

Communication

Photocontrolled radical polymerization from hydridic C–H bonds

Erin E Stache, Veronika Kottisch, and Brett P. Fors

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c00287 • Publication Date (Web): 11 Feb 2020

Downloaded from pubs.acs.org on February 11, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

Photocontrolled radical polymerization from hydridic C–H bonds

Erin E. Stache, Veronika Kottisch[†], and Brett P. Fors^{*}

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States

KEYWORDS (*Word Style "BG_Keywords"*). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval.

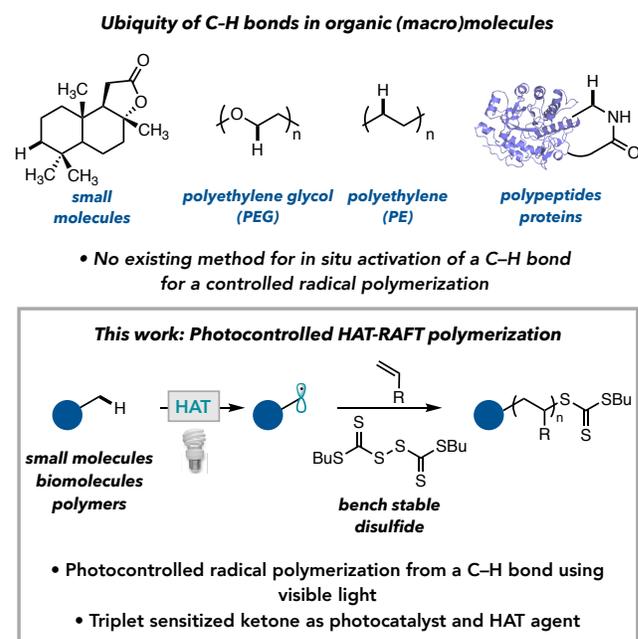
ABSTRACT: Given the ubiquity of carbon-hydrogen bonds in biomolecules and polymer backbones, the development of a photocontrolled polymerization selectively grafting from a C–H bond would represent a powerful strategy for polymer conjugation. This approach would circumvent the need for complex synthetic pathways currently used to introduce functionality at a polymer chain end. On this basis, we have developed a hydrogen-atom abstraction strategy that allows for a controlled polymerization selectively from a hydridic 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. 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.

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/energy transfer (PET-RAFT) processes have been established as a means to exact temporal and spatial control in these processes,^{5–9} finding numerous applications for designing complex 3D architectures.¹⁰ To employ these methods, however, a prefunctionalized initiator/chain transfer agent (CTA) must be installed into a macromolecule, biomolecule, or small molecule for a controlled polymerization. We envisioned a strategy that eliminated the need for the preformation of a CTA and enabled selective grafting of a polymer from hydridic C–H bonds would be an opportunity to streamline macromolecular synthesis (Scheme 1).^{11,12} The development of such a strategy would 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

Hydrogen-atom transfer (HAT) is a burgeoning synthetic strategy to generate carbon centered radicals from C–H bonds.¹⁵ Benzophenone derivatives have been well demonstrated as hydrogen-atom abstraction agents when excited with visible light and the resultant ketyl radical acts as an electron donor.^{16,17} We hypothesized that radical polymerizations could be initiated using this mechanism.^{18–20} Importantly, benzophenone derivatives, in the triplet excited state, can chemoselectively abstract electron rich, hydridic C–H bonds, which would allow the precise selection of grafting sites.²¹ The photogenerated electrophilic oxygen-centered radical has been shown to

abstract α -oxy, α -amino, and hydrocarbon C–H bonds in contrast to α -acyl or more acidic C–H bonds. This selectivity will also preclude unwanted C–H abstraction processes from the growing polymer backbone of electron deficient monomers used in controlled radical processes, which could lead to undesirable cross-linking and branching.

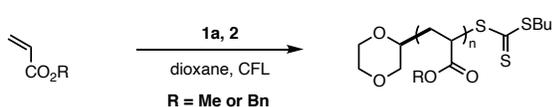
Scheme 1. Design of HAT-RAFT polymerization



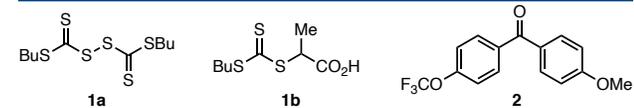
In an approach where we initiate polymerization with C–H abstraction, we envisioned that control over the polymerization could be imbued by a RAFT process via addition of a CTA.

However, the α -chain end of the final polymer would arise from the chain end of the CTA, rather than the C–H bond initiator. Therefore, to achieve efficient grafting we needed to develop a method where the CTA was synthesized *in situ* from the radical formed through C–H abstraction. We hypothesized that the use of a precursor disulfide could effectively generate the CTA *in situ* and provide the desired α -chain end (Scheme 1). Additionally, this strategy should allow the employment of multiple monomer classes with a single disulfide precursor, without matching designed CTAs to a specific monomer, as a macro-CTA would be generated *in situ*. 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



entry ^a	monomer	[M]:[1a]:[2]	M_n^{theo} (kg/mol)	M_n^{exp} (kg/mol)	D
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	MA	100:1:0	0.0	n.d.	n.d.
8	BnA	100:1:0.5	16.0	19.0	1.23



^a Monomer (filtered through basic alumina), disulfide **1a**, and photocatalyst **2** dissolved in dioxane (0.04 M in **1a**), degassed and irradiated with a CFL. ^b CTA **1b**, used in place of **1a** and 1,2-dichloroethane used as a solvent.

We began our studies employing disulfide **1a**, photocatalyst **2**,¹⁶ 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 compact fluorescent lamp (CFL) with a narrow dispersity (D) (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. We were able to identify initiation from dioxane as the major chain end by MALDI-TOF (see supporting information for more details). In the absence of disulfide, the polymerization is rapid and uncontrolled; however, in the absence of light or H-atom source (1,2-dichloroethane used as a solvent), no conversion of MA is observed (see supporting information for more details). Additionally, we could effectively target different molecular

weights by changing the disulfide to monomer ratio (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.²² Furthermore, when the polymerization was conducted without photocatalyst, no conversion was observed, precluding direct excitation of the disulfide to induce polymerization (entry 7). 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 8). Methacrylates could be polymerized under these reaction conditions, but similar results were obtained in the absence of photocatalyst or HAT source suggesting a competitive iniferter process.^{22,23}

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). Unlike traditional radical RAFT processes, we observed a small increase in dispersity over time. We attribute this increase to continued generation of alkyl radical and termination events. We also 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 macro-CTA 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-*b*-PBnA copolymer with good matching of M_n^{theo} and M_n^{exp} and narrow D . The GPC trace did indicate some remaining PMA macro-CTA, and we attribute the incomplete conversion to reductive termination events during the HAT-RAFT polymerization. Based on GPC data of isolated homopolymer and copolymer, we estimate 78% chain extension.

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**). Alternatively, the electrophilic chain end can add to disulfide **1a** and generate **III**. The remaining radical (**III**) can be subsequently reduced by the photocatalyst radical **V** to generate the trithiocarbonic acid and turnover the catalyst. Upon formation of **IV**, we propose that additional alkyl radicals are generated from excitation of the photocatalyst to maintain a

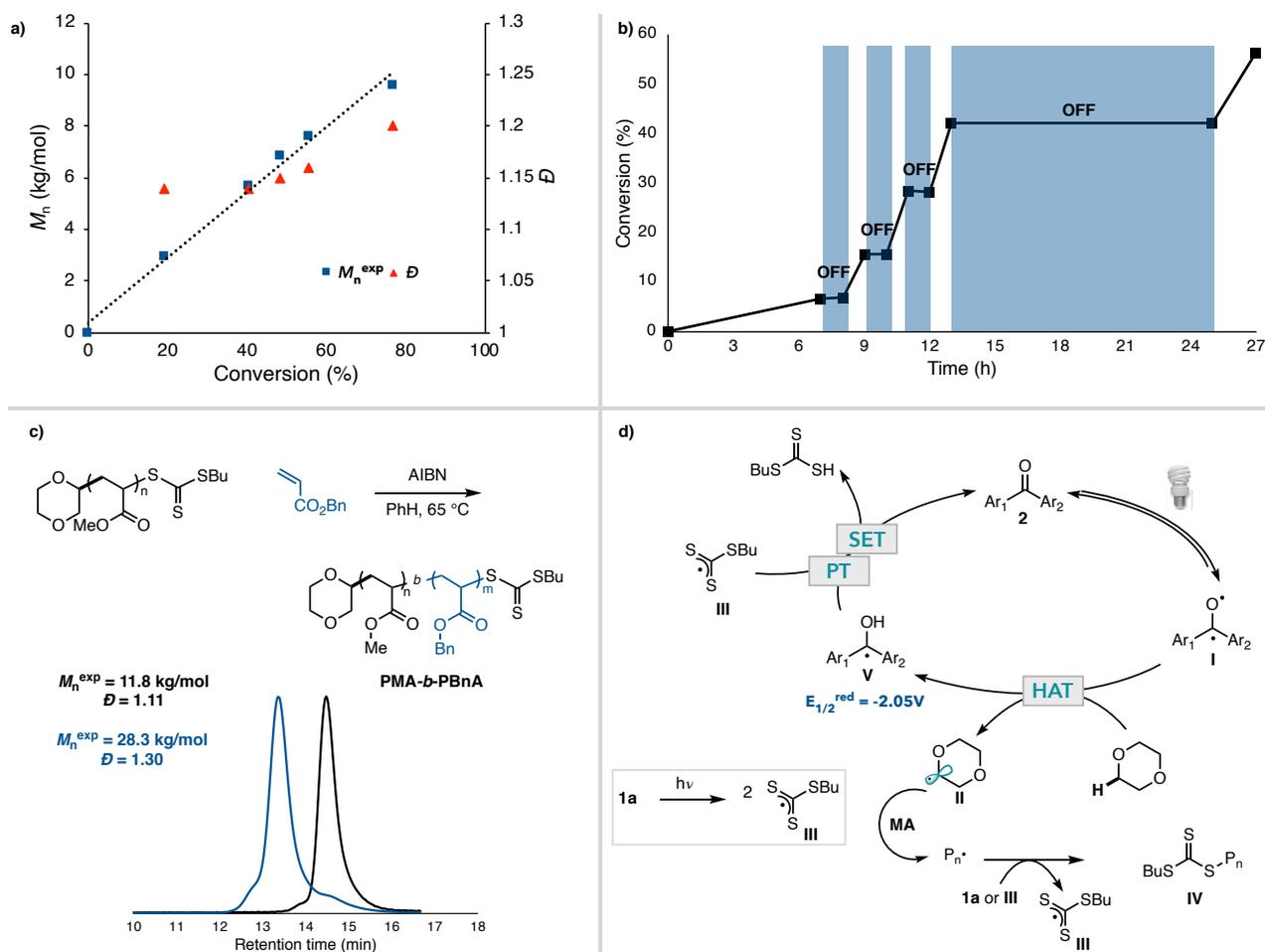


Figure 1. a) Linear growth of molecular weight vs. conversion. b) Temporal control of polymerization with intermittent light. c) Thermal RAFT chain extension of PMA with BnA. d) Proposed mechanism; see Figure S47 for a full description of the proposed mechanism.

active RAFT process (see supporting information 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 radical-radical 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.^{16, 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 suggests that unwanted abstraction from the backbone of the polymer chain can be avoided.³⁰ 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-

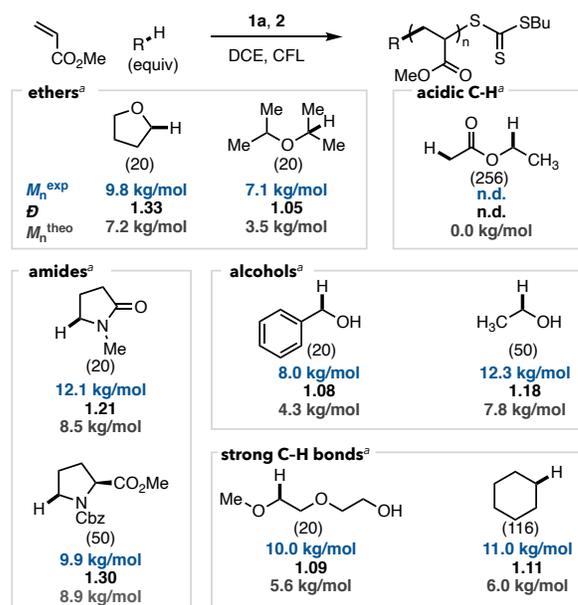


Figure 2. Examples of C–H initiators to mediate HAT-RAFT polymerization, including controlled grafting from PEG. *a* MA (100 equiv, filtered through basic alumina), disulfide **1a** (1 equiv), **2** (0.75–1.0 equiv) and C–H coupling partner (20–116 equiv) dissolved in DCE (0.04 M in **1a**), degassed and irradiated with a CFL.

controlled polymerization, suggesting that biomolecules may serve as C–H initiators in bioconjugation. Alcohols were also demonstrated to function as initiators in this chemistry, with benzyl alcohol and ethanol affording well controlled polymerizations.³¹ 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.^{14,32}

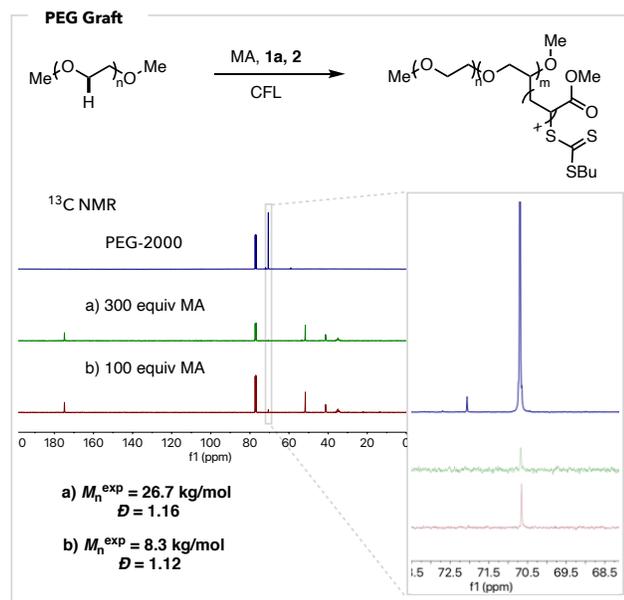


Figure 3. MA (100 or 300 equiv), poly(ethylene glycol) dimethyl ether (3 equiv, MW = 2.0 kg/mol), **1a** (1.0 equiv), **2** (1.0 equiv), degassed and irradiated with a CFL.

Lastly, we demonstrated that a PEG polymer could also serve as a C–H initiator (Figure 3). 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. Currently, 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 ¹³C NMR of the precipitated polymer.³³ Furthermore, no PEG degradation is observed via GPC analysis, highlighting the advantage of our method for functionalizing PEG, where the installation of thiocarbonyl compounds results in PEG decomposition.

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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

brief description (file type, i.e., PDF)

AUTHOR INFORMATION

Corresponding Author

* bpf46@cornell.edu

Present Addresses

† Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, United States

Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

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. This work made use of the Cornell Center for Materials Research Facilities supported by the National Science Foundation under Award Number DMR-1719875. 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. RAFT agent design and synthesis. *Macromolecules* **2012**, *45*, 5321–5342.
- (2) Perrier, S. *50th Anniversary Perspective: RAFT–A user guide. 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. Beyond traditional RAFT: Alternative activation of thiocarbonylthio compounds for controlled polymerization. *Adv. Sci.* **2016**, *3*, 1500394. b) Wu, C.; Corrigan, N.; Lim, C.-H.; Jung, K.; Zhu, J.; Miyake, G.; Xu, J.; Boyer, C. Guiding the design of organic photocatalyst for PET-RAFT polymerization: Halogenated xanthene dyes. *Macromolecules* **2019**, *52*, 236–248.
- (4) Lorandi, F.; Fantin, M.; Shanmugam, S.; Wang, Y.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K. Toward electrochemically mediated reversible addition–fragmentation chain-transfer (eRAFT) polymerization: Can propagating radicals be efficiently electrogenerated from RAFT agents? *Macromolecules* **2019**, *52*, 1479–1488.
- (5) Otsu, T.; Yoshida, M. Role of initiator-transfer agent-terminator (iniferter) in radical polymerizations: Polymer design by organic disulfides as iniferters. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 127–132.
- (6) Otsu, T. J. Iniferter concept and living radical polymerization. *Polym. Sci. Part A: Polym. Chem.* **2000**, *38*, 2121–2136.
- (7) Xu, J.; Jung, K.; Atme, A.; Shanmugam, S.; Boyer, C. A robust and versatile photoinduced living polymerization of conjugated and

unconjugated monomers and its oxygen tolerance. *J. Am. Chem. Soc.* **2014**, *136*, 5508-5519.

(8) Dadashi-Silab, S.; Doran, S.; Yagci, Y. Photoinduced electron transfer reactions for macromolecular syntheses. *Chem. Rev.* **2016**, *116*, 10212-10275.

(9) Corrigan, N.; Yeow, J.; Judzewitsch, P.; Xu, J.; Boyer, C. Seeing the light: Advancing materials chemistry through photopolymerization. *Angew. Chem. Int. Ed.* **2019**, *58*, 5170-5189.

(10) a) Chen, M.; Zhong, M.; Johnson, J. A. Light-Controlled Radical Polymerization: Mechanisms, Methods, and Applications. *Chem. Rev.* **2016**, *116*, 10167. b) Zhang, Z.; Corrigan, N.; Bagheri, A.; Jin, J.; Boyer, C. A versatile 3D and 4D printing system through photocontrolled RAFT polymerization. *Angew. Chem. Int. Ed.* **2019**, *58*, 17954-17963.

(11) Williamson, J. B.; Czaplowski, W. L.; Alexanian, E. J.; Leibfarth, F. A. Regioselective C–H xanthylation as a platform for polyolefin functionalization. *Angew. Chem. Int. Ed.* **2018**, *57*, 6261-6265.

(12) Tasdelen, M. A.; Moszner, N.; Yagci, Y. The use of poly(ethylene oxide) as hydrogen donor in type II photoinitiated free radical polymerization. *Polym. Bull.* **2009**, *63*, 173-183.

(13) Ko, J. H.; Maynard, H. D. A guide to maximizing the therapeutic potential of protein–polymer conjugates by rational design. *Chem. Soc. Rev.* **2018**, *47*, 8998-9014.

(14) Williamson, J. B.; Lewis, S.E.; Johnson III, R. R.; Manning, M.; Leibfarth, F. A. C–H functionalization of commodity polymers. *Angew. Chem. Int. Ed.* **2019**, *58*, 8654-8668.

(15) Capaldo, L.; Ravelli, D. Hydrogen atom transfer (HAT): A versatile strategy for substrate activation in photocatalyzed organic synthesis. *Eur. J. Org. Chem.* **2017**, 2056-2071.

(16) Shen, Y.; Gu, Y.; Martin, R. *sp*³ C–H Arylation and alkylation enabled by the synergy of triplet excited ketones and nickel catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 12200-12209.

(17) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, *116*, 10075-10166.

(18) Yagci, Y.; Jockusch, S.; Turro, N. J. Photoinitiated polymerization: Advances, challenges, and opportunities. *Macromolecules* **2010**, *43*, 6245-6260.

(19) Block, H.; Ledwith, A.; Taylor, A. R. Polymerization of methyl methacrylate photosensitized by benzophenones. *Polymer* **1971**, *12*, 271-288.

(20) Sandner, M. R.; Osborn, C. L.; Trecker, D. J. Benzophenone/triethylamine-photoinitiated polymerization of methyl acrylate. *J. Polym. Sci. Part A-1: Polym. Chem.* **1972**, *10*, 3173-3181.

(21) Roberts, B. P. Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25-35.

(22) a) Singh, A.; Kuksenok, O.; Johnson, J. A.; Balazs, A. C. Tailoring the structure of polymer networks with iniferter-mediated photogrowth. *Polym. Chem.* **2016**, *76*, 2955-2964. b) McKenzie, T. G.; Fu, Q.; Wong, E. H. H.; Dunstan, D. E.; Qiao, G. G. Visible light mediated controlled radical polymerization in the absence of exogenous radical sources or catalysts. *Macromolecules* **2015**, *48*, 3864-3872. c) Shanmugam, S.; Cuthbert, J.; Flum, J.; Fantin, M.; Boyer, C.; Kowalewski, T.; Matyjaszewski, K. Transformation of gels *via* catalyst-free selective RAFT photoactivation. *Polym. Chem.* **2019**, *10*, 2477-2483.

(23) We observed a background reaction that gives similar results to the HAT-RAFT process in the absence of dioxane (DCE used as a solvent) or photocatalyst for MMA and BMA. This is likely due to direct excitation of the disulfide and resultant CTA through an iniferter process, see Ref. 5,6, 21.

(24) Bortolamei, N.; Isse, A. A.; Gennaro, A. Estimation of standard reduction potentials of alkyl radicals involved in atom transfer radical polymerization. *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. O–H Hydrogen bonding promotes H-atom transfer from a C–H bonds for C-alkylation of alcohols. *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. Direct arylation of strong aliphatic C–H bonds. *Nature* **2018**, *560*, 70-75.

(28) Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. Direct C–C bond formation from alkanes using Ni-photoredox catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14059-14063.

(29) Vleeschouwer, F. D.; Speybroeck, V. V.; Waroquier, M.; Geerlings, P.; De Proft, F. Electrophilicity and Nucleophilicity Index for Radicals. *Org. Lett.* **2007**, *9*, 2721-2724.

(30) We conducted experiments on macro-CTAs to test for branching in the polymer backbone and observed no considerable polymerization suggesting that abstraction from the backbone is not a major pathway. See supporting information for more details.

(31) Benzyl alcohol chain ends are identified by ¹H NMR; see supporting information for more details.

(32) Williamson, J. B.; Na, C. G.; Johnson III, R. R.; Alexanian, E. J.; Leibfarth, F. A. Chemo- and regioselective functionalization of isotactic polypropylene: A mechanistic and structure–property study. *J. Am. Chem. Soc.* **2019**, *141*, 12815-12823.

(33) See supporting information Figures S47 and S50 for GPC chromatograms.

1 Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title,
2 should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem,
3 etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.
4

