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A simple copper salt catalysed the coupling of imidazole with arylboronic acids in protic solvent†

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In the presence of a catalytic amount of a simple copper salt, the coupling of imidazole with arylboronic acids was performed in methanol to give corresponding *N*-arylimidazoles in almost quantitative yields; this coupling reaction could also be performed in aqueous solutions to give *N*-arylimidazoles in excellent yields.

N-Arylimidazoles are important compounds because of their significant pharmaceutical,[1] biological,[2] and chemical activities.[3] The development of mild and highly efficient method for synthesis of *N*-arylimidazoles has recently gained considerable attention in synthetic chemistry, such as nucleophilic aromatic substitution,[1a,2a,b] and traditional Ullmann reaction,[1b,2b,c,4c] as well as the coupling of imidazoles with aryllead, arylbismuth, arylborane or arylsilane.[4a,b,d,e] The use of arylboronic acids is a significant improvement over previous methods. A recent series of developments by Chan and Lam' group have shown that the coupling of arylboronic acids with imidazole was effective when stoichiometric quantities of $Cu(OAc)_2$ and base were used.[5c] A more important discovery by Collman has demonstrated that this coupling reaction can be rendered when a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ was used.[6] However, both methods had been conducted usually in halogenated hydrocarbon or other non-protic solvents and with the use of complex copper salts and other additives. Therefore, it is important to develop more simple and efficient catalytic systems to prepare *N*-arylimidazoles in the absence of additional ligands and bases.

As a part of our ongoing research on imidazole and imidazolium cyclophanes,[7] we present the first example of the use of simple copper salts to catalyse the coupling of imidazole with arylboronic acids in protic solvents. By using only 5% mol of a simple copper salt, without the addition of any bases or other ligands, the coupling reaction was performed in methanol to give corresponding *N*-arylimidazoles in almost quantitative yields. This coupling reaction could also be performed in aqueous solution to give *N*-arylimidazoles in high yields. To the best of our knowledge, the coupling of imidazole with arylboronic acids conducted in protic solvents and with the use of simple copper salts has not been explored previously, this represents an advance over the use of complex copper salts together with a substantial amount of a base in non-protic solvent.

To select proper solvent is very important in this reaction. In view of previous methods, CH_2Cl_2 is the optimum solvent for the coupling of arylboronic acids with imidazole, and no product was observed when CH_3OH was used as solvent.[5,6a,6c] We firstly selected CH_2Cl_2, $ClCH_2CH_2Cl$, $PhCH_3$, THF, CH_3COCH_3, CH_3CN as reaction solvents, unfortunately, none of desired product was obtained in the catalytic system of a simple copper salt. However, when CH_3OH was employed as solvent, *N*-arylimidazoles were obtained in almost quantitative yields in the system of simple copper salts.

The effect of reaction temperature on chemical yield was also examined. High yield was obtained when the coupling reaction was carried out in methanol and refluxed 3 h. The coupling reaction at room temperature for 5 days gave only trace of desired product.

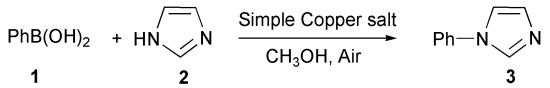
† Dedicated to Professor Xie Ming-Gui on the occasion of his 65th birthday.

We then made a survey of the effect of different simple copper salts and their amounts on the coupling of phenylboronic acid with imidazole in methanol. As shown in Table 1, no product was formed in the absence of CuCl, and only trace product was observed using 0.1% mol CuCl (Table 1, Entry 1, 2). However, when 3–5% mol of CuCl were used, the *N*-phenylimidazole was obtained in 98% yield (Table 1, Entry 5, 6). All the copper (I) salts gave the product with essentially the same high level of yield (> 97%). As such, the counterion does not play a significant role. In the case of copper (II) salts, this coupling reaction took longer time to accomplish. As the same with copper (I), $CuCl_2\cdot 2H_2O$ and $Cu(OAc)_2\cdot H_2O$ also gave almost quantitative yield. (Table 1, entry 10, 11)

The ratio of imidazole–phenylboronic acid is an important factor for this intermolecular reaction. We found that when the ratio is more than 1.2 : 1, *N*-phenylimidazole was obtained in almost quantitative yield (Table 2, Entreis 3, 4 and 5). Decreasing the ratio to 1 : 1, *N*-phenylimidazole was obtained in 89% yield (Table 2, Entry 1). This result is much better than previous report.[6c]

The catalytic system has also been proved to be highly efficient for other arylboronic acids (Table 3). It is worth mentioned that all

Table 1 Effect of copper salts and their amount on the coupling reaction



1 2 3

Entry	Copper salt	Amount (mol %)	Yield(%)[a]
1	CuCl	0	0
2	CuCl	0.1	trace
3	CuCl	1	40
4	CuCl	2	93
5	CuCl	3	98
6	CuCl	5	98
7	CuBr	5	98
8	CuI	5	98
9	$CuClO_4$	5	97
10[b]	$CuCl_2\cdot 2H_2O$	5	96
11[b]	$Cu(OAc)_2\cdot H_2O$	5	98
12[c]	$Cu(NO_3)_2\cdot 3H_2O$	5	81

[a] Isolated yield, purity confirmed by HPLC, MS and ^1H NMR. [b] Reflux 5 h. [c] Reflux 12 h.

Table 2 Effect of the ratio of imidazole–phenylboronic acid on the coupling reaction[a]

Entry	Imidazole–phenylboronic Acid[b]	Yield(%)[c]
1	1	89
2	1.1	94
3	1.2	98
4	1.5	98
5	2	98

[a] 5% mol of CuCl was used. [b] mol/mol. [c] Isolated yield, purity confirmed by HPLC, MS and ^1H NMR.

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the *o*-, *m*- and *p*-tolylboronic acids were used, the corresponding N-arylation products were obtained in almost quantitative yields (Table 3, Entries 2, 3 and 4). Completed conversion was readily obtained for naphthylboronic acid and to give *N*-naphthylimidazole in 98% yield (Table 3, Entry 7). Although a slightly longer reaction time compared with the phenylboronic acid was required, which is consistent with the general trend that the latter is less steric hindrance of the reaction center than the former. In particular with the *o*-methoxyarylboronic acids, the coupling yields was only in 5% in previous work,[6c] but it was also obtained in excellent yields in the catalytic system of simple copper salts. (Table 3, Entry 5, 8)

In recent years, many chemists devoted to the use of water as a reaction medium for organic synthesis.[9] However, very few examples of N-arylation accomplished in aqueous media have been reported.[5b]

We then set out to explore the coupling reaction in aqueous solution, and found when water was used solely, the yields were depressed (Table 4, Entry 1, 2). This may be attributed to the poor solubility of reactants in water. In view of the excellent yield while the coupling reaction was performed in CH_3OH, we tried to study this coupling in mixed protic solvent, as can be seen from Table 4, a small quantity of CH_3OH was added, the coupling yield was still poor, and when a 1 : 1 ratio of H_2O–CH_3OH was used, the coupling yield came to 90% (Table 4, Entry 3, 4). The results encouraged us to study the coupling reaction in other mixed solvents such as C_2H_5OH–H_2O, THF–H_2O or CH_3COCH_3–H_2O in 1 : 1 ratio, respectively, the coupling product was also obtained in the same high yield (Table 4, Entreis 5, 6 and 7). Obviously, it can be considered that solvent effect was one of the most important factors in the coupling of arylboronic acids with imidazole. Protic solvents were essential to the coupling reaction in the catalytic system of simple copper salts.

In conclusion, we have developed a novel and highly efficient catalytic system for preparing a variety of *N*-arylimidazoles in excellent yields through the cross coupling of arylboronic acids with imidazole in protic solvents and in the presence of a catalytic amount of simple copper salts. In addition, this system also works well with pyrazole, anilines, and imides. The further work and the study on mechanism are being in progress.

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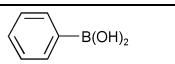
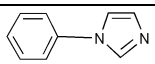
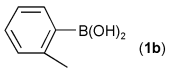
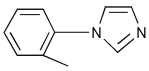
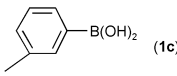
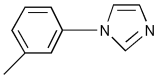
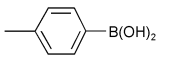
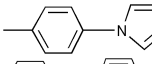
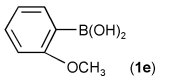
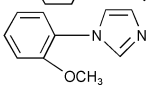
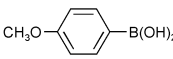
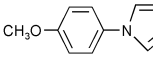
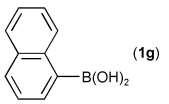
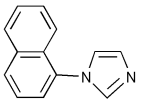
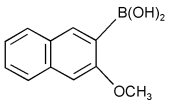
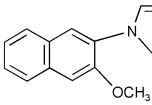
Table 3 Synthesis of a variety of *N*-arylimidazoles[a]

Entry	**1**	*N*-arylimidazoles (**3**)	Yield (%)[b]
1	 (**1a**)	 (**3a**)	98
2	 (**1b**)	 (**3b**)	98
3	 (**1c**)	 (**3c**)	97
4	 (**1d**)	 (**3d**)	98
5[c]	 (**1e**)	 (**3e**)	93
6[c]	 (**1f**)	 (**3f**)	92
7[c]	 (**1g**)	 (**3g**)	98
8[c]	 (**1h**)	 (**3h**)	92

[a] 5% mol of CuCl was used. [b] Isolated yield, purity confirmed by HPLC, MS and ^{1}H NMR. [c] Reflux 6 h.

Table 4 Coupling reaction in different aqueous solution[a]

Entry	Solvent (V/V)	Yield (%)[b]
1	H_2O	22
2[c]	H_2O	10
3	H_2O–CH_3OH (10 : 1)	22
4	H_2O–CH_3OH (1 : 1)	90
5	H_2O–C_2H_5OH (1 : 1)	90
6	H_2O–THF (1 : 1)	92
7	H_2O–CH_3COCH_3 (1 : 1)	88
8	H_2O-CH_3CN (1 : 1)	58

[a] 5% mol of $Cu(OAc)_2.H_2O$ was used and refluxed 6 h. [b] Isolated yield, purity confirmed by HPLC, MS and ^{1}H NMR. [c] 5% mol of CuCl was used.

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8 Typical procedure for the cross coupling reaction: a mixture of 2 mmol of arylboronic acid (**1**), 2.4 mmol of imidazole (**2**), and a catalytic amount of copper salt in 10 ml dry methanol was stirred under an atmosphere of air and refluxed 3 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography using CH_2Cl_2–C_2H_5OH as the eluent to give *N*-arylimidazole (**3**). *N*-(2-methoxynaphthyl)imidazole (**3h**) is a new compound and its spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.78–7.80 (m, 2H), 7.74 (s, 1H), 7.49–7.54 (m, 1H), 7.40–7.44 (m, 1H), 7.30–7.31 (d, 2H), 7.22 (s, 1H), 3.96 (s, 3H) ppm; M/S (*m*/*z*): 224(M^+, 100), 196, 182, 169, 152, 139, 127, 113, 101, 84, 77, 58; elemental analysis calcd. (%) for $C_{14}H_{12}N_2O$ (224.26): C 74.98, H 5.39, N 12.49; found C 74.62, H 5.32, N 12.35%.

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