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The 25th Anniversary of the Buchwald−Hartwig Amination: Development, Applications, and Outlook

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ABSTRACT: The palladium-catalyzed cross-coupling of amines and aryl (pseudo)halides, now commonly known as the Buchwald−Hartwig amination, was first reported 25 years ago. Since the simultaneous breakthrough reports of Buchwald and Hartwig in 1995, this reaction has transformed the way synthetic chemists think about synthesizing aromatic amines. In this highlight article, a short showcasing discussion about the genesis of this reaction is provided, along with selected examples showing the impact of this transformation in synthetic chemistry in both academic and industrial settings.

KEYWORDS: *carbon−nitrogen coupling, amine synthesis, methodology, rational ligand design, Buchwald−Hartwig amination*

Aromatic amines are fundamental products and building blocks in chemistry with particular importance for the pharmaceutical and agrochemical industries.[1] Their formation traditionally relied on different strategies, such as nitration followed by a reduction step, nucleophilic aromatic substitution of activated substrates, or copper-mediated Ullmann-type coupling of amines and aryl halides (Scheme 1).[2] While useful strategies, all of these transformations show limited scope and functional group tolerance. Nitration is an economical and well-established technology but suffers from poor step economy in the overall synthesis of aromatic amines. Nucleophilic aromatic substitution requires strong activating electron-withdrawing groups on the aromatic substrate in order to achieve reactivity. The Ullmann-type couplings can require up to stoichiometric amounts of copper, elevated temperatures, and display competing biaryl formation. Subsequently, milder alternatives are of particular interest and value, from both the academic point of view and the industrial perspective. It has to be mentioned that immense progress has been made in recent years in this area, particularly with the Chan−Evans−Lam modifications[3] and the catalytic systems developed by Ma that allowed dramatic reductions of the catalyst loading and temperature.[4] The palladium-catalyzed formation of carbon−nitrogen bonds, now commonly known as the Buchwald−Hartwig amination, has drastically transformed this area of chemistry. It is now a fundamental transformation in synthetic chemistry and one of the most widely used transformations in the pharmaceutical and agrochemical industries.[5−7]

This reaction has its root in early reports by Migita in 1983 about the palladium-catalyzed coupling of aryl bromides and tin amides.[8] In 1994 two independent reports appeared, one by the Hartwig group, who examined the reaction intermediates and catalytic species of this reaction,[9] and the other by the Buchwald group, who described an improved method to avoid the isolation of toxic and sensitive tin amides.[10] A year later, both Buchwald and Hartwig reported protocols for what is now the prototypical C−N coupling reaction of an amine with an aryl halide using a palladium catalyst and a hindered base (Scheme 2).[11,12] After these initial reports, the reaction quickly took off and was adopted in a variety of academic and industrial settings. In 2016, it was reported that about 10% of all medicinal chemistry papers in the year 2014 used a Buchwald−Hartwig coupling at least once, showing the importance of this transformation in the pharmaceutical industry at early-stage discovery.[13]

Early studies by Hartwig established the following general mechanism using $P(Ar)_3$-type ligands (Scheme 3).[12] Oxidative insertion of Pd(0) species **I** into the aryl halide substrate affords a dimeric species of type **II**. Coordination of the amine significantly increases its acidity, allowing its deprotonation by a hindered base such as *t*BuONa or LiHMDS, forming palladium amide complex **IV**, which undergoes reductive elimination to give the arylated amine product and the regenerated Pd(0) catalyst **I**. Extensive mechanistic investigations by both groups led to a better understanding of the factors governing the reaction efficiency, from the oxidative addition process to the reductive elimination process, as well as the competing β-hydride elimination side reactions.[14−17] Understanding these factors led to the rational development of a large number of catalytic systems,[18,19] vastly improving the reactivity and scope compared with the $P(o\text{-tolyl})_3$ phosphine ligands used in the original reports (Scheme 4).

The bidentate ligand **CyPF-*t*-Bu** (**1**) developed by Hartwig and the family of biaryl phosphine ligands developed by Buchwald, such as **BrettPhos** (**2**) and **RuPhos** (**3**),[20] are now considered standard and highly efficient ligands, and all of them are commercially available. Buchwald notably published a user's guide of the numerous biaryl phosphine ligands developed by his group and their preferred applications in order to aid selection of reaction conditions and further optimization.[21] Several other ligands performing C−N

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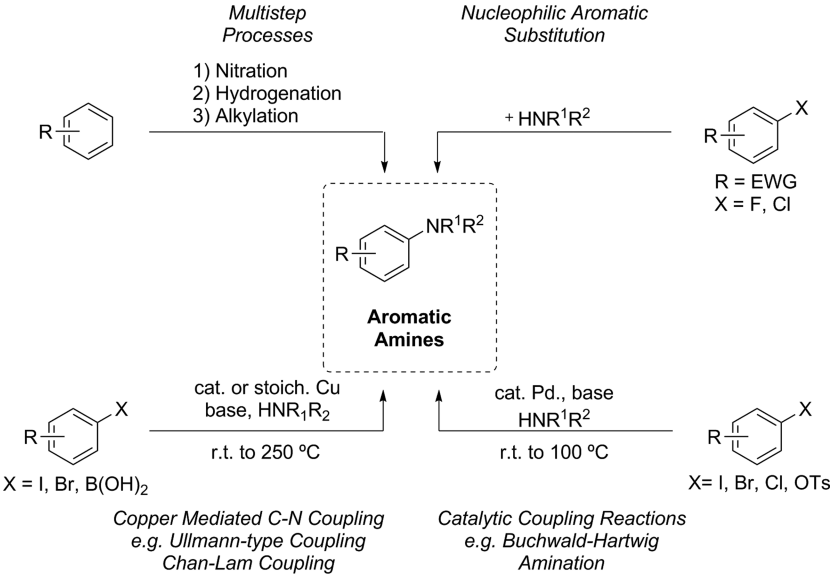
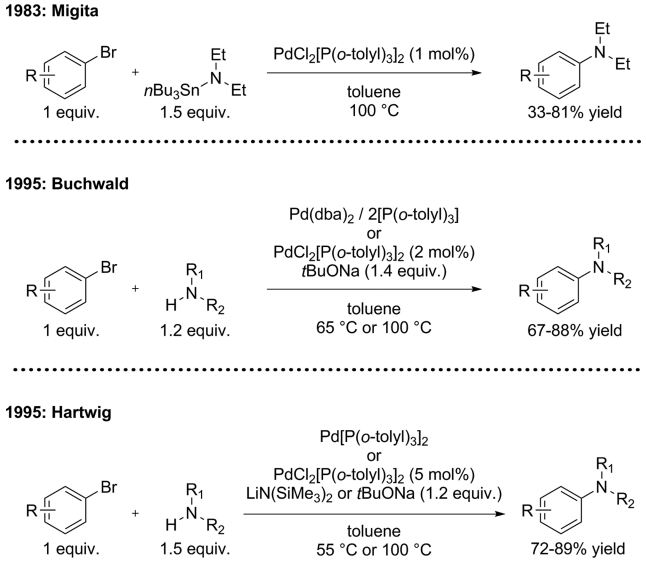
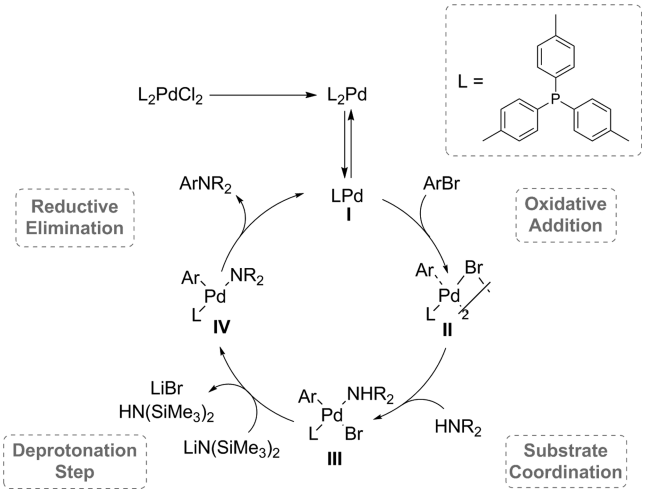
Scheme 1. Common Strategies for the Synthesis of Aromatic Amines



Scheme 2. Early Reports of Palladium-Catalyzed C−N Bond-Forming Reactions



Scheme 3. Mechanistic Framework of the Palladium-Catalyzed C−N Cross-Coupling Reaction[12]



couplings with very broad scopes have been reported, such as **BippyPhos** (**4**)[22] and the N-heterocyclic carbene ligand ***i*Pr-HCl** (**5**),[23] which are commercially available. Nowadays it is possible to conduct C−N couplings of a very wide variety of (hetero)aryl (pseudo)halides with amines, amides, and N−H heterocycles, often at relatively low temperatures and catalyst loadings, even on the order of parts per million.[24,25] As additional proof of the robustness of this chemistry, it is also possible to use more challenging sources of nitrogen, such as fluoroalkylamines,[26] or even ammonia as a direct coupling partner.[27,28]

As a consequence, a variety of industrial processes making use of the C−N coupling technology on multikilogram scales have been reported (Scheme 5).[6,7] As selected examples, in 2004 a hydrazonation was reported by a team from Rhodia that made use of **MePhos** (**12**) as ligand for the synthesis of *N*-(*p*-tolyl)benzophenone hydrazone (**11**) from chlorotoluene (**9**) and benzophenone hydrazone (**10**) on a 3.4 kg scale.[29]

The same year, researchers from AstraZeneca reported the large-scale synthesis of an intermediate to a 5-HT receptor antagonist. In this case, the use of racemic **BINAP** (**16**) as the ligand, cesium carbonate as the base, and anisole as the solvent allowed an efficient and economical reaction to proceed in 6 h, giving 24 kg of the desired intermediate **15**.[30] In 2012, a team from Eli Lilly reported a first optimized system for the synthesis of compound **19**. Using a 0.4 mol % loading of a catalyst combination consisting of $Pd_2(dba)_3$ and **Xantphos** (**20**) as a bidentate phosphine ligand, they obtained 82 kg of the desired coupling product.[31] Further refinement of the process at manufacturing scale, particularly an investigation of the sensitivity of the reaction toward oxygen, allowed them to transfer the same reaction to 8000 L reactors and a 250 kg scale.[32] Using racemic **16** as ligand, researchers from Pfizer demonstrated the reaction of bromide **21** with the amino alcohol **22**, delivering **23** in 80% yield on a 2.5 kg scale.[33] Remarkably, the primary alcohol contained in **22** did not need protection and could be used as such without interference in the desired C−N coupling. In 2015, a team from Amgen

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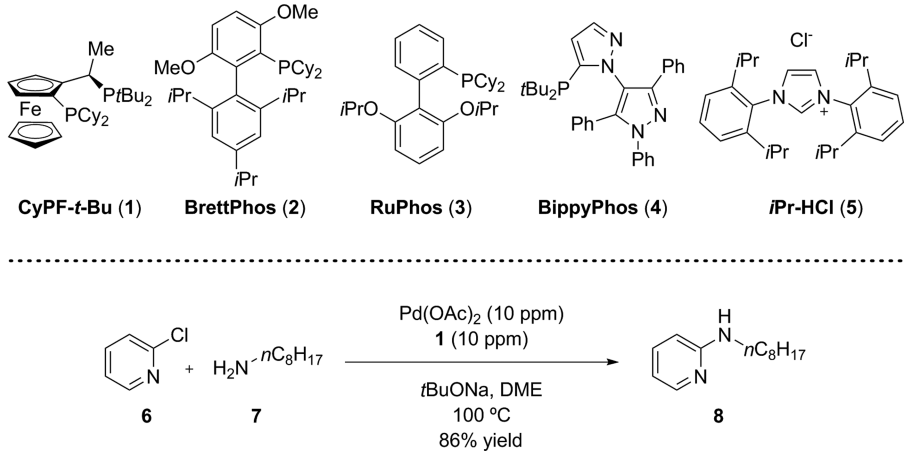
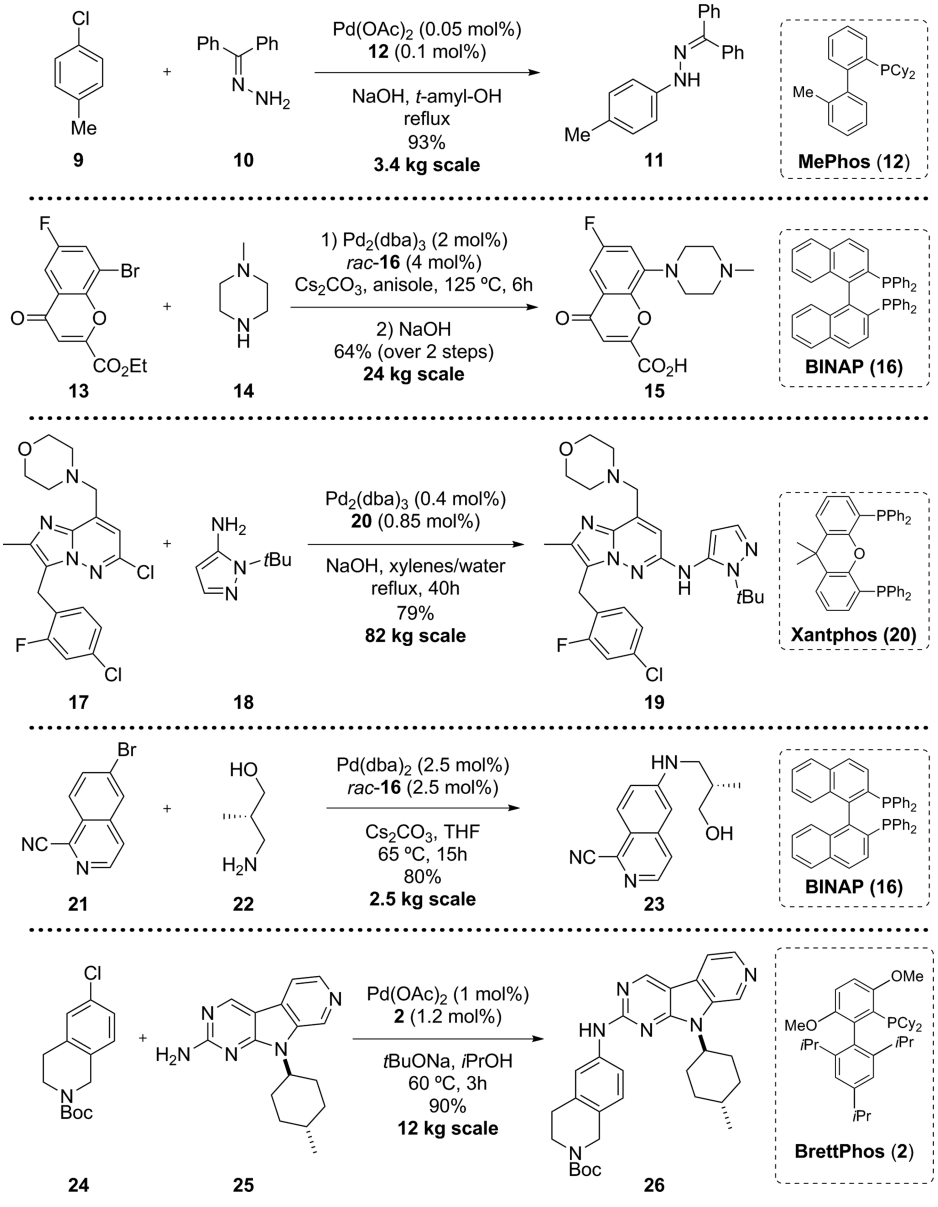
Scheme 4. Examples of Optimized Ligands for the C−N Coupling Reaction and the Amination of 2-Chloropyridine Using Parts per Million Catalyst Loading



Scheme 5. Selected Examples of Industrially Relevant Processes Making Use of the C−N Coupling Technology



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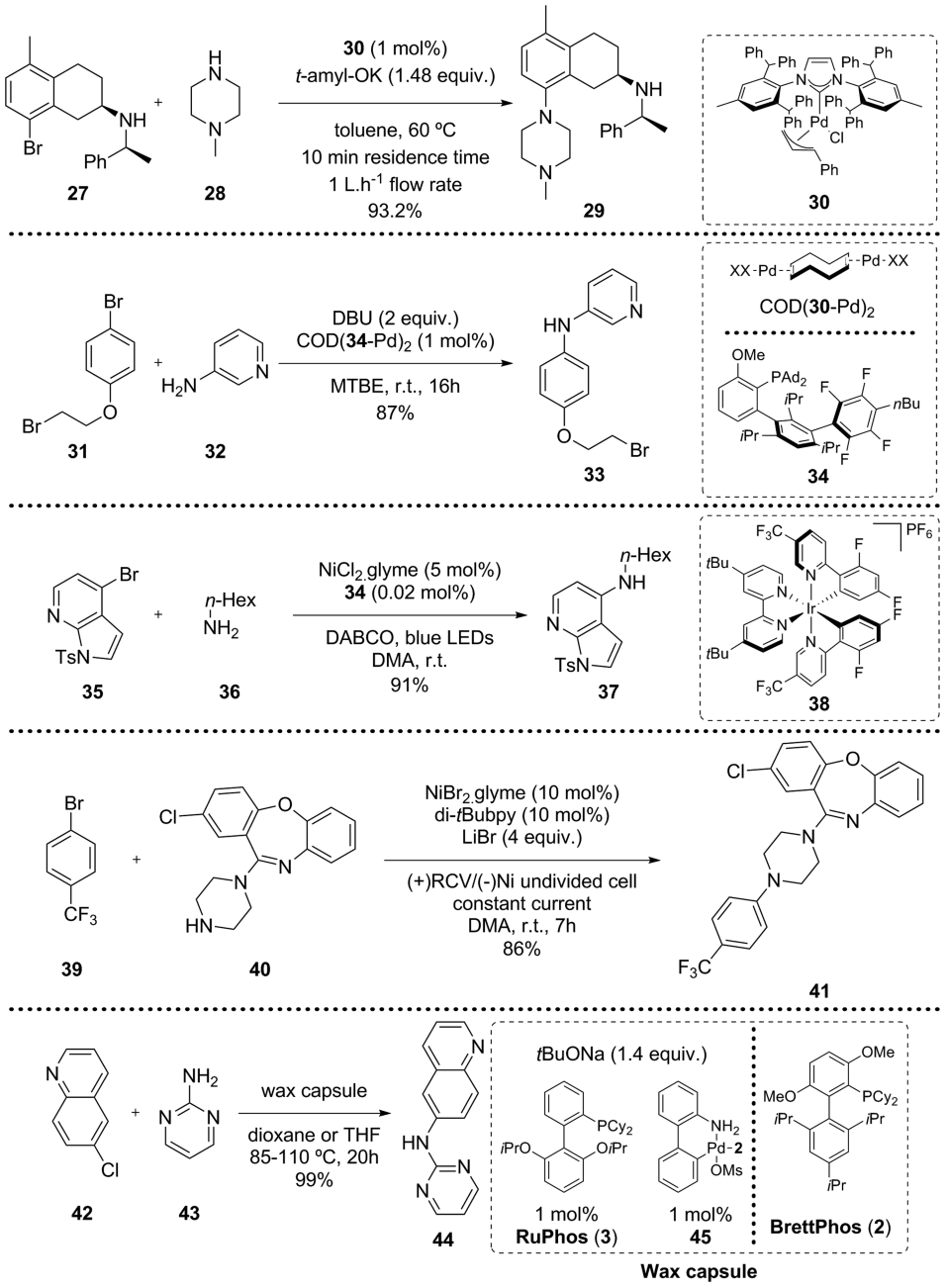
Scheme 6. Examples of Recent Advances in the Field of C−N Coupling Reactions



reported the synthesis of the drug candidate AMG 925 required for early clinical studies that relied on an early-stage amination of tetrahydroisoquinoline **24** with **25** on a 12 kg scale.[34] The use of the biaryl ligand **Brettphos** (**2**) along with *t*BuONa as the base allowed the reaction to proceed at a low temperature of 60 °C with a short reaction time of 3 h to deliver 12 kg of **26** in 90% yield. These selected examples showcase the industrial utility of the C−N coupling reaction beyond the early stages of discovery and its applicability in process chemistry.

While already well-established as a synthetic tool for the formation of C−N bonds, further development in this area is continuing, aimed at further improving the efficiency and scope of the reaction (Scheme 6). An interesting example was reported by researchers from AstraZeneca referring to the use of flow reactors, which showed promising results for the implementation of continuous manufacturing techniques, including catalyst recycling, for the Buchwald−Hartwig coupling reaction leading to product **29**.[35] A recent report by the Buchwald group described the use of tertiary amine bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), allowing reactions to be conducted at room temperature in the presence of base-sensitive functionalities, as in the synthesis of **33**.[36] Likewise, some attention has been directed toward photocatalytic strategies, notably allowing reactions to be conducted at room temperature[37,38] or in the absence of supporting ligands, as in the nickel-catalyzed arylation of amines reported by the MacMillan and Buchwald groups in collaboration with the Merck process chemistry laboratories.[39] This methodology allowed the synthesis of **37** at room temperature using photocatalyst **38** at a loading of 0.02 mol %. An alternative method reported by the Baran group in

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collaboration with Asymchem and Pfizer makes use of electrochemistry for a variety of coupling reactions, including modification of the drug amoxapine **40** to give **41**.[40] The Buchwald group reported the use of wax capsules in order to deliver oxygen- and moisture-sensitive catalysts and reagents.[41] For example, they demonstrated the coupling of chloroquinoline **42** with **43** in quantitative yield using a wax capsule containing all of the reagents required for the reaction, i.e., *t*BuONa as the base and a combination of the ligand **RuPhos** (**3**) and the base-activated precatalyst **45** bearing **BrettPhos** (**2**) as a ligand.[42] Remarkably, yields obtained with a wax capsule that had been stored on the bench for 8 months were similar to or even higher than those obtained when the same reaction was set up in a glovebox without the wax capsule technique. Finally, the use of machine learning techniques has recently been reported as a tool to predict the performance of catalytic systems in C−N coupling reactions,[43] showing both the importance of the transformation itself and its established relevance as a benchmark reaction in modern catalysis development.

Twenty-five years ago, Buchwald and Hartwig revolutionized the field of C−N coupling reactions with their seminal reports. This transformation has now become one of the main tools for organic synthesis, at the same level as other palladium-catalyzed processes such as the Suzuki−Miyaura and Sonogashira coupling reactions.[13] As such, it has found countless applications in academia and industry alike, and vibrant research is still being performed to push the limits of this transformation even further.

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The manuscript was written through contributions of both authors. Both authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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