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Synthesis of Di(hetero)arylamines from Nitrosoarenes and Boronic Acids: A General, Mild, and Transition-Metal-Free Coupling

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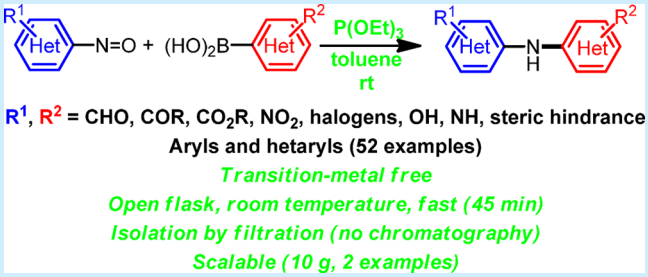
Supporting Information

ABSTRACT: The synthesis of di(hetero)arylamines by a transition-metal-free cross-coupling between nitrosoarenes and boronic acids is reported. The procedure is experimentally simple, fast, mild, and scalable and has a wide functional group tolerance, including carbonyls, nitro, halogens, free OH and NH groups. It also permits the synthesis of sterically hindered compounds.

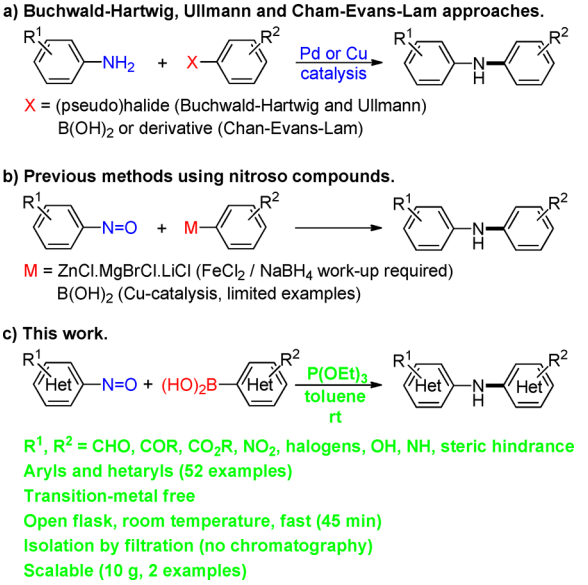


Due to the ubiquity of nitrogen-containing compounds in functional materials, natural products, and active pharmaceutical ingredients, the search for alternative methods for the easy construction of carbon−nitrogen bonds is an active area of research. Methods that require the use of transition metals are usually characterized by a reduced sustainability. On the other hand, transition-metal-free processes spare the need to remove undesired metal contamination, which is important in many applications, such as in the pharmaceutical industry.[1]

Di(hetero)arylamines are highly important chemicals, frequently found among drugs, agrochemicals, dyes, radical-trapping antioxidants, electroluminescent materials, and ligands for transition-metal catalysis.[2] On the one hand, the synthesis of di(hetero)arylamines under simple, mild, and eco-friendly conditions remains highly desirable, and on the other, extending the scope of the synthetically valuable reactions of user-friendly boronic acids under transition-metal-free conditions is a matter of current interest with wide utility from a green perspective. In this paper, we report the coupling of nitrosoarenes with arylboronic acids under neutral and transition-metal-free conditions as a general method for the synthesis of di(hetero)arylamines. The procedure is experimentally simple, fast, mild, scalable, and has a wide functional group tolerance, including aldehydes, ketones, esters, nitro, and halogens, which are often incompatible with other previous methods for di(hetero)arylamine synthesis. It also permits the presence of unprotected NH and OH groups, as well as the assembly of sterically hindered diarylamines, which are usually challenging issues.

The most popular current syntheses of diarylamines are based on transition-metal-catalyzed couplings of anilines with aryl halides under Cu-catalysis[3,4] (Ullmann−Goldberg reaction) or Pd-catalysis[5] (Buchwald−Hartwig reaction), and with boronic acids under Cu-catalysis[3] (Cham−Evans−Lam reaction).[6,7] See Scheme 1. Although these cross-coupling reactions exhibit wide substrate scope, they require the use of expensive and toxic metallic catalysts, the presence of ligands, and extensive individual optimization of reaction conditions. In addition, these methods are usually inadequate to prepare sterically hindered diarylamines[8] and can be rather limited by the synthetic availability of the starting anilines.[9]

Scheme 1. Different Approaches to Di(hetero)aryl Amines



Other typical approaches make use of electrophilic nitrogen reagents and their reaction with carbon nucleophiles.[10] In this regard, nitroso aromatic compounds stand out as attractive starting materials, as they can be easily obtained by a wide range

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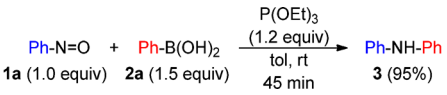
of complementary procedures,[11] such as nitrosation of aromatics, oxidation of anilines or hydroxylamines, reduction of nitrobenzenes, or nitrosation of (het)aryltrifluoroborates.[12] In addition, the functionalization of the aryl moiety of nitrosobenzenes is also feasible.[13] In particular, the nucleophilic addition of main-group organometallics to nitroso compounds has been used for the synthesis of diarylamines,[14] however, this method has a somewhat limited functional group scope due to the high reactivity of the carbon−metal bond. This is especially important when dealing with OH or NH groups, which must be protected. In addition, the transformation of the primary addition products (Ar_2N-OM) into the final diarylamines requires further elaboration (reduction of the N−O bond).

In contrast to main-group organometallics, boronic acids are quite bench-stable reagents that can be used without the need for protection from humidity, and are compatible with functional groups, such as OH or NH.[15] In connection with the synthesis of diarylamines using boronic acid derivatives under transition-metal-catalysis, apart from the aforementioned Chan−Evans−Lam coupling,[6] boronic acids have also been made to react with *N*-chloro-*N*-arylacetamides,[16] with aryl azides,[17] and with a narrow set of nitrosobenzenes.[18] On the other hand, when it comes to transition metal-free procedures,[19] to the best of our knowledge, the synthesis of diarylamines using boronic acid derivatives has been elusive.

We started our research by considering the possibility of activating nitroso compounds toward cross-coupling with phenylboronic acid derivatives using a trivalent phosphorus species.[20] After some experimentation,[21] we found that diphenylamine (**3**) could be synthesized by the reaction of nitrosobenzene (**1a**) with phenylboronic acid (**2a**) in the presence of inexpensive $P(OEt)_3$ (eq 1). The best yield in **3** (95%) was obtained in toluene solution at rt, after 45 min. The reaction did not require anhydrous solvent or inert atmosphere, and the isolation of the product was accomplished by filtration over a pad of silica-gel, without the need for chromatography.[21]



(1)

Under optimum reaction conditions for the synthesis of **3**, we looked into the scope of this metal-free cross-coupling reaction with regard to the arylboronic acid component **2**, using nitrosobenzene (**1a**) as reagent (Figure 1).

We observed that the reaction was general, either with electron-donor or electron-acceptor substituents on the benzene ring of the arylboronic acids **2** (Figure 1). With regard to steric hindrance in the presence of *o*-substituents, we observed that a single *o*-MeO substituent was tolerated, although the yield was slightly lower in comparison to *p*-substitution (**4**−**6**). However, double *o*-substitution by MeO (**7**) was not permitted.[22] On the other hand, double *o*-substitution by Me (**8**) was possible. Ph was also allowed at the *o*-position (**9**). The reaction was compatible with functional groups typically reactive against organolithiums or Grignard reagents, such as ketone, ester or aldehyde, even at the *o*-position (**10**−**13**), as well as the NO_2 group (**14**). With regard to halogenated compounds, F, Cl, Br and I were accepted (**15**−**21**). This is an important issue, particularly because Br and I were attached to the C(sp^2) present in the orthogonal interaction in the typical Pd or Cu-catalyzed syntheses of diarylamines.[3−6] Whereas, when a phenolic OH group was tolerated (**22**), the reaction did not take place with NH_2 or

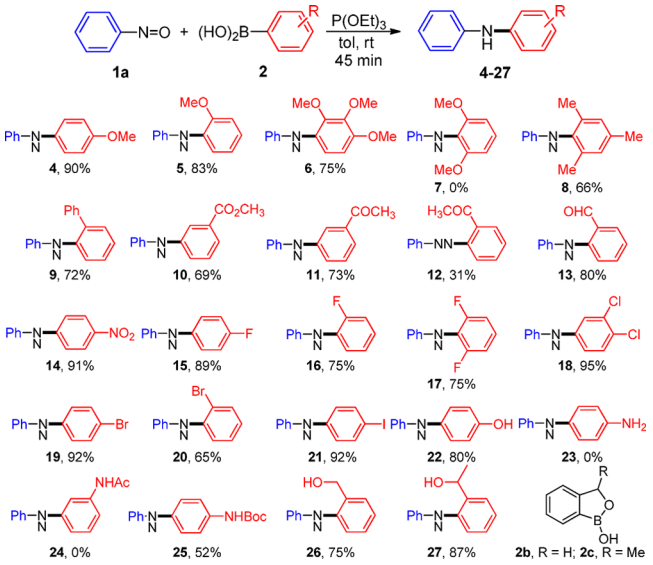


Figure 1. Cross-coupling between nitrosobenzene **1a** and arylboronic acids (**2**). Reaction conditions: PhNO (**1a**, 0.28 mmol), $ArB(OH)_2$ (**2**, 1.5 equiv), $P(OEt)_3$ (1.2 equiv), tol (0.6 mL), and rt, for 45 min.

NHAc (**23**, **24**) as substituents of the arylboronic acid component.[22] However, Boc-protection permitted the synthesis of **25** with moderate yield. Finally, compounds **26** and **27**, with alcoholic OH groups, were synthesized starting from benzoxaboroles **2b** and **2c**.

Next, we looked into the scope of the cross-coupling reaction with regard to the nitrosobenzene component **1**, using phenylboronic acid (**2a**) as reagent (Figure 2). For the sake

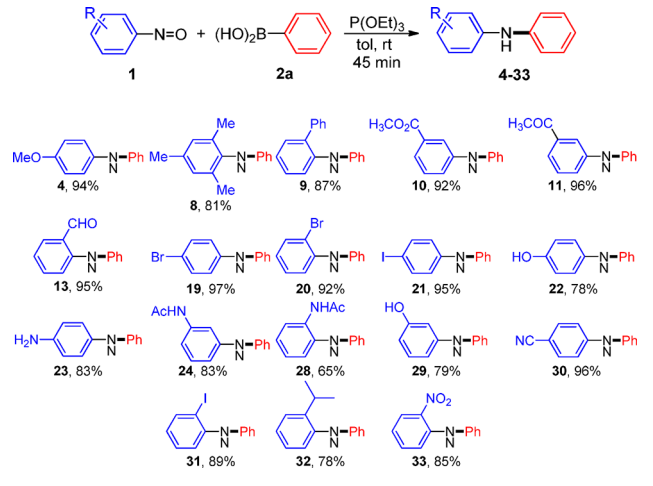


Figure 2. Cross-coupling between nitrosobenzenes **1** and phenylboronic acid (**2a**). Reaction conditions: ArNO (**1**, 0.28 mmol), $ArB(OH)_2$ (**2a**, 1.5 equiv), $P(OEt)_3$ (1.2 equiv), tol (0.6 mL), and rt, for 45 min.

of comparison, we started by synthesizing several representative examples (**4**, **8** − **11**, **13**, **19**−**24**) that had already been prepared the other way round, i.e., by the reaction of **1a** with the boronic acids **2** (results gathered in Figure 1). The comparison of results put forward that compounds **4**, **8**−**11**, **13**, **19**, **20**, and **21** could be synthesized with a slight increase in yield when starting with substituted nitroso compounds **1**. The phenol **22** was synthesized in similar yield. However, we were pleased to find that, opposite to the previous situation, free

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NH_2 was tolerated as substituent when installed on the nitrosobenzene moiety (**23**), as well as NHAc (**24**). In particular, **23** is an important industrial antioxidant used in the manufacture of car tires.[23] The synthesis of **23** has been scaled to 10 g of starting material with a slight loss in yield (74%).

For completeness, some additional new cases (**28** − **33**) were included in the study (Figure 2) to show the scope of the method further with regard to the nitrosobenzene counterpart, including examples with NH, OH and halogens, among others. All reactions took place in good yields, including those carrying *o*-substituents.

Then, we considered the coupling of nitrosobenzenes **1** and arylboronic acids **2** carrying substituents on each ring. As previously stated,[8] the synthesis of sterically hindered diarylamines, i.e., those carrying *ortho*-substituents on both aromatic rings, is often challenging. Therefore, we have focused on evaluating the performance of this cross-coupling procedure with nitrosobenzenes and arylboronic acids carrying at least one *ortho*-substituent each (Figure 3).

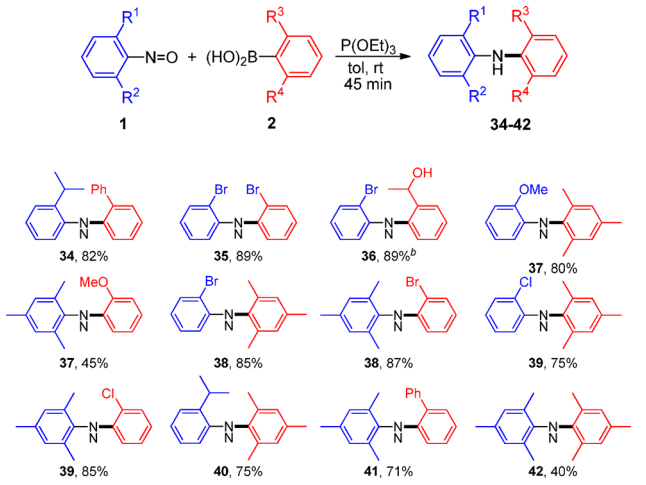


Figure 3. Synthesis of sterically hindered diarylamines. Reaction conditions: ArNO (**1**, 0.28 mmol), $ArB(OH)_2$ (**2**, 1.5 equiv), $P(OEt)_3$ (1.2 equiv), tol (0.6 mL), rt, 45 min.

The results gathered in Figure 3 put forward that this cross-coupling reaction admits the presence of two (**34** − **36**) and three (**37** − **41**) *o*-substituents with good yields. However, **42**, with four Me *o*-substituents, was synthesized in moderate yield.

Finally, we were pleased to find that the reaction was also useful for the assembly of heterocyclic amines, either starting with heterocyclic nitroso compounds or with heterocyclic boronic acids (Figure 4); many of them were π-excessive or π-deficient. The tolerance of unprotected NH in indoles is noteworthy (**44**, **51**).

To test the scaling possibilities, in addition to the synthesis of **23** (*vide supra*), we have carried out the 10-g scale synthesis of phentolamine (**57**) (Regitine, Vasomax), a reversible, non-selective α-adrenergic antagonist used clinically to control hypertensive emergencies (Scheme 2).[24] The procedure benefits from the tolerance of the OH group in the cross-coupling reaction leading to **55**.

Based on the above considerations and the literature information,[20] we propose the mechanism for the amination, as illustrated in Scheme 3 for the synthesis of diphenylamine (**3**). Nucleophilic addition of $P(OEt)_3$ to the oxygen atom of

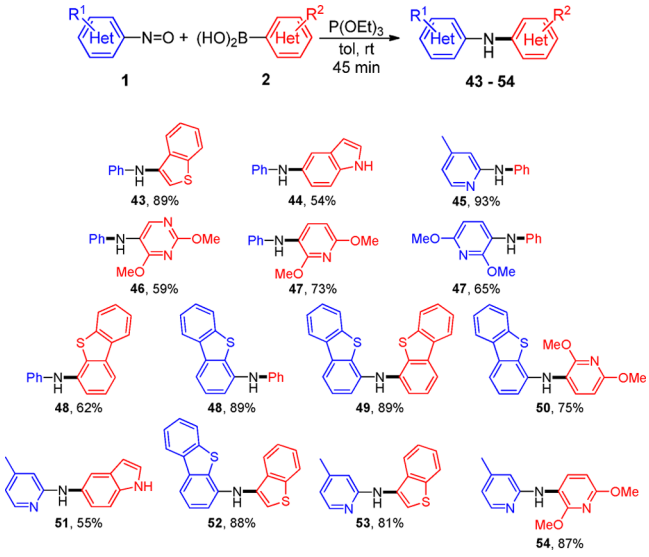
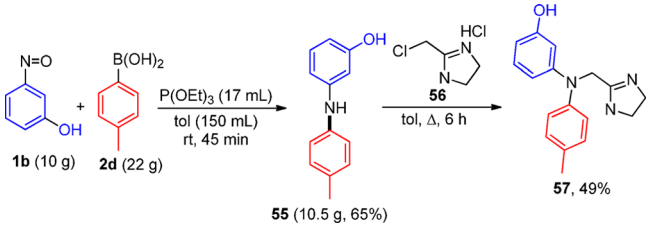
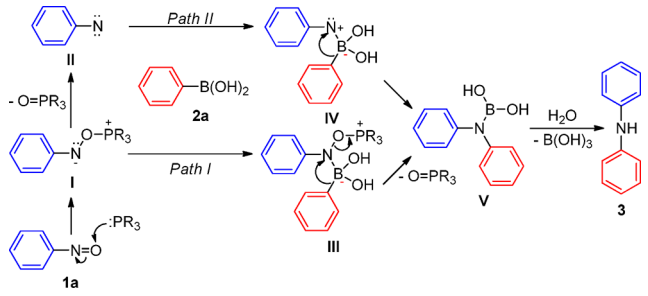


Figure 4. Synthesis of heterocyclic amines. Reaction conditions: (Het)ArNO (**1**, 0.28 mmol), $(Het)ArB(OH)_2$ (**2**, 1.5 equiv), $P(OEt)_3$ (1.2 equiv), tol (0.6 mL), and rt, for 45 min.

Scheme 2. Synthesis of Phentolamine (57)



Scheme 3. Plausible Reaction Course



the nitroso group in **1a** leads to a tetravalent phosphorus intermediate (**I**), which can be transformed into a nitrene by elimination of $O{=}P(OEt)_3$ (**II**). Either (**I**, **II**) can add to the vacant orbital on boron in **2a**, giving rise to a boronate species (**III**, **IV**) able to transfer the nucleophilic phenyl group to the electrophilic nitrogen. Protonation of the final aminoboronate **V** upon filtration affords diphenylamine (**3**), together with boric acid as byproduct.

In conclusion, we have developed for the first time the transition metal-free cross-coupling between nitrosobenzenes and boronic acids. The reaction tolerates functional groups that are incompatible with other methods for the synthesis of di(hetetro)aryamines (carbonyls, nitro, halogens, free OH and NH_2), and permits the synthesis of diaryl- and diheteroaryl-amines, including sterically encumbered compounds. The experimental procedure is simple and inexpensive [open flask, $P(OEt)_3$], mild (base-free, toluene, rt), fast (45 min), and

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scalable (10 g), and the reaction products are recovered by simple filtration without the need for separation by chromatography.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00473.

Synthesis of starting materials, optimization of reaction conditions between **1a** and **2a**, full experimental details, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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