. The rapid reaction of electron-rich enol ethers with the propagating Ru alkylidene (appending ring-opened NBE) substantially suppressed NBE homopropagation, which allowed an even distribution of DHF along the polymer chain to result in fully degradable copolymers with controlled MWs, low dispersities and high conversions. We also synthesized NBE-DHF copolymers that are water soluble, functionalizable and/or crosslinkable. All these

copolymers can be completely hydrolysed into small molecules or oligomers under mildly acidic conditions.

This strategy for the synthesis of degradable ROMP polymers has several distinct advantages: (1) the simplicity of adding commercially available DHF to NBEs under otherwise common living ROMP conditions, (2) an even distribution of degradable linkages, which leads to a complete polymer degradation into small molecules and oligomers, (3) facile degradation under mildly acidic conditions at room temperature, (4) good MW control and (5) the generality to apply to the large repertoire of NBEs. The new family of degradable copolymers enabled by this strategy will find applications that range from nanolithography to drug delivery to sustainable plastics.

Online content

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Methods

Copolymer synthesis. In a nitrogen-charged glove box, NBE monomers 1–5 and 7 and DHF were dissolved in THF at 0.15 M for each monomer. For copolymers with an unequal monomer loading, the initial concentration of the more abundant monomer was 0.15 M. For **P1c**, 5 equiv. 3-bromopyridine was added to the monomer solution. A stock solution of the **G3** catalyst in THF (10 mg ml⁻¹) was prepared in a separate vial. The desired amount of catalyst was injected into the monomer solution and the reaction was stirred at room temperature until the desired monomer conversion was reached. The polymerization was then quenched with several drops of ethyl vinyl ether and stirred for 10 min. Polymers were precipitated into a poor solvent (cold diethyl ether for copolymers of 5, and MeOH for all the others), collected by centrifugation (3,300 r.p.m., 10 min), and dried under vacuum.

Preparation of crosslinked acrylate-bearing copolymers. Terpolymers of monomers **1** (270 or 290 equiv.), **7** (30 or 10 equiv.) and DHF (300 equiv.) were dissolved in DCM with a small amount of azobisisobutyronitrile (~0.5 mg) and transferred to a silanized Petri dish. The Petri dish was covered and the solvent was allowed to evaporate overnight. The dish was then transferred to a vacuum oven and heated to 70 °C under vacuum for 20 h. After cooling, the polymer film was removed from the Petri dish and cut with a razor into samples for mechanical testing.

Polymer degradation. To a 5 mg ml⁻¹ solution of degradable polymer in 1 ml of THF was added one drop of 1 M HCl. The homogeneous solution was swirled and allowed to stand for 30 min. The crude mixture was analysed by GPC.

Data availability

All data supporting the findings of this study are available within the Article and its Supplementary Information. Source data are provided with this paper.

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Author contributions

J.D.F. and Y.X. conceived this project. J.D.F. performed the majority of the experiments and D.C.L. synthesized and characterized the water-soluble copolymers. J.D.F. and Y.X. wrote the manuscript with input from D.C.L.

Competing interests

J.D.F. and Y.X. are named inventors on a patent application (US Provisional Application 63/169,588) filed by Stanford University on the copolymerization method described in this work.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41557-021-00810-2>.

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