ACS Macro Letters

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Phosphonium Tetraphenylborate: A Photocatalyst for Visible-Light-Induced, Nucleophile-Initiated Thiol-Michael Addition Photopolymerization

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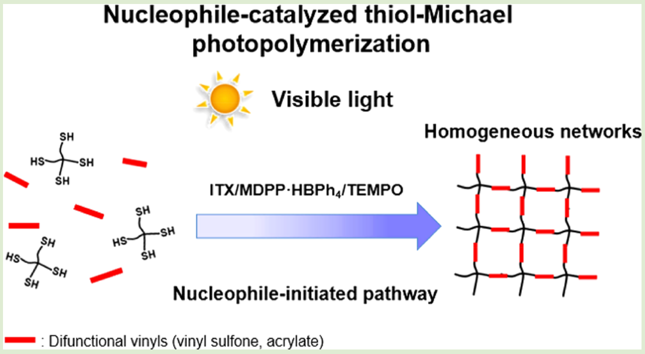
Cite This: *ACS Macro Lett.* 2021, 10, 84−89

ABSTRACT: A photoinitiation system that utilizes phosphonium tetraphenylborate as the key component was developed for the visible light-triggered nucleophile-catalyzed thiol-Michael addition reaction. This highly reactive catalyst was composed of a photocaged phosphine (methyldiphenylphosphonium tetraphenylborate, MDPP·$HBPh_4$), a photosensitizer (isopropylthioxanthone, ITX), and a radical scavenger (TEMPO). Unlike the prevailing photobase catalysts, this photoactivatable phosphine system triggers the thiol-Michael addition polymerization by a nucleophile-catalyzed mechanism and provides a controlled stoichiometric reaction between the thiol and the vinyl precursors. This approach enables the formation of homogeneous polymer networks upon low-energy visible light exposure and, thus, broadens its potential applications in bulk polymer materials synthesis and UV-sensitive bioscaffold formation.



The thiol-Michael addition reaction is a highly efficient "click" reaction that affords quantitative yields, high reaction rates, and the ability to be performed under mild reaction conditions.[1,2] The thiol-Michael addition reaction is readily initiated by either a base or a nucleophile and proceeds through an anion-mediated propagation mechanism.[3] With relatively stable reaction intermediates (thiolate and enolate anions), the thiol-Michael addition reaction is highly robust and negligibly influenced by water or oxygen and widely implemented in many hybrid and orthogonal systems when utilized with other types of reactions.[4,5] In the past few decades, the thiol-Michael "click" reaction has drawn a great deal of attention and seen broad applications, including bioconjugation,[6] organic synthesis,[7] material synthesis,[8] and dendrimer/polymer modification.[9−11]

Additionally, the utilization of light in the "click" reaction provides distinct advantages, including rapid reaction kinetics, the ability to control the desired reactions temporally and spatially, and the environmental benefits of avoiding the use of volatile organic solvents.[12] For example, in the advent of the diversified radical photoinitiator library, photocontrolled reactions have been widely used in (meth)acrylate photopolymerizations,[13] cationic reactions,[14] the thiol−ene/thiol−yne radical reactions,[15,16] and the copper(I) catalyzed azide alkyne cycloaddition (CuAAC) reactions,[17,18] among others. In contrast, the phototriggered thiol-Michael "click" reaction is challenging to achieve since the photolysis process often involves radicals leading to the homopolymerization of the vinyl moieties, often rendering it ineffective for stoichiometric Michael addition.

One promising strategy to photoinitiate thiol-Michael reactions is to implement photocaged bases, which generate limited or no radicals during photocleavage.[19] Upon light exposure, photobase generators release the organic bases (typically amines and guanidines) to deprotonate the thiol and initiate the alternating thiol-Michael propagation and chain transfer steps.[20] Photobases, for example, nitrobenzyl- and coumarin-protected organic bases, showed high catalytic efficiency toward the thiol-Michael addition reaction through the base-initiation pathway.[4] However, there are no light-mediated methods reported to trigger the thiol-Michael addition reaction through the nucleophile-mediated pathway.

As noted, in addition to base catalysts, the thiol-Michael addition reaction can also be catalyzed by using strong nucleophiles (e.g., phosphines).[21] Chan and co-workers investigated the effect of organocatalysts on the nucleophile-initiated thiol-Michael reaction and demonstrated extremely rapid, subsecond-scale, thiol-Michael reactions by using only 0.0004 mol % phosphine catalysts (i.e., methyldiphenylphos-

Received: November 18, 2020
Accepted: December 17, 2020
Published: December 18, 2020

https://dx.doi.org/10.1021/acsmacrolett.0c00809

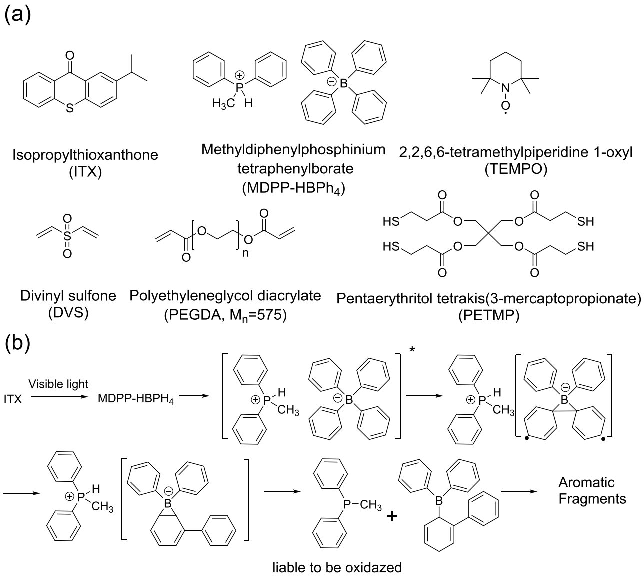
phine and dimethylphenylphosphine).[3] As such, the development of the corresponding photoactivatable phosphine would afford a new photoinitiation methodology for the photoinduced thiol-Michael reactions and, therefore, diversifying the light-mediated "click" reaction toolbox. Besides the exceptional use in "click" chemistry and material science, the phosphine species are also readily exploited as bioactive probes in cell imaging and pharmacology.[22] For example, a series of carbocyanine−phosphonium adducts was reported as photoactivatable phosphine probes to induce intracellular reductive stress in individual cells with minimal disturbance to neighboring cells.[23]

Here, we introduce phosphonium tetraphenylborates as photoinitiators for the nucleophile-catalyzed, light-triggered thiol-Michael addition reaction. Previous studies utilized tetraphenylborate-protected bicyclic guanidines as the efficient photobase catalysts for the living anionic ring-opening polymerization of cyclic esters.[24] In this study, strong phosphine nucleophiles, that is, methyldiphenylphosphine (MDPP), were implemented to form tetraphenylborate salts ($MDPP\cdot HBPh_4$) as the photoactivatable phosphine catalyst. Furthermore, $MDPP\cdot HBPh_4$ was then incorporated with a visible light sensitizer, isopropylthioxanthone (ITX), and a radical inhibitor, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), as a three-component initiation system for the visible light induced thiol-Michael addition reaction. The visible light sensitizer ITX is capable of absorbing lights at longer wavelengths (>400 nm) and allows the phosphonium tetraphenylborates to perform photochemical reactions upon visible light exposure via triplet energy transfer from the sensitizer to the phosphonium salt.[24] Lastly, the implementation of TEMPO avoids the radical-mediated homopolymerization of the vinyl groups by quenching the radicals generated from the photoreaction of ITX and phosphonium salts and, thus, facilitates a stoichiometric thiol-Michael addition reaction.[25]

Scheme 1a shows the structures of the chemicals used in this study. Basically, the phosphine, hydrochloric acid (HCl), and $NaBPh_4$ were mixed in water, followed by filtration and appropriate solvent wash, giving the phosphonium tetraphenylborates in high yields (80−90%; the compound was confirmed by ^1H NMR and ^{31}P NMR). The absorption spectra of the MDPP, $MDPP\cdot HBPh_4$, and ITX are shown in Figure 1. The phosphonium tetraphenylborate, that is, $MDPP\cdot HBPh_4$, does not exhibit light absorption above 330 nm. However, a deep UV exposure to $MDPP\cdot HBPh_4$ salt can lead to the problem of photoinduced phosphine oxidation. As such, the photosensitizer ITX, which has a long-wavelength absorption band tailing into the visible light region (above 420 nm), was implemented to trigger photolysis of the $MDPP\cdot HBPh_4$ upon visible light induction. Irradiation by long-wavelength light not only increases curing depths in polymeric material synthesis but also minimizes the light damage to UV-sensitive cells or materials in pharmaceutical, biological, or materials applications.[26]

The proposed mechanism of the ITX-sensitized tetraphenylborate photodeprotection is shown in Scheme 1b. Upon photoactivation, ITX transfers the triplet energy to excite the phosphonium tetraphenylborate. Previous studies on tetraphenylborate photoprotection elucidated that the photolysis of the BPh_4 type salt proceeds via the same pathway as $NaBPh_4$.[24] In the excited state, the BPh_4 ion rearranges and abstracts a proton from the neighboring cation $MDPP\cdot H^+$ to release the phosphine and then further decomposes to aromatic fragments. Due to the photoinduced phosphine oxidation effect,[27] the direct measurement of the phosphine generation from the phosphonium salts is challenging. Previous reports on photoactivatable phosphines utilized indirect methods to monitor the photoinduced phosphine generation, such as measuring the evolution of the reductive stress and chemically trapping the photoreleased phosphines (e.g., by the Staudinger-Bertozzi ligation reaction).[23,28] In this study, the photogenerated phosphine from phosphonium tetraphenylborate was examined in the glutathione disulfide (GSSG) reduction reaction. GSSG aqueous solution was mixed with $ITX/MDPP\cdot HBPh_4$, followed by 10 min of 405 nm LED irradiation. The generation of the reduced form, that is, glutathione (GSH), was observed via an LC-MS experiment, indicating the reductive stress induced by phosphonium tetraphenylborate within the system (Figure S1).

Scheme 1. (a) Chemical Structures of Monomers and Initiators Used in This Study; (b) Proposed Mechanism for the Photogeneration of MDPP from $MDPP\cdot HBPh_4$[a]



[a]MDPP is liable to be photo-oxidized upon light exposure, making it a challenge to be measured directly.

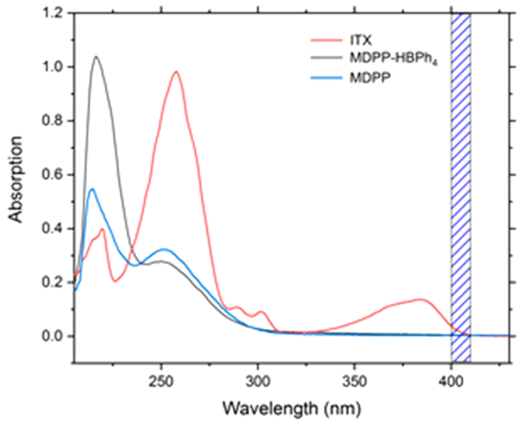


Figure 1. UV−vis absorption evaluation of the photosensitizer ITX, MDPP, and photocaged $MDPP\cdot HBPh_4$ in methanol, along with the wavelength regions of the applied 405 nm LED and 400−500 nm light sources.

Besides being used as active reducing agents, phosphine species, for example, MDPP and dimethylphenylphosphine (DMPP), are also strong nucleophiles that trigger thiol-Michael addition reactions efficiently. A series of different monofunctional thiols and vinyl moieties were implemented as model substrates to study the catalyzing efficiency of the photoactivatable phosphine in thiol-Michael reactions (Table 1). ITX/MDPP·$HBPh_4$/TEMPO was added into stoichiometric thiol and vinyl mixtures, and the ultimate yields of the photoinduced thiol-Michael couplings were determined by ^1H NMR (Figure S2). The results in Table 1 indicate that, with only 2 wt % phosphonium tetraphenylborate catalyst loading, all analyzed systems achieved near-quantitative conversions in a short time (less than 20 min). In addition, the control experiments (entries 6 and 7) indicate that the photocatalyst and the visible light are both required to initiate the reaction.

Table 1. Stoichiometric Mixtures of Different Monofunctional Thiol and Vinyl Moieties Catalyzed with 1/2/2 wt % ITX/MDPP·$HBPh_4$/TEMPO Irradiated with 40 mW/cm^2 Visible Light of 400−500 nm[a]

entry	thiol	vinyl	yield (%)
1	butyl 3-mercaptopropionate	divinyl sulfone	94
2	1-hexanethiol	divinyl sulfone	99
3	methyl thioglycolate	divinyl sulfone	93
4	1-hexanethiol	butyl acrylate	99
5	butyl 3-mercaptopropionate	butyl acrylate	99
6[b]	butyl 3-mercaptopropionate	butyl acrylate	0
7[c]	butyl 3-mercaptopropionate	butyl acrylate	0

[a] After 20 min of irradiation, the crude product from the photoreaction was evaluated by ^1H NMR to determine the remaining reactant and reaction yield. [b] No ITX in the system. [c] No irradiation.

The photoinitiation efficiency of the photoactivatable phosphine for the thiol-Michael polymerization reactions was further investigated in stoichiometric PETMP and DVS formation. The thiol-vinyl sulfone photopolymerization was monitored by real time FT-IR. The decreasing thiol peak (2500−2600 cm^{-1}), acrylate peak (780−820 cm^{-1}), and vinyl peak (3050−3150 cm^{-1}) were measured to evaluate the photopolymerization kinetics during the experiments. TEMPO, as a common radical scavenger, was used to optimize the initiation step of the ITX photosensitized thiol-Michael reactions by eliminating the radical-mediated pathway. Figure 2a shows the photopolymerization kinetics of PETMP/DVS mixture using ITX/DMPP·$HBPh_4$/TEMPO (1/2/2 wt %) and ITX/DMPP·$HBPh_4$ (1/2 wt %) as photoinitiation systems and irradiated by 40 mW/cm^2, 405 nm LED light. Both phosphonium tetraphenylborate systems (with and without TEMPO) catalyzed efficient thiol-Michael photopolymerization and achieved over 80% conversion within 20 min. However, the system with TEMPO (solid lines) is superior to the system without TEMPO (dash lines), as it not only afforded a higher final conversion of the monomer, but also allows for more rapid photoreaction kinetics. Additionally, the final conversion of thiol in the ITX/MDPP·$HBPh_4$ catalyzed system is about 20% lower than that of vinyl moieties due to the extra vinyl consumption from radical-mediated homopolymerization. In contrast, the presence of TEMPO significantly elevated the thiol-Michael reaction rate with stoichiometric thiol and vinyl conversion, facilitating the formation of more homogeneous polymer networks by eliminating radical-mediated side reactions.

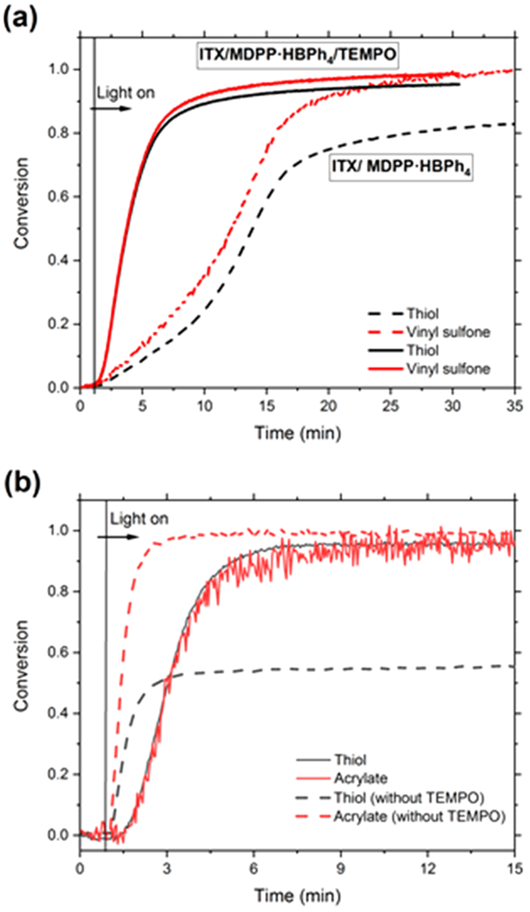


Figure 2. Conversions of thiol and vinyl moieties as a function of reaction time for (a) stoichiometric PETMP and DVS mixture and (b) stoichiometric PETMP and PEGDA (M_n = 575) mixture. All photopolymerization reactions were photocured using either ITX/DMPP·$HBPh_4$/TEMPO (1/2/2 wt %) or ITX/MDPP·$HBPh_4$ (1/2 wt %) and initiated with 40 mW/cm^2, 405 nm LED light.

Compared to highly electron deficient vinyl sulfone moieties, acrylate monomers are generally less reactive in the thiol-Michael reaction, and more likely to homopolymerize with even minimal amounts of radicals present in the system. Herein, eliminating the radical side reactions in the thiol−acrylate system is critical to achieve stoichiometric reaction and highly uniform polymer matrix. In this case, ITX/DMPP·$HBPh_4$/TEMPO (1/2/2 wt %) and ITX/DMPP·$HBPh_4$ (1/2 wt %) were added into stoichiometric PETMP/PEGDA (M_n = 575) formulations and photocured at the same exposure conditions (40 mW/cm^2, 405 nm LED light; Figure 2b). In the thiol−acrylate system initiated by ITX/DMPP·$HBPh_4$/TEMPO (solid line), the conversions of the thiol and acrylate monomers were almost identical during the photopolymerization process. After 5 min of irradiation, the orthogonal thiol-Michael network was readily achieved with quantitative monomer consumption. However, the absence of TEMPO (dash lines) resulted in a significant difference between the thiol and acrylate conversions. The conversions of thiol and vinyl reached 54% and 99%, respectively, after 5 min of irradiation. Compared to vinyl sulfones (dash lines in Figure 2a), acrylate species are less electron-deficient, making them react more rapidly in radical homopolymerization (dash lines in Figure 2b). This is attributed to a photoinduced radical generation in the photoinitiation step. Upon 400−500 nm light exposure, the ITX sensitizer not only induces the photolysis of DMPP·$HBPh_4$, releasing phosphine as the nucleophile initiator for the thiol-Michael reaction, but also generates radicals via proton absorption.[29] These radical species initiate a series of radical-meditated reactions, including thiol−acrylate addition and acrylate homopolymerization. In fact, without TEMPO present, the acrylate homopolymerization consumes almost half of the vinyl groups that react with the remainder, reacting via either Michael addition or radical-mediated thiol−acrylate addition. In contrast, in the presence of the radical scavenger TEMPO, the radical-mediated side reactions were greatly suppressed, and the nucleophile-initiated thiol-Michael reaction proceeded with stochiometric thiol and acrylate conversions. As such, TEMPO plays an important role in promoting homogeneity of the phosphonium tetraphenylborate-catalyzed thiol-Michael photopolymerization.

Except for suppressing radical-mediated side reactions, another crucial aspect of triggering orthogonal, rapid thiol-Michael polymerization is photo releasing a strong nucleophile in the initiation step. To prove this concept, a weak nucleophile, triethylamine (TEA, $pK_a = 10.7$), was photocaged with tetraphenylborate and investigated in the PETMP/PEGDA system. (Figure S3) Compared to the DMPP·$HBPh_4$ catalyzed system, ITX/TEA·$HBPh_4$/TEMPO (1/2/2 wt %) catalyzed the thiol−acrylate reaction with relatively slow photoreaction kinetics, in which the conversion of thiol and vinyl reached 53 and 97%, respectively, after 20 min of irradiation. The distinct difference in thiol and acrylate consumption indicates that the radical-mediated thiol−acrylate and acrylate−acrylate reaction dominated during the photocuring process. This result implies that the importance of photocaging strong nucleophiles (e.g., DMPP and MDPP) as the photoinitiation species for the photo-thiol-Michael addition reaction.

It is worth noticing that the phosphonium tetraphenylborate induced thiol-Michael polymerization is triggered by a nucleophile-initiation mechanism, as all the photoinitiation components, that is, ITX, DMPP·$HBPh_4$, and TEMPO, are weakly basic. Propagation in the thiol-Michael polymerization involves anionic species as reactive intermediates, which are still active even after the cessation of irradiation. This "living" characteristic was confirmed in a photoinitiated PETMP/DVS system using ITX/DMPP·$HBPh_4$/TEMPO (1/2/2 wt %). Figure 3a implies, after 2 min of irradiation, the phosphonium tetraphenylborate-triggered thiol-Michael polymerization continues in the dark, in which the thiol conversion increased from 30% to 78% after the cessation of light. This continuous curing kinetics also indicates that the thiol-vinyl reactions were induced by the nucleophile initiation pathway rather than the radical pathway due to the extremely limited lifetimes of radical species in the dark.

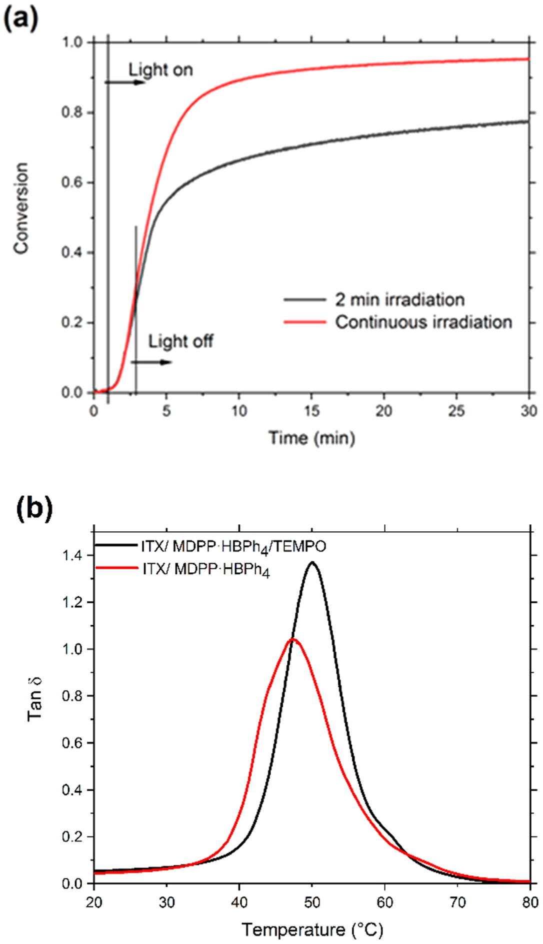


Figure 3. Tan δ plots for the PETMP and DVS polymer film initiated with the ITX/MDPP·$HBPh_4$/TEMPO (1/2/2 wt %) and ITX/MDPP·$HBPh_4$ (1/2 wt %) and initiator system. By suppressing the radical-mediated side reactions in the initiation step, ITX/MDPP·$HBPh_4$/TEMPO photoinitiation gives a more homogeneous polymer network, which was achieved with a narrower tan δ peak.

Finally, the thermomechanical performance of the photocured thiol-Michael polymers was evaluated. Two photoinitiation systems, that is, ITX/MDPP·$HBPh_4$ (1/2 wt %) and ITX/TBD·$HBPh_4$/TEMPO (1/2/2 wt %), were added into the PETMP/DVS mixture and then photocured under 405 nm LED light with an intensity of 40 mW/cm^2. The tan δ and modulus curves of the polymer were shown in Figures 3b and S4. The elastic moduli of the evaluated materials were similar, being slightly affected by a 20% difference in thiol and vinyl conversion according to the FT-IR result. Compared to the polymer networks without TEMPO, the PETMP/DVS film synthesized using ITX/TBD·$HBPh_4$/TEMPO exhibited a relatively narrower tan δ peak and higher T_g. The difference in the mechanical performance of the two systems indicates that the radical-mediated side reactions are detrimental to the thermomechanical properties.[30] Furthermore, the remaining functional groups, mainly thiol moieties, in heterogeneous polymer networks (photocured with ITX/MDPP·$HBPh_4$) would also affect the biocompatibility and long-term stability of the material.[31,32]

In summary, a photoactivatable phosphine system, that is, ITX/MDPP·$HBPh_4$/TEMPO, was developed and evaluated as a photoinitiator for the visible light-induced thiol-Michael photopolymerization. A series of kinetic studies of the thiol-vinyl sulfone and thiol−acrylate system proved that the photosensitizer, ITX, the photocaged strong nucleophile, MDPP, and the radical scavenger, TEMPO, are each a critical component of the photoinitiation system. This visible light photocuring method provides a controlled stoichiometric reaction between thiols and vinyl moieties and, as a result, generates a highly uniform polymer network with enhanced mechanical performance. Together, this photoinitiation system opens a new avenue for photomediated nucleophile-catalyzed reactions, including thiol-Michael addition polymerization, allowing them to be performed under mild visible light irradiation conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.0c00809.

Experimental section and Figures S1−S4 (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the NIH (1U01DE023777-01), NSF CHE 1808484, and the Industry/University Cooperative Research Center for Fundamentals and Applications of Photopolymerizations for providing funding for this research.

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