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Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation: An Efficient Method for the Synthesis of 2-Aminobenzimidazoles†

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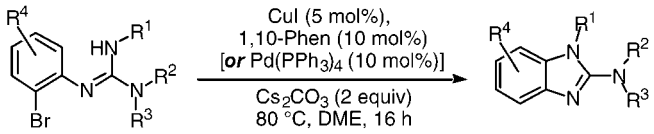
ABSTRACT



The formation of 2-aminobenzimidazoles via intramolecular C–N bond formation between an aryl halide and a guanidine moiety can be achieved using either copper or palladium catalysis. Inexpensive copper salts such as CuI are generally superior to the use of palladium catalysts. Regioselective cyclizations, where $R^3 = H$, can be achieved in high yield under CuI/1,10-phenanthroline-catalyzed conditions, whereas palladium catalysis results in the formation of regioisomeric products.

There have been a number of groundbreaking advances in cross-coupling methodology over the past few years. One significant area of improvement is that of metal-catalyzed C−N bond and other carbon-heteroatom bond formations. In particular, the palladium-catalyzed amination of aryl halides, pioneered by the laboratories of Hartwig and Buchwald, has been enthusiastically adopted in the pharmaceutical industry.[1] While some limitations still exist, it is clear that metal-catalyzed cross-coupling reactions will increasingly occupy a key position among the armamentarium of carbon−heteroatom bond-forming reactions.[2]

Our interest in guanidine chemistry[3] and cyclization reactions led us to consider the feasibility of intramolecular cross-coupling between a guanidine residue and an aryl halide for the formation of 2-aminobenzimidazoles, which are known to display a range of biological activities.[4,5] The vast majority of methods for the synthesis of 2-aminobenzimidazoles originate from *o*-phenylenediamine precursors. For example, a recent example from Senanayake and co-workers utilized palladium-catalyzed aryl amination of 2-chlorobenzimidazoles, which are *o*-phenylenediamine derived.[6] Kerr and co-workers have synthesized aminobenzimidazoles through a high-pressure S_NAr reaction between 2-chlorobenzimidazoles and alkylamines.[7] More recently,

† This paper is dedicated to our friend and colleague, Professor J. Bryan Jones, on the occasion of his 65th birthday.

(1) Reviews: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

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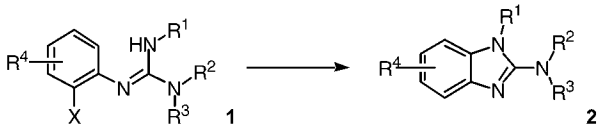
Sun and co-workers have used a rapid microwave-assisted liquid-phase combinatorial approach from *o*-phenylenediamine and isothiocynanates.[8]

Despite these approaches, a general method for the generation of 2-aminobenzimidazoles under mild conditions is desirable, particularly when the corresponding *o*-phenylenediamines are not readily available. We envisaged that the cyclization reaction of tri/tetrasubstituted guanidines **1** via an intramolecular aryl guanidinylation, analogous to Buchwald and Hartwig aryl amination chemistry, would generate mono/disubstituted 2-aminobenzimidazoles **2** (Scheme 1).[1,9] Intramolecular palladium-catalyzed cross-couplings

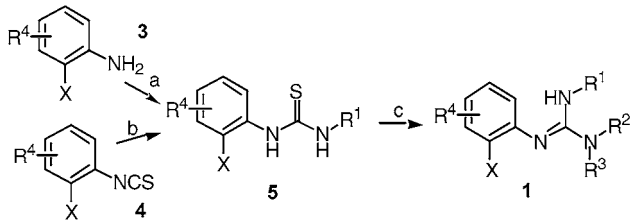
Scheme 1



resulting in C−N bond formation and cyclization are known for the generation of a variety of heterocycles such as indoles, pyrido[2,3-*b*]indoles, phenazines, indazoles, and several alkaloid backbones.[10]

The requisite cyclization precursors are readily synthesized from commercially available *o*-haloaryl isothiocyanates or *o*-haloanilines (Scheme 2). Reaction of *o*-haloaniline **3** with

Scheme 2[a]

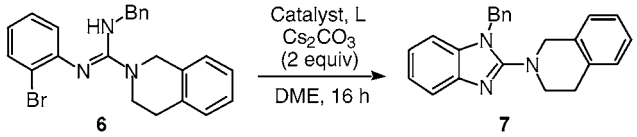


[a] Key: (a) R^1NCS, DMF, 12−48 h; (b) R^1NH_2, MeCN, 10 min; (c) $HgCl_2$, Et_3N, R^2R^3NH, 3−24 h.

an isothiocyanate in DMF gave thiourea **5** in 12−48 h. Alternatively, thiourea **5** can be synthesized in quantitative yield from *o*-halophenyl isothiocyanate **4** in acetonitrile in less than 10 min. Treatment of **5** with $HgCl_2$ under basic conditions in the presence of a primary/secondary amine generated tri/tetrasubstituted guanidine **1** following filtration through Celite and aqueous workup with aqueous ammonium chloride. Dehydrothiolation of thiourea **5** could also be achieved via Mukaiyama's reagent, silver salts, or EDCI.

Bromophenyl guanidine **6** was chosen as a representative substrate, and optimization studies of palladium source, ligand, solvent, and temperature were undertaken (Table 1).

Table 1. Palladium-Catalyzed Aryl Guanidinylation: Catalyst, Ligand, and Temperature Effects on the Cyclization of Guanidine **6** to Benzimidazole **7**



entry	catalyst	mol %	L	mol %	temp (°C)	conversion[a] (%)
1					80	0
2	$Pd_2(dba)_3$	10	PPh_3	20	80	47
3	$Pd_2(dba)_3$	10	PPh_3	40	80	55
4	$Pd_2(dba)_3$	10	$(o\text{-tol})_3P$	20	80	71
5	$Pd(OAc)_2$	10	$(o\text{-tol})_3P$	20	80	30
6	$Pd_2(dba)_3$	10	**8**	20	80	85
7	$Pd_2(dba)_3$	10	**8**	40	80	27
8	$Pd(PPh_3)_4$	10			80	>98
9	$Pd_2(dba)_3$	10	PPh_3	20	rt	0
10	$Pd_2(dba)_3$	10	$(o\text{-tol})_3P$	20	rt	8
11	$Pd_2(dba)_3$	10	**8**	20	rt	7
12	$Pd_2(dba)_3$	10	$(o\text{-tol})_3P$	20	50	21
13	$Pd(PPh_3)_4$	10			50	5
14	$Pd(PPh_3)_4$	5			80	17
15	$Pd(PPh_3)_4$	2			80	8

[a] Conversions determined by ^1H NMR.

Intramolecular cyclization of **6** using $Pd_2(dba)_3$ (10 mol %), PPh_3 (20 mol %), and Cs_2CO_3 (2 equiv) at 80 °C was investigated with various solvents, including toluene, CH_3CN, DMA, DMF, and DME. Good conversion of **6** to 2-aminobenzimidazole **7** (as analyzed by ^1H NMR) was observed with DMF, DMA, and DME solvents, with DME being superior (Table 1, entries 2 and 3). Use of tri-*o*-tolylphosphine or Buchwald's ligand (di-*tert*-butylphosphinobiphenyl) **8** led to higher conversions at 80 °C (Table 1, entries 4 and 6). The use of $Pd(OAc)_2$ or a greater amount of **8** both resulted in poorer conversions (Table 1, entries 5 and 7). However, $Pd(PPh_3)_4$ (10 mol %) showed complete conversion at 80 °C. Reactions at lower temperatures resulted in poorer conversions for a variety of Pd/ligand combinations (Table 1, entries 9−13), as did lowering the amount of $Pd(PPh_3)_4$ catalyst (Table 1, entries 14 and 15). Brain and co-

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(9) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (d) Zhao, S.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463−4466. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135. (f) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546. (g) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519−521.

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workers have also synthesized a single example of a 2-aminobenzimidazole through an analogous approach using $Pd(PPh_3)_4$ catalyst.[11]

While the palladium-catalyzed reaction was encouraging, the relatively high catalyst loadings are not ideal. Copper(I) has recently been used in C−C and C−N bond formation.[12,13] Application of copper chemistry to the intramolecular aryl guanidinylation reaction of **6** was therefore investigated. Using CuI without any ligand at 80 °C gave partial conversion to the desired product (Table 2, entry 1).

Table 2. Copper-Catalyzed Aryl Guanidinylation: Catalyst, Ligand, and Temperature Effects on the Cyclization of Guanidine **6** to Benzimidazole **7**

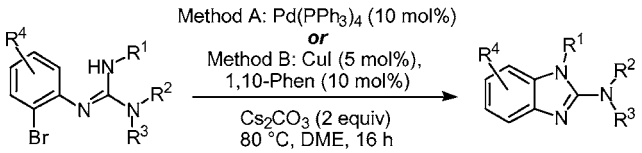
entry	catalyst	mol %	L	mol %	temp (°C)	conversion[a] (%)
1	CuI	5			80	40
2	CuI	5	9	10	80	>98
3	$CuSO_4 \cdot 5H_2O$	5	9	10	80	95
4	$CuBr_2$	5	9	10	80	>98
5	$Cu(OAc)_2 \cdot H_2O$	5	9	10	80	95
6	CuI	5	9	10	rt	3
7	CuI	5	9	10	50	65
8	CuI	1	9	2	80	66
9	CuI	2.5	9	5	80	95

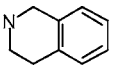
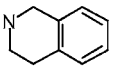
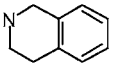
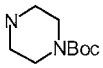
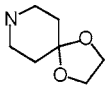
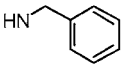
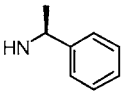
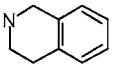
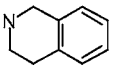
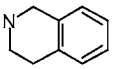
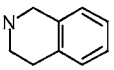
[a] Conversions determined by ^1H NMR.

Investigation of various copper salts as a catalyst (5 mol %) and 1,10-phenanthroline **9** (10 mol %) as a ligand resulted in excellent conversions, with CuI and $CuBr_2$ achieving complete conversion (Table 2, entries 2−5). Reaction of **6** at lower temperatures or the use of lower catalyst loadings resulted in poorer conversions (Table 2, entries 6−8). However, reaction with the corresponding iodide resulted in 50% and complete conversions at room temperature and 50 °C, respectively, illustrating the greater reactivity of the iodide substrates. To our knowledge, this is the first catalytic intramolecular aryl guanidinylation using copper salts.

The intramolecular aryl guanidinylation was applied to various aryl bromide substrates (Table 3) using the two sets of optimized conditions, method A for palladium catalysis (Table 1, entry 8) and method B for copper catalysis (Table 2, entry 2).[14] In general, both sets of conditions resulted in product formation, with the copper-catalyzed conditions

Table 3. Intramolecular Aryl Guanidinylation of Aryl Bromides with $Pd(PPh_3)_4$ (Method A) and CuI (Method B)



entry	R^1	NR^2R^3	R^4	method A yield[a] (%) (conversion[b]) (%)	method B yield[a] (%) (conversion[b]) (%)
1	Bn		H	88 (>98)	83 (>98)
2	Ph		H	84 (>95)	58 (>95)
3	4-MeOBn		H	63 (65)	66 (95)
4	4-MeOBn		H	93 (>98)	97 (>98)
5	Bn		H	93 (>98)	96 (>98)
6	Bn	$MeN(CH_2)_2CN$	H	31 (40)	87 (>98)
7	Ph		H	n.d. (17)	83 (>98)
8	Bn		H	n.d. (85)[c,d]	97 (>98)[c]
9	Bn		4-Me	66 (70)	90 (95)
10	Bn		6-Br-4-Me	76 (76)[e]	98 (>98)
11	Bn		4-Cl	81 (95)	88 (90)
12	Bn		5-CF_3	87 (>98)	88 (95)

[a] All yields are reported after column chromatography. [b] Conversions determined by ^1H NMR. [c] Reaction was refluxed for 16 h. [d] Product was obtained as a 1:1 mixture of isomers. [e] Product was obtained as a 1:1 mixture of mono-Br and debrominated products.

sometimes achieving higher conversions, and with product purification being more readily accomplished. In cases where the regioselectivity of cyclization is an issue, the copper-catalyzed method gives better results (Table 3, entries 7 and 8). Preferential cyclization of guanidine occurs from an NH-

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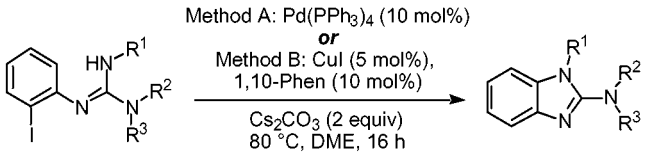
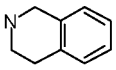
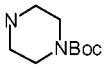
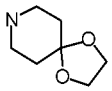
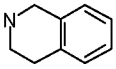
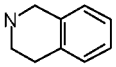
(12) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805. (c) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269−272. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (e) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428.

(13) For an earlier review of copper-assisted nucleophilic substitutions of aryl halides, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.

(14) **General Synthetic Procedure.** To a mixture of guanidine (0.20 mmol), CuI (0.01 mmol, 0.05 equiv), 1,10-phenanthroline (0.02 mmol, 0.10 equiv), and Cs_2CO_3 (0.40 mmol, 2.0 equiv) was added reagent-grade dimethoxyethane (4 mL). The reaction mixture was heated at 80 ° C for 16 h under nitrogen. The reaction was diluted with EtOAc (25 mL) and washed with H_2O (2 × 25 mL) and saturated NaCl (1 × 25 mL). The organic layer was dried over $MgSO_4$, and then the solvent was removed in vacuo. The crude product was purified using silica gel column chromatography. For the $Pd(PPh_3)_4$ (23.1 mg, 0.1 equiv) catalyzed reactions, dried dimethoxyethane (from 4 Å molecular sieves) was used as a solvent.

Table 4. Intramolecular Aryl Guanidinylation of Aryl Iodides with $Pd(PPh_3)_4$ (Method A) and CuI (Method B)



entry	R^1	NR^2R^3	method A	method B
			yield[a] (%) (conversion[b]) (%)	
1	Bn		86 (95)	96 (>98)
2	Bn		84 (98)	95 (98)
3	4-MeOBn		82 (90)	94 (>98)
4	4-MeOBn		41 (45)	80 (>98)
5	3,4-$(MeO)_2$Ph-CH_2CH_2-		50 (60)	70 (90)
6	3,4-$(MeO)_2$Ph-CH_2CH_2-	$MeN(CH_2)_2CN$	22 (25)	80 (95)

[a] All yields are reported after column chromatography. [b] Conversions determined by ^1H NMR.

aryl rather than an NH-alkyl group (Table 3, entry 7). Significantly, whereas copper-catalyzed reaction of a substrate bearing an NH-benzyl group and an NH-α methylbenzyl group results in completely regioselective cyclization through the less sterically encumbered NH-benzyl group, the palladium-catalyzed reaction is unselective (Table 3, entry 8). Also, reaction of a susbstrate incorporating two *o*-bromo substituents gave a mixture of bromo and debrominated aminobenzimidazoles with palladium catalysis, while the copper-catalyzed variant gave clean reaction without competing debromination (Table 3, entry 10). These results may suggest that precoordination of the guanidine is necessary before oxidative addition of copper into the Ar−Br bond occurs, a process that is perhaps less important for palladium.

Further investigation of the intramolecular aryl guanidinylation with aryl iodides using the optimized conditions was also pursued (Table 4). Results for the application of these conditions to various substrates were analogous to those obtained using aryl bromides, with copper catalysis again being superior (Table 4).

In summary, we have demonstrated an intramolecular aryl guanidinylation to form biologically relevant 2-aminobenzimidazoles using both palladium and copper catalysts. The use of inexpensive copper salts such as CuI is shown to be superior to their palladium counterparts, both in terms of yields and selectivities. To our knowledge, this is the first report of the use of copper salts in aryl guanidinylation. We anticipate that such catalytic cross-coupling with copper will allow the synthesis of interesting heterocycles in a manner suitable for combinatorial library generation. Further studies toward this end will be reported in due course.

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