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**CRITICAL REVIEW**

# Transition metal-catalyzed N-arylations of amidines and guanidines

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Although several recent reviews dealt with transition metal catalyzed N-arylation of amines (all classes), to date no specific review covering the N-arylation of amidines and guanidines appeared. Amidines and guanidines are considered as fundamental entities in medicinal chemistry. The appearance of these functional groups in drugs, agrochemicals and natural products justifies a separate description of the current status of the literature on the N-arylation of the amidine and guanidine functionalities. Both acyclic and cyclic derivatives are taken into account. For cyclic amidines/guanidines only systems which possess an exocyclic nitrogen atom are considered. This *critical review* is largely organized by the type of amidine/guanidine and transition metal used and covers literature up to May 2011 (200 references).

## 1. Introduction

The amidine and guanidine functionalities represent important structural motifs. They turn up as a structural part in various drugs and agrochemicals (for examples see Fig. 1). Several of these drugs are actually top selling pharmaceuticals and appeared in the top 200 prescription list of 2010. Examples are Rosuvastatin (Crestor), Quetiapine (Seroquel), and Lamotrigine (Lamictal) which were, respectively, number 6, 15 and 181 on that list.[1] A variety of natural products are also based on these entities.[2] Natural guanidines from marine invertebrates for instance represent a group of bioactive secondary metabolites that revealed prominent pharmacological activities. Recently, Ziconotide (Prialt), a synthetic form of the marine-derived peptide (ω-conotoxin MVIIA) comprising a guanidine moiety, has been approved for the treatment of chronic pain.[3,4] Amidines and guanidines are also important precursors used as reagents in the synthesis of heteroaromatics such as

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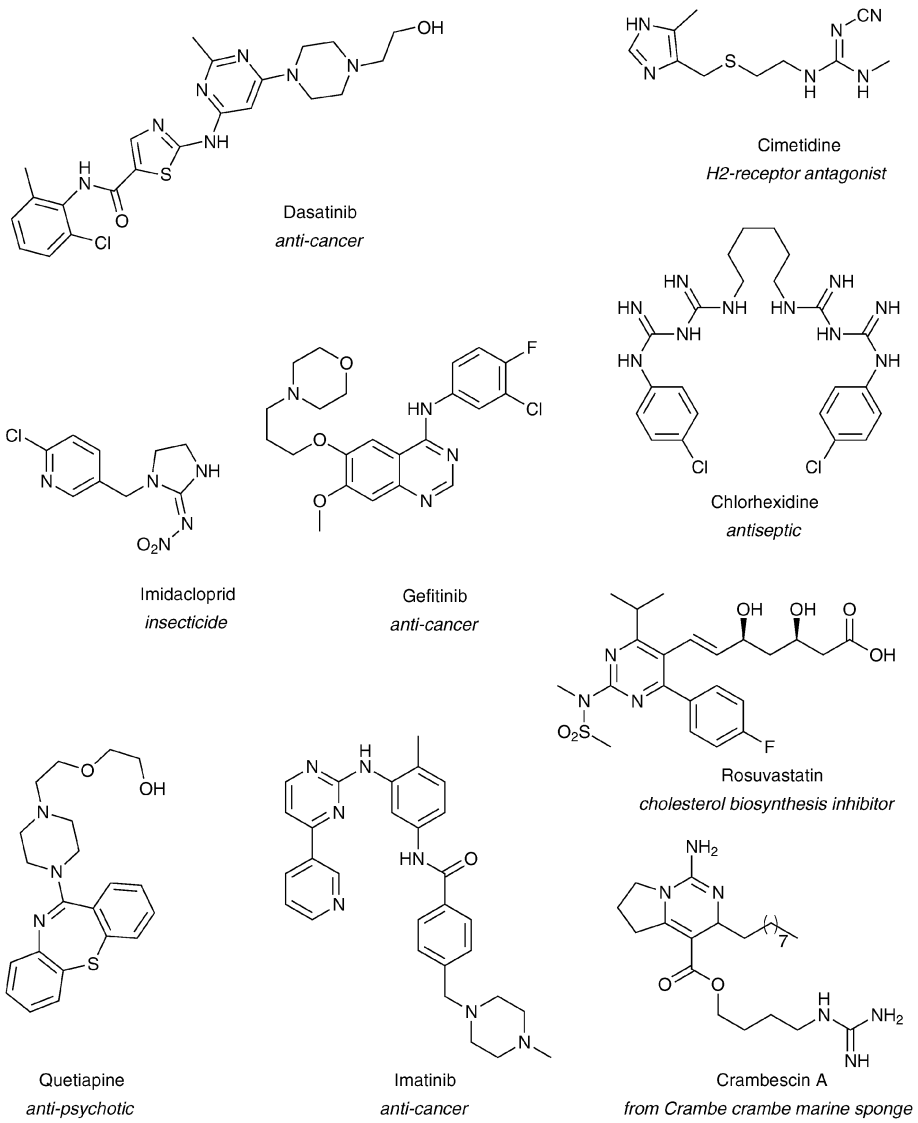



**Fig. 1** Selected examples of amidine and guanidine containing drugs, agrochemicals and natural products.

benzimidazoles[5] and quinazolines.[6,7] N-Arylation of amidines and guanidines can therefore be considered as an important way to construct new chemical entities with promising biological activities. After all, amidines and guanidines are considered as fundamental entities in medicinal chemistry which is not surprising taking into account their occurrence in the nucleobases.[8]

Transition metal-catalyzed N-arylations using amidines and guanidines as a coupling partner are not so straightforward, when compared with the N-arylation of other amine classes, as these functionalities coordinate strongly with transition metals[9–13] and are relatively basic.[14] This is nicely illustrated by the fact that, among other amidines, pyridin-2-amine can for instance be used as a ligand for copper in an Ullmann etherification reaction.[15] Additionally, in pioneering work by Lam on the Chan–Evans–Lam reaction, amidine coordination of pyridin-2-amine to the Cu-catalyst negatively influenced the reaction outcome.[16] Often the amidines/guanidines are added as salts to the reaction mixture and the reagent therefore is generated *in situ* by deprotonation with base. Although no comparative data are published, this might create a kind of controlled release hereby avoiding catalyst deactivation by the large excess of amidine/guanidine. When a sulfur atom is incorporated in the amidine/guanidine containing compounds, poisoning of the catalyst can also occur. Examples are 1,3-thiazol-2-amine derivatives which have shown to be able to shut down Pd-catalyzed amination reactions.[17] The stability of the amidine/guanidine under the reaction conditions applied can also be a limiting factor. However sometimes this can be turned into an advantage as amidines have been used as ammonia surrogates.[18] Finally, the bad solubility of amidines/guanidines in solvents typically used for transition metal-catalyzed C–N bond forming processes with classical amines is sometimes an additional problem. We can discern 3 distinct methods hitherto used for the introduction of aryl groups on amidine and guanidine nitrogens: transition metal-catalyzed amination with aryl (pseudo)halides (Pd, Cu, Ni) (Buchwald–Hartwig reaction,[19,20,21–24] Ullmann type reaction[25,26]), Cu-catalyzed cross-coupling with arylboronic acids (Chan–Evans–Lam reaction[27–29]) and finally direct amination *via* transition metal-catalyzed C($sp^2$)–H activation.

This review aims to describe the current status of literature on the N-arylation of the amidine and guanidine functionalities.

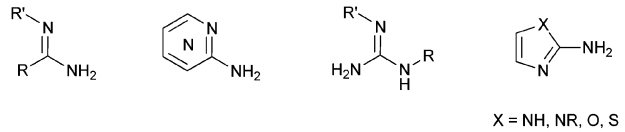


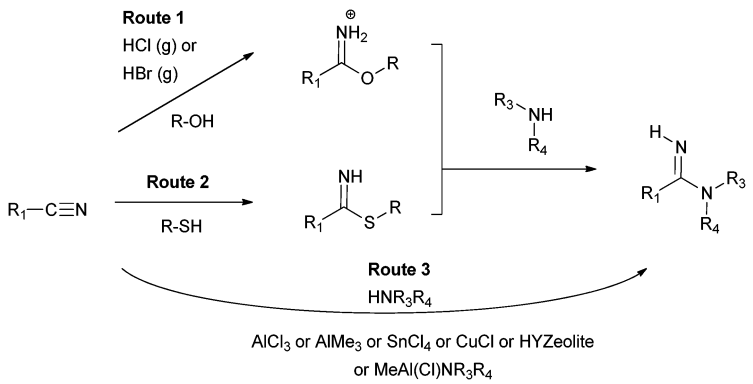

**Fig. 2** Overview of cyclic and acyclic amidine and guanidine coupling partners covered in this review.

Both acyclic and cyclic derivatives are taken into account (Fig. 2). For cyclic coupling partners only systems which possess an exocyclic nitrogen atom are considered. Thus, the N-arylation of imidazoles and benzimidazoles is not covered in this literature overview. Other recent reviews cover this topic.[25,30,31] The review is subdivided into two sections. The first section deals with the N-arylation of amidines and guanidines which are not part of a heteroaromatic ring system. Both inter- and intramolecular reactions are discussed. The same organization is also used for the second part describing the N-arylation of amidines and guanidines which are incorporated in a heteroaromatic system (*e.g.* pyrimidin-2-amine). In those cases where transition metal-catalyzed tandem amination is occurring, the reaction is covered in the intermolecular section.

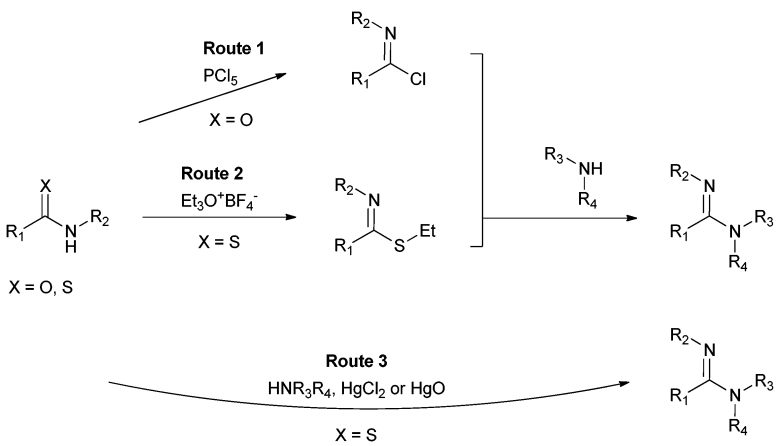
## 2. Synthesis of amidine and guanidine coupling partners

A brief overview of the most common ways to prepare amidines and guanidines is given in this section.[32–34] Only those amidines and guanidines which are not part of a heteroaromatic ring system are covered and the overview is by no means exhaustive. Heteroaromatic amidines and guanidines can be synthesized in various ways including $S_NAr$, $S_NH$[35–37] and ring construction. For these synthetic methods we refer to specialized literature.[34] The most common methods for the amidine synthesis start from nitriles, amides, and thioamides. All these methods involve disconnection of the product to an iminium/imine synthon and a nitrogen nucleophile.

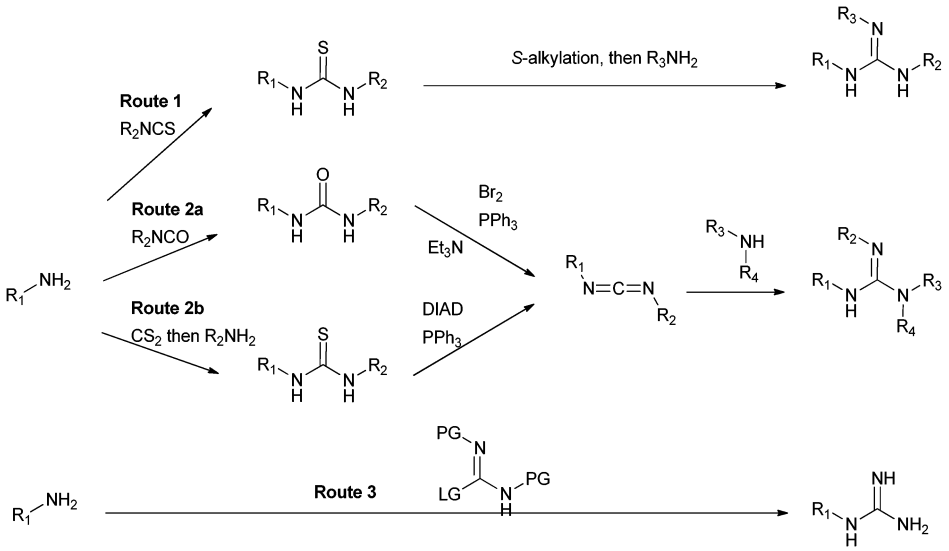
The Pinner reaction remains the most common way of making primary and secondary amidines.[38] This involves treatment of a nitrile with an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide to form the imidic ester salt. Subsequent reaction with amines gives the corresponding amidine (Scheme 1, Route 1). A modification of the Pinner synthesis involves the formation of the thioimidic ester. Reaction of the isolable thioimidic ester with amines or their acetate salts forms amidines (Scheme 1, Route 2).[39] A method which has been widely used to prepare *N*-substituted or *N*,*N*-disubstituted amidines is to heat the nitrile with a primary or secondary amine in the presence of aluminium chloride[40] (Scheme 1, Route 3). Other Lewis acids[41] such as methylchloro-aluminium amide[42] are also used to activate the nitrile but also metal salts[43] and zeolites[44] can be employed (Scheme 1, Route 3). When the nitrile is substituted with electron withdrawing groups, it can react directly with amines to give the corresponding amidine without any activation.




**Scheme 1** Primary and secondary amidine syntheses.




**Scheme 2** Secondary and tertiary amidine syntheses.




**Scheme 3** General scheme for guanidine synthesis.

Tertiary amidines cannot be formed *via* reaction with nitriles. Tertiary amidines and *N*,*N*′-secondary amidines are generally prepared from amides or thioamides (Scheme 2). Activation of the monosubstituted amide to give the imidoyl chloride is most frequently done with phosphorus pentachloride.[45] The imidoyl chloride can then be reacted with an amine to produce an amidine (Scheme 2, Route 1).[46] The condensation of an amine with a thioamide directly gives an amidine without activation.[47] The reaction can be improved by the addition of a sulfide scavenger such as $HgBr_2$ or HgO (Scheme 2, Route 3).[48] Activation *via* alkylation of thioamides with alkyl halides or triethyloxonium tetrafluoroborate gives thioimidic esters which react more readily with amines to give amidines (Scheme 2, Route 2).[49]

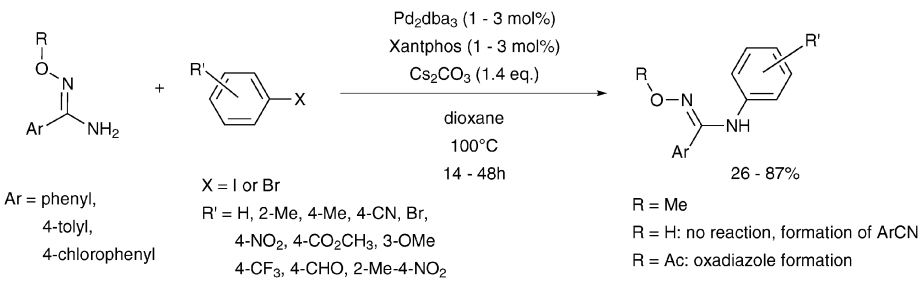
Di-, tri- or tetrasubstituted acyclic guanidines are generally prepared from the corresponding amines through thiourea (Scheme 3, Route 1) or carbodiimide intermediates (Scheme 3, Route 2). Also monocyclic guanidines can be prepared by application of these methods. Recently, polysubstituted guanidines were prepared in good yields by a catalytic bismuth-promoted synthesis through reaction of *N*-benzoyl or *N*-phenylthioureas with primary and secondary amines.[50] Furthermore, it was found that rare earth metal complexes can serve as catalyst for the addition of various primary and secondary amines to carbodiimides, efficiently yielding a series of guanidines.[51] Other reagents have been used for the transformation of amines into their corresponding guanidines such as *S*-methylisothiourea,[52] protected guanidine,[53] pyrazole-1-carboxamidine[54] and benzotriazole-1-carboxamidine derivatives[55] (Scheme 3, Route 3). Cyanogen bromide can also be used as a source of the iminium synthon for the guanidinyl functional group synthesis when reacted with primary or secondary amines. In this way acyclic[56] and monocyclic systems can be constructed (not shown).[57]

## 3. Amidines/guanidines which are not part of a heteroaromatic system

### 3.1 Intermolecular N-arylations

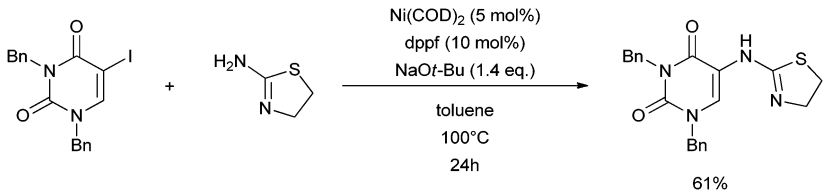
**3.1.1 Pd-catalyzed N-arylations.** In 2002, the synthesis of *N*-aryl-*O*-methylbenzamidoximes *via* intermolecular Pd-catalyzed amination of *O*-methylbenzamidoximes with aryl bromides and aryl iodides was reported.[58] Electron withdrawing and moderate electron donating groups were well tolerated while electron-rich aryl halides gave far worse results. Thus, 4-bromoanisole could not be coupled under these reaction conditions, nor did 4-iodoanisole (Scheme 4). Notably, benzamidoxime failed to undergo coupling and *O*-acetylbenzamidoxime cyclized into the corresponding 1,2,4-oxadiazole. The coupling reaction failed to proceed when $Pd_2dba_3$/BINAP or $Pd(OAc)_2$/Xantphos were used as precatalyst system, or when $K_2CO_3$ was added as base instead of $Cs_2CO_3$.

**3.1.2 Ni-catalyzed N-arylations.** Ni-catalyzed N-arylation of 4,5-dihydro-1,3-thiazol-2-amine with 1,3-dibenyl-5-iodouracil




**Scheme 4** Pd-catalyzed N-arylation of *O*-methylbenzamidoximes.




**Scheme 5** Ni-catalyzed N-arylation of 4,5-dihydro-1,3-thiazol-2-amine.



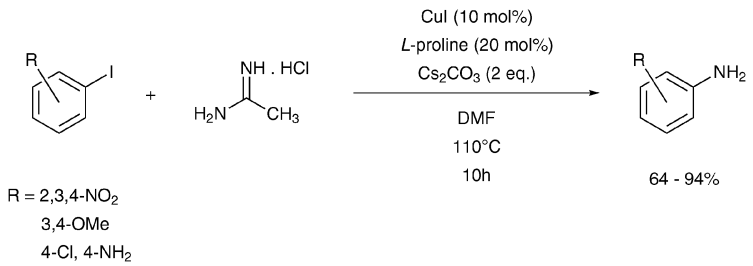
employing $Ni(COD)_2$/dppf was published in 2001 (Scheme 5).[59] The same conditions were also used to N-arylate imidazole (52% yield). In both cases the yield of the desired reaction product was moderate due to a competitive hydrodehalogenation side reaction.

### 3.1.3 Cu-catalyzed N-arylations

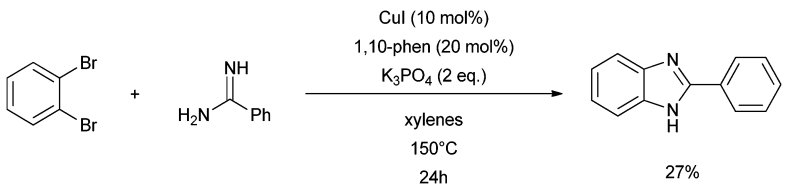
*3.1.3.1 Ullmann type coupling*. Cu-catalyzed N-arylations of amidines/guanidines have been much more investigated in comparison with Ni and Pd catalysis. Intermolecular amination of iodoarenes with acetamidine interestingly did not give the corresponding *N*-arylated derivatives but instead anilines were obtained *via in situ* hydrolysis.[18] The acetamidine therefore acted as an ammonia surrogate under these reaction conditions. Both aryl iodides containing an electron withdrawing or electron donating group could be used (Scheme 6). Electron withdrawing groups gave the best yields. Benzamidine and butyramidine can also be used as a coupling partner, but gave lower yields of the corresponding anilines.

In 2008 the first example of a tandem Cu-catalyzed inter- and intramolecular amination with amidines was reported; reaction of 1,2-dibromobenzene with benzamidine (Scheme 7).[60] For this tandem protocol the authors started from reaction conditions similar to those reported by Altenhoff and Glorius,[61] however, they switched to a CuI/1,10-phenanthroline (1,10-phen) catalytic system.

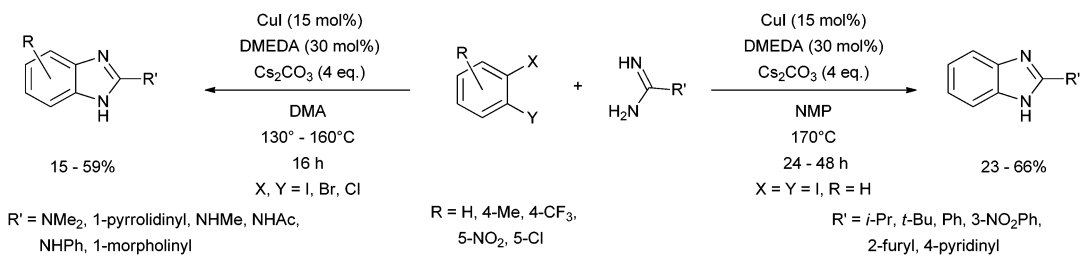
A more recent report on inter- and intramolecular amination using both amidines and guanidines as coupling partners was reported in 2009 by Deng *et al*.[62] CuI/*N*,*N*′-dimethylethylenediamine (DMEDA) proved to be a reasonably efficient catalyst system for the amination of aryl halides with guanidines. Pd-catalysis using Buchwald's biphenyl ligands failed to give any amination product. Intermolecular amination of substituted iodobenzenes with morpholine-4-carboxamidine, for instance, required 15% of catalyst to access the corresponding *N*-arylguanidines at 100 °C. The same catalyst system was then successfully applied to the one-step synthesis of 1*H*-benzimidazol-2-amines through tandem amination of 1,2-dihalobenzenes with guanidines (Scheme 8). An increased temperature was found to be essential to access the benzimidazolamine target compounds in modest yields. As can be expected, diiodobenzene



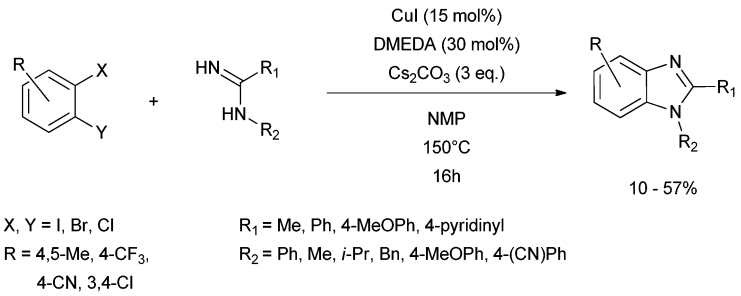

**Scheme 6** Synthesis of anilines *via* Cu-catalyzed N-arylation of acetamidine.




**Scheme 7** Synthesis of 2-phenyl-1*H*-benzimidazole *via* Cu-catalyzed tandem amination with benzamidine.




**Scheme 8** Synthesis of 1*H*-benzimidazoles *via* Cu-catalyzed tandem amination with guanidines and amidines.



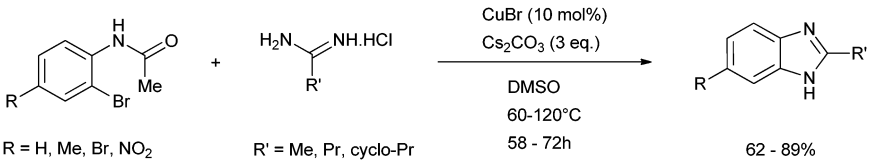

**Scheme 9** Synthesis of 1*H*-benzimidazoles *via* regioselective Cu-catalyzed tandem amination with *N*-substituted amidines.

reacted better than iodobromobenzene and iodochlorobenzene. Dichlorobenzene did not give any conversion at all. This methodology is also applicable for the preparation of 2-aryl- or 2-alkyl-1*H*-benzimidazoles using an amidine as a coupling partner (Scheme 8). However, NMP at 170 °C was necessary to obtain reasonable conversions and in almost all cases in addition to the desired 1*H*-benzimidazole products, the uncyclized hydrodehalogenated *N*-arylamidines were observed as side products. The method also allows us to synthesize 1,2-substituted benzimidazoles as exemplified by the synthesis of 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole and 1,2-diphenylbenzimidazole (not shown).

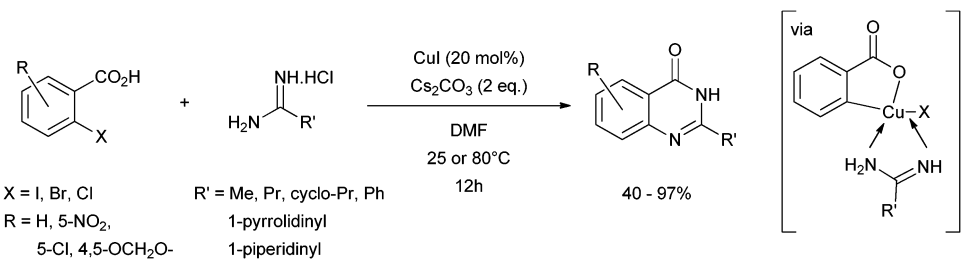
A year later Deng and Mani published an extension of the benzimidazole synthesis.[63] Regioselectivity in the tandem amination reaction of 1,2-dihaloarenes with *N*-substituted amidines was achieved (Scheme 9). The regiochemical outcome of this Cu-catalyzed reaction is achieved through a double chemoselectivity control: different reactivity of the unsubstituted and substituted nitrogen in the amidine and different reactivity of $X_1$ and $X_2$ in the 1,2-dihaloarene coupling partner (see also Section 4.1.1). The intermolecular amination is shown to go first on the unsubstituted nitrogen of the amidine and proceeds best with iodoarenes, while chloroarenes are unreactive. Yields remain moderate (57% utmost) but a small variety in substituents was tolerated on the arene as well on the amidine. A noteworthy example uses a 2-iminopiperidine yielding tricyclic 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole.

1*H*-Benzimidazoles can alternatively be build up *via* tandem reaction of *o*-haloacetanilides with amidines.[64] The protocol uses 10 mol% CuBr as catalyst and $Cs_2CO_3$ as the base. No ligand is required but presumably the solvent (DMSO) fulfills this role (Scheme 10). The mechanism proceeds *via* the sequential intermolecular arylation of the amidine followed by *in situ* hydrolysis of the acetanilide and subsequent cyclization *via* addition elimination with concomitant loss of $NH_3$. Interestingly, 2,4-dibromoacetanilide as substrate only gave *ortho* functionalization, pointing towards the acetanilide directing effect in the C–N bond forming process. *o*-Iodoacetanilide reacted faster than the corresponding bromide in the amination reaction, but overall the protocol requires long reaction times due to the time necessary for the second (hydrolysis (48 h)) and third (cyclization) reactions of the cascade.

An efficient Cu-catalyzed method for the synthesis of quinazolin-4(3*H*)-one derivatives appeared in 2009.[65] These were obtained *via* reaction of 2-bromo- and 2-iodobenzoic acid derivatives with amidines and guanidines. The reaction could be performed at room temperature with CuI as catalyst without the addition of a ligand (Scheme 11). Non-reactive coupling partners such as 2-chlorobenzoic acid and guanidines did allow to obtain the desired quinazolin-4(3*H*)-ones when the reaction temperature was raised to 80 °C. A mechanistic rationale for reaction at room temperature was also given pointing to the formation of a Cu–carboxylate prior to the carbon halogen bond activation step *via* oxidative addition (see inset, Scheme 11). Coordination with amidine followed by deprotonation and reductive elimination yields *N*-(2-carboxyphenyl)amidines. These intermediate amination products could however not be isolated and give the target molecules *via* instantaneous intramolecular condensation.

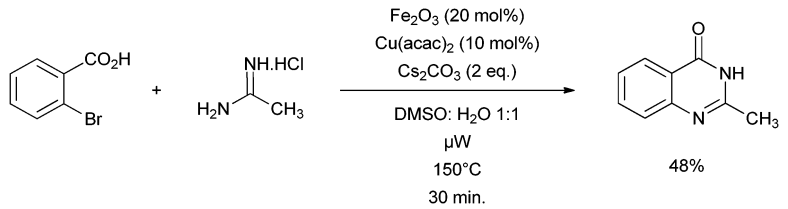



**Scheme 10** 1*H*-Benzimidazole synthesis based on tandem reaction of *o*-haloacetanilides with amidines.




**Scheme 11** Quinazolin-4(3*H*)-one synthesis *via* tandem reaction of 2-halobenzoic acids with amidines and guanidines.




**Scheme 12** 2-Methylquinazolin-4(3*H*)-one synthesis *via* tandem reaction of 2-bromobenzoic acid with acetamidine.

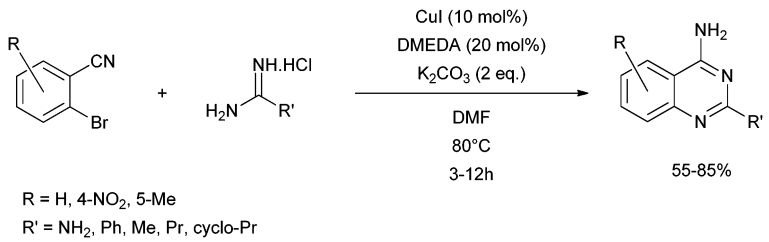
Similarly, a more recent paper shows the formation of 2-methylquinazolin-4(3*H*)-one *via* reaction of 2-bromobenzoic acid with acetamidine (Scheme 12).[66] Besides a copper catalyst a readily available iron co-catalyst was used. The actual role of this co-catalyst is unclear. The reaction conditions applied were actually developed for the amination of aryl iodides with alkylamines. The catalytic system to synthesize 2-methylquinazolin-4(3*H*)-one from 2-bromobenzoic acid is however less efficient than the one disclosed by Liu *et al.*[65] (Scheme 11) because of the need of the iron co-catalyst and the higher reaction temperature employed. Moreover, the obtained yield is lower (48% *vs.* 81%).

Quinazolin-4-amines and quinazolin-2,4-diamines can also be built up by reaction of *o*-bromobenzonitriles with amidines and guanidines, respectively.[67] A CuI/DMEDA catalyst system with $K_2CO_3$ as base gave reasonable yields (Scheme 13). $K_2CO_3$ gave better results than $Na_2CO_3$, $Cs_2CO_3$ or $K_3PO_4$ and the introduction of a nitro-substituent on the benzonitrile accelerated the reaction to a great extent as the required reaction times dropped significantly. The authors suggested a mechanism involving a tandem reaction involving a Cu-catalyzed amination with amidine/guanidine, followed by an intramolecular nucleophilic addition on the *o*-cyano group.

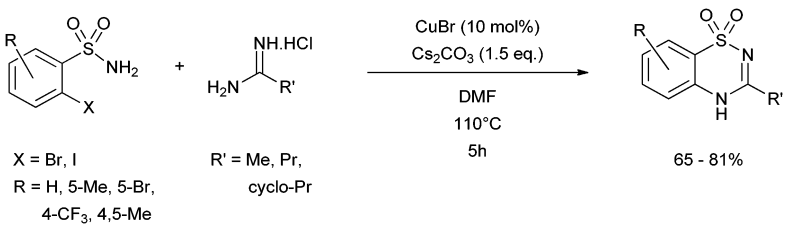
The *ortho* substituent can also act as a nucleophile. A recent report showed that 1,2,4-benzothiadiazine-1,1-dioxides can be accessed *via* a tandem reaction consisting of N-arylation of amidines with substituted *o*-halobenzenesulfonamides followed by a nucleophilic attack of the sulfonamide nitrogen on the amidine resulting in the ring closure with concomitant extrusion of ammonia. A mechanistic study using $^{15}N$ labeled 2-bromobenzenesulfonamide as substrate confirmed this. CuBr was used as catalyst for the transformation (Scheme 14).[68]

Good intermolecular N-arylation processes for guanidines and amidines also appeared. A Cu-catalyzed N-arylation protocol of guanidines with aryl iodides was reported in 2010.[69] Reaction of commercially available guanidinium nitrate with various aryl iodides using CuI/*N*,*N*-diethylsalicylamide in the presence of $K_3PO_4$ gave symmetrical *N*,*N*′-diarylated guanidines in reasonable to good yields (Scheme 15). *N*,*N*-Diethylsalicylamide proved to be the best ligand for this transformation. Other classically used ligands for CuI such as *trans*-cyclohexane-1,2-diamine (CHDA), 1,10-phen and *L*-proline gave far worse results. The use of acetonitrile as solvent was shown to be essential.

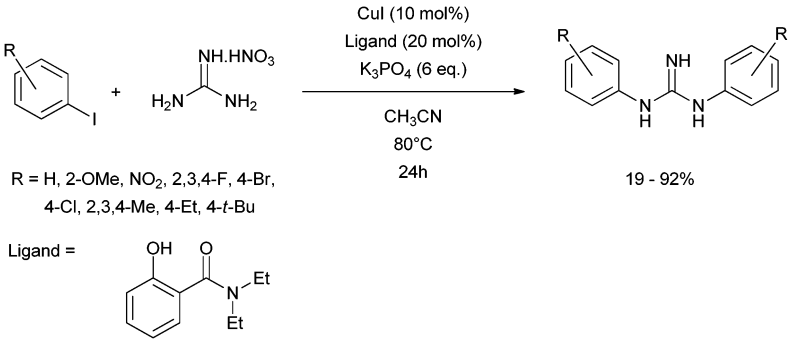
For the N-arylation of amidines on the other hand, very recently the intermolecular arylation of benzamidine and acetamidine was described.[70] In contrast to what was observed for guanidine in this case N-monoarylated products were obtained in moderate to high yields. CuI was used as catalyst under ligand free conditions (Scheme 16). For the arylation of benzamidines DMF proved to be the superior solvent, while acetonitrile worked best for the arylation of acetamidine. Notable is the use of 2 eq. of $Cs_2CO_3$, as other bases or different stoichiometries just gave worse results. The reactivity trend observed in the coupling of iodotoluenes being *ortho* > *meta* > *para*. It was also observed that isonicotinamidine hydrochloride could also be arylated, albeit in lower yield (37%). Interesting to specifically address is that the applied reaction conditions are crucial in coupling reactions with acetamidine with respect to the



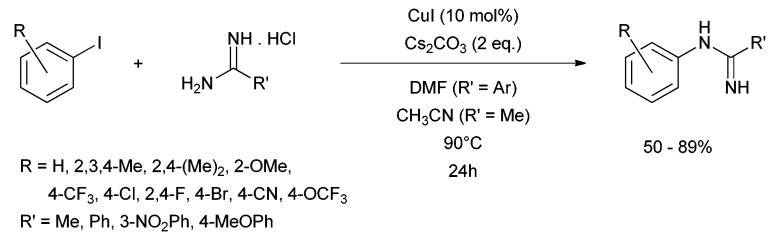

**Scheme 13** Synthesis of quinazolin-4-amines and quinazolin-2,4-diamines *via* tandem reaction of 2-bromobenzonitriles with amidines and guanidines, respectively.




**Scheme 14** Synthesis of benzothiadiazines-1,1-dioxides *via* tandem reaction of *o*-halobenzenesulfonamides with amidines.




**Scheme 15** Synthesis of symmetrical *N*,*N*′-diarylated guanidines *via* Cu-catalyzed N-arylation of guanidine.




**Scheme 16** Synthesis of N-arylated amidines *via* Cu-catalyzed N-arylation of amidines.

obtained reaction product as we showed in Scheme 6 that acetamidine also can serve as an ammonia surrogate yielding anilines.

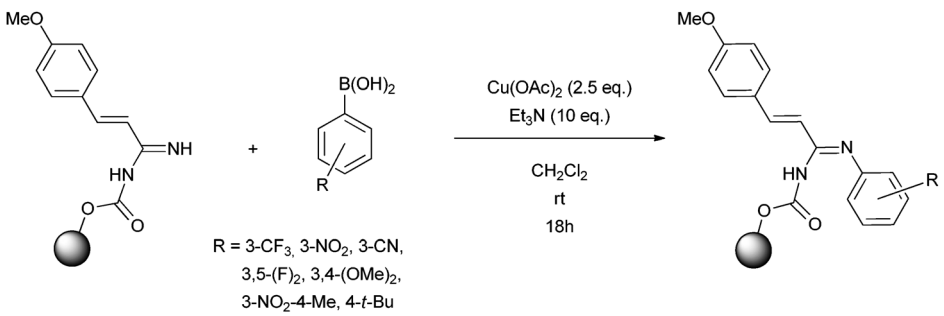
*3.1.3.2 Chan–Evans–Lam type coupling*. A US patent described the use of a resin linked amidine (*via* a carbamate) as nitrogen nucleophile in a Chan–Evans–Lam type coupling under standard reaction conditions.[71] Various substituted phenylboronic acids were coupled including 3-nitrophenylboronic acid, 3,4-dimethoxyphenylboronic acid, 3,5-difluorophenylboronic acid and 4-bromophenylboronic acid (Scheme 17). The resin could be cleaved off using TFA, yielding the *N*-arylated amidines. No yields are mentioned.

**3.1.4 Fe-catalyzed N-arylations.** In 2009 Chinese researchers showed the use of $FeCl_3$ or $Fe_2(acac)_3$ as a catalyst for the formation of quinazolin-4(3*H*)-ones from 2-halobenzoic acids (Scheme 18).[72] The reactions could be performed in water or DMF under microwave irradiation with or without the addition of ligands classically used for Cu-catalyzed N-arylations. 2-Iodobenzoic acids reacted better than 2-bromo- and 2-chlorobenzoic acids. Different amidines as well as guanidines could be employed as reagents. The authors gave no details about the reaction mechanism. A Cu-catalyzed and Cu/Fe-catalyzed version of the same transformation was also reported (Schemes 11 and 12).[65,66] Whether the reactions presented in Scheme 18 are catalyzed by homeopathic amounts of copper present in the iron sources or not was not considered/investigated by the authors.

## 3.2 Intramolecular N-arylations

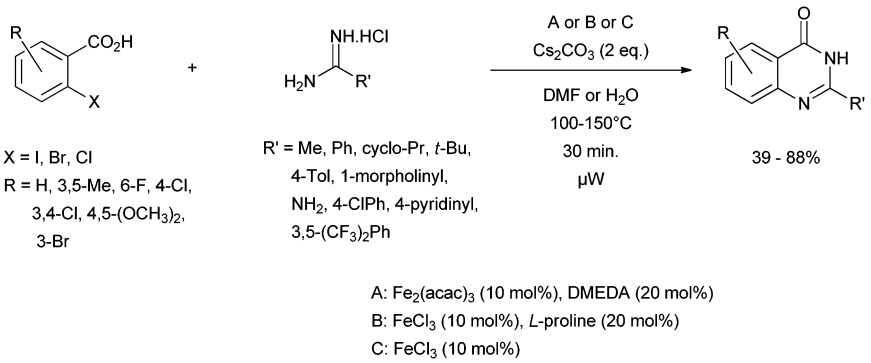
**3.2.1 Pd-catalyzed N-arylations.** In 2002 Brain and Brunton reported a novel synthesis of 1*H*-benzimidazoles by Pd-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)amidines (Scheme 19).[73] The use of $Pd(PPh_3)_4$ and a mix of NaO*t*-Bu and $K_2CO_3$ proved to be essential for the success of the reaction protocol. One example in which a *N*-(*o*-bromophenyl)guanidine ($R_3$ = 1-pyrrolidinyl) was used, creating a 1*H*-benzimidazol-2-amine, was also provided.

A follow up article in 2003 described a further optimization of the reaction conditions; the catalyst loading could be decreased and the use of a combination of bases was avoided by using NaOH in a $H_2O$/DME solvent mixture (Scheme 20).[74]

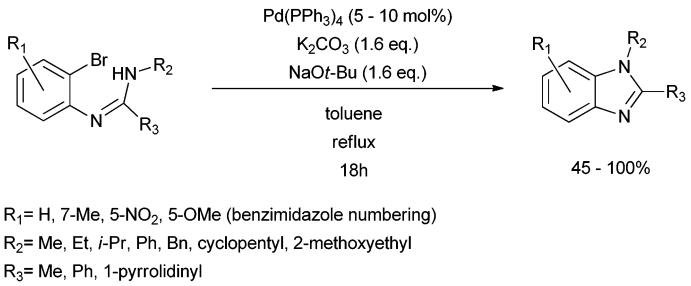



**Scheme 17** Cu-catalyzed N-arylation of resin-linked amidine.




**Scheme 18** Fe-catalyzed quinazolin-4(3*H*)-one synthesis.




**Scheme 19** Pd-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)amidines.

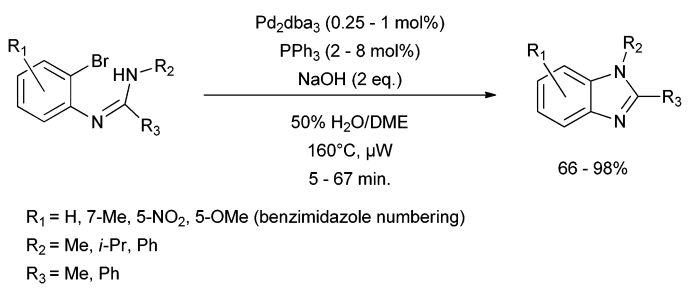
Moreover, by switching to microwave irradiation shorter reaction times were achieved provided a higher reaction temperature was applied. The phosphine residues were removed with a "catch and release" operation using Amberlyst 15. Electron-poor amidines gave the fastest reactions requiring the lowest catalyst loadings.

Analogously to the Brain team,[73] Evindar and Batey reported the use of $Pd(PPh_3)_4$ as a catalyst for the Pd-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)guanidines.[75] Only a different base ($Cs_2CO_3$) was used. A range of guanidines could be cyclized in low to very good yields (Scheme 21). However, as the required catalyst loading was quite high (10 mol%), a Cu-catalyzed variant for these transformations was developed which gave essentially the same results employing a lower catalyst loading (see Section 3.2.2), except for the 2,6-dibrominated substrate where the Pd catalysis provoked hydrodebromination while the Cu-catalyzed variant did not. Also *N*-(*o*-iodophenyl)-guanidines can be used in the transformation. Here also the Cu-catalyzed reaction conditions proved to be superior.

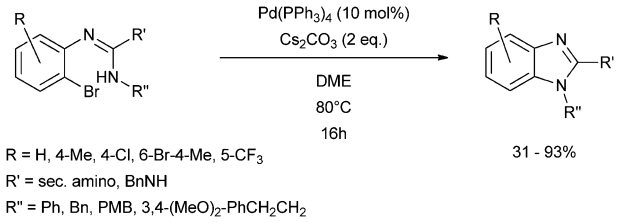
Substituted 1*H*-benzimidazoles can also be constructed *via* Pd-catalyzed intramolecular N-arylation of *N*-(*o*-chloroaryl)-amidines (Scheme 22).[76] Cyclization under the conditions of Brain and Brunton[73] (PhMe, 80 °C, 5 to 10 mol% $Pd(PPh_3)_4$) gave low yields. Optimal conditions were found by employing xylenes or DMF as solvent at a higher temperature.

Candito and Lautens showed the use of *N*-silyl-*N*′,*N*′-dialkyl-2-chlorobenzamidines for the synthesis of phenanthridin-6-amines *via* tandem catalysis (example given in Scheme 23).[77] The mechanism involves a Pd-catalyzed intermolecular N-arylation based on C($sp^2$)–H activation *via* norbornene assistance, followed by Pd-catalyzed intramolecular amination with the *N*-silylamidine moiety. The silylamidines are cleaved under the reaction conditions giving rise to a reactive nitrogen atom which participates in the Pd-catalyzed intramolecular amination reaction.

In 2009 Yang and Shi disclosed a method for the construction of 2-phenyl-1*H*-benzimidazoles from *N*-phenylbenzamidines *via* a Pd-catalyzed C–H activation approach (Scheme 24).[78] Evidence for a mechanism involving a palladacycle from which TMTU (tetramethylthiourea) promotes the reductive elimination is given. $Cu(OAc)_2$ serves as an oxidant shuttle for the reoxidation of Pd(0) formed after the reductive elimination, thereby rendering the transformation a catalytic process. Strongly electron withdrawing groups (both R and R′) are not




**Scheme 20** Second generation reaction conditions for the Pd-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)amidines.




**Scheme 21** Pd-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)guanidines.

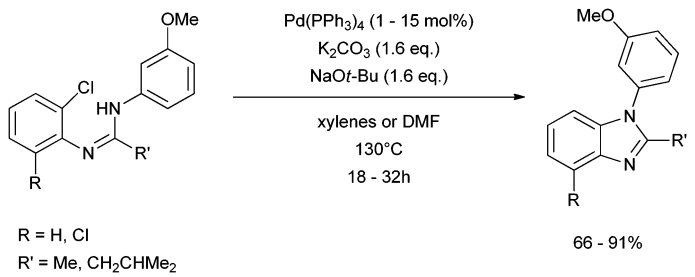
tolerated and *N,N′*-diphenylguanidine failed to cyclize as did *N*-phenylacetamidine. The observation that no desired product was formed from *N′*-phenylated *N*-phenylbenzamidine under the given reaction conditions indicates that a free imine N–H is necessary for this process.

### 3.2.2 Cu-catalyzed N-arylations

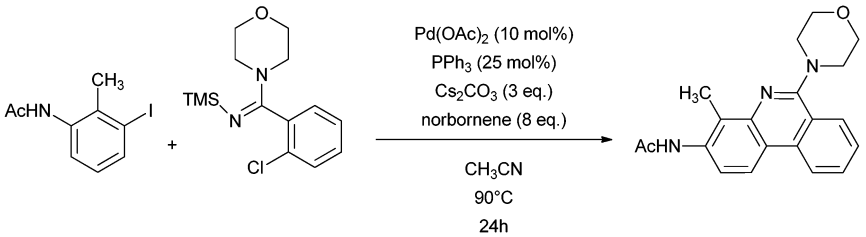
*3.2.2.1 Cu-catalyzed C–X amination*. As already referred above, Evindar and Batey also published a route to 1*H*-benzimidazoles *via* Cu-catalyzed intramolecular amination of *N*-(*o*-bromophenyl)guanidines using 1,10-phenanthroline (1,10-phen) as ligand in combination with CuI.[75] In this way the relatively high catalyst loading for the analogous Pd-catalyzed ring closure reaction (see Section 3.2.1) could be circumvented. By applying this protocol various *N*-(*o*-bromophenyl)guanidines could be cyclized into the corresponding 1*H*-benzimidazol-2-amines in good yields (Scheme 25). Also *N*-(*o*-iodophenyl)-guanidines can be used in the transformation.

Complementary, intramolecular arylation of *N*-(*o*-bromoaryl)-formamidines were reported by Glorius *et al.*[79] The 2-unsubstituted 1*H*-benzimidazoles synthesized in this way were obtained in excellent yields (Scheme 26). Sixteen examples bearing sterically demanding substituents (R′) on the nitrogen atom involved in the cyclization (*e.g.* mesityl, 2,6-diisopropylphenyl, 2-*tert*-butylphenyl group) were given and indicate the utility of this method. Intramolecular amination took readily place on brominated substrates, but also 2 examples of chlorinated substrates were provided. In the latter case the reaction times became very long (up to 190 h), yet reasonable yields were preserved.

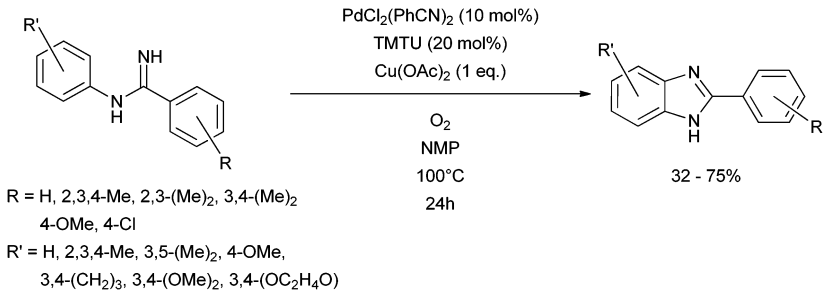
A Cu-catalyzed method in water as solvent has also been developed for the synthesis of the 1*H*-benzimidazole ring system.[80] Intramolecular arylation with $Cu_2O$ (5 mol%) as the catalyst, DMEDA (10 mol%) as ligand and $K_2CO_3$ as the base, gave the corresponding 1*H*-benzimidazoles starting from *N*-(*o*-halophenyl)-amidines (Scheme 27). The paper mentions also a single example on 1*H*-benzimidazole formation starting from a chlorinated substrate. *N*-(*o*-Chlorophenyl)-2-methylbenzamidine was successfully cyclized, but the yield was low (23%). Other chlorinated substrates gave decomposition of the starting material.




**Scheme 22** 1*H*-Benzimidazole synthesis *via* Pd-catalyzed intramolecular C–Cl amination.

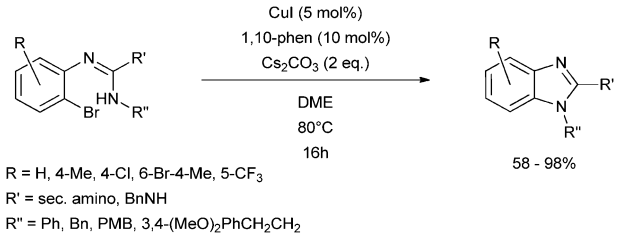



**Scheme 23** Example of a phenantridin-6-amine synthesis starting from *N*-silyl-*N′*,*N′*-dialkyl-2-chlorobenzamidines.



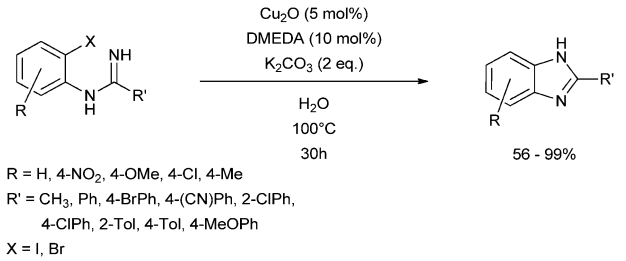

**Scheme 24** 2-Aryl-1*H*-benzimidazole construction *via* oxidative Pd-catalyzed C–H amination.




**Scheme 25** Cu-catalyzed intramolecular amination of *N*-(*o*-bromophenyl)guanidines.


**Scheme 26** Synthesis of 2-unsubstituted 1*H*-benzimidazoles by Cu-catalyzed intramolecular amination.




**Scheme 27** 1*H*-Benzimidazole synthesis *via* Cu-catalyzed intramolecular N-arylation of *N*-(*o*-halophenyl)amidines in water.

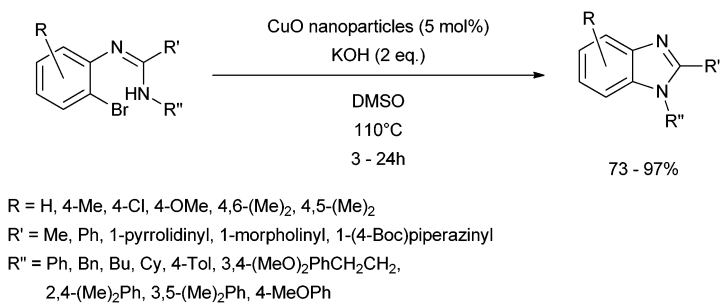
Copper(II)oxide nanoparticles can also serve as catalyst for the intramolecular amination of *N*-(*o*-bromophenyl)amidines (Scheme 28).[81] The cyclization of *N*-(*o*-halophenyl)amidines and guanidines was shown to be most effective using KOH in DMSO, while DMF, dioxane or toluene gave worse results. Cyclizations of substrates containing R′ = phenyl went faster and were better yielding than substrates bearing R′ = methyl or sec. amino group.

Aza-analogues of 1*H*-benzimidazoles have also been synthesized employing Cu catalysis.[82] The ligandless Cu-catalyzed intramolecular N-arylation of *N*-(5-bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)guanidines using CuI yielded xanthines (Scheme 29). Attempts to utilize Pd-catalysis or acidic conditions for the ring closure failed to give any product. Other electron-deficient brominated systems such as a pyridazinone, quinone, and maleimide (only pyridazinone shown in Scheme 29) all proceeded under similar conditions. Sodium hydride was the base of choice, but alkoxides and $Cs_2CO_3$ also promoted ring closure effectively in aprotic solvents. The guanidine substrates were synthesized *via* an addition–elimination reaction and when an aprotic solvent was used for this substitution reaction, a one pot sequence involving substitution and subsequent ring closure could be performed. Also *N*-(5-bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzamidine could be cyclized using the same reaction conditions. A limited range of more electron rich brominated substrates such as *N*-(*o*-bromophenyl)butyramidine were also tested. These required higher temperatures for the ring closure, but were nonetheless converted to the desired reaction product, albeit in a lower yield.

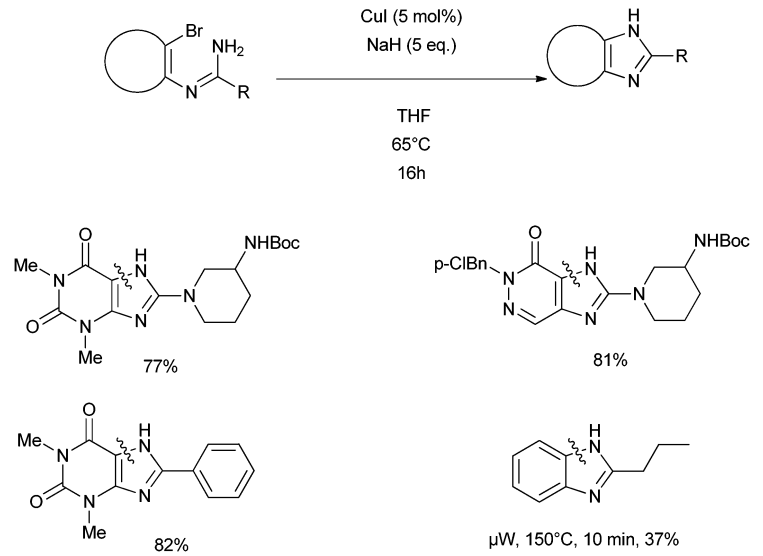
Besides 2-halobenzoic acids and 2-halobenzonitriles (Schemes 11–13), *o*-iodobenzaldehydes have also been used to build up the quinazoline core (Scheme 30).[83] Starting from *o*-iodobenzaldehydes a tandem reaction involving condensation and subsequent intramolecular amination occurred. This is in contrast to the tandem procedures starting from 2-halobenzoic acids and 2-halobenzonitriles which involved an intermolecular N-arylation as the first step. A ligandless approach was adopted since the addition of typically used ligands for C–N bond formation *via* Cu-catalyzed arylation such as DMEDA, *L*-proline or 8-hydroxyquinoline gave only modest yields. A variety of substituted benzamidines, a heteroaromatic analogue and an alkylamidine were found to be compatible with the reaction conditions (Scheme 30). No *o*-substituted benzamidines were tested and *o*-bromobenzaldehyde turned out to be a troublesome substrate, even at elevated temperatures.

The problematic *o*-bromobenzaldehyde substrate could however be coupled successfully when *L*-proline was added to assist in the Cu-catalyzed intramolecular amination. Also switching from MeOH to DMF, allowing a reaction at higher temperature (110 °C), proved to be beneficial.[84] Interestingly, under the same reaction conditions 2-bromophenylketones were also viable substrates (Scheme 31).

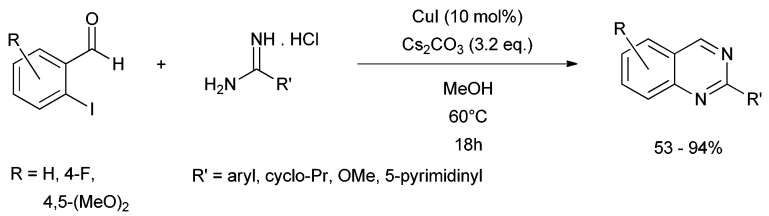
This catalytic system could be extended to the formation of quinazolin-4(3*H*)-ones when starting from methyl *o*-bromobenzoates or *o*-chlorobenzoates (Scheme 32). A lower temperature could be applied *versus* starting from *o*-bromobenzaldehydes (80 °C). Interestingly, methyl 2-chloronicotinate could equally well be used as substrate. The authors proposed a mechanism



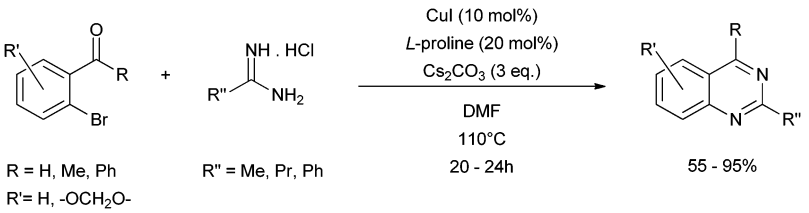

**Scheme 28** CuO-catalyzed 1*H*-benzimidazole formation.




**Scheme 29** Fused imidazole systems prepared from acyclic guanidines and amidines by Cu-catalyzed intramolecular N-arylation.




**Scheme 30** Synthesis of quinazolines *via* tandem reaction of *o*-iodobenzaldehydes with amidines.




**Scheme 31** Quinazoline formation *via* tandem reaction of 2-bromophenylketones with amidines.

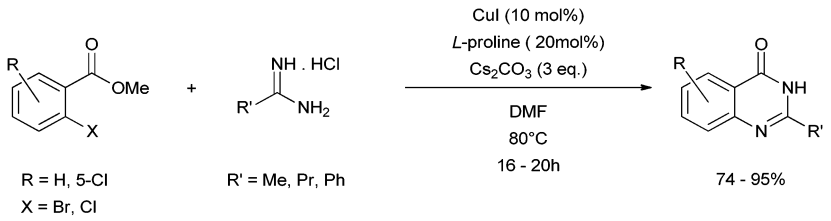
for the quinazolin-4(3*H*)-one formation based on a tandem reaction consisting of ester aminolysis by the amidine followed by Cu-catalyzed intramolecular amination.

In 2010 a novel synthetic route for the preparation of candesartan cilexetil was described. One of the key steps was the formation of the 2-ethoxybenzimidazole moiety *via* intramolecular Cu-catalyzed N-arylation of an *N*-(*o*-bromophenyl)-*O*-propylisourea.[85] Also here *L*-proline was used as ligand for CuI, in combination with $K_2CO_3$ as base (Scheme 33). The transformation however required a very high catalyst loading (0.5 eq.). The authors also reported that for the same transformation CuI/NaH could be used in refluxing THF, but that this base should be avoided for industrial applications (for the use of NaH see also Schemes 29 and 94).[82]

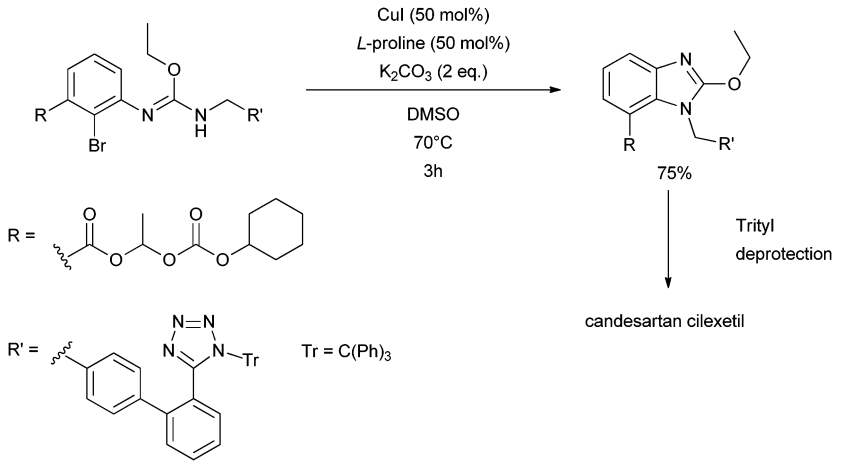
Similarly *S*-alkylated, benzylated and allylated isothioureas have also been used as substrates yielding the corresponding *S*-alkylated, benzylated and allylated 2-mercaptobenzimidazoles (Scheme 34).[86] *N*-(*o*-Bromophenyl)-*N*′-(*o*-iodophenyl)thiourea led, after alkylation with MeI, under standard Cu-catalyzed ring closure conditions to a mixture of brominated and iodinated derivatives. However, when the reaction was performed at lower temperature, 1-(*o*-bromophenyl)-2-(methylthio)benzimidazole was produced with a good selectivity. 1,3-Dihydro-2*H*-benzimidazole-2-thiones are also accessible by using a protection/deprotection strategy using the PMB protective group.

*N*-Sulfonyl-1*H*-benzimidazoles could be obtained by a Cu-catalyzed three-component reaction of sulfonyl azides, alkynes and 2-bromoanilines followed by a Cu-catalyzed intramolecular N-arylation of the formed *N*-sulfonylamidines in a one-pot sequence (Scheme 35).[87] A single example of 2-iodoaniline is given, while 2-chloroaniline could not be coupled under these conditions. Also heteroaromatic substrates, 2-bromopyridin-3-amine and 3-bromo-6-methylpyridin-2-amine, can be used as substrates (not shown). A plausible mechanism was proposed for this cascade process involving a ketenimine species formed by CuI catalyzed condensation of the sulfonazide and the alkyne. This ketenimine is quickly attacked by the aniline to generate a *N*-sulfonylamidine, which is cyclized in the next step.

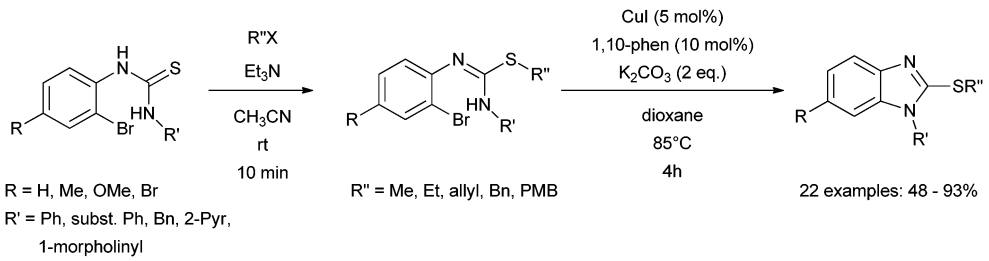
 




**Scheme 32** Quinazolinone formation *via* tandem reaction of methyl 2-halobenzoates with amidines.



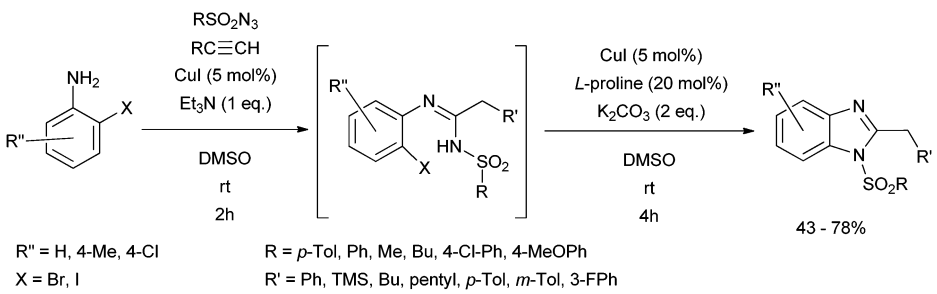

**Scheme 33** Synthesis of candesartan cilexetil.



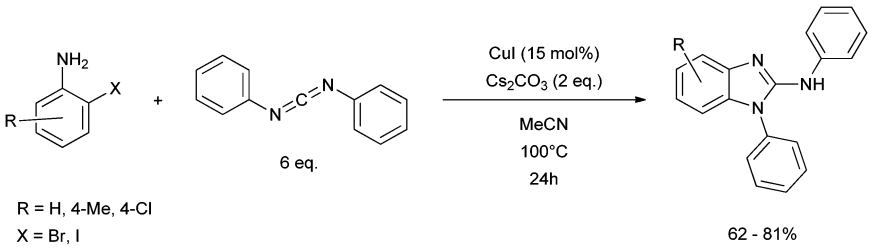

**Scheme 34** Synthesis of *S*-alkylated, benzylated and allylated 2-mercapto-1*H*-benzimidazoles *via* Cu-catalyzed intramolecular N-arylation of the corresponding *S*-alkylated, benzylated and allylated *N*-(*o*-bromophenyl)isothioureas.

A concise way of constructing *N*,1-diphenyl-1*H*-benzimidazol-2-amines from 2-haloanilines and diphenyl carbodiimide was presented in 2010.[88] The 1*H*-benzimidazoles could be obtained *via* a cascade addition/cyclization reaction promoted by ligandless CuI in acetonitrile (Scheme 36). A possible downside is the need for an excess of diphenyl carbodiimide, which had to be added portionwise to the reaction mixture over a period of 18 h in order to consume all of the aniline. Also, a single example using *N*-methyl-2-iodoaniline as substrate is presented and the method can be applied to construct *N*-(3-phenylbenzo-[*d*]oxazol-2(3*H*)-ylidene)anilines from 2-halophenols.

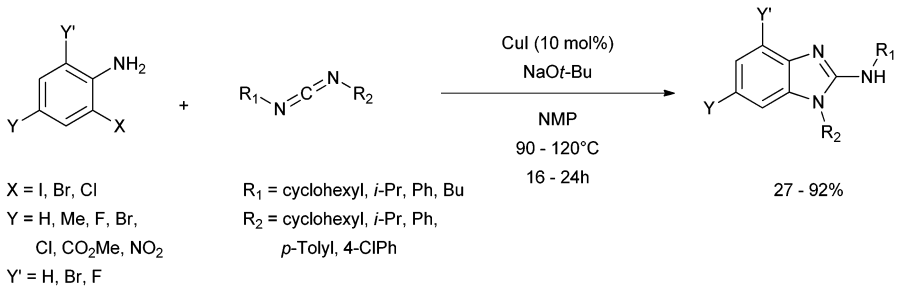
Other substituted benzimidazol-2-amines can also be constructed *via* a similar synthetic approach but under slightly modified conditions (Scheme 37).[89] Optimal reaction conditions consist also of the use of a ligandless CuI catalyst, but using a stronger base in another solvent (NMP). When the




**Scheme 35** Tandem Cu-catalyzed synthesis of *N*-sulfonyl-1*H*-benzimidazoles from sulfonyl azides, alkynes and 2-bromoanilines.




**Scheme 36** Cu-catalyzed one-pot synthesis of *N*,1-diphenyl-1*H*-benzimidazol-2-amines.




**Scheme 37** Synthesis of benzimidazol-2-amines from symmetrical and unsymmetrical carbodiimides and *o*-haloanilines.

reaction was performed with unsymmetrically substituted carbodiimides ($R_1$ = alkyl, $R_2$ = aryl), preferential cyclization occurred on the aryl-NH group rather than on the alkyl-NH group.

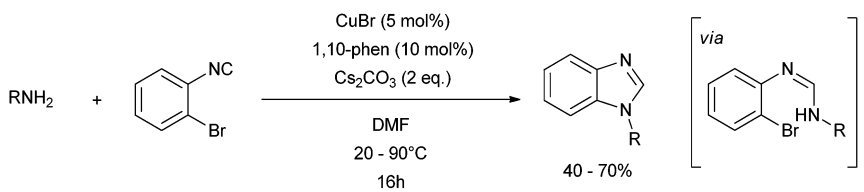
Lygin and de Meijere envisioned the synthesis of 2-unsubstituted 1*H*-benzimidazoles from *o*-bromophenyl isocyanide employing copper catalysis.[90] Isocyanides are well known to give amidines after reaction with amines in the presence of a copper catalyst.[91] A Cu-catalyzed intramolecular amination from the *in situ* formed amidines can then give access to the benzimidazole core. As both steps require the same type of catalyst, a tandem procedure was developed (Scheme 38). The reaction of *o*-bromophenylisocyanide with *tert*-butylamine surprisingly gave rise to 1-(2-bromophenyl)-1*H*-benzimidazole (38%) and no *N*-(*tert*-butyl)-1*H*-benzimidazole. An extension of the reaction scope with respect to the substrate was also given. Three examples yielding 3-substituted 3*H*-thieno[2,3-*d*]-imidazoles starting from 2-bromo-3-isocyanothiophene as substrate were also included (Scheme 39).

Takayama *et al*. proposed a retrosynthetic approach towards the trimeric indole alkaloid (±)-psychotrimine based on the formation of the saturated pyrroloindole core through the use of an intramolecular CuI mediated N-arylation reaction.[92] The authors undertook a careful optimization of the reaction parameters (ligand, solvent, and base). In this particular case, diamine ligands DMEDA and CHDA as well as 1,10-phen proved to be completely inefficient, which was attributed to the very low reactivity of the amidine nitrogen. Switching to ligandless conditions and stoichiometric copper overcame this issue, yielding the cyclized product in high yield (Scheme 40).

*3.2.2.2 Cu-catalyzed C–H amination*. Brasche and Buchwald disclosed a new $Cu(OAc)_2$ catalyzed synthesis of 2-aryl-1*H*-benzimidazoles and 2-*tert*-butyl-1*H*-benzimidazoles from *N*-arylamidines through an intramolecular direct C–H amination process which uses oxygen as the stoichiometric oxidant and generates water as the only direct waste product (Scheme 41).[93] The procedure requires the use of 5 equivalents of acetic acid. Various functional groups on the aryl moieties are well tolerated. While the method is generally applicable for benzamidines, currently only a *tert*-butyl group can be employed as a representative of an alkyl group creating 2-alkyl-1*H*-benzimidazoles. Also, *N*-methyl-2-aryl-1*H*-benzimidazoles can be constructed this way from *N*-alkyl-*N*-arylamidines.

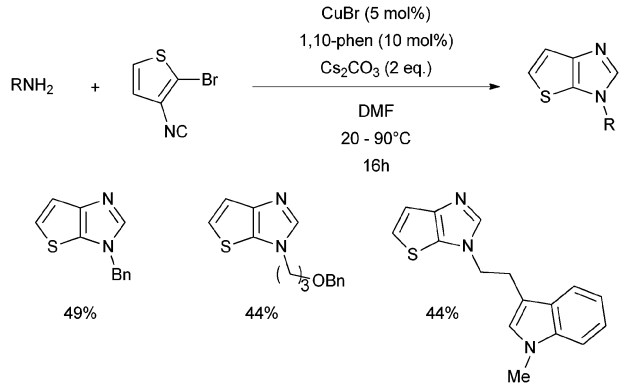
Inspired by this publication by Brasche and Buchwald, Bao *et al*. was able construct 1,2-substituted 1*H*-benzimidazoles directly from the reaction of diphenyl carbodiimides with different nitrogen and oxygen nucleophiles *via* an addition/C–H amination cascade process catalyzed by $Cu(OAc)_2$ with $O_2$ as the stoichiometric oxidant (Scheme 42).[94]

In 2011 the transformation of *N*-benzyl bisarylhydrazones to functionalized 2-aryl-*N*-benzyl-1*H*-benzimidazoles was




**Scheme 38** Tandem Cu-catalyzed synthesis of *N*-substituted 1*H*-benzimidazoles from *o*-bromoarylisocyanides.

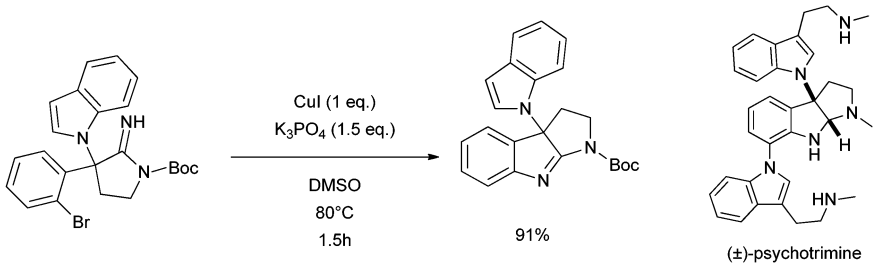
 



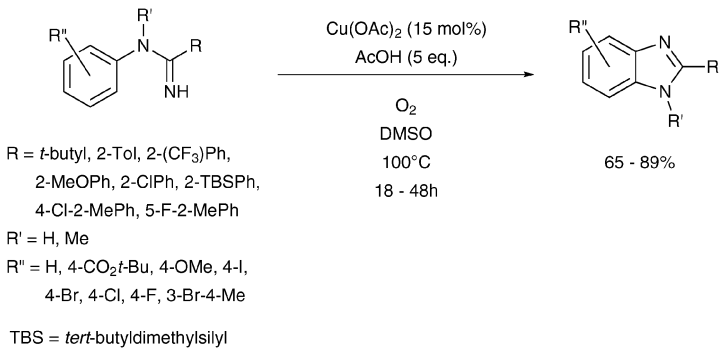

**Scheme 39** Tandem Cu-catalyzed synthesis of 3-substituted 3*H*-thieno[2,3-*d*]imidazoles from 2-bromo-3-isocyanothiophene.

published (Scheme 43).[95] A stoichiometric amount of $Cu(OTf)_2$ in refluxing toluene was employed to access the benzimidazoles in moderate to good yields. A variety of substituents, both electron donating and electron withdrawing were tolerated but an extreme case such as with $R_1 = NO_2$ gave no desired benzimidazole. The reaction is proposed to proceed *via ortho*-metalation in the $R_2$ containing arene induced by nitrile formation *via* scission of the N–N bond. The benzonitrile formed (still coordinated to Cu) is then attacked by the generated imine, forming an amidine. Upon reductive elimination benzimidazole is formed (Scheme 44).

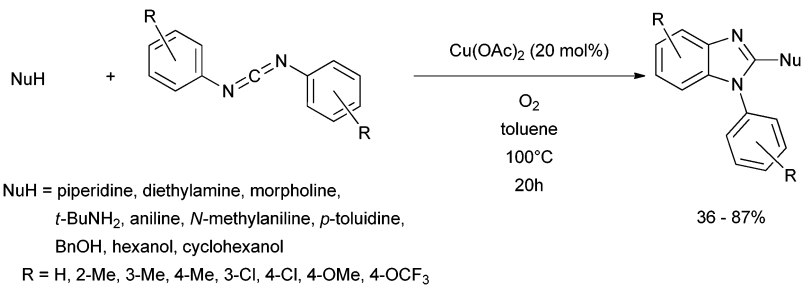
*3.2.2.3 Cu-catalyzed* N *amination*. A one-step synthesis of 1,2,4-triazolo annulated pyridines by Cu-catalyzed oxidative coupling reaction of pyridin-2-amines and benzonitriles was described in 2009.[96] The key step in the tandem reaction consists of a Cu-catalyzed N–N bond forming step. Starting from pyridin-2-amines and (hetero)aromatic nitriles the corresponding 1,2,4-triazolo[1,5-*a*]pyridines could be obtained in moderate to good yields (Scheme 45). The addition of $ZnI_2$ and the use of 1,2-dichlorobenzene (DCB) as solvent enhanced the reaction to a great extent. The authors also gave a single example using isoquinolin-1-amine. Moreover alkanimidamides or arenecarboximidamides can also be used as a coupling partner, yielding 2,3-disubstituted 1,2,4-triazoles (not shown).



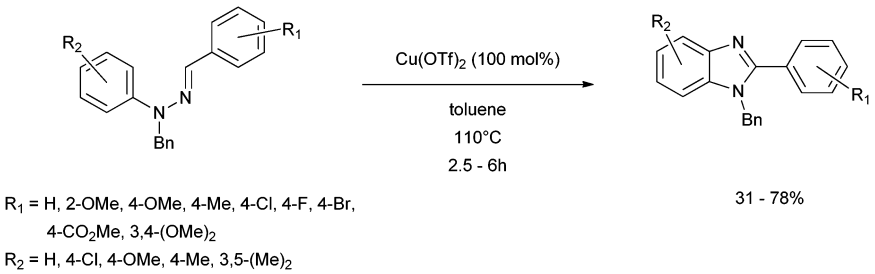

**Scheme 40** Synthesis of the (±)-psychotrymine pyrroloindole core *via* Cu-mediated intramolecular N-arylation.



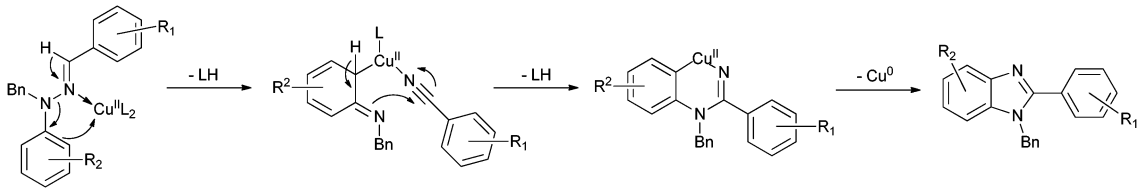

**Scheme 41** Oxidative Cu-catalyzed intramolecular C–H amination of *N*-arylamidines.



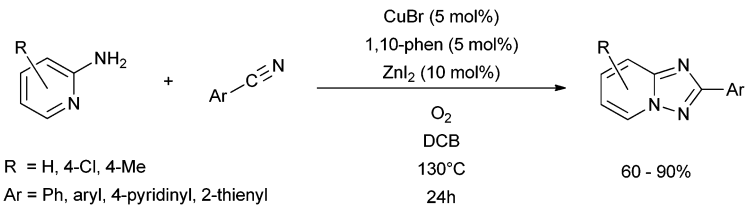

**Scheme 42** Oxidative Cu-catalyzed synthesis of 1,2-substituted 1*H*-benzimidazoles through an addition/C–H amination cascade with nitrogen and oxygen nucleophiles and diaryl carbodiimides as substrate.




**Scheme 43** Synthesis of 2-aryl-*N*-benzyl-1*H*-benzimidazoles by Cu-mediated transformation of *N*-benzyl bisarylhydrazones.




**Scheme 44** Proposed mechanism.




**Scheme 45** Oxidative Cu-catalyzed synthesis of 1,2,4-triazolo[1,5-*a*]pyridines from pyridin-2-amines and (hetero)aromatic nitriles.

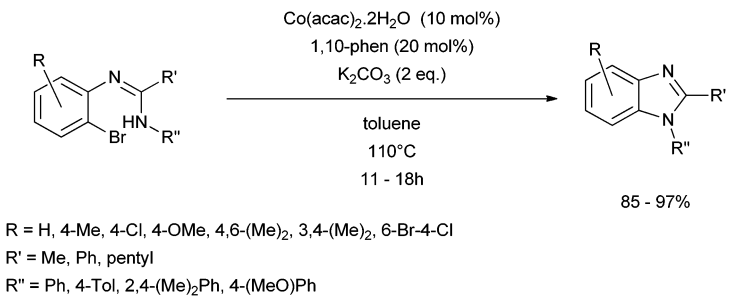
**3.2.3 Co-catalyzed N-arylations.** The intramolecular Co-catalyzed C–N bond formation in *N*-(*o*-bromophenyl)-*N*′-phenylamidines in the presence of $K_2CO_3$ as base was disclosed in 2010 (Scheme 46).[97] 1,10-Phenanthroline proved to be a better ligand than *L*-proline, ethylene glycol and 8-hydroxyquinaldine. *N*-(*o*-Iodophenyl)-*N*′-phenylbenzamidine exhibited a greater reactivity affording the desired 1*H*-benzimidazole in 6 h with quantitative yield, whereas *N*-(*o*-chlorophenyl)-*N*′-phenylbenzamidine showed no reaction. The cobalt source was screened for trace amounts of copper as these proved to be the active catalyst in Fe-catalyzed cross-couplings,[98] but none was detected.

## 4. Amidines/guanidines which are part of a heteroaromatic system

### 4.1 Intermolecular N-arylations

**4.1.1 Pd-catalyzed N-arylations.** For amidines which are part of a heteroaromatic ring system, in contrast to their acyclic counterparts, Pd-catalyzed amination is much more explored. Catalyst systems comprise mainly Pd/BINAP and Pd/Xantphos, based on chelating ligands. In this way for example 2-amino(benzo)thiazoles are coupled with a wide variety of (hetero)aryl halides.[99,100–139] The ferrocenyl based ligand CyPF-*t*-Bu shows also a very good catalytic activity for the arylation of such nitrogen systems.[140,141] Only three catalyst systems which do not contain chelating ligands have been successfully employed, namely Pd/XPhos, Pd/*t*-Bu-XPhos, and Pd/BrettPhos. This section is divided into two parts: intermolecular N-arylation based on the use of a chelating ligand (Section 4.1.1.1) and a part which deals with the Pd-catalyzed amination employing a monodentate ligand (Section 4.1.1.2).

*4.1.1.1 Pd-catalyzed N-arylations employing a chelating ligand.* In 2001 Maes *et al.* reported the amination of 2,3-dichloropyridine with (di)azinamines.[142] Employing a Pd/BINAP catalyst system and an excess of carbonate base a C2 regioselective amination could be smoothly achieved (Scheme 47). Employing the same




**Scheme 46** Co-catalyzed intramolecular N-arylation of *N*-(*o*-bromophenyl)-*N*′-phenylamidines.

reaction conditions 2,6-dichloropyridine could also be aminated with pyridin-2-amine.

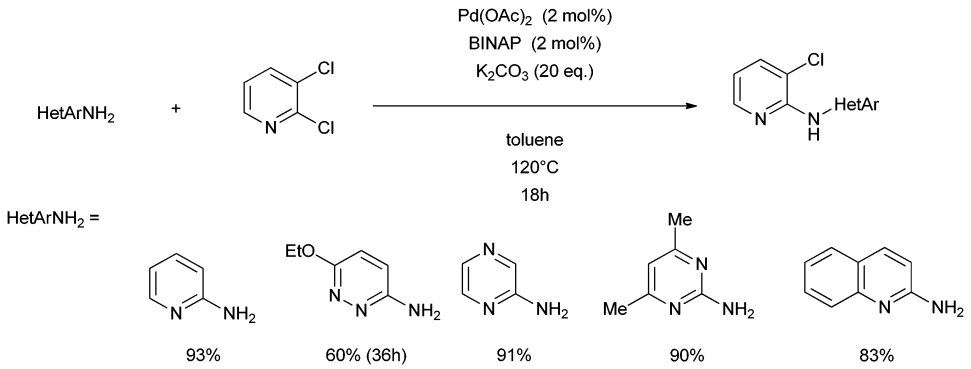
A special case of amination using pyridin-2-amine was published in 2005. Kanbara *et al.* reported the synthesis of new heterocalixarenes, *N*-(*p*-tolyl)azacalix[*n*](2,6)pyridines ($n$ = 3–8, and 10), constituted of various numbers of pyridin-amine units *via* Cu- and Pd-catalyzed amination reactions.[143] One of the reported synthetic routes for the oligo-α-amino-pyridines goes *via* the Pd-catalyzed homo-coupling of 6-bromo-*N*-(4-methylphenyl)pyridin-2-amine with $Pd_2(dba)_3$/Xantphos as catalyst and NaO*t*-Bu as base (Scheme 48).

Another pioneering article dealing with Pd-catalyzed N-arylation reactions involving heteroarenamines was published in 2002 by Yin *et al.* from Merck.[144] Xantphos proved to be the best ligand in comparison with dppe and BINAP, and $Cs_2CO_3$ was the base of choice in dioxane. Selected examples are shown in Scheme 49. Notably, they succeeded in coupling thiazol-2-amines and derivatives under slightly modified reaction conditions. These aminations imply a higher catalyst loading (up to 8 mol% Pd), using NaO*t*-Bu, $K_3PO_4$ or $Na_2CO_3$ as base, and in some cases toluene as solvent (selected examples in Scheme 50).

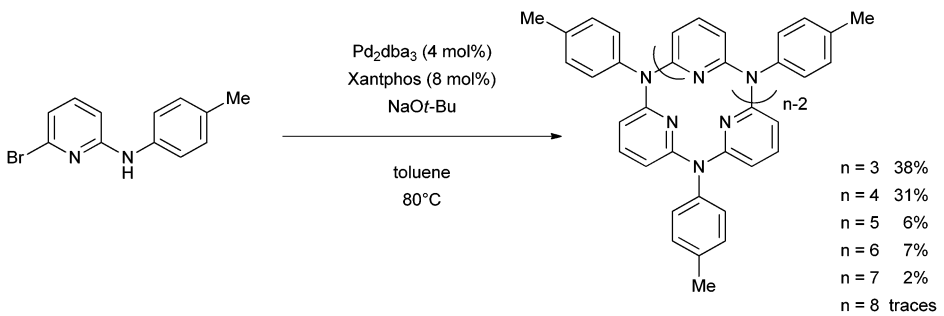
Zhang *et al.* also published an amination reaction involving 1,3-benzothiazol-2-amine with 2-chloro-5-ethylpyrimidine as substrate using microwave irradiation to heat the reaction mixture.[145] Pd-catalysis with Xantphos as ligand in dioxane was used since acid-catalyzed $S_NAr$ failed (Scheme 51).

An ICAGEN patent described Pd-catalyzed aminations with other azolamines (1*H*-diazol-3-amine and 1,2-oxazol-3-amine) (Scheme 52).[112]

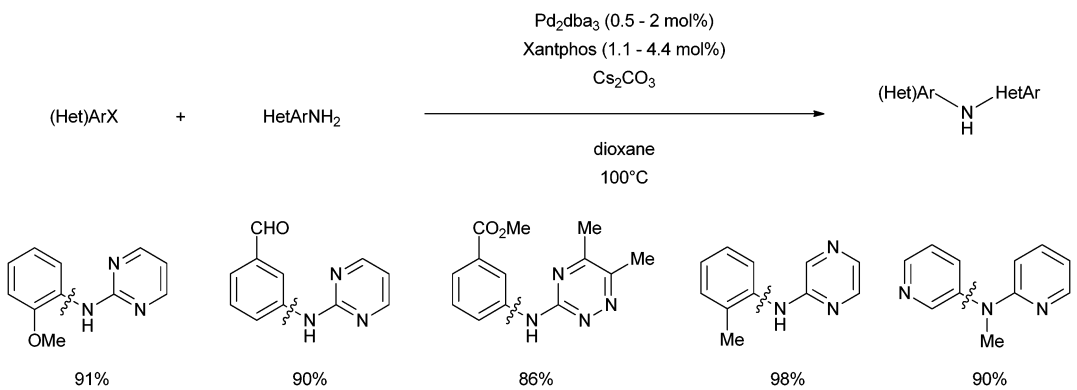
In 2004 Maes *et al.* reported a tandem amination protocol for the (aza)dipyridoimidazole synthesis *via* coupling of 2-chloro-3-iodopyridine with various azin- and diazinamines (Scheme 53).[146] BINAP or Xantphos were used as ligands and



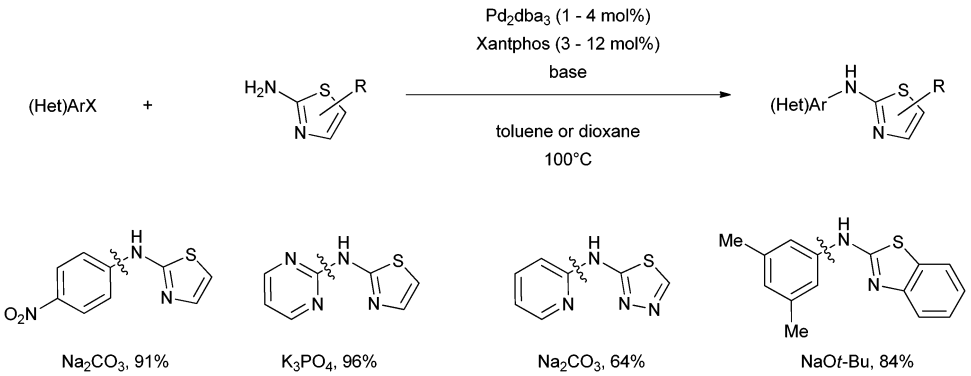

**Scheme 47** Regioselective Pd-catalyzed amination of 2,3-dichloropyridine with amidine/guanidine containing heteroaromatic amines.



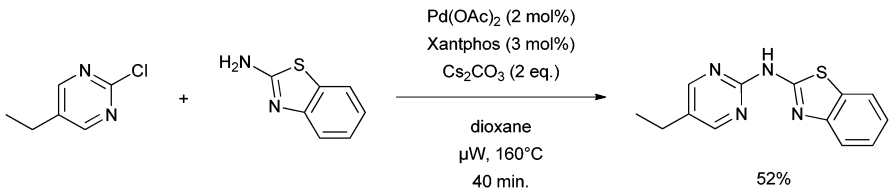

**Scheme 48** Synthesis of *N*-(*p*-tolyl)azacalix[*n*](2,6)pyridines.




**Scheme 49** Pd-catalyzed N-arylation involving (di)azin- and triazinamines.




**Scheme 50** Pd-catalyzed N-arylations involving thiazol-2-amines, benzothiazol-2-amine and [1,3,4]thiadiazol-2-amine.

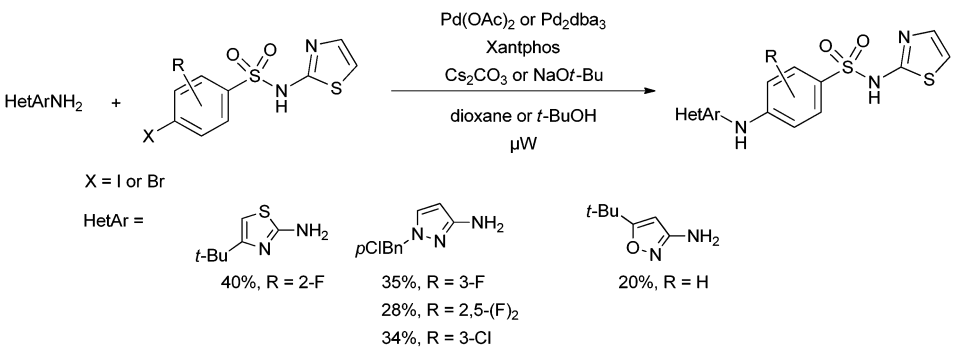



**Scheme 51** Synthesis of *N*-(5-ethylpyrimidin-2-yl)-1,3-benzothiazol-2-amine *via* Pd-catalyzed amination of 2-chloro-5-ethylpyrimidine with benzothiazol-2-amine.

$Cs_2CO_3$ as base to effect the transformation. After a chemoselective intermolecular amination with the exocyclic amino group, an intramolecular amination involving the endocyclic nitrogen spontaneously occurred. The large excess of base, although almost completely insoluble in the solvent used (toluene), was essential to obtain high cross-coupling rates. An interphase deprotonation of the palladium(II)–amine intermediate formed in the catalytic cycle is the basis for this remarkable 'base effect'.[147]

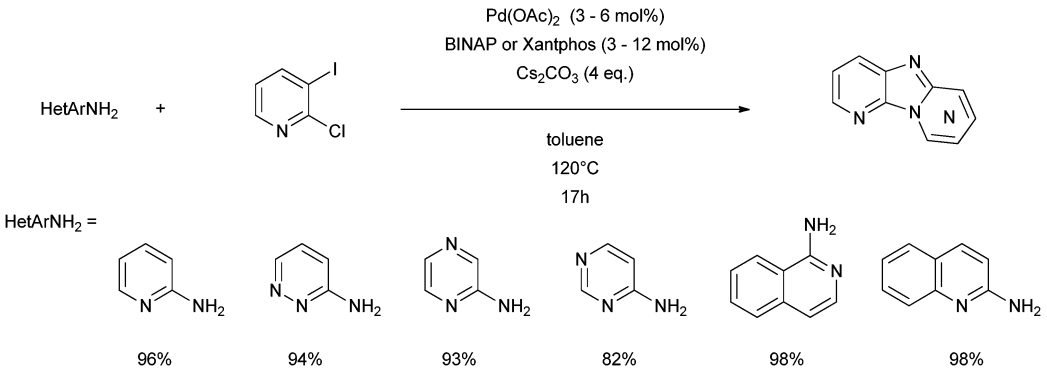
A subsequent article dealt with the construction of the regioisomers of (aza)dipyrido[1,2-*a*:3′,2′-*d*]imidazole.[148] The synthesis of these regioisomers could be accomplished in one step with the same (di)azinamines starting from commercially available 2,3-dibromopyridine. The ring closure reaction did however not occur with the same Pd-catalyst as used previously and only allowed smooth and selective C2 intermolecular amination in this case (Scheme 54). The regioselectivity was shown *via* dehalogenation. A Cu catalyst was required to achieve the aimed cyclization (Scheme 54). Pd and Cu catalyst could be simultaneously added providing an example of orthogonal tandem catalysis.

These tandem amination procedures could be extended to the benzo-analogs of the pyridine substrates, 2-chloro-3-iodoquinoline and 2,3-dibromoquinoline (Scheme 55).[149] Again tandem amination on 2-chloro-3-iodoquinoline required only Pd-catalysis while those on 2,3-dibromoquinoline generally required the action of a Pd- and a Cu-catalyst. For the double amination of 2,3-dibromoquinoline with quinolin-2-amine, isoquinolin-1-amine, and pyridazin-3-amine the use of $Pd_2dba_3$/Xantphos was surprisingly sufficient. Following this at first glance strange observation, a study was performed to assess whether the mechanism of the intramolecular amination step was indeed always transition metal-catalyzed or in some cases rather a base-assisted nucleophilic aromatic substitution.[150] It was found that nucleophilic aromatic substitution is indeed possible as alternative mechanism and its occurrence depends on the aromaticity of the amidine containing heteroaromatic ring. The heteroarenes with the lowest resonance energy therefore gave access to their cyclized counterparts without the interference of a transition metal catalyst. In addition, for those intramolecular aminations that occured *via* the involvement of

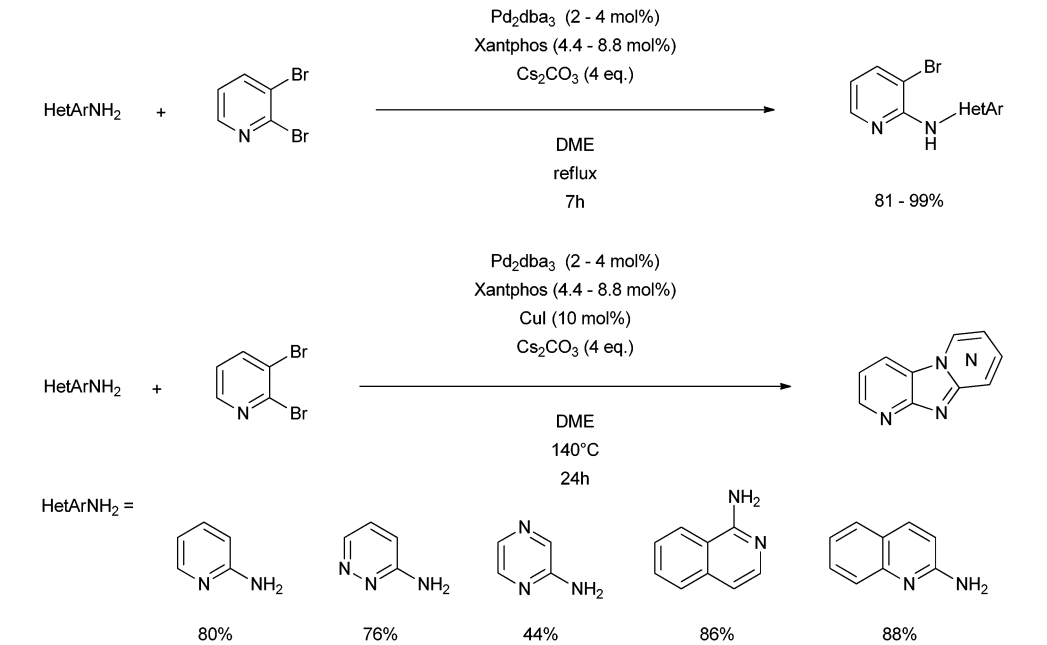



**Scheme 52** Pd-catalyzed aminations with 4-*tert*-butyl-1,3-thiazol-2-amine, 1-(4-chlorobenzyl)-1*H*-1,2-diazol-3-amine and 5-*tert*-butyl-1,2-oxazol-3-amine.

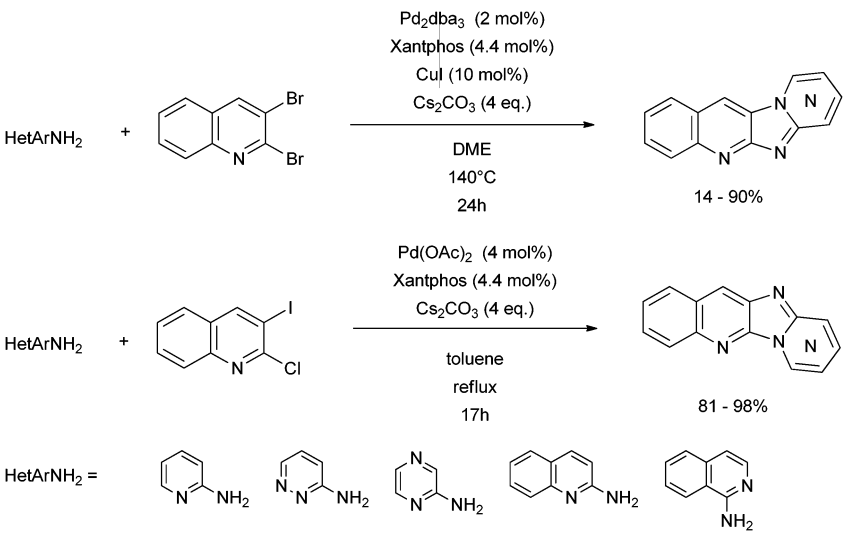
 




**Scheme 53** (Aza)dipyrido[1,2-*a*:3′,2′-*d*]imidazole synthesis *via* tandem amination of 2-chloro-3-iodopyridine with (di)azinamines.




**Scheme 54** (Aza)dipyrido[1,2-*a*:2′,3′-*d*]imidazole synthesis *via* tandem amination of 2,3-dibromopyridine with (di)azinamines.




**Scheme 55** Tandem amination of 2-chloro-3-iodoquinoline and 2,3-dibromoquinoline with (di)azinamines.

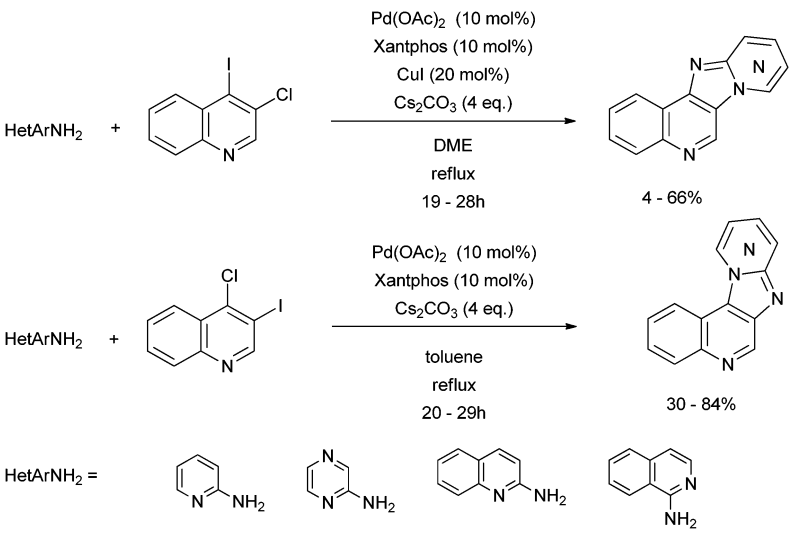
a transition metal catalyst, evidence was gained based on DFT calculations that the imine type nitrogen in the heteroarene is involved in the catalytic cycle. No prior tautomerization is occurring.

Based on the work of Maes, Bogányi and Kámán studied a tandem inter- and intramolecular Pd-catalyzed amination protocol on 4-chloro-3-iodoquinoline and 3-chloro-4-iodoquinoline as substrates with different heteroarenamines (Scheme 56).[151] Tri- and tetraazabenzo[*c*]fluorenes could be obtained from 3-iodo-4-chloroquinoline by employing a Pd/Xantphos catalyst system. For the coupling with 4-iodo-3-chloroquinoline, a tandem approach based on two catalysts (Pd and Cu-catalysis) had to be used to affect the double inter- and intramolecular amination.

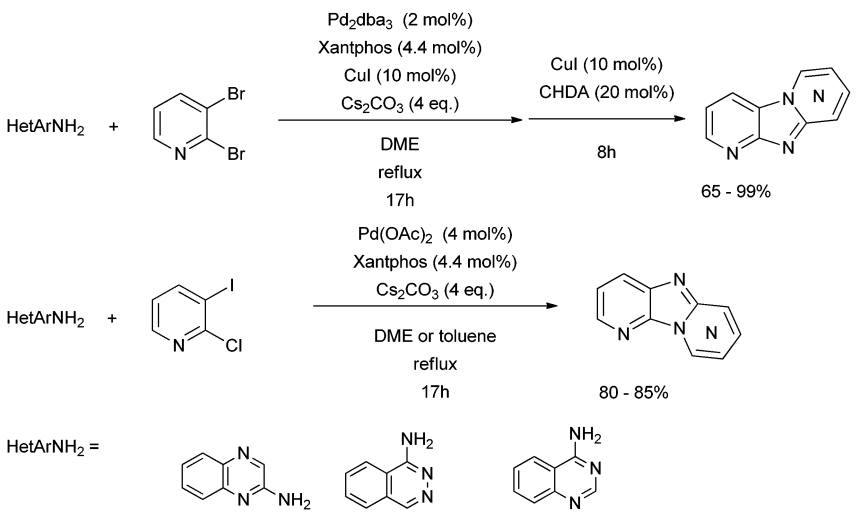
More recently, Maes reported a further extension of the scope of the transition metal-catalyzed double amination of dihalopyridines using the benzodiazinamines phthalazin-1-amine, quinazolin-4-amine and quinoxalin-2-amine as coupling partners.[152] These benzodiazinamines were reacted with 2-chloro-3-iodopyridine and 2,3-dibromopyridine employing Pd- and Pd/Cu-catalysis (Scheme 57). The use of *trans*-cyclohexane-1,2-diamine (CHDA) as ligand for the copper catalyst allowed the intramolecular amination on the *N*-(3-bromopyridin-2-yl)benzodiazinamines to take place at a lower reaction temperature, but required the performance of the intermolecular and intramolecular reaction in a sequential manner (one pot). Also for the ring closure reaction of the intermediate *N*-(2-chloropyridin-3-yl)quinazolin-4-amine the same copper catalyst system was employed since reaction at high temperature gave an unexpected Smiles rearrangement.

A remarkable example of tandem catalysis was reported in 2010. Bispyrazino[2″,3″:4′,5′]imidazo[1′,2′:1,6]pyrazino[2,3-*b*:2′,3′-*e*]pyrazines were prepared by $Pd(OAc)_2$/BINAP-catalyzed C–N coupling reactions involving 5-aryl-3-bromopyrazin-2-amines (Scheme 58).[153] Yields were low, but an impressive structural motif could be obtained from a single starting material.

A Pd-catalyzed amination using substituted pyrimidin-2-amines was published by Korean researchers in 2008 (Scheme 59).[154] The precatalyst $(PPh_3)_2PdCl_2$ is used to ensure the dissolution of the otherwise insoluble $PdCl_2$ in the

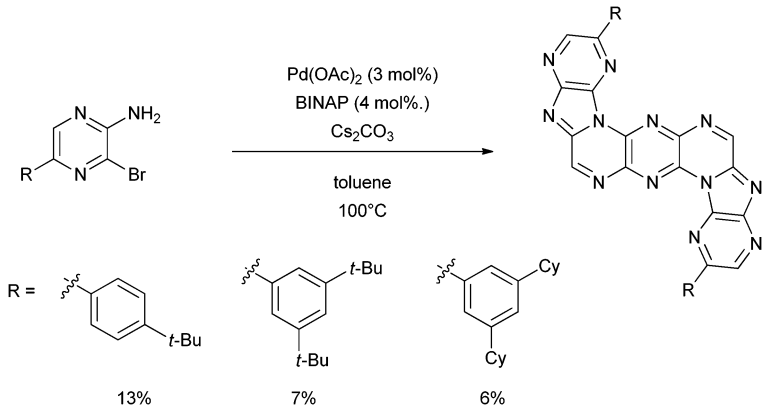



**Scheme 56** Tandem aminations of 3-chloro-4-iodoquinoline and 4-chloro-3-iodoquinoline with (di)azinamines.




**Scheme 57** Tandem amination of 2-chloro-3-iodopyridine and 2,3-dibromopyridine with benzodiazinamines.




**Scheme 58** Bis(pyrazino[2′,3′:4,5]imidazole)-fused 1,2,5,6-tetrahydro-1,4,5,8,9,10-hexaazaanthracenes synthesis *via* Pd-catalyzed amination involving 5-aryl-3-bromopyrazin-2-amines.

reaction mixture. A follow up paper also used some other substituted bromoarenes for the same transformation.[155] Mexican researchers employed a Pd/Xantphos catalyst system to achieve N-arylation on similar substrates but this time generated from $Pd(dba)_2$ precatalyst.[156] By employing a weaker base they succeeded in the construction of some new, albeit cytotoxic, CDK inhibitor compounds.

The Buchwald group published the use of (hetero)aryl nonaflates as coupling partners for various amidine containing heteroaromatics (Scheme 60).[157] Microwave irradiation ensured short reaction times at higher temperatures. Noteworthy is the use of an organic base, MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), which is a good microwave absorber allowing the reactions to be run at higher temperature in non-polar solvents.

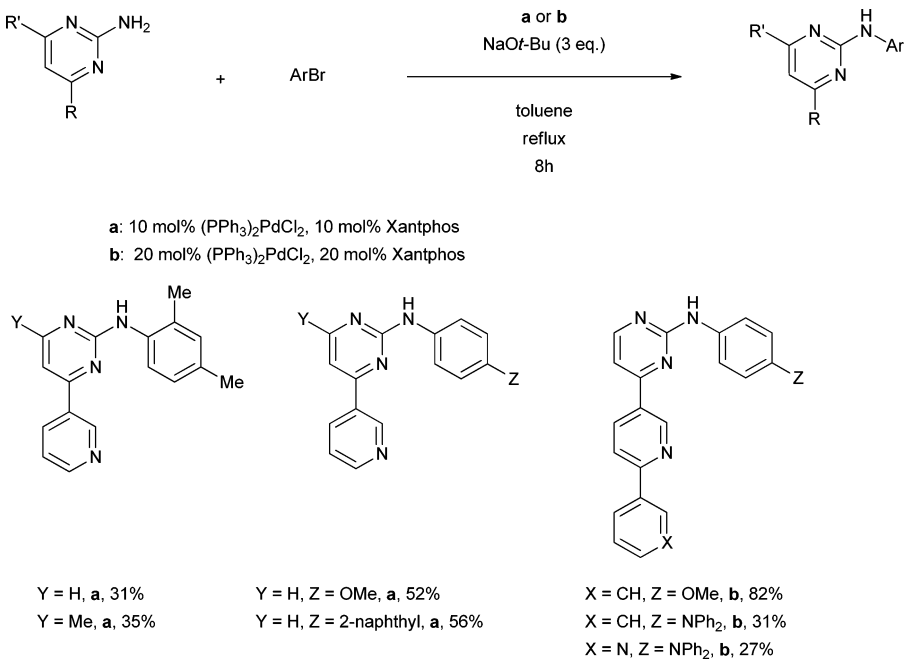
Noronha *et al.* described the amination of various bromobenzenes with benzo[1,2,4]triazin-3-amines using a $Pd_2dba_3$/Xantphos catalyst system (Scheme 61).[158]

During the search for a quinazoline glucokinase activator, Japanese researchers used a Pd/BINAP catalyst system to aminate 6-acetoxy-4-chloroquinazoline with various heteroaromatic amidines (Scheme 62).[159]

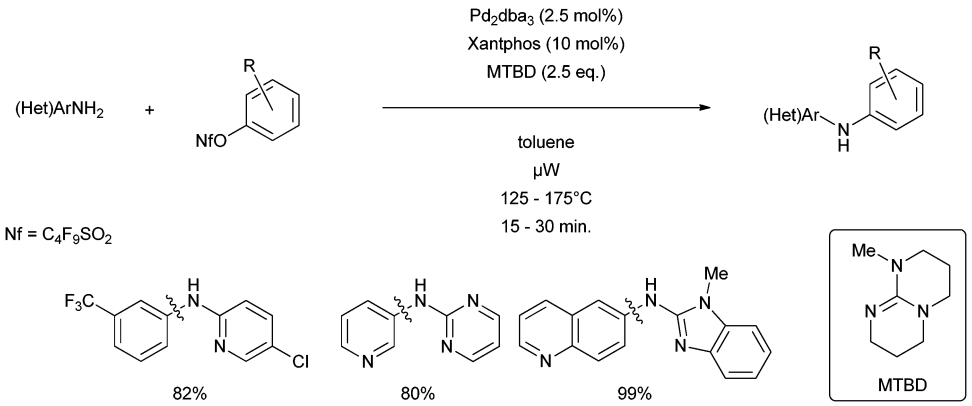
Ogata and Hartwig reported the amination of (hetero)aryl tosylates using CyPF-*t*-Bu as ligand.[140] Reactions were run with a low loading of Pd and at room temperature. Under these conditions, the amidine pyridin-2-amine could be coupled with phenyl tosylate in good yield (Scheme 63).

The same ligand was also employed for the arylation of pyrazin-2-amine with 3-chloropyridine.[141] Some differences with the previous conditions were applied: toluene was substituted for DME and a different precatalyst ((CyPF-*t*-Bu)$PdCl_2$) was used at higher temperature. Again, only a low catalyst loading (1 mol%) was needed for the transformation. In the same year Hartwig *et al.* reported a more thorough study on the scope of the use of CyPF-*t*-Bu as ligand for Pd-catalyzed amination reactions.[160] Again catalyst loading did not exceed 1 mol%, and heteroaromatic amidines seemed to be well tolerated (Scheme 64).

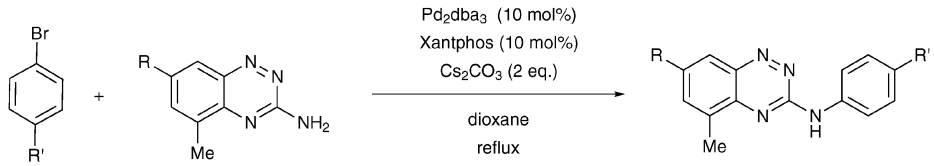
A patent filed in 2006 described the Pd-catalyzed coupling of 2-(2-*tert*-butylphenoxy)-3-iodopyridine with pyrimidin-4-amine




**Scheme 59** Pd-catalyzed amination of aryl bromides with pyrimidin-2-amines using a Pd/Xantphos catalytic system.



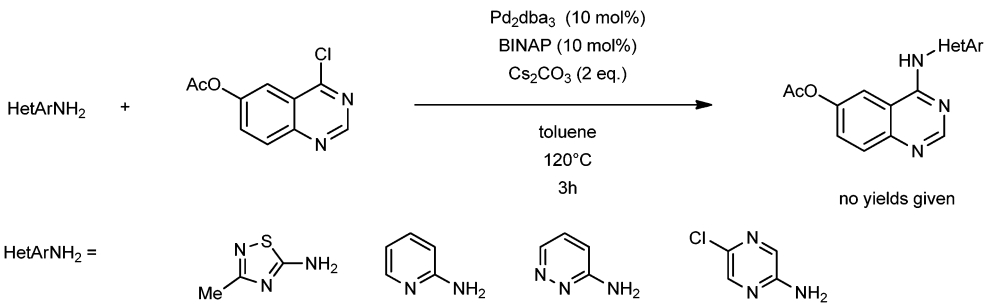

**Scheme 60** Pd-catalyzed amination of (hetero)aryl nonaflates with several heteroaromatic amidines.




R = 2,6-$(Cl)_2$-5-(OH)Ph, 2-Cl-6-F-5-(OH)Ph, 2,6-$(F)_2$-5-(OH)Ph, 2-Br-5-(OH)Ph, 1*H*-indol-4-yl, 5-$(NH_2)$-2-ClPh, 2-Cl-6-(OH)Ph

R'= 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propyl, 2-(pyrrolidin-1-yl)ethylaminocarbonyl, piperazin-1-ylcarbonyl, (4-methylpiperazin-1-yl)carbonyl, (1,1-dioxothiomorpholin-4-yl)carbonyl, $SO_2NH_2$, (2-pyrrolidin-1-ylethyl)sulfonamido, *N*-methyl-*N*-(2-pyrrolidin-1-ylethyl)sulfonamido, *N*-ethyl-*N*-(2-pyrrolidin-1-ylethyl)sulfonamido, *N*-*i*-propyl-*N*-(2-pyrrolidin-1-ylethyl)sulfonamido, *N*-methyl-*N*-(2-morpholino-4-ylethyl)sulfonamido, piperazin-1-ylsulfonyl, (3-pyrrolidin-1-ylpropyl)sulfonyl, piperidin-4-ylsulfonyl, {1-[2-(diethylamino)ethyl]piperdin-4-yl}sulfonyl

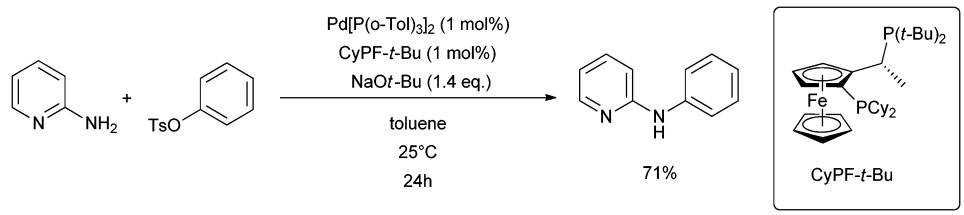
**Scheme 61** Pd-catalyzed amination of bromobenzenes with benzo-1,2,4-triazin-3-amines.




**Scheme 62** Pd-catalyzed amination of 6-acetoxy-4-chloroquinazoline with diazinamines and 3-methyl-1,2,4-thiadiazol-5-amine.

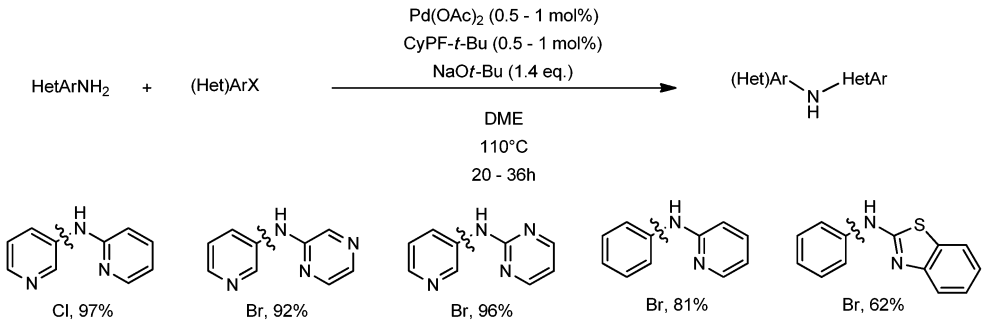
and 5-phenyl-1,2,4-thiadiazol-3-amine.[134] Dppf was used in combination with NaO*t*-Bu as base in toluene (Scheme 65).

An interesting class of molecules which have been used are the aminopurines. N-Arylation of adenines was reported by French researchers in 2009.[161] Utilizing $Pd(OH)_2$ on charcoal in combination with Xantphos they succeeded in the *N*6-arylation of *N*9-benzylated adenines (Scheme 66). The reactions were run at high temperatures in NMP. Heteroaryl halides such as

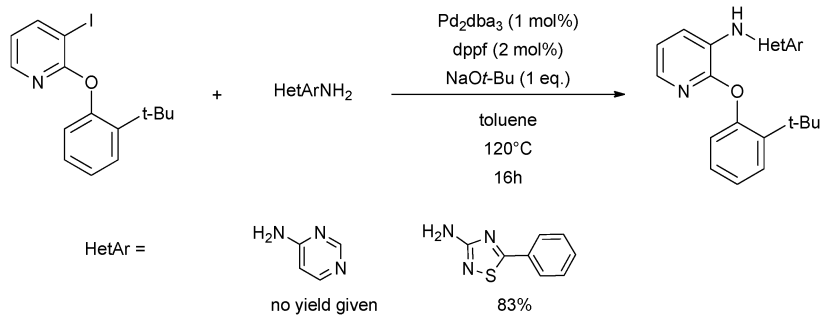



**Scheme 63** Pd-catalyzed amination of phenyl tosylate with pyridin-2-amine using Pd/CyPF-*t*-Bu as catalytic system.




**Scheme 64** Pd-catalyzed amination of (hetero)aryl halides with heteroaromatic amidines using Pd/CyPF-*t*-Bu as catalytic system.




**Scheme 65** Pd-catalyzed amination of 2-(2-*tert*-butylphenoxy)-3-iodopyridine with pyrimidin-4-amine and 5-phenyl-1,2,4-thiadiazol-3-amine using Pd/dppf as catalytic system.

3-iodopyridine and 2-bromopyridine could also be used as substrates in this reaction as well as bromonaphthalene. Interestingly, the amination step could be performed in a one pot fashion after the selective arylation at C8 performed with $Pd(OH)_2$ in combination with CuI. Thus, introducing the aryl halide and Xantphos (making use of the same Pd) after the first reaction step resulted in the subsequent *N*6-arylation.

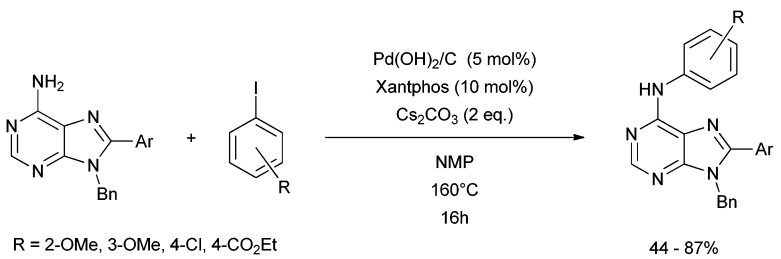
In continuation of their research on adenines, arylation of the exocyclic amino group of nucleosides, with Pd/Xantphos was attempted. Successful arylation of suitable protected 2′-deoxyguanosine (Scheme 67) and 2′-deoxyadenosine (Scheme 68) with a wide range of aryl bromides was disclosed.[162]

In 2006 Takamura-Enya *et al.* reported the Pd-catalyzed N-arylation of the nucleobases of several nucleosides for the convenient synthesis of DNA adducts with carcinogenic compounds.[163] Using $Pd_2dba_3$/Xantphos as Pd-catalyst and tetraethylammonium fluoride (TEAF) as base in DMSO, several iodonitroarenes could be coupled with 2′-deoxyguanosine, 2′-deoxyadenosine, and 2′-deoxycytidine (Scheme 69). DPEphos, BINAP and some other ligands were also tested but gave worse results or no reaction at all. Employing a $Pd_2dba_3$/Xantphos catalyst system also gave a smooth coupling between a protected 2′-deoxyguanosine and 1-iodonaphthalene and 3-iodobiphenyl respectively.

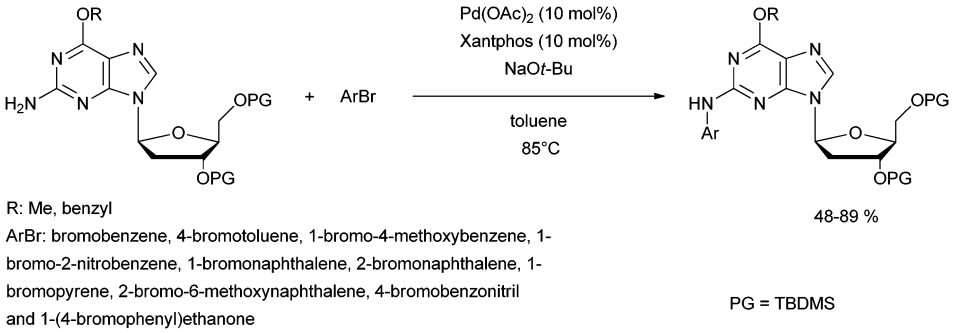
In 2004 Rizzo focused his research on the adducts of the highly mutagenic heterocyclic amine 3-methyl-3*H*-imidazo-[4,5-*f*]quinolin-2-amine (IQ) with nucleosides and nucleotides. He described the coupling of 5-bromo-3-methyl-2-nitro-3*H*-imidazo[4,5-*f*]quinoline with protected 2′-deoxyguanosine using $Pd(OAc)_2$/BINAP in combination with $Cs_2CO_3$ (Scheme 70).[164]

Halogenated purines were also used as substrates.[165] The amination on the C-8 brominated position of a protected 2′-deoxyguanosine with 3-methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine (IQ) was catalyzed by the same Pd/BINAP system. In this case, LiHMDS was used as a base instead of $Cs_2CO_3$ (Scheme 71). The authors found that both *N*2-protected (STABASE = 1,1,4,4-tetramethyldisilylazacyclopentane[166]) and unprotected guanosines can be used for the transformation.

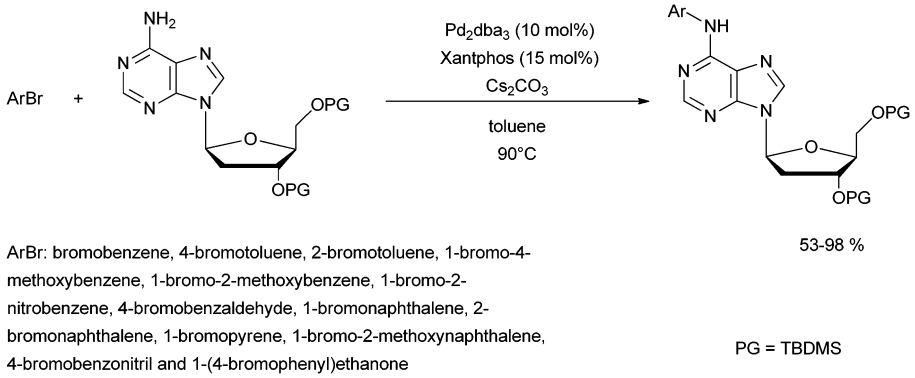
*4.1.1.2 Pd-catalyzed N-arylations employing a monodentate ligand.* Buchwald *et al.* found that the monodentate *t*-Bu-XPhos ligand (Scheme 72, inset) can be successfully employed for the arylation of heteroaromatic systems which contain an amidine functionality (Scheme 72).[17] The fact that a monodentate can be




**Scheme 66** *N*6-Arylation of *N*9-protected adenines with (hetero)aryl halides.




**Scheme 67** Pd-catalyzed N-arylation of protected 2′-deoxyguanosine.

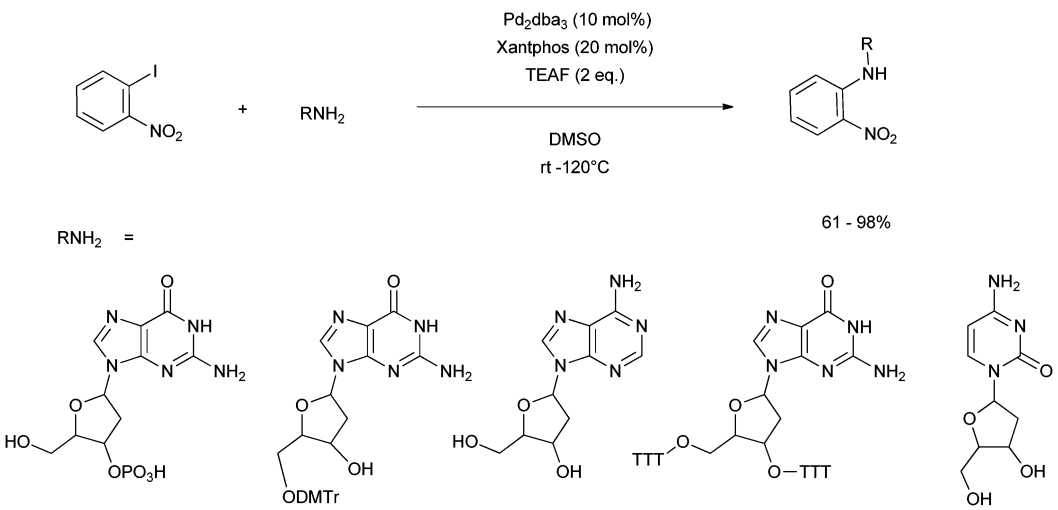



**Scheme 68** Pd-catalyzed N-arylation of protected 2′-deoxyadenosine.

used as ligand took away the belief that a bidentate ligand was essential for success by preventing $\kappa^2$ coordination to the Pd(II) species by the amidine moiety. This same coordination pattern has been reported to hamper amide N-arylations employing a Pd catalyst.[167,168] Notably an unactivated chlorinated substrate (4-chlorophenol) could be coupled in very good yield.

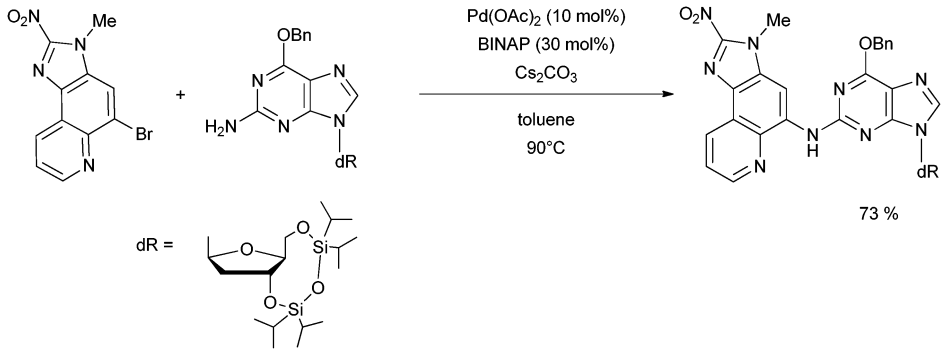
A concise synthesis of Imatinib (Glivec) using a flow based Pd-catalyzed amination step was recently disclosed. The final step employed a Buchwald–Hartwig reaction between an aryl bromide and a pyrimidin-2-amine (Scheme 73).[169] This transformation had previously been achieved in batch mode in 72% yield using 10 mol% $Pd_2dba_3{\cdot}CHCl_3$, NaO*t*-Bu and BINAP in xylene.[170] Unfortunately, these conditions could not be used in flow since traditional non-polar solvents for the Buchwald–Hartwig reaction do not fully solubilise the starting materials. Switching to reaction conditions similar to those used for the synthesis of Nilotinib[171] (1,4-dioxane/*t*-BuOH, $Pd_2dba_3$, Xantphos) gave precipitation of Pd black and NaBr. Finally, this problem was overcome by the use of BrettPhos–Pd precatalyst.[172,173]

The synthesis of *N*2,*N*2-dialkyl-*N*4-heteroarylpyrimidine-2,4,6-triamines was achieved by successive $S_NAr$ and Pd-catalyzed amination reactions starting from commercially available 2,6-dichloropyrimidin-4-amine.[174] This strategy could introduce a

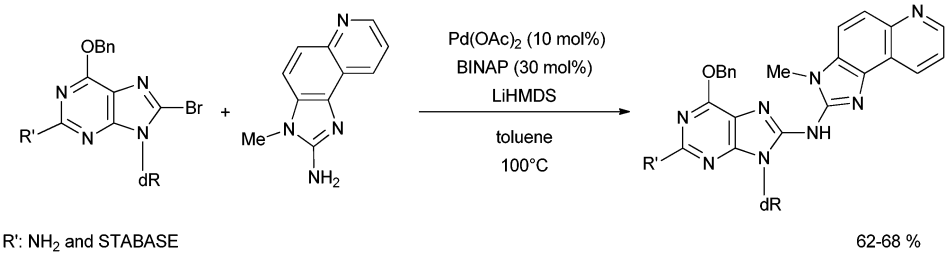



**Scheme 69** Pd-catalyzed N-arylation of several nucleosides with iodonitrobenzenes.

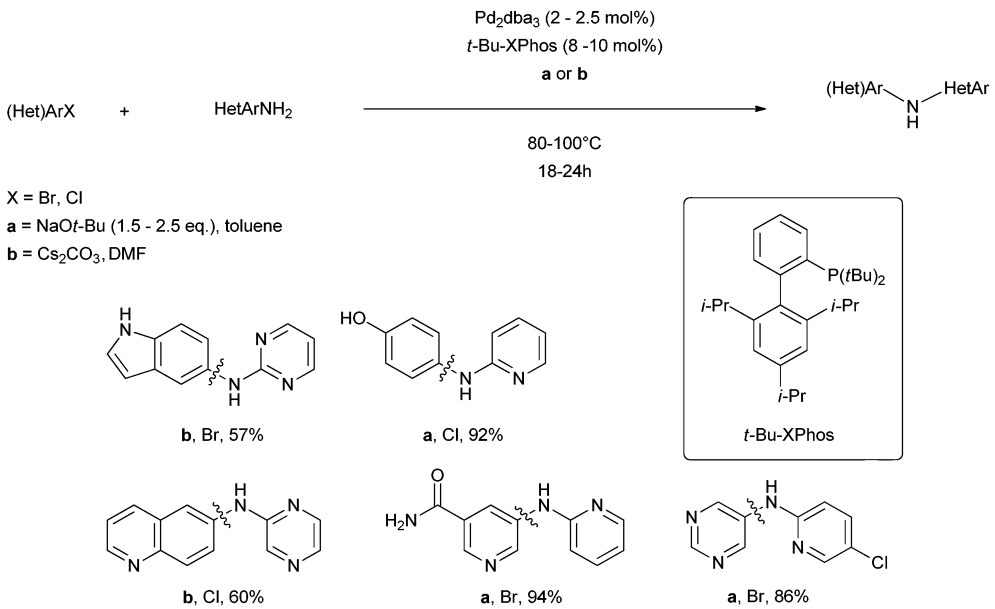
 




**Scheme 70** Pd-catalyzed N-arylation of protected 2′-deoxyadenosine with 5-bromo-3-methyl-2-nitro-3*H*-imidazo[4,5-*f*]quinoline.




**Scheme 71** Pd-catalyzed amination of protected and C8 brominated 2′-deoxyguanosine with 3-methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine.



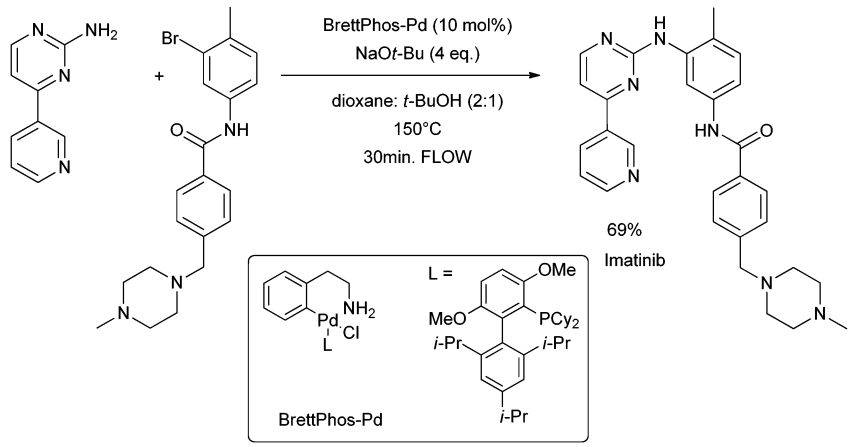

**Scheme 72** Pd-catalyzed N-arylation of heteroaromatic amidines using Pd/*t*-Bu-XPhos as catalytic system.

diverse set of secondary amines at the 2-position and heteroarylamines with amidine entity at the 6-position of the pyrimidine ring (Scheme 74). The authors reported also a further functionalization *via* N-arylation using the Boc deprotected *N*4 amino group of the reaction products which also belong to an amidine moiety. Standard Pd-catalyzed amination reactions gave regioselective coupling products with high yields. Also heteroaryl bromides such as bromopyridines and bromopyrimidine gave high yielding reactions. The catalyst loading required for the latter transformation however is quite high: 20 mol% Pd.

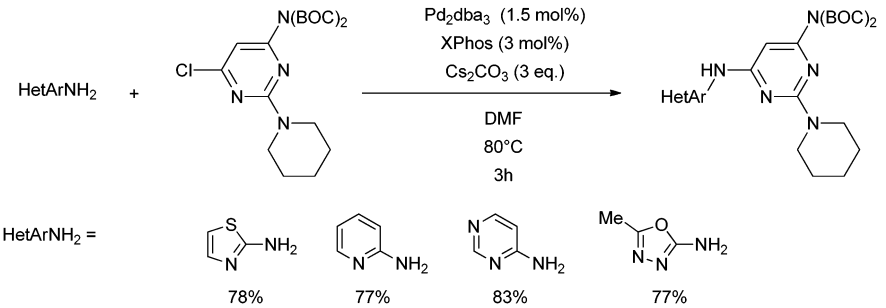
### 4.1.2 Cu-catalyzed N-arylations

*4.1.2.1 Ullmann type coupling*. Arterburn *et al*. investigated the coupling of 5-iodouracil with some heteroaromatic, one aromatic and some aliphatic amines.[59] A catalyst system comprising $Cu(OTf)_2$, 1,10-phenanthroline and dba was utilized in *p*-xylene (Scheme 75) for the coupling. The same catalyst system failed to couple 1,3-thiazolin-2-amine, so for this substrate Ni-catalysis was employed (see Section 3.1.2).

*N*-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine, a key intermediate for the synthesis of Imatinib, was prepared by Cu-catalyzed arylation of 5-(pyridin-3-yl)pyrimidin-2-amine with




**Scheme 73** Synthesis of Imatinib based on a flow based Pd-catalyzed amination reaction.



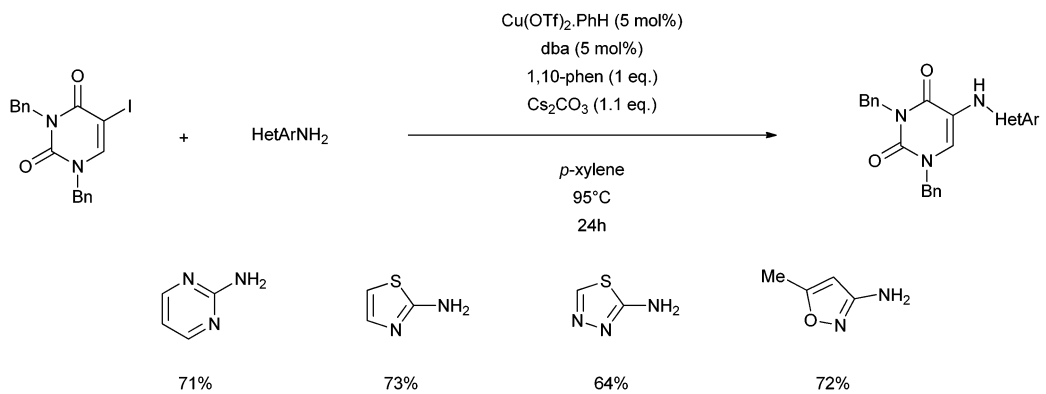

**Scheme 74** Pd-catalyzed amination of di-*tert*-butyl (6-chloro-2-piperidin-1-ylpyrimidin-4-yl)imidodicarbonate with heteroaromatic amidines.

1-bromo-2-methyl-5-nitrobenzene in 82% yield (Scheme 76).[175] Copper catalysis was used instead of the more expensive palladium catalysis (20 mol% Pd, see Scheme 59).[170] A similar approach was utilized to construct Imatinib analogues under slightly modified reaction conditions by Kalesh *et al.*[176,177]

An intermolecular amination of 4-chlorophthalazines with substituted thiazol-2-amines using CuI/TMEDA was reported in a patent describing the preparation of modulators of steroid hormone nuclear receptors.[124] These reactions are mostly performed under microwave irradiation allowing short reaction times.

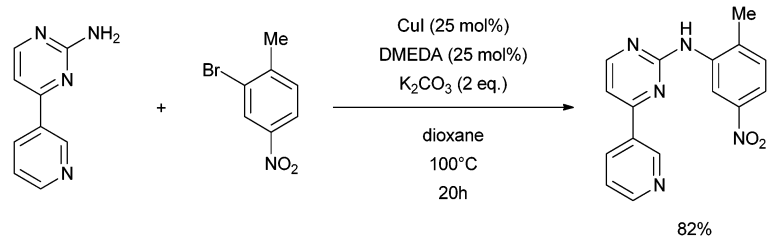
A Cu-catalyzed method for the *N*6-arylation of 2′-deoxyadenosine with aryl iodides and bromides was described by Ran *et al.*[178] The method can be applied for the coupling with aryl halides containing either electron donating or electron withdrawing groups (Scheme 77). Reactions of the aryl bromides were significantly enhanced when 1 eq. of NaI was added to the reaction mixture. The faster rates presumably originate from the *in situ* halide exchange of the bromine atom for an iodine atom, which is a known Cu-catalyzed process.[179] In contrast to a Chan–Evans–Lam approach (see Section 4.1.2.2), reaction of *O*6-benzyl-2′-deoxyguanosine with 4-iodoanisole under these conditions occurred smoothly affording the *N*2-aryl-dG adduct in good yield (79%). However, the arylation of the unprotected 2′-deoxyguanosine failed under these conditions.

Immobilized CuO nanoparticles can also be used for the arylation of heteroaromatic amidines.[180] CuO hollow nanospheres were immobilized on acetylene black (AB) or charcoal to allow easy reuse. Pyridin-2-amine and pyrimidin-2-amine

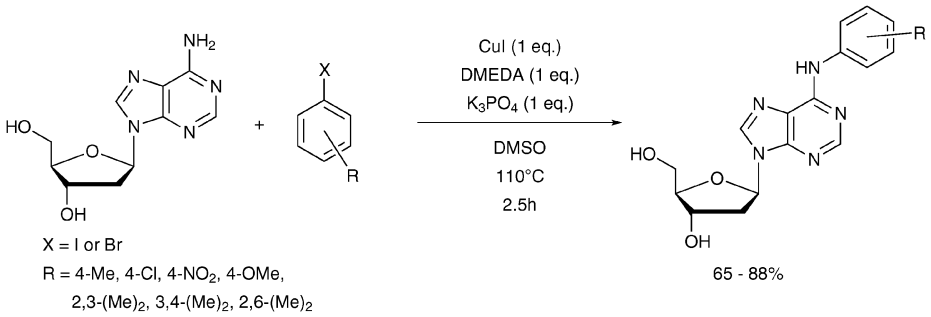



**Scheme 75** Cu-catalyzed amination of 5-iodouracil with heteroaromatic amidines.




**Scheme 76** Synthesis of a key intermediate in the Imatinib synthesis using Cu-catalyzed amination.

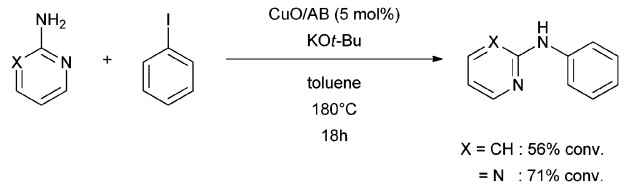



**Scheme 77** Cu-catalyzed amination of aryl halides with 2′-deoxyadenosine.

were shown to be suitable amidines for arylation with iodobenzene (Scheme 78). The authors unfortunately only reported conversions based on $^1$H-NMR spectra for these transformations.

1,3,4-Oxadiazol-2-amines were also successfully used in amination reactions with iodoarenes (Scheme 79).[181] For these transformations Buchwald's protocol developed for the arylation of amides and NH-heterocycles was applied based on a CuI/CHDA (= *trans*-cyclohexane-1,2-diamine) catalytic system.[182]

A novel acid dye, obtained *via* the Cu-catalyzed reaction of bromamine acid with 6-nitrobenzothiazol-2-amine, was reported to give good UV radiation absorption and dyeing properties on silk.[183] 1-Amino-4-[(6-nitro-2-benzothiazolyl)-amino]-9,10-anthraquinone-2-sulfonic acid was obtained in good yield (Scheme 80). The combination of Cu and Cu(II)$SO_4$ probably yields a catalytically active Cu(I) species *via* comproportionation in water.[184,185]

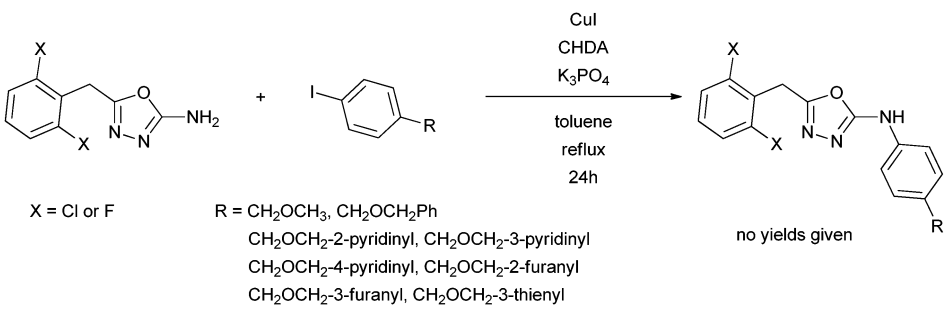



**Scheme 78** CuO immobilized nanoparticles used for Cu-catalyzed N-arylation of heteroaromatic amidines.

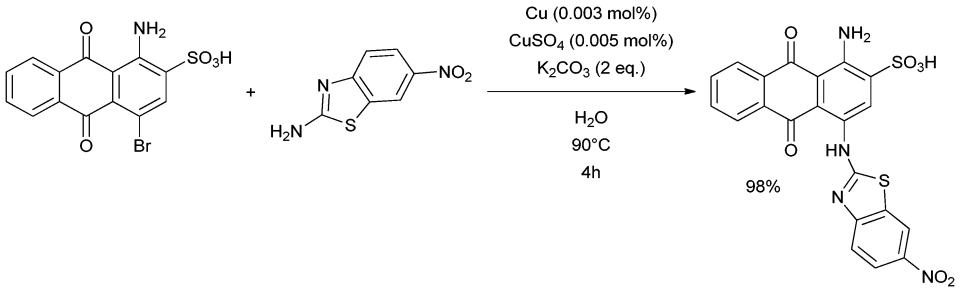
*4.1.2.2 Chan–Evans–Lam type coupling*. Chan and Lam researched the coupling of various heteroarylamines with *p*-tolylboronic acid.[16] They concluded that, in general, electron-rich N-nucleophiles tend to give better results but the presence of a chelating nitrogen atom can sometimes influence the chemistry significantly. Compared to the coupling of pyridine-3-amine with *p*-tolylboronic acid, the pyridin-2-amine for instance gave far worse results. In the case of pyridin-4-amine the reaction was even completely shut down. The heteraromatic amidines covered in the paper are summarized in Scheme 81.

Hong *et al.* described a Chan–Evans–Lam coupling of pyridin-2,5-diamines with arylboronic acids under standard conditions (Scheme 82).[186] Yields were low however, probably due to a too strong coordination of the amidine to the catalytically active Cu-species. Standard Chan–Evans–Lam conditions were also suitable to N-arylate ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate with arylboronic acids.[187] Only mono-arylation was observed.

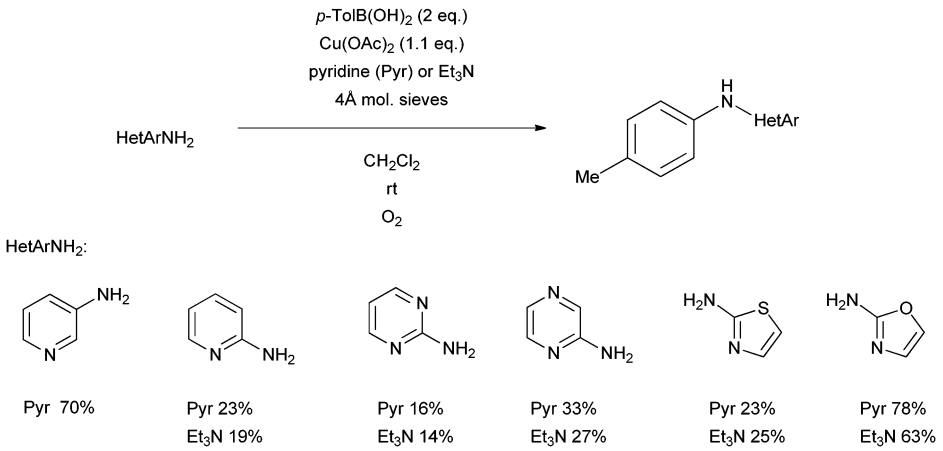
For the preparation of 2-phenoxy-*N*-(1,3,4-thiadiazol-2-yl)-pyridin-3-amine derivatives as new P2Y1 receptor inhibitors




**Scheme 79** Cu-catalyzed N-arylation of 1,3,4-oxadiazol-2-amines with iodoarenes.




**Scheme 80** Synthesis of an acid dye by a Cu-catalyzed amination of bromamine acid with 6-nitrobenzothiazol-2-amine.



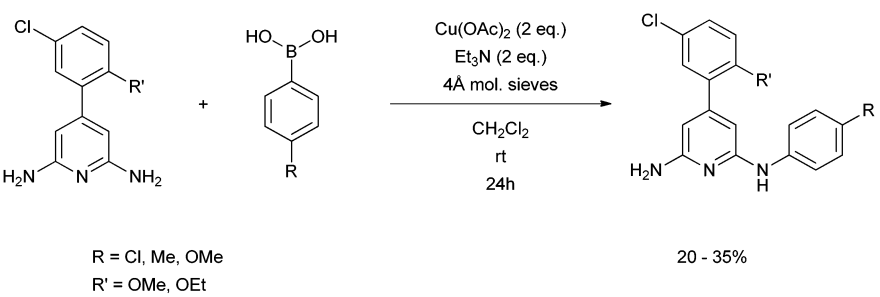

**Scheme 81** Cu-mediated N-arylation of heteroaromatic amidines with arylboronic acids studied by Chan and Lam.

researchers at the Bristol-Myers Squibb company used a standard Chan–Evans–Lam coupling between 2-(2-*tert*-butylphenoxy)pyridine-3-boronic acid and 1,3-thiazol-2-amines and 1,3-oxazol-2-amines (Scheme 83).[134]

A communication dealing with the Cu-mediated coupling between arylboronic acids and a guanidine derivative, 5-methyl-2-methylthiopyrimidin-4-amine and 4-chloro-2-methylthiopyrimidin-6-amine was published in 2004 (Scheme 84).[188]

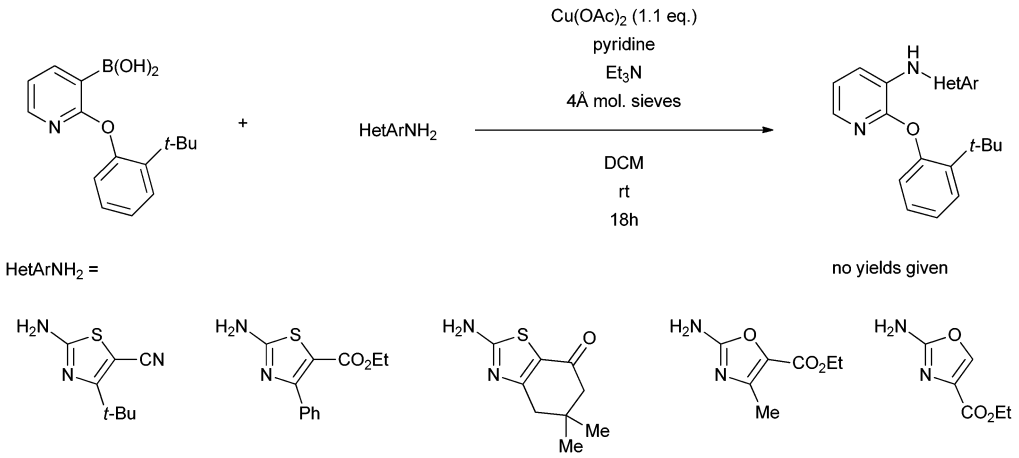
Dai *et al*. described the regioselective arylation of 2′-deoxyguanosine by Cu-mediated coupling with arylboronic acids (Scheme 85).[189] Selective *N*3-arylation was observed leaving the exocyclic amino group untouched. Noteworthy is that a benzyl ether derivative of 2′-deoxyguanosine didn't react under Chan–Evans–Lam reaction conditions mediated by $Cu(OAc)_2$. In this report also reactions of 2′-deoxycytidine and 2′-deoxyadenosine, which both possess an exocyclic amino group but lack an amido functionality, were included. In those cases the exocyclic nitrogen was arylated, albeit in lower yield in comparison with the other 2′-deoxyribonucleosides (Scheme 86). Several bases (1,10-phen, pyridine, $Et_3N$) were tested in DMSO as solvent with 4-methylphenylboronic acid as coupling partner.

Triazolamine acyclonucleosides can be N-arylated using various arylboronic acids.[190] By varying the copper source ($Cu(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$, $CuBr_2$, CuI, CuCl), base ($Et_3N$, $EtN(i\text{-}Pr)_2$, pyridine, NaH, pyridine/$Et_3N$, *etc*.) and solvent (*e.g*. $CH_2Cl_2$, DMF, toluene, MeOH/$H_2O$) optimal reaction conditions were attained for the N-arylation of methyl 3-amino-1-{[2-(benzoyloxy)ethoxy]methyl}-1*H*-1,2,4-triazole-5-carboxylate (Scheme 87). Arylation of the 3-$NH_2$ group was obtained with various substituted arylboronic acids, however *ortho*-substitution of the boronic acid is not tolerated. Noteworthy is the fact that when 3-amino-1-[(2-hydroxyexthoxy)methyl]-1*H*-1,2,4-triazole-5-carboxamide is used as substrate, only the amide nitrogen is chemoselectively N-arylated in yields up to 60%.

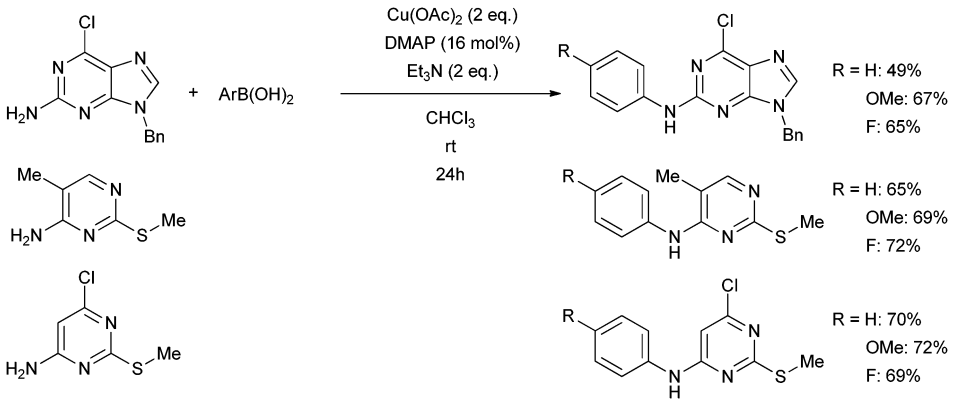



**Scheme 82** Chan–Lam–Evans coupling of pyridin-2,6-diamines with arylboronic acids.

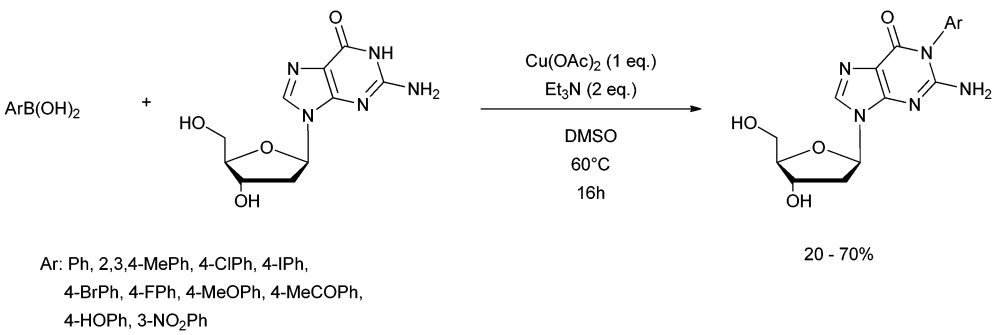
 




**Scheme 83** Chan–Evans–Lam coupling used at Bristol-Myers Squibb to prepare P2Y1 receptor inhibitors.




**Scheme 84** Cu-mediated coupling of purinamines and pyrimidinamines with arylboronic acids.



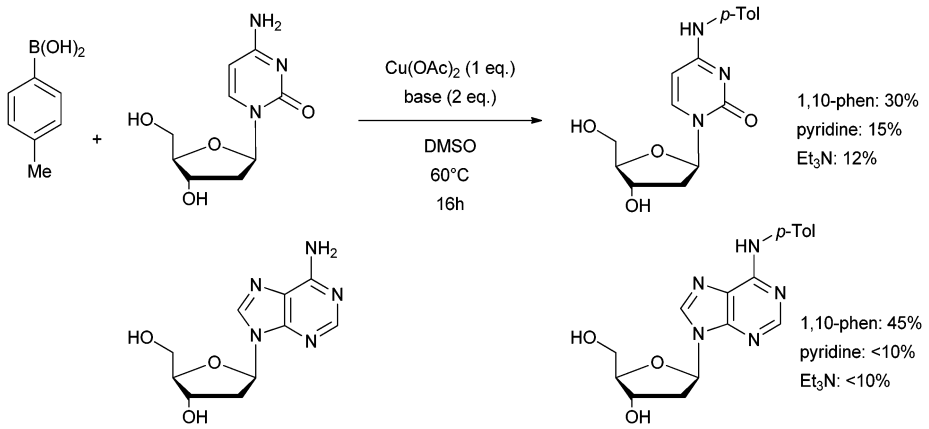

**Scheme 85** N3-arylation of 2′-deoxyguanosine with arylboronic acids.

Later the same group also reported the N-arylation of triazol-3-amine ribonucleosides under Chan–Evans–Lam conditions (Scheme 88).[191] Similarly to the arylation of the acyclic counterparts, *o*-substituents on the boronic acid were not tolerated.

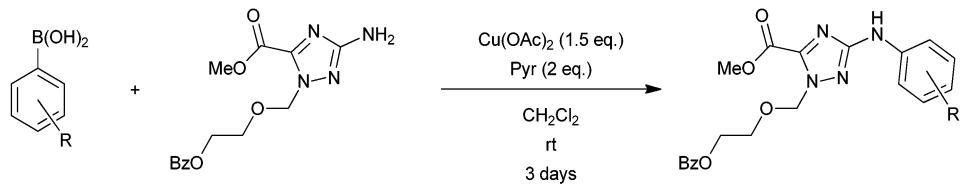
A patent described the use of pyrazin-2-amines as substrate in a Chan–Evans–Lam type coupling with various arylboronic acids (Scheme 89).[192] This method provides the advantage over the Ullmann type coupling and the Buchwald–Hartwig reaction that a halogen present remains untouched under the reaction conditions.

Although formally no Chan–Evans–Lam reaction we also mention the coupling of 1,3-thiazol-2-amine and benzothiazol-2-amine derivatives with the triphenylbismuth diacetate/$Cu(OAc)_2$ system in this section. Arylbismuths introduced by Barton *et al.*[193] are one of the mildest reagents for N-arylation reactions.[194] Reaction with the 1,3-thiazol-2-amine system shows a unique behavior as diphenylation is favored over monophenylation of the exocyclic nitrogen (Scheme 90). Moreover, after the first phenylation of the exocyclic nitrogen atom, the second phenylation takes place on the endocyclic rather than on the exocyclic nitrogen atom which is unique in intermolecular arylations.

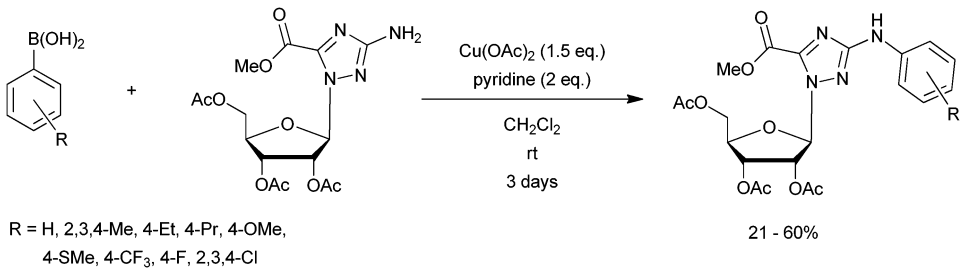
**4.1.3 Rh-catalyzed N-arylations.** A Rh-catalyzed amination reaction of aryl halides with several classes of amines has been developed using a N-heterocyclic carbene (NHC) ligand.[195]



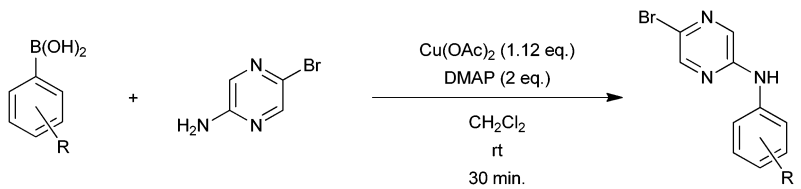

**Scheme 86** Cu-mediated N-arylation of 2′-deoxyribonucleosides.




**Scheme 87** Cu-mediated N-arylation of triazol-3-amine acyclonucleosides with arylboronic acids.




**Scheme 88** Cu-mediated N-arylation of triazol-3-amine ribonucleosides with arylboronic acids.




**Scheme 89** Cu-mediated N-arylation of 5-bromopyrazin-2-amine with arylboronic acids.

I*i*Pr·HCl proved to be the ligand precursor of choice since either IMes·HCl or a phosphine ligand ($PCy_3$) failed to give any conversion. A single example of an amidine arylation was also included in their set. Bromobenzene was reacted with 6-methylpyridin-2-amine yielding the desired *N*-phenylated product in high yield (Scheme 91). A downside of the protocol is the need for 3 equivalents of the amine.

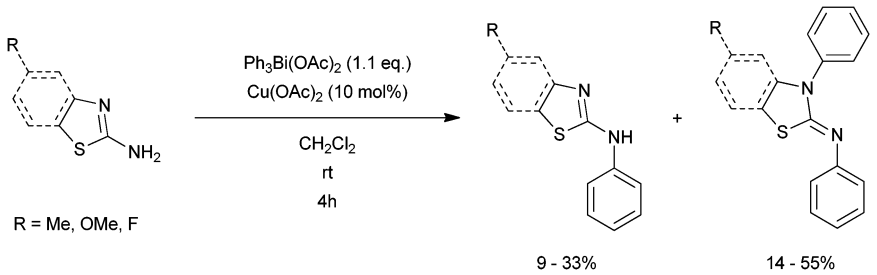
## 4.2 Intramolecular N-arylations

**4.2.1 Pd-catalyzed N-arylations.** Benzimidazo[1,2-*a*]quinolines have been synthesized *via* Pd-catalyzed heterocyclization of *N*-(2-bromophenyl)quinolin-2-amines (Scheme 92).[196] An optimization study revealed that $Pd(PPh_3)_4$ is preferred over $PdCl_2$/dppp or $Pd(OAc)_2$/P(*o*-Tol)$_3$ systems.

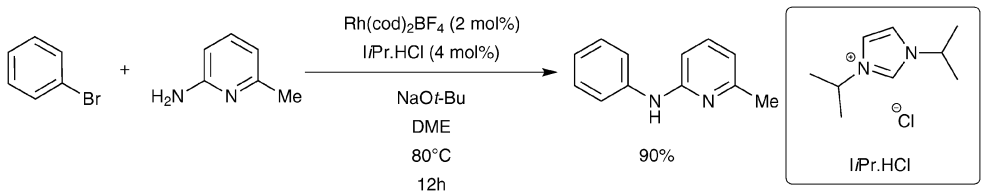
The same conditions were used by De Borggraeve and co-workers to obtain pyrazino[1,2-*a*]benzimidazol-1(2*H*)-ones.[197] In this case, microwave irradiation at high temperature did allow the reactions to be run in just 25 min (Scheme 93).

**4.2.2 Cu-catalyzed N-arylations.** Some copper catalyzed intramolecular arylations have already been covered in Section 4.1.1. These are part of tandem amination reactions of 2,3-dibromopyridine (Schemes 54 and 57), 2,3-dibromoquinoline

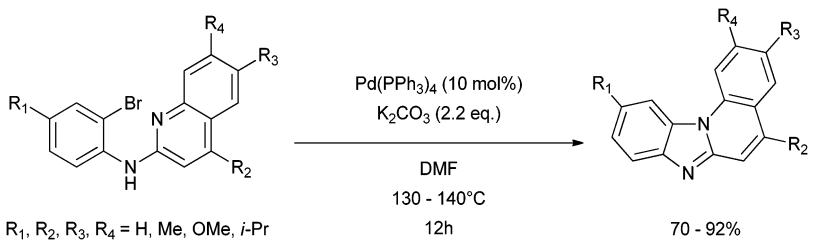
 



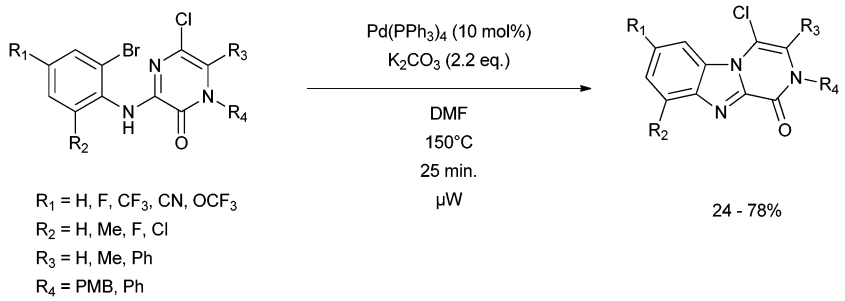

**Scheme 90** Cu-catalyzed N-arylation of (benzo)thiazol-2-amines with triphenylbismuth diacetate reagent.




**Scheme 91** Rh-catalyzed N-phenylation of 6-methylpyridin-2-amine.




**Scheme 92** Benzimidazo[1,2-*a*]quinoline synthesis *via* Pd-catalyzed cyclization of *N*-(2-bromophenyl)quinolin-2-amines.



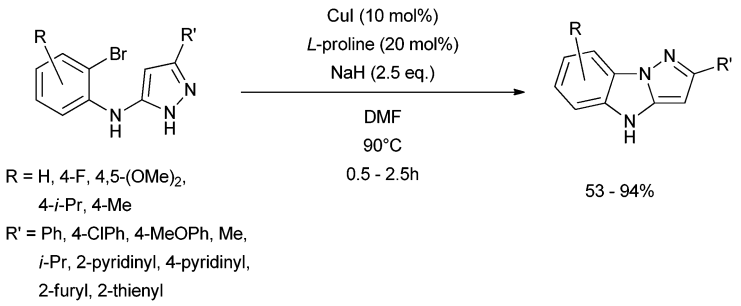

**Scheme 93** Microwave assisted Pd-catalyzed intramolecular amination.

(Scheme 55), and 4-iodo-3-chloroquinoline with heteroaromatic amines (Scheme 56).

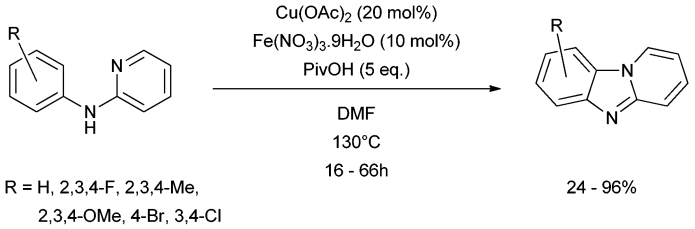
Ila *et al.* reported in 2009 the Cu-catalyzed cyclization of *N*-(2-bromophenyl)-1*H*-pyrazol-5-amines (Scheme 94).[198] Sodium hydride was chosen as base since $K_2CO_3$ and $K_3PO_4$ gave rise to hydrodehalogenation of the starting material as well as incomplete conversions. Remarkably, *N*-(2-bromo-4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-amine failed to cyclize under these conditions.

A recent paper of Chinese researchers showed that pyrido[1,2-*a*]benzimidazoles can be built up from *N*-arylpyridin-2-amines by intramolecular C–H amination.[199] By using an excess of pivalic acid and an iron co-catalyst, a Cu-catalyzed intramolecular amination was performed on various substrates bearing a substituent on the aniline ring (Scheme 95). Electron withdrawing substituents on the pyridine ring gave incomplete reactions. Only methyl substituents on the pyridine ring gave rise to the corresponding pyridobenzimidazoles in good yield. The authors stipulate that the iron co-catalyst facilitates the formation of a more electrophilic Cu(III) species. As electron withdrawing groups on the aniline retarded the reaction rate, the suggestion of a $S_EAr$ mechanism was made by the authors. However, a kinetic isotope effect was found which is very rare for $S_EAr$ reactions.

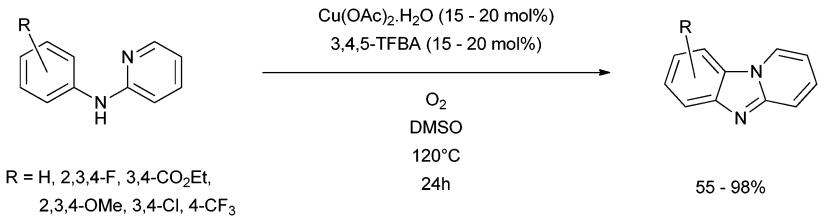
Simultaneously, a new catalyst system based on 3,4,5-trifluorobenzoic acid (3,4,5-TFBA) as additive was developed for the same transformation by Maes and co-workers.[200] By employing $Cu(OAc)_2{\cdot}H_2O$ and 3,4,5-trifluorobenzoic acid under oxygen atmosphere 6-, 7- and 8-substituted pyrido[1,2-*a*]benzimidazoles could be constructed without the need for an additional metal (Scheme 96). When the aniline moiety was substituted in the 3-position regioselectivity was obtained for




**Scheme 94** 4*H*-Pyrazolo[1,5-*a*]benzimidazole synthesis *via* Cu-catalyzed cyclization of *N*-(2-bromophenyl)-1*H*-pyrazol-5-amines.

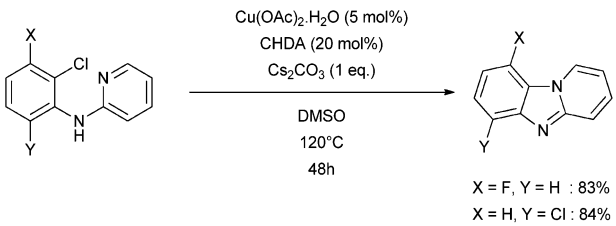



**Scheme 95** Cu-catalyzed intramolecular C–H amination of *N*-arylpyridin-2-amines.




**Scheme 96** Synthesis of 6-, 7- and 8-substituted pyrido[1,2-*a*]benzimidazoles *via* Cu-catalyzed intramolecular C–H amination.

C–H amination on the less hindered site (C6). The type of carboxylic acid additive proved to be essential as 3,4,5-trifluorobenzoic acid gives higher yields than when a classical carboxylic acid like acetic or pivalic acid was used. A mechanism comprising an *anti*-aza cupration was suggested based on the observed kinetic isotope effects, $k_{obsd}$ values and DFT calculations. Also, a competitive C–Cl amination was found for substrates bearing an *o*-chloro substituent such as *N*-(2-chloro-5-methoxyphenyl)pyridin-2-amine. This C–Cl amination reaction was optimized for the preparation of 9-substituted pyrido-[1,2-*a*]benzimidazoles, as exemplified for the 9-fluoro derivative, showing the complementarity of the C–H and C–Cl amination methods (Scheme 97).




**Scheme 97** Synthesis of 9-substituted pyrido[1,2-*a*]benzimidazoles *via* Cu-catalyzed intramolecular C–Cl amination.

## 5. Conclusions

Despite the occurrence of the amidine and guanidine structural motifs in many important compounds, metal-catalyzed N-arylations involving these entities still remain less explored in the field of transition metal-catalyzed C–N bond formation. Probably this is due to the fact that obtaining catalysis with amidine and guanidine moieties, appearing both in reagent and reaction product, is just problematic as these structural entities can easily act as chelators. This definitely creates a major challenge in the development of catalytic systems with a broad scope. One can conclude that mostly copper and palladium based catalysts have hitherto been explored to achieve the N-arylations, as only four papers describe the use of another transition metal (Ni, Rh, Co and Fe). Especially data on intermolecular coupling reactions with amidines and guanidines which are not part of a heteroaromatic system are very limited, although tandem reactions allowing a smooth heteroarene synthesis *via* a subsequent reaction received considerable attention. Achieving chemoselectivity in coupling reactions with unsymmetrically substituted amidines/guanidines has yet only briefly been researched. For the heteroaromatic amidines and guanidines much more literature appeared to date with very challenging applications already realized, such as those involving nucleosides and (deoxy)nucleotides as the coupling partners. Generally, there is a clear need for further development of better N-arylation protocols with broad scope requiring mild reaction conditions. Some interesting challenges remain for the future for the N-arylation of non-heteroaromatic amidines

and guanidines, such as the use of unactivated aryl chlorides as substrates and the further development of direct C–H amination approaches, with an emphasis on intermolecular reactions.

## List of abbreviations

| | |
|---|---|
| Acac | acetoacetate |
| Ad | adamantyl |
| COD | 1,5-cyclooctadiene |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppf | 1,1′-bis(diphenylphosphino)ferrocene |
| dppp | 1,3-bis(diphenylphosphino)propane |
| Xantphos | 9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene |
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-dinaphthalene |
| 1,10-phen | 1,10-phenanthroline |
| DMEDA | *N*,*N*′-dimethylethylenediamine |
| TMEDA | *N*,*N*,*N*′,*N*′-tetramethylethylenediamine |
| CHDA | *trans*-cyclohexane-1,2-diamine |
| dba | dibenzylideneacetone |
| PMB | *p*-methoxybenzyl |
| MTBD | 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene |
| TEAF | tetraethylammonium fluoride |
| DMAP | *N*,*N*-dimethylpyridin-4-amine |
| I*i*Pr·HCl | *N*,*N*′-diisopropylimidazolium chloride |
| Bz | benzoyl |
| Bn | benzyl |
| Tol | Tolyl |
| DPEphos | bis(2-diphenylphosphinophenyl)ether |
| Pyr | Pyridine |
| TMTU | *N*,*N*,*N*′,*N*′-tetramethylthiourea |
| TTT | thymidine oligonucleotide (3 units) |
| DMTr | di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl |

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