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Synthesis of Secondary Arylamines through Copper-Mediated Intermolecular Aryl Amination

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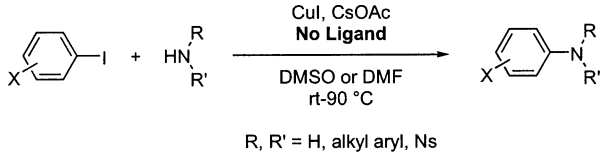
ABSTRACT



A mild intermolecular copper-mediated amination of aryl iodides has been developed. The reaction takes place at room temperature or heating at 90 °C and tolerates halogens attached to the aromatic ring. Its synthetic applications include a synthetic protocol for unsymmetrical *N*,*N*′-dialkylated phenylenediamines and both a stepwise and a general synthetic method for *N*-aryl secondary amines via Ns-anilides (readily obtained by reaction of the Ns-amide).

The copper-catalyzed Ullmann−Goldberg coupling, a well-known reaction for the introduction of amine functionality using aromatic halides, proceeds under severe reaction conditions such as heating at high temperatures without a solvent.[1] While milder reactions using transmetallating agents such as triarylbismuth,[2] aryllead triacetates,[3] arylboronic acids,[4] and hypervalent aryl siloxanes[5] have been developed, the utility of these variants is limited since the preparation of highly functionalized substrates usually requires multistep sequences. Recent improvements using palladium-catalyzed amination of aryl halides appear to be greatly superior in terms of practical utility and mild reaction conditions.[6] For instance, with the right choice of an efficient phosphine ligand, N-arylation can be performed at room temperature. More recently, mild Ullmann-type N-arylations have been investigated, in which a variety of nitrogen substrates, including anilines,[7] amides,[8] imidazoles,[9] nitrogen heterocycles,[10] hydrazides,[11] and α- or β-amino acids[12] could be

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arylated under mild conditions. In addition, copper-catalyzed aminations using easily prepared, efficient ligands have been reported.[13]

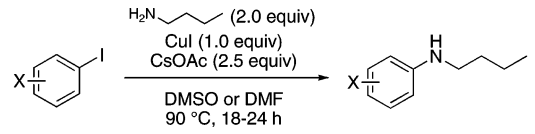
During the course of our synthetic studies on indole alkaloids, we have discovered an exceptionally mild copper-mediated intramolecular amination of aryl halides, which was effected by a combination of copper iodide and cesium acetate without ligands.[14] Use of this reaction allowed asymmetric total syntheses of the duocarmycins to be achieved.[15] The unusually facile amination might be attributed to the use of soluble CuOAc, generated in situ, and appropriate solvents without using ligands. To examine the generality of this reaction, we turned our attention to its application to an intermolecular process. In this paper, we describe a copper-mediated intermolecular amination of aryl iodides. In addition, we report its application to a general protocol for the synthesis of secondary *N*-arylalkylamines, exploiting *o*-nitrobenzenesulfonamide (Ns-amide) chemistry.

First, *n*-butylamine and iodobenzene were chosen as the test substrates and subjected to the conditions previously established,[14,15] namely, 1.0 equiv of CuI and 2.5 equiv of CsOAc in degassed DMSO.[16] Unfortunately, the reaction afforded only a minute amount of the desired product (**1a**). After extensive optimization, we found that a relatively high concentration (ca. 1.0 M) in DMSO or DMF was essential for obtaining satisfactory yields. Thus, the reaction at room temperature for 18 h afforded 70% yield of *N*-butylaniline (Table 1, entry 1), which was improved to 93% by elevating the reaction temperature to 90 °C (entry 2). In the case of a large-scale reaction with several grams of substrate, use of inexpensive lower grade CuI (95% purity) and nondegassed DMSO provided **1a** at the same level of yield, indicating the practical utility of this condition (entry 3).[17] Furthermore, a limited amount (1.2 equiv) of amine and a substoichiometric amount (20 mol %) of CuI provided acceptable results (entries 4, 5).

Having established the optimal conditions, we then investigated the substitution effects of aryl iodides (Table 1). All of the para-substituted compounds, including those bearing electron-donating and electron-withdrawing substituents, gave good to excellent yields of the products (entries 2, 6−10). One advantage over palladium-mediated reactions[14] was that a selective monoamination took place in the cases of the 4-bromoiodobenzene and 1,4-diiodobenzene, and the 4-bromo or 4-iodo substituent was mostly retained after the reaction. The amination reaction of the meta-substituted iodobenzenes also gave the corresponding secondary amines in good yields (entries 11−13).[18] As observed in para-substituted diiodobenzene, selective monoamination took place. On the other hand, the reaction was strongly hampered by ortho-substituents, and ortho-substituted iodobenzenes afforded the desired compounds (entries 14−17) in only modest yields. Steric rather than electronic effects may be the principal factor for these low yields.

Taking advantage of the selective monoamination that occurs when using diiodobenzenes, we then applied this process to successive diamination to construct unsymmetrical N,N′-dialkylated phenylenediamines (Scheme 1). Following

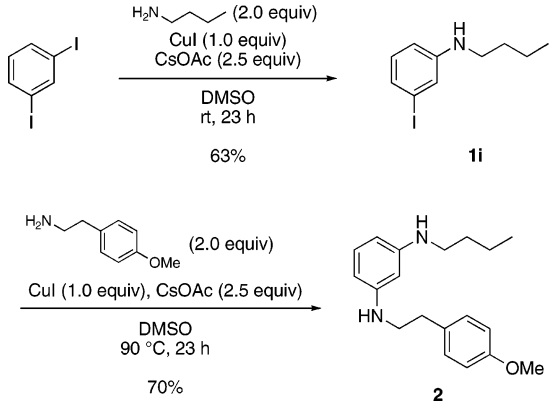
Table 1. Amination of Monosubstituted Aryl Iodides with Butylamine[a]



entry	product		yield (%)	entry	product		yield (%)
1	X = H	(**1a**)	70[b]	11	X = OMe	(**1g**)	80
2			93	12	Me	(**1h**)	77
3			96[c,d]	13	I	(**1i**)	63[b,c]
4			87[c,e]				
5			82[c,f]				
6	OMe	(**1b**)	85				
7	Me	(**1c**)	76	14	X = OMe	(**1j**)	30[h]
8	NO_2	(**1d**)	89	15	Me	(**1k**)	20[c]
9	Br	(**1e**)	77[b,g]	16	NO_2	(**1l**)	8[i]
10	I	(**1f**)	74[b,c]	17	F	(**1m**)	20[c]

[a] Reaction conditions: 0.50 mmol of aryl iodide, 1.0 mmol of butylamine, 0.50 mmol of CuI, 1.25 mmol of CsOAc, degassed DMF (0.50 mL), under Ar. [b] Room temperature. [c] DMSO was used as a solvent. [d] Iodobenzene (18 mmol), CuI (1.0 equiv, 95% purity). [e] Iodobenzene (9.8 mmol), butylamine (1.2 equiv). [f] Iodobenzene (6.9 mmol), CuI (20 mol %), 48 h. [g] Inseparable butyl-(4-iodo-phenyl)amine (4%) was observed by ^{1}H NMR. [h] 2,2′-Dimethoxy-1,1′-biphenyl (26%; homocoupling product) was obtained. [i] 2,2′-Dinitro-1,1′-biphenyl (25%; homocoupling product) was obtained.

Scheme 1. Successive Amination of 1,3-Diiodobenzene



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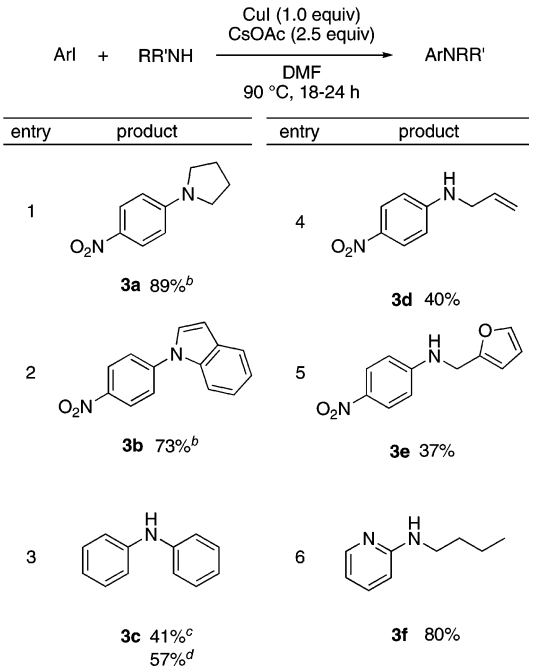
(16) Use of 1 equiv of CuOAc instead of CuI and CsOAc afforded *N*-butylaniline in 70% yield.
(17) For the large-scale procedure, see Supporting Information.

the preparation of *N*-butyl-3-iodoaniline **1** by selective monoamination, the second amination was carried out smoothly to give the phenylenediamine derivative **2** in good yield. This protocol could be quite useful since, to the best of our knowledge, the synthesis of unsymmetrical N,N′-dialkylated phenylenediamines has not been well-established. For example, an approach starting with phenylenediamines would have difficulty in discriminating the two amines, and starting with the corresponding nitroanilines would require a lengthy synthesis involving protection and deprotection of the nitrogens.

The substrates in our amination reaction are not limited to primary alkylamines (Table 2). Cyclic secondary amines,

Table 2. Amination of Functionalized Aryl Halides with Various Amines[a]



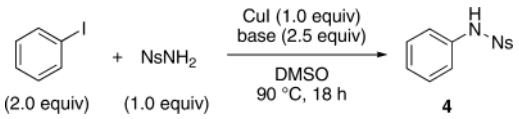
[a] Reaction conditions: 0.50 mmol of aryl iodide, 1.0 mmol of amine, 0.50 mmol of CuI, 1.25 mmol of CsOAc, degassed DMF (0.50 mL), under Ar. [b] Performed with 2.5 mmol of an amine. [c] $T = 120$ °C. [d] $T = 150$ °C.

and even an indole nitrogen, could be introduced to the aromatic ring in good yields (entries 1, 2). However, less reactive amines, e.g., aniline and allylamine, provided the amination product in moderate yields (entries 3, 4). In addition to the iodobenzene derivatives, 2-iodopyridine is amenable to amination, and the 2-amino pyridine derivative was obtained in 80% yield (entry 6).

Although we have established the conditions in which to introduce amines to the aromatic ring, amines, especially functionalized amines, are not always commercially available. The most widely used preparations of amines include the Gabriel method[19] or reduction of alkyl azides,[20] both of which are easily accessible from halides or alcohols. In addition to these conventional methods, we have reported a method for the synthesis of primary[21] and secondary amines[22] using 2-nitrobenzenesulfonamides ($NsNH_2$). We thought that a combination of the amination reported here and Ns chemistry could lead to a general protocol for the synthesis of aromatic amines. Thus, a nitrogen function would be introduced into the aromatic ring by the amination of $NsNH_2$ with aromatic iodides to afford Ns-anilides, to which various residues would be introduced by the Ns protocol to provide a range of functionalized anilines.

First, we examined the intermolecular amination of aryl iodides with $NsNH_2$ using our reaction conditions (Table 3).

Table 3. Selection of Bases on Introduction of an Ns Group[a]



entry	base	yield[b] (%)	recovered $NsNH_2$ (%)
1	CsOAc	30	69
2	K_3PO_4	53	45
3	K_2CO_3	26	72
4	Cs_2CO_3	70	25
5	Cs_2CO_3	91[c]	none

[a] Reaction conditions: 1.0 mmol of iodobenzene, 0.50 mmol of $NsNH_2$, 0.50 mmol of CuI, 1.25 mmol of a base, degassed DMSO (0.50 mL), under Ar. [b] Yields are based on $NsNH_2$. [c] Performed with 1.0 mmol of CuI and 2.5 mmol of Cs_2CO_3.

The conventional conditions using CsOAc provided the desired Ns-anilide (**4**) in only 30% yield with a recovery of 69% of $NsNH_2$ (entry 1). To address this problem, we briefly screened bases and found that Cs_2CO_3 was the best choice (entry 4). Finally, the yield of **4** was improved to 91% by use of 2-fold amounts of CuI and Cs_2CO_3 (entry 5).

Then, an alkyl side chain could be efficiently introduced either by alkylation with alkyl halides or by the Mitsunobu reaction.[23] After amination with Ns-amide, we conducted a one-pot N-alkylation and deprotection. The Ns-anilide **5**, derived from methyl 4-iodobenzoate, was treated with phenylpropyl bromide in the presence of K_2CO_3 and a catalytic amount of Bu_4NI in DMF, followed by addition of PhSH, to furnish methyl 4-(3-phenylpropylamino)benzoate (**6**) in 85% yield over two steps (Scheme 2).

(18) Typical Procedure. An oven-dried Pyrex screw-tube was charged with CsOAc (2.02 g, 10.5 mmol, 2.5 equiv), CuI (801 mg, 4.21 mmol, 1.0 equiv), and ca. 0.3 mL of dried benzene. The tube was evacuated and back-filled with argon. To the mixture was added degassed DMF (4.2 mL), 1,3-diiodobenzene (1.39 g, 4.21 mmol, 1.0 equiv), and *n*-butylamine (0.82 mL, 8.4 mmol, 2.0 equiv). After stirring at room temperature for 23 h, the mixture was partitioned between EtOAc and 5% NaCl in 10% NH_4OH. The aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a crude material. Purification by flash column chromatography on silica gel (20−50% CH_2Cl_2 in hexanes, gradient) gave 3-iodo-*N*-butylaniline (730 mg, 2.65 mmol, 63%).

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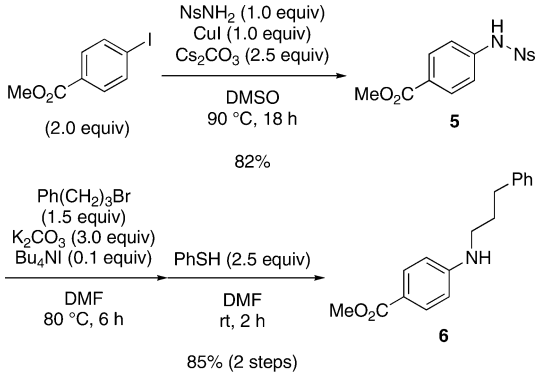
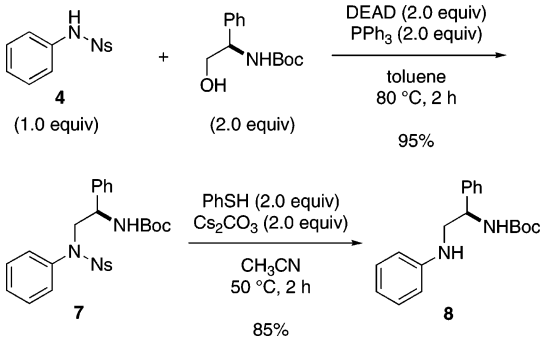
Scheme 2. Synthesis of an *N*-Aryl Secondary Amine



Scheme 3. Synthesis of a Chiral β-Diamine



In another approach utilizing the Ns strategy, N-alkylation by the Mitsunobu reaction was performed (Scheme 3). The Mitsunobu reaction of the relatively less reactive Ns-anilide (**4**) with *N*-Boc-(*R*)-phenylglycinol took place on heating, and the subsequent deprotection of the Ns group gave the chiral β-diamine derivative (**8**) in high yield. This method is applicable to the general synthesis of chiral *N*-aryl-1,2-diamines since various chiral amino alcohols are easily accessible by reduction of α-amino acids.

In summary, we have developed a copper-mediated intermolecular amination. Furthermore, Ns-anilides, which were obtained by amination using Ns-amides, have proven to be particularly useful for the stepwise synthesis of functionalized *N*-aryl secondary amines. Finally, we developed a synthetic protocol for unsymmetrical phenylenediamine derivatives. Because of the mild reaction conditions and the chemoselectivity, we believe that this reaction will be useful for the synthesis of a variety of *N*-arylamines.

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Supporting Information Available: Experimental details, characterization data details, synthetic procedures, and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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