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An Efficient Copper-Catalyzed Amination of Aryl Halides by Aqueous Ammonia

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Abstract: The copper(I) bromide/1-(5,6,7,8-tetrahydroquinolin-8-yl)-2-methylpropan-1-one (CuBr-**L3**) combination catalyzed the cross-coupling reactions between aryl or heteroaryl halides and aqueous ammonia with high yields to produce primary aromatic or heteroaromatic amines at room temperature or under mild conditions.

Keywords: amination; aqueous ammonia; aryl halides; copper catalysis; primary anilines

Due to its great abundance and extremely low cost, ammonia has been considered as one of the most important nitrogen sources for the production of organic or inorganic fertilizers and nitrogen-containing intermediates for pharmaceuticals, agrochemicals and polymers.^[1] Primary aromatic amines represent one class of such important intermediates. The traditional preparation of primary aromatic amines by coupling of aryl halides with ammonia needs high temperature and high pressure.^[2] In recent years, transition metal-mediated reactions such as palladium- or copper-catalyzed couplings of aryl halides with ammonia or ammonia surrogates to afford the desired anilines under mild conditions have been reported.^[3,4] More recently, Fu et al.^[5] reported a ligand-free copper-catalyzed arylation of aqueous ammonia with aromatic boronic acids at room temperature. However, the Pd-catalyzed synthesis of anilines from ammonia or ammonia surrogates usually requires the use of strong bases, toxic phosphorus ligands and rare metallic catalysts. There are only few successful examples of the copper-catalyzed coupling of aryl halides with aqueous ammonia under mild conditions.^[4a,c] It is highly desirable to develop new efficient methods to further improve

the efficiency and generality of the copper-catalyzed preparation of primary aromatic amines.

We have identified 2-pyridinyl- β -ketones (Figure 1) as new supporting ligands for the Cu-catalyzed Ullmann coupling reaction at room temperature.^[6,7] In this paper, we report an efficient room-temperature arylation of aqueous ammonia to afford anilines under the catalysis of 5% CuBr and 10% 2-pyridinyl- β -ketone ligands.

The study was initiated by an investigation of the amination of 4-iodochlorobenzene under the previously optimized conditions (Table 1, entry 1).^[6] It was found that the CuI-**L2** combination successfully promoted the coupling reaction in a yield of 62% at room temperature whereas only a 21% yield of 4-chlorobenzeneamine was obtained without the ligand under similar conditions (Table 1, entry 2). The catalytic efficiency of the other ligands was also evaluated in the same reaction system. 1-(5,6,7,8-Tetrahydroquinolin-8-yl)-2-methylpropan-1-one (**L3**), a close analogue of **L2**, displayed the best catalytic activity (Table 1, entry 4). Thus, **L3** was chosen as the ligand for the following optimization of the reaction conditions.

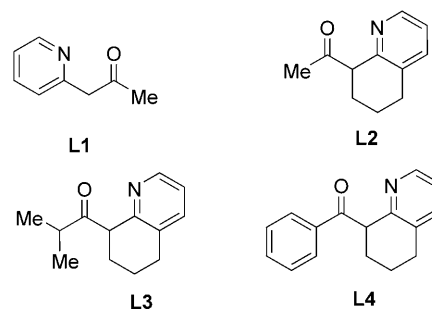


Figure 1. Structures of 2-pyridinyl- β -ketones **L1**–**L4**.

Table 1. Amination of 4-iodochlorobenzene: optimization of the catalytic conditions.^[a]

Entry	[Cu]	Ligand	Base	Solvent	Yield [%] ^[b]
1	CuI	L2	Cs ₂ CO ₃	DMF	62
2	CuI	–	Cs ₂ CO ₃	DMF	21
3	CuI	L1	Cs ₂ CO ₃	DMF	41
4	CuI	L3	Cs ₂ CO ₃	DMF	71
5	CuI	L4	Cs ₂ CO ₃	DMF	45
6	CuBr	L3	Cs ₂ CO ₃	DMF	79
7	CuCl	L3	Cs ₂ CO ₃	DMF	69
8	Cu(acac) ₂	L3	Cs ₂ CO ₃	DMF	34
9	Cu ₂ O	L3	Cs ₂ CO ₃	DMF	49
10	CuO	L3	Cs ₂ CO ₃	DMF	6
11	–	L3	Cs ₂ CO ₃	DMF	0
12	CuBr	L3	Cs ₂ CO ₃	THF	trace
13	CuBr	L3	Cs ₂ CO ₃	H ₂ O	0
14	CuBr	L3	Cs ₂ CO ₃	EtOH	32
15	CuBr	L3	Cs ₂ CO ₃	DMSO	97
16	CuBr	L3	K ₃ PO ₄	DMSO	97
17	CuBr	L3	K ₂ CO ₃	DMSO	93
18	CuBr	L3	Na ₂ CO ₃	DMSO	81
19	CuBr	L3	–	DMSO	79
20	CuBr	L3	K ₃ PO ₄	DMSO	70 ^[c]
21	CuBr	L3	K ₃ PO ₄	DMSO	90 ^[d]
22	CuBr	L3	K ₃ PO ₄	DMSO	75 ^[e]

^[a] Reaction conditions: 4-iodochlorobenzene (1.0 mmol), commercial 28% aqueous NH₃ (5.0 equiv., 0.3 mL), [Cu] 10 mol%, ligand 20 mol%, base (2.5 mmol), solvent (2.0 mL) stirred at room temperature (25°C) for 12 h under argon.

^[b] Isolated yield.

^[c] CuBr (5 mol%), ligand (10 mol%).

^[d] CuBr (5 mol%), ligand (10 mol%), 24 h.

^[e] CuBr (2 mol%), ligand (5 mol%), 24 h, 2.0 mmol scale.

Among various copper sources examined, CuBr was more effective when combined with **L3** (Table 1, entry 6). Further investigation revealed that DMSO was the optimal solvent for the room-temperature CuBr-**L3** catalyzed arylation of aqueous ammonia (Table 1, entry 15). The following conditions screening suggested that both Cs₂CO₃ and K₃PO₄ were highly efficient for the reaction (Table 1, entries 15 and 16). Although a decrease of additives had a highly negative influence on the reaction (Table 1, comparing entry 16 with 20), it could be compensated for by a longer reaction time. For example, the coupling of 4-iodochlorobenzene and aqueous ammonia only gave a 70% isolated yield under the catalysis of 5% CuBr and 10% **L3** in 12 h, but the yield was significantly

improved to 90% when the reaction was continued for 24 h (Table 1, entry 21). It is noteworthy that a good yield (75%) was obtained when the reaction was carried out using a combination of 2% CuBr and 5% **L3** (Table 1, entry 22). The optimal conditions of 5% CuBr, 10% **L3** and 250% inexpensive K₃PO₄ in DMSO at room temperature were used for further investigations.

Under these optimized conditions, the scope of the amination of aryl iodides with aqueous ammonia was explored (Table 2). In general, all the aryl iodides yielded the corresponding N-protected anilines with good to excellent yields. The results indicated that electron-withdrawing groups (Table 2, entries 1–5 and 10) favoured the CuBr-catalyzed amination. Although the amination of electron-rich aryl iodides was more difficult, and led to lower yields, the yields were significantly improved by increasing the amounts of additives (Table 2, entries 8 and 9). Table 2 also clearly shows that steric hindrance has a huge influence on the coupling reaction (Table 2, entries 13–15). For example, when 2-methyliodobenzene was aminated at room temperature, only a 27% isolated yield was obtained. Fortunately, the reaction was significantly accelerated at an elevated temperature (Table 2, entry 14).

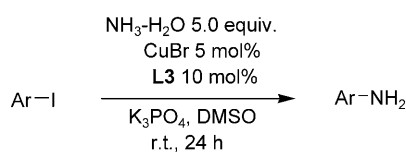
In addition, the CuBr-**L3** catalytic system displayed a great tolerance to multiple functional groups such as ketone, cyano, nitro, carboxylic ester, acetamino and hydroxy (Table 2, entries 2, 3, 5, 10, 11 and 12). Furthermore, the room-temperature amination of heteroaromatic iodides was examined with great success. All the pyridinyl or thienyl iodides tested coupled with aqueous ammonia to afford the corresponding anilines with satisfactory yields (Table 2, entries 16–19).

Although no *p*-chloroaniline was detected when *p*-chlorobromobenzene was reacted with aqueous ammonia at room temperature, a 79% yield was obtained when the reaction was carried out at 110°C (Table 3, entry 1). Furthermore, *p*-chloroaniline was produced with 95% yield when 10% CuBr and 20% **L3** were applied (Table 3, entry 1). Thus, the CuBr-catalyzed amination of aryl bromides was investigated under the new conditions (10% CuBr, 20% **L3**, 110°C). As shown in Table 3, all the aryl and heteroaryl bromides examined coupled with aqueous ammonia to afford the corresponding anilines with good to excellent yields.

In summary, a general and highly efficient copper-catalyzed synthesis of primary aromatic amines was developed. The CuBr-**L3** [1-(5,6,7,8-tetrahydroquinolin-8-yl)-2-methylpropan-1-one] combination successfully promotes the cross-coupling reaction between aryl or heteroaryl halides and aqueous ammonia at room temperature or under mild conditions. Furthermore, the reaction exhibits excellent functional group

Table 2. Copper-catalyzed amination of aryl iodides at room temperature.^[a]

Entry	Ar-I	Ar-NH ₂	Yield [%] ^[b]
1			90
2			95
3			93
4			90
5			92
6			75, 85 ^[c]
7			68, 83 ^[c]
8			75, 87 ^[c]
9			70, 81 ^[c]
10			89

**Table 2.** (Continued)

Entry	Ar-I	Ar-NH ₂	Yield [%] ^[b]
11			90
12			66, 79 ^[c]
13			37, 93 ^[d]
14			27, 70 ^[d]
15			45, ^[d] 60 ^[c,d]
16			89
17			81
18			79
19			80

^[a] Reaction conditions: Ar-I (1.0 mmol), commercial 28% aqueous NH₃ (5.0 equiv., 0.3 mL), CuBr 5 mol%, **L3** 10 mol%, K₃PO₄ (2.5 mmol), DMSO (2.0 mL) stirred at room temperature (25 °C) for 24 h under argon.

^[b] Isolated yield.

^[c] CuBr (10 mol%), ligand **3** (20 mol%).

^[d] At 80 °C.

compatibility. Our report provides an attractive strategy for the synthesis of aniline derivatives.

Experimental Section

General Procedure for the Coupling of Aryl and Heteroaryl Iodides with Aqueous Ammonia

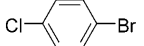
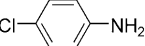
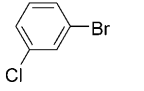
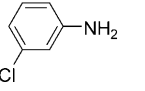
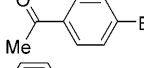
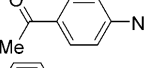
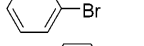
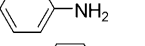
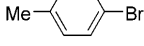
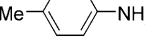
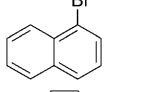
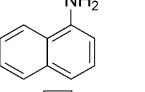
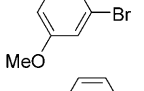
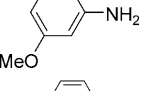
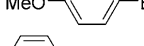
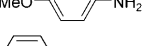
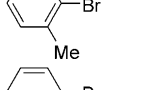
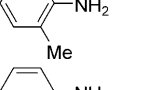
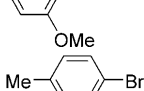
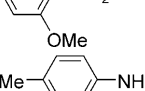
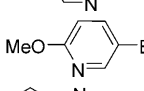
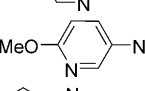
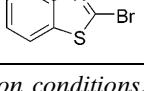
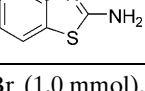
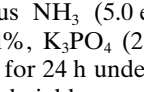
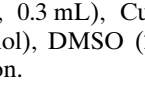
A 10-mL flask equipped with a Teflon valve was charged with a magnetic stir bar, CuBr (8 mg, 5 mol%), K₃PO₄ (530 mg, 2.5 mmol) and solid aryl iodide (1.0 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, DMSO (2.0 mL), 1.0 mmol aryl iodide (if liquid), 0.3 mL (5.0 mmol) aqueous ammonia (28%) and **L3** (21 mg, 10 mol%) were added by syringe. The tube was sealed. The reaction mixture was allowed to stir under argon at ambient temperature (25 °C) for 24 h. Then the mixture was diluted with dichloromethane and passed through a fritted glass filter, the filter cake being further washed with dichloromethane. The filtrate was washed twice with water. The com-

bined aqueous phases were extracted with dichloromethane five times. The organic layers were collected, dried over Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent.

General Procedure for the Coupling of Aryl and Heteroaryl Bromides with Aqueous Ammonia

A 10-mL sealed tube equipped with a Teflon valve was charged with a magnetic stir bar, CuBr (15 mg, 10 mol%), K₃PO₄ (530 mg, 2.5 mmol) and solid aryl bromide (1.0 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, DMSO (2.0 mL), 1.0 mmol aryl bromide (if liquid), 0.3 mL (5.0 mmol) aqueous ammonia (28%) and **L3** (41 mg, 20 mol%) were added by syringe. The tube was sealed. The reaction mixture was heated to the indicated temperature (110 °C) and stirred for 24 h. After cooling to room temperature, the mixture was diluted with dichloromethane and passed through a fritted glass filter, the filter cake was further washed with dichlorome-

Table 3. Copper-catalyzed amination of aryl bromides.^[a]

Entry	Ar-Br	Ar-NH ₂	Yield [%] ^[b]
1			79, ^[c] 95
2			93
3			96
4			70, ^[c] 85
5			86
6			89
7			87
8			82
9			52
10			60
11			85
12			86
13			81

^[a] Reaction conditions: Ar-Br (1.0 mmol), commercial 28% aqueous NH₃ (5.0 equiv., 0.3 mL), CuBr 10 mol%, **L3** 20 mol%, K₃PO₄ (2.5 mmol), DMSO (2.0 mL) stirred at 110 °C for 24 h under argon.

^[b] Isolated yield.

^[c] CuBr (5 mol%), ligand **3** (10 mol%).

thane. The filtrate was washed twice with water. The combined aqueous phases were extracted with dichloromethane five times. The organic layers were collected, dried over Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel with an eluent of petroleum ether and ethyl acetate.

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