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Synthesis of Primary Aryl Amines Through a Copper-Assisted Aromatic Substitution Reaction with Sodium Azide

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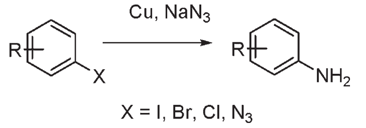
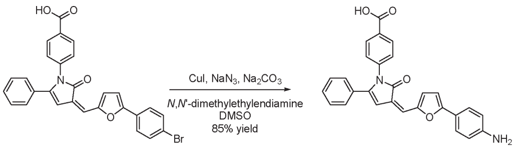


A method is presented by which aryl halides and azides are converted to the corresponding primary aryl amines with copper(I) and sodium azide.

Metal-promoted transformations of aryl halides and pseudohalides to various heteroatomic functional groups is an ever-expanding class of reactions in synthetic chemistry. These reactions provide new routes to many compounds of medicinal and industrial importance. Among these reactions, several methods for the formation of carbon−nitrogen bonds have become especially prominent.[1]

In the course of a medicinal chemistry effort, we had need for such a reaction to convert a complex aromatic bromide to the corresponding azide to serve as an affinity probe. In an attempt to employ previously reported conditions to accomplish this transformation,[2] we unexpectedly obtained an amine instead of the azide as the product in high yield (eq 1).[3]



(1)

We were able to obtain the desired azide via subsequent diazotization reaction of the amine. The formation of the amine as the initial product led us to consider whether this reaction could provide general access to aryl amines as a complement to existing procedures for aromatic amination most commonly with copper or palladium catalysts and either masked nitrogen sources[4] or ammonia directly.[5]

The previous literature on the use of sodium azide in aromatic substitution reactions consists of a confusing variety of results with respect to whether the products are aryl azides or amines. Ma reported the reaction of a variety of electron-rich or electron-poor aryl iodides, aryl bromides, and alkenyl iodides with excess NaN_3 and catalytic quantities of CuI and proline to form the corresponding azides.[2a] Similar results were obtained by Liang using diamine ligands in place of proline[2b] and by Ackermann for the in situ generation of aryl azides as participants in a cascade reaction sequence involving “click” [3+2] cycloadditions.[6] Similarly, Molander and Ham described the use of stoichiometric NaN_3, Cs_2CO_3, catalytic CuBr, and *N*,*N*′-dimethylethylenediamine (DMEDA) in a general procedure for conversion of potassium haloaryltrifluoroborates into the corresponding azidoaryltrifluoroborates, but in a small number of cases, the corresponding amines were instead obtained without a clear pattern of dependence on substituent effects.[7] Fu and Qiao found a pronounced substituent effect when employing excess NaN_3, Cs_2CO_3, or K_2CO_3, and catalytic CuI whereby aryl-halides bearing *o*-carboxyl, -carboxamide, or -aminocarbonyl groups underwent conversion to the corresponding aryl amines, but other substitution patterns led either to an azide or to lack of reactivity of the halide. Of relevance to later discussion (vide infra), nitro substituents survived unchanged under the Fu and Qiao amination conditions without concomitant reduction.[8] Thatcher reported a single isolated example of the conversion of a fairly complex aryl bromide into an aryl amine using excess NaN_3 and stoichiometric NaOH, CuI, and proline.[9] Sajiki recently published a method employing trimethylsilyl azide and CuF_2, which has broad scope for the synthesis of aryl amines without formation of azides.[10] Finally, there have also been reports of reactions of NaN_3 without a catalyst to convert aryl halides into amines[11] and of nitroaromatics into aryl azides.[12] With the backdrop of this bewildering array of reports, we sought

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(1) (a) Kienle, M.; Dubbaka, R. S.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (c) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

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(4) (a) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367. (b) Lee, D.-Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.

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(6) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084.

(7) Cho, Y. A.; Kim, D.-S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, 4330.

(8) Zhao, H.; Fu, H.; Qiao, R. *J. Org. Chem.* **2010**, *75*, 3311.

(9) Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682.

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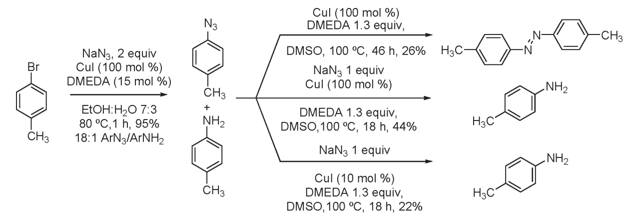
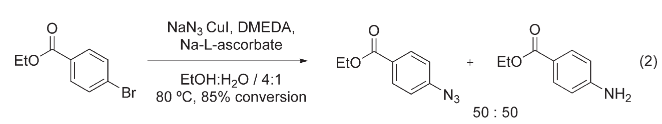
SCHEME 1



to determine whether conditions could be found for generalization of the copper-promoted amination that we had observed (eq 1).[3] In the present paper, we report that this reaction is indeed of wide scope for conversion of aryl halides into amines, and that the same copper-based conditions also effect reduction of aryl azides into the amines.

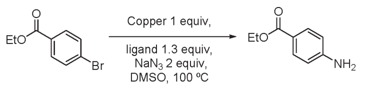
We began this investigation by applying Ma[2a] and Liang's[2b] conditions for the generation of aryl azide **2** from **1**, but we obtained a substantial amount of the corresponding amine **3** (eq 2). The ratio of the amine **3** to azide **2** varied with time and temperature, but the azide **2** was never a predominant product of this reaction.



Because the Ma and Liang conditions had also been used with electron-rich aryl halides, we attempted to reproduce Liang's results in particular using 4-bromotoluene as a substrate.[13] Under microwave conditions as used by Liang, we obtained a mixture of the azide and amine in a 7:1 ratio in 89% yield, whereas Liang reported formation of only the azide. We also performed the reaction with conventional heating to obtain an 18:1 ratio of the azide and amine in 95% overall yield (Scheme 1).

We subsequently attempted to find conditions to transform the azide further into the amine (Scheme 1). The azide was untouched after being heated in DMSO for 72 h, contrary to earlier suggestions that the formation of amines may be due to thermal decomposition of azides.[9,14] When we treated the azide with 100 mol % CuI in the presence of DMEDA, we isolated neither the azide nor the amine but rather the corresponding azo compound. The azide was successfully reduced to the amine when treated with 100 mol % NaN_3 along with either 100 or 10 mol % CuI. There are few previous reports of NaN_3 serving as a reducing agent. An example is the reduction of quinones.[15] Heating the azide in the absence of copper but in the presence of 2 equiv of NaN_3 resulted in no reaction, suggesting the present transformation is catalyzed by copper.

TABLE 1. Effect of Varying Amounts of Reagents



entry	CuI (mol %)	NaN_3 (equiv)	ligand[a]	time (h)	yield (%)[b]
1	0	2		48	7
2	10	2	DMEDA	48	32
3	25	2	DMEDA	8	29
4	50	2	DMEDA	3	56
5	100	2	DMEDA	1	82[c]
6	10	2	proline	75	38
7	25	2	proline	28	66
8	50	2	proline	13	83
9	100	2	proline	13	93[c]
10	100	4	proline	20	87
11	100	1	proline	56	30
12	400	2	proline	35	58

[a] 1.3 equiv of ligand was used for each equiv of CuI. [b] Yields measured by ^1H NMR with mesitylene as an internal standard unless otherwise noted. Complete consuption of the starting material was observed for all reactions. [c] Isolated yield.

We then optimized the reaction conditions (solvent, copper source, ligand, mol % of copper, and mol % NaN_3) for direct conversion of aryl halides to amines using ethyl 4-bromobenzoate as a model compound. Starting with the solvent, we observed complete consumption of the starting material only when polar solvents were used. DMSO or water/DMSO mixtures provide the best solvent medium for this reaction.[16] The effect of varying amounts of CuI and NaN_3 was studied next (Table 1). The reaction works best with 100 mol % of CuI while either a large excess of CuI or a low catalyst loading increases the amount of impurities. We found an excess of NaN_3 to be the most critical factor leading to high yields of the reduced amine products (compare entries 9−11).

We identified two optimal ligands, proline and DMEDA, with complementary profiles in terms of rate and cleanliness of the reaction (Table 1; Table 2, entries 5 and 9). While the copper complex with DMEDA reacts over a shorter time period, the crude products after aqueous workup had small quantities of several impurities (total of ca. 10−15% with 100 mol % CuI). We made similar observations with the analogous diamine ligands in entries 2−5. We also found diamine ligands that lack a hydrogen bond donor are less effective as evident in the drop in activity from DMEDA to *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (Table 2, entries 5 and 6). The heteroaromatic chelating ligands, bipyridine and phenanthroline, were not as effective as the top performing diamine ligands (entries 7 and 8). Although extended reaction times were required with proline, the amounts of impurities in the crude product were diminished (<5% with 100 mol % CuI) leading to a higher yield of the amine. DMEDA led to increased impurities, but its advantages become apparent when performing the reaction at a lower temperature. At 60 °C, the reaction with DMEDA gave a 71% yield of the amine after 32 h while the reaction with proline as a ligand failed to go to completion. The addition of bases such as

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(11) (a) Kitahara, Y.; Tamura, F.; Kubo, A. *Tetrahedron Lett.* **1997**, *38*, 4441. (b) Vicker, N.; Burgess, L.; Chuckowree, I. S.; Dodd, R.; Folkes, A. J.; Hardick, D. J.; Hancox, T. C.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S. P.; Charlton, P. A.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A. J.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 721. (c) Delfourne, E.; Darro, F.; Portefaix, P.; Galaup, C.; Bayssade, S.; Bouteillé, A.; Le Corre, L.; Bastide, J.; Collignon, F.; Lesur, B.; Frydman, A.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 3765. (d) Delfourne, E.; Kiss, R.; Le Corre, L.; Merza, J.; Bastide, J.; Frydman, A.; Darro, F. *Bioorg. Med. Chem.* **2003**, *11*, 4351.

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(13) See Table 3, entry 2, of ref 2b.

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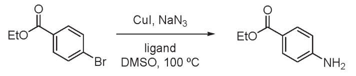
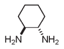
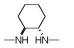
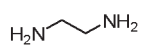
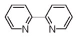
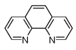
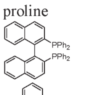
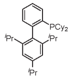
(15) (a) Couladouros, E. A.; Plyta, Z. F.; Haroutounian, S. A.; Papageorgiou, V. P. *J. Org. Chem.* **1997**, *62*, 6. (b) Pokhilo, N. D.; Shuvalova, M. I.; Lebedko, M. V.; Sopelnyak, G. I.; Yakubovskaya, A. Y.; Mischenko, N. P.; Fedoreyev, S. A.; Anufriev, V. P. *J. Nat. Prod.* **2006**, *69*, 1125.

(16) See Table 1 in the Supporting Information1.

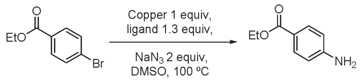
TABLE 2. Effect of the Ligand



entry	ligand	time (h)	yield (%)[a]
1	none	96	22
2		1.5	48
3		1	81
4		1.5	57
5	DMEDA	1	82[b]
6	TMEDA	25	52
7		25	41[b]
8		8	69[b]
9	proline	16	79[b]
10		48	<10
11		48	<10

[a]Yields measured by ^{1}H NMR with mesitylene as an internal standard unless otherwise noted. Complete consuption of the starting material was observed for all reactions. [b]Isolated yield.

TABLE 3. Performance of Different Forms of Cu



entry	Cu source	ligand	time (h)	yield (%)[a]
1	CuI	DMEDA	1	72
2	CuOTf	DMEDA	1	67
3	Cu_2O	DMEDA	1	26
4	CuTc	none	34	24[b]
5	CuTc	DMEDA	1	36
6	CuI	proline	11	88
7	CuBr	proline	11	85
8	Cu_2O	proline	2	91
9	CuOTf	proline	11	83
10	CuCl	proline	13	90
11	Cu powder	proline	13	89

[a]Yields measured by ^{1}H NMR with mesitylene as an internal standard. Complete consuption of the starting material was observed for all reactions unless otherwise noted. [b]87% conversion.

Na_2CO_3 had no effect on the progress of the reaction. (±)-BINAP and X-Phos did not afford products in any appreciable yield (entries 9 and 10).

Next, several different copper sources were investigated (Table 3). With DMEDA as the ligand, disappearance of the starting material ensued at nearly equal rates for all copper sources. However, the amount of impurities was vastly greater for some copper sources (entries 3 and 5), leading to diminished yields. Proline tolerated a wider range of copper sources, giving essentially the same pure product in good yields. As an exception to this ligand reactivity trend, copper(I) oxide mitigated some of the rate problems seen with proline and maintained the same purity profile. Reactions did not go to completion with CuTc (thiophene-2-carboxylate as the only ligand), whereas when DMEDA was added, the reaction did go to completion but gave a poor yield of the amine (entry 4 without ligand and entry 5 with DMEDA).[17] Taken together, these results point to 1 equiv of Cu_2O/proline in DMSO as preferred conditions for generation of aryl amines. Lastly, we explored the scope of the reaction with a variety of aryl halides (Table 4). In general, good yields of amines were obtained in many cases in which either electron-donating or -withdrawing substituents were present. However, electron-withdrawing substituents resulted in increased reaction rates. Steric hindrance adjacent to the aryl halide leads to long reaction times and diminished yields (compare entries 16 and 17). *p*-Bromochlorobenzene reacted with preferential displacement of the bromide to form *p*-chloroaniline (entry 4).

The reaction of methyl 4-chloro-2-nitrobenzoate afforded a mixture with the amino chloride as the major product and small amounts of the corresponding nitroamine and diamine products (entry 10) in contrast with an earlier report in which nitro groups were unaffected.[8] We found the transformation of a nitro group to an amine to be sluggish under these conditions as indicated by entries 11 and 12. The *o*-biphenyl bromide gave the expected amine without any carbazole, which could have been produced if these reactions occurred via a singlet nitrene (entry 17). 2,2′-Dibromo-1,1′-binaphthyl reacted with 2 equiv of Cu_2O to form only trace amounts of the mono- and diamino compounds (not in the table), whereas when treated with large excesses of CuI and NaN_3, a 1:1 mixture of 2,2′-diamino-1,1′-binaphthyl and dibenzocarbazole was isolated in good yield (entry 21).

In conclusion, we have shown that copper-promoted substitution of aromatic halides with NaN_3 is a method of broad generality for the production of aryl amines. We have also demonstrated that aryl azides and nitro groups are transformed into primary aryl amines under these conditions. In agreement with the finding of others, we have found that proline and DMEDA are effective ligands. We have shown the use of DMSO as a solvent and Cu_2O as a copper source greatly improves the efficiency of this transformation compared to previously reported conditions. Although the pathway by which azides are reduced to amines is not clear at this time, we have found that a large excess of azide ion is crucial to obtain amines in high yield.

There is still substantial room for improvement of this method, including reducing the amount of copper to substoichiometric quantities while maintaining high yields, perhaps by identification of other ligands to improve efficiency. Nonetheless, at its present state of development, this method provides a convenient and inexpensive means for the direct conversion of aryl halides into aryl amines. *Due to the ever-present potential for explosions when working with azides, we do not recommend use of this method for large-scale conversions.* Nonetheless, for routine, small-scale research applications, including the use of valuable, highly functionalized substrates, this procedure should find wide utility. Among the principal competitive methods from which to choose are the copper- and palladium-catalyzed aminations employing ammonia,[5] but the latter metal is disadvantaged by economic considerations.

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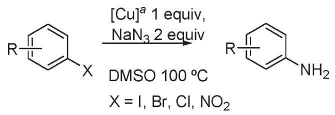
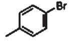
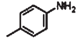
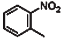
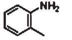
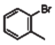
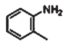
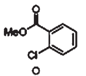
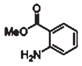
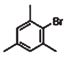
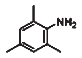
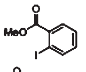
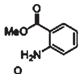
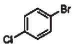
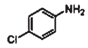
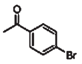
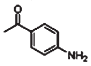
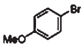
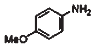
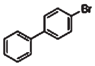
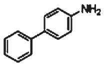
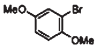
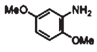
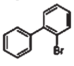
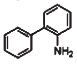
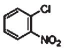
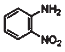
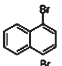
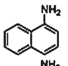
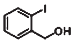
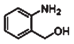
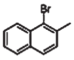
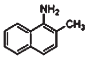
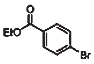
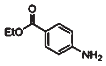
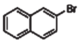
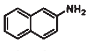
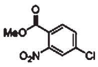
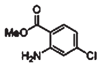
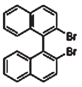
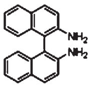
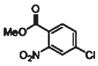
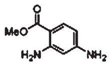
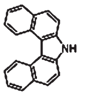
[17] Ligand exchange transpires when DMEDA and CuTc are combined to form a new reactive species (Table 3, entries 4 and 5).

TABLE 4. Scope of the Amination with Various Aryl Halides



entry	starting material	time [h] (method)[a]	product	yield (%)[b]	entry	starting material	time [h] (method)[a]	product	yield (%)[b]
1		16 (C)		84	12		144 (C)[d]		43[d]
2		18 (B)		70	13		12 (C)		40
3		10 (A)		72	14		0.25 (C)		64
4		3 (B)		73	15		7 (C)		87
5		16 (C)		46	16		14 (C)		82
6		6 (C)		71	17		18 (A) 36 (B)		73 40
7		5 (C)		75	18		12 (C)		59
8		3 (C)		87	19		14 (C)		76
9		2 (C)		93	20		12 (C)		83
10		2 (C)		29	21		48 (A)[e]		48
11		48 (C)[c]		20					48

[a] Method A: CuI/DMEDA. Method B: CuI/proline. Method C: Cu$_2$O/proline [b] Isolated yield unless otherwise noted. Complete consuption of the starting material was observed for all reactions. [c] 4 equiv of CuI and 9 equiv of NaN$_3$ were used. [d] Yield measured by ^{1}H NMR with mesitylene as an internal standard. [e] 6 equiv of Cu$_2$O and 12 equiv of NaN$_3$ were used.

Experimental Section

A representative procedure for the amination of an aryl bromide with CuI/proline and NaN$_3$ is presented here. For other examples, see the Supporting Information.

Ethyl 4-Aminobenzoate (3). Proline (150 mg, 1.30 mmol, 1.3 equiv), NaN$_3$ (130 mg, 2.00 mmol, 2 equiv),[18] CuI (190 mg, 1.0 mmol, 1.0 equiv), and ethyl 4-bromobenzoate (228 mg, 1.0 mmol, 1 equiv) were combined in a flask that was then purged with argon. Degassed DMSO (2.0 mL) was added while flushing with argon. The flask was then placed in an oil bath maintained at 100 °C. The solution turned from dark red to dark brown over the course of the reaction. After completion of the reaction as judged by TLC, the dark solution was cooled to 22 °C and quenched by the addition of satd aq NH$_4$Cl (3 mL) and EtOAc (2 mL). This biphasic mixture was stirred at 22 °C for 1 h. The resulting dark green solution was filtered through a pad of Celite, which was subsequently washed with EtOAc and water. The filtrate was extracted with EtOAc and washed with brine. Finally the organic phases were combined, dried with MgSO$_4$, filtered, and concentrated to afford **3** (152 mg, 93%) as a pale yellow solid. The crude product was found to be satisfactorily pure: mp 88.5−89.0 °C (lit.[19] mp 89−90 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 4.08 (br s, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 166.8, 150.9, 131.5, 119.8, 113.7, 60.3, 14.4.

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Supporting Information Available: Results with varying solvents, LCMS identification of impurities, experimental procedures, characterization data for the products, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Sodium azide was weighed by using a plastic spatula.

(19) van de Graaf, B.; Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1981**, *46*, 653.