Copper-Catalyzed Direct Amination of Halo(hetero)arenes with Sodium Azide as the Amino Source

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Abstract: In the synthesis of primary (hetero)aryl amines through copper-catalysis, the ammonia surrogates or aqueous ammonia nucleophilic partners can be replaced by sodium azide. Recent efforts in copper-mediated transformation of (hetero)aryl halides to (hetero)aryl amines using azide anion as the amino source are discussed in these highlights.

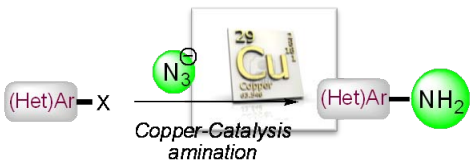
Keywords: Amination, Anilines,·Aminoheterocycles, Sodium azide, Copper.

INTRODUCTION

A wide array of primary anilines are produced by fine–chemical industries, and these molecules containing aryl- and heteroarylamine units are widely used in the synthesis of natural products, pharmaceuticals compounds as well as in material science. Therefore, synthetic methods for the efficient formation of C(sp^2)–NH_2 bond have attracted increasing attention. Over the last decades, transition metal-catalyzed reactions offer a versatile strategy for the C–N bond formation using various nitrogen sources. In this context, several catalytic methods have been used, particulary palladium-catalyzed Buchwald-Hartwig reactions and copper-catalyzed Ullmann-type transformations.

Initial synthesis of primary anilines has been performed through coupling of aryl halides with benzophenone imine, [1] $Li[N(SiMe_3)_2]$ [2,3] or $Zn[N(SiMe_3)_2]$ [3] under palladium-catalysis. Other nitrogen sources have been used as suitably masked forms of ammonia in cross-coupling aminations; they include allylamine, [4] *tert*-butyl carbamate, [5] solid-supported ammonia surrogates, [6] the fluoroalkyl benzophenone imine reagents, [7] *N*-substituted-^{F}Boc carbamate (^{F}Boc: fluorous Boc), [8] amidines [9] and lithium amide [10]. Although these protocols are useful to prepare primary anilines, most of them require an extra step for the cleavage of protecting groups.

An alternative to the use of ammonia surrogates is the palladium-catalyzed amination of aryl halides with ammonia [10,11]. The requirement of high pressure and elevate temperature hampers their wide application. Concurrent with the use of palladium catalysts, attention is currently directed to the utilisation of copper salts, which proved to be an efficient catalyst for the coupling of aryl halides with ammonia, including aqueous ammonia and ammonium chloride [12]. This topic has been the subject of a recent review [13] and will not be covered here. Instead, this highlight will focus on the use of azide [14] anion as a new amino source in the copper-catalyzed direct amination of halo(hetero)arenes (Scheme **1**).



Scheme 1.

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EARLY EVIDENCES OF THE USE OF NaN_3 IN THE DIRECT AMINATION

The pioneering observation of a copper-mediated [15] *in situ* direct formation of anilines from aryl bromides and sodium azide was reported in 2007 by Thatcher and co-workers [16]. The authors described a single isolated example of the transformation of 4'-bromo-4'-desmethoxyarzoxifene **1** into its corresponding aniline **2** using excess NaN_3 (12 equiv) and stoichiometric NaOH, CuI and L-proline (Scheme **2**). The reaction was achieved in DMSO/ethanol at 110 °C, and the amine **2** was formed as a single product, which was attributed to the instability of the aryl azide intermediate at high temperature.

In the course of a medicinal chemistry program, a related observation was reported by Helquist, [17] describing the conversion of a complex aromatic bromide **3** to the corresponding amine **4** by the use of a stoichiometric amount of CuI and *N*,*N*′-dimethylethylenediamine (DMEDA) in place of L-proline (Scheme **3**).

Similarly, during the preparation of potassium azidoaryltrifluoroborates from their corresponding bromoaryltrifluoroborates, under standard azidation conditions, [18] Molander and Ham [19] noted in four cases that only aminotrifluoroborate products were formed in good yields instead of azidoaryltrifluoroborates (Scheme **4**). Although the influence of several parameters (catalyst, ligand, etc.) on the outcome of the reaction was not investigated, this reductive amination seems to be highly dependent on the substitution patterns of the substrate and the reaction time.

DIRECT AMINATION OF (HETERO)ARENES WITH SODIUM AZIDE AS THE AMINO SOURCE

In 2010, five publications describing a systematic investigations of the copper-mediated direct amination of (hetero)aryl halides with azide anion as the amino source were reported.

In the first report, Sajiki and co-workers [20] detailed for the direct amination of aryl bromides the use of trimethylsilyl azide ($TMSN_3$) in the presence of CuF_2 (2 equiv) and Et_3N or 2-aminoethanol (2.5 equiv). The scope and limitations of this reductive amination, in DMA at 95 °C, were demonstrated by the amination of various aryl bromides. Bromoarenes containing an electron-withdrawing group effectively reacted with $TMSN_3$, regardless of the position of the substituent on the aromatic ring to give the corresponding anilines in good to excellent yields (Scheme **5**). In the cases of electron-rich bromoarenes, the protocol was also effective when Cu^0 was used in place of CuF_2, NaN_3 was employed in place of $TMSN_3$, and the reaction was carried out at 120 °C. Noteworthy, the amination of iodoarenes and activated chloroarenes worked as

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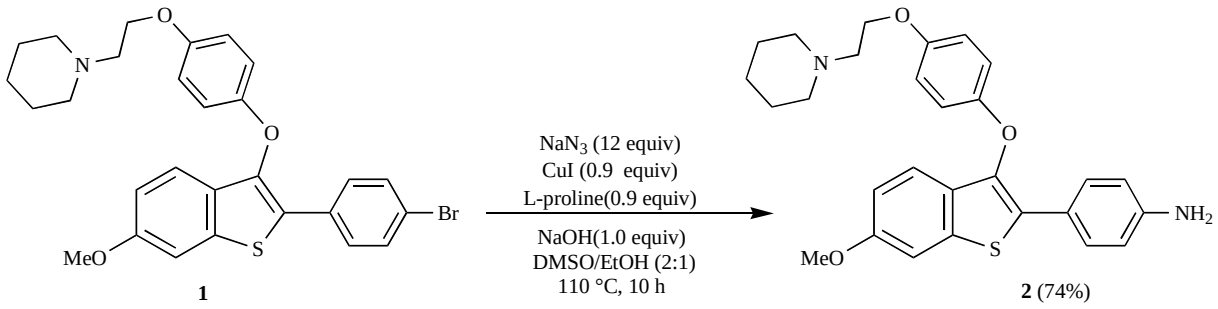
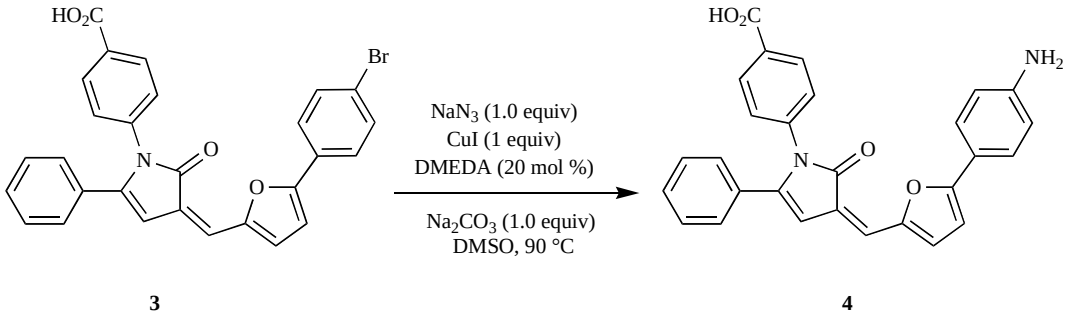
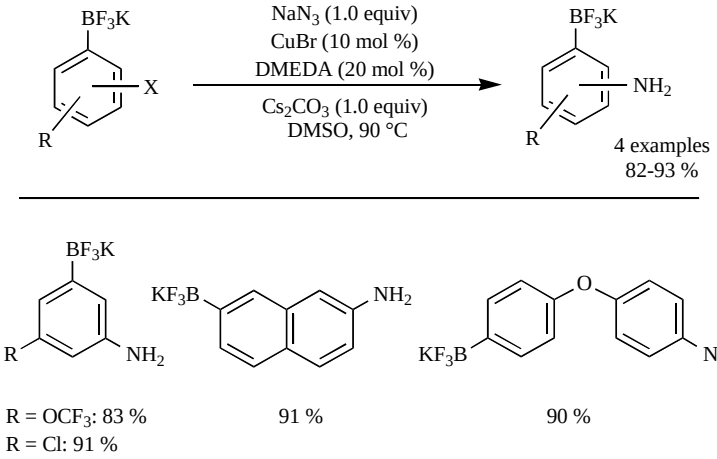


Scheme 2. Synthesis of the amine **2** according to Thatcher *et al.* [16].



Scheme 3. Synthesis of **4** according to Helquist *et al.* [17].



Scheme 4. Copper-catalyzed synthesis of potassium aminotrifluoroborates according to Molander *et al.* [19].

well, although the yields were slightly lower compared to bromoarenes.

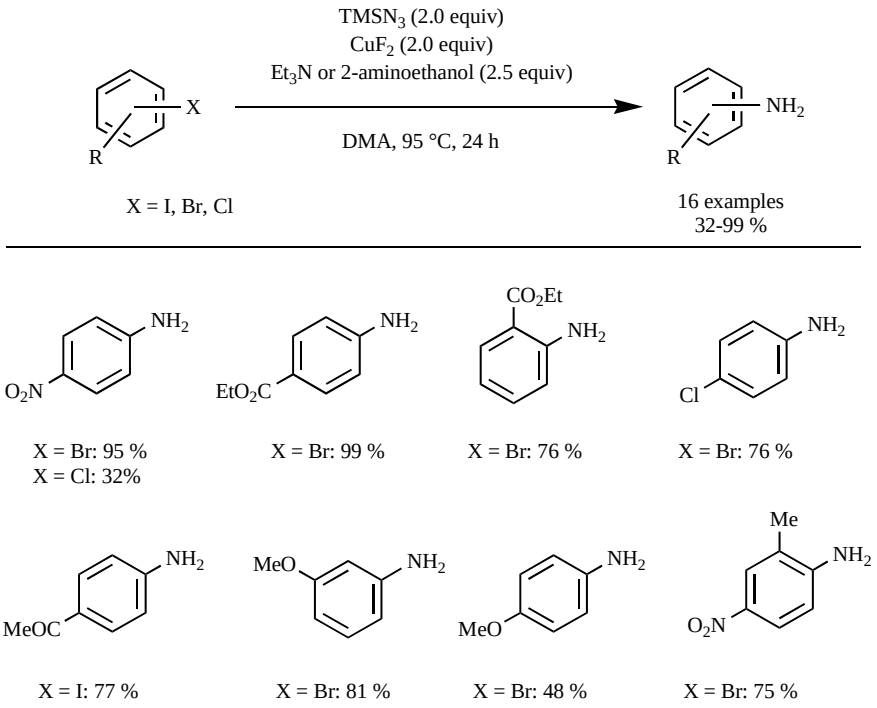
The authors suggested that the reductive amination of haloarenes does not chiefly proceed through an aryl azide intermediate, since exposure of ethyl 4-azidobenzoate to the optimal amination conditions scarcely promoted the reduction of the azide functionality, and the corresponding aniline derivative was only obtained in 5% yield (Scheme **6**).

Qiao and co-workers [21] developed closely related reaction conditions for the direct amination of *ortho*-functionalized haloarenes employing NaN_3 as the amino source in ethanol (Scheme **7**). All haloarenes studied contain an *ortho*-functionalized group (*e.g.;* -COOH, -$CONH_2$, -NHCOR) that have been shown to be critical for the outcome of the reaction. In the case of 2-bromobenzoic and 2-bromobenzamide derivatives, the optimized conditions required the use of CuI (10 mol%) as the catalyst and Cs_2CO_3 (2 equiv) as the base. For 2-chlorobenzoic acid and 2-chlorobenzamides derivatives, an additional ligand, 20 mol% of DMEDA was required to promote their reactivity because of lower activity of the C–Cl bond (Scheme **7**).

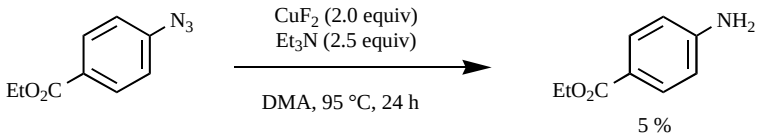
In the case of 2-halobenzoic acid derivatives, the authors proposed an *ortho*-coordination of the carboxyl group with CuI to give the intermediate **I**. Intramolecular oxidative addition deliver metallacycle **II** which, upon exchange of X^- with N_3^- gives **III**. Reductive elimination leads to the azide intermediate **IV**, which evolve after a coordination/oxidation-reduction sequence to aniline **2** (Scheme **8**).

In continuation of his study, Helquist [22] investigated in detail the influence of several parameters (catalyst, ligand, etc.) of its earlier protocol [17]. The best results, with yields up to 93%, were obtained when applying Cu_2O or CuI as the copper source, L-proline or DMEDA as ligand, in DMSO at 100 °C (Scheme **9**).

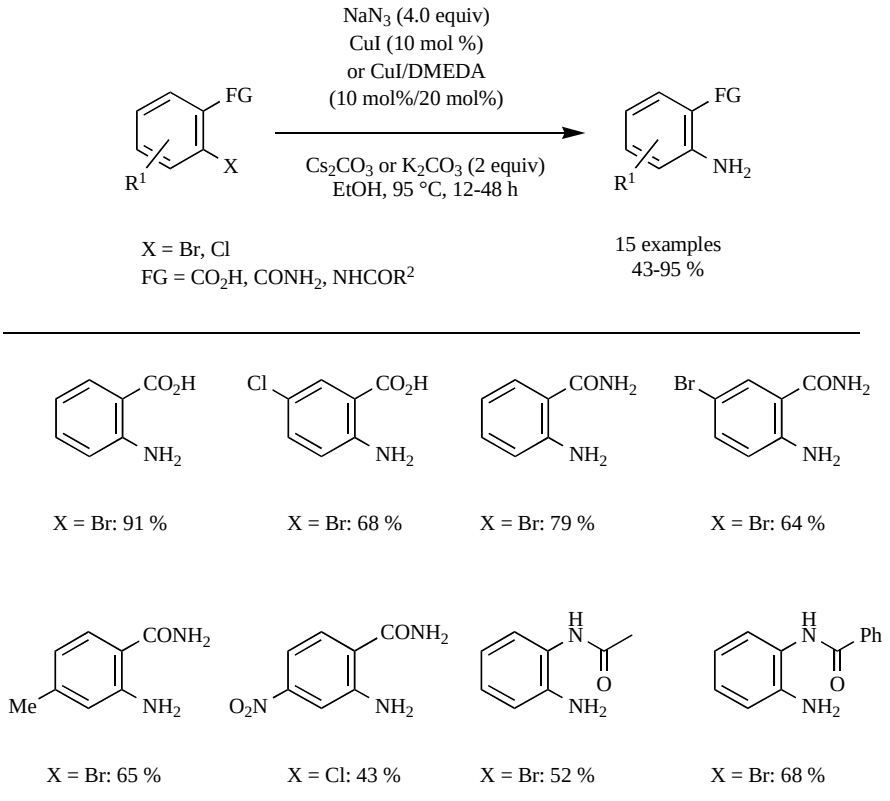
The scope of the reaction with a variety of aryl halides was explored with 1 equiv of Cu_2O and L-proline in DMSO as preferred conditions (Scheme **9**). In general, good yields of anilines were obtained with haloarenes in which either electron-donating or -



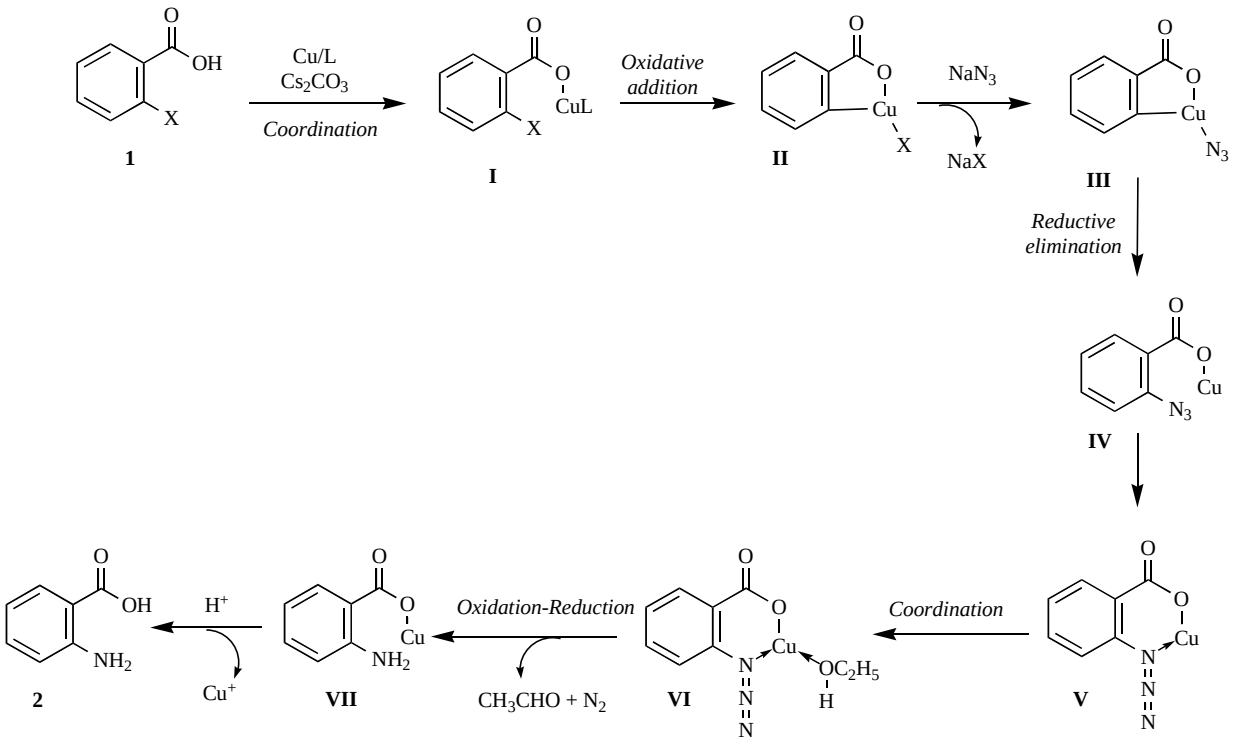
Scheme 5. Copper-mediated reductive amination of aryl halides according to Sajiki *et al*. [20].



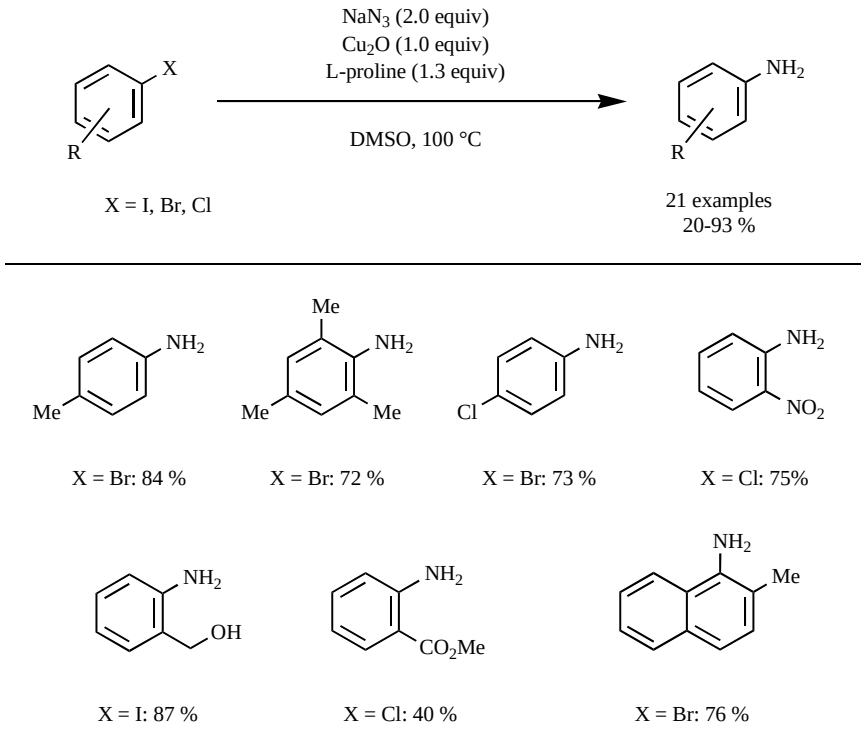
Scheme 6. Exposure of ethyl 4-azidobenzoate to the amination conditions according to Sajiki *et al.* [20].



Scheme 7. Copper-catalyzed direct amination of *ortho*-functionalized haloarenes according to Qiao *et al.* [21].



Scheme 8. Proposed mechanism for the copper-catalyzed direct amination of *ortho*-functionalized haloarenes with sodium azide [21].

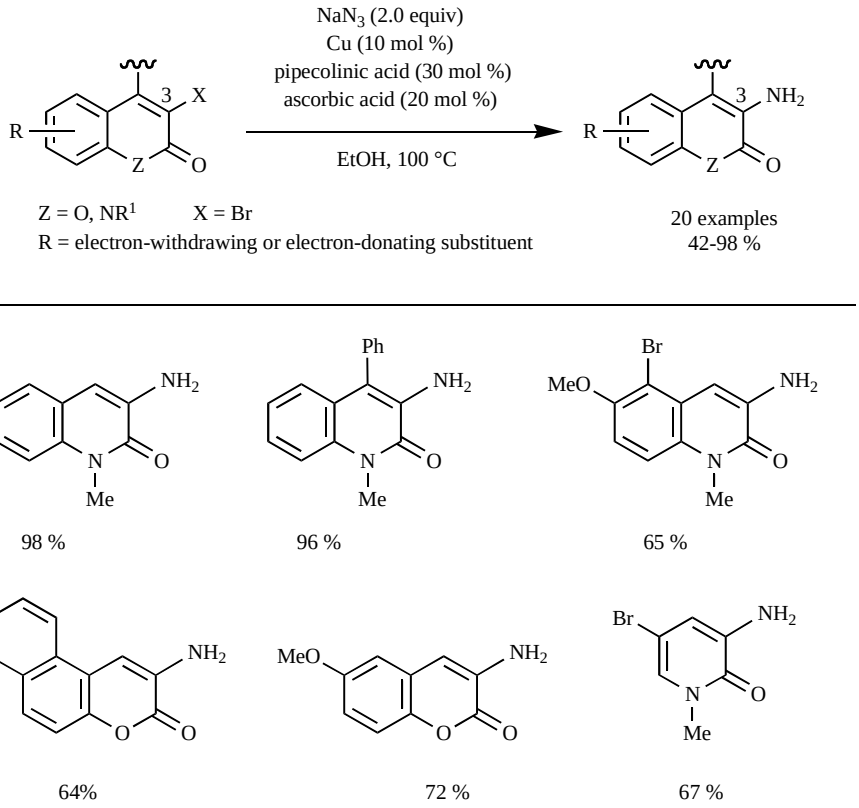


Scheme 9. Copper-mediated reductive amination of aryl halides according to Helquist *et al.* [22].

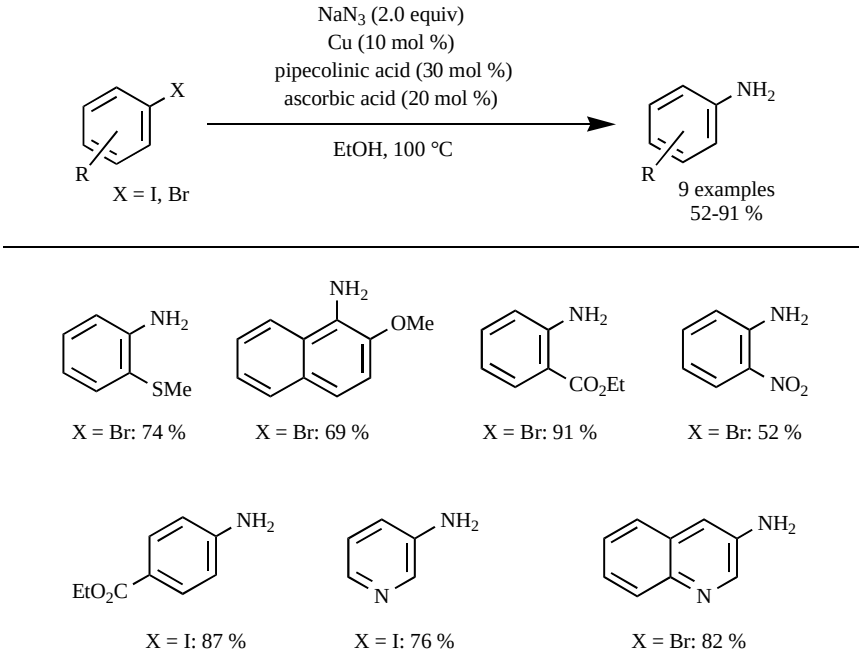
withdrawing substituents were present. Electron-withdrawing substituents resulted in increased reaction rates; whereas, steric hindrance adjacent to the aryl halide leads to longer reaction times and diminished yields.

In a study on this subject, our research group [23] reported the first examples of a copper-catalyzed direct amination of heterocycles (Scheme **10**). Thus, in the presence of Cu^0 powder/pipecolinic acid as the catalytic system, NaN_3 as the amino source and environmentally benign EtOH as the solvent, 3-bromoquinolones, 3-bromopyrolidinones and 3-bromocoumarins were efficiently and regioselectively aminated at the C-3 position in good to excellent yields. Representative examples are illustrated in Scheme **10**.

The generality and efficiency of this protocol was also demonstrated in the case of functionalized (hetero)aryl halides, including



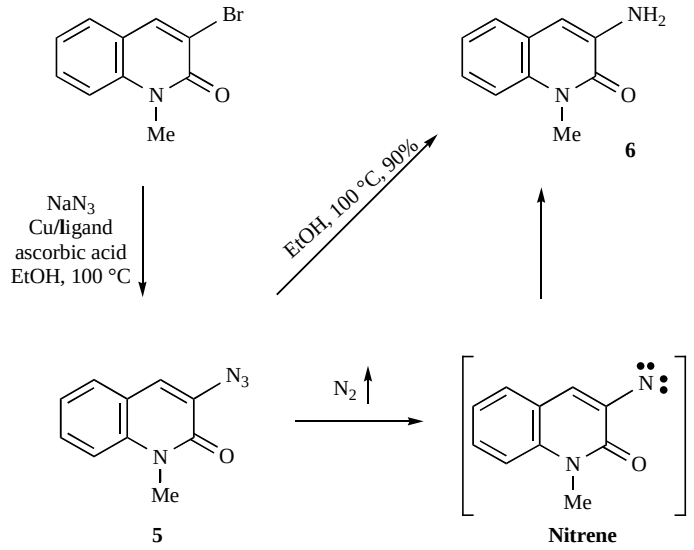
Scheme 10. Copper-catalyzed direct amination of heterocyclic halides according to Alami *et al.* [23].



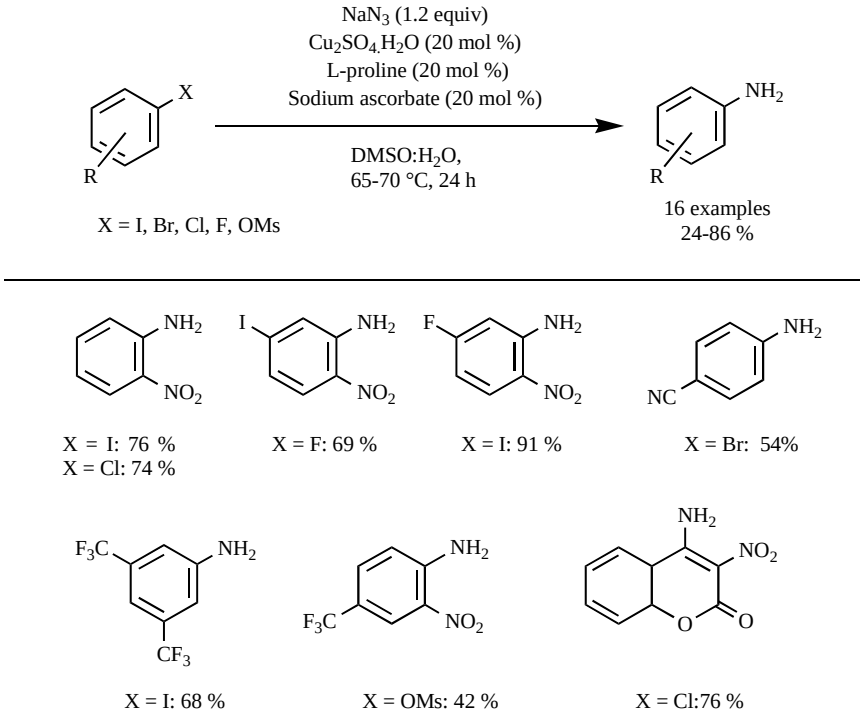
Scheme 11. Copper-catalyzed direct amination of (hetero)aryl halides according to Alami *et al.* [23].

sterically hindered substrates, and those containing base-sensitive functional groups, to provide efficiently the corresponding primary (hetero)aryl amines (Scheme **11**).

Although there is no clear experimental evidence, we suppose that 3-azidoquinolone **5** is formed which evolve into aminoquinolone **6** through a thermally-generated nitrene intermediate. Further experiments concerning the reaction mechanism demonstrated that upon heating **5** in a sealed Schlenk tube in EtOH (oil bath at 100 °C), **6** was formed in 90% yield, suggesting that reactants (Cu^0, ascorbic acid, pipecolinic acid) have no effect on the outcome of the reduction step of azide **5** to amine **6** (Scheme **12**). Attempted *in situ* trapping of the intermediate **5** by an alkyne to obtain the corresponding triazole failed, indicating that the transformation of **5** into **6** is faster than the Huisgen cycloaddition.



Scheme 12. Proposed mechanism according to Alami *et al.* [23].



Scheme 13. Copper-catalyzed direct amination of aryl halides according to Ramana *et al.* [24].

Finally, Ramana and co-workers [24] studied the Cu-catalyzed amination of deactivated aryl halides with sodium azide. The authors reported that the reaction conditions [$CuSO_4.5H_2O$ (20 mol%), L-proline (20 mol%), sodium ascorbate (15 mol%), Na_2CO_3 in DMSO/H_2O at 65-70 °C] are affective only with electron-deficient aryl halides containing-NO_2, CN or CF_3 groups (Scheme **13**). Noteworthy, the reactions are facile when the electron-withdrawing groups are placed either *ortho*- or *para*- to the leaving halo group, whereas with electron-rich haloarenes, only starting material was recovered unchanged or resulted in azides or sometimes dehalogenation of the haloarene. On the basis of these results, the authors suggested that this transformation proceeds through a S_NAr-azidation-reduction process. Control experiments revealed that the presence of sodium ascorbate is essential for the azide reduction, and that the rate of the reaction is enhanced by the presence of the copper salt and L-proline.

In summary, we have highlighted Ullmann-type coupling procedures for the preparation of anilines and aminoheterocycles using (hetero)aryl halides as the coupling partners, and azide anion as the amino source. We believe that this methodology complements the existing procedures, and should find broad applications in synthetic organic chemistry, as well as combinatorial and pharmaceutical sciences. Although the pathway by which azides are reduced to amines is not clear at this time, a closer examination of the reaction mechanism would lead to a deeper understanding of the reaction. Finally, a lowering of the reaction temperature and finding a way to decrease the catalyst loadings will be worthwhile.

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