Design and Synthesis of a Caged Carboxylic Acid with a Donor-π-Donor Coumarin Structure: One-photon and Two- photon Uncaging Reactions Using Visible and Near-Infrared Lights

Youhei Chitose, Manabu Abe, Ko Furukawa, Jhe-Yi Lin, Tzu-Chau Lin, Claudine Katan

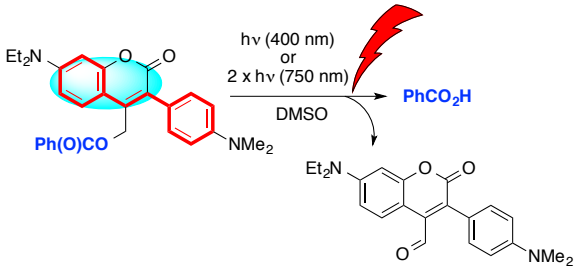
DOI: 10.1021/acs.orglett.7b00957 Org. Lett. 2017, 19, 2622–2625

Design and Synthesis of a Caged Carboxylic Acid with a Donor-π-Donor Coumarin Structure: One-photon and Two-photon Uncaging Reactions Using Visible and Near-Infrared Lights

Youhei Chitose[1], Manabu Abe*[1], Ko Furukawa[2], Jhe-Yi Lin ,[3] Tzu-Chau Lin,*[3] Claudine Katan*[4]

[1]*Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima, Hiroshima 739-8526, Japan.* [2]*Centre for Instrumental Analysis, Niigata University, 8050 Ikarashi 2-no-cho, Nishi-ku, Niigata 950-2181, Japan.* [3]*Photonic Materials Research Laboratory, Department of Chemistry, National Central University, Jhong-Li District, Taoyuan City 32001, Taiwan.* [4]*Institut des Sciences Chimiques de Rennes, UMR 6226, CNRS, Université Rennes 1, 35042 Rennes, France*

ABSTRACT: A caged carboxylic acid with a novel TP-responsive D(donor)-π-D coumarin backbone with a quadrupolar nature was designed and synthesized in this study. The newly synthesized coumarin derivative showed a strong one-photon (OP) absorption band (ε ~29000 cm^{-1} M^{-1}) in the visible region (> ~400 nm). Time-dependent density functional theory calculations predicted a sizable TP absorption cross-section with a maximum at ~650 nm significantly lager than that related to the OP absorption band. This is confirmed experimentally using TP excited fluorescence in the fs regime that leads to TPA cross-section of 18 GM and 5.6 GM at 680 nm and 760 nm, respectively. The OP photolysis (400 nm) and NIR-TP photolysis (750 nm) of the caged benzoic acid resulted in a clean formation of benzoic acid and an aldehyde.



Caged compounds, which are temporally inactivated forms of bioactive substances by photolabile-protecting groups (PPGs), are widely used in various studies to understand the behaviors of bioactive compounds.[1–4] The phototriggered release of bioactive molecules (drugs) without using any chemical reagents plays an important role in physiological studies.

Coumarin-based caged compounds (CM-drug) were developed by Givens and Matuszewski (Figure 1).[5] The fast release of bioactive compounds (drug) from the singlet excited state, ^{1}[CM-drug]*, is an advantage that allows their use in physiological studies.[6,7] However, coumarins exhibit absorption wavelength in the region 280–300 nm.[8,9] UV irradiation is needed to generate the excited state using one-photon (OP) excitation, causing cell damage. The unfavorable damage can be avoided by red-shifting the absorption maximum to the visible-light region. This has been achieved by the introduction of electron-donating and/or withdrawing substituents at the C5–C8 positions.[10–12]

Two-photon (TP) excitation processes using light in the near-infrared (NIR) region, 650–1050 nm, are advantageous for physiological studies, because deep penetration and a high spatial resolution can be achieved.[13–16] The development of new NIR-TP-responsive chromophores is currently a state-of-the-art challenge. Several π-extended coumarin derivatives with TP absorption (TPA) character have been synthesized.[17–22] Furuta *et al.* developed a TP-responsive (6-bromo-7-hydroxycoumarin-4yl)methyl (Bhc) group (Figure 1),[17] which has a TP uncaging efficiency (δ_u) of ~1 GM at 740 nm ($\delta_u = \sigma_2$

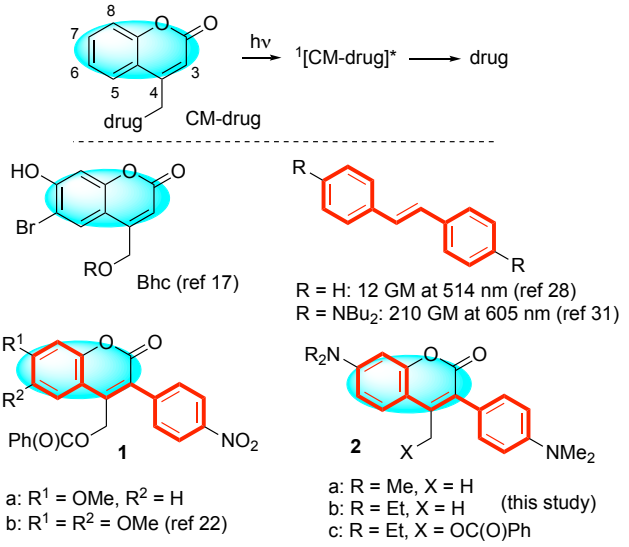


Figure 1. Photochemical uncaging reaction. Coumarin-based Chromophores with TPA character.

× ϕ_u, where σ_2 is the TPA cross-section (GM)[23] and ϕ_u is the uncaging quantum yield). A higher TP efficiency would be better for physiological studies.[24]

So far, we have designed and synthesized TP chromophores with a stilbene core as the platform,[25–27] because stilbene itself has a relatively large TPA cross-section, 12 GM at 514 nm, despite a small π conjugation system.[28] Donor (D)–acceptor (A) π-conjugated[29] coumarin derivatives **1** (Figure 1) showed TP-induced uncaging in the NIR region, in which an electron-withdrawing group was introduced at the C3 position.[22] However, low quantum yields of 0.09 and 0.03 were observed for the uncaging reactions of **1a** and **1b**, respectively, decreasing the efficiency of the TP-induced uncaging reactions.

This paper describes the synthesis and reactivity of a novel D-π-D conjugated coumarin-based caged compound **2** (Figure 1), in which the D-substitution at the C3 position was achieved for the first time. The D-π-D structural motifs were reported to significantly enhance the TPA character in stilbene cores because of a large change in quadrupole moment during the electronic excitation process.[30,31] For example, 4,4′-bis(di-*n*-butylamino)-*E*-stilbene was reported to exhibit a large TP cross-section of 210 GM at 605 nm (Figure 1). Such a high TP cross-section due to the D-π-D structural motif is worthy of application in caged compounds. The D-π-D structural motif by introducing the donating substituent at the C3 position has not been applied so far to coumarin-4ylmethyl type of caged compounds.

First, the OP absorption (OPA) and TPA spectra of a coumarin derivative **2a** were predicted using density functional theory (DFT) and time-dependent (TD) DFT approaches (Figure 2). The computational details are provided in Supporting Information. The predicted first absorption maximum of 7-dimethylamino-substituted coumarin (S_0 ➔ S_1 transition) is slightly blue-shifted compared to its D-π-A analogue **1a** (Figure S19)[22]. As expected for a D-π-D chromophores, a large TPA cross-section (of ca. 700 GM at this level of theory, see discussion on the supporting information for more details) was found for **2a** near 650 nm, corresponding to the S_0 ➔ S_2 electronic transition. Such a larger TPA cross-section of the second electronic transition (S_0 ➔ S_2) as compared to that of the first electronic transition (S_0 ➔ S_1) is similar to the one reported on 4,4′-bis(di-*n*-butylamino)-*E*-stilbene[31]. These computational predictions inspired us to synthesize caged benzoic acid **2c**, in which the OPA should occur in the visible region whereas TP uncaging should be possible using excitation in the NIR region.

7-(Diethylamino)-3-(4-(dimethylamino)phenyl)-4-methyl-2*H*-chromen-2-one (**2b**) with a D-π-D π-conjugated coumarin chromophore was synthesized as shown in Scheme 1. Bromination of commercially available 7-diethylamino-substituted coumarin **3** gave compound **4**;[21] subsequent coupling with the pinacol ester of 4-dimethylaminophenyl boronic acid afforded **2b**. Consistently with the TD-DFT prediction, compound **2b** showed a first OPA band with an absorption maximum at 386 nm (ε = 28861 cm^{-1} M^{-1}) in DMSO (Figure S11).

The TPA spectrum of compound **2b** (1.0 × 10^{-4} M) was measured using the TP excitation fluorescence method in toluene, even though the dynamic tuning range of our laser system for the measurements is limited over 680-nm excitation wavelength (Figure 3). As predicted by the TD-DFT calculations (Figure 2), the TPA cross-section of the second electronic transition (S_0 ➔ S_2, < 680 nm) was much larger than that of the first electronic transition (S_0 ➔ S_1, ~760 nm), i.e., 5.6 GM at 760 nm and 18 GM at 680 nm.

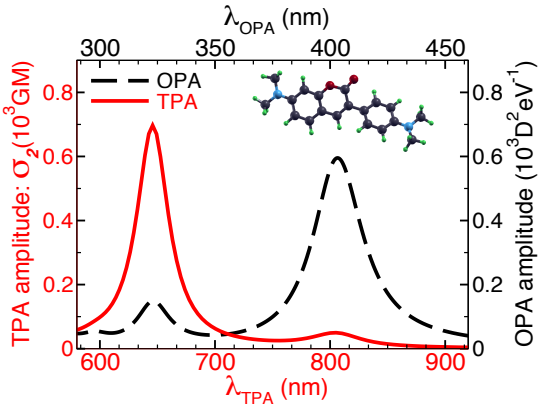
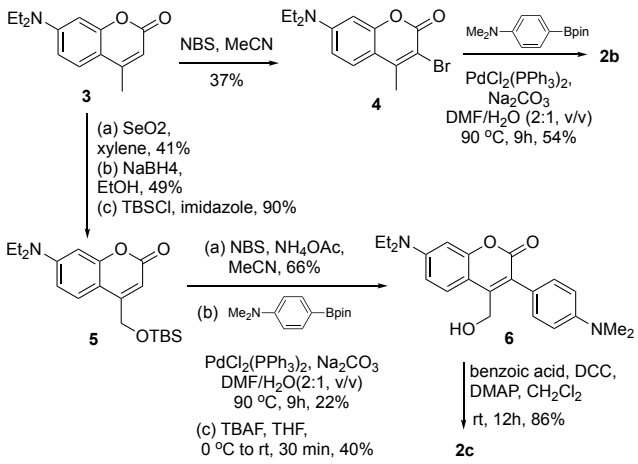


Figure 2. Computed OPA (right-hand axis) and TPA (left-hand axis) spectra at the TD-B3LYP/6-31G(d)//B3LYP/6-31G(d) level of theory for a coumarin derivative **2a**, in vacuum and using a damping factor of 0.10 eV to simulate the finite linewidth in the resonant spectra.

Scheme 1. Synthesis of compound **2b** and **2c**.



Compound **2c** was also synthesized from compound **3** (Scheme 1). After the oxidation of **3** with SeO_2 and pro- tection of the alcohol, the rigid D-π-D stilbene structure was prepared by introducing the electron-donating group at the C3 position using the coupling of the bromide with the commercially available pinacol ester of 4-dimethylaminophenyl boronic acid. The corresponding 4- hydroxy methyl derivative **6** was synthesized by deprotection. Caged benzoic acid **2c** was obtained by condensation with benzoic acid in a high yield (86%). The UV–visible absorption spectrum of compound **2c** showed the maximum absorption at 407 nm (ε_{407nm} = 28493 M^{-1} cm^{-1}) in DMSO (Figure S14).

DOI: 10.1021/acs.orglett.7b00957 Org. Lett. 2017, 19, 2622–2625

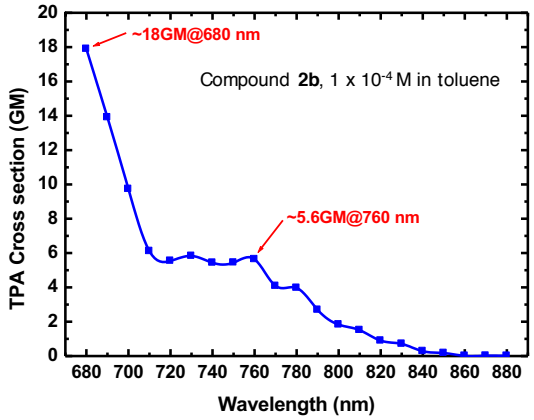
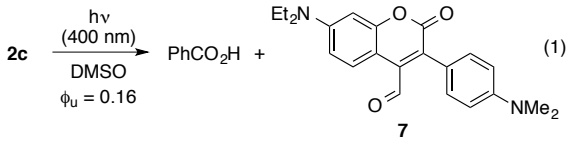


Figure 3. TPA spectrum, 680–880 nm, of compound **2b** (1.0 × 10^{-4} M) in toluene.

The OP photolysis of compound **2c** was conducted using a Xe lamp at 400 ± 10 nm in DMSO-d_6 (1.8 mM), resulting in the quantitative uncaging of benzoic acid (Eq. 1, Figure 4). The quantum yield (ϕ_u) was determined to be 0.16. After 2-h irradiation, the photoproduct 4- carboxaldehyde coumarin **7** was isolated in 70% yield along with benzoic acid (~95%). The formation of an aldehyde was observed for the first time in related uncaging reactions using coumarin derivatives. The clean photochemical transformation of **2c** was also confirmed by analysis of UV–visible absorption spectra (Figure 5). Thus, aldehyde **7** with λ_{max} = 482 nm (ε 23178 cm^{-1} M^{-1}) was observed with a concomitant decay of the band of **2c** with λ_{max} 407 nm.



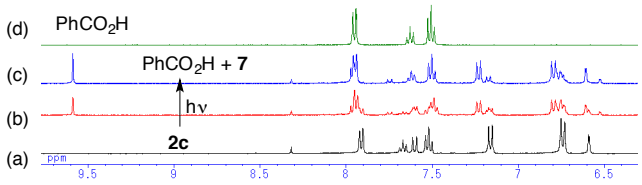


Figure 4. OP uncaging reaction of compound **2c** at 400 ± 10 nm in DMSO-d_6; (a) ^{1}HNMR spectrum of compound **2c** in DMSO-d_6 before the irradiation; (b) after 1-h photolysis using 400 nm (b); after 2-h photolysis; (c) ^{1}HNMR spectrum of benzoic acid in DMSO-d_6.

The effect of solvent on the OP photolysis of compound **2c** was investigated using methanol, DMSO with 5% Tris buffer, and DMSO with 5% distilled water (Figure 6). The uncaging reaction rates of coumarin-4ylmethyl type caged compounds were reported to be fast in the presence of water in solvents.[18] Interestingly, the uncaging reaction of **2c** in methanol was slower than the reaction in anhydrous or wet DMSO (5% tris buffer) by a factor of 1.6 (Figure 6). However, the reaction rate of uncaging of **2c** in wet DMSO (5% water) was slightly faster than anhydrous DMSO by a factor of 1.2 (Figure 6). 4-Hydroxymethyl derivative **6** was isolated in 76% isolated yield in wet DMSO in place of aldehyde **7** in anhydrous DMSO (Scheme 2). The formation of photoproducts clearly suggests that carbocation **8** is generated in the photochemical reaction, which is trapped by DMSO or H_2O, affording aldehyde **7** or alcohol **6** (Scheme 2).[6] The significantly short lifetime of ^{1}**2c*** fluorescence (577 ps in DMSO) in comparison with ^{1}**2b*** (3.1 ns, Figures S12,S13) supports the fast release of benzoic acid from ^{1}**2c*** (Figures S15, S16).

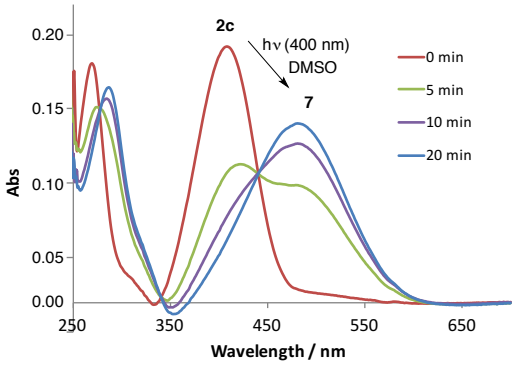


Figure 5. UV–visible spectroscopic analysis of OP uncaging reaction of caged benzoate **2c** at 400 ± 10 nm irradiation in DMSO.

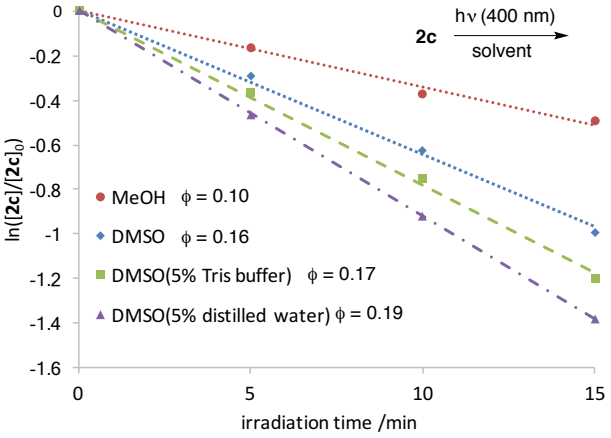


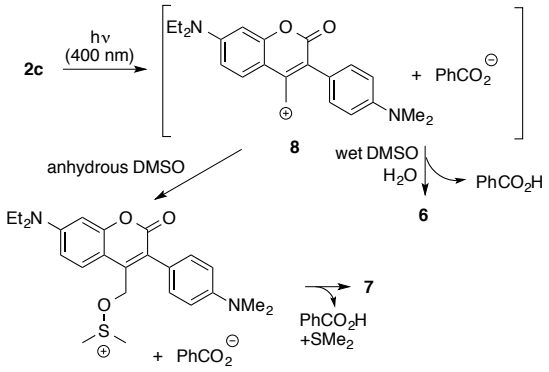
Figure 6. Time profile of the OP uncaging of compound **2c**, ln[**2c**]/[**2c**]$_o$ vs. irradiation time (min) at a wavelength of 400 nm using a Xe lamp in various solvents.

Finally, the TP photolysis of compound **2c** (5 × 10^{-2} mM) was carried out in DMSO using 750-nm light obtained from a Ti:sapphire laser (pulse width 100 fs, 80 MHz) at an average power of 700 mW (Figure S17). The TP-uncaging reaction of **2c** was observed at 750 nm, and the uncaging rate was determined to be k_{750} = 1.9 × 10^{-6} s^{-1}. The TPA cross-section of **2c** was extrapolated to ~7 GM at 750 nm by comparing the uncaging rate constant of 9.4 × 10^{-6} s^{-1} of the standard compound NPBF-BA (σ_2 = 54 GM and ϕ_u = 0.09)[26]. This TPA cross-section is consistent with the TPA spectrum recorded for **2b** (Figure 3). Although we cannot experimentally measure the TPA cross-section value of **2b** below 680 nm, due to the limitation of our laser setup, the cross-section at the maximum can be extrapolated from the computationally predicted cross-sections by using simple proportionality method as described in the SI. Therefore, the maximal TPA cross-section of compound **2c** can be estimated to reach ~100 GM around 650 nm. The corresponding TP uncaging efficiency was then estimated to be ~16 GM (= 100 x 0.16), which is one order of magnitude larger than that of related dipolar coumarin derivatives.

DOI: 10.1021/acs.orglett.7b00957 Org. Lett. 2017, 19, 2622–2625

In this study, a novel caged carboxylic acid with a TP-responsive D-π-D coumarin backbone was designed and synthesized. The newly synthesized D-π-D-substituted coumarin derivative showed a strong OPA band (ε~29000 cm^{-1} M^{-1}) in the visible region (> ~400 nm). TD-DFT calculations predicted that the TP excitation process of the second electronic transition is allowed, with a maximum of several hundreds of GM at ~650 nm. Meanwhile, the TPA cross-section of the first electronic transition close to 800 nm was predicted to be much smaller, as a result of the quadrupolar nature of the investigated compound. In fact, the experimental TPA cross-section at 680 nm was found three times larger (18 GM) than that recorded in the vicinity of twice the wavelength of the main OPA band (5.6 GM at 760 nm). The OP photolysis of **2c** with a D-π-D coumarin backbone in DMSO resulted in a clean formation of benzoic acid and an aldehyde **7**, hitherto unknown in coumarin-4yl methyl type uncaging reactions. The quantum yield of 0.16 was much higher than the D-π-A-substituted coumarin derivative. In the presence of H_2O, alcohol **6** was formed in place of the aldehyde, suggesting the generation of coumarin 4-ylmethyl cation **8** in the uncaging reaction. This new platform for the TP-induced uncaging reaction can be applied to future *in vivo* physiological studies.

Scheme 2. Mechanism for the uncaging reaction of **2c** in anhydrous DMSO and wet DMSO.



Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Computational and experimental details, ^1H and ^{13}C NMR spectra for new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

mabe@hiroshima-u.ac.jp
tclin@ncu.edu.tw
claudine.katan@univ-rennes1.fr

ACKNOWLEDGMENT

NMR and MS measurements were performed at N-BARD, Hiroshima University. M.A. gratefully acknowledges the financial support by a Grant- in-Aid for Science Research on Innovative Areas “Stimuli-responsive Chemical Species (No. 2408)” (JSPS KAKENHI Grant No. JP24109008) and JP17H0302200. TCL acknowledges the financial support from the Ministry of Science and Technology (MOST), Taiwan (Grant No. MOST 105-2113-M-008-004). C.K. acknowledges the HPC resources of CINES and IDRIS under the allocations 2016-[x2016080649] made by GENCI.

REFERENCES

(1) In *Dynamic Studies in Biology*, Eds. Goeldner, M.; Givens, R., Wiley-VCH, 2005.
(2) Engels, J.; Schlager, E.-J. *J. Med. Chem.* **1977**, *20*, 907-911.
(3) Kaplan, H.; Forbush, B.; Hpffmann, J. F. *Biochemistry*, **1978**, *17*, 1929-1935.
(4) Klán, P.; Šolomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. *Chem. Rev.* **2013**, *113*, 119-191.
(5) (a) Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984**, *106*, 6860-6861. (b) Kamatham, N.; Mendes, D. C.; Da Silva, J. P.; Givens, R. S.; Ramamurthy, V. *Org. Lett.* **2016**, *18*, 5480-5483.
(6) Schmidt, R.; Geissler, D.; Hagen, V.; Bendig, J. *J. Phys. Chem. A*, **2007**, *111*, 5768-5774.
(7) Atta, S.; Jana, A.; Ananthakirshnan, R.; Dhuleep, P. S. N. *J. Agric. Food Chem.* **2010**, *58*, 11844-11851.
(8) Wheelock, C. E. *J. Am. Chem. Soc.* **1959**, *81*, 1348-1352.
(9) Jivaramonaikul, W.; Rashatasakhon, P.; Wanichwecharungruang, S. *Photochem. Photobiol. Sci.* **2010**, *9*, 1120-1125.
(10) Givens, R. S.; Rubina, M.; Wirz, J. *Photochem. Photobiol. Sci*. **2012**, *11*, 472-488.
(11) Li, J.; Zhang, C.-F.; Yang, S.-H.; Yang, W.-C.; Yang, G.-F. *Anal. Chem.* **2014**, *86*, 3037-3042.
(12) Furuta, T. In *Dynamic Studies in Biology*, Eds. Goeldner, M.; Givens, R., Wiley-VCH, **2005**, 29-55.
(13) Matsuzaki, M.; Ellis-Davies, G. C. R.; Nemoto, T.; Miyashita, Y.; Iino, M.; Kasai, H. *Nat. Neurosci*. **2001**, *4*, 1086.
(14) Ellis-Davies, G. C. R. *Nat Methods*. **2007**, *4*(8), 619–628.
(15) Brieke, C.; Rohrbach, F.; Gottschalk, A.; Mayer G.; Heckel, A. *Angew. Chem., Int. Ed.*, **2012**, *51*, 8446–8476
(16) Bort, G.; Gallavardin, T.; Ogden, D.; Dalko, P. I. *Angew. Chem. Int. Ed.* **2013**, *52*, 4526-4537.
(17) Furuta, T.; Wang, S. S.-H.; Dantzker, J. L.; Dore, T. M.; Bybee, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 1193-1200.
(18) Suzuki, A. Z.; Watanabe, T.; Kawamoto, M.; Nishiyama, K.; Yamashita, H.; Ishii, M.; Iwamura, M.; Furuta, T. *Org. Lett*., **2003**, *5*, 4867-4870
(19) Bao, C.; Fan, G.; Lin, Q.; Li, B.; Cheng, S.; Huang, Q.; Zhu, L. *Org. Lett.*, **2012**, *14*, 572-575.
(20) Sakamoto, Y.; Boinapally, S.; Katan, C.; Abe, M. *Tetrahedron Lett.*, **2013**, *54*, 7171-7174.
(21) Olson, J. P.; Banghart, M. R.; Sabatini, B. L.; Ellis-Davies, G. C. R. *J. Am. Chem. Soc*. **2013**, *135*, 15948−15954.
(22) Chitose, Y.; Abe, M.; Furukawa, K.; Katan, C. *Chem. Lett*. **2016**, *45*, 1186–1188.
(23) Göppert-Mayer, M. *Ann. Phys*. **1931**, *401*, 273−294.
(24) Kiskin, N. I.; Chillingworth, R.; McCray, J. A.; Piston, D.; Ogden, D. *Eur. Biophys. J*. **2002**, *30*, 588-604.
(25) Boinapally, S.; Huang, B.; Abe, M.; Katan, C.; Noguchi, J.; Watanabe, S.; Kasai, H.; Xue, B.; Kobayashi, T. *J. Org. Chem*. **2014**, *79*, 7822-7830.
(26) Komori, N.; Jakkampudi, S.; Motoishi, R.; Abe, M.; Kamada, K.; Furukawa, K.;Katan, C.; Sawada, W.; Takahashi, N.; Kasai, H.; Xue, B.; Kobayashi, T. *Chem. Commun.* **2016**, *52*, 331-334.
(27) Jakkampudi, S.; Abe, M.; Komori, N.; Takagi, R.; Furukawa, K.; Katan, C.; Sawada, W.; Takahashi, N.; Kasai, H. *ACS Omega*, **2016**, *1*, 193-201.
(28) Anderson, R. J. M.; Holtom, G. R.; McClain, W. M. *J. Chem. Phys.* **1979**, *70*, 4310-4315.
(29) Boyd, R. W. In *Nonlinear Optics*, 2nd ed., **2003**, 515.
(30) Wang, X.; Wang, D.; Zhou, G.Y.; Yu, W. T.; Zhou, Y. F.; Fang, Q.; Jiang, M. H. *J. Mater. Chem*., **2001**, *11*, 1600–1605.
(31) Albota, M.; Beljonne, D.; Bre´das, J. L.; Ehrlich, J. E.; Fu, J. Y.; Heikal, A. A.; Hess, S. E.; Kogej, T.; Levin, M. D.; Marder, S. R.; Maughon, D. M. C.; Perry, J. W.; Röckel, H.; Rumi, M.; Subramaniam, G.; Webb, W. W.; Wu, X. L.; Xu, C. *Science*, **1998**, *281*, 1653-1656.