OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 5713–5718

pubs.acs.org/OrgLett

Preparation of Viscosity-Sensitive Isoxazoline/Isoxazolyl-Based Molecular Rotors and Directly Linked BODIPY–Fulleroisoxazoline from the Stable *meso*-(Nitrile Oxide)-Substituted BODIPY

Yuriy V. Zatsikha,[†] Natalia O. Didukh,[†,‡] Rachel K. Swedin,[§] Viktor P. Yakubovskyi,[‡] Tanner S. Blesener,[†] Andrew T. Healy,[§] David E. Herbert,[†] David A. Blank,*[,§] Victor N. Nemykin,*[,†] and Yuriy P. Kovtun*[,‡]

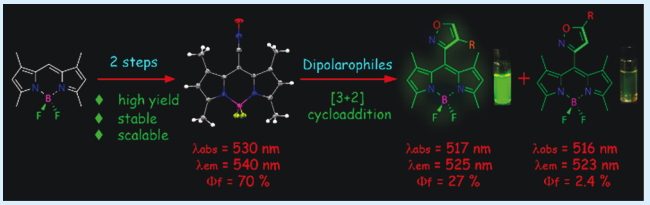
[†]Department of Chemistry, University of Manitoba, Winnipeg, MB R3T 2N2, Canada

[‡]Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska str., 02660 Kyiv, Ukraine

[§]Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455, United States

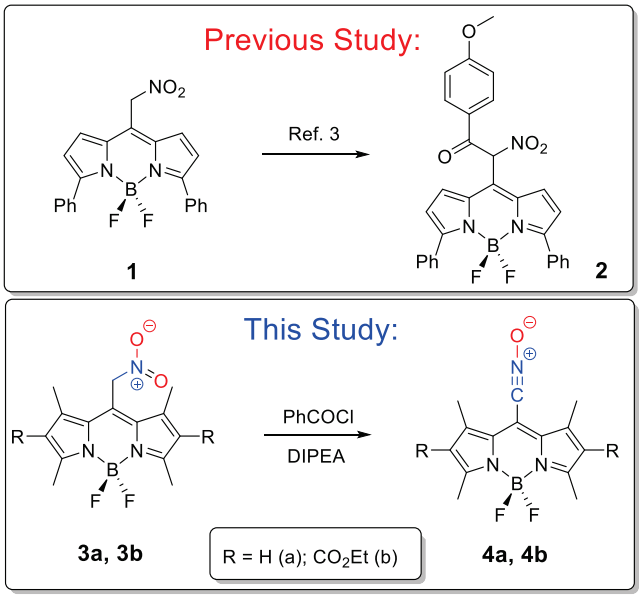
Supporting Information

ABSTRACT: We developed a simple methodology for the preparation of stable *meso*-(nitrile oxide)-substituted BODIPYs, which were characterized by spectroscopic methods and X-ray crystallography. These compounds were used for the preparation of isoxazoline– or isoxazolyl–BODIPYs by 1,3-dipolar cycloaddition reaction with dipolarophiles. Several BODIPYs possess molecular rotor behavior, including viscosity-dependent fluorescence. Transient absorption spectroscopy and time-resolved fluorescence are indicative of a 3 orders of magnitude difference in the excited-state lifetime for dichloromethane and glycerol solutions.



Dyes derived from the boron dipyrromethene (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, BODIPY) attracted considerable attention over the past decades because of their excellent thermal, chemical, and photochemical stability as well as prominent and tunable optical absorption and fluorescence properties, general insensitivity to both solvent polarity and pH, large two-photon cross sections for multiphoton excitation, lack of ionic charge, and good solubility.[1] Because properties of this chromophore can be tuned via functionalization of the *α*-, *β*-, or *meso*-positions of the BODIPY core, it is not surprising to see an extensive array of well-developed synthetic procedures reported on chemical modification of these dyes.[2] Recently, we have developed a convenient synthetic methodology to the preparation of *meso*-nitromethyl-substituted BODIPYs that is based on the addition of nitromethane to the *meso*-unsubstituted boron dipyrromethene in the presence of base followed by the further oxidation of the corresponding intermediate.[3] The *meso*-nitromethyl group in these BODIPYs was then used for further modification of the chromophore core via reduction or condensation reactions. In particular, sterically nonhindered BODIPY (**1**) can be easily benzoylated using anizoyl chloride in the presence of DIPEA to form BODIPY **2**. In the case of 1,7-diphenyl-substituted BODIPY derivatives, a similar reaction leads only to the degradation of the BODIPY core. To our surprise, however, in the case of less sterically crowded 1,7-dimethyl-substituted BODIPYs **3a** and **3b**, a similar reaction resulted in the formation of the stable BODIPY nitrile oxides **4a** and **4b** (Scheme 1 and Figure 1).

Scheme 1. Preparation of Stable BODIPY Nitrile Oxides 4a and 4b



We might speculate that in the case of sterically nonhindered BODIPY **1**, the benzoylation reaction involves the accessible

Received: June 17, 2019
Published: July 8, 2019

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713–5718

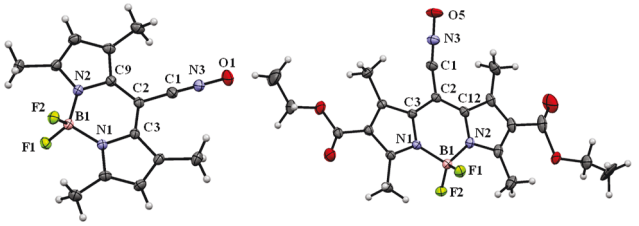


Figure 1. ORTEP of the X-ray structures of **4a** (left; one out of two crystallographically independent molecules is shown) and **4b** (right) at 50% ellipsoid probabilities. See Supporting Information for further details.

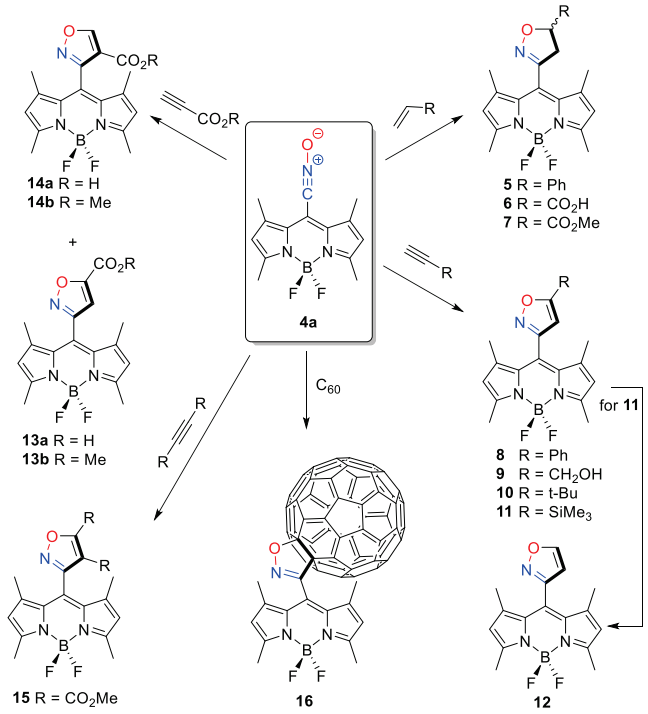
carbon atom of the *meso*-nitromethyl fragment, whereas in the case of more sterically hindered BODIPYs **3a** and **3b**, the less sterically crowded oxygen atom of the *meso*-nitromethyl group participates in the reaction. In the latter case, such a reaction mechanism leads to the formation of nitrile oxide BODIPYs **4a** and **4b**.

Nitrile oxides are known to be among the most reactive species in organic chemistry and can undergo regioselective and stereospecific cycloaddition with 1,3-dipolarophiles (alkenes or alkynes) yielding isoxazoline or isoxazolyl derivatives.[4] The cycloaddition between nitrile oxides and alkynes represents a metal-free ligation reaction that has been employed for polymer end-group modifications.[5] Nitrile oxides usually are prepared from oxime precursors by either dehydrohalogenation of hydroximoyl halides (Huisgen's reaction)[6] or by oxidation with sodium hypochlorite or *N*-bromosuccinimide.[7] Because of their rapid dimerization to 1,2,5-oxadiazole 2-oxides (furoxans), they are usually prepared in situ, which often limits their use in organic synthesis. The spontaneous dimerization to furoxans can be prevented by steric shielding of the nitrile oxide fragment facilitated by the nearby substituents, in particular, by methyl groups.[8]

In comparison, preparation of the nitrile oxides by dehydration of activated primary nitroalkanes (Mukaiyama reaction) is less common. An aryl isocyanate in the presence of a base is typically used for this purpose.[9] In our case, BODIPYs **4a** and **4b** can also be formed using phenyl isocyanate as the dehydration reagent. However, the use of benzoyl chloride is preferential, as no substantial byproducts are formed (Supporting Information). The presence of a 1,7-dimethyl substitution pattern is key for the formation and stability of BODIPYs **4a** and **4b**. Indeed, both compounds are stable for a prolonged time in a solid state, can be purified by the conventional chromatography methods, and are recrystallized using a variety of organic solvents. Because of their excellent stability, we were able to obtain a single crystal structure of **4a** and **4b** (Figure 1). The BODIPY core in **4a** and **4b** was found to be planar. In the case of **4b**, the two ester groups were almost coplanar with the plane of the BODIPY core. The bond distances in the nitrile oxide fragments in **4a** and **4b** (C_{meso}–CNO = 1.4214(18)–1.427(2), C≡N = 1.1403(18)–1.150(2), and N–O = 1.2156(19)–1.2232(16) Å) are close to those reported for the very limited number of known nitrile oxides.[10] The nitrile oxide is linear in **4a** (C–C≡N = 177.82(14)–179.13(16)° and C≡N–O = 179.15(15)–179.57(17)°) and slightly bent in **4b** (C_2–C_1≡N_3 = 169.06(18)° and C_1≡N_3–O_5 = 179.5(2)°). In both molecules, nitrile oxide is nearly coplanar with the BODIPY core. The nitrile oxide in **4a** and **4b** is also well-shielded by steric interactions with the neighboring methyl groups with the closest contacts observed at ~2.273 (ONC–H_{CH3}) and ~2.576 (N–H_{CH3}) Å.

To explore the synthetic potential of the BODIPY nitrile oxide synthons, we focused on the chemistry of BODIPY **4a** as a more readily available compound (Scheme 2).

Scheme 2. Utilization of 4a in 1,3-Dipolar Cycloaddition Reactions



The reaction between nitrile oxide **4a** and monosubstituted alkenes is fast and results in the stereoselective formation of BODIPYs **5**–**7** (Scheme 2). Indeed, BODIPYs **5**–**7** can be formed in high yields from the equimolar amounts of reagents just in 15 min in boiling toluene. New BODIPY–isoxazolines can be purified using conventional chromatographic methods. During purification steps for BODIPYs **5**–**7**, we found only negligible amounts of colored (i.e., BODIPY-containing) side products. BODIPY **4a** also reacts similarly with electron-rich alkynes to form BODIPY-isoxazoles **8**–**11**. The reaction is very clean in the case of BODIPYs **10** and **11**. Because the alkyne precursors for BODIPYs **10** and **11** are liquids with low boiling points, room temperature and a prolonged reaction time were used for the formation of these compounds in high yields. Finally, BODIPY **12** was formed by the elimination of the –$Si(CH_3)_3$ group from **11** by treatment with a catalytic amount of K_2CO_3 in methanol.

The analogous reaction between **4a** and electron-deficient alkynes was found to be less stereoselective. When BODIPY **4a** reacts with propargylic acid or its methyl ester, both possible C4- and C5-substituted isoxazolyl stereoisomers (**13a**/**14a** and **13b**/**14b**) were observed to form. The C4-substituted isoxazolyl isomer (**14a** or **14b**) is highly fluorescent, whereas the C5-substituted isomer (**13a** or **13b**) is nonfluorescent when judged by the naked eye. Stereoisomers **13a** and **14a** can be easily separated, as the BODIPY **14a** has very low solubility in toluene, while remaining in solution, **13a** can be purified by the conventional chromatographic methods. The ratio between analytically pure isomers **13a** and **14a** is close to 4:1. In

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713–5718

contrast with BODIPYs **13a** and **14a**, compounds **13b** and **14b** have similar solubility and R_f values, which makes their separation more challenging. Again, based on the ^{1}H NMR spectrum of the reaction mixture, the ratio between two isomers is close to 2:1 (**13b**/**14b**) (Scheme 2).

Recently, in situ generated BODIPY nitrile oxide located at the *para*-position of the BODIPY's *meso*-phenyl substituent was used for the formation of BODIPY−C_{60} fullerene dyad.[11] Thus, we tested nitrile oxide **4a** in a similar 1,3-dipolar cycloaddition reaction with C_{60} fullerene. The reaction between equimolar amounts of **4a** and C_{60} in boiling toluene under an inert atmosphere resulted in the formation of new chromophore **16** (Scheme 2). BODIPY **16** was purified by flash column chromatography and has a λ_{max} (538 nm) between those of nitrile oxides **4a** and **4b** (~560 nm) and BODIPYs **5**−**15** (~520 nm). In addition, the UV−vis spectrum of BODIPY **16** has clear spectroscopic signatures of fullerene in the UV region (Figure 2). Fluorescence from

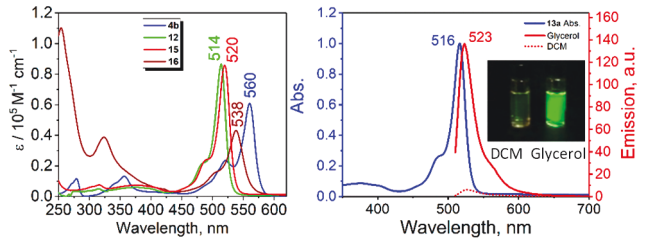


Figure 2. Selected UV−vis (DCM) and fluorescence (DCM and glycerol/MeOH (9:1 v/v)) spectra of new BODIPYs.

the BODIPY chromophore in **16** is quenched; however, we were able to observe weak fluorescence associated with the fullerene chromophore (Figure S63). High-resolution mass spectra of BODIPY **16** confirm its molecular composition. It is interesting that under negative atmospheric-pressure chemical ionization (APCI) mode, apart from the molecular ion of **16**, the ions of the retro-cycloaddition reaction products **4a** and C_{60} can be observed in the spectrum. At the same time, it appeared to be more stable under positive mode ionization (Figures S46 and S47). The BODIPY **16** has the shortest C_{60}−BODIPY donor−acceptor distance among all known BODIPY−fullerene dyads, and its exciting photophysical properties will be reported later along with the other similar systems.

The UV−vis spectra of all new BODIPYs resemble those observed for the reported earlier *meso*-aryl-substituted systems and are dominated by the strong BODIPY-type absorption between 515 and 540 nm (Figure 2). On the other hand, it is possible to observe, even with the naked eye, that the fluorescence of C4-substituted isoxazolyl BODIPYs **14a**, **14b**, and **15** (in all of these systems, C4-substituents prevent the rotation of the isoxazole unit) is significantly stronger when compared to that in all other BODIPYs reported here. Indeed, the fluorescence quantum yields measured in DCM for **14a**, **14b**, and **15** were found to be between 0.09 and 0.27, whereas those for the other BODIPYs vary between 0.014 and 0.05 in the same solvent (Table 1). Such behavior is characteristic of BODIPY-based molecular rotors (including those with five-membered nonconjugated heterocycles located at the *meso*-position reported earlier),[12] in which twisted intramolecular charge transfer (TICT) plays a dominant role in suppressing of fluorescence. BODIPY-based molecular rotors gained a lot of attention, as they turn on their fluorescence in response to the

Table 1. Spectroscopic Properties of Novel BODIPY Dyes

dye	λ_{abs} ($\varepsilon \times 10^{-3}$, M^{-1} cm^{-1})[a]	λ_{em} (Φ_f)[a]	λ_{em} (Φ_f)[b]
4a	560 (60)	570 (0.70)	-
4b	560 (72)	572 (0.48)	-
5	515 (85.4)	524 (0.014)	524 (0.13)
6	516 (83.2)	527 (0.024)	525 (0.15)
7	516 (80.8)	525 (0.027)	525 (0.10)
8	514 (85.3)	522 (0.026)	523 (0.21)
9	514 (81.5)	523 (0.024)	523 (0.39)
10	513 (79)	523 (0.050)	523 (0.43)
11	512 (81.2)	521 (0.036)	521 (0.34)
12	514 (86)	522 (0.042)	522 (0.27)
13a	516 (80.1)	523 (0.024)	523 (0.38)
14a	517 (76.7)	525 (0.27)	525 (0.76)
13b	518 (83)	525 (0.027)	525 (0.26)
14b	518 (80.2)	529 (0.27)	527 (0.72)
15	520 (85.8)	528 (0.085)	528 (0.37)
16	538 (43.1)	-	-
	324 (38.8)		

[a]DCM as a solvent. [b]Glycerol/MeOH (90:10 v/v) as a solvent.

changes in viscosity and offer a high sensitivity tool to map the viscosity within biomolecules and lipid membranes.[13] The fluorescence quantum yields of BODIPYs **5**−**12** and **13a** and **13b** increase dramatically in glycerol compared to in DCM (Figure 3 and Table 1). Our DFT calculations agree well with

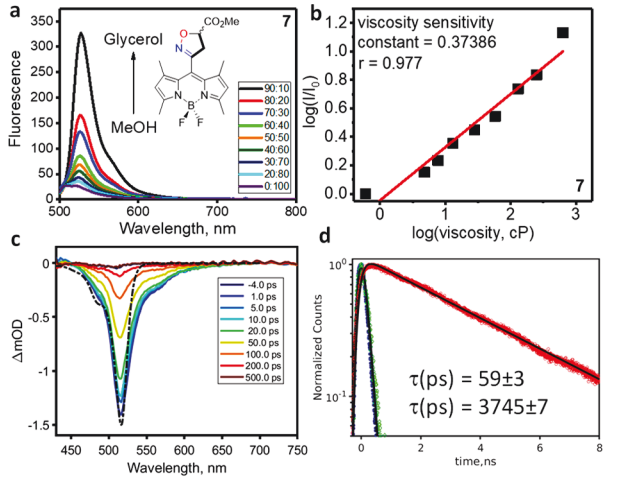


Figure 3. (a) Selected steady-state fluorescence, (b) linear dependency of the fluorescence versus viscosity, (c) transient pump−probe in DCM following excitation at 515 nm. The dash−dot line is the inverted absorption spectrum scaled for comparison. (d) Time-correlated single photon counting (TCSPC) measured at 560 nm following excitation at 465 nm in DCM (green) and glycerol (maroon). The instrument response is shown in blue.

the experimental fluorescence data. The DFT-predicted rotational barrier for well-known *meso*-phenyl BODIPY **17** (Figure 4), which has no TICT properties[14] and has more or less solvent-independent fluorescence quantum yields, was found to be prohibitively high compared to that in BODIPYs **7** and **13a**. To prove the TICT nature of the fluorescence quantum yields in new molecular rotors, we subsequently investigated the photophysics of BODIPY **7** in a MeOH/glycerol mixture using steady-state fluorescence as well as transient absorption spectroscopy for DCM and glycerol solutions (Figure 3).

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713−5718

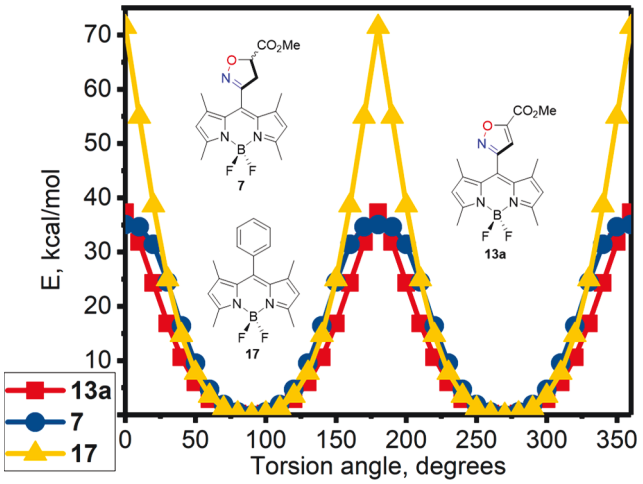


Figure 4. DFT-predicted rotational barriers for BODIPYs **7**, **13a**, and **17**.

In the case of steady-state experiments, the integrated fluorescence intensity increased linearly with solvent viscosity. Transient pump−probe spectra were a combination of a ground-state bleach and stimulated emission. There was no evidence of absorption from any additional intermediates, and the signals exponentially returned to the ground state, indicating first-order decay of the initially excited state directly back to the ground state. The lifetime of the excited state was quantified using time-correlated single photon counting (TCSPC). The data was well-fitted with a single exponential decay convoluted with the instrument response function. The excited-state lifetime was 59 ± 3 ps in DCM and 3745 ± 7 ps in glycerol. The solvent dependence of the emission quantum yields and excited-state lifetimes are consistent with the TICT molecular rotors, and the BODIPY dyes reported here represent a new type of fluorogenic viscosity-driven responsive probes.

In conclusion, we report here a simple, scalable method for the preparation of stable *meso*-(nitrile oxide)-substituted BODIPYs. The critical requirement for this methodology's success was the presence of moderately bulky methyl groups at positions 1 and 7 of the BODIPY core: these not only facilitate the formation of nitrile oxides but also stabilize these resulting molecules in solution and the solid-state. New nitrile oxide **4a** can be introduced in a variety of cycloaddition reactions with 1,3-dipolarophiles (alkenes, alkynes, and C_{60} fullerene), which leads to the formation of BODIPY−isoxazoline and BODIPY−isoxazolyl derivatives in mild conditions and excellent yields. The majority of new BODIPYs possess prominent molecular rotor properties, with high sensitivity to the solvent viscosity. The excited-state lifetime was increased by three-orders of magnitude when going from a DCM solution to a glycerol solution. The new BODIPY−C_{60} system **16** with the fullerene acceptor directly linked to the *meso*-position of BODIPY represent a new class of donor−acceptor dyads with potentially interesting electron-transfer properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02082.

Experimental procedures, additional information, and characterization data (PDF)

Accession Codes

CCDC 1918705−1918706 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: Viktor.Nemykin@umanitoba.ca. (V.N.N.)
*E-mail: kovtun@ioch.kiev.ua. (Y.P.K.)
*E-mail: blank@umn.edu. (D.A.B.)

ORCID

Yuriy V. Zatsikha: 0000-0002-9770-7007
David E. Herbert: 0000-0001-8190-2468
David A. Blank: 0000-0003-2582-1537
Victor N. Nemykin: 0000-0003-4345-0848

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support from the Minnesota Supercomputing Institute, NSERC, CFI, NSF (CHE-1464711), the University of Manitoba, and WestGrid Canada to V.N.N. is greatly appreciated. Generous support from the NSF support (DMR-1708177) to D.A.B. is greatly appreciated. Generous support from NAS of Ukraine to Y.P.K. is greatly appreciated.

■ REFERENCES

(1) (a) Nemykin, V. N.; Blesener, T. S.; Ziegler, C. J. Photophysics, Redox Processes, and Electronic Structures of Ferrocenyl-Containing BODIPYs, aza-BODIPYs, BOPHYs, Transition-Metal Dipyrromethenes and aza-Dipyrromethenes. *Makrogeterotsikly* **2017**, *10*, 9−26. (b) Vecchi, A.; Galloni, P.; Floris, B.; Dudkin, S. V.; Nemykin, V. N. Metallocenes meet porphyrinoids: Consequences of a "fusion. *Coord. Chem. Rev.* **2015**, *291*, 95−171. (c) Vecchi, A.; Galloni, P.; Floris, B.; Nemykin, V. N. New developments in chemistry of organometallic porphyrins and their analogs. *J. Porphyrins Phthalocyanines* **2013**, *17*, 165−196. (d) Ulrich, G.; Ziessel, R.; Harriman, A. The chemistry of fluorescent bodipy dyes: versatility unsurpassed. *Angew. Chem., Int. Ed.* **2008**, *47*, 1184−1201. (e) Ziessel, R.; Ulrich, G.; Harriman, A. The chemistry of Bodipy: a new El Dorado for fluorescence tools. *New J. Chem.* **2007**, *31*, 496−501. (f) Durantini, A. M.; Heredia, D. A.; Durantini, J. E.; Durantini, E. N. BODIPYs to the rescue: potential applications in photodynamic inactivation. *Eur. J. Med. Chem.* **2018**, *144*, 651−661.

(2) (a) Zatsikha, Y. V.; Kovtun, Y. P. In *Handbook of Porphyrin Science With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine: Volume 36: BODIPYs and Chlorins: Powerful Related Porphyrin Fluorophores*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific: Singapore, 2016; pp 151−257. (b) Didukh, N. O.; Yakubovskyi, V. P.; Zatsikha, Y. V.; Rohde, G. T.; Nemykin, V. N.; Kovtun, Y. P. Flexible BODIPY Platform that Offers an Unexpected Regioselective Heterocyclization Reaction Toward Preparation of 2-Pyridone [a]-Fused BODIPYs. *J. Org. Chem.* **2019**, *84*, 2133−2147. (c) Zatsikha, Y. V.; Maligaspe, E.; Purchel, A. A.; Didukh, N. O.; Wang, Y.; Kovtun, Y. P.; Blank, D. A.; Nemykin, V. N. Tuning electronic structure, redox, and photophysical properties in asymmetric NIR-absorbing organometallic BODIPYs. *Inorg. Chem.* **2015**, *54*, 7915−7928. (d) Jean-Gerard, L.; Vasseur, W.; Scherninski,

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713−5718

F.; Andrioletti, B. Recent advances in the synthesis of [a]-benzo-fused BODIPY fluorophores. *Chem. Commun.* **2018**, *54*, 12914−12929. (e) Lu, H.; Mack, J.; Nyokong, T.; Kobayashi, N.; Shen, Z. Optically active BODIPYs. *Coord. Chem. Rev.* **2016**, *318*, 1−15. (f) Boens, N.; Verbelen, B.; Dehaen, W. Postfunctionalization of the BODIPY core: synthesis and spectroscopy. *Eur. J. Org. Chem.* **2015**, *2015*, 6577−6595. (g) Lakshmi, V.; Rajeswara Rao, M.; Ravikanth, M. Halogenated boron-dipyrromethenes: synthesis, properties and applications. *Org. Biomol. Chem.* **2015**, *13*, 2501−2517. (h) Ni, Y.; Wu, J. Far-red and near infrared BODIPY dyes: synthesis and applications for fluorescent pH probes and bio-imaging. *Org. Biomol. Chem.* **2014**, *12*, 3774−3791. (i) Loudet, A.; Burgess, K. BODIPY dyes and their derivatives: syntheses and spectroscopic properties. *Chem. Rev.* **2007**, *107*, 4891−4932.

(3) Didukh, N. O.; Yakubovskyi, V. P.; Zatsikha, Y. V.; Nemykin, V. N.; Kovtun, Y. P. *meso*-Nitromethyl-Substituted BODIPYs−A new type of water switchable fluorogenic dyes useful for further core modifications. *Dyes Pigm.* **2018**, *149*, 774−782.

(4) (a) Roscales, S.; Plumet, J. Metal-catalyzed 1, 3-dipolar cycloaddition reactions of nitrile oxides. *Org. Biomol. Chem.* **2018**, *16*, 8446−8461. (b) Giustiniano, M.; Novellino, E.; Tron, G. C. Nitrile N-Oxides and Nitrile Imines as New Fuels for the Discovery of Novel Isocyanide-Based Multicomponent Reactions. *Synthesis* **2016**, *48*, 2721−2731. (c) Vitale, P.; Scilimati, A. Functional 3-arylisoxazoles and 3-aryl-2-isoxazolines from reaction of aryl nitrile oxides and enolates: synthesis and reactivity. *Synthesis* **2013**, *45*, 2940−2948. (d) Heaney, F. Nitrile Oxide/Alkyne Cycloadditions−A Credible Platform for Synthesis of Bioinspired Molecules by Metal-Free Molecular Clicking. *Eur. J. Org. Chem.* **2012**, *2012*, 3043−3058.

(5) Altintas, O.; Glassner, M.; Rodriguez-Emmenegger, C.; Welle, A.; Trouillet, V.; Barner-Kowollik, C. Macromolecular surface design: photopatterning of functional stable nitrile oxides. *Angew. Chem., Int. Ed.* **2015**, *54*, 5777−5783.

(6) (a) Singh, I.; Zarafshani, Z.; Heaney, F.; Lutz, J.-F. Orthogonal modification of polymer chain-ends via sequential nitrile oxide−alkyne and azide−alkyne Huisgen cycloadditions. *Polym. Chem.* **2011**, *2*, 372−375. (b) Rajagopalan, P.; Talaty, C. N. Dipolar addition reactions of nitrileoxides. IV. The cycloaddition of nitrileoxides to ketene animals. *Tetrahedron Lett.* **1966**, *7*, 4877−4881.

(7) (a) Jakubiec, D.; Przypis, L.; Suwinski, J. W.; Walczak, K. Z. Synthesis of 5-hetaryluracil derivatives via 1, 3-dipolar cycloaddition reaction. *ARKIVOC* **2017**, *2017* (2), 149−161. (b) Dondoni, A.; Giovannini, P. P. Formyl C-glycosides as precursors to glycosyl nitrile oxides and nitrones. *Synthesis* **2002**, *2002*, 1701−1706. (c) Moriya, O.; Takenaka, H.; Urata, Y.; Endo, T. Generation of nitrite oxides via O-tributylstannyl aldoximes; application to the synthesis of isoxazolines and isoxazoles. *J. Chem. Soc., Chem. Commun.* **1991**, 1671−1672. (d) Grundmann, C.; Richter, R. Nitrile oxides. X. Improved method for the prepared of nitrile oxides from aldoximes. *J. Org. Chem.* **1968**, *33*, 476−478.

(8) (a) Poh, J.-S.; Garcia-Ruiz, C.; Zuniga, A.; Meroni, F.; Blakemore, D. C.; Browne, D. L.; Ley, S. V. Synthesis of trifluoromethylated isoxazoles and their elaboration through inter- and intra-molecular C−H arylation. *Org. Biomol. Chem.* **2016**, *14*, 5983−5991. (b) Kim, T. K.; Lee, B. W.; Lee, H. W.; Chung, K.-H.; Kim, J. S. Synthesis and Characterization of Bisimidazolylfuroxan Derivatives. *Bull. Korean Chem. Soc.* **2013**, *34*, 1864−1866. (c) Mitchell, W. R.; Paton, R. M. Flash vacuum pyrolysis of 1, 2, 5-oxadiazole 2-oxides and 1, 2, 3-triazole 1-oxides. *ARKIVOC* **2010**, *2010* (10), 34−54. (d) Itoh, K.; Horiuchi, C. A. Formation of isoxazole derivatives via nitrile oxide using ammonium cerium nitrate (CAN): a novel one-pot synthesis of 3-acetyl-and 3-benzoylisoxazole derivatives. *Tetrahedron* **2004**, *60*, 1671−1681.

(9) (a) Zagozda, M.; Plenkiewicz, J. Derivados de 4, 5-diidroisoxazóis: Métodos de síntese e aplicações farmacológicas. *Tetrahedron: Asymmetry* **2007**, *18*, 1457−1464. (b) Fenk, C. J. Synthesis and 1, 3-dipolar cycloaddition reactions of 4-methyl-1-nitromethyl-2, 6, 7-trioxabicyclo [2.2. 2] octane. *Tetrahedron Lett.* **1999**, *40*, 7955−7959. (c) Lee, S. Y.; Lee, B. S.; Lee, C.-W.; Oh, D. Y. Cycloaddition of Nitrile Oxides to Unsaturated Phosphonates. *Synth. Commun.* **1999**, *29*, 3621−3626.

(10) (a) Dhami, J. K.; Idzorek, K. M.; Johnson, R. B.; Van Auken, K. S.; Ojala, W. H. Intramolecular geometry and intermolecular interactions of the CNO group of crystalline benzonitrile oxides: a comparison with phenyl cyanates, phenyl isocyanates, and phenyl azides. *CrystEngComm* **2019**, *21*, 908−916. (b) Tsutsuba, T.; Sogawa, H.; Kuwata, S.; Takata, T. Kinetically Stabilized Aliphatic Nitrile N-Oxides as Click Agents: Synthesis, Structure, and Reactivity. *Chem. Lett.* **2017**, *46*, 315−318. (c) Shiro, M.; Yamakawa, M.; Kubota, T. The structures of 4-methoxy-2, 6-dimethylbenzonitrile N-oxide (I), 4-bromo-2, 6-dimethylbenzonitrile N-oxide (II) and 2, 4, 6-trimethylbenzonitrile N-oxide (III). *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1979**, *35*, 712−716. (d) Stoyanovich, F. M.; Krayushkin, M. M.; Mamaeva, O. O.; Yufit, D. S.; Struchkov, Y. T. Stable o-Sulfamoylbenzonitrile Oxides. *Gazz. Chim. Ital.* **1993**, *123*, 39−44. (e) Hashimoto, Y.; Takada, A.; Takikawa, H.; Suzuki, K. Synthesis of isoxazoles en route to semi-aromatized polyketides: dehydrogenation of benzonitrile oxide−para-quinone acetal cycloadducts. *Org. Biomol. Chem.* **2012**, *10*, 6003−6009. (f) Groundwater, P. W.; Nyerges, M.; Fejes, I.; Hibbs, D. E.; Bendell, D.; Anderson, R. J.; McKillop, A.; Sharif, T.; Zhang, W. Preparation and reactivity of some stable nitrile oxides and nitrones. *ARKIVOC* **2000**, *2000* (5), 684−697.

(11) (a) Cabrera-Espinoza, A.; Insuasty, B.; Ortiz, A. Novel BODIPY-C60 derivatives with tuned photophysical and electron-acceptor properties: Isoxazolino [60] fullerene and pyrrolidino [60] fullerene. *J. Lumin.* **2018**, *194*, 729−738. (b) Cabrera-Espinoza, A.; Insuasty, B.; Ortiz, A. Synthesis, the electronic properties and efficient photoinduced electron transfer of new pyrrolidine [60] fullerene-and isoxazoline [60] fullerene-BODIPY dyads: nitrile oxide cycloaddition under mild conditions using PIFA. *New J. Chem.* **2017**, *41*, 9061−9069.

(12) (a) Lee, S.-C.; Heo, J.; Woo, H. C.; Lee, J.-A.; Seo, Y. H.; Lee, C.-L.; Kim, S.; Kwon, O.-P. Fluorescent molecular rotors for viscosity sensors. *Chem. - Eur. J.* **2018**, *24*, 13706−13718. (b) Wu, Y.; Stefl, M.; Olzynska, A.; Hof, M.; Yahioglu, G.; Yip, P.; Casey, D. R.; Ces, O.; Humpolickova, J.; Kuimova, M. K. Molecular rheometry: direct determination of viscosity in L o and L d lipid phases via fluorescence lifetime imaging. *Phys. Chem. Chem. Phys.* **2013**, *15*, 14986−14993. (c) Bahaidarah, E.; Harriman, A.; Stachelek, P.; Rihn, S.; Heyer, E.; Ziessel, R. Fluorescent molecular rotors based on the BODIPY motif: effect of remote substituents. *Photochem. Photobiol. Sci.* **2014**, *13*, 1397−1401. (d) Kubankova, M.; Lopez-Duarte, I.; Kiryushko, D.; Kuimova, M. K. Molecular rotors report on changes in live cell plasma membrane microviscosity upon interaction with beta-amyloid aggregates. *Soft Matter* **2018**, *14*, 9466−9474. (e) Lou, Z.; Hou, Y.; Chen, K.; Zhao, J.; Ji, S.; Zhong, F.; Dede, Y.; Dick, B. Different Quenching Effect of Intramolecular Rotation on the Singlet and Triplet Excited States of Bodipy. *J. Phys. Chem. C* **2018**, *122*, 185−193. (f) Mika, J. T.; Thompson, A. J.; Dent, M. R.; Brooks, N. J.; Michiels, J.; Hofkens, J.; Kuimova, M. K. Measuring the viscosity of the Escherichia coli plasma membrane using molecular rotors. *Biophys. J.* **2016**, *111*, 1528−1540. (g) Xochitiotzi-Flores, E.; Jimenez-Sanchez, A.; Garcia-Ortega, H.; Sanchez-Puig, N.; Romero-Avila, M.; Santillan, R.; Farfan, N. Optical properties of two fluorene derived BODIPY molecular rotors as fluorescent ratiometric viscosity probes. *New J. Chem.* **2016**, *40*, 4500−4512. (h) Dziuba, D.; Jurkiewicz, P.; Cebecauer, M.; Hof, M.; Hocek, M. A Rotational BODIPY Nucleotide: An Environment-Sensitive Fluorescence-Lifetime Probe for DNA Interactions and Applications in Live-Cell Microscopy. *Angew. Chem., Int. Ed.* **2016**, *55*, 174−178. (i) Lincoln, R.; Greene, L. E.; Bain, C.; Flores-Rizo, J. O.; Bohle, D. S.; Cosa, G. When push comes to shove: unravelling the mechanism and scope of nonemissive meso-unsaturated BODIPY dyes. *J. Phys. Chem. B* **2015**, *119* (13), 4758−4765. (j) Zhu, H.; Fan, J.; Li, M.; Cao, J.; Wang, J.; Peng, X. A "Distorted-BODIPY"-Based Fluorescent Probe for Imaging of Cellular Viscosity in Live Cells. *Chem. - Eur. J.* **2014**, *20* (16), 4691−4696. (k) Yu, C.; Huang, Z.; Gu, W.; Wu, Q.-H.; Hao, E.; Xiao,

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713−5718

Y.; Jiao, L.; Wong, W.-Y. R. A novel family of AIE-active *meso*-2-ketopyrrolylBODIPYs: Bright solid-state red fluorescence, morphological properties and application as viscosimeters in live cells. *Mater. Chem. Front.* **2019**, Accepted Manuscript. (l) Wang, J.; Li, Y.; Gong, Q.; Wang, H.; Hao, E.; Lo, P. C.; Jiao, L. *β*-AlkenylBODIPY Dyes: Regioselective Synthesis via Oxidative C−H Olefination, Photophysical Properties, and Bioimaging Studies. *J. Org. Chem.* **2019**, *84* (9), 5078−5090.

(13) (a) Benniston, A. C.; Harriman, A.; Whittle, V. L.; Zelzer, M. Molecular rotors based on the boron dipyrromethene fluorophore. *Eur. J. Org. Chem.* **2010**, *2010*, 523−530. (b) Alamiry, M. A. H.; Bahaidarah, E.; Harriman, A.; Bura, T.; Ziessel, R. Fluorescent molecular rotors under pressure: synergistic effects of an inert polymer. *RSC Adv.* **2012**, *2*, 9851−9859. (c) He, Y.; Shin, J.; Gong, W.; Das, P.; Qu, J.; Yang, Z.; Liu, W.; Kang, C.; Qu, J.; Kim, J. S. Dual-functional fluorescent molecular rotor for endoplasmic reticulum microviscosity imaging during reticulophagy. *Chem. Commun.* **2019**, *55*, 2453−2456. (d) Rao, B. O.; Shrivastava, S.; Pal, S.; Chattopadhyay, A. Effect of Local Anesthetics on the Organization and Dynamics of Hippocampal Membranes: A Fluorescence Approach. *J. Phys. Chem. B* **2019**, *123*, 639−647. (e) Suhina, T.; Amirjalayer, S.; Woutersen, S.; Bonn, D.; Brouwer, A. M. Ultrafast dynamics and solvent-dependent deactivation kinetics of BODIPY molecular rotors. *Phys. Chem. Chem. Phys.* **2017**, *19*, 19998−20007. (f) Vysniauskas, A.; Lopez-Duarte, I.; Duchemin, N.; Vu, T.-T.; Wu, Y.; Budynina, E. M.; Volkova, Y. A.; Pena Cabrera, E.; Ramirez-Ornelas, D. E.; Kuimova, M. K. Exploring viscosity, polarity and temperature sensitivity of BODIPY-based molecular rotors. *Phys. Chem. Chem. Phys.* **2017**, *19*, 25252−25259. (g) Vu, T. T.; Meallet-Renault, R.; Clavier, G.; Trofimov, B. A.; Kuimova, M. K. Tuning BODIPY molecular rotors into the red: sensitivity to viscosity vs. temperature. *J. Mater. Chem. C* **2016**, *4*, 2828−2833. (h) Dent, M. R.; Lopez-Duarte, I.; Dickson, C. J.; Geoghegan, N. D.; Cooper, J. M.; Gould, I. R.; Krams, R.; Bull, J. A.; Brooks, N. J.; Kuimova, M. K. *Phys. Chem. Chem. Phys.* **2015**, *17*, 18393−18402. (i) Kimball, J. D.; Raut, S.; Jameson, L. P.; Smith, N. M.; Gryczynski, Z.; Dzyuba, S. V. A triazine-based BODIPY trimer as a molecular viscometer. *RSC Adv.* **2015**, *5*, 19508−19511.

(14) (a) Kuimova, M. K.; Yahioglu, G.; Levitt, J. A.; Suhling, K. Molecular rotor measures viscosity of live cells via fluorescence lifetime imaging. *J. Am. Chem. Soc.* **2008**, *130*, 6672−6673. (b) Marfin, Y. S.; Vodyanova, O. S.; Merkushev, D. A.; Usoltsev, S. D.; Kurzin, V. O.; Rumyantsev, E. V. Effect of *π*-extended substituents on photophysical properties of BODIPY dyes in solutions. *J. Fluoresc.* **2016**, *26*, 1975−1985.

DOI: 10.1021/acs.orglett.9b02082
Org. Lett. 2019, 21, 5713−5718