Tetrahedron Letters 53 (2012) 1265–1270

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Solvent-free copper-catalyzed N-arylation of amino alcohols and diamines with aryl halides

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ARTICLE INFO

Article history:
Received 11 October 2011
Revised 22 December 2011
Accepted 30 December 2011
Available online 5 January 2012

Keywords:
Copper-catalyzed
N-arylation
Solvent-free
Amino alcohols
Diamines

ABSTRACT

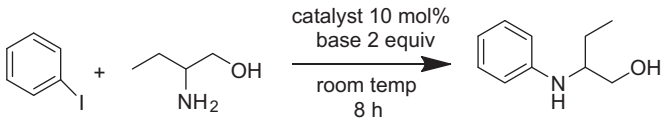
A simple and mild method for the coupling of aryl halides with amino alcohols and diamines is described. The reactions can be performed under ligand-free and solvent-free conditions, and generate the products in good yield.

Transition-metal-catalyzed amination of aryl halides represents an important method and is widely used in the synthesis of many substances including drugs, materials, natural products, agrochemicals, and optical devices.[1] Typically, C–N bonds are formed by Ullmann-type coupling processes. However, the classical coupling reaction generally suffers from several shortcomings including high reaction temperatures, moderate yields, extended reaction times, and poor substrate generality.[2] A breakthrough by Buchwald and co-workers discovered that the Cu-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides could be achieved in good yields under mild conditions in the presence of bidentate *N*,*N*-ligands.[3] Following the work of Buchwald, a number of Cu-catalyzed coupling reactions with various ligands have been reported, such as organic phosphanes,[4] N-containing aromatic heterocycles,[5] diamines,[6] diols,[7] triols,[8] rac-binols,[9] salicylamides,[10] β-diketones,[11] β-keto esters,[12] imines,[13] amino acids,[14] amino phosphates,[15] and diazaphospholanes.[16] Notably, most ligands are hard to synthesize and the solvent is difficult to remove. Therefore, it is important to develop a simpler and more efficient catalytic system for the amination of aryl halides.

Recently, several 'ligand-free' systems have emerged for the N-arylation of aromatic N-heterocycles and amino acids catalyzed by copper compounds.[17] However, there are few reports covering amino alcohols and diamines. Buchwald investigated selective *N*-aryl and *O*-aryl reactions of β-amino alcohols as reactants with different solvents and bases,[18] however, this method was limited by the narrow substrate scope. They found the substrate scope was extended by adding β-keto esters as ligands.[19] Twieg reported that deanol was used as an efficient solvent and ligand for the copper-catalyzed amination reaction.[20]

We were interested in developing a mild and effective method for the N-arylation of amine derivatives. Herein, we report the efficient Cu-catalyzed N-arylation of amino alcohols and diamines with aryl halides under ligand-free and solvent-free conditions.

Table 1
Screening reaction conditions for copper-catalyzed N-arylation of 2-amino-1-butanol with iodobenzene



Entry	Cu source	Base	Yield[a] (%)
1	CuCl	Cs_2CO_3	30
2	CuCl	K_2CO_3	20
3	CuCl	K_3PO_4	25
4	CuCl	NaOH	61
5	CuCl	KOH	91
6	CuBr	KOH	85
7	Cu_2O	KOH	80
8	CuI	KOH	72
9	$Cu(OAc)_2$	KOH	27
10[b]	CuCl	KOH	Trace

[a] Isolated yield.
[b] 2 ml DMSO added.

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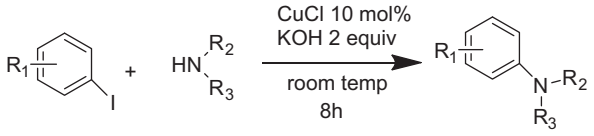
doi:10.1016/j.tetlet.2011.12.130

In our initial screening experiments, iodobenzene and 2-amino-1-butanol were used as the prototypical substrates for the discovery of suitable reaction conditions. The standardized protocol was performed using iodobenzene (1 equiv), 2-amino-1-butanol (3 equiv), base (2 equiv), and Cu source (10 mol %) stirred at room temperature for 8 h. The results are shown in Table 1.

At first, iodobenzene (1 equiv) was treated with 2-amino-1-butanol (3 equiv) and stirred at room temperature for 8 h with CuCl (0.1 equiv) and Cs_2CO_3 (2 equiv), and the corresponding *N*-arylated 2-amino-1-butanol was formed only in a 30% yield (Table 1, entry 1). Replacement of Cs_2CO_3 with K_2CO_3 and K_3PO_4 also gave low yields (Table 1, entries 2–3), but NaOH gave a good yield (Table 1, entry 4).

Table 2
Catalyzed N-arylation of amino alcohols with various iodobenzenes[a]



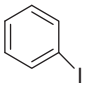
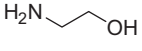
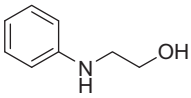
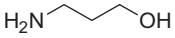
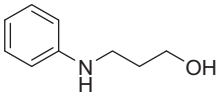
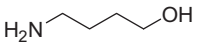
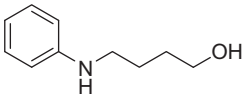
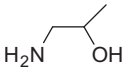
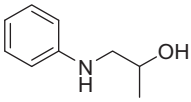
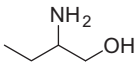
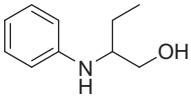
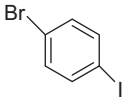
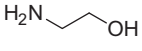
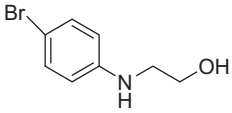
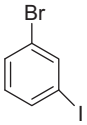
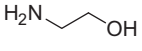
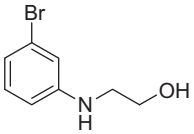
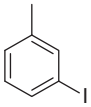
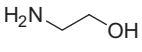
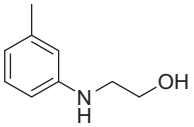
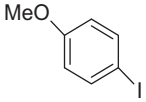
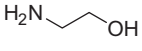
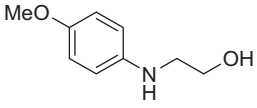
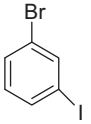
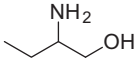
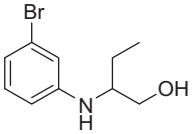
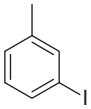
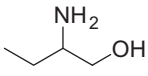
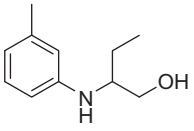
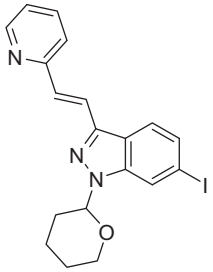
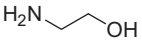
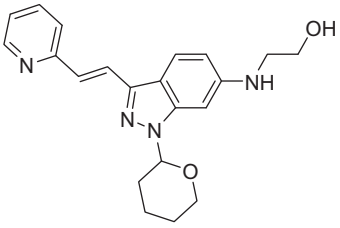
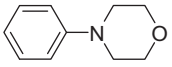
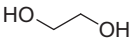
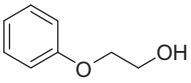
Entry	Aryl halide	Amine	Product	Yield[b] (%)
1				99
2				97
3[c]				73
4				82
5				91
6				92
7				95
8				92
9				90
10				98
11				64

Table 2 (*continued*)

Entry	Aryl halide	Amine	Product	Yield[b] (%)
12				82
13				Trace
14				0

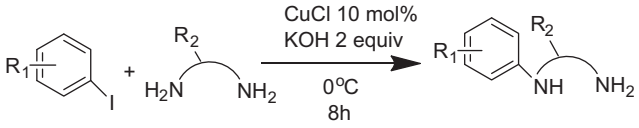
[a] Reaction and conditions: CuCl (0.1 mmol, 10 mol %), ArI (1.0 mmol), amine (3.0 mmol), and KOH (2.0 mmol) at room temperature under air (no solvent added).
[b] Isolated yield
[c] Reaction time: 12 h

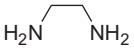
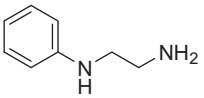
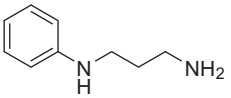
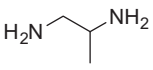
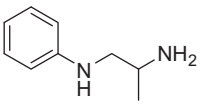
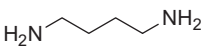
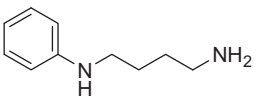
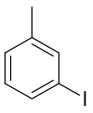
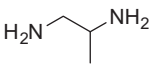
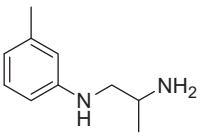
An extremely good yield of 91% was obtained when only KOH was used (Table 1, entry 5). Other copper compounds (CuBr, CuI, Cu_2O and $Cu(OAc)_2$) were also evaluated under KOH conditions but proved less effective than CuCl. Notably, $Cu(OAc)_2$ gave a product yield of only 27% (Table 1, entries 6–9).

The solvent usually plays an important role in the coupling reaction. Surprisingly, it was found that DMSO, the reported effective solvent, had a deleterious effect on the reaction using this catalytic system (Table 1, entry 10).

Having established an effective catalytic protocol for the coupling reaction, we then examined the scope of the process with respect to various amino alcohols.[21] We noticed that all the amino alcohols we explored worked well; in particular, ethanolamine and propanolamine showed high yields (Table 2, entries 1–2). When 4-aminobutanol was used, a good yield was obtained (Table 2. entry 3). Even simple amino alcohols with substituents provided high yields (Table 2, entries 4–5). To explore the scope of the process with respect to aryl halides, a variety of substituted aryl halides

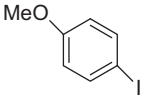
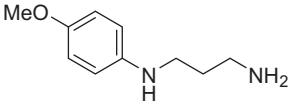
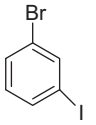
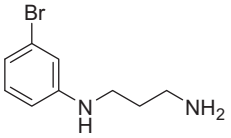
Table 3
Catalyzed N-arylation of diamines with iodobenzenes[a]



Entry	Aryl Halide	Amine	Product	Yield[b] (%)
1				98
2				92
3				62
4[c]				15
5				41

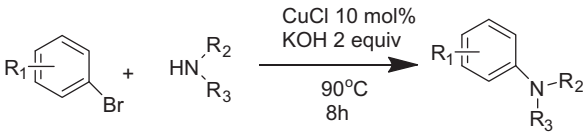
(*continued on next page*)

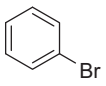
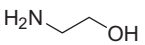
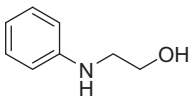
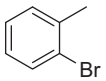
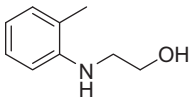
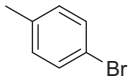
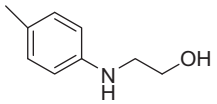
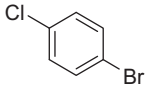
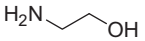
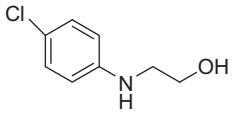
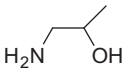
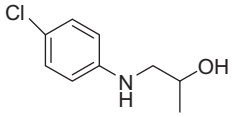
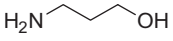
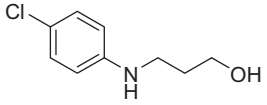
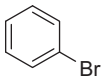
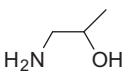
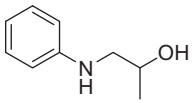
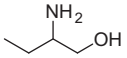
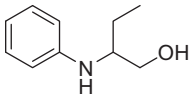
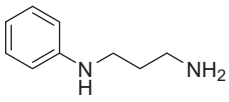
Table 3 (*continued*)

Entry	Aryl Halide	Amine	Product	Yield[b] (%)
6				65
7				56

[a] Reaction and conditions: CuCl (0.1 mmol, 10 mol %), ArI (1.0 mmol), amine (3.0 mmol), and KOH (2.0 mmol) at 0 °C under air (no solent added).
[b] Isolated yield.
[c] Reaction time: 24 h.

Table 4
Catalyzed N-arylation of amino alcohols and diamines with various bromides[a]



Entry	Aryl halide	Amine	Product	Yield[b] (%)
1				99
2				97
3				97
4				99
5				72
6				73
7				62
8[c]				42
9[d]				24

[a] Reaction conditions: CuCl (0.1 mmol, 10 mol %), ArI (1.0 mmol), amine (3.0 mmol), and KOH (2.0 mmol) at 90 °C under air (no solvent added).
[b] Isolated yield.
[c] Reaction temperature: 110 °C.
[d] Reaction time: 24 h.

under the optimized reaction conditions were tested. Selecting ethanolamine as the model amine, the corresponding N-arylation products were obtained in high yields (Table 2, entries 6–9). When 2-aminobutanol was chosen, significant electronic effects were observed for the electron-poor and electron-rich substituted aryl halides (Table 2, entries 10–11). Electron-donating substituents showed lower reactivity than electron-withdrawing substituents. In addition, we found that more complicated aryl iodides worked well, affording the amination product in an excellent yield (Table 2, entry 12).

In view of these interesting results, we further investigated the scope of the reaction using various substrates. When ethylene glycol or morpholine was used, no product was observed (Table 2, entries 13–14). However, when ethylenediamine was used, the desired amination products were obtained in an 82% yield at room temperature, and a yield of 98% was obtained when the reaction was performed at 0 °C (Table 3, entry 1).[22] Diamines are a special class of amines that are capable of forming stable chelates with a metal atom, whereas their use as substrates in reactions normally fails because the formation of chelates may hinder the catalytic process. Guilard and co-workers reported a selective, convenient palladium-catalyzed introduction of aryl moieties into diamines without using any protecting group.[23]

With the optimized reaction conditions identified for ethylenediamine, the other diamines were examined. A high yield was observed for 1,3-propanediamine (Table 3, entry 2), and a moderate yield was observed for 1,2-propanediamine (Table 3, entry 3). 1,4-Butanediamine gave a poor yield (Table 3, entry 4). We then evaluated a variety of aryl halides, in which both electron-withdrawing and -donating groups were tolerated (Table 3, entries 5–7).

Furthermore, we investigated the coupling reaction of aryl bromides with amino alcohols and diamines. Almost no desired product was attained at room temperature, but when the reaction temperature was increased to 90 °C, bromobenzene and ethanolamine gave a 99% yield of the product (Table 4, entry 1). The efficacy of the system for various bromides with ethanolamine was further evaluated. Both electron-withdrawing and electron-donating groups worked well (Table 4, entries 2–4). Other amino alcohols were then used as substrates, and all of them afforded moderate to good yields (Table 4, entries 5–7). However, a lower yield was observed for 2-aminobutanol, even at temperatures as high as 110 °C (Table 4, entry 8). In addition, chlorides failed to undergo this transformation under the standard reaction conditions, and the coupling reaction of aryl bromides with diamines afforded much lower yields even with an extended reaction time of 24 h (Table 4, entry 9).

On the basis of the presented results, we propose a possible mechanism for the reactions (Fig. 1). The mechanism of the reaction may be similar to amino acid promoted copper catalysis. The reaction of amine substrates with CuCl produced a five- or six-membered chelator **I**, and subsequent oxidative addition of the chelator **I** with an aryl halide led to the formation of intermediate **II**. Treatment of the amine substrates with **II** in the presence of KOH provided complex **III**, and then reductive elimination of **III** gave the N-arylation product and the chelator **I**. The mechanism not only explains the reactivity order of aryl halides, ArI > ArBr > ArCl, but also the lower reactivity of steric amines. This mechanism can also rationalize the failure of morpholine as the substrate, because it must be in boat conformation in order to form chelator **I** with Cu, which however, is disfavored. In addition, relative lower yield of 4-aminobutanol can be explained with the more difficulty in the formation of seven-membered chelator **I** with Cu, compared to five- or six-membered ring.

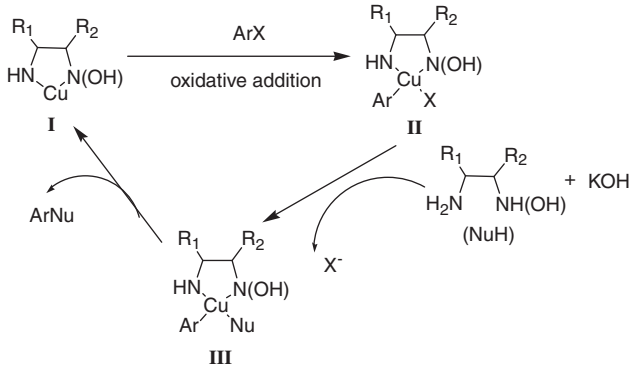


Figure 1. Proposed Mechanism.

In summary, we have developed a simple and facile method for the C–N cross-coupling of amino alcohols and diamines with aryl halides using CuCl under ligand-free and solvent-free conditions. This method is convenient, cost effective, environmentally friendly, and the work-up is easy. The reactions are efficient, affording the cross-coupled products in short reaction times with high yields. Currently, we are exploring substrate scope and the application of the Cu-catalyzed N-arylation under ligand-free and solvent-free conditions with regard to the synthesis of pharmaceutical molecules.

Acknowledgments

We thank to the National Natural Science Foundation of China for supporting this research (Grant No. 20942006, Grant No. 21072095) and the research grants provided by the open fund of key laboratory of Synthetic Chemistry of Natural Substance, Shanghai Institute of Organic Chemistry, CAS.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.130.

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21. *General procedure for Cu-catalyzed N-arylation of amino alcohols with iodobenzenes*: CuCl (10 mg, 0.1 mmol), Aryl iodide (if solid, 1.0 mmol), and KOH (112 mg, 2.0 mmol) were added to a screw-capped test tube. Aryl iodide (if liquid, 1.0 mmol), and amino alcohol (3 mmol) were added by syringe at room temperature. The reaction mixture was stirred at room temperature for 8–12 h. The resulting mixture was diluted with water (2 mL) before extraction with ethyl acetate (3×5 mL), and dried over Na_2SO_4, the filtrate was concentrated under reduced pressure, and the mixture was purified by flash chromatography on silica gel to afford the desired product. Selected spectral data for 2-(3-Tolylamino)butan-1-butanol (Table 2, entry 11): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (m, 1H), 6.54 (d, 1H, J = 7.6 Hz), 6.46 (d, 2H, J = 7.6 Hz), 3.72 (dd, 1H, J = 4.2 Hz, J = 10.8 Hz), 3.5 (dd, 1H, J = 5.9 Hz, J = 10.8 Hz), 3.38 (m, 1H), 2.28 (s, 3H), 1.54 (m, 2H), 0.95 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.2, 118.8, 114.5, 110.8, 64.1, 56.7, 29.7, 24.9, 21.6, 10.5; ESI-MS m/z 180.2 [M^++H].
22. *General procedure for Cu-catalyzed N-arylation of dimines with iodobenzenes*: CuCl (10 mg, 0.1 mmol), aryl iodide (if solid, 1.0 mmol), and KOH (112 mg, 2.0 mmol) were added to a screw-capped test tube. Aryl iodide (if liquid, 1.0 mmol), and dimine (3 mmol) were added by syringe. The reaction mixture was stirred at 0 °C for 8 h. The resulting mixture was diluted with water (2 mL) before extraction with methylene chloride (3×5 mL), and dried over Na_2SO_4, the filtrate was concentrated under reduced pressure, and the mixture was purified by flash chromatography on silica gel to afford the desired product. Selected spectral data for *N*-Phenyl-1,2-diaminoethane (Table 3, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, 2H, J = 7.8 Hz), 6.72 (t, 1H, J = 7.3 Hz), 6.64 (d, 2H, J = 7.8 Hz), 3.16 (t, 2H, J = 5.7 Hz), 2.91 (t, 2H, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 129.0, 117.1, 112.7, 46.2, 40.9.
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