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Synthesis of Benzannulated N-Heterocycles by a Palladium-Catalyzed C–C/C–N Coupling of Bromoalkylamines

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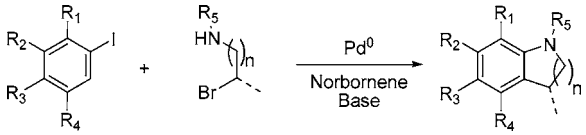
ABSTRACT



A palladium-catalyzed domino intermolecular alkylation/intramolecular amination of functionalized aryl iodides represents a new strategy for the synthesis of benzannulated N-heterocycles, affording functionalized indolines and tetrahydroquinolines from simple precursors.

In our continuing efforts to discover novel approaches to heterocycles, we have developed a method to synthesize indolines by palladium-catalyzed sequential C−C and C−N bond formations between bromoalkylamines and iodoarenes. Indolines are a biologically active motif found in alkaloids[1] and pharmaceuticals.[2] Commonly synthesized by cyclization of 2-substituted or N-substituted anilines through either metal-catalyzed processes,[3] non-metal-catalyzed processes,[4] or radical means,[5] numerous steps are often required either to synthesize the starting precursors or the indoline itself. Furthermore, few methods exist in which the functionality on the benzenoid ring can be easily varied.[6] Typically, either C−C or C−N bond formation occurs in the key transformation, but to the best of our knowledge, there are no previously reported strategies for indoline synthesis that accomplish both C−C and C−N bond formations in one step.

We have shown that palladium-catalyzed *ortho*-alkylation-based methodologies are compatible with a variety of terminal bond-forming reactions. Each of these sequences involves the formation of a new C−C[7] or C−H[8] bond; however, the introduction of a new carbon−heteroatom bond

(1) For oxaline, see: (a) Steyn, P. S. *Tetrahedron* **1970**, *26*, 51. (b) Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2005**, *7*, 941. For neoxaline, see: (c) Hirano, A.; Iwai, Y.; Masuma, R.; Tei, K.; Ōmura, S. *J. Antibiot.* **1979**, *32*, 781. For mersicarpine, see: (d) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995. For anhydrolycorinone, see: (e) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003. For oxoassoanine, see: (f) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637.

(2) For 5-hydroxytryptamine receptor antagonists, see: (a) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929. For muscarine receptor agonists and antagonists, see: (b) Adachi, S.; Koike, K.; Takayanagi, I. *Pharmacology* **1996**, *53*, 250. For DPP-IV inhibitors, see: (c) Sakashita, H.; Akahoshi, F.; Yoshida, T.; Kitajima, H.; Hayashi, Y.; Ishii, S.; Takashina, Y.; Tsutsumiuchi, R.; Ono, S. *Bioorg. Med. Chem.* **2007**, *15*, 641.

(3) For examples, see: (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (b) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068. (c) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777. (d) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130. (e) Liu, P.; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 2307.

(4) For examples, see: (a) Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett.* **2003**, *44*, 5305. (b) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316.

(5) For examples, see: (a) Moutrille, C.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 4631. (b) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943.

(6) For the synthesis of indoles and indolines that are highly substituted on the benzenoid ring, see: Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776.

(7) For selected examples with the Heck reaction, see: (a) Piguel, S.; Lautens, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (b) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827. (c) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. With cyanation, see: (d) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436. With direct arylation, see: (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (f) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827.

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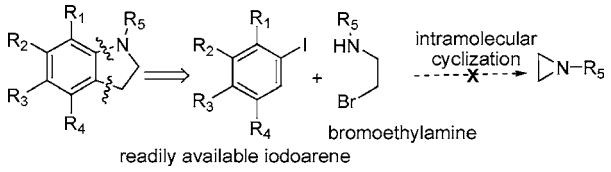
is less studied.[9] Herein we report our first example of a carbon-nitrogen bond-forming reaction in this domino sequence.

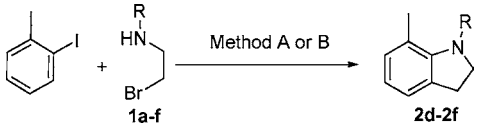
To realize our goal of making highly substituted indolines, we required bromoethylamines with a limited tendency to form aziridines (Scheme 1). The nucleophilicity of the amine

Scheme 1. Our Strategy for the Synthesis of Substituted Indolines



was suppressed by testing various nitrogen-protecting groups. These substrates were subjected to *ortho*-alkylation conditions with 2-iodotoluene (Table 1). Using method A, the Boc, Bz, and Ts groups led exclusively to decomposition or aziridination products (entries 1−3). However, moderate yields of the indoline were obtained with the ethyl carbamate (CO_2Et), phenyl (Ph), and 4-nitrophenyl (4-$NO_2C_6H_4$) groups (entries 4−6), and these were explored further. Switching to method B for the 4-$NO_2C_6H_4$-protected amine (**1f**) increased the yield to 88% with respect to the limiting reagent (entry 7), and decreasing the equivalents of base up to half the original amount had minimal effect (entry 8). The Ph-protected amine (**1e**) had similar reactivity under these conditions (method B, Table 1) compared to method A (entry 9), but the CO_2Et-protected substrate (**1d**) gave a lower yield of desired product **2d** (entry 10). Thus, the conditions used in entry 8 were chosen as the optimized reaction conditions.

Table 1. Optimization of Domino Alkylation/Amination Reaction

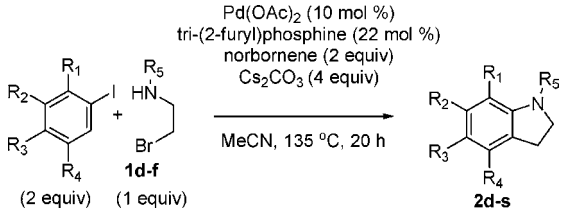


entry	R	method[a]	product	yield (%)
1	Boc (**1a**)	A	—	—
2	Bz (**1b**)	A	—	—
3	Ts (**1c**)	A	—	—
4	CO_2Et (**1d**)	A	**2d**	45
5	Ph (**1e**)	A	**2e**	62
6	4-$NO_2C_6H_4$ (**1f**)	A	**2f**	60
7	4-$NO_2C_6H_4$ (**1f**)	B	**2f**	88
8[c]	4-$NO_2C_6H_4$ (**1f**)	B	**2f**	**86**
9	Ph (**1e**)	B	**2e**	60
10	CO_2Et (**1d**)	B	**2d**	12

[a] Method A: iodoarene (1 equiv), bromoethylamine (2 equiv), $Pd(OAc)_2$ (10 mol %), tri(2-furyl)phosphine (22 mol %), norbornene (2 equiv), Cs_2CO_3 (8 equiv), acetonitrile (0.1 M), microwave 180 °C for 5 min. Method B: iodoarene (2 equiv), bromoethylamine (1 equiv), $Pd(OAc)_2$ (10 mol %), tri(2-furyl)phosphine (22 mol %), norbornene (2 equiv), Cs_2CO_3 (8 equiv), acetonitrile (0.1 M), 135 °C for 20 h. [b] With 1 equiv of iodoarene and 2 equiv of bromoalkylamine. [c] With 4 equiv of Cs_2CO_3.

We then examined the scope of this reaction with a variety of iodoarenes (Table 2). Well-tolerated functional groups at the 2-position of the arene include methyl, trifluoromethyl, fluoro, chloro, and TBS-protected benzyl alcohol (entries 1−5, 7). In addition, 1-iodonaphthalene gave the benzoindoline **2k** in 62% yield (entry 6). The reaction also tolerated arenes containing a C−F bond (entries 7 and 8) or a C−Cl bond (entries 4, 9, and 10). The latter substrates furnished indolines with aryl−Cl bonds at the 2-, 3-, or 5-positions of the benzenoid ring which are useful for post-modification. Strongly electron-donating groups at the 2-position are not tolerated under the optimized conditions (entry 11), increasing the importance of these C−Cl bonds which can be converted into electron-rich alcohols, amines, and thiols in one step.[10] Using bromoethylamines **1d** and **1e** (entries 13−16), higher temperatures and larger amounts of base were required for appreciable product yields. Only iodoarenes containing *ortho*-substituents have been investigated thus far, although we do have precedence for using external alkyl halides in palladium-catalyzed *ortho*, *ortho′* substitution reactions.[11]

Table 2. Scope of Domino Alkylation/Amination Reaction



entry	R_1	R_2	R_3	R_4	1	2	yield (%)
1	Me	H	H	H	**1f**	**2f**	86
2	Me	H	H	Me	**1f**	**2g**	24
3	CF_3	H	H	H	**1f**	**2h**	53
4	Cl	H	H	H	**1f**	**2i**	54
5	CH_2OTBS	H	H	H	**1f**	**2j**	30
6	2,3-benzo		H	H	**1f**	**2k**	62
7	F	H	H	H	**1f**	**2l**	40
8	Me	H	H	F	**1f**	**2m**	64
9	Me	Cl	H	H	**1f**	**2n**	80
10	Cl	H	H	Cl	**1f**	**2o**	50
11	OMe	H	H	H	**1f**	**2p**	0
12	NO_2	H	H	H	**1f**	**2q**	0
13[a]	Me	H	H	H	**1d**	**2d**	45
14[a]	2,3-benzo		H	H	**1d**	**2r**	43
15	Me	H	H	H	**1e**	**2e**	62
16	2,3-benzo		H	H	**1e**	**2s**	46

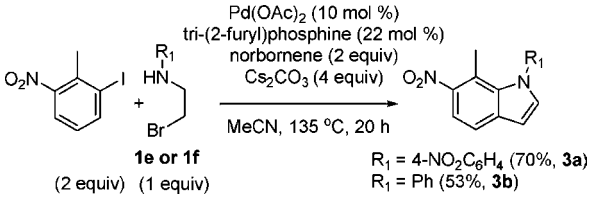
[a] Using method A in Table 1.

(8) (a) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053. (b) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939.

(9) Catellani has reported a domino *ortho*-arylation/amidation reaction: Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759.

While 2-nitroiodobenzene failed to give product (entry 12), 3-nitro-2-methyliodobenzene produced the *indole* (**3a**) in 70% yield (Scheme 2). Though the Pd-catalyzed dehydrogenation of indolines to indoles is known,[12] we do not observe indole formation with any of the other iodoarenes tested. We are currently investigating the possibility that another mechanism might be operating that is substrate-dependent. However, we have shown that this process is protecting-group dependent; phenyl-protected substrate **1e** also gave indole **3b** in 53% yield, while CO_2Et substrate **1d** gave only indoline in 20% yield.

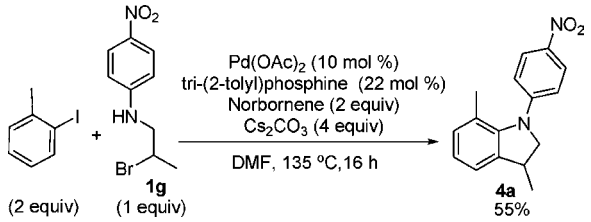
Scheme 2. Synthesis of Indoles



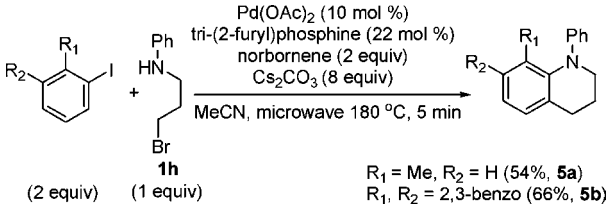
We next investigated the use of secondary bromoalkylamines to furnish 3-methylindolines. Although secondary alkyl halides decrease the rate of oxidative addition,[13] we hoped that, more importantly, aziridination would be discouraged. We have reported that secondary alkyl halides participate in an intramolecular palladium-catalyzed annulation reaction.[7c] However, there is limited information on the intermolecular process.[14] Compared with the primary alkyl halides, optimization studies revealed that changing the solvent to DMF and the ligand to tri(*p*-tolyl)phosphine increased the product yield. Thus, *N*-(2-bromopropyl)-4-nitrobenzenamine (**1g**) coupled with 2-iodotoluene in DMF at 135 °C in the presence of $Pd(OAc)_2$, tri(*p*-tolyl)phosphine, norbornene, and Cs_2CO_3 to give 3-methylindoline **4a** in 55% isolated yield (Scheme 3).[15]

We also extended the methodology to N-protected bromopropylamines to produce tetrahydroquinolines, another common alkaloid scaffold.[16] Previous approaches to this heterocycle largely focused on insertion reactions, ring expansions, and ring contractions.[15] Phenyl-protected propylamine (**1h**) was the optimal substrate for this process,[17] reacting with 2-iodotoluene and 1-iodonaphthalene to give tetrahydroquinolines **5a** and **5b** in 54 and 66% yields, respectively (Scheme 4).

Scheme 3. Example of the Use of Secondary Alkyl Halides

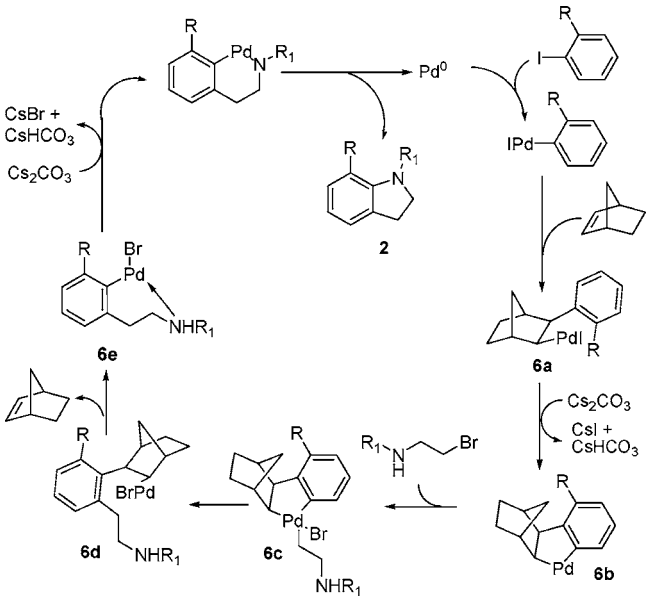


Scheme 4. Synthesis of Tetrahydroquinolines



A proposed mechanism for the synthesis of indoline **2** is shown in Scheme 5. Pd(0) inserts into the aryl−iodide bond of the iodoarene, followed by carbopalladation of norbornene to give **6a**. C−H activation of the 2-position of the arene forms palladacycle **6b**. Oxidative addition of the bromoethylamine leads to the Pd(IV) species **6c**,[18] and reductive elimination generates *ortho*-alkylated product **6d**. Extrusion

Scheme 5. Proposed Mechanism



(10) For the coupling of ammonia and $LiNH_2$ with aryl halides, see: (a) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028. For the coupling of aryl halides with KOH, see: (b) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. For the coupling of silyl-protected arenethiols with aryl halides, see: (c) Kreis, M.; Bräse, S. *Adv. Synth. Catal.* **2005**, *47*, 313.

(11) For examples, see: (a) Ref 7b. (b) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601. (c) Martins, A.; Marquardt, U.; Kasravi, N.; Alberico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4837.

(12) For examples, see: (a) Moores, A.; Poyatas, M.; Luo, Y.; Crabtree, R. H. *New J. Chem.* **2006**, *30*, 1675. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403. (c) Hara, T.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 6207.

(13) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749.

(14) Catellani reported that isopropyl iodide could be used in the *ortho*-alkylation/vinylation reaction with 31% conversion using a large excess of the halide: Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595.

(15) Preliminary results show that reaction with 3-nitro-2-methyliodobenzene produces the indole in 27% unoptimized yield.

of norbornene due to steric congestion gives aryl−Pd(II) complex **6e**. Last, an intramolecular Buchwald−Hartwig reaction with **6e** yields product **2**.

In summary, we have tuned the reactivity of the amine moiety in various bromoethylamines to allow these substrates to participate in a novel palladium-catalyzed domino *ortho*-alkylation/aromatic amination with substituted iodoarenes or 1-iodonaphthalene. The resulting highly functionalized indolines or benzoindolines are formed in moderate to good yields. In some cases, in situ formation of the indole was possible and proceeded in good yields. Using a N-protected bromoethylamine with a secondary alkyl bromide successfully produces 3-methylindoline, while N-protected bromopropylamines can be used to yield tetrahydroquinolines. Broadening of the reaction scope and improving the conditions for bromoalkylamines with removal N-protecting groups is currently under investigation and will be reported in due course.

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

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(16) For virantmycin, see: (a) Ōmura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiot.* **1980**, *33*, 1395. For isoschizogaline, see: (b) Kariba, R. M.; Houghton, P. J.; Yenesew, A. *J. Nat. Prod.* **2002**, *65*, 566. (c) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(17) Reaction with 4-$NO_2C_6H_4$-protected amine gave 24 and 35% of **a** and **b**, respectively, and CO_2Et-protected amine gave no products.

(18) Based on the mechanistic proposal of Catellani and co-workers, see ref 13 and references therein.