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Modern Amination Reactions

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday[‡]

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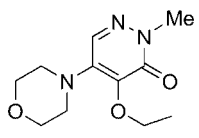
The synthesis of functionalized aromatic and heteroaromatic amines has attracted much interest due to their importance as building blocks for pharmaceuticals, polymers, or materials. In this microreview, new developments involving palladium-, nickel-, and copper-catalyzed amination reactions are discussed. The synthesis of functionalized secondary amines or diarylamines by addition of polyfunctionalized arylmagnesium reagents to nitroarenes or arylazo tosylates is also presented. Finally, primary, secondary, and tertiary amines prepared by the oxidative coupling of polyfunctional lithium amidocuprates using chloranil as oxidant are highlighted.

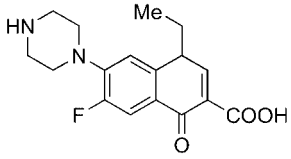
1. Introduction

Functionalized aromatic and heteroaromatic amines are important building blocks for the synthesis of pharmaceuticals,[1] polymers, or materials.[2] Emorfazone (**1**), for example, is a potent analgesic anti-inflammatory agent.[3] Norfloxacin (**2**) is a well known member of the family of quinolone antibiotics showing high activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*.[4] Mirtazapine (**3**),[5] an antidepressant, Olanzapine (**4**),[6] a neuroleptic, and Timolol (**5**),[7] a nonselective beta-adrenergic receptor blocker, are further medicinally active compounds, which show the need for efficient synthetic methods allowing the preparation of functionalized amines.

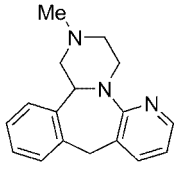
This microreview highlights recent developments relating to transition metal-catalyzed amination reactions using palladium, nickel, and copper, as well as the use of Grignard reagents for the synthesis of arylamines through addition to nitro- or nitroso-arenes or arylazo tosylates. It also includes the oxidative coupling of amidocuprates, which allows a very general approach to polyfunctional amines.



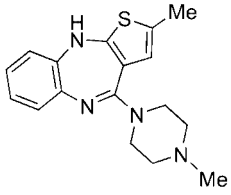
Emorfazone (**1**)



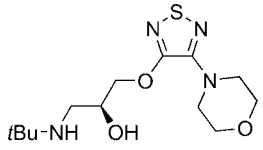
Norfloxacin (**2**)



Mirtazapine (**3**)



Olanzapine (**4**)



Timolol (**5**)

2. Transition Metal-Catalyzed Amination Reactions

2.1 Palladium

The palladium-catalyzed coupling of aryl halides with amines or other nitrogen-containing substrates has become a versatile method for the preparation of arylamines.[8] The first palladium-catalyzed C(sp^2)–N bond formation was re-

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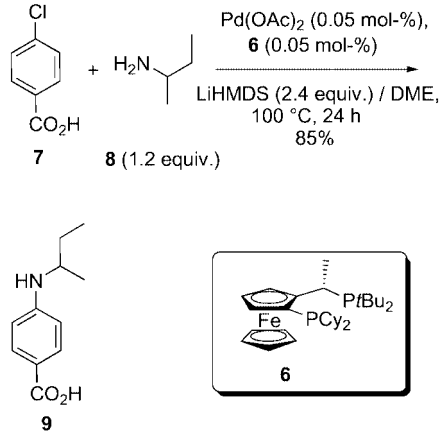
ported in 1983 by Migita et al. Treatment of aryl bromides with aminotin compounds in the presence of catalytic amount of palladium provides the corresponding aniline derivatives in moderate to good yields.[9a]

The limitations associated with the use of toxic tin derivatives were overcome by Buchwald and Hartwig in 1995.[9b–9c] Among all the efforts to increase the scope of substrates and the efficiency of the reaction, fine tuning of the ligands has shown the biggest impact. Recent developments have led to two main and complementary ligand classes: chelating bisphosphane ligands and biaryl monophosphane ligands. In the presence of the commercially available Josiphos-type ligand **6**[9] and with LiHMDS [LiN(SiMe$_3$)$_2$] as base, the aryl chloride **7**, with a free carboxylic acid function, reacts with primary alkylamine **8** to afford the secondary amine **9** (Scheme 1).[10]



Scheme 1.

The steric hindrance, strong electron donation, and tight chelation of the palladium center with ligand **6** result in a catalyst system possessing a long lifetime and a high reactivity for reactions of primary nitrogen nucleophiles with aryl and heteroaryl chlorides. This catalyst system even allows the direct use of ammonia in the palladium-catalyzed amination reaction, opening new pathways for the synthesis of primary arylamines.[11] In a typical reaction, the sterically hindered aryl bromide **10** reacts with ammonia to yield the arylamine **11** (Scheme 2). This reaction can be extended to aryl chlorides instead of aryl

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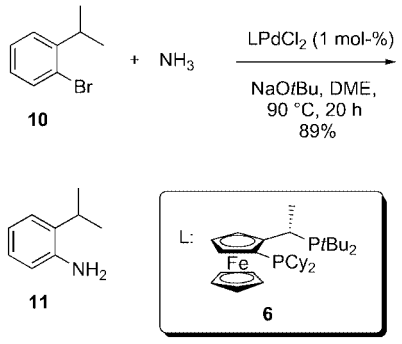
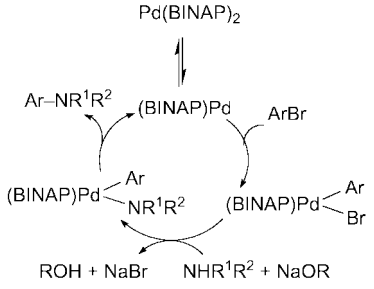
bromides. Lithium amide ($LiNH_2$) is a more convenient nitrogen source than gaseous NH_3, which may not be practical in some cases.



Scheme 2.

Buchwald, Blackmond, and Hartwig have recently reported a detailed study of the mechanism of amination of aryl halides in the presence of palladium complexes of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP).[12] Identification of the Pd-BINAP complexes present in the reaction mixture, together with rate measurements, revealed that the oxidative addition of the bromoarene to [Pd(BINAP)] occurs prior to the amine addition. The reaction with the amine and the base with [Pd(BINAP)(Ar)(Br)] follows. The catalytic cycle is completed by a reductive elimination of the resulting amido complex, providing the desired arylamine (Scheme 3).

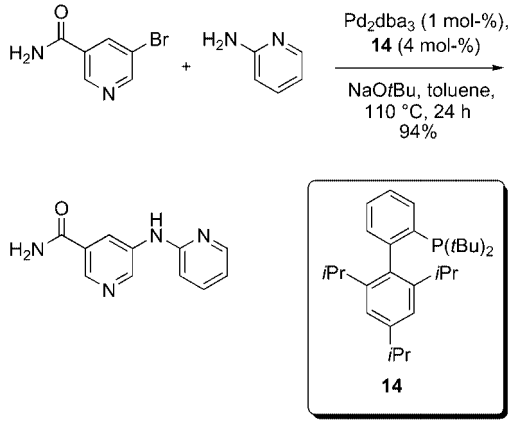


Scheme 3.

Monophosphane ligands can also be successfully applied to palladium-catalyzed aminations.[13] Among them, biaryl ligands have proven to be particularly efficient.[14] Progress in the coupling of heteroaryl halides allows access to a large variety of biologically and pharmaceutically important heteroarylamines.[15] Moreover, a range of highly active, bulky, and electron-rich biaryl ligands are commercially available.[16]

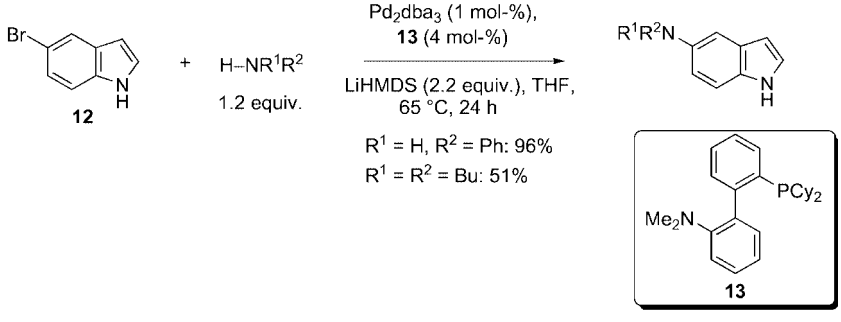
5-Bromoindole (**12**) reacts with aniline and acyclic or cyclic secondary alkylamines in satisfactory yields in the presence of ligand **13** (Scheme 4).[17] Protection of the free NH function is not necessary in such aminations.

Later generations of monodentate biaryl ligands possess bulky substituents at the 2,2′-positions for prevention of palladacycle formation[18] and additionally shift the equilibrium between [L_2Pd^0] and [L_1Pd^0] in the direction of the latter, more reactive, complex. Such palladium catalysts display high chemoselectivity towards the reaction of an aniline NH_2 group over that of a primary amide.[14b] Ligand **14** further allows the use of 2-amino-substituted heterocycles as nucleophiles (Scheme 5).[19] The presence of a bidentate ligand prevents coordination of this "amidine-like" nucleophile to palladium.[20]

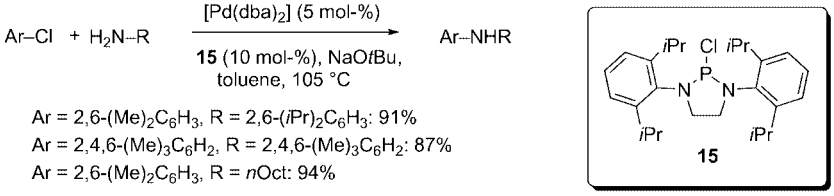


Scheme 5.

An alternative to tertiary phosphane ligands is represented by a new class of sterically hindered diaminochlorophosphanes, showing high efficiency in the arylation reactions of amines.[21] With ligand **15**, for example, sterically demanding aniline derivatives and acyclic alkylamines can be coupled with electron-rich aryl chlorides and bromides in high yields (Scheme 6).



Scheme 4.

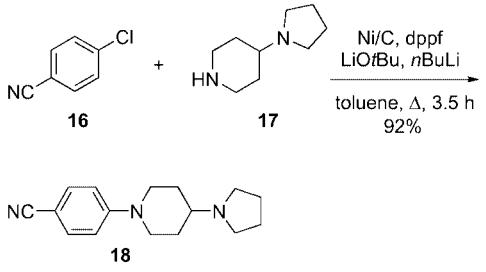


Scheme 6.

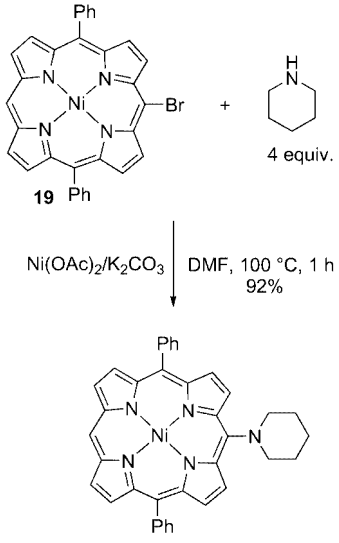
2.2 Nickel

Though palladium complexes certainly represent the most widely used class of catalysts for amination reactions, many challenges still remain. One of these is the coupling of the readily available aryl chlorides, which often requires the use of specially tailored ligands.[22] Despite the fact that Ni^0 easily inserts into aryl chlorides without the need for expensive ligands, relatively little work on their use in amination reactions has been done.[23]

Lipshutz has developed an industrially attractive catalyst system that shows high efficiency for C–C, C–N, and C–H bond formation reactions.[24] The catalyst consists of nickel atoms embedded in a charcoal matrix (Ni/C). Addition of *n*BuLi to Ni^{II}/C in the presence of 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) generates the phosphane-ligated active Ni^0/C catalyst, which shows very little bleeding into the reaction medium (0.15% relative to the substrate).[25]



Scheme 7.



Scheme 8.

The catalyst is readily stored and can simply be filtered off after reaction. A wide range of aryl halides can be converted into their corresponding aniline derivatives with reaction times as short as 2.5 h, although long reaction times are still needed for the coupling of electron-rich aryl chlorides such as 4-chloroanisole (52 h).[25] In a typical reaction, aryl chloride **16** and the cyclic secondary amine **17** are coupled to provide the corresponding arylamine **18** in 92% yield (Scheme 7).

Nickel(II) can further be successfully applied to the ligand-free catalyzed amination of *meso*-bromoporphyrin **19** with primary or secondary aliphatic amines as nucleophiles (Scheme 8).[26]

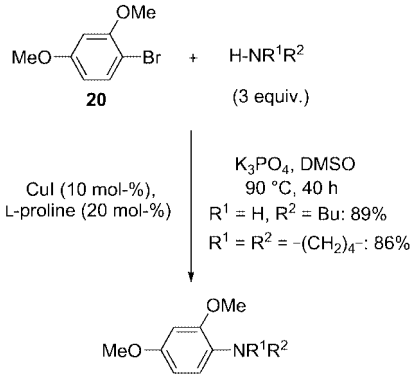
2.3 Copper

Great efforts have been made to improve the Ullmann condensation reaction[27] and to turn it into a viable alternative to the commoner Pd-catalyzed reactions.[28] The harsh reaction conditions (high temperatures, long reaction times, the presence of strong bases, and the use of stoichiometric amounts of copper or copper salts) make the Ullmann coupling unattractive. Excellent overviews are available, showing that a variety of aryl organometallics [boronic acids, halides, siloxanes, stannanes, iodonium salts, lead(IV) triacetates, pentavalent organobismuth, and organotrifluoroborate reagents] successfully participate in copper-mediated amination reactions.[29]

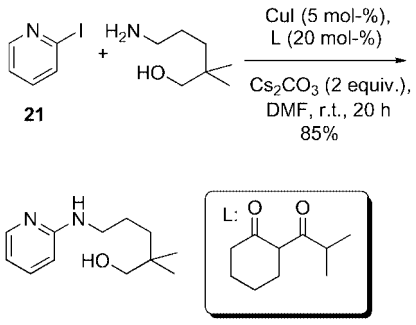
Significant progress towards the development of milder reaction conditions has been achieved with the use of bidentate ligands such as aliphatic diamines,[30] ethylene glycol,[31] diethylsalicylamide,[32] 1,10-phenanthroline and its derivatives,[33] amino acids,[34] and amino alcohols.[35] With L-proline as promoter, for example, the coupling of aryl iodides or bromides such as **20** with aliphatic primary amines, aliphatic cyclic secondary amines, or electron-rich primary arylamines can be carried out at temperatures between 60 and 90 °C (Scheme 9).[36]

The long reaction times can be shortened by using β-diketones as ligands, avoiding possible catalyst deactivation.[37] A catalyst system generated in situ from CuI and 2-isobutyrylcyclohexanone as ligand allows the amination of aryl or heteroaryl iodides such as **21** to proceed at room temperature (Scheme 10).[37]

Furthermore, copper-catalyzed amination has developed into a valuable method for the synthesis of nitrogen-containing heterocycles from common starting building blocks. Recently, Buchwald and Altman reported the Cu-catalyzed

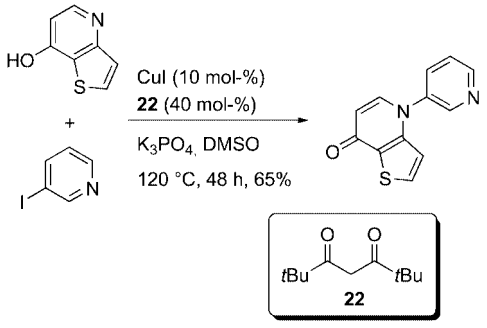


Scheme 9.



Scheme 10.

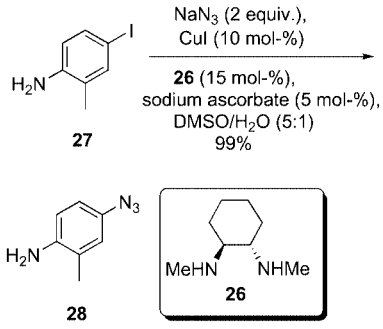
N-arylation of 4-hydroxypyridine with aryl bromides and iodides.[38] The resulting pyridine-4(1*H*)-one structure is found in natural products or biologically active compounds. These Cu-catalyzed couplings of 4-hydroxypyridine with a variety of aryl and heteroaryl iodides and bromides showed complete selectivity for reaction at nitrogen in the presence of the ligand **22** (Scheme 11).



Scheme 11.

Buchwald developed a highly flexible Cu-catalyzed domino C–N coupling/hydroamination protocol for the synthesis of pyrroles and pyrazoles.[39] This approach proceeds through an initial Cu-catalyzed amidation of a reactive haloenyne with an intramolecular hydroamidation. In a typical reaction, starting from iodoenyne **23**, pyrrole **24** and pyrazole **25** are obtained in high yields, depending on the nitrogen nucleophile used (Scheme 12).

Complementary to the Pd-catalyzed procedures is a new method for the preparation of aryl azides from aryl halides.[40] Aryl azides are versatile starting materials for the synthesis of anilines, nitrenes,[41] and a variety of nitrogen-containing heterocycles.[42] In the presence of copper iodide and diamine **26**, the functionalized aryl iodide **27** is converted into the corresponding azide **28** at room temperature in high yields (Scheme 13).



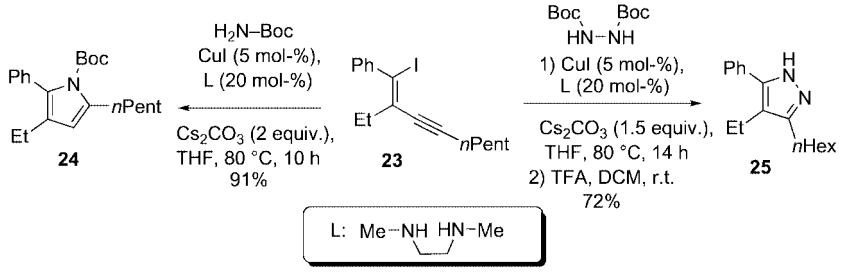
Scheme 13.

Recent developments in the copper(I)-catalyzed aminations of aryl halides nowadays allow the use of mild bases (exp. Cs_2CO_3) and low reaction temperatures.[43] Despite these advantages, difficulties remain for the coupling of aryl chlorides, and high catalyst loadings are often required.

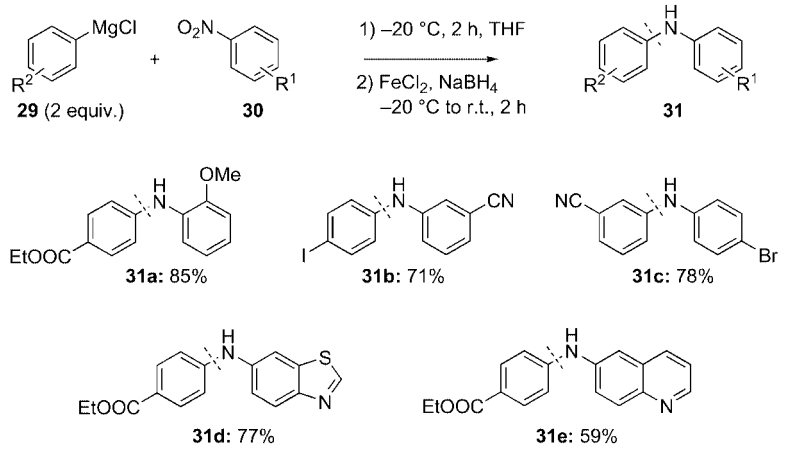
3. Other Methods

3.1 Functionalized Amines through Electrophilic Amination Reactions

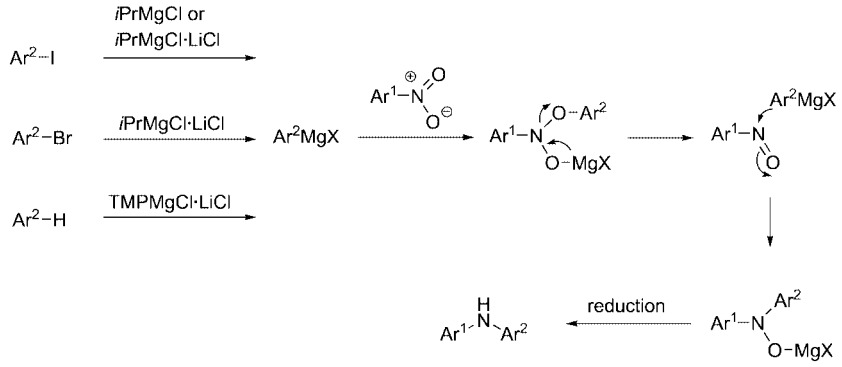
Besides the transition metal-catalyzed amination protocols described above, in which a nucleophilic amino synthon is combined with an electrophilic aromatic reagent, reactions between Grignard reagents and aromatic nitrogen compounds in a higher oxidation state have proven to be a versatile alternative for the synthesis of functionalized di-



Scheme 12.



Scheme 14.

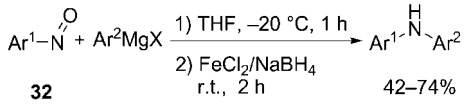


Scheme 15.

arylamines.[44] In such reactions the aromatic organometallic species acts as a nucleophile, while the nitroarene plays the role of an electrophile. Treatment of a functionalized arylmagnesium species **29** with nitroarene **30** thus provides (after reductive workup[45]) polyfunctionalized diarylamines **31a**–**c** in good yields (Scheme 14). Even heterocycles bearing nitro groups can be successfully transformed into the corresponding heterocyclic amines **31d**–**e**.

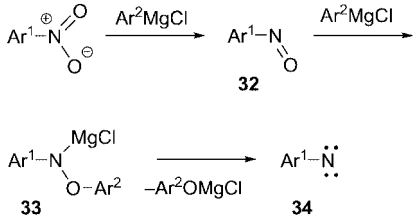
Functionalized Grignard reagents Ar^2MgCl are conveniently prepared by halogen–magnesium exchange reactions[46] starting from aryl iodides[47] or aryl bromides through the use of *i*PrMgCl·LiCl (Scheme 15).[48] Aromatic rings bearing acidic protons can be magnesiated by treatment with TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl).[49] The use of two equivalents of the Grignard reagent was found to be crucial for obtaining complete conversion, as explained by considering the reaction mechanism (Scheme 15).[44,50]

Addition of the first equivalent of Grignard reagent to the nitroarene leads, after elimination of a magnesium phenolate, to the intermediate formation of an arylnitroso derivative **32**, which reacts with a second equivalent of Grignard reagent to provide the desired diarylamine after reductive workup. The first equivalent of arylmagnesium reagent is used to generate the reactive nitrosoarene **32**, a drawback overcome by directly using nitrosoarenes as starting materials. This allows the synthesis of various functionalized diarylamines (Scheme 16).[51]

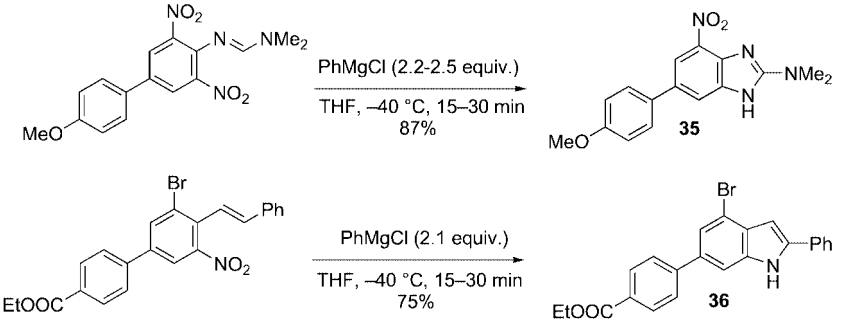


Scheme 16.

Nitroarenes bearing bulky substituents next to their nitro functions are not reduced to the corresponding diarylamines.[52] Although the formation of the intermediate nitrosoarene **32** is still observed, because of steric hindrance a second equivalent of the Grignard reagent does not add to the nitrogen atom, but rather to oxygen, resulting in the formation of the magnesium-nitrenoid **33** (Scheme 17).



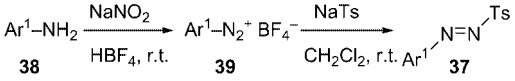
Scheme 17.



Scheme 18.

Intermediate **33** furnishes a nitrene **34** that can be used for the mild synthesis of benzimidazoles such as **35** or indoles such as **36**, with a broad range of functional groups being tolerated (Scheme 18).

Alternatively, arylazo tosylates of type **37** can be used in electrophilic aminations.[53a] They are conveniently prepared from aniline derivatives such as **38** in a two-step procedure involving a diazotization[54] and subsequent conversion of the resulting diazonium tetrafluoroborates **39** with sodium *p*-toluenesulfinate (NaTs) (Scheme 19).

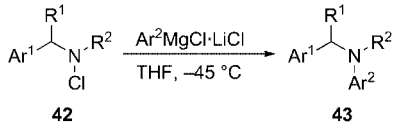


Scheme 19.

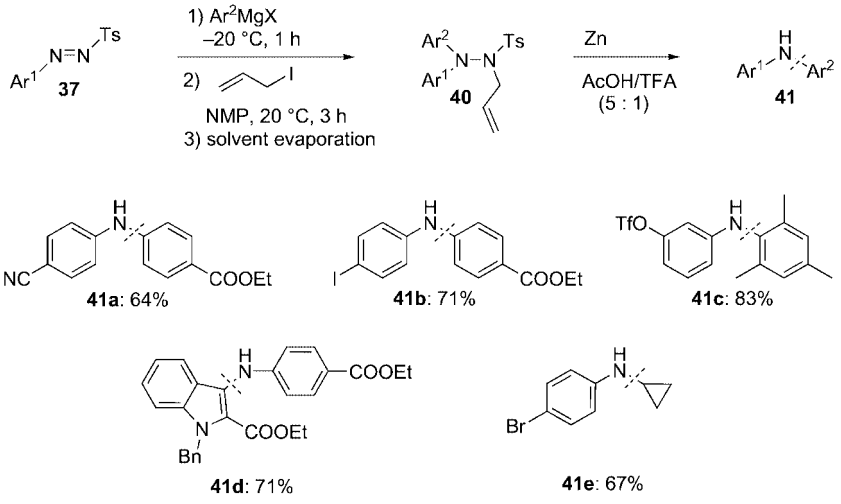
Compounds **37** react with a broad range of functionalized Grignard reagents under mild conditions (–20 °C, 1 h). Subsequent allylation of the addition products with allyl iodide in *N*-methylpyrrolidinone (NMP), followed by reductive cleavage of the resulting hydrazine derivatives **40** with zinc in a mixture of acetic acid and trifluoroacetic acid (TFA), furnishes polyfunctionalized diarylamines **41** in high yields (Scheme 20).[53a]

This amination protocol is complementary to the transition metal-catalyzed amination reactions with respect to the functional groups that can be tolerated. Reactive functional groups such as nitriles, esters (**41a**), iodides (**41b**), bromides, or even triflates (**41c**) are all tolerated. Even heterocyclic amines (**41d**) and bulky alkyl arylamines (**41e**) can be obtained.

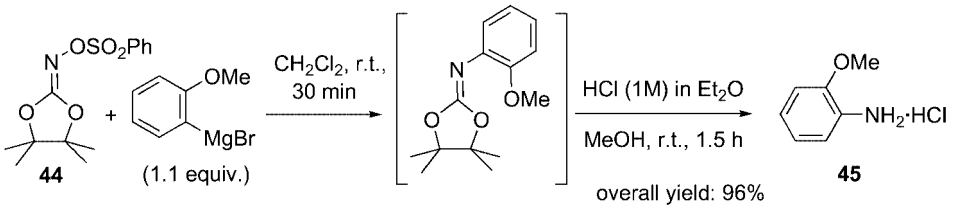
The electrophilic amination of organometallic species with mono-, di-, and trihaloamines has attracted a lot of attention for the synthesis of amines. Only a few cases using alkylchloroamines as precursors for the synthesis of tertiary amines have been reported. Functionalized arylmagnesium compounds react rapidly with benzyl-*N*-chloroamines **42** at –45 °C to provide polyfunctional tertiary amines **43** in good yields (Scheme 21).[53b] The procedure was also applied for the preparation of chiral *N*-chloroamines with retention of chirality at the α-carbon. However, the amination process



Scheme 21.



Scheme 20.



44 **45**

Scheme 22.

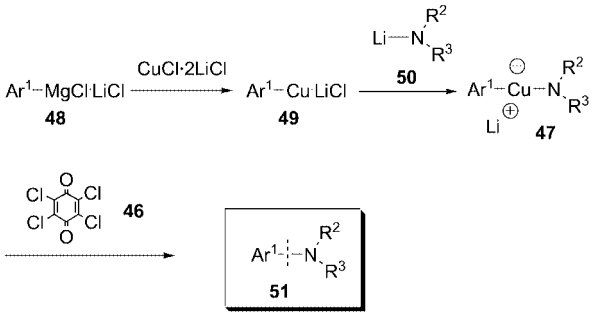
is limited to benzyl-*N*-chloroamines only. This method offers a possible alternative strategy to transition metal-catalyzed amination reactions.

Narasaka[55] reported a useful amination through a substitution reaction at nitrogen. 4,4,5,5-Tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfoxime (**44**) proved suitable for the amination of alkyl- and arylmagnesium reagents, affording the corresponding primary alkyl- or arylamines such as **45** in high yields (Scheme 22).

3.2 Oxidative Coupling of Polyfunctional Aryl and Heteroaryl Amidocuprates

The oxidative amination of amidocuprates is a further complement to transition metal-catalyzed and electrophilic amination reactions. Previous studies by Yamamoto and Maruoka[56] and by Ricci et al.[57] focused on the use of oxygen as oxidant for converting amidocuprates into various amines.

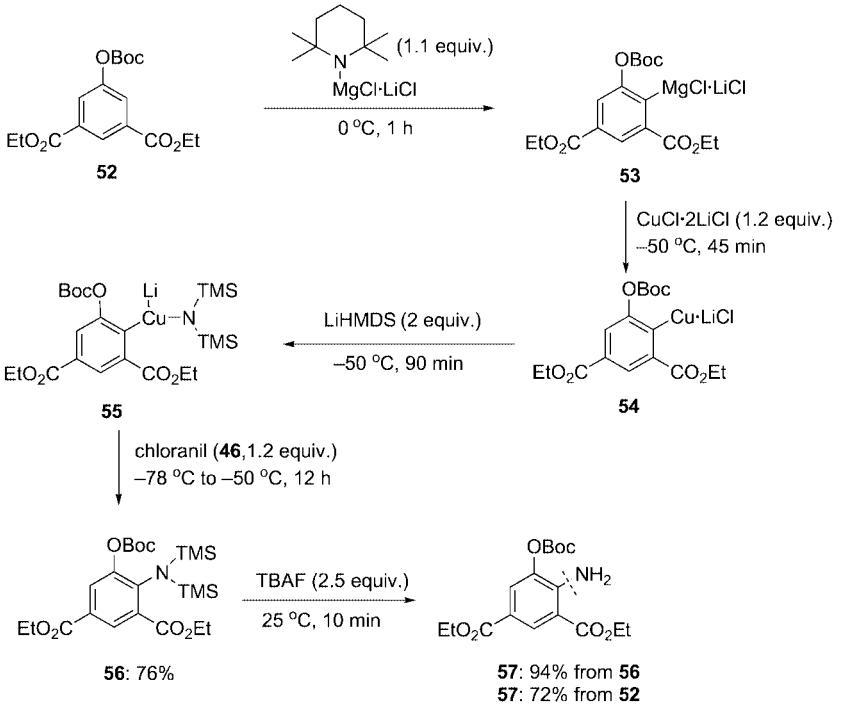
In a new synthetic protocol for the preparation of polyfunctional primary, secondary, and tertiary aryl- and heteroarylamines by oxidative coupling of amidocuprates, chloranil (**46**) proved to be an efficient oxidant.[58] The required functionalized amidocuprates **47** are prepared from the starting organomagnesium reagents **48**. Compounds **48** are transmetallated with CuCl·2 LiCl to afford the corresponding copper derivatives **49**, which after treatment with a lithium amide of type **50** results in the formation of amidocuprates **47**. Oxidation with chloranil (**46**) finally affords the amines **51** in high yields (Scheme 23).



48 **49** **47**

Scheme 23.

For the synthesis of primary amines, the diester **52** was magnesiated with TMPMgCl·LiCl, leading to the arylmagnesium derivative **53**, which was treated with CuCl·2 LiCl



52 **53** **54** **55**

56: 76%

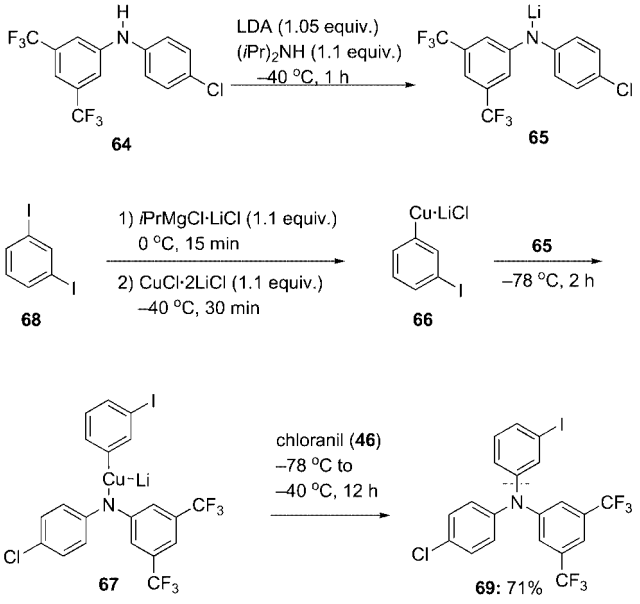
57: 94% from **56**
57: 72% from **52**

Scheme 24.

to afford the corresponding arylcopper derivative **54**, with subsequent addition of LiHMDS furnishing the amidocuprate **55**. This copper reagent reacted with chloranil (**46**) to provide the *N*,*N*-bis(trimethylsilyl)amine derivative **56** in 76% yield. A facile desilylation was achieved with TBAF, giving the arylamine **57** in 94% yield (Scheme 24).

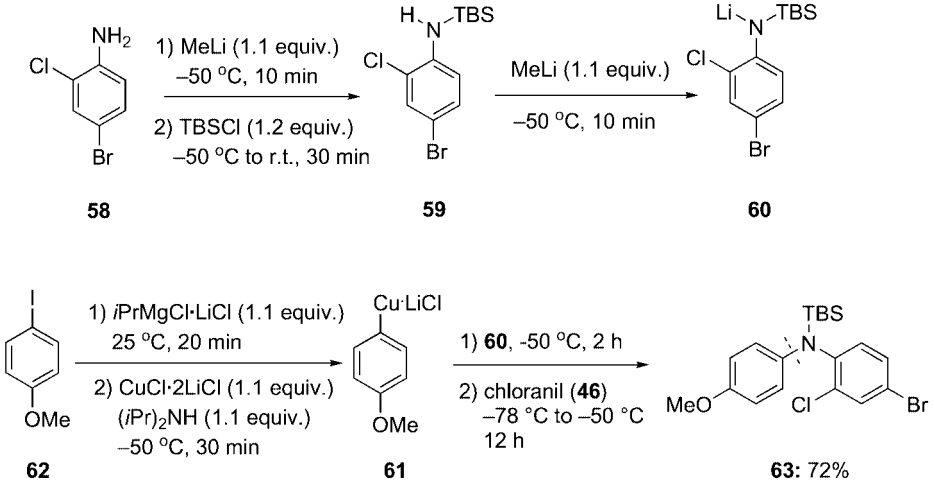
Secondary amines were prepared from aniline derivatives such as **58** (Scheme 25). Its in situ protection with a *tert*-butyldimethylsilyl (TBS) group was performed by lithiation with MeLi followed by the addition of TBSCl, leading to the *N*-silylaniline **59**. Further treatment with MeLi provided the lithium amide **60**, which was treated with the arylcopper reagent **61**. [This copper reagent was prepared from 4-iodoanisole (**62**) by an I/Mg exchange reaction with *i*PrMgCl·LiCl, followed by the addition of CuCl·2 LiCl in the presence of $i\text{Pr}_2\text{NH}$.] The resulting lithium amidocuprate was treated with chloranil (**46**) to provide the silyl-protected polyfunctional diarylamine **63** in 72% yield (Scheme 25). This reaction proved to be quite general, and a number of functionalized aromatic and heteroaromatic Grignard reagents variously bearing cyano, trifluoromethyl, or bromine substituents were found to undergo smooth oxidative amination with lithiated *N*-TBS anilines bearing various functional groups such as chloride, methoxy, or ester functions.

Finally, the preparation of polyfunctional triarylamines can be performed by the same approach. As an example, the lithiation of the secondary amine **64** with LDA in the presence of an additional equivalent of $i\text{Pr}_2\text{NH}$ provided the lithium amide **65**, which reacted with the copper reagent **66** to afford the lithium amidocuprate **67**. This copper reagent **66** was prepared by an I/Mg exchange on 1,3-diiodobenzene (**68**) with *i*PrMgCl·LiCl, followed by transmetallation with CuCl·2 LiCl. The resulting lithium amidocuprate **67** was treated with chloranil (**46**), providing the polyfunctional triarylamine **69** in 71% yield (Scheme 26). This sequence can be performed with several arylmagnesium reagents bearing various functional groups, such as methoxy, iodide, or amide groups, as well as with various lithium amides bearing functional groups such as bromide, nitrile, or ester groups, leading to the tertiary amines in acceptable yields.

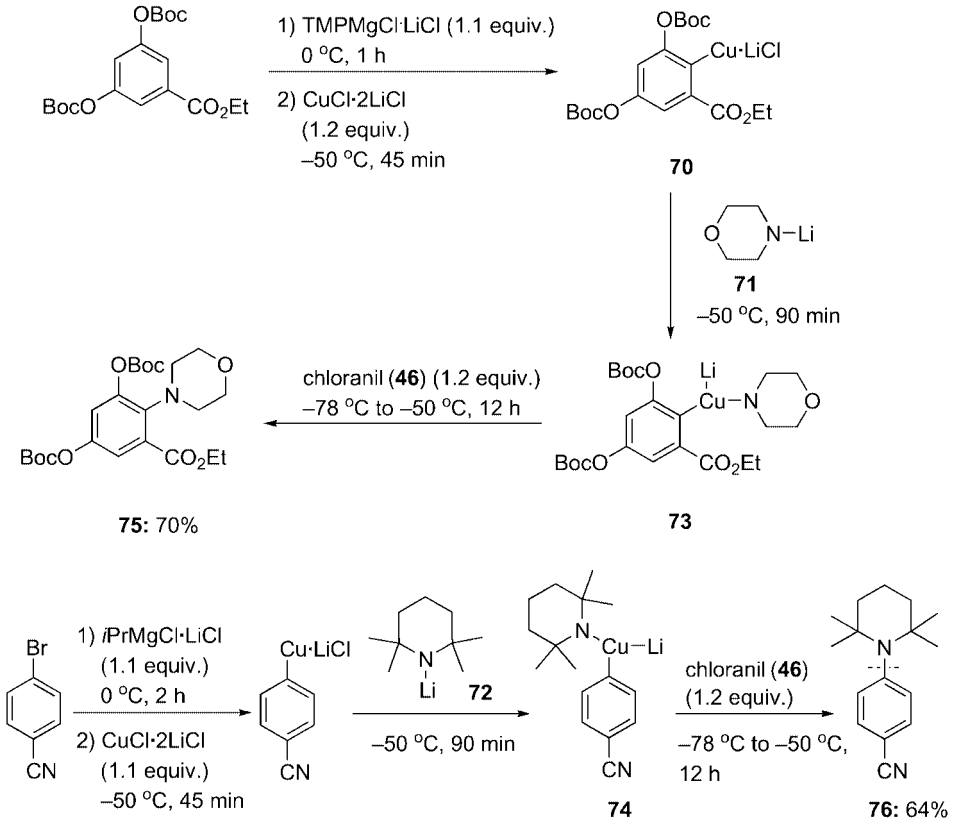


Scheme 26.

Remarkably, this amination reaction can be extended to the preparation of very sterically hindered copper reagents by use either of sterically hindered copper reagents such as **70** with the lithium amide **71** or of a sterically hindered lithium amide such as lithium 2,2,6,6-tetramethylpiperidide (**72**), through the oxidative couplings of the lithium amidocuprates **73** and **74**. The expected tertiary amines **75** and **76** are obtained in 70 and 64% yields, respectively (Scheme 27).



Scheme 25.



Scheme 27.

4. Conclusion

The importance of aromatic and heteroaromatic amines as target molecules for the synthesis of pharmaceuticals, xerographic and photographic materials,[59] conducting polymers, or materials precursors is the major driving force behind the rapidly developing field of modern amination reactions. This microreview presents the numerous synthetic tools currently available including transition metal-catalyzed amination reactions using palladium (Buchwald–Hartwig amination), nickel, and copper (Ullmann condensation reaction), as well as electrophilic amination reactions and oxidative couplings of amidocuprates. With these synthetic protocols, many long-standing challenges, such as the use of aryl chlorides and sterically hindered compounds, have been overcome. Improved compatibility with sensitive functional groups, while using milder and more environmentally friendly compounds has also been achieved.

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