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Pd-Catalyzed Tandem C–N/C–C Coupling of *gem*-Dihalovinyl Systems: A Modular Synthesis of 2-Substituted Indoles

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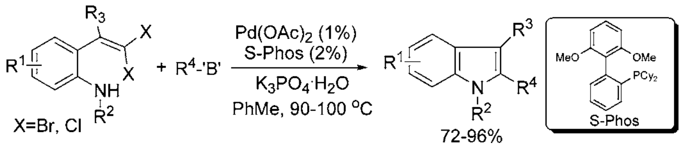
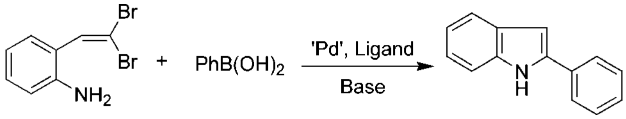
ABSTRACT



2-Substituted indoles were synthesized via a Pd-catalyzed tandem C–N/Suzuki–Miyaura coupling from readily prepared *ortho-gem*-dihalovinylanilines. Optimal conditions used a Pd(OAc)$_2$/S-Phos catalyst in the presence of K$_3$PO$_4$·H$_2$O and an organoboron reagent, which included boronic acids, esters, alkyl 9-BBN derivatives, and trialkylboranes. Yields of the desired indoles were good to excellent using low catalyst loadings (typically 1 mol %).

Over the past several decades, palladium has emerged as one of the most versatile catalysts for the formation of carbon−carbon, carbon−heteroatom, and carbon−metalloid bonds.[1] A usual protocol involves coupling an sp^2 carbon-halide and various nucleophiles. The reactivity difference between halides (I > Br ≫ Cl, F usually inert) is significant to give stepwise couplings of multihalogenated substrates using different catalyst systems.[2] However, regioselective coupling of the same halogen is usually rather difficult. In our previous studies, we successfully applied a strategy to couple a dibromoaryl system selectively using an intramolecular and intermolecular tandem Heck reaction.[3] We therefore decided to extend our method toward the selective tandem coupling of *gem*-dihalovinyl systems, which can be easily obtained via a Ramirez−Corey olefination reaction.[4] By tethering a *gem*-dibromovinyl group *ortho* to aniline, we envisaged a modular indole synthesis via a tandem Pd-catalyzed intramolecular C−N (Buchwald−Hartwig amination)[5] and intermolecular C−C bond (Suzuki−Miyaura coupling)[6] formation (Scheme 1).[7] Since the resulting indole moiety is a privileged structural motif exhibiting broad pharmacological properties in numerous therapeutic agents and natural products,[8] a modular synthetic method, which allows rapid access to a new class of indole derivatives, is very attractive to synthetic and medicinal chemists.[9]

Scheme 1



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(1) For a comprehensive monograph, see: Tsuji, J. *Palladium Reagents and Catalysis*; John Wiley & Sons Ltd.: Chichester, U.K., 2004.

(2) Wu, T. Y. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett.* **2001**, *3*, 3827.

(3) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679.

(4) For a review on the preparation of *gem*-dibromovinyl compounds, see: Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, 185−213.

(5) (a) Muci, A.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051.

(6) (a) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

10.1021/ol051286l CCC: $30.25

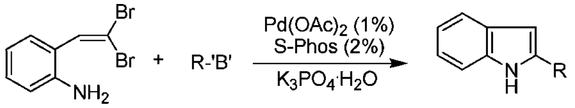
Although recent work suggested that activation of the aniline N-H using an electron-withdrawing Ac group was essential,[7] we found that free anilines afforded the desired indole product directly and in higher yield. Herein, we report a highly efficient and modular synthesis of 2-substituted indoles from *ortho*-*gem*-dihalovinylanilines.[10]

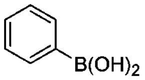
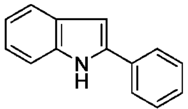
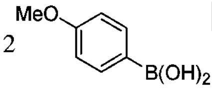
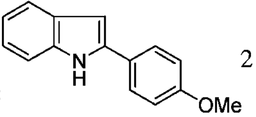
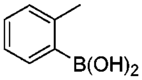
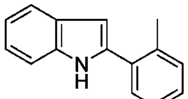
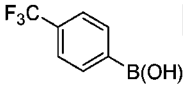
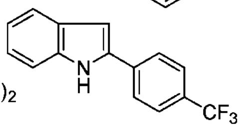
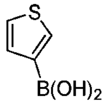
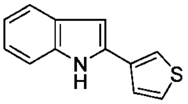
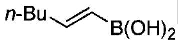
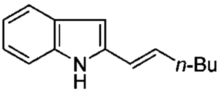
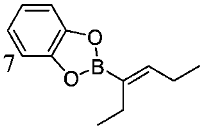
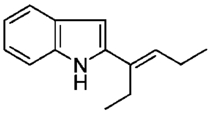
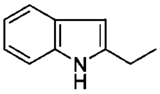
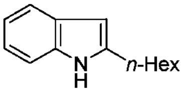
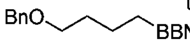
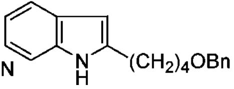
Initial studies focused on screening the activating groups on nitrogen, inorganic bases, phosphine ligands, and Pd sources. Preliminary results gave a yield of 75% using *N*-acetyl-2-*gem*-dibromovinylaniline, $Pd_2(dba)_3/P(o\text{-tol})_3$, and K_2CO_3. However, the range of boronic acids was very limited and yields did not increase despite further optimization. We later found that comparable yields for a broader variety of boronic acids could be obtained by simply using the free amino group. Gratifyingly, $Pd(OAc)_2$ coupled with Buchwald's S-Phos ligand[11] in the presence of $K_3PO_4{\cdot}H_2O$ in toluene at 90 °C gave 2-phenylindole in good yield (84%) with an attractively low catalyst loading (1 mol % Pd).

Using these optimized reaction conditions, various commercially available aryl and heteroarylboronic acids of different electronic and steric character were evaluated (Table 1, entries 1−5). For all cases, the expected 2-substituted indoles were isolated in good yields. Extension to alkenyl boronic acids and alkenyl catechol boronate esters (Table 1, entries 6 and 7) also gave the desired products in good yield.

One of the merits of the Suzuki−Miyaura coupling reaction is its ability to couple sp^2 and sp^3 carbons.[12] Therefore, we decided to examine commercially available trialkylboron or functionalized alkyl 9-BBN reagents (prepared in situ by premixing a terminal alkene and 9-BBN overnight at 20 °C). Under mild reaction conditions (60 °C in THF), the desired indoles were obtained in good yield (Table 1, entries 8−10).

Table 1. Scope of Organoboron Reagents



entry	R-'B'	indoles	time (h)	yield (%) [a]
1			6	84
2			2	83
3			4	82
4			7	75
5			12	86 [b]
6			5	80 [b]
7			6	73 [c]
8	Et_3B		2	77 [d]
9	*n*-HexBBN		3	79 [d]
10			4	78 [d]

[a] Isolated yields using $Pd(OAc)_2$ (1%), S-Phos (2%), $ArB(OH)_2$ (1.5 equiv), and $K_3PO_4{\cdot}H_2O$ (5 equiv) in PhMe at 90 °C. [b] Catalyst loading (3%). [c] $Pd(OAc)_2$ (3%), S-Phos (6%), R-B (2.5 equiv), and $K_3PO_4{\cdot}H_2O$ (5 equiv) in PhMe at 90 °C. [d] $Pd(OAc)_2$ (2%), S-Phos (5%), R-B (1.5 equiv), and $K_3PO_4{\cdot}H_2O$ (5 equiv) in THF at 60 °C.

Various substituted *ortho*-*gem*-dibromovinylanilines were also evaluated with phenylboronic acid under the reaction conditions. This method proved to be very general and efficient to prepare a variety of benzo-functionalized indoles (Table 2, entries 1−8). In particular, preparation of 4-substituted indoles (entries 1−2, 7), which are generally regarded as challenging targets by traditional Fischer indole methods, were prepared from their corresponding anilines in good yield. One of the synthetic advantages of this method is its compatibility with a broad spectrum of electron-withdrawing

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(7) During our investigation, Bisseret and co-workers disclosed a related example of this reaction yielding *N*-acetyl-2-arylindole in moderate yield. Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907. The scope of this reaction was not reported.

(8) For recent reviews on indole-containing natural products, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) For recent reports on indole-containing pharmaceuticals, see: Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175.

(9) For reviews see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045 and references therein. (b) *Indoles*; Sundberg, R. J., Ed.; Academic Press: San Diego, 1996. For recent reports on Pd-catalyzed indole synthesis, see: (c) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (d) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (e) Nazare, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526. (f) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230. (g) Larock, R. C.; Yum, E. K.; Refvic, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(10) *ortho-gem*-Dibromovinylanilines are readily accessible via Ramirez−Corey olefination, followed by reduction to the aniline. For example, *ortho-gem*-dibromovinylaniline can be easily obtained from 2-nitrobenzaldehyde by treatment with CBr_4/PPh_3 (95%), followed by $SnCl_2{\cdot}2H_2O$ (90%) or Fe/HOAc (85%) reduction. This can also be carried out in a convenient one-pot preparation on a relatively large scale (>40 g) in 85% overall isolated yield. For experimental procedures for the preparation of all substrates in Table 2, please refer to Supporting Information.

(11) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(12) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745.

Table 2. Scope of *ortho-gem*-Dihalovinylaniline Substrates

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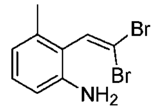
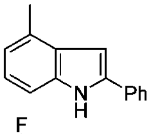
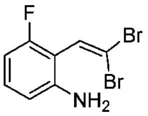
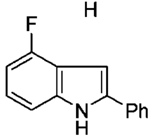
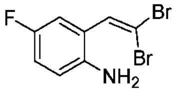
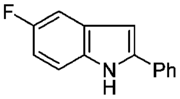
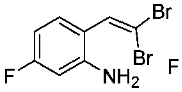
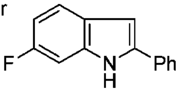
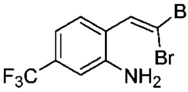
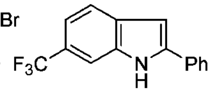
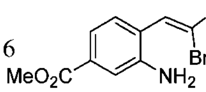
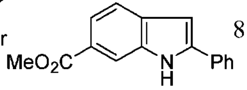
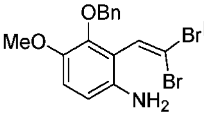
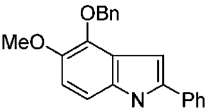
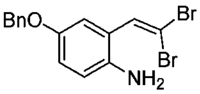
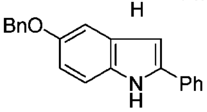
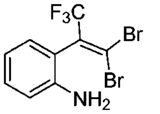
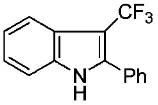
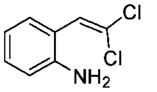
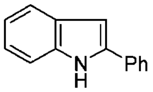
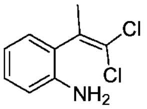
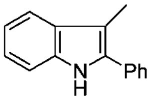
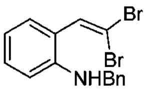
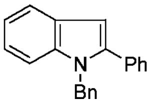
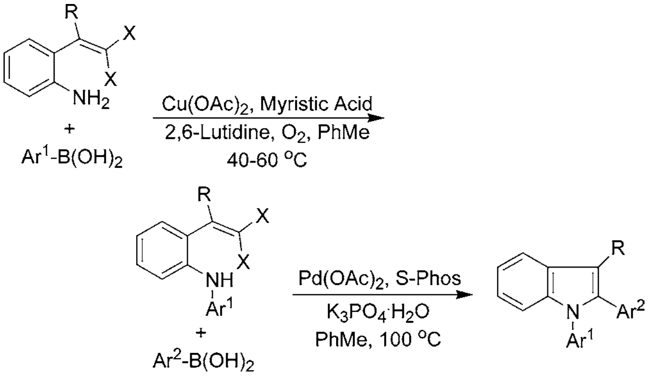
1			2	77[b]
2			14	88
3			2	87
4			2.5	80[d]
5			2.5	90
6			8.5	90
7			2	72[c]
8			3	86[d]
9			1	79[c]
10			2	95[b]
11			2	96[c]
12			4	82

[a] Isolated yields using $Pd(OAc)_2$ (1%), S-Phos (2%), $PhB(OH)_2$ (1.5 equiv), and $K_3PO_4 \cdot H_2O$ (5 equiv) in PhMe at 90 °C. [b] Catalyst loading (5%), 90 °C. [c] Catalyst loading (3%), 100 °C. [d] Catalyst loading (2%), 90 °C.

and electron-donating functionalities, presumably resulting from the distance from the reaction sites.

We also sought to extend our method toward the preparation of synthetically important 2,3-disubstituted indoles.[13] Using our standard conditions, 3-alkyl-substituted indoles (Table 2, entries 9 and 11) could be obtained from the corresponding dihalovinyl substrates in good to excellent yields. In particular, we note that use of *ortho-gem*-dichlorovinylanilines[14] (Table 2, entries 10 and 11) gave near quantitative yields of the expected indole, suggesting that these two C−Cl bonds were more selective in the two new bond formations than their C−Br analogues.[15]

Table 3. Metal-Controlled Orthogonal Combinatorial Approach To Synthesize 1,2-Diarylindoles



entry	R	X	$Ar^1B(OH)_2$	yield (%)[a]	$Ar^2B(OH)_2$	yield (%)[b]
1	H	Br	$PhB(OH)_2$	89	$PhB(OH)_2$	90
2	H	Br	$PhB(OH)_2$	89	$4\text{-}FPhB(OH)_2$	86[c]
3	H	Br	$4\text{-}FPhB(OH)_2$	69	$PhB(OH)_2$	90
4	Me	Cl	$PhB(OH)_2$	98	$4\text{-}FPhB(OH)_2$	96
5	Me	Cl	$4\text{-}FPhB(OH)_2$	65	$PhB(OH)_2$	94

[a] Isolated yields using $ArB(OH)_2$ (2 equiv), $Cu(OAc)_2$ (1 equiv), myristic acid (0.4 equiv), 2,6-lutidine (1.07 equiv), and PhMe, 40−60 °C. [b] Isolated yields using $Pd(OAc)_2$ (3%), S-Phos (6%), $ArB(OH)_2$ (1.5 equiv), and $K_3PO_4 \cdot H_2O$ (5 equiv) in PhMe at 100 °C. [c] Mixed base of KOH (2 equiv) and $K_3PO_4 \cdot H_2O$ (1 equiv) instead of $K_3PO_4 \cdot H_2O$ (5 equiv).

Substitution on the aniline nitrogen using an *N*-benzyl-substituted secondary amine worked almost as well as the primary amine substrate (Table 2, entry 12). In contrast, we found that use of an activating acetyl or tosyl protecting group gave very low yields under the optimized conditions.

We also wanted to explore an orthogonal combinatorial approach to synthesize 1,2-disubstituted or 1,2,3-trisubstituted indoles because these compounds generally exhibit a broad range of application in the pharmaceutical (COX-II inhibitors,[16] estrogen agonists and antagonists[17]) and material science (electroluminescence[18]) industries. While initial attempts to prepare the *N*-arylated starting material using Buchwald's catalytic conditions gave moderate to low yields, use of stoichiometric Cu(II) and higher reaction temperature was found to circumvent this problem.[19] The *N*-arylated substrates were subsequently subjected to the Pd-catalyzed tandem coupling reaction conditions, affording the indole

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products in good to excellent yields (Table 3). Such a catalyst-controlled combinatorial approach allows the facile and rapid generation of a diverse and broad library using a limited number of reagents by simply switching the addition sequence of the boronic acids in the reactions.[20]

In conclusion, we have found a very efficient and modular de novo indole synthesis via a formal intramolecular Buchwald−Hartwig C−N/intermolecular Suzuki−Miyaura C−C coupling reaction. Further study of the mechanism, exploration of scope, application to library synthesis, and synthesis of biologically active targets are currently under investigation.

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Supporting Information Available: Full experimental details and characterization including ^{1}H and ^{13}C NMR spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Aldrich currently supplies a special catalog of more than 250 boronic acids and esters. This can be found at http://www.aldrich-sigma.com.