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A Route to Annulated Indoles via a Palladium-Catalyzed Tandem Alkylation/Direct Arylation Reaction

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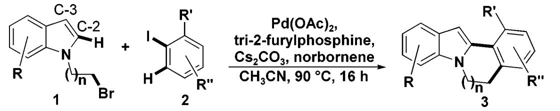
Traditionally, catalytic methods for biaryl formation involve transition metal-catalyzed coupling between an organometallic component with an aryl halide or pseudohalide.[1] More recently, considerable attention has been given to the direct arylation of heteroarenes, achieved via cross-coupling of heteroaromatic sp[2] C−H bonds and aryl halides.[2] A direct arylation approach allows for carbon−carbon bond formation without the need for prior functionalization of the heteroarene via metalation. One important application of direct arylation is the functionalization of indoles since many biologically active natural products as well as pharmaceutically important compounds contain this privileged motif.[3] Although such an approach is highly desirable, few examples have been reported for the direct arylation of indoles with aryl halides.[4]

We have reported a palladium-catalyzed reaction based on modified Catellani conditions[5] for the synthesis of carbocycles and heterocycles from aryl iodides, alkyl halides, and Heck acceptors.[6] This methodology is based on a norbornene-mediated tandem aromatic alkylation/Heck reaction. Herein, we report a modification of this sequence by using bromoalkyl indole **1**, so that an intramolecular direct arylation can follow the *ortho* alkylation. In this highly efficient approach, two carbon−carbon bonds are created from two carbon−hydrogen bonds in a one-pot process. In addition, a wide range of functionalized annulated indoles **3** can be rapidly synthesized in a convergent manner from relatively simple and accessible starting materials (Scheme 1).

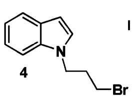
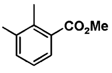
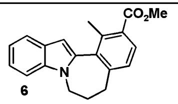
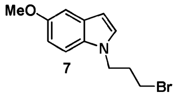
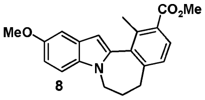
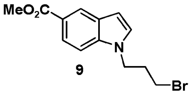
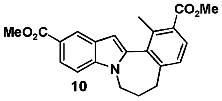
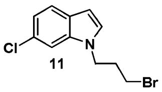
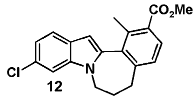
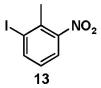
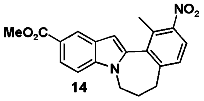
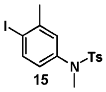
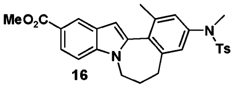
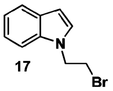
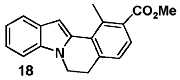
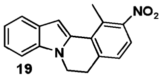
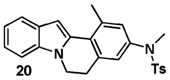
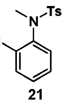
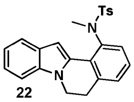
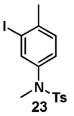
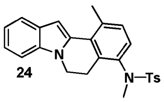
Scheme 1. Synthesis of Annulated Indoles



Our initial attempts to effect a tandem alkylation/direct arylation employed bromoalkyl indole **4**. Use of aryl iodide **5** under the optimized reaction conditions [iodoarene (1 equiv), Pd(OAc)$_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs$_2$CO$_3$ (2 equiv), norbornene (2 equiv), and bromoalkyl indole (2 equiv) in acetonitrile (0.1 M) at 90 °C in a sealed tube for 16 h] afforded the seven-membered ring annulated indole **6** in 80% yield (entry 1, Table 1).

The generality of this reaction sequence was first demonstrated for the seven-membered ring annulated indole by varying the substituents on the bromoalkyl indole. Both electron-withdrawing and electron-donating substituents are tolerated at various positions on the bromoalkyl indole when reacted with aryl iodide **5**. Reaction of methoxy containing bromoalkyl indole **7** provided **8** in 83% yield (entry 2). For bromoalkyl indole **9** containing an ester, **10** was produced in 79% yield (entry 3). Substrate **11**, bearing a chloro substituent, gave a more modest yield of **12** (entry 4). Substituents on the aryl iodide moiety were readily tolerated (entries 5 and 6). Reaction of 1-iodo-2-methyl-3-nitrobenzene with **9** resulted in an 86% yield of **14** (entry 5). A *N*-methyl tosyl substituent at position 4 of the aryl iodide gave a similar yield of **16** (entry 6).

Table 1. Synthesis of Annulated Indoles via Palladium-Catalyzed Tandem Alkylation/Direct Arylation Reaction[a]

entry	substrate	aryl iodide	product	yield(%)[b]
1	 **4**	 **5**	 **6**	80
2	 **7**	**5**	 **8**	83
3	 **9**	**5**	 **10**	79
4	 **11**	**5**	 **12**	54
5	**9**	 **13**	 **14**	86
6	**9**	 **15**	 **16**	85
7	 **17**	**5**	 **18**	79
8	**17**	**13**	 **19**	88
9	**17**	**15**	 **20**	93
10	**17**	 **21**	 **22**	76
11	**17**	 **23**	 **24**	38

[a] All reactions were run under the following conditions: iodoarene (0.20 mmol, 1 equiv), Pd(OAc)$_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs$_2$CO$_3$ (2 equiv), norbornene (2 equiv), and bromoalkyl indole (2 equiv) in acetonitrile (2 mL) were heated in a sealed tube at 90 °C for 16 h. [b] Isolated yield.

We next investigated the synthesis of six-membered ring annulated indoles. A variety of polysubstituted aryl iodides were

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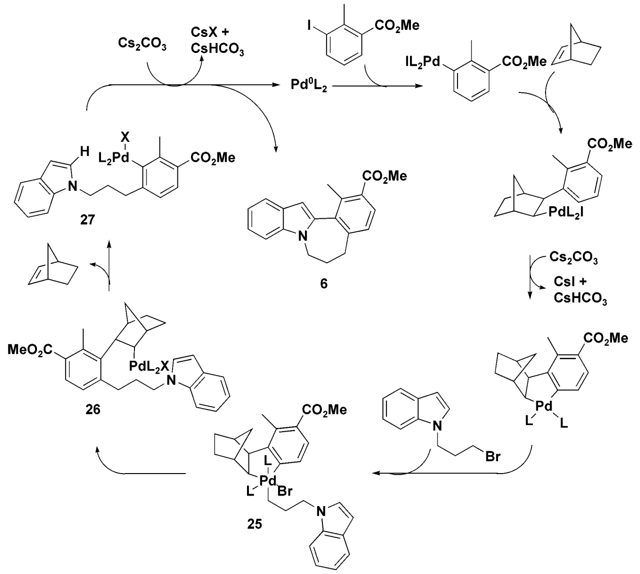
Scheme 2. Proposed Mechanism for the Synthesis of Annulated Indoles



reacted with bromoalkyl indole **17**. Ester, nitro, and *N*-methyl tosyl substituents gave good to excellent yields (entries 7−9). Having a *N*-methyl tosyl substituent as the *ortho* blocking group afforded **22** in 76% yield (entry 10). However, when this substituent was placed at position 5 of the aryl iodide, **24** was obtained in only 38% yield (entry 11), presumably due to steric effects.

The *ortho* alkylation likely proceeds through the mechanism previously described by Catellani[5a] and is illustrated in Scheme 2. Intermediate **27** arises from the reductive elimination of the proposed Pd(IV) complex **25** to give **26**, followed by expulsion of norbornene. Heteroaryl−aryl coupling of **27** via C−H functionalization of the indole C-2 hydrogen follows to provide annulated indole **6**.

Several mechanisms have been suggested for C−H functionalization α to the heteroatom in heteroaromatic compounds.[4c,7] Possible pathways for the intramolecular C-2 indole arylation include (1) a Heck-type process[4d,e] involving a carbopalladation followed by an atypical *anti*-*β*-hydride elimination,[8] (2) a direct C-2 palladation via a nonelectrophilic pathway,[9] and (3) an electrophilic substitution at the C-3 position, followed by a C-3 to C-2 palladium migration and reductive elimination.[4c] Direct C-2 palladation via a nonelectrophilic pathway has been reported but requires a coordinating heteroatom on the N- or C-3 substituent as a directing group.[9] Sames recently reported mechanistic investigations for the palladium-catalyzed intermolecular C-2 arylation of indoles and concluded through kinetic studies and a Hammett plot that the most likely pathway is an electrophilic substitution at the C-3 position, followed by a C-3 to C-2 palladium migration.[4c] Although this may be the most probable mechanism for the intermolecular C-2 arylation, we cannot exclude a Heck-type process for the intramolecular reaction.

In summary, we have developed a new approach to highly substituted six- and seven-membered ring annulated indoles, where an alkyl−aryl bond and a heteroaryl−aryl bond are formed in one pot. This process involves a norbornene-mediated tandem *ortho* alkylation/C−H functionalization between an aryl iodide and a bromoalkyl indole. We are currently exploring the application of this methodology to the synthesis of other heterocyclic compounds.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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