Fast Photoreactions

International Edition: DOI: 10.1002/anie.201504716
German Edition: DOI: 10.1002/ange.201504716

Visible-Light-Induced Click Chemistry**

Jan O. Mueller, Friedrich G. Schmidt, James P. Blinco, and Christopher Barner-Kowollik**

Abstract: *A rapid and catalyst-free cycloaddition system for visible-light-induced click chemistry is reported. A readily accessible photoreactive 2H-azirine moiety was designed to absorb light at wavelengths above 400 nm. Irradiation with low-energy light sources thus enables efficient small-molecule synthesis with a diverse range of multiple-bond-containing compounds. Moreover, in order to demonstrate the efficiency of the current approach, quantitative ligation of the photo-activatable chromophore with functional polymeric substrates was performed and full conversion with irradiation times of only 1 min at ambient conditions was achieved. The current report thus presents a highly efficient method for applications involving selective cycloaddition to electron-deficient multiple-bond-containing materials.*

In contemporary chemistry, the design of highly efficient reactions has become one of the dominating aspects for the development of novel technologies. Properties such as atom efficiency, sustainability, and environmentally benign conditions have become highly desired.[1] In particular, irradiation-induced processes represent a sustainable approach for efficient ligation reactions and their exceptional importance is validated by recent reports.[2] Thus, a large variety of photochemical techniques—almost exclusively relying on biologically harmful UV irradiation—have been established that fuse the favorable properties of cycloaddition reactions with the benefits of light-induced chemistry,[3] namely, spatial and temporal control. Although UV-activated ligation systems offer several advantages over conventional cycloaddition systems, the ability to employ the ubiquitously available energy of environmental light (visible-light region: 390–700 nm) represents a major goal of contemporary synthetic photochemistry.[4] Milestones regarding the development of systems utilizing visible-light-induced chemistry have been achieved through photoredox catalysis, which is a versatile tool in organic chemistry.[5] Moreover, efficient dipolar cycloaddition reactions have been conducted that employ metal-based as well as metal-free visible-light-triggered photoredox catalysts.[6] Nevertheless, an approach for catalyst-free ligation induced by visible light, as reported in the current study, had yet to be developed.

In order to obtain a photoreactive compound that can be ligated by visible light, two key points must be addressed: the moiety must absorb light in the desired wavelength region and the reactive species needs to be generated efficiently. We combined the absorption properties of a visible-light-absorbing chromophore (pyrene) and the photochemical reactivity of azirine compounds to provide an elegant solution to address both challenges simultaneously. The photochemistry of 2*H*-azirine moieties has been investigated intensely in former studies.[7] Upon irradiation, 2*H*-azirines undergo ring opening to generate nitrile ylides[8]—1,3-dipoles—in a reaction that shows extremely high photon efficiency.[9] Since 1,3-dipoles naturally form cycloadducts in the presence of electron-deficient multiple bonds,[10] nitrogen-containing five-membered heterocycles can be synthesized very efficiently and the properties, reaction kinetics, and scope of these reactions have been studied.[11] Lin and co-workers have previously demonstrated that azirine-based ligation is suitable for the rapid bioorthogonal conjugation of polymers and peptides in aqueous media.[12] Our work expands the available excitation wavelength for azirine ligations to the visible-light region, thus enhancing this rapid and efficient cycloaddition reaction to give a powerful new synthetic method (Scheme 1).

In terms of the absorption wavelength, the properties of the final photoreactive compound (**az-py**) need to be judiciously designed. Although absorption in the visible-light region is indispensable, rapid decomposition of the

---

[*] J. O. Mueller, Prof. C. Barner-Kowollik
Preparative Macromolecular Chemistry
Institut für Technische Chemie und Polymerchemie
Karlsruhe Institute of Technology (KIT)
Engesserstrasse 18, 76128 Karlsruhe (Germany)
E-mail: christopher.barner-kowollik@kit.edu

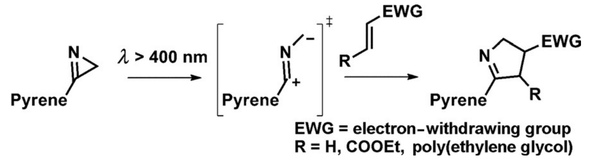
J. O. Mueller, Prof. C. Barner-Kowollik
Institut für Biologische Grenzflächen
Karlsruhe Institute of Technology (KIT)
Hermann-von-Helmholtz-Platz 1
76344 Eggenstein-Leopoldshafen (Germany)

Dr. F. G. Schmidt
Evonik Industries AG
Paul-Baumann-Strasse 1, 45764 Marl (Germany)

Dr. J. P. Blinco, Prof. C. Barner-Kowollik
Queensland University of Technology
School of Chemistry, Physics and Mechanical Engineering
2 George St, Brisbane, Queensland 4001 (Australia)
E-mail: j.blinco@qut.edu.au

[**] C.B.-K. acknowledges continued financial support from Evonik Industries as well as the excellent collaboration. In addition, funding from the Helmholtz association in the context of the STN and BIF programs as well as the German Research Council (DFG) (Orbitrap mass spectrometer) is acknowledged. J.B. acknowledges the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology. J.M. acknowledges financial support from the Karlsruhe House of Young Scientists (KHYS) funding a research stay in the laboratories of J.B.

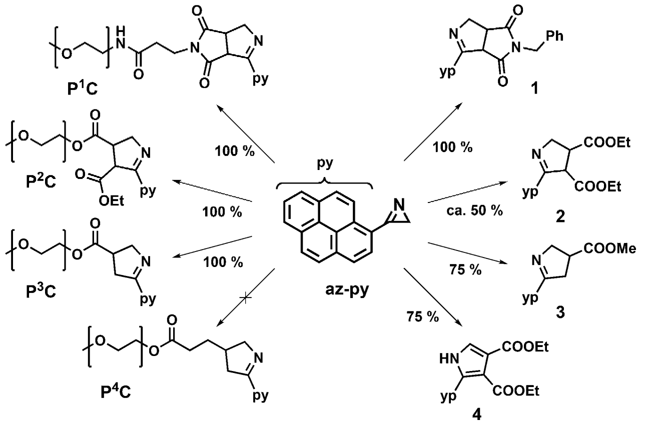
Supporting information for this article (experimental details, materials, instrumentation, and additional spectroscopic data) is available on the WWW under http://dx.doi.org/10.1002/anie.201504716.



Scheme 1. General reaction scheme for the catalyst-free azirine-based visible-light-induced cycloaddition reaction.

target compound in the presence of ambient light should be suppressed. Therefore, the current photoreactive entity was designed to absorb just sufficient light in the region of 400 nm (see Figure S2 in the Supporting Information for the UV/Vis spectrum) to enable efficient activation with low-energy visible-light sources while avoiding handling problems during synthesis or sample preparation. Moreover, the pyrene group is not only crucial for light absorption, but is incorporated into the cycloadducts carbon framework, thereby providing additional desirable features such as a built-in fluorescent marker or anchor for π–π stacking.[13]

To demonstrate the versatility of our visible-light-induced ligation reaction, the cycloaddition of **az-py** was utilized for organic synthesis, as well as the conjugation reaction of **az-py** with polymeric species (Scheme 2). To confirm the successful cycloaddition processes and provide evidence for the accessibility of diverse types of dipolarophiles, small-molecule cycloaddition reactions with the most commonly employed classes of functional groups were conducted. Fumarate, maleimide, and acrylate derivatives represent feasible vinyl moieties, and activated acetylenes enable the synthesis of pyrrole derivatives.



Scheme 2. Overview of the reactions performed with **az-py** (middle), which was irradiated with a visible-light LED setup ($\lambda = 410$–420 nm) in the presence of small molecules (right) or polymeric species (left).

The combined NMR and ESI-MS results for the generated cycloadducts unambiguously reveal successful formation of the desired products (Figure 1). Figure 1 a displays selected sections of their ^{1}H NMR spectra (see Figure S4–S8 for full spectra). The aromatic region (9.5–7.5 ppm) of the **az-py** spectrum contains two doublets assigned to the protons a and b, which are mostly affected by changes to the azirine group, implying a shift upon successful photoreaction. Signal a, for instance, is shifted up-field (**1**, **2**) or down-field (**3**), or it was found to overlap with the large number of aromatic resonances b^4 and c^4 (**4**). Proton b is subjected to similarly obvious changes: a down-field shift for **1** and **2**, and overlapping resonances with the c^3 and c^4 signals for **3** and **4**. Moreover, a new set of signals appears in the region of 5.0–3.5 ppm, which were labeled d^x and e^x. These correspond to protons adjacent to the newly generated five-membered heterocycle or substituents of the dipolarophile. The cyclic structure of the products, as well as the potential formation of stereoisomers, broadens the resonances in this region and they thus cannot be assigned specifically, however, the overall integration values correspond to the correct number of protons. Interestingly, the signals d^4 differ from the other d signals (**1**–**3**) since they appear in the aromatic region owing to a rearrangement occurring subsequent to the cycloaddition, which generates an aromatic pyrrole derivative.[6d] Figure 1 b displays the ESI-MS characterization of **az-py** and the corresponding cycloadducts. Clean spectra provide unambiguous evidence for the successful generation of the desired products. Furthermore, the experimentally obtained m/z values match the theoretically calculated exact mass values almost perfectly ($\Delta m/z < 0.03$, Table S1 in the Supporting Information). A decreased signal-to-noise ratio for the spectrum of **az-py** is caused by an absence of polar functionalities to support the ionization process. The combined results of NMR and ESI-MS analysis provide unambiguous evidence for successful visible-light-triggered reaction. In addition, UV/Vis analysis (Figure S2), fluorescence spectrometry data (Figure S3), and carbon NMR spectra (Figure S9–S11) provide further evidence for the purity of **1**, **2**, **3**, and **4**.

For monitoring the reaction progress, HPLC was employed because it is a facile yet highly sensitive technique. Moreover, UV absorbance and fluorescence can be detected simultaneously, thus enabling a detailed analysis of the photoreaction process. HPLC analysis for the reaction of **az-py** with benzyl-maleimide is depicted as an example (Figure 2), and very similar results were obtained for the synthesis of **2**, **3**, and **4** (Figures S15, S16). Figure 2 shows that the reaction proceeds to full conversion since the intensity of the starting material signal decreases with increasing reaction time until it vanishes completely. Furthermore, the visible-light-induced cycloaddition is highly efficient and no side products were detected either in fluorescence or in absorption mode (Figure S14). Moreover, complete conversion of the product is achieved after 30 min, thus demonstrating our light-induced process to be remarkably clean and highly efficient.

Post-polymerization modification of synthetic polymer strands is highly important for a multitude of advanced applications.[14] However, an as yet limited number of (light-induced) systems[15] fulfill the required criteria.[1b] Polymer ligation thus allows us to demonstrate the strength of our visible-light-induced cycloaddition approach. Poly(ethylene glycol) (PEG) moieties containing different dipolarophilic termini were subjected to reactions with **az-py**. PEG provides several beneficial properties: 1) Excellent ionization characteristics allow precise ESI-MS measurements, 2) PEG substrates can be purchased with versatile end groups, and

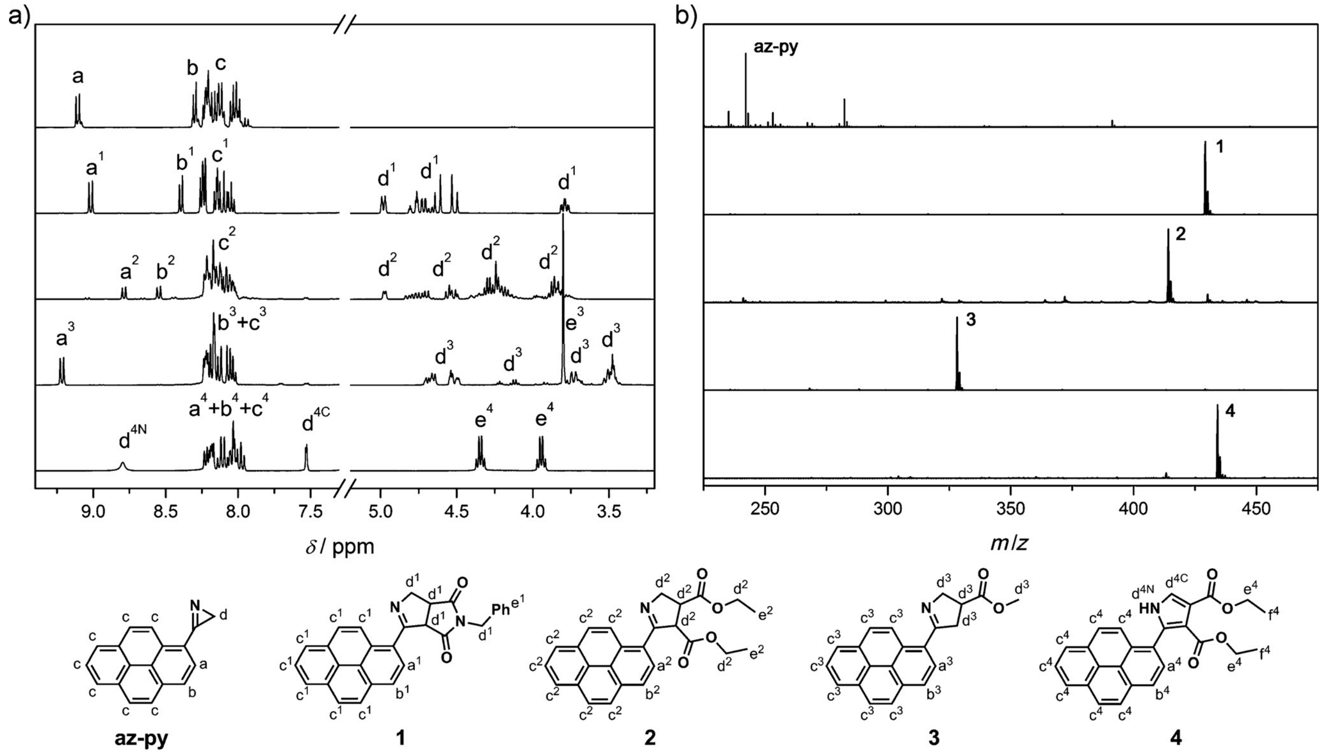


Figure 1. Comparison of ^{1}H NMR (a) and ESI-MS (b) spectra of isolated photoreaction products. From top to bottom, the spectra refer to compounds **az-py**, **1**, **2**, **3**, and **4**. The corresponding structures are depicted below.

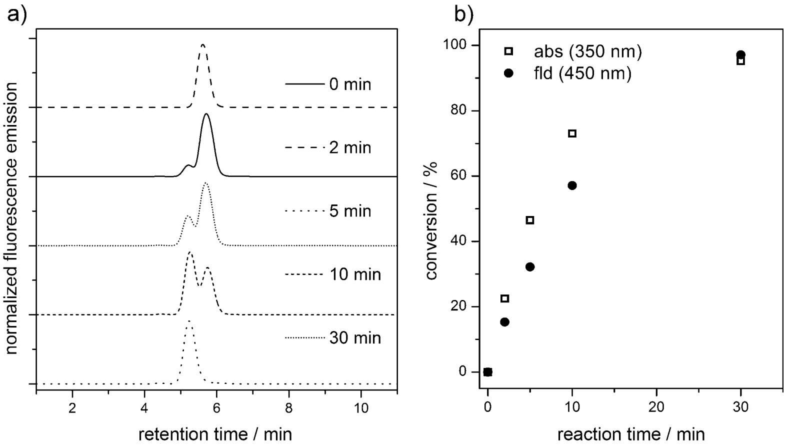


Figure 2. HPLC analysis for the reaction of benzylmaleimide and **az-py** in the visible-light-induced process. a) HPLC chromatograms with fluorescence detection at 450 nm ($\lambda_{ex}=350$ nm). b) Kinetics plot depicting the conversion determined by fluorescence and absorbance detection as a function of time.

3) specific end groups can be introduced via facile esterification of the commercially available hydroxy-terminated PEG. Four PEG compounds, two commercial and two synthesized samples, containing end groups with varying reactivity towards dipoles were tested and the light-triggered process was monitored via high resolution ESI-MS (Figure 3). Figure 3a,b shows the reactions between **az-py** and the polymers **P^1** and **P^2**. Two polymer repeating units in the single-charge region are displayed at three stages of the reaction: prior to irradiation, at close to 50% conversion, and upon complete conversion. For both polymers, a rapid photochemical reaction was observed to yield the desired cycloaddition product with exceptional purity. The signals corresponding to the starting polymers (labeled **P^1** and **P^2**) disappeared entirely after only 1 min. Simultaneously, the product signals (labeled **P^{1}C** and **P^{2}C**) emerge at similar intensity as the starting compound ones after 30 s, and after 1 min, remarkably clean spectra of the end group modified polymers were observed. A shift of the entire polymeric distributions in multiply charged regions is clearly discernible in the spectra presented in Figures S17 and S18. In addition, NMR and a detailed collision induced dissociation (CID)-ESI-MS characterization of **P^{2}C** confirm the nature of the cycloaddition product, where only the expected resonances were found in the ^{1}H NMR spectrum (Figure S11) and exclusively assignable dissociation products were observed in the CID-ESI-MS spectrum (Figure S21). In Figure 3c, the reaction of **az-py** with a commercially available PEG acrylate of a shorter chain length is displayed. The signals for the starting polymer **P^3** disappeared after 2 min and two product distributions—proton ionized (**P^{3}CH$^+$**) and sodium ionized species (**P^{3}CNa$^+$**)—emerge. A small amount of nonfunctional impurity (**P^{3X}**) remains through all of the spectra. The increased reaction time (2 min to full conversion) can be explained by a reduced reactivity of the acrylate functional group compared to maleimide or fumarate functions. How-

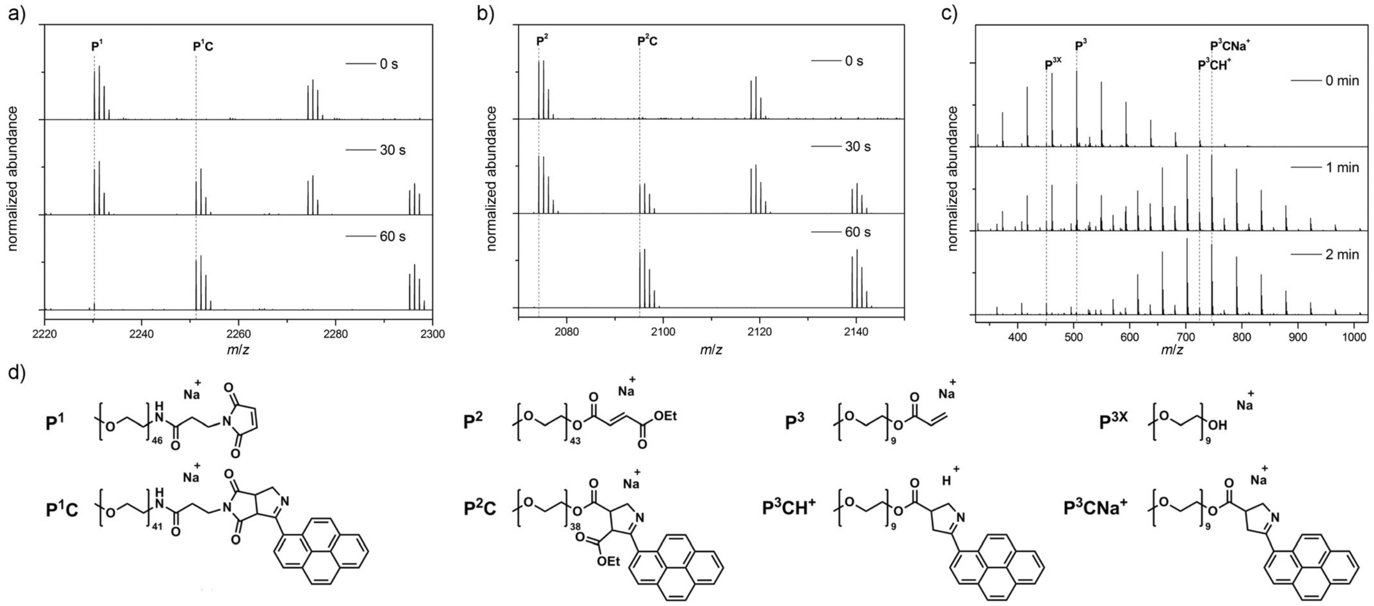


Figure 3. High-resolution ESI-MS spectra following the reaction of **az-py** with P^1 (a), P^2 (b), and P^3 (c). d) The structures associated with the respective signals.

ever, in comparison to the small-molecule study, the reaction times for the polymer ligation reactions are generally much shorter owing to higher dilution and smaller molar amounts of material (see experimental section in the Supporting Information for details). The structures and mass values corresponding to the signals displayed in Figure 3 a–c are depicted in Figure 3 d and Table S2. The three successful ligation reactions noted above demonstrate the exceptional properties of our method by linking a fluorescent dye to a polymer chain with extraordinary efficiency. Moreover, selectivity for electron-deficient dipolarophiles could be demonstrated by the reaction of **az-py** with $\mathbf{P^4}$, which contains a non-activated alkene as the chain terminus, for which no conversion could be observed even after 90 min of irradiation (Figure S19). Finally, control reactions were conducted in the dark and under standard laboratory illumination to demonstrate the necessity of a suitable light source (Figure S20).

In summary, we herein present the design of a photoreactive compound that can be activated for rapid and efficient cycloaddition reactions with visible light (> 390 nm). An azirine-based moiety that is activated by visible light was applied to organic synthesis, as well as polymer ligation, without the need for a catalyst. The reactions proceeded under ambient conditions and were not sensitive to oxygen or water. Photochemical organic synthesis was found to be efficient with representatives of the most common reactive groups (maleimide, fumarate, acrylate, and acetylene). Moreover, the advanced demands of polymer ligation reactions were satisfied with the current system, as demonstrated by the efficient linkage of a fluorescent dye (pyrene) to PEG chains with different termini. Selective, clean, and complete end-group modification of polymers could be achieved within irradiation times of 1 min under ambient conditions.

Keywords: azirine · click chemistry · photochemistry · polymer ligation · visible light

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10284–10288
Angew. Chem. **2015**, *127*, 10423–10427

---

[1] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; *Angew. Chem.* **2001**, *113*, 2056; b) C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp, *Angew. Chem. Int. Ed.* **2011**, *50*, 60; *Angew. Chem.* **2011**, *123*, 61.

[2] M. A. Tasdelen, Y. Yagci, *Angew. Chem. Int. Ed.* **2013**, *52*, 5930; *Angew. Chem.* **2013**, *125*, 6044.

[3] a) Z. Liu, T. Liu, Q. Lin, C. Bao, L. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 174; *Angew. Chem.* **2015**, *127*, 176; b) Z. Liu, Q. Lin, Y. Sun, T. Liu, C. Bao, F. Li, L. Zhu, *Adv. Mater.* **2014**, *26*, 3912; c) Z. Yu, T. Y. Ohulchanskyy, P. An, P. N. Prasad, Q. Lin, *J. Am. Chem. Soc.* **2013**, *135*, 16766; d) S. V. Orski, A. A. Poloukhtine, S. Arumugam, L. Mao, V. V. Popik, J. Locklin, *J. Am. Chem. Soc.* **2010**, *132*, 11024; e) T. Pauloehrl, G. Delaittre, M. Bruns, M. Meißler, H. G. Börner, M. Bastmeyer, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2012**, *51*, 9181; *Angew. Chem.* **2012**, *124*, 9316; f) K. K. Oehlenschlaeger, J. O. Mueller, N. B. Heine, M. Glassner, N. K. Guimard, G. Delaittre, F. G. Schmidt, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2013**, *52*, 762; *Angew. Chem.* **2013**, *125*, 791.

[4] T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527.

[5] a) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; *Angew. Chem.* **2012**, *124*, 6934; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.

[6] a) Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 7171; *Angew. Chem.* **2011**, *123*, 7309; b) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615; c) S. Maity, M. Zhu, R. S. Shinabery, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 222; *Angew. Chem.* **2012**, *124*, 226; d) J. Xuan, X.-D. Xia, T.-T. Zeng, Z.-J. Feng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 5653; *Angew. Chem.* **2014**, *126*, 5759.

[7] A. Padwa, *Acc. Chem. Res.* **1976**, *9*, 371.

[8] A. Padwa, J. Smolanoff, *J. Am. Chem. Soc.* **1971**, *93*, 548.

[9] E. Albrecht, J. Mattay, S. Steenken, *J. Am. Chem. Soc.* **1997**, *119*, 11605.

[10] A. Padwa, M. Dharan, J. Smolanoff, S. I. Wetmore, *J. Am. Chem. Soc.* **1973**, *95*, 1945.

[11] a) A. Padwa, M. Dharan, J. Smolanoff, S. I. Wetmore, *J. Am. Chem. Soc.* **1973**, *95*, 1954; b) A. Padwa, J. Smolanoff, S. I. Wetmore, *J. Org. Chem.* **1973**, *38*, 1333; c) A. Padwa, S. I. Wetmore, *J. Org. Chem.* **1974**, *39*, 1396; d) N. J. Turro, D. A. Hrovat, I. R. Gould, A. Padwa, W. Dent, R. J. Rosenthal, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 625; *Angew. Chem.* **1983**, *95*, 647.

[12] R. K. V. Lim, Q. Lin, *Chem. Commun.* **2010**, *46*, 7993.

[13] a) O. P. Lee, A. T. Yiu, P. M. Beaujuge, C. H. Woo, T. W. Holcombe, J. E. Millstone, J. D. Douglas, M. S. Chen, J. M. J. Fréchet, *Adv. Mater.* **2011**, *23*, 5359; b) S. Burattini, B. W. Greenland, D. H. Merino, W. Weng, J. Seppala, H. M. Colquhoun, W. Hayes, M. E. Mackay, I. W. Hamley, S. J. Rowan, *J. Am. Chem. Soc.* **2010**, *132*, 12051; c) Z. Xu, N. J. Singh, J. Lim, J. Pan, H. N. Kim, S. Park, K. S. Kim, J. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 15528.

[14] A. S. Goldmann, M. Glassner, A. J. Inglis, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2013**, *34*, 810.

[15] S. Chatani, C. J. Kloxin, C. N. Bowman, *Polym. Chem.* **2014**, *5*, 2187.

Received: May 27, 2015