Room-Temperature Copper-Catalyzed Synthesis of Primary Arylamines from Aryl Halides and Aqueous Ammonia

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Abstract: Primary arylamines can be prepared via a copper-catalyzed cross-coupling between aryl halides and aqueous ammonia using K_3PO_4 as a base and DMF as a solvent at room temperature.

Key words: copper, catalysis, cross-coupling, room temperature, aqueous ammonia, primary arylamine

Primary arylamines are important intermediates in the manufacture of agrochemicals, pharmaceuticals, dyes, pigments, and rubber.[1] Their preparation has attracted increasing attention. These compounds were traditionally synthesized through the amination of aryl halides using ammonia as the nucleophile,[2] but high pressure and high temperature are necessary to achieve good yields. Several groups have recently studied the possibility of using transition metals to catalyze the synthesis of primary arylamines from aryl halides. For instance, palladium- and copper-catalyzed synthesis has been achieved with ammonia surrogates. The nitrogen sources include allylamines,[3a] benzophenone imines,[3b,c] *tert*-butyl carbamates,[3d,e] Li[N(SiMe$_3$)$_2$],[3f,g] Zn[N(SiMe$_3$)$_2$]$_2$,[3h] amidines,[3i] 2,2,2-trifluoroacetamide.[3j] However, the use of masked ammonia suffers from low atom economy and needs an additional cleavage step to liberate the primary arylamine. Recently, Hartwig[4a,b] and Buchwald[4c] reported palladium-catalyzed coupling reactions of aryl halides and free ammonia, in which bulky ferrocene or electron-rich phosphine ligands were used. These methods provide a highly efficient route to anilines and can be carried out without the ammonia surrogates. More recently, progress has also been achieved in the copper-catalyzed coupling ammonia with aryl halides,[5] such as CuI/L-proline,[5b] CuI/2,4-pentanedione,[5c] CuI/*N,N*-dimethylglycine/organic base,[5d] CuBr/2-pyridinyl β-ketone,[5e] and CuI/4-hydroxy-L-proline[5f] catalytic systems. Wolf and Xu also introduced a copper-catalyzed amination protocol in the solvent of H_2O/NMP at 80 °C.[5g] The efficiency of all the above catalytic reactions using ammonia as the nucleophile is highly dependent on the involvement of suitable ligands and elevated temperatures (80–110 °C).[4,5]
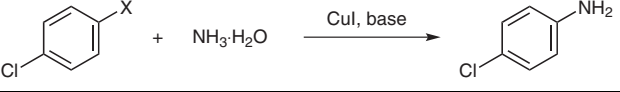
In the meantime, Fu et al. reported a mild copper-catalyzed coupling of aryl boronic acids and aqueous ammonia (Scheme 1).[6] The reaction proceeds at room temperature without ligands, bases, or other additives, and many functional groups are tolerated under mild conditions. However, the cost and availability of the aryl boronic acids, particularly the highly functionalized ones, hampers their applications. Usually aryl halides are preferred substrates because these electrophiles tend to be cheaper and easier to prepare. Thus, we set out to develop more economical, practical, and efficient protocols for the synthesis of primary arylamines from aryl halides under mild conditions.

As part of our studies on the copper-catalyzed arylation of nucleophiles,[3j,7] we now report that the synthesis of primary arylamines can be achieved by the copper-catalyzed cross-coupling between aryl halides and aqueous ammonia at room temperature (Scheme 1).
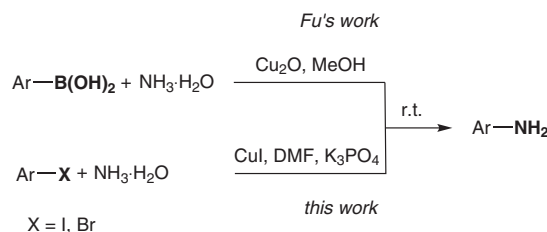
Scheme 1 Room-temperature copper-catalyzed synthesis of primary arylamines

1-Chloro-4-iodobenzene was selected as a model substrate for optimization of the reaction conditions at room temperature. As shown in Table 1, using CuI as a catalyst under ligand-free and base-free conditions, different solvents were screened for arylation of ammonia (entries 1–5). Low yields of the desired products were obtained in alcohol, acetone, toluene, and dioxane, while the use of DMF led to a fair yield (40%) of the cross-coupling product (entry 5). Generally, in the copper-catalyzed carbon–nitrogen bond formation of aryl halides, additional bases were essential.[8] Although ammonia itself could play the role of a base in the catalyst system, we speculated that the basicity of reaction system was not strong enough. Then, with DMF as solvent, several bases such as Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, and NaOH were introduced into the reaction mixture. We were delighted to find that the

Table 1 Copper-Catalyzed Coupling of 1-Chloro-4-halobenzene with Aqueous Ammonia: Optimization of the Reaction Conditions[a]

Entry	X	Cat.	Base	Solvent	Temp	Yield (%)[b]
1	I	CuI	–	MeOH	r.t.	6
2	I	CuI	–	acetone	r.t.	7
3	I	CuI	–	toluene	r.t.	5
4	I	CuI	–	dioxane	r.t.	10
5	I	CuI	–	DMF	r.t.	40
6	I	CuI	Na_2CO_3	DMF	r.t.	57
7	I	CuI	K_2CO_3	DMF	r.t.	66
8	I	CuI	K_3PO_4	DMF	r.t.	80 (87[c])
9	I	CuI	Cs_2CO_3	DMF	r.t.	69
10	I	CuI	NaOH	DMF	r.t.	62
11	I	Free	K_3PO_4	DMF	r.t.	0
12	I	CuCl	K_3PO_4	DMF	r.t.	45
13	I	CuBr	K_3PO_4	DMF	r.t.	33
14	I	Cu_2O	K_3PO_4	DMF	r.t.	15
15	I	CuO	K_3PO_4	DMF	r.t.	0
16	I	Cu_2SO_4	K_3PO_4	DMF	r.t.	0
17	Br	CuI	K_3PO_4	DMF	r.t.	29 (40[c], 5[d])

[a] Reaction conditions: 1-chloro-4-halobenzene (1.0 mmol), 25% aq NH_3 (6.5 mmol, 0.5 mL), catalyst (10 mol%), base (2.0 mmol), solvent (1 mL), nitrogen atmosphere, 24 h.
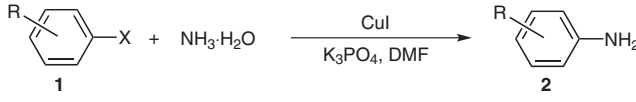[b] Isolated yields.
[c] Reaction time: 48 h.
[d] At 80 °C.

coupling yields can be increased to 60% (entries 6–10). Gratifyingly, the use of K_3PO_4, an inexpensive base, resulted in the coupled product in 80% yield. At this point we screened the copper sources including CuCl, CuBr, Cu_2O, CuO, and $CuSO_4$ (entries 11–16). The yields indicated that CuI was the best catalyst.

When 1-chloro-4-iodobenzene was replaced by 1-bromo-4-chlorobenzene, however, the reaction was less effective providing 4-chloroaniline in 29% yield (entries 17). Surprisingly, when the reaction temperature was raised to 80 °C for the aryl bromide, only 5% yield was obtained. It is noteworthy that in previous reports, an elevated temperature (up to 80 °C) was usually necessary for aryl bromides. However, in our catalytic system, elevating the reaction temperature results in a reduction of the product yield. We presumed that the low reactivity results from the decreased solubility of ammonia in the solvent. Therefore, our optimal reaction condition for room-temperature synthesis of primary arylamines was as follows: 10 mol%

of CuI as the catalyst and aqueous ammonia (6.5 equiv) as the amino source, relative to the aryl halide, DMF as the solvent and K_3PO_4 as the base at room temperature.[9]

Having identified the catalytic system of CuI, K_3PO_4 and DMF, we next examined whether the same catalytic system could be applied to the coupling of aqueous ammonia with various aryl iodides and bromides with different electronic and steric properties (Table 2). It was found that the coupling of aryl iodides containing electron-donating groups with ammonia afforded anilines in moderate yields (entries 1–3). Aryl iodide carrying electron-withdrawing groups could be smoothly converted to the desired products with good to excellent isolated yields (83–98%, entries 4–13). It is noteworthy that many functional groups including ether, cyano, nitro, keto, ester, and free carboxylic acid moiety were tolerated under these mild conditions. However, aryl iodide carrying an *ortho* substituent was not found to be a good substrate in the reaction (entry 14, 15). Only when a neighboring carboxylic acid group was present, aryl iodide could be readily converted to aniline in 84% yield (entry 16). This finding was consistent with the well-known accelerating effect of the carboxylate group on copper-catalyzed aryl halide exchange reactions.[10] Although nonactivated aryl bromide reacted sluggishly with ammonia (entry 17), satisfactory yields (40–89%) of primary arylamines were obtained when the electron-deficient aryl bromides (entries 18–23) were utilized.

Table 2 Copper(I) Iodide Catalyzed Cross-Coupling of Aryl Halides **1** with Aqueous Ammonia at Room Temperature[a]
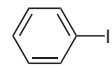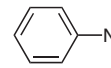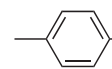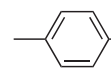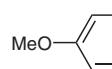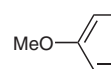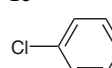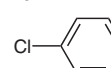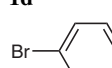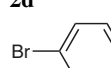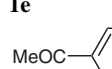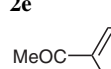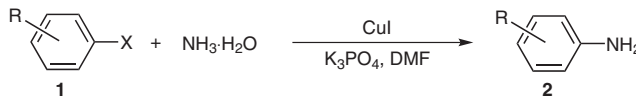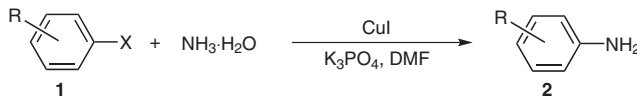

Entry	Aryl halide	Product	Yield (%)[b]
1	**1a**	**2a**	69
2	**1b**	**2b**	61
3	**1c**	**2c**	50
4	**1d**	**2d**	87
5	**1e**	**2e**	83
6	**1f**	**2f**	84

Table 2 Copper(I) Iodide Catalyzed Cross-Coupling of Aryl Halides **1** with Aqueous Ammonia at Room Temperature[a] (continued)

Entry	Aryl halide	Product	Yield (%)[b]
7	EtOOC—C6H4—I **1g**	EtOOC—C6H4—NH2 **2g**	90
8	NC—C6H4—I **1h**	NC—C6H4—NH2 **2h**	92
9	HOOC—C6H4—I **1i**	HOOC—C6H4—NH2 **2i**	88
10	O2N—C6H4—I **1j**	O2N—C6H4—NH2 **2j**	98
11	Cl, I **1k**	Cl, NH2 **2k**	85
12	MeOOC, I **1l**	MeOOC, NH2 **2l**	93
13	O2N, I **1m**	O2N, NH2 **2m**	90
14	Me, I **1n**	Me, NH2 **2n**	11
15	NO2, I **1o**	NO2, NH2 **2o**	20
16	COOH, I **1p**	COOH, NH2 **2p**	84
17	Ph—C6H4—Br **1q**	Ph—C6H4—NH2 **2q**	24
18	Cl—C6H4—Br **1r**	Cl—C6H4—NH2 **2a**	40
19	MeOC—C6H4—Br **1s**	MeOC—C6H4—NH2 **2f**	61

Entry	Aryl halide	Product	Yield (%)[b]
20	NC—C6H4—Br **1t**	NC—C6H4—NH2 **2h**	76
21	O2N—C6H4—Br **1u**	O2N—C6H4—NH2 **2j**	89
22	NC, Br **1v**	NC, NH2 **2r**	50
23	O2N, Br **1w**	O2N, NH2 **2m**	66

[a] Reaction conditions: aryl halide (1.0 mmol), 25% aq NH_3 (6.5 mmol, 0.5 mL), CuI (10 mol%), K_3PO_4 (2.0 mmol), DMF (1 mL), r.t., nitrogen atmosphere, 36–48 h.
[b] Isolated yields.

A possible mechanism for the present catalytic reaction was proposed. It has been proposed that the function of the base in the copper-catalyzed C–N couplings is to remove the proton from the NH group in the amine-coordinated Cu intermediate.[8] We can reasonably assume that when the coupling reaction was carried out at room temperature, the basicity of aqueous ammonia was not strong enough. Therefore, addition of a base can drastically promote the reaction. However, the difference between the effect of K_3PO_4 and of other bases suggested that K_3PO_4 may not only act as a base, but also played a role as a ligand in the catalysis. This phenomenon was consistent with our earlier report[7b] on copper-catalyzed, ligand-free cross-couplings.

To summarize, herein we report a convenient, practical, and efficient copper-catalyzed method for the synthesis of primary arylamines from couplings of aryl halides and inexpensive aqueous ammonia. It was found that by using K_3PO_4 as the base, DMF as the solvent, the cross-coupling could proceed successfully at room temperature for aryl iodides and bromides. The present procedure is mild and tolerant of a variety of functional groups, thus allowing for a practical route to primary aryl amines. The convenience of aqueous ammonia and low cost of the catalytic copper system make this method readily adaptable to production on an industrial scale.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Coupling of Aryl Halides with Aqueous Ammonia at Room Temperature – General Procedure**
An oven-dried Schlenk tube was charged with CuI (18 mg, 10 mol%), K_3PO_4 (424 mg, 2.0 mmol), and aryl halide (1.0 mmol). The tube was evacuated and backfilled with nitrogen. Then, aq NH_3 (6.5 mmol, 0.5 mL) and DMF (1.0 mL) were added under nitrogen. The tube was sealed, and the reaction mixture was stirred at r.t. for 36–48 h. The reaction mixture was quenched with H_2O, extracted with Et_2O, and dried over anhyd $MgSO_4$. The solvents were removed under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc–PE) to afford the product.

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