Organic LETTERS

Letter

pubs.acs.org/OrgLett

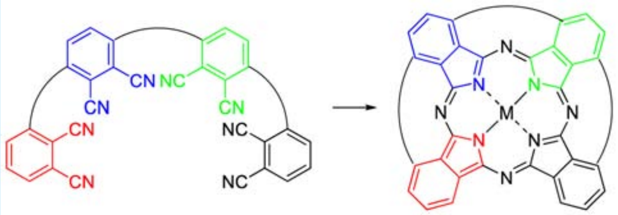
Synthesis of an ABCD-Type Phthalocyanine by Intramolecular Cyclization Reaction

Sun Y. S. Chow and Dennis K. P. Ng*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China

Supporting Information

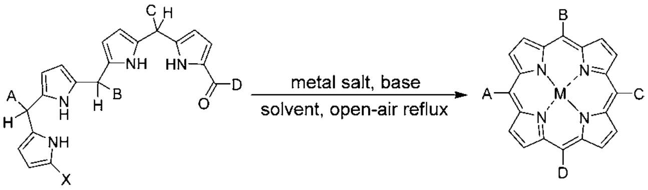
ABSTRACT: Unsymmetrical phthalocyanines with a low symmetry can exhibit unique and intriguing properties that can facilitate their applications in certain disciplines. The synthesis of these compounds, however, has posed a great difficulty. A novel and unprecedented approach for phthalocyanine synthesis is reported that involves intramolecular cyclization of prelinked tetrakisphthalonitriles. By using this strategy, the first ABCD-type phthalocyanine has been prepared in 7.2% yield.



Being a versatile class of functional dyes, phthalocyanines possess intriguing and tunable optoelectronic, photophysical, catalytic, and self-assembly properties.[1] These characteristics, together with their high stability, render them useful as advanced materials,[2] selective sensors,[3] efficient catalysts,[4] and promising theranostic agents[5] for various practical/potential applications. The properties of these macrocyclic compounds depend largely on the metal center and the axial and/or peripheral substituents. Both the nature and position of the substituents are important, which, apart from imparting their intrinsic characteristics to the parent macrocycles, can control the molecular architecture, which in turn can alter their physical properties. Therefore, there has been considerable interest in controlled synthesis of phthalocyanines, particularly the low-symmetry analogues, which could exhibit unique properties that cannot be found in the symmetrical counterparts,[6] as well as revealing their structure−property−activity relationships.

Phthalocyanines are usually prepared by cyclotetramerization of phthalonitriles or their derivatives, such as 1,3-diiminoisoindolines, phthalimides, and phthalic anhydrides.[7] While these methodologies can effectively produce a wide range of symmetrical phthalocyanines with four identical aza-linked isoindole units, the preparation of the unsymmetrical analogues by mixed condensation of two of these precursors inevitably gives a mixture of products that may not be separated readily. A careful selection of precursors and optimization of their ratio and experimental conditions are crucial to facilitate the isolation and purification of the A_3B-type products.[8] Mixed condensation with more than two of these precursors is not feasible to prepare phthalocyanines with an even lower symmetry. To circumvent this problem, a number of alternative synthetic pathways have been developed for low-symmetry phthalocyanines, such as ring expansion of subphthalocyanines,[9] polymer-supported synthesis,[10] cross condensation of 1,3,3-trichloro-6/7-nitroisoindolenine and 1,3-diiminoisoindolines,[11] use of sterically demanding precursors,[12] the "half-phthalocyanine" approach,[13] and cyclization of bisphthalonitriles.[14] Unfortunately, all these methods still suffer from various deficiencies and limitations, which preclude them to be employed generally. Phthalocyanines with more than two different isoindole units remain extremely rare.[15] We report herein a programmed synthetic strategy for low-symmetry phthalocyanines, which involves a preselection and conjugation of four phthalonitrile precursors followed by a base-promoted intramolecular cyclization in the presence of a metal template. This controlled pathway allows tailor-made phthalocyanines to be synthesized and the preparation of low-symmetry analogues that cannot be synthesized readily by conventional methods, including the ABCD-type phthalocyanines. A similar approach has been reported for the preparation of porphyrins that contain four different meso-substituents.[16] As shown in Scheme 1, 1-protected 19-acylbilanes undergo intramolecular condensation under a metal-templating and basic condition to give the corresponding ABCD-type porphyrins.

Scheme 1. Preparation of ABCD-Type Porphyrins



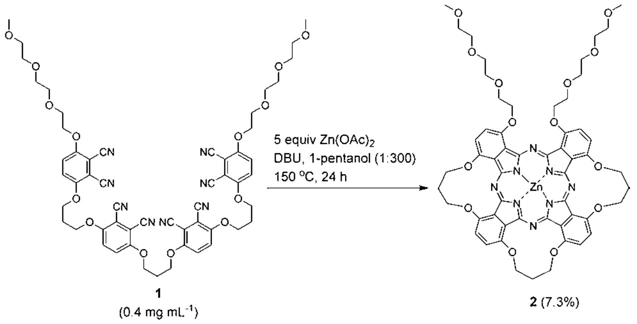
To assess the feasibility of this approach, we first prepared the tetrakisphthalonitrile **1** through a series of nucleophilic substitution reactions as shown in Scheme S1 in the Supporting Information (SI). The four phthalonitrile units were connected by three 1,3-dioxypropylene linkers, and two tetraethylene glycol chains were introduced to the ends to increase the solubility of the resulting phthalocyanine that can facilitate the

Received: May 23, 2016
Published: June 16, 2016

DOI: 10.1021/acs.orglett.6b01489

purification. By using conventional base-promoted cyclization conditions in the presence of $Zn(OAc)_2$ in 1-pentanol, the desired product **2** could be isolated. Attempts were made to optimize the yield by changing the reaction conditions, including the concentration of **1** (0.1−2.0 mg mL^{-1}), nature of the base [1,8-diazabicylo[5.4.0]undec-7-ene (DBU) or lithium], ratio of DBU to solvent (1:200 or 1:300), reaction temperature (140 or 150 °C), and reaction time (up to 48 h). While the use of lithium and a highly diluted solution (at 0.1 mg mL^{-1}) could not yield the expected product, the yields of **2** were in the range of 2.6−7.3% in the other conditions. The optimized conditions as given in Scheme 2 and the Experimental Section in SI could afford **2** in a quite satisfactory yield (7.3%). As these conditions are typical for preparation of other metallophthalocyanines,[7] the effect of metal salts was not examined.

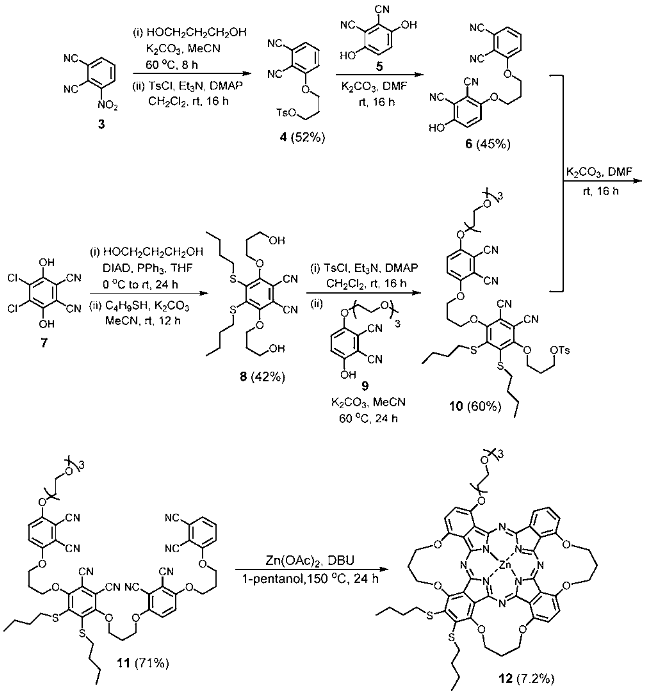
Scheme 2. Preparation of Phthalocyanine 2 by Intramolecular Cyclization of Tetrakisphthalonitrile 1



It was found that a relatively low concentration of tetrakisphthalonitrile **1** (at 0.4 mg mL^{-1}) was still needed to promote intramolecular cyclization. In fact, apart from the phthalocyanine product, which has a characteristic green color, some very polar, dark brown compounds were also formed and trapped in the silica gel column. They are supposed to be the undesired polymeric isoindoles formed by intermolecular condensation reaction. As compound **2** was the major, if not the only, phthalocyanine product, its isolation and purification could be performed readily by column chromatography. This is a great advantage for phthalocyanine synthesis.

With these encouraging results, we attempted to prepare a phthalocyanine with four different isoindole units, i.e., an ABCD-type phthalocyanine. Scheme 3 shows the convergent route used to prepare this compound. The first half of the phthalocyanine was derived from bisphthalonitrile **6**, which was prepared from 3-nitrophthalonitrile (**3**) through aromatic nucleophilic substitution with 1,3-propanediol, tosylation using 4-dimethylaminopyridine (DMAP) as the base, and then monosubstitution with 2,3-dicyanohydroquinone (**5**). To prepare the other half, 4,5-dichloro-3,6-dihydroxyphthalonitrile (**7**) underwent Mitsunobu reaction with 1,3-propanediol, diisopropyl azodicarboxylate (DIAD), and triphenylphosphine,[17] followed by aromatic nucleophilic substitution with 1-butanethiol to give **8**. This compound was then converted to the ditosylate, and one of these moieties was then substituted with the previously reported phthalonitrile **9**[8c] to yield the bisphthalonitrile **10**. The two bisphthalonitriles **6** and **10** were then coupled by aliphatic nucleophilic substitution reaction to give the tetrakisphthalonitrile **11** in 71% yield. By using the same cyclization conditions as reported in Scheme 2, the ABCD-type phthalocyanine **12** was isolated as an isomerically pure product in 7.2% yield. Again, this compound could be purified readily by silica gel column chromatography. To our knowledge, ABCD-type phthalocyanines have never been reported so far.

Scheme 3. Preparation of ABCD-Type Phthalocyanine 12



All the new compounds were unambiguously characterized with various spectroscopic methods (see the Experimental Section in SI). For phthalocyanines **2** and **12**, the electrospray ionization (ESI) mass spectra showed an intense cluster due to the molecular ion with correct exact mass and isotopic pattern (Figures S1 and S2 in SI). Their ^1H NMR spectra in $CDCl_3$ with a trace amount of pyridine-d_5 displayed well-resolved signals, indicating that the compounds were not significantly aggregated even in a millimolar range of concentration. For **12**, the aromatic signals were well-separated and resolved, including a doublet at δ 9.17 for the only α proton of the phthalocyanine ring and a virtual triplet at δ 8.03, three doublets at δ 7.77, 7.73, and 7.53, as well as a singlet at δ 7.66 (two protons) for the six β ring protons, which could be assigned readily as shown in Figure 1.

The UV−vis spectrum of **2** in *N*,*N*-dimethylformamide (DMF) (Figure S3 in SI) showed an intense and sharp Q-band at 713 nm, which is blue-shifted by ca. 20 nm compared with those of typical octa-α-alkoxy zinc(II) phthalocyanines.[18] It is not clear if this is due to the ring strain that may be imposed by the linkers. With seven α-substituents and two β-substituents, phthalocyanine **12** gave the Q-band at 716 nm (Figure 2). It has been reported that both the substitution of alkoxy groups at the α-positions and that of alkylthio groups at the β-positions of phthalocyanines will shift the Q-bands to the red.[19] The similar spectral features of **2** and **12** suggest that the effect of two additional β-butylthio groups can counteract the effect of one α-alkoxy group on the Q-band absorption. As expected, for both of these compounds, the Q-band strictly followed the Lambert−Beer law, revealing their nonaggregated characteristic. Upon excitation at 610 nm, compound **12** showed a fluorescence emission at 725 nm with a fluorescence quantum

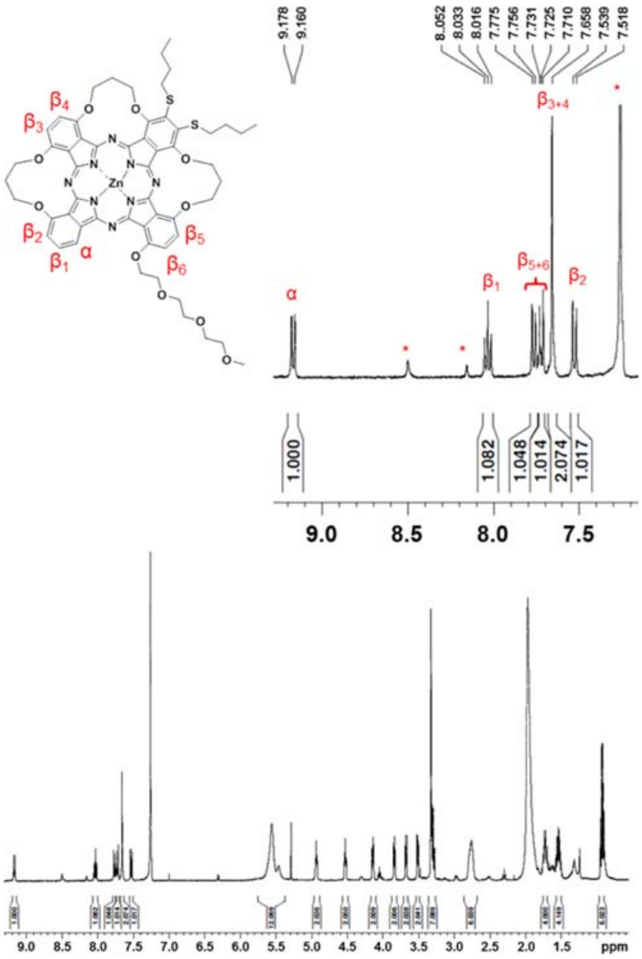


Figure 1. ^1H NMR spectrum of **12** in $CDCl_3$ with a trace amount of pyridine-d_5; the residual solvents' signals are marked with an asterisk.

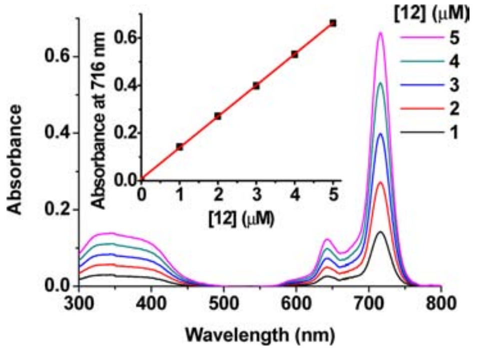


Figure 2. UV−vis spectra of **12** at different concentrations in DMF.

yield of 0.10 relative to unsubstituted zinc(II) phthalocyanine ($\Phi_f = 0.28$).[8c] The fluorescence lifetime was found to be 2.18 ns, which is typical for nonaggregated zinc(II) phthalocyanines.[20]

According to this synthetic pathway, the disposition of the four isoindole units of phthalocyanine depends on the sequence of the four phthalonitrile units in the tetrakisphthalonitrile. Hence, it can be envisaged that the ABCD rings can actually be rearranged, and this approach can be regarded as a programmed synthetic strategy for low-symmetry phthalocyanines. Although additional steps are involved, this approach can have a good control in the sequence of the four isoindole units and produce low-symmetry phthalocyanines that cannot be prepared by conventional methodologies. In addition, the sole phthalocyanine products are isomerically pure, which can greatly facilitate the isolation and purification.

In summary, we have developed a new strategy for the controlled synthesis of phthalocyanines. It involves conjugation of four preselected phthalonitrile units followed by base-promoted intramolecular cyclization in the presence of a metal template. The resulting phthalocyanines can be obtained in about 7% yield. This approach is particularly useful for synthesis of exotic phthalocyanines with a very low symmetry. Owing to the potential intriguing properties of these compounds, it is envisaged that this approach can greatly enrich the chemistry of phthalocyanines.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01489.

Experimental details, synthetic scheme for **1**, and additional spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dkpn@cuhk.edu.hk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Sunny Y. K. Ng of our Department for preparing some of the intermediate products and The Chinese University of Hong Kong for financial support.

■ DEDICATION

Dedicated to Professor Tien-Yau Luh on the occasion of his 70th birthday.

■ REFERENCES

(1) (a) Claessens, C. G.; Hahn, U.; Torres, T. *Chem. Rec.* **2008**, *8*, 75−97. (b) de la Torre, G.; Bottari, G.; Sekita, M.; Hausmann, A.; Guldi, D. M.; Torres, T. *Chem. Soc. Rev.* **2013**, *42*, 8049−8105.

(2) (a) Katoh, K.; Isshiki, H.; Komeda, T.; Yamashita, M. *Chem. - Asian J.* **2012**, *7*, 1154−1160. (b) Oni, J.; Ozoemena, K. I. *J. Porphyrins Phthalocyanines* **2012**, *16*, 754−760. (c) Ragoussi, M.-E.; Ince, M.; Torres, T. *Eur. J. Org. Chem.* **2013**, *2013*, 6475−6489. (d) Martin-Gomis, L.; Fernandez-Lazaro, F.; Sastre-Santos, A. *J. Mater. Chem. A* **2014**, *2*, 15672−15682. (e) Singh, V. K.; Kanaparthi, R. K.; Giribabu, L. *RSC Adv.* **2014**, *4*, 6970−6984. (f) Melville, O. A.; Lessard, B. H.; Bender, T. P. *ACS Appl. Mater. Interfaces* **2015**, *7*, 13105−13118. (g) Basova, T.; Hassan, A.; Durmus, M.; Gurek, A. G.; Ahsen, V. *Coord. Chem. Rev.* **2016**, *310*, 131−153.

(3) (a) Bouvet, M.; Gaudillat, P.; Suisse, J.-M. *J. Porphyrins Phthalocyanines* **2013**, *17*, 913−919. (b) Venkatramaiah, N.; Rocha, D. M. G. C.; Srikanth, P.; Paz, F. A. A.; Tomé, J. P. C. *J. Mater. Chem. C* **2015**, *3*, 1056−1067. (c) Zhang, J.; Chen, Z.; Wu, H.; Wu, F.; He, C.; Wang, B.; Wu, Y.; Ren, Z. *J. Mater. Chem. B* **2016**, *4*, 1310−1317. (d) Lochman, L.; Svec, J.; Roh, J.; Kirakci, K.; Lang, K.; Zimcik, P.; Novakova, V. *Chem. - Eur. J.* **2016**, *22*, 2417−2426.

(4) (a) Zagal, J. H.; Griveau, S.; Silva, J. F.; Nyokong, T.; Bedioui, F. *Coord. Chem. Rev.* **2010**, *254*, 2755−2791. (b) Sorokin, A. B. *Chem. Rev.* **2013**, *113*, 8152−8191. (c) Das, S.; Daud, W. M. A. W. *RSC Adv.*

2014, *4*, 20856−20893. (d) Jack, R. S.; Ayoko, G. A.; Adebajo, M. O.; Frost, R. L. *Environ. Sci. Pollut. Res.* **2015**, *22*, 7439−7449.

(5) (a) Josefsen, L. B.; Boyle, R. W. *Theranostics* **2012**, *2*, 916−966. (b) Iqbal, Z.; Chen, J.; Chen, Z.; Huang, M. *Curr. Drug Metab.* **2015**, *16*, 816−832. (c) Zhang, C.; Gao, L.; Cai, Y.; Liu, H.; Gao, D.; Lai, J.; Jia, B.; Wang, F.; Liu, Z. *Biomaterials* **2016**, *84*, 1−12. (d) Lo, P.-C.; Chow, S. Y. S.; Ng, D. K. P. In *Handbook of Photodynamic Therapy - Updates on Recent Applications of Porphyrin-Based Compounds*; Pandey, R. K., Kessel, D., Dougherty, T. J., Eds.; World Scientific: Hackensack, 2016; pp 237−272.

(6) (a) Mack, J.; Kobayashi, N. *Chem. Rev.* **2011**, *111*, 281−321. (b) Wang, A.; Long, L.; Zhang, C. *Tetrahedron* **2012**, *68*, 2433−2451. (c) Nemykin, V. N.; Dudkin, S. V.; Dumoulin, F.; Hirel, C.; Gürek, A. G.; Ahsen, V. *ARKIVOC* **2014**, 142−204.

(7) McKeown, N. B. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2003; Vol. *15*, pp 61−124.

(8) (a) Bai, M.; Lo, P.-C.; Ye, J.; Wu, C.; Fong, W.-P.; Ng, D. K. P. *Org. Biomol. Chem.* **2011**, *9*, 7028−7032. (b) Lau, J. T. F.; Lo, P.-C.; Fong, W.-P.; Ng, D. K. P. *J. Med. Chem.* **2012**, *55*, 5446−5454. (c) Ke, M.-R.; Yeung, S.-L.; Fong, W.-P.; Ng, D. K. P.; Lo, P.-C. *Chem. - Eur. J.* **2012**, *18*, 4225−4233.

(9) (a) Kobayashi, N.; Kondo, R.; Nakajima, S.-i.; Osa, T. *J. Am. Chem. Soc.* **1990**, *112*, 9640−9641. (b) Kobayashi, N.; Ishizaki, T.; Ishii, K.; Konami, H. *J. Am. Chem. Soc.* **1999**, *121*, 9096−9110. (c) Vagin, S. I.; Frickenschmidt, A.; Kammerer, B.; Hanack, M. *Chem. - Eur. J.* **2005**, *11*, 6568−6573. (d) Zhao, L.; Wang, K.; Shang, H.; Jiang, J. *Dyes Pigm.* **2015**, *120*, 52−56.

(10) (a) Hall, T. W.; Greenberg, S.; McArthur, C. R.; Khouw, B.; Leznoff, C. C. *Nouv. J. Chim.* **1982**, *6*, 653−658. (b) Erdem, S. S.; Nesterova, I. V.; Soper, S. A.; Hammer, R. P. *J. Org. Chem.* **2008**, *73*, 5003−5007.

(11) (a) Young, J. G.; Onyebuagu, W. *J. Org. Chem.* **1990**, *55*, 2155−2159. (b) Ayhan, M. M.; Singh, A.; Hirel, C.; Gürek, A. G.; Ahsen, V.; Jeanneau, E.; Ledoux-Rak, I.; Zyss, J.; Andraud, C.; Bretonnière, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3655−3658. (c) Dong, S.; Bao, C.; Tian, H.; Yan, D.; Geng, Y.; Wang, F. *Adv. Mater.* **2013**, *25*, 1165−1169.

(12) (a) Kobayashi, N.; Ashida, T.; Osa, T. *Chem. Lett.* **1992**, 2031−2034. (b) Yang, J.; Van De Mark, M. R. *J. Heterocycl. Chem.* **1995**, *32*, 1521−1524. (c) Fazio, E.; Jaramillo-García, J.; de la Torre, G.; Torres, T. *Org. Lett.* **2014**, *16*, 4706−4709.

(13) (a) Nolan, K. J. M.; Hu, M.; Leznoff, C. C. *Synlett* **1997**, *1997*, 593−594. (b) Fukuda, T.; Kobayashi, N. *Chem. Lett.* **2002**, 866−867. (c) Kobayashi, N.; Fukuda, T. *J. Am. Chem. Soc.* **2002**, *124*, 8021−8034.

(14) (a) Kobayashi, N. *Chem. Commun.* **1998**, 487−488. (b) Miwa, H.; Kobayashi, N. *Chem. Lett.* **1999**, 1303−1304. (c) Kobayashi, N.; Miwa, H.; Nemykin, V. N. *J. Am. Chem. Soc.* **2002**, *124*, 8007−8020. (d) Chen, X.-W.; Ke, M.-R.; Li, X.-S.; Lan, W.-L.; Zhang, M.-F.; Huang, J.-D. *Chem. - Asian J.* **2013**, *8*, 3063−3070.

(15) Dumoulin, F.; Zorlu, Y.; Ayhan, M. M.; Hirel, C.; Isci, Ü.; Ahsen, V. *J. Porphyrins Phthalocyanines* **2009**, *13*, 161−165.

(16) Dogutan, D. K.; Zaidi, S. H. H.; Thamyongkit, P.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 7701−7714.

(17) Al-Raqa, S. Y. *Dyes Pigm.* **2008**, *77*, 259−265.

(18) (a) Lin, M.-J.; Wang, J.-D.; Chen, N.-S.; Huang, J.-L. *Z. Anorg. Allg. Chem.* **2006**, *632*, 2315−2320. (b) Goslinski, T.; Osmalek, T.; Konopka, K.; Wierzchowski, M.; Fita, P.; Mielcarek, J. *Polyhedron* **2011**, *30*, 1538−1546. (c) Kucinska, M.; Skupin-Mrugalska, P.; Szczolko, W.; Sobotta, L.; Sciepura, M.; Tykarska, E.; Wierzchowski, M.; Teubert, A.; Fedoruk-Wyszomirska, A.; Wyszko, E.; Gdaniec, M.; Kaczmarek, M.; Goslinski, T.; Mielcarek, J.; Murias, M. *J. Med. Chem.* **2015**, *58*, 2240−2255.

(19) Fukuda, T.; Kobayashi, N. In *Handbook of Porphyrin Science*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific: Singapore, 2010; Vol. *9*, pp 1−644.

(20) Shen, T.; Yuan, Z.; Xu, H. *Dyes Pigm.* **1989**, *11*, 77−80.