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Palladium Catalysis

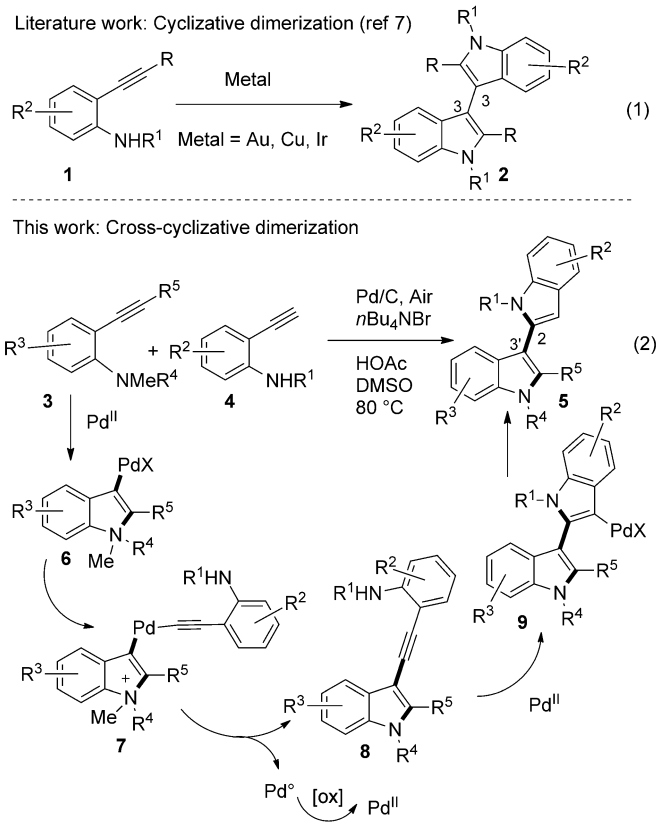
Pd/C-Catalyzed Cyclizative Cross-Coupling of Two *ortho*-Alkynylanilines under Aerobic Conditions: Synthesis of 2,3′-Bisindoles

Bo Yao, Qian Wang, and Jieping Zhu*[a]

Abstract: A palladium-catalyzed cyclizative cross-coupling of two *o*-alkynylanilines to 2,3′-bisindoles under aerobic oxidative conditions was developed. Mechanistic studies suggested that the two catalytic cycles, namely the formation of 3-alkynylindoles **8** and their subsequent cyclization to bisindoles **5**, are temporally separated. The aminopalladation of 3-alkynylindoles **8** occurred only after all the *N*,*N*-dialkyl-*o*-alkynylanilines were consumed. The solid support (activated charcoal) played a crucial role in the second intramolecular aminopalladation process.

Bisindoles are important structural motifs found in bioactive natural products,[1] pharmaceuticals,[2] and functional materials.[3] Different synthetic methodologies including Pd-catalyzed cross-coupling of two appropriate functionalized indoles,[4] double cyclization of 1,4-di-(*o*-aminophenyl)-1,3-diynes,[5] homo-dimerization of indoles,[6] and cyclizative homo-dimerization of *o*-alkynylanilines **1** to bisindoles **2** ([Eq. (1)], Scheme 1)[7] have been developed.[8] Except for the cross-coupling methodology, most of the one-step protocols allow access to 3,3′- and 2,2′-bisindoles rather than the 2,3′-bisindoles. Synthesis of unsymmetrical 2,3′-bisindoles directly from two different linear starting materials has, to the best of our knowledge, never been reported.

Palladium-catalyzed cyclization of *N*,*N*-dimethyl *o*-alkynylanilines is an efficient strategy for the synthesis of indoles.[9] Taking advantage of their high propensity to undergo Pd-catalyzed oxidative cyclization under aerobic conditions, we have recently reported a cross-cyclizative dimerization between *o*-alkynylanilines and *o*-alkynylbenzamides for the synthesis of bis-heterocycles tethered by a double bond.[10,11] As a continuation of this work, we report herein the synthesis of 2,3′-bisindoles by a cyclizative cross-coupling of two *o*-alkynylaniline derivatives **3** and **4** ([Eq. (2)], Scheme 1). The underlying principle is shown in Scheme 1. Selective aminopalladation of **3** would afford the σ-indolylpalladium(II) intermediate **6** that upon ligand exchange would provide **7**. Reductive elimination followed by *N*-demethylation would then furnish 3-alkynylindole **8** and Pd°.[12] Oxidation of Pd° to Pd^{II} followed by a second aminopalladation would afford **9** that upon proto-demetallation, was expected to deliver the 2,3′-bisindole **5**. To ensure the smooth occurrence of the desired domino process, the following competitive reaction pathways needed to be circumvented: a) the protonation and dimerization of intermediate **6**; b) the sequence initiated by Pd^{II}-catalyzed aminopalladation of alkynes **4**; c) Glaser type oxidative dimerization of terminal alkyne **4**,[13] and d) the dimerization of intermediate **9**.



Scheme 1. Strategies for the synthesis of bisindoles.

The reaction between *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline (**3a**; 1.0 equiv) and *o*-ethynylanline derivative **4** (2.0 equiv) with different *N*-protecting groups was first examined to find the best-matched reaction partners. Under our previous optimized conditions [$Pd(OAc)_2$ (0.05 equiv), nBu_4NI (1.0 equiv), HOAc (1.0 equiv), DMSO, air, 80 °C], reaction of **3a** with **4a**

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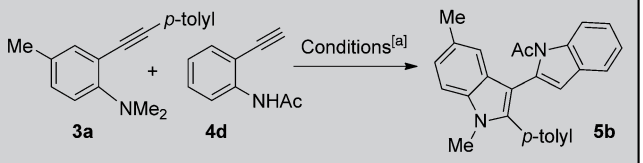
($R^1 = R^2 = H$) provided the desired bisindole **5a** in about 40% yield (based on NMR spectroscopy). On the other hand, reaction of **4b** ($R^1 = Me$, $R^2 = H$) or **4c** ($R^1 = Bn$, $R^2 = H$) with **3a** afforded a complex reaction mixture.[14] The most promising result was obtained by reaction of **3a** with **4d** ($R^1 = Ac$, $R^2 = H$) affording bisindole **5b** in 43% isolated yield. Therefore, the reaction between **3a** and **4d** was chosen for further survey of the reaction conditions (Table 1). The key results are summarized as follows: a) nBu$_4$NI was a better additive than nBu$_4$NBr when Pd(OAc)$_2$ was used as a catalyst (Table 1, entries 1 vs. 2); b) Pd/C was an excellent pre-catalyst and interestingly, nBu$_4$NBr was a better additive (Table 1, entry 4) than nBu$_4$NI (Table 1, entry 3) in this case. LiBr and KBr were also effective additives (Table 1, entries 6, 7), while addition of nBu$_4$NCl completely inhibited the desired transformation (Table 1, entry 8);[15] c) other Pd^{II} (Table 1, entries 9, 10) and Pd$^{\circ}$ species (Table 1, entry 11) can also catalyze the reaction, albeit with reduced catalytic efficiency relative to Pd/C. Overall, the optimized conditions consisted of heating a DMSO ($c = 0.1$ M) solution of **3a** (0.05 mmol) and **4d** (3.0 equiv) in the presence of Pd/C (0.025 equiv, 10 wt% on activated charcoal), nBu$_4$NBr (0.5 equiv), and HOAc (1.0 equiv) at 80 °C under air (sealed tube). Under these reaction conditions, the cyclizative cross-coupling product **5b** was isolated in 70% yield together with **2b**, a homo-dimer of **3a**, in 14% yield (**5b**/**2b** = 5:1). We note that there are only a few examples of using Pd/C as a pre-catalyst for Pd^{II}-catalyzed oxidative transformations.[16]

Table 1. Survey of conditions for the cyclizative cross-coupling reaction.

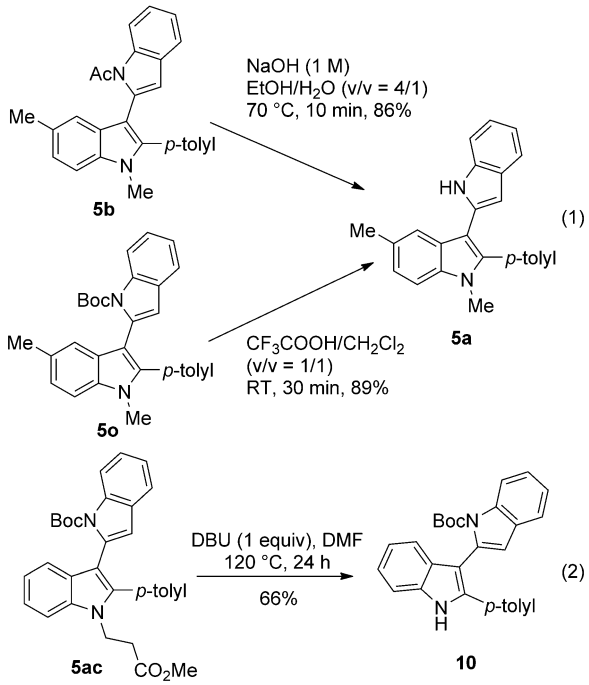


Entry	Pd [equiv]	Additive [equiv]	Time [h]	Yield [%] (ratio)[b]
1	Pd(OAc)$_2$ (0.025)	nBu$_4$NI (0.25)	24	59 (2.5:1)
2	Pd(OAc)$_2$ (0.05)	nBu$_4$NBr (0.25)	33	–
3	Pd/C (0.025)	nBu$_4$NI (0.25)	52	41 (2:1)
4	Pd/C (0.025)	nBu$_4$NBr (0.25)	26	69 (3:1)
5	**Pd/C (0.025)**	**nBu$_4$NBr (0.5)**	**23**	**77 (5:1)**[c]
6	Pd/C (0.05)	LiBr (1.0)	44	67 (5:1)
7	Pd/C (0.025)	KBr (0.5)	44	72 (4:1)
8	Pd/C (0.025)	nBu$_4$NCl (0.5)	24	n.d.[d]
9	[Na$_2$PdCl$_4$] (0.05)	nBu$_4$NBr (0.5)	21	31 (0.8:1)
10	[Pd(PPh$_3$)$_2$Cl$_2$] (0.05)	nBu$_4$NBr (0.5)	21	40 (1: 1)
11	[Pd$_2$(dba)$_3$] (0.025)	nBu$_4$NBr (0.5)	21	50 (1:1)

[a] Conditions: **3a** (0.05 mmol), **4d** (0.15 mmol), Pd catalyst, additive, HOAc (1.0 equiv), DMSO (0.5 mL), air (1 atm), 80 °C, 700 rpm. [b] NMR yields of **5b** and ratios of **5b** to **2b** (in parentheses) were calculated based on ^{1}H NMR spectra using CH_2Br_2 as the internal standard. [c] 70% isolated yield of **5b**. [d] **5b** was not detected.

With the optimum conditions in hand, the scope of the reaction was next examined (Table 2). These conditions were applicable not only to *N*-acetyl-*o*-ethynylanilines, but also to *N*-benzoyl- (**5n**) and *N*-Boc-*o*-ethynylanilines with *N*-Boc-*o*-ethynylanilines being in general the best substrates. With respect to the scope of *o*-alkynylanilines **3**, both aromatic and aliphatic substituents attached on the C_{sp} carbon atom (R^5 = aryl or alkyl) were well tolerated. The reaction was insensitive to the electronic properties of the aniline moieties of the two starting materials. When *N*-methyl-*N*-alkylanilines **3** (R^4 = alkyl) were used as substrates, the reaction delivered the *N*-demethylated bisindoles selectively (**5ab**, **5ac**). Finally, a variety of functional groups including fluoride, chloride, bromide, hydroxyl, amide, and ester were compatible with the reaction conditions to provide bisindoles with a handle for further transformations.

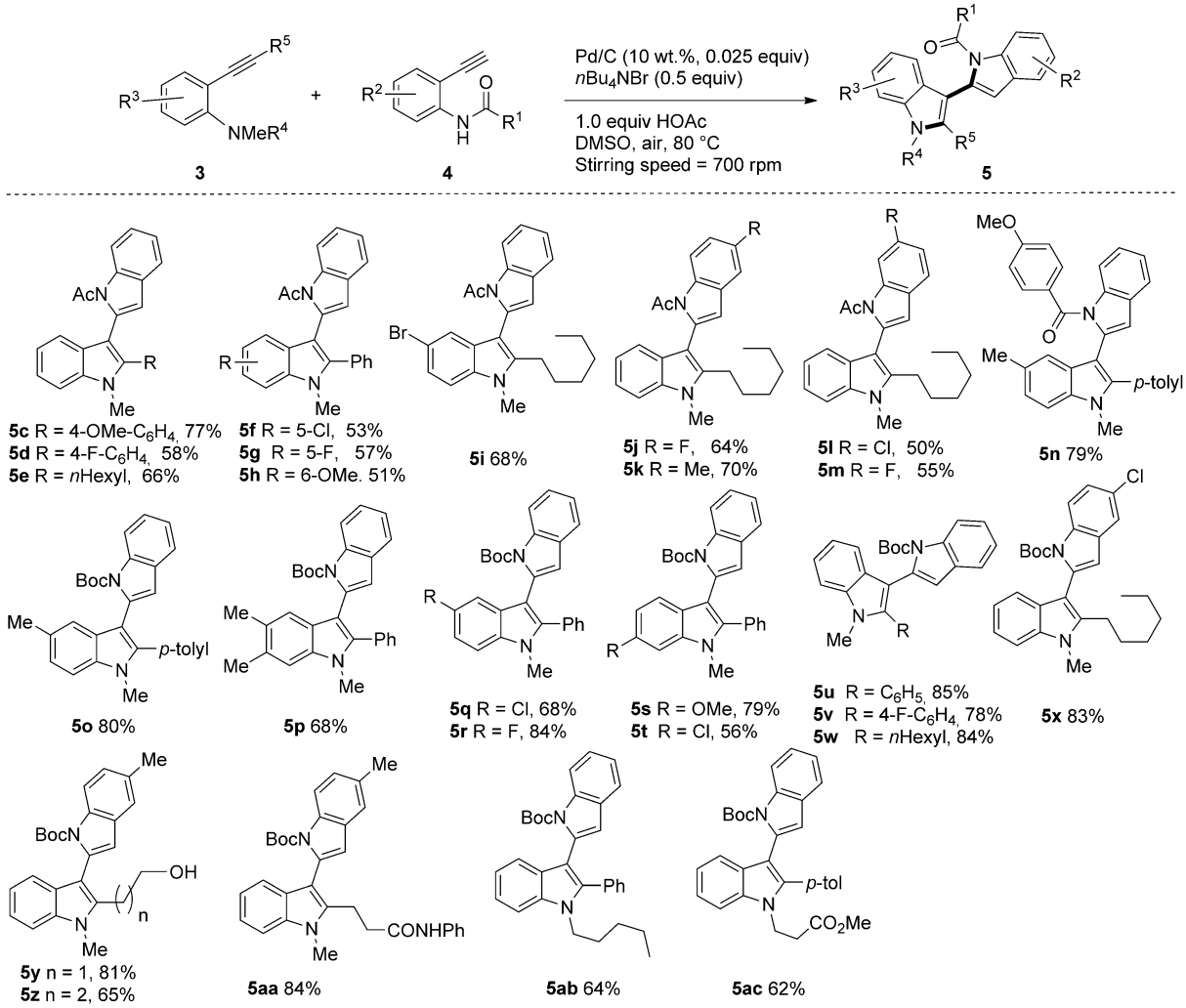
The indolyl *N*-protecting groups can be removed under standard conditions (Scheme 2). Hydrolysis of the *N*-acetyl bisindole **5b** under basic conditions delivered 2,3′-bisindole **5a** in 86% yield,[17] while cleavage of the *N*-Boc-bisindole **5o** under acidic conditions gave **5a** in 89% yield.[18] The *N*-methoxycarbonylethyl protecting group in **5ac** was selectively removed under basic conditions through a retro-Michael reaction to afford **10** in 66% yield.[19]



Scheme 2. Selective *N*-deprotection of bisindoles **5**.

There are two catalytic cycles according to our working hypothesis: formation of 3-alkynylindoles **8** and their subsequent conversion to bisindoles **5** (see Scheme 1). To gain mechanistic insights on this novel transformation, the reaction between **3a** and **4d** was carefully monitored. As shown in Figure 1, cyclizative alkynylation of **3a** with **4d** took place rapidly to deliver 3-alkynylindole **8b**. Only after the total consumption of aniline **3a** (6 h) was the cyclization of **8b** initiated to afford, after another 16 h, the bisindole **5b**. This kinetic data clearly suggested a temporal separation of the two catalytic cycles.[20] The aminopalladation of *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline (**3a**) is apparently much faster than that of the acetanilide **8b** due presumably to the higher nucleophilicity of the aniline nitrogen.[21] We note here that in DMSO, acetic acid is not acidic

Table 2. Scope of cyclizative cross-coupling between *o*-alkynylanilines **3** and *o*-ethynylaniline derivatives **4**.[a,b]



[a] Reaction conditions: **3** (0.05 mmol), **4** (0.15 mmol), Pd/C (0.025 equiv, 1.33 mg, 10 wt% on activated charcoal), nBu_4NBr (0.5 equiv, 8.1 mg), HOAc (1.0 equiv, 2.9 μL) and DMSO (0.5 mL) were heated at 80 °C under air atmosphere (1 atm) at the stirring speed of 700 rpm. [b] Yields of isolated products.

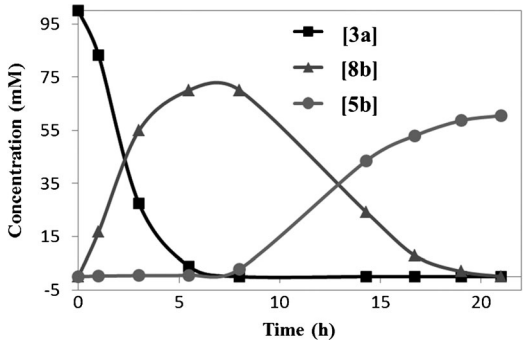


Figure 1. Kinetic profile for the reaction of **3a** with **4d**.

enough to protonate the *N*,*N*-dimethylaniline.[22] The role of the solid support in the reaction was next explored by hot filtration experiments.[23] The reaction mixture of **3a** with **4d** at 28% conversion (23% yield of **8b**) was filtered through a short pad of Celite and the evolution of the filtrate was monitored. After 3.5 h, the filtrate showed a conversion and yield of **8b** similar to that of the parallel experiment without filtration. However, after 23 h, the filtrate delivered **8b** (66%) together with only a trace amount of **5b**. These results suggested that Pd^{II}, leached into the solution, can catalyze the reaction between **3a** and **4d** leading to 3-alkynylindole **8b**, but was inefficient in catalyzing the aminopalladation of **8b** in the absence of solid support. This last assumption was born out by the following control experiments. In two parallel reactions of **3a** with **4d**, the one catalyzed by $Pd(OAc)_2$ and activated charcoal afforded, after 44 h, the 2,3′-bisindole **5b** as the major isolable product in 30% yield, while the other one catalyzed by $Pd(OAc)_2$ alone afforded only a trace amount of **5b**.

In conclusion, we developed a novel palladium-catalyzed cyclizative cross-coupling reaction between two different *o*-alkynylanilines under aerobic oxidative conditions for the synthesis of unsymmetrical 2,3′-bisindoles. Mechanistic studies suggested that the reaction went through cyclizative alkynylation to

form 3-alkynylindoles **8** followed by a second aminopalladation process to give 2,3′-bisindoles. The two catalytic cycles are temporally separated and the solid support (charcoal) played a key role in the cyclization of 3-alkynylindoles **8** to bisindoles **5**. This work represents a rare example of Pd/C acting as pre-catalyst for Pd^{II}-catalyzed oxidative transformations.[24]

Experimental Section

General procedure for the synthesis of 2,3′-bisindoles: A vial (5.0 mL) was charged with **3a** (12.8 mg, 0.05 mmol), **4d** (23.8 mg, 0.15 mmol), Pd/C (1.33 mg, 2.5 mol%, 10 wt%), nBu$_4$NBr (8.1 mg, 0.5 equiv), acetic acid (2.9 μL, 1.0 equiv), and DMSO (0.5 mL). The reaction mixture was heated at 80 °C under air (1 atm). The reaction mixture was quenched with water, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, petroleum ether/dichloromethane = 2/1) to give the desired product **5b** as a foam (13.7 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.40$ (d, $J = 8.2$ Hz, 1H), 7.52–7.49 (m, 1H), 7.36–7.21 (m, 6H), 7.21–7.10 (m, 3H), 6.56 (s, 1H), 3.73 (s, 3H), 2.44 (s, 3H), 2.36 (s, 3H), 2.06 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 171.6$, 139.8, 138.6, 137.4, 135.8, 133.2, 130.6, 130.1, 129.6, 129.5, 128.7, 127.9, 124.5 (two carbons overlapped), 123.4, 120.0, 119.0, 116.6, 113.2, 109.7, 106.8, 31.6, 26.0, 21.6, 21.5 ppm; ATR-IR: $\tilde{\nu} = 1699$ (w), 1450 (w), 1366 (m), 1302 (m), 908 (w), 823 (w), 794 (w), 730 cm^{-1} (s); HRMS (ESI) calcd for $C_{27}H_{25}N_2O^+$ $[M+H]^+$ 393.1961; found 393.1947.

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Keywords: aerobic oxidative conditions · bisindoles · cyclizative cross-coupling · *o*-alkynylaniline · palladium

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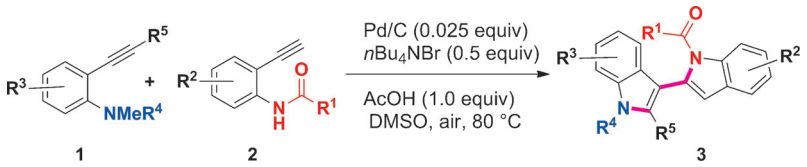

Good to excellent yields of the 2,3′-bisindoles **3** were obtained, through the formation of three chemical bonds (two C–N, one C–C), in the Pd-catalyzed reaction of two *o*-alkynylanilines **1** and **2** under mild aerobic conditions. Mechanistic studies suggested that the two catalytic cycles leading to two indole rings were temporally separated. The aminopalladation of 3-alkynylindoles, the product of the first catalytic cycle occurred only after all the *N*,*N*-dialkyl-*o*-alkynylanilines **1** were consumed. This work represents a rare example in which Pd/C was used as a pre-catalyst for the Pd^{II}-catalyzed oxidative transformations.

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Pd/C-Catalyzed Cyclizative Cross-Coupling of Two *ortho*-Alkynylanilines under Aerobic Conditions: Synthesis of 2,3′-Bisindoles