Light-Controlled Orthogonal Covalent Bond Formation at Two Different Wavelengths

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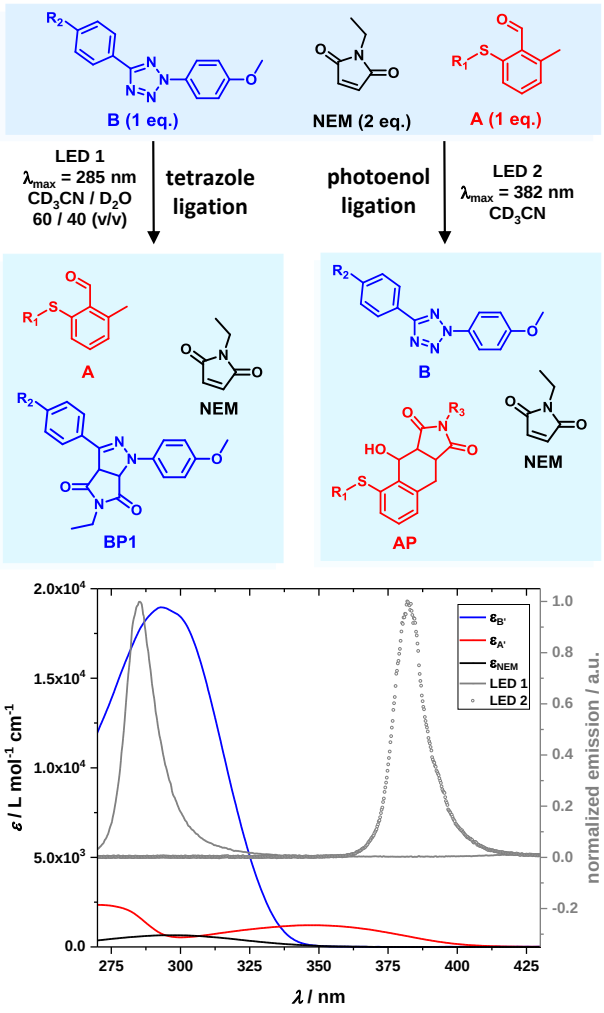
Jan P. Menzel,[a] Florian Feist,[a], [b] Bryan Tuten,[a] Tanja Weil,[b] James P. Blinco*[a], [c] and Christopher Barner-Kowollik*[a], [c]

Abstract: We report light-induced reactions in a two chromophore system capable of sequence independent λ-orthogonal reactivity relying solely on the choice of wavelength and solvent. In a solution of water and acetonitrile, light of an LED, λ_{max} = 285 nm, leads to full conversion of 2,5-diphenyltetrazoles with *N*-ethylmaleimide to the pyrazoline ligation products. Simultaneously present *o*-methylbenzaldehyde thioethers are retained. Conversely, LED light, λ_{max} = 382 nm, is used to induce ligation of the *o*-methylbenzaldehydes in acetonitrile via *o*-quinodimethanes with *N*-ethylmaleimide, while also present 2,5-diphenyltetrazoles are retained. This unprecedented photochemical selectivity is achieved through control of the amount and wavelength of incident photons as well as favorable optical properties and quantum yields of the reactants in their environment.

Photoinduced ligation reactions in a one pot system that can be controlled by choice of irradiation wavelength without the need of additives or catalysts are highly desirable tools in fields of organic, biological and macromolecular chemistry as well as materials science. Until recently, this orthogonality, also described as λ-orthogonality,[1] wavelength selectivity[2] or chromatic orthogonality[3] has, with the exception of photo-cleavage or photodeprotection systems,[4] the use of additional protecting groups,[5] added catalysts,[6] release from plasmon resonant liposomes[7] and photo-isomerization systems (photo switches),[3, 8] been achieved in only a sequence dependent fashion.[1-2, 9] Clearly, the design of a catalyst free, sequence independent orthogonal ligation system is a formidable challenge.[10] Generally, sequence-dependent λ-orthogonality is possible, if one photoactivatable chromophore absorbs light in a region of the ultraviolet-visible spectrum, where the other chromophore does not absorb (long wavelength irradiation induces first reaction). The inverted order (short wavelength irradiation induces first reaction) of photoreactions usually results in undesired non-selective activation of both chromophores. In 2000, Bochet and coworkers introduced a pair of protecting groups that can be cleaved with different wavelengths in a one pot system with acceptable selectivity:[4a, 4b] One of the photoactivatable substances was converted with 254 nm light to 92%, while the other photo-cleavable compound was retained to a degree of 83%. In the wavelength inverted approach, the latter substance can be converted by 420 nm light to 93%, while 92% of the first compound is retained. While this selectivity for a photodeprotection is notable, it is far from being quantitative and addresses bond cleavage rather than formation.



Scheme 1. Tetrazoles and *o*-methylbenzaldehydes enable λ-orthogonal reactivity: Photons within defined wavelength ranges and control of the water content of the solution allow selective conversion of one substrate at each wavelength, whereas the other is retained. From top to bottom: Composition of the mixture before and after irradiation with the shorter and the longer wavelength, respectively; emission spectra of LEDs and UV/Vis spectra of all chromophores (to increase the accuracy of molar attenuation coefficients ε, spectra of the chromophores as small molecule derivatives without long PEG chains A' and B' are depicted, refer to the Supporting Information, section 1.7).

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Examples that show control over ligation reactions with different colors of light without the limitation of sequence dependence are scarce: It was shown indirectly by combining a visible light triggered 'off-switch' of a thermal ligation reaction with a UV light induced ligation reaction.[11] Orthogonal labelling of biomolecules was reported employing 9,10-phenanthrenequinones and tetrazoles, although no study with thorough evidence, such as NMR spectroscopic or mass spectrometric proof of the orthogonality of the reactions was shown.[12] Recently, the reversibility of the styrylpyrene dimerization was exploited to enable chain ligation and single chain coupling[13] as well as crosslinking of polymer networks[14] in a sequence-independent λ-orthogonal fashion.

Here, we present a catalyst free ligation system forming covalent bonds, where the color of light and the solvent environment determine the reaction outcome, independent of which colour is employed first and despite overlapping absorption spectra of the chromophores. Such sequence-independent λ-orthogonality may open avenues to remote controlling reaction outcomes in applications ranging from multi-material 3D direct laser lithography,[15] synthesis of sequence defined macromolecules[16] to *in-vivo* ligation.[17] Our previous work[18] led us to assess the potential λ-orthogonality of diaryltetrazoles and *o*-methylbenzaldehydes as substrates for reaction with electron poor dienophiles. The combination of *o*-methylbenzaldehyde thioether **A** (R_1 = $CH_3(O(CH_2)_2)_n$-, 31<*n*<64; Scheme 1), methoxy-substituted diphenyltetrazole **B** (R_2 = $CH_3(O(CH_2)_2)_n$NHCO-, 31<*n*<64) and *N*-ethylmaleimide was found to be the most promising system according to the observed absorptivity and reactivity of the chromophores. As has been highlighted by Feringa and coworkers,[19] to achieve sequence-independent wavelength selective (λ-orthogonal) photoreactivity not only the absorption properties have to be considered, but also the quantum yields Φ_λ (defined as the number of product molecules formed divided by the number of monochromatic photons absorbed by the respective chromophore) of the reactions. On the one hand, the molar attenuation coefficient of tetrazole **B'** (R_2 = CH_3OCO-) at 285 nm is 10.6 times higher than the one of *o*-methylbenzaldehyde **A'** (R_1 = $HO((CH_2)_2O)_5(CH_2)_2$-) ($\varepsilon_{\mathbf{B'},285\ nm}$=1.76 * 10^4 $Lmol^{-1}cm^{-1}$; $\varepsilon_{\mathbf{A'},285nm}$=1.7 * 10^3 $Lmol^{-1}cm^{-1}$). On the other hand, the reaction quantum yield of the ligation of methoxy-substituted tetrazole **B** is estimated to be equal to that of a diphenyltetrazole, $\Phi_{Tet,285\ nm}$≥0.55±0.06.[18a] It is therefore even 34 times higher than the reaction quantum yield of the ligation of *o*-methylbenzaldehyde **A** with *N*-ethylmaleimide (in a solvent mixture containing 40% water), $\Phi_{A,285\ nm}$=0.016±0.002 (see the Supporting Information, Section 2.1). In acetonitrile with a water content of less than 1% the quantum yield of the photoenol ligation is found to be significantly higher ($\Phi_{A,285nm}$=0.057±0.007) than in the water containing mixture, limiting the orthogonal conversion of the two substrates. To gain an in-depth understanding of the selectivity and to predict reaction outcomes, an iterative simulation was conceived by modifying already established python source code (see also the Supporting Information, Section 2.2).[18a, 20] With known concentrations of starting materials **A**, **B** and *N*-ethylmaleimide, molar attenuation coefficients and quantum yields, the progress of the competing reaction pathways can be simulated: The volume of the sample solution is treated as a stack of thin segments (wafers / slices). Within each segment, a defined amount of photons (either a laser pulse or a defined time increment in case of continuous LED irradiation) changes the local concentrations of compounds according to light absorption and reactivity. The outcome of the simulation is a calculated overall conversion as a function of the irradiation time (time increments *k*). The simulation was executed for varied quantum yields of photoenol ligation, corresponding to the change in quantum yield in different environments (see Figure 1 and the Supporting Information, Section 2.2. If the photon number input of the light source in the experiment is known, as in a tunable laser experiment with controlled photon count, the simulation has predictive power regarding the conversion of each component resulting in a selectivity at a certain time of irradiation. In case of an LED experiment, the simulation is slightly less precise, especially regarding the *x*-axis, because differences in wavelength dependent quantum yields as well as the width of the emission spectrum are not taken into account in the simulation. Yet, the calculated selectivities indicate the viability of sequence independent λ-orthogonal conversion of the substrates **A**, **B** and **NEM** in a selected solvent environment.

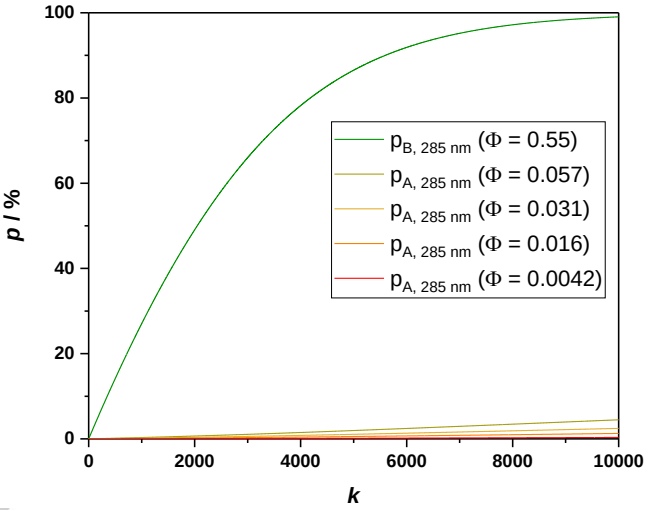

Figure 1. Simulated progress of the photoreactions for the tetrazole and photoenol ligation at 285 nm under varied solvent conditions with the respective quantum yield. While the tetrazole is converted to the pyrazoline ligation product (green line, $p_{B,\ k\ =\ 10000}$ > 99%), the photoenol conversion is calculated to reach values between 0.34% ($\Phi_{A,\ 285\ nm}$ = 0.0042) and 4.5% ($\Phi_{B,\ 285\ nm}$ = 0.057) depending on the quantum yield of photoenol ligation.

While tetrazole **B** does not absorb light with wavelengths longer than 345 nm, the photoenol-ligation can be successfully triggered with light up to 430 nm,[18b] enabling the already well established λ-orthogonal ligation sequence (photoenol ligation before tetrazole ligation).[1] Irradiation was in each case carried out with readily available light emitting diodes (For details see Supporting Information, section 1.5 and 2.3). Figure 2 evidences the proposed orthogonal reactivity.

A stock solution containing 1.0 eq. (1.7 mmol L^{-1}) of *o*-methylbenzaldehyde **A**, 1.0 eq. (1.7 mmol L^{-1}) of tetrazole **B**, and 2.2 eq. (3.9 mmol L^{-1}) *N*-ethylmaleimide in CD_3CN was prepared. In case of the first irradiation step with LED 1, D_2O and in case of irradiation with LED 2, CD_3CN was added, as the water content reduces the quantum yield of photoenol ligation, but at higher photon counts leads to the formation of side products (for details see the Supporting Information, Section 2.1 and 2.6).

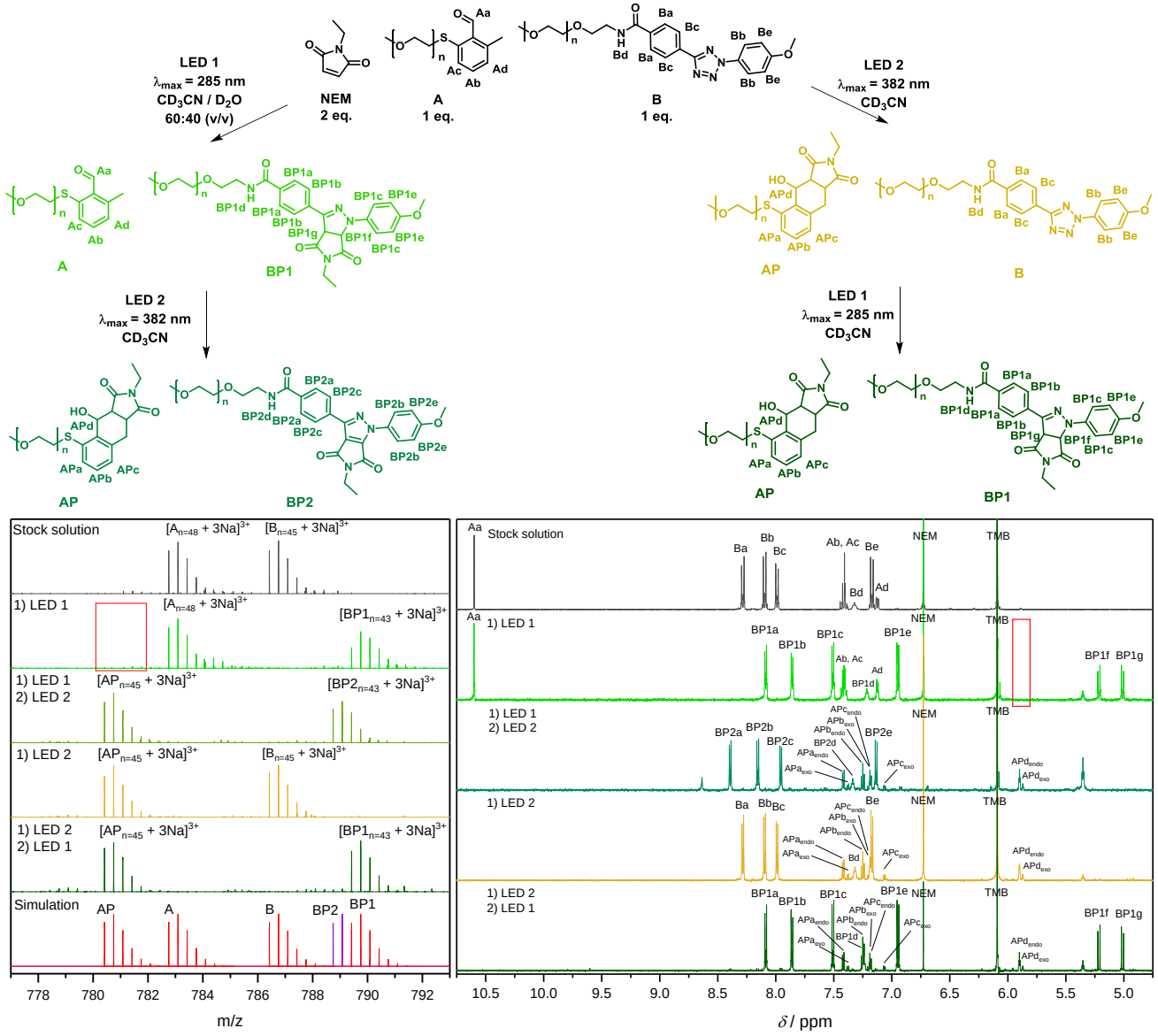

Figure 2. Orthogonal reactivity evidenced by nuclear magnetic resonance spectroscopic and high resolution electrospray ionization mass spectrometric analysis. Above: Reaction scheme – fractions of a stock solution of 1.0 eq. (1.0 mmol L^{-1}) of *o*-methylbenzaldehyde **A**, 1.0 eq. (1.0 mmol L^{-1}) of tetrazole **B**, and 2.2 eq. (2.3 mmol L^{-1}) *N*-ethylmaleimide were subjected to LED light, first either LED 1 (λ_{max} = 285 nm, solvent mixture of 60 % CD_3CN and 40 % D_2O) or LED 2 (λ_{max} = 382 nm, CD_3CN) and second with the other respective LED wavelengths (both in CD_3CN). All spectra were obtained without purification except for the removal of water / volatiles. Right: Expansion of selected regions of mass spectra obtained prior and after the respective irradiation as well as simulated peak patterns. Left: Expansion of NMR spectra of the mixture before and after each irradiation (For details, see the Supporting Information, Section 2.3).

The excess of *N*-ethylmaleimide guarantees that any activated species, in case it is formed, can find a reaction partner. Prior to irradiation, the stock solution was deoxygenated by a stream of nitrogen. Conversion for each ligation reaction is quantified by nuclear magnetic resonance spectroscopy and the results are qualitatively verified by high resolution electrospray ionization mass spectrometry directly after collection of the sample (see Figure 2). After removal of volatiles from the water-containing sample and addition of *N*-ethylmaleimide, the following irradiation step was each performed in CD_3CN. Both mass spectra as well as NMR spectra indicate that each reaction can be performed with full conversion, while the other compound is retained. The determination of full conversion and full retention is limited by the sensitivity of the NMR measurement. Yet, the integrals of the signals of **A** (**Aa**, **Ab**, **Ac** and **Ad**) in the NMR spectrum obtained after irradiation with LED 1 (λ_{max} = 285 nm, second spectrum from the top in Figure 1 (see also the Supporting Information, Section 1.5) show that no significant amount of **A** was consumed, while the tetrazole **B** was converted to the pyrazoline cycloadduct **BP1**. The red rectangles highlight the region in the NMR and mass spectrum showing no detectable conversion to the photoenol ligation product **AP**, despite the respective *o*-methylbenzaldehyde absorbing light at 285 nm. During the subsequent photoreaction at λ_{max} = 382 nm the *o*-methylbenzaldehyde **A** was fully converted to its ligation product **AP**, here observed in an endo/exo ratio of 80:20 and the pyrazoline **BP1** rearomatized to the pyrazole **BP2**. The same endo/exo ratio for **AP** is found, when the inverted irradiation sequence is applied. In this case the pyrazoline **BP1** is the end-product of the tetrazole ligation, as it is converted last. The results are each confirmed by the mass spectral results, impressively showing the binary character

of the λ-orthogonal ligation reactions despite the overlapping absorption spectra (Scheme 1).

To establish the limitations of the orthogonal bond formation system, a number of further experiments were carried out. If the sequences are carried out without water addition, minor amounts of undesired photoenol ligation product can be detected in high resolution mass spectra after irradiation of a stock solution of **A**, **B** and **NEM** with LED 1 (see the Supporting Information, Section 2.4). The product could not be detected by NMR spectroscopy, thus preventing quantification of the undesired reactivity, as potential ionization biases in electrospray ionization allow only a semi-quantitative assessment of conversion. With the previously noted limitation of side products being formed (see the Supporting Information, section 2.6), both sequences were successfully carried out in a mixture of acetonitrile and water (see the Supporting Information, section 2.5). The sequence employing LED 1 first, in a water containing mixture, was additionally carried out in the presence of oxygen (see the Supporting Information, section 2.7). While the first reaction remarkably shows uncompromised selectivity, albeit at a slower reaction rate of tetrazole ligation, subsequent photoenol ligation leads to side products. Yet, the majority of the mass spectrometrically found and identified species can be assigned to partially oxidized ligation products, thus revealing the potential of the λ-orthogonal bond formation system for bio-applications. Further, instead of being carried out orthogonally in a sequential fashion, both ligations can be carried out simultaneously, without interference of the intermediate states (see the Supporting Information, Section 2.8).

Although the identity of the cycloadducts **BP1** and **BP2** varies depending on the sequence, for a large variety of applications only the formation of a covalent bond matters, be it λ-orthogonal labelling of biomolecules, the tying of linkage points in 3D direct laser lithography or the photopatterning of thin films. In case of λ-orthogonal network formation, a side reaction resulting in crosslinking of *o*-methylbenzaldehyde functionalities may not at all be problematic, allowing the use of water containing media throughout all reaction sequences. It was demonstrated recently that dimerization of *o*-quinodimethanes can be exploited for crosslinking of polymer networks.[21] A study investigating λ-orthogonal network formation employing tetrazoles and *o*-methylbenzaldehyde thioethers is currently underway in our laboratories.

In summary, we have shown how the precise determination of quantum yields can aid in the computational prediction of photochemical selectivity, leading to an example of sequence independent λ-orthogonal bond formation, despite the inherent obstacle of overlapping absorption spectra. Expanding the toolbox of orthogonally addressable chromophores will enable precision photochemical control of synthetic challenges in a multitude of scientific fields.

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Keywords: λ-orthogonal photoligation • wavelength selective photochemistry • photoenol • tetrazole • chromatic orthogonality • photochemical simulation

[1] K. Hiltebrandt, T. Pauloehrl, J. P. Blinco, K. Linkert, H. G. Börner, C. Barner‐Kowollik, *Angew. Chem. Int. Ed.* **2015**, *54*, 2838-2843.

[2] A. Eibel, D. E. Fast, J. Sattelkow, M. Zalibera, J. Wang, A. Huber, G. Müller, D. Neshchadin, K. Dietliker, H. Plank, H. Grützmacher, G. Gescheidt, *Angew. Chem. Int. Ed.* **2017**, *56*, 14306-14309.

[3] M. M. Lerch, M. J. Hansen, W. A. Velema, W. Szymanski, B. L. Feringa, *Nat. Commun.* **2016**, *7*, 12054.

[4] a) C. G. Bochet, *Tetrahedron Lett.* **2000**, *41*, 6341-6346; b) C. G. Bochet, *Angew. Chem. Int. Ed.* **2001**, *40*, 2071-2073; c) M. N. Stanton-Humphreys, R. D. T. Taylor, C. McDougall, M. L. Hart, C. T. A. Brown, N. J. Emptage, S. J. Conway, *Chem. Commun.* **2012**, *48*, 657-659; d) V. San Miguel, C. G. Bochet, A. del Campo, *J. Am. Chem. Soc.* **2011**, *133*, 5380-5388; e) A. Gautier, C. Gauron, M. Volovitch, D. Bensimon, L. Jullien, S. Vriz, *Nat. Chem. Biol.* **2014**, *10*, 533; f) L. Fournier, C. Gauron, L. Xu, I. Aujard, T. Le Saux, N. Gagey-Eilstein, S. Maurin, S. Dubruille, J.-B. Baudin, D. Bensimon, M. Volovitch, S. Vriz, L. Jullien, *ACS Chem. Biol.* **2013**, *8*, 1528-1536; g) M. A. Azagarsamy, K. S. Anseth, *Angew. Chem. Int. Ed.* **2013**, *52*, 13803-13807; h) J. P. Olson, M. R. Banghart, B. L. Sabatini, G. C. R. Ellis-Davies, *J. Am. Chem. Soc.* **2013**, *135*, 15948-15954; i) W. A. Velema, J. P. van der Berg, W. Szymanski, A. J. M. Driessen, B. L. Feringa, *ACS Chem. Biol.* **2014**, *9*, 1969-1974; j) M. A. H. Fichte, X. M. M. Weyel, S. Junek, F. Schäfer, C. Herbivo, M. Goeldner, A. Specht, J. Wachtveitl, A. Heckel, *Angew. Chem. Int. Ed.* **2016**, *55*, 8948-8952.

[5] K. Hiltebrandt, M. Kaupp, E. Molle, J. P. Menzel, J. P. Blinco, C. Barner-Kowollik, *Chem. Commun.* **2016**, *52*, 9426-9429.

[6] a) S. Hurrle, A. Lauer, H. Gliemann, H. Mutlu, C. Wöll, A. S. Goldmann, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2016**, *38*, 1600598; b) M. A. Tasdelen, O. S. Taskin, C. Celik, *Macromol. Rapid Commun.* **2016**, *37*, 521-526.

[7] S. J. Leung, X. M. Kachur, M. C. Bobnick, M. Romanowski, *Adv. Funct. Mater.* **2011**, *21*, 1113-1121.

[8] a) J. R. Hemmer, S. O. Poelma, N. Treat, Z. A. Page, N. D. Dolinski, Y. J. Diaz, W. Tomlinson, K. D. Clark, J. P. Hooper, C. Hawker, J. Read de Alaniz, *J. Am. Chem. Soc.* **2016**, *138*, 13960-13966; b) S. Ishida, T. Fukaminato, D. Kitagawa, S. Kobatake, S. Kim, T. Ogata, S. Kurihara, *Chem. Commun.* **2017**, *53*, 8268-8271.

[9] a) P. Lederhose, D. Abt, A. Welle, R. Müller, C. Barner-Kowollik, J. P. Blinco, *Chem. Eur. J.* **2017**, *24*, 576-580; b) C. Menge, A. Heckel, *Org. Lett.* **2011**, *13*, 4620-4623; c) N. Kotzur, B. Briand, M. Beyermann, V. Hagen, *J. Am. Chem. Soc.* **2009**, *131*, 16927-16931; d) T. F. Scott, B. A. Kowalski, A. C. Sullivan, C. N. Bowman, R. R. McLeod, *Science* **2009**, *324*, 913-917; e) D. Klinger, K. Landfester, *Soft Matter* **2011**, *7*, 1426-1440; f) M. A. Priestman, L. Sun, D. S. Lawrence, *ACS Chem. Biol.* **2011**, *6*, 377-384; g) B. N. Goguen, A. Aemissegger, B. Imperiali, *J. Am. Chem. Soc.* **2011**, *133*, 11038-11041; h) C. A. DeForest, K. S. Anseth, *Nat. Chem.* **2011**, *3*, 925; i) D. R. Griffin, A. M. Kasko, *ACS Macro Lett.* **2012**, *1*, 1330-1334; j) L. García-Fernández, C. Herbivo, V. S. M. Arranz, D. Warther, L. Donato, A. Specht, A. del Campo, *Adv. Mater.* **2014**, *26*, 5012-5017; k) S. Yamazoe, Q. Liu, L. E. McQuade, A. Deiters, J. K. Chen, *Angew. Chem. Int. Ed.* **2014**, *53*, 10114-10118; l) M. Kaupp, K. Hiltebrandt, V. Trouillet, P. Mueller, A. S. Quick, M. Wegener, C. Barner-Kowollik, *Chem. Commun.* **2016**, *52*, 1975-1978; m) L. Yu, Q. Wang, J. Sun, C. Li, C. Zou, Z. He, Z. Wang, L. Zhou, L. Zhang, H. Yang, *J. Mater. Chem. A* **2015**, *3*, 13953-13961; n) K. Morihiro, T. Kodama, S. Mori, S. Tsunoda, S. Obika, *Org. Biomol. Chem.* **2016**, *14*, 1555-1558; o) O. Eivgi, E. Levin, N. G. Lemcoff, *Org. Lett.* **2015**, *17*, 740-743; p) A. M. Schenzel, N. Moszner, C. Barner-Kowollik, *ACS Macro Lett.* **2017**, *6*, 16-20; q) X. Hu, Z. Qureishi, S. W. Thomas, *Chem. Mater.* **2017**, *29*, 2951-2960; r) X. Zhang, W. Xi, S. Huang, K. Long, C. N. Bowman, *Macromolecules* **2017**, *50*, 5652-5660; s) R. R.

Batchelor, E. Blasco, K. N. R. Wuest, H. Lu, M. Wegener, C. Barner-Kowollik, M. H. Stenzel, *Chem. Commun.* **2018**, *54*, 2436-2439; t) M. Wu, X. Lin, X. Tan, J. Li, Z. Wei, D. Zhang, Y. Zheng, A.-x. Zheng, B. Zhao, Y. Zeng, X. Liu, J. Liu, *ACS Appl. Mater. Interfaces* **2018**, *10*, 19416-19427.

[10] H. Frisch, D. E. Marschner, A. S. Goldmann, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2017**, *57*, 2036-2045.

[11] H. A. Houck, F. E. Du Prez, C. Barner-Kowollik, *Nat. Commun.* **2017**, *8*, 1869.

[12] J. Li, H. Kong, L. Huang, B. Cheng, K. Qin, M. Zheng, Z. Yan, Y. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 14542-14546.

[13] H. Frisch, F. R. Bloesser, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2019**, *58*, 3604-3609.

[14] S. Bialas, L. Michalek, D. E. Marschner, T. Krappitz, M. Wegener, J. Blinco, E. Blasco, H. Frisch, C. Barner-Kowollik, *Adv. Mater.* **2019**, *31*, 1807288.

[15] M. M. Zieger, P. Mueller, A. S. Quick, M. Wegener, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2017**, *56*, 5625-5629.

[16] N. Zydziak, W. Konrad, F. Feist, S. Afonin, S. Weidner, C. Barner-Kowollik, *Nat. Commun.* **2016**, *7*, 13672.

[17] a) Y. Wang, W. Song, W. J. Hu, Q. Lin, *Angew. Chem.* **2009**, *121*, 5434-5437; b) P. An, T. M. Lewandowski, T. G. Erbay, P. Liu, Q. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 4860-4868.

[18] a) J. P. Menzel, B. B. Noble, A. Lauer, M. L. Coote, J. P. Blinco, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2017**, *139*, 15812-15820; b) F. Feist, J. P. Menzel, T. Weil, J. P. Blinco, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2018**, *140*, 11848-11854.

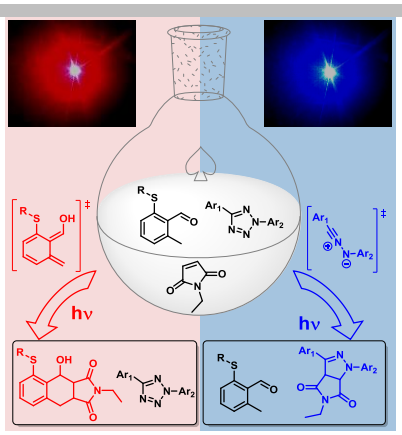
[19] M. J. Hansen, W. A. Velema, M. M. Lerch, W. Szymanski, B. L. Feringa, *Chem. Soc. Rev.* **2015**, *44*, 3358-3377.

[20] a) T. Gegenhuber, L. De Keer, A. S. Goldmann, P. H. M. Van Steenberge, J. O. Mueller, M.-F. Reyniers, J. P. Menzel, D. R. D'hooge, C. Barner-Kowollik, *Macromolecules* **2017**, *50*, 6451-6467; b) H. Frisch, J. P. Menzel, F. R. Bloesser, D. E. Marschner, K. Mundsinger, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2018**, *140*, 9551-9557.

[21] T. Krappitz, F. Feist, I. Lamparth, N. Moszner, H. John, J. P. Blinco, T. R. Dargaville, C. Barner-Kowollik, *Materials Horizons* **2019**, *6*, 81-89.

COMMUNICATION

Light and water define opposite outcomes: Two colours of light are able to selectively activate each one substrate in a two chromophore system for light induced ligation. Control over which of the two ligation reactions takes place is achieved through the chosen wavelength of irradiated light and the water content of the solution.



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