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Synthesis of 2-Vinylic Indoles and Derivatives via a Pd-Catalyzed Tandem Coupling Reaction

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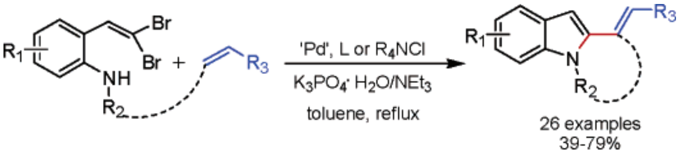
ABSTRACT



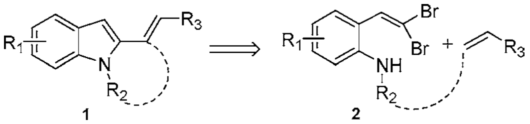
A novel one-step synthesis of valuable 2-vinylic indoles and their tricycle derivatives is described. This reaction, which utilizes a *gem*-dibromovinyl unit as a readily available starting material, occurs via an efficient Pd-catalyzed tandem Buchwald–Hartwig/Heck reaction.

gem-Dihalovinyl systems are important, versatile synthons in organopalladium chemistry, and they have been used in many different cross-coupling reactions with organostannane,[1] organomagnesium,[2] organoborane,[3] organozinc,[4] and also organocopper[5] reagents as coupling partners.

The *gem*-dihalovinyl moiety also represents a very attractive key unit for the syntheses of various heterocycles and carbocycles by judicious selection of the coupling partners and well-designed starting materials. Despite this great potential, relatively few reports utilizing palladium-catalyzed chemistry have been published in this area.[6]

In the context of developing a selective tandem coupling of *gem*-dihalovinyl systems,[7] our previous studies showed that *ortho*-*gem*-dibromovinylanilines can undergo a Pd-catalyzed tandem C−N/Suzuki−Miyaura coupling to provide 2-substituted indoles[8] or Cu-catalyzed tandem intramolecular amidation to provide imidazoindolones.[9] Herein, we describe an extension to this concept where a tandem Pd-catalyzed C−N[10]/Heck reaction[11] is involved to provide a novel, highly efficient, and modular synthesis of 2-vinylic indoles[12] and their tricyclic derivatives (Scheme 1).[13,14]

Scheme 1



Vinylic indoles are valuable building blocks and are used in the synthesis of biologically significant compounds such

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(1) (a) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (b) Zapata, A. J.; Rúiz, J. *J. Organomet. Chem.* **1994**, *479*, c6.

(2) (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052. (c) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912.

(3) (a) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (b) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russel, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. (c) Kabalka, G. W.; Dong, G.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 763. (d) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493.

(4) (a) Shi, J.-C.; Negishi, E. *J. Organomet. Chem.* **2003**, *687*, 518. (b) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762.

(5) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.

(6) Indole and benzofuran syntheses: (a) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907. Isocoumarin syntheses: (b) Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625. Six-membered carbocycle syntheses: (c) Soderquist, J. A.; Léon, G.; Colberg, J. C.; Martínez, I. *Tetrahedron Lett.* **1995**, *36*, 3119. Fused bicycle syntheses: (d) Ma, S.; Xu, B.; Ni, B. *J. Org. Chem.* **2000**, *65*, 8532. (e) Ma, S.; Xu, B. *J. Org. Chem.* **1998**, *63*, 9156. (f) McAlonan, H.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1996**, *37*, 7151. Phenanthrene syntheses: (g) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

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as indole alkaloids, carbazoles, and carbolines.[15] They are also present in medicinally important compounds such as fluvastatin[16] (cholesterol-lowering drug) or SB-242782[17] (treatment for osteoporosis; Figure 1).

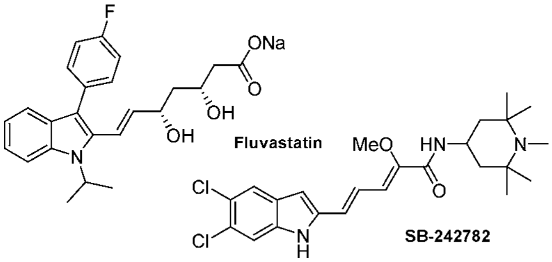
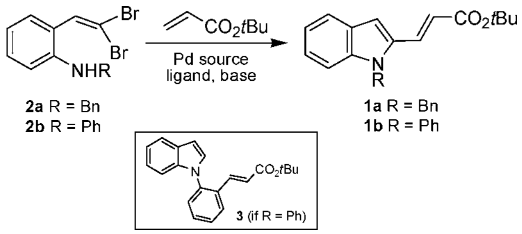


Figure 1. Biologically active 2-vinylic indoles.

The existing synthetic methods present some limitations, such as the necessity of introducing a functional group on the heterocycle prior to the vinylation step resulting in longer linear syntheses and limited ability to introduce significant molecular diversity.[18]

This novel tandem Pd-catalyzed C−N/Heck reaction was first investigated using **2a** and **2b**[19] with *tert*-butyl acrylate to screen different Pd sources, ligands, organic and inorganic bases, additives, and temperatures (Scheme 2). Catalyst systems comprising different palladium sources ($Pd(OAc)_2$, Pd_2dba_3, $Pd(PPh_3)_4$, Pd/C), ligands ($HP(tBu)_3{\cdot}BF_4$, $P(tBu)_3$, PCy_3, P(*o*-tolyl)$_3$, PPh_3, P(*o*-tolyl-*p*-OMe)$_3$, X-Phos, DavePhos, S-Phos), and additives have been tested.

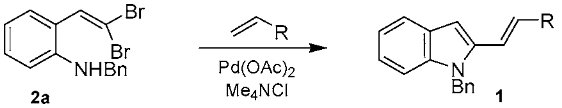
Scheme 2

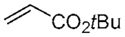
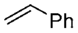
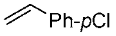
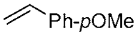
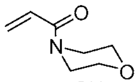
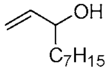
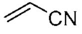
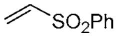


Three catalyst systems were discovered to give good results depending on the substituent on the nitrogen. The use of $Pd(OAc)_2$ (4 mol %) and P(*o*-tolyl)$_3$ (8 mol %) with *N*-benzyl-vinylaniline **2a** gave a 71% yield of 2-vinylic indole **1a** (Scheme 2). The use of Jeffery's conditions (4 mol % of $Pd(OAc)_2$, Me_4NCl)[20] which avoid the use of expensive phosphines is even better as **1a** is obtained in 79% yield. Although longer reaction times are usually required under Jeffery's conditions, yields are generally much better than those obtained with P(*o*-tolyl)$_3$. Using $Pd(OAc)_2$/P(*o*-tolyl)$_3$ with *N*-aryl-vinylaniline **2b** gave 50% of vinylic indole **1b** and 40% of an interesting byproduct **3** (Scheme 2). This product (**3**) is probably the result of a 1,4-migration palladium species, followed by a Heck reaction, as shown by Larock and Gallagher with a biaryl system.[21] Additional screening showed that the use of Pd_2dba_3 (3 mol %) and S-Phos[22] (12 mol %) with **2b** avoids the formation of the indole **3** and provides **1b** in 78% yield. Toluene was found to be the best solvent, and reflux was the optimum temperature for a complete and rapid conversion. Screening a range of bases revealed that a combination of organic and inorganic bases (Et_3N and $K_3PO_4{\cdot}H_2O$) provided the best yields.

The optimized conditions were then applied to various commercially available alkenes of different electronic character using *N*-benzyl-*ortho*-*gem*-dibromovinylaniline (**2a**). In all cases, the expected 2-vinylic indoles were isolated in good yields (Table 1, entries 1−8). The reaction tolerates a wide variety of alkene reagents containing ester, amide, nitrile, sulfone, and alcohol moieties (Table 1, entries 1 and 4−8)

Table 1. Scope of Alkene Reagents



entry	alkene	product **1**/yield[a, b]
1	 CO2tBu	**1a** 79%
2	 Ph	**1c** 65%
3	 Ph-*p*Cl	**1d** 71%
4	 Ph-*p*OMe	**1e** 73%[c]
5		**1f** 63%
6		**1g** 82%[d]
7	 CN	**1h** 70%[c, e]
8	 SO2Ph	**1i** 40%

[a] Isolated yields. [b] Alkene (2.0 equiv), $Pd(OAc)_2$ (4 mol %), Me_4NCl (1.0 equiv), $K_3PO_4{\cdot}H_2O$ (2.0 equiv), NEt_3 (2.0 equiv), reflux, toluene. [c] P(*o*-tolyl)$_3$ (8 mol %) instead of Me_4NCl. [d] Mixture of ketone/allylic alcohol: 3:1. [e] 80% conversion.

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(7) (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769. For a review on the preparation of *gem*-dibromovinyl compounds, see: (c) Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, 185.

(8) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549.

(9) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

(10) For a review on Pd-catalyzed C−N couplings, see: (a) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; John Wiley & Sons: Weinheim, 2004. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley-Interscience: Weinheim, 2002. (c) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.

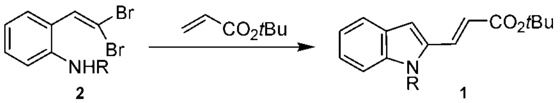
(11) For a review on Heck reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(12) For reviews on indoles, see: (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Servien, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol.2, p 207. (b) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (c) For a review on Pd-catalyzed indole syntheses, see: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

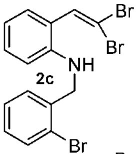
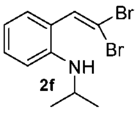
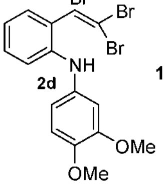
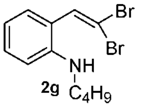
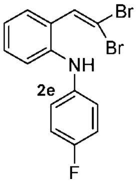
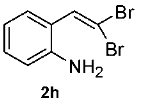
and also phenyl moieties with different electronic properties (Table 1, entries 2−4).

The effect of substitution on the aniline nitrogen of the *gem*-dibromovinylaniline has also been studied using *tert*-butyl acrylate under the standard reaction conditions (Table 2, entries 1−6). The coupling with both the electron-rich and the electron-deficient *N*-aryl substrate and *N*-benzyl derivative proceeded smoothly to afford the desired product in good yields (Table 2, entries 1−3). In addition, *N*-alkyl-substituted anilines with different steric hindrance (entries 4 and 5) also reacted efficiently. The use of the unsubstituted aniline (**2h**), which allows flexibility, gave the expected product, but in lower yield (Table 2, entry 6).

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



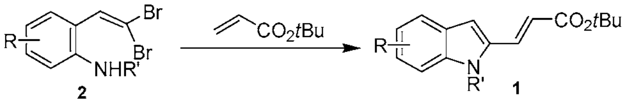
2 **1**

entry	subtrate **2**	product **1** yield$^{a,\,b}$	entry	subtrate **2**	product **1** yield$^{a,\,b}$
1	 **2c**	**1j** 62%	4	 **2f**	**1m** 69%
2	 **2d**	**1k** 60%^{c}	5	 **2g**	**1n** 67%
3	 **2e**	**1l** 60%^{c}	6	 **2h**	**1o** 50%^{d}

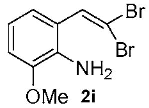
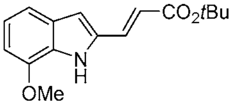
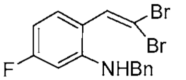
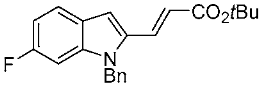
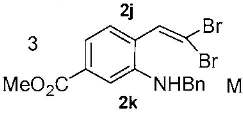
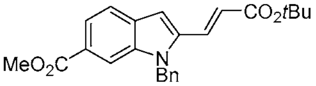
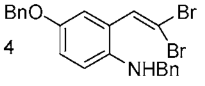
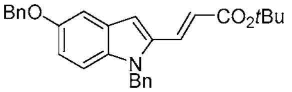
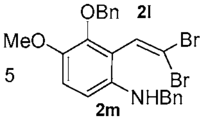
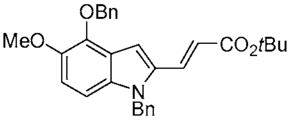
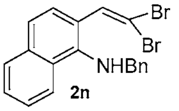
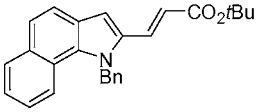
^{a} Isolated yields. ^{b} *tert*-Butyl acrylate (2.0 equiv), Pd(OAc)$_2$ (4 mol %), Me$_4$NCl (1.0 equiv), K$_3$PO$_4$·H$_2$O (2.0 equiv), NEt$_3$ (2.0 equiv), reflux, toluene. ^{c} Pd$_2$dba$_3$ (3 mol %), S-Phos (12 mol %). ^{d} Pd(OAc)$_2$ (4 mol %), P(*o*-tolyl)$_3$ (8 mol %).

Various dibromovinylanilines substituted on the phenyl ring were also evaluated with *tert*-butyl acrylate (Table 3, entries 1−6). This methodology proved to be a very general and efficient method to prepare functionalized indoles. Electronic factors and steric hindrance had little effect on the yield. A broad spectrum of electron-donating and electron-withdrawing functionalities in different positions around the phenyl ring is tolerated. The only limitation of this reaction is in the formation of 3-substituted indoles, as yields were poor when attempts were made with the corresponding substituted dibromovinylanilines.

Table 3. Scope of *ortho*-*gem*-Dibromovinylaniline Substrates



2 **1**

entry	subtrate **2**	product **1**	yield$^{a,\,b}$
1	 **2i**		**1p** 53%^{c}
2	 **2j**		**1q** 70%
3	 **2k**		**1r** 71%
4	 **2l**		**1s** 64%^{c}
5	 **2m**		**1t** 39%
6	 **2n**		**1u** 43%^{c}

^{a} Isolated yields. ^{b} *tert*-Butyl acrylate (2.0 equiv), Pd(OAc)$_2$ (4 mol %), Me$_4$NCl (1.0 equiv), K$_3$PO$_4$·H$_2$O (2.0 equiv), NEt$_3$ (2.0 equiv), reflux, toluene. ^{c} Pd(OAc)$_2$ (4 mol %), P(*o*-tolyl)$_3$ (8 mol %).

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(13) For a synthesis of indoles occurring via a tandem Pd-catalyzed Heck reaction/amination, see: Barluenga, J.; Fernández, A. M.; Aznar, F.; Valdés, C. *Chem.−Eur. J.* **2005**, *11*, 2276.

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(15) For some recent applications, see: (a) Laronze, M.; Sapi, J. *Tetrahedron Lett.* **2002**, *43*, 7925. (b) Wiest, O.; Steckhan, E. *Angew. Chem., Int. Ed.* **1993**, *32*, 901. (c) Noland, W. E.; Xia, G. M.; Gee, K. R.; Konkel, M. J.; Wahlstrom, M. J.; Condoluci, J. J.; Rieger, D. L. *Tetrahedron* **1996**, *52*, 4555. (d) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193. (e) Padwa, A.; Lynch, S. M.; Mejia-Oneta, J. M.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 2206. (f) Rawat, M.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329. (g) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586.

(16) Repic, O.; Prasad, K.; Lee, G. T. *Org. Process Res. Dev.* **2001**, *5*, 519.

(17) Conde, J. J.; McGuire, M.; Wallace, M. *Tetrahedron Lett.* **2003**, *44*, 3081.

(18) Synthesis of 2-vinyl indole via C−H functionalization: (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (b) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. Via a Stille cross-coupling reaction: (c) Hudkins, R. L.; Diebold, J. L.; Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218. (d) Beccalli, E. M.; Marchesini, A. *Tetrahedron* **1995**, *51*, 2353. Via Wittig reaction: (e) Eitel, M.; Pindur, U. *Synthesis* **1989**, 364. (f) Nagarathnam, D. *Synthesis* **1992**, 743. Via a hetero-Cope rearrangement: (g) Wilkens, J.; Kühling, A.; Blechert, S. *Tetrahedron* **1987** *43*, 3237. (h) Macor, J. E.; Newman, M. E.; Ryan, K. *Tetrahedron Lett.* **1989**, *30*, 2509.

(19) For the preparation of the *gem*-dibromovinylaniline system, see Supporting Information and also the Supporting Information of ref 8.

(20) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(21) (a) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (b) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. For a review on 1,4-migration on biaryl systems, see: (c) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512.

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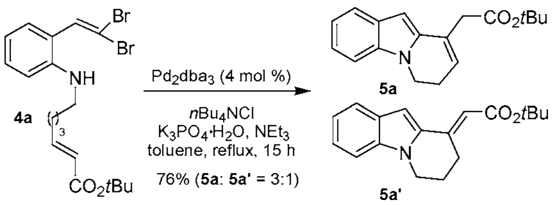
An intramolecular version of this methodology was developed to provide more elaborate heterocycles using substrates where the alkene moiety is tethered to the nitrogen of the *ortho*-*gem*-dibromovinylaniline. The enoate **4a**[23] was used for this study, and different palladium sources and ligands were screened. Pd_2dba_3 (4 mol %) with $n$$Bu_4NCl$ (1 equiv) in the presence of $NEt_3/K_3PO_4{\cdot}H_2O$ in toluene at 120 °C gave the desired tricyclic adduct in good yield (76%) as a mixture of two easily separable isomers (**5a** and **5a′**; Scheme 3).

Scheme 3



The generality of the intramolecular process was explored as shown in Figure 2. Substituents on the aromatic ring with different electronic properties have been used successfully (examples **5a**−**c**), and it is also possible to use a nonactivated alkene (**5e**). Moreover, a compound with a seven-membered ring attached to the indole unit has been readily obtained using the amination−Heck sequence. It is worth noting that these interesting pyrido and azepino-indole skeletons are simultaneously constructed from the corresponding acyclic precursors in just one step, which is distinctive from the traditional ring-by-ring approach.[24]

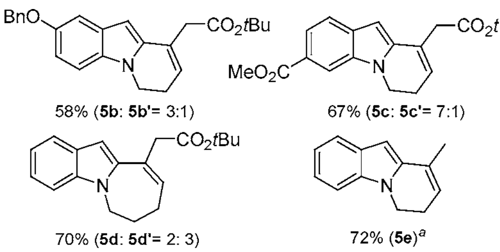
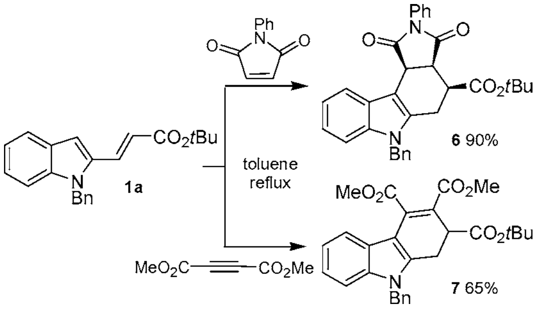


Figure 2. Scope of the intramolecular version. (Isolated yields. Conditions: Pd_2dba_3 (4 mol %), $n$$Bu_4NCl$ (1 equiv), $K_3PO_4{\cdot}H_2O$ (2 equiv), NEt_3 (2 equiv), toluene, reflux. ^{a}Pd(OAc)$_2$ (4 mol %), P(o-tolyl)$_3$ (8 mol %).)

2-Vinyl indole moieties have been shown to be versatile dienes in Diels−Alder reactions for the regioselective and stereoselective syntheses of indole alkaloids, carbazoles, and nonnatural annulated indole derivatives of pharmological interest.[25] The reactivity of 2-vinylic indoles **1a** was briefly examined using *N*-phenylmaleiimide and dimethyl acetylenedicarboxylate as a dienophile in toluene at reflux. The interesting carbazole derivatives **6** and **7** were obtained in good yields (Scheme 4).[26]

Scheme 4. Utility of a 2-Vinylic Indole Building Block



In conclusion, we have developed an efficient and modular one-pot procedure giving rapid access to a wide range of substituted 2-vinylic indoles from readily accessible *gem*-dibromovinylaniline substrates via a palladium-catalyzed tandem Buchwald−Hartwig amination/Heck reaction. The intramolecular variant of this reaction leads to the formation of interesting cyclic compounds including pyrido and azepino indole derivatives.

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Supporting Information Available: Full experimental details and characterization including ^{1}H and ^{13}C 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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[23] For syntheses of **4**, see the Supporting Information.

[24] For some examples, see: (a) Germain, A. L.; Gilchrist, T. L.; Kemmitt, P. D. *Heterocycles* **1994**, *37*, 697. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. (b) Conzález-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002**, *43*, 4765. (c) Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042. (d) Bit, R. A.; Davis, P. D.; Hill, C. H.; Keech, E.; Vesey, D. R. *Tetrahedron* **1991**, *47*, 4645.

[25] For reviews of Diels−Alder reactions of vinyl indoles, see: (a) Pindur, U. *Heterocycles* **1988**, *27*, 1253. (b) Pindur, U. *Chimia* **1990**, *44*, 406.

[26] Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368.