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TAD Click Chemistry on Aliphatic Polycarbonates: A First Step Toward Tailor-Made Materials

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For the first time, the effectiveness of triazolinedione (TAD) click chemistry onto aliphatic polycarbonates (APC) is demonstrated. Statistic copolymers carrying click-reactive conjugated diene (in a ratio of 10%) are synthesized via organocatalyzed ring-opening polymerization. The highly efficient click reaction of TADs carrying simple butyl and phenyl functions are confirmed by ^{1}H-NMR and DSC. Network formation using a bivalent TAD is also performed and simply characterized by DSC. This post-polymerization functionalization of biocompatible and biodegradable APC pave the way to easy and versatile "on-demand" materials design.

Alongside polyesters, aliphatic polycarbonates (APC) are well-known for their ability to be biodegradable and biocompatible,[1,2] which makes them good candidates for biomedical uses.[3–7] During the past 10 years, their synthesis by ring-opening polymerization (ROP) of cyclic carbonate monomers (CC) using metal-free catalysts was fully investigated.[8–12] More specifically, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was shown to promote the ROP of CC by activation of an initiating alcohol in a pseudo-anionic polymerization mechanism, resulting in a high control over polymer molecular weight, dispersity, and end-group fidelity.[13–15] This amine-based catalyst was proven to be noncytotoxic[16] which is interesting for further bio-utilization of the material. Also, this "green" catalyst answers to the need to answer to environmental concerns.

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Compared to lactones, cyclic carbonate monomers are more easily functionalized. Their (co-)polymerization aims to design specific macromolecules able to, for example, overcome biological barriers.[17–20] Various functions can be directly attached on the CC monomer by means of a mastered synthetic route, starting from 2,2-bishydroxy(methyl) propionic acid (bis-MPA).[21] However, some functional groups are incompatible with the ROP process or limit its activity[13] and post-polymerization functionalization is therefore a more versatile and powerful approach. Among the existing post-polymerization processes, the concept of "click chemistry" has been widely explored since Sharpless, Kolb, and Finn introduced it in 2001.[22] This relatively recent chemistry concept is characterized by specific and versatile transformations, leading to a very efficient and reliable covalent coupling. APCs already proved their capability to withstand alkyne-azide, thiol-ene, or Diels-Alder reactions[23] but their use with 1,2,4-triazoline-3,5-diones (TAD) was not yet investigated. Since the work of Du Prez's team,[24] demonstrating that TAD reactions met the criteria of click chemistry, this metal-free "grafting onto" approach gained more and more interest in the fields of material chemistry.[25,26]

TAD compounds are known to be among the strongest -enophiles and -dienophiles in organic chemistry[27] and they have high reactivity toward conjugated dienes in a Diels-Alder-like reaction.[24,25] This reaction can be performed at room temperature, which is significantly advantageous when heat-sensitive polymers are concerned. Moreover, TADs show a strong absorption in the visible light spectrum exhibited by a deep red color which disappears upon reaction. The visual monitoring of the reaction, the lack of need for a catalyst or an initiator, and the absence of smelly products (as thiols), constitute the major advantages of the TAD click chemistry compared to others. This strategy has recently been applied in a wide range of applications, such as self-healing,[28] surface chemistry,[29] post-modification of unsaturated ADMET polymers,[30] and in areas where both temperature[31] and light[32] can be used as reaction trigger. Even if the synthesis toward TAD compounds is a multistep process, a recently developed one-pot synthetic route broadened the range of possible TAD compounds, making it more industrially interesting.[33] Besides, the phenyl-TAD compound is commercially available, confirming the interest of the scientific community for this chemistry.

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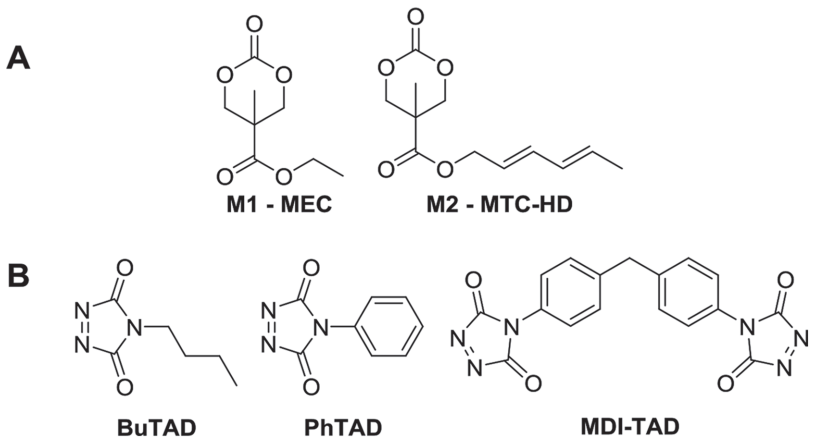

Figure 1. A) Chemical structures of the two monomers MEC (M1) and MTC-HD (M2). B) Chemical structures of the synthesized mono- and divalent TAD compounds.

This work demonstrates the application of TAD click chemistry for the post-polymerization functionalization of APC. For the first time, a CC monomer carrying a conjugated diene (5-methyl-5-hexadienoxycarbonyl-1,3-dioxane-2-one, MTC-HD) was synthesized and copolymerized with a nonfunctionalized monomer (5-methyl-5-ethyloxycarbonyl-1,3-dioxane-2-one, MEC) in a controlled organocatalyzed ROP. Subsequently, a study of the modification of these copolymers with 4-butyl-TAD (BuTAD) or 4-phenyl-TAD (PhTAD) was realized, focusing on the effect of these functional groups on thermal properties (glass transition (T_g) before and after modification). The versatility of the concept was highlighted with a bivalent TAD compound based on 4,4′-methylene bis(phenyl isocyanate) (MDI-TAD), leading to cross-linked polycarbonate materials.

The MEC monomer (M1, **Figure 1**A) was prepared based on the protocol suggested by Fukushima et al.[34] However, the highly toxic triphosgene was replaced by ethyl chloroformate and triethylamine was used for the ring closure reaction of the diol. A pure product was obtained (yield = 40%). The MTC-HD monomer (M2, Figure 1B) was synthesized for the first time via a strategy introduced by Hedrick and coworkers,[13,21] starting from 2,2-bis(hydroxymethyl)propionic acid (bis-MPA). The obtained monomers were carefully dried before use in ROP, since water traces can interfere in the ROP-process. The full synthetic protocols and characterization can be found in the Supporting Information.

The statistic copolymerization of M1 and M2 by ROP was initiated by benzyl alcohol (BnOH) in CH_2Cl_2 for a targeted DP of 100. A monomer solution was prepared with a feed ratio of M1/M2 = 90/10 to keep a low concentration of conjugated diene. The nonfunctionalized monomer units (M1) were acting as diluting agents, making reactive dienes more reachable by the TAD counterpart. The polymerization was catalyzed with DBU (ratio DBU:BnOH = 3:1) and was quenched with benzoic acid (BnCOOH, 5 mg / mg of DBU) after 3 h. At this point of the polymerization, a monomer conversion of 93% was calculated with a ratio MTCH-HD:MEC in accordance with the feed ratio (Figure S8, Supporting Information). A longer time of polymerization is not recommended since trans-acylation or trans-esterification could occur. Precipitation in cold methanol led to a polymer batch without any traces of monomer, quencher, and catalyst (Figure S10, Supporting Information). The batch purity is an important point since the click-reaction could be impaired by the presence of contaminants. The obtained TAD-reactive polymer (P1) was fully characterized by SEC (Figure S9 and Table S2, Supporting Information), ^{1}H-NMR (Figure S10 and Table S2, Supporting Information) and differential scanning calorimetry (DSC) (Figure 4).

Triazolinediones were typically prepared via oxidation of the corresponding bench-stable urazoles. Different synthesis routes to these urazoles have been reported and summarized in a recent review.[25] The typical urazole synthesis started from the isocyanate as an auxiliary compound,[24] as was used in this work for the synthesis of 4-phenyl-TAD, 4-butyl-TAD, and the bivalent compound MDI-TAD. All structures can be found in Figure 1B while experimental procedures and ^{1}H-NMR spectra can be found in Supporting Info.

The effectiveness of TAD click chemistry onto APCs was proved by three observations done after reaction: i) the disappearance of the deep red color; ii) the loss of the characteristic diene peaks on ^{1}H-NMR; iii) the evolution of the glass transition temperature (T_g). Concerning the cross-linking with the bivalent MDI-TAD, the qualitative observation of the gel formation, supported by the rise in the T_g, would confirm the feasibility. Full network characterizations (such as swelling) could be done in a devoted study of several network syntheses, evaluations, and applications.

TADs were weighed in a ratio of 1 molar equivalence to the diene present on the polymer backbone (determined by ^{1}H-NMR). This ratio complies with the requirement of a quantitative addition proper to click chemistry. The polymer and the TAD compounds were dissolved separately in CH_2Cl_2 and the TAD solution was added dropwise under stirring to ensure control over this fast reaction. The synthetic pathway is presented in **Figure 2**. The color disappearance was observed within seconds, confirming the ultrafast addition on a conjugated diene.[24] However, the solution was stirred for another 30 min to guarantee reaction completeness.

Before the functionalization, the ^{1}H-NMR intensity of the diene peaks (δ = 5.5–6.3 ppm) was equal to 10% of the ethyl side chains (δ = 4.2 ppm) (complete ^{1}H-NMR spectra on Figure S12, Supporting Information). A total disappearance (**Figure 3**) was an indication of a quantitative reaction. Simultaneously, the signals related to the new alkene bond formed upon click reaction appeared with the right integration (δ = 5.7–6.0 ppm). In other words, these results confirmed the successful click-reaction between alkyl-TADs and the diene containing APCs.

Thermal analysis of the crude and modified polymers, using DSC, depicted the effect of BuTAD and PhTAD functionalization. While the nonfunctionalized polymer P1 had a T_g of −31 °C, this value increased to −20 °C and −3 °C after functionalization with BuTAD (P1a) and PhTAD (P1b), respectively (**Figure 4**). In each case, the polymers were totally amorphous. The π–π stacking interaction of PhTAD groups induced macromolecular

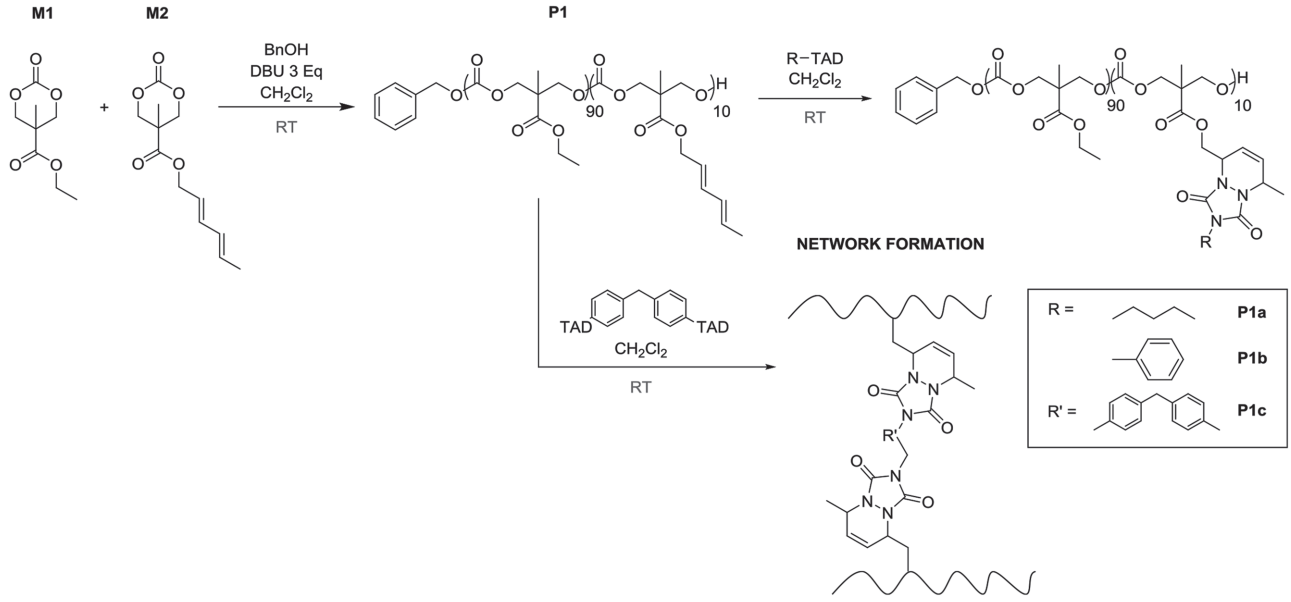

Figure 2. Synthetic pathway followed in this study including the post-polymerization functionalization of a clickable APC using TAD-chemistry. P1a and P1b are functionalized with BuTAD and PhTAD respectively. The network P1c was prepared using the bivalent MDI-TAD.

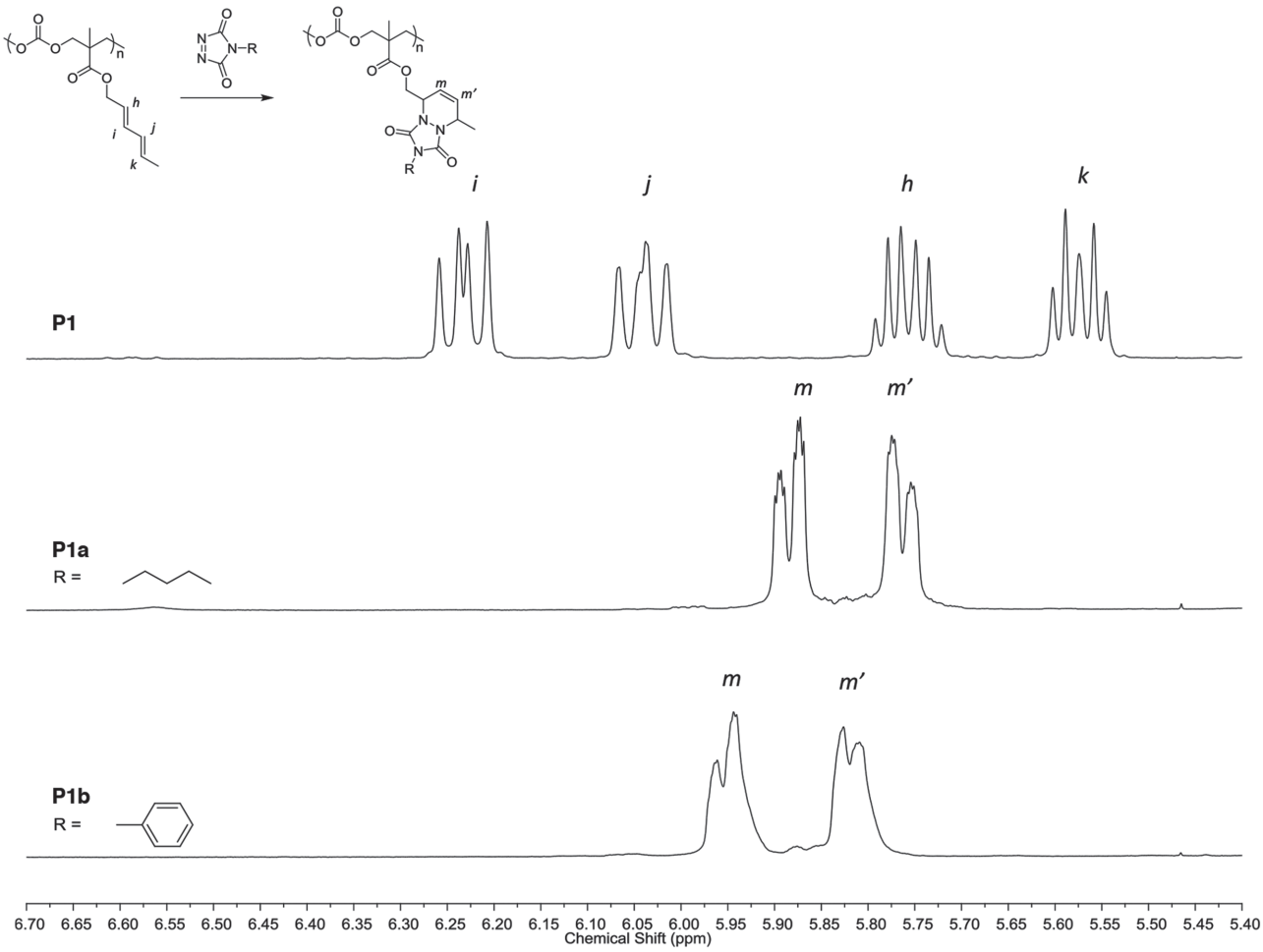

Figure 3. ^{1}H-NMR in $CDCl_3$ of BnO-P(MEC_{90}-co-MTC-HD_{10}) statistic copolymer functionalized with BuTAD (P1a) and PhTAD (P1b).

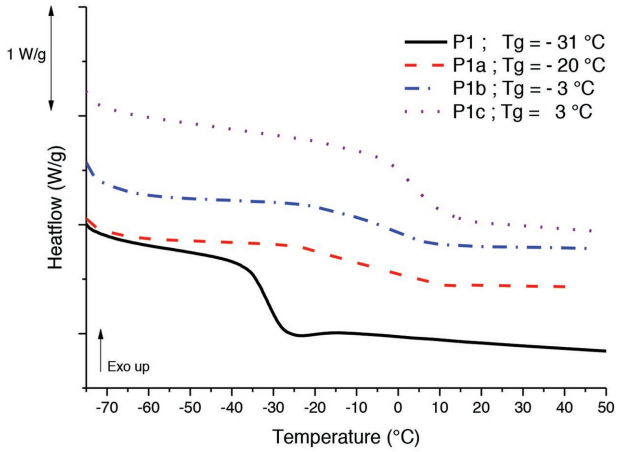

Figure 4. Differential scanning calorimetry thermograms of BnO-P(MEC_{90}-co-MTC-HD_{10}) before (P1, plain black line) and after functionalization with BuTAD (P1a dashed red line) and PhTAD (P1b dashed—point blue line). P1c (point purple line) is the network obtained with the cross-linker MDI-TAD.

interactions[30] that decreased the chain mobility and thus increased the T_g. This confirmed the effect of the functionalization onto the backbone, even for a ratio as low as 10%.

To broaden the scope of the post-polymerization functionalization of APCs by TAD click chemistry, cross-linking of the chains using the bivalent MDI-TAD was considered. Indeed, APCs are very interesting under their gel form for biomedical and environmental applications, such as controlled drug release[35–38] or heavy metal ions sequestration.[39] The polymer P1 was dissolved in a minimum of THF to reach a high concentration of active species. A solution of MDI-TAD in THF was added dropwise onto the polymer. The solution was not stirred to avoid breakage of the forming network. After the first drops, the color disappearance was noted in less than a second as well as gel formation (Figure S13, Supporting Information). A remaining red color was observed (in the gel), which was ascribed to a possible overestimation of the number of moles of the conjugated dienes and/or to the entrapment of unreacted MDI-TAD. The DSC analysis of the vacuum-dried network highlighted the typical rise in the T_g value from −31 °C to 3 °C, in accordance with a network formation.

To conclude, a new cyclic carbonate monomer bearing a conjugated diene pendant chain was presented and fully characterized. Its copolymerization by ROP with another cyclic carbonate monomer using a basic organic catalyst had been successfully realized. The ratio of the two monomers in the final material was confirmed by ^{1}H-NMR after purification of the unreacted compounds. The diene lateral functional groups reacted quantitatively with different TAD compounds within few seconds, leading to functionalized polymers with different thermal properties.

The successful preparation of a clickable diene monomer, the well-controlled copolymerization and the growing library of TAD compounds paved the way for easy, fast, and versatile post-polymerization functionalization of biocompatible APC. Specifically, TAD compounds bearing bio-relevant functions[40,41] could be clicked on demand for nano-vector design in aim to perform drug delivery.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

aliphatic polycarbonates, click chemistry, ring-opening polymerization, triazoline diones

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[1] K. J. Zhu, R. W. Hendren, K. Jensen, C. G. Pitt, *Macromolecules* **1991**, *24*, 1736.
[2] Z. Zhang, R. Kuijer, S. K. Bulstra, D. W. Grijpma, J. Feijen, *Biomaterials* **2006**, *27*, 1741.
[3] J. Feng, R. X. Zhuo, X. Z. Zhang, *Prog. Polym. Sci.* **2012**, *37*, 211.
[4] J. Xu, E. Feng, J. Song, *J. Appl. Polym. Sci.* **2014**, *131*, 1.
[5] K. Fukushima, *Biomater. Sci.* **2016**, *4*, 9.
[6] H. Ajiro, Y. Haramiishi, N. Chanthaset, M. Akashi, *Polym. J.* **2016**, *48*, 751.
[7] C. M. Agrawal, R. B. Ray, *J. Biomed. Mater. Res.* **2001**, *55*, 141.
[8] N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813.
[9] F. Suriano, O. Coulembier, J. L. Hedrick, P. Dubois, *Polym. Chem.* **2011**, *2*, 528.
[10] A. P. Dove, *ACS Macro Lett.* **2012**, *1*, 1409.
[11] S. Tempelaar, L. Mespouille, O. Coulembier, P. Dubois, A. P. Dove, *Chem. Soc. Rev.* **2013**, *42*, 1312.
[12] L. Mespouille, O. Coulembier, M. Kawalec, A. P. Dove, P. Dubois, *Prog. Polym. Sci.* **2014**, *39*, 1144.
[13] F. Nederberg, B. G. G. Lohmeijer, F. Leibfarth, R. C. Pratt, J. Choi, A. P. Dove, R. M. Waymouth, J. L. Hedrick, *Biomacromolecules* **2007**, *8*, 153.
[14] B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 8574.
[15] T. Endo, K. Kakimoto, B. Ochiai, D. Nagai, *Macromolecules* **2005**, *38*, 8177.
[16] A. Nachtergael, O. Coulembier, P. Dubois, M. Helvenstein, P. Duez, B. Blankert, L. Mespouille, *Biomacromolecules* **2015**, *16*, 507.
[17] A. Aied, U. Greiser, A. Pandit, W. Wang, *Drug Discov. Today* **2013**, *18*, 1090.
[18] H. Hillaireau, P. Couvreur, *Cell. Mol. Life Sci.* **2009**, *66*, 2873.
[19] E. Blanco, H. Shen, M. Ferrari, *Nat. Biotechnol.* **2015**, *33*, 941.
[20] J. Zhou, K. T. Shum, J. C. Burnett, J. J. Rossi, *Pharmaceuticals* **2013**, *6*, 85.

[21] R. C. Pratt, F. Nederberg, R. M. Waymouth, J. L. Hedrick, *Chem. Commun.* **2008**, *2*, 114.
[22] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chemie Int. Ed.* **2001**, *40*, 2004.
[23] Y. Dai, X. Zhang, F. Xia, *Macromol. Rapid Commun.* **2017**, *38*, 1700357.
[24] S. Billiet, K. De Bruycker, F. Driessen, H. Goossens, V. Van Speybroeck, J. M. Winne, F. E. Du Prez, *Nat. Chem.* **2014**, *6*, 815.
[25] K. De Bruycker, S. Billiet, H. A. Houck, S. Chattopadhyay, J. M. Winne, F. E. Du Prez, *Chem. Rev.* **2016**, *116*, 3919.
[26] P. Espeel, F. E. Du Prez, *Macromolecules* **2015**, *48*, 2.
[27] R. C. Cookson, S. S. H. Gilani, I. D. R. Stevens, *Tetrahedron Lett.* **1962**, *3*, 615.
[28] N. Van Herck, F. E. Du Prez, *Macromolecules* **2018**, *51*, 3405.
[29] K. De Bruycker, M. Delahaye, P. Cools, J. Winne, F. E. Du Prez, *Macromol. Rapid Commun.* **2017**, *38*, 1.
[30] L. Vlaminck, K. De Bruycker, O. Türünç, F. E. Du Prez, *Polym. Chem.* **2016**, *7*, 5655.
[31] H. A. Houck, K. De Bruycker, C. Barner-Kowollik, J. M. Winne, F. E. Du Prez, *Macromolecules* **2018**, *51*, 3156.
[32] H. A. Houck, F. E. Du Prez, C. Barner-Kowollik, *Nat. Commun.* **2017**, *8*, 1.
[33] L. Vlaminck, B. Van De Voorde, F. E. Du Prez, *Green Chem.* **2017**, *19*, 5659.
[34] K. Fukushima, R. C. Pratt, F. Nederberg, J. P. K. Tan, Y. Y. Yang, R. M. Waymouth, J. L. Hedrick, *Biomacromolecules* **2008**, *9*, 3051.
[35] C. Bartolini, L. Mespouille, I. Verbruggen, R. Willem, P. Dubois, *Soft Matter* **2011**, *7*, 9628.
[36] S. H. Kim, J. P. K. Tan, F. Nederberg, K. Fukushima, J. Colson, C. Yang, A. Nelson, Y. Y. Yang, J. L. Hedrick, *Biomaterials* **2010**, *31*, 8063.
[37] T. F. Al-Azemi, K. S. Bisht, *Polymer* **2002**, *43*, 2161.
[38] A. Pascual, J. P. K. Tan, A. Yuen, J. M. W. Chan, D. J. Coady, D. Mecerreyes, J. L. Hedrick, Y. Y. Yang, H. Sardon, *Biomacromolecules* **2015**, *16*, 1169.
[39] M. Kawalec, A. P. Dove, L. Mespouille, P. Dubois, *Polym. Chem.* **2013**, *4*, 1260.
[40] S. Vandewalle, R. De Coen, B. G. De Geest, F. E. Du Prez, *ACS Macro Lett.* **2017**, *6*, 1368.
[41] P. Wilke, T. Kunde, S. Chattopadhyay, N. ten Brummelhuis, F. E. Du Prez, H. G. Börner, *Chem. Commun.* **2017**, *53*, 593.