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Copper-catalyzed synthesis of primary arylamines from aryl halides and 2,2,2-trifluoroacetamide

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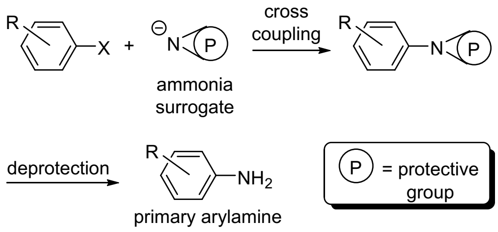
Abstract—A catalytic method was developed to synthesize primary arylamines from the corresponding aryl bromides and iodides under mild conditions (yields = 80–99%). Crystalline 2,2,2-trifluoroacetamide was used as ammonia surrogate and CuI/*N*,*N*′-dimethyl ethylenediamine was used as catalyst to achieve the C–N cross-coupling.

Primary arylamines are important intermediates in the manufacture of agrochemicals, pharmaceuticals, dyes, pigments, and rubber.[1] These compounds were traditionally synthesized through the aryne route by amination of the corresponding aryl halides using ammonia as the nucleophile.[2] A problem associated with this synthetic method is that the reaction has to be carried out under fairly high temperature and pressure. Besides, the amination reaction is often complicated by other products arising from the highly unstable aryne intermediates.[3] Due to these reasons, several groups have recently studied the possibility of using transition metals to catalyze the synthesis of primary arylamines from aryl halides. For instance, in 2001 Lang et al. reported Cu-catalyzed coupling reactions between aryl bromides and NH_3 under 100 psi.[4] In 2006 Hartwig and Shen reported Pd-catalyzed coupling of NH_3 with aryl halides under 80 psi.[5] More recently Buchwald and Surry also reported Pd-catalyzed coupling of NH_3 (0.5 M in dioxane) with aryl halides at 80 °C in a sealed test tube.[6]

Unfortunately all the above catalytic reactions using NH_3 as the nucleophile were still performed under a relatively high pressure of NH_3 at elevated temperatures. A sealed reaction vessel had to be used under these conditions and therefore, the procedures might not be operationally simple or safe from the application's perspective. Besides, several functional groups (such as esters) cannot tolerate the above amination reaction conditions (namely, concentrated NH_3 + elevated temperature), which further limits the applicability of the above methods. To overcome the problem of using NH_3, a number of authors have recently proposed the use of non-volatile ammonia surrogates in the transition-metal catalyzed synthesis of primary arylamines. Previously reported surrogates included benzophenone imine,[7] allylamines,[8] lithium bis(trimethylsilyl)amide,[9] *N*-trialkyl-silylimines,[10] and zinc trimethylsilylamide.[11] These compounds were demonstrated to be sufficiently active in the Pd-catalyzed C–N cross-coupling with aryl halides under relatively mild conditions.[7–11] The corresponding C–N cross-coupling products could subsequently be converted to the desired primary arylamines after removing the protective groups (Scheme 1).



Scheme 1. Synthesis of primary arylamines by using ammonia surrogates as the nucleophile through transition-metal catalyzed cross-coupling reactions.

Keywords: Copper catalysis; Ammonia surrogate; Cross coupling; Primary arylamines.

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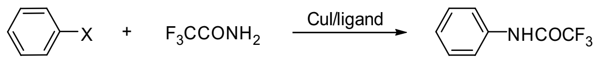
It is worth noting that the ammonia surrogate approach has only been tested with the Pd catalysts.[7–11] However, the use of Pd catalysts may not be optimal from the economic point of view because Pd is expensive and contamination of the product by Pd has to be tightly controlled.[12] Besides, it is well known that expensive phosphine ligands such as 2-dicyclohexylphosphinobiphenyl are usually needed to effect the Pd-catalyzed C–N cross coupling.[13] Due to these reasons, we are interested in developing a Cu-catalyzed approach to achieve the ammonia surrogate strategy in the synthesis of primary arylamines. This approach is expected to be economically efficient because Cu-catalyzed C–N cross-coupling reactions have been shown to proceed under much less expensive conditions than Pd.[14] In addition, to further reduce the cost of the arylamine synthesis we seek to use 2,2,2-trifluoroacetamide as ammonia surrogate. This particular compound has not been tested in the previous Pd-catalyzed approaches, but we expect it to be an ideal ammonia surrogate because the trifluoroacetyl group can be readily removed under very mild conditions.[15]

Evidently the key point of the Cu-catalyzed primary arylamine synthesis using 2,2,2-trifluoroacetamide as ammonia surrogate is the cross coupling between this particular amide and aryl halides. Although a number of catalytic systems (such as CuI/1,2-diamines and CuI/1,10-phenanthroline)[16] have been shown to promote the Cu-catalyzed amidation of aryl halides, it remains unclear how the trifluoroacetyl group would affect the amidation efficiency. Thus we systematically evaluate the ligands in the cross coupling of iodobenzene and bromobenzene with 2,2,2-trifluoroacetamide (Table 1). It is found that the amidation yield is zero when no ligand is added (entry 1). Surprisingly, it is also found that the amidation yield remains to be zero in the presence of glycine and *N*,*N*-dimethylglycine (entries 2 and 3), despite the fact that these amino acids ligands were previously shown to be able to promote the amidation

Table 1. Copper-catalyzed cross-coupling of iodobenzene and bromobenzene with 2,2,2-trifluoroacetamide[a]



Entry	X	Ligand	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
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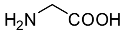
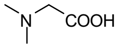
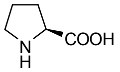
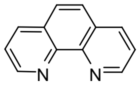
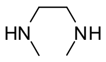
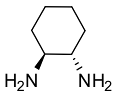
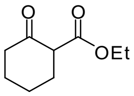
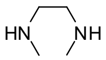
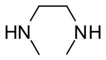
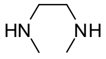
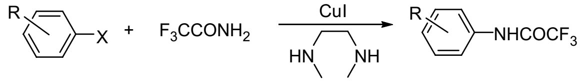
2	I		K_3PO_4	DMF	45	24	0
3	I		K_3PO_4	DMF	45	24	0
4	I		K_3PO_4	DMF	45	24	35
5	I		K_3PO_4	DMF	45	24	0
6	I		K_3PO_4	DMF	45	24	**95**
7	I		K_3PO_4	DMF	45	24	40
8	I		K_3PO_4	DMF	45	24	0
9	Br		K_3PO_4	DMF	75	24	0
10	Br		K_2CO_3	DMF	75	24	36
11	Br		K_2CO_3	Dioxane	75	24	**96**

[a] General conditions: PhX = 1.0 mmol, F_3CCONH_2 = 1.5 mmol, CuI = 5 mol %, ligand = 10 mol %, base = 2.0 equiv, solvent = 1.0 mL, 4 ÅMS = 500 mg.

[b] Isolated yield.

Table 2. Cu-catalyzed cross-coupling of substituted iodobenzenes and bromobenzenes with 2,2,2-trifluoroacetamide[a]



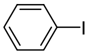
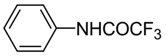
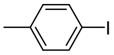
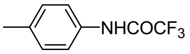
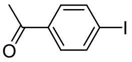
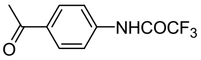
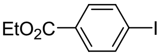
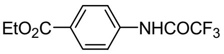
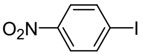
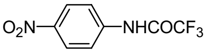
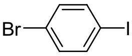
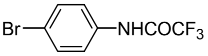
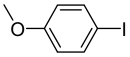
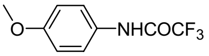
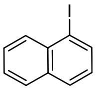
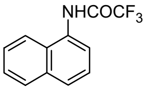
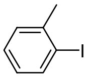
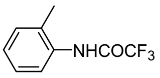
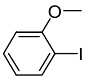
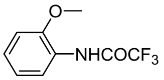
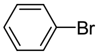
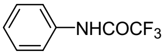
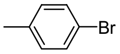
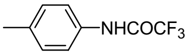
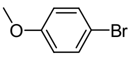
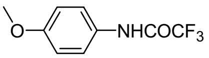
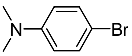
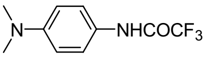
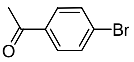
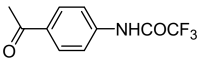
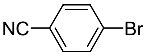
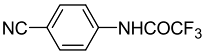
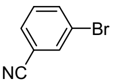
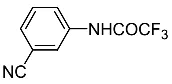
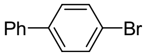
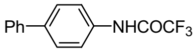
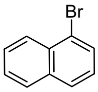
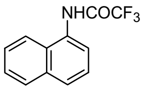
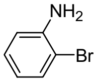
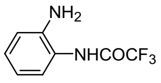
Entry	Aryl halide	Product	Temp (°C)	Yield[b] (%)
1			45	95
2			45	94
3			45	90
4			45	83
5			45	80
6			45	95
7			45	93
8			45	21[c]
9			45	15[c]
10			45	26[c]
11			75	96
12			75	93
13			75	90
14			75	99
15			75	81
16			75	84
17			75	83

Table 2 (*continued*)

Entry	Aryl halide	Product	Temp (°C)	Yield[b] (%)
18			75	98
19			75	61[c]
20			75	6

[a] Conditions: ArX = 1.0 mmol, F_3CCONH_2 = 1.5 mmol, CuI = 5 mol %, *N*,*N*′-dimethylethylenediamine = 10 mol %, base = 2.0 equiv, solvent = 1.0 mL, 4 ÅMS = 500 mg.

[b] Isolated yield.

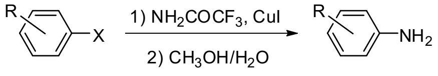
[c] CuI = 10 mol %.

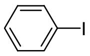
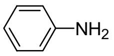
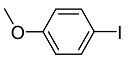
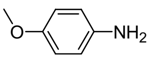
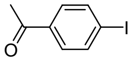
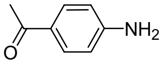
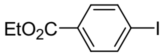
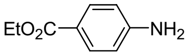
of phenyl halide by acetamide and benzamide.[17] The addition of proline as ligand can increase the yield to 35% (entry 4). However, 1,10-phenanthroline, an excellent ligand in many Cu-catalyzed cross coupling reactions,[18] is completely inactive in this particular transformation (entry 5). At this point, we are pleased to find that *N*,*N*′-dimethyl ethylenediamine (DMEDA) can dramatically increase the coupling yield to 95% (entry 6). On the other hand, *trans*-cyclohexane-1,2-diamine and ethyl 2-oxocyclohexanecarboxylate (an excellent ligand recently highlighted by Bao and Lv[19]) are not found to be active enough (entries 7 and 8). All the above observations indicate that 2,2,2-trifluoroacetamide has a very different ligand demand as compared to the ordinary amides. Furthermore, it should be noted that although 45 °C is sufficient for the amidation of an aryl iodide, the reaction temperature has to be raised to 75 °C for an aryl bromide (entries 9–11). The solvent also has to be changed to dioxane, where the amidation yield is as high as 96%.

Having identified the CuI/DMEDA catalytic system, we next examined whether the same catalytic system can be applied to the coupling of 2,2,2-trifluoroacetamide with various aryl iodides and bromides having different electronic and steric properties (Table 2).[20] It is found that both electron-rich and electron-deficient aryl halides can be smoothly converted to the desired products with satisfactory isolated yields (i.e. 80–95% for aryl iodides and 81–99% for aryl bromides, respectively). However, aryl halides carrying an *ortho*-substituent are not found to readily participate in the reaction. For instance, 2-iodotoluene can only give an isolated yield of 15% even in the presence of 10% CuI (entry 9), whereas the amidation yield for 2-bromoaniline is as low as 6% (entry 20). Similarly, the amidation yield is only 21% for 1-iodo-naphthalene (entry 8) and 61% for 1-bromonaphthalene (entry 19), which are values significantly lower than the phenyl cases. Thus the steric effect has a much stronger influence than the electronic effect in the cross-coupling with 2,2,2-trifluoroacetamide.

Certainly the above amidation products can now be readily converted to the target primary arylamines using the standard deprotection methods for the trifluoroacetyl group.[15] However, in our hands we find fortuitously

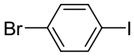
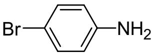
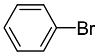
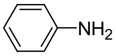
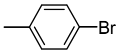
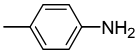
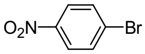
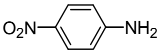
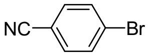
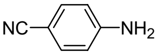
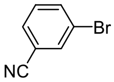
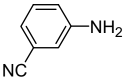
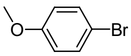
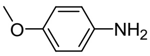
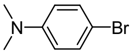
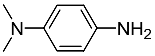
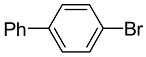
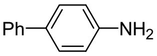
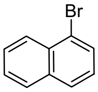
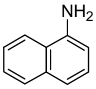
Table 3. Copper-catalyzed one-pot synthesis of primary arylamines from aryl halides[a]



Entry	Aryl halide	Product	Temp (°C)	Yield[b] (%)
1			45	91
2			45	95
3			45	98
4			45	99

(*continued on next page*)

Table 3 (*continued*)

Entry	Aryl halide	Product	Temp (°C)	Yield[b] (%)
5			45	80
6			75	93
7			75	91
8			75	93
9			75	99
10			75	95
11			75	87
12			75	90
13			75	93
14			75	50[c]

[a] Conditions: (1) ArX = 1.0 mmol, F_3CCONH_2 = 1.5 mmol, CuI = 5 mol %, *N*,*N*′-dimethylethylenediamine = 10 mol %, base = 2.0 equiv, solvent = 1.0 mL, 4 ÅMS = 500 mg. (2) $MeOH/H_2O$ = 3.0 mL:3.0 mL.

[b] Isolated yield.

[c] CuI = 10 mol %.

that the trifluoroacetyl group can be removed directly after the amidation step by adding CH_3OH and H_2O to the reaction vessel. The success of this method is presumably due to the use of K_3PO_4 or K_2CO_3 in the amidation step, which promotes the hydrolysis of the trifluoroacetyl group once water is added. Taking advantage of this finding, we developed a one-pot method for the synthesis of primary arylamines from aryl halides without the need to separate any intermediate.[21] As shown in Table 3, this one-pot method can be successfully applied to a variety of aryl iodides and bromides (entries 1–13, yields = 80–99%). 1-bromonaphthalene can also be successfully converted to 1-naphthalenamine with a yield of 50% (entry 14).

To conclude, in the present study we report a novel method for the synthesis of primary arylamines from the corresponding aryl halides. 2,2,2-Trifluoro-acetamide is used as ammonia surrogate and CuI is used as the catalyst to achieve the C–N coupling under mild conditions. Given the fact that primary arylamines are becoming increasingly more important intermediates in the synthesis of functional materials,[1] the method described in the present report may be found useful in a number of fields such as pharmaceutical research and organic material design.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.012.

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19. Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863.
20. *General procedure for the amidation*: An over-dried Schlenk tube was charged with CuI (10 mg), base (2.0 mmol, K_3PO_4 for ArI and K_2CO_3 for ArBr), and 4 ÅMS (500 mg). The tube was evacuated and backfilled with Ar. Then aryl halide (1.0 mmol), trifluoroacetamide (170 mg), DMEDA (12 μL), and solvent (1.0 mL, DMF for ArI and dioxane for ArBr) were added under Ar. The reaction mixture was stirred for 24–36 h at 45 °C (for ArI) or 75 °C (for ArBr). The resulting suspension was cooled to room temperature and filtered through a pad of silica gel with the help of 100 mL of ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography to afford the product.
21. *General procedure for the one-pot synthesis of primary arylamines*: An over-dried Schlenk tube was charged with CuI (10 mg), base (2.0 mmol, K_3PO_4 for ArI and K_2CO_3 for ArBr), and 4 ÅMS (500 mg). The tube was evacuated and backfilled with Ar. Then aryl halide (1.0 mmol), trifluoro-acetamide (170 mg), DMEDA (12 μL) and solvent (1.0 mL, DMF for ArI and dioxane for ArBr) were added under Ar. The reaction mixture was stirred for 24–48 h at 45 °C (for ArI) or 75 °C (for ArBr). Subsequently to the reaction mixture was added CH_3OH/H_2O (3.0 mL/3.0 mL) under Ar. The reaction was further stirred for 5–12 h. The resulting suspension was cooled to room temperature, concentrated and extracted with ethyl acetate (20 mL × 3). The combined organic layers were concentrated and the residue was purified by column chromatography to afford the product.