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Copper-catalyzed regioselective 2-amination of *o*-haloanilides with aqueous ammonia

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ABSTRACT

An efficient Cu(II)-vasicine catalytic system has been developed for intramolecular C—N bond formation. In this way, regioselective 2-amination of *o*-haloanilides with aqueous ammonia in EtOH has been achieved. This strategy provides several advantages, such as good regioselectivity, high yields and functional group tolerance.

Nitrogen containing compounds are of great importance in natural products, pharmaceutical agents, materials as well as synthetic intermediates [1]. Therefore, the formation of the C—N bond has attracted more and more attention [2]. In the past decades, many significant methods have been developed in C—N coupling reactions [3], especially the transition metal-catalyzed synthetic strategy has been considered as one of the most efficient manners, such as copper [4], palladium [5], cobalt [6], nickel [7] and silver [8]. Among them, Cu is the most commonly used metal for C—N bond forming cross-coupling reactions, which was first reported by Ullmann and Goldberg [9]. In recent years, various copper salts were introduced in C—N bond formation in the presence of ligands and bases [4,10].

o-Phenylenediamines are important intermediates in synthesis of medicines or natural products [11]. In general, there are two commonly used methods for preparation of *o*-phenylenediamines. The classical method is the reduction of nitrobenzene [12], and the other is the metal-catalyzed amination of functionalized aryl halides [13], especially the amination of *o*-haloanilides is the more green and efficient strategy. However, there are very few reports about C—N cross-couplings of *o*-haloanilides to give 2-aminoanilides so far [14]. In 2009, Ma et al. have reported CuI/L-proline catalyzed cross-coupling of aqueous ammonia with 2-iodoanilides to form 2-aminoanilides [14a]. In 2010, Fu et al. have developed CuI-catalyzed direct amination of *ortho*-functionalized 2-halobenzamide with NaN_3 as the amino source [14b]. From reported methods, we could see that there were still some limitations including limited substrate scope, low yields and toxic solvents. In addition, it was very difficult to achieve direct 2-amination of multihaloanilides. Therefore, it is worthwhile to explore a more efficient protocol for regioselective synthesis of 2-aminoanilides from *o*-haloanilides with aqueous ammonia *via* C—N cross-coupling reactions in green condition. Vasicine is a bioactive natural product of alkaloid isolated from leaves and stems of *A. vasica*, which could be used as small organic molecule catalyst in methodology in recent years [15]. In present work, we have explored an efficient Cu(II)-vasicine catalytic system, and achieved regioselective 2-amination of o-haloanilides with aqueous ammonia *via* intramolecular C—N bond coupling using environmentally friendly EtOH as the solvent.

Initially, N-(2-bromophenyl) benzamide (**1aa**) was chosen as a model substrate to identify and check the optimal Ullmann coupling conditions including Cu sources, ligands, bases and temperature, the results were shown in Table 1. First of all, **1aa** was carried out using different Cu sources (CuI, $CuBr_2$, $CuSO_4$, $Cu(OAc)_2$ and $Cu(OTf)_2$) and ligands (L1-L4) in presence of K_2CO_3 in EtOH at 90 °C (Table 1, Entry 1–20). The results showed that benzoxazole **2a** was easy to form from **1aa** *via* Cu-catalyzed intramolecular *O*-arylation, but regioselective 2-amination and chemoselective Ullmann condensation of **1aa** were hard to perform on the whole. When CuI was introduced, **3a** was obtained in 65% and 32% yield using CuI/L2 or CuI/L4 catalysts (Table 1, Entry 1–4). In addition, there was no difference between $CuBr_2$, $CuSO_4$ and $Cu(OAc)_2$ in presence of

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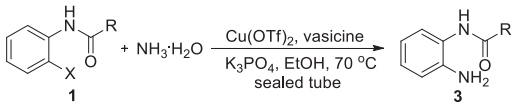
0040-4039/

Table 1
Optimization of reaction conditions for Ullmann coupling of **1aa** with aqueous ammonia.[a,b]



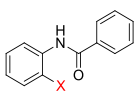
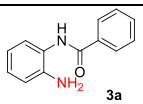
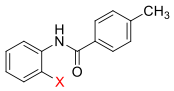
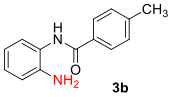
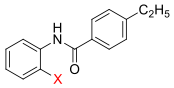
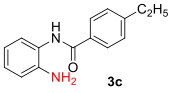
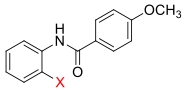
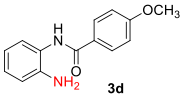
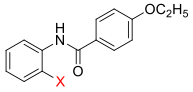
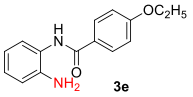
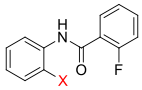
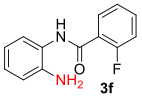
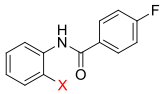
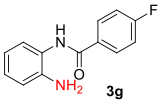
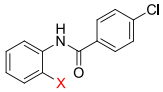
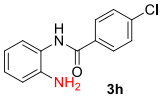
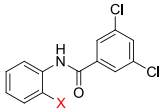
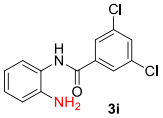
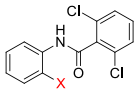
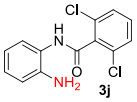
Entry	[Cu]	L	Base	Solvent	*T* (°C)	Yield (%)		
						2a	**3a**	**4a**
1	CuI	L1	K_2CO_3	EtOH	90	58	NR[c]	NR
2	CuI	L2	K_2CO_3	EtOH	90	20	65	NR
3	CuI	L3	K_2CO_3	EtOH	90	52	Trace	NR
4	CuI	L4	K_2CO_3	EtOH	90	45	32	NR
5	$CuBr_2$	L1	K_2CO_3	EtOH	90	36	NR	NR
6	$CuBr_2$	L2	K_2CO_3	EtOH	90	NR	NR	NR
7	$CuBr_2$	L3	K_2CO_3	EtOH	90	34	NR	NR
8	$CuBr_2$	L4	K_2CO_3	EtOH	90	22	Trace	NR
9	$CuSO_4$	L1	K_2CO_3	EtOH	90	47	NR	NR
10	$CuSO_4$	L2	K_2CO_3	EtOH	90	trace	NR	NR
11	$CuSO_4$	L3	K_2CO_3	EtOH	90	25	NR	NR
12	$CuSO_4$	L4	K_2CO_3	EtOH	90	44	NR	NR
13	$Cu(OAc)_2$	L1	K_2CO_3	EtOH	90	77	NR	NR
14	$Cu(OAc)_2$	L2	K_2CO_3	EtOH	90	53	Trace	NR
15	$Cu(OAc)_2$	L3	K_2CO_3	EtOH	90	60	Trace	NR
16	$Cu(OAc)_2$	L4	K_2CO_3	EtOH	90	48	20	12
17	$Cu(OTf)_2$	L1	K_2CO_3	EtOH	90	64	15	trace
18	$Cu(OTf)_2$	L2	K_2CO_3	EtOH	90	20	34	NR
19	$Cu(OTf)_2$	L3	K_2CO_3	EtOH	90	14	41	trace
20	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	90	trace	50	32
21	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	60	NR	63	NR
22	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	70	NR	87	NR
23	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	80	trace	62	18
24	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	100	trace	Trace	83
25	$Cu(OTf)_2$	L4	K_2CO_3	EtOH	110	trace	Trace	83
26	**$Cu(OTf)_2$**	**L4**	**K_3PO_4**	**EtOH**	**70**	**NR**	**88**	**NR**
27	$Cu(OTf)_2$	L4	Et_3N	EtOH	70	trace	61	NR
28	$Cu(OTf)_2$	L4	DIPEA	EtOH	70	13	58	NR

[a] All reactions were performed using **1aa** (1 mmol), [**Cu**] (0.05 mmol), **L** (0.1 mmol), base (2 mmol), ammonia (25% wt, 1 mL), solvent (4 mL) in a sealed tube for 12 h.
[b] Isolated yield after chromatographic purification.
[c] NR represented no title product.

L1-L4, benzoxazole **2a** was obtained in most case except $Cu(OAc)_2$-L4 catalyst (Table 1, Entry 5–16). To our delight, when $Cu(OTf)_2$ was used, the yield of 2-aminoanilide **3a** was obviously increased and **2a** was decreased in presence of four ligands (Table 1, Entry 17–20). These results indicated that Cu(II)-vasicine complex could promote regioselective synthesis of 2-aminoanilides from *o*-haloanilides with aqueous ammonia. On this basis, we studied the effect of temperature on the Ullmann coupling. With the temperature increasing from 60 to 110 °C, the rate of **4a** was increased (Table 1, Entry 21–25). Especially, when the reaction was carried out at 70 °C or 100 °C, the yield of **3a** or **4a** was the best than others (up to 87% and 83%, respectively). The results revealed that Cu/vasicine-catalyzed Ullmann coupling of *o*-haloanilides with aqueous ammonia could be achieved. In order to investigate the effect of different bases on Ullmann coupling of *o*-haloanilides, other three bases (K_3PO_4, Et_3N and DIPEA) were tested to check the catalytic system at 70 °C, and the results were quite different. Among them, K_3PO_4 contributed to **3a** in higher yields (88%) than that of other bases. Therefore, it was quite clear that $Cu(OTf)_2$-vasicine catalyst was beneficial to Ullmann coupling of *o*-haloanilides with aqueous ammonia using K_3PO_4 as base in EtOH, which could achieve regioselective preparation of 2-aminoanilides from *o*-haloanilides.

With the optimal reaction conditions in hand, various kinds of *o*-haloanilides were chosen to examine the scope of 2-amination at 70 °C, the results were shown in Table 2. Firstly, in order to study the reactivity of different halogens, 2-chloro, 2-bromo and 2-iodo anilides were performed under optimal reaction conditions (Table 2, Entry 1–2). To our delight, although 2-chloroanilides did not form corresponding 2-aminoanilides, 2-bromoanilides and 2-iodoanilides gave title products **3a** and **3b** in good yields (84–90%), and the activity of 2-iodoanilides was better than that of 2-bromoanilides (Table 2). This indicated that the $Cu(OTf)_2$/vasicine catalyst system was chemoselective to 2-Br and 2-I. In addition, the influence of various substituted groups was examined as well, and *o*-haloanilides bearing electron donating groups (CH_3, C_2H_5, CH_3O, X, *etc*) and electron withdrawing group (CF_3, NO_2) were carried out. From the results, we found that the developed strategy was effective to all 2-bromoanilides and 2-iodoanilides to form 2-aminoanilides in good to high yields. Besides, the protocol was tolerable to both EDG and EWG, and there was no obvious difference. For instance, N-(2-iodophenyl)benzamide gave **3a** in 90% yield, N-(2-iodophenyl)-4-chlorobenzamide formed **3h** in 85% yield, and N-(2-iodophenyl)-4-trifluoromethylbenzamide formed **3n** in 84% yield. Moreover, the position of the substituents had been studied, and there was obvious influence on Ullmann coupling of *o*-haloanilides with aqueous ammonia using the $Cu(OTf)_2$/vasicine catalyst. On the whole, the yields of *para* substituted *o*-haloanilides were higher than that of *meta*,

Table 2
Substrates scope of 2-aminoanilides.[a,b]

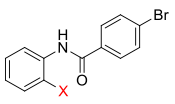
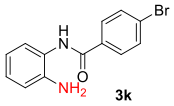
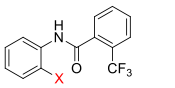
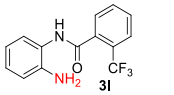
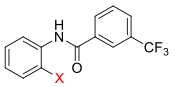
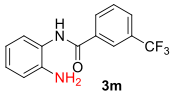
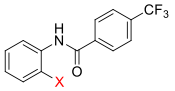
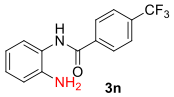
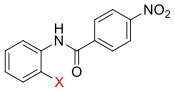
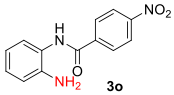
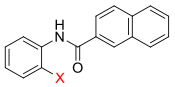
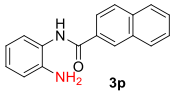
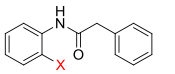
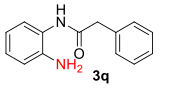
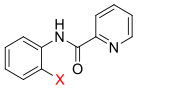
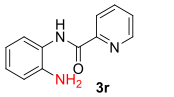
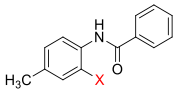
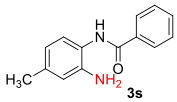
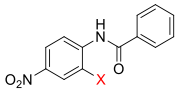
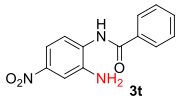
1		 **3a**	X=Cl, trace X=Br, 88 X=I, 90
2		 **3b**	X=Cl, trace X=Br, 84 X=I, 88
3		 **3c**	X=Br, 83 X=I, 89
4		 **3d**	X=Br, 84 X=I, 88
5		 **3e**	X=Br, 87 X=I, 90
6		 **3f**	X=Br, 77 X=I, 78
7		 **3g**	X=Br, 83 X=I, 84
8		 **3h**	X=Br, 83 X=I, 85
9		 **3i**	X=Br, 79 X=I, 82
10		 **3j**	X=Br, 72 X=I, 74

and the yields of *ortho* substituted *o*-haloanilides were lower than others. For example, N-(2-bromophenyl)-2-fluorobenzamide, N-(2-bromophenyl)-2,6-dichlorobenzamide and N-(2-bromophenyl)-2-trifluoromethylbenzamide gave **3f**, **3j** and **3l** in 77%, 72% and 74% yield under standard conditions, respectively. Moreover, alkyl amide and heterocyclic acylamide were tested to check the optimal reaction conditions, and **3q** and **3r** were obtained in high yields (83–90%). Finally, different electrical property (electron donating and withdrawing groups) on the halogenated benzene had an obvious influence on 2-amination of *o*-haloanilides. EWG (NO_2) on the halogenated benzene was more beneficial to 2-amination than EDG (CH_3), and **3t** was obtained in up to 92% yield (Entry 19–20). Therefore, it was verified that Cu(II)-vasicine catalytic system could be used in regioselective 2-amination of 2-bromoanilides and 2-iodoanilides with ammonia.

Besides, we studied the applicability of other aryl halides using the present catalytic conditions. As shown in Scheme 1, **5a** was performed by copper catalytic conditions, but only trace **6a** was obtained. In addition, substrates without bearing a neighboring amide moiety were tested to verify substrate scope. However, **5b** and **5c** were not converted to amination product. Based on this, the present $Cu(acac)_2$-vasicine catalyst was regioselective for 2-amination of *o*-haloanilides.

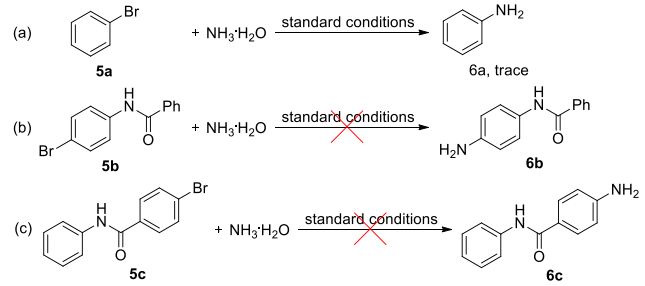
In addition, to explore the possible amination mechanism, many control reactions were carried out (Scheme 2). First of all, in the absence of vasicine, **1ab** was not converted to title product (Scheme 2a). When the reaction was carried out by not using base, only **2a** (14%) was formed (Scheme 2b). As reaction temperature rising to 100 °C, the yiled of 2-amination decreased to 62%, and **4a** was obtained (Scheme 2c). Therefore, the possible catalytic amination mechanism according to the above results is as follows. *o*-Halobenzanilides complex react with CuL to form intermediate II, which gives III *via* oxidative addition. Subsequently, substitution of III with NH_3 provides coordinate IV. Reduction elimination of IV leads to 2-aminoanilides with release of CuL for reuse (Scheme 3).

In conclusion, we have developed an efficient Cu-vasicine catalytic system for C—N bond formation. This strategy is applicable to synthesis of a wide variety of 2-aminoanilides from

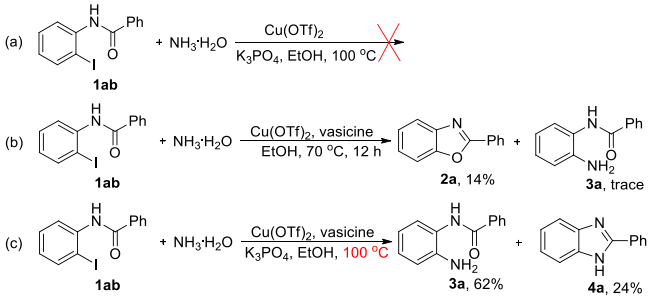
11		 3k	X=Br, 83 X=I, 86
12		 3l	X=Br, 74 X=I, 76
13		 3m	X=Br, 80 X=I, 81
14		 3n	X=Br, 82 X=I, 84
15		 3o	X=Br, 72 X=I, 74
16		 3p	X=Br, 88 X=I, 91
17		 3q	X=Br, 83 X=I, 90
18		 3r	X=Br, 83 X=I, 87
19		 3s	X=Br, 54 X=I, 62
20		 3t	X=Br, 88 X=I, 92

[a] All reactions were carried out using *o*-haloanilides (1 mmol), $Cu(OTf)_2$ (0.05 mmol), vasicine (0.1 mmol), K_3PO_4 (2 mmol), ammonia (25% wt, 1 mL), EtOH (4 mL) in a sealed tube at 70 °C for 12 h.

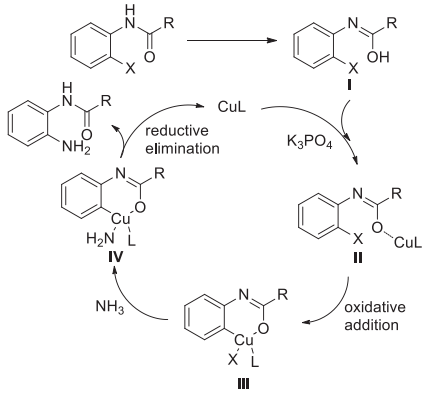
[b] Isolated yield.



Scheme 1. Substrate scope of other Ar-X.



Scheme 2. Control reactions of mechanistic studies.



Scheme 3. Possible mechanism.

o-haloanilides by regioselective Cu-catalyzed Ullmann coupling under mild and green conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153001.

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