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Selected Patented Cross-Coupling Reaction Technologies

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1. Introduction

Many significant products (drugs, materials, optical devices, etc.) commercialized or in the development phase, possess aromatic carbon−carbon and aromatic carbon−nitrogen bonds which can be assembled by organometallic catalyst cross-coupling reactions. So, the scale-up of any new and general technology for the formation of these bonds can be of great industrial significance. Our main objective here is to propose an analysis of the relevant patent literature, which could be of interest for industrial and academic chemists. Furthermore, given the exponential number of papers in this field, we have decided to focus on aromatic C−C and C−N bond formation.

This is a difficult exercise, since it is not always easy from such an analysis to identify what is really relevant from an industrial point of view, what has been exploited or not, and which difficulties have been met during the scale-up of the process. So, we had to refer to our own industrial experience in this field, more specifically in the development of the ABF (aromatic bond formation, referring to Buchwald's technology to form aromatic bonds). Rhodia's motivation in developing the ABF compared to some other competitive technologies was its ability to fulfill the requirements of a sustainable development (defined in the Brundtland Report of 1987 as a development "that meets the needs of the present without compromising the ability of future generations to meet their own needs"): high productivity, low metal content, atom economy, potential recycling of the catalyst, low energy consumption, mild conditions, low waste production, and safe solvents.

2. Aromatic Bond Formation

The aromatic bond formation (ABF) offers the advantage of any organometallic catalysis and at the same time brings the opportunity of designing much more convergent syntheses than those of traditional chemistry, thanks to its ability

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Jean-Pierre Corbet was born in 1953. He studied at Annecy (France) and then at the Mulhouse National Chemical School, and he received his Ph.D. from Strasbourg University in 1980 in Prof. Claude Benezra's laboratory (in the Natural Substances Laboratory, under the supervision of Prof. Guy Ourisson). He spent 3 years in the Discovery Department of the Health Division of Rhône-Poulenc in Paris and then 6 years as lab manager and 2 years as the head of the Organic Chemistry and Analysis Department in the Rhône-Poulenc Research Center in Lyon. In 1993 he became R&D Director of Inorganic Applications and then of the Paper, Coatings and Construction Materials sectors of Rhône-Poulenc in Paris (silica, titanium dioxide, latexes, polyisocyanates, organic and inorganic additives). From 1999 to 2002 he was the head of the Rhodia Research Center in Lyon (organic intermediates and polyamides), and he is now the R&D Director of Rhodia Pharma Solution, in charge of the industrial development of new technologies for the pharmaceutical industry (for example: biotransformations, fluoro intermediates, hydrolytic kinetic resolution from Prof. E. Jacobsen, aromatic bond formation from Prof. S. Buchwald) and of new routes to pharmaceutical compounds.

Gérard Mignani studied chemistry at Orsay and Rennes Universities (Lavoisier Medal in 1977), where he received his Ph.D (Docteur Ingénieur) in 1980 and his “Thèse d'Etat” in 1982 in the field of organometallic chemistry and homogeneous catalysis, especially in steroid chemistry (Rhône-Poulenc Grant) on Prof. Dabard's team. He joined the Rhône-Poulenc Research group in Lyon in 1980, where he developed new processes in organic and terpene chemistry and in homogeneous and heterogeneous catalysis. Thereafter he performed postdoctoral research with Prof. Seyferth at the Massachusetts Institute of Technology (Cambridge, MA) on ceramic precursors and organosilicon chemistry. He came back to Rhône-Poulenc research, where he developed new ceramic precursors, new nonlinear optic derivatives, polymers, and homogeneous catalysis processes. He spent 10 years as a Group Leader in Silicon Chemistry. His research interests were the polyfunctionalization of polysiloxanes, new organometallic catalysis for organosilicon applications, and the functionalization of mineral charges. Now, his research interests are new processes and scale-up in organic chemistry, organometallic catalysis (homogeneous and heterogeneous), and new methodologies in chemistry synthesis. He received the “Prix de la Recherche” in 1995, in 2001 the “Prix RHODIA Group”, and in 2004 the “Prix Centre de Recherches-RHODIA”. Dr. Gérard Mignani has contributed to about 60 international scientific publications and more than 120 patents.

to couple two sophisticated moieties under mild conditions. This is due to its high flexibility toward functional groups. For instance, in the case of the carbon−nitrogen bond formation, the carbon−nitrogen coupling of an aza heterocycle with a halo aromatic is often much faster, more cost efficient, and more atom economical than building the heterocycle from the amino group of the corresponding aniline.

But the ABF also requires taking into account as early as possible a number of significant criteria such as the access to the starting materials, the nature of the catalyst (metal, ligand), the reaction conditions, and the isolation step, including metal recycling or removal and solvent recycling. One of the starting materials is usually a halo aromatic, and questions such as the selectivity of the chlorination step (and consecutive purification) or waste management are of paramount importance for the overall economy of the process. This means the pertinence of using the ABF compared to traditional chemistry should be evaluated at the perimeter of the whole multistep synthesis.

If the catalyst turnover is a key parameter, recycling is often of paramount importance. We generally consider it more efficient to spend R&D resources to enhance the catalyst efficiency to an extent where it is no longer necessary to recycle it (energy economy, productivity), rather than to make cumbersome and lengthy recycling step studies. Usually, a recycling step has a strong economic impact on the cost of the product and requires sophisticated technologies. In the case of ABF, we have generally found it possible to reach a compromise between the metal, ligand, solvent, base, and reaction conditions allowing the use of less than 1000 ppm of metal, thus making the recycling generally unnecessary.

But whatever the solution (recycling or not), the regulation requirements linked to toxicity and environmental issues make the removal of any traces of metal (generally below 1 ppm) mandatory. In the case of the ABF, as the catalytic step can take place at the last step of the convergent synthesis, a failure at this stage could kill the whole process. Rhodia[1] and Merck[2] have independently developed an automated system to rapidly screen metal removal conditions in order to propose viable solutions in the early stages of the development.

The difficulties linked to the scale-up of the catalytic coupling reactions (exothermicity, instability, toxicity, productivity, metal contamination, etc.) are well described by Pfizer in their presentation of a robust, safe, and environmentally friendly process using the Sonogashira, Miyaura-Suzuki, and Heck reactions for the multikilo synthesis of CP-724 714, an anticancer drug candidate.[3] Sometimes a longer route, and even lower yields, can be preferred to overcome these difficulties.

Finally, to rapidly provide a safe, scalable, and cost efficient process, we should take into account the following items as early as possible in the development phase:

General route selection: compare the convergent syntheses based on the coupling technology to traditional linear chemistry, not only in terms of steps saving but also considering the whole process (starting material availability, HSE, etc.).

Parameters determination: identify the metal/ligand couple, the nature of the base, solvent, and concentration effects, temperature, addition order, mass and energy transfer effects, kinetics, etc.

Safety study: make a hazard evaluation, stability study, and thermal data acquisition.

Metal removal: this can be the killer of the whole process and must be treated as such (as early as possible in the project and with required resources).

Process intensiveness: some catalytic steps can be advantageously made continuous, and this decision should not be the result of an optimization study but that of an early kinetic study and an analysis of the identification of potential bottlenecking. This will shorten the process development studies and increase the overall project profitability.

Aromatic C−C and aromatic C−N bond formation are among the most significant reactions in organic chemistry. Even if outstanding progress has been made, there are still significant challenges which could explain the constant interest aroused by such technologies among academic and industrial teams worldwide. It is noteworthy that the main advances in the area result from close collaboration between academics and industrialists and even from partnerships between companies with the upstream support of academic labs. The tripartite collaboration between Rhodia, Lanxess, and S. Buchwald from MIT is a good example of how the industrialization of a technology (ABF) can be speeded up.[4]

3. C–C Cross-Coupling Technology

This section will mainly focus on the C−C coupling reactions for aryl−aryl, aryl−heteroaryl, and heteroaryl−heteroaryl bond formation.

3.1. Introduction and Classification of Carbon–Carbon Coupling Reactions

The catalyzed C−C coupling reactions are very powerful and well-known chemical tools. In their review of the GMP bulk reactions run in the Groton site between 1985 and 2002, Ripin et al., from Pfizer, found that the use of Pd-catalyzed cross-coupling reactions has significantly increased among the methods to make C−C bonds.[5] Widely reviewed in the traditional academic journals and books, it is our understanding that they have not really been analyzed through the patent literature. Many variants of the C−C coupling reactions have been described, particularly in the modern organic synthesis literature, such as the Miyaura−Suzuki (boron-mediated),[6] Corriu−Kumada−Tamao (magnesium-mediated),[7] Kosugi−Migita−Stille (tin-mediated),[8] Neghishi (zinc-mediated),[9] Sonogashira (copper-mediated),[10] Heck−Mizokori (Pd-mediated),[11] and Hiyama (Pd-mediated)[12] coupling reactions. Other C−C coupling reactions using Mn-mediated catalysts were also described, particularly in the case of the acylation reaction.[13] The fundamental role of the ligand in C−C coupling reaction was presented in a pertinent review by van Leeuwen.[14]

Two excellent reviews were published: one devoted to the industrial R&D of catalytic C−C and C−N coupling reactions and the second devoted to the status and trends of fine chemical synthesis.[15]

Historically, one of the first examples of the use of transition metals such as Pd and Ni in catalytic reactions of soft nonorganometallic carbon nucleophiles was reported in 1973 by Semmelhack.[16] The lithium salt of acetophenone reacted with the oxidative product of iodobenzene and $Ni(PPh_3)_4$ to give a mixture of the aryl ketones and the homocoupled biphenyl. An intramolecular version of this reaction was described by the same author to prepare cephalotaxinime in 30% yield using a stoichiometric amount of $Ni(COD)_2$.[17]

3.2. Portfolio of Carbon–Carbon Coupling Reaction Technologies

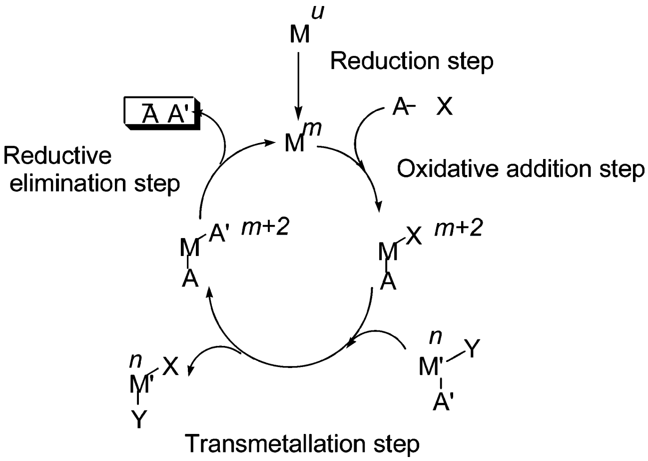
Since then, a lot of C−C coupling reaction technologies have been developed, and Table 1 presents their main characteristics: scope and limitations, experimental complexity, tolerance to functions, etc.

The facile redox interchange of Pd(II)/Pd(0) and Cu(I)/Cu(0) or/and Cu(I)/Cu(II) oxidation states is mainly responsible for the catalytic efficiently of Pd and Cu species during the catalytic cycle.

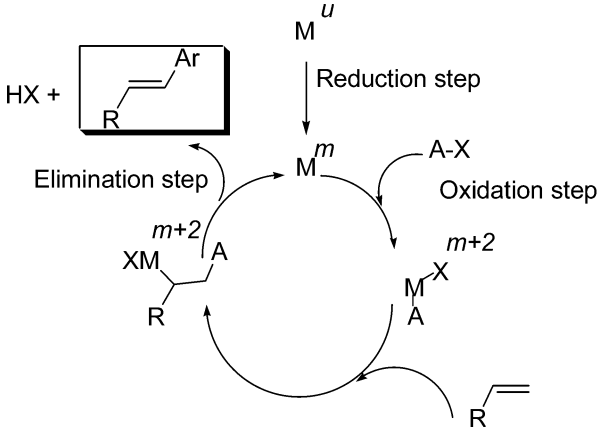
3.3. C–C Coupling Reaction Mechanisms

The mechanistic aspects of these reactions have largely been described in the literature.[18] For instance, noteworthy electrochemical and kinetic approaches have been used to elucidate the key steps of the catalytic cycle.[19] Schemes 1 and 2 show the postulated mechanism involving a transmetalation step (Miyaura−Suzuki reaction type) and an insertion step (Heck−Mizokori reaction type).

Scheme 1. Postulated Miyaura−Suzuki Reaction Mechanim



Scheme 2. Postulated Heck−Mizokori Reaction Mechanism



The organometallic fundamental steps of the metal (M)-catalyzed C−C coupling reaction of a halo-aromatic or vinylic (A−X) are now well established.

Table 1. Portfolio of Well-Established C−C Coupling Reaction Technologies

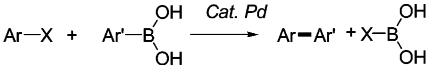
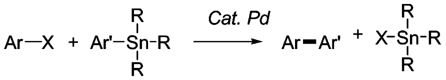
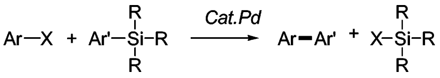
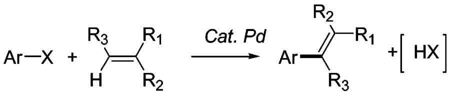
strengths	limitations
Miyaura−Suzuki Reaction:  $\mathrm{Ar{-}X + Ar'{-}B(OH)_2 \xrightarrow{Cat.\ Pd} Ar{-}Ar' + X{-}B(OH)_2}$	
commercial availability on laboratory scale of many boronic acids and esters bearing a large panel of organic and inorganic functions—possibility to use boroxine derivatives good yield and selectivity very low amount of catalyst, with or without ligands stability of boronic acids to heat, oxygen, and water flexibility toward functional group easy handling; mild experimental conditions—water as solvent, low temperature heterogeneous catalyst (Pd/C) can be used functionalized arylchlorides can be used in place of generally more expensive aryl bromides or iodides vinyl halides work easy separation of inorganic boron from the reaction mixture	few commercially available (on a large scale) boronic acids or esters, except $\mathrm{PhB(OH)_2}$ organoboranes are expensive due to their synthesis via Grignard intermediate or B−B and B−H derivatives the starting boronic acid can be difficult to purify when Ni is used, toxicity of Ni complexes toxicity of boric acid and borates derivatives[a]
Kosugi−Migita−Stille Reaction:  $\mathrm{Ar{-}X + Ar'{-}SnR_3 \xrightarrow{Cat.\ Pd} Ar{-}Ar' + X{-}SnR_3}$	
air and moisture stability of catalytic system and products neutral experimental conditions excellent functional group compatibility good yield and selectivity	unsuitable for pilot and plant production due to the use of stoichiometric Sn quantities (toxicity, waste) waste treatment not easy organostannanes are expensive
Negishi Reaction: $\mathrm{Ar{-}X + Ar'{-}Zn\text{-}Y \xrightarrow{cat.\ Pd\ or\ Ni} Ar{-}Ar' + X{-}Zn\text{-}Y}$	
large panel of organozinc derivatives available, with functionalized aryl, alkenyl, and alkyl moieties flexibility toward functional group—neutral medium good yield and selectivity mild experimental conditions organozinc can be prepared in situ Zn/Cu and Zn dust can be used	zinc derivative and coupling reaction medium are water sensitive specific treatment of large amounts of Zn waste safety issues linked to Grignard reaction
Sonogashira Reaction: $\mathrm{Ar{-}X + H{-}C{\equiv}C{-}R \xrightarrow{cat.\ Pd} Ar{-}C{\equiv}C{-}R + HX}$	
Pd−Cu, Pd, and less expensive Cu complexes can be used good yield and selectivity flexibility toward functional groups reduced organometallic waste stoichiometric amount of Cu acetylides (as in the Castro reaction) can be avoided	safety issues due to the use of alkynyl derivatives on pilot and plant scales
Kumada−Corriu−Tamao Reaction: $\mathrm{Ar{-}X + Ar'{-}Mg{\cdot}Y \xrightarrow{cat.\ Ni} Ar{-}Ar' + X{\cdot}Mg\text{-}Y}$	
mild experimental conditions nonsophisticated Pd ligand generally used good yield and selectivity Ni complexes can be used as catalyst Grignard reagents easily available on laboratory, pilot, andplant scales	moisture sensitivity and low versatility to functional groups toxicity of Ni complexes safety issues due to the use of Grignard reagents waste treatment of large quantities of Mg
Hiyama Reaction:  $\mathrm{Ar{-}X + Ar'{-}SiR_3 \xrightarrow{Cat.Pd} Ar{-}Ar' + X{-}SiR_3}$	
mild experimental conditions—generally do not need any organic or inorganic base nonsophisticated Pd ligand generally used good yield and selectivity phenyl and vinyl silanes and polysiloxanes are available on industrial scale low toxicity of Si derivatives functionalized aryl and vinyl Si can be easily prepared via Si−Si derivatives or via a hydrosilylation process	the stoichiometric amount of activator such as fluoride anion requires the use of a specific reactor functionalized aryl and vinyl silanes or polysiloxanes not available on the industrial scale low functional tolerance in the aryl−Si synthesis through Grignard reagents or when hydroxide anion is used as an activator

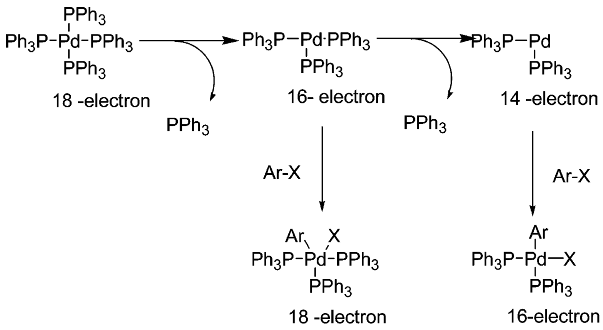
Table 1 (Continued)

strengths	limitations
Heck−Mizokori Reaction:	
	
large scope	works with Pd catalysts only
mild experimental conditions—no activator—no organometallic intermediates	concerns vinylhalide coupling only
generally does not need any sophisticated Pd ligand	
good yield and selectivity	
very large panel of functionalized alkenes are available on laboratory, pilot, and industrial scales	
flexibility toward functional group	
cheap aryl chlorides work when using bulky phosphines	
pseudohalides such as diazonium salts can be used	
acyl halides, carboxyclic anhydrides, and aldehydes can be used	
reduced organometallic waste	
intramolecular reactions are possible (cyclization)	

[a] Boric acid and borate derivatives are considered as reprotoxic category 2 materials according to the classification proposal as in 30 ATP (Adaptation to Technical Progress) to Dangerous Substances Directive (67/548/EEC). For details see http://ecb.jrc.it/DOCUMENTS/Classification-Labelling/ATPS_OF_DIRECTIVE_67-548-EEC/30TH_ATP_DRAFT_SUBSTANCE_ANNEXES/Annex-1H_new_entries_non-conf.doc.

3.3.1. Oxidative Addition

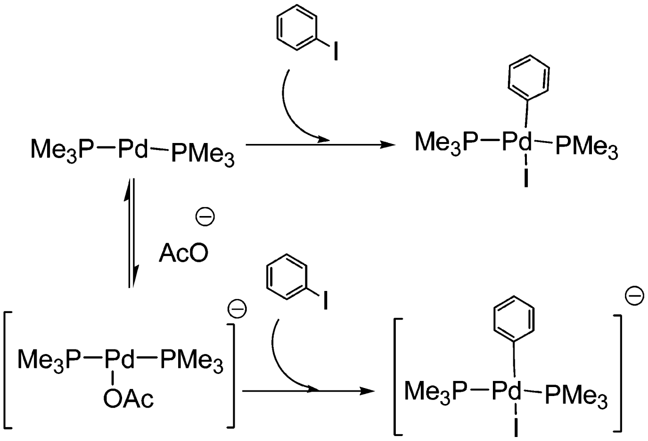
This step corresponds to the insertion of M^n ($n = 0$, I, II, depending on the electronic state of M) in the A−X bond (with A = aryl or heteroaryl moieties, X = halide or pseudohalide groups) and cleavage of this σ bond into two new bonds M^{n+2}(A)(X). 16-electron and 18-electron species can be formed using respectively 14-electron or 16-electron starting organometallic complexes. M^0 being Pd(0) coordinated with PPh_3 represents a typical example (eq 1).



(1)

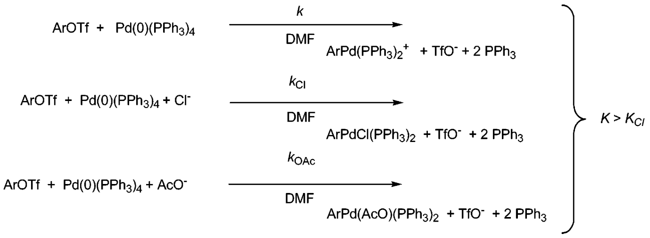
In many cases, the oxidative addition step of aryl halides to Pd(0) complexes is considered to be rate-determining.[20] A representative example of a 14-electron linear complex is $Pd[P(o\text{-}C_6H_4Me)_3]_2$, well-synthesized, -characterized, and developed in catalysis by Hartwig.[21] The mechanistic pathways of the oxidative addition of aryl halide to Pd(0) complexes have been described using density functional theory (DFT).[23] Jutand and Amatore demonstrated that the three-coordinated anionic Pd(0) species $[Pd(PR_3)_2(OAc)]^-$ or $[Pd(PR_3)_2(Cl)]^-$ were formed, instead of the classical two-coordinated complex, by the reaction of Pd(II) salts with phosphine and are involved in the oxidative addition step.[22] The Amatore−Jutand stable intermediate $[Pd(0)(PMe_3)_2OAc]^-$ is confirmed as the starting Pd(0) complex of the catalytic cycle before the oxidative addition step. Stable four-coordinated intermediates were found in place of five-coordinated Pd(II) complexes during the cis−trans oxidative addition step, in which the aryl halides coordinate linearly to the Pd via the halide atom (Scheme 3). As proved by the Amatore−Jutand work, the reactivity of the Pd(0) species during the oxidative step was strongly influenced by the presence of a neutral ligand (such as dba) or anions (Cl^- or AcO^-). The following reactive order was found by Jutand, Amatore, Carré, and Medjour.[24]

Scheme 3. Coordination of Pd(0) Intermediates to Phenyl Iodide



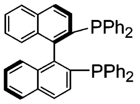
$$\mathrm{ArI} > \mathrm{ArOTf} > \mathrm{ArBr} \gg \mathrm{ArCl}$$

The aryl triflates form into the medium cationic species that are neutralized by the presence of AcO^- or/and Cl^- anions (eq 2).

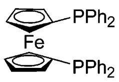


Oxidative addition is facilitated by the higher electron density of M^n. σ-donor ligands such as phosphines attached to M^n facilitate the oxidative step. π-acceptors such as CO and alkenes tend to reduce or suppress this oxidative step.[25]

Polar and nonpolar Ar−X bonds can undergo the oxidative insertion of Mn. The classical reactive order C−I > C−Br ≫ C−Cl ≫ C−F is contradicted by using electron-rich ligands such as P(*t*-Bu)$_3$, Arduengo's N-heterocyclic carbenes, Bertrand's carbenes, and Buchwald and Hartwig's ligands and other new types of ligands.[26] In the case of Pd(dba)$_2$−bidentate ligand [(*R*)-BINAP ((*R*)-1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine) (**1**)), DPPF (1,1′-bis-diphenylphosphinoferrocene (**2**)), etc.] catalytic systems, Jutand and Amatore identified the key reactive intermediate complexes of the oxidative addition step. Pd(0)−bidentate ligand complexes are the more reactive species in the oxidative addition of phenyl iodide.[27] The exact role of the bidentate bite angle parameter is not very clear.[18]



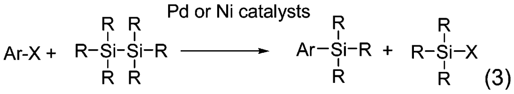
1



2

Diazonium salts, triflates, acyl halides, and sulfonyl halides can give the oxidative addition.[28] The cross-coupling of unactivated alkyl halide, such as fluoride, and pseudohalide bonds has been recently described using Ni(0) catalysts, but the activation of the C−F bond remains an interesting challenge. The Kumada group described for the first time the C−F activation of fluorobenzene using NiCl$_2$(dmpe)$_2$ (dmpe = 1,2-bis(dimethylphosphino)ethane (**132f**)) as the catalyst. Recently, the Herrmann (Ni-carbene), Mongin (Ni-dppe or Ni-dppp) (dppe = 1,2-bis(diphenylphosphino)ethane (**132d**), dppp = 1,3-bis(diphenylphosphino)propane (**132e**)), and Dankwardt (Ni-microwaves) groups developed new C−C coupling reactions using aryl fluorides as starting materials.[29]

The oxidative addition also works with Si−Si, Sn−Sn, and B−B derivatives. For example, patents from Dow-Corning in 1971[30] and Rhône-Poulenc in 1976[31] claimed the Ni- and Pd-catalyzed reaction of aryl halides with $Cl^{x}Me_{y}Si-SiCl_{x}Me_{y}$[30] or $(OR)_{x}Me_{y}Si-Si(OR)_{x}(Me)_{y}$ ($x + y = 3$),[31] via an oxidative addition intermediate Si−M−Si (eq 3), to give the corresponding $Ar-SiCl_{x}(Me)_{y}$ and $Ar-Si(OR)_{x}Me_{y}$ products.



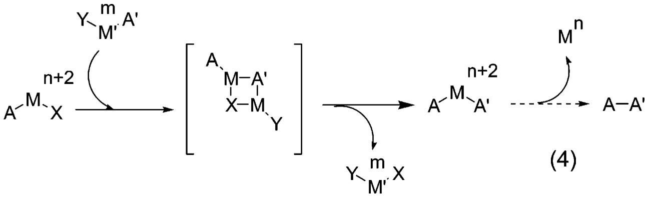
$$Ar\text{-}X + R_3Si-SiR_3 \xrightarrow{\text{Pd or Ni catalysts}} Ar-SiR_3 + R_3Si-X \tag{3}$$

Functionalized aryl silanes can be prepared using this process with some economical advantage compared to the classical routes through Grignard or organolithium intermediates.[32]

3.3.2. Transmetalation

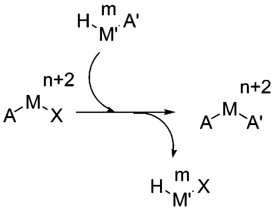
A′−M′^{m}(Y) and H−M′^{m}(A′) adducts (with A′ = aryl or heteroaryl groups) of main group metals, M′ = Mg, Zn, B, Al, Sn, Si, Hg, and Bi, react with the oxidative adduct M^{n+2}(A)(X) to create new derivatives M^{n+2}(A)(A′) and M′^{m}(X)(Y) having formally the same oxidation states respectively as those of the starting derivatives ($m + 2$ and m). The driving force of the transmetalation step is due to the difference in the electronegativities between M^{n+2} and the main group metal (M′^{m}). Usually, M species are more electronegative than the main group metal (M′). Some examples are provided below.[33] The Pauling electronegativity scale is as follows: Pd (2.20), Ni (1.91), Mg (1.31), Zn (1.65), B (2.04), Al (1.61), Sn (1.96), Si (1.90), Hg (2.00), and Bi (2.02).

In the transmetalation step, it is reasonable to consider the formation of a four-center intermediate (eq 4).



(4)

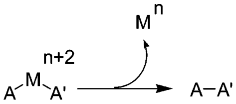
When (A′)M′^{m}−H hydride is used instead of AM^{n+2}(X), the reaction proceeds in the same way (eq 5).



(5)

3.3.3. Reductive Elimination

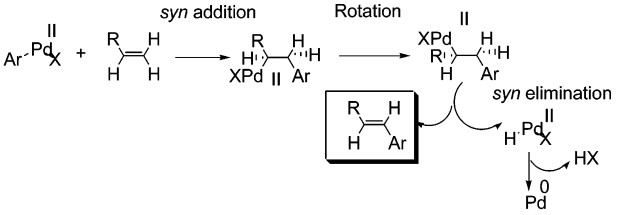
Reductive elimination is a unimolecular reaction, which can be considered as the reverse of the oxidation step. During this step, the central metal M^{n+2} is normally reduced to M^{n} (eq 6). The regenerated M^{n} species repeats the oxidative addition step to complete the catalytic cycle. No reductive elimination occurs with Mg, Zn, Si, B, and Sn metals. This is the main difference in behavior between metal transition complexes and the main metal compounds group. At the opposite, in the oxidative addition, this reductive elimination step is promoted by the reduced electron density of the central metal M in the A−M^{m+2}−A′ intermediate, by a strong π-acceptor ligand such as CO, electron deficient alkenes, and bulky ligands.



(6)

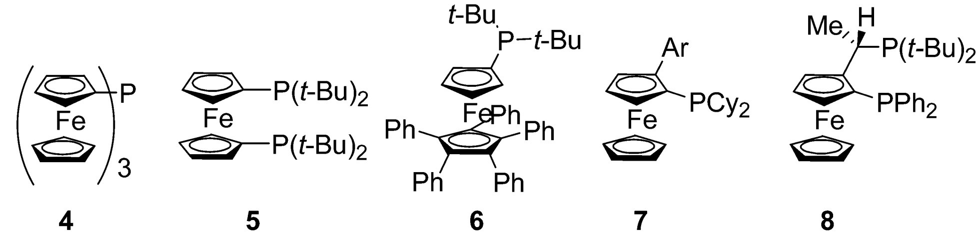
3.3.4. Insertion Step

The α,β-insertion is a reversible step. In the case of Pd, there is, first of all, a *syn* addition of the oxidative adduct to the C=C bond, leading to the formation of a σ-(β-aryl) alkylPd intermediate. Then, an internal rotation and a *syn* β-H elimination give the *trans*-alkene (eq 7).



(7)

This carbometalation is generally controlled by several factors such as the oxidation state of the M^{n+2}(A)(X). A faster process is observed when a cationic complex is used (for instance by the addition of a Ag(I) salt to a halogeno complex) due to a better coordination between the alkene



Ar= Ph, 2-MeOPh, 1-naphthyl, 9-phenanthrenyl

Figure 1. Some representative Hartwig family ligands.

and the organometallic species. Another solution to enhance the activity is sometimes to use bulky, electron-rich phosphines such as $P(t\text{-Bu})_3$ or carbenes as ligands[34] or supported heterogeneous Pd catalysts with or without phosphines.[35] This insertion step was demonstrated in the Heck−Mizokori coupling reaction. Recent theoretical studies have shown that the β-hydrogen elimination in the $[L_2PdCH_2CH_2X]^+$ complex ($L_2 = H_2PCH_2CH_2PH_2$; X = halides, OH, OMe, OAc) is kinetically more favorable than the β-heteroatom elimination (β-OR). An excess of halide ions block the empty coordination site presenting the β-H elimination, and the acidic conditions favor the elimination of the OR moiety via HOR formation.[36]

3.4. Representative Catalytic Systems

The Ullmann reaction, discovered one century ago, is one of the very first examples from the patent literature of a metal which promotes aryl−aryl and aryl−hetroaryl bond formation. Cu was used in stoichiometric or quasi stoichiometric quantities. The somewhat drastic conditions (high temperature) and waste formation, along with the large amount of metal, limit the applications of this technology. An excellent review was recently published by Lemaire discussing the aryl−aryl Ullmann reaction.[37]

The revolution in C−C cross-coupling came from the use of very reactive ligated organometallic species (Pd, Cu, Ni as centered metal) as catalysts of the reaction of aryl halides, aryl-pseudo halides, or vinyl halides with organometallic compounds (B, Mg, Si, Zn, and Sn) or with alkenes. These new catalytic systems widened the scope of the C−C bond formation, thanks to its acceptance of a larger variety of functional groups and to milder reaction conditions. Nevertheless, there are still some limitations in large scale applications due to the nature and reactivity of the functional groups, to the type of aryl halides, ..., and to physical aspects (e.g. solubility, accessibility of the reactive sites, and chain mobility for polymers), which can necessitate the use of too large amounts of costly metals and ligands.

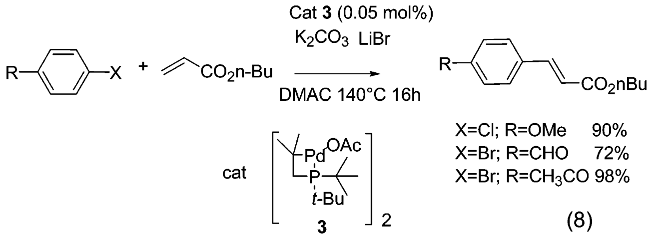
New technologies for the heterogenization of the catalyst can boost the development of the C−C bond cross-coupling in the industry. We can see more and more examples of the use of heterogeneous catalysts such as Pd/C or Pd/alumina, without ligand, and some new promising results have recently been published using Pd/C, Pd spheres, and Pd nanoparticules as catalyst in organic solvent or, better, in water.[38]

3.4.1. Homogeneous Catalysts

Pd, Cu, and Ni associated with bulky ligands are the most efficient catalytic compositions to create C−C bonds. We report in this chapter the most typical examples of this coupling reaction.

3.4.1.1. Pd/Heck−Mizokori Reaction. This reaction was independently discovered by the Mizoroki and Heck groups in 1971−1973.[39] This reaction is probably the most general and useful technology to create a C−C bond involving a sp[2] carbon. Many reviews have already been published.[40] One of the first patented examples (1973) using a Heck−Mizokori like reaction process concerns the vinylation process of PhCl or $PhNO_2$, PhMe or PhH with styrene at 80 °C under 300 psig pressure during 5−6 h using $Pd(OAc)_2$ as catalyst to give stilbene.[41]

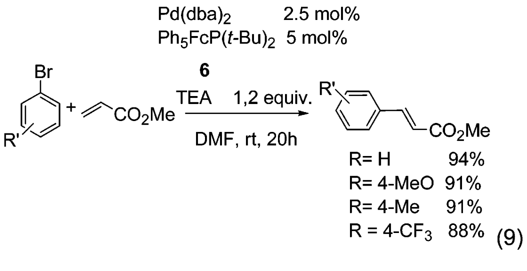
In 1996 Hoechst patented the synthesis of functionalized alkenes by the Heck−Mizokori reaction using palladaphosphacyclobutanes as catalyst[42] and K_2CO_3 as the best base. Very good isolated yields were observed with functionalized aryl bromides and (less reactive) aryl chlorides (eq 8).[43] These palladaphosphacyclobutanes **3** were obtained by reacting $Pd(OAc)_2$ with $P(t\text{-Bu})_3$ (**22**).



(8)

Pd(II) di-*tert*-butylphenylphosphine catalyst was patented by Bayer in a C−C cross coupling reaction of aryl chloride and acrylamides in dipolar aprotic solvent ($AcNMe_2$).[44] Very good results were obtained when a bulky base such as cyclohexyldimethylamine was used. For example, $4\text{-}CF_3C_6H_4CH{=}CHCONH_2$ was isolated in 99% isolated yield by reacting acrylamide with 4-chlorotrifluoromethylbenzene.[45]

Hartwig developed and patented in 2000 the synthesis and application of air-stable, new electron-rich ligands of the family of ferrocenylphosphines in Pd-catalyzed Heck−Mizokori, Miyaura−Suzuki, and Buchwald−Hartwig coupling reactions.[46] The structures of the most relevant Harwig ligands (**4**−**8**) are presented in Figure 1. Pd(0)/**6** gives particularly good results in the Heck−Mizokori coupling reaction (mild conditions, acceptance of a wide variety of substituents) (eq 9).



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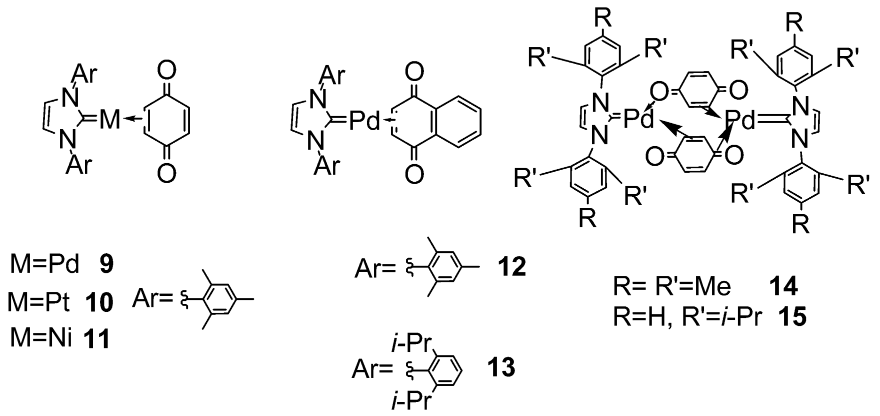
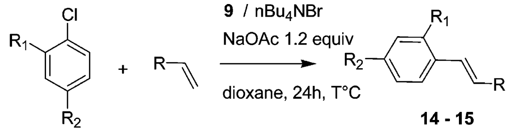


Figure 2. Palladocarbene examples.

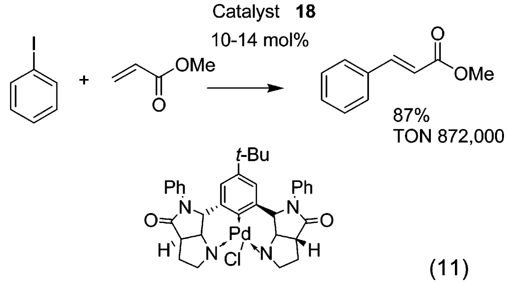
Umicore patented in 2002 new, useful metallocarbene complexes of Pd, Ni, or Pt.[47] The palladocarbene complexes **9**−**13** were tested in the C−C Heck−Mizokori coupling reaction between aryl halides and styrenes or acrylates (Figure 2). Moderate to good isolated yields were obtained using aryl chloride as starting material (eq 10). These experimental conditions can tolerate a large range of organic functions. Bis palladocarbene complexes **14**−**15** are also claimed.



	R	R_1	R_2	T°C	%		R	R_1	R_2	T°C	%
16a	Ph	H	H	140	62	**17a**	$CO_2CHEtBu$	CN	H	140	99
16a	Ph	H	H	160	67	**17b**	$CO_2CHEtBu$	H	NO_2	140	98
16b	Ph	H	OMe	160	52	**17c**	$CO_2CHEtBu$	H	COMe	140	99
16c	Ph	H	NO_2	140	88	**17d**	$CO_2CHEtBu$	H	CF_3	140	90
16d	Ph	H	Me	160	62						
16e	Ph	H	CF_3	140	84						
16f	Ph	CN	H	140	99						

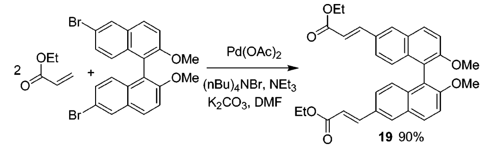
(10)

New Pd pincers such as **18**, which have a good thermal stability and are very efficient in the Heck−Mizokori reaction, have been also described (eq 11).[48] **18** was prepared in 98% isolated yield by the reaction of 4,2,6-*t*-Bu(OHC)$_2$C$_6$H$_2$-PdCl(PPh$_3$)$_2$ with (*S*)-2-anilinocarbonylpyrrolidine in refluxing MeCN during 94 h.



18

In some specific examples, much simpler catalytic systems can work. For instance, the Heck−Mizokori synthesis in good yields of functionalized binaphthol **19**, an intermediate in the synthesis of cholesteric liquid crystal compounds, has been claimed by Fuji Photo Film using Pd(OAc)$_2$/(^{n}Bu)4NBr as the catalyst (eq 12).[49] Recently, Gaunt developed new Fujiwara−Moritani oxidative experimental conditions to control the selectivity of the intermolecular alkenylation of indoles by the nature of the solvent[50] (eq 13). Large quantities of Pd(OAc)$_2$ were needed. These oxidative coupling reactions will be reviewed below.



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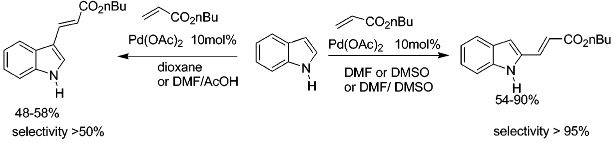

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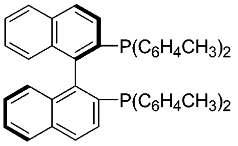
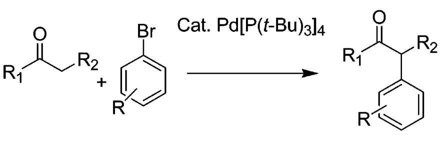
3.4.1.2. Pd/C−C Coupling Reactions Involving Activated C−H Derivatives.

Arylation and vinylation of activated methyl, methylene, and methine carbons with aryl halides and vinyl halides are performed using bulky phosphines such as BINAP (**1**) and Tol-BINAP (**20**) developed by Buchwald[51] or PCy$_3$ (**21**) and P(*t*-Bu)$_3$ (**22**) from Hartwig,[52] which are the best ligands of Pd(0) and Ni(II) species (eq 14).



20
(R)-Tol-BINAP

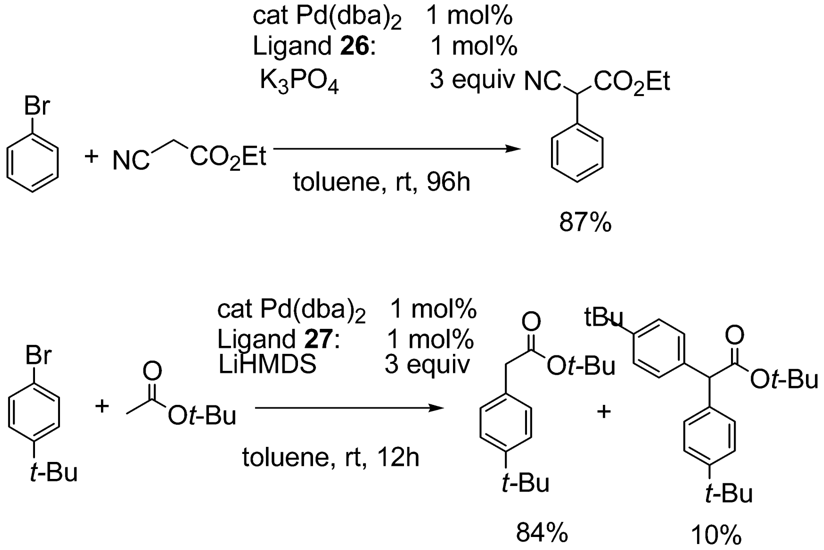


(14)

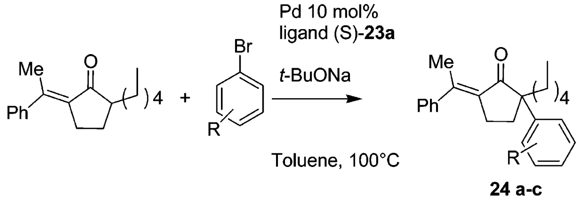
For example, with his ligands, Hartwig obtained excellent yields (70−97%) of a range of α-monoaryl ketones by the reaction of unsubstituted or substituted ArBr (mostly *p*-methoxy) and alkyl ketones (mainly alkylphenyl ketones but cyclohexanone is included) or malonates[52] (reaction conditions: Pd(OAc)$_2$ or Pd(dba)$_2$ 1 mol %, Pd/ligand 1/1 mol/mol, t-BuONa 2 equiv, Ar−Br/ketone or malonate 1/1.1 mol/mol, THF, 2−24 h, 20−70 °C).

Comparatively, under similar conditions, more catalyst is needed with the BINAP series. A large variety of Ar−Br

Scheme 4. Representative Examples in C−C Coupling Reactions Using Pd(0)−Hartwig Ligands



compounds, such as protected bromoanilines (imine forms) or acetals of bromobenzaldehyde, have been tested in this case with good results. Interestingly, good yields and ee% are obtained in the asymmetric α-arylation of the cyclopentanone of eq 15 with (S)-BINAP (**23a**), but a large amount of catalyst is required (eq 15).[51]

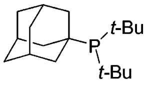


24 a-c

R		Catalyst	(S)-23 %	Yield %	ee %
24 a	H	$Pd_2(dba)_3$	15	93	93
24 b	3-Me	$Pd(OAc)_2$	10	100	99
24 c	4-CF_3	$Pd_2(dba)_3$	10	100	90

(15)

In 2000 Hartwig patented new adamanthyl, bulky and electron-rich monophosphine ligands such as **25**−**27**.[53] These ligands allow an efficient C−C coupling reaction between cyanoesters, esters, ketones, and aryl halides. Scheme 4 shows some representatives examples. P(*t*-Bu)(Ada)$_2$ (**26**) gives the monoarylation product while disubstitution occurs using P(Ada)(*t*-Bu)$_2$ (**27**). Under the same experimental conditions, PCy$_2$(*t*-Bu) and PCy(*t*-Bu)$_2$ give similar results. Beller patented the same ligand family for Miyaura−Suzuki cross-coupling reactions.[54]



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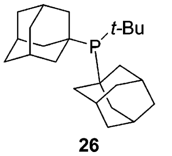

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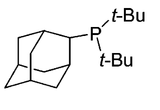
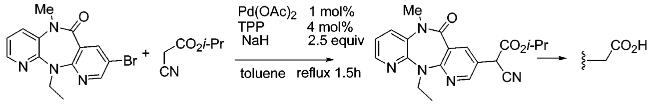


27

Much simpler ligands such as triphenylphosphine can work in some specific examples. For instance, Boerhringer Ingelheim patented in 2002 the synthesis of an intermediate of non-nucleoside HIV-1 reverse transcriptase inhibitor drugs **28**[55] where the acetyl moiety was introduced by a Pd(OAc)$_2$−PPh$_3$-catalyzed coupling reaction of cyanomalonate with a 3-bromopyridyl group. The coupled product was hydrolyzed to give the corresponding acetic intermediate in excellent overall yields (eq 16).

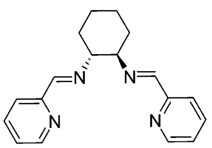


>90%

28

(16)

Cu catalysts have been used also in the C−C coupling of activated C−H and aryl halides. Powerful Cu bidentate ligands such as **29**−**33** patented by Rhodia and Cristau−Taillefer are particularly effective in the coupling of malonates or malononitriles when aryl iodides are the starting materials (eq 17). Phenyl malonates **34**−**36** were obtained in almost quantitative yields.[56]



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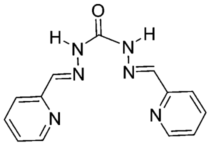

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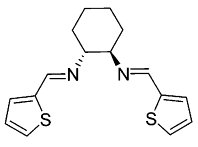

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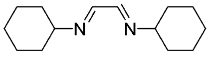

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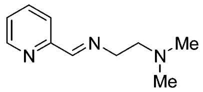

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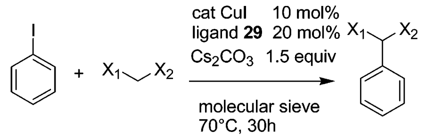


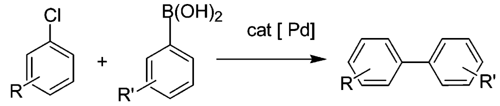
X1= X_2 =CO_2Et	**34**	93%
X1=CO_2Et, X_2=CN	**35**	92%
X1=CN, X_2=CN	**36**	62%

(17)

3.4.1.3. Pd/Miyaura−Suzuki Reaction.

The Pd-catalyzed C−C coupling reaction between organoboron compounds and aryl, alkenyl, and alkynyl halides has been intensively developed since the first results of the Miyaura and Heck groups (eq 18).[57a−c] O-boronic acid synthesis via an elegant direct ortho lithiation and related C−C coupling reaction was rewieved by Snieckus.[57d]

A considerable number of papers and patents claiming new, extremely powerful catalysts associated with mild

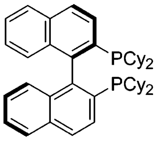


(18)

reaction conditions have been published since and applied in many fields. The most noteworthy progress in this coupling reaction involved the use of bulky phosphines such as PCy_3 (**21**) or $P(t\text{-}Bu)_3$ (**22**). Classical triarylphosphines are inefficient ligands in the C−C coupling reaction with aryl halides.[58]

a. Ligand Families for the Miyaura−Suzuki Reaction. The Pd(0)−PCy_3 or similar couples give very good results, even with bulky aryl chlorides or triflates and bulky boronic acids. Pd(0)−$P(t\text{-}Bu)_3$ is also excellent except with aryl triflates. Fu discovered that $P(t\text{-}Bu)_3$ (**22**), a highly air sensitive ligand, can be advantageously released in situ from an air-stable phosphonium salt precursor $[P(t\text{-}Bu)_3H]BF_4$.[59] Bidentate phosphorus ligands such as (*R*)-BINAP (**1**), or (*S*)-BINAP (**23a**) or racemate (**23b)** or tol-BINAP (**20**), originally developed by Buchwald,[60] and DPPF (**2**), developed by Hartwig,[46] form strongly chelated organometallic intermediates, accelerating the oxidative addition and preventing the *β*-elimination (see mechanism section). Hartwig observed a monochelated intermediate in the coupling reaction with 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF) ligand **37**.[61]

b. First Generation of Buchwald Ligands. Buchwald patented in 1998 several BINAP derivatives of the *o*-(dialkylphosphino)biphenyl type such as **38** and **39**, which are efficient Pd ligands in the Miyaura−Suzuki cross-coupling reaction.[62] This reaction can work at room temperature with very low amounts of Pd complexes (less than 0.02 mol % for **38**). A wide variety of functional groups are tolerated, and electron-rich or electron-poor aryl bromides or chlorides, even *o*-substituted ones, work (Scheme 5; typical conditions: ArX 1 equiv, boronic acid 1.5 equiv, KF 3 equiv, $Pd(OAc)_2$ <1 mol %, *o*-(di-*tert*-buthylphosphino)-biphenyl (**39**) 2 mol %, THF, rt).



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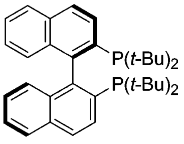

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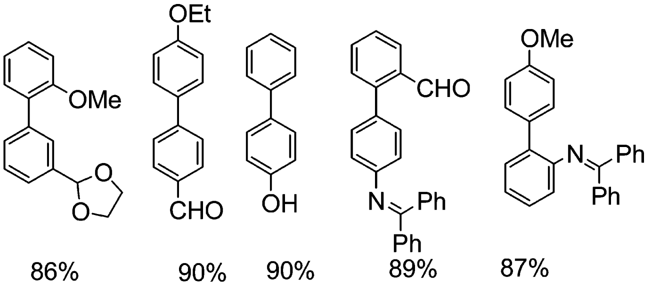
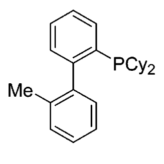
Scheme 5. Examples of Biphenyls Obtained with C−C Coupling Reactions Using Ligand 39



c. Second Generation of Buchwald Ligands. Patents report the use in C−C (and C−N) cross-coupling reactions of new alkyl substituted biaryl phosphine ligands such as Me-Phos (**40**), NMe_2-Phos (**41),** and X-phos (**42**),[62,63] which were commercialized by Rhodia, or alkoxy substituted S-Phos (**43** and **44**)[64] (second generation Buchwald ligands). These ligands work well in the Miyaura−Suzuki coupling to give both biaryl and alkylaryl products, allow arylations or vinylations α to carbonyl groups, and can also be used in the C−O bond coupling. In the Miyaura−Suzuki coupling, they are efficient with deactivated and/or hindered aryl chlorides or aryl boronic acids. The most effective bases are K_3PO_4, CsF, and Cs_2CO_3 (eq 19). For example, methoxybiphenyl, methylbiphenyl, and 4-methyl-2′-methoxybiphenyl are obtained in 94%, 95%, and 99% yields, respectively. Other representative examples with CsF (aryl halides) and *t*-BuONa (ketones) as bases are shown in Table 2. Good yields are obtained with electron donor and electron acceptor substituents on aryl halides and boronic acid or ketone derivatives. No yield decrease was observed with bulky aryl halides or boronic acids.



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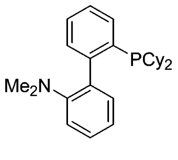

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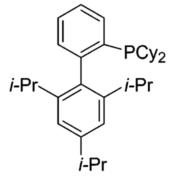

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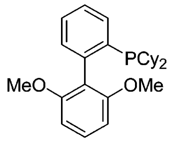

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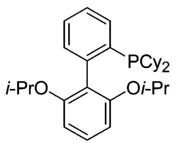

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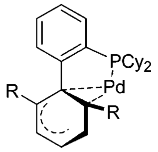

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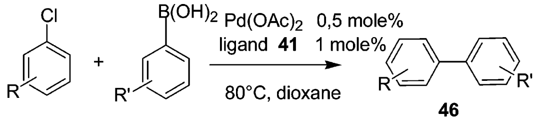


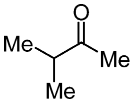
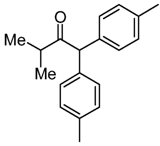
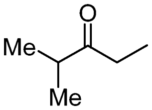
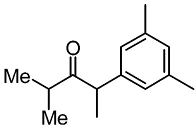
(19)

The observed high reactivity of Buchwald’s ligands is a function of their steric bulk and high electron density. It has been postulated that the *π* system of the biaryl group interacts with the Pd center. When orthometalation is possible (unsubstituted ortho positions of the biphenyl), too stable complexes are formed which inhibit the catalytic activity. To prevent this, substituents have been introduced in these ortho positions and much more active “cyclopropane” species such as **45** are formed. Furthermore, methoxy, isopropyloxy, and isopropyl groups increase both the steric bulk and the electronic density of the biphenyl moiety, thus stabilizing even more the corresponding Pd complex **45**. X-ray data of **45**-like complexes have been published by Buchwald.[65]

These catalytic systems have unprecedented activity in the Miyaura−Suzuki coupling reaction. For example, the coupling reaction between 4-*tert*-butylbromobenzene and 2-methylphenylboronic acid using only 10 ppm of $Pd(OAc)_2$ and 20 ppm of **43** (K_3PO_4; 100 °C; 1.5 h) gives 98% yield of the biaryl. Various bulky, electron-rich and electron-poor substituents are tolerated on the two aromatic partners. Aryl chlorides and aryl bromides gave similar results. Scheme 6 shows some selected examples using ligand **42**.

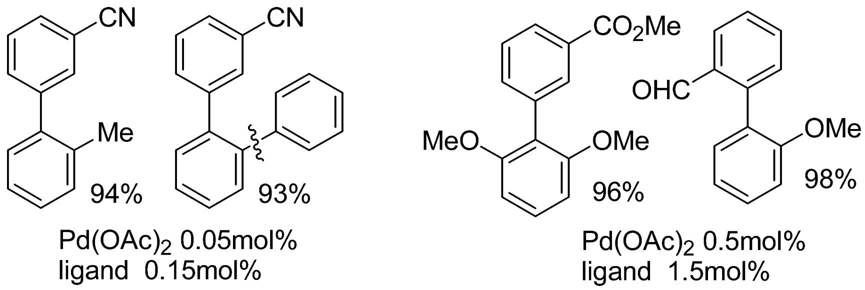
Pradhan published mild experimental conditions in the Miyaura−Suzuki arylation process of nucleoside C-6 arylsulfonates using $Pd(OAc)_2$−2-(dicyclohexylphosphino)biphenyl (**47**) as catalyst (eq 20).[66] **48** or **49** was characterized in the ^1H NMR technique as a plausible intermediate (eq 21).

Table 2. C−C Cross-Coupling Reactions Using MMe$_2$-Phos Ligand (41)[a]

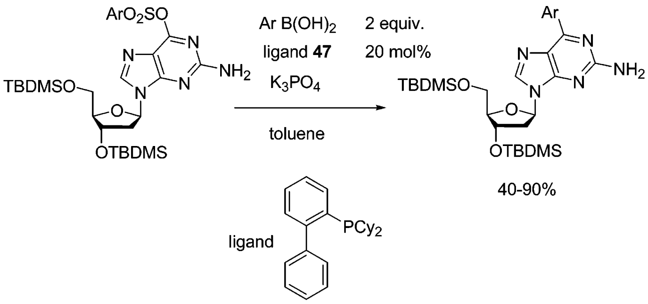
halide	boronic acid	T (°C)	mol % Pd	yield (%)	product
4-MePhCl	PhB(OH)$_2$	100	0.5	96	4-MePh−Ph (**46a**)
4-MePhCl	PhB(OH)$_2$	rt	2	94	4-MePh−Ph (**46a**)
4-(MeO)PhCl	PhB(OH)$_2$	100	0.5	93	4-(MeO)Ph−Ph (**46b**)
4-(MeO)PhCl	PhB(OH)$_2$	rt	2	92	4-(MeO)Ph−Ph (**46b**)
3,5-(Me)$_2$PhBr	PhB(OH)$_2$	rt	1	92	3,5-(Me)$_2$Ph−Ph (**46c**)
2,5-(Me)$_2$PhCl	3-tolyl-B(OH)$_2$	rt	2	94	2,5-(Me)$_2$Ph−3-(Me)Ph (**46d**)
4-(MeCO$_2$)PhCl	PhB(OH)$_2$	rt	2	90	4-(MeCO$_2$)Ph−Ph (**46e**)
4-MeCOPhCl	3-tolyl-B(OH)$_2$	rt	2	92	4-MeCOPh−3-(Me)Ph (**46f**)
4-MePhCl	4-(MeO)PhB(OH)$_2$	100	1	94	4-(MeO)Ph−4-(Me)Ph (**46g**)
4-MePhCl	 Base: *t*-BuONa	80	3	79	 **46h**
3,5-(Me)$_2$PhBr	 Base: *t*-BuONa	rt	3	82	 **46i**

[a] Reaction conditions: 1.0 equiv aryl halide, 1.5 equiv boronic acid, 3 equiv CsF, Pd(OAc)$_2$, 1.5 L/Pd, dioxane.

Scheme 6. Some Biphenyls Obtained by the Miyaura−Suzuki Coupling Reaction Using Buchwald's Ligand 42



d. Hartwig Ligands. As discussed before, Hartwig patented the electron-rich ferrocenylphosphines as air-stable ligands for the Pd-catalyzed C−C and C−N coupling reactions.[46] The catalytic system Pd(0)/Ph$_5$FcP(t-Bu)$_2$ (**6**) gives high yield (>90%) in the Miyaura−Suzuki cross-coupling reaction of aryl bromides and chlorides (eq 22). No major electronic and steric effects are observed on the arylboronic: −CF$_3$, halogeno, or MeO− can be present in the para or ortho positons. The paper describes mostly electroattractive groups (cyano, keto, nitro) on the aryl halide partner. Fair yields are obtained using alkyl or cycloalkyl boronic acids.



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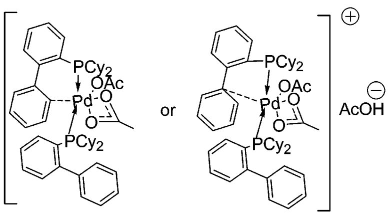
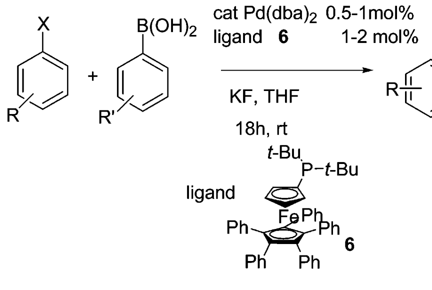
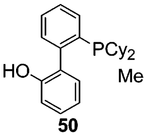


48 **49** (21)



(22)

e. Clariant Ligands. Pd and Ni complexes of 2-(dicyclohexylphosphino)-2′-hydroxybiphenyl phosphine (**50**) and related **51**−**54** phosphines and their applications in catalytic coupling reactions have been patented in 1999 by Clariant.[67]



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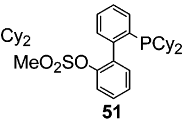

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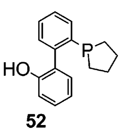

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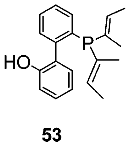

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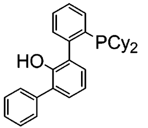
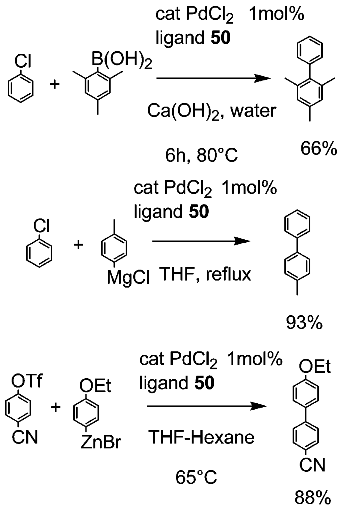


54

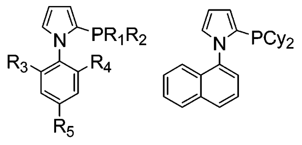
The hydroxyl function, under basic conditions, increases the global electronic density of these ligands, which can account for their activity. A second hypothesis is to consider a stabilization by interaction between the hydroxy or its salt and the Pd species. These new complexes are efficient in C−C, C−N, and C−O cross-coupling reactions, even with aryl chlorides (e.g. for Miyaura−Suzuki, Corriu−Kumada−Tamao, or Hiyama and Heck−Mizokori coupling reactions) (eq 23).



(23)

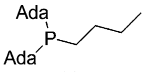
f. Beller−Degussa Ligands. Another interesting ligand family **55 (56−61)** for the Miyaura−Suzuki C−C coupling reaction was discovered by Beller and patented by Degussa.[68] Various electron-rich or electron-poor aryl and heterocyclic chlorides can be used as starting materials under mild reaction conditions. Using these ligands with very small amounts of Pd (less than 0.1 mol %), a high yield of biaryls is obtained when Ar−Cl or hetero-Cl (RC_6H_6Cl: R = 4-COMe, 2-COMe, 2-CN, 4-CN, H, 4-Me, 2-OMe, or hetero-Cl: 4-OMe, 2-CF_3, 3-chloropyridine,5-chloroindole, 2-chloroquinoline, 5-chlorofurfural) is reacted with phenyl boronic acid (K_3PO_4, $Pd(OAc)_2$/**56** = 1/2, toluene, 20 h at 60−100 °C). But there are some exceptions since under the same conditions, when R is the 2,6-Me_2 or 2-chlorobenzoxazolyl or 3-chlorothiophenyl group, there is a strong drop in the yield.

R_1=R_2=*t*-Bu; R_3=R_4=R_5=H **56**
R_1=R_2=Ada; R_3=R_4=R_5=H **57**
R_1=R_2=Cy; R_3=R_4=R_5=H **58**
R1=R_2=Cy; R_3= R_4=R_5=Me **59**
R1=R_2=Cy; R_3=MeO, R_4,R_5=H **60**



55 **61**

The very bulky and σ-electron donor phosphines bearing adamantyl groups **62** and **25** can be used with an even lower amount of Pd (~0.005% mol %/substrate).[54] For instance, Pd/**25**-catalyzed Miyaura−Suzuki reaction of 4-chloroanisole and phenylboronic acid gave the coupled product in 96% in only 5 min.[69] This is one of the few examples where KOH is used as base in the Miyaura−Suzuki reaction.



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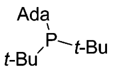


25

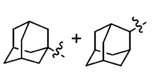
Ada =


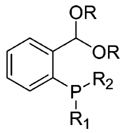
Table 3. Influence of the Nature of Aryl Chloride Derivatives Using Beller−Degussa Ligands 62[a]

coupled product	R	yield (%)	TON
46a	4-Me	87	17 400
46a	4-Me	74	14 800
63	2-Me	85	17 000
64	2,6-Me_2	68	13 600
65	H	80	16 000
66	2-F	96	19 200
46b	4-(MeO)	64	12 800
67	3-(MeO)	58	11 600
68	2-(CN)	100	20 000
69	3-pyridine	99	19 800

[a] Reaction conditions: RPhCl + $PhB(OH)_2$, $Pd(OAc)_2$ 0.005 mol %, ligand **62** with L/Pd = 2, 100 °C in toluene, K_3PO_4.

Ligand **62** is similar to $P(t\text{-}Bu)_3$ and compares favorably to other ligands such as PPh_3, $PhPCy_2$, (2-tolyl)PCy_2, or PCy_3 in the coupling reaction of $PhB(OH)_2$ with 4-MePhCl. There is no significant influence of substituents on the aryl chloride. In all cases, high TON values were observed (Table 3). This catalytic system is also very powerful in the amination reaction of arylamides (see below).

g. Symyx Ligands. Symyx Technologies patented new bidentate ligands with general structure **70 (72−76)** and **71** and related Pd complexes useful for C−N and C−C coupling reactions.[70] A typical complex of Pd is shown in **77**.



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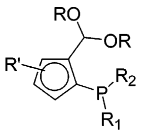

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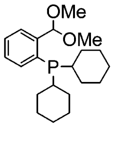

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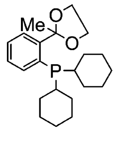

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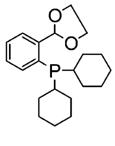

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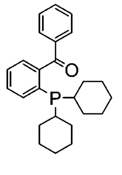

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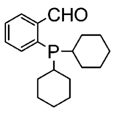

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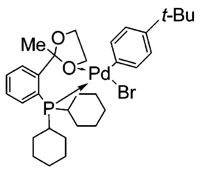
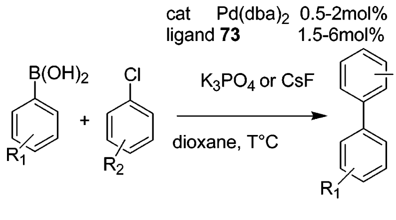


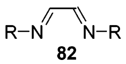
77

These new bidentate ligands were used in C−C coupling reactions of aryl chlorides and boronic acids (eq 24). Typical examples are given in Table 4.



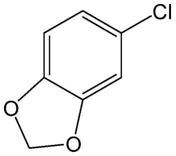
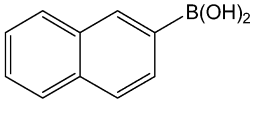
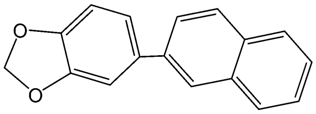
(24)

h. Nolan-diimine Ligands. Bidentate *N*,*N*′-dialkyl- or *N*,*N*′-dicycloalkyl-1,4-diazabutadienes (**82**) represent a new class



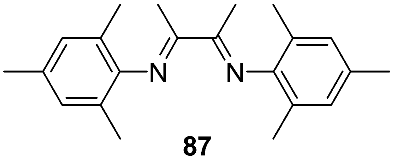
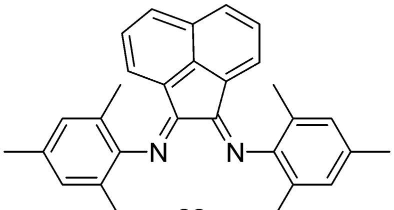
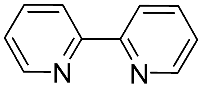
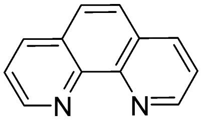
82

Table 4. C−C Coupling Reaction Results Using Symyx Ligand 73[a]

R_2	R_1	T (°C)	mol % Pd	biphenyl product	yield (%)
4-CF_3	H	80	0.5	**78**	92
4-CF_3	4′-CF_3	100	1	**79**	94
4-COMe	4′-Me	100	1	**80**	96
2-CN	H	100	1	**68**	91
		100	1	 **81**	90

[a] Reaction conditions: $Pd(OAc)_2$ 0.5−1 mol %, dioxane, K_3PO_4, or CsF.

Table 5. Comparative Results Using Family 82 and Bipyridine and 1,10-Phenanthroline Ligands[a]

ligand	yield (%)	ligand	yield (%)
no ligand	30	 **87**	78
83 (R = Cy)	99	 **88**	79
84 (R = Ada)	93	 **89**	13
85 (R = 2,2′-(*i*-Pr)$_2$Ph	80	 **90**	no reaction
86 (R = 2,2′,4-(Me)$_3$Ph	85		

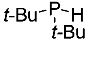
[a] Reaction conditions: 4-MePhBr + $PhB(OH)_2$, 3 mol % $Pd(OAc)_2$/L, Cs_2CO_3, 3 h, 80 °C, dioxane.

of Pd ligands in the Miyaura−Suzuki reaction.[71] Very good yields are obtained with **83** (R = cyclohexyl).

Using the $Pd(OAc)_2$/*N*,*N*′-dicyclohexyl-1,4-diazabutadiene (**83**) catalytic system, the coupling reaction between 4-bromotoluene and phenylboronic acid gives 4-phenyltoluene in 99% yield. Bipyridine (**89**) and 1,10-phenanthroline (**90**), which could have been been of industrial interest, do not work (Table 5).

i. Du Pont Ligands. Phosphine oxides such as **91** and **92** were claimed by Du Pont as very good ligands of Pd complexes in the Miyaura−Suzuki reaction.[72] These ligands stabilize Pd(II) salts through P−O···H···O−P interactions in the Pd complex to give air-stable Pd complexes **93** and **94**; this accelerates the rate-determining oxidative addition to aryl halides.[73] These complexes are efficient catalysts for a variety of Miyaura−Suzuki (and Neghishi) C−C cross coupling reactions. Representative results are shown in Table 6.

j. Substituted Aminomethylphosphine Ligands. Symyx has prepared, by a tricomponent reaction (R_2PH + $R'-NH_2$ + $R''-CHO$), a large library of new ligands of general structure **96** which have been used in the Miyaura−Suzuki cross-coupling reaction (polymerization and others) through complexes **97** obtained from (COD)PdMeCl.[74]



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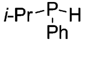

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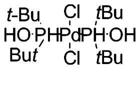

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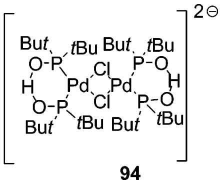

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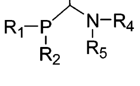

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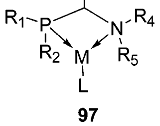


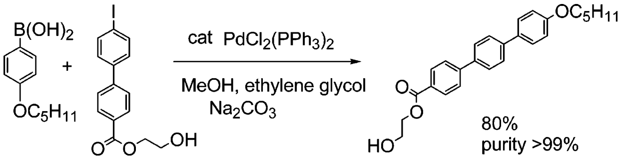
97

Table 6. C−C Coupling Reaction Using Du Pont Ligands[a]

phosphine oxide ligand	aryl compound	boronic acid	final product	yield %
91	Ph-Cl	$PhB(OH)_2$	biphenyl (**65**)	88
91	4-MePhCl	$PhB(OH)_2$	4-phenyltoluene (**46a**)	63
92	4-MePhCl	$PhB(OH)_2$	4-phenyltoluene (**46a**)	31
91	4-(MeO)PhCl	$PhB(OH)_2$	4-phenylanisole (**46b**)	97
91	2-(MeO)PhCl	4-(Me)$PhB(OH)_2$	2-(4-methylphenyl)anisole (**95**)	83
92	4-(MeO)PhCl	4-(Me)$PhB(OH)_2$	4-(4-methylphenyl)anisole (**46g**)	99
$(Me_2CH)PH(O)(2,4\text{-}(MeO)_2C_6H_3)$ (**92a**)	4-(Me)PhCl	4-(MeO)$PhB(OH)_2$	4-(4-methylphenyl)anisole (**46g**)	99

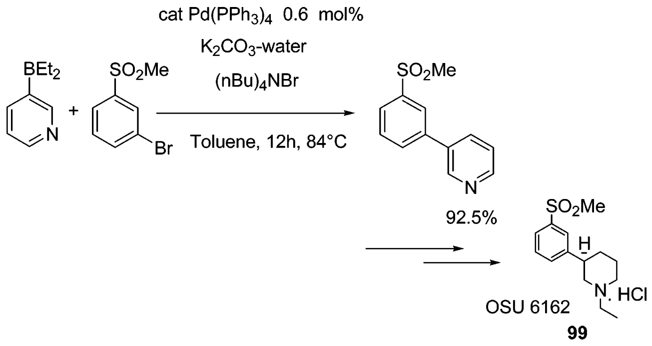
[a] Reaction conditions: $Pd_2(dba)_3$/dioxane, room temperature, Cs_2CO_3.

3.4.1.4. Selected Patented Examples of the Miyaura−Suzuki Reaction. *a. Pd−Phosphine Complexes.* The synthesis of terphenyls from arylboronate esters and biphenyl derivatives was described by Clariant using a $PdCl_2(PPh_3)_2$/Na_2CO_3/MeOH/ethylene glycol system.[75] For example, polyphenyl **98** was prepared in 80% isolated yield (eq 25).



98 (25)

Pharmacia has implemented at several hundred kilo scale a Miyaura−Suzuki coupling reaction between (3-pyridyl)-borane and 3-bromophenyl methyl sulfone in the key step of the synthesis of OSU 6162, a chiral 3-arylpiperidine with potential indications for diskinesia. The final conditions (0.3 mol % $Pd(PPh_3)_4$/K_2CO_3/H_2O) gave a 92−96% isolated yield of the corresponding sulfone **99** (eq 26).[76]

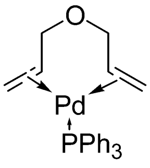


(26)

Interestingly, 2-aryl-2-(methoxyimino) acetate **100** can be obtained by the $Pd(PPh_3)_4$-catalyzed cross-coupling reaction of arylboronic acid with 2-bromo-2-(methoxyimino)acetate esters as shown in eq 27. This has been patented by Ciba-Geigy in 1995.[77]

b. Chelated Pd−Phosphine Complexes. In 2001 OMG and Beller patented a new class of catalysts **101**−**105** for the C−C cross-coupling reaction between aryl chlorides and boronic acids (Table 7).[78] Better results are observed when electron acceptor substituents are present on aryl halides.

Table 7. Cross-Coupling Reaction Results Using Chelated Pd−Phosphine Complexes[a]



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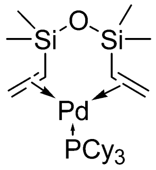

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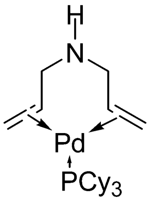

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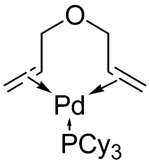

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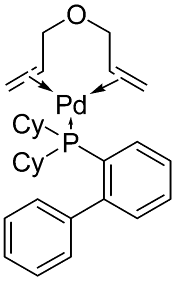
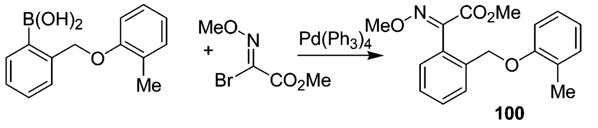


105

aryl halide	adduct	catalyst	yield (%)	TON
4-(F)PhCl	**66a**	**102**	15	300
4-(F)PhCl	**66a**	**103**	34	680
4-(F)PhCl	**66a**	**104**	34	689
4-(F)PhCl	**66a**	**105**	67	1340
4-(MeO)PhCl	**46b**	**102**	28	560
4-(MeO)PhCl	**46b**	**103**	48	960
4-(MeO)PhCl	**46b**	**104**	56	1120
4-(MeO)PhCl	**46b**	**105**	72	1440
2-(CN)PhCl	**68**	**102**	96	1920
2-(CN)PhCl	**68**	**103**	95	1900
2-(CN)PhCl	**68**	**104**	96	1920
2-(CN)PhCl	**68**	**105**	97	1940
2-(CN)PhCl	**68**	**101**	32	65 0.5 mol % catalyst
2-(CN)PhCl	**68**	**101**	16	160 0.1 mol % catalyst

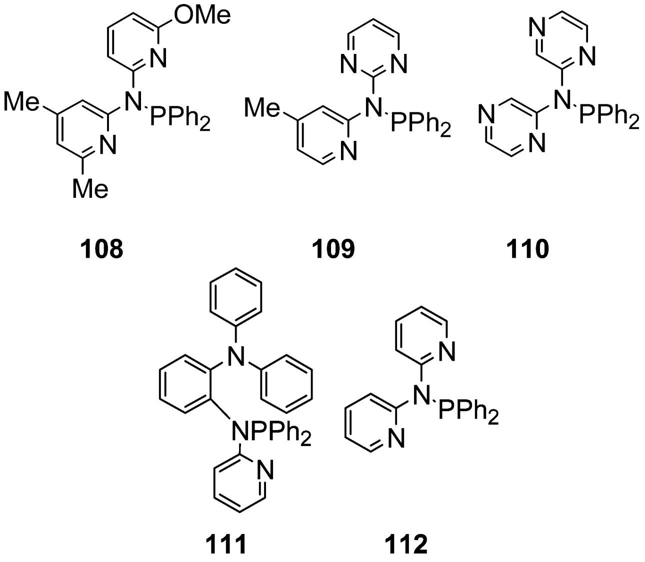
[a] Reaction conditions: aryl halide/$PhB(OH)_2$ = 1/1.3, K_3PO_4 1 equiv, and KF 1 equiv/aryl halide, THF, 100 °C, catalyst: 0.05 mol %.

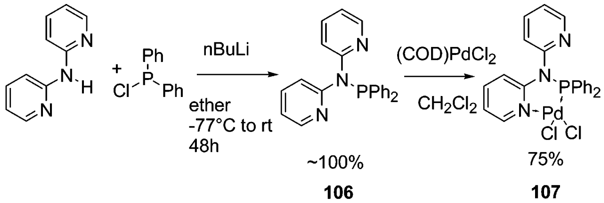


(27)

Degussa patented a new electon-rich bidentate ligand family (**106** and **108−112)** and related Pd(II) and Ni(0) complexes[79] such as **107** (eq 28 and Scheme 7). In the Miyaura−Suzuki and Kumada−Corriu−Tamao coupling reactions, good yields are obtained only when electron−acceptor substituents are present on aryl halides. Fair results were observed with heteroaryl halides.

Scheme 7. Typical Patented Degussa Ligands

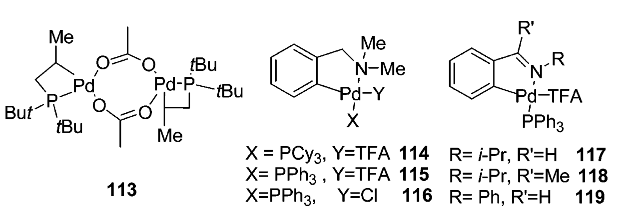




(28)

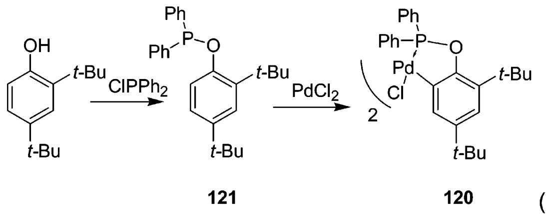
c. Palladacycle Catalysts. In palladacycles, states II and 0 of Pd are stabilized. The easy Pd(II)/Pd(0) redox interchange explains the efficiency of Pd species during the catalytic cycle. A plethora of palladocycles have been prepared, but few have been tested in homogeneous catalysis; some examples are found in reactions such as allylic rearrangement, C−C bond creation, cyclopropanation, aldolization, amino palladation, and Michael reaction. A review has been recently published by Spencer.[80]

Palladaphosphacyclobutane catalyzes the Miyaura−Suzuki cross-coupling reaction to give good yields of bis-aryl derivatives.[81] For example, reaction of 2-chloropyridine with 2-pyridylboronic acid glycol ester in refluxed THF (KOH as base and Bu_4NCl as phase transfer catalyst) gave the 2,2′-bipyridine in 91% yield when Pd complex **113** was used as a catalyst. In the same area, Bedford patented new palladacyclopentane complexes **114−119** useful to create C−C, C−S, C−O, and C−N bonds.[82]



Under typical conditions (Cs_2CO_3 2 equiv, toluene, 110 °C, 17 h), **114** gives better results than the other complexes **115−119**. A large range of substituents (OMe, Me, NO_2, COMe) can be present on the aryl chlorides. In some instances, for example with electron-poor ArCl, a very low loading (0.01−0.0001 mol %) of **114** is needed. Cs_2CO_3 in dioxane is the preferred base.

In 2002 Johnson Matthey claimed palladacycles such as **120** in the Miyaura−Suzuki and Heck−Mizokori C−C cross-coupling reactions (eq 29).[83] **120** is easily prepared through the corresponding phosphinate **121.** Some interesting synergies between ligands of the same family have been seen. For instance, high turnovers (100 000 to 100 000 000) have been reached in the reaction of Ph-$B(OH)_2$ with 3-bromoanisole, 4-bromoacetophenone, or 2-bromotoluene (PhB-$(OH)_2$/aryl halides 1.5/1 mol/mol, K_2CO_3, toluene, 130 °C, 18 h) when a mixture of ligands is used.



(29)

In 2000 Solvias patented new combinations of Pd salts and palladacycles−bulky dialkylphosphines−as powerful catalysts in Miyaura−Suzuki coupling reactions.[84] Scheme 8 shows comparative results using different Pd sources and dinorbornylphosphine (**122**) or di-*tert*-butylphosphine as

Scheme 8. Comparative Results Using Pd Complex−Dinorbornylphosphine Associations

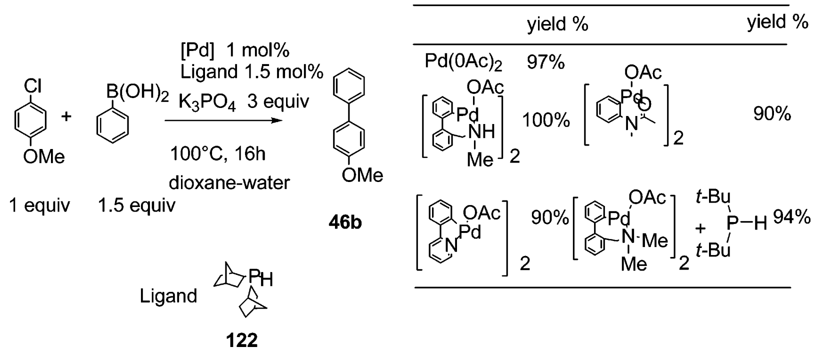


Table 8. Bayer's Carbene 124 Results[a]

final compd	aryl chloride	aryl-B(OH)$_2$	time	temp	yield (%)
46a	4-MePhCl	Ph-B(OH)$_2$	6 h	RT	>95
			20 min	80 °C	>95
46c	4-MePhCl	3-(MeO)PhB(OH)$_2$	25 h	RT	80
			2 h	80 °C	88
78	1-chloro-4-trifluoromethylbenzene	Ph-B(OH)$_2$	2 h	RT	95
78a	1-chloro-4-trifluoromethylbenzene	3-(MeO)PhB(OH)$_2$	25 h	RT	73
			2 h		>95
80a	4-acetyl-1-chlorobenzene	3-(MeO)PhB(OH)$_2$	25 h	RT	95
46b	1-chloro-4-methoxybenzene	Ph-B(OH)$_2$	6 h	RT	>95

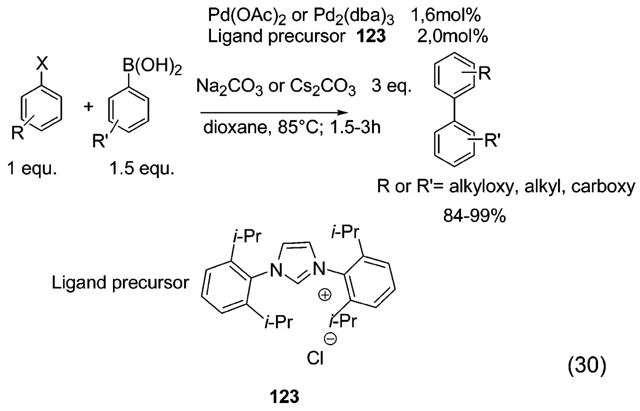
[a] Reaction conditions: aryl chloride/boronic acid 1/1.5, CsF, dioxane, biscarbene **124** 3% mol/Ar−Cl.

ligands. Dialkylphosphines can be advantageously used in place of trialkyl phosphines (no real difference in activity and lower cost). These catalytic systems are also effective in the Mizoroki−Heck coupling reaction.

d. Pd−Carbene Catalysts. Carbenes bind to metals in low or high oxidation states. They bring to the metal the right stabilization/availability balance during the catalytic cycle;[85] this explains the high activity of the catalytic system using these ligands. It is obvious that the well-established organo phosphorus ligands will be progressively complemented or even replaced by a new generation of carbene ligands. The examples below are representative of the recent patent literature in this field.

The preparation of 1,3-disubstituted imidazolium salts was patented by Arduengo in 1990,[86] and in 2000 related NHC carbenes were used in the preparation of ionic liquids.[87] Immobilized NHC carbene precursors with alkoxysilane moieties have been used by Merck and in some coupling reactions.[88] BASF has recently patented new stable carbene/imine bidentate ligands and related organometallic complexes (Pd, Ru, Ir, Ni, ...).[89]

In 2000 Nolan patented the use of metallocarbene complexes (NHC type) as catalysts for the C−C and C−N coupling reactions.[90] The metallocarbenes were produced in situ using a weak base such as K_2CO_3 or Cs_2CO_3 and an imidazolium salt as **123** (eq 30). With these catalysts, no significant difference in reactivity was observed between aryl halides, heteroaryl halides (Cl, Br), and aryl triflates, and a wide range of functions on the boronic acid and aryl halide or pseudohalide rings are accepted. The precursor imidazolium salts of biscarbenes are also claimed in this patent, but they give results similar to those for the monocarbenes.



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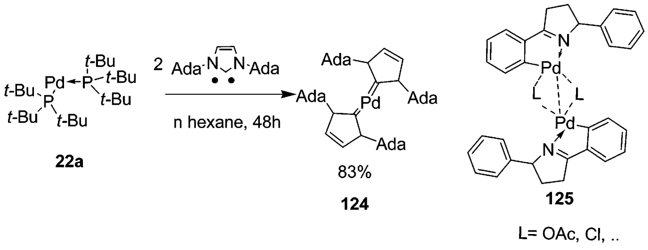
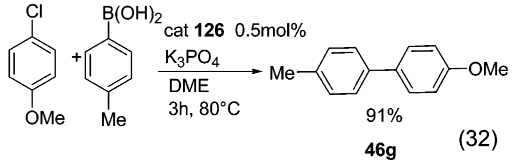
Biscarbene **124**, patented by Bayer,[91] was prepared by reaction of the 14-electron complex Pd(P(*t*-Bu)$_3$)$_2$ (**22a**) with free carbene (eq 31) and gave the corresponding bisaryl in good yield (eq 31). Good to excellent results were obtained with a variety of substrates as shown in Table 8. Bayer also patented the synthesis of the bis-Pd carbene complexes **125** by the quantitative reaction between 2,5-diphenyl-3,4-dihydro-2H-pyrrole and $Pd(OAc)_2$ in THF.[92]



(31)

Finally, as discussed above, Umicore patented new palladocarbene complexes of type **9** having similar performances.

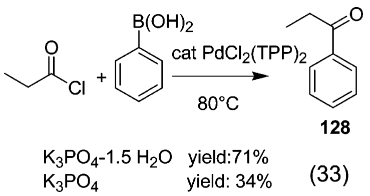
e. Ni Catalyst. $Ni(NO_3)_2-6H_2O/PPh_3$ combination **126** was also claimed by Sumitomo in 2003 for the Miyaura−Suzuki cross-coupling reaction.[93] Using it, functionalized bisaryl derivatives **46g** were economically prepared in very good yield and under mild conditions from aryl chlorides (eq 32). Only 1% of the homocoupling reaction was observed.



(32)

Aryl−aryl products were prepared using a Ni(0) catalyst generated in situ by Mn reduction of Ni(II) salt in DMF and bipyridine/cyclohexadiene ligands.[94] Under these conditions, 2,2′-dimethylbiphenyl (**127**) was obtained in 94% isolated yield from 2-bromotoluene.

3.4.1.5. Other Related Miyaura−Suzuki-like Carbon−Carbon Coupling Reactions. Pd(II) complexes catalyze the acylation reaction of boronic acid with acid chlorides to produce the corresponding alkyl aryl ketones such as **128** (eq 33).[95] The best yields are obtained using hydrated K_3PO_4 in place of anhydrous K_3PO_4.



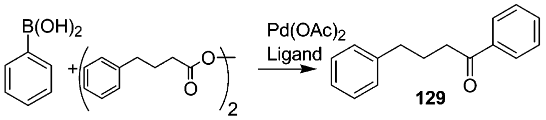
(33)

Table 9. Arylation of Anhydrides Using Boronic Acid[a]

ligand	solvent	water/Ph(BOH)$_2$ mol/mol	yield of **129** (%)
DPPF (**2**)	THF	2.5/12	83
PPh$_3$	THF	0	29
PPh$_3$	THF	2.5/12	97
PPh$_3$	THF	10/12	38
PPh$_3$	DME	2.5/12	53
PPh$_3$	DMF	2.5/12	92
PPh$_3$	toluene	2.5/12	77
PPh$_3$	CH$_3$CN	2.5/12	54
PCy$_3$ (**21**)	THF	2.5/12	91
P(2-Toly)$_3$	THF	2.5/12	31
BINAP (**1**) (ligand/Pd = 1 mol/mol)	THF	2.5/12	<5
P(4-MeOPh)$_3$	THF	2.5/12	97
P(*t*-Bu)$_3$ (**22**)	THF	2.5/12	28

[a] Reaction conditions: PhB(OH)$_2$/pivalic anhydride 1.2 mol, Pd(OAc)$_2$, ligand/Pd = 2.3 mole ratio, 60 °C, THF, water (or not).

This new acylation reaction is potentially interesting when traditional methods such as Friedel−Crafts or Grignard reactions cannot be used, for example in the presence of interfering groups. Similarly, aromatic ketones **129** were prepared in good yields by the Pd-, Ni-, Pd-, or Cu-catalyzed reaction of boronic acids with carboxylic acid anhydrides.[96] The best results were obtained using water as coreactant (to increase the solubility of the base) and PPh$_3$, PCy$_3$, or P(4-MeOPh)$_3$ as ligand in THF or DMF (Table 9 and eq 34).



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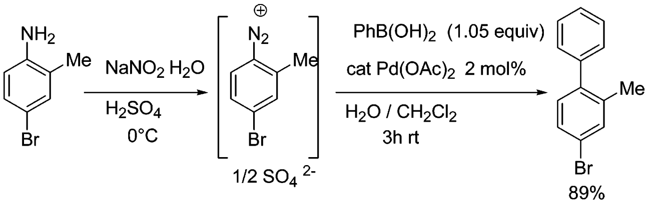
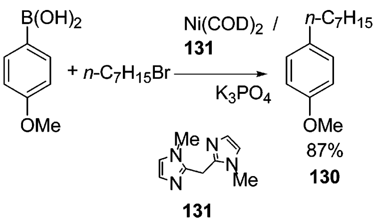
Theoretical DFT calculations of the Pd-catalyzed cross-coupling between boronic acid and anhydrides were recently published.[97] It is noteworthy that, in two key steps of the catalytic cycle, the square-planar Pd(II)−diphosphine intermediates (such as the anionic Amatore−Jutand complex [Pd(0)L$_2$X]$^-$ which has been identified) have a cis-configuration.

In 2000 Rhodia patented the cross-coupling reaction between aryldiazonium sulfates or hydrogenosulfates and arylboronic acids (eq 35).[98] A scalable one-pot process starting from the corresponding arylamines was described. This procedure allows the use of diazonium salts which are cheaper and safer than other previously described tetrafluoroborate diazonium salts. Furthermore, no Pd ligand is needed.



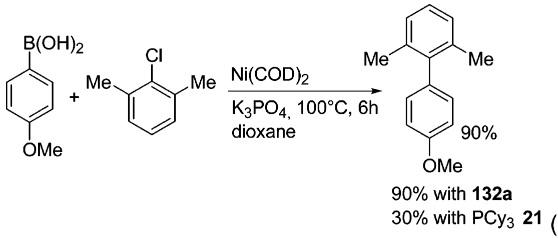
(35)

3.4.1.6. Ni/Miyaura−Suzuki Reaction. Alkylarenes such as **130** (eq 36) were prepared via a Miyaura−Suzuki cross-coupling reaction using an Ni(0)/bidentate bisimidazol **131** catalytic system.[99] This is one of the few examples of the Ni-catalyzed Miyaura−Suzuki reaction yielding sp^2−sp^3 bonds.



(36)

1,3-Bis(dicyclohexylphosphino)propane **132a** and butane **132b**, or bis(dicyclohexylphosphino)ferrocene **2a**, ligands are more efficient than traditional ligands such as tricyclohexylphosphine in the Ni(0)-catalyzed Miyaura−Suzuki reaction.[100] This system runs efficiently with aryl chlorides (eq 37).



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3.4.1.7. Carbon−Carbon Coupling Reactions Involving C−H Activation. CDC stands for the "cross-dehalogenative coupling" process between sp^2 C−H or sp^2 C−X on one hand and sp^2 C−H or sp^3 C−H on the other hand (see Table 10).[101] Metals are reoxidized by addition of oxidizing agents such as peroxides (for Cu catalysis) or oxygen (for Pd catalysis). These new direct coupling reactions could become in the future an economically and industrially attractive alternative to standard cross-coupling methods which require a preactivated species formation. No boronic acid, Grignard, zinc, or silane intermediates are needed. But unfortunatel,y large amounts of catalyst are still required.

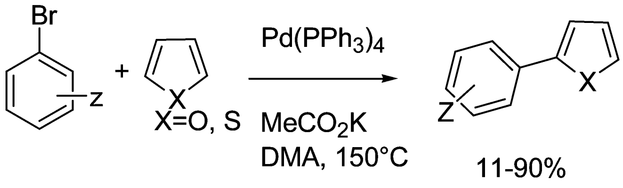
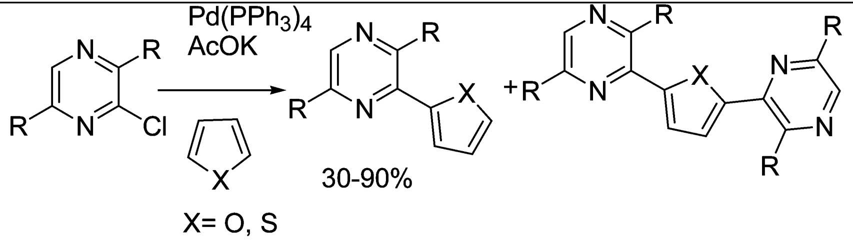
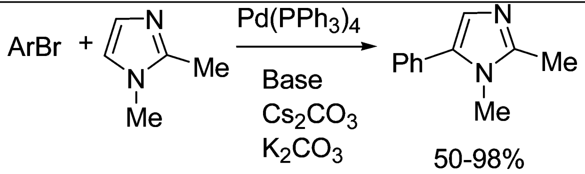
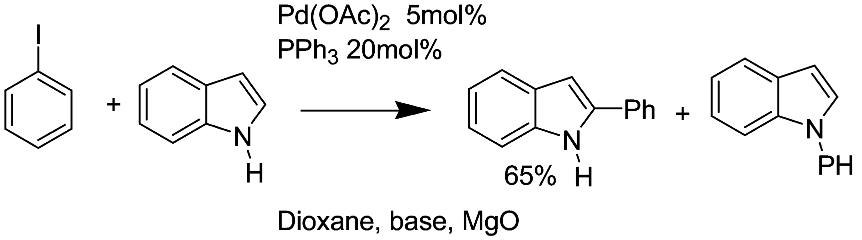
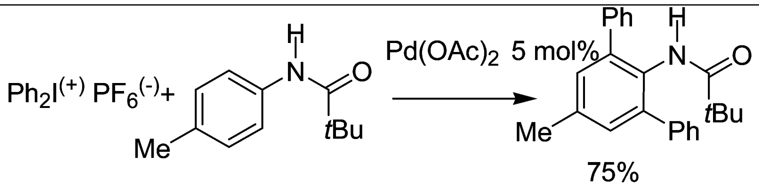
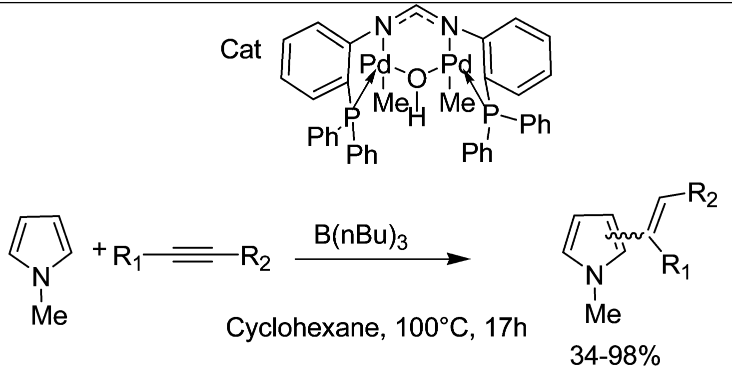
Pd (and now Au or Cu) catalysts for sp^3 C−H and sp^3 C−H[101] are efficient catalysts for these coupling reactions. A few selected examples from the literature are presented in Table 10. In each case, moderate to good yields are obtained. The regioselectivity is dependent on the nature of the metals and on the experimental conditions. The recent Pd-catalyzed addition of C−H to alkyne is also presented in Table 10. Catalytic C−H activation offers a very promising route to the C−C bond formation.

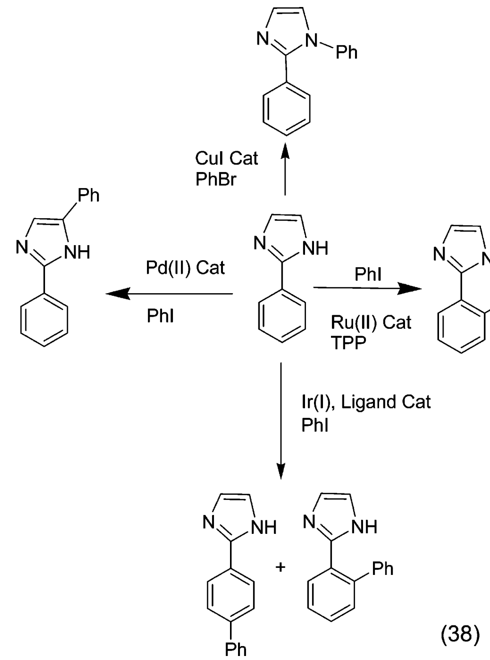
Interestingly, some selectivity can be seen as a function of the metal (eq 38).[105] Recently, this strategy was applied to the arylation of imidazo [1,2-*b*][1,2,4] triazine, an intermediate in the synthesis of $\alpha_{2/3}$-selective GABA agonist **133** (eq 39).[108] Another example is a direct indolization of tetrahydroisoquinolines under mild conditions with a cheap Cu salt using the CDC methodology (eq 40).[109] **134** was obtained in good yield when an excess of oxidant (*t*-BuOOH) was used.

Preparation of functionalized 2-arylindenes **135**−**139** in fair yields by the Pd(OAc)$_2$-catalyzed coupling reaction of indenes with aryl iodide was patented in 1998 (eq 41).[110] No activation of the indene is necessary.

Another example of C−H activation by Pd, using PMe(*t*-Bu)$_2$ or P(*t*-Bu)$_3$ as the best ligand, has been reported in the intramolecular C−C bond formation between various arenes and aryl halides (X = I, Br, and Cl).[111]

Table 10. C−C Cross-coupling Reactions Involving C−H Activation

Reaction	Reference
	102
	103
	104
	105
	106
 *Addition of C-H bond to alkynes*	107



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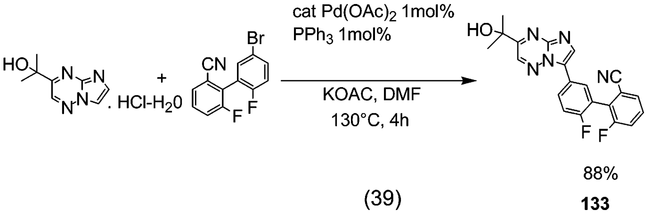

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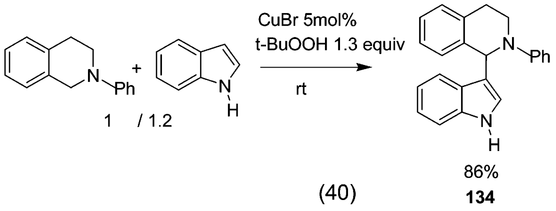

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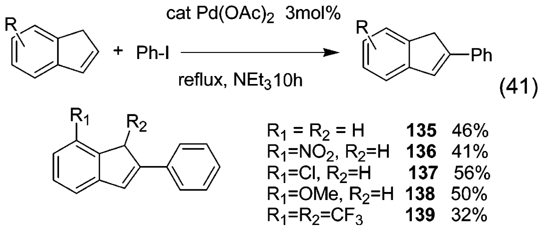
134



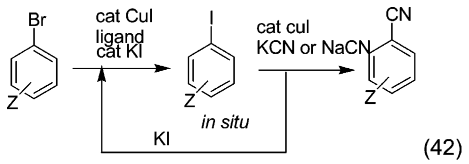
(41)

$R_1 = R_2 = H$	**135**	46%
R_1=NO_2, R_2=H	**136**	41%
R_1=Cl, R_2=H	**137**	56%
R_1=OMe, R_2=H	**138**	50%
R_1=R_2=CF_3	**139**	32%

3.4.1.8. Copper, Palladium, and Nickel Catalysts in Cyanation Processes. The cyanation process is an important and useful tool to introduce functionality in aromatic and heteroaromatic rings. Since the first Rosenmund and Von Braun works in 1916 and 1931,[112] a very large range of experimental conditions and reagents have been described in the literature. For some interesting reviews, see refs 113 and 114.

a. Cu Catalysts. An industrial scale cyanation process was described first by Buchwald.[115] Aryl bromides are transformed into the corresponding aryl cyanides using CuI as catalyst (eq 42). Iodide acts as a cocatalyst, and *N*,*N*′-dimethylethylenediamine is described as the best Cu(I) ligand. This process tolerates a large range of functions and avoids the use of expansive aryl iodides.

The following examples demonstrate the interest of this procedure. Derivatives **140**, **68**, and **142**−**144** were obtained in reasonable to good isolated yields (eq 43).



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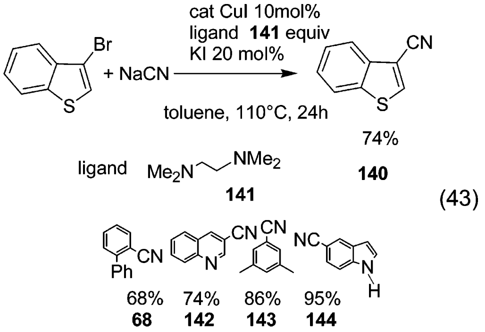
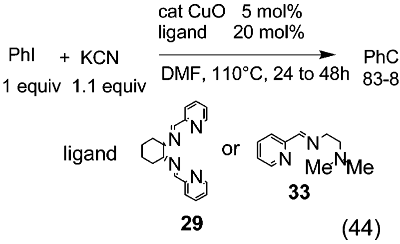


(43)

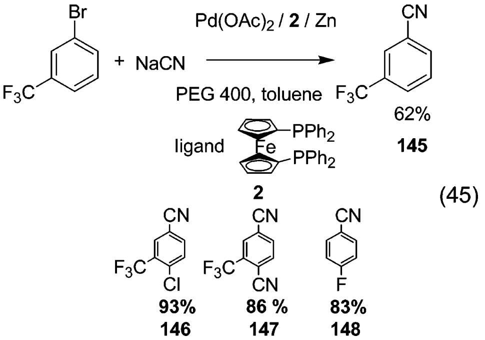
Cu ligated with **29** and **33** is able to catalyze the cyanation of iodobenzene in good yield (eq 44).[56]



(44)

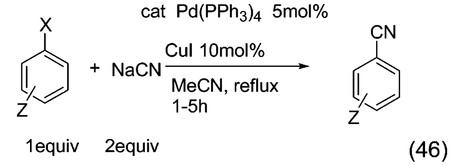
b. Pd Catalysts. The Pd-catalyzed cyanation is very sensitive to cyanide in soultion. An excess of cyanide has a negative impact on the catalytic cycle.[116] To overcome this issue, Merck has developed a cyanation process using $Zn(CN)_2$ in DMF.[117]

In 2002 Bayer patented an inexpensive (NaCN or KCN is used in place of $Zn(CN)_2$) and robust cyanation process using Pd/dppf in the presence of Zn (reductor) and polyethers (PEG400, PEG 200) as extractant.[118] A typical example is given in eq 45, where **145**−**148** are obtained in moderate to good yields. Under these conditions, dicyanation is possible. For example, **147** is obtained in 86% isolated yield starting from 5-bromo-2-chlorobenzotrifluoride (eq 45).



(45)

Lilly Research Laboratory published the effect of ZnI_2 and CuI in the cyanation process (eq 46).[119] A large range of aromatic and heteroaromatic products containing various functionalities were synthesized in good yields starting from aryl halides (I, Br), vinyl bromides, or aryl triflates **149**−**152**.



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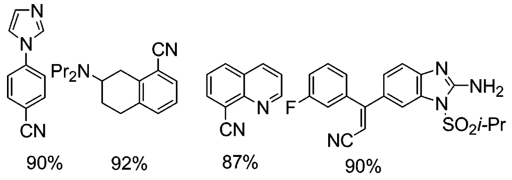


149 **150** **151** **152**

Pd(PPh$_3$)$_4$ 10mol%, CuI 20%mol

Two catalytic cycles (A and B) have been proposed to explain the role of Cu−Pd complexes (Scheme 9). The key intermediate relay is the soluble complexe M(CN)$_n$.

A recent paper describes the use of only 0.6 equiv of Zn(CN)$_2$ per mole of aryl halide with Pd(0) as catalyst.[120a]

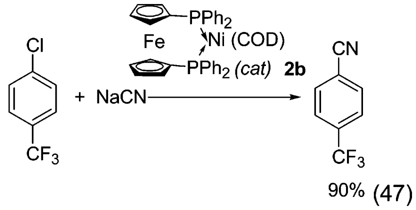
A practical ligand free cyanation process of aryl bromides using a nontoxic cyanide source such as K$_4$[Fe(CN)$_6$] and Pd(0) as catalyst was recently published. Good yields and TON were attained.[120b]

A very convenient procedure for the palladium-catalyzed cyanation of halides was published by Beller's group using acetone cyanohydrin as cyanide source. This protocol permit use of a small amount of palladium catalyst (0.5 mol %), and exellent yield and selectivity (in general >90%) were obtained.[120c]

c. *Ni Catalysts.* In 1989 Occidental Chemical patented a cyanation process via the in situ production of Ni(0)/PPh$_3$ starting from Ni(II) salts and Zn as reductor.[121] An electrochemical process was also used to reduce Ni(II) to Ni(0).[122] Some typical examples of Ni-catalyzed cyanation processes are given below.

4-Chlorobenzophenone has been converted at high temperature (180 °C) in diethylacetamide to the corresponding cyano derivative using a Pd(II)−Ni(II)/1,4-(diphenylphosphino)butane **132c**/NaBr system.[123] In another example, aryl trifluoromethanesulfonates were cyanated in refluxing MeCN using NiCl$_2$(PPh$_3$)$_2$/PPh$_3$ in the presence of Zn as reductor.[124] In 1993 Duphar patented new ligated Ni(0) catalysts **2b** shown in eq 47.[125] These catalysts are less sensitive to CN$^-$ inhibition.

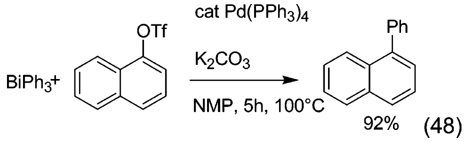
Some other representative patented examples of Ni-catalyzed cyanation processes are presented in Table 11.



(47)

3.4.1.9. C−C Coupling Reaction Using Arylbismuth Derivatives.

Arylbismuth compounds have been sometimes used as nucleophile in the Pd-catalyzed C−C coupling reaction. A typical example is given in eq 48.[131] The toxicity and high cost of arylbismuth derivatives do not make this process very attractive.



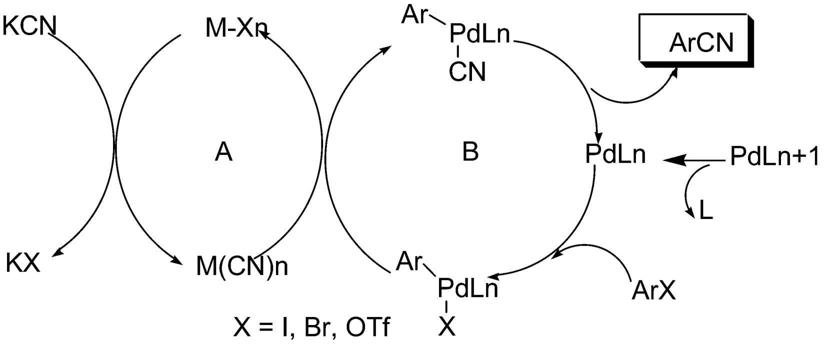
(48)

3.4.1.10. Pd/Hiyama Reaction.

Hiyama's group[132] has reported that functionalized organosilanes (aryl- and/or alkenylfluorosilanes), fluorosiliconates, and orthosiliconates do engage efficiently in C−C cross-coupling reactions using conventional Pd catalysts or new catalysts such as Pd-phosphinous acids.[133] Silanols have also proved to be appropriate coupling "partners".[134] At the genuine works, the coupling reaction occurred when Ag$_2$O was used as an activator. Fluorine ion is the best activator for functionalized alcoxyvinyl silanes.[135] A useful review was published by Holms, who compares the hypervalency by explaining the stereochemistry and the reactivity of silicon and phosphorus centers.[136]

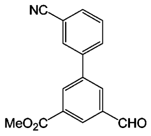
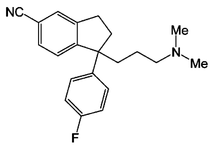
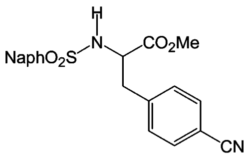
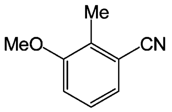
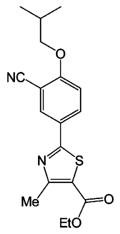
The Denmark and DeSong groups are very active in this field. Functionalized silanols, chlorosilanes, vinylsilanes, or vinyl or phenyl silicones (as phenyl or vinyl sources) react with functional aryl halides under mild conditions using Pd(dba)$_2$, Pd$_2$(dba)$_3$[(allyl)PdCl]$_2$, or Pd(OAc)$_2$ as the best Pd source. TBAF (tetrabutylammonium fluoride) is a very effective activator through probably a pentacoordinated silane intermediate. Various donor and bulk ligands (tri(*tert*-butyl)-phosphine and tricyclohexylphosphine) were claimed to facilitate the transmetalation and avoid the homocoupling. The scope of the reaction was investigated with a variety of aryl iodides and bromides bearing electron-withdrawing or -donating groups (carbethoxy, acetyl, nitro, cyano, etc.) in the para, meta, or ortho positions. Each time, the desired unsymmetrical biaryls were obtained in good to excellent yields.[133,134]

Scheme 9. Postulated Catalytic Cycles of the Cyanation Reaction

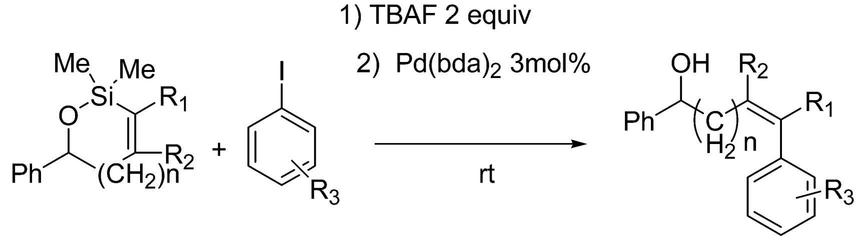


X = I, Br, OTf
M = Zn, Cu, Sn

Table 11. Representative Patented Examples of Ni Catalyzed Reactions

Targets	Experimental condition	Reference
5-(3-cyanophenyl)-3-formylbenzoic acid  Intermediate for factor Xa inhibitors	KCN ,NiBr$_2$, PPh$_3$ and Zn in THF at 55°C for 3 h.	126
Citalopram  55% yield	NaCN, NiCl$_2$, PPh$_3$ in AcCN in the presence of a catalytic quantity of Zn.	127
4- and/or 3-substituted cyanophenylalanine derivatives  89% yield	KCN, Ni(PPh$_3$)$_2$Cl$_2$, PPh$_3$ and Zn in NMP for 2.5 h at 55°C .	128
Benzoic acids derivatives  92.6% yield Chemical intermediates	KCN, NiBr$_2$, Zn and Ph$_3$, in THF at 60°C for 18 h.	129
2-(3-cyanophenyl)thiazoles  73% yield Treatment of gout and hyperuricemia	KCN, Ni(PPh$_3$)$_2$Cl$_2$, PPh$_3$ and Zn in DMF at 80°C for 16 h.	130

Scheme 10. Cross-coupling Reaction Involving Cyclic Vinyl Siloxanes



154

n	R1	R2	R3	% yield	time	Products
0	H	H	4-CO_2Me	85%	0.5h	**154a**
1	H	Me	2-Me	83%	0.75h	**154b**
2	H	H	2-OMe	85%	0.5 h	**154c**

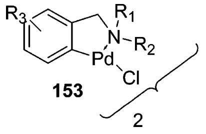
(49)

DeSong published a new route to Colchinine using the Hiyama reaction between 5-bromotropolone and functionalized aryl alcoxy silanes catalyzed by $Pd(OAc)_2$−PPh_3 (5 mol % Pd and 15 mol % ligand).[137] Good isolated yields were obtained. In this publication, an interesting comparison between the three C−C methodologies (boronic acid, alcoxy silane, and tin reagents) was investigated. Aryl siloxanes and aryl boronic acids produce similar results in the preparation of functionalized biaryl compounds with the exception of *o*-methoxy containing siloxanes. In this case, a rapid protodesilylation occurs.

The cross-coupling reaction with organofluorosilanes was patented by Sagami Chemical Research in 1989 to prepare alkenyl derivatives by treating RCH=CH−SiF_3 derivatives with alkyltriflates catalyzed by Pd(0)−TPP in the presence of fluorine anion.[138]

Fort's group published interesting results for the Hiyama cross-coupling reaction between choro or fluoro aryl derivatives or heteroaromatic iodides and methoxypyridyltrimethylsilanes at room temperature using $PdCl_2(PPh_3)_2$−PPh_3−CuI−TBAF in DMF.[139]

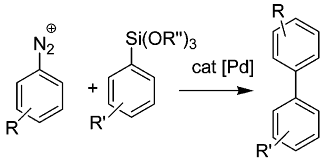
Palladocycles such as **160** (<0.1% molar), without phosphine ligand, were claimed by Rhodia for the mild coupling of arylmethyldichlorosilane with aryl halides.[140] NaOH was used as the base and activator. For example, (4′-trifluoromethyl)phenylbenzene can be isolated in 95% yield by reacting a mixture of Ph_2SiCl_2 and NaOH at 100 °C in dioxane with (4-trifluoromethyl)bromobenzene in the presence of **153** and tetrabutylammonium bromide.



153

In 2000 Denmark patented the cross-coupling reaction using organosilicone derivatives as nucleophiles, a Pd catalyst, and an activator such as fluoride, hydroxide, hydride, or siloxides.[141] This patent describes many aspects of Denmark's works including functionalized vinylsilanols and silacyclobutane derivatives as nucleophiles (eq 49). Scheme 10 shows one example of the potential of these synthetic strategies. In this case, no Pd ligand was needed.

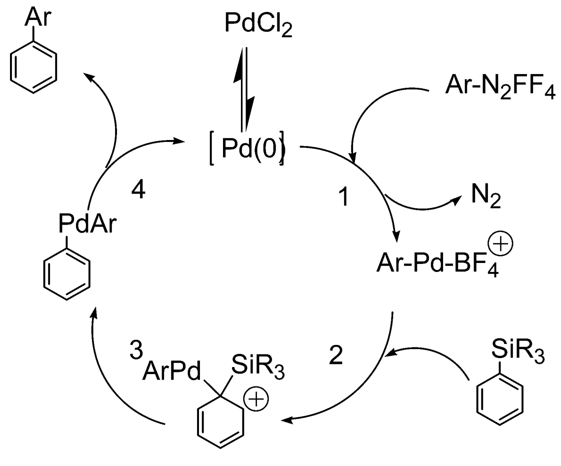
Pd-catalyzed cross-coupling of aryldiazonium salts with alcoxyarylsilanes has been patented (eq 50).[142] This new reaction is environmentally friendly compared to that of the tin intermediate used before, and it does not need any ligand.



(50)

To achieve good yields, the aryldiazonium salt must bear electroattracting substituents and a large amount of catalyst (Pd 10 mol %) is needed, and depending on the substituents on the ring, an excess of one of the two reagents is needed. The mechanism shown in Scheme 11 was proposed including successively oxidative addition (step 1), electrophilic addition (step 2), silyl elimination (step 3), and reductive elimination (step 4).

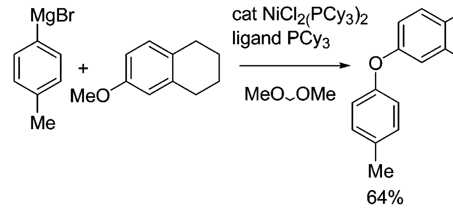
Scheme 11. Postulated C−C Cross-coupling Reaction Mechanism Involving a Diazonium Derivative and an Aryl Silane



3.4.1.11. Ni/Kumada−Corriu−Tamao Reaction.

a. Ni Catalyst. Ni/phosphorus ligands are quite general systems for catalytic cross-coupling of aryl Grignard reagents with a large range of aromatic, vinylic, and allylic halides or pseudohalides. This versatility is demonstrated in the following examples.

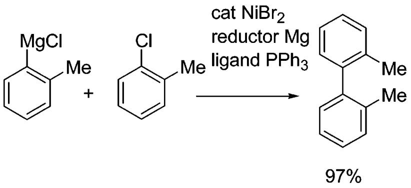
Ni organometallic complexes coordinated by a bulky and σ-donor monophosphine such as $NiCl_2(PCy_3)_2$ + PCy_3 were patented by DSM.[143] Under these conditions the methoxy becomes a good living group (eq 51).



(51)

Bidentate ligand $PPh_2CH_2CH_2PPh_2$ **132d** has been used in the $NiCl_2$-catalyzed coupling reaction of allyl chloride with PhMgBr; the corresponding 3-phenylpropene was obtained in 86% yield.[144] Aryl halides and vinyl halides give functionalized vinyl−aryl derivatives under similar conditions.[145]

A Ni(0) (obtained by Mg reduction of Ni(II) salts)/TPP system was claimed as a good catalyst of the coupling reaction of Grignard reagents with aryl halides to obtain functionalized and bulky biaryl compounds **46j** in high yields (eq 52).[146]



46j (52)

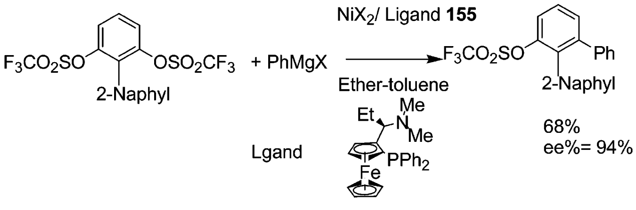
In the same area, aryl pyridines, as materials for electrically conductive polymers, were obtained by the $NiCl_2$-catalyzed reaction of halo pyridine with an aryl Grignard.[147]

The electron-rich bidentate ligands from Degussa[79] discussed before work well in the Kumada−Corriu−Tamao reaction. Typical examples as shown in Scheme 12.

Biaryls were also prepared by the Ni/Me-imidazole-catalyzed cross-coupling reaction of Grignard reagents in ether solvents such as the ether of diethylene glycol.[148]

On his side, Sumitomo patented the synthesis of optically active 1-biphenylnaphthalenes via a cross-coupling reaction between PhMgBr and phenylnaphthalene in the presence of a chiral ferrocene **155** and Ni[149] and Pd salts.[150] Better ee% values were obtained with the Ni−**155** complex (ee% = 94%) than with the Pd−**155** complex (ee% = 46%) (eq 53).

Nickel/magnesium bimetallic cooperation is key in the Ni-catalyzed C−C cross-coupling reaction of aryl fluorides and chlorides with Grignard reagents.[151]

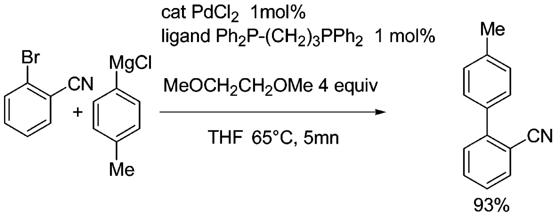


155 (53)

b. Pd Catalysts. The following examples show the versatility of the Pd-catalyzed Kumada−Corriu−Tamao reaction; Pd loading is in the 1−5 mol % range.

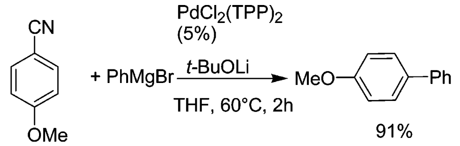
2-Arylpyrroles have been obtained by the $PdCl_2/Ph_2P(CH_2)_4$-PPh_2-catalyzed coupling reaction between an *N*-alkylpyrrole Grignard reagent and an aryl iodide in around 80% yield.[152]

A patent describes the synthesis of a key intermediate of Sartan family drugs via the $PdCl_2$/1,3-bis(diphenylphosphino)propane-catalyzed C−C cross-coupling reaction of 4-tolylmagnesium halide and 2-bromobenzonitrile (eq 54).[153] Less than 3.5 mol % of the homocoupling product is observed. Ni(0) ($Ni(PPh_3)_4$) and Mn ($MnCl_2$, $MnCl_4Li_2$) catalysts are also claimed. The next step is the transformation of the nitrile into the tetrazole ring.



(54)

An original C−C cross-coupling reaction catalyzed by Pd−phosphine or Ni−phosphine complexes results in the substitution of the nitrile group of aryl nitriles by Grignard or zinc reagents (DSM patent).[154] 4-Phenylanisole **46b** was prepared in good yield using this procedure (eq 55).

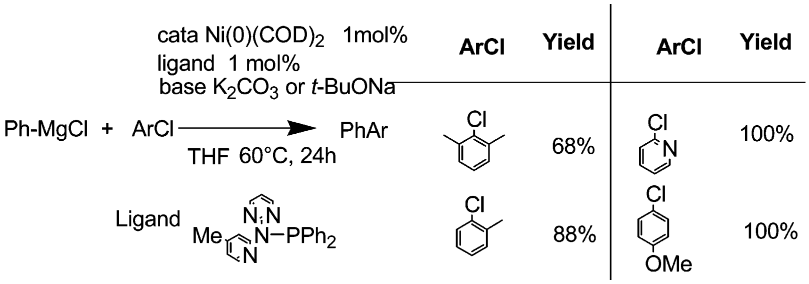


46b (55)

The more hindered the phosphine, the less active the catalyst (PMe_3 > PEt_3 > $P(Cy)_3$), and arylphosphines such as PPh_3 or $MePPh_2$ usually provide less active Ni catalysts.

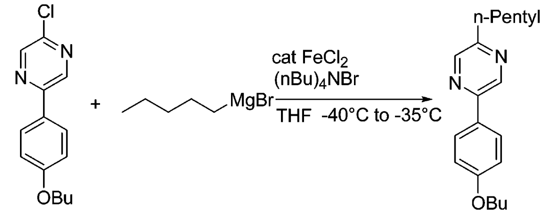
Recently, Hartwig published economical C−C cross-coupling reactions between aryl Grignard derivatives and aryl and vinyl tosylates at room temperature using a Pd(0)/Josiphos ligand.[155] This “phenol” (from which aryl tosylates

Scheme 12. Kumada−Corriu−Tamao Coupling Reaction Using Ni(0)−Degussa Ligands



are obtained) route to the coupling reaction is of particular interest when the corresponding halide is not easily accessible.

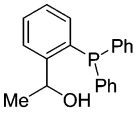
3.4.1.12. Fe/Kochi Coupling Reaction. Iron is the most abundant metal after aluminum in the earth's crust (5%), has a low toxicity, and is cheaper than Pt, Pd, or Ni. Two excellent reviews on Fe-catalyzed cross-coupling reactions have been recently published.[156,157] The first example of a Fe-catalyzed C−C coupling reaction between a Grignard reagent and alkyl halides was described by Kochi and Tamura.[158] Interestingly, functional groups sensitive to Grignard reagents do not react under these conditions. More recently, Cahiez[159a] and Fürstner[159b] have developed new synthetic approaches using iron catalysts to create efficiently and regioselectively $sp^3{-}sp^3$ and $sp^2{-}sp^3$ C−C bonds.[159c] In 1984, Ube Industries patented a $FeCl_2$-catalyzed $sp^3{-}sp^2$ coupling reaction of alkyl Grignard and heteroaryl derivatives (eq 56).[159d]



(56)

Tosoh patented the synthesis of 4-allyl-*tert*-butoxybenzene by the reaction of 4-*tert*-butoxyphenylmagnesium chloride with allyl chloride catalyzed by $FeCl_2{-}P(t\text{-}Bu)_3$.[160] A $FeCl_3{-}AlEt_3$-catalyzed vinylation process has been patented by the same company in 1999. 4-Chlorostyrene was obtained in 62% yield by the reaction in THF of 4-chlorophenylmagnesium bromide with vinyl chloride.[161] In this case, the active catalyst may be a small heterogeneous iron species. $FeCl_3$/TMEDA has been used as the catalyst in the cross-coupling reaction of primary or secondary alkyl halides with aryl Grignard reagents in THF. Good yields are obtained (>88%) under mild conditions, and many organic functions such as esters can be present.[162]

$Ni(acac)_2$/bidentate phosphine **156** was recently described as a very efficient catalyst in the C−C coupling reaction between aryl fluorides or aryl chlorides and Grignard reagents at low temperature.[163] This catalytic system is able to activate the Ar−F bond, and in the case of aryl bromides and aryl chlorides, 0.2−0.05 mol % catalyst loading has been reached.



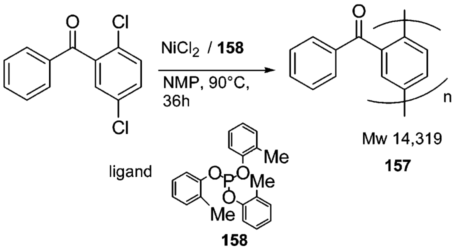
156

It seems that the bimetallic synergy between Ni and Mg species accelerates the kinetics. The actual catalytic species is still a matter of speculation; the formations of Fe(0), Fe(I),[164] and the super-ates of Fe(II) complexes have been proposed.[165]

There is no doubt that the Fe-catalyzed cross-coupling reaction is a big but exciting challenge, but to progress, a better knowledge of its mechanism is needed.

3.4.1.13. Ni(II)/Reductor−Homo-coupling Reaction. The C−C homo-coupling reaction of aryl halides was patented in 1979 by Union Carbide using $NiCl_2/PPh_3$ as catalyst.[166] In the case of PhCl, in DMAC, very good yields (>98%) and fast kinetics were observed with NaI as promoter (0.01 mol/2 mL PhCl). Reductor efficiency was as follows: Zn > Mg > Mn. $NiCl_2$, NiI_2, $Ni(acac)_2$, and $Ni(OAc)_2$ were used as Ni sources with the same excellent yields.

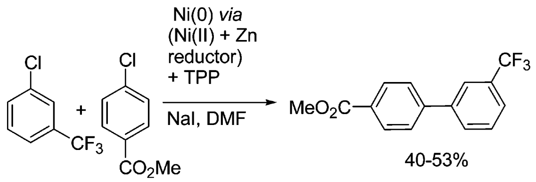
Polyaryl oligomomers **157** with high M_w values were obtained by the Ni(II)/phosphite (**158**)-catalyzed homocoupling reaction of bis aryl halide using Zn dust as reductor (eq 57).[167]



(57)

In 1998 Fort's group patented the combination of metal and ultrafine oxide particles, such as Ni/Fe_2O_3, in C−C homocoupling reactions.[168,169]

3.4.1.14. Hetero-coupling Reaction. Polyfunctionalized biaryl derivatives are prepared in moderate yields via the hetero-coupling reaction between two different functionalized aryl halides using Ni(II)/phosphine as catalyst and Zn, Mn, or Mg as reductor (eq 58).[170] But some homo-coupling occurs (20%).



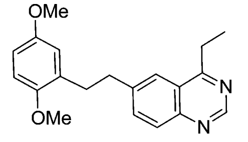
(58)

The aryl−Ni complex intermediate was prepared in situ by the electroreduction at −1.9 V of NiX_2 in the presence of ArX. This intermediate was trapped by the addition of $BrCH_2CO_2Et$ to give a mixture of $PhCH_2CO_2Et$ (main product) and Ph−Ph (minor product), resulting in a homocoupling reaction.[171] A NaH-*t*-AmONa−$Ni(OAc)_2$ combination, in the presence of 2,2′-bipyridyl and KI, was described as an efficient system for the one-pot cross-coupling reaction of aryl halides.[172]

3.4.1.15. Cu and Pd/Sonogashira Reaction. The first process (Castro reaction) to graft an alkyne group to aryl or vinyl derivatives was described in 1963 using stoichiometric Cu acetylenide complexes.[173] Then, three subsequent catalytic systems were described: (a) Pd(0)−phosphine in the presence of an amine by Heck, Dieck, and Cassar.[174,175] (b) Pd(0)−CuI in the presence of an amine by Sonogashira, Tohda, and Hagihara. The addition of CuI as cocatalyst increases the reactivity.[176] (c) Pd(0)−phosphine in an atmosphere of hydrogen gas diluted with nitrogen or argon; this can reduce the homo-coupling of terminal acetylenes.[177]

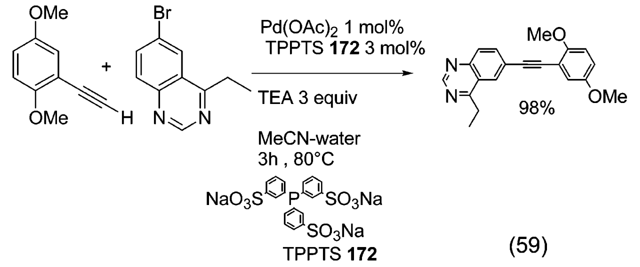
A recent excellent review was published in 2003 by Negishi and Anastasia.[178] We report herein just a few additional examples from the patent literature.

Novartis published a practical and scalable synthesis of 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-ethylquinazoline (**159**), a key intermediate in the formation of an antimitotic agent, using a Sonogashira step.[179]



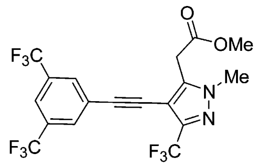
159

Another interesting Sonogashira procedure consists of using the water-soluble Pd(II)−TPPTS complex in acetonitrile−water (eq 59). Pd scavenger agents such as *N*-acetylcysteine or thiourea were used to remove the residual Pd species from the final product.



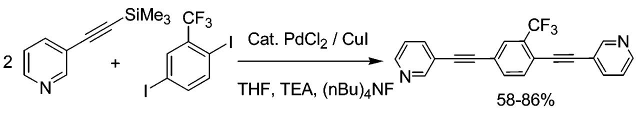
TPPTS **172** (59)

Cu-catalyzed reaction of halopyrazoles with arylacetylenes was mentioned as a low cost process to get the corresponding bisarylacetylene **160** in fair yield.[180]



160

The “one-pot”, Pd-catalyzed Sonogashira coupling reaction between silylated arylalkynes and aryl halides gives high yields (**161**) and does not require the use of a base (formation of Me_3SiI) as in the traditional procedure, as shown in eq 60.[181] This procedure was used to prepare 1D or 2D polymeric architectures.



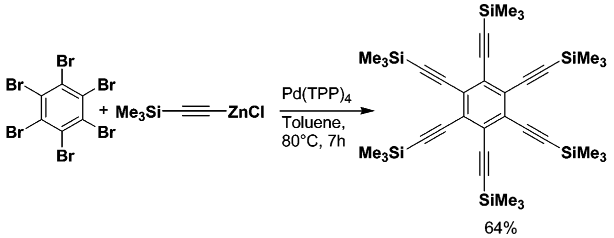
161 (60)

New conditions, without Cu, were recently described in the literature using 3 mol % of $PdCl_2(PPh_3)_2$ in the presence of 3 equiv of TBAF or KF as base. Aryl iodides and aryl bromides give almost quantitative coupling (aryl chlorides give 40−70% yields).[182]

A $CuI/Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ (2/3/6 mol %) system in dioxane works at room temperature:[183] Phenylacetylene derivatives are isolated in moderate to excellent yields (63−95%).

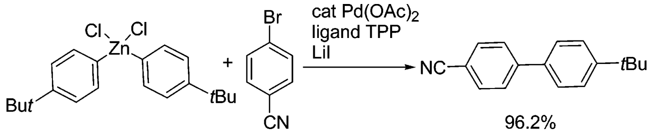
3.4.1.16. Pd/Negishi Reaction. Thank’s to Buchwald ligands, Pd is by far the most common metal used in the Negishi coupling reaction. Nevertheless, Ni catalysts open new perspectives due to the easy oxidative addition of the metal into aryl halide bonds.

a. Pd Catalysts. Polyethynyl derivatives **162** were obtained via the Pd(TPP)$_4$-catalyzed coupling reaction between halobenzenes and ethynylzinc halides (eq 61).[184]



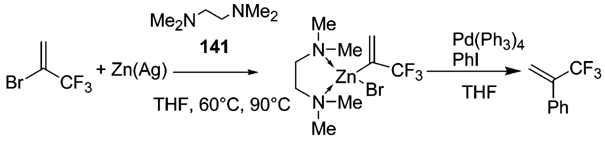
64%
162 (61)

The Pd(OAc)$_2$/PPh$_3$/LiI combination was used in a Negishi cross-coupling reaction patented by Tosoh Corp. (eq 62).[185] The cyano biphenyl **163** was obtained in very good yield.



96.2%
163 (62)

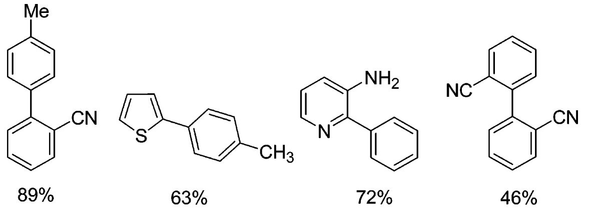
The Shanghai Institute of Organic Chemistry has patented the efficient preparation of trifluoromethylstyrene **164** from the coupling reaction between trifluoroisopropenylzinc **164a** and aryl halides (eq 63).[186]



93%
164a
96%
164 (63)

Recently, Buchwald published new results for a Pd−Negishi reaction using bulky and electron-rich ligands **43**. Only 0.01−0.1 mol % Pd is necessary, and a wide range of functional and/or bulky groups may be present.[63] Furthermore, the possible use of aryl chlorides as starting materials and the mild experimental conditions make it attractive from an industrial point of view.

b. Ni Catalysts. In 1997 Catalytica Inc. patented the Ni(acac)$_2$/PPh$_3$-catalyzed synthesis of biaryl derivatives by reaction of arylzinc compounds with aryl chlorides.[187] This procedure was used to prepare cyano biphenyls and other biphenyls in good yields.



3.4.2. Heterogeneous Catalysts

The main advantages of heterogeneous catalysis from an industrial point of view are well-known: generally, no ligand is needed, it is easier to remove and recycle the catalyst with less metallic pollution of the final products, and, finally, costs are lower than those for the corresponding homogeneous catalysis. The main limitations are the mass-transfer management during the process, physical specificities such as porosity (nano/micro) or granulometry, acid or basic effects on the solid surface, and, sometimes, metal leaching from the surface to the solution.

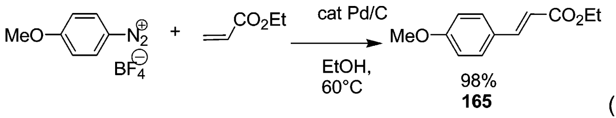
3.4.2.1. Heterogeneous Pd Catalysts. *a. General C−C Coupling Reactions.* The new heterogeneous nano Pd(0) catalysts are supposed to be more environmentally friendly and economical than soluble Pd catalysts; the so-obtained products are usually free of any traces of Pd. Layered double hydroxide supported nano Pd catalysts were used in the Heck−Mizokori, Miyaura−Suzuki, Sonogashira, and Kosugi−Migita−Stille-type coupling reactions with even unreactive aryl halides.[188] They can be supported by hydroxylapatites such as $Ca_{10-z}(HPO_4)_z(PO_4)_{6-z}(OH)_{2-z}$ [$z = 0.1-1$]. For instance, $Ca_9(HPO_4)(PO_4)_5(OH)$ has been patented by Koei Chemical for the C−C Miyaura−Suzuki cross-coupling.[189]

A solution to protect Pd catalyst from dissolved oxygen is to use polyphasic systems; this has been patented by Koei Chemical for the preparation of aryl-substituted heterocyclic compounds.[190]

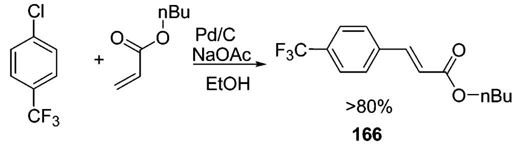
b. Heck−Mizokori Reaction. In 2000 Degussa patented the use of supported catalysts such as Pd/C in the Heck−Mizokori coupling reaction.[191] For example, *E*-stilbene was prepared in moderate to good yields depending of the nature of the inorganic support, the solvent, and the reaction temperature (eq 64). The leaching of Pd strongly depends on the nature of the inorganic support and the catalyst synthesis process.

$$\text{Ph-Br} + \text{Ph-CH=CH}_2 \xrightarrow[\text{NMP/DMAC/Tol/H}_2\text{O, 120°C, 1h}]{\text{Pd/C (5\%) 0.2 mol\%, NaOH}} \underset{trans}{\text{Ph-CH=CH-Ph}} \qquad (64)$$

Hoechst A-G patented the high yield synthesis of functionalized phenylalkenes **165** by the Pd/C-catalyzed reaction between functionalized phenyldiazonium salts and activated olefins such as acrylates under mild and practical conditions (eq 65).[192] A similar coupling reaction but with functionalized chlorophenyls has also been claimed. For example, **166** was obtained in good yield using Pd/C as catalyst and NaOAc as base (eq 66).[193]



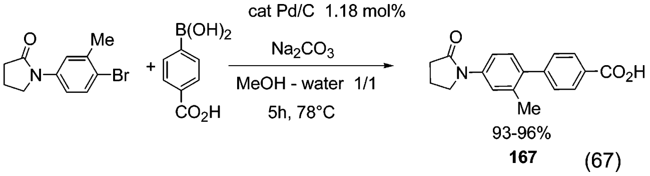
(65)



(66)

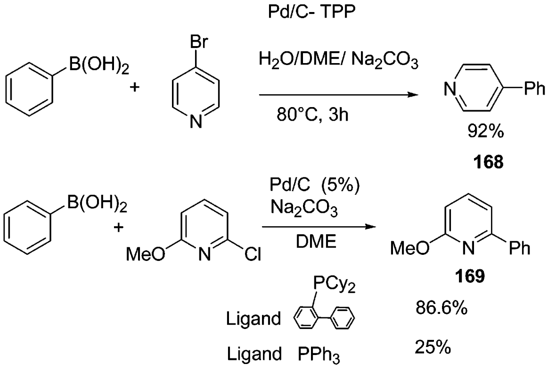
A new heterogeneous Pd catalyst on organic polymer was prepared in two steps: polymerization of endo-2-norbornene-5-*N*,*N*-α,α-bipyridylcarbamide using a Mo catalyst and then complexation with H_2PdCl_4. The amount of Pd in the final insoluble polymer is about 0.25 mmol Pd/g of polymer.[194] This catalyst was used in Heck−Mizokori coupling and amination reactions.

c. Miyaura−Suzuki Reaction. Smith Kline Beecham published a robust multikilogram-scale synthesis of a biphenyl carboxylic acid **167**, an intermediate in the synthesis of antidepressor SB-245570, via a Pd/C-catalyzed Miyaura−Suzuki reaction (eq 67).[195] Finely dispersed heterogeneous Pd/C catalysts allow the production of aryl- or heteroaryl-alkenes in high yield and selectivity.[196] In water and still without any ligand, Pd/C 5% catalyses also the Miyaura−Suzuki reaction of tetrarylborates with aryl bromides.[197] Very good yields (>90%) and turnover were obtained with less than 0.05 mol % of Pd, which imparts a great industrial potential to this reaction.



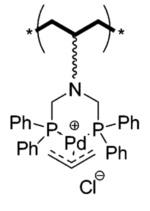
(67)

Arylpyridines **168** result from the Pd/C−triarylphosphine-catalyzed reaction of halo-substituted pyridines with arylboronic acid. No inhibition effect of the pyridine is observed (eq 68).[198] Similarly, the use of Pd/C−(dicyclohexylphosphino)biphenyl in the Miyaura−Suzuki reaction of 3-chloropyridine was patented in 2001 by Koei Chemicals Co. For instance, 3-phenylpyridine **169** was obtained in good yield (eq 69).[199] The (dicyclohexylphosphino)biphenyl ligand seems to stabilize strongly Pd species at the charcoal surface; this is not the case of triphenylphosphine, which gives low yields. This ligand effect was also observed in homogeneous catalysis.



(68 and 69)

Another solution is to support Pd (or Rh) on a solid phase such as ArgoGelNH2−bidentate phosphine grafted **170** (Nissan patent).[200]



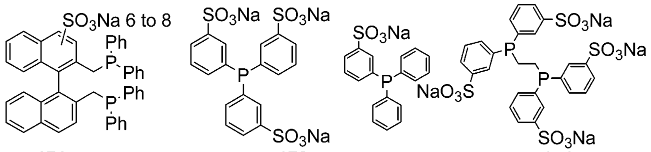
170

d. Kumada−Corriu−Tamao Reaction. Bayer has patented the use of inexpensive Ni/C−PPh_3 for the C−C cross-coupling reaction of aryl Grignards and aryl bromides (eq 70).[201] Very good results were also obtained with aryl chlorides. Lipshutz has also described Ni/C−PPh_3 as a catalyst in Kumada−Corriu−Tamao reactions; it is believed that Ni/C is a reservoir of active Ni(0) species for the solution.[202]

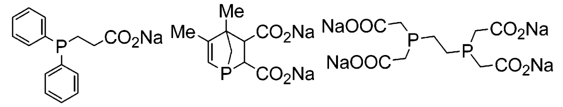
$$m\text{-MePhBr} + \text{PhMgBr} \xrightarrow[\text{THF, 2h reflux}]{\text{cat Ni/C, ligand PPh}_3} \underset{98\%}{m\text{-MePh-Ph}} \qquad (70)$$

3.4.2.2. Biphasic Catalytic Systems. Reactions in multiphasic systems can offer some advantage for the recycling of the catalysts, for product recovery, or to overcome solubility issues. The global performance of the reaction must be evaluated taking into account the potential physical limitations (such as mass transfer, effects at the interface, etc.). This means that parameters such as stirring efficiency are of paramount importance; nevertheless, they are not always mentioned in the literature, thus making comparative studies difficult.

a. Hydrosoluble Pd Catalysts. Reactions in aqueous media using hydrosoluble starting materials and metal−ligand systems or in water−organic solvent biphasic systems using hydrosoluble metal−ligand catalysts have strong advantages[203] (catalyst recycling, product isolation, etc.). Sulfonated phosphines such as TPPTS **172** discovered by Rhône-Poulenc (Rhodia) are the most popular water-soluble ligands and are now utilized in several industrial processes. Other sulfonated ligands (such as **171**, **173**, and **174**) have been published so far, as well as carboxyl (such as **175**−**177**) or glycosyl ligands (such as **178**−**180**). A review has been published in this field by Li.[204]



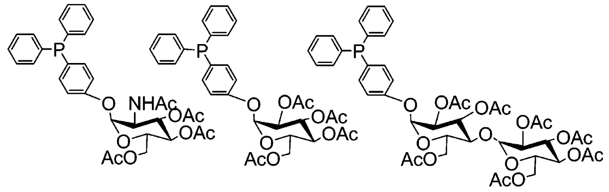
171 **172** **173** **174**



175 **176** **177**

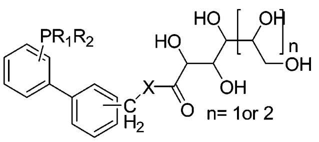
The examples reported below are representative of the work done by several companies in the area.

Hydrosoluble glycoside phosphines **178**−**180** ligated to Pd catalysts were developed to prepare substituted biphenyls or stilbenes.



178 **179** **180**

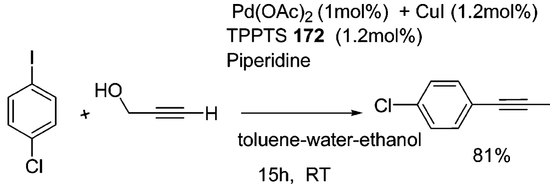
Other water-soluble bisaryl alkylphosphines bearing oligosaccharide **181** moieties have been used in the Pd- or Ni-catalyzed Miyaura−Suzuki reaction of aryl halides or aryl triflates with arylboronic salts in water (eq 71).[205]



181

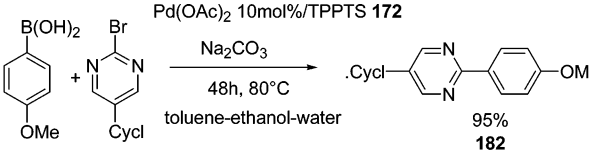
$$p\text{-MePhB(OH)}_2 + p\text{-ClPh-COMe} \xrightarrow[\text{water}\quad K_3PO_4]{\text{Pd(OAc)}_2\quad \mathbf{181}\ (R_1{=}R_2{=}\text{cyclohexyl},\ n = 1,\ X = \text{NH})} p\text{-MePh-}(p'\text{-COMe})\text{Ph}\quad \begin{matrix}95\%\\ \mathbf{80}\end{matrix} \qquad (71)$$

A liquid/liquid-phase system (toluene/water/ethanol) with TPPTS (**172**) or BINAS (**171**) was described by Hoechst to cross-couple halo- or perfluoroalkanesulfono aromatics with terminal alkynes (eq 72).[206] A second patent described the DMSO−ethylene glycol−water system.[207] Pd(II)−TPPTS in water−xylene−DMSO has been used to prepare high yields of cyanobiphenyl intermediates **68a** of the Sartan family (eq 73).[208] Similarly, Aventis patented a synthesis of 2-arylpyrimidines **182** under biphasic conditions, with good yields (93−96%). In this case, large amounts of Pd are needed (eq 74).[209]



(72)

$$\underset{1\ \text{equiv}}{o\text{-ClPhCN}} + \underset{1.1\ \text{equiv}}{p\text{-MePhB(OH)}_2} \xrightarrow[\text{DMSO/ xylene/ water}\quad \text{5h, reflux}]{\text{PdCl}_2\ (3\ \text{mol\%})/\text{TPPTS}\ \mathbf{172}\quad Na_2CO_3} p\text{-MePh-}(o\text{-CN})\text{Ph}\quad \begin{matrix}85\%\\ \mathbf{68a}\end{matrix} \qquad (73)$$



(74)

Rhodia patented in 1999 a simple and robust access to polyaromatic compounds via a Miyaura−Suzuki cross-coupling reaction in organic solvent or water in the presence of a phase-transfer agent such as ammonium or phosphonium salts (eq 75).[210] Functionalized biphenyl derivatives such as **68b** are obtained in good yields.

$$p\text{-BrPhCN} + \text{PhB(OH)}_2 \xrightarrow[\text{toluene or DME}\quad 60\text{-}85°\text{C 3h}]{\text{cat Pd(PPh}_3)_4\ 2\ \text{mol\%}\quad Na_2CO_3\ 1.4\ \text{equiv}\quad \text{Aliquat 336}\ 0.05\ \text{equiv}} (p\text{-CN})\text{Ph-Ph}\quad \begin{matrix}93\%\\ \mathbf{68b}\end{matrix} \qquad (75)$$

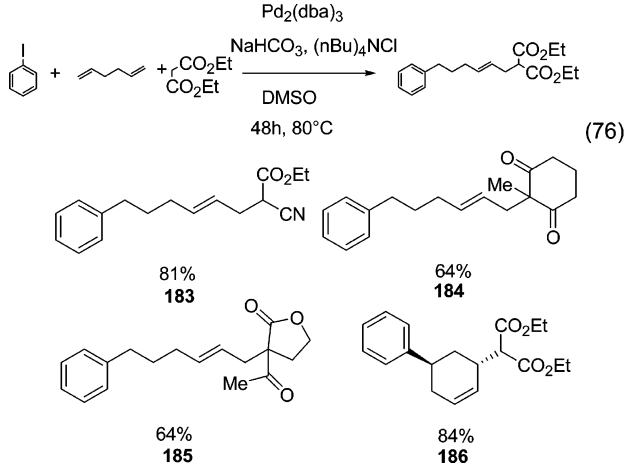


Table 12. Modification of the Ar−Cl Structure in Eq 87[a]

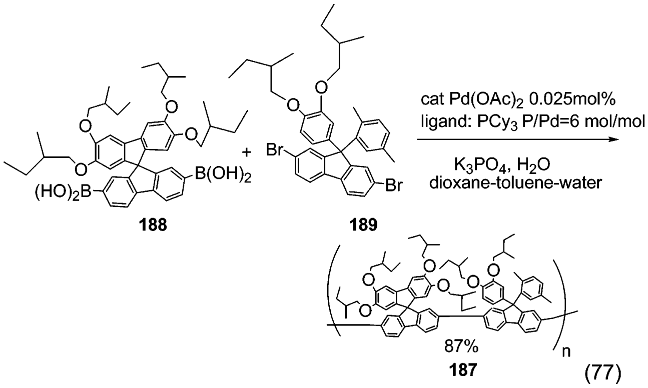
R	solvent	T (°C)	product	yield (%)
4-COMe	1,4-dioxane	50	**190**	79
4-CHO	1,4-dioxane	50	**191**	81
4-COPh	1,4-dioxane	50	**192**	70
4-CF_3	DMF	80	**78**	80
4-Me	NMP	80	**46a**	70

[a] Reaction conditions: $NiCl_2(dppe)$ 10 mol %, TPPTS **172** 50 mol %, Zn 50 mol %, solvent water, K_3PO_4 3 equiv, Ph-$B(OH)_2$/Ar−Cl = 1.1 mol/mol.

A low cost Miyaura−Suzuki C−C coupling reaction with $PdCl_2$−EDTA (1/1 mol/mol) in water has been published.[211] Aryls or heteroaryls and hetero(aryl)boronic acids give the corresponding functionalized biphenyl in good yields (turnover up to 97 000).

Nonconjugated dienes react with aryl halides and malonates in the presence of Pd(0) and Bu_4NCl to give the corresponding adduct **183**−**186** in moderate to good yields (60−85%) (eq 76). Under these experimental conditions, no racemization was observed.[212]

An efficient Miyaura−Suzuki process to prepare high M_n and M_w bulky polymers **187** from monomers **188** and **189** under multiphase conditions (dioxane−toluene−water) was patented by Covion Organic Semiconductors (eq 77).[213]

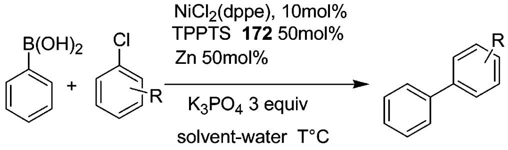


(77)

These new polymers have potential application in polymeric light-emitting diodes, organic solar cells, and organic ICs.

b. Hydrosoluble Ni Catalysts. Rhodia patented the hydrosoluble Ni(0) salts/TPPTS **172** catalyst for the Miyaura−Susuki reaction between aryl chlorides and boronic acids.

The Ni(0) complexes were prepared in situ using Zn as reductor (eq 78).[214] This avoids the need to use an expensive Pd catalyst.

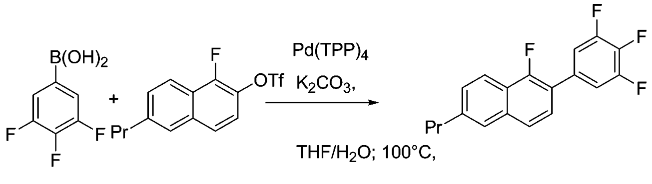


(78)

Typical results are shown in Tables 12 and 13. Using this procedure, bulky biaryl and electron-rich biaryl derivatives were prepared in good yields.

3.5. Specific Conditions of the C–C Cross-Coupling Reaction

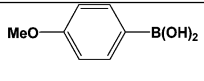
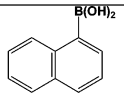
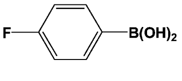
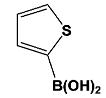
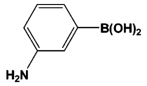
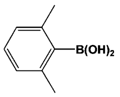
Dainippon patented a preparation of biaryls (liquid crystals application) by a Miyaura−Suzuki coupling reaction in water/THF under high pressure (≥500 kPa) and temperature (eq 79).[215]



300kPa, 2h (79)

Merck patented the use of microreactor technology for the Heck−Mizokori coupling reaction.[218] When iodobenzene was reacted with styrene in the presence of catalysts (e.g., Pd diacetate, triphenylphosphine, NMP, and tributylamine) in a microreactor, *trans*-stilbene was obtained in very good yield and productivity. Microreactor technology was successfully applied in the Pd-catalyzed C−N cross-coupling reaction between 4-bromotoluene and piperidine. Excellent conversions and selectivity were obtained without any byproduct formation in a continuous reactor.[219] More generally, microreactors have proven to be highly valuable tools in organic chemistry.[216] Key advantages are a large flexibility of operating conditions with efficient heat transfer, optimized mixing, and easy reaction control. Microreactors are available in several designs and models, but only a few examples of pilot plant implementation are reported.[217]

Table 13. Modification of the the Boronic Acid Structure in Eq 87[a] **(R = 4-COMe)**

Ar-$B(OH)_2$	Product	Yield %	Ar-$B(OH)_2$	Product	Yield %
	**193**	81		**197**	99
	**194**	86		**198**	72
	**195**	47		**196**	94

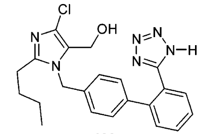
[a] Reaction conditions: $NiCl_2(dppe)$ 10 mol %, TPPTS **172** 50 mol %, Zn 50 mol %, solvent water, K_3PO_4 3 equiv, Ar−$B(OH)_2$/4-MeCOPhCl = 1.1 mol/mol in dioxane−water at 50 °C.

3.6. Selected Representative Syntheses of Pharmaceutical, Agrochemical, and Material Science Patented Compounds

The following examples recently described in the patent literature illustrate the wide range of applications of the C−C cross-coupling reactions using organometallic catalysts (Table 14).

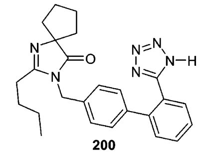
3.7. Application to the Biphenyl Family

The biaryl family is one of the backbones of the drug universe. A nice representative is the Sartan group, the fastest growing class of prescription drugs for hypertension, which accounts for 230 patents and for 8 (Losartan (**199**),[265] Irbesartan **(200)**,[266,153] Candesartan, Telmisartan, Olmesartan, Valsartan (**201**),[404] and two coformulations) out of the 21 biaryl drugs on the market with a total sales of 8 billion U.S. dollars in 2004.



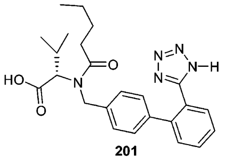
199

Losartan (Dupont-Merck)



200

Irbesartan (Sanofi-Aventis)



201

Valsartan (Novartis)

These biaryl families can be structurally divided into different chemical groups (Table 15): mature products (like Sartan), early stage of development products (around 100), and clinical phase products (8). Therefore, we can anticipate that several new biaryl derivatives will enter the development pipe of pharmaceutical companies in the coming years. About 10 should be launched in the next 5 years, mainly in the disubstituted group, but outside the Sartan family.

The routes to Losartan[265] and other Sartan family members have largely been covered by patents from Merck-Dupont, Merck, Mikuni, and others. Note that there are no less than 90 patents claiming routes to 2-(4-tolyl)benzonitrile, the key building block of the Sartan family, most of them using B, Mg, and Zn coupling of the tolyl group with 2-halogenobenzonitriles. Zn coupling has been developed by DSM Catalytica to overcome interference with the cyano group which occurs when using the Grignard alone (Miyaura−Suzuki coupling).

Sanofi-Synthelabo has developed its own original route to Irbesartan (**200**) where the key step is the preparation of the 2-(4-tolyl)benzonitrile by the one-step C−C coupling reaction of 4-toluylmagnesium bromide with benzonitrile in the presence of $MnCl_2$ or $PdCl_2$−bis phosphine.[153,266]

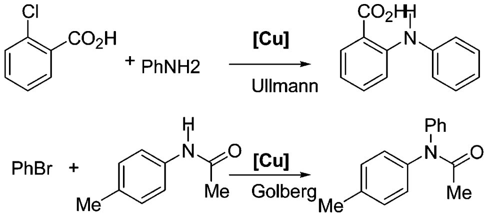
A Pd-catalyzed coupling reaction between a zinc tetrazole intermediate and a functionalized aryl bromide has been patented by American Home Products Corporation. The best catalyst was prepared by reacting $Pd(PPh_3)_2Cl_2$ with DIBAL in THF.[267]

4. Carbon–Nitrogen Coupling Reaction Technologies

4.1. Introduction and Classification of Coupling Reactions

Carbon−nitrogen bond formation catalyzed by organometallic complexes is now classical in organic synthesis. Metal-catalyzed amination of aryl halides and pseudohalides has already been reviewed several times, but it is our understanding that no extensive patent literature analysis, which would give an estimate of the industrial interest (products, processes, and applications) in the technology, is available today.[268]

One of the first examples of the amination and amidification of aryl halides using organometallic complexes is the synthesis of substituted diphenylamines catalyzed by Cu salts; these products are key intermediates in the syntheses of acridones (eq 80), as described separately by Ullmann and Goldberg in 1903 and 1906, respectively.[269]



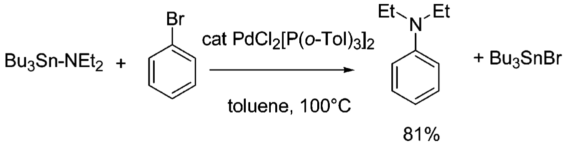
(80)

The Ullmann or Goldberg reaction usually requires drastic experimental conditions such as high temperature (150−300 °C) and large amounts of catalysts to get acceptable kinetics. The following reactivity trend was observed: I > Br ≫ Cl, and fluoro derivatives usually do not react under the reaction conditions. The aryl halide can bear various substituents and even reactive moieties. Usually, electron-donating substituents on the aromatic ring do not drastically affect the reaction rate. The reactivity of the Cu species strongly depends on its method of preparation. CuO and Cu_2O can be used without base addition. There are a few typical side reactions of the aryl halide, such as reductive dehalogenation or biaryl homocoupling and halogen exchange with a Cu(I) salt.

Some modifications of the electrophile were proposed to reduce the harsh character of the original experimental conditions: (a) Chan−Evan−Lam modifications−use of aryl boronic acids with TEA or pyridine and $Cu(OAc)_2$ (Molecular sieves were also used in this reaction.[270]); (b) Batey modifications−use of ligand- or base-free copper(II) systems with aryltrifluoroboronates;[271] (c) Beringer−Kang modifications−use of aryl iodonium salts;[272] (d) Barton plumbane modifications−use of lead derivatives;[273] (e) Barton modifications−use of bismuth derivatives.[274]

As most of these modifications cannot be applied industrially for economical, toxicity, safety, and environmental reasons, there has been a strong need for better processes.

In 1983 Kosugi−Kameyama−Migita published their first report on the intermolecular carbon−nitrogen bond formation using tin amide derivatives in the presence of a bulky P(*o*-Tol)$_3$ ligand. Vinyl bromides and aryl bromides containing electron-donating or electron-withdrawing groups gave coupled products in low to good yields (5−87%) (eq 81).[275]



(81)

Table 14. Selected Applications of the C−C Cross-Coupling Reactions

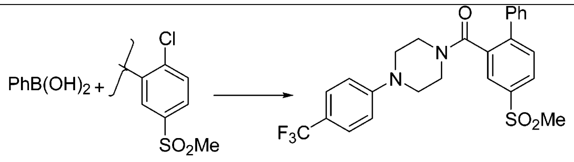
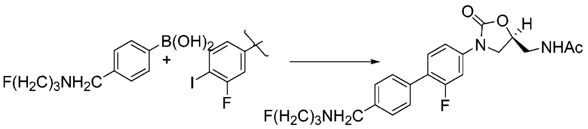
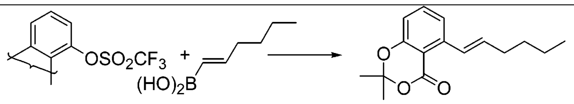
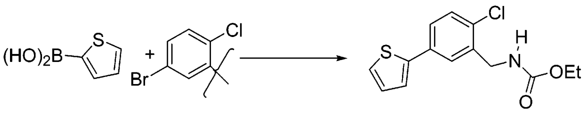
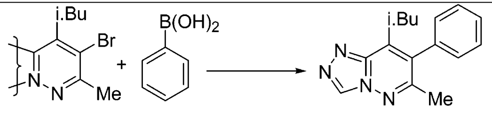
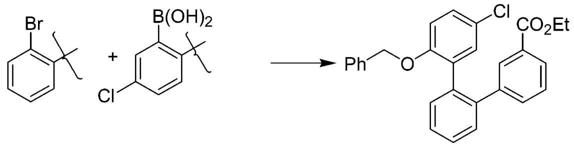
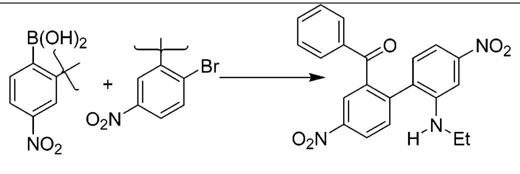
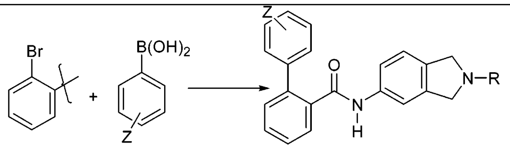
Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd(P(tBu)_3)_2$	Dioxane, KF, 19h-90°C >80%	 *Glycine transporter 1 (GlyT-1) inhibitors*	220
$Pd(PPh_3)_4$	K_2CO_3 Toluene-EtOH, H_2O Reflux, 8h 65%	 *Antiinfective, antiproliferative, anti-inflammatory and prokinetic properties*	221
$Pd(PPh_3)_4$	K_2CO_3, THF, H_2O reflux	 *Protein tyrosine phosphorylation activators*	222
$Pd(PPh_3)_4$	Na_2CO_3 Toluene, ethanol,4h reflux 75%	 *Bactericides*	223
$Pd(PPh_3)_4$	$NaHCO_3$, THF, H_2O, 24h reflux	 *Fungicides*	224
$Pd(PPh_3)_4$	K_2CO_3 Toluene-EtOH 90°C, 3-5h 35-50%	 *EP1 receptor antagonist's activity (treatment of prostaglandin mediated diseases)*	225
$Pd(PPh_3)_4$	Na_2CO_3, DME, H_2O 20h reflux 15-20%	 *DNA intercalator*	226
$Pd(PPh_3)_4$	Na_2CO_3, THF, reflux	 *Apolipoprotein B secretion inhibitors*	227

Table 14 (Continued)

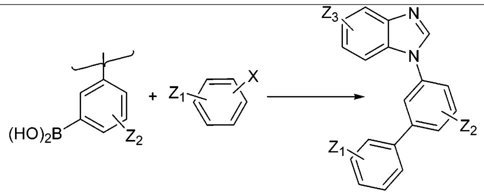
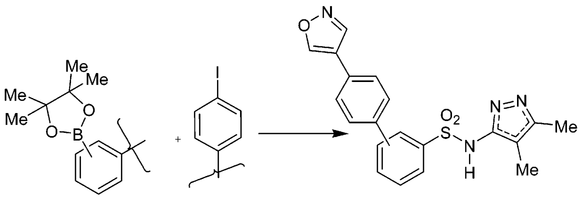
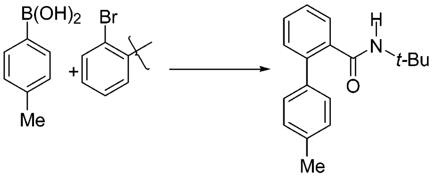
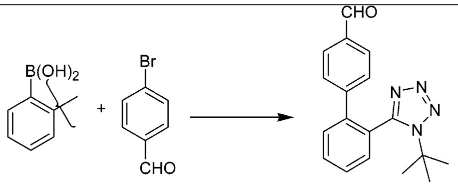
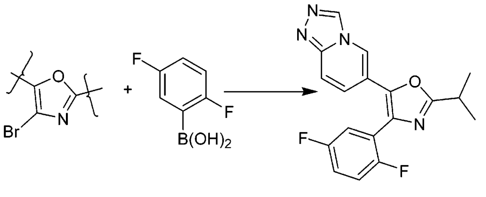
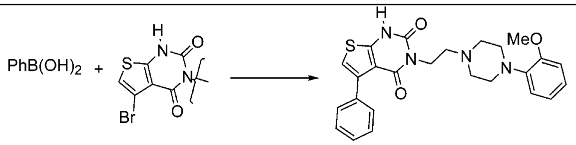
Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd(PPh_3)_4$	$NaHCO_3$ DME, H_2O 90°C >90%	 *Treatment of stroke, ischemia, anoxia, migraine and psychosis*	228
$Pd(OAc)_2$-PPh_3	Na_2CO_3 THF, reflux >70%	 *Pharmaceutical intermediate drugs*	229
Pd/C	NaOH Toluene, MeOH reflux	 *Angiotensin converting enzyme II inhibitors*	230
$Pd_2(dba)_3$ PPh_3	Na_2CO_3 THF, reflux > 70%	 *Intermediates of angiotensin II receptor antagonists.Sartan family*	231
$Pd(PPh_3)_4$	TEA EtOH,H_2O 65-70°C 40%	 *Mitogen-activated protein (MAP) kinases*	232
$Pd(PPh_3)_4$	Na_2CO_3, THF	 *Depression treatment*	233

Table 14 (Continued)

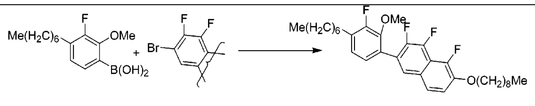
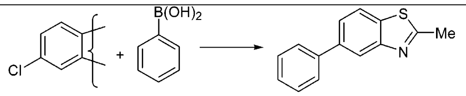
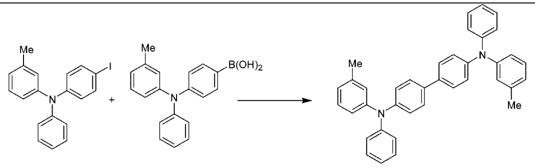
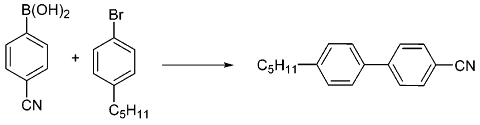
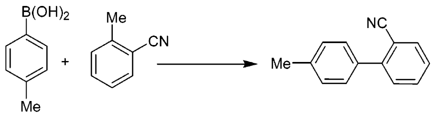
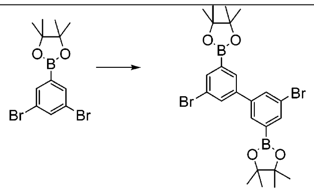
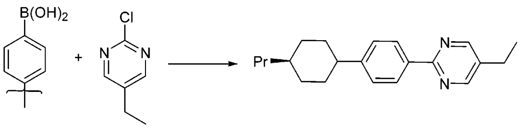
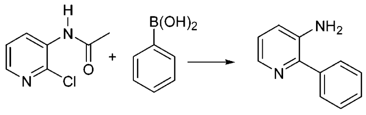
Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd_2(dba)_3$ + TPPTS	Na_2CO_3 80°C, 12h	 *Smectic liquid crystal*	234
$Pd(OAc)_2$+ PCy_3	K_2CO_3, toluene reflux,8h 66%	 *Photographic additives*	235
$Pd(OAc)_2$, P(*o*-MePh)$_3$	TEA DMF,100°C 2h, 75%	 *Materials for organic electroluminescent, electrophotographic, and optical recording materials*	236
Ni-Raney	K_2CO_3 Toluene, Ethanol 4h reflux 85%	 *Used in material sciences*	237
$PdCl_2$ Hydrosoluble phosphine	Na_2CO_3 Ethylene glycol, H_2O 74%	 *Pharmaceutical intermediate as Sartan*	238
$Pd_2(dba)_3$ P(*t*-Bu)$_3$	K_3PO_4 Xylene reflux 16h >60%	 *Functionalized polymer*	239
Pd/C (5%)	K_2CO_3 $(nBu)_4NBr$ Toluene, Ethanol Reflux, 6h 80%	 *Useful as drugs, agrochemicals. or their intermediates, or as liquid crystal materials.*	240 see also 241 242
$Pd(PPh_3)_4$	Na_2CO_3 Toluene, H_2O Reflux, 8h 86%	 *Intermediate for NK1 receptor such as CP-99,994 and GR203040*	243

Table 14 (Continued)

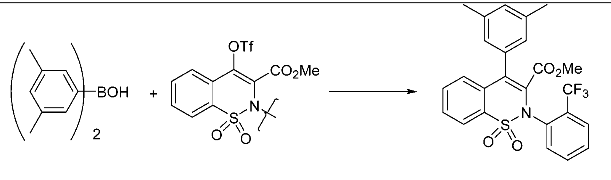
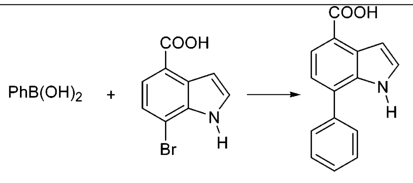
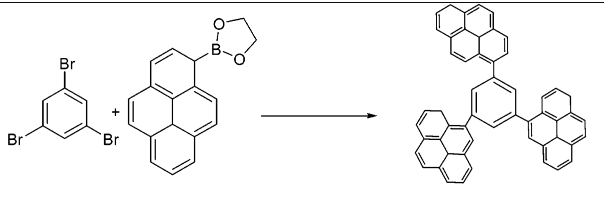
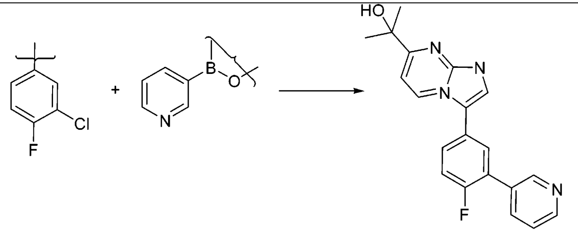
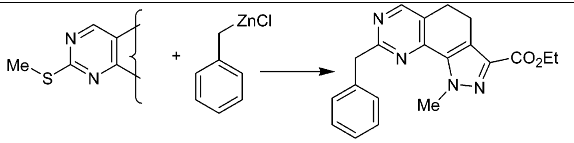
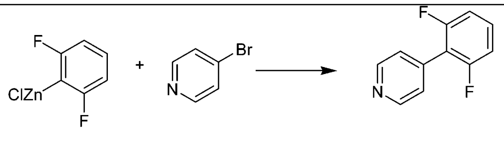
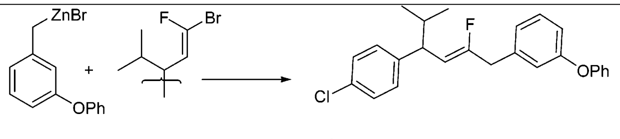
Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd(PPh_3)_4$	K_2CO_3 THF-H2O 91%	 *Intermediate for Endothelin receptor antagonists*	244
$Pd_2(dba)_3$ + carbene (NHC) or P(*t*-Bu)$_3$	$CsHCO_3$ dioxane, 70%	 *Intermediate for pharmaceutical drugs*	245
$Pd(OAc)_2$ di-*tert*-butyl-2'-methyl-2-biphenylphosphine	K_2CO_3 Toluene, H_2O Reflux, 3h	 *Electroluminescent devices*	246
$Pd(OAc)_2$ PPh_3	Cs_2CO_3 THF	 *Receptor ligands for the treatment of deleterious mental disorders*	247
$Pd(PPh_3)_4$	THF 20h, 60°C	 *Inhibitors of protein kinases*	248
$Pd(PPh_3)_4$	THF, 40°C, 12h >73%	 *Bactericides*	249
$Pd(PPh_3)_4$	THF, reflux	 *Pesticides*	250

Table 14 (Continued)

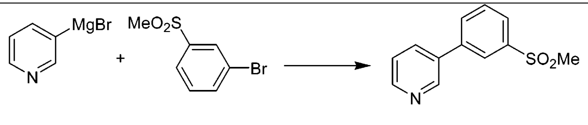
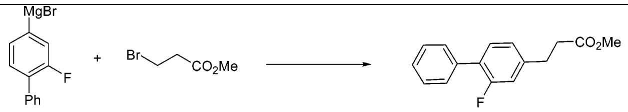
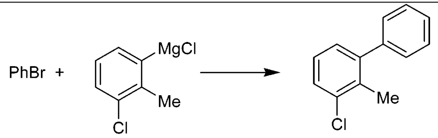
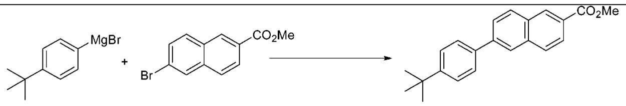
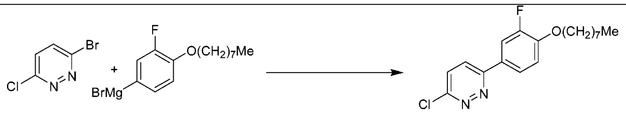
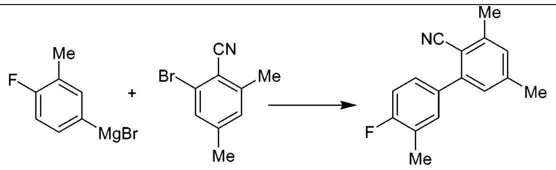
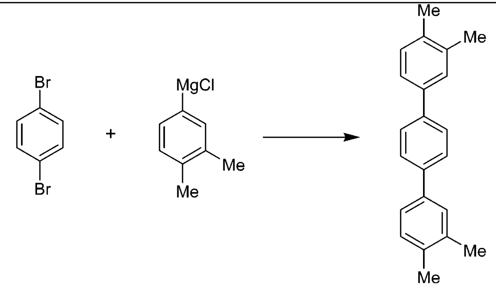
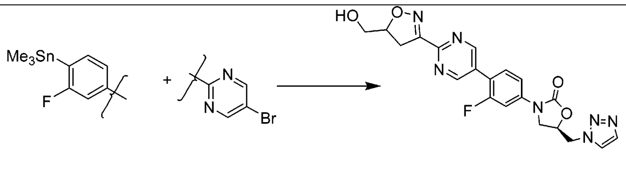
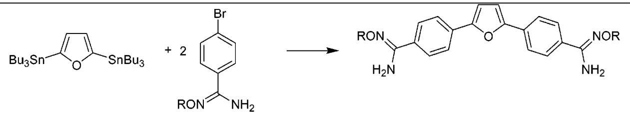
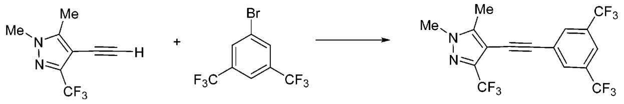
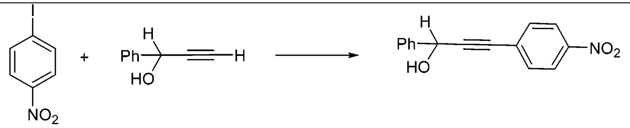
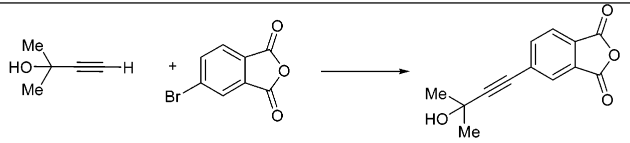
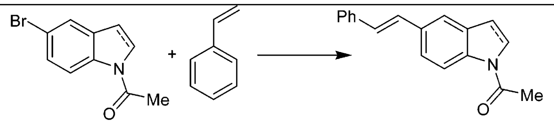
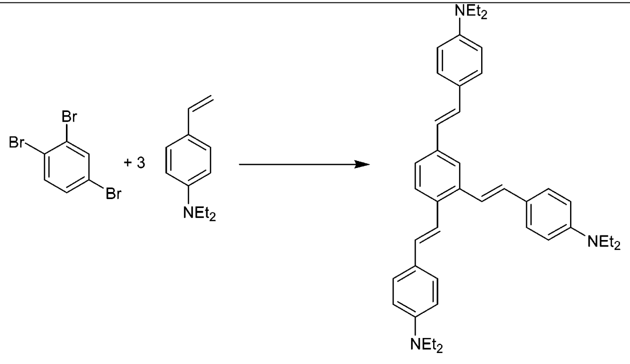
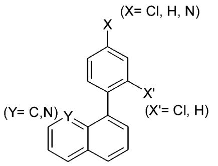
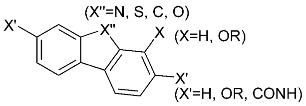
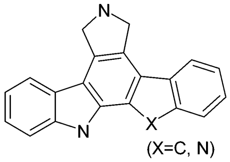
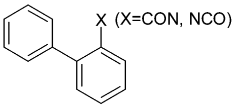
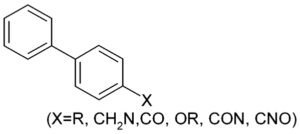
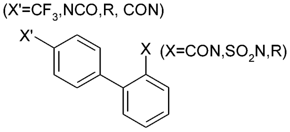
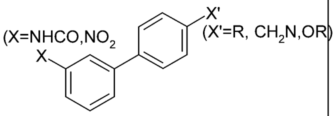
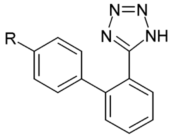
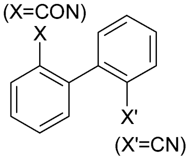
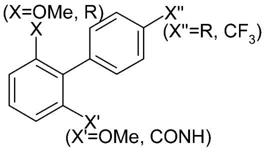
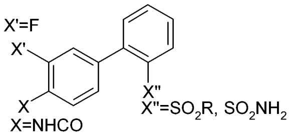
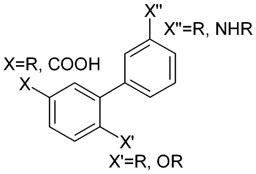
Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd(PPh_3)_4$	THF, $ZnCl_2$ 50°C, 4h 80%	 *Nervous diseases*	251
$NiCl_2(PPh_3)_2$	THF, -25°C 78%	 *Anti-inflammatory agents Example: Flurbiprofen*	252
$NiCl_2$	THF 50-60°C 89%	 *Chemical intermediates*	253
$NiCl_2$ $Ph_2P(CH_2)PPh_2$	THF, rt, 30mn 54%	 *Pharmacy and cosmetics intermediates*	254
$PdCl_2(Ph_2P$ $(CH_2)_4PPh_2)$	THF, >80%	 Raw materials for pharmaceuticals, agrochemicals, and liquid crystal.	255
Ni(0) *via* $NiCl_2(PPh_3)_2$ with $(Me_2CHCH_2)_2$ AlH	THF	 *Antihypercholesterolemic agents*	256
$NiCl_2$	THF, 50°C- 60°C 30mn 68%	 *Conductive polymers*	257
$Pd_2(dba)_2$ P(2-fury)$_3$	Dioxane, 95°C 12h > 70%	 *Antibacterial agents*	258

Table 14 (Continued)

Catalyst	Experimental conditions	Reaction / *Application*	Reference
$Pd(PPh_3)_4$	Dioxane 16, 100°C 60-65%	 *Effective against human Africain trypanosomiasis*	259
$Pd(OAc)_2$ + CuI $PhP(tBu)_2$	DMAC $Cy(NH_2)_2$ 12h, 110°C 85%	 *Insecticides or acaricides*	260
$PdCl_2(PPh_3)_2$ + CuI	TEA THF, reflux 92%	 *Chemical intermediates*	261
$PdCl_2(PPh_3)_2$ + CuCl	TEA Reflux, 4h 38%	 *Monomers for thermosetting resins, liquid crystals, nonlinear optical materials, or photographic additives.*	262
$Pd(OAc)_2$ + $P(o\text{-}MeC_6H_4)_3$	Acetonitrile/ NEt_3, 100°C 50%.	 *Intermediates for perfumes, drugs, and agrochemicals applications*	263
$Pd(OAc)_2$ + $P(o\text{-}MeC_6H_4)_3$	DMF, $n\text{-}Bu_3N$ 100°C, 4h 92%	 *Charge-transport agents for electrophotographic photoreceptors applications*	264

Based on this discovery, interest has grown in the area of Pd-catalyzed C−N bond-forming reactions. In particular, methods for accomplishing “tin-free” cross-coupling that circumvented use of toxic derivatives were investigated. Much of the development in this area stemmed from fundamental studies conducted by numerous research groups such as those of Buchwald, Hartwig, and others.[276] The original set of experimental conditions, involving a Pd catalyst and $P(o\text{-}Tol)_3$ as ligand, was developed with *t*-BuONa or $LiN(SiMe_3)_2$ as base and toluene as solvent.[277] This methodology suffers from some limitations such as the necessity to use electron-rich aryl bromides (with the formation of large amounts of reduction derivatives) and the poor yield observed with primary and secondary acyclic amines or aryl triflates. A major projection carried out independently by Hartwig and Buchwald consisted of using

Table 15. Some Chemical Groups of the Biaryl Family Including Sartan

Chemical groups	Typical examples		
Poly-biaryl derivatives			
"Mono functional" biaryl derivatives:.			
"Bi-functional" biaryl derivatives	 	 SARTAN	
"Tri- functional" biaryl derivatives			

chelating diphosphine ligands such as dppf and BINAP.[278] These ligands increased the catalytic stability and preserved the formation of reduction product via a β-elimination process; they widen the scope of the amination reactions including the use of primary and secondary aryl- and alkylamines, anilines, heteroaromatic halides, or triflates. Fort's group developed the in situ generated Ni−(NHC) carbene complexes in coupling reactions of aryl chlorides with amines and piperazines.[279]

4.2. Advantages and Limitations of Well-Established C–N Coupling Reactions

Table 16 shows the main advantages and limitations of the well-established C−N coupling technologies.

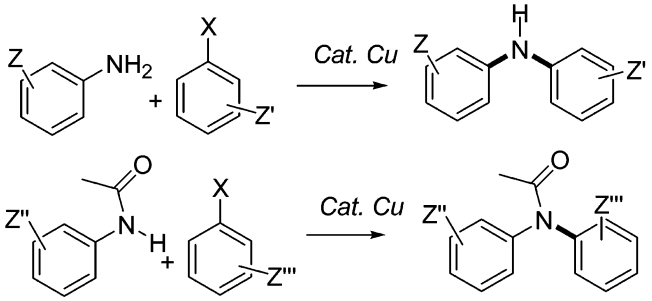
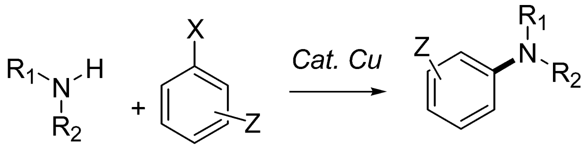
4.3. C–N Coupling Reaction Mechanisms

The mechanism of the catalytic C−N bond formation depends on the nature of the metal involved.

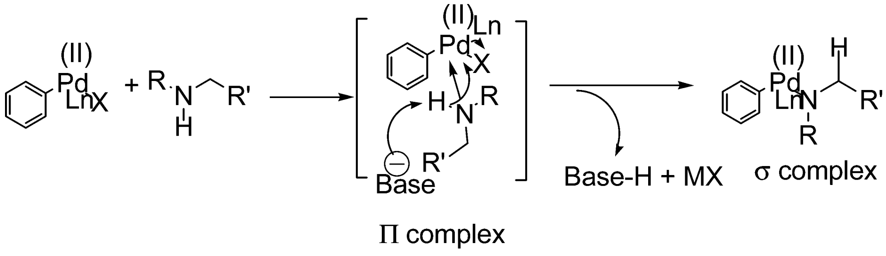
4.3.1. Palladium Catalysis

The mechanism of the C−N coupling reaction involving Pd species is well described in the literature.[280] It involves four main steps (Scheme 13): (1) First an *oxidative addition step*; as described previously, the reaction between Pd(0) complex and aryl halide generates an aryl−Pd complex. (2) Then the a*mine coordination and proton abstraction step*; a σ-aryl Pd amide intermediate is obtained by the proton abstraction of the coordinated amine ($^2\eta$ or π amine−Pd(II) complex). The ability of the base to abstract the proton is a key parameter (Scheme 14). As proved by Amatore and Jutand and discussed above, the starting complex is $[PdL_2X]^-$ with X = AcO or/and Cl.[19,23] (3) Then there is *a reductive elimination step* to obtain the arylamine and the ligated Pd(0); this is the rate-determining step. (4) The last step is a *β-elimination* to give an imine and a Pd−H complex which can produce an arene byproduct by reductive β-elimination. The use of chelating ligands can strongly decrease this side

Table 16. Evaluation of Well-Established Carbon−Nitrogen Coupling Technologies

advantages	limitations
Ullmann−Goldberg Coupling Reaction 	
commercial availability of many arylamines, heteroarylamines, arylamides , aryl halides, and heteroaryl halides	high temperature → slight flexibility toward functional group—sometimes formation of tare products
a large variety of aryl halides or pseudohalides and amines or amides can be used	sometimes difficulties in purifying final product due to the medium complexity
easy handling	low to moderate yields
many examples described in the literature	works well only with aryl derivatives
heterogeneous catalyst (metal, oxides, ...) and mixture of metals can be used	usually a large amount of catalyst is needed: cost, toxicity, (especially Ni), environment
functionalized halides—with some limitation—can be used	purification and recycling not easy
scalability from the lab to pilot and industrial scales	sometimes requires specific solvents (high boiling point, polar, ...)—sometimes difficulty in removing the solvent from the medium
rather cheap technology	waste treatment (formation of inorganic salts)
Hartwig−Buchwald Coupling Reaction 	
commercial availability on a lab scale, large range of arylamines, heteroarylamines, arylamides, aryl halides, and heteroaryl halides	ligand specific to the metal, electrophile, and nucleophile
	base specific to the catalytic system, electrophile, and nucleophile
	metal removal
pseudohalides (triflates, ...) can be used	waste treatment (formation of inorganic salts)
works well with alkyl halides	
very active catalytic systems—low amount of catalyst	
large flexibility toward functional group	
mild experimental conditions	
handling without specific precautions	
many examples described in the literature	
usually good yield and selectivity	
large variety of ligands to coordinate the metal	
classical solvents can be used	
large range of applications (pharma, polymers, materials)	

Scheme 13. Formation of the σ-Aryl Pd Amide Intermediate



reaction. As described by Amatore and Jutand, the nucleophile can often form a new complex with the Pd which can totally inhibit the catalytic activity.[281]

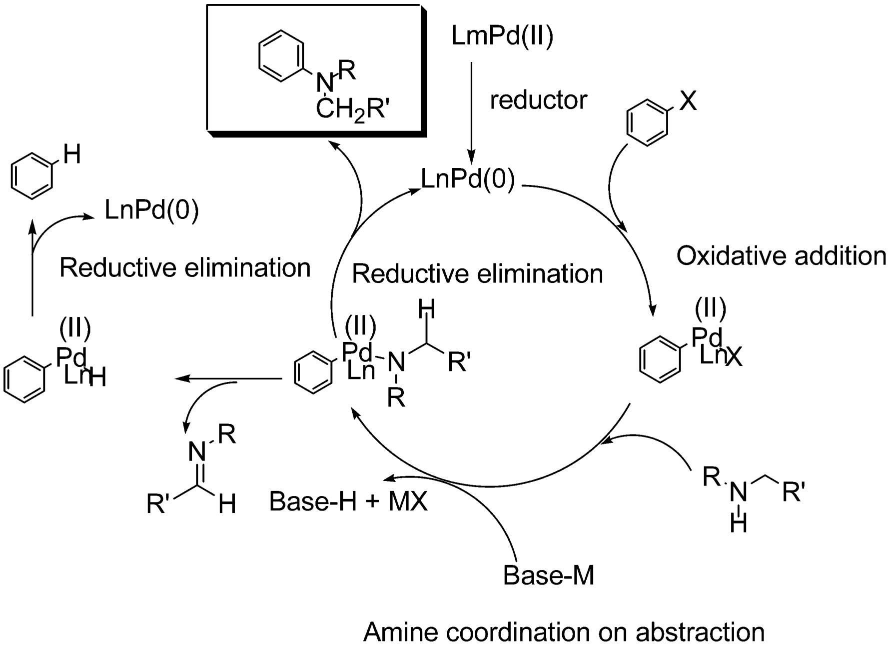
4.3.2. Copper Catalysis

The mechanism elucidation is not total, but radical scavenge experiments have shown that radicals are involved in some steps. The two speculated and concomitant mechanisms usually used to interpret experimental results are shown in Scheme 15.[282] Cu(0) and Cu(I) starting materials and Cu(I), Cu(II), and Cu(III) intermediates can be involved in these coupling processes.

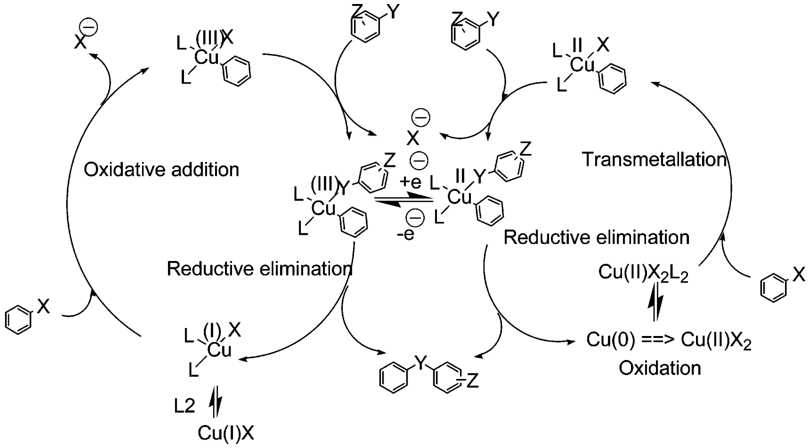
4.4. Palladium Catalysis: The Choice of the Ligand

The catalyst (metal + ligand) is a major contributor to the cost of the catalytic C−N bond formation. In December 2005, the bulk Pd price on the international metal market

Scheme 14. Simplified Catalytic Cycle in a Pd Amination Reaction



Scheme 15. Simplified and Postulated Interpenetrated Catalytic Cycle in a Cu Catalyst Coupling Reaction



was roughly 2000 times that of the bulk Cu. Therefore, based solely on metal costs, the aforementioned transformations would be orders of magnitude more appealing if they could be achieved with catalysts comprising Cu rather than Pd. Nevertheless, even if Cu catalysts usually need less sophisticated and costly ligands than other metals, a good compromise between the ligand, the solvent, and the base can make Pd a good choice given the low amount of metal required under the best conditions. We will review here the main ligands from the literature for Pd first and then Cu homogeneous and heterogeneous catalysis.

4.4.1. Bulky and Electron-Rich Monodentate Ligand Coupling Reactions

4.4.1.1. PPh$_3$ and P(*t*-Bu)$_3$ Ligands. Table 17 shows the main representative patented examples using simple PPh$_3$ or P(*t*-Bu)$_3$ **22** as Pd ligands and related palladacycles. These two ligands are easily accessible. But on a large scale, P(*t*-Bu)$_3$ has some limitations due to its sensitivity to oxidation. In 1996 Tosoh patented the first examples of synthesis of arylamines via a C−N cross-coupling reaction using Pd complexes and bulky phosphines such as P(*t*-Bu)$_3$ **22**. The Pd(P(*t*-Bu)$_3$)$_4$ complex and its family were also claimed.[283] No steric and electronic effects of the substituents on aryl bromide were observed. Scheme 16 shows several representative examples (**202**−**206**).

The use of electron-rich P(*t*-Bu)$_3$, thanks to its ability to stabilize Pd species during the catalytic cycle, has been described in many applications: (i) polyarylamines;[296] (ii) halotriarylamines and vinyltriarylamines for hole-transporting materials;[297] (iii) triarylamines and diarylaminophenyl methacrylates with a hydroxyl function useful as monomers for electroluminescent and electrophotographic materials;[298] (iv) bisarylaminofluorenes;[299] (v) formyltriarylamines;[300] (vi) *N*-substituted (diarylamino)pyrroles;[301] (vii) diarylaminothiophenes;[302] (viii) 4-*tert*-butoxy-4′-cyanobiphenyl and 4-hydroxy-4′-cyanobiphenyl as materials for liquid crystals and polymers.[303]

The ability of P(*t*-Bu)$_3$ to stabilize Cu has been applied in the vaporization process of MOCVD coatings (Tosoh's patent):[287,304] cyclopentadienyl Cu complexes ligated with P(*t*-Bu)$_3$ show good enough heat resistance for this application.

4.4.1.2. Symyx Monophosphines. Symyx patented C−N and C−C (Miyaura−Suzuki) coupling reactions with the bulky alkyl aryl monophosphines **207** (eq 82), **208**, **209**, **210**,

Table 17. Selected Examples of Pd/PPh$_3$, Pd/P(*t*-Bu)$_3$, and Palladacycle Applications in C−N Bond Formation

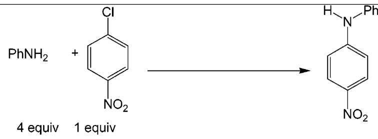
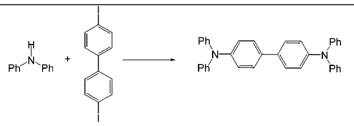
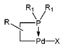
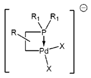
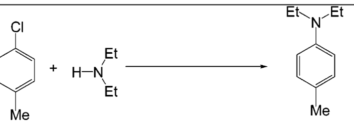
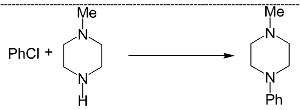
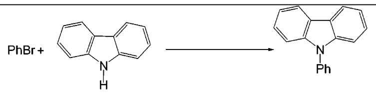
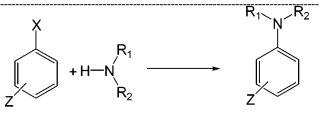
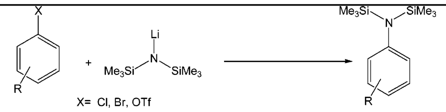
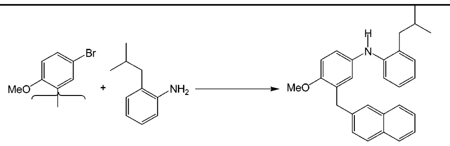
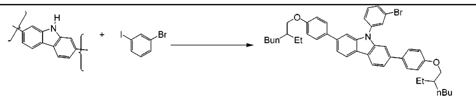
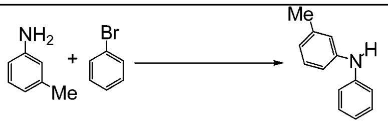
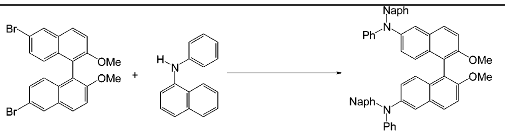
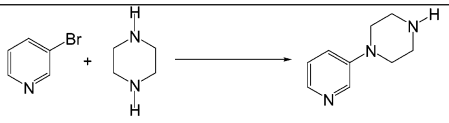
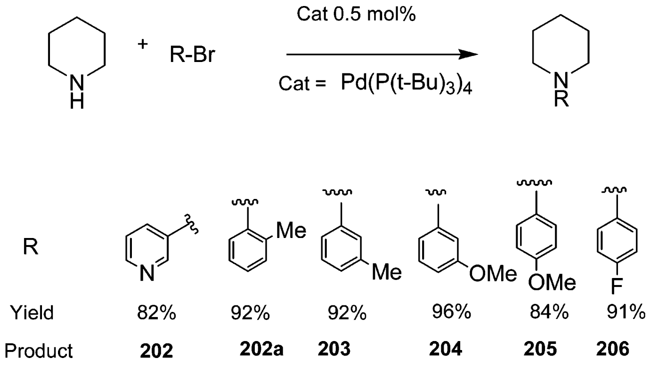
Catalyst	Experimental conditions	Reaction / *Application*	Reference
Pd-PPh$_3$ *with activated starting materials*	Pd(OAc)$_2$ –PPh$_3$ *t*-BuOK or *t*-BuONa 170°C, 1h ~100%	 *Chemical intermediates*	284
Pd-PPh$_3$ *with non activated starting materials*	Pd(OAc)$_2$ –PPh$_3$ *t*-BuOK or *t*-BuONa xylene, 130°C, 1h 89%	 *Limitation to reactive functionnalized derivative and aryl iodides as staring materials*	285
Pd-phosphacylo butane complex  	Palladacycle *t*-BuOK or *t*-BuONa toluene, reflux 24h 87%	 *Intermediate*	286
	PdCl$_2$((P(*t*-Bu)$_3$)$_2$ Toluene, 120°C; *t*BuONa 120°C, 8h 95%	 *Intermediate*	287
Pd-P(t-Bu)$_3$ P(t-Bu)$_3$ and other electron rich phosphines	Pd(OAc)$_2$ + P(*t*-Bu)$_3$ K$_2$CO$_3$ Xylene, 120°C, 8h 95%	 *Organic photosensitive materials, hole-transport agents for organic electroluminescent devices*	288
	Pd(dba)$_2$ + P(*t*-Bu)$_3$ *t*-BuONa Toluene, reflux Amine : >80% Azole : > 60%	 *Intermediate*	289

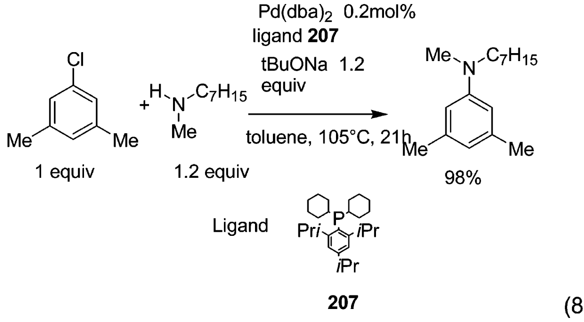
Table 17 (Continued)

Catalyst	Experimental conditions	Reaction / *Application*	Reference
Pd-P(t-Bu)$_3$ ***P(t-Bu)$_3$ and other electron rich phosphines***	Pd(dba)$_2$ + P(*t*-*Bu*)$_3$ Toluene 50-100°C 75-90%	 *Intermediate*	290
	Pd$_2$(dba)$_3$ + PCy$_3$ *t*-BuONa, THF 16h, 70°C 47%	 *Derivatives for antiviral HIV treatment*	291
	Pd$_2$(dba)$_3$ + P(*t*-Bu)$_3$ *t*-BuONa, toluene 70°C, 63h 52%	 *Intermediate to organometallic dendrimers (G2 and G3) useful in electro-optic devices*	292
	Pd(OAc)$_2$ + P(*t*-Bu)$_3$ *t*-BuONa, toluene, reflux 2.5h 95-97%	 *The second step is a C-C coupling reaction using as catalyst ligated Ni(0) by bipyridine and PPh$_3$*	293
	Pd(OAc)$_2$ + P(*t*-Bu)$_3$ *t*BuONa, toluene, reflux 81%	 *Ligand*	294
	Pd(OAc)$_2$ + P(*t*-Bu)$_3$ P(*t*-Bu)$_3$, *o*-xylene 82%	 *Intermediates*	295

Scheme 16. Example of a C−N Coupling Reaction between Piperazine and Aryl Bromide

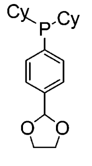


and **211**.[305] Very good yields were obtained even with low amounts of Pd catalyst (0.2 mol %).

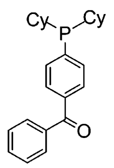


207

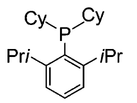
(82)



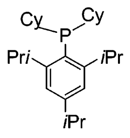
208



209



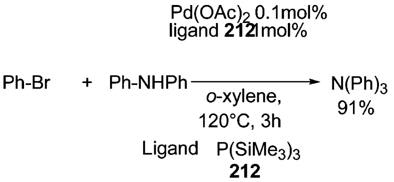
210



211

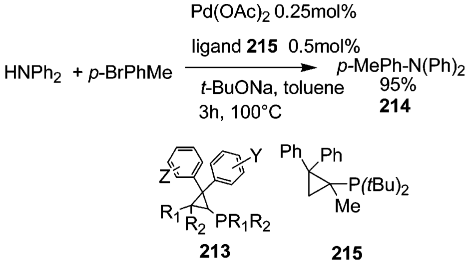
As described before, Symyx patented new bidentate phosphine ligands and related complexes **72**−**74**. These ligands have an acetal ligand in the position β to the phosphorus center and are very convenient to ligate Pd species in the amination reaction of aryl halides.[70] Secondary amines were tested with 4-bromobiphenyl derivatives using 2 mol % of $Pd(OAc)_2$ and 4 mol % of Symyx ligands at 105−110 °C during 5−90 min. In all cases, ligand **73** gives the best results.

4.4.1.3. Pd−P(SiMe$_3$)$_3$ Ligand. Syntec patented the synthesis of diarylamines by reaction between arylamines and aryl halides in the presence of a particularly low amount of Pd using a new powerful silylphosphine **212** which boosts the reaction rate (eq 83).[306]



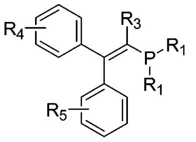
(83)

4.1.4.4. Takasago Pd−Phosphinocyclopropane Ligand. Takasago patented a new phosphinocyclopropane family of ligands **213** for the Pd-catalyzed C−N bond formation (eq 84).[307] The triphenylamino derivative **214** and phenylcarbazol were prepared in very good yield using Pd−phosphinocyclopropane **215**.

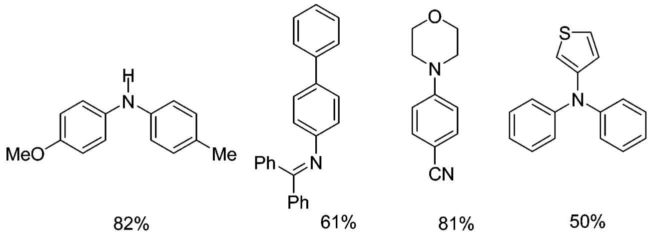


(84)

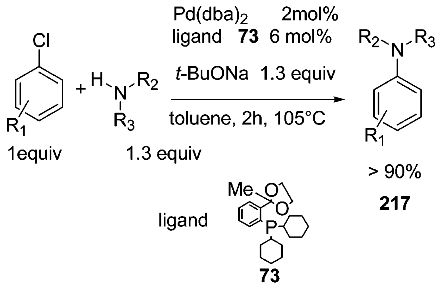
4.4.1.5. Takasago 2,2-(Diaryl)vinylphosphine Ligand. Tagasago patented new 2,2-(diaryl)vinylphosphine**s** of general formula **216** as ligands of Pd in the C−N coupling reaction.[308] These catalysts are more efficient than other Pd/ligand systems in the amination reaction of aryl bromides and chlorides. The following derivatives were prepared in moderate to good yields with 0.25 mol % $Pd(OAc)_2$ and 1 mol % ligand in toluene/*t*-BuONa (100 °C, 8 h). In a typical example, ligands **216** gave >85% yield while under the same conditions BINAP (**1**) gave 22%, PCy_3 (**21**) gave 37%, and PPh_3 gave 10%.



216



4.4.1.6. Symyx Bidentate Ligand. Symyx Technologies patented in 1999 new bidentate Pd ligands **73** and related complexes useful for C−N and C−C coupling reactions (see C−C cross-coupling reactions).[70] These new bidentate ligands were used in C−N coupling reaction of a large variety of aryl chlorides (with fluoro, cyano, and carboxy substituents) **217** with alkyl and aromatic amines in >90% yield (eq 85).



(85)

4.4.2. Pd–BINAP and Pd–Buchwald/Hartwig Ligands and Related Bidentate Ligands in C–N Bond Formation

4.4.2.1. Hartwig Ligands. The first generation of Hartwig's ligand is represented by the air-stable bidentate 1,1′-bis(diphenylphosphino)ferrocene (DPPF; **2**). The Pd(II)/dppf system was patented in 1997 by Hartwig as a catalyst for the high yield *N*-arylation of pyrrole, carbazole, indole, and

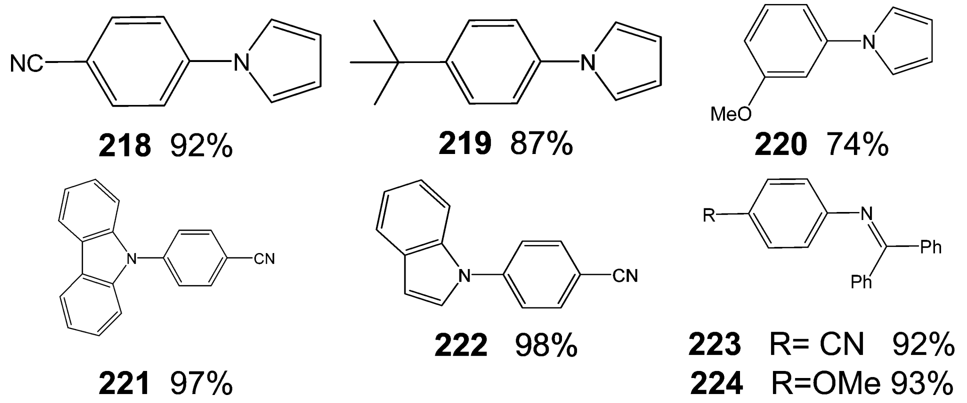


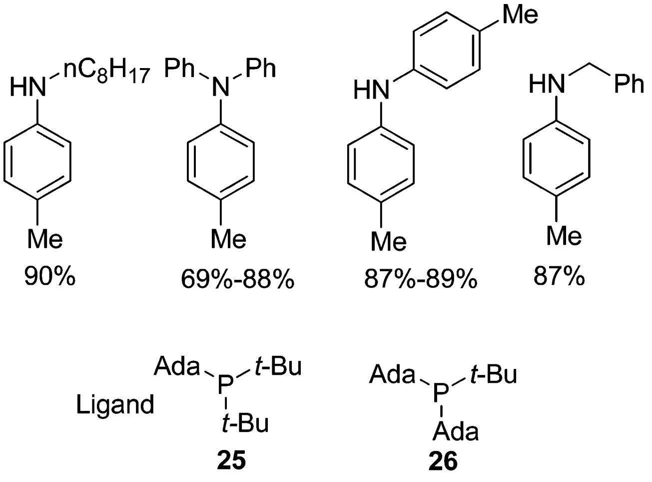
Figure 3. Selected examples using Pd-dppf catalyst.

Table 18. Some Representative Examples Using Pd−$Ph_5FcP(t\text{-}Bu)_2$ 6 Catalyst[a]

Ar−X	amine	product	conditions	yield (%)
PhBr	$HNPh_2$	NPh_3	1 mol % Pd rt, 1 h	99
PhCl			1 mol % Pd 100 °C, 21 h	98
4-MeOPhCl		4-MeOPhN$(Ph)_2$	1 mol % Pd rt to 80 °C	99
2-MePhBr	morpholine	2-MePh-(morpholino)	1 mol % Pd 100 °C, 2 h	40
4-MePhCl		4-MePh-(morpholino)	2 mol % Pd rt to 80 °C	85
4-CNPhCl		4-(CN)Ph-(morpholino)	1 mol % Pd 45 °C, 24 h	82
4-*t*-BuPhBr	HN(*n*-Bu)$_2$	4-*t*-BuPhN(*n*-Bu)$_2$	1 mol % Pd rt to 60 °C	89
4-($MeCO_2$)PhCl	H_2N(*n*-hexyl)	4-($MeCO_2$)PhNH(*n*-hexyl)	2 mol % Pd 4 mol % ligand K_3PO_4, DME 100 °C, 20 h	86

[a] Reaction conditions: $Pd(dba)_2/Ph_5FcP(t\text{-}Bu)_2$ 1/2 mol/mol, t-BuONa 1.5 equiv, toluene.

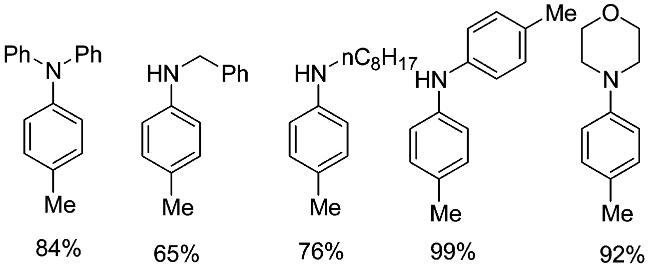
Scheme 17. C−N Coupling Reaction Examples Using Pd Adamantyl Phosphine Catalysts



$HN{=}CPh_2$ with an excess (1.2−1.5 equiv) of substituted (with CN, MeO, or *t*-Bu) aryl bromides[309] and aryl triflates.[310] The preferred bases are Cs_2CO_3 or *t*-BuONa. In the selected examples of Figure 3 (**218**−**224**), good yields are obtained in all cases using the following typical procedure: ArX, azole or imine with ArX/azole = 1.2/1 mol/mol, Cs_2CO_3 1.2 equiv, $Pd(OAc)_2$ 1 mol %, DPPF (**2**) 1.2 mol %, 100 °C, 12 h.

As described before, Hartwig patented new bulky and electron-rich ligands such as $Ph_5FcP(t\text{-}Bu)_2$ (**6**)[46] for C−C and C−N coupling reactions. Selected examples of C−N coupling reactions using Pd−$Ph_5FcP(t\text{-}Bu)_2$ catalyst are presented in Table 18. This procedure tolerates a large variety of organic functions and amines.

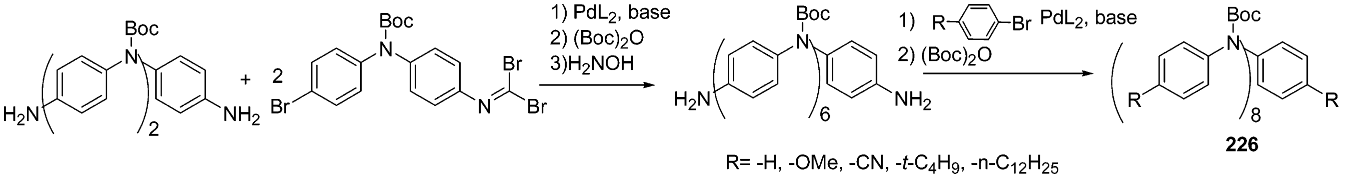
Scheme 18. C−N Coupling Reaction Examples Using Pd Tris(1,1-dimethylpropyl)phosphine 225



Hartwig patented the new adamantyl monophosphines **25**−**26** and related phosphine copmplexes in C−N coupling reactions.[53] Some typical examples are presented in Scheme 17 (Conditions: $Pd(dba)_2$ 1 mol %, ligand 1 mol %, 4-chlorotoluene 1 equiv, amine 1.5 equiv, *t*-BuONa 1.5 equiv, toluene, 80 °C). Similar results are obtained using the two types of adamantyl phosphine or another bulky monophosphine such as tris(1,1-dimethylpropyl)phosphine **255** (Scheme 18) (Conditions: $Pd(dba)_2$ 1 mol %, ligand 1 mol %, 4-chlorotoluene 1 equiv, amine 1.5 equiv, *t*-BuONa 1.5 equiv, toluene, 80 °C).

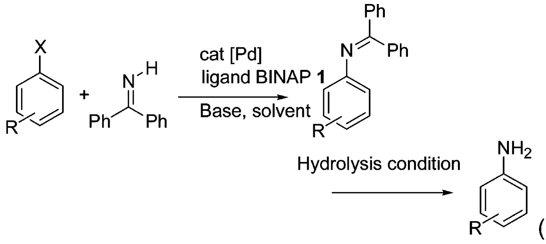
4.4.2.2. Buchwald BINAP Ligand. BINAP (**1**) associated with Pd also constitutes an efficient catalytic system to create

Scheme 19. C−N Coupling Reaction[a]



[a] Reaction Conditions: $Pd_2(dba)_3$ or $Pd(OAc)_2$ 1−6 mol %, BINAP 10 mol %, *t*-BuONa 1 equiv/ArX, THF, reflux.

a C−N bond between aryl halides or triflates and an imine (eq 86).[311,51] This is a good process to obtain free arylamines, after hydrolysis.

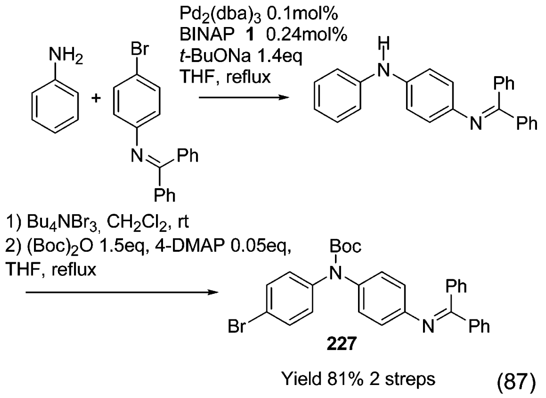


(86)

The mild experimental conditions are compatible with a large range of functional groups. Furthermore, the possible use of aromatic triflates can be of great industrial interest since they come from the very rich phenol or naphthol tree which is quite complementary to the aromatic halide series. For instance, 2-naphthyltriflate gives 85% of the imine by heating in THF at 65 °C during 16 h with $Pd(OAc)_2$ (1 mol %), BINAP (**1**) (1.5 mol %), and Cs_2CO_3 (1.4 equiv). Ester or nitrile functions can be tolerant. Triflates of 3- and 4-hydroxybenzoic acid methyl ester give under similar conditions (the 4-isomer being more reactive) high yields of the corresponding amino benzoate after hydrolysis. 4-Bromo methylbenzoate gives 75% yields of 4-aminobenzoate, and 4-bromo benzonitrile gives 97% of the 4-amino benzonitrile after hydrolysis under similar conditions.

On the other hand, 3-chloropyridine requires the use of a Ni/dppf catalyst: Ni(COD) (25 mol %), dppf (10 mol %), and *t*-BuONa 1.4 equiv in toluene at 100 °C provides more than 80% yield of the 3-aminopyridine.

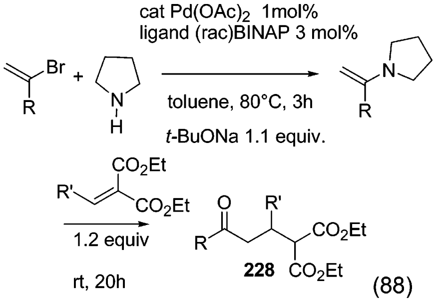
Using the same approach, oligoaniline **226** with low polydispersity has been prepared by Buchwald (Scheme 19).[312] The starting material **227** was prepared by the same methodology (eq 87). The thermal deprotection of *N*-Boc to N−H was realized at 180 °C for 7 h.



(87)

Many other polymers, with various applications (functionalized polyaniline as an organic conducting polymer, components in rechargeable batteries, electromagnetic interference shielding, photolithography, chemical sensors, and anticorrosion coatings), can be prepared using this methodology.

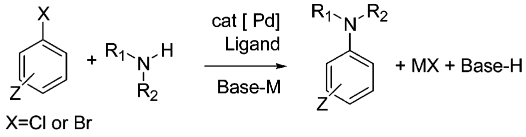
Recently, an elegant synthesis of enamines was described via a C−N coupling reaction with Pd−(rac)BINAP as catalytic system (eq 88).[313] This sp[2] C−Br amination affords



(88)

an interesting route to functionalized building blocs **228**. Other representative examples are given in Table 19.

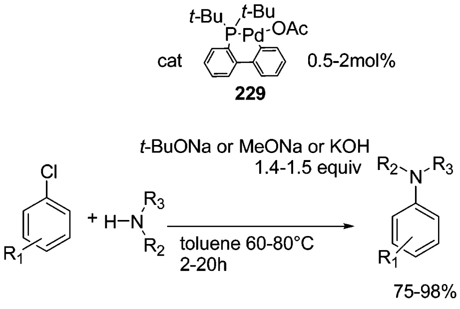
4.4.2.3. Buchwald Me$_2$N−Phos Ligands and other Biphenyl Phosphine Ligands. As discussed before, Buchwald's ligands such as Me-Phos (**40**), NMe$_2$-Phos (**41**), and X-phos (**42**) are very good ligands of Pd to create C−N bonds under mild conditions (eq 89).[321]



(89)

In the case of Me$_2$N-Phos (**41**), in toluene or DME at 25−80 °C, isolated yields are usually >90% for a variety of aryl halides (X = Cl, Br and Z = H, Me, OMe, CO_2Me, CN) and amines (HN(^{n}Bu)$_2$, HN(Me)Ph, morpholine).

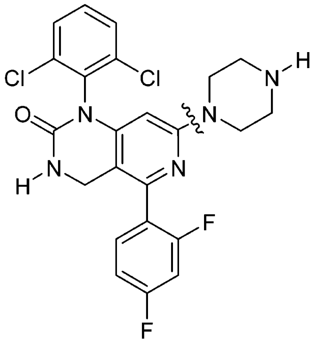
The air- and moisture-stable isolated palladacycle **229** was used in high yield C−N coupling reactions (eq 90).[322] Aryl chlorides work, and a simple base such as KOH can be used.



(90)

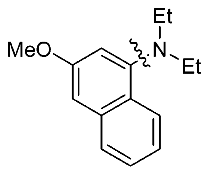
Buchwald described the use of supported dialkylphosphinobiphenyl ligand **230** in C−N and C−C coupling reactions (eq 91).[323]

Table 19. Representative Examples of the Pd/BINAP Catalyst Applications in C−N Bond Formation



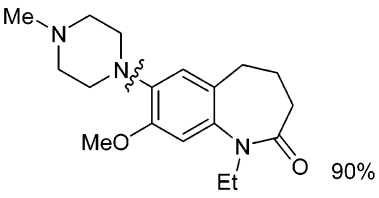
$Pd(OAc)_2$,BINAP,Cs_2CO_3, dioxane, 100°C

P38 kinase inhibiting agents **Ref 314**



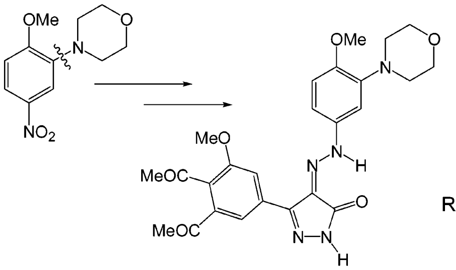
$Pd_2(dba)_3$ 0.5mol%, S-BINAP 1.5mol%,,*t*-BuONa 3.3 equiv, toluene, 16h, 80°C

Fluorescent labels in the non-radioactive detection of biological analytes **Ref 315**



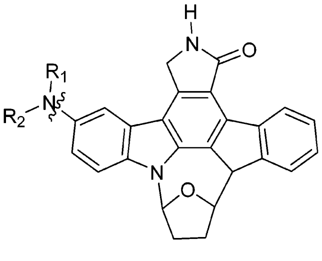
$Pd(OAc)_2$ 10mol%, BINAP 15mol%
Cs_2CO_3 1.4equiv, Toluene, 100°C

New antibacterial agents **Ref 316**

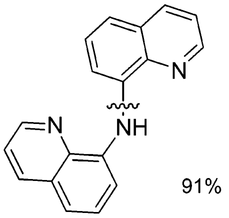


$Pd_2(dba)_3$ 0.5mol%, BINAP 1.5mol%
Cs_2CO_3 1.4equiv, dioxane, 80°C, 6h

Potential treatment of diabetes and Alzheimer **Ref 317**

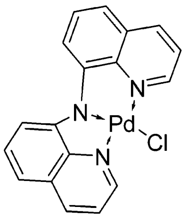


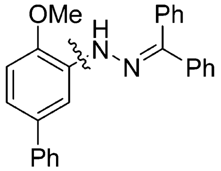
Inhibition of trkA tyrosine kinase activity **Ref 318**



$Pd_2(dba)_3$ 2 mol%
BINAP 4 mol%, *t*-BuONa 1.5 equiv
toluene, 36h, 110°C

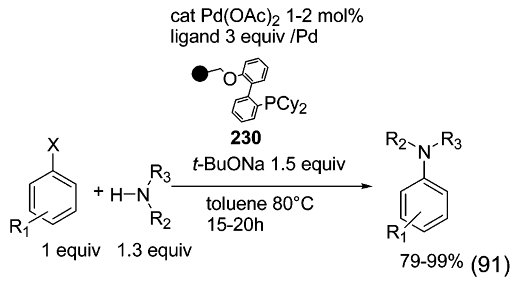
Ligand synthesis for Pd, Pt,Ti,..metals **Ref 319**





$Pd(OAc)_2$
BINAP,*t*-BuONa

Tire intermediates, bifenazate **Ref 320**



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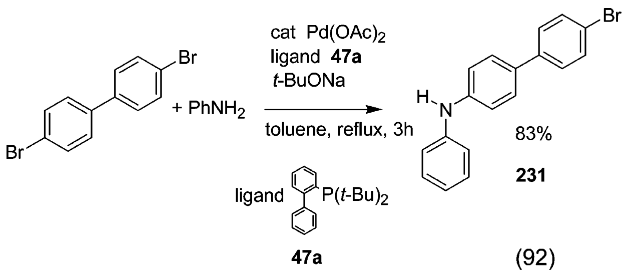

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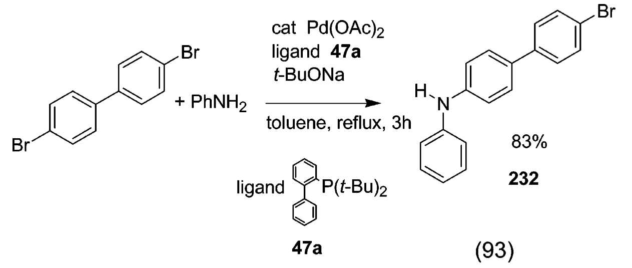


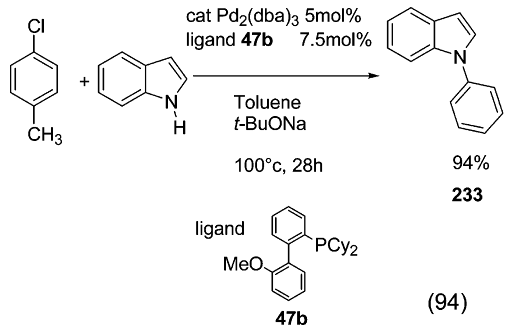
(93)

The bulky and electron-rich ligand di-*tert*-butyl-*o*-biphenylphosphine **47a** is an excellent ligand of Pd(0) in the synthesis of biphenylcarbazol **231** via a double C−N coupling reaction The same ligand was used with Pd(II) to prepare selectively halogenated arylamines (eq 92).[324]

The same ligand **47a** was used to prepare with high selectivity aryl biphenylamine **232** (eq 93).[325]

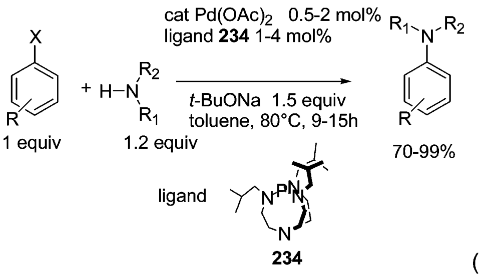
High yields of aryl indole **233** has been observed in the Pd/ligand (bulky and electron-rich **47b**)-catalyzed reaction of indole with aryl chloride (eq 94).[326]

4.4.2.4. Verkade Ligand. Bicyclic triaminophosphine P(*i*-$BuNCH_2CH_2)_3N$ (**234**) is an effective ligand in the Pd-catalyzed amination of aryl halides. The pK_a of this phosphine is approximately 33 in acetonitrile. Its strong basicity



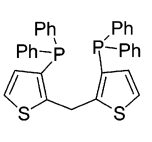
(94)

facilitates the oxidation step in the catalytic cycle. The bulky effect could assist the reductive elimination step. The isolated yields of this amination process are around 70−99% with a range of amines (primary, secondary, aniline, substituted anilines, ...) and aryl halides (eq 95).[327] The high donating effect of the phosphorus atom comes from a transannular bonding between the bridgehead nitrogen and the phosphorus atom.



(95)

4.4.2.5. Pd−Hetero Bidentate Phosphino Ligand. Bis(thiophene) based diphosphine bidentate ligands **235** and the related Pd complex **236**,[328] and new bidentate heteroaryl−aryldiphosphines **237**−**238** have been used for C−C and C−N coupling reactions.[329]



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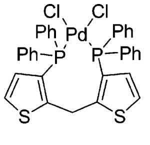

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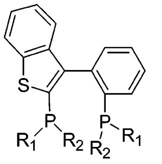

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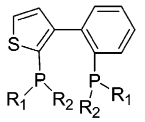
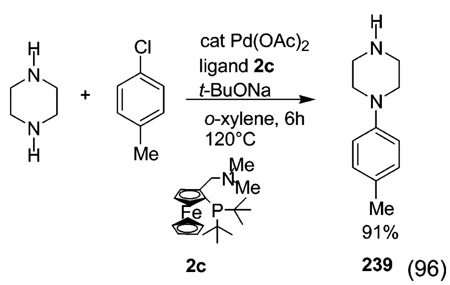


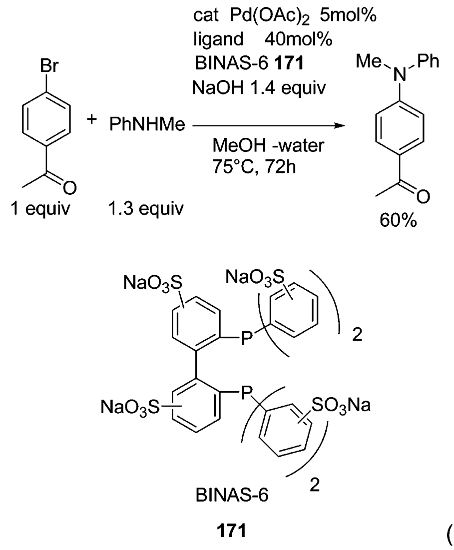
238

4.4.2.6. Tosoh Bidentate Ligand. In 1999 Tosoh patented a new generation of Pd bidentate ligand **2c** useful in highly selective C−N cross-coupling reactions of aryl chloride and piperazine (eq 96).[330] Only monoalkylated piperazine **239** is obtained.



(96)

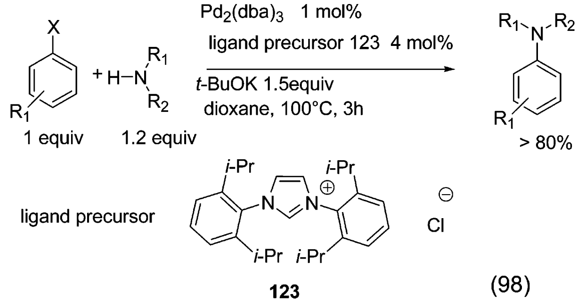
4.4.2.7. Hydrosoluble Bidentate Ligand. Celanese patented the use of Pd hydrosoluble bidentate ligand (BINAS-6 (**171**), TPPTS (**172**)) in C−N coupling reactions (eq 97).[331]



(97)

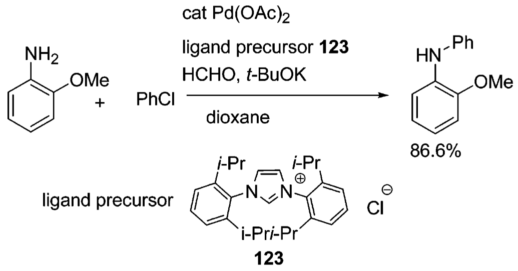
4.4.3. Pd–Carbene Catalytic Systems

As discussed before, carbene ligands are more and more used in new catalytic systems. Nolan's experimental procedure described before gives very good isolated yields of C−N product with a wide range of functions in the aromatic ring (eq 98).[90] Dialkylamines and cycloalkylamines react as well. Unlike the cases of C−C coupling reactions, aryl trifates give poorer results than the corresponding aryl halides.



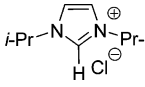
(98)

Diarylamines can be obtained via a Pd(II)-catalyzed cross-coupling reaction between an amine and an aryl chloride in the presence of imidazolidium salt **123** (Mitsui Chemical Co. patent). The carbene ligand was prepared in situ (eq 99).[332] This process provides an effective and cheap route to diarylamines.



(99)

Other types of carbene precursors such as difluoroimidazoline have also been patented (eq 120).[333] Buchwald reports the use of metallo (Ni, Pd, or Pt) carbene (in situ generation from **123** or **240**) catalysts for C−N coupling reactions to produce *N*-aryl amines and *N*-aryl amides.[334]



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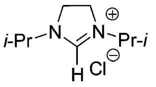
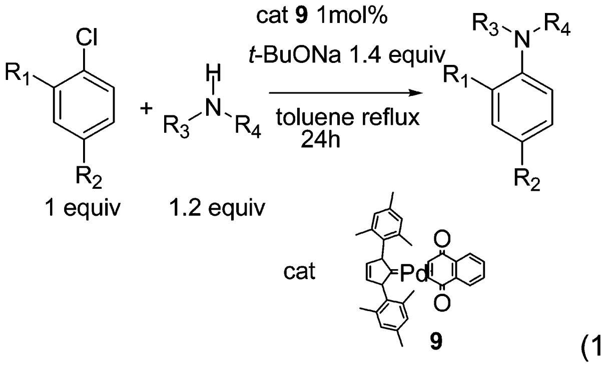


240

An electron-acceptor group on the aryl chloride (for example: 2- or 4-chloronitrobenzene) and an electron-donor group on the amine (for example: 4-methoxy aniline) are necessary to obtain good yields. Moderate yields were observed using morpholine, indole, and alkyl amines as nucleophile.

As presented before, Umicore patented new metallocarbene complexes (Pd, Ni, Pt) **9**−**15** which give moderate to good yields in the C−N bond formation when aryl chlorides (bearing Me, CO_2Et, CN, or CF_3 substituents) and simple amines (aniline, butylamine) are the starting materials (eq 100 and Table 20).[335]

Table 20. C−N Coupling Reaction Results Using Umicore's Carbene Catalysts 9[a]



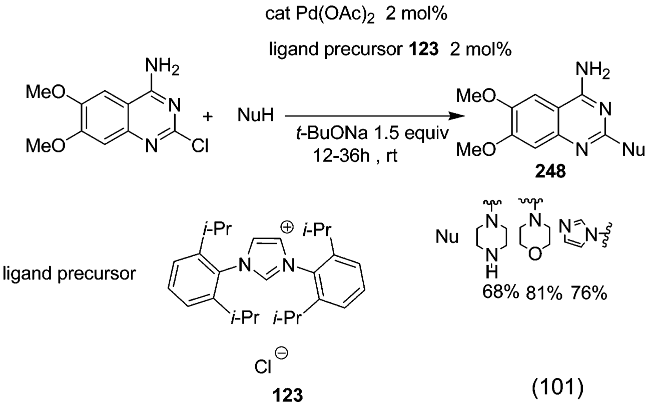
(100)

final compound	R_1	R_2	R_3	R_4	conversion (%)	yield (%)
241	H	COMe	Ph	H	93	81
242	H	H	c-(C_2H_5)		73	69
243	H	Me	Ph	Me	77	74
244	H	OMe	mesityl	H	64	62
245	H	CF_3	Bu	Bu	84	78
246	CN	H	Ph	H	100	89

[a] Reaction conditions: 1 mol % 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene-1,4-naphthoquinone **13**, ArCl 1 equiv, amine 1.2 equiv, *t*-BuONa 1.4 equiv, toluene reflux, 24 h.

Bayer patented the synthesis of new immobilized Pd−carbene **247** complexes as described in Scheme 20.[336] The support is a copolymer of aminoethylstyrene and divinylbenzene. These heterogeneous catalysts were used in the C−N coupling reaction between 4-bromobenzonitrile and aniline (*t*BuONa, 120 °C, xylene). A 70% yield of the corresponding aniline was obtained when Pd (2 mol %) was used.

In the same area, a convergent route to the antihypertension drug iodoazidoaryl prazozin **248** (eq 101) involving a Pd-carbene-catalyzed C−N coupling reaction between acylated piperazine and 2-chloroquinazoline has been published.[337]



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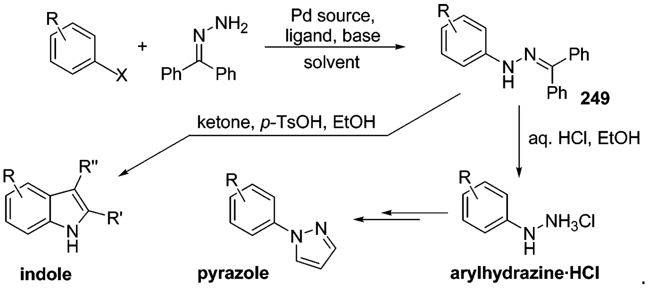
4.4.4. Application of the Pd-Catalyzed C−N Bond Formation to the Synthesis of Arylhydrazines

Arylhydrazines **249** are key industrial intermediates to pyrazoles and, most significantly, to indoles through the Fischer synthesis. They are typically produced by Sn(II) or sulfite reduction of diazonium salts, but these are low yielding transformations that generate large volumes of harmful wastes. Pd-catalyzed hydrazonation or aryl halides followed by hydrolysis can be an excellent industrial alternative, developed by Buchwald and Rhodia (Scheme 21).[4]

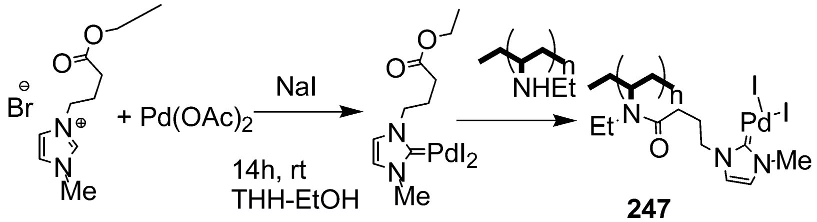
Scheme 21. Pd-Catalyzed Hydrazonation, a Route to Pyrazoles and Indoles

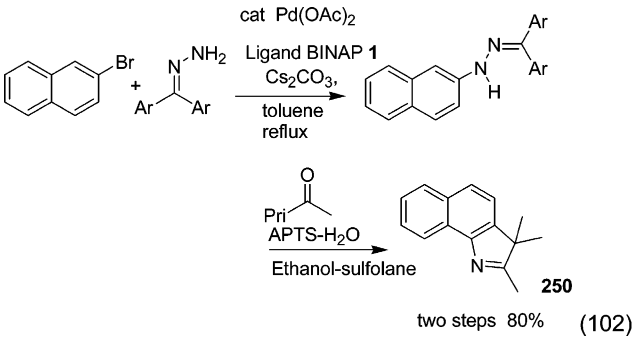


Fuji Photo Film Co. patented the synthesis of benzindolenine **250** by the reaction between diaryl hydrazone and halonaphthalene in the presence of a Pd catalyst such as $Pd(OAc)_2$−BINAP **1**.[338] The resulting naphthylhydrazine hydrazone was reacted with ketone $R_2R_3CHCOR_1$ in the presence of acid to yield the desired benzindolenine (eq 102). This process does not use naphthylhydrazines, which are suspected to be explosive and have a cancer-causing effect.

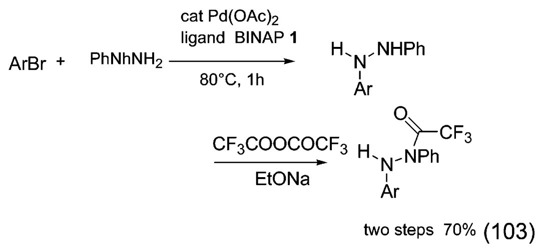
In 1998, Buchwald patented the arylation of hydrazone, hydroxylamine, and oxime using $Pd(OAc)_2$−BINAP **1** as

Scheme 20. Bayer's Supported Metallocarbene

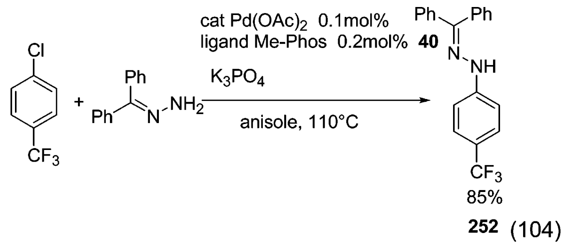




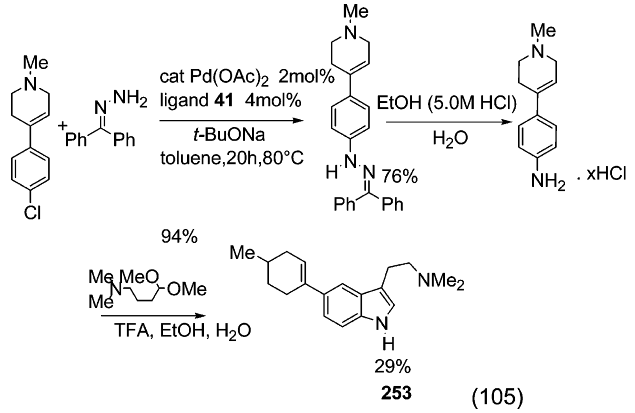
catalytic system in the presence of *t*-BuONa as base (eq 103).[339] Various arylhydrazones have similarly been produced via a highly efficient Pd-catalyzed cross-coupling reaction between functionalized aryl halides and benzophenone hydrazone, using Buchwald's ligands such as Me-Phos (**40**) or bidentate Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; **251**). Rhodia developed an economical process for this reaction; studies to scale-up this reaction led to mild conditions cheap conditions. Very mild experimental conditions using an inexpensive base such ground NaOH and less than 0.05 mol % Pd in a nonaromatic and safe solvent such as *tert*-amyl alcohol were patented and scaled up by Rhodia (Scheme 22).[340]



Different aspects of these reactions have been investigated in order to provide a safe, scalable, and cost efficient process. Very good results were obtained in *tert*-amyl alcohol using ground NaOH or, better, a ground NaOH/*tert*-amyl alcohol paste. Toluene and xylene are not good solvents. In the case of *o*-bromochlorobenzene, no coupling occurred at the chloro position. Moreover, aryl-triflates are totally unreactive. The hydrazones were then hydrolyzed at room temperature (HCl, water−EtOH) to give the corresponding hydrazine salts in quasi quantitative yield. This approach was applied to the preparation of trifluoromethylphenyl hydrazines **252**, which are important pharmaceutical and agrochemical intermediates (eq 104).



Rhodia patented the synthesis of functionalized indole derivatives via the strategy described above (eq 105).[341] The final indole derivative **253** is useful in the treatment of migraines.[342]



4.4.5. Other Applications of the Pd-Catalyzed C–N Bond Formation to Important Classes of Products

Table 21 summarizes some other applications of the Pd-catalyzed C−N bond formation. The high flexibility of this C−N coupling reaction can be illustrated by the preparation of a class of new antiinflammatory drugs shown in Scheme 23.[349]

4.5. Cu Catalysis: A Promising Technology

The Ullmann biaryl condensations between arylamines and aryl halides and the Goldberg condensation between aryl amide and aryl halides were discovered at the beginning of last century. Since Cu has a strong advantage in terms of cost and toxicity compared to other traditional metals (Pd, Rd, Ru, Ni, ...), during the last 10 years, extensive work has been done to make these reactions safer and more efficient (Cu loading) and to widen their scope. In the first part below, we describe the progress made these few last years on the catalytic system, and in the second part, we will try to draw

Scheme 22. Route to Functionalized Phenyl Hydrazines

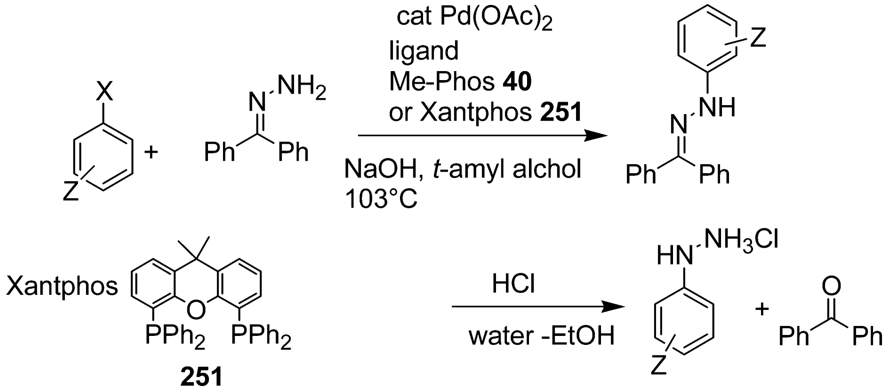


Table 21. Miscellaneous Applications of the Pd Catalyzed C−N Bond Formation from the Patent Literature

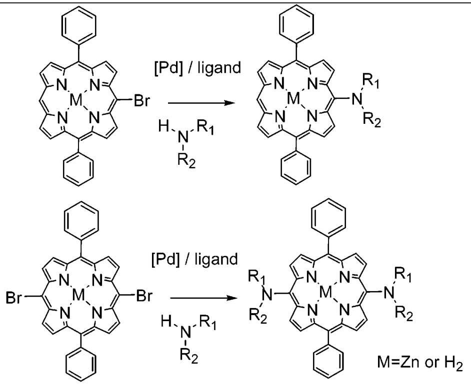
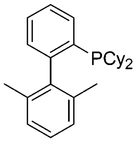
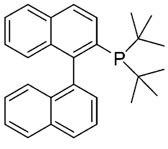
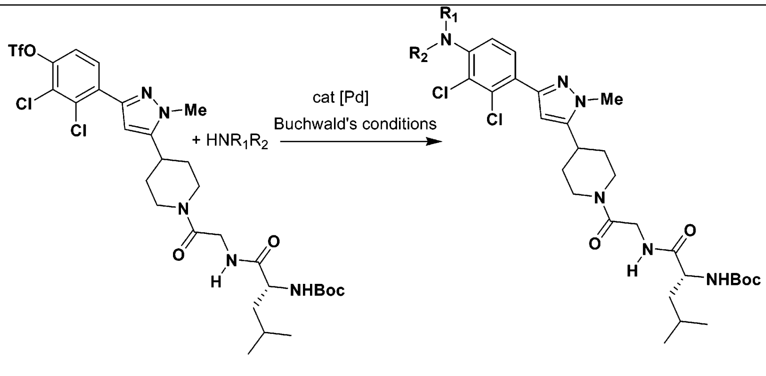
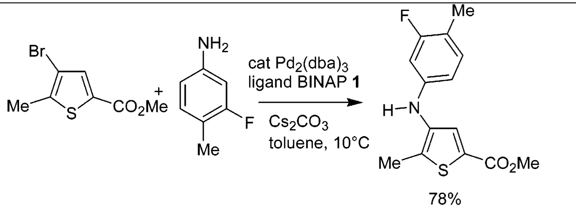
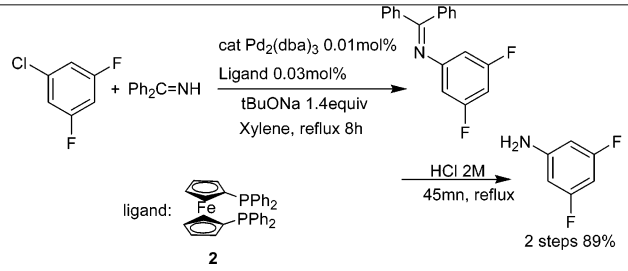
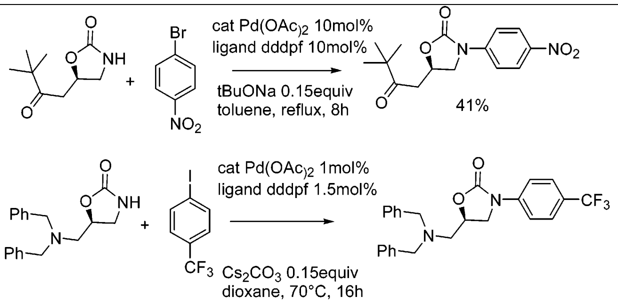
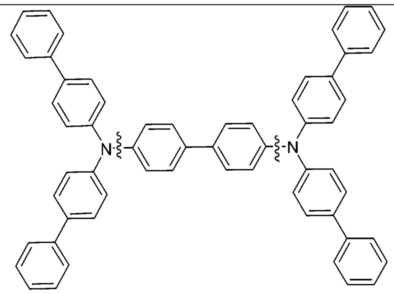
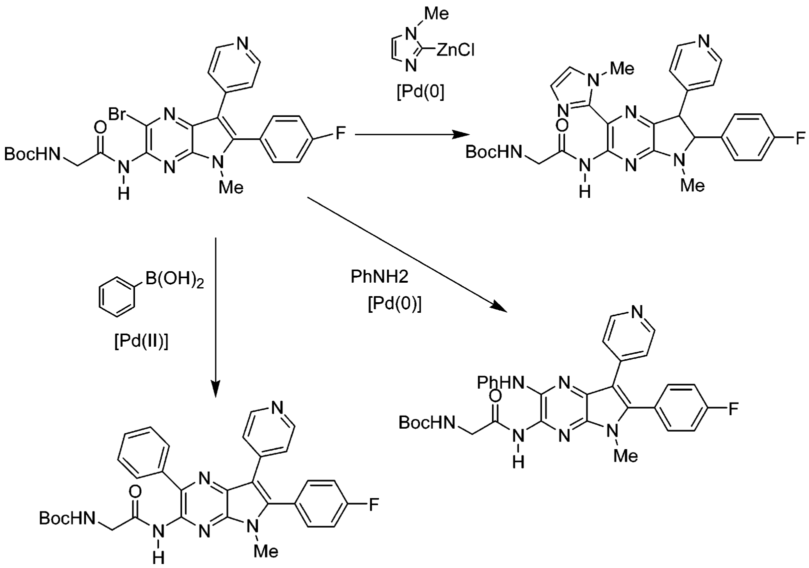
Reaction / *Application*	Reference
 *Conditions: Pd(OAc)$_2$ (5mol%), ligand (7.5mol%), /tBuONa or Cs$_2$CO$_3$/ toluene or THF; 48h ,80°C* *R1=Ph, R_2=H* *ligand = BINAP* **1** *R1=4-MeO-Ph, R_2=H* } *R1=nBu; R_2=H* } ligand= **254- 255** HNR$_1$R$_2$= morpholine Yield; 60-90%  **254**  **255**	343
 *Inhibitors of Interleukin-2*	344
 *New inhibitors of prostheses, especially trypsin-like serine prostheses*	345

Table 21 (Continued)

Reaction / *Application*	Reference
 *Protein kinase inhibitory activity*	346
 *Antimicrobial agent resistant strains of Gram positive bacteria.*	347
 *Charge transporting materials for electrophotog. photoreceptors and org. electroluminescence devices.*	348

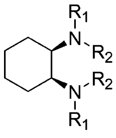
Scheme 23. Mixed Miyaura−Suzuki, Hartwig−Buchwald, and Neghishi Technologies in Multistep Syntheses



a Cu−ligand−reaction−application matrix, which could help the chemist in making the best choice of catalyst and conditions.

4.5.1. Cu–Diamine Ligand

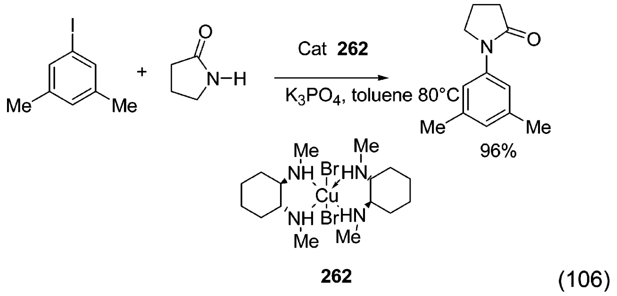
In 2002, Buchwald patented the use of diamines **256**−**261** as ligand of Cu salts (Cu(0), Cu(I), or Cu(II)) to prepare in situ efficient catalysts for the C−N bond formation. When aryl iodide is the starting material, a broad range of primary amides, amines, and azoles (pyrrole, indole, ...) react under mild conditions.[350] The following ligands are patented:



R_1=R_2=H *cis* **256**
R1=R2=H *trans* **257**
mixture *cis* + *trans* **258**
R_1 =Me, R_2=H *cis* **259**
R_2=Me, R_2=H *trans* **260**
R_1= Tol, R_2=H *mixture cis* + *trans* **261**

When using the standard conditions (CuI (1 mol %), rac *trans*-cyclohexyldiamine (10 mol %), Ar−I (1.0 equiv), K_3PO_4 or Cs_2CO_3, dioxane 23 h), lactames, benzamides or pyrroles, pyrazoles, and indoles react with iodobenzenes and iodothiophene bearing methoxy, amino, or alkyl groups in excellent yields. N-Boc hydrazine works well when using CuI−phenanthroline as the catalytic system. 4-Iodoaniline is an interesting case since the iodo reacts selectively with the amide (no NH_2 interference).

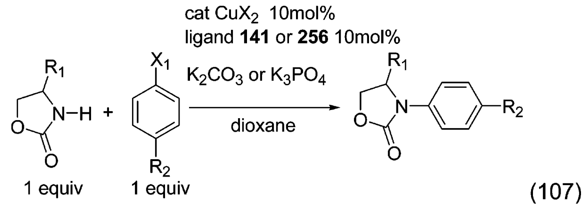
Preformation of a organometallic complex such as bis-(*trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine)Cu(II) bromide **262** cancels the induction period otherwise observed (eq 106).



(106)

Aryl halide can give a high yield of the corresponding arylcyanide with the same catalytic system, thus avoiding the use of expensive Pd-based catalyst or of stoichiometric amounts of Cu or Ni cyanides (difficult recycling, harmful wastes). This method is applicable to a large range of aryl halides and hetero halides, aryl heteroaryl halides, vinyl halides, or sulfonates.

N-Aryl oxazolidinones were prepared in high yields via the Cu-catalyzed cross-coupling reaction between oxazolidinones and aryl halides (oxazolidinone 1 equiv, ArX 1 equiv, Cu 0.1 equiv, ligand 0.1 equiv, K_2CO_3 or K_3PO_4).[351] The best ligands are $MeNHCH_2CH_2NHMe$ **141** and 1,2-diaminocyclohexane **256** (eq 107).

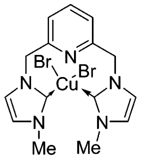


(107)

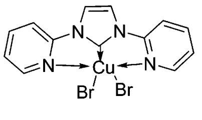
4.5.2. Cu–Carbene Ligand

The use of Cu−carbene catalytic systems is economically and industrially attractive. The low cost of Cu salts associated with the specific ligand properties of carbene contribute to the interest. As mentioned before, one of the advantages of carbene ligands is their ability to stabilize different oxidation states of the same metal. On the other hand, the Cu atom has close energetic levels which, coupled with the strong σ-donor property of the carbene, can contribute to stabilize organometallic species during the catalytic cycle. Some typical applications are given below.

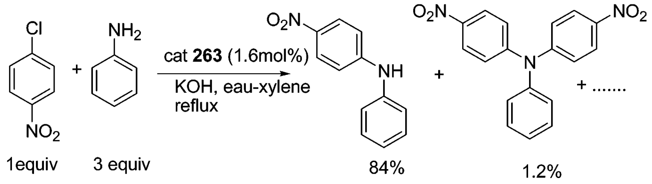
Nitrodiphenylamines were obtained via a Cu/bis-carbene **263** and Cu/mono-carbene **264** catalysis coupling reaction. This catalyst is prepared by treating the corresponding bisimidazolium salt with *t*BuOK and $CuBr_2$ (eq 108).[352]



263

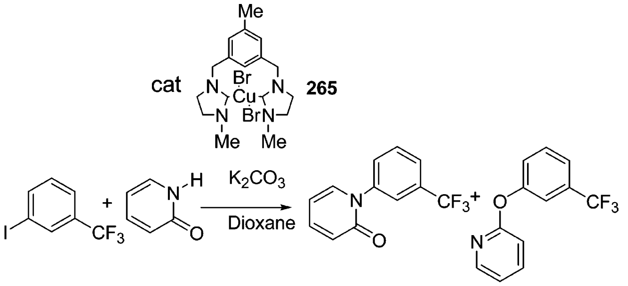


264



(108)

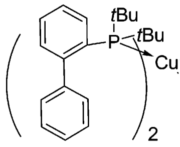
Bayer recently patented a new type of Cu−carbene complex **265** for the C−N and C−O bond formation (eq 109).[353]



(109)

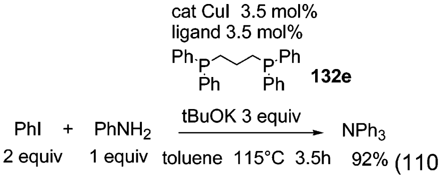
4.5.3. Cu–Phosphine Ligand

Nitrodiphenylamines were prepared in very good isolated yields by the reaction of nitrohalobenzenes with anilines in the presence of a Cu(II) complex **266** with bulky, electron-rich biphenylphosphine.[354]



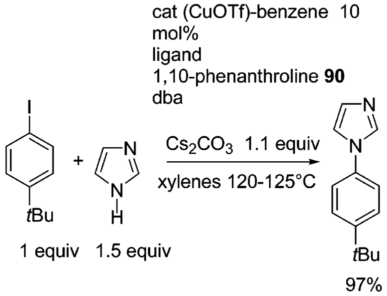
266

A rapid amination process of iodobenzene using a Cu/bis-phosphine such as 1,3-bis(diphenylphosphino)propane **132e** has been patented in 2003 (eq 110).[355]

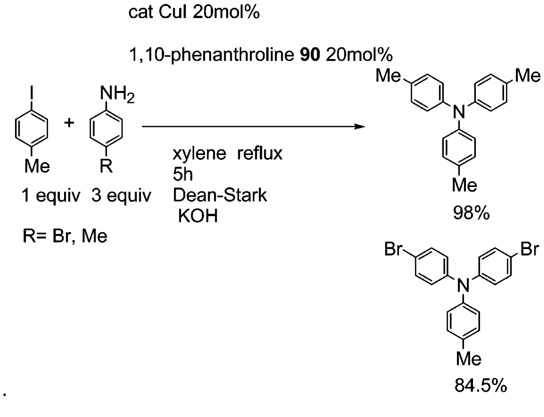

(110)

4.5.4. Cu–Phenanthroline, Cu–Hydroxyquinoline, and Related Ligands

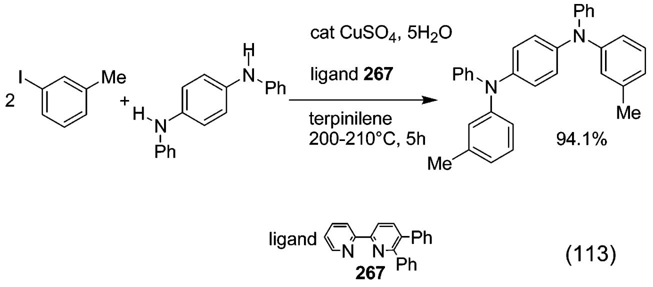
Buchwald published the new combination of a Cu(I) salt such as Cu(OTf)·benzene and a mixture of ligand 1,10-phenanthroline **90** and *trans*,*trans*-dibenzylideneacetone (dba) in a C−N coupling reaction between imidazole and aryl bromides (eq 111).[356] The products, *N*-arylimidazoles, were isolated in high yields. A large range of *N*-arylimidazoles were prepared, and in each case, the presence of the two ligands proved to be necessary.


(111)

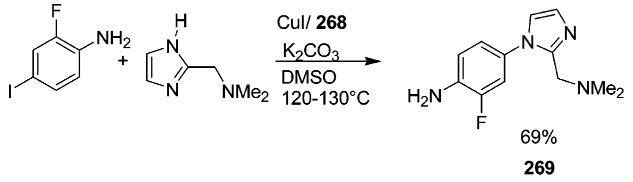
Cu(I)/1,10-phenanthroline has been used as the catalyst of the reaction of anilines with haloaromatics to obtain various triarylamines (eq 112).[357]


(112)

Functionalized bipyridines **267** as ligands of Cu salts have been described in the Ullmann coupling reaction at 200−210 °C (eq 113).[358]


(113)

8-Hydroxyquinoline **268** and analogues were claimed in the Ullmann coupling reaction of anilines and azoles (eq 114).[359] The coupling products **269** are intermediates of factor Xa inhibitors.

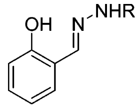

(114)

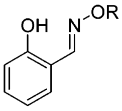
N-Arylation of imidazole derivatives by aryl halides was efficiently performed using the quasi-soluble catalytic system 8-hydroxyquinoline/CuI and $((Et_4)N)_2CO_3$ as organo soluble base.[360]

4.5.5. Cu–Bis Imine and Related Ligands

Powerful Cu ligands such as **29**−**33** have been patented by Rhodia and the Cristau−Taillefer group for the high yield *N*-arylation and *N*-vinylation of various azoles (pyrrole, indole, imidazole, triazole, ...) and amides.[56,361] Some representative examples are given in Scheme 24.

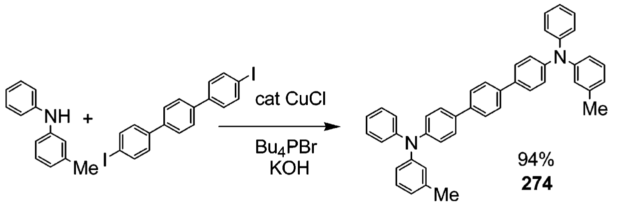
Salzone (**270**), Me-Salzone (**271**), Salox (**272**), and Me-Salox (**273**) are other examples of good ligands.


R=H **270**
R=Me **271**


R=H **272**
R=Me **273**

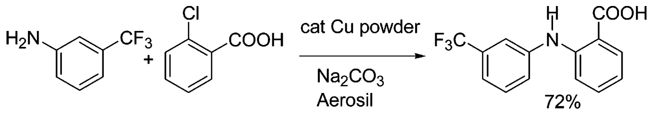
4.5.6. Cu–Ammonium Salt System

Sankio Chemicals patented the low cost and scalable synthesis of polyaryl diamines **274** using KOH, CuCl (catalyst), and Bu_4PBr (eq 115).[362]


(115)

4.5.7. Cu Powder

Cu powder as catalyst was used in a C−N coupling reaction to prepare efficiently flufenamic acid by reaction of *o*-chlorobenzoic acid with 3-trifluoromethylaniline in the presence of Na_2CO_3 and a soluble wetting agent such as aerosil (eq 116).[363]


(116)

4.5.8. Sources of Cu

Compared to the case of Pd catalysis, the low complexity and cost of the ligand (amines, bis amines, quinolines, pyridines, and now carbenes can be used), as well as the low cost of Cu and salts, make this catalysis very attractive from an industrial point of view. Furthermore, Cu sources

Scheme 24. C−N Representative Examples Using the Cristau−Taillefer Ligand

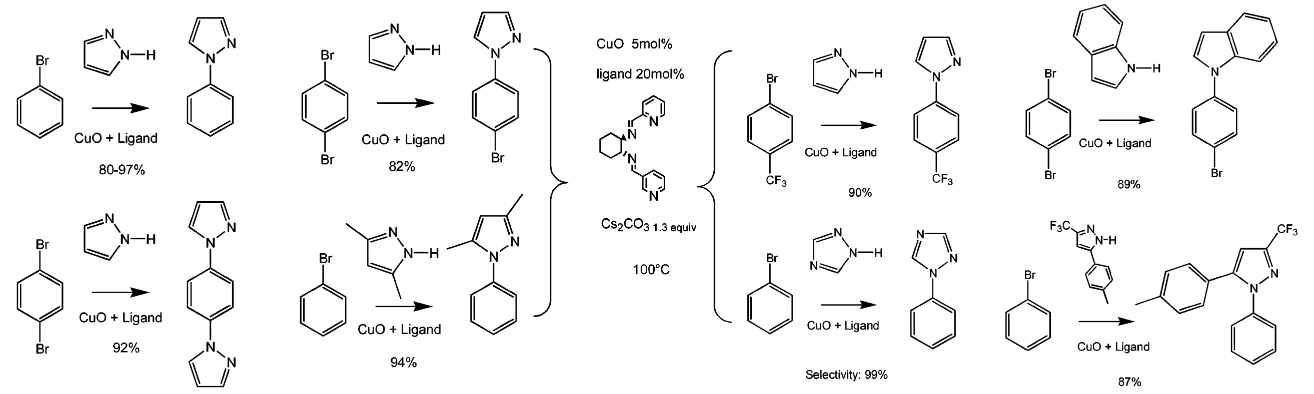
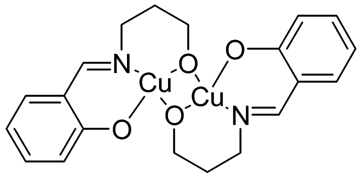


Table 22. Source of Cu Matrix

Cu species	ref	Cu species	ref
CuCl	364	Cu catalyst in a solvent of ionization potential of 8.0−9.0 eV sucah as terpene	377
CuCl + Cu powder	365	CuCl + PBu_3	362
CuCl + $MgCl_2$	366	CuI	379
CuI + di(aminomethyl)cyclohexane	367	CuI + anthranilic acid	380
CuI + Cu	368	CuBr	381
Cu metal	369	Cu + iodine + 1,3-dimethyl-2-imidazolidinone	382
powdered Cu in nitrobenzene	370	CuO	383
Cu_2O	371	CuO + phosphonium	384
CuO−DMF	372	CuO−NMP	385
$CuSO_4{\cdot}5H_2O$ + glucose	373	$CuSO_4$ + pyridine	386
$CuSO_4$−$PhNMe_2$	374	$CuNO_3$ + bis(1,10-phenanthroline)	387
CuCl + 1,10-phenanthroline	375, 378	CuCN + polyethers	388
	376	Cu propanetricarboxylate	376

can be of great diversity, widening the industrial scope of the reaction. Some examples are given in Table 22.[389]

5. Metal Removal Processes

Residual metals need to be removed from the reaction mixture, as they can interfere with subsequent transformations and they can be a problem for the shelf life and use of the final product and for safety and environmental reasons.[390] The removal of organometallic species has now become a critical step for all new development strategies involving metal complexes catalysis, not only in pharmaceutical but also in agrochemical, polymer, and material science, applications.

Homogeneous metal catalysis frequently requires the removal of metal transition species such as Pd, Pt, Rh, Ni, Cu, ... from the final product. Heterogeneous metal catalysts can often be removed by a simple filtration step, except when leaching metal from the catalytic surface to the medium occurs.

Current classical processes for removing metal complexes from the reaction medium involve distillation, crystallization, and/or extraction steps. These well-known industrial-scale techniques for metal removal are not always suitable, and sometimes it is necessary to use absorbents at least as a complementary solution to remove the last traces. The choice of absorbent and the knowledge of hydrodynamic parameters are crucial for a successful development. Today, a large variety of absorbents such as activated carbon, alumina, clay, and functionalized chelating resins[391] are available at a laboratory scale or a multi-kilo scale. For example, Acticarbon (Ceca-Atofina), Waterlink and Scavnet (Engelhard), Smopex (Johnson Matthey), Diaion (Mitsubishi), Dowex (Dow Chemical), Deloxan (Degussa), Silicycle (Sigma-Aldrich-Silicycle), Fibercat (BB), Lewatit (Bayer), Octolig (Meter-General Inc.), QuadraPureTU (Avecia), and many other adsorbents have been developed but only a few of them are available on a large scale. The use of specific nanofiltration membranes was developed by Livingston to remove very efficiently Pd and Rh species from the catalysis medium.[392] Some metals, such as Pb(II), Cd(II), and Cr(VI) in aqueous solution, can be eliminated via a bioadsorption technology using bacteria and activated carbon.[393] Other described approaches consist of using homogeneous recoverable organometallic catalysis based on ligated organometallic complexes with ligand grafted on a specific polymer backbone. Polium Technologie Inc. developed and patented this strategy (Rexalyst).[394] These catalytic systems can be used in normal and inverted thermomorphic systems, depending on the structure of the initial polymers. This technology was well demonstrated for Heck−Mizokori and Miyaura−Suzuki cross-coupling reactions. Examples of other patented metal removal techniques are given in Table 23.

Recently, Sumitomo Chemical Company patented an interesting and simple process to remove Pd complexes from

Table 23. Representative Patented Metal Removal Technologies

metal	technologies	ref (selection)
Ru, Co, Pd, ...	phosphine treatment	395
	hydrosoluble phosphine treatment	396
Ru, Rh, Os, ...	treatment with specific organic derivatives: oximes, diamines, pyridine, thiol, ...	397
Co, Rh, Ru, Pd, ... metal carbonyl	treatment with functionalized copolymers, polymers, or resins: vinyl, thiol, ...	398
Pd, Ir, Pt, Rh, ...	thermal treatment at 1000−1500 °C → oxides → phosphates or other compounds	399
all metals	electrochemical treatment	400
Pd, Rh, ...	polyesters treatments	401
Pd	treatment with ammonium salts	402
Pd	zolithe treatment	402

an organic medium.[403] The process consists of reacting the solution containing a Pd complex with a layered clay compound or a zeolite having a pore diameter of 0.6−2 nm at room temperature. In the examples, the final Pd content in the concentrated solution was less than 5 ppb, and the percentage of Pd removal was more than 99.9%.

Merck presented a microtube screening approach to select rapidly the more pertinent metal scavengers in Miyaura−Suzuki and hydrogenation processes.[2]

Rhodia has developed a methodology, based on thermodynamic data (isotherm absorption) and transfer data, to set up a metal removal automated process allowing the screening of a large range of commercially available scavengers under different conditions (temperature, solvent, dilution, ...) In many examples of catalytic aromatic bond formation, a content of less than 0.5 ppm of various metals [Pd, Cu, Zn, Co, Fe, Ni] has been reached in a short period of time.[1]

6. Conclusions and Outlook

Catalytic coupling technologies are expanding as a result of high levels of performance (scope of application, selectivity, soft operating conditions, high catalyst turnovers, application to convergent multistep syntheses, etc.), and they offer increasingly attractive industrial prospects in terms of sustainable development. This was made possible by various essential research projects, which allowed a better understanding of implemented catalytic processes and, therefore, a better control of the catalysis. Thus, we note, as a consequence, more and more industrial applications of the catalyzed C−C and C−N aromatic coupling reactions, for both pharmaceutical and agrochemical needs, and electronic or optical materials.

There has been outstanding progress in connection with catalytic systems in the creation of C−C and C−N aromatic ligands, since the development, fairly recently, of sterically bulky and high electron density ligands, coupled with a wide range of transition metals. Consequently, C−C (Miyaura−Suzuki) and C−N (Buchwald−Hartwig) coupling technologies have constantly been improved and allow a partial tackling of reactivity and selectivity problems. Recent ligands such as Andergo or Bertrand carbenes stabilize catalytic species at variable oxidation degrees and may be considered as relatively universal.

But the best compromise between metal/ligand/base/solvent still strongly depends on the nature of the involved substrates, and its identification sometimes requires long screening times, which may be reduced via automation. Another difficulty obviously lies in the use of metal. The economic success of a coupling reaction will then depend either on metal (and sometimes ligand) recycling and/or catalyst performance. This is a common feature to any organometallic catalyst. Heterogeneous or polymeric catalysts may be an answer, but sometimes they need long development surveys, which are often recommended and conducted by specialized companies. In any case, the removal of any traces of metal will require a particular evaluation methodology of scavengers, which can also be automated.

Direct activation of C−H bond, which does not require the use of “relay species” (B, Si, Mg, Zn, ... derivatives), and creation of C−C and C−N bonds via the oxidative processes C−H + H−C and C−H + H−N remain future major challenges. Another challenge consists of elaborating new efficient organometallic catalysis based on cheap metals such as Cu, Fe, Co, ... and more universal ligands such as carbenes.

To conclude, Ullmann and Goldberg had possibly never imagined that their pioneering research would arouse, more than a century after their publications, so much interest in both the industrial and academic worlds. Despite many views, Organic Chemistry, far from being a mature science, demonstrates in this example that it can reinvent itself and adapt to new needs of our Society.

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