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Palladium-Catalyzed Domino C,N-Coupling/Carbonylation/Suzuki Coupling Reaction: An Efficient Synthesis of 2-Aroyl-/Heteroaroylindoles

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ABSTRACT

A convenient one-pot synthesis of 2-aroylindoles using a domino palladium-catalyzed C,N-coupling/carbonylation/C,C-coupling sequence is described. The reaction involved easily prepared 2-*gem*-dibromovinylanilines and boronic acids under carbon monoxide. Optimized reaction conditions allowed the construction of a wide variety of highly functionalized 2-aroyl-/heteroaroylindoles in satisfactory yields.

The indole scaffold is prevalent in a plethora of natural and synthetic compounds characterized by a variety of biological and pharmacological activities.[1] In particular, the 2-aroylindole moiety is presented in several potent tubulin polymerization inhibitors.[2] In connection with our ongoing studies[3] on the synthesis of new vascular disrupting agents,[4] we were especially interested in the construction of polysubstituted indoles bearing a 2-aroyl or 2-heteroaroyl group.

Relatively few methods for the synthesis of the 2-aroylindole skeleton have been reported. The most common synthetic route involves regioselective addition of a variety of acyl electrophiles on an N-protected 2-lithioindole species.[5] Other synthetic pathways include (a) cyclization of chalcones bearing a 2-nitrogen group,[6] (b) palladium-catalyzed coupling reactions with an acid chloride,[7] and (c) palladium carbonylative cross-coupling with indoylborate.[8] Moreover, these methodologies require the "de novo" construction of conveniently N-protected indoles or highly functionalized precursors.

In this context, we became interested in the development of a reliable approach for the synthesis of polysubstituted 2-aroylindoles. The palladium-catalyzed domino reaction appears as an attractive synthetic route that prevents the tedious construction of elaborated precursors and enhances

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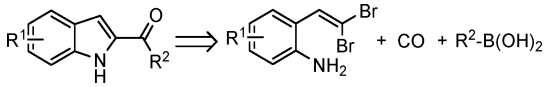
the efficiency of reaching the target molecules. Recently, some interesting syntheses of 2-substituted indoles via palladium-catalyzed tandem reactions, starting from 2-*gem*-dibromovinylanilines, have emerged in the literature.[9] Lautens and co-workers reported several C,N/C,C sequences providing 2-aryl,[10] 2-heteroaryl,[11] 2-alkenyl,[12] or 2-alkynyl[13] indoles. Interestingly, a tandem C,N/carbonylation reaction published by Alper and co-workers allowed access to various methyl-2-indolecarboxylates.[14] Accordingly, we envisioned that 2-bromoindole—reported as a potential intermediate in these tandem reactions—could generate, by the migratory insertion of carbon monoxide, an acylpalladium species which could undergo transmetalation with a boronic acid.[15,16]

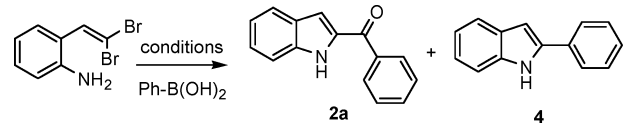
Herein, we report an effective domino C,N-coupling/carbonylation/C,C-coupling sequence as a new route to 2-aroyl-/heteroaroylindoles bearing a variety of functional groups. The reaction involves 2-*gem*-dibromovinylanilines,[17] carbon monoxide, and boronic acids using palladium catalysis (Scheme 1).

Scheme 1. Strategic Approach to the Synthesis of 2-Acylindoles



The 2-*gem*-dibromovinylaniline **1a** and phenylboronic acid **3a** were chosen to investigate the feasibility of the projected reaction (Table 1). Thus, using $Pd(PPh_3)_4$, K_3PO_4 as a base, and toluene as the solvent under 1 atm of CO at 90 °C until consumption of the starting aniline, the desired aroylindole **2a**[5b] could be isolated in 29% yield, but along with the 2-phenylindole[18] **4** (15% yield) arising from a C,N/Suzuki reaction (entry 1). Several bases were next examined, and

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base[a]	CO	catalyst	temp (°C)/time (h)	yield **2a**/**4** (%)[b]
1	toluene	K_3PO_4	balloon	$Pd(PPh_3)_4$	90/6	29/15
2	toluene	K_2CO_3	balloon	$Pd(PPh_3)_4$	90/24	45/7
3	toluene	Cs_2CO_3	balloon	$Pd(PPh_3)_4$	90/24	25/2
4	toluene	CsF	balloon	$Pd(PPh_3)_4$	90/48	trace
5	toluene	K_2CO_3	balloon	$Pd(PPh_3)_4$[c]	90/2	45/25
6	toluene	K_2CO_3	balloon	$PdCl_2$dppf[c]	90/18	28/8
7	toluene	K_2CO_3	balloon	Pd_2dba_3/ Xantphos[c]	90/18	12/6
8	toluene	K_2CO_3	12 bar	$Pd(PPh_3)_4$	110/16	44/0
9	dioxane	K_2CO_3	12 bar	$Pd(PPh_3)_4$	100/16	61/0
10	dioxane	K_2CO_3	12 bar	$Pd(PPh_3)_4$	85/24	54/0
11	dioxane	K_2CO_3	12 bar	$Pd(PPh_3)_4$	85/48	62/0
12	dioxane	K_2CO_3	12 bar	$Pd(PPh_3)_4$	85/60	70/0

[a] All reactions were performed on a 1 mmol scale using 5 mol % of catalyst, 5 equiv of base, and 1.1 equiv of phenylboronic acid. [b] Isolated yield after column chromatography. [c] 3 equiv of KI was added.

K_2CO_3 proved to be the most efficient (entries 2—45% yield—vs 1, 3, and 4).

Other catalyst systems did not favor the expected three-step tandem process (entries 5—7).[19] To promote the carbonylation step, the domino reaction was performed under 12 bar of CO (entries 8—12). Using this relatively low pressure, the sequence provided exclusively 2-benzoylindole **2a** (entry 8, 44% yield). Exchanging toluene to dioxane at 100 °C resulted in a higher yield of **2a** (entry 9, 61%), but a longer heating time did not improve the coupling efficiency (data not shown). Reducing the temperature to 85 °C resulted in a slight diminution of the yield (entry 10, 54%), while heating for a longer time (48 or 60 h) allowed recovery of up to 70% yield for product **2a** (entries 11 and 12). Modification of the catalytic system also failed to improve the yield (data not shown).

To examine the scope of this one-pot protocol, we selected the optimized reaction conditions (K_2CO_3, $Pd(PPh_3)_4$, CO 12 bar, dioxane) and chose the temperature/time parameters with respect to the nature of the engaged substrates.

For substituted anilines **1b**—**1g**,[20] which are prone to degradation, domino reactions were conducted at 85 °C for 24 h. As highlighted in Table 2, several functional groups are tolerated including chlorine (entry 1, 68%), the electron-withdrawing methoxycarbonyl group (entry 2, 50%), or electron-releasing groups (entries 4—6) to produce benzoylindoles **2b**—**2f**[2b,6a] in good yields. The reaction can also be conducted with the polysubstituted aniline **1g** to provide 2-benzoyl-4,5,6-trimethoxindole **2g** in

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(10) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.
(11) Fang, Y.-Q.; Karish, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341.
(12) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203.
(13) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.
(14) Viera, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899.
(15) Carbonylative cross-coupling reactions had proved to be an efficient tool for the preparation of unsymmetrical ketones. See: (a) Brunet, J.-J.; Chauvin, R. *Chem. Soc. Rev* **1995**, *24*, 89. (b) Neigishi, E.-i. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Ed.;Wiley-Interscience: New York, 2002; Part IV, p 2309. (c) O'Keefe, B. M.; Simmons, N.; Martin, S. F. *Org. Lett.* **2008**, *10*, 5301. (d) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.
(16) For recent examples of carbonylation used in combination with alternative palladium-catalyzed reactions, see: (a) Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11*, 3210. (b) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583. (c) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987. (d) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102, and references cited therein. (e) Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 7175. (f) Grigg, R.; Sridharan, V.; Saha, M.; Mutton, S.; Kilner, C.; Macpherson, D.; Milner, P. *J. Org. Chem.* **2008**, *73*, 8352.
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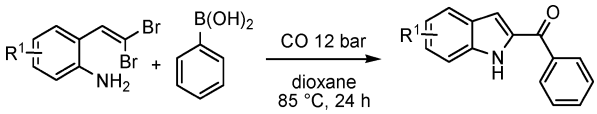
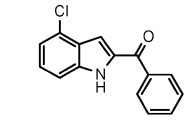
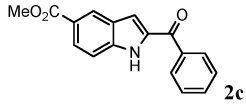
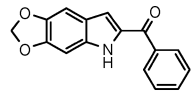
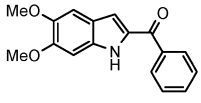
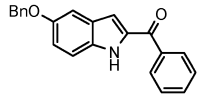
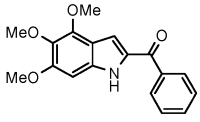
(19) KI and dppf complex were reported to enhance the carbon monoxide insertion vs the transmetalation of boronic acids, see: Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.
(20) *gem*-Dibromovinylanilines **1b**—**1g** were prepared in a two-step sequence (Ramirez olefination, reduction using $SnCl_2{\cdot}2H_2O$) from *o*-nitrobenzaldehyde derivatives according to Fang and Lautens (see ref 10).

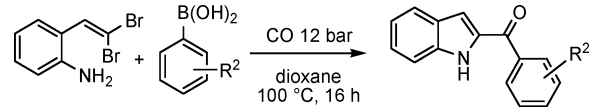
Table 2. Variation of the 2-*gem*-Dibromovinylanilines[a]

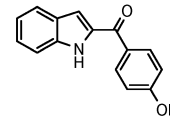
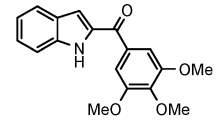
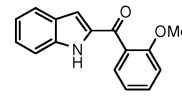
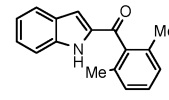
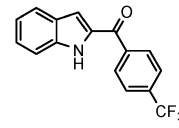
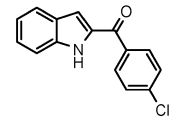
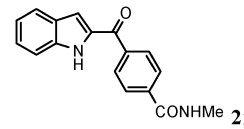
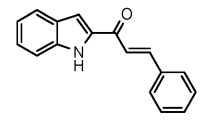


entry	substrate (R^1)	product	yield (%)[b]
1	3-Cl **1b**	 **2b**	68
2	4-CO_2Me **1c**	 **2c**	50
3	4,5-OCH_2O- **1d**	 **2d**	56
4	4,5-diOMe **1e**	 **2e**	55
5	4-OBn **1f**	 **2f**	73
6	3,4,5-triOMe **1g**	 **2g**	65 (51)[c]

[a] All reactions were performed on a 1 mmol scale using 5 mol % of $Pd(PPh_3)_4$, 5 equiv of K_2CO_3, and 1.1 equiv of phenyl boronic acid under an atmosphere of CO (12 bar). [b] Isolated yield after column chromatography. [c] Reaction run at 100 °C for 16 h.

Table 3. Scope of Aryl Boronic Acids[a]



entry	substrate (R^2)	product	yield (%)[b]
1	4-OMe **3h**	 **2h**	61
2	3,4,5-triOMe **3i**	 **2i**	63
3	2-OMe **3j**	 **2j**	40
4	2,6-diMe **3k**	 **2k**	-
5	4-CF_3 **3l**	 **2l**	73
6	4-Cl **3m**	 **2m**	70
7	4-CONHMe **3n**	 **2n**	29
8	Styryl **3o**	 **2o**	67

[a] All reactions were performed on a 1 mmol scale using 5 mol % of $Pd(PPh_3)_4$, 5 equiv of K_2CO_3, and 1.1 equiv of boronic acid under an atmosphere of CO (12 bar). [b] Isolated yield after column chromatography.

good yield (entry 6, 65%). It is noteworthy that yields could be further enhanced by increasing the reaction time. We then turned our attention to the scope of aryl boronic acids. Since the starting aniline **1a** was robust enough, these reactions were conducted at higher temperature (100 °C) for 16 h using several commercially available boronic acids **3h**−**3o** (Table 3).

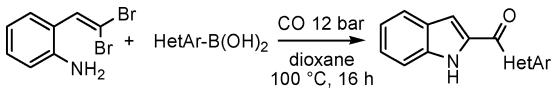
Electron-rich partners, such as 4-methoxyphenyl or 3,4,5-trimethoxyphenyl boronic acids, performed well under the optimized conditions (entries 1 and 2).[2b,21] The reaction seems to be sensitive to steric hindrance imposed by the *o*-substitution of the boronic acid. For example, 2-methoxyphenylboronic acid **3j** furnished the aroylindole **2j**[21] in modest yield (entry 3, 40%), whereas with the 2,6-dimethylphenylboronic acid, an attempt to isolated indole **2k** was unsuccessful despite complete consumption of aniline **1a** (entry 4). Electron-deficient substrates, such as 4-trifluoromethyl or 4-chlorophenylboronic acids, react smoothly (entries 5−6, 73 and 70%, respectively).[22] Boronic acid **3n**, bearing an amido group, participates in the reaction albeit in a lower yield (entry 7, 29%). Phenylvinylboronic acid also proved to be an efficient partner of the domino reaction providing indol-2-ylchalcone **2o** in good yield (entry 8, 67%).

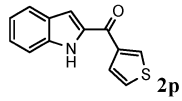
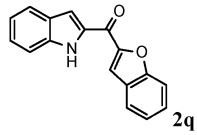
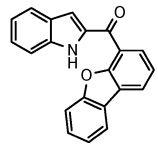
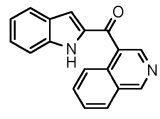
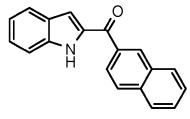
Finally, we explored the application of the domino reaction to heteroarylboronic acids (Table 4). The reaction proved to be compatible with various substrates such as thiophen-3-, benzofuran-2-, or dibenzofuran-4-boronic acids providing 2-heteroaroylindoles **2p**−**2s**[2b,23] in fair to good yields (entries 1−3, 58−71%). Reaction with isoquinolin-3-boronic acid was less efficient providing indole **2s** in low yield, probably due to the nitrogen of the boronic acid (entry 4, 21%).

(21) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935.

(22) Takeda, Y.; Kikuchi, A.; Terashima, M. *Heterocycles* **1993**, *35*, 573.

Table 4. Scope of Heteroaryl Boronic Acids[a]



entry	HetAr	product	yield[b] (%)
1	thiophen-3-yl **3p**	 **2p**	67
2	benzo furan-2-yl **3q**	 **2q**	58
3	dibenzo furan-4-yl **3r**	 **2r**	71
4	isoquinolin-3-yl **3s**	 **2s**	21
5	naphtalen-2-yl **3t**	 **2t**	70

[a] All reactions were performed on a 1 mmol scale using 5 mol % of $Pd(PPh_3)_4$, 5 equiv of K_2CO_3, and 1.1 equiv of boronic acid under an atmosphere of CO (12 bar). [b] Isolated yield after column chromatography.

2-Naphthylboronic acid also participated in the domino process leading to polycyclic compound **2t**[24] in good yield (entry 5, 70%).

In summary, we have established a novel and efficient protocol for the preparation of 2-aroylindoles in moderate to good yields, through a one-pot palladium-catalyzed C,N-coupling/carbonylation/Suzuki coupling sequence. The reaction tolerates various functional groups, thus providing a practical access to a wide range of 2-aroyl- or 2-heteroaroylindoles from readily accessible starting materials. The application of this methodology to the synthesis of bioactive compounds is underway in our laboratory.

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Supporting Information Available: Synthetic procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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