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Amination and Formation of sp^2 C–N Bonds

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Amination and Formation of sp^2 C–N Bonds

Volume Editors: Marc Taillefer and Dawei Ma

With Contributions by

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Preface

The use of transition metal catalysis has provided organic chemists with a wide and quasi-exhaustive toolbox to create selectively the C(sp^2)-N bonds, essential not only for the development of bioactive molecules but also for materials engineering. Drawing on the bountiful number of publications related to this topic in the last 10 years, this volume mainly focuses on the most significant results and important breakthroughs.

The volume highlights in the first chapter, written by Lemen and Wolfe, the discovery and the development of original palladium-based catalysts for C(sp^2)-N bond formation via the coupling of nitrogen nucleophiles and aryl/alkenyl halides and pseudohalides. The authors also report various applications of these transformations to the synthesis of useful compounds, including biologically active molecules and materials.

In the second chapter, Correa and Bolm discuss a powerful set of protocols involving C(sp^2)-N bond formation which have emerged as reliable and convenient alternatives for the assembly of enamines and enamides. The authors also describe palladium-catalyzed oxidative amination of alkenes and both palladium- and copper-catalyzed cross-couplings generally between vinyl halides or pseudohalides and amines or amides.

Owing to their importance for pharmaceutical and material sciences, N-containing heterocycles have received great attention from the synthetic community. Another masterpiece of this volume "Assembly of N-Containing Heterocycles via Pd and Cu-Catalyzed C–N Bond Formation Reactions", presented by Jiang and Ma, covers the original and last contributions on the development of Pd- and Cu-catalysts for the assembly of N-heterocycles such as indoles, benzimidazoles, pyrroles, indazoles, indolines, lactams, quizolinones, heterobenzazepines, and other N-containing heterocycles.

By far the greatest number of reports on the modern catalytic Ullmann-type reactions has dealt with the creation of C–N bonds. Kantam et al. present, in their chapter, the recent developments in heterogeneous or recyclable copper-catalysts available to selectively form this C(sp^2)-N bond. The challenges and opportunities

in copper-catalyzed heterogeneous catalysis are enormous as less research has been carried out in this area compared to homogeneous systems. This part covers the recent recyclable protocols for the C−N bond forming reactions between aromatic, heterocyclic, and aliphatic-amines with aryl iodides, bromides, chlorides, and arylboronic acids employing copper mediated systems.

The last chapter by Monnier and Taillefer focuses on the copper-catalyzed formation of $C(sp^2)$-N bond via the coupling of nitrogen nucleophiles (N-heterocycles, amines, anilines, amides, ammonia, azides, hydroxylamines, nitrites salts, phosphonic amides) with aryl halides. The authors also present C (aryl)–N bond formation as a result of the coupling between these nucleophiles and aryl-boronic acids (the Chan–Lam reaction).

We would like to thank the authors for their diligent work on this hot topic.

Montpellier, France — Marc Taillefer
Shanghai, China — Dawei Ma

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Palladium-Catalyzed sp^2 C–N Bond Forming Reactions: Recent Developments and Applications

Georgia S. Lemen and John P. Wolfe

Abstract This review describes recent developments in the field of Pd-catalyzed sp^2 C–N bond formation that were reported in the primary literature between 2004 and 2008. These transformations have found widespread application in both academia and industry. A brief history of the field is presented, followed by recent improvements and extensions of the methodology. Applications of these transformations to the synthesis of useful compounds, including biologically active molecules, and materials, are described.

Keywords Arylamines · Cross-coupling · Heterocycles · Materials · *N*-Arylation · Natural products

Contents

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Abbreviations

μW	Microwave
Cy	Cyclohexyl
Dba	Dibenzylideneacetone
Dppe	1,2-Bis(diphenylphosphinoethane)
Dppp	1,3-Bis(diphenylphosphinopropane)
Hex	*n*-Hexyl
HMDS	Hexamethyldisilazide
IPr	*N*,*N*′-Bis(2,6-diisopropylphenyl)imadalol-2-ylidene
i-Pr	Isopropyl
PMP	4-Methoxyphenyl
SAR	Structure–activity relationship
TBS	*tert*-Butyldimethylsilyl

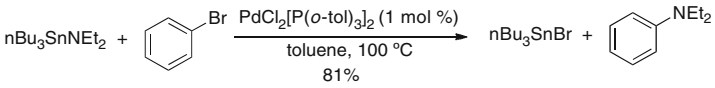
1 Introduction and Scope

Molecules that contain aryl C–N bonds play important roles in many different areas of chemistry, including materials and pharmaceuticals. For example, a number of top-selling drugs, including Lipitor [1], Abilify [2], and Celebrex [3], contain this functional unit. Over the past 15 years, Pd-catalyzed coupling reactions between aryl halides and amines have developed into broadly utilized methods for sp^2 C–N bond formation. These transformations have been used on both small academic scales and very large industrial scales. Due to the significance of this field, a number of reviews have been previously published describing various stages of its development ([4–11]; for a comprehensive review on the Buchwald biaryl phosphine ligands, see [12]; for a review on the utility of Josiphos-type ligands in Pd-catalyzed N-arylation reactions, see [13]; [14–21]). This review outlines key aspects of Pd-catalyzed sp^2 C–N bond forming cross-coupling reactions of nitrogen nucleophiles and aryl/alkenyl halides and pseudohalides that were reported in the literature between 2004 and 2008. Although this review is focused primarily on synthetic aspects of the chemistry, a very brief description of reaction mechanism along with a brief historical background is provided to place the current work in context and aid the reader.

2 Early Work Prior to 2004

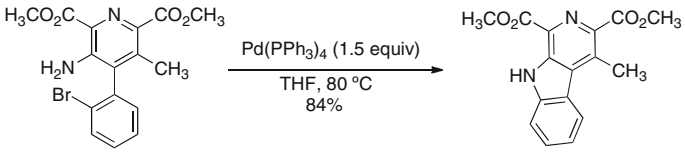
The first example of the formation of an aryl C–N bond via a Pd-catalyzed cross-coupling reaction of an aryl halide was reported in 1983 by Migita and coworkers [22, 23]. During the course of their studies on the reactivity of organotin compounds,

this group discovered that bromobenzene could be converted to *N*,*N*-diethylaniline by treatment with (*N*,*N*-diethylamino)tributylstannane and a palladium catalyst (Eq. 1). The scope of this reaction was quite limited. For example, efforts to use iodobenzene and chlorobenzene as electrophiles failed to generate the aniline product. Although the field of Pd-catalyzed cross-coupling reactions was relatively new at this time, the authors did suggest that the reaction proceeded via a sequence of three basic organometallic transformations: oxidative-addition, transmetallation, and reductive-elimination, which were combined into a catalytic cycle.



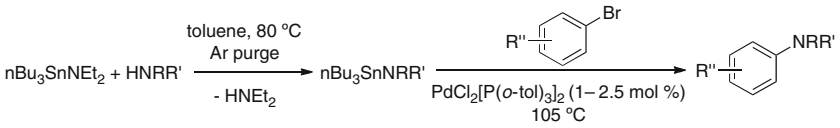
(1)

One year later, Boger and Panek [24–26] described the first synthesis of a natural product in which a Pd-mediated reaction was employed for the construction of an aryl C–N bond (Eq. 2). In this pioneering study, the D ring of lavendamycin methyl ester was generated from an intramolecular reaction between an aryl bromide and an aminopyridine. A stoichiometric amount of palladium was required for this transformation, and attempts to achieve catalytic turnover were unsuccessful. Thus, this study demonstrated the great potential synthetic utility of the C–N bond forming process, but also highlighted the need for development of more reactive palladium complexes that could function as catalysts with broad scope, rather than as stoichiometric reagents.



(2)

Interestingly, despite the considerable potential utility of a Pd-catalyzed C–N bond forming reaction with broad scope, the field lay inactive for the better part of 10 years, until attracting the attention of two research groups in the mid-1990s. Two significant papers emerged in 1994 that provided the necessary spark for continued development in this area. A detailed investigation into the mechanism of the Migita aminostannane cross-coupling reaction was reported by Hartwig and coworkers [27]. Although the field of Pd-catalyzed cross-coupling had undergone intensive investigation between the early-1980s and the mid-1990s, no study had ever explored Migita's proposed mechanism for C–N bond formation via reductive elimination from a palladium(II) (aryl)(amido) complex. In addition, relatively few late transition metal complexes bearing metal–heteroatom bonds had been prepared, and a significant number of organometallic chemists believed that these complexes would be inherently unstable due to electron–electron repulsion [28]. In this initial publication, Hartwig demonstrated that isolable dimeric (o-tol_3P)Pd(Ar)(Br) complexes were converted to $ArNMe_2$ products when heated with Bu_3SnNMe_2. This provided support for Migita's

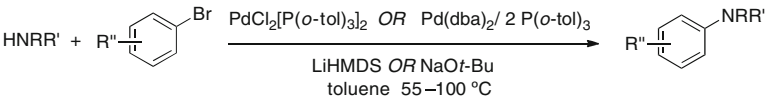


Scheme 1 In Situ Generation of Aminostannanes for Pd-Catalyzed N-Arylation Reactions

mechanism that involved transmetallation of the NMe_2 group followed by C–N bond-forming reductive elimination.

Also in the mid-1994, Buchwald and coworkers developed a means to significantly expand the scope of the Migita reaction through an in situ transamination protocol that exchanged the dimethylamino group of Bu_3SnNMe_2 with various amines [29]. This allowed access to a broader array of substituted aniline derivatives (Scheme 1).

Despite these findings, the use of aminostannanes in Pd-catalyzed *N*-arylation reactions had significant drawbacks. The Bu_3SnNMe_2 reagent is quite moisture sensitive, and both the reagent and the tin-containing by-products of the cross-coupling reaction are toxic. A major advance in the field came in 1995, when Buchwald [30] and Hartwig [31] independently demonstrated that amines can be directly coupled with aryl bromides in the presence of a strong base and a Pd/P(*o*-tol)$_3$ catalyst (Eq. 3). This alleviated the need for stoichiometric amounts of tin, which led to a practical procedure that would be useful in both academic and industrial settings.

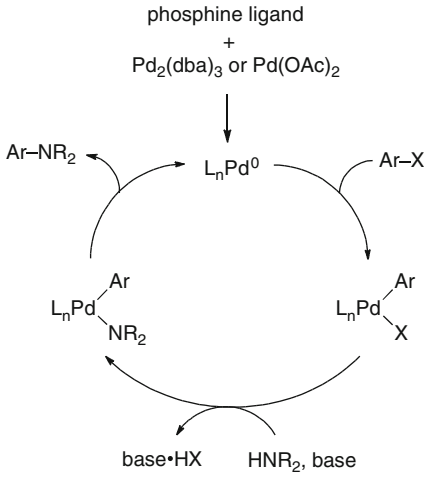


(3)

A number of studies have examined the mechanism of base-mediated Pd-catalyzed amination reactions [32–44]. A simplified catalytic cycle is illustrated below (Scheme 2). However, the precise, detailed mechanism for any Pd-catalyzed *N*-arylation reaction is highly dependent on ligand structure, amine basicity, and base strength [32–44]. In general, the transformation is initiated by oxidative addition of the aryl halide to a Pd(0) complex, which is frequently generated in situ from mixtures of a phosphine ligand and a precatalyst such as $Pd_2(dba)_3$ or $Pd(OAc)_2$. The resulting $L_nPd(Ar)(Br)$ intermediate is converted into a $L_nPd(Ar)(NR_2)$ complex upon reaction with amine in the presence of base. The $L_nPd(Ar)(NR_2)$ complex then undergoes C–N bond-forming reductive elimination (for a recent review, see [45]; [46, 47]) to afford the desired product with concomitant regeneration of the catalyst. The most common side reaction observed in this process is competing β-hydride elimination from the $L_nPd(Ar)(NR_2)$ complex, which leads to reduction of the aryl bromide substrate.

Although the new tin-free conditions represented a major advance, the scope of the *N*-arylation reactions was still quite limited with the original Pd/P(*o*-tol)$_3$ catalyst system. Over the next several years, a series of experiments illustrated that the nature of the phosphine ligand played a key role in reactivity and selectivity. Thus, a number of ligands were subsequently employed that allowed for efficient coupling of a broad

Scheme 2 General Mechanism of Pd-Catalyzed N-Arylation Reactions



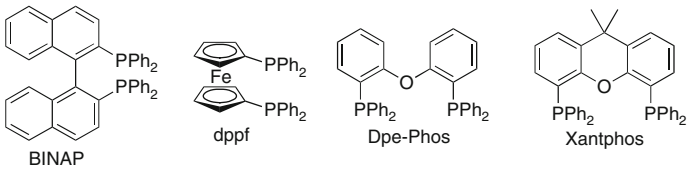


Fig. 1 Chelating Ligands Used in Second-Generation Catalysts for Pd-Catalyzed N-Arylation Reactions

array of amines and aryl or heteroaryl halides. These include BINAP [48], dppf [49], Dpe-Phos [50], and Xantphos [51] (Fig. 1). In addition to expanding the types of amine nucleophiles that could be effectively coupled, the use of these ligands also broadened the range of electrophiles (ArI, ArBr, ArOTf) for these reactions. Moreover, many of the catalysts generated in situ from these ligands were sufficiently reactive to allow for use of weak bases such as Cs_2CO_3, which greatly improved the functional group tolerance of the *N*-arylation reactions.

Although use of these chelating bis(triaryl)phosphine ligands led to a significant expansion in the scope of this method, an important class of electrophiles could not be employed. The use of aryl chlorides would allow for large-scale reactions to be conducted much more economically due to the low cost of these electrophiles. However, aryl chlorides typically do not undergo oxidative addition to palladium complexes derived from triaryl phosphines. It was known that more electron-rich phosphines not only facilitate the oxidative addition but also decrease the rate of reductive elimination. Thus, the use of a ligand such as PCy_3 would improve one step of the catalytic cycle while hindering another. To overcome this problem, several groups investigated the use of a new class of ligands that were both electron-rich and sterically bulky (to facilitate reductive elimination) for aryl chloride aminations (Fig. 2). Among the most widely utilized of these ligands are biaryl (dialkyl) phosphines that were developed by Buchwald (Fig. 2) ([12]; [52]). Hartwig illustrated

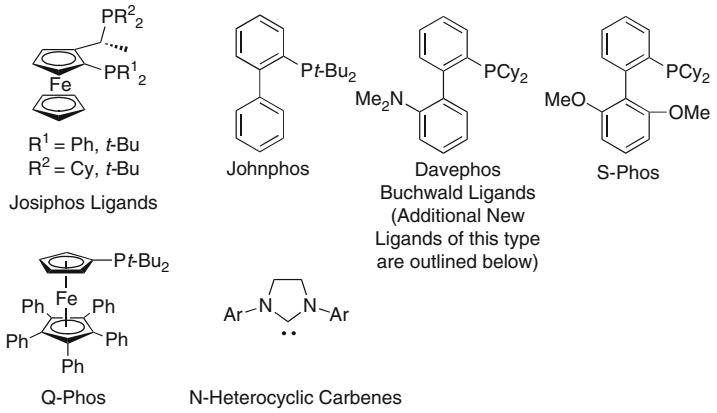


Fig. 2 Third Generation Ligands for Pd-Catalyzed N-Arylation Reactions

that Q-phos [53] and Josiphos ligands were also effective for these transformations ([13]), and the simple monodentate ligand P(*t*-Bu)$_3$ [54, 55] has also been employed in several applications. The utility of *N*-heterocyclic carbene ligands in Pd-catalyzed *N*-arylation reactions has also been investigated [56, 57], although they are used less frequently than phosphines. The specific details on each of these classes of ligands have been outlined in prior reviews ([4–11]; for a comprehensive review on the Buchwald biaryl phosphine ligands, see [12]; for a review on the utility of Josiphos-type ligands in Pd-catalyzed N-arylation reactions, see [13]; [14–21]).

3 Improvements and Extensions of Pd-Catalyzed *N*-Arylation Methods

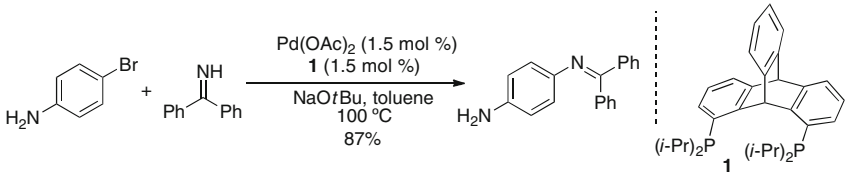
3.1 New Ligands and Continued Exploration of Existing Ligands

Further exploration of scope and utility of the ligands described above has led to many interesting new results in this field. In addition, the development of new ligands for Pd-catalyzed *N*-arylation reactions has remained an area with significant research activity. In some instances, direct comparisons of different ligands have been reported [58–61], and although no single ligand provides the best results for all substrate combinations, nearly all transformations can be achieved with at least one ligand. The new ligands highlighted below are a subset of those that appeared in the literature between 2004 and 2008, with a focus on those that provide reactivity complementary or superior to that of existing ligands. A few studies have explored the utility of supported/reusable catalysts for these reactions [62–67], but these

types of catalysts have not yet found widespread appeal or applications and are therefore not covered in detail.

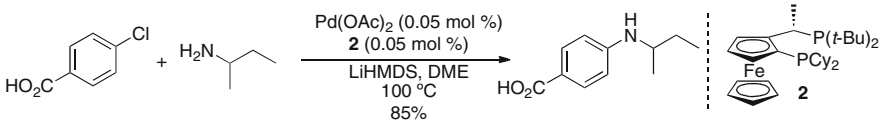
3.1.1 Bidentate Phosphines

The efficacy of dppf, BINAP, Josiphos, and other chelating ligands in Pd-catalyzed *N*-arylation has prompted further exploration of bidentate ligands. An interesting trans-chelating ligand **1** was recently prepared for *N*-arylation reactions of benzophenone imine [68]. For example, the selective cross-coupling of 4-bromoaniline with benzophenone imine was achieved in 87% yield using a catalyst composed of **1**/Pd $(OAc)_2$ (Eq. 4). Competing oligomerization of the 4-bromoaniline was not observed. Direct comparison of ligand **1** with other chelating phosphines suggests this ligand is more efficient than dppf or BINAP for benzophenone imine *N*-arylation reactions, but is of comparable reactivity to Xantphos when $Pd_2(dba)_3$ is used as the precatalyst.



(4)

The Hartwig group has continued to examine the reactivity of catalysts supported by the Josiphos ligands [13, 69]. The use of **2** has allowed for the coupling of highly functionalized aryl chlorides with primary amines and benzophenone imine. Amides, enolizable ketones, phenols, alcohols, and carboxylic acids are tolerated in these reactions. For example, a catalyst composed of $Pd(OAc)_2$/**2** effected the coupling of 4-chlorobenzoic acid with *sec*-butylamine in 85% yield (Eq. 5). In addition, catalysts supported by this ligand are relatively long-lived, and catalyst loadings as low as 0.001 mol% Pd can be employed in some instances. This ligand is also effective for the *N*-arylation of aryl and heteroaryl tosylates at rt [70]. Hartwig has also developed an air- and moisture-stable L_1PdCl_2-complex of **2** that serves as a user-friendly precatalyst [71]. This complex exhibits similar reactivity to mixtures of $Pd(OAc)_2$/**2**.



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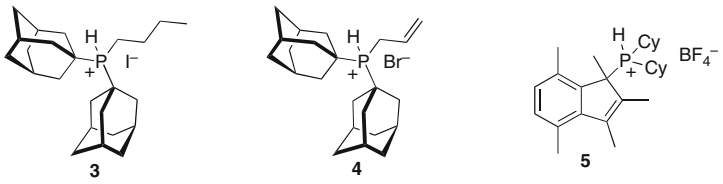
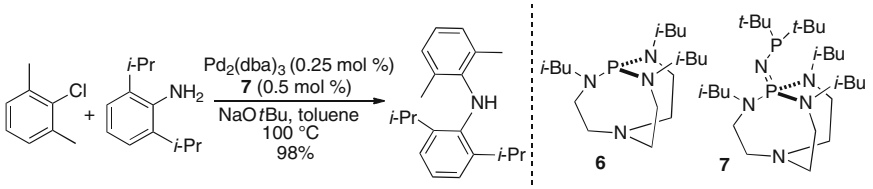


Fig. 3 Bulky, Electron-Rich Ligands for Pd-Catalyzed N-Arylation Reactions

3.1.2 Monodentate Phosphines

Following initial reports on the utility of the bulky monodentate ligand P(*t*-Bu)$_3$, several groups have examined other sterically encumbered trialkylphosphines (Fig. 3) in Pd-catalyzed coupling reactions between amines and aryl halides. For example, Shaughnessy has reported that (neopentyl)P(*t*-Bu)$_2$ has similar activity as P(*t*Bu)$_3$ in these transformations [72]. Beller has illustrated that bulky, electron-rich phosphines **3** and **4** are useful in Pd-catalyzed *N*-arylation reactions [73, 74]. In some instances catalyst loadings as low as 0.01 mol% Pd can be employed. Indene-derived trialkylphosphine **5** has also been used for arylation reactions of aryl chloride electrophiles [75, 76]. The reactivity of catalysts supported by this ligand appears to be similar to that of many existing Pd/ligand systems, although the first example of aminoferrocene *N*-arylation was carried out using **5** [75]. All three of these ligands are typically introduced to reaction mixtures as air-stable phosphonium salts, which are converted into the corresponding free phosphines in the presence of base.

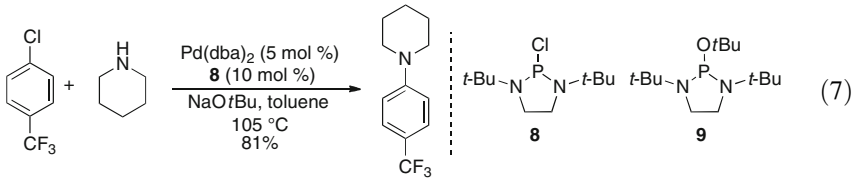
The Verkade group has conducted extensive studies on the synthesis and reactivity of phosphazenes, which are strong, non-nucleophilic bases [77]. More recently this group has employed these types of compounds (e.g., **6**–**7**) as ligands for Pd-catalyzed *N*-arylation reactions [78–80]. These ligands are effective with a broad range of substrates, including sterically hindered aryl halides, and 2,6-disubstituted aniline derivatives (Eq. 6). However, efforts to use these ligands for reactions of primary aliphatic amines have been unsuccessful.



(6)

During the past several years the use of secondary phosphine oxides, chlorophosphines, and related species as ligands for late-transition metal catalysts has been explored by several groups (reviews [81, 82]). Catalysts supported by these unusual ligands have shown some utility in Pd-catalyzed *N*-arylation reactions. For example, treatment of 4-chlorobenzotrifluoride with piperidine and NaO*t*Bu in the presence

of $Pd_2(dba)_3$ and **8** afforded the coupled product in 81% yield (Eq. 7) [83]. The chlorophosphine **8** likely functions as a pre-ligand, which is transformed to *t*-butoxyphosphine **9** under the reaction conditions. Although these ligands are conceptually interesting, their reactivity does not appear to approach that of other phosphines more commonly employed in *N*-arylation reactions.

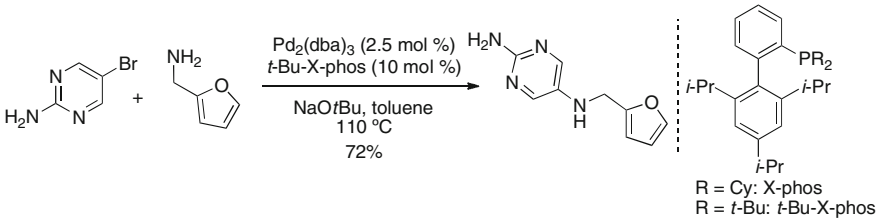


(7)

3.1.3 Hemilabile Phosphine Ligands

Catalysts supported by the Buchwald biaryl phosphine ligands have exhibited both excellent reactivity and excellent generality with a broad range of coupling partners. The ligands are commercially available air-stable crystalline solids that are easy to handle. The unique reactivity of these ligands is attributed to their hemilabile nature. The *ortho*-aromatic group is positioned to allow a weak binding interaction between the metal and the ligand π-system that imparts added stability to the catalysts, but is sufficiently labile to allow access to highly reactive 3-coordinate intermediates. Since the initial report by Buchwald and coworkers on the use of hemilabile *ortho*-biphenyl phosphine derivatives [52], several other related ligands have been developed. The chemistry of these ligands has been extensively described in two recent reviews ([12]; [19]). As such, they are only briefly covered in this section.

Buchwald has shown that X-Phos and *t*-Bu-X-Phos are good ligands for the coupling of highly functionalized aryl chlorides and bromides with primary amines, primary anilines, and nitrogen containing aromatic heterocycles [84]. For example, the coupling of furan-2-ylmethylamine with 2-amino-5-bromopyrimidine proceeded in 72% yield using *t*-Bu-X-Phos as ligand (Eq. 8). The X-Phos series of ligands have also shown utility in reactions of aryl nonaflate electrophiles [85].



(8)

Four other new biarylphosphine ligands have recently been developed by the Buchwald group that are effective in very challenging coupling reactions. Brettphos exhibits outstanding reactivity with electrophiles such as aryl mesylates that are unreactive towards other catalyst systems (Fig. 4) [86]. This ligand is also effective

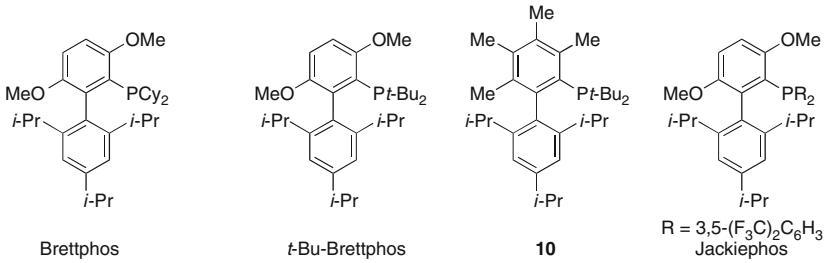
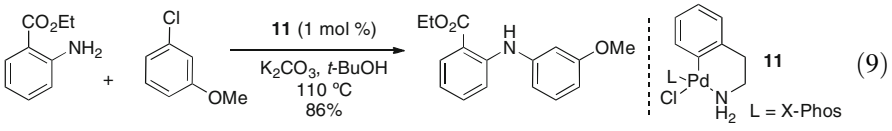


Fig. 4 Hemilabile biaryl phosphine ligands for Pd-catalyzed N-arylation reactions

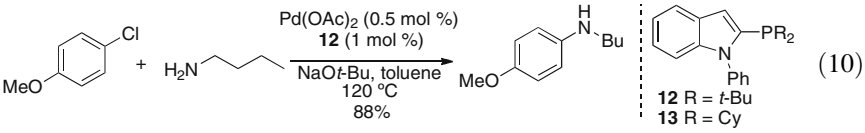
for *N*-arylation reactions of aryl iodides, which can be difficult to achieve as catalyst deactivation often occurs when other ligands are employed [87]. The related ligands *t*-Bu-Brettphos and methylated analog **10** are useful for coupling reactions of amides with aryl chlorides [88–90]. Jackiephos is effective for the *N*-arylation of a broad array of secondary amide, urea, carbamate, and sulfonamide substrates [91]. Several binaphthyl (MOP-type) analogs of the Buchwald ligands have been examined by Zhang in *N*-arylation reactions [92], although it is not clear these are superior to the biaryl-derived phosphines.

Mechanistic studies have illustrated that monophosphine palladium complexes (L_1Pd) exhibit considerably higher reactivity than analogous bis(phosphine) complexes (L_2Pd) ([4–21]). However, in most instances the catalysts employed in *N*-arylation reactions are generated in situ from mixtures of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and a phosphine ligand. This frequently leads to mixtures of different palladium complexes (both L_1Pd and L_2Pd) and reactivity that is less than that theoretically possible. To overcome this limitation, several studies have explored the development of precatalysts bearing a single phosphine that are cleanly converted into L_1Pd complexes in situ. The Buchwald group has recently prepared a new series of palladacycles (e.g., **11**) derived from phenethylamine that are supported by biarylphosphines such as X-Phos and others described above. These palladacycles serve as precursors to L_1Pd catalysts that are sufficiently reactive to couple sterically hindered electron deficient anilines with aryl chlorides (Eq. 9) [93, 94]. In addition, many *N*-arylation reactions can be carried out at room temperature using these complexes. Related palladacycles derived from ferrocenylimines have also been employed for room-temperature amination reactions [95]. In addition, a series of dinuclear palladium complexes supported by the Buchwald biaryl ligands have been developed, and their reactivity is superior to that of complexes generated in situ from mixtures of ligand + $Pd(OAc)_2$ or $Pd_2(dba)_3$ [96].



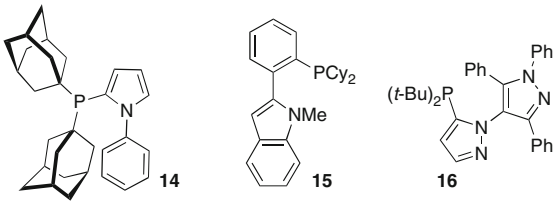
(9)

Several groups have investigated the utility of hemilabile biaryl phosphine ligands in which one or both aryl units are heteroaromatic. Beller and coworkers have developed *N*-phenyl 2-phosphinoindole ligands (e.g., **12**–**13**) for *N*-arylation reactions [97]. These ligands allow for the coupling of electron-rich, electron-poor, and heteroaromatic aryl chlorides with primary amines, anilines, and cyclic amines with good yields (88–99%). For example, the Pd/**12**-catalyzed coupling of butylamine with 4-chloroanisole proceeded in 88% yield (Eq. 10). A series of related dialkylphosphinoimidazole ligands such as **14** (Fig. 5) have also been explored and exhibit reactivity similar to the indole-based ligands [98, 99]. The 2-phenylindole-derived ligand **15** has shown utility for amination reactions of aryl mesylates [100]. Singer and coworkers from Pfizer have developed a non-proprietary bipyrazole phosphine ligand (**16**) [101–103]. Although catalysts supported by **16** appear to be less reactive than those derived from the Buchwald biaryl phosphines, they still have useful activity in *N*-arylation reactions of aryl bromides and chlorides.

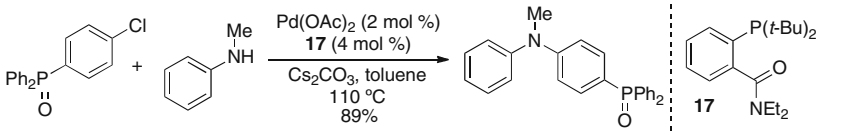


(10)

Fig. 5 Hemilabile Heterobiaryl Phosphine LIgands for Pd-Catalyzed N-Arylation Reactions



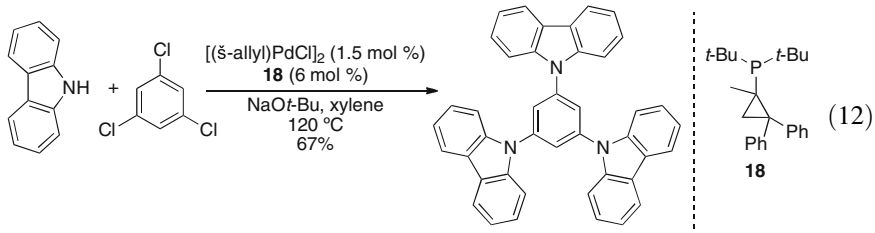
The vast majority of hemilabile ligands employ an *o*-aryl or heteroaryl group appended to an aryl(dialkylphosphine) as the weakly coordinating moiety. However, recent studies from two research groups have explored alternative ligand structures with hemilabile binding groups. Kwong and coworkers have developed an aryl(di-*t*-butyl)phosphine bearing an *ortho*-amide substituent (**17**) [104]. Use of this ligand for the *N*-arylation of 4-chlorotriphenylphosphine oxide with *N*-methylaniline led to an 89% yield of the desired product (Eq. 11)



(11)

Another structurally interesting hemilabile ligand was developed by Suzuki and coworkers and is based on a 2,2-diphenyl-1-(di-*t*-butylphosphino)-1-

methylcyclobutane scaffold (**18**). The phenyl substituent that is oriented *cis* to the phosphine can bind palladium through a M-π interaction similar to the biarylphosphines described above. This ligand is effective for the coupling of diarylamines and carbazole with aryl bromides and chlorides [105]. For example, 1,3,5-trichlorobenzene can be coupled with 3 equiv of carbazole to yield a compound with interesting photoluminescent properties (Eq. 12). Hemilabile ligands based on a [2,2-diarylvinyl]phosphine scaffold have also been examined by this group [106].



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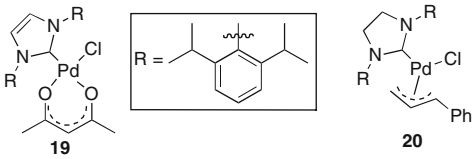
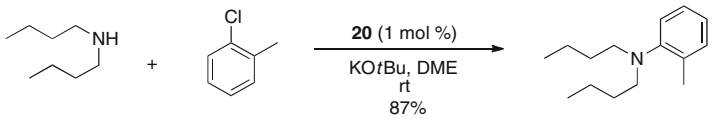


Fig. 6 N-Heterocyclic Carbene Precatalysts for Pd-Catalyzed N-Arylation Reactions

3.1.4 *N*-Heterocyclic Carbenes

As noted above, *N*-heterocyclic carbenes (NHCs) have been investigated as alternatives to phosphines in Pd-catalyzed *N*-arylation reactions. These ligands have not been employed as frequently as phosphines, and head-to-head comparisons suggest that phosphines may be more generally effective [107]. However, the NHC ligands have shown some utility in reactions with aryl chloride electrophiles. Recent studies in this area have led to several new catalyst systems (Fig. 6). For example, Nolan has demonstrated that the (NHC)Pd(Cl)(acac) complex **19** provides good results in a number of Pd-catalyzed *N*-arylation reactions [108–110]. The related (NHC)Pd(Cl)(cinnamyl) complex **20** is sufficiently reactive to catalyze the coupling of dibutylamine with 2-chlorotoluene at rt (Eq. 13) [111–113]. The reactivity of NHC-ligated cyclopalladated complexes of *N*,*N*-dimethyl-2-phenylaniline has also been examined [114]. Organ and coworkers have developed (NHC)$PdCl_2$(3-chloropyridine) complexes **21** that have shown useful reactivity in *N*-arylations [115, 116]. For example, the coupling of 2-chloro-5-methoxypyridine with *N*-methyl aniline proceeded in 94% yield using **21** as catalyst and Cs_2CO_3 as a mild base (Eq. 14). Although most Pd-NHC complexes are generated through ligand exchange processes, Fürstner has illustrated these species can also be formed via oxidative addition of 2-chloroimidazolium salts to Pd(0) [117]. This allows access to catalysts that cannot be easily prepared via other methods.



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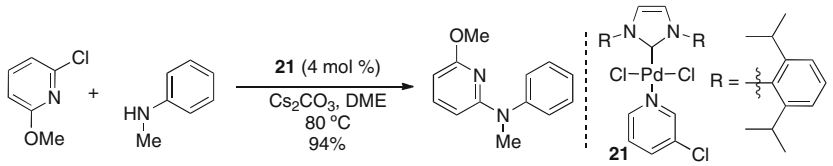


(14)

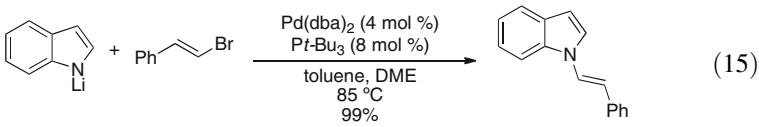
3.2 *Modified Reaction Conditions or Techniques That Facilitate Pd-Catalyzed* N*-Arylations*

Several studies have explored the influence of modified reaction conditions or special techniques to facilitate Pd-catalyzed *N*-arylation reactions. For example, Buchwald has demonstrated that water can be used to preactivate $Pd(OAc)_2$/biarylphosphine catalyst systems, which leads to enhanced reactivity in *N*-arylations [118]. The addition of small amounts of water has been shown to accelerate Pd/Xantphos-catalyzed *N*-arylations of amide nucleophiles when Cs_2CO_3 is used as base [119]. Particle size, shape, and molar excess also have a large influence on reaction rates for Cs_2CO_3-mediated reactions [120]. The use of microwave irradiation to facilitate *N*-arylation has been explored [121–124], and transformations have been conducted in continuous flow microreactors [125], or with supercritical CO_2 as solvent [126].

3.3 *New Nucleophiles and Electrophiles or Improved Reactions of Previously Studied Nucleophiles and Electrophiles*

3.3.1 Alkenyl Halides

In 2002, the expansion of the Buchwald-Hartwig amination reaction to alkenyl halide electrophiles was reported. This has proven to be a useful method for the construction of enamines or imines that are difficult to prepare using traditional condensation reactions [127]. For example, Voskoboynikov and coworkers [128] demonstrated that azoles could be stereoselectively coupled with either *E*- or *Z*-β-bromostyrene to generate enamines using a catalyst composed of $Pd(dba)_2$ and P(*t*-Bu)$_3$ (Eq. 15). In the same year, Mori and Kozawa reported $Pd(OAc)_2$/DPE-Phos catalyzed intramolecular *N*-alkenylation reactions that afforded bicyclic β-lactams (Eq. 16) [129].



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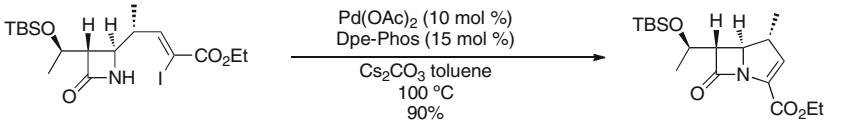
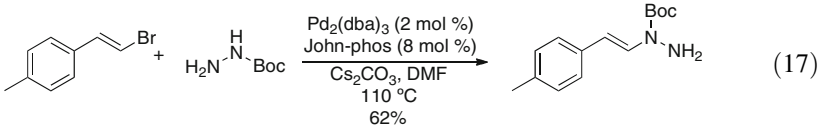


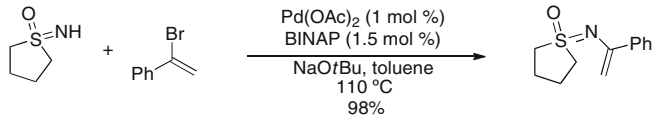
(16)

Barluenga and Willis have independently demonstrated that secondary amines can be coupled with alkenyl bromides or triflates using a Pd/BINAP catalyst to generate enamines [130–132]. Imines can also be accessed through the use of primary amines as nucleophiles. Alkenyl chlorides or chlorodienes can be coupled with amines using the Buchwald biaryl phosphines as ligands for palladium [133, 134]. As noted above, these transformations have significant utility. For example, Pd-catalyzed *N*-alkenylation reactions of *t*-butylcarbazide lead to selective reaction of the Boc protected nitrogen atom (Eq. 17). The N^1-Boc-N^1-alkenylhydrazine products cannot be prepared via condensation of *t*-butylcarbazide with aldehydes or ketones, as the unsubstituted nitrogen is more nucleophilic. The observed regioselectivity in the Pd-catalyzed reactions is due to deprotonation of the NH-Boc group under the reaction conditions, which affords the requisite intermediate palladium amido complex [135]. The related coupling of arylhydrazines with β-bromovinyl aldehydes has been employed in the synthesis of pyrazoles ([136]; for analogous reactions of 2-bromobenzaldehyde derivatives, see [137]). The Buchwald ligands are also effective for coupling reactions of alkenyl tosylate substrates [138]. Verkade's proazaphosphatane ligands have been used in Pd-catalyzed amination reactions with alkenyl bromides and chlorides [139].



(17)

A variety of nitrogen nucleophiles have been utilized in Pd-catalyzed *N*-alkenylation reactions. For example, Bolm has employed *N*-alkenylation reactions for the preparation of *N*-alkenyl sulfoximines (Eq. 18) [140], and Yudin has applied this method to the synthesis of *N*-alkenyl aziridines (Eq. 19) [141]. Analogous *N*-arylation reactions of sulfoximines and aziridines have also been developed [142, 143]. Movassaghi has effected *N*-alkenylation reactions between functionalized alkenyl triflates and several aromatic nitrogen heterocycles including indoles and pyrroles (Eq. 20) [144]. The use of β-chloroacrolein derivatives as substrates in *N*-alkenylation reactions has also been illustrated [145, 146].



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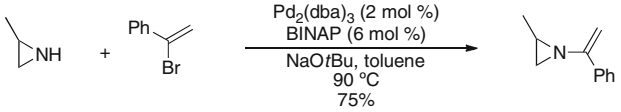

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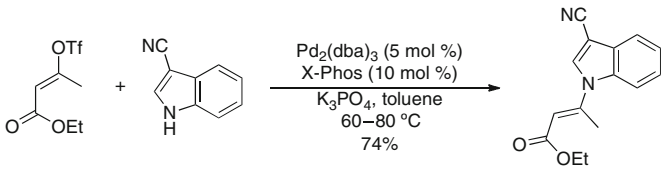
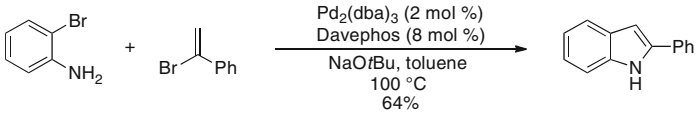


(20)

The synthesis of many different aromatic heterocycles has been accomplished through *N*-akenylation of amines or amides followed by subsequent ring formation [147–150]. For example, several new strategies for the preparation of indoles have been reported that involve cascade or multicomponent couplings. Barluenga has developed a sequential palladium-catalyzed *N*-alkenylation followed by intramolecular Heck reaction of 2-bromoaniline derivatives [151] (Eq. 21). Willis has employed tandem *N*-alkenylation/*N*-arylation reactions of 2-(2-haloalkenyl)-aryl halides with primary amines for indole synthesis [152, 153] (Eq. 22). Lautens has developed several different sequenced *N*-arylation/cross coupling reactions for the preparation of indoles from *ortho-gem*-dihalovinylanilines [154–159]. For example, treatment of 2-*gem*-dibromovinylaniline with 4-methoxyphenylboronic acid in the presence of a Pd/S-phos catalyst and K_3PO_4 afforded a 2-arylindole in 83% yield via cascade *N*-arylation/Suzuki coupling [154] (Eq. 23). This strategy has also been applied to the synthesis of other heterocycles [158].



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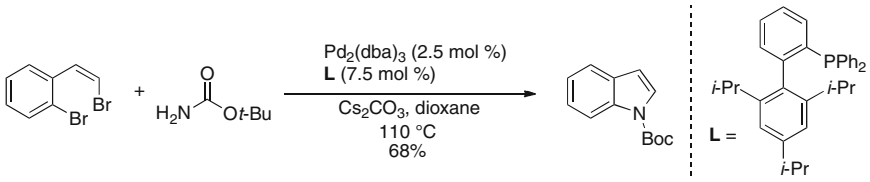

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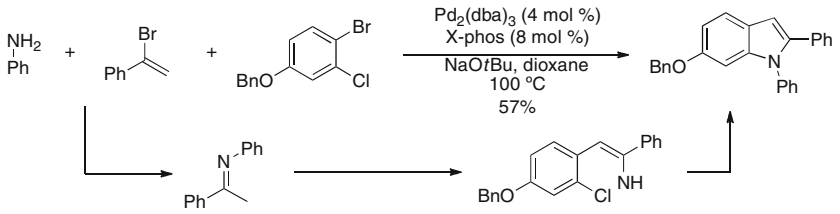
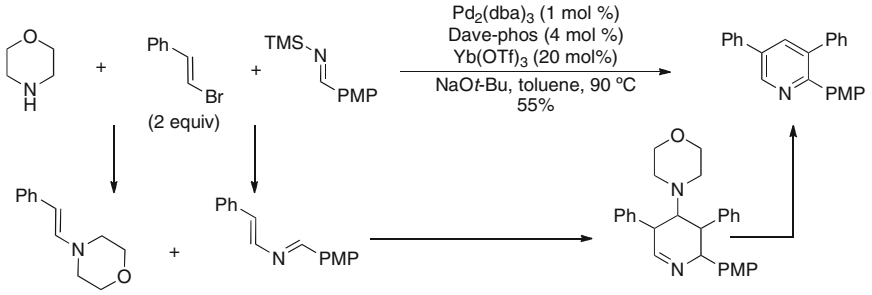
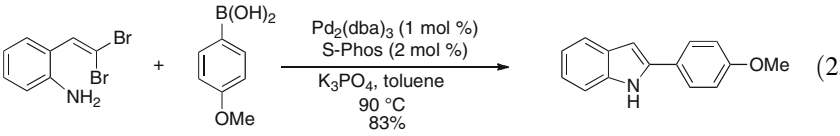


Scheme 3 Multicomponent Synthesis of Indoles via Sequential Pd-Catalyzed C–C and C–N Bond-Forming Reactions



Scheme 4 Multicomponent Synthesis of Pyridines via Pd-Catalyzed N-alkenylation/Hetero Diels-Alder Reactions



(23)

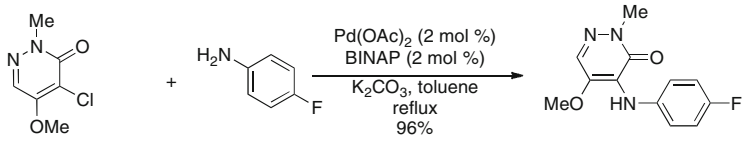
Enamines generated by Pd-catalyzed coupling reactions have been employed in several cascade processes. An interesting approach to the synthesis of indoles involves a three-component coupling between an amine, an alkenyl halide, and a 1,2-dihalobenzene [160]. An initial *N*-alkenylation reaction provides an intermediate imine, which undergoes α-arylation to yield an enamine. Intramolecular *N*-arylation subsequently occurs to afford the indole product (Scheme 3). A related multicomponent reaction was reported for the generation of pyridines (Scheme 4) [161]. This transformation proceeds via *N*-alkenylation of morpholine to generate an enamine, which occurs simultaneously as desilylation and *N*-alkenylation of an *N*-silyl imine to give a heterodiene. A [4+2] cycloaddition followed by elimination then yields the heterocyclic product. The Pd-catalyzed formation of enamines followed by reaction with Michael acceptors to afford substituted malonate derivatives has also been described [162].

3.3.2 Heteroaromatic Halides and Heteroaromatic Amines

A large number of interesting biologically active compounds and pharmaceutical targets contain heteroaromatic groups. Thus, Pd-catalyzed *N*-arylation reactions

involving heteroaryl halides, heteroaryl amines, and azoles have been of longstanding interest. These substrates can be quite challenging to employ, as pyridine and related nitrogen heterocycles are good ligands for palladium and can cause catalyst deactivation. Thus, the proper choice of catalyst is essential for successful coupling of these derivatives. Early studies on the use of heteroaryl halides indicated that chelating ligands or bulky, electron-rich ligands provided satisfactory results in many cases [163–165]. Azoles, including pyrrole and indole, can also be *N*-arylated under appropriate conditions [166, 167].

Heterocycle amination has continued to be an active area of research [168–170]. For example, Mátyus and coworkers have demonstrated that aniline derivatives can be coupled with chloromethoxypyridazine-3(2H)-ones in excellent yields (Eq. 24) [171]. Buchwald and coworkers have coupled chlorothiophenes, 5-bromopyrimidine, haloindoles, chlorobenzoxazoles and chlorobenzothiazoles with anilines, cyclic amines, and indole using *o*-biphenyl ligands [172]. Interestingly, unprotected haloindoles can be coupled with amines without competing *N*-arylation of the indole nitrogen atom (Eq. 25) [172]. Hartwig has demonstrated that the Josiphos-type ligands are also effective for heteroaryl chloride amination reactions [69] and has shown that coupling of amides with heteroaryl chlorides can be facilitated by added BEt_3 [173]. Gueiffier and coworkers have effected the coupling of 2-(4-fluorophenyl)-8-iodoimidazo[1,2-*a*]pyridine with primary amines and cyclic amines using either copper or palladium catalysts. However, palladium catalysts provided superior yields in these transformations (Eq. 26) [174].



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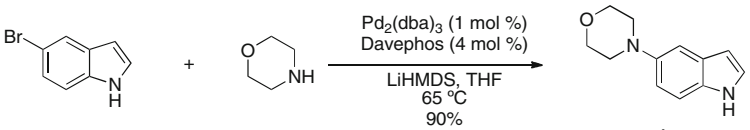

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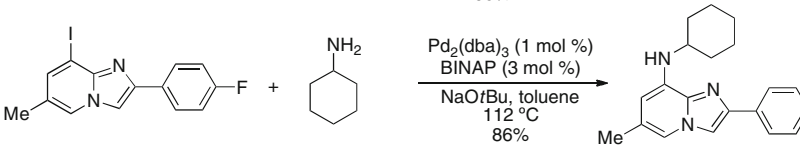
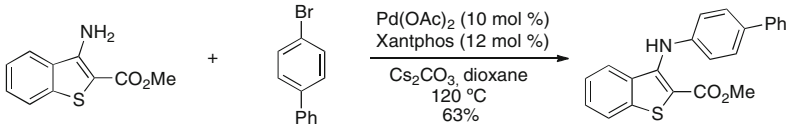


(26)

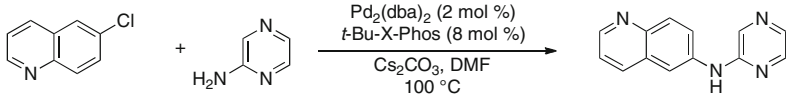
In addition to the examples described above, many other heteroaromatic substrates have been employed in *N*-arylation reactions, including triazines [175], thiophenes and benzothiophenes [176–180], pyridines and pyridones [181–183], quinolines and quinolones [184, 185], coumarins [186, 187], chromenes and chromones [188, 189], pyridazines [190], azaindoles [191], pyrroles and pyrazolo-heteroarenes [192, 193], indazoles [194], indolizinones [195], triazines [196], and

naphthyridines [197]. The *N*-arylation of aminobenzothiophine derivatives has also been accomplished (Eq. 27) [176].



(27)

Conducting efficient *N*-arylation reactions of 2-aminopyridines and related nucleophiles is particularly challenging, as coordination of the metal between the two nitrogen atoms can lead to catalyst deactivation. However, several catalysts have been developed that efficiently transform these substrates. For example, Buchwald has illustrated that X-phos is an excellent ligand for *N*-arylation of 2-aminoheteroarenes (Eq. 28) [84], and Hartwig has employed Josiphos for related coupling reactions (Eq. 29) [59]. In some instances other ligands have also proven useful (see below in Eq. 31). A number of other aminoheterocycles [198–201], including purine and guanosine nucleosides [202–208], have been *N*-arylated using palladium catalysts.



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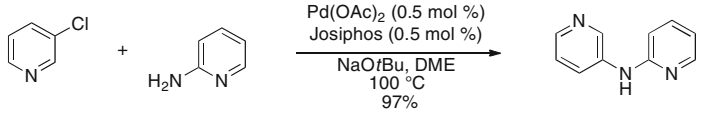
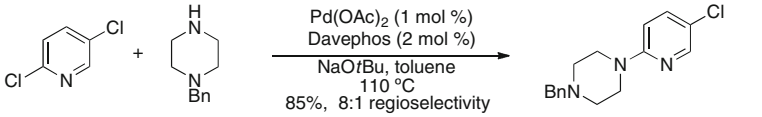


(29)

Several studies have explored the reactivity of heteroarenes bearing two halogen atoms [209–216]. For example, Beller has shown that 2,5-dichloropyridine can be coupled with piperazine derivatives with good regioselectivity using Davephos as ligand (Eq. 30) [217]. Vaquero has demonstrated that the variolin core can be selectively aminated with substitution of the activated chloro group in preference to the bromide (Eq. 31) [218]. Beletskaya has illustrated that 6-bromo-4-chloroquinoline can be sequentially *N*-arylated with two different amines (Scheme 5) [219]. Use of a palladium catalyst with a modified dppf ligand leads to initial substitution of the bromide group, with the second transformation occurring at the chlorine-bearing carbon.



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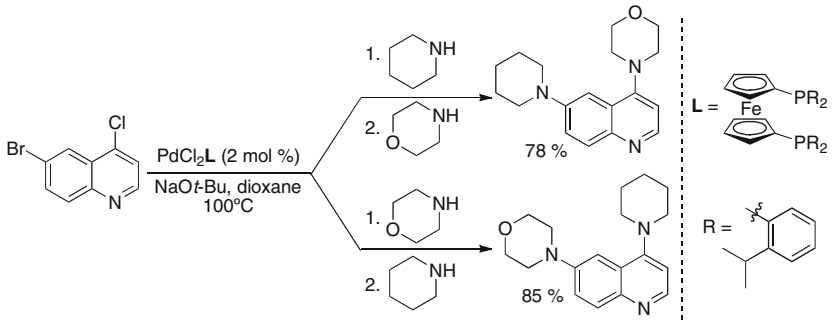
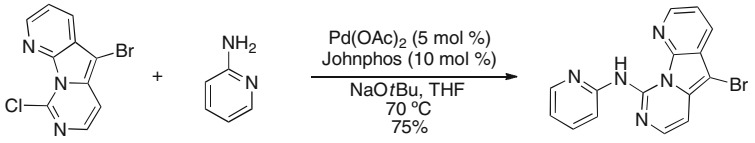
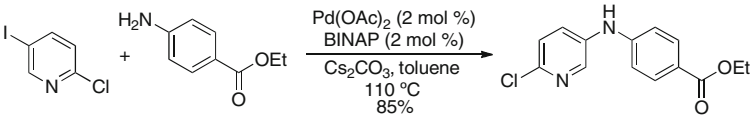


Scheme 5 Sequential Chemoselective N-Arylation of 6-Bromo-4-Chloroquinoline



(31)

Amide and electron-poor aniline nucleophiles have also been employed in heteroaryl halide amination reactions. For example, an organic synthesis procedure was recently reported for the synthesis of ethyl 4-[(6-chloropyridin-3-yl)amino] benzoate via *N*-arylation of ethyl 4-aminobenzoate with 2-chloro-4-iodopyridine (Eq. 32) [220]. Beletskaya has illustrated that bromoindole derivatives can be coupled with amides utilizing either Xantphos or 3,5-$(CF_3)_2$Xantphos (**22**) as the ligand in good yield (Eq. 33) [169].



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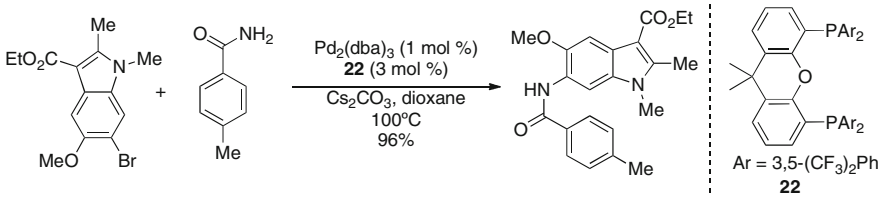

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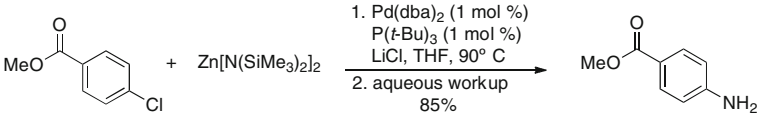
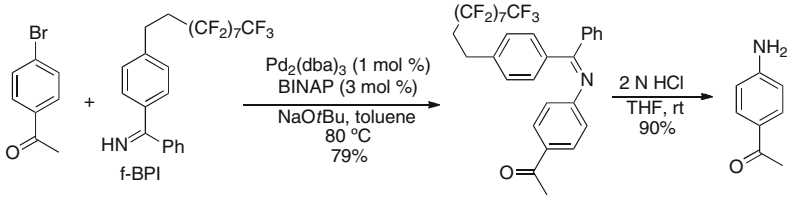
3.3.3 Ammonia and Ammonia Surrogates

Primary anilines are useful building blocks with applications in many areas of chemistry. As such, Pd-catalyzed *N*-arylation reactions of ammonia have been of longstanding interest [221, 222]. However, coupling of ammonia has proven challenging due to its volatility and its propensity to generate catalytically inactive palladium complexes. Thus, a considerable number of studies have focused on the use of ammonia surrogates in Pd-catalyzed amination reactions. These include benzophenone imine, allylamine, benzylamine, trimethylsilylamine, lithium hexamethyldisilylazide, and lithium amide [9, 223]. In many instances use of these ammonia surrogates adds an additional synthetic step (protecting group cleavage) as well as additional purification steps (after coupling and after deprotection). The use of silyl protecting groups allows for deprotection with a simple acidic workup. However, LiHMDS is strongly basic, which limits functional group tolerance. In order to address this limitation, Hartwig and coworkers have devised a protocol to couple $Zn(HMDS)_2$ with aryl halides and triflates. The zinc reagent is less basic and less nucleophilic than LiHMDS, and several functional groups are tolerated in these reactions (Eq. 34) [224].



(34)

Two fluorinated ammonia surrogates have been developed that allow product purification through fluorous separation techniques. The first is a benzophenone imine derivative bearing a fluorinated alkyl side-chain (f-BPI) (Eq. 35) [225]. The second is a fluorinated Boc derivative (^{F}Boc) (Eq. 36) [226]. Both of these can be *N*-arylated using standard conditions. Cleavage of the f-BPI group was achieved using aqueous HCl, and the ^{F}Boc group can be removed with TFA.



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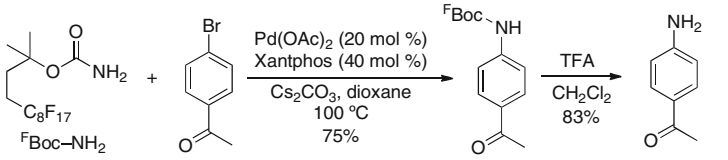

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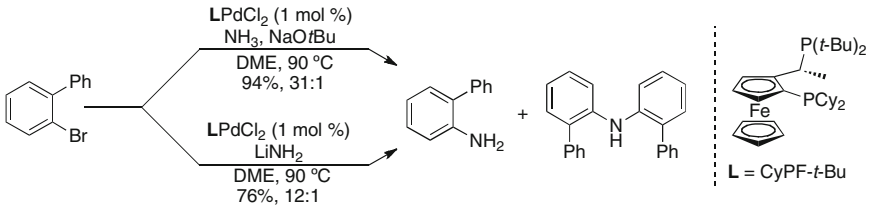
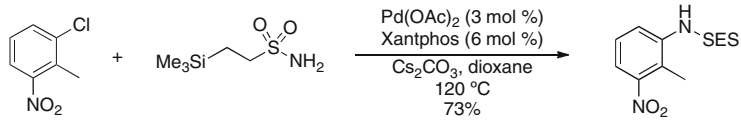


Scheme 6 Palladium-Catalyzed N-Arylation of Ammonia Using Josiphos Ligands

Ureas and sulfonamides have occasionally been employed as ammonia surrogates. For example, 2-(trimethylsilyl)ethanesulfonyl amide (SES-NH_2) can be arylated with electron-poor or electron-neutral aryl halides in the presence of Cs_2CO_3 and a catalyst composed of $Pd(OAc)_2$/Xantphos (Eq. 37) [227]. The SES group can subsequently be cleaved with CsF, which allows other sensitive functional groups to remain intact. Beletskaya has reported use of urea as an NH_3 equivalent in the generation of symmetrical di- and triarylamines [228, 229]. The authors found that *para*- and *meta*-substituted aryl halides afforded triarylated products, whereas diarylated anilines were generated when ortho substituted aryl halides were employed (Eq. 38). These results are similar to those reported by Buchwald for *N*-arylation reactions of lithium amide [230].



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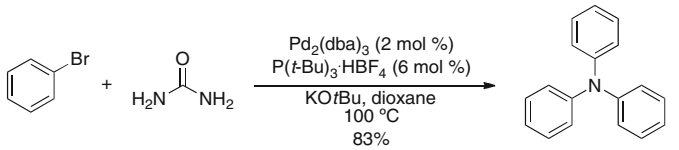
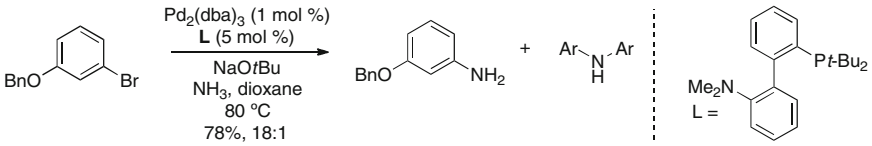


(38)

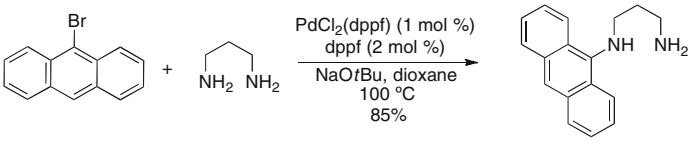
Despite the utility of the ammonia surrogates described above, the use of protected ammonia derivatives is inherently inefficient with respect to atom economy, and added steps are required for deprotection. However, recent studies with highly active palladium catalysts have illustrated that ammonia can be efficiently monoarylated under appropriate conditions. For example, Hartwig and coworkers employed the CyPF-*t*-Bu Josiphos ligand to effect coupling of aryl bromides with ammonia at moderate pressures (80 psi), selectively generating primary anilines (Scheme 6) [231]. They also demonstrated that primary anilines could be obtained via *N*-arylation of lithium amide, albeit with slightly lower selectivity. Buchwald and coworkers illustrated that commercially available solutions of ammonia in dioxane could be employed for the selective synthesis of mono-, di-, or triarylated amines (Eq. 39) [232]. Unsymmetrical diarylamines could be generated by evaporating excess ammonia after monoarylation, and then adding a different aryl halide and ligand. Triarylamines with three different aryl groups could also be prepared using a similar one-flask procedure.



(39)

3.3.4 Diamines as Nucleophiles

Palladium-catalyzed *N*-arylation reactions of diamines have been employed in the synthesis of a number of interesting compounds. For example, Beletskaya and coworkers have demonstrated that selective monoarylation (Eq. 40) or diarylation (Eq. 41) of diamines can be achieved using dppf or BINAP as ligand [233]. The selective arylation of the primary amino group of 3-aminopiperidines and pyrrolidines has also been described [234, 235]. Diamines with polyether linkers or polyamine linkers can be converted into macrocycles through *N*-arylation with bishalobenzene derivatives (Eq. 42) [236–239]. In general, the yields of these transformations are modest due to competing side reactions, such as polymerization. However, very interesting structures can be accessed with this chemistry.



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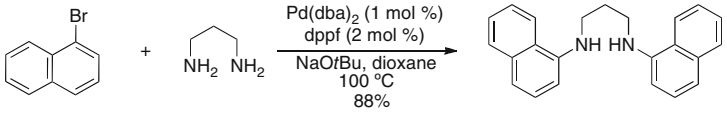

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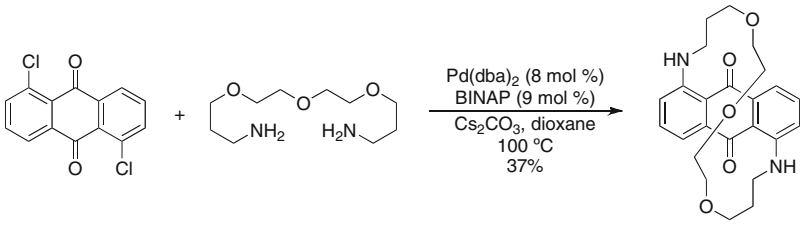
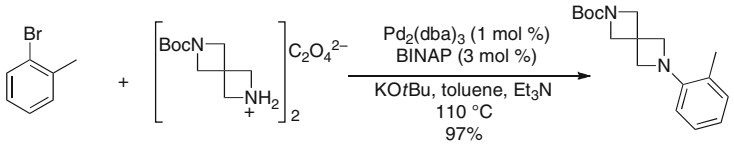


(42)

Carreira has recently described Pd-catalyzed *N*-arylation reactions of *N*-Boc-2,6-diazaspiro[3.3]heptane [240]. For example, the coupling of this nucleophile with 2-bromotoluene proceeded in 97% yield using the $Pd_2(dba)_3$/BINAP catalyst system (Eq. 43). This core may serve as a useful structural analog to the piperazine ring, which is a common moiety in many biologically active molecules and pharmaceuticals. A number of studies have examined Pd-catalyzed *N*-arylation reactions of piperazine derivatives [217, 241, 242] and other rigid cyclic diamine

[243–245] or triamine [246] scaffolds. A synthesis of peptide helix mimics based on a 1,4-dipiperazinobenzene scaffold was also accomplished through Pd-catalyzed *N*-arylation of substituted piperazines [247].



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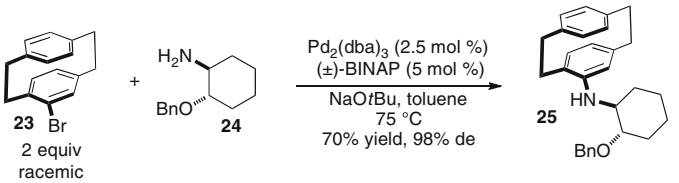
3.3.5 Stereoselective *N*-Arylation Reactions

Palladium-catalyzed *N*-arylation reactions are typically used in transformations that do not present issues of stereocontrol. However, a few studies have explored diastereoselective or enantioselective *N*-arylation reactions that show considerable potential utility. For example, Bräse has developed a diastereoselective coupling of enantiopure amine **24** with (±)-**23** (2 equiv) that affords **25** in 70% yield and 98% de (Eq. 44) [248]. A related study on kinetic resolution via Pd-catalyzed *N*-arylations of racemic amines with 0.42 equiv of an aryl bromide demonstrated that up to 80% ee could be obtained for certain combinations of substrates when (*R*)-Tol-BINAP was employed as ligand [249]. However, most reactions proceeded with considerably lower selectivity (5–72% ee). Kitagawa and Taguchi have developed a new approach to the synthesis of axially chiral *N*-(*p*-nitrophenyl)anilides. The Pd/(*R*)-DTBM-SEGPHOS catalyzed coupling of *o*-*tert*-butylanilides with *p*-iodonitrobenzene generates these compounds in good yield with excellent enantioselectivity (88–96% ee) (Eq. 45) [250].



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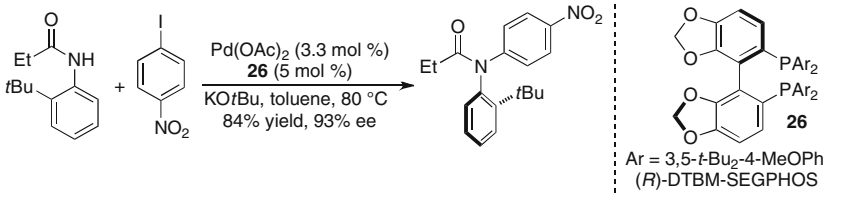

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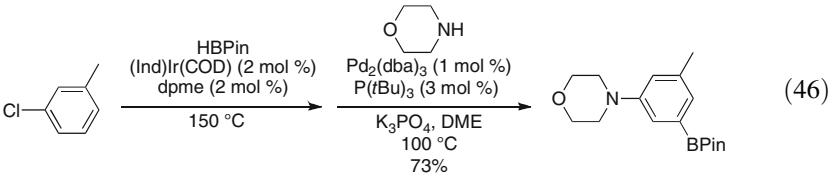
3.3.6 Miscellaneous Transformations of Interest

In addition to the broad categories of nucleophiles and electrophiles outlined above, several examples of coupling reactions involving interesting substrates were reported in the literature between 2004 and 2008. For example, Beletskaya has described the

Pd-catalyzed amination of a *B*-iodocarborane with various amine nucleophiles [251]. Smith and Maleczka have developed a one-pot synthesis of arylamine boronate esters via sequential C–H borylation followed by Pd-catalyzed *N*-arylation (Eq. 46) [252]. The preparation of ^{18}F-labeled-*N*-arylindoles was accomplished through coupling reactions of *p*-^{18}F-C_6H_4I (Eq. 47) [253]. Importantly, these transformations were effected in only 20 min, as the half-life of ^{18}F is short. Near stoichiometric quantities of palladium were employed, but the reactions were conducted on extremely small scale (7 mg of substrate), and the use of high catalyst loadings may have been due to convenience rather than necessity. Pd-catalyzed sp^2 C–N bond forming reactions involving halogenated naphthoquinones [254], ketal-protected piperidones [255], sulfamides [256, 257], and *N*,*N*-dialkylhydrazines [258] have also been described.



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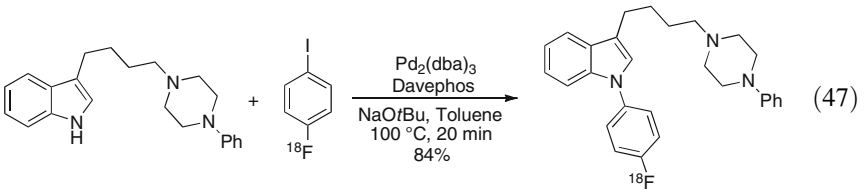


(47)

4 Applications

4.1 *Synthesis of Heterocycles via Reaction Sequences Involving* N-*Arylation*

Palladium catalyzed *N*-arylation reactions have been employed in a number of ring-forming reactions that generate heterocyclic products [259–262]. In one of the earliest publications on tin-free Pd-catalyzed *N*-arylation reactions, a number indolines, tetrahydroquinolines, and benzoazepines were prepared via intramolecular *N*-arylation [263]. This strategy has subsequently been used for the generation of several other clases of nitrogen heterocycles [264–271], including benzocazocenes (e.g., **27**) [272] and benzimidazo[1,2-*a*]quinolines (e.g., **28**) [273] (Fig. 7).

The use of 1,2-dihaloarenes has been a key component of several recent annulation reactions that afford nitrogen heterocycles [274–276]. For example, indoles were prepared via a tandem amination/Heck reaction sequence between allylic amines and *o*-bromoiodobenzene derivatives (Eq. 48) [277]. A synthesis of heterocycles bearing three or more nitrogen atoms has been developed that proceeds via intermolecular *N*-arylation of a 3-aminopyridazine followed by intramolecular *N*-arylation of the resulting product (Eq. 49) [278]. This latter strategy has also been applied to the construction of other nitrogen-containing heterocycles [279].

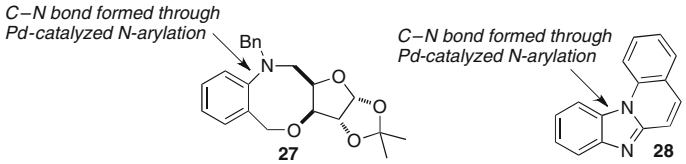
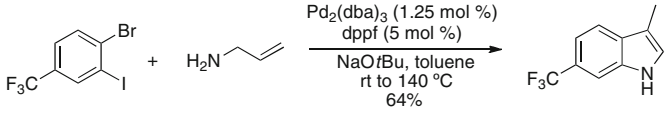


Fig. 7 Synthesis of nitrogen heterocycles via intramolecular Pd-catalyzed N-arylation



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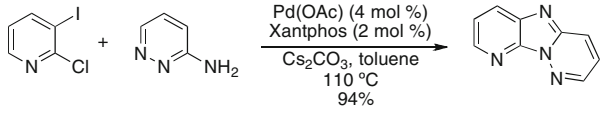
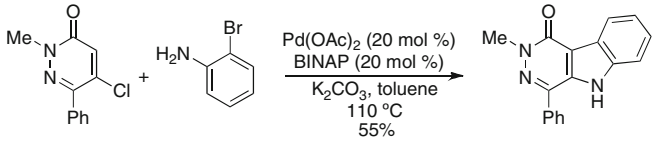


(49)

The use of *o*-haloarylamine derivatives as substrates has played a central role in many different annulation strategies that yield heterocyclic products [280]. For example, a tandem *N*-arylation/Heck reaction sequence involving 2-bromoaniline has been employed for the generation of carbazole derivatives (Eq. 50) [281]. Heterocycles have also been prepared from Boc-protected 2-chloro-3-aminopyridine via intermolecular *N*-arylation followed by intramolecular acylation (Eq. 51) [282]. Buchwald has reported a high-yielding synthesis of substituted benzimidazoles from 2-bromoacetamide derivatives via *N*-arylation followed by condensation (Eq. 52) [283]. In contrast to direct *N*-arylations of benzimidazole derivatives, which typically effect substitution at the least hindered nitrogen atom, this strategy allows for the generation of products in which the more sterically hindered nitrogen atom is arylated. Bedford and Betham have developed a tandem *N*-arylation/C–H activation between 2-bromoanisole and a 2-chloroaniline derivative that was employed in a synthesis of the natural product Clausine P (Eq. 53) [284]. Pd-catalyzed *N*-arylation reactions have also played a central role the construction of numerous other carbazoles, including alkaloid natural products [285–291].



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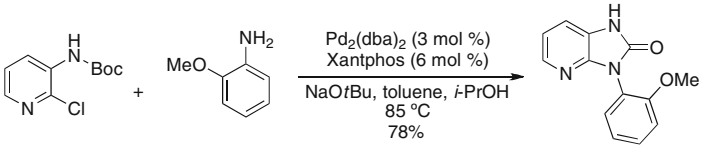

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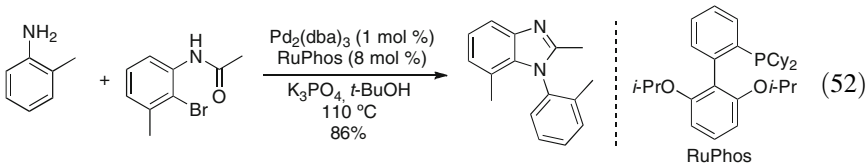

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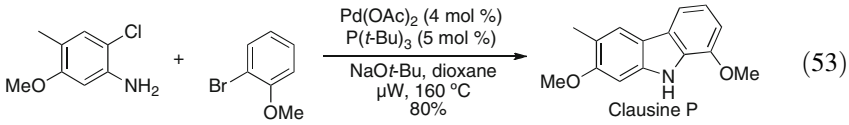
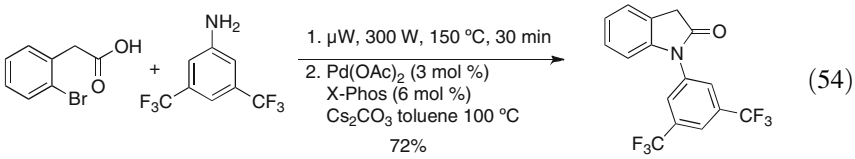


(53)

Several strategies have been developed for the synthesis nitrogen heterocycles from aryl bromides bearing pendant carbonyl functionality. For example, microwave-promoted acylation of primary amines or anilines followed by intramolecular *N*-arylation of the resulting amides was employed for the construction of oxindoles (Eq. 54) [292]. Intermolecular amidation of 2′-bromoacetophenone derivatives followed by base mediated intramolecular condensation has been used to generate 4-quinolones (Eq. 55) [293]. The preparation of 2-quinolones has been achieved via a cascade intermolecular Heck arylation/intramolecular *N*-arylation sequence between *o*-bromocinnamide and aryl iodides [294]. The synthesis of quinazolinediones via a tandem acylation/Pd-catalyzed *N*-arylation reaction between *o*-halobenzoates and monoalkylureas has also been described [295]. An interesting cascade reaction involving Pd-catalyzed C–C and C–N bond formation effects the conversion of 2-bromobenzamide derivatives (2 equiv) to phenanthridones (Eq. 56) [296].



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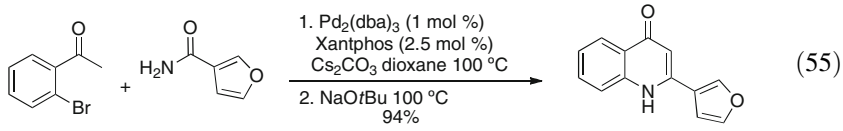

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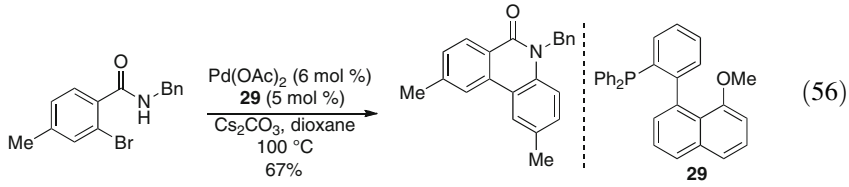

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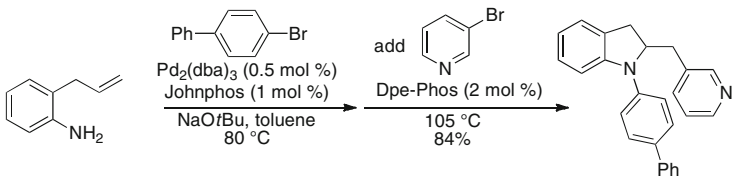
Our group has developed cascade Pd-catalyzed *N*-arylation/alkene carboamination reactions of 2-allylanilines that afford indoline products [297, 298]. For example, treatment of 2-allylaniline with 4-bromobiphenyl in the presence of NaO*t*Bu and a

Pd/Johnphos catalyst at 80°C for 30 min, followed by addition of Dpe-Phos and 3-bromopyridine, affords an *N*-aryl-2-benzylindoline derivative (Eq. 57). This method has also been extended to the synthesis of *N*-aryl-2-benzylpyrrolidines [299].



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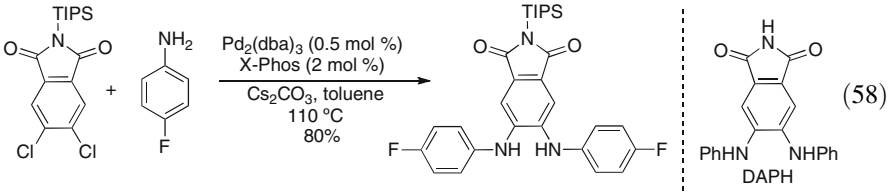
4.2 *Synthesis of Natural Products and Pharmaceutical Target Molecules*

Palladium catalyzed *N*-arylation reactions have been widely employed in both academia and industry for the construction of biologically active molecules, including compounds of pharmaceutical relevance [300–311]. Importantly, since a wide variety of amines and aryl/heteroaryl halides are readily available, generation of analogs of lead compounds for SAR studies and optimization of biological properties is relatively facile. For example, Buchwald and Hennessy have used this method to synthesize analogs of 4,5-dianilinophthalimide (DAPH), which has been investigated as a potential treatment of Alzheimer's disease (Eq. 58) [312]. Scientists at Leo Pharma employed a Pd-catalyzed amination reaction to synthesize analogs of known p38 MAP kinase inhibitor **30** (Eq. 59) [313]. Microwave heating was shown to facilitate rapid reactions. The use of Pd-catalyzed *N*-arylation reactions with solid-supported substrates for combinatorial chemistry applications has been explored [314–318], and Pd-catalyzed amination reactions have been employed for the modification of peptides [319, 320] and hormones [321].



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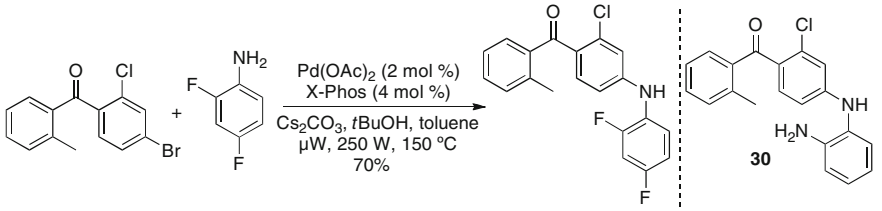
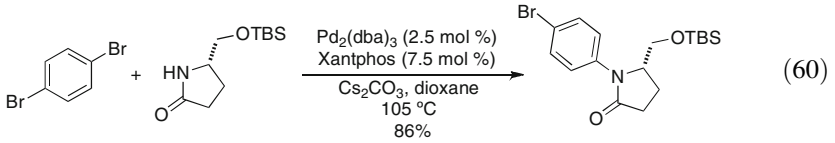


(59)

Transformations involving amides or carbamates as nucleophiles have played a central role in the synthesis of several natural products. For example, Lovely and coworkers generated *N*-aryl lactams via Pd-catalyzed *N*-arylation reactions using the Xantphos ligand (Eq. 60) [322]. These products were used as intermediates in the synthesis of the *Martinella* alkaloids. Bringmann and coworkers utilized the coupling of *t*-butylcarbamate with a bromonaphthalene derivative as part of a convergent synthesis of Ancisheynine (Scheme 7) [323]. Ganton and Kerr have demonstrated that the CPI subunit of CC-1065, which has shown antitumor activity, can be synthesized using an intramolecular amidation as one of the key transformations (Eq. 61) [324].



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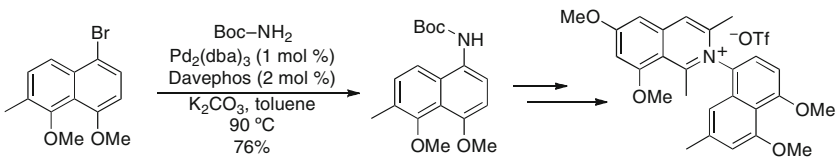
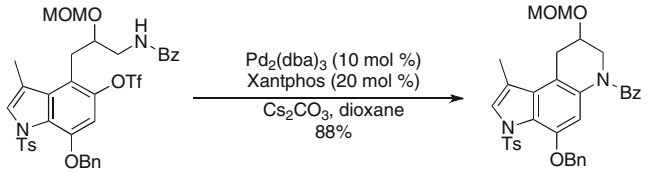
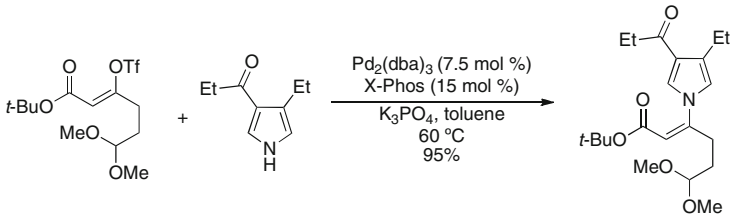


Scheme 7 Palladium-Catalyzed N-Arylation in the Synthesis of Ancisheynine



(61)

Alkenyl halides and triflates have also been employed in the generation of biologically active compounds and natural products. For example, Movassaghi and Ondrus have utilized a Pd-catalyzed *N*-alkenylation reaction as a key step in the synthesis of several *Myrmicarin* alkaloids (Eq. 62) [325, 326]. The alkenyl triflate is easily generated from a β-ketoester and the coupling reaction proceeded in high yield on a 7 g scale. Wu reported the synthesis of 4-aryl-3-aminoquinoline-2(1H)-ones using palladium catalyzed amination of a bromoalkene (Eq. 63) [327]. Several members of this class of compounds have shown biological activity. Bergman, Ellman and coworkers have prepared a protein kinase C inhibitor using a Pd-catalyzed *N*-arylation reaction of a heterocyclic alkenyl bromide (Eq. 64) [328].



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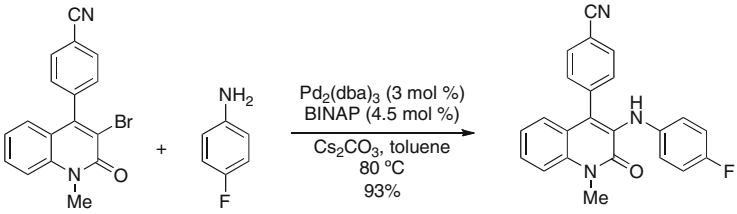

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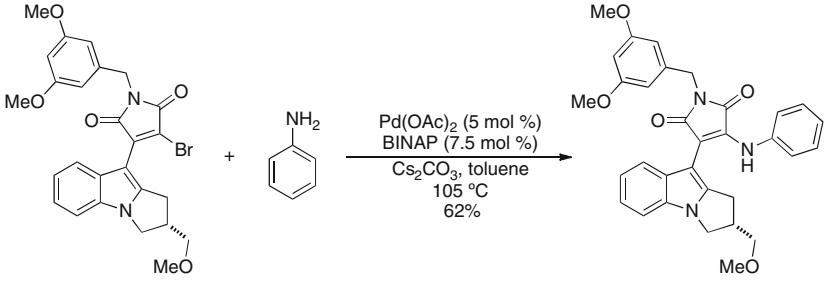


(64)

In addition to the examples outlined above, Pd-catalyzed *N*-arylation reactions have been employed in the synthesis of a number of natural products (Fig. 8), such as the indole alkaloids anhydrolycorinone, hippadine (**31**), oxoassoanine, and pratosine [329]. The *N*-arylation of 2-alkylpiperidines played a central role in the synthesis of solenopsin A and dihydropinidine (**32**), with an *N*-phenyl moiety serving as a nitrogen protecting group [330]. Other noteworthy work in this area includes syntheses of hydroxyphenazine (**33**, a precursor to methanophenazine) [331], nigellicene (**34**) [332], the core of nodulisporic acid A (**35**) [333], and dapiramicin B (**36**) [334]. Additional representative applications of *N*-arylation reactions towards the synthesis of pharmaceutical lead compounds, including AMN107 (**37**, Ariad) [335], benzoxazine **38** (an intermediate in the preparation of levofloxacin) [336], Lck inhibitor **39** (Amgen) [337], BMS-566419 (**40**, Bristol-Myers Squibb) [338], and KDR kinase inhibitor **41** (Merck) [339], are illustrated in Fig. 9.

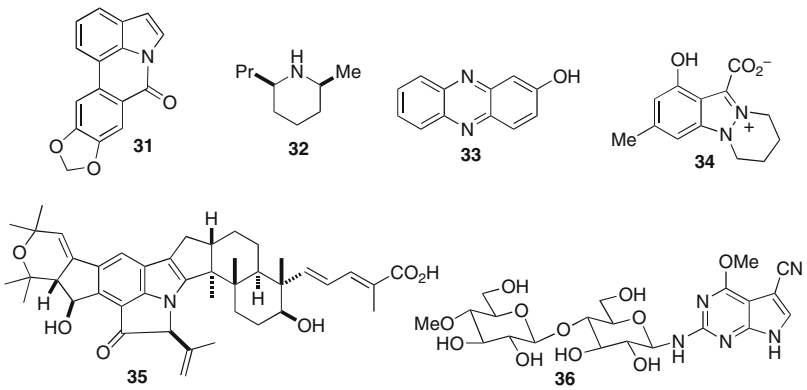


Fig. 8 Natural Products Synthesized Using Pd-Catalyzed N-Arylation as a Key Step

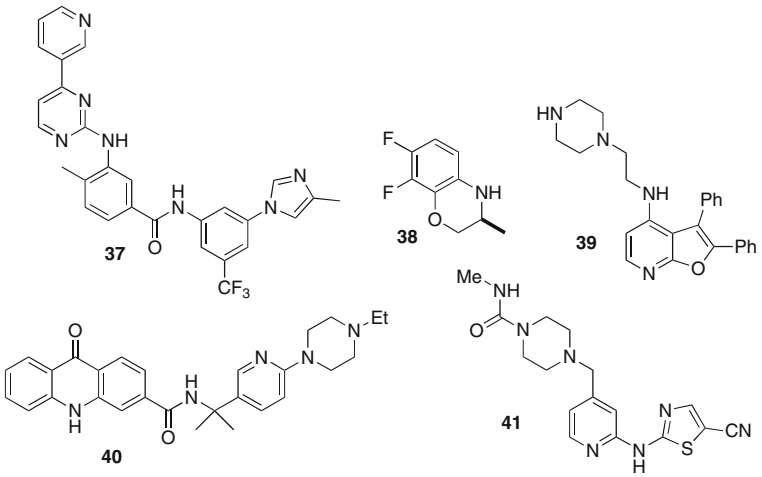


Fig. 9 Pharmaceutical Lead Compounds Synthesized Using Pd-Catalyzed N-Arylation as a Key Step

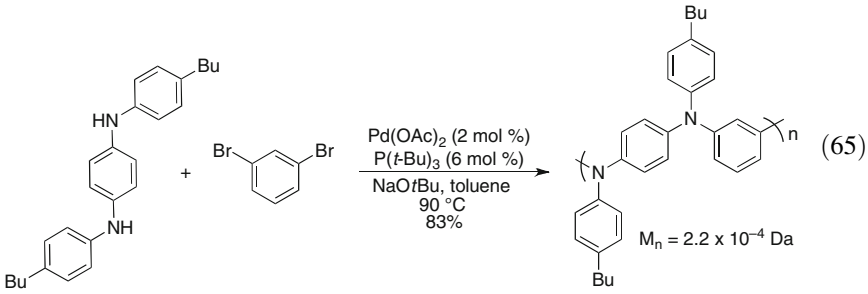
4.3 Synthesis of Molecules with Potential Materials Chemistry Applications

4.3.1 Synthesis of Oligomers and Polymers

The application of palladium-catalyzed *N*-arylation reactions to the synthesis of polymers has attracted considerable attention due to the interesting electronic properties of these materials [6, 8, 11]. For example, polyaniline has been utilized in anti-static materials, flexible electronics, and as electromagnetic shielding material. The first application of palladium-catalyzed amination reactions in polymer

synthesis involved the coupling of 1,3- and 1,4-dibromobenzene derivatives with piperazine or alkyl-linked bis-piperidines [340]. These early experiments, which employed a Pd/P(*o*-tol)$_3$ catalyst system, did not afford high molecular weight materials ($M_n = 4.5 \times 10^{-3}$ Da), but illustrated the potential for oligomer formation with this method. Early work in this area by Buchwald led to the synthesis of oligoanilines with well-defined lengths (Fig. 10) [341, 342], as well as the synthesis of high molecular weight polyaniline through Pd-catalyzed *N*-arylation chemistry [343].

Due to the utility of the methods and the significance of the materials, the use of Pd-catalyzed *N*-arylation reactions in oligoaniline and polyaniline synthesis has remained an active area of research [344, 345]. For example, in recent work Kulszewicz-Bajer and coworkers have employed Pd-catalyzed amination reactions for the synthesis of *N*-aryl poly(*m*,-*p*-aniline) derivatives that can be oxidized to high-spin radical cations [346, 347]. The preparation of these materials was accomplished by coupling 1,3-dibromobenzene with *N*,*N*′-diarylphenylenediamine derivatives (Eq. 65). Palladium-catalyzed *N*-arylation reactions have also been employed for the preparation of partially annulated poly(*m*-anilines) [348] and other triarylamine-derived polymers [349, 350].



(65)

Hirao and coworkers have prepared two types of short aniline oligomers that contain fused heterocyclic units (Fig. 11, **42** and **43**) [351]. The synthesis of these materials was accomplished by Pd-catalyzed *N*-arylation of 4,7-dibromo-2,1,3-benzoliadiazole or 5,8-dibromoquinoxaline with an appropriate aniline derivative. The electrochemical properties of these oligomers were found to be dependent on the heterocycle, its position in the chain, and the chain length.

The synthesis of oligoaniline ladder molecules **46** has been accomplished through sequential inter- and intramolecular Pd-catalyzed *N*-arylations (Scheme 8) [352]. The coupling of 3-bromochlorobenzene with phenylenediamine afforded **44** in 89% yield. This bis(triarylamine) was then coupled with 4 equiv of a substituted aniline to give **45**. The final rungs of the ladder were installed by double *N*-arylation of 2 equiv of 1,4-dibromobenzene. This synthesis illustrates that high chemoselectivity can be achieved in *N*-arylation reactions with proper control of conditions. These materials exhibit interesting electronic and photophysical properties. Structurally related polymers that act as hydrogen storage materials have also been prepared using Pd-catalyzed *N*-arylations [353].

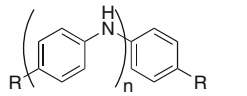


Fig. 10 Oligoanilines Prepared via Pd-Catalyzed N-Arylation

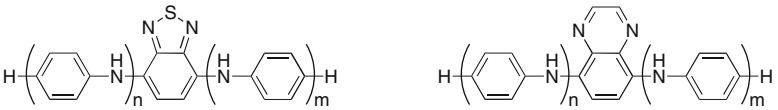
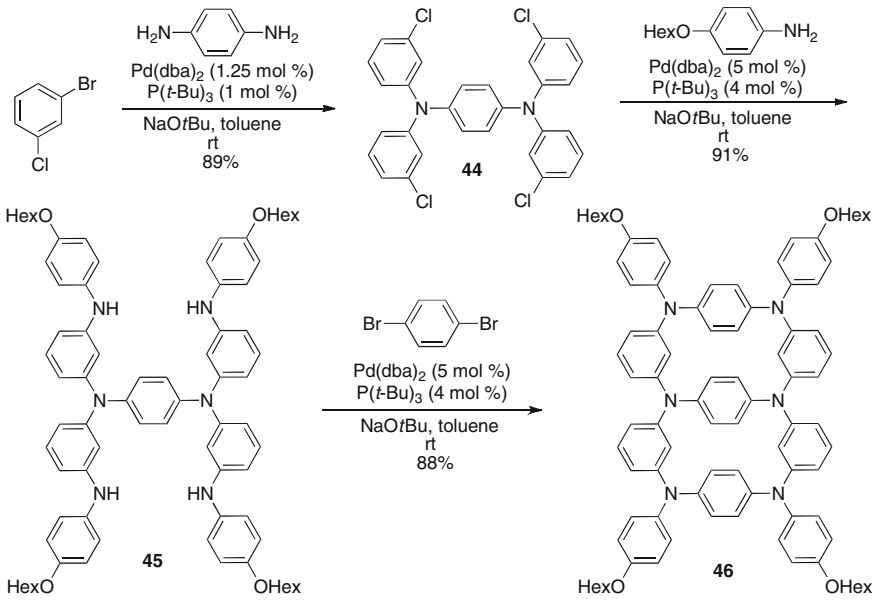


Fig. 11 Heteroaryl Aniline Oligomers Prepared via Pd-Catalyzed N-Arylation



Scheme 8 Synthesis of Oligoaniline Ladder Molecules via Pd-Catalyzed N-Arylation

A series of triarylamines containing azulene units (Fig. 12, **47**–**48**) have been prepared through *N*-arylation of phenylendiamine or amination of dihaloarenes [354–357]. These molecules exhibit interesting redox and optical properties and have been employed as hole-injecting materials in organic light-emitting devices. Triarylamines bearing fluorene cores (e.g., **49**) that serve as light-harvesting materials have also been synthesized via Pd-catalyzed *N*-arylation reactions [358–360].

The synthesis of oligoaniline-based dendrimers has also been carried out using Pd-catalyzed *N*-arylation reactions. Early work in this area by the Hartwig group led to the preparation of **51** (X=Me) through sequential Pd-catalyzed *N*-arylation reactions [361]. The final step in the synthesis involved the coupling of amine

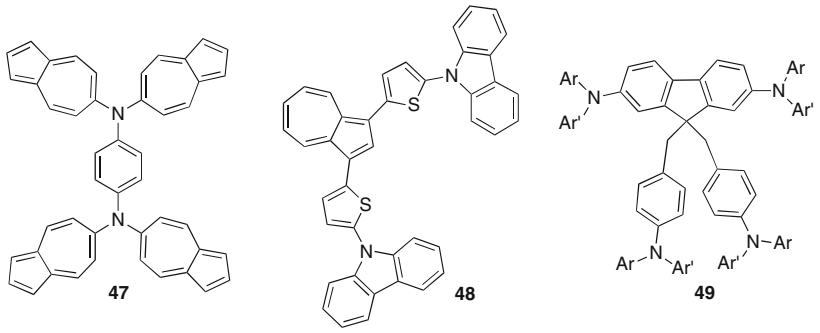
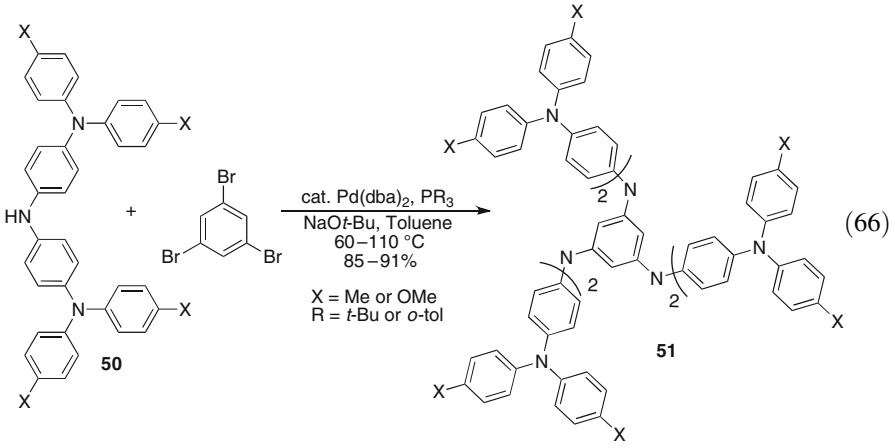


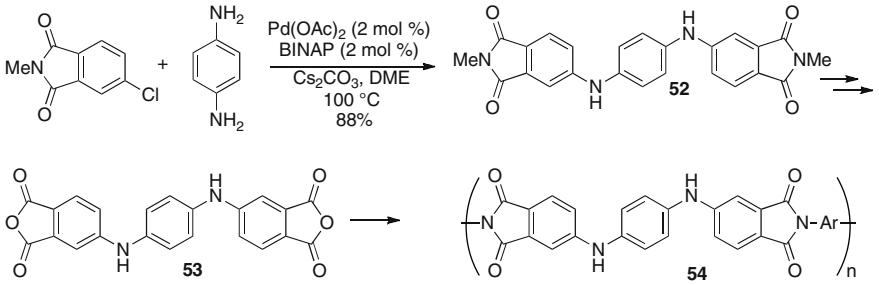
Fig. 12 Synthesis of light-harvesting or light-emitting materials via Pd-catalyzed N-arylation

50 with 1,3,5-tribromobenzene (Eq. 66). Related dendrimers bearing different X-groups have been prepared in an analogous manner by Ito, who has also examined intramolecular charge transfer processes of these materials [362, 363].



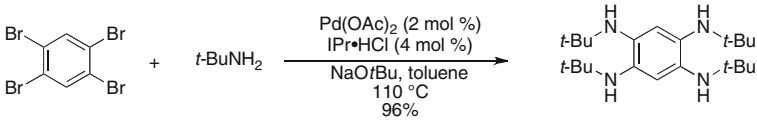
(66)

In addition to their use in the synthesis of oligo- and polyanilines, Pd-catalyzed *N*-arylation reactions have also been employed for the construction of other nitrogen-containing polymers. For example, poly(amine-imide) **54** was prepared from key building block **52**, which was generated via the coupling of *p*-phenylenediamine with *N*-methyl-4-chlorophthalimide. Conversion of **52** to the corresponding cyclic bis-anhydride **53** followed by treatment with *p*-phenylendiamine provided the polymer (Scheme 9) [364]. Analogous materials derived from *m*-phenylendiamine were prepared in a similar manner. The synthesis of poly(aminophthalimide) dimers and trimers via coupling of 3-aminophthalimide with 3,6-dichlorophthalimide has also been reported [365]. In addition, poly(imino) ketones have been synthesized through *N*-arylation of phenylenediamine derivatives with aromatic dibromoketones [366].



Scheme 9 Synthesis of Poly(Amine-Imide) Molecules via Pd-Catalyzed N-Arylation

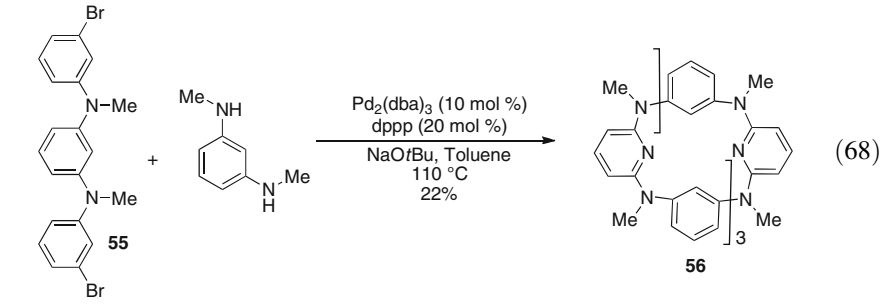
Bielawski has utilized bis(imidazoylidenes) as building blocks in the synthesis of a number of interesting materials [367, 368], including organometallic polymers and fluorescent compounds [369]. Palladium-catalyzed *N*-arylation reactions of 1,2,4,5-tetrabromobenzene have played a key role in the construction of many of these species ([370, 371]; for recent studies on the selective monoamination of dihalogenated benzenes, see [372]). For example, this approach was used to generate a tetraaminobenzene derivative in 96% yield (Eq. 67).



(67)

4.3.2 Synthesis of Azacalixarenes, Aza-Crowns, Porphryins, and Related Compounds

Palladium-catalyzed *N*-arylation reactions have been employed in the synthesis or derivatization of a number of nitrogen-containing macrocycles, including azacalixarenes [373], aza-crown ethers [374], aza-cyclophanes [375, 376], and porphryins [377–379]. For example, Wang and coworkers have prepared azacalixarenes **56** that are capable of binding fullerenes using a cyclocondensation of *N*,*N*′-dimethyl-1,3-phenylenediamine with dibromide **55** (Eq. 68) [380, 381]. The synthesis of *N*-methylated azacalix[4]arene (**58**) was conducted using a sequence of three separate Pd-catalyzed *N*-arylation reactions [382]. The macrocyclic ring was formed in the third transformation through intramolecular *N*-arylation of intermediate **57** (Eq. 69). A structurally analogous azacalix[8]arene was also prepared in a similar fashion [383].



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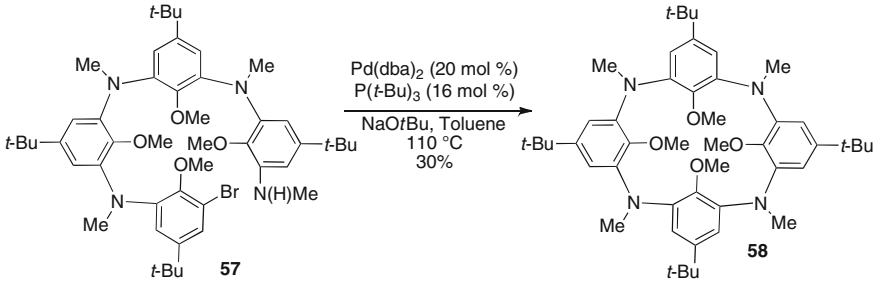
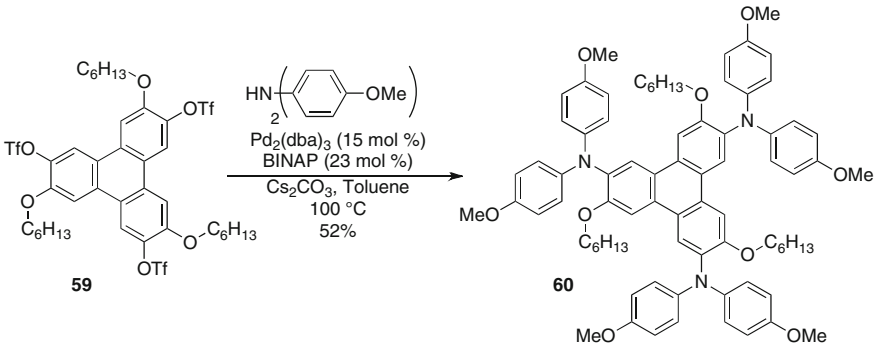


(69)

4.3.3 Synthesis of Molecules with Useful Magnetic or Photophysical Properties

A number of molecules that contain aryl C–N bonds have both interesting and useful magnetic, optical, or photophysical properties [384–396]. For example, the synthesis of high-spin organic molecules has attracted considerable attention due to potential applications of these compounds for the construction of organic magnets. Palladium-catalyzed aryl C–N bond formation has provided a powerful means to access these types of compounds. In a representative example, Nishide effected the triple *N*-arylation of tris-triflate **59** with 4,4′-dimethoxyphenylenediamine, to generate **60** in 52% yield (Eq. 70). Oxidation of **60** with $AgBF_4$ afforded a stable high spin triradical trication with magnetic properties at room temperature [397, 398].



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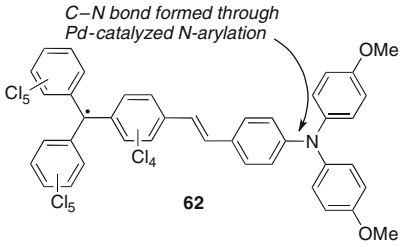
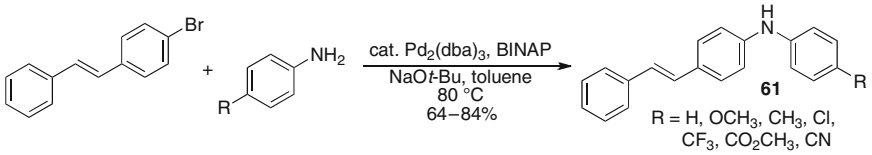


Fig. 13 A Stable Radical Mixed-Valence Compound Generated via Pd-Catalyzed N-Arylation

The synthesis of *N*-arylamino stilbene derivatives that have interesting electronic and photophysical properties has also been accomplished using Pd-catalyzed *N*-arylation reactions [399–403]. For example, the coupling of *E*-4-bromostilbene with *p*-substituted anilines afforded compounds with the general structure **61** (Eq. 71) [399]. These molecules exhibit intramolecular charge transfer characteristics in their excited states, which may be useful in nonlinear optics, chemical sensors, and fluorescence probe applications. A similar strategy was employed for the synthesis of related triarylamine derivatives from substituted 4-bromostilbenes. Treatment of the triarylamine products with base followed by chloranil yields stable radical mixed-valence compound **62** (Fig. 13) [404]. These types of species may find applications as molecular switches that function through intermolecular electron-transfer processes. Related compounds bearing crown ether functionality have been employed as sensors for metal ions [405].



(71)

A series of boron-containing heterocycles (e.g. **66**) have been prepared using Pd-catalyzed *N*-arylation reactions between polyhalogenated aromatic amines **63** and **64**. (Fig. 14) [406]. Selective reactivity of the aryl iodide cleanly provided the desired product **65**, which was transformed to **66** in subsequent steps. Spectroscopic studies indicate these materials have extended conjugated π-systems.

The synthesis of *N*-arylated porphryin derivatives that serve as light-harvesting molecules has been achieved using Pd-catalyzed *N*-arylation reactions. For example, porphyrin-phthalocyanine dyad **67** was prepared using this method [407] (Fig. 15). At 425 nm, the fluorescence quantum yields of this molecule are close to quantitative. A metal cation sensor bearing subporphyrin and amino-crown ether subunits (**68**) was also generated via this strategy [408]. Cation binding to this compound leads to changes in absorption at visible light wavelengths.

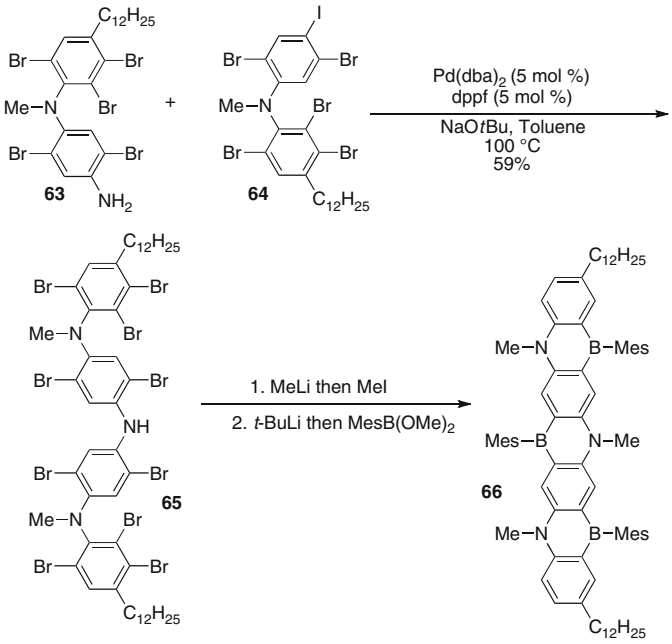
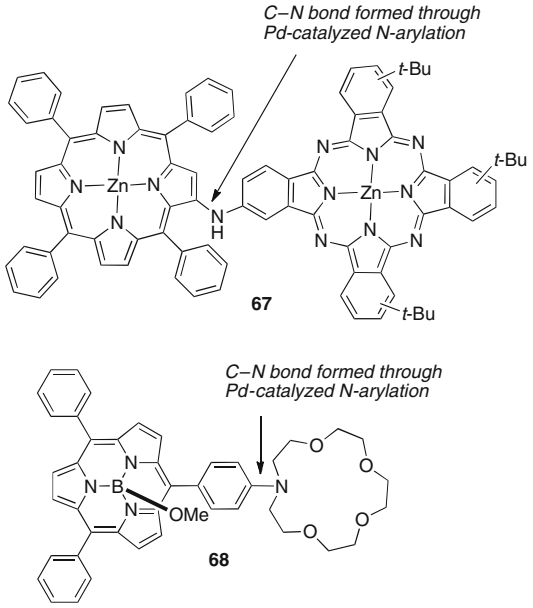


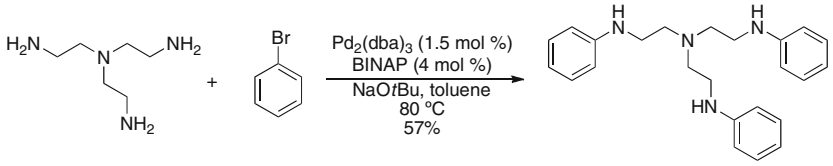
Fig. 14 Synthesis of Boron-Containing Fused Heterocycles via Pd-Catalyzed N-Arylation

Fig. 15 Synthesis of N-Arylated Porphryins via Pd-Catalyzed Coupling Reactions



4.4 *Use of* N*-Arylation Reactions for the Synthesis of Ligands for Metal Complexes and Catalysts*

A number of transition metal catalysts with interesting reactivity are supported by nitrogen containing ligands. Palladium-catalyzed *N*-arylation reactions have proven to be very useful for the synthesis of ligands for metal complexes [11]. For example, an early application in this area was reported by Schrock, who effected the triple Pd-catalyzed *N*-arylation of tris(2-aminoethyl)amine to generate ligands for molybdenum complexes (Eq. 72) [409–411]. More recent work on the synthesis of chelating amine ligands involved the *N*-arylation of 2-aminoarylimines derived from acetophenone (Eq. 73) [412]. The products of these reactions have been employed as ligands for Ti- and Zr-complexes. Other chelating amine ligands generated by *N*-arylation include macrocycles bearing 2-aminoarylimine subunits [413], dipyridylamine ligands [414, 415], and aminoterpyridine ligands [416].



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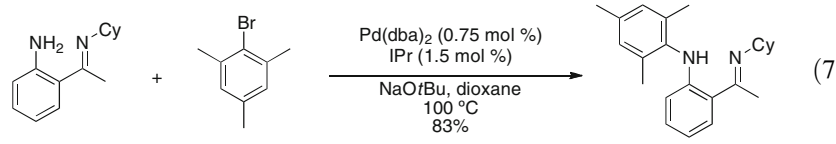
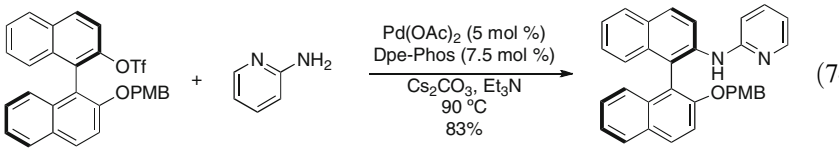


(73)

Cross-coupling reactions between amines and aryl halides or pseudohalides have been employed for the preparation of a number of chiral, nonracemic ligands for asymmetric catalysis. For example, early studies by Buchwald illustrated that chiral amino binaphthol derivatives could be generated by Pd-catalyzed *N*-arylation of binaphthol-derived triflates (Eq. 74) [417]. A similar strategy was employed by Bräse for the synthesis of planar-chiral [2.2]paracyclophane ligands (Eq. 75) [418]. The *N*-arylation of [2.2]paracyclophane-derived triflates has also been used for the construction of planar-chiral benzimidazoles [419]. The *N*-arylation of a substituted pyrrolidine with 4-bromopyridine played a key role in the synthesis of a chiral nucleophilic catalyst related to DMAP [420].



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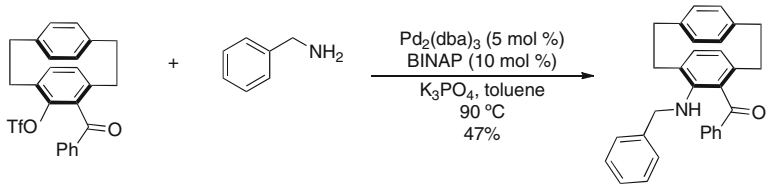
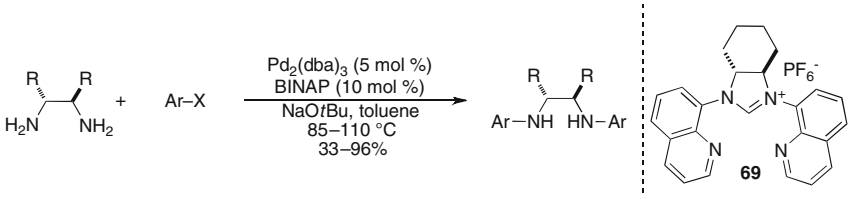


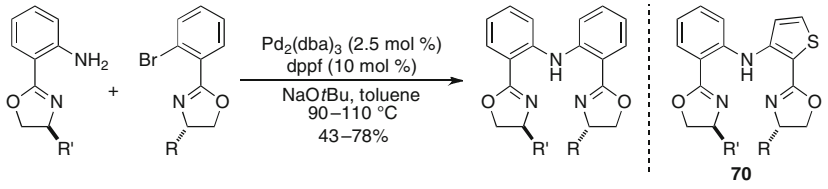
(75)

A series of C2 symmetric *N*,*N*′-bis(aryl)diamines, which have been broadly employed in asymmetric catalysis, were prepared via *N*-arylation of chiral 1,2-diamines (Eq. 76) [421]. Importantly, the stereochemical purity of the chiral diamine is retained in the coupling reaction. In addition to the utility of the arylated products as chelating nitrogen ligands, they have also been transformed into enantiopure NHC's such as **69** [422]. The tetra-*N*-arylation of optically active 1,1-binaphthyl-2,2′-diamine has also been reported [423].



(76)

A number of recent studies have used Pd-catalyzed *N*-arylation reactions for the preparation of chiral ligands with a diphenylamine-derived backbone. For example, Guiry and coworkers have synthesized chiral bis(oxazoline) ligands derived from substituted diarylamines through coupling of an *o*-bromophenyl oxaxoline with an *o*-aminophenyl oxaxoline (Eq. 77) [424]. A similar strategy was applied to the synthesis of thiophene derivatives such as **70** [425] and bis(2-pyrdiyl)amine ligands **71**–**73** (Fig. 16) [414]. This approach was also used for the synthesis of **74** from 2 equiv of an *o*-bromophenyl oxaxoline and 1 equiv of 2,2′-diaminobiphenyl [426]. The double *N*-arylation of 2,2′-diaminobiphenyl with bromoanisole derivatives has been employed in the construction of ligands for yttrium hydroamination catalysts [427]. The *N*-arylation of *o*-bromophenyloxazolines with simple aniline derivatives has provided ligands for zinc-based polymerization catalysts [428].



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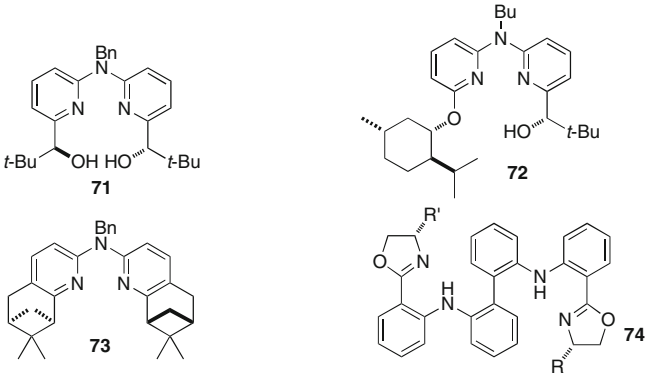


Fig. 16 Synthesis of Chiral Nitrogen-Containing Ligands via Pd-Catalyzed N-Arylation

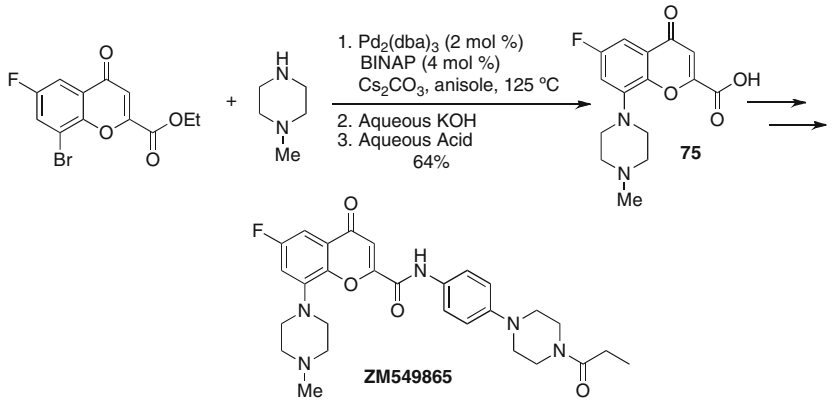
4.5 Process Scale Applications of Pd-Catalyzed N*-Arylation Reactions*

The Pd-catalyzed *N*-arylation of amines has proven to be amenable to large scale synthesis in a number of industrial applications [429–431]. For example, a collaboration between Lanxess, Rhodia, and Buchwald resulted in several applications of Pd-catalyzed amination reactions to the large-scale synthesis of both pharmaceutically relevant molecules and precursors for materials applications. A detailed description of this work was published in a recent review [432].

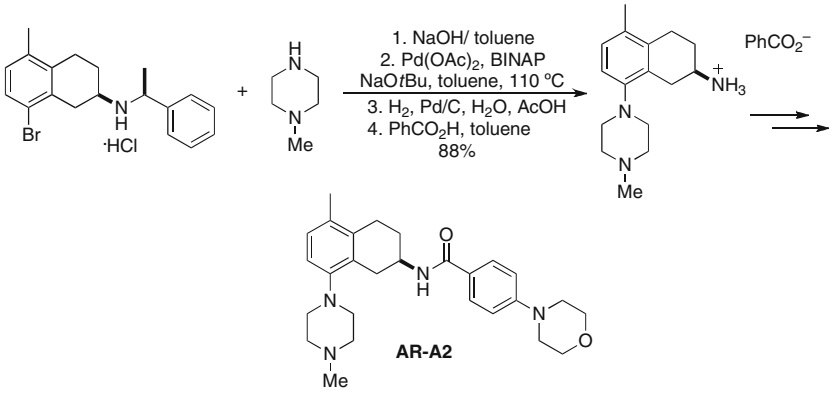
In the production of ZM549865, which is a 5-HT_{1B} receptor antagonist, Robinson and coworkers at AstraZeneca effected the Pd-catalyzed coupling of *N*-methyl piperazine with a functionalized bromo-chromenone derivative (Scheme 10) [433]. Hydrolysis of the product with aqueous KOH followed by acidification afforded carboxylic acid **75**, which served as a key intermediate in the synthesis of the desired target. During initial manufacturing, three batches of **75** were produced from 116 kg of the bromo-chromenone.

A related synthesis of another 5-HT_{1B} receptor antagonist, AR-A2, was also carried out by scientists at AstraZeneca (Scheme 11) [434, 435]. The coupling of *N*-methyl piperazine with a bromotetrahydronaphthalene derivative was successfully executed on a 1 kg scale using only 0.47 mol% of the palladium catalyst (Scheme 11). Scientists at Abbot Pharmaceuticals conducted an eight-step preparation of 2.1 g of the glucuronide metabolite of ABT-74, a D_4 Dopamine receptor antagonist [436]. The key *N*-arylation reaction was effected on a 19 g scale (Scheme 12).

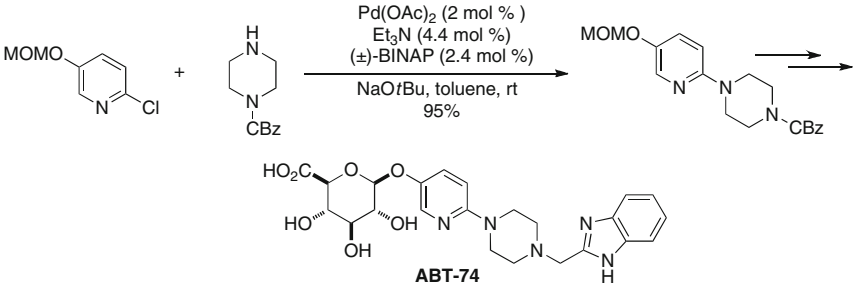
Torcetrapib, a compound designed by Pfizer to increase HDL cholesterol was synthesized in the final process using a key palladium catalyzed *N*-arylation reaction [437]. As shown below (Scheme 13), the coupling of (*R*)-3-aminopentanenitrile with 4-chlorobenzotrifluoride proceeded in 75–79% yield on a 3 kg scale. This route allowed for the use of enantiopure starting material, which avoided a late-stage resolution step. In addition, this approach also avoided the use of



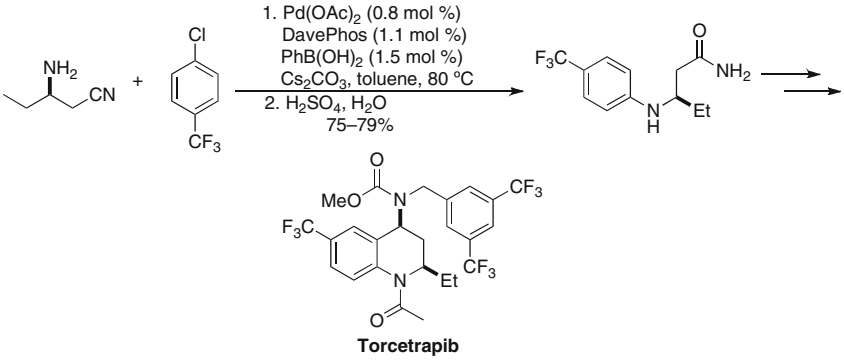
Scheme 10 Large-Scale Synthesis of ZM549865 via Pd-Catalyzed N-Arylation



Scheme 11 Large-Scale Synthesis of AR-A2 via Pd-Catalyzed N-Arylation



Scheme 12 Large-Scale Synthesis of ABT-74 via Pd-Catalyzed N-Arylation



Scheme 13 Large-Scale Synthesis of Torcetrapib via Pd-Catalyzed N-Arylation

4-trifluoromethylaniline, which cannot be stored for long periods of time. Unfortunately, torcetrapib was dropped during the late stages of development.

5 Conclusion

The field of Pd-catalyzed *N*-arylation reactions has expanded rapidly since the early studies of Migita, Boger, Buchwald, and Hartwig. Advances in catalyst design have led to significantly improved scope, utility, and applicability of these transformations to numerous areas of chemistry. It is likely that continued research in this area will lead to further enhancement of catalyst activity, expansion of generality, and continued applications to important problems in synthetic chemistry.

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Metal-Catalyzed C(sp^2)–N Bond Formation

Arkaitz Correa and Carsten Bolm

Abstract During the last decades a powerful set of protocols featuring C(sp^2)–N bond formation have emerged as convenient alternatives for the assembly of enamine and enamides. Those methods consist of mostly palladium-catalyzed oxidative amidations of alkenes and both palladium- and copper-catalyzed cross-couplings between generally vinyl halides or pseudohalides and amines or amides. In this review recent advances in both types of processes will be disclosed. Additionally, the synthetic value of the title processes will be illustrated by describing relevant total syntheses of natural products involving vinylation process as the key step.

Keywords Copper · Cross-coupling · Enamide · Enamine · Metal catalysis · Palladium · Vinylation

Contents

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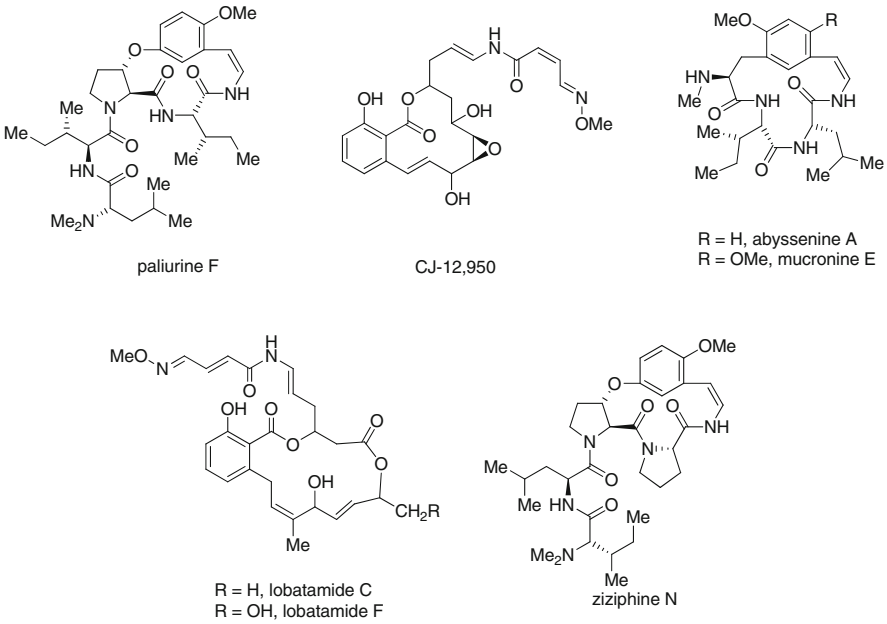


Fig. 1 Important compounds bearing enamide backbone

1 Introduction

Enamines and enamides are widely present as key structural motifs in a large number of natural products of great biological and medicinal importance such as the antibiotics and antitumor cyclopeptide alkaloids outlined in Fig. 1 [1]. Besides, they have found numerous applications as highly versatile intermediates in organic synthesis [2, 3] being found of utmost significance in Heck reactions [4–6], 1,3-dipolar cycloadditions [7], C–H activation processes [8–13], asymmetric fluorinations [14], and ring-closing metathesis [15, 16]. Furthermore, they are established as powerful nucleophiles in asymmetric Michael addition reactions [17] and other valuable stereoselective C–C [18] and C–N bond forming processes [19].

On one hand, conventional approaches for the preparation of enamines involve acid-catalyzed condensations of secondary amines with carbonyl compounds [20, 21]. However, the commonly required severe reaction conditions imply low functional group tolerance and lack of stereoselectivity. Other alternative routes include the hydroamination of alkynes [22, 23], and dehydrogenation of tertiary [24] and secondary amines [25]. On the other hand, numerous methods for the preparation of enamide-type compounds have been devised including ruthenium-[26–28] and rhenium-catalyzed amidation of alkynes [29], metal-catalyzed isomerizations of *N*-allylamides [30–32], ruthenium-catalyzed co-oligomerizations of *N*-vinylamides and alkenes or alkynes [33], reductive acylations of oximes [34, 35], *N*-acylations of imines [16], Wittig olefinations of *N*-formylimides [36], and Pd-catalyzed chloroallylation of ynamides [37], among others.

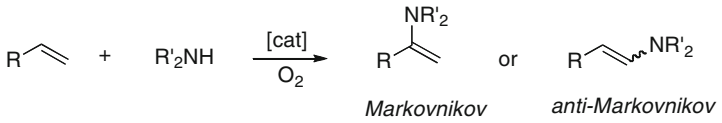
In the last years a powerful set of protocols involving C(sp^2)–N bond formation have emerged as reliable and convenient alternatives for the assembly of enamine and enamides. The latter methods consist of mostly palladium-catalyzed oxidative amidations of alkenes [38] and both palladium-[39] and copper-catalyzed cross-couplings [40] between generally vinyl halides or pseudohalides and amines or amides. In this review, recent advances in both types of processes will be disclosed illustrating, likewise, their synthetic value by describing total syntheses of natural products of high structural complexity.

2 Oxidative Amination/Amidation of Alkenes

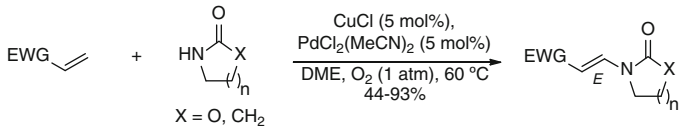
Metal-catalyzed oxidative addition of nitrogen nucleophiles such as amines and amides to olefins represents a straightforward atom economical approach for the preparation of enamines and enamides, respectively. These amination processes may proceed with Markovnikov or anti-Markovnikov regioselectivity and in the latter case such products can be obtained as either *E* or *Z* isomers (Scheme 1). Therefore, the ability of the catalyst to control that regiochemistry and stereoselectivity constitutes a challenging issue for synthetic chemists.

In 1992 Murahashi, Hosokawa, and co-workers described the anti-Markovnikov oxidative addition of amides and carbamates to electron-deficient olefins by applying a palladium and copper cooperative catalysis under oxygen atmosphere [41]. The proposed mechanism involved a σ-bonded palladium(II) intermediate resulting from the addition of the nucleophile to the olefin, and subsequent β-palladium hydride elimination to yield the functionalized alkene. Interestingly, both lactams and cyclic carbamates gave predominantly the corresponding *E*-enamide derivatives. Acyclic amides, conversely, afforded *E*/*Z* mixtures of products. The addition of a catalytic amount (5 mol%) of hexamethylphosphoric triamide (HMPA) was found notably beneficial for the reaction of 5-membered lactams and reduced the reaction time of such particular oxidative amidations (Scheme 2).

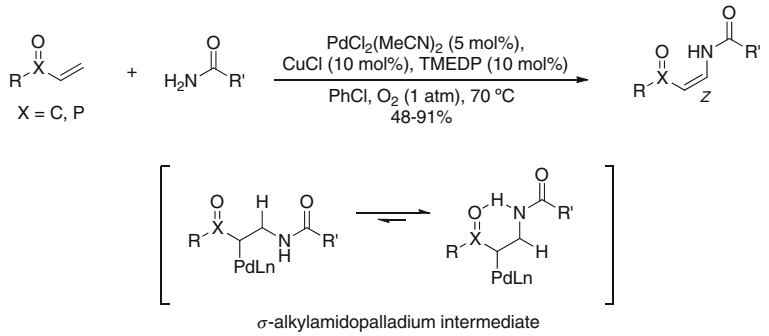
A highly stereoselective synthesis of *Z*-enamides was further developed by Chang, Kim, and co-workers via palladium/copper co-catalyzed anti-Markovnikov amidation of conjugated olefins [42]. The authors attributed the preferential formation of *Z*- vs *E*-enamides to the favorable β-palladium hydride elimination from the indicated σ-bonded palladium(II) intermediate which places an intramolecular hydrogen-bond between the amido proton and the carbonyl oxygen (Scheme 3). This oxidative amidation performed under Wacker-type conditions had a broad substrate scope and proved efficient for the reactions of different kind of amides (including aliphatic, aromatic, and vinyl substrates) with terminal olefins conjugated with keto, ester, amide, and phosphonate moieties. However, simple aliphatic olefins, styrene derivatives, and internal alkenes as well as carbamates proved unsuitable substrates under this oxidative amidation protocol. Importantly, the use of tetraethyl methylenediphosphonate (TEMDP) as additive not only resulted in a clear improvement of the yields but also inhibited the formation of undesired side products (cyclized enamides).



Scheme 1 Oxidative amination of olefins

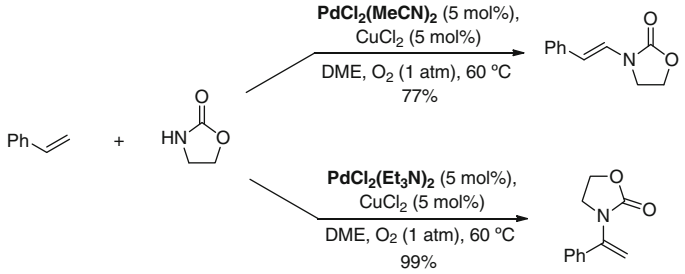


Scheme 2 Synthesis of *E*-enamides



Scheme 3 Synthesis of *Z*-enamides

Stahl and co-workers demonstrated that the regiochemistry between Markovnikov and anti-Markovnikov products in such amination processes could be entirely controlled by the proper choice of the palladium-catalyst system [43]. In particular, they first observed that the amination of styrene with oxazolidinone was easily directed toward the formation of each regioisomer by modifying the nature of the Pd-catalyst [44]. Thus, while the use of $PdCl_2(MeCN)_2$ in the presence of $CuCl_2$ as co-catalyst led to the selective formation of the anti-Markovnikov derivative (as *E*-isomer), the Markovnikov enecarbamate was regioselectively obtained when utilizing either such palladium catalyst in combination with $(NBu_4)OAc$ or when using $PdCl_2(Et_3N)_2$ as catalyst together, in both cases, with $CuCl_2$ as co-catalyst (Scheme 4). Kinetic studies supported a Brønsted base-modulated mechanism to justify this switch in regiochemistry [45]. In addition, they observed that other nitrogen nucleophiles such as cyclic imides, lactams, and sulfonamides were suitable substrates to accomplish the Markovnikov aerobic amination of various styrene derivatives. However, less acidic nucleophiles (morpholine, pyperidine, and anilines) proved unreactive under such conditions. Alternatively, co-catalyst-free oxidative aminations of



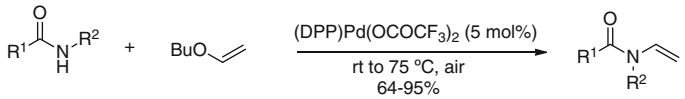
Scheme 4 Pd-catalyst effect in the regiochemistry

unactivated alkenes were developed by the same authors and the use of 5 mol% of $Pd(OAc)_2$ as catalyst provided the Markovnikov addition products in high yields when imides and sulfonamides were used as nucleophiles [46].

The major drawback of the protocols commented above is the requirement for large excess of alkenes to ensure high conversions, and this issue has been recently circumvented by a modification of the reaction conditions. Thus, use of a higher catalyst loading (10 mol% of $Pd(OAc)_2$) and high pressure (4 atm) of oxygen, which acts as stoichiometric oxidant, was found essential to allow the efficient oxidative amination of alkenes using the latter substrates as the limiting reagent [47].

In the course of these studies on the palladium-catalyzed oxidative aminations of olefins, Stahl observed that vinyl ethers did not undergo the expected oxidative amination under aerobic conditions and a vinyl transfer to the nitrogen nucleophile occurred instead [48]. They further explored such unexpected reactivity and developed a novel approach toward the synthesis of enamides and related derivatives involving a formal cross-coupling reaction between the corresponding nitrogen nucleophile and vinyl ethers. Remarkably, palladium-catalyzed cross-couplings are generally incompatible with the presence of oxygen and, besides, vinyl ethers unlikely undergo efficient oxidative addition to palladium(0). Therefore, the authors proposed a mechanism in which the palladium source remains in the +2 oxidation state throughout the catalytic cycle and anticipated the role of oxygen as oxidizer of any catalyst that could be reduced to palladium(0) during the process. Screening studies led to the identification of (4,7-diphenyl-1, 10-phenanthroline)palladium(II) trifluoroacetate complex as the best catalyst (Scheme 5).

Rhodium catalysts have also found application in oxidative aminations of styrenes. Beller and co-workers observed that numerous styrenes reacted with various kinds of secondary aliphatic amines in the presence of the cationic rhodium complexe $[Rh(cod)_2]BF_4$ and PPh_3. Regioselectively the corresponding anti-Markovnikov products (*E*-enamines) were formed [49]. While the Markovnikov product was never observed under such conditions, the target enamine was mostly obtained along with hydrogenated olefin, and in some cases even small amounts of hydroaminated products were detected [50].



Scheme 5 Palladium-catalyzed vinyl transfer reaction

3 Cross-Coupling Reactions

3.1 Palladium-Catalyzed Cross-Couplings

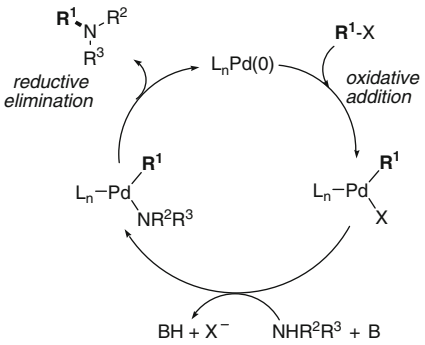
The palladium-catalyzed cross-coupling of amines with aryl halides, often named Buchwald–Hartwig amination, is nowadays one of the most powerful transformation in organic synthesis for the assembly of C–N linkages. Likewise, this methodology has recently matured from a standard laboratory procedure into a general, practical, and daily used technique in industrial environments [51–53]. However, the related palladium-catalyzed vinylation process has been comparatively less explored and not until 2000 did the first examples appear in the literature. Although its mechanism still remains unexplored and detailed studies have not been so far performed, it is reasonably accepted that a similar reaction pathway to *N*-arylation processes should operate when vinyl halides are used [54]. The generally accepted mechanism (Scheme 6) involves an initial oxidative addition of the aryl halide to the palladium (0) complex, which is obtained either by reduction of the Pd(II) source or by simple ligand exchange from a Pd(0) source. The resulting Pd(II) complex is then converted by coordination with the amine and followed by deprotonation into the corresponding amido Pd complex, which eventually releases the coupling product through reductive elimination and regenerates hence the starting Pd(0) complex.

It must be emphasized that the success of palladium-catalyzed cross-couplings is crucially restricted to the use of phosphine-type ligands [55], some of which are shown in Fig. 2.

3.1.1 Synthesis of Enamines

In 2000 Brookhart and Hicks reported one of the very first examples of palladium-catalyzed cross-coupling reactions between a nitrogen nucleophile and a vinylic substrate (Scheme 7). They found that the coupling conditions developed by Buchwald and Hartwig for the *N*-arylation of amines with aryl triflates were suitable for the synthesis of 2-anilinotropone derivatives by amination of 2-triflatropone with a wide range of anilines [56]. In fact, as aryl triflates, vinyl triflates have proven to be more active substrates than the corresponding alkenyl bromides toward oxidative addition to palladium(0) complexes in a coordinating solvent such as DMF and are hence much more reactive electrophilic coupling partners [57]. This methodology was found efficient for the preparation of a variety of 2-anilinotropone derivatives,

Scheme 6 General mechanism for palladium-catalyzed cross-couplings



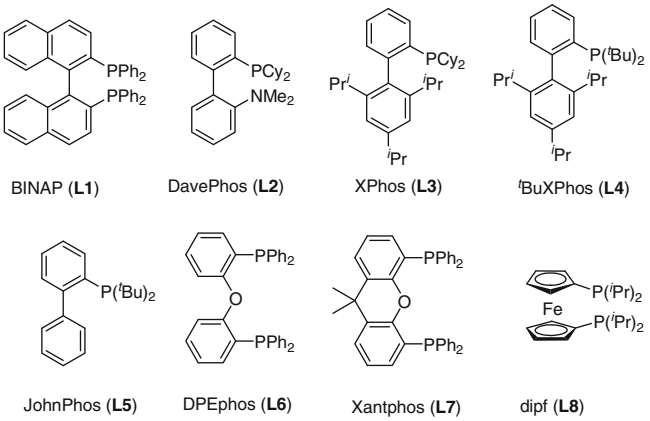
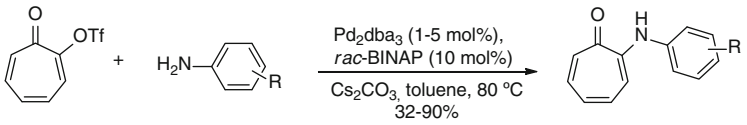


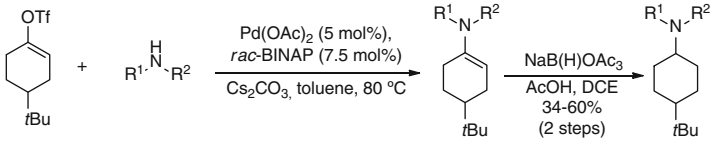
Fig. 2 Typical phosphine-type ligands in cross-couplings



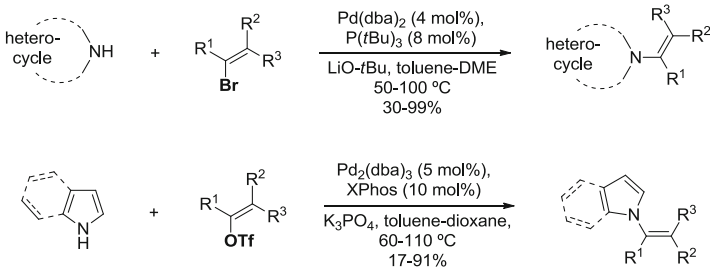
Scheme 7 Palladium-catalyzed coupling of anilines and vinyl triflates

even when sterically hindered anilines were employed. Moreover, electron poor 2,6-dihaloanilines provided regioselectively the desired tropone derivatives and side products due to competitive coupling reactions were not observed.

Similar reaction conditions were further utilized by Willis and Brace to conduct the synthesis of enamines from cyclic vinyl triflates and secondary amines [58]. Although the use of Cs_2CO_3 as base at 80°C delivered satisfactorily the target enamines, the effectiveness of using a strong base such as KO-*t*Bu at room temperature was also demonstrated and moderate to good conversions were achieved in those



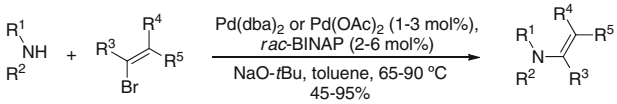
Scheme 8 Palladium-catalyzed coupling of secondary amines and vinyl triflates



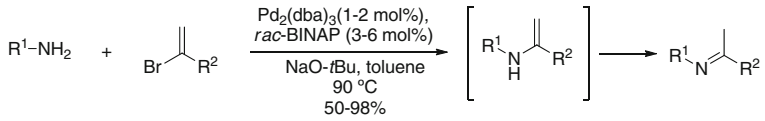
Scheme 9 *N*-alkenylation of heterocycles with vinyl bromides and triflates

cases. In view of the decomposition of the resulting enamines during their purification, they were in situ reduced to the corresponding amines by treatment with $NaB(H)OAc_3$ and AcOH in DCE (Scheme 8). Alternatively, they treated the crude enamines with aqueous acid to yield the corresponding ketones rendering thus such protocol a mild hydrolysis procedure of enol triflates, which usually constitutes a difficult task in organic synthesis.

In 2002 Voskoboynikov and Barluenga independently reported for the first time the use of alkenyl halides as electrophilic component in palladium-catalyzed vinylation processes. Voskoboynikov described the synthesis of *N*-vinyl azoles by means of palladium-catalyzed alkenylations of *NH*-azoles [59]. After screening of the reaction conditions with indole and *trans*-*β*-bromostyrene as a model system, a combination of $Pd(dba)_2$ and $P(tBu)_3$ as catalyst in a mixture of toluene and DME at 85°C proved optimal for the coupling. Notably, side products due to competitive *β*-eliminations in the starting styrene were avoided by the selection of a proper base. Hence use of either LiO-*t*Bu or a preformed indolyllithium regioselectively led to the target *N*-vinylic compound. The reaction occurred with complete retention of configuration in the double bond and both *cis*- and *trans*-*β*-bromostyrenes afforded stereospecifically the corresponding products. Other alkenyl bromides (α-bromostyrene, 2-bromopropene, and vinyl bromide) and other *N*-heterocycles (pyrrole, phenothiazine, carbazole and derivatives) smoothly underwent the desired vinylation at temperatures ranging from 50°C to 100°C (Scheme 9). In 2005 an alternative palladium-catalyzed synthesis of *N*-vinyl azoles using vinyl triflates as electrophilic counterpart was described by Movassaghi [60]. There, a combination of $Pd_2(dba)_3$ and XPhos afforded the best results and provided the stereospecific coupling of both cyclic and acyclic triflates with pyrrole and indole derivatives. Noteworthy, the formation of side products was minimized by using rigorously



Scheme 10 Palladium-catalyzed coupling of secondary amines and alkenyl bromides



Scheme 11 Palladium-catalyzed coupling of primary amines and alkenyl bromides

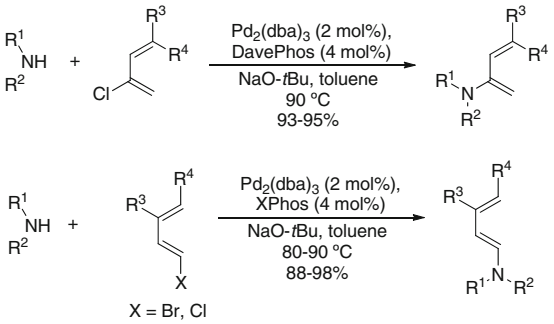
dried anhydrous K_3PO_4 and, unlike in the former protocol, the use of preformed pyrrolyllithium under such conditions gave predominantly undesired elimination product.

Barluenga further expanded upon these initial results and reported palladium-catalyzed cross-couplings of alkenyl halides and a wide range of amines. They first developed efficient intermolecular vinylation reactions of secondary amines to afford valuable enamine derivatives [61]. Selecting the reaction of α-bromostyrene and morpholine as a model system, they established that a combination of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and BINAP as catalyst system allowed such transformation in the presence of NaO-*t*Bu as base and toluene as solvent. Under those conditions, the coupling of *N*-methylaniline and dialkyl amines with various alkenyl bromides satisfactorily proceeded to provide the corresponding enamine derivatives (Scheme 10). Owing to the acid and water sensitivity of the resulting compounds, a particularly remarkable feature was that the workup consisted of simple filtration through celite of the reaction crude to yield pure products and hence conventional chromatography purification was not necessary.

Next, they studied the coupling of vinyl bromides with primary amines (anilines and benzylamines) under such reaction conditions and in those cases the corresponding imines were obtained after tautomerization of the initially formed enamines in nearly quantitative yields (Scheme 11) and in shorter reactions times than when using secondary amines (15 min vs 6 h) [62].

Despite the lower reactivity that vinyl chlorides usually display in cross-couplings due to their lower tendency toward oxidative additions to metals, Barluenga and co-workers described their successful application in coupling reactions with amines to yield imines and enamines [63]. In this case, the catalyst of choice turned out to be a combination of $Pd_2(dba)_3$ and the phosphine-type ligand DavePhos. Couplings between alkenyl bromides and secondary amines furnished the corresponding enamines in high yields, except when utilizing sterically hindered substrates. Primary amines led to the corresponding imine derivatives after the enamine-imine tautomerism indicated before (Scheme 12). The high practical value of using vinyl chlorides in such palladium-catalyzed processes was illustrated by the advantageous synthesis of 2-amino-1,3-butadienes through coupling between amines and 2-chlorodienes,

Scheme 12 Amination of vinyl chlorides and 2-chlorodienes



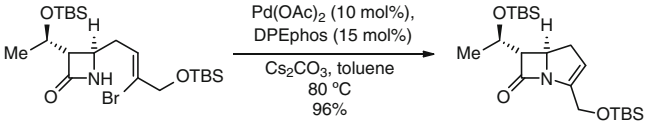
which remained inaccessible when utilizing more reactive albeit more stable related bromide derivatives. The latter protocol was further extended to the preparation of analogous 1-amino-1,3-butadienes (conjugated dienamines). In those cases XPhos was the ligand of choice. Interestingly, not only 1-chloro-1,3-butadienes but also the corresponding bromo-compounds efficiently underwent the latter process [64].

3.1.2 Synthesis of Enamides

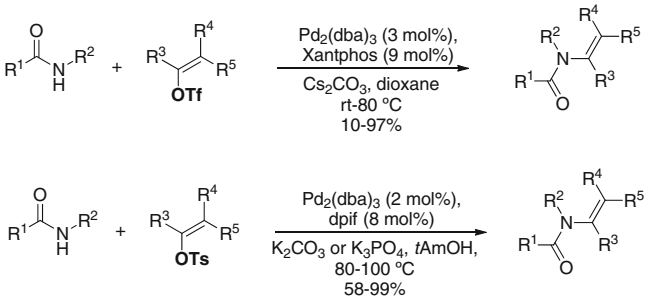
In 2002 Mori reported for the first time intramolecular palladium-catalyzed cross-couplings of β-lactams and vinyl halides to yield enamide-type compounds [65], and their application as key step in the synthesis of valuable carbapenem antibiotics (Scheme 13) [66]. The catalyst of choice was a combination of $Pd(OAc)_2$ and DPEphos. Noteworthy, control experiments revealed that the generation of the Pd(0) had to occur in the absence of the base to ensure high yields.

Intermolecular palladium-catalyzed amidations were further explored by a research group at Merck employing enol sulfonates as electrophilic coupling partners. They first described the amidation of enol triflates in the presence of $Pd_2(dba)_3$ and Xantphos. This vinylation protocol was also suitable for carbamates and sulfonamides [67]. Interestingly, when the corresponding enamides were obtained as mixtures of regioisomers, performing the reaction at room temperature allowed for retention of the configuration at the double bond of the starting enol triflate (Scheme 14). The same group extended this transformation to more advantageous enol tosylates, which are prepared also from the corresponding ketones but using much lower cost reagents and generally isolated as crystalline solids [68]. Ligand screening proved 1,1′-diisopropylphosphino ferrocene (dpif) as the most general supporting ligand to effect this challenging transformation. In this case, the rate of isomerization could be substantially minimized by using either shorter reaction times or bulkier amides as coupling partners.

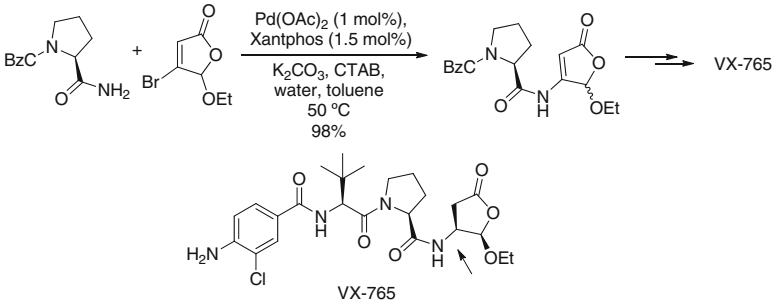
The major drawback of the latter protocols relies on the fact that the success of the process was limited to the use of enol triflates or tosylates bearing an aryl substituent or an electron-withdrawing group in the β-position. This substrate limitation was shortly after overcome by Willis, who introduced alternative palladium catalysts involving other phosphine-type ligands that also assisted the



Scheme 13 Intramolecular coupling of β-lactams and vinyl bromides



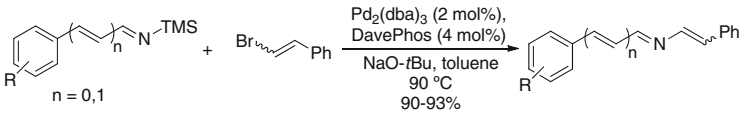
Scheme 14 Amidations of vinyl triflates and tosylates



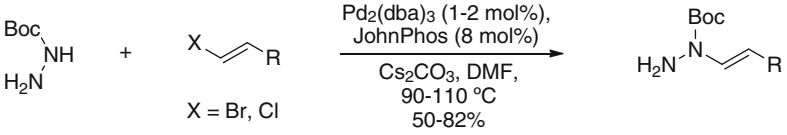
Scheme 15 Synthesis of VX-765

amidation of unactivated vinyl triflates and tosylates. Thus, using $Pd_2(dba)_3$ in combination with a ligand with a biphenyl scaffold such as DavePhos or tBuXPhos led to the coupling of triflates and tosylates that shown unreactive before yielding a wide range of vinylated amides, carbamates, and amines [69].

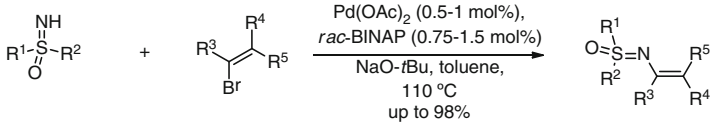
Recently, a research group from Vertex Pharmaceuticals has reported a general Pd-catalyzed protocol for the coupling of carbamates and amides (both aliphatic and aromatic ones) with *β*-bromoenoates (Scheme 15) [70]. The utility of the method was shown by performing the process on a 1 kg scale and by applying it as the key step in the total synthesis of VX-765, a potent inhibitor of the enzyme ICE which is currently under clinical studies in autoinflammatory disorders. They carefully optimized the reaction conditions to be compatible with the use of base-sensitive bromides. Finally, they concluded that the combination of $Pd(OAc)_2$ and Xantphos gave an effective catalyst when performing the amidation reaction under aqueous conditions in the presence of cetyltrimethylammonium bromide (CTAB) as phase transfer catalyst.



Scheme 16 Palladium-catalyzed vinylations of *N*-trialkylsilyl imines



Scheme 17 Palladium-catalyzed vinylations of *tert*-butylcarbazate



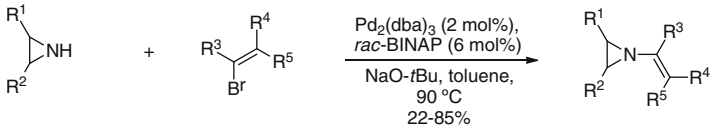
Scheme 18 Palladium-catalyzed vinylations of *NH*-sulfoximines

3.1.3 Other Nitrogen Compounds

Without doubt, amines and amides are the most common nitrogen coupling components in palladium-catalyzed vinylation reactions. However, cross-couplings of such type proved rather versatile and tolerant to the employment of other nitrogen compounds too. In this respect, Barluenga introduced the readily available *N*-trialkylsilyl imines as synthetic equivalents of the highly unstable *NH*-aldimines and reported their efficient application in C–N bond forming processes (Scheme 16) [71]. The use of $Pd_2(dba)_3$ in combination with either BINAP or DavePhos assisted the reaction of *β*-bromostyrene with silyl imines derived from benzaldehyde and cinnamaldehyde to afford the corresponding 2-azadienes and 3-azatrienes, respectively, in high yields.

More recently, they have reported the coupling of vinyl halides with *tert*-butyl carbazate to yield rather functionalized and unusual types of hydrazines (Scheme 17) [72]. In this case, the success of the process relied on the use of the phosphine-type ligand Johnphos in combination with $Pd_2(dba)_3$. Furthermore, the proper choice of base played a determinant role in circumventing the formation of the Ullmann-type homocoupling compound as a side product. Under the optimized conditions, a wide range of vinyl halides (*β*-bromostyrene, 1-bromodienes, 4-bromoenynes, and even less-reactive 1-chlorodienes) smoothly underwent the coupling process to furnish the target *N*-alkenylhydrazines.

Bolm employed *NH*-sulfoximines as nitrogen nucleophiles in palladium-catalyzed vinylations (Scheme 18) [73]. These kinds of derivatives are of utmost synthetic



Scheme 19 Palladium-catalyzed vinylations of aziridines

importance owing to their application as chiral ligands in the field of asymmetric catalysis [74]. They found that the methodology introduced by Buchwald and Hartwig for the *N*-arylation of amines and amides was suitable for the vinylation of these appealing substrates affording hence previously unknown *N*-vinyl sulfoximines. Thus, a mixture of $Pd(OAc)_2$ and BINAP in the presence of NaO-*t*-Bu proved highly efficient for the coupling of sulfoximine derivatives and vinyl bromides. Interestingly, a vinyl triflate was also utilized in such cross-coupling. In that case the replacement of the strong base by the weaker one Cs_2CO_3 was required in order to avoid the hydrolysis of the vinylic substrate.

Yudin and co-workers used aziridines as the amino partner in palladium-catalyzed alkenylations with vinyl halides developing thus a straightforward method for the synthesis of *N*-alkenyl aziridines (Scheme 19) [75]. They observed that copper catalysts provided comparatively lower yields, albeit allowed for the preparation of some aziridines inaccessible with a palladium catalyst. Due to the sensitivity of the coupling products toward aziridine ring opening on silica gel, the crude reactions had to be purified by either distillation or flash chromatography on alumina to ensure acceptable yields.

3.2 Copper-Catalyzed Cross-Couplings

Despite the efficiency of palladium catalysts, their high cost and air sensitivity sometimes limit their application to large- and industrial-scale synthesis. In this respect, the tremendously fast development of palladium catalysis was followed by an outstanding resurgence of copper-catalyzed reactions, endowing hence today a plethora of copper-catalyzed cross-coupling protocols as valuable alternatives to perform related processes [76–81]. While early attempts on copper-assisted couplings between amines or amides and aryl halides (Ullmann and Goldberg condensations, respectively) implied the use of harsh reaction conditions and stoichiometric amounts of copper, the methods currently available are catalytic in copper and involve much milder reaction conditions. Although some *ligand-free* copper-catalyzed methods have been reported in the literature [82–86], copper catalysts generally result from combining copper salts with certain supporting ligands, some of which are shown in Fig. 3.

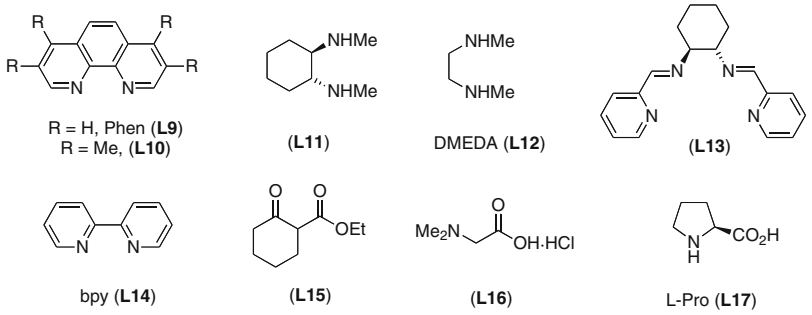


Fig. 3 Commonly used ligands in copper-catalyzed cross-couplings

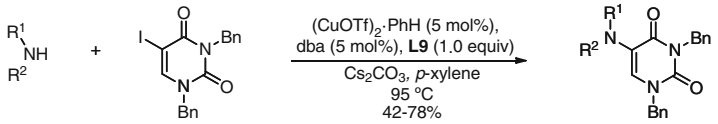
3.2.1 Synthesis of Enamines

While palladium-catalyzed alkenylation reactions involving amines as nucleophiles have been extensively explored, the related copper-catalyzed processes are rare and only few examples have been reported in the literature. The first example was described in 2001 and implied the particular use of 1,3-dibenzyl-5-iodouracil as electrophilic counterpart for the access of enamine-type products with potential pharmacological activity (Scheme 20) [87]. The authors demonstrated that the conditions previously reported by Buchwald for the arylation of imidazoles [88] were suitable for the vinylation of numerous amines (including primary heteroaromatic substrates and both primary and secondary aliphatic ones) to yield thus the corresponding 5-aminouracil derivatives in yields up to 78%.

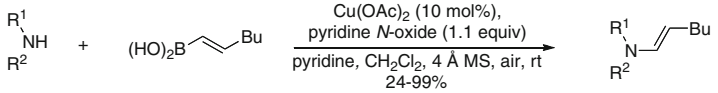
A very mild copper-catalyzed vinylation of amines, which involved the use of advantageous vinyl boronic acids at room temperature, was developed by Lam (Scheme 21) [89]. They proved that a combination of $Cu(OAc)_2$ and pyridine *N*-oxide was an efficient catalyst system for the coupling of *trans*-1-hexenyl boronic acid with certain amines. In this respect, not only *N*-heterocycles such as benzimidazole and indazole but also numerous ureas and lactams underwent the cross-coupling under similar conditions.

Bao reported the Ullmann-type coupling of vinyl bromides and imidazoles in ionic liquids (Scheme 22) [90]. A combination of copper iodide and L-proline was found highly effective as catalyst in the presence of $[Bmim]BF_4$ as solvent. This protocol was sensitive to the geometry of the starting vinyl bromide and only *E*-isomers were found reactive under such conditions. Interestingly, this method featured the possibility of recycling the catalyst system which was immobilized in the ionic liquid and hence the same media containing the active catalyst was utilized up to four times without any significant variation in the reaction outcome.

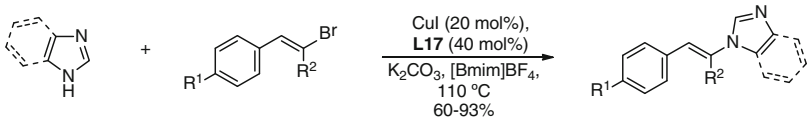
More recently, the latter authors developed a more simple protocol for the coupling of vinyl bromides and imidazoles involving the use of the cheaper Cu_2O along with a β-keto ester (ethyl 2-oxocyclohexanecarboxylate) as the catalyst of choice (Scheme 23) [91]. It was found that β-bromostyrenes bearing both electron-donating and electron-withdrawing groups were suitable for the cross-coupling, and



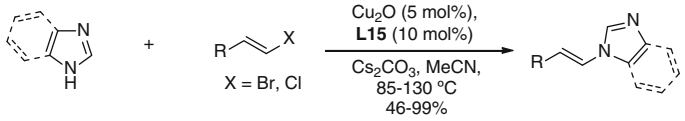
Scheme 20 Cross-coupling of amines and 1,3-dibenzyl-5-iodouracil



Scheme 21 Cross-coupling of amines and vinyl boronic acids



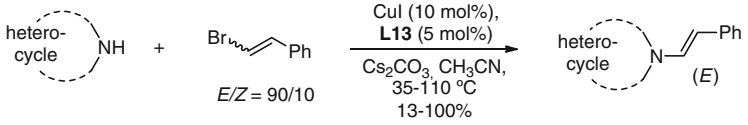
Scheme 22 Alkenylations of imidazoles with bromostyrenes



Scheme 23 Alkenylations of imidazoles with vinyl halides

even some vinyl chlorides were successfully coupled under modified conditions (higher reaction temperature and longer reaction time). Notably, the reaction was stereoselective for the (*E*)-alkenyl halides.

Early preliminary results on the N-vinylation of heterocycles[92, 93] were extended in 2006 by Taillefer and co-workers. There, a versatile catalytic strategy toward the preparation of *N*-vinyl azoles based on a copper-catalyzed *N*-vinylation of numerous azoles with (E)-b-bromostyrene as vinyl source [94] was introduced. The catalyst system involved the use of CuI together with the tetradentate ligand **L13** (Scheme 24) and was applicable for the conversion of pyrrole, pyrazole, indole, imidazole, benzimidazole, indazole, and several triazoles. β-Bromostyrene was utilized as a mixture of isomers ($E/Z = 90/10$) and the authors observed that whatever the nature of the nitrogen heterocycle the (*Z*)-β-bromostyrene always led to the formation of byproducts (competitive dehydrobromination reaction). Therefore, being the (*E*)-isomer the only reactive species, the corresponding *N*-alkenyl azoles were in all cases obtained as the (*E*)-compounds. Later on, the same authors demonstrated that the catalytic effect of the copper source could be enhanced by



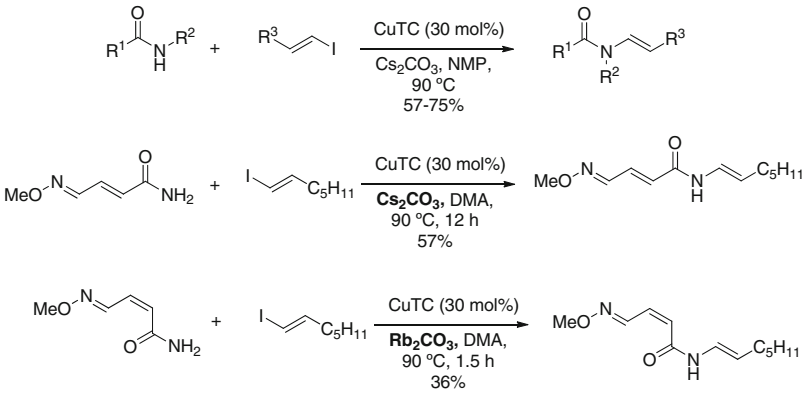
Scheme 24 *N*-vinylations of azoles with (*E*)-β-bromostyrene

using dendrimer-bound iminopyridine ligands and described the vinylation of pyrazole with (*E*)-*β*-bromostyrene utilizing phosphorus dendrimers as ligands [95].

In 2008 an alternative *ligand-free* copper-catalyzed protocol for the *N*-vinylation of *N*-heterocycles was reported by Mao [96]. The latter procedure implied the use of 10 mol% of CuI in DMF as solvent and Cs_2CO_3 as base at 120°C. Under such conditions imidazoles, pyrroles, indoles, benzimidazoles, and pyrazoles were efficiently coupled with (*E*)-*β*-bromostyrenes. Interestingly, the protocol was compatible with the use of cheaper vinyl chlorides albeit higher temperature (140°C) was required. More recently, the same authors described a complementary procedure for the coupling of vinyl halides and imidazoles that featured the use of 10 mol% of $FeCl_3$ in DMSO as solvent and K_3PO_4 as base at 120°C. Interestingly, this alternative iron-catalyzed protocol made possible the preparation of previously inaccessible (*Z*)-products when starting from (*E*)-vinyl bromides but, in striking contrast, the use of (*E*)-vinyl chlorides led to the preferential formation of (*E*)-products [97].

3.2.2 Synthesis of Enamides

Early experiments on the synthesis of enamides by means of copper-promoted substitutions of vinyl bromides and potassium amides were reported by Ogawa and Suzuki in 1991 [98]. However, the requirement of stoichiometric amounts of copper iodide under rather harsh reaction conditions (in HMPA at 130°C) rendered such approach highly inconvenient. Not until 2000 did an improved procedure for the copper-mediated coupling of alkenyl halides and amides appear in the literature [99]. Then, Porco and co-workers established that the use of Liebeskind's copper(I) thiophenecarboxylate (CuTC) [100, 101] in the absence of any further ligand led to the pursuit of a more convenient approach toward enamides. In particular, it consisted of using catalytic amounts of CuTC and Cs_2CO_3 as base in a polar aprotic solvent such as NMP or DMSO at 90°C. Under these conditions, both styrenyl and alkenyl iodides were suitable partners affording the corresponding enamides in moderate to good yields. Likewise, with the aim of assembling enamides related to salicylate antitumor macrolides, conjugated enamides such as 2,4-hexadienamide were tested as coupling partners. Interestingly, they observed that the nature of the base played a determinant role in the stereoselectivity of the process. While under the optimized conditions the (*E*)-amide (Scheme 25) yielded

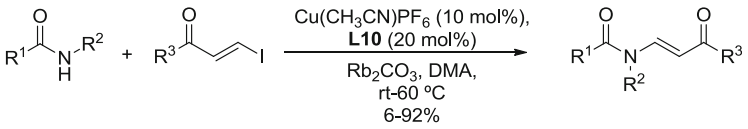


Scheme 25 Cross-couplings of amides and vinyl iodides with CuTC

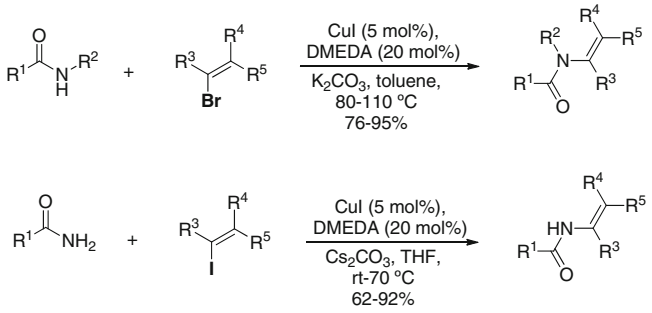
the desired enamide, Rb_2CO_3 was found to be required for the conversion of the corresponding (*Z*)-isomer.

Some years later, Porco extended this C–N bond formation methodology to the cross-coupling of numerous amides with *β*-iodo-acrylates to prepare both *N*-acyl vinylogous carbamic acids and ureas (Scheme 26) [102]. In this case, a combination of $Cu(CH_3CN)_4PF_6$ and 3,4,7,8-tetramethyl-1,10-phenanthroline was identified as the most efficient catalyst system and remarkably the coupling underwent at comparatively lower temperatures (45–60°C). With 2-pyrrolodinone as nitrogen coupling partner the reaction even proceeded at room temperature. Mostly, the enamide-type compounds were obtained as the (*E*)-isomers. Only when conjugated amides were coupled with 3-iodo-*N*-benzyl-2-propenamide the thermodynamic (*Z*)-isomers were observed. The authors proposed that this preference may be related to the higher acidity of the *NH* in conjugated amines, which stabilized the *Z*-isomer by formation of intramolecular hydrogen bond. Besides, the synthetic value of the protocol was demonstrated by its application as the key step in the preparation of the antibiotic CJ-15,801.

Buchwald developed a general cross-coupling protocol for the synthesis of enamide-type compounds which involved the use of 5 mol% of CuI and 20 mol% of *N*,*N*′-dimethylethylendiamine (DMEDA) as the active catalyst system [103]. When utilizing unactivated vinyl bromides, the process implied the use of K_2CO_3 as base in toluene at 110°C. Conversely, the amidation of vinyl iodides proceeded under milder conditions and implied the use of Cs_2CO_3 in THF at temperatures ranging from room temperature to 70°C (Scheme 27). Importantly, four-, five-, and six-membered lactams and carbamates efficiently coupled. Furthermore, acyclic primary amides were also found as suitable substrates under such reaction conditions. Of particular synthetic interest was the chemoselectivity observed toward the vinylation of an amide moiety in the presence of a free-amino group. Presumably due to steric hindrance, acyclic secondary amides proved to be unsuitable substrates as nitrogen coupling partners, whereas fully substituted vinyl



Scheme 26 Cross-couplings of amides and β-iodoacrylates

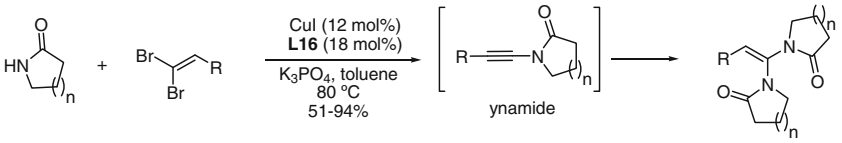


Scheme 27 Cross-coupling of amides and vinyl halides with CuI/DMEDA

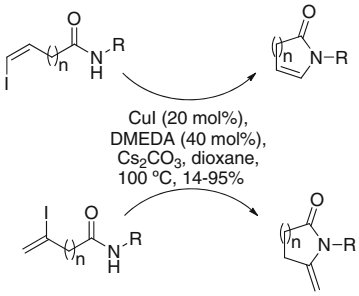
bromides performed well affording the corresponding enamides in good to high yields. Remarkably, the double bond geometry of the vinyl halides was retained in all cases. This protocol was recently applied for the preparation of amino acid-derived enamides by coupling of vinyl iodides and amino amides [104]. Notably, Buchwald further described the efficient coupling of numerous *β*-iodoenoates with azaheterocycles by applying a slightly modified copper-catalyzed vinylation process [105]. In the latter case, the target enamine and enamide-type products were obtained when using the key combination CuI/DMEDA in the presence of K_3PO_4 as base and toluene as solvent at 65°C.

Similar results were reported by Ma and co-workers, who utilized a combination of CuI and *N*,*N*′-dimethylglycine·HCl (**L16**) as catalyst system in dioxane as solvent and Cs_2CO_3 as base [106]. This alternative vinylation protocol was effective for the coupling of vinyl iodides and bromides with numerous amides and carbamates (both cyclic and acyclic substrates). Importantly, a wide range of functional groups (ketone, ester, and dienoic amides) were found compatible with the reaction conditions. Like in the protocol developed by Buchwald, the geometry of the double bond of the starting vinyl halide was retained during the reaction course.

Interestingly, a related copper catalyst system was recently utilized by Evano and co-workers for the synthesis of *N*,*N*-acetals when coupling 1,1-dibromoalkenes with certain amides [107]. Unexpectedly, this particular transformation did not proceed through two consecutive copper-catalyzed C–N bond formations and experiments conducted on ynamides under the same experimental conditions supported the plausible role of the latter species as active intermediates in the amidation process (Scheme 28). The mechanism pathway proposed by the authors consists of a first C–N cross-coupling of the alkene with the amide, followed by dehydrobromination of the coupling product and subsequent hydroamidation of the



Scheme 28 Cross-coupling of amides and 1,1,-dibromoalkenes



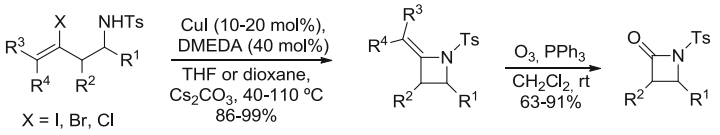
Scheme 29 Copper-catalyzed intramolecular vinylations of amides

resulting ynamide. Curiously, when the process was performed with Cs_2CO_3 as base the reaction was entirely selective toward the formation of ynamides [108].

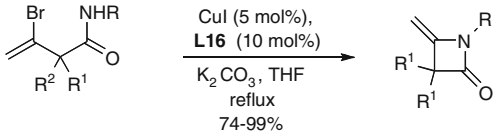
Copper-catalyzed *intramolecular* vinylations of amides for the assembly of five- to seven-membered lactams were further reported by Li (Scheme 29) [109]. The combination of CuI and DMEDA was identified as the catalyst of choice when using Cs_2CO_3 as base in dioxane at 100°C. Under such conditions numerous iodoenamides [both with (*Z*)-vinylic iodine substitution and bearing the iodine on the internal side of the double bond] underwent the cyclization furnishing the corresponding lactams in good to high yields. Notably, not only primary amides but also *N*-phenyl-substituted ones were found suitable substrates. In contrast to the parent intermolecular couplings, attempts to accomplish cyclizations under bromoenamides were all unsuccessful and low yields were obtained.

Importantly, four-membered ring closures to yield azetidine derivatives were also achieved by applying that copper-catalyzed protocol on sulfonamides placing a vinyl halide motif (Scheme 30) [110]. It is worth noting that cyclizations with substrates incorporating all iodo, bromo, and even challenging chloro groups proceeded smoothly to afford the desired 2-alkylideneazetidines. As expected, with vinyl iodides the reactions took place under milder reaction conditions (lower catalyst loading and temperature) than when employing the analogous chlorides and bromides. Along the entire process the configuration of the C=C double bond was retained. Additionally, the resulting 2-azetidine derivatives were converted into the corresponding β-lactams by conventional oxidation procedures proving evidence for the high synthetic value of such nitrogen compounds. Shortly after, they extended such methodology for the assembly of heterocyclic enamine derivatives of different sizes in both *exo* and *endo* cyclization modes [111].

More recently, the same authors have proved that the combination of CuI/*N,N′*-dimethylglycine·HCl (**L16**) efficiently catalyzed the conversion of 3-bromobut-



Scheme 30 Intramolecular vinylations of sulfonamides

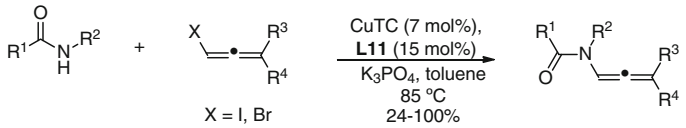


Scheme 31 Intramolecular vinylations of amides

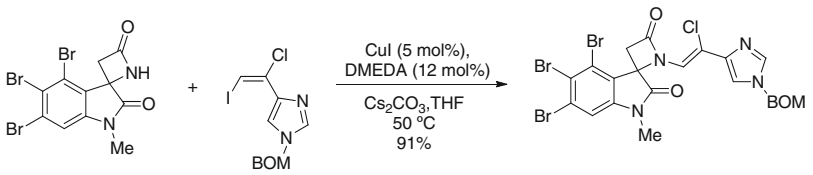
3-enamides into the corresponding 4-alkyliden-2-azetidinones through an intramolecular 4-*exo* cyclization process (Scheme 31) [112]. Importantly, experiments performed with substrates having two possible modes of ring-closure revealed a strong preference for the uncommon 4-*exo* cyclization mode vs competing 5-*exo*, 6-*exo*, or 6-*endo* cyclization modes. Notably, the treatment of primary amides under the optimized conditions yielded the corresponding *β*-lactams vinylated at the nitrogen atom resulting from a tandem process consisting of intra- and subsequent intermolecular *N*-vinylation reaction. The same authors have subsequently explored the application of this copper-catalyzed cyclization for the synthesis of related heterocycles by coupling of vinyl halides with other nucleophiles such as thiols [113], carboxylic acids [114], and methylene compounds [115].

Although vinyl halides as such are the most widespread utilized vinyl sources in this kind of copper-catalyzed C–N bond forming processes, the use of other related compounds such as allenyl halides and 1,2-dihaloalkenes have also been investigated. In this respect, Trost established a catalytic access to numerous allenamides based on the Ullmann-type coupling between allenyl halides and amides, carbamates and ureas (Scheme 32) [116]. The process was assisted by copper thiophenecarboxylate (CuTC) along with *trans-N,N′*-dimethylcyclohexyldiamine as ligand in the presence of K_3PO_4 as base and toluene as solvent. While under such conditions carbamates and ureas smoothly underwent the coupling reaction with allenyl iodides and bromides, both acyclic and cyclic amides were found less reactive and full conversion was never achieved.

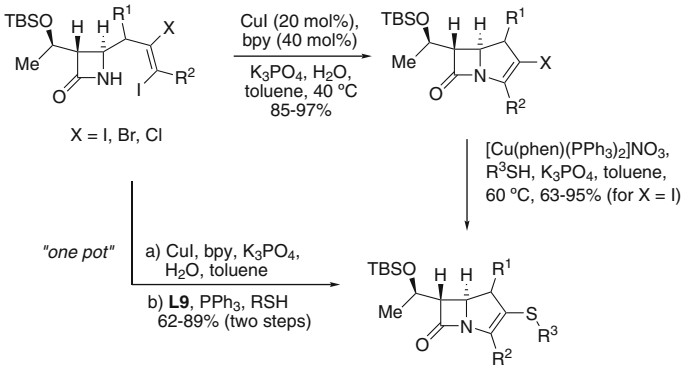
Particularly interesting as vinyl sources are 1,2-dihaloalkenes, which have lately found appealing applications in domino cross-coupling processes. The first single example was described by Isobe, who found that the coupling protocol developed by Buchwald for simple vinyl halides could be extended for the reaction of a *β*-lactam and (*E*)-*β*-chloro vinyl iodide [117]. However, in that case a mixture of enamide derivatives was obtained due to a nonselective coupling on the iodo and the chloro atom. This lack of selectivity was not observed by Weinreb, who reported the stereocontrolled synthesis of *β*-haloenamides via coupling of lactams and (*E*)-*β*-chloro and (*E*)-*β*-bromo vinyl iodides under the conditions previously reported by Buchwald (Scheme 33) [118]. In the latter case, the couplings were entirely selective toward the iodo group. Remarkably, the coupling could be affected in an intramolecular fashion to yield valuable seven-membered bicycles. More recently,



Scheme 32 Copper-catalyzed amidations of allenyl halides



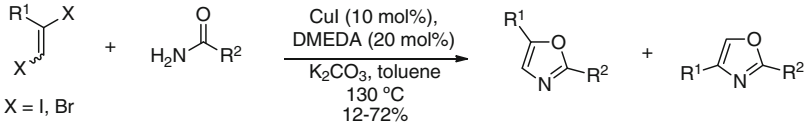
Scheme 33 Coupling of β-haloenamides and lactams



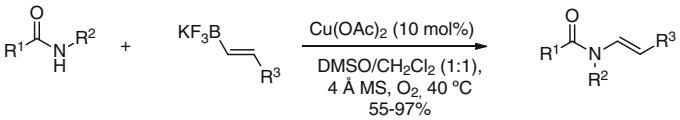
Scheme 34 Synthesis of carbapenem antibiotics

1,2-diiodoethene was utilized as vinyl source in couplings with cyclic and acyclic amides to furnish *β*-iodoenamides under Buchwald conditions [119].

An elegant approach for the preparation of carbapenem antibiotics featured the use of 1,2-dihaloalkenes which allowed two successive copper-catalyzed cross-couplings to take place in one pot [120]. By screening experiments the combination CuI and 2,2′-bipyridine was identified as the best catalyst for the intramolecular coupling of a *β*-lactam with a *trans*-diiodoalkene to provide the key intermediate 2-halocarbepenem in high yields. The latter iodo-functionalized heterocycles smoothly underwent intermolecular copper-catalyzed reactions with various thiols to thereby incorporate the desired sulfur chains by C–S cross-coupling (Scheme 34). In preliminary studies $[Cu(phen)(PPh_3)_2]NO_3$ was used as catalyst, which proved efficient for the conversion of alkyl, aryl, and heteroaryl thiols. Both couplings could also be performed without isolating the monoiodocarbapenem compound.



Scheme 35 Synthesis of oxazoles



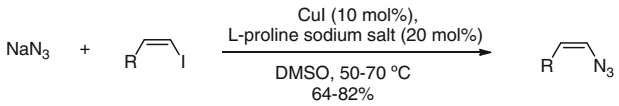
Scheme 36 Copper-catalyzed amidations of alkenyltrifluoroborates

Then, 1,10-phenanthroline, PPh_3, and the corresponding thiol were added to the reaction mixture once the first *N*-vinylation was complete.

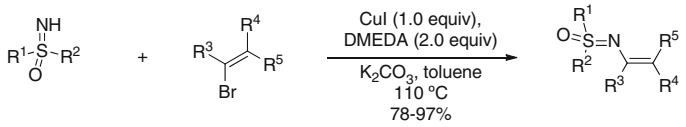
Likewise, a domino C–N/C–O cross-coupling process for the assembly of oxazoles was reported using 1,2-dihaloalkenes as the electrophilic partners [121]. When starting from dibromoalkenes a strong preference for the formation of 2,5-disubstituted oxazoles was observed (ratios up to 11:1). The more reactive diiodoalkenes reacted unselectively at both positions (Scheme 35).

Very recently potassium alkenyltrifluoroborate salts have been introduced by Batey as advantageous alternative coupling components in copper-catalyzed vinylations for the assembly of enamide-type derivatives (Scheme 36) [122, 123]. The use of such salts allowed the cross-coupling to occur under mild base-free conditions and at rather low temperatures (40°C). It was found that a combination of $Cu(OAc)_2$ and *N*-methylimidazole was very effective for the coupling of phthalimide and potassium hexenyltrifluoroborate. While other related compounds such as 2-hydroxypyridine and isatin proved suitable substrates under such conditions, attempts to use benzamides and lactams led to the formation of the corresponding enamide derivative in unsatisfactory yields (0–22%). Interestingly, the removal of the ligand and the addition of DMSO as co-solvent led to a more general protocol which was indeed suitable for the vinylation of numerous cyclic and acyclic amides as well as certain carbamates. All reactions were highly stereoselective and yielded the *trans*-enamides in good to excellent yields when starting from *trans*-alkenyl salts.

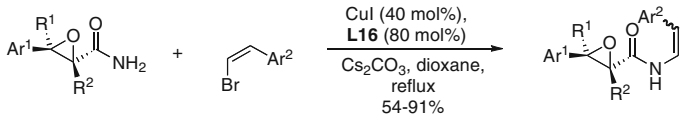
Alternatively, Arsenyan employed trimethoxyvinylsilane as vinyl source in copper-promoted *N*-vinylation of amides, but the use of stoichiometric amounts of $Cu(OAc)_2$ are required [124].



Scheme 37 Copper-catalyzed vinylation of azides



Scheme 38 Copper-catalyzed vinylation of *NH*-sulfoximines



Scheme 39 Coupling of oxirane carboxamides and vinyl bromides

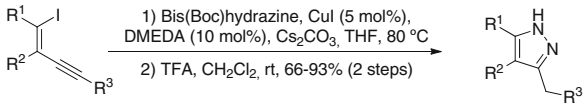
3.2.3 Other Nitrogen Compounds

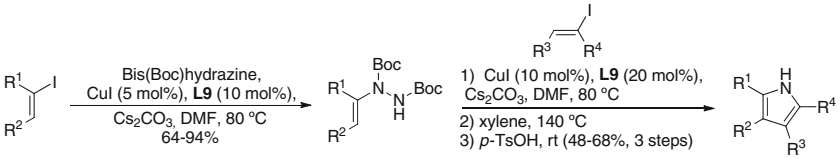
Although the vast majority of vinylation reactions involving copper catalysts are accomplished with amines and amides as nitrogen coupling partners, the reactivity of other less common nitrogen species has also been studied. Ma introduced the use of sodium azide in copper-catalyzed cross-couplings leading to aryl and vinyl azides [125]. The use of CuI along with L-proline sodium salt gave a very active catalyst that enabled both arylations and vinylations of sodium azide in high yields (Scheme 37). Noteworthy, the protocol was suitable for the conversions of *cis*-vinyl iodides bearing either aromatic or aliphatic substituents. Importantly, the stereochemistry of the C–C double bond was retained in all cases.

Bolm prepared a wide range of *N*-vinyl sulfoximine derivatives by means of copper-promoted coupling of *NH*-sulfoximines and vinyl bromides (Scheme 38) [126]. The major drawback of such protocol, which relied on the use of stoichiometric amounts of both copper and diamine ligands, was balanced by the fact that the present method exhibited broader scope than the one involving palladium-catalyst [73] being found compatible with the conversion of di-, tri-, and even tetra-substituted vinyl bromides.

Wang disclosed an efficient copper-catalyzed cross-coupling of oxirane carboxamides with vinyl bromides (Scheme 39) [127]. After screening studies, they came to a similar system to that reported by Ma for vinylations of amides. In most cases, the stereoselectivity of the process was good to high with the ratio of *Z*-enamide over *E*-enamide ranging from 85:15 to 95:5. Notably, the protocol was successfully applied in the synthesis of valuable *Clausena* alkaloids.

Scheme 40 Copper-catalyzed vinylation of hydrazydes





Scheme 41 Synthesis of pyrroles

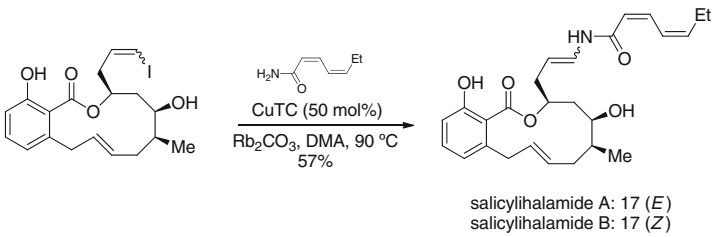
Hydrazides have been also utilized as nucleophilic component in these copper-catalyzed vinylations. On one hand, Kabalka reported the synthesis of diprotected monosubstituted hydrazynes by means of cross-couplings between *tert*-butyl carbazate and boronic acids [128]. The reaction required the use of CuCl as catalyst, took place at room temperature, and accommodated a wide range of functional groups. In most cases aryl boronic acids were employed, and only one example of a vinylic substrate was described. On the other hand, Buchwald reported elegant approaches toward the assembly of both pyrroles and pyrazoles by copper-catalyzed reactions of hydrazides with vinyl halides. They first combined an initial cross-coupling between either amides or hydrazydes and haloenynes followed by an in situ intramolecular hydroamidation of the resulting alkyne to yield pyrroles and pyrazoles, respectively [129] (Scheme 40).

In a subsequent report, they described an alternative synthesis of pyrroles through a two sequential copper-catalyzed vinylations of hydrazydes/cyclization strategy (Scheme 41) [130]. Alternatively, the synthesis of various *N*-acylpyrroles was accomplished by Li through a copper-catalyzed double *N*-alkenylation of amides [131]. For more details see the chapter devoted to the synthesis of heterocycles by means of arylation/vinylations.

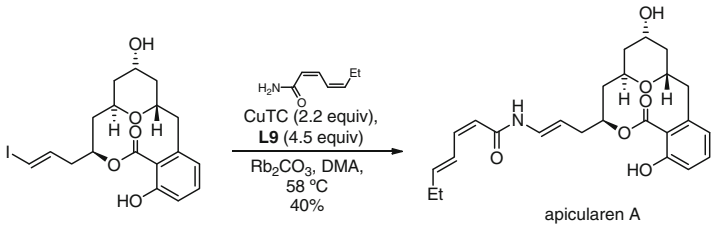
3.2.4 Applications in Synthesis of Natural Products

Copper-catalyzed alkenylations have lately found highly practical applications in the total synthesis of a vast array of natural products and evolved hence into a viable alternative to the usually practiced palladium reactions. Major reasons for the success of the latter catalysts are their comparatively lower price, excellent compatibility with a variety of functional groups and the ability to control the stereoselectivity of the process.

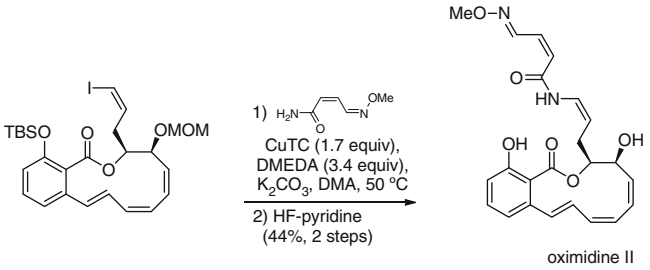
The protocol developed by Porco for the construction of an enamide motif was further expanded and applied by other research groups as the key step in various total syntheses. In 2001 Fürstner described the concise syntheses of the potent cytotoxic marine alkaloids salicylihalamide A and B utilizing a copper-catalyzed



Scheme 42 Synthesis of alkaloids salicylihalamide A and B



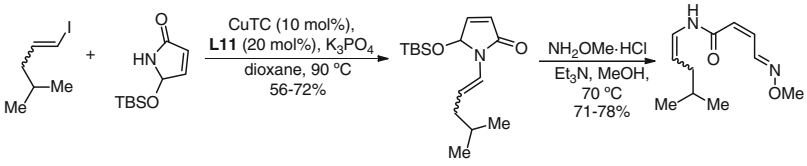
Scheme 43 Synthesis of polyketide apicularen A



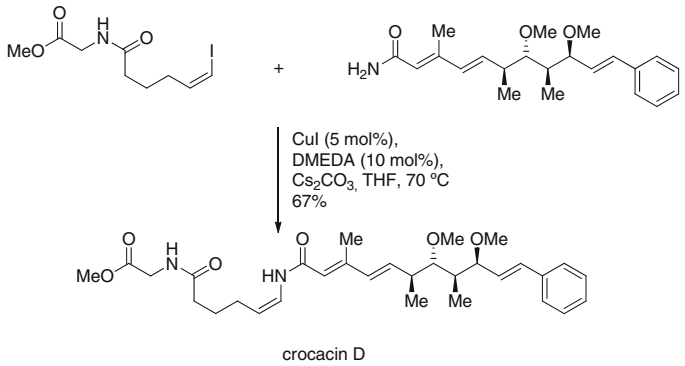
Scheme 44 Synthesis of oximidine II

vinylation as the final step (Scheme 42) [132]. The required vinyl iodide was used as a mixture of isomers (E:Z = 9:1). Unfortunately, an isomerization of the double bond occurred in the course of the coupling to yield the target product as a 2.5:1 mixture of E:Z-isomers, which could then be separated by HPLC.

Likewise, Nicolaou observed such isomerization when attempting a copper-mediated vinylation under modified Porco's conditions in the total synthesis of the polyketide apicularen A [133, 134]. Thus, when starting from a vinyl iodide consisting of a 9:1 mixture of E:Z isomers the target enamide was obtained as a 10:1 mixture (E:Z). The final product was then obtained after chromatographic separation. Alternatively, Panek described the total synthesis of the same natural product using a copper-promoted vinylation at the late stage of synthesis (Scheme 43) [135]. Isomerization of the double bond accompanied the target enamide formation and a mixture of iodides (E:Z = 6:1) furnished the desired apicularen A as an 8:1 E:Z mixture. Remarkably, the addition of 1,10-phenanthroline and reaction temperature proved essential parameters for the reaction outcome.



Scheme 45 Stereospecific copper-catalyzed vinylations

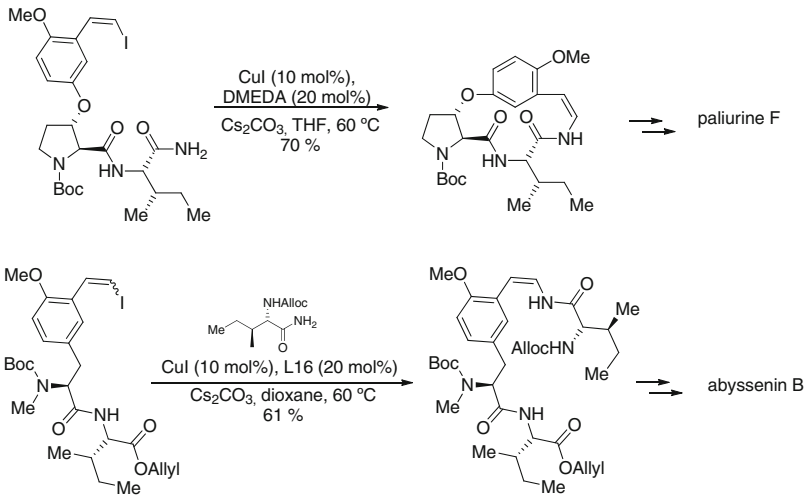


Scheme 46 Synthesis of crocacin D

Porco employed his methodology in the preparation of the salicylate antitumor macrolides lobatamide C [136, 137] and Oximidine II (Scheme 44) [138]. In both cases, re-optimization of the reaction conditions was required, and it was observed that the addition of a stoichiometric amount of diamine ligand (1,10-phenanthroline and DMEDA) was essential for the process to occur. It is noteworthy that when starting from a *Z*-vinyl iodide (synthesis of oximidine II) the amidation proceeded stereoselectively. Conversely, when starting from a *E*-vinyl iodide (synthesis of lobatamide C) a mixture of enamide isomers was obtained.

Some drawbacks of the former total syntheses such as the lack of stereoselectivity and the use of overstoichiometric amounts of the metal catalyst were circumvented by the protocol developed by Coleman, who reported a unified strategy for the divergent and stereocontrolled introduction of enamide chains in natural products [139]. Thus, a stereospecific copper-catalyzed vinylation of a protected maleimide hemiaminal delivered the key enamide intermediate whose further deprotection and treatment with *O*-methylhydroxylamine provided the corresponding ring-opened *O*-methyloxime ethers (Scheme 45). The latter are characteristic fragments in the structure of oximidines I/II/III, salicylihalamides A/B, lobatamides A/D, and CJ-12,950. In those cases, Liebeskind's CuTC together with *trans-N,N′*-dimethyl-1,2-cyclohexanediamine was recognized as the best catalyst system, and the optimized conditions involved the use of K_3PO_4 in dioxane at 90°C.

Owing to their high degree of stereoselectivity and mild reaction conditions the protocols independently developed by Buchwald and Ma have lately found significant applications too. In this respect, the total syntheses of numerous natural products have been achieved by applying such protocols in both inter- and



Scheme 47 Synthesis of macrocycles paliurine F and abyssenin B

intramolecular fashion. In 2005 the total synthesis of (+)-crocacin D was described based on an intermolecular copper-catalyzed *N*-vinylation, which provided efficiently the challenging (*Z*)-enamide moiety (Scheme 46) [140]. The use of both Buchwald's and Ma's conditions led to similar results.

Other impressive applications of the protocol developed by Buchwald in natural product synthesis were displayed by Evano, who reported the total syntheses of the alkaloids paliurine F [141], abyssenine A [142], and mucronine E [143] by means of intramolecular copper-catalyzed vinylation as the key step for the assembly of such relevant 13- and 15-membered macrocycles. Likewise, some of the latter cyclopeptide alkaloids such as abyssenine B and mucronine E [144], and other significant ones like ziziphine N [145], were prepared by Ma performing the key enamide formation under his previously reported copper-catalyzed cross-coupling (Scheme 47). All these elegant approaches proceeded with complete regioselectivity toward the construction of the required (*Z*)-enamide motif, without any isomerization of the starting alkenyl iodide and, importantly, without any epimerization of the multiple stereogenic centers present in molecules of such structural complexity.

4 Conclusion and Outlook

Owing to the prevalence of C(sp^2)–N bonds as enamine and enamide moieties in numerous valuable natural products, the construction of such functionalities poses a challenging target for organic chemists and has hence stimulated the development of a vast array of methodologies. In this respect, palladium-catalyzed oxidative

amination of alkenes and both palladium- and copper-catalyzed *N*-vinylation of generally amines and amides stand out today as reliable and efficient protocols for the assembly of such type of compounds. In particular, based on the mild reaction conditions, broad functional group tolerance, and mostly the high degree of stereospecificity, copper-catalyzed cross-couplings between vinyl halides and amides have been broadly identified as the method of choice in the field of natural product synthesis. Therefore, continued growth and advances of paramount synthetic importance in the field can be anticipated.

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Assembly of *N*-Containing Heterocycles via Pd- and Cu-Catalyzed C–N Bond Formation Reactions

Yongwen Jiang and Dawei Ma

Abstract Some newly developed methods for assembling N-containing heterocycles are summarized here. The key transformations in these methods are Pd- or Cu-catalyzed N-arylation and N-vinylation. The heterocycles include indoles, benzimidazoles, pyrroles, indazoles, indolines, lactams, quinazolinones and heterobenzazepines. These conceptually-novel and reliable methods should find applications in the synthesis of bioactive compounds and material molecules.

Keywords Palladium · Copper · Cross-coupling · C–N bond formation · N-containing heterocycles · Synthesis

Contents

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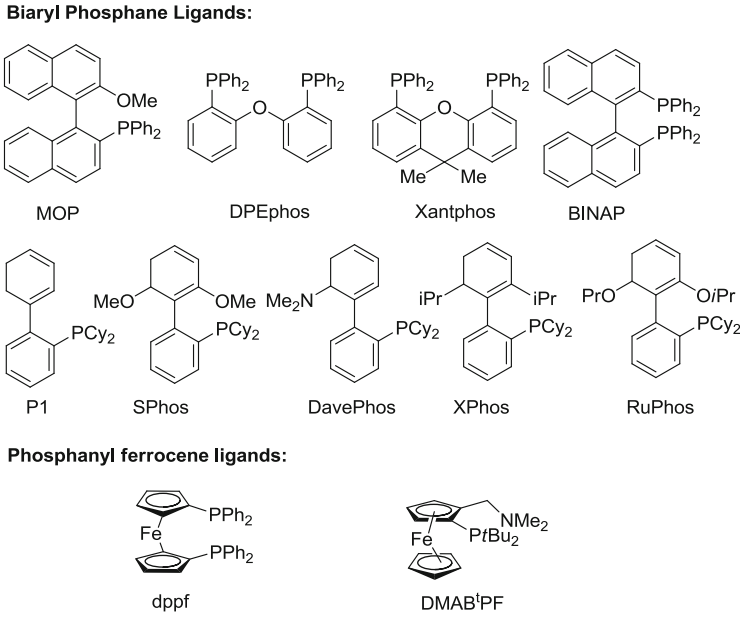


Fig. 1 Typical ligands for Pd-catalyzed *N*-arylation and *N*-vinylation

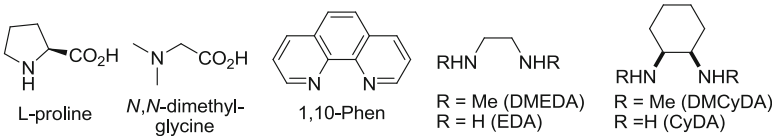
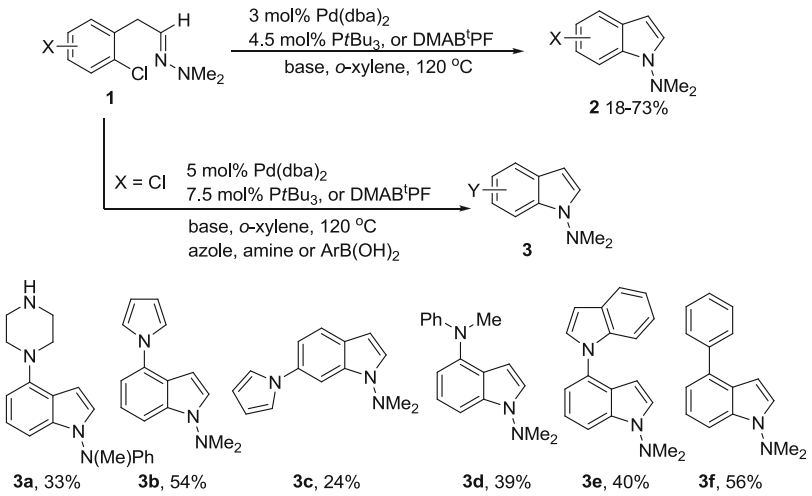


Fig. 2 Typical ligands for Cu-catalyzed *N*-arylation and *N*-vinylation

1 Introduction

Owing to their importance for pharmaceutical and material sciences, *N*-containing heterocycles have received great attention from the synthetic community [1, 2]. Although numerous methods have been developed for the synthesis of *N*-containing heterocycles, novel approaches that allow more diverse synthesis are still required. In recent years, we have witnessed great progress in metal-catalyzed *N*-arylation and *N*-vinylation. These new reactions provide abundant opportunity for discovering new methodologies to elaborate *N*-containing heterocycles. During the past decade, using Pd- and Cu-catalyzed *N*-arylation and *N*-vinylation as the key steps, a number of methods have been developed for assembling indoles, benzimidazoles, pyrroles, indazoles, indolines, lactams, quinazolinones, heterobenzazepines and other *N*-containing heterocycles (for Pd-catalyzed coupling reaction reviews, see: [3–11]; for Cu-catalyzed coupling



Scheme 1 Synthesis of 1-amino indoles via Palladium-catalyzed intramolecular C–N bond formation

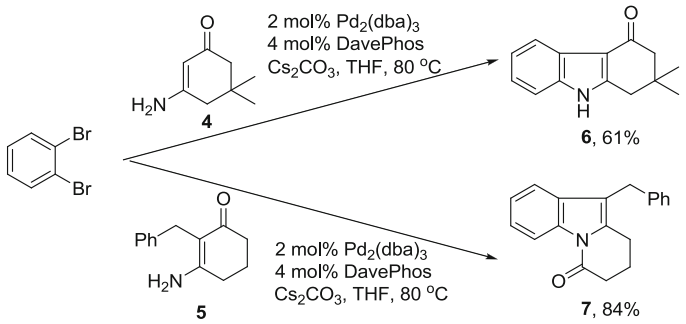
reaction reviews, see: [12–18]). In this review, we wish to summarize these results. The often used ligands in this article are outlined in Fig. 1 (for Pd-catalyzed reactions) and Fig. 2 (for Cu-catalyzed reactions).

2 Indoles and Related Heterocycles

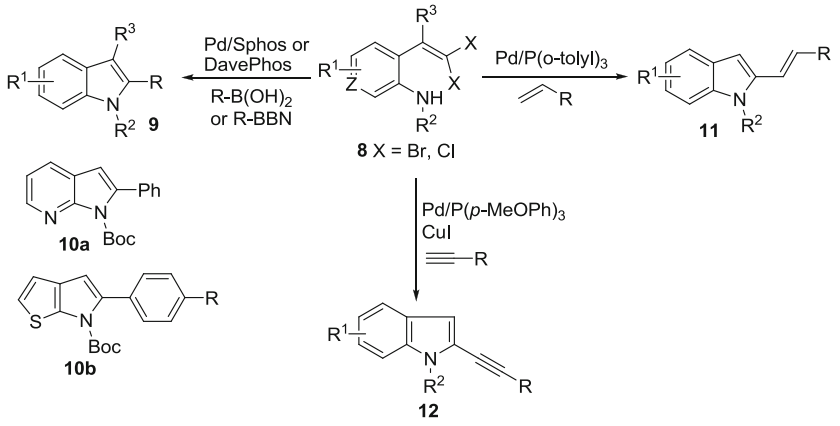
The indole moiety exists widely in bioactive natural products and artificial molecules. Establishing efficient methods for constructing the indole compounds has been an active area in organic synthesis for over 100 years (for reviews, see: [19–23]). The newly developed C–N bond formation reactions allow indole synthesis using aryl halides as starting materials. Watanabe et al. found that intramolecular aryl amination of aryl halides bearing a hydrazone moiety could be catalyzed by Pd/P*t*Bu$_3$ or Pd/DMAB*t*PF to afford 1-aminoindole derivatives (Scheme 1) [24]. It seemed that an additional chloride group in benzene ring does not affect this cyclization, and therefore further coupling with amines, azoles or phenylboronic acid could be carried out in one-pot to provide more complex products.

A Merck research group discovered that the cross-coupling reaction between aryl halides and vinylogous amides could take place under the catalysis of Pd/DavePhos. When 1,2-dibromobenzene was used, a cascade intermolecular C–N bond coupling and intramolecular Heck reaction occurred to provide 2,3-disubstituted indoles (Scheme 2) [25].

Using *ortho-gem*-dihalovinylanilines as substrates, the Lautens group developed a series of methods for the synthesis of 2-substituted indoles by Pd-catalyzed cascade reactions. For examples, intramolecular C–N bond formation and subsequent Suzuki–Miyara coupling reaction of *ortho-gem*-dihalovinylanilines with boric reagents provided 2-substituted indoles **9**, azaindole **10a** and thienopyrroles **10b** (Scheme 3) [26–28]. In the latter two cases, *ortho-gem*-dichlorovinylanilines were



Scheme 2 Synthesis of 2,3-disubstituted indoles via Pd-catalyzed cascade intermolecular C–N bond formation and intramolecular Heck reaction



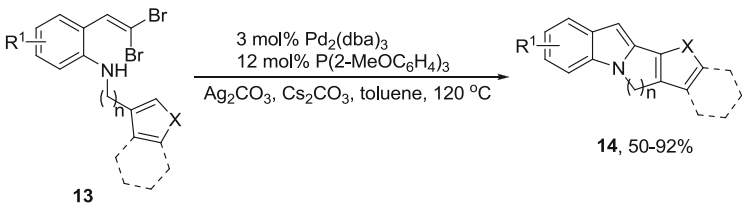
Scheme 3 Synthesis of 2-aryl indoles, 2-vinylic indoles and 2-alkynyl indoles via Pd-catalyzed intramolecular N-arylation

better substrates than *ortho-gem*-dibromovinylanilines, although the reason was not so clear. Through a cascade intramolecular aryl amination and intermolecular Heck reaction, 2-vinylic indoles **11** could be obtained with good yields [29]. Additionally, 2-alkynyl indoles **12** could be assembled via a cascade aryl amination/Sonogashira reaction process [30].

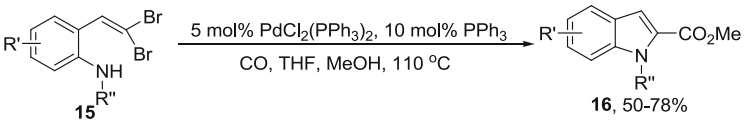
Based on the same strategy, Lautens et al. developed a method for synthesizing indole embodied polycyclic heteroaromatics **14**, in which a silver-promoted domino Pd-catalyzed intramolecular amination and C–H activation arylation were involved (Scheme 4) [31].

Recently, Alper et al. added Pd-catalyzed carbonylation to the above domino process and developed a concise route for the synthesis of 2-carboxyindoles **16** from *ortho-gem*-dibromovinylanilines **15** (Scheme 5) [32].

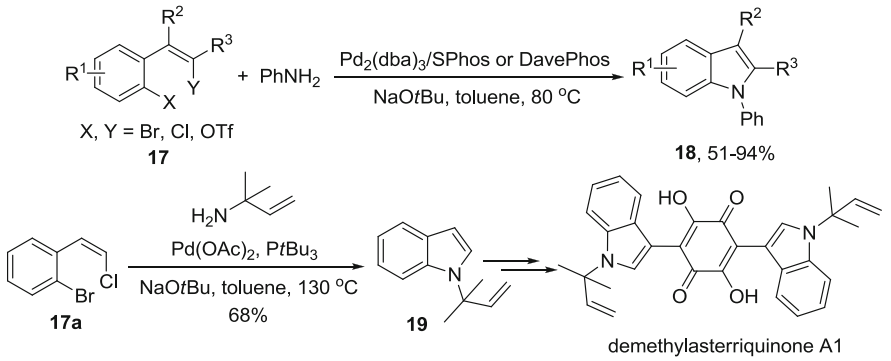
Using 2-(2-haloalkenyl)aryl halides **17** as coupling partners, the Willis group discovered an alternative route to indoles (Scheme 6) [33, 34]. Thus, Pd-catalyzed double amination of **17** with aniline delivered 1-phenyl indoles **18** in good yields.



Scheme 4 Silver-promoted domino Pd-catalyzed intramolecular amination and C–H activation



Scheme 5 Synthesis of 2-carboxyindoles via Pd-catalyzed intramolecular coupling and carbonylation from *ortho-gem*-dibromovinylanilines

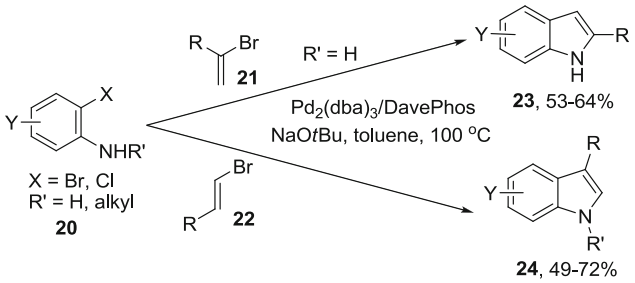


Scheme 6 Pd-catalyzed double amination of 2-(2-haloalkenyl)aryl halides

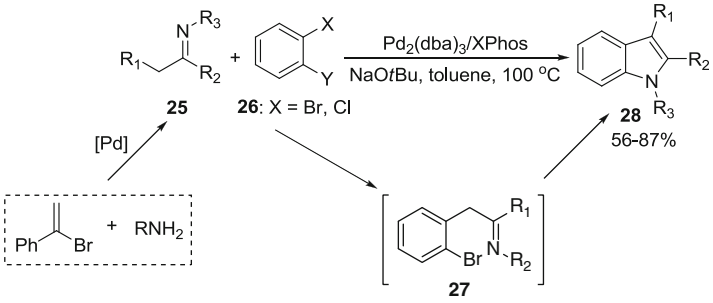
When sterically demanding *N*-nucleophiles were used, bulky and electron-rich phosphine P*t*Bu$_3$ and higher reaction temperatures were required to ensure complete conversion [34]. The product **19** thus formed could be easily transformed into natural product demethylasterriquinone A1.

Another approach to the indole core was developed by Barluenga. The reaction of 2-bromophenylamines **20** and alkenyl halides (**21** or **22**) underwent a cascade Pd-catalyzed intermolecular vinyl amination and intramolecular Heck reaction process to provide 2-substituted or 1,3-disubstituted indoles (**23** or **24**) (Scheme 7) [35].

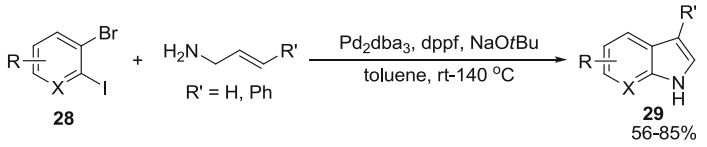
Subsequently, the same group reported a more practical method for preparing indoles by using the azaallylic anion as a synthon (Scheme 8) [36]. They found that imines **25** could couple with *o*-dihalobenzenes **26** to produce intermediates **27**, which underwent an intramolecular aryl amination to afford 1,2,3-trisubstituted indoles **28**. Because the azaallylic anion could be prepared by a Pd-catalyzed reaction of alkenyl halides and primary amines, they were able to develop a domino three-component synthesis of indoles.



Scheme 7 Assembly of 2-substituted and 1,3-disubstituted indoles via Pd-catalyzed intermolecular vinyl amination and intramolecular Heck reaction



Scheme 8 Synthesis of polysubstituted indoles via Pd-catalyzed intermolecular C–C bond formation and subsequent intramolecular N-arylation

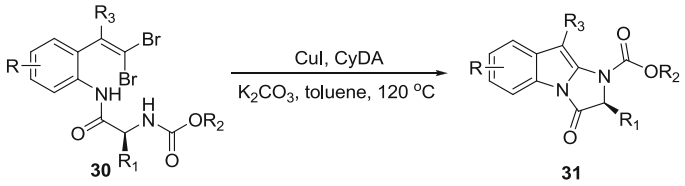


Scheme 9 Indole synthesis via Pd-catalyzed N-arylation and intramolecular Heck reaction

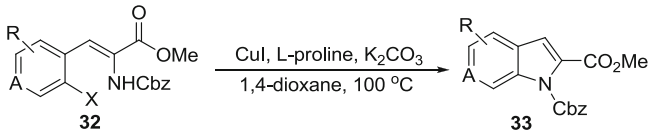
Pd-catalyzed reaction of allylamines with 2-bromoiodobenzenes **28** could also provide indoles **29** (Scheme 9) [37]. This process obviously contains an aryl amination and an intramolecular Heck reaction. The catalytic system of Pd_2dba_3 with dppf was proved to be the most efficient for both selectivity and yield. The nitrogen of indole could be further functionalized by in situ *N*-arylation.

Based on their Pd-catalyzed synthesis for the indole ring system, Lautens et al. developed a method for assembling imidazoindoles **31**, which relied on CuI-catalyzed double vinyl amidation of *gem*-dibromovinyl compounds **30** (Scheme 10) [38]. Normally this reaction required 2.5 mol% CuI. For sterically hindered substrates (R^3 = 4–F–C_6H_4), increasing catalytic loading was necessary to get better yields.

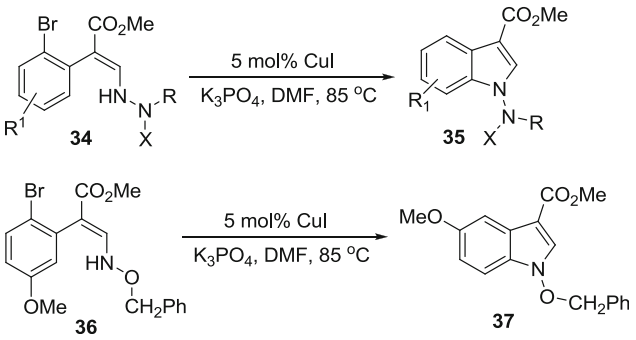
CuI/L-proline was found by Abbott chemists to be able to catalyze the intramolecular C–N bond formation of ene-carbamates **32**, affording 2-substituted indoles **33** [39] (Scheme 11). Using $Pd_2(dba)_3$/*t*Bu_3P as the catalyst gave similar results.



Scheme 10 Imidazoindole formation via CuI-catalyzed double vinyl amidation



Scheme 11 Assembly of 2-substituted indoles via CuI/L-proline-catalyzed intramolecular C–N bond formation

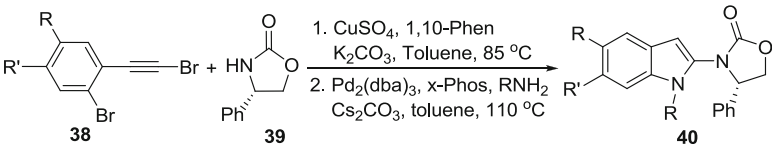


Scheme 12 Synthesis of 1-amino-1H-indole-3-carboxylates and 1-benzoxy-1*H*-indole-3-carboxylates from hydrazone and hydroxyamine derivatives

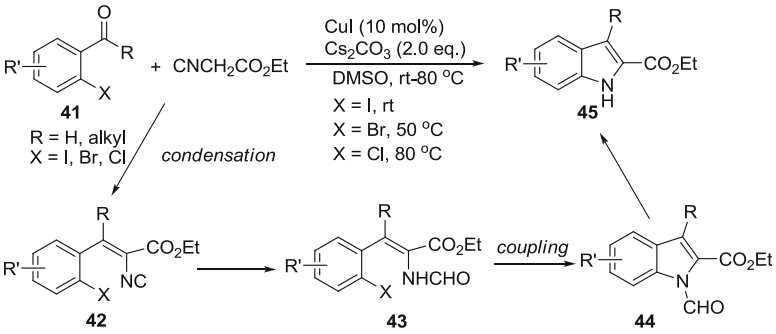
Karchava et al. reported that CuI-catalyzed intramolecular coupling of hydrazone derivatives **34** could produce 1-amino-1*H*-indole-3-carboxylates **35** (Scheme 12) [40]. The addition of ligand is not necessary for this conversion. A hydroxyamine derivative **36** was also an available substrate for this cyclization, affording 1-benzoxy-1*H*-indole-3-carboxylates **37** with 87% yield.

Through a sequential metal-catalyzed C–N bond formation, 2-amidoindoles **40** were conveniently constructed from *o*-haloaryl acetylenic bromides **38**, carbamate **39** and primary amines (Scheme 13) [41]. It is believed that Cu-catalyzed intermolecular amidation occurred first, and the resultant *o*-haloaryl substituted ynamides were coupled with primary amines, affording indoles **40** after intramolecular nucleophilic attack.

Cai and Ding designed a smart cascade process to construct indole-2-carboxylic acid esters **45** [42]. The possible reaction sequence is as follows: (1) condensation of 2-haloaryl aldehydes (or ketones) **41** and ethyl isocyanoacetate to produce olefins **42**;



Scheme 13 Synthesis of 2-amidoindoles via a sequential metal-catalyzed C–N bond formation



Scheme 14 CuI-catalyzed cascade process for synthesizing indole-2-carboxylic acid esters

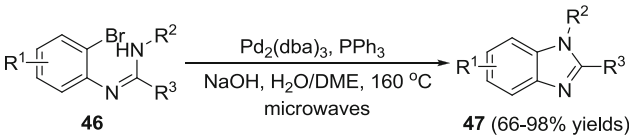
(2) condensation of **42** with water to give enamides **43**; (3) CuI-catalyzed intramolecular aryl amidation to form cyclization products **44**; and (4) deformylation of **44** to deliver indoles **45**. Noteworthy is that no special ligand was required for this transformation, and 2-iodo, 2-bromo, 2-chloro aryl aldehydes all worked for this process, although different reaction temperatures were required (Scheme 14).

3 Benzimidazoles and Related Heterocycles

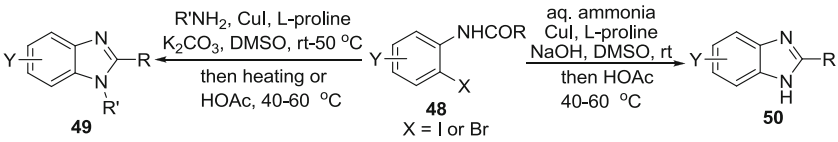
Benzimidazole is another privileged structure for pharmaceutical science. A great number of bioactive molecules contain this moiety. The classical methods for synthesizing substituted benzimidazoles are highly relied on using *o*-aminoanilines as the key intermediates, which limits the diverse synthesis because of inconvenient availability of substituted *o*-aminoanilines. The discovery of mind conditions for aryl amination opens a new avenue for getting access to this class of heterocycles.

In 2002, the Brain group reported that Pd-catalyzed intramolecular aryl amination of (2-bromophenyl)amidines **46** worked in refluxing toluene to afford substituted benzimidazoles **47** [43]. Subsequently, they found that the reaction could proceed better by using the catalytic system of $Pd_2(dba)_3/PPh_3$ under the promotion of microwave (Scheme 15) [44].

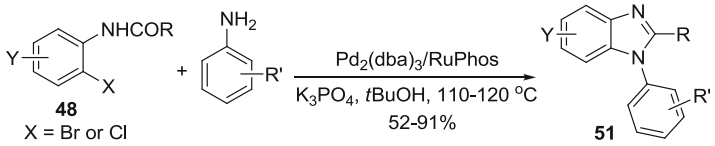
The Ma group revealed that an *ortho*-substituent effect caused by amido groups exists in many Cu-catalyzed coupling reactions. Taking the advantage of this effect, they were able to carry out aryl amination of 2-haloanilides **48**



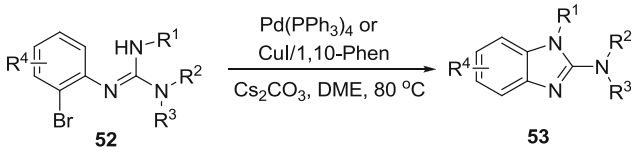
Scheme 15 Pd-catalyzed intramolecular N-arylation of (2-bromophenyl)amidines



Scheme 16 CuI/L-proline-catalyzed synthesis of substituted benzimidazoles from 2-haloanilides



Scheme 17 Pd-catalyzed synthesis of N-aryl benzimidazoles from *o*-haloanilides and anilines

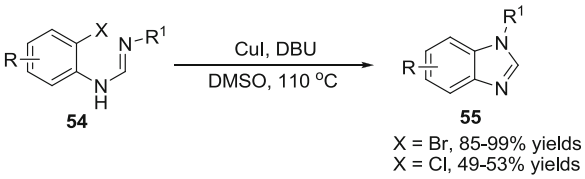


Scheme 18 Synthesis of 2-aminobenzimidazoles via Pd- or Cu-catalyzed intramolecular C–N bond formation

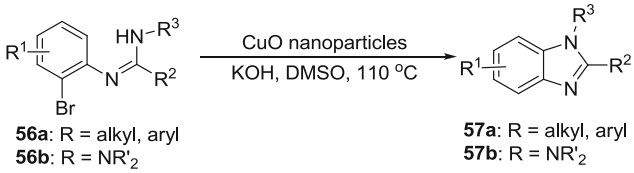
and primary amines at rt −50°C (Scheme 16). Upon heating or exposure on acetic acid, the coupling mixture could be in situ converted into 1,2-disubstituted benzimidazoles **49** with good to excellent yields [45]. Using aqueous ammonia as a coupling partner, a number of 1*H*-benzimidazoles **50** were constructed under the similar reaction conditions [46].

Using *o*-haloanilides **48** and anilines as coupling partners, Buchwald et al. developed a Pd-catalyzed approach to prepare *N*-aryl benzimidazoles **51**, which involves a cascade aryl amination/intramolecular condensation process (Scheme 17) [47]. Both aryl bromides and aryl chlorides could be used as substrates. However, when primary aliphatic amines were used, this reaction failed to give *N*-alkyl benzimidazoles in reasonable yields.

The Batey group found that both $Pd(PPh_3)_4$ and CuI/1,10-Phen could promote the intramolecular C–N coupling of guanidines **52**, providing 2-aminobenzimidazoles **53** with 22–98% yields (Scheme 18) [48]. The copper catalytic system was found superior to the palladium catalytic system in terms of yields and regioselectivity.



Scheme 19 CuI-catalyzed intramolecular coupling for preparing benzimidazoles from imines



Scheme 20 CuO-catalyzed intramolecular N-arylation of *o*-bromoarylamidines

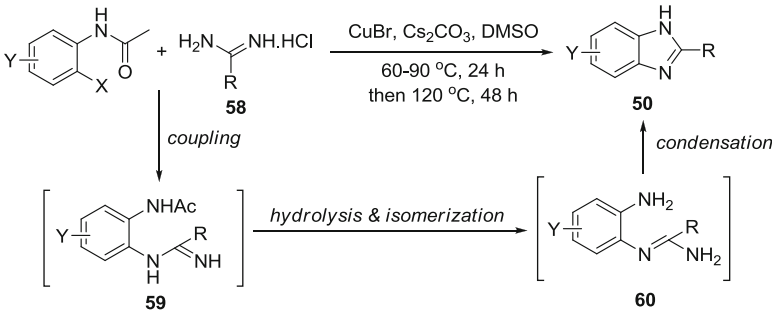
Glorius et al. used a CuI-catalyzed intramolecular coupling strategy to construct 2-unsubtituted *N*-substituted benzimidazoles **55** from imines **54** (Scheme 19) [49], which are useful *N*-heterocyclic carbene precursors. The reaction could proceed smoothly without special ligand, and various substrates including those containing sterically demanding substituents on nitrogen and functional groups were tolerated under the reaction conditions. In cases of aryl chloride as substrates, the corresponding benzimidazoles could be obtained in moderate yields.

Using CuO nanoparticles as the catalyst, Punniyamurthy et al. reported another ligand-free method for the synthesis of substituted benzimidazoles (Scheme 20) [50]. From *o*-bromoarylamidines **56a**, 2-alkyl and 2-aryl substituted benzimidazoles **57a** could be obtained, while 2-amino substituted benzimidazoles **56b** were prepared from the cyclization of *o*-bromoarylguanidines **57b**.

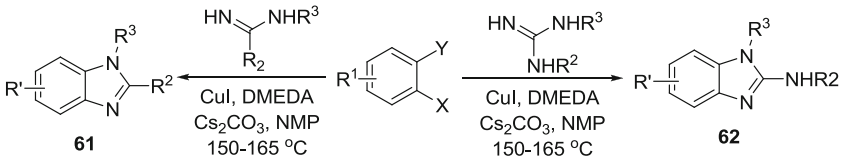
Using amidine hydrochloride as the ammonia surrogates, the Fu group developed an efficient entry to 1*H*-benzimidazoles **50**. In their reaction, Cu-catalyzed coupling of *o*-haloacetanilides with amidine hydrochlorides **58** proceeded at 60–90°C to afford arylation products **59**, which underwent hydrolysis and isomerization upon further heating to provide intermediates **60**. Intramolecular condensation of **60** produced benzimidazoles **50** (Scheme 21) [51].

In a recent paper, Deng et al. described that CuI-catalyzed amination of 1,2-dihaloarenes with amidines proceeded smoothly under the assistance of some ligands, delivering 1-*H*-2-substituted benzimidazoles (R^3 = H) or 1,2-disubstituted benzimidazoles (Scheme 22) [52, 53]. Among the ligands tested, DMEDA gave best results. When guanidines were employed as the coupling partners, this reaction delivered 2-amino benzimidazoles **62** with reasonable yields [53].

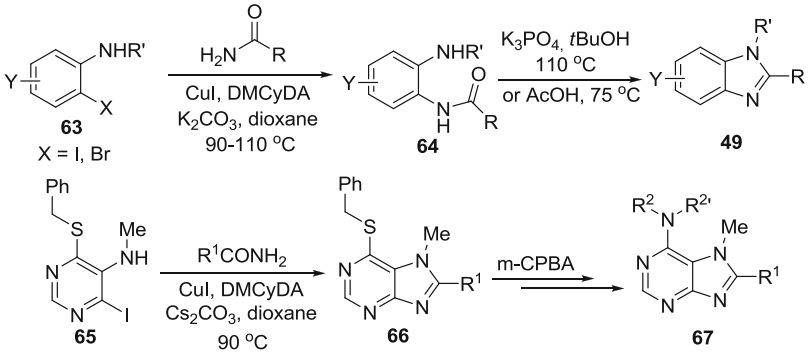
CuI/DMCyDA-catalyzed coupling of *o*-haloanilines **63** with amides provided an alternative approach to *N*-alkyl benzimidazoles **49** (Scheme 23) [54]. In this case, intermolecular aryl amidation took place first, and the resulting coupling products **64** were heated in *t*BuOH in the presence of K_3PO_4, or in AcOH to produce the



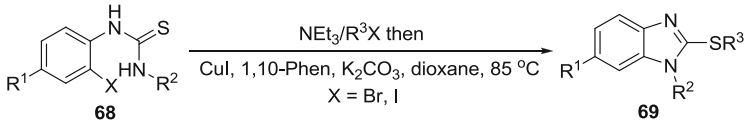
Scheme 21 CuBr-catalyzed synthesis of 1*H*-benzimidazoles from *o*-haloacetanilides and amidine hydrochlorides



Scheme 22 CuI-DMEDA-catalyzed synthesis of 1*H*-2-substituted benzimidazoles from 1,2-dihaloarenes, amidines and guanidines



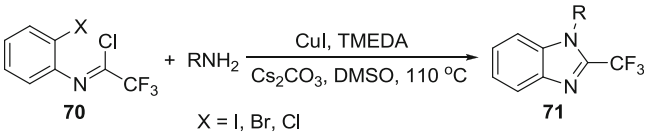
Scheme 23 CuI/DMCyDA catalyzed coupling of *o*-haloanilines with amides



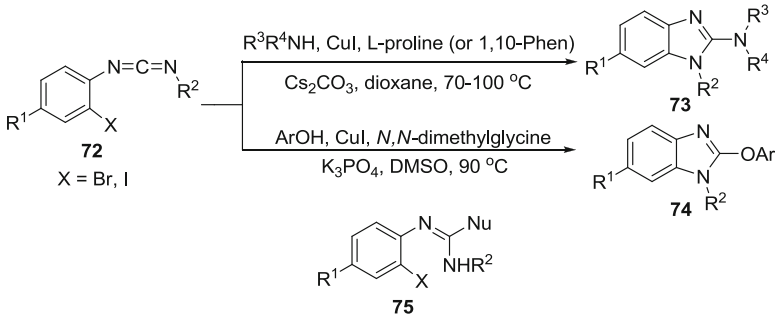
Scheme 24 CuI-catalyzed synthesis of substituted 2-mercapto benzimidazoles

target molecules. This strategy has been applied by Legraverend and Ibrahim in the preparation of 6,7,8-trisubstituted purines **66** and **67** from aryl iodides **65** [55].

Le Bras et al. recently reported an efficient method for preparing 2-mercapto benzimidazoles (Scheme 24) [56]. In their process, *S*-alkylation of thioureas **45**



Scheme 25 CuI-catalyzed synthesis of 2-trifluoromethyl substituted benzimidazoles from *N*-(2-haloaryl)trifluoroacetimidoyl chlorides



Scheme 26 Copper-catalyzed synthesis of substituted benzimidazoles from *o*-haloarylcarbodiimides

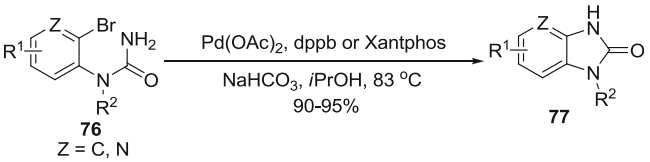
followed by Cu-catalyzed intramolecular *N*-arylation furnished various substituted 2-mercapto benzimidazoles. Among ligands examined for this process, 1,10-Phen gave a best result.

Zhang et al. designed a tandem C–N bond formation reaction for the assembly of 2-trifluoromethyl substituted benzimidazoles **71** from *N*-(2-haloaryl) trifluoroacetimidoyl chlorides **70** (Scheme 25) [57]. CuI/TMEDA-catalyzed cross coupling of **70** with primary amines following by intramolecular condensation produced **71** with 62–98% yields.

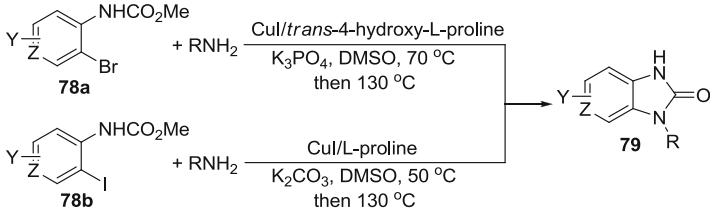
Bao et al. reported a cascade addition/cyclization process for preparing 2-heteroatom substituted benzimidazoles from *o*-haloarylcarbodiimides **72**. Upon nucleophilic addition with amines, imidazoles and phenols, intermediates **75** might form, which in turn underwent intramolecular C–N bond formation to provide 2-amino benzimidazoles **73** and 2-aryloxy benzimidazoles **74** (Scheme 26) [58].

4 Benzimidazol-2-Ones

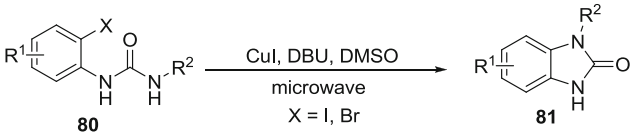
The 1,3-dihydrobenzimidazol-2-one moiety can be found in many pharmaceutically important molecules that possess a wide range of biological activities. Three examples of synthesizing these heterocycles via metal-catalyzed C–N formation have been disclosed. Mclaughlin et al. found that Pd-catalyzed aryl amidation of (2-bromobenzyl)ureas **76** could provide *N*-substituted 1,3-dihydrobenzimidazol-2-ones **77** (Scheme 27) [59]. For the pyridine substrates, the catalytic system of $Pd(OAc)_2$/dppb worked well, providing the corresponding cyclization products in



Scheme 27 Scheme 27 Pd-catalyzed aryl amidation of (2-bromobenzyl)ureas



Scheme 28 Cu-catalyzed synthesis of 1,3-dihydrobenzimidazol-2-ones from methyl *o*-haloarylcarbamates



Scheme 29 CuI-catalyzed synthesis of 1,3-dihydrobenzimidazol-2-ones under microwave irradiation

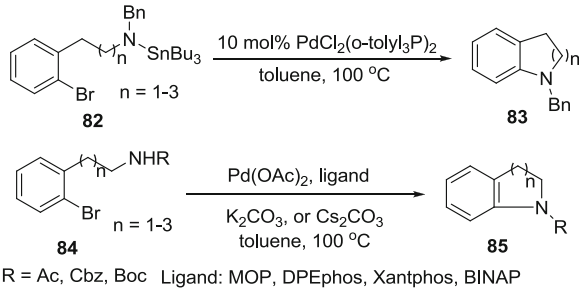
almost quantitative yield. But for haloaniline substrates, X-phos was a better ligand for this cyclization.

From methyl *o*-haloarylcarbamates **78**, 1,3-dihydrobenzimidazol-2-ones **79** could be obtained via a cascade coupling/condensation process (Scheme 28) [60]. For aryl bromides, *trans*-4-hydroxy-L-proline was found to be a better ligand than L-proline. In the case of aryl iodides, L-proline is good enough for promoting the coupling reaction. After coupling reaction, reaction mixture was directly heated at 130°C to afford **79** with good yields. Noteworthy is that reaction temperatures for coupling step are slightly lower than typical CuI/amino acid-catalyzed aryl amination, indicating that the carbamate could provide weak *ortho*-assistance in this case.

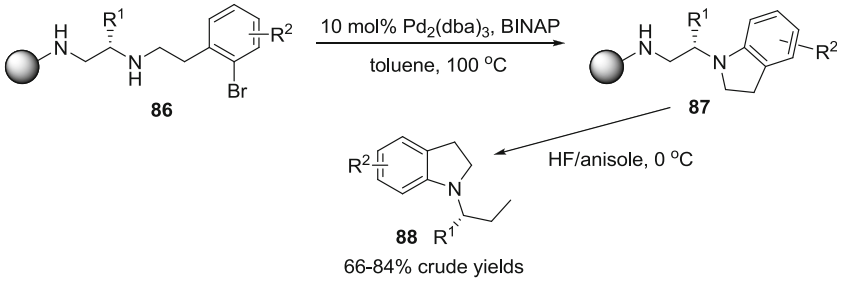
The Liu group reported that a CuI-catalyzed intramolecular C–N bond formation between aryl halide and urea moiety in ureas **80** occurred under microwave irradiation, providing 1,3-dihydrobenzimidazol-2-ones **81** with 59–95% yields (Scheme 29) [61]. No special ligand was needed because of microwave irradiation, and organic base (DBU) was the best choice.

5 Indolines

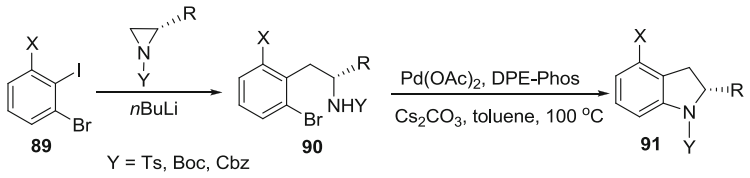
Initial studies from the Buchwald group indicated that aryl halides with an stannylamine moiety **82** could lead to the formation of indolines **83** ($n = 1$) under the catalysis of $PdCl_2(o\text{-tolyl}_3P)_2$. Other heterocycles with six- or seven-membered



Scheme 30 Pd-catalyzed synthesis of indolines and related heterocycles



Scheme 31 Solid-phase synthesis of indolines via Pd-catalyzed intramolecular C–N bond formation

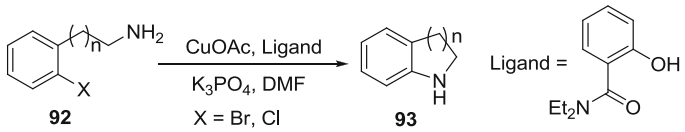


Scheme 32 Synthesis of 2-substituted indolines via ring opening of aziridines and subsequent Pd-catalyzed intramolecular amination

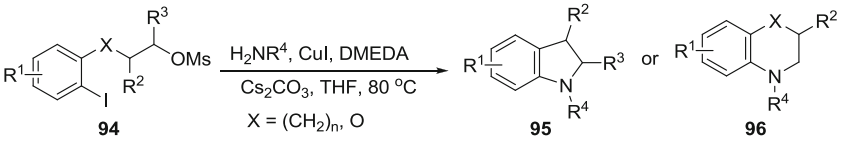
ring could also be obtained using this method (Scheme 30) [62]. Further investigations revealed that the straight intramolecular coupling of amino group and aryl halides could be affected by using different combination of $Pd_2(dba)_3$ (or $Pd(OAc)_2$) with P(2-furyl)$_3$, P(o-tolyl)$_3$, DPEphos, MOP, Xantphos or BINAP to give the corresponding indolines and other *N*-containing heterocycles **85** [63].

Using the same strategy, Houghten et al. developed a solid-phase synthesis for indolines (Scheme 31) [64]. When enantiopure amines were used, cyclization conditions did not lead to the racemization of the products.

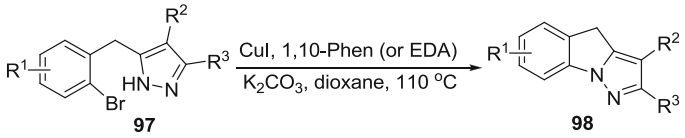
Dineen and Michaelis reported a new method for synthesizing 2-substituted indolines. They prepared the amination substrates **90** via ring opening of aziridines with *o*-bromophenyl metal reagents, which were subjected to $Pd(OAc)_2$/DPE-Phos-catalyzed intramolecular amination to afford enantiopure indolines **91** (Scheme 32) [65].



Scheme 33 Copper-catalyzed synthesis of indolines and related heterocycles



Scheme 34 CuI-catalyzed amidation/nucleophilic substitution for assembling polysubstituted indolines



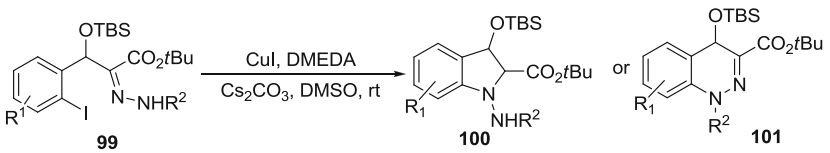
Scheme 35 CuI/1,10-phenanthroline-catalyzed synthesis of pyrazole[1,5-a]indoles

The first example for the copper-catalyzed synthesis of indoline and analogous heterocycles was reported by Buchwald in 2003 [66]. It was found that the intramolecular reaction of amines **92** could carry out under milder reaction conditions comparing to the intermolecular coupling reactions (Scheme 33). Even less reactive aryl chlorides could also provide the corresponding products by prolonging reaction time and increasing reaction temperatures. So after that, the Ma group found that CuI/L-proline could also promote this intramolecular coupling reaction deliver indoline ($n = 1$) in 70% yield [67].

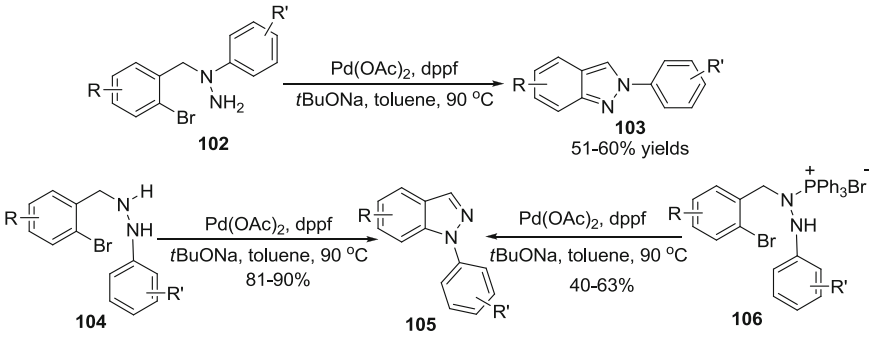
Subsequently, Buchwald et al. developed a more efficient one-pot procedure for the synthesis of indolines **95** and their homologues **96** based on a domino Cu-catalyzed amidation/nucleophilic substitution reaction of aryl iodides **94** and primary amines (Scheme 34) [68]. Polysubstituted indolines could be obtained in good yields.

Under the promotion of 1,10-Phen, CuI-catalyzed intramolecular coupling of aryl bromides **97** provided pyrazole[1,5-a]indoles **98** with good diversity (Scheme 35) [69]. Changing the ligand to EDA and increasing its amount to 30 mol% made some problematic substrates give moderate yield.

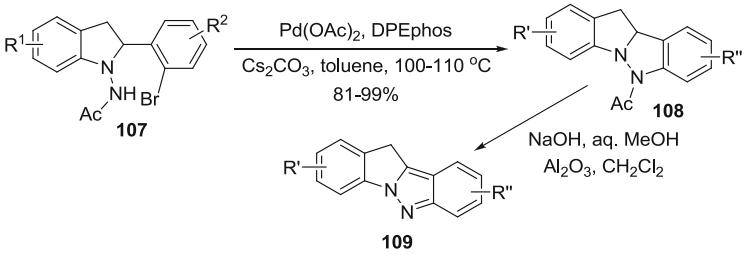
Nishida et al. found that hydrazones **99** could undergo intramolecular amination under the catalysis of CuI and DMEDA to provide 1-aminoindoles **100** or cinnolines **101**. Interestingly, regioselectivity of this coupling reaction was highly relied on the protecting groups of the hydrazone part. When R^2 = Bz, indolines **100** were produced exclusively, while cinnolines **101** were the major products in the case of R^2 = Ac (Scheme 36) [70].



Scheme 36 CuI/DMEDA-catalyzed synthesis of 1-aminoindolines and cinnolines



Scheme 37 Synthesis of 2-aryl-2*H*-indazoles and 1-aryl-1*H*-indazoles via Pd-catalyzed intramolecular C–N bond formation

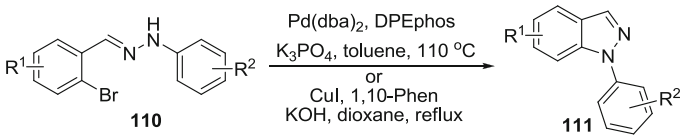


Scheme 38 Pd-catalyzed synthesis of tetracyclic heterocycles

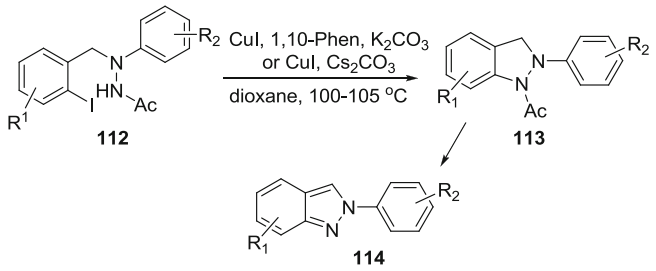
6 Indazoles and Related Heterocycles

Song and et al. discovered that *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines **102** or *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines **104** could be effected by the $Pd(OAc)_2$/dppf catalytic system to afford 2-aryl-2*H*-indazoles **103** [71] and 1-aryl-1*H*-indazoles **105** [72] with reasonable yields (Scheme 37). Further investigations indicated that [*N*-aryl-*N*′-(*o*-bromobenzyl)hydrazinato-*N*′]-triphenylphosphonium bromides **106** were also suitable substrates for this reaction, affording 1-aryl-1*H*-indazoles **105** in moderate yields.

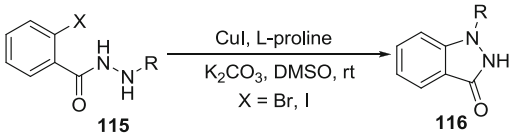
The Katayama group applied the similar strategy for the construction of tetracyclic heterocycles **108** (Scheme 38) [73]. Their amination substrates **107** were treated with $Pd(OAc)_2$/DPEphos to deliver coupling products **108**. After deprotection and



Scheme 39 Pd-catalyzed synthesis of 1-aryl-1*H*-indazoles from N-aryl-N-(*o*-bromobenzyl) hydrazones



Scheme 40 CuI/1,10-phenanthroline-catalyzed synthesis of 2-aryl-2*H*-indazoles



Scheme 41 CuI/L-proline-catalyzed synthesis of 1-substituted indazolones

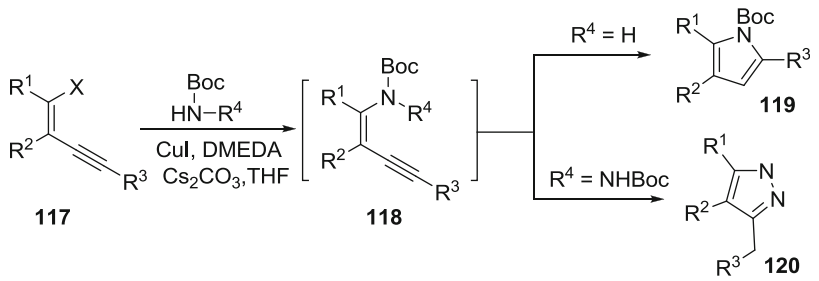
oxidation, indolo[1,2-b]indazole derivatives **109** were isolated, which are potential inhibitors for DNA topoisomers I and II.

Using *N*-aryl-*N*-(*o*-bromobenzyl)hydrazones **110** as the starting materials, Voskoboynikov et al. were able to prepare 1-aryl-1*H*-indazoles **111** via a Pd-catalyzed amination (Scheme 39) [74]. This reaction was found workable when the catalytic system was switched to CuI/1,10-Phen [75].

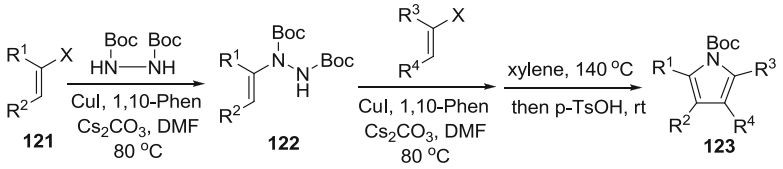
Two other Cu-catalyzed reactions have been reported for preparing 2-aryl-2*H*-indazoles **114** (Scheme 40) [76] and 1-substituted indazolones **116** (Scheme 41) [77]. The first one started from protected hydrazines **112**, which underwent intramolecular amidation and subsequent deacylation and oxidation to afford **114** with moderate yields. In this case, if base was switched from K_2CO_3 to Cs_2CO_3, no ligand was required. The secondary one using amides **115** as substrates, which were catalyzed by CuI/L-proline to provide **116** with good yields.

7 Pyrroles and Related Heterocycles

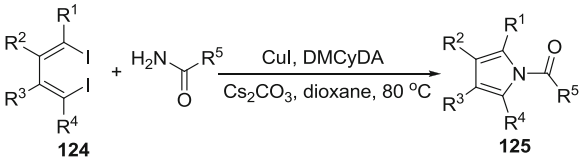
Based on the CuI-catalyzed C–N coupling reaction, Buchwald et al. developed a domino coupling/cyclization process for synthesizing substituted pyrroles **119** from vinyl halides **117** and Boc-protected amines (Scheme 42) [78]. When Boc-protected



Scheme 42 CuI-catalyzed synthesis of substituted pyrroles from vinyl halides and Boc-protected amines



Scheme 43 CuI-catalyzed synthesis of highly substituted pyrroles



Scheme 44 CuI-catalyzed synthesis of substituted N-acylpyrroles

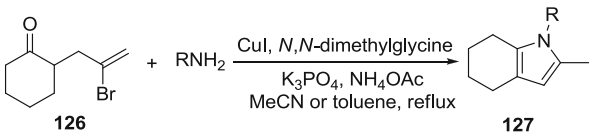
hydrazine was employed as a coupling partner, substituted pyrazoles **120** were obtained in good yields.

Further investigations from the same group indicated that highly substituted pyrroles **123** could be obtained through two sequential copper-catalyzed vinylation reactions of bis-Boc-hydrazine followed by thermal rearrangement/cyclization (Scheme 43) [79].

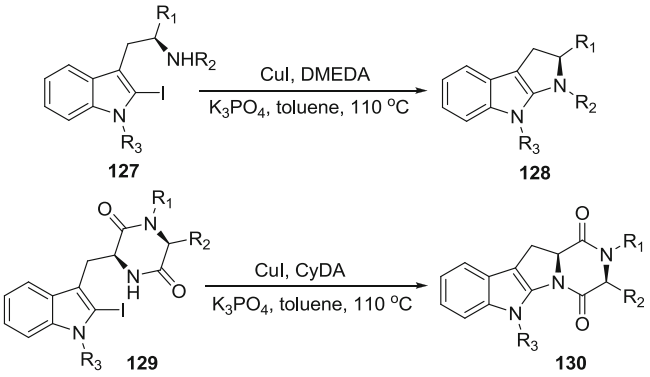
Double alkenylation of amides with (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes **124** could produce di- or trisubstituted *N*-acylpyrroles **125** with good to excellent yields (Scheme 44) [80]. The same idea has been applied in the synthesis of dihydropyrroles and carbazoles [81].

Another efficient method for the synthesis of polysubstituted pyrroles was described by Li et al. They found that CuI/*N*,*N*-dimethylglycine-catalyzed reaction of amines with γ-bromo-substituted γ,δ-unsaturated ketone **126** underwent a condensation/coupling process to afford pyrroles **127** (Scheme 45) [82].

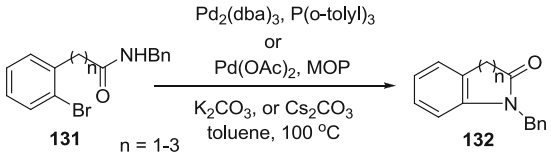
The intramolecular coupling of 2-iodo substituted tryptophan derivatives **127** could take place in the presence of CuI/DMEDA, affording the corresponding pyrroloindoles. This tricyclic system has been found in a considerable number of



Scheme 45 CuI/*N*,*N*-dimethylglycine catalyzed synthesis of pyrroles



Scheme 46 CuI/DMEDA-catalyzed synthesis of pyrroloindoles

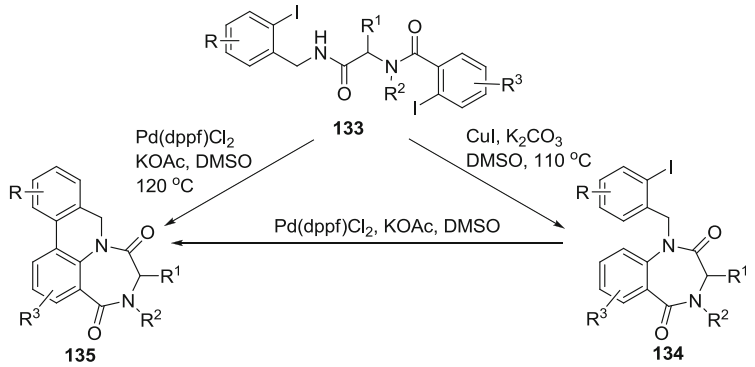


Scheme 47 Pd-catalyzed synthesis of benzolactams

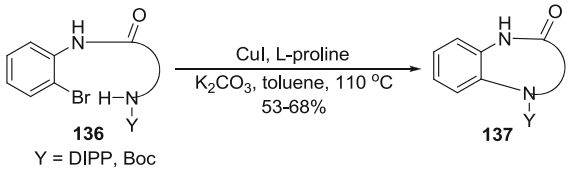
biologically active alkaloids (Scheme 46) [83]. The mild reaction conditions allow the formation of enantioenriched products when optical pure substrates were used. When CyDA was used as a ligand, more complex diketopiperazines **129** were also applicable for this cyclization process, resulting in tetra- or penta-polycyclic compounds **130**.

8 Lactams

The Buchwald group found that intramolecular amidation of 2-bromoaryl with secondary amide moiety in **131** was found workable under that catalysis of $Pd_2(dba)_3$/P(o-tolyl)$_3$ [62] or $Pd(OAc)_2$/MOP [63], providing the corresponding benzolactams **132** with good yields (Scheme 47).



Scheme 48 Synthesis of polyheterocycles

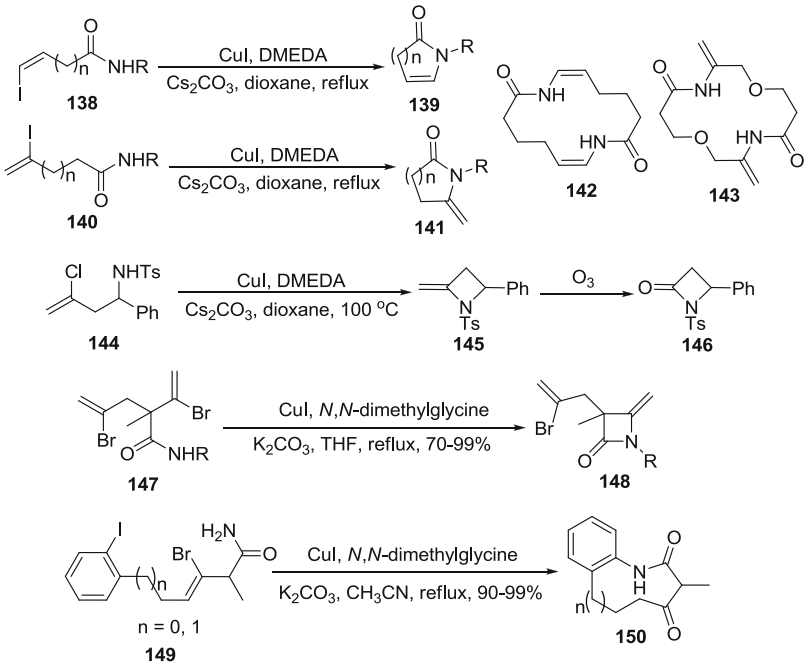


Scheme 49 CuI/L-proline catalyzed synthesis of medium- and large-sized nitrogen heterocycles

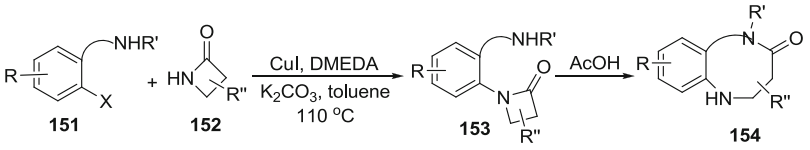
Under different reaction conditions, diamides **133** that were generated via Ugi reaction could give either benzodiazepinediones **134** or polyheterocycles **135** (Scheme 48) [84–86]. The former ones were formed via a simple CuI-catalyzed intramolecular amidation, while the latter ones were resulted from a cascade Pd-catalyzed *N*-arylation/C–H activation/aryl–aryl bond formation process. Conversion of **134** to **135** was found possible upon exposure on Pd catalyst.

Fu et al. revealed that CuI/L-proline-catalyzed intramolecular cyclization of amides **136** could proceed smoothly to afford medium- and large-sized nitrogen heterocycles **137** (Scheme 49) [87]. The introduction of a phosphoryl or *tert*-butoxycarbonyl group at *N*-termini was found essential for this macrocyclization.

By using Cu-catalyzed intramolecular vinyl amidation as the key step, the Li group developed some methods for elaborating lactams with different size (Scheme 50) [88–90]. For examples, intramolecular coupling of iodoenamides **138** and **140** under the catalysis of CuI/DMEDA provided five-, six- and seven-membered *N*-vinylic lactams **139** and **141**, respectively. Increasing the amount of CuI and DMEDA to 100 mol% and 200 mol% could lead to bimolecular reaction of *N*-unsubstituted iodoenamides, affording to the corresponding macrocyclization products **142** and **143** [88]. Further investigations demonstrated that CuI/DMEDA-catalyzed intramolecular coupling of *N*-tosyl-3-halo-3-butenylamines **144** could deliver 2-alkylidenazetidines **145**. It is notable that vinyl chlorides also worked well for this transformation. Upon oxidation, these cyclization products could



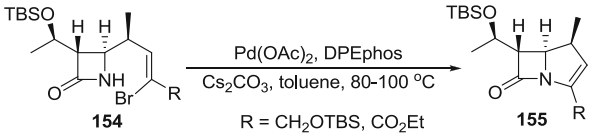
Scheme 50 CuI-catalyzed elaboration of lactams



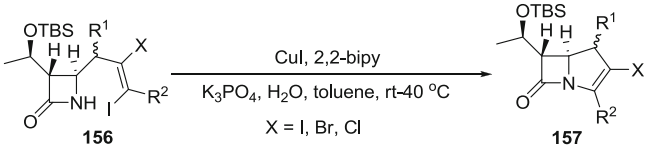
Scheme 51 Synthesis of medium ring nitrogen heterocycles via Cu-catalyzed C–N bond formation

be converted to the corresponding *β*-lactams **146** [89]. Later, they found that *β*-lactams could be directly obtained via amidation of amides **147** under the catalysis of CuI/*N*,*N*-dimethylglycine. This catalytic system was proven powerful for double amidation of amides **149**, affording macrolactams **150** with excellent yields after hydrolysis [90].

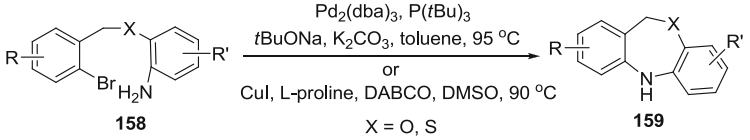
CuI/DMEDA-catalyzed coupling of *β*-lactam **152** with 2-halophenylamines, 2-halobenzylamines and related aryl halides worked at 110°C, yielding aryl amides **153**, which underwent ring expansion under the assistance of acetic acid to produce lactams **154**. This method was proven useful for assembling seven-, eight-, nine-, and ten-membered heterocycles (Scheme 51) [91].



Scheme 52 Synthesis of carbapenems via Pd-catalyzed intramolecular N-vinylation



Scheme 53 Synthesis of carbapenems via CuI-catalyzed intramolecular N-vinylation



Scheme 54 Synthesis of heterobenzazepines via Pd- or Cu-catalyzed intramolecular C–N bond formation

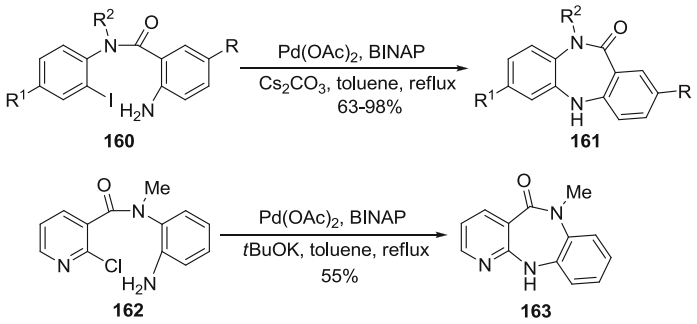
9 Carbapenems

Two reports on the synthesis of carbapenems via *N*-vinylation have been disclosed. Mori et al. found that Pd/DPEphos-catalyzed intramolecular amination of vinyl bromides 154 could take place at 80–100°C to afford 3-substituted 1β-methylcarbapenems **155** (Scheme 52) [92, 93].

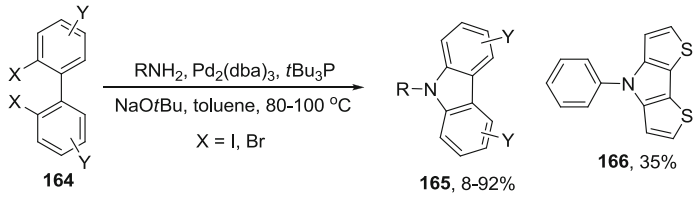
The Jiang group discovered that the combination of CuI and several bidentate ligands could also be used for promoting the similar transformation. In their case, the substrates were more reactive vinyl iodides **156**, and the vinyl halide part in carbapenems **157** allows further functionalization via other coupling reactions (Scheme 53) [94].

10 Heterobenzazepines

Rogers et al. reported that heterobenzazepines **159** could be assembled by a Pd-catalyzed intramolecular coupling of aryl bromides **158** (Scheme 54) [95]. For particularly problematic substrates, increasing the amount of ligand or changing ligand to BINAP could make the yield higher. CuI/L-proline was found applicable for catalyzing this transformation [96]. Noteworthy is that in this case DABCO was a better base compared to inorganic bases like Na_2CO_3 and K_3PO_4.



Scheme 55 Elaboration of dibenzo[*b*,*e*][1,4]diazepines and benzopyrido-analogues via Pd-catalyzed intramolecular aryl amination



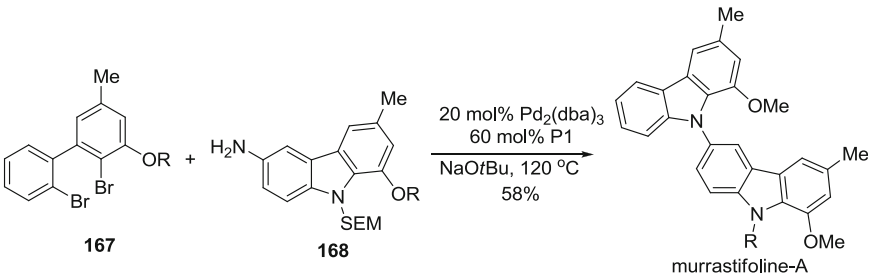
Scheme 56 Synthesis of polysubstituted carbazoles via Pd-catalyzed double N-arylation

Pd-catalyzed intramolecular aryl amination could be applied in elaboration of dibenzo[*b*,*e*][1, 4]diazepines **161**, started from aryl iodides **160**. This method is also suitable for the synthesis of benzopyrido-analogues, as demonstrated by transformation from aryl chloride **162** to cyclization product **163** (Scheme 55) [97].

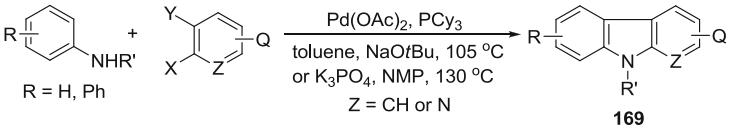
11 Carbazoles and Related Heterocycles

The double *N*-arylation of 2,2′-dihalobiphenyl compounds **164** with primary amines occurred under the catalysis of $Pd(dba)_2/tBu_3P$, delivering polysubstituted carbazoles **165** (Scheme 56) [98]. 2,2′-Bibromobithiophene was also suitable for the reaction, producing heterocarbazole **166** with 35% yield. This method has been applied in the total synthesis of murrastifoline-A, a biscarbazole alkaloid, via coupling of dibromide **167** with aryl amine **168** (Scheme 57) [99].

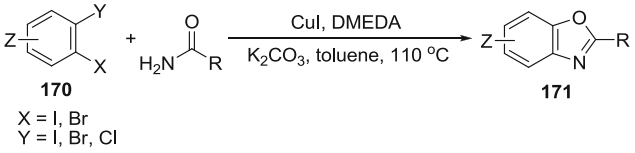
Ackermann et al. found that a domino amination/C–H bond activation process could be used for the preparation of carbazoles **169** (Scheme 58) [100]. The readily available anilines and 1,2-dihaloarenes make this method suitable for diverse synthesis.



Scheme 57 Total synthesis of murrastifoline-A via Pd-catalyzed double N-arylation



Scheme 58 Carbazole synthesis via a Pd-catalyzed domino amination/C–H bond activation process



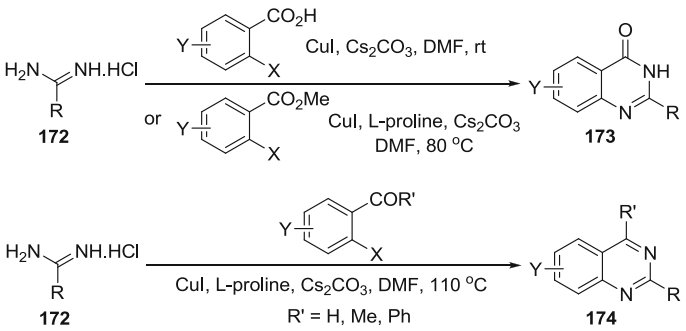
Scheme 59 CuI-catalyzed synthesis of benzoxazoles from dihalobenzenes and amides

12 Benzoxazoles

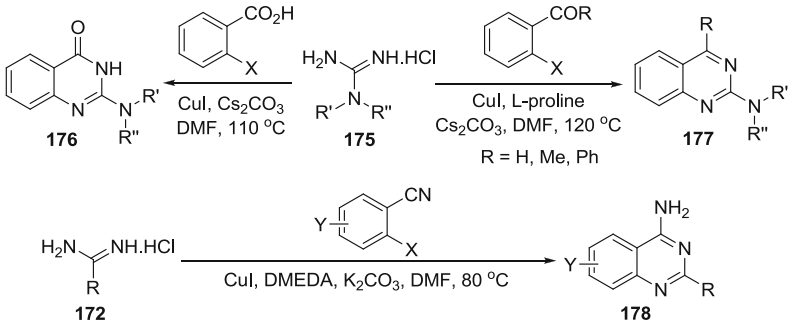
Glorius et al. reported a Cu-catalyzed domino C–N and C–O bond formation to elaborate benzoxazoles from dihalobenzenes and amides (Scheme 59) [101]. 1,2-Diiodobenzenes and 1,2-dibromobenzenes displayed well for this process. Differently substituted benzoxazoles could regioselectively be formed from the corresponding 1-bromo-2-chlorobenzenes. The amidation occurred selectively at the C–Br position and then C–O bond formation took place at the C–Cl moiety. No product was isolated when 1,2-dichlorobenzene was used, indicating that chloride was only reactive for the intramolecular cyclization step.

13 Quinazolinones and Related Heterocycles

CuI-catalyzed coupling of amidine hydrochloride salts **172** with 2-halobenzoic acid and subsequent condensative cyclization worked well to provide 2-substituted quinazolinones **173** at room temperature (Scheme 60) [102, 103]. The *ortho*-substituent effect directed by the carboxylic acid group should be the reason of



Scheme 60 Synthesis of 2-substituted quinazolinones and quinazolines via CuI-catalyzed N-arylation of amidines

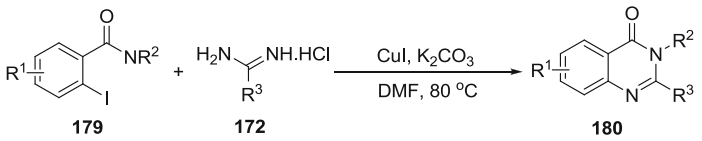


Scheme 61 Synthesis of 2-amino-4(3*H*)-quinazolinones, 2-aminoquinazolines and 4-aminoquinazolines via CuI-catalyzed N-arylation of guanidines

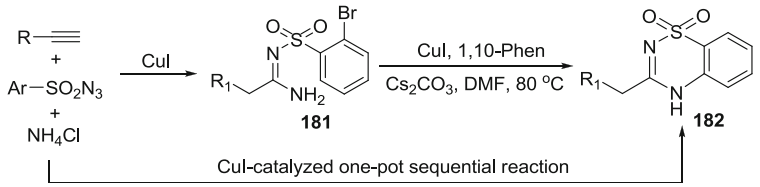
that the coupling reaction worked under this mildconditions, because higher reaction temperatures and ligand promotion were required to facilitate the coupling/condensative cyclization of the corresponding esters with **172**. When 2-bromobenzaldehyde and 2-bromophenylketones were used, further increasing reaction temperatures were needed to ensure complete coupling. In this case, substituted quinazolines 174 were obtained with good yields. Truong reported if using methanol as solvent, CuI-catalyzed reaction amidine hydrochloride salts with 2-iodobenzaldehyde could proceed under ligand-free conditions to afford the corresponding quinazolines [104].

Fu et al. have extended the above strategy to the synthesis of 2-amino-4(3*H*)-quinazolinones **176** and 2-aminoquinazolines **177** by using guanidines **175** as the coupling partners [105], and assembly of 4-aminoquinazolines **178** by coupling amidine hydrochloride salts **172** with 2-bromobenzonitrile [106] (Scheme 61).

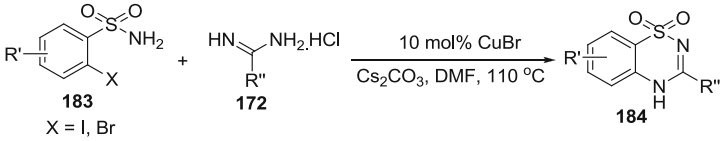
Ding found that coupling of 2-iodobenzobenzamides and amidine hydrochloride salts **172** led to formation of 2,3-substituted quinazolinones (Scheme 62) [107].



Scheme 62 Synthesis of 2,3-substituted quinzolinones via CuI-catalyzed coupling of 2-iodobenzobenzamides and amidine



Scheme 63 CuI-catalyzed three-component reaction for assembling 1,2,4-benzothiadiazine 1,1-dioxides



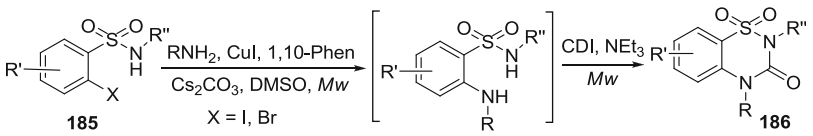
Scheme 64 CuBr-catalyzed synthesis of 1,2,4-benzothiadiazine 1,1-dioxides from 2-halobenzensulfonamides and amidines

14 Benzothiadiazine 1,1-Dioxides

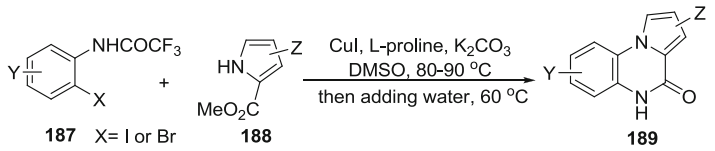
A CuI/DMEDA-catalyzed intramolecular coupling of *N*-unprotective amidines **181** has been used for assembling 1,2,4-Benzothiadiazine 1,1-dioxides **182**, another important class of heterocycles for pharmaceutical design (Scheme 63) [108]. Because the preparation of the amidines **181** could be achieved via a CuI-catalyzed three-component reaction of 1-alkynes, ammonium salts and aryl sulfonyl azides, a more efficient one-pot sequential process has been developed for the synthesis of **182** from these reagents.

The Fu group developed another efficient cascade process for synthesizing substituted 1,2,4-benzothiadiazine 1,1-dioxides **184**, in which the coupling of 2-halobenzensulfonamides **183** and amidines **172** was employed as the key step (Scheme 64) [110].

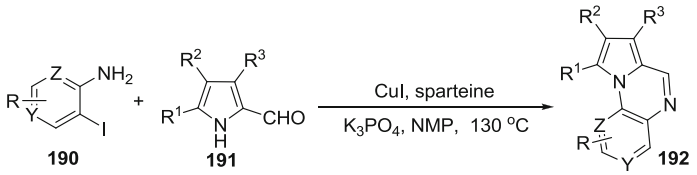
Using a microwave-assisted sequential one-pot *N*-arylation/condensative cyclization process, Hanson and Rolf developed a facile method for preparing benzothiadiazin-3-one-1,1-dioxides **186** from sulfonamides **185** (Scheme 65) [109].



Scheme 65 Synthesis of benzothiadiazin-3-one-1,1-dioxides via a microwave-assisted sequential N-arylation/condensative cyclization process



Scheme 66 Pyrrolo[1,2-a]quinoxaline formation via CuI/L-proline catalyzed coupling of 2-halotrifluoroacetanilides and pyrrole-2-carboxylate esters



Scheme 67 Synthesis of pyrrolo[1,2-*a*]quinoxalines via CuI-catalyzed intramolecular N-arylation

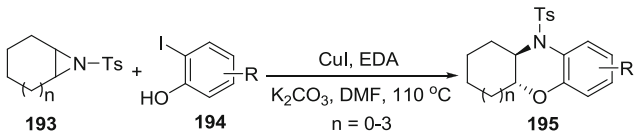
15 Miscellaneous

CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides **187** with pyrrole-2-carboxylate esters **188** in dimethyl sulfoxide (DMSO) at 80–90°C followed by in situ hydrolysis and condensative cyclization at 60°C afforded pyrrolo[1,2-*a*]quinoxalines **189** with good yields (Scheme 66) [111]. Indole-2-carboxylate esters underwent the same process smoothly to provide the corresponding tetracyclic products.

Reaction of *o*-aminoiodoarenes **190** with 2-formylazoles **191** could go through a cascade condensation and Cu-catalyzed intramolecular *N*-arylation process to afford pyrrolo[1,2-*a*]quinoxalines and related heterocycles with structures of **192** (Scheme 67) [112]. Noteworthy is that sparteine was used first time as a ligand for *N*-arylation.

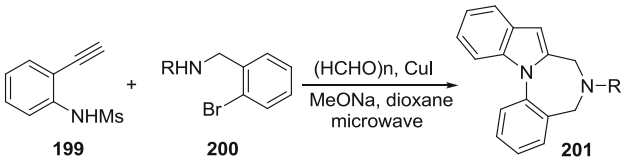
The *trans*-3,4-dihydro-2*H*-1,4-benzoxazines could be obtained conveniently by ring opening of aziridines **193** with *o*-iodophenols **194** and subsequent copper-catalyzed intramolecular *N*-arylation (Scheme 68) [113].

Liu et al. developed an one-pot process for preparing *N*-substituted dihydro-2*H*-1,4-benzoxazine-3-(4*H*)-ones **198** using 2-halophenols **196** and 2-chloroacetamides **197** as the starting materials. In this case, an S_N2 reaction occurred first, following by CuI-catalyzed *N*-arylation to afford **198** (Scheme 69) [114].

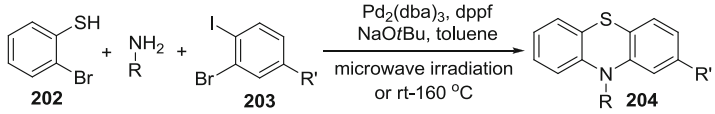


Scheme 68 Synthesis of *trans*-3,4-dihydro-2*H*-1,4-benzoxazines via copper-catalyzed intramolecular N-arylation

Scheme 69 CuI-catalyzed synthesis N-substituted dihydro-2*H*-1,4-benzoxazine-3-(4*H*)-ones from 2-halophenols and 2-chloroacetamides



Scheme 70 CuI-catalyzed synthesis of indole-fused 1,4-diazepines from 2-ethynylanilines and *o*-bromobenzylamines

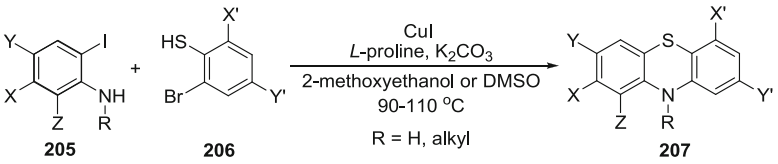


Scheme 71 Synthesis of phenothiazines via a Pd-catalyzed three-component reaction

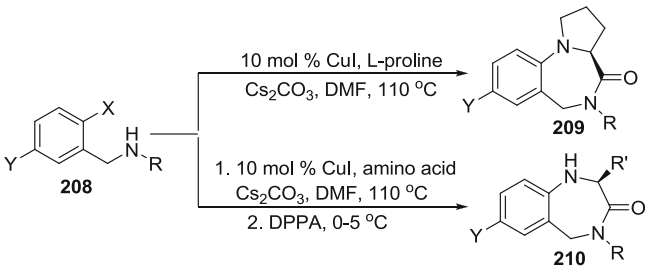
Starting from simple 2-ethynylanilines **199** and *o*-bromobenzylamines **200**, complex indole-fused 1,4-diazepines **201** were easily and directly synthesized in a single reaction vessel (Scheme 70) [115]. This transformation included a sequential Cu-catalyzed three-component condensation/indole formation/*N*-arylation process. *o*-Bromoheteroarylamines were also available for this domino process and various indole-fused tetracyclic compounds were obtained.

Jørgensen reported an efficient three-component approach for synthesizing phenothiazines (Scheme 71) [116], in which a C–S bond and two C–N bonds were formed in one-pot under the catalysis of Pd_2dba_3/dppf. The transformation required either microwave or conventional heating.

Ma et al. developed a sequentially controlled CuI/L-proline-catalyzed cascade C–S and C–N bond formation process for assembly substituted phenothiazines **207** (Scheme 72) [117]. In this case using substituted 2-iodoanilines **205** and 2-bromobenzenethiols **206** as the coupling partners are essential for controlling regioselectivity.



Scheme 72 Synthesis of phenothiazines via a CuI/L-proline-catalyzed cascade C–S and C–N bond formation process



Scheme 73 Synthesis of pyrrole-fused 1,4-benzodiazepin-3-ones via CuI-catalyzed coupling of *o*-bromobenzylamines and amino acids

CuI-catalyzed coupling of *o*-bromobenzylamines **208** with L-proline at 110°C afforded pyrrole-fused 1,4-benzodiazepin-3-ones **209** directly (Scheme 73) [118]. Other amino acids were found suitable for *N*-arylation reaction, but did not give cyclization products directly. However, through treatment of the coupling mixture with diphenylphosphoryl azide (DPPA), the desired 1,4-benzodiazepin-3-ones **210** could be prepared in 35–60% yields.

16 Conclusion and Outlook

In this chapter, we have described some newly developed methods for assembling *N*-containing heterocycles, which highly relied on Pd- or Cu-catalyzed *N*-arylation and *N*-vinylation. These heterocycles include indoles, benzimidazoles, pyrroles, indazoles, indolines, lactams, quinazolinones and heterobenzazepines. Some of these new methods may find a number of applications in organic synthesis because they provide powerful approaches for preparing *N*-containing heterocycles from conveniently available starting materials in mild conditions. Further studies are still needed to extend the reaction scope of these methods and discover new approaches for synthesizing *N*-containing heterocycles.

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Recent Developments in Recyclable Copper Catalyst Systems for C–N Bond Forming Cross-Coupling Reactions Using Aryl Halides and Arylboronic Acids

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Abstract This review covers the recent recyclable protocols for the C–N bond forming reactions between aromatic, heterocyclic and aliphatic amines such as imidazoles, benzimidazoles, benzylamines, piperidine, pyrrole, imides, anilines, hexyl, cyclohexyl amines, and amides as coupling partners with aryl iodides, bromides, chlorides, and arylboronic acids employing copper-mediated systems. The physical properties and characterization of the catalysts and their use in organic synthesis will be outlined. Most importantly, these recyclable versions developed by many groups in the recent years are potential candidates for commercial exploitation. The effect of additives, solvents, temperature, base, the nature of aryl halides on reactivity, and recycle studies of the heterogeneous catalysts are included in this

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review. We believe that this information is beneficial for the people who are doing similar studies in this field. Catalyst optimization is of critical importance to catalyst development, thus the information we have included in this review contains very valuable information for the newcomers to the field. To our knowledge this is the first review that covers the title chemistry.

Keywords Aryl halides · C-N bond formation · Copper catalyst · Cross-Coupling · Heterocycles · Heterogeneous · Reusable catalysts

Contents

1 Heterogeneous or Reusable Catalysis

Organic synthesis employing heterogeneous catalysts has several beneficial effects to the environment. Because it involves the reuse of precious metal catalysts, it forms less waste and results in lower metal contamination in the final pharmaceutically important molecules. However, solid-supported catalysts are complex assemblies. Their preparation and characterization are challenging tasks. Minor changes to their preparation conditions can significantly influence the delicate balance of conflicting demands: high activity, high selectivity, and a long lifetime [1]. Several varieties of heterogeneous or reusable catalytic systems are known depending on the type of application.

2 Green Chemistry of Coupling Reactions

The coupling reactions were carried out mostly under homogeneous conditions [2]. Although homogeneous reactions have tremendous benefits in terms of ready availability of the catalyst and defined structure, the separation of the catalyst from the reaction products poses a problem. Some copper-catalyzed homogeneous methods require stoichiometric amounts of additional base that generates copious amounts of solid waste as a by-product. In general, few reports are available on heterogeneous cross-coupling reactions compared to the homogeneous reactions. Some of the heterogeneous methods have also been considered as atom economic [3].

3 Copper-Catalyzed Coupling Reactions in Organic Synthesis

Homogeneous copper-catalyzed coupling reactions have been successfully applied in the natural product synthesis. An excellent up-to-date review on the application of copper-catalyzed methods in medicinal chemistry was recently published by Evano, Blanchard, and Toumi [4]. Some selected examples are listed in Fig. 1, wherein C–N bond formation was mediated by copper species.

Copper-catalyzed C–N bond formation was first applied in the total synthesis by Ma et al. [5] for the synthesis of benzolactam **1** (Fig. 1), a protein kinase C inhibitor, involving a coupling reaction between valine and aryl iodide. The compound structure **2** shown is an intermediate for the synthesis of lotrafiban, a potent glycoprotein IIb/IIIa receptor antagonist [6]. Copper-catalyzed methodology was successfully utilized for the synthesis of compound **3**, a potential intermediate for the synthesis of tetrahydroquinoline alkaloid and martinellic acid [7]. Coupling of cyclic aliphatic amines with iodoarenes was reported for the synthesis of cyclopropanated iprodione, an analogous intermediate compound shown in **4** [8]. Compounds **5** and **6** are active intermediates for the synthesis of antibiotics, namely, linezolid and toloxatone [9], prepared by the coupling of carbamate with aryl bromides in the presence of copper and ligand. Furstner et al. have successfully employed the copper-catalyzed protocol for the synthesis of compound **7,** which is an intermediate for the total synthesis of macrocyclic spermidine alkaloid isooncinotine [10]. Ghosh et al. developed a method for the synthesis of compound **8** on a large scale using a copper catalyst and a ligand from oxazolidinone [11]. Buchwald and Chae reported the total synthesis of U86192, a potent hypertensive agent via a step involving the copper catalyst for the synthesis of compound **9** using aryl bromide and *N*-aryl, *N*-Boc hydrazide [12]. A biologically active compound Nilotinib, (AMN107) useful for chronic myelogenous leukemia, shown in structure **10** was prepared by employing a copper-catalyzed protocol [13]. Compound **11** is an intermediate for the synthesis of the naphthalenoid H3 antagonist prepared in multi-gram scale from the corresponding bromo derivative and pyridazinone using

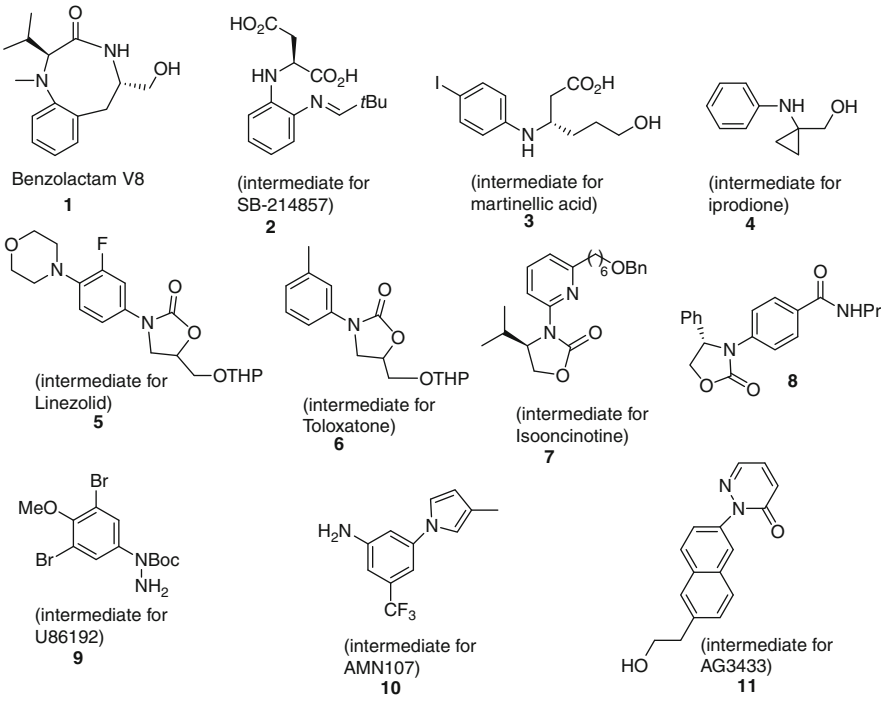


Fig. 1 Selected precursors for biologically important molecules involving copper-catalyzed C–N formation

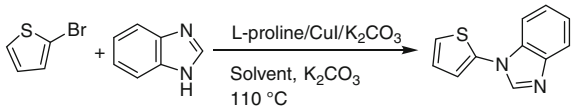
a copper catalyst. This method was quite impressive since palladium-based catalytic systems failed to produce compound **11** [14].

4 CuI/L-Proline/[Bmim][BF_4] Ionic Liquids with Aryl/Heteroaryl Bromides

Room temperature ionic liquids (RTILs) are a class of nonmolecular ionic solvents. The intrinsic properties of RTILs such as low vapor pressure, high polarity, solubility of metal salts, and reusability have made them more attractive candidates for solvents in the last two decades [15]. Bao et al. reported the use of RTILs in C–N bond forming reactions of aryl/heteroaryl bromides with imidazoles and benzimidazoles using a combination of CuI and L-proline at 105–115°C in the presence of K_2CO_3 to give the coupled products in good yields. They found the use of RTILs, for example, [Bmim]BF_4 gave slightly improved yields over bench top organic solvents (Table 1).

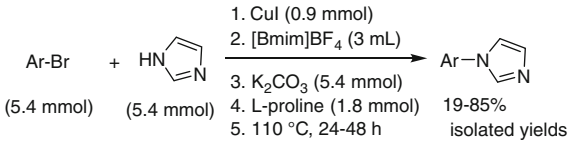
The scope of the method was thoroughly explored using a variety of aryl bromides with imidazole, and the selected examples are listed in Table 2. In most cases, good yields of products were obtained, except in the case of *o*-substituted

Table 1 Solvent effect in copper-catalyzed coupling reactions



Entry	Solvent	Isolated yield (%)
1	$[Bmim]BF_4$	76
2	DMF	66
3	DMSO	71

Table 2 Copper-mediated coupling of imidazole with various aryl bromides



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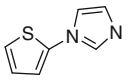
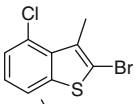
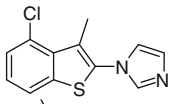
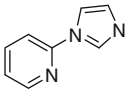
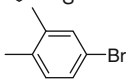
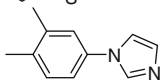
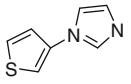
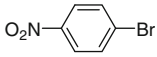
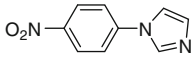
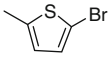
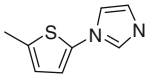
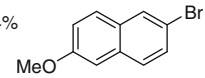
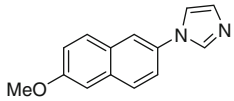
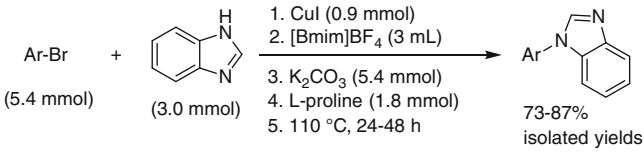
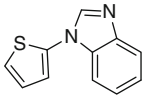
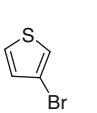
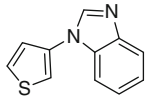
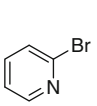
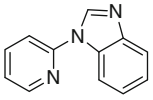
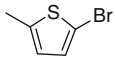
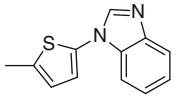
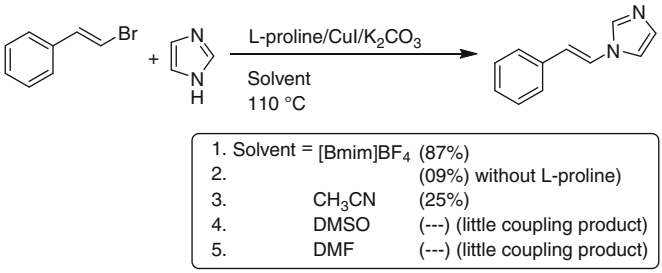
		74%			19%
		76%			70%
		72%			62%
		74%			85%

heterocycle bromides such as 2-bromo-4-chloro-3-methylbenzo[*b*]thiophene which is much more difficult to couple with imidazole (see Table 2, right column first entry), probably because the methyl group on the 3-position hinders the coplanarity of the imidazole and the thiophene moieties which gives a negative effect on product formation (19% yield). Prolonging the reaction time from 48 to 72 h did not substantially improve the yield. As can be seen from Table 2, aryl halides containing electron-withdrawing groups gave slightly lower yields compared to those containing electron-donating groups. This method is also applicable to the coupling of benzimidazole moieties with a variety of heterocyclic halides under the conditions mentioned in the Scheme of Table 3.

Table 3 Copper-mediated coupling of benzimidazole with various aryl bromides



Ar-Br	Product	Yield	Ar-Br	Product	Yield
		76%			75%
		87%			73%

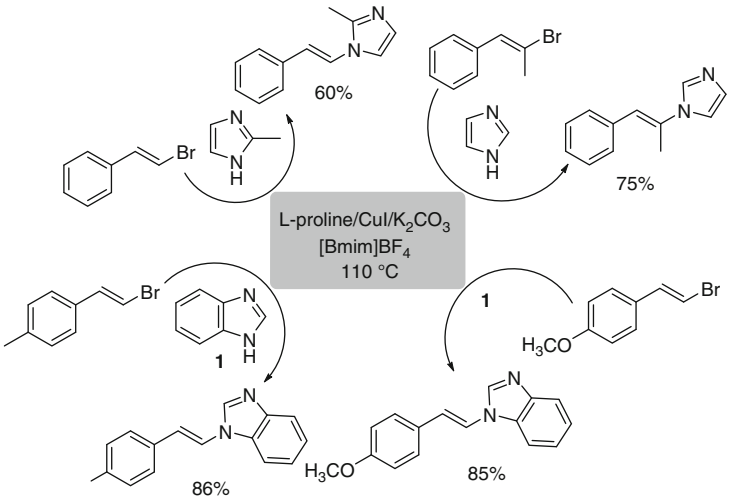


Scheme 1 Optimization conditions for the synthesis of N-vinylimidazoles

5 CuI/L-Proline/[Bmim]BF_4 Ionic Liquids with Vinyl Halides

Owing to the usefulness of N-vinylimidazoles in organic synthesis as valuable intermediates, Bao and coworkers developed a method for the coupling of vinyl bromides with imidazoles [16] using a combination of reagents, L-proline, and potassium carbonate in ionic liquids in the presence of CuI catalyst (Scheme 1) at 110°C. They found that L-proline has a significant effect in cross-coupling reactions, for example, only 9% (entry 2 of Scheme 1) of isolated product was obtained in the absence of L-proline compared to 87% when L-proline is added (Scheme 1, entry 1). Several other ionic liquids were investigated, and [Bmim]BF_4 was found to be the best solvent. Conventional organic solvents such as DMSO and DMF were incompatible for the formation of coupling products; only 25% of coupled product was isolated using CH_3CN as solvent. It was also reported that Z-vinyl bromides were ineffective under these conditions due to their increased level of steric hindrance.

Product yields were in the range of 60–91% in the coupling of a variety of vinyl bromides with simple and substituted imidazoles and benzimidazoles (Scheme 2). Bao et al. have also reported the reusability of the copper/L-proline/[Bmim]BF_4



Scheme 2 Synthetic approaches for the preparation of N-vinylimidazoles and benzimidazoles

system by adding additional base quantities for each successive cycle. The system was quite capable of performing at least four catalytic cycles using β-bromostyrene and imidazole, albeit with a mild decrease in yield.

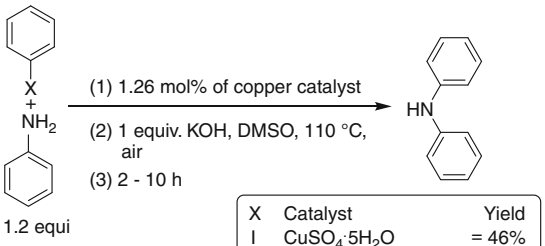
6 CuO Nanoparticles

In 2007, Punniamurthy et al. [17] reported the use of commercially available CuO nanoparticles (Aldrich, particle size 33 nm and surface area 29 m^2/g) for C–N coupling of halobenzene with simple aniline derivatives (Scheme 3). CuO nanoparticles were found to be the best performing copper source under the conditions given in Scheme 3. Under these reaction conditions, bromo- and chloroarenes gave moderate yields of the coupled products. The scope of the catalyst was well examined, for example, amines containing electron-donating groups showed greater reactivity compared to those possessing electron-withdrawing groups when coupled with iodobenzene (Scheme 4).

Aliphatic amines are known to be difficult substrates in C–N coupling reactions, however, using CuO nanoparticles, good to excellent yields of coupled products were obtained employing the reactions conditions shown in Scheme 5.

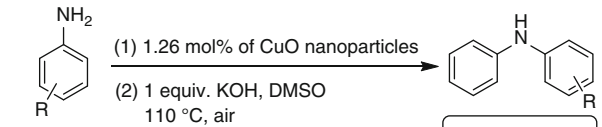
CuO nanoparticles were also found to be effective for the coupling of heterocyclic amines such as imidazole, 2-methylimidazole, and benzimidazole with iodobenzene using 2.5 mol% of catalyst, whereas 1.26 mol% of catalyst was sufficient for pyrrole and indole (Fig. 2).

The coupling of substituted iodobenzenes containing an electron-donating group such as 4-iodoanisole with aniline gave 22% yield using 1.26 mol% of catalyst.



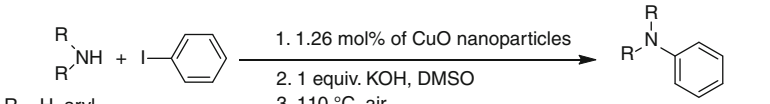
X	Catalyst	Yield
I	$CuSO_4 \cdot 5H_2O$	= 46%
I	$Cu(OAc)_2 \cdot H_2O$	= 33%
I	CuO	= 35%
I	CuO nanoparticles	= 95%
Br	CuO nanoparticles	= 95%
Cl	CuO nanoparticles	= 95%

Scheme 3 Optimization studies using various copper catalysts



R	Yield
p-Cl	= 92%
p-Br	= 83%
p-OMe	= 94%
p-NO_2	= 70%
o-Me	= 96%

Scheme 4 Coupling of aryl amines with iodobenzene catalyzed by CuO nanoparticles



Amine	Yield
Benzylamine	= 90%
Furfurylamine	= 85%
n-Butylamine (80 °C)	= 91%
Cyclohexylamine	= 93%
Pyrrolidine	= 93%
Morpholine	= 89%

Scheme 5 Coupling of aryl amines with iodobenzene catalyzed by CuO nanoparticles

CuO nanoparticles were recycled three times efficiently (first cycle 95%, third cycle 91%), with a catalyst recoverability of 95% in the first cycle and 81% in the third cycle by simple centrifugation.

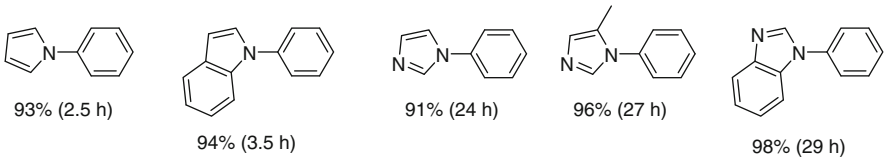
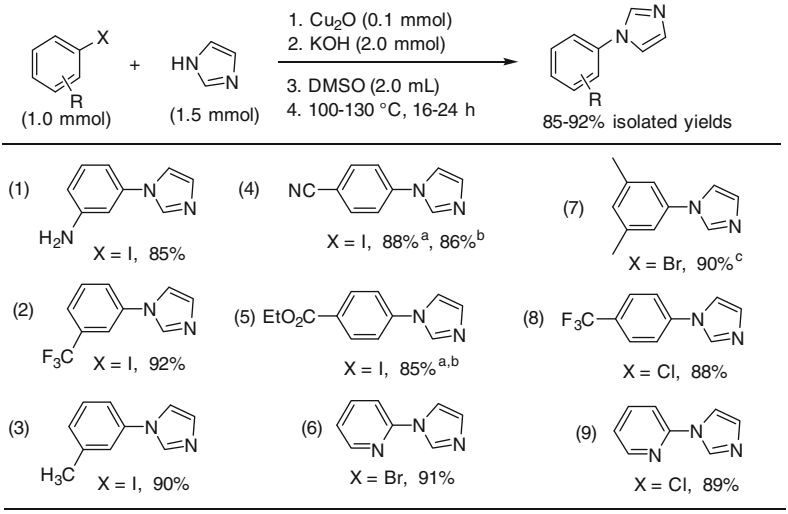


Fig. 2 Coupled products of heterocyclic amines (*left* to *right*) pyrrole, indole, imidazole, 2-methylimidazole, and benzimidazole with iodobenzene catalyzed by CuO nanoparticles

Table 4 Cu_2O-catalyzed coupling of imidazole with various aryl halides



[a]200 mg of 4 Ä molecular sieves were added
[b]Cs_2CO_3 used in place of KOH
[c]0.2 mmol of Cu_2O used

7 Cu_2O Catalyst

In 2008, Xu et al. [18] reported the use of simple Cu_2O (10 mol%) as an efficient reusable catalyst for the *N*-arylation of various heterocycles such as imidazole, benzimidazole, indole, pyrazole, and pyrrole with aryl iodides, whereas bromides and chlorides react with imidazole in the presence of two equivalents of a base, typically KOH. Other bases such as Cs_2CO_3, K_3PO_4, and K_2CO_3 resulted in moderate to poor yields. Significantly, poor conversion (ca. 24%) was observed under these reaction conditions when using CuO as catalyst.

The efficacy of Cu_2O for general *N*-arylation of imidazole with diverse aryl halides was examined, and selected examples are listed in Table 4. Interestingly, imidazole can be selectively arylated in the presence of a free $–NH_2$ group (Table 4, entry 1). Cyano and ester functionalized aryl iodides (Table 4, entry 4 and 5) equally participated in the coupling reaction by simply replacing KOH with

Cs_2CO_3. Other imidazoles such as benzimidazole, indole, pyrazole, and pyrrole were successfully coupled with iodobenzene to give the corresponding *N*-arylated products in good yields employing 10 mol% of Cu_2O. The catalyst was reused for four times with consistent activity for the coupling of iodobenzene with imidazole at 120°C. In the first cycle 90% yield was obtained while in the fourth cycle 88% yield was obtained.

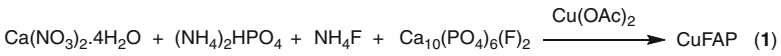
8 Copper-Exchanged Fluorapatite

Choudary et al. have chosen [19] a weakly amphoteric apatite as support, since various kinds of cations and anions can be readily introduced into their framework due to their large ion exchange ability. Such exchanged apatites are already in use for several organic transformations [20]. A schematic representation of copper-exchanged fluorapatite (**1**) by incorporating the basic species F^- in apatite in situ by co-precipitation and subsequent exchange with Cu (II) is shown (Scheme 6). *N*-Arylation of imidazoles and other heterocycles with chloroarenes and fluoroarenes to afford good to excellent yields of aryl heterocycles by using CuFAP catalyst is described.

The method is general and amenable to the *N*-arylation of imidazole with a wide range of chloro- and fluoroarenes using catalyst **1** (Table 5). As illustrated in Table 5, chloroarenes (electron withdrawing), 2-chloropyridine, and 2-chloropyrimidine provided excellent yields in shorter reaction times than chlorobenzene and chloroarenes (electron donating) (entries 1–11). Cyano, nitro, and trifluoromethyl groups are well tolerated (entries 1, 3, and 4). The *N*-arylation results of deactivated chloroarenes using K_2CO_3 as a base are quite impressive over the unreactive system using nanocopper and Cs_2CO_3 base [21]. Another significant feature is that under similar conditions, the *N*-arylation of imidazole with chlorobenzene afforded moderate yields, which could be further improved by the addition of KO^tBu (entry 9). *N*-Arylation of heterocycles developed here using the less expensive chloroarenes is more attractive than the methods using the expensive bromo- and iodoarenes in terms of economic feasibility. The catalyst is recycled four times with a slight decrease in activity (entry 1). Interestingly, fluoroarenes composed of several *o*- or *p*-electron-withdrawing (EW) groups (entries 12–15) are also coupled with imidazole to afford the corresponding *N*-arylated products in excellent yields. Faster reactivity over the chloroarenes (entries 1, 5, 13 and 14) and selective coupling involving C–F activation only in chlorofluoroarene (entry 15) are reported.

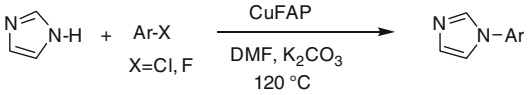
As shown in Table 6, benzimidazole, pyrrole, pyrazole, and piperidine are also coupled with 1-chloro-4-nitrobenzene and 1-fluoro-4-nitrobenzene to give the corresponding *N*-arylated products in excellent yields.

To understand the mechanism of the *N*-arylation of imidazole, a series of experiments were conducted. The reaction of catalyst (**1**) with imidazole gives a deep blue Cu-imidazole complex (**3**), which is considered to be the first step of the



Scheme 6 Preparation of Catalyst CuFAP (**1**)

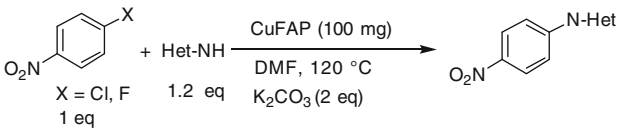
Table 5 *N*-Arylation of imidazole with chloro- and fluoroarenes[a]



Entry	Ar–X	Time (h)	Yield (%)[b]
1	1-Chloro-4-nitrobenzene	1	100 (90) 90[c]
2	1-Chloro-2-nitrobenzene	3	100 (88)
3	4-Chlorobenzonitrile	6	98 (95)
4	2-Chloro-5-(trifluoromethyl) benzonitrile	3	100 (92)
5	4-Chlorobenzaldehyde	10	88 (82)
6	2-Chloropyridine	7	96 (92)
7	2-Chloropyrimidine	1	100 (90)
8	4-Chlorobenzophenone	6	96 (88)
9	Chlorobenzene	36	72 (60) 85[d]
10	4-Chlorotoluene	36	65 (55)
11	4-Chloroanisole	36	62 (52)
12	2-Fluorobenzonitrile	1	95 (82)
13	4-Fluorobenzaldehyde	1	92 (80)
14	1-Fluoro-4-nitrobenzene	0.5	100 (85)
15	3-Chloro-4-fluoronitrobenzene	1	95 (85)

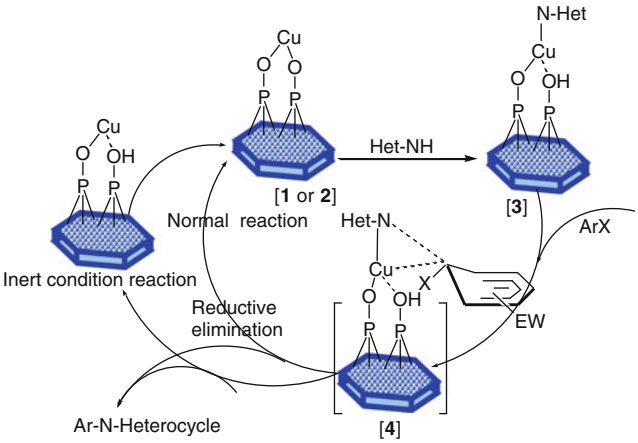
[a]Aryl halide (1 mmol), imidazole (1.2 mmol), catalyst (100 mg), K_2CO_3 (2 mmol), DMF (4 mL), 120°C
[b]Yields refer to GC yields and yields in parentheses refer to isolated yields
[c]GC yield after fourth recycle
[d]GC yield obtained by using 10 mol% of KO^{t}Bu

Table 6 *N*-Arylation of imidazole with chloro- and fluoroarenes[a]



		X=Cl		X=F	
Entry	Het-NH	Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	Pyrrole	4	90 (80)	2	95 (85)
2	Pyrazole	3	95 (85)	1	90 (80)
3	Benzimidazole	12	85 (72)	9	85 (75)
4	Piperidine	5	90 (80)	1	95 (85)

[a]Yields refer to GC yields and yields in parenthesis refer to isolated yields

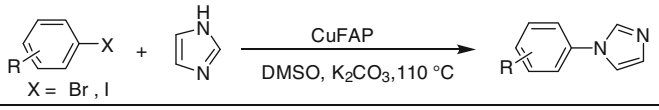


Scheme 7 Possible mechanism for the *N*-arylation of heterocycles. Reproduced with permission from [19]. American Chemical Society

catalytic cycle as described in Scheme 7, since there was no reaction between the catalyst and chloro- or fluorobenzaldehyde. The XPS of N 1s **(3)** lines appear at 401.8 and 399.6 eV, which are assigned to the Cu–N and C=N bonds, respectively [22]. The FTIR of **3** shows a P-OH vibration at 867 cm^{-1} which is in agreement with the similar hydride(enolato)ruthenium(II)apatite complex reported earlier [23]. Subsequent reaction of complex **3** with chloro- or fluorobenzaldehyde afforded the final product *N*-arylimidazole instantly, leaving the [Cu(II)] catalyst in normal conditions and Cu(I) in nitrogen atmosphere. The FTIR spectrum of the used catalyst **1,** obtained in normal conditions, shows the disappearance of the P-OH stretching indicating the regeneration of 1 to initiate another cycle. Although we are unable to isolate any intermediate complexes, the identification of Cu(I) complex in a nitrogen atmosphere presumes copper assisted nucleophilic displacement of X^- of the arene by N^--Het providing the coupled product via transient **4**. In normal conditions, the formed Cu(I) may be reoxidized to **1**. Similarly, in a reaction with the chloroarene**,** the deep blue complex 3 obtained from 2 also provides the coupling product. The deep blue complex formed on the treatment of a simple copper hydroxyapatite with imidazole is inert in the coupling reaction with the chlorobenzaldehyde. The above results and the identification of intermediates provide a better understanding of the mechanism and the necessity of strong basic sites in the apatite for the transformation of **3** to give the coupled product.

The same catalyst showed good activity for the *N*-arylation of bromo- and iodoarenes using K_2CO_3 as base (Table 7) [24]. To identify the best system for *N*-arylation of imidazole with bromobenzene, a variety of bases were screened and it was found that the CuFAP catalyst with K_2CO_3 (2 eq) afforded good yields (90%) in DMSO at 110°C. A control reaction conducted under identical conditions devoid of CuFAP gave no coupled product. CuFAP was recovered quantitatively by simple filtration and reused, which gave consistent activity even after the fourth cycle

Table 7 *N*-Arylation of imidazole with bromo- or iodoarenes[a]



(1)	92%, (6), X = I	(5)	90%, (10), 89%[b] X = Br
(2)	90%, (14), X = I	(6)	88%, (15), X = Br
(3)	91%, (14), X = I	(7)	85%, (15), X = Br
(4)	95%, (3), X = I	(8)	95%, (4), X = Br
(9)	90%, (8), X = Br		
(10)	98%, (2), X = Br		
(11)	92%, (6), X = Br		

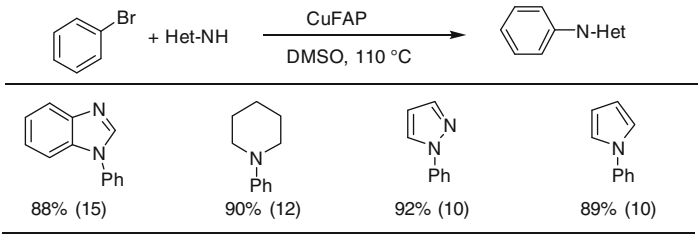
[a]Reaction conditions: aryl halide (1 mmol), imidazole (1.2 mmol), CuF AP (0.1 g), DMSO (5 mL), and K_2CO_3 (2 equiv.) at 110°C. Isolated yields and reactions times are in parenthesis
[b]Yield after fourth cycle

(Table 7, entry 5). Moreover the absence of copper in the filtrate was confirmed by AAS, which reiterates that no leaching of copper occurred during the reaction and provides evidence for heterogeneity throughout the reaction.

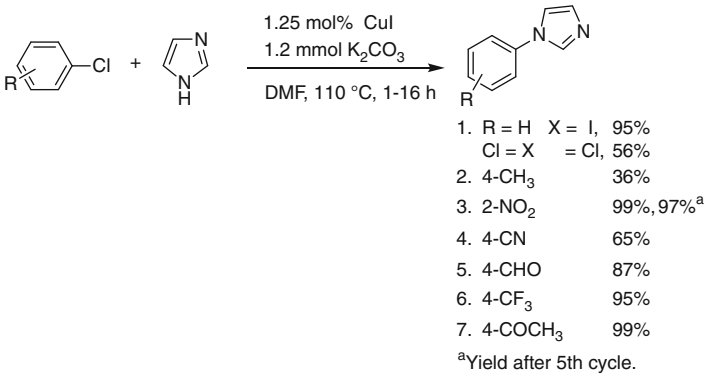
The generality of the CuFAP promoted *N*-arylation of imidazole with K_2CO_3 as base is shown in Table 7. 4-Bromopyridine, 2-bromopyrimidine, and bromobenzenes with electron-withdrawing groups, such as 4-nitrobromobenzene and 4-bromobenzaldehyde, gave excellent yields of coupled products in short reaction times (Table 7, entries 8–11) compared with bromobenzene. Bromobenzenes with electron-donating groups such as 4-bromotoluene and 4-bromoanisole required longer reaction times and gave moderate yields (Table 7, entries 6 and 7). Among the iodoarenes tested, iodobenzenes with electron-withdrawing groups (Table 7, entry 4) underwent smooth reaction with excellent yields compared to iodobenzenes with electron-donating groups (Table 7, entries 2 and 3). As expected, iodobenzene provided good yields in a shorter time than bromobenzene (Table 7, entry 1).

In order to expand the scope of the reaction, a variety of other nitrogen-containing heterocycles such as benzimidazole, pyrrole, pyrazole, and piperidine were successfully coupled with bromobenzene to give the corresponding *N*-arylated products in good yields. Among these heterocycles, piperidine and pyrrole gave the corresponding *N*-arylated products in good yields in short periods (Table 8, entries 3 and 4).

Table 8 *N*-Arylation of various nitrogen heterocycles[a]



[a]Reaction conditions: aryl halide (1 mmol), Het-NH (1.2 mmol), CuFAP (0.1 g), DMSO (5 mL), K_2CO_3 (2 equiv), 110°C. Isolated yields and reactions times are in parenthesis



Scheme 8 *N*-Arylation of imidazole with chlorobenzenes

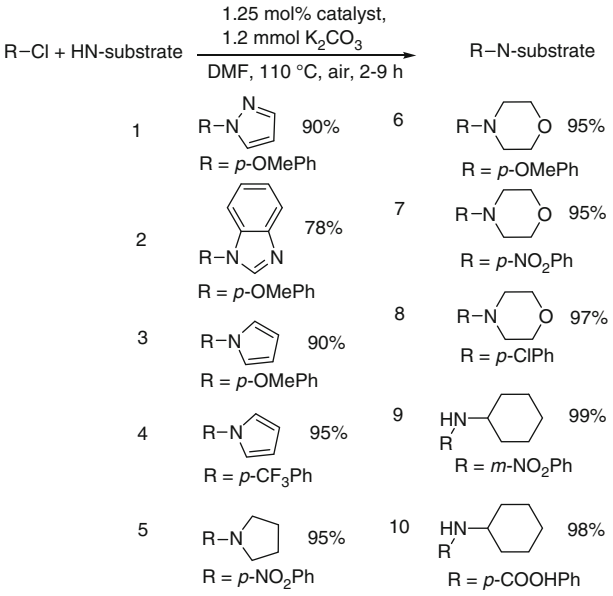
9 CuI Nanoparticles

In 2009, Sreedhar et al. reported [25] the use of CuI nanoparticles for the coupling of aryl bromides and chlorides with various azoles in the absence of both ligands and strong bases in DMF solvent. Specifically, this method uses inexpensive aryl chlorides [26].

Aryl chlorides possessing electron-donating (ED) or electron-withdrawing (EW) groups are coupled using CuI nanoparticles with imidazole, and the results are shown in Scheme 8. Aryl chlorides with ED group show poor activity (entry 2) compared to EW groups.

Various other substituted azoles such as pyrazoles, benzimidazoles, and primary and secondary aliphatic cyclic amines were also successfully coupled with chlorobenzenes to afford *N*-arylated products in fair yields (Scheme 9, entries 1–10).

Impressively, many azoles such as pyrazoles, pyrrole, and benzimidazoles reacted equally well with substituted chlorobenzenes to yield the corresponding *N*-arylated products in good yields (Scheme 9, entries 1–4). 1H-benzimidazole seemed to be a little sluggish to react with aryl chloride compared to imidazole



Scheme 9 *N*-Arylation of pyrazole, pyrrole and alkylamines with chlorobenzenes

(Scheme 9, entry 2). The authors have observed that air is necessary in the coupling process, which involves oxidative addition followed by reductive elimination; however, more data is required to propose a reaction pathway.

10 Cu(II)-NaY Zeolite

Zeolites are very useful catalysts for a large variety of reactions, from acid to base and redox catalysis [27]. Hutchings et al. reported that bis(oxazoline)-modified Cu (II)-HY catalysts are effective for asymmetric carbonyl- and imino-ene reactions and aziridination of styrene [28, 29]. Recently Djakovitch and Kohler [30–34] found that Pd(II)-NaY zeolite activates aryl halides towards Heck olefination, α-arylation of malonate, and amination reactions. It is well known that alkali-exchanged faujasite zeolites are solid base catalysts [35]. Owing to the usefulness of zeolites in organic chemistry, and our interest, we recently reported the use of modified alkali-exchanged zeolite Y, NaY zeolite [36] with electron rich copper catalyst in the *N*-arylation of nitrogen heterocycles with aryl halides to afford *N*-arylheterocycles in excellent yields under mild conditions without the use of any additive.

Catalyst preparation: Cu(II)-NaY zeolite was prepared by ion exchange of zeolite NaY (10 g) with a solution of copper(II) acetate (2.86 g, 15.75 mmol in deionized water 150 mL) for 24 h at room temperature. The material was recovered

by filtration, dried (110°C), and calcined (550°C) in a flow of air. Atomic absorption spectroscopy analysis showed that the zeolite contained 6.84 wt% of Cu.

As can be seen from Table 9, *N*-arylation of imidazole with chloroarenes containing electron-withdrawing groups such as nitro-, cyano-, and trifluoromethyl- gave quantitative yields (entries 1–3) in shorter reaction times when compared with 4-chloroacetophenone (entry 4). Bromoarenes containing electron-donating groups afforded the corresponding *N*-arylated products in high yields after 36 h (entries 5–8). The reaction with iodoarenes resulted in complete conversion in shorter reaction times (entries 9–11). Reaction of 1-chloro-4-iodobenzene with imidazole gave selectively N-(4-chlorophenyl)imidazole (entry 12). The catalyst was used for four cycles successfully with minimal loss of activity (Table 9, entry 7).

After completion of the reaction, the catalyst was separated by simple filtration and washed with DMF and then with acetone and dried in an oven. AAS results of the used Cu(II)-NaY catalyst indicate leaching of 1.8% of copper in the *N*-arylation reaction of imidazole with 4-bromotoluene after the first cycle and 6.2% leaching after the fourth cycle. When a fresh reaction was conducted with the filtrate obtained at the end of the *N*-arylation reaction, no product formation was observed.

The application of this catalytic system for the coupling of nitrogen-containing heterocycles with 4-bromo- and 4-iodotoluene was also explored and the desired *N*-arylated products were obtained in excellent yields (Table 10). The reaction of 4-chlorotoluene with nitrogen heterocycles provided the products in only trace amounts even after 48 h.

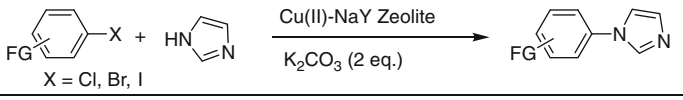
11 Nanocrystalline Copper(II) Oxide

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases, the destruction of hazardous chemicals [37, 38], and catalysts for various organic transformations [39–43]. Recently, we reported the use of nano-CuO as a catalyst for C–N bond forming reactions [44]. Nano-CuO samples were obtained from NanoScale Materials, Inc., having a surface area of 136 m^2/g and crystallite size of 7–9 nm.

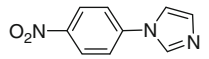
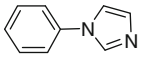
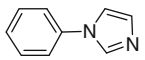
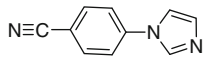
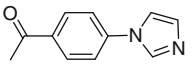
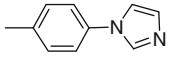
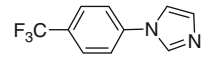
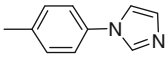
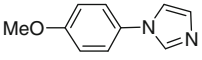
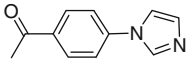
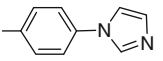
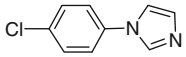
As illustrated in Table 11, the catalytic system (10 mol% of nano-CuO, K_2CO_3, DMF at 120°C) proved to be highly efficient with other activated chloroarenes. When *o*-, *m*-, and *p*-nitrochlorobenzenes were used, the corresponding *N*-arylated products were obtained in excellent yields (Table 11, entries 1, 2 and 3). Cyano, nitro, and aldehyde groups are well tolerated (Table 11, entries 1, 4, and 6).

2-Chloropyridine, 4-chloropyridine, and 2-chloropyrimidine also provided excellent yields as can be seen from Table 11 (entries 7, 8, and 10). The sterically bulky 4-chlorobenzophenone was converted to the corresponding *N*-arylated product (Table 11, entry 9) with excellent yields. This catalytic system is completely inactive in the case of deactivated chloroarenes such as chlorobenzene (Table 11, entry 12). The activity of nano-CuO is lower than the Cu(II) fluoroapatite catalyst

Table 9 Cu(II)-NaY-catalyzed coupling reactions of aryl halides with imidazole[a]



X = Cl, Br, I

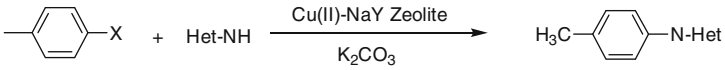
(1)	 92%[b] (20 h), X = Cl	(5)	 99% (30 h), X = Br	(9)	 99% (24 h), X = I
(2)	 99% (24 h), X = Cl	(6)	 99% (20 h), X = Br	(10)	 99% (24 h), X = I
(3)	 97% (30 h), X = Cl	(7)	 90%[b] (84%)[c] (36 h), X = Br	(11)	 99% (36 h), X = I
(4)	 95% (48 h), X = Cl	(8)	 85% (48 h), X = Br	(12)	 99% (40 h), X = I

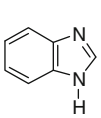
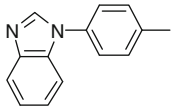
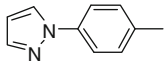
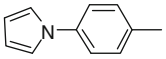
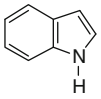
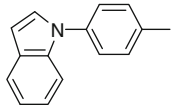
[a]Reaction conditions: aryl halide (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol), Cu(II)-NaY (100 mg) in 3 mL of DMF, GC yields unless otherwise stated, and reactions times are reported in parenthesis

[b]Isolated yields

[c]Isolated yield after third recycle

Table 10 *N*-Arylation of various nitrogen heterocycles[a]

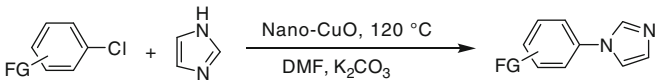


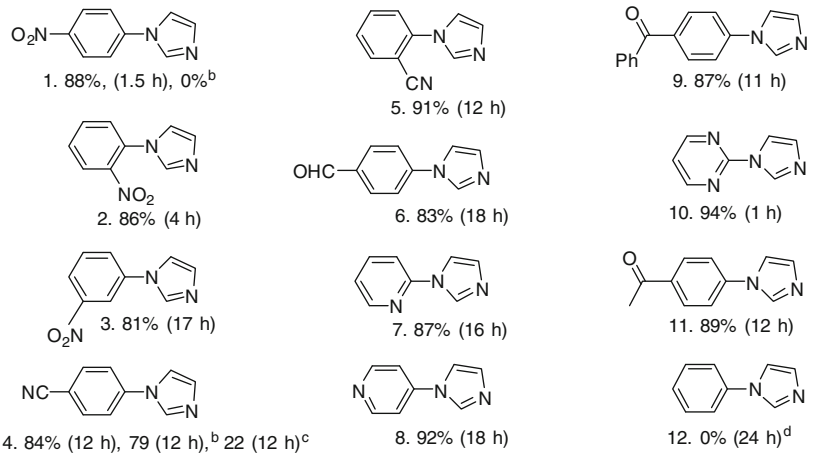
Entry	Nitrogen hetrocycle	Product	X = Br		X = I	
			Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1			48	99	36	99
2			36	99	22	99
3			24	99	20	99
4			20	99	22	99

[a]Reaction conditions: aryl halide (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol), Cu(II)-NaY (100 mg) in 3 mL of DMF

[b]GC yields

Table 11 *N*-Arylation of imidazole using different chloroarenes[a]





[a]Reaction conditions: Ar–Cl (1 mmol), imidazole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL), 120°C, isolated yields; reaction times are in parenthesis in hours
[b]Recycle 4
[c]Using commercial CuO
[d]Yield without catalyst

previously reported by us [19] and comparable with Cu_2O-coated Cu nanoparticles reported by Hyeon [21].

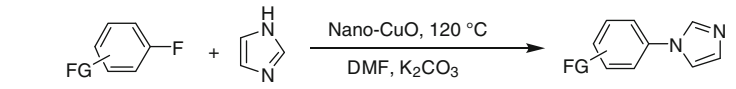
Particularly noteworthy is that fluoroarenes composed of *o*- or *p*-electron-withdrawing groups are also coupled with imidazole to afford the corresponding *N*-arylated products in excellent yields (Table 12). Similar behavior has been observed for greater reactivity of C–F over C–Cl bonds for fluoroarenes in the Suzuki reaction [45].

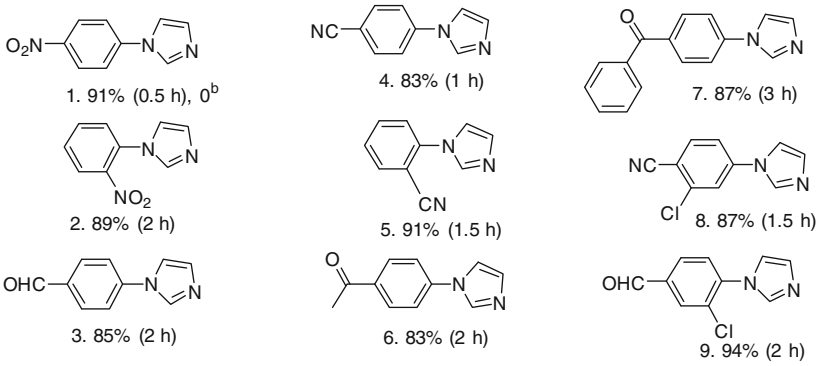
Chloro-4-nitrobenzene, 4-chlorobenzonitrile, 2-chlorobenzonitrile, 2-chloropyrimidine, and 2-chloropyridine are coupled with indole to give the corresponding *N*-arylated products in good to excellent yields (Table 13, entries 1, 2, 3, 4, and 5). The *N*-arylated product was obtained in 20% yield by coupling indole with 4-chloroacetophenone using nano-CuO catalyst, while a complex mixture was obtained in the case of Cu_2O-coated Cu nanoparticles [21].

As can be seen from Table 14, other nitrogen-containing heterocycles like benzimidazole, pyrrole, and pyrazole gave the corresponding *N*-arylated products with 1-chloro-4-nitrobenzene and 1-fluoro-4-nitrobenzene in excellent yields.

The nano-CuO catalyst was recovered by centrifugation and reused for several cycles without any significant loss of activity. Transmission electron microscopy

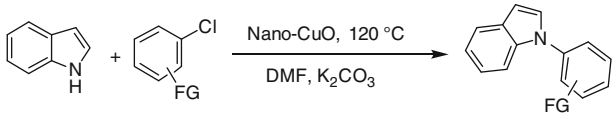
Table 12 *N*-Arylation of imidazole using different fluoroarenes[a]

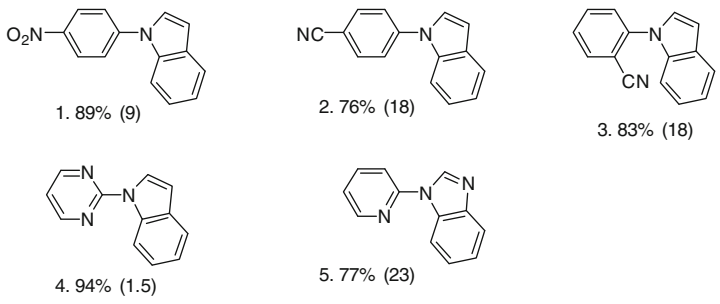




[a]Reaction conditions: Ar–F (1 mmol), imidazole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL), isolated yields; reaction times are in parenthesis
[b]Yield without catalyst

Table 13 *N*-Arylation of indole with different chloroarenes[a]

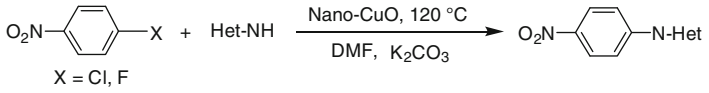




[a]Reaction conditions: Ar–Cl (1 mmol), indole (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL). Isolated yields, reactions times are in hours

(TEM) studies of both fresh and used catalysts were carried out to determine the shape and size of the particles. Interestingly, it is observed that the shape and size of the particles remain unchanged. This confirms that the morphology of the catalyst remains same even after recycling.

Table 14 *N*-Arylation of various nitrogen heterocycles[a]



		X=Cl		X=F	
Entry	Net-NH	Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	Pyrrole	8	82, 0[c]	2	84, 0[c]
2	Benzimidazole	4.5	87	3	81
3	Pyrazole	5	84	2	94

[a]Reaction conditions: ArX (1 mmol), Net-NH (1.2 mmol), nano-CuO (10 mol%), K_2CO_3 (2 mmol), DMF (4 mL)
[b]Isolated yields
[c]Yield without catalyst

12 Cu_2O-Coated Cu Nanoparticles

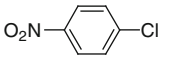
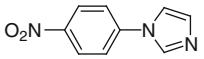
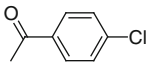
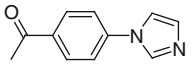
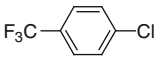
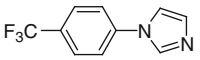
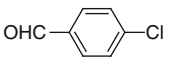
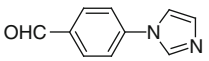
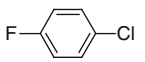
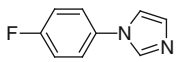
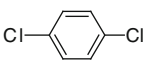
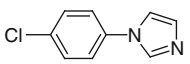
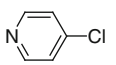
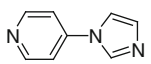
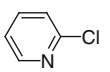
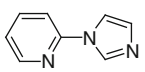
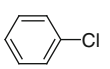
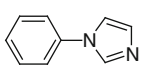
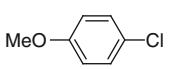
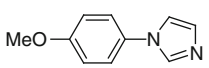
Hyeon [21] synthesized uniform Cu_2O-coated Cu nanoparticles from the thermal decomposition of copper acetylacetone followed by air oxidation and used these nanoparticles as catalysts for Ullmann-type amination coupling reaction of aryl chlorides.

Ullmann-type amination reaction of imidazole with various aryl chlorides having electron-withdrawing groups were conducted using the Cu_2O coated copper nanoparticles as catalysts, the reactions proceeded very well (Table 15, entries 1–8). The high catalytic activity of the Cu_2O-coated Cu nanoparticles seems to result from the high surface area derived from the nanoparticles. In the case of unactivated aryl chlorides such as chlorobenzene and 4-methoxychlorobenzene, there is no reaction (Table 15, entries 9 and 10). Various amines were screened to obtain the coupled products with 4-chloroacetophenone (Table 16). In the case of benzimidazole, pyrazole, and pyrrole, the yield of the product is good to moderate.

13 Resin-Supported Sulfonato-Cu-(salen) Complex

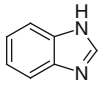
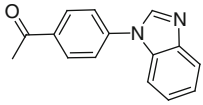
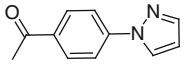
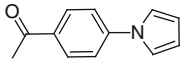
Salen ligands are recognized as efficient auxiliaries, and many metallosalen complexes have been found to serve as excellent catalysts for various organic transformations [46]. Styring et al. have reported the Suzuki–Miyaura cross-coupling reaction by using a polymer-supported salen-type palladium complex [47, 48]. Taillefer et al. examined the efficiency of salen ligands in the *N*-arylation of imidazole with bromobenzene in moderate yields [49, 50]. We synthesized a resin-supported sulfonato-Cu(salen) catalyst **1** (Scheme 10) from **2** (Scheme 11) [51] and tested for the *N*-arylation of heterocycles with chloro- and fluoroarenes in the presence of an inexpensive and mild base K_2CO_3.

Table 15 Catalytic reactions using Cu_2O-coated nanoparticles for Ullmann coupling of imidazole with various aryl chlorides[a]

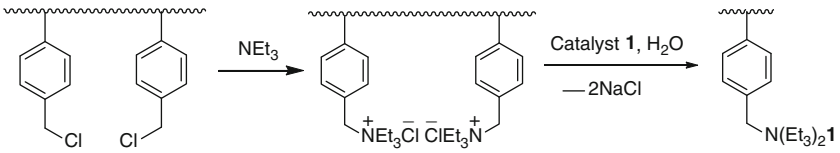
Entry	Reactant	Product	Yield (%)[b]
1			95
2			91
3			90
4			85
5			97
6			69
7			86
8			88
9			0
10			0

[a]5 mol% Cu_2O-coated nanoparticles and 2 eq. imidazole used, Cs_2CO_3, DMSO, 150°C, 18 h
[b]Isolated yield

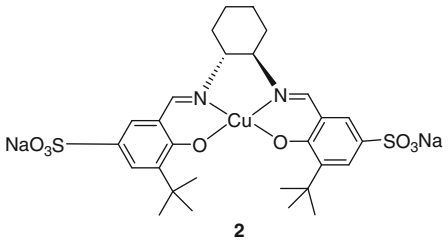
Table 16 Catalytic reactions using Cu_2O-coated Cu nano particles for Ullmann coupling of 4-chloroacetophenone with various amines[a]

Entry	Reactant	Product	Yield(%)[b]
1			84
2			86
3			63

[a]5 mol% Cu_2O-coated Cu nanoparticles used, Cs_2CO_3, DMSO, 150°C,18 h
[b]Isolated yield

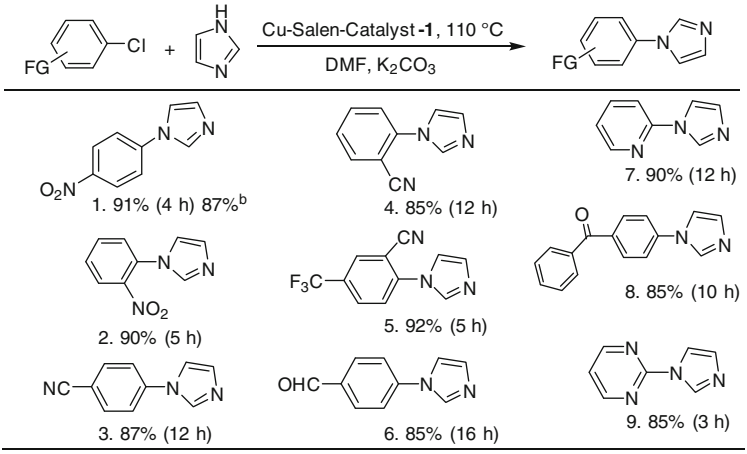


Scheme 10 Schematic representation of synthesis of resin-supported catalyst **1**



Scheme 11 Schematic representation of homogeneous catalyst **2** precursor for the synthesis of Merrifield resin catalyst **1**

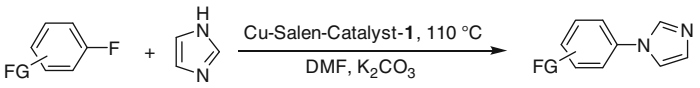
Table 17 *N*-Arylation of imidazole with chloroarenes

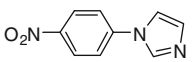


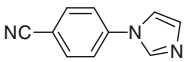
[a]Reaction conditions: catalyst resin 2 (1 mol%), ArCl (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol), DMF (4 mL), 110°C. Reaction times are in parenthesis
[b]Yield after third cycle

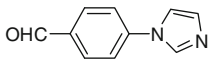
After optimizing the reaction conditions (see foot note *a* of Table 17), the reaction scope was extended with various aryl halides and azoles. A variety of substituted chloro- and fluoroarenes possessing a wide range of functional groups are examined. As illustrated in Table 17, when *o*- and *p*-chloronitrobenzenes were used, the corresponding *N*-arylated products were obtained in excellent yields (entries 1 and 2). Cyano, nitro, and aldehyde groups are well tolerated. 2-Chloropyridine and

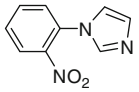
Table 18 *N*-Arylation of imidazole using different fluoroarenes[a]

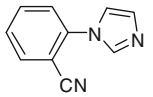


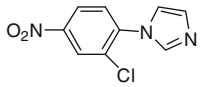

1. 92% (3 h)


3. 91% (2.5 h)


5. 91% (3 h)

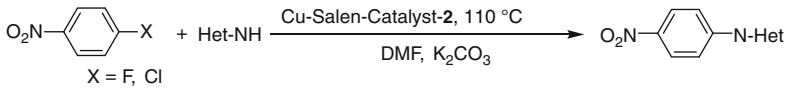

2. 90% (4 h)

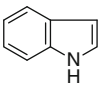

4. 90% (3 h)


6. 90% (3 h)

[a]Reaction conditions: catalyst resin 2 (1 mol%), ArF (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol), DMF (4 mL), 110°C, isolated yields. Reaction times are in parenthesis

Table 19 *N*-Arylation of various nitrogen heterocycles[a]



Entry	Het-NH	X = F		X = Cl	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1		3	85	7	87
2		4	82	10	80
3		12	80	18	82
4		3	87	12	83

[a]Reaction conditions: catalyst resin **2** (1 mol%), ArX (1 mmol), Het-NH (1.2 mmol), K_2CO_3 (2 mmol), DMF (3 mL), 110°C. Isolated yields

2-chloropyrimidine also provided excellent yields, as can be seen from Table 17 (entries 7 and 9). The sterically bulky 4-chlorobenzophenone was converted to the corresponding *N*-arylated product (entry 8) with excellent yields. This catalytic system is completely inactive in the case of un-activated chloroarenes such as chlorobenzene.

Particularly, noteworthy is that fluoroarenes containing *o*- or *p*-electron-withdrawing groups are also coupled with imidazole to afford the corresponding *N*-arylated products in excellent yields (Table 18).

As can be seen from Table 19, other nitrogen-containing heterocycles like pyrrole, pyrazole, indole, and piperidine gave the corresponding *N*-arylated products with 1-chloro-4-nitrobenzene and 1-fluoro-4-nitrobenzene in excellent yields. Lower reaction rates but comparable yields were observed with resin supported **1** compared to its homogeneous counterpart. The resin supported **1** can be recovered by simple filtration and reused for three cycles with consistent activity.

14 Silica Immobilized Copper Complexes

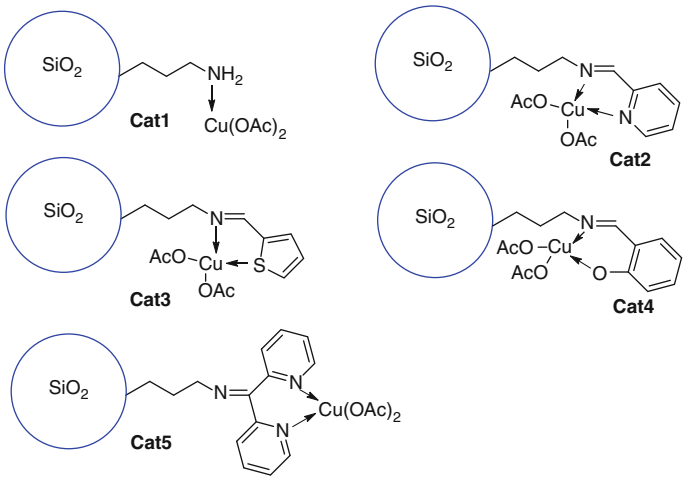
Silica modified with different functionalities such as -NH_2, -SH, diamines, and amino acids is reported to be a good support for various metals like Pd, Cu, Sc, Ru, Pt, and V for different organic transformations [52]. Recently, Likhar et al. [52] reported the *N*-arylation of N(H)-heterocycles and benzylamines with aryl halides and arylboronic acids using silica immobilized copper complexes (Scheme 12).

The FTIR spectrum of chemically modified silica (imine) shows a peak due to the C=N bond around 1,640 cm^{-1}, which on complexation with copper shifts to a lower value. The lowering in frequencies of the C=N peak is indicative of the formation of the metal–ligand bond. The difference in the values of the C=N stretching band before and after complexation for all the catalysts is shown in Table 20.

XPS analysis of the catalysts shows that in catalysts cat1-cat5, two intense peaks appear at 933–935 eV and 952–954 eV. These peaks are attributable to the Cu $2p_{3/2}$ and Cu $2p_{1/2}$ levels of $Cu^{0-\delta+}$ species, which may be due to the formation of the mono/bi/multidentate copper complexes with nitrogen ligands [53, 54]. A simplified catalyst structure is shown in Scheme 12. The copper content of the catalysts were estimated by using ICP-AES, and the results are shown in Table 20.

To find the best catalyst for the *N*-arylation reaction, all the catalysts (5 mol% Cu) were screened for the reaction of iodobenzene with imidazole using Cs_2CO_3 at 100°C under nitrogen atmosphere in toluene, and the results are summarized in Table 21. From Table 21, it can be seen that the catalysts derived from pyridine-2-carboxaldehyde (**Cat2**) and 2-bipyridyl ketone (**Cat5**) were equally good; **Cat3** showed moderate activities whereas **Cat1** and **Cat4** gave poor yields**.** Interestingly, when neat $Cu(OAc)_2$, was used there was almost no reaction (Table 21, entry 6).

To explore the scope and limitations of the current catalyst (**Cat2**), several haloarenes were used for the arylation of the imidazole under the optimized conditions, and the results are summarized in Table 22. It was observed that iodoarenes with an electron-withdrawing group (entries 3 and 4) reacted at a faster rate than iodoarenes with an electron-donating group (entry 2). Decreasing the amount of catalyst from 5 mol% to 2 mol% gave good yields only after 24 h (entry1). Interestingly, heterogeneous **Cat2** afforded a comparable yield in shorter duration when compared with the Buchwalds CuOTf-1,10-phenanthroline system (entry 3) [55]. To expand the scope of the catalyst, a variety of other nitrogen-containing heterocycles such as benzimidazole, pyrrole, and pyrazole were successfully coupled with iodoarenes to give the corresponding *N*-arylated products in

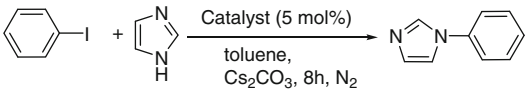


Scheme 12 Structure of silica tethered copper catalysts

Table 20 Characterization of silica-supported copper catalysts

Entry	Catalyst	Stretching frequency of C=N (cm^{-1}) before complexation	Change in C=N bands (cm^{-1}) after complexation	Loading of Cu (mmol/g)
1	**Cat1**	–	–	0.38
2	**Cat2**	1,640	1,631	0.43
3	**Cat3**	1,641	1,338	0.41
4	**Cat4**	1,645	1,631	0.41
5	**Cat5**	1,643	Almost no shift	0.39

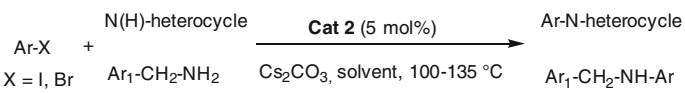
Table 21 Screening of different copper catalysts for *N*-arylation of imidazole with iodobenzene[a]



Entry	Catalyst	Yield (%)	Leaching of Cu (%)[b]
1	**Cat1**	23	25
2	**Cat2**	92	2.5
3	**Cat3**	69	7
4	**Cat4**	31	9
5	**Cat5**	91	6.5
6	$Cu(OAc)_2$	3	–

[a]Reaction conditions: iodobenzene (1 mmol), imidazole (1.2 mmol), Cs_2CO_3 (2 mmol), toluene (3 mL), catalyst (5 mol%), 100°C, N_2 atmosphere. GC yields
[b]Determined by ICP-AES and expressed as percentage of the total copper charged

Table 22 *N*-Arylation of N(H)-heterocylces and benzylamines with aryl halides using **Cat 2**[a]



Entry	Aryl halide	N(H)-heterocycle/amine	Time (h)	Yield (%)
1	C_6H_5-I	Imidazole	8	89, 72[b]
2	4-MeO-C_6H_4-I	Imidazole	16, 24[c]	94, 96[c]
3	4-MeCO-C_6H_4-I	Imidazole	4	92
4	4-NO_2-C_6H_4-I	Imidazole	3	90
5[d]	4-I-C_6H_4-I	Imidazole	16	85
6	C_6H_5-I	Benzimidazole	14	88
7	C_6H_5-I	Pyrazole	12	90
8	C_6H_5-I	Pyrrole	10	82
9	C_6H_5-I	Benzylamine	12	90
10	C_6H_5-I	Dibenzyl amine	16	0
11	4-MeO-C_6H_4-I	Benzylamine	18	72
12	C_6H_5-Br	Imidazole	24	78
13	4-MeCO-C_6H_4-Br	Imidazole	18	90
14	4-NO_2-C_6H_4-Br	Imidazole	12	90
15	4-Me-C_6H_4-Br	Imidazole	24	20

[a]Reaction conditions: aryl halide (1 mmol), amine (1.2 mmol), C at2 (5 mol%), Cs_2CO_3 (2 mmol), toluene or xylene (2 mL), 100 or 135°C, N_2 atmosphere, isolated yield
[b]**Cat2** (2 mol%), reaction time 24 h
[c]Cited from reference 4
[d]3 mmol imidazole used

good yields. Next, benzylamine was reacted with iodobenzene and a good yield was obtained after 14 h. Benzylamine with electron-donating moieties was found to be more active than simple benzylamine (entry 9). When dibenzylamine was employed in the reaction, no product formation was observed (entry 10). This may be due to the steric hindrance of the benzylamine. Bromoarenes were found to be unreactive but an increase in temperature from 100°C to 135°C and a change in solvent from toluene to xylene gave excellent yield of product for bromoarenes with an electron-withdrawing group (entries 13 and 14). Bromobenzene gave a satisfactory yield after 24 h (entry 12), whereas bromoarenes with an electron-donating group gave low yield (entry 15).

Catalyst recyclability: For any heterogeneous system, it is important to know the ease of catalyst separation and possible reuse. The catalyst (**Cat2**) can easily be separated by filtration. The recovered catalyst after washing with acetone followed by drying at 60°C was used in the next run and minimal decrease in activity was observed (first cycle: 92%, fifth cycle: 86%) (Fig. 3). This decrease in activity may be due to the leaching or deactivation of the metal center. To see whether the reaction was occurring mainly due to the leached metal or the supported catalyst, a reaction between imidazole and iodobenzene was terminated after a small conversion (45 min, 18% conversion), the catalyst was filtered off by hot filtration, and the

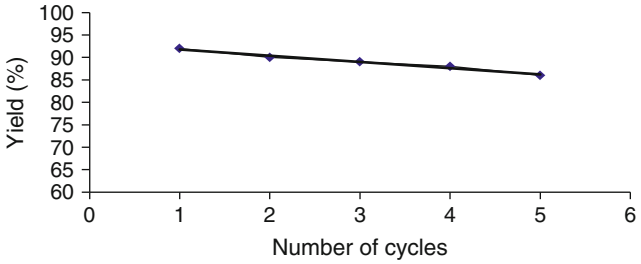


Fig. 3 Reusability study of **Cat2** for the *N*-arylation of imidazole with iodobenzene. Reproduced with permission from [52]. Copyright 2007, Elsevier

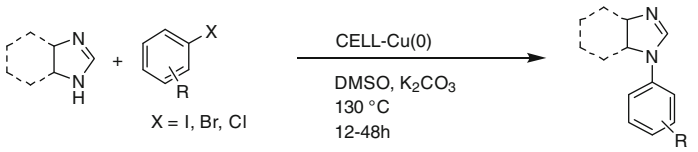
reaction was continued with the filtrate for 10 h. Almost no change in the conversion of iodobenzene was observed. These studies and the non-activity of $Cu(OAc)_2$ in *N*-arylation of imidazole clearly prove that the reaction occurred heterogeneously. Lipshutz et al. [56] also reported that significant amount of supported metal can be dissolved during the reaction and would redeposit quickly on the solid during the filtration as a result of unavoidable minor temperature differences during the filtration. It also may be assumed in this case that during filtration, the solid matrix (silica) traps the copper species leached from the catalyst during the reaction.

15 Bio-degradable Cellulose-Supported Copper(0) Catalyst

Cellulose is a natural biopolymer, which is biodegradable, environmentally safe, widely abundant, inexpensive, and easy to handle [57]. Cellulose and its derivatives are widely used in chemical and bio-chemical applications and also as supports for the synthesis of organic molecules [58]. Interestingly, the cellulose fibers also act as a nanoreactor for the stabilization of metal nanoparticles [59]. However, its use as a support for catalytic applications is not well explored. Recently, Choplin and coworkers reported cellulose as the support for water soluble $Pd(OAc)_2$/5 TPPTS system in the Trost–Tsuji allylic alkylation reaction [60]. To corroborate the above concept in the cross coupling of aryl halides and boronic acids, we reported *N*-arylation of imidazoles with aryl halides using a cellulose-supported Cu(0) catalyst (CELL-Cu(0) [61] . The prepared catalyst was well characterized using various instrumental techniques. For example, the X-ray diffraction pattern of CELL-Cu(0) catalyst clearly indicates the presence of Cu (111) and Cu (200) phases which are attributed to Cu(0) [46]. Further, the high resolution XPS narrow scan spectrum of the fresh CELL-Cu(0) catalyst shows a Cu 2p3/2 peak at 932.72 ev, which is attributed to Cu (0) [22].

The scope of the cellulose-supported copper catalyst has been examined in the case of aryl halides, and the results are summarized in Table 23. A very good yield (89%) was observed for the reaction of imidazole with 4-iodoanisole

Table 23 *N*-Arylation of nitrogen heterocycles with aryl halides using CELL-Cu(0) catalyst[a]



1 95%, 90%[b], <10[c], X = I

2 89% (85%)b, X = I

3 40%, X = I

4 70%, X = Br

5 70%, X = Br

6 95% (91%)[b] X = Cl

7 50%, X = Cl

8 20%[d], X = Cl

9 40%, X = I

10 60%, X = I

11 85%, X = Cl

[a]Reaction conditions: 2 mmol of aryl halide, 2 mmol of imidazole, 4 mmol of K_2CO_3, CELL-Cu(0) catalyst (0.05 g) DMSO, 130°C
[b]Yield after fourth cycle
[c]Reaction temperature 80°C
[d]Reaction with 0.1 g of CELL-Cu(0) catalyst

(Table 23, entry 2). On the other hand, 2-iodoanisole gave lower yields, which may be because of steric factors (Table 23, entry 3). In the case of bromoderivatives, 4-bromoacetophenone and bromobenzene afforded 70% of the coupled product (Table 23, entries 4 and 5). Further, the catalyst was screened for chloroderivatives (Table 23, entries 6–8) for the *N*-arylation of imidazole. Among them *p*-nitrochlorobenzene with a strong electron-withdrawing group resulted in quantitative yield (Table 23, entry 6), whereas 4-chloroacetophenone only gave low yield (Table 23, entry 7). *N*-Arylation of imidazole with chlorobenzene gave no coupled product under the above conditions. However, an increase of catalyst loading (0.1 g) with a longer reaction time provided 20% yield of the coupled product (Table 23, entry 8). The catalytic couplings of benzimidazole and indole resulted in good yields of products (Table 23, entries 9–11).

Reusability of the catalyst: The catalyst was recovered by simple filtration and washed with acetone and oven dried. The recovered catalyst was reused for *N*-arylation of imidazole and aryl halide (Table 23, entries 1, 2 and 6). These results indicate that the CELL-Cu(0) catalyst can be used for several cycles successfully with minimal loss of activity. The high resolution XPS narrow scan spectrum of the used CELL-Cu(0) catalyst shows two peaks at 932.72 and 935.25 for Cu 2p3/2, which are attributed to Cu(0) and Cu(II), respectively. ICP-AES results of the used CELL-Cu(0) catalyst indicate leaching of 0.8% of copper in the *N*-arylation

reaction of imidazole with iodobenzene after the first cycle and 3.5% after the fourth cycle.

16 Polyaniline-Cu Catalyst

Polyaniline (PANI) is one of the most widely studied conducting polymers for electronic and optical applications. It is also receiving considerable attention in modern organic synthesis as a support and a promoter for metal-catalyzed organic transformations due to its easy preparative protocol from inexpensive starting material, high environmental stability, easy acid–base doping–dedoping, and redox properties [62]. Recently, Choudary et al. have reported polyaniline-supported Os-, Sc-, In-, and Pd-catalyzed organic transformations [63]. Later, we reported [64] the preparation, characterization, and catalytic properties of polyaniline-supported cuprous iodide (Scheme 13) in the *N*-arylation of N(H)-heterocycles and benzylamines with aryl halides and arylboronic acids.

PANI-Cu was prepared by stirring CuI and polyaniline in acetonitrile for 24 h followed by filtration. The prepared PANI-Cu was fully characterized using FTIR, XPS, ICP-AES, SEM, and EDAX. The most important bands in the FTIR spectrum of PANI are located at 1,584, 1,494, 1,376, 1,308, 1,163, and 830 cm^{-1}. They are attributed to the stretching vibrations of quinoid ($\upsilon_{C=N} + \upsilon_{C=C}$), benzenoid ($\upsilon_{C=C}$) units of the polymer, deformations of the C–N bond, stretching vibrations of the C–N bond, in-plane deformations of CH bonds present in the aromatic rings of the undoped polymer, and the out-of-plane deformations of CH bonds in the 1,4-substituted aromatic ring, respectively [65]. Upon incorporation of CuI into PANI, no appreciable shifts in the quinoid or benzenoid ring bands positions have been observed. XPS analysis of PANI-Cu showed a Cu $2p_{3/2}$ line at 932.4 eV and Cu $2p_{1/2}$ line at 952 eV, which confirmed the oxidation state of copper in PANI-Cu to be +I [22]. The PANI catalyst was analyzed by XPS for the N 1s, and it showed three types of N, namely, -N (398 eV, proportion 45%), $-NH^-$ (399.4 eV, proportion 45%), and $-N^+$ (402 eV, proportion 10%). Similarly, PANI-Cu showed the presence of -N (397.7 eV, proportion 13%), $-NH^-$ (400 eV, proportion 65%), and $-N^+$ (401.9 eV, proportion 22%). The decrease of imine nitrogen indicates that more of the copper was bound with the PANI via imine nitrogen than the amine nitrogen.

To explore the scope and limitations of the current catalytic protocol for *N*-arylation, several haloarenes and nitrogen-containing heterocycles were allowed to react under the optimized conditions, and the results are summarized in Table 24. It was observed that iodoarenes with electron-withdrawing groups (Table 24, entries 4 and 5) reacted at a faster rate than iodoarenes with electron-donating groups (Table 24, entries 2 and 3). Sterically hindered 2-iodotoluene took a longer time to afford a good yield (Table 24, entry 6). Benzylamine with electron-donating moieties was found to be more active than the simple benzylamine (Table 24, entries 11 and 12). When dibenzylamine was employed, no product formation was observed (Table 24, entry 13). This is may be due to steric hindrance of the

Scheme 13 Possible structure of PANI-Cu

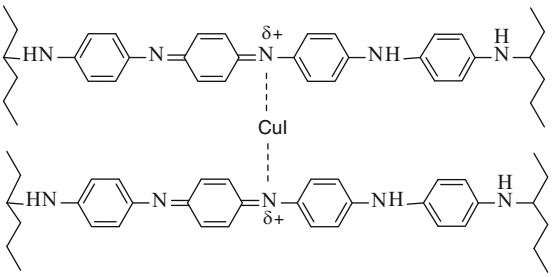


Table 24 *N*-Arylation of N(H)-heterocycles and benzylamines with aryl halides using PANI-Cu[a]

Entry	Aryl halide	N(H)-heterocycle/amine	Time (h)	Yield (%)
1	C_6H5-I	Imidazole	12	92, (90, 89, 90, 87)[b]
2	4-Me-C_6H_4-I	Imidazole	16	85
3	4-MeO-C_6H_4-I	Imidazole	18	82
4	4-MeCO-C_6H_4-I	Imidazole	8	98
5	4-NO_2-C_6H_4-I	Imidazole	6	95
6	2-Me-C_6H_4-I	Imidazole	24	65
7	C_6H_5-I	Benzimidazole	16	84
8	C_6H_5-I	Pyrazole	14	92
9	C_6H_5-I	Pyrrole	12	88
10	C_6H_5-I	Benzylamine	15	90
11	C_6H_5-I	4-Methylbenzylamine	12	92
12	C_6H_5-I	4-Methoxybenzylamine	10	90
13	C_6H_5-I	Dibenzyl amine	24	0
14[c]	C_6H_5-Br	Imidazole	15	90 (80, 65)[b]
15[c]	4-MeCO-C_6H_4-Br	Imidazole	10	95
16[c]	4-NO_2-C_6H_4-Br	Imidazole	8	90
17[c]	4-Me-C_6H_4-Br	Imidazole	18	90
18[c]	4-MeO-C_6H_4-Br	Imidazole	30	88

[a]Reaction conditions: aryl halide (1 mmol), amine (1.2 mmol), PANI-Cu (2.5 mol%), Cs_2CO_3 (3 mmol), CH_3CN (2 mL), 80°C, N_2 atmosphere, isolated yield
[b]Yields after consecutive cycles
[c]DMF used as solvent and reaction temperature 100°C

benzylamine. Bromoarenes react at 100°C in DMF to give good yields of products (Table 24, entries 16–22). The recovered catalyst, after washing with acetone followed by drying at 80°C, was used in the next run. Almost consistent activity was observed over five cycles in the reaction of iodobenzene with imidazole (Table 24, entry 1). The difference between the copper content of the fresh catalyst and the used catalyst (fifth cycle) is only 2.4%.

17 Copper–Aluminum Hydrotalcite

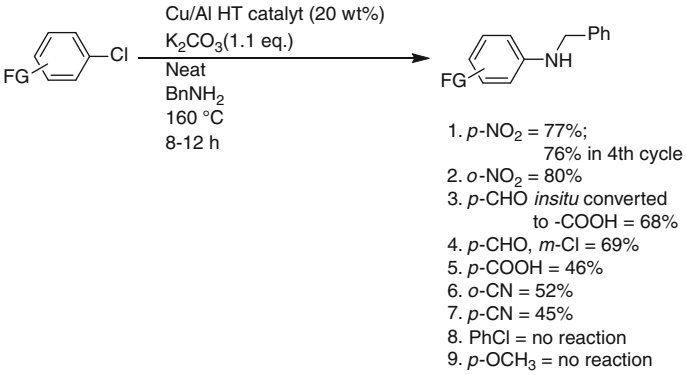
Hydrotalcites are a class of layered materials of current interest. They are represented by a general formula $[M(II)_{1-x}\ M(III)_x\ (OH)_2]^{n-}\ A^{n-}{}_{x/n.y}\ H_2O$, where M(II) and M(III) are divalent and trivalent cations such as Cu^{2+}, Mg^{2+}, and Al^{3+}, respectively. The compensating anions may be OH^-, Cl^-, $NO_3{}^-$, $CO_3{}^{2-}$, etc. (see for a recent review [66]). Copper-containing LDHs act as the best heterogeneous catalysts for the production of substituted amines via Ullmann-type cross-coupling reactions of unreactive aryl chlorides with aryl and aliphatic amines under ligand-free conditions [67]. This method tolerates a variety of functional groups and does not require any additive (Schemes 14 and 15).

Chlorobenzenes with electron-withdrawing groups substituted at *para* and *ortho* provided moderate to good yields (Scheme 14, entries 1–7). In the case of 2,4-dichlorobenzaldehyde, the chloro group at the *ortho* position was *N*-arylated (Scheme 14, entry 4). The C–N coupling product bearing an aldehyde group is oxidized to an acid (Scheme 14, entry 3) while in the case of 2,4-dichlorobenzaldehyde, no oxidation of the aldehyde group occurred (Scheme 14, entry 3 vs. 4). Electron-neutral and electron-donating chloroarenes such as chlorobenzene and 4-chloroanisole (Scheme 14, entries 8 and 9) did not form any coupled products under these conditions.

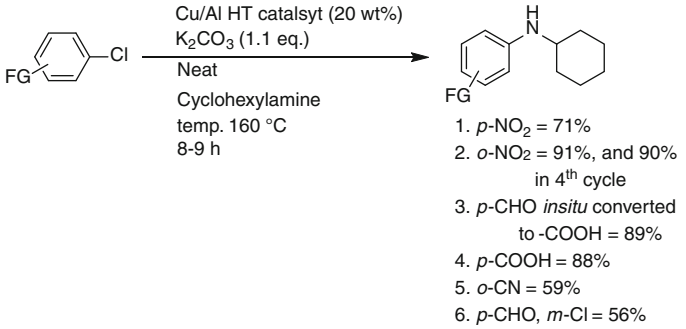
This protocol was successfully applied to cycloalkylamines (Scheme 15) using the amine as self-solvent, with good isolated yields and negligible amount of Cu leaching. Cu/Al-HT was recovered quantitatively by simple filtration and reused. Consistent activity is observed even after the fourth cycle (91% in the first cycle and 90% in the fourth cycle) (Scheme 15, entry 1) for the coupling reaction between *o*-nitrochlorobenzene and cyclohexylamine. A similar observation was made when a C–N coupling product bearing an aldehyde in the *para*-position was oxidized to an acid, while in the case of 2,4-dichlorobenzaldehyde, no oxidation of the aldehyde group occurred (Scheme 15, entry 3 vs. 6).

In 2009, Sreedhar et al. [68] expanded the scope of amination with various amines and aryl halides using Cu/Al-HT. In this study, the authors had chosen a coupling reaction between octylamine and 2-nitro-chlorobenzene (Scheme 16) with a catalytic amount of Cu catalyst under ligand-free conditions. From Table 25, it can be seen that Cu/Al-HTB is the best catalyst among the catalysts screened (Table 25, entry 6). The catalysts screened were (Cu-(HAP) copper hydroxyapatite, Cu-(FAP) copper flouroapatite, and Cu/Al-HTs (HT, Hydrotalcite of Cu/Al in different ratios) Cu/Al-HTA, 3:1(Cu: Al); Cu/Al-HTB, 2.5:1; and Cu/Al-HTC, 2:1)

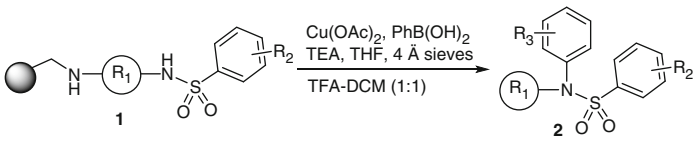
The scope of the methodology was examined on many aryl chlorides using the Cu/Al-HTB as catalyst. Selected examples are listed in Table 26. Although this method works for variety of amines, some of the aryl chlorides, for example chlorobenzene and 2-methyl chlorobenzene, did not participate in the coupling of cyclopentyl and octylamine under the same reaction conditions. As can be seen, aryl chlorides with electron-donating and electron-withdrawing groups coupled with equal ease in many cases.



Scheme 14 Cu/Al LDHs-catalyzed C–N bond forming reactions beween benzylamine and chloro arenes



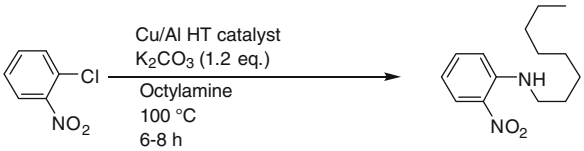
Scheme 15 Cu/Al LDHs-catalyzed C–N bond forming reactions beween cyclohexylamine and chloroarenes



Scheme 16 *N*-Arylation of solid-supported sulfonamides with phenylboronic acid catalyzed by $Cu(OAc)_2$

Using the same catalyst system, Cu/Al-HTB, the scope was extended in the case of heterocyclic amines such as imidazole, benzimidazole, pyrazole, and morpholine with aryl chlorides, bromides, and iodides in good to excellent isolated yields. Selected examples are listed in Table 27. However, some of the chlorides either participated sluggishly or were unreactive towards coupling reactions under the same reaction conditions. Many examples of the methodology were studied for coupling partners on both sides.

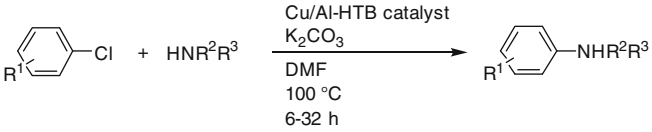
Table 25 Cu/AI LDHs-catalyzed C–N bond forming reactions between octylamine and 2-nitro chlorobenzene[a]



Entry	Catalyst[b]	Yield (%)
1	Cu(HAP)	n.r.[c]
2	Cu(FAP)	n.r.[c]
3	Cu(II)-NaY	32
4	SiO_2-$Cu(OAc)_2$	36
5	Cu/Al-HTA	65
6	Cu/Al-HTB	96,97[d]
7	Cu/Al-HTC	90

[a]1-Chloro-2-nitrobenzene (1.0 mmol), amine (1.2 mmol), catalyst (2.5 mol%), K_2CO_3 (1.2 mmol) DMF (2.0 mL) stirred at 100°C
[b]Cu-(HAP), copper hydroxyapatite; Cu-(FAP) copper flouroapatite, Cu/Al-HTs (HT, Hydrotalcite of Cu/Al in different ratios) Cu/Al-HTA, 3:1(Cu: Al); Cu/Al-HTB, 2.5:1; and Cu/Al-HTC, 2:1)
[c]n.r = no reaction
[d]Isolated yield after fifth cycle

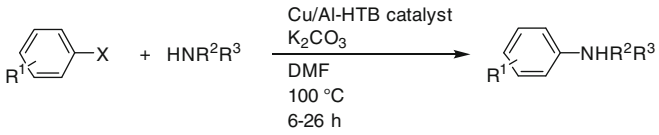
Table 26 Coupling of aryl chlorides with amines catalyzed by Cu/Al-HTB[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)
1	2-Me	H	n-C_8H_{17}	32	42
2	4-COOH	H	n-C_8H_{17}	8	97
3	4-Cl-2-CHO	H	n-C_8H_{17}	8	95
4	H	H	Cyclopentyl	16	n.r.[b]
5	2-Me	H	Cyclopentyl	20	n.r.[b]
6	4-COOH	H	Cyclohexyl	14	73
7	4-Me	$-(CH_2)_5^-$		28	52
8	4-I	$-(CH_2)_5^-$		9	81

[a]Aryl chloride (1.0 mmol), amine (1.2 mmol), catalyst (2.5 mol%), K_2CO_3 (1.2 mmol), DMF (2.0 mL) stirred at 100°C
[b]n.r = no reaction

Table 27 Coupling of aryl halides with N(H) heterocyclic amines catalyzed by Cu/Al-HTB



Entry	X	R^1	$-NR^2R^3$	Time (h)	Yield (%)[a]
1	Cl	H	Imidazol-1-yl	18	n.r.[b] (92, 80)
2	Cl	4-Me	Imidazol-1-yl	12	27 (89)
3	Cl	4-NO_2	Imidazol-1-yl	8	90 (95)
4	Cl	CN	Imidazol-1-yl	12	95
5	Cl	2-CF_3	Imidazol-1-yl	7	97
6	Br	4-Cl	Imidazol-1-yl	8	98
7	I	4-COMe	Benzimidazol-1-yl	15	88
8	I	4-OMe	Benzimidazol-1-yl	18	85
9	L	4-OMe	Pyrazol-1-yl	20	80
10	Cl	H	Morpholino	26	n.r.[b]

[a]Isolated yields in parenthesis are of iodo- and bromoarenes, respectively
[b]n.r = no reaction

18 C–N Bond Forming Cross-Coupling Reactions Using Arylboronic Acids

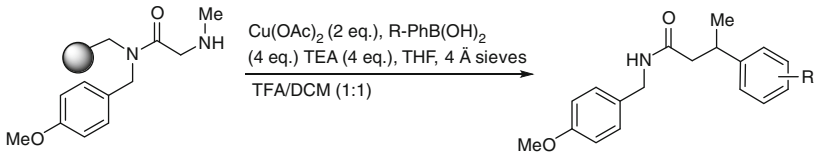
Significant improvement in copper-catalyzed *N*-arylation is realized after the introduction of arylboronic acids as the aryl donors independently by Lam et al. [69, 70], Chan et al. [71], and Evans et al. [72] utilizing stoichiometric amount of $Cu(OAc)_2$.

Combs et al. [73] reported the first examples of polymer-supported aryl-heteroaryl C–N cross-coupling reactions and dramatically decreased reaction times upon microwave irradiation. The methodology provides easy access to *N*-arylated heterocycles from heterocycles bearing an N–H bond and readily available arylboronic acids in the presence of copper(II) acetate and pyridine.

Later Combs et al. [74] reported a general and mild method for the *N*-arylation of sulfonamides on solid supports. Copper acetate, triethylamine-mediated coupling of arylboronic acids at room temperature to solid-supported sulfonamides gave good to excellent yields of the desired *N*-arylsulfonamides. Sulfonamide bond cleavage of the *o*, *p*-dinitrobenzene(*N*-aryl) sulfonamide provides a route to *N*-arylated secondary amine products.

N-arylated primary and secondary aliphatic amines are important substituents in many biologically active compounds. The predominance of arylpiperidines and arylpiperazines in CNS drugs is particularly noteworthy [75–77].

Copper acetate, triethylamine-mediated CN cross-coupling reaction of arylboronic acids at room temperature to solid-supported primary and secondary amines gave good to excellent yields of the desired *N*-arylated products [78]. This method demonstrates the generality of this methodology for the solid-phase synthesis of combinatorial libraries (Scheme 17).



Scheme 17 *N*-Arylation of solid-supported secondary amines with arylboronic acids catalyzed by $Cu(OAc)_2$

Chiang et al [79] reported the preparation of polymer-supported copper complex by immobilization of copper on to modified Wang resin. This catalyst is effective in cross-coupling reactions between N- or O-containing substrates and arylboronic acids. The copper catalyst is air stable and can be recycled with minimal loss of activity. A series of N-containing substrates and phenols were tested (Table 28), and the reactions were complete after 24 h, with yields varying between 48% and 93%. The reaction is not general for amides and only starting material was recovered. (entries 8 and 9). Both electron-withdrawing and –donating phenols worked well (entries 11–13) and the phenolic OH group can be arylated in the presence of an amide group (entry 14).

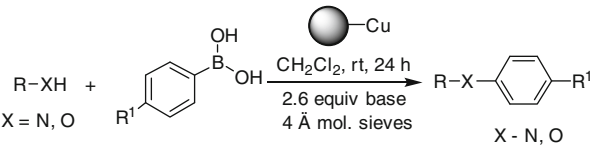
We have reported [80] the coupling of imides with various arylboronic acids using Cu–Al hydrotalcite in refluxing methanol with continuous bubbling of air through the mixture without employing base or ligand to afford *N*-arylated products in very good yields (Scheme 18, Table 29). Cu–Al hydrotalcite is used for four cycles successfully with minimal loss of activity.

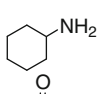
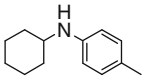
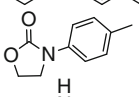
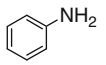
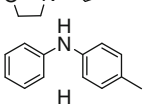
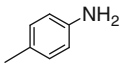
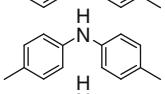
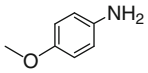
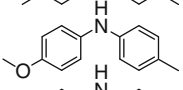
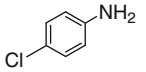
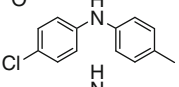
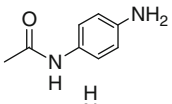
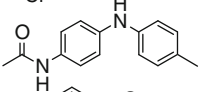
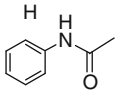
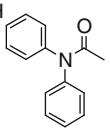
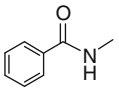
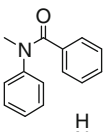
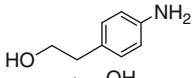
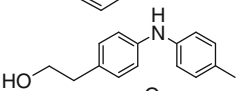
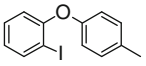
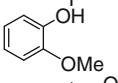
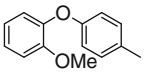
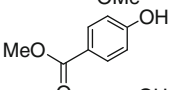
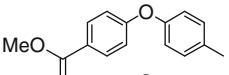
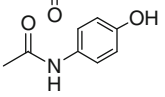
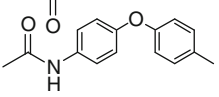
Wang Lei et al. [81] reported the Ar–N coupling of arylboronic acids with imidazoles by using 3-(2-aminoethylamino)propyl functionalized silica gel immobilized copper(II) catalyst (10 mol%) in methanol without any additives and bases. The reactions generated the corresponding cross-coupling products in good yields. Furthermore, silica-supported copper can be recovered and recycled by a simple filtration procedure and used for five consecutive trials without decrease in activity.

We reported [82] the *N*-arylation of imidazoles and amines with arylboronic acids with copper-exchanged fluorapatite (Cu-FAP) in methanol at room temperature. The products *N*-arylimidazoles and *N*-arylamines were isolated in good to excellent yields. A variety of arylboronic acids were converted to the corresponding *N*-arylimidazoles and *N*-arylamines, demonstrating the versatility of the reaction.

In an effort to evolve a better catalytic system, various catalysts were screened for *N*-arylation of imidazole and phenylboronic acid in methanol at room temperature. The results are summarized in Table 30. Homogeneous Cu catalyst, $Cu(OAc)_2$ and CuI gave very low yield (Table 30, entries 1–2). Copper-exchanged hydroxyapatite (CuHAP) also gave a very low yield (Table 30, entry 4), while CuFAP afforded a very good yield (Table 30, entry 5). Moreover, the controlled *N*-arylation reaction conducted under identical conditions devoid of CuFAP gave no coupled product despite prolonged reaction time (Table 30, entry 6). CuFAP was recovered quantitatively by simple filtration and was reused several times, with consistent

Table 28 Copper-mediated coupling of N- and O-containing compounds with arylboronic acids using the generalized conditions[a]

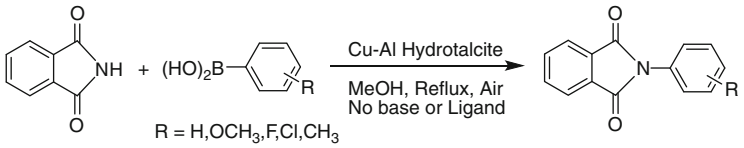


Entry	Starting material	R^1	Product	Isolated yield (%)
1		Me		54
2		Me		48
3		Me		66[b]
4		Me		93[b]
5		Me		78
6		Me		54[b]
7		Me		55[b]
8		H		0
9		H		0
10		Me		75[b]
11		Me		56[b,c]
12		Me		83[b,c]
13		Me		67[c]
14		Me		50[c]

[a]All reactions were run using 1.5 equiv of catalyst, 3 equiv of arylboronic acid, and NEt_3 as the base

[b]Recycled catalyst

[c]Performed with 4 equiv of boronic acid



Scheme 18 *N*-Arylation of pthalimide with arylboronic acids using Cu–Al hydrotalcite

activity even after the fourth cycle (Table 30, entry 5). The absence of copper in the filtrate was confirmed by Atomic Absorption Spectroscopy which confirms no leaching of copper during the reaction and provides evidence for heterogeneity throughout the reaction.

Our method was successfully amenable to a wide range of arylboronic acids, allowing preparation of *N*-arylimidazoles and *N*-arylbenzimidazoles in high yield and the results are shown in Table 31. Phenylboronic acids with an electron-donating group afforded better yields (Table 31, entries 2–4) than with electron-withdrawing groups (Table 31, entries 5–7). Similar observation was made when benzimidazoles were used in place of imidazoles to obtain the corresponding *N*-arylbenzimidazoles (Table 31, entries 8–10), but the reactions took longer time compared to imidazoles.

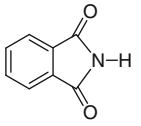
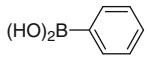
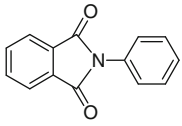
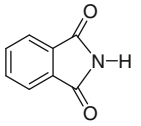
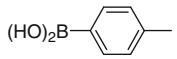
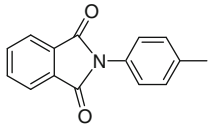
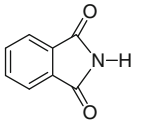
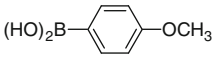
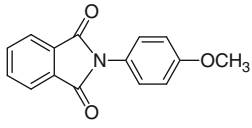
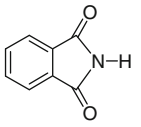
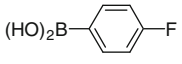
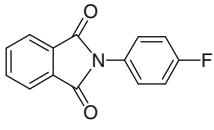
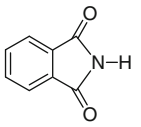
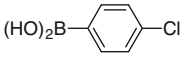
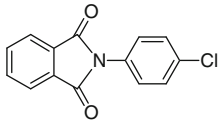
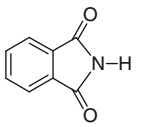
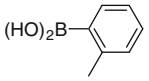
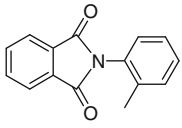
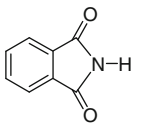
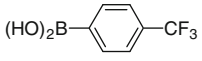
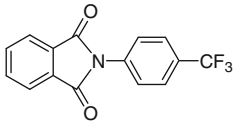
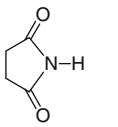
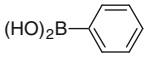
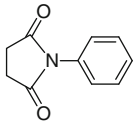
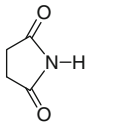
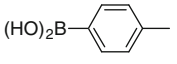
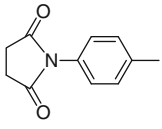
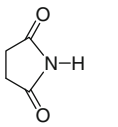
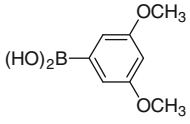
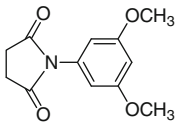
After achieving excellent results with imidazoles, we further applied this catalytic system for the *N*-arylation of aromatic amines and aliphatic amines. The results are shown in Table 32 and Table 33. Table 32 shows the results of *N*-arylation of aniline with several arylboronic acids.

It is clear from Table 32 that *N*-arylation proceeds very effectively and afforded the corresponding *N*-arylated products in good to excellent yields under very mild conditions. No spectacular electronic effects were observed in *N*-arylation of aniline; only a slight decrease in the reaction rate was noted with the 3-nitrophenylboronic acid. Next we examined the *N*-arylation of various primary amines such as aliphatic, cyclohexyl and heterocyclic amines with phenylboronic acid using CuFAP catalyst at room temperature, and the results are listed in Table 33. All the reactions proceeded very efficiently at room temperature and yielded the corresponding *N*-arylated products. It was interesting to note that the formation of the conceivable diarylated product is not observed in our conditions.

We [83] reported the *N*-arylation of nitrogen heterocycles with a variety of arylboronic acids to afford the corresponding coupled products in good to excellent yields without using external ligands or additives as promoters using cellulose-supported Cu(0) catalyst. The catalyst was recovered by simple filtration and reused for several cycles.

Preliminary experiments are carried out by taking phenylboronic acid as a test molecule for the *N*-arylation of imidazole (Scheme 19). In order to determine the best reaction medium, we tested different solvents and methanol is found to be the best solvent for the *N*-arylation of imidazole (98%). The nature of base has a pronounced effect in these reactions. Reaction of imidazole with phenylboronic acid in presence of K_2CO_3 and KO^{t}Bu gave no coupled product, while

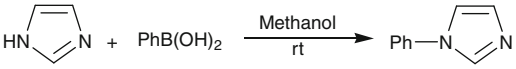
Table 29 *N*-Arylation of imides with boronic acids by Cu–Al hydrotalcite[a]

Entry	Imide	Aryl boronic acid	Time [h]	Product	Yield [%][b]
1			5		91
2			6		90
3			6		90
4			6		87
5			6		91
6			7		87
7			7		88
8			4		91
9			4		90
10			4		89

[a]Reaction conditions: phthalimide (1.2 mmol), arylboronic acid (1 mmol), catalyst (0.15 g) in refluxing methanol

[b]Isolated yields after chromatography

Table 30 *N*-Arylation of imidazoles using different copper catalysts[a]



Entry	Catalyst	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2$	6	25
2	CuI	6	30
3	Cu power	6	25
4	CuHAP	6	20
5	CuFAP	6	88, 82[c]
6	None	24	0

[a]Conditions: imidazole (1.2 mmol), phenylboronic acid (1 mmol, Methanol (3 mL), rt
[b]Isolated yields
[c]Yield after fourth cycle

triethylamine and pyridine provided good yield. However, we continued the reactions in triethylamine instead of pyridine because of toxicity reasons.

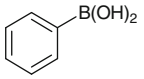
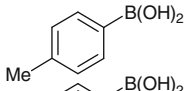
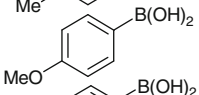
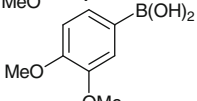
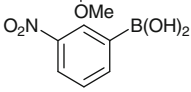
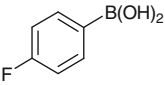
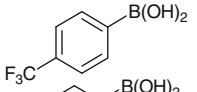
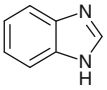
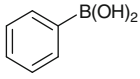
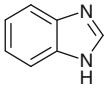
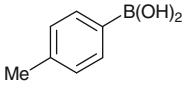
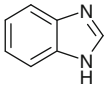
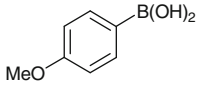
The reaction temperature plays an important role, the reaction at room temperature afforded 80% of the coupled product after 18 h (87%, 24 h), while the duration of the reaction is drastically decreased to 2.5 h under reflux conditions to provide quantitative yields (Table 34, entry 1). After optimizing the reaction conditions**,** different arylboronic acids were coupled with imidazole using CELL-Cu(0) catalyst, triethylamine as base and methanol as solvent under refluxing conditions, and the results are summarized in Table 34. Various structurally and electronically diverse arylboronic acids gave the corresponding *N*-arylated products in high yields. However, methyl-, acetyl-, and methoxy-substituted boronic acids required longer reaction times (Table 34, entries 5, 6 and 8) compared to chloro-, fluoro-, and trifluoromethyl-substituted boronic acids (Table 34, entries 2, 3 and 4). *o*- and *p*-substituted arylboronic acids were equally effective for the coupling with imidazoles (Table 34, entries 7 and 8).

Later we reported [84] the *N*-arylation of imidazoles, imides, amines, amides, and sulfonamides with arylboronic acids using a recyclable $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system in the absence of a base or additive to afford the corresponding *N*-arylated products in good to excellent yields.

Similarly, the cross-coupling reaction between imidazole and phenylboronic acid was performed with different ILs, and the results are grouped in Fig. 4. Among the ILs tested, hydrophilic [bmim][BF_4] was found to be superior (95% yield) than that of hydrophobic [bmim][PF_6] (80% yield), whereas the cross-coupling reaction was not successful in other molten salts such as *n*-tetrabutylammonium bromide (*n*-Bu_4Br) and 1-*n*-butyl-3-methylimidazolium bromide, [bmim][Br], under similar reactions conditions. These results clearly indicate that both the cation and anion play a significant role in this cross-coupling reactions.

Under optimized reaction conditions, a wide range of structurally diverse arylboronic acids were coupled with imidazole (Table 35, entries 1–7) using

Table 31 *N*-Arylation of imidazoles with different arylboronic acids[a]

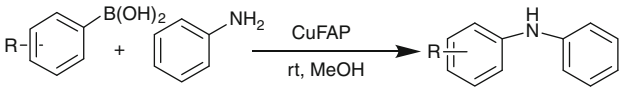
Entry	Imidazole	Arylboronic acid	Time (h)	Yield (%)[b]
1			5	88 (25)[c] 80[d]
2			4	86
3			5	90
4			5	85
5			8	78
6			5	85
7			8	80
8			12	88 (25)[c] 83[d]
9			12	85
10			12	86

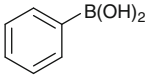
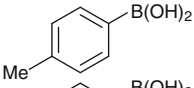
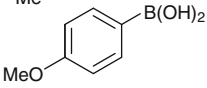
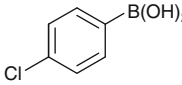
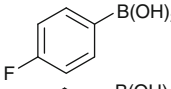
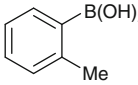
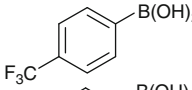
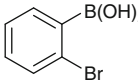
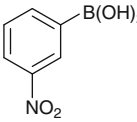
[a]Reaction conditions: imidazole (1.2 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL), r.t
[b]Isolated yields
[c]$Cu(OAc)_2$ homogeneous reaction under identical conditions
[d]Yield after fourth cycle

$Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system to produce the corresponding substituted *N*-aryl imidazoles in good to excellent yields. Finally, upon completion of the reaction, the ionic liquid phase containing [bmim][BF_4] and catalyst was almost quantitatively recovered by simple extraction of the product with Et_2O. The recovered ionic liquid phase containing the catalyst was reused for several cycles with consistent activity (Table 35, entry 1).

In an endeavor to expand the scope of the above methodology, the catalytic system was applied to imides, amines, amides, and sulfonamides. A series of substituted arylboronic acids were coupled with phthalimide (Table 36, entries

Table 32 *N*-Arylation of aniline with various arylboronic acids[a]



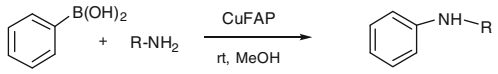
Entry	Arylboronic acid	Time (h)	Yield(%)[b]
1		3	90
2		4	93
3		4	90
4		3	87
5		3	87
6		3	89
7		4	90
8		2	91
9		6	79

[a]Conditions: aniline (1.5 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL)
[b]Isolated yields

1–6) and succinamide (Table 36, entries 7 and 8) under the generalized reaction conditions to afford the corresponding *N*-aryl imides in good to excellent yields.

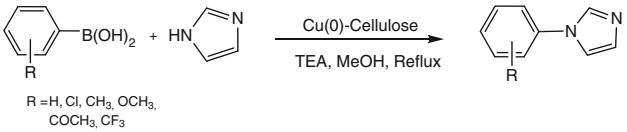
Similarly, aniline was subjected to cross coupling with substituted arylboronic acids and *o*-, *p*-substituted anilines with phenylboronic acid, and the corresponding *N*-aryl amines were obtained in satisfactory yields (Table 37, entries 1–9). The coupling of alkylamines with phenylboronic acid gave the *N*-alkyl anilines in moderate yields (Table 37, entries 10–14). However, the reaction of amides and sulfonamides with phenylboronic acid afforded the corresponding products albeit in lower yields (Table 37, entries 15 and 16).

Table 33 *N*-Arylation of amines with phenylboronic acid[a]



Entry	Amines	Time (h)	Yield (%)[b]
1	*n*-Butylamine	3	93
2	*n*-Hexylamine	4	90
3	*n*-Heptylamine	4	92
4	*n*-Octylamine	4	95
5	Benzylamine	2	90
6	Cyclohexylamine	3	88
7	Allylamine	4	87
8		2	90

[a]Conditions: amine (1.5 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL)
[b]Isolated yields



Scheme 19 *N*-Arylation of imidazole with arylboronic acids using cellulose-supported Cu(0)

In general, the reactions are facile, clean for the synthesis of a variety of *N*-arylated products. Several functional groups such as Cl, CF_3, F, CH_3, $COCH_3$, and OCH_3 remain unaffected under the present reaction conditions.

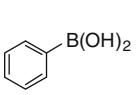
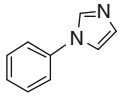
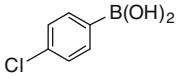
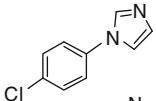
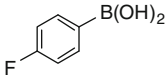
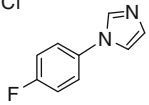
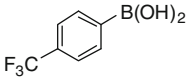
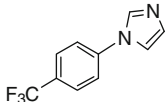
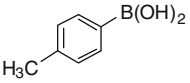
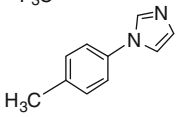
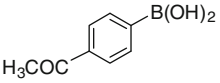
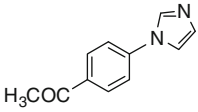
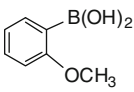
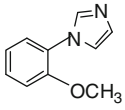
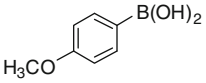
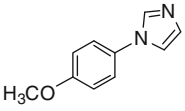
We have used silica tethered copper complexes as reusable catalysts in the *N*-arylation of N(H)-heterocycles and benzylamines with arylboronic acids [85] (Table 38). *N*-arylated products were isolated in good to excellent yields, demonstrating the versatility of the protocol. Moreover the catalyst was easily recovered by simple filtration and reused for several cycles with consistent activity.

19 Recently Reported Copper Heterogeneous Systems

Recently Nageswar et al. reported that copper iodide along with *trans*-1,2-diaminocyclohexane as a ligand (reported by Buchwald in homogeneous conditions) acts in water, as a simple, efficient, cheap, and recyclable catalytic system (Scheme 20) [86].

N-heterocycles like indole, substituted indoles, pyrazole, imidazole, benzamide, morpholine, benzimidazole, thiobenzamide, aniline, benzylaniline, octylaniline, heptylaniline, and cyclohexylaniline couple with aryl iodides and bromides in the

Table 34 *N*-Arylation of imidazole with various arylboronic acids using CELL-Cu(0) catalyst[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			2.5	98 87[c] 80[d]
2			2.5	82
3			2.5	87 83[c]
4			2.5	93
5			4.0	95
6			5.0	80 77[c]
7			5.0	83
8			5.0	86

[a]Reaction conditions: imidazole (1 mmol), triethylamine (2 mmol), CELL-Cu(0) catalyst (0.025 g), phenylboronic acid (1 mmol), methanol (5 ml), reflux
[b]Isolated yields
[c]Yield after fourth cycle
[d]Reaction performed at room temperature for 18 h

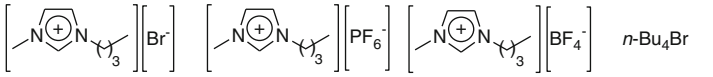
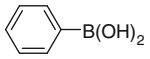
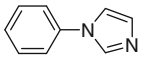
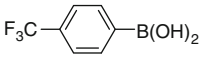
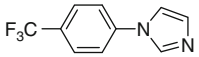
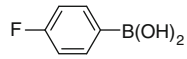
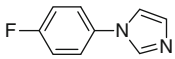
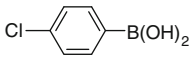
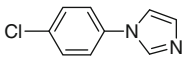
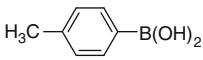
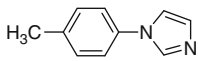
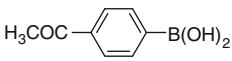
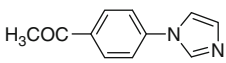
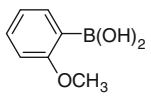
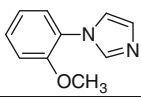


Fig. 4 Screening of ILs for the *N*-arylation of imidazole (1 mmol) with phenylboronic acid (1 mmol) using 10 mol% $Cu(OAc)_2 \cdot H_2O$ at 70°C in 3.0 h

Table 35 *N*-Arylation of imidazole with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system[a]

Entry	Arylboronic acid	Time (h)	Product	Yield (%)[b]
1		3.0		95 (90)[c]
2		4.0		90
3		4.0		85
4		4.0		85
5		4.5		88
6		5.0		80
7		5.0		80

[a]Reaction conditions: imidazole (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), [bmim][BF_4] (1 mL)
[b]Isolated yield
[c]Isolated yield after fourth cycle

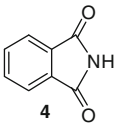
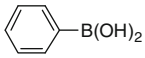
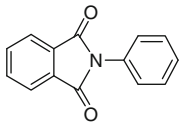
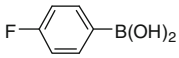
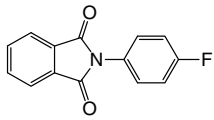
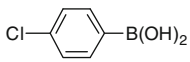
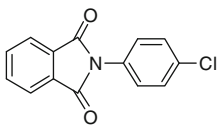
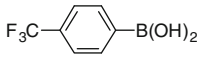
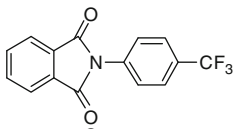
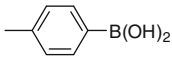
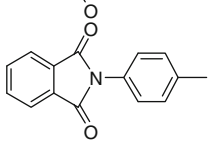
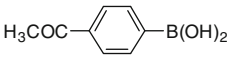
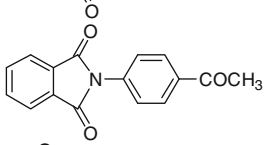
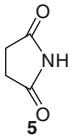
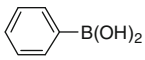
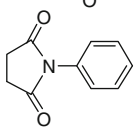
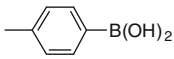
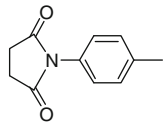
presence of K_2CO_3 as base and water as solvent to give the *N*-arylated products in good to excellent yields. For aryl iodides, the reaction proceeded at 80°C, whereas a higher reaction temperature of 95–100°C was needed to activate aryl bromides. Ortho-substituted aryl iodides afforded poor yields of the product owing to steric reasons.

This copper catalyst system along with the aqueous phase were recyclable up to four times without loss of catalytic activity, and FT-IR spectrum on the used catalyst did not indicate any copper oxide formation.

Chaudhari et al. reported encapsulation of copper complexes in zeolite-Y and MCM-41 or by tethering of copper complexes on various supports like zeolite-Y, silica, charcoal, or clay [87]. These materials were then characterized by a plethora of sophisticated analytical techniques like EPR, diffused reflectance UV–vis, XRD, IAS, ICPES, SEM, and TEM and employed for the amination of aryl iodide to synthesize diphenyl aniline or triphenyl amine (Scheme 21).

For encapsulated catalysts, amination reaction was carried out in a high pressure autoclave containing aniline, iodobenzene, catalyst, and potassium *tert*-butoxide (KO*t*-Bu) at 408 K for 14 h. For tethered catalysts, the amination reaction was carried out in a two necked flask under reflux at 385 K for 10–12 h.

Table 36 *N*-Arylation of imides with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system[a]

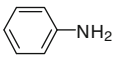
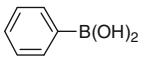
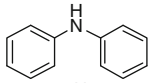
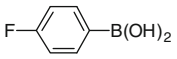
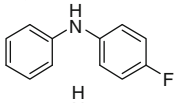
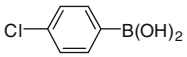
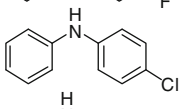
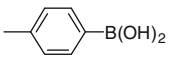
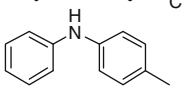
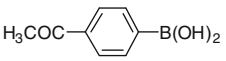
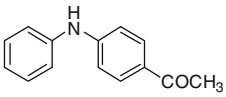
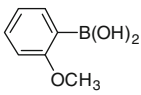
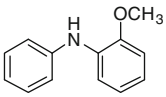
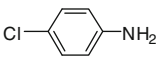
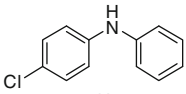
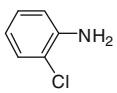
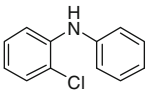
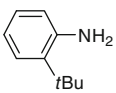
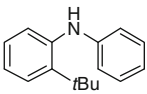
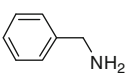
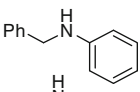
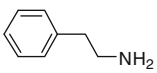
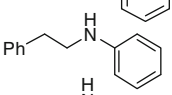
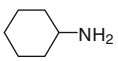
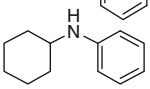
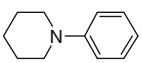
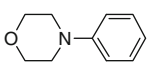
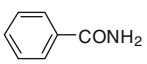
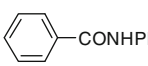
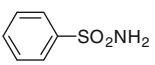
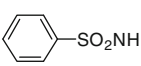
Entry	Imine	Arylboronic acid	Time (h)	Product	Yield (%)[b]
1	 **4**		3.0		92 85[c]
2	**4**		5.0		85
3	**4**		4.0		90
4	**4**		5.0		88
5	**4**		6.0		90
6	**4**		7.0		80
7	 **5**		4.0		90
8	**5**		5.0		88

[a]Reaction conditions: imide (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), [bmim][BF_4] (1 mL)
[b]Isolated yield
[c]Isolated yield after fourth cycle

The results of amination reaction as obtained by different copper catalysts are tabulated in Table 39.

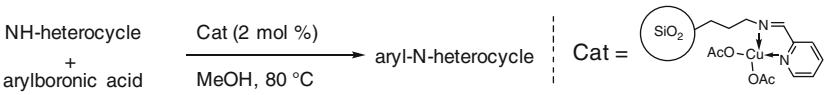
Recyclability and stability studies were carried out for both encapsulated and tethered copper catalysts. For encapsulated Cu(Phen)–Y catalyst, the catalyst

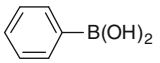
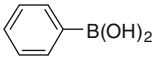
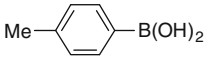
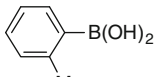
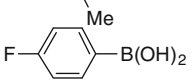
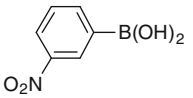
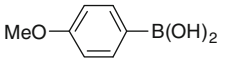
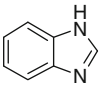
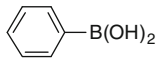
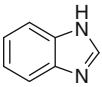
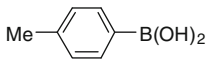
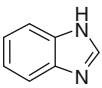
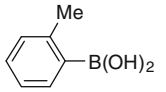
Table 37 *N*-Arylation of various N nucleophiles with various arylboronic acids using $Cu(OAc)_2{\cdot}H_2O$/[bmim][BF_4] system[a]

Entry	Amine	Arylboronic acid	Time (h)	Product	Yield (%)[b]
1	 **6**	 **7**	4.0		75 (70)[c]
2	**6**		4.0		72
3	**6**		4.0		70
4	**6**		4.5		75
5	**6**		5.0		65
6	**6**		5.0		68
7		**7**	5.0		70
8		**7**	5.0		65
9		**7**	5.0		60
10		**7**	4.0		60
11		**7**	4.0		60
12		**7**	5.0		55
13		**7**	5.0		60
14		**7**	5.0		60
15		**7**	6.0		30
16		**7**	6.0		30

[a]Reaction conditions: amine (1 mmol), arylboronic acid (1 mmol), $Cu(OAc)_2$ (10 mol%), [bmim]BF_4 (1 mL)
[b]Isolated yield
[c]Isolated yield after fourth cycle

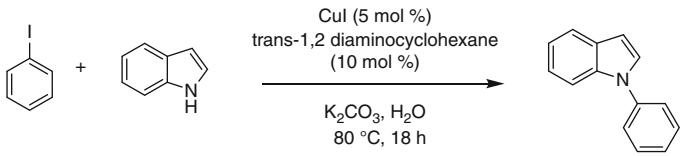
Table 38 *N*-Arylation of N(H)-heterocycles with arylboronic acids using silica tethered Cu-complex[a]



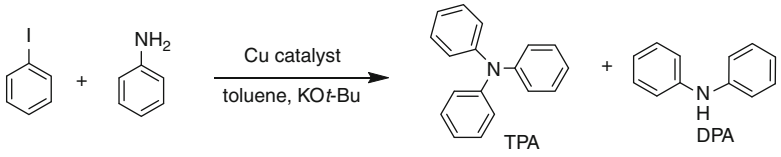
Entry	NH-heterocycle	Arylboronic acid	Time(h)	Yield /%
1			40	92[b]
2			2	91, 88[c]
3			1	90
4			1.5	88
5			2.5	90
6			5	92
7			1	93
8			2.5	90
9			2	94
10			3	90

[a]*Reaction conditions*: N(H)-heterocycle (1 mmol), arylboronic acid (1.2 mmol), Cat (2 mol%), MeOH (2 mL), 80°C, air
[b]Room temperature
[c]Yields after fifth cycle

activity and selectivity remained constant even after five reaction cycles. Encapsulated Cu(Bipy)-MCM-41 lost its catalytic activity with every reuse indicating leaching of copper from the support. This is justified from the fact that wide openings of pore and channel diameter of MCM-41 (~35 A˚˜) results in some washing of copper complex under the reaction conditions. Thus Cu(Bipy)-MCM-41 loses its heterogeneity and performs as a homogeneous catalyst during the course of the reaction. Recyclability experiments on tethered Cu(Phen)(PPh_3)Br-PTA-Y



Scheme 20 Copper-catalyzed C–N cross coupling



Scheme 21 Amination of aryl iodide using copper catalyst

catalyst revealed that the catalyst was stable even after fifth recycle, and no leaching of copper or tungsten occurred. The catalyst was found to give a higher turnover number (TON) of 69 compared to its homogeneous counterparts (TON 27).

The authors also presented a plausible reaction pathway for the amination of aryl iodide catalyzed by zeolite-supported copper complex, wherein they experimentally demonstrated the formation of PhNHK type of salt as an intermediate.

The various types of immobilized copper complexes described in this work aim to eliminate the problems encountered in homogeneous amination of aryl halides. The catalysts displayed good activity and recyclability depending upon the nature of the support.

Islam et al. reported, in 2011, the synthesis of a heterogeneous polystyrene-supported Cu(II) catalyst (Cu-PAR) for the *N*-arylation of N–H heterocycles with aryl halides as well as arylboronic acids to afford the corresponding coupled products in good to excellent yields [88].

Cu-PAR catalyst was employed for the *N*-arylation of imidazole with various aryl halides under N_2 atmosphere at 100°C using DMSO as the solvent and K_2CO_3 as the base (Scheme 22). Iodoarenes with electron-withdrawing groups reacted faster than that with electron-donating groups. Sterically hindered 2-iodotoluene afforded good yield of the corresponding of the *N*-arylated product albeit at longer reaction time (20 h). Bromoarenes as well as other N-containing cycles such as benzimidazole, pyrazole, and pyrrole also reacted well under these reaction conditions.

Cu-PAR catalytic system was also found to be applicable for *N*-arylation of N–H heterocycles with arylboronic acids (Scheme 23) under mild conditions in less time. Methanol was found to be the best solvent as other solvents gave trace amount of the coupled product under identical conditions. No organic co-solvent or additive or base was needed to promote the reaction. Arylboronic acids with electron-withdrawing groups reacted at a slower rate yielding moderate to good yield of the corresponding product. 3-nitrophenylboronic acid, a relatively tough substrate, was also found to be reactive under these reaction conditions. Cu-PAR catalytic

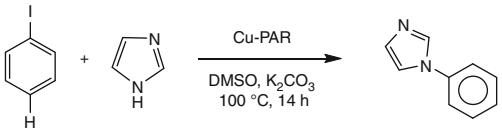
Table 39 Amination of iodobenzene by aniline using heterogenized copper complexes

Sr. No.	Catalyst	Aniline Conv (%)	DPA selectivity (%)	DPA yield (%)	TPA yield (%)	DPA/TPA ratio
[a]Cu(Phen or Bipy) complex encapsulated in NaY						
[b]1	Na–Y	40	58	23	8	2.9
[c]2	4% Cu–Y	60	69	41	7	5.9
[b]3	1% Cu(Phen)–Y	85	80	68	4	17.0
[c]4	4% Cu(Phen)–Y	88	84	74	3	24.7
[c]5	4% Cu(Bipy)–Y	89	87	78	2	39.0
[d]6	8% Cu(Phen)–Y	90	66	60	15	4.0
[e]Cu(Bipy) complex encapsulated in MCM-41						
7	MCM-41	18	16.6	3	6	0.5
8	4% Cu-MCM-41	32	28.1	9	15	0.6
9	4% Cu(Bipy)-MCM-41	80	6.3	5	71	7.0
[f]4% Cu(Phen or neocup)(PPh3) Br complex tethered catalyst						
10	Cu(Phen)(PPh_3) Br-PTA-Y	86	10.5	9	72	0.1
11	Cu(neocup)(PPh_3)Br-PTA-Y	70	15	10.5	60	0.2
12	Cu(Phen)(PPh_3)Br-PTA-alumina	78	10.2	8	55	0.15
13	Cu(Phen)(PPh_3)Br-PTA-titanium oxide	74	17.6	13	26	0.5
14	Cu(Phen)(PPh3)Br-PTA-clay	80	8.8	7	32	0.2
15	Cu(Phen)(PPh3)Br-PTA-charcoal	50	48	24	25	0.96
16	Cu(Phen)(PPh3)Br-PTA-silica	56	35.7	20	22	0.9

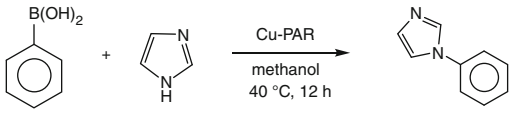
[a]Iodobenzene: 2.0 mmol; aniline: 2.1 mmol; KO*t*-Bu: 6.4 mmol; toluene: 20 ml; temperature 408 K; time: 14 h
[b]Catalyst 900 mg
[c]Catalyst 225 mg
[d]Catalyst 115 mg
[e]Iodobenzene: 2.0 mmol; aniline: 2.1 mmol; KO*t*-Bu: 6.4 mmol; 4% Cu(Bipy)-MCM-41: 225 mg; toluene: 20 ml; temperature: 408 K; time: 14 h
[f]Iodobenzene: 8.2 mmol; aniline: 4.0 mmol; KO*t*-Bu: 16.0 mmol; 4% Cu catalysts: 550 mg; toluene: 20.0 ml; naphthalene (IS); 0.25 g; temperature: 385 K; time: 10 h

system also worked well for imide, amide, phthalimide, and sulfonamide yielding decent yield of the *N*-arylated product.

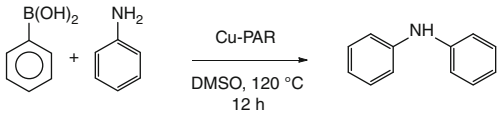
The scope of this catalytic system was even extended for the amination of aromatic amines with boronic acids using DMSO as solvent and KOH as base at



Scheme 22 Cu-PAR-catalyzed *N*-arylation of imidazole with iodobenzene



Scheme 23 Cu-PAR-catalyzed *N*-arylation of imidazole with phenyl-boronic acid



Scheme 24 Cu-PAR-catalyzed amination of aniline with phenylboronic acid

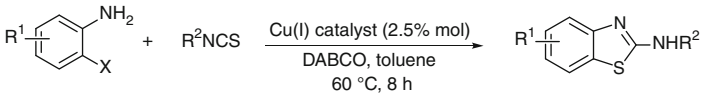
120°C for 12 h (Scheme 24). The amination reaction proceeded smoothly and good to excellent yields of the products were recorded in all cases.

Cu-PAR is a very versatile catalyst and offers excellent stability, activity, and reusability for multiple reaction cycles.

Wang et al. in 2011 [89] developed a polystyrene immobilized phenanthroline–Cu(I) catalyst and applied it successfully for the synthesis of 2-aminobenzothiazoles from 2-halobenzeneamines and phenyl isothiocyanates (Scheme 25).

The optimum reaction conditions were found to be 2.5 mol% copper loading in the catalyst with DABCO as base and toluene as the solvent at 60°C for 8 h. The efficiency of the catalytic system was then tested by using 2-chloroaniline, 2-iodoaniline, and various substituted 2-bromoanilines possessing electron-withdrawing as well as electron-donating groups along with phenyl isocyanate. Even substituted phenyl isocyanates bearing methoxy, chloro, methyl, nitro, and trifluoromethyl groups were found to react appreciably with 2-bromoaniline as well as 2, 4-dibromoaniline. In all cases good to excellent yields (69–95%) of the corresponding 2-aminobenzothiazoles were obtained. Even a less active substrate, 2-bromo-5-trifluoromethylaniline, reacted surprisingly well with phenyl isothiocyanate to give a decent yield (71%) of the corresponding product. The catalytic system was even found to tolerate sterically hindered substrate like 2,4-dibromo-6-fluoroaniline to give an excellent yield (84%) of the corresponding 2-aminobenzothiazole product.

Recyclability studies of the catalyst using 2-iodoaniline and phenyl isothiocyanate as the model substrates demonstrated that the catalyst can be separated from the reaction mixture simply by filtration, washed dried, and reused for at least ten reaction cycles with almost no leaching of copper from the support (<0.20 ppm).



Scheme 25 Synthesis of 2-aminobenzothiazoles from 2-halobenzeneamines and phenyl isothiocyanates catalyzed by Cu(I) catalyst

20 Summary and Outlook

In summary, we have gathered information from the recent published methodologies, wherein heterogeneous or reusable copper-catalyst systems were used for the $C_{(aryl)}$–N bond formation employing aryl halides and arylboronic acids as coupling partners. Among the methods we discussed here for the arylation of aryl halides, most of the reactions were conducted at 100–160°C. To our knowledge no room-temperature reports have appeared under heterogeneous conditions.

The challenges and opportunities in copper-catalyzed heterogeneous catalysis are enormous as less research was carried out compared to homogeneous systems [4, 90]. The development of less expensive and robust new catalysts with higher activities and turnover numbers is desirable. It is also important to exploit these heterogeneous catalysts for the synthesis of biologically important molecules.

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Copper-Catalyzed C(aryl)–N Bond Formation

Florian Monnier and Marc Taillefer

Abstract Although requiring the use of stoichiometric amounts of metal and harsh conditions, the copper-mediated coupling reactions of aryl halides with amines and phenols (Ullmann condensations), amides and carbamates (Ullmann–Goldberg condensations), or activated methylene compounds (Ullmann–Hurtley condensations) have been for a long time useful methods for the formation of C(aryl)–N, C(aryl)–O, and C(aryl)–C bonds. In 2001, a renaissance of the Ullmann reaction has been initiated with the discovery of versatile new copper catalytic systems for C–C, C–N, or C–O coupling under mild temperature conditions.

This chapter covers more specifically the copper-catalyzed C(aryl)–N bond formation via the coupling of aryl halides with nitrogen nucleophiles such as N-heterocycles, amines, anilines, amides, ammonia, azides, hydroxylamines, nitrite salts or phosphonic amides. The C(aryl)–N bond formation as a result of the coupling between these nucleophiles and arylboronic acids (the Chan–Lam reaction) will be also presented. It is worth noting that this chapter mainly focuses on the most significant results and important breakthroughs in this field.

Keywords Copper · Arylation · N-nucleophiles · Catalysis

Contents

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1 Introduction and Scope of the Chapter

For more than a century copper-mediated coupling reactions of aryl halides with amines [1, 2], and phenols [3, 4], (Ullmann condensations), amides and carbamates [5, 6], (Ullmann–Goldberg condensations) or activated methylene compounds [7] (Ullmann–Hurtley condensations) have been three of the most useful and practical methods for the formation of C(aryl)–N, C(aryl)–O and C(aryl)–C bonds [8–16].

Despite its usefulness in life sciences and materials industries, Ullmann-type coupling reactions have not been employed to its full potential for a long time until 2000 due to the harsh reaction conditions, restricted range of substrates and the moderate yields obtained. The synthetic scope of these transformations was often limited because of the high temperatures needed (>200°C) and of the concomitant use of high-boiling-point polar solvents. Another drawback was the use of stoichiometric amounts of copper reagents and of aryl halides activated or substituted by *o*-carboxylic groups [17–27].

However, some studies amongst the literature had shown rate enhancements when arylations were performed in the presence of copper ligands, additives, or substrates bearing chelating groups [28–35]. These latter compounds were supposed to improve the catalyst solubility and stability or to prevent the aggregation of the metal. Finally, a renaissance of Ullmann-coupling reactions has been initiated in 2001 by two academic groups [36–40], with the discovery of the first both versatile and very efficient new copper/ligand systems for C–C, C–N, or C–O coupling which enabled the use of only catalytic amounts of metal under milder temperature conditions. Since these important breakthroughs based on a unique system for all type of coupling, a bountiful number of methods have been described with an extraordinary tolerance of functional groups. Nowadays, revisited copper-catalyzed cross-coupling reactions of aryl halides with nucleophiles are competitive, particularly for aryl iodides and bromides, to the expensive and more toxic palladium-catalyzed procedures.

This chapter covers the C(aryl)–N bond formation via copper-catalyzed coupling of nitrogen nucleophiles (N-heterocycles, amines, anilines, amides, ammonia, azides, hydroxylamines, nitrite salts, phosphonic amides) with aryl halides. The C(aryl)–N bond formation as a result of the coupling between these nucleophiles and arylboronic acids (the Chan–Lam reaction) will be presented, too.

Amongst the bountiful amount of publications related to this topic for about 10 years, this chapter mainly focuses on the most significant results and important breakthroughs. Its scope is to highlight the most efficient homogeneous catalytic system based on the association of a copper source with an original ligand,

when necessary. The systems dealing with the C(vinyl)–N bond formation catalyzed by copper constitute a part of the chapter presented by C. Bolm, as a chapter written by M. L. Kantam is dealing with the related heterogeneous systems.

2 C–N Bond Formation from Aryl Halides

By far the greatest number of reports on the modern catalytic Ullmann-type reactions has dealt with the creation of C–N bonds. Amongst the numerous publications which appeared during the last decade, those that give real improvement in terms of overall efficiency have been selected. Many other systems, though they are very interesting contributions, cannot be included within the scope of this book chapter.

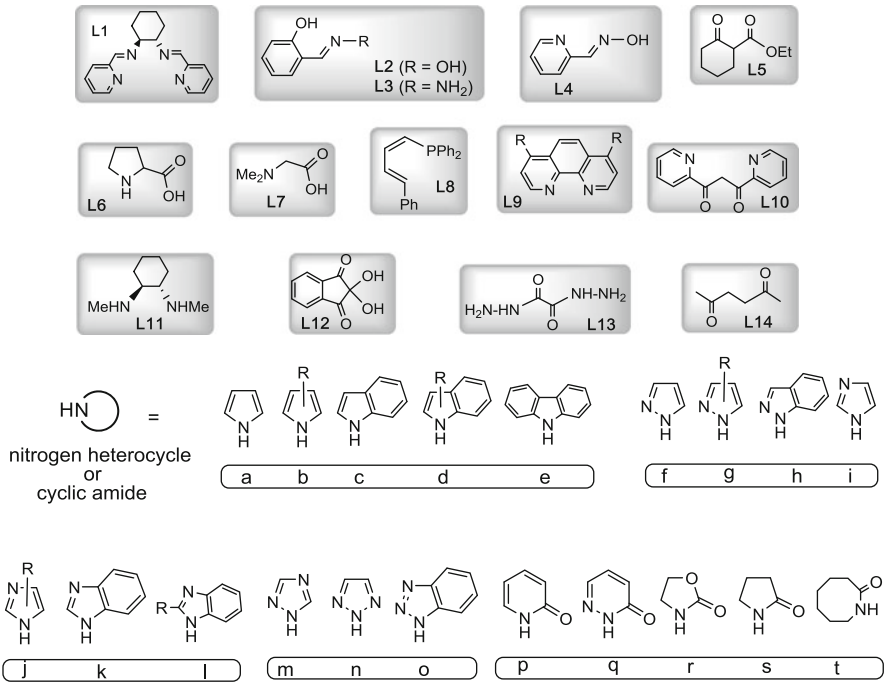
2.1 Coupling Reactions of Aryl Halides with N-Heterocycles and Cyclic Amides

Some years ago we developed novel families of polydentate ligands of Schiff base and oxime type (**L1–L4**). Combining at least one imine with oxygen or nitrogen coordination sites (Scheme 1), they facilitate coupling of numerous azole and cyclic amide derivatives (Table 1, entry 1) with aryl bromides under mild temperature conditions' [36–39], [41–43]. With aryl iodides, some reactions were even performed at 25°C and a turnover of about 1,500 was achieved with pyrazole at higher temperature (80°C). This catalytic system is one of the rare examples amongst modern copper chemistry that has already been industrially applied.

Another catalytic system was developed by Bao using the β-ketoester ligand **L5** (Table 1, entry 2) [44]. Coupling of different N-nucleophiles at mild temperatures with aryliodides or bromides mainly substituted by electron-donating groups was reported. Note that reactions could be conducted at room temperature from phenyl iodide or bromoiodobenzene and pyrrolidinone.

Amino acids, especially L-proline **L6** and *N*,*N*-dimethylglycine **L7**, were shown by Ma and co-workers to be excellent bidentate ligands for copper-catalyzed Ullmann-type reactions [45–48]. They successfully enabled coupling of numerous aryl bromides with various azoles, often in mild temperature conditions (Table 1, entry 3). The low cost of naturally occurring amino acids and their availability provide a real interest to Ma's system.

The butadienylphosphine **L8** and related molecules, obtained from a synthetic method based on the phosphorus ylides, are efficient ligands in Ullmann-type copper-catalyzed arylation reactions, particularly for nitrogen heterocycles (Table 1, entry 4). The reactions often proceed to completion in a very short time.



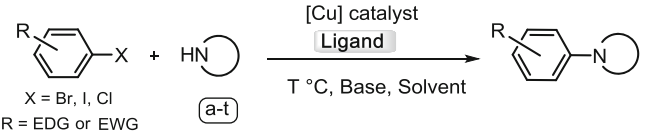
Scheme 1 Selected supporting ligands (**L1–L14**) for the copper-catalyzed coupling of aryl halides with nitrogen heterocycles and cyclic amides (substrates used: **a–t**)

Starting, for example, from pyrazole and aryl bromides, it takes less than four hours. The use of this ligand made it possible to follow the reaction by ^{31}P NMR spectroscopy and thus to propose a mechanism for the Ullmann reaction [49, 50].

The group of Buchwald has developed a copper/4,7-dimethoxy-1,10-phenanthroline system enabling the N-arylation of a various imidazole derivatives (Table 1, entry 5; **L9**, R = OMe) [51, 52]. Note that no general useful palladium catalytic systems have been described for this type of coupling. The use of a solid–liquid phase transfer catalyst, the polyethylene glycol (PEG), and a 2,000 times turnover achieved from iodobenzene and imidazole are interesting features of this procedure.

Another method to be discussed relates to a system based on an iron-copper cooperative catalyst ($Fe(acac)_3$-CuO) allowing the condensation of aryl bromides with a wide range of nitrogen heterocycles at 90°C (Table 1, entry 6). One example involving an activated chloride is also reported. This methodology introduced by Taillefer et al. does not require the presence of an additional supporting ligand [53, 54]. It represents an interesting competitive alternative to the usual Cu/ligand combination (for a review on related Fe/Cu systems which followed this first discovery, see the [55]).

Table 1 Selected copper catalytic systems for the coupling of aryl halides with various nitrogen heterocycles or cyclic amides



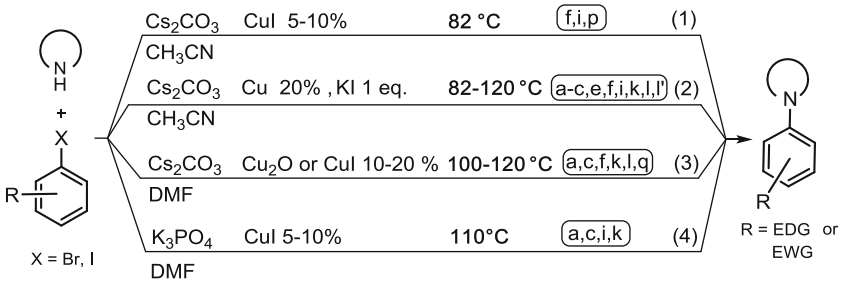
Entry	X	HN	[Cu]/Ligand	Temperature (°C)	Time (h)	Base/solvent
1	Br, I	a–c,f–i,m, p–s	Cu_2O (0.05–5%) **L1,2,3,4** (0.1–5%)	25–82	24–48	Cs_2CO_3/CH_3CN
2	Br, I	i,k,p,s	CuBr (10%) **L5** (20%)	25–80	22–30	Cs_2CO_3/DMSO
3	Br, I	a,c–f,i,k	CuI (10%) **L6-L7** (10–20%)	75–110	22–65	K_2CO_3 or Cs_2CO_3 DMSO
4	Br, I, CI	a,c,f,i,m	CuI (10%) **L8** (20%)	82	4–10	Cs_2CO_3/CH_3CN
5	Br, I	i,j,k,l	Cu_2O (0.025–20%) **L9** (7–20%)	80–150	24–48	Cs_2CO_3/n-PrCN PEG
6	Br, I	a,c,f,i,m, n,s	CuO–$Fe(acac)_3$ (10–30%)	90	30	Cs_2CO_3/DMF
7	Br, Cl	a,c,e,g, i–k,s	CuI (10%) **L10** (10%)	110	24–48	K_2CO_3/DMF
8	Br, I	a–d,f–o	CuI (5%) **L11** (20%)	110	24	K_2CO_3/Toluene
9	Br, I, Cl	a,c,f,i,k	Cu_2O (10%) **L12** (20%)	90–150	24–48	KOH/DMSO
10	CI	f,i,k	CuO (10%) **L13** and **L14** (50 and 100%)	120	48	K_3PO_4/NBu_4Br H_2O

EDG and EWG correspond respectively to electron-donating and electron-withdrawing substituents

An efficient system combining (1,3)-bispyridine-(1,3)-diketone **L10** and CuI, described by Chen et al. (Table 1, entry 7), allowed the coupling of aryl bromides with nitrogen heterocycles [56]. Reaction conditions are slightly harsher than in earlier systems mentioned, but interesting results involving arylation of imidazole from activated chloropyridine derivatives are reported.

In an update [57, 58], of a 2002 report [59], Buchwald et al. described a very competitive catalytic system based on the use of 1,2-diamine ligand **L11** for the coupling of aryl bromides with a very wide range of nitrogen nucleophiles (Table 1, entry 8).

The use of ninhydrin **L12** as ligand associated with Cu_2O has also been reported by Xu et al. for the N-arylation of nitrogen heterocycles. It is interesting to note that in some cases reactions take place with unactivated chlorobenzenes (Table 1, entry 9) with modest yields at a relatively high temperature (150°C) [60].



Scheme 2 Ligand-free copper catalytic systems for the coupling of aryl halides with nitrogen heterocycles

The last example reports the CuO-catalyzed N-arylation of nitrogen heterocycles (and also anilines and ammonia) in water. The procedure, reported by Wan et al., is quite complex. It indeed requires the presence of a very large excess of the nucleophiles, a phase transfer agent (NBu_4Br) and two ligands **L13** (50%) and **L14** (100%). It however represents one of the rare examples of copper-catalyzed coupling applied to nonactivated aryl chlorides [61].

Some years ago, Bolm et al. highlighted the fact that a sub-Mol% loading in copper salt (between 0.05 and 0.001 mol%) was able to successfully promote at 135°C the coupling of the phenyl iodide with the pyrazole and the azaindole in the presence of a large excess of DMEDA ligand (*N*,*N*′-dimethylenediamine, **L26**) [62–65]. The procedure was also applied to other types of nucleophiles such as the phenol, the *S*-methyl-*S*-phenylsulfoximine, and the phenyl acetylene. Note that the use of a low amount of copper for the C–N coupling was reported [15], using the 4,7-dimethoxy-1,10-phenanthroline ligand **L9** (R = Me) [51, 52] or polydentate ligands of Schiff base and oxime type (**L1–L4**) [41–43] (the latter were also efficient with low amount of copper for the C–O coupling [15]).

Some "ligand-free" systems have also appeared for the copper-catalyzed N-arylation of aromatic N-heterocycles. The earliest preliminary results were reported in a 2005 patent (Scheme 2, Eq. (1)) by Taillefer et al. [66]. Arylation from iodo- and bromobenzene was performed without any additional ligand, with 5–10% of a copper source such as CuI in the presence of Cs_2CO_3 as base in a nitrile-type solvent (CH_3CN). Something similar was reported three years later by Hu, but higher loading of the copper source (20 mol%) and the presence of stoichiometric amount of potassium iodide (KI) were employed to permit bromide/iodide exchange for aryl bromides (Scheme 2, Eq. (2)) [67].

A "ligand-free-like" system using 10% of CuI (for ArI) or Cu_2O respectively (for ArI and ArBr) in DMF was also proposed by Yasutsugu [68] and Bolm [69] (Scheme 2, Eq. (3)). Bolm and Gesing more recently reported a system allowing the microwave-assisted ligand-free copper-catalyzed coupling of nitrogen heterocycles or amides with halopyridines [70]. In a related system, Guo et al. [71] used a phosphate (K_3PO_4) as base and suggested that the latter could also promote the oxidative addition of the aryl halide to the copper centre by chelating

Cu(I) (Scheme 2, Eq. (4)). For other interesting results allowing C(Ar)–N coupling in ligand-free conditions and not described in this chapter (see [72–78]).

It is likely that in all these "ligand-free" methods, the solvent and/or the base acts as ligands of copper, though with less efficiency than the chelating ligands presented earlier. Our experience showed that with our ligand-free conditions (5–10% copper loading at 82°C, aromatic bromides) good performance is not always reproducible for reactions conducted on an industrial scale. This problem could be only partially solved by using higher copper loading (20% [Cu]) and/or higher temperatures. However reactions conducted on an industrial scale are questionable with regard to residual toxicity under such conditions. This highlights the fact that ligands do not only allow or accelerate the reactions but also improve their reproducibility and make them inherently safer in terms of operating conditions and residual toxicity.

For interesting results allowing C(Ar)–N(azoles) and/or C(Ar)–N(cyclic amides) formations and not described in Sect. 1, see the following [56, 79–133].

2.2 *Coupling Reactions of Aryl Halides with Alkyl and Aryl Amines and with Noncyclic Amides*

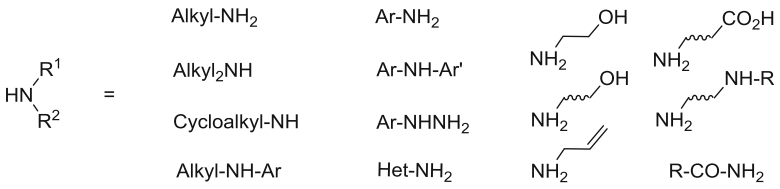
The renaissance of the catalytic Ullmann coupling has also led to numerous new methods allowing the condensation of aryl iodides and bromides, with aliphatic amines, anilines, hydrazines, amino alcohols, noncyclic amides, and other substrates (Scheme 3).

After the first works on the copper-catalyzed arylation of alkyl amines in the presence of ethylene glycol (2 equiv.) **L15** [134] or diethylsalicylamide (5–20 mol%) **L16** [135] as ligands, Buchwald reported in 2006 a room-temperature procedure for this type of reaction (Scheme 4). The condensation of primary or secondary alkyl amines [136, 137], and amino alcohols (selective N- versus O-arylation) with aryl iodides was performed at 25°C, thanks to the help of cheap 1,3-diketone ligands **L17** associated with CuI (5%). Harsher conditions (90°C) had to be applied from aryl bromides (Scheme 4).

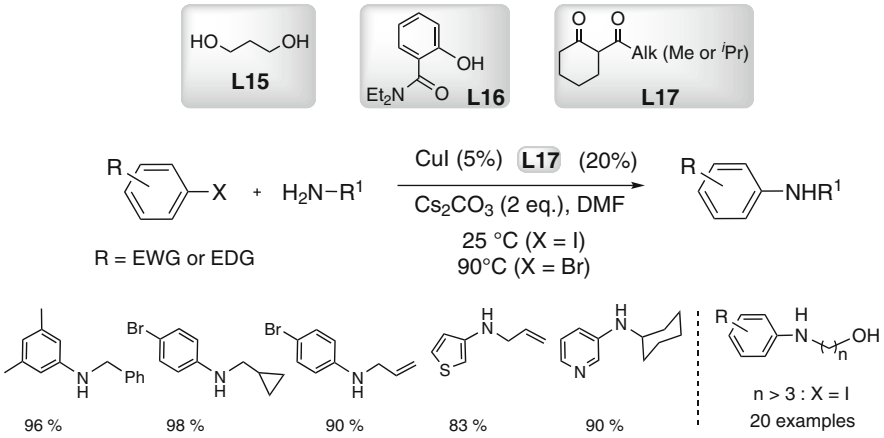
Twieg et al. published in 2003 one of the first examples of a copper catalytic system that was able to promote the coupling of aryl iodides or bromides with alkyl amines. The *N*,*N*-dimethylaminoethanol **L18** associated with CuI as precatalyst (10 mol%) was used at mild temperature conditions (60–90°C) both as solvent and ligand (Scheme 5) [138].

In 2007, Fu reported room-temperature systems based either on *N*-phenyl hydrazone (**L19**) or on *rac*-BINOL (**L20**) (Scheme 6) [139, 140]. These ligands, combined with CuI or CuBr (10 mol%), revealed good reactivity for the N-arylation from aryl iodides of aliphatic amines and/or amino acids.

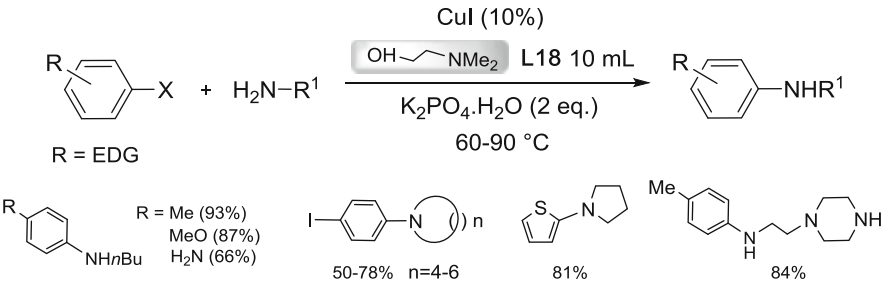
Some years ago Ma showed that amino acid L-proline **L6** and glycine derivatives **L7** were very efficient ligands of copper for the coupling of alkyl amines and aniline



Scheme 3 Substrates used for Cu-catalyzed coupling with aryl halides



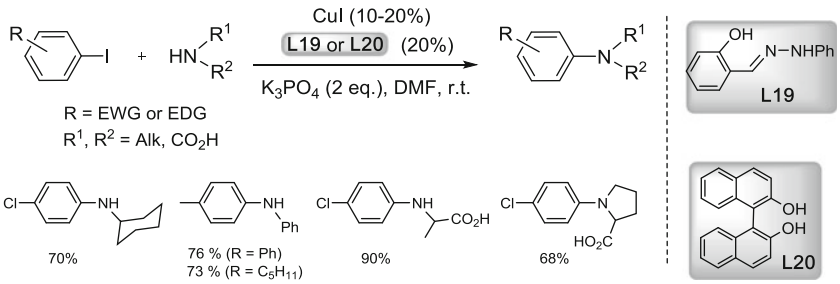
Scheme 4 Copper iodide /**L17**-catalyzed reactions of alkyl amines or and amino alcohols with aryl halides



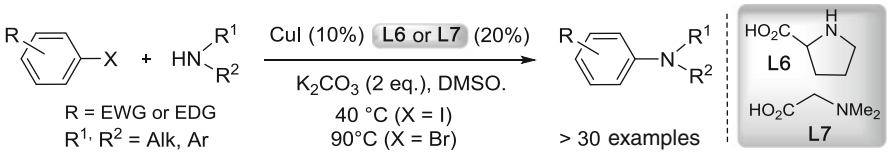
Scheme 5 Copper iodide /**L18**-catalyzed reactions of alkyl amines with aryl halides

derivatives over a range of temperatures from 40°C to 90°C (Scheme 7). The carboxyl and amino groups could make catalytic species (probably a Cu^{I}) more reactive toward a first oxidative addition of the aryl halide, by chelating the metal [47, 48].

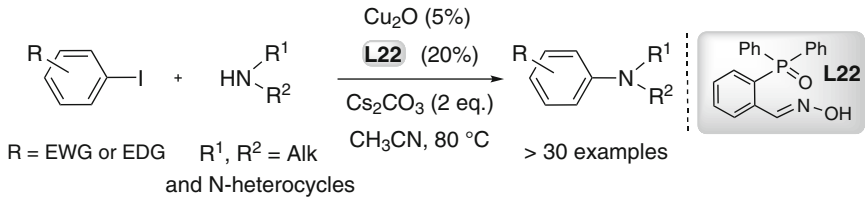
Another elegant route for the room-temperature coupling of aryl iodide (of aryl bromides at 65°C) with aliphatic amides was developed by Ding et al. with the support of a 2 pyridyl β-ketones ligand **L21**. This Cu-based catalytic system permits



Scheme 6 Copper iodide/**L19** or **L20**-catalyzed reactions of alkyl amines or amino acids with aryl iodides

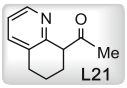


Scheme 7 Copper iodide/**L6** or **L7**-catalyzed reactions of alkyl amines and anilines with aryl halides



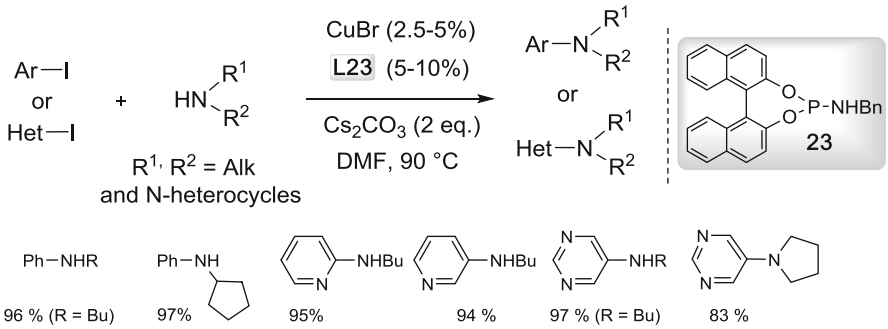
Scheme 8 Copper(I) oxide/**L22**-catalyzed reactions of alkyl amines and N-heterocycles with aryl iodides

obtaining a large amount of aryl amines in good to excellent yields under very smooth reaction conditions [141].

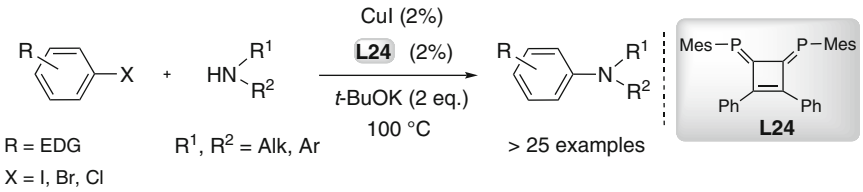


Phosphine-oxime **L22** also proved to be a good ligand for the N-arylation of alkyl amines and N-heterocycles (Scheme 8) [142]. Although product formation takes place only in the case of aryl iodides and at higher temperatures (80°C) than in earlier cited examples, the presence of a phosphorus atom in **L22** constitutes an interesting feature for mechanistic studies (^{31}P NMR).

Wass et al. described another phosphorous-based ligand for the amidation of aryl iodides [143]. The yields were only fair but several well-identified



Scheme 9 Copper bromide/**L23**-catalyzed reactions of alkyl amines and N-heterocycles with aryl or heteroaryl iodides



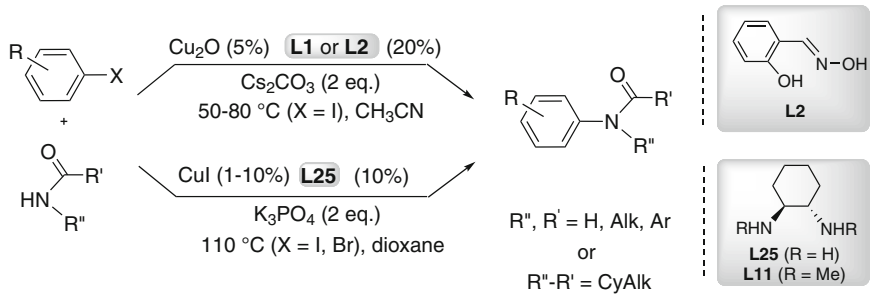
Scheme 10 Copper iodide/**L24**-catalyzed reactions of alkyl and aryl amines with aryl halides

(X-ray structures) copper precatalysts have been isolated from *N*,*N*-bis(diphenylphosphino)amine ligands and CuCl. Wan and co-workers [144, 145], proposed a system with the ability to couple aryl or heteroaryl iodides with a bountiful variety of alkyl amines (Scheme 9). For these reactions, the authors also used a phosphorus ligand (phosphoramidite **L23)** with CuBr in DMF.

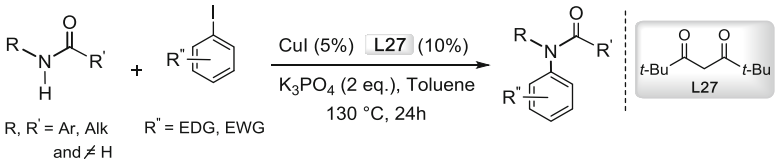
Another system selected for discussion, developed in 2005 by Yoshifuji, involves a diphosphinidenecyclobutene ligand (**L24**) [146]. Although the ligand is rather complex, it enabled the difficult reaction of aniline or morpholine with nonactivated aryl chlorides in solvent-free conditions at a temperature that is moderate for this transformation (Scheme 10).

In 2001 Buchwald et al. [147] showed that the combination of CuI and racemic trans-1,2-cyclohexanediamine (**L25**) in the presence of K_3PO_4 furnishes a general and efficient catalyst system for the N-amidation of aryl and heteroaryl iodides and bromides, as described in Scheme 11 (**L25**). Note that with chlorotoluene used as solvent and substrate, the benzamide could be arylated.

Also in 2001, the group of Taillefer has developed an efficient copper-catalyzed N-arylation procedure for amides that affords corresponding products with excellent yields and selectivity (Scheme 11: **L2**) [36–39, 41]. The reaction was shown to be compatible with various amides, providing the arylated compounds under particularly mild conditions (50–82°C). Ligands employed for this reaction are based on Schiff bases (**L1**, **L2** and derivatives).



Scheme 11 Copper(I) oxide/(**L1** or **L2**) or copper iodide/**L25**-catalyzed coupling of amides with aryl halides



Scheme 12 Copper iodide/**L27**-catalyzed coupling of secondary acyclic amides with aryl iodides

Short after these first works, Kang described in 2002 a procedure with ethylenediamine as ligand for the coupling of some aryl or heteroaryl iodides with benzamides and cyclic amides as nucleophiles [148]. The same year, Buchwald exemplified his method described right above and successfully tested other 1,2-diamine ligands amongst which, for example, **L11** and DMEDA **L26** (*N*,*N*′-dimethylenediamine) [149].

In the following years, other methods based on new ligands appeared in the literature for noncyclic amides. Because the corresponding catalytic systems often also deal with cyclic amides, they have been in fact already described in Sect. 2.1 (or in [150–164]).

The last example discussed concerns secondary acyclic amides, known to be poor nucleophilic partners rarely involved in coupling reactions with aryl halides. Recently a procedure (Taillefer, Monnier et al.) has described a versatile catalytic system allowing their intermolecular N-arylation (Scheme 12) [165]. Overcoming this challenge using a simple copper/diketone (**L27**) system offers a general method for the preparation of acyclic tertiary amides. The structure–activity relationship studies of these important targets are thus facilitated by this method, which complements the known systems based on palladium.

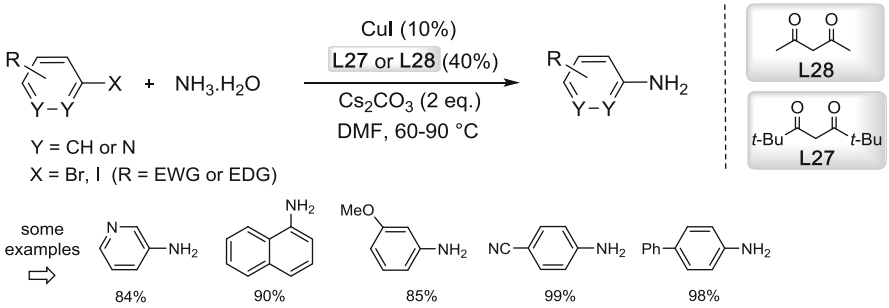
For interesting results allowing C(Ar)–N(aliphatic amines) coupling and not described in the Sect. 2.2, see the following [144, 145, 166–183].

For interesting results allowing C(Ar)–N(anilines) coupling and not described in the Sect. 2.2, see the following [184–197].

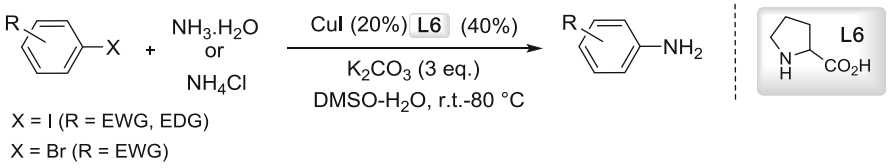
For interesting results allowing C(Ar)–N(noncyclic amides) coupling and not described in the Sect. 2.2, see the following [150–164].

2.3 Coupling Reactions of Aryl Halides with NH_3

Anilines and their derivatives are important building blocks both for the fine and commodity chemistry. Aniline is traditionally produced in a huge scale (>6 million tons/year) from the hydrogenation of nitrobenzene, which requires very hard conditions (300–600°C) in the presence of a transition metal catalyst. The nitrobenzene itself is synthesized from benzene under hard acidic conditions in a mixture of water, nitric acid and sulfuric acid [198]. More sophisticated aniline derivatives have been mainly prepared, particularly in the past decade, via the palladium-catalyzed C–N bond formation resulting from the coupling of aryl halides with ammonia surrogates (for recent reviews on arylation of ammonia by Pd or Cu catalysts, see, e.g., [199–201]). However these efficient methods require a deprotection step to obtain anilines and consequently result in the production of unwanted side products. Therefore, the development of alternative processes for the production of anilines and derivatives is of great importance, particularly in terms of sustainable development. One possibility could be the direct use of ammonia as the nitrogen source [199–201]. Indeed NH_3 is one of the simplest and cheapest bulk chemicals and its use would allow reducing the amounts of waste. The latter has however been rarely involved as a reagent in a catalytic process because of, for example, its strong ability to coordinate transition metals, thus leading to an inactivation of the catalyst. Another potential problem is the selectivity of the reaction with the possible formation of diarylamines, the anilines formed in a catalytic process being usually more reactive than NH_3 [202]. A punctual example has been reported in 1999 by Vedej et al. in an intermediate step for the synthesis of substituted isoquinolines [203]. A coupling between ammonia and a substituted aryl bromide was obtained in the presence of an almost stoichiometric amount of copper. As another limitation, the reaction was performed in 5 days under high pressure in liquid NH_3. Another protocol involving catalytic amount of copper was later reported by a researcher at Merck [204] (for a more recent example of Cu-catalyzed coupling between aryl halides and liquid ammonia, see also the [205]). As drawbacks, the reaction was performed under pressure with liquid ammonia and the scope was mainly limited to activated aromatic or heteroaromatic bromide. Moreover, the presence of ethylene glycol being necessary for the success of the reaction, the method encounters in all cases problems with the selectivity because of competitive C–O arylation of the alcoholic solvent. After 2006, palladium catalysts appeared as serious candidates for the coupling involving aryl halides and NH_3. The efficient direct synthesis of aniline derivatives has thus been reported from ammonia and, depending on the method, aryl bromides, aryl chlorides, or aryl tosylates [202, 206–209]. Drawbacks regarding these catalytic systems include the use of toxic and expensive metal and sophisticated supporting ligands and the use of strong bases and ammonia pressure in some cases. Finally,



Scheme 13 Copper iodide/**L27** or **L28**-catalyzed reactions of aqueous ammonia with aryl or heteroaryl halides

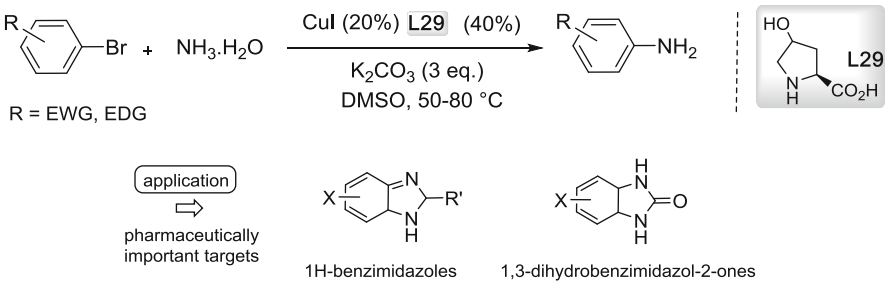


Scheme 14 Copper iodide/**L6**-catalyzed reactions of aqueous ammonia or ammonium chloride with aryl halides

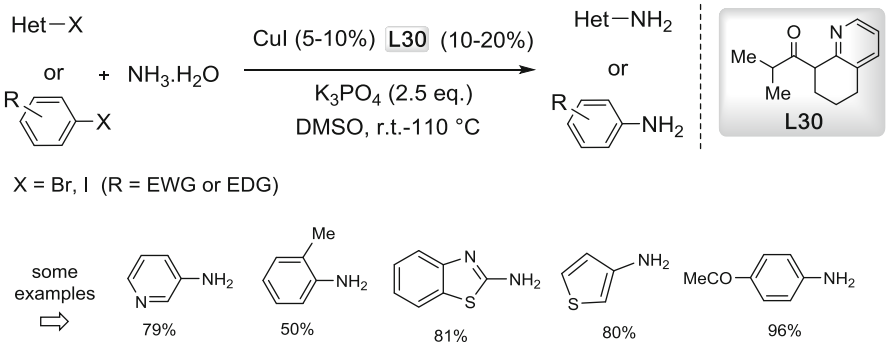
from 2007, general, selective easy-handling and cheaper methodologies involving copper catalysts appeared to overcome the challenge of the direct arylation of NH_3.

In 2007, the group of Taillefer described an efficient and very simple system for the direct amination of aryl halides with the assistance of a catalytic amount of CuI (10%) and ligands **L28** or **L27** of diketone type (Scheme 13) [210, 211]. They used aqueous ammonia ($NH_3.H_2O$) as a very easy-to-handle ammonia source and were able to efficiently couple a wide range of activated (R = EWG) or nonactivated (R = EDG) aryl iodides and aryl or heteroaryl bromides at 60–90°C. The reaction was fully selective, no di- or triarylated amine being observed. It is noteworthy that the key factor for the efficiency of the system is its biphasic character, observed on heating. The reaction would take place in the organic phase, whereas the aqueous phase would serve as a reservoir for ammonia and the copper precatalysts, such as $[Cu(NH_3)_4]^{2+}$.

In 2008, Chang et al. reported a related system allowing the synthesis of aniline derivatives from aryl halides coupled with ammonia or equivalent substrates (Scheme 14) [212]. For this cross-coupling reaction, they used a catalytic system based on twice the amount of CuI (20%), L-proline **L6** as ligand and NH_4Cl or $NH_3.H_2O$ as ammonia sources. They efficiently performed the coupling from aryl iodides at room temperature and at 80°C for two activated aryl bromides (R = *p*-CN and *p*-OCH_3). The more challenging nonactivated aryl bromides (R = EDG) show low reactivity even in the presence of 20% of CuI at 80°C, as illustrated in one example involving the *p*-bromoanisole (R = *p*-OMe).



Scheme 15 Copper iodide/**L29**-catalyzed reactions of aqueous ammonia with aryl bromides

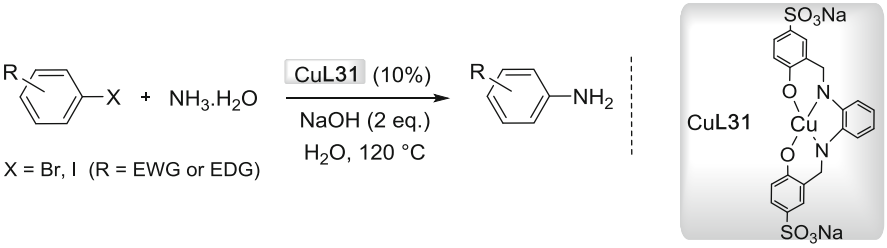


Scheme 16 Copper iodide/**L30**-catalyzed reactions of aqueous ammonia with aryl or heteroaryl halides

In 2009, Ma and co-workers in their continuing effort to develop Ullmann reactions involving amino acid ligands [213] slightly modified the precedent system using the 4-hydroxy-L-proline **L29** (Scheme 15) [214, 215]. This lone modification allowed to overcome the low reactivity observed by Chang with the ligand **L6** for nonactivated aryl bromides (R = EDG). Authors also adapted this system starting from 2-iodoacetanilides and aqueous ammonia, for an intramolecular synthesis of pharmaceutically important heterocycles such as 1*H*-benzimidazoles or 1,3-dihydrobenzimidazol-2-ones [214]. L-proline was preferred as ligand in this case.

Another system associating the copper with the ligand 2-pyridinyl-β-ketone **L30** was described in 2009 by Ding et al. for the amination of aryl or heteroaryl halides. The corresponding anilines were obtained at room temperature from activated or nonactivated aryl iodides (R = EWG or EDG), a higher temperature of 80°C being necessary from sterically hindered iodides, for example, the *o*-iodotoluene. On the other hand this catalytic system was rather disappointing, as a high temperature of 110°C is needed to perform this coupling with aryl bromides (Scheme 16) [216].

An interesting update has been proposed by the group of Zhou in 2010 by employing a hydrosoluble preformed sulfonato-Cu(salen) catalyst Cu**L31** [217]. The latter was able to couple aqueous ammonia with aryl iodides and bromides in neat water in the presence of NaOH as base (Scheme 17). This



Scheme 17 Hydrosoluble sulfonato-Cu(salen)-catalyzed reactions of aqueous ammonia with aryl halides

environmentally benign system has been also applied for other nucleophiles such as nitrogen heterocycles [218].

Other systems describing the copper-catalyzed coupling of aryl halides with aqueous ammonia appeared in the literature. Although very interesting, they correspond to variations of the methods described above and will not be described here [205, 219–228].

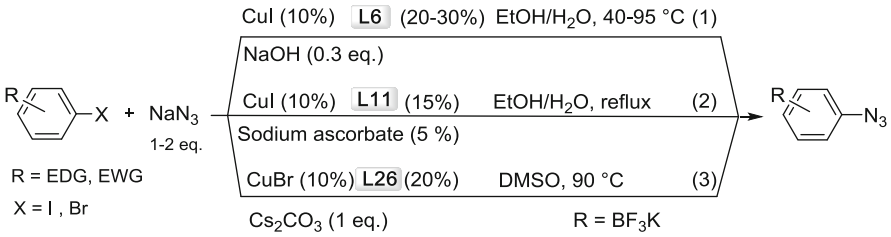
Some methods concern specific categories of substrates. For example, Renaud et al. in the field of their continuing efforts to prepare dipyridylamine (dpa) ligands, described in 2008 and more recently the copper-catalyzed arylation of bromopyridine and bromopyrimidine derivatives in the presence of aqueous ammonia [229, 230].

Also note the results of Tao, Zhao [231] and Fu and Liu [232] who performed in mild temperature conditions the arylation of, (1) activated aryl iodides or strongly activated aryl bromides in long reaction times and (2) some aryl iodides or bromides (often activated) in the presence of *N*,*N*-dimethylglycine as a ligand and additive salts of phosphonium malonate type (in stoichiometric amounts), respectively.

The works of Wolf et al. describing the arylation of ammonia from aryl bromide at 80–110°C in ligandless conditions (the N-methyl pyrrolidone is the co-solvent with water) or from aryl chlorides under microwave irradiation can be cited (233) (for comments on this system see ref 201 and 208). Worth noting that recently the Chan–Lam reaction was adapted by Fu et al. for the synthesis of aniline derivatives via the copper-catalyzed coupling of arylboronic acid with aqueous ammonia (cf. Sect. 3) [234–236]. Another alternative has been described by Darcel et al. [237, 238] on the basis of the Fe/Cu Taillefer's co-catalytic system [53, 239, 240], known to allow the coupling of various aryl halides with C-, O-, and N-nucleophiles including NH_3. Authors, by tuning of the conditions of this work, could obtain anilines in EtOH at 90°C, avoiding the use of ligands. The system was however limited to aryl iodides as starting reagent.

Other authors presented methods based on surrogates of ammonia such as amidine hydrochlorides [241], 2,2,2-trifluoroacetamides [156], benzophenone imine [242] and sodium azide (cf. Sect. 2.4.1) [243–248]. Although efficient, these systems require an additional deprotection step to get anilines and sometimes the use of stoichiometric amounts of a copper precursor.

All the efficient methods reported above describing the copper-catalyzed production of anilines from NH_3 have been discovered in only 5 years. Important



Scheme 18 Copper-catalyzed reactions of sodium azide with aryl halides

challenges still remain to be overcome such as the arylation in mild conditions of ammonia from aryl chlorides or sulfonates or the comprehension of the mechanism, a recurrent objective in catalytic Ullmann reactions. However in a very short time the purpose of discovering sustainable processes as credible alternatives to the traditional methods has been achieved.

2.4 Miscellaneous Coupling Reactions of Aryl Halides with N-Nucleophiles

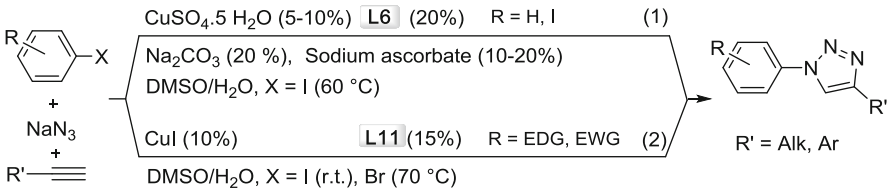
Ullmann-type coupling reactions also offer the possibility to couple N-nucleophiles such as azide salts, hydroxylamines, nitrite salts, sulfonimidamides or phosphinic amides.

2.4.1 Coupling Reactions of Aryl Halides with Azides

Since the renaissance of the [3+2] Huisgen cycloaddition [249], the azide group has attracted many attention because its condensation with alkynes, leading to 1,2,3-triazole derivatives, is one of the most powerful tools to reach these compounds which found various applications, for example, as pharmaceuticals, agrochemicals, or dyes.

The literature concerning the copper-catalyzed arylation of sodium azide describes the formation, depending on the reaction conditions, of aryl and vinyl azides, 1-aryl-1,2,3-triazoles or aryl amines.

Thus, in 2004 Ma and co-workers have developed a very simple route to aryl and vinyl azides from sodium azide through a copper-mediated reaction (Scheme 18, Eq. (1)). In the presence of 10% of CuI and 20–30% of proline **L6**, they obtained coupling products in good yields at 40–70°C from aryl and vinyl iodides and at 95°C from aryl bromides [250, 251]. In a similar way, Liang et al. developed in 2005 a nice route to aryl azides with the assistance of 10% of CuI and 15% of the diamine ligand **L11** (Scheme 18, Eq. (2)) [252]. The authors observed that the addition of catalytic amount of sodium ascorbate has a stabilizing effect on the catalyst thus allowing to obtain excellent yields in aryl azides.

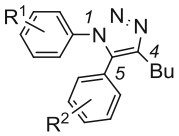


Scheme 19 Copper-catalyzed synthesis of substituted triazoles via arylation of sodium azide and cycloaddition with alkynes

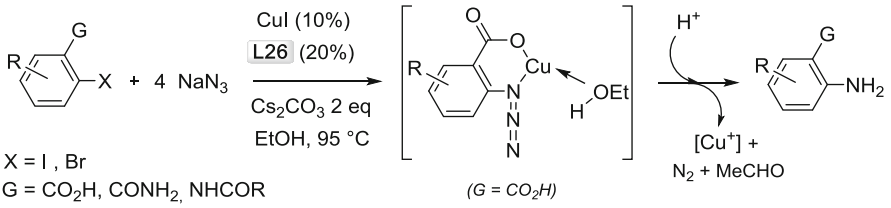
More recently in 2009, Ham, Molander and co-workers showed the efficiency of DMEDA **L26** as ligand of copper to synthesize potassium azidoaryltrifluoroborates (Scheme 18, Eq. (3)) [253]. They successfully conducted the Suzuki–Miyaura cross coupling of the latter with aryl halides in the presence of palladium catalyst and obtained various azido-functionalized biaryl compounds.

A procedure for trapping the in situ formed aryl azides was described in 2004 by Fokin and co-workers (Scheme 19, Eq. (1)) [254, 255]. In an original one-pot two-step method, they combined the copper-catalyzed arylation of sodium azide with a 1,3-cycloaddition with terminal alkynes, thus leading to the direct and selective synthesis of various 1,4-disubstituted 1,2,3-triazoles. Worth noting is that the cycloaddition of the second step was already known to be catalyzed by copper(I) [256, 257]. L-proline **L6** associated with $CuSO_4$ was used as the catalytic system. One year later, Liang et al. improved their azidonation of aryl halides method [252] and described the one-pot synthesis of a large array of 1-aryl-1,2,3-triazoles following a similar strategy (Scheme 19, Eq. (2)) [258]. This procedure allows the preparation from aryl bromides in very mild temperature conditions of these important pharmaceutical and agrochemical targets.

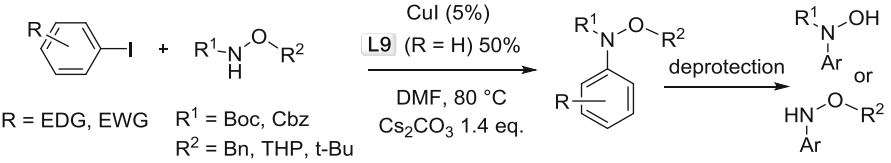
In 2008, Ackerman and co-workers applied these methods for the synthesis of fully decorated triazoles [259]. Their studies revealed that a single copper system based on CuI and DMEDA **L26** ligand was able to catalyze in a one-pot procedure the arylation of sodium azide and the subsequent in situ arylation in position 5 of the resulting triazole, via a sustainable C–H functionalization. Based on the same type of strategy, various organo-[1,2,3]-triazol-1-aryl-trifluoroborates were recently prepared by Ham and subsequently used as substrates in Suzuki–Miyaura cross-coupling reactions [260].



The utilization of in situ generated aryl azides is not restrictive to [3+2] Huisgen condensation-type reactions. These compounds could also play the role of ammonia surrogate for the synthesis of aniline derivatives. Thus in 2004 Fu, Qiao and co-workers described conditions involving CuI with or without DMEDA **L26**



Scheme 20 Copper-catalyzed amination of ortho-functionalized aryl halides using NaN_3 as amino source



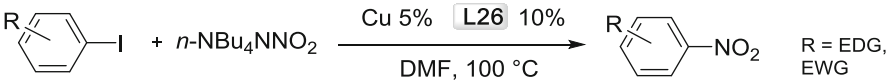
Scheme 21 Copper iodide/**L9**-catalyzed N-arylation of N,O-diprotected hydroxylamines

ligand, allowing the direct amination of ortho-functionalized aryl halides using NaN_3 as amino source [243]. Authors propose the formation of an intermediate complex of the copper (Scheme 20) after a first azidonation step. The complex then allows the formation of the corresponding aniline by an oxidation-reduction reaction in the presence of the base followed by acidification of the medium.

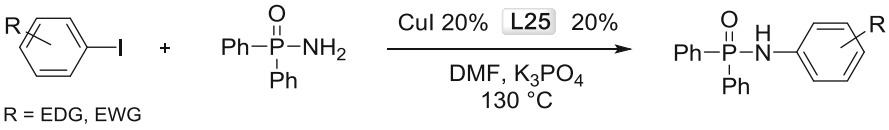
The same year Alami et al. described the synthesis of various 3-aminoquinolinones, 3-aminocoumarines and some anilines based on a similar strategy involving an intermediate arylation of sodium azide. Experimental evidence obtained from the azidonation of quinolone seems to indicate that the reaction proceeds via the intermediate formation of nitrene species [261, 262]. More recently, Sajiki et al. published related procedures affording aniline derivatives by arylation of trimethylsilyl azide ($TMSN_3$). The interest on the method was very limited by the use of stoichiometric amounts of copper source (CuF_2 or Cu) [244, 245]. A similar drawback was also met in the recent works of Helquist et al. using stoichiometric amount of copper associated with ligand DMEDA (**L26**) or proline (**L6**) in the synthesis of aniline derivatives from NaN_3 and aryl halides [246, 247]. In 2011 Sekar et al. presented a related method requiring the presence of only catalytic amounts of the copper salt and ligand (the D-glucosamine). In this case, an additional equimolar amount of potassium iodide was necessary to obtain anilines [248].

2.4.2 Coupling Reactions of Aryl Halides with N,O-Diprotected Hydroxylamines

In 2008, Tomkinson et al. have described a method allowing the copper-catalyzed N-arylation of N,O-diprotected hydroxylamines [263]. By using 5% of CuI and 50% of 1,10-phenanthroline as ligand, they were able to synthesize various N-aryl



Scheme 22 Copper bronze/**L26**-catalyzed nitration of aryl iodides



Scheme 23 Copper iodide/**L25**-catalyzed reactions of phosphinic amides with aryl iodides

hydroxylamines which are valuable intermediates, for example, in nitrone and aziridine synthesis. The products could be N- or O-deprotected thus affording the further possibility of a selective N- or O-functionalization (Scheme 21).

2.4.3 Coupling Reactions of Aryl Halides with Nitrite Salts

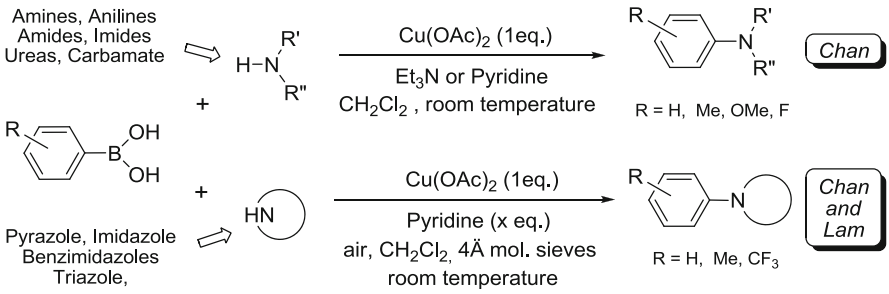
In 2005, Saito et al. described the nitration of aryl halides catalyzed by 5% of copper bronze, using tetra-*n*-butylammonium nitrite as a nitrating agent and the DMEDA **L26** as ligand [264]. This efficient system, which offers the aromatic nitro compounds in fair to excellent yields, constitutes an interesting alternative to the traditional more drastic industrial method involving the electrophilic nitration of aromatic compounds (Scheme 22).

2.4.4 Coupling Reactions of Aryl Halides with Phosphinic Amide

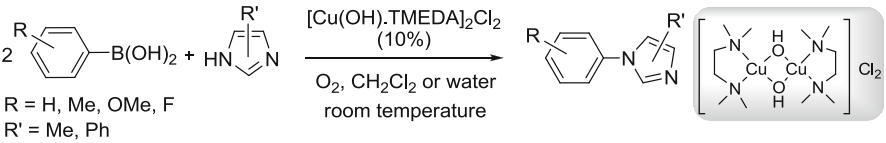
Guo and co-workers presented in 2007 the copper-catalyzed coupling between phosphinic amides and aryl iodides in the presence of the cyclohexylenediamine **L25** ligand in DMF at 130°C with K_3PO_4 as base [265]. This methodology gave access for arylated phosphinic amides, which are usually obtained by amidation of phosphinic chlorides and are interesting compounds for medicinal applications or ligand design (Scheme 23).

3 C–N Bond Formation from Arylboronic Acids and Derivatives

The copper-catalyzed cross couplings between arylboronic acids and various N-nucleophiles, first described in two reports [266, 267], have emerged recently as an efficient tool for forming C(aryl)–N bonds in mild conditions. Thus Chan et al. in



Scheme 24 Copper-mediated coupling of arylboronic acids with N-nucleophiles

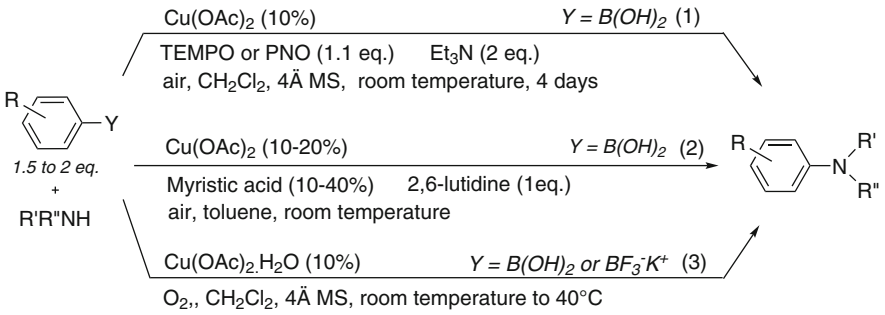


Scheme 25 Copper-catalyzed coupling of arylboronic acids with imidazoles

1998, using stoichiometric amount of $Cu(OAc)_2$ and arylboronic acids as the aryl source, presented a system allowing the coupling of amines, anilines, amides, imides, ureas and carbamates at room temperature under air (Scheme 24) [266]. In a back-to-back publication [267], Chan, Lam et al. reported that aromatic N-heterocycles coupled efficiently with arylboronic acids as aryl donors in the presence of an almost similar system (Scheme 24). It is worth noting that at the same time Evans et al. also described a very closed copper system allowing the synthesis of diaryl ethers from phenol and arylboronic acids [268, 269].

Although this novel methodology opened the scope to a new family of coupling partners, it suffered from the amount of copper needed, which is often more than equimolar. However, Collman et al. reported in 2000 the first catalytic version of this smooth C–N bond formation [270]. Indeed, they were able to generate, always proceeding at room temperature, various N-arylated molecules from boronic acids and imidazoles in the presence of only 10% of a copper precatalyst $[Cu(OH).TMEDA]_2Cl_2$ (Scheme 25). The authors carried out the same type of coupling in water, obtaining the N-arylimidazoles in moderate yields [271], and studied the influence of nitrogen-chelating bidentate ligands on the course of the reaction [272].

All these authors proposed that the mechanism bears some similarity to the copper-mediated arylation of amines from triarylbismuth compounds, described by Barton et al. [273]. Thus, the reaction would proceed via the formation of a cupric acetate complex with the nucleophile followed by a transmetallation with arylboronic acid playing the role of the triarylbismuth, before affording the N-arylated compound by reductive elimination. This last step would be facilitated by prior oxidation by dioxygene of a copper II intermediate to a copper III intermediate [266–270, 274]. Some authors reported that the addition of molecular



⟹ R'R"NH =

(1) phthalimide, piperidine, indazole, aniline, pyridone, sulfonamide, benzimidazole (*R = Me*)

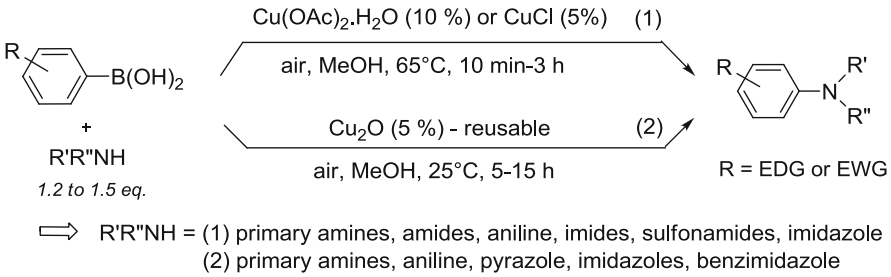
(2) primary and secondary amines, aniline *(R = EDG or EWG*)

(3) primary and secondary amines, aniline, pyrole, α-amino acid *(R = EDG or EWG)*

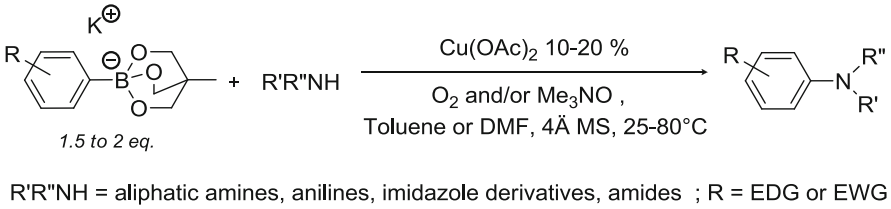
Scheme 26 Copper acetate-catalyzed coupling of arylboronic acids or potassium aryltrifluoroborate salts with N-nucleophiles

sieves increases the yields of coupling products, avoiding the formation of side products such as phenols or diaryl ethers arising from the arylation of water. The latter would be generated through the triarylboroxine formation from the corresponding arylboronic acid [267, 268, 274, 275].

In 2001, Lam et al. postulated that the addition of a mild oxidizing agent such as pyridine N-oxide (PNO) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the reaction mixture could favor the last reductive elimination step (by in situ oxidation of Cu^{II} in Cu^{III}), thus leading more efficiently to the coupling products. They thus described a mild and in air performed copper-catalyzed coupling method of arylboronic acids with various NH but also OH-containing substrates (Scheme 26, Eq. (1)) [276]. It is worth noting that these authors also presented the first example of a C–N coupling between a vinyl boronic acid and a nitrogen nucleophile. The same year, Buchwald et al. reported that, by addition of catalytic amounts of $Cu(OAc)_2$ in association with myristic acid, they were able to couple different substituted anilines with arylboronic acids in good yields (Scheme 26, Eq. (2)) [277]. In the presence of aliphatic amines, the aryl amines were obtained only in fair yields. The myristic acid was supposed to increase the solubility of the catalyst by coordination to the copper. The efficiency of the system, performed in air, would also be due to the use of oversized reaction flasks relative to the solvent volume and due to a vigorous stirring, those conditions allowing a more efficient oxidation of copper intermediates. It is worth noting that a similar system was used for the synthesis of N-aryl aziridines [278]. An original complementary methodology allowing the coupling of primary and secondary amines with arylboronic acids or potassium aryltrifluoroborate was developed by Batey et al. in 2003 [279]. This novel catalytic system, base- and ligand-free, is very practical to obtain aliphatic amines. Moreover potassium aryltrifluoroborate salts offer an air- and moisture-stable alternative to other organoboron compounds (Scheme 26, Eq. (3)).



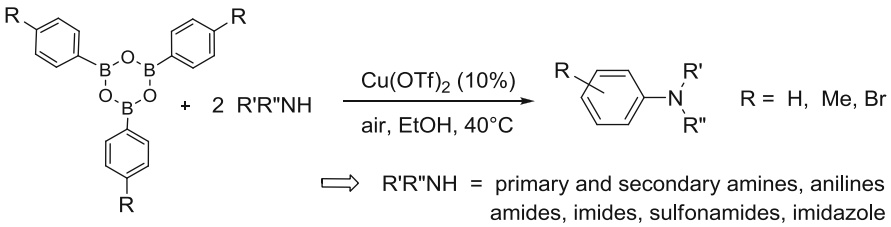
Scheme 27 Copper acetate- or copper oxide-catalyzed coupling of arylboronic acids with N-nucleophiles



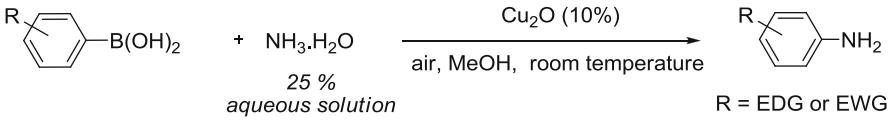
Scheme 28 Copper acetate- coupling of cyclic potassium aryl triolborates with N-nucleophiles

After these first reports on the catalytic version of the Chan–Lam reaction, a lot of other research groups presented efficient systems for the coupling of a wide range of nitrogen nucleophiles. Even if it is difficult to choose amongst them, we will focus on catalytic ones as, for example, the system presented by Xie et al. based on the use of catalytic amounts of copper acetate or copper chloride. The method, base- and ligand-free as in the Batey's system, allows the coupling in methanol of arylboronic acids with amines, anilines, imides, sulfonamides or imidazoles (Scheme 27, Eq. (1)) [280, 281]. Also worthy of note is the system recently reported by Sreedhar et al., which shows that in heterogeneous conditions, catalytic amounts of Cu_2O are able to allow the coupling of various azoles and amines with arylboronic acids in methanol. Performed at room temperature, this extremely simple method exhibits as another interesting feature the possibility to recycle and reuse the catalyst without any loss of the reactivity (Scheme 27, Eq. (2)) [282].

In 2008, Miyaura et al. discovered novel cyclic potassium triolborates of high nucleophilicity, both stable in air and water. These compounds were able to provide various coupling products with aliphatic amines, anilines, amides and imidazole derivatives, in the presence of copper catalysts. Depending on the N-nucleophile, the reaction was performed under oxygen atmosphere with or without a trimethylamine N-oxide as an additional oxidant (Scheme 28) [283, 284]. These triolborates were found to be more reactive than their potassium aryl trifluoroborate analogs or than traditional arylboronic acids, as illustrated in the N-arylation of piperidine.



Scheme 29 Copper triflate-catalyzed reactions of arylboroxines with N-nucleophiles

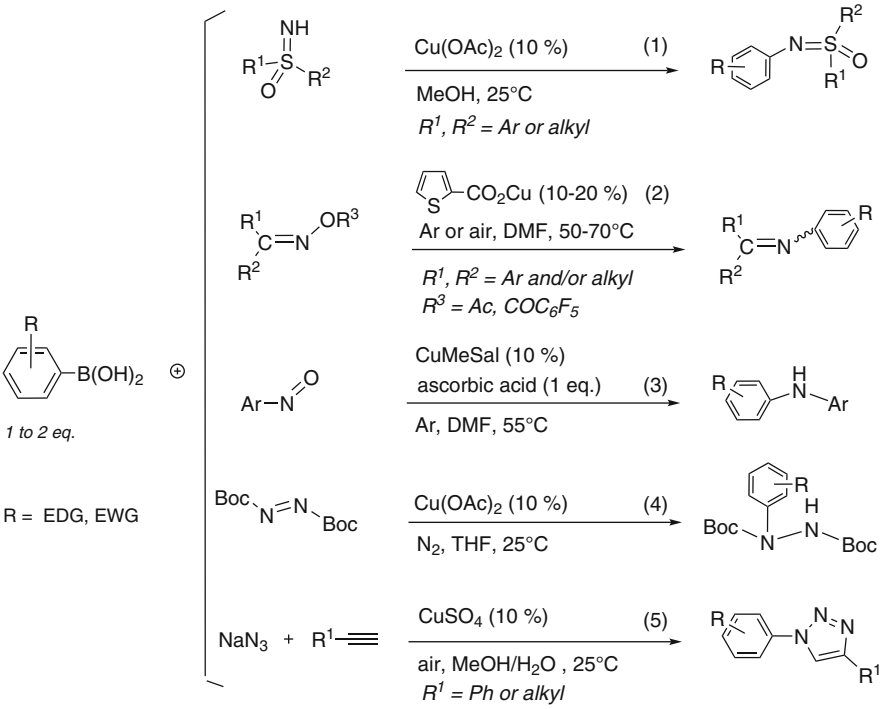


Scheme 30 Copper oxide-catalyzed coupling of arylboronic acids with aqueous ammonia

It is worthy of note that in addition to triolborates and trifluoroborates [279], boronic esters and the triphenylboroxine have also been used in place of arylboronic acids. The performances of the systems, first described by Chan and Lam, were however not overwhelming and the copper was used in stoichiometric amount [285]. A catalytic version was recently introduced by Yu et al. who presented a very simple method allowing in absence of the additive, the base and the ligand, the coupling of several arylboroxines with a large panel of N-nucleophiles, in fair to excellent yields (Scheme 29) [286].

Recently, the Chan–Lam reaction was also adapted for the synthesis of aniline derivatives. Indeed, in 2009, Fu et al. described the base- and ligand-free copper-catalyzed coupling of arylboronic acids with aqueous ammonia (Scheme 30) [234]. This very simple system used 10% of Cu_2O under air at room temperature and affords the corresponding aniline derivatives in very good yields. The reaction can also be carried out from arylboronic acid esters. A related reaction, performed in water with $CuSO_4.5H_2O$ as catalyst, was more recently reported by Wu [235]. Fu et al. also reported a quite similar system [236].

Other nitrogen nucleophiles, less common in the copper-catalyzed coupling, have also been engaged with boronic acids. For example, the latter react with sulfoximines in base-free conditions to give at room temperature the corresponding N-arylated compounds (Scheme 31, Eq. (1)) [287]. Oxime O-carboxylates have also proven to be an excellent candidate for the Chan–Lam reaction, leading in the presence of boronic acids to the formation of N-aryl imines, in base-free and under nonoxidizing conditions (Scheme 31, Eq. (2)) [288]. Indeed, the oxidant is replaced by the N–O bond of the oxime (R^3 = Ac or COC_6F_6) probably able to generate a key copper III intermediate ($R^1R^2C{=}N)Cu(X)(OR^3$). The product would be obtained from the latter after transmetallation of the arylboronic acid followed by a reductive elimination. An extension of this method to the synthesis of highly substituted pyridines has been



Scheme 31 Copper-catalyzed reactions of arylboronic acids with sulfoximines, oximes, nitroso aromatic compounds, azodicarboxylates and aryl azides

recently reported [289]. Other nucleophiles such as nitroso aromatic compounds (Scheme 31, Eq. (3)) [290], azodicarboxylates (Scheme 31, Eq. (4)) [291], and aryl azides (Scheme 31, Eq. (5)) [292] also involved in Chan–Lam C–N coupling, allow the synthesis of respectively dissymmetric diarylamines, aryl-substituted hydrazines, aryl azides, and 1-aryl triazoles.

Almost all the methods presented above belong to the field of homogeneous catalysis. It is worthy of note that a lot of other catalytic systems, not detailed and discussed in this chapter, have been developed by other groups. For other interesting results for the Chan–Lam–Evans reaction, see, for example, the following [285, 293–303] (for reviews or book chapters see, [304–306]). The particular case of the coupling of arylboronic acid with nucleobases, mainly described in the presence of stoichiometric amount of copper complexes, has not been described in this chapter (for examples of publications, see, [307–318]). The heterogeneous systems allowing the coupling of arylboronic acid with nucleophiles will be presented in the chapter written by M. L. Kantam (for some examples of heterogeneous systems see, [319–327]), and the coupling of vinylboronic acid derivatives with various N-nucleophiles will be detailed in the chapter of C. Bolm (for some examples see [276, 328–330]).

4 Conclusions

Since a decade, impressive progressions have been accomplished for the copper-catalyzed formation of C(sp^2)–N bonds. Both Ullmann and Chan–Lam reactions have permitted the coupling of a wide array of nitrogen nucleophiles with aryl/vinyl halides and boronic acids, respectively. The simplicity of the ligands, when necessary, their commercial availability and the low cost of copper make these reactions very attractive compared to palladium cross coupling, though the latter are considered complementary one to another.

Nevertheless, Cu-catalyzed cross-coupling methodologies display several drawbacks.

Compared to the well-established C–N coupling catalyzed by palladium, the copper systems present lower turnover numbers and frequencies. This is particularly the case for the Chan–Lam-type reaction which often still requires stoichiometric amounts of metal. A lot of additives like the oxidant and bases, and sometimes co-oxidants, are also often needed in stoichiometric or higher quantities.

In the catalytic version of the Ullmann reaction the situation is different, the challenge being to obtain acceptable turnover frequencies at low temperatures (25–80°C).

In both reactions, the goal is the reduction of metallic waste and the residual levels of copper in final products. The same objective could be also reached by the development of recyclable and reusable catalytic systems.

The copper systems are especially efficient with the aryl iodides or bromides. The arylation of N-nucleophiles from the less reactive but also much less expensive aryl chlorides in mild conditions remains a stimulating challenge.

As far as the industrial application of this copper chemistry is concerned, it is difficult to gather some information. However, at least the Rhodia and the Shasun Chemical companies tested the Ullmann reaction in its catalytic version and produced several tones of various target compounds.

Finally, a very important challenge for copper-catalyzed C–N bond formation and in a general point of view for all types of Cu-catalyzed carbon nucleophile (O, C, S) coupling is a better understanding of the mechanism. In comparison, one of the reasons which permitted the palladium-catalyzed reaction to become the method of choice for C(sp^2)–N bond formation is the clear description of the different steps in the catalytic cycle. We hope to be able in the near future to correlate some mechanistic understanding with this exciting area of copper chemistry.

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