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Cross Coupling of Arylboronic Acids with Imidazoles by Sulfonatocopper(II)(salen) Complex in Water

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A mild and clean protocol for the cross coupling reactions between imidazoles and arylboronic acids has been developed in good to excellent yields up to 98% in the presence of sulfonatocopper(II)(salen) catalyst in water without addition of other additives and bases.

Carbon–nitrogen bond forming reactions are one of the most widely used methodologies for the synthesis of biologically active molecules.[1] *N*-Arylimidazole subunit is a commonly found structural motif in agrochemical, pharmaceutical, and biological compounds because of their biomedical applications as thromboxane synthase inhibitors[2] and has been exploited as important precursors of versatile *N*-heterocyclic carbenes,[3] a powerful class of ligands for transition-metal catalysis[4] or room-temperature ionic liquids.[5] Previously, Chan, Lam and co-workers developed an efficient method for coupling of azoles and arylboronic acids for the synthesis of *N*-arylazoles by using stoichiometric $Cu(OAc)_2$ and pyridine as base.[6] Later, Collman and co-workers demonstrated the use of a catalytic amount of $[Cu(OH)tmeda]_2Cl_2$ for the coupling of arylboronic acid with imidazole in dichloromethane and water at room temperature.[7] Thereafter, simple copper salt catalyzed coupling of imidazoles with arylboronic acids in methanol was reported.[8] A recent notable achievement has been made by using copper(I) oxide as catalyst in *N*-arylation of azoles and amines with arylboronic acids at room temperature in methanol.[9] Despite the synthetic elegance the vast majority of the existing protocols were generally operated in volatile organic solvents. To make the catalysis in a "greener" approach, organic reactions in water have recently attracted much attention on account of the environmental friendliness.[10]

Recently, we reported the first example of *N*-arylation of imidazoles with iodobenzene catalyzed by sulfonatocopper(II)-(salen) complex **1** (Figure 1) under mild conditions in water with satisfactory results.[11] To determine the applicability of the complex catalyzed C–N coupling reaction, *N*-arylation reactions of imidazoles with arylboronic acids in the presence this complex were carried out in this work.

To identify the best catalytic system for *N*-arylation reactions of imidazoles with arylboronic acids, in our initial study, the reaction between phenylboronic acid (2 equiv) and imidazole (1 equiv) in water (3 mL) was chosen as a model without any additives and bases, a variety of different catalyst loadings and reaction temperatures were screened, and the results of optimization are listed in Table 1.

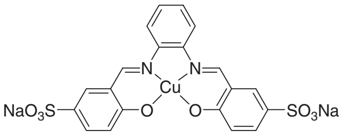
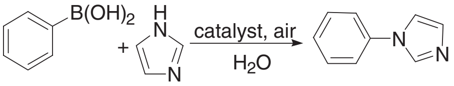


Figure 1. Structure of sulfonatocopper(II)(salen) complex **1**.

Table 1. Screening reaction conditions for the *N*-arylation of imidazole with arylboronic acid



Entry	Time/h	Temp/°C	Catalyst/%	Yield[a]/%
1	24	100	10	97
2	12	100	10	97
3	6	100	10	98
4	4	100	10	90
5	1	100	10	81
6	6	100	5	71
7	6	100	2	49
8	6	100	—	trace
9	6	80	10	87
10	6	60	10	45
11	6	25	10	<10

[a]Yields were determined by GC using 1,4-dichlrobenzene as internal standard.

Comparison of the various reaction times indicated that 6 h was enough for the catalysis with 98% yield (Table 1, Entry 3). Meanwhile, the control experiments indicated that the presence of catalyst was crucial for the reaction, 10% catalyst loading was proven to be essential in the procedure, and only trace of product was detected in the absence of catalyst (Table 1, Entries 6–8). Furthermore, lower temperature than 100 °C decelerated the reaction and led to lower yields (Table 1, Entries 9–11).

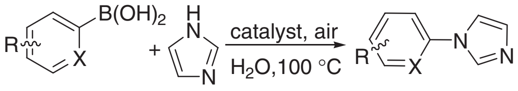
Thus, the optimized reaction conditions for the *N*-arylation involved 6 h, 100 °C, and 10% catalyst loading. Then, the scope of arylboronic acids was investigated under these reaction conditions.[12]

As shown in Table 2, most of the substituted arylboronic acids can give moderate to excellent yields. Also, electron-deficient arylboronic acids resulted in excellent yields ranging from 83 to 93% (Table 2, Entries 6–11), while electron-rich arylboronic acids depressed the reaction to a certain degree in lower yields (43–68%). On the other hand, steric hindrance was another important factor to affect the results (Table 2, Entries 1–5). Heteroarylboronic acid was also tried in a yield of 83%.

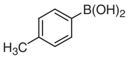
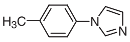
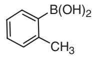
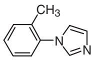
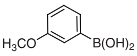
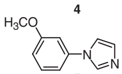
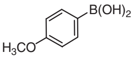
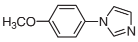
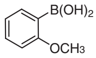
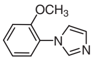
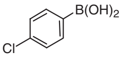
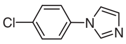
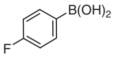
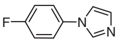
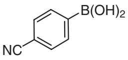
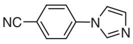
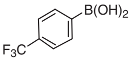
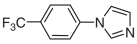
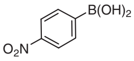
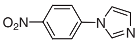
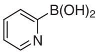
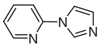
Encouraged by these results, a variety of imidazole derivatives were applied in catalytic coupling reactions with arylboronic acids, and the results are listed in Table 3.

To our delight, most of the corresponding cross-coupling products can be afforded in good to excellent yields (77–95%) under the optimized reaction conditions. Sterically hindered 2-methylimidazole and 2-ethyl-4-methylimidazole could also undergo selective *N*-arylation with heteroarylboronic acid to give good yields (Table 3, Entries 7–9). The results indicated that arylboronic acid could be a proper substituent of iodobenzene in the catalytic coupling reactions.

Table 2. *N*-Arylation of imidazole with different arylboronic acids catalyzed by complex **1**[a]

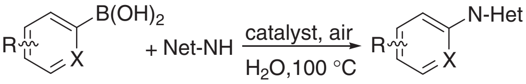


X=C, N **3-13**

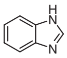
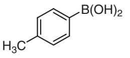
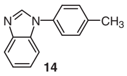
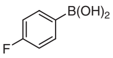
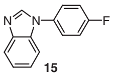
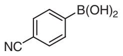
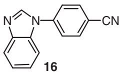
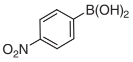
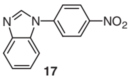
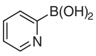
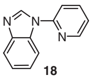
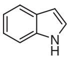
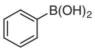
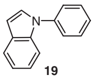
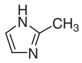
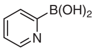
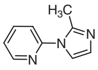
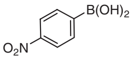
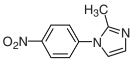
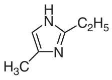
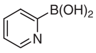
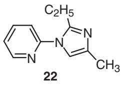
Entry	Arylboronic acid	Product	Yield[b] /%
1		 **3**	68
2		 **4**	65
3		 **5**	55
4		 **6**	54
5		 **7**	43
6		 **8**	83
7		 **9**	93
8		 **10**	83
9		 **11**	92
10		 **12**	90
11		 **13**	83

[a] Reaction condition: arylboronic acid (1.0 mmol), imidazole (0.5 mmol), complex **1** (0.05 mmol), H_2O (3 mL), 100 °C, 6 h. [b] Isolated yield.

Table 3. The coupling of imidazoles and different arylboronic acids catalyzed by complex **1**[a]



X=C, N **14-22**

Entry	Het-NH	Arylboronic acid	Product	Yield[b] /%
1			 **14**	77
2			 **15**	88
3			 **16**	92
4			 **17**	95
5			 **18**	90
6			 **19**	88
7			 **20**	80
8			 **21**	85
9			 **22**	75

[a] Reaction condition: arylboronic acid (1.0 mmol), imidazole derivatives (0.5 mmol), complex **1** (0.05 mmol), H_2O (3 mL), 100 °C, 6 h. [b] Isolated yield.

In conclusion, we have discovered a new protocol of sulfonatocopper(II)(salen) catalyzed cross coupling of arylboronic acids with imidazoles, this method proceeds under mild conditions which is beneficial for operation. Furthermore, the procedure is performed in water without addition of other additives and bases.

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