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Published in:
Angewandte Chemie-International Edition

DOI:
[10.1002/anie.201904795](https://doi.org/10.1002/anie.201904795)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Dorel, R., Grugel, C. P., & Haydl, A. M. (2019). The Buchwald-Hartwig Amination After 25 Years. *Angewandte Chemie-International Edition*, 58(48), 17118-17129. <https://doi.org/10.1002/anie.201904795>

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Cross-Coupling

International Edition: DOI: 10.1002/anie.201904795
German Edition: DOI: 10.1002/ange.201904795

The Buchwald–Hartwig Amination After 25 Years

Ruth Dorel,* Christian P. Grugel, and Alexander M. Haydl*

Keywords:

arenes · amination ·
cross-coupling · palladium ·
reaction mechanisms

Dedicated to Dr. Friedhelm Balkenhohl

The Pd-catalyzed coupling of aryl (pseudo)halides and amines is one of the most powerful approaches for the formation of C(sp²)–N bonds. The pioneering reports from Migita and subsequently Buchwald and Hartwig on the coupling of aminostannanes and aryl bromides rapidly evolved into general and practical tin-free protocols with broad substrate scope, which led to the establishment of what is now known as the Buchwald–Hartwig amination. This Minireview summarizes the evolution of this cross-coupling reaction over the course of the past 25 years and illustrates some of the most recent applications of this well-established methodology.

1. Introduction

Over the past 25 years the Pd-catalyzed amination of aryl halides and pseudohalides has become a fundamental tool in organic synthesis for the formation of C(sp²)–N bonds.^[1] The ubiquitous nature of aryl amines and related heterocycles in natural products, pharmaceuticals, agrochemicals, and organic molecules relevant for materials science has prompted the development of improved catalysts and general methodologies, which nowadays find applications in both academic research and industrial processes.^[2]

Historically, the formation of C(sp²)–N bonds has been achieved by means of either nucleophilic aromatic substitutions (S_NAr) or by copper-mediated processes pioneered by Goldberg^[3] and Ullmann^[4] at the beginning of the 20th century. However, these methods typically suffer from a narrow substrate scope and require high temperatures, long reaction times, toxic solvents and, in the latter case, high copper loadings. In recent years, some of these drawbacks have been overcome through the use of copper-based catalysts (often) bearing chelating ligands.^[5]

The use of palladium complexes as catalysts for the formation of C(sp²)–N bonds was pioneered in 1983 by Migita and co-workers, who reported that palladium complexes of P(*o*-tol)₃ catalyze the formation of aryl amines from aryl bromides and aminostannanes.^[6] The limitations associated with both the narrow substrate scope achieved in this seminal work and the use of toxic aminostannanes were later circumvented by Stephen L. Buchwald and John F. Hartwig, who independently reported first, in 1994, an improved protocol for the coupling of aryl bromides and aminostannanes^[7] and later, in 1995, a tin-free Pd-catalyzed coupling of aryl bromides with amines.^[8] This breakthrough, together with subsequent efforts from both groups towards a general and efficient methodology for C–N bond formation and a deep mechanistic understanding of the process, led to the establishment of what nowadays is known as the Buchwald–Hartwig amination reaction.

The aim of this Minireview is to give an overview of the evolution of the Buchwald–Hartwig amination from its discovery to the state of the art protocols, including recent applications of this methodology in both academic and industrial contexts. The main focus will therefore be on the Pd-catalyzed formation of C(sp²)–N bonds, and consequently, neither the use of other transition metals as catalysts for this

transformation^[5,9] nor the Pd-catalyzed formation of other C(sp²)–heteroatom bonds^[10] will be discussed.

2. Evolution of the Catalyst and Implications for the Substrate Scope

The scope of the Buchwald–Hartwig amination has been widely illustrated for a variety of arene and amine coupling partners. Nonetheless, the choice of the catalyst is largely dependent on the geometric and electronic

features of the substrates. As a consequence, the catalytic system initially established for the Pd-catalyzed coupling of aryl bromides with aminostannanes^[7] has gradually evolved into several generations of catalysts with distinct advantages and limitations.

2.1. First Generation: Tri-*o*-Tolylphosphine as a Ligand

The seminal reports by Migita and co-workers^[6] inspired the development of the first general procedures for the coupling of aryl bromides and free amines in the absence of toxic aminostannane reagents, which relied on the use of a Pd⁰/P(*o*-tol)₃ complex as the catalytically active species in the presence of a base, and the use of either toluene or THF as the solvent (Scheme 1).^[8] These protocols enabled the preparation of a range of arylamines from the corresponding dialkyl or alkylaryl secondary amines and functionalized bromoarenes. However, primary amines could not be effi-

Scheme 1. Pd-catalyzed coupling of aryl bromides and secondary amines using P(*o*-tol)₃ as the ligand. THF = tetrahydrofuran.

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<https://doi.org/10.1002/anie.201904795>.

ciently coupled due to a competitive β -hydride elimination process leading to the formation of the reduced arene from an $\text{Ar-Pd}^{\text{II}}\text{-H}$ intermediate. As in the case of the coupling with aminostannanes,^[7a] aryl iodides provided lower yields of the coupled arylamines, which was later circumvented by the use of 1,4-dioxane as the reaction medium.^[11] In contrast, aryl iodides proved to be superior substrates for the intramolecular version of this reaction.

The use of $\text{Pd}_2(\text{dba})_3$ in combination with $\text{P}(o\text{-tol})_3$ successfully promoted the intramolecular C–N coupling of enantiomerically enriched α -substituted secondary amine and amide substrates with no erosion of their optical activity.^[12] The utility of this method was illustrated with the synthesis of **2**, which is a key intermediate in the synthesis of the angiotensin converting enzyme (ACE) inhibitor **3** (Scheme 2). Nonetheless, the intermolecular version of this protocol led to (partial) racemization because of a competitive β -hydride elimination.

Scheme 2. Intramolecular C–N coupling of enantiomerically enriched α -substituted secondary amine **1**.

2.2. Aromatic Bisphosphine Ligands

The use of aromatic bisphosphines as ligands for Pd-catalyzed C–N couplings constituted the first step towards the generalization of this method. Hence, the utilization of palladium complexes of either DPPF^[13] or BINAP^[14] as catalysts in the presence of NaOtBu led to a general improvement of the yields previously reported, as well as to the successful arylation of primary amines (Scheme 3). A key feature of the success of these ligands was the fact that the reductive elimination of the coupled products was favored over β -hydride elimination due to the chelating effect of the bisphosphine ligands to the metal center. Subsequent studies demonstrated that, under similar reaction conditions, these

Scheme 3. Pd-catalyzed C–N coupling using aromatic bisphosphine ligands. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

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complexes promoted the coupling of not only aryl bromides and iodides but also aryl triflates.^[15] Furthermore, the use of more sterically hindered ferrocene-based dialkylphosphines, such as 1,1'-bis(di-*tert*-butylphosphino)ferrocene (DtBPF), resulted in an enhancement of the coupling rates and, more importantly, allowed for both the first amination of aryl tosylates and the amination of aryl chlorides under mild reaction conditions.^[16] Concurrently, the amination of aryl chlorides with both primary and secondary amines was also accomplished through the use of $\text{Ni}(\text{COD})_2$ (COD = cyclo-1,5-octadiene) in combination with DPPF^[17] and other bidentate ligands such as 2,2'-bipyridine.^[18] In addition, the use of a well-defined BINAP-containing Ni^0 complex later allowed for the Ni-catalyzed amination of (hetero)aryl halides with primary aliphatic amines.^[19]

Unlike in the case of $\text{P}(o\text{-tol})_3$, the use of either BINAP or DPPF as ligands in the Pd-catalyzed intermolecular N-arylation of enantiomerically enriched α -substituted amines provided the coupled products with no loss of enantiomeric purity.^[12] As in the coupling of primary amines, these results were attributed to the bidentate coordination of the bisphosphine ligand to the palladium center, which precludes the equilibration between palladium imine complexes that

result from β -hydride elimination. Other N-nucleophiles such as imines,^[20] azoles,^[21] lactams,^[22] and sulfoximines^[23] could also be efficiently arylated under related reaction conditions. In this context, the arylation of benzophenone hydrazones was coupled to hydrolysis and trapping with an excess of either aldehydes or ketones, which led to a novel entry into the Fischer indole synthesis.^[24] Furthermore, alkenyl bromides^[25] and triflates^[26] could also be used as coupling partners to form enamines and imines upon Pd-catalyzed amination using BINAP as ligand.

POP-type phosphines were also examined as ligands in Pd-catalyzed C–N couplings (Figure 1). The palladium complex of bis[2-(diphenylphosphino)phenyl] ether (DPEphos) proved to be a highly competent catalyst for the coupling of

Figure 1. POP-type ligands used in the Buchwald–Hartwig amination.

anilines with aryl bromides, with an activity that either equals or exceeds that of the corresponding BINAP and DPPF complexes.^[27] The structurally related Xantphos ligand in combination with a palladium source promoted the coupling of aryl halides with different N-nucleophiles, such as amines,^[28] amides,^[29] sultams,^[30] and ureas.^[31] More recently, the use of Xantphos enabled the Pd-catalyzed coupling of aniline with aryl fluorosulfonates.^[32] It was also found that the use of catalytic amounts of metal triflates accelerates the coupling of aryl halides with amides when Pd(dba)₂/XantPhos is used as the catalyst.^[33] Furthermore, unactivated aryl chlorides have been coupled to secondary amines using the phenoxazine-based NiXantphos ligand.^[34]

2.3. Sterically Hindered Monophosphine Ligands

The limited success in the amination of aryl chlorides initially encountered through the use of bidentate aromatic bisphosphine ligands, together with the high temperatures typically required for C–N couplings, prompted the quest for ligands that generate more active catalysts to achieve both a broader substrate scope and milder reaction conditions. It was expected that more-electron-rich bidentate phosphines would facilitate the rate-limiting oxidative addition step by increasing the electron density around the metal center. In this context, the aminophosphine ligand Davephos (**4**) was initially synthesized by Buchwald and co-workers and explored in Pd-catalyzed C–N coupling reactions, which led to a highly active catalyst for the amination of aryl bromides and chlorides (Scheme 4).^[35] The superior activity of this system allowed the amination of a number of aryl bromides, and even one activated aryl chloride at room temperature.

Scheme 4. Pd-catalyzed C–N coupling using ligand **4**. dba = dibenzylideneacetone, DME = dimethoxyethane.

Subsequent studies on the use of **4** as a ligand for Pd-catalyzed C–O bond-forming reactions revealed no need for the coordination of the amino group to achieve effective catalysis,^[36] which ultimately led to the development of a new series of biaryl phosphane ligands that would play a pivotal role in C–N coupling reactions (Figure 2).^[37] As illustrative

Figure 2. Representative biaryl phosphane ligands for C–N coupling.

examples, the Pd-catalyzed amination of a range of aryl chlorides was accomplished with a variety of amine coupling partners through the use of either JohnPhos (**5**) or CyJohnPhos (**6**) as ligands.^[38] The more sterically demanding XPhos ligand (**7**) enabled the expansion of the scope of the amination of aryl halides, the development of protocols for both the amination and amidation of aryl sulfonates, as well as the first aqueous amination that does not necessitate the use of a co-solvent.^[39] This ligand also proved to be effective in the Pd-catalyzed amination of heteroaryl halides^[40] and allowed for the selective formation of either di- or triarylamines from aryl halides and ammonia.^[41] A major breakthrough came with the discovery of BrettPhos (**8**), which promoted the amination of aryl mesylates and the selective monoarylation of primary amines with aryl chlorides.^[42] Structurally related *t*BuBrettPhos (**9**) enabled the coupling of amides with aryl chlorides.^[43] In addition, RuPhos (**10**) turned out to be a superior ligand for the coupling of secondary amines with aryl chlorides.^[44] This series of dialkylbiaryl phosphane ligands was not only suitable for the amination and amidation of arenes, but also alkenyl halides and triflates could be converted into imines, enamines,^[25,45] and enamides^[46] by Pd-catalyzed coupling with the corresponding nitrogen-based nucleophile.

In a more recent example, reaction progress kinetic analysis led to the design of an improved ligand (**11**) for the Pd-catalyzed coupling of encumbered α,α,α -trisubstituted primary amines (Scheme 5).^[47] Weak organic amine bases could also be used as substitutes for strong inorganic bases in the presence of an electron-deficient palladium complex (**12**) containing a dialkyl triarylphosphine ligand.^[48] Moreover, the

Scheme 5. Monophosphine ligands for the Pd-catalyzed C–N coupling of encumbered primary amines (**11**) and for the C–N coupling using weak organic bases (**12**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MTBE = methyl *tert*-butyl ether.

*t*BuXPhos ligand has been utilized to prepare stable oxidative addition palladium complexes of densely functionalized aryl halide substrates, complexes which then engaged in a series of couplings, including C–N couplings, in the context of drug discovery.^[49]

Concurrent with the development of biaryl monophosphine ligands, Hartwig and co-workers examined the use of bulky trialkylphosphines as ligands for the Pd-catalyzed amination of aryl halides. Thus, the use of PrBu_3 in a ratio 0.8:1 with respect to a Pd^0 source initially allowed for the amination of aryl bromides and chlorides at either room temperature or slightly above, and enabled both the arylation of indoles and carbamates.^[50] Further studies led to an improved catalyst through the use of air-stable dimeric palladium(I) complexes $[\text{PdBrL}]_2$ (**13**; $\text{L} = \text{PrBu}_2(1\text{-Ad})$ or PrBu_3), which promoted the coupling of secondary alkylamines with aryl chlorides at room temperature within minutes (Scheme 6).^[51] The use of $\text{Pd}(\text{dba})_2$ and $\text{P}(\text{tBu})_3$ was

Scheme 6. Pd-catalyzed C–N coupling using Pd^{I} dimers and QPhos ligand.

also effective in the coupling of aryl halides with $\text{LiN}(\text{SiMe}_3)_2$, which upon hydrolysis led to the formation of the corresponding anilines.^[52] Moreover, the addition of a phase-transfer catalyst allowed the use of aqueous hydroxide as a base.^[53] The palladium complex of the ferrocenyl-based ligand QPhos (**14**) also turned out to be remarkably active for the C–N coupling of both aryl bromides and chlorides with secondary and also primary amines, affording the latter monoarylated products with high selectivity.^[54]

Following these pioneering achievements, numerous novel monophosphines,^[55] including triaminophosphines,^[56] have been designed and successfully applied to Pd-catalyzed C–N couplings over the last years. In addition, the solvent-free Pd-

catalyzed Buchwald–Hartwig amination has recently been accomplished for solid substrates using mechanochemistry as an alternative to classic in-solution chemistry.^[57] The key was the use of $\text{Pd}(\text{OAc})_2/\text{PrBu}_3$ as the catalyst combined with olefin additives, which act as dispersants for the palladium catalyst to prevent its deactivation. This method allowed for the amination of a range of π -extended aryl bromides, which could also be conducted on gram scale, and its potential utility was exemplified with the synthesis of hole-transporting materials.

2.4. Josiphos-Based Bidentate Ligands

In spite of the remarkable progress accomplished in the field of C–N coupling through the use of catalysts containing the biarylmonophosphine ligands described in the previous subsection, those protocols still suffer from some limitations, such as the low selectivity towards the monoarylation of primary amines or high catalyst loadings typically required for the amination of heteroaromatic halides. In this context, Hartwig and co-workers envisioned that the steric and electronic properties of bidentate Josiphos-type ligands offered unparalleled opportunities to overcome those limitations.^[58] It was anticipated that the bulky groups surrounding the coordinating sites could prevent a second arylation in the case of primary amine substrates, thus improving the selectivity towards monoarylated products. In addition, the bidentate nature of these ligands was expected to create catalysts less prone to undergo ligand displacement by basic heterocycles and primary amines, therefore improving the coupling of halopyridines and other challenging substrates.

Initial studies revealed that the combination of the CyPFrBu JosiPhos ligand **15** with $\text{Pd}(\text{OAc})_2$ was an effective catalyst for the coupling of heteroaryl chlorides with primary nitrogen nucleophiles including amines, amides, imines, and hydrazones (Scheme 7).^[59] The same catalyst also promoted the coupling of aryl chlorides and primary amines with high turnover numbers and excellent functional-group compatibility and selectivity towards monoarylation products. Furthermore, aryl bromides and iodides,^[60] as well as (hetero)aryl tosylates^[61] were successfully aminated under related reaction conditions.

Scheme 7. Pd-catalyzed arylation of primary amines using JosiPhos ligand **15**.

The use of a preformed palladium(II) complex of **15** led, in 2006, to the first coupling of (hetero)aryl halides with ammonia to form primary anilines.^[62] The coupling with lithium amide proceeded under related reaction conditions to afford primary aromatic and heteroaromatic amines. Furthermore, the scope of this transformation was later expanded to the amination of a variety of aryl chlorides, bromides, iodides, and sulfonates with only 5 equivalents of ammonia through the use of $\text{Pd}[\text{P}(o\text{-tol})_3]_2$ as the catalyst precursor in combination with equimolar amounts of **15**.^[63] Ammonium salts of ammonia and gaseous amines could likewise be coupled to aryl halides,^[64] which was also later accomplished using a Ni^0 complex of **15** as the catalyst.^[65] The Pd-catalyzed amination of aryl halides with ammonia has also been described using monophosphine ligands.^[41,66] More recently, the in situ formed palladium complex of the P,N-ligand MorDaIPhos proved to be effective in the monoarylation of ammonia^[67] and hydrazine.^[68]

2.5. N-Heterocyclic Carbene (NHC) Ligands

Well-defined palladium(II) complexes of NHC ligands are attractive catalyst precursors in cross-coupling reactions because of their robustness and high degree of tunability.^[69] Following early reports on the C–N coupling of chloroarenes catalyzed by Pd–NHC complexes generated in situ,^[70] $[\text{Pd}(\text{IPr})\text{Cl}_2]$ (**16**),^[71] the NHC-containing palladacycle **17**,^[72] and $[\text{PdCl}(\eta^3\text{-allyl})(\text{IPr})]$ (**18**)^[73] were initially used as catalyst precursors in the arylation of amines (Figure 3). The coupling

Figure 3. Well-defined Pd^{II} complexes of NHC ligands used in C–N coupling.

of (hetero)aryl bromides and chlorides proceeded effectively with both secondary amines and anilines in the presence of **16**, although this complex did not catalyze the coupling of aryl triflates and base-sensitive substrates. Remarkably, these reactions could be conducted under aerobic conditions. Aryl tosylates could be coupled using either **17** or **18**, and further structural modifications of the latter led to significant improvements regarding substrate scope, reaction times, and temperatures. As illustrative examples, the replacement of the allyl fragment in **18** by a cinnamyl ligand to form **19** allowed for the amination of unactivated aryl chlorides at room temperature within minutes,^[74] the use of low catalyst

loadings,^[75] and the coupling of sterically demanding substrates.^[73b] Another structural variation consisted of the replacement of the allyl group by an acetylacetonate (acac) moiety.^[76] The resulting $[\text{Pd}(\text{NHC})(\text{acac})\text{Cl}]$ complexes, such as **20**, turned out to be highly active in the amination of a series of substrates including sterically encumbered arenes and heterocyclic aryl chlorides.

The quest for improved NHC-containing precatalysts for Pd-catalyzed cross-coupling reactions led to the development of Pd-PEPPSI complexes of type **21** (PEPPSI = pyridine-enhanced, precatalyst preparation, stabilization, and initiation), which were first applied in C–N coupling in 2008.^[77] Modifications of the backbone of the NHC ligands in Pd-PEPPSI precatalysts allowed for the expansion of the substrate scope and the use of milder reaction conditions.^[78] Polymer-supported Pd-PEPPSI precatalysts^[79] as well as a mechanochemical method based on the use of Pd-PEPPSI-IPent^[80] have also been recently developed for C–N couplings. In addition, the use of a NHC-containing palladacycle enabled the amination of diaryl sulfoxides, which could be regioselectively conducted by means of steric bias.^[81]

3. Mechanistic Studies

The reaction mechanism of the Buchwald–Hartwig amination has been extensively studied throughout its development,^[82] which has led to the proposal of different catalytic cycles depending on the nature of the ligand and the reacting partners.

3.1. Monophosphine Ligands

The mechanism of the initial Pd-catalyzed amination of aryl bromides with aminostannanes reported by Migita^[6] was first studied in detail by Hartwig and co-workers (Scheme 8).^[7b] The Pd^0 complex **A**, containing two $\text{P}(o\text{-tol})_3$ ligands, was independently prepared and tested as a catalyst in the C–

Scheme 8. Catalytic cycle proposed for the Pd-catalyzed amination of aryl bromides using $\text{P}(o\text{-tol})_3$ as the ligand.

N bond formation reaction, which gave rise to the coupled products in yields comparable to those obtained from the Pd^{II} precursor. The reaction of **A** with aryl bromides led to the isolation of the dimeric species **C**, which turned out to be the resting state of the catalyst. However, this transformation was retarded by the addition of an excess of $\text{P}(o\text{-tol})_3$, which pointed towards the intermediacy of **B** through initial reversible dissociation of one phosphine ligand. In addition, **C** or its corresponding monomer reacted with aminostannanes in what appeared to be the rate-limiting step to form **E**, which upon reductive elimination would release the coupled product and regenerate the Pd^0 catalyst. This mechanism for the Pd-catalyzed coupling of aryl bromides with aminostannanes was further studied through a combination of independent synthesis of reaction intermediates and stoichiometric transformations, which led to the first identification of the three-coordinate Pd^{II} alkylamido complex **E** as the intermediate that subsequently undergoes reductive elimination to form the C–N bond.^[83] In addition, complexes of type **E** could also be prepared from **C** through the addition of lithium amides, and pointed towards the possibility of a catalytic cycle that would not require the presence of aminostannane reagents, which eventually led to the development of the tin-free coupling of aryl bromides with amines.^[8] Indeed, it was demonstrated that the dimeric complexes **C** are cleaved in the presence of amines to form the monomeric species **D**, bearing one phosphine and one amine ligand, which due to the enhanced acidity that results from the coordination to the palladium center can be deprotonated with either $\text{MO}t\text{Bu}$ ($\text{M}=\text{Li}, \text{Na}$) or $\text{LiN}(\text{SiMe}_3)_2$. The resulting amido complex **E** undergoes rapid reductive elimination at room temperature to afford the coupled aniline product.^[8a] In the case of using $\text{LiN}(\text{SiMe}_3)_2$ as the base, **A** was found to be the resting state of the catalyst and therefore the oxidative addition appeared to be the rate-limiting step. In contrast, the reactions conducted in the presence of $\text{MO}t\text{Bu}$ were limited by the generation and reductive elimination of **E**.

The low yields obtained for the coupling of primary amines using $\text{P}(o\text{-tol})_3$ could be rationalized on the basis of some of the results derived from these mechanistic studies.^[8] On the one hand, a β -hydride elimination process may compete with the reductive elimination from **E** in the cases where the alkylamido group possesses β -hydrogen atoms, which leads to the formation of the corresponding imine and concomitant reduction of the aryl halide. The selectivity towards reductive elimination could be improved through the use of either bulkier phosphine ligands, more nucleophilic amines, or electron-deficient aryl bromides,^[84] yet mixtures of amination and reduction products were typically obtained when primary amines were used as nucleophiles. On the other hand, it was found that primary amines have a great tendency to form catalytically incompetent palladium bis(amine) complexes by the reaction of **C** with an excess of the amine.^[85]

While the cleavage of **C** readily proceeds in the presence of an amine to form **D**, the process to cleave the iodide-bridged analogue was found to be endergonic, which might be responsible for the lower efficiency observed in the amination of aryl iodides compared to aryl bromides.^[85] Thus, it was

hypothesized that the use of ligands such as biarylphosphines, which prevent the formation of such dimers, would favor the coupling of aryl iodides.^[86] In addition, further investigations unveiled that NaI , which is generated as a byproduct, inhibits the Pd-catalyzed coupling of aryl iodides with amines by binding to Pd^{II} intermediates. Consequently, the use of solvents in which the iodide is insoluble led to suppression of the inhibition effect and therefore to a more efficient coupling of aryl iodides.

3.2. Bisphosphine Ligands

As discussed in the previous section, the use of chelating ligands was found to be a viable alternative to $\text{P}(o\text{-tol})_3$ ^[13,14] to prevent competing β -hydride elimination during the amination of aryl halides.^[87] The effect of the bite angle and steric and electronic properties of a series of bidentate phosphine ligands on the product ratios that result from the amination of aryl bromides was systematically examined, concluding that the formation of the reduced arene and diarylation side products was significantly diminished through the use of electron-rich, hindered phosphines with small bite angles.^[16,88]

The isolation of several reaction intermediates led to the postulation of the catalytic cycle depicted in Scheme 9. When

Scheme 9. Catalytic cycle proposed for the Pd-catalyzed amination of aryl bromides using chelating bisphosphines as the ligands.

BINAP was used as the bidentate ligand, the Pd^{II} complex **G** could be independently synthesized by the reaction of BINAP with **C**.^[14a] The corresponding $\text{Pd}(\text{BINAP})(\text{dba})$ complex was also isolated. Both complexes proved to be catalytically competent and rendered the coupled products in yields and product distributions similar to those obtained when a combination of $\text{Pd}_2(\text{dba})_3$ and BINAP was used as the catalyst. Additionally, the Pd^{II} amido complexes **I**, containing DPPF as the chelating ligand, could also be isolated.^[13,89] These four-coordinate complexes underwent reductive elimination upon heating in the case of secondary amides and even at room temperature when primary amides containing β -hydrogen atoms were bound to the palladium center, which presumably

results from the *cis* configuration of the aryl and amido moieties.^[90] Further mechanistic studies from the groups of both Hartwig^[91] and Buchwald^[92] led eventually to a revised mechanistic picture for the amination of aryl bromides catalyzed by Pd-BINAP complexes.^[93] Hence, the bromoarene appears to react with [Pd(BINAP)] rather than [Pd-(BINAP)₂], which is an off-cycle intermediate and generates the active species by reversible dissociation of one of the BINAP ligands. Moreover, it was also demonstrated that the structure of the inorganic base plays a key role in the reaction rate in the cases where a rate-limiting deprotonation step is involved.^[94]

Contrary to the aryl- and alkylamido complexes **1** containing either BINAP or DPPF ligands, the corresponding parent amido complexes neither formed nor underwent reductive elimination with anilines,^[95] which is consistent with the fact that these ligands are ineffective in the coupling of aryl halides with ammonia. In contrast, the parent Pd^{II} amido complex **22**, bearing **15** as a ligand, could be generated and slowly underwent reductive elimination at room temperature in the presence of PPh₃ (Scheme 10).

Scheme 10. Reductive elimination from parent amido complexes **22**.

4. Recent Applications

The modern protocols developed for Pd-catalyzed coupling of amines and aryl (pseudo)halides exhibit in general broad substrate scope, high reproducibility, and scalability, which makes them appealing methods for the preparation of aryl amines in both academic research and industrial production. The number of applications in fields such as natural product synthesis, material sciences, agrochemicals, or synthesis of ligands has grown exponentially since the first coupling protocols were disclosed.^[2] In this section, some of the most recent illustrative applications of the Buchwald–Hartwig amination, with a particular focus on applied research, will be summarized with the aim of exemplifying the state-of-the-art and the potential of this methodology.

4.1. Applications in Basic Research

The Pd-catalyzed amination of aryl halides is typically one of the most straightforward disconnections to obtain aryl amines, which are key building blocks in numerous molecules with either relevant biological or optoelectronic properties. A comprehensive review covering a broad assortment of applications of C–N bond formation has been recently published.^[2a] Thus, only some representative examples described over the course of the past two years are presented in this subsection (Figure 4). In the context of total synthesis of natural products, an intramolecular C–N coupling catalyzed

Figure 4. Selected recent applications of the Buchwald–Hartwig amination in basic research.

by Pd/BINAP was used as one of the key steps in the synthesis of structurally related 7-isovaleryloxy-8-methoxygirinimbine (**23**)^[96] and furoclausine-B (**24**).^[97] This strategy has also been applied in the preparation of B,N-containing polycyclic aromatic hydrocarbons such as **25**,^[98] which are of potential relevance for implementation in optoelectronic devices. Additionally, the amination of the vertexes of well-defined nanographenes provided an entry to reversed donor-acceptor conjugates such as **26**,^[99] whose electron-deficient cavity can host electron-rich guests as a result of intermolecular charge transfer. In a different example, the sixfold Buchwald–Hartwig amination of a 9,10-diaminoanthracene derivative with 1,4-dibromobenzene afforded hexaaza[1₆]paracyclophane **27**.^[100] This compound was converted into the corresponding triradical trication upon oxidation, which was found to be a spin-frustrated three-spin system.

4.2. Applications in Scale-Up Processes

In addition to being an indispensable tool in basic research, Pd-catalyzed cross-coupling reactions have also become crucial in industry.^[2c–e,101] As such, Pd-catalyzed C–N couplings have found applications in the large-scale production of pharmaceuticals and agrochemicals. In this subsection, a selection of examples reported over the course of the past five years are discussed.^[102]

Chemists at Pfizer reported in 2014 the scale-up of the coupling of 6-bromoisoquinoline-1-carbonitrile (**28**), featuring a potentially base-labile nitrile group, with (*S*)-3-amino-2-methylpropan-1-ol (**29**) to provide pharmaceutical intermediate **30** in 80% yield on a 2.5 kilogram scale (Scheme 11).^[103] Notably, the competing formation of the corresponding diarylated amine was significantly circumvented and **30** was obtained in 94.8% purity, containing less than 5% of this byproduct.

A multi-kilogram scale protocol for synthesis of the potential drug candidate AMG 925 (**34**) was developed by taking advantage of a Buchwald–Hartwig amination as one of the key steps (Scheme 12).^[104] Thus, chloropyridine **32** was coupled with aminopyrimidine **31** using a catalyst generated

Scheme 11. Kilogram-scale synthesis of the pharmaceutical intermediate **30**.

Scheme 12. Kilogram-scale synthesis of the AMG 925 precursor **33**.

from $\text{Pd}(\text{OAc})_2$ and BrettPhos, which gave rise to 12 kilograms of intermediate **33** in a single batch with a palladium content lower than 5 ppm.

The most efficient large-scale synthesis of broad-spectrum fungicide sedaxane (**37**) includes the Buchwald–Hartwig coupling of chloroarene **35** and benzylamine, the product of which is subsequently cleaved to afford the corresponding aniline **36** (Scheme 13).^[105]

Scheme 13. Scale-up synthesis of sedaxane (**37**).

A scalable synthesis of venetoclax (**41**), which is an active pharmaceutical ingredient, has also been developed based on a key Buchwald–Hartwig coupling between **38** and **39** (Scheme 14).^[106] This new protocol led to a significant reduction of the production cost with an overall yield that exceeds double that obtained in the first-generation synthesis, and allowed the preparation of up to 8.5 kilograms of **41** in a single batch.^[107]

Scheme 14. Scale-up synthesis of venetoclax (**41**).

In addition to batch processes, Pd-catalyzed couplings of aryl halides with amines have also been conducted in continuous flow on a multi-kilogram scale.^[107]

5. Summary and Outlook

The noteworthy progress achieved in the Buchwald–Hartwig amination over the past 25 years has turned it into a well-established and remarkably convenient methodology to form aniline derivatives from aryl (pseudo)halides and amines. The pioneering reports on the coupling of amino-stannanes with aryl halides rapidly evolved into tin-free protocols with impressive substrate scope, encompassing, among others, aryl halides and phenol derivatives, which can be coupled with a range of N-nucleophiles including ammonia. In addition, the reaction development was accompanied by in-depth mechanistic studies, which not only unveiled reaction intermediates and unprecedented elementary steps, but also contributed to further innovations in catalyst design. Notably, even though some motifs appear to be privileged in the structure of the ligands employed in Buchwald–Hartwig aminations, none of them has proved to be superior as an all-purpose ligand.

The widespread occurrence of aniline derivatives in a broad spectrum of research areas makes the Buchwald–Hartwig amination a tremendously useful method for both academic research and industrial processes. The operational simplicity and availability of the required ligands have also been decisive factors for the rapid implementation of this methodology. Furthermore, there is a growing interest in the development of first-row transition-metal-catalyzed alternatives to palladium catalysis for this transformation^[9] including their coupling to photochemical^[9e,108] or electrochemical processes.^[109] In contrast to basic research, the number of applications on large scale still remains somehow limited compared to Pd-catalyzed C–C cross-coupling methodologies. Nonetheless, the importance of aminated building blocks together with the fundamental developments accomplished over the past years certainly hold potential for additional future industrial applications.

Acknowledgements

A.M.H. thanks BASF SE, particularly Dr. Johann-Peter Melder, Dr. Xenia Beyrich-Graf, and Dr. Detlef Kratz for general support. C.P.G. is grateful for a PhD fellowship from the Fonds der Chemischen Industrie. The Ramón Areces Foundation is also gratefully acknowledged for a postdoctoral fellowship to R.D.

Conflict of interest

The authors declare no conflict of interest.

How to cite: *Angew. Chem. Int. Ed.* **2019**, 58, 17118–17129
Angew. Chem. **2019**, 131, 17276–17287

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Manuscript received: April 17, 2019

Accepted manuscript online: June 5, 2019

Version of record online: September 18, 2019