Aromatic amines are compounds that have found widespread use in medicinal applications and materials science; consequently, their manufacture is one of the fastest-growing sectors in the chemical industry worldwide. The current trend in the industry is cost reduction and environmental compliance (sustainability); for that reason, the demand for new, green, and economic methods for the synthesis of these compounds has been intensified. This book provides a detailed description of a new method for the synthesis of functionalized secondary arylamines starting from nitrosoarenes and boronic acids in the presence of triethyl phosphite under metal-free-conditions. The plethora of research substained in the book will provide a detailed outlook on synthetic applications of this cross-coupling reaction and will open new horizons to extend the methodology development. The operational ease, broad functional group tolerance and scalability of the reaction make it suitable for adoption in both academic and industrial settings. The book should be specially useful to chemists or anyone else who may be interested in the synthesis of amines or in the reactivity of nitrosoarenes or boronic acids.

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# Transition-Metal-Free Synthesis of Amines from Nitrosoarenes

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## 1. Introduction

Amines are an important class of compounds which find uses as a basis or constituent for pharmaceutical compounds, crop protection chemicals, agricultural products, fine chemicals, solvents, dyes and pigments.[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 organic scaffolds, secondary arylamines are important building blocks that are useful in various fields such as pharmaceutical or chemical industries; in fact, secondary amines are by far one of the most used classes of reagents in medicinal chemistry.[3] Consequently, their manufacture as raw materials and as end products is one of the fastest-growing sectors in the chemical industry worldwide.[4] According to a report by Grand View Research, Inc. global amine market was assessed $14.4 billion during year 2016 and is expected to raise up to $29.3 billion by year 2025.[5]

Methods for commercial manufacture of amines vary depending on the specific amine to be produced and on the raw materials employed. Often, there are multiple processes used for manufacturing a particular amine or family of amines. Most processes result in the synthesis of an equilibrium distribution of primary, secondary and tertiary amines, which is different for every family of amines.[6] The current trend in the chemical and pharmaceutical industries is cost reduction and environmental compliance (sustainability);[7] for that reason, the demand for new, robust, selective, and economic methods has been intensified. Traditionally, the synthesis of secondary arylamines has been achieved using transition-metal catalysis.[8] Despite the robust catalytic capability of these metals, some drawbacks have been gradually realized in transition metal-mediated reactions. For instance, metal catalysts are often air- and/or moisture-sensitive. The toxicity of metals and incremental cost are major shortfalls for their applications in the large-scale synthesis. The technologies developed by now using those metals are unsustainable in the future due to their limited availability affecting the future supply.[9] Moreover, residual transition metals can be difficult as well as costly to remove, but the need to obtain final product free of metal contamination is crucial in many applications, such as in the pharmaceutical industry.[10] Consequently, transition-metal-free processes have emerged as valuable alternatives to more conventional transition-metal-catalyzed reactions. According to the volume of today's literature several innovative methodologies under metal-free conditions have been reported that can compete with metal-catalyzed methods.[11]

The emerging area of transition-metal-free reaction strategy provides an opportunity to make industrially useful, significantly cost-reducing and ecologically acceptable the synthesis of secondary arylamines. This book is devoted to the detailed description of a new method for the synthesis of secondary arylamines starting from nitrosoarenes and boronic acids in the presence of triethyl phosphite under metal-free-conditions. Accordingly, the next three chapters address general aspects of the structure, properties and reactivity of nitrosoarenes and boronic acids. Chapters 5 and 6 are dedicated to explaining in detail the scope and limitations of a new transition-metal-free method for the synthesis of secondary di(hetero)arylamines and alkylarylamines using nitrosoarenes and boronic acids as starting materials. Next chapter is devoted to the gram-scale synthesis of secondary anilines with industrial interest by using this new method in the absence of transition metals. Finally, the last chapter is a results overview.

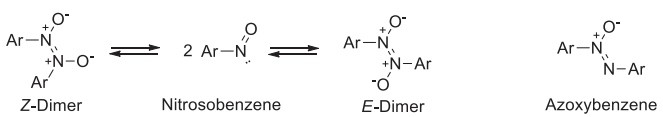
## 2. Nitrosoarenes

### 2.1. Structure and Properties

C-Nitroso compounds[12] are organic compounds with a nitroso group bounded to a carbon atom (R−N=O). Although with the same functional group, there is difference between aromatic (R = aryl) and aliphatic (R = alkyl) nitroso compounds, not only in their basic structural characteristics, but also in their use and importance in synthetic chemistry, and specially, in their biologically interesting activities. Aliphatic nitroso compounds are not so stable and tend to undergo a facile rearrangement to the corresponding oximes by hydrogen shift from the α-carbon atom. Furthermore, aliphatic nitroso compounds show a strong tendency to form dimers. On the other hand, aromatic nitroso compounds[13] have a rich history in chemistry and biology.

The nitroso group is strongly electron-withdrawing, which combined with the presence of a lone pair on nitrogen, makes that nitroso compounds tend to be in equilibrium with dimers in solution (Scheme 1).[14] Generally, the blue- or green-colored monomeric form dominates, but the extent of the equilibrium mainly depends on the nature, but in particular by the positions of substituents of the ring. Substitution can basically have two kinds of influences on chemical behaviour: Steric effect (which is important with *o*-substituents and affect the orientation of the NO group relative to the plane of the benzene ring; the dimer formation is most favored in the presence of substituents in the *o*-position) and electronic effect (which affects to the reactivity of the NO group: while electron donors substituents deactive the nitroso group, the electron-withdrawing substituents enhance its reactivity, specially towards dimerization). The dimers, which are often colorless or pale-yellow, are often favored in the solid state, whereas the monomers are favored in dilute solution or at higher temperatures. Dimers exist as *Z*- and *E*-isomers. Protonation on one of the oxygen atoms of any of these dimers followed by dehydroxylation gives rise to stable azoxybenzenes.[15]






**Scheme 1**. Equilibrium between monomeric and dimeric forms of nitrosoarenes

The recent attention in nitrosoarenes has been focused in their many applications in synthetic organic chemistry, their role as reactive metabolites (nitrosoaromatic compounds appear in biological systems as intermediates, mostly on the pathway of either oxidation of amines or reduction of nitro compounds),[16] and their use as spin traps.[17] Nitrosobenzenes have been utilized as radical scavengers,[18] antioxidants in lubricating oil,[19] and antiviral compounds.[20]

## 2.2. Synthesis

As a consequence of the high reactivity of nitroso group, the synthesis of nitrosoarenes has two main difficulties: First is finding proper conditions under which the reaction will not continue to the final oxidation or reduction product, but instead, will stop when the nitroso is formed. A further consideration to be borne in mind is the possibility of reaction of the nitroso compound with the starting material and/or preparative reagents. The second problem has its origin in the tendency of intermediates to form dimers as byproducts. To avoid these difficulties, besides the optimized classical synthetic pathways, a series of specific reagents as well as methods have been developed.



Nitroso aromatic compounds can be obtained by a wide range of complementary procedures (Scheme 2).[21] The nitrosation of electron-rich aromatics (Scheme 2, a) consists of a $S_E$Ar reaction that can be carried out using various nitrosating agents as electrophiles through a Wheland intermediate. Substitution normally occurs *para* to an activating group, such as amino, alkoxy, or hydroxyl. The most commonly employed nitrosating reagent is nitrous acid, derived from the action of an acid upon sodium nitrite. To minimize side reactions, nitrosations are usually carried out at temperatures around 0ºC or below. A large excess of nitrosating reagent should be avoided to prevent the formation of nitro compounds through further reactions of the nitrosoarenes.

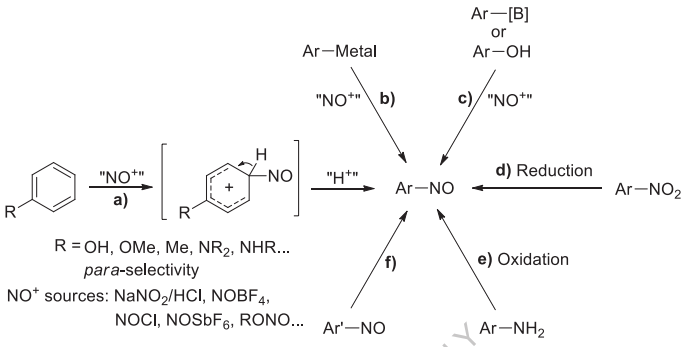
While nitrosation by electrophilic displacement of hydrogen is only suited for arenes bearing highly activating substituents, less activated nitrosoarenes can be prepared by electrophilic nitrosation of aryl metallic compounds (Scheme 2, b). The polarization of the metal-carbon bond and the formation of a stabilized metal cation as leaving group facilitate the electrophilic displacement. Magnesium, silicon, tin, thallium, or mercury compounds, among others, have been used as starting materials with various nitrosating reagents.

An alternative to toxic and air- and moisture-sensitive organometallic species for the synthesis of functionalized aryl and heteroaryl nitroso compounds is the use of boronic acid derivatives as starting materials (Scheme 2, c). Molander and Cavalcanti disclosed the facile *ipso*-nitrosation of aryl and heteroaryltrifluoroborates using nitrosonium tetrafluoroborate.[22] Later, the *ipso*-nitrosation of aryl boronic acids using chlorotrimethylsilane-sodium nitrite unison as nitrosation reagent system was also reported.[23] Most recently, Alaniz and coworkers developed a synthesis of aromatic nitroso derivatives by using an *ipso*-oxidative aromatic substitution process starting from substituted phenols.[24] The reaction starts with the use of phenyliodoso diacetate in MeOH for the oxidative dearomatization of the phenol derivatives to have access to a quinone monoketals; treatment of these intermediates with hydroxylamine sulphate and pyridine allows the one-pot synthesis of nitrosobenzenes from phenols through a tandem dearomatization/condensation/rearomatization process.

A common pathway for the synthesis of nitrosoarenes is the reduction of nitro compounds (Scheme 2, d). The most frequent protocol consists of a two-step procedure that involves reduction of the nitro group to a hydroxylamine (Zn, HCl), which is subsequently oxidized (most frequently using Fe(III) salts) to the nitroso compound. There are also reported some methods that allow the synthesis of nitrosoarenes from nitro compounds consisting on photochemical or acid- or base-catalyzed rearrangements. Most of the usual conditions employed to reduce nitro compounds also reduce the more susceptible nitrosoarenes. In turn, the nitrosoarenes may combine with *N*-arylhydroxylamines to give diaryldiazene *N*-oxides and this can become a dominant reaction. However, the separation of the nitroso compound as it is formed is often effective in preventing this undesired side reaction and allows the direct reduction of selected nitroarenes to the corresponding nitroso compounds.

A variety of stoichiometric and catalytic methods exist for the oxidation of aromatic amines to nitrosoarenes (Scheme 2, e). A broad range of oxidants has been used under appropriate reaction conditions such as oxone, 3-chloroperoxybenzoic acid, and hydrogen peroxide, among others. The oxidation of anilines or hydroxylamines is restricted to benzenes that do not carry other substituents prone to oxidation. Reaction conditions may vary greatly depending upon the substrate and should be chosen carefully, in order to avoid the overoxidation to nitroarenes or the formation of azocompounds by the reaction of the starting aniline with the nitroso compound. In addition, the formation of byproducts can also occur during the work-up or purification of oxidation-sensitive compounds.

Nitrosoarenes are very reactive compounds and undergo a broad range of reactions involving the nitroso group. It follows, therefore, that transformations of functional groups in the presence of a nitroso group are uncommon. However, the functionalization of the aryl moiety of some selected nitrosobenzenes is also feasible (Scheme 2, f).[25]




**Scheme 2**. Main methods for the synthesis of nitrosoarenes



The major difficulty in nitroso chemistry is that the high reactivity of these compounds necessarily imposes constraints upon the methods employed for their preparation, particularly with regard to the yield of the desired product. However, and as aforementioned, there is a considerable variety of synthetic routes available for the high-yield preparations of nitroso compounds (monomers or dimers), some of which have been in regular use.

## 2.3. Reactivity

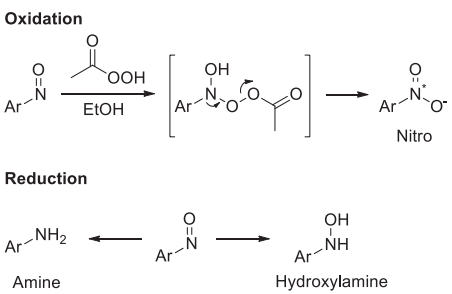
In recent years, nitroso compounds have become of great importance in organic synthesis as a viable alternative to other nitrogen-containing reagents. Nitrosoarenes are highly reactive compounds and display interesting intra- and intermolecular dimerization processes and addition reactions with unsaturated compounds. The fact that nitroso function possesses two heteroatoms with *n*-electrons, and also $\pi$-electrons in the N=O double bond, is used for the synthesis of a wide variety of metal complexes, therefore, its coordination chemistry is noteworthy.[26] Furthermore,

nitrosoarenes are not only interesting starting substrates, but they also participate as reagents in different reactions.[27]

Bearing a lone pair of electrons on nitrogen and a highly polarized N=O double bond, nitroso compounds can act both as nucleophiles and electrophiles. First of all, in dimerization, nitroso molecules show their ambivalent nature: one of nitroso partners behaves as the nucleophile, but the other plays the role of the target for the nucleophile attachment. Such dually reactive nature allows nitrosoarenes to participate in many chemical transformations which include additions, isomerizations, oxidations, as well as reductions.[28] The polarization of the N=O bond results in a susceptibility of the nitroso group to additions of nucleophiles on the nitrogen atom predominantly. However, under appropriate reaction conditions, additions on the oxygen atom are also possible. On the other hand, the free electron pair on nitrogen enables nitrosobenzenes to act as nucleophiles and add to activated doubled bonds. This property gives nitroso compounds a special role in the synthesis of heterocyclic compounds.

Among the reactions of nitrosoarenes, oxidation to the corresponding nitroarenes or reduction to give the corresponding amines or hydroxylamines are common transformations (Scheme 3). Oxidation of nitrosobenzenes to nitro compounds can be achieved by numerous oxidizing agents, such as permanganate, chromate, hexacyanoferrate, Caro's acid, nitric acid, nitrogen dioxide or nitrogen monoxide. Some attention has been paid to the oxidation of nitrosobenzene with peroxocarboxylic acids.[29] Reduction of nitrosobenzenes yields aryl hydroxylamines or anilines and can occur electrochemically, by hydrated electrons, or by chemical reducing agents, including zinc and tin in acidic media, sodium in diethyl ether, or boranes. Reduction can also be carried out by catalytic hydrogenation.



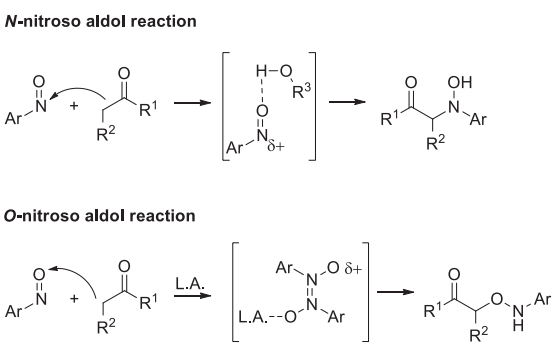



**Scheme 3**. Oxidation and reduction reactions of nitrosoarenes

Nitrosobenzenes readily participate as an electrophile in nucleophilic addition reactions. Carbon-based nucleophiles are commonly used and, depending upon the nucleophile and type of reaction, either C–N or C–O bond formation is possible. Nitroso compounds are the prototype of ambident electrophiles, with reactions proceeding through the oxygen or the nitrogen atom. Thus, both C–O and C–N bonds are accessible from a single source.

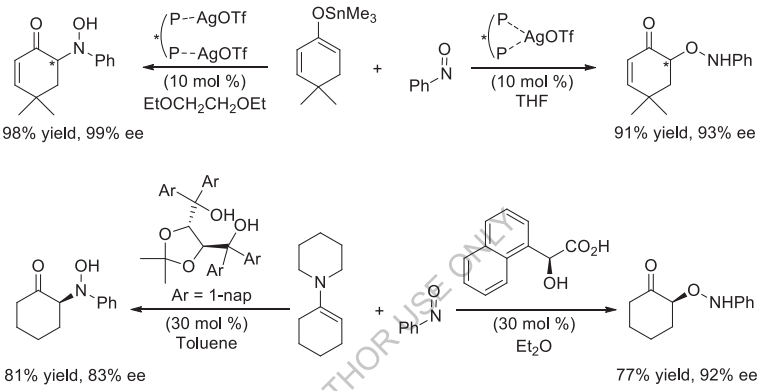
The reaction of aromatic nitroso derivatives with enolizable carbonyl compounds (nitroso aldol reaction) is an important synthetic method (Scheme 4).[30] The main problem of the nitroso aldol reaction is its regioselectivity. If the addition takes place on the nitrogen atom of the nitroso group, α-amino carbonyls are obtained through an α-oxyamination process. On the other hand, when the addition takes place on the oxygen atom of the nitroso group, α-hydroxy carbonyls are obtained through an α-aminoxylation reaction. In general, the regioselectivity of the reaction can be controlled by the action (or absence) of an acid. Whereas the reaction proceeds through *N*-addition with *in situ* generated or preformed enolates (usually, lithium, tin, or silicon), *O*-addition is observed if the reaction is catalyzed by a Lewis acid or Brønsted acid. It has been suggested that in the Lewis acid promoted reaction, the aminoxy compounds could come from a nitroso dimer generated *in situ* in the presence of the Lewis acid. The same rationale can be applied to the reactions catalyzed by a Brønsted acid. Strong Brønsted acids interact with the more basic nitrogen atom to facilitate attack at the oxygen center, whereas weak acids, such as alcohols, prefer to interact with the oxygen and direct the nucleophilic attack on the nitrogen center. Simple enolates would give rise to hydroxyamino compounds through the nitroso monomer.






**Scheme 4**. *N*-nitroso and *O*-nitroso aldol reactions

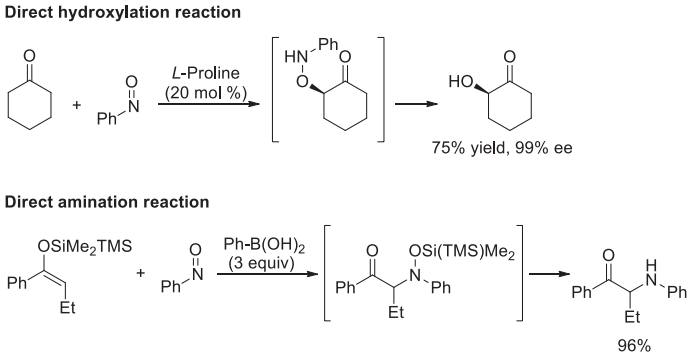
In recent years, remarkable advances have been made in the use of nitroso compounds for preparing α-hydroxy and α-amino carbonyl compounds in an enantioselective way through asymmetric α-aminoxylation and α-oxyamination reactions, respectively. Several examples of this reaction have been reported, including the use of enamines as enolate equivalents. By employing metal[31] and organic catalysts[32] a range of α-amino and α-hydroxy carbonyl derivatives can be generated with total regioselectivity and high levels of enantiomeric excess (Scheme 5). [33]






**Scheme 5**. Stereoselective nitroso aldol reactions

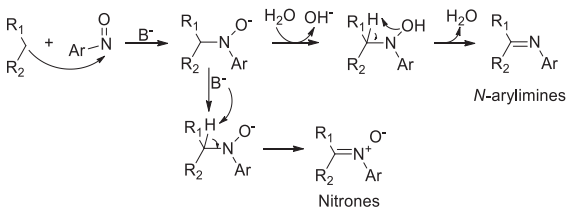
In last few years, there has been also little progress in the one-pot cleavage of the N–O bond for direct hydroxylation or amination processes, and under optimized conditions, *α*-aminooxy carbonyl compounds can be transformed into the corresponding *α*-hydroxy compounds, or hydroxylamines are transformed into the corresponding amines (Scheme 6).[34]




**Scheme 6**. Nitroso aldol reactions: one-pot cleavage of the N-O bond

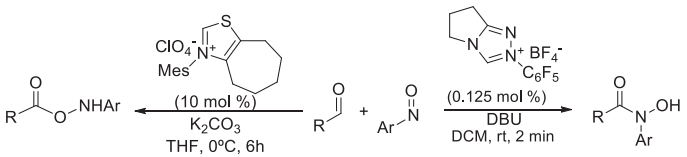
When nucleophilic addition to arylnitroso compounds involves a carbanion derived from active methylene compounds the reaction is denoted Ehrlich-Sachs reaction (Scheme 7).[35] This reaction can be initiated by acid or simply heating, but in most cases, it is triggered by a base. The reaction has been reported catalyzed by a variety of bases and occurs with various active methylene components, including arenemethyl cyanides, malonic esters, β-keto esters, β-diketones, fluorenes, and cyclopentadienes. In this reaction, two competing products can be formed: the dehydrate azomethine derivative[36] and the oxidized nitrone derivative.[37] Azomethine formation tends to be favored over nitrone formation when strong basic catalysts are used but, it is known that the reaction conditions, the acidity of the methylene group, and the structure of compounds with the methylene group all affect the reaction outcome. The predominance of formation of azomethine derivatives in the Ehrlich-Sachs reaction seems to be mainly caused by the electronic effects of the activating groups, which destabilize the adduct and favor rapid elimination of $OH^-$ or $H_2O$.






**Scheme 7**. Ehrlich-Sachs reaction

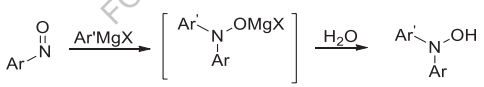
Nitrosobenzenes are also able to undergo crossed benzoin-type reactions with aldehydes, which are frequently catalyzed by *N*-heterocyclic carbenes (NHCs) (Scheme 8). A variety of alkyl, alkenyl, aryl, and heterocyclic aldehydes have been found to undergo the reaction. *N*-Phenylhydroxamic acids can be formed directly from aldehydes by reaction with nitrosobenzene under NHC-catalysis.[38] The Breslow intermediate in these reactions undergoes nucleophilic addition to the nitrogen center of nitrosobenzene. A different NHC catalyst leads to *O*-acyl hydroxylamines through a nucleophilic addition of the Breslow intermediate to the oxygen center of nitrosobenzenes.[39]




**Scheme 8**. Crossed benzoin-type condensations with aldehydes

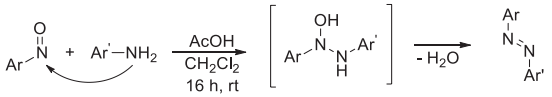


With regard the reactivity of organometallic compounds with nitrosobenzenes, reaction of aryl magnesium halides yields *N,N*-diarylhydroxylamines, indicating nucleophilic addition and reacting as carbonyl analogues (Scheme 9).[40]



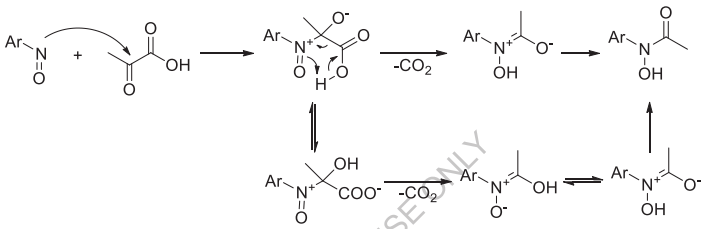

**Scheme 9**. Nucleophilic addition of Grignard reagents

Nitrosoarenes also react with nitrogen nucleophiles such as amines,[41] hydroxylamines or hydrazines. The condensation reaction of nitrosoarenes and anilines, denoted Mills reaction, yields diarylazoxy derivatives (Scheme 10).[42]




**Scheme 10**. Nucleophilic addition of anilines

Due to the free electron pair on nitrogen, nitrosobenzenes can act in some instances as nucleophiles. For the addition of nitrosoarenes to a carbonyl group, the presence of a leaving group capable of heterolytic cleavage adjacent to the carbonyl carbon is essential,[43] or the reaction must be carried out in the presence of a powerful catalyst. An example is the reaction of benzaldehyde with nitrosobenzene in the presence of aluminum propoxide.[44] In the presence of an acid as catalyst, nitrosoarenes add to formaldehyde, acetaldehyde, trifluoroacetaldehyde, glyoxylic acid, and pyruvic acid to give the corresponding *N*-arylhydroxamic acids (Scheme 11).[45] Regarding the mechanism, the first step is a nucleophilic attack of the nitroso group on the carbonyl group, followed by a decarbonylation of the intermediate and protonation.

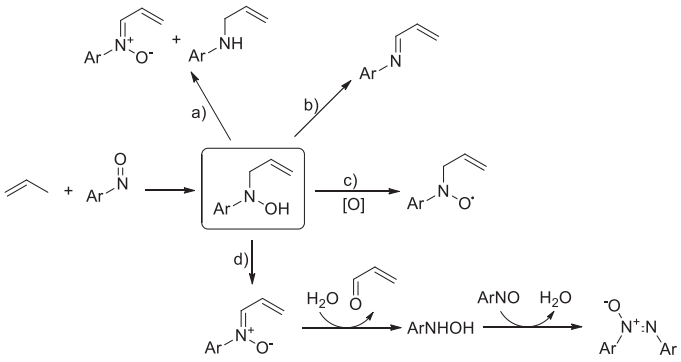



**Scheme 11**. Nitrosoarenes as nucleophiles



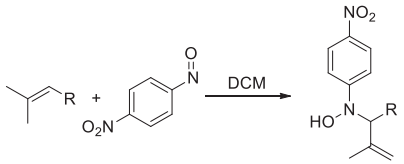
As a consequence of their low LUMO energy, nitroso compounds belong to the class of most reactive enophiles. The mode selectivity of the nitroso reactions with double bonds has not been systematically studied: with dienes, a [4+2] cycloaddition is usually the exclusive pathway; with alkenes that bear an allylic hydrogen atom, an ene reaction usually prevails.

The nitroso ene reaction constitutes a mild, valuable methodology for the direct regio- and stereoselective allylic nitrogen functionalization of alkenes.[46] Usually, the initially formed hydroxylamine ene products undergo subsequent *in situ* reaction such as oxidation, disproportionation, and elimination. As a result, nitrones, nitroxides, imines, amines, and azoxy compounds can be the final products of these reactions (Scheme 12).




**Scheme 12**. *In situ* transformations of the hydroxylamines derived from the nitroso ene reaction

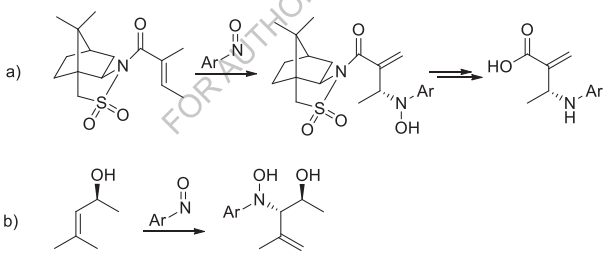
Ene products derived from electron-rich nitroso compounds (e.g., 4-nitrosophenol, *N,N*-dimethyl-4- nitrosoaniline) undergo almost entirely disproportionation along path a. On treatment with acids and bases or on heating, the resulting hydroxylamine dehydrates to the corresponding imine (path b). The oxidation of the ene products from nitrosoarenes by adventitious oxygen or by an "excess" of nitroso compound leads to the relatively persistent nitrosyl radicals path c. Hydroxylamines that bear a hydrogen atom at the *N*-substituted carbon may be further oxidized to nitrones (path d), which are labile species and undergo polymerizations, 1,3-cycloadditions, or are solvolyzed. The solvolysis leads to the respective carbonyl compound and the hydroxylamine; the latter condenses with another equivalent of the nitroso compound to an azoxyarene. Fortunately, electron-withdrawing groups at the nitroso functionality not only increase the enophilic reactivity, but also afford relatively persistent hydroxylamine products. Therefore, most work on the nitroso ene reaction has employed electron-poor enophiles such as α-chloro nitroso compounds, acyl nitroso compounds, pentafluoronitrosobenzene and 4-nitronitrosobenzene (Scheme 13).[47] In recent years, the efforts are been centered in the implementation of nitroso-ene reactions in the synthesis of natural products.[48]




**Scheme 13**. Ene reactivity of lone-substituted 2-methyl-2-butenes with 4-nitronitrosobenzene

A large number of publications have appeared on the mechanism of this pericyclic process, nevertheless, the nature of the involved intermediates and the structures of the transition states are not well resolved. The complex reaction pathways are dependent on the substituents. Evidently, both steric and electronic interactions with the substituents of the alkene control the regioselectivity. In general, the stereoselectivity of the ene reaction may be controlled by steric or electrostatic shielding of one π face of the double bond. To achieve stereochemical control, despite several successful chiral auxiliary-based systems (Scheme 14, a),[49] the use of inherent chirality adjacent to the reactive site has been explored (Scheme 14, b).[50]

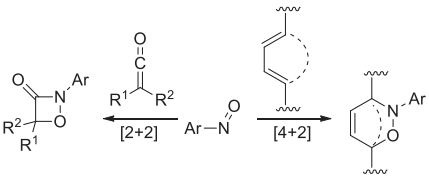





**Scheme 14**. Stereoselectivity control in nitroso ene reactions

In addition to nitroso-ene reaction, further electrocyclic reactions include [2+2] and [4+2] cycloadditions. The nitroso hetero-Diels–Alder reaction involves the formation of the 3,6-dihydro-*2H*-1,2-oxazines in a single step from nitroso dienophiles and dienes in a [4+2] cycloaddition reaction (Scheme 15). The resulting adducts are useful compounds and allow further functionalization towards various derivatives, which shows their versatility in organic synthesis. The nitroso Diels–Alder reaction has become a general tool to synthesize a great number of important compounds. The success of this methodology may be explained in part by the high

selectivity of this reaction. The observed high regioselectivity results from various electronic effects and the stereoselectivity can be influenced by the use of chiral dienes or dienophiles or the application of asymmetric catalysis. Several groups have made great contributions to the development of this transformation and many aspects of the nitroso hetero-Diels-Alder reaction have been reviewed.[51] The high regio- and stereoselective implantation of nitrogen and oxygen functionalities to 1,3-diene systems has resulted in the reaction often being an important step in the synthesis of natural products and biologically active compounds.[52]




**Scheme 15**. [4+2] and [2+2] cycloaddition reactions



Whereas the [4+2] cycloaddition of nitroso compounds with dienes has been intensively used in organic synthesis, the [2+2] cycloaddition of nitroso derivatives with olefins is not well investigated. Scarce examples of stereoselective catalyzed cycloadditions of ketenes with aryl nitroso derivatives have been reported, and 1,2-oxazetidine-3-ones are obtained in good selectivities (Scheme 15).[53] Ketenimines[54] and electron-rich olefins[55] also undergo [2+2] cycloadditions with nitroso derivatives.

Nitrosoarenes are valuable building blocks in heterocycle-forming reactions. In addition to the heterocycles formed directly as a result of cycloaddition reactions, or by subsequent transformations on the obtained adducts, nitrosobenzenes are also readily converted into substituted nitrones, which participate in [3+2] cycloadditions with electron-deficient alkenes to form isoxazolidines.[56] Nitroso compounds can also be converted into substituted indoles through annulation reactions with alkynes.[57] [3+2]-Annulations of *N*-hydroxy allenylamines with nitrosoarenes allow the one-pot synthesis of substituted indole products through nitrosyl radicals generated in the presence of a copper catalyst and $O_2$.[58]

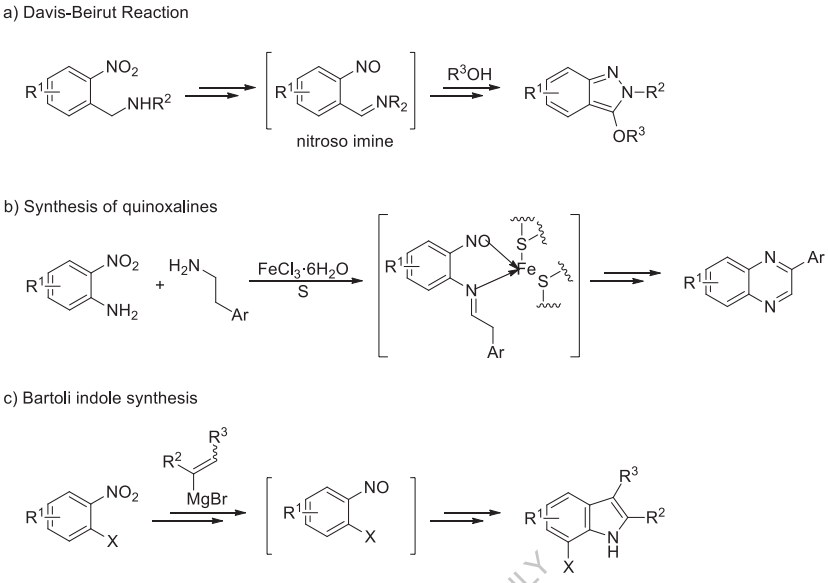
In addition to processes involving participation of electron pairs, nitrosobenzenes are also susceptible to one-electron processes, involving radicals and radical ions. Nitrosobenzenes can be converted into radicals by some oxidizing or reducing agents, photochemically, or by electrochemical processes. Electronic structure of NO group

with high energy HOMO orbital and possibility of n<-π* and π<-π* transition is responsible for pronounced photochemical and electrochemical reactivity. They also react readily with other free radicals and act as radical traps.[17] This reactivity is the base of a great number of reactions of nitroso compounds; for example, the synthesis of unsymmetrical aromatic azoxy compounds by silver-mediated oxidative coupling of aromatic amines with nitrosoarenes reported recently take place through a radical pathway.[59]

Nitroso compounds are also important as intermediates in organic reactions,[60] specially when nitro compounds participate (Scheme 16). Most nitroso compounds are typically generated *in situ* because of their instability and high reactivity. The nitro group can be employed as a good nitroso precursor for the generation of reactive nitroso surrogates. For example, the Davis-Beirut reaction is a method that exploits the diverse chemistries of a key nitroso imine intermediate generated *in situ*.[61] The resulting N-N bond-forming heterocyclization between nucleophilic and electrophilic nitrogens can be leveraged for the synthesis of *2H*-indazoles (Scheme 16, a). This reaction was further expanded to produce a variety of indazole derivatives from a broad range of starting materials under acidic or basic conditions.[62]

Nitrosoarenes are also intermediates in the synthesis of other nitrogen-containing heterocycles. For example, nitroso group participates in the generation of quinoxalines through an iron/sulfur co-catalyzed redox condensation reaction between *o*-nitroanilines and phenethylamines (Scheme 16, b).[63]

Nitrosoarenes are also intermediates in the Bartoli indole synthesis which make use of vinyl magnesium halides and *o*-substituted nitroarenes (Scheme 16, c).[64] Three equivalents of the vinyl Grignard reagent are necessary for the reaction to achieve full conversion. The first step in the mechanism reaction consists of the nitro group reduction to the nitroso derivative.[65] The steric bulk of the group in the *ortho* position assists in the [3,3]-sigmatropic rearrangement required for product formation. One advantage of the Bartoli indole synthesis is the ability to produce indoles substituted on both the carbocyclic ring and the pyrrole ring.



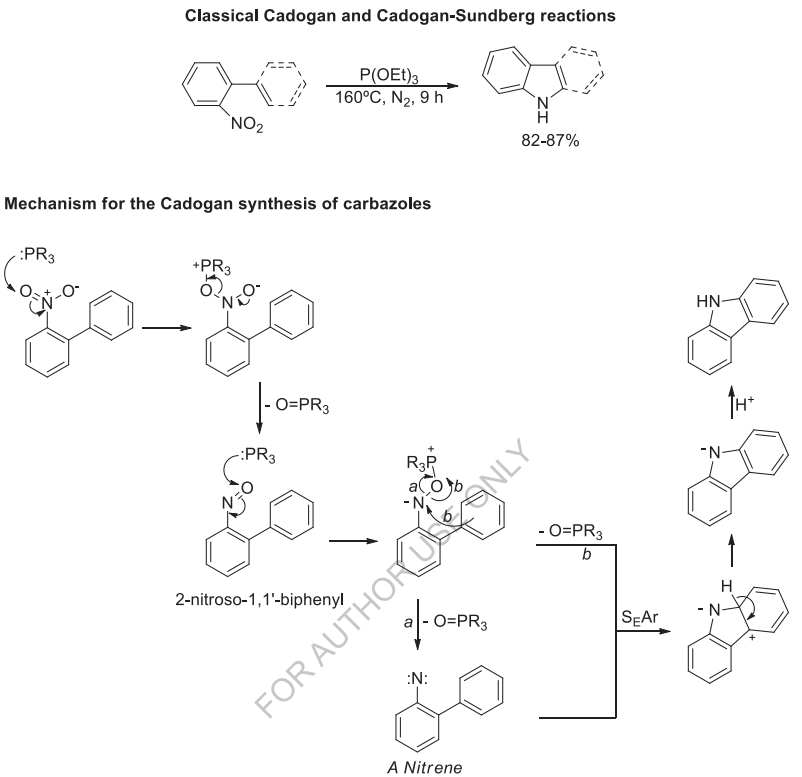

**Scheme 16**. Examples of nitrosoarenes as intermediates in reactions of nitro compounds



Nitrosoarenes are intermediates in the Cadogan synthesis of indole derivatives. Cadogan/Cadogan-Sundberg cyclization reaction has been reported as one of the most efficient routes for the synthesis of a wide variety of *N*-heterocycles from nitroarenes by treating with trivalent phosphorus compounds (trialkyl- or triarylphosphines or trialkylphosphites). Cadogan and Bunyan carried out reductive annulation of 2-nitrobiaryls by heating them with $P(OEt)_3$ leading to the formation of carbazoles. Sundberg extended the ring annulation strategy for the synthesis of indole from *o*-nitrostyrene under Cadogan conditions (Scheme 17).[66] The driving force of the process is the formation of the strong, thermodynamically favored O=P bond in $O{=}PR_3$.[67] The formation of the product involves the nucleophilic attack of a lone pair of $PR_3$ on the oxygen atom of the starting nitro group followed by removal of $O{=}PR_3$ and resulted in the formation of nitroso intermediate. The nucleophilic attack of $PR_3$ on oxygen atom of nitroso group affords an intermediate which may undergo a $S_E$Ar reaction via any of the two pathways involving nitrene (a) or non-nitrene (b).

The reductive cyclization of nitroarenes using trivalent phosphorous reagents to synthesize heterocycles via nitroso intermediates have been extensively studied.

Substituted carbazoles, indoles, indazoles and other nitrogen-containing heterocycles have been efficiently prepared by using this methodology.[68]

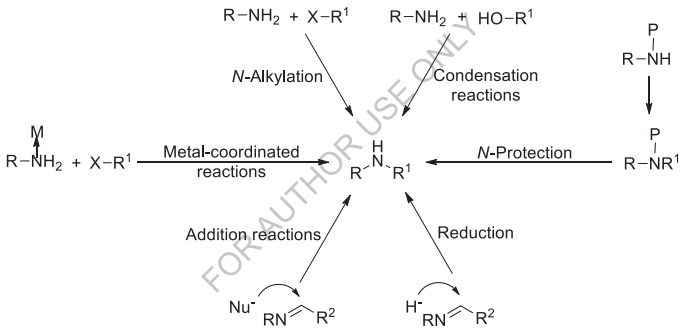



**Scheme 17**. Cadogan synthesis of carbazoles

The reactions detailed in this chapter clearly demonstrate that nitrosoarenes are very powerful and efficient building blocks in organic synthesis. Transition-metal-catalyzed or alternatively metal-free nitroso reactions provide versatile access to an impressive array of substituted *N*/*O*-heterocycles. The versatile reactivity of nitroso group results in numerous side reactions, which is one of the reasons why nitroso compounds have received limited attention in organic synthesis; nevertheless, such diversity should be advantageous for developing new and efficient synthetic methods based on nitroso chemistry.

## 3. Synthesis of Secondary Amines from Nitrosoarenes

Syntheses of amines have perhaps received more attention than the preparation of many other compounds in organic chemistry. With the growing repertoire of biologically relevant nitrogenous molecules, so is the need for efficient synthetic methods to prepare amines as useful intermediates. Due to their interesting physiological activities, secondary amines in particular are extremely important pharmacophores in numerous biologically active compounds, which have greatly been touted in the area of drug discovery. The most general transformations to prepare secondary (hetero)arylamines include direct alkylation of anilines with alkyl halides,[69] C-N cross-coupling reactions,[70] electrophilic aminations,[71] and reductive amination reactions.[72] Illustrated in Scheme 18 is a brief classification for the major traditional methods for the synthesis of secondary amines.




**Scheme 18**. Traditional methods for the synthesis of secondary amines

### 3.1. Synthesis of Alkylarylamines

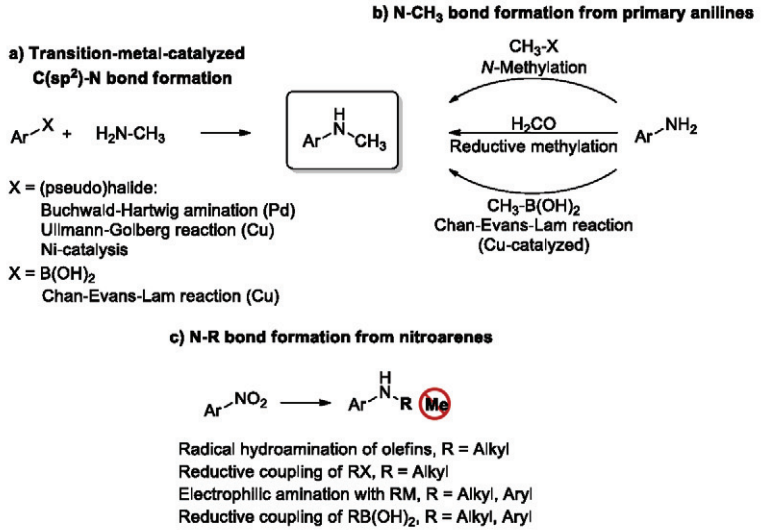
#### 3.1.1. General Methods for the Synthesis of Methylarylamines and Other Alkylarylamines

Traditionally, secondary alkylarylamines have been prepared by *N*-alkylation of primary arylamines by treatment with an alkyl halide in the presence of a base.[69, 73] However, selective synthesis of *N*-alkylanilines is often intricate due to the difficulty in preventing the formation of the corresponding tertiary *N,N*-dialkylarylamine.

Direct alkylation with excess aniline in the presence of an alkyl halide is not feasible in order to prepare secondary amines in good yields simply because the formation of tertiary amines and quaternary ammonium salts is usually the dominant reaction process. To avoid overalkylation, aniline derivatives can be protected and subsequent alkylation is performed. Although dialkylation is avoided, protection/deprotection steps are needed. Also, alcohol condensation with aromatic amines has enjoyed great synthetic utility in the introduction of alkyl functionality on nitrogen. Numerous catalysts have been explored in the reaction of aromatic primary amines with alcohols to form the product containing substantially *N*-alkyl monosubstituted aromatic amines.[74] In addition, secondary *N*-alkylated anilines can be prepared by reductive alkylation of a primary aromatic amine with different carbonyl compounds.[75]

Among secondary alkylarylamines, mono-*N*-methyl aromatic amines are relevant compounds due to they are common scaffolds among pharmaceutical, dye, and agrochemical compounds.[76] Despite the apparent simplicity of the NHMe functionality, the synthesis of this motif is far from easy. Most general methods to prepare these compounds are based on the construction of the C($sp^2$)−N or the N−Me bonds and use free amines as starting materials (Scheme 19).

The most frequent approaches centered on the construction of the C($sp^2$)−N bond make use of methylamine and functionalized aryl electrophiles under transition-metal catalysis (Scheme 19, a).[77] A few examples of the synthesis of mono-*N*-methylaniline derivatives by the Cham−Evans−Lam reaction using arylboronic acids have been reported,[78] and specific Pd-based[79] (Buchwald−Hartwig amination) and Cu-based[80] (Ullmann−Goldberg reaction) systems have been developed for the coupling reactions of methylamine with aryl (pseudo)halides. Some scattered examples under Ni catalysis have been also reported,[81] as well as the use of aryl organometallics together with nitrogen electrophiles.[82] In limited cases, transition-metal-free reactions between methylamine and activated substrates are possible by $S_NAr$ or via benzyne intermediates.[83] However, because of its small size, methylamine is a particularly challenging amine to monoarylate by these procedures due to its tendency to diarylate.




**Scheme 19**. Common strategies for the synthesis of secondary methylanilines and other alkylanilines



The strategy based on the construction of the N–Me bond (Scheme 19, b) makes use of primary anilines as starting materials. Reactions of primary arylamines with $S_N2$-methylating agents[84] are usually hampered by overmethylation, due to the small steric hindrance of the methyl group and the increased nucleophilicity of the monomethylated secondary aromatic amine in comparison to the nonmethylated starting material. To control overalkylation, the use of acyl[85] or sulfonyl[86] derivatives of the starting amines as precursors is frequent, but this requires the inclusion of protection/deprotection steps in the reaction sequence, which may be cumbersome. Reductive amination approaches for methylation require the use of formaldehyde as a carbon source together with a reducing agent.[87] Also, the reduction of carbamates[88] or formamides[89] is feasible. However, some of these reduction procedures may be incompatible with the presence of other labile functional groups. To circumvent some of these issues, recent methods that make use of carbon dioxide[90] or MeOH[91] have been developed. Even so, these methods require high temperatures and the use of transition metals and complex ligands. In addition to these procedures, the alkylation of (hetero)arylamines can also be accomplished by the Cu-catalyzed Chan–Evans–Lam reaction using alkylboronic acids.[92] However, when applied to

methylation, the method requires overstoichiometric quantities of copper salts and methylboronic acid and dimethylation is frequent under these reaction conditions.[93]

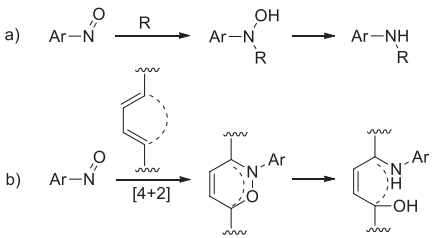
In many occasions, the primary arylamines used as starting materials for the construction of the N−C bond are prepared in advance by the reduction of other nitrogen-containing functional groups (Scheme 19, c). Therefore, the direct engagement of these functionalities in amine formation has emerged as a relevant strategy for the synthesis of secondary arylamines because it eliminates the previous reduction step and avoids protection of functional groups that may be labile to the reduction conditions. In this realm, nitro compounds have been used most frequently.[94] For example, it has been described the Fe-catalyzed synthesis of *N*-alkylanilines through an *in situ* generated nitroso intermediate, which is subsequently trapped by highly reactive alkyl radicals derived from alkenes[95] or alkyl halides.[96] Although successful for the synthesis of various alkylarylamines and diarylamines, this sort of strategy has been elusive for the particular case of the NHMe group.[97]

As a consequence of the prevalence of alkylarylamines in the industry new synthetic methods for their synthesis are constantly emerging.[98]



## 3.1.2. Synthesis of Alkylarylamines from Nitroso Compounds

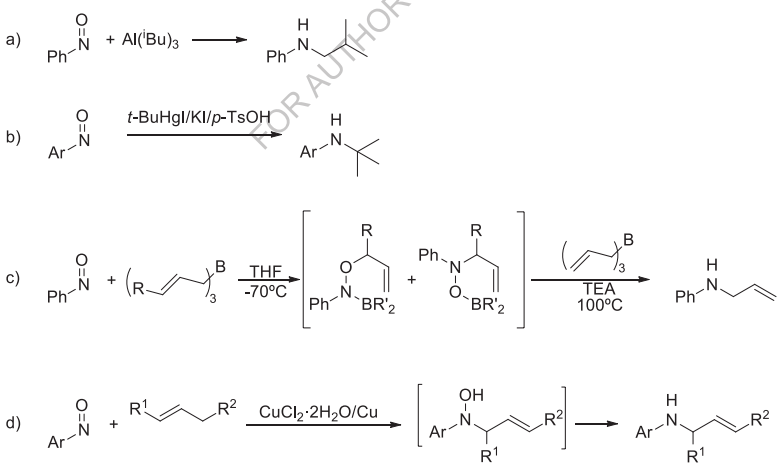
Nitrosoarenes have been used as nitrogen source in the synthesis of secondary anilines. The synthesis frequently requires two reactions. In a first step, nitrogen atom on nitrosoarenes reacts with the corresponding substrate and a hydroxylamine is formed. Reduction of this functional group allows the obtention of the secondary amine (Scheme 20, a).[99] An alternative is that the nitrosoarene undergoes a cycloaddition reaction as first step. The cleavage of the N-O bond in the final adduct affords the secondary amine (Scheme 20, b).[100]




**Scheme 20**. Synthesis of secondary anilines from nitrosoarenes in two reactions

Both protocols are well established and are usually used. However, the direct synthesis of secondary amines form nitroso compounds is not so common, but some examples have been reported. Reactions with organometallic reagents or the use of metal catalysis are the most common strategies for these synthesis. In the beginnings, reactions of nitrosoarenes with different alkylating reagents were investigated and often mixtures of products were obtained, among them, the corresponding secondary amines. For example, nitrosobenzene reacts vigorously with $^{i}Bu_3Al$ in benzene to give, after hydrolysis, a mixture of products including diamine (40%), aniline (20%) and azobenzene (12%) (Scheme 21, a).[101] Deoxigenation of nitrosoaromatics by photolysis with *t*-BuHgI/KI/*p*-TsOH afforded through a radical addition pathway, *t*-butylanilines in good yields (Scheme 21, b).[102] The allylic amination of nitrosoarenes has been achieved using triallylboranes (Scheme 21, c).[103] The allylboration of nitrosobenzene resulted in the formation of *N*- and *O*-allyl derivatives of *N*-phenylhydrazine, which were reduced with a second allylborane molecule to *N*-allylaniline above 100°C. Allylanilines are also synthesized by ene reaction of nitrosoarenes with alkenes[104] to produce *N*-allylhydroxylamines, which can deoxygenate *in situ* with Cu(I) (Scheme 21, d).[105]



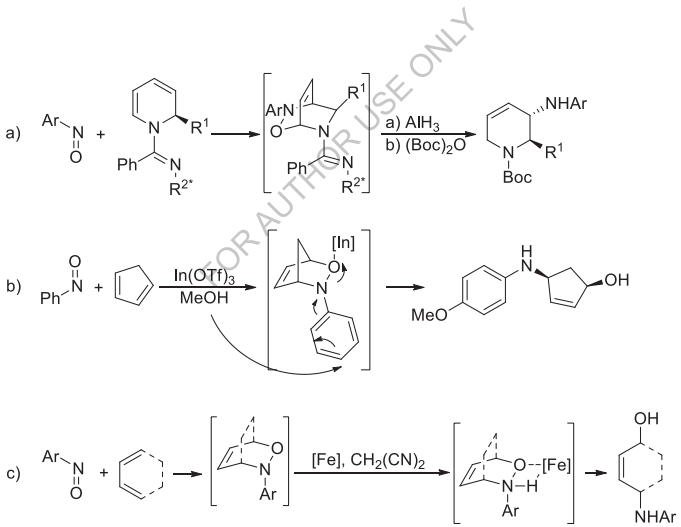



**Scheme 21**. Synthesis of secondary alkylarylamines from nitrosoarenes

Synthesis of alkylarylamines with functional groups in the alkyl chain are usually carried out in one-pot processes having the cleavage of a N-O bond as final step. The cycloadducts resulting of the [4+2] cycloaddition reaction of nitrosoarenes with

cyclic alkenes are frequently used as intermediates in the synthesis of alkylamines with amine or hydroxyl groups. For example, the stereoselective synthesis of *trans*-2-substituted 3-amino-1,2,3,6-tetrahydropyridines was achieved by cycloaddition of nitrosobenzenes with 2-substituted 1,2-dihydropyridines followed by *in situ* chemoselective reduction of the cycloadducts (Scheme 22, a).[106] Indium triflate-assisted nucleophilic aromatic substitution reactions of nitrosobezene-derived cycloadducts in the presence of alcohols afford secondary amines with free hydroxyl groups in their structures (Scheme 22, b).[107] The reaction might be initiated by coordination between the oxygen atom in intermediate oxazine and indium to generate an electron-deficient intermediate, which is susceptible to the addition of methanol to the aromatic ring. Tautomerization of the resulting imines and rearomatization afford the final aniline. On the other hand, a consecutive [4+2]-cycloaddition/N–O-bond cleavage catalyzed by a Fe-complex using malononitrile as reductant allow an efficient way for the synthesis of 1,4-aminoalcohols (Scheme 22, c).[108]

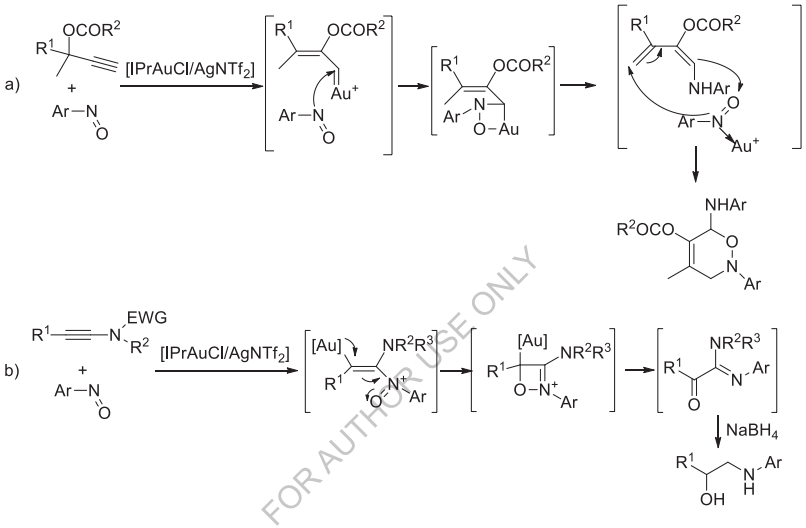





**Scheme 22**. Synthesis of secondary alkylarylamines from nitrosoarenes with [4+2] cycloaddition reactions as key step

Alkenylgold carbenoids are useful intermediates in reactions with nitrosobenzenes. These species are formed by interaction of alkynes with a gold catalyst. The synthesis of some oxazines have been achieved using this methodology (Scheme 23, a). Nitrosobenzene initially attacks at the C(1)-carbene carbon to generate nitrosonium

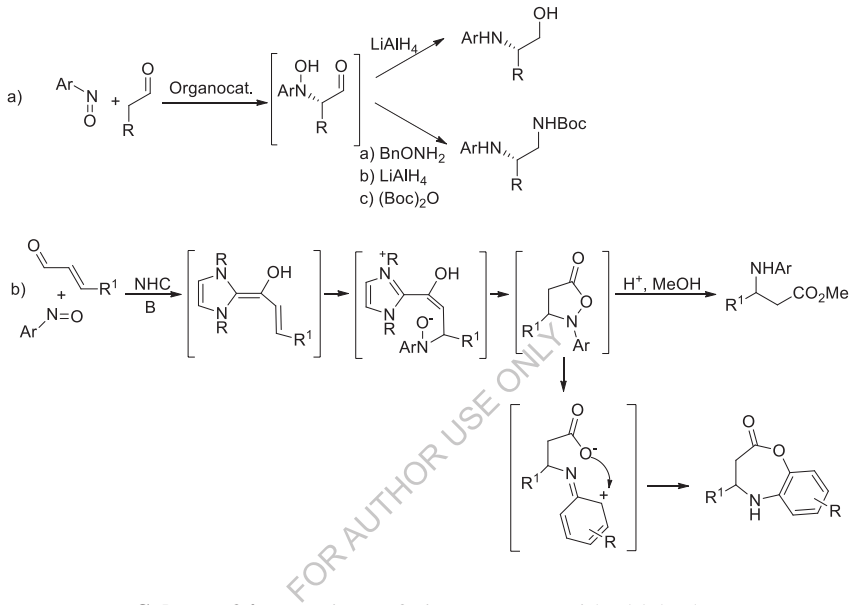
species that subsequently forms gold-containing oxazetidines via a metathesis pathway. Gold-coordinate nitrosobenzene is highly electrophilic and becomes attacked by 1-aminodiene to give the observed oxazines ultimately.[109] On the other hand, using an aminoalkyne and gold catalysts, a distinct 1,2-difunctionalization using nitrosobenzene was observed (Scheme 23, b). Through an alkyne/nitroso metathesis, an oxoimination product was obtained, and 1,2-aminoalcohols were obtained via $NaBH_4$ reduction *in situ*.[110]




**Scheme 23**. Reactions of nitrosoarenes and alkynes under gold catalysis

An alternative to achieve 1,2-difunctionalization in the alkyl chain of secondary anilines, are the one-pot procedures developed to prepare α-amino alcohols or 1,2-diamines starting from nitrosobenzenes and aldehydes in the presence of an amine as quiral organocatalyst (Scheme 24, a).[111] The resulting hydroxyamination product was treated with $LiAlH_4$ and an amino alcohol was obtained. The same intermediate could be converted to the fully protected 1,2-diamine without loss of enantiopurity by the one-pot procedure including *O*-benzyloxime formation, reduction of the N=C double bond and reductive cleavage of two N-O bonds with $LiAlH_4$, and Boc protection. Reaction of α,β-unsaturated aldehydes and nitrosobenzenes can be catalyzed by *N*-heterocyclic carbenes (Scheme 24, b). Under NHC catalysis conditions, enals react with nitroso compounds via homoenolate intermediates to give isoxazolidin-5-ones

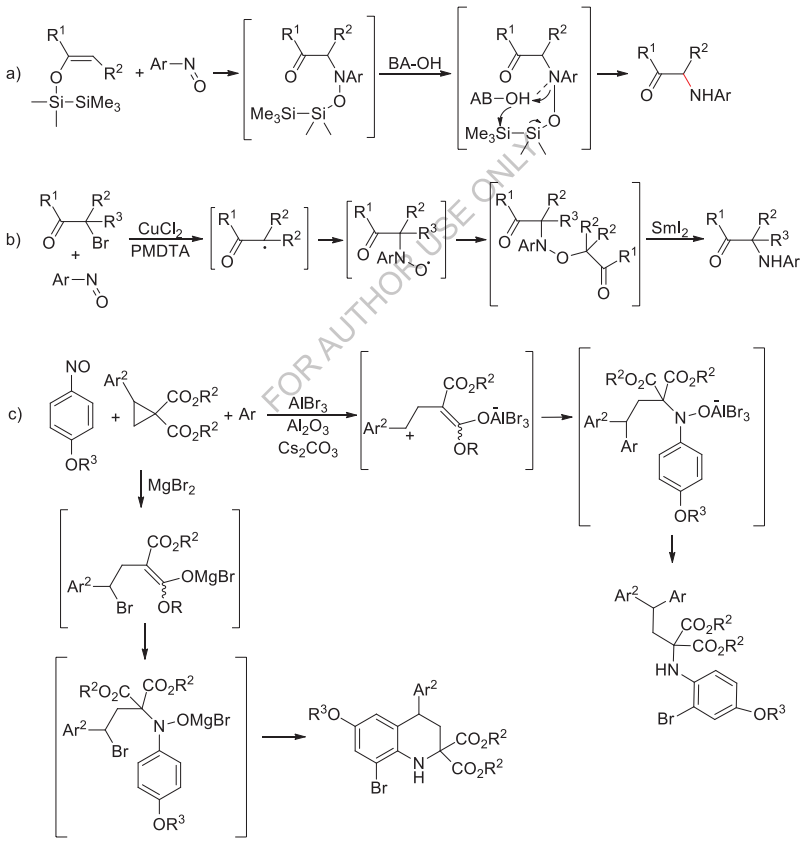
that can be easily converted into the corresponding β-amino acid derivatives by an esterification/Bamberger-like rearrangement sequence.[112] On the other hand, the use of a different *N*-heterocyclic carbene in the presence of DBU as a base catalyzed the annulation of enals with nitroso compounds and seven-membered 4-azalactones were formed.[113]




**Scheme 24**. Reactions of nitrosoarenes with aldehydes

The synthesis of α-amino carbonyls compounds using nitrosoarenes as nitrogen source is a common transformation. For example, the Brønsted acid mediated N-O bond cleavage for α-amination of ketones has been developed through the aromatic nitroso aldol reaction of nitrosoarenes and silyl enol ethers having a disilane backbone (Scheme 25, a).[114] This transformation affords structurally diverse α-amino ketones in high yields. On the other hand, the Cu-catalyzed radical addition with *in situ* generated nitroso compounds has allowed the synthesis of sterically hindered amines (specifically α-amino carbonyls) directly from readily available materials (Scheme 25, b).[115] The synthesis of amines with two carbonyl substituents at α-position has been achieved by $AlBr_3$-mediated multicomponenet 1,3-bifunctionalization of donor-acceptor cyclopropanes using arenes and nitrosoarenes as coupling partners.[116] This reaction affords γ,γ-disubstituted *N*-arylated α-amino esters as products (Scheme 25, c).

Ring-opening of the cyclopropanes with $AlBr_3$ generates a reactive benzylic cation, which directly undergoes Friedel−Crafts type alkylation. The resulting enolate further reacts with *p*-alkoxynitrosobenzene. N−O bond cleavage is assisted by the alkoxy group in *para* position. Notably, reaction with $MgBr_2$ occurs *via* a different pathway.[117] Ring-opening with $MgBr_2$ provides a benzylic bromide. As in the alumininum chemistry, the Mg-enolate is then α-aminated by the nitrosoarene. *o*-Bromination and N−O bond cleavage and subsequent intramolecular Friedel-Crafts alkylation affords a tetrahydroquinoline. Hence, the difference in the bromination aptitude of the Lewis acid in the initial ring-opening step determines the reaction outcome to give either the 1,3- bifunctionalization products or tetrahydroquinolines.





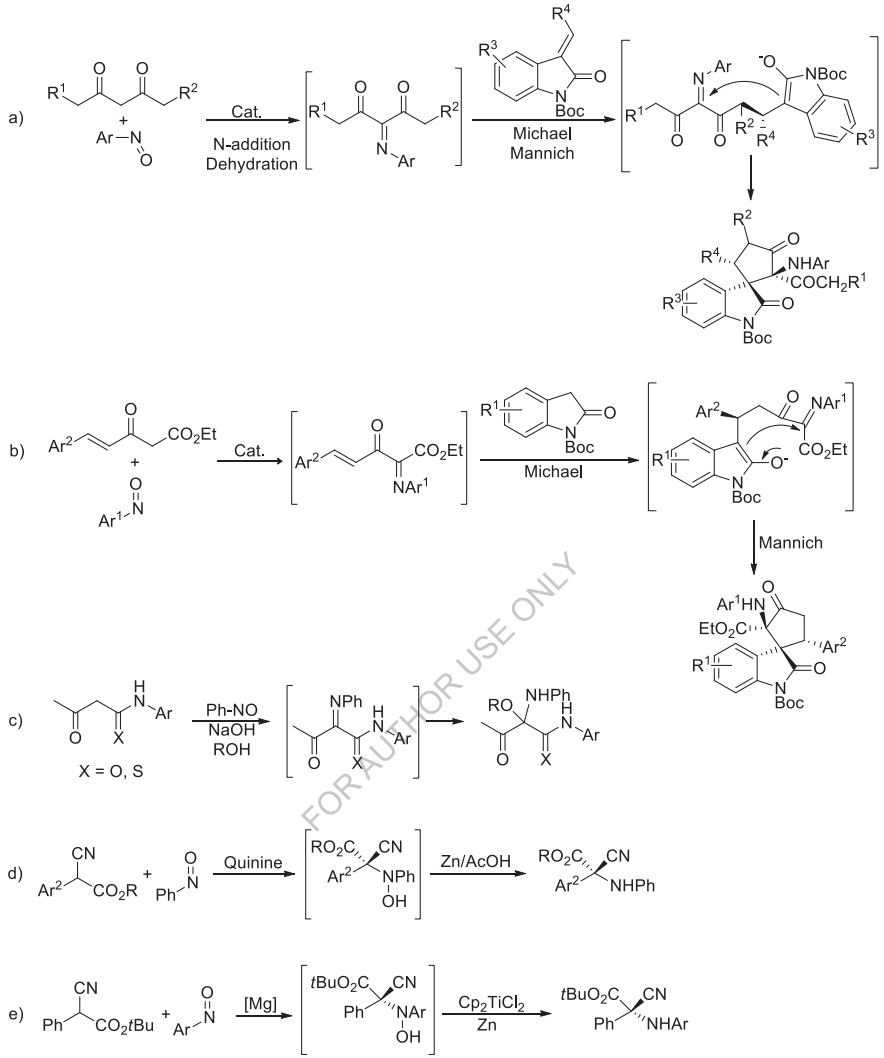

**Scheme 25**. Synthesis of α-amino carbonyls compounds

The synthesis of α-imino-β-dicarbonyl compounds has been also achieved using nitrosoarenes and 1,3-dicarbonyl compounds. In 2015, a one-pot reaction was performed in the presence of a bifunctional quinine-derived squaramide catalyst and provides simple and efficient access to five-membered spirocyclic oxindoles bearing three contiguous stereocenters and two adjacent quaternary centers in excellent yields and stereoselectivities (up to>20:1 dr, >99% ee) (Scheme 26, a).[118] The process starts with a *N*-selective addition to nitrosobenzene. Subsequent intermolecular Michael addition of the resulting ketimine with methyleneindolinone followed by the final cyclization afford the products. Later, this protocol has allowed the enantioselective construction of multifunctionalized spirocyclopentane oxindoles bearing α,α-bisubstituted α-amino-β-keto esters (Scheme 26, b).[119] The reaction is initiated by base-catalyzed *N*-selective addition of the Nazarov reagent on nitrosobenzene. Subsequently, enolization of the oxindole is promoted by the tertiary amine group and the α,β-unsaturated ketone moiety is activated by the same catalyst. This initiated the cascade intermolecular Michael/Mannich reaction to furnish the final annulation product.

In addition, other 1,3-dicarbonyl compounds have been used for the synthesis of secondary amines. The study on the reactivity of *N*-(2′-aryl)acetoacetamides with nitrosobenzene furnished the expected amines in the presence of alcohols (Scheme 26, c).[120]



In 2007, Jørgensen and coworkers reported the amination of α-aryl-α-cyanoacetates with nitrosobenzene in high yields but moderate enantioselectivity (22–59% ee values) using a cinchona alkaloid as catalyst (Scheme 26, d).[121] The process is catalyzed by quinine and shows *N*-chemoselectivity, giving the corresponding (*S*)-α-arylamine after *in situ* reduction of the hydroxylamine precursors. Recently, highly enantioselective amination of α-aryl-α-cyanoacetates with 2-nitrosoarenes by using an efficient *N,N*'-dioxide/$Mg(OTf)_2$ complex as catalyst has been achieved (71-92% ee) (Scheme 26, e).[122] The N-O bond cleavage was achieved by the use of Zn and a titanium catalyst.





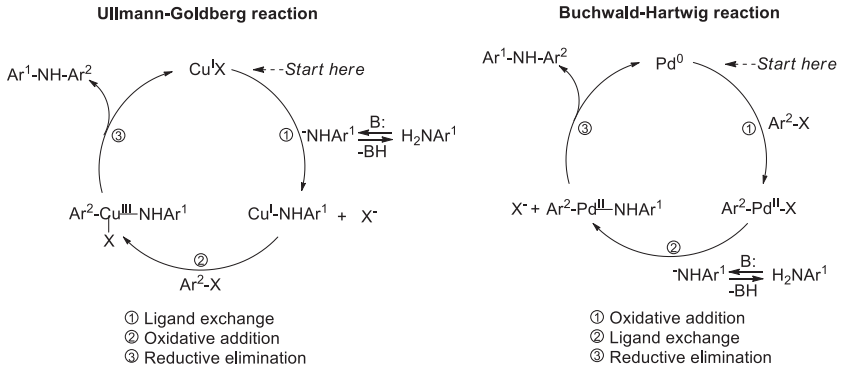

**Scheme 26**. Synthesis of α-imino-β-dicarbonyl compounds

## 3.2. Synthesis of Diarylamines

### 3.2.1. General Methods for the Synthesis of Diarylamines

Diarylamines constitute an important class of organic compounds, frequently found among drugs, agrochemicals, dyes, radical-trapping antioxidants, electroluminescent materials, and ligands for transition-metal catalysis.[123] The most popular current methods for the synthesis of diarylamines make use of anilines and aryl halides as starting materials in transition-metal-catalyzed coupling reactions. The most important procedures are the Ullmann-Goldberg[124, 125] and the Buchwald-Hartwig[126] reactions (Scheme 27). Both reactions share in common the *in situ* generation of an organometallic species of the type $Ar^1NH\text{-}M^{(n+2)}\text{-}Ar^2$ by the interaction of $Ar^1NH_2$ and an aryl halide ($Ar^2X$) with an organometallic catalyst ($M^nL$, L = ligands). The Ullmann-Goldberg reaction requires $Cu^I$ species, while the Buchwald-Hartwig reaction requires $Pd^0$ species. Both reactions are carried out in the presence of a base which is needed to equilibrate the starting aniline with the corresponding amide, which is nucleophilic enough to displace an anionic ligand from an electrophilic metallic intermediate (ligand exchange). The dummy ligands are crucial because they serve to stabilize the metallic intermediates in solution, avoiding the precipitation of elemental Cu or Pd. The $Ar^1NH\text{-}M^{(n+2)}\text{-}Ar^2$ key intermediate is generated by oxidative addition. Reductive elimination gives the final product ($Ar^1\text{-}NH\text{-}Ar^2$) and regenerates the catalytically active species ($M^nL$).



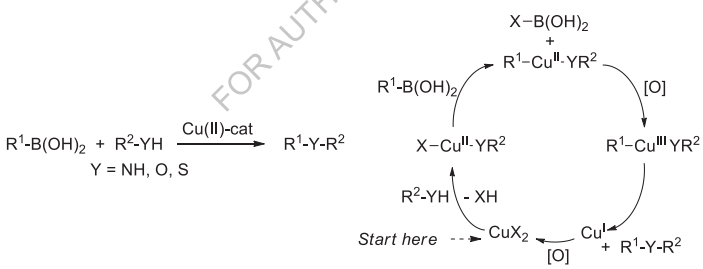



**Scheme 27**. The Ullmann-Goldberg and Buchwald-Hartwig reactions

In the Ullmann-Goldberg reaction ($Cu^{I}/Cu^{III}$ catalytic cycle), the amide displaces a ligand from a $Cu^{I}$ species to generate a $Cu^{I}$-$NHAr^{1}$ intermediate. In the oxidative addition step, the $Cu^{I}$-$NHAr^{1}$ species interacts with the aryl halide to generate a $Cu^{III}$ intermediate ($Ar^{2}$-$Cu^{III}(X)$-$NHAr^{1}$) which evolves to the final product by reductive elimination. This step regenerates the catalytically active $Cu^{I}$ species. In the Buchwald-Hartwig reaction[127] ($Pd^{0}/Pd^{II}$ catalytic cycle), the oxidative addition step (generation of $Ar^{2}$-$Pd^{II}$-X) goes first. Ligand exchange followed by reductive elimination renders the final product together with recovery of the catalytically active $Pd^{0}$ species.

The Chan-Evans-Lam reaction[128] is one of the most popular methods for the formation of C-N bonds (Scheme 28). This cross-coupling is generally performed by reaction of boronic acids derivatives as carbon source with substrates involving nitrogen containing functional groups such as amines, amides, ureas, hydrazine, carbamates, sulfonamides or different heterocycles (imidazole, pyrazole, indole). It requires a stoichiometric amount of copper (II) or a catalytic amount of a copper catalyst. In this case, an oxidant is needed to ensure the catalytic cycle. The reaction with a stoichiometric amount of copper (II) is also facilitated by oxygen, because reductive elimination from a copper (III) species is faster.






**Scheme 28**. Chan-Evans-Lam reaction

The Chan-Evans-Lam reaction ($Cu^{I}/Cu^{II}/Cu^{III}$ catalytic cycle) can be understood starting by ligand exchange between $CuX_2$ and $R^{2}$-YH (in many occasions a base is included to equilibrate $R^{2}$-YH with the corresponding anion, which is more nucleophilic, and thus more active in the ligand exchange process). This gives rise to a new $Cu^{II}$ species (X-$Cu^{II}$-$YR^{2}$). A second ligand exchange (transmetalation of $R^{1}$ from B to Cu) affords another $Cu^{II}$ intermediate ($R^{1}$-$Cu^{II}$-$YR^{2}$). In order for coupling between $R^{1}$ and $YR^{2}$ to occur smoothly (reductive elimination), oxidation (air) to a

$Cu^{III}$ species is required. Reductive elimination affords the coupling product and $Cu^{I}$, which must be oxidized (air) to regenerate the active $Cu^{II}$ catalyst. The reaction can also be performed with boronic esters and potassium organotrifluoroborates. This synthesis of amines offers many advantages over others such as mild reaction conditions, inexpensive catalyst, good functional group tolerance, use of air and variety of substrates. In addition to the formation of C-N bonds, the Chan-Evans-Lam reaction is also a method for the formation of C-O and C-S bonds using boronic acids and phenols or thiols, respectively.

In addition to the synthesis of diarylamines, the aforementioned metal-catalyzed reactions of amines (Cham-Evans-Lam, Ullmann-Goldberg and Buchwald-Hartwig) have been also used for the synthesis of secondary alkylarylamines. Although general, these cross-coupling reactions require the use of expensive metallic catalysts. Many of them are highly toxic and sensitive to air and/or moisture. Residual traces of heavy metals in the final product can be difficult to remove. Due to their potential toxicity, this is not acceptable in pharmaceutical applications. In addition, these methods are usually inadequate to prepare sterically hindered diarylamines[129] and can be rather limited by the synthetic availability of the starting anilines.

Other typical approaches for the synthesis of diarylamines make use of electrophilic nitrogen reagents and their reaction with carbon nucleophiles.[130] In general, the nucleophilic addition of main-group organometallics to *N*-containing compounds have been extensively used for the synthesis of diarylamines.[131] For example, reactions of arylmagnesium compounds with nitroarenes,[94] arylazatosylates,[94] or azides under Cu catalysis[132] have been reported. In general, copper-catalyzed coupling reactions have been recognized as one of the most useful strategies for the formation of C–N bonds.[133] However, given the importance of diarylamines in the industry, new approaches for their synthesis are continuously being reported.[134]



### 3.2.2. Synthesis of Diarylamines from Nitroso Compounds

Direct synthesis of diarylamines from nitrosoarenes has not received much attention and there are only scarce examples reported in the literature. The addition of functionalized arylmagnesium reagents to nitrosoarenes furnishes after a reductive workup with $FeCl_2$ and $NaBH_4$ polyfunctional diarylamines in 43-74% yield (Scheme 29, a).[135] Addition of functionalized aryl or heteroaryl zinc reagents to various

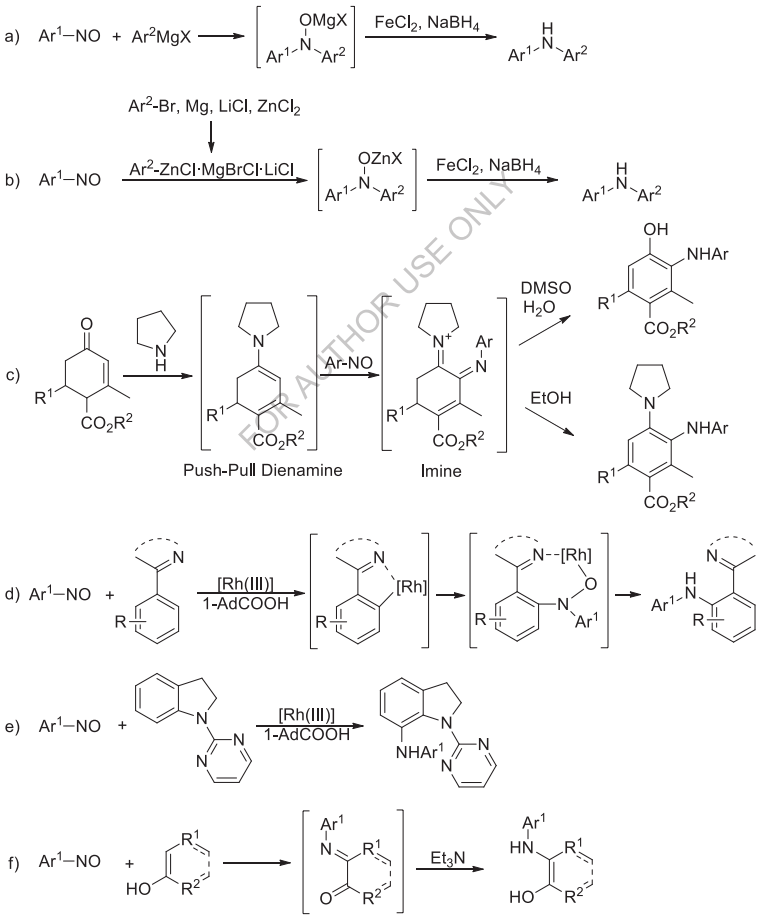
nitrosoarenes in the presence of magnesium salts and LiCl in THF produces after a reductive work-up the corresponding di(hetero)arylamines in high yields (Scheme 29, b).[136] However, these methods have a somewhat limited functional group scope due to the high reactivity of the carbon-metal bond. This is specially 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).

Other methods reported for the direct synthesis of diarylamines from nitroso compounds require the presence of heteroatom in the arene structure to achieve the C-N bond formation. For example, a one-pot organocatalytic selective process for the cascade synthesis of highly substituted *o*-hydroxydiarylamines and *o*-pyrrolidin-1-yldiarylamines have been reported (Scheme 29, c).[137] The cascade enamine amination/isoaromatization reaction furnished highly functionalized anilines with high yields. Different products can be obtained depends on the reaction conditions. The possible reaction mechanism starts with the formation of the dienamine thermodynamic stable as major product. The reaction of push-pull dienamine with nitrosoarenes furnishes the selectively nitroso aldol product, which will give an imine product by losing the hydroxide ion. Hydrolysis followed by isoaromatization of imine product converted into highly substituted *o*-hydroxydiarylamine. On the other hand, imine was transformed into highly substituted *o*-pyrrolidin1-yldiarylamines via isoaromatization under suitable conditions (EtOH and MS 4A). Hydrolysis of imine intermediate is more solvent dependent, which means this hydrolysis step is faster in DMSO than in EtOH, perhaps due to more interactions with water. Later, the cascade enamine amination/isoaromatization/*O*-allylation sequence by using this methodology was reported.[138]



An alternative route to diarylamines starting from nitrosobenzenes is the Rh(III)-catalyzed direct amination of arenes bearing a nitrogen containing substituent (Scheme 29, d).[139] Different directing groups, such as *N*-based heterocycles and ketoximes, can be used in this C-H amination process. Coordination of the nitrogen atom with the rhodium catalyst, and subsequent *o*-directed C-H bond activation, results in a rhodacycle. Then, coordination and subsequent nucleophilic addition (or N=O insertion) of nitroso compound takes place. The N-O bond cleavage in the resulting hydroxylamine takes place by a radical pathway in the presence of $O_2$. In a related work, the synthesis of 7-amino-substituted indolines by using this procedure was described (Scheme 29, e).[140]

Recently, an unprecedented metal free arylamination reaction involving nitrosoarenes as the electrophilic aminating agents has been reported (Scheme 29, f).[141] The direct arylamination of a broad range of substrates, such as naphthols, hydroxyquinolines, hydroxyquinones, coumarins and 1,3-cyclohexadienones was achieved under mild conditions without the aid of additional reagents/steps for N–O bond reduction. A plausible reaction course for this metal-free reductive arylamination process starts with the formation of an iminoquinone by the reaction between the naphthol derivative and nitrosoarene. $Et_3N$ reduced this intermediate to produce the desired aminated product.




**Scheme 29**. Synthesis of diarylamines from nitrosoarenes

# 4. Reactions of Nitrosoarenes with Boronic Acids

## 4.1. Structure, Properties and Reactivity of Boronic Acids

Boronic acids[142] are trivalent boron compounds that possess one carbon-based substituent and two hydroxyl groups, which are oriented in a trigonal planar geometry (Figure 1). With six valence electrons, the $sp^2$ hybridized boron atom has a low-energy empty *p* orbital, which is orthogonal to the three substituents. Therefore, they can act as a mild class of organic Lewis acid capable of coordinating nucleophiles (Lewis bases). When doing so, the resulting tetrahedral adducts, called borates, acquire a carbon-like configuration (rehybridization to generate a $sp^3$ boron). The reactivity and properties of boronic acids highly depend upon the nature of their single variable substituent R, more specifically, on the type of carbon group directly bonded to boron. Based on this substituent, boronic acids can be classified into subtypes such as alkyl-, alkenyl-, alkynyl-, and arylboronic acids. Of all of them, the latter are the most well-known class of boronic acids; their popularity is in large part due to their role as cross-coupling partners for the synthesis of biaryl units, which are present in the structure of several pharmaceutical drugs.



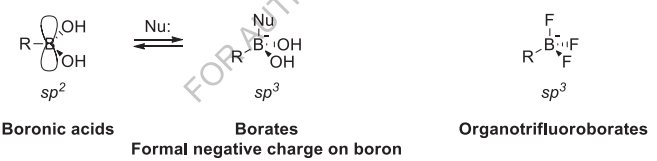



**Figure 1**. Boronic acids, borates and organotrifluoroborates

Most boronic acids exist as solids that can be manipulated in ambient air without special precautions. These compounds are also stable in water in a wide range of pH. At ambient temperature, boronic acids are chemically stable and most display shelf stability for long periods of time, although boronic acids tend to exist as mixtures of oligomeric anhydrides, in particular, the cyclic six-membered boroxines (Figure 2). Boronic esters (or boronates) are boronic acid derivatives formed between a boronic acid and an alcohol. These derivatives possess similar characteristics and properties than boronic acids, and are used in similar way in organic reactions.

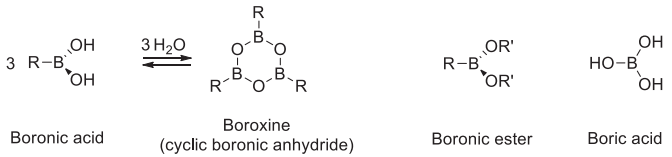



**Figure 2**. Boroxine, boronic ester and boric acid

Among the stable tetracoordinated adducts, the organotrifluoroborate salts[143] are a class of boronic acid derivatives that can be easily prepared from boronic acids with a concentrated solution of potassium bifluoride ($KHF_2$) (Figure 3). These crystalline derivatives are easy to handle and are competent substrates in many of the same reactions that employ free boronic acids.

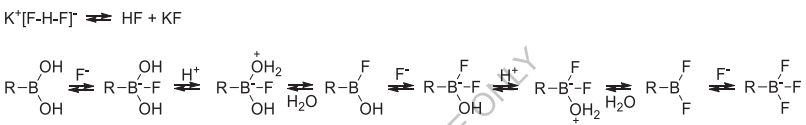



**Figure 3**. Synthesis of organotrifluoroborates from boronic acids



Most boronic acids present no particular toxicity compared to other organic compounds,[144] and do not require a particular environmental threat, because boronic acids in air and aqueous media undergo slow oxidation into boric acid (a very stable and relatively benign compound to humans, Figure 2), a relatively innocuous compound, which may be toxic only under high daily doses.[145] Their properties and reactivity as Lewis acids, coupled with their stability and ease of handling, are what make boronic acids a particularly attractive class of synthetic intermediates. Moreover, because of their low toxicity and their ultimate degradation into boric acid, boronic acids can be regarded as green (environment-friendly) compounds.

In addition to their use as synthetic intermediates, boronic acids have other many applications in chemistry as catalysts and promoters[146] and their use have been extended to fields such as chemical biology and molecular recognition,[147] materials science,[148] and medicine.[149] This increasing importance has motivated the development of efficient methods to provide access to these compounds. Although methods like the oxidation or hydrolysis of trialkylboranes bear a significant historical and fundamental relevance, modern methods of practical value for synthetic

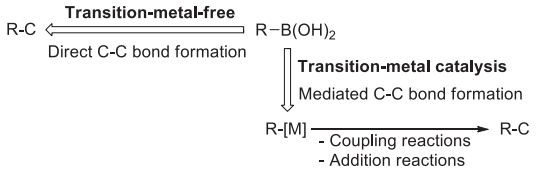
chemists has been developed in recent years.[150] Traditionally, boronic acids are prepared through transformations that involve transmetalation from highly reactive organometallic intermediates, such as organolithium or organomagnesium species (accessible through halogen-metal exchange from organic halides), that react with trialkylborates. Another approach for the synthesis of boronic acids has been the transition-metal-catalyzed borylation reactions of C–X and C–H bonds. In recent years, the use of transition-metal-free methods for the synthesis of organoboron compounds has also received much attention.[151] As a consequence of their growing popularity and advances in methods available for their preparation, a few thousands of functionalized boronic acids have become available from several commercial sources.

Boronic acids and their derivatives can act as carbon nucleophiles, like Grignard reagents, organolithiums or cuprates, which are among the most common carbon nucleophiles used in organic synthesis. However, these popular reagents are air and water sensitive and they must be used under inert gas atmosphere and in anhydrous solvents. In addition, most cuprates must be generated *in situ* and are sensitive to temperature. In contrast to main-group organometallics, and as mentioned above, boronic acids are bench-stable carbon nucleophiles that do not require handling under inert atmosphere or in anhydrous solvents. Additionally, they are compatible with many functional groups readily attacked by conventional organometallic reagents, such as carbonyl, OH or NH groups, thus avoiding additional protection/deprotection steps. However, these boron reagents are less nucleophilic than conventional organometallics. Mayr and coworkers evaluated the nucleophilicity of organoboron compounds towards the design of transition-metal-free C–C bond forming reactions.[152] The comparison of the nucleophilicity of boron reagents with other carbon nucleophiles has put forward nucleophilicity of boronic acids in between that of organolithiums and organosilicons.



As a result of its moderate nucleophilicity, the most popular reactions of boronic acids require catalysis by transition metals and proceed by transmetalation to generate intermediate C-Metal species, which are the actual nucleophiles (Scheme 30); boronic acid acts as an ultimate carrier of the carbon framework and the transition-metal being the true species responsible for the bond forming process. Thus, the most popular C–C forming reactions of these reagents such as couplings with aryl- and alkenylhalides and surrogates (the Suzuki–Miyaura reaction),[153] couplings with alkenes and alkynes (Heck-type reactions), conjugate additions (Hayashi–Miyaura

reaction),[154] and additions to C=O and C=N bonds are usually catalyzed by transition metals.[155]

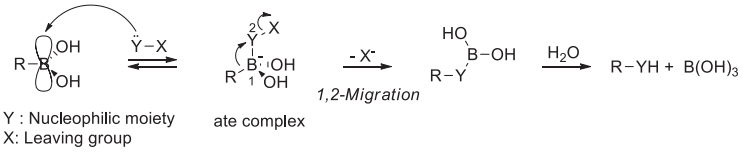



**Scheme 30**. Methods for C–C bond formation with boronic acids

However, boronic acids are nucleophilic enough to participate in several C-C and C-heteroatom bond formation processes directly without the need for metal catalysis. This aspect of the reactivity of boronic acids is less well-known and is currently an active area of research. Activation of boronic acids by transformation into borates (Figure 1) enhances their ability to transfer their carbon backbone to electrophilic sites inter- or intramolecularly. The uncatalyzed addition of boronic acids to imines and iminiums (the Petasis reactions and its variants) for the synthesis of substituted amines was disclosed in 1993 and has been extensively reviewed.[156] Several new methods for C–C bond formation using boronic acids under transition-metal-free conditions have emerged in recent years.[157] Comparatively, C-Heteroatom bond-forming reactions under metal-free conditions have remained scarce until recently.[158]



In many occasions, the process of *ipso*-substitution in boronic acids and their derivatives is achieved without the need of the assistance of transition metals (Scheme 31). Addition of a nucleophile specie Y-X (where Y is a heteroatom-based nucleophilic center and X a moiety that can act as a leaving group) to the vacant *p*-orbital of the boronic acid generates a tetravalent boron "ate" complex. The heightened electron density on the boron and increased steric crowding in the borate facilitate R-B bond dissociation and subsequent 1,2-migration of the carbon backbone from boron to the adjacent acceptor atom with simultaneous detachment of the leaving group X.[159] Protonation ($H_2O$) renders the final product and boric acid.




**Scheme 31**. The *ipso*-substitution reaction in boronic acids

Extending the scope of the synthetically valuable reactions of user-friendly boronic acids under transition-metal-free conditions for the formation of C-N bonds is a matter of current interest with wide utility from a green perspective.

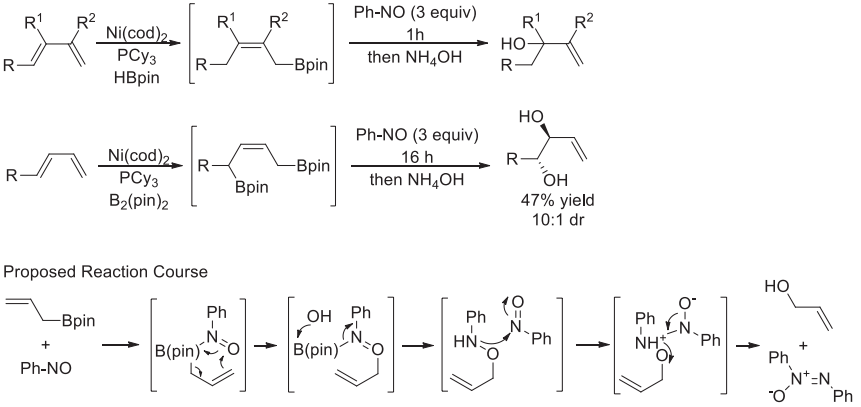
## 4.2. Reactions of Nitrosoarenes with Boronic Acids Derivatives

To date, reactions of nitrosoarenes have been only reported with two classes of boronic acid derivatives: allylboronic esters and arylboronic acids.



### 4.2.1. Reactions with Allylboronates

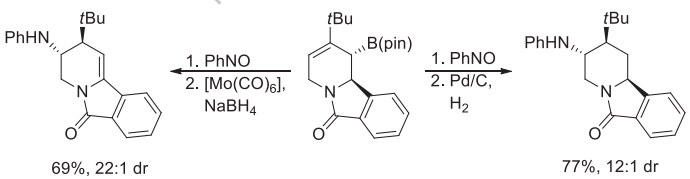
In 2010, Morken reported the allylation of nitrosobenzene with pinacol allylboronates.[160] Addition of nitrosobenzene to pinacol allylboronates leads to oxidation of the organoboron with concomitant rearrangement of the substrate alkene. Remarkably, the N-O bond was cleaved during the reaction such that simple alcohols are the final reaction products (Scheme 32). Different substrates were explored in the tandem hydroboration/oxidation sequence. To study the capacity for diastereoinduction in the nitrosobenzene-mediated allylboronate oxidation reaction, a chiral 1,4-diboryl-2-alkene was generated by Ni-catalyzed diene diboration and subjected to the nitrosobenzene allylation reaction. When nitrosobenzene was added to diboronate and followed by oxidative work-up, the diol was isolated in 10:1 *anti:syn* stereoselection and in moderate yield. The predominant reaction pathway occurs by addition of the allylboron to the oxygen atom of the nitrosobenezene. Presumably, the enhanced basicity of nitrogen relative to oxygen results in N-B bonded complex wherein nitrosobenzene has coordinated to the boronate. It was surmised that a second molecule of nitrosobenzene and the Brønsted base might conspire to cleave the N-O bond of the initial allylation product.




**Scheme 32**. Synthesis of alcohols by allylation of nitrosobenzene

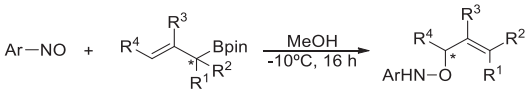
Later, Ready and coworkers studied the reactivity of dihydropyridine boronic esters.[161] As part of their research, they carried out the amination of an allyl boronic ester with nitrosobenzene followed by reduction with $[Mo(CO)_6]/NaBH_4$. An enamide was generated with very high diastereoselectivity. Alternatively, hydrogenation with Pd/C gave a tetrasubstituted piperidine with a dr value of 12:1. By contrast of previous results reported by Morken, they observed complete *N*-selectivity to afford the indicated amine products instead of alcohols (Scheme 33).






**Scheme 33**. Synthesis of amines by allylation of nitrosobenzene

In 2015, Studer and coworkers reported an efficient approach to chiral allyloxyamines by stereospecific allylation of nitrosoarenes with chiral allylboronates (Scheme 34).[162] The bond forming reaction features complete regioselectivity (O-selectivity) and excellent chirality transfer. The products of this *O*-allylation reaction were obtained with excellent stereospecificity and in most cases very high *E/Z* selectivity.

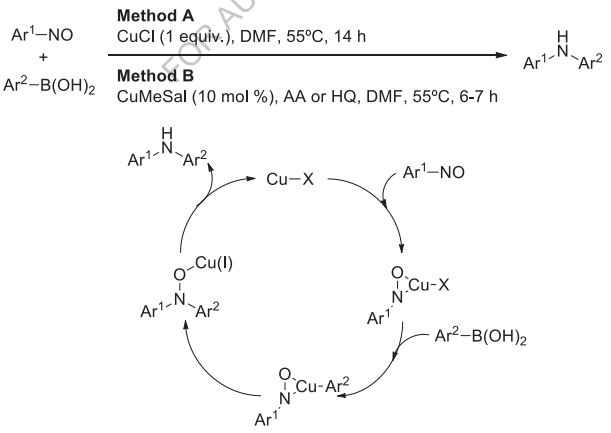



**Scheme 34**. Synthesis of allyloxyamines by allylation of nitrosoarenes

## 4.2.2. Reactions with Arylboronic Acids

In 2002, the group of Liebeskind developed a catalytic reaction of aryl or alkyl boronic acids with *N*-thioimide derivatives to selectively produce thioethers under neutral conditions.[163] Based on this discovery, the same group further explored the copper-catalyzed reactions of various aromatic nitroso compounds with boronic acids, which provided an interesting synthetic complement to existing procedures for C-N bond-formation reactions.[164] The Cu(I)-mediated reductive amination of arylboronic acids with nitroso aromatics reported by Liebeskind is mediated by a stoichiometric amount of CuCl as both a catalyst and a reducing agent. Alternatively, 10% Cu(I)-3-methylsalicylate (CuMeSal) catalyzes the same reaction in the presence of either ascorbic acid or hydroquinone as the terminal reducing agent. Diarylamines were obtained in good yields (65-87%) (Scheme 35).



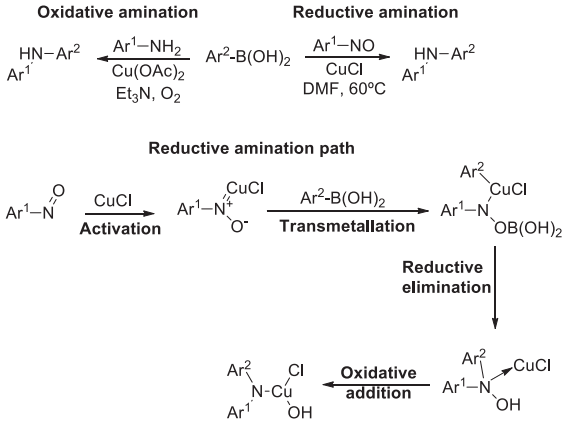



**Scheme 35**. Synthesis of diarylamines from nitrosoarenes and arylboronic acids under Cu(I) catalysis

A suggested mechanism for the reaction starts with the side-on complexation of Cu(I) with the nitroso moiety, which generates a formal Cu(III) intermediate that would be susceptible to transmetalation by the boronic acid. Reductive elimination would then generate a Cu(I) alkoxide of an *N*,*N*-diarylhydroxylamine. This intermediate would suffer an internal redox generating the diarylamine and an oxidized Cu species. Under conditions catalytic in copper, the oxidized Cu species would be reduced by ascorbic acid or hydroquinone to a catalytically active form of Cu(I).

Although the yields were very good, this transformation was applied to the synthesis of few diarylamines; three nitrosoarenes and eight arylboronic acids were tested, so only nine different diarylamines were synthesized in total. Later, this procedure has been used in a few cases for the synthesis of some diarylamines.[165]

A comparative investigation of copper-assisted oxidative and reductive amination of aryl boronic acids with arylamines or nitroso benzenes respectively, for the synthesis of bulky diarylamines was performed (Scheme 36).[166] The investigation of the oxidative and reductive approaches indicated that, to obtain sterically demanding diarylamines, reductive amination is preferable. A DFT study of the influence of the electronic properties of the substituents in both reactants on the activation energy revealed that the optimal combination for the synthesis of unsymmetrical diarylamines to provide better yields was an electron-rich aryl boronic acid and an electron-deficient nitroso compound; using these helpful guidelines six bulky (*o*-substituted) diarylamines were obtained. According to the DFT data, the reductive amination reaction path consists of four main steps: activation of the nitrosoarene with copper(I); transmetalation, yielding a copper(II) complex with the transfer of the $B(OH)_2$ group to the oxygen atom of the nitroso; reductive elimination, which restores copper(I) species; and oxidative addition of copper(I) to the N-O bond, which produces the copper(III) complex again.




**Scheme 36**. Synthesis of diarylamines by copper-assisted oxidative and reductive amination of aryl boronic acids with arylamines or nitroso benzenes respectively

However, this methodology, in addition to the use of metal, has been only applied for the synthesis of a limited number of diarylamines. Given the green properties of boronic acids and high reactivity of nitrosoarenes mentioned in previous paragraphs, the general synthesis of secondary amines using these compounds as starting materials in the absence of transition metals is a synthetic method that has great value for synthetic chemists.

## 5. Transition-Metal-Free C-N Bond-Forming Reaction of Arylboronic Acids and Nitrosoarenes: Synthesis of Di(hetero)arylamines[167]

Di(hetero)arylamines are an important scaffold in organic chemistry. This type of secondary amines are frequently found in the chemical structure of compounds with a wide variety of properties and applications in chemical, pharmaceutical and manufacturing industries, among others.[1, 123] For that reason, the development of new methods that allow the synthesis of di(hetero)arylamines under simple, mild, and eco-friendly conditions remains highly desirable. As previously stated, the use of nitrosoarenes in the synthesis of diarylamines has not received much attention and is limited to reactions with heteroatom-substituted arenes[137, 138, 139, 140] and arylmagnesium[135] or arylzinc reagents[136] (so some functional groups in the aromatic rings are not tolerated). Reactions with arylboronic acids promoted by Cu(I) have been only used for the synthesis of a few scope of diarylamines.[164, 165, 166] However, the use of nitrosoarenes and arylboronic acids under adequate reaction conditions could allow the synthesis of a wide variety of substituted di(heteroaryl)amines.

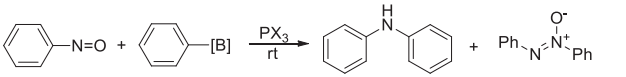


### 5.1. Synthesis of Diarylamines

Based on the proposed mechanism for the Cadogan synthesis of carbazoles from nitroarenes in the presence of trialkyl phosphite species (Scheme 17), in which a nitrosoarene is postulated as an intermediate, the research started by considering the possibility of activating nitroso compounds toward cross-coupling with phenylboronic acid derivatives using trivalent phosphorus species.[68] Under the hypothesis that the intermediate species formed from the nucleophilic attack of $PR_3$ to the nitrosoarene are Lewis bases and can coordinate to the vacant orbital of boronic acid, the studies began by considering the reaction of nitrosobenzene with phenylboronic acid in the presence of $PR_3$ species.[67] $PPh_3$ and $P(OEt)_3$ are the most frequent trivalent phosphorus species used for the activation of nitro compounds in the synthesis of indole derivatives. Both are inexpensive chemicals commonly used in chemistry labs, therefore were selected as promoters of the reaction.

Some optimization studies for the synthesis of diphenylamine by reaction of nitrosobenzene with phenylboronic acid derivatives in the presence of trivalent phosphorous species were carried out and are gathered in Table 1.

**Table 1**. Metal-free cross-coupling between nitrosobenzene and phenylboronic acid derivatives.




Diphenylamine (**D**) Azoxybenzene (**A**)

| Entry | [B] (equiv.) | $PX_3$ (equiv.) | Solvent | D : A ratio | Yield D (%) |
|---|---|---|---|---|---|
| 1 | $B(OH)_2$ (1.0) | $PPh_3$ (2.0) | Toluene | 75 : 25 | 65 |
| 2 | $B(OH)_2$ (1.5) | $PPh_3$ (1.5) | Toluene | 84 : 16 | 69 |
| 3 | $B(OH)_2$ (1.5) | $PPh_3$ (1.2) | Toluene | 95 : 05 | 89 |
| 4 | $B(OH)_2$ (1.5) | $P(OEt)_3$ (1.2) | Toluene | 100 : 00 | 95 |
| 5 | $B(OH)_2$ (1.5) | $P(OEt)_3$ (1.2) | Acetonitrile | 97: 03 | 71 |
| 6 | $B(OH)_2$ (1.5) | $P(OEt)_3$ (1.2) | THF | 100 : 00 | 95 |
| 7 | $B(OH)_2$ (1.5) | $P(OEt)_3$ (1.2) | $CH_2Cl_2$ | 98 : 02 | 93 |
| 8 | $BF_3K$ (1.5) | $P(OEt)_3$ (1.2) | Toluene | 00 : 100 | -- |
| 9 | Bpin (1.5) | $P(OEt)_3$ (1.2) | Toluene | 00 : 100 | -- |



The use of $PPh_3$ in toluene as solvent at room temperature (entries 1-3) affords a mixture of diarylamine and azoxybenzene.[15] When the reaction was promoted by $P(OEt)_3$ instead of $PPh_3$ (entries 4-7) a complete selectivity in favour of the obtention of diarylamine was observed, together with a high isolated yield. In addition to toluene, reaction could also be carried out using alternative solvents as acetonitrile, THF or $CH_2Cl_2$ with good selectivity. The possibility of using boronic acid derivatives was also tested, and potassium phenyltrifluoroborate and phenylboronic acid pinacol ester were used as coupling partners in the reaction with nitrosobenzene (entries 8-9). However, the diamine was not formed when using these compounds.

Therefore, diphenylamine could be synthesized by the reaction of nitrosobenzene with phenylboronic acid in the presence of inexpensive $P(OEt)_3$. The best yield (95%) was obtained in toluene solution at room temperature, 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.

The synthesis of diarylamines bearing substituents in one aromatic ring was achieved using this new metal-free cross-coupling reaction between nitrosobenzene and different arylboronic acids under optimum reaction conditions for the synthesis of diphenylamine (Figure 4).

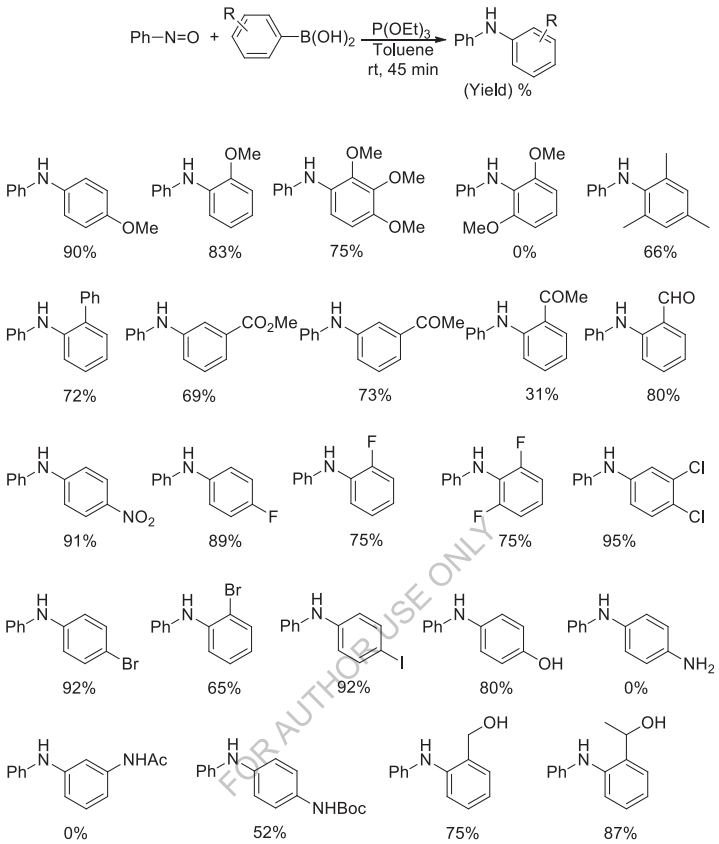





**Figure 4**. Amines synthesized by cross-coupling reaction between nitrosobenzene and arylboronic acids

The reaction was general, either with electron-donor or electron-acceptor substituents on the benzene ring of the arylboronic acids, which is important due to aryl boronic acids bearing electron-withdrawing substituents are often reluctant substrates for the Chan-Evans-Lam synthesis or diarylamines.[168] Some diarylamines with steric hindrance were also prepared by this method; this way, diphenylamines with an *o*-methoxy substituent were synthesized (75-83% yield), although the yield was slightly lower in comparison to *p*-substitution (90%). Unfortunately, double *o*-substitution by methoxy was not permitted and, in this case, only the azoxybenzene

was observed. On the other hand, the diarylamine with double *o*-substitution by a methyl group was synthesized in 66% yield and the amine with *o*-substitution by a phenyl group was obtained in 72% yield. It is important to highlight the fact that the reaction is compatible with functional groups typically reactive against traditional organometallic compounds such as organolithiums or Grignard reagents, such as ester, ketone, or aldehyde, even at the *o*-position (31-80% yield), as well as the $NO_2$ group (91% yield). Tolerance to these functional groups is advantageous, since it avoids protection/deprotection steps. Furthermore, the presence of these groups in the final diarylamine allows further transformations to obtain new diarylamines with more complex structures. With regard to halogenated compounds, diarylamines bearing one or two atoms of F, Cl, Br and I in *ortho*-, *meta*-, or *para*-positions of the aromatic ring could be prepared in good yields (65-92%). 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.[124, 126] The tolerance to free phenolic OH groups were demonstrated with the synthesis of 4-(phenylamino)phenol in 80% yield. Compounds with free alcoholic OH groups were also synthesized starting from the corresponding benzoxaboroles in good yields (75-87%). On the other hand, the reaction did not take place with $NH_2$ or NHAc as substituents of the arylboronic acid component, however, Boc-protection permitted the obtention of the diarylamine with moderate yield (52%).



The synthesis of diarylamines bearing substituents in one aromatic ring could be also carried out using a different approach of this new metal-free cross-coupling reaction, i.e., reaction between phenylboronic acid and different nitrosoarenes (Figure 5). For the sake of comparison, several representative examples that had already been prepared the other way round, i.e., by the reaction of nitrosobenzene with boronic acids (Figure 4), were synthesized. The comparison of results put forward that, in general, diarylamines could be synthesized with a slight increase in yield when starting with substituted nitroso compounds. This approach towards the synthesis of diarylamines with substituents in one aromatic ring proved to be also general for the synthesis of amines with *o*-susbtitution and the presence of functional groups such as ester, ketone, aldehyde, nitro and cyano were well tolerated and amines were obtained with excellent yields (78-96%). Amines bearing halogens or free OH groups could be also prepared by this way (78-97% yields). However, it is important to highlight that, opposite to the previous situation, free $NH_2$ was tolerated as substituent when installed on the nitrosobenzene moiety, and $N^1$-phenylbenzene-1,4-diamine could be prepared in 83% yield. This is an important issue due to anilines are

substrates for the aforementioned metal-catalyzed reactions (Cham-Evans-Lam, Ullmann-Goldberg and Buchwald-Hartwig reactions) for the synthesis of secondary amines, allowing access to more complex diamines. Also, NHAc group was tolerated as substituent in *meta*- and *ortho*-positions, and the corresponding diarylamines were obtained with 83 and 65% yield, respectively. In addition to avoid protection/deprotection steps, tolerance to free OH and $NH_2$ groups is noteworthy due to further transformations of these substituents allow the synthesis of new, more complex molecules.

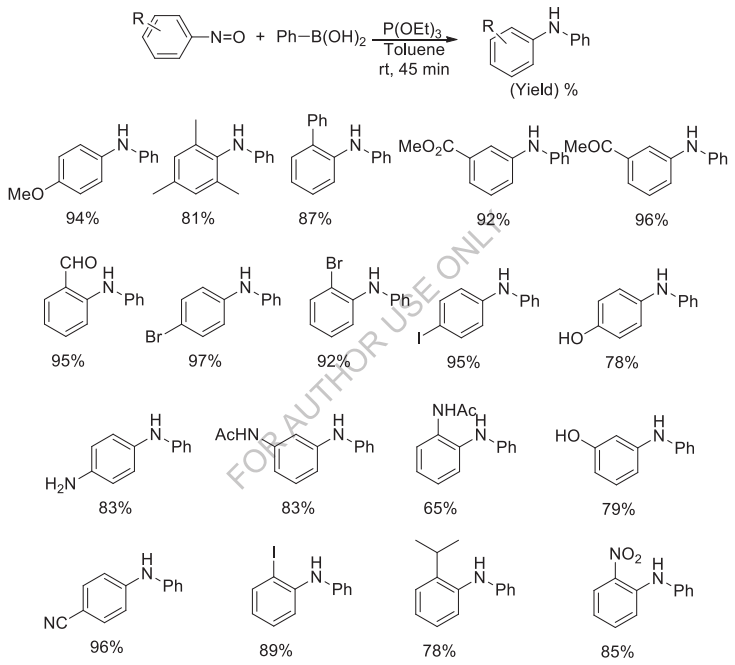



**Figure 5**. Amines synthesized by cross-coupling reaction between nitrosobenzenes and phenylboronic acid

## 5.2. Synthesis of Sterically Hindered Diarylamines

As previously stated, the synthesis of sterically hindered diarylamines,[129, 166] i.e., those carrying *o*-substituents on both aromatic rings, is often challenging. Therefore, the attention was focused on evaluating the performance of this cross-coupling

procedure with nitrosobenzenes and arylboronic acids carrying at least one *o*-substituent each. The results gathered in Figure 6 put forward that this cross-coupling reaction admits the presence of two *o*-substituents with good yields (82-89%), including the bulky isopropyl group. Amines with three *o*-substituents were obtained with good yields (45-87%); a wide variety of substituents was tested, including methyl, isopropyl, phenyl, methoxy, Cl, and Br. In addition, the diarylamine with four methyl *o*-substituents was synthesized by this method but in moderate yield (40%).

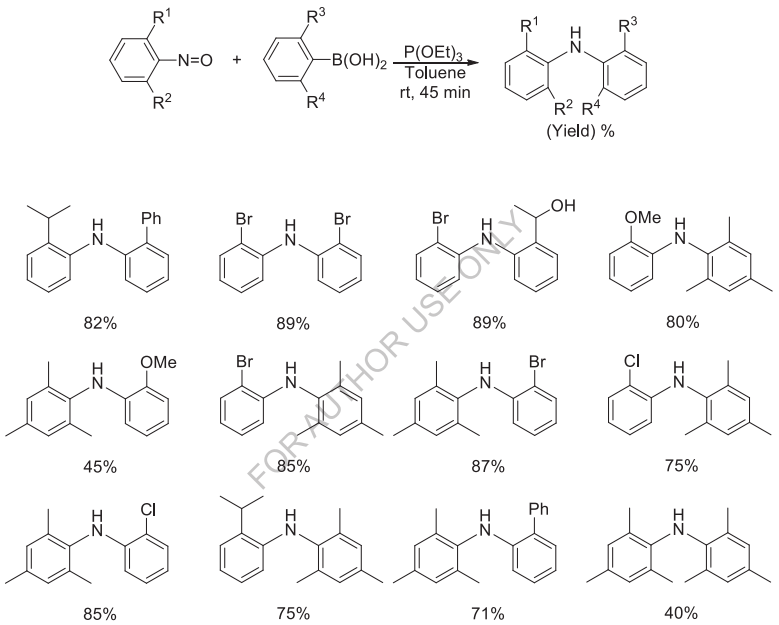



**Figure 6**. Sterically hindered diarylamines synthesized by cross-coupling reaction between nitrosobenzenes and arylboronic acids

## 5.3. Synthesis of Di(hetero)arylamines

Only one example of di(hetero)arylamine was prepared using the coupling of nitrosobenzes with arylboronic acids under Cu(I) catalysis.[164] 2-dibenzofuranylboronic acid reacts with phenylbenzene under Cu(I) catalysis in 80% yield. Due to the ubiquity of amines with heteroaryl groups in biologically active

compounds and drugs[169] as well as functional materials[170] and synthetic intermediates,[171] the next goal was the possibility of preparing secondary amines bearing a heteroaryl moiety by this metal-free cross-coupling reaction (Figure 7). The reaction was useful for the assembly of heterocyclic amines, either starting with heterocyclic nitroso compounds or with heterocyclic boronic acids, many of them were π-excessive or π-deficient, with a phenyl ring (54-93% yields). Even more, amines bearing two heterocyclic rings could be synthesized efficiently (55-89% yields), demonstrating the versatility and robustness of the method. The tolerance of unprotected NH in indoles is noteworthy.

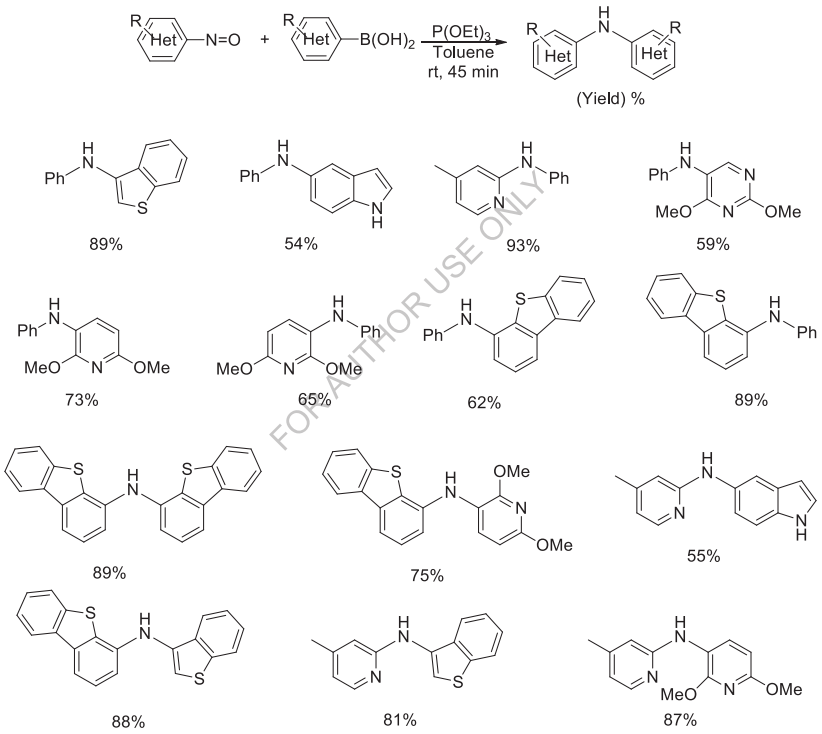





**Figure 7**. Heterocyclic amines synthesized by cross-coupling reaction between nitrosobenzenes and arylboronic acids

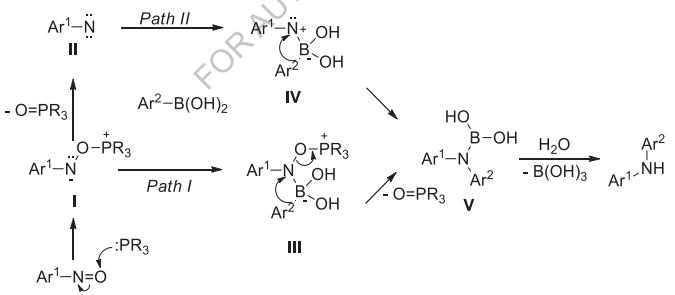
Di(hetero)arylamines with privileged heterocyclic scaffolds were selected as target molecules. The term privileged structure makes reference to chemical scaffolds

capable of providing useful ligands for more than one receptor in chemical biology and drug discovery. Indoles constitute one of the most relevant types of privileged structures in drug design.[172] Pyridine and pyrimidine derivatives are also well-known privileged scaffolds[173] and benzo[*b*]thiophene scaffold is also included in this category and this core exhibits various biological activities.[174]

## 5.4. Proposed Reaction Course, Experimental Considerations and Summary

Based on the above considerations and the literature information,[68] a plausible reaction course for the amination process has been proposed (Scheme 37). Nucleophilic addition of $P(OEt)_3$ to the oxygen atom of the nitroso group in nitrosoarene leads to a tetravalent phosphorus intermediate (I), which can be transformed into a nitrene (II) by elimination of $O{=}P(OEt)_3$. Either unsaturated species (I, II) can add to the vacant orbital on boron in arylboronic acid, giving rise to a boronate species (III, IV) able to transfer the nucleophilic aryl group from boron to the electrophilic nitrogen. Protonation of the final aminoboronate V upon filtration affords diarylamine, together with boric acid as byproduct.






**Scheme 37**. Plausible reaction course

An important aspect of the method is the fact that experimentally it is very simple. The general procedure for the reaction is described in the next lines: "*P(OEt)₃ (58 μL, 0.34 mmol, 1.2 equiv) was added to a solution of nitrosoarene (0.28 mmol, 1.0 equiv) and boronic acid (0.42 mmol, 1.5 equiv) in toluene (0.6 mL), and the mixture was stirred at rt for 45 min. The reaction mixture was filtered through a small plug of*

*silica, eluting with Hexane:AcOEt or $CH_2Cl_2$:AcOEt. The product was obtained after evaporation of the solvent.*" The reaction is fast, and no dried solvent or inert atmosphere are necessaries. Furthermore, most diarylamines could be purified by filtration without the need for separation by chromatography. All these characteristics make the method interesting for its application in the industry.

To sum up, the transition metal-free cross-coupling between nitrosobenzenes and arylboronic acids has been developed for the first time. The reaction tolerates functional groups that are incompatible with other methods for the synthesis of di(hetero)arylamines (carbonyls, nitro, halogens, free OH and $NH_2$), and permits the synthesis of diaryl- and diheteroarylamines, including sterically encumbered compounds. All reactions took place in good yields, including those carrying *o*-substituents. The experimental procedure is simple and inexpensive (open flask, $P(OEt)_3$), mild (base-free, rt), fast (45 min), and the reaction products are recovered by simple filtration without the need for separation by chromatography.

# 6. Transition-Metal-Free C-N Bond-Forming Reaction of Alkylboronic Acids and Nitrosoarenes: Synthesis of Alkylarylamines[175]

The reaction of nitrosoarenes with boronic acids promoted by Cu(I) was only applied to the synthesis of diarylamines and the use al alkylboronic acid was not reported.[164] Furthermore, reactions of nitrosobenzenes with alkylboronic acids derivatives are limited to the use of allylic boronic esters.[160, 161, 162] The synthesis of secondary alkylarylamines from nitrosoarenes are usually limited to alkyl chains with functional groups. The scattered reported examples of the synthesis of amines with simple carbon chains usually afford a mixture of products,[101, 102] or are allylic chains.[103, 104, 105] Moreover, there are no references in the literature for the synthesis of mono-*N*-methylanilines starting from nitroso compounds.

Based on the excellent results obtained for the synthesis of di(hetero)arylamines described in the previous chapter, this new transition metal-free cross-coupling reaction of boronic acids with nitrosoarenes has been extended to the synthesis of secondary alkylarylamines.



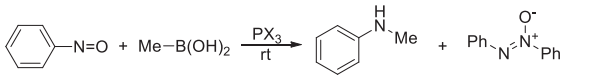
## 6.1. Synthesis of Mono-*N*-Methyl Aromatic Amines

As explained in Chapter 3, the synthesis of secondary methyl anilines presents a series of difficulties; specially overmethylation or diarylation byproducts are frequents as a consequence of the small size of the NHMe group. In this chapter, it has been addressed this issue and developed conditions that permit the transformation of nitrosoarenes into mono-*N*-methyl arylamines easily.

Based on the previous experience in the synthesis of di(hetero)arylamines with P(III) species as oxygen scavengers (Chapter 5), some optimization studies were made to adapt the reaction conditions towards the direct synthesis of *N*-methylaniline starting from nitrosobenzene and methylboronic (Table 2). When phosphines ($PPh_3$ or dppe) were used as promoters, extensive formation of the azoxybenzene[15] was observed (entries 1-2); however, the use of $P(OEt)_3$ significantly increased the ratio of methylaniline (entries 3-7). Taking into account the balance between the amount of methylboronic acid, the products ratio, and the isolated yield in methylaniline, the best conditions (82% yield) were found when using 1.1 equiv of $P(OEt)_3$ in toluene

(entry 4). The reactions in tetrahydrofuran (THF) or dichloromethane (DCM) afforded more azoxybenzene and lower yield in diamine.

**Table 2**. Metal-free cross-coupling between nitrosobenzene and methylboronic acid.




Methylaniline (M) Azoxybenzene (A)

| Entry | Equiv. $MeB(OH)_2$ | $PX_3$ (equiv) | Solvent | M : A | Yield M (%) |
|---|---|---|---|---|---|
| 1 | 1.0 | $PPh_3$ (1.1) | Toluene | 51 : 49 | 32 |
| 2 | 1.0 | dppe (1.1) | Toluene | 60 : 40 | 49 |
| 3 | 1.0 | $P(OEt)_3$ (1.0) | Toluene | 95 : 05 | 71 |
| 4 | 1.5 | $P(OEt)_3$ (1.1) | Toluene | 98 : 02 | 82 |
| 5 | 2.0 | $P(OEt)_3$ (1.1) | Toluene | 99: 01 | 83 |
| 6 | 1.5 | $P(OEt)_3$ (1.1) | THF | 65 : 35 | 62 |
| 7 | 1.5 | $P(OEt)_3$ (1.1) | $CH_2Cl_2$ | 95 : 05 | 72 |



Under optimum reaction conditions for the synthesis of mono *N*-methylamine (Table 2, entry 4), the synthesis of a variety of methylanilines starting from the corresponding nitrosoarenes and methylboronic acid was carried out (Figure 8). In general, nitrosoarenes carrying electron-donating or electron-withdrawing groups were selectively monomethylated to form the secondary amines in good yields. Electron-donating substituents, such as methyl, methoxy, isopropyl, or phenyl performed well, including when one of them is place in the *o*-position of the starting nitrosoarene (57-75% yields). This constitutes an important feature, because sterically demanding substrates are in general less active in *N*-methylation processes compared to *para*- or *meta*-substituted ones.[176] Unfortunately, double *o*-substitution in the aromatic ring by methyl was not permitted. This result contrasts with that previously observed for the arylation reaction of 1,3,5-trimethyl-2-nitrosobenzene using arylboronic acid (Figure 5); 2,4,6-trimethyl-*N*-phenylaniline could be prepared in 81% yield and the results showed in Figure 6 put forward that the cross-coupling arylation reaction admits the presence of two or three *o*-substituents in the aromatic rings of diarylamines. These results show a greater influence of steric hindrance in methylation reaction than in the arylation process.

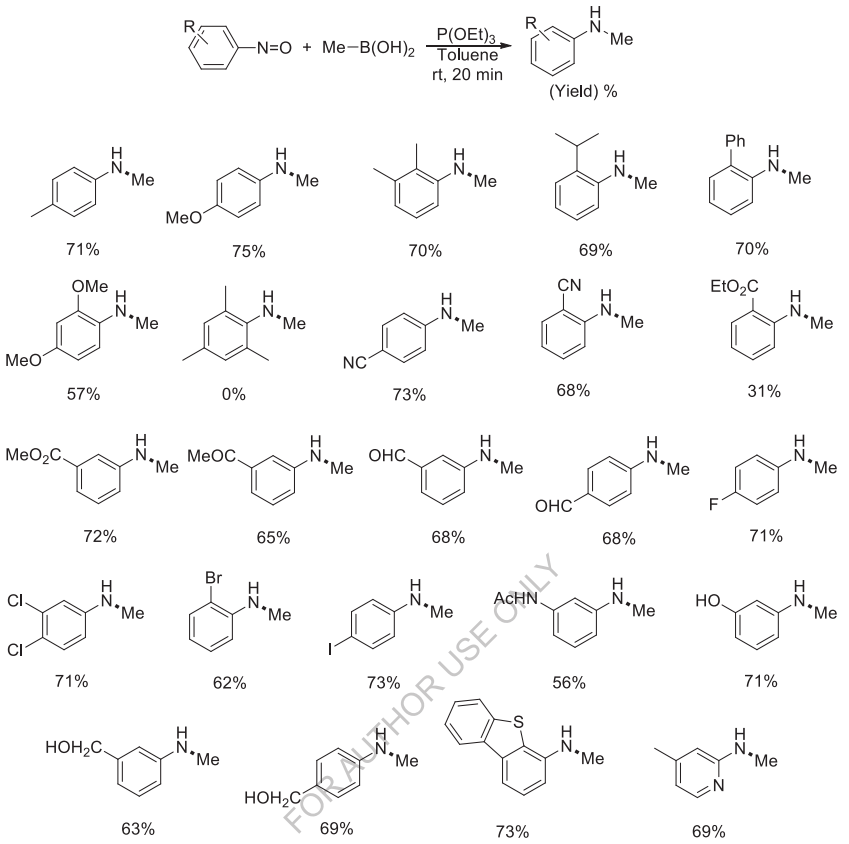





**Figure 8**. Mono-*N*-methyl aromatic amines synthesized by cross-coupling reaction between nitrosobenzenes and methylboronic acid

Notably, the reaction could also be applied to substrates bearing labile functional groups such as cyano, ester, ketone, as well as aldehyde in *ortho*-, *meta*- or *para*-positions (31-72% yield). Mono- or disubstituted aryl halides were also well tolerated (62-73% yields), thus opening the possibility of further functionalization of the resulting methylamines by conventional cross coupling reactions of the aryl halide. With regard to the presence of NH and OH groups, *N*-methylarylamines containing NHAc, unprotected phenolic OH, and compounds with free alcoholic OH groups were synthesized in good yields, thus avoiding protection/deprotection reactions that are frequent among other syntheses of *N*-methylanilines (56-71% yields). Finally,

heterocyclic nitroso compounds were also efficiently monomethylated: *N*-methyldibenzo[*b*,*d*]thiophen-4-amine was synthesized in 73% yield, and the methylation of 4-methyl-2-nitrosopyridine took place in 69% yield, thus demonstrating that the synthesis of secondary methylheteroarylamines is possible using this methodology.

## 6.2. Synthesis of other-*N*-Alkyl Aromatic Amines

In addition to methylation, the metal-free cross-coupling reaction between nitrosoarenes and boronic acid activated by P(III) species is also useful for the synthesis of other secondary *N*-alkylamines different from methylarylamines (Figure 9). The reaction of different alkylboronic acids using nitrosobenzene as a reagent was tested under optimum reaction conditions for the synthesis of methylaniline. Secondary *N*-alkylarylamines were obtained in good yields with primary linear (75% yield) and branched (74% yield) alkyl boronic acids. However, the reaction of nitrosobenzene with a secondary alkyl boronic acids gave a lower yield (50%). On the other hand, the use of cyclic boronic acids such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl, permitted the synthesis of secondary *N*-alkylaryl amines with good yields (59-78%). This is an important issue specially for the sometimes challenging synthesis of *N*-arylcyclopropylamines.[177] Due to the inherent properties of the cyclopropyl ring, the synthesis of arylcyclopropylamines is not easy, however, by using the coupling of nitrosoarenes with cyclopropylboronic acid in the presence of $P(OEt)_3$, various cyclopropylanilines could be prepared in good yields (66-78%). In addition to nitrosobenzene, the synthesis of some additional new alkylarylamines were included in the study with differently functionalized nitrosoarenes using cyclopropyl- and cyclohexylboronic acids as reagents, to test for compatibility with halogens and reactive functional groups as cyano, ester or ketone, among others. All reactions took place in good yields (59-77%), including those carrying *o*-substituents.

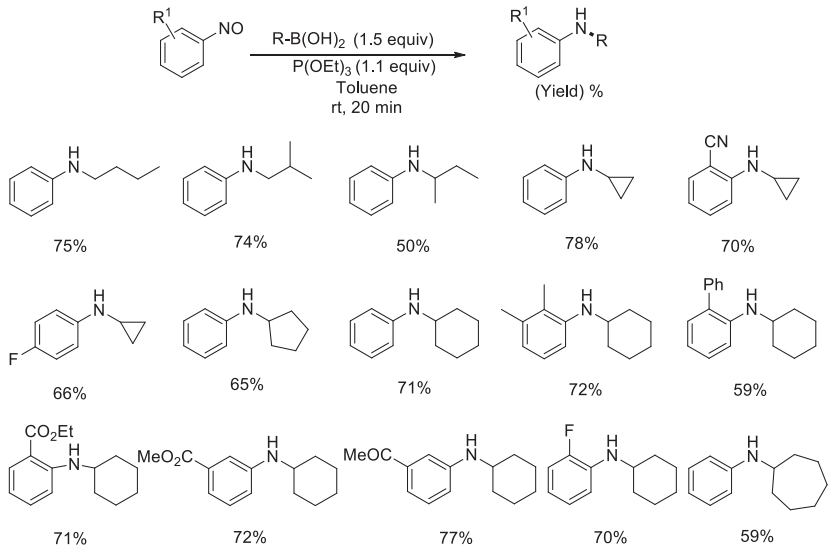
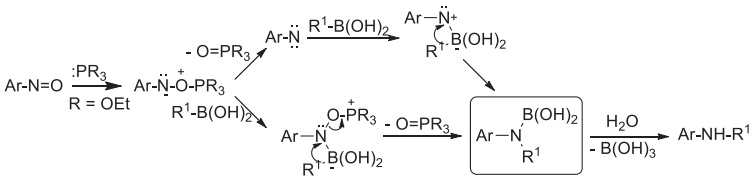



**Figure 9**. Mono-*N*-alkylanilines synthesized by cross-coupling reaction between nitrosobenzenes and alkylboronic acids



## 6.3. Proposed Reaction Course, Experimental Considerations and Summary

Based on previous considerations[68] and in a similar way to the arylation process (Scheme 37), the reaction can be understood (Scheme 38) by the formation of a key arylalkylaminoboronate from the nucleophilic attack of $P(OEt)_3$ to the starting nitrosobenzene followed by borylation of the resulting intermediate (either the initial tetravalent phosphorous species or a nitrene, the latter generated by unimolecular extrusion of triethyl phosphate).




**Scheme 38**. Proposed reaction course

As in the previous synthesis of diarylamines, an important aspect of the method for the synthesis of alkylanilines is the fact that experimentally it is very simple. The general procedure for the reaction is described in the next lines: "*$P(OEt)_3$ (0.31 mmol, 1.1 equiv) was added to a solution of nitrosoarene (0.28 mmol, 1.0 equiv) and boronic acid (0.42 mmol, 1.5 equiv) in toluene (1.1 mL), and the mixture was stirred at rt for 20 min. The reaction mixture was purified by flash column chromatography eluting with hexane/AcOEt or $CH_2Cl_2$/AcOEt.*"

In summary, the results presented in this chapter permit the synthesis of mono-*N*-methyl aromatic amines and other mono-*N*-alkyl aromatic amines directly from nitroso compounds and alkylboronic acids without overfunctionalization to tertiary amines or ammonium salts. The reactions promoted by $P(OEt)_3$ are transition-metal-free and take place in only 20 min at rt, without the need of specially dried solvents, anhydrous conditions, reducing agents, bases, or other additives.

# 7. Transition-Metal-Free C-N Bond-Forming Reaction of Boronic Acids and Nitrosoarenes: Synthesis of Amines with Industrial and Academic Interest

The formation of C-N bonds for the preparation of aromatic amines is among the top five reactions carried out globally for the production of high-value materials, ranging from bulk chemicals to pharmaceuticals and polymers. As a result of this ubiquity and diversity, methods for their preparation impact the full spectrum of chemical syntheses in academia and industry.[1] The metal free cross-coupling reaction between nitrosoarenes and boronic acids promoted by $P(OEt)_3$ has demonstrated to be an excellent method for the synthesis of secondary (hetero)aromatic amines bearing a great variety of substituents in the aromatic rings. Given the importance of secondary arylamines in different fields as pharmaceutical or material sciences, the present method has been used for the gram-scale synthesis of some selected examples of amines with industrial interest.

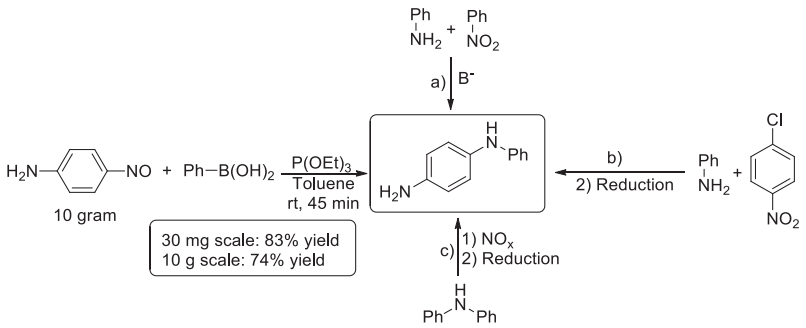


## 7.1. *N*-phenyl-*p*-phenylenediamine

*N*-phenyl-*p*-phenylenediamine (*N*$^1$-phenylbenzene-1,4-diamine) (Scheme 39) is an important industrial antioxidant used in the manufacture of car tires.[178] This diarylamine belongs to the most important family of antidegradants-antiozonants for rubber goods. The start of application of this diamine and its *N*-alkylated derivatives as antidegradants was in the 50' of the last century and its world annual production (2017) is about 300.000 t/a.[179] There are different industrially interesting ways for the preparation of this compound; its most popular synthesis is the condensation of aniline with nitrobenzene in the presence of a base (Scheme 39, a). Alternatives to this synthesis are the reaction of 4-chloronitrobenzene with aniline, followed by reduction of the formed 4-nitrodiphenylamine to the target compound (Scheme 39, b) or the *N*-nitrosation of diphenylamine followed by Hepp's rearrangement to 4-nitrosodiphenylamine and its final reduction (Scheme 39, c).

As shown Figure 5 in Chapter 5, *N*-phenyl-*p*-phenylenediamine could be prepared in 83% yield by the metal-free cross-coupling reaction of 4-nitrosoaniline with phenylboronic acid. This one step synthesis has been scaled to 10 g of starting nitrosoarene with a slight loss in yield (74%) (Scheme 39). This procedure benefits

from the tolerance of the unprotected $NH_2$ group in the cross-coupling reaction leading to diarylamine that avoids reduction or protection/deprotection steps.

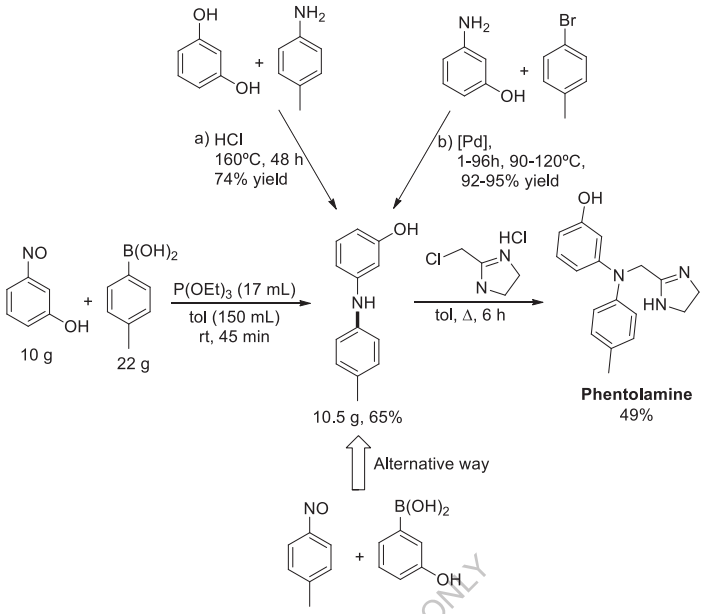



**Scheme 39**. Synthesis of *N*-phenyl-*p*-phenylenediamine

## 7.2. Phentolamine



Phentolamine (Regitine, Vasomax) is a reversible, nonselective α-adrenergic antagonist used clinically to control hypertensive emergencies (Scheme 40).[180] This drug is a tertiary amine that is prepared by alkylation of 3-(4-methylanilino)phenol using 2-chloromethylimidazoline at reflux.[181] The synthesis of the diarylamine necessary as substrate for the final alkylation step has been carried out by reaction of *p*-toluidine with resorcinol (Scheme 40, a)[182] or by reaction of 3-aminophenol and 1-bromo-4-methylbenzene catalyzed by Pd (Scheme 40, b).[183] Though these procedures allow the synthesis of 3-(4-methylanilino)phenol in good yields, high reaction temperatures and long times are usually needed. Direct reaction of 10 grams of 3-nitrosophenol with 22 grams of *p*-tolylboronic acid in the presence of 17 mL of $P(OEt)_3$ allows the synthesis of 3-(4-methylanilino)phenol in 65% yield after 45 min at rt, and phentolamine can be prepared in two steps in 32% overall yield. An interesting point of this strategy for the synthesis of phentolamine is that 3-(4-methylanilino)phenol could be prepared by an alternative way, i.e., by the cross-coupling reaction of 1-methyl-4-nitrosobenzene with (3-hydroxyphenyl)boronic acid. A direct comparison of the yields of both cross-coupling reactions, the prices and/or characteristics of the procedures for the synthesis of the starting nitrosoarenes and boronic acids, would allow to design a new optimized route for obtaining this drug.



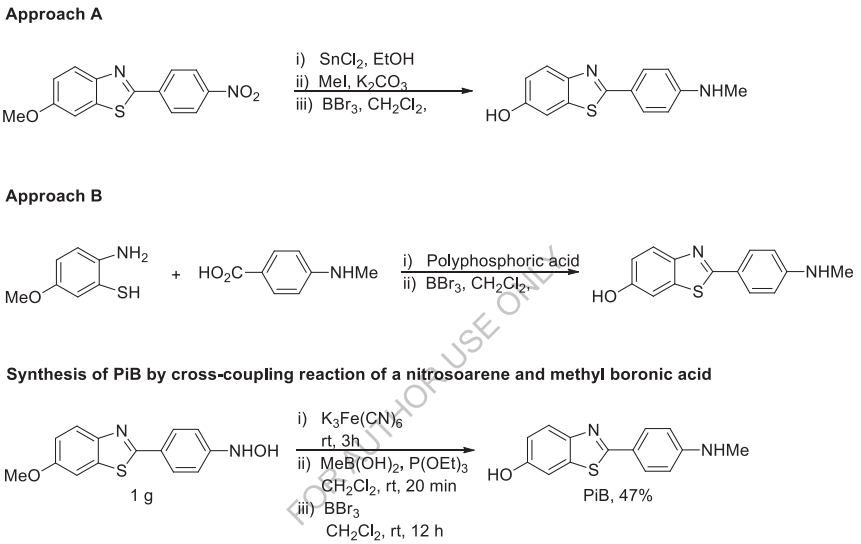

**Scheme 40**. Synthesis of phentolamine



## 7.3. Pittsburgh Compound B (PiB)

In order to test the scaling possibilities for the *N*-methylation reaction, the 1 gram-scale synthesis of the benzothiazole-aniline derivative Pittsburgh compound B (PiB) has been carried out (Scheme 41). $^{11}$C-PiB is currently the most studied radioligand for positron emission tomography (PET) imaging of cerebral amyloid beta (Aβ) deposits for investigational studies of Alzheimer's disease. The functionalization of its hydroxyl group has permitted the synthesis of a variety of other derivatives with improved pharmacokinetics useful as probes for Aβ by different imaging techniques.[184] Two different approaches to synthesize this family of compounds have been taken. In approach A, reduction of nitro group to the amine and subsequent *N*-methylation reaction are the key steps, and a final *O*-demethylation is needed. In approach B, 5-methoxy-*o*-aminothiophenol was reacted with *p*-(methylamino)benzoic acid followed by *O*-demethylation. The cross-coupling reaction of methylboronic acid with nitrosoarenes allows the synthesis of this compound: PiB was prepared directly from 1 g of hydroxylamine in a 47% overall

yield without purification of intermediates. Thus, hydroxylamine was converted with $K_3Fe(CN)_6$ into the corresponding nitroso compound. Without purification, methyl boronic acid and $P(OEt)_3$ were added to obtain the corresponding *N*-methylarylamine, and the phenolic methyl group was removed *in situ* using $BBr_3$. The procedure benefits from the short methylation reaction time (only 20 minutes), so this approach may be of interest for the future development of new radiomethylation reactions with carbon 11, and it could be applied to the synthesis of new radiotracers.[185]






**Scheme 41**. Synthesis of PiB

## 7.4. Flufenamic Acid[186]

Finally, as an example of the interest of the metal-free cross-coupling reaction of nitrosoarenes with boronic acids in both the academy and the industry, a method for the synthesis of flufenamic acid (Figure 10),[187] a nonstereoidal anti-inflammatory drug (NSAID) of the fenamate family, has been described as an experiment for the upper-division undergraduate organic chemistry laboratory. The key step is the formation of the diarylamine moiety of flufenamic acid by the reaction consisting of the coupling of nitrosobenzenes with boronic acids under transition-metal-free conditions.

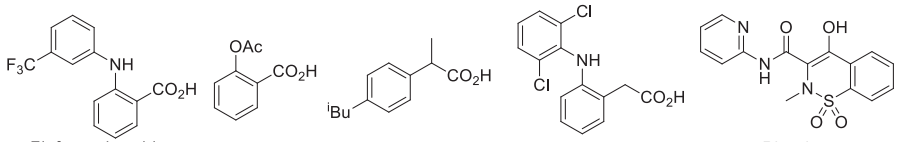



**Figure 10**. Structures of flufenamic acid and other common NSAIDs

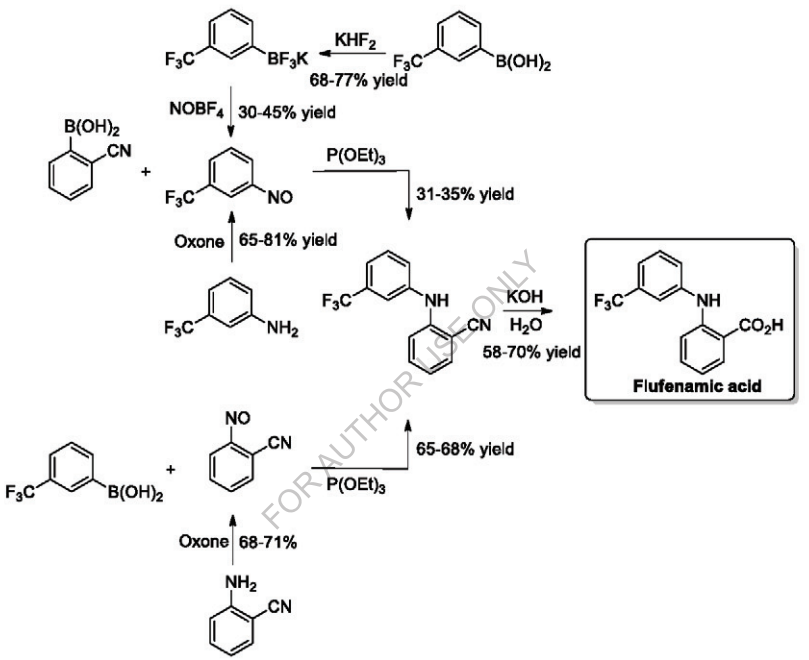
NSAIDs are among the best-selling drugs worldwide (there is an estimate of more than 100 million prescriptions per year in the USA alone). Their importance relies on their anti-inflammatory, analgesic and anti-fever actions. The therapeutic activity of NSAIDs is thought to result from their ability to hinder the synthesis of prostaglandins by inhibiting the enzymes cyclooxygenases. Aspirin, a derivative of salicylic acid (salicylates) is the most well-known example of NSAIDs. Besides, most relevant commercial NSAIDs approved for use in humans belong to the families of fenamic acid derivatives (fenamates), propionic acid derivatives (profens), acetic acid derivatives, and enolic acid derivatives (oxicams). In particular, flufenamic acid is effective in treating rheumatism, arthritis and other musculoskeletal inflammatory disorders very effectively. Esterification with diethyleneglycol affords etofenamate, another NSAID of the fenamate family with improved skin absorption, widely found in topical formulations.[188] Flufenamic acid has also shown activity against other targets different from cyclooxygenases, and the core of flufenamic acid is found as well in drugs that belong to other therapeutic areas.[189]



Multiple laboratory experiments have been reported for the preparation of aspirin,[190] and some laboratory experiments are also available for the preparation of other NSAIDs such as acetaminophen or ibuprofen.[191] However, no synthesis of fenamates had been reported at a student level. Flufenamic acid and other *N*-arylanthranilic acids have been synthesized by the Ullmann-Goldberg condensation between *o*-halobenzoic acids and anilines.[124, 192] The reactions usually require harsh conditions, long reaction times, and yields are low. To the best of our knowledge, the synthesis of flufenamic acid has not been reported by neither a Buchwald-Hartwig nor a Cham-Lam approach.

In the proposed experiment for the students, the key step was the construction of the diarylamine moiety of flufenamic acid using arylboronic acids and nitrosobenzenes as reaction partners in the C-N bond-forming reaction carried out under transition-metal-free conditions. This reaction simultaneously exploits the

electrophilicity of the nitroso group and the nucleophilicity of a boronic acid that has been activated as an ate complex by coordination to nitrogen (Scheme 37). The reaction is promoted by $P(OEt)_3$, which serves as an oxygen scavenger because of the formation of a strong P=O bond.[67] The subproduct of the reaction, triethyl phosphate, is much less toxic than transition-metal wastes. Boric acid, another subproduct of the reaction, is of low toxicity. Therefore, the experiment minimizes the generation of hazardous substances. The overall synthetic route is given in Scheme 42.




**Scheme 42.** Overall synthetic scheme for the synthesis of flufenamic acid

The experiment was carried out by two groups of students that follow two complementary approaches to converge on key intermediate 2-[[3-(trifluoromethyl)phenyl]-amino]benzonitrile. The difference between both approaches relies on the substitution patterns of the reaction partners: A group of students prepared the diarylamine by reacting 2-(cyanophenyl)boronic acid with 1-nitroso-3-(trifluoromethyl)benzene, while students in the other group prepared the amine by reacting [3-(trifluoromethyl)phenyl]boronic acid with 2-nitrosobenzonitrile.

Additionally, students compared the performance of two methods for the preparation of two different nitrosobenzenes: *ipso*-$S_E$Ar reaction on potassium organotrifluoroborate using $NOBF_4$[22, 193] (acetonitrile, room temperature, 30 min) (30-45% yields) and oxidation of anilines using oxone (dichloromethane/$H_2O$, room temperature, 1.5 h) (65-81% yields).[194] The reaction time tended to favor the method that used an organotrifluoroborate as starting material. However, yields of the oxidation procedure were higher. Also, obtaining 2-nitrosobenzonitrile with the corresponding azoxybenzene (approximately 10%) was compared to obtaining 1-nitroso-3-(trifluoromethyl)benzene almost pure. This may be attributed to the electronic effect of the *o*-CN group, which makes the nitroso group of 2-nitrosobenzonitrile more electron deficient, thus favoring dimerization.[15]

Students also compared the yields of the two complementary examples for the transition-metal-free C−N coupling reaction between two commercial boronic acids and prepared nitrosobenzenes (tetrahydrofuran, room temperature, 20 min). The yields for the coupling of (2-cyanophenyl)boronic acid with 1-nitroso-3-(trifluoromethyl)benzene were rather low, ranging between 31 and 35% after purification. A small amount of the azoxybenzene derived from 1-nitroso-3-(trifluoromethyl)benzene was formed during the coupling reaction. On the other hand, the yields for the coupling of (3-(trifluoromethyl)phenyl)boronic acid with 2-nitrosobenzonitrile were much higher, ranging between 65 and 68%. When comparing the yields, the second reaction was clearly favored. This can be explained by the higher electrophilicity of the nitroso group in 2-nitrosobenzonitrile, which may favour the step in which $P(OEt)_3$ bonds to nitrogen (Scheme 37). In addition, the boron group of (3-(trifluoromethyl)phenyl)boronic acid is less sterically hindered than that of (2-cyanophenyl)boronic acid, which may favor the step in which the N−B bond is formed.

Finally, students set up the basic hydrolysis of the nitrile group in the diarylamine to obtain flufenamic acid with yields ranged between 58 and 70%. The product was isolated by acidification followed by extraction and chromatography. It is important to note that none of the transformations in the sequence involved the use of any transition metals, and are carried out without the need of inert gas atmosphere or specially dried solvents.

Grading of lab questionnaires and discussion with instructors during the lab sessions put forward that the students that participated in this experiment consolidated their knowledge of the reactivity of nitroso compounds and boronic

acids, their ability to understand reaction mechanisms and their preparation skills in a multistep sequence.

To sum up, the C-N bond forming reaction using boronic acids and nitrosoarenes in the absence of transition metals is a robust method which can be apply in a gram-scale to the synthesis of secondary anilines with industrial interest. As an example of the interest of the method in the academia, the synthesis of flufenamic acid using nitrosobenzenes and boronic acids under transition-metal-free conditions was described to be used in the upper-division organic chemistry laboratory course.

## 8. Outlook and Conclusions

In summary, this book is devoted to the coupling of nitrosoarenes with (hetero)aryl and alkylboronic acids under neutral and transition-metal-free conditions as a general method for the synthesis of functionalized secondary di(hetero)arylamines and alkylarylamines. The procedure is experimentally simple, fast, mild, scalable, and has a wide functional group tolerance, including aldehydes, ketones, esters, cyano, and nitro, which are often incompatible with other previous methods for secondary 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 ability to tolerate halogen and $NH_2$ functionalities makes the method orthogonal to other cross-coupling reactions.

This method permits the selective synthesis of substituted secondary diarylamines (41 examples reported, 31−97% yield), di(hetero)arylamines (12 examples reported, 54−93% yield), mono-*N*-methyl aromatic amines (25 examples reported, 31−82% yield) and other *N*-alkyl aromatic amines (15 examples reported, 50−78% yield) directly from nitrosoarenes and boronic acids without overfunctionalization to tertiary amines or ammonium salts. Using the coupling of nitrosobenzenes with boronic acids as key step, some selected examples of secondary amines with industrial interest have been prepared and the synthesis of flufenamic acid has been described to be used in the upper-division organic chemistry laboratory course. The reactions promoted by inexpensive $P(OEt)_3$ are transition-metal-free and take place in only 20-45 min at rt, without the need of specially dried solvents, anhydrous conditions, gas inert atmosphere, reducing agents, bases, or other additives. The subproducts of the reaction, triethyl phosphate and boric acid, are of low toxicity, thus minimizing the generation of hazardous substances, as required in contemporary industrial applications, and the starting boronic acids are considered as “green” compounds due its low inherent toxicity and relatively quick degradation in the environment. Therefore, the target amines are constructed efficiently under environmentally benign reaction conditions and the procedure is of interest in pharmaceutical, agricultural, material, and chemical industries.

The plethora of research substained in this book will provide a detailed outlook on synthetic applications of this cross-coupling reaction and will open new horizons to extend the methodology development. Considering the fact that secondary anilines are by far one of the most used class of compounds in various industries including

chemical, food, agricultural, cosmetics, and pharmaceuticals, a methodology able to synthesize these compounds in a single step has the potential to bypass lengthy synthetic routes and, more importantly, to provide increased capacity for chemical space exploration around high-value molecules. This C-N coupling strategy represents a general method for the fast preparation of secondary aromatic amines and for the efficient generation of chemical diversity. The tolerance to a great variety of functional groups, in addition to avoid protection/deprotection steps, allows subsequent transformations of these functional groups, thus being able to synthesize structurally more complex molecules. The potential in late-stage functionalization has been demonstrated by the synthesis of drugs as phentolamine or flufenamic acid. The transformation has been scaled effectively to gram-scale. The operational ease, broad functional group tolerance and scalability of this reaction make it suitable for adoption in both academic and industrial settings.

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