Organic LETTERS

Letter

pubs.acs.org/OrgLett

Neo-N-confused Phlorins and Phlorinone: Rational Synthesis and Tunable Properties

Jiahui Kong,[†,⊥] Jiewei Shao,[†,⊥] Chengjie Li,[*,†] Dongdong Qi,[‡] Minzhi Li,[§] Xu Liang,[§] Weihua Zhu,[§] Jianzhuang Jiang,[‡] and Yongshu Xie[*,†]

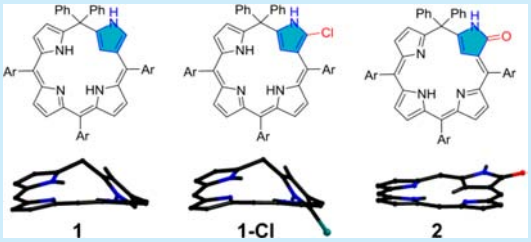
[†]Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China

[‡]Department of Chemistry, University of Science and Technology Beijing, Beijing 100083, China

[§]School of Chemistry & Chemical Engineering, Jiangsu University, Zhenjiang 212013, China

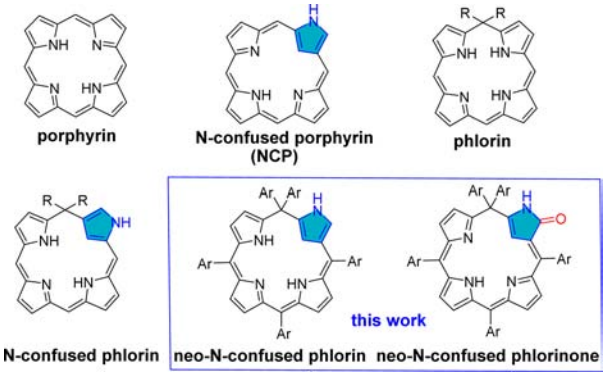
Supporting Information

ABSTRACT: By the acid-catalyzed [2 + 2] condensation, an unprecedented neo-N-confused phlorin (neo-NCphlorin **1**) was successfully synthesized. By treating 1 with *N*-chlorosuccinimide, the corresponding chloro-substituted neo-NCphlorin (1-Cl) was obtained. The oxidization of 1 with $FeCl_3$ afforded the neo-N-confused phlorinone (neo-NCphlorinone **2**), which bears a relatively coplanar conformation, different from the highly distorted ones observed for **1** and **1-Cl**. Notably, **2** shows striking long-wavelength absorption beyond 1300 nm upon addition of TBAF.



As a class of naturally occurring macrocycles, porphyrins exhibit outstanding photophysical, redox, and optoelectronic properties, applicable in many fields.[1−4] In recent years, interesting porphyrin analogues developed through contraction, confusion, and interruption of the porphyrin conjugation frameworks (Scheme 1) have aroused intensive interest in expanding the structures and properties of porphyrins. For example, N-confused porphyrins (NCPs) are featured with a pyrrolic unit incorporated into the macrocycle through the linkage of its α,β'-positions rather than that of α,α'-positions for normal porphyrins (Scheme 1).[5,6] Because of the presence of peripheral NH and inner CH moieties and the possibility of coordinating as trianionic ligands, NCPs have been extensively used as anion sensors, building blocks for constructing supramolecular assemblies, and reagents for stabilizing high valent metal ions which may find applications in catalysis.[7] Unlike fully conjugated porphyrin analogues, phlorins and calixpyrroles contain one or more sp^3 *meso*-carbons[8,9] which interrupt the conjugated macrocycles, resulting in the tendency of adopting nonplanar structures, which will be favorable for binding and sensing anions at the NH moieties.[10,11] In contrast to the extensively investigated calixpyrroles, phlorins, especially N-confused phlorins (NCphlorins), remain relatively unexplored.[12] Studies on rational and controllable syntheses and properties of N-confused types of phlorins are thus highly desired.

Scheme 1. Chemical Structures of Porphyrin and Its Analogues



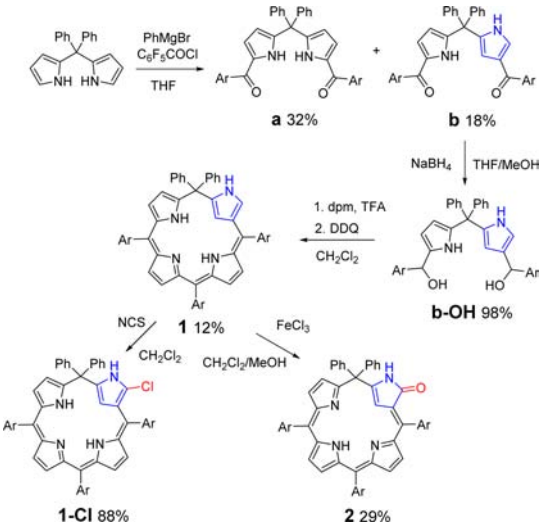
Herein, we report the efficient and rational syntheses of neo-N-confused phlorin (**1**), its chloro derivative (**1-Cl**), and further oxidized product neo-N-confused phlorinone (**2**). X-ray analyses revealed more distorted conformations for the neo-N-confused phlorins **1** and **1-Cl** relative to that of normal phlorins and roughly planar conformation of neo-N-confused phlorinone (**2**). The F^--detecting behavior and electrochemistry of these compounds have also been explored.

The synthetic routes are depicted in Scheme 2. Compound **b** is a key intermediate for constructing the "N-confused" part. Interestingly, the synthesis of **b** is highly dependent on the reaction media. As expected, the acylation of 5,5′-diphenyldipyrromethane with C_6F_5COCl in toluene affords the corresponding α,α'-diacylated product.[8c,9c] When we changed the reaction media to THF, in addition to the α,α'-diacylated product (**a**, 32% yield, see the Supporting Information), the

Received: December 22, 2016
Published: January 23, 2017

DOI: 10.1021/acs.orglett.6b03816
Org. Lett. 2017, 19, 650−653

Scheme 2. Syntheses of Neo-N-confused Phlorin and Its Derivatives (Ar = C_6F_5, dpm = 5-Pentafluorophenyldipyrromethane)



desired α,β'-diacylated compound **b** was separated as a more polar fraction in a yield of 18%. Compared with the symmetric molecule **a**, the ^{1}H NMR spectrum of **b** exhibits an unsymmetric character, with the pyrrolic NH peaks at δ = 9.25 and 8.55 ppm, respectively (Figures S1 and S9). The remaining pyrrolic α-CH appears at a relatively downfield region with δ = 7.21 ppm because of the electron-withdrawing effect of the neighboring β-acyl group.[13] Reduction of **b** with $NaBH_4$ in THF/MeOH (3/1) generated the corresponding dicarbinol, which was condensed with 5-(pentafluorophenyl)-dipyrromethane in CH_2Cl_2 using TFA as the catalyst followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the neo-N-confused phlorin **1** in 12% yield.

In the HRMS of **1**, a molecular ion peak was observed at m/z = 963.1603 ($[M + H]^+$), consistent with the neo-N-confused phlorin framework. The ^{1}H NMR spectrum of **1** revealed that the π-conjugation interrupted macrocycle exhibits pyrrolic-CH signals with typical nonaromatic features, locating between 5.6 and 6.9 ppm. The outer NH appears at δ = 8.27 ppm, and the inner NH moieties appears at lower fields with δ = 9.26 and 9.38 ppm, respectively, owing to the presence of intramolecular hydrogen bonds, as clearly evidenced in its crystal structure (vide infra). By treating **1** with *N*-chlorosuccinimide (NCS), a slightly less polar compound **1-Cl** was obtained in a high yield of 88%, showing its molecular ion peak at m/z = 997.1212 in its HRMS, and its ^{1}H NMR spectrum shows almost the same pattern as that of **1**, except for the disappearance of the pyrrolic α-CH signal (Figure S3). These observations are consistent with the chlorination of compound **1**.

Considering the presence of the reactive free α position of the confused pyrrolic unit in **1**, it is anticipated that **1** may be susceptible to further oxidation reactions. Consistent with this expectation, when **1** was treated with anhydrous $FeCl_3$ in CH_2Cl_2/MeOH for 4 h, a more polar product **2** was obtained in a yield of 27%. The MS of **2** showed a molecular ion peak at m/z = 975.13, indicative of the attachment of an oxygen atom. In the ^{1}H NMR spectrum of **2** (Figure S4), an inner NH and an outer NH were observed at δ = 12.12 and 8.98 ppm, respectively. In addition, the outer pyrrolic α-CH disappeared. These observations are in agreement with the phlorinone structure of **2**.

With the purpose of further elucidating the structural identity of the compounds, we successfully obtained the single crystals by slow evaporation of the dichloromethane/hexane solutions for **1** and **1-Cl** and the dichloromethane/heptane solution for **2**. Single-crystal X-ray diffraction analyses[14] revealed that the tetrapyrrolic macrocycles of **1** and **1-Cl** adopt similarly distorted conformations. Notably, a confused pyrrole unit is present in the phlorin frameworks (Figure 1 and Figure S10).

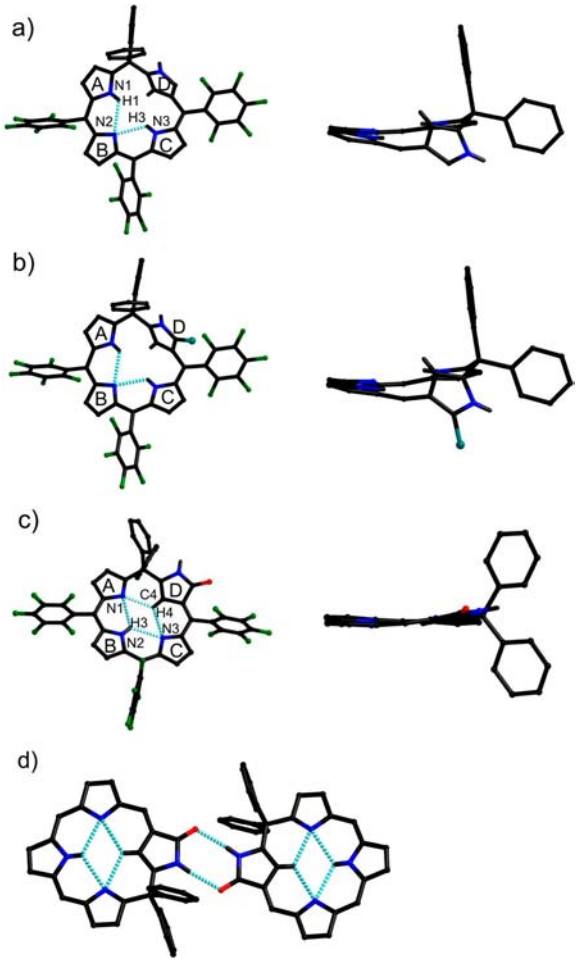


Figure 1. Crystal structures of compounds **1** (a), **1-Cl** (b), and **2** (c). The hydrogen-bonded dimer for **2** is shown in (d). C_6F_5 groups and the hydrogens attached to carbons except that of the confused pyrrole unit are omitted for clarity.

For **1** (Figure 1a), the pyrrolic rings B and C, opposite to the sp^3-hybridized carbon atom, are essentially coplanar. The remaining two pyrroles A and D are obviously distorted from the mean plane of B and C, with dihedral angles of 20.5° and 48.3°, respectively. These data indicate that the confused pyrrole unit D is inclined to be tilted from the macrocycle owing to the steric hindrance between its CH moiety and the NH moieties within the macrocycle as well as the absence of hydrogen bonds involving the CH moiety. Within the macrocycle, N2 is hydrogen bonded to H1 and H3 with the N2···N1 and N2···N3 distances of 2.988(5) and 2.891(5) Å, respectively. In the crystal of **1-Cl** (Figure 1b), pyrroles A and D are tilted from the mean plane of rings B and C with dihedral angles of 17.0° and 53.8°, respectively, indicative of a distorted

DOI: 10.1021/acs.orglett.6b03816
Org. Lett. 2017, 19, 650−653

structure similar to that of **1**. The crystal structure of **2** (Figure 1c) clearly indicates that the confused pyrrole unit has been oxidized to the corresponding pyrrinone with an oxygen atom attached at its α position. Interestingly, the slight modification at the confused pyrrole ring leads to significant effects on the conformation of the tetrapyrrolic framework. Unlike the severely distorted conformation of the phlorins **1** and **1-Cl**, **2** displays a relatively coplanar conformation in which pyrrole rings A–C are essentially coplanar, with the confused pyrrole unit D slightly tilted from the plane with a small dihedral angle of 12.2°. Interestingly, four intramolecular hydrogen bonds exist within the macrocycle involving both the NH and CH moieties. Thus, H-bonds N1···H3, N3···H3, N1···H4, and N4···H4 are observed with N1···N2, N2···N3, N1···C4, and C4···N4 distances of 2.940(6), 2.971(6), 2.975(6), and 2.897(6) Å, respectively. The multiple intramolecular hydrogen bonds may be favorable for improving the planarity of **2**. In addition, intermolecular hydrogen bonds are also observed between the two lactam-like moieties of two neighboring molecules, affording hydrogen-bonded dimers (Figure 1d).

Consistent with the nonconjugated and nonaromatic structures, the dark green neo-N-confused phlorins **1** and **1-Cl** exhibit typical nonaromatic absorption spectra, which feature a split absorption around 400 nm and an absorption peak around 670 nm with comparable intensities (Figure 2). In addition to the typical absorption bands for **1** and **1-Cl**, neo-N-confused phlorinone **2** exhibits a stronger peak at 342 nm and a shoulder peak at 450 nm, and the peak around 680 nm is extremely broad.

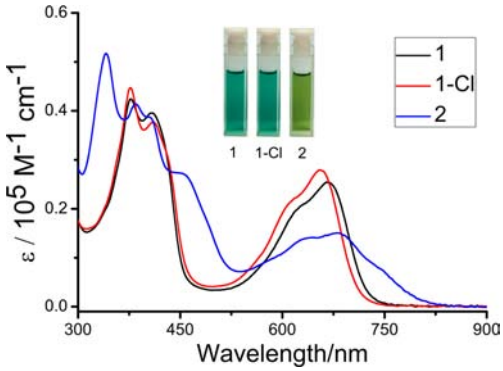


Figure 2. UV–vis–NIR spectra of **1**, **1-Cl**, and **2** in CH_2Cl_2. The inset shows the phtographs of these compounds in CH_2Cl_2.

The redox properties of neo-N-confused phlorins (**1** and **1-Cl**) and phlorinone **2** were investigated by cyclic voltammetry in CH_2Cl_2 under an inert atmosphere by using 0.1 M tetra-*n*-butylammonium perchlorate (TBAP) as the electrolyte and a saturated calomel reference electrode (SCE) as the reference electrode. Compound **1** displays two oxidation and two reduction processes. Similar behavior was observed for compounds **1-Cl** and **2**. The HOMO–LUMO gaps were electrochemically obtained to be 1.84, 1.79, and 1.53 eV for **1**, **1-Cl**, and **2**, respectively (Figure S11 and Table S1).

Theoretically, both **1** and **2** have some potential tautomeric isomers, **1a–d** and **2a–f** (Figure 3 and Figure S12). In fact, only **1a** and **2a** were observed in their respective crystal structures (vide supra). DFT calculations can be used to rationalize these results by evaluating the relative energies of all the possible isomers.[15] Thus, **1a** has the lowest energy among all its proposed isomers, with the others showing energies 3.3 to 19.0 kJ/mol higher relative to **1a** (Figure 3). Similar results were obtained for **2a** (Figure S12).

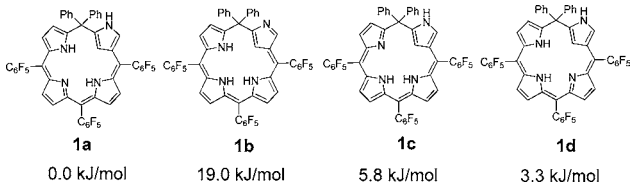


Figure 3. Relative energies of the four possible isomers of compound **1**.

Oligopyrroles are well known for their abilities to detect fluoride ions using the pyrrolic NH moieties.[10,11] As shown in Figure 4a, the gradual addition of tetra-*n*-butylammonium fluoride (TBAF) to the solution of **1** in CH_2Cl_2 resulted in absorption spectral changes with a set of isosbestic points at 321, 410, 525, and 709 nm, indicating that a distinct species was formed. The addition of F^- to the solution of **1-Cl** exhibited similar results (Figure S13). In contrast, addition of F^- to **2** caused a strikingly long-wavelength absorption up to 1350 nm (Figure 4b and Figures S14–S16), which may be potentially applicable in bioimaging and other relevant areas. The ^{1}H NMR spectral changes of **1**, **1-Cl**, and **2** upon addition of TBAF (Figures S17–S19) demonstrate that the F^- anion may act as a base to deprotonate the compounds, which are accompanied by the development of absorption peaks at wavelengths beyond 800 nm.

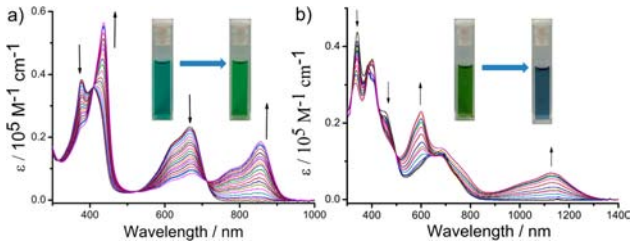


Figure 4. Changes in the absorption spectra of (a) **1** and (b) **2** (10 μM in CH_2Cl_2) upon titration with TBAF (0–200 equiv for **1** and 0–2000 equiv for **2**) in CH_2Cl_2. The inset shows the phtographs of these compounds in CH_2Cl_2.

In summary, we herein report the facile and efficient syntheses of a neo-N-confused phlorin **1** and its chloro-derivative **1-Cl**. The further oxidation of **1** with $FeCl_3$ affords a neo-N-confused phlorinone **2**. X-ray analyses revealed that both **1** and **1-Cl** exhibit highly distorted conformations. In contrast, **2** displays a relatively coplanar structure. The structural differences result in different absorption spectra and F^- detecting behavior. Interestingly, accompanying by the addition of F^-, the absorption spectra of **2** were dramatically extended to 1350 nm.

These results lead us to propose a convenient and efficient approach for the syntheses of neo-N-confused phlorins and phlorinone, and the striking long-wavelength absorption induced by F^- may find applications in bioimaging and relevant areas.

DOI: 10.1021/acs.orglett.6b03816
Org. Lett. 2017, 19, 650–653

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03816.

Complete experimental details; crystallographic details for **1**, **1-Cl**, and **2**; spectroscopic and analytical data; details on DFT calculations (PDF)
X-ray data for **1** (CIF)
X-ray data for **1-Cl** (CIF)
X-ray data for **2** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chengjie.li@ecust.edu.cn.
*E-mail: yshxie@ecust.edu.cn.

ORCID

Yongshu Xie: 0000-0001-8230-7599

Author Contributions

⊥These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by NSFC (21472047, 91227201), the Program for Professor of Special Appointment (Eastern Scholar, GZ2016006) at Shanghai Institutions of Higher Learning, and the Fundamental Research Funds for the Central Universities (WK1616004).

■ REFERENCES

(1) (a) O'Sullivan, M. C.; Sprafke, J. K.; Kondratuk, D. V.; Rinfray, C.; Claridge, T. D. W.; Saywell, A.; Blunt, M. O.; O'Shea, J. N.; Beton, P. H.; Malfois, M.; Anderson, H. L. *Nature* **2011**, *469*, 72. (b) Tsuda, A.; Osuka, A. *Science* **2001**, *293*, 79. (c) Saito, S.; Osuka, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4342. (d) Roznyatovskiy, V. V.; Lee, C. H.; Sessler, J. L. *Chem. Soc. Rev.* **2013**, *42*, 1921. (e) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134. (f) Stepien, M.; Sprutta, N.; Latos-Grażyński, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4288.

(2) (a) Ito, T.; Hayashi, Y.; Shimizu, S.; Shin, J. Y.; Kobayashi, N.; Shinokubo, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8542. (b) KC, C. B.; Lim, N. G.; D'Souza, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 5088. (c) Lash, T. D.; Lammer, A. D.; Ferrence, G. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9718. (d) Xie, Y. S.; Hill, J. P.; Charvet, R.; Ariga, K. *J. Nanosci. Nanotechnol.* **2007**, *7*, 2969. (e) Nozawa, R.; Yamamoto, K.; Shin, J.-Y.; Hiroto, S.; Shinokubo, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 8454.

(3) (a) Xie, Y. S.; Yamaguchi, K.; Toganoh, M.; Uno, H.; Suzuki, M.; Mori, S.; Saito, S.; Osuka, A.; Furuta, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5496. (b) Ding, Y. B.; Tang, Y. Y.; Zhu, W. H.; Xie, Y. S. *Chem. Soc. Rev.* **2015**, *44*, 1101. (c) Ding, Y. B.; Li, T.; Zhu, W. H.; Xie, Y. S. *Org. Biomol. Chem.* **2012**, *10*, 4201. (d) Wang, Y. Q.; Chen, B.; Wu, W. J.; Li, X.; Zhu, W. H.; Tian, H.; Xie, Y. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 10779. (e) Zhao, C. Q.; Rehman, F. U.; Jiang, H.; Selke, M.; Wang, X. M.; Liu, C.-Y. *Sci. China: Chem.* **2016**, *59*, 637.

(4) (a) Thomas, K. E.; Alemayehu, A. B.; Conradie, J. C.; Beavers, M.; Ghosh, A. *Acc. Chem. Res.* **2012**, *45*, 1203. (b) Kumar, A.; Goldberg, I.; Botoshansky, M.; Buchman, Y.; Gross, Z. *J. Am. Chem. Soc.* **2010**, *132*, 15233. (c) Schweyen, P.; Brandhorst, K.; Wicht, R.; Wolfram, B.; Bröring, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 8213.

(5) (a) Furuta, H.; Asano, T.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 767. (b) Chmielewski, P. J.; Latos-Grażyński, L.; Rachlewicz, K.; Głowiak, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 779. (c) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2001**, *123*, 6435−6436. (d) Toganoh, M.; Furuta, H. *Chem. Commun.* **2012**, *48*, 937.

(6) (a) Xie, Y. S.; Wei, P. C.; Li, X.; Hong, T.; Zhang, K.; Furuta, H. *J. Am. Chem. Soc.* **2013**, *135*, 19119. (b) Wei, P. C.; Zhang, K.; Li, X.; Meng, D. Y.; Ågren, H.; Ou, Z. P.; Ng, S.; Furuta, H.; Xie, Y. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 14069. (c) Zhang, K.; Zhang, J. D.; Li, X.; Guo, R.; Ågren, H.; Ou, Z. P.; Ishida, M.; Furuta, H.; Xie, Y. S. *Org. Lett.* **2015**, *17*, 4806. (d) Li, M.; Wei, P. C.; Ishida, M.; Li, X.; Savage, M.; Guo, R.; Ou, Z. P.; Yang, S. H.; Furuta, H.; Xie, Y. S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3063.

(7) Fujino, K.; Hirata, Y.; Kawabe, Y.; Morimoto, T.; Srinivasan, A.; Toganoh, M.; Miseki, Y.; Kudo, A.; Furuta, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6855.

(8) (a) Sessler, J. L.; Zimmerman, R. S.; Bucher, C.; Kral, V.; Andrioletti, B. *Pure Appl. Chem.* **2001**, *73*, 1041. (b) Dehaen, W. *Top. Heterocycl. Chem.* **2010**, *24*, 75. (c) Pistner, A. J.; Lutterman, D. A.; Ghidiu, M. J.; Walker, E.; Yap, G. P. A.; Rosenthal, J. *J. Phys. Chem. C* **2014**, *118*, 14124.

(9) (a) Pistner, A. J.; Lutterman, D. A.; Ghidiu, M. J.; Ma, Y.-Z.; Rosenthal, J. *J. Am. Chem. Soc.* **2013**, *135*, 6601. (b) Pistner, A. J.; Yap, G. P. A.; Rosenthal, J. *J. Phys. Chem. C* **2012**, *116*, 16918. (c) Bruce, A. M.; Weyburne, E. S.; Engle, J. T.; Ziegler, C. J.; Geier, G. R., III. *J. Org. Chem.* **2014**, *79*, 5664. (d) Kim, D.; Chun, H.-J.; Donnelly, C. C.; Geier, G. R., III. *J. Org. Chem.* **2016**, *81*, 5021.

(10) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140. (b) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1. (c) Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57.

(11) (a) Sessler, J. L.; Cyr, M.; Furuta, H.; Král, V.; Mody, T.; Morishima, T.; Shionoya, M.; Weghorn, S. *Pure Appl. Chem.* **1993**, *65*, 393. (b) Král, V.; Sessler, J. L.; Zimmerman, R. S.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1055. (c) Sessler, J. L.; Zimmerman, R. S.; Bucher, C.; Král, V.; Andrioletti, B. *Pure Appl. Chem.* **2001**, *73*, 1041. (d) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17.

(12) (a) Li, X. F.; Chmielewski, P. J.; Xu, J. L.; Jiang, L.; Li, Y. L.; Liu, H. B.; Zhu, D. B. *J. Org. Chem.* **2006**, *71*, 9739. (b) Liu, B.; Li, X.; Xu, X.; Stępień, M.; Chmielewski, P. J. *J. Org. Chem.* **2013**, *78*, 1354. (c) Furuta, H.; Ishizuka, T.; Osuka, A.; Uwatoko, Y.; Ishikawa, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2323. (d) Furuta, H.; Ishizuka, T.; Osuka, A. *Inorg. Chem. Commun.* **2003**, *6*, 398.

(13) (a) Ding, Y. B.; Li, X.; Li, T.; Zhu, W. H.; Xie, Y. S. *J. Org. Chem.* **2013**, *78*, 5328. (b) Tang, Y. Y.; Ding, Y. B.; Li, X.; Ågren, H.; Li, T.; Zhang, W. B.; Xie, Y. S. *Sens. Actuators, B* **2015**, *206*, 291.

(14) CCDC 1509208 (**1**), 1509209 (**1-Cl**), and 1509210 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) All of the calculations were performed with the Gaussian09 program package. See the Supporting Information for more details.

DOI: 10.1021/acs.orglett.6b03816
Org. Lett. 2017, 19, 650−653