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Palladium-Catalyzed Synthesis of 2,3-Diaryl-*N*-methylindoles from *ortho*-Alkynylanilines and Aryl Pinacol Boronic Esters

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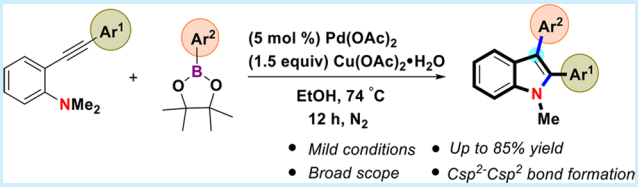
Supporting Information

ABSTRACT: A palladium-catalyzed synthesis of 2,3-diaryl-*N*-methylindoles from *o*-alkynylanilines and aryl pinacol boronic esters was developed. The system possesses high functional group tolerance and a broad substrate scope with a variety of aryl pinacol boronic esters to provide valuable 2,3-diaryl-*N*-methylindoles in moderate to good yields. Remarkably, the sequential reaction controlled by iridium-catalyzed C−H borylation or palladium-catalyzed alkynylation followed by the present palladium-catalyzed C3 arylation reaction provided functionalized 2,3-diaryl-*N*-methylindoles in good yields.



Transition-metal-catalyzed reactions have a significant impact in organic synthesis due to their peculiar synthetic transformations that obtain new chemical compounds.[1] Nitrogen-containing heterocycles are a privileged core unit present in immense bioactive scaffolds. In particular, aryl-fused *N*-heterocycles are well suited to acting as structurally enriched drug discovery entities.[2] In particular, indole skeletons have been found to be a ubiquitous prototypical pattern with widespread applications in natural products,[3] drug discovery,[4] and pharmaceuticals.[5] Unique prevalent molecules containing the indole motif are currently under clinical study[5] and have motivated an ongoing and increasingly intense research effort to overcome the remaining synthetic challenges for obtaining indole patterns. Over the past decades, several classes of pioneering methods have been reported for the synthesis of indole patterns.[6,1a,c] In particular, substituted indoles have attracted considerable attention due to their outstanding biosignificant applications. For example, a U.S.-approved indomethacin drug exhibits anti-inflammatory properties.[7a] Arbidol was demonstrated to be an effective antiviral agent.[7b] Fluvastatin is used to lower the level of LDL cholesterol.[7c,5a] Bazedoxifene is a selective estrogen receptor modulator,[7d] and pravadoline is a potent analgesic agent[7e] (Figure 1).

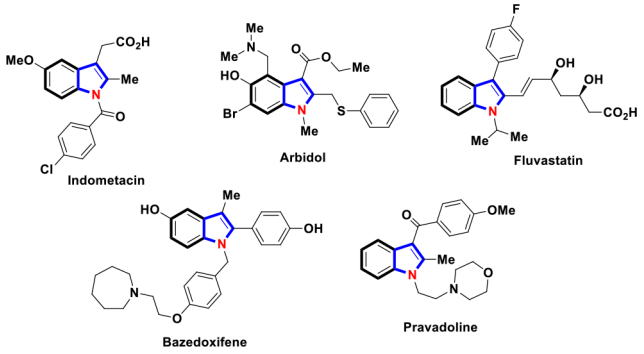


Figure 1. Representative bioactive molecules containing substituted indoles.

Palladium catalysts have played a vital role in intramolecular cyclization of *o*-alkynylanilines for the synthesis of substituted indoles.[8a−g,6a] Alkynyl or aryl halides were reacted with *o*-alkynyanilines to synthesize 3-substituted indoles.[8h,i] Zhu's research group has demonstrated the synthesis of 3-alkynyl-*N*-methylindoles via the reaction between *o*-alkynylanilines and alkynes (Scheme 1a).[9a] Wu's group has reported a strategy of using isocyanides by the amidylation of indoles to 3-amidyl-*N*-methylindoles (Scheme 1b).[9b] Despite the development of these methods, arylation on intramolecular amination of *o*-alkynylanilines is in great demand and remains a challenging step in the synthesis of the highly valuable densely substituted indoles.

Meanwhile, organoboron compounds are well-known as a key component in various chemical transformations[10−12] due to their stability, ease of handling, and ready availability of the starting precursors.[10b,c] Their utilization in a broad range of chemical entities has contributed widely to valuable chemical syntheses.[11] Boron-arylating compounds are highly prominent in various synthetic methodologies. In particular, aryl boronic

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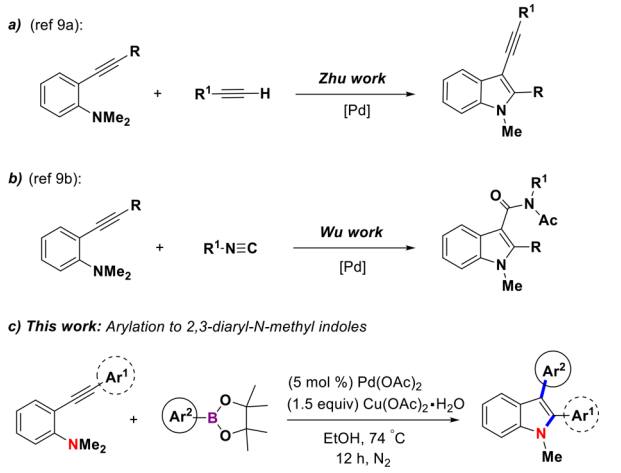
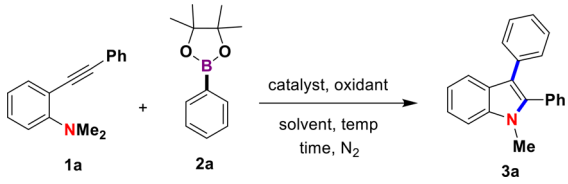
Scheme 1. Different Approaches for the Synthesis of Substituted Indoles



esters have been effectively utilized in diverse coupling reactions.[12,10a,c] We reasoned that aryl boronic esters may be suitable for carrying out the peculiar intermolecular coupling on intramolecular amination of alkynes. Herein we report a direct synthesis of densely substituted 2,3-diaryl-*N*-methyl-indoles by employing *N,N*-dimethyl-*o*-alkynylanilines with aryl pinacol boronic esters via a Pd-catalyzed intramolecular amination followed by intermolecular C3 arylation (Scheme 1c).

Initial studies were performed between **1a** and **2a** to determine the optimal reaction conditions (Table 1). In the presence of 5 mol % $Pd(OAc)_2$ in ^{t}BuOH, a trace amount of product **3a** was detected (Table 1, entry 1). Whereas for the reactions executed in EtOH, IPA, and ^{i}AmOH, product **3a** was afforded in 39%, 30%, and 35% yields, respectively (Table 1, entries 2−4). By raising the temperature to 74 °C in ethanol, **3a** was obtained in 43% yield (Table 1, entry 5). Lower yields were observed when the reactions were performed in ^{i}AmOH and ^{n}BuOH (Table 1, entries 6 and 7). When the reaction was carried out using silver acetate as the oxidant, **3a** was obtained in 48% yield (Table 1, entry 8). By switching the oxidant to $Cu(OAc)_2{\cdot}H_2O$, the product yield was increased to 53% (Table 1, entry 9). No product was observed when $K_2S_2O_8$ was used as the oxidant (Table 1, entry 10). When the reactions were carried out in the presence of peroxide oxidants, the product was formed in lower yields (Table 1, entries 11 and 12). Further reaction with hydrate-free copper acetate afforded a 51% yield (Table 1, entry 13). The reaction was completely ineffective in the absence of a catalyst (Table 1, entry 14). The reaction was also screened with a variety of palladium sources such as $PdCl_2$, $Pd(TFA)_2$, and $Pd(PPh_3)_4$, and the desired product **3a** was obtained in 18−45% yields (Table 1, entries 15−17). By decreasing or increasing the amount of $Pd(OAc)_2$, the product **3a** was furnished in 29% and 50% yields, respectively (Table 1, entries 18 and 19). In the presence of 5 mol % $Pd(OAc)_2$, a reaction time of up to 18 h in ethanol attained a 45% yield, whereas decreasing the reaction time to 12 h significantly increased the yield to 60% (Table 1, entries

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	time (h)	temp (°C)[b]	yield (%)[c]
1	5 mol % $Pd(OAc)_2$	Ag_2CO_3	^{t}BuOH	24	73	trace
2	5 mol % $Pd(OAc)_2$	Ag_2CO_3	EtOH	24	70	39
3	5 mol % $Pd(OAc)_2$	Ag_2CO_3	IPA	24	70	30
4	5 mol % $Pd(OAc)_2$	Ag_2CO_3	^{i}AmOH	24	74	35
5	5 mol % $Pd(OAc)_2$	Ag_2CO_3	EtOH	24	74	43
6	5 mol % $Pd(OAc)_2$	Ag_2CO_3	^{i}AmOH	24	90	<10
7	5 mol % $Pd(OAc)_2$	Ag_2CO_3	^{n}BuOH	24	94	<10
8	5 mol % $Pd(OAc)_2$	AgOAc	EtOH	24	74	48
9	5 mol % $Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	53
10	5 mol % $Pd(OAc)_2$	$K_2S_2O_8$	EtOH	24	74	N.D.
11	5 mol % $Pd(OAc)_2$	DTBP	EtOH	24	74	<10
12	5 mol % $Pd(OAc)_2$	TBHP	EtOH	24	74	<10
13	5 mol % $Pd(OAc)_2$	$Cu(OAc)_2$	EtOH	24	74	51
14	–	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	N.D.
15	5 mol % $PdCl_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	18
16	5 mol % $Pd(TFA)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	39
17	5 mol % $Pd(PPh_3)_4$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	45
18	2 mol % $Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	29
19	10 mol % $Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	74	50
20	5 mol % $Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	18	74	45
21	**5 mol % $Pd(OAc)_2$**	**$Cu(OAc)_2{\cdot}H_2O$**	**EtOH**	**12**	**74**	**60**
22	5 mol % $Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	EtOH	6	74	44

[a]Reactions were performed in 0.2 mmol scale. [b]Internal temperature. [c]Isolated yields. N.D. = not detected.

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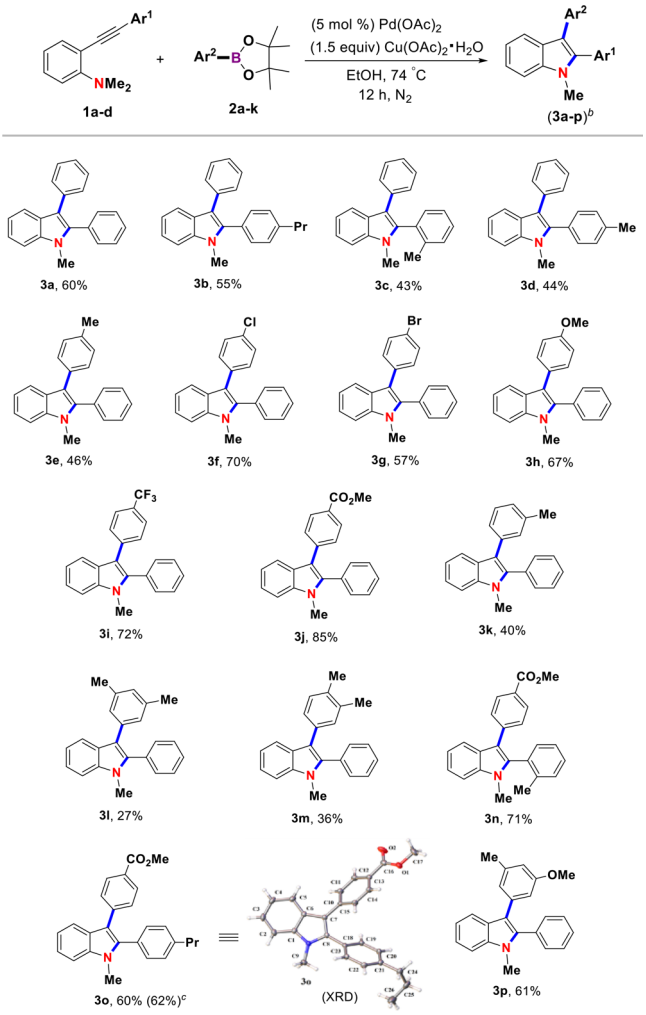
20 and 21). By further decreasing the reaction time, the yield of the product was decreased (Table 1, entry 22). From these optimization studies, we finally determined that the optimal reaction conditions are 5 mol % $Pd(OAc)_2$ with $Cu(OAc)_2 \cdot H_2O$ in ethanol at 74 °C.

With the optimized reaction conditions in hand, the scope of the reaction with various of *N,N*-dimethyl-*o*-alkynylanilines and aryl pinacol boronic esters was investigated (Scheme 2).

Scheme 2. Substrate Scope of *o*-Alkynylanilines and Aryl Boronic Esters[a]

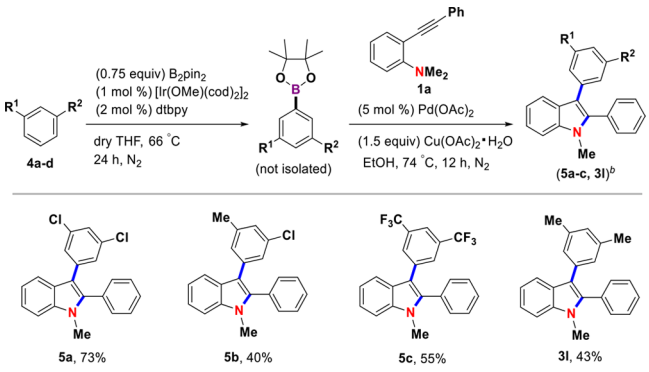


[a]All the reactions were conducted in 0.2 mmol scale in ethanol. [b]Isolated yields. [c]1 mmol scale.

We examined the reaction with different *N,N*-dimethyl-*o*-alkynylanilines (**1a–d**) under the standard reaction conditions, and the desired products **3a–3d** were isolated in 43–60% yields. Furthermore, we conducted the reactions with different *para*-substituted aryl pinacol boronic esters (**2b–g**). In all cases, the reactions proceeded smoothly, showing compatibility with methyl (**3e**), halides (**3f** and **3g**), methoxy (**3h**), trifluoromethyl (**3i**), and ester (**3j**). 3-Methylphenyl, 3,5- or 3,4-dimethylphenyl boronic esters (**2h–j**) reacted well with **1a** in ethanol and furnished the products **3k–3m** in moderate yields. Boronic ester containing ester functional group **2g** undergoing reaction with **1c** afforded the corresponding product **3n** in 71% yield. A similar reaction with **1b** delivered the resultant product **3o** in 60% yield. The structure of **3o** was unambiguously confirmed by single crystal X-ray analysis. The dissimilar disubstituent electronic nature of **2k** was also investigated. It was found that the reaction proceeded well and the desired product **3p** was obtained in 61% yield. It is to be noted that while on reaction with heteroaromatic boronic esters such as 2-(2,5-dimethylfuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine with **1a**, the reactions failed to afford the desired products.

We have inspected a sequential iridium-catalyzed C–H borylation[13] followed by the present synthetic strategy (Scheme 3). The initial reaction was performed with

Scheme 3. Iridium-Catalyzed C–H Borylation Followed by C3 Arylation Reactions[a]

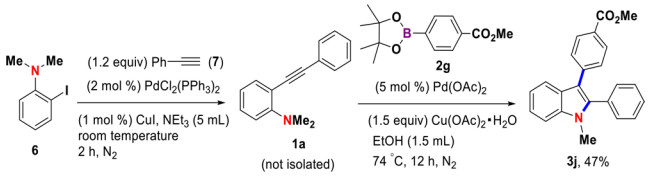


[a]Reactions were performed on 0.2 mmol scale. [b]Isolated yields.

dichloroarene **4a** by a sequential process, affording the product **5a** in 73% yield. Encouraged by this result, we have examined disubstituted arene **4b** by employing the identical sequential method, and the product **5b** was furnished in 40% yield. Further reaction with ditrifluoromethyl or dimethyl arenes afforded the arylation products **5c** and **3l** in 55% and 43% yields, respectively.

Inspired by the above sequential process, we further examined a sequential Sonogashira reaction[8f] followed by the present synthetic protocol (Scheme 4). The initial Csp^2–Csp

Scheme 4. Sequential Coupling Reaction



coupling reaction was performed between **6** and **7** in the conditions for the Sonogashira reaction and was followed by the reaction with **1a** and **2g** in the presence of 5 mol % $Pd(OAc)_2$ with $Cu(OAc)_2 \cdot H_2O$, affording the product **3j** in 47% yield. A competition experiment was carried out between *o*-alkynylaniline (**1c** and **1d**) with **2a** to determine the steric properties of aminoalkynes (Scheme 5a). The sterically congested *ortho* methyl group of **1c** led to the lower amount of the C3 arylation product. On the other hand, a boronic ester competition experiment was undertaken between **1a** with **2a** and **2c** to determine the electronic impact of the boronic ester. It was found that the boronic ester containing an electron-

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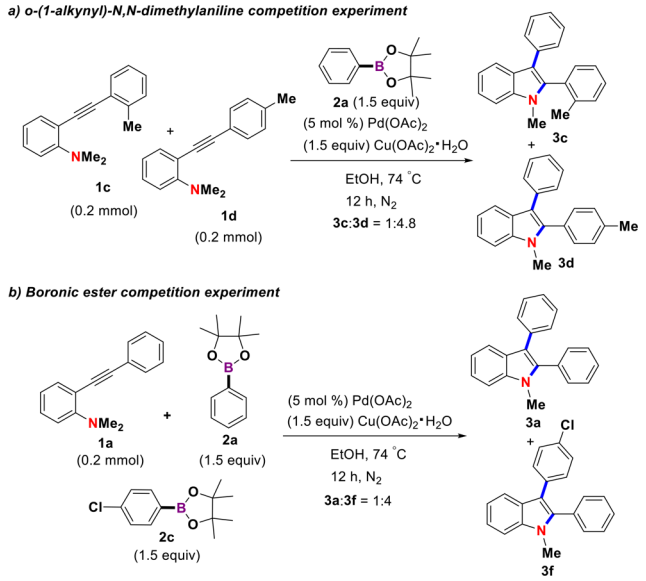
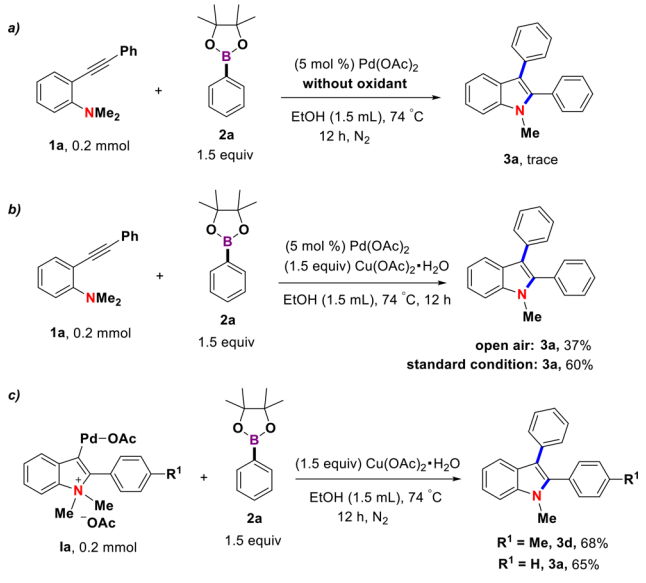
Scheme 5. Competition Experiments



withdrawing group is more favorable for C3 arylation than phenyl boronic ester (Scheme 5b).

Control experiments were also carried out to gain insight into this reaction mechanism. A preliminary reaction without an oxidant was carried out, and only a trace amount of product **3a** was detected. This result indicated that $Cu(OAc)_2{\cdot}H_2O$ is essential for this transformation in this system (Scheme 6a).

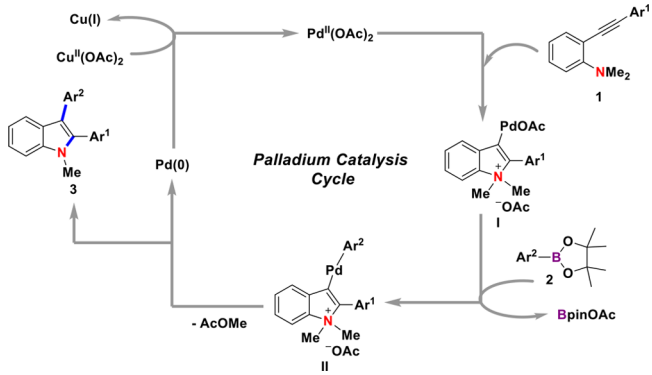
Scheme 6. Control Experiments and Mechanistic Studies



The reaction performed under an open air atmosphere afforded the product with a lower yield which revealed that an inert nitrogen atmosphere is necessary to upturn the yield of the product (Scheme 6b). Intermediate **Ia** was prepared according to the literature,[9] and the reaction was implemented with aryl boronic ester **2a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in ethanol. The desired products **3d** and **3a** were obtained, which evidenced that the reaction mechanism proceeds through an intermediate **I** (Scheme 6c).

Based on the above results, we postulated a plausible mechanism as follows (Scheme 7). First, $Pd(OAc)_2$ reacts with

Scheme 7. Possible Mechanism for the Palladium-Catalyzed Arylation Reaction



o-alkynylaniline **1**, which leads to aminopalladation intermediate **I**. The aryl pinacol boronic ester **2** interacts with **I** to form an intermediate *σ*-aryl-*σ*-indolylpalladium **II** along with the concurrent removal of BpinOAc. The intermediate **II** further undergoes a reductive elimination to afford the desired C3 arylation product **3**, and Pd(0) was oxidized to Pd(II) by Cu(II) to furnish the catalytic cycle.

In conclusion, an efficient method for the synthesis of densely substituted 2,3-diaryl-*N*-methylindoles was achieved by using *o*-alkynylanilines with aryl pinacol boronic esters via palladium-catalyzed arylation on intramolecular amination of *o*-alkynylanilines. The present protocol is compatible with various aryl pinacol boronic esters under mild reaction conditions. A sequential iridium-catalyzed C−H borylation or Sonogashira reaction followed by the present method was used to obtain functionalized 2,3-diaryl-*N*-methylindoles. The reaction is simple to carry out in practice and has high functional group tolerance, and the mechanistic studies implied that the reaction proceeds through an aminopalladation intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02835.

Experimental procedures, spectroscopic data, copies of NMR and crystallographic data (PDF)

Accession Codes

CCDC 1858837 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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