Efficient Copper-Catalyzed Synthesis of 4-Aminoquinazoline and 2,4-Diaminoquinazoline Derivatives

Xiaobo Yang,[a,b] Hongxia Liu,[c] Hua Fu,*[a] Renzhong Qiao,*[b] Yuyang Jiang,[c] Yufen Zhao[a]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China
Fax +86(10)62781695; E-mail: fuhua@mail.tsinghua.edu.cn

[b] State Key Laboratory of Chemical Resource Engineering, Department of Pharmaceutical Engineering, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, P. R. of China
E-mail: qiaorz@mail.buct.edu.cn

[c] Key Laboratory of Chemical Biology, Guangdong Province, College of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. of China

Received 21 September 2009

Abstract: We have developed an efficient copper-catalyzed method for the synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives via reactions of substituted 2-bromobenzonitriles with amidines or guanidine, and the method is of economical and practical advantage.

Key words: copper, Ullmann-type reaction, cross-coupling, quinazoline, synthetic method

Nitrogen-containing heterocycles are ubiquitous in nature and are well-represented among the desirable structures of modern medicinal chemistry. Quinazoline derivatives have been used as powerful inhibitors of the epidermal growth factor (EGF) receptors of tyrosine kinase,[1] ligands for benzodiazepine and GABA receptors in the CNS system[2] or as DNA binders,[3] and some of quinazoline derivatives have shown remarkable activity as anticancer,[4] antiviral,[5] and antitubercular agents.[6] The quinazoline derivatives with different substituted groups show different biological and medicinal activity. 4-Aminoquinazoline derivatives (**A** in Figure 1) have been applied as fungicides,[7] anti-inflammatory,[8] anti-cancer,[9] anti-microbial, and anti-hypertensive agents.[10] 2,4-Diaminoquinazoline derivatives have also shown unique biological and medicinal functions. For example trimetrexate (**B**)[11] and piritrexim (**C**)[12] in Figure 1, two lipophilic agents originally developed against cancer,[13] are now used in clinic as second-line therapy in moderate to severe PCP.[14] Some 2,4-diaminoquinazoline derivatives have been used as dihydrofolate reductase inhibitors,[15] potent and selective inhibitors of the leishmanial and trypanosomal enzymes and SMN2 promoter activators (such as **D** and **E** in Figure 1) for the potential treatment of spinal muscular atrophy.[16] Some of them have exhibited potent growth inhibition of the clinically relevant life-cycle stage of the intact parasite[17] and antitumor activity (such as **F** in Figure 1).[18] For the synthesis of 4-aminoquinazoline derivatives, most of them start from reactions of cyanophenyltriazenes,[19] *o*-azidobenzonitriles with nitriles,[20] aromatic nitriles with 2-aminobenzonitriles,[21] and 2-aminobenzonitrile and orthoesters with ammonium acetate.[22] The preparation of 2,4-diaminoquinazoline derivatives commonly uses reaction of substituted 2-fluorobenzonitriles with guanidine carbonate,[16] substituted 2-aminobenzonitriles with guani-

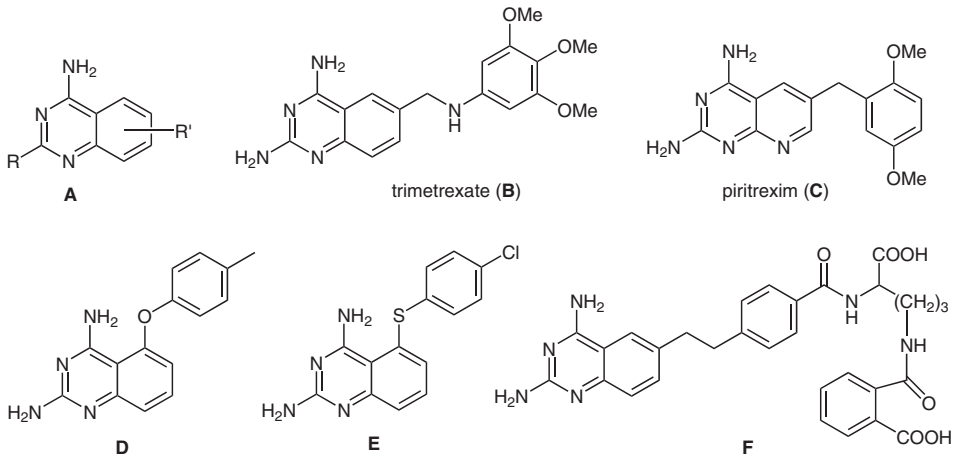


Figure 1 4-Aminoquinazoline and 2,4-diaminoquinazoline derivatives with important biological and medicinal activity

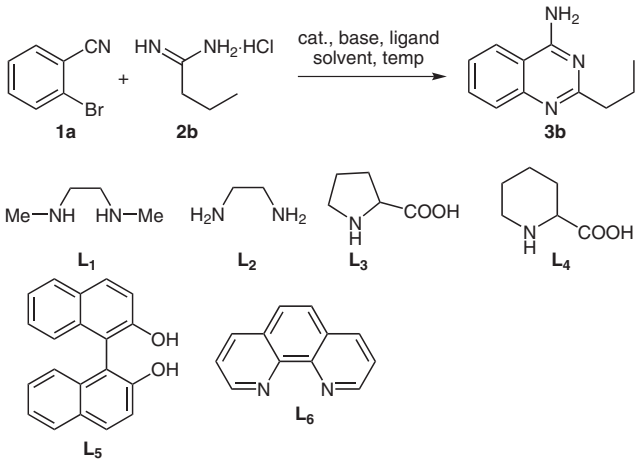
SYNLETT 2009, No. x, pp 000A–000F
Advanced online publication: xx.xx.2009
DOI: 10.1055/s-0029-1218530; Art ID: W15209ST

dine hydrochloride[15c] and chloroformamidine hydrochloride.[23] Although the previous methods for the synthesis of 2-aminoquinazoline and 2,4-aminoquinazoline derivatives are efficient, the starting materials often are not readily available or difficult to prepare. Recently, copper-catalyzed Ullmann-type N-arylations have made great progress,[24] and the N-arylation strategy has been used to make N-heterocycles.[25] We have also developed some copper-catalyzed methods for synthesis of N-heterocycles via the Ullmann-type coupling.[26] Herein, we report a simple, convenient one-pot copper-catalyzed cascade method for the synthesis of 2-aminoquinazoline and 2,4-aminoquinazoline derivatives under mild conditions.

Initially, 2-bromobenzonitrile and butyramidine hydrochloride were chosen as the model substrates to optimize reaction conditions including the catalysts, bases, and solvents under nitrogen atmosphere. As shown in Table 1, five copper catalysts were tested at 80 °C using 20 mol% *N*,*N*′-dimethylethylenediamine (DMEDA) as the ligand, 2 equiv of K_2CO_3 as the base (relative to amount of 2-bromobenzonitrile) in DMF (entries 1–5), and CuI showed the best activity (entry 1). We attempted other ligands (entries 6–10), and *N*,*N*′-dimethylethylenediamine was proved to be the most effective. Only small amount of the target product was obtained in the absence of ligand (entry 11). The effect of bases was investigated, and K_2CO_3 displayed the best results (compare entries 1, 12–14). Several solvents, DMF, DMSO, and toluene, were screened, and DMF was found to be the most effective (compare entries 1, 15, and 16). Reaction temperature was also changed, high temperature (more than 100 °C) led to small amount of unknown byproducts, but lower temperature (<60 °C) provided lower yields.

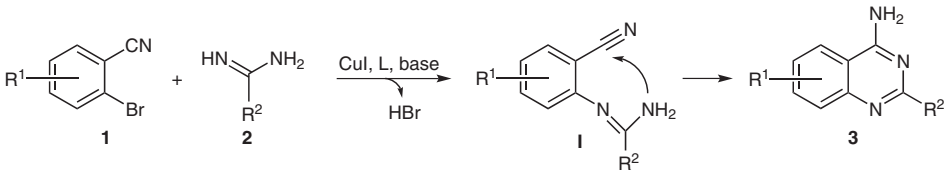
The scope of copper-catalyzed reactions of the substituted 2-bromobenzonitriles with amidines was investigated under the optimized conditions (10 mol% CuI, 20 mol% DMEDA, 2 equiv of K_2CO_3).[27] As shown in Table 2, most of the substrates examined provided good yields at 80 °C within 3–12 hours. For the substituted 2-bromobenzonitriles, the electron effect of the substituent groups could affect the reactivity of the substrates. For example, 2-bromo-4-nitrobenzonitrile showed higher reaction rates than the substrates containing electron-rich or electron-neutral groups. Aliphatic and aromatic amidines provided higher yields. Couplings of the substituted 2-bromobenzonitriles with guanidine almost quantitatively transferred into the corresponding 2,4-diaminoquinazolines, and only moderate to good isolated yields were obtained because of high polarity of the target products (entries 11–13 in Table 2).

Table 1 Copper-Catalyzed Coupling of 2-Bromobenzonitrile with Butyramidine Hydrochloride: Optimization of Conditions[a]



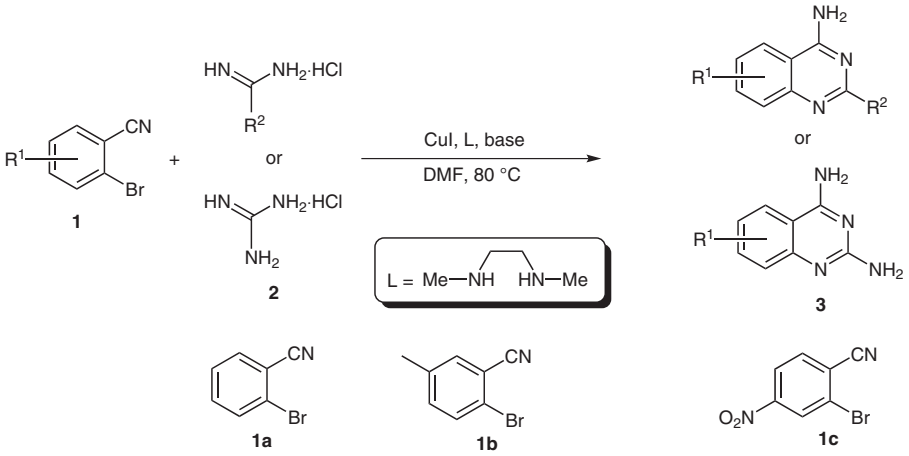
Entry	Cat.	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	**L**$_1$	K_2CO_3	DMF	79
2	CuBr	**L**$_1$	K_2CO_3	DMF	63
3	CuCl	**L**$_1$	K_2CO_3	DMF	64
4	$CuCl_2$	**L**$_1$	K_2CO_3	DMF	46
5	Cu	**L**$_1$	K_2CO_3	DMF	33
6	CuI	**L**$_2$	K_2CO_3	DMF	32
7	CuI	**L**$_3$	K_2CO_3	DMF	21
8	CuI	**L**$_4$	K_2CO_3	DMF	64
9	CuI	**L**$_5$	K_2CO_3	DMF	63
10	CuI	**L**$_6$	K_2CO_3	DMF	42
11	CuI	–	K_2CO_3	DMF	21
12	CuI	**L**$_1$	Na_2CO_3	DMF	32
13	CuI	**L**$_1$	Cs_2CO_3	DMF	57
14	CuI	**L**$_1$	K_3PO_4	DMF	19
15	CuI	**L**$_1$	K_2CO_3	DMSO	53
16	CuI	**L**$_1$	K_2CO_3	toluene	trace

[a] Reaction conditions: 2-bromobenzonitrile (1 mmol), butyramidine hydrochloride (1.2 mmol), catalyst (0.1 mmol), base (2 mmol), solvent (3 mL), 80 °C, nitrogen atmosphere, 12 h.
[b] Isolated yield.



Scheme 1 Possible formation mechanism of 4-aminoquinazoline derivatives

Table 2 Copper-Catalyzed Synthesis of 4-Aminoquinazoline and 2,4-Diaminoquinazoline Derivatives via Reactions of Substituted 2-Bromobenzonitriles with Amidines or Guanidine[a]



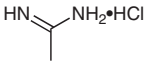
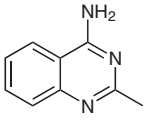
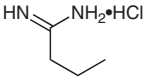
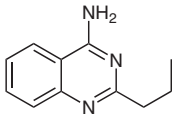
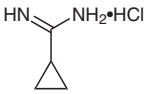
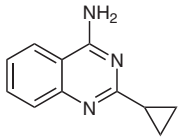
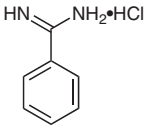
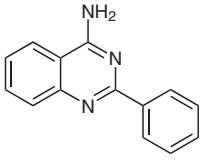
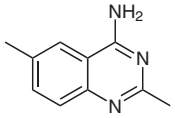
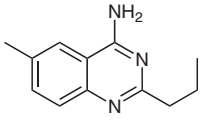
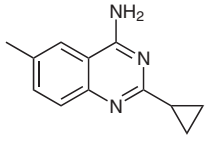
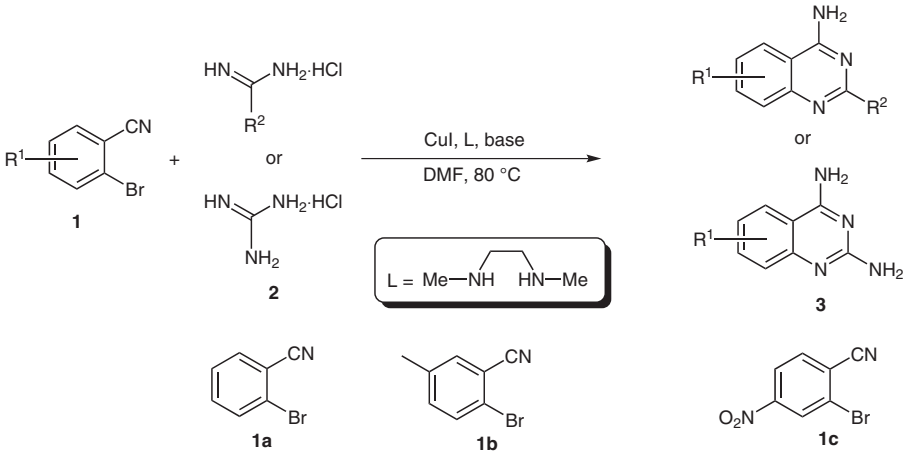
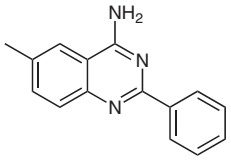
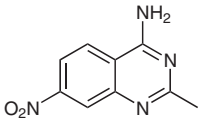
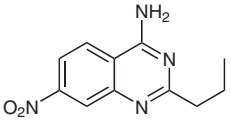
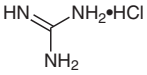
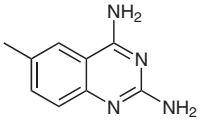
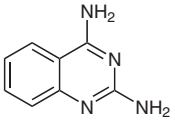
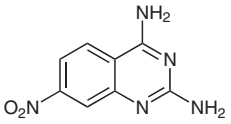
Entry	**2**	Time (h)	Product (**3**)	Yield (%)[b]
1	 **2a**	12	 **3a**	69
2	 **2b**	12	 **3b**	79
3	 **2c**	12	 **3c**	72
4	 **2d**	12	 **3d**	85
5	**2a**	12	 **3e**	75
6	**2b**	12	 **3f**	79
7	**2c**	12	 **3g**	55

Table 2 Copper-Catalyzed Synthesis of 4-Aminoquinazoline and 2,4-Diaminoquinazoline Derivatives via Reactions of Substituted 2-Bromobenzonitriles with Amidines or Guanidine[a] (continued)



Entry	2	Time (h)	Product (3)	Yield (%)[b]
8	**2d**	12	 **3h**	67
9	**2a**	3	 **3i**	63
10	**2b**	3	 **3j**	76
11	 **2e**	12	 **3k**	66
12	**2e**	12	 **3l**	57
13	**2e**	8	 **3m**	85

[a] Reaction conditions: substituted 2-bromobenzonitrile (1 mmol), amidine hydrochloride (1.2 mmol), CuI (0.1 mmol), DMEDA (0.2 mmol), base (2 mmol, Cs_2CO_3 for acetamidine hydrochloride; K_2CO_3 for others), DMF (3 mL), 80 °C, nitrogen atmosphere.
[b] Isolated yield.

A possible formation mechanism of 4-aminoquinazoline derivatives was proposed in Scheme 1. The Ullmann-type coupling reaction of the substituted 2-bromobenzonitrile with amidine first provides intermediate **I** under catalysis of CuI in the presence of base (K_2CO_3 or Cs_2CO_3). Intramolecular nucleophilic attack of amino group to *ortho*-cyano group in **I** affords the target product **3**.

In summary, we have developed a simple and efficient method for the synthesis of 2-aminoquinazoline and 2,4-diaminoquinazoline derivatives. The couplings of substituted 2-bromobenzonitriles with amidines or guanidine were performed well under mild conditions, and the target products were obtained in good yields when reaction temperature was raised to 80 °C. The present method shows economical, practical, and starting material readily available advantages over the previous methods, so it will provide opportunity for construction of diverse and useful molecules in organic chemistry and medicinal chemistry.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (Grant No. 20672065, 20732004, 20872010, 20972083), Chinese 863 Project (Grant No. 2007AA02Z160, 2006DFA43030), and the Key Subject Foundation from Beijing Department of Education (XK100030514).

References and Notes

(1) Ple, P. A.; Green, T. P.; Hennequin, L. F.; Curwen, J.; Fennell, M.; Allen, J.; Lambertvan der Brempt, C.; Costello, G. *J. Med. Chem.* **2004**, *47*, 871.

(2) (a) Colotta, V.; Catarzi, D.; Varano, F.; Lenzi, O.; Filacchioni, G.; Costagli, C.; Galli, A.; Ghelardini, C.; Galeotti, N.; Gratteri, P.; Sgrignani, J.; Deflorian, F.; Moro, S. *J. Med. Chem.* **2006**, *49*, 6015. (b) Lewerenz, A.; Hentschel, S.; Vissiennon, Z.; Michael, S.; Nieber, K. *Drug Dev. Res.* **2003**, *58*, 420.

(3) Malecki, N.; Carato, P.; Rigo, G.; Goossens, J. F.; Houssin, R.; Bailly, C.; Henichart, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 641.

(4) (a) Doyle, L. A.; Ross, D. D. *Oncogene* **2003**, *22*, 7340. (b) Henderson, E. A.; Bavetsias, V.; Theti, D. S.; Wilson, S. C.; Clauss, R.; Jackman, A. L. *Bioorg. Med. Chem.* **2006**, *14*, 5020.

(5) (a) Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem. Pharm. Bull.* **2004**, *52*, 1422. (b) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 4154.

(6) (a) Waisser, K.; Gregor, J.; Dostal, H.; Kunes, J.; Kubicova, L.; Klimesova, V.; Kaustova, J. *Farmaco* **2001**, *56*, 803. (b) Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. *Farmaco* **2000**, *55*, 725.

(7) (a) Nakagami, K.; Yokoi, S.; Nishimura, K.; Nagai, S.; Honda, T.; Oda, K.; Fujii, K.; Kobayashi, R.; Kojima, M. US 4323680, **1982**. (b) Haley, G. J. US 5373011, **1994**.

(8) (a) Palanki, M. S. S.; Suto, M. J. US 5939421, **1999**. (b) Myers, M. R.; Spada, A. P.; Maguire, M. P.; Persons, P. E.; Zilberstein, A.; Hsu, C.-Y.-J.; Johnson, S. E. US 5714493, **1998**.

(9) (a) Barker, A. J. US 5942514, **1999**. (b) Barker, A. J. US 5932574, **1999**.

(10) (a) Nauta, W. T. US 3980650, **1976**. (b) Mizogami, S.; Hiranuma, H.; Sekiya, T.; Hanazuka, M. US 4607034, **1986**.

(11) (a) Elslager, E. F.; Davoll, J. In *Lectures in Heterocyclic Chemistry 2*; Castle, R. N.; Townsend, L. B., Eds.; Hetero Corp.: Orem Utah (USA), **1974**. (b) Elslager, E. F.; Johnson, J. L.; Werbel, L. M. *J. Med. Chem.* **1983**, *26*, 1753.

(12) Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327.

(13) (a) Bertino, J. R.; Sawacki, W. L.; Moroson, B. A.; Cashmore, A. R.; Elslager, E. F. *Biochem. Pharmacol.* **1979**, *28*, 1983. (b) Weir, E. C.; Cashmore, A. R.; Dreyer, R. N.; Graham, M. L.; Hsiao, N.; Moroson, B. A.; Sawacki, W. L.; Bertino, J. R. *Cancer Res.* **1982**, *42*, 1696. (c) Duch, D. S.; Edelstein, M. P.; Bowers, S. W.; Nichol, C. A. *Cancer Res.* **1982**, *42*, 3987. (d) Lin, J. T.; Cashmore, A. R.; Baker, M.; Dreyer, R. N.; Ernstoff, M.; Marsh, J. C.; Bertino, J. R.; Whitfield, L. R.; Delap, R.; Grillo-Lopez, A. *Cancer Res.* **1987**, *47*, 609. (e) Kovacs, J. A.; Allegra, C. A.; Swan, J. C.; Drake, J. C.; Parillo, J. E.; Chabner, B. A.; Masur, H. *Antimicrob. Agents Chemother.* **1988**, *32*, 430.

(14) *Am. J. Hosp. Pharm.* **1994**, *51*, 591.

(15) (a) Graffner-Nordberg, M.; Fyfe, M.; Brattsand, R.; Mellgård, B.; Hallberg, A. *J. Med. Chem.* **2003**, *46*, 3455. (b) Graffner-Nordberg, M.; Marelius, J.; Ohlsson, S.; Persson, A.; Swedberg, G.; Andersson, P.; Andersson, S. E.; Åqvist, J.; Hallberg, A. *J. Med. Chem.* **2000**, *43*, 3852. (c) Graffner-Nordberg, M.; Kolmodin, K.; Åqvist, J.; Queener, S. F.; Hallberg, A. *J. Med. Chem.* **2001**, *44*, 2391.

(16) Thurmond, J.; Butchbach, M. E. R.; Palomo, M.; Pease, B.; Rao, M.; Bedell, L.; Keyvan, M.; Pai, G.; Mishra, R.; Haraldsson, M.; Andresson, T.; Bragason, G.; Thosteinsdottir, M.; Bjornsson, J. M.; Coovert, D. D.; Burghes, A. H. M.; Gurney, M. E.; Singh, J. *J. Med. Chem.* **2008**, *51*, 449.

(17) (a) Chowdhury, S. F.; Villamor, V. B.; Guerrero, R. H.; Leal, I.; Brun, R.; Croft, S. L.; Goodman, J. M.; Maes, L.; Ruiz-Pérez, L. M.; Pacanowska, D. G.; Gilbert, I. H. *J. Med. Chem.* **1999**, *42*, 4300. (b) Chowdhury, S. F.; Guerrero, R. H.; Brun, R.; Ruiz-Pérez, L. M.; Pacanowska, D. G.; Gilbert, I. H. *J. Enzym. Inhib. Med. Chem.* **2002**, *17*, 293. (c) Pez, D.; Leal, I.; Zuccotto, F.; Boussard, C.; Brun, R.; Croft, S. L.; Yardley, V.; Ruiz-Pérez, L. M.; Gonzalez-Pacanowska, D.; Gilbert, I. H. *Bioorg. Med. Chem.* **2003**, *11*, 4693.

(18) Vaidya, C. M.; Wright, J. E.; Rosowsky, A. *J. Med. Chem.* **2002**, *45*, 1690.

(19) Stevens, M. F. G. *J. Chem. Soc. C* **1967**, 1096.

(20) Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 534.

(21) Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215.

(22) Rad-Moghadam, K.; Samavi, L. *J. Heterocycl. Chem.* **2006**, *43*, 913.

(23) Rosowsky, A.; Chen, H. *J. Org. Chem.* **2001**, *66*, 7522.

(24) For recent reviews on copper-catalyzed *N*-arylation, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054; and references cited therein.

(25) For recent studies on the synthesis of N-heterocycles through Ullmann-type couplings, see: (a) Martin, R.; Rodríguez, R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351. (d) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2598. (e) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510.

(26) (a) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 348. (b) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333. (c) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 7841.

(27) **General Procedure for the Synthesis of Compounds 3a–m**

A 25 mL round-bottom flask was charged with a magnetic stirrer and DMF (3 mL), substituted 2-bromobenzonitrile (**1**, 1 mmol), amidine hydrochloride (**2**, 1.2 mmol), DMEDA (0.2 mmol, 18 mg), and K_2CO_3 (2 mmol, 138 mg) [2 mmol (656 mg) of Cs_2CO_3 were used for acetamidine hydrochloride] after stirring of the mixture for 15 min under nitrogen atmosphere, and CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was stirred at 80 °C for the time indicated in Table 2. The resulting mixture was cooled to r.t. and filtered. The solid was washed with DMF (2 × 3 mL), and the combined filtrate was concentrated by the rotary evaporator, and the residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH (40:1 to 5:1) as eluent to give the desired product.

Cyclopropyl-4-aminoquinazoline (3c)

Eluent $CHCl_3$–MeOH (40:1). Yield 134 mg (72%). White solid; mp 198–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.12 (d, 1 H, *J* = 7.9 Hz), 7.58 (m, 4 H), 7.34 (t, 1 H, *J* = 7.4 Hz), 1.99 (m, 1 H, *J* = 7.5 Hz), 1.05–0.87 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.6, 162.3, 150.5, 133.2, 126.9, 124.5, 124.0, 113.4, 18.4, 9.4. HRMS: *m/z* calcd for $C_{11}H_{11}N_3$ $[M + H]^+$: 186.1031; found: 186.1037.