ORGANIC LETTERS

2000
Vol. 2, No. 9
1233−1236

An Efficient Diamine·Copper Complex-Catalyzed Coupling of Arylboronic Acids with Imidazoles

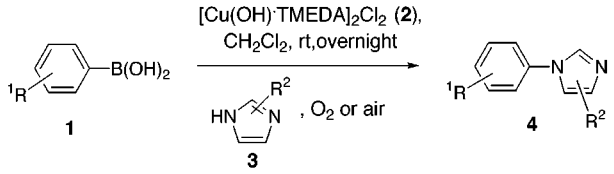
James P. Collman* and Min Zhong

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

jpc@chem.stanford.edu

Received February 15, 2000

ABSTRACT



A novel diamine·copper complex-catalyzed intermolecular coupling of arylboronic acids (1) with imidazoles (3) is described. In the presence of a catalytic amount of [Cu(OH)·TMEDA]$_2$Cl$_2$ (2), arylboronic acids (1) react smoothly with imidazoles (3) in dichloromethane at room temperature to give a variety of *N*-arylimidazoles (4) in good to excellent yields.

The *N*-arylimidazole subunit is a commonly found motif in pharmaceutical molecules. A huge number of drugs bearing *N*-arylimidazolyl moieties have been reported to have a broad range of significant biological activities, which include cyclic AMP phosphodiesterase inhibitors,[1a,b] thromboxane synthase inhibitors,[1b−d] cardiotonic agents,[1e−g] topical antiglaucoma agents,[1h] and AMPA receptors antagonists.[1i] Accordingly, the development of efficient methods for constructing *N*-arylimidazole units remains an important area of organic synthesis.

The direct coupling of imidazoles with functionalized arenes is the most efficient approach to *N*-arylimidazole units. Although palladium- or nickel-catalyzed *N*-arylations of a variety of amines and anilines with both electron-rich and electron-deficient aryl halides have been well-documented by Hartwig,[2] Buchwald,[3] and others,[4] mild and efficient methods for the arylation of N−H-containing heterocycles are still not satisfactory. The nucleophilic aromatic substitution[1d,f,g,i,5] of imidazoles with aryl halides is one of the most commonly used methods for constructing *N*-arylimi-

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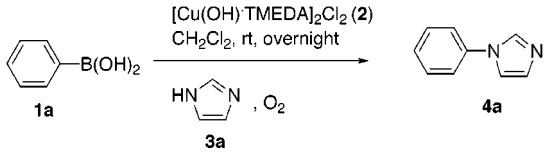
10.1021/ol000033j CCC: $19.00
Published on Web 04/13/2000

dazolyl moieties; however, this approach requires aryl halides containing electron-withdrawing substituents, which limits its scope. Another popular method for constructing *N*-arylimidazoles is the traditional Ullmann-type coupling[1a−c,e,g,h,j] of imidazoles with aryl halides. This coupling is successful for a broader range of aryl halides, but it is usually performed at high temperatures and gives varying yields. Recently, Buchwald[6] reported that this type of condensation can be accomplished in a $(CuOTf)_2$·benzene/1,10-phenanthroline/*trans*,*trans*-dibenzylideneacetone/Cs_2CO_3 system at relatively low temperatures (110−125 °C). In addition to these examples employing aryl halides, several couplings of other activated aryls under mild conditions have also been established. López-Alvarado,[7] for example, has described *N*-arylation of imidazoles with *p*-tolyllead triacetate using a catalytic amount of $Cu(OAc)_2$ at 90 °C. However, this method is limited to *p*-tolyllead, and also it produces toxic organolead byproducts. Chan and Lam[8] have reported a Cu(II) salt-promoted coupling to various *N*-arylimidazoles at room temperature. This process is usually carried out by treatment of commercially available arylboronic acids and imidazoles with more than equimolar amounts of $Cu(OAc)_2$ and either triethylamine or pyridine under ambient conditions.[9] The use of arylboronic acids is a significant improvement over previous methods, although no catalytic process of this coupling for preparing *N*-arylimidazoles has been reported to date to our knowledge. We present here an efficient diamine·copper complex-catalyzed *N*-arylation of imidazoles.

Readily available Cu(OH)Cl·TMEDA[10] has been successfully employed in aerobic oxidative coupling of 2-naphthols,[11] where dioxygen plays a critical role to regenerate the active catalyst in the catalytic cycle. We believe that this catalyst could be an excellent replacement for the Cu(II) salts and tertiary amines that are used in Chan and Lam's system.[8] We have successfully employed and optimized this catalytic system for the cross-coupling reaction of arylboronic acids with imidazoles.

In a preliminary study, we selected pure dioxygen gas as a dioxygen source rather than ambient air because of the importance of dioxygen for regenerating Cu(OH)Cl·TMEDA in the catalytic cycle,[11] and used a 2/1 ratio of phenylboronic acid (**1a**)/imidazole (**3a**) for the coupling according to Chan and Lam's studies.[8] A general procedure for optimizing the reaction condition is described as follows: 2 equiv of phenylboronic acid (**1a**) are stirred overnight with 1 equiv of imidazole (**3a**) and a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) in dry dichloromethane under an atmosphere of O_2. As shown in Table 1, reaction yields were found to be dependent on the amount of **2**. When 0.1 equiv of **2** was used, the anticipated *N*-phenylimidazole (**4a**) was obtained in 71% yield (entry 4, Table 1). However, only a trace amount of **4a** was formed using 0.02 equiv of **2** (entry 1, Table 1). Moreover, no significant improvement of the yield of **4a** was observed even employing more than 0.1 equiv of **2** (entries 5 and 6, Table 1).

Table 1. Effect of the Amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) on the Coupling



1a 3a 4a

entry[a]	catalyst **2** (mol %)	yield (%)[b]
1	2	5
2	5	54
3	7.5	62
4	10	71
5	15	73
6	20	72

[a] A typical procedure: A mixture of 2 mmol of phenylboronic acid (**1a**), 1 mmol of imidazole (**3a**), and a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) in 4 mL of dry dichloromethane is stirred at room temperature overnight under an atmosphere of O_2. [b] Isolated yields of *N*-phenylimidazole (**4a**) represent the average of two runs.

We have also investigated effects of varying the concentration and ratio of reactants, the reaction atmosphere and the addition of molecular sieves on the coupling reaction. Varying concentrations of the reaction mixture over a given range (0.1−0.5 M of **3a**, 0.2−1.0 M of **1a**) has no notable effect on the reaction yield (entries 1−4, Table 2). On the other hand, the ratio of phenylboronic acid (**1a**)/imidazole (**3a**) is an important factor for this intermolecular reaction. The optimal ratio of **1a**/**3a** is 2/1 (entry 4, Table 1), which gives the product in a higher yield compared to a 1/1 ratio (entry 5, Table 2). However, none of the desired product was obtained when a $^1/_2$ ratio of **1a**/**3a** was employed (entry 6, Table 2). Another variable is the reaction atmosphere. We found that the reaction also succeeds under ambient conditions, although a lower yield was found compared with that using pure O_2 (entries 2 and 7, Table 2). Not surprisingly, none of the desired coupling product was generated under N_2 (entry 8, Table 2). Attempts to increase the reaction yield by prolonging the reaction time were not effective. Overnight stirring is optimal. The addition of 4 Å molecular sieves

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Table 2. Effects of the Ratio of Phenylboronic Acid (**1a**)/Imidazole (**3a**), the Concentration of Reactants, the Reaction Atmosphere, and Molecular Sieves (MS) on the Coupling

entry[a]	*C* (M)[b]	**1a**/**3a**	atmosphere	MS (mg)[c]	yield (%)[d]
1	0.5	2/1	O_2	none	70
2	0.25	2/1	O_2	none	71
3	0.125	2/1	O_2	none	69
4	0.1	2/1	O_2	none	71
5	0.25	1/1	O_2	none	52
6	0.25	1/2	O_2	none	0
7	0.25	2/1	air	none	62
8	0.25	2/1	N_2	none	0
9	0.25	2/1	O_2	100	81
10	0.25	2/1	O_2	200	4

[a] A typical procedure: A mixture of phenylboronic acid (**1a**), 1 mmol of imidazole (**3a**), and 0.1 mmol of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) in dry dichloromethane is stirred at room temperature overnight. [b] The concentration of reaction mixture is based on imidazole (**3a**) (1 mmol of **3a**/mL of dichloromethane). [c] The amount of 4 Å molecular sieves is based on imidazole (**3a**) (mg of 4 Å MS/1 mmol of **3a**). [d] Isolated yields of *N*-phenylimidazole (**4a**) represent the average of two runs.

powder (100 mg of 4 Å MS/1 mmol of **3a**) to the reaction mixture results in a moderate improvement of the reaction yield (entry 9, Table 2), which is consistent with Evans' observation.[12] However, molecular sieves inhibit the reaction when greater quantities are used (200 mg of 4 Å MS/1 mmol of **3a**) (entry 10, Table 2).

Subsequently, a number of structurally and electronically diverse substrates have been employed for this catalytic coupling (Table 3). When either *o*- or *p*-tolylboronic acid (**1c** or **1b**) was used, the corresponding *N*-arylation products were obtained in good yields (entries 1, 2, 6, and 9, Table 3). Upon treatment of *p*-fluorophenylboronic acid (**1d**) with imidazole (**3a**), a fluoronated *N*-phenylimidazole (**4d**) was formed in 58% yield (entry 3, Table 3). However, the cross-coupling yields are depressed for methoxyphenylboronic acids (entries 4, 5, and 10, Table 3). When *o*-methoxyphenylboronic acid (**1f**) was applied to this coupling, only a trace amount of the coupling product was obtained. However, the yield of this coupling was improved dramatically by adding a third equivalent of **1f** (entry 4, Table 3). In fact, *o*-methoxyphenylboronic acid (**1f**) shows a propensity to decompose under the reaction conditions, which may account for the low conversion.[13] 2-Methylimidazole (**3b**) also reacts with **1b** to yield a single coupling product in good yield (entry 6, Table 3).

To test the regioselectivity of the *N*-arylation reaction, 4(5)-substituted imidazoles were treated with *o*-tolylboronic acid (**1c**). When 4(5)-methylimidazole (**3c**) was used, a mixture of coupling compounds **4h** and **4h′** was obtained in 66% yield with a 2.5/1 ratio. Furthermore, the **4h**/**4h′** ratio increased to 3.8/1 with a decreased reaction yield (37%) by employing a 1/1 ratio of **1c**/**3c** (entry 7, Table 3). Changing

(12) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

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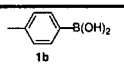
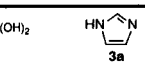
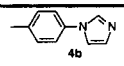
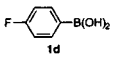
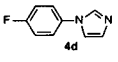
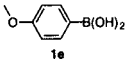
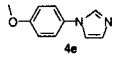
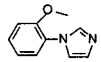
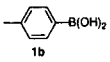
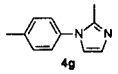
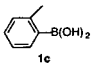
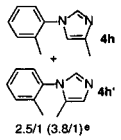
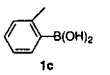
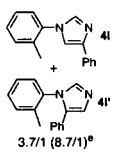
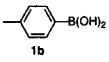
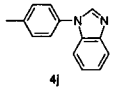
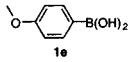
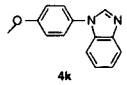
Table 3. Synthesis of a Variety of *N*-Arylimidazoles (**4**) by $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) Catalyzed *N*-Arylation of Arylboronic Acids (**1**) with Imidazoles (**3**)

entry[a]	ArB(OH)$_2$ (**1**)	Imidazole (**3**)	N-arylimidazole (**4**)	yield (%)[b]
1				71
2				74
3				58 (2[c])
4				63
5				5 (52[d])
6				64
7				68 (37[e])
8				94 (77[e])
9				98 (19[f])
10				69

[a] A typical procedure: A mixture of 2 mmol of arylboronic acid (**1**), 1 mmol of imidazole (**3**), and 0.1 mmol of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**) in 4 mL of dry dichloromethane is stirred at room temperature overnight under an atmosphere of O_2. [b] Isolated yields of *N*-arylimidazoles (**4**) represent the average of two runs. [c] A total of 1 mmol of 4-fluorophenylboronic acid (**1d**) was used. [d] A total of 3 mmol of 2-methoxyphenylboronic acid (**1f**) was used. [e] A total of 1 mmol of 2-tolylboronic acid (**1c**) was used. [f] A total of 100 mg of 4 Å MS was added, and the reaction mixture was stirred under ambient conditions.

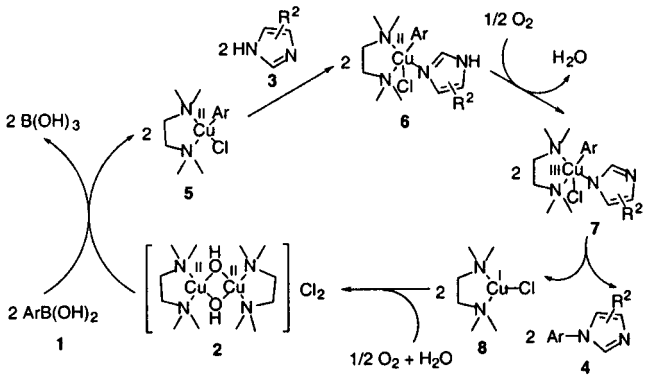
the methyl substituent on imidazole to a phenyl group further increases the regioselectivity. When a 1/1 ratio of *o*-tolylboronic acid (**1c**)/4(5)-phenylimidazole (**3d**) was employed, coupling products **4i** and **4i′** were generated in 77% yield with a ratio of 8.7/1. An additional equivalent of **1c** resulted in a lower ratio of **4i**/**4i′** (3.7/1), but a higher reaction yield (94%) (entry 8, Table 3).

Moreover, benzimidazole (**3e**) reacts with arylboronic acids to yield the corresponding *N*-arylbenzimidazoles (**4j,k**) in good yields. However, when the coupling of *p*-tolylboronic acid (**1b**) with **3e** was performed under ambient conditions

with the addition of 4 Å molecular sieves, **4k** was generated only in 19% yield (entries 9 and 10, Table 3). It should be noted that when 4,5-dicyanoimidazole and methyl 4(5)-imidazolyl-carboxylate were employed for the coupling, none of the desired product was obtained.

The speculated mechanism in Scheme 1 stems from Evans' postulation for coupling arylboronic acids (**1**) with phenols.[12] The initial transmetalation of **1** with catalyst **2** would generate **5**. The imidazole (**3**) could coordinate to the Cu(II) to generate **6**, thus reducing the reduction potential[14] of the Cu(III)/Cu(II) couple. In the presence of O_2, the Cu(II) in **6** should be readily oxidized to Cu(III), thereby forming a putative Cu(III) intermediate (**7**) which would subsequently undergo reductive elimination to give the *N*-arylimidazole (**4**) along with the Cu(I) complex (**8**). The latter, should readily regenerate catalyst **2**[10a,b] (Scheme 1). It was reported that **1** can release H_2O through triarylboroxine formation,[15] which could result in the competitive arylation of water and the subsequent competition of phenol with imidazole substrates, thereby diminishing yields of the desired coupling products. Presumably, during the oxidation of Cu(II) to Cu(III), hydrogen peroxide would also be produced, which could decompose **1**.[16] These could explain the use of more than 1 equiv of **1** in the coupling to obtain synthetically useful yields. We have not attempted to analyze the intermediates and byproducts produced or involved in the coupling. The mechanism described here is speculation and the actual pathway of the coupling may be elucidated in due course.

Scheme 1



In summary, we have developed a novel system for preparing a variety of *N*-arylimidazoles (**4**) in good to excellent yields through cross coupling arylboronic acids (**1**) with imidazole compounds (**3**) in the presence of a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ (**2**).

Acknowledgment. This work was supported by the NIH (grant GM17880). We thank the Mass Spectrometry Facility at the UCSF supported by the NIH (grants RR 04112 and RR 01614).We also thank Professor Scott E. Denmark for helpful discussion.

Supporting Information Available: Experimental procedures and characterizations for compounds **4a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000033J

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