Synthesis of Functionalizable and Degradable Polymers by ROMP

Joshua M. Fishman and **Laura L. Kiessling**[*]

Keywords

ROMP; degradable polymer; metathesis; oxazinone; Click chemistry

A valuable approach for creating synthetic polymers is the ring-opening metathesis polymerization (ROMP).[1,2] Well-defined metal carbene catalysts have been devised that afford control over the polymer chain length and architecture.[3–6] In addition, ruthenium carbene intiators have been developed with excellent air stability and functional group tolerance.[6,7] These catalysts enable the synthesis of polymers with a range of functionality,[8–15] thereby providing access to polymers for diverse applications.[16–19]

Extant polymers from ROMP, like the majority of synthetic polymers, are non-degradable. They therefore lead to refuse accumulation. A functional and degradable polymer from ROMP would allow the synthetically useful traits of ROMP reactions to be combined with the growing need for new degradable polymer scaffolds. To date, efforts to prepare degradable materials using ROMP have afforded polymers that are either functional or partially hydrolysable, but not both (Figure 1). For example, cargo can be attached via a linker such that it can be released from the polymer backbone by photolysis or hydrolysis in acid.[16,20–22] Still, the polymeric backbone persists. Alternatively, partially degradable polymers have been generated. A block copolymer can be generated from a modifiable monomer and a sacrificial dioxepine or dithiepine monomer.[8,23,24] In this scenario, one block is composed of a non-hydrolysable backbone and the degradable block contains acid-labile acetals or thioacetals that can be cleaved by hydrogenation. Polymers of this type only undergo partial degradation, as one block persists. The current state-of-the-art therefore demands a compromise between generating polymers that can be customized and polymers that can be easily degraded.

Applying ROMP to synthesize a modifiable homopolymer with a degradable backbone requires a monomer with three important attributes. First, it must be a strained cyclic or bicyclic olefin, so that it undergoes polymerization.[25] Second, it must contain core functionality that gives rise to a polymer that can be degraded. Third, a means to append desired functionality onto the monomer or polymer is needed to enable polymer diversification. Monomers with all of these attributes have been elusive. Many strained olefinic heterocycles spontaneously aromatize.[26,27] In addition, attempts to incorporate handles for diversification can further increase monomer instability.[28] Thus, traditional monomers used in ROMP cannot be simply modified to instil polymer degradability.

[*]Prof. Laura L. Kiessling, Department of Chemistry, Departments of Biochemistry, University of Wisconsin – Madison, 1101 University Ave., Madison, WI 53706, Kiessling@chem.wisc.edu.

We sought a new class of monomers that would give rise to degradable materials. The generation of substrates with an 8-*oxo*-2-azabicylo[3.2.1]oct-6-en-3-one framework through a novel *aza*-[4+3] cycloaddition was recently reported (Scheme 1A).[29] We postulated that this bicyclic oxazinone would be a substrate for ROMP. Calculations suggest that this framework has a ring strain of 13.4 kcal/mol, which is comparable to that of *trans*-cyclooctene (a monomer that has favourable kinetics of polymerization using ROMP).[25,30] Reports of successful ring-opening cross metathesis on architecturally analogous 8-*oxo*-bicyclo[3.2.1.]oct-6-en-3-ones provided additional impetus.[31,32] Significantly, if the bicyclic oxazinone serves as a monomer in ROMP, the resulting framework should be both acid and base labile (Scheme 1B). Moreover, we postulated that we could modify this core monomer at a site distal to the polymerizable moieties and bridgehead carbons. Thus, without destabilizing the heterocycle, we could tailor the properties of the resulting materials.

Despite our optimism that bicyclic oxazinones would serve as a monomer, we had concerns that its polymerization would yield highly oxygenated polymer products that would facilitate backbiting.[34,35] Our initial results confirmed our suspicions. The reaction of **3a** using Grubbs' second generation catalyst (**GII**)[33] in chloroform afforded polymer **4a** (Table 1, entry 1), but we observed a concomitant increase in the PDI and decrease in the number averaged molecular weight (M_n) of the products as the polymerization progressed (Supporting Information, Table S1). One strategy to mitigate backbiting is to raise the reaction temperature to disrupt dative bonds.[36,37] However, in our system, an increase in temperature did not reduce backbiting (Table 1, entry 2). The problem of backbiting, nevertheless, was solved. We performed the polymerization reaction in tetrahydrofuran (THF), a solvent system that can compete with the polymer for catalyst coordination. We also employed catalyst **5**, which has superior polymerization kinetics to **GII**.[7,36] These changes afforded dramatic improvements in the polymerization. We obtained stable M_n or PDI values even at long reaction times (Table 1, entry 5–6). In addition, the M_n increased proportionally to monomer to catalyst loading (Table 1, entry 3–7), and the degree of polyerization was found to be in good agreement with monomer conversion. Thus, structures such as compound **3a** undergo ROMP to afford polymer scaffolds with a repeating oxazinane backbone.

We next investigated the degradability of the new polyoxazinone scaffold. Small molecule oxazinones have been used to generate -hydroxy carboxylic acids,[37,38] but the conditions used for ring opening have been harsh (i.e. extreme pH and high temperatures). We assessed more mild conditions. Utilizing gel permeation chromatography (GPC), we monitored the decomposition of polymer **4e** under a range of acidic and basic conditions at room temperature (Figure 2). No appreciable breakdown occurred at pH values between 4.6 and 9.1 over 48 hours. This observation indicates that the oxazinane backbone is able to withstand exposure to a wide range of conditions, thereby facilitating polymer handling or modification. Still, the polymers are vulnerable under specific conditions. At pH values less than 1.0, degradation is fast with complete decomposition occurring in under an hour. The acid-catalyzed backbone decomposition also occurs readily at pH 2.5, with 66% of the polymer mass lost in 6 h. At pH values up to 4.5, slower degradation occurs. We also observed polymer backbone cleavage under basic conditions. Thus, either acid or base can promote degradation of polymers with an *N*-alkoxy-oxazinone backbone. These data indicate that these oxazinone polymers represent a unique class of backbone degradable ROMP polymer that is stable at neutral pH values but labile in either acidic or basic environments.

Further studies were conducted to characterize the degradation products. Because obtaining the necessary quantities of specific polymer degradation fragments for characterization is

difficult, we employed a model. Specifically,, compound **3e** was subjected to a ring-opening cross metathesis reaction with 1-hexene to yield heterocycle **9**. When the product was exposed to an acidic methanol solution, ring-cleavage occurred to afford hydroxamic acid **10** (Scheme 2).[37] This mode of reactivity would promote fragmentation of the polyoxazinone backbone causing polymer degradation. It is expected that hydroxamic ester **10** undergoes further hydrolysis to a -hydroxy carboxylic acid, however this species was not isolated.

Bicylic oxazinones can be used to access a new class of degradable polymers. However, the aforementioned monomers do not provide the means to imbue polymers with desired functional properties. To expand the utility of our strategy, we devised a monomer that can be further elaborated. We envisioned a facile and modular strategy to impart new functionality into the monomer is to use a bifunctional hydroxylamine. This approach facilitates the introduction of additional groups at a site distal from the monomer's core polymerizable group. Moreover, no changes to the synthetic route are required (Scheme 1).

Starting with bromine functionalized hydroxylamine **1b**, monomer **3b** was accessed using the same synthetic strategy as monomer **3a**.[29] Monomer **3b** was also a substrate for ROMP, leading to polymer **4b**. Additionally, monomer **3b** can be elaborated through nucleophilic displacement of its alkyl bromide functionality. As a proof of concept, we exposed the bromine to sodium azide to yield compound **3c**, which is a substrate for the azide-alkyne [3+2] cycloaddition (AAC). Because of the exquisite chemoselectivity of this Click chemistry reaction, it is widely used to introduce new functionality into polymers.[39–43] Azides, however, have been found to be incompatible with ruthenium catalysts.[22,44] Therefore, compound **3c** was conjugated to 1-propargyl- -*D*-mannose-2, 3, 4, 6-tetraacetate using a copper-catalyzed AAC to afford monomer **6** (Scheme 3). The functionalized monomer that resulted could undergo ROMP to afford polymer **7**. The acetate groups were hydrolyzed to produce mannose-substituted polymer **8**. The water solubility of this polymer facilitated analysis of its degradation in aqueous solution. At pH values similar to those that led to the loss of polymer **4e**, we observed decomposition of **8**.[45]

Substituents can be added to influence a polymer's bioactivity or its mechanical or optical properties. To illustrate the generality of our strategy, we generated polymers from *O*-octyl hydroxylamine (**1a**), *O*-ethyl hydroxylamine (**1d**) or *O*-benzyl hydroxylamine (**1e**) starting materials. In this way, polymers **4a4d** and **4e**[46] with modified hydrocarbon functionality were generated. Additionally, pyrene conjugated hydroxylamine **1f** was leveraged to assemble polymer **4f** (Scheme 1B), which could serve as an optical sensor. This substance exhibited a red-shifted fluorescence spectrum indicative of pyrene exciplex emission (Supporting Information, Figure S1).[47] When polymer **4f** undergoes hydrolytic degradation, a monomeric pyrene derivative is released from the backbone thereby diminishing exciplex emission. Changes in the ratio of fluorescence intensity of monomeric pyrene ($_{max}$=377 nm) and polymeric exciplex ($_{max}$=480 nm) over time report on the extent of backbone hydrolysis. We followed this spectral change to reveal that exposure to acidic conditions for 3 hours resulted in the degradation of approximately 80% of the polymer (Figure 3).

In conclusion, ROMP can be used to synthesize a new class of degradable polymers. These polymers possess a backbone that is labile under either acidic or basic conditions. In addition, the polymers can be decorated through a modular monomer synthesis using bifunctional hydroxylamine building blocks. The process we describe affords functional and degradable polymers that can be used in specific applications. We envision that polymers of this type may yield new degradable plastics or resins. ROMP can be used on an industrial scale to generate new materials; therefore, the strategy described here could generate consumables with properties that complement those currently generated by ROMP.[2] In this

way, ROMP can give rise to stable species or materials that can be broken down to simple building blocks. Furthermore, degradable and functional polymers can serve as scaffolds for directed drug delivery or regenerative medicine.[16,48,49] Therefore, we foresee that these polymers may find utility as novel biomaterials as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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46. Monomer **3e** was a poorer substrate than the other monomers tested. See the Supporting Information for details.

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Previous Polymers: partially degradable and functionalizable

A

B
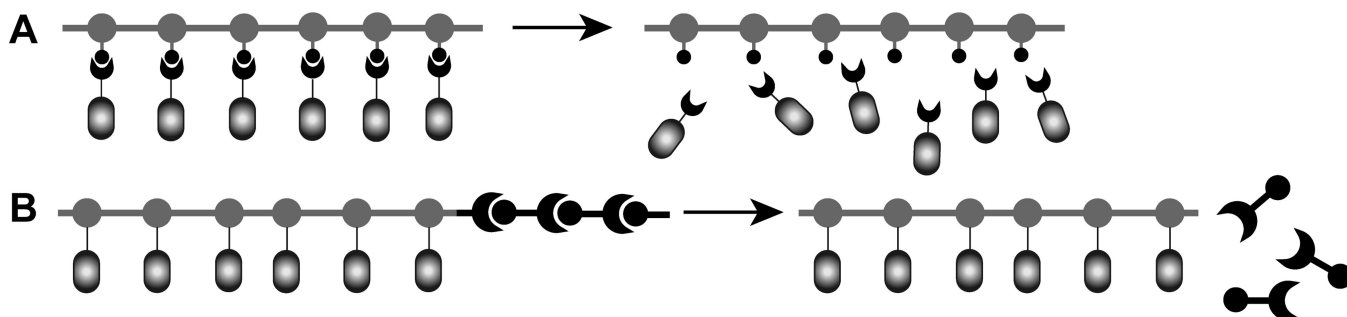
New Polymers: fully backbone degradable and functionalizable

C
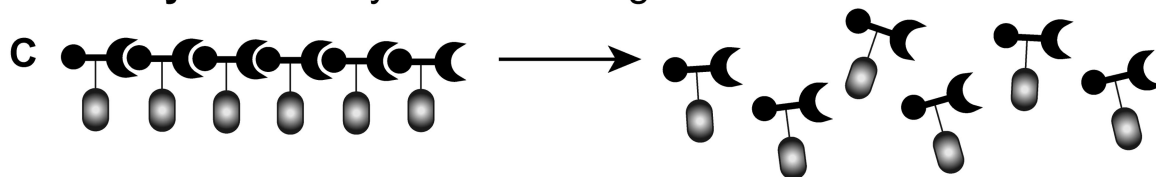
Figure 1.
Strategies to synthesize functionalizable and degradable ROMP polymers: a) ligand attachment via a cleavable linker, b) copolymerization with a sacrificial monomer, and c) homopolymerization of a functionalizable, heterocyclic oxazinone.
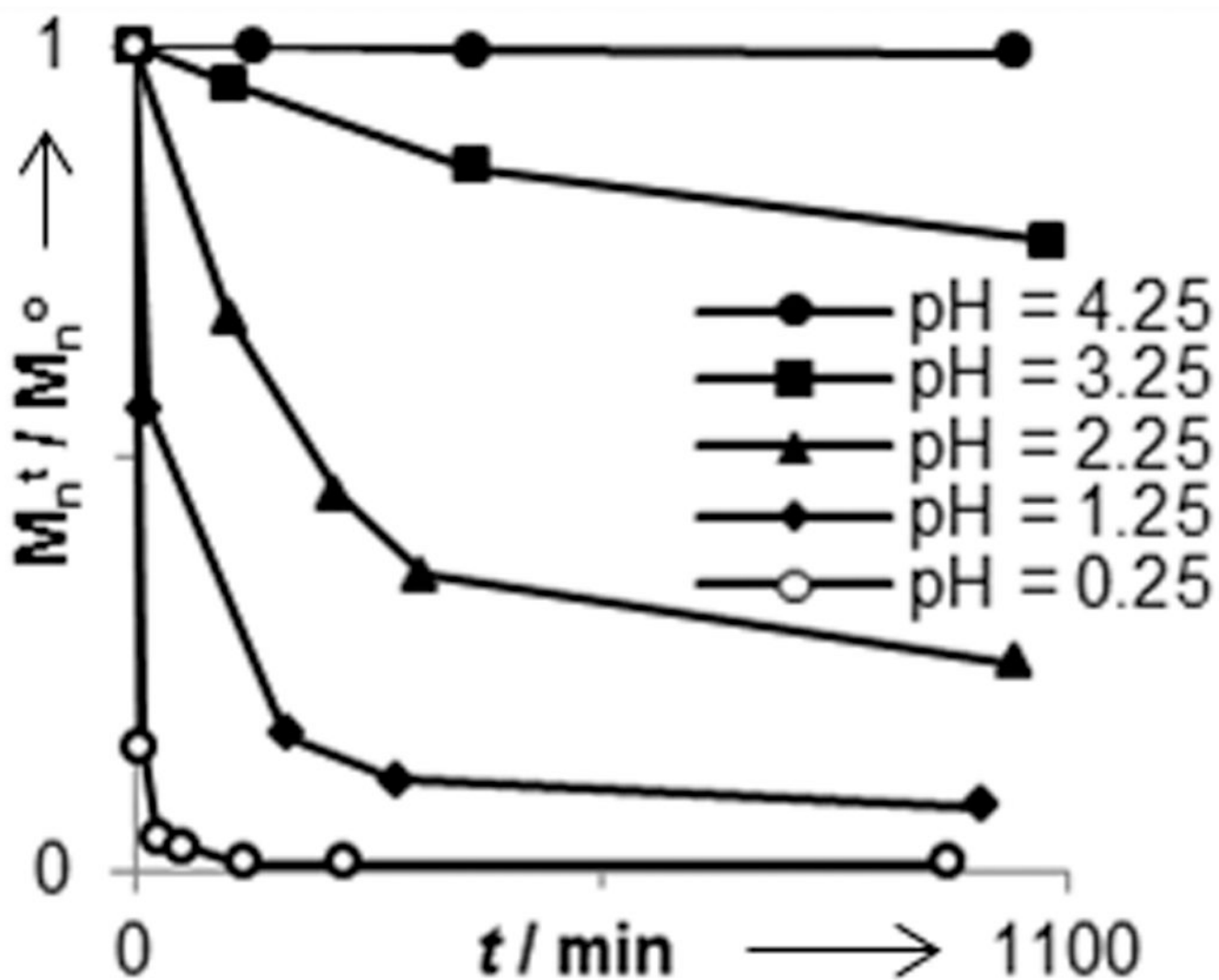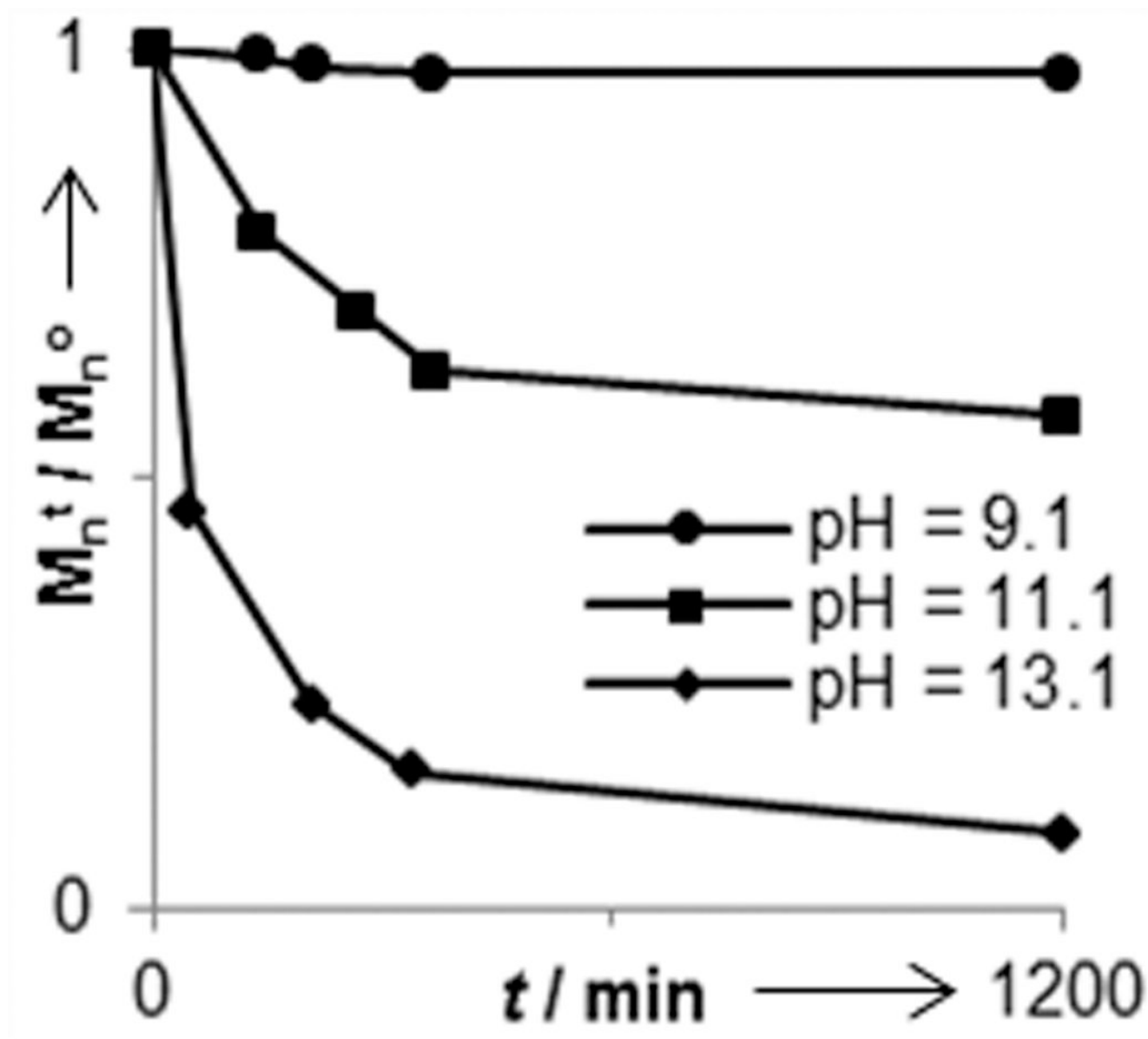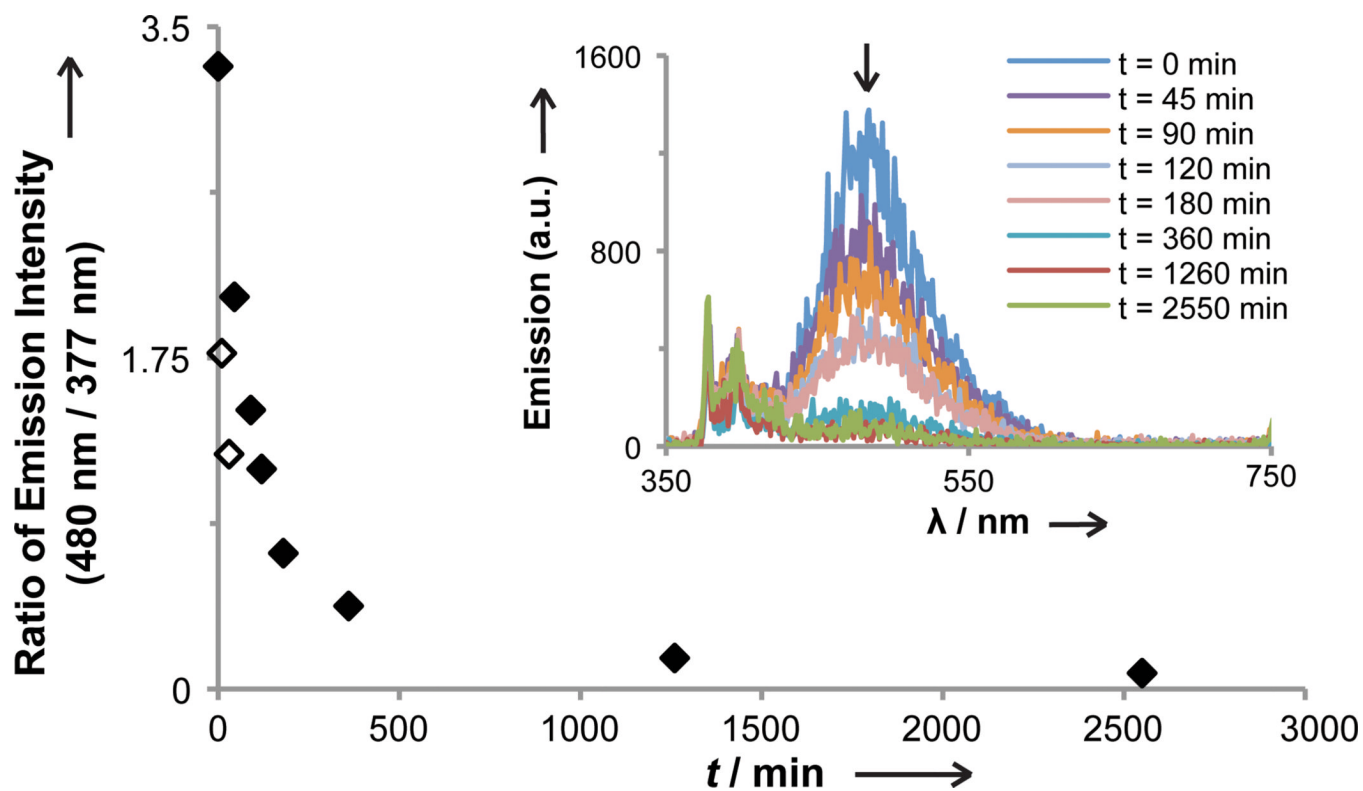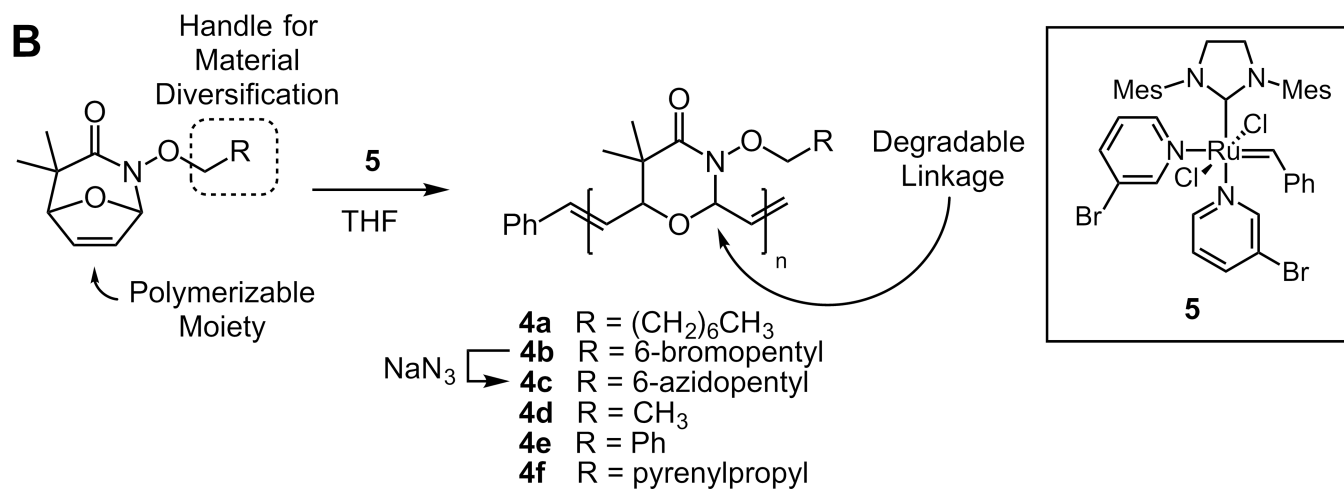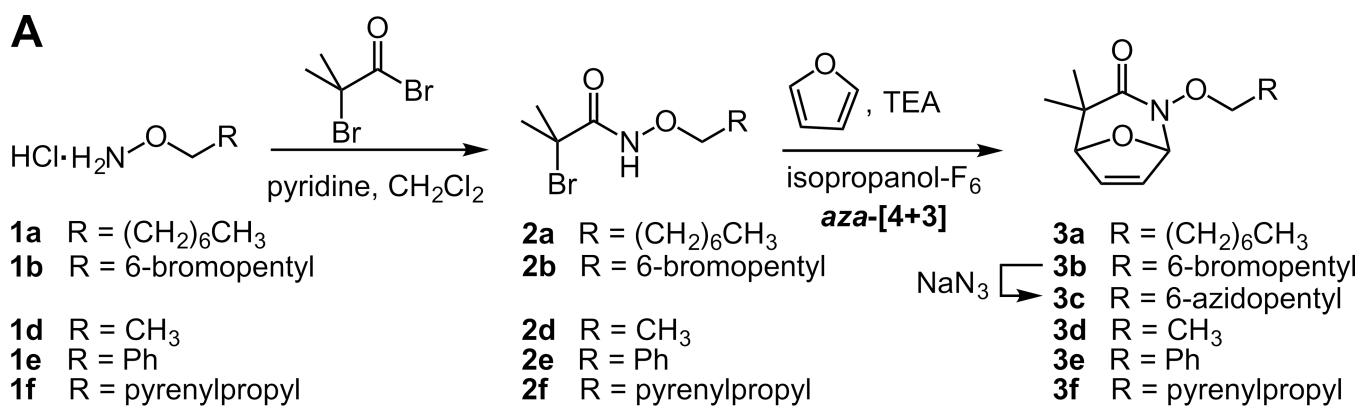
Figure 2.
Degradation profile of polymer **4e** under acidic and basic conditions. $M_n^o = 18, 500$ g/mol.

Figure 3.
Degradation of **4f** was monitored by comparing the ratio of polymeric pyrene exiplex emission (λ_{max} = 480 nm) to monomeric pyrene emission (λ_{max} = 377 nm). λ_{ex} = 250 nm, pH = 0.25 (3:1 THF:MeOH). Unfilled diamonds represent low emission ratios due to initial low polymer solubility; polymer completely dissolved in solution within 40 min.

A

1a R = (CH$_2$)$_6$CH$_3$
1b R = 6-bromopentyl

1d R = CH$_3$
1e R = Ph
1f R = pyrenylpropyl

2a R = (CH$_2$)$_6$CH$_3$
2b R = 6-bromopentyl

2d R = CH$_3$
2e R = Ph
2f R = pyrenylpropyl

3a R = (CH$_2$)$_6$CH$_3$
3b R = 6-bromopentyl
NaN$_3$ **3c** R = 6-azidopentyl
3d R = CH$_3$
3e R = Ph
3f R = pyrenylpropyl

B

Handle for Material Diversification

Polymerizable Moiety

5

THF

Degradable Linkage

5

4a R = (CH$_2$)$_6$CH$_3$
4b R = 6-bromopentyl
NaN$_3$ **4c** R = 6-azidopentyl
4d R = CH$_3$
4e R = Ph
4f R = pyrenylpropyl

Scheme 1.
Synthesis of bicyclic oxazinones that undergo ROMP to afford degradable polymers.
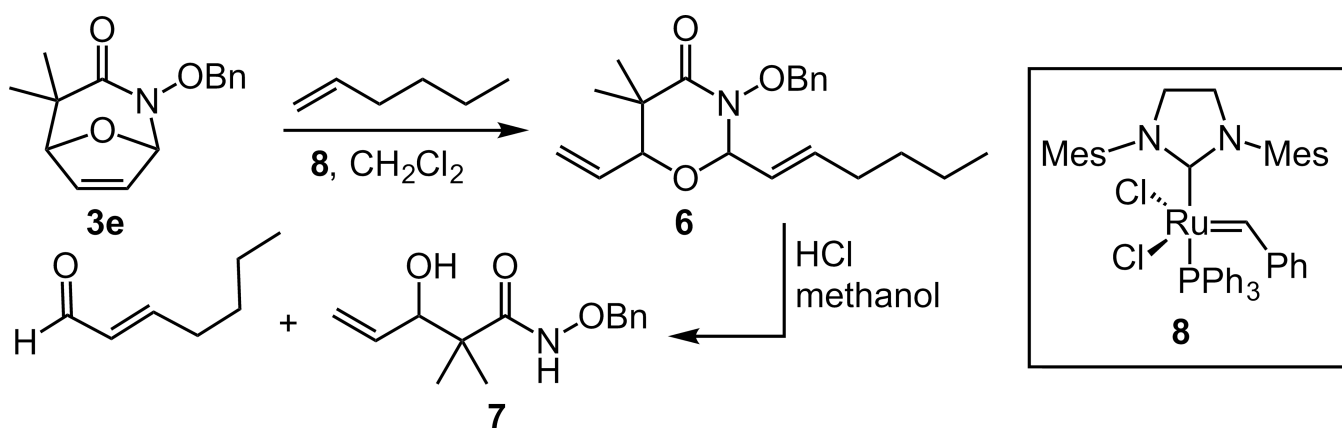
Scheme 2.
Ring-opening cross metathesis of monomer **3a** and subsequent hydrolysis of a 3-alkoxy-1,
3-oxazin-4-one under acid conditions.

Scheme 3.
Synthesis of glycopolymer **8**.

Table 1

Polymerization of monomer **3a** using ROMP

entry	$[M]_0/[I]$	catalyst	solvent[a]	temp (°C)	time (h)	conversion (%)[b]	Yield[c,d]	M_n^{theo} (g/mol)	M_n^{NMR} [e] (g/mol)	M_n^{GPC} [f] (g/mol)	PDI[f] (M_n/M_w)
1	100/1	GII	CHCl$_3$	20	4	84	72	23600	103800	63200	2.8
2	100/1	GII	CHCl$_3$	45	18	81[g]	49	22800	26000	24900	2.6
3	25/1	5	THF	20	1	87	57	6100	6500	9300	1.4
4	50/1	5	THF	20	1	85	71	12000	12500	16300	1.4
5	100/1	5	THF	20	1	81	80	23100	22000	21600	1.4
6	100/1	5	THF	20	18	81	85	23100	22100	22300	1.4
7	200/1	5	THF	20	1	73	83	41000	45200	50300	1.5

[a] $[M]_0 = 1M$.

[b] based off of ^{1}H-NMR integrations of monomer olefin signals to polymer olefin signals.

[c] isolated.

[d] theoretical yield based off of monomer conversion.

[e] based off ^{1}H-NMR integrations of polymers olefin signals and polymers chain-end phenyl signals.

[f] calibrated with polystyrene standards, eluted in THF,

[g] additional 10–15% cyclic dimer (see Supporting Information for structural characterization of byproduct).