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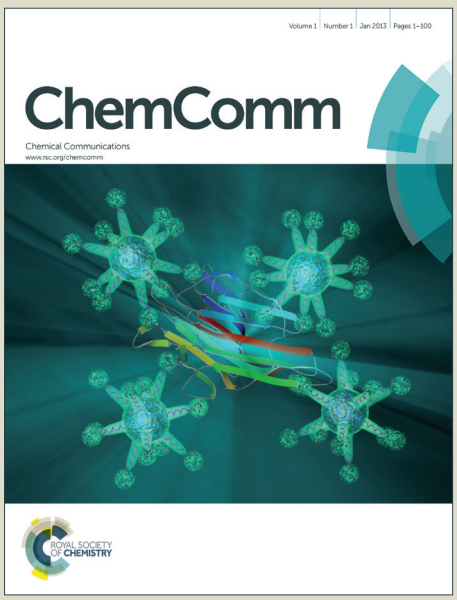





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# COMMUNICATION

# From Slow to Fast – the User Controls the Rate of the Release of Molecules From Masked Forms Using a Photoswitch and Different Types of Light

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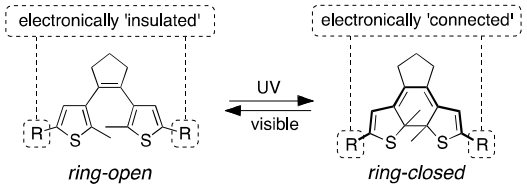
**Exposure to UV light generates a ring-closed isomer of a diarylethene, which undergoes very slow bond breaking and release even after the light is turned off. The rate of release is increased by exposing the isomer to UV and/or visible light.**

Of the many approaches to control where and when a reaction happens, the use of light as the 'on-off trigger' offers distinct advantages. It can be precisely and quickly tuned to induce photochemistry based on its colour and the absorption properties of the photoresponsive chromophore. It can also be just as quickly removed to halt processes induced by light. This explains why light has a rich history as the stimulus to release molecules from 'caged'-compounds where masked forms of biologically relevant species can be transformed into active ones.[1] Our interests in this area include developing systems where the light only has to be on for a short period of time, and then a release reaction continues even after the light is turned off. This is very different from both currently employed photorelease strategies and photodynamic therapy, where continuous exposure to light is required.

Our approach takes advantage of the dithienylethene framework, which is a robust and versatile platform used to develop molecular switching systems. Molecules based on this backbone undergo reversible cyclization reactions when exposed to appropriate wavelengths of light (Scheme 1) and toggle between two isomers exhibiting distinct optoelectronic properties.[2] The ring-open isomers have their π-conjugation localized at the two heterocycles. On the other hand, there is extended π-conjugation running along the molecule's backbone in the ring-closed version (shown in bold in the scheme), which explains why these isomers tend to be coloured. The consequences of this structural change are not only optoelectronic in nature. While the groups attached to the C-5 position of the heterocycles (labeled 'R' in Scheme 1) are electronically 'insulated' from each other in the ring-open isomer, they can 'sense' the presence of each other in the ring-closed analogues (they are electronically connected). This difference is responsible for how the 'R' groups act as molecular magnets, nucleophiles and electro-active components.[3]

In the recent years, we have reported several examples of how photoresponsive dithienylethenes can be used to regulate chemical and biochemical reactivity by controlling Bergman[4] and Diels-Alder cyclization reactions,[5] modulating the reactivity of transition metal catalysts[6] and Lewis acids,[7] triggering epimerization reactions of an amino acid in a biomimetic approach,[8] and regulating enzyme inhibition.[9] All of these examples take advantage of the fact that the ring-closing reaction results in a substantial rearrangement of both the double bonds in the molecular backbone and its steric constraints.

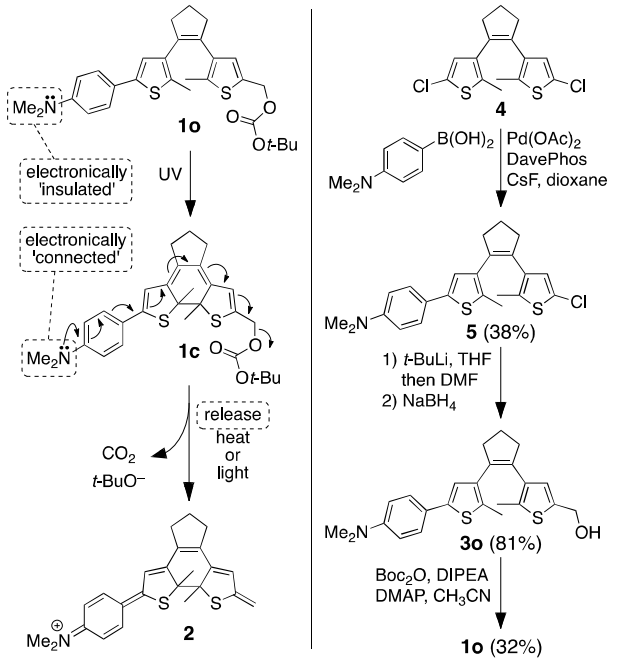



**Scheme 1.** The reversible light-induced cyclization reaction of the dithienylethene backbone between two isomers that have different electronic connectivity between the two arms.

In this report, we describe how the communication of the substituents on the two thiophene rings can be used to regulate specific bond-breaking reactions and release small molecules from 'masked' forms. Our approach is illustrated in Scheme 2. Molecule **1o** possesses an amine substituent on one of the thiophene rings and a carbonate on the opposing heterocycle. As mentioned previously, they should be electronically insulated from each other and the molecule should be immune to spontaneous breakdown. UV-induced ring-closing creates a pathway in isomer **1c** for the amine's lone-pair electrons to 'push' into the conjugated backbone, promoting spontaneous fragmentation of the carbonate, releasing *tert*-butylcarbonate anion and producing the cationic, quinoidal structure **2**.[10] The effectiveness of an amine's lone-pair electrons to fragment carbonates through a π-conjugated system has been reported previously, although these systems do not use light as the trigger.[11] The appeal of our system is that the ring-closing reactions of dithienylethenes tends to be very fast (picosecond),[12] which implies that the light only has to be 'on' for a very short period of time. Even after it is removed, the spontaneous release will continue.

Scheme 2 also illustrates how photoresponsive compound **1o** is prepared, which involves selectively reacting the known dichloride **4** to make a non-symmetric amine (**5**).[13,‡] The alcohol **3o** is a key intermediate in this synthesis and will be used as a control to assess the photochemistry of the carbonate **1o**. The photoresponsive behaviours of carbonate **1o** and alcohol **3o** are

best assessed using UV-vis absorption spectroscopy (Fig 1) as is typically done for photochromic dithienylethenes. When a wet $CH_3CN$ (5% v/v $H_2O$)[ψ] solution of **1o** (20 μM) is exposed to UV light (365 nm),[φ] there is an immediate decrease in the intensity of the high-energy absorption bands between 250 and 350 nm and the appearance of a broad band in the visible region centred at 500 nm (Fig 1a), which explains the colour change of the solution from colourless to red as the ring-closed isomer (**1c**) is generated. These absorption spectra are almost identical to those for the alcohol in both its ring-open (**3o**) and ring-closed (**3c**) forms,[‡] which can be expected considering the carbonate should have a minimal effect on the optical nature of the chromophore.




**Scheme 2.** Spontaneous release is feasible only from the ring-closed isomer (left) of the photoresponsive compound (**1c**). The synthesis of the key photoreactive carbonate **1o** is shown on the right.

This change in absorbance profile under UV irradiation correlates with the appearance of a new set of resonances in the $^1$H-NMR spectrum that demonstrate the formation of the ring-closed dithienylethene isomer (**1c**). According to the $^1$H NMR spectra, a photostationary state is reached after 700 s at this concentration[δ] and contains 80% of the ring-closed isomer.[‡] A similar photostationary state (82% **3c**) is reached when the alcohol (**3o**) is subjected to similar conditions. This is where the similarities between **1o** and **3o** end. While the ring-closed isomer of the alcohol is stable both in the dark and upon continuous exposure to UV light, **1c** is not and the spectrum starts to change even after the light is turned off. In fact, small bands appear as shoulders between (550 and 650 nm) during the first 70 seconds of exposure of the 20 μM solution to UV light when generating the photostationary state (Fig 1a). These bands (centred at 570 nm) are not present in the spectrum of **3o/c** and grow steadily over the next few hours (Fig 1b) and a deep purple solution is produced. The new, more intense, lower-energy bands also have a distinct vibronic structure. We attribute this spectrum to the production of the cationic, quinoidal structure **2**, owing to its larger dipole moment, smaller HOMO-LUMO gap and the rigid, fused polycyclic skeleton of its π-system.

The kinetics of the release reaction (**1o** → **1c** → **2**) are best monitored in a buffered solution (15% v/v mixture of 105 mM Tris buffer (pH 6.5) in $CH_3CN$). This precaution can be rationalized in two ways: (1) the reaction starts from a neutral compound (**1o** or **1c**) and produces an ion pair implying that the ionic strength of the medium will increase as the reaction proceeds, and (2) subsequent decarboxylation will consume protons from the solvent, which will effectively raise the pH of the solution as the reaction progresses and may affect the reaction if proton-transfer has a role in the rate-determining step. Under these conditions, the increase in the intensity of the bands centered at 570 nm stops after about 12 hours at which time they start to decrease again. This is likely due to the trapping of the cationic, quinoid **2** by water or another nucleophile in the system. Using a sequential first-order reaction model (the fit is shown by the line in Fig 1c),[‡] the rate of release can be estimated to be $k_1 = (2.7 \pm 0.02) \times 10^{-3}$ s$^{-1}$, which corresponds to a half-life of 257 seconds. The second reaction is five times slower $k_2 = (5.3 \pm 0.02) \times 10^{-4}$ s$^{-1}$ corresponding to a half-life of 1308 seconds.

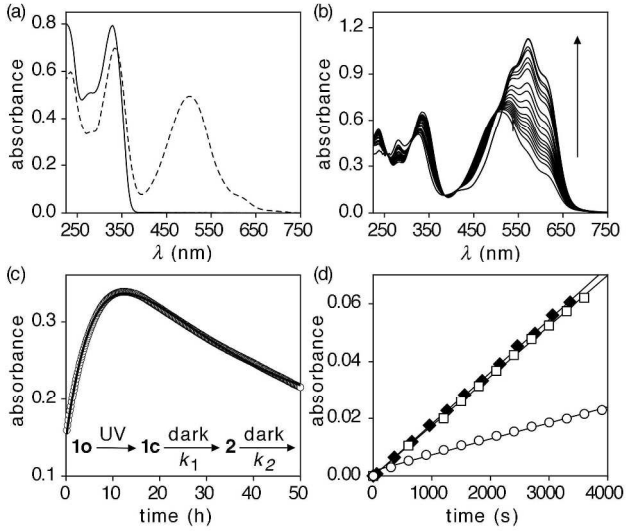



**Fig 1.** (a) UV-vis absorption spectra of a wet $CH_3CN$ solution (5% v/v $H_2O$) of **1o** (20 μM) before (solid line) and after (broken line) irradiation with 365 nm light for 70 s. (b) Changes in the UV-vis absorption spectra when a similar solution is irradiated for 135 s and then stored in the dark for 20 hours. (c) Changes in the absorption intensity at 570 nm of a 20 μM buffered solution of **1o** (15% v/v mixture of 105 mM tris buffer (pH 6.5) in $CH_3CN$) after it is irradiated with 365 nm light for 70 s and then stored in the dark for 50 h. (d) Changes in the absorption intensities at 650 nm of wet $CH_3CN$ solutions (5% v/v $H_2O$) of **1o** (20 μM) after they are irradiated with 365 nm light for 70 s and then stored in the dark (○), exposed to 342 nm light (□) and exposed to visible light (495 nm) (◆). The last two light sources were generated using a monochromator with a 2 nm slit width.

Unlike the ring-closed isomer of the alcohol (**3c**), the analogous isomer for the carbonate (**1c**) does not undergo ring-opening when exposed to visible light. Whereas **3c** can be quantitatively converted back to **3o** by irradiation of a solution containing the photostationary state mixture with light of wavelengths greater than 434 nm,[β] solutions containing **1c** behave exactly as they did when they were stored in the dark. The same bands between 550 and 650 nm appeared in the spectrum indicating that ring-opening (**1c** → **1o**) does not compete with the

spontaneous release (**1c** → **2**). Not only does ring-opening not compete with release, exposure to visible light also promotes the release reaction. This can be demonstrated by comparing the increase in the intensity of the absorbance at 650 nm when wet $CH_3CN$ solutions (5% v/v $H_2O$) of **1o** are irradiated with 365 nm light for 70 seconds to produce their photostationary states and then either kept in the dark or exposed to monochromatic light at 495 nm.[ω] The initial rate of increase in intensity for the sample exposed to visible light ($3.5 \times 10^{-6}$) is three times greater than that for the 'dark' sample ($1.2 \times 10^{-6}$) as shown in Fig 1d. UV light has the same effect and an identical solution of **1c** when exposed to monochromatic 342 nm light had almost the same initial rate ($3.6 \times 10^{-6}$). The use of long-wavelength visible light to trigger the release of carbonates, carboxylates and phosphates from chromophores has been described,[14] The release from our carbonate (**1o**) occurs at a similar energy.

Unfortunately, the chemical species responsible for producing the deep purple solution when the photostationary state of **1o/c** underwent the release process (either in the dark or in the presence of UV or visible light) proved troublesome to characterize. The product of the reaction of this chromophore with solvent (presumably water) is even more elusive. The release of *tert*-butoxy carbonate could be established using $^1$H NMR spectroscopy as shown in Fig 2 and the Supporting Information. When a solution of carbonate **1o** (~7 mM) in $CD_3CN$ (5% v/v $D_2O$) was simultaneously irradiated with 365 nm and light of wavelengths greater than 434 nm,[η] the signal corresponding to the *tert*-butyl $CH_3$ protons in **1o** (1.41 ppm) decreases and a new singlet at $\delta = 1.16$ ppm matching that of the rapidly-formed free *tert*-butanol appears in 60% yield (as calculated by comparison with the integration of *p*-nitroanisole as an internal standard).‡

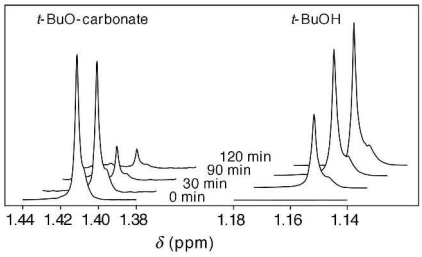



**Fig 2.** Partial $^1$H NMR spectra showing the production of *tert*-butanol with concurrent consumption of the *tert*-butyl carbonate when a solution of **1o** (6.65 mM in 5 v/v % $D_2O/CD_3CN$ / 600 MHz) is simultaneously exposed to 365 nm and light of wavelengths greater that 434 nm.

What is surprising is the fact that no other new signals, including any corresponding to the dithienylethene framework appear in the $^1$H spectrum of the resulting purple photolysis mixture. In fact, the signals corresponding to the carbonate **1o** simply disappear as the reaction progresses. Because our proposed mechanism of release involves the cationic, quinoidal structure **2**, we attempted to characterize it by isolating it from the photolysis mixture by ion-exchange precipitation. The involvement of either radical or polymer species was ruled out due to the EPR silence of the photolysis mixture and the absence of any precipitate upon addition of water. A deep purple solid does form, however, when a bulk photolysis reaction mixture is added drop wise into a vigorously stirred solution containing an excess of ammonium hexafluorophosphate.[π] This fine precipitate could be isolated by centrifugation and purified by repeated re-suspension/centrifugation in hexanes and deionized water in turn.‡ The resulting solid (to which we assign the structure **2•PF$_6$**) is soluble in polar, non-nucleophilic solvents such as acetonitrile, dichloromethane, chloroform and tetrahydrofuran, and forms a deep purple solution in each case. The UV-vis absorption spectra of these solutions are the same as that of the photolysis mixture (Fig 3a shows an example). We ascribe the slope in the baseline to underlying scattering, which may be indicative of the formation of aggregates and help explain the poorly resolved $^1$H NMR spectrum.

The $^1$H NMR spectrum of a very dilute $CD_3CN$ solution (400 μM) of this purple solid shows some signals that are consistent with the postulated structure for **2•PF$_6$** (Fig 3b). The pair of coupled doublets centered on $\delta = 7.54$ ppm and $\delta = 7.29$ ppm are consistent with the presence of a *para*-disubstituted benzene ring ($H_a$ and $H_b$), while the singlet at $\delta = 6.60$ ppm corresponds to one of the alkene backbone protons (either $H_c$ or $H_d$), and the pair of doublets at $\delta = 4.25$ ppm and $\delta = 4.21$ ppm (the former of which seems to exhibit a small coupling constant consistent with a long-range coupling) are indicative of the *exo*-methylene substituent produced upon expulsion of the leaving group ($H_e$ and $H_f$). The two chemically distinct triplets at $\delta = 3.05$ ppm and $\delta = 3.01$ ppm are consistent with the chemically in-equivalent allylic methylene groups of the cyclopentene backbone ($H_g$ and $H_h$), and the singlet at $\delta = 3.59$ ppm corresponds to the *N*-methyl protons of the aniline ($H_j$). The poor signal-to-noise ratio, and the absences of the multiplet expected for the central methylene of the cyclopentene and the singlet of the second alkene backbone proton prevents complete assignment of the structure based on this $^1$H NMR spectrum (although broad, poorly resolved signals at 6.75 and 3.35 ppm may correspond to these protons). The $^{31}$P NMR and $^{19}$F spectra‡ contain the well-resolved heptet and doublet, respectively, corresponding to the $PF_6^-$ counter ion, with an observed $^1J(^{31}P\text{-}^{19}F)$ of 707 Hz as expected. High-resolution mass spectrometry (ESI-(+) mode) contains the molecular ion peak for the proposed cation at m/z = 392.1501.

As already mentioned, compound **2** was not the only elusive one in the release reaction studies. The species produced when the ring-closed isomer (**1c**) underwent its second, slower spontaneous reaction in the dark or by irradiation with UV and/or visible light (presumably through cationic, quinoid **2**) could not be isolated nor characterized. While we assumed that the reaction of **2** with water would produce the alcohol **3c**, we observed no evidence for this. Instead an uncharacterizable brown residue was obtained when the reaction mixture was evaporated to dryness. Quenching experiments using other nucleophiles proved equally fruitless. Any reaction of the purple photolysis product (**2**) with nucleophiles such as NaSEt, KCN, NaSPh, NaOEt, piperidine and water resulted in a reaction mixture containing no tractable products.

The changes in colour throughout the photorelease offer a convenient way to track the progress of the release reaction. The first, light-induced reaction (**1o** → **1c**) is accompanied by a colour change from colourless to red. This provides feedback to the user that the system is 'armed'. By monitoring the change in colour from red to purple, the user can assess and track the release reaction in 'real-time'.

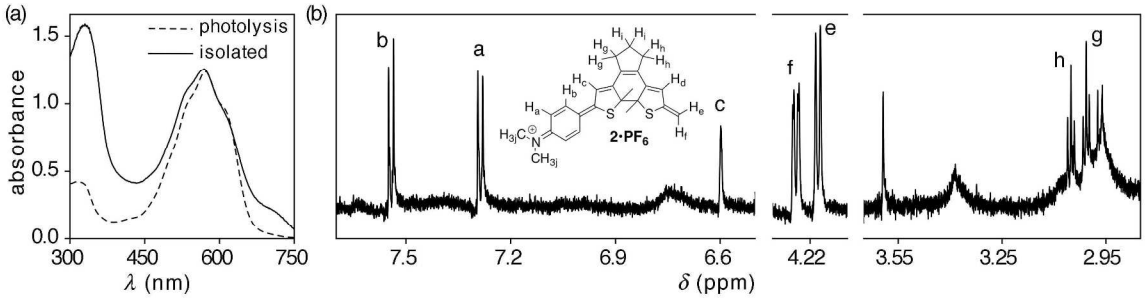



**Fig 3.** (a) Normalized UV-vis absorption spectra of a $CH_3CN$ solution of **2•PF$_6$** isolated from the bulk hydrolysis (solid line) and the spectrum that results when a wet $CH_3CN$ solution (5% v/v $H_2O$) of **1o** is irradiated with 365 nm light for 2200 s (dashed line). (b) $^1$H NMR spectrum ($CD_3CN$, 600 MHz) of **2•PF$_6$** isolated from the bulk hydrolysis after serial dilution to 400 μM. The three regions of the $^1$H NMR spectrum are not shown at the same scale.

Although the final products of the release-and-trapping reaction remain unclear, the analysis strongly suggests the presence of **2** as the key intermediate in the release reaction. Our photoresponsive compound has distinct advantages over other photo-release systems. Relatively brief exposure to UV light quickly and effectively produces a reactive 'armed' system, which undergoes slow but spontaneous fragmentation even in the absence of light. The increase in rate of release when exposed to UV and/or visible light offers a heightened level of control to the user, who can decide when and where the release process should be accelerated. The visible-light-induced photolysis of the ring-closed isomer (**1c**) represents an appealing starting point for the construction of viable visible-light activated cage compounds that harness low-energy visible light.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed descriptions of experimental methods, synthetic procedures, characterization of new compounds and additional absorption spectra. See DOI: 10.1039/b000000x/

‡ See ESI for details.

ψ Carbonate **1o** is not soluble in pure water. When solutions of **1o** in dry acetonitrile were exposed to UV light, ring-closed isomer **1c** was produced, however, the spontaneous release process was not observed. The addition of water is required to increase the static dielectric constant of the medium (see: L. G. Gagliardi, C. B. Castells, C. Rafols, M. Rosés, E. Bosch, *J. Chem. Eng. Data*, 2007, **52**, 1103–1107). Accordingly we suspect that the release of the ion pair is only spontaneous in a sufficiently polar medium.

ϕ Standard hand-held lamps used for visualizing TLC plates were used to carry out the ring-closing and photolysis reactions at 365 nm (1.4 mW/cm$^2$). Irradiation was carried out in low-light conditions to minimize interference from ambient light.

δ While the intensity of light from the UV light source used in the photolyis reactions under conditions suitable for UV-Vis and $^1$H NMR studies is constant, the concentration of carbonate is an order of magnitude higher for the latter studies so a sufficient signal-to-noise ratio is obtained. As a result, irradiation times for $^1$H NMR photolysis experiments are correspondingly longer than those for the UV-Vis absorption experiments.

β Visible light irradiation was carried out using the light of a 150-W tungsten source that was passed through a 434-nm cutoff filter to eliminate higher-energy light. Irradiation was carried out in low-light conditions to minimize interference from ambient light.

ω Irradiation with low-intensity light was generated using the source of a PTI Quantamaster Spectrofluorimeter with a 2 nm slit width.

η Both types of light were used as we have demonstrated the reaction to consume compound **1c** is promoted by visible light.

π The bulk photolysis was carried out on 35 mg of **1o** in 5% v/v degassed water/$CH_3CN$ using a 450 W mercury arc lamp.

(1) R. S. Givens, P. G. Conrad II, A. L. Yousef, J.-I. Lee, "Photoremovable Protecting Groups" in CRC handbook of organic photochemistry and photobiology 2nd Ed., (Eds.: W. M. Horspool, F. Lenci). CRC Press, Boca Raton 2004.

(2) (a) M. Irie *Chem. Rev.* 2000 **100**, 1685–1716. (b) H. Tian, S. J.Yang, *Chem. Soc. Rev.* 2004, **33**, 85–97. (c) C. Warford, V. Lemieux, N. Branda, in Molecular Switches 2nd Edition (Eds.: B. L. Feringa, W. R. Brown), Wiley-VCH, Weinheim, 2011.

(3) (a) L. Sun, H. Tian, *Tetrahedron Lett.* 2006, **47**, 9227–9231. (b) H. Samachetty, N. Branda, *Pure Appl. Chem.* 2006, **78**, 2351–2359. (c) B. Gorodetsky, N. Branda, *Adv. Func. Mater*. 2007, **17**, 786–796.

(4) D. Sud, T. Wigglesworth, N. R. Branda, *Angew. Chem. Int. Ed.* 2007, **46**, 8017–8019.

(5) (a) V. Lemieux, N. R. Branda, *Org. Lett.* 2005, **7**, 2969–2972. (b) V. Lemieux, S. Gauthier, N. R. Branda, *Angew. Chem. Int. Ed.* 2006, **45**, 6820–6824. (c) Z. Erno, A. M. Asadirad, V. Lemieux , N. R. Branda, *Org. Biomol. Chem.* 2012, **10**, 2787–2792.

(6) D. Sud, T. B. Norsten, N. R. Branda, *Angew. Chem. Int. Ed.* 2005, **44**, 2019–2021.

(7) V. Lemieux, M. D. Spantulescu, K. K. Baldridge, N. R. Branda, *Angew. Chem. Int. Ed.* 2008, **120**, 5112–5115.

(8) D. Wilson, N. R. Branda, *Angew. Chem. Int. Ed.* 2012, **51**, 5431–5434.

(9) D. Vomasta, C. Högner, N. R. Branda, B. König, *Angew. Chem. Int. Ed.* 2008, **47**, 7644–7647.

(10) Y. Pocker, B. L. Davison, T. L. Deits, *J. Am. Chem. Soc.* 1978, **100**, 3564–3567.

(11) F. M. H. de Groot, C. Albrecht, R. Koekkoek, P. H. Beusker, H. W. Scheeren, *Angew. Chem. Int. Ed.* 2003, **42**, 4490–4494.

(12) H. Miyasaki, T. Nobuto, A. Itaya, N. Tamai, M. Irie, *Chem. Phys. Lett.* 1997 **269** 281–285.

(13) D. W. Old, J.P. Wolfe, S.L. Buchwald, *J. Am. Chem. Soc.* 1998**, 120**, 9722–9723.

(14) (a) Y. Chen, M.G. Steinmetz, *J. Org. Chem.* 2006, **71**, 6053–6060. (b) C. Bao, G. Fan, Q. Lin, B. Li, S. Cheng, Q. Huang, L. Zhu, *Org. Lett.* 2012, **14**, 572–575. (c) L. Fournier, I. Aujard, T. Le Saux, S. Maurin, S. Beaupierre, J-B. Baudin, L. Jullien, *Chem. Eur. J.* 2013, **19**, 17494–17507. (d) P. Šebej, J. Wintner, P. Muller, T. Slanina, J. Al Anshori, L.A.P. Antony, P. Klan, J. Wirz, *J. Org. Chem.* 2013, **78**, 1833–1843. (e) N. Umeda, H. Takahashi, M. Kamiya, T. Ueno, T. Komatsu, T. Terai, K. Hanaoka, T. Nagano, Y. Urano, *ACS Chem. Biol.* 2014, **9**, 2242–2246. (f) A. P. Gorka, R. R. Nani, J. Zhu, S. Mackem, M. J. Schnermann, *J. Am. Chem. Soc.* 2014, **136**, 14153–14159.

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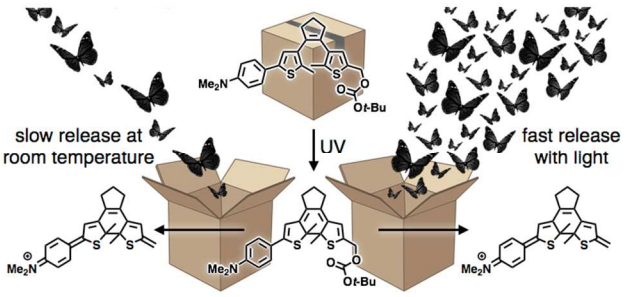


Light-gated release of a small molecule increases when exposed to UV or visible light.