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Synthesis of Hindered Anilines: Three-Component Coupling of Arylboronic Acids, *tert*-Butyl Nitrite, and Alkyl Bromides

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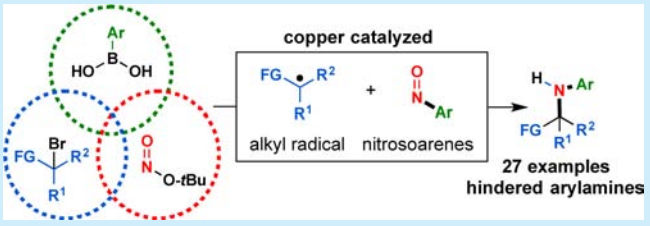
Supporting Information

ABSTRACT: The synthesis of sterically hindered amines has been a significant challenge in organic chemistry. Herein, we report a modular, three-component coupling that constructs two carbon−nitrogen bonds including a sterically hindered C_{sp}^3−N bond using commercially available materials. This process uses an earth-abundant copper catalyst and mild reaction conditions, allowing access to a variety of complex aromatic amines.



Following several decades of study, the development of metal-catalyzed C−N bond formation has had a profound impact on organic synthesis.[1] Often, the synthetic utility of these methods can be attributed to their chemical robustness, generality, and availability of the starting materials. Additional features such as mildness, scalability, and use of earth-abundant metals also play an important role in their widespread use. Notable examples include palladium-catalyzed Buchwald−Hartwig[2] and copper-catalyzed Ullman-type[3] coupling reactions between aryl halides and nitrogen nucleophiles, which have modernized the synthesis of C_{sp}^2−N-containing molecules. Within this context, a number of modern methods for the synthesis of hindered anilines have been reported. Several groups have independently reported coupling reactions involving highly reactive organometallic intermediates, and more recently Lalic disclosed a milder copper-catalyzed addition of arylboronic acids to *O*-benzoylhydroxylamines.[4] Furthermore, Buchwald and co-workers have developed several elegant approaches for the arylation of hindered primary and secondary amines using a newly developed ligand scaffold for palladium (Figure 1a).[5] In contrast, metal-catalyzed methods for the formation of C_{sp}^3−N bonds is a less developed field and remains a worthwhile objective.[6]

The use of alkyl halides as a coupling partner has unique potential in this context, exemplified by the classic substitution reaction (S_N2) between a nitrogen nucleophile and an alkyl halide.[7] Despite their widespread use, N-alkylation reactions have inherent limitations such as overalkylation and poor yields with less reactive alkyl halides (e.g., secondary and tertiary halides).[8] Recently, alkyl halides that are not suitable substrates for classic S_N2 reactions due to steric hindrance have emerged as useful coupling partners for C−N bond formation. For example, the collaborative approach by Peters, Fu, and co-workers employed a photoinduced, copper-catalyzed coupling between alkyl halides and amine nucleophiles (Figure 1b).[9] The amine-coupling partners have thus far been restricted to carbazoles, indoles, and amides.

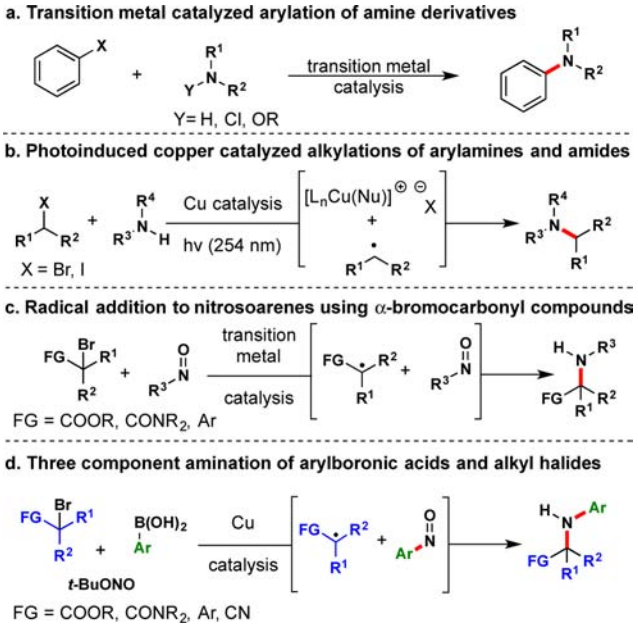


Figure 1. Copper-catalyzed C−N bond formation with alkyl halides.

We[10] and others[11] reported an alternative strategy for C−N bond formation by merging radical reactions with nitroso chemistry (Figure 1c). This process, which has largely been limited to the field of polymer chemistry,[12] utilizes two electrophiles, an alkyl halide and a nitroso compound, and involves the addition of a carbon-centered radical to the nitrosoarene. In principle, this approach should have broad opportunities for synthesizing C_{sp}^3−N bonds by leveraging the use of readily available alkyl halides and employing a range of nitroso compounds. In practice, however, progress has been

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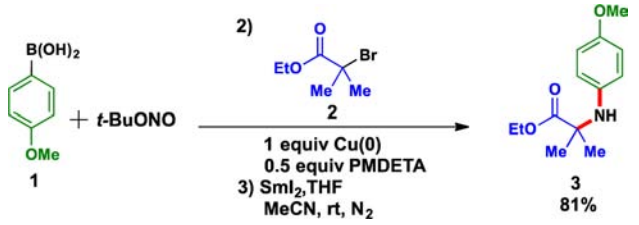
largely restricted to commercially available nitrosobenzene and 2-methyl-2-nitrosopropane,[11] with the exception of the use of *N*-arylhydroxylamines under oxidizing conditions.[10] However, *N*-arylhydroxylamines must be prepared prior to use because they are not commercially available and are often unstable when stored for extended periods of time.[13] Herein, we report that this Cu-mediated radical-based strategy has broader generality and describe the first approach to use a three-component coupling reaction with arylboronic acids, *tert*-butyl nitrite, and various alkyl halides for the synthesis of hindered aniline derivatives (Figure 1d). This modular process occurs under mild reaction conditions, constructs two C−N bonds, uses commercially available starting materials, is compatible with α-bromocarbonyls, α-bromonitriles, and benzyl bromides, and employs earth-abundant copper salts.

Initially, conditions independently developed by the groups of Wu and Yan for the metal-free *ipso*-nitration of arylboronic acids with *tert*-butyl nitrite were evaluated.[14] Specifically, we sought to identify conditions to form exclusively the nitrosoarene intermediate and prevent the competitive over-oxidation to the nitroarene. Running the reaction under inert conditions and reducing the equivalents of *tert*-butyl nitrite (1.5 equiv proved optimal) afforded the 4-methoxyphenylnitrosobenzene in >95% yield. Next, a one-pot, three-component coupling using 4-methoxyphenylboronic acid (0.6 equiv), *tert*-butyl nitrite (0.9 equiv), and ethyl α-bromoisobutyrate (1.0 equiv) was attempted using standard stoichiometric Cu(0) ATRP conditions.[15] Unfortunately, after 24 h only a trace amount of the desired product was produced along with a substantial amount of the nitroarene. Although simultaneous mixing of all reagents was problematic, the undesired formation of the nitroarene could be avoided by sequential reaction of reagents (Scheme 1). Upon consumption of arylboronic acid

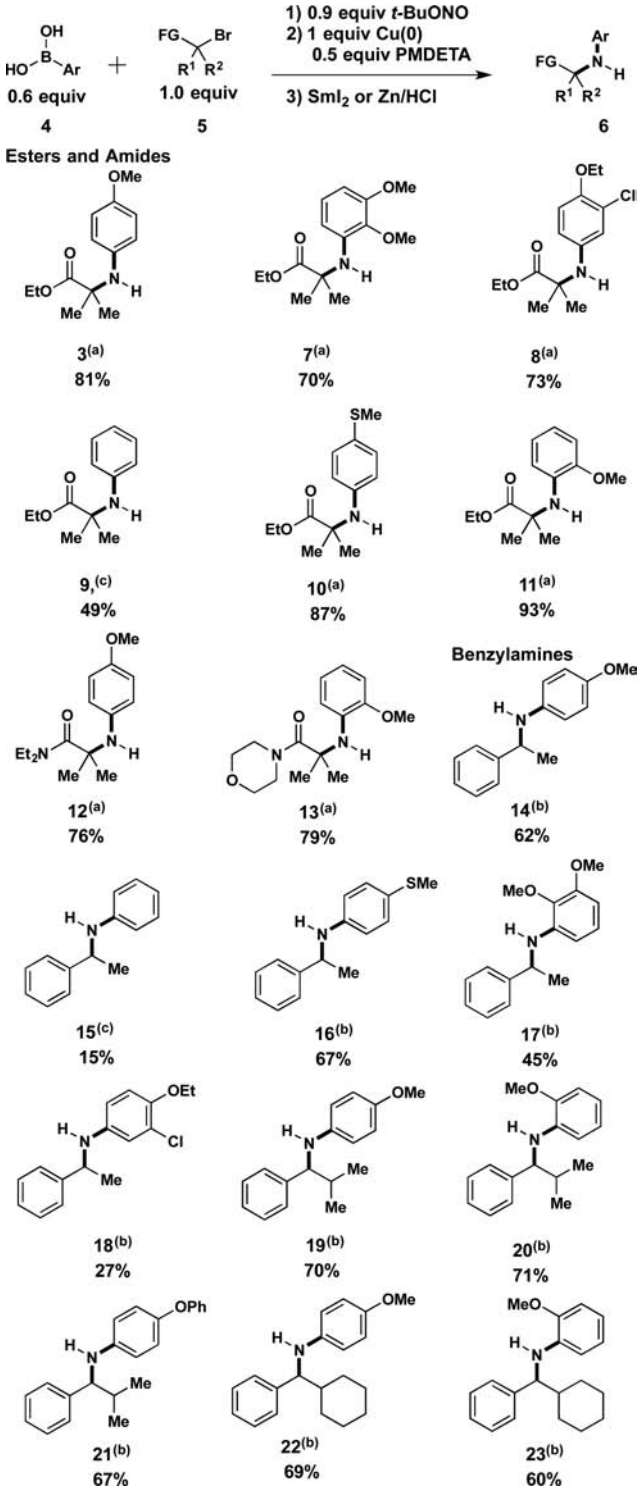
Scheme 1. One-Pot Synthesis of α-Amino Ester



(**1**), ethyl α-bromoisobutyrate, Cu(0), and PMDETA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) were added and allowed to react to completion. Using this protocol and subsequent treatment of the crude reaction mixture with a solution of freshly prepared SmI_2, furnished the α-amino ester (**3**) in 81% yield.

With optimized conditions in hand, we sought to develop the substrate scope. Electron-rich arylboronic acids were well tolerated with both α-bromo esters and amides. For example, those bearing O-alkyl substituents at the 2, 3, and/or 4 positions generated products in high yield (Scheme 2). 4-Ethoxy-3-chlorophenylboronic acid reacted to give **8**, allowing incorporation of a synthetic handle for further manipulation. Aromatic thioethers were also amenable to this process as seen by **10**. Electron-neutral arylboronic acids can be used (**9**); however, excess arylboronic acid is required because oxidation of the nitrosoarene intermediate to the corresponding nitroarene could not be avoided using optimized, one-pot reaction

Scheme 2. Scope of the α-Bromocarbonyls and Benzyl Bromides with Arylboronic Acids



[a]N−O bond cleavage with SmI_2/THF 23 °C. [b]N−O bond cleavage with Zn/HCl in THF at 60 °C. See the Supporting Information for details. [c]3 equiv of phenylboronic acid and 4.5 equiv of *t*-BuONO used. PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine.

conditions. Overoxidation to the corresponding nitroarene is also observed with electron-deficient arylboronic acids.

Utilizing the same conditions, benzyl bromides also underwent the desired three-component, Cu-mediated coupling

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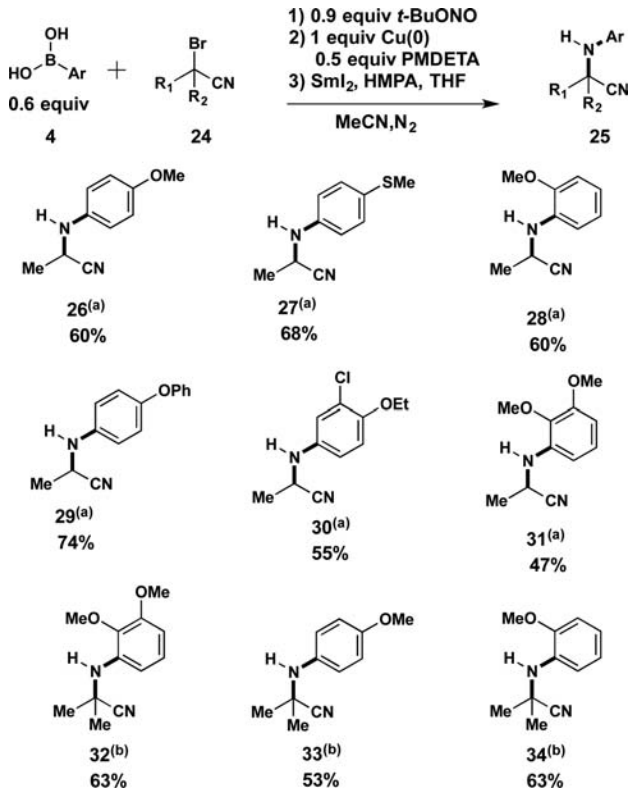
reaction (Scheme 2, **14**–**23**). However, in contrast to the carbonyl derivatives, cleavage of the N–O-alkylated adduct that resulted from the radical-coupling reaction was unsuccessful with SmI_2. As such, to gain access to the desired benzylamine products, reducing Zn/HCl conditions were used to cleave the N–O bond. A range of electron-rich arylboronic acids proved to be suitable coupling partners with the benzyl bromide substrates. In addition, sterically hindered benzyl bromide electrophiles that are typically poor substrates for substitution reactions,[16] including those bearing a α-branched isopropyl (**19**–**21**) and cyclohexyl (**22** and **23**) groups, showed excellent reactivity under the optimized conditions. Because this reaction presumably proceeds via radical intermediates, overalkylation products are never observed.

To further display the versatility of this method, it was applied to the synthesis of α-aminonitriles (Scheme 3),[17]

Scheme 3. Scope of α-Bromonitriles with Electron-Rich Arylboronic Acids

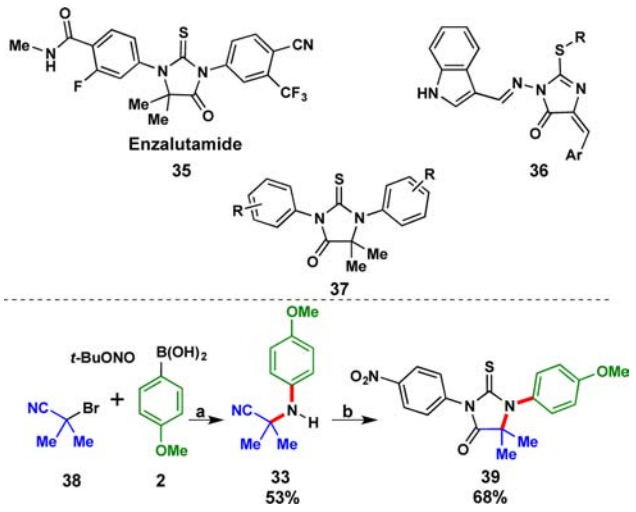


[a]N–O bond cleavage at 23 °C. [b]N–O bond cleavage at 40 °C. See the Supporting Information for details. PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine.

valuable precursors to a wide variety of pharmacologically relevant molecules.[18] Both α-bromopropionitrile and α-bromoisobutyronitrile reacted with 4-methoxyphenylboronic acid and *tert*-butyl nitrite under the optimized reaction conditions to give the N–O alkylated adducts in 75% and 95% yield, respectively. Like the benzylamine N–O alkylated adducts, cleavage of the N–O bond for the nitrile derivatives proved challenging using SmI_2. However, the addition of HMPA, known to increase the reactivity of SmI_2,[19] enabled the cleavage and afforded the desired product in good yield. The amination of secondary (**26**–**31**) and tertiary (**32**–**34**) α-bromonitriles was compatible with electron-rich arylboronic acids substituted in the *ortho, meta, or para* position to generate a range of α-aminonitriles (Scheme 3).

As proof of concept, this copper-mediated, three-component strategy was used to perform the convergent and facile synthesis of the 2-thiohydantoin scaffold (Scheme 4 top),

Scheme 4. Application for the Synthesis of a 2-Thiohydantoin Derivative



[a]Conditions: (a) 0.9 equiv of *t*-BuONO, 0.6 equiv of 4-methoxyphenylboronic acid, 1.0 equiv of Cu(0), 0.5 equiv of PMDETA, MeCN, rt, then SmI_2/HMPA, 60 °C; (b) 2.0 equiv of 4-nitrophenylisothiocyanate, DMF, rt, then 2 N HCl, MeOH, 80 °C.

which has attracted widespread synthetic interest due in part to the chemotherapeutic activity of enzalutamide **35**[20] and antimicrobial activity of **36**.[21] In addition, **37** has been developed as a possible treatment for diabetes.[22] As depicted in Scheme 4, 2-thiohydantoin **39** can be prepared in two steps from commercially available materials. First, by using copper-mediated coupling of 4-methoxyphenylboronic acid (**2**), α-bromoisobutyronitrile (**38**), and *tert*-butyl nitrite, followed by reduction of N–O adduct, α-aminonitrile **33** was produced in 53% yield. Treatment of this product with 4-nitrophenyl isothiocyanate followed by HCl afforded 2-phenylthiohydantoin **39** in 68% yield.

In conclusion, we have developed a general method for the synthesis of hindered secondary anilines through a three-component coupling of electron-rich arylboronic acids with *tert*-butyl nitrite and a variety of alkyl halides. The modularity of the process is illustrated through the synthesis of a variety of α-amino carbonyls, benzylamines, and α-amino nitriles. This method utilizes commercially available starting materials, occurs under mild reaction conditions, and forms two C–N bonds in a single protocol. Finally, the application of this method was demonstrated by convergent synthesis of a biologically active 2-thiohydantoin derivative.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02523.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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