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Graphical Abstract

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Synthesis of bis(pyrrol-2-yl)arenes by Pd-catalyzed cross coupling
Jun-ichiro Setsune,*a Masayuki Toda,a Keigo Watanabe,a Pradeepa K. Panda,b and Takafumi Yoshidab

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bVenture Buisiness Laboratory, Kobe University,
Nada-ku, Kobe 657-8501, Japan

X-(arene)-X
Pd(OAc)2
PPh3
DMF-H2O
K2CO3
80-90 °C, 24 h

1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 4,4'-biphenylene,
2,5-thienylene, 2,6-pyridylene, 9,10-anthracenylene, 2,7-fluorenylene,
2,7-(9-oxofluorenylene), 6,6'-(2,2'-bipyridylene)

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Synthesis of bis(pyrrrol-2-yl)arenes by Pd-catalyzed cross coupling

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Abstract—2-Borylpyrrole was prepared from 2-iodopyrrole almost quantitatively and then reacted with dihaloarenes under typical reaction conditions of Suzuki-Miyaura cross coupling to give bis(pyrrrol-2-yl)arenes in good yields, while the cross coupling reaction of 2-iodopyrrole with 1,4-phenylenebisboronic acid was susceptible to oxidative self-coupling to produce 4,4’-bis(pyrrrol-2-yl)biphenyl as a byproduct. These bis(pyrrrol-2-yl)arenes showed strong fluorescence. © 2007 Elsevier Science. All rights reserved.

Organic materials containing pyrrole are of great interest and the application to π-conjugated polymers such as polypyrroles are well known.1 Bis(pyrrrol-2-yl)arenes have been regarded as useful monomers for electroactive polymeric material.2 Another interesting application of bis(pyrrrol-2-yl)arenes is their use as building blocks for expanded porphyrins.3 In this context, various bipyrrrole derivatives with an aromatic linker such as benzene, pyridine, furan, thiophene, and pyrrole have been reported.4,6 The five-membered heteroaromatic linker between pyrroles was constructed by the cyclization of 1,4-bis(pyrrrol-2-yl)-1,4-diketone.4,5 On the other hand, pyrrole rings were constructed at both sides of the six-membered aromatic core to produce bis(pyrrrol-2-yl)arenes.6 However, these synthetic methods are not satisfactory in the synthesis of bipyrrrole compounds with various substituents.

The Pd-catalyzed cross coupling reaction is a straightforward synthetic method for arylpyrroles. Whereas arylation of N-unprotected pyrrole through C-H activation has recently been reported (Scheme 1. (a); R=M=H, X=halogen),1ır conventional Suzuki-Miyaura cross coupling reactions are favored practically in view of their wide applicability and milder reaction conditions.8,9 There are two options of the reactant combination as shown in Scheme 1; (a) pyrrolylmethyl and haloarene and (b) halopyrrole and arylmetal. While Pd-catalyzed reactions of N-unprotected halopyrrole and borylarene were frequently reported to give arylpyrroles (Scheme 1. (b); R=H, X=halogen, M=B(OR’)2),8 the coupling reaction using N-unprotected borylpyrrole (Scheme 1. (a); R=H, X=halogen, M=B(OR’)2) has never been reported except a few examples.9a N-protected borylpyrroles have usually been employed in the protocol (a).9b,9c Here, we will show convenient preparation of N-unprotected borylpyrrole and its successful application to the synthesis of bis(pyrrrol-2-yl)arenes. The Pd-catalyzed cross coupling of N-unprotected borylpyrrole and dihaloarene was found to be much less susceptible to the oxidative self-coupling reaction in comparison with the reverse combination of halopyrrole and diborylarene.

![Scheme 1](image)

3,4-Dialkyl-2-ethoxycarbonylpyrrole 1 is the choice of pyrrole substrate in this paper since it is frequently used in the porphyrinoid synthesis.10 It is well known that the ester substituent stabilizes pyrrole nucleus against oxidative degradation and is readily removed by the hydrolysis-decarboxylation procedure. When a mixture of 3,4-diethyl-2-ethoxycarbonyl-5-iodopyrrole 2 (2.0 mmol), 1,4-phenylenebisboronic acid (1.0 mmol), K2CO3 (6.6 mol), Pd(OAc)2 (0.10 mmol), and PPh3 (0.20 mmol) in ethanol (10 ml) was heated under argon for 24 h at reflux, 1,4-bis(pyrrrol-2-yl)benzene 3 was obtained in good yield.11 1H NMR analysis after chromatographic purification showed that 3 (80% yield) was contaminated with a byproduct, 4,4’-bis(pyrrrol-2-yl)biphenyl, 4 (5% yield) originated from the self-coupling of the pyrrolylbenezeneboronic acid intermediate (Scheme 2). The compound 4 was identical with the major product of the similar Pd-catalyzed cross coupling reaction of 2 and 4,4’-biphenylenebisboronic acid. The major product 4 in 74% yield was also contaminated with a self-coupling product, bis(pyrrrol-2-yl)quarterphenyl, 5 in 19% yield. The latter was characterized by the MS signal at 693.33 (theory for C46H48N2O4 + H+: 693.37).
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Scheme 2. Pd-catalyzed cross coupling reactions of 2-iodopyrrole 2 and arenebisboronic acid.

The purity of the bis(pyrrol-2-yl)arene is crucial if it is used to generate oligomers and polymers. Therefore, we examined the cross coupling of 2-borylpyrrole and diiodoarenes as a reverse combination in the hope of improving selectivity. 2-Borylpyroles have been prepared by the reaction of N-Boc-protected 2-lithiopyrrole with alkoxyborane.12 Ir-catalyzed direct borylation of pyrrole at the 2-position has recently been reported.13 Since the latter reaction is restricted to sterically unhindered substrates and the former reaction needs protection-deprotection procedure, these methods would not be suitable for 1. Thus, we have tried to convert 2 to 2-borylpyrrole 6 according to the procedure for Pd-catalyzed borylation of aromatic halides.14 A mixture of 2 (4.6 mmol), pinacolborane (5.5 mmol), NEt 3 (11.5 mmol), and PdCl2(PPh3)2 (0.23 mmol) in dioxane (20 ml) was heated at 60 °C for 3 h to give 611 almost quantitatively. The amount of the dehalogenated product 1 was negligible under these reaction conditions. It is worthy of note that PdCl2(PPh3)2 was much more effective than PdCl2(dppf). The latter was reported to be the best catalyst for the borylation of ordinary aromatic iodide.14a Borylation with bispinacolatodiborane instead of pinacolborane did not work well in the case of 2 either as shown in Table 1.

Table 1. Pd-catalyzed borylation of iodopyrrole 2.a)

<table>
<thead>
<tr>
<th>entry</th>
<th>borane</th>
<th>Pd catalyst</th>
<th>base</th>
<th>time (h)</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>HB(pin)</td>
<td>PdCl2(dppf)</td>
<td>Et3N</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>HB(pin)</td>
<td>PdCl2(PPh3)</td>
<td>Et3N</td>
<td>3</td>
<td>98</td>
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<tr>
<td>3</td>
<td>B2(pin)</td>
<td>PdCl2(dppf)</td>
<td>KOAc</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>B2(pin)</td>
<td>PdCl2(PPh3)</td>
<td>KOAc</td>
<td>2</td>
<td>12</td>
</tr>
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</table>

a) The molar ratio: 2/borane/Pd/base = 1.0/1.2/0.05/2.5. b) The yield was determined by 1H NMR.

2-Borylpyrrole 6 (3.0 mmol) after separating ammonium salts and most part of catalyst by filtration was subjected to the Suzuki-Miyaura cross coupling reaction with dihaloarenes (1.25 mmol) in the presence of Pd(OAc)2 (0.13 mmol), PPh3 (0.26 mmol), and K2CO3 (4.1 mmol) in DMF-H2O (15-3 ml) at 80-90 °C for 5 h. The coupling products 3 and 4 free from the self-coupling byproducts were obtained in 69% and 92% yield from 1,4-diodobenzene and 4,4'-diiodobiphenyl, respectively.

Table 2. Pd-catalyzed cross coupling of 2-borylpyrrole 6 and 6' with dihaloarenes.

<table>
<thead>
<tr>
<th>X-(arene)-X</th>
<th>Pd(OAc)2</th>
<th>PPh3</th>
<th>DMF-H2O</th>
<th>K2CO3</th>
<th>80-90 °C, 24 h</th>
<th>product yield (%)</th>
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<tr>
<td>I-I</td>
<td>Et</td>
<td>Et</td>
<td>3</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-I</td>
<td>Et</td>
<td>Et</td>
<td>4</td>
<td>92</td>
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<tr>
<td>I-I</td>
<td>Et</td>
<td>Et</td>
<td>7</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-I</td>
<td>Et</td>
<td>Et</td>
<td>8</td>
<td>81</td>
<td></td>
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</tr>
<tr>
<td>I-I</td>
<td>Et</td>
<td>Et</td>
<td>9</td>
<td>70</td>
<td></td>
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</tr>
<tr>
<td>I-I</td>
<td>i-Bu</td>
<td>Me</td>
<td>11</td>
<td>70</td>
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<td>I-I</td>
<td>i-Bu</td>
<td>Me</td>
<td>14</td>
<td>76</td>
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</table>

Molar ratio: 6(or 6')/dihaloarene/Pd(OAc)2/PPh3/K2CO3 = 2.4/1.0/0.10/0.20/3.3.

It has been shown that oxidative self-coupling of areneboronic acid is accelerated by dioxygen by way of diarylpalladium intermediate.15 Probably because of the steric reason, double transmetallation of 2-borylpyrrole 6 to
Pd(II) seems to be suppressed, as compared with that of pyrrolylareneboronic acid as an intermediate in the cross coupling reaction of 2 and areneboronic acid. Facile formation of 2-borylpyrrole and its clean cross coupling reaction with dihaloarenes lead to a reliable synthetic procedure for bis(pyrrol-2-yl)arenes and bis(pyrrol-2-yl)heteroarenes. Table 2 summarizes the yields of the cross coupling reactions of 6 with m-diodobenzene, o-diodobenzene, 2,5-diodothiophene, and 2,6-dibromopyridine to give the coupling products 7 – 10. It is worthy of note that 1,2-bis(pyrrol-2-yl)benzene derivative could not be prepared by the pyrrole ring forming reaction starting from phthaloyl dichloride.\textsuperscript{a} 2-Borylpyrrole 6\textsuperscript{a} having a sterically demanding iso-butyl group was prepared similarly in more than 90% yield and then gave coupling products 11 – 14 in good yields.

The newly synthesized dipyrrole compounds are fluorescent as shown in Figure 1 and the fluorescence intensity is very high in some cases. For example, the fluorescence efficiency of 4 in ethanol estimated relative to anthracene (Φ\textsubscript{flu} = 0.27)\textsuperscript{b} is 0.89. It is worthy of note that protonation at the pyridine nitrogen of 10 caused red shift of the absorption band from 352 nm to 432 nm and also of the fluorescence band from 392 nm to 490 nm.

![Figure 1. UV-vis absorption (left arrow) and emission spectra (right arrow) of 4, 10, and 10+TFA in CH\textsubscript{2}Cl\textsubscript{2} at room temperature. Emission spectra of 4 (6.8×10\textsuperscript{-3} mol/L), 10 (2.0×10\textsuperscript{-3} mol/L), and 10+TFA (2.0×10\textsuperscript{-3} mol/L) were measured with the excitation at the absorption maxima at 339, 352, and 432 nm, respectively.](image)

In summary, 2-borylpyrrole was readily prepared from 2-iodopyrrole and it was successfully applied to the synthesis of bis(pyrrol-2-yl)arenes by the Pd-catalyzed cross coupling with dihaloarenes. This is in contrast to the reverse combination of 2-halopyrrole and areneboronic acid that was found to be more susceptible to the oxidative self-coupling. In addition to good solubility owing to the alkyl substituents at the pyrrole-β positions, the strong fluorescence augments the utility of these bis(pyrrol-2-yl)arenes and bis(pyrrol-2-yl)heteroarenes as scaffolds for functional π-conjugated materials.

**Acknowledgments**

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**References**


11. 1,4-Bis(pyrrol-2-yl)biphenyl (3) Yield 69%. m. p. 208-210 °C. 1H NMR (400 MHz, d-value, CDCl3) 8.81 (br, 2H, NH), 7.53 (s, 4H, C6H4-linker), 4.35 (q, 4H, J=7.1 Hz, OCH2Me), 2.81, 2.62 (q, 2H, 4Hx2, J=7.4 and 7.5 Hz, CH2Me), 1.38 (t, 6H, J=7.1 Hz, OCH2Me), 1.22, 1.21 (t, 6Hx2, OCH2Me, J=6.7 and 6.9 Hz). 13C NMR (100 MHz, d, CDCl3) 161.56, 138.12, 132.63, 122.26, 83.56, 59.91, 24.71. Analysis calcd. for C28H36N2O4: C, 72.39; H, 7.81; N, 6.03. Found C, 72.36; H, 7.99; N, 5.63.

12. 4,4’-Bis(pyrrol-2-yl)biphenyl (4) Yield 92%. m. p. 260 °C. 1H NMR (400 MHz, d-value, CDCl3) 8.84 (br, 2H, NH), 7.71, 7.56 (dx2, 4Hx2, J=8.2 Hz, (CH2)2-linker), 4.36 (q, 4H, J=7.1 Hz, OCH2Me), 2.82, 2.64 (q, 2H, 4Hx2, J=7.5 and 7.6 Hz, CH2Me), 1.39 (t, 6H, J=7.1 Hz, OCH2Me), 1.23, 1.22 (t, 6Hx2, CH2Me, J=7.5 Hz). 13C NMR (100 MHz, δ, CDCl3) 163.53, 139.35, 134.42, 132.07, 131.78, 127.65, 127.32, 124.24, 118.50, 60.00, 18.40, 17.51, 16.35, 18.58, 14.56. ESI-MS (found/calc'd for C25H21N2O4 + H+) 465.276/465.275. IR (cm⁻¹, in KBr pellet) 1668 (ν(CO)). Analysis calcd. for C25H21N2O4: C, 72.39; H, 7.81; N, 6.03. Found C, 72.36; H, 7.99; N, 5.63.