



Short Communication

Homogenous bimetallic catalysis on amination of ArX and ArX₂ in aqueous medium-synergistic effect of dicopper complexes

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ABSTRACT

A dicopper complex [Cu₂(**bnp**)(OH)(CF₃COO)₃] (**1**) (**bnp** = 2,7-bis(pyridin-2-yl)-1,8-naphthyridine) was found to be an excellent catalyst on amination of aryl halides and aryl dihalides with ammonia in aqueous solutions leading to the corresponding anilines and aryldiamines, respectively. Catalytic activity of **1** toward amination appears to be superior to those of other mono nuclear copper complexes. Furthermore, the bimetallic catalyst **1** gave exclusively diamination product in the reaction of ArX₂ with ammonia, but other copper complexes showed poor selectivity. Kinetic product distribution study suggests that the dicopper metal ions in this catalysis promote the second amination efficiently.

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1. Introduction

Aniline derivatives are highly useful compounds for synthetic, biological, pharmaceutical, and material applications. Conventional methodology for the preparation of anilines starts with aromatic nitration followed by reduction [1], which involves multi-step processes and complicated separations. In order to meet the environmental concern, the development of new methodologies for C–N bond formations by new catalytic systems for tandem reactions has received much attention [1]. Among this context, transition metal-catalyzed C–N bond formations to produce the desired amines, typically palladium-catalyzed Buchwald–Hartwig coupling reactions [2,3] and copper-catalyzed Ullman-type transformations [4–6], have been demonstrated to be a powerful tool for the production of arylamines [2–28]. However, the use of dihaloarenes as the starting source to generate aryldiamines directly via the amination in aqueous system is less reported [27,29].

In terms of catalysts, quite a number of mononuclear copper complexes have been proved to be active in the amination of ArX with ammonia [7–26], some palladium complexes also show such an activity [27,28]. However, there is no precedent report concerning the use of dinuclear metal complexes as catalysts. Dinuclear complexes, where two metal ions are arranged in close proximity, provide an ideal focus for the simultaneous activation of substrates particularly for di-functional substrates, thus increasing the catalytic activity of the complexes. Here we describe the use of a dicopper complex **1** catalyzed amination of aryl halides including dihalides with ammonia in an aqueous solution leading to the corresponding anilines or aryldiamines.

2. Experimental

2.1. General information

Nuclear magnetic resonance spectra were recorded on a Bruker AVANCE 400 spectrometer. All reactions were carried out in a sealed high pressure tube. Chemicals were purchased from commercial source and were used without further purification. All compounds were characterized by ¹H, ¹³C NMR and MS. Dicopper complex **1** was prepared according to the method previously reported [30].

2.2. General procedure for amination

A mixture of substrate (0.25 mmol), complex **1** (2.5 × 10^{−3} mmol), Cs₂CO₃ (1 mmol), Conc. NH_{3(aq)} (0.5 mL) and TBAB (0.25 mmol) in water (0.5 mL) were loaded in a sealed reaction tube. The reaction temperature was increased to 110–140 °C and the reaction mixture was stirred for 8–24 h. After cooling to RT, the reaction mixture was poured into a saturated NaCl solution, extracted with ethyl acetate and dried over anhydrous MgSO₄. After removal of solvents, the residue was re-crystallized or chromatographed on silica gel. All products were characterized by NMR spectroscopy and were consistent with the literature data.

3. Results and discussion

3.1. Mono-amination

Initially, the amination of *p*-methoxyphenyl bromide with ammonia was chosen to examine the catalytic activity of **1** in C–N bond formation.

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Table 1
Amination of *p*-bromoanisole with ammonia catalyzed by **1**.^a

Entry	catalyst	Base (1 mmol)	Additive ^b	Temp (°C)	Yield ^c
1	–	Cs ₂ CO ₃	TBAB	110	5%
2	1	–	–	110	Trace
3	1	Cs ₂ CO ₃	TBAB	110	96%
4	1	Cs ₂ CO ₃	TBAB	30	0
5	1	Cs ₂ CO ₃	TBAB	70	0
6	1	CsF	TBAB	110	0
7	1	Na ₂ CO ₃	TBAB	110	76%
8	1	K ₂ CO ₃	TBAB	110	86%
9 ^d	1	Cs ₂ CO ₃	TBAB	110	70%
10	1	Cs ₂ CO ₃	–	110	Trace

^a Reaction conditions: *p*-MeOC₆H₄Br (0.5 mmol), catalyst (0.005 mmol), conc. NH_{3(aq)} (0.3 mL) and water (0.3 mL) in a sealed tube for 16 h.

^b TBAB = tetrabutylammonium bromide.

^c NMR yield based on ArBr.

^d In DMF as the solvent.

Reactions were conducted with 1.0 mol% of **1** as catalyst in water with an excess of aqueous ammonia, an additional base and tetrabutylammonium bromide. A screening of this model reaction (Table 1) revealed that complex **1** triggered the amination of the aryl bromide with NH₃ smoothly, but additives and bases have a significant impact on the yield of *p*-methoxyaniline. Although ammonia is a basic substance in the aqueous medium, the reaction requires the additional base such as Cs₂CO₃ to promote the reaction. Furthermore, the addition of tetrabutylammonium bromide (TBAB) readily improves the production of the desired product presumably acting as a phase-transfer reagent. The best reaction condition is following: a mixture of *p*-BrC₆H₄OCH₃ (0.5 mmol), Cs₂CO₃ (1 mmol), TBAB (0.25 mmol), concentrated NH_{3(aq)} (0.3 mL) and **1** (1 mol% based on ArBr) in water (0.3 mL) was heated at 110 °C for 16 h (Table 1, entry 3). This result proves that complex **1** can act as a catalyst for C–N bond formation in aqueous medium.

For comparison, we screened various copper catalysts on this model reaction and the results are summarized in Table 2. As expected, most of the copper complexes do exhibit the catalytic activity on the amination of aryl bromide. However, complex **1** appears to be more efficient as compared to other copper catalysts in term of turnover frequency under the similar conditions, suggesting the possible synergistic effect on this dimetallic system.

Having this catalytic system and reaction conditions for the C–N coupling of ammonia with aryl halides, we also explored this amination with a wide range of bromides and iodides (Table 3). It showed good catalytic activities for the amination of both iodides and bromides with various substituents, indicating the potential application of this catalytic system. Excellent isolated yields were achieved with the substrates of *o*-HOC₆H₄I and *m*-HOC₆H₄Br (Table 3, entries 6 and 7). However, chloro-substituted substrates could not be aminated under the catalytic conditions. Thus, reaction of 3-chlorophenyl bromide with ammonia provided 3-chloroaniline in 55% yield (Table 3, entry 9).

Table 2
Comparison of catalytic activity among various copper complexes.^a

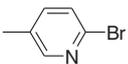
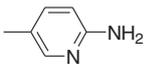
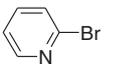
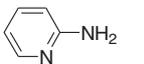
Entry	Catalyst ^b	Yield	TOF ^c
1	Complex 1	96%	6.0
2	CuI	85%	5.3
3	CuCl ₂	83%	5.2
4	CuBr ₂	80%	5.0
5	Cu(OAc) ₂	70%	4.4
6	Cu(ClO ₄) ₂	75%	4.7
7	Cu(CF ₃ COO) ₂	61%	3.8
8	Cu(cyclam) (ClO ₄) ₂	85%	5.3

^a Reaction conditions: *p*-MeOC₆H₄Br (0.5 mmol), catalyst, conc. NH_{3(aq)} (0.3 mL) and water (0.3 mL) in a sealed tube at 110 °C for 16 h.

^b 2 mol% of copper catalyst except complex **1** (1 mol%).

^c TOF: turnover frequency, (mol. of product)/(mol. of catalyst)h.

Table 3
Amination of various aryl halides with ammonia catalyzed by **1**.^a

Entry	Substrate	Product	Yield
1	<i>p</i> -MeOC ₆ H ₄ I	<i>p</i> -MeOC ₆ H ₄ NH ₂	95%
2	<i>m</i> -MeOC ₆ H ₄ I	<i>m</i> -MeOC ₆ H ₄ NH ₂	55%
3	C ₆ H ₅ I	C ₆ H ₅ NH ₂	79%
4	<i>p</i> -MeC ₆ H ₄ I	<i>p</i> -MeC ₆ H ₄ NH ₂	91%
5	<i>p</i> -NO ₂ C ₆ H ₄ I	<i>p</i> -NO ₂ C ₆ H ₄ NH ₂	50%
6	<i>o</i> -HOC ₆ H ₄ I	<i>o</i> -HOC ₆ H ₄ NH ₂	99%
7	<i>m</i> -HOC ₆ H ₄ Br	<i>m</i> -HOC ₆ H ₄ NH ₂	95%
8	<i>o</i> -MeOC ₆ H ₄ Br	<i>o</i> -CH ₃ OC ₆ H ₄ NH ₂	72%
9	3-ClC ₆ H ₄ Br	3-ClC ₆ H ₄ NH ₂	55%
10	2-BrC ₆ H ₄ COOH	2-NH ₂ C ₆ H ₄ COOH	71% ^b
11			100%
12			100%
13	2,4,6-Me ₃ C ₆ H ₂ Br	No reaction	0

^a Reaction conditions: aryl halide (0.5 mmol), catalyst (0.005 mmol), TBAB (0.25 mmol), conc. NH_{3(aq)} (0.3 mL) and water (0.3 mL) in a sealed tube at 110–120 °C for 16 h.

^b 2-NH₂C₆H₄CONH₂ (21%) as the side product.

More interesting, pyridinyl halides also coupled with ammonia to give the corresponding primary amines in excellent yields (Table 3, entries 11–12). It is noticed that 2,4,6-trimethylbromobenzene gave no amination product with the substrate recovered; this is presumably due to the steric hindrance of *ortho* substituents.

3.2. Diamination

The above results provided the impetus to evaluate the preparation of aryl diamines via the copper-catalyzed double amination of aryl dihalide, i.e. one step process. We have explored the double amination of aryl dihalides in the early work [29]. Here, the aim of this study was to evaluate the catalytic efficiency of **1**.

First, we screened a series of copper complexes as catalysts for the amination of *o*-C₆H₄Br₂ with NH_{3(aq)} (Eq. (1)) to establish the degree of bimetallic cooperativity of complex **1**. The reaction yields were determined by ¹H NMR spectroscopy at the end of the reaction, where percentage of products was established by ¹H NMR spectroscopy. Results are summarized in Table 4. It is noticed that all the Cu(II) and Cu(I) salts catalyzed the C–N bond formation, but produced both mono- and di-amination products (**2** and **3**), i.e. poor selectivity. The reaction catalyzed by the dicopper complex [Cu₂(CF₃COO)₄], bridged by CF₃COO[–] ligands, provided the desired product **3** in 60% yield, but still accompanied with 28% of **2** (Table 4, entry 2). On the other hand, complex **1** gave the diamination product exclusively (Table 4,

Table 4
Diamination of *o*-C₆H₄Br₂ catalyzed by various complexes.^a

Entry	Complex	Ligand	Yield (%)	
			2	3
1	1	–	0	100
2	Cu ₂ (CF ₃ COO) ₄	–	28	60
3	Cu(CH ₃ COO) ₂	–	50	25
4	Cu(CH ₃ COO) ₂	TMEDA	38	39
5	CuBr ₂	PPh ₃	40	35
6	CuBr ₂	Bipyridine	42	41
7	CuSO ₄	–	47	41
8	CuCl ₂	–	42	40
9	CuCl	–	44	40
10	CuI	–	54	19
11	CuI	dppe	40	45
12	CuI	TMEDA	35	45

^a Reaction conditions: *o*-C₆H₄Br₂ (0.25 mmol), complex (0.005 mmol), water (0.5 mL), conc. NH_{3(aq)} (0.5 mL), Cs₂CO₃ (1 mmol) and Bu₄NBr (0.25 mmol) at 120 °C for 16 h.

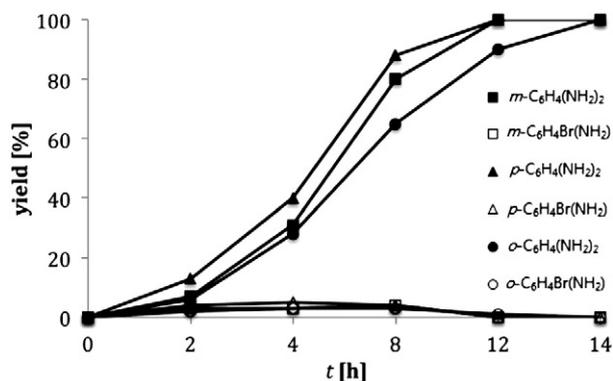
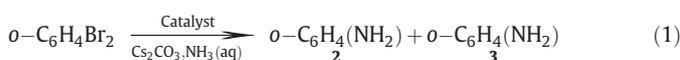


Fig. 1. Product distribution during the amination of *o*-, *m*- and *p*-C₆H₄Br₂.

entry 1), indicating the importance of the chelating ligand **bpnp** on this catalytic reaction.



In order to know more detail, the diaminations of *o*-, *m*- and *p*-C₆H₄Br₂ catalyzed by **1** were monitored to analyze the product distribution and the results are summarized in Fig. 1. It clearly shows the mono-amination product remains in a very low percentage during the reaction, indicating that the second amination via the dicopper

Table 5
Diamination of various aryl dihalides.^a

Entry	Substrate	Product	Yield
1		<i>p</i> -H ₂ NC ₆ H ₄ NH ₂	98%
2	<i>o</i> -C ₆ H ₄ IBr	<i>o</i> -C ₆ H ₄ (NH ₂) ₂	95%
3	<i>m</i> -IC ₆ H ₄ I	<i>m</i> -C ₆ H ₄ (NH ₂) ₂	99%
4			– ^b
5 ^c			96%
6 ^c			94%
7 ^c			55%
8			0%
9			95%
10		Polymer	^d
11		Polymer	^d

^a Reaction conditions: aryl halide (0.5 mmol), catalyst (0.005 mmol), TBAB (0.25 mmol), conc. NH₃(aq) (0.3 mL) and water (0.3 mL) in a sealed tube at 120 °C for 16 h.

^b A mixture of products.

^c Ethylene glycol as solvent at 140 °C.

^d 100% conversion of substrate.

system is a fast step. We believe that the copper ions bound in close proximity of **1** could be one of the key factors for the efficient double amination. Possibly, the intermediate generated by the coordination of the first amination might be responsible for the facilitation of the second amination. More important, the ligand **bpnp** readily confines the metal ions closely, allowing the cooperative interaction between them. In a separated experiment, we found that the rate of amination of *o*-C₆H₄Br(NH₂) was about 3.5 time faster than that of C₆H₅Br under the same amination conditions. This observation provides an evidence to support the proposal.

We have showed the synthetic application of this diamination in a previous report [29]. Here we extended the substrate scope for this catalysis as summarized in Table 5. Besides aryl dibromides, the diamination proceeded smoothly with iodobromobenzenes (Table 5, entries 1, 2 and 5). The replacement of the solvent from water to ethylene glycol may improve the yield (Table 5, entries 4 vs. 5). Dibromides of hetero-aromatic compounds such as thiophene and pyridine also reacted smoothly, producing the corresponding diamines with good to excellent yields (Table 5, entries 6 and 7), but the substituted imidazole did not provide the diamino product (Table 5, entry 8). In the case of 2,5-dihalothiophenes, these substrates yielded a black polymeric material under the amination conditions (Table 5, entries 9–10).

4. Conclusion

In summary, the present study reports a development of highly efficient protocol for amination of ArX and ArX₂ with aqueous ammonia. The dimetallic catalyst was optimized with respect to various parameters, affording excellent yields in amination. Particularly, the synergistic effect of the dimetallic system might play a key role of its activity on aminations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.catcom.2012.11.027>.

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