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Application of Novel Phosphine Ligands in Palladium-Catalyzed Cross-Coupling Reactions

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Abstract

This thesis describes the application of 2-phosphino-*N*-arylindoles, -pyrroles and -imidazoles as ligands in Pd-catalyzed C–C, C–N and C–O bond forming reactions. Based on prior studies, 2-phosphino-*N*-arylindoles and -pyrrols were found to form efficient catalysts with Pd-salts in the Sonogashira-Hagihara coupling of (hetero)aryl bromides and the Pd-catalyzed monoarylation of ammonia. The novel imidazole-based phosphines were prepared after a straightforward modular synthesis and are notably stable towards air. They were successfully employed in the Pd-catalyzed phenol synthesis, the Heck-Cassar coupling of aryl chlorides, and the Pd-catalyzed monoarylation of ammonia. Furthermore, mechanistic studies in the Pd-catalyzed hydroxylation were undertaken.

In der vorliegenden Dissertation wird die Anwendung von Dialkyl-heteroarylphosphinen als Liganden in palladiumkatalysierten Bindungsknüpfungen beschrieben. Die zuvor beschriebenen Indol- und Pyrrol-basierten Phosphine wurden erfolgreich in der Sonogashira-Hagihara-Kupplung von Aryl- und Heteroarylbromiden und der palladiumkatalysierten selektiven Anilinsynthese eingesetzt. Die Imidazolderivate hingegen stellen eine neuartige Ligandenklasse für Kreuzkupplungen dar. Sie konnten mit einer modularen Synthesemethode bequem dargestellt werden und sind äußerst luftstabil. Mit auf ihnen basierenden Palladium-Katalysatoren konnten Arylchloride effizient kupferfrei mit Alkinen umgesetzt, sowie Phenole wie auch Aniline aus Arylhaliden synthetisiert werden. Des weiterten wurden mechanistische Untersuchungen in der palladiumkatalysierten Phenolsynthese durchgeführt.

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List of Abbreviations

a	year
Ac	acetyl
Ad	adamantyl
API	active pharmaceutical ingredient
Ar	aryl
AT_2	angiotensin II
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
Bn	benzyl
BOC	di-*tert*-butyl dicarbonate
Bu	butyl
Cata*CX*ium® A	di-1-adamantyl-*n*-butylphosphine
Cata*CX*ium® PIntB	2-(di-*tert*-butylphosphino)-*N*-phenylindole
Cata*CX*ium® PtB	2-(di-*tert*-butylphosphino)-*N*-phenylpyrrole
CETP	cholesteryl ester transfer protein
CP	ceruloplasmin
COD	cyclooctadieenyl
COX-2	prostaglandin-endoperoxide synthase 2
CNS	central nervous system
Cy	cyclohexyl
D-A	Diels-Alder
dba	*trans*, *trans*-dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DE	dissociation energy
DFT	density functional theory
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene

e.g.	exempli gratia
EP_3	prostaglandin E receptor 3
Et	ethyl
et. al.	et alii
f	fluorinated
g	gramm
Hex	hexyl
HIV	human immunodeficiency virus
H-M	Heck-Mizoroki
5-HT	5-hydroxytryptamine
i	iso
IPA	isopropanol
IPAc	isopropyl acetate
kg	kilogramm
L	ligand; litre
L	laevus
m	meta
Me	methyl
Ms	mesylate
Mt	megaton
mw	microwave
n	natural number
n	normal
NHC	*N*-heterocyclic carbene
NLO	non-linear optical (material)
NPY	neuropeptin Y
o	ortho
OAE	oligo(aryleneethynylene)
p	para
PAE	poly(aryleneethynylene)
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl

R	organic group
rac	racemic
S	sinister
sia	bis(1,2-dimethylpropyl)
SPS	switchable-polarity solvents
t	ton
t	tertiary
TBAB	tetra-*n*-butylammonium bromide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate, trifluoromethanesulfonate
THF	tetrahydrofurane
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl; temperature dependent multi-component solvent
TMSA	trimethylsilylacetylene
TOF	turnover frequency
TON	turnover number
Ts	tosyl, *p*-toluenesulfonyl
X	leaving group, halide
XPhos	2-di-cyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Z	zusammen

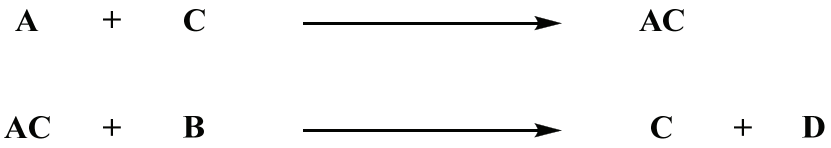
1 Introduction

1.1 Catalysis

A substance, which is accelerating a chemical reaction without being consumed, is called a ‘catalyst’, the process itself ‘catalysis’. The word catalysis has its origin in the Greek word καταλύειν (katálysis) meaning ‘in the presence of break-up’ and was coined out by Jöns Jörg Berzelius in 1835. Various reactions known today to proceed in a catalytic manner had been discovered before that date, for example the ingnition of hydrogen on a platinum sponge being part of a lighter developed by Johann Wolfgang Döbereiner in 1823. However, Berzelius was first to illuminate the common chemical principle of these reactions. He pointed out that these chemical transformations (the *‘break-ups’*) occur *in the presence* of a certain substance not being converted into another during the reaction. The modern definition of a catalyst was given by Wilhelm Ostwald in 1894: *A catalyst is a substance that changes the rate of a reaction without itself appearing in the products*. For his pioneering work in systematically examining and understanding catalytic processes, Ostwald was awarded with the Nobel Prize in Chemistry in 1909. He was followed by many other Nobel laureates contributing to the field of catalysis, for example Haber (1918), Bergius and Bosch (1931), Natta and Ziegler (1963), Fischer and Wilkinson (1973), Knowles, Noyori and Sharpless (2001), Chauvin, Grubbs and Schrock (2005) and, most recently, Ertl (2007).

A catalyst has influence on the kinetics of the reaction but not on the thermodynamics; it does not change the reaction equilibrium. Thus, it is impossible to enable a thermodynamically disfavored reaction by adding a catalyst. The reason for the efficiency of a catalyst is its capability to decrease the activation energy of a reaction. In general, for every chemical reaction to proceed a certain quantity of activation energy is needed; this energy can also be described as the difference of the free enthalpy of the substrate and the free enthalpy of the transition state ($\Delta G^{\ddagger}$). For some reactions this ‘barrier’ is very high; they are kinetically blocked or slowed down and can not be observed to a significant extend even if they are thermodynamically favored. Now, a catalyst can provide an alternative reaction mechanism involving a different transition state and lower activation

energy. This transition state can constitute a complex **AC** of the substrate **A** and the catalyst **C** (Scheme 1).



Scheme 1: The princple of catalysis.

The complex reacts with substrate **B** to give the product **D** while releasing the catalyst **C**. This sequence consisting of the generation of the substrate-catalyst-complex, the product formation and the release of the catalyst is called a catalytic cycle. After the catalyst is released, it can reenter the cycle. As an important consequence, only small amounts of catalyst are needed for enabling a reaction; theoretically, it is possible to convert all starting material molecules with the help of just one catalyst molecule. However, the probability of the reaction of a substrate molecule and a catalyst molecule in a certain reaction volume increases with the number of catalyst molecules (so-called active centers) being present in this volume. Moreover, catalysts are often deactivated over the course of the reaction due to side reactions or degradation processes and are then not able to take part in the catalytic cycle again. Hence, the productivity of a catalyst can be displayed by the number of cycles each catalyst molecule is going through, till it is deactivated or the reaction is finished. This turnover number (*TON*) equals the ratio of the substrate concentration to the active catalyst concentration; referring to the turnover per unit time, the term of turnover frequency (*TOF*) is used. Substances, which are directly converted into the catalytically active species, are called precatalysts; those compounds are often easy to store.

Catalytic processes can be divided into three different parts depending if the substrate(s) and the catalyst exist in the same phase or not. If they are present in the same phase, the term *homogeneous catalysis* is used. In most cases, the catalyst and the substrate are dissolved in a liquid phase, in which the reaction takes place. In *heterogeneously catalyzed reactions*, the catalyst exists in a different phase than the substrate(s), mostly in the solid phase. Herein, the active centers of the catalyst are dispersed over the surface of solid material, which is often just supporting material but has no catalytic activity on its own. The substrates exist in the liquid or gas phase; they diffuse to the surface of the catalyst and adsorb onto it in order to react. After the reaction, the products have to desorb from the surface and diffuse back into the origin phase, so that the catalyst can enter a

new catalytic cycle. Often, these not chemical but physical reaction steps are rate-determining for the whole reaction. The third part of catalyzed reactions constitutes the transformations promoted by biomolecules, namely enzymes. Thus, nature can be considered as the world's leading catalyst designer providing the most selective, active and complex catalysts. *Biocatalysis* is often defined as a 'blend' of homogeneous and heterogeneous catalysis; especially enzymes are macromolecules, and therefore it is sometimes difficult to decide whether they are in the same phase as the substrates or not.

Catalysis is a main issue for both academic research and chemical industry. Today, in the manufacture of over 80 % of the chemical products at least one catalytic step is involved.[1] Especially heterogeneous catalysis plays an important role since 75 % of all catalytic processes are heterogeneous. In fact, the most widely used industrial catalysts are inorganic solids, e.g. metals, metal oxides, or metal sulphides, which are sometimes used in combination of each other.[2] In commodity chemical production, where often drastic reaction conditions are required in order to convert the natural occurring substrates to basic chemicals, thermal stable and easy-to-recycle catalysts are generally used. Most prominent examples including heterogeneous catalysts are the synthesis of ammonia promoted by alkali metal supported iron catalysts (Haber-Bosch-process), the V_2O_5-catalyzed SO_2 oxidation in the production of sulphuric acid (contact process) and elementary processes in petrol chemical refinement like hydrocracking.

With respect to stability, cost, and the ability of being recycled, heterogeneous metal catalysts have advantages compared to their homogeneous counterparts. However, being less selective, for many applications they are not suitable. The construction of complex molecules possessing various functional groups, for instance, requires mild reaction conditions, selective reagents and therefore often selective catalysts. A homogeneous catalyst may be able to be active at low temperature and promote one specific transformation on such a molecule, neglecting other reaction pathways. Therefore, homogeneous catalysts find their application in fine chemical industry and pharmaceutical industry rather than heterogeneous ones. The fact that they are often less cost-efficient is carrying less weight for these applications, since the products are more valuable than bulk chemicals.

It is important to note that the discovery of a new catalytic transformation is followed by new possible synthetic routes to molecules of commercial interest. Often, these new pathways exclude the usage of highly reactive and therefore hazardous reagents needed in the former procedures. Moreover, with the help of catalysis, fewer steps are required to

get to a target molecule by enabling the reaction of former relatively inert substrates. In general, catalytic reactions proceed at milder conditions, produce less waste, and are less energy and time-consuming than their stoichiometric analogues.

1.2 Homogeneous Catalysis

Brønsted acids are 'classic' homogeneous catalysts. Two of the first discovered acid-catalyzed reactions were the cleavage of glycogen to give glucose discovered by Parmentier in 1781, and the formation of esters from carboxylic acids and alcohols in the presence of acid (Scheele 1782). A particular example for *Brønsted acid catalysis* in current industrial chemistry is the usage of hydrogen iodide as co-catalyst in the Monsanto-process for the production of acetic acid.[3]

In contrast to inorganic salts and acids, the catalytic potential of small organic molecules was revealed in small steps. The Hajos-Parrish-Eder-Sauer-Wiechert reaction, independently developed by two industrial groups in the early 1970s,[4] was an exceptional effective organo-catalyzed transformation. The whole area of *organocatalysis* took then a remarkable development in the early 2000s.[5] In particular, many efficient methods to generate chrial building blocks *via* asymmetric organocatalysis have been developed. It is undeniable that organocatalysis has become an interesting counterpart to metal catalysis during the last decade.

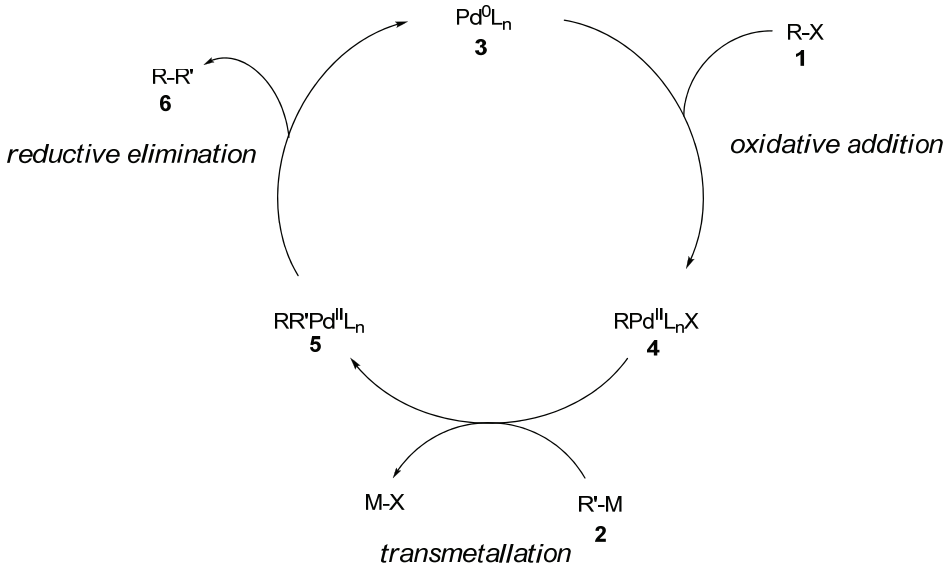
On the other hand, *homogeneous metal catalysis* is established since centuries. The field may be divided into metal complex-catalyzed reactions and those catalyzed by Lewis acids. Metal cations and metalloid-based Lewis acids are commonly used homogeneous catalysts, which is exemplified by the versatility of Friedel-Crafts chemistry.[6] Ethylbenzene, which world production capacity is estimated to ca. 27 megatons per year (Mt/a), is commercially manufactured by $AlCl_3$/HCl-catalyzed alkylation of benzene with ethylene. Similarly, cumene, a major intermediate to phenol, is formed by reaction of propylene and benzene with a world capacity of ca. 10 Mt/a. Despite the fact, that both procedures are nowadays more or less replaced by heterogeneous methods like the usage of zeolithes, they still constitute one of the few metal-catalyzed processes involving a non-transition metal in homogeneous media where conventional chemistry has been transferred to a large commercial scale.[7] On the contrary, the application of transition metals, especially of transition metal complexes, has indeed become the largest sector of homogeneous catalysis.[8] It was basically initiated by three industrial processes

developed during the time from 1930-1960. The first to mention is the so-called oxo-process invented by Roelen in 1938.[9] It represents the $Co_2(CO)_8$-catalyzed conversion of an alkene with synthesis gas to an aldehyde, and is also known as the hydroformylation reaction. Today, hydroformylation is conducted with the more active but more expensive Rh instead of Co.[10] The second milestone in the evolution of transition metal complex catalysis was the invention of Ziegler-Natta catalysts, a combination of Et_3Al and $TiCl_3$ or $TiCl_4$ in 1955; it was used in the polymerization of polyethylene and isotactic polypropylene, respectively.[11] Third, the establishment of the Wacker process constituting the first industrial application of a homogeneous Pd catalyst.[12] Interestingly, it had been known since 1894 that ethylene can be oxidized to acetic acid in the presence of stoichioimetric amounts of $PdCl_2$.[13] The crucial point was to find a way to regenerate the Pd^0 species to the active Pd^{II} species in order to make the reaction catalytic. Now, in the Wacker process, developed between 1957 and 1959 by Wacker and Hoechst, $CuCl_2$ was added as an oxidant enabling the conversion of Pd^0 back to Pd^{II}. The Pd^{II} species can enter the catalytic cycle again, while the Cu^I species is oxidized by molecular oxygen. After reaching his maximum production capacity in the mid 1970s, the importance of the Wacker process as a method to synthesize acetic acid decreased with the upcoming Monsanto-process. Nevertheless, the Wacker process can be seen as a starting point for the industrial application of homogeneous Pd catalysis. Before that, palladium was used in the first place as a part of heterogeneous catalysts promoting hydrogenations, for example of carbonyl compounds.[14] But from that point on, homogeneous palladium catalysts became more and more attractive for both industry and academic. In the 1960s, on the basis of mechanistic considerations of the Wacker process, the first Pd-mediated C–C coupling processes were developed, namely the stoichiometric versions[15],[16] of the Tsuji-Trost reaction and the Heck-Mizoroki coupling. First Pd-catalyzed carbonylations were also conducted during that time.[17] After the birth of the Heck-Mizoroki reaction,[18],[19] the application of palladium compounds as homogeneous catalysts in C–C cross couplings started to evolve in the mid 1970s. First systematic studies were conducted by Negishi *et al.*,[20] while standard protocols of nowadays famous coupling reactions involving tin[21] and boron[22] were established in 1978 and 1979, respectively. Today, homogeneous Pd-catalyzed cross-coupling reactions are standard methods in forming carbon-carbon or carbon-heteroatom bonds. With respect to these reaction types, but also other efficient applications of palladium, the synthetic value of this metal can be considered as exponentiated since its discovery.

1.3 The Role of Palladium in Homogeneous Catalysis

Palladium was discovered in 1803 by Wollaston and is named after the asteroid Pallas. Although palladium is a rare[23] and therefore expensive metal, its chemistry is part of modern organic synthesis. It is almost impossible not to find a publication incorporating palladium chemistry in the latest issues of journals presenting organic chemistry, homogeneous catalysis or related topics. There are different reasons for the applicability of palladium in transition metal catalysis; all of them are based on the size and the electronic configuration of this metal.[24] Palladium possesses the atomic number 46 and is therefore on the one hand part of the second row transition metals, on the other hand part of the Ni triad. While Ni complex-catalyzed reactions are often single electron transfer processes sometimes lacking selectivity, the stability of Pt complexes, mostly Pt^{IV} octahedral ones, is often too high and therefore incapacitating them as (pre)catalysts. In the case of palladium, activity and stability are obviously quite balanced. The metal favours the oxidation states 0 and +2; as it was already depicted in the description of the Wacker process, one form can be easily converted to the other in the presence of a proper oxidant or reducant, respectively. This has two consequences: first, the easy switch between the two oxidation states guarantees the (re)creation of an active species and therefore the establishment of a catalytic cycle. Second, by not being involved in single electron transfer and radical processes, palladium catalysts can provide high chemoselectivities. Another important feature is palladium's relative high electronegativity of 2.20 (according to Pauling).[25] Consequently, Pd–C bonds are quite unpolar, and organopalladium complexes are relatively stable. As a late transition metal, palladium is able to form d^8 and d^{10} complexes. With this high d-electron count and the low oxidation states, compared with the moderate size, the metal can be considered as 'soft'. Because of its tendency to form coordinatively unsaturated species, palladium can provide at least one empty and one filled non-bonding molecular orbital. Thus, it possesses a high affinity towards nonpolar π-compounds (alkenes, alkynes) and forms at the same time readily σ-bonds with n-donors like phosphines. Taking these points into account, it may become understandable why palladium complexes are frequently used and established as efficient catalysts. Especially in promoting the formation of C–C bonds, palladium catalysts have an extraordinary high potential. Next to the telomerisation reaction,[26] the Tsuji-Trost reaction[27] and Heck-type couplings, the field of palladium-catalyzed cross-couplings represents the most important type herein. In general, C–C cross coupling can be understood as the metal-catalyzed reaction of organic halide or

pseudohalide R–X **1** (R = alkyl, alkenyl, alkynyl, aryl; X = Cl, Br, I, N_2^+, COCl, SO_2Cl, $CO_2C(O)R$, OSO_2R_f, OMs) and an organometallic compound R'–M **2** (R' = alkyl, alkenyl, alkynyl, aryl) resulting in the generation of a new C–C bond present in the product R–R'. Cross-couplings are mainly catalyzed by Ni, Cu, and Fe next to palladium. A simplified catalytic cycle of a palladium mediated C–C cross-coupling reaction is depicted in Scheme 2.



Scheme 2: Catalytic cycle of a Pd-catalyzed C–C cross-coupling.

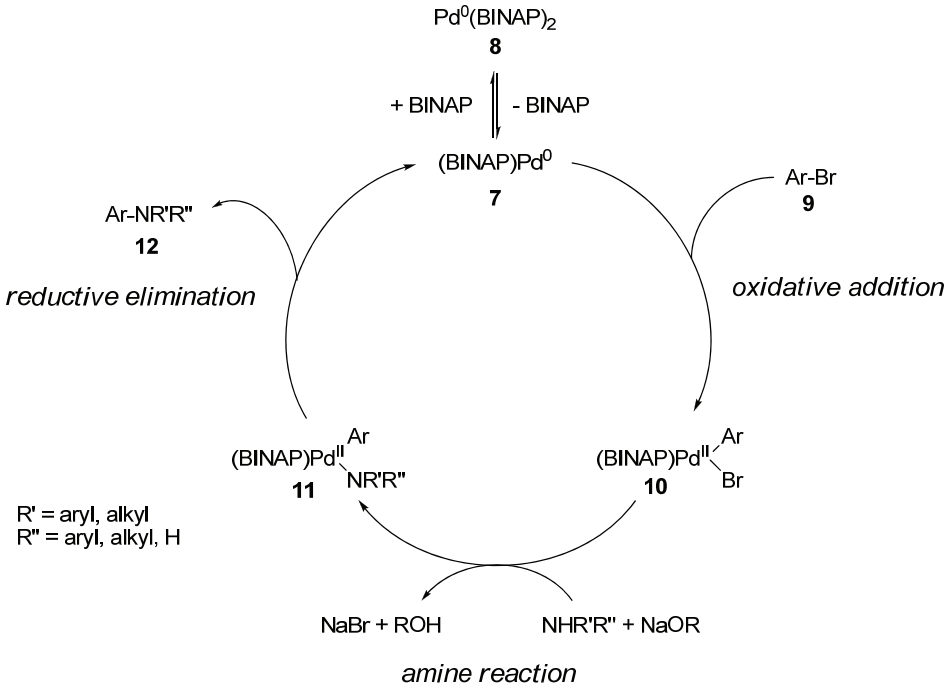
The active Pd^0 species **3**, in most cases supported by a number n of ligands L, is generated from a Pd^{II} or Pd^0 precatalyst.[28] This formation is not fully understood in most reactions, especially if it occurs *via* reduction from Pd^{II} precatalysts. Sometimes, there are various possible reductants of Pd^{II} in the reaction mixture of palladium-catalyzed cross-coupling reactions: phosphines (applied as ligands), amines (substrates, products, and bases), and ethers (products, solvents). The Pd^0L_n species enters the catalytic cycle as it reacts with the organic halide **1** *via* oxidative addition to give the $RPd^{II}L_nX$ complex **4**. The oxidative addition is a typical reaction of transition metal complexes, in which the formal oxidation state of the metal is increased after the reaction of the complex with a substrate molecule. While the reaction occurs, substrate bonds are often cleaved (as in the cross-coupling) but not in general (e. g. as in oxidative cyclizations). The oxidative addition is facilitated, if a high electron density is present on the metal centre and σ-donor ligands are attached to it, while π-acceptor ligands on the metal suppress the reaction. For cross-couplings and similar reactions, the use of electron rich phosphines as ligands has turned out to be effective. It is important that the catalyst complex possesses free coordination sites; in Pd-

catalyzed cross-couplings, 14-electron and 12-electron complexes are discussed as active catalysts.[29] With respect to the organic halide, the oxidative addition becomes faster with decreasing C–X (X = I, Br, Cl) bond dissociation energy *DE* ($DE_{CCl} > DE_{CBr} > DE_{CI}$): while aryl iodides ($DE_{CI}$ ca. 51 kcal/mol) react readily to give oxidative addition complexes, there were only a very few examples of the activation of aryl chlorides (DE_{CCl} ca. 81 kcal/mol) by Pd^0 species ten years ago. On the other hand, the rate of oxidative addition is decreased by high electron density on the C–X carbon atom; aryl halides bearing electron-donating groups ('deactivated' aryl halides), for instance, react slower than aryl halides with electron-withdrawing groups ('activated' aryl halides). In analogy to that, alkyl halides are generally less reactive in oxidative additions than substrates bearing a $C(sp^2)$–X bond like aryl and vinyl halides.

As the subsequent step to the oxidative addition in the catalytic cycle the so-called transmetallation occurs. Basically, transmetallation is known as the transfer of an organic group (or a hydride) from one metal centre (mostly a main group metal) to another (mostly a transition metal). The driving force for this transformation is the difference in the electronegativities of the involved metals as the main group metal is normally more electropositive than the transition metal. In Pd-catalyzed C–C cross-coupling reactions, organometallics based on various metals have been applied as nucleophiles. These metals include magnesium (Murahashi coupling),[30] boron (Suzuki-Miyaura coupling),[22] tin (Stille coupling),[21] zinc (Negishi coupling),[20] copper (Sonogashira-Hagihara coupling)[31] and silicon (Hiyama coupling)[32] among others. From the $RR'Pd^{II}L_n$ complex **5**, the catalytic species Pd^0L_n is regenerated by reductive elimination of the coupling product **6**. Reductive elimination from a transition-metal complex can only occur if the moieties being eliminated are *cis* to each other; therefore, the transmetallation is often followed by an isomerisation step in the case of monodentate ligands. Bidentate ancillary ligands, for example bisphosphines force the two other ligands bound to Pd^{II} in *cis* coordination and are therefore known to accelerate reductive elimination per se. π-Acceptor ligands also support reductive elimination in accordance to the fact, that the back reaction of a reductive elimination is always an oxidative addition and *vice versa*. However, reductive elimination of $C(sp^2)$ carbons is faster than of $C(sp^3)$; thus, the cross-coupling of alkyl halides is difficult with respect to oxidative addition as well as with respect to reductive elimination. In complexes with ligands bearing *β*-hydrogens, the transfer of a *β*-hydride to the palladium centre competes with the reductive elimination of the coupling product. This so-called *β*-hydride elimination and the insertion of an alkene

into a metal hydride are reversible steps. Again bidenate ligands, but also very bulky monodenate ones can effect the suppression of *β*-hydride elimination *via* acceleration of the competing reductive elimination. Pd-catalyzed C–C cross couplings are generally performed under basic conditions.

In reactions strongly related to the palladium-catalyzed C–C cross coupling, similar reaction mechanisms and catalytic cycles are proposed. The catalytic cycle of the so-called Buchwald-Hartwig[33] amination with BINAP in the presence of an alkoxide base was proposed by Blackmond, Buchwald, Hartwig *et al.* in 2006[34] and is shown in Scheme 3. The catalytically active species **7** herein is a Pd^0 complex with a single 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (BINAP) ligand generated from a catalytically inactive bisligated species **8**. Oxidative addition occurs in analogy to the C–C cross-coupling. Now, the oxidative addition complex **10** reacts with an amine in the presence of base to give the amido complex $ArPd^{II}(BINAP)NR'R''$ **11**, which then reductively eliminates the arylated amine **12** under regeneration of **7**.



Scheme 3: Catalytic cycle of a Buchwald-Hartwig amination with BINAP.[34]

The Buchwald-Hartwig amination follows roughly the same principles as Pd-catalyzed C–C cross-couplings. Therefore, similar reaction conditions (solvents, bases, ligands, Pd-sources) have been successfully applied. However, it can be stated, that reductive elimination of the C–N coupling product from an amido complex is generally considered to be slower than a C–C coupling product from the corresponding complex. The choice of

base is crucial: for instance, it has been found, that the application of strong bases likes NaO*t*-Bu in the arylation of pyrrols and related compounds hamper the coupling reaction while generating high concentrations of azolyl anions, which form catalytically non-active, anionic complexes with Pd^0.[35]

In analogy to the Buchwald-Hartwig amination, Pd-catalyzed cross-coupling with O-nucleophiles[36] is possible giving access to aryl-aryl ethers, alkyl-aryl ethers and phenols. However, those reactions have not attracted as much attention as Pd-catalyzed C–N couplings. This is on the one hand due to the fact, that the coupling products are of less commercial interest, on the other hand especially C–O bond formation is more difficult to achieve for several reasons. In particular, the reductive elimination of a coupling product from an oxido-complex is even slower than from the analogue amido-complex. That is why *β*-hydride elimination as a side reaction is often an issue in the coupling of aryl halides with secondary alcohols, for instance.

Several investigations have been undertaken in order to shed light on the mechanisms of palladium-catalyzed bond forming processes.[37] These include the isolation and characterization of possible organometallic reaction intermediates or resting states,[38] DFT calculations[39] as well as spectroscopic and electrochemical methods.[40] Although much data was collected in the past decade, a lot of questions remain unanswered. For most reactions, the active catalytic species is only proposed but not identified. The interaction of metal and ligand as well as the coordination number of the active species play an important role. Even though the active complex may be monomeric and may contain only one ligand, e.g. a bulky monophosphine, a two-fold or even higher ratio of ligand to palladium may have to be applied to the reaction mixture. Another problematic issue is the prediction of the rate-determing step of the overall coupling reaction. Moreover, there are a number of factors having influence on the transformation including solvents, bases, additives, etc., which have to be examined. These are the reasons why mechanistic work will remain the fundament of all Pd catalysis research. The ‘understanding’ of a Pd-catalyzed bond formation process may lead to higher efficiencies of its applications in both industrial and academic surroundings.

1.4 Industrial Applications of Pd-catalyzed C–C and C–N Bond Formations

On laboratory scale, palladium-catalyzed coupling processes in homogenous media have become an indispensable tool for synthetic chemists.[41] Particularly, in natural product synthesis and for the preparation of versatile organic building blocks, Heck-Mizoroki reactions, C–C cross-couplings and C–N cross-couplings (Buchwald-Hartwig aminations) are now state-of-the-art methods.[42] The reasons for that are obvious: Most of these transformations make use of easily available substrates and allow for shorter and more selective reaction sequences to substituted arenes and alkenes compared to non-catalytic, classic pathways. In addition, they are predictable and offer high chemoselectivity, and broad functional group tolerance. Furthermore, the versatility of palladium catalysts is depicted by its application in various reaction types besides C–C and C–N cross-coupling including carbopalladation, hydrogenation, carbonylation, isomerisation, etc. Considering these facts, it is not surprising that several examples of Pd catalysis have been implemented in the last decade into the industrial manufacture of pharmaceuticals and fine chemicals.

As metal for cross-coupling processes, palladium competes strongly with non-precious metals like copper,[43] nickel,[44] and, more recently, iron.[45] Even though nickel,[46] copper[47] and more important iron, are truly more cost-effective, the advantages of palladium-catalyzed bond formations remain. Noteably, palladium catalysts generally possess a much higher activity than their metal competitors enabling the conversion of less reactive substrates,[48] the performance at relatively low temperatures[49] and catalyst turnover numbers (TONs) up to 10^6.[50]

Despite the vast number of applications of homogeneous palladium-catalysts on laboratory scale and the widespread research interest concerning this issue, comparably few industrial applications have been realized since now.[51] The main reasons for this discrepancy are on the one hand the high costs of palladium and its compounds, on the other hand the constraints concerning the content of ‘heavy metals’ like palladium in pharmaceutical products. Therefore, when using catalytic methods based on palladium (or transition metals with comparable economic and ecologic properties) in fine chemical industry, specific points have to be considered: (a) the *productivity* of the catalyst system, (b) its *activity*, (c) its *selectivity*, and finally (d) the *contamination* of the product with metal and ligand.[52] As a rule of thumb for the production of fine chemicals, catalyst

TONs of ca. 1000-10000 are needed if the catalytic route should be competitive with established non-catalytic ones.[53] Assuming an hypothetical organic product in fine chemistry (e.g. intermediate for an active pharmaceutical ingredient (API), food additive, fragrance, dye, etc.) with an molecular weight of 200 g/mol palladium costs are in the range of $ 3 per kg product (TON = 1000).[54] If the output of this product would be 10 t/a[55] at a total production cost of $ 1000 per kg, the cost of the pure palladium in this process will be $ 3000 per year, that means only 0.3 % of the total production costs. Nevertheless, besides the palladium there are the expenses for the ligands, which are often sophisticated (e.g. for asymmetric synthesis) and therefore more expensive than the precious metal itself.[56]

The second point which has to be taken into account is the activity of the catalytic system: Here, fine chemical production is believed to require palladium catalysts with turnover frequencies of 200-500 h^{-1}. In an ideal process, these numbers should be achieved by stable catalyst systems with long persistence; consequently, when designing a catalyst, a perfect balance between activity and stability has to be found.

In general, the selectivity of the Pd catalyst is also of significant importance: Still, the synthesis of pharmaceutical intermediates causes large amounts of by-products (up to 100 kg per kg of product). Therefore, from an economical as well as an ecological point of view, the transition of not only active but also selective catalytic methods to industrial application is necessary.

The contamination of the product with ligands and the metal is a problematic issue, especially in the case of pharmaceuticals. Usually, the amount of heavy metal in an API has to be controlled to levels below 10 ppm.[57] If higher, recycling strategies of the catalyst have to be developed,[58] which again produce costs. Recent approaches including nanofiltration,[59] the application of temperature depending multi-component solvent systems (TMS-systems)[60] or switchable-polarity solvents (SPS)[61] are fascinating from the academic point of view, but not yet readily developed to be part of industrial processes. In cases where it is either unwanted or impossible to recycle the Pd-catalyst, scavenging methods constitute an effective tool for an efficient removal of palladium from post reaction solutions.[62] Problems can arise not only from API-palladium and API-adsorbent binding, but also from strong interactions of the palladium to its ligands or to other additives. Through these stabilizing effects it is possible that the Pd may remain in solution rather than being adsorbed.[63] This disadvantage of ligand (especially phosphine) supported Pd catalysis is also an issue

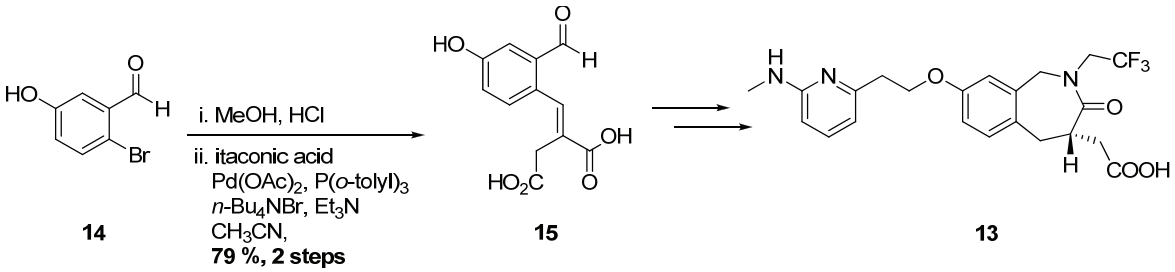
concerning other separation methods, e.g. filtration. To circumvent this, so called 'ligand-less' palladium systems are used: an active Pd^0 species is not surrounded by ancillary ligands such as phosphines, but aggregated as small colloids dispended in the reaction media.[64] Recovery of the pure noble metal is more feasible compared to the recycling of ligand-containing palladium catalysts.[65] The main disadvantage of these procedures is the short lifetime of the catalyst tending to further aggregate and form inactive 'Pd-black';[66] the higher the Pd load is, the faster the deactivation relative to the catalytic process occurs. Moreover, for challenging substrates like aryl chlorides or alkyl halides ligands are urgently required. Especially the use of bulky, electron-rich monophosphines[67] has significantly contributed to the success of cross-coupling and opened the way to new concepts in the construction of complex molecules. On the other hand, for the conversion of simple, active substrates, 'ligandless' approaches can very attractive for industry by reducing costs dramatically. It is also possible to stabilize the Pd colloids with additives tetraalkylammonium salts,[68] organic carbonates,[69] etc. in order to increase the lifetime of the catalyst.[70]

In summary, a Pd-catalyzed reaction has to comply with a lot of conditions in order to become part of an industrial process. In the following chapters different Pd-catalyzed coupling reactions are highlighted. All of them were run on kilogram scale by chemical companies, but only a few were commercialized in the end.

1.4.1 Heck-Mizoroki Reactions

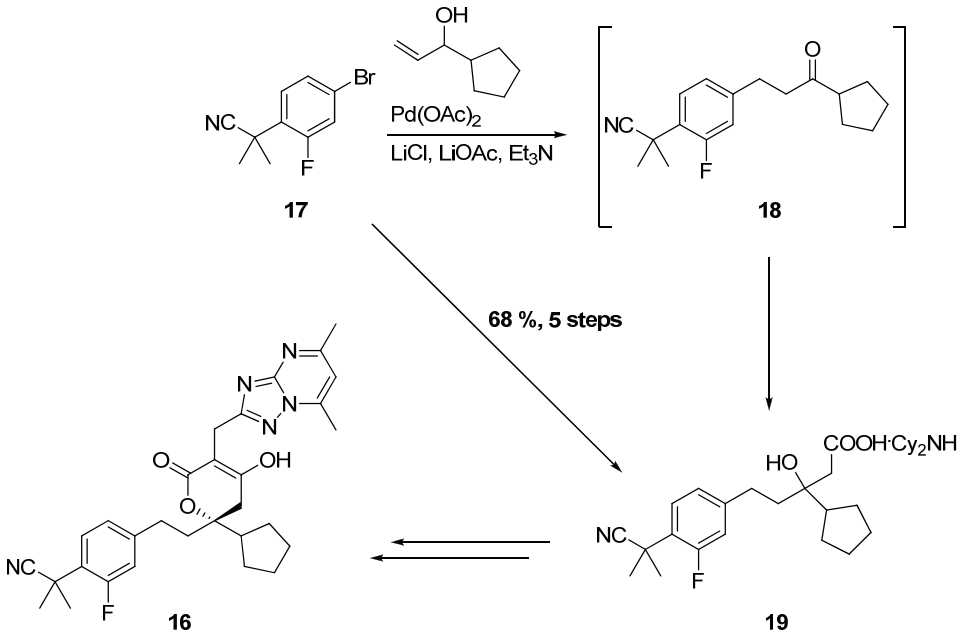
As mentioned above, the Pd-catalyzed vinylic substitution reaction in which vinylic hydrogen is replaced by an aryl, alkenyl, or benzyl moiety is known as the Heck-Mizoroki (H-M) reaction. It was independently discovered by Mizoroki and Heck in the early 1970s.[18],[19] Today, the Heck-Mizoroki reaction is probably one of the best investigated and most frequently applied Pd-catalyzed coupling reactions.[71] The efficiency of the H-M reaction is pictured not only by numerous contributions of research groups and the widespread small-scale applications, but also by some industrial applications[72] including the manufacture of the herbicide Prosulfuron (Ciba-Geigy, Novartis),[73] the anti-inflammatory drug Naproxen (Albermarle, Hoechst AG),[74] the asthma drug Singulair (Merck),[75] the 5-$HT_{1D\text{-like}}$ partial antagonist Eletriptan (Pfizer),[76] and the production of high-purity 2- and 4-vinyltoluenes as co-monomers for styrene polymers (Dow chemicals).[77] During the last eight years, the fine chemical industry continued spending effort in the development of kilogram applications of this powerful

C–C bond formation method. As an example in 2004, researchers at GlaxoSmithKline reported the multikilogram-scale synthesis of the Vitronectin receptor antagonist SB-273005 (**13**) including the coupling of itaconic acid with 4-bromo-4-hydroxybenzaldehyde (**14**) as a key step (Scheme 4).[78] Because of an intramolecular aldol side reaction, the H-M coupling was not performed directly with **14**, but after treatment with catalytic amounts of acid in methanol, with the corresponding dimethylacetal yielding 61 kg of product **15** (79 %). It was pointed out by the authors, that this synthesis is the first example of an H-M coupling of itaconic acid with a structural complex aryl bromide such as **14**.



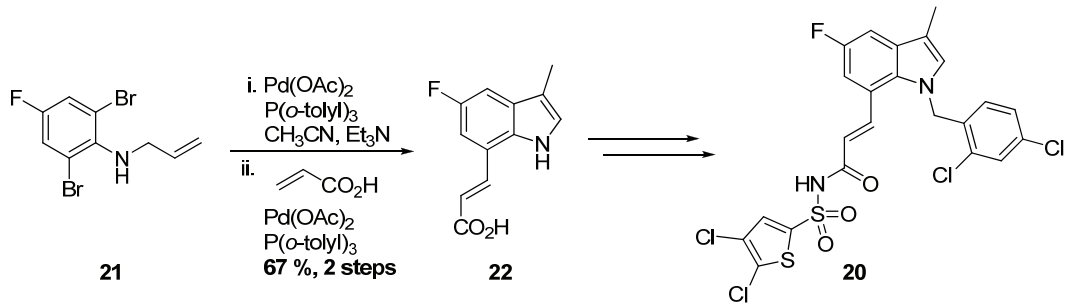
Scheme 4: H-M reaction on the way to SB-273005.

Scott and co-workers from PfizerGlobal R&D developed a valuable synthetic process for hepatitis C polymerase inhibitor **16** on kilogram scale (Scheme 5).[79] The initial synthesis, patented in 2004, contained a Sonogashira coupling, which was quite effective.[80] However, the whole process did not make the transition to large-scale manufacture because of the instability of the alkyne intermediate produced during the cross-coupling reaction. In the new alternate route, the H-M coupling was performed instead of the alkyne transformation: Bromide **17** was reacted with an allylalcohol in presence of $Pd(OAc)_2$, LiCl and triethylamine (Et_3N).



Scheme 5: Phosphine-free Heck coupling in the synthesis of **16**.

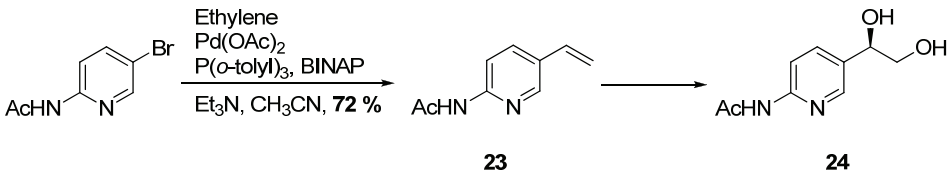
Interestingly, the amine had to be dosed to slow down the reaction: The determination of a high adiabatic temperature rise caused the reaction to be modified. However, limitations of the amine concentration in the reaction mixture resulted in stability problems of the catalyst. To circumvent this, LiOAc was added as a co-base allowing the performance of the reaction on 40 kg scale. The oily product **18** was directly converted to **19** in 68 % yield over five steps. Another nice example for a large scale one-pot double H-M reaction was provided by Zembower *et al.* in 2007.[81] For the synthesis of the EP_3 receptor antagonist DG-041 **20** a double H-M reaction on **21** led to intermediate **22** (Scheme 6). The one-pot procedure gave ca. 1 kg of the desired product in acceptable yield using $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ for both transformations.



Scheme 6: Synthesis of DG-041 intermediate **22** *via* double H-M reaction.

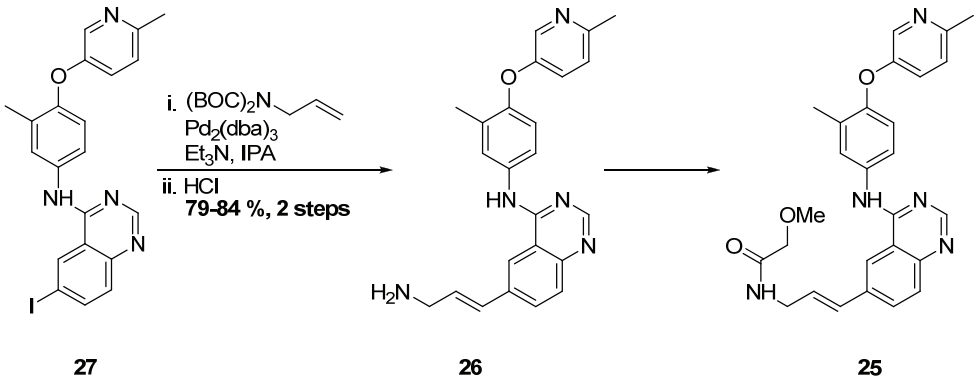
The introduction of ethylene into complex molecules through catalysis is a challenging issue for synthetic organic chemists. By using the relatively *rac*-BINAP ligand in

combination with $Pd(OAc)_2$ and P(*o*-tolyl)$_3$, an effective multikilogram-scale synthesis of **23** was realized at Pfizer laboratories (Scheme 7).[82] Sharpless dihydroxylation of **23** led to 2-acetamido-5-vinylpyridine (**24**), a key intermediate for their drug candidates.



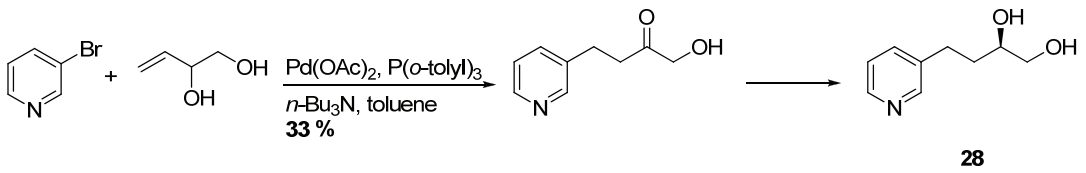
Scheme 7: H-M reaction with ethylene to give **23**.

On the route to oncology candidate CP-724,714 **25** different Pd-coupling strategies were investigated on pilot plant scale, including Heck couplings next to Suzuki and Sonogashira-type transformations (Scheme 8).[83] With respect to efficiency, safety issues and the amount of waste produced during the whole process, the so-called 'second-generation' H-M route remained superior among the others. With a Pd loading of 1 mol% ($Pd_2(dba)_3$ as catalyst precursor), 96 kg of product **26** were obtained by reacting **27** and BOC-protected allylamine with subsequent deprotection.



Scheme 8: 'Second generation' H-M route to CP-724,714.

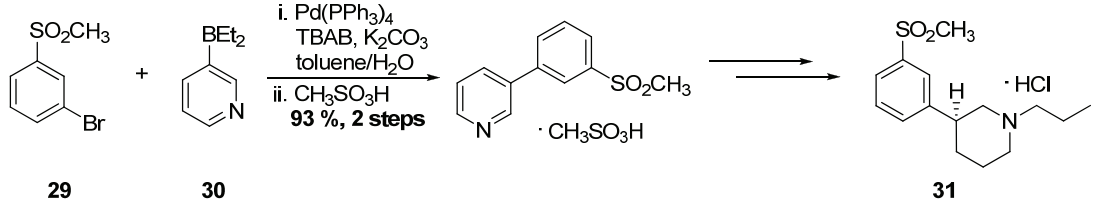
AstraZeneca developed in 2002 a manufacture route to their key intermediate **28** (Scheme 9). Here, the H-M coupling was performed in order to link the pyridine ring to a C_4 chain.[84] The authors reported an overall yield of only 33 % on a 3 kg scale, which was addressed to catalyst decomposition during the reaction. Despite the moderate yield, this synthesis constitutes an excellent example for the shortening of a synthetic route by application of catalytic methods. Instead of five steps with the former routes incorporating aldol and Wittig chemistry, respectively, it only takes two steps with this so-called third-generation route to obtain **28**.



Scheme 9: Synthesis of **28** by AstraZeneca.

1.4.2 Suzuki-Miyaura Reactions

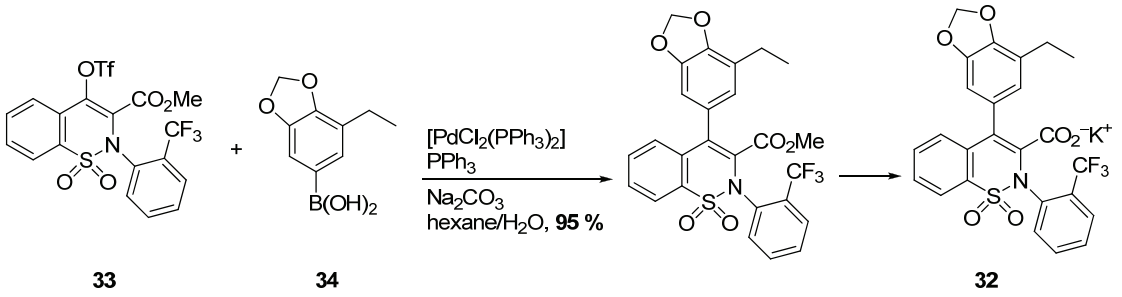
Next to the Heck reaction, Pd-catalyzed cross-coupling reactions of a boronic acids or esters with organic halides,[22] the Suzuki-Miyaura couplings,[85] have become a highly attractive tool for industrial chemists to use in fine chemical manufacture. Important industrial processes until 2001 were highlighted previously, including the synthesis of the important AT_2 receptor antagonist intermediate 2-cyano-4'-methylbiphenyl at Clariant,[86] the alternative route to Losartan developed by Merck in 1994,[87] and the production of non-linear optical (NLO) materials.[88] Since then, there is a continued interest in large scale applications of this practical coupling protocol. For example, researchers at Pharmacia Corporation, in collaboration with Dow, were able to scale up the Suzuki coupling of **29** with pyridine **30** in the synthesis of **31**, a potential CNS agent (Scheme 10). Problems aroused because a high palladium loading was needed for the reaction in a mixture of water and tetrahydrofurane (THF). However, optimization of the solvent system (toluene/water) allowed a significantly improved process with only 0.7 mol% of Pd catalyst. It was assumed that a less polar media is beneficial for the lifetime of the catalyst.[89]



29 **30** **31**

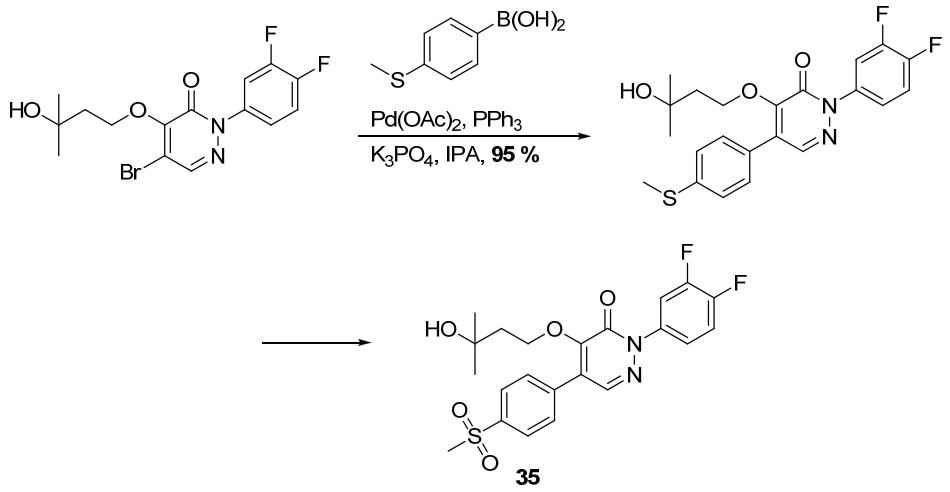
Scheme 10: OSU 6162-key intermediate synthesis *via* Suzuki coupling.

Due to the low atom efficiency of their transformations, triflates are rarely used in industrial coupling processes compared to aryl halides. Notably, Jacks *et al.* from Pfizer showed a reliable mulitkilogram-scale route to **32**, an Endothelin antagonist including a Suzuki coupling of triflate **33** with boronic acid **34** as a key step (Scheme 11).[90] Different surrogates for the triflate were also tested in the coupling; however, for their full conversion higher Pd loadings (>0.3 mol%) were required.



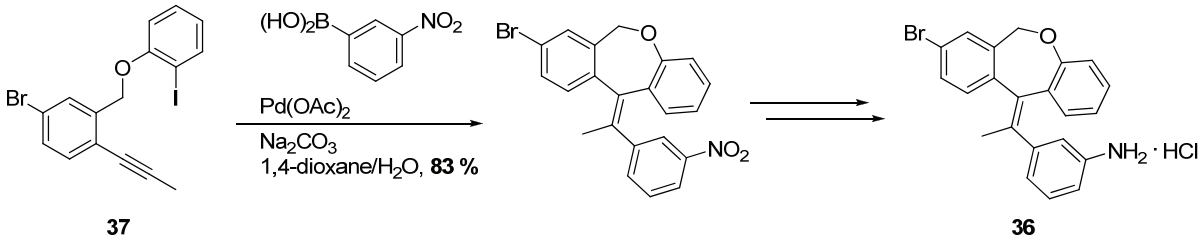
Scheme 11: Pfizers' route to Cl-1034 using Suzuki coupling.

Another multikilogram-scale Suzuki reaction was reported by Kerdesky *et al.*[91] ABT-963 **35**, a potent COX-2 inhibitor, was prepared in 36 % overall yield in four steps from commercially available materials. In step three the biaryl coupling proceeded smoothly by using a mixture of $Pd(OAc)_2$ and triphenylphosphine (Scheme 12). Palladium catalysts bearing other phosphine ligands, e.g. P(*o*-tolyl)$_3$ provided high yields at lower loadings. However, if working with these low loadings, higher temperatures and prolonged reaction times were needed in order to reach full conversion; therefore, PPh_3 remained the ligand of choice.



Scheme 12: Suzuki coupling in the preparation of ABT-963.

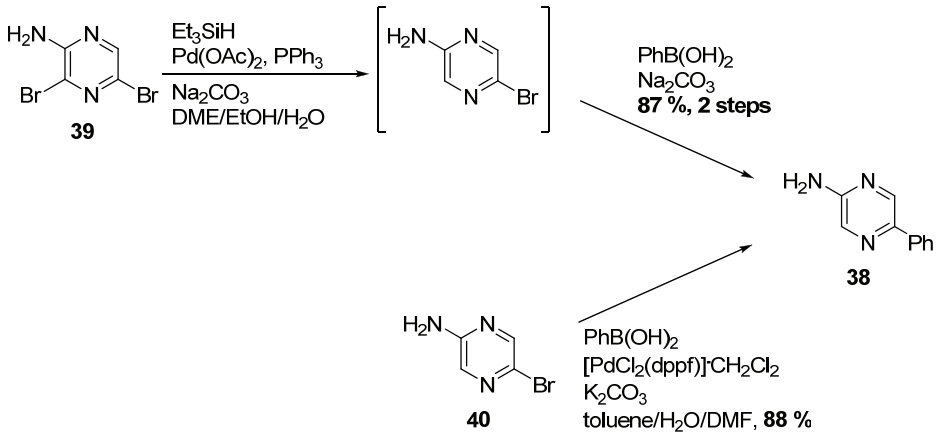
As part of cascade reactions, Suzuki couplings can play an important role for a quick and easy construction of more complicated target molecules. In this respect, a Pd-catalyzed alkyne carbometalation-Suzuki coupling cascade has recently been reported as part of a 2 kg-scale synthesis of dibenzoxapine **36** (Scheme 13).[92] This product **36** was described as a key intermediate on the route to selective nuclear hormone receptor modulators.



Scheme 13: Cascade reaction in the kg-scale manufacture of **36**.

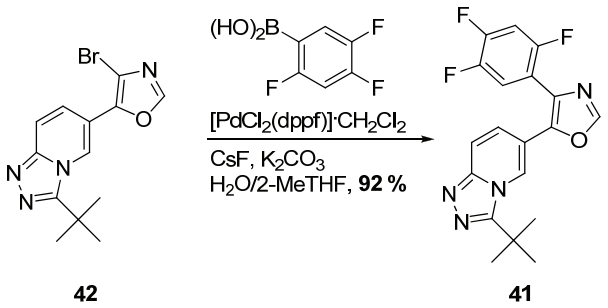
Applying only 0.1 mol% of $Pd(OAc)_2$, the reaction of iodide **37**with *m*-nitroboronic acid did not result in biaryl coupling but formation of the seven-membered ring in 83 %. The authors reported an overall yield of 48 % over five steps starting form commercially available material and a Pd content of <10 ppm in the final product.

An elegant one-pot synthesis incorporating two palladium-catalyzed transformations was described by Itho, Zhao, *et al*. (Scheme 14).[93] The synthesis of 2-amino-5-phenylpyrazine **38** a key intermediate of selective NPY-5 receptor antagonist, proceeded via reduction of dibromide **39** and subsequent Suzuki coupling. Alternatively, 2 kg of product **38** were obtained by coupling of the monobromide **40**. Notably, the bisphosphine 1,1'-bis(diphenylphosphino)ferrocene (dppf) was used herein as ancillary ligand.



Scheme 14: Alternative routes to **38**.

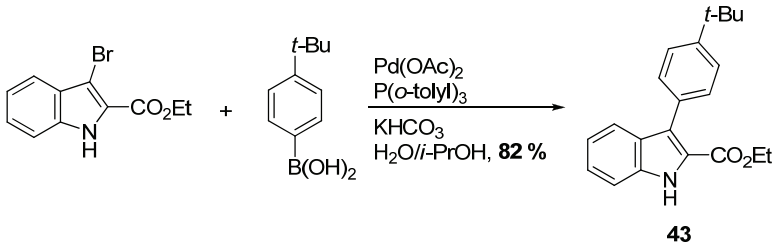
Another example for the use of dppf in a Suzuki coupling reaction on industrial scale is the manufacture of kinase inhibitor **41** at Pfizer's laboratories.[94] After regioselective bromination of the oxazole ring at the 5-position Suzuki coupling of **42** with 1,3,4-trifluorophenyl-6-boronic acid was performed successfully on 3-kg scale (Scheme 15).



42 41

Scheme 15: Synthesis of kinase inhibitor **41**.

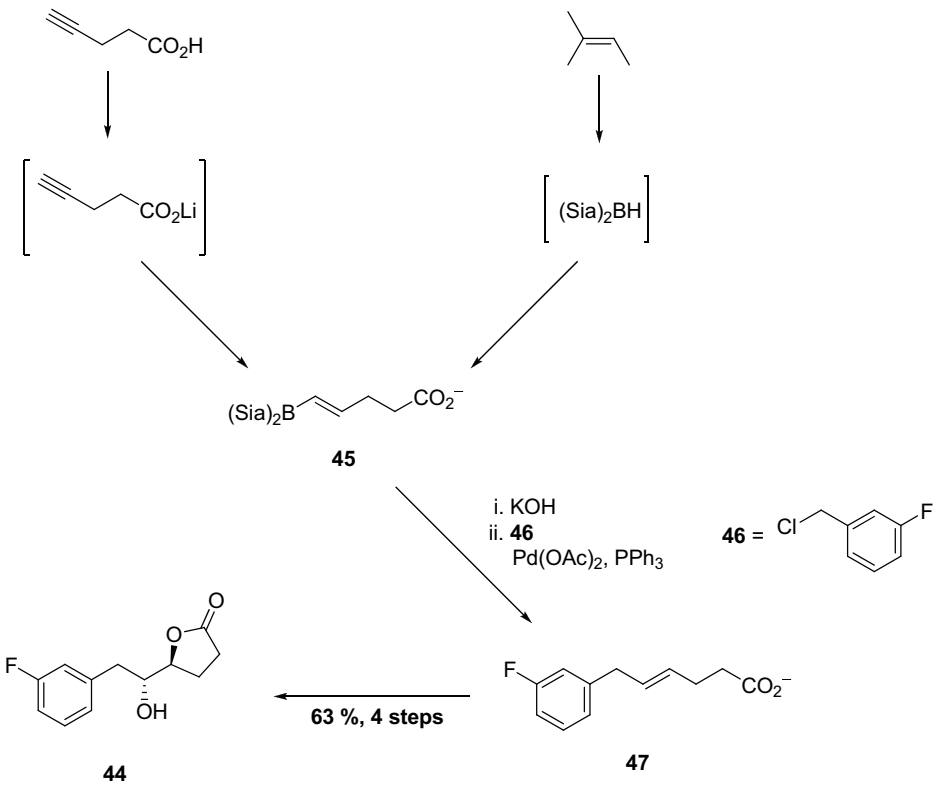
For the preparation of ethyl [3-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylate (**43**), researchers at GlaxoSmithKline[95] also chose dppf as ligand in the first place. However, the reaction had several drawbacks including a moderate yield, formation of the reduced indole in significant amounts, and high levels of residual phosphorus and iron in the final product. After an extensive ligand-solvent-base screening study, P(*o*-tolyl)$_3$ was identified as the most efficient ligand in combination with palladium acetate and $NaHCO_3$ as base. Followed by a palladium removal technique, the optimized reaction conditions were demonstrated successfully on 20-L scale yielding 82 % of pure product with 100 ppm residual palladium (Scheme 16).



43

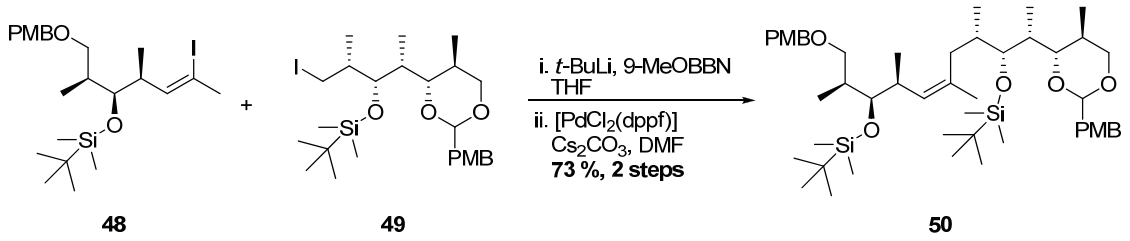
Scheme 16: Large-scale synthesis of **43** by GlaxoSmithKline.

The application of Suzuki protocols is not limited to the coupling of heteroaromatic aryl halides and aryl boronic acids or *vice versa*. The versatility of this reaction also allows the linkage of a C(sp^2)-center and a C(sp^3)-center, even on industrial scale. Ager and co-workers at DSM identified and developed an elegant method to produce large amounts of lactone **44**, a presursor to potential HIV drugs and blood pressure modulation agents.[96] On pilot plant scale, the disiamylborane **45** was reacted with 3-fluorobenzyl chloride (**46**) to give **47** using the 'standard' precatalyst $Pd(OAc)_2/PPh_3$ (Scheme 17). Then, the Suzuki coupling product **46** was transformed into **44** *via* organocatalytic Shi epoxidation.



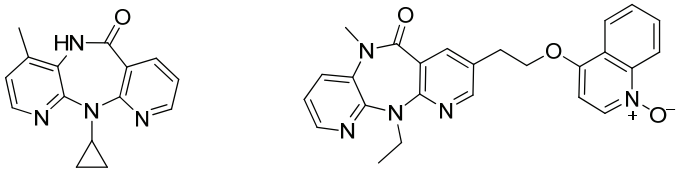
Scheme 17: Suzuki benzylation on the way to **44**.

In 2004, Mickel and co-workers from Novartis published together with colleagues from Cambridge University the large scale preparation of the $C_{7\text{-}24}$ fragment of the polyketide natural product (+)-discodermolide, which is a potent cancer cell growth inhibitor.[97] The linkage of the $C_{9\text{-}14}$ and the $C_{15\text{-}21}$ fragment was realized *via* Suzuki cross-coupling: Addition of a mixture of compound **48**, *t*-BuLi, and 9-methoxy-9-BBN to the alkyl iodide **49** in DMF containing 10 mol% of [$PdCl_2$(dppf)] catalyst and Cs_2CO_3 as base gave about 1 kg of olefin **50** (Scheme 18).



Scheme 18: Synthesis of the $C_{9\text{-}21}$ fragment of (+)-discodermolide.

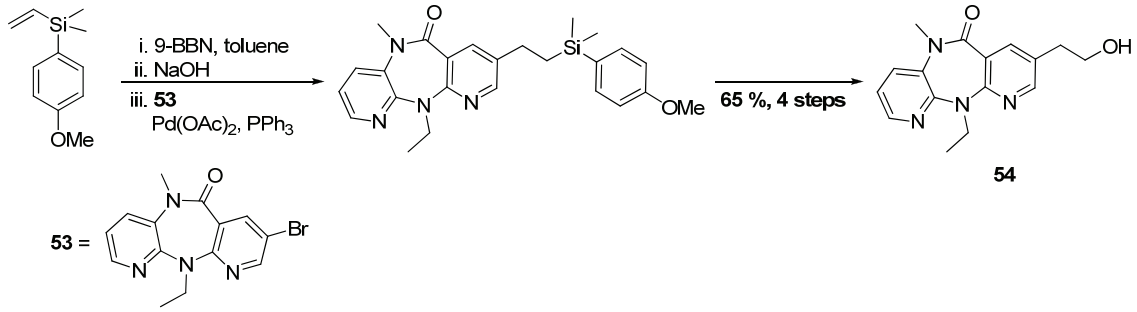
For the analogue **51** of Nevirapine **52**, a transcriptase inhibitor used for the treatment of HIV infection (Scheme 19), a pilot plant process was developed by Boehringer-Ingelheim.[98]



52 51

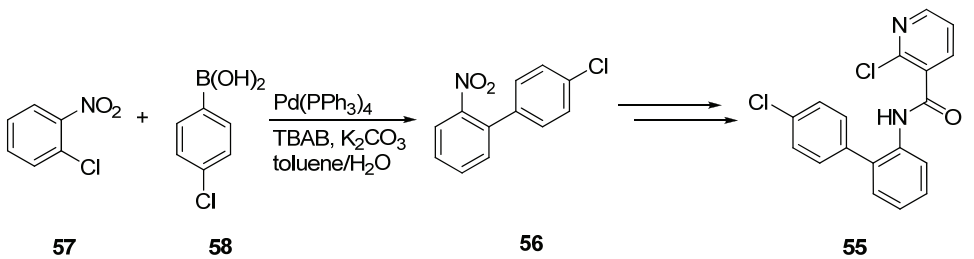
Scheme 19: Transcriptase inhibitors nevirapine and its analogue **51**.

Herein, three different routes were elaborated in order to couple an ethanol surrogate with bromide **53**, giving **54**, the direct precursor to the target molecule. Interestingly, for each route Pd catalysis was applied: Synthesis of **54** either proceeds by hydroboration/Suzuki chemistry (Scheme 20), malonate arylation or cyanoisopropylacetate arylation. The reaction of the malonate required a catalyst with bulky phosphine ligands like tri-*tert*-butylphosphine P(*t*-Bu)$_3$ or Buchwald's biaryl phosphines; unfortunately, those ligands were, despite their outstanding reactivity, not suitable for pilot plant use because of their high costs. In contrast to that, the hydroboration/Suzuki- and malonate surrogate protocol were scaled up to 9 and 20 kilogram, respectively, using relatively inexpensive palladium acetate and triphenylphosphine in both cases.



Scheme 20: Hydroborylation/Suzuki protocol in the large-scale synthesis of **54**.

Being patterned by BASF in 1997 and 1999,[99] respectively, the today's total production volume of the fungizide Boscalid **55** is more than 1000 t per year. The biphenyl intermediate **56** is prepared by Suzuki coupling of 2-nitrochlorobenzene (**57**) and 4-chloroboronic acid (**58**) (Scheme 21).

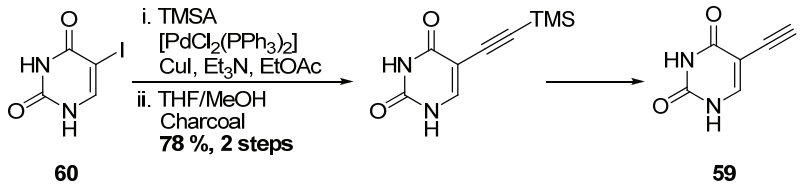


57 58 56 55

Scheme 21: Suzuki biaryl coupling in the manufacture of **54**.

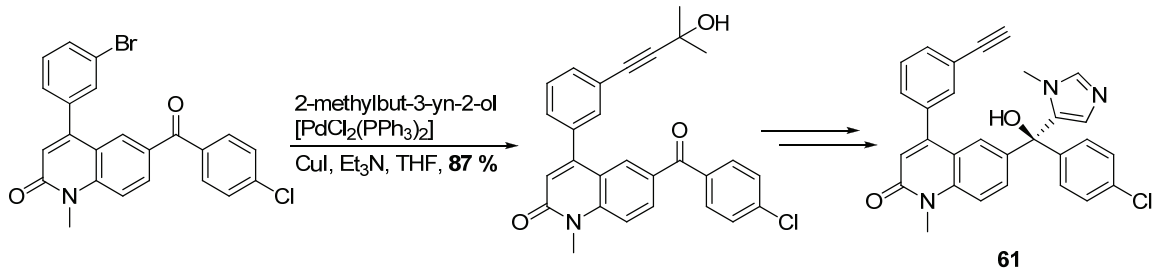
1.4.3 Sonogashira-Hagihara Reactions

In addition to Heck and Suzuki couplings, Sonogashira coupling reactions[100] have been realized on an industrial scale as well. The most prominent example to date is the synthesis of Terbinafin, the active agent of antimyotic Lamisil (Sandoz).[101] The main reason for avoiding a Sonogashira-reaction on large scale is the lability of alkyne intermediates, or, if buyable, their high costs. Therefore, the most common version of this alkyne coupling in large scale synthesis is the reaction of acetylene-surrogates like trimethylsilylacetylene (TMSA) or 2-methylbut-3-yn-2-ol with aryl halides. The TMS-group or the respective acetone moiety is subsequently cleaved off. Thus, this two-step protocol gives an easy access to terminal aryl alkynes. An example for this approach was shown by Cooke *et al.* at GlaxoSmithKline for the synthesis of Enduracil **59**, a dehydrogenase inactivator.[102] Iodide **60** was converted to the corresponding TMSA derivative in presence of 0.5 mol% bis(triphenylphosphine)palladium dichloride [$PdCl_2(PPh_3)_2$] and 0.5 mol% CuI giving 52 kg of product (82 % yield) on pilot plant-scale (Scheme 22). After a purification step and desilylation under basic conditions **59** was obtained in high purity with a palladium content <2 ppm and a copper content <1 ppm.



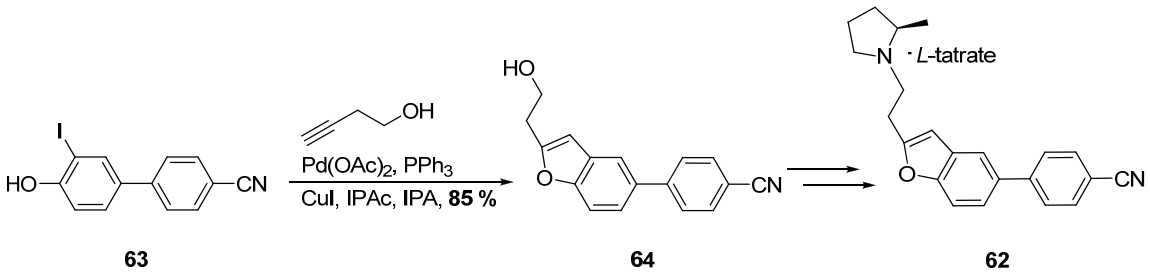
Scheme 22: Synthesis of Enduracil *via* Sonogashira coupling.

The application of 2-methylbut-3-yn-2-ol in a Sonogashira reaction on kg-scale was shown by Pfizer's researchers while developing a streamlined process for the synthesis of Farnesyl transferase inhibitor **61** (Scheme 23).[103]



Scheme 23: Sonogashira coupling in the manufacture of **61**.

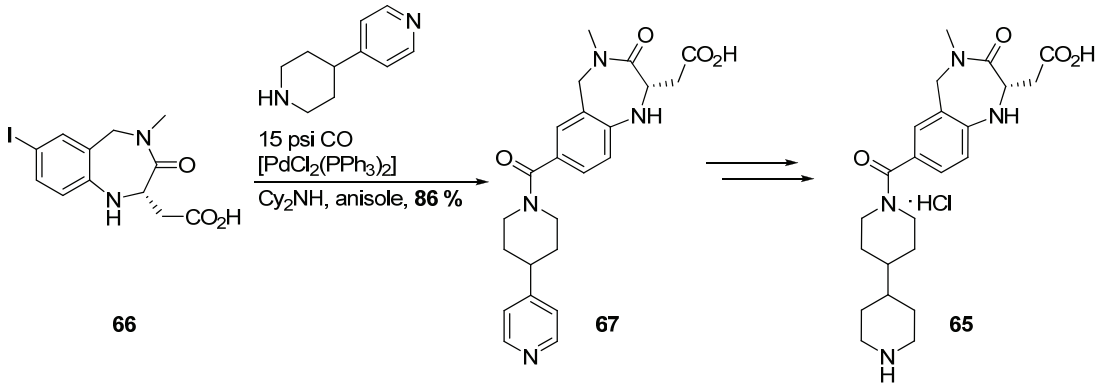
Again, $[PdCl_2(PPh_3)_2]$ (2.5 mol%) was the catalyst of choice in combination with CuI (2.5 mol%). The implementation of a Sonogashira coupling in a large scale reaction cascade was demonstrated by Pu *et. al.* in the manufacture of ABT-239 **62**.[104] ABT-239 is a histamine H_3 receptor antagonist bearing a 2-substitituted benzofurane scaffold, which can be easily constructed *via* coupling of an alkyne with a 2-halo-substituted phenol and subsequent ring formation. Thus, the reaction of **63** with butyn-3-ol was successfully applied and scaled up in the synthesis of precursor **64** using a combination of $Pd(OAc)_2$ (1 mol%), PPh_3 (2 mol%) and CuI (2 mol%) (Scheme 24).



Scheme 24: Large scale reaction cascade to give ABT-239 intermediate **64**.

1.4.4 Carbonylations

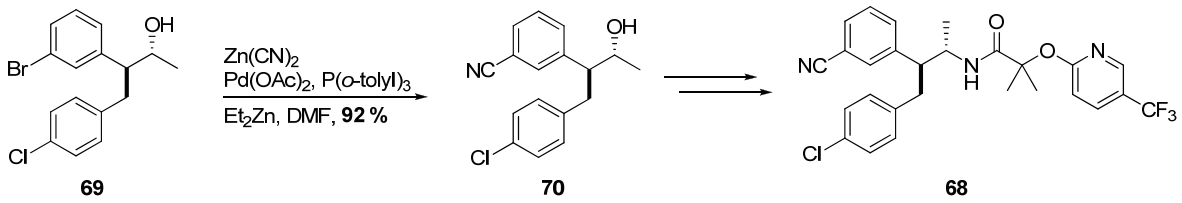
Pd-catalyzed carbonylations[105] are an attractive tool for fine chemical industry, since carbon monoxide is an inexpensive reagent and the resulting carboxylic acid derivatives represent versatile products. By changing the nucleophile in this three-component reaction, an enormous variety of carbonyl compounds are accessible. For fine chemical production, a number of processes are known including the production of the anti-inflammatory drug Ibuprofen (Hoechst-Celanese),[106] the monoamine oxidase B inhibitor Lazabemide (Hoffmann-LaRoche),[107] as well as the manufacture of intermediates like phenyl acetic acid[108] and *N*-acetyl phenyl alanine[109] from benzyl chloride or isochroman-3-one from *o*-xylene dichloride (Clariant).[110] In 2006, an efficient reductive carbonylation of aryl halides using $Pd(OAc)_2$ and bulky di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A)[111] was published by us.[112] This protocol was successfully applied for the synthesis of aromatic aldehydes[113] on to >100 kg-scale.
In addition, Carey and co-workers from GlaxoSmithKline reported in 2003 an aminocarbonylation on the route to GP IIb/IIa receptor antagonist SB-214857-A **65** on 40 kg-scale.[114] For the conversion of iodide **66** to amide **67** a catalyst loading of 1.8 mol% $[PdCl_2(PPh_3)_2]$ and a CO pressure of 15 psi were required (Scheme 25).



Scheme 25: Pd-catalyzed aminocarbonylation in the synthesis of SB-214857-A.

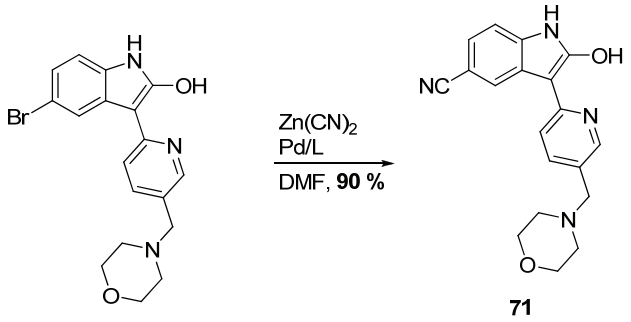
1.4.5 Cyanations

The introduction of a cyano group into an arene moiety by catalytic means is a challenging synthetic approach to aromatic nitriles.[115] Nonetheless, there are some examples of Pd-catalyzed cyanations scaled up to at least some kilogram. In 2006, the chiral amide MK-0364 **68** was found to be a cannabinoid-1 receptor inverse agonist and is therefore a candidate for the treatment of obesity at Merck Research Laboratories.[116] One year later, the development and demonstration of a process for its preparation on multi-kilogram scale was reported.[117] This process included an efficient and selective conversion of bromide **69** to nitrile **70**. Applying 2 mol% of $Pd(OAc)_2$ and 8 mol% of P(*o*-tolyl)$_3$, 3 kg of **70** could be produced (Scheme 26).



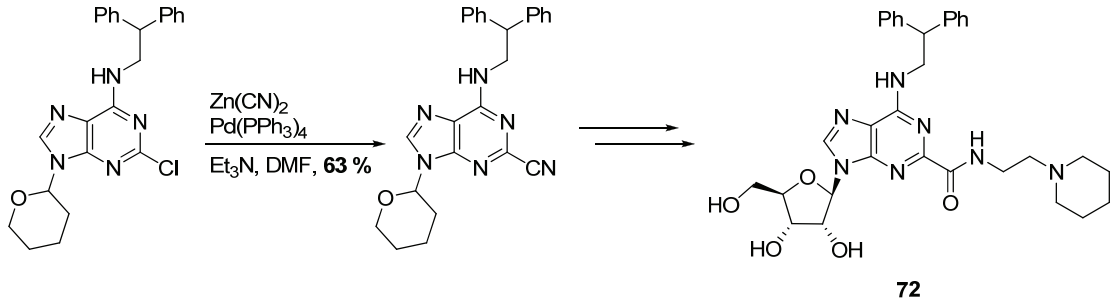
Scheme 26: Palladium-catalyzed cyanation of **69** by Merck.

Ryberg recently showed a robust and mild method for the cyanation of indole **71** (Scheme 27).[118] A catalyst derived from di-μ-bromobis(tri-*t*-butylphosphine)dipalladium(I) (1.25 mol%) gave a superb performance and the reaction was scaled up to more than 5 kg. Other ligands including P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$ and Buchwald's biphenyl phosphines showed a similar reactivity. Notably, adding the CN-source after the catalyst turned out to be essential for a clean reaction.



Scheme 27: Preparation of **71** *via* Pd-catalyzed cyanation.

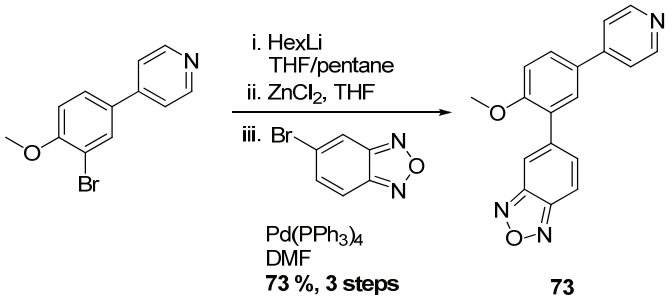
Smith and co-workers from Pfizer reported the development of palladium catalyzed cyanation as a part of the kg-scale process for the production of adenosine A_{2A} receptor agonist UK-371,104 **72** (Scheme 28).[119] In contrast to the applications described above, the nitrile group was not part of the target molecule but hydrolyzed to the acid after the coupling step.



Scheme 28: Cyanation as part of the large scale synthesis of UK-371,104.

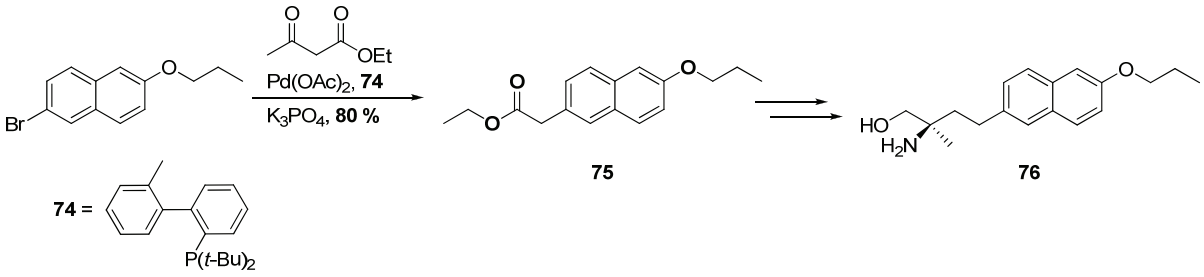
1.4.6 Other Pd-Catalyzed C–C Coupling Reactions

Manley, Acemoglu, and co-workers from Novartis reported in 2003 the application of a Negishi protocol[20],[120] in the manufacture of phosphodiesterase type 4D inhibitor PDE472 **73**. As an alternative to the analogue Suzuki coupling, the Negishi approach proved to be more successful yielding the benzoxadiazole in 73 % yield on a 4.5 kg scale (Scheme 29).[121] Herein, 0.8 mol% tetrakispalladium(triphenylphosphine) $Pd(PPh_3)_4$ served as the precatalyst. After crystallisation of **73** as the hemi-maleate salt, a Pd-content <2 ppm was detected in the target compound.



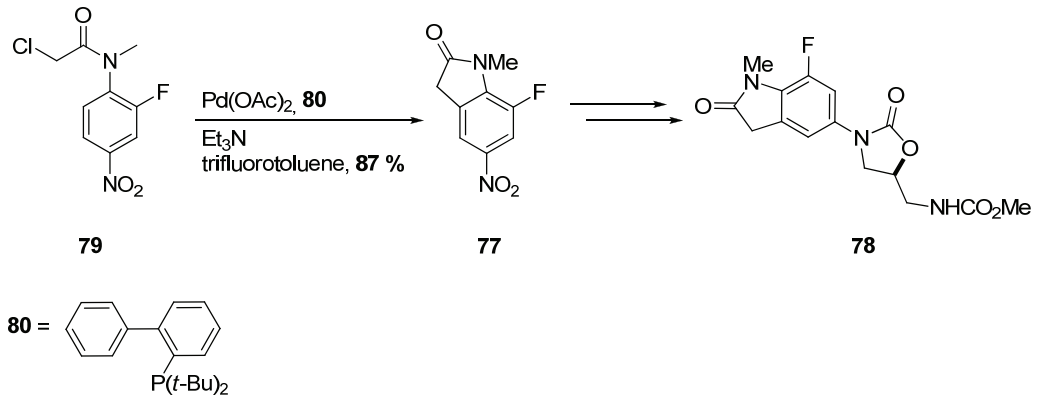
Scheme 29: Negishi coupling in the large scale production of PDE472.

In the field of palladium-catalyzed α-arylation of CH-acidic compounds, a tremendous progress is observed during the past eight years.[122] Using a mixture of $Pd(OAc)_2$ (1 mol%) and a bulky, electron-rich phosphine **74** (2 mol%), scientists at Novartis were able to furnish ester **75** by α-arylation of ethylacetoacetate and subsequent deacylation on 14 kg scale (Scheme 30).[123] **75** was later converted into the chiral analogue **76** of immunomodulator FTY720 with 22 % overall yield.



Scheme 30: Synthesis of intermediate **75** by Novartis.

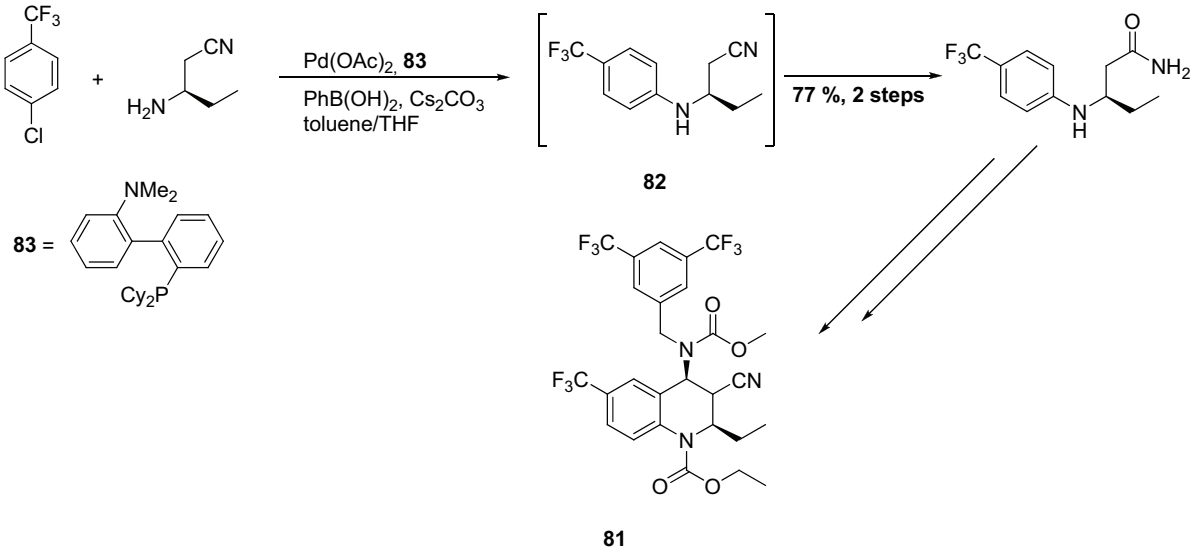
For the formation of oxindole **77**, the precursor for antibacterial **78**, an exceptional approach was chosen by Pamment *et al.* They used Buchwald's method of Pd-catalyzed oxindole ring closure starting from α-chloroamide **79**.[124] With 3 mol% of Pd source and 6 mol% of JohnPhos **80**, the reaction proceeded smoothly to give 87 % of **77** on a 5 kg scale (Scheme 31). It was pointed out that the rather uncommon solvent trifluorotoluene outperformed other tested solvents.



Scheme 31: Oxindol formation on the route to antibacterial **78**.

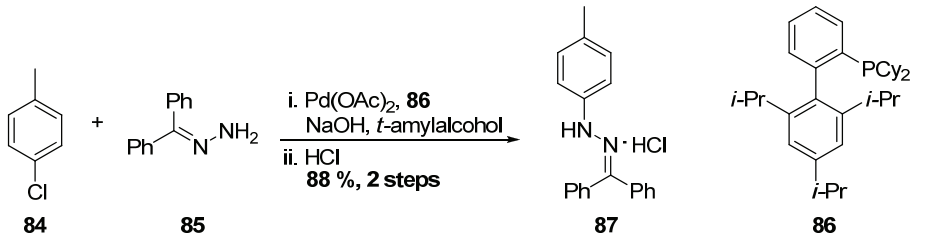
1.4.7 Buchwald-Hartwig Aminations

Pd-catalyzed C–N coupling was pioneered by Kosugi *et al.* in the 1980s[125] using tin amides as N-nucleophiles. In 1995, Buchwald[126] and Hartwig[127] independently improved the reaction by the usage of free amines. Because of its numerous applications the reaction is today known as the Buchwald-Hartwig amination.[33] The aryl amines formed *via* this process are important building blocks for industrial products. Therefore, there is not only an academic but also a strong commercial interest in the Buchwald-Hartwig amination, a fact which was recently pointed out by Schlummer and Scholz.[128] The authors reported that 'several C–N couplings have already been run at a production scale of multi-hundred kgs', although in the literature a somewhat smaller number of processes has appeared. One example is the synthesis of CETP inhibitor CP 529,414 **81** patented by Pfizer.[129] Herein, intermediate **82** was prepared by Buchwald-Hartwig coupling applying $Pd(OAc)_2$ and Buchwald's DavePhos **83** on a 3 kg-scale (Scheme 32).[130] Interestingly, catalytic amounts of phenyl boronic acid were needed in order to pre-activate the catalyst.



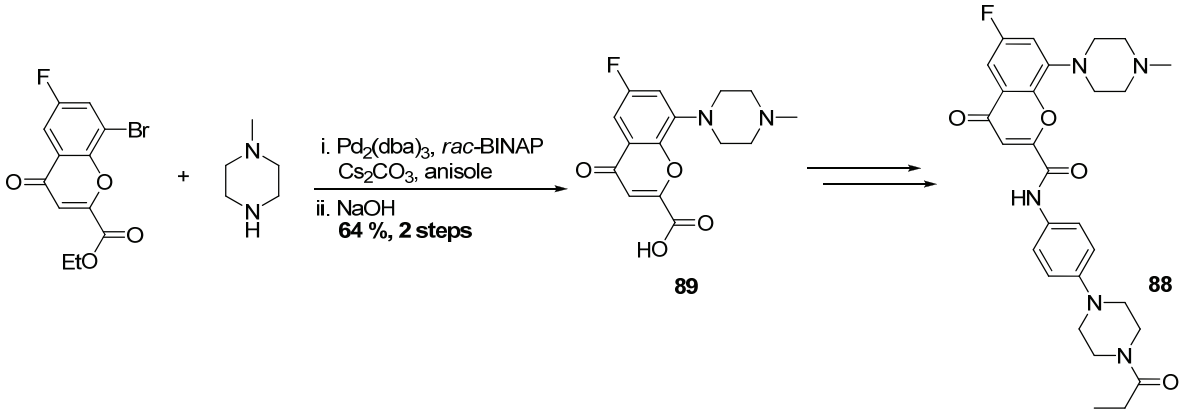
Scheme 32: Large-scale Buchwald-Hartwig amination yielding precursor **82**.

In a personal account, Buchwald *et al.* reported the usage of similar bulky biarylphosphines for the synthesis of arylhydrazones, arylpiperazines and diarylamines.[131] For instance, the reaction of 4-chlorotoluene (**84**) with benzophenone hydrazine (**85**), catalyzed by a complex generated from $Pd(OAc)_2$ (0.5 mol%) and XPhos **86** (1 mol%), was successfully scaled up and directly converted into the hydrochloride salt **87** after treatment with hydrochloric acid (Scheme 33). The final compound contained less than 10 ppm of residual palladium.[132]



Scheme 33: Coupling of 4-chlorotoluene with hydrazone **85**.

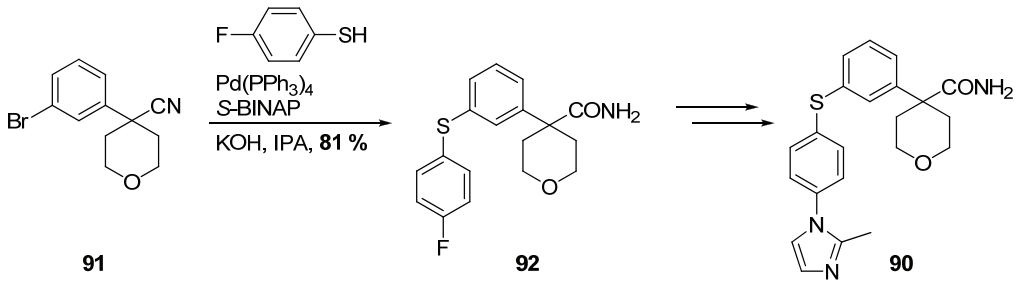
A Buchwald-Hartwig amination with a less sophisticated but more ‘classic’ catalyst was performed as a part of the preparation of 5-HT antagonist ZM549865 **88** (Scheme 34).[133] With 2 mol% of catalyst generated from $Pd_2(dba)_3$ and *rac*-BINAP, the process was scaled up in a pilot plant to give 24 kg of the key intermediate **89**.



Scheme 34: Preparation of key intermediate **89** on a 24-kg scale.

1.4.8 Miscellaneous

Next to their nitrogen and carbon counterparts, sulphur nucleophiles can take part in Pd-catalyzed coupling reactions as well. In the original paper published by Migita,[134] a high-yielding route to diarylthioethers by reaction of aryl iodides with thiophenols in the presence of catalytic amounts of $Pd(PPh_3)_4$ was described. For the large scale manufacture of former antiasthma drug candidate **90**, researchers at Pfizer reacted nitrile **91** with 4-fluorothiophenol furnishing 40 kg of thioether **92** (Scheme 35).[135] Remarkably, bidentate phosphorus ligands were found to accelerate the reaction: In the optimized coupling protocol, a mixture of 0.5 mol% $Pd(PPh_3)_4$ and 1 mol% of *rac*-BINAP constituted the precatalyst. Under the strong basic conditions (KOH), the desired hydrolysis of the nitrile group yielding the amide also occurred during this step.



Scheme 35: Pfizer's Migita-protocol for the synthesis of **90**.

1.4.9 Conclusions and Outlook

The ongoing success of palladium-catalyzed cross-coupling is not only documented by the high number of publications in the past years, but also by the increasing interest of the fine chemical and pharmaceutical industry in applications of these powerful methods. Especially Suzuki-Miyaura couplings have become best practices when it comes to

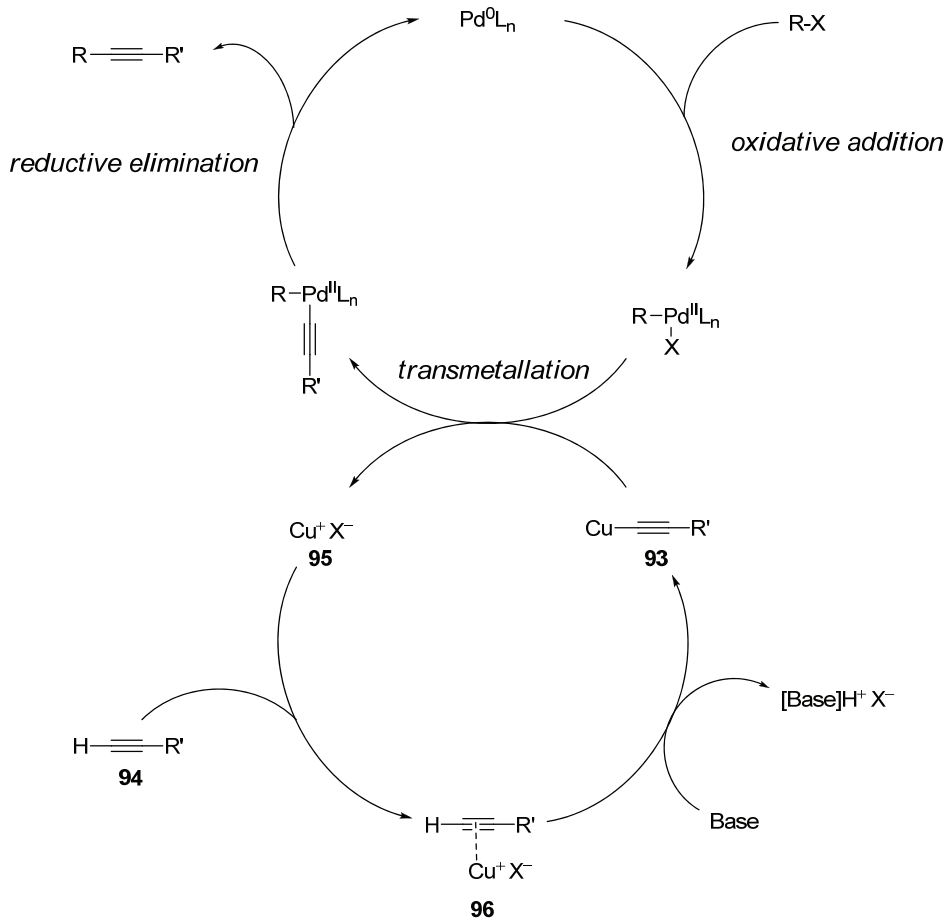
carbon-carbon bond formations. Like almost every type of chemical transformation, the cross-coupling reactions have disadvantages: Besides the cost for the precious metal palladium and the problem of product contamination, the reaction produces at least one equivalent of inorganic salt as waste during the reaction. Nevertheless, there are useful ways of recycling especially bromide salts.

In some cases the cost of the catalyst itself can indeed be a problem. On the contrary to the catalyst activities and productivities claimed for industrial application to be worthwhile, TONs $>10^3$ in large scale palladium catalysis are still rare. However, an extensive know-how in catalyst optimization strategies has emerged during the last two decades. Moreover, from the technologic standpoint, for most coupling reactions using aryl bromides, catalyst costs are no longer the limiting factor. Because of the tremendous advances in the field of aryl chloride coupling, this may also be true for commercial conversion of these substrates in the near future. Summing up the processes presented in this chapter, it becomes clear, that in most of these reactions the cost-efficient triphenylphosphine is favoured as a ligand of choice. Despite this, it is most likely that the recent advances in the development of new ligands and their synthetic abilities on lab scale result in more commercial applications. Novel designed ligands and/or catalysts may not always meet the challenges regarding high TON and TOF. However, especially with recent developed phosphine based systems, progress has been made with respect to functional group tolerance and the activation of aryl chlorides in C–C cross couplings like the Sonogashira-Hagihara coupling. Moreover, in recent years with the help of new ligands it became possible to introduce challenging nucleophilic coupling partners like ammonia or hydroxide to produce anilines and phenols, respectively.

1.5 Sonogashira-Hagihara Reaction and Heck-Cassar Coupling

1.5.1 Basic Principles

The Sonogashira-Hagihara reaction was discovered in 1975[31] and is today defined as Pd-catalyzed reaction of a terminal alkyne and an organic halide with a copper source as co-catalyst, while the copper-free variant is often called Heck-Cassar[136] coupling. Both C–C cross-couplings constitute standard methods for the construction of C(sp^2)–C(sp) bonds.[100] The ‘textbook’ catalytic cycle of the Sonogashira-Hagihara reaction is shown in Scheme 36.



Scheme 36: Catalytic cycle of the Sonogashira-Hagihara coupling.

It incorporates the basic steps of Pd-catalyzed cross-coupling: oxidative addition, transmetallation and reductive elimination (see chapter 1.3). The transmetallation is suggested to take place from a copper acetylide **93** formed in a second cycle from the alkyne **94** and the copper source **95** in the presence of base.[137] Since many bases are not strong enough to deprotonate the alkyne but are successfully applied in the coupling reaction (e.g. amines), a π-complex **96** is supposed to be part of the catalytic cycle. While the Cu^+-ion withdraws electron density from the alkynyl carbon, the terminal proton becomes easier to abstract. Copper(I) iodide is the most commonly applied Cu^I source; its efficacy may be due to its moderate solubility in organic solvents. Even though the transmetallation is often supposed to be the rate determining step in the reaction, the addition of copper co-catalyst is not always a benefit for the overall reaction. Indeed, Cu^+ can hamper the coupling reaction by promoting the oligomerization of the alkyne. On the other hand, alkyne coupling can proceed without copper; herein, the activation of the alkyne is believed to be realized by a Pd^{II} species.[138]

1.5.2 Catalysts and Reaction Conditions

In the original protocol from 1975,[31] bis(triphenylphosphine)palladium dichloride [$PdCl_2(PPh_3)_2$] and CuI were applied as Pd- and Cu-source, respectively. Various aryl iodides, bromoalkenes and bromopyridines were reacted in diethylamine with different alkenes including acetylene gas. On the contrary to the previously reported procedures by Heck and Cassar, reaction conditions were notably mild. The couplings were completed after 3-6 hours stirring at room temperature. This catalytic system has varied over the last three decades regarding catalyst, solvent and base. Depending on the nature of the substrate and the economical as well as ecological background, new catalytic systems were developed and tested in combination with various bases, solvents, and additives often followed by replacement of the original components.

For instance, *N-heterocyclic carbenes* (NHCs) gave outstanding performances in challenging Sonogashira couplings,[139] for example in the coupling of unactivated alkyl halides.[140]

Complexes bearing *multidentate ligands* have also extensively applied in the Sonogashira coupling reaction, especially bidentate ones. Apart from 'classic' bisphosphines like dppf, recently synthesized chelating P,P,[141] N,N,[142] and P,N[143] ligands were successfully applied in high turnover catalysis. Notably, some of these ligands promote the conversion of aryl chlorides even without copper co-catalysis. There are also examples of Pd-complexes incorporating tri- and tetradentate ligands acting as catalysts in Sonogashira couplings.[144],[145]

The usage of *palladacycles* as catalysts in Sonogashira couplings often requires high temperatures.[146] This is due to the fact that palladacycles are precatalysts; their conversion into the active, low coordinate Pd^0 species occurs *via* thermal decomposition.[147]

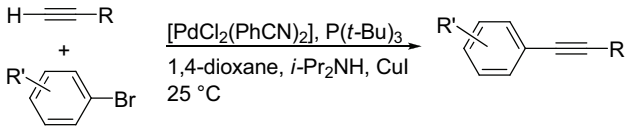
Furthermore it is noteworthy, that there are also so-called *'ligand-free'* versions of the Sonogashira reaction.[148]

Monodentate phosphines as part of homogeneous catalysts for Pd-catalyzed alkyne couplings are still representing the most important ligand family. Most of them, especially triarylphosphines, are commercially available while being cost-effective. However, for the activation of less reactive substrates like aryl chlorides, PPh_3 or other triarylphosphines proved to be more or less ineffective. Herein, the more electron rich alkyl substituted phosphines have outperformed other monodentate ligands. Those monophosphines are often not buyable, but they are easier accessible than multidentate ligands. Their syntheses

often comprise less than three steps and are modular; these features offer the possibility to fine-tune the ligand. Thus, ligand families can be created; a very important factor, since little changes of the substrate in Pd-catalyzed coupling reactions can cause the requirement of a different catalytic system.

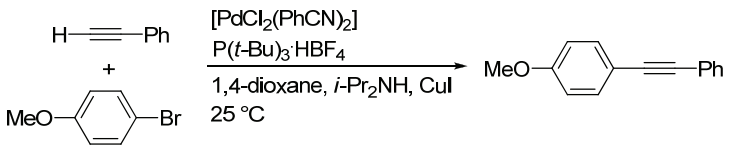
1.5.3 Catalysts Bearing Monodentate Alkyl-Substituted Phosphines

Trialkyl-substituted phosphines are often sensitive towards moisture and air.[149] Despite its pyrophobic nature, the bulky P(*t*-Bu)$_3$ ligand has been used intensively in Pd-catalyzed cross-coupling reactions. In 2000, Fu, Buchwald *et al.* showed its efficiency in the Sonogashira-Hagihara coupling of aryl bromides at room temperature.[150] Both electron rich and deficient substrates were successfully alkynylated in the presence of 3 mol% catalyst (Scheme 37).



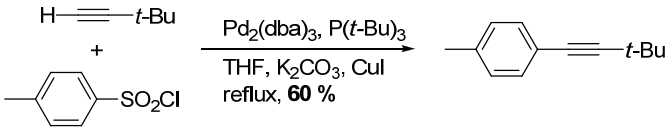
Scheme 37: Sonogashira coupling of aryl bromides using a Pd/P(*t*-Bu)$_3$ system.

To circumvent the problem of ligand oxidation, the ligand was converted into air-stable phosphonium salts, which can also be successfully applied in the Sonogashira reaction as a 'masked' ligand: the free phosphine is released from the salt under the basic reaction conditions (Scheme 38).[151]



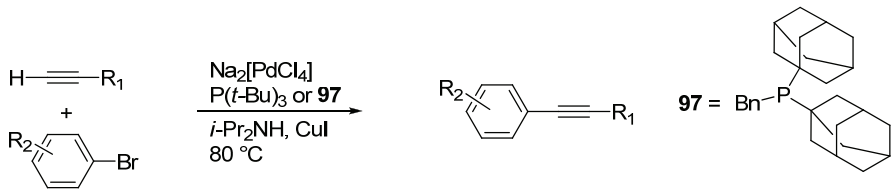
Scheme 38: Application of P(*t*-Bu)$_3$·HBF$_4$ in the coupling of 4-bromoanisol.

For the conversion of arene sulfonyl chlorides, free P(*t*-Bu)$_3$ was used in combination with Pd$_2$(dba)$_3$.[152] For instance, *p*-toluenesulfonyl chloride was coupled with *tert*-butyl acetylene in 60 % yield with 3 mol% of Pd source and 10 mol% of ligand applied (Scheme 39).



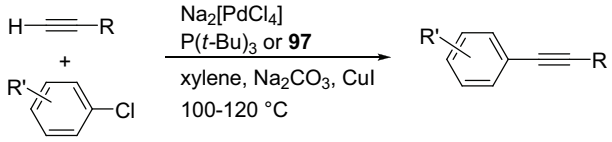
Scheme 39: Application of P(*t*-Bu)$_3$ in the coupling of *p*-toluenesulfonyl chloride.

Putting emphasis on increasing the turnover number in the coupling of aryl bromides, Plenio *et al.* applied P(*t*-Bu)$_3$ at higher temperatures.[153] Indeed, when using a mixture of $Na_2[PdCl_4]$/P(*t*-Bu)$_3$/CuI in diisopropylamine at 80 °C, TONs of $>10^5$ were achieved (Scheme 40). Next to P(*t*-Bu)$_3$, the (1-Ad)$_2$PBn ligand (**97**) performed also well while being less sensitive to oxidation and therefore easier to handle.



Scheme 40: Sonogashira coupling of aryl bromides using a Pd/P(*t*-Bu)$_3$ and Pd/(1-Ad)$_2$PBn systems.

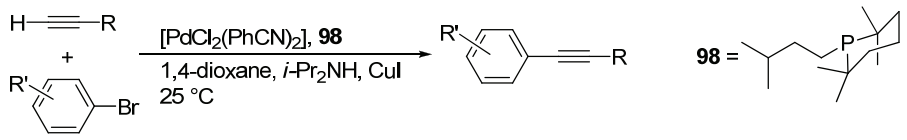
Their steric as well as their electronic properties are the reasons for the high activity of bulky alkyl-substituted phosphanes like P(*t*-Bu)$_3$ in the Pd-catalyzed cross-coupling of aryl chlorides. The high electron density on the phosphorus enables oxidative addition to the C–Cl bond, while the steric bulk facilitates reductive elimination. Moreover, sterical congested phosphines tend to form monoligated 12-electron Pd complexes, which are very active catalytic species because of the high number of open coordination sites. Consequently, application of both P(*t*-Bu)$_3$ and (1-Ad)$_2$PBn in the Sonogashira-Hagihara reaction of aryl chlorides remained successful at 100-120 °C and 2 mol% Pd loading (Scheme 41).[154]



Scheme 41: Sonogashira coupling of aryl chlorids using a Pd/P(*t*-Bu)$_3$ and Pd/(1-Ad)$_2$PBn systems.

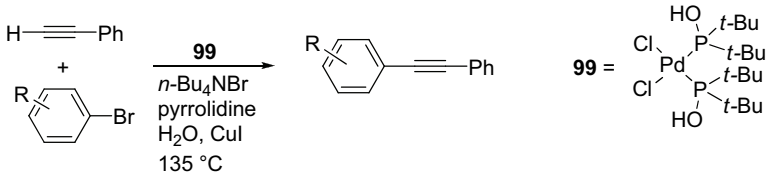
By immobilization and also other modifications of these catalysts, various recycling procedures were examined.[155]

Capretta and co-workers demonstrated the usefulness of the unsymmetrical triarylphosphine **98** in the room-temperature coupling of aryl bromides (Scheme 42).[156]



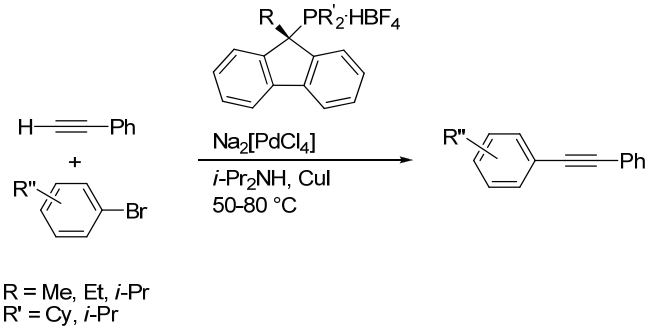
Scheme 42: Sonogashira coupling of aryl chlorids using a Pd/phosphorinane system.

A phosphinous acid in combination with a palladium source **99** constituted the catalyst for the alkynylation of aryl bromides in an aqueous system without the need for an organic cosolvent.[157] A high catalyst loading and elevated temperature had to be applied in order to convert the substrates completely, even if activated bromides are used (Scheme 43).

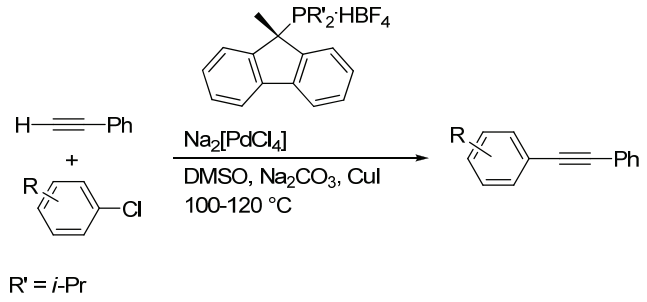


Scheme 43: Alkynylation in water employing a palladium/phosphinous acid complex.

Plenio and Fleckenstein reported in 2007 the synthesis of novel 9-fluorenylphosphines and their application in Pd-mediated cross-coupling reactions.[158] The ligands were conveniently obtained in three steps from commercial available material and found to effectively catalyze the Sonogashira coupling of aryl bromides and chlorides with phenyl acetylene. TONs up to 26400 were achieved in the case of bromides (Scheme 44) whereas 1 mol% of catalyst was needed to convert activated aryl chlorides (Scheme 45). The reaction of the electron rich 4-chloroanisol ended up in a somewhat lower yield (73 %).

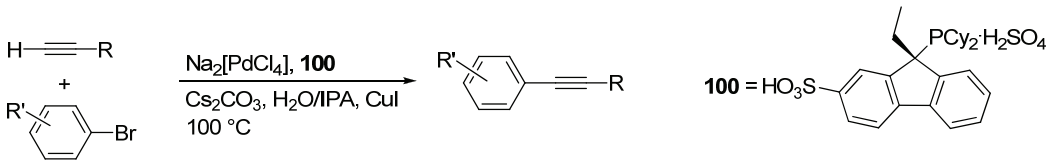


Scheme 44: Sonogashira coupling of aryl bromides using 9-fluorenylphosphines.



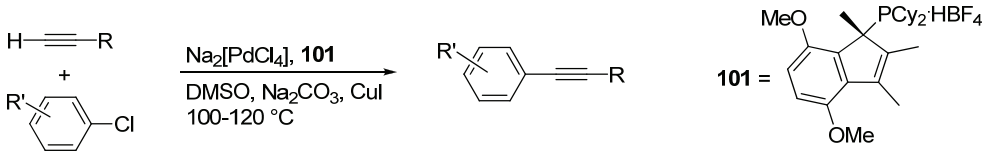
Scheme 45: Sonogashira coupling of aryl chlorides using 9-fluorenylphosphines.

A sulfonated phosphine **100** was also successfully tested in the Sonogashira-Hagihara coupling of aryl bromides with different alkynes in aqueous phase at 1 mol% Pd loading (Scheme 46).



Scheme 46: Sonogashira coupling applying Pd/**100** in a water/IPA mixture.

Based on the fluorenyl phosphine framework, 1-indenyldialkylphosphines and cyclopentadienyldialkylphosphines were developed by the same group.[159] Although being active in the coupling of aryl chlorides (Scheme 47), the application of ligand **101** did not constitute a significant improvement compared to the performances by fluorenylphosphine ligands.

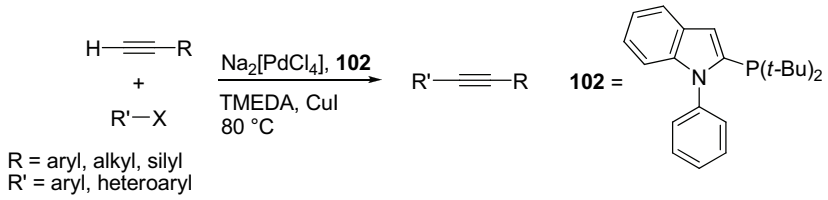


Scheme 47: Sonogashira coupling of aryl chlorides using a Pd/1-indenyldialkylphosphine system.

By linkage of two phosphine units, a small library of bidentate fluorenylphosphine ligands for cross-couplings was also established.[160]

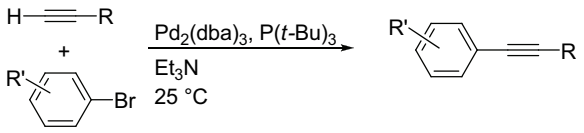
A very selective system for the Sonogashira-Hagihara coupling of aryl and heteroaryl bromides was recently presented by us.[161] The use of the commercially available Cata*CX*ium® PIntB ligand **102** offered high activity and functional group tolerance in tetramethylethylene diamine (TMEDA) at 80 °C (Scheme 48). Even hydroxo- and amino-

substituted arenes were converted completely at a 0.5 mol% Pd loading. In the coupling of activated bromides like 4-bromo-acetophenone, TONs up to 14100 were achieved.



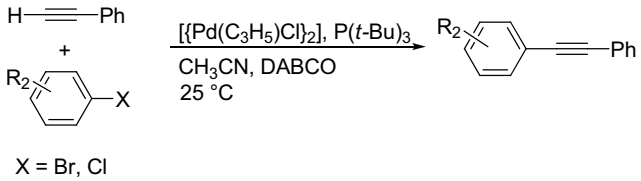
Scheme 48: Sonogashira coupling of (hetero)aryl bromides employing a Pd/Cata*CX*ium® PIntB system.

In the past few years, an increasing number of Heck-Cassar couplings with catalysts bearing alkyl-substituted phosphine ligands were reported. Already in 2000, Böhm and Herrmann showed that copper-free alkyne coupling of electron-rich as well as sterically congested aryl bromides is possible at room temperature. For these transformations, only 0.5 mol% of both $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ were needed (Scheme 49).[162]



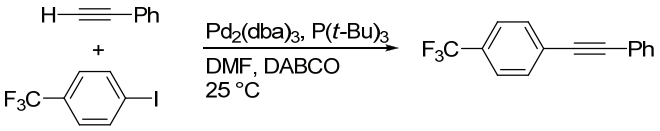
Scheme 49: Heck-Cassar coupling of aryl bromides using a Pd/P(*t*-Bu)$_3$ system.

Following the reports by Fu, Buchwald and Herrmann, Sohelli *et al.* developed a copper-free alkynylation procedure for aryl bromides with P(*t*-Bu)$_3$ at room temperature (Scheme 50). Under slightly different reaction conditions compared to Herrmann's procedure ($Pd(allyl)_2$, DABCO, acetonitrile), lower TONs were observed. However, the reaction of an aryl chloride (4-chloroacetophenone) was also reported.[163]



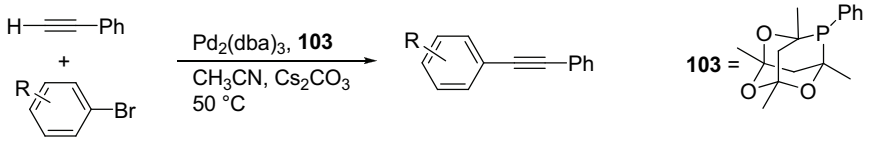
Scheme 50: Heck-Cassar coupling of aryl bromides and chlorides using a Pd/P(*t*-Bu)$_3$ system.

Among other ligands (e.g. $AsPh_3$), P(*t*-Bu)$_3$ was applied in the Heck-Cassar coupling of 4-trifluoromethyliodobenzene with phenylacetylene at room temperature (Scheme 51).[164]



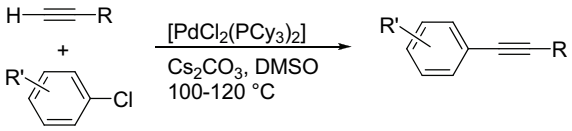
Scheme 51: Heck-Cassar coupling of an aryl iodide using a Pd/P(*t*-Bu)$_3$ system.

A palladium complex of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (**103**) showed a similar activity as P(*t*-Bu)$_3$ in the Heck-Cassar coupling of aryl bromides at 50 °C (Scheme 52).[165]



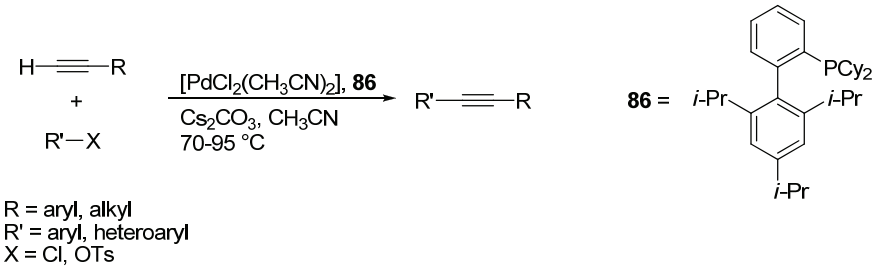
Scheme 52: Heck-Cassar alkynylation of aryl bromides using a Pd/phosphaadamantane system.

The coupling of aryl chlorides with terminal alkynes is also possible under copper-free conditions. Yi and Hua reported in 2006, that 3 mol% of the [$PdCl_2(PCy_3)_2$] complex enables the conversion of a variety of aryl chlorides including esters and alcohols (Scheme 53).[166]



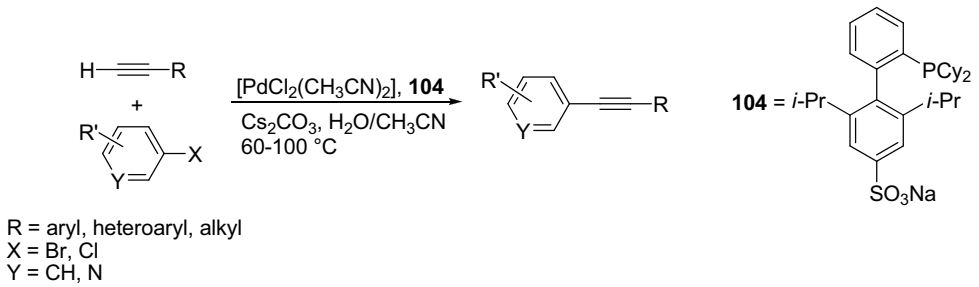
Scheme 53: Copper-free alkynylation of aryl chlorides using [$PdCl_2(PCy_3)_2$] complex.

Being probably the most active system in the copper-free Pd-catalyzed alkyne coupling with aryl chlorides reported hitherto, a combination of [$PdCl_2(CH_3CN)_2$] and Buchwald's XPhos (**86**) ligand showed great functional group tolerance and a remarkable activity.[167] Only 0.1-1 mol% of catalyst was required to obtain various coupling products in high yields (Scheme 54). This catalyst system was also capable of catalyzing the Heck-Cassar coupling of aryl tosylates, although higher loadings were needed (5 mol%). Moreover, the authors were the first to report that the addition of a Cu-source can inhibit a Sonogashira reaction.



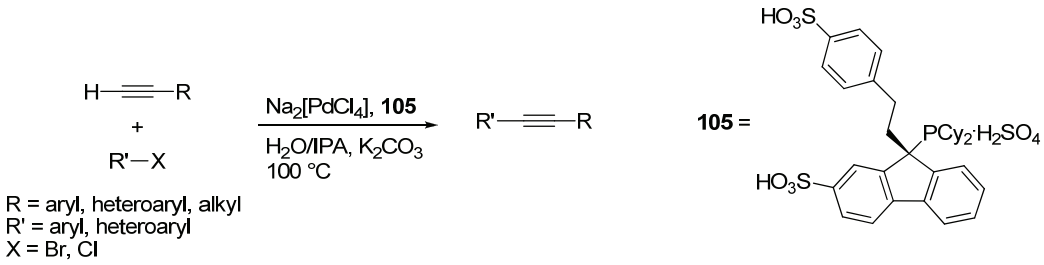
Scheme 54: Copper-free alkynylation of aryl chlorides and tosylates using a Pd/XPhos system.

A sulfonated version of XPhos **104** was also applied in the Heck-Cassar coupling of aryl bromides and chlorides in water (Scheme 55).[168]



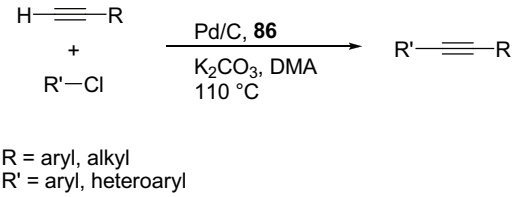
Scheme 55: Copper-free alkynylation of (hetero)aryls in an aqueous phase catalyzed by a Pd/**104** system.

Plenio's fluorenylphosphine ligand **105** was shown to be effective in the coupling of heteroaryl substrates in a similar aqueous system (Scheme 56).[169]



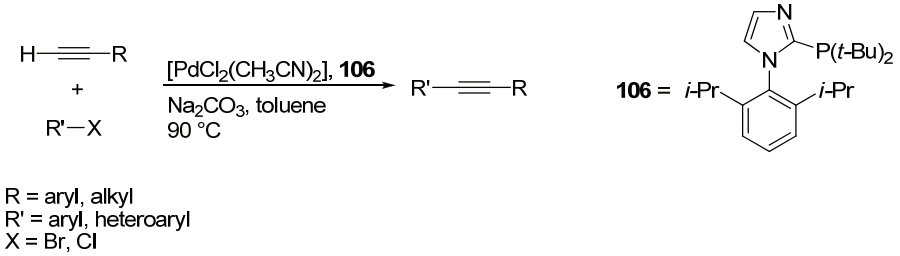
Scheme 56: Copper-free alkynylation of (hetero)aryls in aqueous phase catalyzed by a Pd/**105** system.

Komároni and Novák used XPhos for the Heck-Cassar coupling of aryl chlorides in combination with palladium on charcoal.[170] The alkynylation of various substrates, including thiophenes, pyridines and aromatic amides was realized using 1 mol% of ligand and 1 mol% of Pd source (Scheme 57).



Scheme 57: Copper-free alkynylation of aryl chlorides and tosylates using a Pd/C/XPhos system.

Inspired by Buchwald's biaryl phosphines, we developed a new class of imidazole-based phosphine ligands.[67] [*N*-(2,6-diisopropylphenyl)-2-imidazolyl]-di-*tert*-butylphosphine (**106**) gave an excellent performance in the Heck-Cassar coupling of aryl chlorides (Scheme 58).[67] Compared to Buchwald's system, there were some drawbacks with respect to the substrate scope; in particular, chloropyridines as well as di-*ortho*-substituted substrates are not fully converted. However, next to esters and nitriles, the system tolerates also amino groups, while a cleavage of the silyl group of TMSA, as observed in Buchwald's system, did not occur.

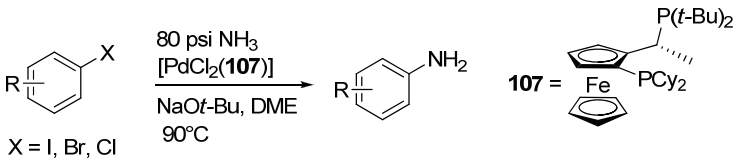


Scheme 58: Heck-Cassar coupling of aryl halides employing a Pd/**106** system as catalyst.

1.6 Palladium-Catalyzed Coupling of Ammonia and Hydroxide with Aryl Halides

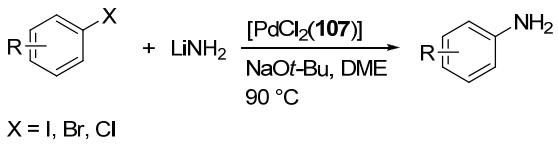
On the contrary to established Pd-catalyzed cross-couplings, the reaction of aryl halides with a) ammonia and b) hydroxide to form primary anilines or phenols, respectively, remained unexplored for a long time.[171] Despite this, there is a strong need for an easy, cost-effective and environmentally benign access to such substance classes, as they are starting materials for pharmaceuticals or bulk commodities like dyes and polymers.[33],[172] The Buchwald-Hartwig amination is known as one of the first Pd-catalyzed carbon-heteroatom bond formations. Since its discovery, the scope of the Buchwald-Hartwig reaction has broadened very fast and a high number of nitrogen containing compounds can be readily coupled with aryl halides by using Pd catalysis

today. The monoarylation of ammonia, however, was a challenge for several reasons: first of all, the reagent ammonia tends to form stable complexes with the metal palladium, which are catalytically inactive. Due to the stability of Pd-amido complexes, reductive elimination is also disfavored and therefore very slow. Moreover, if the primary aniline is formed, it has a higher nucleophilicity compared to ammonia. Consequently, double- or triple-arylation is likely to occur. To circumvent this, ammonia surrogates were often used in the coupling reaction.[173] The disadvantages of these procedures are obvious: the surrogates are much more expensive than ammonia, and their application is less atom-efficient. Furthermore, an additional step is needed, as the unwanted part of the surrogate needs to be cleaved off. In 2006, Hartwig and Shen reported the first palladium-catalyzed monoarylation of ammonia.[174] By using a preformed Pd-dichloro complex incorporating the bulky Josiphos ligand **107**, the authors were able to convert different alkyl-substituted aryl halides as well as 4- and 5-bromoisoquinoline to the corresponding anilines (Scheme 59). High yields (69-94%) were obtained at 1 mol% Pd loading and 90 °C in DME. Interestingly, a high selectivity towards the monoarylated product was observed, even though an excess of ammonia need to be used (80 psi).



Scheme 59: Coupling of aryl halides with ammonia, employing [$PdCl_2$(**107**)] as precatalyst.

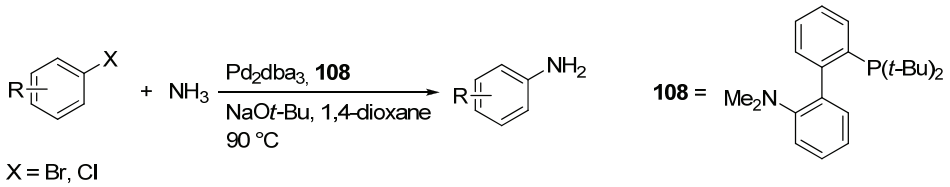
Next to ammonia, lithium amide was also used in order to form anilines (Scheme 60). The substrate variation in this reaction was similar to the scope of the monoarylation of ammonia. Moreover, 4-chlorobromobenzene was selectively converted to the Br-substituted aniline, while the reaction of 2,2'-dibromobiphenyl ended up in the formation of carbazole.



Scheme 60: Coupling of aryl halides with lithium amide, employing [$PdCl_2$(**107**)] as precatalyst.

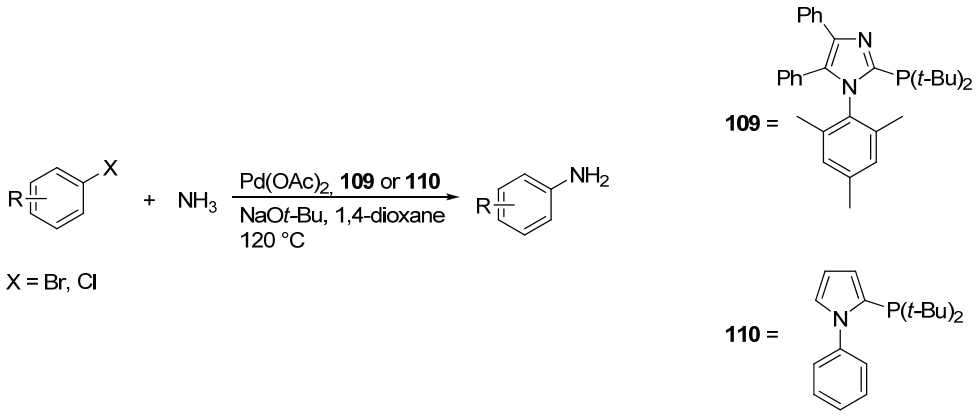
The authors also reported the preparation of an arylpalladium amido complex containing the Josiphos ligand as well as the reductive elimination of both primary and secondary aniline from it. However, these studies did not give a satisfactory explanation for the remarkable selectivity towards the monoarylated product in the coupling reactions.

One year later, Buchwald and Surry described the use of bulky dialkyl-biarylphophines in the monoarylation of ammonia as well as in the synthesis of symmetrical and unsymmetrical di- and triarylamines.[175] From the ligands tested, the highest selectivity towards the primary aryl amine was observed with ligand **108**. The scope of the protocol was quite narrow; only five aryl bromides were presented being successfully converted, including alkyl, aryl and alkoxy-substituted substrates. In contrast to Hartwig's procedure, ammonia was not applied as a gas but as easy-to-handle solution in 1,4-dioxane. The monoarylation reactions were performed with 1 mol% $Pd_2(dba)_3$, 5 mol% of ligand 102 and NaO*t*-Bu as base in 1,4-dioxane at 80 °C (Scheme 61). Notably, for the formation of di- and triarylamines, XPhos was used as ancillary ligand instead of **108**.



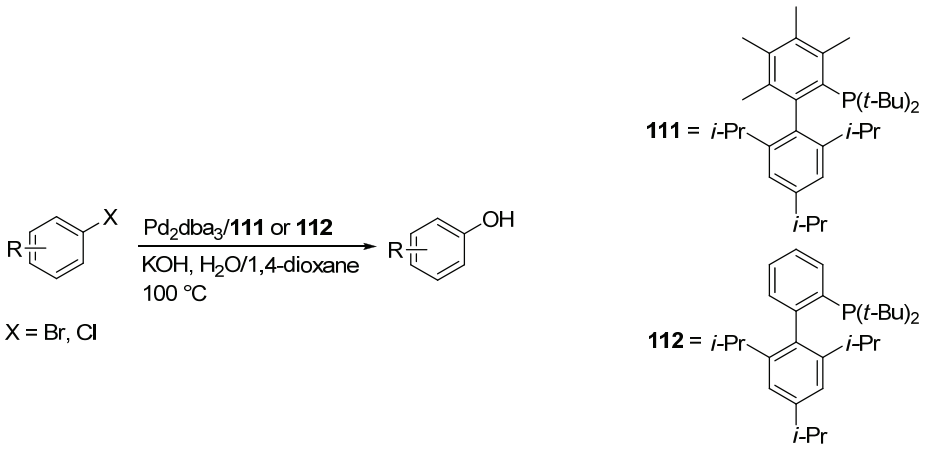
Scheme 61: Monoarylation of ammonia catalyzed by a Pd/biarylmonophosphine system.

Despite the fact that Buchwald's and Hartwig's procedures worked efficiently for certain substrates, both methods were lacking of a broad scope including the conversion of more functionalized substrates. A more general protocol was published by us for the Pd-catalyzed monoarylation of ammonia in 2009.[67] Herein, a complex derived *in situ* from $Pd(OAc)_2$ (1-4 mol%) and ligand **109** (4-16 mol%) catalyzed the amination of various aryl halides, e.g. halostyrenes, haloindoles and aminoaryl halides. In some cases, application of commercially available ligand **110** (cata*CX*ium® PtB) also succeeded (Scheme 62). Similar to Buchwald's procedure, the ammonia was provided as a 0.5 M solution in 1,4-dioxane as well as NaO*t*-Bu was used as base. The reactions were generally performed in a steel autoclave at 120 °C and 10 bar N_2 atmosphere, although amination was shown to be possible also at ambient pressure. It was noted that the steric and electronic features of the ligands are possible reasons for the excellent productivity and selectivity of the catalyst system.



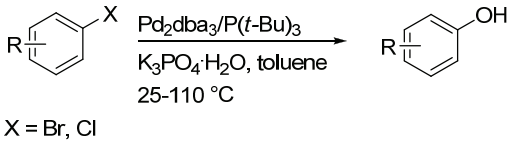
Scheme 62: Monoarylation of ammonia using cata*CX*ium® P ligand **110** and novel **109**.

Pd-catalyzed C–O bond constructions have emerged as effective methods for the synthesis of diaryl and alkyl aryl ethers.[36] However, like the Pd-catalyzed synthesis of anilines from aryl halides and ammonia, the use of hydroxide salts as nucleophiles in a similar coupling process had never been reported before 2006. With respect to the lower rate of reductive elimination, this transformation was considered as even more challenging. By application of sterically demanding monophosphines **111**/**112**, Buchwald *et al.* were able to furnish a number of phenols starting from aryl halides and potassium hydroxide in a water/1,4-dioxane mixture at 100 °C (Scheme 63).[176] With 1-4 mol% of catalyst, a variety of aryl chlorides and bromides were efficiently coupled in short reaction time and high yields. The catalyst system tolerated nitrile-, keto-, hydroxo-, and carboxo-groups as well as enabled the hydroxylation of halo-substituted anisols, styrenes, pyridines and aldehyds. Next to the phenol syntheses, the authors also demonstrated the application of the hydroxylation protocol in tandem reactions. First, a convenient method for alkyl aryl ether synthesis was established. The phenolate formed *in situ* after the hydroxylation step was further reacted with an alkyl halide by addition of cetyltrimethylammonium bromide as a phase transfer catalyst. Moreover, the hydroxylation of 2-chloroaryl alkynes led to benzofuranes in good yields. It was pointed out, that an excess of hydroxide base (2 equiv.) was necessary to convert the substrate to the phenol, while the application of other inorganic bases like K_3PO_4 led to diarylether formation.



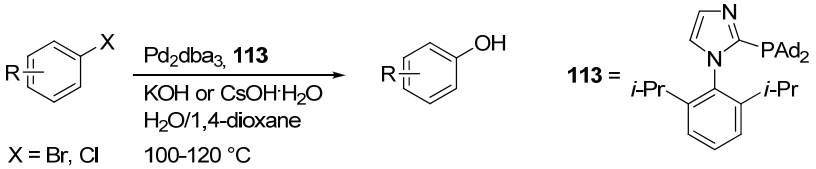
Scheme 63: Pd/biarylphosphine catalyzed synthesis of phenols from aryl halides.

Kwong *et al.* reported one year later the $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalyzed formation of phenols from highly activated aryl halides (Scheme 64).[177] Interestingly, potassium phosphate used as base served herein well. The reactions were performed in toluene at 25-100 °C with a 2 mol% catalyst loading.



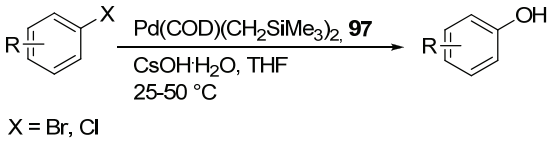
Scheme 64: Pd/P(*t*-Bu)$_3$ catalyzed synthesis of phenols from aryl halides.

Our group chose the palladium-catalyzed hydroxylation of aryl halides as a challenging model reaction for their new developed imidazole-based phosphines (Scheme 65).[67] A mixture of $Pd_2(dba)_3$ (0.5-4 mol%) and ligand **113** (4-16 mol%) was found to be the most active catalyst. The reaction conditions were comparable to those reported by Buchwald, although in the case of some substrates the use of CsOH·H_2O proved to be more beneficial. The system featured higher catalyst productivity in some cases compared to Buchwald's procedure, but a lower functional group tolerance.



Scheme 65: Pd-catalyzed hydroxylation of aryl halides catalyzed by a Pd/arylimidazole phosphine system.

In a subsequent publication, we presented also mechanistic investigations.[178] After mixing [Pd(COD)(CH_2SiMe_3)$_2$] complex with ligand **113** and mesityl bromide in THF at room temperature, the oxidative addition complex was isolated in 60 % yield. X-Ray analysis of this complex revealed a remarkable P,N chelation, which had also been observed in similar complexes.[179],[67] Attempts to synthesize a [Pd(2,4,6-$Me_3C_6H_2$)(**113**)(OH)] complex failed, as reductive elimination was also found to take place at room temperature. Consequently, catalytic reactions were conducted at 25-50 °C, applying 1-4 mol% of [Pd(COD)(CH_2SiMe_3)$_2$] and 1.5-6 mol% of ligand **113** (Scheme 66).



Scheme 66: Pd-catalyzed hydroxylation of aryl halides catalyzed by a Pd/arylimidazole phosphine system at room temperature.

It was pointed out that this unusual catalyst precursor outperformed common used Pd sources. $CsOH{\cdot}H_2O$ was applied as base/hydroxide source; other hydroxides remained inferior, presumably because of lacking solubility in THF. Compared to the protocol of hydroxylation at elevated temperatures, the scope of reaction was expanded, as the catalytic system allowed the selective transformation of nitrile- and trifluoromethyl-substituted aryl halides.

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3 Objectives of this Work

Bulky, electron-rich phosphines are effective ligands in palladium-catalyzed cross-coupling reactions, which are most useful organic transformations. For industrial palladium-catalyzed processes, (phosphine) ligands have to be stable and easy to be synthesized from cost-effective starting materials. In former projects, 2-phosphino-*N*-arylindoles and -pyrroles were conveniently prepared by a modular synthesis and successfully tested in the Suzuki coupling and the Buchwald-Hartwig amination. Their efficiency prompted us to explore their applicability in other cross coupling reactions like the Sonogashira-Hagihara reaction, which is a reliable and widely used method to form C(sp)–C(sp^2) bonds. However, the selective conversion of highly functionalized aryl halides and heteroaryl halides is still a challenging goal. By using 2-(di-*tert*-butylphosphino)-*N*-phenylindole as ligand, a mild and efficient protocol for the selective Sonogashira coupling of a variety of such aryl and heteroaryl bromides with different aryl and alkyl acetylenes was established (*ChemSusChem* **2008**, *1*, 91-96).

We then set our focus on the development of novel phosphine ligands being suitable for Pd-catalyzed cross couplings. Encouraged by the success of the indol- and pyrrol-based phosphines, 2-phosphino-*N*-arylimidazoles were prepared in high yields and purity by a convenient lithiation-phosphorylation method. They are remarkably stable towards air and were found to form highly active catalysts in the Pd-catalyzed selective hydroxylation of aryl halides, a novel and challenging cross coupling reaction producing phenols (*Angew. Chem.* **2009**, *121*, 936-939; *Angew. Chem. Int. Ed.* **2009**, *48*, 918-921).

Mechanistic studies of the Pd-catalyzed hydroxylation with the new catalyst system followed (*Angew. Chem.* **2009**, *121*, 7731-7735; *Angew. Chem. Int. Ed.* **2009**, *48*, 7595-7599). Herein, it was demonstrated that all steps of the catalytic cycle of the Pd-catalyzed hydroxylation can proceed under very mild conditions. Based on these findings, the first room temperature synthesis of phenols was presented.

Systematically, the scope of the novel phosphine ligands was expanded to other useful but challenging coupling reactions.

In the Heck-Cassar coupling of aryl chlorides, [*N*-(2,6-diisopropylphenyl)-2-imidazolyl]-di-*tert*-butylphosphine showed an excellence performance. (*Chem. Eur. J.* **2009**, *15*, 1329-1336). Various aryl and heteroaryl chlorides were reacted in good to excellent yields with

aryl and alkyl acetylenes. This Pd-catalyzed alkynylation procedure was cost-effective with respect to solvent, base and the avoiding of copper source. Moreover, mechanistic investigations were undertaken regarding the influence of the solvent propylene carbonate on the activity of the catalyst.

In another Pd-catalyzed reaction, the selective monoarylation of ammonia, catalysts derived from the novel ligands proved to be very active (*Chem. Eur. J.* **2009**, *15*, 4528-4533). A general coupling protocol allowed the selective conversion of deactivated, electron-neutral and activated halides, *o*-, *m*- and *p*-substituted substrates, aryl chlorides as well as heterocycles. Besides the novel imidazole-based ligands, 2-(di-*tert*-butylphosphino)-*N*-phenylpyrrole also performed excellent.

4 Publications

4.1 Palladium Catalysts for Highly Selective Sonogashira Reactions of Aryl and Heteroaryl Bromides

ChemSusChem **2008**, *1*, 91-96.

Christian Torborg, Alexander Zapf, and Matthias Beller*

C.T. conducted all the experiments and prepared the manuscript. The work of C.T. to this publication accounts to approximately 90 %.

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Palladium Catalysts for Highly Selective Sonogashira Reactions of Aryl and Heteroaryl Bromides

Christian Torborg, Alexander Zapf, and Matthias Beller*[a]

*Palladium catalysts have been studied for the Sonogashira–Hagihara coupling of aryl and heteroaryl bromides with terminal alkynes. Among the different biarylphosphines tested, 2-(di-*tert*-butylphosphino)-N-phenylindole (cataCXium PIntb) allows the efficient coupling of both activated and deactivated (hetero)aryl bromides in the presence of sodium tetrachloropalladate in tetramethylethylenediamine (TMEDA) at 80 °C. The catalyst system gives high turnover numbers (up to 14100) and shows a broad tolerance towards functional groups such as OH and NH_2, as well as heterocycles.*

Introduction

Palladium-catalyzed coupling processes of aryl–X compounds (X = Cl, Br, I, N_2^+, COCl, SO_2Cl, $CO_2C(O)R$, OSO_2R_f, OSO_2CH_3) such as the Heck and Suzuki reactions, the Stille and Sonogashira coupling reactions, and similar carbonylation reactions are important methods for forming carbon–carbon bonds.[1] Owing to their generality and broad tolerance of functional groups, these methods have become powerful tools for organic synthesis and have been used extensively over the last three decades for the synthesis of building blocks and natural products. Besides their use in laboratory-scale synthesis, these methods offer shorter and more selective routes to a number of currently used industrial fine chemicals as compared to classic stoichiometric organic transformations.[2] Moreover, such applied catalysis is in most cases cost-efficient and sustainable in terms of shorter reaction times, lower reaction temperatures, and reduced amounts of expensive metals needed as catalyst precursors.

For some years, we have been interested in the development of more efficient palladium catalysts for applications in coupling reactions on both the laboratory and industrial scale.[3] In this respect, we have developed palladacycles,[4] adamantylphosphines,[5] and carbene ligands.[6] In 2004, based on the success of Buchwald's biaryl ligands, we reported the synthesis of 2-phosphino-*N*-arylindoles and -pyrroles and their application in cross-coupling reactions of aryl chlorides.[7] Nowadays, these ligands are commercially available under the trade name cataCXium P. They are easy to prepare, even on the kilogram scale, are remarkably stable to air, and afford efficient catalysts in the Suzuki reaction and amination of various aryl chlorides. Here, we report for the first time the use of such heteroaryl-arylphosphines, and in particular 2-(di-*tert*-butylphosphino)-*N*-phenylindole, in Sonogashira reactions.

The Sonogashira coupling of unsaturated organic halides with alkynes is the most general method for the synthesis of conjugated acetylenes. The original protocol reported by Sonogashira et al. in 1975 described the coupling of aryl bromides and iodides in the presence of catalytic amounts of $[(PPh_3)_2PdCl_2]$ and CuI in $HNEt_2$ at room temperature.[8] Since then, various catalyst systems have been applied in the Sonogashira reaction, including palladium monophosphine systems, palladacycles, chelating diphosphines, diamines, and P,N ligands, as well as carbene ligands.[9] Until recently, highly productive Sonogashira couplings of aryl halides were performed in the presence of tricyclohexylphosphine[10] or tri-*tert*-butylphosphine (**1**; Figure 1).[11] Notably, Plenio and Köllhofer obtained high catalyst turnover numbers (TONs up to 20000) in the coupling of aryl bromides when using tri-*tert*-butylphosphonium tetrafluoroborate as ligand precursor.[11c] Plenio and co-workers also described efficient Sonogashira reactions of aryl chlorides using di-1-adamantylphosphines such as **2**[11b] and later on 9-fluorenylphosphines **3**–**6**.[12] Moreover, successful applications of homogeneous catalysts supported on polymers as well as ionic-phase-tagged catalysts were reported.[13] In all these reactions, CuI is applied as co-catalyst in dimethyl sulfoxide (DMSO) with sodium carbonate as base. Interestingly, Gelman and Buchwald reported that CuI inhibited the reaction when cesium carbonate was used in acetonitrile. However, use of the highly sterically demanding ligand **7** under copper-free conditions led to high catalyst productivity.[14] Recently, Doucet, Santelli, and co-workers reported that ferrocenylphosphine ligands **8** and **9**, as well as their tetraphosphine ligand tedicyp (**10**), showed exceptionally high catalyst TONs (up to 920000) for the conversion of strongly activated aryl bromides.[15] Noteworthy, tedicyp (**10**) also performs well in the coupling of alkynes with activated aryl chlorides.[16] Despite these impressive developments, Sonogashira reactions of more functionalized substrates as well as heteroaryl halides remain challenging.[14,17] For example, only a few reports deal with the coupling of oxygen and sulfur heterocycles or hydroxy-substituted halobenzenes.[18]

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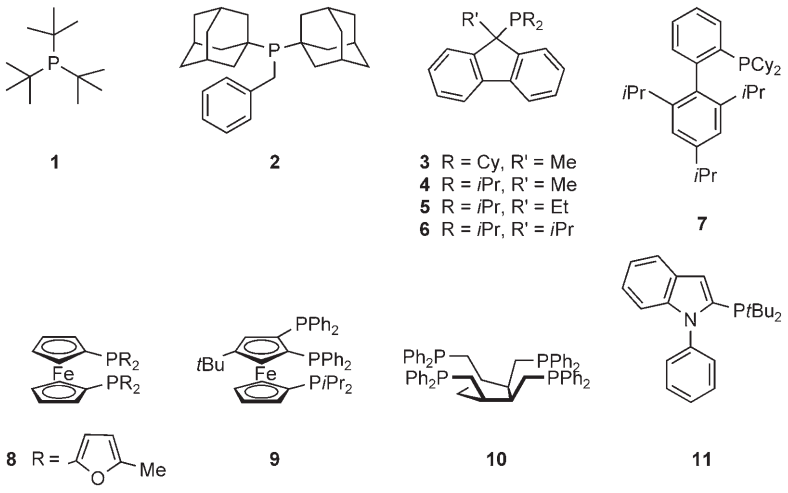


Figure 1. Selected efficient ligands for Sonogashira reactions (Cy = cyclohexyl).

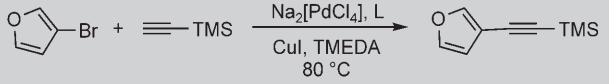
Results and Discussion

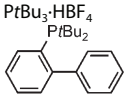
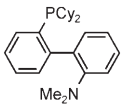
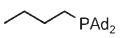
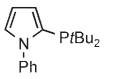
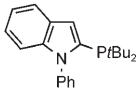
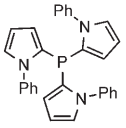
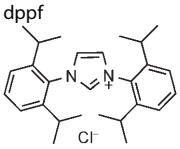
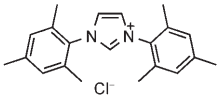
Initially, we investigated the coupling of 3-bromofuran with trimethylsilylacetylene as a more challenging coupling reaction. Exploratory experiments revealed that this Sonogashira reaction proceeded in the presence of palladium and triphenylphosphine in moderate yield. Hence, this constitutes a useful model system for testing different ligands. Selected results from screening experiments are shown in Table 1. In general 0.5 mol% of $Na_2[PdCl_4]$ was applied as palladium precursor in the presence of 1 mol% of the corresponding ligand. Among the 10 different phosphine and two carbene ligands tested, 2-(di-*tert*-butylphosphino)-*N*-phenylindole (**11**, cataCXium Pintb) and 2-(di-*tert*-butylphosphino)biphenyl followed by tri-*tert*-butylphosphonium tetrafluoroborate were found to perform best with CuI as co-catalyst and tetramethylethylenediamine (TMEDA) as solvent at 80 °C. Next, we investigated the Sonogashira coupling of 3-bromofuran with trimethylsilylacetylene in the presence of ligand **11** under milder conditions and at lower catalyst concentrations. Thus, different reaction conditions were tested in combination with the novel catalyst system.

As shown in Table 2, the role of TMEDA as solvent and base is crucial for the success of this reaction. When other amines such as triethylamine (Table 2, entries 2 and 3), 1,4-diazabicyclo[2.2.2]octane (DABCO; Table 2, entry 7), and diisopropylamine (Table 2, entry 1) were applied, only low yields were obtained. The use of Na_2CO_3 (Table 2, entries 4, 5, and 8) and Cs_2CO_3 (Table 2, entry 6) in different solvents gave no conversion at all. At room temperature, the reaction proceeds only slowly (Table 2, entry 13). Lowering the catalyst concentration to 0.1 mol% Pd decreased the yield to 70%, which corresponds to a turnover number of 700 (Table 2, entry 10). However, a further decrease in the catalyst concentration to 0.01 mol% Pd even at 120 °C resulted in low conversion and yield (Table 2, entry 14).

With optimized reaction conditions in hand, we focused on the general applicability of $Na_2[PdCl_4]$/**11** in the Sonogashira reaction of different aryl and heteroaryl bromides with trimethylsilylacetylene. As shown in Table 3, in all cases good to excellent conversions and yields were obtained with a catalyst concentration of 0.5 mol%. Activated aryl bromides such as 4-bromoacetophenone and 2-bromobenzonitrile are efficiently coupled at lower catalyst concentrations (Table 3, entries 1 and 3). Hence, in the case of 4-bromoacetophenone a turnover number of 14100 was observed. Attempts of coupling electron-rich bromides (Table 3, entries 4 and 6) were also successful, while substrates with *ortho* substitutents gave somewhat lower conversions (Table 3, entries 8 and 9). Notably, the catalyst system showed a high tolerance towards unprotected hydroxy and amino groups (97% and 81%, respectively; Table 3, entries 5 and 7). Here, no competitive palladium-catalyzed amination or aryl ether formation was observed. With respect to biologi-

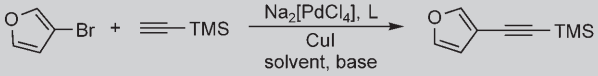
Table 1. Sonogashira coupling of 3-bromofuran and trimethylsilylacetylene in the presence of different ligands (L).[a]



Entry	Ligand	Conv. [%]	Yield [%][b]
1	PPh_3	65	57
2	PCy_3	4	4
3	$PtBu_3 \cdot HBF_4$	92	78
4		87	86
5		49	24
6		66	55
7		75	71
8		91	86
9		3	3
10	dppf	64	60
11		3	2
12		37	36

[a] Reaction conditions: 3-bromofuran (1 equiv), trimethylsilylacetylene (1.2 equiv), $Na_2[PdCl_4]$ (0.5 mol%), ligand (1 mol%), CuI (1 mol%), TMEDA (1 M), 80 °C, 20 h. TMS = trimethylsilyl, Ad = adamantyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene. [b] Yields determined by GC.

Table 2. Investigation of solvents and bases on the model reaction in the presence of ligand **11**.[a]



Entry	Solvent	Base	Pd source	Pd [mol%]	L [mol%]	T [°C]	Conv. [%]	Yield [%][b]
1	$HNiPr_2$	–	$Na_2[PdCl_4]$	0.5	1	80	7	7
2	PC	NEt_3	$Na_2[PdCl_4]$	0.5	1	80	14	14
3	NEt_3	–	$Na_2[PdCl_4]$	0.5	1	80	1	1
4	Toluene	Na_2CO_3	$Na_2[PdCl_4]$	0.5	1	80	1	1
5	DMSO	Na_2CO_3	$Na_2[PdCl_4]$	0.5	1	80	1	1
6	CH_3CN	Cs_2CO_3	$Na_2[PdCl_4]$	0.5	1	80	0	0
7	CH_3CN	DABCO	$Na_2[PdCl_4]$	0.5	1	80	22	21
8	Dioxane	Na_2CO_3	$Na_2[PdCl_4]$	0.5	1	80	4	4
9	TMEDA	–	$Na_2[PdCl_4]$	0.5	1	80	91	86
10	TMEDA	–	$Pd(OAc)_2$	0.1	1	80	84	70
11	TMEDA	–	$Na_2[PdCl_4]$	0.01	0.1	80	0	0
12	TMEDA	–	$Na_2[PdCl_4]$	0.5	1	24	15	15
13	TMEDA	–	$Na_2[PdCl_4]$	0.5	0.5	80	90	73
14	TMEDA	–	$Pd(OAc)_2$	0.01	0.1	120	10	8

[a] Reaction conditions: 3-bromofuran (1 equiv), trimethylsilylacetylene (1.2 equiv), CuI (1 mol%), solvent (1 M), base (2 equiv), 80 °C, 20 h (reaction times not optimized). PC = propylene carbonate. [b] Yields determined by GC.

cally active compounds, it is important that heterocycles afford the desired products in high yield. Six-membered nitrogen heterocycles such as pyridines (67–93%; Table 3, entries 13–15) were as easily coupled as five-membered sulfur and oxygen heterocycles (86–99%; Table 3, entries 10–11).

3-Bromopyrimidine (Table 3, entry 12) required a somewhat higher reaction temperature of 110 °C to give a satisfying yield of 77%. To our delight, the Sonogashira coupling of 5-bromoindole gave the corresponding 5-(trimethylsilylethynyl)indole in excellent yield (93%). Again, the coupling proceeded highly chemoselectively without the need for protecting groups on the indole nitrogen atom.

Finally, we investigated the coupling reaction of 3-bromothiophene with four different alkynes (Table 4). In all cases, the desired products were obtained in high yield (83–96%) using 0.5 mol% Pd and 1 mol% **11** at 80 °C. Alkynes bearing an aliphatic side chain (Table 4, entries 1, 3, and 4) were converted into the corresponding alkynyl-thiophenes, as was the simple phenylacetylene (87%; Table 4, entry 2). The reaction of 2-methylbut-3-yn-2-ol and 3-bromothiophene proceeded smoothly with high chemoselectivity (94%; Table 4, entry 1); in this case, only traces (< 1%) of the corresponding aryl-propargylic ether were detected.

Summary

In conclusion, we have described for the first time the use of N-substituted heteroarylphosphines in Sonogashira reactions. In general, good to excellent results were obtained for the coupling of a variety of aryl and heteroaryl bromides using a mixture of sodium tetrachloropalladate and 2-(di-*tert*-butylphosphino)-*N*-arylindole (**11**) in TMEDA at 80 °C. This novel catalyst system offers high chemoselectivity and functional group tolerance, which makes it especially useful for applications in the area of biologically active compounds.

Experimental Section

All reactions were performed under argon atmosphere using standard Schlenk techniques. All starting materials and reactants were used as received from commercial suppliers, except TMEDA, which was distilled from calcium hydride under argon before use.

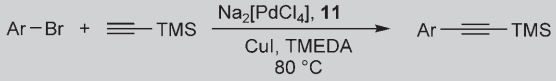
General Procedure for the Sonogashira Coupling

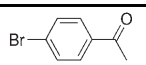
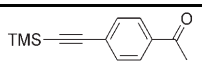
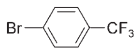
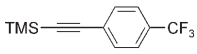
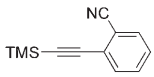
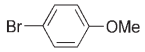
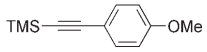
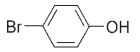
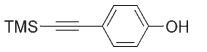
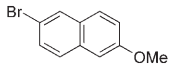
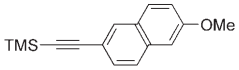
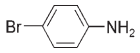
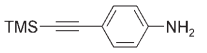
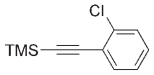
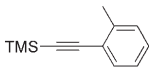
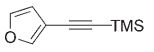
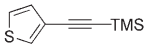
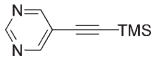
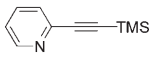
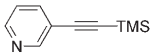
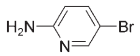
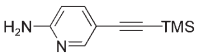
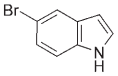
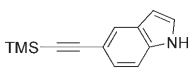
A 25-mL Schlenk tube was evacuated and backfilled with argon. The flask was charged with sodium tetrachloropalladate (1.47 mg, 0.005 mmol), ligand (0.01 mmol), and copper iodide (1.90 mg, 0.01 mmol). Then, TMEDA (1 mL), (hetero)aryl halide (1 mmol), and the acetylene substrate (1.2 mmol) were added successively under argon atmosphere. The mixture was stirred for 20 h at 80 °C, during which time a white precipitate formed. After cooling the contents to room temperature, the mixture was quenched with water (3 mL) and the aqueous phase was extracted with diethyl ether (3 × 3 mL). The organic phases were combined and concentrated, and the desired product was isolated by column chromatography (hexane or hexane/ethyl acetate 20:1). Alternatively, the reaction mixture was quenched with water (3 mL) and diluted with diethyl ether (7 mL). Hexadecane was then added as internal standard, and quantitative analysis was performed by using gas chromatography. Commercially available products were identified by comparison of their GC-MS data with the data of authentic samples; all known products were characterized by NMR spectroscopy, mass spectrometry (EI MS), and high-resolution mass spectrometry (HRMS).

(4-Trimethylsilylethynyl)acetophenone: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 2H; $2H_{arom}$), 7.41–7.35 (m, 2H; $2H_{arom}$), 2.43 (s, 3H; $CH_3C{=}O$), 0.11 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5 ($CH_3C{=}O$), 136.5 (C_{arom}), 132.2 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 104.2 (C_{acetyl}-C_{arom}), 98.3 ($CSi(CH_3)$), 26.8 ($CH_3C{=}O$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 216 (18) $[M]^+$, 201 (100), 158 (9), 143 (7). HRMS: calcd for $C_{13}H_{16}OSi$: 216.09649; found: 216.09620.

(4-Methoxyphenylethynyl)trimethylsilane: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.35 (m, 2H; $2H_{arom}$), 6.85–6.75 (m, 2H; $2H_{arom}$),

Table 3. Sonogashira coupling of trimethylsilylacetylene with different aryl and heteroaryl bromides.[a]



Entry	Substrate	Product	Conv. [%]	Yield [%][b]
1			100	71[c,d]
2			100	93
3			100	90[e]
4			100	83
5			100	97
6			100	99
7			100	81
8			90	78
9			90	68
10			95	86[d]
11			100	99[d]
12			100	77[f]
13			90	67
14			90	73
15			100	93
16			100	93

[a] Reaction conditions: aryl bromide (1 equiv), trimethylsilylacetylene (1.2 equiv), $Na_2[PdCl_4]$ (0.5 mol%), **11** (1 mol%), CuI (1 mol%), TMEDA (1 M), 80 °C, 20 h (reaction times not optimized). [b] Yield of isolated product. [c] Reaction run with 0.005 mol% Pd source. [d] Yield determined by GC. [e] Reaction run with 0.05 mol% Pd source. [f] Reaction run at 110 °C.

3.78 (s, 3H; CH_3O), 0.26 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.7$ (C_{arom}), 133.4 (C_{arom}), 115.2 (C_{arom}), 113.7 (C_{arom}), 105.1 (C_{acetyl}-C_{arom}), 92.3 ($CSi(CH_3)$), 55.2 (CH_3O), 0.00 ppm ($Si(CH_3)_3$). MS (%): 204 (31) $[M]^+$, 189 (100), 174 (8), 146 (7). HRMS: calcd for $C_{12}H_{16}OSi$: 204.09649; found: 204.09609.

(4-Trifluoromethylphenylethynyl)trimethylsilane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.55–7.5$ (m, 4H; $4H_{arom}$), 0.24 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 132.4$ (C_{arom}), 130.6 (C_{arom}), 130.1 (C_{arom}), 127.1 (C_{arom}), 125.9 (CF_3), 125.3 (C_{arom}), 103.6 (C_{acetyl}-C_{arom}), 97.4 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 242 (12) $[M]^+$, 227 (100), 197 (6). HRMS: calcd for $C_{12}H_{13}F_3Si$: 242.07331; found: 242.07317.

(2-Chlorophenylethynyl)trimethylsilane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.20–7.15$ (m, 1H; H_{arom}), 7.07–7.04 (m, 1H; H_{arom}), 6.95–6.84 (m, 2H; H_{arom}), 0.00 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.3$ (C_{arom}), 133.7 (C_{arom}), 129.6 (C_{arom}), 129.3 (C_{arom}), 126.4 (C_{arom}), 123.2 (C_{arom}), 101.4 (C_{acetyl}-C_{arom}), 100.34 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 208 (21) $[M]^+$, 193 (100), 165 (7), 129 (5), 115 (16), 63 (10). HRMS: calcd for $C_{11}H_{13}ClSi$: 208.04696; found: 242.04700.

(2-Tolylethynyl)trimethylsilane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.30–7.13$ (m, 2H; H_{arom}), 7.49–7.46 (m, 2H; H_{arom}), 2.49 (s, 3H; CH_3), 0.32 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.5$ (C_{arom}), 132.0 (C_{arom}), 129.3-(C_{arom}), 128.4 (C_{arom}), 125.3 (C_{arom}), 122.8 (C_{arom}), 104.0 (C_{acetyl}-C_{arom}), 98.1 ($CSi(CH_3)_3$), 20.56 (CH_3-C_{arom}), 0.37 ppm ($Si(CH_3)_3$). MS (%): 188 (25) $[M]^+$, 173 (100), 145 (14), 86 (7). HRMS: calcd for $C_{12}H_{16}Si$: 188.10158; found: 188.10136.

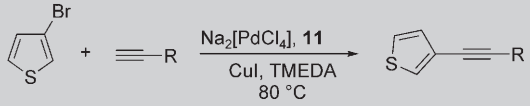
5-(Trimethylsilylethynyl)pyrimidine: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.10–9.05$ (m, 1H; H_{arom}), 8.78–8.72 (m, 2H; $2H_{arom}$), 0.24 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$ (C_{arom}), 157.0 (C_{arom}), 120.1 (C_{arom}), 103.3 (C_{acetyl}-C_{arom}), 97.9 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 176 (19) $[M]^+$, 161 (100), 107 (7), 77 (6). HRMS: calcd for $C_9H_{12}N_2Si$: 176.07643; found: 176.07665.

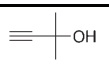
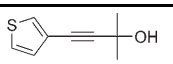
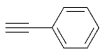
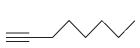
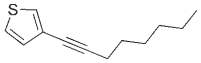
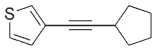
4-(Trimethylsilylethynyl)aniline: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.27–7.22$ (m, 2H; $2H_{arom}$), 6.57–6.52 (m, 2H; $2H_{arom}$), 3.77 (bs, 2H; NH_2), 0.21 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.6$ (C_{arom}), 133.2 (C_{arom}), 114.4 (C_{arom}), 112.3 (C_{arom}), 105.9 (C_{acetyl}-C_{arom}), 91.2 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 189 (42) $[M]^+$, 174 (100), 144 (7), 150 (5), 87 (7). HRMS: calcd for $C_{11}H_{15}NSi$: 189.09683; found: 189.09642.

(3-Thiophenylethynyl)trimethylsilane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.45–7.42$ (m, 1H; H_{arom}), 7.23–7.18 (m, 1H; H_{arom}), 7.10–7.07 (m, 1H; H_{arom}), 0.20 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 130.1$ (C_{arom}), 129.6 (C_{arom}), 125.2 (C_{arom}), 122.4 (C_{arom}), 99.9 (C_{acetyl}-C_{arom}), 93.9 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 180 (27) $[M]^+$, 165 (100), 135 (6). HRMS: calcd for $C_9H_{12}SSi$: 180.04235; found: 180.04177.

(3-Furylethynyl)trimethylsilane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61–7.60$ (m, 1H; H_{arom}), 7.32–7.31 (m, 1H; H_{arom}), 6.43–6.42 (m, 1H; H_{arom}), 0.21 (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.4$ (C_{arom}), 142.7 (C_{arom}), 112.7 (C_{arom}), 107.7 (C_{arom}), 96.4 (C_{acetyl}-C_{arom}),

Table 4. Sonogashira coupling of 3-bromothiophene with different alkynes.[a]



Entry	Alkyne	Product	Conv. [%]	Yield [%][b]
1			100	94
2			95	87
3			85	82
4			100	96

[a] Reaction conditions: 3-bromothiophene (1 equiv), alkyne (1.2 equiv), $Na_2[PdCl_4]$ (0.5 mol%), **11** (1 mol%), CuI (1 mol%), TMEDA (1 M), 80 °C, 20 h (reaction times not optimized). [b] Yield of isolated product.

96.1 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 164 (21) $[M]^+$, 149 (100). HRMS: calcd for $C_9H_{12}OSi$: 164.06519; found: 164.06572.

2-(Trimethylsilylethynyl)pyridine: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.57–8.50 (m, 1H; H_{arom}), 7.61–7.56 (m, 1H; H_{arom}), 7.43–7.38 (m, 1H; H_{arom}), 7.19–7.15 (m, 1H; H_{arom}), 0.23 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$150.2 (C_{arom}), 143.4 (C_{arom}), 136.3 (C_{arom}), 127.5 (C_{arom}), 123.9 (C_{arom}), 103.9 (C_{acetyl}-C_{arom}), 95.0 ($CSi(CH_3)_3$), 0.37 ppm ($Si(CH_3)_3$). MS (%): 175 (25) $[M]^+$, 160 (100), 132 (8), 106 (9). HRMS: calcd for $C_{10}H_{13}NSi$: 175.08118; found: 175.08166.

3-(Trimethylsilylethynyl)pyridine: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.70–8.60 (m, 1H; H_{arom}), 8.48–8.46 (m, 1H; H_{arom}), 7.69–7.66 (m, 1H; H_{arom}), 7.21–7.15 (m, 1H; H_{arom}), 0.22 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$152.8 (C_{arom}), 148.9 (C_{arom}), 139.0 (C_{arom}), 123.1 (C_{arom}), 120.5 (C_{arom}), 101.7 (C_{acetyl}-C_{arom}), 98.4 ($CSi(CH_3)_3$), 0.37 ppm ($Si(CH_3)_3$). MS (%): 175 (22) $[M]^+$, 160 (100), 130 (5). HRMS: calcd for $C_{10}H_{13}NSi$: 175.08118; found: 175.08140.

2-(Trimethylsilylethynyl)benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.61–7.58 (m, 1H; H_{arom}), 7.55–7.46 (m, 2H; $2H_{arom}$), 7.39–7.34 (m, 1H; H_{arom}), 0.27 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$132.9 (C_{arom}), 132.8 (C_{arom}), 132.6 (C_{arom}), 139.0 (C_{arom}), 128.8 (C_{arom}), 127.3 (C_{arom}), 117.6 (C_{arom}), 116.1 (CN), 102.5 (C_{acetyl}-C_{arom}), 100.9 ($CSi(CH_3)_3$), 0.37 ($Si(CH_3)_3$). MS (%): 199 (12) $[M]^+$, 184 (100), 168 (5), 154 (25), 130 (6), 84 (5). HRMS: calcd for $C_{12}H_{13}NSi$: 199.08118; found: 199.08130.

5-(Trimethylsilylethynyl)-1*H*-indole: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.11 (bs, 1H; NH), 7.75–7.74 (m, 1H; H_{arom}), 7.25–7.18 (m, 2H; $2H_{arom}$), 7.14–7.12 (m, 1H; H_{arom}), 7.14–7.12 (m, 1H; H_{arom}), 6.47–6.44 (m, 1H; H_{arom}), 0.20 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$135.4 (C_{arom}), 127.4 (C_{arom}), 125.8 (C_{arom}), 125.0 (C_{arom}), 124.8 (C_{arom}), 114.1 (C_{arom}), 110.1 (C_{arom}), 106.8 (C_{acetyl}-C_{arom}), 102.8 (C_{arom}), 90.9 ($CSi(CH_3)_3$) 0.00 ppm ($Si(CH_3)_3$). MS (%): 213 (39) $[M]^+$, 198 (100), 168 (6), 154 (5), 99 (8). HRMS: calcd for $C_{13}H_{15}NSi$: 213.09683; found: 213.09633.

(6-Methoxy-2-naphthylethynyl)trimethylsilane: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.94–7.89 (m, 1H; H_{arom}), 7.69–7.59 (m, 2H; $2\times H_{arom}$), 7.49–7.42 (m, 1H; H_{arom}), 7.16–7.05 (m, 2H; $2H_{arom}$), 3.90 (s, 3H; OCH_3), 0.26 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 158.3 (C_{arom}), 134.2 (C_{arom}), 131.8 (C_{arom}), 129.3 (C_{arom}), 129.1 (C_{arom}), 128.3 (C_{arom}), 126.6 (C_{arom}), 119.3 (C_{arom}), 117.9 (C_{arom}), 105.7 (C_{arom}), 105.6 (C_{acetyl}-C_{arom}), 93.6 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 254 (55) $[M]^+$, 239 (100), 224 (5), 196 (12), 119 (10), 98 (5). HRMS: calcd for $C_{16}H_{18}OSi$: 254.11214; found: 254.11209.

2-Amino-5-(trimethylsilylethynyl)pyridine: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$8.18–8.16 (m, 1H; H_{arom}), 7.48–7.41 (m, 1H; H_{arom}), 6.39–6.34 (m, 1H; H_{arom}), 4.62 (bs, 2H; NH_2), 0.20 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$157.5 (C_{arom}), 152.0 (C_{arom}), 140.7 (C_{arom}), 109.8 (C_{arom}), 107.7 (C_{arom}), 102.7 (C_{acetyl}-C_{arom}), 94.5 ($CSi(CH_3)_3$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 190 (57) $[M]^+$, 175 (100), 149 (6), 145 (5), 74 (6). HRMS: calcd for $C_{10}H_{14}N_2Si$: 190.09208; found: 190.09173.

3-(Phenylethynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.49–7.39 (m, 3H; $3\times H_{arom}$), 7.33–7.19 (m, 4H; $4H_{arom}$), 7.16–7.09 ppm (m, 2H; $2H_{arom}$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$131.6 (C_{arom}), 129.9 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 125.4 (C_{arom}), 123.2 (C_{arom}), 122.3 (C_{arom}), 88.9 (C_{acetyl}), 84.5 ppm (C_{acetyl}). MS (%): 184 (100) $[M]^+$, 152 (11), 139 (24). HRMS: calcd for $C_{12}H_8S$: 184.03412; found: 184.03381.

3-(1-Cyclopentylethynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.36–7.28 (m, 1H; H_{arom}), 7.23–7.16 (m, 1H; H_{arom}), 7.08–7.01 (m, 1H; H_{arom}), 2.78 (quin, 1H, $J=8$ Hz; -CH-), 2.07–1.85 (m, 2H), 1.84–1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$130.1 (C_{arom}), 127.4 (C_{arom}), 124.9 (C_{arom}), 123.1 (C_{arom}), 94.1 (C_{acetyl}), 75.1 (C_{acetyl}), 33.9 (CH-CH_2), 30.8 (CH), 25.1 ppm ($CH(CH_2)CH_2$). MS (%): 176 (87) $[M]^+$, 161 (13), 147 (100), 134 (30) 128 (18), 121 (18), 115 (18), 108 (23), 97 (10), 91 (11), 77 (9), 69 (8), 63 (11), 45 (10). HRMS: calcd for $C_{11}H_{12}S$: 176.06542; found: 176.06560.

3-(1-Octynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.35–7.29 (m, 1H; H_{arom}), 7.23–7.16 (m, 1H; H_{arom}), 7.07–7.01 (m, 1H; H_{arom}), 2.36 (t, 2H, $J=7$ Hz; C_{acetyl}-CH_2), 1.65–1.19 (m, 8H; $(CH_2)_4CH_3$), 0.89 ppm (t, 3H, $J=7$ Hz; $(CH_2)_4CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 130.1 (C_{arom}), 127.5 (C_{arom}), 125.0 (C_{arom}), 123.1 (C_{arom}), 90.0 (C_{acetyl}-C_{arom}), 75.6 (C_{acetyl}-CH_2), 31.4, 28.8, 28.7, 22.6, 19.4 (C_{acetyl}-CH_2), 14.1 ppm ($(CH_2)_4CH_3$). MS (%): 192 (54) $[M]^+$, 163 (22), 149 (45), 135 (61), 123 (100), 115 (52), 108 (22), 97 (32), 91 (17), 77 (26), 63 (13), 45 (17). HRMS: calcd for $C_{12}H_{16}S$: 192.09672; found: 176.09644.

4-(Trimethylsilylethynyl)phenol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.38–7.28 (m, 2H; $2H_{arom}$), 6.77–6.68 (m, 2H; $2H_{arom}$), 5.15 (bs, 1H; OH), 0.21 ppm (s, 9H; $Si(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$155.8 (C_{arom}), 133.7 (C_{arom}), 115.4 (C_{arom}), 115.3 (C_{arom}), 105.0 (C_{acetyl}-C_{arom}), 92.5 ($CSi(CH_3)$), 0.00 ppm ($Si(CH_3)_3$). MS (%): 190 (33) $[M]^+$, 175 (100), 145 (8), 115 (6), 88 (7). HRMS: calcd for $C_{11}H_{14}OSi$: 190.08084; found: 190.08046.

2-Methyl-4-(3-thiophenyl)-3-butyn-2-ol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.36–7.32 (m, 1H; H_{arom}), 7.20–7.14 (m, 1H; H_{arom}), 7.04–6.99 (m, 1H; H_{arom}), 2.19 (bs, 1H; OH), 1.53 ppm (s, 6H; $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$129.9 (C_{arom}), 128.7 (C_{arom}), 125.3 (C_{arom}), 121.8 (C_{arom}), 93.4 (C_{acetyl}-$C(CH_3)_2OH$), 77.3 (C_{acetyl}-C_{arom}), 65.7 (C-$(CH_3)_2OH$), 31.5 ($(CH_3)_2$). MS (%): 166 (33) $[M]^+$, 151 (100), 135 (7), 123 (10), 108 (13), 89 (6), 75 (6), 69 (6), 63 (11) 43 (59). HRMS: calcd for $C_9H_{10}OS$: 166.04469; found: 166.04494.

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4.2 Practical Imidazole-Based Phosphine Ligands for the Selective Palladium-Catalyzed Hydroxylation of Aryl Halides

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Synthetic Methods

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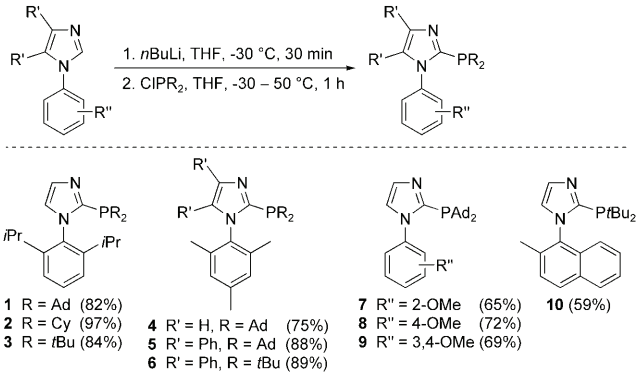
Practical Imidazole-Based Phosphine Ligands for Selective Palladium-Catalyzed Hydroxylation of Aryl Halides**

*Thomas Schulz, Christian Torborg, Benjamin Schäffner, Jun Huang, Alexander Zapf, Renat Kadyrov, Armin Börner, and Matthias Beller**

Phenols are an integral part of numerous pharmaceuticals, polymers, and natural products.[1] In the past the non-oxidative preparation of this class of compounds involved nucleophilic aromatic substitution of activated aryl halides, often under harsh reaction conditions.[2] Smith, Maleczka, and co-workers reported the preparation of non-*ortho*-substituted phenols under milder conditions.[3] However, two steps, CH-activation/borylation and oxidation, were required for the desired transformation. In contrast to well-established palladium-catalyzed aryl ether formations,[4–6] the direct hydroxylation of aryl halides has been a major challenge in coupling chemistry. Buchwald and co-workers achieved this goal for the first time,[7a,b] applying their bulky, monodentate ligands[8] which facilitate C–O reductive elimination. Chen and co-workers[7c] reported the Pd-catalyzed hydroxylation of highly activated aryl bromides in the presence of P(*t*Bu)$_3$.[9]

Despite these developments, there is a need for easily available ligands which lead to generally applicable, more active catalyst systems for this coupling reaction. Clearly, for selective hydroxylation it is important that the subsequent coupling reaction of the phenol towards diaryl ethers is controlled.

Herein, we describe the synthesis of new, sterically demanding phosphine ligands based on *N*-arylated imidazoles (Scheme 1), and their use in the synthesis of phenols from the corresponding aryl halides. Various dialkyl-2-(*N*-arylimidazolyl)-phosphines (**1**–**10**) were synthesized in one or two reaction steps. Notably, the most active 1-(2,6-diisopropylphenyl)-1*H*-imidazole-based phosphine ligands (**1**–**3**) can be readily prepared on 100 g scale. The corresponding *N*-aryl-1*H*-imidazole unit, which is present in many natural products, including amino acids, nucleic acids, and imidazole-based alkaloids,[10] is easily available by various synthetic strategies and allows high tunability.[11]



Scheme 1. Synthesis of dialkyl-2-(*N*-arylimidazolyl)phosphines.

Ligands **1**–**10** are synthesized using either a copper-catalyzed Ullmann reaction[12] or by a four-component condensation of the corresponding aniline with paraformaldehyde, ammonium acetate, and an α-dicarbonyl component (glyoxal or benzil).[13] The resultant *N*-arylated imidazoles were regioselectively deprotonated with *n*-butyl lithium in THF at −30 °C, and the resulting carbanion subsequently quenched with the corresponding dialkylchlorophosphines to give the desired phosphines in good-to-excellent yields after aqueous work up and single recrystallization from H_2O/EtOH (Scheme 1). Unlike the known *N*-aryl-2-(dialkylphosphino)-(benz)imidazoles,[14,15] the addition of N,N,N′,N′-tetramethylethylenediamine (TMEDA) was not required for selective metalation.[6,16]

The novel phosphine ligands were treated with selenium to give the corresponding phosphine selenides. The magnitude of the coupling constant between the phosphorus and selenium atoms was strongly dependent upon the nature of the organic substituents bound to phosphorus.[17] The values of the coupling constants of **1**–**10** are in the same range as Buchwald's biaryl phosphines **13** and **14** (Table 1), suggesting that the electronic and steric effect of both ligand classes is comparable.

To test the new ligands and their applicability to cross-coupling reactions, the palladium-catalyzed hydroxylation of aryl halides was carried out. Initially, a catalyst derived from [Pd(dba)$_2$] (dba = dibenzylideneacetone) and ligand **4** showed moderate activity in the hydroxylation of mesityl bromide with sodium hydroxide in a 1:1 mixture of water and 1,4-dioxane at 100 °C (Table 2). The use of potassium hydroxide in place of sodium hydroxide gave slightly improved results, as did NaO*t*Bu and CsOH, whereas triethylamine, K_3PO_4, and inorganic carbonates were ineffective in the reaction. In combination with KOH, 1,4-dioxane was by far the most

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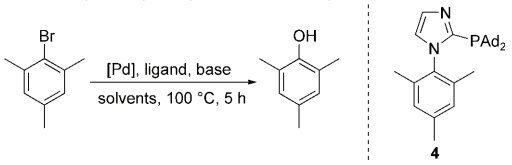
Table 1: Chemical shifts and $^{31}P{=}^{77}Se$ coupling constants for 2-(*N*-arylimidazolyl)phosphine selenides.[a]

Ligand	δ [ppm]	$^1J_{P=Se}$ [Hz]
1	59.3	718
2	40.3	732
3	62.2	726
4	58.9	712
5	60.0	713
6	63.0	724
7	59.0	715
8	58.9	716
9	59.0	717
10	62.2	726
13	45.2	710
14	71.1	742

[a] The corresponding ligand (0.03 mmol) and selenium (2 equivalents) were dissolved in $CDCl_3$ (0.7 mL) in a NMR tube, heated for a short time at 50 °C and submitted to ^{31}P NMR spectroscopy.

Table 2: Pd-catalyzed hydroxylation of mesityl bromide.



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Base[a]	Conversion [%]	Yield [%]
NaOH	51	43
KOH	57	55
$CsOH{\cdot}H_2O$	66	50
Na_2CO_3	< 5	< 5
K_2CO_3	5	5
Cs_2CO_3	14	8
K_3PO_4	7	7
NaO*t*Bu	55	46
NEt_3	90	< 1
–	< 5	< 1
Solvent[b]	**Conversion [%]**	**Yield [%]**
1,4-dioxane	57	55
THF	36	36
MeOH	95	14
DMSO	20	20
Toluene	9	9
DMF	43	< 1%
Pd source[c]	**Conversion [%]**	**Yield [%]**
$[Pd(dba)_2]$	57	55
$Pd(OAc)_2$	29	29
$[Pd(CH_3CN)_2Cl_2]$	12	12
$[Pd(PPh_3)_4]$	< 5	< 5

[a] $[Pd(dba)_2]$ (1 mol%), ligand **4** (4 mol%), base (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h; [b] $[Pd(dba)_2]$ (1 mol%), ligand **4** (4 mol%), KOH (3 equivalents), H_2O/organic solvent (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h; [c] [Pd] (1 mol%), ligand **4** (4 mol%), KOH (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 5 h.

effective organic cosolvent. The other palladium sources investigated were inferior to $[Pd(dba)_2]$.

Next, different ligands were applied to the model hydroxylation reaction, and compared with commercially available ligands (Table 3). In general, the more bulky ligands

Table 3: Ligands for Pd-catalyzed hydroxylation of mesityl bromide.[a]

Entry	Ligand	R	R′	R″	Yield [%]
1	**1**	Ad			77; 72;[b] 88[c]
2	**2**	Cy			0
3	**3**	*t*Bu			49
4	**4**	Ad	H		56
5	**5**	Ad	Ph		75
6	**6**	*t*Bu	Ph		62
7	**7**			2-OMe	0
8	**8**			4-OMe	0
9	**9**			3,4-OMe	0
10	**10**				58
11	**11**				0
12	**12**				0
13	**13**	Cy			1
14	**14**	*t*Bu			8[d]
15	$PtBu_3{\cdot}HBF_4$				3
16	**16**				0

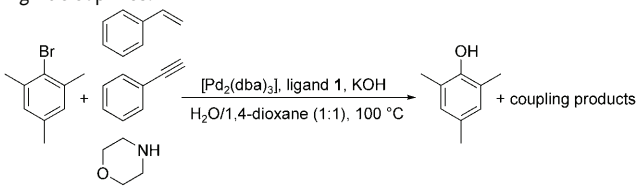
[a] $[Pd_2(dba)_3]$ (1 mol%), ligand (4 mol%), KOH (3 equivalents), H_2O/1,4-dioxane (1:1, 1.2 mL, 0.8 M), 100 °C, 20 h; [b] toluene as organic cosolvent; [c] with $CsOH{\cdot}H_2O$ (3 equivalents) as base, no addition of water; [d] under Buchwald's reaction conditions (mesityl bromide (1 mmol), $[Pd_2(dba)_3]$ (2 mol%), ligand **14** (8 mol%), KOH (3 equivalents), 1,4-dioxane, H_2O, 100 °C, 6 h), a yield of 88% was verified.[7a]

gave better results. For example, adamantyl-substituted ligands proved superior compared to the *tert*-butyl-substituted ligands, whereas cyclohexyl-substituted phosphines led to no reactivity at all (Table 3, entries 1–3). Moreover, for reaction to proceed, substitution at both *ortho*-positions on the aryl ring was necessary (Table 3, entries 7–9). Ligands with a less sterically demanding substitution pattern (mesityl, Table 3, entry 4) were inferior to more bulky ones (2,6-diisopropylphenyl, Table 3, entry 1). Consequently, combining these positive structural features, that is, 1-adamantyl groups attached to phosphorus and isopropyl groups at the 2- and 6-positions of the aryl ring, led to the highest yield in the model reaction (Table 3, entry 1; 77%).

Advantageously, substituents on the imidazole ring could also be altered to improve reactivity (Table 3, entries 5, 6). It is important to note that the commercially available ligands tested led to low or no reactivity (Table 3, entries 11, 12, 15, and 16). Furthermore, only trace amounts of product were detected from the reaction with Buchwald's XPhos ligands under these conditions (Table 3, entries 13, 14).

To understand the behavior of the new catalysts, competitive experiments were carried out in the presence of olefins, alkynes and amines (Table 4). One equivalent (with respect to mesityl bromide) of styrene, phenylacetylene, or morpholine was added to the reaction mixture without optimization. Surprisingly, in the presence of styrene, the potential Heck reaction did not occur and the hydroxylated product was formed in 74% yield. Similarly, the coupling reaction in the presence of morpholine is highly chemoselective, albeit with a reduced conversion. Conversely, the alkyne–arene coupling competed with the hydroxylation. Nevertheless, 55% of the desired phenol was obtained, with 22% of the diarylalkyne. These experiments demonstrate for the first time the high specificity of a palladium catalyst system towards hydroxylation reactions.

Table 4: Selectivity of the hydroxylation reaction in presence of competing nucleophiles.[a]

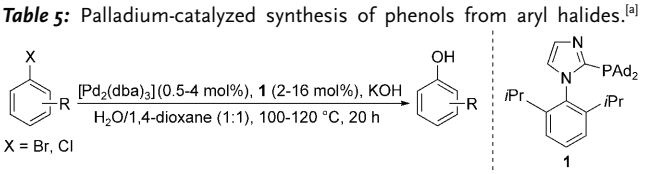


Nucleophile	Yield of phenol [%]	Ratio (phenol/coupling product)
	74	>15:1
	55	2.5:1
	16	>50:1

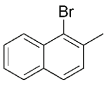
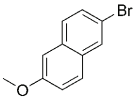
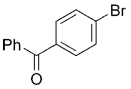
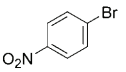
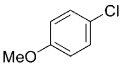
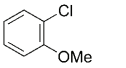
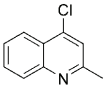
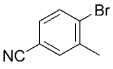
[a] Mesityl bromide (1 mmol), competing nucleophile (1 mmol), [$Pd_2(dba)_3$] (1 mol%), ligand **1** (4 mol%), KOH (3 equivalents), 1,4-dioxane (0.6 mL), H_2O (0.6 mL), 100°C, 20 h.

Finally, the scope of the catalyst system [$Pd_2(dba)_3$]/ligand **1** was examined by treating various aryl bromides and chlorides with KOH in water/1,4-dioxane (Table 5). Different alkyl-substituted aryl bromides and chlorides were converted into the corresponding phenols in good-to-excellent yields (Table 5, entries 1–6; 73–93%). Both activated substrates, such as 4′-bromobenzophenone (Table 5, entry 8; 91%) and 4-bromonitrobenzene (Table 5, entry 9; 99%), and deactivated arenes, such as anisoles and thioanisoles (Table 5, entries 10–12; 88–94%), were fully converted. For aryl chloride substrates, the use of CsOH as a base led to better results and full conversion. In comparison with 2- and 4-chloroanisole, the hydroxylation of 2-bromo-6-methoxynaphthalene was less selective and afforded the corresponding naphthalene-2-ol in moderate yield (Table 5, entry 7; 50%). On using 1-bromo-2-chlorobenzene as the substrate, as expected when substitution of bromide competes with the substitution of chloride, substitution of bromide occurred preferentially (Table 5, entry 13), and only a small amount (<5%) of the chloride-substituted product could be detected. For full conversion of 4-chloroquinaldine, only 1 mol% of palladium (0.5 mol% of [$Pd_2(dba)_3$]) was required (Table 5, entry 14; 99%). Conversely, complete hydroxylation in the presence of a nitrile group necessitated a higher catalyst loading (Table 5, entry 15; 68%).

Table 5: Palladium-catalyzed synthesis of phenols from aryl halides.[a]



1

Entry	Substrate	Yield [%]
1		88[b]
2		93
3		90[c]
4		83
5		73
6		80[c]
7		50
8		91
9		99
10		94[b]
11		90[b]
12		88
13		78[d]
14		99[e]
15		68[f]

[a] Substrate (1 mmol), [$Pd_2(dba)_3$] (1 mol%), ligand **1** (4 mol%), KOH (3 equivalents), 1,4-dioxane (0.6 mL), H_2O (0.6 mL), 100°C, 20 h; [b] CsOH·H_2O (3 equivalents) as base with 1,4-dioxane (1.2 mL) and no addition of water, 120°C; [c] [$Pd_2(dba)_3$] (2 mol%), ligand **1** (8 mol%); [d] product = 2-chlorophenol; [e] [$Pd_2(dba)_3$] (0.5 mol%), ligand **1** (2 mol%); [f] [$Pd_2(dba)_3$] (4 mol%), ligand **1** (16 mol%).

In summary, we synthesized a series of novel imidazole-based phosphine ligands. These phosphines were readily generated in high yields and purities from the corresponding imidazole precursors, by a convenient lithiation–phosphorylation method. Notably, the preparations could be easily scaled up to afford the phosphines on 100 g scale for potential applications. The ligands are remarkably stable towards air and were successfully applied as ligands in the palladium-catalyzed selective hydroxylation of aryl halides with low palladium loadings in the majority of cases. The hydroxylation procedure was uncomplicated and did not require special reagents.[3] Further applications of these ligands are currently under investigation in our laboratories.

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4.3 Palladium-Catalyzed Hydroxylations of Aryl Halides under Ambient Conditions

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C.T. planned and executed several catalytic experiments. C.T. was involved in mechanistic discussions. The work of C.T. to this publication accounts to approximately 30 %.

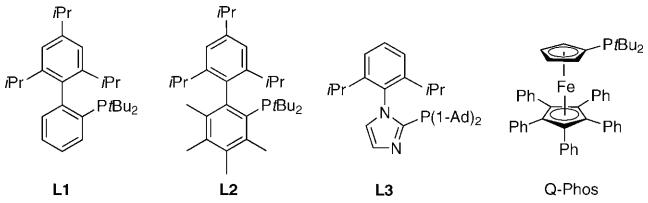
Palladium Catalysis

DOI: 10.1002/anie.200902148

Palladium-Catalyzed Hydroxylation of Aryl Halides under Ambient Conditions**

*Alexey G. Sergeev, Thomas Schulz, Christian Torborg, Anke Spannenberg, Helfried Neumann, and Matthias Beller**

Phenols are found in various natural products ranging from coal tar containing simple phenols to red wine possessing numerous colored polyphenols with antioxidant properties.[1,2] In organic synthesis the development of mild, general, and efficient methods for the preparation of phenols still constitutes a significant challenge. Considering the availability of starting materials, the direct nucleophilic substitution of a halogen atom in aryl halides is an appealing approach to the synthesis of substituted phenols.[3,4] However, reactions of non-activated substrates typically proceed under harsh reaction conditions (200–350 °C).[1] Hence, the development of a milder catalytic phenol synthesis through a two-step coupling procedure by Hartwig and co-workers was an important advancement.[5] Recently, the direct hydroxylation of aryl halides was developed by Buchwald and co-workers as well as by Chan and co-workers using palladium catalysts with bulky tri-*tert*-butylphosphine and biphenylphosphines (**L1**, **L2**).[6,7]

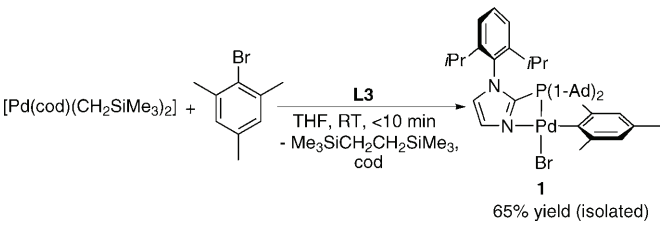


L1 **L2** **L3** Q-Phos

Among the various catalytic systems studied, palladium complexes based on ligands **L1** and **L2** allowed C–O coupling of both activated and non-activated aryl halides at 80–100 °C.[7] Inspired by the efficiency of palladium/biphenylphosphine catalysts, we recently demonstrated the hydroxylation of aryl halides in the presence of imidazole-based ligands.[8] Although progress in palladium-catalyzed C–O bond-forming reactions made it possible to arylate alcohols under milder conditions,[9,10] the coupling using water remained problematic.[4] Indeed, no examples of phenol syntheses from non-activated aryl halides at ambient temperature have been described to date,[11] and the mechanistic understanding of this coupling reaction is limited.

Herein we report the first room temperature palladium-catalyzed hydroxylation of aryl chlorides and bromides as deduced from studies of the elementary steps of the catalytic cycle. In the presence of a novel palladium precursor and the imidazolylphosphine ligand **L3** (Ad = adamantyl), a variety of phenols can be obtained from aryl halides in excellent yield.

Initially, we were interested in the structure and reactivity of palladium complexes of the bulky ligand **L3**, which was previously involved in the hydroxylation of aryl halides. To prepare the corresponding oxidative addition complex, bromomesitylene was reacted with different palladium sources and ligand **L3** in THF at room temperature. Notably, only $[Pd(cod)(CH_2SiMe_3)_2]$ allowed isolation of the desired oxidative addition product in pure form. The oxidative addition of bromomesitylene in the presence of $[Pd(cod)(CH_2SiMe_3)_2]$ and **L3** took place within 10 minutes at room temperature to give complex **1** in 65 % yield (Scheme 1). In contrast, the



Scheme 1. Synthesis of complex **1**. cod = 1,5-cyclooctadiene.

reaction with $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) proceeded more slowly (14 h) to give the oxidative addition complex in moderate yield (44 %) upon isolation.[12] Recent attempts to synthesize related [Pd(Ar)(X)(L)] (X = halogen) complexes bearing 2-dialkylphosphino-2,4,6-tri*iso*-propylbiphenyl ligands (X-Phos-type phosphines including **L1** and **L2**) were not successful.[13,14] However, the use of a ligand having methoxy groups introduced into the 3,6-positions of X-Phos allowed the synthesis of the stable oxidative addition complexes.[14] Thus, introduction of additional donor atoms may play a profound role in the improved stability of the oxidative addition intermediate.

The crystal structure of the oxidative addition complex **1** is shown in Figure 1.[15] Complex **1** contains a single phosphine ligand coordinated to the metal through both the phosphorous and nitrogen atoms, thereby forming a four-membered P,N-chelate ring.[16] The additional coordination of the nitro-

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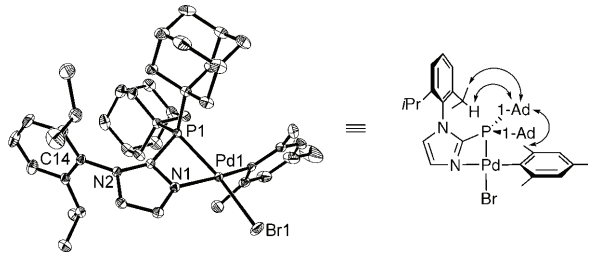
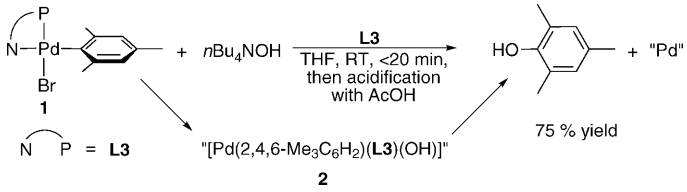


Figure 1. Crystal structure and important through-space interactions in NOESY NMR spectrum of complex **1** (see the Supporting Information for details). The thermal ellipsoids are set at 30% probability.

gen atom "freezes" the rather sterically unfavorable conformation of the coordinated phosphine with bulky di*iso*-propylphenyl and di-1-adamantylphosphino groups facing each other.

Thus, one side of the complex is sterically overcrowded with the phosphine, whereas the opposite side is relatively open for nucleophilic attack. As determined by NOESY NMR experiments **1** exists in a single form in solution,[17] which corresponds to that found in the solid state (Figure 1).[18]

Next, we investigated the preparation of the corresponding hydroxo complex "[Pd(Ar)(OH)(**L3**)]" (**2**), which is the key catalytic intermediate for the formation of phenol. Thus, **1** was reacted with an excess of nBu$_4$NOH·30 H$_2$O in THF at room temperature. The starting complex **1** was completely consumed within less than 20 minutes. To our surprise instead of the desired hydroxo complex **2**, 2,4,6-trimethylphenol was formed in 75% yield (Scheme 2). Apparently, complex **2** immediately underwent C–O bond-forming reductive elimi-

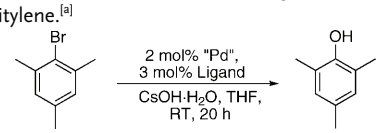


Scheme 2. Reaction of **1** with tetra-*n*-butyl ammonium hydroxide.

nation at room temperature. To the best of our knowledge such direct reductive elimination of phenols from palladium has not been reported until now.[19] It is this step that is considered as the "bottle-neck" of the palladium-catalyzed hydroxylation and which is responsible for rather high reaction temperatures ($\geq$80 °C).[6,7]

Apparently, the combination of [Pd(cod)(CH$_2$SiMe$_3$)$_2$]/**L3** allows all steps of the catalytic cycle to proceed at room temperature within minutes. These findings encouraged us to study the corresponding catalytic reaction in the presence of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] and other palladium precursors (Table 1). To our delight the reaction of bromo mesitylene with an excess of CsOH·H$_2$O in the presence of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] and **L3** in THF gave mesitol in nearly quantitative yield (Table 1, entry 2). The oxidative addition complex **1** as catalyst led to the product in identical yield

Table 1: Variation of palladium sources and ligands in the hydroxylation of bromomesitylene.[a]



Entry	Ligand	"Pd" source	Yield [%][b]
1	–	**1**	99
2	**L3**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	98 (88)[c]
3	**L3**	[Pd$_2$(dba)$_3$]	76 (44)[c]
4	**L3**	[Pd(allyl)(Cp)]	37
5	**L3**	[Pd(TMEDA)(Me)$_2$]	35
6	**L3**	Pd(OAc)$_2$	30
7	**L1**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	1
8	**L2**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
9	PtBu$_3$	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
10	Q-Phos	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
11	**L4**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	11

[a] Reaction conditions: bromomesitylene (1 mmol), CsOH·H$_2$O (3 mmol), [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (2 mol%), phosphine ligand (3 mol%), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h. [b] Yields determined by using GC methods. [c] In parentheses: 1 mol% of Pd and 1.5 mol% of a ligand was used. Cp = cyclopentadiene, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

(Table 1, entry 1). Notably, all other palladium precursors tested with **L3** are considerably less efficient (Table 1, entries 3–6). The advantage of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] in the room temperature hydroxylation is explained by the efficient generation of the corresponding palladium (0) complex (PdL) by rapid substitution of 1,5-cyclooctadiene for the bulky phosphine ligand L and a subsequent fast reductive elimination of bis(trimethylsilyl)ethane.[20] As a result, the oxidative addition occurs fast at room temperature. Inferior results with the common palladium(0) precursor, [Pd$_2$(dba)$_3$] in the catalytic reaction (Table 1, entry 3) are attributed to a much slower oxidative addition of the aryl bromide (see below). This deceleration should be caused by the stronger coordination of the electron-poor olefin (dibenzylidenacetone) to the palladium center.[21] Similar unfavorable effects of dba in palladium-catalyzed reactions are well documented in the literature.[22]

Notably, despite applications of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (R = Me, Ph) in organometallic synthesis,[14,20] these complexes have never been used in catalytic reactions.[23] The ability of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] to generate catalytically active species in situ under mild reaction conditions and in a one-step synthesis from commercially available precursor[20] make this complex an appealing tool for catalysis of cross-coupling reactions at room temperature.[24]

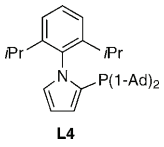
Furthermore, the palladium(0) precursor was tested with other ligands, which were successfully employed for hydroxylation of aryl halides at high temperature (**L1**, **L2**, and PtBu$_3$). For comparison, we also employed Q-Phos which is the unique ligand for arylation of tBuOH and tBuMe$_2$SiOH at room temperature.[10] However, none of these tests led to the product at room temperature, demonstrating the superiority of **L3** for this reaction (Table 1, entries 7–10).

We suppose that the improved activity of the **L3**-based catalyst in the room temperature hydroxylation stems from a

favorable combination of the steric bulk of the biphenyl-type backbone and alkyl substituents bound to the phosphorous center, as well as the ability to coordinate to the metal through the sp^2-nitrogen atom. The favorable effect of increased steric bulk of biphenyl-type ligands has already been highlighted.[8,25] Indeed, in the hydroxylation at elevated temperatures (80–100 °C), the efficiency of the catalysts based on bulky biphenyl ligands (**L1**, **L2**), and their arylimidazolyl congeners with a similar backbone is rather close.[7,8] However, in the room temperature reaction the novel palladium precursor and imidazolyl ligand **L3** exhibits an enormous difference in efficiency relative to reaction runs with the biphenyl phosphines **L1** and **L2** (Table 1, entries 2 and 7–8).

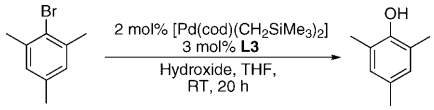
The main reason for this different catalytic behavior is seen in the ability of **L3** to coordinate to the palladium through both the P and N atoms (Figure 1). In agreement with this assumption, the pyrrole-based ligand **L4** which has the same framework as **L3**, but contains no second nitrogen atom available for coordination, provided only 11 % yield of phenol versus 98 % in the presence of **L3** (Table 1, entries 11 and 2).

Next, we optimized the reaction conditions for room temperature hydroxylation of bromomesitylene (Table 2). Among the various hydroxides tested, the best results were obtained in the presence of $CsOH{\cdot}H_2O$ (Table 2, entry 3). The mediocre performance of nBu$_4$NOH·30H$_2$O in the catalytic reaction (Table 2, entry 5) compared to the reaction using stoichiometric amounts of nBu$_4$NOH·30H$_2$O (Scheme 2) is attributed to the formation of a biphasic mixture resulting from the high water content in the commercial hydroxide.



L4

Table 2: Variation of hydroxides in the hydroxylation of bromomesitylene.[a]

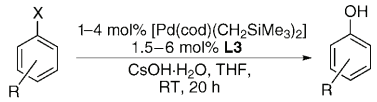


Entry	Hydroxide	Conversion [%][b]	Yield [%][b]
1	LiOH	7	0
2	KOH	37	27
3	$CsOH{\cdot}H_2O$	100	98
4	$Me_4NOH{\cdot}5H_2O$	98	87
5	nBu$_4$NOH·30H$_2$O	41	36

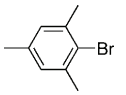
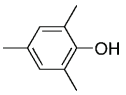
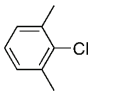
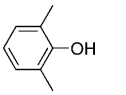
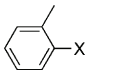
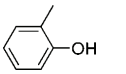
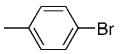
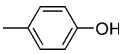
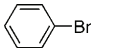
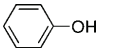
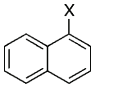
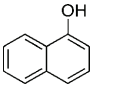
[a] Reaction conditions: bromomesitylene (1 mmol), base (3 mmol), [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (2 mol %), **L3** (3 mol %), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h. [b] Determined by GC methods.

Finally, we applied the optimized reaction conditions to the hydroxylation of various aryl halides at ambient conditions. As shown in Table 3, different aryl bromides and even aryl chlorides are transformed into the corresponding phenols in good to excellent yields (isolated; 67–99 %). In all cases, aryl chlorides were as active as the corresponding bromides and no noticeable amounts of diphenyl ethers were detected. Aryl halides containing electron-withdrawing substituents in the *ortho* and *para* positions reacted smoothly (Table 3, entries 10–16). Functional groups such as cyano, nitro, and

Table 3: Palladium-catalyzed hydroxylation of aryl halides at room temperature.[a]



X = halogen

Entry	Aryl Halide		Product	"Pd" [mol %]	Yield [%][b]
1				1 2	n.d. (88) 93 (98)
2				2	96
3		X = Br		2	92
4		X = Cl		2	92
5				4	70[c]
6				2	72 (97)[c,d]
7		X = Br		2	85
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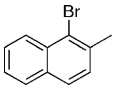
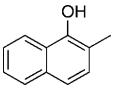
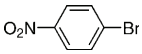
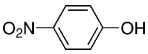
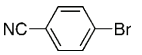
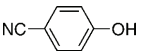
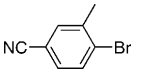
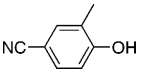
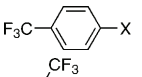
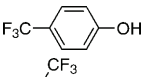
9				2	87
10				2	94
11				4	88
12				1	99
13		X = Br		2	83 (89)[d]
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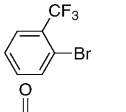
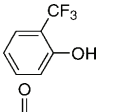
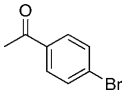
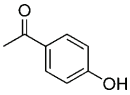
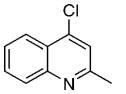
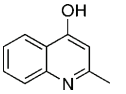
15				4	67 (72)[d]
16				2	95
17				2	99

[a] Reaction conditions: aryl halide (1 mmol), CsOH·H$_2$O (3 mmol), [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (1–4 mol %), **L3** (1.5–6 mol %), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h; reaction time is not optimized. [b] Yields for isolated product, and yields given in parentheses were determined by using GC methods. The reported yields refer to independent runs. [c] The reaction was carried out at 50 °C. [d] Volatile compound.

keto substituents are well tolerated. Moreover, the room temperature hydroxylation has a broader functional group scope compared to the reaction run at elevated temperature. For example, at 100 °C, we have observed only limited tolerance to nitriles.[26] In contrast, the present mild protocol enables preservation of nitrile group in all cases. Indeed, hydroxylation of 4-bromo-3-methylbenzonitrile and 4-bromobenzonitrile gave phenols in 88 % and 99 % yields,

respectively, using lower catalyst loadings (Table 3, entries 11 and 12). Previously, all attempts to hydroxylate aryl halides possessing a CF_3 substituent at elevated temperatures failed because of the hydrolysis of the CF_3 group. Under the present set of conditions both *para*- and *ortho*-aryl halides possessing CF_3 groups were coupled successfully at room temperature in good yields (Table 3, entries 13–15). In addition, a heterocyclic derivative, such as 4-chloro-2-methylquinoline, is smoothly transformed into the corresponding phenol in quantitative yield (Table 3, entry 17). With regard to limitations of the present method, we found that CO_2H and OH groups are not tolerated presumably because of the formation poorly soluble salts.

The novel protocol was also successfully applied for the hydroxylation of various non-activated aryl bromides including bromobenzene, *ortho*- and *para*-substituted halobenzenes, and 1-halonaphthalenes to give substituted phenols in 70–93% yields (Table 3, entries 1–9). Bromo- and chloronaphthalenes smoothly reacted at room temperature affording naphthols in 75–87% yields (Table 3, entries 7–9). Bromobenzene and 4-bromotoluene were somewhat less reactive and required a reaction temperature of 50°C (Table 3, entries 5–6). The introduction of one or two methyl groups in *ortho* positions of halobenzenes increased the reactivity of the halides, allowing the reaction again to proceed at room temperature with excellent yields (Table 3, entries 1–4). For example, bromomesitylene and 2-bromotoluene furnished phenols in 93% and 92% yields, respectively. Hydroxylation of similar chloro derivatives also proceeded under the same conditions (Table 3, entries 2 and 4). Acceleration of the reaction by *ortho* substituents in haloarenes, as well as the similar reactivity of aryl bromides and aryl chlorides, makes it likely that reductive elimination is the rate limiting step for this hydroxylation reaction. Indeed, it is known that carbon–heteroatom bond-forming reductive elimination from arylpalladium complexes is accelerated by *ortho* substituents in aryl halides.[27] However, we found that the further increase in the steric bulk of the *ortho* substituents, for example, from methyl to *iso*-propyl decelerates the reaction. Hence, room temperature hydroxylation of 2-bromo-*iso*-propylbenzene proceeded only to 10% conversion, whereas the reaction of 2,4,6-tri*iso*-propylbromobenzene did not occur at all and led to decomposition of the catalyst.

This effect of the different *ortho* substituents on the rate of the hydroxylation may imply a change of the rate-determining step.

In summary, we demonstrated for the first time that all steps of the catalytic cycle of the palladium-catalyzed hydroxylation of aryl chlorides and bromides can proceed at room temperature. Based on these findings, the catalytic synthesis of phenols occurs under unprecedented mild conditions. The key to the success is the combination of the novel palladium precursor $[Pd(cod)(CH_2SiMe_3)_2]$ and the imidazole-based ligand **L3**, which should be useful for numerous other catalytic coupling reactions as well.

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Keywords: homogeneous catalysis · hydrolysis · hydroxylation · palladium · phenols

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[12] In addition to the main product some minor side-products were formed (5–10%), which could not be removed by recrystallization. Reaction with [Pd(TMEDA)(Me)$_2$] gave a mixture of [Pd(**L3**)(2,4,6-Me$_3$C$_6$H$_2$)(Br)] (**1**) and [Pd(TMEDA)(2,4,6-Me$_3$C$_6$H$_2$)(Br)] in the 2.57:1 ratio.
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[15] CCDC 728525 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[17] Complex **1** exhibits no dynamic behavior in the temperature range of 25–(−80)°C as evidenced by the ^{1}H and ^{31}P{^{1}H} NMR spectra in [D$_8$]THF (see the Supporting Information).
[18] In contrast to **1**, oxidative addition palladium complexes bearing related biphenyl ligands show equilibrium between two forms, where one of them exhibits interaction of palladium atom and second arene ring of the biphenyl ligand, see reference [14] and

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[20] Y. Pan, G. B. Young, *J. Organomet. Chem.* **1999**, *577*, 257 – 264.
[21] Indeed, dibenzylidenacetone is more strongly bound to Pd^0 compared to 1,5-cyclooctadiene. Palladium (0) complexes of dibenzylidenacetone ([$Pd(dba)_2$] and [$Pd_2(dba)_3$]) are stable and commercially available, whereas the corresponding complex with 1,5-cyclooctadiene ([$Pd(cod)_2$]) decomposes above −30 °C: a) M. Green, J. A. K. Howard, J. L. Spencer, F. G. A. Stone, *J. Chem. Soc. Chem. Commun.* **1975**, 449 – 451; b) E. Sturm, H. Reinhard, K.-J. Kreutz (Air Products & Chemicals Inc.), DE2555374A1, **1975**.
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[24] Recently, Buchwald et al. reported an alternative phosphine ligated palladium pre-catalyst which forms PdL species at low temperature (−40 °C). However, multistep synthesis is required for the each of these phosphine-containing precursors: M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686 – 6687.
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4.4 Improved Palladium-Catalyzed Sonogashira Reactions of Aryl Chlorides

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C.T. planned and conducted most of the experiments, and prepared the manuscript. The work of C.T. to this publication accounts to approximately 70 %.

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Improved Palladium-Catalyzed Sonogashira Coupling Reactions of Aryl Chlorides

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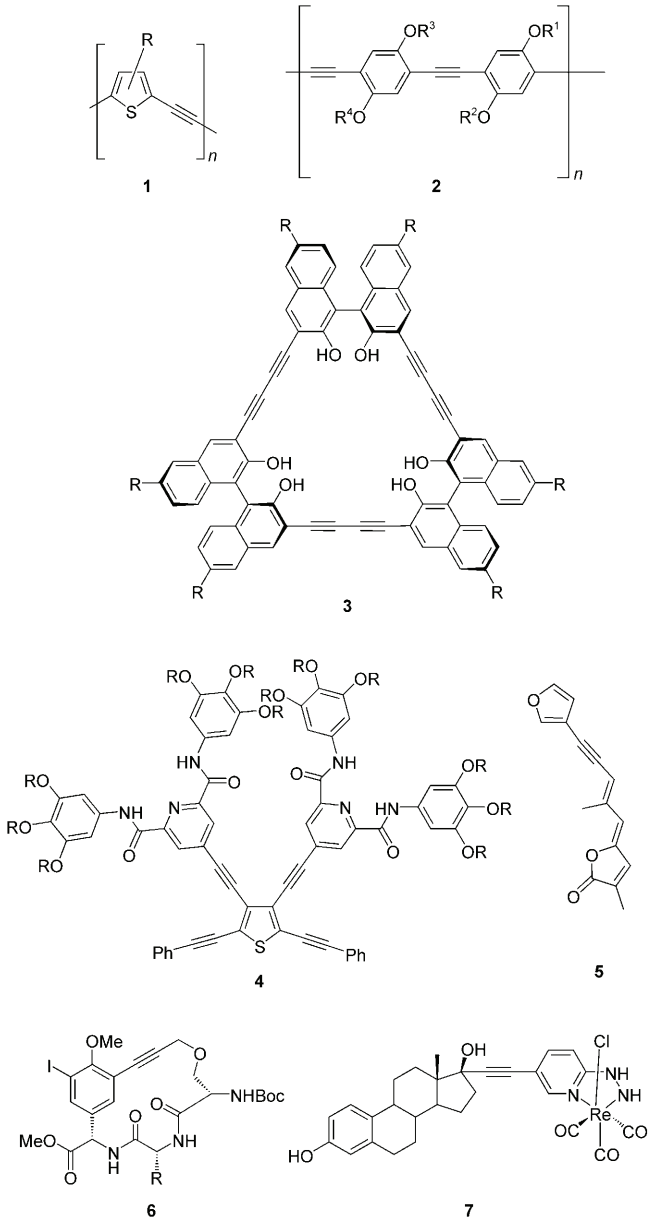
The construction of C_{sp}–(aryl)C_{sp^2} bonds is an important transformation in organic chemistry. The resulting aryl alkynes are building blocks often encountered within natural products, pharmaceutical products, and molecular materials.[1] Due to the highly conjugated π system, this structural motif is found in organic semiconductors, and the respective products act as molecular sensors, light-emitting diodes, or polarizers for liquid-crystalline displays.[2] In recent years polyaryleneethynylenes (PAEs) and oligoaryleneethynylenes (OAEs) such as **1** and **2** (Scheme 1) have become an established class of conjugated polymers in addition to poly(*p*-phenylenevinylene)s (PPVs) and polyacetylenes. Moreover, arylene–ethynylene macrocycles (AEMs) (e.g. **3**) and macromolecules such as **4** possess interesting electronic properties and lead to defined nanostructures.[3,4] Apart from material science, the construction of aryl alkynes plays an important role in the synthesis of complex molecules of pharmaceutical and agrochemical interest (e.g. **5**,[5] **6**,[6] **7**[7]), even though the arylene–ethynylene structure itself does not often occur in natural products, which is in marked contrast to the corresponding vinylene–ethynylene motif.[8] However, the alkynylation of aromatic halides and subsequent cyclization is a widely used method for the synthesis of carbo-[9] and heterocycles[10] as well as intermediates of natural products.[11] It is undeniable that the most effective way to form aryl–alkyne bonds is still palladium-catalyzed coupling reactions of aromatic halides with alkynes in the presence of base and copper co-catalysts. Although this reaction was independently discovered by Cassar, Heck, and Sonogashira in 1975,[12] today it is generally known as the Sonogashira reaction, and numerous catalytic systems have been reported for this



Scheme 1. Examples for structures bearing the arylene–ethynylene motif.

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transformation.[13] During the last few years important catalyst developments have been described such as the minimization of the catalyst amount,[14] the activation of less-reactive starting materials (aryl chlorides, alkyl halides),[15] the selective transformation of more functionalized substrates,[16] and the application of cost effective and/or sustainable methods.[17] With respect to the latter point, aryl–alkyne coupling methods catalyzed by more cost-effective metals such as iron[18] or copper[19] have become an interesting alternative to Pd-catalyzed procedures regarding the efficient coupling of aryl iodides. However, so far there is no general procedure for the efficient coupling of deactivated aryl bromides and inexpensive aryl chlorides with these metals. A generally accepted mechanism[20] of the Sonogashira reaction consists of two catalytic cycles: a) the 'classic' palladium-based coupling reaction that involves the oxidative addition of an aryl (vinyl) halide (or triflate) R^1–X to a low-coordinate palladium(0) complex, then transmetalation of a copper-acetylide (formed in the second catalytic cycle) to generate a $R^1Pd(-C\equiv CR^2)L_2$ species, which subsequently undergoes a *cis–trans* isomerzation and reductive elimination to give the aryl (vinyl)–alkyne and the regenerated catalyst; and b) the so-called 'copper-cycle', in which the copper–acetylide is generated from the free alkyne in the presence of a base, which is often an amine. This latter cycle is poorly understood: for example, the in situ formation of a copper acetylide is not proven yet, although recently indirect evidence has been found.[21] In fact, most of the amines used are not basic enough to deprotonate the alkyne to provide an anionic species which can further react to the corresponding copper acetylide. Therefore, a π-alkyne–Cu complex, which makes the alkyne proton more acidic, is often proposed as an intermediate. With respect to further catalyst developments the application of copper-free (and also amine-free) protocols is of importance due to the environmental and economical advantages. However, to date, only a few examples of Sonogashira reactions without copper source have been described. Notably, Gelman and Buchwald discovered in 2003 a catalyst system consisting of $[PdCl_2(CH_3CN)_2]$ and the so-called XPhos ligand, which allowed a general coupling of aryl chlorides and aryl tosylates with various terminal alkynes.[15c,22] Although desilylation of trimethylsilylacetylene, an important substrate in the synthesis of larger molecules, was observed during the reaction, an excellent substrate scope was demonstrated. Interestingly from a mechanistic viewpoint, the same authors reported that the presence of copper iodide in the coupling of aryl chlorides with alkynes inhibits coupling reactions. Copper-free Sonogashira reactions were also described in water.[23] More recently, Yi et al. reported in 2006 the application of $[PdCl_2(PCy_3)_2]$ in the coupling of various aryl chlorides with alkynes under copper-free conditions with 3 mol% catalyst at 100–150 °C.[24] Activation of the alkyne without copper is supposed to proceed via formation of a $(\eta^2\text{-}RC\equiv CH)Pd^0L_2$ species.[25,26] However, the term 'copper-free' should be considered carefully, since commercially available palladium salts can contain traces of copper.[27]

For some years we have been interested in the development of palladium catalysts that can be applied for coupling reactions on both laboratory as well as industrial scale. In this respect we have developed palladacycles,[28] adamantylphosphines,[29] carbene ligands,[30] and 2-phosphino-*N*-arylindoles and -pyrroles.[31] More recently, we also reported the synthesis of 2-phosphino-*N*-arylimidazoles and their application in cross-coupling reactions of aryl chlorides and bromides.[32] Importantly, such monodentate *N*-substituted heteroaryl phosphines are conveniently synthesized by selective metalation at the 2-position of the respective *N*-substituted heterocycle (pyrrole, indole, imidazole). Thus, a variety of novel ligands is easily available and can be efficiently prepared in a modular synthesis. This is an important aspect, since the application of palladium-catalyzed coupling reactions in the fine chemical and pharmaceutical industry requires in general a fine-tuning of the catalytic system. Here, we describe for the first time the use of *N*-aryl-heteroarylphosphines in Sonogashira coupling reactions of aryl chlorides without the necessity to add copper salts. Inspired by the work of the Buchwald group on XPhos,[33] we synthesized the novel ligand [*N*-(2,6-diisopropylphenyl)-2-imidazolyl]-di-*tert*-butylphosphine L1 (Figure 1).

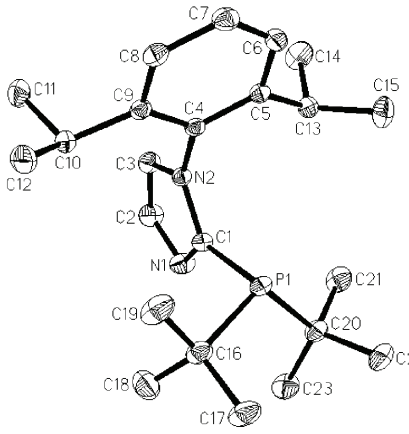
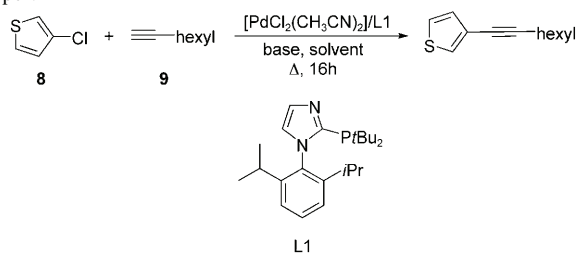


Figure 1. Molecular structure of L1. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability.

Advantageously, this ligand is formed straightforwardly from easily available substrates (2,6-diisopropylamine, glyoxal, formaldehyde,[34] and chloro-di-*tert*-butylphosphine) in two steps. For our catalytic studies we chose the reaction of 3-chlorothiophene (**8**) and 1-octyne (**9**), which is a more challenging coupling reaction. Propylene carbonate (PC) was first chosen as solvent for the reaction. Its usage in coupling reactions offers several advantages including the possibility of catalyst recycling a) via extraction of the nonpolar product with nonpolar solvents from the reaction mixture[35] or b) as PC can form part of temperature-dependent multicomponent solvent systems (TMS systems).[36] To our delight the reaction proceeded with 1 mol% $[PdCl_2(CH_3CN)_2]$ and 8 mol% of phosphine ligand L1 in 76% yield at 90 °C (Table 1, entry 1).[37] Unfortunately, decreasing the Pd/ligand

Table 1. Sonogashira coupling of 3-chlorothiophene and 1-octyne without copper.[a]



Entry	Pd [mol%]	L [mol%]	Solvent	Base	Conv. [%]	Yield [%][b]
1	1	8	PC	Cs_2CO_3	8	76
2	1	3	PC	Cs_2CO_3	3	25
3	2	6	PC	Cs_2CO_3	4	30
4	1	8	toluene	Na_2CO_3	80	71
5	1	3	toluene	Na_2CO_3	73	68
6	1	2	toluene	Na_2CO_3	18	18
7	1	1	toluene	Na_2CO_3	10	10
8[c]	1	3	toluene	Na_2CO_3	90	87
9[d]	1	3	toluene	Na_2CO_3	45	45
10[e]	1	3	toluene	Na_2CO_3	18	2
11[f]	1	1	toluene	Na_2CO_3	60	40
12[g]	1	3	toluene	Na_2CO_3	90	86

[a] Reaction conditions: 3-chlorothiophene (1 equiv), 1-octyne (1.3 equiv), base (2.6 equiv), solvent (0.5 M), 16 h (reaction times not optimized). [b] GC yields (internal standard: hexadecane). [c] 2 equiv of 1-octyne and 4 equiv of base. [d] $Pd(OAc)_2$. [e] 1 mol% of CuI. [f] 2 equiv of 1-octyne and 4 equiv of base, 1 mol% of complex **10**. [g] 2 equiv of 1-octyne and 4 equiv of base, 1 mol% of complex **10**, 2 mol% L1.

ratio from 1:8 to 1:3 lowered the product yield (Table 1, entries 2 and 3) significantly. Apparently, the reaction in propylene carbonate needs an excess of ligand, which may be explained by partial displacement of the ligand by solvent molecules.[38] In contrast to the reaction in propylene carbonate, the Sonogashira coupling in toluene with sodium carbonate as base yielded the desired 3-octinylthiophene in good yield at lower ligand concentration (Table 1, entries 4 and 5). However, an excess of ligand is obviously needed (Table 1, entries 6 and 7). The best yield is obtained by addition of two equivalents of the alkyne (Table 1, entry 9, 87% yield); most likely because the Pd^{II} species is reduced to the catalytically active Pd^0 species by the alkyne in the first place. After a standard procedure,[39] complex **10** was prepared from one equivalent of $[PdCl_2(CH_3CN)_2]$ and one equivalent of L1. Remarkably, X-ray analysis showed a η^2-P,N chelation of L1 to the metal center (Figure 2).[40] Time-dependent ^{31}P NMR experiments showed that this complex is also formed from a mixture of one equivalent of $[PdCl_2(CH_3CN)_2]$ and three equivalents of L1 in propylene carbonate as well as in toluene. Therefore it is most likely that it is also present in the reaction mixture and should act as a precursor for a monoligated Pd^0 species. Monoligated Pd^0 species are supposed to be the catalyst in coupling reactions, if bulky biarylphosphines like L1 are applied.[41] With the phosphine already attached to the metal center, the creation of the catalytically active species is considered to be easier from **10** than from a mixture of $[PdCl_2(CH_3CN)_2]$ and L1.

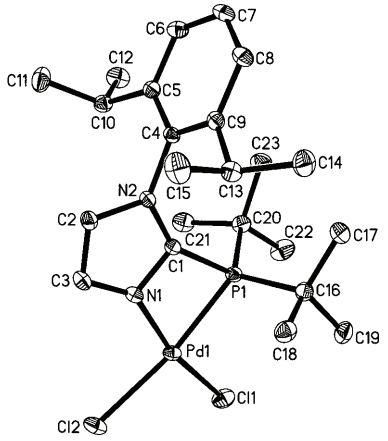
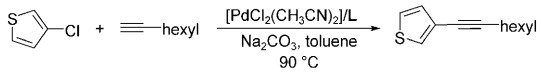
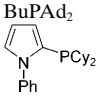
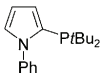
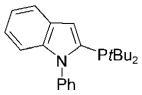
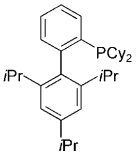
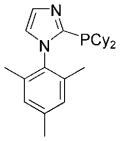
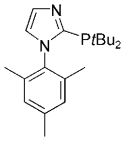
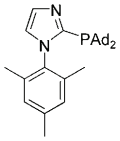
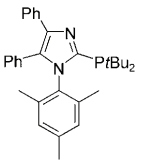
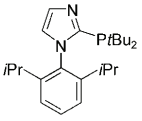
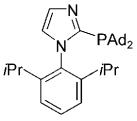


Figure 2. Molecular structure of **10**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability.

For the same reasons, an excess of ligand is not necessary any more. Hence, complex **10** was directly applied in the reaction (Table 1, entry 11). However, the reaction yielded only 40% of the coupling product under optimized conditions; with an additional 2 mol% of L1, the same activity of the catalyst was observed as with 1 mol% of $[PdCl_2(CH_3CN)_2]$ and 3 mol% of L1 (Table 1, entry 12). In agreement with the observation by Buchwald et al., inhibition of the reaction is observed when CuI was applied as co-catalyst (Table 1, entry 10). Next, a series of commercially available phosphines and novel dialkyl-2-(*N*-arylimidazolyl)phosphines were compared in the model reaction. Selected results of this ligand screening are shown in Table 2. Not surprisingly, triphenylphosphine (Table 2, entry 1), but also sterically hindered, basic ligands such as tri-*tert*-butylphosphine (employed as the HBF_4 salt; Table 2, entry 2) and cataCXium A (Table 2, entry 3) showed no reactivity without any copper co-catalyst, too. Similarly, *N*-aryl-2-phosphinopyrroles and *N*-aryl-2-phosphinoindoles (Table 2, entries 4–6) gave no conversion. Unexpectedly, even XPhos (Table 2, entry 7) showed only low reactivity under these conditions. However, significant amounts of the desired coupling product are obtained in the presence of the tested imidazole-based phosphine ligands. Among this class of ligands the following trends can be observed: within the applied *N*-mesityl-substituted ligands the di-1-adamantyl derivative gave the best result (Table 2, entry 10, 55% yield), while the yield drops significantly going over the corresponding 2-(di-*tert*- butylphosphino)imidazole ligand (Table 2, entry 9) to the sterically less demanding 2-(dicyclohexylphosphino)imidazole (Table 2, entry 8). Evidently, the more sterically hindered ligands gave favorable catalytic results probably because they accelerate the reductive elimination. Comparing entries 9 and 11 in Table 2, the ligand substituted with two phenyl rings in the backbone gave a better yield and selectivity (47% yield; 58% conversion). However, ligand L1 (Table 2, entry 12) showed the best performance compared to all other ligands tested. Interestingly, the corresponding 2-(di-1-adamantyl)phosphine (Table 2, entry 13) gave only

Table 2. Reaction of 3-chlorothiophene and 1-octyne using different phosphine ligands.[a]

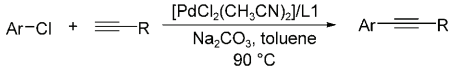


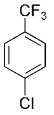
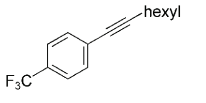
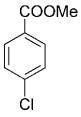
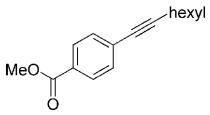
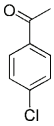
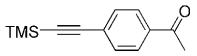
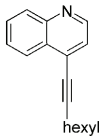
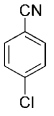
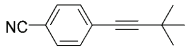
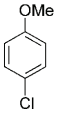
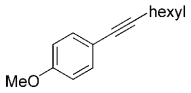
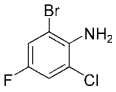
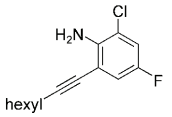
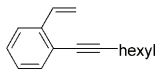
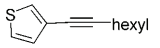
Entry	Ligand	Conversion [%]	Yield [%][b]
1	PPh_3	0	0
2	$P(tBu)_3$*HBF_4	3	0
3	$BuPAd_2$	0	0
4		2	0
5		3	0
6		7	0
7		34	6
8		19	1
9		76	21
10		63	55
11		58	47
12		73	68
13		31	25

[a] Reaction conditions: 3-chlorothiophene (1 equiv), 1-octyne (1.3 equiv), Na_2CO_3 (2.6 equiv), $[PdCl_2(CH_3CN)_2]$ (1 mol%), ligand (3 mol%), toluene (0.5 M), 90 °C, 16 h (reaction times not optimized). [b] GC yields (internal standard: hexadecane).

25% yield, even though it is considered to be more bulky. Finally, the Sonogashira reaction without added copper co-catalyst in the presence of ligand L1 was studied in more detail. Table 3 demonstrates that good to excellent results can be obtained under mild conditions in the case of activated aryl and heteroaryl chlorides using 1 mol% catalyst

Table 3. Sonogashira coupling of various aryl and heteroaryl chlorides with different alkynes.[a]



Entry	Aryl chloride	Alkyne	Product	Yield [%][b]
1				97
2				93
3				75
4				97
5[c]				42
6				87
7				64
8				31
9				87
10				73
11				77
12[c]				83
13[c]				45

[a] Reaction conditions: 3-chlorothiophene (1 equiv), 1-octyne (2 equiv), Na_2CO_3 (4 equiv), $[PdCl_2(CH_3CN)_2]$ (1 mol%), L1 (3 mol%), toluene (0.5 M), 90 °C, 16 h (reaction times not optimized). [b] Yield of isolated product. [c] 0.5 mol% $[PdCl_2(CH_3CN)_2]$, 1.5 mol% L1. [d] 2 equiv aryl halide, 1 equiv alkyne.

(Table 3, entries 1–4; 75–97% yield). Moreover, electron-rich aryl chlorides such as 4-chloroanisole react readily with 1-octyne in 87% yield (Table 3, entry 6). Notably, amino groups are tolerated under these conditions as shown by the reaction of 2-bromo-6-chloro-4-fluoroaniline, which is converted into the corresponding 2-subsituted product (Table 3, entry 7). The reaction of 2-chlorostyrene with 1-octyne gave an interesting highly conjugated coupling product (Table 3, entry 8). This reaction also shows that the catalyst system is chemoselective for the coupling of the alkyne, as no stilbene or stilbene oligomers are observed. Finally, 3-chlorothiophene was allowed to react with various alkynes. In addition to the reaction of 1-octyne (87%; Table 3, entry 9) also reactions with cyclopentyl-, triethylsilyl-, and phenylacetylene proceeded smoothly (73–83%; Table 3, entries 10–12).

In summary, palladium-catalyzed Sonogashira couplings have been performed in the presence of *N*-substituted heteroaryl phosphines without copper co-catalysts for the first time. In general, good to excellent coupling results of a variety of aryl and heteroaryl chlorides—including challenging substrates—have been obtained in the presence of [*N*-(2,6-diisopropylphenyl)-2-imidazolyl]-di-*tert*-butylphosphine L1 at low catalyst loading. Various functional groups including amino, silyl, and vinyl groups are tolerated under these conditions, in contrast to previously reported copper-free procedures. The novel procedure is cost effective and benign with respect to solvent, base, and avoiding the addition of copper salts.

Experimental Section

General: All reactions were performed under an argon atmosphere using standard Schlenk techniques. All starting materials and reactants were used as received from commercial suppliers, except toluene, which was distilled from sodium and stored under argon before use. Phosphine ligands and complexes were stored in Schlenk flasks but weighed under air. NMR spectra were recorded on an ARX300 (Bruker) spectrometer; chemical shifts are given in ppm and are referenced to the residual solvent peak. Mass spectra were recorded on an AMD 402 double-focusing, magnetic sector spectrometer (AMD Intectra). GC-MS spectra were recorded on a HP 5989A (Hewlett Packard) chromatograph equipped with a quadropole analyzer. Gas chromatography analyses were realized on a HP 6890 (Hewlett Packard) chromatograph using a HP 5 column. Melting points were measured on a SMP3 (Stuart) and are not corrected.

X-ray structure determinations: Data were collected with a STOE-IPDS diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The structures were solved by direct methods [SHELXS-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**] and refined by full-matrix least-squares techniques against F^2 [SHELXL-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**]. XP (Bruker AXS) was used for graphical representations.

CCDC-712744 (L1) and CCDC-712745 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Sonogashira reaction of aryl chlorides: A 25 mL Schlenk tube was evacuated and backfilled with argon. It was charged with $[PdCl_2(CH_3CN)_2]$ (2.59 mg, 0.01 mmol), L1 (11.2 mg, 0.03 mmol), and Na_2CO_3 (424 mg, 4 mmol). If it was a solid, the (hetero)aryl chloride was also added at that point. Then, toluene (2 mL), the corresponding (hetero)aryl chloride (if liquid) (1 mmol), and the alkyne (2 mmol) were added successively under argon atmosphere. The reaction mixture was heated up to 90°C for 16 h (reaction times not optimized) while it was stirred vigorously. After cooling to room temperature, the mixture was then quenched with water (3 mL), and the aqueous phase was extracted with diethyl ether (3×4 mL). The organic phases were combined, concentrated, and the desired product was isolated by column chromatography (cyclohexane or cyclohexane/ethyl acetate mixtures). Alternatively, the reaction mixture was quenched with water (3 mL) and diluted with diethyl ether (8 mL). Hexadecane was then added as an internal standard and quantitative analysis was performed by gas chromatography.

(4-Acetylphenylethynyl)trimethylsilane: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 2H, 2×H_{arom}), 7.41–7.35 (m, 2H, 2×H_{arom}), 2.43 (s, 3H, CH_3(C=O)), 0.11 ppm (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5 (CH_3(*C*=O)), 136.5 (C_{arom}), 132.2 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 104.2 (C_{acetyl}–C_{arom}), 98.3 (*C*-Si(CH_3)), 26.8 (*C*H_3(C=O)), 0.00 ppm (Si(*C*H_3)$_3$); MS (70 eV): *m/z* (%): 216 (18) [M^+], 201 (100), 158 (9), 143 (7); HRMS: calcd for $C_{13}H_{16}$OSi: 216.09649; found: 216.09620.

3-(Phenylethynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.39 (m, 3H, 3×H_{arom}), 7.33–7.19 (m, 4H, 4×H_{arom}), 7.16–7.09 ppm (m, 1H, 2×H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.6 (C_{arom}), 129.9 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 125.4 (C_{arom}), 123.2 (C_{arom}), 122.3 (C_{arom}), 88.9 (C_{acetyl}), 84.5 ppm (C_{acetyl}); MS (70 eV): *m/z* (%): 184 (100) [M^+], 152 (11), 139 (24); HRMS: calcd for $C_{12}H_8S$: 184.03412; found: 184.03381.

3-(Cyclopentylethynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 1H, H_{arom}), 7.23–7.16 (m, 1H, H_{arom}), 7.08–7.01 (m, 1H, H_{arom}), 2.78 (quin, J = 8.0 Hz, 1H, CH), 2.07–1.85 (m, 2H), 1.84–1.43 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.1 (C_{arom}), 127.4 (C_{arom}), 124.9 (C_{arom}), 123.1 (C_{arom}), 94.1 (C_{acetyl}), 75.1 (C_{acetyl}), 33.9 (CH-*C*H_2), 30.8 (CH), 25.1 ppm (CH(CH_2)*C*H_2);. MS (70 eV): *m/z* (%): 176 (87) [M^+], 161 (13), 147 (100), 134 (30) 128 (18), 121 (18), 115 (18), 108 (23), 97 (10), 91 (11), 77 (9), 69 (8), 63 (11), 45 (10); HRMS: calcd for $C_{11}H_{12}S$: 176.06542; found: 176.06560.

3-(1-Octynyl)thiophene: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 1H, H_{arom}), 7.23–7.16 (m, 1H, H_{arom}), 7.07–7.01 (m, 1H, H_{arom}), 2.36 (t, J = 7.0 Hz, 2H, C_{acetyl}-*C*H_2), 1.65–1.19 (m, 8H, (*C*H_2)$_4$$CH_3$), 0.89 ppm (t, J = 7.0 Hz, 3H, (CH_2)$_4$*C*H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.1 (C_{arom}), 127.5 (C_{arom}), 125.0 (C_{arom}), 123.1 (C_{arom}), 90.0 (C_{acetyl}-C_{arom}), 75.6 (C_{acetyl}-CH_2), 31.4, 28.8, 28.7, 22.6, 19.4 (C_{acetyl}-*C*H_2), 14.1 ppm ((CH_2)$_4$*C*H_3); MS (70 eV): *m/z* (%): 192 (54) [M^+], 163 (22), 149 (45), 135 (61), 123 (100), 115 (52), 108 (22), 97 (32), 91 (17), 77 (26), 63 (13), 45 (17); HRMS: calcd for $C_{12}H_{16}S$: 192.09644; found: 192.09672.

2-Methyl-4-(3-thiophenyl)-3-butyn-2-ol: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 1H, H_{arom}), 7.20–7.14 (m, 1H, H_{arom}), 7.04–6.99 (m, 1H, H_{arom}), 2.19 (br s, 1H, OH), 1.53 ppm (s, 6H, 2× CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.9 (C_{arom}), 128.7 (C_{arom}), 125.3 (C_{arom}), 121.8 (C_{arom}), 93.4 (C_{acetyl}-C(CH_3)$_2$OH), 77.3 (C_{acetyl}-C_{arom}), 65.7 (*C*-(CH_3)$_2$OH), 31.5 ppm ((CH_3)$_2$); MS (70 eV): *m/z* (%): 166 (33) [M^+], 151 (100), 135 (7), 123 (10), 108 (13), 89 (6), 75 (6), 69 (6), 63 (11) 43 (59); HRMS: calcd for C_9H_{10}OS: 166.04469; found: 166.04494.

1-Methoxy-4-(oct-1-ynyl)benzene: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 2H, 2×H_{arom}), 6.83–6.75 (m, 2H, 2×H_{arom}), 3.78 (s, 3H, OCH_3), 2.36 (t, J = 6.9 Hz, 2H, *C*H_2(C_5H_{11})), 1.63–1.18 (m, 8H, CH_2(C_4H_8)CH_3), 0.88 ppm (t, J = 6.9 Hz, 3H, CH_2(C_4H_8)*C*H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 132.9, 116.3, 113.8, 88.9, 80.2, 55.3, 31.4, 28.9, 28.7, 22.6, 19.5, 14.1 ppm; MS (70 eV): *m/z* (%): 216 (51) [M^+], 187 (19), 173 (38), 159 (38), 145 (100), 130 (15), 115 (29), 102 (28); HRMS: calcd for $C_{15}H_{20}$O: 216.15087; found: 216.15080.

Methyl-4-(oct-1-ynyl)benzoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.87 (m, 2H, 2×H_{arom}), 7.44–7.37 m, 2H, 2×H_{arom}), 3.86 (s, 3H, *C*H_3(C=O)), 2.38 (t, J = 7.0 Hz, 2H, *C*H_2(C_5H_{11})), 1.64–1.20 (m, 8H, CH_2-(C_4H_8)CH_3), 0.87 ppm (t, J = 7.0 Hz, 3H, CH_2(C_4H_8)*C*H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (CH_3O(*C*=O)), 131.5 (C_{arom}), 129.4 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 94.0 (C_{acetyl}-CH_2), 80.1 (C_{acetyl}-C_{arom}), 52.1 (*C*H_3O(C=O)), 31.4, 28.6, 28.6, 22.6, 19.5 (C_{acetyl}-*C*H_2), 14.1 ppm ((CH_2)$_4$*C*H_3); MS (70 eV): *m/z* (%): 244 (36) [M^+], 213 (29), 201 (45),

173 (35), 143 (52), 129 (100), 115 (43); HRMS: calcd for $C_{16}H_{20}O_2$: 244.14578; found: 244.14578.

3-Chloro-5-fluoro-2-(oct-1-ynyl)aniline: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.98–6.86 (m, 2H, 2×H_{arom}), 4.60–4.00 (br s, 2H, 2×NH_2), 2.48 (t, $J =$ 7.0 Hz, 2H, $CH_2(C_5H_{11})$), 1.66–1.25 (m, 8H, $CH_2(C_4H_8)CH_3$), 0.88 ppm (t, $J =$7.0 Hz, 3H, $CH_2(C_4H_8)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 155.6, 152.4, 141.1 (d, $J =$2.4 Hz), 118.6 (d, $J =$11.5 Hz), 116.6 (dd, $J =$ 39.4 Hz, 24.5 Hz), 110.3 (d, $J =$10.1), 97.8, 75.9 (d, $J =$3.6), 31.4, 28.7, 28.7, 22.6, 19.6, 14.1 ppm; IR (ATR): $\tilde{\nu} =$3484, 3385, 3082, 2955, 2928, 2857, 2223, 1589, 1572, 1469, 1301, 1201, 1157, 1069, 850, 793, 728 cm^{-1}; MS (70 eV): *m/z* (%): 253 (87) [M^+], 224 (20), 210 (18), 196 (26), 182 (100), 175 (19), 158 (29), 149 (44), 126 (23); HRMS: calcd for $C_{14}H_{17}ClFN$: 253.10281; found: 253.10287.

4-(3,3-Dimethylbut-1-ynyl)benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.56–7.49 (m, 2H, 2×H_{arom}), 7.55–7.38 (m, 2H, 2×H_{arom}), 1.29 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$132.1, 131.9, 129.2, 118.7, 110.7, 103.5, 78.0, 30.8, 28.2. MS (70 eV): *m/z* (%): 183 (20) [M^+], 168 (100), 153 (31), 140 (13); HRMS: calcd for $C_{13}H_{13}N$: 183.10425; found: 183.10477.

1-(Oct-1-ynyl)-2-vinylbenzene: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.58–7.52 (m, 1H, 1×H_{arom}), 7.43–7.35 (m, 1H, 1×H_{arom}), 7.30–7.12 (m, 3H, 2×H_{arom}, 1×H_{vinyl}), 5.78 (dd, $J =$17.7 Hz, 1.2 Hz, 1H, 1×H_{vinyl}), 5.32 (dd, $J =$11.0 Hz, 1.2 Hz, 1H, 1×H_{vinyl}), 2.46 (t, $J =$6.9 Hz, 2H, $CH_2(C_5H_{11})$), 1.70–1.20 (m, 8H, $CH_2(C_4H_8)CH_3$), 0.91 ppm (t, $J =$6.9 Hz, 3H, $CH_2(C_4H_8)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$138.8, 135.2, 132.5, 127.7, 127.4, 124.5, 122.9, 115.0, 95.4, 78.9, 31.4, 28.8, 28.7, 22.6, 19.6, 14.1 ppm; MS (70 eV): *m/z* (%): 212 (1) [M^+], 169 (16), 155 (59), 141 (100), 128 (44), 115 (67); HRMS: calcd for $C_{16}H_{20}$: 212.15595; found: 212.15596.

1-(Oct-1-ynyl)-4-(trifluoromethyl)benzene: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$7.54–7.42 (m, 4H, 4×H_{arom}), 2.40 (t, $J =$7.1 Hz, 2H, 2×C_{acetyl}-CH_2), 1.67–1.21 (m, 8H, $(CH_2)_4CH_3$), 0.89 ppm (t, $J =$4.6 Hz, 3H, $(CH_2)_4CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$131.8, 129.2 (q, $J =$23.6 Hz), 128.0, 125.2 (q, $J =$3.8 Hz), 124.1 (q, $J =$272.1 Hz), 93.4, 79.5, 31.4, 28.6, 28.5, 22.6, 19.5, 14.1 ppm; MS (70 eV): *m/z* (%): 254 (44) [M^+], 235 (26), 225 (81), 211 (98), 197 (45), 183 (100), 170 (37), 159 (62), 129 (78) 115 (40); HRMS: calcd for $C_{15}H_{17}F_3$: 254.12769; found: 254.12722.

Triethyl(thiophen-3-ylethynyl)silane: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.46 (dd, $J =$3.0 Hz, 1.1 Hz, 1H, 1×H_{arom}), 7.22 (dd, $J =$5.0 Hz, 3.0 Hz, 1H, 1×H_{arom}), 7.11 (dd, $J =$5.0 Hz, 1.2 Hz, 1H, 1×H_{arom}), 1.03 (t, $J =$ 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.66 ppm (t, $J =$4.9 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$130.3, 129.5, 125.1, 122.6, 101.1, 91.4, 7.5, 4.5 ppm; IR (ATR): $\tilde{\nu} =$3109, 2953, 2934, 2910, 2873, 2151, 1005, 945, 869, 779, 722, 680 cm^{-1}; MS (70 eV): *m/z* (%): 222 (13) [M^+], 193 (99), 165 (100), 137 (83), 111 (16); HRMS: calcd for $C_{12}H_{18}SSi$: 222.08930; found: 222.08877.

4-(Oct-1-ynyl)quinoline: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$8.79 (d, $J =$ 4.5 Hz, 1H, 1×H_{arom}), 8.29–8.01 (m, 2H, 2×H_{arom}), 7.75–7.48 (m, 2H, 2×H_{arom}), 7.39 (d, $J =$4.5 Hz, 1H, 1×H_{arom}), 2.53 (t, $J =$7.1 Hz, 2H, C_{acetyl}-CH_2), 1.74–1.23 (m, 8H, $(CH_2)_4CH_3$), 0.95–0.79 ppm (m, 3H, $(CH_2)_4CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$149.8, 148.1, 130.8, 129.8, 129.7, 128.2, 126.9, 126.1, 123.6, 101.1, 31.4, 28.7, 28.5, 22.6, 19.8, 14.1 ppm; MS (70 eV): *m/z* (%): 237 (100) [M^+], 208 (34), 194 (52), 180 (59), 166 (71), 153 (45), 139 (36); HRMS: calcd for $C_{17}H_{19}N$: 237.15120; found: 237.15135.

Complex 10: m.p. >245 °C (decomp); ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta =$ 7.57 (dd, $J =$2.6 Hz, 1.5 Hz, 1H, H_{imid}), 7.49 (t, $J =$7.8 Hz, 1H, 4-H_{arom}), 7.27 (d, $J =$7.8 Hz, 2H, 3-H_{arom}, 5-H_{arom}), 7.02 (dd, $J =$1.5 Hz, 0.6 Hz, 1H, H_{imid}), 2.29 (sep, $J =$6.8 Hz, 2H, 2×$CH(CH_3)_2$), 1.42 (s, 9H, $C(CH_3)_3$), 1.37 (s, 9H, $C(CH_3)_3$), 1.23 (d, $J =$6.9 Hz, 6H, $CH(CH_3)_2$), 0.97 ppm (d, $J =$6.9 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta =$146.6, 132.5, 131.9, 128.2, 128.1, 127.7, 125.0, 38.9 (d, $J =$9.6 Hz), 30.0 (d, $J =$3.8 Hz), 29.4, 27.6, 21.3 ppm; ^{31}P NMR (120 MHz, CD_2Cl_2): $\delta =$53.7; IR (ATR): $\tilde{\nu} =$3162, 3140, 2962, 2923, 2866, 1457, 1444, 1173, 1132, 813, 805, 787, 770, 763 cm^{-1}; HRMS (ESI, [M^+ Na^+]): calcd for $C_{23}H_{37}Cl_2N_2NaPPd$: 573.10026; found: 573.09955.

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4.5 A General Palladium-Catalyzed Amination of Aryl Halides with Ammonia

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A General Palladium-Catalyzed Amination of Aryl Halides with Ammonia

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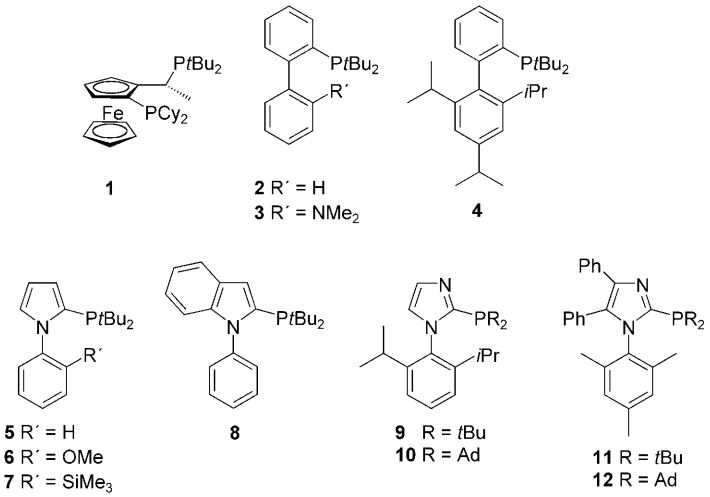
Anilines are important intermediates in the manufacture of agrochemicals, dyes, pharmaceuticals, and other industrial products.[1] Hence, there is a continuing interest in easier and more cost-efficient preparations.[2] In the past decade transition-metal-catalyzed C–N bond-forming reactions have emerged as a potent tool for the production of aryl amines. Due to the seminal contributions of the groups of Buchwald and Hartwig, palladium-catalyzed C–N cross-coupling reactions of aryl halides with various *N*-nucleophiles have become one of the most valuable organic transformations.[3] Despite the impressive results in the production of secondary and tertiary amines,[4] relatively little work has been done on the amination of aryl halides to produce primary aryl amines. Problems encountered with the direct utilization of ammonia are: 1) the displacement of the ligand bound to the Pd center by ammonia leading to a catalytically non-reactive complex,[5] 2) the tendency of complexes bearing an amido group to form stable bridging structures,[6] and 3) the increased activity of a resulting primary aniline compared to ammonia leading to diaryl amines. To avoid these problems synthetic equivalents of ammonia have been employed including allyl,[7] benzyl,[8] and silyl amines,[9] imines,[10] and amides.[11] Unfortunately, the corresponding coupling products have to be cleaved after the reaction, which leads to unwanted side products.[12] Hence, the use of ammonia as an *N*-nucleophile is still by far the most desired approach[13] because of its inherent atom economy, and the low cost and availability of ammonia.[14]

In 2006, Hartwig and Shen[15] published the first selective palladium-catalyzed monoarylation of ammonia employing the bulky Josiphos bisphosphine **1** as ancillary ligand (Scheme 1). Simple alkyl-substituted aryl iodides, bromides, and even chlorides were converted successfully to the corresponding anilines in good yields. In addition, the isolation of the first organopalladium complex with a terminal NH_2-functionalized ligand and its reductive elimination of aryl amine were reported. Afterwards, Buchwald and Surry[16] published a Pd-catalyzed synthesis of anilines with ammonia using monophosphines **2**–**4**. Here, a mixture of $[Pd_2(dba)_3]$ (dba = *trans,trans*-dibenzylideneacetone) and dialkylphosphinobiphenyl ligand **3** gave the highest selectivity in the formation of anilines from the corresponding aryl bromides of all applied ligands. Although being quite efficient in the conversion of the substrates tested, both Hartwig and Buchwald[17] have not reported the conversion of more challenging substrates such as aminoaryl halides, halostyrenes, halopyridines, and functionalized aryl chlorides. Hence, there is still interest for more general procedures in the Pd-catalyzed monoarylation of ammonia.



Scheme 1. Active phosphine ligands for selective Pd-catalyzed amination of aryl halides.

It is important to note that besides palladium, the amination of aryl halides with ammonia is possible under copper

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catalysis. However, these procedures are limited to aryl iodides[18] and some bromides.[19] To date, efficient Cu-catalyzed coupling protocols of ammonia with aryl chlorides are not known.[20]

We have been interested in the development of new ancillary ligands for Pd-catalyzed coupling reactions for some time. Examples include di-1-adamantylphosphines (cata*CX*ium A),[21] carbene ligands,[22] and 2-phosphino-*N*-arylindoles and -pyrroles (cata*CX*ium P).[23] The latter ligands can be easily prepared by a two-step lithiation–phosphorylation method from the corresponding heterocycles. Such a modular synthesis is important in the fine chemical and pharmaceutical industry, since fine-tuning catalysts in cross-coupling reactions is often required. Recently, our group reported an efficient approach for the synthesis of novel bulky, electron-rich imidazole-based monophosphines[24] and their successful application in the Pd-catalyzed hydroxylation of aryl halides. Here, we report for the first time that 2-phosphino-*N*-arylpyrroles **5** and **7**, 2-phosphino-*N*-arylindole **8** , and dialkyl-2-(*N*-arylimidazolyl)phosphines **11** and **12** work well in the selective Pd-catalyzed amination of aryl halides to the corresponding aniline derivatives (Scheme 1).

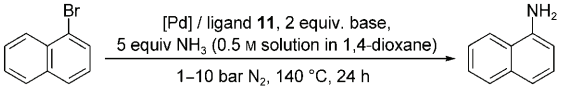
After some exploratory testing a catalyst derived from $[Pd(CH_3CN)_2Cl_2]$ and ligand **11** showed good activity in the amination of 1-bromonaphthalene with NaO*t*Bu and a 0.5 M solution of ammonia in 1,4-dioxane at 140 °C under a nitrogen atmosphere of 5 bar (Table 1). To determine the optimal reaction conditions different parameters such as palladium source, base, and nitrogen pressure were then screened. The use of NaO*t*Bu gave the best results in the model reaction, whereas all other tested bases including different inorganic phosphates, carbonates, and hydroxides remained ineffective. Interestingly, KO*t*Bu showed much worse results in C–N bond formation than NaO*t*Bu although the starting material was fully converted with both bases. Except for palladium on charcoal, the palladium source had no significant influence on the reaction; good to excellent yields (79–95 %) were achieved under all the reaction conditions studied. Increasing the pressure up to 10 bar gave slightly improved yield compared to 1 bar and 5 bar, respectively.

In comparison to the amination protocol adopted by Hartwig and Shen,[15] the preparation of a pre-catalyst system formed from the corresponding palladium source and phosphine and handling in a dry box under inert atmosphere are not required. The novel palladium/monophosphine catalyst system is formed in situ from the air- and moisture-stable *N*-aryl-2-(dialkylphosphino)imidazoles and the palladium source.

Next, different phosphine ligands were investigated in the model amination reaction and compared with commercially available ligands (Table 2). The *N*-phenylpyrrole/indole-substituted (**5**, **7**, and **8**)[23a,b] and the more sterically demanding imidazole-based phosphines **11** and **12**[24b] resulted in the highest yields up to 82 %. The 2-methoxy-functionalized ligand **6** showed a lower yield than the trimethylsilyl-substituted one, which is explained by the different electronic properties of both ligands. Evidently, small changes in the phosphine ligand have a significant influence on the catalytically active system. The very bulky ligands **9**, **10**, **13**, and **15** confirm this conclusion and gave the monoarylated amine in moderate yields (24–56 %). Notably, the more bulky adamantyl-substituted ligands are inferior compared to *tert*-butyl- and cyclohexyl-substituted ones (**9**, **10**, **13**), whereas ligands **11** and **12** do not show this dependency. The comparison of phosphine **14** and the 4,5-diphenyl-functionalized derivative **12** demonstrates that the phenyl backbone is responsible for an increase of the yield. This can be explained by steric as well as electronic factors. The bulkiness of **11** becomes evident considering Figure 1, in which its molecular structure (determined by X-ray analysis) is depicted. The commercially available ligands cata*CX*ium A (**16**) and tri-*tert*-butylphosphine (**17**) turned out to be ineffective for this transformation.

Finally, the scope of the catalyst system $Pd(OAc)_2$/**11** was examined by reacting various aryl bromides and chlorides with ammonia (available as a 0.5 M solution in 1,4-dioxane) in the presence of NaO*t*Bu as base at 120 °C and a nitrogen atmosphere of 10 bar. In some cases the use of the "simple" ligand **5** showed similar results and in one case (Table 3, entry 22) gave much better yield. Different alkyl- and aryl-

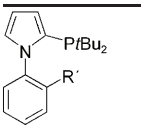
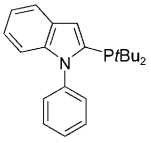
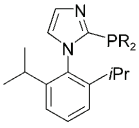
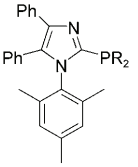
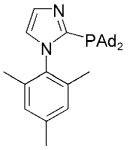
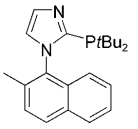
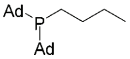
Table 1. Influence of different reaction parameters on the Pd-catalyzed amination of 1-bromonaphthalene.



	Conv. [%]	Yield [%][d]
Base[a]		
NaO*t*Bu	>99	79
NaOH	50	13
Na_3PO_4	<5	<1
Na_2CO_3	<5	<1
KO*t*Bu	>99	10
K_3PO_4	79	14
K_2CO_3	15	3
Cs_2CO_3	36	9
none	<10	<1
[Pd] source[b]		
$Pd(OAc)_2$	>99	95
$[Pd(dba)_2]$	>99	93
$[Pd(CH_3CN)_2Cl_2]$	>99	79
$PdCl_2$	>99	80
Pd/C	59	2
$p(N_2)$ [bar][c]		
1	>99	78
5	>99	79
10	>99	86

[a] 5 mol % $[Pd(CH_3CN)_2Cl_2]$, 10 mol % ligand **11**, 2 equiv base, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [b] 5 mol % [Pd], 10 mol % ligand **11**, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [c] 5 mol % $[Pd(CH_3CN)_2Cl_2]$, 10 mol % ligand **11**, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 1–10 bar N_2, 140 °C, 24 h. [d] GC yields (internal standard: hexadecane).

Table 2. Ligands for Pd-catalyzed amination of 1-bromonaphthalene.[a]

Ligand		R	R′	Yield [%][b]
	**5**		H	80
	6		OMe	50
	7		$SiMe_3$	76
	**8**			80
	**9**	*t*Bu		51
	10	Ad		24
	13	Cy		56
	**11**	*t*Bu		82
	12	Ad		78
	**14**			50
	**15**			44
	**16**			2
$PtBu_3/HBF_4$	**17**			13

[a] 5 mol% $[Pd(CH_3CN)_2Cl_2]$, 10 mol% ligand, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [b] GC yields (internal standard: hexadecane).

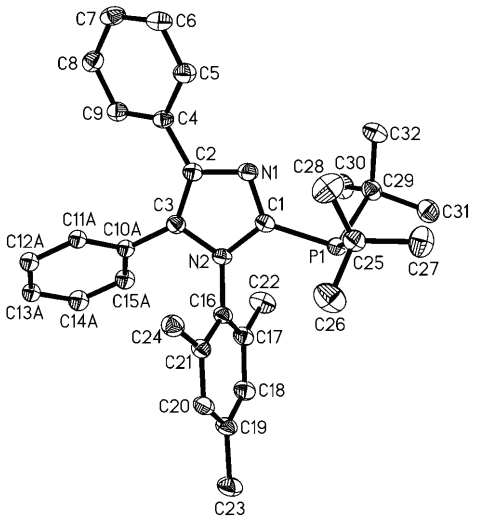
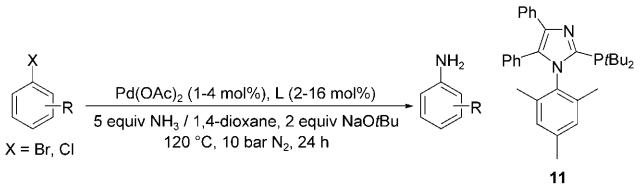
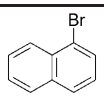
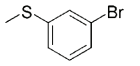
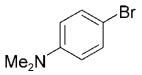
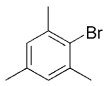
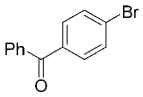
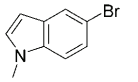
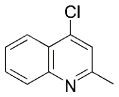
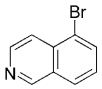
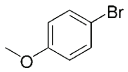
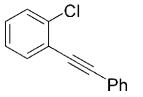


Figure 1. Molecular structure of ligand **11**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability.

Table 3. Palladium-catalyzed amination of aryl halides.[a]



Entry	Substrate	Yield [%][b]	Entry	Substrate	Yield [%][b]
1		93[c]			
2		67[d]	17		66[g]
3		93[e]			
4		90	18		70
5		95[c]			
6		95[e]	19		86[j]
7		70[f]			
8		96			
9		95[e]	20		80
10		72[f]			
11		75[g]	21		90
12		71	22		> 99[k]
13		68[h]	23		70[l]
14		> 99[i]	24		28[m]
15		89[i]	25		30[m]
16		68	26		53[n]

[a] 0.2 mmol aryl halide, 2 mol% $Pd(OAc)_2$, 8 mol% ligand **11**, 2 equiv NaO*t*Bu, 2.0 mL 0.5 M NH_3/1,4-dioxane, 10 bar N_2, 120 °C, 24 h. [b] GC yields (internal standard: hexadecane). [c] With ligand **5**, 96% yield. [d] Carried out in a pressure tube under an atmospheric pressure of argon. [e] 1 mol% $Pd(OAc)_2$, 4 mol% ligand **11**. [f] 1 mol% $Pd(OAc)_2$, 2 mol% ligand **11**. [g] With 16 mol% of ligand **11**. [h] Product: 2-chloroaniline. [i] Product: 2-aminoaryl halide. [j] With ligand **5**, 89% yield. [k] With ligand **5**; with ligand **11**, 48% yield. [l] With ligand **5**, 78% yield. [m] With 4 mol% $Pd(OAc)_2$, 16 mol% ligand **11**. [n] Isolated yield.

substituted bromides and chlorides (Table 3, entries 1, 4, 5, 8, 11) were allowed to react to give the corresponding aniline derivatives in good to excellent yields (75–96%). Notably, the monoarylation with ammonia also proceeds under atmospheric pressure in a pressure tube under argon at 120 °C. The formation of 1-naphthylamine was observed in a slightly lower yield of 67% (Table 3, entry 2). For selected aryl bromides and chlorides (Table 3, entries 3, 6, and 9) it could be shown that with a lower catalyst loading (1 mol% $Pd(OAc)_2$, 4 mol% ligand **11**) excellent results can be ob-

tained, too, whereas a Pd/ligand ratio of 1:2 (Table 3, entries 7 and 10) gives yields of around 70% under otherwise identical reaction conditions. To our delight, 2-chlorostyrene was converted to the corresponding 2-aminostyrene in good yield (71%; Table 3, entry 12). As expected, the substitution of bromide is preferred, if a bromide ligand competes with a chloride ligand, and no significant amount Cl-substituted product is formed (Table 3, entry 13; 68% yield). Noteworthy is that the reaction of the corresponding 1,2-dihalides selectively yielded the monoaminated products in excellent yields (Table 3, entries 14, 15; 89–99%). The activated 4-bromobenzophenone (Table 3, entry 20; 80% yield) and deactivated bromoarenes such as anisole, thioanisole, and *N*,*N*-dimethylbenzene (Table 3, entries 16–18; 66–70% yield) were also fully converted. The conversion of 2-bromoaniline proceeded smoothly to give the corresponding 1,2-diaminobenzene in 86% yield (Table 3, entry 19). Next, some *N*-heteroaryl bromides and chlorides were investigated.

Full conversion is observed for *N*-methylindole and isoquinoline (Table 3, entries 21 and 23; 70–90% yield), whereas the reaction of pyridine (Table 3, entries 24 and 25; 28–30% yield) gave the desired products in only moderate yields. Notably, in comparison to ligand **11**, the pyrrole-based phosphine **5** gave much better results in the amination of 4-chloroquinaldine (Table 3, entry 22; >99% yield). 1-Chloro-2-(phenylethynyl)benzene (Table 3, entry 26), which was synthesized by a Sonogashira reaction of phenylacetylene and 1-bromo-2-chlorobenzene with ligand **10**, is successfully converted to the corresponding amine in 53% yield.[25]

In summary, a new robust palladium/phosphine catalyst system for the selective monoarylation of ammonia with different aryl bromides and chlorides has been developed. The active catalyst is formed in situ from $Pd(OAc)_2$ and air- and moisture stable phosphines as easy-to-handle pre-catalysts. The productivity of the catalyst system is comparable to that of competitive Pd/phosphine systems;[15,16] full conversion is achieved with most substrates with 1–2 mol% of Pd source and a fourfold excess of ligand. One can conclude that the novel electron-rich and sterically demanding phosphine ligands cannot be displaced from the palladium by ammonia to a significant extent; thus, the deactivation of the catalyst is prevented by the ligands. Furthermore, a subsequent reaction of the resulting aniline derivatives to the corresponding diaryl amines was not observed. Although giving a slightly lower yield of the aniline product, it is demonstrated that the Pd-catalyzed amination process also works at ambient pressure. Notably, the optimized system showed an excellent substrate scope including deactivated, electron-neutral, and activated halides, *o*-, *m*-, and *p*-substituted substrates, aryl chlorides, as well as heterocycles. In contrast to the previously reported Pd-catalyzed procedures, the effective conversion of halostyrenes, haloindoles, and aminoaryl halides is possible with this system. The most active ligands are either commercially available (ligands **5**, **8**)[26] or can be easily synthesized by the previously reported procedure (ligands **11**, **12**).[24b]

Experimental Section

General: All reactions were performed under a nitrogen atmosphere (1–10 bar) using an eightfold parallel autoclave. All starting materials and reactants were used as received from commercial suppliers. Phosphine ligands were stored in Schlenk flasks but weighed under air. NMR spectra were recorded on an ARX300 (Bruker) spectrometer; chemical shifts are given in ppm and are referenced to TMS or the residual non-deuterated solvent as internal standard. Mass spectra were recorded on an AMD 402 double focusing, magnetic sector spectrometer (AMD Intectra). GC-MS spectra were recorded on a HP 5989 A (Hewlett Packard) chromatograph equipped with a quadropole analyzer. Gas chromatography analyses were performed on a HP 6890 (Hewlett Packard) chromatograph using a HP 5 column. All yields were determined by calibration of the corresponding anilines with hexadecane as internal standard and analysis by using gas chromatography.

X-ray structure determination: $C_{32}H_{39}N_2P$, $M_r = 482.62$, colorless crystal, $0.50 \times 0.30 \times 0.13$ mm, orthorhombic, space group $P2_12_12_1$, $a = 10.3780(3)$ Å, $b = 10.7916(3)$ Å, $c = 25.6151(6)$ Å, $V = 2868.76(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.117$ g cm^{-3}, $\mu = 0.117$ mm^{-1}, $T = 200$ K, 41 509 measured, 5645 independent reflections ($R_{int} = 0.0439$), of which 4297 were observed ($I > 2\sigma(I)$), $R_1 = 0.0302$ ($I > 2\sigma(I)$), $wR_2 = 0.0595$ (all data), 296 refined parameters. Data were collected on a STOE IPDS II diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The structure was solved by direct methods (SHELXS-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**) and refined by full-matrix least-squares techniques on F^2 (SHELXL-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**). XP (Bruker AXS) was used for graphical representation. All fully occupied non-hydrogen atoms were refined anisotropically. One phenyl ring (C10–C15) is disordered nearly equally over two sites. Hydrogen atoms were placed in idealized positions and refined by using a riding model. CCDC-713326 (**11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

General procedure for the amination of aryl halides: A 3.0 mL autoclave was charged with $Pd(OAc)_2$ (0.9 mg, 2 mol%), ligand **11** (7.7 mg, 8 mol%) or ligand **5** (4.6 mg, 8 mol%), and NaO*t*Bu (38.4 mg, 2 equiv). If it was a solid, the (hetero)aryl halide was also added at that point. The filled autoclave was placed into the autoclave device, evacuated, backfilled with argon, and then 1,4-dioxane (0.2 mL) was added and the mixture was stirred at room temperature for 5 min. Then, the corresponding aryl halide (if liquid) (0.2 mmol) and a 0.5 M NH_3 solution (2.0 mL) in 1,4-dioxane (5 equiv NH_3) were added successively under an argon atmosphere. The reaction mixture was pressurized with 10 bar N_2 and heated up to 120 °C for 24 h. After the mixture had been cooled to room temperature, it was laced with hexadecane (20 μL) as an internal standard. The mixture was filtered and the yield was determined by gas chromatography.

2-(Phenylethynyl)aniline (Table 3, entry 21): Following the reaction and cooling to room temperature, the reaction mixture was purified by column chromatography (cyclohexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.45 (m, 2H), 7.32–7.24 (m, 4H), 7.10–7.04 (m, 1H), 6.72–6.65 (m, 2H), 4.60 ppm (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.0$, 132.2, 131.5, 129.8, 128.4, 128.3, 123.3, 118.6, 114.8, 108.5, 94.9, 85.7 ppm; MS (EI): 193 (100) $[M]^+$, 165 (34), 139 (4), 89 (11); HRMS: calcd for $C_{14}H_{11}N$: 193.08860; found:193.08853.

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Scientific Work

Publications

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Poster Contributions

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den 03.04.2009

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