ORGANIC
LETTERS

2007
Vol. 9, No. 13
2493−2496

Synthesis of *meso*-5-Azaindolyl-Appended Zn(II) Porphyrins via Pd-Catalyzed Annulation

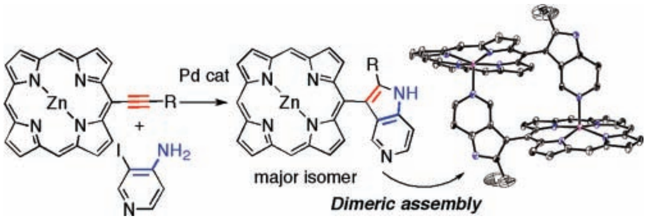
Chihiro Maeda, Hiroshi Shinokubo,* and Atsuhiro Osuka*

*Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku,
Kyoto 606-8502, Japan*

osuka@kuchem.kyoto-u.ac.jp; hshino@kuchem.kyoto-u.ac.jp

Received April 16, 2007

ABSTRACT



Pd-catalyzed annulation reaction of *meso*-hexynyl Zn(II) porphyrin with 4-amino-3-iodopyridine efficiently provides *meso*-3-(5-azaindolyl)-substituted Zn(II) porphyrin as a major product, which assembles to form a slipped cofacial dimer by the complementary coordination of the pyridine moiety to the Zn(II) center. 2-Iodoaniline and 2-iodophenol also undergo this [3 + 2] annulation with the *meso*-hexynyl Zn(II) porphyrin to furnish *meso*-indolyl- and benzofuranyl-substituted Zn(II) porphyrins, respectively.

In recent years, extensive efforts have been made toward construction of discrete supramolecular assemblies of porphyrins,[1] which are appealing as models of photosynthetic special pairs due to considerably lowered excitation energy levels,[2] as models of photosynthetic antennae due to efficient excitation energy hopping,[3] as porous materials,[4] and as nonlinear optical materials due to large nonlinear optical responses.[5] Complementary coordination interactions between central metals and coordinating sidearms often play an important role in these assembling processes. Among these, we reported self-sorting assembling of pyridine-appended *meso*−*meso*-linked zinc(II) diporphyrins, where the angle of the coordinating atom with regard to the porphyrin plane controls the size and thus structures of the assemblies.[6] In particular, we found that *meso*-cinchomeronimide-appended *meso*−*meso*-linked zinc(II) diporphyrins exhibit high-fidelity self-sorting assembling to form discrete cyclic trimers, tetramers, and pentamers through almost perfect discrimination of enantiomeric and conformational differences of the cinchomeronimide substituents (Scheme 1).[6c] These supramolecular cyclic porphyrin arrays are structurally attractive but display significant fluorescence quenching, probably due to intramolecular electron transfer from the photoexcited zinc(II) porphyrin moieties to the appended imide moieties. This is a serious drawback as

---

(1) (a) Imamura, T.; Fukushima, K. *Coord. Chem. Rev.* **2000**, *198*, 133. (b) Wojaczynski, J.; Latos-Grazynski, L. *Coord. Chem. Rev.* **2000**, *204*, 113. (c) Ingeno, E.; Zangrando, E.; Alessio, E. *Eur. J. Inorg. Chem.* **2003**, 2371. (d) Satake, A.; Kobuke, Y. *Tetrahedron* **2005**, *61*, 13.

(2) (a) Kobuke, Y.; Miyaji, H. *J. Am. Chem. Soc.* **1994**, *116*, 4111. (b) Stibrany, R. T.; Vasudevan, J.; Knapp, S.; Potenza, J. A.; Emge, T.; Schugar, H. J. *J. Am. Chem. Soc.* **1996**, *118*, 3980.

(3) (a) Hwang, I.-W.; Yoon, Z. S.; Kim, J.; Kamada, T.; Ahn, T. K.; Aratani, N.; Osuka, A.; Kim, D. *J. Photochem. Photobiol. A* **2006**, *178*, 130. (b) Hajjaj, F.; Yoon, Z. Y.; Yoon, M.-C.; Park, J.; Satake, A.; Kim, D.; Kobuke, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4612.

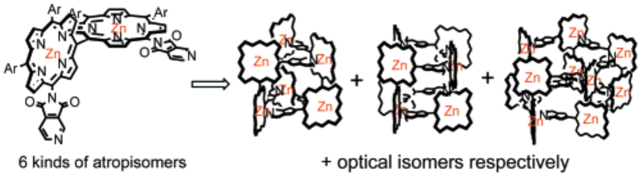
(4) (a) Belanger, S.; Hupp, J. T.; Stern, C. L.; Slone, R. V.; Watson, D. F.; Carrell, T. G. *J. Am. Chem. Soc.* **1999**, *121*, 557. (b) Mines, G. A.; Tzeng, B.-C.; Stevenson, K. J.; Li, J.; Hupp, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 154.

(5) (a) Screen, T. E.; Throne, J. R. G.; Denning, R. G.; Buchnall, D. G.; Anderson, H. L. *J. Am. Chem. Soc.* **2002**, *124*, 9712. (b) Ogawa, K.; Ohashi, A.; Kobuke, Y.; Kamada, K.; Ohta, K. *J. Am. Chem. Soc.* **2003**, *125*, 13356.

(6) (a) Tsuda, A.; Nakamura, T.; Sakamoto, S.; Yamaguchi, K.; Osuka, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2817. (b) Hwang, I.-W.; Kamada, T.; Ahn, T. K.; Ko, D. M.; Nakamura, T.; Tsuda, A.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2004**, *126*, 16187. (c) Kamada, T.; Aratani, N.; Ikeda, T.; Shibata, N.; Higuchi, Y.; Wakamiya, A.; Yamaguchi, S.; Kim, K. S.; Yoon, Z. S.; Kim, D.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 7670.

10.1021/ol070885k CCC: $37.00

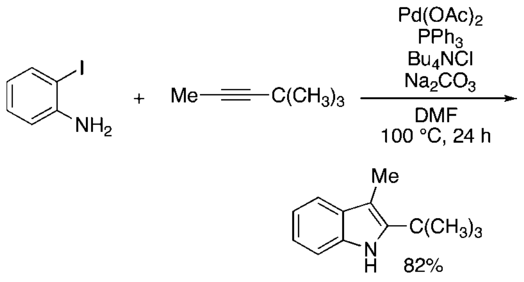
Scheme 1. Self-Sorting Assembling of *meso*-Cinchomeronimide-Appended Zn(II) Diporphyrins



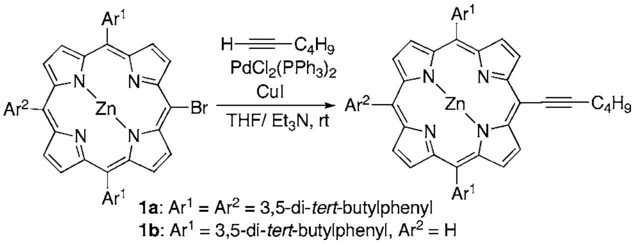
photosynthetic antenna models. We then came up with a 5-azaindolyl-appended porphyrin as a fluorescent building block for similar self-sorting assembling. However, the literature has shown that there is no report on the synthesis of such porphyrins. Even *meso*-indolyl-appended porphyrins are not known. Here it is worth noting that the synthesis of such functionalized porphyrins as pyridine-derivative-appended porphyrins is not trivial through the acid-catalyzed condensation method.

We propose a transition-metal-catalyzed cyclization on a side chain of porphyrins for the synthesis of functionalized porphyrins, demonstrated by the efficient synthesis of *meso*-(5-azaindolyl)-substituted porphyrins via the Pd-catalyzed [3 + 2] annulation reaction of *meso*-hexynyl porphyrin and 4-amino-3-iodopyridine. This type of approach is logically feasible but has not been investigated so far in porphyrin synthesis. The [3 + 2] annulation of alkynes with 2-iodoanilines and related iodoheteroaromatics, which has been mainly developed by Larock et al., is a convenient and selective method for the synthesis of a variety of indole derivatives (Scheme 2).[7]

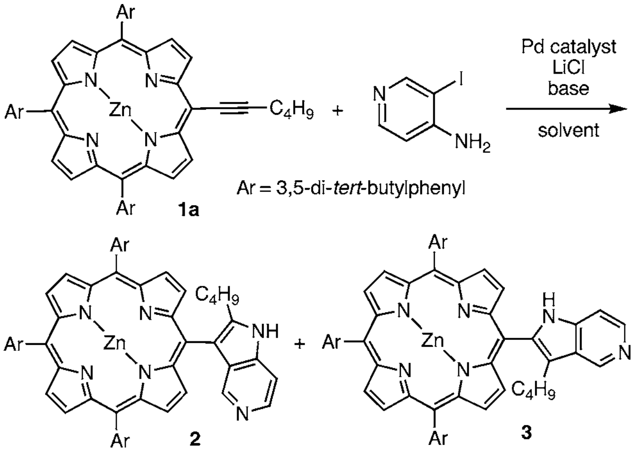
Scheme 2. Larock's [3 + 2] Annulation of Alkynes with 2-Iodoaniline



Scheme 3. Synthesis of *meso*-Hexynyl Zn(II) Porphyrin **1**



Scheme 4. Pd-Catalyzed Annulation Reaction of *meso*-Hexynyl Zn(II) Porphyrin with 4-Amino-3-iodopyridine



meso-Hexynyl Zn(II) porphyrins **1a** and **1b** were prepared by the Sonogashira coupling reaction of *meso*-bromoporphyrin with 1-hexyne (Scheme 3). The reaction of hexynyl porphyrin **1a** with 4-amino-3-iodopyridine (4 equiv), LiCl (1 equiv), and Na_2CO_3 (2 equiv) in the presence of 20 mol % of $PdCl_2(dppf)$ as the catalyst in DMF gave one major product **2** and a trace amount of byproduct **3**. These compounds showed their parent ion peaks both at $m/z = 1109.61$ by ESI-TOF mass spectroscopy that matched well with the azaindolyl-substituted porphyrins (calcd for $C_{77}H_{85}N_6Zn = 1109.61$) (Scheme 4). In $CDCl_3$, the ^1H NMR spectrum of **2** shows a simple set of peaks with large upfield shifts for the pyridine protons, suggesting the formation of aggregates via the coordination of the pyridine moiety to the Zn(II) porphyrin core. In contrast, that of **3** displays several broad signals, including upfield-shifted protons, probably because of nondiscrete assemblies (Supporting Information, SI). Both **2** and **3** display sharp ^1H NMR spectra in pyridine-d_5 (SI). Initially, we anticipated that compound **3** would be the major isomer on the basis of the previous works,[7] where a more sterically demanding substituent is located at the 2-position of indoles (Scheme 2). Contrary to our expectation, however, X-ray diffraction analysis unambiguously elucidated that the major product is 3-(5-azaindolyl)-substituted Zn(II) porphyrin **2**, which forms a dimeric assembly **2**$_2$ constructed by the coordination between nitrogen and zinc atoms (Figure 1).[8] On the other hand, although the data were preliminary, X-ray diffraction analysis of **3** shows that **3** formed a linear assembly as expected from the ^1H NMR spectrum (SI). After several examinations, the use of a catalyst combination of $Pd_2(dba)_3-P(o\text{-tol})_3$ and a toluene−

---

(7) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc*. **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem*. **1998**, *63*, 7652. (c) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (d) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Cytonowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823. (e) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471. (f) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627.

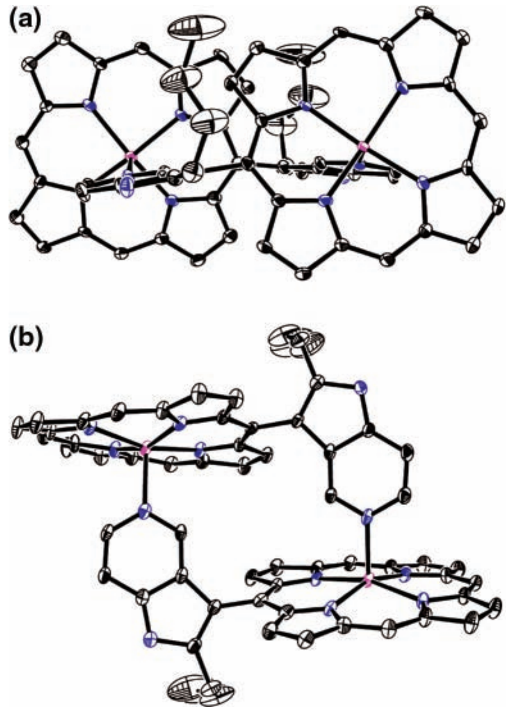


Figure 1. X-ray crystal structure of the dimeric assembly of $\mathbf{2}_2$. (a) Top view and (b) side view. Hydrogen atoms and *meso*-aryl groups were omitted for clarity. The thermal ellipsoids were at the 50% probability level.

Table 1. Optimization of the Reaction Conditions[a]

Pd source	ligand	solvent	yield (**2**/**3**/**1a**)
$PdCl_2$(dppf)	none	DMF	50/2/13
$Pd_2(dba)_3$	none	DMF	27/2/30
$Pd_2(dba)_3$	dppf	DMF	–/–/–[b]
$Pd_2(dba)_3$	P(*o*-tol)$_3$	DMF	–/–/–[b]
$PdCl_2$(dppf)	none	DMF/toluene	36/6/38
$Pd_2(dba)_3$	none	DMF/toluene	28/3/57
$Pd_2(dba)_3$	PPh_3	DMF/toluene	24/–[b]/70
$Pd_2(dba)_3$	dppf	DMF/toluene	18/–[b]/61
$Pd_2(dba)_3$	P(*o*-tol)$_3$	DMF/toluene	51/–[b]/49

[a] Reaction conditions: **1a** (10 μmol), 4-amino-3-iodopyridine (4 equiv), Pd source (20 mol %, as palladium), ligand (80 mol %), LiCl (1 equiv), Na_2CO_3 (2 equiv), in DMF (1 mL) or DMF/toluene (1 mL/1 mL), 100 °C, 48 h. [b] Not detected.

DMF mixed solvent turned out to be optimal among the various reaction conditions we investigated (Tables 1 and 2). On the other hand, Ni(II) porphyrin and free-base porphyrin were almost unreactive under the same reaction conditions.

Table 2. Optimization of the Reaction Conditions[a]

base	temp, time	yield (**2**/**3**/**1a**)
Na_2CO_3	100 °C, 48 h	51/–[b]/49
K_2CO_3	100 °C, 48 h	47/5/32
Cs_2CO_3	100 °C, 48 h	40/2/49
Na_2CO_3	80 °C, 48 h	23/–[b]/77
Na_2CO_3	120 °C, 48 h	16/–[b]/52
Na_2CO_3	100 °C, 96 h	61/5/31

[a] Reaction conditions: **1a** (10 μmol), 4-amino-3-iodopyridine (4 equiv), $Pd_2(dba)_3$ (10 mol %), P(*o*-tol)$_3$ (80 mol %), LiCl (1 equiv), base (2 equiv), in DMF/toluene (1 mL/1 mL), 100 °C, 48 h. [b] Not detected.

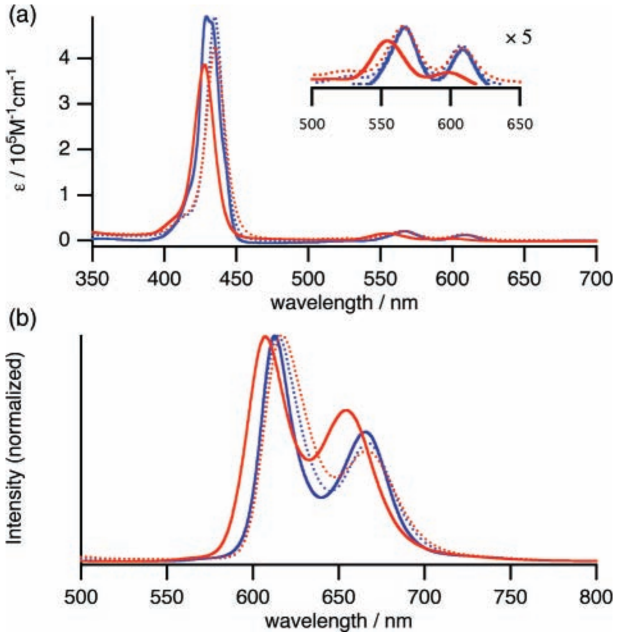


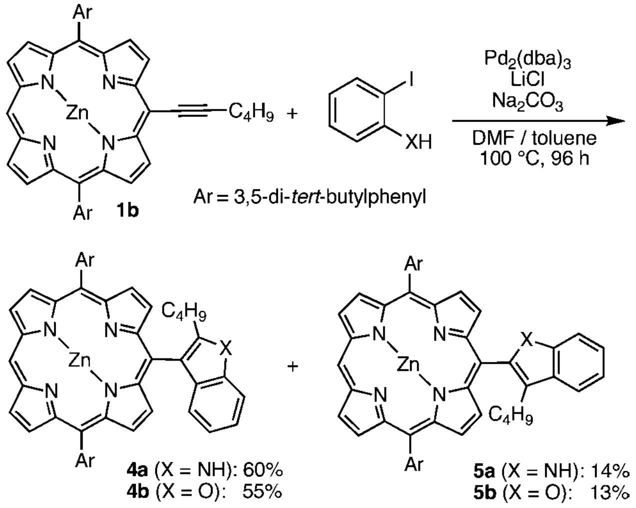
Figure 2. (a) UV−vis absorption and (b) fluorescence spectra of **2** and **3** (blue solid line is **2** in $CHCl_3$ (1.8×10^{-6} M), blue dashed line is **2** in pyridine, red solid line is **3** in $CHCl_3$ (1.9×10^{-6} M), red dashed line is **3** in pyridine).

UV−vis absorption and fluorescence spectra of these azaindolyl-appended Zn(II) porphyrins are shown in Figure 2. The absorption spectrum of **2** in $CHCl_3$ shows a small splitting of the Soret band at 430 nm and almost the same Q bands as the spectra of **2** and **3** in pyridine, indicating pyridine coordination to the zinc porphyrin. These suggest that **2** forms the dimeric assembly even in such a highly diluted solution. In contrast, the aggregate of **3** is completely dissociated in this concentration. The fluorescence spectrum of **2** in $CHCl_3$ is concentration dependent in the range of roughly 10^{-8} to 10^{-7} M (SI). On the basis of absorption spectra in pyridine, the lower energy bands at 655 nm at $<10^{-8}$ M and at 665 nm at $>10^{-7}$ M can be ascribed to four-coordinate and five-coordinate zinc porphyrin units, respectively. A good fit for the observed sigmoidal curve is obtained by assuming porphyrin dimer formation ($\mathbf{2}_2$), which

---

(8) Crystallographic data for **2**: $C_{77}H_{94}N_6Cl_3OZn$, M_w = 1291.30, triclinic, space group $P\bar{1}$ (No. 2), a = 11.7096(19), b = 20.183(3), c = 31.905(5) Å, α = 98.296(3), β = 94.448(3), γ = 96.059(3)°, V = 7387(2) Å^3, T = 90 K, D_{calcd} = 1.161 g cm^{-3}, Z = 2. For 35370 reflections measured; R_1 = 0.093, wR_2 = 0.170 for 25307 reflections with [$I > 2\sigma(I)$], GOF = 1.065.

Scheme 5. Pd-Catalyzed Annulation Reaction of *meso*-Hexynyl Zn(II) Porphyrin with 2-Iodoaniline and 2-Iodophenol



gives an association constant of $K_2 = 1.0 \times 10^8\ M^{-1}$. On the other hand, the fluorescence spectrum of **3** is not concentration dependent in the range of 10^{-6} M or lower, and the association constant is estimated to be lower than $K_2 = 1.0 \times 10^5\ M^{-1}$ (SI). These results are in good agreement with the results of absorption spectra of **2** and **3**. Their quantum yields in toluene were 4.3% for **2** and 5.7% for **3**.[9] Owing to a lack of significant quenching processes, assemblies based on these molecules are expected to work as photosynthetic antenna models.

2-Iodoaniline and 2-iodophenol also undergo similar [3 + 2] annulation to furnish *meso*-indolyl- and benzofuranyl-substituted porphyrins **4** and **5** (Scheme 5). In these cases, the addition of tri(*o*-tolyl)phosphine as the ligand lowered yields of **4** and **5**. *meso*-3-Indolyl-substituted porphyrin **4a** was obtained as a major product, of which assignment was determined on the basis of the chemical shifts of protons on the indole ring compared to the nonsubstituted indole. The ^{1}H NMR spectrum of **4a** exhibits a slight downfield shift for the 4-position of the indole ring, probably because of the ring current effect of the porphyrin core, while peaks of **5a** stay in the same region for indole protons as the nonsubstituted indole. *meso*-3-Benzofuranyl porphyrin **4b** was also obtained in good yield as the major isomer.

In summary, the efficient synthesis of *meso*-5-azaindolyl-, indolyl-, and benzofuranyl-substituted porphyrins has been achieved through a Pd-catalyzed annulation reaction. *meso*-5-Azaindolyl Zn(II) porphyrin forms a dimeric assembly by the coordination of the pyridyl moiety to the Zn(II) center. This type of modification on porphyrin substituents after porphyrin synthesis would be useful to gain highly functionalized porphyrinic molecules. Further investigations on the supramolecular chemistry and photochemistry of porphyrin arrays obtained by this protocol are currently being investigated in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures, compound data, association constants for **2** and **3**, preliminary X-ray structure for **3**, and crystallographic data for **2** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070885K

---

[9] The quantum yield was determined in comparison with Zn(II) tetraphenylporphyrin ($\Phi_F = 0.033$) as the standard sample.