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Photochemical Formation of Dibenzosilacyclohept-4-yne for Cu-Free Click Chemistry with Azides and 1,2,4,5-Tetrazines

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Supporting Information

ABSTRACT: Photochemical generation of dibenzosilacyclohept-4-yne **3** from the corresponding cyclopropenone **1** and its copper-free click reactions are reported. Steady-state irradiation, kinetic, and transient absorption spectroscopy studies revealed that strained alkyne **3** is rapidly (<5 ns) and efficiently (Φ = 0.58−0.71) photoreleased from **1** and undergoes remarkably fast, selective, and high-yielding 1,3-dipolar cycloaddition with benzyl azide (~20 M^{-1} s^{-1}) or [4 + 2] inverse-electron-demand Diels−Alder reaction with 1,2,4,5-tetrazines (~260 M^{-1} s^{-1}) in both methanol and acetonitrile.

Angle-strained cycloalkynes are important molecular motifs for click chemistry.[1] Their high reactivity due to the ring strain allows for their efficient copper-free click chemistry via facile 1,3-dipolar cycloaddition[2] with various substrates, for example, azides or tetrazines.[1a] When such reactions occur in biological systems and do not interfere with native biochemical processes, they are termed bioorthogonal reactions.[1a,3] However, the rates of these cycloadditions are generally lower than those of Cu-catalyzed processes.[4]

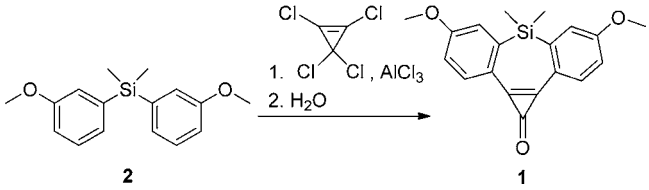
To increase the rates of strain-promoted cycloadditions, structural modifications to the cycloalkyne scaffold have been explored, including efforts for the preparation of highly strained cycloheptynes.[5] The demand for reasonably stable but still reactive cycloalkynes resulted in the development of temporary protection of the triple bond by its complexation with Cu(I) salts[6] or octacarbonyldicobalt.[7]

Popik and co-workers, who combined rapid photorelease of the triple bond of dibenzocyclooctynes from cyclopropenones via clean and efficient decarbonylation with a subsequent Cu-free click reaction, demonstrated an elegant solution to spatial and temporal control of the reactivity of cycloalkynes.[8] Bertozzi and co-workers studied photorelease of analogous dibenzoselenacycloheptynes and their in situ trapping with benzyl azide.[9]

Here we present the click chemistry of a highly strained seven-membered dibenzosilacyclohept-4-yne derivative, photogenerated from the corresponding cyclopropenone, with benzyl azide and 1,2,4,5-tetrazines. The mechanism and kinetics of the reaction steps were evaluated by steady-state and transient absorption spectroscopy experiments.

The 4-silabicyclo[5.1.0]octatrienone derivative **1** was prepared using a procedure analogous to that employed for the synthesis of a 4-selenabicyclo[5.1.0]octatrienone derivative by Bertozzi and co-workers[9] (Scheme 1). The first step involved a coupling of two 3-bromoanisole molecules using *n*-butyllithium and dichlorodimethylsilane to give dimethyldiphenylsilane **2**. Two consecutive Friedel−Crafts alkylation reactions of **2** with

Scheme 1. Synthesis of Cyclopropenone 1



commercially available tetrachlorocyclopropene in the presence of a Lewis acid and subsequent in situ hydrolysis afforded strained cyclopropenone derivative **1** in an overall chemical yield of 30%.

The absorption spectra of **1** in methanol and acetonitrile possess two intense close-lying absorption bands (in methanol: λ_{max} = 337 and 354 nm, $\varepsilon \approx 2.6 \times 10^4$ mol^{-1} dm^3 cm^{-1}, Figure S13; in acetonitrile: λ_{max} = 336 and 353 nm, $\varepsilon \approx 1.8 \times 10^4$ mol^{-1} dm^3 cm^{-1}, Figure S14), analogous to those of structurally similar bicyclo[6.1.0]nonatrien-9-one derivatives.[8a] Compound **1** is only weakly fluorescent (λ_{max} = 387 nm in methanol; Figure S13); the quantum yield of fluorescence was below 0.01. We found that **1** in both solutions undergoes partial but still significant (<20%) photochemical degradation during the acquisition of the spectra; therefore, only three scans of freshly prepared samples were averaged to obtain the final spectrum.

Upon irradiation at 375 nm, efficient photodecarbonylation of **1** was observed in both methanol (Φ = 0.58 ± 0.01) and acetonitrile (Φ = 0.71 ± 0.01) to give silacycloheptyne **3** (Scheme 2). This compound exhibits two distinct bands (in methanol: λ_{max} = 315 and 334 nm; in acetonitrile: λ_{max} = 316 and 335 nm) in its absorption spectra (Figure S15), analogous to those of cyclooctyne derivatives.[8a]

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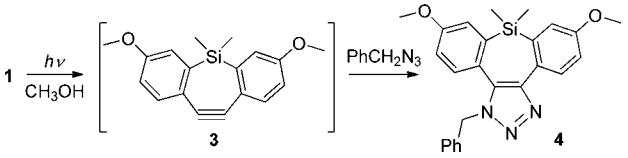
Scheme 2. Formation of Intermediate 3 and Its Reaction with Benzyl Azide



Transient absorption spectra were obtained with **1** in methanol (c = 6.5 × 10^{-4} M) in 100 fs steps up to a 180 ps delay after the pump pulse (λ_{exc} = 250 nm; Figure S23). Fitting with two single-exponential functions (the A → B and C → D model) using global analysis gave the spectra of three species (B does not absorb in the study range; Figures 1 and S24). The

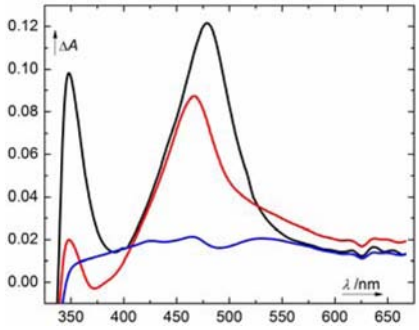


Figure 1. Transient absorption spectra of the singlet excited state of **1** (black line; A) and the singlet (red line; C) and triplet excited states of **3** (blue line; D) obtained by photolysis of **1** in methanol. The spectra were determined by global analysis of the data set using two single-exponential kinetic equations.

assignment of these spectra was based on comparison with those obtained by laser flash photolysis of several 2,3-disubstituted cyclopropenones studied by Poloukhtine and Popik.[8b] The spectrum of a species formed immediately after excitation (A) possesses two maxima at 348 and 480 nm (Figure 1, black line) and is attributed to the singlet excited state of **1** with a lifetime of (1.50 ± 0.03) ps (Figure S24). The second transient absorption spectrum (C) has a maximum at 465 nm and a lifetime of (28.99 ± 0.39) ps (Figure S24), and the species is assigned to the singlet excited state of the photoproduct alkyne **3** (Figure 1, red line), which is converted to its triplet state (D), characterized by an almost featureless broad signal in the range of 350−500 nm (Figure 1, blue line) with a lifetime exceeding 1.5 ns (the longest time delay of our pump−probe setup). The same kinetics and transient absorption spectra of C and D were obtained for **3** initially generated by steady-state photolysis of **1** in methanol (c = 6.5 × 10^{-4} M) at 375 nm to complete conversion. Because of the exceptionally fast photolysis of **1**, the alkyne **3** formed in the flow cell was most probably excited by the pump pulse used for the excitation of **1**. We could not avoid direct excitation of **3** even at the highest achievable flow rate of the solution through our flow cell. Our measurements thus indicate that photochemical decarbonylation of **1** is complete on a time scale similar to that reported for other cyclopropenones.[8b] In addition, our nanosecond flash photolysis measurements (for details, see the Supporting Information and Figures S25 and S26) confirmed that **3** is formed faster than the time resolution of the transient absorption setup (5 ns).

When a solution of cyclopropenone **1** (0.15 mmol) and benzyl azide (0.15 mmol) in methanol or acetonitrile was irradiated at 375 nm, a sole product, triazole derivative **4**, was isolated in excellent yields (93% and 97% in methanol and acetonitrile, respectively). The exclusive formation of the click product **4** was also observed during irradiation of **1** in methanol-d_4 using NMR spectroscopy (Figure S17). This indicates that the rates of 1,3-dipolar cycloaddition were significantly higher than those of any side reactions of alkyne **3** (second-order rate constants of (22.5 ± 0.7) and (15.8 ± 0.9) M^{-1} s^{-1} were obtained for methanol and acetonitrile, respectively; for more details, see the Supporting Information). The presence of air oxygen did not have any effect on the course of the reaction.

In addition, we studied the stability of **1** and its photo-triggered click process with benzyl azide in an aqueous solution (because of the limited solubility of **1** in water, we used a 1:1 (v/v) water/methanol mixture) to evaluate whether the reaction could also be carried out in biologically relevant aqueous media. Cyclopropenone **1** was found to be stable in this solution for 72 h in the dark, and the photochemical click process resulted in the formation of triazole **4** in 80% chemical yield.

Because relatively efficient hydrogen transfer from H-atom-donating compounds or solvents to some cycloheptynes has been reported,[9,10] posing a potential obstacle in any click reaction applications, we examined whether it plays any role in the case of **3**. Fortunately, we did not identify any products of hydrogen atom transfer from the solvents, benzyl azide, or even an excess of benzyl alcohol (20 molar equiv) added as a hydrogen atom donor to the solution of **3** on the time scale needed for click reaction completion.

Furthermore, as the irradiation wavelength (375 nm, Figure S18) overlaps slightly with an absorption tail of alkyne **3**, we tested its photostability. We found that **3** is slowly photochemically decomposed; however, as this process is several orders of magnitude slower than the corresponding cycloaddition reaction, it does not interfere with the click process. Upon extensive (72 h) irradiation of **1** in methanol (c = 3.0 × 10^{-2} M) at 375 nm, an orange solid precipitated. ^{1}H, ^{13}C, and 2D NMR as well as HRMS experiments suggested that the solid is composed of oligomeric compounds consisting of at least two parent subunits. On the other hand, the structures anticipated as the products of alkyne trimerization[11] or aryne insertion into the carbonyl bond,[12] reported for analogous compounds, were not observed in our case. We also attempted to trap **3** in situ with other dienes, such as furan and *N*-methyl-α-phenylnitrone. Unfortunately, both reactions resulted in complex mixtures of unidentified products.

Together with azides, tetrazines have also gained importance as versatile reagents for in vivo click labeling[13] because of their exceptionally fast [4 + 2] cycloadditions with strained alkenes and alkynes.[4] First, we attempted to trap silacycloheptyne **3**, formed in situ by photolysis of **1** (c_1 = 0.050 M) in chloroform, with 3,6-diphenyltetrazine **5a** (1 equiv) (Scheme 3). Pyridazine derivative **6a** was obtained in 84% yield via an inverse-electron-demand Diels−Alder reaction. Because of the limited solubility of **5a** in polar solvents such as methanol and acetonitrile, we chose to study the cyclization reaction of **3** (c_3 ≈ 0.050 M) with more soluble 3,6-dimethoxycarbonyltetrazine (**5b**) and 5-[4-(1,2,4,5-tetrazin-3-yl)benzylamino]-5-oxopentanoic acid (**5c**) (Scheme 3). Both reactions provided the anticipated pyridazine derivatives **6b** and **6c** in excellent isolated yields (92 and 93%,

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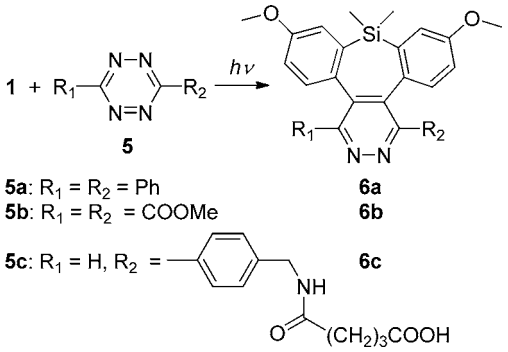
Scheme 3. Trapping of in Situ-Generated Silacycloheptyne 3 with Tetrazines 5



respectively). The rate constant for the reaction leading to pyridazine **6b** in acetonitrile was found to be (2.58 ± 0.15) × 10^2 M^{-1} s^{-1}.

Inverse-electron-demand cycloaddition reactions between strained alkynes and tetrazines, used also for chemoselective labeling of biomolecules, are usually much faster (10^1–10^5 M^{-1} s^{-1}) than strain-promoted alkyne–azide cycloadditions.[4,14] Indeed, the rate constant of the reaction of **3** with **5b** is 1 order of magnitude larger than that of an unsubstituted cyclooctyne with **5b**[14a] or that for the reaction between **3** and benzyl azide found in this work. Its reactivity toward tetrazines is comparable only to that of difluorocyclooctynes and bicyclononynes.[15] Interestingly, structurally similar dibenzocyclooctynes,[16] fluorocyclooctyne,[17] and probably tetramethylthiacycloheptyne[18] were reported to react only with azides but not with tetrazines.

For comparison, we carried out analogous photochemical trapping of **5a** with cycloalkynes photochemically generated from two recently reported cyclopropenones, bicyclo[6.1.0]-nonen-9-one derivative **7**[19] and 4-selenabicyclo[5.1.0]-octatrienone derivative **8**[9] (Figure 2). Surprisingly, even

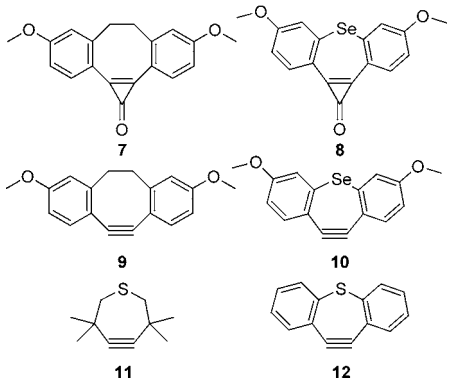


Figure 2. Cyclopropenones and strained cycloalkynes.

extensive irradiation (2 h) of an equimolar mixture of **7** and **5a** in chloroform at 375 nm did not lead to any cyclization product; only the formation of a stable alkyne **9** was observed (a structurally similar alkyne was reported to be sufficiently stable to be isolated from the solution),[8a] whereas the starting tetrazine remained unchanged in the solution (UV–vis and NMR) even when the reaction temperature was increased to 60 °C; therefore, **9** is not sufficiently reactive for the reaction with **5a**. No other photochemical side reactions were involved. In contrast, irradiation of **8** in the presence of **5a** under the same conditions gave a complex mixture of unidentified products; thus we did not investigate this reaction further. This is not a surprising result, as irradiation of a mixture of cyclopropenone **8** and benzyl azide in THF was reported to form **10**, which undergoes a hydrogen atom transfer from a poor H-atom-donor (the solvent) rather than cycloaddition.[9] This side reaction had to be suppressed by introducing the *o*-methyl groups in diaryl cycloalkyne **10** to shield the reactive triple bond.[9] Hydrogen abstraction reactions of strained cycloalkynes from H-atom-donating substrates, such as thiols or alkanols,[10] can be connected with a partial biradical character of the triple bond.[9] For example, the half-lives of **11** in an excess of benzyl alcohol or methanol are <3 min or 3.4 h, respectively.[20] The fact that cycloheptyne **3** showed no tendency to abstract hydrogen from good hydrogen donors can be related to the presence of an electropositive dimethylsila group in the ring compared to the more electronegative S and Se atoms in **10** and **11**.

Handling unstable cycloheptynes as reactants for click reactions is difficult because of their high reactivity in solutions;[5c,d] however, their controlled photorelease from cyclopropenone precursors in situ[8] overcomes such limitations. Inspired by the work of Bertozzi and co-workers on photorelease of seven-membered selenacycloheptyne **10** from **8**,[9] we chose to investigate the analogous silacyclohept-4-yne derivative **3** photoliberated from its precursor **1** for this work. There are not many literature reports available describing the synthesis of silacycloheptyne derivatives.[21] A thermal generation of 1,1-dimethylsilacyclohept-4-yne and its in situ trapping by cyclopenta-2,4-dienone was reported in the 1970s,[22] and the authors mentioned that the compound is fairly stable in diluted dichloromethane solutions (~100 h). The atomic radius of silicon is only slightly smaller than that of selenium, and thus, the ring strain in **3** is expected to be similar to that in **10** but certainly higher than that of eight-membered dibenzocyclooctyne. Although an aliphatic analogue, tetramethylthiacycloheptyne (**11**), is a stable and isolable molecule,[5c,20] two fused phenyl rings in the cycloheptyne significantly increase the strain, making dibenzothiacycloheptyne (**12**) a highly reactive molecule.[23] Therefore, we were not surprised that the second-order rate constant of the reaction of **3** with benzyl azide in methanol (22.5 M^{-1} s^{-1}) is nearly 300 times higher than that of substituted dibenzocyclooctyne in the same solvent (7.6 × 10^{-2} M^{-1} s^{-1})[8a] and even of thiacycloheptyne derivative **11** (4.0 M^{-1} s^{-1}, in acetonitrile),[5c] but it is comparable to those of oxadibenzocyclooctynes (2–45 M^{-1} s^{-1})[24] and 1 order of magnitude lower than that of a pyrrolocyclooctyne derivative (>400 M^{-1} s^{-1}).[25] Our alkyne **3** thus exhibits one of the fastest reported noncatalyzed cycloalkyne–azide click reactions, with rate constants that are comparable to those of common Cu-catalyzed alkyne–azide cycloadditions.[4]

We have shown that strained and reactive dibenzosilacyclohept-4-yne **3**, photogenerated from the corresponding cyclopropenone **1**, undergoes remarkably rapid and selective Cu-free click reactions with azides and 1,2,4,5-tetrazines in both methanol and acetonitrile. A well-balanced combination of reactivity and stability of **3** even in aqueous solutions is an important attribute for its successful click reaction applications, and we suggest that this system could be used for bioorthogonal in vivo labeling.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02367.

Materials, methods, synthesis, spectra, and kinetic data (PDF)

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Notes

The authors declare no competing financial interest.

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