# The [Cu(OH)·TMEDA]$_2$Cl$_2$-Catalyzed Coupling of Arylboronic Acids with Imidazoles in Water

James P. Collman,* Min Zhong, Li Zeng, and Simona Costanzo

*Department of Chemistry, Stanford University, Stanford, California 94305-5080*

*jpc@stanford.edu*

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## Introduction

Establishing efficient methods for constructing the *N*-arylimidazole subunit is currently an active area in organic synthesis. *N*-Arylimidazoles are not only important structures in biological systems but also common moieties in pharmaceutical research. A significant number of *N*-arylimidazole derivatives have been reported to have biomedical applications, serving as cyclic AMP phosphodiesterase inhibitors,[1] AMPA receptor antagonists,[2] cardiotonic agents,[3] thromboxane synthase inhibitors,[1b,4] and topical antiglaucoma agents.[5] Furthermore, recent high-resolution X-ray analyses have shown a *N*-(2-hydroxyphenyl)imidazole motif, formed by histidine (His$^{240}$) and tyrosine (Tyr$^{244}$) residues through a C−N linkage, in the active site of cytochrome *c* oxidase (C*c*O).[6] C*c*O is a heme−copper oxidase and the terminal respiratory enzyme of mitochondria and aerobic bacteria.[7] This phenol-functionalized imidazole is speculated to participate in the proton and electron-transfer steps during the reduction cycle of oxygen to water.[8] Our long-term program on C*c*O required *N*-arylimidazole intermediates for the construction of new C*c*O active-site models.[9,10] Accordingly, we became interested in developing new approaches to *N*-arylimidazoles by directly coupling imidazoles with activated aryl substrates.

*N*-Arylimidazoles have been prepared by two types of direct-coupling, i.e. nucleophilic aromatic substitution[2,3b,c,4b,11] and Ullman-type coupling.[1,3a,3c,4a,5,12] The former method requires substrates bearing electron-withdrawing substituents and the latter coupling is usually carried out at high temperatures. Other efficient methods for generating *N*-arylimidazoles using aryllead, arylborane, and arylsilane reagents instead of aryl halides under mild reaction conditions have also been established. For instance, López-Alvarado[13] and Konopelski[14] have reported the coupling of aryllead triacetate with imidazoles in the presence of a catalytic amount of Cu(OAc)$_2$; however, this method produces toxic organolead byproducts. Chan and Lam[15] have described a Cu(OAc)$_2$-promoted N-arylation of commercially available arylboronic acids with imidazoles at room temperature.[16] Recently, we demonstrated that the same coupling can be accomplished in the presence of a catalytic amount of [Cu(OH)·TMEDA]$_2$Cl$_2$ without the addition of any base at room temperature.[17] Alternatively, Lam[18] has recently described the coupling of phenyl trimethoxysilane with benzimidazole to *N*-phenylbenzimidazole, promoted by tetrabutylammoniun fluoride (TBAF) and an equimolar amount of Cu(OAc)$_2$. Although this method is quite mild, aryl trimethoxysilanes are not readily available and their preparation involves highly toxic trimethoxysilane.

In recent years, much effort has been devoted to the use of water as a reaction medium for organic synthesis.[19] A number of studies have shown that many organic reactions that are traditionally carried out exclusively in organic solvents can be also performed in aqueous media. Ayrlboronic acid mediated Suzuki-type cross coupling for forming C−C bonds is one of the successful

* To whom correspondence should be addressed. Tel: (650) 725-0283. Fax: (650) 725-0259

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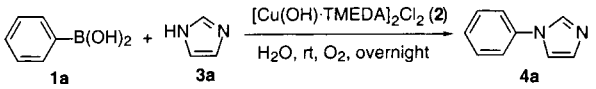
**Table 1. Effect of the Amount of [Cu(OH)·TMEDA]$_2$Cl$_2$ (2) on the Coupling in Water**




1a 3a 4a

| entry[a] | catalyst **2** (mol %) | yield of **4a** (%) |
|---|---|---|
| 1 | 2 | 2 |
| 2 | 5 | 18 |
| 3 | 10 | 42 |
| 4 | 15 | 44 |
| 5 | 20 | 42 |
| 6 | 25 | 43 |

[a] A typical procedure: a mixture of 2 mmol of phenylboronic acid (**1a**), 1 mmol of imidazole (**3a**), and a catalytic amount of [Cu(OH)·TMEDA]$_2$Cl$_2$ (**2**) in 10 mL of water is vigorously stirred at room temperature overnight under an atmosphere of $O_2$.

cases.[20] However, few examples of N-arylation[21] accomplished in aqueous media have been reported. Recently, Davydov[22] has described a palladium- and copper-catalyzed coupling of substituted iodobenzenes with carbazole using a water−*n*-butanol emulsion stabilized by cetyltrimethylammonium bromide. To the best of our knowledge, N-arylation of imidazoles in aqueous media has not been explored. Herein, we present the first example of N-arylation of imidazoles in water.

## Results and Discussion

In our previous catalytic system for preparing *N*-arylimidazoles, arylboronic acids were coupled with imidazoles in the presence of a catalytic amount of [Cu(OH)·TMEDA]$_2$Cl$_2$ in dichloromethane. Since all three reactants are either partially or completely soluble in water, we were encouraged to study the coupling in water. An initial study was carried out following our previously published procedure but with the single change of the solvent. A general procedure is described as follows: 2 equiv of phenylboronic acid (**1a**) is vigorously stirred overnight with 1 equiv of imidazole (**3a**) in the presence of 0.1 equiv of [Cu(OH)·TMEDA]$_2$Cl$_2$ (**2**) in 10 mL of water under an atmosphere of $O_2$.

As shown in Table 1, we tested the effect of the amount of the catalyst (**2**) on the coupling reaction in water. When 0.1 equiv of the catalyst **2** is used, a 42% yield of *N*-phenylimidazole (**4a**) is obtained, which is lower than that in $CH_2Cl_2$ (71%).[17] When less than 0.1 equiv of **2** is employed in the coupling, the yield dramatically decreases. Moreover, no significant improvement of the coupling yield is observed when more than 0.1 equiv of **2** is used (Table 1).

Considering the importance of phase-transfer catalysts (PTC) for aqueous media reactions,[19] we investigated the effect of PTC on this coupling reaction. As summarized in Table 2, the addition of a PTC into the reaction mixture slightly reduces the coupling yield—PTC probably increases both the N-arylation and side-reaction rates to a similar extent. No significant variation of the coupling yield has been observed by changing the PTC counterion from $Cl^-$ to $Br^-$ (Table 2).

**Table 2. Effect of the Addition of Phase-Transfer Catalysts (PTC) on the Coupling**

| entry[a] | PTC | yield of **4a** (%) |
|---|---|---|
| 1 | none | 42 |
| 2 | $Bu_4NBr$ | 40 |
| 3 | $Bu_4NCl$ | 44 |
| 4 | $Heptyl_4NBr$ | 34 |
| 5 | $BzEt_3NCl$ | 37 |
| 6 | $BzBu_3Cl$ | 39 |
| 7 | $BzMe_2$tetradecylNCl | 36 |

[a] A typical procedure: a mixture of 2 mmol of phenylboronic acid (**1a**), 1 mmol of imidazole (**3a**), 0.1 mmol of [Cu(OH)·TMEDA]$_2$Cl$_2$ (**2**), and 0.1 mmol of PTC in 10 mL of water is vigorously stirred at room temperature overnight under an atmosphere of $O_2$.

**Table 3. Effect of the pH Value of the Aqueous Medium on the Coupling**

| entry[a] | reaction medium | yield of **4a** (%) |
|---|---|---|
| 1 | $H_2O$ | 42 |
| 2 | HOAc + NaOAc + $H_2O$ (pH = 4.63) | 30 |
| 3 | $Na_2HPO_4$ + $NaH_2PO_4$ + $H_2O$ (pH = 7.00) | 42 |
| 4 | $NaHCO_3$ + $Na_2CO_3$ + $H_2O$ (pH = 9.00) | 30 |

[a] A typical procedure: a mixture of 2 mmol of phenylboronic acid (**1a**), 1 mmol of imidazole (**3a**), and 0.1 mmol of [Cu(OH)·TMEDA]$_2$Cl$_2$ (**2**) in 10 mL of solvent is vigorously stirred at room temperature overnight under an atmosphere of $O_2$.

Moreover, we studied the effect of the pH value of the aqueous medium on the coupling. When the reaction is accomplished in aqueous buffer solutions at pH 4.63 (NaOAc/HOAc), 7.00 ($NaH_2PO_4$/$Na_2HPO_4$), and 9.00 ($NaHCO_3$/$Na_2CO_3$), lower yields are obtained in both acidic and basic media compared to that in neutral medium. The coupling product (**4a**) is generated in the same yield when the reaction is carried out in either water or $NaH_2PO_4$/$Na_2HPO_4$ aqueous buffer (Table 3).

Subsequently, we applied a number of arylboronic acids and imidazoles to [Cu(OH)·TMEDA]$_2$Cl$_2$ (**2**)-catalyzed coupling in water. As presented in Table 4, when *p*- or *o*-tolylboronic acids are used, the corresponding coupling products **4b** and **4c** are obtained in 63% and 55% yields, respectively (entries 1 and 2). *p*-Methoxyphenylboronic acid also gives a good yield of **4d** (entry 3). However, when *p*-fluorophenylboronic acid is employed, the yield is remarkably depressed (entry 4).

The regioselectivity of this coupling was also investigated. When *o*-tolylboronic acid (**1b**) reacts with 4(5)-methylimidazole (**3b**) in a 2/1 ratio, a mixture of the coupling products **4f** and **4f′** is obtained in 35% yield with a 3.2/1 ratio. The **4f**/**4f′** ratio slightly increases to 3.7/1 by employing a 1/1 ratio of the reactants (entry 5). Alternatively, a 4.6/1 ratio of the **4g**/**4g′** is obtained when 2 equiv of *o*-tolylboronic acid (**1b**) is treated with 1 equiv of 4(5)-phenylimidazole (**3c**). No attempt has been made to further increase the coupling yield by adding additional amounts of arylboronic acid to the reaction mixture.

Furthermore, the couplings of benzimidazole (**3d**) with arylboronic acids were tested (entires 7−9). *N*-Phenylbenzimidazole (**4h**), *N*-*p*-tolylbenzimidazole (**4i**), and *N*-*p*-methoxyphenyl-benzimidazole (**4j**) are formed in 46%, 44%, and 28% yields, respectively (Table 4).

This N-arylation system for preparing *N*-arylimidazoles in water seems to be more complex than that in

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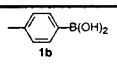
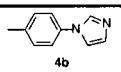
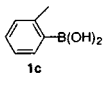
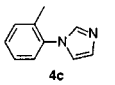
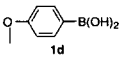
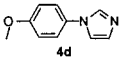
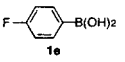
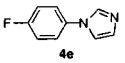
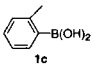
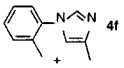
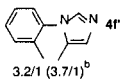
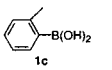
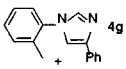
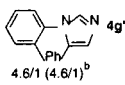
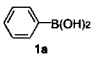
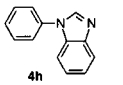
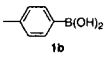
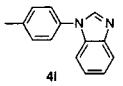
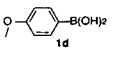
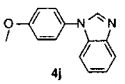
**Table 4. Synthesis of *N*-Arylimidazoles (4) by the [Cu(OH)•TMEDA]$_2$Cl$_2$ (2)-catalyzed Coupling of Arylboronic Acids (1) with Imidazoles (3) in Water**

| entry[a] | 1 | 3 | 4 | yield (%) |
|---|---|---|---|---|
| 1 |  1b |  3a |  4b | 63 |
| 2 |  1c | |  4c | 55 |
| 3 |  1d | |  4d | 51 |
| 4 |  1e | |  4e | 26 |
| 5 |  1c |  3b |  4f  4f' 3.2/1 (3.7/1)[b] | 35 (10)[t] |
| 6 |  1c |  3c |  4g  4g' 4.6/1 (4.6/1)[b] | 21 (8)[b] |
| 7 |  1a |  3d |  4h | 46 |
| 8 |  1b | |  4i | 44 |
| 9 |  1d | |  4j | 28 |

[a] A typical procedure: a mixture of 2 mmol of arylboronic acid (**1**), 1 mmol of imidazole (**3**), and 0.1 mmol of [Cu(OH)•TMEDA]$_2$Cl$_2$ (**2**) in 10 mL of water is vigorously stirred at room temperature overnight under an atmosphere of $O_2$. [b] 1 mmol of 2-methylphenylboronic acid (**1c**) is used.

$CH_2Cl_2$. According to the experimental results, the main reactions in the catalytic system are the Cu(II) complex-catalyzed N-arylation of imidazoles (Scheme 1, eq 1) and the subsequent regeneration of the catalyst **2** (equation 2).[17] The lower coupling yield is due to several possible side reactions. As shown in Scheme 1, it has been reported that arylboronic acids can be oxidized by copper (II) in the presence of water to form the corresponding phenols (equation 3),[23] which can be subsequently converted to quinone-type derivatives (equation 4).[24] Moreover, arylboronic acids can undergo deboronation in the presence of water (equation 5).[23]

**Scheme 1. Reactions in the Catalytic System**

Main reactions:

(1) $2ArB(OH)_2 + [Cu(OH)\cdot TMEDA]_2Cl_2 + 1/2\ O_2 + 2$  $\longrightarrow 2$  $+ 2CuCl\cdot TMEDA + H_2O + 2B(OH)_3$

(2) $2CuCl\cdot TMEDA + H_2O + 1/2\ O_2 \longrightarrow [Cu(OH)\cdot TMEDA]_2Cl_2$

Possible side reactions:

(3) $Ar\text{-}B(OH)_2 \xrightarrow{Cu(II),\ H_2O} Ar\text{-}OH + B(OH)_3$

(4) $Ar\text{-}OH \xrightarrow{Cu(II)}$ Quinone-type derivatives

(5) $ArB(OH)_2 + H_2O \longrightarrow ArH + B(OH)_3$

The decreased coupling yield at both basic and acidic pHs could be due to the deboronation reaction (equation 5), which is known to proceed more rapidly in basic or acidic medium.[23] Moreover, the copper (II)-catalyzed oxidation of arylboronic acids to phenols (equation 3)[23] at pH 9.00 should be favored compared to that at neutral pH, resulting in a lower coupling yield (Scheme 1).

In summary, we have successfully carried out the [Cu(OH)•TMEDA]$_2$Cl$_2$-catalyzed coupling of arylboronic acids with imidazoles in water instead of $CH_2Cl_2$. This appears to be the first example of N-arylation of imidazoles in water to date.

## Experimental Section

All reagents were used as supplied commercially without further purification. $^1$H NMR spectra were recorded on Varian XL-400 instruments. Mass spectra were measured by the Mass Spectrometry Facility at the University of California, San Francisco.

**General Procedure for the N-Arylation of Imidazoles**: A mixture of 2 mmol of arylboronic acid (**1**), 1 mmol of imidazole substrate (**3**), and 0.1 mmol of [Cu(OH)•TMEDA]$_2$Cl$_2$ (**2**) in 10 mL of water was vigorously stirred under an atmosphere of $O_2$ at room temperature overnight. The reaction mixture was extracted with $CHCl_3$, and the organic phase was combined, dried over anhydrous $MgSO_4$, filtered, and evaporated. Subsequently, the residue was subjected to preparative chromatography on a silica gel plate using $CHCl_3$/hexanes = 1/1 (*v*/*v*) (saturated with $NH_3$ gas) as the eluent to give *N*-arylimidazole (**4**).

***N*-Phenylimidazole (4a).** Yield 42%; $^1$H NMR ($CDCl_3$) $\delta$ 7.84 (s, 1H), 7.43−7.47 (m, 2H), 7.32−7.37 (m, 3H), 7.26 (s, 1H), 7.19 (s, 1H) ppm; MS (*m*/*z*) 144($M^+$, 100), 117, 90, 77, 69, 57; HRMS calcd. for $C_9H_8N_2$ ($M^+$) 144.069, found 144.069.

***N*-(4-Methyl-1-phenyl)imidazole (4b).** Yield 63%; $^1$H NMR ($CDCl_3$) $\delta$ 7.86 (s, 1H), 7.28 (s, 3H), 7.63 (s, 2H), 7.21 (s, 1H), 2.41 (s, 3H) ppm; $^1$H NMR ($CD_3CN$) $\delta$ 8.44(s, 1H), 7.96 (s, 1H), 7.93 (d. $J$ = 8.0 Hz, 2H), 7.85 (d. $J$ = 8.0 Hz, 2H), 2.92 (s, 3H) ppm; MS (*m*/*z*) 158($M^+$, 100), 131, 104, 91, 77, 65, 57; HRMS calcd. for $C_{10}H_{10}N_2$ ($M^+$) 158.084, found 158.084.

***N*-(2-Methyl-1-phenyl)imidazole (4c).** Yield 55%; $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (s, 1H), 7.21−7.36 (m, 5H), 7.07 (s, 1H), 2,19 (s, 3H) ppm; MS (*m*/*z*) 158($M^+$), 130, 107, 91, 83, 69(100); HRMS calcd. for $C_{10}H_{10}N_2$ ($M^+$) 158.084, found 158.084.

***N*-(4-Methoxy-1-phenyl)imidazole (4d).** Yield 51%; $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (s, 1H), 7.31 (d, $J$ = 8.0 Hz, 2H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.00 (s, 1H), 6.98 (s, 1H), 3.85 (s, 3H) ppm; MS

(23) Lappert, M. F. *Chem. Rev.* **1956**, 959 and references therein.
(24) Mijs, W. J.; de Jonge, C. R. H. I. *Organic Syntheses by Oxidation with Metal Compounds*; Plenum Press, Inc.: New York, 1986.

(*m*/*z*) 174($M^+$, 100), 159, 147, 132, 120, 104, 92, 77, 63; HRMS calcd for $C_{10}H_{10}N_2O(M^+)$ 174.079, found 174.079.

***N*-(4-Fluoro-1-phenyl)imidazole (4e).** Yield 26%; $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (s, 1H), 7.33−7.36 (m, 2H), 7.14−7.21 (m, 4H) ppm; MS (*m*/*z*) 162($M^+$, 100), 141, 135, 129, 108, 95, 83, 71, 57; HRMS calcd for $C_9H_7FN_2$ ($M^+$) 162.059, found 162.059.

**Mixture of *N*-(2-Methyl-1-phenyl)-4(5)-methylimidazole (4f + 4f′).** Yield 35%; $^1$H NMR ($CDCl_3$) $\delta$ 7.48 and 7.45 (s, 1H), 7.16−7.38 (m, 4H), 6.93 and 6.77 (s, s, 1H), 2.32 and 2.05(s, s, 3H), 2.20 and 1.99 (s, s, 3H) ppm; MS (*m*/*z*) 172($M^+$), 111, 97, 83, 69, 57(100); HRMS calcd for $C_{11}H_{12}N_2$ ($M^+$) 172.100, found 172.100.

**Mixture of *N*-(2-Methyl-1-phenyl)-4(5)-phenylimidazole (4g + 4g′).** Yield 21%; $^1$H NMR ($CDCl_3$) $\delta$ 7.84−7.86 (m, 2H), 7.62 and 7.65 (s, s, 1H), 7.09−7.43 (m, 8H), 2.26 and 1.93(s, s, 3H) ppm; MS (*m*/*z*) 235($M^+ + 1$), 234($M^+$), 233($M^+ - 1$), 206, 130-(100), 117, 104, 91, 77, 65; HRMS calcd for $C_{16}H_{14}N_2$ ($M^+$) 234.116, found 234.116.

***N*-Phenylbenzimidazole (4h).** Yield 46%; $^1$H NMR ($CDCl_3$) $\delta$ 8.11 (s, 1H), 7.87−7.89 (m, 1H), 7.46−7.58 (m, 6H), 7.31−7.35 (m, 2H) ppm; MS (*m*/*z*) 194($M^+ + 1$, 100), 166, 139, 105, 77; HRMS calcd for $C_{14}H_{11}N_2(M^+)$ 193.089, found 193.089.

***N*-(4-Methyl-1-phenyl)benzimidazole (4i).** Yield 44%; $^1$H NMR ($CDCl_3$) $\delta$ 8.10 (s, 1H), 7.87−7.89 (m, 1H), 7.50−7.53 (m, 1H), 7.32−7.41 (m, 6H), 2.46 (s, 3H) ppm; MS (*m*/*z*) 209($M^+ + 1$), 208($M^+$), 207($M^+$-1), 192, 180, 166, 152, 104, 91(100), 77, 65; HRMS calcd for $C_{14}H_{12}N_2(M^+)$ 208.100, found 208.100.

***N*-(4-Methoxy-1-phenyl)benzimidazole (4j).** Yield 28%; $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (s, 1H), 7.86−7.88 (m, 1H), 7.45−7.47 (m, 1H), 7.41 (d, $J$ = 9.0 Hz, 2H), 7.30−7.33 (m, 2H), 7.06 (d, $J$ = 9.0 Hz, 2H), 3.88 (s, 3H) ppm; MS (*m*/*z*) 224($M^+$, 100), 209, 192, 181, 154, 128, 112, 102, 92, 77, 64; HRMS calcd for $C_{14}H_{12}N_2O$-($M^+$) 224.095, found 224.095.

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