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Sulfonato–Cu(salen) Complex Catalyzed *N*-Arylation of Aliphatic Amines with Aryl Halides in Water

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A water-soluble sulfonato-Cu(salen) complex catalyzed procedure for the *N*-arylation of simple aliphatic amines, amino alcohols and amino acids in pure water have been developed. A variety of substituted aryl iodides, bromides and electron-deficient chlorides were found to be applicable, and 1,2-disubstituted benzimidazoles could be prepared easily by a cascade amination/condensation process in this catalytic system.

Introduction

The copper-catalyzed C–N bond formation by the pioneering work of Ullmann and Goldberg has became one of the most powerful synthetic strategies for the construction of nitrogen-containing intermediates, which are key structural motifs for the synthesis of pharmaceuticals, agrochemicals, polymers, or materials.[1] Over the past decade, many efforts have been devoted to this methodology to improve its efficiency and selectivity by demonstrating the use of chelating ligands,[2] including 1,3-diketones,[3] 1,2-diamines,[4] phenanthrolines,[5] bipyridines,[6] α-amino acids,[7] diols,[8] salicylamides[9] and others.[10] Recently, Buchwald and Hartwig and co-workers made significant progresses in the mechanism study of diamine ligands promoted Ullmann-type C–N cross coupling.[11] Although important advances have been made in the aforementioned transformations, it is still highly desired to develop readily available, economic and environmentally friendly protocols for this type of reactions.

In general, organic solvents are used extensively for organic transformations, which lead to various environmental and health concerns.[12] Considering the requirement of green chemistry, various cleaner solvents have been evaluated as replacement, such as water,[13] supercritical fluids[14] and ionic liquids.[15] As a natural solvent, the nontoxic, cheap, and readily available water is obviously the most attractive one for both academic and industrial settings. Therefore, there has been increased interest in catalytic cross-coupling reactions in aqueous medium by water-soluble transition metal complexes recently.[16,17] On the other hand, salen ligands and related transition metal complexes are well known for enabling a broad array of organic transformations. However, it is rarely used in Ullmann-type cross-coupling reactions to date. In 2004, Taillefer and coworkers described an efficient copper-catalyzed *N*-arylation of heterocycles with aryl halides under mild conditions supported by tetradentate Schiff base ligands in an organic medium.[18] Inspired by this pioneering work, we have recently prepared a water-soluble sulfonato–Cu(salen) complex, which was successfully applied in the catalytic *N*-arylation of imidazoles and aqueous ammonia with aryl halides in water without an inert gas.[19] Encouraged by these precedents, we envisioned such catalyst may be applied in other types of C–N bond-forming processes. Thus, a series of aliphatic N-nucleophiles including simple aliphatic amines, amino alcohols and amino acids was employed to react with aryl halides in water. Herein, we wish to disclose the results.

Results and Discussion

Our first effort was devoted to the preparation of a variety of substituted sulfonato–Cu(salen) complexes as indicated in Figure 1. Complexes **1**–**6** could be conveniently synthesized by condensation of the corresponding diamines with 5-sulfonatosalicylaldehydes and a sequential addition of copper acetate in good yields.

To evaluate the catalytic efficiency of the catalyst, 4-iodotoluene and cyclohexylamine were chosen as model substrates for the reaction catalyzed by copper complex (10 mol-%) in the presence of NaOH (2 equiv.) in water at 120 °C as shown in Table 1. Gratifyingly, the substrates were transformed into the desired *N*-arylated products in

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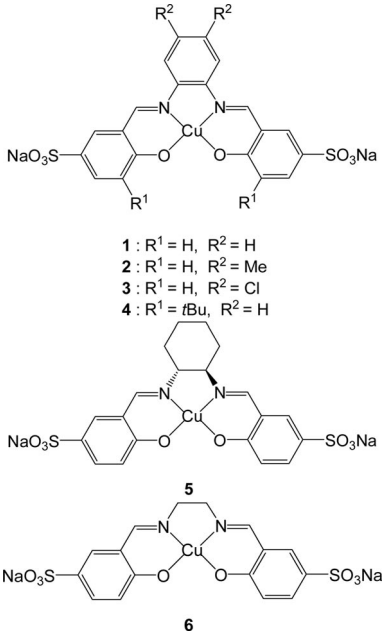
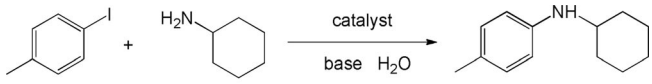


Figure 1. Structures of sulfonato–Cu(salen) complexes **1**–**6**.

comparable moderate yields ranging from 70 to 80% in the presence of complexes **1**–**4**, which indicates that the substituents of the benzene ring have only a small effect on the catalysis (Table 1, Entries 1–4). However, when the diamine was changed from diaminobenzene to diaminocyclohexane or 1,2-ethylenediamine, the yields dropped dramatically to around 40% (Entries 5–6). Thus, complex **1** was selected as catalyst in the following studies. The temperature was a key parameter in the process, and attempts to lower it resulted in a decreased yield (Table 1, Entry 7). Furthermore, the base is another important factor for the *N*-arylation reaction; a control experiment showed that the yield decreased to 41% in the absence of any base (Table 1, Entry 8). The following base screening showed that Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4 and NaOH were all effective and gave quite similar results; CH_3COONa, $NaHCO_3$ and organic bases such as triethylamine resulted in lower yields (Table 1, Entries 9–15). Moreover, the extension of the reaction time to 15 h improved the yield to 89% (Table 1, Entries 16–18). The addition of phase-transfer catalysts (PTCs) seemed to be not necessary in this case with almost the same result (Table 1, Entries 17 and 19). Test experiments carried out in the absence of catalyst led to trace yields of the desired product, which illustrates the key role of the water-soluble sulfonato–Cu(salen) complexes in this transformation (Table 1, Entry 21).

Next, a variety of aryl halides were tested under the optimized reaction conditions. As shown in Table 2, all the aryl iodides and most of the bromides reacted with cyclohexylamine smoothly, leading to the desired products in moderate to excellent yields. Electron-withdrawing groups seemed to be a little beneficial for the catalysis compared to electron-donating ones. For example, 1-bromo-4-nitrobenzene and 1-bromo-4-methoxybenzene led to the corresponding arylated products in 90% and 85% yields, respectively (Table 2, Entries 3 and 6). Notably, sterically demanding *ortho* substituents did not hamper the arylation reaction (Table 2, Entries 8 and 9). Heterocyclic aryl halides could also be coupled with cyclohexylamine to afford the corresponding products in excellent yields (Table 2, Entries 10 and 11). Then, we were intrigued by the possibility of using the aryl chlorides as coupling partner, which have been proven to be problematic substrates in Ullmann-type cross couplings. To our pleasure, several electron-deficient aryl chlorides afforded the corresponding products in moderate yields (Table 2, Entries 3 and 11). 2-chlorobenzoic acid also exhibited a high activity due to the possible *ortho*-substituent effect, which might greatly expand the application of this methodology (Table 2, Entry 12).[20]

Table 1. Optimization of sulfonato–Cu(salen) complex catalyzed cross coupling between 4-iodotoluene and cyclohexylamine in water.[a]



7a 8a 9a

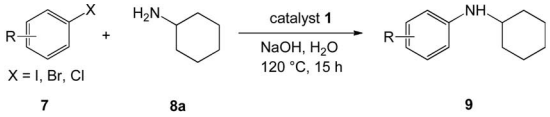
Entry	Catalyst (mol-%)	Base	*T* [h]	Yield [%][b]
1	**1** (10)	NaOH	12	79
2	**2** (10)	NaOH	12	70
3	**3** (10)	NaOH	12	80
4	**4** (10)	NaOH	12	77
5	**5** (10)	NaOH	12	40
6	**6** (10)	NaOH	12	41
7[c]	**1** (10)	NaOH	12	52
8	**1** (10)	–	12	41
9	**1** (10)	Na_2CO_3	12	79
10	**1** (10)	K_2CO_3	12	79
11	**1** (10)	Cs_2CO_3	12	81
12	**1** (10)	K_3PO_4	12	81
13	**1** (10)	CH_3COONa	12	43
14	**1** (10)	$NaHCO_3$	12	47
15	**1** (10)	$N(Et)_3$	12	42
16	**1** (10)	NaOH	9	62
17	**1** (10)	NaOH	15	89
18	**1** (10)	NaOH	20	88
19[d]	**1** (10)	NaOH	15	89
20	**1** (5)	NaOH	15	70
21	–	NaOH	15	trace

[a] Unless otherwise noted, the reaction was carried out with 4-iodotoluene (0.5 mmol), amine (2 mmol), and base (1 mmol) in water (2 mL) at 120 °C. [b] Isolated yields. [c] Performed at 100 °C. [d] nBu_4NBr (20 mol-%) was added as PTC.

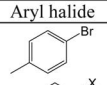
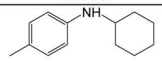
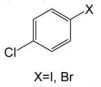
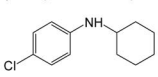
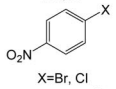
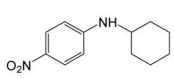
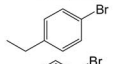
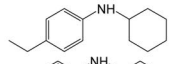
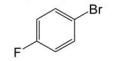
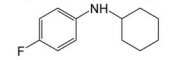
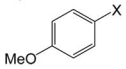
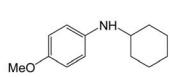
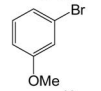
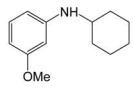
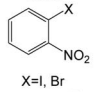
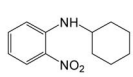
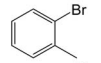
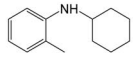
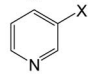
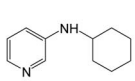
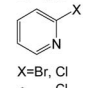
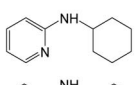
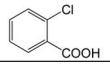
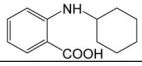
In order to expand the scope of the catalysis, a series of aliphatic N-nucleophiles was employed to react with 4-iodotoluene. As shown in Table 3, all the examined linear and branched aliphatic amines afforded the corresponding *N*-arylated products in good to excellent yields (Table 3, Entries 1–6). Notably, amino alcohols selectively form the *N*-arylated product with satisfactory yield, which is of great interest in medicinal chemistry (Table 3, Entry 7).[21]

Among numerous functionalized amines, the ubiquitous amino acids and their derivatives are important chemical building blocks in organic and biological chemistry.[22] Therefore, the *N*-arylation of amino acids has attracted much attention in recent years.[23] In this work, both α- and

Table 2. *N*-arylation of cyclohexylamine with aryl halides in water catalyzed by sulfonato–Cu(salen) complex **1**.[a]



7 8a 9

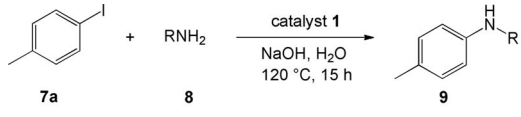
Entry	Aryl halide	Product		Yield (%)[b]
1			**9a**	80
2	 X=I, Br		**9b**	89 (X = I) 82 (X = Br)
3	 X=Br, Cl		**9c**	90 (X = Br) 80 (X = Cl) 68[c] (X = Cl)
4			**9d**	79
5			**9e**	83
6	 X=I, Br		**9f**	85 (X = I) 80 (X = Br)
7			**9g**	78
8	 X=I, Br		**9h**	90 (X = I) 89 (X = Br)
9			**9i**	69
10	 X=I, Br		**9j**	91 (X = I) 88 (X = Br)
11	 X=Br, Cl		**9k**	90 (X = Br) 72 (X = Cl) trace[c] (X = Cl)
12			**9l**	75 trace[c]

[a] Reaction conditions: aryl halide (0.5 mmol), amine (2 mmol), catalyst **1** (10 mol-%), base (1 mmol), H_2O (2 mL), 120 °C, 15 h. [b] Isolated yields. [c] Without catalyst.

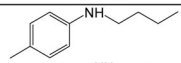
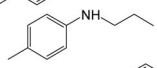
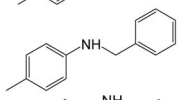
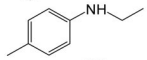
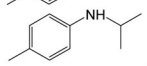
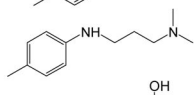
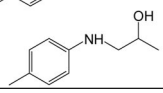
β-amino acids could be employed as coupling partner to give good yields as shown in Scheme 1.

Furthermore, 1,2-disubstituted benzimidazoles are important heterocycles found in a variety of natural products and exhibit a wide range of biological properties.[24] Although a variety of synthetic methods for the synthesis of these important frameworks has been developed, exploring of straightforward and general methods for the synthesis of 1,2-disubstituted benzimidazoles from easily available precursors is still in demand.[25] Recently, we have demonstrated that substituted 1*H*-benzimidazole could be easily prepared by a cascade amination/condensation process in the presence of sulfonato–Cu(salen) complex **1**.[19b] Subsequent to this discovery, we discovered that the 1,2-disubstituted benzimidazoles could also be prepared by utilizing this catalytic protocol; both 2-iodoacetanilide and 2-bromoacetanilide were applicable as substrates (Scheme 2).

Table 3. *N*-Arylation of aliphatic amines with 4-iodotoluene in water catalyzed by sulfonato–Cu(salen) complex **1**.[a]



7a 8 9

Entry	Amine	Product		Yield (%)[b]
1			**9m**	91
2			**9n**	85
3			**9o**	79
4			**9p**	68
5			**9q**	81
6			**9r**	89
7			**9s**	85

[a] Reaction conditions: 4-iodotoluene (0.5 mmol), amine (2 mmol), catalyst **1** (10 mol-%), base (1 mmol), H_2O (2 mL), 120 °C, 15 h. [b] Isolated yields.

Scheme 1. *N*-Arylation of amino acids in water catalyzed by sulfonato–Cu(salen) complex **1**.

Scheme 2. Synthesis of 1,2-disubstituted benzimidazoles in water.

Conclusions

We have developed a simple and efficient catalytic *N*-arylation protocol of aliphatic amines promoted by an inexpensive water-soluble sulfonato–Cu(salen) complex in pure water. The environmentally benign process contains several noteworthy features, including: (1) the protocol utilizes the

"green" water as solvent; (2) convenient operation, performed without addition PTC and under an inert gas; (3) a variety of aryl iodides and bromides, even some electron-deficient chlorides were found to be applicable with excellent functional-group compatibility; (4) a series of aliphatic *N*-nucleophiles, including simple aliphatic amines, amino alcohols and amino acids provided high selectivity with good to excellent yields. Furthermore, 1,2-disubstituted benzimidazoles could be prepared conveniently by a cascade amination/condensation process in this water system. We believe this report will provide an attractive approach for the preparing of *N*-arylated aliphatic amines. Further application of the catalyst for other types of coupling reactions is currently under investigation in this laboratory.

Experimental Section

General Procedure for the *N*-Arylation of Simple Aliphatic Amines in Water: Catalyst (0.05 mmol), aryl halide (0.5 mmol), NaOH (1 mmol), amine (2 mmol) and water (2 mL) were added to a sealed tube. The reaction mixture was stirred at 120 °C for 15 h (20 h for the synthesis of 1,2-disubstituted benzimidazoles), cooled to room temperature, and then extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was then removed under reduced pressure. The *N*-arylated product was finally obtained by column chromatography on silica gel.

General Procedure for the *N*-Arylation of Amino Acids in Water: Catalyst (0.05 mmol), aryl halide (0.5 mmol), NaOH (2 mmol), amino acid (1 mmol) and water (2 mL) were added to a sealed tube. The reaction mixture was stirred at 120 °C for 20 h and then cooled to room temperature. 2 N HCl was added to adjust the pH to 3, and then extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was then removed under reduced pressure. Column chromatography on silica gel afforded the desired *N*-arylated product.

Supporting Information (see footnote on the first page of this article): Complete experimental procedures, NMR spectra of coupling products.

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