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Catalyst-Controlled Chemoselective Arylation of 2-Aminobenzimidazoles

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Abstract

The chemoselective and complementary Pd-and Cu-catalyzed N-arylation of 2-aminobenzimidazoles is described. Selective N-arylation of the amino-group was achieved with a Pd-catalyzed method, while selective N-arylation of azole nitrogen was achieved with a Cu-catalyzed procedure. The utility of these complementary sets of conditions is demonstrated in several two-step, selective syntheses of di-arylated aminoazoles.

Keywords

palladium; copper; C-N coupling; aminoazole; *N*-arylation

Transition-metal catalyzed heteroatom-arylation reactions are emerging as valuable tools in organic synthesis, fuelled by the identification of more efficient catalyst systems with increased substrate scopes.[1] The synthetic utility of these transformations is increased if catalysts are both highly reactive and selective. This is particularly important for substrates with multiple heteroatom sites capable of undergoing reaction. Furthermore, the development of complementary sets of catalysts or conditions for the selective arylation of substrates possessing multiple nucleophilic sites enables the rapid, protecting group-free generation of molecular complexity with minimal synthetic manipulations. In this context, we have developed sets of procedures for the Pd- and Cu-catalyzed chemoselective arylation of aminobenzamides,[2a] 5-aminoindole,[2a] 4-(2-aminoethyl)aniline,[2a] amino alcohols,[2b] oxindoles[2c] and aminophenols. [2d]

During our work on the N-arylation of nitrogen-containing heterocycles,[3] we became interested in the use of 2-aminobenzimidazoles as potential substrates for chemoselective N-arylation reactions. Both N^1-aryl-2-aminobenzimidazoles and 2-arylaminobenzimidazoles are found in a variety of medicinally important compounds including integrin $\alpha_4\beta_1$ antagonists,[4] mTOR inhibitors,[5] aurora kinase inhibitors,[6] Tie-2 kinase inhibitors,[7] Ca channel blockers,[8] and CXCR2 antagonists.[9 Thus, the selective syntheses of both of these isomers from a common core structure represent attractive alternatives to other previously-employed routes[10–11] and could provide rapid access to a diverse array of potentially bioactive 2-aminobenzimidazole derivatives (Scheme 1).

While the efficient Cu-[12] and Pd-catalyzed[13] N^1-arylations of some benzimidazole derivatives with aryl halides have been described, the chemoselective N-arylation of

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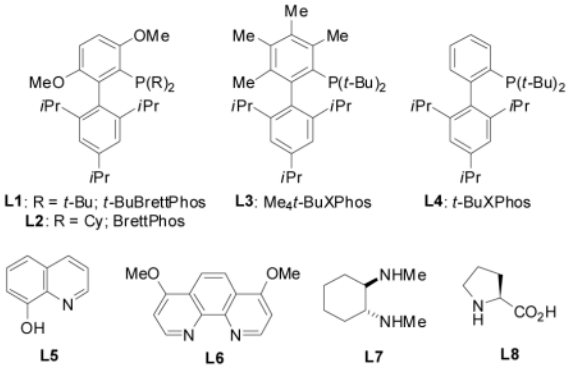
unprotected 2-aminobenzimidazoles with aryl halides has received little attention. [14–16] Potential challenges of such an approach include the formation of regioisomers and/or poly-arylated products due to the presence of three adjacent nucleophilic nitrogens (N^1, N^3 and C^2-amino group), as well as the tautomeric nature of 2-aminobenzimidazoles. Herein, we report the successful development of an orthogonal set of Pd- and Cu-catalyzed chemoselective conditions for the N-arylation of unprotected 2-aminobenzimidazoles and related aminoazoles.



We initiated our investigation by examining the Pd-catalyzed coupling of 2-aminobenzimidazole and bromobenzene (Table 1). With $Pd_2(dba)_3$ (0.1 mol%), **L1** (0.2 mol %), and K_3PO_4, the N-arylation went smoothly to give 2-anilinobenzimidazole **1a** in 92% yield and without formation of regioisomer **1b** or poly-arylated products (entry 1). The use of other biaryl phosphine ligands (**L2**–**L4**) provided low yields of product under these conditions. Replacing K_3PO_4 with other bases also resulted in lower yield of the product (entries 5–6).

Turning our attention to finding conditions for the selective formation of the the N^1-arylated product (**2a**), we found that reactions with a Cu-catalyst system (iodobenzene/ bromobenzene, CuI, **L5**,[17] and Cs_2CO_3) were completely chemoselective, providing no trace either of regioisomer **1a** or of any poly-arylated products (entries 7–8). The use of other ligands (**L6**–**L8**) and bases did not alter this chemoselectivity, but rather gave lower yields of **1b** (entries 9–13). Thus, complete selectivity and complementarity can be achieved using Pd- and Cu-based catalyst systems.

We next explored the scope of the Pd-catalyzed selective *N*-arylation of aminoazoles, and found that a variety of 2-aminobenzimidazoles and 2-aminoimidazole could be coupled chemoselectively with both electron-rich and electron-poor aryl halides, as well as with an *ortho*-substituted aryl halide (Table 2, 1b–1h).[18] For 3-amino-5-alkylpyrazoles the primary amino groups were also selectively and efficiently arylated using 0.2–0.5 mol% catalyst. Though the selective Pd-catalyzed N-arylation of 3-aminopyrazoles has been previously reported, relatively high catalyst loadings (5 mol% Pd and 10 mol% **L4**) and the use of a strong base (NaO*t*Bu) were required.[13a]

The scope of the Cu-catalyzed N^1-selective arylation was also investigated (Table 3). Reactions of 2-aminobenzimidazoles and 2-aminoimidazole with a variety of functionalized aryl iodides gave N^1-arylated products **2b**–**2f** and **2i** selectively and in good yields. The N-arylation of unsymmetrical 2-amino-4-methylbenzimidazole reacted at the less sterically-hindered N^1-position to provide **2g**. Both electron-rich, **2e**, **g** and electron-deficient aryl halides reacted smoothly to give products in high yield. Lastly, reactions of 2-

alkylaminobenzimidazoles gave N^1-arylated products **2j** and **2k** in good yields. Not surprisingly, the process showed good functional group compatibility.

Having established a complementary set of Pd- and Cu-catalyzed chemoselective arylation methods, we sought to apply our methods to selective two-step syntheses of diarylaminoazoles from unprotected aminoazoles using sequential Pd- and Cu-catalyzed reactions (or vice versa). Parent 2-aminobenzimidazole could be selectively arylated via an initial Pd-catalyzed N-arylation of 2-aminobenzimidazole, followed by a subsequent Cu-catalyzed arylation to give **3**. Diarylated 3-aminoindazole **4** was prepared via a Cu-catalyzed reaction of 3-aminoindazole, followed by arylation via the Pd-catalyzed method. In both cases, the reaction order was important. In the first case, only a trace amount of **3** was obtained when the Pd-catalyzed system was used as the second step. For the synthesis of **4**, the use of a Pd-catalyst for the first arylation of 3-amioindazole gave a mixture of mono- and di-arylated products.[19]

In summary, we have developed an orthogonal set of Pd- and Cu-catalyzed N-arylations of 2-aminobenzimidazoles and related aminoazoles. Selective N-arylation of the primary amino-group of 2-aminobenzimidazoles was achieved via Pd-catalyzed methods, while selective N-arylation of the azole nitrogen was achieved with Cu-catalysis. These general protocols are compatible with a variety of aryl halides and give facile access to an array of both isomers of N-arylaminoazoles from common aminoazole precursors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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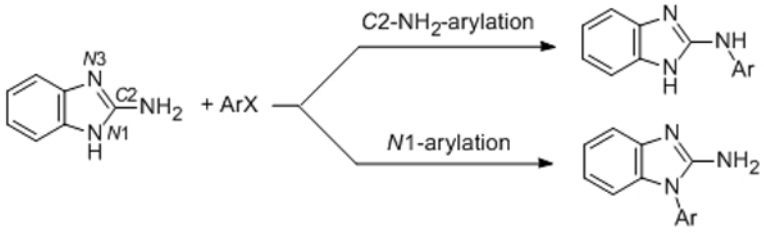
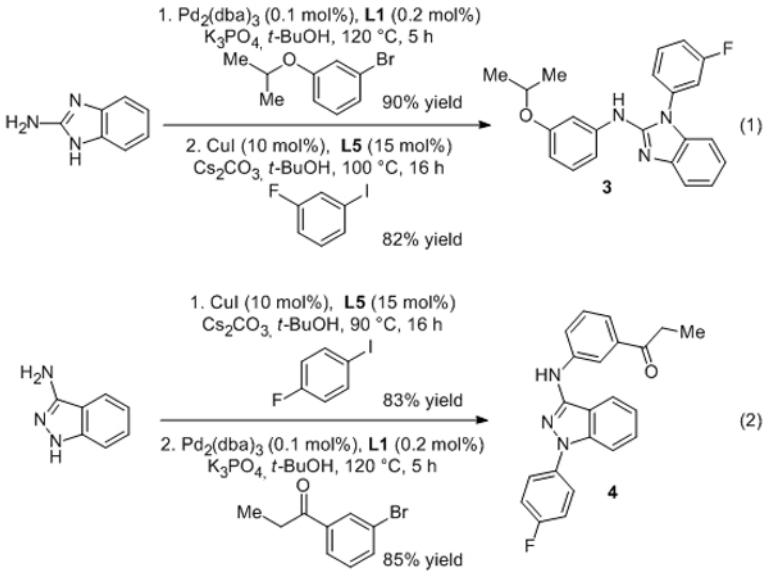
18. For the arylation of 2-aminoimidazole sulfate, the use of DMF as solvent was crucial to obtain the desired product **1h**.
19. See supporting information for details.



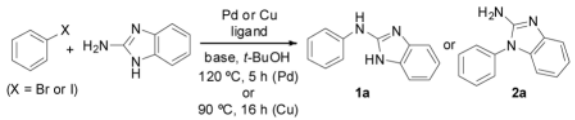
Scheme 1.
Chemoselective arylation of 2-aminobenzimidazole



Scheme 2.
Selective syntheses of diarylaminoazoles

Table 1

Reaction optimization[a]



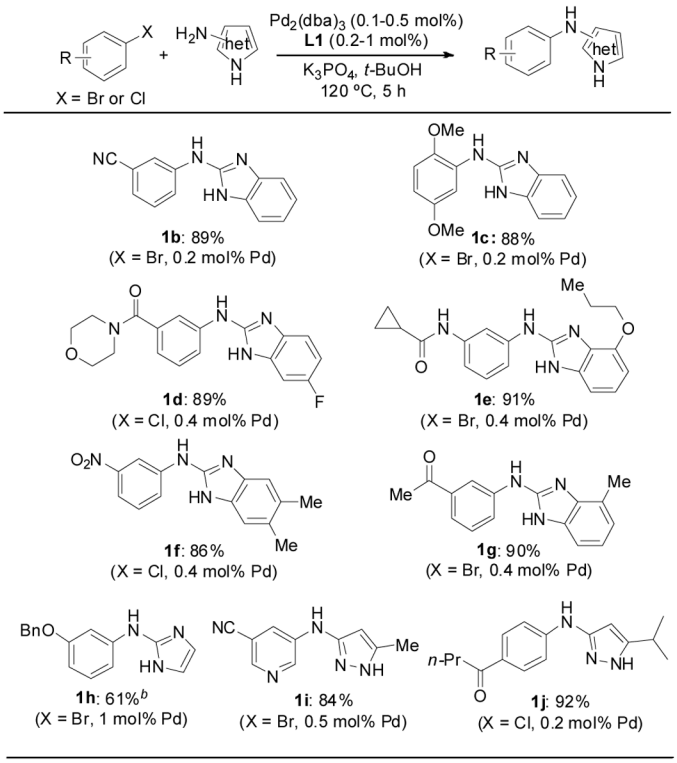
entry	metal source (mol %)	ligand (mol %)	X	base (1.5 eq.)	yield (%)
1	$Pd_2(dba)_3$ (0.1)	**L1** (0.2)	Br	K_3PO_4	**1a**/92
2	$Pd_2(dba)_3$ (0.1)	**L2** (0.2)	Br	K_3PO_4	**1a**/<5
3	$Pd_2(dba)_3$ (0.1)	**L3** (0.2)	Br	K_3PO_4	**1a**/23
4	$Pd_2(dba)_3$ (0.1)	**L4** (0.2)	Br	K_3PO_4	**1a**/<5
5	$Pd_2(dba)_3$ (0.1)	**L1** (0.2)	Br	Cs_2CO_3	**1a**/14
6	$Pd_2(dba)_3$ (0.1)	**L1** (0.2)	Br	NaO*t*-Bu	**1a**/<5
7	CuI (10)	**L5** (15)	I	Cs_2CO_3	**2a**/89
8[b]	CuI (10)	**L5** (15)	Br	Cs_2CO_3	**2a**/70
9	CuI (10)	**L6** (15)	I	Cs_2CO_3	**2a**/10
10	CuI (10)	**L7** (15)	I	Cs_2CO_3	**2a**/45
11	CuI (10)	**L8** (15)	I	Cs_2CO_3	**2a**/<5
12	CuI (10)	**L5** (15)	I	K_2CO_3	**2a**/45
13	CuI (10)	**L5** (15)	I	K_3PO_4	**2a**/39

[a]Conditions for entries 1–6: PhBr (1 mmol), 2-aminobenzimidazole (1.1 mmol), base (1.5 mmol), $Pd_2(dba)_3$ (0.1 mol%), ligand (0.2 mol%), *t*-BuOH (1.5 mL), 120 °C, 5 h. Conditions for entries 7–13: PhI or PhBr (1 mmol), 2-aminobenzimidazole (1.1 mmol), base (1.5 mmol), CuI (10 mol%), ligand (15 mol%), *t*-BuOH (1.5 mL), 90 °C, 16 h.

[b]Reaction was performed at 120 °C.

Table 2

Scope of the Pd-catalyzed N-arylation[a]

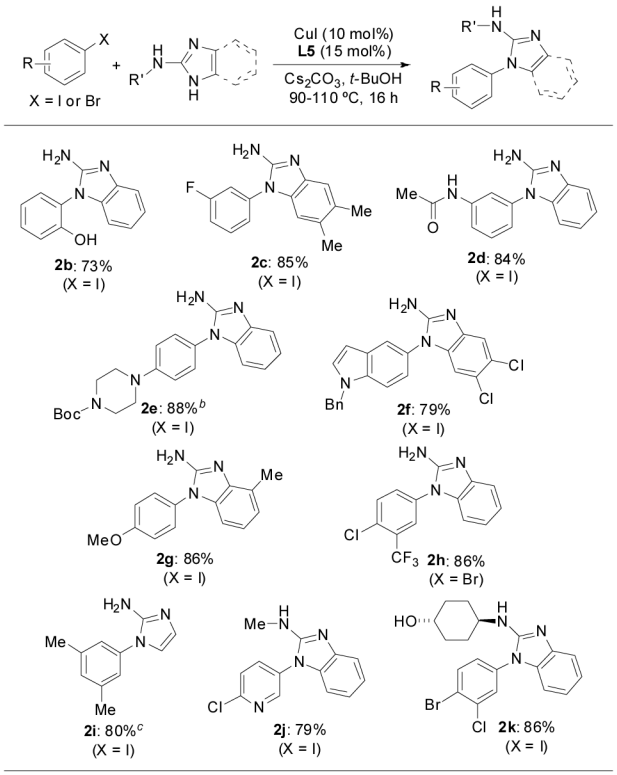


[a] aryl halide (1 mmol), aminoazole (1.1 mmol), K_3PO_4 (1.5 mmol), $Pd_2(dba)_3$ (0.1–0.5 mol%), **L1** (0.2–1 mol%), *t*-BuOH (1.5 mL), 120 °C, 5 h. Yield of isolated product, average of two runs.

[b] 2-aminoimidazole sulfate (1.1 mmol), K_3PO_4 (2.5 mmol) and DMF were used.

Table 3

Scope of the Cu-catalyzed N-arylation[a]



[a]aryl halide (1 mmol), aminoazole (1.1 mmol), Cs_2CO_3 (1.5 mmol), CuI (10 mol%), **L5** (15 mol%), *t*-BuOH (1.5 mL), 90–110 °C, 16 h. Yield of isolated product, average of two runs.

[b]0.5 mmol scale.

[c]2-aminoimidazole sulfate (1.1 mmol), Cs_2CO_3 (2.5 mmol) were used.