



Feature Article

[2+2] Photo-cycloadditions for polymer modification and surface decoration



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ABSTRACT

Photo-induced reactions play an important role in precision polymer design. Photoreactions are often cost-effective reactions that proceed under relatively mild reaction conditions. Additionally, photo reactions add spatial and temporal control over reactions, which gives rise to a large number of applications that would otherwise be inaccessible. Among the various photochemistries available, [2+2] cycloadditions are a prominent example for effective conversions. In the field of polymer chemistry, such reactions are often used for crosslinking. If reaction conditions are chosen carefully, they can, however, also be employed for advanced polymer transformations, such as polymer endgroup modification or specific ligation to substrates. Especially when applying flow chemistry approaches, very high reaction efficiencies are gained, bringing [2+2] cycloadditions close in use to other well known click-like techniques such as thiol–ene chemistry.

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1. Introduction

The advent of click chemistry has brought a profound paradigm shift into the field of synthetic polymer chemistry [1]. The ability to combine controlled polymerization

techniques (sequential approaches) with the highly efficient ligation chemistries (modular design approach) such as (hetero) Diels–Alder and 1,3 dipolar cycloadditions (to name only the most prominent examples for click-type transformations) has led to an almost infinite number of polymeric materials that can be achieved [2–5]. Almost any macromolecular structure that is imagined can also be synthesized, whereby limitations are only set by how cost- and time-consuming a certain synthesis procedure may be. Focus of research has thus in recent years shifted

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from development of procedures for novel targets to the optimization and simplification of existing synthesis concepts or the development of more efficient methods for the synthesis of known structures. Among the many approaches especially photo-induced reactions have gained significant interest – for conjugation reactions as well as for controlling polymerizations. Photo-triggered reversible addition fragmentation chain transfer (RAFT) polymerization [6], atom transfer radical polymerization (ATRP) [7–10] and nitroxide-mediated polymerizations (NMP) [11,12] have been developed. The advantage of such photo-activation methodologies is evident: reactions can be switched on and off by will, which adds a further dimension to the control over the reactions. Additionally, photo-control does not only imply temporal control, but also spatial containment and may hence be used to build up two- or three dimensional scaffolds with ease and thus deliver a significant added value over purely thermal reactions.

As mentioned, not only photoinduced polymerizations play an important role, also photoconjugation reactions have gained significant prominence. Light-mediated modular design gives similar advantages as described above with respect to tempo-spatial control of reactions, but is also interesting with respect to orthogonality of reactions. Within the realm of click chemistry, not only reaction efficiency is important, but also chemical selectivity, especially when a variety of different approaches are supposed to be combined in a synthesis sequence. Being able to switch between a thermal and a photochemical activation would thus enable to work more efficiently with complementary reactions that may even be based on the same functional groups (see Scheme 1).

In here, an overview will be given over the recent advances in the field of photoconjugation reactions. Special focus will thereby be given to [2+2] cycloadditions as a representative of truly photoinduced reactions. [2+2] cycloadditions are often regarded to be less efficient when compared to other photo-triggered reactions. The potential, especially in the realm of material science is, however, large and with optimization of reaction conditions and choice of suitable reaction conditions, even click like behavior can be reached for the reaction, making it thus a convenient tool for a multitude of applications, in principle ranging from polymer modification reactions to surface patterning.

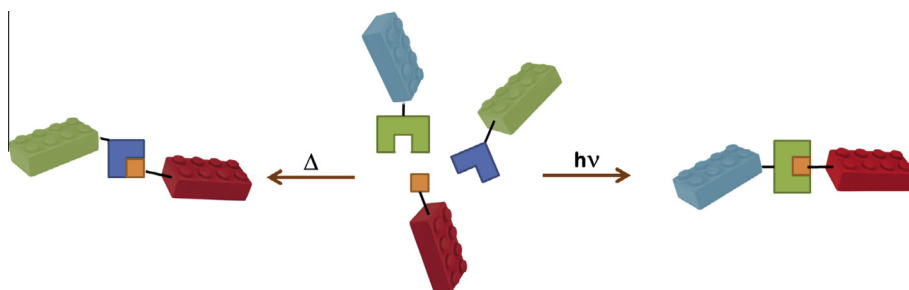
2. Photoligation chemistries

Generally, two types of reactions may be differentiated with respect to photo-triggered ligation chemistries. The first class entails reactions where a photo-reaction precedes an actual conjugation reaction; in other words, such reactions proceed via two distinct reaction steps, where the light incidence creates a reactive species that then leads to conjugation in a classical (thermally activated) reaction. A typical example for such reaction is the photo-induced thiol-ene reaction (see below), where only the initiation of the system proceeds via photoinitiation, but where the remaining reaction steps proceed under thermal activation. The second class consists of reactions that are truly photo-controlled in the sense that the actual ligation step is activated by light. Examples for the latter class are sparser, but generally cycloaddition reactions can be counted in there. The important difference between the two classes is that for the first a thermal activation still exist. The kinetics of the ligation is dominated by the activation energy of the following reaction step(s). Only in the second class, a truly temperature-independent reaction is achieved.

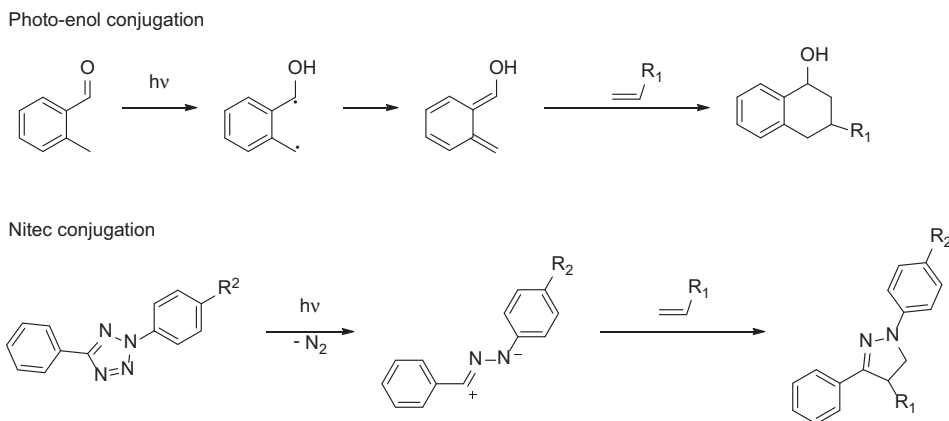
As noted above, the focus of this overview are [2+2] cycloadditions, thus a representative of the second class. However, before moving to these reactions, some prominent examples for polymer ligation reaction via the first class of reactions is given. It should be noted that this should be seen as an arbitrary reference point for the further discussion, not as a detailed overview over all existing photoreactions.

Thiol-ene reactions are very popular conjugation reactions and are used in a broad range of applications [13,14]. Among the various modes of the reaction, also a photo-triggered reaction pathway exists, where either the reaction is autoinitiated by UV and/or visible light, or where a conventional photoinitiator is added to start the thiol-ene chain reaction. Reactions are efficient, but due to the radical chain mechanism, the reaction is immanently prone to termination reactions, which results in the requirement of using the thiol component always in excess [15,16]. This requirement is not a particular property of the photo reaction, but a general limitation of thiol-ene as such.

Among other photoligations, two click-like reactions have gained significant prominence for their high



Scheme 1. Schematic representation of UV/thermal orthogonality of reactions. Depending on the mode of activation a different reaction occurs for the same substrate.



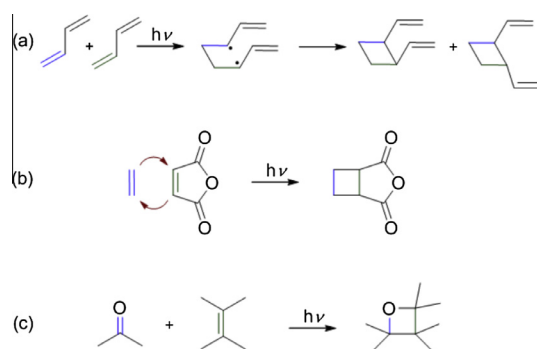
Scheme 2. Reaction schemes for the so-called photo-enol and NITEC conjugation reactions.

efficiency on polymer systems as well as for the particularly fast reaction rates (see [Scheme 2](#) for reaction schemes). In the so-called NITEC (nitrile imine tetrazole-ene cycloaddition) [17–20] reaction, ligation is achieved via UV-induced activation of a tetrazole, which splits off nitrogen to form a reactive intermediate, which can then react with an ene in a 1,3 dipolar cycloaddition with activated or non-activated enes. This reaction is particularly effective and allows for facile conversions of polymeric substrate as well as for bioconjugation. Also for conjugation of enes, the photo-enol reaction may be employed. In the photo-enol concept, a highly reactive *o*-quinodimethane is formed from the triplet state of a *o*-methyl benzaldehyde. This intermediate – due to the loss of its aromatic ring structure – is highly susceptible towards Diels–Alder reactions and reacts thus almost immediately after UV activation [21–23]. While both NITEC as well as photo-enol constitute highly efficient reactions that can be considered to allow for click-type modification, both are essentially thermal cycloaddition reactions.

3. [2+2] Cycloadditions

Photoinduced [2+2] cycloadditions take place between a variety of substrates. Any 4 electron system can in principle be activated, even though not all compounds exhibit sufficient reactivity [24,25]. Cycloadditions can proceed via a concerted mechanism, or via a radical two-step pathway, where the activated triplet state of the photo-activated double bond adds to the other pi system, which is then only in a second step followed by ring-closure. The reaction products are cyclobutane rings (or oxetanes if one ene was a carbonyl functionality), a common motive in natural product synthesis [26]. Interestingly, the reactions are under certain conditions reversible and allow for dynamic switching between the alkene and the cyclobutane state.

Whether reactions occur via concerted or via a radical intermediate mechanism has large impact on the stereo- and regioselectivity of the reaction. Since often both mechanisms proceed simultaneously, often complex product mixtures are obtained, which complicates the use of the



Scheme 3. Examples for a photoinduced [2+2] cycloaddition; (a) homocyclization of butadiene, (b) selective cyclization of an alkene with an enone and (c) the Paternò–Büchi reaction between a carbonyl compound with an alkene.

reaction in organic synthesis. For material science, however, the stereochemistry plays a minor role, and the exact mechanism is without consequences when the reaction is only used as a conjugation tool. A stable carbon–carbon bond between the reaction partners is formed in any way, making the reaction thus suitable to link two building blocks to each other.

[Scheme 3](#) depicts common examples for [2+2] cycloadditions. Often, cycloaddition is observed in homo-dimerization reactions. Prominent examples to undergo such reaction is cinnamic acid and its derivatives, which motive can be found as photo-crosslinkers in a number of applications, however, also anthracenes, acrylates, coumarins, maleimides or as shown in the scheme butadiene is prone to dimerization. Landfester and coworkers gave a good overview over reversible (nanoparticle) crosslinking via homodimerization [2+2] cycloadditions [27]. For example by using anthracene moieties as crosslinkers, conjugation can be reached at wavelengths above 350 nm, whereby light at 250 nm will trigger the reverse reaction.

The latter two [2+2] cycloaddition modes, that is the alkene–enone conjugation [28] as well as the Paternò–Büchi reaction [29] between an aldehyde or ketone and an alkene differ from the homodimerization in that a

differentiation between activator and quencher can be made. Activated enes and carbonyl compounds such as maleic anhydride or benzaldehyde are more susceptible to triplet activation compared to unactivated alkenes and hence act as the activator for a [2+2] reaction. The non-activated reaction partner then acts as a quencher and is hence often used in excess in order to avoid side-product formation. This is important when targeting polymer conjugation reactions since it is favorable to have the quencher compound in higher concentration compared to the activatable ene.

With respect to precision engineering of polymer materials, fewer examples are found in literature where [2+2] cycloadditions are applied. The reason for this lack can be seen in the perceived efficiency of the reaction. In cross-linking applications, incomplete conversion of functional groups as well as missing selectivity (as seen in homodimerizations) can be tolerated. When the reaction is supposed to be employed at specific loci of a polymer chain, close to 100% efficiency is required in order to achieve good reaction outcomes. In order to see if such higher reaction efficiency could be reached, polymer endgroup modifications were investigated via the Paterno–Büchi reaction pathway [29]. The advantage of the Paterno–Büchi pathway is that carbonyl compounds do not show self-dimerization, thus eliminating an unwanted side reaction from the scheme. Therefore, polyacrylates carrying a carbonyl functionality at the chain end were synthesized via ATRP employing a benzaldehyde-based initiator and then subjected to endgroup modification in [2+2] cycloadditions [30]. Reaction conditions were optimized by using 1-octene as a test substrate. Even though reaction velocities were low and large molar excesses of the alkene compound were required to drive the reaction to completion, quantitative conversion of the carbonyl group could be observed via NMR and via soft-ionization mass spectrometry. To perform the reactions, removal of oxygen prior to illumination was required, which underpins the radical character of the reaction. Up to 50 eq. of the alkene had to be employed as quencher to avoid unwanted side reactions or residual aldehyde functionalities after reaction. A polymer with a terminal aldehyde group was here targeted for the sake of simplicity, extrapolation of the results to more complex systems where the aldehyde may be located at remote position should be possible.

Regardless, the endgroup modification proceeds under the chosen reaction conditions well. Functional group tolerance is high and not only octene can be added to the terminal aldehyde, but also multifunctional alcohols, cyanurate or branched alkenes could be successfully implemented (see Table 1).

An obvious drawback of the endgroup modification described above is the large concentration of quencher that is required in the reaction as well as the relatively high reaction times between 1 and 2 days illumination. Both constraints make the reaction somewhat uneconomical, and also limit its application to cases where indeed a large excess of one compound could be used. Further optimization of the reaction was thus mandatory.

All light-induced reactions suffer from issues stemming from light intensity gradients in the reaction vessel.

Table 1

Yields of reaction of endgroup modification of aldehyde-functional poly(isobornyl acrylate) with various alkenes (see Scheme 4 for structures).

Alkene	C _{C=C} /C _{C=O}	Yield, %
1-Octene (a)	1:40	95
Allylamine (b)	1:50	60
3-Buten-1-ol (c)	1:50	34
Trimethylolpropane allyl ether (d)	1:50	88
Triallyl cyanurate (e)	1:50	86
2-Methylpentene (f)	1:50	90

Depending on the absorption coefficient and the pathlength (i.e. diameter of the reaction flask), reduced light intensities apply to relatively large parts of the reactors, which is reflected in different concentrations of activated species at any given point in time. If the overall absorption is high and significant reaction flask sizes are used, some parts of the reaction solution may entirely be in the dark. While this concentration gradient can be compensated by vigorous stirring, it still inevitably leads to inefficient light use. This phenomenon can be prevented by keeping optical pathways small (in the order of micro to millimetres) to ensure homogeneous irradiation of samples. While this is well possible for kinetic investigations, such small volumes are impractical for synthesis purposes. A convenient way to avoid this problem is the application of flow chemistry [31]. In flow reactors, especially in microstructured devices, pathlengths can be at all times kept low, while still substantial amounts of materials are processed over time. Flow reactors with 10 mL or more internal volume – concomitantly not exceeding pathlengths of 1 mm – can be easily set up using conventional UV light sources [32]. Not surprisingly, in such reactor devices, much faster reactions are observed compared to its batch counterparts and reduction of reaction times from hours to mere minutes are commonly observed [33].

For the optimization of the [2+2] cycloadditions, application of the flow chemistry concept was tested, employing a non-sophisticated flow reactor [34]. Initially, the reaction between unfunctionalized maleimide with various alkenes, hence an alkene–enone reaction, was tested in order to establish reactivity differences between batch and flow mode. Indeed, a very significant acceleration of the reaction could be observed (see Fig. 1). The alkene–enone reaction proceeds in batch slightly more efficient than the above described Paterno–Büchi reaction. The excess in alkene could be reduced to 20 eq and the reaction time could be kept between 10 and 20 h when using the same batch reaction conditions. When the same reaction is performed in flow, full enone conversion is observed within 4 min, using a comparable light source with respect to emission spectrum and intensity. Not surprisingly, slightly faster reactions were observed at 360 nm peak wavelength compared to 250 nm. Nevertheless, also at the lower wavelength, full conversions could be achieved, demonstrating that the conjugation product is photo-stable. Moreover, no excess of the alkene compound was required. Tests with various amounts of alkene showed that more than 98% conversion of the maleimide is already reached under equimolar reaction conditions. The reaction – under flow conditions – proceeds thus with an efficiency

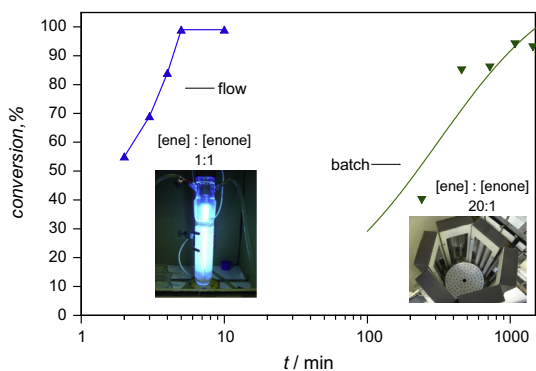


Fig. 1. Comparison of reaction rate for the alkene–enone cycloaddition between maleimide and 1-octene in a flow reactor compared to a batch reactor. In flow, equimolar ratios of reactants are used while in batch a 20-fold excess of the alkene was employed.

as is normally associated with a click reaction: following a single reaction trajectory, being very fast even at room temperature and selective, and additionally proceeding under equimolar conditions. Interestingly, no homodimer product of the maleimide was identified as would normally be expected under the chosen reaction conditions. It may be hypothesized that the homodimerization product is – in contrast to the desired product – not stable at the lower wavelength, which would explain the absence of dimer as well as the full conversion of the alkene.

Consequently, the same concept was then extended to a polymer substrate [35]. Therefore, a poly(butyl acrylate) was synthesized with a pendant maleimide endgroup to remain consistent with the earlier Paterno–Büchi study (see Scheme 5), via a activated ester approach [35]. A reduced reaction rate could be observed for the polymeric substrate, which may be attributed to steric hindrance and viscous effects on the reaction. Yet, fast reactions, reaching full conversion within 1 min reaction time, were achieved again by additionally adding a photosensitizer, thioxanthone (TXS) [36]. However, 5 equivalents of the alkene had to be added in order to achieve this result. Under equimolar reaction conditions still a fast reaction is observed on the timescale of minutes. Yet, the reactions prematurely stop at around 60–80% conversion. The precise amount of TXS plays a significant role. If too high concentrations are used (above 10 mol%), fast degradation of the polymer

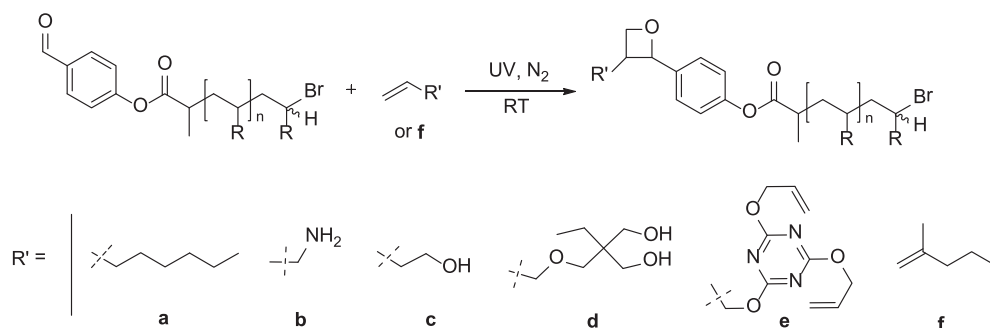
backbone is observed, even at low reactor residence times. If too little TXS is added, slow reactions occur. Yet, also when using TXS, large acceleration of the reaction is achieved simply by employing the flow reactor setup. Also in presence of TXS, reactions take several hours to completion when being performed in batch.

Regarding functional group tolerance and overall efficiency, the alkene–enone reaction is relatively similar to the Paterno–Büchi reaction, as can be seen from Table 2, if not even slightly better. Good conjugation efficiencies are observed for a broad range of functional alkenes, all under identical reaction conditions.

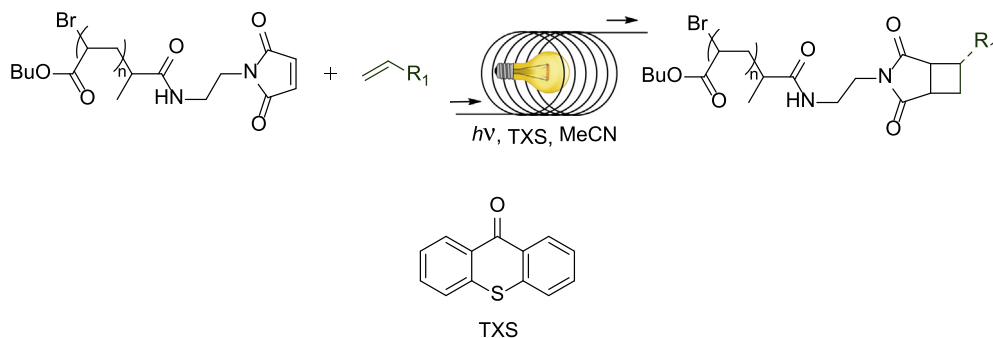
As mentioned above, one of the key advantages of photo-induced reactions is that spatial control can be easily achieved. Thus, the [2+2] conjugation concept was consequently extended towards surface modification reactions, both employing alkene moieties as binding motifs on the surface as well as carbonyl functions in order to test both possible routes. In principle, best results should be observed when the UV-activatable group is attached to surfaces, since this allows to directly activate specific areas rather than relying on the slow diffusion. Regardless, as will be demonstrated, both routes can be taken without penalty.

As example for a homogeneous surface modification, cellulose sheets were chosen as substrate. Cellulose modification benefits largely from UV-modification since mild reaction conditions are a prerequisite in order not to disintegrate the cellulose material during reaction. To carry out Paterno–Büchi reactions, the free C6 hydroxygroup of cellulose was modified by tosylation and subsequent introduction of p-hydroxy benzaldehyde (see Scheme 6 for structure) [37].

The Paterno–Büchi reaction could thereby be successfully used to modify the cellulose sheets with a variety of functional alkenes, comparable to the ones given in Scheme 4. Reactions proceeded efficiently as was evidenced by ATR-IR. Also, polymers bearing a non-activated vinyl endgroup were prepared via a functional RAFT initiator approach in order to graft polymers directly to the surface. Both poly(butyl acrylate) as well as poly(N-isopropylacrylamide) (NIPAAm) were in this manner ligated. Especially the attachment of NIPAAm yielded a material with interesting surface properties. At temperatures below the LCST, the cellulose sheet soaks up water, while at temperatures above 40 °C, a hydrophobic surface is created with a contact angle above 90° (see Scheme 7).



Scheme 4. Endgroup modification of aldehyde-terminal polymers via [2+2] Paterno–Büchi cycloadditions.



Scheme 5. [2+2] photo-induced alkene–enone polymer cycloaddition in flow in presence of a photosensitizer (TXS).

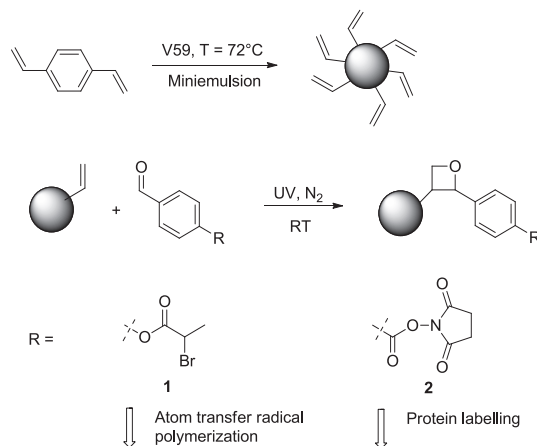
Table 2

Yields of the photocycloaddition reaction in flow of pBA-maleimide with various functional alkenes given in presence of 0.1 equiv. photosensitizer TXS, irradiation at 365 nm (400 W) and a residence time of 1.1 min at 4 °C.

Alkene	Equiv. TXS	Equiv. alkene	Yield _[2+2] /%
2-Methyl pentene	0.1	4	≥95
1-Octene	0.1	5	≥95
COE	0.1	5	≥95
Allylamine	0.1	5	–
Buten-3-ol	0.1	5	≥85
Allyl ethylether	0.1	5	≥90
Styrene	0.1	5	24
Triallyl cyanurate	0.1	1 ^a	80

^a 3 equiv. with respect to number of functional groups.

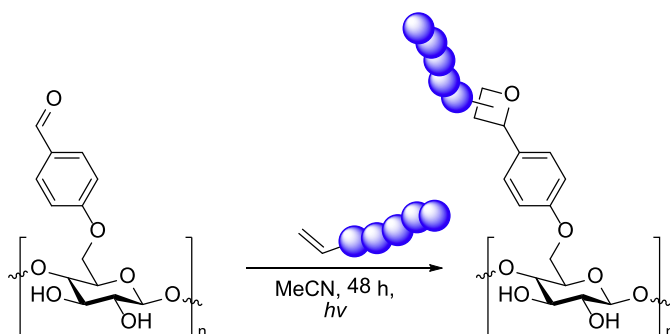
In the other approach, nanoparticles that were obtained by polymerization of divinyl benzene (DVB) in miniemulsion were decorated with either an ATRP initiator functionality or with NHS groups, likewise via a Paterno–Büchi reaction [38]. DVB nanoparticles carry unreacted double bonds on the surface that are available for cycloadditions. The two functionalities that were introduced to the particle were attached to benzaldehyde to keep a comparable reactivity with the previous studies. Via the ATRP initiator, butyl acrylate was grafted, allowing to study the grafting (and thus photoconjugation) density on the particles. via different methods, that elemental analysis, gravimetry and XPS spectroscopy, high grafting densities of at least 4 chains per nm² were confirmed, which is comparatively high for such reaction [39]. As the surface is covered with



Scheme 7. Surface modification of divinylbenzene based nanoparticles obtained from miniemulsion via the Paterno–Büchi reaction. Figure reproduced with kind permission from RSC.

the quencher moiety rather than the activatable carbonyl functionality, this result came somewhat surprising, especially, keeping in mind that the functional counterpart to the DVB-bound double bonds (styrene) exhibited only limited reactivity in the previous studies on polymer end-group modification.

Further, the pendant NHS groups that were then introduced to the surface could be used for bioconjugation. Attachment of gold-labeled antibodies could be easily



Scheme 6. UV-induced [2+2] cycloaddition between benzaldehyde functionalized cellulose and alkene-terminal polymers.

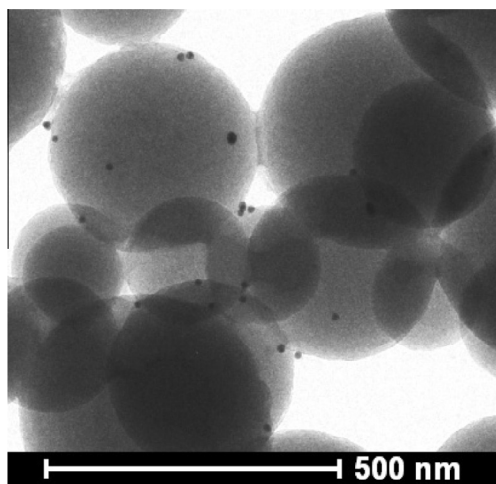


Fig. 2. TEM image of polyDVB particles after UV conjugation with NHS-aldehyde followed by gold-labeled antibody coupling [38]. Figure reproduced with kind permission from RSC.

achieved by dispersing the photo-modified particles in a protein solution, which was followed by addition of a relatively large number of antibodies per nanoparticle (see Fig. 2). It must thereby be noted that low concentrations of protein was used for economic reasons and that thus grafting densities are consequently lower and not in the same range as for the acrylate grafts.

4. Conclusions

Photoligation chemistries, especially [2+2] photocycloadditions open versatile pathways for polymer and surface modification reactions. This type of reaction can be used in facile manner as photocrosslinker, but also allows for dedicated functional group conversions for example in end-group modification reactions. Reaction efficiencies, which under normal circumstances are limited in terms of reaction time and amount of alkene needed to push the reaction to completion, can be increased tremendously when the process is carried out in flow reactors. Reaction times are reduced from several hours to just minutes and reactions become almost as efficient as classical click transformations. [2+2] cycloadditions can be also used efficiently in polymer ligation to surfaces, as is demonstrated by the grafting of nanoparticles and cellulose sheets.

The foundation to use alkene–enone or Paterno–Büchi reactions also for more advanced synthesis targets is put and the role that this reaction can play in precision polymer design has been demonstrated. Especially interesting, even if not studied in detail yet, is the fact that the herein discussed chemistries are photo-orthogonal to other reactions. All enes described in here can also be employed in classical thiol–ene reactions. The carbonyl functionalities are able to undergo bio-ligation in oxime formations. Most prominently, the maleimides used in the alkene–enone reaction are also very reactive functionalities for Diels–Alder conjugations, which might hold the biggest potential for further investigations into the photo-orthogonality.

Applications where a substrate is first (partially) functionalized under spatial control in a [2+2] cycloaddition followed by a second reaction step in which the substrate is further reacted in thermal ligations can be envisaged. In this way, access is given to fast structuring of surfaces in a non-demanding way.

In future work also a broader variety of modification reactions can be targeted, such as backbone functionalization or bioconjugation, not unlike photo-induced thiol–ene conjugations. Other fields of interest are also to apply [2+2] cycloadditions towards surface patterning to fully exploit the advantages of photo-controlled processes and to give access to advanced applications.

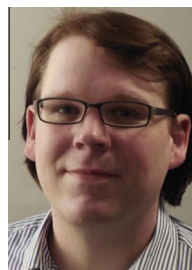
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