Photocontrolled radical polymerization from hydridic C–H bonds

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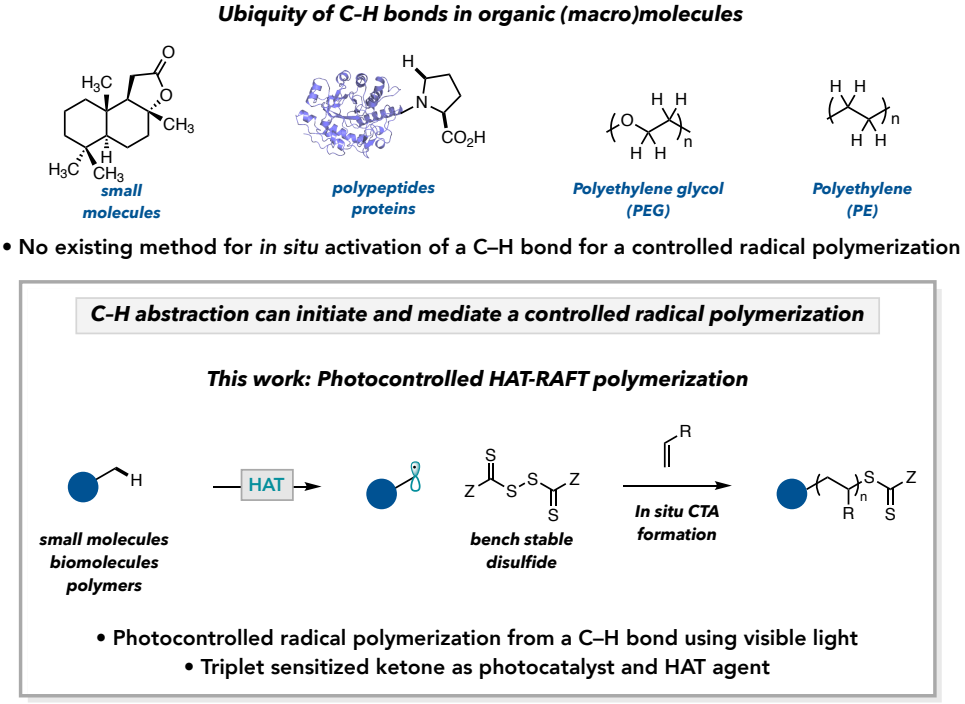
Abstract:

Given the ubiquity of C–H bonds in biomolecules and polymer backbones, the development of a photocontrolled polymerization from a C–H bond would represent a powerful strategy for selective polymer conjugation precluding several synthetic steps to introduce complex functionality. We have developed a hydrogen-atom abstraction strategy that allows for a controlled polymerization from a C–H bond using a benzophenone photocatalyst, a trithiocarbonate-derived disulfide, and visible light. We perform the polymerization from a variety of ethers, alkanes, unactivated C–H bonds, and alcohols as well as showcase the applicability of the method to several monomer classes. Our method lends itself to photocontrol which has important implications for building advanced macromolecular architectures. Finally, we demonstrate that we can graft polymer chains controllably from poly(ethylene glycol) showcasing the potential application of this method for controlled grafting from C–H bonds of commodity polymers.

Main Text:

Reversible-deactivation radical polymerizations (RDRPs) represent one of the most versatile strategies for controlling macromolecular architecture. Numerous synthetic methods have been developed to obtain control over chain length and dispersity. Reversible addition-fragmentation chain transfer (RAFT) has emerged as a powerful tool for controlling radical polymerizations.[1-4] Additionally, photoinduced electron transfer (PET-RAFT) processes have been established as a means to exact temporal and spatial control, finding numerous applications in photopatterning for designing complex 3D architectures.[5-10] To employ these methods, however, a prefunctionalized initiator must be installed into a macromolecule, biomolecule, or small molecule for a controlled polymerization. Despite the ubiquity of C–H bonds, a method for controlling polymerization from a C–H bond has not been demonstrated.[11,12] The development of such a strategy could allow the direct formation of protein-polymer bioconjugates or drug-polymer conjugates without prefunctionalization.[13] Furthermore, complex macromolecular architectures could be controllably accessed via grafting from existing polymers in a single step with spatial and temporal control.[14]

Scheme 1. Design of HAT-RAFT Polymerization

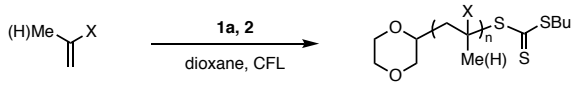


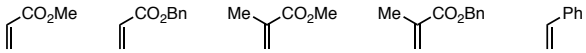
Hydrogen-atom transfer (HAT) is a burgeoning synthetic strategy to generate carbon centered radicals from C–H bonds. Benzophenone derivatives have been well demonstrated as hydrogen-atom abstraction agents as well as an electron donor when irradiated with visible light.[15,16] We hypothesized that radical polymerizations could be initiated using this mechanism.[17-19] Through careful selection of the hydrogen atom abstractor, high levels of chemoselectivty can be achieved.[20] In the case of a benzophenone derivative, in the triplet excited state, it can chemoselectively abstract electron rich, hydridic C–H bonds. This selectivity will preclude unwanted C–H abstraction processes from the growing polymer backbone of electron deficient polymers, which could lead to undesirable cross-linking and branching.

We envisioned that control over the polymerization could be imbued by a RAFT process via addition of a chain transfer agent (CTA). However, the α-chain end would arise from the chain end of the CTA, rather than the C–H bond initiator. We propose employing a precursor disulfide to generate the effective CTA *in situ* to obtain the desired α-chain end. Additionally, this strategy should allow the employment of multiple monomer classes with a single disulfide precursor, without matching specific chain ends to a specific monomer. To access controlled polymerizations of more or less active monomers, it should be possible to vary the Z group of the disulfide. After formation of the CTA, further generation of radicals via HAT would grow polymer chains controllably. The radical concentration could be controlled by both the photocatalyst and the H-atom source loading. This process could also lend itself to

photocontrol, as in the absence of light, radical chains would become dormant. Upon generation of radical initiators via the light gated HAT process, a photocontrolled radical polymerization, initiated from a ubiquitous C–H bond, would be obtained.

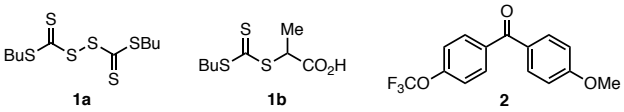
Table 1. HAT-mediated polymerization of acrylates, methacrylates, and styrene





MA **BnA** **MMA** **BnMA** **St**

entry[a]	monomer	[M]:[**1a**]:[**2**]	M_n^{theo} (kg/mol)	M_n^{exp} (kg/mol)	$Đ$
1	**MA**	100:1:0.5	5.3	8.9	1.12
2	**MA**	50:1:0.5	2.4	4.6	1.26
3	**MA**	200:1:0.5	10.2	13.8	1.15
4	**MA**	400:1:0.5	17.8	21.8	1.17
5	**MA**	1000:1:0.5	54.3	51.5	1.13
6[b]	**MA**	100:1:0.5	0.0	n.d.	n.d.
7	**BnA**	100:1:0.5	16.0	19.0	1.23
8	**MMA**	100:1:0.5	5.4	3.0	1.19
9	**BnMA**	100:1:0.5	16.0	15.7	1.30
10[c]	**St**	400:1:1.0	4.4	5.8	1.29



1a **1b** **2**

[a] Monomer (filtered through basic alumina), disulfide **1a**, and photocatalyst **2** dissolved in dioxane (4M), degassed and irradiated with a CFL. [b] CTA **1b**, used in place of **1a** and 1,2-dichloroethane used as a solvent [c] 50 equiv THF used in place of dioxane, no additional solvent.

We began our studies employing disulfide **1a**, photocatalyst **2**, and dioxane as both the solvent and H-atom source. We hypothesized that we could control the radical concentration of this process by simply modifying the concentration of photocatalyst while using the solvent as an H-atom source. Methyl acrylate (MA) was efficiently polymerized in the presence of a CFL with a narrow dispersity ($Đ$) (Table 1, entry 1). The experimental molecular weight (M_n^{exp}) showed good agreement with theoretical molecular weight (M_n^{theo}), which was calculated such that one disulfide gives one polymer chain. In the absence of disulfide, the polymerization is rapid and uncontrolled; however, in the absence of light, photocatalyst or H-atom source (1,2-dichloroethane used as a solvent), no conversion of MA is observed (see SI for details). We observed good agreement between theoretical and experimental molecular weights when targeting specific molecular weights (entries 2-5). When CTA **1b** was used in place of the disulfide and in the absence of H-atom source, we observed no polymerization (entry 6), suggesting that the excited state of the photocatalyst cannot

engage in PET-RAFT processes, nor is direct excitation of the CTA responsible for polymerization under standard conditions.[21]

With the optimized conditions, we sought to explore the scope of the method to other monomer classes. Benzyl acrylate (BnA) was efficiently polymerized with good agreement between theoretical and experimental molecular weight with excellent control over molecular weight distribution (Table 1, entry 7). Both methyl methacrylate (MMA) and benzyl methacrylate (BnMA) were also efficiently polymerized to give PMMA and PBnMA with good control over dispersity (entries 8-9).[22] Styrene was also polymerized using the HAT-RAFT strategy, albeit under slightly different reaction conditions, using tetrahydrofuran (THF) as the H-atom source and conducting the polymerization in the absence of solvent (entry 10). This led to a well-controlled polymerization to afford polystyrene. We observed that in the absence of H-atom source, however, similar results were obtained, suggesting a mechanism other than HAT-RAFT.[23]

When monitoring the reaction, we observed an induction period prior to polymerization. After this initial period, it was observed that M_n increased linearly with conversion, suggesting a controlled radical process (Figure 1a). We hypothesized that the system may also be amenable to temporal control, rather than just a photoinitiated process, if a traditional radical RAFT mechanism is invoked. To test this hypothesis, the polymerization was intermittently exposed to light while monitoring conversion (Figure 1b). Gratifyingly, we observed that conversion ceased upon removal from irradiation. Moreover, polymerization continued upon additional irradiation. This process was repeated, including a long "off" period, in which polymerization was only observed in the presence of the CFL.

To test the trithiocarbonate chain end fidelity of our polymers, we isolated a sample of PMA synthesized under our standard polymerization conditions. We then subjected the macroinitiator to a solution of AIBN and BnA monomer in benzene at 65 °C (Figure 1c). We observed efficient chain extension under these conditions, obtaining a PMA-*co*-PBnA copolymer with good matching of M_n^{theo} and M_n^{exp} and narrow $Đ$. The GPC trace did indicate some remaining PMA homopolymer, and we attribute this incomplete conversion of the macroinitiator to C–H chain ends, resulting from reductive termination events during the HAT-RAFT polymerization.

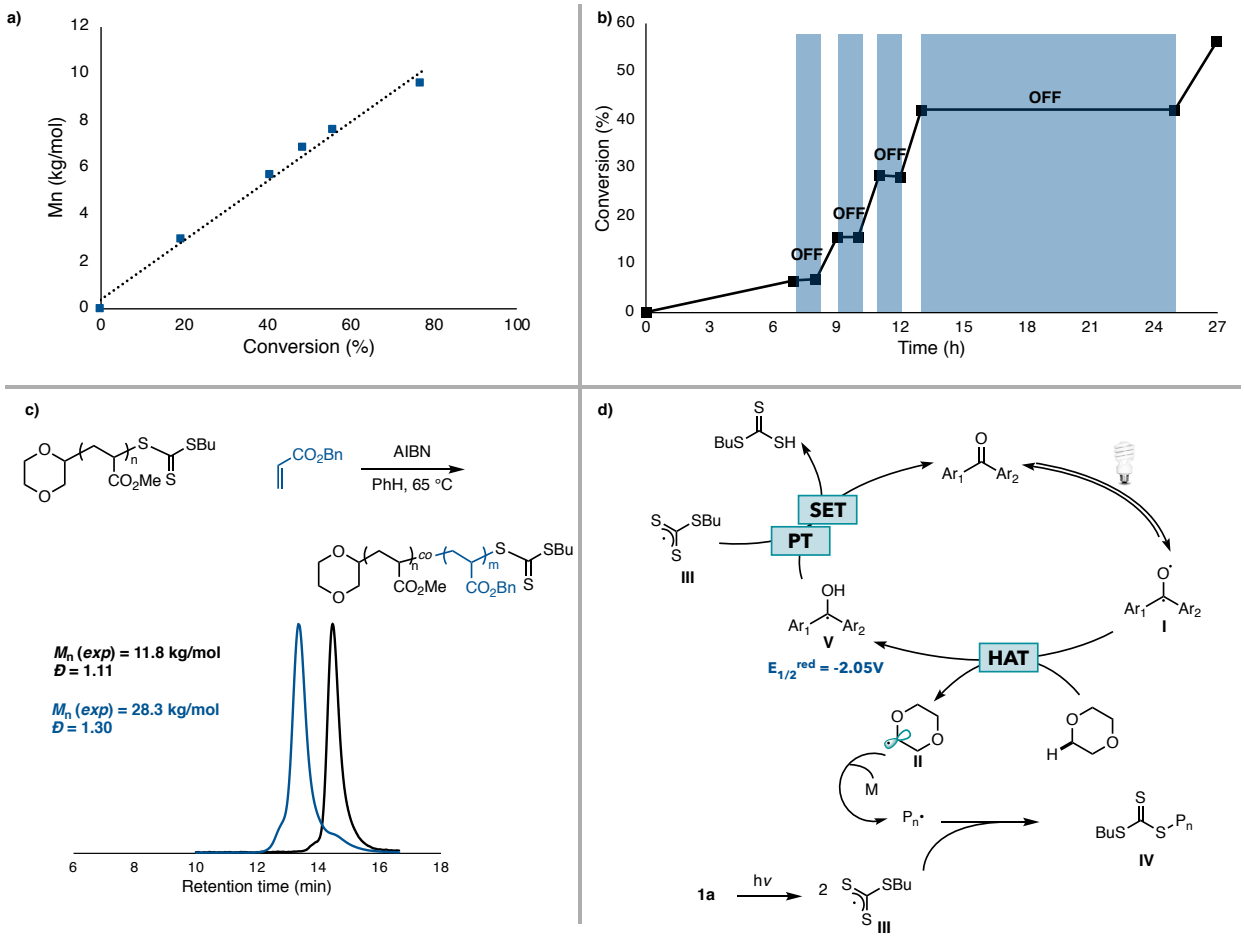


Figure 1. a) Linear growth of molecular weight vs. conversion. b) Temporal control of polymerization with intermittent light. c) Thermal RAFT chain extension of PMA with BnA. d) Proposed mechanism.

Given these results, we propose the following mechanism (Figure 1d). Upon excitation with visible light, photocatalyst **2** forms triplet excited state **I**. This diradical will abstract a hydridic C–H bond to form alkyl radical **II**, which will subsequently add to monomer to form a propagating polymer chain. After homolysis with visible light, disulfide **1a** can form two trithiocarbonyl radicals (**III**), one of which can combine with the electrophilic chain end to form macro-CTA (**IV**). The remaining radical (**III**) can be subsequently reduced by the photocatalyst radical **V** to generate the trithiocarbonic acid. Upon formation of IV, we propose that additional alkyl radicals are generated from excitation of the photocatalyst to maintain an active RAFT process (see SI for a full proposed mechanism). In the absence of light, termination events generate an inactive polymerization state, but upon generation of additional radical with irradiation, the RAFT process can be restarted. Termination events include reduction of an active chain end to form an anion which will be rapidly protonated, in addition to chain-chain coupling.[24,25]

To apply this method to various applications, such as grafting from an existing polymer or biomolecule, we recognized that using solvent quantities of C–H coupling partner may be inefficient.[15,26-28] We therefore examined a number of C–H initiators in reagent quantities relative to disulfide. In C–H initiators with lower BDEs or more hydridic C–H bonds,[29] radical initiation becomes more facile and when THF was used as a solvent in a similar manner to Table 1, a completely uncontrolled polymerization was observed. For THF, we found that by reducing the C–H initiator concentration to 20 equivalents, we were able to achieve a controlled polymerization (Figure 2). When ethyl acetate was used as the H-atom source, even in solvent quantities, no polymerization was observed. Given the lack of hydridic C–H bonds in ethyl acetate, this result is consistent with highly selective HAT processes and unwanted abstraction from the backbone of the polymer chain can be avoided. Amides also served as C–H initiators, with *N*-methyl pyrrolidinone affording similar results to THF, and even Cbz-(*L*)-proline methyl ester afforded a well-controlled polymerization, suggesting that biomolecules may serve as C–H initiators in bioconjugation. Alcohols were also demonstrated to function as initators in this chemistry, with benzyl alcohol and ethanol affording well controlled polymerizations. Excitingly, diethylene glycol monomethyl ether, a mimic for poly(ethylene glycol) (PEG) afforded a well-controlled polymerization. Furthermore, cyclohexane, with a C–H BDE of 100 kcal/mol afforded the desired PMA, albeit at higher C–H initiator loadings. Cyclohexane is representative of a polyolefin, such as polyethylene, and provides future opportunities for grafting from commodity polymers.[14,30]

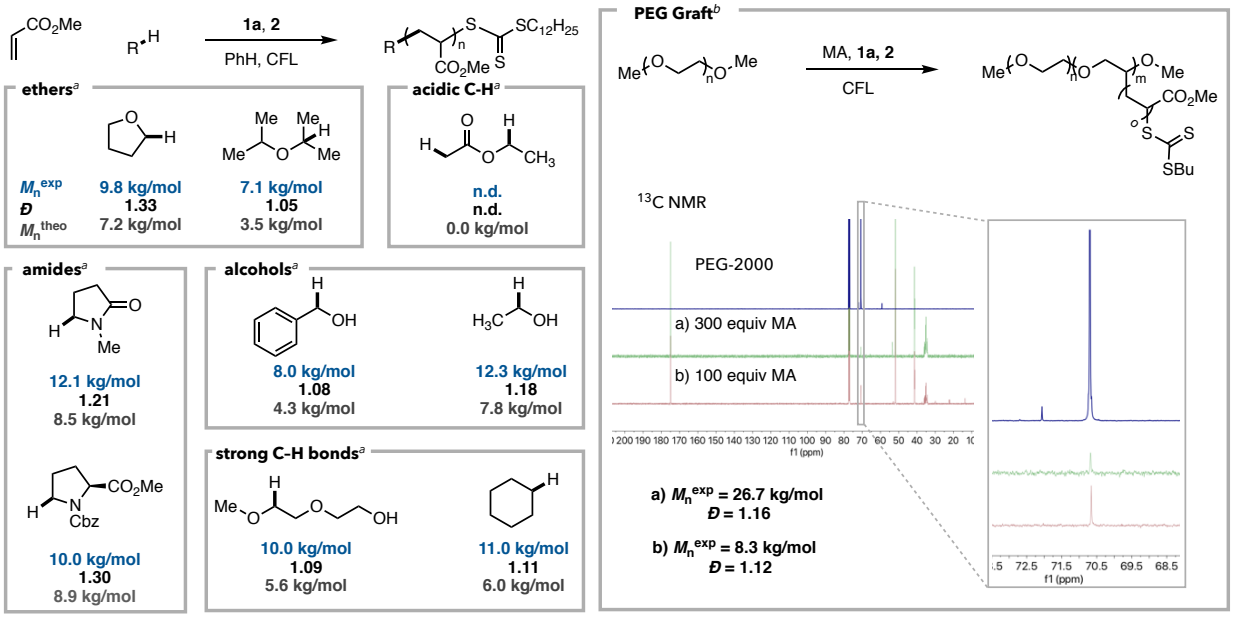


Figure 2. Examples of C–H initiators to mediate HAT-RAFT polymerization, including controlled grafting from PEG. [a] MA (100 equiv, filtered through basic alumina), disulfide **1a** (1 equiv), **2** (0. 5-1.0 equiv) and C–H coupling partner (20-116 equiv) dissolved in DCE (4M), degassed and irradiated with a CFL. [b] MA

(100 or 300 equiv), poly(ethylene glycol) dimethyl ether (3 equiv, MW = 2.0 kg/mol), **1a** (1.0 equiv), **2** (1.0 equiv), degassed and irradiated with a CFL.

Lastly, we demonstrated that a PEG polymer could also serve as a C–H initiator (Figure 2). Under slightly modified conditions, we employed 3 equivalents of a 2.0 kg/mol PEG-dimethyl ether and obtained well controlled MA polymerizations. With increasing amounts of C–H initiator polymer, we observed increased conversion and molecular weight (see SI for more details). We also observed that we could achieve graft copolymers of designed molecular weight, 8.3 kg/mol to 26.7 kg/mol, by altering the equivalents of monomer. To our knowledge, there are no other examples of *in situ* controlled grafting from a C–H bond of a PEG polymer.[11,12] Excitingly, we observe that even after precipitation, and removal of PEG confirmed via GPC analysis, that a signal for PEG is observed in the ^{13}C NMR of the precipitated polymer.

We have demonstrated that ubiquitous C–H bonds can serve as radical initiators for controlled radical polymerizations via use of a benzophenone derivative and visible light. We can access a controlled polymerization by employing a RAFT process, which can be accessed via an inexpensive and easily modifiable disulfide. We have highlighted future applications of this method in controlled polymerization from biomolecules as well as commercial or commodity polymers.

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Notes: The authors declare no competing financial interests.

Acknowledgements

This work was supported by the NSF under the award number CHE-1752140 (B.P.F). Additionally, this work made use of the NMR Facility at Cornell University and is supported, in part, by the NSF under the award number CHE-1531632. B.P.F. thanks 3M for a Non-Tenured Faculty Award and the Alfred P. Sloan Foundation for a Sloan Research Fellowship. E.E.S acknowledges the Cornell Presidential Postdoctoral Fellowship for financial support.

References

(1) Keddie, D. J.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2012**, *45*, 5321-5342.
(2) Perrier, S. *Macromolecules* **2017**, *50*, 7433-7447.

(3) a) McKenzie, T. G.; Fu, Q.; Uchiyama, M.; Satoh, K.; Xu, J.; Boyer, C.; Kamigaito, M.; Qiao, G. G. *Adv. Sci.* **2016**, *3*, 1500394. b) Wu, C.; Corrigan, N.; Lim, C.-H.; Jung, K.; Zhu, J.; Miyake, G.; Xu, J.; Boyer, C. *Macromolecules* **2019**, *52*, 236-248.
(4) Lorandi, F.; Fantin, M.; Shanmugam, S.; Wang, Y.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K. *Macromoelcules* **2019**, *52*, 1479-1488.
(5) Otsu, T.; Yoshida, M. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 127-132.
(6) Otsu, T. J. Polym. Sci. Part A: Polym. Chem. **2000**, 38, 2121-2136.
(7) Xu, J.; Jung, K.; Atme, A.; Shanmugam, S.; Boyer, C. *J. Am. Chem. Soc.* **2014**, *136*, 5508.
(8) Chen, M.; Zhong, M.; Johnson, J. A. *Chem. Rev.* **2016**, *116*, 10167.
(9) Corrigan, N.; Yeow, J.; Judzewitsch, P.; Xu, J.; Boyer, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 5170-5189.
(10) Dadashi-Silab, S.; Doran, S.; Yagci, Y. *Chem. Rev.* **2016***, 116*, 10212-10275.
(11) Williamson, J. B.; Czaplyski, W. L.; Alexanian, E. J.; Leibfarth, F. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 6261-6265.
(12) Tasdelen, M. A.; Moszner, N.; Yagci, Y. *Polym. Bull.* **2009**, *63*, 173.
(13) Ko, J. H.; Maynard, H. D. *Chem. Soc. Rev.* **2018**, *47*, 8998.
(14) Williamson, J. B.; Lewis, S.E.; Johnson III, R. R.; Manning, M.; Leibfarth, F. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 8654-8668.
(15) Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.
(16) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116,* 10075.
(17) Yagci, Y.; Jockusch, S.; Turro, N. J. *Macromolecules* **2010***, 43*, 6245-6260.
(18) Block, H.; Ledwith, A.; Taylor, A. R. *Polymer* **1971**, *12*, 271-288.
(19) Sandner, M. R.; Osborn, C. L.; Trecker, D. J. *J. Polym. Sci. Part A-1: Polym. Chem.* **1972**, *10*, 3173-3181.
(20) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.
(21) a) Singh, A.; Kuksenok, O.; Johnson, J. A.; Balazs, A. C. *Polym. Chem.* **2016***, 76*, 2955-2964. b) McKenzie, T. G.; Fu, Q.; Wong, E. H. H.; Dunstan, D. E.; Qiao, G. G. *Macromolecules* **2015***, 48*, 3864-3872. c) Shanmugam, S.; Cuthbert, J.; Flum, J.; Fantin, M.; Boyer, C.; Kowalewski, T.; Matyjaszewski, K. *Polym. Chem.* **2019**, *10*, 2477-2483.
(22) We observed a background reaction in the absence of dioxane (DCE used as a solvent) for MMA and BMA, likely due to an iniferter process. See SI for more details.
(23) THF based chain ends were not observed in the ^{1}H NMR. Given the relative triplet energies of 2 vs. stryene (E_T = 67.7 vs. 60 kcal/mol), initiation may be occurring via direction sensitization of styrene rather than HAT.
(24) Bortolamei, N.; Isse, A. A.; Gennaro, A. *Electrochimica Acta* **2010**, *55*, 8312-8318.
(25) See supporting information for more details on the proposed mechanism.
(26) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532-1536.
(27) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. *Nature* **2018**, *560*, 70-75.
(28) Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. *J. Am. Chem. Soc.* **2018**, *140*, 14059-14063.
(29) Vleeschouwer, F. D.; Speybroeck, V. V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* **2007**, *9*, 2721-2724. Radical nucleophilicity will also dictate the % of C–H α-chain ends.
(30) Williamson, J. B.; Na, C. G.; Johnson III, R. R.; Alexanian, E. J.; Leibfarth, F. A. *J. Am. Chem. Soc.* **2019**, *141*, 12815-12823.