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A Palladium-Catalyzed Alkylation/Direct Arylation Synthesis of Nitrogen-Containing Heterocycles

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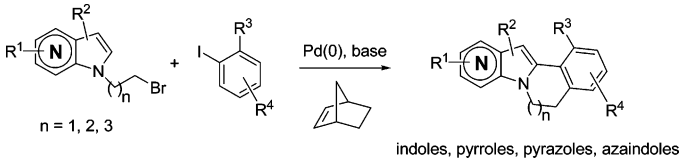
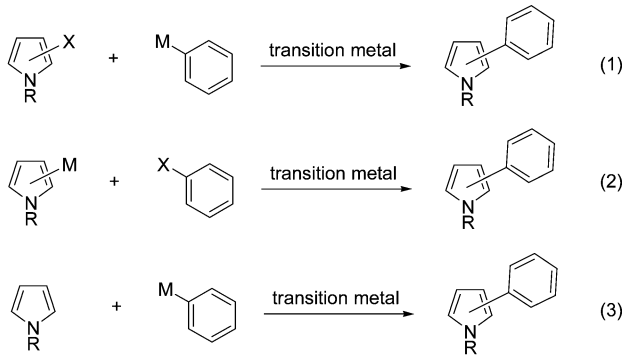


A norbornene-mediated palladium-catalyzed sequence is described in which an alkyl-aryl bond and an aryl-heteroaryl bond are formed in one reaction vessel. The aryl-heteroaryl bond-forming step occurs via a direct arylation reaction. A number of six-, seven-, and eight-membered ring-annulated indoles, pyrroles, pyrazoles, and azaindoles were synthesized from the corresponding bromoalkyl azole and an aryl iodide.

Introduction

The aryl-*N*-heteroaryl bond is found in many bioactive molecules, pharmaceuticals, and organic materials. Among the various methods that exist for the synthesis of this bond, metal-catalyzed cross-coupling reactions between aryl (or heteroaryl) halides and heteroaryl (or aryl) organometallic compounds offer the advantages of relatively mild reaction conditions and high functional group tolerance (Scheme 1, eqs 1 and 2).[1] More recently, transition-metal-catalyzed direct arylation reactions have emerged as an efficient alternative to traditional cross-coupling reactions.[2,3] This method generates a C−C bond from an aryl halide and a heteroaryl C−H bond (Scheme 1, eq 3).

SCHEME 1. Aryl-*N*-Heteroaryl Bond Formation via Cross-Coupling and Direct Arylation Reactions



Unlike cross-coupling reactions, direct arylation reactions avoid the need for stoichiometric amounts of organometallic reagents, resulting in fewer reaction steps and reduced waste. However, due to the ubiquitous nature of C−H bonds, one of the

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(1) (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (d) Anastasia, L.; Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002; pp 311−334. For reviews on cross-coupling reactions involving nitrogen-containing heterocycles, see: (e) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043. (f) Schnürch, M.; Flasik, R.; Farooq Khan, A.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (g) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000.

(2) For reviews on direct arylation reactions, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (f) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (g) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625. (h) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, O. *Synlett* **2003**, 585. (i) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (j) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699.

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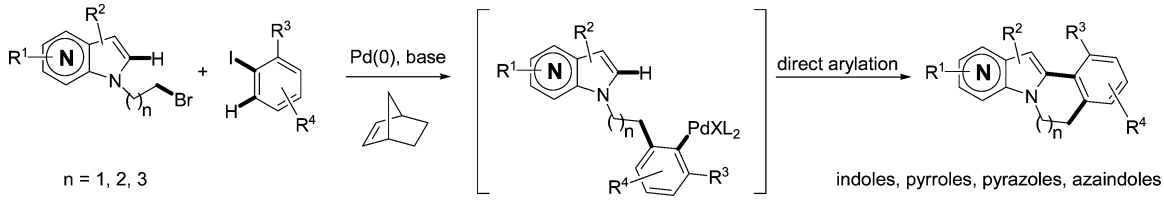
SCHEME 2. Synthesis of Annulated Nitrogen-Containing Heterocycles via a Tandem Norbornene-Mediated Palladium-Catalyzed Alkylation/Direct Arylation Reaction



challenges associated with direct arylation reactions is controlling chemoselectivity in terms of which C−H bond undergoes the reaction. This obstacle can often be overcome by using a tether to limit the degree of freedom in the system (intramolecular direct arylation), exploiting the electronic nature of the heterocycle (intermolecular), or employing a directing group (semi-intermolecular).[2a]

Our group has utilized direct arylation reactions to generate annulated nitrogen-containing heterocycles.[4] The method involves a norbornene-mediated palladium-catalyzed intermolecular *ortho*-alkylation of an aromatic C−H bond with an *N*-bromoalkyl heterocycle, generating a tethered intermediate (Scheme 2). The mechanism for the initial step is based upon the findings of Catellani and involves a Pd(II)/Pd(IV)[5] catalytic cycle.[6,7] The resulting species then undergoes an intramolecular direct arylation reaction forming the aryl-*N*-heteroaryl bond at the 2 position of the *N*-heteroaryl compound.[8] Herein, we report the details of our studies whereby functionalized annulated indoles, pyrroles, pyrazoles, and azaindoles are generated from readily available *N*-bromoalkyl heterocycles and *ortho*-substituted aryl iodides.[9] In addition, we show that the annulated products can be further functionalized via subsequent cross-coupling methodologies.

(3) For recent papers on the direct arylation of nitrogen-containing heterocycles, see: (a) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (c) Marcia de Figueiredo, R.; Thoret, S.; Huet, C.; Dubois, J. *Synlett* **2007**, 529. (d) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (e) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (f) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (g) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389. (h) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (i) Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, 3170. (j) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synlett* **2006**, 3237. (k) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

(4) (a) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043. (b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. For the synthesis of annulated furans and thiophenes, see: (c) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827.

(5) For a discussion on Pd(II)/Pd(IV) reactions, see: Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924 and references therein.

(6) For mechanistic studies and for related norbornene-mediated palladium-catalyzed reactions, see: (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. (c) Catellani, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; John Wiley & Sons: Hoboken, NJ, 2002; pp 1479−1489. (d) Catellani, M. *Synlett* **2003**, 298. (e) Tsuji, J. *Palladium Reagents and Catalysis−New Perspectives for the 21st Century*; John Wiley & Sons: New York, 2004; pp 409−416. (f) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21.

(7) For the proposed catalytic cycle as it relates to this reaction, see ref 4.

(8) For a discussion on the possible mechanisms of the direct arylation of heterocycles, see refs 2a and 2b and references therein.

(9) For preliminary studies, see refs 4a and 4b.

Results and Discussion

Typical reaction conditions involve heating a solution of the aryl iodide (1 equiv), *N*-bromoalkyl heterocycle (2 equiv), palladium catalyst ($Pd(OAc)_2$ or $PdCl_2$, 10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) in acetonitrile (0.1 M) in a sealed tube at 90 °C for 16−24 h. In addition to the desired annulated products, a number of side products were observed in some reactions, often in trace amounts (Figure 1). For example, displacement of the bromide of the *N*-bromoalkyl heterocycles with an iodide or acetate ion afforded **1** and **2**, respectively. Compound **2** was only observed with $Pd(OAc)_2$ and could be eliminated by using $PdCl_2$. For *N*-bromoalkyl heterocycles with $n = 1$, the elimination alkene product **3** was formed with some substrates. The *ortho*-alkylated/*ipso*-reduced product **4** was also observed, especially for *N*-bromoalkyl heterocycles with $n = 3$. The *ortho*-insertion of the *N*-bromoalkyl heterocycle followed by reduction, wherein the alkyl halide is the hydride source (the desired final cyclization being presumably much slower in that case), is proposed to be responsible for formation of the product.[10] This observation is very important since it strongly suggests that the *ortho*-alkylation precedes the final aryl-heteroaryl coupling.[4b] Finally, in addition to the side products illustrated in Figure 1, various norbornane-containing aromatic compounds are usually formed in trace amounts.[11]

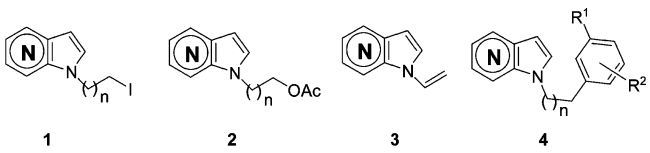


FIGURE 1. Various side products observed.

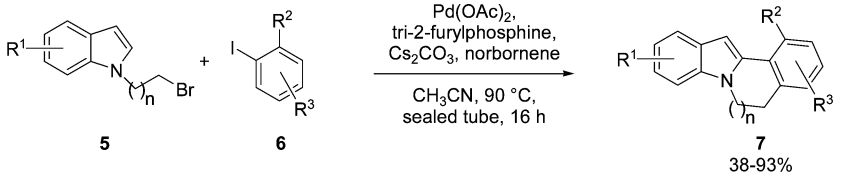
Synthesis of Annulated Indoles. We previously reported the synthesis of six- and seven-membered ring-annulated indoles.[4b,12] A number of bromoalkyl indoles with electron-donating or electron-withdrawing substituents were prepared. These substrates were reacted with both electron-rich and electron-poor aryl iodides, affording a variety of annulated indoles in moderate to good yields (Scheme 3). Various substituents are tolerated under the reaction conditions including ester, amine, methyl, methoxy, nitro, and chloride. The electronic nature of the substituents seemed to have little effect on the product yields. However, a *N*-methyl tosyl substituent at the *meta*-position of the aryl iodide resulted in only 38% yield, presumably due to steric interactions.[4b]

(10) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053.

(11) For examples, see ref 6d and: Motti, E.; Ippomei, C. P.; Deledda, S.; Catellani, M. *Synthesis* **2003**, 2671.

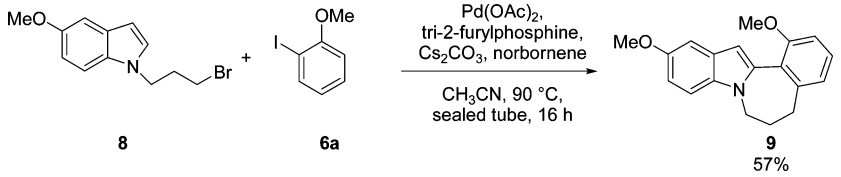
(12) For reviews on the synthesis and functionalization of indoles, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

SCHEME 3. Synthesis of Six- and Seven-Membered Ring-Annulated Indoles



n = 1, 2
R^1 = H, OMe, CO_2Me, Cl
R^2 = Me, NMeTs
R^3 = H, CO_2Me, NO_2, NMeTs

SCHEME 4. Synthesis of Methoxy-Substituted Annulated Indole



SCHEME 5. Attempted Formation of Eight-Membered Ring-Annulated Indoles

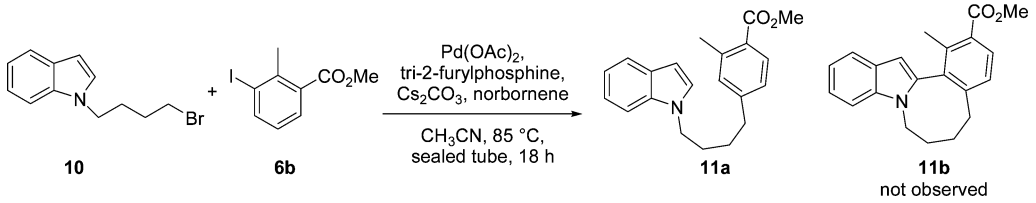
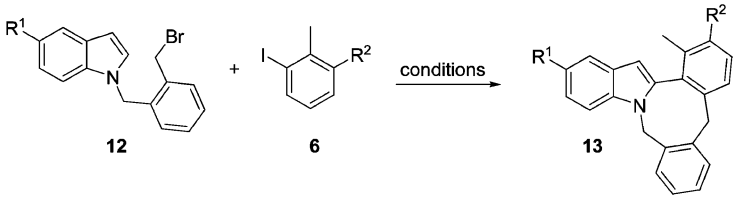


TABLE 1. Synthesis of Eight-Membered Ring-Annulated Indoles[a]



entry	bromoalkyl indole	aryl iodide	product	isolated yield (%)
1	**12a** R^1 = H	**6c** R^2 = NO_2	**13a**	24
2	**12b** R^1 = CO_2Me	**6c** R^2 = NO_2	**13b**	50
3	**12b** R^1 = CO_2Me	**6d** R^2 = H	**13c**	50

[a] Unless otherwise specified, all reactions were run under the following conditions: aryl iodide (1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) in acetonitrile (0.1 M) were heated at 90 °C, and bromoalkyl indole (2 equiv, 0.07 M in MeCN) was added dropwise via syringe pump over 12 h.

It should be noted that, when 2-iodoanisole was used as a coupling partner in this reaction, lower yields of the products were obtained (Scheme 4). It has been shown that aryl palladium species with the palladium *ortho* to a methoxy group can undergo C−H activation with the methoxy C−H bond to form a stable five-membered palladacycle.[13] This or other similar reactions may be occurring, thereby preventing the desired steps in the catalytic cycle.

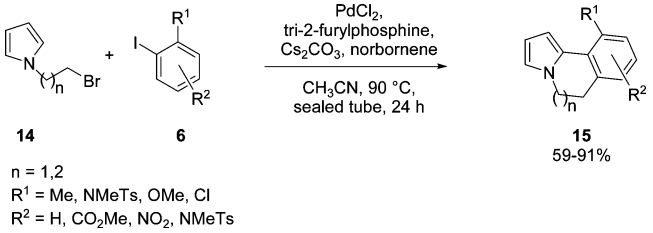
The synthesis of eight-membered ring-annulated indoles proved to be more difficult. When **10** was subjected to the reaction conditions, no desired eight-membered ring compound **11b** was isolated (Scheme 5).[14] Rather, the acyclic *ortho*-inserted product **11a** was observed. Therefore, to promote the sluggish cyclization step, we envisaged limiting the degrees of freedom of the alkyl chain. Thus, **12a** and **12b** were prepared and subjected to the standard reaction conditions, which involves mixing all of the reagents and heating. Unfortunately, only low yields (<20%) of product were isolated. Fortunately, we found that the yield could be increased by adding the bromoalkyl indole dropwise over 12 h. Ultimately, we could achieve the formation of eight-membered ring compounds, albeit in modest yields (Table 1). There are very few reports of *ortho*-alkylation using benzylic halides, so the success in this instance is noteworthy.

Synthesis of Annulated Pyrroles. We also investigated the synthesis of six- and seven-membered ring-annulated pyrroles (Scheme 6).[4a] Reaction of unsubstituted bromoalkyl pyrroles **14** with a number of aryl iodides was conducted using $PdCl_2$ as the catalyst. Good yields of product were generally obtained with various electron-rich and electron-poor aryl iodides. Silyl-protected aryl iodides are also compatible under the reaction conditions and can be deprotected in situ to give the corresponding alcohol product (Scheme 7, eq 1). Notably, aryl iodide **6f** afforded an excellent yield of annulated pyrrole **18** (Scheme 7, eq 2). This compound is found in the core of biologically active compounds including Lettowianthine and Lamellarin.[15]

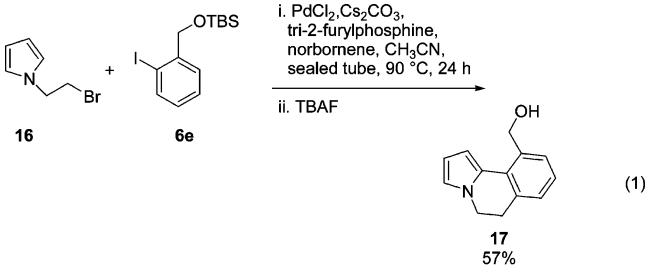
More highly functionalized six-membered ring-annulated pyrroles could be prepared using substituted bromoalkyl pyrroles. Pyrroles substituted with an ester in the 2 position underwent cyclization with a number of aryl iodides (Table 2). In order to simplify the purification process for certain substrates, the ester moiety was converted to the corresponding alcohol using lithium aluminum hydride (entries 4−7). The scope of aryl iodides was expanded to include fluoride substituents. 1-Fluoro-2-iodobenzene (**6k**) afforded the annulated product **20f** in 43% (entry 6), while the arene substituted with a fluorine atom *ortho* to where the alkylation occurs (**6i**) resulted in a lower yield of 21% (entry 4). Finally, pyrroles substituted in the 3 position with an acetyl moiety furnished an 8:1 mixture of annulated product, favoring the less sterically encumbered 4-substituted acetyl product (entry 8).

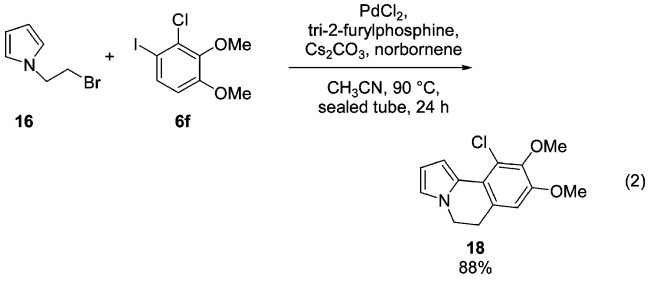
Larger ring sizes are also accessible for the pyrrole series. An eight-membered ring compound was formed, albeit in low yield (Scheme 8).

SCHEME 6. Synthesis of Six- and Seven-Membered Ring-Annulated Pyrroles

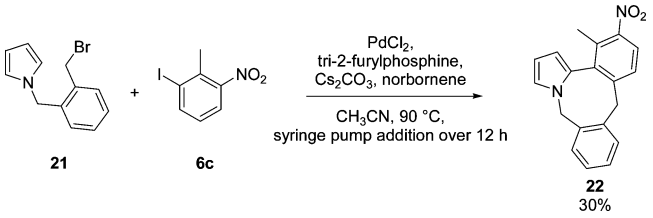


SCHEME 7. Synthesis of Functionalized Annulated Pyrroles





SCHEME 8. Synthesis of an Eight-Membered Ring-Annulated Pyrrole



Synthesis of Annulated Azaindoles. Having successfully generated annulated products from indoles and pyrroles, we next investigated the effect of using heterocycles containing more than one nitrogen atom.[16] We initially examined the reaction of 7-azaindole **23a** with 2-iodotoluene (Table 3, entry 1). Unfortunately **24a** was isolated in only 32% yield, which may be a result of the adjacent pyridyl nitrogen coordinating to one of the palladium intermediates in the catalytic cycle. When 6-azaindole **23b**, which contains the pyridyl nitrogen at a position where chelation to palladium is impossible, is reacted, the derived products **24b−j** are generally isolated in higher yields (Table 3). Azaindole **23b** was prepared by reacting commercially available 2-chloro-3-nitropyridine with vinylmagnesium bromide, followed by alkylation with 1,2-dibromoethane.

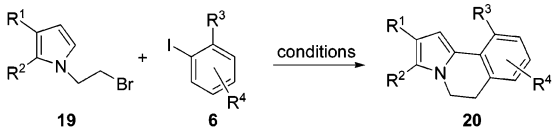
(13) (a) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023.

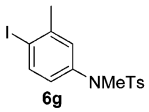
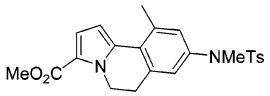
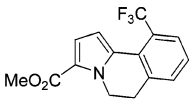
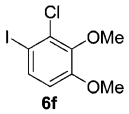
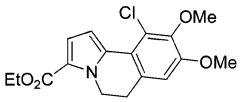
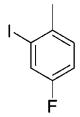
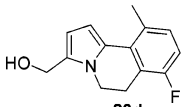
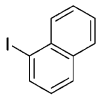
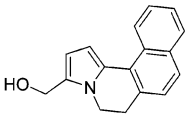
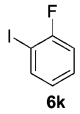
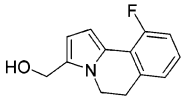
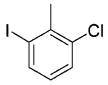
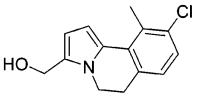
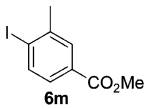
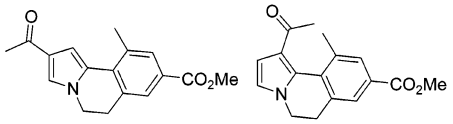
(14) In addition, no eight-membered ring product was observed by adding the bromoalkyl indole dropwise over 12 h.

(15) Lettowianthine: (a) Nkunya, M. H. H.; Jonker, S. A.; Makangara, J. J.; Waibel, R.; Achenbach, H. *Phytochemistry* **2000**, *53*, 1067. Lamellarin D: (b) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392. (c) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2005**, *70*, 8231.

(16) For a review on the synthesis and functionalization of azaindoles, see: Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.

TABLE 2. Synthesis of Six-Membered Ring-Annulated Pyrroles from Functionalized Bromoalkyl Pyrroles[a]



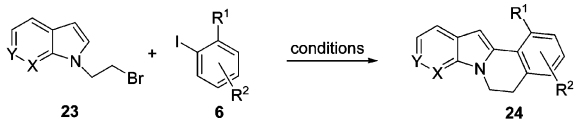
entry	bromoalkyl indole	aryl iodide	product	isolated yield (%)
1	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6g**	 **20a**	58
2	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6h**	 **20b**	40
3	**19b** $R^1 = H$, $R^2 = CO_2Et$	 **6f**	 **20c**	59
4	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6i**	 **20d**	21[b]
5	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6j**	 **20e**	41[b]
6	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6k**	 **20f**	43[b]
7	**19a** $R^1 = H$, $R^2 = CO_2Me$	 **6l**	 **20g**	45[b]
8	**19c** $R^1 = C(O)Me$, $R^2 = H$	 **6m**	 **20h** **20i**	**20h** = 40 **20i** = 5

[a] Unless otherwise specified, all reactions were run under the following conditions: aryl iodide (1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl pyrrole (2 equiv) in acetonitrile (0.1 M) were heated in a sealed tube at 90 °C for 24 h. [b] Lithium aluminum hydride was added after 24 h.

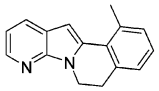
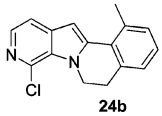
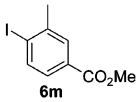
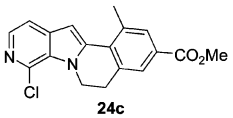
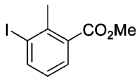
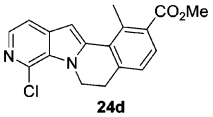
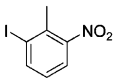
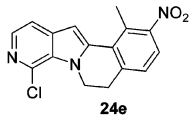
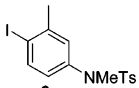
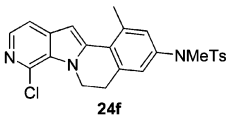
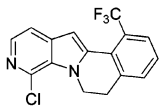
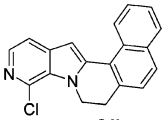
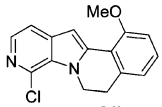
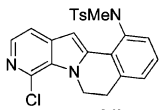
Synthesis of Annulated Pyrazoles. We were also interested in examining the reaction of pyrazoles because of the important properties and uses of annulated pyrazoles as insecticides and CB_1 receptor antagonists[17] and since, to the best of our knowledge, there are no reported cases of direct arylations of pyrazoles. Initial studies were conducted with the unsubstituted *N*-bromoalkyl pyrazole **25**, which was easily prepared by the alkylation of pyrazole with 1,2-dibromoethane. Under the typical reaction conditions, which involve mixing all of the reagents followed by heating the mixture, very low yields of products were obtained. After exploring and altering various aspects of the reaction conditions, we found that the dropwise addition of the pyrazole substrate over 17 h significantly improved the yield of the reaction. Once again, a variety of electron-rich and electron-poor aryl iodides were explored and generally gave moderate to good yields of annulated pyrazoles in one step (Table 4).

(17) (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467. (b) Stoit, A. R.; Lange, J. H. M.; den Hartog, A. P.; Ronken, E.; Tipker, K.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.* **2002**, *50*, 1109.

TABLE 3. Synthesis of Annulated Azaindoles[a]



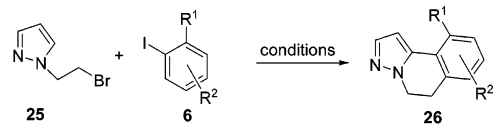
23 6 24

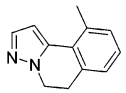
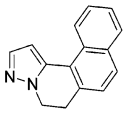
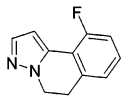
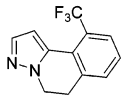
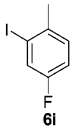
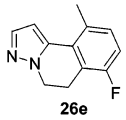
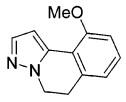
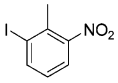
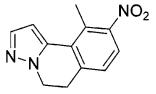
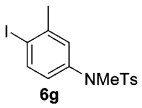
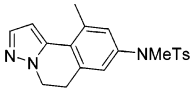
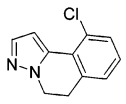
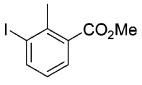
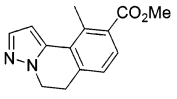
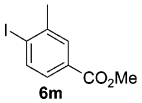
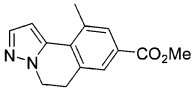
entry	bromoalkyl indole	aryl iodide	product	isolated yield (%)
1	**23a** X = N Y = CH	 **6d**	 **24a**	32
2	**23b** X = CCl Y = N	 **6d**	 **24b**	65
3	**23b** X = CCl Y = N	 **6m**	 **24c**	77
4	**23b** X = CCl Y = N	 **6b**	 **24d**	61
5	**23b** X = CCl Y = N	 **6c**	 **24e**	56
6	**23b** X = CCl Y = N	 **6g**	 **24f**	62
7	**23b** X = CCl Y = N	 **6h**	 **24g**	66
8	**23b** X = CCl Y = N	 **6j**	 **24h**	57
9	**23b** X = CCl Y = N	 **6a**	 **24i**	36
10	**23b** X = CCl Y = N	 **6n**	 **24j**	41

[a] Unless otherwise specified, all reactions were run under the following conditions: aryl iodide (1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl azaindole (2 equiv) in acetonitrile (0.1 M) were heated in a sealed tube at 90 °C for 24 h.

Functionalized *N*-bromoalkyl pyrazoles were also successful partners in the reaction. Various substituents were introduced at the 4 position of the pyrazole including nitro, iodo, and chloro. These substrates were readily prepared by treating pyrazole **25** with HNO_3 and H_2SO_4, I_2 and CAN, and NaOCl, respectively. Nitro-substituted pyrazole **27a** gave comparable yields to the unsubstituted pyrazole **25** (Table 5, entries 1−5), while halo-substituted pyrazoles **27b** and **27c** gave slightly lower yields (entries 6−8). We were delighted to see that both chloro- and iodo-substituted pyrazoles were tolerated under the reaction

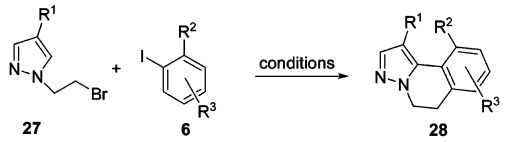
TABLE 4. Synthesis of Six-Membered Ring-Annulated Pyrazoles[a]

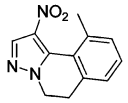
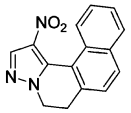
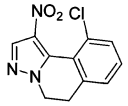
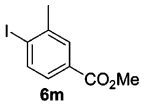
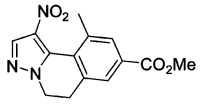
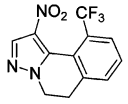
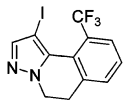
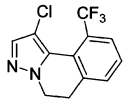
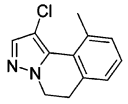


entry	aryl iodide	product	isolated yield (%)
1	 **6d**	 **26a**	54
2	 **6j**	 **26b**	51
3	 **6k**	 **26c**	49
4	 **6h**	 **26d**	42
5	 **6i**	 **26e**	43
6	 **6a**	 **26f**	32
7	 **6c**	 **26g**	27
8	 **6g**	 **26h**	37
9	 **6o**	 **26i**	60
10	 **6b**	 **26j**	38
11	 **6m**	 **26k**	55

[a] Unless otherwise specified, all reactions were run under the following conditions: aryl iodide (1.5 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) in acetonitrile (0.3 M relative to the aryl iodide) were heated at 90 °C, and a 0.1 M acetonitrile solution of bromoalkyl pyrazole (1 equiv) was added dropwise via syringe pump over 17 h and then heated for an additional 3 h.

TABLE 5. Synthesis of Six-Membered Ring-Annulated Pyrazoles from Functionalized Bromoalkyl Pyrazoles[a]



entry	bromoalkyl indole	aryl iodide	product	isolated yield (%)
1	**27a** $R^1 = NO_2$	 **6d**	 **28a**	61
2	**27a** $R^1 = NO_2$	 **6j**	 **28b**	55
3	**27a** $R^1 = NO_2$	 **6o**	 **28c**	62
4	**27a** $R^1 = NO_2$	 **6m**	 **28d**	45
5	**27a** $R^1 = NO_2$	 **6h**	 **28e**	64
6	**27b** $R^1 = I$	 **6f**	 **28f**	42
7	**27c** $R^1 = Cl$	 **6h**	 **28g**	54
8	**27c** $R^1 = Cl$	 **6d**	 **28h**	51

[a] Unless otherwise specified, all reactions were run under the following conditions: aryl iodide (1.5 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) in acetonitrile (0.3 M relative to the aryl iodide) were heated at 90 °C, and a 0.1 M acetonitrile solution of bromoalkyl pyrazole (1 equiv) was added dropwise via syringe pump over 17 h and then heated for an additional 3 h.

conditions and were not affected by the active palladium species in solution.

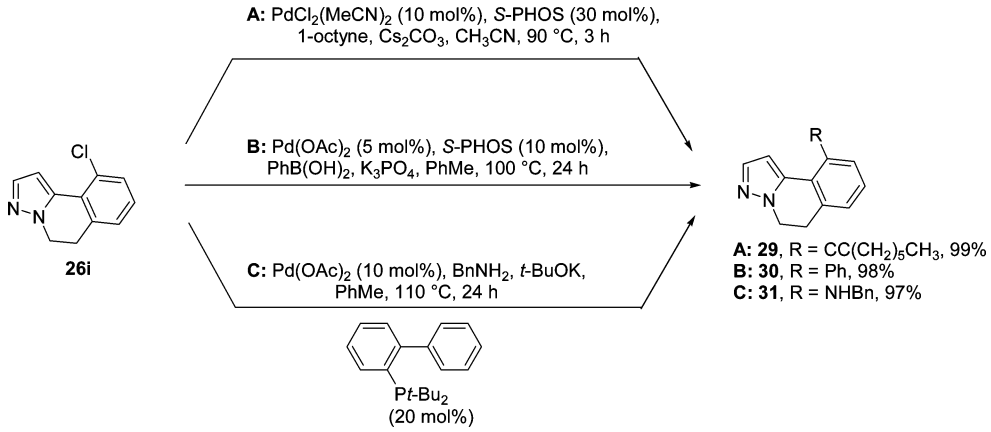
One of the advantages of having halogen substituents on the annulated heterocycles is that they can be easily converted into other substituents via a number of metal-catalyzed coupling reactions. For example alkyne, aryl, and amine substituents were easily introduced onto the arene moiety of **26i** via palladium-catalyzed Sonogashira,[18] Suzuki,[19] and amine coupling reactions,[20] respectively (Scheme 9). Likewise, new functionality can be efficiently added to the heterocyclic moiety of the annulated product by subjecting chloro-substituted **28h** to

(18) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.

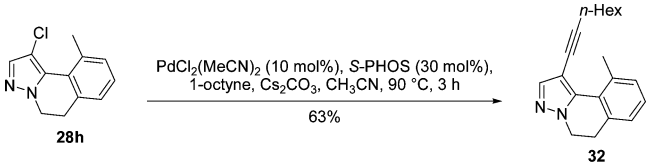
(19) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(20) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

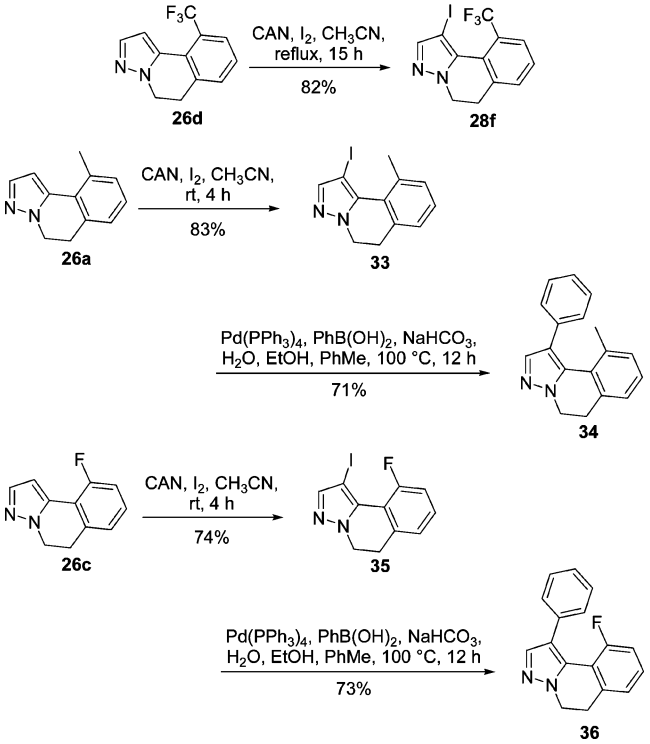
SCHEME 9. Further Functionalization of the Arene Moiety of the Annulated Pyrazoles



SCHEME 10. Further Functionalization of the Pyrazole Moiety of the Annulated Pyrazoles



SCHEME 11. Iodination of the Annulated Pyrazoles and Further Functionalization



palladium-catalyzed coupling conditions (Scheme 10). Finally, we showed an alternative route to similar products by introducing the halogen after the cyclization reaction by treating the annulated product with I_2 and CAN.[21] These iodinated pyrazoles were then subjected to Suzuki conditions[22] and resulted in the arylation of the pyrazole moiety in good yields (Scheme 11).

(21) Rodríguez-Franco, M. I.; Dorronsoro, I.; Hernández-Higueras, A. I.; Antequera, G. *Tetrahedron Lett.* **2001**, *42*, 863.

(22) Meegalla, S. K.; Doller, D.; Sha, D.; Soll, R.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4949.

Conclusion

We have developed a route to highly functionalized six-, seven-, and eight-membered ring-annulated indoles, azaindoles, pyrroles, and pyrazoles using a palladium-catalyzed norbornene-mediated tandem process involving an intermolecular *ortho*-alkylation of an aromatic C−H bond followed by an intramolecular direct arylation reaction. The reaction tolerates a number of substituents on both the *N*-bromoalkyl heterocycle and aryl iodide including ester, nitro, amine, alkyl, methoxy, trifluoromethyl, chloro, and fluoro. Furthermore, we showed that diverse functionality can be introduced by treating the halo-containing annulated products in palladium-catalyzed cross-coupling reactions.

Experimental Section

The following represents general experimental procedures toward the synthesis of annulated products. Specific experimental details and characterization data for the aforementioned compounds and other new compounds can be found in the Supporting Information.

General Procedure for the Synthesis of Six- and Seven-Membered Ring-Annulated Indoles, Azaindoles, and Pyrroles. A vial equipped with a stir bar was charged with aryl iodide (1 equiv), Cs_2CO_3 (2 equiv), norbornene (2 equiv), palladium catalyst (10 mol %; $Pd(OAc)_2$ was used for indoles, and $PdCl_2$ was used for pyrroles and azaindoles), and tri-2-furylphosphine (22 mol %). A solution of bromoalkyl indole, pyrrole, or azaindole (2 equiv) in CH_3CN (0.1 M) was then added, and the vial was capped and purged with nitrogen. The resulting mixture was heated in an oil bath at 90 °C for 16−24 h, cooled to room temperature, and then filtered through a short plug of silica. Removal of the solvent gave a crude product that was purified by flash chromatography.

General Procedure for the Synthesis of Eight-Membered Ring-Annulated Indoles and Pyrroles. A solution of the appropriate bromoalkyl indole or pyrrole (0.200 mmol, 2 equiv) in CH_3CN (6 mL) was added dropwise over 12 h to a solution of $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and the aryl iodide (1 equiv) in CH_3CN (1 mL) at 80 °C. The reaction was then stirred at 80 °C for 3 h. Once cooled to room temperature, the reaction was diluted with CH_2Cl_2, filtered through Celite, and washed with CH_2Cl_2. Removal of the solvent gave a crude product that was purified by flash chromatography.

General Procedure for the Synthesis of Six-Membered Ring-Annulated Pyrazoles. A 10 mL round-bottom flask equipped with a reflux condenser was charged with aryl iodide (0.600 mmol, 1.5 equiv), tri-2-furylphosphine (22 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (10 mol %), and CH_3CN (2 mL). The resulting mixture was heated to reflux, and then a solution of

bromoalkyl pyrazole (1.0 equiv) in CH_3CN (2 mL) was added dropwise (17 h syringe-pump addition). After the addition, the resulting mixture was heated for an additional 3 h, allowed to cool to room temperature, diluted with EtOAC, and filtered through a short plug of silica (EtOAc washings). Removal of the solvent gave a crude mixture that was purified by flash column chromatography.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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