JOC*Note*

A Soluble Base for the Copper-Catalyzed Imidazole N-Arylations with Aryl Halides†

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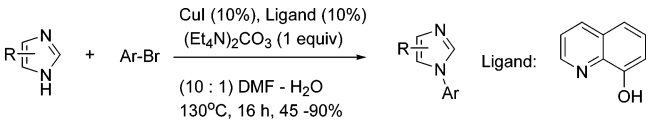

CuI-catalyzed N-arylation of imidazoles with aryl bromides has been achieved in a near-homogeneous system that utilizes tetraethylammonium carbonate as base, 8-hydroxyquinoline as ligand, and H_2O as cosolvent. Preliminary results with aryl chlorides are also reported.

Copper-catalyzed C−N, C−O, and C−S bond formations between aryl halides and NH, OH, SH-containing heterocycles have evolved as a major method for the synthesis of novel heterocyclic compounds.[1] One exception, however, has been the imidazole N-arylation with aryl halides.

N-Arylimidazoles have been recorded in medicinal,[2] biological,[3] and recently, in the area of N-heterocyclic carbene chemistry.[4] Traditionally, these compounds were synthesized via S_NAr substitution of imidazoles with aryl halides bearing electron-withdrawing substituents[5] or via the Ullmann-type coupling at high temperatures.[6] The Lam−Chan reaction (Cu-catalyzed cross-coupling between imidazoles and aryl boronic acids) has emerged as a method of choice partly because it requires much lower temperatures.[7] However, it is often necessary to optimize the conditions (solvent,[8] base,[9] additive,[10] and substrate types[11]) for a given reaction. In addition, one is limited by the high cost and poor availability of functionalized boronic acids.

Other types of cross-coupling reagent for the synthesis of *N*-arylimidazoles include (*p*-Tol)$Pb(OAc)_3$,[12] $(Ph)_3Bi$,[13] $ArSnR_3$,[14] $ArSi(OR)_3F^-$,[15] and Ar_2IBr.[16] These reagents are generally less accessible, and some are highly toxic. Therefore, methods that circumvent these limitations are highly desirable.

In 1999, Buchwald reported the first catalytic Ullmann coupling of imidazoles with aryl halides at low temperatures (110 °C) with $(CuOTf)_2$−PhH as catalyst.[17] Key features of the Buchwald protocol are (1) the use of

† This article is dedicated to Prof. Gilbert Stork on the occasion of his 84th birthday.

(1) For reviews on Cu-catalyzed coupling reactions, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364. For recent examples of Cu-catalyzed N-arylations with aryl halides, see: (e) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428 and references therein. (f) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987−4990. (g) Kwong, F. Y.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 793−796. (h) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385−3386.

(2) For examples of cAMP PDE inhibitor, see: (a) Venuti, M. C.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M. *J. Med. Chem.* **1988**, *31*, 2136−2145. Thromboxane synthase inhibitor: (b) Martinez, G. R.; Walker, K. A. M.; Hirschfeld, D. R.; Bruno, J. J.; Yang, D. S.; Maloney, P. J. *J. Med. Chem.* **1992**, *35*, 620−628. (c) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M. *J. Med. Chem*. **1981**, *24*, 1139−1148. (d) Cozzi, P.; Carganico, G.; Fusar, D.; Grossoni, M.; Menichincheri, M.; Pinciroli, V.; Tonani, R.; Vaghi, F.; Salvati, P. *J. Med. Chem.* **1993**, *36*, 2964−2972. (e) Qiao, J. X.; Cheng, X.; Modi, D. P.; Rossi, K. A.; Luettgen, J. M.; Knabb, R. M.; Jadhav, P. K.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 29−35. Angiotensin-II agonist: (f) Wan, Y.; Wallinder, C.; Plouffe, B.; Beaudry, H.; Mahalingam, A. K.; Wu, X.; Johansson, B.; Holm, M.; Botoros, M.; Karlen, A.; Pettersson, A.; Nyberg, F.; Faendriks, L.; Gallo-Payet, N.; Hallberg, A.; Alterman, M. *J. Med. Chem*. **2004**, *47*, 5995−6008. Cardiotonic agent: (g) Sircar, I.; Weishaar, R. E.; Kobylarz, D.; Moos, W. H.; Bristol, J. A. *J. Med. Chem*. **1987**, *30*, 1955−1962 and references therein. (h) Güngör, T.; Fouquet, A.; Teulon, J.-M.; Provost, D.; Cazes, M.; Cloarec, A. *J. Med. Chem*. **1992**, *35*, 4455−4463. Carbonic anhydrase inhibitor: (i) Lo, Y. S.; Nolan, J. C.; Maren, T. H.; Welstead, W. J., Jr.; Gripshover, D. F.; Shamblee, D. A. *J. Med. Chem*. **1992**, *35*, 4790−4794. AMPA antagonist: (j) Ohmori, J.; Shimizu-Sasamata, M.; Okada, M.; Sakamoto, S. *J. Med. Chem*. **1996**, *39*, 3971−3979. COX inhibitor: (k) Almansa, C.; Bartroli, J.; Belloc, J.; Cavalcanti, F. L.; Ferrando, R.; Gomez, L. A.; Ramis, I.; Carceller, E.; Merlos, M.; Garcia-Rafanell, J. *J. Med. Chem*. **2004**, *47*, 5579−5582. PDE-4 inhibitor: (l) Jiang, W.; Guan, J.; Macielag, M. J.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2005**, *48*, 2126−2133. Bradykinin B1 antagonist: (m) Su, D.-S.; Markowitz, M. K.; Murphy, K. L.; Wan, B.-L.; Zrada, M. M.; Harrell, C. M.; O'Malley, S. S.; Hess, J. F.; Ransom, R. W.; Chang, R. S.; Wallace, M. A.; Raab, C. E.; Dean, D. C.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6045−6048. CB-1 antagonist: (n) Lange, J. H. M.; van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Looff, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823−1838. PDGFR inhibitors: (o) Zhong C.; He, J.; Xue, C.; Li, Y. *Bioorg. Med. Chem*. **2004**, *12*, 4009−4015 and references therein.

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(8) For reactions performed in H_2O or MeOH, see: (a) Collman, J. P.; Zhong M.; Zeng, Li.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528−1531. (b) Lan, J.-B.; Chen, L.; Yu, X.-Q.; You, J.-S.; Xie, R. G. *Chem. Commun.* **2004**, *2*, 188−189.

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(11) Electron-rich substrates may result in low yield under the oxidative condition (Collman J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236), except with excess $ArB(OH)_2$ or in protic solvents (cf. ref 8b).

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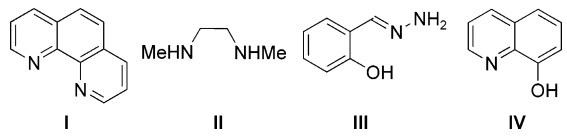
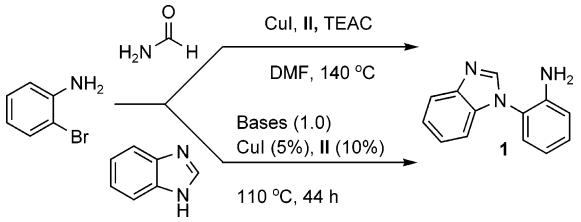


FIGURE 1. Ligands for Cu-catalyzed N-arylations of imidazoles.

stoichiometric amount (relative to halide) of 1,10-phenanthraline (**I**, Figure 1) along with a secondary ligand, dibenzylidene acetone (dba, 5%), for maintaining reproducibility, (2) high substrate concentrations ([ArX] $\approx$ 2.5−5 M), and (3) the use of relatively insoluble inorganic base (Cs_2CO_3) in nonpolar solvent (xylenes). This procedure was modified by Hanzlik, who used DMF (20%) as cosolvent to accommodate the poor solubility of functionalized substrate (N-Ac-L-His-OMe) in the synthesis of N^{τ}-arylhistidine derivatives (12% yield from iodobenzene).[18]

Subsequently, Buchwald has shown that 1,2-diamines (10%, such as **II**), in combination with catalytic amounts of **I** (10−20%), promoted CuI-catalyzed coupling of imidazoles with aryl iodides in dioxane or DMF.[19] Recently, Cristau et al.[20] reported that salicylaldehyde-derived ligands such as **III** (20%) promoted Cu_2O-catalyzed N-arylations of imidazoles with aryl halides in MeCN. These examples represented significant advances in the synthesis of *N*-arylazoles in general and *N*-arylimidazoles in particular. Most importantly, they demonstrated the critical role of ligands in Cu-catalyzed cross-coupling reactions with aryl halides. However, both Buchwald and Cristau's systems still rely on the use of excess Cs_2CO_3 at high substrate concentrations (>1.7 M). As a result, maintaining efficient mixing of these highly heterogeneous, multicomponent systems presents an operational challenge that may affect the reproducibility of these reactions, especially on large scales. So far, most of the aryl halides reported in the N-arylation of imidazoles, already limited in examples, were aryl iodides,[21] with only four tested substrates being aryl bromides.[22] Clearly there is a need to develop a process that allows direct coupling of a wide range of aryl halides with imidazoles,

SCHEME 1



by far the least reactive NH-containing azoles in cross-coupling reactions. We wish to disclose an alternative system that employs a *soluble* base (1.1 equiv) and a readily available ligand for the CuI-catalyzed N-arylation of imidazoles with aryl iodides, aryl bromides, and even aryl chlorides.

During a study on the Goldberg amidation under the Buchwald protocol,[23] we discovered that bis(tetraethylammonium) carbonate, $(Et_4N)_2CO_3$ (TEAC),[24] which unlike K_2CO_3 or Cs_2CO_3 dissolves in the mixture, promotes the CuI-catalyzed N-arylation of benzimidazoles with aryl halides in DMF. For example, the reaction between 2-bromoaniline and formamide led to 2-(1*H*-benzo[*d*]-imidazol-1-yl)benzenamine (**1**) as the major product (Scheme 1).[25] Presumably, the initial amidation product was converted in situ into benzimidazole,[26] the latter then underwent *rapid* N-arylation with the remaining aryl bromide to form the observed end product (**1**).

Support for the above hypothesis can be drawn from the reaction between *benzimidazole* and 2-bromoaniline: the desired product (**1**) was formed cleanly in high yield with TEAC (96%) in contrast to low (~40%) conversion with other bases such as K_2CO_3.[27]

The superiority of TEAC as base for the N-arylation is further illustrated in Table 1. Under the conditions of Buchwald,[17,19a,b] 1-iodo-3,5-bis(trifluoromethyl)benzene was converted to **2** in >97% yield after 10 h with TEAC, whereas twice as much time was needed to reach similar conversion with Cs_2CO_3 as base. Similarly, with the less reactive substrate 1-bromo-3,5-dimethylbenzene, the use of TEAC resulted in higher conversion to **3** (61%) than of Cs_2CO_3 (44%).[27] To the best of our knowledge, this is the first time an organic carbonate salt had been reported in metal-catalyzed cross-coupling with aryl halides.[28] Most significantly, the improved efficiency in the reaction of 1-*bromo*-3,5-dimethylbenzene suggested that TEAC as a base might be useful in expanding the scope of

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(19) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. A later publication suggested that either *trans*-1,2-cyclohexanediamine or 1,10-phenanthroline was sufficient for aryl iodides: (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578−5587.

(20) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.−Eur. J.* **2004**, *10*, 5607−5622. This report appeared after the completion of our own work. As a result, we have not performed direct comparison with ligand **III**.

(21) Proline-promoted Ullmann coupling: (a) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496−499. (b) Ma, D.; Cai, Q. *Synlett* **2004**, 128−130.

(22) A ligandless N-arylation of (*S*)-1-(3-bromophenyl)-ethylamine under microwave heating (195 °C and 2−3 h): Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* **2003**, *44*, 4217−4218.

(23) See ref 1e and references therein.

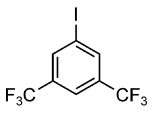
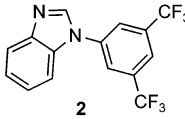
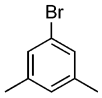
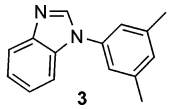
(24) (a) TEAC is very soluble in most organic solvents and gives nearly homogeneous reaction mixtures. The commercial material from Fluka (90% or 95%) was used in this study. (b) Other soluble bases such as pyridine and TBAF did not yield any products.

(25) Based on LC−MS analyses. Some optimizations were carried out under microwave heating at various temperatures.

(26) This type of in situ conversion to benzimidazole had been observed before (personal communication with Prof. Stephen L. Buchwald at MIT, 2004).

(27) (a) Conversion based on LC−MS analyses. The isolated yield of **1** was 63% from TEAC. (b) These reactions were run in a sealed tube without using any inert gases. (c) Examples of other inorganic bases screened include Cs_2CO_3, K_3PO_4, $CaCO_3$, and MgO. These experiments were conducted under microwave heating (Smith Synthesizer, from Personal Chemistry, 180 °C, 20 min total) under identical conditions (CuI, **IV**, DMF).

TABLE 1. Effect of Bases on Reaction Rate[a,e]

aryl Halide	product	base (equiv)	conversion (yd) %
	 **2**	TEAC (1.0)	>97 (76)[b]
		Cs_2CO_3 (2.0)	87[b] 94 (70)[c]
	 **3**	TEAC (1.0)	61 (32)[d]
		Cs_2CO_3 (2.0)	44 (20)[d]

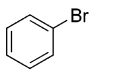
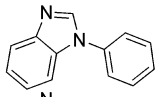
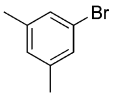
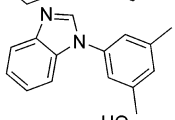
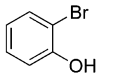
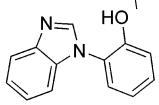
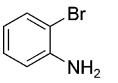
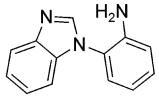
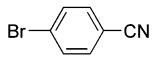
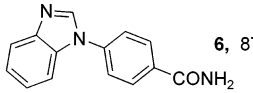
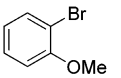
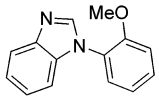
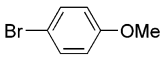
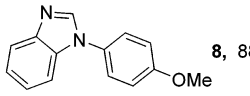
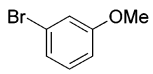
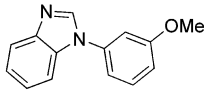
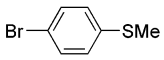
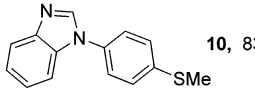
[a] 110 °C, ArX (1.0), BzImd (1.15), CuI (10%), ligand (20%), DMF (1.0 mL). [b] 10 h. [c] 22 h. [d] 60 h. [e] **I** was used with Cs_2CO_3, whereas **II** (cf. ref 19a) was used for TEAC.

imidazolyl N-arylations from traditional aryl iodides as substrates to include aryl bromides in general.

Indeed, further optimization of the reaction conditions led to the following observations: (1) 8-hydroxyquinoline (**IV**)[29] is more effective as a ligand than either 1,10-phenanthroline (**I**)[17] or the 1,2-diamine ligands (**II**);[19] (2) the ratio of **IV** to CuI (10% mol) can be reduced from the conventional 2:1 to 1:1 without noticeable reduction in the reaction yield; (3) addition of a small amount of H_2O as cosolvent significantly accelerates the N-arylation reaction.[30] These findings have made it possible, for the first time, to effectively *convert nonactivated*[31] *aryl bromides to N-aryl benzimidazoles at reasonable temperatures (130 °C).* Table 2 summarizes the reaction of benzimidazole with a wide range of aryl bromides under the current protocol.[32,33] The reaction worked well with aryl bromides bearing both nonpolar and polar (OH, NH_2, OMe, SMe) groups except for the nitrile group that was hydrolyzed to the carboxyamide (**6**, entry 5).

Cu-catalyzed N-arylations are known to be very sensitive to steric hindrance. In Table 3, substrates with varying degrees of substitution proximal to the reaction centers (excluding chelating groups[31]) were examined. When either *o*-alkyl-substituted aryl bromides or 2-alkyl imidazoles were reacted with their nonhindered counterparts, modest yields were still achieved (entries 2−5).[33]

TABLE 2. N-Arylation of Benzimidazole with ArBr[a]

entry	Ar-X	product	yield
1			**4**, 85[b]
2			**3**, 90[c]
3			**5**, 62
4			**1**, 67
5			**6**, 87
6			**7**, 64[d]
7			**8**, 88
8			**9**, 87
9			**10**, 83

[a] Conditions: 130 °C for 16 h, ArBr (1.0), BzImd (1.15), TEAC (1.0), CuI (10%), **IV** (10%), DMF (1.0 mL), H_2O (0.1 mL). [b] 24 h. [c] 70 h at 120 °C. [d] 64 h, (∼10% **5** was formed).

However, only a trace of the product was observed when 2-phenyl imidazole and 2-bromotoluene (entry 6) were coupled, suggesting that concurrent steric hindrance from both substrates is incompatible in the current system.

Preliminary results also suggest that the current system can be applied to aryl chlorides. For example *p*-CF_3-PhCl and *m*-Me-PhCl[34] were converted to **17** and **18** in 50 and 40% isolated yields, respectively (Figure 2). To date, this constitutes *the first soluble copper-ligand system that at relatively low temperatures catalyzes the N-arylation of an imidazole by ArCl.*[35]

In summary, a near homogeneous system for the synthesis of *N*-arylimidazoles has been established that features the use of a readily available, crystalline ligand (**IV**), H_2O as cosolvent, and a soluble carbonate (TEAC) as base. The system is effective for aryl iodide, aryl bromides, and, to a less extent, for simple aryl chlorides. It is anticipated that, because it is homogeneous, this

(28) (a) $(NH_4)_2CO_3$ and polymer-supported carbonate were ineffective. (b) TEAC as carboxylating reagents: Arcadi, A.; Inesi, A.; Marinelli, F.; Rossi, L.; Verdecchia, M. *Synlett* **2005**, 67−70 and references therein. (c) TEAC as base for sulfide synthesis: Feroci, M.; Inesi, A.; Rossi, L. *Synth. Commun.* **1999**, *29,* 2611−2615.

(29) For use of quinolinol ligands in biaryl ether synthesis, see: Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051.

(30) (a) We found the optimal ratio to be 10−26% H_2O in DMF (v/v). H_2O also accelerates reactions with Cs_2CO_3 to a smaller extent. For example, **3** (Table 2) reached 80 and 60% after 7 h with TEAC and Cs_2CO_3 (Aldrich) as bases, respectively. Both reactions went to completion after 24 h. (b) Effect of H_2O on the amination reactions has been controversial. For a recent example, see: Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010−6017.

(31) A comparison between Scheme 1 and Table 1 offers an example of possible chelation (substrate based) assisted Cu catalysis. We suspect that this was the case in the N-arylation of purine (ref 19b).

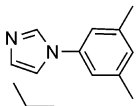
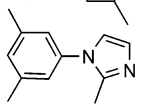
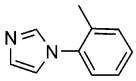
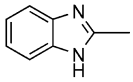
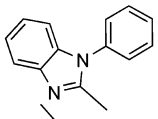
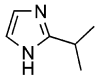
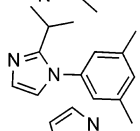
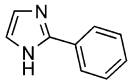
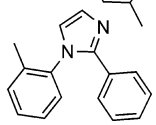
(32) A small amount of ethylation products (5−10%), likely by TEAC, of benzimidazole or **IV**, was observed (LC−MS), especially with long reaction times. 8-MeO-quinoline (Trécourt, F.; Mallet, M.; Mongin, F.; Quéguiner, G. *Synthesis* **1995**, 1159−1162) as ligand is somewhat less, but still, effective for the reaction.

(33) Lower yields were often obtained for polar imidazoloids (see Table 2, entries 3 and 4), partially due to loss of products during workup and purifications.

(34) (a) No regioisomers were detected. (b) In the absence of TEAC and ligand (**IV**), only a trace amount of **18** was formed.

(35) (a) Nanoparticles of Cu coated with Cu_2O were reported to catalyze N-arylation of imidazole with activated chlorides (DMSO, 150 °C): Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778−779. (b) Cu(II) apatites were recently reported in the N-arylation of imidazoles with chloroarenes: Choudary, B. C.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948−9949.

TABLE 3. N-Arylation of Imidazoles with Aryl Bromides[d]

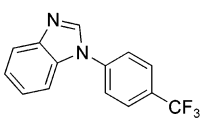
entry	imidazole	product	yield
1			**11,** 80[a]
2			**12,** 64
3			**13,** 47[b]
4			**14,** 45[c]
5			**15,** 40
6			**16**, trace

[a] Cs_2CO_3 was used as base (cf. ref 30a). [b] 74% when 2-methyl iodobenzene was used. [c] 36 h. [d] Conditions: 130 °C for 16 h (unless otherwise noted), TEAC (1.0), CuI (10%), **IV** (10%), DMF−H_2O (1.0−0.1 mL).

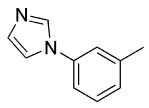
system will make it possible for copper-catalyzed N-arylations to be studied spectroscopically. It also promises to lead to the discovery of even better catalyst systems.

Experimental Section

Typical Experimental Procedure for Table 2. In a pressure reaction vessel (a 10-mL microwave tube was used in this case) equipped with a magnetic stirring bar was added benzimidazole (0.17 g, 1.43 mmol), CuI (0.019 g, 0.1 mmol), 8-hydroxyquinoline (**IV**, 0.015 g, 0.1 mmol), bis(tetraethylammonium) carbonate (TEAC, 95%, 0.37 g, 1.1 mmol), and aryl bromide (1.0 mmol). DMF (1.0 mL) and H_2O (0.1 mL) were added, and the vessel was capped with a rubber septum. The system was stirred while degassed under vacuum and purged with nitrogen three times. The septum was either replaced with a pressure cap or kept if the system was allowed to remain connected to nitrogen supply. The reaction mixture was heated to 130 °C in an oil bath for 16 h whereby an aliquot was taken for HPLC and LC−MS analyses. Upon cooling to room temperature, the mixture was subject to one of the following procedures for product isolation. The purified product was subject to ^1H NMR, HPLC, LC−MS, HRMS, ^{13}C NMR, or elemental analyses.



17 (50%)



18 (40%)

FIGURE 2. N-Arylimidazoles from aryl chlorides (130 °C, 60 h).

Method A. The almost homogeneous mixture was loaded onto a silica column (with MeOH/CH_2Cl_2 rinse) and eluded first with 1:1 mixture of hexanes/EtOAc, then with either MeOH in EtOAc or MeOH (for very polar products 2 N NH_3 in MeOH was used) in CH_2Cl_2.

Method B. The mixture was diluted with EtOAc (20 mL) and washed with H_2O, NH_4Cl (saturated), H_2O, and $NaHCO_3$ (saturated). The organic layer was dried over Na_2SO_4, concentrated, and subject to flash chromatography.

Acknowledgment. We thank Prof. Stephen L. Buchwald for providing helpful suggestions and encouragement.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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