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

Ghotas Evindar, Robert A. Batey*

Davenport Research Laboratories, Department of Chemistry, University of Toronto,
80 St. George Street, Toronto, Ontario, M5S 3H6, Canada

rbatey@chem.utoronto.ca

Received Date (will be automatically inserted after manuscript is accepted)

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 R³ = 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 amongst the armamentarium of carbon-heteroatom bond forming reactions.²

Our interest in guanidine chemistry³ 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-

[†] 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. Engl.* **1998**, *37*, 2046-2067. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125-146.

(2) (a) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035-2038.

(b) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101-1104. (c) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381-4384. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539-2541.

(3) (a) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362-2363. (b) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913-2916.

(4) Ellingboe, J. W.; Spinelli, W.; Winkley, M. W.; Nguyen, T. T.; Parsons, R. W.; Moubarak, I. F.; Kitzen, J. M.; Von Engen, D.; Bagli, J. F. *J. Med. Chem.* **1992**, *35*, 705-716.

(5) (a) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1934-1943. (b) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925-1933. (c) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1943-1947.

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, Sun and coworkers have used a rapid microwave-assisted liquid-phase combinatorial approach from *o*-phenylenediamine and isothiocyanates.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

Scheme 1

palladium catalyzed cross-couplings 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 an isothiocyanate in DMF gave thiourea **5** in 12–48 hours. Alternatively, thiourea **5** can be synthesized in quantitative yield from *o*-halophenyl

Scheme 2^a

^a Key: (a) R¹NCS, DMF, 12–48 h; (b) R¹NH₂, MeCN, 10 min; (c) HgCl₂, Et₃N, R²R³NH, 3–24 h.

isothiocyanate **4** in acetonitrile in less than 10 minutes. Treatment of **5** with HgCl₂ under basic conditions in the presence of a primary/secondary amine generated tri/tetrasubstituted guanidine **1** following filtration through Celite and aqueous work-up 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 for palladium source, ligand, solvent and temperature were undertaken (Table 1). Intramolecular cyclization of **6** using Pd₂(dba)₃ (10 mol%), PPh₃ (20 mol%) and Cs₂CO₃ (2 equiv.) at 80 °C was investigated with various solvents including toluene, CH₃CN, 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(PPh₃)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(PPh₃)₄ catalyst (Table 1, entries 14 and 15). Brain and co-workers have also synthesized a single example of a 2-aminobenzimidazole through an analogous approach using Pd(PPh₃)₄ catalyst.¹¹

Whilst 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

(6) Hong, Y.; Tanoury, G. J.; Wilkinson, S. H.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607–5610.

(7) Barrett, I. C.; Kerr, M. A. *Tetrahedron Lett.* **1999**, *40*, 2439–2442.

(8) Bendale, P. M.; Sun, C.-M. *J. Comb. Chem.* **2002**, *4*, 359–361.

(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.

(10) (a) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028–1030. (b) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068–3073. (c) Abouabdellah, A.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 2119–2122. (d) Emoto, T.; Kubosaki, N.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **2000**, *41*, 355–358. (e) Brown, J. K. *Tetrahedron Lett.* **2000**, *41*, 1623–1626. (f) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519–521. (g) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937–2940. (h) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415. (i) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475.

(11) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893–1895.

(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.

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)	conv. ^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	(<i>o</i> -tol) ₃ P	20	80	71
5	Pd(OAc) ₂	10	(<i>o</i> -tol) ₃ P	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	(<i>o</i> -tol) ₃ P	20	rt	8
11	Pd ₂ (dba) ₃	10	8	20	rt	7
12	Pd ₂ (dba) ₃	10	(<i>o</i> -tol) ₃ P	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.

80 °C gave partial conversion to the desired product (Table 2, entry 1). Investigation of various copper salts as catalyst (5 mol%) and 1,10-phenanthroline **9** (10 mol%) as a ligand resulted in excellent conversions, with CuI and CuBr₂ 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 conversion 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

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)	conv. ^a (%)
1	CuI	5	—	—	80	40
2	CuI	5	9	10	80	>98
3	CuSO ₄ ·5H ₂ O	5	9	10	80	95
4	CuBr ₂	5	9	10	80	>98
5	Cu(OAc) ₂ ·H ₂ O	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.

product formation, with the copper catalyzed conditions sometimes achieving higher conversions, and with product purification being more readily accomplished. In the case where regioselectivity of cyclization is an issue, the copper catalyzed method gives better results (Table 3, entries 7 and 8). Preferential cyclization of the guanidine occurs from an NH–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–alpha 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 substrate incorporating two ortho-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 were 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).

(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 Cs₂CO₃ (0.40 mmol, 2.0 equiv) was added reagent grade dimethoxyethane (4 mL). The reaction mixture was heated at 80 °C for 16 hours under nitrogen. The reaction was diluted with EtOAc (25

mL) and washed with H₂O (2 x 25 mL), sat. NaCl (1 x 25 mL). The organic layer was dried over MgSO₄ then the solvent was removed *in vacuo*. The crude product was purified using silica gel column chromatography. For the Pd(PPh₃)₄ (23.1 mg, 0.1 equiv) catalyzed reactions, dried dimethoxyethane (from molecular sieves 4 Å) was used as solvent.

Table 3. Intramolecular aryl guanidinylation of aryl bromides with Pd(PPh₃)₄ (Method A) and CuI (Method B).

Method A: Pd(PPh₃)₄ (10 mol%)
or
Method B: CuI (5 mol%),
1,10-Phen (10 mol%)
Cs₂CO₃ (2 equiv)
80 °C, DME, 16 h

entry	R ¹	NR ² R 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) ₂ CN	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 hours. ^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.

Table 4. Intramolecular aryl guanidinylation of aryl iodides with Pd(PPh₃)₄ (Method A) and CuI (Method B).

Method A: Pd(PPh₃)₄ (10 mol%)
or
Method B: CuI (5 mol%),
1,10-Phen (10 mol%)
Cs₂CO₃ (2 equiv)
80 °C, DME, 16 h

entry	R ¹	NR ² R ³	method A yield ^a (%) (conversion ^b) (%)	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 ₂ CH ₂ -		50 (60)	70 (90)
6	3,4-(MeO) ₂ Ph-CH ₂ CH ₂ -	MeN(CH ₂) ₂ CN	22 (25)	80 (95)

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

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.

Acknowledgment. This work was supported by Crompton Co., the Natural Sciences and Engineering Research Council of Canada (NSERC), the Ontario Research and Development Challenge Fund, and the Environmental Science and Technology Alliance of Canada. G.E. thanks the University of Toronto for fellowship support. R.A.B gratefully acknowledges receipt of a Premier's Research Excellence Award. We thank Dr. A. B. Young for mass spectrometric analysis.

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