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A Simple and Efficient Catalytic System for N-Arylation of Imidazoles in Water

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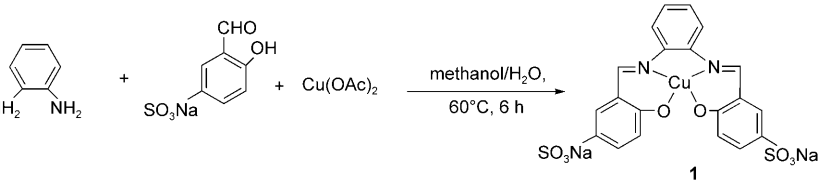
N-Aryl imidazoles are key structural motifs in a wide range of agrochemicals, pharmaceuticals, and biologically active compounds[1] and have been exploited as important precursors of versatile N-heterocyclic carbenes,[2] a powerful class of ligands for transition-metal catalysis[3] or room-temperature ionic liquids.[4] A traditional method of introducing this functionality is nucleophilic aromatic substitution of imidazole with activated aryl halides (S_NAr reactions) or classic Ullmann-type coupling reactions.[5] However, these well-known methods suffer from several drawbacks, such as high reaction temperature, stiochiometric amounts of metal reagents, and low functional-group tolerance, which has limited their applications. Recently, Buchwald et al.[6] and Taillefer et al.[7] found several N- and O-based ligands could greatly facilitate the copper-catalyzed path for the N-arylation of imidazoles. After the discovery of these ligands, interest in this field has increased spectacularly in the last few years[8] and resulted in the golden age of copper-catalyzed Ullmann-type coupling reactions. While many important results have been achieved via this methodology, it is worth noting that these protocols are generally operated in volatile organic solvents with transition-metal ions. From the standpoint of green chemistry, the development of more environmentally benign reaction media, such as water, in place of organic solvents would be desirable.[9] Henceforth, as part of our endeavors toward the development of environmentally friendly protocols, efforts were directed towards performing the N-arylation reaction by using water as the sole reaction medium.

To date, salen ligands have been recognized as one of the most efficient auxiliaries, and many metallosalen complexes are used as excellent catalysts in various organic transformations.[10] Herein we report the first example the N-arylation of imidazoles directly catalyzed by sulfonato–Cu(salen) complex **1** under mild conditions in water with satisfactory results. This catalytic system contains several advantages: 1) Water, a green solvent, is used in place of volatile organic solvents; 2) the catalysis reactions could be performed without an inert gas atmosphere and with low catalyst loading; 3) the work-up procedure is simple with excellent yields; 4) the catalyst could be easily recovered and used again.

As shown in Scheme 1, catalyst **1** could be conveniently synthesized in 82% yield by a one-pot reaction of three components, *o*-phenylenediamine, 5-sulfonatosalicylaldehyde, and copper acetate, in methanol/H_2O according to a modified literature method.[11] The complex is remarkably soluble in water and stable in air and did not decompose even after several months.



Scheme 1. Preparation of catalyst **1**.

To optimize the reaction conditions, the catalyzed N-arylation was performed with imidazole (1.1 equiv) and iodobenzene (1 equiv) in the presence of complex **1** (2 mol%), a base (2 equiv), and $(n\mathrm{Bu})_4\mathrm{NBr}$ as the phase-transfer catalyst (PTC; 5 mol%) in water. As shown in Table 1, comparison of the various bases revealed that NaOH and KOH gave the best yields of around 100% (Table 1, entries 3 and 4), whereas only a trace amount of product was found when or-

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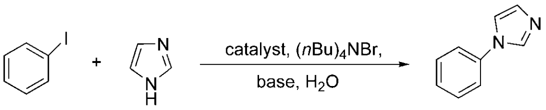
Table 1. Screening reaction conditions for N-arylation of imidazole with iodobenzene.



2

Entry	Catalyst [%]	PTC [%]	Base	*t* [h]	*T* [°C]	Yield[a] [%]
1	2	5	Cs_2CO_3	18	100	88
2	2			18	100	75
3	2	5	NaOH	12	100	100
4	2	5	KOH	12	100	100
5	2	5	Et_3N	24	100	<1
6	2	5	Pyridine	24	100	<1
7	–	5	NaOH	12	100	0
8	2	–	NaOH	12	100	32
9	2	5	NaOH	24	25	5
10	2	5	NaOH	24	50	23
11	2	5	NaOH	18	80	91

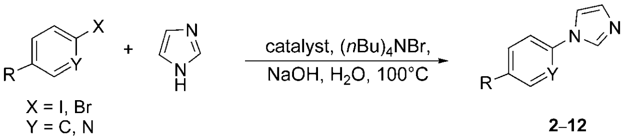
[a] Yields were determined by GC/MS with 1,4-dichlrobenzene as internal standard.

ganic bases, such as triethylamine or pyridine, were used (Table 1, entries 5 and 6). Therefore, the more inexpensive NaOH was chosen for further catalysis reactions. Meanwhile, the control experiments showed that the presence of catalyst and PTC was crucial for the catalysis. No product was detected in the absence of catalyst, and only a 32% yield was obtained in the absence of the PTC (Table 1, entries 7 and 8). In addition, low temperatures decelerated the reaction rate and led to lower yields (Table 1, entries 9–11).

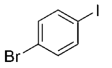
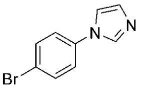
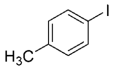
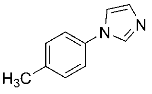
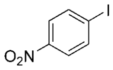
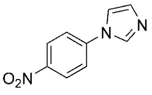
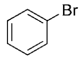
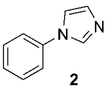
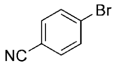
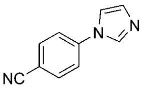
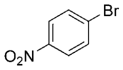
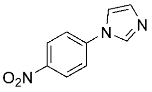
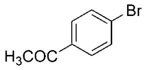
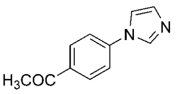
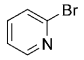
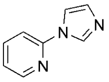
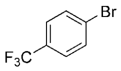
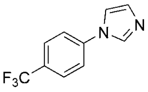
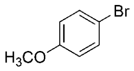
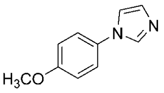
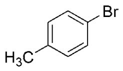
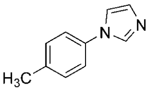
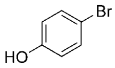
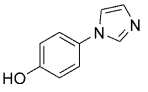
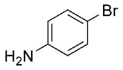
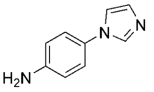
The scope of aryl halide substrates was then investigated by using the catalytic system under the optimized reaction conditions. As shown in Table 2, most of the substituted aryl iodides and electron-deficient aryl bromides afforded N-aryl imidazole products **2**–**12** in water with excellent yields ranged from 78 to 93%. However, the arylation of electron-rich aryl bromides resulted in lower yields (41–64%) even with a longer reaction time of 24 h (Table 2, entries 10–13). Furthermore, the catalytic system could tolerate a variety of functionalized aryl halides in the reaction, including nitrile, nitro, acetyl, and ether groups (Table 2, entries 5–7, 10). On the other hand, imidazole could be selectively arylated by aryl halides with hydroxyl or amino group in good yields without formation of diaryl ether or diaryl amine (Table 2, entries 12 and 13); usually these functional groups should be protected before catalysis, as reported previously.[12]

In an endeavor to expand the scope of the methodology, this new catalytic system was applied to a variety of imidazole derivatives (see Table 3). To our delight, most of the imidazole derivatives and indole exclusively afforded the corresponding products in good to excellent yields (73–97%) under the optimized reaction conditions. Note that the sterically hindered 2-methylimidazole could undergo selective N-arylation with 4-nitrobromobenzene and 2-bromopyridine to give yields of 82 and 80%, respectively (Table 3, entries 6 and 7). The more sterically hindered 2-ethyl-4-methylimidazole was also coupled with 2-bromopyridine to

Table 2. N-arylation of imidazole with different aryl halides catalyzed by complex **1**.

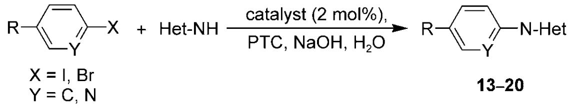


2–**12**

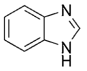
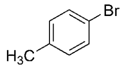
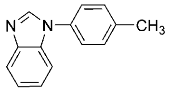
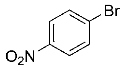
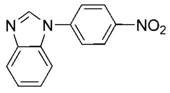
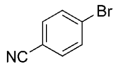
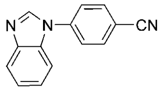
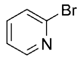
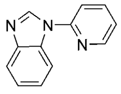
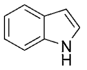
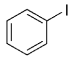
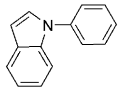
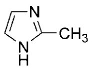
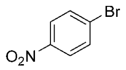
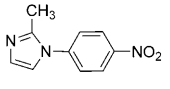
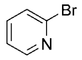
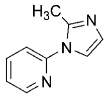
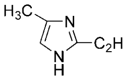
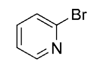
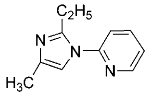
Entry	ArX	Product	Yield[a] [%]
1		 **3**	86
2		 **4**	78
3		 **5**	93
4		 **2**	85
5		 **6**	82
6		 **5**	85
7		 **7**	79
8		 **8**	81
9		 **9**	88
10		 **10**	41[b]
11		 **4**	47[b]
12		 **11**	58[b]
13		 **12**	64[b]

[a] Isolated yields. [b] Reaction time: 24 h.

Table 3. Sulfonato–Cu(salen)-catalyzed N-arylation of aryl halides with other imidazoles.[a]



13–20

Entry	Het-NH	ArX	Product	Yield[b] [%]
1			 **13**	81
2			 **14**	97
3			 **15**	92
4			 **16**	88
5			 **17**	94
6			 **18**	82
7			 **19**	80
8			 **20**	73

[a] The reactions were carried out by using the general procedure (see the Experimental Section). [b] Isolated yields.

give 1-phenyl-2-ethyl-4-methylimidazole **20** in 73% yield (Table 3, entry 8), which is the first example of the copper-catalyzed N-arylation of a substituted imidazole in water.

Furthermore, the catalyst could be easily recovered and reused. For example, after the first coupling reaction between 4-trifluoromethylbromobenzene and imidazole, which gave a yield of 88%, the product could be easily separated from the reaction mixture by extraction with ethyl acetate. Substrates, PTC, and base were then added to the remaining aqueous solution that contained the catalyst for the next reaction. The recycled catalyst could be reused at least three times and gave quite stable yields of 87, 85, and 84%. The reusability study of the catalyst indeed constitutes a challenge of considerable economic and environmental importance.

In summary, we have developed a simple, highly efficient, and environmentally friendly protocol of sulfonato–Cu-(salen)-catalyzed N-arylation of imidazoles in water with a low catalyst loading (2%) and cheap base. This method avoids the use of stringent inert conditions. In addition, the catalyst can be easily recovered and reused. Overall, we believe that this catalyst system could provide an important complement to the Pd- or Cu-catalyzed methods that have already been used in a number of applications.

Experimental Section

Preparation of catalyst 1: $Cu(OAc)_2$ (0.012 mol, 2.18 g) was added to a solution of *o*-phenylenediamine (0.01 mol, 1.08 g) and 5-sulfonatosalicylaldehyde (0.02 mol, 4.5 g) in methanol/H_2O (10:1, 30 mL). The mixture was stirred at 60°C for 6 h and then filtered. After filtration, the precipitate was washed with dichloromethane to remove unreacted $Cu(OAc)_2$. The solid product was collected and dried under vacuum to afford the desired complex **1** (4.7 g; 82% yield). IR (Nujol): $\tilde{\nu}=1610$ (C=N); 1036, 1116 (SO_3); 443 cm^{-1}(Cu-N); MS (negative): *m/z* (%): 536 (100%?) $[M-2Na]^+$; elemental analysis calcd (%) for $C_{20}H_{12}N_2O_8S_2Na_2Cu$: C 41.28, H 2.08, N 4.81; found: C 41.35, H 2.21, N 4.80.

Typical procedure for the catalysis: Imidazole (1.1 mmol), catalyst (12 mg, 0.02 mmol), $(nBu)_4NBr$ (16 mg, 0.05 mmol), aryl halide (1 mmol), NaOH (80 mg, 2 mmol), and water (3 mL) were added to a sealed tube. The reaction mixture was stirred at 100°C for 12 h and then cooled to room temperature and extracted with ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The N-arylated product was finally obtained by column chromatography on silica gel. All the products were confirmed by ^1H and ^{13}C NMR spectroscopic analysis. See the Supporting Information for full details.

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Keywords: copper · cross-coupling · homogeneous catalysis · sulfonates · water chemistry

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