JOC*Note*

2-Aminopyrimidine-4,6-diol as an Efficient Ligand for Solvent-Free Copper-Catalyzed N-Arylations of Imidazoles with Aryl and Heteroaryl Halides

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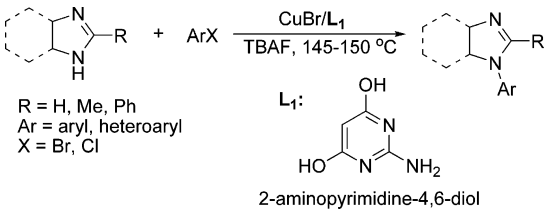
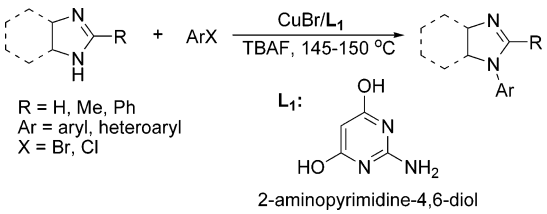


Efficient and solvent-free copper-catalyzed N-arylations of imidazoles with aryl and heteroaryl halides have been demonstrated. In the presence of CuBr, 2-aminopyrimidine-4,6-diol, and TBAF (*n*-Bu_4NF), a variety of imidazoles underwent the N-arylation reaction with aryl and heteroaryl halides smoothly in moderate to excellent yields. Noteworthy is that the reaction is conducted under solvent-free conditions.

N-Aryl imidazoles play an important role as structural and functional units in many natural products and biologically active compounds.[1] Accordingly, many efficient and selective methods have been provided for their synthesis.[2−7] Recently, the copper-catalyzed N-arylations of imidazoles with aryl halides promoted by a ligand attracted much attention due to its economy and efficiency.[3−5] These highly efficient ligands included 1,10-phenanthroline derivatives,[5a−d] diamines,[5e−g] aminoarenethiol,[5h] amino acid derivatives,[5i−k] 8-hydroxyquinoline,[5l] pyrrolidine-2-phosphonate,[5m] oxime-phosphine oxides,[5n] and phosphoramidite.[5o] Although these ligands combined with copper as efficient catalytic systems for the N-arylations of imidazoles with aryl iodides and bromides with a range of electronic and steric properties are now extensively developed, only a few catalysts extended the scope to both hindered substrates and less active aryl halides (aryl bromides and aryl chlorides). In particular, few papers on the N-arylations of imidazoles with heteroaryl halides catalyzed by copper have been reported.[5j,k,n−q] Moreover, harmful solvents were required in almost all cases.[5,8] Very recently, we found that pyrimidines were effective ligands to improve the palladium-catalyzed cross-coupling reactions.[9] On the other hand, we have also discovered that TBAF is a suitable base for some solvent-free palladium-catalyzed cross-couplings.[10] As a continued interest in developing efficient and greener processes, we expected to apply these ligands and base in the N-arylation reaction. As expected, both aryl and heteroaryl halides underwent the solvent-free N-arylation reaction with imidazoles smoothly in the present of TBAF when a combination of CuBr and 2-aminopyrimidine-4,6-diol was employed as the catalytic system (Scheme 1). In addition, it was found that DMF, the reported effective solvent,[5] has a deleterious effect on the reaction.

SCHEME 1



The N-arylation of imidazole (**1a**) with 1-bromo-4-methoxybenzene (**2a**) in the presence of 3 equiv of TBAF was studied to identify a suitable catalyst and ligand. As shown in Table 1, a number of pyrimidines as the ligand were first tested. The results demonstrated that the reactivity of the ligands was dependent on the substituents on the pyrimidine ring and that

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(3) For selected reviews on the use of copper as the catalyst, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

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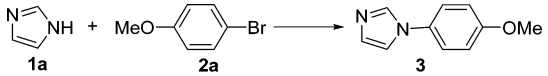
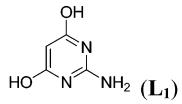
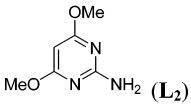
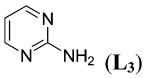
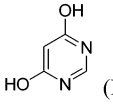
TABLE 1. Screening Reaction Conditions for Copper-Catalyzed N-Arylation of Imidazole (1a) with 1-Bromo-4-methoxybenzene (2a)[a]



1a **2a** **3**

entry	[Cu]	ligand	yield (%)[b]
1	CuI	—	trace
2	CuI	 (**L$_1$**)	68
3	CuI	 (**L$_2$**)	47
4	CuI	 (**L$_3$**)	43
5	CuI	 (**L$_4$**)	42
6	CuBr	(**L$_1$**)	90
7	CuCl	(**L$_1$**)	36
8	Cu_2O	(**L$_1$**)	15
9[c]	CuBr	(**L$_1$**)	38
10[d]	CuBr	(**L$_1$**)	10
11[e]	CuBr	(**L$_1$**)	12
12[f]	CuBr	(**L$_1$**)	32
13[g]	CuBr	(**L$_1$**)	20
14[h]	CuBr	(**L$_1$**)	trace

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), [Cu] (10 mol %), ligand (20 mol %) and TBAF (3 mmol) under Ar atmosphere at 145−150 °C for 24 h. [b] Isolated yield. [c] DMF (1 mL) was added. [d] Cs_2CO_3 (3 mmol) instead of TBAF. [e] KF (3 mmol) instead of TBAF. [f] TEAC ($(Et_4N)_2CO_3$; 3 mmol) instead of TBAF. [g] Et_3N (3 mmol) instead of TBAF. [h] At 100 °C.

2-aminopyrimidine-4,6-diol (**L$_1$**) bearing both hydroxyl and amino group was the most effective ligand (entries 1−5). Without the aid of any ligands, treatment of substrate **1a** with **2a**, CuI, and TBAF afforded a trace amount of the corresponding desired product **3** after 24 h (entry 1), whereas the yield of **3** was enhanced sharply to 68% in 24 h when 20 mol % of 2-aminopyrimidine-4,6-diol, a ligand, was added (entry 2). Other ligands, such as **L$_2$** and **L$_3$** without a free hydroxyl group and **L$_4$** having no amino group, gave the target product **3** under a 50% isolated yield (entries 3−5). Other copper compounds were then evaluated (entries 6−8). We were happy to observe that the yield of **3** was increased dramatically to 90% when CuBr was used as the catalyst instead of CuI (entries 2 and 6). However, both CuCl and Cu_2O are inferior to CuI (entries 7 and 8). To our surprise, DMF, the reported effective solvent,[5] suppressed the reaction (entries 6 vs 9). The effect of bases was also investigated, and TBAF provided the best results (entries 10−13). It was disclosed that the reaction temperature had a fundamental influence on the reaction, and almost no reaction was observed at 100 °C (entry 14).

The efficacy of the CuBr/**L$_1$**/TBAF system for general N-arylations of imidazoles with aryl and heteroaryl halides was further evaluated, and the results are summarized in Table 2. In the presence of CuBr (10 mol %), **L$_1$** (20 mol %), and TBAF (3 equiv), the N-arylation of imidazole (**1a**) with aryl bromide **2b** or heteroaryl bromide **2c** was conducted smoothly to afford the corresponding products **4** and **5** in 96 and 80% yields, respectively (entries 1 and 2). However, the reaction of substrate **1a** with chloride **2d** was unsuccessful (entry 3). Gratifyingly, we found that substrate **1a** reacted efficiently with 2-chloropyrimidine (**2e**), a heteroaryl chloride, in a 90% yield (entry 4). Encouraged by these results, a variety of aryl and heteroaryl halides **2a**−**m** was then treated with benzimidazole (**1b**) under the standard reaction conditions (entries 5−17). The results indicated that both aryl and heteroaryl halides all work well with substrate **1b** to generate the corresponding products in moderate to excellent yields. For example, the less activated bromide **2a** was reacted with **1b** in an 81% yield (entry 5). A 40% yield was still achieved even in the N-arylation of **1b** with chlorobenzene (**2l**) (entry 16). Satisfactory results were also obtained for nitrogen- and/or sulfur-containing heteroaryl halides (entries 7, 9, 12−15, and 17). Gratifyingly, substrate **1c** or **1d**, two hindered 2-methylimidazoles, underwent the N-arylation reaction with **2c** and/or **2e** smoothly in good yields (entries 18−

(5) For papers on the copper-catalyzed N-arylations of imidazoles with aryl halides, see: (a) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; Kamer van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405. (c) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779. (d) Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405. (e) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (f) Alcalde, E.; Dinarès, I.; Rodríguez, S.; Garcia de Miguel, C. *Eur. J. Org. Chem.* **2005**, 1637. (g) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (h) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241. (i) Ma, D.; Cai, Q. *Synlett* **2004**, 128. (j) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (k) Lv, X.; Wang, Z.; Bao, W. *Tetrahedron* **2006**, *62*, 4756. (l) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135. (m) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107. (n) Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553. (o) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435. (p) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948. (q) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778.

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(8) For a paper on the solvent-free copper-catalyzed amination reactions of aryl halides with amines, see: Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Chem. Commun.* **2004**, 1994.

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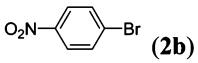
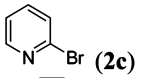
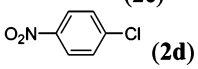
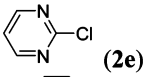
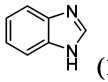
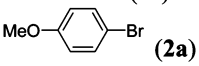
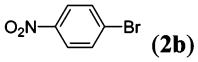
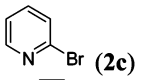
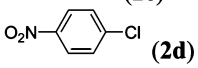
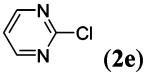
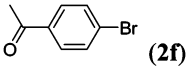
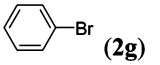
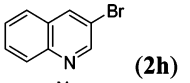
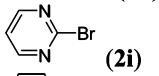
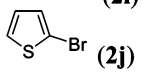
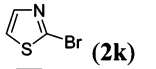
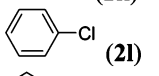
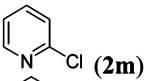
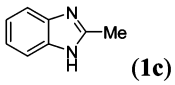
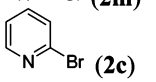
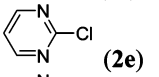
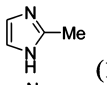
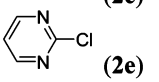
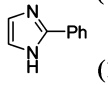
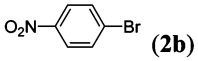
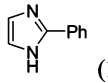
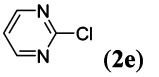
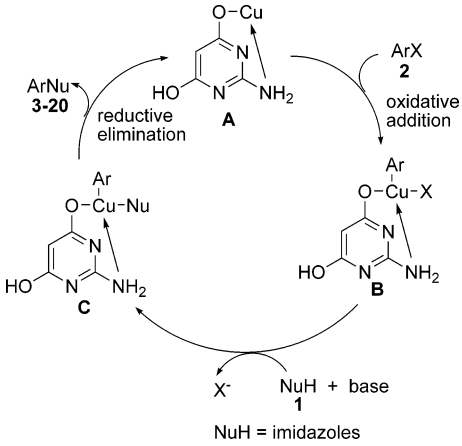
TABLE 2. N-Arylations of Imidazoles (1) with Aryl or Heteroaryl Halides (2) in the Presence of CuBr, L_1, and TBAF[a]

entry	imidazole	halide	yield(%)
1	 (**1a**)	 (**2b**)	96 (**4**)
2	(**1a**)	 (**2c**)	80 (**5**)
3	(**1a**)	 (**2d**)	trace (**4**)
4	(**1a**)	 (**2e**)	90 (**6**)
5	 (**1b**)	 (**2a**)	81 (**7**)
6	(**1b**)	 (**2b**)	95 (**8**)
7	(**1b**)	 (**2c**)	99 (**9**)
8	(**1b**)	 (**2d**)	74 (**8**)
9	(**1b**)	 (**2e**)	100 (**10**)
10	(**1b**)	 (**2f**)	92 (**11**)
11	(**1b**)	 (**2g**)	86 (**12**)
12	(**1b**)	 (**2h**)	63 (**13**)
13	(**1b**)	 (**2i**)	100 (**10**)
14	(**1b**)	 (**2j**)	62 (**14**)
15	(**1b**)	 (**2k**)	55 (**15**)
16	(**1b**)	 (**2l**)	40 (**12**)
17	(**1b**)	 (**2m**)	56 (**9**)
18	 (**1c**)	 (**2c**)	95 (**16**)
19	(**1c**)	 (**2e**)	78 (**17**)
20	 (**1d**)	 (**2e**)	100 (**18**)
21	 (**1e**)	 (**2b**)	30 (**19**)
22	 (**1e**)	 (**2e**)	trace (**20**)

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CuBr (10 mol %), L_1 (20 mol %), and TBAF (3 mmol) under Ar atmosphere at 145−150 °C for 24 h. [b] Isolated yield.

SCHEME 2



20). However, the N-arylation of 2-phenylimidazole (**1e**) was unsuccessful (entries 21 and 22). For example, treatment of substrate **1e** with the activated bromide **2b**, CuBr (10 mol %), L_1 (20 mol %), and TBAF (3 equiv) provided the target product **19** in a low yield (a 30% isolated yield; entry 21).

As described in Scheme 2, we have formulated a working mechanism for the solvent-free copper-catalyzed N-arylations of imidazoles that is based on the previously proposed mechanism.[3,5,11,12] The chelation of Cu(I) with an 2-aminopyrimidine-4,6-diol occurs to make the Cu(I) species more reactive toward oxidative addition and/or stabilized intermediate **B**[12] that was generated from the oxidative addition of **A** with aryl halides. In the presence of base, imidazoles reacted with intermediate **B** readily to afford intermediate **C**, followed by reductive elimination to provide the desired product and regenerate the active Cu(I) species. We inferred that CuBr is the best catalyst for the present reaction by virtue of its insensitivity to light and air. Study of the accurate mechanism is in progress.

In summary, we have disclosed that 2-aminopyrimidine-4,6-diol acted as an efficient and general ligand for the solvent-free copper-catalyzed N-arylations of imidazoles, including 2-substituted imidazoles, with a diverse range of aryl and heteroaryl halides providing moderate to excellent yields. It is noteworthy that the present reaction is conducted under solvent-free conditions. Moreover, the presence of DMF has a deleterious effect on the reaction. Overall, the present protocol significantly advances the scope of N-arylations of imidazoles and is of great value to the research and development efforts in the pharmaceutical industry. Efforts to extend the applications of the CuBr/pyrimidine/TBAF system in the formation of other C−N bond transformations are currently underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Solvent-Free Copper-Catalyzed N-Arylation of Imidazoles. A mixture of imidazole **1** (1.0 mmol), aryl halide **2** (1.2 mmol), CuBr (10 mol %), 2-aminopyrimidine-4,6-diol (L_1, 20 mol %), and TBAF (3 mmol)

(11) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, *15*, 3555. (c) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496. (d) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565.

(12) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

was stirred at 145−150 °C for 24 h until complete consumption of starting material was monitored by TLC. After the reaction was finished, ethyl acetate was poured into the mixture, then washed with water, extracted with diethyl ether, dried over anhydrous Na_2SO_4, and evaporated under vacuum, and the residue was purified by flash column chromatography (ethyl acetate or hexane/ethyl acetate) to afford the desired product.

1-(Pyrimidin-2-yl)-1*H*-benzimidazole (10): White solid, mp 108.4 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.79 (d, J = 4.8 Hz, 2H), 8.62 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.46−7.38 (m, 2H), 7.23 (t, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 156.4, 145.1, 141.8, 131.9, 124.6, 123.8, 120.4, 118.0, 115.6; LRMS (EI, 20 eV) *m*/*z* (%) 196 (M^+, 100); HRMS (EI) for $C_{11}H_8N_4$ (M^+) calcd 196.0749, found 196.0749.

1-(Thiazol-2-yl)-1*H*-benzimidazole (15): Yellow solid, mp 100.9 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 7.49−7.41 (m, 2H), 7.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 144.2, 141.2, 140.5, 131.9, 125.0, 124.1, 121.0, 115.1, 112.3; LRMS (EI, 20 eV) *m*/*z* (%) 201 (M^+, 100); HRMS (EI) for $C_{10}H_7N_3S$ (M^+) calcd 201.0361, found 201.0360.

2-Methyl-1-(pyrimidin-2-yl)-1*H*-benzimidazole (17): Slight yellow solid, mp 77.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 2H), 8.26 (t, J = 3.0 Hz, 1H), 7.74−7.72 (m, 1H), 7.33−7.22 (m, 3H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.2, 152.7, 142.7, 134.0, 123.4, 119.0, 118.0, 114.4, 18.4; LRMS (EI, 20 eV) *m*/*z* (%) 210 (M^+, 100); HRMS (EI) for $C_{12}H_{10}N_4$ (M^+) calcd 210.0906, found 210.0905.

2-(2-Methyl-1*H*-imidazol-1-yl)pyrimidine (18): Slight yellow solid, mp 90.3−90.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75−8.70 (m, 2H), 7.85 (d, J = 6.0 Hz, 1H), 7.19 (t, J = 9.7 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.3, 146.7, 127.5, 118.4, 118.2, 18.0; LRMS (EI, 20 eV) *m*/*z* (%) 160 (M^+, 100); HRMS (EI) for $C_8H_8N_4$ (M^+) calcd 160.0749, found 160.0747.

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Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for products **3**−**19**, and typical procedure for the solvent-free copper-catalyzed N-arylation of imidazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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