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Fluorescent Diarylindoles by Palladium-Catalyzed Direct and Decarboxylative Arylations of Carboxyindoles

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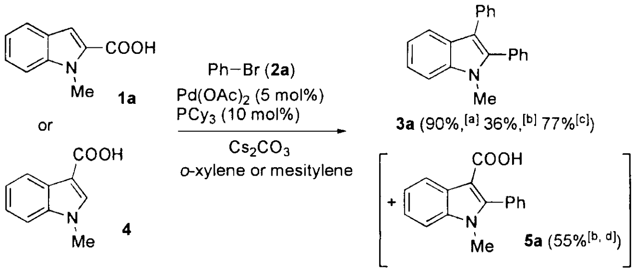
The indole nucleus is found in a large number of biologically active natural and unnatural compounds, and the synthesis of its derivatives is of considerable importance in organic chemistry.[1] In addition, as tryptophan is an intrinsic fluorescent probe in proteins, indole derivatives are known to display fascinating photophysical properties.[2] Thus, suitably arylated indoles may be considered to exhibit fluorescence, and the wavelength and intensity may depend on the nature of the aryl substituents. A literature search indicates that some 2,3-diarylindoles, for example 2,3-bis(4-methoxy- and hydroxyphenyl)indoles, show not only interesting biological activities,[3a–g] but also fluorescence in the blue region,[3e–h] whereas very little is known about their fluorescent efficiency. Accordingly, as the development of efficient blue emitters is currently one of the important subjects in materials chemistry,[4,5] the synthesis of various related compounds is of particular interest in terms of their physical features and their biological behavior.

Transition-metal-catalyzed biaryl cross-coupling with aryl halides and aryl metal reagents is one of the most reliable methods for the synthesis of indoles having a variety of aryl functions,[6] and recent advances in the metal-mediated direct C–H arylation reactions of heteroarenes[7] provide an efficient access to C2- or C3-monoarylated indoles.[8,9] However, the 2,3-diarylation reactions on an indole scaffold are quite rare.[10] Thus, efficient methods for installing identical and different aryl groups at the 2- and 3-positions are required.[11] During our studies on the palladium-catalyzed direct arylation of heteroarenes with aryl halides, we achieved the 2,3-diarylation of 3-hydroxymethyl- and carboxythiophenes by cleavage of C–H and C–C bonds.[12] This synthetic strategy involves sequential *ortho*- and *ipso*-arylations,[12–14] and gratifyingly, it has been successfully utilized in carboxyindole systems. Herein, we report the palladium-catalyzed 2,3-diarylation of carboxyindole derivatives with aryl bromides, as well as a practical route to 2,3-diarylindoles having different aryl substituents by performing ester hydrolysis in the sequence. As a result of these studies, we have found a highly fluorescent 2,3-diarylindole among the products, and its photoluminescent properties are described.[15,16]

In a typical synthesis, treatment of 1-methyl-1*H*-indole-2-carboxylic acid (**1a**) with bromobenzene (**2a**) (3 equiv) in the presence of $Pd(OAc)_2$ (5 mol%), PCy_3 (Cy = cyclohexyl, 10 mol%), and Cs_2CO_3 (4 equiv) in refluxing *o*-xylene for 4 h afforded 1-methyl-2,3-diphenyl-1*H*-indole (**3a**) in 90% yield (Scheme 1). In the reaction of 1-methyl-1*H*-indole-3-carboxylic acid (**4**) in place of **1a** under the same conditions, formation of the 2-monophenylated product, 1-methyl-2-phenyl-1*H*-indole-3-carboxylic acid (**5a**) (55%) was observed together with **3a** (36%). Thus, the second *ipso*-phenylation at the 3-position appears to be a relatively slower process. The reaction of **4** at a higher temperature using me-



Scheme 1. Phenylation of carboxyindole **1a** or **4** with **2a**. Reaction conditions: **1a** or **4** (0.5 mmol), **2a** (1.5 mmol), and Cs_2CO_3 (2 mmol) at 170 °C (bath temp) for 4 h. [a] Reaction of **1a** in *o*-xylene. [b] Reaction of **4** in *o*-xylene. [c] Reaction of **4** in mesitylene with addition of MS 4A (150 mg). [d] Determined by GC as its methyl ester **7a** after methylation with MeI.

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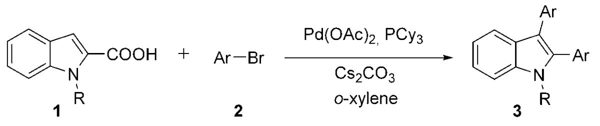
sitylene as a solvent, however, gave **3a** in an acceptable yield (77 %).

Various aryl bromides having an electron-donating or -withdrawing group could be employed for the diarylation reaction of **1a** (entries 1–5, Table 1). The reaction using other 2-carboxyindoles was also undertaken. Under the standard reaction conditions, *N*-methoxymethyl(MOM)-protection and *N*-phenyl-substitution were tolerated, and thus, carboxyindoles **1b** and **1c** coupled with **2a** to give the expected products **3f** and **3g** (entries 6 and 7, Table 1).

Table 1. Reaction of 2-carboxyindoles **1** with aryl bromides **2**.[a]

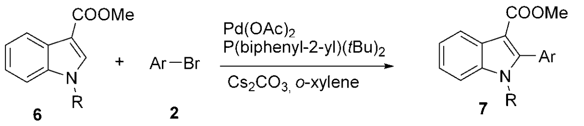


Entry	**1**, R	**2**, Ar	**3**, Yield [%][b]
1	**1a**, Me	**2a**, Ph	**3a**, 90
2	**1a**, Me	**2b**, 4-MeC$_6$H$_4$	**3b**, 86
3	**1a**, Me	**2c**, 4-MeOC$_6$H$_4$	**3c**, 93
4	**1a**, Me	**2d**, 4-CF$_3$C$_6$H$_4$	**3d**, 78
5	**1a**, Me	**2e**, 4-FC$_6$H$_4$	**3e**, 79
6	**1b**, MOM	**2a**, Ph	**3f**, 82
7[c]	**1c**, Ph	**2a**, Ph	**3g**, 79

[a] Reaction conditions: [**1**]:[**2**]:[Pd(OAc)$_2$]:[PCy$_3$]:[Cs$_2$CO$_3$] = 0.5:1.5:0.025:0.05:2 (in mmol), in refluxing *o*-xylene under N$_2$ for 4 h. [b] Yield of isolated product. [c] With 0.0125 mmol of Pd(OAc)$_2$ and 0.025 mmol of P(biphenyl-2-yl)Cy$_2$.

To achieve the selective synthesis of indoles having different aryl groups at the 2- and 3-positions, we examined a stepwise diarylation with methyl esters of **1a** and **4** as the starting materials, as an ester function is inert under the present conditions. The latter ester, methyl 1-methyl-1*H*-indole-3-carboxylate (**6a**) was effectively monoarylated with **2a**, **2c**, and **2d** using P(biphenyl-2-yl)(*t*Bu)$_2$ as a ligand to give the corresponding 2-arylated products **7a–c** with good yields (entries 1–3, Table 2), whereas the former ester did not react at all. The ligand PCy$_3$ was less effective in this case (entry 4, Table 2). MOM-protected indole **6b** was also available for use (entry 5, Table 2). Then, **7a**, **7c**, and **7d** were hydrolyzed with ethanolic KOH to quantitatively afford the corresponding carboxylic acids. Subsequently, the acids were subjected to the second arylation accompanied by decarboxylation in mesitylene, and diarylindoles **8a**–**8f** were obtained in good yields (Table 3).

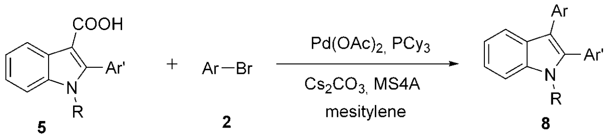
Table 2. Reaction of 3-(methoxycarbonyl)indoles **6** with aryl bromides **2**.[a]



Entry	**6**, R	**2**, Ar	**7**, Yield [%][b]
1	**6a**, Me	**2a**, Ph	**7a**, 82
2	**6a**, Me	**2c**, 4-MeOC$_6$H$_4$	**7b**, 90
3	**6a**, Me	**2d**, 4-CF$_3$C$_6$H$_4$	**7c**, 79
4[c]	**6a**, Me	**2a**, Ph	**7a**, 57
5	**6b**, MOM	**2a**, Ph	**7d**, 73

[a] Reaction conditions: [**6**]:[**2**]:[Pd(OAc)$_2$]:[P(biphenyl-2-yl)(*t*Bu)$_2$]:[Cs$_2$CO$_3$] = 0.5:1.0:0.025:0.05:1.0 (in mmol), in refluxing *o*-xylene under N$_2$ for 6 h. [b] Yield of isolated product. [c] PCy$_3$ was used as a ligand.

Table 3. Decarboxylative arylation of **5**.[a]



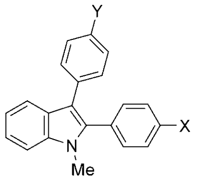
Entry	**5**, R, Ar′	**2**, Ar	**8**, Yield [%][b]
1	**5a**, Me, Ph	**2b**, 4-MeC$_6$H$_4$	**8a**, 84
2	**5a**, Me, Ph	**2d**, 4-CF$_3$C$_6$H$_4$	**8b**, 60
3	**5a**, Me, Ph	**2f**, 4-EtOCOC$_6$H$_4$	**8c**, 89
4	**5a**, Me, Ph	**2g**, 4-PhC$_6$H$_4$	**8d**, 94
5	**5b**, Me, 4-CF$_3$C$_6$H$_4$	**2a**, Ph	**8e**, 55
6	**5c**, MOM, Ph	**2b**, 4-MeC$_6$H$_4$	**8f**, 70

[a] Reaction conditions: [**5**]:[**2**]:[Pd(OAc)$_2$]:[PCy$_3$]:[Cs$_2$CO$_3$] = 0.5:1.0:0.025:0.05:1.0 (in mmol) with MS4 A (150 mg), in mesitylene at 170 °C under N$_2$ for 6 h. [b] Yield of isolated product based on **5**.

With the above 2,3-diarylindoles **3** and **8** in hand, a preliminary survey of their solid-state photoluminescence by using a UV lamp was carried out. It was found that 1-methyl-2,3-bis(4-trifluoromethylphenyl)-1*H*-indole (**3d**) was especially luminescent.

Consequently, the photoluminescence spectra of **3d** and, to examine the substituent effects on the aryl groups, those of **3a**, **3c**, **8b**, and **8e** as well as their absorption spectra were measured for their ethanol solutions and solid powders (Table 4 and Figure 1). Accordingly, diarylindole **3d** is

Table 4. Optical properties of 1-methyl-2,3-diarylindoles.



3a; X = Y = H
3c; X = Y = MeO
3d; X = Y = CF$_3$
8b, X = H, Y = CF$_3$
8e; X = CF$_3$, Y = H

Entry	**3** or **8**	λ_{abs-sl} [nm][a]	log ε	λ_{em-sl} [nm][b]	Φ_{f-sl}[c]	λ_{em-pw} [nm][d]	Φ_{f-pw}[e]
1	**3a**	225 298	4.63 4.24	418	0.51	419	0.65
2	**3c**	248 299	4.48 4.22	421	0.13	441	0.44
3	**3d**	225 286	4.80 4.46	436	0.90	422	0.97
4	**8b**	225 296	4.66 4.30	419	0.37	420	0.56
5	**8e**	225 303	4.63 4.12	438	0.64	426	0.76

[a] Absorption maximum in EtOH. [b] Emission maximum in EtOH. [c] Determined by comparison with ethanol solution of anthracene (Φ_f = 0.30) excited at 254 nm. [d] Emission maximum of solid powder excited at 350 nm. [e] Absolute quantum yield determined by an integrating sphere system.

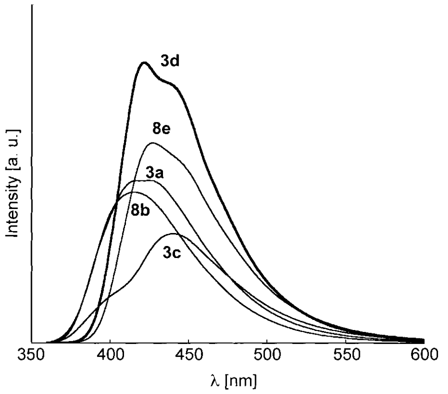


Figure 1. Photoluminescence spectra of the powders of 1-methyl-2,3-diarylindoles **3** and **8**.

highly luminescent with emission maxima at 436 nm and 422 nm and with quantum yields of 0.90 and 0.97, in solution and as a solid, respectively. The quantum efficiency of the solid samples decreased in the following order: **3d**>**8e**>**3a**>**8b**>**3c**. This trend is the same as that in solution. In each case, the discrepancy between the emission maxima in solution and in the solid state is relatively small. These facts suggest that the solid-state luminescence in each case is essentially based on the intrinsic structure and electronic conjugation of individual molecules. This was, at least in the case of **3d**, supported by the crystal structure and packing determined by single-crystal X-ray diffraction (Figure 2).[17]

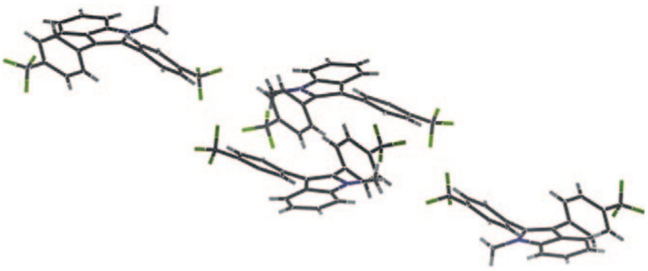


Figure 2. Molecular structure of **3d** and its packing ($P2_1/n$) within the crystal determined by single-crystal X-ray diffraction.

The torsion angles between the indole plane and the C2 and C3 aryl groups are 45° and 43°, respectively, which appear to prevent intermolecular electronic interactions. In this case, the presence of two CF_3 substituents also appears to be an important factor in allowing the almost perfect quantum yield in the solid (Table 4). However, further studies are needed to gain a better understanding of the observed remarkable effect of the substituents on the luminescent efficiency.

In summary, physically and biologically interesting 2,3-diarylindoles can be readily prepared by palladium-catalyzed direct and decarboxylative arylations using commercially available carboxyindoles. This approach has led to the discovery of a highly luminescent solid blue emitter.

Experimental Section

Typical synthetic procedure (preparation of compound 3d, entry 4 in Table 1): In a 20 mL two-necked flask were added 4-bromobenzotrifluoride **(2d)** (1.5 mmol, 338 mg), 2-carboxyindole **1a** (0.5 mmol, 87 mg), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), PCy_3 (0.05 mmol, 14 mg), Cs_2CO_3 (2 mmol, 652 mg), and *o*-xylene (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 170 °C (bath temperature) for 4 h. Compound **3d** (163 mg, 78 %) was isolated by filtration of the mixture through a filter paper by using diethyl ether as eluent, followed by evaporation of the solvents, and chromatography on silica gel using hexane–ethyl acetate (98:2, v/v). M.p. 170–172 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.69$ (s, 3 H), 7.23 (t, $J = 6.6$ Hz, 1 H), 7.34–7.38 (m, 3 H), 7.44 (d, $J = 7.3$ Hz, 3 H), 7.53 (d, $J = 8.5$ Hz, 2 H), 7.67 (d, $J = 8.0$ Hz, 2 H), 7.75 ppm (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.1$, 109.9, 114.8, 119.5, 121.0, 123.1, 124.0 (q, $J = 270$ Hz), 124.4 (q, $J = 270$ Hz), 125.3 (q, $J = 3.8$ Hz), 125.6 (q, $J = 3.8$ Hz), 126.6, 127.8 (q, $J = 32$ Hz), 130.4, 129.5 (q, $J = 32$ Hz), 131.4, 135.2, 136.6, 137.7, 138.6 ppm; elemental analysis calcd (%) for $C_{23}H_{15}F_6N$: C 65.87, H 3.61, N 3.34; found: C 65.60, H 3.59, N 3.36.

Acknowledgements

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Keywords: arylation · C–C coupling · indoles · luminescence · palladium

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[15] During the preparation of this manuscript, an efficient blue emitter involving an indole unit was reported by Shimizu, Mochida, and Hiyama.[5]

[16] Related to this is our approach to fluorescent condensed aromatics by catalytic direct coupling with alkynes: N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem.* **2008**, *120*, 4083; *Angew. Chem. Int. Ed.* **2008**, *47*, 4019.

[17] CCDC-713262 (**3d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif See also the Supporting Information. Albeit not high crystallinity, it is obvious that there is no interactive pile between the indole planes.

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