Catalytic Activities of Cu(II) Complexes with Nitrogen-Chelating Bidentate Ligands in the Coupling of Imidazoles with Arylboronic Acids

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Introduction

N-Arylimidazoles are common motifs in pharmaceutical research because of their biomedical use as thromboxane synthase inhibitors,[1] AMP phosphodiesterase inhibitors,[2] AMPA receptor antagonists,[3] cardiotonic[4] and topical antiglaucoma agents,[5] etc. Moreover, recent high-resolution X-ray diffraction analyses have revealed in the Cu_B site of cytochrome *c* oxidase (CcO), the terminal respiratory enzyme of mitochondria and aerobic bacteria,[6] a tyrosine-histidine (Tyr^{244}-His^{240}) cross-linked through a C−N bond.[7] This functionalized phenol has been postulated to serve as a hydrogen atom donor during the $4H^+$, $4e^-$ reduction of O_2 to H_2O.[8] Thus, in the course of our efforts in developing new active-site models of C*c*O,[9] we became interested in studying direct C−N coupling reactions for preparing *N*-arylimidazoles as building blocks[10] of new model compounds incorporating *N*-(2′-hydroxyphenyl)imidazole moieties as Cu_B site mimics.

Numerous reports describe copper-promoted N-arylation of imidazoles with arylmetalloids to furnish *N*-arylimidazoles. Traditional Ullman-type coupling of imidazole with aryl halides,[1−5,11] one of the most usually used methods, requires high temperatures. A few approaches have also been developed using aryllead, arylborane, or arylsilane reagents in the presence of $Cu(OAc)_2$ under milder conditions. For example, López-Alvarado[12] described the coupling of imidazoles with *p*-tolyllead triacetate in the presence of a stoichiometric amount of $Cu(OAc)_2$ at 90 °C. Interestingly, Konopelski[13] found that imidazoles react with *o*- or *p*-methoxyphenyllead triacetate to give the corresponding C−N coupling products in good yields in the presence of 10% mol of $Cu(OAc)_2$ at room temperature. However, it should be noted that both procedures produce toxic organolead byproducts. Moreover, Chan and Lam[14] established an efficient approach to *N*-arylimidazoles via $Cu(OAc)_2$-mediated coupling of imidazoles with readily available arylboronic acids at room temperature,[15] and Lam[16] extended this methodology to phenyl trimethoxysilane. Although both methods are quite mild, they suffer from two main drawbacks: more than an equimolar amount of $Cu(OAc)_2$ and either Et_3N or pyridine are employed to promote the coupling; moreover, the synthesis of phenyl trimethoxysilane involves the use of highly toxic trimethoxysilane.[17] Very recently, both Lam[18] and Buchwald[19] reported the synthesis of *N*-arylimidazoles through the coupling of imidazoles with *p*-tolylboronic acid using 10% mol of Cu-

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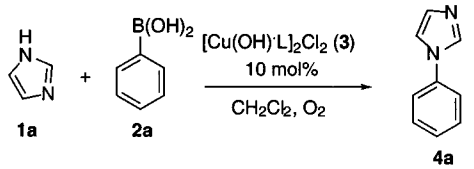
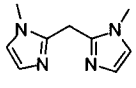
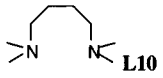
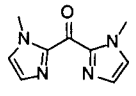
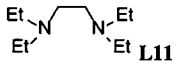
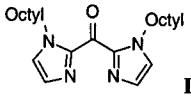
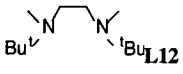
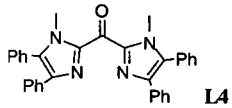
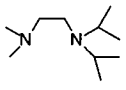
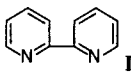
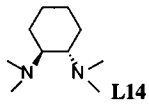
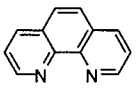
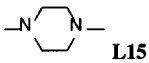
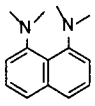
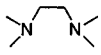
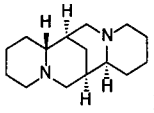
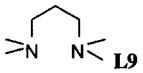
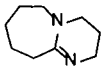
Table 1. Effect of the Bidentate Ligand on the Reactivity of Complex 3 in the N-Arylation of Imidazole (1a) with Phenylboronic Acid (2a)



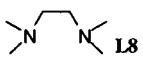
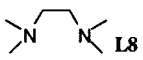
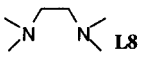
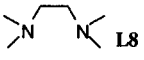
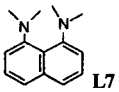
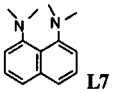
entry[a]	L	color of **3**	yield of **4a** (%)[b]	entry[a]	L	color of **3**	yield of **4a** (%)[b]
1	 L1	blue	52	10	 L10	mustard yellow	63
2	 L2	green	48	11	 L11	green	60
3	 L3	green	42	12	 L12	pea green	45
4	 L4	green	19	13	 L13	green	60
5	 L5	blue	59	14	 L14	blue-green	54
6	 L6	blue	40	15	 L15	pea green	60
7	 L7	light green	61	16	 L16	orange	46
8	 L8	brown	71	17	 L17	light green	50
9	 L9	light green	52	18	 L18	pea green	32

[a] A typical procedure: a mixture of 1 mmol of imidazole (**1a**), 2 mmol of phenylboronic acid (**2a**), and 0.1 mmol of Cu(II) complex (**3**) in 4 mL of dry CH_2Cl_2 was stirred at room temperature overnight under an atmosphere of dioxygen. [b] Isolated yield.

$(OAc)_2$. However, Lam's method requires more than a stoichiometric amount of oxidant, such as pyridine *N*-oxide, TEMPO, or NMO etc., as well as Et_3N or pyridine, and elevated temperature (65 °C), whereas the system described by Buchwald requires the addition of a stoichiometric amount of 2,6-lutidine as well as myristic acid and gives a low yield (32%). Accordingly, it is important to develop more efficient catalytic systems to prepare *N*-arylimidazoles under mild reaction conditions—at room temperature, with a small amount of the catalyst, and in the absence of base.

Recently, we carried out the coupling of imidazoles with arylboronic acids at room temperature using only 10% mol of $[Cu(OH)\cdot TMEDA]_2Cl_2$, without the addition of base in CH_2Cl_2.[20a] We also demonstrated that this coupling could be performed in water to give *N*-arylimidazoles in moderate yields.[20b] To the best of our knowledge, this catalytic system is one of the most efficient

Table 2. Effect of the Counterion on the Reactivity of Complex 3 in the N-Arylation of Imidazole (1a) with Phenylboronic Acid (2a)

entry[a]	L	CuX	color of **3**	yield of **4a** (%)[b]
1	 **L8**	CuCl	brown	71
2	 **L8**	CuBr	brown	62
3	 **L8**	CuI	brown	63
4	 **L8**	CuOTf	blue	72
5	 **L7**	CuCl	blue	61
6	 **L7**	CuBr	green	39

[a] A typical procedure: a mixture of 1 mmol of imidazole (**1a**), 2 mmol of phenylboronic acid (**2a**), and 0.1 mmol of Cu(II) complex (**3**) in 4 mL of dry CH_2Cl_2 was stirred at room temperature overnight under an atmosphere of dioxygen. [b] Isolated yield.

approaches to *N*-arylimidazoles to date. To design and synthesize more efficient catalysts for this important C−N coupling, it is necessary to understand the effects of bidentate ligands as well as counterions on the activities of the μ-hydroxo Cu(II) complexes. Thus, a series of μ-hydroxo Cu(II) complexes with nitrogen chelating bidentate ligands were prepared and applied to the coupling of imidazoles with arylboronic acids.

Results and Discussion

$[Cu(OH)\cdot TMEDA]_2Cl_2$ is a binuclear bis-μ-hydroxo copper(II) complex.[21] It has been demonstrated to be an efficient catalyst for oxidative coupling reactions of naphthols[22] or terminal alkynes.[23] In our studies, all Cu(II) complexes (**3**) were prepared[24] by stirring 1 equiv of the bidentate ligand (**L**) with 1 equiv of CuX (X = Cl^-, Br^-, I^-, or TfO^-) in 95% aqueous ethanol at room temperature overnight under an atmosphere of dioxygen. These Cu(II) complexes (**3**) were used in the C−N coupling reaction following our previously published procedure:[20a] a mixture of 1 mmol of imidazole (**1a**), 2 equiv of phenylboronic acid (**2a**), and 0.1 equiv of Cu(II) complex (**3**) in 4 mL of dry CH_2Cl_2 was stirred at room temperature overnight under an atmosphere of dioxygen.

As shown in Table 1, several bisimidazole-type ligands **L1**−**4** were initially investigated. The coupling yield of *N*-phenylimidazole (**4a**) is not significantly affected by either replacing the methylene with a carbonyl group or changing the *N*-methyl to *N*-octyl groups of ligand **L1**. However, the increase of the substituents' bulk on the carbons adjacent to the imidazole sp^2-N atoms, serving as chelating centers, results in a significantly decreased yield of compound **4a** (entries 1−4, Table 1). Other types of sp^2-N bidentate ligands have also been tested. The Cu(II) complexes with 2,2′-pyridyl (**L5**) or 1,10-phenatholine (**L6**) also catalyze the coupling to give compound **4a** in moderate yields (entries 5 and 6, Table 1). However, no coupling product is formed when employing 2, 2′-dipyridylmethane or 2, 2′-dipyridyl ketone as the ligand.

A series of sp^3-N bidentate ligands were also investigated. A 61% yield of *N*-phenylimidazole (**4a**) is obtained when Proton Sponge (**L7**) is used (entry 7, Table 1). Both increasing the distance between the two dimethylamino groups and replacing one or both dimethylamino groups with bulkier dialkylamino groups on the TMEDA (**L8**) backbone result in decreased coupling yields (entries 8−13, Table 1). The Cu(II) complexes prepared from readily available ring-containing alkyldiamines, such as tetramethylcyclohexanediamine (**L14**), *N*,*N*-dimethylpiperazine (**L15**), Dabco (**L16**), and (−)-sparteine (**L17**) give moderate coupling yields (entries 14−17, Table 1). A relatively low yield of compound **4a** is obtained when DBU (**L18**) is used as a ligand (entry 18, Table 1).

The activity of Cu(II) complexes with different counterions were also tested (Table 2). Only small variations of the coupling yield are observed using TMEDA (**L8**) as a ligand with different counterions, such as Cl^-, Br^-, I^-, and TfO^-. However, in the case of Proton Sponge (**L7**), the coupling yield significantly drops when CuCl is replaced with CuBr. It should be noted that the complex derived from 1,10-phenatholene (**L6**) with CuBr or CuI does not give compound **4a**. Some studies have shown that strongly coordinating counterions, such as halides, can affect the rate of reoxidation by acting as bridging ligands and thus favoring the formation of the active dinuclear bis-μ-hydroxo Cu(II) system.[25] This could explain the variation in activity of the Cu(II) complexes in the presence of different counterions.

Since regioselectivity is one of the major issues in various coupling reactions, Cu(II) complexes (**3**) with different ligands were applied to the coupling of equimolar amounts of 4(5)-substituted imidazole (**1b** or **1c**) with *o*-tolylboronic acid (**2b**) (Table 3). The increase of either the number of carbons or the bulk of the substituents on the nitrogen atoms of TMEDA (**L8**) results in small variations of the selectivity. No obvious linear correlation is observed between steric hindrance in the bidentate ligands and the regio-selectivity of the coupling products. In general, better coupling yields and selectivities are obtained by employing 4(5)-phenylimidazole (**1c**) instead of 4(5)-methylimidazole (**1b**) as a substrate.

In our proposed mechanism for the C−N coupling of imidazoles, phenylboronic acid (**2**) initially undergoes transmetalation with complex **3** to generate boric acid (**5**) and intermediate **6**, which then coordinates the imidazole substrate (**1**) forming complex **7**. In the pres-

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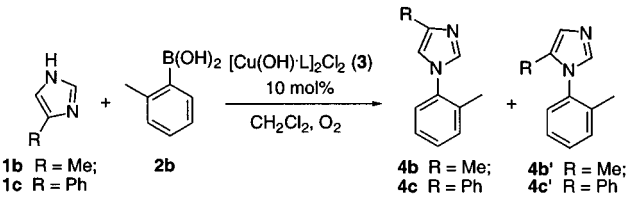
Table 3. Effect of the Ligand of Cu(II) Complex (3) on the Regioselectivity of the Coupling Reaction of 4(5)-Substituted Imidazole (1b or 1c) with *O*-Tolylboronic Acid (2b)



entry[a]	L	yield (%)[b]	ratio of **4b/4b'**[c]	entry[a]	L	yield (%)[b]	ratio of **4c/4c'**[c]
1	**L8**	37	3.8/1.0	11	**L8**	77	8.7/1.0
2	**L9**	37	2.9/1.0	12	**L9**	54	4.0/1.0
3	**L10**	19	4.4/1.0	13	**L10**	54	4.1/1.0
4	**L11**	21	3.5/1.0	14	**L11**	44	4.9/1.0
5	**L12**	33	3.2/1.0	15	**L12**	48	4.8/1.0
6	**L13**	19	4.0/1.0	16	**L13**	43	7.5/1.0
7	**L14**	23	3.5/1.0	17	**L14**	48	6.8/1.0
8	**L15**	37	1.9/1.0	18	**L15**	68	3.2/1.0
9	**L16**	41	2.8/1.0	19	**L16**	56	3.8/1.0
10	**L7**	29	2.5/1.0	20	**L7**	60	3.2/1.0

[a] A typical procedure: a mixture of 1 mmol of 4(5)-substituted imidazole (**1b** or **1c**), 1 mmol of *o*-tolylboronic acid (**2b**), and 0.1 mmol of Cu(II) complex (**3**) in 4 mL of dry CH_2Cl_2 was stirred at room temperature overnight under an atmosphere of dioxygen. [b] Isolated yield. [c] The ratio of compounds **4b** and **4b′**, as well as **4c** and **4c′**, was determined by the comparison of the respective methyl group signals in the corresponding ^{1}H NMR spectrum using $CDCl_3$ as the solvent; see the Supporting Information of ref 20a.

ence of dioxygen, complex **7** is proposed to be oxidized forming a putative Cu(III) intermediate **8**, which undergoes reductive elimination yielding *N*-phenylimidazole **4** and complex **9**. The latter can be reconverted to bis-μ-hydroxo Cu(II) complex **3** in the presence of dioxygen and water.[26] It is most likely that less sterically hindered bidentate ligands form intermediate **7** or **8** more easily compared with hindered ligands, resulting in higher yields of coupling product **4** (Scheme 1).

The regioselectivity of coupling is dependent on the interaction between R_L and R_S on the bidentate ligands, R^3 on the phenyl and R^4 on imidazole rings. As shown in Scheme 2, regardless of the bulk of the substituents R_L and R_S, the intermediates **7F** and **7F′** are more geometrically favored than the intermediates **7U** and **7U′**, resulting in a higher yield of **4b** or **4c** compared with **4b′** or **4c′**. Moreover, in the case of ethylenediamine-based ligands, TMEDA (**L8**) gives the highest selectivity compared with other more hindered ligands (**L11**−**L13**). It is possible that the increase in the bulk of R_L enhances the interactions between R_L, R^3, R^4, and the counterion,

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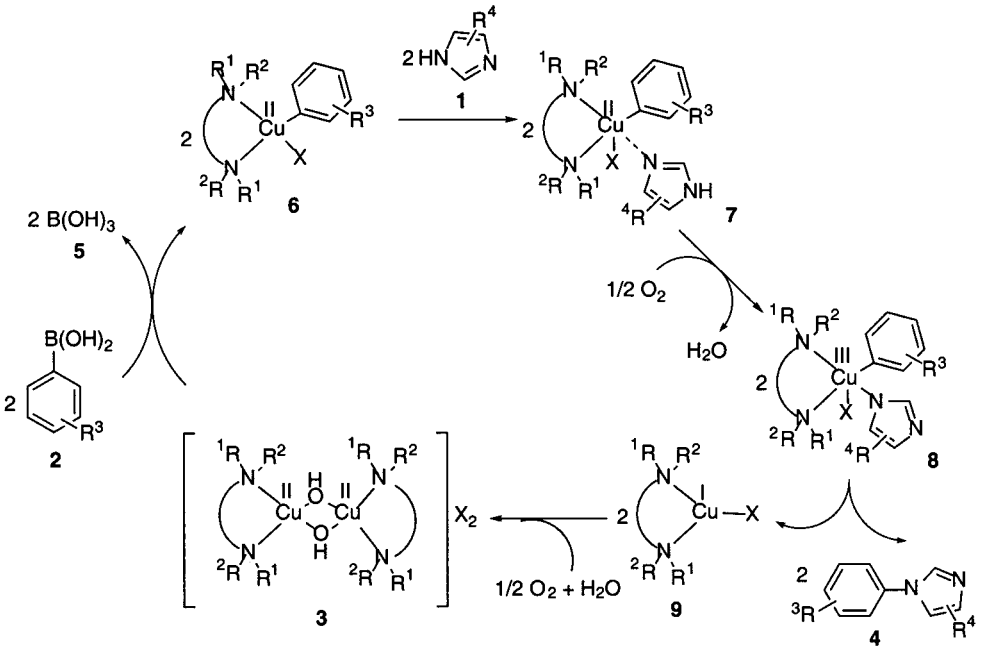
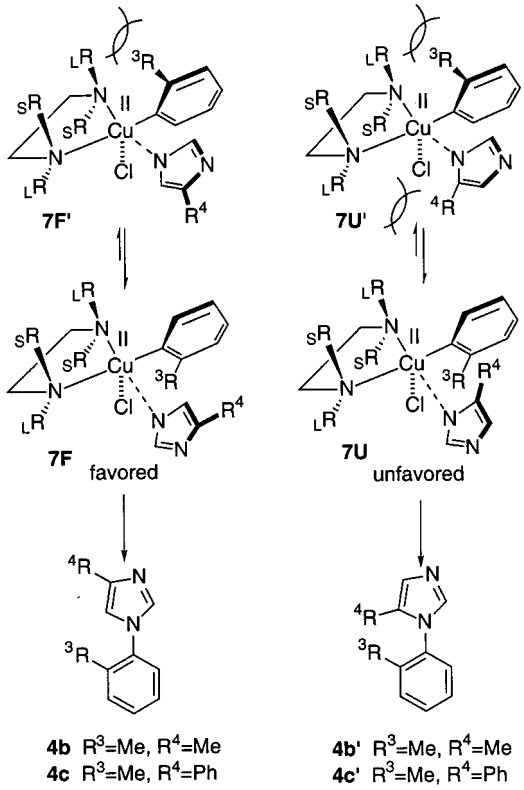
Scheme 1



Scheme 2



reducing the number of stable conformations of intermediates **7U** and **7F** and therefore yielding lower ratios of **4b**/**4b′** or **4c**/**4c′** compared with TMEDA (**L8**).

In summary, we have demonstrated that a series of nitrogen chelating bidentate ligands (**L**) can react with Cu(I) salt and water in the presence of dioxygen to generate Cu(II) complexes (**3**) that efficiently catalyze the coupling reaction of imidazoles with arylboronic acids under mild conditions. The activities of the Cu(II) complexes (**3**) are dependent both on the nature of the bidentate ligands (**L**) and the counterions employed and TMEDA (**L8**) appears to be the best ligand for the coupling reaction. Detailed mechanistic studies of the reaction and the application of these new catalysts to the coupling of other NH− containing substrates[27] with arylboronic acids are being investigated and will be reported in due course.

Experimental Section

All reagents were used as supplied commercially without further purification unless otherwise noted.Bis[2-(1-methylimidazolyl)]methane (**L1**),[28] bis[2-(1-methylimidazolyl)]ketone (**L2**),[28] bis[2-(1-octylimidazolyl)]ketone (**L3**),[9f] bis[2-(4,5-diphenyl-1-methylimidazolyl)]ketone (**L4**),[9f] *N*,*N*′-*tert*-butyl-*N*,*N*′-dimethylethylenediamine (**L12**),[29] and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (**L14**)[30] were prepared following reported procedures. ^{1}H and ^{13}C 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.

***N*,*N*-Diisopropyl-*N*′,*N*′-dimethylethylenediamine (L13).** This compound was prepared following the procedure for the synthesis of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (**L14**)[30] using *N*,*N*-diisopropylethylenediamine as starting material. Colorless liquid, 67% yield. ^{1}H NMR ($CDCl_3$): δ 2.99 (m, 2H), 2.52 (m, 2H), 2.30 (m, 2H), 2.24 (s, 6H), 1.00 (d, J = 6.5 Hz, 12H) ppm. ^{13}C NMR ($CDCl_3$): δ 61.8, 49.3, 45.9, 43.9, 20.6 ppm. MS (*m*/*z*): 172 (M^+), 162, 143, 114 (100), 82, 72, 58. HRMS: calcd for $C_{10}H_{24}N_2$ (M^+) 172.194, found 172.195.

General Procedure for the Preparation of Bidentate Ligand·Cu(II) Complexes (3). A mixture of 3 mmol of bidentate ligand (**L**) and 3 mmol of CuX (X = Cl^-, Br^-, I^-, or TfO^-) in 6 mL of 95% aqueous ethanol was stirred vigorously at room temperature overnight under an atmosphere of dioxygen. The precipitates were filtered off, washed with a small amount of 95% ethanol, and dried in vacuo over P_2O_5. In some cases, the complexes are soluble in 95% aqueous ethanol and they were obtained by concentrating to dryness and dried in vacuo over

(27) Lam recently disclosed that $[Cu(OH)\cdot TMEDA]_2Cl_2$ can also catalyze the C−N coupling reactions of phenyl trimethoxysiloxane with benzoimidazole (ref 16) and *p*-tolylboronic acid with various NH-containing heterocycles (ref 18) in moderate yields.

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P_2O_5. These complexes were used for the coupling reaction without further purification and all the molecular weights of these complexes were calculated on the basis of the formula of $[Cu(OH)\cdot L]_2X_2$.

General Procedure for the N-Arylation of Imidazoles. A mixture of 1 mmol of imidazole (**1**), 2 mmol of arylboronic acid (**2**), and 0.1 mmol of μ-hydroxo Cu(II) complex **3** in 4 mL of dry CH_2Cl_2 was vigorously stirred at room temperature overnight under an atmosphere of dioxygen. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by preparative thin-layer chromatography on a 1000 μm silica gel plate using a mixed solvent of $CHCl_3$ and *n*-hexane (1/1 volume ratio, saturated with NH_3 gas) to give *N*-arylimidazole (**4**).

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