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

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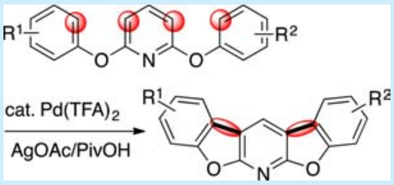
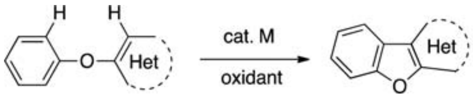
Supporting Information

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.



Polycondensed heteroacenes are increasingly important as organic functional materials. Besides the well-established benzothiophene-fused series of thienoacenes,[1] benzofuran-fused polyaromatic compounds[2] and O,X-mixed heteroacenes (X = S, N, P, etc.) such as benzofuro[3,2,*b*]benzothiophenes,[3] -indoles,[4] and -benzophospholes[4] 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 activities[5] 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]



(1)

In the context of our continuous studies of direct C−H functionalization chemistry, we recently reported that 3-aryloxy-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 2,6-diphenoxypyridines **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

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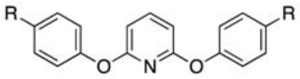
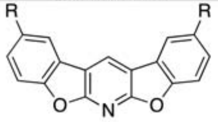
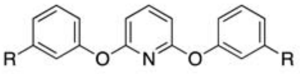
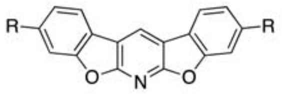
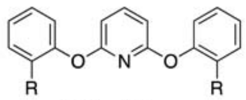
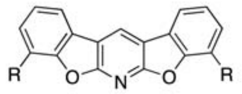
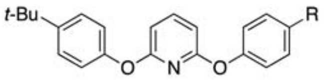
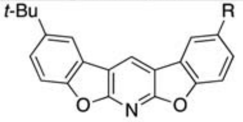
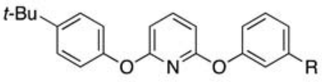
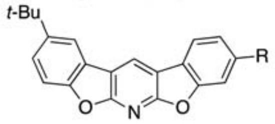
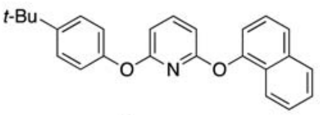
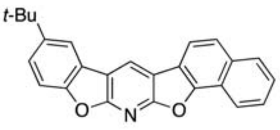
Table 1. Double Cyclization of 2,6-Diaryloxypyridines 1a–1k[a]

substrate	product, yield[b]
 **1a**: R = H **1b**: R = Me **1c**: R = *n*-C_3H_7 **1d**: R = *i*-C_3H_7 **1e**: R = *t*-Bu **1f**: R = OMe **1g**: R = CF_3	 **2a**: R = H, 61% (73%)[c] **2b**: R = Me, 64% **2c**: R = *n*-C_3H_7, 66% **2d**: R = *i*-C_3H_7, 74% **2e**: R = *t*-Bu, 73% **2f**: R = OMe, 31% **2g**: R = CF_3, 62%
 **1h**: R = Me **1i**: R = *t*-Bu	 **2h**: R = Me, 63% **2i**: R = *t*-Bu, 71%
 **1j**: R = Me **1k**: R = *t*-Bu	 **2j**: R = Me, 66% **2k**: R = *t*-Bu, 55%

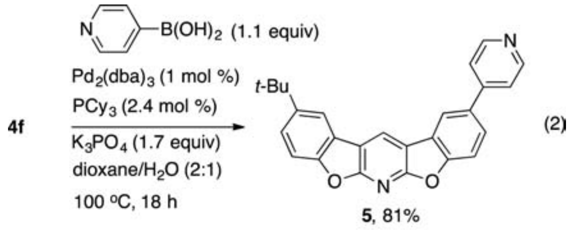
[a]Reaction conditions: **1** (0.20 mmol), Pd(TFA)$_2$ (0.006 mmol, 3 mol %), and AgOAc (0.8 mmol, 4 equiv) in PivOH (2 mL) in a 10 mL Schlenk tube at 150 °C for 6 h under air. [b]Isolated yield. [c]**1** (1.0 mmol), Pd(TFA)$_2$ (0.1 mmol, 10 mol %), and AgOAc (4.0 mmol, 4 equiv) in PivOH (10 mL) in a 50 mL Schlenk tube at 150 °C for 6 h under air.

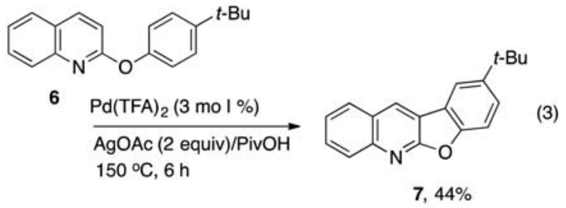
Table 2. Double Cyclization of Unsymmetrically Substituted 2,6-Diaryloxypyridines 3a–3j[a]

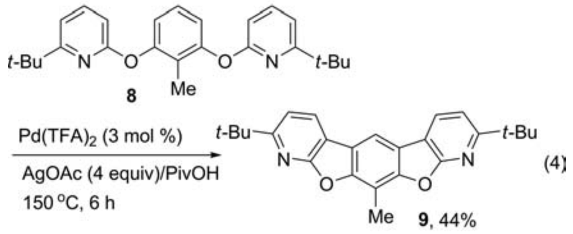
substrate	product, yield[b]
 **3a**: R = H **3b**: R = Me **3c**: R = OMe **3d**: R = CH_2Ph **3e**: R = Ph **3f**: R = Cl **3g**: R = C(=O)Ph	 **4a**: R = H, 69% **4b**: R = Me, 71% **4c**: R = OMe, 61% **4d**: R = CH_2Ph, 65% **4e**: R = Ph, 71% **4f**: R = Cl, 70% **4g**: R = C(=O)Ph, 63%
 **3h**: R = Cl **3i**: R = NO_2	 **4h**: R = Cl, 63% **4i**: R = NO_2, 71%
 **3j**	 **4j**, 68%

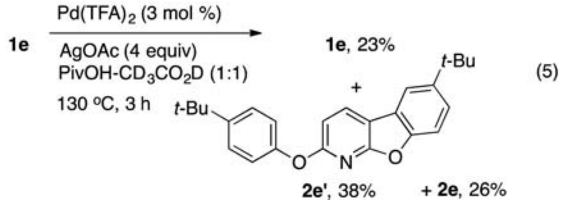
[a]Reaction conditions: **3** (0.20 mmol), Pd(TFA)$_2$ (0.006 mmol, 3 mol %), and AgOAc (0.8 mmol, 4 equiv) in PivOH (2 mL) in a 10 mL Schlenk tube at 150 °C for 6 h under air. [b]Isolated yield.

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-2-pyridinyloxy)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 six-membered 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/

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-3,5-diiodopyridine 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/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 ($CHCl_3$, $\Phi_F = 0.70$), indicating a relatively small Stokes shift. Interestingly, the phosphorescence spectrum (77 K, $CHCl_3$−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_{HOMO} (E_{OX} in CV), E_g (UV/vis), and E_T (phosphorescence spectrum) of **2e** were estimated to be −6.11, 3.44, and 2.88 eV, respectively, indicating a wide HOMO/LUMO energy gap and a relatively high E_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 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).

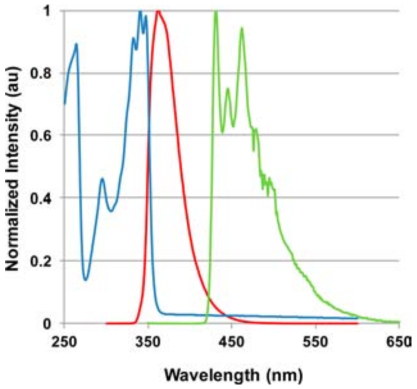


Figure 1. Normalized absorption (left, 1.0×10^{-5} M, $CHCl_3$), fluorescence (center, 1.0×10^{-6} M, $CHCl_3$), and phosphorescence spectra (right, 1.0×10^{-4} M, $CHCl_3$/EtOH 1:4 v/v at 77 K) spectra of **2e**.

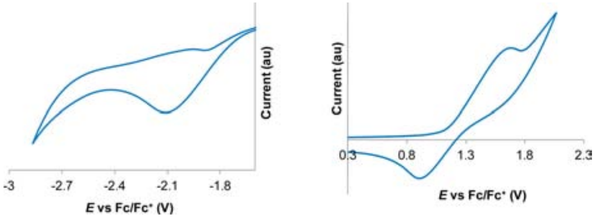


Figure 2. Cyclic voltammogram of **2e** in *o*-dichlorobenzene/acetonitrile (10:1, v/v) containing 0.1 M Bu_4NPF_6 at a scan rate of 100 mV s^{-1}.

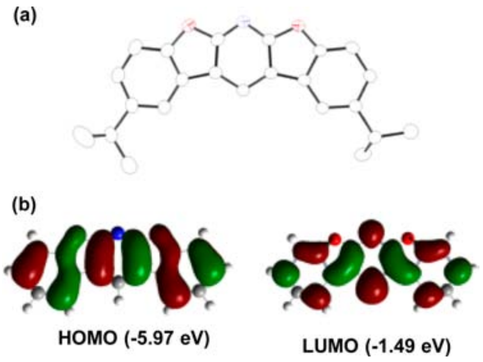


Figure 3. X-ray structure of **2e** (a) and HOMO and LUMO of **2a** calculated at B3LYP/6-31G(d) level of theory (b).

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.orglett.7b00323.

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

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Notes

The authors declare no competing financial interest.

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