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Enhancement of phlorin stability by the incorporation of *meso*-mesityl substituents

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Abstract—The effect of sterically bulky mesityl substituents on the stability of *meso*-substituted phlorins was examined. Three different phlorins bearing zero, two or three mesityl substituents were prepared via alkylation of the appropriate porphyrins. The stability of each phlorin was examined by UV–vis spectral monitoring of dilute solutions exposed to ambient light and air. UV–vis and mass spectral analyses performed after decomposition revealed qualitative differences in the degradation products. This study shows that the selection and positioning of peripheral substituents can enhance phlorin stability.

Phlorins are porphyrinic macrocycles that differ from porphyrins by the presence of an sp^3 hybridized carbon atom at one of the four *meso*-positions (Fig. 1). Phlorins bearing a hydrogen atom at the sp^3 hybridized position are dihydroporphyrins and they are tautomeric with chlorins. The presence of the sp^3 hybridized *meso*-position has a profound effect on the properties of phlorins as it disrupts the conjugation of the macrocycle and it distorts the structure from planarity. Phlorins were first identified in the course of Woodward's landmark studies of macrocycles related to chlorophyll a.[1] In the years following that classic work, phlorins have been of significance in a number of contexts. The importance of phlorins in studies of the reduction of porphyrins and metalloporphyrins by photochemical,[2] radiolytic,[3] electrochemical[4] and chemical[5] means is well established. The equilibrium between phlorin and chlorin tautomers has been investigated.[6] Phlorins have been proposed as intermediates in some syntheses of porphyrins[7] and chlorins.[8] Phlorins have been relevant in model studies of coenzyme F430,[9] and a phlorin intermediate has been proposed in the catalytic cycle of haem P460 of hydroxylamine oxidoreductase.[10] Photosensitized electron transfer catalysis of the Mukaiyama aldol reaction by a *N*,*N*′-bridged porphyrin has been shown to proceed through a phlorin intermediate.[11] Studies of the deactivation of molybdenum-based hydrodesulfurization catalysts by metalloporphyrins revealed that the catalyst bound porphyrin is reduced to a phlorin.[12] Phlorins are important species in investigation of reactions of porphyrins and metalloporphyrins with nucleophiles,[13] including thorough studies of reactions with alkyl lithium reagents.[14] Phlorins have been obtained serendipitously upon attempted oxidative cyclization of pentapyrrane species.[15] There has been a growing interest in the preparation of phlorins from small molecule precursors.[16] These recent studies have been motivated, in part, by the anion binding properties of phlorins[15,16b]

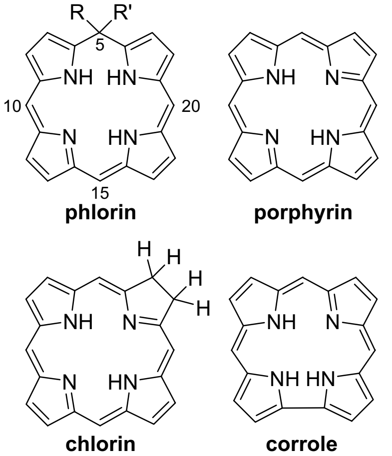

Figure 1. Structures of phlorin, porphyrin, chlorin and corrole.

Keywords: Phlorin; Porphotrimethene; Stability; *meso*-Substituted porphyrin; Alkylation.

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and by the longer wavelength absorption of phlorins relative to porphyrins.

Although the aforementioned studies establish the importance of phlorins within the broader family of porphyrinoids, these studies have also revealed challenges that must be overcome to fully develop phlorin chemistry. Arguably, the most significant of these challenges is the poor stability of most phlorins. Phlorins bearing a hydrogen atom at the sp^3 hybridized *meso*-position are subject to facile oxidation under ambient light and air affording the corresponding aromatic porphyrins. Phlorins for which that pathway is blocked by the incorporation of two substituents at the sp^3 hybridized position are subject to oxidation to ring opened biladienone species. Callot and co-workers have shown that oxidative attack takes place at a *meso*-position adjacent to the sp^3 hybridized atom[17] (i.e., position 10 in Fig. 1).

The small subset of phlorins that is sufficiently stable for isolation and characterization have generally possessed either an electronegative central metal ion (e.g., gold(III)[18]) or structurally distorting, bulky substituents/tethers on one or more of the nitrogen atoms within the core of the macrocycle.[19–21] Both insertion of a metal ion or the addition of core nitrogen substituents impact the interior core of the macrocycle. Only Woodward's observation of a phlorin stabilized by the steric bulk of β-pyrrole substituents adjacent to the sp^3 hybridized atom has demonstrated the potential to improve phlorin stability by the use of peripheral substituents.[1]

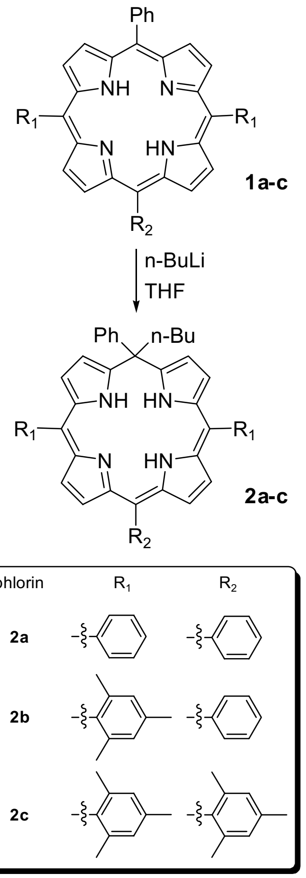
We became interested in phlorins in the course of our studies of *meso*-substituted corroles.[22] Corroles lack one of the four bridging *meso*-positions and their inner core contains three N–H type nitrogen atoms (Fig. 1). The contracted core size of corroles and their trianionic character upon deprotonation and metal insertion facilitate the stabilization of metal ions in high oxidation states.[23] Like corroles, the core of phlorins has three N–H type nitrogen atoms, but unlike corroles, the size of the core is more similar to that of porphyrins—albeit with distortion from planarity. Thus, exploration of phlorin coordination chemistry could prove interesting. Additionally, our observation of a significant effect of different *meso*-substituents on the stability of corroles[22] piqued our curiosity towards the potential impact of peripheral *meso*-substituents on the stability of phlorins. Stable phlorins obtained by a judicious selection of *meso*-substituents would complement those species that have been obtained by the insertion of an electronegative metal ion or by incorporation of structurally distorting *N*-substituents.

Towards that end, we have been investigating the preparation of phlorins bearing different types of *meso*-substituents—in particular, electron withdrawing (e.g., pentafluorophenyl) and sterically bulky (e.g., mesityl) substituents. Electron withdrawing groups are expected to render the *meso*-positions electron poor and therefore less prone to oxidation as has been demonstrated with other porphyrinoids such as corrole.[22] Bulky substituents are expected to sterically shield the *meso*-positions.

Our initial efforts described herein were focused on studies of phlorins bearing sterically bulky mesityl substituents. This starting point was attractive as we suspected that an appropriate series of *meso*-mesityl substituted phlorins could be obtained via Krattinger and Callot's published methodology for the preparation of 5-butyl-5,10,15,20-tetraphenylphlorin **2a** from *meso*-tetraphenylporphyrin (TPP, **1a**) by alkylation with *n*-BuLi (Scheme 1).[24] It was anticipated that alkylation of porphyrins **1b** and **1c** with *n*-BuLi would occur at a *meso*-position bearing a phenyl substituent due to the steric bulk of the mesityl groups.

The known phlorin **2a** lacks any mesityl substituents, and has been reported to be sensitive towards light and air.[24] 5-Butyl-10,20-dimesityl-5,15-diphenylphlorin **2b** has mesityl substituents at the two *meso*-positions adjacent to the sp^3 hybridized atom. These positions have been shown to be sites of oxidative ring opening.[17] 5-Butyl-10,15,20-trimesityl-5-phenylphlorin **2c** has mesityl substituents at all three sp^2 hybridized *meso*-positions.

Of the three porphyrin precursors required for this study, only the preparation of **1c** posed significant difficulty. Porphyrin **1a** is commercially available, and **1b**



Scheme 1. Preparation of phlorins via alkylation of porphyrins.

was prepared via the condensation of 5-mesityldipyrromethane with benzaldehyde as described by Lindsey and co-workers.[25] Unfortunately, the pattern of mesityl substituents present in porphyrin **1c** is not amenable to rational, stepwise synthesis.[26] Thus, we prepared this porphyrin by a mixed aldehyde condensation of mesitaldehyde and benzaldehyde (3:1) with pyrrole according to the BF_3-etherate/ethanol cocatalytic conditions reported by Lindsey and co-workers for the preparation of *meso*-tetramesitylporphyrin.[27] Porphyrin **1c** was isolated from the mixture of porphyrins by silica gel chromatography in a yield of 10% (90 mg). Analysis of **1c** by TLC, laser desorption mass spectrometry (LD-MS) and ^{1}H NMR spectroscopy was consistent with the absence of other porphyrins (see Supplementary data).

Our initial attempts to prepare phlorin **2a** via the conditions of Krattinger and Callot[24] [**1a** in anhydrous THF (10 mg **1a** to 1 mL THF), 3 equiv of *n*-BuLi, −78 °C, 30 min] resulted in inconsistent conversion of the starting material. Our difficulties potentially stemmed from the 2 to 30-fold lower scale employed in our reactions, increasing susceptibility towards adventitious water and to variations in the concentration of *n*-BuLi. Reactions of **1a** were performed on a modest scale in preparation for alkylations of porphyrins **1b** and **1c**, which were available in limited quantities. After a brief survey of reaction conditions (quantity of *n*-BuLi, temperature, solvent volume and time), we found that an elevated temperature of −42 °C, an excess of *n*-BuLi (16 equiv), and a longer reaction time (1 h) provided more consistent formation of **2a**, which was isolated in yields of ~5%. Our modest isolated yield is, in part, due to decomposition of the phlorin during purification (vide infra). The modified conditions were successfully applied to the preparation of **2c** in a yield of 11%. Alkylation conditions for the preparation of **2b** had to be further altered due to the poor solubility of porphyrin **1b** in THF. A reaction temperature of 0 °C and a ~20-fold increase in the volume of THF were employed. The quantity of *n*-BuLi was also increased due to the higher dilution of the reaction. Under these conditions, **2b** was obtained in a yield of 7%. Overall, we found the alkylation of <50 mg quantities of porphyrin to be quite challenging. In each case, a fairly complex reaction mixture was obtained such that extensive chromatography was required to purify the phlorin. All steps were performed under conditions of near total darkness to limit decomposition of the phlorins.

Phlorins **2a**–**c** were initially identified by their UV–vis spectra showing characteristic peaks at ~416, 438 and 675 nm. Analysis of each phlorin by LD-MS and high resolution FAB MS was satisfactory. In addition to the molecular ion, LD-MS analysis of each phlorin showed a peak consistent with loss of the butyl group. ^{1}H NMR analysis of phlorin **2a** was consistent with published data[24] with the exception of improved resolution of the phenyl protons in our spectrum. ^{1}H NMR analysis of phlorins **2b**,**c** provided clear evidence for alkylation at a *meso*-position bearing a phenyl rather than a mesityl substituent. Figure 2 shows key regions of the ^{1}H NMR spectra of phlorins **2a** and **2c**. Each phlorin provided a resonance at 6.3 ppm, consistent with the *ortho*-protons of a phenyl substituent at the sp^3 hybridized position. In addition, the number and integration of mesityl $-CH_3$ resonances were consistent with the proposed phlorin structures. Phlorin **2b** provided three $-CH_3$ resonances of equal area, and **2c** provided six $-CH_3$ resonances with integrated peak areas of 2:2:2:1:1:1.

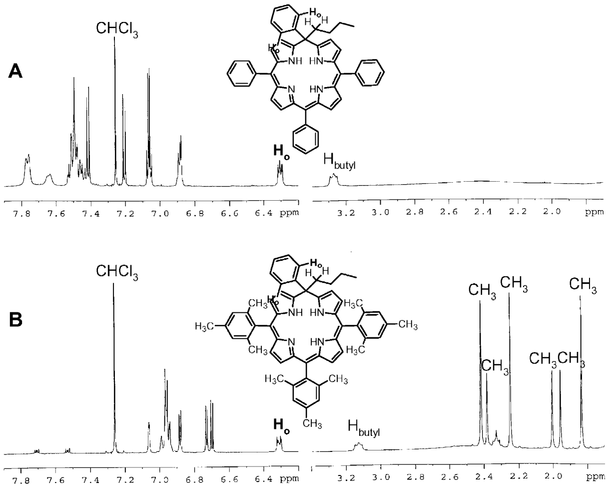


Figure 2. ^{1}H NMR spectra of phlorins: (A) **2a** and (B) **2c**.

The stability of freshly purified samples of each phlorin was assessed in side-by-side experiments. Dilute solutions of phlorins were prepared in the dark in toluene, CH_2Cl_2, acetone, THF, ethyl acetate or acetonitrile. Each solution was transferred to a cuvette and the concentration was adjusted so that the absorbance of the visible band was between 0.4 and 0.8. The samples were then exposed to room lights, and decomposition was monitored by UV–vis spectroscopy. After exposure to light, the absorbance of the visible band with λ_{max} 650–675 nm was observed to decrease (Fig. 3, see the Supplementary data for the complete set of spectra). The absorbance of this band was plotted as a function of time of exposure to light. Representative plots are provided in Figure 4 (see the Supplementary data for the complete set of plots). Once phlorin decomposition was complete, the samples were concentrated and analyzed by LD-MS. The low quantity of phlorins available for these studies precluded a more detailed analysis of the products of degradation. Control solutions of phlorins stored in the dark did not undergo decomposition.

The stability studies revealed clear differences between the three phlorins. Phlorin **2c** was found to be much more stable than the other two phlorins. Under a subset of conditions, the half-life of **2c** was greater than 90 min compared to half-lives of generally less than 15 min for the other phlorins. There was less of a difference between the stabilities of phlorins **2a** and **2b**. The enhanced stability of **2c** over **2b** and the similar stability of **2a** and **2b** show that it is not sufficient to sterically shield

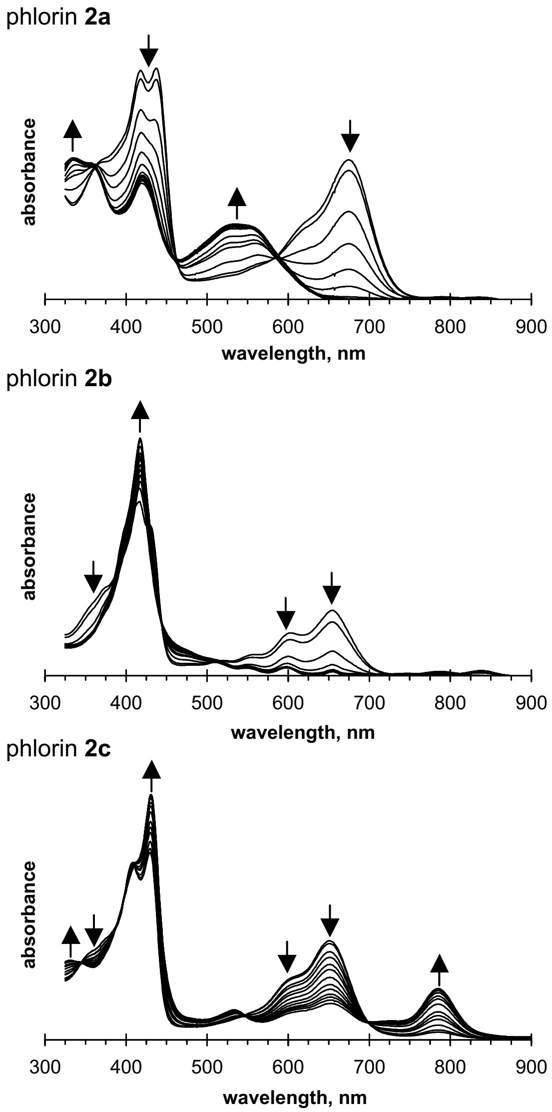


Figure 3. UV–vis spectra of solutions of phlorins **2a**–**c** (CH_2Cl_2) recorded after 0–90 min of exposure to light and air. The arrows indicate the direction of the change.

only the *meso*-positions adjacent to the sp^3 hybridized carbon atom. Degradative pathways are available in addition to that leading to the previously identified biladienones.[17] Differences in the UV–vis spectral changes accompanying the decomposition of **2a**–**c** are consistent with this conclusion (Fig. 3). It is tempting to ascribe the near complete loss of absorbance in the visible region of **2b** to oxidative attack at the unsheltered 15-position, but conclusive evidence for such a pathway remains to be obtained. The appearance of a new absorbance band at longer wavelength in the case of **2c** is interesting, and it defies ready explanation. Although fairly sharp isobestic points were observed in these experiments, analysis by LD-MS provided rather complex spectra. LD-MS analysis revealed qualitative differences between the decomposition products of the three phlorins; however, the complexity of the mass spectra and the possible presence of fragment ions prohibit drawing definitive conclusions.

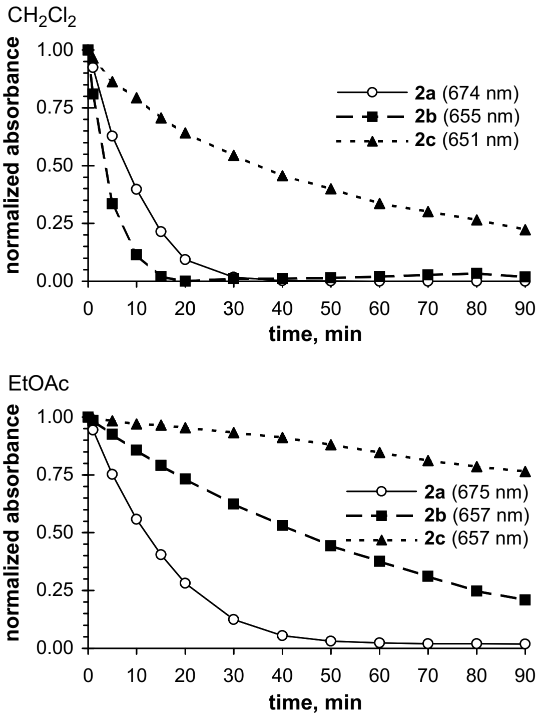


Figure 4. Plots of absorbance as a function of time of exposure to light for solutions of phlorins **2a**–**c** (CH_2Cl_2 or EtOAc). The absorbance wavelengths monitored are indicated on each plot.

The stability studies revealed that the choice of solvent affects phlorin stability. Solvent impacted both the stability of each phlorin and the magnitude of stability differences between the three phlorins. Generally, each phlorin was more stable in solvents of intermediate polarity, and the solvent effect was most pronounced for phlorins **2b** and **2c**. Interestingly, in solvents of lower polarity, **2a** was slightly more stable than **2b**, and in solvents of higher polarity, with the exception of MeCN, the order was reversed. Differences in the dissolved oxygen concentration of each solvent would impact each phlorin equally; thus, it is more likely that the solvent effect stems from other factors such as changes in phlorin conformation and/or reactivity of the excited state. As a practical matter, it is unfortunate that phlorin stability is most poor in non-polar solvents like those used in chromatographic purification. Care must be exercised to rigorously exclude light during purification of each of these phlorins.

In summary, three phlorins were prepared bearing zero, two or three mesityl substituents in defined locations, and the stability of each phlorin towards light and air was compared. The incorporation of sterically bulky mesityl substituents was found to enhance phlorin stability—provided that all three sp^2 hybridized *meso*-positions bear this substituent. The choice of solvent was also found to impact phlorin stability. This study shows that judicious selection of peripheral *meso*-substituents can enhance the stability of phlorins, and thereby provides encouragement for a wider study of phlorins bearing diverse substituents.

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Supplementary data

Complete experimental details, ^{1}H NMR and LD-MS spectra of **1c**, all UV–vis spectra from stability studies of **2a**–**c**, and the complete set plots of phlorin absorbance as a function of time of exposure to light. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.103.

References and notes

1. Woodward, R. B. *Ind. Chim. Belg.* **1962**, *27*, 1293–1308.
2. (a) Mauzerall, D. *J. Am. Chem. Soc.* **1962**, *84*, 2437–2445; (b) Harriman, A. *J. Photochem.* **1985**, *29*, 139–150.
3. (a) Harel, Y.; Meyerstein, D. *J. Am. Chem. Soc.* **1974**, *96*, 2720–2727; (b) Baral, S.; Hambright, P.; Neta, P. *J. Phys. Chem.* **1984**, *88*, 1595–1600; (c) Sutter, T. P. G.; Rahimi, R.; Hambright, P.; Bommer, J. C.; Kumar, R.; Neta, P. *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 495–502.
4. (a) Lanese, J. G.; Wilson, G. S. *J. Electrochem. Soc.* **1972**, *119*, 1039–1043; (b) Langhus, D. L.; Wilson, G. S. *Anal. Chem.* **1979**, *51*, 1139–1144; (c) Marrese, C. A.; Carrano, C. J. *Inorg. Chem.* **1983**, *22*, 1858–1862; (d) Marrese, C. A.; Carrano, C. J. *Inorg. Chem.* **1984**, *23*, 3961–3968; (e) Abou-Gamra, Z.; Harriman, A.; Neta, P. *J. Chem. Soc. Faraday Trans. 2* **1986**, *82*, 2337–2350.
5. (a) Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1963**, *85*, 818–819; (b) Fuhrhop, J.-H.; Mauzerall, D. *J. Am. Chem. Soc.* **1968**, *90*, 3875–3876.
6. Whitlock, H. W.; Oester, M. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5738–5741.
7. (a) Rocha Gonsalves, A. M. d'A.; Pereira, M. M. *J. Heterocycl. Chem.* **1985**, *22*, 931–933; (b) Lash, T. D. *J. Porphyrins Phthalocyanines* **1997**, *1*, 29–44; (c) Lash, T. D. V.; Gandhi, V. *J. Org. Chem.* **2000**, *65*, 8020–8026.
8. (a) Burns, D. H.; Caldwell, T. M.; Burden, M. W. *Tetrahedron Lett.* **1993**, *34*, 2883–2886; (b) Burns, D. H.; Shi, D. C.; Lash, T. D. *Chem. Commun.* **2000**, 299–300.
9. (a) Stolzenberg, A. M.; Stershic, M. T. *Inorg. Chem.* **1987**, *26*, 3082–3083; (b) Stolzenberg, A. M.; Stershic, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 6391–6402.
10. Arciero, D. M.; Hooper, A. B. *Biochem. Soc. Trans.* **1998**, *26*, 385–389.
11. Wada, K.-i.; Yamamoto, M.; Setsune, J.-i. *Tetrahedron Lett.* **1999**, *40*, 2773–2776.
12. Mitchell, P. C. H.; Scott, C. E. *Polyhedron* **1986**, *5*, 237–241.
13. (a) Pandian, R. P.; Chandrashekar, T. K.; Chandrasekhar, V. *Indian J. Chem.* **1991**, *30A*, 579–583; (b) Segawa, H.; Azumi, R.; Shimidzu, T. *J. Am. Chem. Soc.* **1992**, *114*, 7564–7565; (c) Jiang, X.; Nurco, D. J.; Smith, K. M. *Chem. Commun.* **1996**, 1759–1760; (d) Collman, J. P.; Boulatov, R. *J. Am. Chem. Soc.* **2000**, *122*, 11812–11821.
14. (a) Setsune, J.; Yazawa, T.; Ogoshi, H.; Yoshida, Z. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1641–1645; (b) Senge, M. O.; Kalisch, W. W.; Bischoff, I. *Chem. Eur. J.* **2000**, *6*, 2721–2738; (c) Feng, X.; Bischoff, I.; Senge, M. O. *J. Org. Chem.* **2001**, *66*, 8693–8700.
15. Ka, J. W.; Lee, C. H. *Tetrahedron Lett.* **2001**, *42*, 4527–4529.
16. (a) Bucher, C.; Seidel, D.; Lynch, V.; Kral, V.; Sessler, J. L. *Org. Lett.* **2000**, *2*, 3103–3106; (b) Hong, S. J.; Ka, J. W.; Won, D. H.; Lee, C. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 661–663.
17. Jeandon, C.; Krattinger, B.; Ruppert, R.; Callot, H. J. *Inorg. Chem.* **2001**, *40*, 3149–3153.
18. Sugimoto, H. *J. Chem. Soc. Dalton. Trans.* **1982**, 1169–1171.
19. (a) Setsune, J.-i.; Ikeda, M.; Iida, T.; Kitao, T. *J. Am. Chem. Soc.* **1988**, *110*, 6572–6574; (b) Setsune, J.-i.; Ishimaru, Y.; Kitao, T. *Chem. Lett.* **1990**, 1351–1354; (c) Setsune, J.-i.; Yamaji, H.; Kitao, T. *Tetrahedron Lett.* **1990**, *31*, 5057–5060; (d) Setsune, J.-i.; Wada, K.-i.; Higashino, H. *Chem. Lett.* **1994**, 213–216; (e) Setsune, J.-i.; Kashihara, K.; Wada, K.-i. *Chem. Lett.* **2001**, 608–609.
20. (a) Krattinger, B.; Callot, H. J. *Chem. Commun.* **1996**, 1341–1342; (b) Ruppert, R.; Jeandon, C.; Sgambati, A.; Callot, H. J. *Chem. Commun.* **1999**, 2123–2124.
21. Ishimaru, Y.; Sumida, S.; Iida, T. *Tetrahedron Lett.* **2001**, *42*, 419–421.
22. Geier, G. R., III; Chick, J. F. B.; Callinan, J. B.; Reid, C. G.; Auguscinski, W. P. *J. Org. Chem.* **2004**, *69*, 4159–4169.
23. (a) Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, pp 233–300; (b) Gross, Z. *J. Biol. Inorg. Chem.* **2001**, *6*, 733–738.
24. (a) Krattinger, B.; Callot, H. J. *Tetrahedron Lett.* **1996**, *37*, 7699–7702; (b) Krattinger, B.; Callot, H. J. *Eur. J. Chem.* **1999**, 1857–1867.
25. Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864–2872.
26. Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
27. (a) Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1989**, *54*, 828–836; (b) Wagner, R. W.; Li, F.; Du, H.; Lindsey, J. S. *Org. Process Res. Dev.* **1999**, *3*, 28–37.