<u>LETTERS</u>

Construction of Bisbenzofuro[2,3-b:3',2'-e]pyridines by Palladium-Catalyzed Double Intramolecular Oxidative C–H/C–H Coupling

Hiroyuki Kaida,[†] Tsuyoshi Goya,[‡] Yuji Nishii,[§] Koji Hirano,^{†©} Tetsuya Satoh,^{†,||©} and Masahiro Miura^{*,†©}

[†]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[‡]Advanced Materials Research Center, Nippon Shokubai Co. Ltd., 5-8 Nishi Otabi-cho, Suita, Osaka 564-8512, Japan

[§]Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

^{II}Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

(5) Supporting Information

ABSTRACT: The palladium-catalyzed intramolecular oxidative C-H/C-H coupling of 2-aryloxypyridines as challenging substrates is investigated to construct an important class of N,O-mixed heteroacenes, i.e. benzofuropyridines. It is found that 2,6-diaryloxypyridines efficiently undergo double cyclization to provide bisbenzofuro[2,3-b:3',2'-e]pyridines of interest in materials chemistry.

P olycondensed heteroacenes are increasingly important as organic functional materials. Besides the well-established benzothiophene-fused series of thienoacenes,¹ benzofuran-fused polyaromatic compounds² and O,X-mixed heteroacenes (X = S, N, P, etc.) such as benzofuro[3,2,b]benzothiophenes,³ -indoles,⁴ and -benzophospholes⁴ are also attracting attention since they show intriguing photophysical and electrochemical properties. On the other hand, benzofuropyridines are of substantial interest owing to their significant biological activities⁵ as well as physical properties.⁶ Among various methods for constructing the multiring systems, the palladium-catalyzed intramolecular cross-coupling of aryl heteroaryl ethers is promising. In particular, the oxidative C-H/C-H coupling appears to be potentially useful because of its simplicity and atom-economic nature (eq 1).⁷



In the context of our continuous studies of direct C–H functionalization chemistry, we recently reported that 3aryloxy-thiophenes and -benzothiophenes effectively undergo palladium-catalyzed oxidative cyclization in the presence of a silver salt as the terminal oxidant to furnish the corresponding benzofuro[3,2-*b*]thiophenes (Het = 3-thienyl in eq 1).⁸ A similar transformation was independently reported by Kanai and Kuninobu.⁹ Under the palladium catalysis, the double and triple cyclization reactions of diaryloxy- and triaryloxy-benzenes to give rise to benzobis- and benzotris-benzofurans could effectively be performed.¹⁰ We were then interested in the oxidative cyclization of 2-aryloxypyridines (Het = 2-pyridyl in



eq 1): They appear to be particularly challenging substrates bearing an electron-deficient pyridine moiety with coordinating ability, while the starting ethers are readily available by conventional substitution reactions of 2-halopyridines with phenols and the cyclized products may be of potential utility.^{5,6} We herein report that 2,6-diphenoxypyridines efficiently undergo double cyclization under palladium catalysis to provide five-ring-condensed bisbenzofuro[2,3-*b*:3',2'-*e*]pyridines, which are of interest in the area of materials chemistry.⁶ In addition, cardinal optoelectronic properties of the N,O-mixed heteroacene core are also described.

When 2,6-diphenoxypyridine (1a, 0.2 mmol) was treated with 3.0 mol % of $Pd(TFA)_2$ (TFA = trifluoroacetate) and 4.0 equiv of AgOAc in PivOH (pivalic acid) at 150 °C for 6 h, the corresponding doubly cyclized bisbenzofuropyridine 2a was successfully obtained in 61% yield (73% yield with 10 mol % of Pd in a 1.0 mmol scale) (Table 1). Similarly, 4,4'-dimethyl-, dipropyl-, diisopropyl-, and di-tert-butyl-substituted 2,6diphenoxypyridines 1b-1e gave bisbenzofuropyridines 2b-2e. The electron-donating methoxy-substituted 1f was transformed to 2f, albeit in a lower yield. It was of considerable interest that the substitution of electron-withdrawing trifluoromethyl did not hamper the cyclization and bisbenzofuropyridine 2g was obtained in a good yield. 3,3'- or 2,2'-Dimethyl and 3,3'- or 2,2'-di-tert-butyl-substituted 1h-1k also cyclized to furnish 2h-2k. It is worth noting that the reactions of 1h and 1i took place only at the less hindered 6-position.

Next, we examined the synthesis of unsymmetrically substituted bisbenzofuropyridines (Table 2). To gain the

Received: January 30, 2017

product, yield^b substrate 1a B = H 2a: R = H, 61% (73%)^c 1b: R = Me 2b: R = Me, 64% **1c**: $R = n - C_3 H_7$ **2c**: R = *n*-C₃H₇, 66% **2d**: R = *i*-C₃H₇, 74% **1d**: $R = i - C_3 H_7$ 1e: R = t-Bu **2e**: R = *t*-Bu, 73% 1f: B = OMe 2f: R = OMe, 31% 1g: R = CF₃ 2g: R = CF₃, 62% R 1h: R = Me 2h: R = Me. 63% 1i: R = t-Bu 2i: R = t-Bu, 71% 1j: R = Me 1k: R = *t*-Bu **2j**: R = Me, 66% **2k**: R = *t*-Bu, 55%

Table 1. Double Cyclization of 2,6-Diaryloxypyridines $1a-1k^a$



Table 2. Double Cyclization of Unsymmetrically Substituted 2,6-Diaryloxypyridines $3a-3j^a$



^{*a*}Reaction conditions: **3** (0.20 mmol), $Pd(TFA)_2$ (0.006 mmol, 3 mol %), and AgOAc (0.8 mmol, 4 equiv) in PivOH (2 mL) in a 10 mL Schlenk tube at 150 °C for 6 h under air. ^{*b*}Isolated yield.

solubility of products, substrates 3a-3j bearing a 4-*tert*-butyl group were employed. Benzyl, phenyl, chloro, benzoyl, and nitro groups as well as methyl and methoxy groups were tolerable to afford 4a-4i in good yield. 1-Naphthyloxy-substituted 3j selectively gave six-ring-condensed compound 4j. The reactive functional groups in 4 may be further manipulated to afford divergent derivatives. As an example, 4f was subjected to the Suzuki-Miyaura coupling with 4-pyridylboronic acid to lead to compound 5 in 81% yield (eq 2).



The reaction of simple 2-phenoxypyridine itself unfortunately did not occur under the present conditions, and only the substrate was recovered. However, 2-(4-tert-butylphenoxy)quinoline (6) underwent cyclization to produce benzofuroquinoline 7 in 44% yield (eq 3). 2,6-Bis(6-tert-butyl-2pyridinyloxy)toluene (8) could be transformed to compound 9 in 44% yield (eq 4), while only less than 10% of product was formed from the 6-methyl-2-pyridinyloxy analog of 8 (not shown). These results may imply that a sterically demanding circumstance around the pyridyl nitrogen is required for the reaction to proceed smoothly.¹¹

Though the detailed mechanism of the present reaction is not definitive at this stage, the cyclization may be considered to occur through palladation on the phenyl ring followed by that on the pyridyl ring (or its reverse order) to form a sixmembered palladacycle and the subsequent reductive elimination leads to the product. The precedence of the initial palladation would depend on the substituent of the phenyl ring. It should be noted that the reaction of **1e** in acetic acid- d_4 /

Organic Letters

pivalic acid (1:1, v/v) at 130 °C for 3 h gave the monocyclized product 2e' and 2e in 38% and 26% yields, respectively, with recovery of 1e (23%) (eq 5). No incorporation of deuterium was observed in 1e and 2e'. This suggests that the metalation step via C–H cleavage is not reversible, which contrasted the fact that, in the relevant reaction of 1,3,5-tris(4-*tert*-butylphenyloxyl)benzene, significant amounts of deuterium were introduced into the central benzene ring of the starting material and the intermediary mono- and dicyclized products (ca. 50% D in each central-ring hydrogen, not shown).

The synthesis of **2a** and some of its derivatives as candidates of electroluminescent and semiconducting materials was previously described using a sequence of Suzuki–Miyaura coupling/diazonium substitution starting from 2,6-diamino-3,5diiodopyridine in the patent literature.⁶ However, no spectroscopic and electrochemical data were given. Consequently, to provide a basic set of information about optelectronic properties of the bisbenzofuro[2,3-b:3',2'-e]pyridine core, we first measured the absorption and emission spectra of 4,4'-di-tert-butyl-substituted **2e** having substantial solubility as the representative compound (Figure 1). The UV/



Figure 1. Normalized absorption (left, 1.0×10^{-5} M, CHCl₃), fluorescence (center, 1.0×10^{-6} M, CHCl₃), and phosphorescence spectra (right, 1.0×10^{-4} M, CHCl₃/EtOH 1:4 v/v at 77 K) spectra of **2e**.

vis spectrum of **2e** showed intense peaks at 340 and 347 nm, and its fluorescence spectrum showed a band with a maximum at 360 nm (CHCl₃, $\Phi_{\rm F}$ = 0.70), indicating a relatively small Stokes shift. Interestingly, the phosphorescence spectrum (77 K, CHCl₃–EtOH 1:4 v/v) showed a strong peak at 431 nm. The cyclic voltammogram of **2e** indicated its ambipolar character showing both oxidation and reduction peaks (Figure 2). Based on these data, $E_{\rm HOMO}$ ($E_{\rm OX}$ in CV), $E_{\rm g}$ (UV/vis), and $E_{\rm T}$ (phosphorescence spectrum) of **2e** were estimated to be -6.11, 3.44, and 2.88 eV, respectively, indicating a wide



Figure 2. Cyclic voltammogram of 2e in *o*-dichlorobenzene/ acetonitrile (10:1, v/v) containing 0.1 M Bu₄NPF₆ at a scan rate of 100 mV s⁻¹.

HOMO/LUMO energy gap and a relatively high $E_{\rm T}$ value, which may meet requirements in the application to OLED devise materials.^{12,13} The X-ray crystal analysis of **2e** showed that it has a planar structure as expected (Figure 3a). One of



Figure 3. X-ray structure of 2e (a) and HOMO and LUMO of 2a calculated at B3LYP/6-31G(d) level of theory (b).

the major reasons for the wide HOMO/LUMO energy gap is the unique orbital distributions in the HOMO and LUMO: the HOMO has a node without participation of the central perpendicular p orbitals of N and C atoms, while those of the two oxygen atoms are not involved in the LUMO (Figure 3b).

In summary, we have developed an effective method for the flexible construction of N,O-mixed heteroacenes such as bisbenzofuro[2,3-b:3',2'-e]pyridine derivatives by means of double intramolecular oxidative C-H/C-H coupling. The condensed five-ring system appears to be a useful core of organic materials such as OLED components, and fine-tuning of the physical properties by the new synthetic method and the construction of related mixed heteroacene systems are underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b00323.

¹H and ¹³C{¹H} spectra for products (PDF) Crystallographic data for **2e** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: miura@chem.eng.osaka-u.ac.jp. ORCID [®]

Koji Hirano: 0000-0001-9752-1985 Tetsuya Satoh: 0000-0002-1792-140X Masahiro Miura: 0000-0001-8288-6439 Notes

notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported, in part, by JSPS KAKENHI Grant Number JP 24225002 (Grant-in-Aid for Scientific Research (S)) to M.M. and JSPS KAKENHI Grant Number JP16H01037 (in Precisely Designed Catalysts with Customized Scaffolding) and JST (ACT-C), Japan to T.S.

Organic Letters

REFERENCES

(1) For reviews: (a) Murphy, A. R.; Fréchet, J. M. J. Chem. Rev. 2007, 107, 1066. (b) Takimiya, K.; Shinamura, S.; Osaka, I.; Miyazaki, E. Adv. Mater. 2011, 23, 4347. (c) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. Chem. Rev. 2012, 112, 2208. (d) Mei, J.; Diao, Y.; Appleton, A. L.; Fang, L.; Bao, Z. J. Am. Chem. Soc. 2013, 135, 6724. (e) Takimiya, K.; Nakano, M.; Kang, M. J.; Miyazaki, E.; Osaka, I. Eur. J. Org. Chem. 2013, 2013, 217.

(2) (a) Tsuji, H.; Ilies, L.; Nakamura, E. Synlett 2014, 25, 2099.
(b) Mitsui, C.; Tsuji, H.; Sato, Y.; Nakamura, E. Chem. - Asian J. 2012, 7, 1443.
(c) Mitsui, C.; Soeda, J.; Miwa, K.; Tsuji, H.; Nakamura, E. J. Am. Chem. Soc. 2012, 134, 5448.
(d) Mitsui, C.; Tsuji, H.; Takeya, J.; Nakamura, E.; Ota, Y. Bull. Chem. Soc. Jpn. 2015, 88, 776.

(3) (a) Aaron, J.-J.; Svoboda, J.; Pihera, P.; Váchal, P.; Martínez, R. J. Fluoresc. 2011, 21, 2133. (b) Cernovska, K.; Svoboda, J.; Stibor, I.; Glagarova, M.; Vanek, P.; Novotna, V. Ferroelectrics 2000, 241, 231. (c) Chen, X.-K.; Zou, L.-Y.; Ren, A.-M.; Fan, J.-X. Phys. Chem. Chem. Phys. 2011, 13, 19490. (d) Matsumura, M.; Muranaka, A.; Kurihara, R.; Kanai, M.; Yoshida, K.; Kakusawa, N.; Hashizume, D.; Uchiyama, M.; Yasuike, S. Tetrahedron 2016, 72, 8085.

(4) (a) Truong, M. A.; Nakano, K. J. Org. Chem. 2015, 80, 11566.
(b) Takahashi, M.; Nakano, K.; Nozaki, K. J. Org. Chem. 2015, 80, 3790.

(5) (a) Liu, J.; Fitzgerald, A. E.; Mani, N. S. J. Org. Chem. 2008, 73, 2951. (b) Yue, W. S.; Li, J. J. Org. Lett. 2002, 4, 2201. (c) Krug, M.; Wichapong, K.; Erlenkamp, G.; Sippl, W.; Schächtele, C.; Totzke, F.; Hilgeroth, A. ChemMedChem 2011, 6, 63.

(6) Lee, J. Y.; Lee, C. W. Republic Korean Kongkae Taeho Kongbo (2013), KR 2013070431 20130627, CAN 159:205233.

(7) (a) Yoshimoto, H.; Itatani, H. Bull. Chem. Soc. Jpn. 1973, 46, 2490. (b) Shiotani, A.; Itatani, H. Angew. Chem., Int. Ed. Engl. 1974, 13, 471. (c) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. J. Org. Chem. 1975, 40, 1365. Hagelin, H.; Oslob, J. D.; Åkermark, B. Chem. - Eur. J. 1999, 5, 2413. (d) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. J. Org. Chem. 2008, 73, 5022. A related synthesis of dibenzothiophenes: (e) Che, R.; Wu, Z.; Li, Z.; Xiang, H.; Zhou, X. Chem. - Eur. J. 2014, 20, 7258. (f) Oechsle, P.; Paradies, J. Org. Lett. 2014, 16, 4086. A related rhodium-catalyzed method: (g) Okada, T.; Unoh, Y.; Satoh, T.; Miura, M. Chem. Lett. 2015, 44, 1598.

(8) Kaida, H.; Satoh, T.; Hirano, K.; Miura, M. Chem. Lett. 2015, 44, 1125.

(9) Saito, K.; Chikkade, P. K.; Kanai, M.; Kuninobu, Y. Chem. - Eur. J. 2015, 21, 8365.

(10) Kaida, H.; Satoh, T.; Nishii, Y.; Hirano, K.; Miura, M. Chem. Lett. 2016, 45, 1069.

(11) Examples of oxidative C-H coupling on the phenyl ring of 2phenoxypyridines, see: (a) Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. Organometallics **2015**, 34, 953. (b) Raghuvanshi, K.; Rauch, K.; Ackermann, L. Chem. - Eur. J. **2015**, 21, 1790.

(12) (a) Tang, C. W.; Vanslyke, S. A. *Appl. Phys. Lett.* **1987**, *51*, 913. For ambipolar materials, see: (b) Duan, L.; Qiao, J.; Sun, Y.; Qiu, Y. *Adv. Mater.* **2011**, *23*, 1137. (c) Chaskar, A.; Chen, H.-F.; Wong, K.-T. *Adv. Mater.* **2011**, *23*, 3876.

(13) For examples of oxygen-containing heteroacenes with a high $E_{\rm T}$, see: (a) Mitsui, C.; Tanaka, H.; Tsuji, H.; Nakamura, E. *Chem. - Asian J.* **2011**, *6*, 2296. (b) Hirai, H.; Nakajima, K.; Nakatsuka, S.; Shiren, K.; Ni, J.; Nomura, S.; Ikuta, T.; Hatakeyama, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 13581.