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Transition-Metal-Free Three-Component Synthesis of Tertiary Aryl Amines from Nitro Compounds, Boronic Acids, and Trialkyl Phosphites

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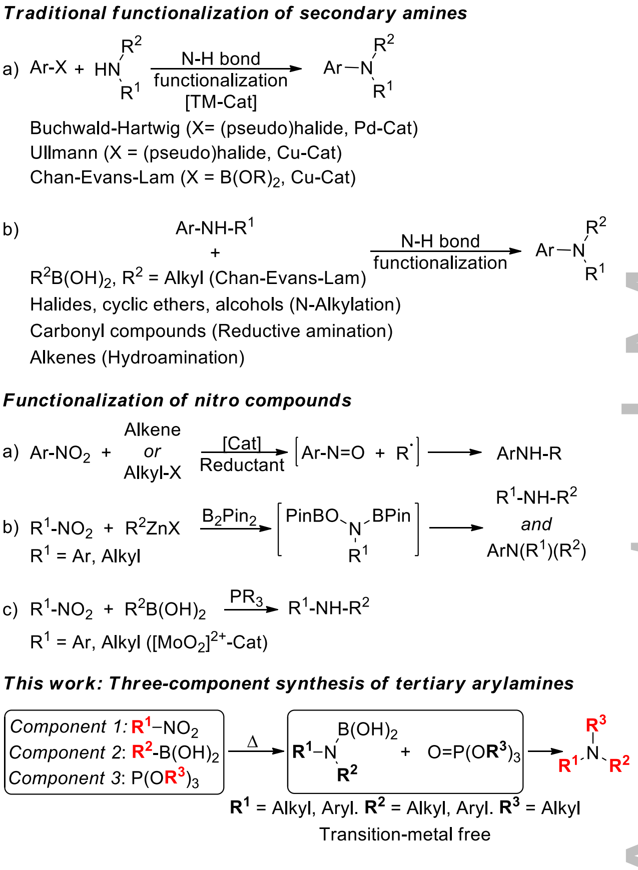
Abstract. The synthesis of aromatic amines is of continuous interest in chemistry. An exceptionally versatile three-component reaction that directly transforms inexpensive nitro compounds, boronic acids, and trialkyl phosphites into tertiary aromatic amines has been realized. The reaction tolerates alkyl and aryl substituents on the nitro and boronic acid moieties, as well as functionalized phosphites. No transition-metal catalysis is required. The method is orthogonal to other classical metal-catalyzed syntheses since it tolerates the presence of halogens, and also permits the synthesis of functionalized compounds such as α-amino ester derivatives.

Keywords: amination; boronic acids; multicomponent reactions; nitro compounds; phosphites

The manufacture of amines as raw materials and as end products is one of the fastest-growing sectors in the chemical industry worldwide.[1] In particular, aromatic amines (also known as arylamines or aniline derivatives) are ubiquitous compounds in nature that have found widespread use in medicinal applications and materials science.[2] Among them, tertiary derivatives are motifs commonly found in molecules of importance to chemistry, biology, and medicine, often found within alkaloid secondary metabolites. We report herein a novel three-component reaction that permits the assembly of tertiary aryl amines with three different substituents by mixing a nitro compound with a boronic acid and a trialkyl phosphite. The target compounds have been used as Lewis bases to form organometallic catalysts, and as Brønsted bases to capture acidic side products in several types of metal-free coupling reactions.[3] The development of efficient methods for the synthesis of arylamines is an issue of continuous interest to the chemistry community.[4]

The synthesis of tertiary derivatives is less straightforward than that of secondary arylamines,[5] requiring a multistep approach. The most general transformations for the synthesis of tertiary arylamines use either secondary anilines or secondary alkylamines as starting materials (Scheme 1).



Scheme 1. State of the art and current proposal.

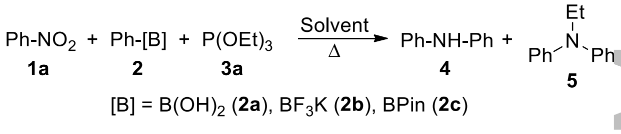
These include the Buchwald-Hartwig[6] or the Ullmann[7] reactions between anilines and (pseudo)aryl halides, the Chan-Evans-Lam amination of boronic acid derivatives, which can be carried out either on N-substituted anilines[8] or on secondary alkylamines,[9] N-alkylation reactions,[10-13] and reductive amination procedures,[14] the last two specific for secondary alkylamines. Besides, some hydroamination procedures of secondary anilines have also been reported.[15] Most of these routes require multiple steps and various purifications, as well as the use of transition-metal catalysts, ligands, and additives, which overall hampers synthetic efficiency. Also, the amines required as starting materials, in particular, the anilines, are frequently obtained by the reduction of nitro compounds. This has led to the development of synthetic methods that directly use readily available and cheap nitro compounds as the nitrogen source. These procedures become more sustainable because they avoid the reduction step and increase functional group compatibility. However, general methods for amine synthesis from nitro compounds remain underdeveloped despite their potential advantages and have been mostly advanced thus far for the synthesis of secondary amines.

Thus, secondary anilines have been prepared from nitroarenes by the radical hydroamination of olefins[16] and alkyl halides[17] using iron catalysts,[18] and by a sequential chainwalking reductive hydroarylamination relay using nickel hydrides as catalysts.[19] Also, using nitroarenes as a nitrogen source,[20] the nucleophilic addition of Grignard reagents followed by reduction of an hydroxylamine intermediate has led to diarylamines.[21] Both aromatic and aliphatic nitro compounds have been transformed into secondary anilines by the reductive coupling of organozinc reagents promoted by B_2Pin_2 via nitrenoids.[22] Boronic acids, although less nucleophilic than Grignard or organozinc reagents, can be used as nucleophiles in organic synthesis. Among their advantages, they are bench-stable compounds that can be used without the need for especially dried solvents or inert atmosphere, are compatible with many labile functional groups such as carbonyls, and tolerate the presence of unprotected OH or NH groups in many of their reactions. Their nucleophilicity can be enhanced by the formation of ate species resulting from coordination with Lewis bases.[23] This property has been exploited to make them react with various nitrenoid species that can be generated *in situ* by the reduction of nitro compounds in the presence of phosphetanes and phosphines.[24,25] Both aliphatic and aromatic nitro compounds have been transformed into secondary anilines by using both an excess of boronic acid and of PPh_3 in combination with a molybdenum catalyst.[26]

Multicomponent reactions[27] constitute a big step forward towards sustainability, a key driver for innovation in industrial research and development, since they provide an alternative to the classical multistep synthesis. Based on this principle and on previous findings,[25] we hypothesized that the activation of either alkyl or aryl nitro compounds with alkyl phosphites in the presence of either alkyl or arylboronic acids could render transient aminoboranes, which are difficult to access through other methods,[22] that could react as nucleophiles with the trialkyl phosphate generated *in-situ* as byproduct of the activation of the nitro group,[28,29] permitting the synthesis of a variety of functionalized tertiary anilines in a sustainable way. The procedure avoids the use of transition-metal catalysis, thus circumventing the drawbacks associated with possible toxicity, cost, need for the design of substrate-depending ligands and risk of product contamination.

We started our investigation by treating nitrobenzene and phenylboronic acid with triethyl phosphite (Table 1, entry 1). Toluene was chosen as the solvent because it had previously been used for the synthesis of diarylamines from nitroso compounds and phenylboronic acid.[25] The temperature was set to 110 ºC (reflux) to favor the alkylation step. However, under these reaction conditions, no conversion of the starting materials was observed. The replacement of toluene by chlorobenzene, together with an increase in the reaction temperature (160 ºC), afforded diphenylamine **4** (entry 2). However, when xylene was used, a mixture of amines **4** and **5** was observed (entry 3). Similar results were obtained upon increasing the reaction time (entry 4) and the molar ratio of phosphite (entry 5). Taking into account that phosphites are inexpensive chemicals, we tried the reaction under neat conditions. Using triethyl phosphite as the solvent (180 ºC) we were able to obtain the tertiary amine **5** in good yield (entry 6). Under similar conditions, no reaction was found when using potassium phenyltrifluoroborate or the corresponding pinacol ester (entries 7, 8).

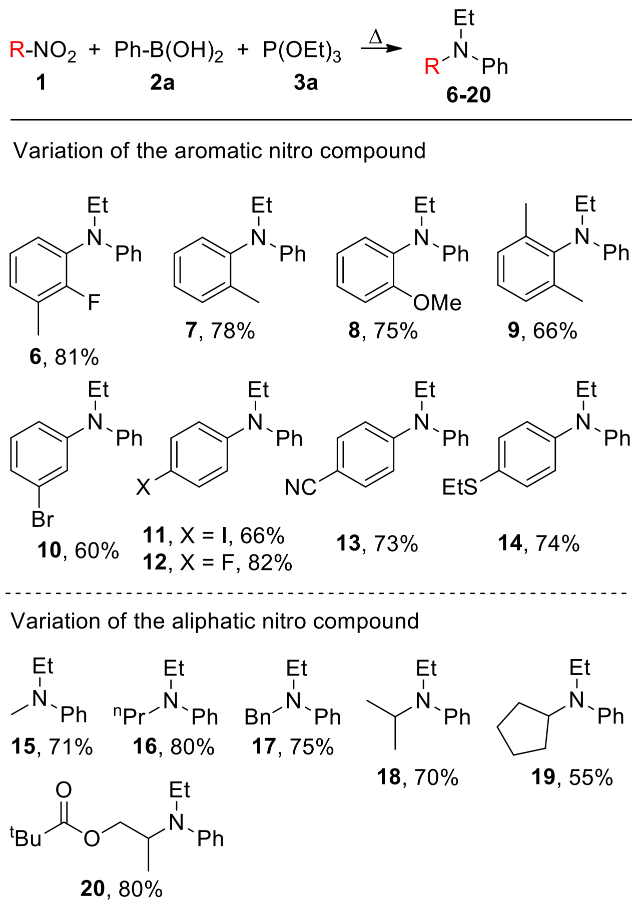
Table 1. Optimization



	2	3a (equiv)	Solvent	Temperature (º C)	Yield [%][c]	
					4	**5**
1	**2a**	3	Toluene	110	0	0
2	**2a**	3	$Cl\text{-}C_6H_5$	160	49	0
3	**2a**	3	Xylene	160	42	15
4	**2a**	3	Xylene[a]	160	41	19
5	**2a**	6	Xylene	160	35	32
6	**2a**	---	**3a**[b]	180	0	83
7	**2b**	---	**3a**[b]	180	0	0
8	**2c**	---	**3a**[b]	180	0	0

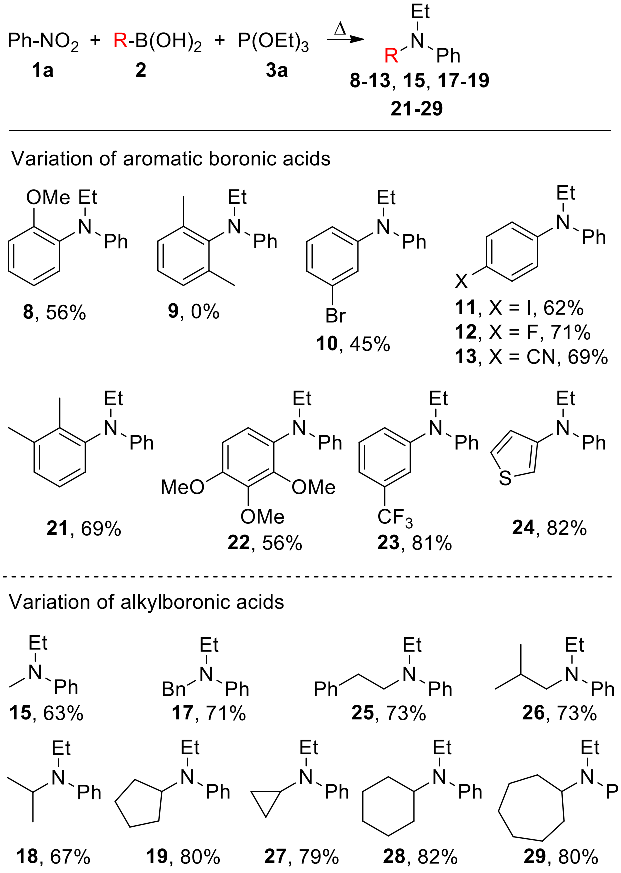
Reaction conditions: **1a** (0.40 mmol), **2** (1.20 mmol), argon atmosphere, sealed tube, 24 h (unless otherwise stated).
[a] 48 h.
[b] 1.2 mL.
[c] Yield of isolated product.

With the optimized conditions in hand (Table 1, entry 5), we began to explore the scope of this three-component transformation by using different nitroarenes (Scheme 2), focusing our attention in examples with steric hindrance at the *ortho* positions (**6-9**), and also compatibility with halogen functionalities (**10-12**), which makes the method orthogonal to transition-metal catalyzed reactions. The reaction could be also applied to substrates bearing a cyano or thioether functional group (**13**, **14**). We were pleased to find that the reaction also tolerated the use of aliphatic nitro compounds including simple linear alkyls such as methyl (**15**), propyl (**16**) or benzyl (**17**) and also examples with ramification at the α-position such as isopropyl (**18**) or cyclopentyl (**19**). Chain-functionalization was also possible (**20**).



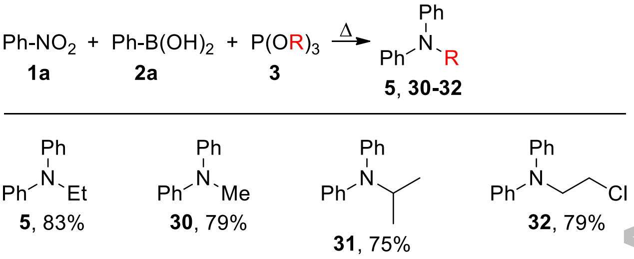
Scheme 2. Initial variations of the nitro group.

Next, we continued to explore the scope of the three-component reaction with respect to the boronic acid (Scheme 3). Starting with arylboronic acids, again we found compatibility with *ortho* substituted rings (**8**, **9**, **21**, **22**) and halogen (**10-12**, **23**) or cyano substitution (**13**). Heterocyclic rings were also possible (**24**). Compounds **8-13** had been previously synthesized from nitroarenes and phenylboronic (Scheme 2). In comparison, higher yields were obtained with substituted nitro compounds and the synthesis of amine **9** was not possible starting from (2,6-dimethylphenyl)boronic acid (Scheme 3). Besides, we found that alkyl boronic acids could also be used in the three-component reaction, both primary (**15**, **17**, **25**, **26**) and secondary (**18**, **19**, **27-29**). Compounds **15**, **17-19** had been previously synthesized from alkyl nitro compounds and phenylboronic acid (Scheme 2). Yields were similar for linear alkyl derivatives following either pathway. On the other hand, the cyclic derivatives were synthesized in higher yields when starting from the corresponding boronic acid.



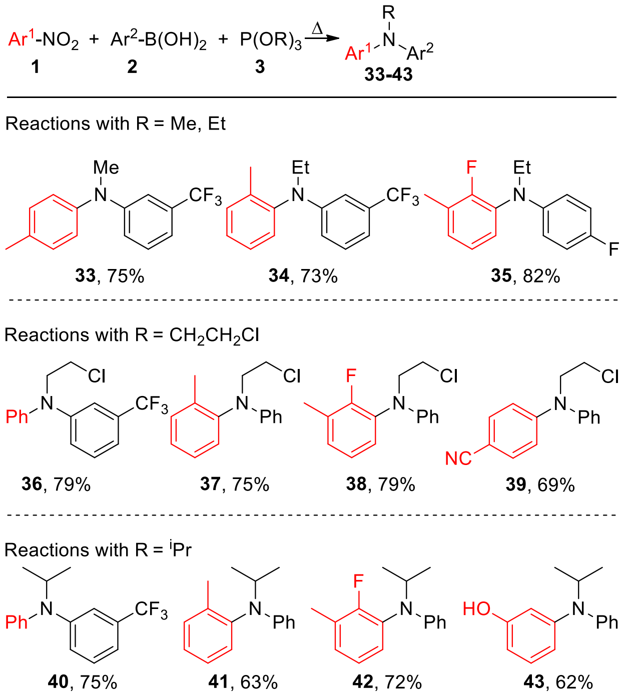
Scheme 3. Initial variations of the boronic acid.

With regard to variations of the phosphite (Scheme 4), we observed that in addition to ethyl (**5**), methyl (**30**), a branched alkyl phosphite (**31**) and a functionalized alkyl phosphite (**32**) could be used as reaction partners, although the synthesis of **31** required an increase in the molar ratio of phosphite (See Supporting Information for details).



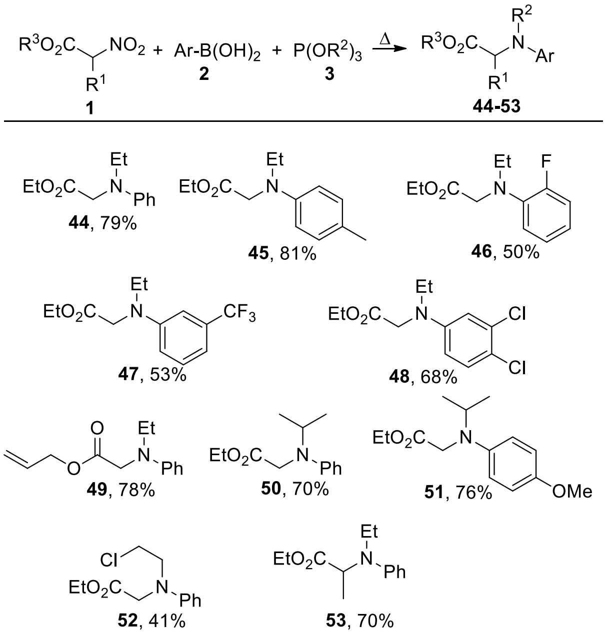
Scheme 4. Variations of the alkyl phosphite.

In light of these results, we accomplished the synthesis of more complicated examples with variation of the nitro compound, the boronic acid, and the phosphite towards the synthesis of N-alkyl diarylamines (Scheme 5). Diarylamines are highly important chemicals found among drugs, agrochemicals, dyes, radical-trapping antioxidants, electroluminescent materials, and ligands for transition-metal catalysis.[2,3] The synthesis of sterically hindered compounds (**41**, **42**) and the tolerance of the unprotected OH group (**43**) are especially noteworthy. In addition, the method was amenable to scaling. As an example, compound **5** has been prepared at 8 mmol scale (1.04 g, 65%).



Scheme 5. Synthesis of N-alkyl diarylamines.

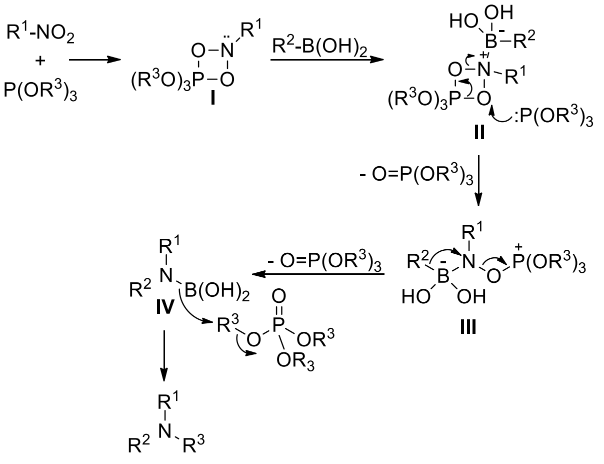
In the context of the ongoing discussion, the case of α-amino acid esters deserves special consideration. It is well known that α-amino acids and their derivatives, the backbone of proteins, have found multiple applications in chemistry.[30]



Scheme 6. Synthesis of α-amino esters.

The N-alkylated derivatives are important elements for the modulation of biological functions.[31] However, methods that permit the synthesis of α-amino acid esters are relatively scarce.[32] The three-component reaction reported herein permits the efficient synthesis of these compounds from readily accessible nitroacetates as starting materials (Scheme 6). The scope of the reaction was put to a test by using ethyl and allyl nitroacetate together with various arylboronic acids and triethyl phosphite (**44**–**49**). Apart from N-ethyl derivatives, it was also possible to prepare isopropyl derivatives (**50**, **51**) and compounds functionalized at the N-alkyl chain (**52**). Also, the reaction was possible when using α-substituted nitroacetate derivatives (**53**).

Based on the above considerations and literature information, we propose the mechanism for the three-component reaction that is gathered in Scheme 7. Initial results by Cadogan and Sundberg[28] put forward the phosphine-mediated deoxygenation of nitrobenzenes with the participation of nitroso intermediates. The successful transformation of aliphatic nitro compounds in our three-component reaction precludes this reaction course since aliphatic nitroso compounds would rapidly tautomerize to oximes. Similar observations have been made by other authors.[24,26]



Scheme 7. Proposed reaction course.

DFT calculations by Radosevich[33] suggested that the direct transfer of oxygen from nitro compounds to P(III) species is energetically disfavored in comparison to a stepwise process with intermediacy of azadioxaphosphetanes. Accordingly, we presume the formation of azadioxaphospetane **I** by the interaction of the trialkyl phosphites with the starting nitro compounds. Coordination of the nitrogen atom in **I** to the low-lying vacant orbital on boron of the boronic acid would render intermediate **II**, in which the boron atom acquires an ate character, and the nitrogen atom becomes highly electrophilic. Ring-opening by an excess of the oxophilic phosphite would deliver intermediate **III** together with the release of a trialkyl phosphate. The boronate character of **III** would then favor the intramolecular 1,2-migration of the carbon backbone as a nucleophile from boron to the electrophilic nitrogen, giving rise to the aminoborane **IV** together with an extra equivalent of phosphate. Finally, alkylation of the aminoborane **IV** with the *in situ* generated phosphate would provide the final product.[34]

In support of this reaction pathway, some control experiments were run (see Supporting Information). Only a diphenylamine was obtained when a mixture of nitrobenzene, phenylboronic acid, and triethyl phosphite was heated in the presence of water, presumably because of protonation of **IV**. Also, the treatment of a solution of diphenylamine in triethyl phosphite with different amounts of triethyl phosphate did only afford traces of **5**. These experiments suggest the participation of **IV** as a reaction intermediate.

In conclusion, we have developed an efficient three-component reaction for the synthesis of tertiary arylamines by heating a mixture of readily available nitro compounds with boronic acids and trialkyl phosphites. The reaction tolerates aryl and alkyl groups both in the nitro and boronic acid moieties and permits the assembly of amines with steric hindrance at the *ortho* positions of the aromatic rings and α-ramification of the alkyl chains. Apart from being scalable, the transformation permits halogen substituents, which makes is orthogonal to traditional transition-metal catalyzed reactions. It also tolerates the presence of ester groups, and in particular, the reaction has proven of use for the synthesis of α-amino esters.

Experimental Section

Standard Procedure for the One-Pot Synthesis of Tertiary Aryl Amines

The nitro compound (0.4 mmol, 1.0 equiv.) and the boronic acid (1.2 mmol, 3.0 equiv.) were dissolved in trialkyl phosphite (1.2–2.4 mL). The mixture was stirred at 180ºC under argon atmosphere for 1–24 hours in a sealed tube. 3 eluting with Hexane:AcOEt or Hexane:DCM.

1g-Scale synthesis of 5

Nitrobenzene **1a** (1.0 g, 8.1 mmol) and phenylboronic acid **2a** (3.0 g, 24.4 mmol) were dissolved in triethyl phosphite (25 mL). The mixture was stirred at 180ºC under argon atmosphere for 30 hours in a sealed tube. After cooling down to room temperature, the resulting mixture was filtered through a celite pad and washed gently with hexane. The filtrate was concentrated *in vacuo* and the resulting mixture was adsorbed on silica and purified by flash column chromatography eluting with hexane:DCM 9:1 (1.04 g, 65%).

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COMMUNICATION

Transition-Metal-Free Three-Component Synthesis of Tertiary Aryl Amines from Nitro Compounds, Boronic Acids, and Trialkyl Phosphites

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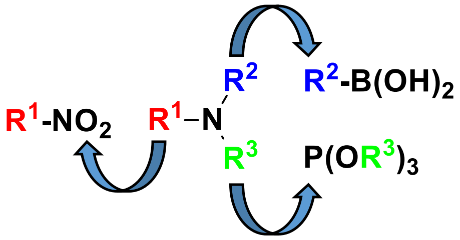

Three-component

R^1, R^2 = Alkyl, Aryl

Transition-metal free