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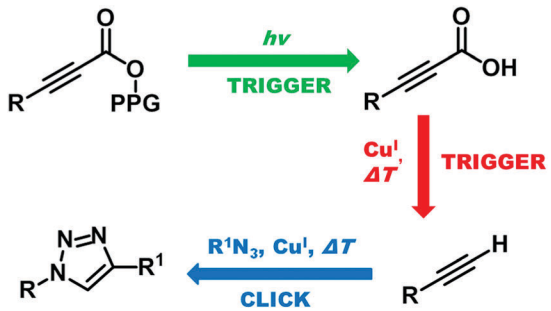

Controlled photorelease of alkynoic acids and their decarboxylative deprotection for copper-catalyzed azide/alkyne cycloaddition

Nikoleta Vohradská, Esther M. Sánchez-Carnerero, Tomáš Pastierik, Ctibor Mazal and Petr Klán*

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COMMUNICATION

Controlled photorelease of alkynoic acids and their decarboxylative deprotection for copper-catalyzed azide/alkyne cycloaddition†

Nikoleta Vohradská, Esther M. Sánchez-Carnerero, Tomáš Pastierik, Ctibor Mazal and Petr Klán *

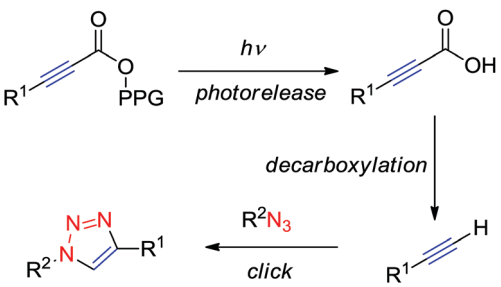
A controlled photorelease of alkynoic acids from the *meso*-methyl BODIPY photoremovable protecting group facilitates their subsequent efficient decarboxylation to give terminal alkynes for a Cu^{I}-catalyzed azide/alkyne cycloaddition. The quantum efficiencies of the photochemical step and the kinetics of the click reaction step are reported.

The 1,3-dipolar cycloaddition of azides and alkynes belongs to the family of "click chemistry" reactions,[1] popular methods to prepare bioconjugates.[2–5] Cu^{I}-catalyzed azide/alkyne cycloaddition (CuAAC) is the most common version of this technique.[6] The reactions of terminal alkynes are feasible under ambient or mild conditions; however, cycloadditions of an organic azide with a 2-alkynoate usually require elevated temperatures and/or long reaction times and exhibit lack of regioselectivity.[7–10] Only a few facile exceptions to the reaction, such as an intramolecular CuAAC[11] or cycloadditions of dimethyl acetylenedicarboxylate with ω-phosphorylalkyl azides in water,[12] were reported. The introduction of an alkoxycarbonyl or aryloxycarbonyl group at the end of terminal alkynes can thus be used for the protection of the triple bond against the azide cycloaddition under reaction conditions typically used in bioconjugation. Indeed, free 2-alkynoic acids react with organic azides upon decarboxylation with similar regioselectivity to that of the corresponding terminal alkynes.[13–17] Heating or a metal,[18] typically Cu^{I},[17] catalysis is usually required for a successful decarboxylation.[19,20]

The controlled release of molecules from photoremovable protecting groups (PPGs; caged groups) has the advantage in spatial and temporal delivery of a great variety of active reagents.[21,22] A significant amount of research effort has been invested in the development and applications of UV-light absorbing PPGs. However, PPGs absorbing chemically benign visible light are much more desired for any application.[22] Such systems have been reported only recently[23–28] because it is difficult to design compounds photoactivatable by a low-energy visible light.[22]

In this work, we introduce a tandem method for the protection of alkynoic acids which are photochemically released upon irradiation with visible light to undergo a subsequent click reaction with an organic azide upon a necessary decarboxylation step (Scheme 1). This method facilitates a chemically inert and spatially and temporally precise trigger for the liberation of alkynoates and their subsequent controlled decarboxylation to produce the corresponding click-reaction-active terminal alkynes.

Synthesis of *meso*-methyl BODIPY alkynoates **3a–3d**. To protect 2-alkynoic acid derivatives, we chose a *meso*-methyl BODIPY PPG, which is easy to prepare, absorbs in the visible part of the spectrum (unlike the protected alkynoic acid derivatives) and possesses a high uncaging cross-section.[27] The synthetic precursor, the *meso*-chloromethyl BODIPY derivative **1**, was prepared from chloroacetyl chloride and 2,4-dimethylpyrrole using a slightly modified procedure described in the literature (Scheme 2).[27,29] Subsequently, esters **3** were synthesized from **1** and the corresponding 2-alkynoic acids **2a–2d** *via* the Finkelstein reaction using a catalytic amount of NaI in the presence of



Scheme 1 Phototriggered release of alkynoates for their subsequent decarboxylation and click reactions.

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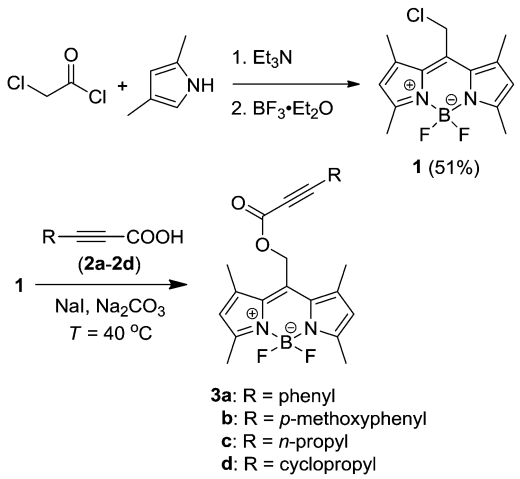
† Electronic supplementary information (ESI) available: Materials, methods, synthesis of the starting compounds, procedures for decarboxylation and click reactions, NMR and MS spectra, and kinetic data. See DOI: 10.1039/c8cc03341b



Scheme 2 Synthesis of BODIPY esters **3**.

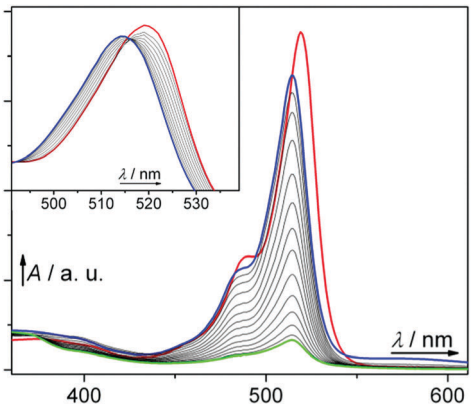


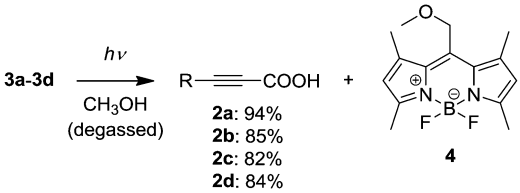
Fig. 1 Irradiation of **3a** in methanol at 525 nm for 13 h (red line: the initial spectrum; blue line: an intermediate formed in 10 min of irradiation (details of the spectra are shown in the inset); green line: the end spectrum after 13 h of irradiation).

Na_2CO_3 as a base in acetonitrile at 40 °C in 77–95% chemical yields (ESI†).

Photochemistry of BODIPY esters **3**. The photoreaction (Scheme 3) chemical yields and efficiencies were determined in both aerated and degassed methanol solutions. Upon irradiation of compounds **3a–3d** ($c \approx 1 \times 10^{-4}$ M) with green light (525 nm, LEDs) in degassed methanol (purging with argon), alkynoic acid derivatives **2** were released in high isolated yields (82–94%; Scheme 3). However, their production in aerated methanol reached only ≈50%. We originally hypothesized that singlet oxygen simultaneously produced by a BODIPY triplet state sensitization destroys the residual starting compound, although it was not observed in the case of the photochemistry of other *meso*-methyl BODIPY carboxylates.[27] In order to find the cause of these lower yields, phenylpropiolic acid (**2a**) was irradiated in the presence of a photochemically stable pentamethyl BODIPY derivative[30] in aerated methanol. However, acid **2a** was not consumed during photolysis. When an excess of phenylpropiolic acid (**2a**, $c = 5.2 \times 10^{-4}$ M) was added to a solution of **3a** ($c = 1.5 \times 10^{-4}$ M) in aerated methanol and the solution was irradiated at 525 nm, a significant portion (60%) of the total amount of **2a** was degraded (Fig. S18, ESI†). We concluded that one of the secondary reaction photoproducts must be responsible for the formation of a reactive intermediate that initiates a reaction involving the **2a** triple bond in the presence of oxygen. As a result, air oxygen was excluded from all further experiments.

The photoreaction progress of **3a** monitored by absorption spectroscopy is shown in Fig. 1. The major band of **3a** (λ_{max} = 519 nm) disappeared during irradiation in several minutes (Fig. 1, inset) to give propiolic acid **2a** and a methoxy-*meso*-methyl BODIPY (photosolvolysis) side-product **4** (Scheme 3; λ_{max} = 514 nm; see also Fig. S19 and S23 (ESI†) for its identification by HPLC and Fig. S24 (ESI†) for its absorption spectrum), observed upon irradiation of different *meso*-methyl BODIPY carboxylates in previous studies.[25,27] When **2a** was released, exhaustive irradiation (hours) of the mixture then led to the destruction of the BODIPY chromophore of **4** and to the disappearance of the absorption bands in the visible part of the spectrum (Fig. 1). The same behavior was observed for all other BODIPY derivatives **3b–d** (the corresponding spectra and chromatograms are shown in Fig. S19–S23, ESI†). The quantum yields of photodecomposition (Φ) of esters **3a–d** were found in the 2.10–0.13% range (Table 1) using a BODIPY-based actinometer (for details see the ESI†). The Φ values are comparable to those reported for other *meso*-methyl BODIPY carboxylates.[31] A lower Φ in the aerated sample is connected to the quenching of a BODIPY chromophore triplet state by oxygen to produce singlet oxygen,[27] which is, however, not substantially involved in the degradation of the starting esters **3** (see above). The differences in the Φ values apparently reflect the quality of the leaving groups[27] (aryl alkynoates are slightly better leaving groups than alkyl alkynoates).

The next step of our proposed tandem reaction sequence (Scheme 1) was the decarboxylation of a photochemically released alkynoic acid/alkynoate. The kinetics of the



Scheme 3 Photochemistry of BODIPY esters **3a–3d**.

Table 1 Photochemistry of BODIPY esters **3a–3d**

Compound	Conditions[a]	Φ_{decomp}/%[b]	ε_{max}[c]
3a	Deg	1.93 ± 0.38	67 000
3a	Aer	0.43 ± 0.02	
3b	Deg	2.10 ± 0.20	36 300
3c	Deg	0.13 ± 0.01	44 700
3d	Deg	1.09 ± 0.24	50 000

[a] In degassed (deg) or aerated (aer) methanol. [b] Determined by irradiation at 507 nm (see the ESI for details). [c] The molar absorption coefficient, ε_{max}/(mol^{-1} dm^{-3} cm^{-1}).

decarboxylation of phenyl propiolic acid[32] as well as propiolic acid[33] and their Group 1 metal salts[34] at high temperature and pressure have already been studied. However, we were more interested in the examples of complex reactions involving the decarboxylation of 2-alkynoates to subsequently exploit the terminal alkynes, which have gained in popularity during the last decade.[19,20,35–37] The most related one was a three-component synthesis of triazoles from inorganic azides, aryl iodides and alkynoic acids first published by Kolarovic and coworkers.[17] This decarboxylation was carried out in the presence of $CuSO_4{\cdot}5H_2O$, ascorbate and K_2CO_3, and the overall reaction needed a rather long reaction time (20–24 h at 65 °C). The contribution of the decarboxylation step to the reaction time was not studied independently; however, in a previous study[38] of the decarboxylation itself, the best results (30 min at 60 °C) were obtained using a CuCl/TEA catalytic system. A subsequent modification of the three-component reaction found Cs_2CO_3[39] to be superior to triethylamine in the CuI/Na ascorbate/base catalytic system to give the reaction yields up to 90%. When CuI and Cs_2CO_3 were used in a decarboxylative cross-coupling of alkynoates with aryl halides, the reaction again needed a long reaction time (12–24 h), even at a higher temperature (130 °C).[35] Because we expected concentration limitations for the photorelease reaction, we decided to test different reagent mixtures and conditions for both the Cu^I-activated decarboxylation and cycloaddition steps.

The decarboxylation of alkynoic acids using a CuI/ascorbate/Cs_2CO_3 system was successful but $CuSO_4$ instead of CuI was eventually chosen for its better solubility in methanol (Scheme 4). The optimized (Table S1, ESI†) conditions (**2**, c_2 = 0.14 M/$CuSO_4{\cdot}5H_2O$/ascorbate/Cs_2CO_3, 1:1:1.2:0.5 equiv.; 60 °C; a slight excess of ascorbate prevents the formation of oxidative homocoupling products[40]) led to nearly quantitative yields of terminal alkynes **5**, whose chemical yields were determined by their trapping with benzyl azide in the next step (see below). The full conversion of the decarboxylation step was achieved in much shorter (≈10 min; Table S1, ESI†)[17,38] or similar[41] experimental times when compared to those reported before. Finally, the kinetic data of the reaction of **2a** under those conditions were fitted with the second-order kinetics (k = 6.4 × 10^{-3} M^{-1} s^{-1}; Fig. S17, ESI†). The second-order kinetics are consistent with the mechanism involving outer-sphere electron transfer observed, for example, in the case of the oxidative decarboxylation of Cu^{II} complexes of aminomalonic acid.[42]

The same (optimized; Table S1, ESI†) experimental conditions found for the decarboxylation of **2** were tested for the subsequent azide–alkyne Huisgen cycloaddition: acids **2a–d** were decarboxylated to give alkynes **5** (without isolation) which were *in situ* trapped by benzyl azide present in the reaction mixture from the beginning. Thus, the reactions of alkynoic acid **2** (c_2 = 0.14 M) and 1.1 equiv. of benzyl azide in a $CuSO_4{\cdot}5H_2O$/ascorbate/Cs_2CO_3 (1:1:1.2:0.75 equiv.) mixture in methanol at 60 °C were carried out. Triazoles **6a–d** were formed in high isolated chemical yields (83–97%; ESI†) after ≈30 min. Although we assumed that the preceding decarboxylation step is necessary for the successful subsequent click process,[7–10] we tested the azide–alkyne cycloaddition starting with the methyl ester of phenylpropiolic acid under the same conditions used in our click chemistry experiments to prove this assumption. No product was formed even upon a prolonged reaction time (4 h). Thus, we conclude that in the transformation of **2** into **6**, the decarboxylation step precedes the click cycloaddition reaction.

Finally, we tested a one-pot arrangement of the overall tandem procedure illustrated in Scheme 1. Methanol solutions of a BODIPY ester (**3a–d**; $c \approx 10^{-3}$ M) were degassed by a freeze–pump–thaw method in a round-bottom flask which rotated to form a thin film of the liquid (see the ESI†), analogous to the method reported recently by George and coworkers.[43] This method allows for shorter irradiation times by reducing the internal filter effect of solutes, such as BODIPY chromophores that possess high molar absorption coefficients. The solutions were subsequently irradiated using white light (LEDs) until the complete conversion of the starting material was achieved to give products **2a–d** in 79–88% chemical yields (Table 2). In the next step, methanol was removed under reduced pressure and a $CuSO_4{\cdot}5H_2O$/ascorbate/Cs_2CO_3/benzyl azide (1:1:2:0.75:1.2 equiv.) system in methanol was added to obtain the same relative reactant concentrations as those under the optimized conditions described in the previous paragraphs. The reaction mixtures were heated at 60 °C for 2 h, and the final chemical yields of triazoles **6a–d** in three steps of the tandem process were 75–84% (Table 2).

In conclusion, we report a tandem procedure for the controlled photorelease of the protected 2-alkynoic acids that decarboxylate to terminal alkynes which subsequently undergo an *in situ* (click chemistry) Cu^I-catalyzed azide/alkyne cycloaddition to give the corresponding 1,2,3-triazoles. The BODIPY-protected 2-alkynoates thus represent photocaged terminal alkynes that can be released by irradiation with visible light to facilitate a ''click reaction'' with organic azides.

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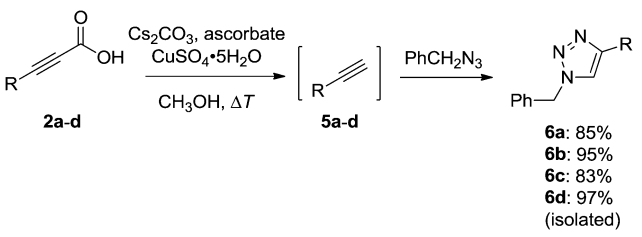

Scheme 4 Decarboxylation and CuAAC steps.

Table 2 One-pot synthesis of **6a–d** from **3a–d**

Starting compound	Yield of **2**/%[a]	Overall yield of **6**/%[b]
3a	88	84
3b	86	79
3c	81	78
3d	79	75

[a] Yields of acids **2** determined by HPLC. [b] Yields of triazoles **6** in three reaction steps determined by HPLC.

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Conflicts of interest

There are no conflicts to declare.

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