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Copper-Catalyzed Synthesis of Primary Arylamines via Cascade Reactions of Aryl Halides with Amidine Hydrochlorides

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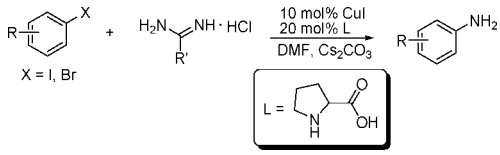
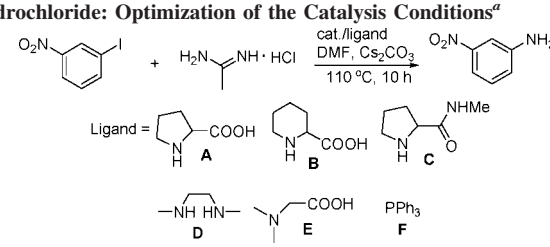


We have developed an efficient method for the synthesis of primary arylamines from aryl halides using amidine hydrochlorides as the ammonia surrogates. The protocol uses 10 mol % CuI as the catalyst, 20 mol % L-proline as the ligand, Cs_2CO_3 as the base, and DMF as the solvent and proceeds the sequential coupling of aryl halides with amidine hydrochlorides and hydrolysis of intermediates to give the target products. This is a convenient, inexpensive, and practical approach to primary arylamines.

The arylamine moiety is a ubiquitous structural element in natural products and pharmaceutical and medicinal compounds, as well as in polymers and materials,[1] and its synthesis has attracted much attention. Although transition-metal-catalyzed synthesis of primary arylamines has been used via reaction of aryl halides with NH_3, high pressure, high temperature, and sealed reaction vessels were required.[2] Therefore, the procedures might not be operationally simple and safe from the application's perspective. The Buchwald−Hartwig palladium-catalyzed amination of aryl halides/triflates has emerged in the past decades as a powerful tool for the synthesis of arylamines,[3] a large variety of amines and nitrogen nucleophiles undergo this reaction, but the use of ammonia as the coupling partner does not afford the corresponding primary anilines.[4] Several ammonia surrogates have been used to overcome this issue, and allylamine,[5a] benzophenone imine,[5b,c] *tert*-butyl carbamate,[5d,e] $Li[N(SiMe_3)_2]$,[5f,g] $Zn[N(SiMe_3)_2]$,[5h] and 2,2,2-trifluoroacetamide[5i] have been found as suitable masked forms of ammonia in cross-coupling amination reactions. Solid-supported ammonia surrogates have also been used in Pd(0)-catalyzed amination reactions showing the advantage of an easy separation of the primary aniline precursors from the reaction byproducts. The final arylamines were obtained after the cleavage step with high purities and reasonable yields.[6] Very recently, a fluoroalkyl

TABLE 1. Copper-Catalyzed Synthesis of N-Nitroaniline via Cascade Reaction of 1-Iodo-3-nitrobenzene with Acetamidine Hydrochloride: Optimization of the Catalysis Conditions[a]



entry	catalyst	ligand	base	solvent	yield [b]
1	CuI	A	Cs_2CO_3	DMF	92
2	CuBr	A	Cs_2CO_3	DMF	83
3	$CuCl_2$	A	Cs_2CO_3	DMF	41
4	CuI	A	Cs_2CO_3	DMSO	56
5	CuI	B	Cs_2CO_3	DMF	43
6	CuI	C	Cs_2CO_3	DMF	22
7	CuI	D	Cs_2CO_3	DMF	29
8	CuI	E	Cs_2CO_3	DMF	7
9	CuI		Cs_2CO_3	DMF	16
10		A	Cs_2CO_3	DMF	0
11	CuI	A	K_2CO_3	DMF	88
12	CuI	A	K_3PO_4	DMF	65
13	$PdCl_2$	F	Cs_2CO_3	DMF	0

[a] Reaction conditions: reaction temperature, 110 °C; reaction time, 10 h); aryl iodide (1 mmol), acetamidine hydrochloride (1.2 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), and solvent (2 mL) under N_2. [b] Isolated yield.

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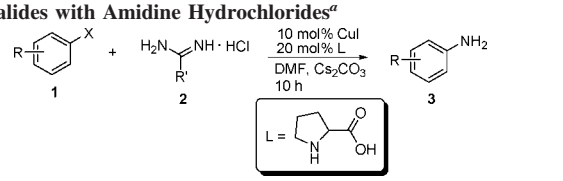
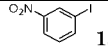
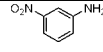
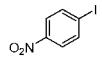
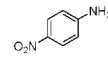
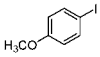
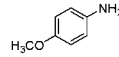
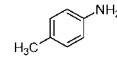
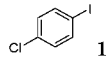
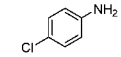
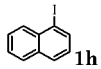
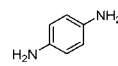
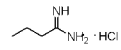
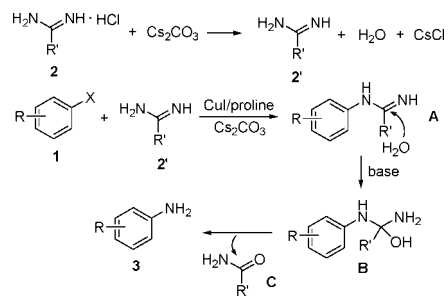
TABLE 2. Copper-Catalyzed Synthesis of Primary Arylamine via Aryl Halides with Amidine Hydrochlorides[a]



entry	aryl halide	amidine hydrochloride	Temp. (°C)	product	yield[b]
1	 **1a**	 **2a**	110	 **3a**	92
2	 **1b**	**2a**	110	 **3b**	88
3	 **1c**	**2a**	110	 **3c**	79
4	 **1d**	**2a**	120	**3b**	75[c]
5	 **1e**	**2a**	120	 **3d**	78[c]
6	 **1f**	**2a**	120	 **3e**	72[c]
7	 **1g**	**2a**	120	 **3f**	72[c]
8	 **1h**	**2a**	120	 **3g**	67[c]
9	 **1i**	**2a**	120	 **3h**	94[c]
10	 **1j**	**2a**	120	 **3i**	64[c]
11	**1b**	 **2b**	110	**3b**	65
12	**1a**	**2b**	110	**3b**	77
13	**1a**	 **2c**	110	**3a**	87
14	**1b**	**2c**	110	**3b**	80

[a] Reaction conditions: aryl iodide (1 mmol), amidine hydrochloride (1.2 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), Cs_2CO_3 (2 mmol), solvent (2 mL) under N_2. [b] Isolated yield. [c] Amidine hydrochloride (2 mmol), Cs_2CO_3 (3 mmol).

SCHEME 1. Possible Mechanism for Copper-Catalyzed Formation of Primary Arylamine



benzophenone imine reagent[7a–c] and *N*-substituted-^{F}Boc carbamate[7d] have been used as the ammonia surrogates. Recently, copper-catalyzed Ullmann *N*-arylation has become an active field,[8] and many research groups[9–11] and we[12] have developed highly efficient catalyst systems to perform aminations of aryl halides. However, the direct use of ammonia as the amino source of primary arylamines is still ineffective in the absence of pressure thus far.[2a] Herein, we report a convenient, inexpensive, and efficient copper-catalyzed method for synthesis of arylamines from aryl halides using readily available amidine hydrochlorides as the ammonia surrogates.

At first, 1-iodo-3-nitrobenzene and acetamidine hydrochloride were chosen as the model substrates to optimize reaction conditions including optimization of the catalysts, ligands, bases, and solvents at 110 °C under nitrogen atmosphere as shown in Table 1, and 3-nitroaniline was synthesized in various yields. Copper salts, CuI, CuBr, and $CuCl_2$ (10 mol % amount relative to 1-iodo-3-nitrobenzene), were tested in DMF (entries 1−3) using 20 mol % L-proline as the ligand and 2 equiv of Cs_2CO_3 as the base, and CuI was found to be the most effective catalyst. We attempted to change solvents to DMSO from DMF (compare entries 1 and 4), and the results showed that DMF was much better than DMSO. The effect of ligands was also investigated (entries 1, 5−8), and L-proline showed the highest activity. Only

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16% yield of 3-nitroaniline was obtained in the absence of ligand (entry 9). No target product was observed in the absence of copper catalyst (entry 10). Several bases, Cs_2CO_3, K_2CO_3, and K_3PO_4, were also screened, and Cs_2CO_3 proved to be the best base (compare entries 1, 11 and 12). We also tried the palladium catalyst $PdCl_2$ in the presence of ligand PPh_3, but no target product was found (entry 13). After the optimization process for catalysts, solvents, ligands, and bases, the various primary arylamines were synthesized under our standard conditions: 10 mol % CuI as the catalyst, 20 mol % L-proline as the ligand, 2 or 3 equiv of Cs_2CO_3 as the base (relative to aryl halides), and DMF as the solvent.

Having established a suitable combination of copper catalyst, ligant, solvent, and base, we explored the scope of this protocol. Reactions of aryl halides containing electron-withdrawing or electron-donating groups with acetamidine hydrochloride in the presence of Cs_2CO_3 were performed, and the corresponding primary arylamines were obtained in good to excellent yields (entries 1−10) as shown in Table 2. Aryl halides containing electron-donating groups showed reactivities slightly weaker than those of ones containing electron-withdrawing groups. For example, aryl iodides containing electron-withdrawing groups were carried out at 110 °C (entries 1−3, 11−14), but amination of aryl iodides containing electron-donating groups could not be performed until the temperature was increased to 120 °C, and 2 equiv of of amidine hydrochlorides relative to aryl iodides was required for entries 5−10. We also investigated reactivity of other amidine hydrochlorides, and reactions of benzamidine hydrochloride or butyramidine hydrochloride with aryl halides also provided the corresponding primary arylamines in good yields (entries 11−14). Compared with acetamidine hydrochloride, benzamidine and butyramidine hydrochlorides showed slightly lower reactivity.

The possible formation mechanism of primary arylamines is proposed in Scheme 1. Reaction of amidine hydrochloride (**2**) with base (Cs_2CO_3) produces free amidine (**2′**) and water, and the Ullmann coupling reaction of **2′** with aryl halide gives *N*-arylamidine (**A**). Addition of **A** with water in base medium provides intermediate **B**, and the following removal of amide **C** from **B** yields the target product (**3**).

In summary, we have developed an efficient method for the synthesis of arylamines, and this protocol uses inexpensive CuI/L-proline as the catalyst, various aryl halides as the substrates, and amidines as the ammonia surrogates, the reactions were performed under simple and safe experimental conditions. Acetamidine hydrochloride is a more economical ammonia surrogate compared with other amidine hydrochlorides. The method provides an important motif for synthesis of natural products and pharmaceutical and medicinal compounds, as well as in polymers and materials.

Experimental Section

General Procedure for Copper-Catalyzed Synthesis of Primary Arylamines. A flask was charged with CuI (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol), and Cs_2CO_3 (2 or 3 mmol) (see Tables 1 and 2) in 2 mL of DMF, and aryl halide (1 mmol) and amidine hydrochloride (1.2 or 2 mmol) (see Tables 1 and 2) were added to the flask at room temperature under nitrogen atmosphere. The mixture was stirred at 110 or 120 °C (see Tables 1 and 2) under nitrogen atmosphere. After the coupling reaction proceeded for 10 h, the resulting solution was cooled to room temperature and diluted with 5 mL of CH_2Cl_2. The solution was filtered, and the inorganic salts were removed. The filtrate was concentrated with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1 to 1:1) as eluent to provide the desired product. Two examples are shown as follows.

4-Nitroaniline (3a). [13] Eluent: petroleum ether/ethyl acetate (10:1). Yield: 127 mg (92%). Yellow solid, mp 113−114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20−7.35 (m, 4H), 5.76 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.62, 149.25, 130.39, 120.46, 110.28, 107.56. MS M^+ *m*/*z* 138.0.

p-Phenylenediamine (3 h). [14] Eluent: petroleum ether/ethyl acetate (1:1). Yield: 102 mg (94%). Brown solid, mp 143−145 °C (lit.[14] 141 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.34 (s, 4H), 4.16 (s, 4H).^{13}C NMR (75 MHz, DMSO-d_6) δ 139.4, 116.0. MS M^+ *m*/*z* 108.1.

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Supporting Information Available: General experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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