Exploring the Photochemical Reactivity of Multifunctional Photocaged Dienes in Continuous Flow

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ABSTRACT

Flow reactors become more and more automated by enabling on-line reaction monitoring and adjusting the process parameters. On-line monitoring of chemical processes is a valuable tool to steer processes, leading to precise engineering of macromolecular materials. Detailed information about specific product patterns, end-group functionality or material composition can be obtained by coupling a flow reactor to a mass spectrometer (e.g. ESI-MS). In this work, we study the deprotection of maleimides and its subsequent photoenol functionalization to synthesize complex macromolecules using a photo flow reactor coupled to an ESI-MS. Using a trapping agent, furan is efficiently removed from the maleimide Diels Alder adduct within just
minutes at 175°C and quantitatively converted into an unreactive species that does not interfere with further reactions of the maleimide. The photoenol reaction was likewise shown to be highly effective to proceed in microreactors, reaching quantitative conversion of trifunctional molecules in as little as 2 minutes.
INTRODUCTION

Continuous flow processes have been increasingly used over the last decade as alternative for conventional batch processes. The excellent heat exchange and control over the reaction parameters, high efficiencies and good reproducibility have gained considerable prominence in the field of organic synthesis. Combined with the easy scalability of the reactions from mg to kg scale, a shift towards advanced macromolecular design has been seen over the last years. \cite{1-8}

Thus, specialized reactor setups, multistep reactions in cascade or looped flow processes are used to explore the synthetic boundaries of continuous flow processes.\cite{9-12} As such, implementation of a plethora of chemical processes in flow has become available, ranging from precision polymer synthesis via reversible deactivation radical polymerization methods \cite{13-18} toward small molecule synthesis (e.g. via cycloadditions, isomerization, or (photo) catalysis).\cite{6, 19}

More recently, flow reactors are automated by enabling on-line reaction monitoring and adjusting the process parameters. On-line monitoring of chemical processes is a valuable tool to steer processes, leading to precise engineering of macromolecular materials.\cite{20} In this way, real-time data enabling rapid kinetic screening and related to that efficient reaction optimization becomes available. On-line monitoring allows for the continuous analysis of the reaction under any given set of reaction conditions. Nowadays, on-line spectroscopy methods such as infrared (IR) \cite{21, 22}, nuclear magnetic resonance (NMR)\cite{23} or UV-Vis \cite{24} are extensively employed for the monitoring and control of chemical processes in order to obtain accurate information of chain sizes. Size exclusion chromatography (SEC) on the other hand is used to determine molecular weight and molecular weight distributions as shown by the groups of Hadziioannou and Schubert.\cite{25-27} More detailed information about specific product patterns, end-group functionality or material composition is obtained by coupling a flow reactor to a mass spectrometer. Although on-line mass spectrometry monitoring is known for more than 30 years \cite{28} it was initially hampered by the limitations in the type of reactions, solvent and low concentrations to be employed.\cite{29} In order to overcome these drawbacks, an electrospray ionization mass spectrometer (ESI-MS) was coupled to a microflow reactor, showing the
versatility of this technique when studying the kinetics of reversible addition-fragmentation chain transfer (RAFT) polymerizations of \(n\)-butyl acrylate.\(^{30, 31}\)

A. 

![Diagram](image1)

**Scheme 1:** General reaction scheme for the photo-enol reaction via an \(\alpha\)-quinodimethane using continuous flow reactors (A) and an overview of the flow diagram (B).

B. 

More recently, *clicking* of polymer endgroups to afford more complex structures including dendrimers and block copolymers otherwise not easily accessible have emerged as an alternative to the reversible-deactivation radical polymerization (RDRP) techniques.\(^{32-35}\) In here, the advantages of click chemistry – high conversion, fast reaction kinetics, simple reaction conditions, chemo and regioselectivity – are combined with the advantages of photo-induced reactions – less side product formation and spatial / temporal resolution.\(^{36-38}\) Within this area, photo-induced Diels-Alder (DA) are very promising, as the reactive moiety – the \(\alpha\)-quinodimethane – neither leads to any side reactions nor to any reactive product.\(^{39, 40}\) In here, the diene moiety is excited by absorption of a photon, leading to a highly reactive triplet state called a \(\alpha\)-quinodimethane (Scheme 1). The diene adds immediately to a present dienophile in a [4+2] DA cycloaddition – thereby regenerating the aromatic structure – leading to a fast and
efficient pathway toward macromolecular structures.\textsuperscript{[39, 41, 42]} By designing a trifunctional core molecule with a dienophile functionality and a bifunctional ‘arm’ molecule with a dienophile and \(\alpha\)-methyl benzaldehyde functionality (Scheme 1), complex architectures can be synthesized in an elegant way using equimolar amounts in a \([4+2]\) cycloaddition approach.\textsuperscript{[43, 44] Using a flow reactor will not only increase the efficiency of the light reaction, but it also allows for rapid kinetic screening and thus reaction optimization (Scheme 2).\textsuperscript{[45, 46]}

\textbf{Scheme 2:} Schematic overview of the deprotection of core \(C_1\) to \(CD_1\).

In the current study, a protocol for the continuous synthesis of complex macromolecules via a photo-induced Diels Alder reaction is developed. A trifunctional maleimide core was chosen as a challenging test for the efficiency of the reaction, see Scheme 2. Maleimides are typically protected as Diels-Alder adducts with furan in polymerization contexts. Thus, at first deprotection of the core \(C_1\) is studied in detail, using a coupled electrospray ionization mass spectrometry (ESI-MS) micro reactor technology (MRT) setup, enabling on-line monitoring. The deprotection is screened for different temperatures, residence times and with respect to the addition of a trapping agent (TA) to capture the released furan. Typically, deprotection requires high temperatures for the retro-Diels Alder reaction to take place over several hours. In a flow reactor under optimized conditions it is the target to reduce this reaction time to mere minutes. After deprotection, macromolecular synthesis is tested via photoenol cycloadditions by the
addition of a monofunctional molecule, leading to an optimized procedure with respect to light intensity and residence time. As a last step a bifunctional molecule is used to demonstrate the versatility and strength of flow reactors, by giving access to an easy, fast and cost-effective method for synthesizing novel complex architectures.

EXPERIMENTAL

Materials and characterization methods, synthesis procedures and compound analysis are described in the supporting information (SI).

Microreactor set-up for de deprotection and photo-enol reaction

Microreactions are performed in the Labtrix® Start R2.2 system (Chemtrix BV, NL) fitted with a glass microreactor (3227, reactor volume 19.5 µL) containing an SOR-2 static micromixer. The system is maintained at 20 bar of back pressure by means of a preset low dead-volume (6 µL) back pressure regulator (Upchurch Scientific). Reactant solutions are introduced into the reactor through three 1 mL gastight syringes (SGE). The pumps are capable of delivering three solutions at flow rates between 0.1 and 40 µL·min⁻¹. The flow rates are controlled via two syringes pumps (Chemyx). The reactor is controlled by a temperature controller MTTC1410 (Melcor Thermal Solutions, temperature range -15 °C to 195 °C).

ESI-MS/Microreactor setup

The ESI-MS / Microreactor set-up was described in detail previously.[47] In short, reactions take place in a conventional microreactor chip. When the microreactor is operated under true synthesis conditions, a reaction mixture is obtained at the reactor outlet that is unsuitable for MS analysis due to a mismatch in sample concentration, solvent, absence of doping agents and flow rate. These issues can, however, be conveniently overcome by a strong dilution of the reactor flow mixture with suitable doped ESI solvent mixtures followed by a flow T-splitter (I) to meet the requirements of the ESI-MS nozzle. Dilution also serves thereby as an effective solvent change next to the decrease in sample concentration down to the micromolar range. One of the
many advantages of such a setup is the high flexibility in terms of concentrations and reaction conditions that can be investigated. A wide concentration window in the microreactor can be accessed; higher flow rates of increased sample concentration can be dynamically compensated by adjusting the dilution factor.

RESULTS AND DISCUSSION

The [4+2] DA cycloaddition consists out of two steps (i) deprotection of maleimide and (ii) coupling of an aldehyde with the maleimide via the so called photoenol reaction. Herein, a trifunctional core was chosen as maleimide (O,O',O"-(benzene-1,3,5-triyltris(methylene)) tris(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) trisuccinate (C₁)) and o-methyl benzaldehyde (A₁) was selected as monofunctional aldehyde moiety. Due to the trifunctional core moiety dendrimer-like structures could thus be obtained (Figure 1).
Figure 1: Chemical structures employed in the current study. (top) core molecule C₁, (bottom) mono A₁-and bifunctional A₂ arm.

On-line monitoring of the deprotection of C₁

Deprotection of the trifunctional core with triple dienophile functionality C₁ – O,O',O"-(benzene-1,3,5-triyltri(methylene)) tris(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) trisuccinate (Figure 1) – was studied on-line using a coupled ESI-MS/MRT set-up. A Labtrix® reactor set-up provided with a 19.5 µL chip reactor enabled optimization of the reactive enone moiety by screening the reaction temperature between 120 - 195 °C and a residence time of 1 -
40 min, when using a total concentration of \([M_i] = 91.4 \text{ mmol·L}^{-1}\) in toluene. The glass syringes were connected to the flow setup and the flow rate was adjusted according to the residence time. Although reactor volumes are small (19.5 \(\mu\text{L}\)), diffusion of reactants at different temperatures and flow rates is negligible in this case.\cite{30} Interestingly, the deprotection of the trifunctional core was monitored in time. Four reaction products were identified in the ESI-MS screening, suggesting either a fully protected core \((m/z = 1064.2889)\), single deprotection of the core \((m/z = 996.2829)\), 2x deprotection of the core \((m/z = 928.2379)\) or a fully deprotected core \((m/z = 860.2124)\), Figure 2 and Table 1. Over time, deprotection progresses and ESI-MS peak intensities were monitored as a function of residence time, leading to an optimal microreactor residence time and temperature for the deprotection of the trifunctional core. The reaction mixture was injected in the ESI-MS nozzle continuously and spectra were measured every 1.33 seconds during the time sweep experiment from 1 to 40 min residence time, allowing to obtain 1.800 data points for each temperature screening. Since ESI-MS is only semi-quantitative – due to the difference in ionization biases of the molecules – no direct correlation can be made between the height of the peaks and the total reactions yield. In here, conclusions were based on a comparison between intensities of similar peaks between different spectra in time during online monitoring of microreactor time sweeps and thus reaction conditions studied.
Figure 2: Ion abundance as a function of residence time in the deprotection of compound C₁ into compound CD₁. The reaction was performed at 120 °C and screened between 1 – 40 minutes of residence time. Conversions were determined as relative fractions using the ESI-MS/MRT on-line setup.

Table 1: ESI-MS analysis results of the stepwise deprotection of the trisuccinate core C₁, based on the ESI-MS results displayed in Figure 2.

| Structure description       | m/z ESI-MS | m/z Theory |
|-----------------------------|------------|------------|
| Fully protected core C₁ (Na⁺) | 1064.2889  | 1064.2629  |
| Deprotection 1x (Na⁺)       | 996.2829   | 996.2430   |
| Deprotection 2x (Na⁺)       | 928.2379   | 928.2180   |
| Fully deprotected core CD₁ (Na⁺) | 860.2124  | 860.1930   |
| Degradation [C₆H₆NO₃] (Na⁺) | 642.2218   | -          |

Although deprotection of the core took place at 120 °C, a maximum conversion of only 42 % was reached after 20 min (Figure 2). Increasing the time frame up to 40 min did not lead to a higher conversion as the product mixtures obviously reach an equilibrium state. An increase in reaction temperature up to 160 °C increased the conversion up to 80 % in just 10 min of residence time, however still no full conversion was reached. Even increasing the reaction temperature to 195 °C did not lead to full conversion. A maximum conversion of ~ 90 % was reached within just minutes, but then again levelled off (Figure S9). Furthermore, partial degradation of the core took place at these high temperatures due to breakage of the ester bonds [C₆H₆NO₃] at elevated
temperatures. This was confirmed by the appearance of an additional peak at \( m/z = 642.2218 \) in the ESI-MS spectra (Figure 2).

The reason for the equilibrium state is that in a flow reactor furan that is freed from the protected maleimide remains in the reaction mixtures, whereas in batch protocols it may be removed by evaporation. Thus, the equilibrium observed is that between the Diels-Alder and retro-Diels-Alder reaction between the maleimide and furan. Increasing the reaction temperature shifts the equilibrium towards the (retroDA) product side, yet never reaches full conversion as shown above.\(^{48, 49}\) Thus, in order to find conditions that allow for full deprotection without risking high-temperature degradation of molecules, a different strategy needed to be found. Furan cannot be removed efficiently from the flow channel during the reaction, yet it can be converted by use of a trapping agent. A suitable TA is a dienophile forming a more stable DA adduct than maleimide, and hence will not undergo a retroDA in the temperature range as used in here. A variety of TAs are available ranging from thietene 1,1-dioxide to morpholine or tetracyanoethylene (TCE).\(^{50, 51}\) Herein, TCE was selected as trapping agent. Due to TCE being insoluble in toluene, ethyl acetate was used as solvent while keeping all other parameter identical. Temperatures in the range of 120 - 195 °C were screened via time sweeps from 1 to 10 minutes (Figure S10) in the online-microreactor setup. The results immediately indicated the profound effect of TCE on the maximum obtainable conversion at each temperature. Reaction temperatures of 160 °C or higher were sufficient to conveniently reach full conversion (> 98 %) within 10 minutes of residence time. Even better results were obtained when the temperature was increased to 175 °C with reactions proceeding in less than 5 minutes to full conversion without formation of any significant byproduct (Figure 3). Of course, the furan DA adduct with TCE remains in the reaction solution, yet this species is unreactive and will not disturb further (photo)reactions. Deprotection in batch typically takes place at 110 °C, leading to full conversions in 15 h when using a TA. Using our flow method this time is thus reduced by a factor of 180, while providing scalability of the reaction.
On-line monitoring of the photo-induced Diels Alder reaction

Next, the photoenol cycloaddition using a trifunctional core with triple dienophile functionality \( \text{C}_1 \) and a mono functional arm with photo-enol functionality – \( o \)-methyl benzaldehyde \( \text{A}_1 \) (Figure 1) – was performed in flow using a compact fluorescent lamp (\( \lambda_{\text{max}} = 365 \) nm, Scheme 2). The conjugation reaction led to a dendrimer-like molecule (\( \text{D}_1 \)) and again, the kinetics of the reaction were followed by on-line using a similar ESI-MR/MRT set-up as described for the deprotection of core \( \text{C}_1 \). The deprotected core \( \text{CD}_1 \) and arm \( \text{A}_1 \) were separately dissolved in acetonitrile (ACN) – using a total concentration of \([M] = 29.1 \) mmol·L\(^{-1}\) and injected into the flow reactor at room temperature. A slight excess of the arm molecules was used to ensure full conversion (1.1 equiv. per reactive dienophile). Kinetic screening of the reaction with respect to UV light intensities (8.2 mW/cm\(^2\) to 36 mW/cm\(^2\)) as well as residence times (1 – 5 min) was enabled, together with the on-line monitoring of the conjugation reaction.

![Figure 3: ESI-MS spectrum of core \( \text{CD}_1 \) obtained after deprotection of the core at 175 °C after 5 minutes of residence time in the micro flow reactor using TCE as TA.](image-url)
Figure 4: (A) core molecule \( D_1 \). (B) Zoom into the ESI-MS spectra of the synthesis of \( D_1 \) using a UV light intensity (\( \lambda_{\text{max}} = 365 \text{ nm} \)) of 36 mW/cm\(^2\) and a microreactor residence time of 2 minutes.

Table 2: ESI-MS analysis results of the stepwise attachment of arm molecule \( A_1 \) to core molecule \( CD_1 \), based on the ESI-MS results displayed in Figure 4.

| Structure description       | ESI-MS       | Theory      |
|----------------------------|--------------|-------------|
| Cluster of 2 arms          | 591.1969     | 591.1196    |
| Core + 1 arm               | 1144.3171    | 1144.3729   |
| Core + 2 arms              | 1428.4467    | 1428.4028   |
| Core + 3 arms (\( D_1 \))  | 1712.5370    | 1712.5077   |

As expected, the conjugation reaction proceeds in a stepwise fashion, in which first one arm and subsequently the second and third arm are attached. Therefore, the ESI-MS results clearly demonstrate the presence of both starting components (\( m/z = 307.0935 \) and \( m/z = 860.1998 \) for the arm and core molecule respectively) as well as 3 product peaks (\( m/z = 1144.3189 \), \( m/z = 1496.4494 \) and \( m/z = 1712.5401 \) with 1, 2 or 3 arms attached to the core respectively) in the ESI-MS spectra Figure 4 and Table 2). In addition, a 6th peak was observed at \( m/z = 591.9840 \), which could be attributed to a cluster of 2 arm molecules.

Screening of the photoenol cycloaddition was performed by varying the residence time and the UV light intensity up to 5 min or 36 mW·cm\(^{-2}\) respectively. It was evident that, according to ESI-MS, both peaks of the starting components were fully consumed after just 2 minutes of
residence time (Figure S11 & S12) using an intensity of 18 mW·cm². However, the results also showed the presence of some amounts of mono- and di-functionalized core molecules. In order to confirm that the presence of these peaks was due to the difference in ionization of biases of the molecules and not due to a lowered conversion, (D₁ molecule), SEC measurements were performed to confirm the success of the photoenol reaction, see Figure S13. Elugrams showed a shift towards lower elution volumes and the product peak is mostly monomodal, underpinning that only minute amounts of unreacted arms are present in the product. The peaks at higher elution volumes in the elugrams are due to the small excess of the arm molecules (1.1 equiv. per reactive dienophile). Thus, by using flow chemistry, easy access to the synthesis of complex architectures thus becomes available using photoenol cycloadditions. Within 2 min of residence time and a UV intensity of 18.5 mW/cm² almost full conversion was obtained, without the need for intermediate purification.

A logical extension of this success is to target further generation dendrimer structures by using bifunctional arm molecules – such as (bis(2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl) O,O'-(2-((3-((4-((2-formyl-3-methylphenoxy)methyl)benzoyl)oxy)propoxy)carbonyl)-2-methylpropane-1,3-diyl) disuccinate A₂. This proved, however, to be unsuccessful even after extended reaction optimization. The limiting factor in these reactions is by far not the deprotection or the efficiency of the photoenol reaction, but the limited solubility of the D₂G₁ species in common (non)-organic solvents.

**CONCLUSIONS**

The results presented herein demonstrate how deprotection of maleimides as well as subsequent photoenol functionalization of complex molecules is feasible, allowing for rapid formation of products on a lower minute time scale. Using a trapping agent, furan is efficiently removed from the maleimide DA adduct and quantitatively converted into an unreactive species that does not interfere with further reactions of the maleimide. This procedure is universal for maleimide deprotections and may be useful for a series of click-like modifications involving maleimide moieties in precision macromolecular design. The photoenol reaction was likewise shown to be
highly effective to proceed in microreactors, reaching quantitative conversion of trifunctional molecules in as little as 2 minutes. Further exploration of the reaction will require though additional design of molecules to increase solubility of the photoenol products as this was identified as the limiting factor in order to use the above reaction in dendrimer synthesis.

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ABBREVIATIONS

$A_1 = o$-methyl benzaldehyde; $A_2 =$ bis((1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)ethyl)O,O'-(2-((3-((4-((2-formyl-3-methylphenoxy)methyl)-benzoyl)oxy)propoxy)carbonyl)-2-methylpropane-1,3-diyl) disuccinate; API = active pharmaceutical ingredients; °C = degrees Celsius; $C_1 =$ O,O',O''-(benzene-1,3,5-triyltris(methylene))tris(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)trisuccinate; $CD_1 =$ O,O',O''-(benzene-1,3,5-triyltris(methylene))tris(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)trisuccinate; $CHCl_2$ / DCM = dichloromethane; CuSO$_4 \cdot 5$ H$_2$O = copper sulfate pentahydrate; $D_1$ = photoenol product of core $CD_1$ and arm $A_1$; $D_2$ = photoenol product of core $CD_1$ and arm $A_2$; DA = Diels-Alder; DMF = dimethylformamide; DMAP = 4-$N,N$-dimethylaminopyridine; EDC*HCl = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; ESI-MS = electrospray ionization mass spectrometer; IR = infrared; K$_2$CO$_3$ = potassium carbonate; $\lambda_{max}$ = wavelength at maximum absorbance; MgSO$_4$ = magnesium sulfate; MRT = micro reactor technology; min. = minutes; $[M_t]$ = total molar concentration; NaHCO$_3$ = sodium bicarbonate; Na$_2$SO$_4$ = sodium sulfate; NH$_4$Cl = ammonium chloride; AlCl$_3$ = aluminum chloride; NMR = nuclear magnetic resonance; RAFT = reversible addition fragmentation chain transfer; RDRP = reversible-deactivation radical
polymerizations; SEC = size exclusion chromatography; TA = trapping agent; TCE = tetracyanoethylene; THF = tetrahydrofuran; TLC = Thin layer chromatography

REFERENCES

1. C. Tonhauser, A. Natalello, H. Löwe, H. Frey. *Macromolecules* 2012, **45**, 9551-9570.
2. D. Wilms, J. Klos, H. Frey. *Macromol Chem Phys* 2008, **209**, 343-356.
3. K. Jahnisch, V. Hessel, H. Lowe, M. Baerns. *Angew Chem Int Ed Engl* 2004, **43**, 406-46.
4. T. Junkers. *Macromol Chem Phys* 2017, **218**.
5. H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel. *Chem Soc Rev* 2016, **45**, 83-117.
6. D. Cambie, C. Botteccia, N. J. Straathof, V. Hessel, T. Noel. *Chem Rev* 2016, **116**, 10276-341.
7. M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger. *Chem Soc Rev* 2016, **45**, 83-117.
8. H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel. *Chem Soc Rev* 2016, **45**, 83-117.
9. D. Wilms, J. Klos, H. Frey. *Macromol Chem Phys* 2008, **209**, 343-356.
10. K. Jahnisch, V. Hessel, H. Lowe, M. Baerns. *Angew Chem Int Ed Engl* 2004, **43**, 406-46.
11. T. Junkers. *Macromol Chem Phys* 2017, **218**.
12. H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel. *Chem Soc Rev* 2016, **45**, 83-117.
13. D. Cambie, C. Botteccia, N. J. Straathof, V. Hessel, T. Noel. *Chem Rev* 2016, **116**, 10276-341.
14. M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger. *Chem Soc Rev* 2016, **45**, 83-117.
15. H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel. *Chem Soc Rev* 2016, **45**, 83-117.
16. D. Cambie, C. Botteccia, N. J. Straathof, V. Hessel, T. Noel. *Chem Rev* 2016, **116**, 10276-341.
17. M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger. *Chem Soc Rev* 2016, **45**, 83-117.
18. H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel. *Chem Soc Rev* 2016, **45**, 83-117.
19. D. Cambie, C. Botteccia, N. J. Straathof, V. Hessel, T. Noel. *Chem Rev* 2016, **116**, 10276-341.
38. C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp. *Angew Chem Int Ed Engl* 2011, 50, 60-2.
39. T. Gruendling, K. K. Oehlenschlaeger, E. Frick, M. Glassner, C. Schmid, C. Barner-Kowollik. *Macromol Rapid Commun* 2011, 32, 807-12.
40. H. Frisch, J. P. Menzel, F. R. Bloesser, D. E. Marschner, K. Mundusinger, C. Barner-Kowollik. *J Am Chem Soc* 2018, 140, 9551-9557.
41. S. Arumugam, S. V. Orski, J. Locklin, V. V. Popik. *J Am Chem Soc* 2012, 134, 179-82.
42. P. Wessig, G. Müller, A. Kühn, R. Herre, H. Blumenthal, S. Troelenberg. *Synthesis* 2005, 1445-1454.
43. K. K. Oehlenschlaeger, J. O. Mueller, N. B. Heine, M. Glassner, N. K. Guimard, G. Delattre, F. G. Schmidt, C. Barner-Kowollik. *Angew Chem Int Ed Engl* 2013, 52, 762-6.
44. T. Junkers, B. Wenn. *React Chem Eng* 2016, 1, 60-64.
45. M. Kaupp, T. Tischer, A. F. Hirschbiel, A. P. Vogt, U. Geckle, V. Trouillet, T. Hofe, M. H. Stenzel, C. Barner-Kowollik. *Macromolecules* 2013, 46, 6858-6872.
46. J. J. Haven, J. Vandenbergh, T. Junkers. *Chem Commun* 2015, 51, 4611-4.
47. T. M. Lacerda, A. J. F. Carvalho, A. Gandini. *RSC Adv* 2016, 6, 45696-45700.
48. K. Alder, H. F. Rickert. *Justus Liebigs Ann. Chem.* 1936, 524, 180-189.
49. D. M. X. Donnelly, M. J. Meegan, Furans and their Benzo Derivatives (iii) Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*, 1984, Vol. 4, pp 657-712.
50. G. Mloston, H. Heimgartner. *Beilstein J Org Chem* 2017, 13, 2235-2251.
Via a coupled photo flow – ESI-MS setup, the deprotection of maleimides and its subsequent photoenol functionalization is studied to synthesize complex macromolecules. The reactions are shown to be highly effective reaching quantitative conversion of trifunctional molecules in just minutes.