

Department Chemie der Technische Universität München

# C-C Coupling Reactions Catalyzed by Supported Palladium in Liquid Phase

SAEEDA SHAHID SOOMRO

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Vorsitzender: Univ.-Prof. Dr. Michael Schuster

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“By three methods we may learn wisdom: First, by reflection,  
which is noblest; Second, by imitation, which is easiest; and  
Third, by experience, which is the bitterest.”

– Confucius

“All things are difficult before they are easy.”

– My father

*to Shahid*

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für die hervorragende Betreuung der Arbeit,  
für das von Anfang an entgegengebrachte Vertrauen,  
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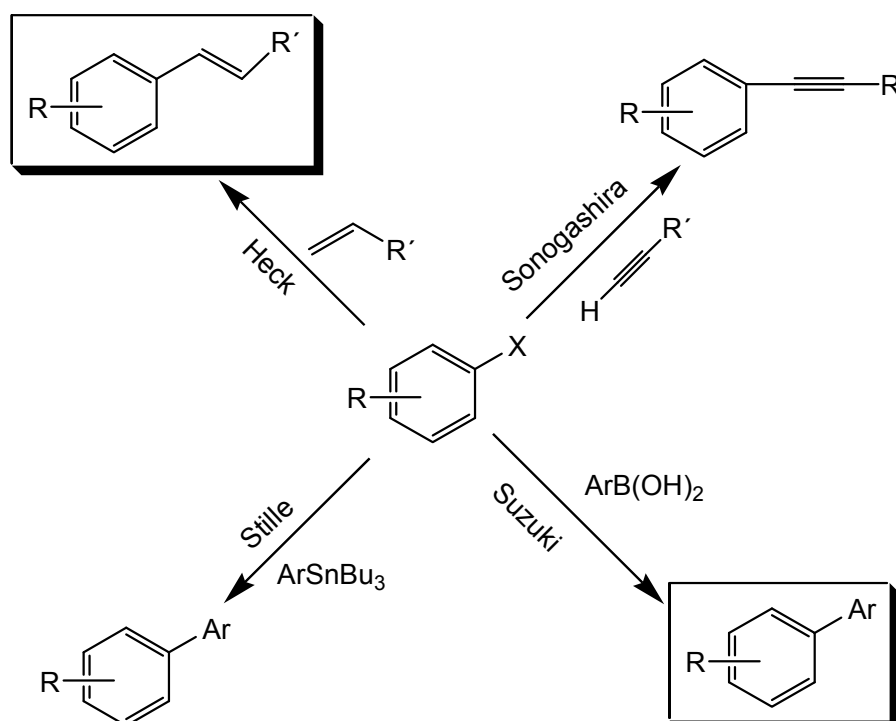
**List of abbreviations**

AAS	atomic absorption spectroscopy
Ar	aryl group
BA	butyl acrylate
BQ	benzoquinone
Co-cat.	co-catalyst
Conv.	conversion (of aryl halide)
DBA	dibenzyl amine
EA	ethyl acetate
EC	ethyl cinnamate
EPR	electron paramagnet resonance
equiv.	equivalents
GC	gas chromatography
HPA	heteropoly acid
MA	methyl acrylate
Me	methyl group
MO <sub>x</sub>	metal oxide
NaY	sodium exchanged zeolite Y
NMP	1-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance (spectroscopy)
2-OH-Pyr	2-hydroxy pyridine
PEG	polyethylene glycol
Ph	phenyl group
ppb	parts per billion (10 <sup>-7</sup> %)
ppm	parts per million (10 <sup>-4</sup> %)
r.t	room temperature
t	reaction time
T	reaction temperature
TEM	Transmission Electron Microscopy
TBAB	tetra- <i>n</i> -butylamonium bromide
TOF	turnover frequency (mol <sub>converted reactants</sub> /(mol <sub>catalys</sub> *h))
TON	turnover number (mol <sub>converted reactants</sub> /(mol <sub>catalys</sub> ))
X	leaving group (halide)

**Supported Palladium Catalysts  
for C-C Coupling Reactions:  
*Problems and Perspectives***

## 1.1 General Introduction

Aromatic carbon-carbon bond coupling reactions have recently emerged as exceedingly important methodologies for the preparation of complex organic molecules such as pharmaceuticals and other fine chemicals. Palladium catalysts offer the most promising systems for these transformations since they feature tolerance towards a variety of functional groups and, thus, offer an abundance of possibilities. Of the many commonly used coupling reactions such as Heck, Suzuki, Sonogashira and Stille reactions, perhaps the two most important are the Heck and Suzuki reactions (Scheme 1.1). The Heck and Suzuki couplings are fascinating reactions from a catalysis science perspective. An enormous number of new Pd complexes, organometallic compounds, and supported Pd catalysts for these reactions have been reported in the last 10 years. Virtually all forms of palladium can be used as pre-catalysts for the simpler reactions (e.g., activation of aryl iodides), yet specifically designed catalysts are required for activation of bulky or electronically unactivated substrates.



**Scheme 1.1** Palladium catalyzed C-C coupling reactions of aryl halides.

Additionally, in many cases, extremely small amounts of palladium (ppm or ppb levels) are sufficient resulting in very high turnover frequencies, whereas in others, higher pre-catalyst loadings (up to 10%) are required to obtain sufficient product yields.

The quest for commercially viable, highly active, recoverable, and reusable palladium catalysts for Heck and Suzuki reactions is still ongoing despite the vast number of attempts and strategies used to date. Most of the C-C coupling reactions described in the open as well as in the patent literature are carried out with homogeneous Pd catalysts, either with or without organic ligands. This is mainly because homogeneous catalysts display high activity and are better defined and understood as compared to heterogeneous palladium catalysts.

**Table 1.1** Strong and weak points of homogeneous and heterogeneous palladium catalysts.

	<b>Homogeneous Catalysts</b>	<b>Heterogeneous Catalysts</b>
<b>Strong points</b>	Defined on molecular level (close to organic chemistry), Variability (design), Activity (turnover number)	Separation, recovery, recycling Stability, handling
<b>Weak points</b>	Sensitivity (handling, stability to air and moisture), Separation	Characterization (understanding on molecular level), Preparation, Reproducibility

One critical question that has repeatedly been brought into focus in modern research is how to minimize the catalyst cost (economics of the process) and metal contamination of the product (strict requirement for active pharmaceutical product). These cost and purification pressures have spurred significant research in two distinct areas: (i) immobilization of palladium so that it can be recovered and reused and (ii) development of highly active catalysts that are active at ppm metal concentrations.

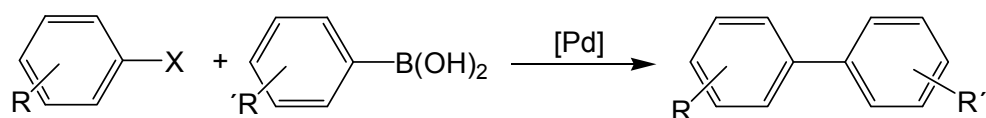
From an industrial point of view, palladium catalysts immobilized on solid supports (heterogeneous catalysts) have the inherent advantage of easy separation and very often also of better handling properties (for a short comparison see Table 1.1). Whereas an enormous number of reports have been published mainly focusing on

this obvious advantage of supported catalysts in C-C coupling reactions, it is only recently that the nature of true, catalytic palladium species has been brought into focus. The studies of catalytic activity of the heterogenized Pd catalysts in Heck reactions have demonstrated the existence of significant Pd-leaching and important contribution of a soluble catalyst in the main reaction course. However, in some cases, the nature of the true catalyst is still ambiguous. In particular for Suzuki reactions, claims exist in the literature supporting both “soluble molecular catalysts” as well as “truly heterogeneous”, insoluble Pd catalysts. One of the main problems exists in the fact that in general, truly active species is only generated *in situ* whereas the “initial catalyst” can just be regarded as a “precursor”. While experimentally proven ideas of this *in situ* generation of catalytically active species have been developed in homogeneous catalysis (e.g. pre-reduction of the active metal or ligand dissociation), the situation is by far more complex in heterogeneous catalysis. In fact, identifying the true active catalytic species is critically important for future advances in the rational design of coupling catalysts.

In addition to above mentioned elementary knowledge about the nature of catalytically active species, specific properties of support material (surface area, morphology, porosity) and active centers (dispersion, metal-support interactions, mobility on the surface, oxidation state) have to be taken into account when heterogenized palladium catalysts are used. In principle, all these factors may have influence on adsorption, reaction and desorption of reactants and products. Furthermore, with respect to active metal leaching, agglomeration and redox processes during the catalytic cycle have to be considered. A reliable estimation of the level (and dynamics) of metal leaching is also of the utmost importance in order to determine the economics of the process. Hence, the design of highly efficient supported palladium catalysts for C-C bond formation reactions is, to a large extent, dependent on the understanding of all the elementary processes involved in the reactions.

## 1.2 Suzuki Coupling Reaction

The Suzuki-Miyaura cross-coupling reaction of organoboron compounds and organic halides or pseudohalides (Scheme 1.2) can be considered as one of the most efficient methods for the construction of aromatic carbon-carbon bonds.



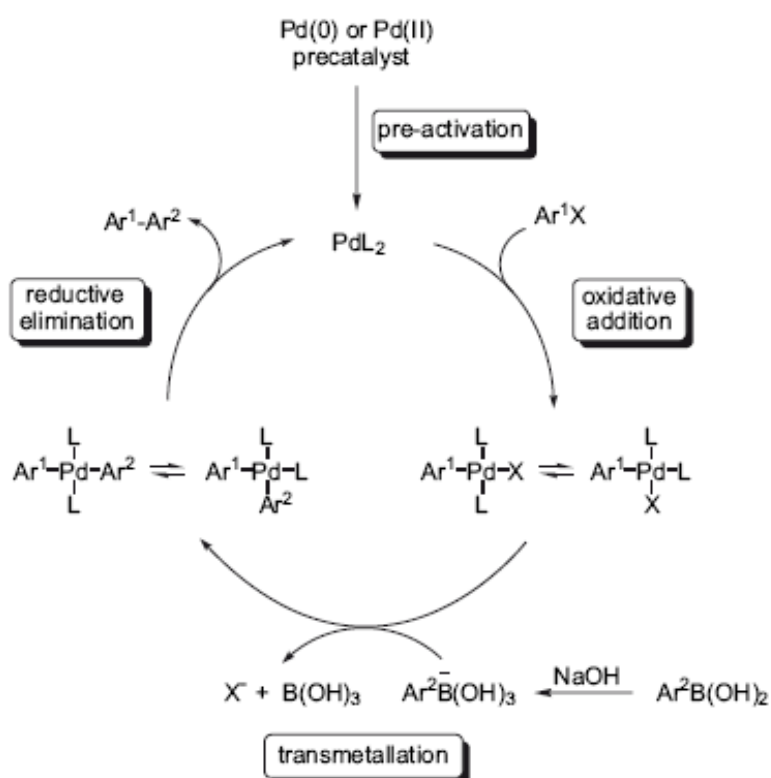
**Scheme 1.2** Suzuki couplings of aryl halides and phenylboronic acid.

In general, the commercial availability of the starting materials, the relatively mild reaction conditions required, the tolerance of a broad range of functionalities and the insignificant effect of steric hindrance, makes the reaction feasible. In addition, the ease of handling and removal of the nontoxic boron-containing by-products, as well as the possibility of using water as a solvent or co-solvent, have widened the scope of this reaction. Because of all these features, it has gained prominence in recent years at an industrial level, mainly in the synthesis of pharmaceuticals and fine chemicals. In academic laboratories, it has been largely applied as the key step in the total synthesis of natural products and polymer synthesis. Various modifications, however, have been recently introduced involving catalysts, substrates, reaction media, reaction conditions, synthetic techniques, etc. in order to develop environmentally friendly and more efficient Suzuki cross-coupling reactions. One current limitation in the scope of the Suzuki reaction is the lower activity of aryl chlorides. The low reactivity of chlorides is usually attributed to the strength of the C-Cl bond (bond dissociation energies for Ph-X: Cl: 96 kcalmol<sup>-1</sup>; Br: 81 kcalmol<sup>-1</sup>; I: 65 kcalmol<sup>-1</sup>). In view of broad availability and decreased expense of aryl chlorides relative to aryl bromides and iodides, it is highly desirable to develop the catalytic systems that utilize aryl chlorides as substrates.



### 1.2.1 Mechanism

The commonly accepted mechanism of the Suzuki-Miyaura coupling reaction (Scheme 1.3) involves an initial *oxidative addition* of the aryl halide to active palladium(0) species followed by transfer of the aryl group from the boronic acid to the palladium(II) centre (*transmetalation*). Base is required to generate quarternized boron species in order to enhance the nucleophilicity of aryl group on boron; a pre-requirement for transmetalation step. In aqueous alkaline solutions, the transmetalation was proposed to proceed through the interaction of the hydroxoboronate anion  $\text{Ar}^2\text{B}(\text{OH})_3^-$  with the oxidative addition product  $[\text{PdX}(\text{Ar})(\text{L})_2]$ .



**Scheme 1.3** General mechanism of palladium catalyzed Suzuki coupling reactions.

An alternative mechanism involves the reaction of the arylboronic acid with the complex  $[\text{Pd}(\text{OR})(\text{Ar})(\text{L})_2]$  *in situ* formed by ligand exchange between  $[\text{PdX}(\text{Ar})(\text{L})_2]$  and the base  $\text{RO}^-$  (alkoxide, hydroxide or carboxylate anion). Finally, *reductive elimination* leads to the biaryl product and regenerates the catalytically active palladium(0) species ( $\text{PdL}_2$ ).

In general, oxidative addition step is considered as the rate-determining step; however, there exist some reports where transmetallation step has been regarded as the most important step.

### 1.2.2 Catalytic Systems

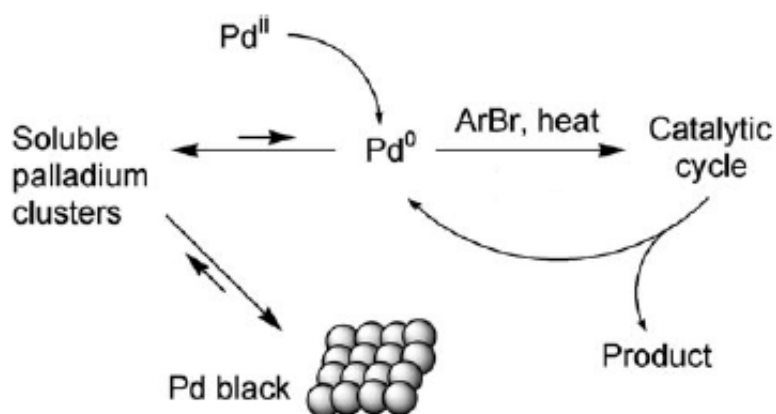
It is obvious that the selection of a proper catalytic system is fundamental for achieving the best efficiency in a given Suzuki reaction. However the catalyst efficiency is not only uniquely related to its catalytic activity or selectivity, but also to the possibility of recovery and re-utilisation of its components. At the same time, it is also desirable in every case to minimise the generation of waste and the environmental impact, especially for possible applications on an industrial scale. According to these very basic principles, significant efforts have been made in recent years to develop more simple, but efficient, catalytic systems.

In 2003, Leadbeater and Marco discovered the so called 'transition metal-free' Suzuki reaction via a microwave promoted coupling methodology that did not require the addition of a palladium catalyst. This spectacular finding was a subject of debate and controversy for some time. Further experiments, however, provided conclusive evidence that the reactions were palladium catalyzed after all by the action of very low levels of palladium (about 50 ppb) contained in the commercially available sodium carbonate used. The work represents a nice example about the activity of the simplest form of palladium for Suzuki coupling reactions under the given conditions.

#### 1.2.2.1 Ligand-free systems

Ligandless approach for the carbon-carbon cross-coupling reaction was pioneered independently by Beletskaya and Jeffery and has attracted increased attention in the recent years due to low cost. Simple Pd sources ( $\text{Pd}(\text{OAc})_2$ ,  $\text{PdCl}_2$ , etc.) can be used at very low palladium loadings (0.01-0.1%, commonly referred as homeopathic palladium). Ligand-free Pd catalysts (such as  $\text{Pd}(\text{OAc})_2$ ) have been applied to Suzuki coupling reactions under a variety of conditions. The collected data on ligand-free, homeopathic palladium studies are consistent with the view that catalysis is achieved by molecular (monomeric or dimeric), Pd(0) species that are in equilibrium with Pd(0)

nanoparticles (Scheme 1.4). Although the ligandless Pd catalyzed Suzuki reaction often achieves significantly fast coupling in aqueous media, complete conversion cannot always be possible, especially for the slow reactions of electron-rich and sterically hindered haloarenes as the active Pd(0) species tend to agglomerate quickly under these conditions.



**Scheme 1.4** The catalytic cycle that involves active molecular Pd species in equilibrium with soluble Pd clusters as proposed by Reetz and de Vries in 2004.

### 1.2.2.2 Homogeneous catalysts

Since its discovery in 1979, a multitude of homogeneous catalysts has been reported for Suzuki coupling reactions. As a consequence, a plethora of Pd-catalyst systems featuring a Pd-bound ligand are now accessible, some of which are capable to activate aryl chlorides. Typically, sterically hindered and electronically rich phosphine ligands have been often applied for these reactions. In addition, N-heterocyclic carbenes have emerged as efficient donor ligands for palladium catalyzed Suzuki coupling reactions. The groups of Buchwald, Beller, and Herrmann, have synthesized fascinating ligands based on nitrogen and/or phosphorus for potential applications in Suzuki coupling reactions. Well known electronic properties of ligand-based systems allow tuning of the catalyst properties for a variety of substrates. However, the removal of noble metal and the ligand from product stream is still a challenging task. Moreover, the sensitivity of ligands towards air and moisture, their tedious multistep synthesis and the use of various additives curtail the applications of these homogeneous systems.

Herrmann and Beller introduced the use of palladacycles to activate aryl chlorides in C-C coupling reactions. A variety of NC, SC and PC palladacycles pre-catalysts has been synthesized and applied to aryl-aryl coupling reactions. The application of palladacycles as catalysts for cross-coupling and similar reactions is reviewed by Beletskaya. In the majority of cases, palladacycles are likely to serve as a source of highly active but unstable Pd(0) species. In this respect, the palladacycles resemble the so-called ligand-free catalysts. Through extensive studies on aryl chloride activation in Suzuki coupling reactions, Bedford *et al.* have demonstrated that the efficiency of the catalytic system involving palladacycles depends on the long-term stability of reduced Pd(0) species and can be enhanced by the use of additives such as ammonium or phosphonium salts.

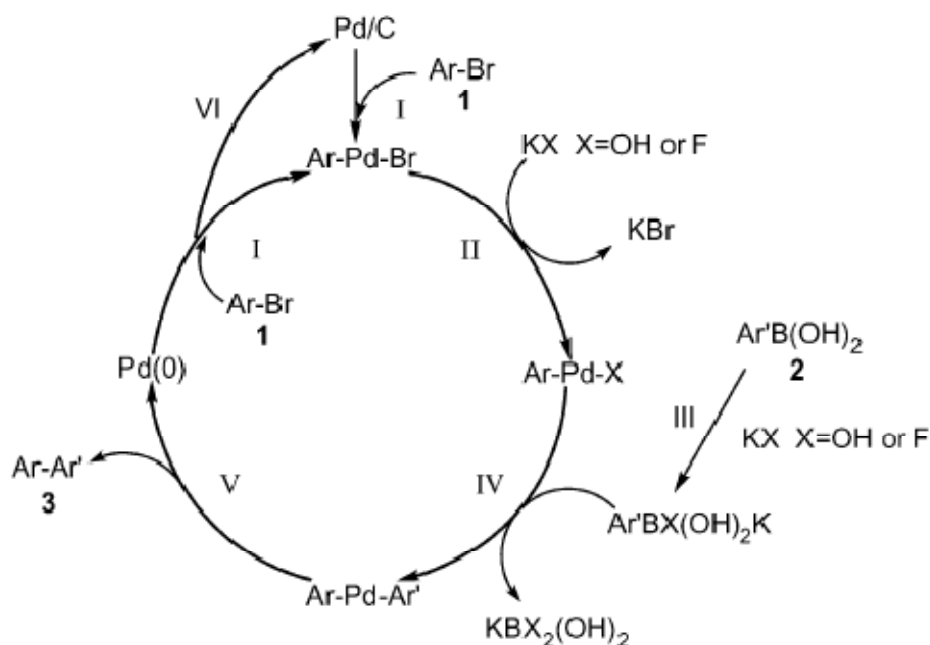
### 1.2.2.3 Supported catalysts

Solid catalysts for C-C coupling reactions have been primarily developed as a means to separate the reaction products from the catalyst, potentially facilitating decreased process cost due to reduced catalyst loss and simplified product purification. It is only rarely that highly active heterogeneous systems are accompanied by serious mechanistic studies about the real nature of catalysis.

There is an ongoing interest in immobilizing catalysts on polymeric supports in carbon-carbon coupling reactions. Uozumi *et al.* immobilized Pd(II) complexes on poly(ethylene glycol)-poly(styrene) graft copolymers and utilized the materials in the Suzuki coupling of aryl iodides and bromides with arylboronic acids. Shieh and co-workers studied the Suzuki coupling of 2-bromoanisole and phenylboronic acid using a commercial triarylphosphine-poly(styrene) resin. The polymer was loaded with PdCl<sub>2</sub> and the effect of the reaction conditions on catalyst leaching was studied. The authors ascribed the activity to 14-electron Pd(PPh<sub>3</sub>)<sub>2</sub> complexes attached to the solid support. Plenio developed a soluble polymer-immobilized triarylphosphine-Pd(II) material and demonstrated its use in Heck, Sonogashira and Suzuki couplings in conjunction with a nanofiltration membrane for catalyst sequestration. Several polymer-supported palladium/*N*-heterocyclic carbene complexes have been prepared and utilized as efficient heterogeneous catalysts for Suzuki coupling reactions.

Palladium on carbon (Pd/C) is one of the most frequently investigated catalysts for the Suzuki reaction. Zhang has demonstrated that a mixture of EtOH/H<sub>2</sub>O with Na<sub>2</sub>CO<sub>3</sub> forms a very active catalytic system with 10% Pd/C (3.5 mol%). The authors pointed out that the alcohol/H<sub>2</sub>O volumetric ratio is critical for the success of the cross-coupling reactions, with a low water concentration resulting only in a partial conversion. High activity of Pd/C in Suzuki reactions has been reported by Koehler *et al.* Furthermore, Sajiki *et al.* have presented Pd/C catalyzed Suzuki couplings of aryl and heteroaryl substrates. They proposed heterogeneous catalysis based on inductively coupled plasma (ICP) mass-spectrometric analysis of the filtrate that showed negligible Pd content in the filtrate at the end of the reaction. Pd-leaching in Pd/C-catalyzed Suzuki couplings in *i*PrOH/H<sub>2</sub>O solvent was investigated by Chen *et al.* using filtration test. Oxidative addition of aryl-bromides was declared as the main cause for Pd-leaching, which was independent of the reaction solvent and temperature. However, it was indicated that phenylboronic acid is another cause of Pd-leaching. Conlon *et al.* have recently proposed a *quasi* homogeneous mechanism for Pd/C catalyzed Suzuki coupling reactions (Scheme 1.5) whereby leached palladium species actually participate in the catalytic cycles.

A large variety of metal oxides (MO<sub>x</sub>) has been explored as support for palladium in Suzuki-Miyaura coupling reactions. Both reports of catalysis by leached, soluble species and truly heterogeneous catalyst systems are abundant. Mercapto-modified mesoporous silica has been utilized as effective support for Pd and resulting catalyst was shown to be highly active for Suzuki-Miyaura coupling reactions. Heterogeneous catalysis by surface-bound palladium was proposed on the basis of low levels of leaching observed after the reaction. The group of Artok has used a Pd(II)-exchanged NaY zeolite for the Suzuki reaction under very mild reaction conditions. Aryl bromides and iodides were coupled, in moderate-to-high yields, with three different arylboronic acids in a DMF/H<sub>2</sub>O mixture for only 1 h at room temperature. Activated aryl chlorides could also be coupled at 100 °C with modest yields. The authors demonstrated that the reaction was heterogeneous and that it did not take place within the zeolite. Various Pd/MO<sub>x</sub> catalysts have been demonstrated as effective and selective catalysts in Suzuki coupling reactions by Heidenreich *et al.* and a solution phase mechanism is proposed on the basis of Pd-leaching during the reaction.



**Scheme 1.5** Catalytic cycle for the Pd/C-catalyzed Suzuki-Miyaura cross-coupling.

In spite of the many reported claims of heterogeneous catalysis, it is now increasingly accepted that supported catalysts actually act as *quasi* homogeneous ones in liquid phase. The quality and reliability of the results and the related interpretations is highly dependent on the experimental techniques chosen for this purpose.

**Hot filtration test:** Most of the reports claiming “true heterogeneous” catalysis provide proofs in the form of hot filtration test whereby the reaction is stopped at low conversions, is filtered and the reaction is allowed to continue after removal of solid catalyst. The loss of activity in filtrate is declared as a proof of “leach proof” catalyst. However, in other cases, it has been demonstrated that inactive filtrate does not indicate heterogeneity as the leached species can be deposited or deactivated during filtration.

**Catalyst poisoning:** Catalyst poisoning has recently emerged as useful technique to assess true catalytic species in CC coupling reactions. However, the fact that extremely low amounts of Pd (ppm or ppb) can catalyze the reaction limits the practical application of the technique.

Analysis before and after the reaction: “Quantitative” catalyst recovery (same Pd loading) also is a way to measure the recyclability of a system. While this methodology has real bearing on practical reuse of the catalysts, it does not provide strong evidence for a truly heterogeneous palladium coupling catalyst when solid catalysts are used. This is because the leached palladium species can, for the most part, re-deposit on to the support after the reactants have been consumed, as has earlier been demonstrated for Heck reactions. In addition, in highly active systems, where ppt or ppb levels of Pd can efficiently catalyze the reaction, Pd loss in the catalyst cannot be detected by rudimentary elemental analysis.

Similarly, unchanged Pd particle size distributions on the catalyst has also been regarded as a measure of heterogeneity; however, as mentioned above, depending on the optimized reaction conditions, the efficient re-deposition of Pd on solid surface can leave the catalyst with minimum visible change in the particle size distributions, as will be demonstrated latter in this chapter.

3-Phase test: Using this test, one reagent is immobilized on a solid support and the catalyst is immobilized on a second, different solid support. The rest of the reagents are then added to the solution. Ideally, if there is no background reaction in the absence of catalyst, the immobilized reagent should only be converted if there is catalyst or substrate leaching. This is a very useful test to assess homogeneous catalysis and is sometimes used in conjunction with filtration tests. There are subtleties involved, however. For example, it must be insured that the species needed to induce leaching are present in the solution phase. Thus, if leaching proceeds via oxidative addition of aryl halide to immobilized Pd(0), the aryl halide or another free aryl halide must be present in the reaction solution. In case of Suzuki reactions, it has been indicated that not only aryl halides but also arylboronic acid cause Pd-leaching in solution. Investigations, related to influence of reaction parameters on Pd-leaching, in this work provide a proof for this assumption. Thus, 3-phase test is not a suitable test to assure the heterogeneous nature of catalysis.

Correlation of reaction rate with concentration of palladium in solution: Determination of Pd content in the reaction mixture with simultaneous analysis for the conversion of aryl halides is a direct and unambiguous way to show the homogeneous nature of

catalysis for C-C coupling reactions catalyzed by supported Pd catalysts. The technique has successfully been applied to the Heck reaction and provides powerful evidence for Pd dissolution-re-deposition processes during the catalytic reaction. Present investigations are therefore focused on this last rather extensive method to assess real nature of catalysis in Suzuki coupling reactions (Section 2.2).

### 1.2.3 Suzuki Coupling Reactions in Water

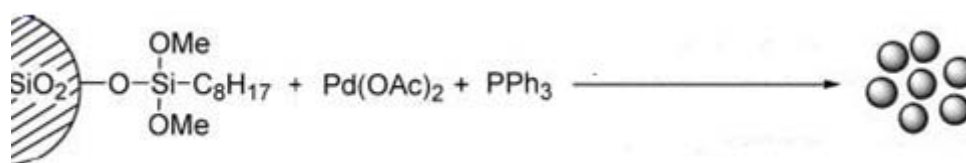
With the increasing interest in “Green Chemistry Processing” the replacement of expensive, toxic and flammable organic solvents by water as the preferred solvent is highly desirable due to economical as well as safety related process engineering reasons. Whereas most of the catalysts mentioned above have been applied in organic solvents or in organic/H<sub>2</sub>O mixtures, an increasing number of research groups have recently focused on the development of new catalytic systems to be used in Suzuki coupling reactions in water as the only solvent. One approach to increase potential of water as solvent in Suzuki reactions is to develop water soluble Pd catalysts and ligands. Moreover, surfactant mediated micellar catalysis has been developed recently by Lipschutz *et al.* Use of homogeneous Pd complexes along with dilute aqueous solution of nonionic amphiphile allowed efficient Suzuki-Miyaura cross-couplings of arylboronic acids with aryl halides. Ligandless Pd(OAc)<sub>2</sub> catalyzed Suzuki coupling reactions of aryl iodides and aryl triflates has been reported in water in the presence of tetra-*n*-butylammonium bromide (TBAB) as additive. Bhattacharya has also reported the use of ligandless Pd(OAc)<sub>2</sub> in Suzuki reactions mediated by cetyltrimethylammonium bromide (CTAB) in water. Aryl bromides and aryl iodides were coupled to give 80-95% yield. The additives are believed to stabilize the active palladium species in water.

Over the last few years, there has been an increasing interest to focus on new supported catalysts for this purpose. Polymers are among the most applied supports for palladium catalysts in water. A variety of polymeric materials, in particular amphiphilic polymers have increasingly been brought into focus for Suzuki coupling reactions. Lysen has reported a highly efficient catalyst system comprising Pd/C in combination with TBAB system for couplings of aryl bromides as well as aryl chlorides at 100-140 °C. Pd/C has also been proved to be an efficient catalyst for



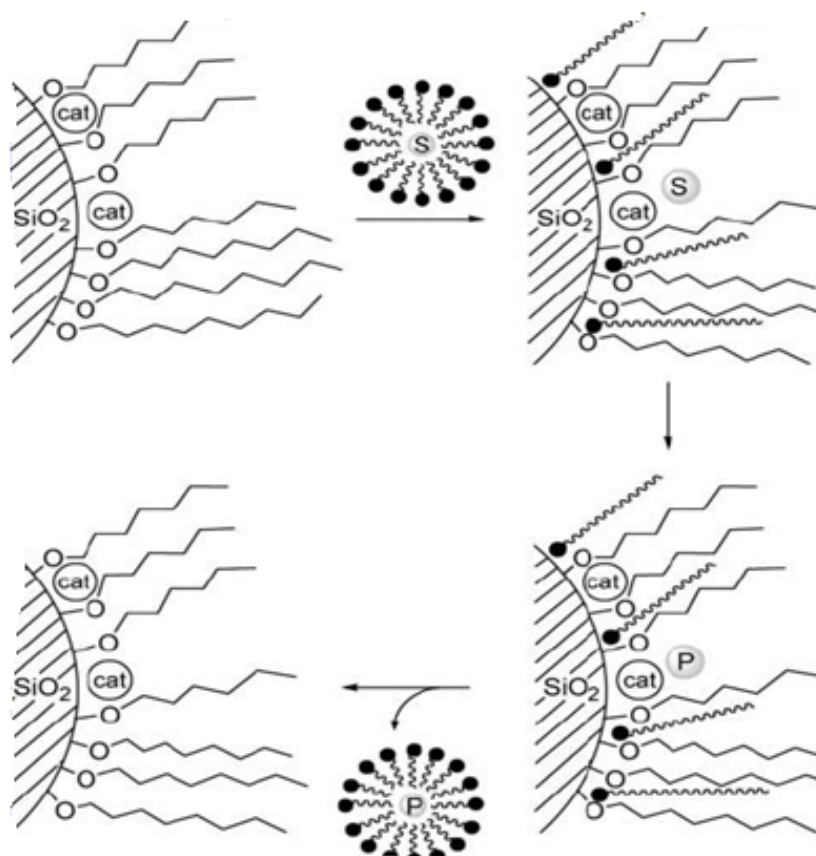
Suzuki reactions in water. Metal oxides, have rarely been exploited for such reactions in water mainly due to difficulties associated with conversion of the non-hydrophilic substrates.

Among a large number of reports dealing with modified or unmodified supports for Pd catalyzed Suzuki reactions in water, the illustrations about the possible influence of the support (surface properties, surface area etc) can hardly be found. However, an interesting example about the Heck reaction can be considered here being more relevant to the investigations carried out for Suzuki reactions in present work. Williams and co-workers reported the use of reverse-phase silica in the Heck reaction. The catalyst was prepared by treatment of derivatized silica with palladium acetate and triphenylphosphine in cyclohexane (Scheme 1.6).



**Scheme 1.6** Preparation of the silica supported catalyst for Heck reaction in water.

Coupling between iodobenzene and acrylic acid was carried out to give the desired product in 90% yield and very little leaching of palladium into the bulk aqueous phase was reported by authors. However, coupling of nonpolar substrate was only possible in the presence of MeOH as a co-solvent. To solve this problem, surfactants were used as carrier for the lipophilic substrates. In the presence of a surfactant, the hydrophobic substrate forms an emulsion in water and the powdered catalytic material is dispersed in the emulsion. Avnir and Blum termed this process emulsion-solid transport (EST). A schematic representation of EST process is given in Scheme 1.7 as presented by Minakata and Komatsu in a recent review.

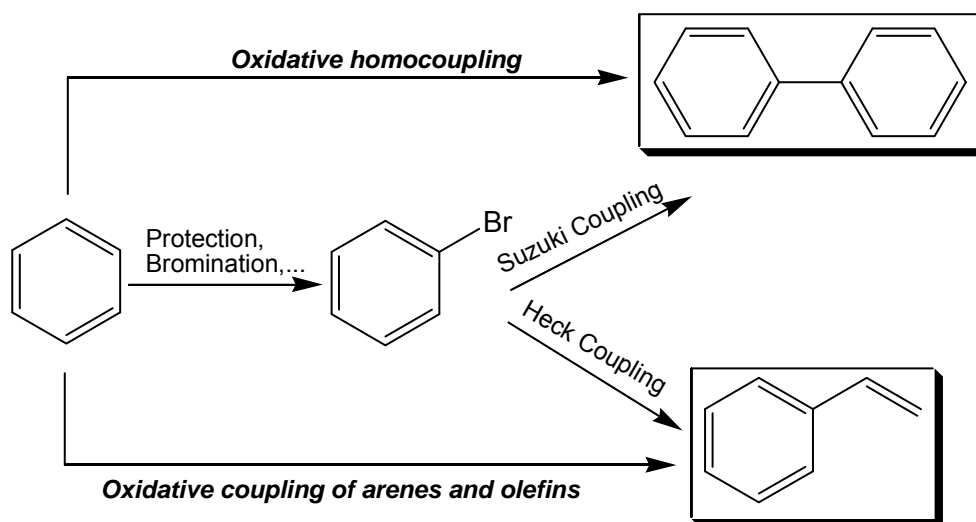


**Scheme 1.7** Illustration of the transport, reaction, and adsorption/desorption steps of the heterogeneously catalyzed and surfactant mediated reactions in water: S=Substrate, P=Product, Cat=Catalyst.

As mentioned above, a deeper understanding of various processes involved in a catalytic cycle is a key to develop highly active systems. A brief exemplary illustration of these considerations is given in present work for Suzuki coupling reactions in water involving different supported Pd catalysts.

### 1.3 Oxidative C-C Coupling Reactions

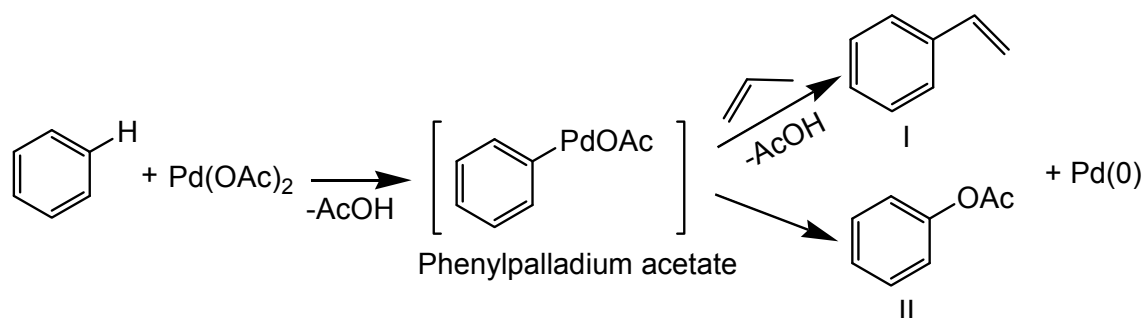
Arenes such as benzenes, naphthalenes, phenols, and anilines are large-quantity chemicals manufactured by chemical industries. Catalytically efficient activation of aromatic C–H bonds leading to useful organic reactions such as new C–C bond formation is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge to chemists. The strategy, commonly known as *oxidative coupling*, would provide simple, clean, and economic methods for making aryl-substituted compounds directly from simple arenes. In contrast to conventional C-C coupling reactions (e.g., Heck and Suzuki reactions), no prefunctionalization such as halogenation is involved (Scheme 1.8) in this case. The activation of aryl C-H bonds is a demanding task as C-H bond strength of arenes ( $D^{\circ}_{298}(\text{C}_6\text{H}_5\text{-H}) = 464 \text{ J/mol}$ ) is higher as compared to that of C-X bond involved in the conventional C-C coupling reactions. The catalytic systems for such a purpose have been sought for many years, although there are many examples of stoichiometric reactions of aromatic C–H bonds with transition metal compounds.



**Scheme 1.8** Atom economy of oxidative coupling

$\text{Pd}(\text{OAc})_2$  promoted oxidative coupling reaction of arenes and olefins (Heck type reaction) via aryl C-H activation was first reported in late 1960s by Fujiwara and Moritani. The reaction provides a convenient method for the synthesis of a wide variety of arylated olefins. In contrast to classical Heck reaction, oxidative coupling of

arenes does not require stoichiometric amount of base or inert reaction conditions. Typically, activation of aryl C-H bonds by Pd(OAc)<sub>2</sub> generates reactive arylpalladium acetate that gives the cross coupled product in the presence of olefins (Scheme 1.9). In addition, formation of acetoxybenzene (II) is possible under these conditions and has to be minimized in order to achieve high selectivity towards desired cross coupled product (I). The control of selectivity in these reactions is more problematic than in conventional coupling reactions. When substituted arenes are applied as substrates, a mixture of products is obtained due to availability of more than one aryl C-H bonds having similar reactivity.



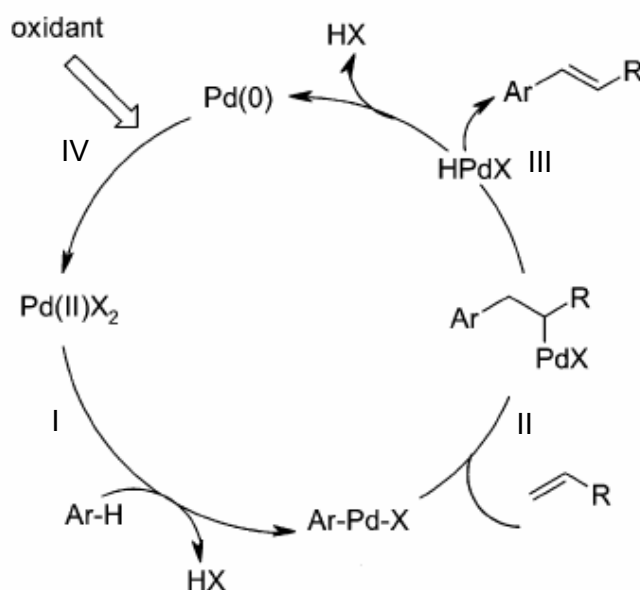
**Scheme 1.9** Generation of phenylpalladium acetate and possible products.

Pd(II) is reduced to Pd(0) during the reaction. For useful synthetic methods it is important that expensive Pd compounds are not consumed in stoichiometric amounts. Much effort has been made to find efficient reoxidation systems to regenerate Pd(II) in situ from Pd(0). Obviously, O<sub>2</sub> is the most environmentally friendly; however, in the absence of a co-catalyst, it fails to achieve a complete oxidation of palladium, as in general, the formation of inactive bulk metal is a competing process.

### 1.3.1 Mechanistic Details

As mentioned in introduction, the reaction proceeds via electrophilic palladation of the aryl C-H bond (Scheme 1.9). The concept was first presented by Fujiwara *et al.* in 1969 on the basis of substituent effects of monosubstituted benzenes. The aromatic substitution of olefins in homogeneous solutions of palladium acetate, aromatic compound (large excess), and acetic acid gave 10-90% yields of arylated products along with reduced metallic palladium. Substituted benzenes preferentially

induced ortho/para orientation with electron-donating groups and meta orientation with electron-withdrawing groups. The order of reactivity found with benzene, naphthalene, ferrocene, and furan were similar to that of the electrophilic aromatic substitution. Even if the reactivity was not influenced as much as in a typical aromatic substitution reaction, this tended to show electrophilic metalation as the first step. The isolation, 20 years later, of diphenyltripalladium(II) complexes obtained by the C-H activation reaction of benzene with palladium acetate dialkylsulfide systems partially confirmed this hypothesis.



**Scheme 1.10** Catalytic cycle for oxidative coupling of arenes and olefins in the presence of Pd(II) salts.

The generally accepted mechanism of oxidative coupling involves the activation of aromatic C-H bonds through electrophilic metalation of aromatic C-H bonds by Pd(II) complexes to give  $\delta$ -aryl-Pd complexes (Scheme 1.10, Step I). The  $\delta$ -aryl-Pd complexes undergo cis arylpalladation to C=C bonds (Step II) followed by Pd- $\beta$ -hydride elimination (Step III) to give aryl alkenes and metallic palladium. For this system, in situ regeneration of Pd(II) from Pd(0) is the crucial step for the catalytic cycle (Step IV) that requires an efficient oxidizing agent. The observed reactivity of aromatics and heteroaromatics as well as the observed selectivity with monosubstituted benzenes indicates that the reaction depends on the nucleophilic nature of the arenes used in the catalytic system. Thus, the formation of the  $\delta$ -aryl-

Pd(II) complexes via electrophilic metalation is believed to be the rate-determining step.

### 1.3.2 Catalytic Systems for Oxidative Coupling of Benzene (derivatives) with Olefins

Although with very low yields (maximum turnover number achieved was 2), the first catalytic protocol for arylation of alkenes was reported by *Fujiwara* and *Moritani* in 1969. Application of  $\text{Cu}(\text{OAc})_2$  or  $\text{AgOAc}$  as reoxidant for Pd(0) species facilitated the lowering of the Pd amount to 10 mol% based on the reactants. Several efforts were made thereafter to develop the reaction. Recent investigations focus mainly on coupling reactions of benzene or substituted benzenes with acrylic esters or their derivatives (Table 1.2).

To date, the best results in terms of turnovers were obtained with a related system using peroxide as hydrogen acceptor. In the presence of palladium acetate and benzoquinone (BQ) with tert-butyl hydroperoxide ( $t\text{BuOOH}$ ) as the oxidant, the oxidative coupling of benzene and ethyl (*E*)-cinnamate can be achieved in up to 280 turnovers.

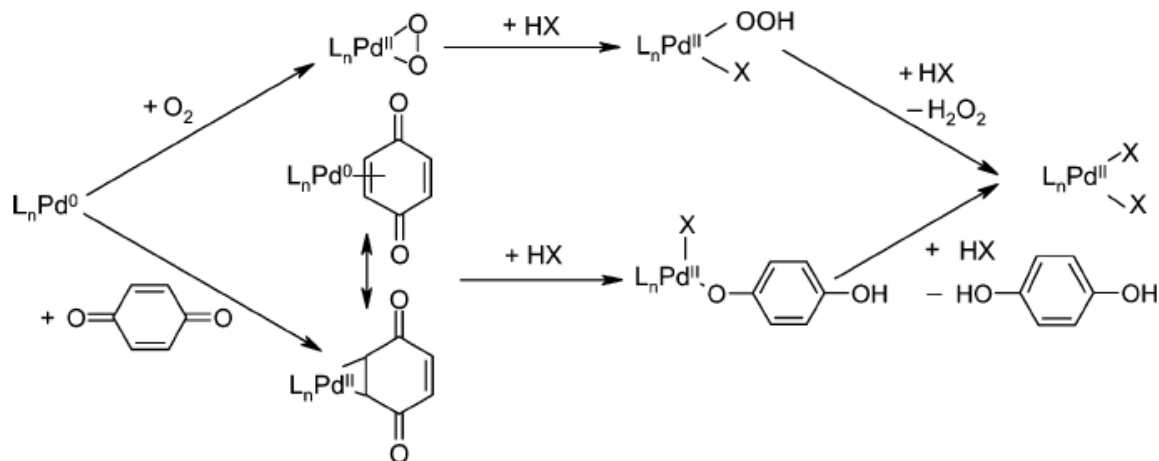
The groups of de Vries and van Leeuwen were able to achieve high *ortho*-selectivity in oxidative coupling reactions of anilides with olefins using benzoquinone as oxidant. No other isomer was formed because of the strong *ortho*-directing effect of the amide group. *Prasad et al.* extended the substrate scope towards halogenated acetanilides under similar conditions. The mechanistic resemblance between benzoquinone (BQ) and dioxygen ( $\text{O}_2$ ) as oxidant have been highlighted by *Stahl et al.* (Scheme 1.11) for these reactions.

**Table 1.2** Comparison of catalytic systems applied in oxidative coupling of benzene and olefins in the presence of Pd(OAc)<sub>2</sub>.

Ref.	Pd (mol%)	Oxidant/Co-cat. (mol%)	Atm. (P, atm)	Olefin	Solv.	T (°C)	t (h)	Yield (%)
10		Cu(OAc) <sub>2</sub> (10)	O <sub>2</sub> (50 atm)	Styrene	AcOH	80	8	45
1		<sup>t</sup> BuOOH/BQ <sup>c)</sup> (200/10)	Air (1 atm)	EC <sup>a)</sup>	AcOH	90	15	81
2		BQ <sup>c)</sup> (100)	Air (1 atm)	BA <sup>b)</sup>	AcOH	RT	16	85
5		BQ <sup>c)</sup> (100)	Air (1 atm)	BA <sup>b)</sup>	AcOH	RT	17	82
6.67		H <sub>4</sub> PVMo <sub>11</sub> O <sub>40</sub> (1.33)	O <sub>2</sub> (1 atm)	Acrolein	EtCOOH	90	1.5	59
1		Mn(OAc) <sub>3</sub> (4)	O <sub>2</sub> (8 atm)	EC <sup>a)</sup>	C <sub>6</sub> H <sub>6</sub>	90	90	92
10		none	O <sub>2</sub> (3.4 atm)	Styrene	C <sub>6</sub> H <sub>6</sub>	55	20	56

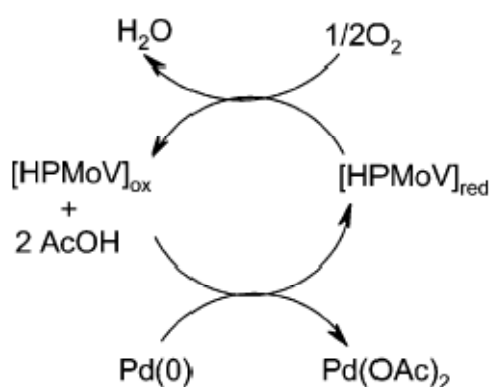
<sup>a)</sup>Ethyl cinnamate; <sup>b)</sup>Butyl acrylate; <sup>c)</sup>Bezoquinone

Several approaches have been made to use molecular oxygen as reoxidant to regenerate catalytically active Pd(II) in the reaction mixture. Typically, a direct reoxidation of Pd(0) is not possible under oxygen atmosphere alone; but is facilitated in the presence of another oxidant. It is highly desirable that the amount of this oxidizing agent is reduced to catalytic level (co-catalyst) and is regenerated by molecular oxygen (Scheme 1.12).



**Scheme 1.11** Mechanistic relationship between the oxidation of palladium(0) by molecular oxygen and benzoquinone.

A catalytic mixture of  $\text{Pd}(\text{OAc})_2$  and the molybdovanadophosphoric heteropolyacid system as a palladium re-oxidant was employed in the reaction of benzene with olefins bearing an electron-withdrawing group. The method was extended to the coupling of various arenes with  $\alpha$ - $\beta$ -unsaturated esters and aldehydes. Reactions were performed in acetic acid using catalytic amounts of Pd and heteropoly acid. Acetylacetonate was used as ligand for Pd and NaOAc was the base of choice.  $[\text{HPMoV}]_{\text{red}}$  is oxidized to  $[\text{HPMoV}]_{\text{ox}}$  with  $\text{O}_2$  as shown in Scheme 1.12.



**Scheme 1.12** Molybdovanadophosphoric heteropolyacid mediated regeneration of  $\text{Pd}(\text{OAc})_2$  with molecular oxygen in acetic acid.



Jacobs *et al.* investigated the reaction of arenes and *trans*-cinnamates in presence of 1 mol% Pd(OAc)<sub>2</sub> and different additives. They found Mn(OAc)<sub>3</sub> to be an effective co-catalyst which potentiated electron transfer from Pd(0) to O<sub>2</sub>. In general, quite long reaction times (20-165 h) had to be applied in these couplings. In absence of a co-catalyst, the reaction reached completion too, but only after an induction period of 2.5 h (reaction time 22-24 h). Park and Hwang reported oxidative coupling of benzene and styrene, which is less reactive than acrylic esters. Good yields were obtained by using 10 mol% Pd(OAc)<sub>2</sub> and phosphine ligands. High selectivity towards desired product (stilbene) was achieved at low temperatures (55 °C) under oxygen pressure (3.5 atm) after reaction time of 20 h.

## 1.4 Aim of Work

Motivated by the need to develop and improve the understanding of the fundamental processes involved in heterogeneously catalyzed C-C coupling reactions, investigations on Suzuki coupling reactions were planned with a particular focus on noble metal leaching and related dissolution-re-deposition phenomena. A comprehensive survey of these investigations will be presented in Section 2. Careful interpretations of the results led to assess the real nature of catalytic species in heterogeneously catalyzed Suzuki coupling reactions – the crucial point for the rational design of coupling catalysts. In addition, detailed investigations on optimization of the reaction protocol as well as influence of reaction parameters on Pd-leaching will be presented for Suzuki coupling reactions under mild reaction conditions (65 °C). The results display highly efficient Suzuki coupling reactions with the clear mechanistic evidence related to solution phase catalysis. The reaction parameters as well as specific characteristics of the chosen catalysts influence the elementary processes (see Section 1.1) involved in a catalytic cycle and hence are of utmost importance to develop efficient reaction protocol.

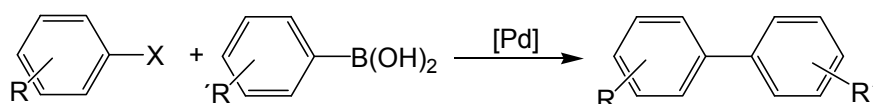
Further investigations were focused on increasing the potential of water as the only solvent in heterogeneously catalyzed Suzuki coupling reactions. An elaborative study regarding influence of surface properties of the supported catalysts on Suzuki coupling reactions in water will be presented in latter sections (Section 2.3). It will be elucidated that interaction of the substrates with supported catalysts as well as solubility of the educts in water can be controlled via careful selection of the reaction parameters.

Direct oxidative C-C coupling of benzene and styrene will be discussed as a promising alternative to “conventional” Heck reactions in Section 3. Homogeneous and heterogeneous Pd catalysts will be presented which feature high activity towards oxidative coupling reactions. A significant impact of the reaction parameters will be demonstrated for this reaction type as well. The choice of oxidant for the regeneration of Pd catalyst is crucial for the activity of the resulting catalytic systems.

## **Suzuki Coupling Reactions**

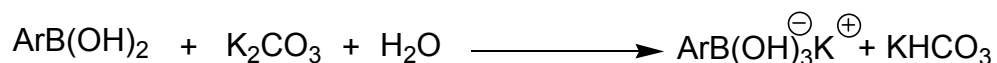
## 2.1 General Introduction

Aromatic carbon–carbon bond formation during the coupling of aryl halides with arylboronic acids (Suzuki reaction, Scheme 2.1) has become an efficient and clean strategy for the preparation of unsymmetrical biphenyls, which are important building blocks for pharmaceutical and agricultural compounds. In the past few years, a number of attempts and strategies have been used to get a commercially viable, highly active, recoverable, and reusable palladium catalyst for Suzuki reactions. A substantial number of reports claiming “true” heterogeneous catalysis by supported palladium (i.e. on the noble metal surface) in Suzuki reactions have been published. Other authors found that Suzuki reactions are catalyzed by palladium dissolved in solution (leaching).



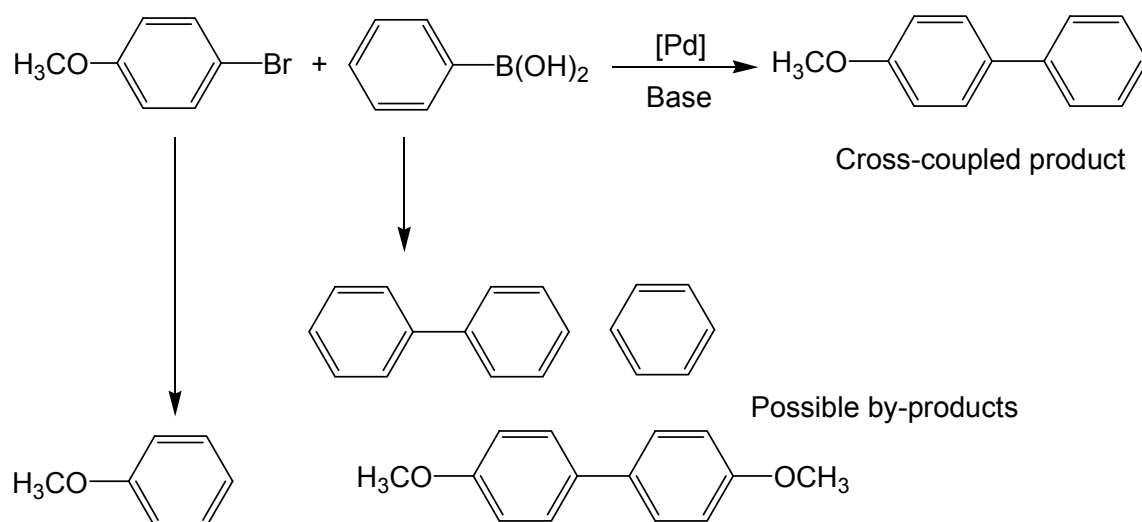
**Scheme 2.1** Suzuki couplings of aryl halides and phenylboronic acid.

Traditionally, Suzuki coupling reactions are carried out in organic solvent/water mixtures. Whereas organic solvents favor the reaction by dissolving organic aryl halides, water is considered necessary to dissolve base for activation of the arylboronic acids. In early mechanistic investigations, Smith *et al.* suggested that one mole of water and one mole of base are required to activate phenylboronic acid (Scheme 2.2) before it enters the transmetalation step of catalytic cycle (general mechanism is given in introduction; Scheme 1.3).



**Scheme 2.2** Activation of phenylboronic acid by base in the presence of water

The reaction proceeds smoothly in mix solvents; however, the relative amount of organic solvent and water must be optimized in order to get high selectivity towards cross coupled product.



**Scheme 2.3** Main product and by-products in the Suzuki coupling reaction of 4-bromoanisole and phenylboronic acid.

In general, Suzuki coupling reactions, under optimized reaction conditions, lead exclusively or mainly to desired cross coupling of two aryl substrates. The possible by-products in Suzuki coupling reactions are given in Scheme 2.3.

Even though a large number of research efforts have been dedicated to develop and study heterogeneous Pd pre-catalysts for Suzuki coupling reactions, the goal of developing a catalyst that is stable, recoverable, and reusable is still sought after. Present investigations on Suzuki coupling reactions are aimed mainly at the understanding of the reaction mechanism under optimized reaction conditions. The study is focused on two main aspects:

- i) Development and optimization of heterogeneous catalysts for Suzuki coupling reactions in NMP/water with a detailed study on homogeneous/heterogeneous mechanism of the reaction under different reaction conditions (120 °C or 65 °C); Section 2.2.
- ii) Suzuki coupling reactions catalyzed by supported palladium in pure water under mild reaction conditions (65 °C). The focal point is the determination of the role of support, if any, on the catalyst activity; Section 2.3.

## 2.2 Suzuki Coupling Reactions in NMP/Water

### 2.2.1 Suzuki Reactions of Aryl Bromides at 120 °C

Previous investigations by Heidenreich in our lab led to the development of highly active Pd/C (5% Pd on activated carbon, 50.5% water content) catalyst for the Suzuki reaction at 120 °C. The commercially available Pd/C, without any catalyst pre-treatment, was demonstrated as highly active heterogeneous catalyst for coupling the phenylboronic acid with various aryl bromides in NMP/water (NMP = 1-methyl-2-pyrrolidone) mixture as solvent. Further experiments were performed in order to explore the mechanistic aspects of the reaction.

#### 2.2.1.1 Non-treated vs. treated catalysts

The Pd/C catalyst was treated at high temperatures in inert (nitrogen) or reducing (hydrogen) environment and the resulting catalysts were utilized in Suzuki coupling reactions. The results of catalytic reactions are summarized in Table 2.1. The thermally treated catalysts showed only small catalytic activity in the Suzuki reaction of 4-bromoanisole and phenylboronic acid (entries 2-4). TON (Turn Over Number) and TOF (TOF = Turn Over Frequency) decreased by at least two orders of magnitude compared to the values of the non-reduced catalyst. These catalysts contain mainly or exclusively palladium in its reduced state Pd(0) clearly indicating that catalysts with higher oxidation states (i.e. Pd<sup>2+</sup>) are better precursors for high activity under these reaction conditions. Moreover, the water content of the catalyst is important for high activity.

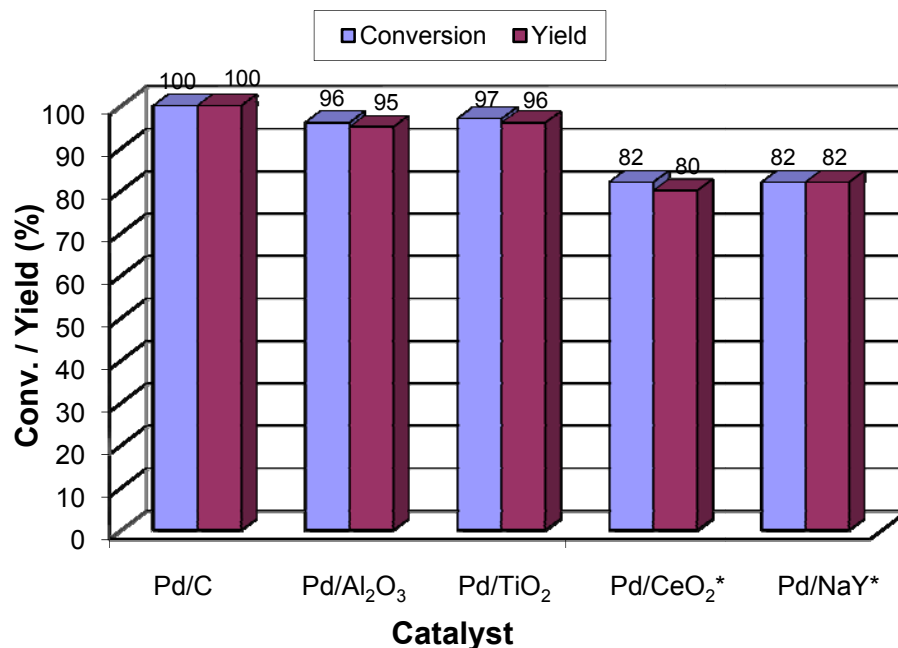
**Table 2.1** Conversion and yield of non-treated and thermally pre-treated Pd/C catalysts in Suzuki coupling of 4-bromoanisole and phenylboronic acid.<sup>a)</sup>

Entry	Pretreatment conditions	Catalyst (mol%)	t (h)	Yield <sup>b)</sup> (%)	TON	TOF (h <sup>-1</sup> )
1	Non-treated Pd/C	0.01	2	100	20,000	10,000
2	pretreated under H <sub>2</sub> at 300 °C	0.2	2	67	335	168
3	pretreated under H <sub>2</sub> at 300 °C	0.2	4	68	340	85
4	pretreated under N <sub>2</sub> at 500 °C	0.2	2	33	165	83
5	pretreated under N <sub>2</sub> at 500 °C	0.2	4	34	170	43

<sup>a)</sup> Reaction conditions: 10 mmol 4-bromoanisole, 11 mmol phenylboronic acid, 12 mmol Na<sub>2</sub>CO<sub>3</sub>, 10 mL NMP, 4 mL H<sub>2</sub>O, T = 120 °C, Pd (E 105 CA/W 5% Pd/C, thermally pre-treated at 300 °C or 500 °C). <sup>b)</sup>GC yield of 4-methoxy biphenyl (500 mg diethyleneglycol dibutyl ether as internal standard).

### 2.2.1.2 Comparison of different supported materials

Continued with these promising results, further investigations were focused on the activity of different Pd precursors under the optimized reaction conditions. In a series of experiments it was investigated whether different surface properties of the support material of the supported materials influence the activity of the corresponding catalysts. The reaction of 4-bromoanisole and phenylboronic acid was chosen as a model reaction. The activity of previously reported Pd/C was compared with different Pd/MO<sub>x</sub> catalysts prepared by controlled immobilization of Pd(OH)<sub>2</sub> on metal oxide supports. The results of catalytic reactions are depicted in Figure 2.1.



**Figure 2.1** Comparison of different supported Pd catalysts in Suzuki coupling reaction of 4-bromoanisole and phenylboronic acid. Reaction conditions: 10 mmol 4-bromoanisole, 11 mmol phenylboronic acid, 12 mmol Na<sub>2</sub>CO<sub>3</sub>, 0.005 mol% [Pd], 500 mg diethyleneglycol dibutyl ether (GC standard), 10 mL NMP, 4 mL H<sub>2</sub>O, T = 120 °C, 2 h. \*Reaction time is 4 h.

All Pd/MO<sub>x</sub> catalysts (Pd/Al<sub>2</sub>O<sub>3</sub>, Pd/TiO<sub>2</sub>, Pd/CeO<sub>2</sub>) as well as Pd/NaY were found active and they showed high conversions of 4-bromoanisole under the optimized reaction conditions (NMP/water, 120 °C). In particular, palladium supported on alumina and titania showed the same high activity as Pd/C. After 2 hours, nearly complete conversion is reached with 100% selectivity towards desired product (4-methoxy biphenyl). Pd/CeO<sub>2</sub> and palladium incorporated into NaY required somewhat longer reaction times to reach high yields. The results imply that nature of the support has a negligible influence on the activity of the catalysts under given reaction conditions. Instead, the preparation procedures and the resulting properties of the catalyst (dispersion, oxidation state of Pd, water content) can be regarded as main factor for high catalyst activity.



### 2.2.1.3 Recycling experiments

Recycling of the catalyst can be of considerable importance for practical applications. The Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed Suzuki reaction of 4-bromoanisole was investigated for catalyst recycling. In particular in the reactions with used catalysts, the application of 0.1 mmol of I<sub>2</sub> led to very satisfying results. Iodine serves as efficient partner in this reaction for partial re-oxidation of reduced palladium as reported by de Vries *et al.*

**Table 2.2** Recycling of Pd/Al<sub>2</sub>O<sub>3</sub> in the Suzuki coupling of 4-bromoanisole and phenylboronic acid.<sup>a)</sup>

Cycle	Conversion <sup>b)</sup> (%)	Yield <sup>c)</sup> (%)
Fresh Catalyst	96	95
*1 <sup>st</sup> . recycle	76	76
*2 <sup>nd</sup> . recycle	71	71
*3 <sup>rd</sup> . recycle	66	66
*4 <sup>th</sup> . recycle	69	69

<sup>a)</sup> Reaction conditions: 10 mmol 4-bromoanisole, 11 mmol phenylboronic acid, 12 mmol sodium carbonate, 10 mmol NMP, 4 mL H<sub>2</sub>O, 0.2 mol% Pd (5% Pd/Al<sub>2</sub>O<sub>3</sub>), 500 mg diethyleneglycol dibutyl ether as internal GC standard; T = 120 °C, 4 h, \*0.1 mmol of I<sub>2</sub>. <sup>b)</sup> Total conversion of 4-bromoanisole. <sup>c)</sup> GC yield of cross coupled product (4-methoxy biphenyl)

A slight gradual decrease in activity was observed during five successful runs and the fifth run corresponded to 69% conversion with 100% selectivity to cross-coupled product (Table 2.2). Probable reasons for the loss of activity are only partial re-oxidation of Pd(0) to Pd(II) by I<sub>2</sub> and somewhat lower palladium dispersion after re-deposition.

### 2.2.2 Suzuki Reactions of Aryl Chlorides at 120 °C

It is well known that the Suzuki coupling of aryl chlorides is clearly more demanding. Applying the same optimized catalyst, it would be necessary to change reaction

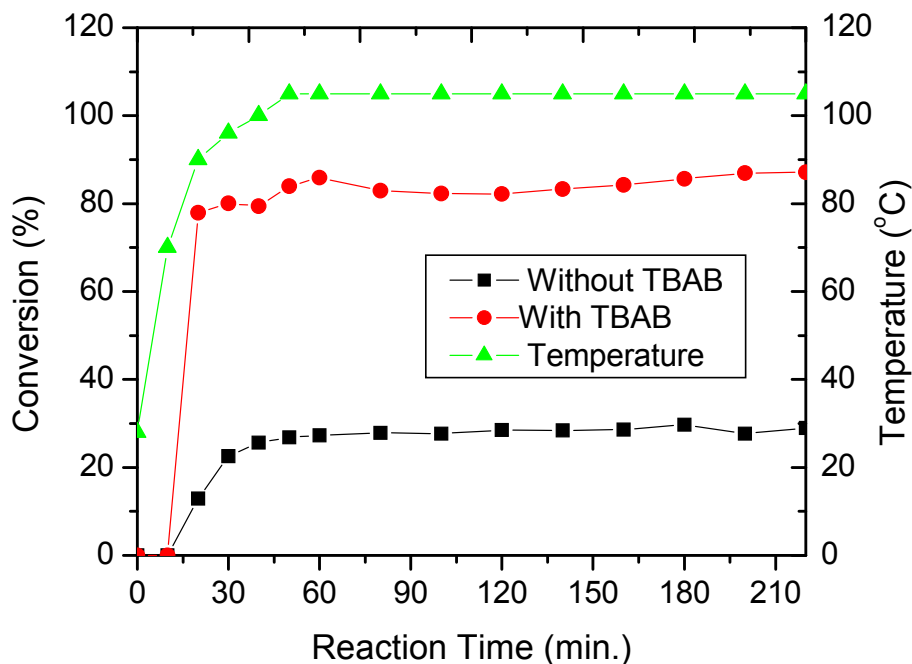
parameters. Most important factors are the addition of tetra-*n*-butylammonium bromide (TBAB) and changing the base from Na<sub>2</sub>CO<sub>3</sub> to NaOH. These small changes resulted in remarkably high conversion of 4'-chloroacetophenone (Table 2.3) with Pd/C as well as with Pd/Al<sub>2</sub>O<sub>3</sub>. 4'-chloroacetophenone has been chosen as aryl chloride substrate because it can more easily be activated as compared to aryl chlorides with electron donating substituents and thus is better comparable to bromoanisole.

**Table 2.3** Heterogeneous Suzuki coupling of 4'-chloroacetophenone with phenylboronic acid.<sup>a)</sup>

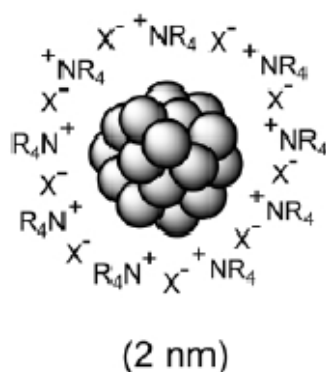
Entry	Catalyst	Additive	Yield (4-acetylbiphenyl) <sup>b)</sup> (%)
1	Pd/Al <sub>2</sub> O <sub>3</sub>	none	30
2	Pd/Al <sub>2</sub> O <sub>3</sub>	TBAB	88
3	Pd/C	TBAB	100

<sup>a)</sup> Reaction conditions: 10 mmol 4'-chloroacetophenone, 11 mmol phenylboronic acid, 12 mmol sodium hydroxide, 3 mmol TBAB (where mentioned), NMP (10 mL), water (3 mL), 0.1 mol% Pd catalyst, 500 mg diethyleneglycol dibutyl ether as internal GC standard, argon, T = 120 °C, 2 h <sup>b)</sup> GC Yield

Conversion as a function of reaction time is illustrated in Figure 2.2 for the reaction of 4'-chloroacetophenone with phenylboronic acid shows this dramatic influence clearly. A sharp increase in reaction yield with the addition of TBAB may be due to stabilization of dissolved palladium species (against agglomeration) in the reaction mixture as has been proposed by Jeffery for Heck reactions. Similarly, Reetz and de Vries have demonstrated that the surfactants prevent undesired agglomeration of Pd metal colloids by forming a monomolecular layer around the metal core (Figure 2.3).



**Figure 2.2** Time dependent conversion of 4'-chloroacetophenone in Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed Suzuki coupling reaction with or without TBAB. Reaction conditions: 29 mmol 4'-chloroacetophenone, 32 mmol PhB(OH)<sub>2</sub>, 32 mmol NaOH, 10 mmol TBAB (optional), 0.1 mol% Pd (1% Pd/Al<sub>2</sub>O<sub>3</sub>). 120 °C oil bath temperature.



**Figure 2.3** Stabilization of nano-sized Pd colloids by tetra-*n*-butylammonium bromide (TBAB).

On the other hand, Calo' *et al.* showed that the *in situ* generated underligated Pd(0) species would most probably afford anionic 16 electron Pd complex  $[L_2Pd(0)Br]^{(-)}$   $(^+)NR_4$  that acts as catalytically active species according to Amatore-Jutand mechanism. In any case, the catalytic activity is referred to the stability of the active Pd species dissolved in the reaction mixture.

### 2.2.3 Pd-leaching Investigations at 120 °C

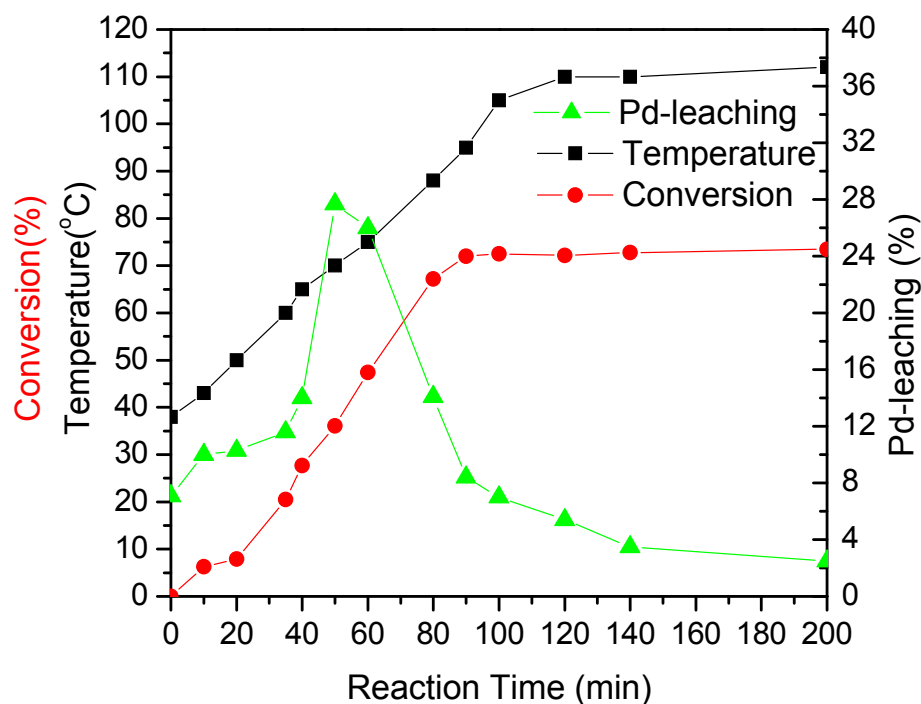
As mentioned earlier, some of the (probably) wrong conclusions in the literature claiming a “truly” heterogeneous character of Suzuki reactions (surface bound Pd is considered to be active species) stem from the fact that measurable amounts of palladium are often observed in solution only during the reaction. Because of re-deposition, the palladium concentration in the solution is very small or undetectable at the end of the reaction. Thus, the approach based on the analysis of the catalyst (or the reaction mixture) before and after the reaction may lead to ambiguous results.

A variety of different experimental approaches demonstrated rather clearly that – for Heck reactions – supported palladium catalysts serve as a reservoir for active palladium species leached into solution. A better understanding of analogous phenomena in heterogeneously catalyzed Suzuki reactions is of particular relevance for future design of commercially viable, highly active, recoverable, and reusable supported palladium catalysts.

In order to address the homogeneous or heterogeneous nature of the reaction, an inclusive experiment was planned with simultaneous determination of Pd concentration as well as conversion in the Suzuki coupling reaction. Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed coupling of 4-bromoanisole with phenylboronic acid was chosen as a model reaction. The experiment was carried out in a 500 mL flask under the optimized reaction conditions (NMP/water, Na<sub>2</sub>CO<sub>3</sub>, 120 °C). The samples were taken from the reaction mixture in short intervals with careful observation of any rise in temperature. One part of the sampled reaction mixture was hot filtered directly into a small round bottom flask to determine palladium content of the solution (elemental analysis), while the remaining part was extracted with dichloromethane to get the conversion of 4-bromoanisole (GC).

The results (Figure 2.4) show a direct correlation between the reaction progress and the amount of dissolved palladium species in solution. A sharp increase in the conversion of 4-bromoanisole is related to the maximum palladium amount leached into the solution. It is interesting to note that this happens at temperatures lower than 100 °C. This is in contrast to analogous experiments carried out for Heck reactions, where – for the same substrates – palladium leaching and conversion started only at

temperatures of or above 140 °C. The outcome of these studies indicates that whereas higher temperature (> 120 °C) is responsible for the generation of active Pd(0) species in Heck reactions, some additional factors are involved in Suzuki reactions that allow the Pd-leaching at temperatures lower than 100 °C.



**Figure 2.4** Time dependent correlation of palladium-leaching and conversion in Suzuki coupling reaction of 4-bromoanisole and phenylboronic acid at 120 °C. Reaction conditions: 116 mmol 4-bromoanisole (1 equiv.), 128 mmol PhB(OH)<sub>2</sub> (1.1 equiv.), 128 mmol Na<sub>2</sub>CO<sub>3</sub> (1.1 equiv.), 0.1 mol% Pd (1% Pd/Al<sub>2</sub>O<sub>3</sub>), 9 g GC standard (diethyleneglycol dibutyl ether, NMP:water 250:100 mL, argon, maximum temperature of oil bath: 120°C).

Although the phenomenon of leaching during the reaction is the same, (Pd is dissolved from the support and catalyzes the reaction in solution, finally re-depositing on the support when the reactants have been consumed), it was hypothesized that the mechanism of Pd-leaching is different for Heck and Suzuki reactions.

### 2.2.4 Suzuki Reactions of Aryl Bromides at 65 °C

The investigations on Suzuki coupling reactions at 120 °C prompted to study the reaction at lower temperatures. As demonstrated by Pd-leaching investigations at 120 °C (Figure 2.4), the reaction in fact starts at temperatures clearly below 100 °C. Lower reaction temperatures are also important with respect to applications of Suzuki coupling reactions in the pharmaceutical industry where low temperature reactions are encouraged to achieve high stereoselectivity for biologically active molecules. Thus, a series of experiments were performed in order to optimize the reaction conditions for Suzuki coupling reactions of aryl bromides at 65 °C. Finally, Pd-leaching investigations were carried out under the optimized reaction conditions. Following sections present the details of these investigations.

#### 2.2.4.1 Comparison of different Pd precursors

First, the activity of various supported catalysts was compared for Suzuki coupling of 4-bromoanisole with phenylboronic acid at 65 °C in NMP/water mixture. The results are summarized in Table 2.4. Ligandless palladium salts (entries 1 and 2, Table 2.4) gave low yields, apparently due to fast agglomeration of palladium species in the reaction mixture. In fact, palladium black appeared in this case in short time after mixing the substrates. As proposed by Reetz and de Vries, under ligandless conditions, active Pd species are in equilibrium with soluble Pd clusters and need to be stabilized by some additives to avoid the formation of inactive Pd black. The homogeneous Pd complex ( $[\text{Pd}(\text{PPh}_3)_2]\text{Cl}_2$ , entry 3) showed highest activity under given reaction conditions. The yields obtained with Pd/Al<sub>2</sub>O<sub>3</sub> (entry 4) were comparable to those obtained with Pd/C (entry 5) whereas Pd/NaY showed comparatively low activity.

**Table 2.4** Activity of different catalysts in Suzuki coupling reactions of 4-bromoanisole with phenylboronic acid.

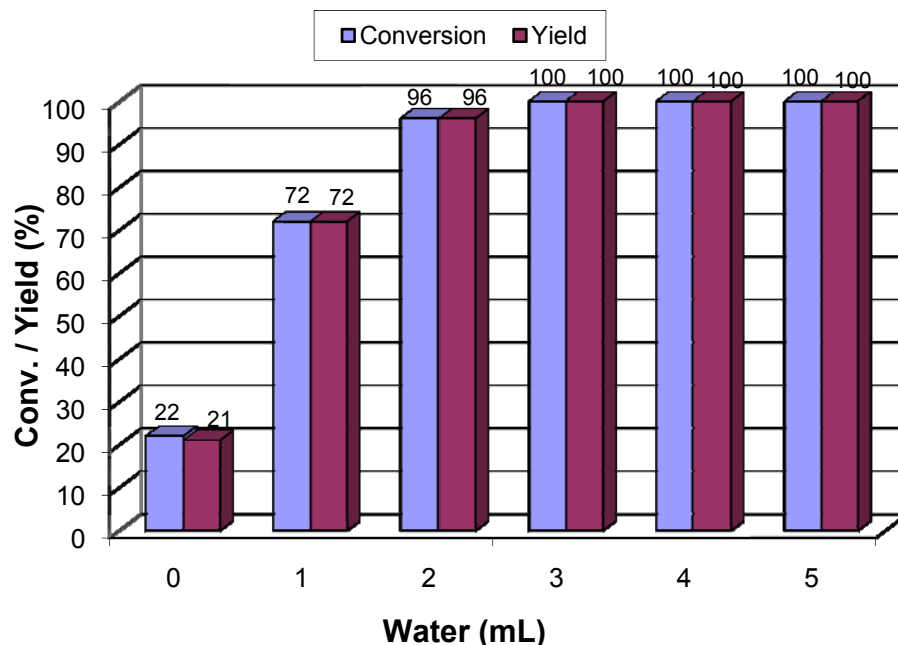
Entry	Catalyst	Conversion <sup>a)</sup> (%)	Yield <sup>b)</sup> (%)
1	Pd(OAc) <sub>2</sub>	15	11
2	PdCl <sub>2</sub>	7	7
3	[Pd(PPh <sub>3</sub> ) <sub>2</sub> ]Cl <sub>2</sub>	80	80
4	Pd/Al <sub>2</sub> O <sub>3</sub>	65	64
5	Pd/C	69	68
6	Pd/NaY	55	53

Reaction Conditions: 2.9 mmol 4-Bromoanisole, 3.2 mmol sodium carbonate, 3.2 mmol phenylboronic acid, 0.1 mol% Pd, NMP:water 5:2 mL, 65 °C, 4h, argon. <sup>a)</sup> Conversion of 4-bromoanisole <sup>b)</sup> GC-yield of the cross-coupled product

Pd/Al<sub>2</sub>O<sub>3</sub> was used as a catalyst for further investigations on Suzuki coupling reaction as it represents rarely used catalyst under mild reaction conditions and also less studied solid catalyst for Pd-leaching investigations.

#### 2.2.4.2 Influence of added water

Further, a large number of experiments were performed, aimed at the optimization of the reaction conditions in order to get simplified but active reaction protocol for Suzuki coupling reactions. First, the investigations were carried out in order to observe possible influence of the amount of water. As pictured in Figure 2.5, the reaction carried out in pure organic solvent (NMP), without addition of water, resulted in considerable decrease in the catalyst activity. Addition of 2 mL water increased the reaction yield to a great extent (96%). Further addition of water (up to 5 mL) had no special influence. The increase in the reaction yield with the addition of water is attributed to the solubility of the base and resulting salts (by-product) in water that allows fast reaction in organic phase.

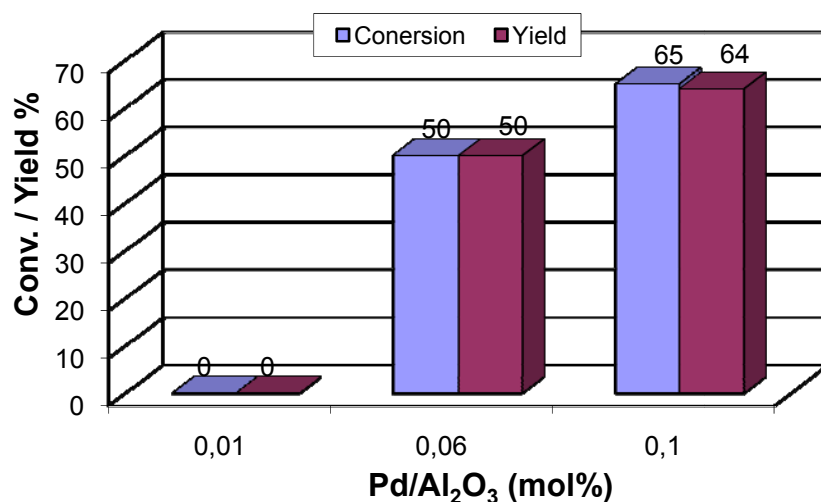


**Figure 2.5** Influence of quantity of water on Suzuki reaction of 4'-bromoacetophenone with phenylboronic acid. Reaction conditions: 2.9 mmol 4'-bromoacetophenone, 3.2 mmol  $\text{Na}_2\text{CO}_3$ , 3.2 mmol phenylboronic acid, 250 mg GC standard (diethyleneglycol dibutyl ether), 0.1 % Pd/ $\text{Al}_2\text{O}_3$ , 5 mL NMP, 4 h, argon, 65 °C.

#### 2.2.4.3 Influence of the catalyst amount and pretreatment

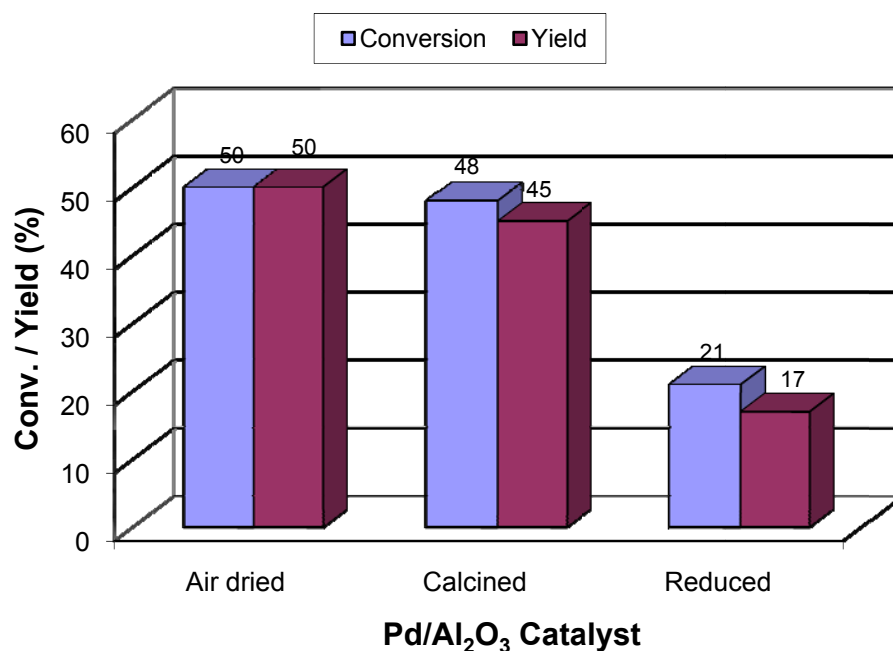
Next, the influence of different Pd concentration was observed in the Suzuki coupling reaction of 4-bromoanisole and phenylboronic acid at 65 °C (Figure 2.6). This is important for the economical as well as process engineering reasons as the excessive amount of Pd would not only lead to high reaction costs but hinder the efficiency of the catalytic process (Pd agglomeration, separation etc.). For the reaction of 4-bromoanisole with phenylboronic acid, 0.1 mol% Pd was found to be optimum Pd concentration resulting in 80% conversion within 4 h. Very low Pd concentrations (0.01 mol%) did not show any catalyst activity at this temperature. The reactivity was low when 0.06 mol% of supported Pd was used in the reaction and it furnished only 50% yield.





**Figure 2.6** Influence of Pd concentration on Suzuki coupling reaction of 4-bromoanisole with phenylboronic acid. Reaction conditions: 2.9 mmol 4-bromoanisole, 3.2 mmol phenylboronic acid, 3.2 mmol sodium carbonate, 1% Pd/Al<sub>2</sub>O<sub>3</sub>, 250 mg GC standard (diethyleneglycol dibutyl ether), NMP:water 5:2 mL, 65 °C, argon, 4h.

Further, influence of the pre-treatment procedures on the catalyst activity was verified in the Suzuki reaction of 4-bromoanisole with phenylboronic acid. Calcination in air at high temperature (500 °C) led to removal of water from the catalyst (brown catalyst), and additional reduction with hydrogen (at 350 °C) resulted in reduction of Pd(II) to palladium(0) particles on alumina support (dark grey powder). The results of Suzuki coupling reaction between 4-bromoanisole and phenylboronic acid are depicted in Figure 2.7. In fact Pd(II) species contribute towards high activity of the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst. Simple air dried catalyst resulted in 50% yield of cross coupled product (4-methoxybiphenyl) with 100% selectivity (no by-product formation); whereas activity and selectivity of the reaction was disturbed by using calcined catalyst under the same reaction conditions. Reduced catalyst furnished only 21% yield along with 5% biphenyl as by-product.



**Figure 2.7** Influence of the catalyst pre-treatment on the Suzuki reaction of 4-bromoanisole with phenylboronic acid. Reaction Conditions: 2.9 mmol 4-bromoanisole, 3.2 mmol sodium carbonate, 3.2 mmol phenylboronic acid, 0.06 mol% of Pd (0.6% Pd/Al<sub>2</sub>O<sub>3</sub>), NMP:water 5:2 mL, 65 °C, 4h, argon. (Conv. stands for the conversion of 4-bromoanisole; Yield refers to the Suzuki product: 4-methoxy biphenyl), Air dried = Catalyst used after drying at r.t. for 24 h, Calcined = Catalyst calcined at 500 °C for 2 h, Reduced = Catalyst reduced under pure H<sub>2</sub>, at 350 °C for 2 h.

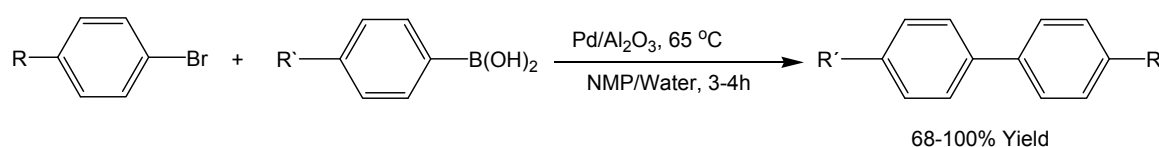
These experiments indicate that the catalysts with higher Pd oxidation state i.e. Pd(II) are better precursors to achieve high activity under these reaction conditions. Similar observations have been presented earlier in literature when alumina-zirconia mixed oxides were used as support for Suzuki coupling reactions; although the pre-reduced catalysts were mainly utilized in investigations.

#### 2.2.4.4 Scope of Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed Suzuki coupling reactions at 65 °C

A variety of substrates, including activated or deactivated aryl bromides could effectively be coupled under mild reaction conditions using 0.1 mol% Pd/Al<sub>2</sub>O<sub>3</sub> (Table 2.5). The reactions were performed after purging argon for five minutes through the reaction mixture in a pressure tube. However, in latter experiments it was found that the exclusion of air was not necessary; instead, better reaction yields were obtained when the reaction was carried out in an air atmosphere. Also the selectivity towards

desired cross coupled product was improved under these conditions (entry 10 in comparison to entry 3). Chloro- and fluoro- groups do not interfere with the catalytic activity of aryl bromides (entries 7 and 9); hence, the reaction conditions can selectively be applied for attack at the carbon-bromine bond.

**Table 2.5** Scope of Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed Suzuki coupling reaction of aryl bromides at 65 °C.

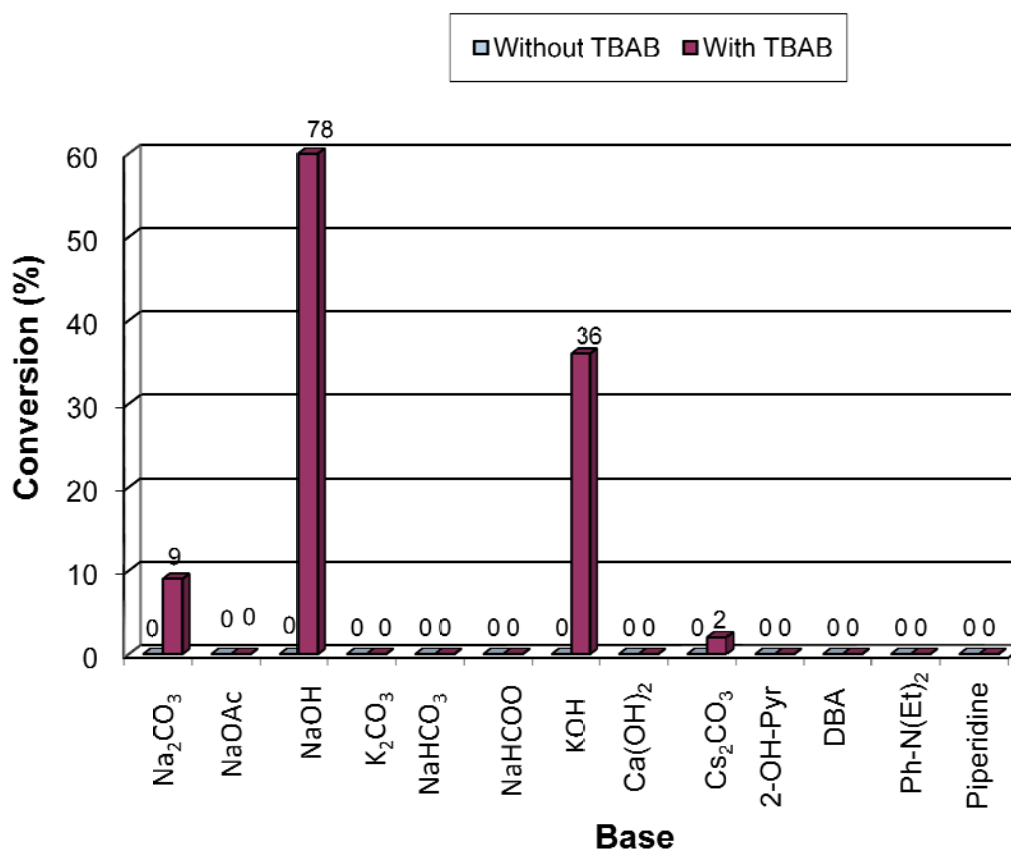


Entry	R	R'	Conversion <sup>a)</sup>	Yield <sup>b)</sup>
1	COCH <sub>3</sub>	H	100	100
2	H	H	95	95
3	OCH <sub>3</sub>	H	68	68
4	COCH <sub>3</sub>	CH <sub>3</sub>	100	100
5	H	CH <sub>3</sub>	87	87
6	NO <sub>2</sub>	H	100	100
7	Cl	H	95	95
8	CHO	H	100	100
9	F	H	96	96
<sup>c)</sup> 10	OCH <sub>3</sub>	H	80	80

Reaction conditions: 2.9 mmol aryl bromide, 3.2 mmol sodium carbonate, 3.2 mmol arylboronic acid, 0.1 mol% of Pd (1% air dried Pd/Al<sub>2</sub>O<sub>3</sub>), NMP:water 5:2 mL, 250 mg GC standard (diethyleneglycol dibutyl ether), 65 °C, argon, 4h. <sup>a)</sup> Conversion of aryl bromide; <sup>b)</sup> GC-yield of cross-coupled product; <sup>c)</sup> the reaction was performed without purging with argon.

### 2.2.5 Suzuki Reactions of Aryl Chlorides at 65 °C

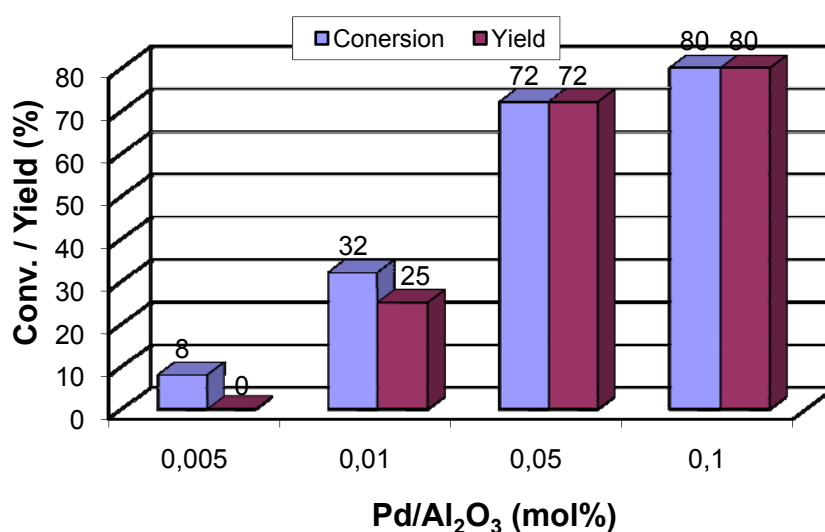
As shown in Table 2.5, chloro- group on aromatic ring remained unaffected (entry 7, Table 2.5) under the given reaction conditions. In general, activation of the aryl chlorides is more demanding and till now has only been realized in the presence of bulky ligands and/or at higher temperatures. The Suzuki coupling reaction of 4'-chloroacetophenone was tried with varying reaction parameters including the change of base and addition of tetra-*n*-butylammonium bromide (TBAB). The results are summarized in Figure 2.8. When sodium hydroxide was used as a base in presence of TBAB, 4'-chloroacetophenone was converted to the desired cross coupling product with high yield (78%). However, argon atmosphere was indispensable to facilitate the reaction.



**Figure 2.8** Variation of reaction conditions for Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid at 65 °C. Reaction conditions: 2.9 mmol 4'-chloroacetophenone, 4.5 mmol base, 3.2 mmol phenylboronic acid, 1 mmol TBAB, 0.1 mol% of Pd (1% Pd/Al<sub>2</sub>O<sub>3</sub>), 250 mg GC standard (diethyleneglycol dibutyl ether), NMP:water 5:2, argon, 4 h, 65 °C. 2-OH-Pyr= 2-hydroxypyridine, DBA= dibenzyl amine.

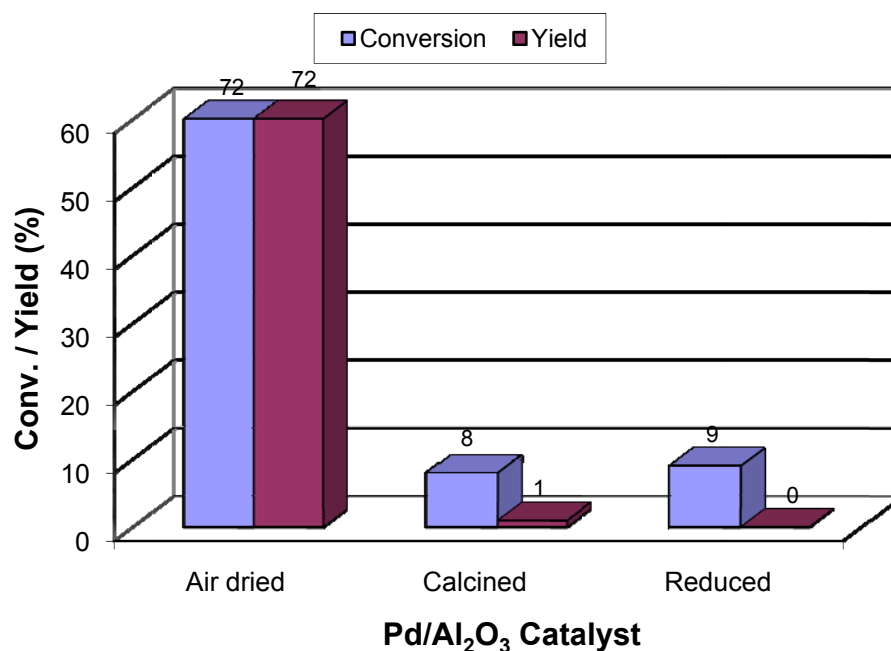
### 2.2.5.1 Influence of catalyst amount and pretreatment

A series of reactions was performed with lower catalyst amounts in order to test the reaction feasibility with lower Pd concentrations. The results are summarized in Figure 2.9. Conversion of 4'-chloroacetophenone dropped to 72% when the catalyst amount was reduced to one half (0.05% Pd). Further lowering of the catalyst amount resulted in loss of activity as well as selectivity of the reaction. No product could be obtained with 0.005 mol% Pd.



**Figure 2.9** Variation of the catalyst amount for Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid at 65 °C. Reaction conditions: 2.9 mmol 4'-chloroacetophenone, 4.5 mmol base, 3.2 mmol phenylboronic acid, 1 mmol TBAB, 1% Pd/Al<sub>2</sub>O<sub>3</sub>, NMP:water 5:2, argon, 4 h, 65 °C.

In another series of experiments, influence of the pretreatment (calcinations or reduction) procedures on the catalyst activity was verified in the Suzuki coupling reaction of 4'-chloroacetophenone. As shown in Figure 2.10, treatment of Pd/Al<sub>2</sub>O<sub>3</sub> catalyst at high temperatures in air (calcined at 500 °C for 2h) or in hydrogen atmosphere (reduced at 350 °C for 2h) resulted in severe loss of activity. The Suzuki coupling reaction yielded only 1% 4-acetylbiphenyl (desired product) with calcined catalyst whereas no product could be obtained with reduced catalyst. It indicates that the +2 oxidation state of Pd and some water content in the catalyst is necessary for the catalytic reaction.



**Figure 2.10** Influence of the catalyst pre-treatment on the Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid. Reaction Conditions: 2.9 mmol 4'-chloroacetophenone, 4.5 mmol sodium hydroxide, 3.2 mmol phenylboronic acid, 0.05 mol% of Pd (0.6% Pd/Al<sub>2</sub>O<sub>3</sub>), NMP:water 5:2 mL, 65 °C, 4h, argon. Air dried = Catalyst dried at r.t. for 24 h; Calcined = Catalyst calcined at 500 °C for 2 h; Reduced = Catalyst reduced under pure H<sub>2</sub>, at 350 °C for 2 h.

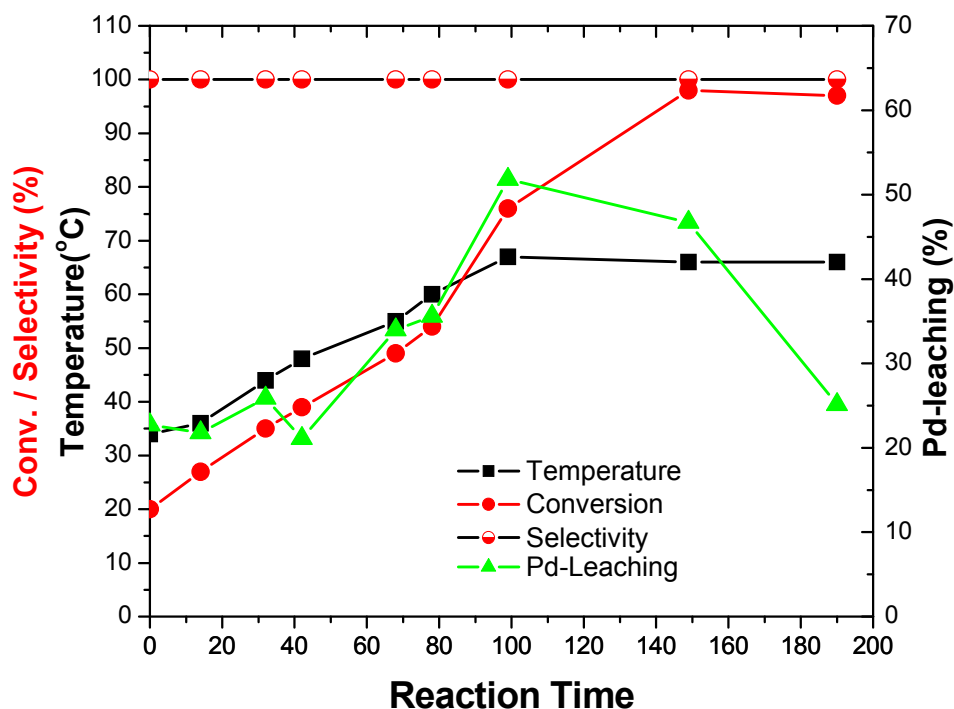
Further optimizations studies (variation of base, solvent, Pd precursors and catalyst concentration) to activate electron rich aryl chlorides were not successful at 65 °C. The activation of these substrates requires clearly higher temperatures as reported earlier.

## 2.2.6 Pd-leaching Investigations at 65 °C

### 2.2.6.1 Kinetic experiments on correlation of Pd-leaching and conversion

As earlier demonstrated, for Suzuki reactions at higher temperatures (120°C), that palladium is dissolved from the support during the reaction and (for the most part) re-deposited onto the support at the end of the reaction (Figure 2.4) when the substrates had been consumed. Such observations have already been given for

Heck reactions at 120-140 °C. The studies leave an open question whether or not the Pd leaching is possible under mild reaction conditions.

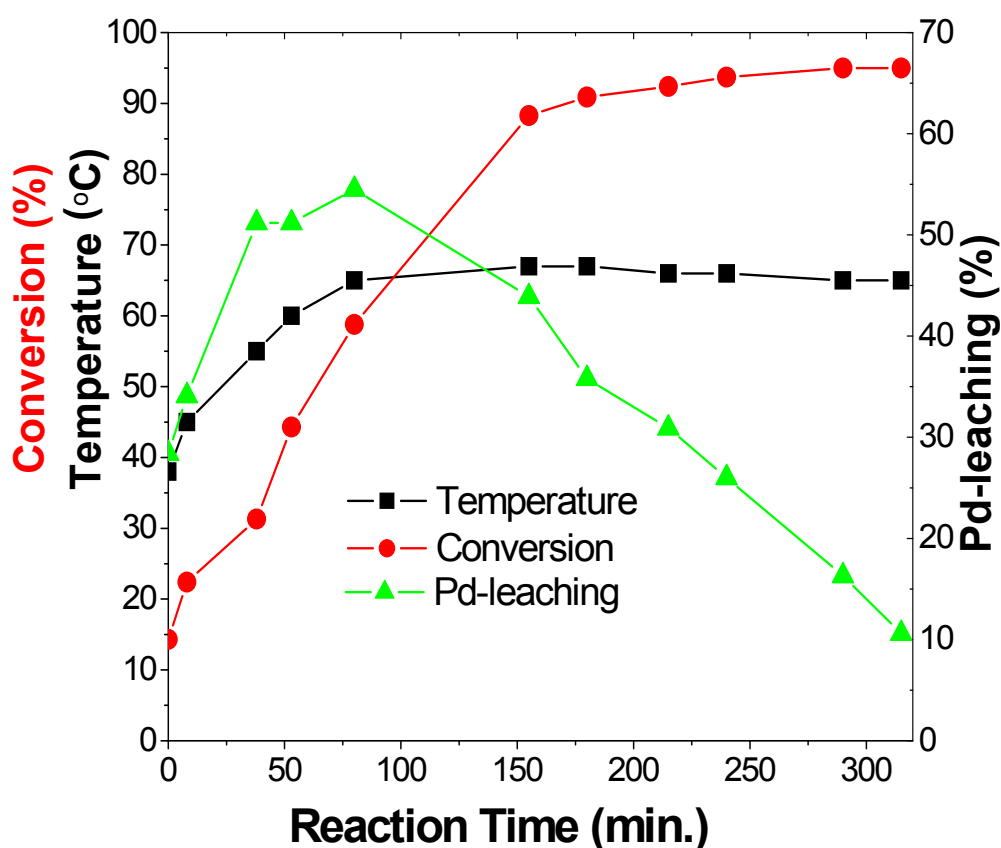


**Figure 2.11** Correlation of Pd-leaching with conversion of 4'-bromoacetophenone in Pd/Al<sub>2</sub>O<sub>3</sub> catalyzed Suzuki coupling reaction. Reaction conditions: 116 mmol 4'-bromoacetophenone, 128 mmol Na<sub>2</sub>CO<sub>3</sub>, 128 mmol PhB(OH)<sub>2</sub>, 9 g GC standard (diethyleneglycol dibutyl ether), NMP:Water 250:100 mL, 0.1 mol% Pd, (1% Pd/Al<sub>2</sub>O<sub>3</sub>), T= 65 °C.

To answer the above mentioned question, the investigations were performed at 65 °C, choosing Suzuki coupling reaction of 4'-bromoacetophenone with phenylboronic acid. As pictured in Figure 2.11, the reaction shows the same general trend, namely dissolution of Pd from the support followed by simultaneous conversion of the aryl halide. Pd concentration in solution decreases when aryl halide has been consumed to give Suzuki product (4-acetylbiphenyl). However, the Pd-leaching curve did not follow a smooth path, probably owing to rapid rise in temperature and/or due to substrate effect (4'-bromoacetophenone is highly activated aryl bromide). Nonetheless, it came out from this study that the leaching curve is different as compared with that at 120 °C; *i.e.* higher amount of Pd is dissolved during the

reaction (up to 50% as compared to 30% at higher temperature) and Pd re-deposition process is slower at lower temperature.

In order to understand the phenomenon in more detail, another kinetic experiment was designed with relatively simple substrate (bromobenzene) and with extended reaction time. Figure 2.12 represents the results of analogous experiments for Suzuki coupling reactions catalyzed by Pd on alumina at 65 °C. Bromobenzene as the aryl halide has been found to be the best substrate for these experiments in preliminary tests. In Figure 2.12, the palladium concentration in solution as well as the conversion of bromobenzene is presented as a function of reaction time and temperature.



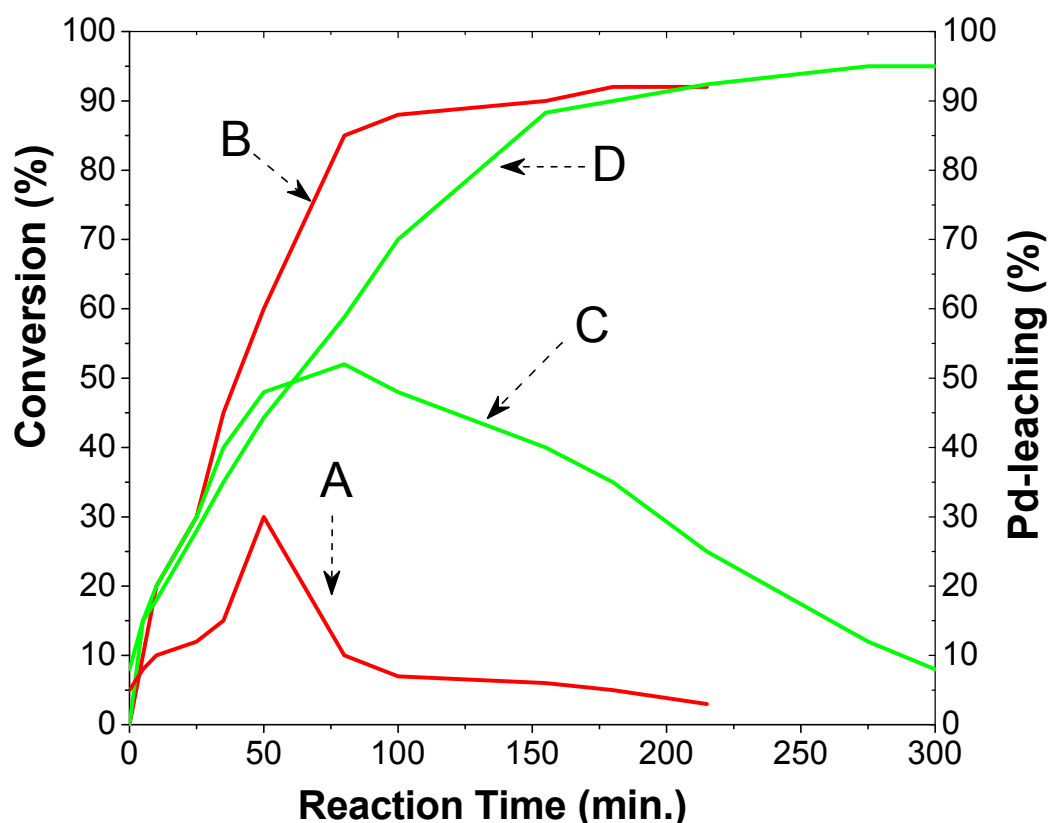
**Figure 2.12** Correlation of Pd-leaching and conversion in the Suzuki reaction of bromobenzene with phenylboronic acid. Reaction conditions: 116 mmol bromobenzene (1 equiv.), 128 mmol  $\text{Na}_2\text{CO}_3$  (1.1 equiv.), 128 mmol  $\text{PhB}(\text{OH})_2$  (1.1 equiv.), 9 g GC standard (diethyleneglycol dibutyl ether), NMP:water 250:100 mL, 0.1 mol% of Pd (1% Pd/ $\text{Al}_2\text{O}_3$ ),  $T = 65^\circ\text{C}$ .



Importantly, an oxidative addition of the aryl halide to a surface-bound palladium atom cannot be the driving force of palladium dissolution at this temperature as often hypothesized for Heck reactions at 140 °C. Higher temperature (more than 120 °C) is believed to generate active Pd(0) species that enter into catalytic cycle at that temperature. The conversion as well as Pd-leaching at 65 °C in Suzuki reaction suggests clearly some different mechanism associated with generation of the catalytically active species.

Analogous curves for palladium dissolution as a function of reaction time were observed for the Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid (not shown here). As expected on the basis of lower reaction rate with the aryl chloride and lower conversion (remaining substrate), the leaching curve was even broader, the amount of Pd in solution was lower (maximum being 25% of total Pd) and re-deposition is less efficient (considerable amount of Pd remained dissolved at the end of 5 hours reaction) for the aryl chloride compared to aryl bromides.

When comparing Pd-leaching at different temperatures, e.g. at 65 °C and 140 °C, it must be taken into account that the stability of the palladium complexes in solution is higher at lower temperatures. In contrast, higher temperatures force reduction to Pd(0) as well as precipitation of palladium (black). Also, the leaching at those higher temperatures is more difficult and *vice versa*, Pd re-deposits on the support more quickly. This effect has been applied for more efficient catalyst separation to avoid product contaminations e.g. in the pharmaceutical industry. Thus, different leaching mechanisms could be expected in different temperature ranges (Figure 2.13).



**Figure 2.13** A presentation of Pd-leaching and conversion in Suzuki coupling reactions at different temperature ranges; A: Pd-leaching at 120 °C, B: Conversion of aryl bromide at 120 °C, C: Pd-leaching at 65 °C, D: Conversion of aryl bromide at 65 °C.

#### 2.2.6.2 Palladium leaching as function of reaction parameters

Several reaction parameters that are different for Suzuki and Heck reactions (temperature, boronic acid/styrene, solvent (mixture), base, etc.) might be responsible for different leaching behavior in both reactions. This is the reason why a number of additional experiments were performed in order to observe the influence of various reaction parameters on the dissolution of palladium from the surface.

Table 2.6 summarizes experimentally determined palladium concentrations in solution observed in suspensions of the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst depending on solvent and on the presence or absence of additives (base, TBAB) and substrates (aryl halides, phenyl boronic acid). In all leaching experiments, the mixtures were stirred at 65 °C for one hour (i.e. the time when maximum palladium leaching was observed during

the Suzuki reaction, see Figure 2.12). The palladium content in the liquid phase was determined by AAS (all numbers in Table 2.6 are mean values of repeated measurements).

*Influence of the solvent (water, NMP, mixtures):* No palladium was detected in water. The concentration of Pd dissolved in NMP (1  $\mu\text{g/mL}$ ; 2%) and in NMP/water mixtures (2.5  $\mu\text{g/mL}$ ; 8%) is very low. Obviously some but only very low amounts of Pd can be dissolved by the chosen solvents under the given conditions.

*Influence of additives (base, TBAB):* The presence of TBAB (14  $\mu\text{g/mL}$ ; 47%) as well as the base sodium carbonate (11.4  $\mu\text{g/mL}$ ; 38%) gives rise to substantial dissolution of Pd from the support. This is in good agreement with the observation that base and TBAB play a crucial role for efficient Suzuki coupling reactions, being relevant in particular for difficult substrate (aryl chlorides, see Figure 2.8). It should be noted here that the present results concern experiments at 65 °C. It has been reported that for leaching experiments at higher temperatures, even the combined action of several additives does not dissolve Pd(II) or Pd(0) for Heck reactions up to 140 °C. The influence of base and temperature on Pd-leaching has been reported for Heck reactions at higher temperatures.

*Influence of the substrates (aryl halide,  $\text{PhB(OH)}_2$ ):* Mixing of phenylboronic acid with the catalyst in NMP/water resulted in visible palladium-black formation under the given conditions, indicating agglomeration of the leached palladium species (Table 4, entry 7). This implies that considerable palladium leaching occurs into solution due to phenylboronic acid. In the absence of additional substrates, (e.g. bromobenzene), the leached palladium species agglomerate to form palladium black. This is expected to occur due to subsequent dissolution, reduction (to Pd(0)) and agglomeration of palladium. Accordingly, Pd stabilized in solution by the base  $\text{Na}_2\text{CO}_3$  forms palladium-black if phenylboronic acid is additionally present due to reduction of Pd(II) to Pd(0) (entry 8). Pd-leaching in the presence of phenylboronic acid has recently been noticed (not determined) in Suzuki reactions catalyzed by Pd/C. Pd-leaching in the presence of either bromobenzene (3.6  $\mu\text{g/mL}$ ; 12%) or 4'-chloroacetophenone (3.0  $\mu\text{g/mL}$ ; 10%) is rather low and very similar in both cases. Simultaneous presence of aryl halide and base results in increased Pd-leaching in comparison to that observed for the aryl halide alone (entries 5 and 6).

**Table 2.6** Effect of different reagents on the palladium leaching under mild reaction conditions.

Entry	Solvent(s)	Catalyst	Additives, Substrates	Total Pd in mixture <sup>a)</sup> (mg)	[Pd] in solution <sup>b)</sup> (µg/mL)	% of total Pd in solution
1	NMP	1% Pd/Al <sub>2</sub> O <sub>3</sub>	---	0.284	1.0	2
2	H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	---	0.292	0	0
3	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	---	0.283	2.5	8
4	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	0.283	11.4	38
5	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	PhBr	0.285	3.6	12
6	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub> , PhBr	0.283	8.6	29
7	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	PhB(OH) <sub>2</sub>	0.288	1.2*	--
8	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub> , PhB(OH) <sub>2</sub>	0.284	0.6*	--
9	H <sub>2</sub> O	5% Pd/C (with 50.5% water)	--	0.285	0	0
10	NMP/H <sub>2</sub> O	Pd/C (with 50.5% water)	---	0.285	<2	N.D
11	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	NaOH	0.286	2.2	7
12	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	TBAB	0.283	14.0	47
13	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	CIPhCOCH <sub>3</sub>	0.284	3.0	10
14	NMP/H <sub>2</sub> O	1% Pd/Al <sub>2</sub> O <sub>3</sub>	NaOH, CIPhCOCH <sub>3</sub>	0.270	5.4	18

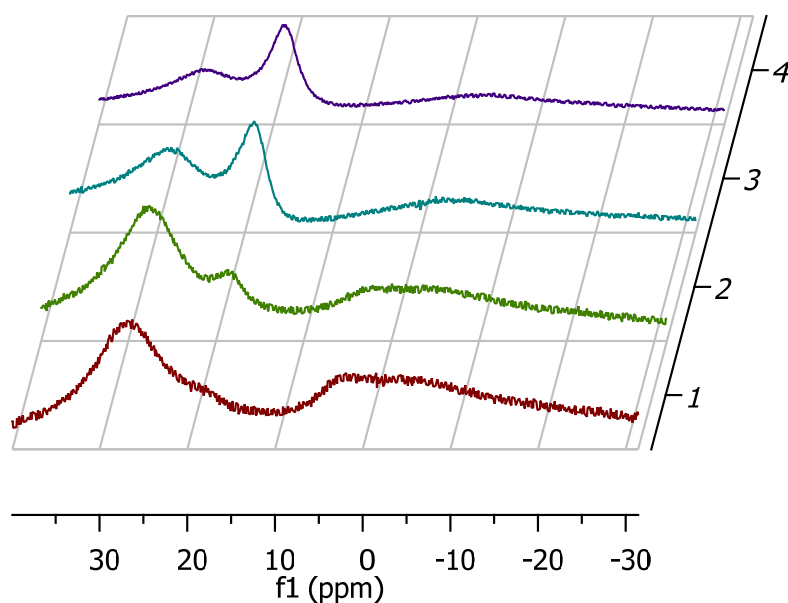
Conditions: The quantities used here are the same as used in the original Suzuki coupling reactions. NMP (5 mL), H<sub>2</sub>O (2 mL), ArX (2.9 mmol), Na<sub>2</sub>CO<sub>3</sub> (3.2 mmol), TBAB (1 mmol), PhB(OH)<sub>2</sub> (3.2 mmol), 0.0029 mmol Pd. <sup>a)</sup> Actual palladium content used in the mixture.

<sup>b)</sup> Palladium content was determined after heating the test mixtures at 65 °C for 1 h and subsequently filtering the hot mixture into the sample flask. \* Palladium black formation.

The experimental results demonstrate that all factors that influence the catalytic activity (substrates, additives, base and solvent) affect the Pd-leaching; however to clearly different extents for different substrates. Whereas very low or no leaching is observed in pure solvents at 65 °C, addition of base or TBAB brings around 40 to 50% of the total palladium present in the system into solution. Aryl halides alone cause very low Pd dissolution. They, however, play a crucial role in combination with phenylboronic acid. The latter causes substantial leaching of palladium accompanied by reduction and subsequent formation of palladium black. If however both substrates are present, the Pd(0) species in solution formed by the phenylboronic acid convert the aryl halide and are not precipitated as palladium black. The effect of the various parameters that influence Pd-leaching during the reaction is in good agreement with the parameters which need to be optimized for an efficient reaction, underlining the important role Pd-leaching plays for Suzuki reactions with supported catalysts.

### 2.2.7 <sup>11</sup>B NMR Experiment

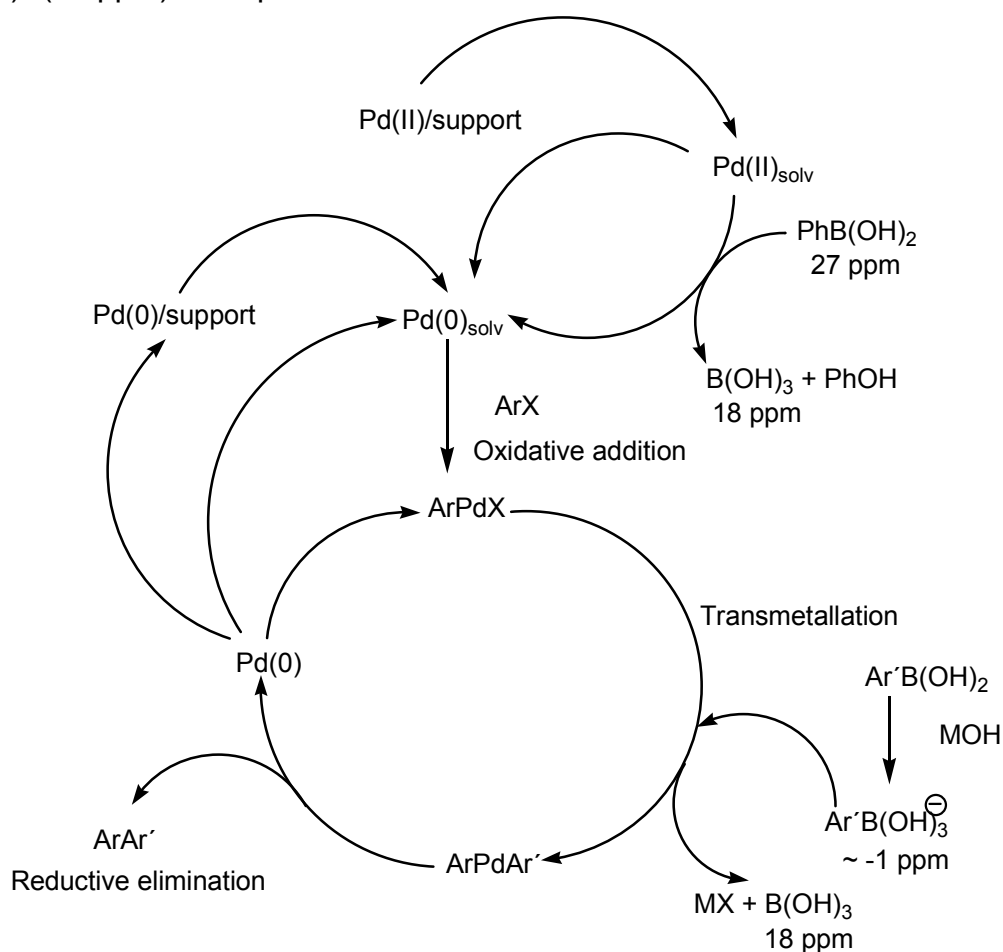
Boron NMR studies were carried out in order to get additional information on the role of boronic acid in Pd-leaching and in the reaction as a whole. Figure 2.14 shows the <sup>11</sup>B NMR spectra of the samples taken from the reaction mixture (Suzuki coupling reaction of bromobenzene with phenylboronic acid under given conditions) at different time intervals. Initially, the boron NMR spectrum of the reaction mixture was recorded without adding the catalyst.



**Figure 2.14**  $^{11}\text{B}$  NMR spectra of the reaction mixture recorded at different reaction times. 1. Stirring the reaction mixture at RT for 30 min without catalyst. 2. After adding catalyst, reaction mixture heated to 65 °C, reaction time: 5min. 3. Reaction time: 35 min. 4. Reaction time = 65 min.

As shown in Figure 2.14 (bottom), two main signals appear in the NMR spectrum: a relatively sharp signal (27.8 ppm) due to phenylboronic acid and a broader upfield signal (-1.0 ppm) representing a tetra coordinated boron species generated in the presence of base. A new boron signal starts appearing at about 18 ppm, indicating the formation of  $\text{B}(\text{OH})_3$  just after the addition of the catalyst ( $\text{Pd}/\text{Al}_2\text{O}_3$ ). The immediate formation of  $\text{B}(\text{OH})_3$  like species implies the initial interaction of the noble metal with the boron species (generation of  $\text{Pd}(0)$  species) in the reaction mixture. As the reaction proceeds further, the signal for  $\text{B}(\text{OH})_3$  (18 ppm) quickly grows ( $\text{B}(\text{OH})_3$  formation via repeated transmetalation steps). At the same time, the signal of  $\text{PhB}(\text{OH})_2$  (around 27 ppm) decreases considerably. On the other hand, the intensity of the broad signal for tetra coordinated species remains almost constant.

The observations imply that phenylboronic acid reacts quickly with  $\text{Pd}^{\text{II}}/\text{Al}_2\text{O}_3$  to produce boric acid ( $\text{B}(\text{OH})_3$ ) and possibly phenol ( $\text{PhOH}$ ). At the same time  $\text{Pd}(\text{II})$  is reduced to catalytically active  $\text{Pd}(0)$ . In the presence of an aryl halide, these active species enter the catalytic cycle (oxidative addition). Alternatively, when no active substrate is present,  $\text{Pd}(0)$  species aggregate to give palladium black as observed in the  $\text{Pd}$ -leaching tests (see Table 2.6).  $\text{B}(\text{OH})_3$  (signal at 18 ppm) is continuously generated in the transmetalation step of the catalytic cycle with consumption of  $\text{PhB}(\text{OH})_2$  (27 ppm) as depicted in Scheme 2.4.



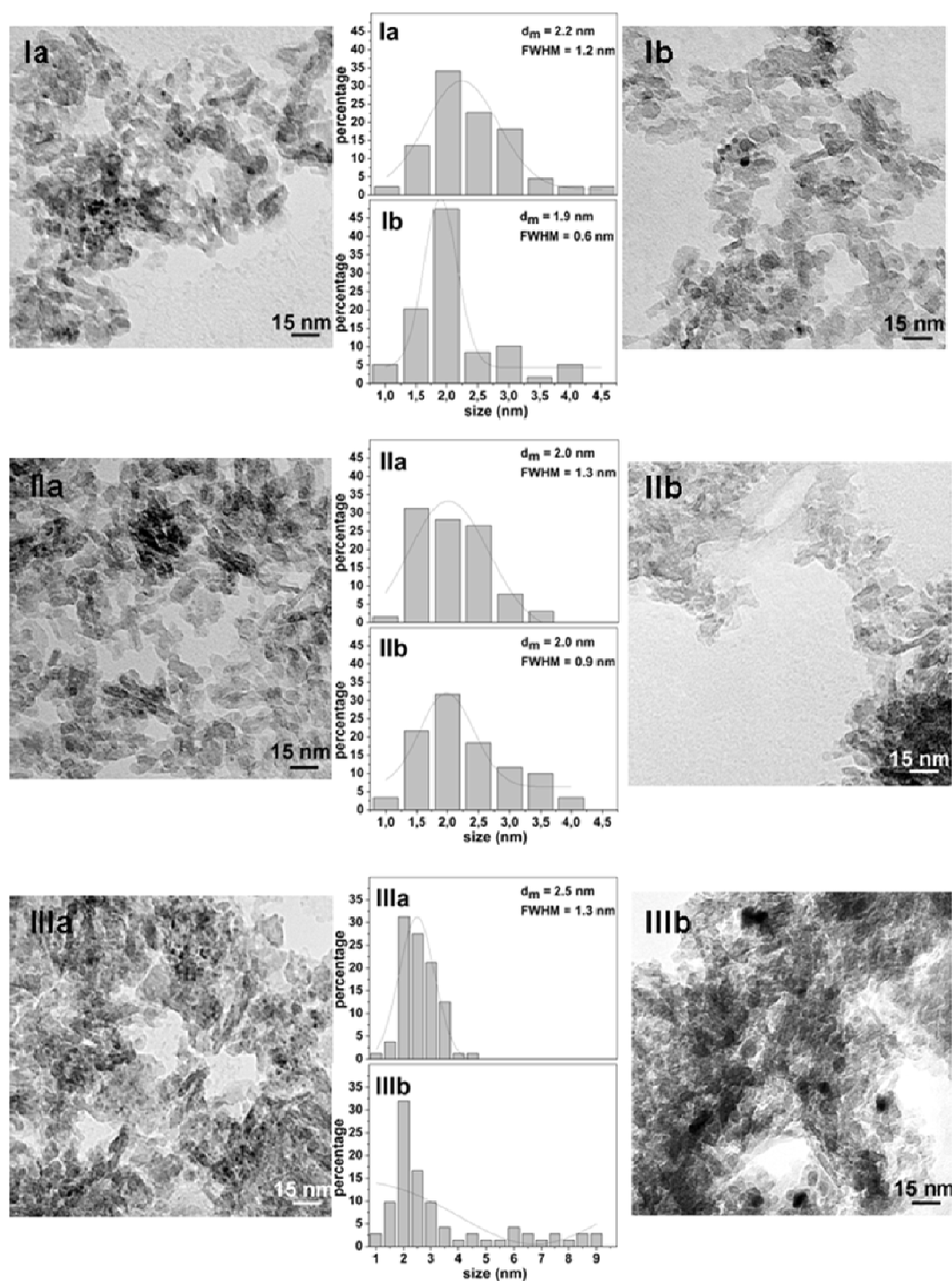
**Scheme 2.4** Catalytic cycle of Suzuki cross coupling reactions catalyzed by supported Pd catalysts at mild reaction temperatures deduced from leaching experiments and  $^{11}\text{B}$  NMR studies.

Although, the reduction of  $\text{Pd}(\text{II})$  to  $\text{Pd}(0)$  has been shown to take place in the presence of phenylboronic acids, however, the investigations present a mechanistic approach to evaluate the leaching phenomena and to correlate with corresponding solution-phase mechanism of the reaction.

### 2.2.8 TEM characterization of the catalyst before and after Suzuki coupling reactions

The experimental results described in section 2.2.6 (Figure 2.12) clearly show that the Suzuki coupling reaction involving supported catalysts is accompanied by Pd dissolution-re-deposition processes. The question arises whether the reaction affects the morphology and dispersion of the palladium particles on the surface of the support. Figure 2.15 represents TEM figures of fresh and spent catalysts with different palladium loadings (0.6 wt%, 2 wt% and 5 wt% Pd/Al<sub>2</sub>O<sub>3</sub>) used in Suzuki coupling reactions. Due to controlled immobilization procedures (identical in all cases), the fresh catalysts (Figure 2.15, Ia-IIIa) exhibit a high Pd dispersion and uniform particle size distribution. This uniform distribution of particle sizes can also be observed in the used catalysts (especially in Figures Ib-IIb) after almost 100% of the aryl bromide was converted into the desired product (Table 2.7, entry 1-2). Close observation of the Figures IIa and IIb (2 wt% Pd) indicates that the particle size distribution is even improved in the spent catalyst as compared to the fresh catalyst. This is important for the desired reusability of the catalyst. In contrast, the TEM figures of 5% Pd/Al<sub>2</sub>O<sub>3</sub> indicate that the initial uniform particle size distribution in the fresh catalyst (IIIa) is destroyed after the reaction (IIIb) corresponding to lower conversions (Table 2.7, entry 3). Similar observations have been reported for 5 wt% Pd/C catalysts used in Heck reactions. This illustrates the remarkable influence of palladium loading on the properties of the catalysts being relevant for recycling and re-use. Catalysts with higher Pd loadings leach more palladium into the solution. Higher total Pd concentrations in solution at a given time lead to less-controlled re-deposition processes. This results in a decrease in Pd dispersion during the reaction, leading to a significant decrease in the catalytic activity (50% conversion in 5 h, see Table 2.7, entry 3 vs. 80% conversion in 4 h, see Table 2.5, entry 10).





**Figure 2.15** TEM pictures of the Pd/Al<sub>2</sub>O<sub>3</sub> catalysts with different initial palladium-loading, before (left column) and after (right column) the Suzuki coupling reaction (for reaction conditions and yields see Table 2.7), showing nearly uniformly dispersed palladium nanoparticles (exception: IIIb). Pd particle size distributions are shown in the middle column. **Ia:** 0.6% Pd/Al<sub>2</sub>O<sub>3</sub> fresh catalyst, **Ib:** 0.6% Pd/Al<sub>2</sub>O<sub>3</sub> after reaction, **IIa:** 2.0% Pd/Al<sub>2</sub>O<sub>3</sub> fresh catalyst, **IIb:** 2.0% Pd/Al<sub>2</sub>O<sub>3</sub> after reaction, **IIIa:** 5.0% Pd/Al<sub>2</sub>O<sub>3</sub> fresh catalyst, **IIIb:** 5.0% Pd/Al<sub>2</sub>O<sub>3</sub> after reaction.

It can be concluded that the re-deposition process can be controlled by choosing the right catalyst (higher surface to metal ratio) and a carefully optimized reaction protocol.

**Table 2.7** Particle size distribution in palladium on alumina catalysts.

Entry	Pd/Al <sub>2</sub> O <sub>3</sub> loading (%)	Aryl halide; Conditions	Reaction Yield	Particle size (nm) determined from TEM	
				fresh catalyst	after reaction
1	0.6	PhBr; NMP/water, Na <sub>2</sub> CO <sub>3</sub> , 0.1 mol% Pd, 65 °C, air, 6h.	99%	2.2 ± 1.2	1.9 ± 0.6
2	2.0	PhBr; NMP/water, Na <sub>2</sub> CO <sub>3</sub> , 0.11 mol% Pd, 65 °C, air 6h.	100%	2.0 ± 1.3	2.0 ± 0.9
3	5.0	MeOPhBr; NMP/water, Na <sub>2</sub> CO <sub>3</sub> , 0.1 mol% Pd, 65 °C, air, 5h.	53%	2.5 ± 1.3	3,3 (no uniform distribution)

This concept can efficiently be used to improve the catalyst activity as well as reuse for practical applications. The results also clearly demonstrate that unchanged particle size distribution cannot be considered as a criterion for the heterogeneous mechanism of the reaction as has been claimed in some articles related to Suzuki reactions.

### 2.2.9 Conclusive Remarks: Suzuki coupling reactions in NMP/water at 65 °C

Supported palladium catalysts like Pd/Al<sub>2</sub>O<sub>3</sub> prepared by controlled precipitation of Pd(II) salts are highly active and selective catalysts for Suzuki cross couplings of aryl bromides and activated aryl chlorides under mild reaction conditions (65 °C, NMP/Water). Thermal treatment and reduction of the catalyst at higher temperatures cause substantial loss of activity and should be avoided for efficient catalysis. It has

been clearly demonstrated that palladium leaching during the reaction correlates directly to the progress of the reaction. The corresponding dissolved molecular palladium species are the active species in the reaction and a pre-requisite for high activity and selectivity. The palladium amount in solution depends in a complex manner on a variety of parameters. Base, additives, boronic acid and substrates differently contribute to palladium leaching. Temperature plays a crucial role in Pd-leaching; fast dissolution and re-deposition processes as higher temperature than at lower temperature. Under optimized reaction conditions, the reaction is slower at lower temperature; however it leads to favorable controlled Pd re-deposition process, bringing minimum change to the catalyst morphology. Hence, the Pd dispersion and particle size distribution on the support can be maintained or even improved by careful choice of catalyst (loading) and reaction parameters (relative substrate concentrations, solvent, temperature, base, additive). Accordingly, a variety of tests demonstrating the heterogeneous character of the catalytic cycle proposed and performed in the literature (as mentioned in Section 2.1) cannot be regarded as useful or sufficient. Palladium determination during the reaction represents a clearly more expressive and convincing experiment to elucidate the real nature of catalytically active species under given reaction conditions.

## 2.3 Suzuki Coupling Reactions in Pure Water

### 2.3.1 General Introduction

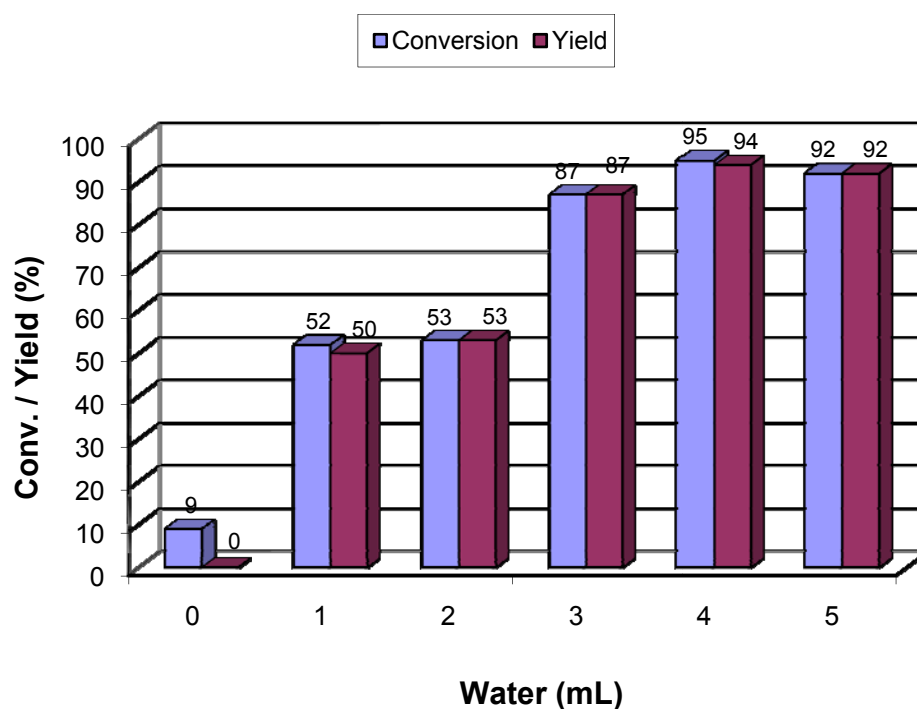
In the past few years, a number of strategies have been used to get commercially viable and highly active “green” catalysts for these reactions. Several strategies have been adopted with approach towards increasing the potentials of water as solvent for organic transformations. Water as a reaction medium offers many advantages as it is cheap, safe, non-toxic and easily available. In the recent years, there has been an increasing drift to utilize water as the only solvent medium for Suzuki coupling reactions. This section summarizes the results and mechanistic aspects of the Suzuki coupling reactions using heterogeneous Pd catalysts in water.

Earlier, high activity in Pd/activated carbon catalyzed Suzuki coupling reaction was demonstrated and reported by Lysen in our lab. A large variety of substrates including activated or un-activated aryl chlorides were efficiently coupled with arylboronic acids in pure water at 100-140 °C. Further study was focused on understanding of the reaction mechanism whereby Pd/C showed high activity in water. Thus, various heterogeneous palladium catalysts, having different surface properties, were tested for Suzuki coupling reactions in water. The reactions were carried out at low temperature (65 °C) for a number of related advantages. In general, heterogeneous palladium catalysts show high activity at higher reaction temperatures (> 100 °C). However, synthesis of the stereoselective biaryls, which constitute main part of many natural products, entail lower reaction temperatures. Regarding practical use of heterogeneous Suzuki coupling reactions for such reactions, it is highly desirable to develop catalytic protocol that could work at low temperatures. Moreover, influence of various reaction parameters and the support can better be understood at low temperatures as according to de Vries, the temperatures higher than 120 °C would always lead to the reduction of Pd (II) to Pd(0) species; a pre-requisite for the catalytic reaction. Present investigations are aimed to develop general understanding about the role of support for Suzuki coupling reactions in water. The optimization of the reaction conditions and the related support effects are described in the following paragraphs.

### 2.3.2 Pd/C Catalyzed Suzuki Coupling Reactions in Water under Mild Conditions

#### 2.3.2.1 Variation of amount of water

The effect of water as solvent was verified by carrying out the Suzuki coupling reaction of 4'-chloroacetophenone in varying amount of water (Figure 2.16). No yield of cross coupled product was obtained in the absence of water. The yield increased smoothly with increasing the volume of water in the reaction mixture and reached maximum (95%) in the presence of 4 mL of water. The results show that water as reaction medium is important, most probably because it can dissolve the by-products (salts), facilitating the product formation.

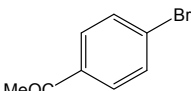
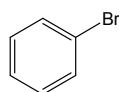
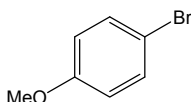
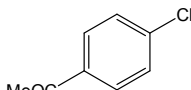


**Figure 2.16** Influence of amount of water on Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid. Reaction conditions: 2.9 mmol 4'-chloroacetophenone, 3.2 mmol phenylboronic acid, 4.5 mmol sodium hydroxide, 1 mmol TBAB, 0.1 mol% Pd/C, 250 mg GC standard (diethyleneglycol dibutyl ether), air, 65 °C, 4h.

### 2.3.2.2 Substrate scope for Pd/C catalyzed Suzuki coupling reactions of aryl bromides in water

Table 2.8 represents the results obtained in Suzuki coupling reactions of various aryl halides with phenylboronic acid. As expected, 4'-bromoacetophenone was converted to desired coupling product with 100% yield. Being hydrophilic in nature, acetyl group on the aromatic ring may be responsible for promoting the Suzuki coupling reactions in water. In addition, the substrates not bearing any hydrophilic substituent (entries 2-3) were also coupled in excellent yield under these conditions. The results emphasize involvement of the factors other than water miscibility of the reactants.

**Table 2.8** Pd/C catalyzed Suzuki couplings of aryl halides with phenylboronic acid.<sup>a)</sup>

Entry	Aryl halide	Conversion	Yield <sup>b)</sup> (%)
1		100	100
2		99	98
3		94	94
4		95	95

<sup>a)</sup>Reaction conditions: 2.9 mmol aryl halide (1 equiv.), 3.2 mmol phenylboronic acid (1.1 equiv.), 4.4 mmol NaOH (1.5 equiv.), 1 mmol TBAB, H<sub>2</sub>O (4 mL), 0.1 mol% of 5 % Pd/C (E 105 CA/W), 250 mg GC standard (diethyleneglycol dibutyl ether), 65 °C, 4 h (not optimized).

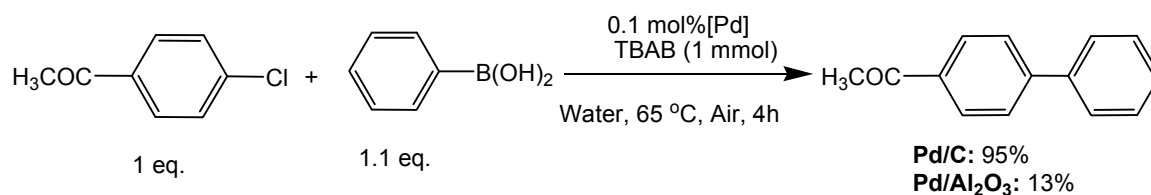
<sup>b)</sup>GC Yield of cross coupled product using diethyleneglycol dibutyl ether as internal standard.

### **2.3.3 Pd/MO<sub>x</sub> Catalyzed Suzuki Coupling Reactions in water at 65 °C**

The Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid was chosen as a model reaction for these investigations.

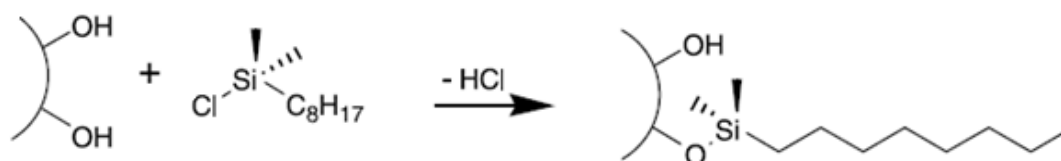
### 2.3.3.1 Influence of metal oxide support

In comparison to Pd/C, when the reaction of 4'-chloroacetophenone with phenylboronic acid was performed with Pd/Al<sub>2</sub>O<sub>3</sub> catalyst that had been demonstrated as highly active catalyst in NMP/water at 65 °C (Section 2.2), only low yield of cross coupled product was obtained (Scheme 2.5).



**Scheme 2.5** Comparison of the yield in Suzuki coupling reaction of 4'-chloroacetophenone catalyzed by Pd/C or Pd/Al<sub>2</sub>O<sub>3</sub> in water.

Considering the possible support effects in these reactions, it was hypothesized that hydrophobic nature of the activated carbon may be manipulating the reaction by increasing association with the organic substrate. This concept has earlier been applied to the hydrogenation and the Heck reaction in two phase reactions. It was demonstrated that, depending on the nature of the surface (hydrophilic or lipophilic), the catalyst resides in one of the two immiscible phases (one of them being water). To test this hypothesis, surface of alumina was hydrophobized (Scheme 2.6) before immobilization of the Pd on it.



**Scheme 2.6** Silylation of metal oxides (Al<sub>2</sub>O<sub>3</sub>-C<sub>8</sub> preparation).

Furthermore, other metal oxide supports possessing different surface properties were also utilized to prepare supported Pd catalysts for better comparison. Table 2.9 summarizes the characteristics of metal oxide materials used for this purpose.

**Table 2.9** Metal oxides used as supports for palladium in this study.

Support	Surface, Characteristics	Particle Size
Al <sub>2</sub> O <sub>3</sub> , C	100 m <sup>2</sup> /g, Hydrophilic, hydroxyl groups on the surface	13 nm
Al <sub>2</sub> O <sub>3</sub> -C <sub>8</sub>	100 m <sup>2</sup> /g, Hydrophobic, modified using n-octyl-dimethylchlorosilane before using it for catalyst preparation.	13 nm
TiO <sub>2</sub> (P-25)	90 m <sup>2</sup> /g, Hydrophilic, hydroxyl groups on the surface	~ 30 nm
T805	50 m <sup>2</sup> /g Hydrophobic, trimethoxy octyl silane coating on the surface	15-20 nm
T2000	Amphiphilic, Titania (80%) surface is coated with Al <sub>2</sub> O <sub>3</sub> (~8%) and Simethicone (a mixture of silica gel (~3%) and polydimethylsiloxane). primary particles aggregate to give roughly 100 nm sized needles.	10-15 nm

The Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid was carried out with a range of Pd catalysts supported on hydrophilic (Al<sub>2</sub>O<sub>3</sub> and TiO<sub>2</sub>), hydrophobic (Al<sub>2</sub>O<sub>3</sub>-C<sub>8</sub> and T805) and amphiphilic (T2000) metal oxide supports.

**Table 2.10** Heterogeneous Suzuki coupling of 4'-chloroacetophenone and phenylboronic acid catalyzed by different Pd/MO<sub>x</sub> catalysts.<sup>a)</sup>

Entry	Catalyst (mol%)	Surface	Conversion <sup>b)</sup>	Yield <sup>c)</sup>
1	Pd/Al <sub>2</sub> O <sub>3</sub> (0.1)	Hydrophilic	13	13
2	Pd/Al <sub>2</sub> O <sub>3</sub> -C <sub>8</sub> (0.1)	Hydrophobic	22	22
3	Pd/TiO <sub>2</sub> (0.1)	Hydrophilic	23	22
4	Pd/T805 (0.1)	Hydrophobic	45	45
5	Pd/T2000 (0.1)	Amphiphilic	41	40

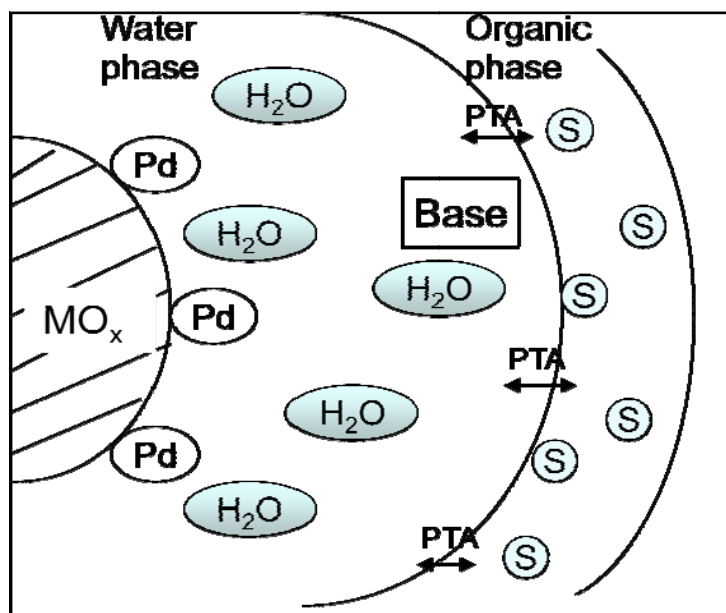
<sup>a)</sup> Reaction conditions: 2.9 mmol 4'-chloroacetophenone (1 equiv.), 3.2 mmol phenylboronic acid (1.1 equiv.), 4.4 mmol NaOH (1.5 equiv.), 1 mmol TBAB, 4 mL water, 65 °C, air, 4h. <sup>b)</sup> Conversion of 4'-chloroacetophenone; <sup>c)</sup> GC yield of cross coupled product using diethylene glycol dibutyl ether as internal standard.



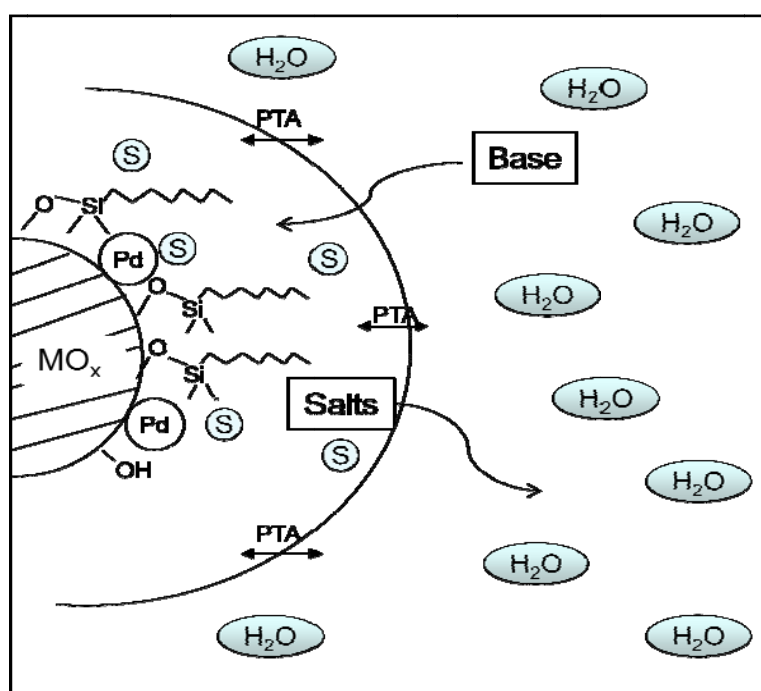
The results are displayed in Table 2.10. Relatively higher yield of the desired cross coupling product (4-acetylbiphenyl) was obtained when Pd on hydrophobically modified alumina was used (entry 2) in place of simple Pd/Al<sub>2</sub>O<sub>3</sub> catalyst (entry 1).

Pd/T805 (hydrophobic surface) and Pd/T2000 (amphiphilic surface) were found to be more active (40-45% yield in four hours) compared to other catalysts investigated under these conditions. The process can be visualized analogous to the so called *phase boundary catalysis* (PBC). Owing to strong hydrophobic effects, the organic substrates form a separate phase in water. Therefore, a catalyst that resides at the phase boundary (due to specific surface characteristics) would have a close contact with both phases and, ultimately, better catalytic activity for the reactions of lipophilic substrates in water. The phenomenon has been postulated for epoxidation reactions in aqueous H<sub>2</sub>O<sub>2</sub> where phase modified zeolites have been used as phase boundary catalysts.

According to this concept, heterogeneous Suzuki coupling reactions carried out in water can be viewed as 3-phase system: A solid catalyst, a lipophilic phase comprising organic substrates and an aqueous phase of water. The hydrophilic catalysts (like Pd/Al<sub>2</sub>O<sub>3</sub>) would more likely be confined in the aqueous phase with minimum possible contact with the organic substrates. Under these conditions, the catalytic activity will be low, strictly depending on the transport of the substrates to the aqueous phase. The presence of phase transfer agent (PTA) can bring some activity in this case as depicted in Figure 2.17. On the other hand, the catalyst possessing hydrophobically modified surface would have an increased contact with lipophilic substrates (S), resulting an ultimate increase in catalyst activity. An appropriate amount of water is required for the simultaneous extraction of salts generated during the catalytic reaction (Figure 2.18).



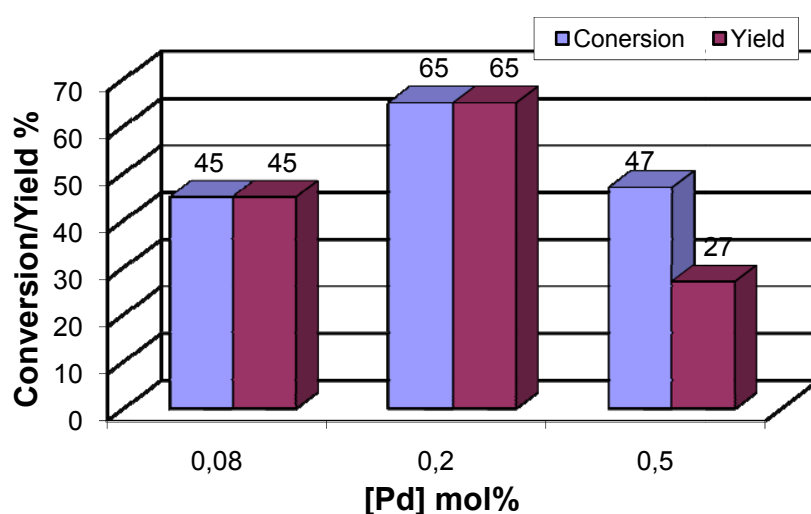
**Figure 2.17** Schematic representation of Suzuki coupling reaction catalyzed by Pd immobilized on hydrophilic metal oxide supports. S=Substrate, PTA= Phase Transfer Agent (TBAB in present case).



**Figure 2.18** Schematic representation of the transport phenomenon in Suzuki coupling reactions catalyzed by Pd catalysts possessing modified surface.

### 2.3.3.2 Variation of catalyst amount

With encouraging results in hand, the Suzuki coupling reaction of 4'-chloroacetophenone was further investigated with varying amount of Pd/T805 (hydrophobic surface) catalyst. Figure 2.19 shows that an increase in the amount of Pd catalyst resulted in an increase in yield of the cross coupled product (65% with 0.2 mol% Pd catalyst); however, still the change was not as much pronounced as compared with 0.08 mol% Pd. A further increase in Pd concentration up to 0.5 mol% resulted in considerable loss of catalyst activity due to obvious agglomeration of Pd in the reaction mixture; only 27% yield of the cross coupled product (4-acetylbiphenyl) was obtained accompanied by 20% biphenyl as a by-product. These results also suggest a possible link of Pd black with biphenyl formation. Possibly, the cross coupling reaction takes place at the phase boundary, whereas side reaction (biphenyl formation) results from surface catalysis.



**Figure 2.19** Influence of Pd concentration on the Suzuki coupling reaction of 4'-chloroacetophenone with phenylboronic acid. Reaction conditions: 2.9 mmol 4'-chloroacetophenone (1 equiv.), 3.2 mmol phenylboronic acid (1.1 equiv.), 4.4 mmol NaOH (1.5 equiv.), 1 mmol TBAB, 250 mg GC standard (diethyleneglycol dibutyl ether), 0.8% Pd/T805, 4 mL water, 65 °C, air, 4h.

### 2.3.3.3 Optimization of reaction parameters

Increasing the amount of base had a remarkable influence on the reaction yield (Table 2.11). Furthermore, purging the reaction mixture with argon before reaction

led to quantitative conversion of 4'-chloroacetophenone (entry 3). In addition to amphiphilic Pd/T2000, the hydrophobic catalysts (Pd/T805 and Pd/Al<sub>2</sub>O<sub>3</sub>) also showed high activity under these conditions. Thus, 80-100% yield of desired coupling product was possible for Suzuki coupling reaction of 4'-chloroacetophenone in water at 65 °C.

**Table 2.11** Optimization of reaction conditions for Pd/MO<sub>x</sub> catalyzed reaction of 4'-chloroacetophenone with phenylboronic acid<sup>a)</sup>

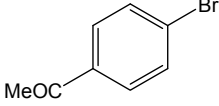
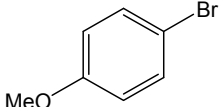
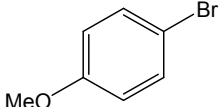
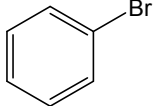
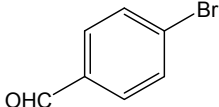
Entry	Catalyst	Atmosphere	Time	Yield <sup>b)</sup> (%)
1	Pd/T2000	Air	4	53
2	Pd/T2000	Argon	4	88
3	Pd/T2000	Argon	5	100
4	Pd/T805	Argon	5	95
5	Pd/Al <sub>2</sub> O <sub>3</sub> -C <sub>8</sub>	Argon	5	80

<sup>a)</sup> Reaction conditions: 2.9 mmol 4'-chloroacetophenone (1 equiv.), 3.2 mmol phenylboronic acid (1.1 equiv.), 1 mmol TBAB, 8.7 mmol NaOH (3 equiv.) 4 mL water, 0.2 mol% Pd catalyst, 65 °C. <sup>b)</sup> GC yield using diethylene glycol dibutyl ether as internal standard.

#### 2.3.3.4 Pd/modified metal oxides catalyzed Suzuki coupling reactions of aryl bromides in water

Further investigations were focused on application of the optimized reaction conditions to Suzuki coupling reactions of aryl bromides. The results for related experiments are summarized in Table 2.12. Various substrates including activated and deactivated aryl bromides could be coupled in good reaction yields (76-100%). The reaction of 4'-bromoacetophenone, as expected, was highly efficient and could be performed without addition of TBAB. However for other substrates, TBAB was mandatory to realize the high yielding catalytic reactions.

**Table 2.12** Suzuki couplings of aryl bromides with phenylboronic acid using palladium supported on metal oxides

Entry	Catalyst (mol%)	Base (equiv.)	Additive (mmol)	Aryl bromide	Time <sup>a)</sup> (h)	Yield (Suzuki-product) (%)
1 <sup>a</sup>	Pd/Al <sub>2</sub> O <sub>3</sub> -C <sub>8</sub> (0.1)	Na <sub>2</sub> CO <sub>3</sub> (1.1)	None		4	100
2 <sup>b</sup>	Pd/T2000 (0.2)	NaOH (3)	TBAB (1)		5	76
3 <sup>b</sup>	Pd/T805 (0.2)	NaOH (3)	TBAB (1)		5	76
4 <sup>b</sup>	Pd/T2000 (0.2)	NaOH (3)	TBAB (1)		5	88
5 <sup>a,b</sup>	Pd/T2000 (0.2)	NaOH (3)	TBAB (1)		4	100

Reaction conditions: 2.9 mmol aryl bromide (1 equiv.), 3.2 mmol phenylboronic acid (1.1 equiv.), 65 °C, 4 mL water. <sup>a</sup> Reaction time is not optimized; <sup>b</sup> under argon.

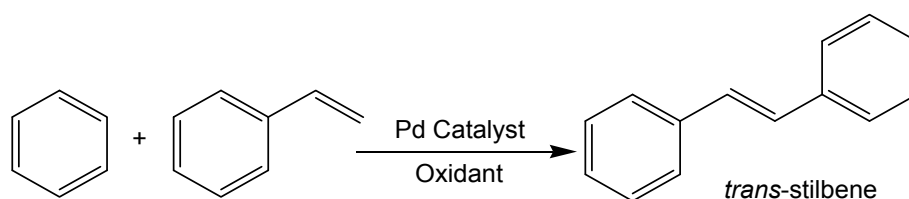
### 2.3.4 Conclusive Remarks: Suzuki coupling reactions in water

Suzuki coupling reaction of aryl bromides and activated aryl chlorides was successfully performed in pure water at 65 °C. By using a range of supported catalysts having different surface properties (hydrophilic, hydrophobic, amphiphilic), it has been verified that the surface properties of the support materials have a pronounced influence on the catalyst activity. It has been demonstrated that hydrophobic support facilitates the Suzuki coupling reaction under mild reaction conditions. It is suggested that the reaction takes place at the phase boundary near the catalyst surface.

## **Oxidative Coupling Reactions**

### 3.1 General Introduction

This section summarizes the investigations on oxidative coupling reactions using homogeneous (mainly  $\text{Pd}(\text{OAc})_2$ ) as well as heterogeneous ( $\text{Pd}/\text{zeolites}$ ,  $\text{Pd}/\text{C}$ ,  $\text{Pd}/\text{Al}_2\text{O}_3$ ) palladium catalysts in small amounts (1.5 mol%). The oxidative coupling of benzene and styrene, an olefin which has not often been used in literature up to now, has been chosen as a model reaction (Scheme 3.1). In comparison to acrylic esters, which are used more frequently, coupling reaction of styrene is more demanding due to its lower reactivity. Moreover, stilbene and its derivatives are desirable reaction products due to their long range applications in chemical industry.



**Scheme 3.1** Oxidative coupling of benzene and styrene.

These investigations led to the development of efficient catalytic reaction protocols for oxidative coupling reactions. The choice of an appropriate oxidant in adequate amounts was crucial to get high reaction yields. Reduced  $\text{Pd}(0)$  species generated during the oxidative coupling reactions could efficiently be reactivated in presence of vanadium(V) oxide as stoichiometric oxidant. In addition to  $\text{Pd}(\text{OAc})_2$ , several heterogeneous catalysts ( $\text{Pd}/\text{Al}_2\text{O}_3$ ,  $\text{Pd}/\text{NaY}$ ,  $\text{Pd}/\text{C}$ ) showed comparable reactivity for these reactions.  $\text{Pd}(\text{OAc})_2$  in the presence of benzoquinone as co-catalyst proved to be the best catalyst for oxidative coupling reaction of benzene with styrene (87% yield of *trans*-stilbene in 5 h). In addition, a catalytic protocol based on the use of TEMPO (2,2,6,6-Tetramethylpiperidine-1-oxyl) as stoichiometric oxidant also led to high reaction yields (up to 84% conversion, 64% selectivity) using 1.5 mol% of  $\text{Pd}(\text{OAc})_2$  as catalyst. Heterogeneous palladium catalyst ( $\text{Pd}/\text{NaY}$ ) could also be utilized to couple benzene and styrene in the presence of TEMPO as oxidant. The study represents a valuable contribution towards environmentally benign chemical reactions, being fundamental for the production of fine chemical synthesis.

Several other oxidants (metal salts) were tested using Pd/HPA catalytic system; only a few of them showed reasonable reactivity. The reactions involving peroxides ( $\text{H}_2\text{O}_2$  or  $t\text{BuOOH}$ ) as oxidants suffered from poor selectivity towards desired coupling product (*trans*-stilbene) possibly due to early oxidation of substrate (styrene). A detailed survey of these investigations is given in the following paragraphs.

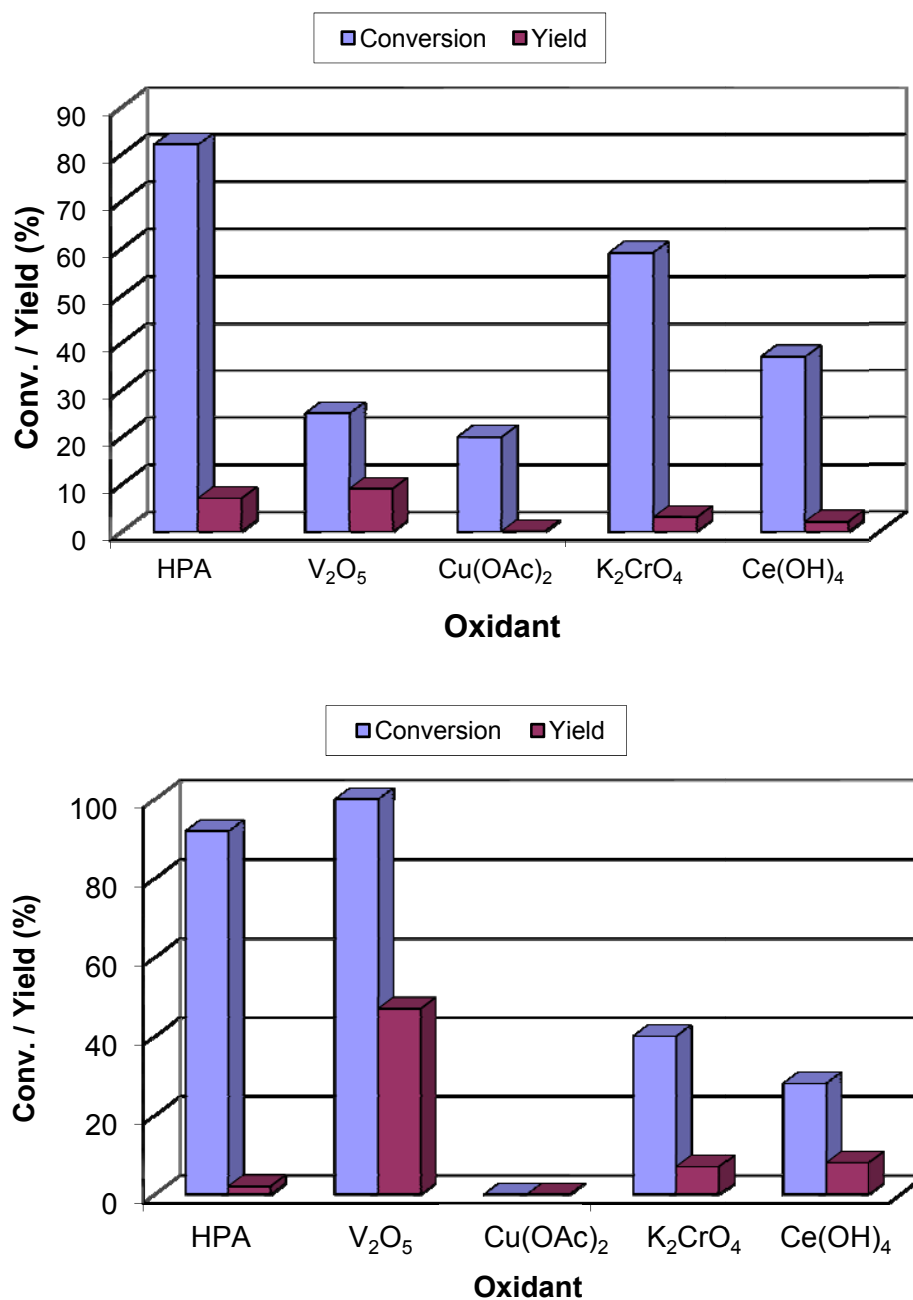
### 3.1.1 Screening of oxidants at different temperatures

First series of experiments was performed starting with the similar reaction conditions which have been reported in literature for oxidative coupling of benzene and acrylates. Various oxidizing agents were utilized in stoichiometric amounts using  $\text{Pd}(\text{OAc})_2$  as catalyst in oxidative coupling of benzene and styrene at different temperatures. Two electrons are released when one molecule of styrene and one molecule of benzene react to give stilbene. If a stoichiometric oxidation of 1.5 mmol of styrene is to be performed, the molar amount of oxidant has to be chosen in a way that 3 mmol of electrons can be absorbed (Table 3.1).

**Table 3.1** Molar amounts of different oxidants needed for oxidative coupling of 1.5 mmol of styrene and benzene (3 mmol of electrons).

Entry	Oxidants	Oxidation States	Transferred Electrons per mole	n (Oxidant) mmol
1	$\text{H}_4\text{PVMo}_{11}\text{O}_{40}$ (HPA)	+6/+4 (Mo) and +5/+4 (V)	23	0.13
2	$\text{V}_2\text{O}_5$	+5/+4 (V)	2	1.5
3	$\text{Cu}(\text{OAc})_2$	+2/+1 (Cu)	1	3
4	$\text{K}_2\text{CrO}_4$	+6/+3 (Cr)	3	1
5	$\text{Ce}(\text{OH})_4$	+4/+3 (Ce)	1	3





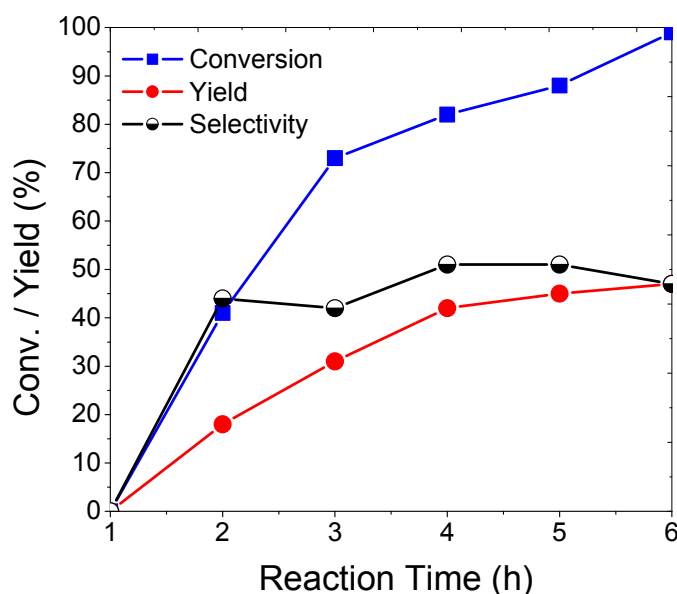
**Figure 3.1** Screening of oxidizing agents for oxidative coupling of benzene and styrene using various oxidizing agents at 90 °C (above) or 120 °C (below). Reaction Conditions: 1.5 mmol styrene, 0.1 mmol NaOAc, 2 redox equivalents of oxidant (V<sub>2</sub>O<sub>5</sub>: 1.5 mmol, Ce(OH)<sub>4</sub>: (3 mmol), Cu(OAc)<sub>2</sub>: 3 mmol, K<sub>2</sub>CrO<sub>4</sub> (1 mmol), HPA (0.13 mmol)), 0.1 mmol acetylacetone as ligand, 125 mg of GC standard (*n*-hexadecane), 1.5 mol% Pd(OAc)<sub>2</sub>, 30 mmol benzene (20 equiv.), 5 ml of acetic acid, 5 h.

As shown in Figure 3.1, in almost all cases, comparatively higher yields were obtained at 120 °C than at 90 °C. The reaction using heteropoly acid (HPA) as oxidant is favored at lower temperature; however the reaction is slow in this case.

Among the other oxidants tested under same conditions, vanadium(V) oxide emerged as the most appropriate oxidant (47% yield of *trans*-stilbene) at 120 °C. Besides,  $K_2CrO_4$  (7% yield) and  $Ce(OH)_4$  (8% yield) exhibit reasonable reactivity as oxidant in these reactions. The reaction was further optimized using  $V_2O_5$  as oxidant.

### 3.1.2 Time-dependant correlation of activity and selectivity in oxidative coupling reactions

Figure 3.2 presents a time-dependant correlation of conversion and yield for oxidative coupling reaction of benzene and styrene carried out with stoichiometric amount of  $V_2O_5$  as oxidant. A linear increase in conversion (up to 73%) could be noticed in first three hours. Subsequently, the conversion curve inclines gently, finally meeting 100% conversion in six hours. On the other hand, a linear increase in the formation of stilbene is observed in first four hours (45% yield), with no considerable change in the next two hours (47%).

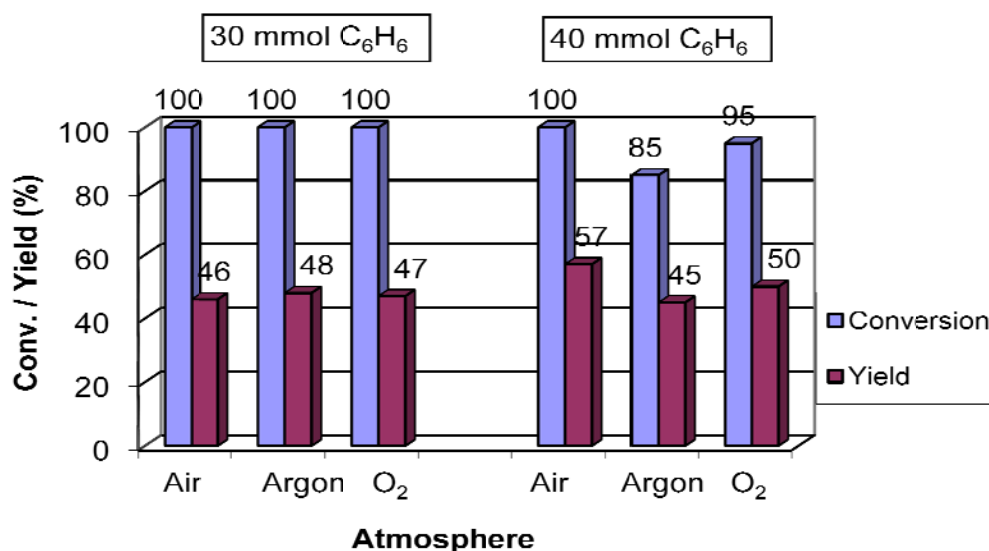


**Figure 3.2** Time-dependant correlation of conversion and yield in oxidative coupling of benzene and styrene. Reaction conditions: 1.5 mmol styrene, 0.1 mmol NaOAc, 1.5 mmol  $V_2O_5$ , 0.1 mmol acetylacetone as ligand, 125 mg of GC standard (*n*-hexadecane), 30 mmol (20 equiv.) benzene, 1.5 mol%  $Pd(OAc)_2$ , 5 ml of acetic acid, 120 °C.

The selectivity towards main product (*trans*-stilbene) remains almost constant (about 50%) under these conditions, suggesting the involvement of a mechanism where two competing pathways (leading to formation of product and side-product respectively) are operating side by side. From a practical point of view, higher selectivity is a main key for development of efficient catalytic systems. Thus, it is important to suppress the formation of side products (mainly oligomerization of styrene).

### 3.1.3 Influence of molar excess of benzene and reaction atmosphere

A large excess of benzene in comparison to olefin is believed to suppress the side reaction involving oligomerization of the latter in oxidative coupling reactions and thus can be helpful to increase selectivity towards desired cross coupling product. Moreover, in most of the oxidative coupling reactions reported in literature up to now, a high pressure of oxygen was maintained in autoclaves to get high conversions. Thus, a series of experiments were carried out in order to observe the effect of reaction atmosphere.

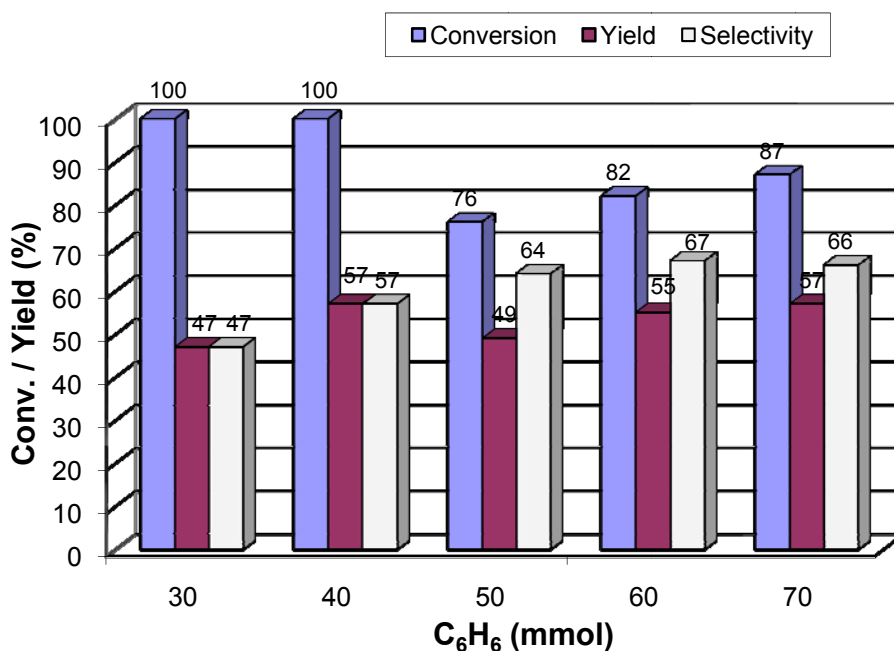


**Figure 3.3** Influence of reaction atmosphere on oxidative coupling reaction using stoichiometric amount of  $V_2O_5$  as main oxidant and different concentrations of benzene. Reaction conditions: 1.5 mmol styrene, 0.1 mmol NaOAc, 1.5 mmol  $V_2O_5$ , 0.1 mmol acetylacetonate as ligand, 125 mg of GC standard (*n*-hexadecane), 30 or 40 mmol benzene, 1.5 mol%  $Pd(OAc)_2$ , 5 ml of acetic acid, 120 °C, 4 h.

The reactions were carried out in two sets using 20 equivalents (30 mmol) or 25 equivalents (40 mmol) of benzene as compared to styrene (1.5 mmol). Whereas the reaction mixture in the pressure tube was purged with argon or oxygen for five minutes and closed tightly before bringing into a pre-heated oil bath (120 °C), the experiments under air atmosphere were performed without gas purging.

Figure 3.3 represents the influence of atmosphere on the oxidative coupling of benzene and styrene. High conversion of styrene was observed in all cases. The reaction atmosphere had a little effect on the reaction yield; however, as expected, the selectivity to desired cross coupled product (yield of *trans*-stilbene as compared to total conversion of styrene) was improved when 40 mmol of benzene were added instead of 30 mmol. The reaction proceeded very well in air corresponding to 57% yield in four hours.

As higher molar concentration of benzene led to higher reaction yields (Figure 3.3), a set of reactions were performed using large excess of benzene. Figure 3.4 presents a comparison of yield obtained with different molar amounts of benzene in oxidative coupling reaction. The selectivity towards desired cross-coupled product increased gradually when higher molar concentrations of benzene were applied. A maximum selectivity of 67% was achieved in the reaction where 60 mmol of benzene (40 equivalents based on styrene) were used.

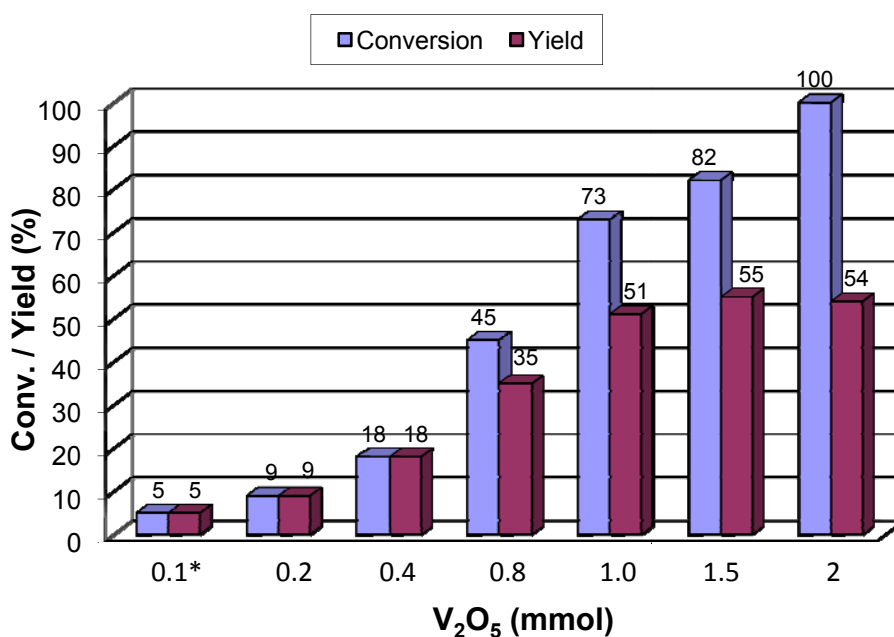


**Figure 3.4** Influence of molar concentrations of benzene on oxidative coupling of benzene and styrene using  $V_2O_5$  as oxidant. Reaction conditions: 1.5 mmol styrene, 1.5 mol%  $Pd(OAc)_2$ , 0.1 mmol  $NaOAc$ , 1.5 mmol  $V_2O_5$ , 0.1 mmol acetylacetone as ligand, 125 mg of GC standard (*n*-hexadecane), excess of benzene, 5 ml of acetic acid, 120 °C, Air atmosphere, 4 h.

### 3.1.4 Variation of oxidant amount

All oxidative coupling reactions presented up to now using vanadium(V) oxide as oxidizing agent have been carried out in presence of stoichiometric amount of oxidant (1.5 mmol  $V_2O_5$  corresponding to 3 mmol of electrons). However, for potential practical applications, it is highly desirable to reduce the oxidant amount to catalytic level. The general idea exists in reoxidation of the spent catalyst by molecular oxygen, which then acts as stoichiometric oxidizing agent. Thus, a reaction of benzene with styrene was tried in presence of catalytic amount of  $V_2O_5$  (0.1 mmol, 5 mol%). The reaction mixture was purged with  $O_2$  for five minutes before bringing into preheated oil bath at 120 °C. As shown in Figure 3.5, the attempt turn into significant lowering of the reaction yield and only 5% conversion could be achieved in four hours. In other words, under the chosen reaction conditions,  $V_2O_5$  acts as a stoichiometric oxidant which is hard to recycle with the help of molecular oxygen.

In addition, a series of experiments were carried with a gradual increase in the amount of oxidant in air atmosphere. Although lower concentrations of  $V_2O_5$  (up to 0.4 mmol  $V_2O_5$ ) helped to avoid the formation of the side-products, the reaction was considerably slow (18% conversion) in this case. One equivalent of  $V_2O_5$  (1.5 mmol), chosen on the basis of number of electrons required for the redox process (See Table 3.1), in fact proved the ideal concentration to obtain high yields in the reaction (Figure 3.5). Still higher molar concentration of  $V_2O_5$  was also not helpful to get high reaction yields.

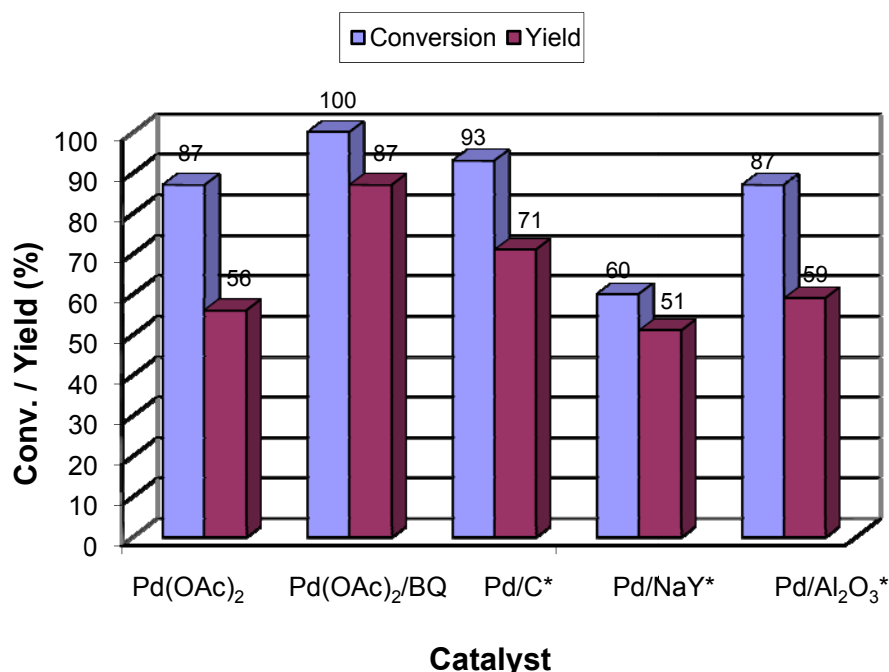


**Figure 3.5** Influence of molar concentrations of  $V_2O_5$  on oxidative coupling of benzene and styrene. Reaction conditions: 1.5 mmol styrene, 0.1 mmol NaOAc,  $V_2O_5$ , 0.1 mmol acetylacetonate as ligand, 125 mg of GC standard (*n*-hexadecane), 60 mmol benzene (5.3 mL), 1.5 mol%  $Pd(OAc)_2$ , 5 ml of acetic acid, 120 °C, Air atmosphere, 4 h. \*reaction mixture was purged with  $O_2$  for 5 min ( $P_{O_2} \approx 0.6$  atm).<sup>1</sup>

<sup>1</sup> Standard volume of 1 mole of an ideal gas at STP: 22.4 liters ( $V_{STP}$ ), Assuming that out of total volume of the pressure tube (50 mL), 10.5 mL is occupied by the solvent and liquid substrates (benzene and styrene), and the rest ( $V_i = 39.5$  mL) by the purged  $O_2$ , the  $O_2$  pressure  $P_i$  can be calculated from the relationship:  $P_i V_i / T_i = nR = P_{std} V_{STP} / T_{std}$ , where  $P_{std}$  and  $T_{std}$  are standard pressure (1 atm) and temperature (273 K) respectively and  $T_i$  is the initial temperature (298 K) at which  $O_2$  is purged into the reaction mixture.

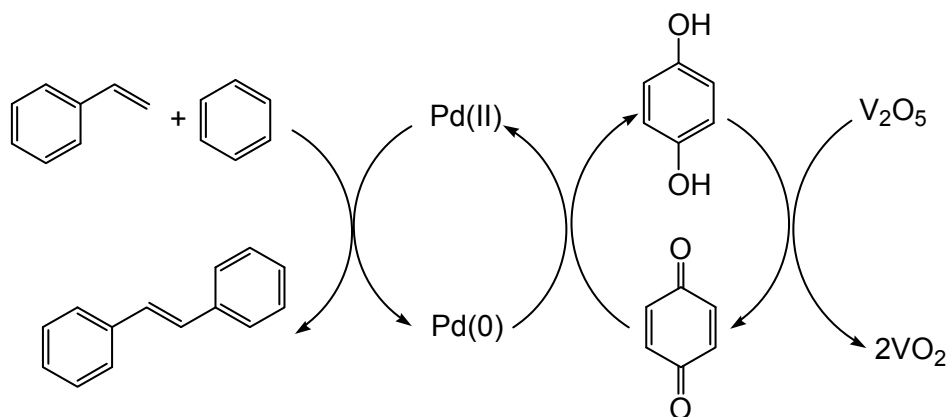
### 3.1.5 Varying the Pd-source in oxidative coupling reactions

Various Pd sources including homogeneous Pd(OAc)<sub>2</sub> alone or Pd(OAc)<sub>2</sub> in presence of catalytic amount (3 mol%, 0.046 mmol) of benzoquinone) as well as heterogeneous (1% Pd/Al<sub>2</sub>O<sub>3</sub>, 1% Pd/NaY, 5% Pd/C) were investigated as potential catalysts for oxidative coupling of benzene and styrene. The reactions were performed for an extended reaction time (5 h instead of 4 h) at two different reaction temperatures (120 °C for homogeneous reactions and at 140 °C for reactions with heterogeneous catalysts). The results of these experiments are summarized in Figure 3.6. A high yield of *trans*-stilbene (87%) was achieved in the homogeneous coupling reaction (1.5 mol% Pd(OAc)<sub>2</sub>) using 3 mol% benzoquinone (BQ) as a co-catalyst. Earlier, the use of benzoquinone as co-catalyst for such reactions has been reported in the presence of <sup>t</sup>BuOOH as a stoichiometric oxidant. In addition, benzoquinone as co-catalyst has also been reported for palladium-catalyzed oxidation of 1,3-dienes in acetic acid using a metal oxide (MnO<sub>2</sub>) as an oxidant. A high activity of Pd(OAc)<sub>2</sub> in combination of benzoquinone can be attributed to the efficient oxidation-reduction process associated with benzoquinone.



**Figure 3.6** Variation of catalysts for oxidative coupling of benzene and styrene. Reaction conditions: 1.5 mmol styrene, 0.1 mmol NaOAc, 1.5 mmol V<sub>2</sub>O<sub>5</sub>, 0.1 mmol acetylacetone as ligand, 125 mg of GC standard (*n*-hexadecane), 70 mmol benzene (6.2 mL), 1.5 mol% Pd-catalyst, 3 mol% benzoquinone (BQ, where mentioned), 5 ml of acetic acid, 120 °C, Air atmosphere, 5 h. \*reaction was carried out at 140 °C.

It can be suggested that benzoquinone acts as an oxidant for *in situ* generated Pd(0) species to give active Pd(II) species and is, in turn, reduced to its hydroxy form (hydroquinone). The continuous regeneration of benzoquinone is possible by stoichiometric amount of  $V_2O_5$  which is in turn reduced to V(IV) species (Scheme 3.2). It should be pointed out here that the efforts to use benzoquinone alone as stoichiometric oxidant for these reactions did not furnish considerable yields.



**Scheme 3.2** A plausible pathway for the Pd catalyzed oxidative coupling reaction of benzene and styrene promoted by benzoquinone as co-catalyst and vanadium(V) oxide as an oxidizing agent.

Moreover, heterogeneous catalysts also showed remarkable activity for oxidative coupling of benzene and styrene at slightly higher temperature (140 °C). The comparable activity of heterogeneous catalysts as compared to  $Pd(OAc)_2$  implies the similarities in the reaction mechanism in both cases. Heterogeneous Pd-catalysts might be acting as a reservoir for soluble active palladium species that catalyze the reaction under suitable reaction conditions.

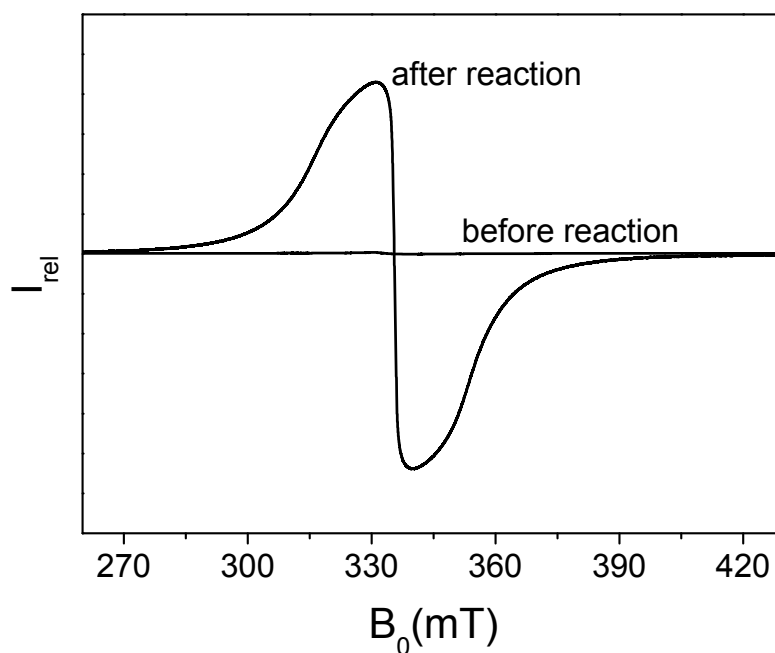
### 3.1.6 Conclusive Remarks: $V_2O_5$ as oxidant for oxidative coupling reaction of benzene and styrene

Highly efficient catalytic protocol has been developed for oxidative coupling of benzene and styrene in presence of  $V_2O_5$  as an oxidant. A high yield of trans-stilbene (87%) could be achieved in short reaction times (5 h) in presence of relatively low Pd concentrations (1.5 mol%) as compared to that required for most of the published reaction procedures. The reaction proceeds well with homogeneous as well as



heterogeneous palladium catalysts. The presence of benzoquinone facilitates the reaction as co-catalyst. Comparable activity of homogeneous and heterogeneous catalysts indicates that the reaction follows similar mechanism and is catalyzed by dissolved palladium species generated *in situ* from heterogeneous palladium catalyst. However, this speculation requires further mechanistic investigations.

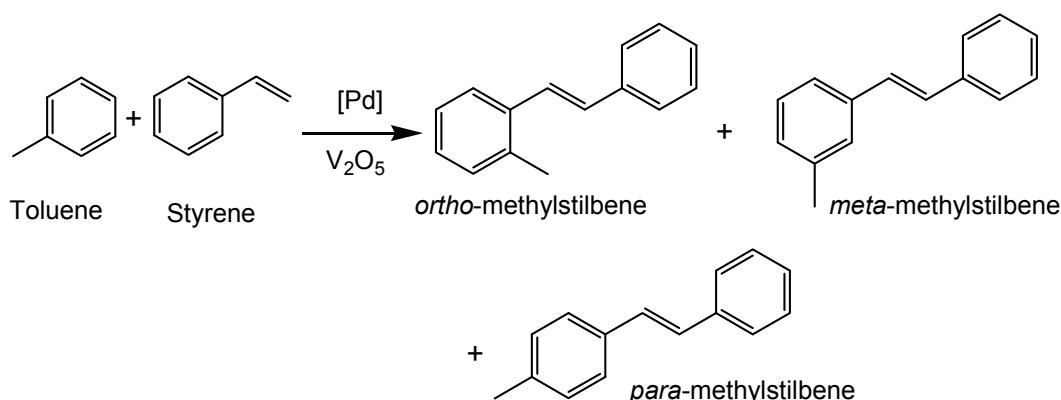
Under chosen reaction conditions,  $V_2O_5$  acts as a stoichiometric oxidizing agent for oxidative coupling reactions. EPR investigations (Figure 3.7) indicate that a significant part of the vanadium present in the reaction mixture is reduced to paramagnetic V(IV) species at the end of the reaction.



**Figure 3.7** X-band EPR spectra of  $V_2O_5$  recorded at r.t. before and after the oxidative coupling of benzene and styrene.

### 3.1.7 Oxidative coupling of toluene with styrene using $V_2O_5$ as oxidant

A number of Pd catalysts were tried for the oxidative coupling of toluene and benzene using  $V_2O_5$  as oxidant. As shown in Table 3.2, a good yield (about 50%) of cross coupled product could be obtained when heterogeneous catalysts (Pd/NaY, entry 4; Pd/C, entry 5) were used at higher temperature (140 °C). However, in each case, a mixture of products is formed corresponding to three regioisomers namely *ortho*-, *meta*- and *para*-methylstilbene (Scheme 3.3).



**Scheme 3.3** Palladium catalyzed oxidative coupling of toluene and styrene using  $V_2O_5$  as oxidant.

The formation of *meta*- product in addition to the expected *ortho*- and *para*- products indicates that electrophilic palladation of benzene may not be the rate determining step under these conditions which would normally lead to the formation of more *ortho*- and *para*- product than *meta*- product (methyl is an ortho para directing group). Instead, the re-oxidation of Pd(0) by  $V_2O_5$  (electron transfer) may be the most important step. This is also supported by the fact that the nature of oxidant has a remarkable influence on the reaction yield (see Figure 3.1). The production of mixture of products represents the main drawback of the reaction.

**Table 3.2** Reaction of styrene with toluene using different homogeneous and heterogeneous catalysts

Entry	Catalyst	<i>T</i> (°C)	Conversion %	Yield %	Selectivity (%) <sup>a)</sup> <i>o</i> -, <i>m</i> -, <i>p</i> - Stilbene	TON
1	Pd(OAc) <sub>2</sub>	120	62	30	26, 37, 37	37
2	Pd/Na-Mordenite	120	20	12	25, 33, 42	14
3	Pd/NaY	120	64	35	31, 38, 31	42
4	Pd/NaY	140	88	49	33, 38, 29	61
5	Pd/C	140	92	49	29, 39, 32	63

Reaction conditions: 1.5 mmol styrene, 0.1 mmol Na<sub>2</sub>CO<sub>3</sub>, 1.5 mmol V<sub>2</sub>O<sub>5</sub>, 0.1 mmol of acetylacetone as ligand, 20 equivalents of toluene (30 mmol) and 125 mg of n-hexadecane as internal GC standard, 1.5 mol% of Pd-catalyst, 5 mL acetic acid, 5 h. <sup>a)</sup> is calculated from total yield.

### 3.2 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) as Potential Oxidant for Oxidative Coupling Reactions

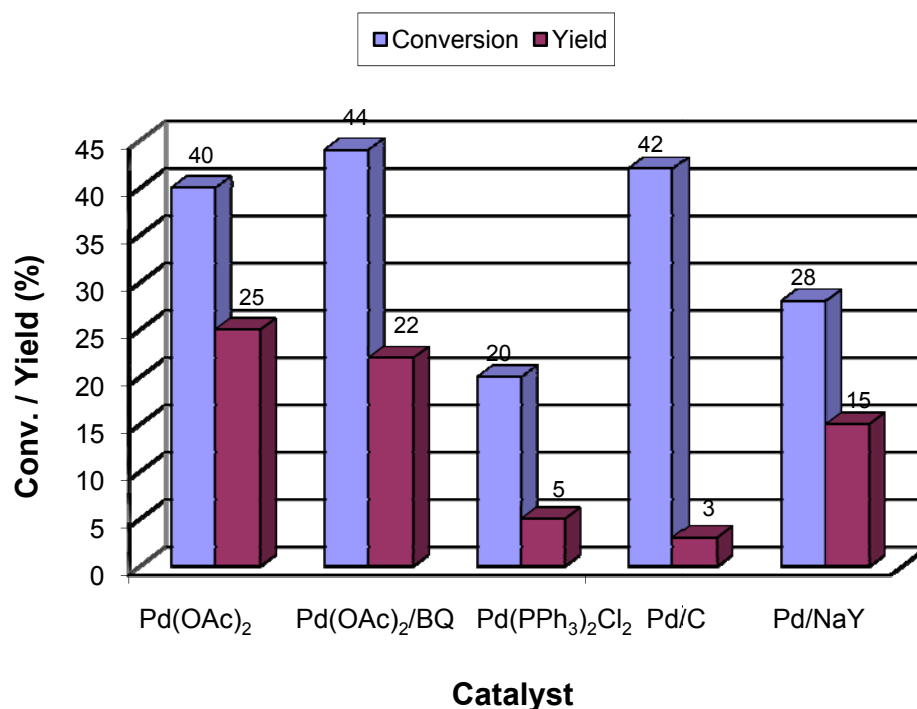
2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO), a stable, nonconjugated nitroxyl radical was first reported in 1961. The unpaired electron is delocalized over the nitrogen–oxygen bond which accounts for its high stability (they can be stored for long periods of time without decomposition). A wide variety of this type of stable free radical has since been reported and forms the subject of several reviews. TEMPO and its derivatives have found wide application as catalysts for the oxidation of alcohols. More recently, Pd(OAc)<sub>2</sub> catalyzed oxidative coupling of arenes and thiophene with arylboronic acids has been reported using TEMPO as an oxidant. Present study is focused on the use of TEMPO as environmentally benign oxidant for oxidative arene-olefin bond formation.

### 3.2.1 Variation of reaction conditions

Several reactions were performed using one equivalent (1.5 mmol) of TEMPO as an oxidant for Pd(OAc)<sub>2</sub> catalyzed coupling reaction of benzene and styrene using different solvents (DMF, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, NMP and CH<sub>3</sub>CN). The reactions were conducted at 90 °C and 120 °C in parallel series. The desired coupling product (*trans*-stilbene) could be obtained only in acetic acid as solvent. A 10% yield was possible when the reaction was carried out at 90 °C for five hours however it increased to 25% at 120 °C for otherwise the same reaction conditions. Thus, further investigations were carried out at 120 °C in acetic acid.

### 3.2.2 Variation of Pd sources

A set of reactions was performed using homogeneous Pd(OAc)<sub>2</sub> alone or with benzoquinone (BQ) as co-catalyst, and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and heterogeneous (Pd/NaY and Pd/C) palladium catalysts. The results pictured in Figure 3.8 indicate that Pd(OAc)<sub>2</sub> is the most active catalyst under these conditions (25% yield, >60% selectivity to *trans*-stilbene). The addition of BQ as co-catalyst was not effective perhaps due to in-efficiency of TEMPO to re-oxidize hydroquinone that is generated *in situ* in the reaction. Palladium complex of triphenylphosphine and Pd/C showed lower catalytic activity; whereas Pd/NaY gave reasonable yield under the same reaction conditions.

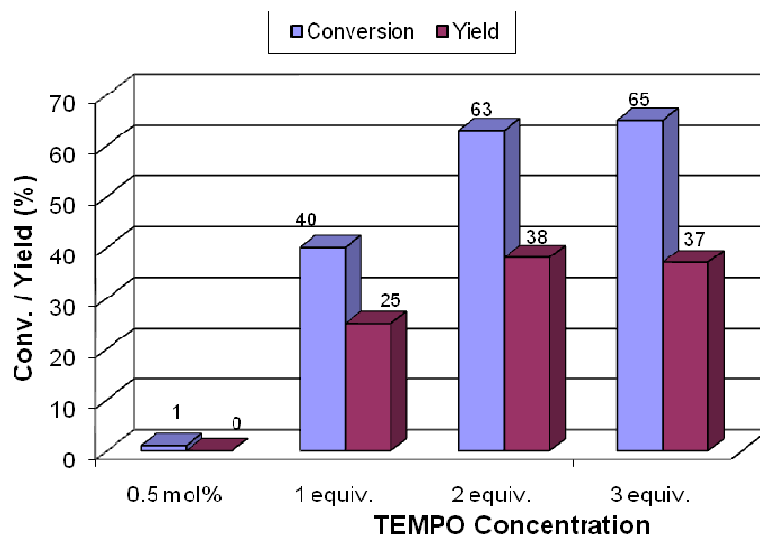


**Figure 3.8** Variation of palladium source for oxidative coupling of benzene and styrene using TEMPO as an oxidant. Reaction conditions: 1.5 mmol styrene, 30 equivalents of benzene (4 mL), 0.1 mmol NaOAc, 0.1 mmol ligand (acetylacetone), 125 mg *n*-hexadecane as GC standard, 1.5 mmol TEMPO, 1.5 mol% Pd-Catalyst, 3 mol% BQ (where given), 5 mL AcOH, 120 °C, 5h.

### 3.2.3 Variation of oxidant amount

In section 3.1, it has been demonstrated that the amount of oxidant is a critical parameter for the success of the oxidative coupling reaction. Moreover, a catalytic amount of oxidant is highly desirable on the basis of atom economy. Thus, a series of reactions was performed using different amounts of oxidizing agent (TEMPO). The results displayed in Figure 3.9 indicate clearly that lowering of TEMPO amount to catalytic level corresponds to a loss of activity. Higher yields are obtained when amount of the oxidant is raised from one equivalent to two equivalents (38% yield); however, the reaction does not reach completion in five hours in any case.

The results imply that stoichiometric amounts of TEMPO are obligatory for the reaction to take place. Moreover, two equivalents (3 mmol) of TEMPO correspond exactly to the amount required for the absorption of 3 mmol of electrons released in the oxidative coupling reaction of benzene and styrene (see Table 3.1).



**Figure 3.9** Influence of the oxidant amount on oxidative coupling of benzene and styrene. Reaction conditions: 1.5 mmol styrene, 30 equivalents of benzene (4 mL), 0.1 mmol NaOAc, 0.1 mmol ligand (acetylacetonone), 125 mg *n*-hexadecane as GC standard, 1.5 mol% Pd(OAc)<sub>2</sub>, 5 mL AcOH, 120 °C, 5h.

### 3.2.4 Variation of ligand and base

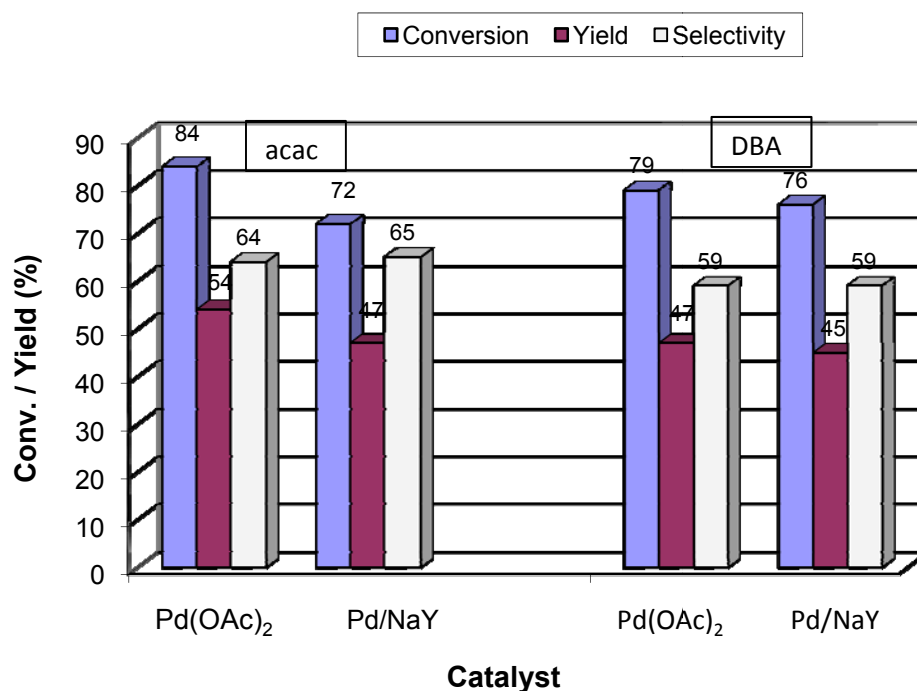
Table 3.3 summarizes the results of the oxidative coupling reactions in presence of various ligands. Interestingly, the reaction proceeded well in the absence of base (entries 2-4). Triphenylphosphine (PPh<sub>3</sub>) was not a ligand of choice for these reactions perhaps due to its degradation under strongly oxidizing conditions. Dibenzylidene acetone (DBA) was effective as a ligand and showed 26% yield as compared to 36% yield when acetylacetonone (acac) was used as ligand.

**Table 3.3** Influence of additive and base in oxidative coupling of benzene and styrene mediated by TEMPO as an oxidant.

Entry	Base	Ligand	Conversion	Yield	Selectivity
1	NaOAc	acac	63	38	60
2	None	acac	65	36	55
3	None	PPh <sub>3</sub>	22	12	55
4	None	DBA	40	26	65

Reaction conditions: 1.5 mmol styrene, 30 equivalents of benzene (4 mL), 0.1 mmol NaOAc, 0.1 mmol ligand, 125 mg *n*-hexadecane as GC standard, 3 mmol TEMPO, 1.5 mol% Pd(OAc)<sub>2</sub>, 5 mL AcOH, 120 °C, 5h.

Further, the reaction time was extended to 17 h with aim to get high reaction yields. Figure 3.10 shows the results of the oxidative coupling reactions carried out with selected homogeneous (Pd(OAc)<sub>2</sub>) and heterogeneous (Pd/NaY) catalysts in the absence of base. Relatively high conversion of styrene (84%) and good selectivity towards desired cross coupling product (*trans*-stilbene; 64%) was observed when Pd(OAc)<sub>2</sub> was used as catalyst. However, the comparable activity of Pd/NaY is important with respect to practical applications where often heterogeneous catalysts are preferred over homogeneous catalyst. Almost similar results were obtained when dibenzylidene acetone was applied as ligand instead of acetylacetone (Figure 3.10, right).

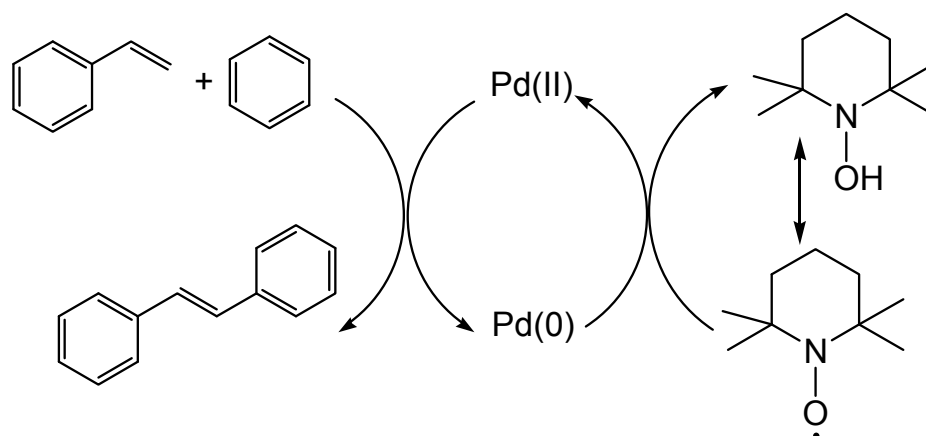


**Figure 3.10** Influence of Pd precursor and ligand on oxidative coupling reaction of benzene and styrene using TEMPO as oxidant. Reaction conditions: 1.5 mmol styrene, 30 equivalents of benzene (4 mL), 0.1 mmol ligand, 125 mg *n*-hexadecane as GC standard, 3 mmol TEMPO, 1.5 mol% Pd(OAc)<sub>2</sub> or Pd/NaY, 5 mL AcOH, 120 °C, 17h.

### 3.2.5 Conclusive Remarks: TEMPO as oxidizing agent

It has also been demonstrated that TEMPO, a stable organic free radical, can efficiently be utilized as green oxidant for oxidative coupling of benzene and styrene. High conversion of styrene (84%) could be achieved with 65% selectivity towards *trans*-stilbene. Homogeneous (Pd(OAc)<sub>2</sub>) as well as heterogeneous (Pd/NaY) catalysts were active resulting in high yields under optimized reaction conditions. TEMPO serves as an efficient hydrogen extractor in these reactions (Scheme 3.4). The reaction protocol does not require addition of base which makes it attractive for synthetic purposes.





**Scheme 3.4** Oxidative coupling of benzene and styrene in presence of TEMPO as stoichiometric oxidant.

### 3.3 Investigations on Some Other Catalytic Systems for Oxidative Coupling Reactions

#### 3.3.1 Pd/HPA catalytic system

Applications of heteropolyacids (HPAs) as promoter in Pd catalyzed oxidative coupling reactions have been a matter of interest in the past few years. In present study, a number of oxidizing agents were tested using homogeneous ( $\text{Pd}(\text{OAc})_2$ ,  $\text{PdCl}_2$ ,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ) as well as heterogeneous ( $\text{Pd}/\text{Al}_2\text{O}_3$ ) catalysts in combination with catalytic amount of HPA (1.5 mol%). The results are summarized in Table 3.4. Stoichiometric amount of  $\text{Cu}(\text{OAc})_2$  in presence of  $\text{Pd}(\text{OAc})_2$  and HPA as catalyst (entry 4) emerged as efficient catalytic system corresponding to 29% conversion with 76% selectivity to desired coupling product. In addition, the reaction performed using stoichiometric amount of  $\text{V}_2\text{O}_5$  showed 36% conversion of styrene when  $\text{Pd}/\text{Al}_2\text{O}_3$  in combination with HPA was used as catalyst. However, in nearly all cases the yield is considerably lower as compared to the reaction where no HPA was involved as co-catalyst (see Section 3.1).

**Table 3.4** Variation of oxidant in oxidative coupling reaction of benzene and styrene involving Pd/HPA catalytic system.

Entry	Catalyst	Oxidant	Conv. <sup>a)</sup>	Yield <sup>b)</sup>	Selectivity <sup>c)</sup>
1	Pd(OAc) <sub>2</sub>	V <sub>2</sub> O <sub>5</sub>	62	20	32
2	Pd(OAc) <sub>2</sub>	CrO <sub>3</sub>	61	17	28
3	Pd(OAc) <sub>2</sub>	Ce(OH) <sub>4</sub>	0	0	0
4	Pd(OAc) <sub>2</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	29	22	76
5	PdCl <sub>2</sub>	V <sub>2</sub> O <sub>5</sub>	37	7	19
6	PdCl <sub>2</sub>	CrO <sub>3</sub>	25	0	0
7	PdCl <sub>2</sub>	Ce(OH) <sub>4</sub>	0	0	0
8	PdCl <sub>2</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	9	9	100
9	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	V <sub>2</sub> O <sub>5</sub>	5	0	0
10	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	CrO <sub>3</sub>	48	6	13
11	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Ce(OH) <sub>4</sub>	9	0	0
12	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	30	11	37
13	Pd/Al <sub>2</sub> O <sub>3</sub>	V <sub>2</sub> O <sub>5</sub>	36	26	72
14	Pd/Al <sub>2</sub> O <sub>3</sub>	CrO <sub>3</sub>	53	11	20
15	Pd/Al <sub>2</sub> O <sub>3</sub>	Ce(OH) <sub>4</sub>	50	11	22
16	Pd/Al <sub>2</sub> O <sub>3</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	45	8	18

Reaction conditions: 1.5 mmol styrene, 75 mmol C<sub>6</sub>H<sub>6</sub> (50 equiv.), 1.5 mol% Pd catalyst (0.022 mmol), 1.5 mol% HPA (0.022 mmol), NaOAc (0.1 mmol), oxidant (V<sub>2</sub>O<sub>5</sub>: 1.5 mmol, Ce(OH)<sub>4</sub>: 3 mmol, Cu(OAc)<sub>2</sub>: 3 mmol, CrO<sub>3</sub>: 1.03 mmol), 0.1 mmol acetylacetone, 5 mL AcOH, 120 °C, 4 h. <sup>a)</sup> conversion of styrene; <sup>b)</sup> GC yield of *trans*-stilbene <sup>c)</sup> selectivity towards *trans* stilbene calculated from total conversion of styrene.

### 3.3.2 Peroxides (<sup>t</sup>BuOOH or H<sub>2</sub>O<sub>2</sub>) as oxidants

Peroxides, in particular hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), have got considerable importance as oxidant due to environmentally benign oxidation process associated with them. Typically, water is the only by-product when H<sub>2</sub>O<sub>2</sub> is used as an oxidant. Hydrogen peroxide is the second best choice after O<sub>2</sub> with respect to atom economy, but utilisation, efficiency and narrow range of scope limit its application. In present work, the use of <sup>t</sup>BuOOH and H<sub>2</sub>O<sub>2</sub> as oxidant was explored under different reaction conditions (temperature: 90, 120 and 140 °C). In the presence of <sup>t</sup>BuOOH as oxidant, 60% conversion of styrene could be obtained, with only 10-15% yield of desired coupling product (*trans*-stilbene). The reaction involving Pd(OAc)<sub>2</sub>, Pd/C or Pd/NaY showed similar activity at 140 °C. Changing the base from NaOAc to Na<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> did not affect the reaction yield to a considerable extent.

Several reactions were performed using H<sub>2</sub>O<sub>2</sub> as oxidant. The reactions carried out with Pd(OAc)<sub>2</sub> alone (1.5 mol%) or Pd(OAc)<sub>2</sub> in combination with catalytic amount of benzoquinone (3 mol%) resulted in complete conversion of styrene in five hours with 20-25% yield of *trans*-stilbene. Changing the reaction parameters (additive, oxidant amount, temperature, and reaction time) had a negligible influence on the activity of the catalyst owing to fast oxidation of substrate (styrene) under the reaction conditions.

In short, the nature of oxidant has a remarkable influence on the efficiency of the reaction. Present studies lay a foundation to evaluate the role of various oxidants in the coupling reactions. Highly efficient catalytic system for oxidative coupling of benzene and styrene has been presented based on Pd(OAc)<sub>2</sub> as catalyst in the presence of V<sub>2</sub>O<sub>5</sub> as stoichiometric oxidant and catalytic amount of benzoquinone. However, further investigations are needed to develop practically more efficient and environmentally benign oxidative coupling reactions.

**Summary**

Aromatic carbon-carbon bond coupling reactions have recently emerged as exceedingly important methodologies for the preparation of complex organic molecules such as pharmaceuticals and other fine chemicals. Mostly, these transformations employ palladium catalysts since they feature tolerance towards a variety of functional groups and, thus, offer an abundance of possibilities. Traditionally, Pd catalyzed coupling reactions are performed in the presence of soluble palladium complexes because they are well defined on molecular level and show high activity under mild reaction conditions. However, in the recent years, economical and environmental pressures have spurred great research interests in supported Pd catalysts that exhibit inherent properties of better separation of the noble metal from the products and possibility of catalyst recycling. On the other hand, development of highly active systems is not possible without knowledge of elementary processes involved in a catalytic cycle. This also concerns the true nature of catalytic species. Controversial claims exist in literature about the catalysis on the solid surface or by the dissolved molecular Pd species in solution. In fact, identifying the true active catalytic species is critically important for future advances in the rational design of coupling catalysts. This work is focused on the investigations related to the development of efficient heterogeneous Pd catalysts for C-C coupling reactions and highlights mechanistic aspects of the corresponding catalytic processes.

Section 2 provides a survey of investigations on the elucidation of the mechanism of highly active Suzuki coupling reactions catalyzed by highly active supported Pd catalysts in liquid phase. Various Pd catalysts (Pd/C, Pd/MO<sub>x</sub>, Pd/zeolite) catalyze Suzuki coupling reactions of aryl bromides under optimized reaction conditions (5 mmol aryl bromide, 5.5 mmol phenylboronic acid, 6 mmol sodium carbonate, 120 °C, NMP/water 10:2 mL, 2-4 h) with only a marginal difference in activity, that suggests similar kind of active species being involved in these processes. The reaction protocol offers the advantages of easy and complete Pd separation and recovery, easy handling, and stability against moisture and air. The Pd concentration in solution during the reaction correlates clearly with the progress of the reaction (conversion) and indicates that dissolved molecular palladium represents the catalytically active species. Dissolved Pd is deposited onto the support at the end of the reaction. Activation of aryl chlorides can be achieved by tuning the reaction

parameters including change of the base (sodium hydroxide instead of sodium carbonate) and the addition of additive (tetra-*n*-butylammonium bromide; TBAB). The high activity of supported catalysts for Suzuki coupling reactions could also be achieved under more desirable reaction conditions; i.e.

- i) Mild reaction conditions in conventional solvents (65 °C, NMP/water, air)
- ii) Reactions in pure water at mild reaction temperatures (65 °C)

A detailed survey on the mechanism of Pd-leaching is presented for Suzuki coupling reactions under mild reaction conditions (65 °C, Section 2.2). Palladium leaching during the reaction correlates directly to the progress of the reaction. Dissolution of Pd from support and the conversion of bromobenzene start simultaneously at room temperature and go on increasing, reaching maximum at reaction temperature. Dissolved Pd species re-deposit onto the support after the substrate (aryl bromide) is completely consumed in the reaction at a given reaction temperature. The palladium amount in solution depends in a complex manner on a variety of parameters. Temperature plays a crucial role in the course of Pd-leaching curve which is sharper (quicker dissolution-re-deposition processes) at higher temperature (120 °C) than at lower temperatures (65 °C). Additive and base cause substantial Pd-leaching in the reaction mixture and careful optimization of both is crucial to develop efficient catalytic systems.

The dissolution of Pd from supported catalysts probably generates (to a great extent “naked” or coordinative unsaturated) Pd species which are extremely active in classic Suzuki cycle. The intrinsic nature of these catalytic species is still unknown. For aryl bromides, these systems represent (largely) ligand free catalysts. The reaction is fast enough to be finished before Pd agglomeration or deactivation could occur to a significant extent. For aryl chlorides, additional halide ligands (preferably Br<sup>-</sup>) are necessary to stabilize active Pd species in solution. Accordingly, reactions of aryl chlorides are possible only in the presence of TBAB.

Section 2.3 presents an inclusive study on the desirable catalyst properties with approach to increase the potential of water as the only solvent in Suzuki coupling reactions under mild reaction conditions. Hydrophobic nature of support is found to

influence the reaction via favorable substrate-support interactions. The reaction is believed to take place on the outer rim of the supported catalyst at the phase boundary between aqueous (water) and organic (substrate) layer. An appropriate amount of water is required to dissolve the salts generated during the catalytic cycle. The addition of TBAB facilitates the reactions of lipophilic substrates, possibly via stabilization of the Pd in solution. The investigations present fundamental understanding towards the application of supported Pd catalysts for C-C coupling reactions in pure water.

Direct oxidative coupling of benzene and styrene (Section 3) was investigated as an alternative to the classical Heck reaction where utilization of halogenated arenes as substrates and the production of waste salts as by-products are major problems for practical purposes. The choice of oxidant was found to be crucial for these reactions.  $V_2O_5$  is found to be an excellent stoichiometric oxidant for Pd catalyzed oxidative coupling reactions. The reaction proceeds well with homogeneous ( $Pd(OAc)_2$ ) as well as heterogeneous ( $Pd/C$ ,  $Pd/NaY$ ,  $Pd/Al_2O_3$ ) palladium catalysts. A high yield of *trans*-stilbene could be achieved in short reaction times (5 h) in presence of relatively low Pd concentrations (1.5 mol%) as compared to that required for most of the published reaction procedures. The addition of benzoquinone as co-catalyst facilitates the reaction (87% yield). Whereas  $Pd(OAc)_2$  is a well established catalyst for oxidative C-C coupling reactions, this is the first report on application of supported Pd catalysts for such reactions.

Under similar reaction conditions, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) has also been utilized as an efficient stoichiometric oxidant for oxidative coupling reactions. The reaction of benzene and styrene could efficiently be performed in the absence of base under optimized reaction conditions.  $Pd(OAc)_2$  as well as  $Pd/NaY$  (1.5 mol% Pd) are found to be efficient catalysts in the presence of 3 mmol of TEMPO (as compared to 1.5 mmol of styrene; benzene is used in large excess).

The results presented in this work reveal that right choice of reaction conditions and fundamental knowledge of elementary processes involved in a catalytic cycle (real nature of catalysis) can lead to highly efficient heterogeneous catalytic systems for C-C coupling reactions. Extensive mechanistic investigations provided detailed

information about the active catalytic species in Suzuki coupling reactions catalyzed by heterogeneous Pd catalysts. Homogeneous, dissolved Pd species in fact catalyze the reaction which re-deposit onto the support after the reaction. The optimization of reaction conditions as well as efficiency of the catalytic system is highly dependent on these fundamental processes. In addition, the surface properties of a catalyst are shown to influence the reactions in water to a great extent. Thus the reaction is facilitated by the use of hydrophobic materials as support for Pd. The outcome of these investigations should support synthetic and industrial organic chemists in choosing simple, optimized solid catalysts and reaction conditions for Suzuki coupling reactions. Direct oxidative coupling of benzene and styrene is also presented as an efficient process with respect to atom economy by which simple non-functionalized arenes can be coupled to give Heck-type product with good reaction yield. The goal of developing an economically viable catalytic system, comprising acceptable oxidizing agent or an efficient co-catalyst (to use molecular oxygen as terminal oxidant) is still to be achieved.





**Zusammenfassung**

Aryl-Kohlenstoff-bindungsbildende Reaktionen haben sich in jüngerer Zeit zu ausserordentlich wichtigen Methoden zur Herstellung komplexer organisch-chemischer Moleküle wie Arzneistoffen und anderen Feinchemikalien entwickelt.

In den meisten dieser Verfahren werden Palladium-Katalysatoren verwendet, da diese eine Vielzahl funktioneller Gruppen tolerieren und somit ein breites Spektrum an Einsatzmöglichkeiten bieten. Klassisch wurden Pd-katalysierte Kupplungsreaktionen mit löslichen Pd-Komplexen durchgeführt, die auf molekularer Ebene wohldefiniert sind und hohe Aktivitäten bei milden Reaktionsbedingungen ausweisen. In den letzten Jahren jedoch spornten wirtschaftliche und ökologische Aspekte die Forschung an geträgerten Pd-Katalysatoren an, da diese natürlicherweise die Möglichkeiten einer besseren Abtrennung des Edelmetalls von den Produkten, und einer Wiederverwendung des Katalysators eröffnen. Die Entwicklung hochaktiver Systeme ist jedoch nicht möglich ohne Kenntnis der grundlegenden Vorgänge im Zusammenhang mit dem Katalysezyklus. Dies betrifft auch die tatsächliche Natur der katalytisch aktiven Spezies. In der Literatur gibt es widersprüchliche Aussagen über die Katalyse auf Festphasenoberflächen gegenüber der Katalyse durch gelöste molekulare Pd-Spezies. Die wahre aktive Spezies zu identifizieren ist mit Sicherheit entscheidend für zukünftige Fortschritte im Design von Katalysatoren für Kupplungsreaktionen. Diese Arbeit beschäftigt sich mit Untersuchungen im Zusammenhang mit der Entwicklung effizienter Pd-Katalysatoren für CC-Kupplungsreaktionen und beleuchtet dabei mechanistische Gesichtspunkte der entsprechenden katalytischen Prozesse.

Kapitel 2 gibt eine Reihe von Untersuchungen wieder, die den Mechanismus von Suzuki-Kupplungsreaktionen in Flüssigphasen, katalysiert durch hochaktive geträgerte Pd-Katalysatoren, beleuchten sollen. Verschiedene Pd-Katalysatoren (Pd/C, Pd/MO<sub>x</sub>, Pd/Zeolith) katalysieren die Suzuki-Kupplung von Arylbromiden unter optimierten Reaktionsbedingungen (5 mmol Arylbromid, 5,5 mmol Phenylboronsäure, 6 mmol Natriumcarbonat, 120 °C, NMP:Wasser 10:2 mL, 2-4 h) mit nur geringen Unterschieden in ihrer Aktivität, was jeweils ähnliche Arten der aktiven Spezies vermuten lässt. Diese Reaktionsvorschrift bietet die Vorteile einer einfachen und vollständigen Abtrennung und Rückgewinnung von Pd, einfacher Handhabbarkeit, und Stabilität gegenüber Feuchtigkeit und Luft. Die Pd-Konzentration in Lösung korreliert während der Reaktion eindeutig mit dem Fortschreiten der Reaktion

(Umsatz) und weist darauf hin, dass gelöstes molekulares Palladium die katalytisch aktive Spezies darstellt. Am Ende der Reaktion wird gelöstes Pd wieder auf dem Träger abgeschieden.

Die Aktivierung von Arylchloriden kann durch Verändern der Reaktionsparameter erreicht werden, einschließlich einem Wechsel der Base (Natriumhydroxid statt Natriumcarbonat) und der Zugabe von Additiven (Tetra-*n*-butylammoniumbromid; TBAB). Die hohe Aktivität geträgerter Katalysatoren konnte auch unter erstrebenswerteren Bedingungen erhalten werden, d.h.

- i) unter milderen Bedingungen in konventionellen Lösungsmitteln (65 °C, NMP/Wasser, Luft)
- ii) in Reaktionen in reinem Wasser bei milden Temperaturen (65 °C)

Eine detaillierte Untersuchung über den Mechanismus des Pd-Leaching für Suzuki-Kupplungen unter milden Reaktionsbedingungen (65 °C) wird hier präsentiert (Kapitel 2.2). Das Pd-Leaching während der Reaktion steht in direktem Zusammenhang mit dem Fortschreiten der Reaktion. Das Ablösen von Pd und die Umsetzung von Brombenzol beginnen gleichzeitig bei Raumtemperatur, steigen weiter und erreichen jeweils ihr Maximum bei Reaktionstemperatur. Gelöste Pd-Spezies werden wieder auf dem Träger abgeschieden, nachdem das Substrat (Arylbromid) bei einer bestimmten Temperatur vollständig umgesetzt worden ist. Die Menge an Palladium in Lösung hängt in einer komplexen Art und Weise von einer Reihe von Parametern ab. Die Temperatur spielt eine entscheidende Rolle für den Verlauf des Pd-Leaching, das bei höheren Temperaturen (120 °C) schärfer verläuft (schnellere Lösungs-/Reaktions-/Wiederabscheidungs Vorgänge) als bei niedrigeren Temperaturen (65 °C). Additiv und Base führen ebenfalls zu einem wesentlichen Herauslösen von Pd, und eine sorgfältige Optimierung beider ist entscheidend für die Entwicklung effizienter Katalysatorsysteme.

Das Herauslösen von Palladium vom heterogenen Katalysator erzeugt wahrscheinlich (größtenteils "nackte" oder koordinativ ungesättigte) Pd-Spezies mit extrem hoher Aktivität bezüglich des klassischen Suzuki-Katalysezyklus. Die wahre Beschaffenheit dieser Katalysatorspezies ist noch unbekannt. Für Arylbromide stellen

diese Systeme (weitgehend) ligandenfreie Katalysatoren dar. Die Reaktion ist schnell genug um vollständig zu verlaufen, bevor eine Agglomerisierung und Desaktivierung von Pd in wesentlichem Ausmaß stattfinden kann. Für Arylchloride sind zusätzliche Halogenid-Liganden (vorzugsweise  $\text{Br}^-$ ) notwendig, um aktive Pd-Spezies in Lösung zu stabilisieren. Dementsprechend sind Reaktionen mit Arylchloriden nur in der Gegenwart von TBAB möglich.

Kapitel 2.3 beinhaltet umfassende Untersuchungen zu erstrebenswerten Katalysatoreigenschaften, im Hinblick darauf das Potential von Wasser als alleinigem Lösungsmittel in Suzuki-Kupplungen unter milden Bedingungen zu erhöhen. Wie gezeigt wird, beeinflusst eine hydrophobe Beschaffenheit des Trägers die Reaktion durch begünstigte Substrat-Oberfläche-Wechselwirkungen. Es wird angenommen, dass die Reaktion in der weiteren Umgebung des Katalysators stattfindet, an der Phasengrenze zwischen der wässrigen und der organischen (Substrat-)Schicht. Eine hinreichende Menge Wasser ist zur Lösung der Salze notwendig, die während des Katalysezyklus gebildet werden. Die Zugabe von TBAB unterstützt die Reaktion lipophiler Substrate, wahrscheinlich durch eine Stabilisierung von Pd in Lösung. Die vorliegenden Untersuchungen geben grundlegende Einsichten zur Anwendung geträgerter Pd-Katalysatoren für CC-Kupplungsreaktionen in reinem Wasser wieder.

Die direkte oxidative Kupplung von Styrol und Benzol wurde als Alternative zur klassischen Heck-Reaktion untersucht, wo der Einsatz halogenierter Aromaten als Substrate und die entsprechende Entstehung von Salzabfällen als Nebenprodukte ein großes Problem für praktische Anwendungen darstellt. Wie gezeigt wurde, ist die Wahl des Oxidationsmittels entscheidend für diese Reaktion.  $\text{V}_2\text{O}_5$  stellte sich als hervorragendes stöchiometrisches Oxidationsmittel für Pd-katalysierte oxidative Kupplungsreaktionen heraus. Die Reaktion verläuft mit homogenen (Palladiumacetat) und heterogenen ( $\text{Pd}/\text{C}$ ,  $\text{Pd}/\text{NaY}$ ,  $\text{Pd}/\text{Al}_2\text{O}_3$ ) Katalysatoren. Eine hohe Ausbeute an *trans*-Stilben konnte mit kurzen Reaktionszeiten (5 h) und in der Gegenwart relativ niedriger Pd-Konzentrationen (1,5 mol%) erreicht werden, verglichen mit den Voraussetzungen für die meisten veröffentlichten Reaktionsverfahren. Die Zugabe von Benzophenon als Ko-Katalysator unterstützt die Reaktion (87% Ausbeute). Während  $\text{Pd}(\text{OAc})_2$  ein etablierter Katalysator für oxidative CC-Kupplungsreaktionen

ist, ist dies der erste Bericht einer Anwendung heterogener Pd-Katalysatoren für diese Reaktionen.

Unter vergleichbaren Reaktionsbedingungen wurde auch TEMPO (2,2,6,6-Tetramethylpiperidin-1-oxyl) als wirksames stöchiometrisches Oxidationsmittel für oxidative Kupplungen eingesetzt. Die Reaktion zwischen Benzol und Styrol konnte unter optimierten Bedingungen und in der Gegenwart einer Base effizient durchgeführt werden. Pd(OAc)<sub>2</sub> wie auch Pd/NaY (1,5 mol% Pd) erwiesen sich als leistungsfähige Katalysatoren in der Gegenwart von 3 mmol TEMPO (bezogen auf 1,5 mmol Styrol; Benzol wurde in großem Überschuss eingesetzt).

Die in dieser Arbeit dargestellten Ergebnisse zeigen auf, dass die richtige Wahl der Reaktionsbedingungen und wesentliche Kenntnisse grundlegender Vorgänge im Zusammenhang mit einem Katalysezyklus (wirkliche Form des Katalysators) zu hocheffizienten heterogenen Katalysatorsystemen für CC-Kupplungsreaktionen führen kann. Weitgreifende mechanistische Untersuchungen ergaben detaillierte Informationen über die katalytisch aktive Spezies in heterogen katalysierten Suzuki-Kupplungsreaktionen. Tatsächlich katalysieren homogene, gelöste Pd-Spezies die Reaktion, und scheiden sich nach der Reaktion wieder auf dem Träger ab. Die Optimierung von Reaktionsbedingungen und die Produktivität des Katalysatorsystems hängen sehr von diesen grundlegenden Vorgängen ab. Des Weiteren wurde gezeigt, dass die Oberflächen-Eigenschaften eines Katalysators die Reaktion in Wasser zu einem maßgeblichen Teil beeinflussen. Die Reaktion wird demnach durch den Einsatz hydrophober Materialien als Träger für Pd unterstützt. Die Ergebnisse dieser Untersuchungen sollen synthetisch- und industriell-organische Chemiker darin unterstützen einfache, optimierte Festphasenkatalysatoren und Reaktionsbedingungen für Suzuki-Kupplungsreaktionen zu wählen. Vorgestellt wurde ebenfalls die direkte oxidative Kupplung von Benzol und Styrol als wirksamer Prozess hinsichtlich der Atom-Effizienz, bei der einfache nichtfunktionalisierte Aromaten zu Heck-Produkten mit guten Reaktionsausbeuten gekuppelt werden können. Ein wirtschaftlich sinnvolles Katalysatorsystem, das ein akzeptables Oxidationsmittel oder einen wirksamen Co-Katalysator (zur Nutzung von molekularem Sauerstoff als letztendliches Oxidationsmittel) beinhaltet, ist ein Ziel, das es weiterhin zu erreichen gilt.

**Experimental Section**

## 6.1 General Remarks

All chemicals and solvents were purchased from Aldrich, Fluka, Merck and Degussa and were used as received without further purification. For reactions under inert atmosphere, argon 4.6 (purity 99.996%) was used to purge the reaction mixture. Catalytic experiments were performed in pressure tubes (Ace Company) with a total volume of 50 mL. Kinetic experiments were performed in 500 mL 3-neck flask equipped with condenser and rubber septum. Correlation of oil bath and reaction temperature was proven experimentally.

## 6.2 Analytical Methods

### 6.2.1 Elemental Analysis

Elemental analysis was performed in the Microanalysis Laboratory at TU München. Carbon and hydrogen contents were determined by combustion analysis using a Vario EL elemental analyzer (Elementaranalysensysteme GmbH Hanau). For analysis of Pd-Leaching samples, the solid residue was treated with 2 mL conc.  $\text{H}_2\text{SO}_4$  and heated to reflux for one hour. 1 mL of conc.  $\text{HNO}_3$  and 5 mL of conc.  $\text{HCl}$  were added and refluxed until the solution was clear. 5 mL of an aqueous solution of  $\text{LaCl}_3$  (10%) were added (to avoid chemical interference). Finally the mixture was diluted with bidistilled water to make a total volume of 100 mL. The palladium content was determined using a flame atomic absorption spectrometer Varian SpectrAA 400.

### 6.2.2 Gas Chromatography

Reaction mixtures from catalytic tests were analyzed qualitatively using a gas chromatograph (GC 5890 A) with a mass selective detector MS 5970 B (Hewlett Packard). Identification and quantitative analysis of reactants and products were performed on a gas chromatograph HP 6890 (Hewlett Packard) equipped with a flame ionization detector (FID). Optimum separation of the components could be achieved using a capillary column HP-1 with methyl siloxane as stationary phase



(length: 30 m, inside diameter: 0.25 mm, film thickness: 0.25  $\mu\text{m}$ ) and the following temperature program:

**Table 6.1** Parameters of the temperature program.

Ramp	Heating rate (K/min)	Final temperature (°C)	Initial/final time (min)
Initial temperature	-	100	2
1	15	170	2
2	35	240	10
3	50	270	2
4		Cooling	

Reactants and products were quantified relating to an internal standard. A response factor  $f$  has to be determined for all components. Chromatograms of pure components were taken using exact masses of each component ( $m(\text{C})$ ) and standard ( $m(\text{S})$ ). The corresponding response factors  $f$  were calculated from the resulting peak areas ( $A(\text{C})$  and  $A(\text{S})$ ), according to the following formula:

$$f = \frac{A(\text{S}).m(\text{C})}{A(\text{C}).m(\text{S})}$$

After determination of the response factors, the composition of reaction mixtures from catalytic tests can be evaluated. Masses of reactants and products ( $m(\text{C})$ ) are calculated from  $f$ ,  $m(\text{S})$  and the peak areas ( $A(\text{S})$  and  $A(\text{C})$ ) by rearranging the above equation. Requirements of internal standard are that it does not participate in any reaction and is transferred completely to organic phase during extraction. Diethylene glycol dibutyl ether was used as internal standard for Suzuki coupling reactions and *n*-hexadecan for oxidative coupling reactions. The relative error for conversion and yield is  $\pm 5\%$ .

### 6.2.3 NMR Spectroscopy

Boron NMR spectra of the reaction mixture were recorded on a JEOL JMX-GX 400 spectrometer operating at 400 MHz. The reaction mixture was analyzed directly after

being syringe filtered into the NMR tube without using an external standard or deuterated solvent. Deuterated solvent ( $\text{CDCl}_3$ , 99.8%) was used for  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR samples. All spectra were recorded on Jeol JNM GX 400 (frequencies:  $^1\text{H}$  400 MHz,  $^{13}\text{C}$  100 MHz).

#### 6.2.4 EPR Spectroscopy

EPR spectra were recorded on a JEOL JES-RE2X ESR spectrometer at X-band frequency at 298 K. the spectra were measured at a microwave frequency of 9.05 GHz with a microwave power of 5 mW., with modulation amplitude of 0.4 mT, sweep time 4 min, sweep width 100 mT, time constant 0.1 s and a modulation frequency of 100 kHz.

#### 6.2.5 Transmission Electron Microscopy

The transmission electron microscopy (TEM) measurements were performed on a JEOL 100CX microscope which operates with an accelerating energy of 100kV. The samples were prepared by dispersion of small grains of the catalyst in ethanol and subsequently placed on copper grids coated with a thin carbon layer. In order to determine the particle size distributions, the size of approximately 100 particles in different areas of the grid was measured and then the plots were fitted by means of a Gauss approximation with the use of Microcal Origin. The graphs provided an idea of the uniformity and distribution of particle size in the catalyst.

### 6.3 Catalyst Preparation

#### 6.3.1 Modification of $\text{Al}_2\text{O}_3$ surface ( $\text{Al}_2\text{O}_3\text{-C}_8$ preparation)

Four grams of  $\text{Al}_2\text{O}_3\text{-C}$  were dried in vacuum at 140 °C for 24 h. Under argon atmosphere 15 mL n-hexane were transferred and the mixture was stirred for 10 min. Amount of required silylating agent (*n*-octyl-dimethylchlorosilane) was calculated on the basis of OH groups on metal oxide surface ( $9/\text{nm}^2$ ) and the surface area of alumina-C ( $100 \text{ m}^2/\text{g}$ ). Thus, 0.031 mmol (five times excess of total OH groups) of *n*-

octyl-dimethylchlorosilane was dropped to the suspension within 1 min and the mixture was stirred for 24 h. Subsequently the solid was filtered off and washed six times by n-hexane under argon atmosphere. The silylated product was dried under vacuum for 24 h before its use as support for preparation of the catalysts. The hydrophobicity of the material was estimated by calculating the silylation grade ( $\sigma$ ) which is a measure of silylated versus total number of OH groups on the surface (equations 1 and 2).

$$\sigma (C) = \frac{\xi (C) \cdot N_A}{10 M_C \cdot S_{sp} \cdot N_{OH} / A} \quad (1)$$

$$\sigma (Si) = \frac{\xi (Si) \cdot N_A}{10 M_{Si} \cdot S_{sp} \cdot N_{OH} / A} \quad (2)$$

$\sigma$  = Degree of silylation of the surface OH groups

$\xi$  = mass percent of C (or Si) in the material

$N_A$  = Avogadro's Number ( $6.022 \cdot 10^{23} \text{ mol}^{-1}$ )

$M$  = Molar mass of carbon or Silicon

$S_{sp}$  = Specific surface area of metal oxide ( $\text{Al}_2\text{O}_3\text{-C}$ :  $100 \text{ m}^2/\text{g}$ )

$N_{OH}$  = Number of OH groups on the surface ( $\text{Al}_2\text{O}_3\text{-C}$ :  $9/\text{nm}^2$ )

Table 6.2 shows the elemental analysis of the  $\text{Al}_2\text{O}_3\text{-C}_8$  and T805 and its degree of silylation determined according to given formula. The degree of silylation is a little bit higher when it is measured on the basis of silicon content ( $\sigma(\text{Si})$ ) as compared with that measured from the carbon content ( $\sigma (C)$ ). It may be due to breaking of some carbon bonds during the silylation procedure.

**Table 6.2** Elemental analysis and degree of silylation of  $\text{Al}_2\text{O}_3\text{-C}_8$  and T805 (hydrophobic materials).

Support Material	Si (%)	C (%)	H (%)	$\sigma (C)$ (%)	$\sigma (Si)$ (%)
$\text{Al}_2\text{O}_3\text{-C}_8$	0.6	1.79	0.80	10	14
T805	1.05	3.09	1.1	77	90

### 6.3.2 Preparation of 1 wt% Pd/MO<sub>x</sub>

The metal oxide (Al<sub>2</sub>O<sub>3</sub>: C or TiO<sub>2</sub>: P25; 0.99 g) was suspended in 30 mL of distilled water. Then 2 g of an aqueous solution of PdCl<sub>2</sub> (0.5 wt% Pd in aqueous 5% HCl) were added dropwise, under vigorous stirring. The resulting mixture was allowed to stir at room temperature for one hour. The suspension was then adjusted to pH 10 by autotitrator (736 GP Titrino, Metrohm) using 10% sodium hydroxide solution under continuous stirring. The mixture was stirred for another hour at r. t. before the solid catalyst was separated by filtration. The resulting solid was washed 4 times with 1 mL water and dried for several hours. The water content of resulting catalyst was determined by weight difference of a sample (50 – 100 mg) which is heated at 100 °C, overnight. The final Pd content of the catalyst was determined by atomic absorption spectroscopy (AAS).

### 6.3.3 Preparation of 1 wt% Pd/T2000 (amphiphilic support)

The procedure was the same as given in above section, except that the support material was suspended in water:THF 1:4 mixture instead of pure water.

### 6.3.4 Preparation of Pd/T805 and Pd/Al<sub>2</sub>O<sub>3</sub>-C<sub>8</sub> (hydrophobic supports)

For palladium on hydrophobic surface (T805 and Al<sub>2</sub>O<sub>3</sub>-C<sub>8</sub>), solution of Pd(OAc)<sub>2</sub> in THF was used as catalyst precursor. After stirring the suspension in THF for 24 hours at room temperature, the catalyst was filtered and washed with THF until the filtrate was clear. The catalyst was dried at room temperature before use. The final palladium content of the catalyst was measured through atomic absorption spectroscopy (AAS).

### 6.3.5 Pre-treatment of Pd/Al<sub>2</sub>O<sub>3</sub> Catalyst

Air dried Pd/Al<sub>2</sub>O<sub>3</sub> (prepared as mentioned in Section 6.3.2) was calcined in a Naberthem (30-3000 °C) oven with air flow using a heating rate of 2 K/min from r.t. to

500 °C. The temperature was maintained at 500 °C for 2 h after which it was cooled down to r.t. “Calcined” catalyst was collected as brown coloured powder.

Pd(0)/Al<sub>2</sub>O<sub>3</sub> (“reduced” catalyst) was obtained by treating the “calcined” catalyst with pure hydrogen with a flow rate of 70 mL/min in a U-reactor. The temperature was maintained at 350 °C for 2 h after which the reactor was cooled down to r.t. under a flow of argon.

### 6.3.6 Preparation of 1 wt% Pd/NaY

Zeolite NaY (0.99 g) was suspended in 100 mL water. Subsequently, 0.95 mL of a solution of PdCl<sub>2</sub> (0.1 M) in aqueous NH<sub>3</sub> were added dropwise and the resulting mixture was stirred for 24 hours at r. t. The solid catalyst was separated by filtration, washed with water until no more chloride were found in filtrate (detection: AgNO<sub>3</sub> test) and dried for several hours. As mentioned above, the water content of resulting catalyst was determined by weight difference of a sample (50 – 100 mg) which is heated at 100 °C, overnight. The final Pd content of the catalyst was determined by atomic absorption spectroscopy (AAS).

### 6.3.7 Pd/C catalyst

Experiments with Pd catalysts based on activated carbon were performed using a commercially available Pd/C catalyst (5% Pd, E105 CA/W from Degussa).

## 6.4 General Procedures for Catalytic Tests

### 6.4.1 Suzuki coupling reactions of aryl halides in NMP/water at 120 °C

Bromoarene (5 mmol; usually 4-bromoanisole), phenylboronic acid (5.5 mmol), base (6 mmol), diethylene glycol dibutyl ether (0.250 g, as an internal standard for GC analysis) and 0.005–0.2 mol % of Pd as a heterogeneous catalyst were introduced into a pressure tube. NMP and water added, the mixture was optionally purged with argon and placed in a preheated oil bath. The reaction was performed with vigorous stirring at the specified temperature for 1-2 hours.

For the GLC analyses a sample (1 mL) taken from the reaction mixture before filtration was quenched with water (2 mL) in a test tube. This mixture was extracted with dichloromethane (2 mL), after which the organic layer was filtered and dried over anhydrous  $\text{MgSO}_4$ . The resulting dry organic layer was analyzed by GLC or GC-MS.

The Suzuki coupling reaction of 4'-chloroacetophenone, the aryl chloride (10 mmol), phenylboronic acid (11 mmol), sodium hydroxide (12 mmol) and TBAB (3 mmol), were added to NMP (10 mL) and water (3 mL) solvent mixture in a pressure tube. After adding 0.1 mol% Pd catalyst, the reaction mixture was purged with argon and brought into preheated oil bath at 120 °C. After 4 hours, the reaction mixture was analyzed for the conversion and yield by GC as mentioned for the aryl bromides.

#### 6.4.2 Kinetic experiment in Suzuki coupling reactions at 120 °C

4-Bromoanisole (116 mmol, 1 equiv.),  $\text{Na}_2\text{CO}_3$  (128 mmol, 1.1 equiv.),  $\text{PhB}(\text{OH})_2$  (128 mmol, 1.1 equiv.), and 0.1 mol% of the Pd-catalyst (1% Pd/ $\text{Al}_2\text{O}_3$ ) were weighed into a 500 mL flask. NMP (250 mL) and of water (100 mL) were added along with 9 g GC standard (diethyleneglycol-*n*-dibutylether) and the flask was placed in a preheated oil bath at 80 °C. The reaction mixture (7 mL) was withdrawn at intervals with careful observation of reaction time and temperature. From the withdrawn sample, 5 mL were directly syringe filtered into a 10 mL round bottom flask for palladium analysis and 2 mL were extracted with dichloromethane to get yields from GLC. The temperature of the oil bath was gradually increased up to 120 °C and the sample taking continued for about 3 hours. The filtered samples (5 mL) were evaporated in order to measure Pd content according to procedure given in 6.4.5.

#### 6.4.3 Suzuki coupling reactions of halides in NMP/water at 65 °C

Bromoarene (2.9 mmol, 1 equiv.), phenylboronic acid (3.2 mmol, 1.1 equiv.), sodium carbonate (3.2 mmol, 1.1 equiv.), diethyleneglycol-*n*-dibutylether (250 mg, as an internal standard for GC analysis) and 0.1 mol% of Pd as supported catalyst were introduced into a pressure tube.

In a typical Suzuki reaction of the aryl chloride, 4'-chloroacetophenone (2.9 mmol, 1 equiv.), phenylboronic acid (3.2 mmol, 1.1 equiv.), sodium hydroxide (4.4 mmol, 1.5 equiv. instead of sodium carbonate) was used along with 1 mmol of TBAB (tetra-*n*-butyl ammonium bromide) as additive.

NMP (1-methyl-2-pyrrolidone, 5 mL) and water (2 mL) were added; the mixture was optionally purged with argon and placed in a preheated oil bath. The reaction was performed with vigorous stirring at the specific temperature for 2-4 hours. Argon atmosphere was obligatory to get good yields for the Suzuki coupling reactions of 4'-chloroacetophenone, whereas it was not a requirement for the activation of aryl bromides.

#### 6.4.4 Kinetic experiment in Suzuki coupling reactions at 65 °C

Bromobenzene (116 mmol, 1 equiv.), Na<sub>2</sub>CO<sub>3</sub> (128 mmol, 1.1 equiv.), PhB(OH)<sub>2</sub> (128 mmol, 1.1 equiv.), and 0.1 mol% of the Pd-catalyst (1 % Pd/Al<sub>2</sub>O<sub>3</sub>) were weighed into a 500 mL flask. After the addition of 9 g diethyleneglycol dibutyl ether as internal standard, 250 mL of NMP and 100 mL of water were added. The flask was placed in a preheated oil bath at 65 °C after deaerating the reaction mixture by purging with argon for five minutes. 7 mL of the reaction mixture were withdrawn at intervals with careful observation of the reaction time and temperature. 5 mL of the sample solution were directly syringe filtered into a 10 mL round bottom flask for palladium analysis whereas 2 mL were extracted by dichloromethane to get yields via GLC. The reaction was monitored for five hours and samples were collected after short intervals of time. The procedure adopted for the evaporation of the filtered reaction mixture is mentioned in section 6.4.5.

#### 6.4.5 Evaporation of the hot-filtered samples

The 10 mL round bottom flask containing 5 mL filtered solution was put into a massive aluminium block (height 60 mm, with 5 holes of 50 mm depth) which was fixed on a heating plate. The mixture that has to be evaporated consisted of NMP, water and the aryl bromide; all other components are solid (phenylboronic acid, salts

and the product). To avoid boiling retardation and thus Pd losses, an elaborated temperature program was implemented, according to which the reaction mixture was allowed to evaporate at different temperatures estimated from the boiling point of the components. Table 6.3 presents the temperature at which the heating was maintained for 3-4 hours in order to evaporate a particular reaction component.

**Table 6.3** Boiling points and evaporation temperatures for reaction components in Suzuki coupling reactions.

Component	Boiling point	Evaporation temperature
Water	100	80
Bromobenzene	156	140
NMP	206	190
4-Bromoanisole	223	200
4'-chloroacetophenone	237	220
Diethylene glycol dibutyl ether	256	240

#### 6.4.6 Pd/C catalyzed Suzuki coupling reactions of aryl halides in water

Aryl halide (2.9 mmol, 1 equiv.), phenylboronic acid (3.2 mmol, 1.1 equiv.), NaOH (4.4 mmol, 1.5 equiv.) and TBAB (1 mmol) were introduced in a pressure tube. 5 % Pd/C (E 105 CAW; 0.1 mol%) and 4 mL H<sub>2</sub>O along with 250 mg GC standard (diethyleneglycol dibutyl ether) were added before bringing the pressure tube into a pre-heated oil bath at 65 °C. After the given reaction time (usually 4 hours) the reaction mixture was allowed to cool down to r. t. and was extracted with 3 mL of dichloromethane. Organic layer was separated, dried over MgSO<sub>4</sub> and analyzed by GC.

#### 6.4.7 Pd/MO<sub>x</sub> catalyzed Suzuki coupling reactions of aryl halides in water

The procedure was similar to that applied for Pd/C catalyzed reactions in water (Section 6.4.6) except that for Pd/MO<sub>x</sub> catalyzed reactions, higher molar



concentration of Pd catalysts had to be applied (0.2 mol% Pd). Also 3 equivalent of base (sodium hydroxide) were used instead to 1.5 equivalents.

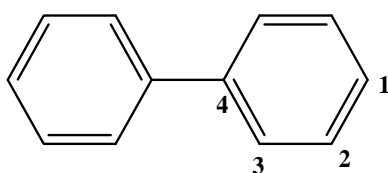
#### 6.4.8 Oxidative coupling of benzene and styrene

Styrene (1.5 mmol), acetylacetone (0.1 mmol), sodium acetate (0.08 mmol), GC-standard (*n*-hexadecane; 125 mg), 1.5 mol% Pd catalyst and the corresponding amount of the oxidant were weighed into a pressure tube. After addition of 5 mL acetic acid and benzene (30-50 mmol), the pressure tube was placed into a pre-heated oil bath at 120 °C for 5 h. After that, the mixture was filtered; 2 mL of filtrate were sampled and extracted with dichloromethane (2 mL) and water (2 mL). The organic layer was dried over MgSO<sub>4</sub> and analyzed for conversion and yield by GC.

#### 6.5 Structural data of reaction products

Analytical data of reaction products which are not mentioned in this section were in good accordance to the spectra known from the literature.

##### Biphenyl

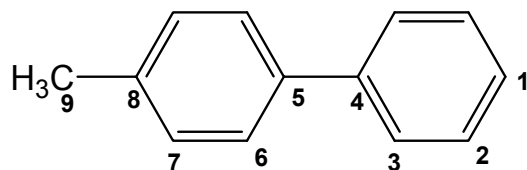


C<sub>12</sub>H<sub>10</sub>, M = 154.21 g/mol

**<sup>1</sup>H-NMR, CDCl<sub>3</sub>, 400.13 MHz:** 7.68 (d, 4H, <sup>3</sup>J = 7.3 Hz, 3-*H*), 7.52 (m, 4H, 2-*H*), 7.42 (m, 4H, 1-*H*).

**<sup>13</sup>C NMR, CDCl<sub>3</sub>, 100.61 MHz:** 141.2 (4-*C*), 128.2 (2-*C*), 127.2 (3-*C*), 127.1 (1-*C*).

**EI-MS:** 154 (M<sup>+</sup>), 76.

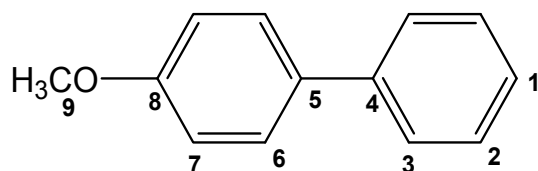
**4-Methyl-biphenyl**

$C_{13}H_{12}$ ,  $M = 168.24$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 7.63 (m, 2H, 3-H), 7.54 (m, 2H, 6-H), 7.47 (m, 2H, 2-H), 7.36 (m, 1H, 1-H), 7.29 (m, 2H, 7-H), 2.44 (s, 3H, 9-H).

**$^{13}C$  NMR,  $CDCl_3$ , 100.61 MHz:** 141.1 (4-C), 138.3 (5-C), 137.0 (8-C), 129.5 (7-C), 128.7 (2-C), 127.0 (3-C), 126.9 (6-C), 126.9 (1-C), 21.1 (9-C).

**EI-MS:** 168 ( $M^+$ ), 152.

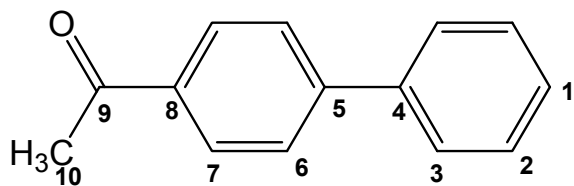
**4-Methoxy-biphenyl**

$C_{13}H_{12}O$ ,  $M = 184.24$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 7.58 (m, 2H, 3-H), 7.56 (m, 2H, 6-H), 7.44 (t, 2H, 2-H), 7.34 (t, 1H, 1-H), 7.29 (dd, 2H, 7-H), 3.86 (s, 3H, 9-H).

**$^{13}C$  NMR,  $CDCl_3$ , 100.61 MHz:** 159.1 (8-C), 140.8 (4-C), 133.7 (5-C), 128.7 (2-C), 128.4 (6-C), 126.7 (1-C), 126.6 (3-C), 114.2 (7-C), 55.3 (9-C).

**EI-MS:** 184 ( $M^+$ ), 169, 141, 115, 63.

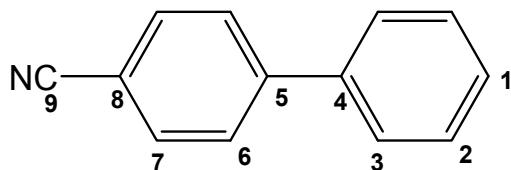
**4-Acetyl-biphenyl**

$C_{14}H_{12}O$ ,  $M = 196.25$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 8.01(d, 2H,  $^3J = 8.2$  Hz, 7-*H*), 7.66(d, 2H,  $^3J = 8.2$  Hz, 6-*H*), 7.62 (d, 2H,  $^3J = 7.3$  Hz, 3-*H*), 7.46(t, 2H, 2-*H*), 7.39 (m, 1H, 1-*H*), 2.62 (s, 3H, 10-*H*).

**$^{13}C$  NMR,  $CDCl_3$ , 100.61 MHz:** 197.7 (9-*C*), 145.7 (5-*C*), 139.8 (4-*C*), 135.8 (8-*C*), 128.9 (2-*C*), 128.7 (3-*C*), 127.2 (6-*C*), 127.1 (1-*C*), 26.6 (10-*C*).

**EI-MS:** 196 ( $M^+$ ), 181, 152, 76, 43.

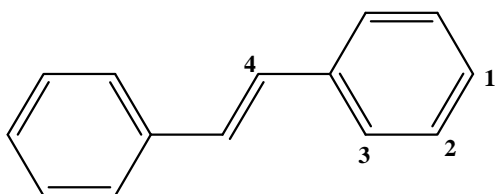
**4-cyano-biphenyl**

$C_{13}H_9N$ ,  $M = 179.22$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 7.70 (d, 2H,  $^3J = 8.2$  Hz, 6-*H*), 7.66 (d, 2H,  $^3J = 8.2$  Hz, 7-*H*), 7.57 (t, 2H,  $^3J = 7.1$  Hz, 3-*H*), 7.47 (t, 1H,  $^3J = 7.2$  Hz, 2-*H*), 7.42 (m, 1H, 1-*H*),.

**$^{13}C$  NMR,  $CDCl_3$ , 100.61 MHz:** 145.6 (5-*C*), 139.1 (4-*C*), 132.5 (7-*C*), 129.0 (2-*C*), 128.6 (1-*C*), 127.9 (6-*C*), 127.1 (3-*C*), 118.9 (9-*C*), 110.8 (8-*C*).

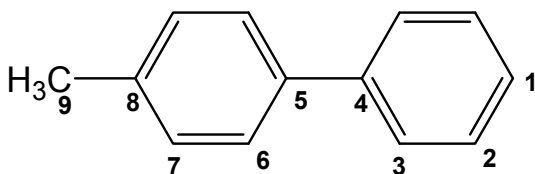
**EI-MS:** 179 ( $M^+$ ), 151, 76.

**E-Stilbene**

$C_{14}H_{12}$ ,  $M = 180.25$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 7.40 (d, 4H,  $^3J = 7.0$  Hz, 3-*H*), 7.25 (t, 4H,  $^3J = 7.5$  Hz, 2-*H*), 7.15 (t, 2H,  $^3J = 7.0$  Hz, 1-*H*), 7.0 (s, 2H, 4-*H*).

**EI-MS:** 180 ( $M^+$ ), 165, 152, 102, 89.

**4-Methyl-E-stilbene**

$C_{15}H_{14}$ ,  $M = 194.28$  g/mol

**$^1H$ -NMR,  $CDCl_3$ , 400.13 MHz:** 7.48 (m, 4H, 3-*H*, 6-*H*), 7.35 (t, 2H,  $^3J = 7.30$  Hz, 2-*H*), 7.23 (m, 1H, 1-*H*), 7.11 (m, 2H, 7-*H*), 7.02 (d, 1H,  $^3J = 10.68$  Hz, 4-*H*), 6.90 (d, 1H,  $^3J = 9.30$  Hz, 5-*H*), 3.83 (s, 3H, 8-*H*).

**Appendix**

### **Publications**

1. "Supported Palladium Catalysts for Suzuki Reactions: Structure-Property Relationships, Optimized Reaction Protocol and Control of Palladium Leaching" K. Köhler, R.G. Heidenreich, **S. S. Soomro**, S. S. Pröckl, *Advanced Synthesis & Catalysis*, **2008**, 350, **2930-6**.

*Highlighted* : Pd on Metal Oxides and activated Carbon for Suzuki-Miyaura Coupling, *Synfacts* **2009**, 3, 343.

### **Poster presentations**

- 40. Jahrestagung Deutscher Katalytiker, Weimer, Germany, **2007**, March 14-16 "Palladium Catalyzed Oxidative Coupling of Benzene and Styrene" **S. Soomro**, W. Kleist, K. Köhler.
- EUROPACAT VIII-From Theory to Industrial Practice **2007**, August 26-31 "Oxidative Coupling of Benzene and Styrene Catalyzed by Palladium in Presence of Various Oxidants" **S. Soomro**, Wolfgang Kleist and Klaus Köhler.
- Vortragstagung der Wöhlervereinigung, München / Garching, **2008**, October, 8-10 "Leaching of Active Palladium Species during Suzuki Reactions Catalyzed by Heterogeneous Palladium Catalysts" **S. Soomro** and K. Köhler.

**References**

- [1] C. E. Tucker, J. G. de Vries, *Top. Catal.* **2002**, *19*, 111.
- [2] J. Tsuji, *Palladium reagents and catalysts: new perspectives for the 21st century*, Wiley, **2004**.
- [3] R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320.
- [4] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.
- [5] J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086.
- [6] A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749.
- [7] N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 1979, 866.
- [8] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
- [9] S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633.
- [10] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett* **1975**, *50*, 4467.
- [11] R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874.
- [12] J. K. Stille, *Angew. Chem, Int. Ed. Engl.* **1986**, *25*, 508.
- [13] H.-U. Blaser, A. Indolese, A. Schnyder, H. Steiner, M. Studer, *J. Mol. Catal. A.* **2001**, *173*, 3.
- [14] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889.
- [15] V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553.
- [16] N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609.
- [17] I. Pryjomska-Ray, A. Gniewek, A. M. Trzeciak, J. J. Ziolkowski, W. Tylus, *Top. Catal.* **2006**, *40*, 173.
- [18] K. Kohler, S. S. Prockl, W. Kleist, *Curr. Org. Chem.* **2006**, *10*, 1585.
- [19] K. Kohler, W. Kleist, S. S. Prockl, *Inorg. Chem.* **2007**, *46*, 1876.
- [20] A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101.
- [21] P. Lloyd-Williams, E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145.
- [22] A. D. Schlüter, *J. Polym. Sci. A: Polym. Chem.* **2001**, *39*, 1533.
- [23] S. Murai, *Activation of unreactive bonds and organic synthesis*, Springer, **1999**.
- [24] N. Miyaura, *J. Organomet. Chem.* **2002**, *653*, 54.
- [25] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2008**, *64*, 3047.
- [26] N. E. Leadbeater, M. Marco, *Angew. Chem., Int. Ed.* **2003**, *42*, 1407.
- [27] R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados, R. D. Singer, *J. Org. Chem.* **2005**, *70*, 161.
- [28] I. P. Beletskaya, *J. Organomet. Chem.* **1983**, *250*, 551.



- [29] T. Jeffery, *Tetrahedron Lett.* **1985**, 26, 2667.
- [30] L. Liu, Y. Zhang, Y. Wang, *J. Org. Chem.* **2005**, 70, 9666.
- [31] N. E. Leadbeater, M. Marco, *Org. Lett.* **2002**, 4, 2973.
- [32] L. M. Klingensmith, N. E. Leadbeater, *Tetrahedron Lett.* **2003**, 44, 765.
- [33] A. Alimardanov, L. Schmieder-van de Vondervoort, A. H. M. de Vries, J. G. de Vries, *Adv. Synth. Catal.* **2004**, 346, 1812.
- [34] M. T. Reetz, J. G. deVries, *Chem. Commun.* **2004**, 1559.
- [35] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, 127, 4685.
- [36] K. W. Anderson, S. L. Buchwald, *Angew. Chem, Int. Ed. Engl.* **2005**, 44, 6173.
- [37] A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, 6, 1830.
- [38] K. Selvakumar, A. Zapf, A. Spannenberg, M. Beller, *Chem. Eur. J.* **2002**, 8.
- [39] A. C. Frisch, A. Zapf, O. Briel, B. Kayser, N. Shaikh, M. Beller, *J. Mol. Catal. A.* **2004**, 214, 231.
- [40] C. W. K. Gstöttmayr, V. P. W. Böhm, E. Herdtweck, M. Grosche, W. A. Herrmann, *Angew. Chem., Int. Ed.* **2002**, 41, 1363.
- [41] W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem, Int. Ed. Engl.* **1993**, 32, 1524.
- [42] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Brossmer, *Angew. Chem, Int. Ed. Engl.* **1995**, 34, 1848.
- [43] J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, 105, 2527.
- [44] W. A. Herrmann, K. Ofele, S. K. Schneider, *J. Organomet. Chem.* **2003**, 687, 229.
- [45] B. B. Robin, in *Palladacycles* (Ed.: D. M. P. Prof. Dr. Jairton Dupont), **2008**, pp. 209.
- [46] R. B. Bedford, *Chem. Commun.* **2003**, 2003, 1787.
- [47] R. B. Bedford, S. L. Welch, *Chem. Commun.* **2001**, 2001, 129.
- [48] I. P. Beletskaya, A. V. Cheprakov, *J. Organomet. Chem.* **2004**, 689, 4055.
- [49] R. B. Bedford, S. M. Draper, P. N. Scully, S. L. Welch, *New J. Chem.* **2000**, 24, 745.
- [50] R. B. Bedford, S. L. Hazelwood, M. E. Limmert, J. M. Brown, S. Ramdeehul, A. R. Cowley, S. J. Coles, M. B. Hursthouse, *Organometallics* **2003**, 22, 1364.
- [51] B. M. Bhanage, M. Arai, *Catal. Rev.* **2001**, 43, 315.
- [52] A. Biffis, M. Zecca, M. Basato, *J. Mol. Catal. A* **2001**, 173, 249.

- [53] N. T. S. Phan, M. Van Der Sluys, Christopher W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609.
- [54] Y. Uozumi, *Top. Curr. Chem.* **2004**, *242*, 77.
- [55] Y. Uozumi, H. Danjo, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384.
- [56] W. C. Shieh, R. Shekhar, T. Blacklock, A. Tedesco, *Synth. Commun.* **2002**, *32*, 1059.
- [57] A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685.
- [58] J. W. Byun, Y. S. Lee, *Tetrahedron Lett.* **2004**, *45*, 1837.
- [59] J. W. Kim, J. H. Kim, D. H. Lee, Y. S. Lee, *Tetrahedron Letters* **2006**, *47*, 4745.
- [60] P. G. Steel, C. W. T. Teasdale, *Tetrahedron Lett.* **2004**, *45*, 8977.
- [61] F. X. Felpin, T. Ayad, S. Mitra, *Eur. J. Org. Chem.* **2006**, *2006*, 2679.
- [62] G. Zhang, *Synthesis* **2005**, 537.
- [63] R. G. Heidenreich, K. Koehler, J. G. E. Krauter, J. Pietsch, *Synlett* **2002**, 1118.
- [64] K. Köhler, R. G. Heidenreich, S. S. Soomro, S. S. Pröckl, *Adv. Synth. Catal.* **2008**, *350*, 2930.
- [65] T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, *Chem. Eur. J.* **2007**, *13*, 5937.
- [66] Y. Kitamura, S. Sako, T. Udzu, A. Tsutsui, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Commun.* **2007**, 5069.
- [67] J. S. Chen, A. N. Vasiliev, A. P. Panarello, J. G. Khinast, *Appl. Catal. A* **2007**, *325*, 76.
- [68] D. A. Conlon, B. Pipik, S. Ferdinand, C. R. LeBlond, J. R. S. Jr., B. Izzo, P. Collins, Guo-Jie Ho, J. M. Williams, Y.-J. Shi, Y. Sun, *Adv. Synth. Catal.* **2003**, *345*, 931.
- [69] C. M. Crudden, M. Sateesh, R. Lewis, *J. Am. Chem. Soc* **2005**, *127*, 10045.
- [70] J. D. Webb, S. MacQuarrie, K. McEleney, C. M. Crudden, *J. Catal.* **2007**, *252*, 97.
- [71] L. Artok, H. Bulut, *Tetrahedron Lett.* **2004**, *45*, 3881.
- [72] H. Bulut, L. Artok, S. Yilmazu, *Tetrahedron Lett.* **2003**, *44*, 289.
- [73] H. C. Hailes, *Org. Process Res. Dev* **2007**, *11*, 114.
- [74] C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68.
- [75] K. H. Shaughnessy, R. B. DeVasher, *Curr. Org. Chem.* **2005**, *9*, 585.

- [76] D.-H. Lee, Y. H. Lee, D. I. Kim, Y. Kim, W. T. Lim, J. M. Harrowfield, P. Thuéry, M.-J. Jin, Y. C. Park, I.-M. Lee, *Tetrahedron* **2008**, *64*, 7178.
- [77] H. Li, Y. Wu, *Appl. Organomet. Chem.* **2008**, *22*, 233.
- [78] E. J. G. Suárez, A. Ruiz, S. Castellón, W. Oberhauser, C. Bianchini, C. Claver, *Dalton Trans.* **2007**, 2859.
- [79] Vilaro, x, Maria, G. Arsequell, G. Valencia, A. Ballesteros, J. Barluenga, *Org. Lett.* **2008**, *10*, 3243.
- [80] C. Fleckenstein, S. Roy, S. Leuthäuser, H. Plenio, *Chem. Commun.* **2007**, 2870.
- [81] B. H. Lipshutz, S. Ghorai, *Aldrichimica Acta* **2008**, *41*, 59.
- [82] B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333.
- [83] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170.
- [84] S. Bhattacharya, A. Srivastava, S. Sengupta, *Tetrahedron Lett.* **2005**, *46*, 3557.
- [85] P. Zheng, W. Zhang, *J. Catal.* **2007**, *250*, 324.
- [86] W. Mai, L. Gao, *Synlett* **2006**, 2553.
- [87] B. J. Gallon, R. W. Kojima, R. B. Kaner, P. L. Diaconescu, *Angew. Chem, Int. Ed. Engl.* **2007**, *46*, 7251.
- [88] K. S. Sivudu, N. M. Reddy, M. N. Prasad, K. M. Raju, Y. M. Mohan, J. S. Yadav, G. Sabitha, D. Shailaja, *J. Mol. Catal. A* **2008**, 295, 10.
- [89] G. Wei, W. Zhang, F. Wen, Y. Wang, M. Zhang, *J. Phys. Chem. C* **2008**, *112*, 10827.
- [90] D. Schönfelder, O. Nuyken, R. Weberskirch, *J. Organomet. Chem.* **2005**, *690*, 4648.
- [91] J.-W. Kim, J.-H. Kim, D.-H. Lee, Y.-S. Lee, *Tetrahedron Lett.* **2006**, *47*, 4745.
- [92] Y. M. A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, *Org. Lett.* **2002**, *4*, 3371.
- [93] M. Lysén, K. Köhler, *Synlett* **2005**, 1671.
- [94] M. Lysen, K. Köhler, *Synthesis* **2006**, 692.
- [95] G. Lu, R. Franzén, Q. Zhang, Y. Xu, *Tetrahedron Lett.* **2005**, *46*, 4255.
- [96] M. Mora, C. Jiménez-Sanchidrián, J. R. Ruiz, *J. Mol. Catal. A* **2008**, 285, 79.
- [97] C. Baleizao, A. Corma, H. Garcia, A. Leyva, *J. Org. Chem.* **2004**, *69*, 439.

- [98] M. S. Anson, A. R. Mirza, L. Tonks, J. M. J. Williams, *Tetrahedron Lett.* **1999**, *40*, 7147.
- [99] S. Minakata, M. Komatsu, *Chem. Rev.* **2008**, *108*, 5035.
- [100] R. Abu-Reziq, D. Avnir, J. Blum, *Angew. Chem, Int. Ed. Engl.* **2002**, *41*, 4132.
- [101] D. R. Lide, *Handbook of chemistry and physics 76th ed*, CRC press, **1995**.
- [102] C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992.
- [103] Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett.* **1968**, *9*, 3863.
- [104] Y. Fujiwara, I. Moritani, S. Danno, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166.
- [105] V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731.
- [106] Y. Fuchita, K. Hiraki, Y. Kamogawa, M. Suenaga, K. Tohgoh, Y. Fujiwara, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081.
- [107] E. M. Beccalli, G. Broggin, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318.
- [108] C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, *1*, 2097.
- [109] M. D. Boele, G. P. v. Strijdonck, A. H. deVries, P. C. Kamer, J. G. deVries, P. W. van-Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586.
- [110] G. T. Lee, X. Jiang, K. Prasad, O. Repic, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*.
- [111] B. V. Popp, J. L. Thorman, S. S. Stahl, *J. Mol. Catal. A* **2006**, *251*, 2.
- [112] M. Yamada, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2005**, *70*, 5471.
- [113] M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem., Int. Ed.* **2003**, *42*, 3512.
- [114] S. B. Park, J. K. Cha, *Org. Lett.* **2000**, *2*, 147.
- [115] T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476.
- [116] M. Tani, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2004**, *69*, 1221.
- [117] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.
- [118] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.
- [119] E. B. Mubofu, J. H. Clark, D. J. Macquarrie, *Green Chem.* **2001**, *3*, 23.
- [120] S. Paul, J. H. Clark, *Green Chem.* **2003**, *5*, 635.

- [121] M. Al-Hashimi, A. Qazi, A. C. Sullivan, J. R. H. Wilson, *J. Mol. Catal. A* **2007**, 278, 160.
- [122] M. Cai, J. Sha, Q. Xu, *J. Mol. Catal. A* **2007**, 268, 82.
- [123] M. Mora, C. Jiménez-Sanchidrián, J. R. Ruiz, *J. Colloid interface Sci.* **2006**, 302, 568.
- [124] Y. M. A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, *J. Org. Chem.* **2003**, 68, 7733.
- [125] S. P. Andrews, A. F. Stepan, H. Tanaka, S. V. Ley, M. D. Smith, *Adv. Synth. Catal.* **2005**, 347, 647.
- [126] Anil V. Gaikwad, A. Holuigue, Mehul B. Thathagar, Johan E. ten Elshof, G. Rothenberg, *Chem. Eur. J.* **2007**, 13, 6908.
- [127] J. M. Richardson, C. W. Jones, *J. Catal.* **2007**, 251, 80.
- [128] A. K. Diallo, C. Ornelas, L. Salmon, J. Ruiz Aranzaes, D. Astruc, *Angew. Chem, Int. Ed. Engl.* **2007**, 119, 8798.
- [129] R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, K. Köhler, *J. Mol. Cat. A.* **2002**, 182, 499.
- [130] K. Koehler, R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, *Chem. Eur. J.* **2002**, 8, 622.
- [131] G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King, T. R. Verhoeven, *J. Org. Chem.* **1994**, 59, 8151.
- [132] A. H. M. de Vries, F. J. Parlevliet, L. S.-v. d. Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. M. Walet, J. G. deVries, *Adv. Synth. Catal.* **2002**, 344, 996.
- [133] T. Jeffery, *Tetrahedron* **1996**, 52, 10113.
- [134] J. G. de Vries, *Dalton Trans.* **2006**, 421.
- [135] A. Gniewek, J. J. Ziolkowski, A. M. Trzeciak, M. Zawadzki, H. Grabowska, J. Wrzyszc, *J. Catal.* **2008**, 254, 121.
- [136] S. S. Pröckl, W. Kleist, M. A. Gruber, K. Köhler, *Angew. Chem, Int. Ed. Engl.* **2004**, 43, 1881.
- [137] F. Zhao, M. Arai, *React. Kinet. Catal. Lett.* **2004**, 81, 281.
- [138] S. Hermanek, *Chem. Rev.* **1992**, 92, 325.
- [139] W. M. Pearlman, *Tetrahedron Lett.* **1967**, 8, 1663.
- [140] R. Narayanan, M. A. El-Sayed, *J. Am. Chem. Soc.* **2003**, 125, 8340.

- [141] M. Gruber, M. Wagner, R. Heidenreich, J. G. E. Krauter, N. Coskun, K. Köhler, *Catal. Lett.* **2004**, *94*, 177.
- [142] H. Nur, S. Ikeda, B. Ohtani, *Chem. Commun.* **2000**, 2235.
- [143] C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, *1*, 2097.
- [144] J. E. Bckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619.
- [145] A. K. Hoffmann, A. T. Henderson, *J. Am. Chem. Soc.* **1961**, *83*, 4671.
- [146] E. G. Rozantsev, B. J. Hazzard, H. Ulrich, *Free nitroxyl radicals*, Plenum press New York, **1970**.
- [147] J. F. W. Keana, *Chem. Rev.* **1978**, *78*, 37.
- [148] E. G. Rozantsev, V. D. Sholle, *Synthesis* **1971**, *1971*, 190.
- [149] E. G. Rozantsev, V. D. Sholle, *Synthesis* **1971**, *1971*, 401.
- [150] R. A. Sheldon, I. Arends, *J. Mol. Cat. A* **2006**, *251*, 200.
- [151] S. Kirchberg, T. Vogler, A. Studer, *Synlett* **2008**, 2841.
- [152] K. Sato, M. Hyodo, J. Takagi, M. Aoki, R. Noyori, *Tetrahedron Letters* **2000**, *41*, 1439.
- [153] G. Grigoropoulou, J. H. Clark, J. A. Elings, *Green Chem.* **2003**, *5*, 1.
- [154] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, *Green Chem.* **2007**, *9*, 411.
- [155] H. Knözinger, *Adv. Catal.* **1976**, *25*, 184.