Light-induced Ligation of *o*-Quinodimethanes with Gated Fluorescence Self-reporting

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ABSTRACT: We introduce a highly efficient photoligation system, affording a pro-fluorescent Diels−Alder product that, on demand, converts into an intensively fluorescent naphthalene via E1 elimination in the presence of catalytic amounts of acid. The Diels−Alder reaction of the photocaged diene (*o*-quinodimethane ether or thioether) with electron-deficient alkynes is induced by UV or visible light. In contrast to previously reported ligation techniques directly leading to fluorescent products, the fluorescence is turned on after the photoligation. Thus, the light absorption of the fluorophore does not undermine the photoligation via competitive absorption, and as a result, photobleaching or side reactions of the fluorophore are not observed. Critically, the gated generation of a fluorescent product allows for fluorometric determination of the conversion. We employ a simple synthesis strategy for heterobifunctional electron-deficient alkynes allowing for facile functionalization of payload molecules.

Photocaged dienes based on *o*-methylbenzaldehydes (*o*-MBAs) are frequently used in various applications, such as polymer network formation,[1] single chain nanoparticle (SCNP) folding,[2] three-dimensional (3D) laser writing,[3] and many more, as they offer the attractive feature of spatiotemporal control and serve as an indispensable tool in contemporary polymer and supramolecular chemistry.[4−7] A limitation of the ligation of *o*-MBAs and electron-deficient enes is the lack of a simple visual feedback that allows for monitoring the reaction progress and selectivity in solution and on surfaces.[8] Many common photoinduced reactions, for instance, the nitrile imine tetrazole ene-reaction click reaction (NITEC)[9] or the reaction of photocaged naphtoquinone-3-methides (*o*-MQMs) with vinylethers[10,11] form fluorescent products (pyrazoles, pyrazolines, and naphtalenes, respectively). Despite this advantage, the direct formation of reaction products that either absorb in the same region or are red-shifted in their absorption compared to their starting materials represents a considerable challenge. The competitive absorption of photons by the reaction products decreases the apparent quantum yield of the reaction[12] and potentially leads to secondary reactions or photobleaching.[13] In particular, for the synthesis of materials such as polymer conjugates,[1] functionalized surfaces,[14] microspheres,[15] sequence-defined macromolecules,[16] or SCNPs,[17] competitive absorption presents a key challenge and limits the selectivity and control over the reaction. (Scheme 1). Herein, we present a strategy using electron-deficient alkynes as dienophiles forming pro-fluorescent 1,4-dihydro-1-naphthols. The naphthols do not absorb in the wavelength range where the respective *o*-MBAs are activated. After the completion of the photoreaction, highly fluorescent naphthalenes are generated rapidly and quantitatively by adding catalytic amounts of acid. The result is a photoreaction that is not disturbed by competitive absorption

Scheme 1[a]
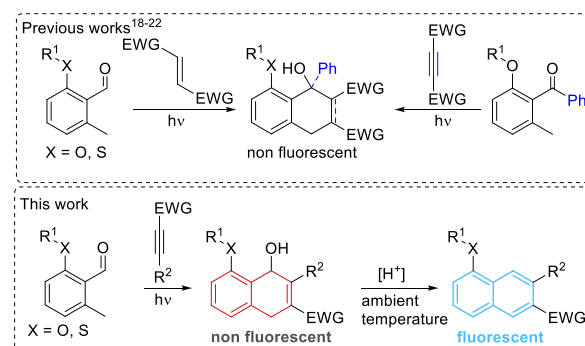
[a](Top) Previous works using *o*-MBAs and electron-deficient alkenes or *o*-methylbenzophenones and alkynes.[18] [22] (Bottom) Approach to fluorescent naphtalenes via non-fluorescent and blue-shifted 1,4-dihydro-1-naphtholes. EWG: electron-withdrawing group.

and is readily traceable by fluorescence spectroscopy due to the controlled formation of the fluorophore.

The reaction of photocaged *o*-QDMs and electron-deficient alkynes was first described by Porter and Tchir.[23] Wallace and co-workers investigated the reaction further and described the isolation of the naphthalenes after reflux in xylene with yields below 40%.[18] On the basis of this pioneering work, the reaction of 2-methyl benzophenones with alkynes was
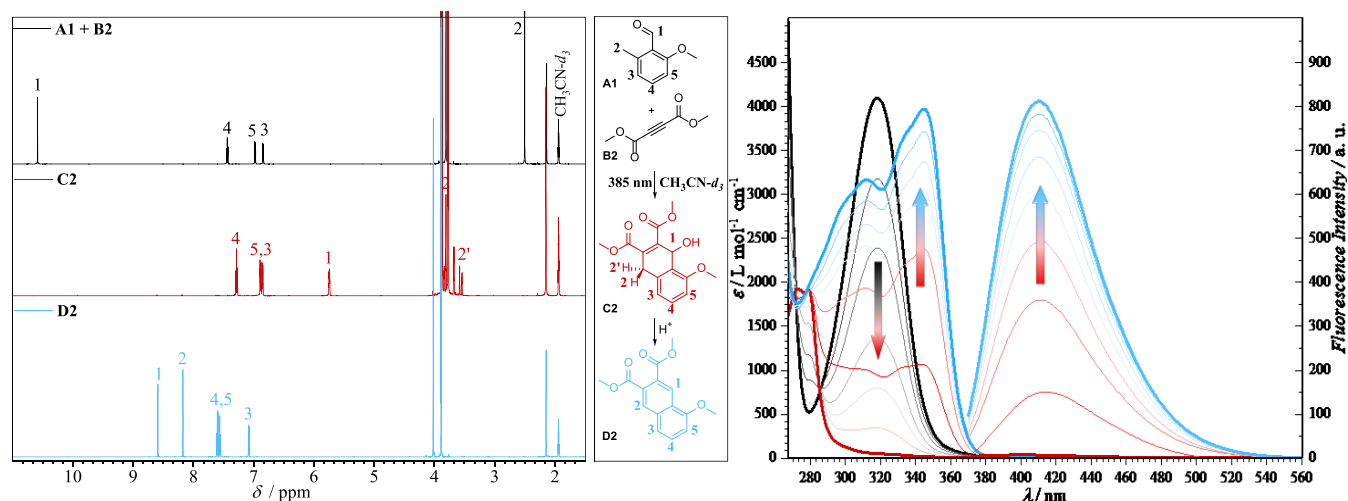
Figure 1. (left) ^{1}H NMR spectra of the reaction between *o*-MBA **A1** and **B2** to form cycloadduct **C2** under irradiation with 385 nm LED (LED-emission spectrum refer to Supporting Information Figure S69) and E1 elimination to **D2** with assigned resonances. (right) UV−vis absorption and fluorescence emission spectra of the reaction mixture (black line), after up to 20 min of irradiation with 385 nm in the quartz cuvette (black to red line) and after addition of 10 mmol % *p*-TsOH and up to 12 min (red to blue line). For detailed analytical information for all compounds depicted in Figure 1 refer to Supporting Information, Figures S25, S26, S29, S30, S57, and S67.

frequently used in synthesis, for instance, to obtain 3-aroylchromones, benzo[*e*]pyrene bisimides, and anthracene diimides using a vast excess of alkynes, strong acids, aprotic solvents, and elevated temperatures.[19−21] Therefore, all the above-mentioned reactions are of limited use for the synthesis of advanced macromolecular architectures including acid- or heat-sensitive structures, in particular, bioconjugates. Bioorthogonal reactions require an exceptional level of chemical selectivity and mild reaction conditions resulting in minimal interference with existing functional groups in biomolecules.[24] Furthermore, no heterobifunctional (nonsymmetric) alkyne substrates have been reported for this reaction, rendering the synthesis of modular linker molecules unexplored. To overcome the limitations described above, we exploit the high driving force toward aromatization of 1,4-dihydro-1-naphtholes (DHNPs). We establish which substrates allow for efficient reaction under mild reaction conditions at concentrations suitable for polymer postfunctionalization or bioligation (0.5 to 50 mmol L^{−1}). Furthermore, we established synthesis strategies for heterobifunctional alkyne linkers. Initially, *o*-MBA (**A1**,[25] 1.00 equiv, 50 mmol L^{−1}) and the electron-deficient acetylenedicarboxylic acid dimethylester (DMAD, **B2**, 1.05 equiv, 52.5 mmol L^{−1}) are irradiated with a 385 nm light-emitting diode (LED) in deuterated acetonitrile (ACN) after deoxygenation. The formation of the intermediate DHNP (**C2**) was observed via ^{1}H NMR spectroscopy (Figure 1). Upon exposure to air, and therefore formation of carbonic acid by absorption of CO_2, the naphthalene **D2** was formed quantitatively within 4 h via E1 elimination. Additionally, the conversion was directly followed by the disappearance of the UV−vis n-π^* band at 320 nm of *o*-MBA and the appearance of a new absorption band at 280 nm associated with the formation of **C2**. After on-demand elimination a new n-π^* band at 345 nm and a fluorescence band at 420 nm was observed, corresponding to **D2**. The absorption spectra impressively show that the intermediate **C2** does not interfere with the photoreaction, as its absorption is shifted to shorter wavelengths. As the stability of **C2** was limited in acetonitrile due to the extremely rapid elimination, ^{13}C and two-dimensional (2D) NMR spectra were recorded in C_6D_6,

where **C2** was observed to be stable (see Supporting Information, Figures S25 and S26). The substrate scope for the reaction was investigated using *o*-MBAs **A1** and **A2**, which exhibit distinctive absorption and reactivity, and can be readily functionalized.[7] Alkynes **B1**−**B5** and diynes **B6** and **B7** are model substrates, and functional analogues can be synthesized using different strategies. Terminal alkynes similar to methyl propiolate **B1** and phenylalkynes similar to **B3** can be readily prepared using propiolic acid or phenylpropiolic acid as precursors, respectively. The synthesis of functional analogues of DMAD (**B2**) is considerably more difficult.[25] 4-Oxo-2-butynoates **B4** and **B5** are readily accessible via Cu(I)-mediated sp-sp[2] coupling of acid halides and propiolates.[26,27] Symmetric and nonsymmetric diynes **B6** and **B7** can be synthesized via different sp-sp coupling reactions and rearrangements.[28] Hay coupling appeared most attractive, as it proceeds in the absence of reactive organometallic compounds.[29] The synthesis and characterization of **A2** and **B4**−**B7** is described in the Supporting Information (Sections 2.2 and 2.3). In Scheme 2, the observed reaction products are depicted and summarized in Table 1.

Scheme 2. Light-induced Reaction Pathways[a]
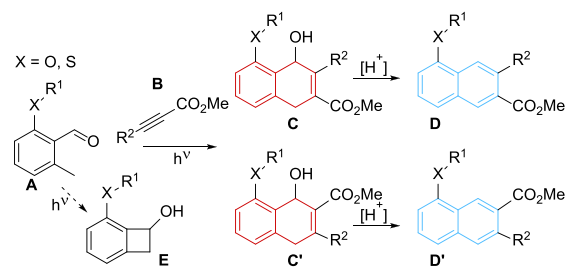
[a]Light-induced reaction pathways of *o*-MBAs **A** in the presence of electron-deficient alkynes **B** to form 1,4-dihydro-1-naphtholes **C** via Diels−Alder reaction or 1-hydroxybenzocyclobutanes **E** via [4π] electrocyclization. 1,4-Dihydro-1-naphtholes **C** can be converted quantitatively to napthalenes **D** with catalytic amounts of acid.

Table 1. Batch Photoligation Experiments[a]

| No.	o-MBA	alkyne	solvent	t [min]	D/E	Y^D	D/D'
1	A1	B1	ACN	20	32:68	25%	100:0
2	A1	B1	toluene	15	76:24	71%	100:0
3	A1	B2	ACN	20	n.d.	96%	
4	A1	B2	toluene	15	n.d.	97%	
5	A2	B1	toluene	30	5:95		100:0
6	A2	B2	ACN	30	13:87		
7	A2	B2	toluene	30	91:9	89%	
8	A1	B3	toluene	30		0%	
9	A1	B4	ACN	30	n.d.	98%	70:30
10	A1	B4	toluene	20	n.d.	97%	65:35
11	A1	B5	ACN	20	n.d.	95%	92:8
12	A1	B5	toluene	15	n.d.	96%	87:13
13	A2	B4	ACN	40	97:3	94%[b]	66:34
14	A2	B4	toluene	20	99:1	96%[b]	54:46
15	A2	B5	ACN	40	n.d.	94%[b]	93:7
16	A2	B5	toluene	20	n.d.	86%[b]	76:24
17	A1	B6	toluene	30	n.d.	96%	99:1
18	A1	B7	toluene	30	55:45	49%	n.d.

[a]Batch photoligation experiments using o-MBAs A1, A2 (5 mmol L^{-1}, 1.00 equiv) and alkynes B1−B5 (5.5 mmol L^{-1}, 1.10 equiv) or diynes B6 and B7 (5.5 mmol L^{-1}, 1.10 equiv), irradiation time (t), Y^D isolated yield. D/E: ratio of the desired Diels-Alder adduct vs the 4π electrocyclization (refer to Scheme 2). D/D' ratio of regioisomers. n.d. not determined. [b]Combined yield after regioisomer separation.

If an alkyne with reduced reactivity is present, a fraction of o-MBA A is converted to benzocyclobutane E upon irradiation. This side reaction was previously described when we studied the photoinduced [4 + 4] cycloaddition of o-MBAs.[30]

Importantly, the ratio of Diels−Alder product C/C' and 4π electrocyclization product E is concentration-dependent (unimolecular vs bimolecular reaction). Furthermore, regioisomers C/C' or D/D' can be formed in the case of nonsymmetric alkynes.

The experiments summarized in Table 1 were conducted in a batch reactor (Scheme 3; setup described in Supporting

Scheme 3. Overview[a]
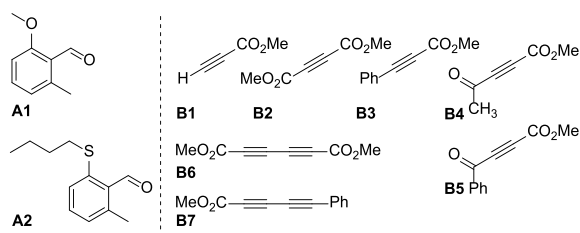
[a]Overview of the o-MBAs A1, A2, and the alkynes B1−B7 utilized in the batch reactions.

Information Figure S1) to facilitate isolation and characterization via NMR spectroscopy and liquid chromatography-mass spectrometry (LCMS) (Supporting Information Figures S27−S66). The two solvents acetonitrile and toluene were chosen to determine the influence of the dipole moment on the reaction. By comparing entries 1 and 2 or 6 and 7, it can be concluded that the ligation reactions of both o-MBAs with alkynes is more efficient in toluene. The more electron-rich B3 and to a lesser extent B1 exhibit low reactivity and therefore result in the formation of benzocyclobutanes (see entries 1, 2, 5, and 8). The same result can be observed comparing diynes

B6 and B7 (entries 17 and 18). o-MBA A1 is more reactive than o-MBA A2 resulting in a lower extent of benzocyclobutane formation (comparison of entries 3 and 6). In general, 4-oxo-2-butynoates B4 and B5 showed the highest reactivity, and no 4π-electrocyclization was observed as a result. The regioselectivity (ratio of C/C' and D/D') is influenced by the steric hindrance and the electronic properties. For the substrate combination A2 and B4 as well as A2 and B5, the resulting products D8, D8', D9, and D9' were separated, and their structures were elucidated via 2D NMR spectroscopy. In addition, the reaction quantum yields for the reaction of A1, A2, and B4 were determined employing a monochromatic light source (refer to Supporting Information, Figures S87−S90); whereas A1 shows a minor dependence on the solvent dipole moment ($\Phi_{R,ACN}$: 0.68 ± 0.02 vs $\Phi_{R,toluene}$: 0.78 ± 0.03), the reaction quantum yield of A2 is highly solvent-dependent ($\Phi_{R,ACN}$: 0.011 ± 0.001 vs $\Phi_{R,toluene}$: 0.14 ± 0.01).

Most fluorophores depicted in Figure 2 do not have structural analogues reported in literature, and therefore the
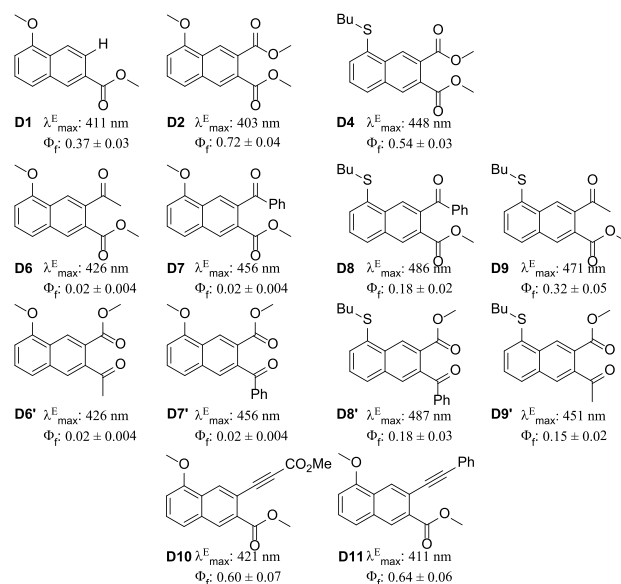

Figure 2. Isolated products from the photoligation experiments summarized in Table 1, including fluorescence emission maxima and fluorescence quantum yields.

fluorescence quantum yields were determined (refer to Supporting Information Figure S71). The emission wavelength of the naphthyl thioethers is, in general, higher than for their naphthylether analogues (for the fluorescence spectra of D1−D11 see Supporting Information, Figures S72−S82). In addition, the photostability of the formed fluorophores was studied. D1, D2, D7, and D10 were irradiated under conditions similar to the photoligation (5 mmol L^{-1}, ACN-d_3, 385 nm LED, and 365 nm LED, respectively; for NMR spectra see Supporting Information, Figures S51−S55). D1, D2, and D7 showed high photostability, whereas D10 was completely converted to various unknown products. This result underlines the advantage of the formation of a nonabsorbing intermediate during the photoreaction, avoiding subsequent reaction or photobleaching.

As reported earlier, o-MBA thioaldehydes such as A2 are performing reasonably well in protic solvents including solvent mixtures containing water.[7] The compatibility with aqueous solutions is crucial for applications involving biomolecules.

Surprisingly, we found that the reaction of **A2** in ACN/H_2O mixtures results in the decrease of 4π electrocyclization compared to pure acetonitrile (refer to Table 2), although

Table 2. Batch Photoligation Experiments[a]

No.	o-MBA	alkyne	λ_{max}[nm]	t [min]	$R^{D/E}$	Y^D	D/D′
1	A2	B2	385	150	98:2	95%	
2	A2	B2	415	360	86:14	75%	
3	A2	B4	415	360	100:0	98%	82:18

[a]Batch photoligation experiments in ACN/H_2O (75:25 v/v) using o-MBA **A2** (5 mmol L^{-1}, 1.00 equiv) and alkyne **B2** or **B4** (5.5 mmol L^{-1}, 1.10 equiv) LED irradiation wavelengths (λ_{max}), irradiation time (t), Y^D isolated yield. **D/E**: ratio of the desired Diels-Alder adduct vs the 4π electrocyclization (see Scheme 2). **D/D′** ratio of regioisomers.

longer reaction times were required, due to the previously reported decrease in the quantum yield of the photoreaction.[31] In addition, from the ACN/H_2O reaction mixture we performed the elimination reaction in a buffer solution at pH 4.2 and monitored the reaction progress via fluorescence spectroscopy (refer to Supporting Information Figure S8). The fact that the elimination takes place at ambient temperature in aqueous solution without the addition of a catalyst is especially important considering potential biological applications.

To use the herein-established reactions, it is essential to have access to functional alkyne linkers. Importantly, alkynoates are reactive toward many nucleophiles. Therefore, we designed two linkers (**L1** and **L2**, Scheme 4) that can be attached to

Scheme 4. Synthesized Linkers[a]
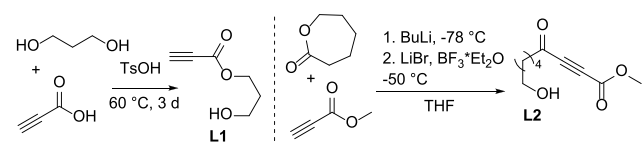
[a]Synthesized linkers **L1** and **L2** exhibiting terminal OH groups for further functionalization (for characterization see Supporting Information, Figures S17−S20).

substrates using well-established ligation methods, such as esterification. **L1** is prepared via esterification of propiolic acid, whereas **L2** is accessible by ring-opening of ε-caprolactone with methyl propiolate following a literature protocol.[32]

In conclusion, we pioneer a light-induced ligation system for o-MBAs that allows for gated fluorescence response. The self-reporting can be triggered quantitatively under very mild conditions, allowing for fluorometric evaluation of the ligation reaction. With the most suitable alkynoate substrates, we designed a linker molecule that can be attached to payload molecules and demonstrated that the reaction can be performed in aqueous media using visible light. We envisage that our technology platform will open new possibilities in biological applications and advanced material synthesis.

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Notes

The authors declare no competing financial interest.

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