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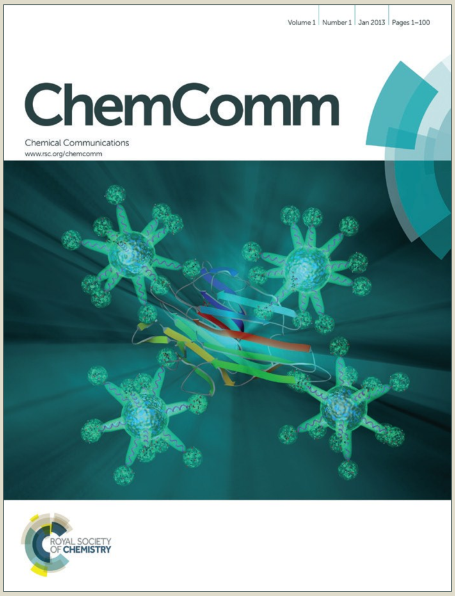

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DOI: 10.1039/C6CC03848D

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Star Polymer Synthesis via *λ*-Orthogonal Photochemistry

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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We introduce a light induced sequence enabling *λ*-orthogonal star polymer formation via an arms-first approach, based on an α,ω-functional polymer carrying tetrazole and *o*-methyl benzaldehyde moieties, which upon irradiation can readily undergo cycloaddition with a trifunctinal maleimide core. Depending on the wavelength, the telechelic strand can be attached to the core at either photo-reactive end.

Star shaped polymers find widespread applications in various scientific and industrial fields.[1] The physical and mechanical properties of the majority of polymers are strongly influenced by the degree of branching of the polymer backbone, thus the properties of star and branched polymers can differ from those of their linear analogues. For example, hyperbranched macromolecules show viscoelastic properties[2] and are used in polymer blends[3] and coatings.[4] In addition, end group modified star polymers have been selectively crosslinked to generate networks via irradiation in discrete wavelength regimes.[5] Well defined star polymers have previously been synthesised using controlled polymerisation techniques such as atom transfer radical polymerisation (ATRP)[6], reversible addition-fragmentation chain transfer (RAFT) polymerisation[7] and nitroxide mediated polymerisation (NMP)[8] directly via multi-arm initiators, yet also in combination with modular ligation strategies.[9] An extension of this concept has been introduced which exploits the advantages of photo-driven click chemistry – high yields, equimolarity, fast reaction kinetics, simple product isolation[10], eco-friendly reactions[11] and uphill photosensitization[12] – yet additionally allows for the independent reaction of multiple photo-click ligations in one pot based solely on the employed activation wavelength. We have termed this process *λ*-orthogonal chemistry. The first *λ*-orthogonal system featured a tetrazole and photoenolisable *o*-methyl benzaldehyde as the photoactive moieties that underwent cycloadditions with electron poor enes such as maleimides. Irradiation in the wavelength range between 260 and 320 nm triggerd transformation of the tetrazole moiety into a nitrile imine reactive intermediate[13] that subsequently undergoes a [3+2] cycloaddition reaction with an ene yielding a 4,5-dihydro-pyrazole.[14] The benzaldehyde moiety is activated in the complimentary wavelength range of 320-360 nm in which a highly reactive diene (*o*-quinodimethane) is formed that undergoes a [4+2]-cycloaddition Diels-Alder reaction.[15] The above system allows for an orthogonal reaction sequence in which benzaldehyde terminated polymers were selectively activated in the presence of tetrazole capped polymers and an equimolar amount of maleimides.[16]

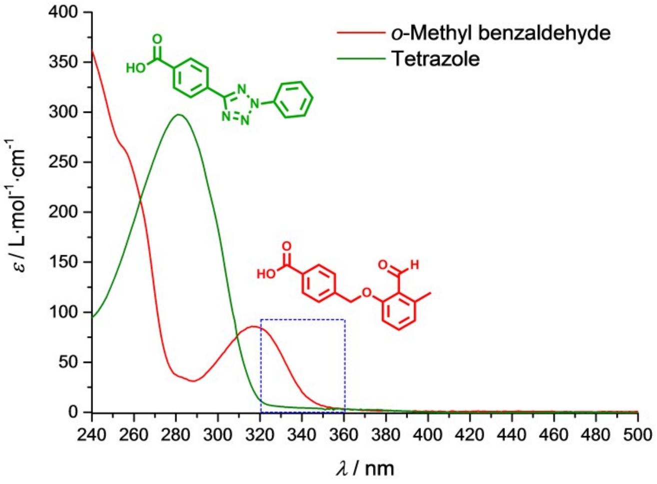

Figure 1: UV/vis absorption spectra of the o-methyl benzaldehyde and a tetrazole moiety. The absorption of both photoactive compounds shows a negligible overlap area between 320-360 nm leading to a selective activation of the benzaldehyde in the presence of tetrazole in the indicated wavelength regime (blue box).

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† Electronic Supplementary Information (ESI) available: Comprehensive experimental and analytical information. See DOI: 10.1039/x0xx00000x

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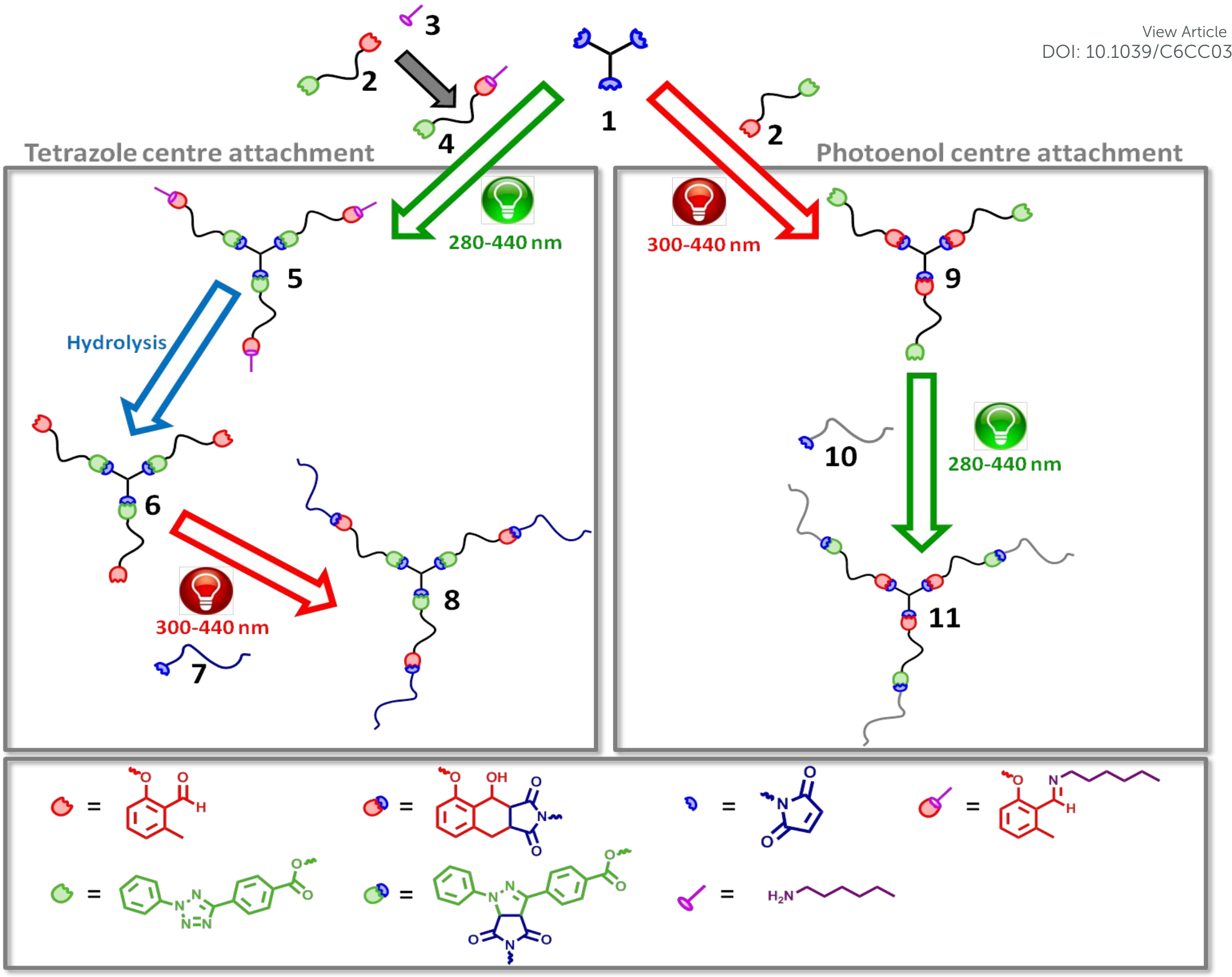

Scheme 1: Light induced orthogonal star polymer synthesis by the selective addition of an α,ω-functional molecule **2** carrying a benzaldehyde (red) and a tetrazole (green) functionality to the trifunctional maleimide centre **1**. The irradiation of **1** (1 eq.) and the imine protected telechelic **4** (3 eq.) at λ = 280-440 nm leads to the selective tetrazole attachment to **1**. The resulting star shaped structure **5** is terminated with an aryl imine. Subsequent imine hydrolysis results in the re-activation of the aldehyde end groups **6**. The star shaped structure containing benzaldehyde end groups **6** (1 eq.) and PEG-maleimide **7** (3 eq.) are irradiated at λ = 300-440 nm yielding the star polymer **8** (left part). The reaction strategy – selective benzaldehyde activation before tetrazole activation – was performed by the photochemical ligation of **2** towards **1** at λ = 300-440 nm according to the photoenol centre attached precursor **9**. The subsequent irradiation of **9** with pL-maleimide **10** at λ = 280-440 nm leads to the star polymer **11** (right).

However, the reverse reaction path – in which the tetrazole polymer is activated first – is not possible within this reaction sequence due to overlapping absorbances in the UV range below 320 nm. A fully λ-orthogonal ligation system requires that the two reaction paths be activated independently of one another using mutually exclusive wavelengths in a one pot reaction system.

The present contribution closes this critical gap, allowing tetrazole activation prior to the benzaldehyde by the reversible deactivation of the aldehyde species with hexylamine yielding an imine prior the irradiation process. As the formed imine is inert to any light induced reactions, the tetrazole is able to react without competition in the range between 260-320 nm. After the complete conversion of the tetrazole functionality in the one pot system, the deprotection of the imine via a fast hydrolysis step freeing the photoactive aldehyde is performed allowing subsequent reaction when irradiated at λ = 320-360 nm.

The combination of the λ-orthogonal chemistry concept including the original wavelength dependent reaction sequence with the novel reaction path constitute a one pot system allowing the synthesis of two different star polymers from identical starting materials in an orthogonal fashion (Scheme 1).

The irradiation of **1** (1 eq.) and the α,ω-functional polymer **2** (3 eq.) at λ = 310-370 nm leads to the selective attachment via the benzaldehyde moiety of the maleimide core **1** yielding the star shaped structure **9**. Maleimide terminated polylactide **10** (3 eq.) and **9** (1 eq.) are subsequently irradiated at λ = 270-310 nm leading to the 3 arm star shaped polymer **11** (right part). This was then followed by the tetrazole activation – the complimentary photoreaction with the λ-orthogonal system – affording a 3 arm star polymer with benzaldehyde at the core and polylactide terminated chains. A collation of the star shaped polymers is depicted in Scheme 2.

The choice of an appropriate light source is key to achieve a selective activation in the aforementioned absorption regions. To demonstrate, tris(2-maleimidoethyl)amine **1** (1 eq.) and the α,ω-functional polymer carrying a benzaldehyde and a tetrazole end group functionality

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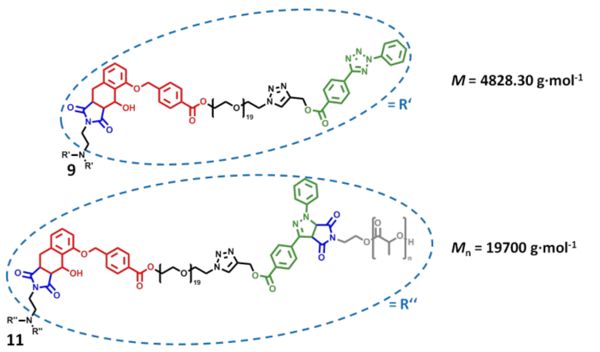


Scheme 2: Star polymer structures **9** and **11**, obtained by the initial benzaldehyde activation and a subsequent tetrazole activation.

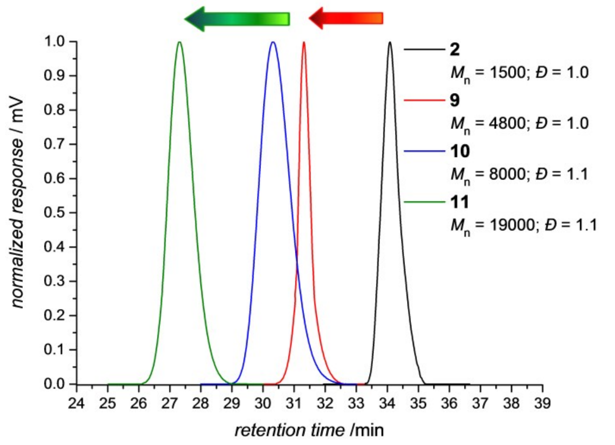
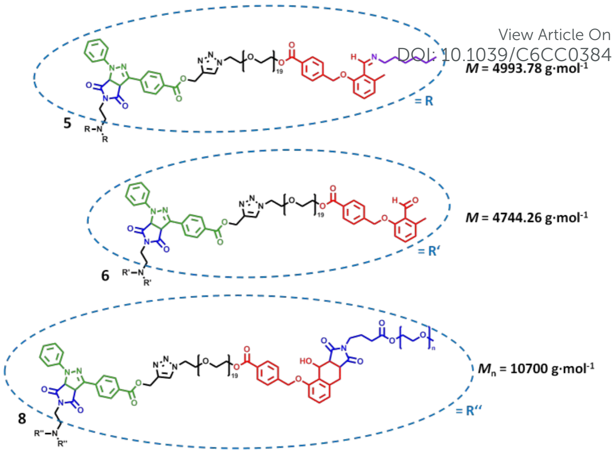


Figure 2: A system consisting of the trifunctional maleimide **1** and the α,ω-functional **2**, carrying the benzaldehyde and tetrazole end group functionalities, was irradiated for 3 h with the PL-L lamp leading to the selective formation of **9**. The star shaped oligomer **9** was subsequently mixed with the maleimide terminated polylactide **10** and irradiated for 13 h at λ = 280-440 nm forming the star polymer **11**. GPC reported to a PS calibration.

2 (3 eq.) were irradiated for 3 h in the wavelength range of 310-440 nm in dichloromethane (ESI Figure S1). Evidence for the successful ligation between the benzaldehyde moiety and the maleimide centre resulting in the star shaped structure terminated with tetrazole moieties **9** was obtained via GPC. The quantitative conversion is illustrated in Figure 2. ^{1}H NMR analysis also evidences the complete benzaldehyde conversion after irradiation, yet it should be noted that a small amount of tetrazole attachment to the maleimide centre (< 4 % conversion) is detectable (refer to ESI S17). Finally, the photoenol cored star precursor **9** carrying three tetrazole end groups was used as starting material for the final ligation step. In this case, **9** and the maleimide terminated polylactide **10** were irradiated for 13 h at λ = 280-440 nm (refer to ESI Figure S1) in the wavelength range of 280-440 nm in dichloromethane. The macromolecular star shaped structure **11** was analysed via GPC in order to evidence the λ-orthogonal ligation steps (refer to Figure 2). A ^{1}H NMR indicates a quantitative NITEC reaction of the tetrazole end groups of **9** with the maleimide functionality of the polylactide **10** (refer to ESI S18). Our novel, inverse λ-orthogonal method allows for the tetrazole attachment initially to the trifunctional maleimide centre by deactivating the benzaldehyde moiety through transformation to an imine. In general, protecting groups in photochemical applications show a photolabile behaviour, where they are removed upon irradiation revealing various functionalities.[17] In addition, systems containing wavelength-selective photolabile protecting groups have been reported.[18] However, the example presented here is not photolabile. The photoactive benzaldehyde species is transformed into an imine leading to the temporary photochemical deactivation of the compound. A shift in the light absorption between the α,ω-functional polymer carrying the benzaldehyde and the subsequently yielded imine end group was recorded via UV/vis spectroscopy (refer to ESI Figure S13).



Scheme 3: Overview of the star polymer structures **5**, **6**, and **8** which are obtained from initial tetrazole activation and subsequent benzaldehyde activation.

The benzaldehyde modification of the α,ω-functional polymer is key for the novel λ-orthogonal reaction sequence – so the tetrazole moiety can react prior to the benzaldehyde activation – before the irradiation procedure can actually start. In this context, the α,ω-functional polymer **2** (1 eq.) and hexylamine **3** (2.8 eq.) were dissolved in dry THF for 3 h yielding quantitative imine formation. The successful imine transformation was evidenced via ^{1}H NMR (refer to ESI Figure S10), Orbitrap ESI-MS (refer to ESI Figure S11), and GPC (refer to ESI Figure S12). The light induced tetrazole reaction was then performed by irradiating tris(2-maleimidoethyl)amine **1** (1 eq.) and the imine containing polymer **4** (3 eq.) for 13 h with the Arimed B6 lamp (refer to ESI Figure S1) in the wavelength range of 280-440 nm in dichloromethane. Evidence for the successful ligation between the tetrazole moiety and the maleimide core resulting in the star shaped structure terminated with aryl imine moieties **5** was determined via GPC. The quantitative conversion is illustrated in Figure 3. ^{1}H NMR underpins the complete and selective tetrazole conversion after the irradiation, whereas the benzaldehyde compound remained unreacted (refer to ESI Figure S14). The stability of the imine protection group under irradiation was additionally demonstrated via the selective addition of maleimide to a benzaldehyde terminated poly(ethylene glycol) with and without hexylamine (refer to ESI Figure S19). The imine hydrolysis was performed by dissolving **5** in dichloromethane and adding wet molecular sieves. The

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hydrolysis overnight led to the benzaldehyde terminated star precursor **6** and according to ^{1}H NMR conversion was quantitative (refer to ESI Figure S15). Finally, the tetrazole core precursor **6** carrying three benzaldehyde end groups was ligated with an ene-terminated polymer. In this example, **6** and the maleimide terminated poly(ethylene glycol) **7** were irradiated for 3 h in the wavelength range of 300-440 nm in dichloromethane (refer to ESI Figure S1). The macromolecular star shaped structure **8** was analysed via GPC in order to display the λ-orthogonal ligation steps (refer to Figure 3). ^{1}H NMR evidences the complete Diels-Alder reaction of **6** with the maleimide functionality of **7** (refer to ESI Figure S16).

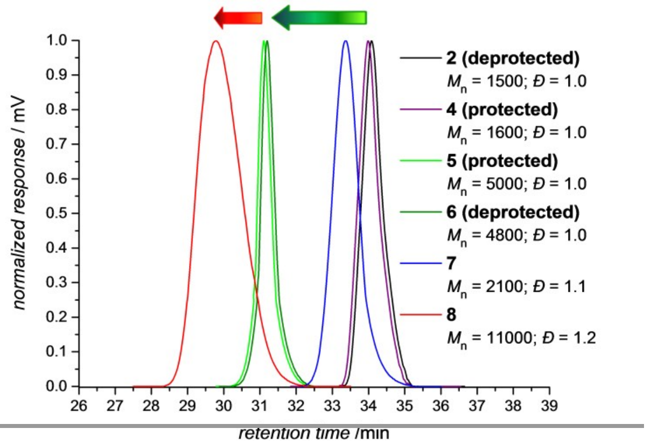

Figure 3: A system consisting of the trimaleimide **1** and the α,ω-functional **4** carrying a deactivated imine and tetrazole end group was irradiated for 13 h at λ = 280-440 nm leading to the selective formation of **5** which was subsequently hydrolysed to **6**. Thus, the benzaldehyde terminated star shaped oligomer **6** was mixed with the maleimide terminated PEG **7** and irradiated for 3 h using the PL-L lamp yielding in the star polymer **8**. GPC reported to a PS calibration.

In summary, we introduce a novel λ-orthogonal strategy for the selective light driven attachment of a bifunctional oligomer carrying two different photoactive termini – a benzaldehyde and tetrazole – to a trifunctional maleimide core. The first reaction path was carried out by an initial photoenol induced Diels-Alder ligation to the maleimide core in the low-energy UV range and then subsequent tetrazole activation leading to the attachment of an ene terminated polymer to the star shaped precursor with more energetic UV light. The reverse reaction path – tetrazole activation prior to the benzaldehyde – was achieved by the specific transformation of the benzaldehyde functionality by adding hexylamine. The obtained imine functionality was temporarily deactivated for the light induced [4+2]-cycloaddition. The imine modified α,ω-functional polymer was selectively attached to the maleimide centre via a tetrazole ligation. The new orthogonal reaction sequence – allowing wavelength-dependant ligation – demonstrates that the photochemical synthesis of complex macromolecular architectures is readily possible.

C.B-K. acknowledges funding from the Karlsruhe Institute of Technology (KIT) in the context of the Helmholtz STN program. K.H.'s PhD studies were partly funded by the Fond der Chemischen Industrie.

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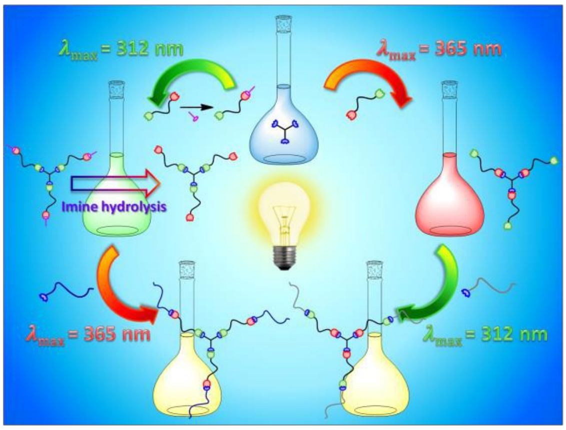

λ-Orthogonal photo-induced ligation in two directions is introduced via a modular, light driven selective star shaped polymer formation.