Palladium-Catalyzed C–N and C–O Coupling – A Practical Guide from an Industrial Vantage Point†

Björn Schlummer, Ulrich Scholz*

Lanxess Deutschland GmbH, Fine Chemicals Research & Development, 51369 Leverkusen, Germany
Fax: (+49)-214-3096-25934, e-mail: ulrich.scholz@lanxess.com

Received: July 6, 2004; Accepted: October 1, 2004

Abstract: The palladium-catalyzed coupling of amines with aryl halides or aryl alcohol derivatives, commonly dubbed Buchwald–Hartwig amination, has matured from a synthetic laboratory procedure to a technique that is widely used in natural product synthesis as well as in other fields of academic interest. Furthermore, due to the versatility and reliability of this reaction, researchers in industrial environments have included this methodology in their toolbox as a standard procedure for the synthesis of amine derivatives. Therefore, it is not surprising that first industrial processes up to ton-scale have been performed using this cross-coupling reaction. The authors who are involved in the application of this reaction to industrial processes on this scale give an overview of the recent developments in this field of chemistry, also including fundamental principles, with a special focus on the industrial approach and issues to be considered relevant in scaling-up this transition metal-catalyzed chemistry. This review differs from the already existing excellent academic reviews by focusing on the practical problems arising during implementing the methodology in an industrial environment as well as giving practical hints to this end.

Keywords: Buchwald–Hartwig amination; C–N bond formation; C–O bond formation; cross-coupling; homogeneous catalysis: palladium; phosphine ligands

1 Introduction

With both chemical industrial and academic research being considered as rather mature fields of science, the question might be raised: what benefit can new research bring to the public community? During the past four decades the great challenges have mainly dealt with questions such as: Can chemists make the same molecules nature can? Can we really make every imaginable molecule? Can we make them elegantly? Can we make them efficiently? Can we make them in an environmentally benign way?

 DOI: 10.1002/adsc.200404216

Björn Schlummer started his studies in chemistry in 1993 at the University of Kiel, Germany. After finishing his diploma thesis in the area of photochemical oxa-di-π-methane rearrangements in the group of Professor J. Mattay in 1998, he moved to the University of Marburg, Germany to join the group of Professor T. Bach. There, he obtained his PhD on iron(II)-catalyzed nitrene transfer reactions in 2000. During his studies he was supported by scholarships from the Studienstiftung des Deutschen Volkes, Graduiertenkolleg Metallorganische Chemie and finally a Kekulé fellowship. To learn more about the fundamentals of organometallic chemistry, he moved to the group of Professor John F. Hartwig at Yale University, New Haven on a DAAD fellowship in the beginning of 2001 to work on palladium-catalyzed hydroaminations. Subsequently, he joined the process development department of the Bayer AG, Leverkusen in 2002 as a project manager for Pharmaceutical Intermediates. Shortly after this, the department was implemented into the Bayer Chemicals AG and is now a part of Lanxess – Fine Chemicals. Together with Ulrich Scholz he works on the application of the Buchwald–Hartwig amination in an industrial environment.

Ulrich Scholz started his studies in chemistry in 1990 at the University of Hannover, Germany. In 1993, he joined Professor Paul A. Wender's research group at Stanford University, California, USA on a DAAD scholarship. After returning to his home town of Hannover, he finished his basic studies in chemistry and received his diploma degree in Professor E. Winterfeldt's research group in 1996 on the synthesis of unsymmetrical pyrazines. He stayed in Professor Winterfeldt's group and spent the subsequent three years on the elaboration of bile acids as potential building blocks for the synthesis of cephalostatin analogues. After graduation he continued as a teaching assistant at Hannover University to finally join the Central Research Department for homogeneous catalysis of Bayer AG at the end of 1999. In 2002, he moved to the process development department of the Bayer Chemicals Company, now Lanxess – Fine Chemicals as a project manager of the Speciality Chemicals Department. Since 2001, he has also headed the Bayer part of an industrial collaboration between Bayer Chemicals, Professor Steve L. Buchwald from MIT and Rhodia Pharma Solutions (formerly Rhodia Chirex) on palladium-catalyzed aromatic aminations.

So with these questions nearly answered in the past, what are the requirements for novel chemical reactions, at least from the view point of the industrial chemist?

One possibility might be: Can we make new molecules with a new methodology in a reliable way, i.e., can we use techniques in the key steps that are both robust and versatile, therefore guaranteeing quick progress in the research? Do we have techniques available that exhibit enough selectivity to allow the construction of highly functionalized, sensitive molecules?

Almost 10 years ago the well known contributions of Buchwald and Hartwig[1] opened a new chapter in the field of transition metal-catalyzed cross-coupling chemistry with a new approach of how to make derivatized anilines and aryl ethers. Although numerous alternatives are available[2] and even the transition metal-catalyzed approach is not a novel approach in general when one looks at metals like copper,[3] these two publications have triggered tremendous activities both in academic and industrial groups.

The intention of this review is to cover the key activities during the past five years. Next to the goal of documenting the milestones in this field, the authors, being industrial chemists, also have a second objective: to show that the palladium-catalyzed C–N and C–O coupling is not only another interesting field to note, but a new reaction that truly fulfills the requirements of a modern synthetic method: versatility, reliability and applicability on small and especially larger scales.

The technique, as mentioned above, is indeed rather young. Still during this time already several reviews have appeared.[4–8,138] While mostly the groups of Buchwald and Hartwig as the pioneers in the field are the contributors, the vantage point so far has usually been the academic researcher. Nevertheless this technology has reached the multi-hundred kg production level in many companies, therefore this article is trying to also cover the concerns of a producer working on that scale.

Although the title includes both C–N and C–O coupling and therefore gives the impression that these two reactions are dealt with in the literature with similar emphasis, it is important to note at this point that about 80% of the covered literature is focused on C–N coupling. As a possible reason for this imbalance one might argue that C–O coupling simply does not work as reliably as amination, furthermore aryl ether formation can

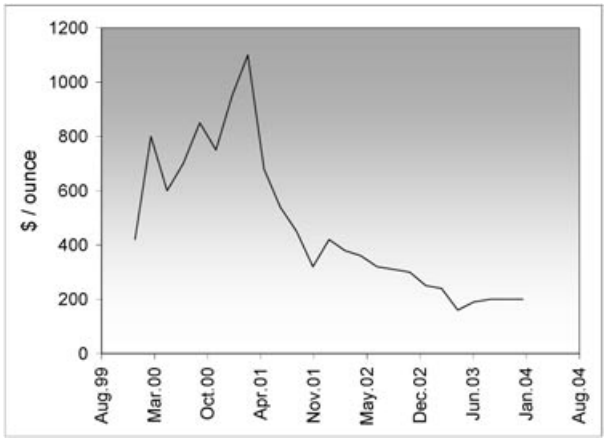


Figure 1. Palladium prices from 2000 to 2004.

also be achieved by alternative approaches, especially copper-catalyzed versions. A last possible answer might be that functionalized anilines might simply be considered to be the more important intermediates compared to aryl ethers.

Another factor that bolsters the interest in palladium-catalyzed coupling reactions is the decline of the precious metal price over the last five years.[9]

While looking at the extremes, the price per ounce from end of 2000 was reduced to one-sixth by the middle of 2003 (Fig. 1), the current development at least keeps economical concerns of this chemistry lower than four years ago.

When looking at the articles that are covered in this review, a point has to be made about comparability. The different contributors present examples with a severely different level of optimization. Only very few authors really compare a large set of different reaction conditions. It seems that many groups prefer some favorite conditions either due to reasons of handling or availability of ligands. Therefore, general statements about which reaction conditions have to be regarded as the most general ones are, in principle, difficult and have to be dealt with certain care.

Positive to note is the fact that the technology has spread from the original inventors into many independent groups, both academic and industrial. Examples are presented that show the strength of this methodology from the viewpoint of the medicinal chemist, who seeks for modular technologies that allow the quick production of a variety of different mg amounts of products for the set-up of structure-activity relations. Also examples from the perspective of total synthesis now appear in the literature, showing reliability of the chemistry with highly functionalized "real-world" problems. Last but not least, more and more groups contribute from the field of the material sciences, therefore showing that this technique offers possibilities for making exciting new functional polymers.

2 Components of the Catalytic System

Due to the proposed mechanism,[8] Buchwald–Hartwig aminations usually require a catalytic system containing four components to efficiently generate the desired C–N bond. A palladium precursor is typically stabilized in solution by an adequate ligand that also raises the electron density at the metal to facilitate oxidative addition and provides sufficient bulkiness to accelerate reductive elimination. A base is required to deprotonate the amine substrate prior to or after coordination to the palladium centre. Owing to the often heterogeneous nature of the reaction due to solubilities of the base or the substrates, the solvent plays a more prominent role than in other transition metal-mediated processes.

These four parameters, visualized in Figure 2, greatly influence the performance of any given C–N coupling reaction and are all of similar importance in designing a screening or reaction set-up. While they are not always independent of each other, it seems nevertheless reasonable to discuss each parameter separately.

The temperature is usually set inside a window typical for activity of the respective ligand or the reactivity of the coupling partners. Further parameters like stirring efficiency, order of addition of components, particle sizes of solids, ratio of ligand to palladium or catalyst loadings have to be taken into account at least before moving to a production scale.

2.1 Ligands

2.1.1 Overview of Ligand Development

Although catalyst systems containing no ligand have been reported over the last years for some organometallic transformations,[10,11] C–N coupling reactions are usually carried out with an added ligand. The ratio of ligand to palladium depends mostly on the ligand employed and can have a distinct influence on the catalytic performance.

The quest for suitable ligands showing higher reactivity and selectivity has been a field of enormous activity over the last years.[4–8] The development of adequate systems has passed through various stages. The first ligands to be used were P(*o*-Tol)$_3$[1,12] and P(*t*-Bu$_3$)[13] (*cf.* Figure 5) The chelating bisphosphines BINAP, DPPF and DtBPF used by Buchwald and Hartwig then defined the state of the art until Buchwald reported the synthesis of monodentate phosphine ligands with a biphenyl backbone in 1998.[14] These ligands greatly enhanced the scope of aminations to aryl chlorides and unactivated aryl halides even under very mild conditions.[15] The

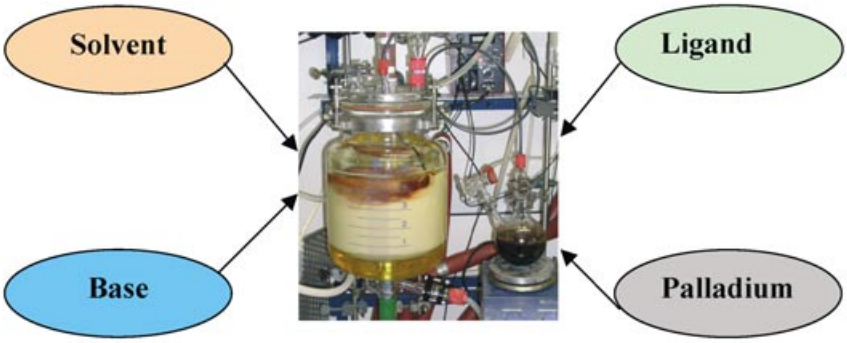


Figure 2. Typical additives for Buchwald–Hartwig aminations.

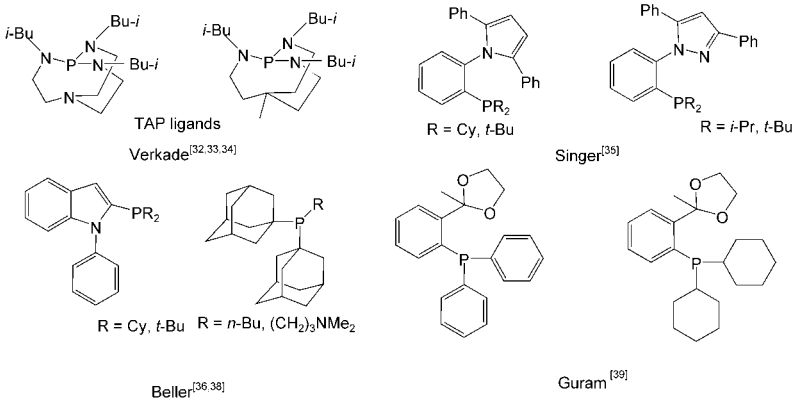


Figure 3. Recently developed ligand systems.

design of the new bulky 2,4,6-triisopropyl-substituted ligand X-Phos led to the most active and stable biphenyl based ligand to date[16] even allowing the use of arenesulfonates and aqueous amination protocols. These biphenyl-based systems can be synthesized easily in a "one-pot" procedure and up to 50 kgs have been prepared.[17,18]

The binaphthyl version of Buchwald's biphenyl ligands, MAP, originally designed and prepared as a ligand for allylic substitution by Kocovský in 1997, could also later be successfully applied in aromatic amination,[19] therefore underlining the privileged nature of the biphenyl type phosphines.

With the advent of carbenes showing outstanding performance in other organometallic transformations as sterically bulky and good electron-donating ligands, these non-phosphorus-based ligand systems increased the variety of ligand architectures.[20–24]

In parallel, van Leeuwen[25] developed XantPhos and DPEPhos (cf. Figure 5) that show especially high activity for coupling of aryl halides with amides,[26–28] hydrazines,[29] oxazolidinones[30] and ureas.[31] These bisphosphines interestingly can act in a *trans*-chelating mode.[26]

Whereas the above-mentioned ligands constitute the most versatile choice with respect to performance and reliability, new lines of ligand design have led to other classes as well.

Verkade reported the use of triaminophosphines as electron-rich ligands with a rigid framework that can be handled in air.[32–34] The scope is very broad including aryl iodides and aryl chlorides.

Heterocyclic subtypes of Buchwald's biphenyl-based ligand systems were reported by Singer[35] in 2003. These pyrrole- and pyrazole-based systems are characterized by the synthetic ease of their formation while their use still requires the combination with the strong base *t*-BuONa. Beller developed these systems further and recently presented new ligands based on *N*-arylindole substructures.[36]

For a potential recycling of the ligand, Buchwald developed a solid-phase bound version of his biphenyl-based ligands.[37] The systems thus obtained allowed aminations down to a loading of 1 mol % palladium and could be recycled at least three times.

Beller reported about adamantyl-substituted alkylphosphines, *n*-BuPAd$_2$, which showed good activity in the activation of aryl chlorides.[38]

Finally, Guram reported the synthesis of phenyl backbone-derived compounds that are efficient for general aminations of aryl chlorides, bromides and iodides.[39] Especially attractive is the synthetic simplicity of these ligands compared to binaphthyl- and ferrocenyl-derived systems.

Recently developed ligands are summarized in Figure 3.

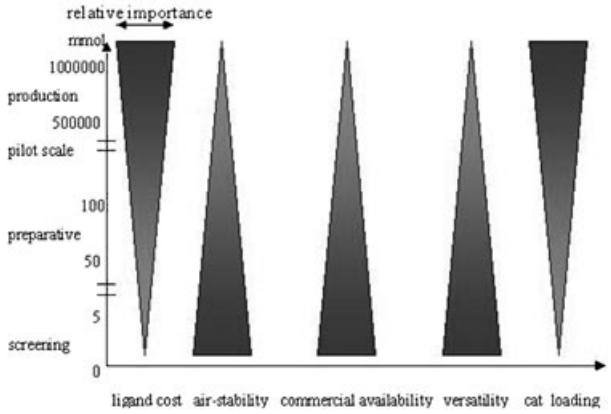


Figure 4. Relative importance of parameters depending on envisaged scale.

2.1.2 Choice of the Right Ligand – Practical Aspects

As outlined in the preceding paragraph, a plethora of ligands with different application profiles has been developed up to date leaving the researcher at a loss about which system to choose for his specific task. A potential ranking has to take different demands into account and can only be seen relative to the problem addressed.

Screening set-ups and also small-scale preparative runs are mostly focused on efficient systems giving good yields in a relatively short time scale due to the demand of the academic researcher or medicinal chemist to have a defined amount of product at hand. Moving to a pilot or production scale, versatility and general performance of the ligand lose some of their importance and availability of the ligand on larger scale (10–50 kg) as well as the ease of its synthesis determining the production costs move into focus. These trends are visualized in Figure 4.

In a screening set-up with typically 1–5 mmol of substrate, a broad variety of ligands is needed that have to be either commercially available or easy to synthesize. Air-stability and ease of handling of catalysts have a stronger impact on results on smaller scales as well. The versatility should be good to cover a broad range of reactivity. Catalyst loading is usually rather high.

In a medium scale of 50–200 mmol, ligand availability and its ease of synthesis, which is also a cost issue, of course, play an even more prominent role while handling usually is easier on this scale. Still, catalyst loading in absolute terms is not a central issue.

If a technical or production scale (1–1000 kg) is aimed at, the large-scale synthesis of the respective ligand as well as catalyst loading (molecular weight of the ligand!) are central points in reaction design. Up to date, ligand costs are one of the determining factors in Buchwald–Hartwig amination processes on the large scale.[18] Air-stability and handling often do not constitute major problems in a typically inertized production vessel environment.

In Figure 5 an overview of the established ligands that have been developed to a mature state and have proven to be versatile ligands in the past is given. While a lot of variations of single ligands have been developed, only the most frequently used ligand variants are shown. The classification of different properties can only provide a general idea, of course, and is not meant to be comprehensive. All of these ligands are used in amination reactions and while some show a broader application profile than others, still many cases exist in which only a single ligand is capable of achieving efficient aminations of a given special substrate.

2.2 Palladium Precursors

2.2.1 Palladium Salts

The choice of a suitable palladium precursor for conducting an amination reaction is far more limited than the choice of the ligand. Typically, Pd(0) or Pd(II) precursors which are reduced if necessary *in situ* to the corresponding zero oxidation state, most often by the amine in the presence of phosphine and base, are used. The most prominent Pd(0) precursors are $Pd_2(dba)_3$ and $Pd(dba)_2$. Nevertheless, the release of dba during the catalysis can have an effect on the performance of the reaction and has to be taken into account.

The most versatile Pd(II) precursor is $Pd(OAc)_2$. Nevertheless, $[allPdCl]_2$ or $Pd(acac)_2$ also show remarkable activity in special cases. If amine substrates lacking β-hydrogens are used as coupling partners, it can be advisable to add a reducing agent to the catalyst mixture. Most versatile additives are phenylboronic acid,[16] alkylamines or sodium formate.[21]

One of the most abundant Pd(II) salts is $PdCl_2$. Nevertheless it is rarely used and only Buchwald reported the use of this precursor in 2001 in the amination of aryl bromides.[40] The effectiveness is comparable to the other precursors when bisphosphine ligands are used but it was incompatible with the use of biphenyl-based monophosphines.

Concerning the catalyst loading, the range is much broader than in other types of cross-coupling reactions. While special substrates can be coupled with palladium loadings down to 0.01 mol %, it is much more typical to start a screening set-up with 1–2 mol % of palladium.

An important point concerning the reliability of the reaction in general is the purity of the components of the catalyst system. Organic or inorganic impurities in the ligand or palladium precursor can have a large impact on the performance of the reaction. Therefore, it is advisable to use material from different suppliers to test for differences in reactivity. Especially when moving to a larger scale, commercial palladium precursors

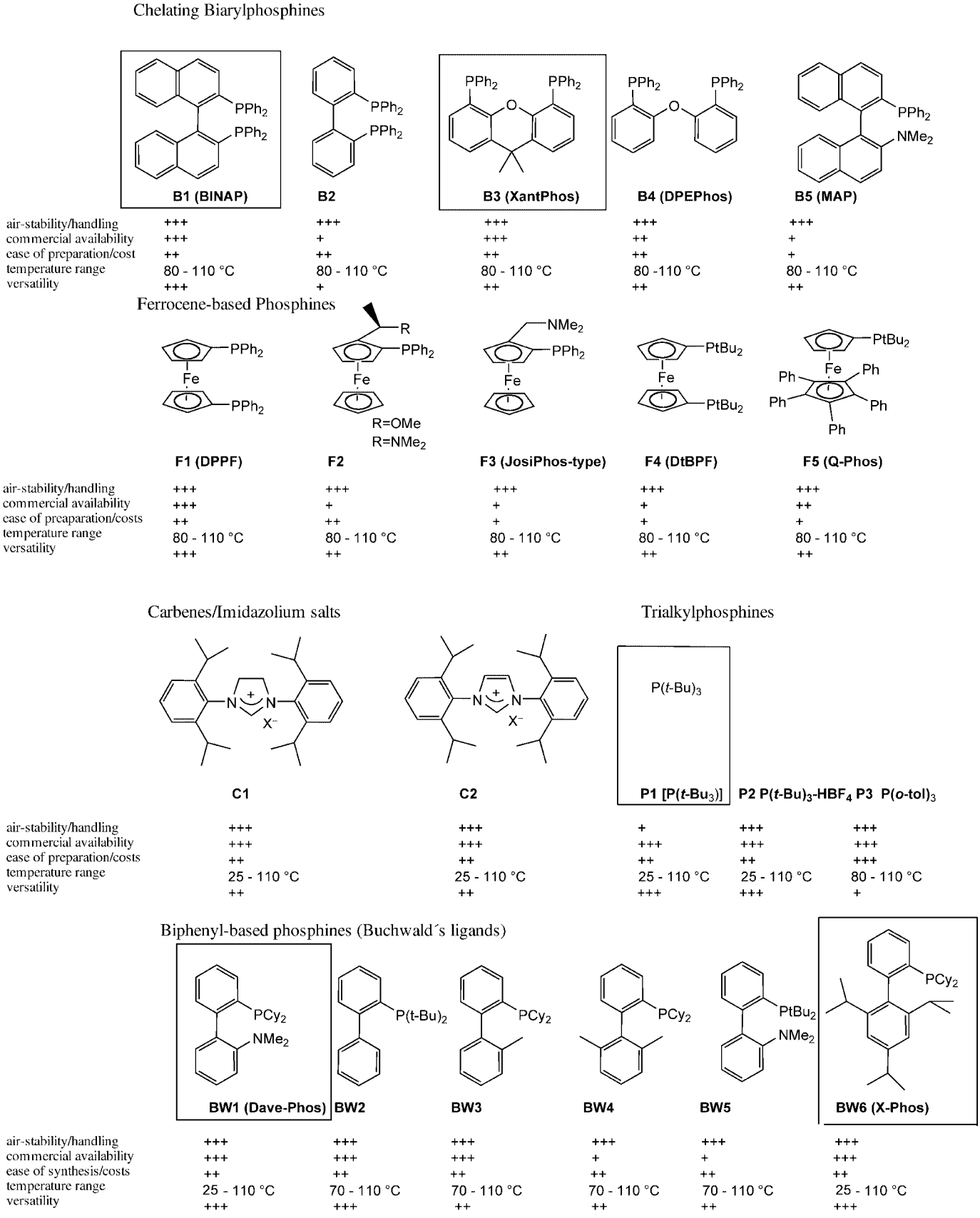


Figure 5. Standard ligands used in C–N coupling chemistry with abbreviations for reference; plus signs indicate relative quality judged by the published literature, most often used ligands are boxed.

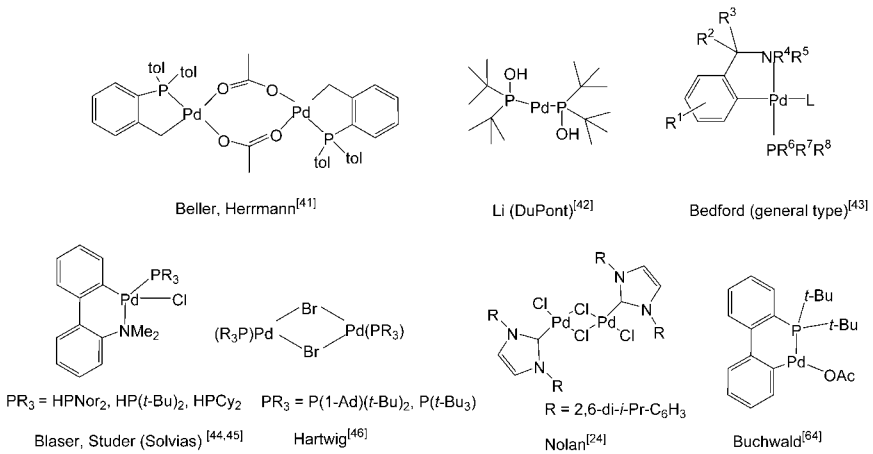


Figure 6. Preformed catalysts.

should be use-tested and a minimum of different palladium batches (ideally one) should be used during a production campaign.

2.2.2 *Preformed Palladium Complexes*

A user-friendly alternative to the more frequently reported *in situ* systems is the use of an isolated palladium complex for the Buchwald–Hartwig amination. Especially in a small-scale synthesis or screening set-up the handling of these mostly air-stable complexes is especially advantageous.

One of the earliest complexes reported for this transformation is the palladacyclic catalyst $[P(o\text{-Tol})_3 PdOAc]_2$ (Figure 6) introduced by Beller and Herrmann which shows a good stability at high temperatures thus also allowing the activation of aryl chlorides.[41]

A very interesting new avenue was paved by Li. He used simple, readily accessible, air-stable palladium(II) complexes ligated with *t*-Bu_2POH.[42] Using these new catalysts, aryl chlorides could be aminated in good yield.

Milstein-type catalysts were investigated by Bedford. These are based on inexpensive precursors and are also viable ligands for the coupling of aryl chlorides.[43]

Blaser et al. used isolated palladacycle-HPR_2 catalysts which are air-stable and easy to handle. These systems also show good performance in the activation of aryl chlorides.[44,45]

Hartwig and Kuwano developed an air-stable palladium(I) dimer that is active for the coupling of various aryl chlorides or bromides within minutes at room temperature.[46]

Nolan reported the use of an isolated N-heterocyclic carbene complex which is air-stable and is reported to show good activity for a variety of C–N coupling reactions involving aryl chlorides even under aerobic conditions.[24]

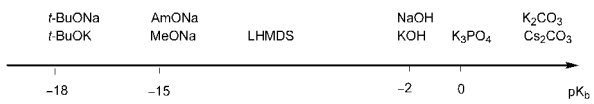


Figure 7. Base strengths of typical bases used in Buchwald–Hartwig aminations.[50]

2.3 Bases

The third crucial component of the reactive system is the base which deprotonates the amine before or after coordination to palladium. Owing to this, at least stoichiometric quantities of this component are needed. Two types can be distinguished: bases that are only sparingly soluble in the typically used apolar solvent (e.g., toluene) and bases that give nearly homogeneous reaction mixtures

The most common bases for C–N couplings are: *t*-BuONa, *t*-BuOK, LHMDS, Cs_2CO_3, K_2CO_3, K_3PO_4, NaOMe, NaOH, KOH and *t*-AmONa. The vast majority of side-reactions to be found in Buchwald–Hartwig aminations are caused by the added base. The functional group tolerance of the strong *tert*-butoxide bases first used in this type of chemistry is inherently low.

The relative base strength determines the functional group tolerance. Unfortunately, direct comparisons of base strengths are difficult owing to heterogeneous mixtures in which solubilities play a significant role, as well as to the broad variety of solvents employed. Nevertheless, a general trend can be outlined.

As already mentioned, solubility plays a crucial role. This is effected by the counterion of the base ($Cs_2CO_3 > K_2CO_3 > Na_2CO_3$) as well as more subtle parameters such as the particle size of the base. Due to the larger surface area, it is usually advantageous to use finely powdered bases for heterogeneous reaction set-ups.

Apart from the strength of the base employed, it is also useful to compare the cost for different bases

Table 1. Relative costs of bases.

Base	MW	€/mol base*
Cs_2CO_3	325.82	110–120
LHMDS	167.33	90–100
t-AmONa	110.13	30–40
t-BuONa	96.11	20–30
t-BuOK	112.22	15–25
K_3PO_4	212.28	6–8
NaOMe	54.02	4–5
K_2CO_3	138.21	4–5
KOH	56.10	1–2
NaOH	40.00	1–2

* Costs are based on lab suppliers, large-scale prices may vary significantly.

when moving to a production scale as well as their availability in large amounts. In the following Table 1 an overview of the costs per mol of active base is given based on commercially available material in small scale (100 g–1 kg).

Apart from the base-sensitivity of the substrate, the combination of base and ligand as well as base/temperature are also important parameters. Regretfully, only very general trends are reported in the literature. Strong bases such as *t*-BuONa have been used very frequently and these are very suitable for low temperature processes and/or low catalyst loadings. Cs_2CO_3 is most effective when chelating bisphosphine ligands are used and many transformations using this base have been reported recently.[15,26–28,30,31,33,51–63] K_3PO_4 tends to show good results with biphenyl-based systems[5,15,48,49] and P(*t*-Bu)$_3$ but is less useful with chelating ligands, which seems to be a general trend.[7] Recently, Hartwig and Buchwald even reported the use of the most inexpensive bases (KOH, NaOH) in aqueous solution which are active in combination with biphenyl-based systems as well as Hartwig's palladium-dimer complex.[16,64,65]

When carbenes are used as ligands, the base also serves as the deprotonating agent for the imdazolium salt precursor, which often requires the use of a strong base.[22,75]

LHMDS proved to be especially useful for the coupling of amines with aryl halides containing hydroxy, amide or enolizable keto groups in conjunction with bulky biphenyl-based ligands at least in catalytic amounts.[66a]

2.4 Solvents/Temperature

Buchwald–Hartwig aminations are usually run within an organic solvent system. The role of the solvent is twofold. Apart from dissolving the coupling partners as well as parts of the base and allowing for a respective temperature window for the reaction, the solvent also plays a crucial role in stabilizing intermediates in the catalytic cycle.

The majority of the reactions reported is run in toluene.[4–8] Frequently, ethers such as DME, THF or dioxane are used. For solubility reasons the polar solvents DMF, NMP or DMSO can also be used for C–N coupling.

The solvents usually have to be dry and deoxygenated but this is strongly dependent on the air-sensitivity of the catalyst system used. In special cases using only slightly air-sensitive phosphines, reactions can be run entirely in air without significant changes in yield.[24] Also, the addition of water can even be beneficial as can be seen from the use of aqueous bases in the amination reaction.[16,65,67] Nevertheless, this only holds true for substrates that are not hydrolyzed under basic conditions. Some aminations can even be run in water as the only solvent.[16]

Other additives reported by Buchwald are alcohols, especially the low nucleophilic *tert*-butyl alcohol to increase conversion.[35,52,68]

Mixed solvent systems can have a great impact mostly on the degree of conversion in certain amination reactions, often owing to the solubilities of the components. Sometimes it is beneficial to premix the catalyst and the ligand in a suitable solvent such as THF to allow time for the formation of the catalytically active complex before adding this to the actual reaction mixture.[15,16b]

Amination reactions can be run even under rather concentrated conditions up to 30% w/w which is important for the space-time yield on a production scale. In most cases the concentration is limited by the undissolved components such as base, starting material or product forming suspensions with stirring becoming a limiting factor.

Regarding the temperature, usually a range between room temperature for the most active ligand systems such as P(*t*-Bu)$_3$,[46] some biphenyl-based systems[15,48] and carbenes[20,23] up to 140 °C for palladacyclic complexes[5,41] is reasonable. The vast majority of reactions is run inside a range of 70–110 °C which can be considered as typical for biphenyl-based ligands.[4–8]

3 C–N Coupling of Amines

3.1 Motivation

Clearly most researchers interested in the palladium-catalyzed aromatic C–N coupling are attracted by the tool of a bond formation between amines and aromatic halides or sulfonic acid esters. Contributions that cover other fascinating aspects of this new methodology like the direct introduction of ammonia equivalents, amide, urea, carbamate, sulfoximine, guanidine, etc. coupling will be covered individually in a later chapter.

3.2 Description of Table 2

To get an overview of the multiple activities over the last five years, we analyzed the literature in a slightly different way compared to the authors of former overview articles.[4–8] In these, the structure of the review is determined by the different types of amines (aromatic, primary, secondary, cyclic, etc.) which is explainable by the history of the palladium-catalyzed amination reaction. Cyclic amines were the easiest coupling partners to start with, taking a few years until either acyclic or electron-deficient amines could be successfully used. Judging by the reported yields of more recent articles, current catalysts show such a high activity that they do not seem to distinguish severely between the amine nucleophiles any more. Therefore we decided to represent the studies in a grid-like table for the quickest reference.

As summarized in Table 2, we screened the number of individual examples in the publications over the last five years and added them up according to the nature of the amine and the nature of the aromatic halide or sulfonic acid ester, respectively. Examples reported with very poor yields were omitted. This table is by no means comprehensive and should be seen as a flashlight over the past five years, therefore overemphasizing recent contributions dealing with more intricate coupling challenges. Attached to this table the examples are cited in a chessboard-like reference scheme following the labels of Table 2. These references also include the major focus of the articles cited. The reader can therefore use this table to find most publications dealing with a specific reaction that were published during the last five years. This table can also be used to visualize the main current activities in the field and also serves to demonstrate the blank spots on the map by looking at the number of examples that were reported, noting that a number alone provides limited information to judge the maturity of a field. Therefore the main goal of this table is to give a fast, unbiased overview on the current status of palladium-catalyzed aromatic amination, for more detailed information covering the entire historical development of this methodology, the other review articles are recommended for reading.[4–8]

3.3 General Statements

While ongoing research in the groups dealing with the methodology of the palladium-catalyzed amination very often focuses on the development of novel, more active catalysts, more and more applications appear in which aromatic amination has been used as a synthetic tool to successfully synthesize a molecule in a multistep synthesis. In the latter kind of publications, Pd-BINAP-based catalysts are still the predominant systems to be used (see chapter on applications). For the former kind of publications, several new catalyst classes are maturing to application, their scope and applicability will be covered in this chapter.

3.4 Aryl Bromides

When looking at the first column of Table 2, one could argue that the amination of aryl bromides has well progressed and has become a standard procedure with no apparent limitations. With a total of around 331 individual examples published in the period regarded, nearly all problems seem to be solvable. Only the use of anilines substituted with an electron-withdrawing group is a field that is seldom visited, however with good yields when examples are reported.[16,33,71] Since aryl bromides have already been intensively investigated during the initial five years since the first description of the technology in 1995,[1] the frontiers in this field were shifted towards broader applicability and generality of the approach. Aryl bromides cannot only be coupled with almost any imaginable nitrogen nucleophile, the reactions very often offer high tolerance to other sensitive functionalities.[66] Even carboxylic acids or alcohols [95] can be present in the starting materials, in those cases the use of LHDMS as base will both serve to deprotonate intermediate amide species as well as serving as temporary protecting group for the acidic position in the molecule.

3.5 Aryl Chlorides

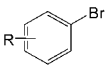
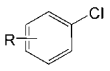
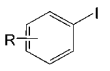
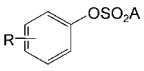
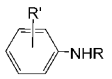
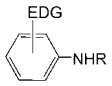
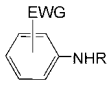
Being the key area of industrial attention due to their abundance and availability on a bulk scale, aryl chlorides have been thoroughly investigated over the past five years. With around 323 published successful examples in our table ranging over all classes of nitrogen nucleophiles, aryl chloride coupling has reached a similar quality as aryl bromide coupling.

An extremely versatile catalyst component for aryl chloride coupling is the Buchwald biphenyl ligand family[16,15,74] or their supported counterparts.[37] Mainly Dave-Phos and the bulky ligand X-Phos have proven their quality in the majority of the published examples.[66,16,42,33] As derivatives of this ligand system, heterocyclic biphenyl ligands first introduced by Singer[35] and further elaborated by Beller[36] show wide scope in the amination of aryl chlorides, with no obvious advantage in reactivity over the biphenyl ligands, however.

New ligand concepts for the coupling of aryl chlorides were demonstrated with Li's dialkylphosphinous oxide ligands[42] and Verkade's TAP ligands.[32,33] While the results are promising, these ligands have so far only been reported by their inventors, therefore for the time being a broader scope of these systems cannot be judged.

Polyphenylated Q-Phos, discovered by the Hartwig group and originally applied for palladium-catalyzed

Table 2. Overview of published single examples from 01/1999 to 01/2004 for the coupling of amines with halo or sulfonic acid ester aromatics.

		1 	**2** 	**3** 	**4** 	**5** 	**6** 	**7** 
A		90	106	18	A = Tol: 2 A = CF_3: 3 A = C_4F_9: 12	4	20	39
B		46	23	8	A = CF_3: 5 A = C_4F_9: 3	–	–	11
C		3	5	1	A = CF_3: 8	–	–	29
D		80	92	15	A = Tol: 4 A = CF_3: 3 A = C_4F_9: 10	13	15	9
E		29	35	6	A = Tol: 1 A = CF_3: 1 A = C_4F_9: 1	1	1	3
F		22	54	7	A = Tol: 1 A = CF_3: 4 A = C_4F_9: 13	–	4	10
G		61	8	–	A = Tol: 2 A = CF_3: 4	3	8	2

The following citations are formatted as: **position in table**: [citation number], range of reported yields, ligand class and special features of article, (number of published examples). Abbreviations used: FGT = functional group tolerance high, Supp. – supported ligands, for the ligands quoted, please refer to Figures 3 and 5.

A1: [66], 80–85%, Dave-Phos – FGT (5); [16], 60–95%, BW (2); [69], 93–99%, Q-Phos (6); [33], 77–96%, TAP (4); [34], 91–99%, TAP (14); [22], 89%, carbene (1); [37], 99%, BW-Supp (1); [15], 89–92%, BW-RT (3); [15], 56–82%, BW (3); [70], 12–62%, P(*t*-Bu)$_3$ (5); [40], 85–92%, DPEPhos/XantPhos (2); [40], 72%, BW-PdCl$_2$ (1); [71], 77–92%, P(*t*-Bu)$_3$ (6); [72], 78–85%, P(*t*-Bu)$_3$-polymerization (3); [23], 89%, carbene (1); [24], 84–92%, carbene (2); [73], 12–93%, P(*t*-Bu)$_3$ (12); [65], 70–98%, P(*t*-Bu)$_3$ (11); [47], 68–82%, BINAP (2); [74], 74–90%, BW (7).

B1: [35], 86%, Singer (1); [66], 57–83%, Dave-Phos – FGT (2); [48], 78–93%, TAP (3); [34], 90–99%, TAP (7); [15], 87–90%, BW-RT (2); [15], 93–97%, BW (5); [40], 93–98%, DPEPhos (8); [75], 47–94%, P(*t*-Bu)$_3$-polymerization (6); [71], 73–99%, P(*t*-Bu)$_3$-polymerization (3); [47], 84–86%, BINAP-NaOMe (3); [46], 82–98%, P(*t*-Bu)$_3$ (3); [39], 88–97%, Guram (3).

C1: [16], 78%, BW (1); [33], 61%, TAP, (1); [71], 97%, P(*t*-Bu)$_3$-polymerization (1).

D1: [35], 93%, Singer (1); [66], 56–90%, Dave-Phos (6); [16], 91%, BW-FGT (1); [69], 54–98%, Q-Phos (6); [33], 42–95%, TAP (7); [34], 82–99%, TAP (9); [22], 83–94%, carbene (2); [37], 84–90%, BW-Supp (2); [15], 80–83%, BW-RT (2); [15], 86–92%, BW (3); [40], 65–93%, BW (3); [71], 63–94%, P(*t*-Bu)$_3$ (18); [23], 83–94%, carbene (3); [24], 71–89%, carbene (5); [65], 95–99%, P(*t*-Bu)$_3$-KOH (2); [47], 66%, BINAP-NaOMe (1); [39], 10–98%, Guram (6).

E1: [35], 83%, Singer (1); [69], 37–94%, Q-Phos (6); [33], 73–95%, TAP (2); [34], 57–70%, TAP (2); [37], 79–93%, BW-Supp (2); [15], 83%, BW-RT (1); [15], 79–89%, BW (3); [40], 83%, BW-PdCl$_2$ (1); [65], 81–92%, P(*t*-Bu)$_3$-KOH (2); [46], 96%, P(*t*-Bu)$_3$ (1); [39], 16–99%, Guram (3).

F1: [35], 83–90%, Singer (3); [69], 85–99%, Q-Phos (4); [33], 85–88%, TAP (4); [15], 52%, BW-RT (4); [15], 86–92%, BW (2); [40], 92%, BW-PdCl$_2$ (1); [40], 85%, BINAP-PdCl$_2$ (1); [71], 98%, P(*t*-Bu)$_3$-polymerization (1); [76], 72%, BINAP (1); [65], 79%, P(*t*-Bu)$_3$-KOH (1); [47], 68–88%, BINAP-NaOMe (3).

G1: [22], 61–99%, carbene (9); [77], 30–99%, BINAP-benzothiophene (5); [78], 43–95%, BW (24); [67], 85–95%, Xantphos (9); [79], 15–96%, P(*t*-Bu)$_3$ (11); [80], 41–99%, P(*t*-Bu)$_3$ (3).

A2: [20], 82–97%, carbene (3); [32], 88–95%, TAP (7); [16], 83–98%, BW (3); [16], 91–96%, X-Phos-water (4); [42], 76–97%, Li (3); [69], 82–99%, Q-Phos (14); [33], 69–97%, TAP (6); [22], 91–99%, carbene (9); [37], 92–95%, BW-Supp (2); [15], 78–98%, BW (13); [71], 82–91%, P(*t*-Bu)$_3$ (2); [23], 94–99%, carbene (5); [64], 96–97%, BW-palladacycle (2); [24], 80–85%, carbene (5); [65], 84–99%, P(*t*-Bu)$_3$-KOH (19); [74], 74–90%, BW (7); [45], 94–99%, Solvias (3); [39], 96%, Guram (1); [81], 33–71%, carbenes (2), [82], 88–91%, BW-microwave (2).

B2: [20], 88%, carbene (1); [32], 87–99%, TAP (3); [16], 92–96%, X-Phos-water (2); [33], 77–97%, TAP (2); [22], 59–85%, carbene (2); [15], 73–77%, BW (6); [38], 70–99%, Beller (5); [23], 59%, carbene (1); [39], 89%, Guram (1).
C2: [16], 71–91%, BW (2); [15], 75–81%, BW (2); [64], 90%, BW-palladacyle (1).
D2: [35], 39–99%, Singer (6); [66], 59–83%. Dave-Phos – FGT (4); [20], 71–99%, carbene (4); [32], 87–95%, TAP (6); [16], 96%, X-Phos-water (1); [16], 80%, BW – FGT (1); [42], 43%, Li (1); [69], 78–97%, Q-Phos (3); [33], 52–98%, TAP (9); [22], 82–96%, carbene (6); [37], 90%, BW-Supp (1); [15], 77–98%, BW (19); [38], 76–87%, Beller (2); [71], 94%, P(*t*-Bu)$_3$ (1); [23], 80–96%, carbene (3); [64], 75–98%, BW-palladacyle (7); [24], 58–95%, carbene (6); [65], 84–94%, P(*t*-Bu)$_3$-KOH (5); [46], 68–92%, P(*t*-Bu)$_3$ (2); [45], 82–99%, Solvias (3); [39], 90–92%, Guram (3), [81], 28%, carbenes (1).
E2: [66], 64–71%, Dave-Phos – FGT (4); [20], 86%, carbene (1); [32], 56%, TAP (1); [69], 93–96%, Q-Phos (3); [22], 95–98%, carbene (4); [37], 94%, BW-Supp. (1); [15], 81%, BW (1); [38], 44–72%, Beller (5); [83], 79–98%, Guram (4); [65], 81–98%, P(*t*-Bu)$_3$-KOH (6), [39], 95–97%, Guram (3).
F2: [16], 84%, X-Phos-water (1); [69], 78–97%, Q-Phos (16); [34], 43–62%, TAP (4); [22], 86%, carbene (1); [52], 70–79%, BW (3); [15], 71–99%, BW (14); [38], 84–93%, Beller (2).
G2: [16], 92%, X-Phos-water (1); [78], 64–88%, BW (5); [67], 91%, Xantphos (1), [79], 71%, P(*t*-Bu)$_3$-enamines (1) ; [81], 6%, carbenes (1).
A3: [33], 71–96%, TAP (6); [34], 75%, TAP (1); [37], 84–95%, BW-Supp (3); [52], 84–99%, BW (6); [84], 90–96%, dppf (1).
B3: [33], 97%, TAP (1); [34], 72–95%, TAP (4); [52], 99%, BW (1); [84], 53–95%, dppf (2).
C3: [52], 91%, BW (1).
D3: [33], 77–93%, TAP (4); [34], 56–89%, TAP (5); [22], 97%, carbene (1); [52], 62–94%, BW (4), [23], 97%, carbene (1).
E3: [33], 60–90%, TAP (3); [52], 70–89%, BW (3).
F3: [34], 43–62%, TAP (4); [52], 70–79%, BW (3).
A4: [16], 92–96%, BW tosylate (2); [48], 85–97%, Dave-Phos nonaflate (12); [15], 76%, BW-RT triflate (2); [85], 73%, BINAP (1).
B4: [48], 89%, Dave-Phos nonaflate (3); [15], 74%, BW-RT triflate, (1); [15], 85–91%, BW triflate (3); [85], 79%, BINAP (1).
C4: [15], 76%, BW (1), [86], 99%, BINAP – selectivity over Ar-Br (1), [85], 38–80%, BINAP or Solvias (6).
D4: [16], 84–99%, BW tosylate (4); [48], 77–94%, BW nonaflate (10); [15], 75–79%, BW triflate (3).
E4: [16], 88%, BW tosylate (1); [48], 86%, BW nonaflate (1); [15], 79%, BW triflate (1).
F4: [16]. 88%, BW tosylate (1); [48], 78–84%, BW nonaflate (13); [15], 81%, BW-RT (1); [15], 68–81%, BW triflate (2); [87], 84%; dppf triflate (1).
G4: [16], 99%, BW tosylate (1); [78], 87–90%, BW (2); [80], 41–48%, P(*t*-Bu)$_3$-enamine (2).
A5: [33], 84–87%, TAP (2); [22], 96–99%, carbene (2).
D5: [33], 93%, TAP (1); [34], 89%, TAP (1); [22], 95%, carbene (1); [15], 76–92%, BW triflate (3); [71], 76%, P(*t*-Bu)$_3$ (1); [88], 36–71%, carbene (6).
E5: [33], 88%, TAP (1).
G5: [78], 81–94%, BW (2); [67], 91%, Xantphos (2).
A6: [32], 53–89%, TAP (2); [33], 84%, TAP (1); [22], 70–97%, carbene (6); [15], 93–97%, BW (2); [89], 60%, BINAP – selectivity (1); [82], 75–89%, BW microwave (7).
D6: [32], 83–90%, TAP (4); [33], 84–87%, TAP (2); [22], 80–99%, carbene (3); [15], 70–95%, BW (3); [24], 84%, carbene (1); [88], 56%, carbene (1), [82], 75%, BW microwave (1).
E6: [15], 77%, BW (1).
F6: [15], 70–98%, BW (4).
G6: [33], 64–95%, Xantphos (7); [89], 80%, BINAP – selectivity (1).
A7: [90] 60–70%, diff. phosphines-bromonucleosides (1); [49], 64–69%, Dave-Phos nucleosides (3); [91], 30–97%, P(*t*-Bu)$_3$-thiophenes/furans (26); [57], 10–78%, BINAP-electron-deficient thiophenes (4); [92], 12–81%, P(*t*-Bu)$_3$-thiophene (4); [82], 80%, BW-microwave (1).
B7: [49], 72%, Dave-Phos nucleoside (1); [77], 50–80%, BINAP-benzothiophenes (5); [93], 89–96%, BINAP-pyridazinones (3), [94], 89–96%, BINAP-pyridazinones (2).
C7: [49], 52–61%, Dave-Phos nucleosides (2); [93], 88–99%, BINAP-pyridazinones (18).
D7: [91], 40–77%, P(*t*-Bu)$_3$-furans, thiophenes, indoles (8); [57], 90, BINAP-electron-deficient thiophenes (1).
E7: [91], 71–77%, P(*t*-Bu)$_3$-furans, thiophenes, indoles (2); [57], 83, BINAP-electron-deficient thiophenes (1).
F7: [57], 7–94%, BINAP-electron-deficient thiophenes (10).
G7: [93], 81%, BINAP-pyridazinones (1); [94], 81%, BINAP-pyridazinones (1).

C–O coupling, shows an interestingly wide scope also for the amination of aryl chlorides.[69]

Conditions rather unusual for traditional ways of organometallic chemistry have been reported, e.g., Hartwig's air stable palladium(I)-(t-Bu$_3$)P dimer is used in aqueous media in combination with sodium hydroxide as base.[65] Also allowing for the use of similar bases like potassium hydroxide in water, Buchwald's X-Phos-ligand proved to be valuable.[16]

Several authors have developed amination reactions using palladium-N-heterocyclic carbene catalysts.[20,22–24,81] These phosphine analogues have shown their strength all over cross-coupling chemistry. From the perception of the industrial chemist, the air-stability and the ease of manufacture of this compound class will surely guarantee ongoing attention in this field.

Also noteworthy are the simple ligand systems introduced by Guram,[39] in which active catalysts are generated using an aryldialkylphosphine without the biphenyl backbone of the Buchwald systems.

As extension of the well established P(t-Bu)$_3$ amination chemistry, Beller published his BuPAd$_2$ ligand system.[38] While not trivial in the preparation, it is described that these ligands show advantageous behavior using bulky aryl chlorides as substrates and are reported to show superior air-stability compared to their parent system.

Palladacyclic intermediates have been used as alternatives for the *in situ* mixtures of palladium and phosphine,[29,45,64] whereas in the case of using complexes of palladacycles with secondary alkylphosphines probably tertiary phosphines are generated *in situ*.[39,45]

3.6 Aryl Iodides

Serving in Heck and other cross-coupling reactions as excellent starting materials, aryl iodides have played only a minor role as starting material in amination chemistry, mostly suited only for intramolecular reactions. This might be explained both by the limited availability of polysubstituted aryl iodides but also due to side reactions that lead to the dehalogenated aromatic system.

The first generation of the Buchwald phosphines (*cf.* BW2 in Figure 5) in combination with strong bases and polar solvents were reported as conditions for aryl iodide coupling.[52] In some cases the use of dppf as ligand[84] or the solid supported version of the Buchwald phosphines[37] were used. Also Verkade's TAP ligand family, still rather new in the literature, proved their wide scope of applicability, however at the expense of high catalyst loadings.[33,34,95]

3.7 Arenesulfonic Acid Esters

With aryl halides now serving as good starting materials in C–N couplings, the use of phenol-based starting materials has always been a worthwhile extension of the methodology. When phenols are transformed to highly activated sulfonic acid esters like trifluoromethanesulfonic acid esters (triflates) or nonafluorobutanesulfonic acid esters (nonaflates), the coupling reaction runs with ease.[15,48,78,87,80]

However, the industrial chemist will be less prone to reduce these systems to practice, since fluorinated sulfonic acid esters are very expensive in their use and disposal. Therefore a milestone in the use of phenol-derived starting materials was the first description of using the cheap sulfonic acid ester, p-toluenesulfonic acid ester, as starting material for aromatic amination by the Hartwig group[96] and the further elaboration of a more general protocol by the Buchwald group.[16]

3.8 Pyridyl Halides

Still an area with very few published examples, pyridyl halides represent one of the white spots on the amination map. So far mainly the simpler cases, for example, coupling with electron neutral anilines proceeded well with the Buchwald ligand system,[15] the TAP ligands[32,33] and with carbenes.[22,88] Cyclic secondary amines as coupling partners could also be utilized by using the same ligand systems, in some cases also the coupling with primary amines is described.[15] Last but not least, pyridyl triflates as starting materials were also described in the literature.[15] When microwave reactors are applied, the Buchwald ligands have demonstrated their versatility.[82]

For the coupling of pyridyl halides with heteroaromatic nitrogen nucleophiles, the XantPhos ligand[33,67] as well as the Buchwald ligands[78] have shown their potential.

No general statement can be made towards the catalyst which serves best for the different substitution patterns of both bromo- and chloropyridines. While BINAP had already been identified as a universal catalyst for the coupling of pyridyl halides in 1996,[97] newer publications have not specifically picked up this point.

3.9 Other Heteroaromatic Halides

Mainly halothiophenes have been the focus of older publications on amination chemistry with heteroaromatic halides. Still they are one of the major fields of interest. P(t-Bu)$_3$ is the ligand of choice for these kinds of transformations which has been shown repeatedly.[91,92] When electron-deficient halothiophenes have to be used as starting materials, BINAP as ligand led to the

best results,[57] which could be extended to benzothiophenes.[77] Hartwig showed in an extensive study that P(*t*-Bu)$_3$ as ligand provided an active catalyst for the coupling of furan, indole, benzothiophene, thiazole, benzimidazole and oxazole halides.[91]

Next to these five-membered ring aromatics, more and more amination problems of nucleoside chemistry could be solved by the use of the palladium-catalyzed methodology.[49,90] Finally, pyridazinones were effectively coupled, again using BINAP as the ligand system.[93,94]

3.10 Catalyst Activity

As a general trend concerning catalytic activity and productivity, so far turnover numbers of about 1000 could only be achieved in combination with very strong bases like alkoxide bases such as sodium *tert*-butoxide. Landmark examples of reactions with low catalyst loading down to 0.05 mol % of palladium were achieved even with electronically neutral aryl chlorides by the use of the Buchwald phosphines (*cf.* Figure 5).[15] Nevertheless, the examples are limited and in an industrial process the robustness and reproducibility play an equally prominent role as rather low catalyst loadings which could potentially increase the sensitivity of a large-scale process.

3.11 Weak Bases

Newer contributions venture for highly active catalysts in combination with weaker bases,[4,28,68] thus rendering procedures allowing for even higher functional group tolerance. However, in cases beyond electron-poor aryl halides and electron-rich cyclic amines, the use of about 0.5 to 1 mol % of palladium in combination with bases like K_3PO_4 or Cs_2CO_3 still seems to be the necessary catalyst concentration.

3.12 Low Temperatures

A similar goal of milder reaction conditions explains the strive for lower temperatures in aromatic amination. This was demonstrated in multiple publications. Carbene ligands showed their potential as low temperature ligands for aryl bromides, aryl chlorides and aryl iodides.[20,22,23] Specifically, halopyridines proved to be good starting materials with carbenes as ligands for the amination reaction.[20] Even broader applicability and generally higher catalytic activity can be attributed to Buchwald's biphenylphosphine family, which allows for room temperature reactions using aryl chlorides, bromides or iodides, but also for the use of nonaflates and triflates.[15,48] Hartwig's dimeric palladium(I)-P(*t*-Bu)$_3$ complex does not only represent a very elegant form of an air-stable P(*t*-Bu)$_3$-type catalyst, it also proved to be extremely valuable for the room temperature amination of aryl bromides and chlorides, with complete formation of product within 15 minutes in some cases.

Nevertheless, the traditional temperature range seldom causes problems in conducting these reactions and the formation of side products can be attributed to the base strength in most cases.

3.13 New Bases

As another interesting trend, the extension of the portfolio of bases that can be used in the reaction is noteworthy. Mild bases like potassium phosphate[48,66] now represent a cheap alternative to the rather expensive cesium carbonate.[31] The fine tuning of the stronger bases also led to a protocol that allows the use of sodium methoxide[47,64] or even more interesting, sodium hydroxide[16,65] as base. In those cases it was understood that next to the catalyst the right combination of base and solvent plays a very important role in the catalytic activity.

3.14 Amine Nucleophiles

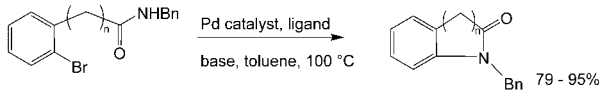
Since amine nucleophiles have been used to structure the field in most other review articles[4–8] we will only briefly touch on this subject. Nearly all catalytic systems could be developed into procedures where acyclic, primary amines as well as secondary acyclic amines can be successfully used. The simpler cases, like cyclic secondary amines or anilines of course are included. More difficult examples are faced when the amine nucleophile is exceptionally electron-poor (Table 2).

From the published literature it is difficult to judge which catalytic system really shows the broadest applicability. Different authors use different standards to manifest the potential of their catalyst. While some compare them by pure GC yields, others will furnish elaborated kinetic studies with isolated yields, the latter procedure being generally preferred in terms of reliability of a process.

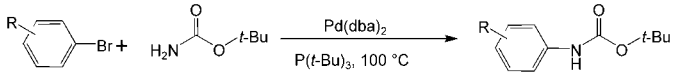
As a general statement still three systems predominate the field, BINAP, P(*t*-Bu)$_3$ and the Buchwald ligand family. By choosing one of these three, positive results for almost any nitrogen nucleophile are most probable.

4 Coupling Reactions with Non-Amine Nucleophiles

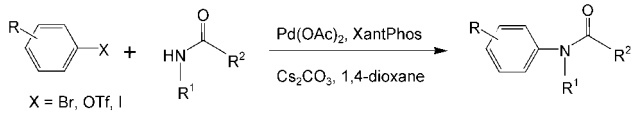
The Buchwald–Hartwig amination methodology has also been expanded to nitrogen nucleophiles carrying electron-withdrawing or -releasing groups directly attached to the amine such as carbonyl, sulfonyl or amino groups. These can also be arylated using catalysts that



Scheme 1.



Scheme 2.



Scheme 3.

are similar to the classical amination systems, although bis-chelating ligands seem to be more versatile for this kind of transformation. Nevertheless, the new biaryl-based phosphines also show a high activity in this reaction.

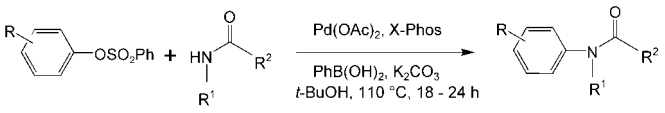
4.1 Coupling of Amides, Sulfonamides, Carbamates and Ureas

A large body of literature regarding the coupling of carbonic acid amides has been reported in the last years. Intramolecular cyclization of bromo-substituted, amide-functionalized arenes was reported in 1999 by Buchwald. Using either MOP, DPEPhos or XantPhos in combination with weak bases such as Cs_2CO_3 and K_2CO_3, efficient cyclizations could be performed (Scheme 1).[28] *N*-Boc and *N*-Cbz protected amines containing carbamate substrates gave the corresponding protected nitrogen heterocycles also in good yield.

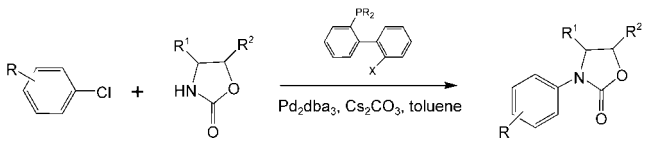
An intermolecular coupling of carbamates with aryl bromides using P(*t*-Bu)$_3$ was reported by Hartwig in 1999.[98] This system allowed for the arylation of *t*-butyl carbamate at 100 °C giving the product in 62–86% yield (Scheme 2).

In 2000, Buchwald outlined the intermolecular coupling of amides with aryl halides using XantPhos as the ligand. Using this procedure, also carbamates and sulfonamides were viable substrates for the coupling reaction. Moreover, the scope was extended from aryl halides to aryl triflates as coupling partners[27] (Scheme 3).

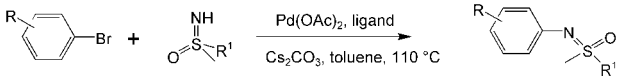
The amidations proceed at 45–110 °C using 1–4 mol % of catalyst. More detailed studies of the mechanism led to the isolation of a palladium (II)-XantPhos complex that shows a *trans*-chelation in the X-ray structure and was active in the amination reaction.[26] As a side reaction, arylation of the nitrogen moiety with the phenyl group attached to the phosphine ligand was detected.



Scheme 4.



Scheme 5.



Scheme 6.

Thus, using the XantPhos/Pd catalyst, Cs_2CO_3 and dioxane (or THF) as solvent, primary and secondary amides, as well as carbamates and sulfonamides can be coupled with activated aryl halides bearing electron-withdrawing groups at *ortho*, *meta* or *para* positions. Unactivated or deactivated aryl halides need more carefully controlled reaction conditions owing to the side reaction mentioned above.

Very recently Buchwald reported the first amidation of arenesulfonates using X-Phos with K_2CO_3 as the base in *tert*-BuOH as the solvent.[16]

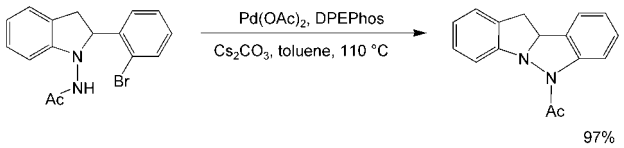
The catalytic addition of phenylboronic acid was necessary to ensure complete conversion of the Pd(II) precursor to the Pd(0) species.

Further examples for the coupling of cyclic carbamates and ureas were provided by Ghosh[99] and Madar.[60] Madar used $Pd_2(dba)_3$ in conjunction with BINAP and cesium carbonate as the base to couple cyclic ureas and carbamates with aryl bromides at 100 °C. Ghosh developed an efficient method for the first intermolecular cross-coupling of oxazolidinones with aryl chlorides using $Pd_2(dba)_3$, Cs_2CO_3 or K_3PO_4 as the base and Buchwald's biaryl ligands (Scheme 5).

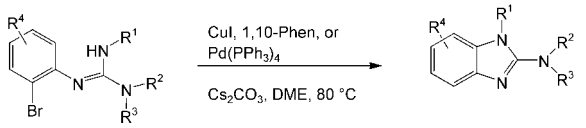
4.2 Coupling with Sulfoximines, Hydrazines and Guanidines

In 2000 Bolm reported the *N*-arylation of sulfoximines with a wide range of aryl bromides in high yield employing chelating ligands such as BINAP, Tol-BINAP, DPPF and DPEPhos[55] (Scheme 6). When aryl dibromides are used, only a monoamination of the arene core takes place. Aryl iodides require lithium or silver salts to undergo the desired coupling reaction.

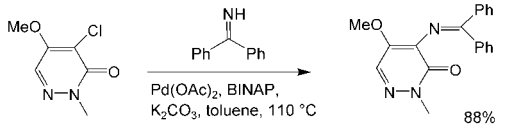
A one-pot transformation yielding benzothiazines using BINAP was reported by Harmata.[100] Regarding the



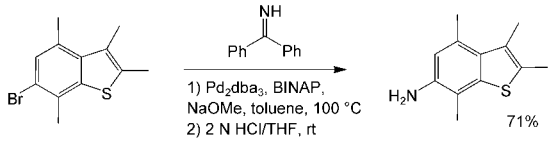
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

arylation of hydrazines, an intramolecular example was reported by Katayama.[63] DPEPhos turned out to be the ligand of choice for the intramolecular cyclization reaction (Scheme 7).

An intermolecular variant was reported by Skerlj who used $Pd_2(dba)_3$, Cs_2CO_3 and DPPF in toluene to achieve the *N*-arylation of *t*-butyl carbazate using electron-deficient aryl bromides as aryl halide.[101]

In 2003, Batey reported an intramolecular guanidinylation.[102] Using $Pd(PPh_3)_4$ almost quantitative yields could be achieved, nevertheless the complementary copper iodide-catalyzed process was found to be superior (Scheme 8).

4.3 Ammonia Surrogates

The most simple amine is ammonia. Nevertheless, C–N coupling reactions with this substrate have not been reported to be successful. While there are a lot of alternatives for the synthesis of anilines or amino-functionalized arenes in general, such as nitration followed by hydrogenation or aminolysis of activated aryl halides, special substitution patterns on the arene rings are sometimes difficult to achieve using classical techniques.[140]

Due to this, palladium-catalyzed aminations with ammonia equivalents have been used to achieve this transformation. The most prominent examples include allyl- and diallylamine,[103] benzyl-[143] and diphenylmethylamine as well as benzophenone imine.[104,105]

In the last years several examples using benzophenone imine have been reported. Lemière used this ammonia surrogate as an alternative for classical nucleophilic substitutions on a chloropyridazine (Scheme 9).[93]

Deprotection giving the free amine was achieved using hydroxyl amine. Furthermore, the same group reported the use of benzophenone imine with Cs_2CO_3 as the base to generate 7-aminoflavones.[62] Most noteworthy is the fact that the precursor was the corresponding aryl triflate. Deprotection of the imine was achieved using $Pd(OH)_2$/charcoal with cyclohexene in ethanol at reflux temperature.

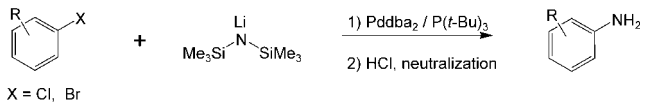
Queiroz employed the reagent for the synthesis of 6-aminobenzo[*b*]thiophenes using BINAP as the ligand and Cs_2CO_3 as the base.[77] Interestingly, the use of NaOMe gave even better results. The imino derivatives were hydrolyzed with HCl in THF to give the parent amine (Scheme 10).

While these reactions show the versatility of the ammonia surrogates reported, especially benzophenone imine has the severe drawback of poor atom economy. With a molecular weight of 181, during the overall transformation the NH_2 moiety with a mass of only 16 atomic units is introduced, so less than 10% of the reagent actually ends up in the product.

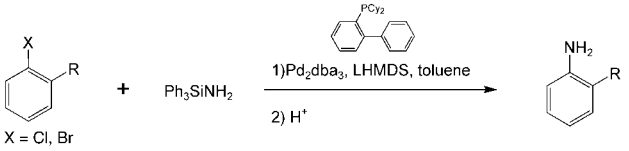
While this is of low importance in small-scale synthesis, it would pose a severe disadvantage in a pilot-plant-scale process.

In 2001 Hartwig as well as Buchwald reported new ammonia equivalents that show a broad versatility. LHMDS was used by Hartwig[106,107] to achieve the conversion of aryl bromides and even aryl chlorides to the parent anilines. The reaction is catalyzed by $Pd(dba)_2$ and P(*t*-Bu)$_3$ and can be run with as little as 0.2 mol % of catalyst. An impressive set of substrates including heteroaromatic halides as well as a broad set of ligands was tested for this transformation. The only limitation was found to be the use of *ortho*-substituted aryl bromides which could not be aminated. Deprotection was very simple due to the nature of the TMS group, which was readily cleaved off during work-up with HCl followed by neutralization. Due to the basicity of LHMDS, generation of benzyne intermediates yielding the amine *via* an addition mechanism was found at higher temperatures (120 °C), but not at the temperatures employed for the metal-catalyzed coupling. The atom economy nevertheless is still poor and only slightly higher than for benzophenone imine (Scheme 11).

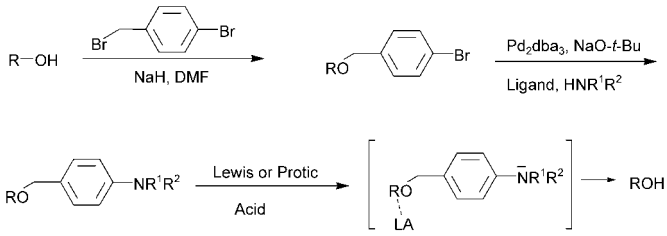
Subsequently, Buchwald also reported the use of LHMDS and an even more versatile reagent, LHMDS in combination with aminotriphenylsilane.[66b] In this study, Buchwald's 2-dicyclohexylphosphinobiphenyl systems proved to be good ligands for the transformation. The addition of the less bulky aminotriphenylsilane



Scheme 11.



Scheme 12.



Scheme 13.

now allowed one to also aminate *ortho*-substituted aryl halides. Presumably an equilibrium exists between the different silyl amides. Nevertheless, the use of at least stoichiometric amounts of LHMDS as well as aminotriphenylsilane is required for the reaction. One of the simplest amine bases, $LiNH_2$, could also be used as an amination agent.[66b] Nevertheless, the aniline formed is arylated immediately again yielding di- and triarylamines, making this a valuable transformation in its own right (Scheme 12).

5 Applications of Buchwald–Hartwig Amination

The versatility and reliability of a newly developed chemical transformation can be deduced from the number of academic and industrial groups using this chemistry in their own field. From this point of view, the success of the C–N coupling methodology is tremendous. This reaction has found its use in the synthesis of natural products and analogues of these, for heterocycle synthesis and material science products as well as in the synthesis of nitrogen-containing ligands. It has proved to be a reliable, robust method that has become a routinely used chemical transformation even on an industrial scale.[18] Nevertheless, it will always be complementary to other methods of amine synthesis such as nitro group reduction or nucleophilic aromatic substitution, which are nevertheless limited to very special cases but can be superior in terms of costs on the large scale.

Even so, the substrate scope of the Buchwald–Hartwig amination for the generation of different arylamines is the broadest of all existing synthetic methods for this class of compounds.

In the following, an overview will be given on the application of the transformation in synthesis.

5.1 Synthesis of Natural Products and Analogues as Active Agents

A plethora of reports has appeared during the last years regarding the application of the C–N coupling methodology for the synthesis of natural products or active ingredients for pharmaceutical or agricultural use. The extent of usage of this methodology by academic as well as industrial groups is very balanced.

5.1.1 Applications from Academic Groups

In Figure 8 some intermediates prepared by C–N coupling are outlined as well as the conditions used and the respective target molecules. The C–N bond forming reaction is shown *via* retrosynthetic bond disassembly.

The application ranges from intermolecular couplings of functionalized amines as well as aryl halides to intramolecular variants for the construction of polycyclic heterocyclic systems. Chelating bisphosphines, especially BINAP, still dominate this field. The reason may not be the better performance of this ligand in general but much more the ready availability of this ligand as well as the lack of a need for extensive optimization of these systems. Nevertheless, newer ligand developments also start to attract attention, such as the use of carbenes by Trudell (Entry 4)[88] or Buchwald's biaryl ligands by Lakshman (Entry 10).[90,49]

An interesting application of C–N coupling as a strategy for the protection of hydroxy groups in sugars was reported by Buchwald and Seeberger.[113] By converting the free hydroxy group to a *para*-halide-substituted benzylic ether, an anchor for C–N coupling is formed. Amination with a suitable amine yields a labile protecting group that can easily be cleaved by Lewis or protic acids. By employing 4-chloro-, 4-bromo- or 4-iodo-substituted benzylic ethers, orthogonal protection is possible and the protecting groups can be removed sequentially. This strategy has found application in the synthesis of trisaccharides. The general methodology is illustrated in Scheme 13.

5.1.2 Applications from Industrial Groups

As can be seen from Figure 9, Buchwald–Hartwig amination is also used in industrial research to a great extent, mostly for pharmaceutically active ingredients.

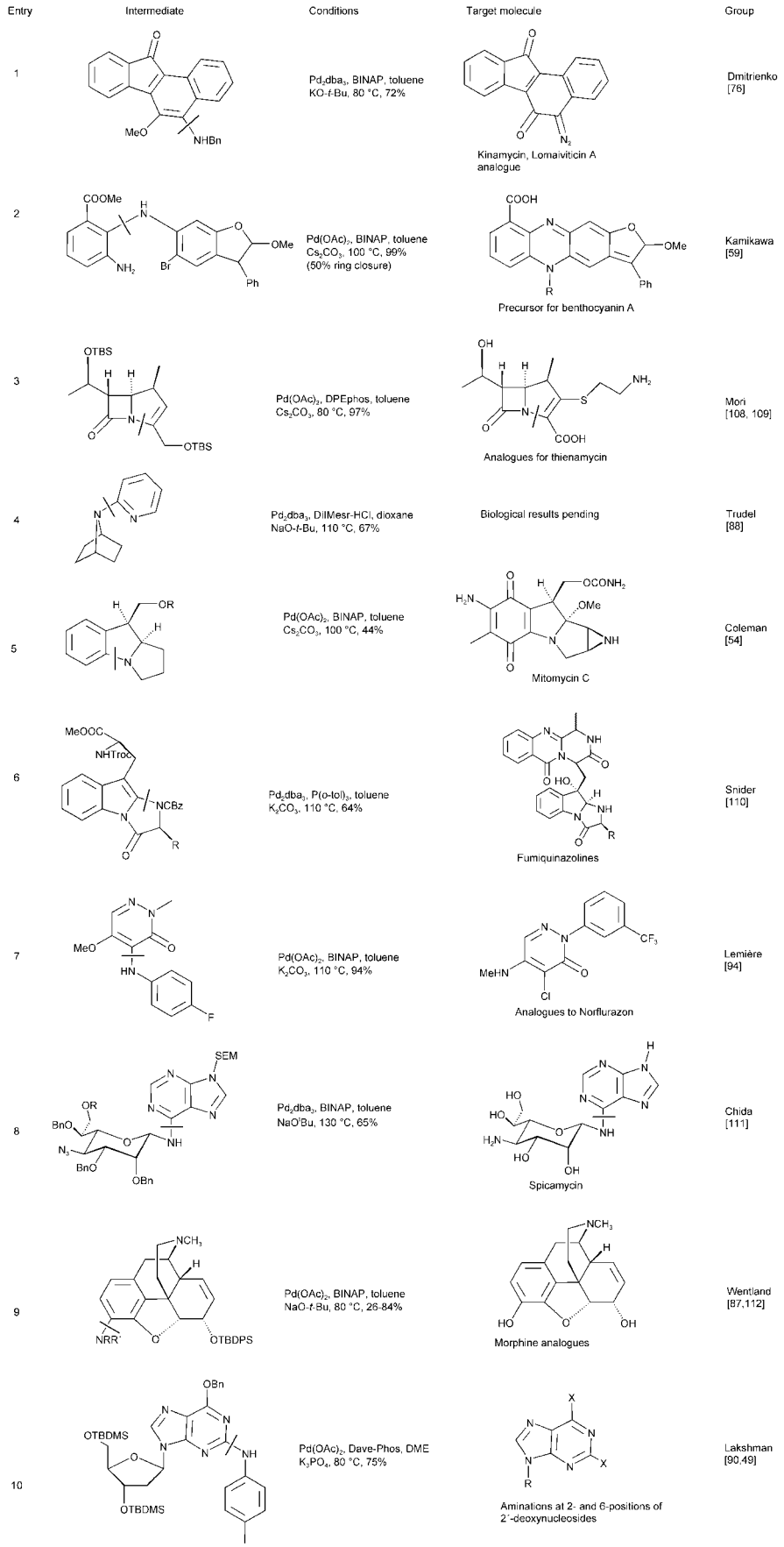
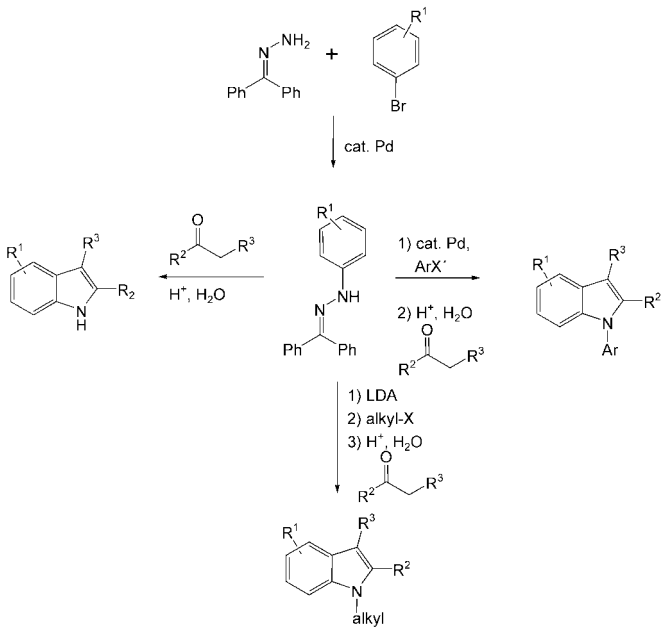
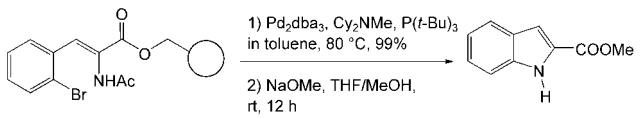


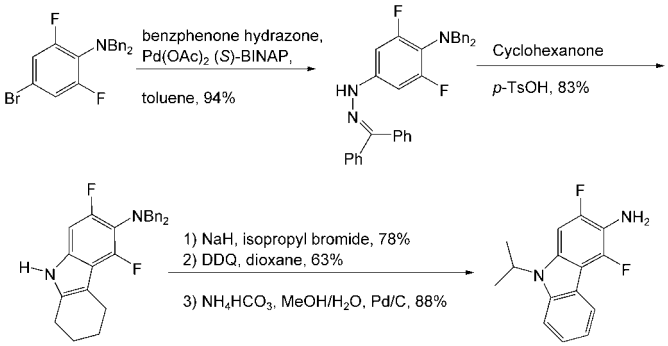
Figure 8. Contributions from academic groups in the synthesis of active ingredients.



Scheme 14. Synthesis of indoles.



Scheme 15. Solid-phase synthesis of indoles.



Scheme 16. Carbazole synthesis.

The ligands used are similar to those used in academic institutions with a slightly stronger focus on monodentate phosphines such as P(*t*-Bu)$_3$ or Buchwald's biaryl ligands. The range of screened conditions is usually broader in examples from industrial laboratories. The scale is also larger owing to the potential scale-up work for future production. For example, Rogers (Entry 4)[116] reports the intramolecular 7-ring formation on a 20-g scale. One of the largest scale applications reported in the literature is the synthesis of CP 529,414 which was published on a 3-kg scale in two patents by Pfizer using Buchwald's ligand Dave-Phos (Entry 7).[118] The commercial volume of this pharmaceutical target which is in clinical development phase III is estimated to be in the multi-ton range and is regarded by analysts as a potential blockbuster.

Nevertheless, owing to intellectual property reasons, the number of examples not published openly will be much larger. Several C–N couplings have already been run at a production scale of multi-hundred kgs.[18]

5.1.3 Synthesis of Indoles and Carbazoles

In 1999, Buchwald described a marvelous one-pot synthesis of indoles using C–N coupling methodology.[29] By reacting benzophenone hydrazone with an aryl halide, a phenyl-substituted hydrazone could be formed. In the beginning of the studies, this intermediate was isolated and then reacted with a substituted ketone under addition of *p*-toluenesulfonic acid. In an equilibrium, benzophenone and the free phenylhydrazine are formed. The hydrazine then reacts with the ketone yielding the cyclization precursor for the classical Fischer indole synthesis. Later, it was found that the isolation of the hydrazone is not necessary and the transformation could be run as a one-pot synthesis. *N*-Alkyl-substituted indoles could be formed by alkylation of the hydrazone precursor. *N*-Aryl-substituted indoles were generated by a very elegant bis-arylation of benzophenone hydrazone. Unsymmetrically substituted *N*-arylindoles were synthesized using a sequential C–N coupling protocol. The catalyst system was either derived from Pd/BINAP or Pd/XantPhos. In Scheme 14, the transformations described above are summarized.

A solid phase synthesis of indoles was described by Kondo in 2002.[80] Here, an intramolecular cyclization reaction of immobilized dehydrohalophenylalaninates was used as the key step for the indole synthesis. The precursor was built up using a Heck-reaction. P(*t*-Bu)$_3$ in toluene was used as the ligand for the C–N coupling (Scheme 15).

Using Buchwald's indole protocol, the analogous synthesis of carbazoles was achieved by Block at Astra Zeneca.[120] For this transformation, (*S*)-BINAP was used as the ligand (Scheme 16).

Sakamoto also reported a palladium-catalyzed strategy for the synthesis of carbolines including carbazoles.[84] He used an intermolecular amination reaction to form the C–N bond using *ortho*-bromoiodobenzene as the coupling partner, followed by intramolecular C–C coupling using Pd(OAc)$_2$. DPPF was used as the ligand for the Buchwald–Hartwig amination.

5.2 Applications in Ligand Synthesis

The Pd/ligand-mediated C–N coupling protocol also found entry to the synthesis of ligands for organometallic transformations themselves (Figure 10).

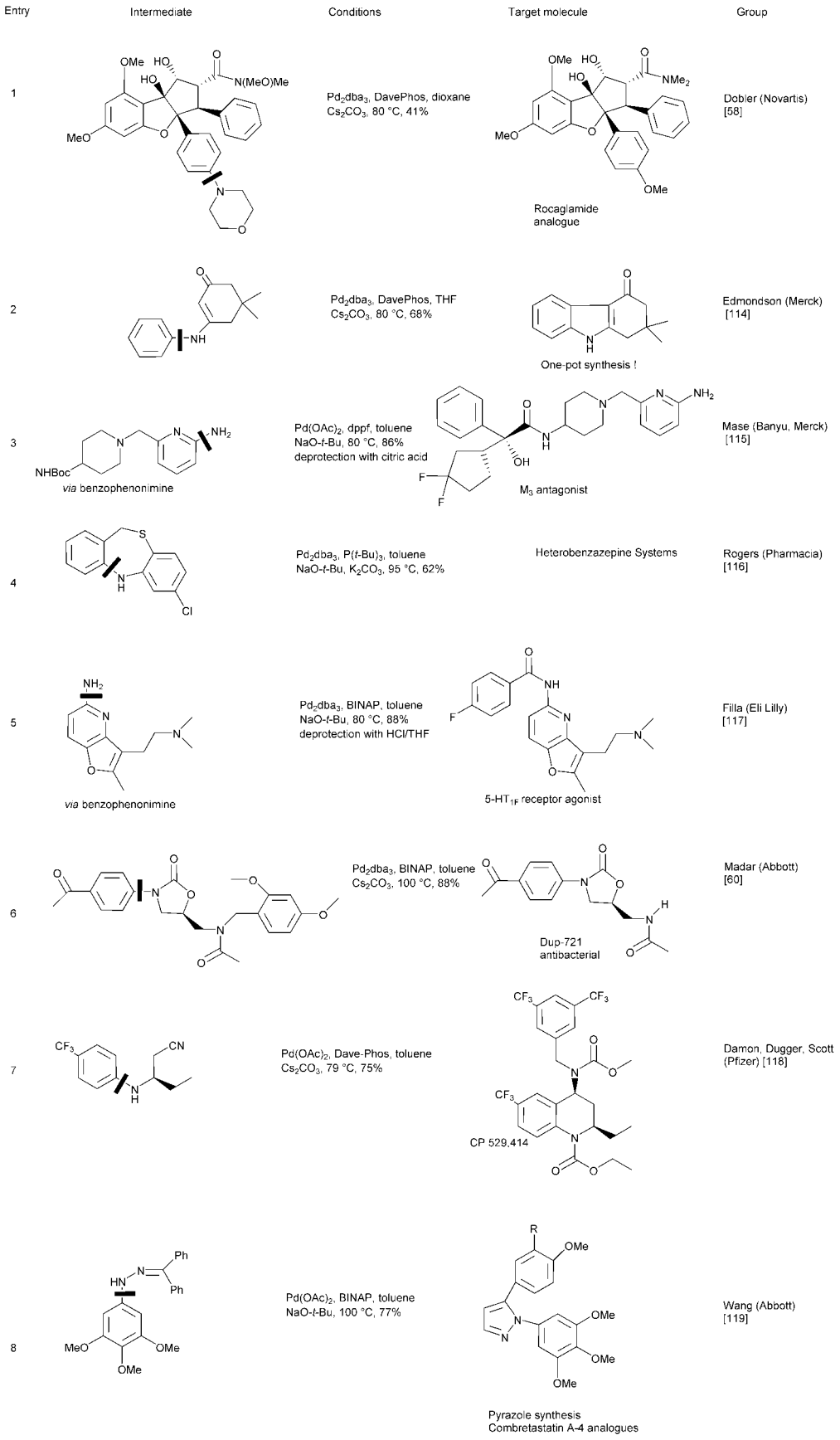


Figure 9. Contributions from industrial groups in the synthesis of active ingredients.

In 1999 Buchwald reported the preparation of *N*-arylated 2-amino-1,1′-binaphthyl derivatives *via* palladium-catalyzed amination (Entry 1).[56] Using DPEPhos as the ligand, an amino or arylamino group could be introduced. Mangeney developed the arylation of diphenyl-substituted ethylendiamines giving *N*-arylated chelating diamino ligands in 1999 (Entry 2).[121] The chiral information was preserved during the reaction and the products were obtained in good yields using BINAP. Heterocyclic aryl bromides could also be coupled. Brookhart coupled 2-triflatotropone with various aromatic amines to obtain 2-anilinotropones as ligands for organometallic transformations (Entry 3).[53]These are inaccessible *via* traditional nucleophilic displacement approaches. Guiry prepared tridentate bis(oxazoline) ligands for asymmetric catalysis in 2002 (Entry 4).[122] The synthesis was optimized using different Pd precursors, ligands, bases and solvents. The best ligand turned out to be DPPF with *t*-BuONa as the base. The reaction times were unusually long (1 week). Finally, Kempe synthesized 60 different P-N ligands using a library of amines generated by Buchwald–Hartwig amination and tested these complexes in the Suzuki reaction.[123]

In Figure 10, the different ligand classes generated by C–N coupling methodology are summarized.

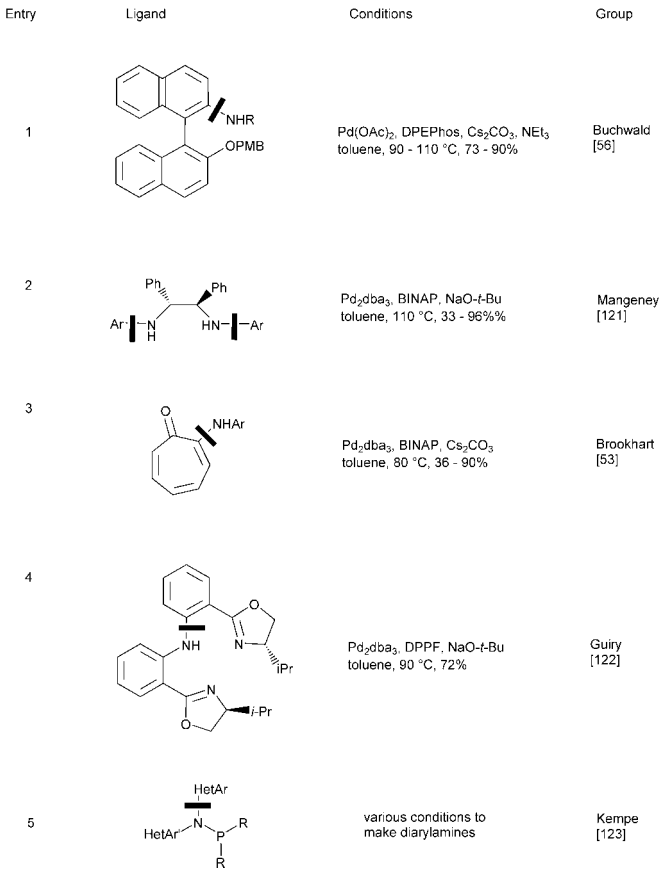


Figure 10. Buchwald-Hartwig amination in ligand synthesis.

5.3 Applications in Material Science

Amines are not only found in small to medium-sized molecules with high diversity that are usually building blocks for biological or chemical applications, but are also a core element of polymers and materials for the electronics and xerographic industry. Only the latest developments are outlined in the following section (Figure 11, for a more comprehensive survey see ref.[6]).

Watanabe synthesized novel bisdiarylaminothiophene oligomers that show intrinsic electronic properties (Entry 1).[92] He also used the methodology to build up 4,4′,4″-tris(*N*-azolyl)triphenylamines as hole transport molecules for light-emitting diodes (Entry 2).[79] While P(*t*-Bu)$_3$ again showed high activity for the transformation, the usage of rather exotic Rb_2CO_3 alongside with K_2CO_3 showed the best performance.

A one-pot synthesis of unsymmetrical triarylamines was reported by Buchwald in 2000 (Entry 3).[74] Using his bis-*tert*-butyl-substituted biphenylphosphine ligand, a sequential arylation protocol of arylamines was developed yielding the desired triarylamines in good to excellent yield. The methodology was used to build up a triarylamine library with a molecular weight range of 299–404.

Nuyken and Meerholz synthesized cross-linkable hole-transporting polymers using the C–N coupling methodology to polymerize N,N′-diphenylbenzidine with aryl dibromides using P(*t*-Bu)$_3$ (Entry 4).[72] Taniguchi reported the synthesis of hyperbranched polytriphenylamines in 2002 (Entry 5)[75]. Again using P(*t*-Bu)$_3$, these molecules could be prepared in medium yields by polymerization of 4,4′-diamino-4″-bromotriphenylamine. In 2002, Hartwig and Goodson reported the synthesis of triarylamine dendrimers using P(*t*-Bu)$_3$ as the ligand. These materials can generate highly delocalized radical cations (Entry 6).[124] Queiroz synthesized diarylamines in the benzo[*b*]thiophene series as electronic or luminescent components in organic materials (Entry 7).[77] In this study, BINAP was used to achieve the coupling in medium to good yields. Finally, P(*t*-Bu)$_3$ was used by Lin and Tao for the synthesis of benzo[*a*]aceanthranylene derivatives for red-emitting electroluminescent materials (Entry 8).[70] Researchers from Tosoh also report synthesis of triarylamines as well as polycondensation of primary amines with aryl dibromides.[13,71]

6 C–O Coupling

Compared to palladium-catalyzed C–N coupling, a first glimpse at Table 3 immediately shows that the field of palladium-catalyzed C–O coupling is by far not as comprehensively elaborated as the former method.

Next to the fact that numerous alternative methods for the synthesis of aryl ethers exist, mechanistically,

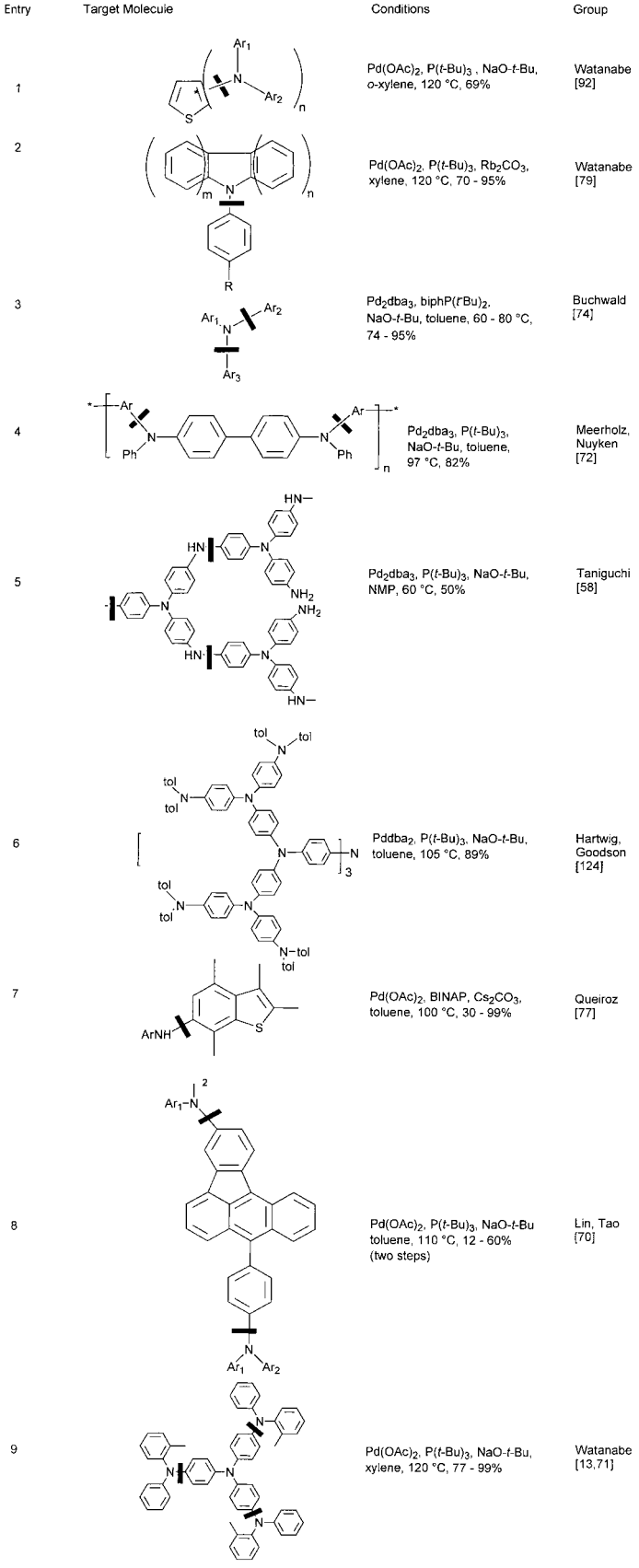


Figure 11. Applications in material sciences.

the slow reductive elimination and a strongly competing β-hydride elimination with primary and secondary alcohols[125] may explain this lack of more general protocols. Still, during the last five years the groups involved in this field have pointed out that the use of monoposphines as catalyst components is one of the key factors for successful C–O coupling.

A good protocol for the preparation of *tert*-butyl ethers from aryl bromides was presented by Watanabe using P(*t*-Bu)$_3$ as ligand.[126] Hartwig's ferrocenyl-dialkylphosphines[127] and especially his Q-Phos Ligand[69,128] proved to be extremely valuable for that protocol. The Buchwald group also published procedures with new ligand structures, usually containing two *tert*-butyl groups and a bulky polyaromatic system.[129,130] These ligands work equally well for aryl chlorides as starting materials[69,126–128,130,131] as for primary alcohols[69,128,130,132,133] with aryl bromides. Interesting to note is the fact that so far aryl chlorides have only been coupled with primary alcohols using the Buchwald ligand family.[130,132,133]

Next to the coupling of aliphatic alcohols with aryl halides, the formation of diaryl ethers has reached good applicability, mainly using Hartwig's Q-Phos[69] or the Buchwald ligands.[129]

For the direct exchange of a halogen with a hydroxy group, either the formation of a *tert*-butyl ether with acidic work-up[127] or the introduction of a silyl-protected alcohol[69,128] were suggested.

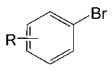
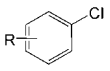
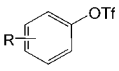
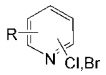
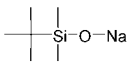
The intramolecular version of the C–O coupling seems to be more facile than the intermolecular reaction and even bisphosphine ligands can be used, as for example demonstrated in the total synthesis of β-decursin.[134] More recent publications, however, also disclosed protocols using both Hartwig's Q-Phos or members of the Buchwald family.[69,128,130,133] Only very few examples of successful coupling of pyridyl halides with aliphatic alcohols have been described, those using either P(*t*-Bu)$_3$[126] or the Buchwald ligands.[132] Only prophyrins as representatives of other heteroaromatic aryl halides have been used to generate the corresponding aryl ethers, in that case using DPEPhos as ligand.[51]

7 Contributions Elucidating the Mechanism

7.1 C–N Coupling

The generally accepted mechanism with two possible pathways that are discussed is depicted in Scheme 17.[4–8] In our impression, different authors agree that there is no general mechanism for palladium-catalyzed C–N coupling, but multiple mechanistic pathways are possible depending not only on the substrate classes that are coupled, but also on the ligand

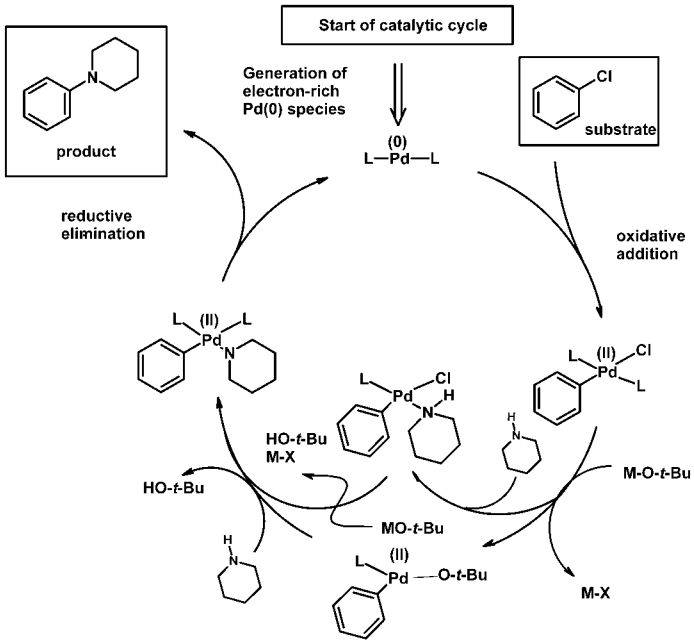
Table 3. Overview of published single examples from 1999 to 2004 for coupling of alcohols with halo or sulfonic acid ester aromatic substrates.

		1 	**2** 	**3** 	**4** 	**5** 	**6** 
A		18	6	2	–	7	–
B		3	2	–	–	2	–
C		–	–	–	–	1	–
D		58	24	–	1	2	–
E		51	22	2	1	1	1
F		7	1	–	–	–	–

The following citations are formatted as: **position in table**: [citation number], range of reported yields, ligand class and special features of article, (number of published examples), for ligand abbreviations, see Figures 3 and 5.
A1: [69], 52–83%, Q-Phos (2), [129], 74–96%, BW (16).
B2: [127], 74–85%, FcP(t-Bu)$_2$ (2); [128], 99%, Q-Phos (1).
D1: [132], 9–99%, BW (35); [133], 71–85%, BW – intramolecular; [69], 58%, Q-Phos – intramolecular (2), [128], 58%, Q-Phos – intramolecular (1); [130], 71–85%, BW – intramolecular (10).
E1: [133], 65–99%, BW – intramolecular (13); [69], 67–98%, Q-Phos (6); [69], 59–93%, Q-Phos – intramolecular (4); [131], 75–90%; BW (8); [126], 20–94%, P(t-Bu)$_3$ (8); [127], 78–84%, FcP(t-Bu)$_2$ (2); [128], 59–98%, Q-Phos (8); [130], 71–79%, BW – intramolecular (2).
F1: [69], 78–99%, Q-Phos (4), [128], 79–99%, Q-Phos (3).
A2: [129], 61–92%; BW (6).
B2: [127], 71–82%; FcP(t-Bu)$_2$ (2).
D2: [132], 88–95%, BW (17); [133], 71–85%, BW – intramolecular (3), [130], 71–85%, BW – intramolecular (4).
E2: [133], 65–78%; BW – intramolecular (4); [69], 92–98%, Q-Phos (3); [131], 84–94%; BW (4), [126], 60–92%, P(t-Bu)$_3$ (4); [127], 68–71%, FcP(t-Bu)$_2$ (2); [128], 78–98%, Q-Phos (3), [130], 75–78%, BW – intramolecular (2).
E3: [134], 80–91%, dppf or Tol-BINAP (2).
F2: [128], 67%, Q-Phos (1).
D4: [132], 79%, BW (1).
E4: [126], 30%, P(t-Bu)$_3$ (1).
A5: [51], 44–89%, DPEPhos – porphyrins (7).
B5: [51], 68–93%, DPEPhos – porphyrins (2).
C5: [51], 78%, DPEPhos – porphyrins (1).
D5: [51], 51–54%, DPEPhos – porphyrins (2).
E5: [51], 50%, DPEPhos – porphyrins (1).
E6: [127], 62%, FcP(t-Bu)$_2$ (1).

class that coordinates to the transition metal. Several authors also make the point that the current generation of catalysts is a result of an understanding of the mechanism and, as a rule of thumb, electron-richness of the ligand increases the ease of oxidative addition, while steric bulk propels reductive elimination. Which factor overweighs the other is a question of the rate-determining step, which is subject to ongoing discussion. Again, as a general rule the rate-determining step may depend on a number of factors, including substrate structure, nature of the halide/triflate substituent, catalyst structure and the base. Therefore each version of this reaction family has to be regarded separately, making generalization difficult.

The incorporation of the mechanistic knowledge into ligand design is best realized by the structures of P(t-Bu)$_3$ and the Buchwald dialkyl-biphenylphosphines. The role of the formation of the Pd–N bond as the rate determining step is also discussed.[15]



Scheme 17. Proposed mechanism of C–N coupling.

Although mechanistic aspects are fundamental for the further development of a method, they are less important for the reduction of a reaction to practice. Therefore, an overview of literature dealing with mechanistic details is given in this chapter for further reading.

Very detailed discussions of the mechanism are summarized in Hartwig's review articles.[6,7] Mechanistic alternatives are discussed and are backed with studies not directly related to C–N coupling chemistry. The three main parts of the catalytic cycle: oxidative addition, formation of amido complexes and reductive elimination with respect to the concurrent β-hydride elimination are summarized separately.

A general overview on the dialkylbiphenylphosphine family has been done by Buchwald et al.[15] While at that time the excellent reactivity and versatility of this ligand class was not fully understood, several calculated models were presented that give an impression on the role of the additional phenyl group as a co-ligand in these ligands. Later, these models were given further support by related crystal structure analyses.[141] Generally, these catalysts are thought to act as monodentate ligands, with the additional phenyl group serving as a co-ligand stabilizing the resting state of the catalyst. The reactivity of aryl bromides *versus* aryl chlorides is discussed, whereas identification of the rate-limiting step for the amination of aryl bromides contrasts older literature, now indicating that complexation of the amine to the catalyst is the rate-determining step rather than oxidative addition. Explanations for this deviation are presented. A recent study on the importance of stable catalyst systems by use of sequential reaction experiments of aryl chloride coupling finally demonstrates the role of substituents on the *o*-phenyl ring of the Buchwald ligand class.[142]

Dedicated to the mechanism of aryl chloride amination with P(*t*-Bu)$_3$ as catalyst is a contribution by the Hartwig group.[135] In this paper, a base-induced oxidative addition is proposed. The operation of two competing pathways is discussed, a neutral and an anionic pathway. The anionic pathway dominates when the ratio of palladium to P(*t*-Bu)$_3$ is set to 1 : 1. All results are backed by NMR studies and kinetic data.

The isolation, modeling and NMR characterization of monomeric arylpalladium(II) halide complexes, possibly real 14-electron intermediates in the catalytic cycle of a C–N coupling, was successfully performed by Hartwig et al.[136] This cleverly isolated complex with, for example, P(*t*-Bu)$_3$ could be used in several transformations, indicating its competence as a catalytic intermediate.

A thorough investigation of the palladium BINAP catalyst was undertaken by Blackmond and Buchwald[137] by the use of reaction calorimetry. This data indicates a rather slow formation of the active catalyst and explains the usually observed induction period. The reaction was measured to be zero order in base and positive order in aryl bromide and amine. The study also indicates that the amine is complexed to the catalyst prior to oxidative addition.

In a kinetic study van Leeuwen and his group discussed different catalytic pathways for C–N coupling of aryl bromides and aryl triflates[25] using diphosphine ligands. Generally, the rate-determining step is dependent on whether cationic intermediates (from aryl triflates) or neutral intermediates (from aryl bromides) appear. In the former case, the rate-determining step is the deprotonation of the Pd-amine complex. In the latter case, the rate-determining step is the formation of the Pd-alkoxide complex. When investigating different ligands, a correlation between bite angle and reactivity could be observed, interestingly laterally reversed when triflate complexes where compared to halide complexes. By the addition of halide salts, the turnover frequency could be increased to a certain extent. The arguments are backed up by kinetic and NMR studies.

Watanabe et al. propose a mechanism for the arylation of piperazine using palladium(II) acetate and P(*t*-Bu)$_3$,[71] with no experimental proof however. In this paper, the arylpiperazine formation is discussed using various monophosphines with different steric and electronic properties and their influence on the mechanism.

The influence of carbene ligands on the mechanism is discussed by the Hartwig group.[20] While catalytic turnover is increased by the use of a dihydrocarbene as ligand, the mechanistic model indicates, like in the publications of other authors,[15] the addition of the nitrogen nucleophile to the catalyst to be the rate-determining step of the catalytic cycle.

7.2 C–Amide Coupling

For the intermolecular amidation of aryl halides, Buchwald discussed the different binding modes of the amide to the palladium using the XantPhos ligand.[27] An explanation of by-products like phenylated amides by phenyl exchange with the ligand is presented.

In a subsequent paper the same group discusses the *trans*-chelating character of the XantPhos ligand in the active palladium complex.[26] These findings are backed both by crystallographic data and by ^{31}P NMR data. The former restriction of the methodology to electron-rich aryl halides could be removed by using $Pd_2(dba)_3$ as precatalyst instead of Pd(II)acetate.

7.3 C–O Coupling

In his review on C–O coupling,[125] Hartwig also discusses the mechanism and a parallel is drawn to the mechanism of C–N coupling. The slower reductive elimination of ether *vs.* amine explains why alkoxy bases can be used in the C–N coupling with no competing C–O coupling. Monophosphines as ligands are essential for C–O, while reductive elimination with bisphosphine ligands was not observed. In another article Hartwig discusses the mechanism of C–O coupling specifically referring to the structural specialties of his Q-Phos ligand with some crystallographic data and thoughts on the rate-determining step.[69]

For the coupling of primary alcohols to aryl halides, Buchwald discusses the mechanism using the group's dialkylbiphenyl ligands.[132] Best results were observed with an optimal dihedral angle and thus the optimal steric shielding of the catalyst is the main success factor for high catalytic activity. The intramolecular case is discussed by the same group in a new method to make benzofurans.[133]

8 Overview of Current Review Articles

As stated in the beginning, already a number of reviews have appeared in the literature.[4–8] The role of this chapter is to give a broad overview on the main focus of each review, so that the reader can decide for him/herself where to look for additional reading.

In 1997 the first extended review in the field was contributed by Hartwig.[138] A strong focus of this work is the mechanism of the reaction, especially compared to earlier work using tin amides as coupling partners. Several crystallographic studies are discussed, including cyclopalladated complexes as possible intermediates of the catalytic cycle. The role of chelating phosphines, especially dppf is presented.

In the same year Beller again reviewed the field[41] with an exclusive view on the cross-coupling of aryl chlorides, including C–N coupling. Generally, the use of palladacylic catalysts as well as N-heterocyclic carbenes is discussed for Heck-like and amination reactions, for the C–N coupling temperatures higher than 120 °C are advised. The effect of salt additions is discussed.

Buchwald et al.[5] summarized in their review the advances in the field before 1999. The review is organized by the product classes that can be generated by the reaction. For the *N*-arylation of secondary amines, the use of chelating ligands is propagated, while ferrocenyl-derived ligands tend to enable more general conditions. Still this substrate class is limited to strong alkoxide bases. New at that time, the dialkylbiphenyl phosphine ligand class with Dave-Phos (cf. Figure 5) as an example is shown to be superior in this reaction, even at room temperature.

The coupling of acylic amines with aryl chlorides is discussed and the catalyst classes that have been reported to that date are summarized. As general point at that time only high temperatures allowed for high yields in aryl chloride coupling. The article also covers *N*-arylation of primary amines, anilines and N-heterocycles like pyrroles. Also the introduction of ammonia by the use of surrogates like benzophenone imine is summarized. The article also includes palladium-catalyzed intramolecular amidations and Buchwald's alternative to the Fischer indole synthesis.

Lakshman et al.[139] described in their 2002 "mini-review" the advances of palladium-catalyzed C–N couplings in purine-nucleoside chemistry. While classically these transformations could be performed using fluorine-substituted purines without transition metals, the new methodology allowed for broader substrate scope. Several ligands are compared with each other for this substrate class, generally Buchwald's bisalkylbiphenylphosphines like Dave-Phos give the most general procedures, although yields vary considerable with respect to the position on the purine ring. The authors address one of the main concerns of many chemists, to deal with a compound class that is strongly coordinating for palladium. A correlation between complexation potential for palladium of the final products and low reaction yields is discussed in this review.

Also appearing in 2002 two rather comprehensive reviews, both as extended book chapters were published individually by the two pioneers Buchwald[8a] and Hartwig.[6]

Buchwald's[8a] review covers both C–N and C–O coupling until the year 2000. The article is organized by the class of amine that is used, i.e., secondary, primary and ammonia, and is substructured by the reactivity of the aryl halide, from aryl bromide to iodide to chloride to sulfonate. By this organization, this contribution can be used in a recipe book-like manner and offers a quick introduction into the field. The article also gives a beautiful historical summary of the chemistry, a brief discus-

sion of mechanistic details and summarizes the different classes of ligands that have been applied over the years. N-Heterocyclic carbenes are summarized just like the well known examples from dialkylbiphenyl phosphines, P(*t*-Bu)$_3$, Xantphos or BINAP. Again obvious is the fact, that C–O coupling did not at that point offer the same generality in the protocols as C–N coupling.

Hartwig[6] in his review covered the literature until the middle of 2001 and extended his older review from 1997[138] with a lot of details. The ligand classes are separated into generations, with triarylphosphines as the 1st, chelating bisphosphines as the 2nd, and trialkyl- and dialkylbiphenyl phosphines as the 3rd generation of ligand. Mechanistic work is discussed with great detail, including the effects of using different solvents and bases. The coupling of base-sensitive aryl chlorides is discussed separately, just like the uses of secondary phosphine oxide, N-heterocyclic carbenes and heterogeneous ligands. Examples for the synthesis of biologically active molecules, molecules with applications in material sciences, and the use of the methodology for synthesis of ligands are presented.

As a summary of this review Hartwig presented a more condensed version in the same year.[7] Again this article can be recommended to the reader who is interested in mechanistic details, since these are beautifully covered in this article. An extended discussion about the correct choice of the base is part of the paper and a concise tabular overview of the possible combinations of aryl halides with different amines is presented and referenced in this paper.

A review dealing with C–O coupling alone was presented, again by Hartwig, in the same year.[125] The most effective catalysts are presented again in a clear, tabular form. The mechanism is discussed, just like the use of fully phenylated ferrocene-based ligands as very versatile catalyst components for this transformation. Next to the use of unactivated aryl halides, Hartwig also summarizes the efforts and history in C–S and C–Se coupling that have been undertaken until 2001.

A comprehensive review article by Prim et al. appeared in 2002. It deals with the more general palladium-catalyzed reaction of aryl halides with soft nucleophiles but also covers the latest developments in C–N and C–O coupling until 2002.[86]

The latest review article on C–N coupling appeared just recently[4] by Buchwald et al. Here the group elaborates in great detail on the parameters of the C–N coupling.

9 Conclusions

Only very rarely does a novel reaction methodology trigger an avalanche of publications in a relatively short time. In this regard, the Buchwald–Hartwig amination has to be named alongside the fundamental organic reactions such as metathesis, Diels–Alder or Wittig reactions.

Even more fascinating is the relatively short period of time from the development in an academic environment over the implementation in pharmaceutical research laboratories up to the almost routine use of this reaction in larger scale production environments.

The reason for this success story is two-fold: the approach of C–N coupling is modular, owing to the variability of both the aryl halide or even sulfonic acid ester and the amine nucleophile, a broad range of amine products is accessible, for which no other comparably versatile methodology is available. Secondly, the reaction conditions are very robust and the reaction shows a high degree of reproducibility if the standard ligands are used and the conditions are optimized. This reliability is one of the central issues for the implementation in an industrial environment.

Further developments will certainly be centered around even more active catalyst systems as well as the use of more demanding coupling partners outlined in Tables 2 and 3. The creation of new ligands is only attractive if they fulfill two criteria: (i) they have to be even easier to synthesize compared with the existing systems and (ii) they have to be more active, thus allowing for even further reduction of catalyst loading also including the use of mild bases. Costs of the ligand as well as the amount of catalyst needed will greatly influence the future prospects of this methodology to be considered a routine tool in industrial small- and large-scale environments.

References and Notes

[†] This review covers the literature from January, 1st, 1999 to January, 1st, 2004.

[1] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 1348–1350; b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, *21*, 3609–3612.

[2] See, for example: a) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, Weinheim, Cambridge, **1989**; b) J. March, *Advanced Organic Chemistry,* 4th edn., Wiley, New York, **1992**.

[3] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174; b) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; c) F. Ullmann, P. Sponagel, *Ber. Dtsch. Chem. Ges.* **1905**, *36*, 2211–2212; d) I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691–1692.

[4] L. Jiang, S. L. Buchwald, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **1998**.

[5] a) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; b) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 853; c) J. F. Hartwig, *Angew. Chem. .Int. Ed.* **1998**, *37*, 2047; d) S. L. Buchwald, *Acc. Chem. Res.* **199 8**, *31*, 805.

[6] J. F. Hartwig, in: *Modern Arene Chemistry*, (Ed.: A. Didier), Wiley-VCH, Weinheim, **2002**, pp. 107–168.
[7] J. F. Hartwig, in: *Handbook of Organopalladium Chemistry for Organopalladium Chemistry of Organic Synthesis*, Vol. 1, Wiley-Interscience, New York, **2002**, pp 1051–1096.
[8] a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem*. **2002**, *219*, 131–209; b) D. Prim, J. M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041–2075.
[9] http://www.kitco.com/charts/livepalladium.html.
[10] A. H. M. DeVries, J. G. DeVries, *WO* 02/057199 A1, 18.1.2001.
[11] Selected examples: a) X. Tao, Y. Zhao, D. Shen, *Synlett* **2004**, *2*, 359–361; b) S. L. Wiskur, A. Korte, G. C. Fu, *J. Am. Chem. Soc*. **2004**, *126*, *1*, 82–83; c) G. Zou, Z. Wang, J. Zhu, J. Tang, Y. M. He, *J. Mol. Cat. A: Chemical* **2003**, *206*, *1–2*, 193–198; d) J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086–1092.
[12] a) M. Kosugi, M. Kameyama, H. Sano, T. Migita, *Chem. Lett*. **1983**, 927–928; b) M. Kosugi, M. Kameyama, H. Sano, T. Migita, *Nippon Kagaku Kaishi* **1985**, 547–551.
[13] a) M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Specialty Chemicals* **1998**, *18*, *10*, 445–450; b) M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett*. **1998**, *39*, 617; c) T. Yamamoto, M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 2367.
[14] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc*. **1998**, *120*, 9722–9723.
[15] a) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158–1174; b) J. P. Wolfe, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413.
[16] a) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc*. **2003**, *125*, 6653–6655; b) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc*. **2003**, *125*, 13978–13980.
[17] a) H. Tomori, J. M. Fox, S. L. Buchwald, *J. Org. Chem*. **2000**, *65*, 5334–5341; b) S. Kaye, J. M. Fox, F. A. Hicks, S. L. Buchwald, *Adv. Synth. Catal*. **2001**, *343*, *8*, 789–794.
[18] Internal Bayer Project.
[19] a) P. Kocovský, *J. Organomet. Chem*. **2003**, *687*, 256–268; b) P. Kocovský, *Tetrahedron Lett.* **1998**, 39, 9289.
[20] S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett*. **2000**, *2*, 1423–1426.
[21] W. A. Herrmann, K. Öfele, D. v. Preysing, S. K. Schneider, *J. Organomet. Chem*. **2003**, *687*, 229–248.
[22] G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem*. **2001**, *66*, 7729–7737.
[23] J. Huang, G. Grasa, S. P. Nolan, *Org. Lett*. **1999**, *1*, 1307–1309.
[24] M. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett*. **2002**, *4*, 2229–2231.
[25] Y. Guari, G. P. F. van Strijdonck, M. D. K. Boele, J. N. H. Reek, P. C. J. Kramer, P. W. N. M. van Leeuwen, *Chem. Eur. J*. **2001**, *7*, 475–482.
[26] J. Yin, S. L. Buchwald, *J. Am. Chem. Soc*. **2002**, *124*, 6043–6048.
[27] J. Yin, S. L. Buchwald, *Org. Lett*. **2000**, *2*, *8*, 1101–1104.
[28] B. H. Yang, S. L. Buchwald, *Org. Lett*. **1999**, *1*, 35–37.
[29] S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc*. **1999**, *121*, 10251–10263.
[30] S. Cacchi, G. Fabrizi, A. Goggiamani, G. Zappia, *Org. Lett*. **2001**, *3*, 2539–2541.
[31] G. A. Artamkina, A. G. Sergeev, I. P. Beletskaya, *Tetrahedron Lett*. **2001**, *42*, 4381–4384.
[32] S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Org. Lett*. **2003**, *5*, 815–818.
[33] S. Urgaonkar, J.-H. Xu, J. G. Verkade, *J. Org. Chem*. **2003**, *68*, 8416–8423.
[34] S. Urgaonkar, M. Nagarajan, J. G. Verkade, *J. Org. Chem*. **2003**, *68*, 452–459.
[35] R. A. Singer, S. Caron, R. E. McDermott, P. Arpin, N. M. Do, *Synthesis* **2003**, 1727–1731.
[36] F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983–2990.
[37] C. A. Parrish, S. L. Buchwald, *J. Org. Chem*. **2001**, *66*, 3820–3827.
[38] A. Ehrentraut, A. Zapf, M. Beller, *J. Mol. Catal. A: Chemical* **2002**, *182–183*, 515–523.
[39] X. Bei, T. Uno, J. Norris, H. W. Turner, W. H. Weinberg, A. S. Guram, *Organometallics* **1999**, *18*, 1840–1853.
[40] X.-X. Zhang, M. C. Harris, J. P. Sadighi, S. L. Buchwald, *Can. J. Chem*. **2001**, *79*, 1799–1805.
[41] T. H. Riermeier, A. Zapf, M. Beller, *Topics in Catalysis* **1997**, *4*, 301–309.
[42] G. Y. Li, G. Zheng, A. F. Noonan, *J. Org. Chem*. **2001**, *66*, 8677–8681.
[43] R. B. Bedford, C. S. J. Cazin, *GB Patent* 2376946 A, 29.6.2001.
[44] M. Thommen, H.-U. Blaser, *Specialty Chemicals* **2002**, *22*, 38–39.
[45] A. Schnyder, A. F. Indolese, M. Studer, H.-U. Blaser, *Angew. Chem. Int. Ed.* **2002**, *41*, 3668–3671.
[46] J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem. Int. Ed*. **2002**, *41*, 4746–4748.
[47] M. Prashad, B. Hu, Y. Lu, R. Draper, D. Har, O. Repic, T. J. Blacklock, *J. Org. Chem*. **2000**, *65*, 2612–2614.
[48] K. W. Anderson, M. Mendez-Perez, J. Priego, S. L. Buchwald, *J. Org. Chem*. **2003**, *68*, 9563–9573.
[49] M. K. Lakshman, J. C. Keeler, J. H. Hilmer, J. Q. Martin, *J. Am. Chem. Soc.* **1999**, *121*, 6090–6091.
[50] See, for example: a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; b) http://daecr1.harvard.edu/pdf/evans_pKa_table.pdf; c) http://www.chem.wisc.edu/areas/reich/pkatable/.
[51] G.-Y. Gao, A. J. Colvin, Y. Chen, X. P. Zhang, *Org. Lett*. **2003**, *5*, 3261–3264.
[52] M. H. Ali, S. L. Buchwald, *J. Org. Chem*. **2001**, *66*, 2560–2565.
[53] F. A. Hicks, M. Brookhart, *Org. Lett*. **2000**, *2*, *2*, 219–221.
[54] R. S. Coleman, W. Chen, *Org. Lett*. **2001**, *3*, *8*, 1141–1144.
[55] C. Bolm, J. P. Hildebrand, *J. Org. Chem*. **2000**, *65*, 169–175.

[56] R. A. Singer, S. L. Buchwald, *Tetrahedron Lett*. **1999**, *40*, 1095–1098.
[57] T. J. Luker, H. G. Beaton, M. Whiting, A. Mete, D. R. Cheshire, *Tetrahedron Lett*. **2000**, *41*, 7731–7735.
[58] M. R. Dobler, I. Bruce, F. Cederbaum, N. G. Cooke, L. J. Diorazio, R. G. Hall, E. Irving, *Tetrahedron Lett*. **2001**, *42*, 8281–8284.
[59] T. Emoto, N. Kubosaki, Y. Yamagiwa, T. Kamikawa, *Tetrahedron Lett*. **2000**, *41*, 355–358.
[60] D. J. Madar, H. Kopecka, D. Pireh, J. Pease, M. Pliushchev, R. J. Sciotti, P. E. Wiedeman, S. W. Djuric, *Tetrahedron Lett*. **2001**, *42*, 3681–3684.
[61] M. C. Willis, G. N. Brace, *Tetrahedron Lett*. **2002**, *43*, 9085–9088.
[62] B.-L. Deng, J. A. Lepoivre, G. Lemière, *Eur. J. Org. Chem*. **1999**, 2683–2688.
[63] Y.-M. Zhu, Y. Kiryu, H. Katayama, *Tetrahedron Lett*. **2002**, *43*, 3577–3580.
[64] D. Zim, S. L. Buchwald, *Org. Lett*. **2003**, *5*, *14*, 2413–2415.
[65] R. Kuwano, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem*. **2002**, *67*, 6479–6486.
[66] a) M. C. Harris, X. Huang, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 17, 2885–2888; b) S. L. Buchwald, X. Huang, *Org. Lett.* **2001**, *3*, 3417.
[67] J. Yin, M. M. Zhao, M. A. Huffman, J. M. McNamara, *Org. Lett*. **2002**, *4*, 3481–3484.
[68] S. R. Stauffer, J. F. Hartwig, *J. Am. Chem. Soc*. **2003**, *125*, 6977–6985.
[69] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem*. **2002**, *67*, 5553–5566.
[70] T. H. Huang, J. T. Lin, Y.-T. Tao, C.-H. Chuen, *Chem. Mater*. **2003**, *15*, 4854–4862.
[71] M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Toso Kenkyu Hokoku* **1999**, *43*, 37–50.
[72] T. Braig, D. C. Müller, M. Groß, K. Meerholz, O. Nuyken, *Macromol. Rapid Commun.* **2000**, *21*, 538–589.
[73] M. Prashad, X. Y. Mak, Y. Liu, O. Repic, *J. Org. Chem.* **2003**, *68*, 1163–1164.
[74] M. C. Harris, S. L. Buchwald, *J. Org. Chem*. **2000**, *65*, 5327–5333.
[75] M. Jikei, R. Mori, S. Kawauchi, M. Kakimoto, Y. Taniguchi, *Polymer Journal* **2002**, *34*, 550–557.
[76] R. S. Laufer, G. I. Dmitrienko, *J. Am. Chem. Soc*. **2002**, *124*, 1854–1855.
[77] I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2003**, *59*, 975–981.
[78] D. W. Old, M. C. Harris, S. L. Buchwald, *Org. Lett*. **2000**, *2*, *10*, 1403–1406.
[79] M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **2000**, *41*, 481–483.
[80] K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2137–2138.
[81] A. C. Frisch, A. Zapf, O.Briel, B. Kayser, N. Shaikh, M. Beller, *J. Mol. Catal. A: Chemical* **2004**, *214*, 231–239.
[82] B. U .W. Maes, K. T. J. Loones, G. L. F. Lemière, R. A. Dommisse, *Synlett* **2003**, 1822–1825.
[83] A. Guram, X. Bei, *US Patent* 6,268,513 B1, 20.8.2004.
[84] T. Iwaki, A. Yasuhara, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1505–1510.
[85] T. Ullrich, F. Giraud, *Tetrahedron Lett*. **2003**, *44*, 4207–4211.
[86] H. J. Knölker, J. Knöll, *Chem. Commun.* **2003**, 1170–1171.
[87] M. P. Wentland, W. Duan, D. J. Cohen, J. M. Bidlack, *J. Med. Chem*. **2000**, *43*, 3558–3565.
[88] J. Cheng, M. L. Trudell, *Org. Lett*. **2001**, *3*, 1371–1374.
[89] T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemière, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommissea, *Synlett* **2003**, *5*, 615–618.
[90] M. K. Lakshman, J. H. Hilmer, J. Q. Martin, J. C. Keeler, Y. Q. V. Dinh, F. N. Ngassa, L. M. Russon, *J. Am. Chem. Soc*. **2001**, *123*, 7779–7787.
[91] M. W. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem*. **2003**, *68*, 2861–2873.
[92] M. Watanabe, T. Yamamoto, M. Nishiyama, *Chem. Commun.* **2000**, 133–134.
[93] B. U. W. Maes, J. Kosmrlj, G. L. F. Lemière, *J. Heterocycl Chem*. **2002**, *39*, 535–543.
[94] J. Kosmrlj, B. U. W. Maes, G. L. F. Lemière, A. Haemers, *Synlett* **2000**, 1581–1584.
[95] S. Urgaonkar, J. G. Verkade, *Adv. Synth. Catal*. **2004**, *346*, 611–616.
[96] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc*. **1998**, *120*, *29*, 7369–7370.
[97] S. Wagaw, S. L. Buchwald, *J. Org. Chem*. **1996**, *61*, 7240–7241.
[98] J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580.
[99] A. Ghosh, J. E. Sieser, M. Riou, W. Cai, L. Rivera-Ruiz, *Org. Lett*. **2003**, *5*, 2207–2210.
[100] M. Harmata, N. Pavri, *Angew. Chem. Int. Ed.* **1999**, *38*, 2419–2421.
[101] Z. Wang, R. T. Skerlj, G. J. Bridger, *Tetrahedron Lett.* **1999**, *40*, 3543–3546.
[102] G. Evindar, R. A. Batey, *Org. Lett*. **2003**, *5*, 133–136.
[103] S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313–1316.
[104] G. Mann, J. F. Hartwig, M. S. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
[105] J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett*. **1997**, *38*, *36*, 6367–6370.
[106] S. Lee, M. Jorgensen, J. F. Hartwig, *Org. Lett*. **2001**, *3*, 2729–2732.
[107] J. F. Hartwig, M. Jorgensen, S. Lee, *WO* 03/006420 A1, 12.7.2001.
[108] Y. Kozawa, M. Mori, *J. Org. Chem*. **2003**, *68*, 3064–3067.
[109] Y. Kozawa, M. Mori, *Tetrahedron Lett*. **2002**, *43*, 111–114.
[110] B. B. Snider, H. Zeng, *Org. Lett*. **2000**, *2*, 4103–4106.
[111] T. Suzuki, S. T. Suzuki, I. Yamada, Y. Koashi, K. Yamada, N. Chida, *J. Org. Chem*. **2002**, *67*, 2874–2880.
[112] M. P. Wentland, G. Xu, C. L. Cioffi, Y. Ye, W. Duan, D. J. Cohen, A. M. Colasurdo, J. M. Bidlack, *Bioorg. Med. Chem. Lett*. **2000**, *10*, 183–187.

[113] O. J. Plante, S. L. Buchwald, P. H. Seeberger, *J. Am. Chem. Soc.* **2000**, *122*, 7148–7149.
[114] S. D. Edmondson, A. Mastracchio, E. R. Parmee, *Org. Lett.* **2000**, *2*, 1109–1112.
[115] T. Mase, Y. Kato, M. Kawasaki, F. Lang, J. Lee, J. Lynch, P. Maligres, A. Molina, T. Nemoto, S. Okada, R. Reamer, J. Z. Song, D. Tschaen, T. Wada, D. Zewge, R. P. Volante, P. J. Reider, K. Tomimoto, *J. Org. Chem.* **2001**, *66*, 6775–6786.
[116] B. J. Margolis, J. J. Swidorski, B. N. Rogers, *J. Org. Chem.* **2003**, *68*, 644–647.
[117] B. M. Mathes, S. A. Filla, *Tetrahedron Lett.* **2003**, *44*, 725–728.
[118] a) D. B. Damon, R. W. Dugger, R. W. Scott, *WO* 2002088085 A2, 30.4.2001; b) D. B. Damon, R. W. Dugger, R. W. Scott, *WO* 2002088069 A2, 30.4.2001.
[119] L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinski-Mozug, D. Frost, S. H. Rosenberg, H. L. Sham, *J. Med. Chem.* **2002**, *45*, 1697–1711.
[120] M. H. Block, S. Boyer, W. Brailsford, D. R. Brittain, D. Carroll, S. Chapman, D. S. Clarke, G. S. Donald, K. M. Foote, L. Godfrey, A. Ladner, P. R. Marsham, D. J. Masters, C. D. Mee, M. R. O'Donovan, J. E. Pease, A. G. Pickup, J. W. Rayner, A. Roberts, P. Schofield, A. Suleman, A. V. Turnbull, *J. Med. Chem.* **2002**, *45*, 3509–3523.
[121] I. Cabanal-Duvillard, P. Mangeney, *Tetrahedron Lett.* **1999**, *40*, 3877–3880.
[122] H. A. McManus, P. J. Guiry, *J. Org. Chem.* **2002**, *67*, 8566–8573.
[123] T. Schareina, R. Kempe, *Angew. Chem. Int. Ed.* **2002**, *41*, 1521–1523.
[124] M. I. Ranasinghe, O. P. Varnavski, J. Pawlas, S. I. Hauck, J. Louie, J. F. Hartwig, T. Goodson, III, *J. Am. Chem. Soc.* **2002**, *124*, 6520–6521.
[125] J. F. Hartwig, in: *Handbook of Organopalladium Chemistry for Organic Synthesis,* (Ed. E.-i. Negishi), J. Wiley & Sons Inc., New York, **2002**, pp. 1097–1106.
[126] M. Watanabe, M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1999**, *40*, 8837–8840.
[127] G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.
[128] Q. Shelby, N. Kataoka, G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
[129] A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.
[130] K. E. Torraca, S. Kuwabe, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.
[131] C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2498–2500.
[132] K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
[133] S.-i. Kuwabe, K. E. Torraca, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.
[134] T. Nemoto, T. Ohshima, M. Shibasaki, *Tetrahedron* **2003**, *59*, 6889–6897.
[135] L. M. Alcazar-Roman, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 12905–12906.
[136] J. P. Stambuli, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 9346–9347.
[137] U. K. Singh, E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14104–14114.
[138] J. F. Hartwig, *Synlett* **1997**, *4*, 329–340.
[139] M. K. Lakshman, *J. Organomet. Chem.* **2002**, *653*, 234–251.
[140] M. B. Smith, J. March, *Advanced Organic Chemistry*, 5th edn. , J. Wiley & Sons, New York, **2001**, pp. 696 and 1552.
[141] J. Yin, M. P. Rainka, X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162.
[142] E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980.
[143] C. W. Lim, S. G. Lee, *Tetrahedron* **2000**, *56*, 5131.

