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Practical Synthesis of Functional Metathesis Initiators Using Enynes

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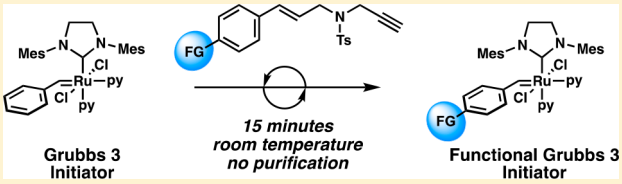
Supporting Information

ABSTRACT: Grubbs-type ruthenium initiators have found extensive use in complex polymer synthesis but are greatly limited to the nonfunctional derivatives that are commercially available. This report describes the design of functional enyne molecules that rapidly and efficiently convert the third-generation Grubbs catalyst (**G3**) into a variety of custom initiators for use in polymer synthesis. The identification of electron-deficient sulfonamide derivatives enables high conversion efficiency (>98%) to functional initiator structures with a minimal number of enyne equivalents (2.5−3 equiv). The catalyst transformations are complete in minutes at room temperature and can be directly used in polymerization without intermediate purification. Through combination with existing termination methods, this technology gives practical entry into well-defined heterotelechelic polymers using metathesis polymerization.

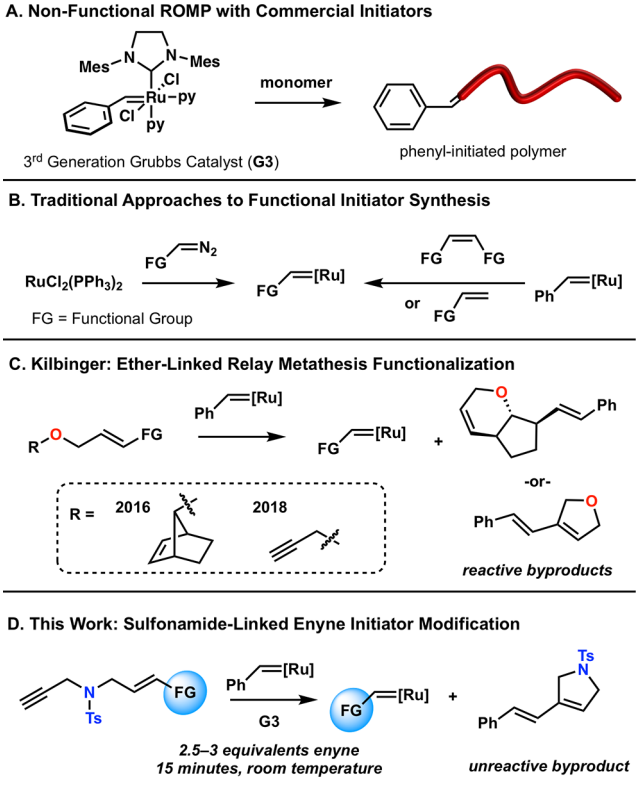


INTRODUCTION

Over the past two decades, metathesis polymerization with Grubbs-type ruthenium initiators has developed into one of the most user-friendly and robust methods in the polymer chemist's toolbox.[1−4] This is a result of the exquisite chemoselectivity and reactivity of the ruthenium alkylidene that permits highly complex and even macromolecular monomers to be polymerized with ease.[5−9] When considering the widespread use of ring-opening metathesis polymerization (ROMP), it is surprising that there are few methods available to modify the initiator structure to generate chain-end functionalized polymers. In the vast majority of polymerizations reported, commercially available Grubbs catalysts are directly employed, resulting in nonfunctional, phenyl-initiated polymer chains (Scheme 1A). Given the significant role of chain-end modified polymers for block polymer synthesis,[10,11] bioconjugation,[12] surface functionalization,[13] and molecular labeling,[14] the invention of a robust method to modify the initiator structure would expand the utility of this already powerful polymerization technology. This study presents the development and optimization of a user-friendly method to prepare custom ruthenium initiators using sulfonamide-linked enyne derivatives.

Historically, chain-end functionalization of ROMP polymers has primarily focused on approaches to terminate the living chain after polymerization.[15−20] Efforts to create custom initiator structures that include functional handles have been far fewer and have generally relied on either independent organometallic synthesis[21,22] or the use of direct cross-metathesis methods (Scheme 1B).[23−32] Other creative approaches have used sacrificial initiating blocks[33] or single monomer addition[34,35] to introduce a functional group (FG) to the initiating end, but these strategies require postpolymerization modification and risk monomer overaddition/underaddition, respectively. A clever strategy by the Kilbinger group

Scheme 1. Approaches to Initiator Functionalized Polymers Using Ruthenium Metathesis



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was reported in 2016 for *in situ* ruthenium initiator functionalization in which a norbornene is used to direct an intramolecular metathesis reaction and generate a new initiator structure (Scheme 1C).[36] While this concept was effective, the small molecule byproduct of the metathesis sequence was also reactive and terminated the living polymer chains. To transform this concept into a more practical system for materials synthesis, this paper reports sulfonamide-tethered enynes as new motifs for relay functionalization that are highly efficient and do not generate reactive byproducts (Scheme 1D). At the same time as our studies, the Kilbinger group also explored terminal alkynes as alternative directing groups for initiator functionalization and recently published a report with ether-linked enynes (Scheme 1C).[37] While superficially very similar to this work, the ether-based enynes display significantly different reactivity with the Grubbs third-generation (**G3**) initiator at room temperature, leading to decomposition of the ruthenium benzylidene. To resolve this issue, Kilbinger performed the reactions at −10 °C for extended periods or added a large excess of 3-bromopyridine ligand (30 equiv) to suppress the catalyst reactivity. Unfortunately, the excess ligand also dramatically affects the rate of polymerization, and the reactions at −10 °C are inconvenient to perform for long reaction times. While ether-linked enynes were also evaluated in this work, our solution to this problem was to explore structural alternatives, leading to the identification of sulfonamide-linked enynes that are devoid of these side reactions. This simple modification permits the transformation of the **G3** initiator to functional derivatives in 15 min at room temperature without significant decomposition observed. In addition, the selection of electron-deficient substituents minimizes the amount of enyne needed for high conversions (2.5−3 equiv) and also presents a convenient handle for introduction of useful end-groups. Overall, this presents a more practical and operationally effective method for initiator modification to generate chain-end modified polymers with ROMP.

EXPERIMENTAL SECTION

Materials. All reactions were performed under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry, degassed dichloromethane (CH_2Cl_2), *N*,*N*-dimethylformamide (DMF), and tetrahydrofuran (THF) were obtained from a JC Meyer solvent purification system. $CDCl_3$ from Cambridge Isotopes was stored under 4 Å molecular sieves to remove water and acid. Unless otherwise stated, all other reagents were purchased at the highest commercial quality and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reactions were monitored by thin layer chromatography (TLC) performed on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and basic aqueous potassium permanganate ($KMnO_4$) and heat as developing agents. E. Merck silica gel (60, particle size 0.043−0.063 mm) was used for flash column chromatography.

Instrumentation. NMR spectra were recorded on Bruker Avance 400, 500, or 700 MHz instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ at 7.26 ppm ^{1}H NMR and 77.16 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) were recorded on LC/MS (Agilent Technologies 1260 Infinity II/6120 Quadrupole) by ESI or a time-of-flight mass spectrometer by matrix-assisted laser desorption/ionization (MALDI) using a *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]-malononitrile (DCTB) matrix and AgTFA ionizing agent. Polymer samples were analyzed using a Tosoh EcoSEC HLC 8320GPC system with TSKgel SuperHZ-L columns eluting $CHCl_3$ containing 0.25% NEt_3 at a flow rate of 0.45 mL/min. All number-average molecular weights and dispersities were calculated from refractive index chromatograms using PStQuick Mp-M polystyrene standards.

General Procedure for the Preparation of Enyne Sulfonamides. Substituted aryl halide (1.5 equiv), *N*-allyl-4-methylbenzenesulfonamide (1.0 equiv), palladium(II) acetate (0.05 equiv), and tri(*o*-tolyl)phosphine (0.15 equiv) were dissolved in acetonitrile (MeCN, 0.2 M) under a N_2 atmosphere. Triethylamine (2.0 equiv) was added via syringe, and the mixture was placed into an oil bath preheated to 70 °C and stirred for 24 h. The reaction was quenched by addition of H_2O (10 mL), and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate in hexanes or MeOH in CH_2Cl_2) to give the product.

To the product obtained above (1.0 equiv) and potassium carbonate (2.0 equiv) was added DMF (0.2 M) at room temperature, followed by the addition of propargyl bromide (1.1 equiv). The mixture was placed in an oil bath that was preheated to 40 °C and stirred for 12 h. The reaction was cooled to room temperature and quenched with H_2O (5 mL), and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate in hexanes or MeOH in CH_2Cl_2) to give the enyne initiator modifier.

General Procedure for Equivalence Test. In separate 4 mL vials (Chemglass, CG-4909-03), solutions of Grubbs third-generation catalyst (18.0 mg/225 μL) and enynes **1**−**14** (1.0 equiv/100 μL) were prepared in degassed $CDCl_3$. In five separate 4 mL vials, equipped with a stir bar, was added appropriate volume (0.5, 1.0, 1.5, 2.0, and 2.5 equiv) of enyne solution under nitrogen. To these stirred solutions was added Grubbs third solution (50 μL, 4.0 mg, 0.0055 mmol, 1.0 equiv). After stirring 10 min at room temperature under nitrogen, NMR samples were directly prepared under a nitrogen atmosphere from the reaction mixture, and the ratio of the benzylidene protons of the two species was measured by ^{1}H NMR.

General Procedure for Polymerization. Enyne molecules **5** and **8**−**14** (3.0 equiv) were added to an 8 mL vial equipped with a stir bar, placed under a nitrogen atmosphere, and dissolved in degassed $CDCl_3$ (200 μL). $CDCl_3$ (200 μL) is added to a second vial in the absence of enyne as a control. A solution of Grubbs third-generation catalyst (50 μL, 2.7 mg, 0.0037 mmol, 1.0 equiv in $CDCl_3$) was rapidly transferred to the stirred enyne solution and control vial using a microliter syringe. After 15 min, a degassed solution of monomer **M1** (20−30 equiv) in 300 μL of $CDCl_3$ was added to both vials. Ethyl vinyl ether (50 uL) was added to each reaction after 5 min to terminate the living polymer. The reaction mixture was concentrated to remove excess EVE, redissolved in $CDCl_3$ to determine conversion by ^{1}H NMR, and precipitated twice into a 15-fold volume of MeOH or hexanes/diethyl ether (1/1). The precipitated polymer was then characterized using GPC, ^{1}H NMR, and MALDI-TOF-MS.

RESULTS AND DISCUSSION

The overall design of the initiator modification system was derived from established enyne metathesis chemistry,[38−40] relay ring-closing metathesis,[41] and Choi's ultrafast polymerization of enyne monomers.[42−44] The proposed mechanism of the relay functionalization sequence is shown in Scheme 2. First, the third-generation Grubbs catalyst (**G3**) reacts rapidly with the terminal alkyne to give a vinyl ruthenium alkylidene intermediate. This positions the ruthenium intermediate for a rapid intramolecular metathesis reaction with the disubstituted olefin to provide a new initiator that contains a functional group (FG) of interest. A byproduct is excised in this process that is expected to be unreactive under the reaction conditions due to the relatively hindered nature of the disubstituted

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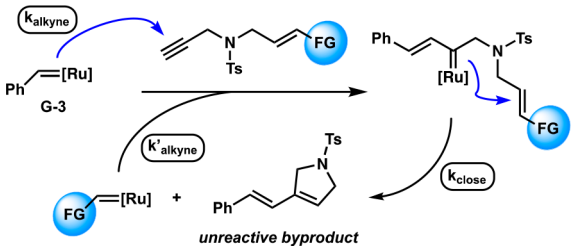
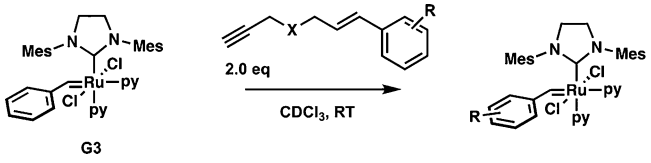
Scheme 2. Mechanism of Functional Initiator Synthesis



styrenic olefin. A potential problem with this approach is that the newly formed initiator competes with **G3** for reaction with the enyne and would likely require several equivalents to achieve complete conversion to a new initiator species. It was reasoned that the number of equivalents required for full conversion could be minimized if the ring closing metathesis step was rate-limiting (k_{close}) or if the new functional initiator had lower reactivity than **G3** ($k_{alkyne} > k'_{alkyne}$). Both of these approaches were explored in the design of a suitable enyne platform.

To test this concept, chloro-enyne **1** was prepared and **G3** was treated with **1** (2 equiv) at room temperature in deuterated chloroform. The enyne was fully consumed in minutes to give 93% conversion to a new chloro-initiator with 7% unreacted **G3** remaining, as judged by ^{1}H NMR (Table 1, entry 1). Following this promising initial result, the enyne structure was modified in terms of linker, sterics, and electronics to increase the conversion efficiency. In each case, 2 equiv of enyne was reacted with **G3** to benchmark the reactivity relative to chloro-enyne **1**. First, exchange of the sulfonamide linkage for an oxygen was explored based on Choi's observations that ether-based enyne monomer derivatives had slower rates of ring closure.[45] Unfortunately, chloro ether **2** did not increase conversion efficiency (85%, entry 2), and significant catalyst decomposition was observed that discouraged further exploration of ether-linked enynes, even when performed at more diluted conditions (see Figure S3). While the loss of benzylidene was initially presumed to be due to intermolecular side reactions before cyclization could occur, Kilbinger also showed that the byproduct produced can react further with the benzylidene through an undetermined mechanism. Next, a series of electronically and sterically modified sulfonamides were tested. The 2-methyl-enyne **3** gave poorer initiator conversion (61%, entry 3), implying the new catalyst had higher reactivity than **G3**. This was presumed to be due to steric blocking of pyridine coordination to the ruthenium center, leading to a higher equilibrium of the active catalyst species.[46] Electron-donating groups such as the 4-methoxy derivative **4** (entry 4) had a small improvement in conversion compared to chloro-enyne **1**, but significant enhancement was observed with 4-carboxymethyl derivative **5**. This implies that the rate of alkyne addition for both electron-rich and electron-poor benzylidenes is slower than the parent phenylbenzylidene, similar to observations by Grubbs for the first-generation catalysts.[47]

Table 1. Effect of Enyne Structure on Conversion Efficiency



entry	compd	R	X	conv[a] (%)
1	**1**	4-Cl	N-Ts	93
2	**2**	4-Cl	O	85
3	**3**	2-Me	N-Ts	61
4	**4**	4-OMe	N-Ts	95
5	**5**	4-CO_2Me	N-Ts	98
6	**6**	3-CO_2Me	N-Ts	95
7	7	2-CO_2Me	N-Ts	>98[b]

[a]Conversion of **G3** determined by ^{1}H NMR. [b]Incomplete consumption of enyne **7** due to inhibited reactivity of chelated benzylidene.

This electron-deficient enyne resulted in 98% conversion to the ester functionalized initiator with only 2 equiv of enyne. The position of the substituent seemed to be important with the *meta* derivative **6** giving slightly lower efficiency (95%, entry 6). Notably, the *ortho*-ester **7** rapidly converts to the modified benzylidene, but the enyne is not fully reacted. The ruthenium center in this catalyst is presumably chelated by the ester which dramatically reduces its metathesis activity, making it unsuitable for use in polymerization.

To further verify the results of entry 5, **G3** was reacted with **5** in varying ratios (Figure 1). Again, rapid conversion to the methyl ester benzylidene was observed with only trace amounts of **G3** remaining by ^{1}H NMR when 2.5 equiv of enyne was employed (>98% conversion). The initiation efficiency of the methyl ester initiator was also investigated, since reducing the reactivity of the benzylidene could negatively impact the dispersity of the polymers prepared due to slower initiation. To test this possibility, the *in situ* formed initiator was reacted with 9 equiv of *exo*-methyl-norbornene imide monomer **M1** and terminated with ethyl vinyl ether (EVE) after 5 min. This gave a low molecular weight ester-initiated polymer **5-P1** to facilitate characterization by chain-end analysis and MALDI-TOF-MS. Concurrently, an identical polymerization was initiated using **G3** to

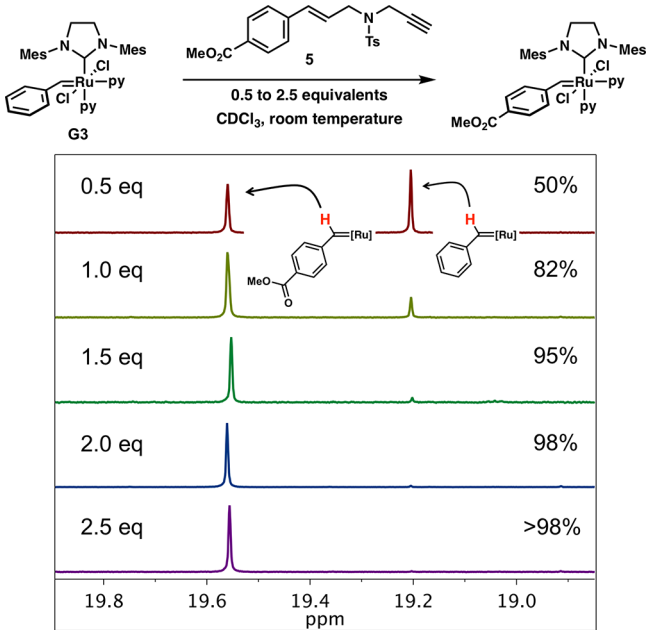


Figure 1. Reaction of **G3** and **5** at different ratios in $CDCl_3$.

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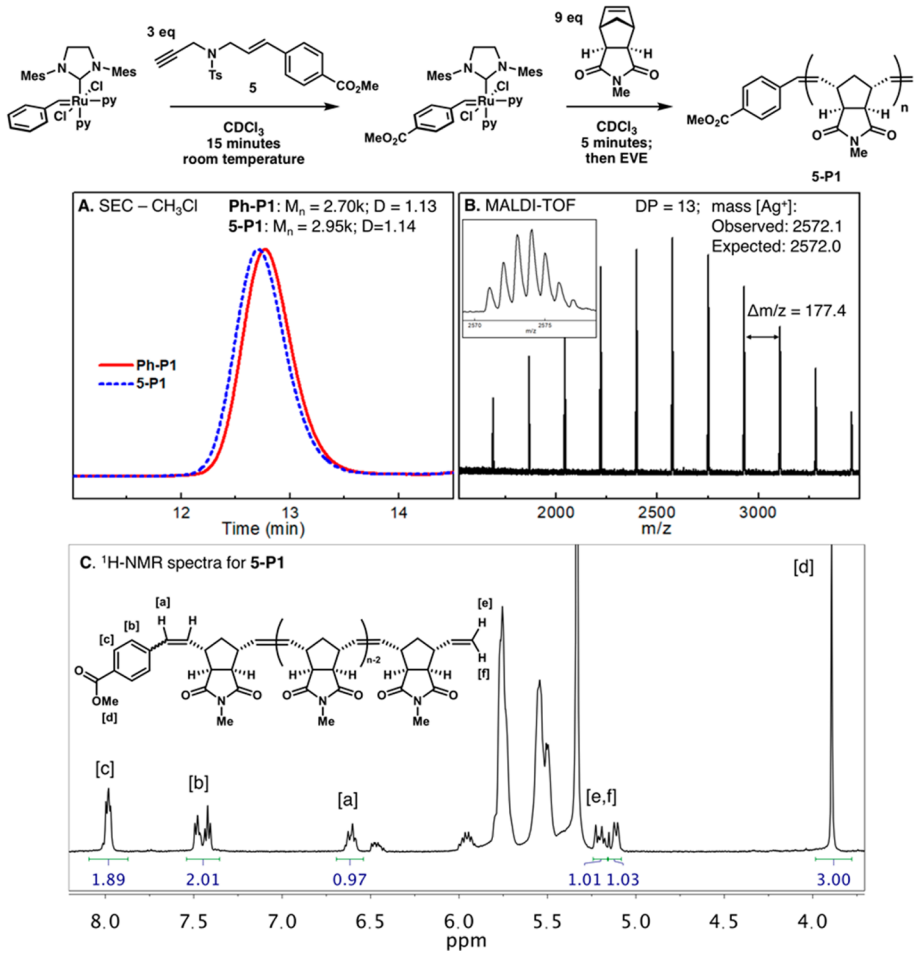
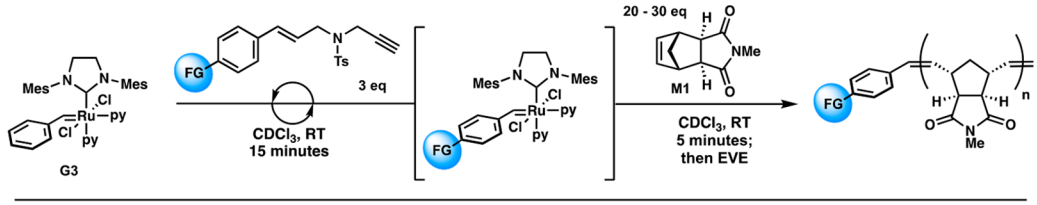
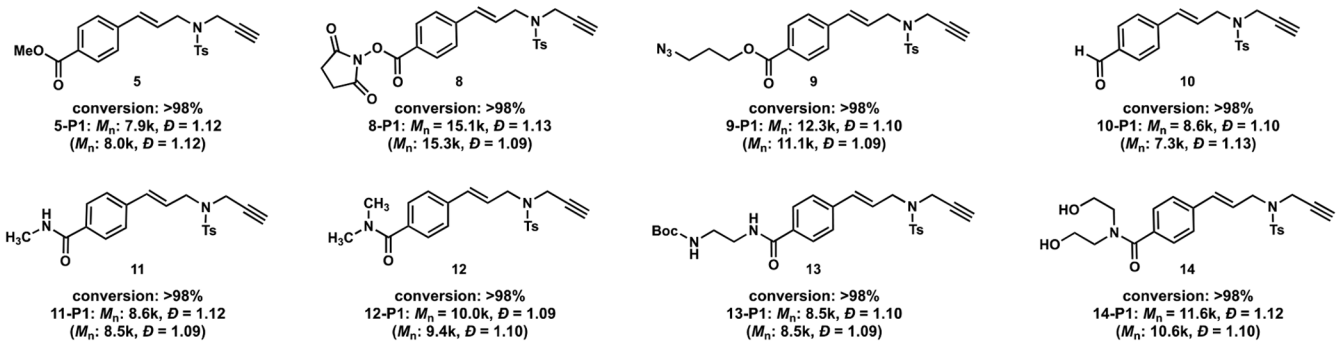


Figure 2. (A) SEC trace of **5-P1**. (B) MALDI-TOF spectrum of **5-P1**. (C) ^{1}H NMR spectrum of **5-P1** showing chain-end analysis in CD_2Cl_2.

Table 2. Scope of the Enyne Metathesis To Generate Useful Functional Initiators[a]





[a]Conversions determined by crude ^{1}H NMR. Molecular weights and dispersities determined using size exclusion chromatography ($CHCl_3$) calibrated with polystyrene standards. Control polymerizations with **G3** listed below in parentheses.

give the control polymer **Ph-P1** for comparison, and the results of both polymerizations are overlaid in Figure 2A. As judged by size-exclusion chromatography (SEC), both of the polymers were very similar in both molecular weight and dispersity. The small difference in molecular weight is likely attributed to slight fractionation of the chain-end-functionalized polymer during

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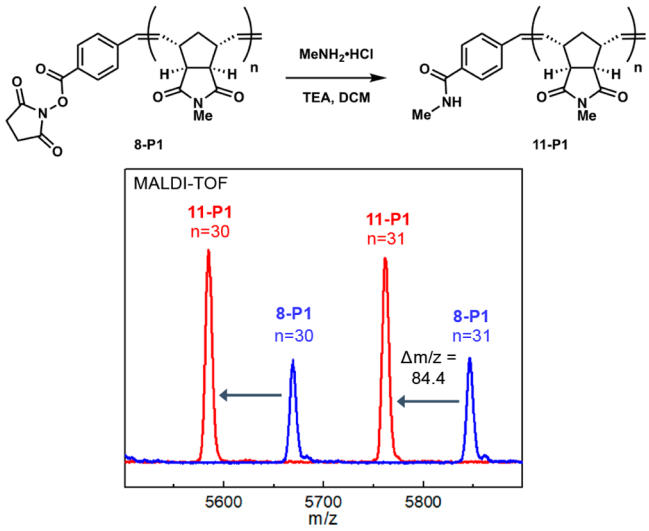
precipitation into methanol. This demonstrates not only that the initiation is sufficiently fast to prepare low-dispersity polymers but also that there is negligible catalyst decomposition during enyne metathesis. Additional experiments with an internal standard demonstrate the lack of initiator degradation even when 5 equiv of enyne is employed (Figure S23). Further evidence of the polymer structure and purity was demonstrated by MALDI-TOF-MS analysis (Figure 2B). A single series of ion peaks were present in the mass spectrum that corresponds to a silver charged polymer series (n = 13, calcd: 2572.0 m/z; obsd: 2572.1 m/z) with a methyl ester-functionalized chain-end. The ^{1}H NMR spectrum of this polymer also demonstrated all of the features expected in a methyl benzoate-initiated structure (Figure 2C). Most clearly identified is the singlet at 3.89 ppm that arises from the methyl ester protons (proton [d]). When setting this integral to three, the relative intensity of the aromatic peaks from the benzoate at 8.0 and 7.4 ppm integrate to the expected value of four (protons [b, c]). The doubling of peaks at 7.4 is likely due to E/Z-isomers of the neighboring styrenic olefin. There is a distinct chemical shift in the **Ph-P1** control for the styrenic olefin that is completely absent in the **5-P1** ^{1}H NMR spectrum, reinforcing the high degree of initiator conversion (Figure S10). Importantly, the terminal olefin protons derived from the ethyl vinyl ether termination integrate to two (protons [e, f]), suggesting high chain-end fidelity without any side reaction with the enyne byproduct. The unreactive nature of the metathesis byproduct **S10** was further demonstrated through independent experiments with the living polymer chain for up to 45 min without any significant changes (see Figure S22).

Based on these findings, the scope of the transformation was explored with a variety of enyne molecules with different functional groups. The superiority of the ester **5** in the structure−activity study was advantageous, as it provides an excellent handle to install various motifs of interest and could be conveniently prepared in two steps using a Heck coupling strategy (see the Supporting Information for synthesis). Table 2 shows the enyne derivatives examined and lists the conversion to the new initiating structure when 3 equiv of enyne is employed. Additionally, each entry reports the corresponding control polymerization experiment to verify initiation quality and evaluate any potential catalyst decomposition (control polymerization listed below in parentheses). Perhaps the most versatile enyne is the *N*-hydroxysuccinimide (NHS) ester **8**. This precursor was used to prepare the amide derivatives **11**−**14** in Table 2 but also can be directly polymerized and reacted afterward with amine nucleophiles. Azide (**9**) and aldehyde (**10**) derivatives were prepared for application in alkyne and oxime "click" chemistry, respectively. Both secondary (**11**) and tertiary (**12**) amides were synthesized from **8** as well as functional amides that contain a Boc-protected primary amine (**13**) and a diethanolamide (**14**) motif. In all of the cases examined, full conversion of **G3** was obtained (>98%) with 3 equiv or less of the enyne (see the Supporting Information for equivalent studies of each). Furthermore, each of the functional initiators could be used to prepare low dispersity polymers with structural verification provided by ^{1}H NMR and MALDI-TOF-MS analysis. With substrates **9**, **10**, and **14**, slightly greater molecular weights were obtained when compared to the control polymerizations, suggesting some possible catalyst decomposition. While the origins of the initiator loss is not clear at this time, the amounts are not significant (less than 20% based on relative M_n values), and the byproducts do not appear to initiate nonfunctional polymer chains. For all other cases, the size exclusion chromatographs of the initiator-modified polymerizations were nearly superimposable with the controls, implying minimal, if any, loss of active initiating benzylidene.

Successful introduction of the functional groups into the initiator structure and further confirmation of the polymer structure were illustrated by a postpolymerization modification sequence (Scheme 3). To do this, the versatile NHS ester

Scheme 3. Postpolymerization Modification of 8-P1



initiated **8-P1** was reacted with methylamine hydrochloride in the presence of triethylamine in DCM. This should lead to the *N*-methylamide initiated polymer, **11-P1**, that was already prepared independently with the *N*-methylamide enyne **11**. After isolation of the polymer, the success of the reaction was clearly observed by MALDI-TOF-MS analysis. A new series of mass signals appeared that each had a reduced molecular weight by 84.4 atomic mass units compared to **8-P1**. This exactly corresponds to the loss of an NHS functionality in exchange for an *N*-methylamide, and the new molecular weight series exactly corresponded to the independently prepared **11-P1** (see the Supporting Information, Figure S20). This also demonstrates how a conveniently prepared parent NHS-ester polymer could be used to divergently prepare a series of amide-functionalized polymers from a common precursor.

With the establishment of a robust protocol for rapid initiator modification, this method can be coupled with existing termination methods to easily produce traditionally challenging heterotelechelic ROMP polymers. To demonstrate this, enyne **5** was prepared according to Table 2 and was terminated with *cis*-2-butene-1,4-diol instead of ethyl vinyl ether to give **5-P1-OH** (Scheme 4). As expected, a new set of peaks were observed in the NMR spectrum of the polymer corresponding to an allylic alcohol chain-end (see the Supporting Information), with further verification characterization by MALDI-TOF-MS. Once again, a single series of ions were observed that directly correlated to polymer chains containing primary allylic alcohol and methyl ester end groups.

CONCLUSION

A new class of optimized, sulfonamide-linked enyne molecules is reported that can be used to convert the third-generation

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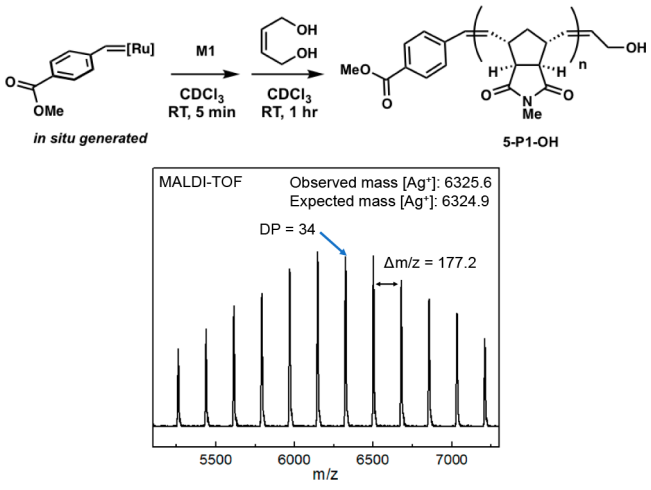
Scheme 4. Synthesis and Characterization of 5-P1-OH



Grubbs initiator (**G3**) into functional derivatives. The reactions proceed at ambient temperature without additional reagents to cleanly deliver functional initiator products in under 15 min. No purification of the newly formed initiators is needed and polymerizations can be directly performed from the crude reaction solutions. This is highlighted through the preparation of a series of new initiators for metathesis that bear useful functionality for further application and derivatization of the resulting polymers. This approach also gives rapid and practical access to heterotelechelic ROMP polymers in a single operation that to date have been difficult to prepare. This study also gives some insight into the effects of structure on the reactivity of NHC-ligated ruthenium complexes, an area that has been significantly missing in the literature to date for nonchelated Grubbs systems and deserves more attention in the future.[47,48] Collectively, this report presents new directions in catalyst design and also will aid in the preparation of new functional materials using ruthenium metathesis polymerization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.8b00866.

Experimental Section, GPC traces, NMR spectra, and MALDI-TOF MS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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