Silica Supported N-Heterocyclic Carbenes: Active and Reusable Heterogeneous Catalysts for Mizoroki-Heck Reactions

by

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ABSTRACT

Carbon-carbon bond formation reactions are among the most important processes in chemistry, as they represent key steps in the synthesis of more complex molecules from simple precursors. This thesis describes mainly the development of novel applications of the mild and versatile palladium-catalyzed carbon-carbon coupling method, commonly known as the Heck reaction. Most of the reactions performed in homogeneous media bearing the difficulty of separation from the reaction mixture. For this reason, N-heterocarbenes (NHCs) that gains scientific interest due to their high catalytic activity and stability were used to combine the practical advantage of a heterogeneous catalyst with the efficiency of a homogeneous system.

Immobilized Pd(NHC) complex **64** (**A**) and its modified derivatives (**B** and **C**), either with trimethylchlorosilane or with imidazolidinium salt **63**, were synthesized. Characterization of the novel materials were performed using elemental analysis, AAS, NMR, DRIFTS and BET analysis.

On the basis of the results, catalyst **C** showed higher activity among the others. The results also verified that the predominant activity of **C** could be ascribed to direct beneficial effect of imidazolidinium salt by being on the silica surface, in the vicinity of the anchored Pd-NHC complex **64**. The catalyst showed high activity and reusability towards the Mizoroki-Heck reactions iodoanisole and bromoarenes (activated, non-activated and deactivated) with styrene, when reactions at 140 °C in the presence of 1.5 molar equivalent NaOAc.3H_2O base and 0.5 % Pd with respect to the aryl halide. The catalyst preserved its original activity for 4-iodoanisole, 4-bromoacetophenone, 4-bromotoluene and even for highly deactivated 4-bromoanisole reagent at least 7 uses. Although the addition of immobilized salt to the catalyst **C** increased the activity, addition of commonly used Bu_4NBr showed no gradual increase in the activity. The catalyst **C** was also active for 4-chloroacetophenone albeit at higher temperature (170°C). The AAS analysis indicated that the reaction was truly heterogeneous.

ÖZ

C-C bag olusumu tepkimeleri, basit öncülerden daha karmasik olanlarin sentezini temsil ettigi için kimyada yer alan proseslerin önemlilerinden biridir. Bu tez, Heck tepkimesi olarak bilinen, çok yönlü paladyum-katalizli karbon-karbon bag olusumu metodunun yeni uygulamalarinin gelistirilmesini anlatmaktadir. Çogu tepkime homojen sistemde gerçeklesmektedir ve ürünlerin tepkime ortamindan ayrilmalari zordur. Bu nedenle, heterojen katalizörlerin uygulama avantajini homojen sistemin verimliligiyle birlestirmek için son yillarda yüksek katalitik aktivitelerinden ve dayanikliliklarindan dolayi büyük ilgi çeken N-Heterokarbenler kullanilmistir.

Immobilize Pd(NHC) kompleksi **64** (**A**) ve onun trimetilklorosilan veya imidazolidin tuzuyla **63** (**B** ve **C**) modifiye olmus türevleri sentezlenmistir. Yeni sentezlenen maddelerin karakterizasyonu elementel analiz, AAS, NMR, DRIFTS ve BET analizi yöntemleriyle gerçeklestirilmistir.

Alinan sonuçlar neticesinde, katalizör **C** digerlerine göre daha yüksek aktivite göstermektedir. Ayrica sonuçlar, **C**’ nin yüksek aktivite göstermesinin nedeninin immobilize olmus Pd-NHC kompleksini **64** çevreleyen silika yüzeyindeki imidazolidin tuzunun yarali etkisine baglanabilecegini göstermektedir. Bu katalizör 140 °C ‘ de aril halojenüre göre baz olarak 1.5 mol esdeger $NaOAc.3H_2O$ ve % 0.5 Pd varliginda iyodoanisol ve bromoarenlerin (aktive olmus, aktive edilmemis ve deaktive olmus) sitiren ile gerçeklestirilen Mizoroki-Heck tepkimelerinde yüksek aktivite ve tekrar kullanilabilirlik göstermistir. Katalizör bastaki aktivitesini 4-iyodoanisol, 4-bromoasetofenon, 4-bromotoluen ve hatta hayli deaktive olmus 4-bromoanisol için en az 7 kullanim boyunca korumustur. Immobilize edilen tuzun katalizör **C**’ ye eklenmesi aktiviteyi arttirirken, genelde kullanilan Bu_4NBr’ ün katalitik aktiviteye kalici bir etkisi gözlenmemistir. Katalizör **C** daha yüksek sicaklik(170°C) kullanilmak kosuluyla 4-kloroasetofenon için de aktiftir. AAS analizleri tepkimelerin tamamen heterojen oldugunu göstermektedir.

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CHAPTER 1

INTRODUCTION

Palladium-catalyzed C-C coupling reactions are widely used for organic synthesis. For instance, vinyl substitution (Mizoroki-Heck reaction (M-H)) is one of the most important, reliable, and general methodology for C-C bond formation that has been applied to a diverse array of fields, ranging from natural products synthesis, bioactive compounds, materials science to high-performance materials [1]. This powerful C-C bond-forming process has been practiced on an industrial scale for the production of compounds such as naproxen [2] and octyl methoxycinnamate [3]. Functional group tolerance and the ready availability and low cost of simple olefins, compared to the vinyl metal compounds that are employed in the corresponding Suzuki, Stille, Kumada, and other cross-coupling reactions, contribute to the exceptional utility of the M-H arylation.

Several ligands such as phosphines, phosphites, carbenes, or thioethers have been successfully employed for this reaction [4-5] The M-H reaction is usually carried out in the presence of bulky phosphine ligands, which give Pd(0) species and accelerate the reaction rate. In contrast to the widely used toxic phosphines complexes, most of the complexes formed with N-heterocyclic carbenes (NHC) are exceptionally stable toward heat, air and moisture and thus attracting interest as possible alternatives to transition-metal phosphine complexes for applications in catalysis. After all, they are easily accessible, and non-toxic. N-heterocyclic carbenes (NHC) have recently emerged as an important family of ligands with strong s-donor electronic properties [6-8]. Indeed, they are tightly bound to the metal thereby avoiding decomposition pathway or deposition of free (and inactive) metal under catalytic conditions. However, many phosphines can be sensitive to air and moisture with conversion to, for example, phosphine oxide species. The latter can poison the metal leading to catalyst decomposition. In such cases, catalyst reuse can be difficult [9]. Hence, the development of phosphine-free recycling catalytic systems is of importance for the M-H reaction [10]. There are also significant economical and environmental reasons for developing recyclable catalytic reactions from both academic and industrial perspectives.

Despite the increasing use of Pd-NHCs in homogeneous systems, there are only a few studies that aimed at recyclization of Pd-NHCs in M-H reactions. Recently, Schwarz et. al. showed that immobilized N-Heterocyclic dicarbene chelate complexes on a functionalized polystyrene (Wang resin) was reusable in the Heck reaction for activated aryl bromide, bromoacetophenone and non-activated aryl bromide, bromobenzene. Although the former could be recycled at least 15 times without any loss in the activity, a noticeable deactivation was observed for the less reactive bromobenzene reagent. However aryl chlorides could not be induced to react even under forcing conditions (170 °C) [11]. Park and Alper displayed that Pd(II)-bisimidazole ligands were effective catalysts for the M-H reaction under phosphine-free conditions using ionic liquids as solvents. This system could be recycled five times without any loss of catalytic activity with various iodoarenes and vinyl moieties; nevertheless the reusability of the catalyst was not satisfactory for the less expensive and more available bromoarene reagents [12].

Several catalyst systems in which miscellaneous palladium catalysts were recoverable for the M-H reactions include either dispersed palladium metals and Pd(II) compounds or immobilized palladium complexes on zeolites [13], on inorganic oxides [14], on C [15], on clays [16], on polymers [17], on silica [18], on a polymeric liquid [19], on molecular sieves [20], on dendrimers [21], on layered double hydroxide supports [22] and on chitosan [23], performed techniques for the recycling of palladium via deposition on a carrier support at the end of the reactions [24], performed reactions on sol-gel entrapped Pd(II) catalysts and a study that was done with supported liquid phase catalysts [25 a].

Among them only a few were shown to be actively recyclable for the M-H reactions of bromoarenes [13 b,c, 19, 18d, 22 a]. Zeolite supported palladium catalysts were displayed to be recyclable for activated bromoarenes while their activity reduced when used for non activated bromobenzene [13 b,c]. Chadasekhar et al. determined that poly(ethylene glycol) formed a reusable solvent medium for palladium catalyzed M-H reaction. The Pd-solvent combination was shown as reusable catalyst system for bromobenzene, albeit there occurred some gradual reduction in activity [19]. Chanthateyanonth and Alper utilized a silica-immobilized tridentate diphosphinoaryl ligand (PCP-type) palladium(II) complex as a catalyst for the M-H reaction. The catalyst was active and reusable for the M-H reaction of aryl iodides and aryl bromides with moderate loss of activity. However, in the reuse of nonactivated and deactivated bromoarene derivatives, (bromobenzene, bromotoluene and bromoanisole) a gradual decrease in the catalytic activity even in the second run was observed [18 d]. In a study by Coudary et al. a layered double hydroxide supported nanopalladium catalyst was determined to be highly active and reusable for bromo- and chloroarenes; however their activity were high only when reactions were carried out in ionic liquids [22 a].

We introduced here a novel catalyst system for the M-H reaction by using a silica anchored saturated Pd-N-Heterocyclic Carbene **64** modified with imidazolidinium salt **63** which was highly active for iodoanisole and several bromoarene derivatives (activated, non activated and deactivated). The catalyst preserved its activity at least for 7 uses in the M-H reaction of 4-iodoanisole, 4-bromoacetophenone, 4-bromotoluene and even highly deactivated 4-bromoanisole without any significant palladium loss.

Before covering the experimental methods and the discussion of the results obtained in this thesis, detailed fundamental information was given in the subsequent chapters.

CHAPTER 2

CATALYSIS

2.1. The Origin of the Catalysis

In 1836 the famous Swedish chemist J. J. Brezelius introduced the concept of catalysis. In the Edinburgh New Philosophical Journal, he proclaimed: “I hence will name it the catalytic force of the substances, and I will name decomposition by this force catalysis. The catalytic force is reflected in the capacity that some substances have, by their mere presence and not by their own reactivity, to awaken activities that are slumbering in molecules at a given temperature” [25 b]. At the beginning of the 20th century, W. Ostwald presented the generally accepted definition of a catalyst as a species which increases the rate of a chemical reaction through the formation of intermediate compounds and which is restored at the end of the reaction. In 1909, Ostwald was awarded the Nobel Prize in Chemistry for his work on catalysis chemical equilibrium and reaction velocities [26].

Catalysis is perhaps one of the most important technologies available, since it plays a critical role in the development of efficient production methods for a wide range of materials, from fuels to polymers, and in the development of more effective and safer pharmaceuticals. Catalysis is the occurrence by which certain chemicals (catalysts) can promote a chemical reaction without undergoing any permanent chemical transformation themselves. Thus, theoretically, recovery of the catalyst is possible after the reaction is completed, enabling it to be recycled. Without the proper catalyst, many reactions proceed infinitely slowly or not all. Moreover, because of its effects on the kinetics of the reaction, which can lead to different chemical entities, the chemical nature of the catalyst can have decisive impact on the selection of reaction manifolds. Over the last few decades, there has been rapid progress in the understanding, especially in homogeneous systems, of the molecular events (micro-steps) leading to the final products in some of these reactions. Subsequently, there has been a striking effect on the number of new catalyst systems currently under development. Combinatorial methods have recently been introduced in the catalyst discovery process for rapid screening of potential homogeneous and heterogeneous catalysts [27].

2.1.1. Catalyst Properties

Irrespective of the constitution of the catalyst, it must be provided with certain properties to be useful. First, it must be highly active, meaning that the reaction must progress with a reasonably high speed. Most catalysts contain so-called ‘active sites’ in their structures. Interactions at the active site permit the reacting molecules to perform a certain chemical reaction at much lower activation energy than would be possible in the absence of such sites. The total number of active sites and their accessibility control the turnover frequency of the process.

A second and very important property is selectivity; catalysts actually govern the product pattern of the reaction as well as increasing the reaction rate. Enzymes, for example, are generally very efficient and selective. Enzymes as well as transition metal based catalysts are capable of recognizing a reacting substrate by its three-dimensional shape and transforming it in a geometrically specific way (i.e. stereospecifically). Third, the catalyst’s lifetime (stability) is an important factor in the design of economical and environmentally considerate chemical processes.

2.1.2. Types of Catalysts

Catalysts can be roughly divided into two main categories: a heterogeneous catalyst is one in which the phase of the catalyst is different from that of the reactants (e.g. car air-exhaust catalyst), a homogeneous catalysts, on the other hand, is one in which the catalyst is in the same phase as the reactants (e.g. acid catalyzed ester cleavages). Presently, heterogeneous catalysis has by far the greater world economic impact and are expected to be very important in the future. This thesis will deal with the latter type, as exemplified by heterogeneous catalytic system using the transition metal palladium N-Heterocyclic carbene (NHC) complex as the active catalyst.

Reactions catalyzed by a transition metal homogeneous system have steadily gained importance in modern chemistry, as powerful synthetic transformations can be facilitated with high selectivity (chemo-, regio-, and enantio-selectivity). Recently, Sharpless, Noyori and Knowles received the 2001 Nobel Prize or their research on homogeneous asymmetric catalysis. Their discoveries have been made use of in the production of chiral selective drugs and materials [28].

From an industrial point of view, catalysts which are not soluble in the same phase as the organic reactant have the inherent advantage of easy separation and very often also of better handling properties, but homogeneous catalysts are better defined and understood (for a short comparison see Table 2.1.).

Table 2.1 Strong and weak points of heterogeneous and homogeneous catalysts

	Homogeneous	**Heterogeneous**
Strong points	Defined on molecular level (close to organic chemistry) Scope, variability (design?) Preparation	Separation, recovery, recycling Stability, handling Many(hydrogenation) catalysts commercially available
Weak points	Sensitivity (handling,stability) Activity, productivity (of many literature procedures) Separation	Characterization (understanding on molecular level) Preparation (needs special know-how), reproducibility Diffusion to and within catalyst

As a rule, heterogeneous catalysts are still chosen on an empirical basis by trial and error, and it is rarely understood why a given catalyst is superior to another one. Many factors influence the catalytic properties of such catalysts, and it is important to realize that even today it is not possible to adequately characterize a heterogeneous catalyst on a molecular level [29].

To minimize waste and the atom economy in the use of raw materials, research on new methods of recycling (♻) the catalyst and the solvent is essential. Every contribution to the development of new “green” techniques, whether small or large, is important if we are to minimize the production of waste.

2.2. Transition Metals as Catalysts in Organic Synthesis

Organometallic compounds are defined as materials that possess direct, more or less polar, π or σ bonds between metals and carbon atoms [30]. The first organometallic π-complex was $K(Pt^{II}Cl_3(h^2 - C_2H_4))$, discovered by W. C. Zeise in 1827, and subsequently named Zeise's salt. The first transition metal σ-complex (Me_3PtI) was not discovered until 82 years later by Pope [29]. After the synthesis of urea at the beginning of the 19th century [31], the first organic compound to be manufactured, organometallic chemistry was begun in earnest in 1887 when Reformatsky developed the first synthetically useful organometallic reaction by applying organozinc in an addition reaction (Figure 2.1.) [32].

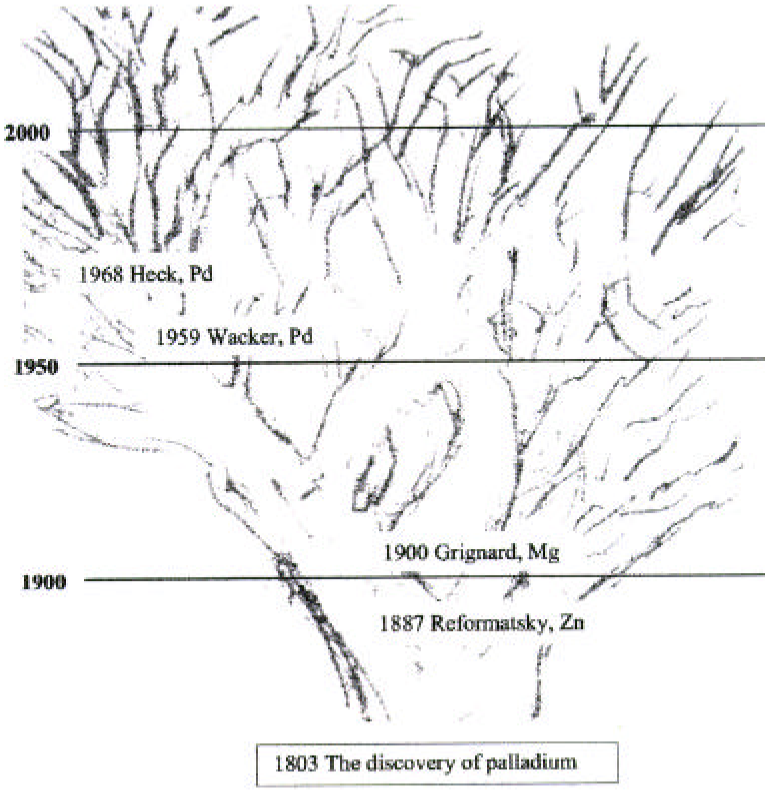
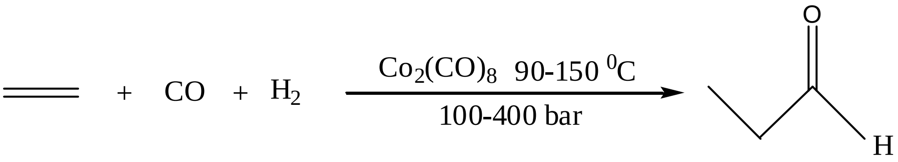


Figure 2.1. The development of organometallic chemistry

Barbier thereafter introduced organomagnesium chemistry in the early 20th century and his student Grignard explored in more detail the reactions with organomagnesium halides [32]. Along with the organolithiums developed later, the

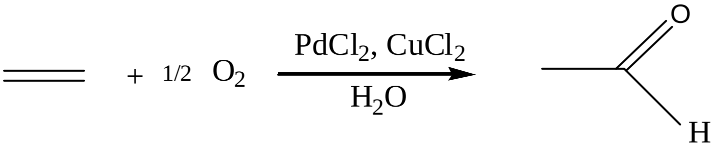
Grignard reagents continue to be one of the most important classes of organometallic compounds. Industrial large-scale applications employing organometallic chemistry started to emerge shortly thereafter. In 1938, O. Roelen discovered the important metal-catalyzed hydroformylation of olefins the oxo process (Scheme 2.1.).



Scheme 2.1. The Classical oxo process utilizing a cobalt catalyst

The oxo process was further developed by Union Carbide, using the transition metal complex $(PPh_3)_3Rh(CO)H$ as the precatalyst. The oxo process is the world's largest-scale homogeneously catalyzed industrial process [30].

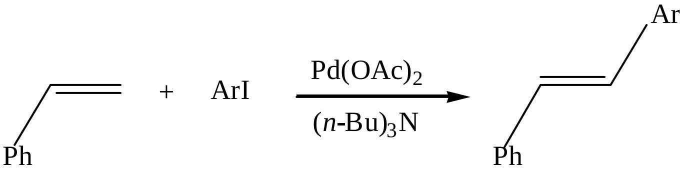
Since transition metals are normally expensive, and sometimes toxic, it is important that they can be used in sub-stoichiometric amounts. A nicely engineered solution is exemplified in the commercially important Wacker process, which was discovered in 1959 by German chemists (Scheme 2.2.).



Scheme 2.2. Palladium-catalyzed oxidation of an olefin, the Wacker process [33,34]

Here, palladium dichloride is used as the catalyst and is regenerated after each cycle with help of catalytic amounts of copper, which in turn is reoxidized by cheap and environmentally friendly oxygen gas.

The very versatile vinylic substitution reaction, the Heck coupling, employing aryl iodides, was developed around a decade later (Scheme 2.3.) [35].



Scheme 2.3. Palladium-catalyzed arylation of an olefin

2.2.1. Transition Metal Chemistry

Transition metals (of which there are 64) occupy the middle portion of the periodic table; they can be defined as metallic elements that have valence electrons in two shells instead of one (Figure 2.2.). These metals are suitable as catalyst because of their ability to change oxidation states during a catalytic cycle and the formation of lower-energy intermediates leading to a reduction of the activation barrier of the catalytic reactions.

One of the most common uses of a transition metal is in the antipollution devices in automobiles; platinum or palladium is used as a heterogeneous catalyst in these systems. The catalytic converter combines carbon monoxide and unburned fuel from a car’s exhaust with oxygen from the air to form carbon dioxide and water vapor. Many of the important transition metals in heterogeneous catalysis are found among the “late transition metals” such as Ru, Co, Rh, Ni, Pd and Pt. The complexes formed by transition metals with ligands allow their catalytic properties to be fine-tuned.

2.2.2. Catalytic Properties of Late Transition Metals

The extended possibility for coordination of ligands as a result of access to partially filled d-orbitals makes transition metals, especially the late, more versatile than the main group metals in a catalytic sense. This partial occupation of the d-orbitals also results in new features such as simultaneous electron-accepting and electron-donating characteristics. The interaction with ligands such as olefins [26], carbon monoxide, arenes, isocyanides, alkynes, nitric oxide etc, which have the same kind of acceptor/donor capabilities, gives rise to a situation where both ‘bonding’ and ‘backbonding’ are possible.

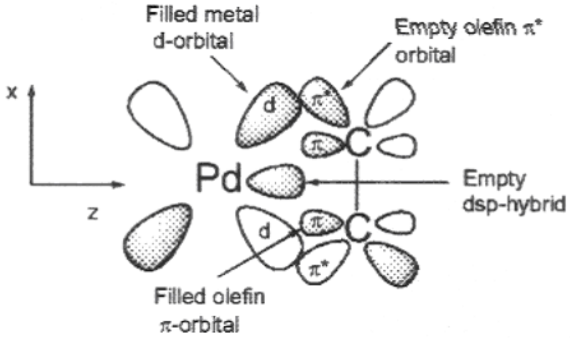
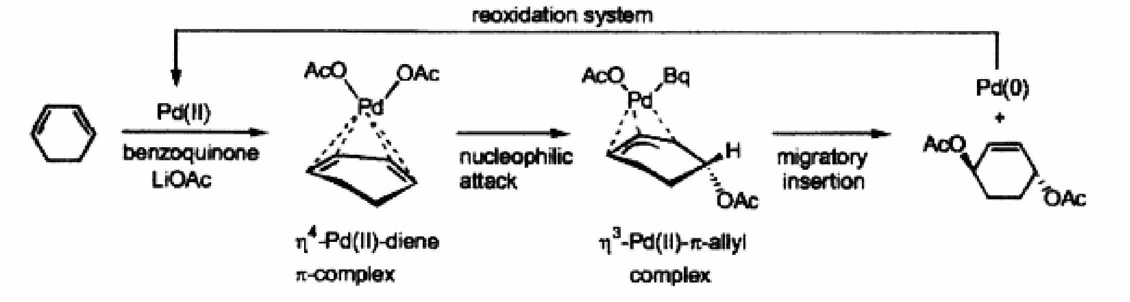


Figure 2.2.
Ethene coordinating palladium in h^{2} - mode, according to the Dewar–Chatt–Duncanson π-bond model.

A 'bonding' interaction (Figure 2.2.) develops between the filled olefin π-orbital and the spd hybrid on the metal, whereas 'backbonding' occurs between the empty olefin antibonding orbital and the filled d_{xz} orbital on the metal. The 'bonding' interaction is classified as a σ-bond, since it is symmetric when rotated around the z-axis. Accordingly, the 'backbonding' interaction is defined as a π-bond (anti-symmetric). In combination with the 18-electron rule, this bonding situation opens up very rich coordination chemistry where the electron density (changes in the HOMO and LUMO levels) on the metal can be easily varied by the judicious choice of ligands. The reactivity and selectivity of the transition metal complex, employed as a homogeneous catalyst, can therefore be fine-tuned.



Scheme 2.4. Coordination to electrophilic palladium facilitates subsequent nucleophilic attack on the diene by acetate anion

Since nearly every organic functional group is potentially capable of coordination to transition metals, there is a good probability of finding a suitable catalyst for the desired transformation. Transition metals can reverse the polarity (i.e electron density) of coordinated functional groups introduce a complementary reactivity (Scheme 2.4.) [37].

2.3. Palladium as Catalyst

In 1803, Wollaston discovered and isolated the precious metal palladium and named it after the asteroid Pallas, the second largest in the asteroids belt which had been discovered the year before [38]. The name Pallas was taken from the Greek goddess of wisdom and learning, Pallas Athena. Palladium is a steel-white metal that does not tarnish in air. Apart from its application as catalyst in organic chemistry (as a finely divided metal), palladium is used in electric components and as an alloy in jewelry.

Palladium is produced mainly in Russia and South Africa. The Pd that is used for chemical applications comprise only 35% of the world's palladium, 5 % of the stock is used in chemistry, while 50 % is used in electric components and 10 % for car-exhaust catalysts. Modern palladium chemistry started with the invention of the Wacker process in 1959, which resulted in palladium becoming a powerful process industrial catalytic tool (Eq. 2.1.). In the palladium-mediated conversion of alkenes to aldehydes it was discovered that Pd(0) could be re-oxidized by oxygen in the presence of $CuCl_2$ [34]. Since the middle of the 20th century, interest in palladium as a catalyst has increased drastically. Among the different types of transformations using late transition metals as catalysts, the reactions catalyzed by palladium are recognized as the most versatile, particularly in reactions involving carbon-carbon bond formations [39-40].

$$H_2C{=}CH_2 + 1/2\ O_2 \xrightarrow{\text{Cat}} CH_3CHO$$

$$\text{Cat} : Pd(II)Cl_2,\ CuCl_2 \qquad (2.1)$$

There are several features, which make reactions involving Pd particularly useful and versatile among many transition metals used for organic synthesis. Palladium is a useful catalyst for many reasons [21, 23]:

- It is the second member of the group nickel triad in the periodic table. The size of palladium contributes to the moderate stability and reactivity in comparison with the more reactive and unselective compounds or the organoplatinum derivatives that often appear to be too stable to be synthetically useful.
- Palladium strongly favors the 0 and +2 oxidation states as they are separated by a relatively narrow energy gap. This feature impends to the palladium to undergo one-electron or radical process and makes palladium a fairly selective catalyst, possibly through the minimization of unwanted side reactions.
- Palladium has comparatively high electronegativity that allows relatively non-polar Pd-C bonds and display low reactivity to polar functional groups, such as ketones, esters, amides, nitro compounds. This quality constitutes a desirable complement to e.g. the Grignard reagents and organolithium compounds that are very reactive to various carbonyl groups.

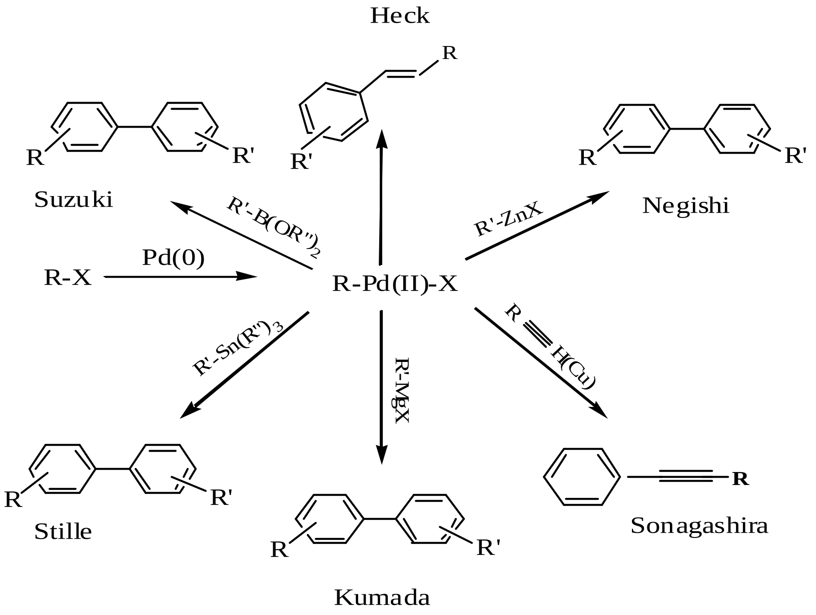
- Most importantly, Pd offers many possibilities of carbon-carbon bond formation. The importance of carbon-carbon bond formation in organic synthesis needs no explanation, and no other transition metals can offer such versatile methods for carbon- carbon bond formation as Pd. Palladium has an impressive functional group tolerance, i.e. chemoselectivity, which makes Pd-catalysis applicable to a large number of different substrates such as carbonyl and hydroxyl groups.Pd-catalysed reactions can be carried out without protection of these functional groups
- Palladium has accessible HOMO and LUMO orbitals, which facilitate concerted reactions of relatively low activation barriers.
- Palladium complexes are usually easy to handle, relatively nontoxic and mostly insensitive to oxygen, moisture and acid. Palladium is rare but less expensive than rhodium, iridium, osmium or platinum. The fact that a number of industrial processes (more than ten at least) based on Pd catalysed reactions have been developed and are now operated reflects these advantages of using Pd catalyst commercially [39].

Palladium catalysts can be divided into two major categories with different reactivities and geometries, namely Pd(0) complexes and Pd(II) salts or complexes (Table 2.2.). The latter unsaturated Pd(II) catalysts are electrophilic and will therefore coordinate to electron-rich organic compounds with a square planer geometry, typically unsaturated hydrocarbons and main group organometallics [1]. Pd(II) complexes form a relatively stable 16-electron complex. Since palladium has a suitable van der Waals radius Pd(0) coordinates to four ligands which allows a tetrahedral coordination and thus fulfill the 18-electron rule. It has recently been proposed that Pd(IV) might be involved in some palladium-mediated systems [41].

Table 2.2. Common oxidation states and coordination numbers for palladium [1]

Oxidation State	**Electronic Configuration**	**Geometry**
0	d^{10}	Tetrahedral
+2	d^8	Square planer
+4, rarely	d^6	Octahedral

2.4. Pd catalyzed C-C Bond Formations

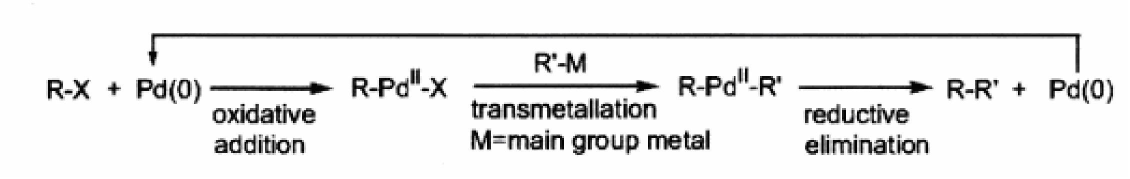


Scheme 2.5. Carbon-Carbon cross coupling reactions

The palladium-catalyzed cross-coupling of aryl and vinyl halides/triflates with organometallic reagents serves as a straightforward and powerful method for formation of carbon-carbon bonds (Scheme 2.5.). The R group of the organometallic reagent can be any of a variety of saturated or unsaturated groups, for example, alkyl, aryl, vinyl, and alkynyl.

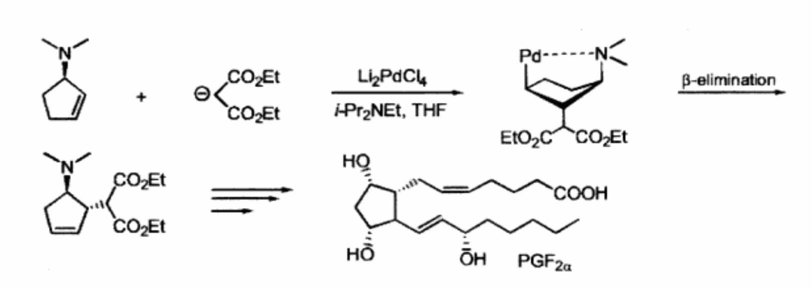
The reactions involved in forming carbon-carbon bonds are unquestionably the most important processes in organic chemistry, as they represent key steps in the building of more complex molecules from carbon-carbon bonds [42]. Metallation procedures are commonly employed to transform carbon into a useful nucleophile for a subsequent reaction with an electron-deficient carbon. The character of the transition metal carbon σ-bond is largely covalent, in contrast to that of the electropositive alkaline and alkaline-earth metals, which have highly polarized metal carbon bonds. Consequently, a part from being merely a carbanion equivalent, new reactivity can be accessed via the proximity effect from the coordination of other ligands due to the higher valency of the transition metal. Furthermore, it is possible to use transition metals in catalytic amounts, in contrast to the group I, II and III metals, which are always depleted in stoichiometric amounts. Palladium is perhaps the most versatile, and easy to handle, carbon-carbon forming metal catalyst in the periodic table.

Organopalladium coupling transformations mainly involve two types of complex: σ- and π-complexes. Among the reactions involving the σ-species are the well known Stille, Suzuki, Sonogashira [39], Kumada and Negishi cross-coupling reactions, which are all catalytic with palladium but also use tin, boron, copper, magnesium and zinc as the respective transmetallating partners (Scheme 2.5.) [1]. The catalytic cycle of all these reactions involves a reductive elimination step, during which the new carbon-carbon bond is created (Scheme 2.6.).



Scheme 2.6. Catalytic cross-coupling process involving a Pd σ-complex

The second type of palladium reaction involves the π-bonded ligands. The usual reaction path involves electrophilic Pd(II) coordination to an electron-rich double bond, causing reduced electron density at the C=C bond, which facilitates subsequent attack by various nucleophiles (Scheme 2.7.).

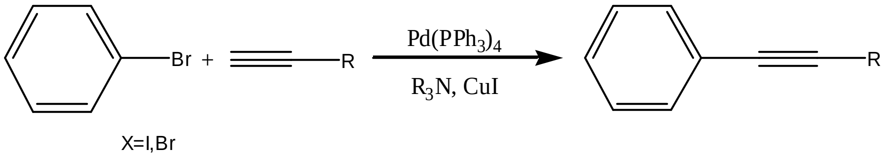


Scheme 2.7. Chelation-controlled carbopalladation of an alkene as a key step in the synthesis of prostaglandin PGF_{2a} [43]

The Heck reaction employs both σ- and π-bonded ligands (Scheme 2.3.). The presented palladium-catalyzed transformations constitute only a small fraction of the immense number of processes involving organopalladium intermediates. This reaction will be fully discussed in Chapter V.

2.4.1. Sonogashira Reaction

Coupling of copper acetylides with halides is known as the Castro reaction. Pd(0)-catalyzed coupling, which is called Sonogashira reaction, proceeds most efficiently by the addition of CuI as a cocatalyst. CuI activates the alkynes by forming the copper acetylide, which undergoes transmetallation with arylpalladium halide to form the alkynyl-arylpalladium species. Its reductive elimination gives the coupling product as the final step with regeneration of Pd(0) and CuI [44].

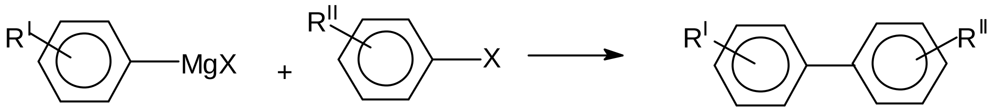


(2.2.)

The Sonogashira cross-coupling of aryl halides and terminal alkynes or arylenes is a useful tool for the synthesis of alkyl–aryl and diaryl-substituted acetylenes (Eq. 2.2.). Functionalized alkynes are important building blocks for the synthesis of biologically active molecules and, surprisingly, are common structural features of natural products that have been isolated from plants and marine organisms, or synthetic drugs. Therefore, the Sonogashira reaction is frequently used as a key step in the synthesis of pharmaceuticals, such as the enediyne antibiotics or the contraceptive pill.

2.4.2. Kumada Reaction

$$Ar^{I}MgX + Ar^{II}X \xrightarrow{Pd,base} Ar^{I}\text{-}Ar^{II}$$



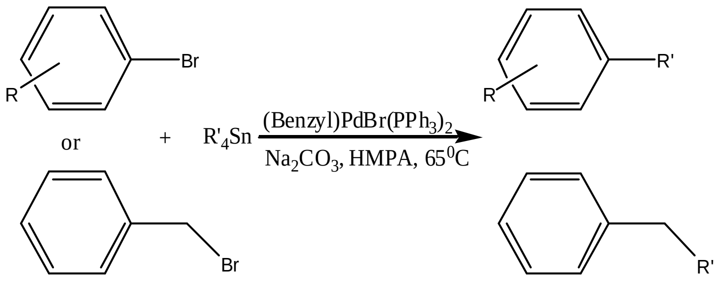
(2.3.)

X: Halogen

Arylboronic acids and other organometallic reagents used in C-C coupling reactions are often synthesized from the corresponding Grignard or organolithium reagents (Eq. 2.3.). A general method employing these reagents directly in cross-coupling would prove valuable. In 1972, Kumada and co workers and Corriu reported independently that the reaction of Grignards with alkenyl or aryl halides (the Kumada reaction) was catalyzed by Ni(II) complexes. The Pd-catalyzed Kumada reaction was first reported by Murahashi in 1975. In recent years several reports have appeared dealing with phosphine modified Pd- or Ni-mediated coupling involving inexpensive aryl halides as substrates [45].

2.4.3. The Stille Reaction

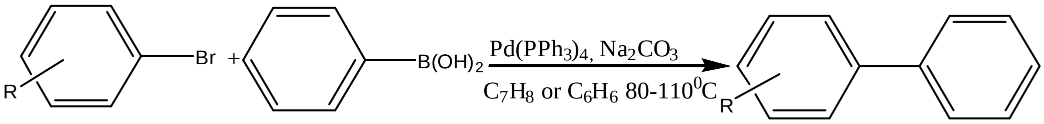
The metal catalyzed cross coupling of organic halides with Organotin reagents is referred to as the Stille reaction [46]. The necessity to develop this reaction arose from the low functional group tolerance of previous metal catalyzed additions of organolithium or organomagnesium reagents to organic halides to form carbon-carbon bonds. In one of the most important initial reports of this reaction, Stille and Milstein coupled benzyl bromide and electronically diverse aryl bromides to various tetrasubstituded Organotin reagents in the presence of a catalytic amount of (Bn)Pd(PPh_3)$_2$Cl (Scheme 2.8.) The generally accepted mechanism of the Stille coupling can be divided into three steps: oxidative addition, transmetallation, and reductive elimination. The factors that control the rate of oxidative addition and reductive elimination are better understood than the factors that control the rate of transmetallation. The mechanism of the step referred to as transmetallation is not clear. The obvious drawback to the Stille reaction is the use of stoichiometric amounts of the organotin reagent. This limitation has not eliminated the use of this cross-coupling reaction as a key step in the synthesis of many biologically active substances [47].



Scheme 2.8. The first example of Stille reaction

2.4.4. The Suzuki Reaction

The Suzuki-Miyaura reaction has become a widely used method to form biaryls without using toxic tin reagents. In 1981, Suzuki and co-workers reported the coupling of aryl iodides or bromides with phenylboronic acid in toluene or benzene in the presence of catalytic $Pd(PPh_3)_4$ and a stoichiometric amount of sodium carbonate (Scheme 2.9.)



Scheme 2.9. The first example of Suzuki-Miyaura Reaction

The reaction proceeds smoothly with phenylboronic acid. However, bulkier arylboronic acids were thought to retard the rate of transmetallation, a proposed step on the catalytic cycle. By increasing the base strength, the coupling of sterically hindered organoboronic acids with aryl halides could be accomplished in high yields. With the abundance of commercially available organoboron reagents and the facile palladium-catalyzed synthesis of boron-functionalized reagents, the Suzuki-Miyaura coupling should remain one of the most widely utilized methods of carbon- carbon bond formation [48].

2.4.5. The Negishi Reaction

The Negishi reaction utilizes aryl zinc reagent and aryl halides. This reaction began to achieve importance in the mid 1970's [39]. The palladium-catalyzed Negishi cross-coupling–the reaction of aryl and vinyl halides/triflates with organozinc reagents–represents a powerful tool for the formation of carbon-carbon bonds because of the ready availability and high functional-group compatibility of organozinc compounds.

As with Suzuki and Stille couplings, there are quite a few examples of heteroaryl chlorides, mainly nitrogen containing species, which participate in the Negishi reaction. Thus, chloropyridines, pyrazines, pyrimidines, and triazines are suitable substrates, as are fused heterocycles such as chloroquinolines, quinazolines, and purines.

CHAPTER 3

HETEROGENATION OF HOMOGENEOUS CATALYST

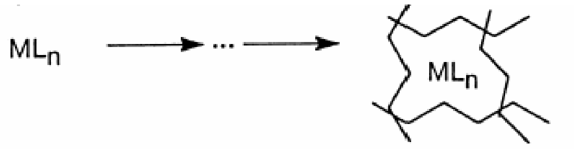
The heterogenization of homogeneous catalysts is a field of continuing interest that is expected to combine the advantages of homogeneous catalysts with the easy product separation and catalyst recovery of heterogeneous ones [49]. Heterogenized catalysts would combine not only the advantages of homogeneous and heterogeneous catalysts but also might minimize the drawbacks of both. The catalytic phase would be well-defined from a molecular scale point of view and all metal atoms could be, in principle, effective. Activity comparable to that of the solution phase has been observed in some cases with equivalent or even enhanced selectivity. Also, easy separation of the products from the reaction medium, along with the recovery and reuse of the expensive catalyst, provide an attractive advantage over homogeneous catalysis. Nevertheless the major drawbacks of these systems concern both their mechanical and chemical stabilities. The nature of the support, the catalytic phase and the anchorage type should be judiciously chosen to be resistant towards solvent and reactant attacks under the reaction conditions used [46]. Thus, unless the activity of the homogeneous catalysts is exceptionally high, their heterogenization is still currently an economical, but also a toxicological and environmental challenge. To reach this goal, many different strategies can and have been considered, which belong to two major classes: (1) Those which preserve as much as possible the coordination sphere of the metal. This is achieved:

- By anchoring the homogeneous catalyst to an inorganic oxide or an organic polymer via bonds between the solid and one (or more) ligand(s) at a position remote from the atom coordinated to the metal center. (Eq. 3.1.)

$$ML_n \rightarrow \quad \rightarrow \; |\!\approx L'ML_{n-1} \qquad L'\approx L \qquad (3.1.)$$

Ligand L' is a ligand L functionalized so as to allow for a reaction with the support of interest.

- By encapsulating or encaging the catalyst in the voids of a porous, inorganic or organic, solid: (Eq. 3.2)



(3.2.)

- Or by immobilizing the homogeneous catalyst in a film of solvent (non volatile or hydrophilic) deposited on a solid, while reactants and products are either in the gas phase or in a second solvent non-miscible to the first one. These are the so-called ‘‘supported liquid (aqueous) phase catalysts’’ (SLPC/SAPC). Formally, all these methods lead to the so-called “supported homogeneous catalysts’’: this means that the structure of the supported organometallic complex is nearly identical to that of the precursor homogeneous catalyst.

(2) Those which anchor the organometallic complex via a direct bond between the metal center and a surface atom: (Eq. 3.3.)

$$ML_n \rightarrow \;\rightarrow \quad |\!\approx ML_{n-i} \qquad (3.3.)$$

This procedure induces important changes of the ligand environment around the metal center, which includes now a ‘‘solid’’ ligand. Two situations ought to be considered separately:

- The precursor organometallic complex is a homogeneous catalyst. Then, the supported complex, whose structure can be very different from not only the precursor complex, but also from any known homogeneous catalyst, is as such a new heterogeneous organometallic catalyst.
- The precursor organometallic complex is not a catalyst. It is chosen so that its reaction with the support leads to a clean and precise anchoring of the metal. In a second step, this supported organometallic complex is chemically transformed into a supported molecular catalyst, designed for a given target reaction.

3.1. Catalysts Anchored on Functionalized Solids

During the 1970s, extensive research was devoted to the anchorage onto insoluble supports of homogeneous catalysts based on metal-transition complexes although the first example did not concern an organometallic complex $[Pt(NH_3)_4^{2+}]$ and used an ionic bond to anchor the complex to the surface (sulfonated silica). One possible strategy to immobilize transition-metal complexes deals with the design of new larger-pore hybrid materials having well-defined pore structures. The grafting of transition-metal complexes by covalent linkage onto the micelle-template silica (MTS) supports. These new materials, recently discovered by Mobil's researchers, feature an ordered mesoporous system of monodispersed pore size and exhibit larger pore aperture than zeolites. They provide new opportunities for grafting catalytic phases on inorganic surfaces [56]. Most of the studies use silica as the support: it presents the advantages to be chemically inert towards many reactants because it has no pronounced surface acidity which would induce secondary reactions, to have surface hydroxyl groups which allow for ligand bonding, to present high specific surface areas and good thermal and mechanical stabilities. Schematically, two different approaches were used, which are represented below: Indirect grafting and direct grafting of metal complexes (Eq. 3.4.–3.5.)

$$\vdash\!\!OH + X\approx L' \rightarrow \vdash\!\!O\approx L' \rightarrow \vdash\!\!O\approx L'\,ML_{n-1} \qquad (3.4.)$$

$$\vdash\!\!OH + (X\approx L')ML_{n-1} \rightarrow \vdash\!\!O\approx L'ML_{n-1} \qquad (3.5.)$$

3.1.1. Indirect grafting

The method consists in functionalizing the surface of silica by reaction between a bifunctional ligand, $X\approx L'$ and the surface silanols. The X group is chosen so as to react easily with hydroxyls; it is generally Cl, $SiCl_3$, $Si(OEt)_3$, OH or $SiR'_2(OR)$. In most cases, L' is a phosphine, PR'_2R, the R alkyl or aryl substituent bearing the X group. With X=OH or $SiR'_2(OR)$, a better control of the surface reaction is claimed: the cross-linking reactions are suppressed (Scheme 3.1.) and the stoichiometry of the

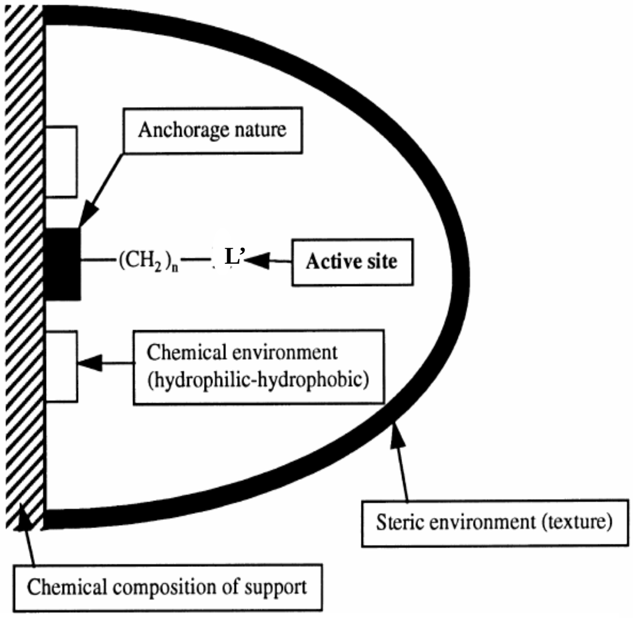
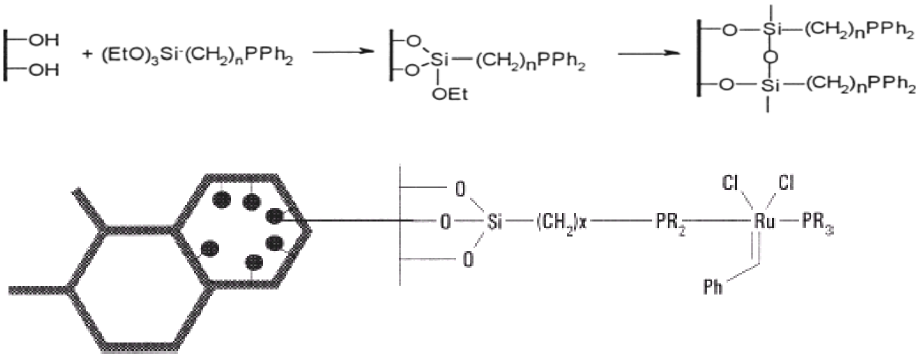


Figure 3.1. Design of organic inorganic mesoporous materials

anchoring reaction is simple. The alkyl chain $(CH_2)_n$ acts as a spacer between the support and the complex: its length allows for a certain mobility of the complex and a partial release of the steric hindrance induced by the support, but it may also be a source, for the larger *n* values, of catalyst deactivation by dimerization of the active species. It has, thus, a major influence on the activity and the selectivity of the catalyst.

$$X\approx L' = X\text{-}(CH_2)_nPPh_2 \text{ or } X\text{-}C_6H_4\text{-}PPh_2$$



Scheme 3.1. Illustration of anchored Ru catalyst in MCM-41

The complex ML_n of interest can also be grafted on the functionalized solid by a ligand exchange reaction with the surface ligands L'. The donor ligand L in the precursor complex is often a phosphine, or any ligand easy to remove from the system, such as CO.

3.1.2. Direct Grafting

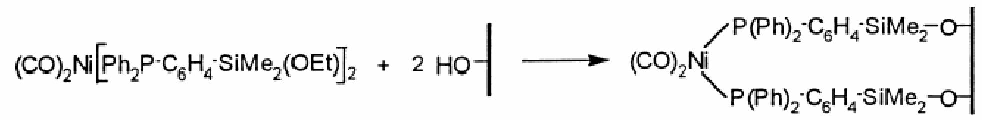
The attachment of guest to the walls of the solid can be achieved by the direct reaction of surface hydroxyl groups with reactive ligands. The approach, described in Eq. (3.5.), consists of synthesizing first the complex ML_xLy', with the desired ratio [functionalized ligand L'] / [M]. This method is only of interest in the cases when the previous one (Eq. 3.4.) does not lead to the desired anchored complex, because the syntheses and isolation of these functionalized complexes are not straightforward (oily products are often obtained). One of the successful examples concerns the synthesis of nickel carbonyl complexes anchored to the surface via two bonds in an attempt to increase their stability through a sort of ''chelate effect''. The simplest method, which consists in reacting $Ni(CO)_4$ with the related phosphinated silica, leads invariably and only to the monophosphine complex, under all tested conditions: (Eq. 3.6.)

$$Ni(CO)_4 + PPh_2-C_6H_4-SiMe_2-O-Si\equiv \rightarrow (CO)_3NiPPh_2-C_6H_4-SiMe_2-O-Si\equiv \quad (3.6)$$

On the other hand, under classical conditions, the complex $(CO)_2Ni[PPh_2(C_6H_4)SiMe_2(OEt)]_2$ reacts with silica mainly via one functionalized ligand as demonstrated by ^{29}Si and ^{31}P CP MAS NMR spectroscopy : (Eq. 3.7)

$$(CO)_2Ni[Ph_2P\text{-}C_6H_4\text{-}SiMe_2(OEt)]_2 + HO\text{-}| \longrightarrow \begin{matrix}(CO)_2Ni(Ph)_2P\text{-}C_6H_4\text{-}SiMe_2\text{-}O\text{-}| \\ (EtO)Me_2Si\text{-}C_6H_4\text{-}PPh_2\end{matrix} \quad (3.7)$$

But, when the solution of the complex is added drop by drop to silica, then the desired di-anchored complex is formed: (Eq. 3.8.)



$$(CO)_2Ni[Ph_2P\text{-}C_6H_4\text{-}SiMe_2(OEt)]_2 + 2\,HO\text{-}| \longrightarrow (CO)_2Ni\begin{matrix}\nearrow P(Ph)_2\text{-}C_6H_4\text{-}SiMe_2\text{-}O\text{-}| \\ \searrow P(Ph)_2\text{-}C_6H_4\text{-}SiMe_2\text{-}O\text{-}|\end{matrix} \quad (3.8.)$$

The success of the method seems, thus, to be very dependent on the precise experimental conditions (surface state of silica, reactivity of the functional ligands, ligand concentration etc.).

3.2. Encapsulated, Intercalated or Entrapped Catalysts

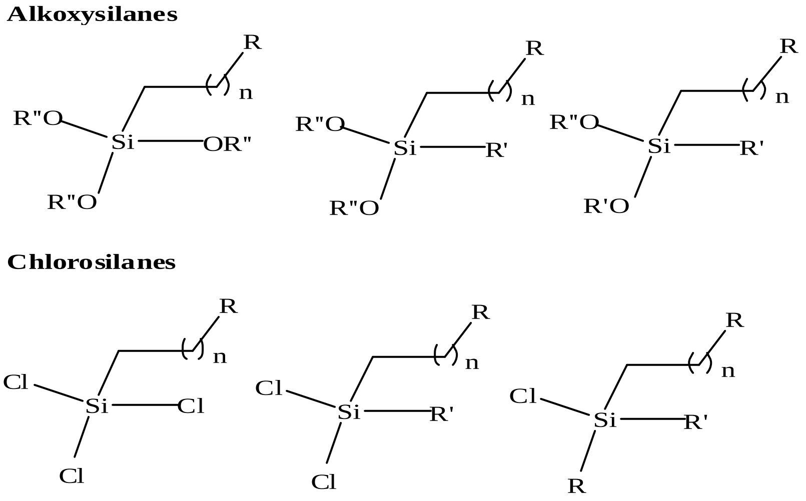
The objective, clearly, is to improve the stability of the metal complex under the reaction conditions by preventing the catalytic species from dimerizing or aggregation, and to tune the selectivity of the reaction using the walls of the pores of the solid via steric effects. The encapsulation of transition metal complexes in inorganic solids was mainly performed by three methods. Two of them introduce (or synthesize) the complex inside the porous network of a pre-formed solid either by encapsulation or by intercalation; the third one uses the complex as one of the reactants in the mixture of synthesis of the solid: the complex is, thus, entrapped inside the pores [51].

3.3. Surface Modification and Activation of Mesoporous Materials

Pure mesoporous materials have a neutral framework limiting their applications to catalysis, supports, molecular sieving, adsorbents, etc. In most cases, a modification step is required to activate the surface towards specific catalytic purposes. The activation can be done by incorporation of heteroelements in the framework structure or by a modification of the surface [52].

The large surface areas of mesoporous materials make these materials very attractive as support for active phases. Silica gel is an amorphous inorganic polymer composed of siloxane groups (Si-O-Si) with silanol groups (Si-OH) distributed on the surface. The modification of silica gel using inorganic or organic functional groups has been a subject of considerable interest. Surface modifications are usually achieved through silanization by using an appropriate organosilane agent. In the last several years, many efforts have also been devoted to the use of ordered mesoporous materials as a support for immobilizing acid and or base sites in order to overcome the low acid strength and stability of Al containing MTS and to broaden the catalytic applications of the MTS materials as heterogeneous base catalysts. Modification of the MTS surface with covalently bonded organic species, especially functional organosilanes, has attracted much attention in order to design MTS materials with engineered properties for advanced applications, e.g. in catalysis, and selective adsorption of organics and metals. At the same time, the grafting of alkylsilane on the MCM-41 surface has provided an opportunity to obtain hydrophobic materials with tailored pore size and high surface area. Important improvements are realized by partial hydrophobization of the MTS surface and by developing materials with thicker and more condensed silicate walls, exemplified by SBA-15 and KIT-1. In addition, several treatments which lead to a decrease in silanol concentration, e.g. silanization, salt effect or coating of the surface, were found to enhance stability [53].

Silanization can be performed on any type of surface displaying hydroxyl groups, such as mica, glass, and metal oxides. Silanization involves the covalent binding of a silane reagent molecule, either a chlorosilane or an alkyloxysilane (Scheme 3.2.), to the surface or to another silane coupling molecule through a siloxane bond. The polymerization of the silane molecules depends on both the number of chloro or alkoxy groups present and the amount of water present on the surface. In this study surface modification was performed by using trimethyl chlorosilane and a Pd(NHC) salt.



R = alkyl, amino alkyl, thioalkyl, alkene, carboxy alkyl...
R'= H,CH_3

Scheme 3.2. Silane molecules used in silanization.

3.4. Catalyst Supports: Silica

The early concept of a support or a carrier was of an inert substance that provided a means of spreading out an expensive catalyst ingredient such as platinum for its most extensive use, or a means of improving the mechanical strength of an inherently weak catalyst. However, the carrier may actually contribute catalytic activity, depending on the reaction and the reaction conditions, and it may react to some extent with other catalyst ingredients during the manufacture process. It can also help to stabilize the catalytically active structure.

The selection of a carrier is based on its having certain desirable characteristics. In addition to possible chemical effects, certain physical properties are important [52]:

1. Inertness to undesired reactions
2. Desirable mechanical properties, including attrition resistance, hardness, and comprehensive strength
3. Stability under reaction and regeneration conditions
4. Surface area (High surface area is usually, but not always, desirable)

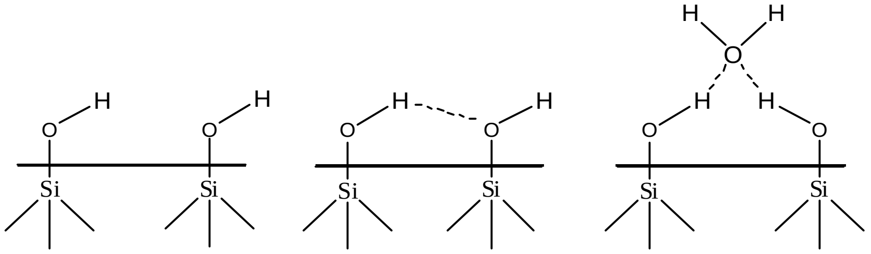
5. Porosity, including average pore size and pore-size distribution (high area implies fine pores but relatively small pores, such as < 2 nm may become plugged in catalyst especially if high loadings are sought)
6. Low cost

Of a wide variety of possible supports, only three combine the four going characteristics in an optimum way and therefore they account for most uses. These are alumina, silica, and activated carbon; titania also has limited uses. In this study amorphous silica was used as the support material.

The first report on the preparation of coherent expanded aerogels was published by Kistler in 1931. He clearly showed that the inorganic gel, when dehydrated under normal conditions, collapses into a powder as a result of the disruption in the pore structure of the gel. However, when the gel was dehydrated under super- critical conditions of temperature and pressure, the liquid-vapor boundary within the pores of the gel no longer existed and the gels did not collapse on drying. Kistler described the formation of gels of silica, alumina, ferric oxide, stannic oxide, tungstic oxide, nickel oxide, and several organic materials [54]. Silica gel chemistry is performed either with an inorganic precursor, like ‘‘water-glass’’ or with organic precursors such as silicon alkoxides, tetraethoxysilane (TEOS) of formula $Si(OC_2H_5)_4$ or tetramethoxysilane (TMOS) of formula $Si(OCH_3)_4$, which are usually engaged as monomers, but partially condensed silica or prepolymers (oligomers) are sometimes also used [55]. Silica gel is most commonly prepared by hydrolyzing an acid, generally hydrochloric acid, with a solution of “water glass” which consists of ortosilicates (Na_4SiO_4), metasilicates (Na_2SiO_3), and related compounds. It was then allowed to set and washed until the chloride was removed. As the pH is lowered, a polymerization and a condensation process takes place, which can be visualized starting with silicic acid [$Si(OH)_4$]. This polymerized with condensation of silane groups (SiOH) to form an ill-defined polymer in which the primary bonds are the siloxane type (Si-O-Si). This precipitates as a gel or as a colloid, the properties of which depend on mixing procedures, the presence of electrolytes, temperature, aging, etc. By proper control, a hydrogel consisting of small micelles that are roughly spherical is obtained. During drying, the micelles do not coalesce appreciably, particularly if the liquid is removed at above critical temperatures and pressures. Under these conditions, no interface forms that could otherwise collapse the structure by the forces of surface tension. The tiny size of the micelles and use of procedures to prevent coalescence leads to a product of high surface area. Commercial material usually has a high area, as high as about 700 m^2/g. The average pore diameter correspondingly very low typically in the range of 2.5 to 5 nm (these pores are however considerably larger than those in zeolites and are substantially greater than the most reactant molecules of interest.)

By varying the manufacturing and aging procedures, silica gels can be made with considerably larger pore diameter and correspondingly lower surface area, perhaps as low as about 100 m^2/g. Silica gel is generally inert. The final dry product should be referred to strictly as a xerogel or porous silica, but the term *silica gel* is in common usage. At ambient temperature the surface consists of a layer of silanol groups (SiOH) plus the physically adsorbed water. Most of the water is removed upon drying in air at 150 to 200 °C. Silanol groups are left on the surface, and these are progressively lost with increased temperature. Some siloxane groups may also be present on the surface [52].

A basic knowledge of the surface structure is of great help in understanding the adsorption behavior and the chemical reactivity of silica in a variety of processes. With respect to the surface of crystalline silica, it was assumed that all of the hydroxyl groups exist as a free or isolated hydroxyl groups (Scheme 3.3.). In contrast, the surface structure of amorphous silica is highly disordered and such a regular arrangement of hydroxyl groups cannot be expected [56].



isolated or free hydroxyl groups

vicinal hydroxyl groups

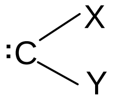
hydroxyl groups bond to water by hydrogen bonding

Scheme 3. 3. Arrangement of hydroxyl groups on a silica surface

CHAPTER 4

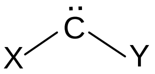
CARBENES

The word "carbene" derives from the name given to free, disubstituded uncharged carbon compounds with general structure **1**, where X and Y may be alkyl, aryl, H, or heteroatoms (O, N, S, halogens). Such compounds are called free carbenes to distinguish them from metal complexes possessing divalent carbon ligands. [57]



1

Carbenes are also regarded as a class of radical like molecules. They possess two nonbonding electrons and six valence electrons [60]. Because the central carbon atom does not possess an octet of electrons, free carbenes are electron deficient and extremely reactive [57]. As it is mentioned before the free carbenes have two unshared electrons. These can be assigned to two nonbonding electrons in two different ways that causes the free carbenes exist in two different electronic states: singlet and triplet, which are represented in structures **2** and **3**. The singlet state has one lone electron pair, while the triplet state has two unpaired electrons. [57]



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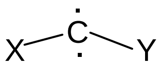

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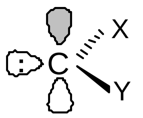

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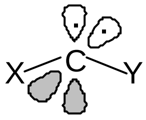
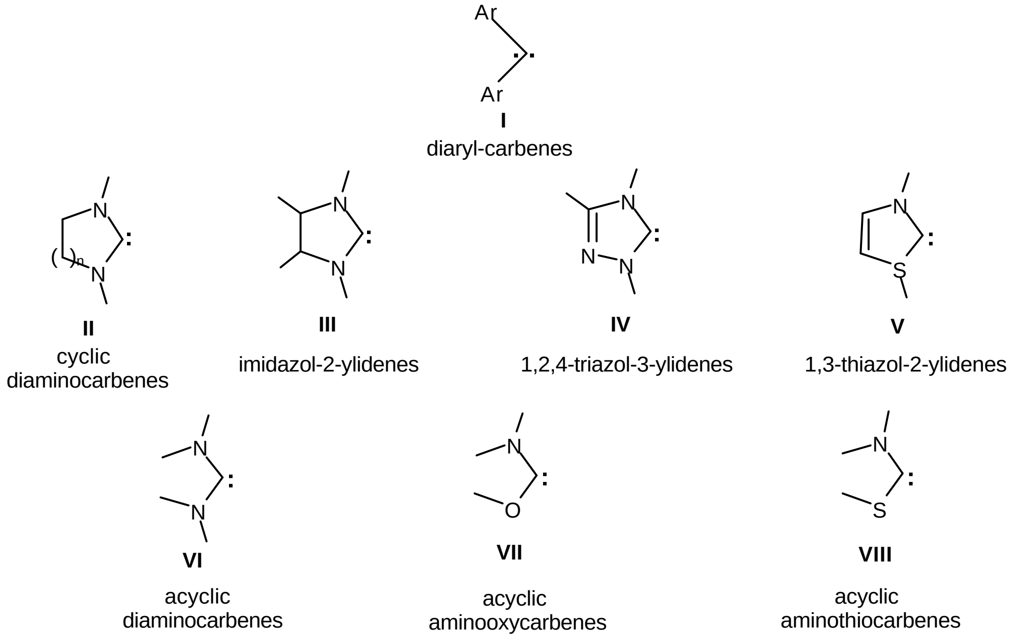


5

Singlet state of a free carbene can be considered as a bent molecule 4 in terms of localized hybrid orbitals. It has three sp^2 (one of which is doubly occupied and nonbonding) and an empty, perpendicularly situated 2*p* orbital. A triplet carbene (really a diradical) would be a less bent species 5 with two singly occupied, orthogonal 2*p* orbitals and two *sp* orbitals that are involved in bonding to substituents.

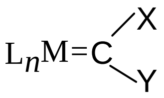
In the last 10 years, our understanding of carbene chemistry has advanced dramatically with the preparation of persistent and the isolation of heteroatoms-substituted singlet carbenes **II-VIII** (Scheme 4.1.) [59].



Scheme 4.1. Triplet I and singlet carbenes II-VIII.

4.1. Metal Carbene Complexes

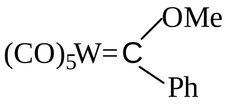
Disubstituted carbon atoms may bind directly to a transition metal producing a formal double bond between the metal and the carbon. Complexes containing these ligands are called *metal-carbene complexes* or *alkylidene complexes*. Metal carbene complexes have the general structure shown in **6**, where L_n is any ligand except for carbene, M is a transition metal and X and Y are same as in **1**.



$$L_nM=C\genfrac{}{}{0pt}{}{X}{Y}$$

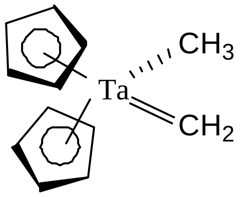
6

It was mentioned that, just as there are two types of free carbenes, there are also two kinds of metal-carbene complexes. The kinds of metal carbene complexes depend upon the nature of the substituents X and Y. When either or both substituents bound to



$(CO)_5W{=}C(OMe)Ph$

7



8

C*carbene* are heteroatomic, the resulting complex is called *Fischer-type carbene complexes* (structure **7** below). The first *Fischer-type carbene* **7** was reported by Fischer and Maasböl in 1964 [60] and since then numerous compounds were synthesized and characterized. Ten years after the first Fischer type complex **7**, Schrock and co-workers discovered a species where the substituents X and Y attached to C*carbene* were H or alkyl. Such metal carbene complexes have since become known as *Schrock-type carbene complexes* **8** or alkylidenes.

The two kinds of carbene complexes differ in several ways. Fischer-type metal-carbene complexes tend to undergo attack at C*carbene* by nucleophiles. While Schrock-type carbene complexes, on the other hand, undergo an attack by electrophiles at C*carbene*, and are more properly called *electrophilic metal-carbene complexes* and Schrock-type carbenes *nucleophilic metal-carbene complexes* Table 4.1. summarizes some other differences between the two carbene complex types.

Table 4.1. Fischer- and Schrock-type carbene complexes

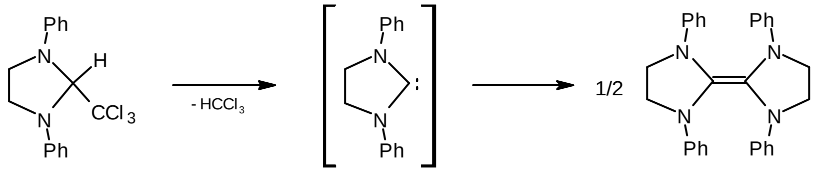
Characteristic	**Fischer-Type**	**Schrock-Type**
Substituents attached to $C_{carbene}$	At least one electronegative heteroatom, *e.g.*, O or N	H or alkyl
Typical ligands also attached to metal	Good π acceptor, *e.g.*, CO	Good σ or π donor, *e.g.*, Cp, Cl, alkyl
Electron count	18 e^-	10 – 18 e^-
Typical chemical Behavior	Nucleophile attacks at $C_{carbene}$	Electrophile attacks at $C_{carbene}$

Despite the increasing interest in persistent intermediates and coordination chemistry of alkylidenes the first singlet carbenes were isolated in 1991. The isolation of these compounds received much attention, among the organometallic chemist. Because they can be used as ligands with almost every element and some of the complexes can catalyze certain organic reactions.

4.2. Aminocarbenes and Their Properties

Carbenes that are widely used in organic synthesis, catalysis and macromolecular chemistry have played an important role in organic chemistry ever since the first firm evidence of their existence. While much of the early chemistry of these laboratory curiosities was established in the 1950s by Skell. It was Fischer and Massböl who introduced carbenes into organometallic chemistry in 1964 and into the organic chemistry by Doering and Hoffmann in the 1950s [61].

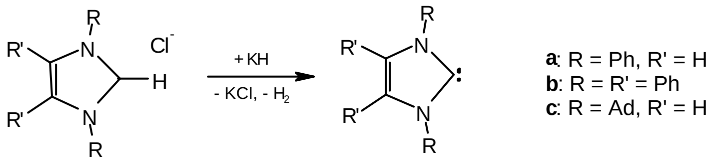
In the early 1960s, Wanzlick realised that the stability of carbenes could be dramatically enhanced by the presence of amino substituents and tried to prepare the 1,3-diphenylimidazolidin-2-ylidene **10** from **9** by thermal elimination of chloroform (Eq. 4.1) [62].



(4.1)

9 **10** **(10)$_2$**

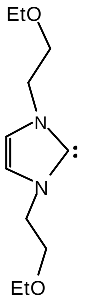
At that time, only the dimeric electron-rich olefin (10)$_2$ was isolated and cross-coupling experiments did not support an equilibrium between (10)$_2$ and two-carbene units [63]. In 1970, Wanzlick and co-workers demonstrated that imidazolium salts **11a,b** could be deprotonated by potassium *tert*-butoxide to afford the corresponding imidazol-2-ylidenes **12a,b** which were trapped but not isolated [64]. Following this principle, almost two decades later Arduengo *et al.* prepared “A Stable Crystalline Carbene” [65]. **12c** was obtained in near quantitative yield by deprotonation of the 1,3-di-1-adamantylimidazolium chloride **11c** with sodium or potassium hydride in the presence of catalytic amounts of either KOBu^t or the dimethyl sulfoxide anion (Eq. 4.2).



11a-c **12a-c**

(4.2)

As expected the deprotonation occurs much faster with liquid ammonia as the solvent (homogeneous phase), and oxygen, nitrogen, and phosphorus *N*-functionalised **13-17** as well as chiral **16** and bis-imidazol-2-ylidenes **17** have been prepared following this procedure.



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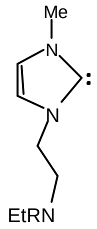

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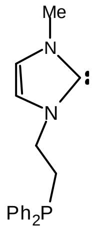

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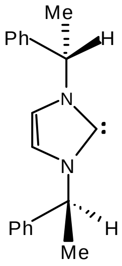

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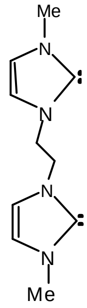
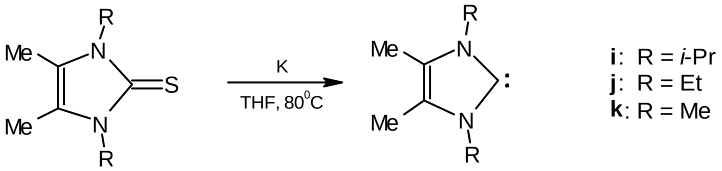


17

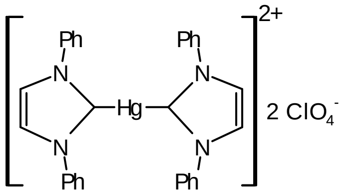
In 1993, Kuhn and co-workers developed a new and versatile approach to the alkyl-substituted *N*-heterocyclic carbenes **19i-k**. This original synthetic strategy relied on the reduction of imidazol-2-thiones **18i-k** with potassium in boiling THF (Eq. 4.3). Compound **17** became the first carbene to be commercially available.



(4.3)

18i-k **19i-k**

Discovery of *N*-heterocyclic carbenes (NHC's) by Wanzlick *et al.* in the 1960s and their first application as ligands in compounds **20-22** by Wanzlick, Öfele and Lappert in 1970s were the basis for carbene complexes as possible catalysts.



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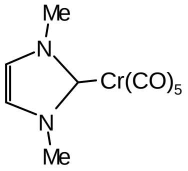

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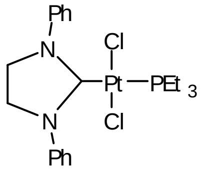


22(1971)

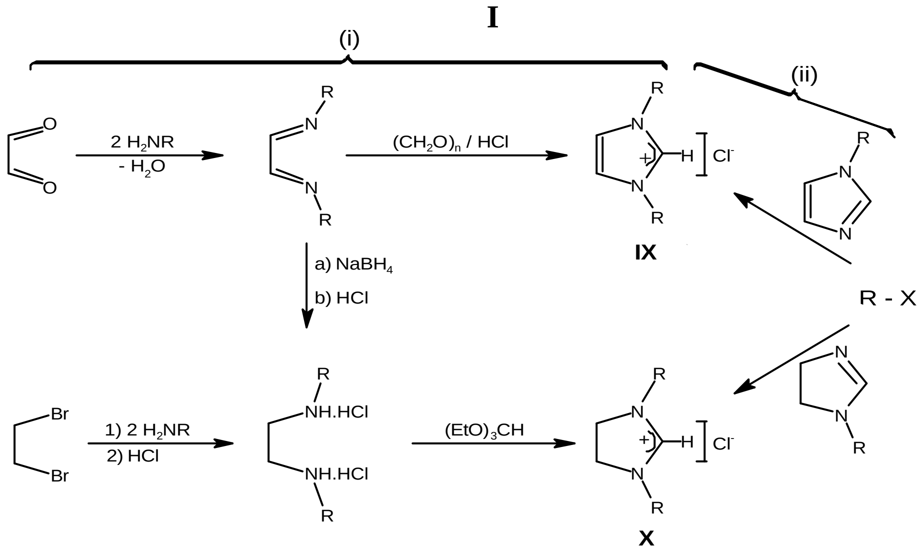
The rest of this section summarizes synthetic methods for the metal complexes containing NHC's and preparation of the relevant carbene precursors. The use of these complexes in transition metal catalysis was discussed. The main emphasis will be on saturated NHC *i.e.* imidazolidin-2-ylidens.

N-Heterocyclic carbenes (NHCs) have become universal ligands in organometallic and inorganic coordination chemistry. They not only bind to any transition metal, be it in low and high oxidation states, but also to main group elements such as beryllium, sulfur, and iodine. Because of their specific coordination chemistry, NHCs both stabilize and activate metal centers in quite different key catalytic steps of organic synthesis; for example, C-H activation, C-C, C-H, C-O, and C-N bond formation. Numerous metal compounds were synthesized and characterized before the free carbene ligands become available through the important work of Arduengo *et al.* [65].

4.3. Precursors for Stable Carbenes

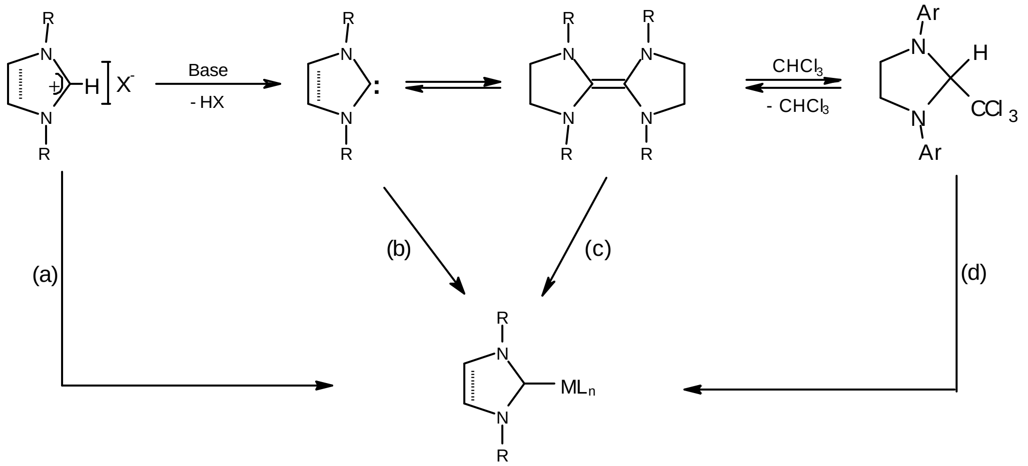
In many cases the synthesis of NHC complexes starts from *N,N′*-disubstitued azoli(ni)um salts (**IX** and **X**). Imidazolium salts as precursors for imidazolin-2-ylidenes are generally accessible by two ways complementing each other: (i) a multicomponent reaction building up the heterocycle with the appropriate substituents in a one-pot reaction or (ii) quaternasition of the alkyl imidazole (Scheme 4.2.).

Imidazolium salts that can be prepared by the first procedure, the alkylation of imidazole, are easy to be obtained and often used for metal complex synthesis. Potassium imidazolide is reacted with the first equivalent of alkyl halide in toluene to give the 1-alkylimidazole. Subsequent alkylation in 3-position is achieved by addition of another equivalent of alkyl halide (Scheme 4.2) [66-67]. The reaction of an ortho-ester, e.g., $HC(OEt)_3$, with a secondary bisamine in the presence of an ammonium salt yields imidazolinium salts (**X**, Scheme 4.2.) [68-69].



Scheme 4.2. Pathways for synthesis of imidazol(in)ium salts as precursors for imidazol(in)-2-ylidenes.

4.4. NHC Complexes of Transition Metals



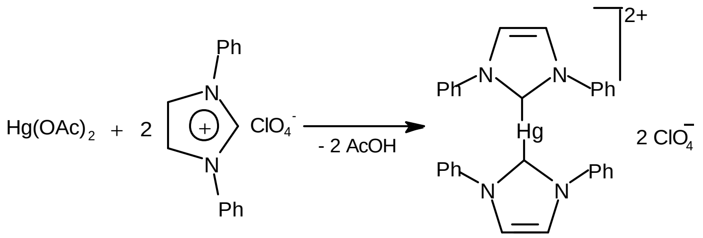
Scheme 4.3. Major synthetic pathways for the generation of transition metal–NHC complexes.

Four major routes were applied for the synthesis of NHC complexes: (a) the *in situ* deprotonation of ligand precursors, (b) complexation of free *N*-heterocyclic carbenes, (c) the cleavage of electron rich-alkenes, (d) elimination of small molecules from neutral ligand precursors (Scheme 4.3.). In this study, since route (a) is followed to synthesize Pd(NHC) complex, it will be documented in detail.

4.4.1. *In Situ* Deprotonation of Ligand Precursors

The *in situ* complexation of the ligand has the advantage of not having to prepare and isolate the free NHC. In cases where the carbene is hardly stable, not yet accessible at all, or difficult to handle, this approach offers the only chance to prepare the desired complex. The *in situ* deprotonation of ligand precursors can be carried out in two different ways; deprotonation by basic anions or deprotonation by external base. Since the first method was used in this study, it will be discussed.

Brönsted basic anions either on the metal precursor or on the azolium salt can form the desired ligand *in situ* by deprotonation. Commercially available metal acetates, acetylacetonates or alkoxylates, which are also easy to prepare, have been used frequently. Wanzlick was the first to use an acetate salt in the synthesis of a mercury bis-NHC complex starting from mercury(II) diacetate (Eq. 4.4) [70]. There are other examples using the same strategy [71]. Exchanging the anionic parts of the mercury precursor and the imidazolium salt, *i.e.*, using $HgCl_2$ and imidazolium acetate, works as well [72].

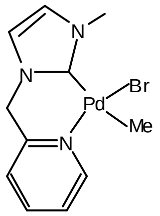


(4.4)

More than 25 years later, this method proved to be especially valuable for palladium(II) and nickel(II) complexes starting at the corresponding metal(II) diacetates and imidazolium or triazolium salts [73,74-35]. For palladium, it is possible to apply the *in situ* deprotonation method even without solvent, [75] but using THF or even better DMSO results in enhanced yields of the complexes.

Since the *in situ* approach seems to tolerate more functional groups in the azolium precursor than does the deprotonation of the azolium salt with NaH, it facilitates the use of bifunctional chelating ligands. Thus, *e.g.*, a hemilabile pyridyl-functionalized NHC

23 has been attached to a palladium(II) center by this route [76]. In certain cases it does not seem to be necessary.



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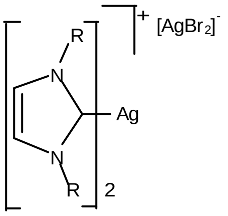
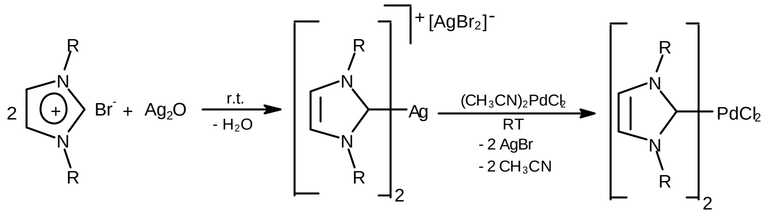


24

Basic silver(I) oxide Ag_2O is a convenient precursor for silver(I) bis(NHC) complexes such as **24** [71,77]. The preparation proceeds even at room temperature. The cationic complex precipitates and is therefore easy to purify. Cationic bis(NHC)silver(I) complexes can be used to transfer both NHC ligands to $[Pd(CH_3CN)_2Cl_2]$ or $[Au(Me_2S)Cl]$ in CH_2Cl_2 at ambient temperature (Eq. 4.5). The silver(I)-NHC complex does not have to be isolated prior to the NHC transfer reaction that makes this method more convenient [78]. The silver(I) halide which forms during the transfer can be filtered off the product solution and can be recycled. Under phase transfer conditions this reaction can be run catalytically in silver (*vide supra*). In certain cases it has been advantageous to use a mixture of CH_2Cl_2 and ethanol as the solvent in this reaction [78]. This procedure has been extended to the preparation of a variety of palladium complexes with donor-functionalized NHCs [79]. Due to its convenience and the broad range of complexes that are accessible, this method is very likely to gain an important role as a synthetic route to NHC complexes.



(4.5.)

4.5. Electronic Properties of NHC Complexes

Due to the presence of two π-donor substituents at the carbene center, the NHCs complexes may be classified, at a first glance, as Fischer-type compounds. However, in contrast to usual Fischer-type complexes, *N*-heterocyclic carbenes and especially imidazol-2-ylidenes **III** and imidazolidin-2-ylidenes **II** bind to transition metals only through σ donation, π-back-bonding being negligible. Photoelectron spectroscopy coupled with density functional calculations have demonstrated that even for group 10 metals, bonding occurs very predominantly through σ donation from the carbene lone pair [80]. These, peculiar binding properties are easily understandable since the energy of the vacant p_π orbital at the carbene center is considerably increased by the strong $N \rightarrow C$ π donation. The CO stretching frequencies of mixed carbene-carbonyl complexes also afford interesting information about the electronic properties of NHC ligands [61]. The ratio of σ donation to π-back-donation for $Fe(CO)_4$-bonded heteroatom-substituted carbenes increases in the order $:C(OR)R < :C(NR_2)R < :C(NR_2)_2$ $\approx$ imidazolidin-2-ylidenes $\approx$ imidazol-2-ylidenes. The π-acceptor ability of diaminocarbene **II-IV** and **VI** lies that of nitriles and pyridine. On the basis of solution calorimetric investigations, a relative enthalpy scale has been established for e series of sterically demanding nucleophilic carbene ligands coordinated to the Cp^*RuCl moiety. Imidazol-2-ylidenes **III** ligands behave as better donors than the best phosphine donor ligands with the exception of the sterically demanding 1,3-di(1-adamantyl)imidazol-2-ylidene.

The X-ray diffraction studies performed on many complexes also reveal the pure σ-donor character of the NHCs. Indeed, elongated single M-C bonds are generally observed. At the same time, the internal ring angle at the carbon atom is slightly larger in coordinated than in free carbenes, although not as large as that in the related imidazolium salts. Similarly, the C-N bond distances lie between those of the free carbenes and imidazolium salts. These data as a whole suggest that the three- and five-center π-delocalization in the imidazolidin-2-ylidenes **II** and imidazol-2-ylidenes **III**, respectively, be increased by coordination of the carbene center.

4.6. Applications in Heterogeneous Catalysis

Recently, transition metal complexes of NHCs have been the focus of considerable attention since they can act as catalyst or catalyst precursors to important transformations, such as Pd-catalyzed Heck type or Suzuki coupling [81], $CO–C_2H_4$ copolymerizations [82], Rh-catalyzed olefin metathesis [83], cyclopropanations [84], furan synthesis [85] and Rh-catalyzed hydrogenation [86], hydroformylation [87] and hydrosilylations [88]. In contrast to the widely used phosphine complexes, they have been shown to be remarkably stable towards heat, oxygen and moisture. The metal–carbon bonds in the carbene complexes are much stronger than the metal-phosphorus bond of typical phosphine complexes. This property eliminates the problems associated with weak ligand–metal interactions including deposition of free metal under catalytic conditions. Homogeneous catalysts have been of somewhat limited use, mainly because of the difficulty of separation from the reaction products [89]. The difficult recycling of catalysts from the reaction mixture represents a major drawback of homogeneous systems compared to heterogeneous catalysts. Many concepts have been developed to overcome this disadvantage of homogeneous catalysts. One of them is the immobilization of homogeneous catalysts on a solid support via an organic linker.

However, the "weak point" of this approach is usually the link between the organic part (polymeric support, linker, and ligand) and the metal i.e., generally the metal-ligand bond. If that bond is weak, the metal will leach out and the catalytic activity will decrease with the number of runs (Figure 4.1.). The high dissociation energy of the NHC ligand should suppress catalyst leaching much more efficiently than an attachment via more labile ligands such as phosphines.

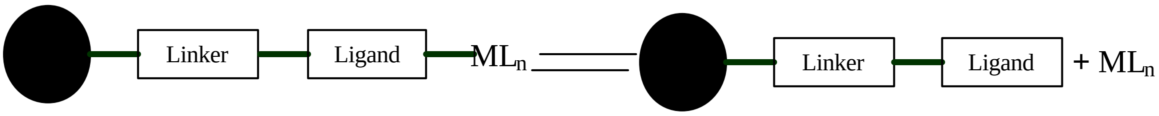
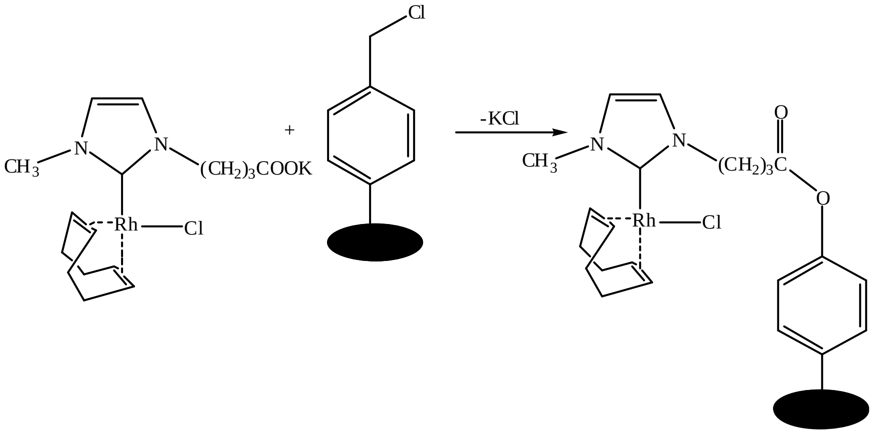


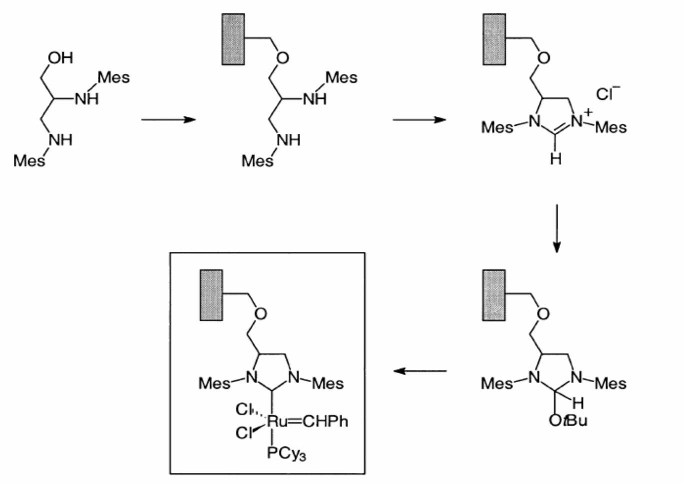
Figure 4.1. Ligand Metal interaction in polymeric supports

Catalytic applications have been reported for a few systems so far: a rhodium complex on a Merrifield resin for hydrosilylation, a Palladium compound for the Mizoroki-Heck coupling on a Wang resin, and a ruthenium complex for olefin metathesis again on a Merrifield polystyrene resin. The first reaction published to be catalyzed by an immobilized NHC catalyst was the hydrosilylation of acetophenone. The triazolium salt precursor was immobilized on a Merrifield resin via a dihydropayran linker and the rhodium(I) catalyst was then prepared in $\mathrm{THF/NEt_3}$ $[(\mu^4\text{-cod})\mathrm{RhCl}]_2$ a chiral triazolium salt gave up to 24 % ee and 80% yield for an asymmetric hydrosilylation reaction (Eq. 4.6.). Recycling was shown to be possible but leaching was not quantified. Immobilized imidazolin-2-yilidene and benzimidazolin-2-yilidene complexes have been applied as well for hydrosilylation. Application of C-C unsaturated NHCs as ligands in M-containing catalysts was disclosed in a series of patents (1994) [59].



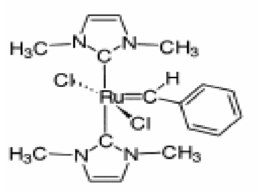
(4.6.)

An alternative strategy was pursued by Blechert et al. to obtain a polymer-supported olefin metathesis catalyst. In this case, the polymer-anchored ligand precursor was built up first and then treated with the catalyst metal compound.



Scheme 4.4. Immobilization of a NHC ruthenium catalyst according to Blechert et al.

Scheme 4.4. outlines this straightforward methodology. Excellent results were obtained in the ring-closing metathesis and the cross-metathesis, for example, yne-ene metathesis. Yao developed a soluble poly(ethylene glycol) (PEG) bound polymer catalyst of type **25** which is immobilized through the phenylalkylidene moiety to a PEG support. Four consecutive ring-closing metathesis steps were achieved by Barrett et al. with the help of recyclable catalysts of type **26**. Here, the classical carbene that initiates the metathesis is itself anchored to the vinylated polystyrene resin by a metathetical step as shown in Equation 4.7.



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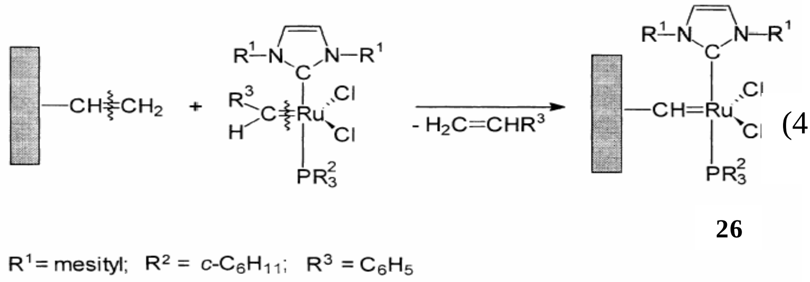
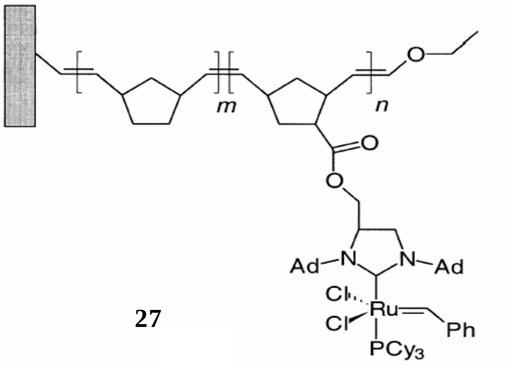


(4.7.)

26

This catalyst is more efficient in olefin metathesis, especially in RCM, than the congener derived from the bis(phosphane) ruthenium complex $[(PR^2{}_3)_2RuCl_2(=CHR^3)]$. The working principle of this new type of “boomerang” catalyst is based on the reversible release of the metallacarbene moiety into the solution phase from the resin, and recovery by the support after reaction. The ruthenium contamination of the products is thus minimized. Beyond that, catalyst recovery and recyclability are improved. An elegant approach to immobilized olefin-metathesis catalysts was reported by Buchmeister et al. They prepared monolithic materials exhibiting a particle diameter of 1.5±0.5 μm, by the metathetic copolymerization of appropriate olefins. The monolithic carrier is then functionalized by “living” NHC-ruthenium termini (from animidazolium precursor and $[Cl_2Ru(PCy_3)_2{=}CHC_6H_5]$) [90].

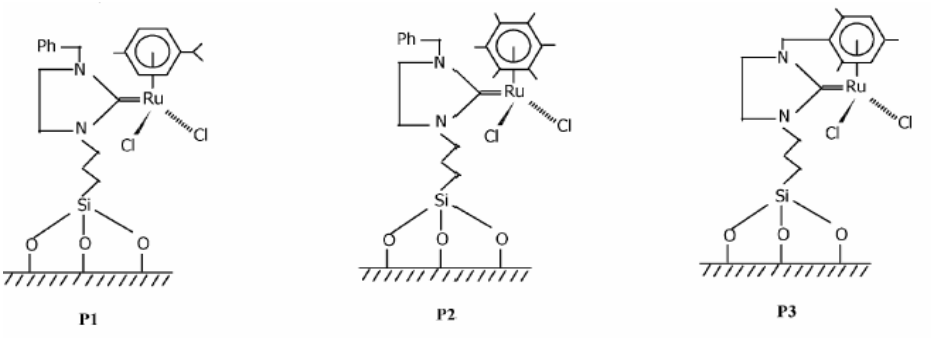


27

The catalyst **27** thus formed shows high activities in both the ring-closing and ring opening metathesis, with cis/trans ratios in the polymeric products that correspond exactly to what has been seen in homogeneous catalysis. The lack of any microporosity in the catalysts **27** minimizes diffusion effects to a large extent, thus giving high turnover frequencies often beyond those of homogeneous catalysts.

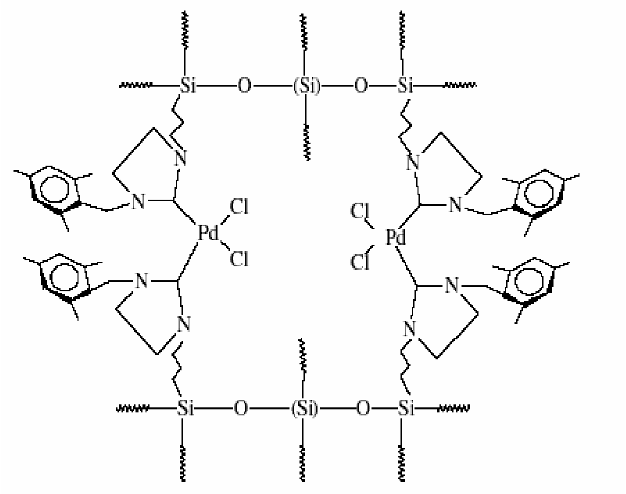
Çetinkaya et al. developed a convenient synthetic route to heterogenize catalytically active NHC complexes by hydrolyzing and condensation of $–Si(OEt)_3$ group attached through $–(CH_2)_3–$ spacer to N atom of the carbene ligand (Scheme 4.5.).

All immobilized complexes display catalytic activity in the furan formation. However, the activity of the mesityl chelated complex is comparable to that of most active binuclear Ru(II) complexes. P3 is the most active among the polymers and can be recycled at least five times [91].



Scheme 4.5. Immobilized Ru carbene complexes

Recently, a novel palladium complex of 1-(2,4,6-trimethylbenzyl)-3-(propyltriethoxysilane) imidazolidinium chloride was grafted onto a silica surface (Scheme 4.6.) to examine the catalytic properties of the Pd(II)–carbene complex in a Suzuki-type cross-coupling reaction of aryl chlorides with phenylboronic acid. p-Chloroanisole and p-chlorobenzaldehyde.reacted very cleanly with phenylboronic acid in high yield (>85%). In all the experiments, where a recycling of catalyst was attempted, a small decrease in activity was observed from one run to the next [92].

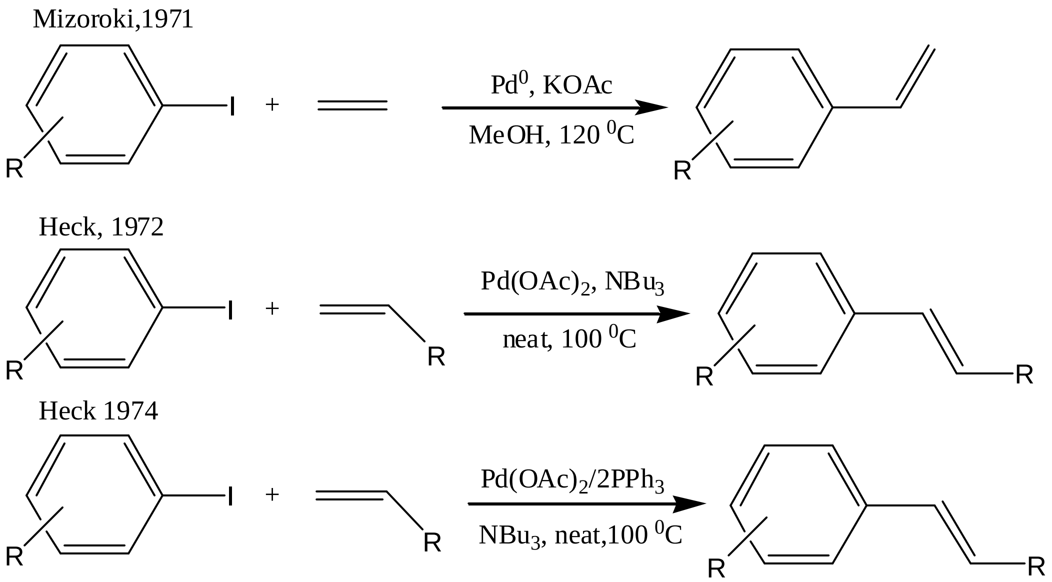


Scheme 4.6. Pd(II)NHC complex grafted on silica.

CHAPTER 5

THE MIZOROKI HECK REACTION

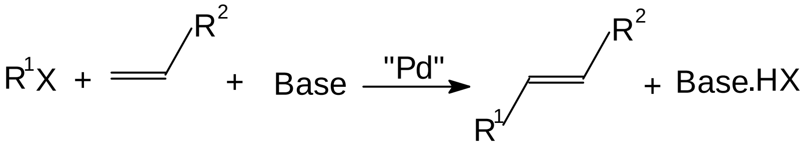
In the early 1970s, two independent research labs discovered that they could use palladium to assist in the coupling of olefins with aryl halides. Mizoroki and co-workers used palladium metal to promote the substitution of vinylic hydrogen of ethylene with iodobenzene to form styrene [4]. The reaction was conducted at 120 °C in methanol using potassium acetate as base (Scheme 5.1.).



Scheme 5.1. Preliminary studies of Mizoroki-Heck reaction

The scope of this reaction was increased when Heck and Nolley reported the use of palladium(II) acetate and tributylamine in a solvent free system that allowed the coupling of aryl iodides with styrene, propene, and methyl acrylate [35]. Both of these processes were improvements over previous olefin arylations, which used toxic lead, mercury, or tin derivatives of aryl halides. The generality of this reaction was increased when Heck used triphenylphosphine ligands in combination with palladium(II) acetate, to catalyze the reaction of olefins with aryl bromides [4 b].

The classical Heck reaction involves bond formation between two sp^2 carbon centers by an overall substitution of a C-H bond of an alkyene by R^1 from the R^1X substrate (where R^1=aryl or vinyl; X=I, Br; R^2 = electron withdrawing or releasing group) under basic conditions. The transformation has since become known as the Heck reaction [31] (Scheme 5.2.).



Scheme 5.2. The Mizoroki-Heck Reaction

In the last twenty-five years, this selective palladium catalyzed C-C bond transformation, has been extensively explored and used in several diverse areas such as the preparation of hydrocarbons, variously substituted olefins and dienes (e.g. stilbenes, cinnamates) many of which are useful as dyes, UV screens and other unsaturated compounds, pharmaceuticals, agrochemicals, and enantioselective synthesis of natural products, for example a fragment of balanol, aspidospermidine, cystisine, cphalotaxine, entgelsedine, vitamin D analogs. The reaction is also useful in polymerization chemistry, giving access to conjugated polymers applicable, e.g., as new materials for optoelectronic devices. [93-99]

Since its discovery, the methodology has been found to be highly versatile and applicable to a wide range of aryl species Ar-X, where X=Cl, Br, I, OTf, OTs and N_2^+. [100] As a great advantage this reaction is not limited to activated alkenes. A diverse range of olefins has also been found to undergo the Heck reaction. The substrate can be a simple olefin (with ethylene being the most reactive one), or it can contain a variety of functional groups (e.g. ester, ether, carboxyl, phenolic, or cyano groups) [101] which also tolerates the presence of water. In many instances, the addition of small amounts of water proved to be beneficial, which leads to improved yields or reaction rates [95]. One out of several bases, both organic and inorganic (e.g. tertiary amines, alkali acetates, carbonates, phosphates), can be used to reduce the Pd(II) precatalyst to Pd(0) and promote reductive elimination of the PdH(X) intermediate by shifting the equilibrium towards Pd(0). This reaction, which brings about the formation of new C–C bonds (Scheme 5.2.), is generally catalyzed in solution by palladium species generated from either Pd(0) compounds, such as [$Pd(PPh_3)_4$] and [$Pd_2(dba)_3$], or Pd(II) salts, such as the acetate and the chloride.[94] The reaction can be catalyzed by palladium complexes with or without phosphine ligands (phosphine assisted vs. phosphine-free catalysis). [93]

One of the major drawbacks of the early homogeneous systems was the precipitation of palladium black, which limited the lifetime of the active species. It was soon discovered that the addition of phosphines greatly improved the stability of the catalytic system, although a large amount of the ligand inhibited the reaction. [93]

A primary role of phosphine ligands is to support palladium in its zero oxidation state in the form of stable PdL_4 or PdL_3 species. The phosphine-assisted method may be regarded as conservative, as it relies not on *a priori* unknown reactivity of palladium catalyst in a given catalytic cycle, but rather on ligands which can sustain the catalytically active species even outside of the catalytic cycle. The phosphine-assisted approach is the classical and well-established method which gives excellent results in a majority of cases.

The reasons of seeking other methods are both economical and chemical. Phosphine ligands are expensive, toxic, and unrecoverable. In large-scale applications on industrial and semi-industrial scale, the phosphines might be a more serious economical burden than even palladium itself, which can be recovered at any stage of production or from wastes. The chemical reason is lower reactivity of fully ligated complexes of palladium, the main result of which is the need for higher loads of catalyst to achieve appropriate rates of reaction and therefore further aggravation of procedure cost. [93]

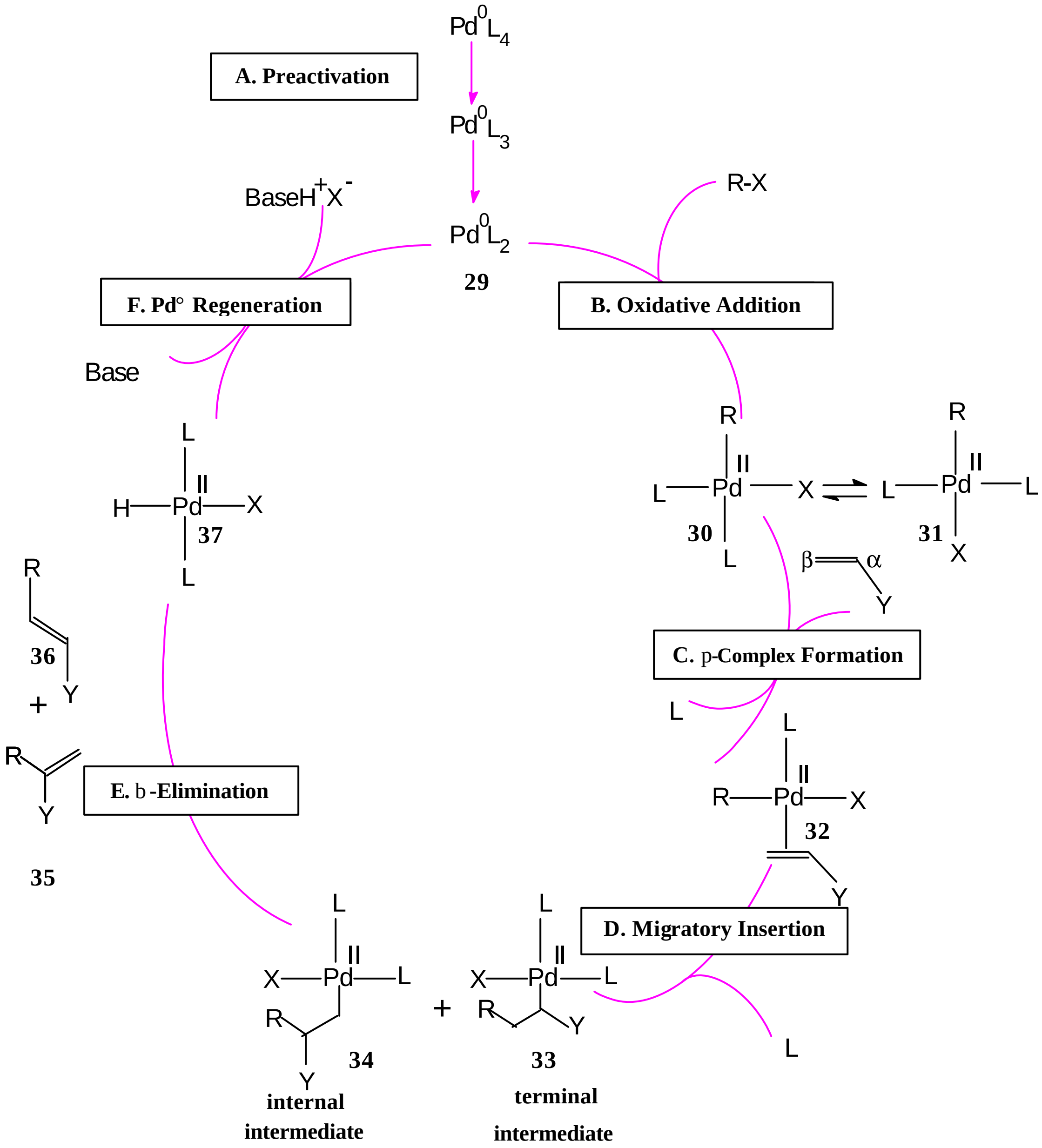
Later investigation demonstrated that heterocyclic carbenes and polymer-supported palladium-carbene complexes as well as carbene-palladacycle [102] systems are suitable for this reaction as well. Several palladacyclic compounds, for example, an oxime palladacycle, a sulfur-containing palladacycle, pyrazole and benzothiazole palladacycles, also showed improved lifetimes and allowed, either on their own or with the aid of promoters, to sustain the reaction for millions of cycles [94]. The formation of palladium nanoparticles was suggested as the active catalyst using cyclopalladated imine catalysts, and was shown to be involved in phosphine-free Heck reactions [95]. Despite displaying many of the benefits usually associated with Pd-mediated reactions (for example ease of scale up and tolerance of water and: or other functional groups), interest in the reaction has been sporadic, largely due to problems of regiocontrol in the case of unsymmetrical alkene substrates and to an incomplete understanding of the reaction mechanism. [101]

5.1 The Catalytic Cycle

Scheme 5.3. gives a simplified scheme introducing the major steps of the Heck catalytic cycle [93]. The standard model for the catalytic cycle, as described in Scheme 5.3, has recently been augmented with alternative mechanisms (e.g. Jutand's new version of the catalytic cycle) and although there is many cases are valid only under special circumstances, there is today a growing awareness that the standard model for the Heck reaction mechanism is not general.

If the catalytic cycle is investigated in detail it is clear that one source of the confusion over the mechanism is the poor understanding of the individual steps. To gain knowledge thereof is a great challenge as there is an inherent difficulty in identifying the catalytically active complexes in a given reaction mechanism. The most stable structures, i.e. those that can be isolated and characterized are in many cases not the conformations responsible for the success of the reaction [103]. The general features of the Pd(0)/Pd(II) catalytic mechanism are presented below; and is currently the most widely accepted, although there has been debate about possible involvement of Pd(IV) species [104-41].

The process starts with a preactivation step **A** in which the palladium (II) salt or a palladium(0) complex is transformed to the commonly assumed, catalytically active 14-electron palladium(0) species **29** (Scheme 5.3.). This underligated and labile palladium(0) complex undergoes an oxidative addition **B** with R-X to form the palladium(II) species, **30** or **31**. Thereafter, the palladium(II) complex undergoes π-coordination **C** to the olefin followed by a migratory insertion **D** in which Pd forms a σ-bond with one of the carbon atoms and the R-group performs a syn migration to the vicinal carbon generating **33** or **34**. A subsequent β-elimination **E** results in the coupling product and furnishes a hydrido palladium(II) complex **37**. Base induced elimination of HX from the palladium hydride regenerates the palladium(0), thereby closing the catalytic circle **F**. These five mechanistic steps are fundamental processes in the palladium-catalyzed Heck reaction. Below, each of them is described more thoroughly to present the key issues that control the reactivity and selectivity of the palladium species, in the overall process.



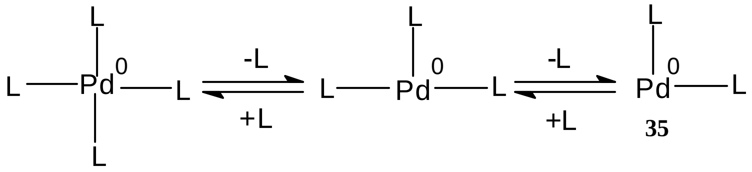
Scheme 5.3. The Mechanism of the Classical Heck Cycle

A. Preactivation: The catalytically active palladium(0) 14-electron complex **29** is unstable. Hence it is the most conveniently prepared in situ from more stable and easily accessible palladium(II) salts, e.g. Pd(OAc)$_2$, PdCl$_2$ or their preformed palladium(II) ligand-mediated complexes e.g. PdCl$_2$(PPh$_3$)$_2$, or a less stable palladium(0) complex, e.g. Pd$_2$dba$_3$, Pd(PPh$_3$)$_4$. There are at least four possible reducing agents in the typical

Heck coupling: the phosphine ligand [105-107], the base [108], the olefin [109-110], or, in some cases, the solvent [111].

There has been some uncertainty over which reducing agent predominates over the other, but convincing evidence has emerged that phosphine ligands, when they are present, are the most active of the four and the agent most likely to reduce Pd(II) [112]. Generally, the Pd(II) salts are reduced to the active complex Pd(0)L_2 primarily by the versatile and widely used phosphine ligands. The reduction is assisted by hard nucleophiles, of which the most common are hydroxide and alkoxide ions, water, and water and acetate ion, though in special cases even fluoride in the presence of water can play the role. It is interesting to note that neither Et_3N nor olefin have any detectable influence on the reduction rate in the presence of phosphine.

In a phosphine free environment, the reduction is preferentially affected by amines, but it is well known that in the absence of phosphine olefins are oxidized by Pd(II) via the first turn of a Waker-type catalytic cycle. Indirect evidence tells that Pd(II) → Pd(0) reduction can also be affected by quaternary ammonium and phosphonium salts, possibly initiated by oxidative addition to C-P or C-N bonds. Thus, Hermann reported that the addition of TBABr eliminated the induction period in the reaction catalyzed by Pd carbene complex. To enter the catalytic cycle through the oxidative addition, palladium(0) species must have a proper coordination shell. No more than two strongly bound ligands are allowed. This requirement places a serious restriction on the choice of ligands and their concentration in the reaction mixture. The active palladium(0) 14-electron complex is assumed to be in equilibrium with the 18-electron palladium(0) species coordinating four ligands (Eq. 5.1.) [93]

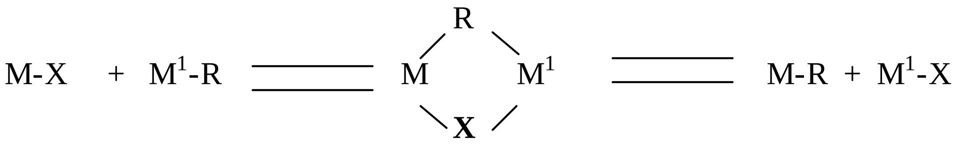


(5.1.)

B. Oxidative Addition: The first step in the Heck reaction concerns the generation of the starting aryl palladium(II) complex **30** from a suitable precursor. There are three distinct ways to generate the required aryl palladium(II) intermediate: transmetallation, electrophilic palladation or oxidative addition procedures. Transmetallation an electrophilic palladation can only occur with Pd(II) species, while oxidative addition takes place with Pd(0).

Transmetallation

Transmetallation of an organic moiety is a fundamental process in organometallic chemistry (Eq. 5.2.), yet little is known about the detailed mechanism. In transmetallation reaction one metal replaces the other metal, which is in the complex. M is more electropositive than M^1 metal. So one metal replaces the other metal, which is less electropositive, in this reaction [39].



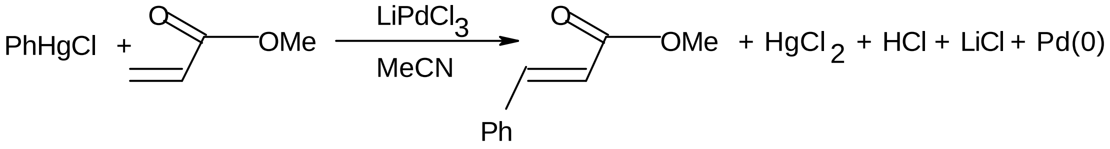
$$\text{M-X} + \text{M}^1\text{-R} \rightleftharpoons \text{M}\overset{\text{R}}{\underset{\text{X}}{\diamond}}\text{M}^1 \rightleftharpoons \text{M-R} + \text{M}^1\text{-X} \quad (5.2.)$$

The physical driving force is the generation of less polar bonds. The transfer of the organic ligand to a more electronegative metal (e.g. from an alkaline earth metal to a transition metal) is always thermodynamically favorable (Scheme 5.4.). The process proceeds smoothly, typically at room temperature.

$$\text{ArMX} + \text{PdX}_2 \longrightarrow \text{'ArPdX'} + \text{MX}_2$$

Scheme 5.4. Transmetallation process involving Pd(II) and a main group metal.

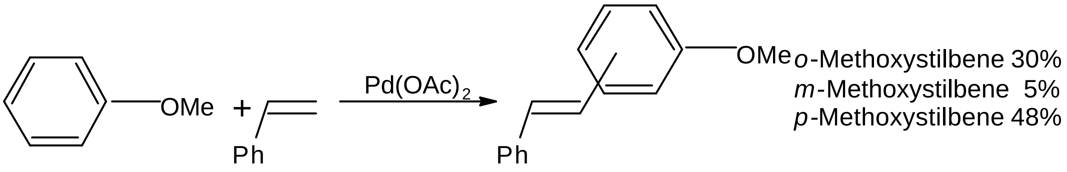
Unfortunately, the transmetallation procedure consumes stoichiometric amounts of palladium, since Pd(0) is produced at the end of the Heck cycle. Therefore, a Wacker type reoxidation of palladium with cupric halides and oxygen was successfully developed to yield a catalytic process [113]. Nevertheless, the transmetallating agent is necessarily used in stoichiometric amounts in conjugation with catalytic amounts of palladium and, therefore, a large amount of metal salt waste is produced. Organomercurials were most commonly used for this purpose in sixties and early seventies (Scheme 5.5.) [114-117] These days, several more suitable and less toxic aryl-metalloid precursors such as organo-boranes [118], silanes [119], stannanes [120], bismuth [121-122], antimony [123] are used, which has resulted in a revitalization of the procedure, especially because of the development of oxygen gas-based oxidation protocols. These procedures are now commonly named oxidative Heck couplings.



Scheme 5.5. Early Heck Coupling Utilizing the Transmetallation Approach and Stoichiometric Amounts of Palladium(II).

Electrophilic Palladation

In 1967, concurrently with Heck's first organomercury protocol for vinylic substitutions, Fujiwara and Moritani discovered a Pd(II)-mediated method of generating the aryl metal intermediate, starting from unfunctionalized arenas (Scheme 5.6.) [124, 125]. If the arene is functionalized, it is difficult to obtain selective ortho-, meta- or para-palladation, and regioisomeric mixtures result.



Scheme 5.6. Pd(II)-mediated Heck reaction

This procedure seems attractive in terms of atom economy, since no stoichiometric metal or organic salt waste is produced, provided an effective palladium(0) reoxidation system is used.

Oxidative Addition

The term “oxidative” may sound strange to organic chemists who are not familiar with organometallic chemistry. The use of this term in organometallic chemistry has a meaning different from the “oxidation” used in organometallic chemistry, such as the oxidation of secondary alcohols to ketones. One of the most fundamental processes in transition metal chemistry is the oxidative addition, which plays an important role in a number of catalytic reactions. An oxidative addition reaction involves the addition of a substrate molecule to a transition metal complex and during the process; the metal center is oxidized by two units. Thus oxidative addition means the reaction of a molecule X-Y with a low valent coordinatively unsaturated metal complex $M_{(n)}L_{(m)}$ to undergo bond cleavage and form two new bonds. As two previously nonbonding electrons of the metal are involved in the new bonding, the metal increases its formal oxidation state by two units, namely, $M_{(n)}$ is oxidized to $M_{(n+2)}$, and increases the coordination number of the metal centre by two (Eq. 5.3) . In oxidative addition, it is defined that the electrons in the two new bonds belong to the two ligands, and not to the metal [39].

$$M(n) + X\text{-}Y \xrightarrow[\text{Addition}]{\text{Oxidative}} X\text{-}M(n+2)\text{-}Y \tag{5.3}$$

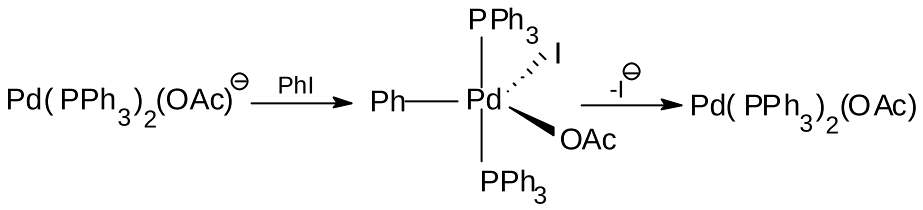
The oxidative addition of low-valent transition metal complexes to carbon halogen bonds is among one of the basic processes of organometallic chemistry [93]. Oxidative addition is a crucial step in the Heck cycle. The tetrahedral Pd(0) complex **35** (Scheme 5.3) is inserted into the R-X bond to generate a square planer cis-$RPd(II)XL_2$ species **30**, which consequently isomerizes to the thermodynamically more stable trans configuration **31** with monodentate ligands [126-127]. X can be a halogen or a pseudohalide. Examples of pseudohalides that have been used in Heck reactions include triflates [128], nonaflates [129], aryldiazonium salts [93] and iodonium salts [93].

The oxidative addition proceeds as a concerted process in which C-X bond rupture is more or less perfectly synchronized with the formation of M-C and M-X bonds. Unlike stepwise addition-elimination mechanisms of nucleophilic aromatic or vinylic substitution in which the addition to the unsaturated system is the primary and often rate-limiting stage while the rupture of C-X bond is fast, the oxidative addition is much less sensitive to the substituents in the unsaturated system but much more sensitive to the nature of nucleophile and the strength of C-X and M-X bonds.

The order of reactivity ArN_2X > I >> OTf >Br >> Cl >>> F, common to oxidative addition, has no precedence in nucleophilic substitution at sp^2-C, in which a roughly opposite order of leaving-group effect is normal [93]. Reactions with aryldiazonium salts are not very common but aryl- and vinyl iodides have been studied extensively. Iodides are usually reactive at room temperature even without the addition of phosphine ligands. Aryl- or vinyl triflates and bromides typically need phosphine ligands, if the reactions are run not run under phase transfer conditions, but are usually quite reactive. It is interesting to note that selectivity between aryl triflates and –bromides has been attained under certain reaction conditions [130]. Aryl chlorides react only with difficulty and at elevated temperatures in standard Heck Couplings and considerable effort is at present made to explore this reaction. One incentive for this exertion is the relative cheapness and availability of aryl chlorides, when compared to aryl triflates and the other aryl halogens, which make the chloro-compounds attractive for industrial scale synthesis [100]. The development of water-soluble catalysts [93] in another research area that is highly interesting for industrial applications.

The choice of the organic moiety that is to be coupled (-R) is limited as it should not have a *cis*-hydrogen on a sp^3-hybridised carbon in the position *b* to the palladium. The desired reaction may be ineffective if this prerequisite is not fulfilled since Pd-H elimination of the *cis*-hydrogen occurs more readily than addition to olefins. Suitable R groups can be e.g. aryl [131], alkenyl [131], benzyl [131], allyl [39], alkynyl [39], sulfonyl [39] or alkoxycarbonyl-methy groups [39].

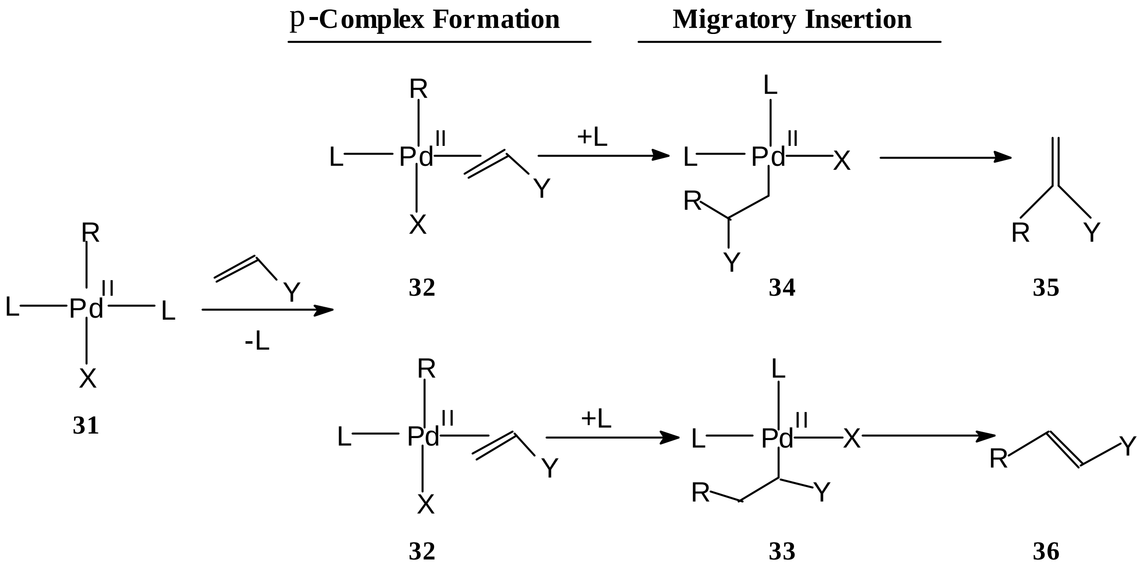
In phosphine-assisted catalysis, C-P bonds of phosphine ligand can compete for Pd(0) with less reactive substrates, leading both to the scrambling of substituents in product and to the depletion and deactivation of catalyst. In most cases except for the complexes with chelating ligands, the isolable product of the oxidative addition possesses *trans*-geometry, though it is obvious that *cis*-complex must be formed first. Moreover, it is *cis*-complex which enters the next stage of the catalytic cycle. Recent studies explicitly revealed both the formation of *cis*-adduct and *cis-trans* isomerization. The latter process can proceed by several independent routes, both through dissociation isomerization-addition and through association pseudo rotation-dissociation.



Scheme 5.7. Oxidative Addition via Pentacoorinated Palladium Species

The availability of the latter route involving five-coordinate complexes (Scheme 5.7.) is of prime importance for complexes with strongly bonded undissociating ligands, which otherwise would be unable to participate in the Heck reaction [93].

C. & D. π-Complex Formation and σ-Complex Formation (Migratory Insertion): Migratory insertion is the product-forming step of the Heck cycle, in which a new C-C bond is formed. It is this step which is most likely responsible for regio- and stereo- discrimination as well as substrate selectivity. Therefore, the understanding of how this step is realized is of prime importance [93]. It is assumed that one ligand (neutral or anionic) coordinating to the palladium dissociates to generate a free coordination site on the unsaturated Pd(II) species. Thus, a syn migratory insertion follows π-coordination of



Scheme 5.8. Internal and Terminal Insertion in the Heck Reaction.

an alkene to palladium to form a new carbon-carbon bond in a presumably concerted fashion (Scheme 5.8.).

The outcome of the two modes of insertion according to the claimed view with neutral intermediates, i.e. the internal **34** (formed by σ-attack) or terminal **33** (formed by β-attack) σ-intermediates, is governed by a delicate balance between electronic (Figure 5.1.) and steric parameters which in tern are affected by the Pd(II) complex, the olefin and the properties of solvent [98], [132].

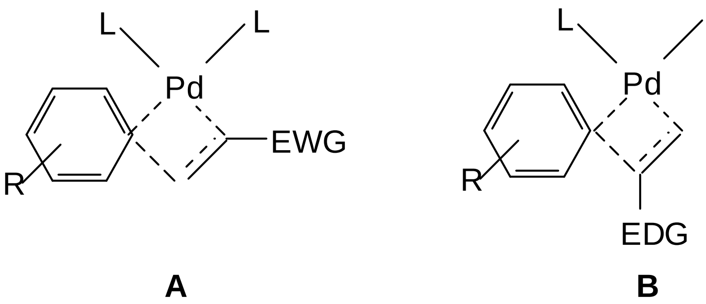
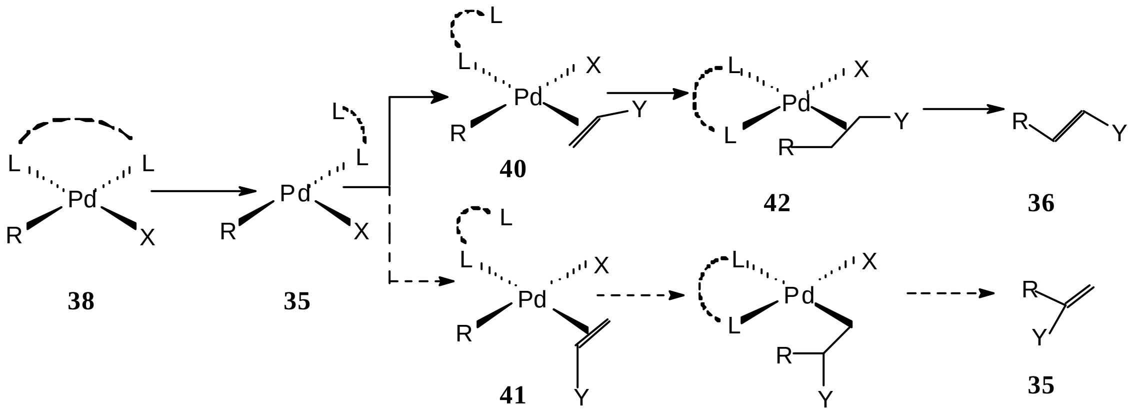


Figure 5.1. Electronic effect directing the olefin in the migratory insertion. **A**) Electron withdrawing group favoring the terminal insertion **B**) Electron donating group promoting the internal insertion [98].

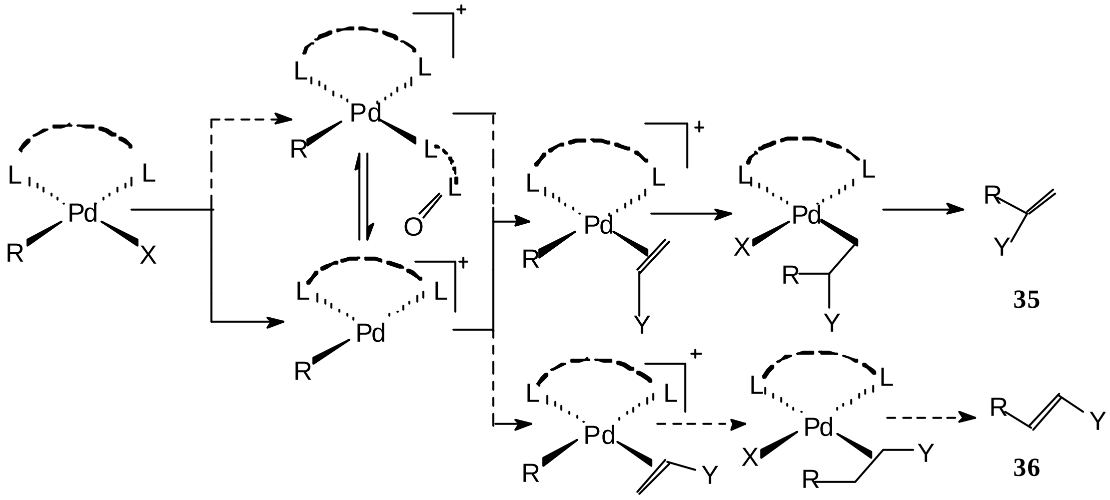
The electronic and steric effects influencing the regiocontrol have recently been investigated using propene and chelating N-N bidentate ligands with density functional methods [133]. To account for the differences in reactivity and enantioselectivity observed in the Heck reactions of unsaturated weakly coordinating pseudohalides (typically triflates) and tightly coordinating halides (typically bromides) two distinct mechanistic pathways, termed “cationic” and “neutral”, have been proposed. The names of these pathways describe the formal charge on the first-formed palladium(II)-alkene complex of each pathway [134]. In a neutral pathway, generally referred as the traditional route, a neutral ligand dissociates from the Pd complex, referentially leads to terminal Heck product with a non-functionalized olefin. In a cationic route proposed independently by Cabri et al.[135] and Hayasi et al. [136] in 1991, where an anionic ligand dissociates from the Pd complex to form the key cationic intermediate which primarily generates the internal product with non-functionalized olefin [98].

The neutral pathway: One of the weakly coordinated neutral ligands (L) (e.g. PAr_3, the solvent or the base) dissociates from the center **38** to create a free coordination site on the Pd(II) species **39**. The process is promoted by the more strongly coordinated halide anion, which has a relatively high trans effect (I>Br>Cl) that weakens the Pd-L bond. For simple non-functionalized olefins, the regioselectivity of the coordination of olefin to the unsaturated neutral Pd complexes **40** and **41** is mainly controlled by steric parameters, and the larger organic group (R) is inserted preferentially into the less substituted vinylic carbon (complex **42**), forming the terminal product **36** (β-attack). Electron-poor olefins enhance the β-attack to form the linear product **36**, while electron-rich olefins are reported to give mixtures of isomers, as a result of an electronic effect (Scheme 5.9) [98].



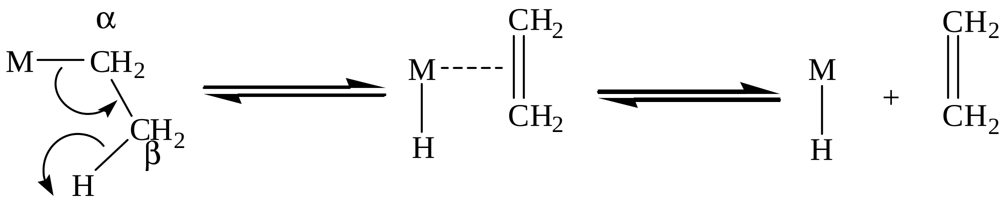
Scheme 5.9. The coordination-insertion process following the neutral pathway.

The cationic pathway: This pathway is generally invoked to describe asymmetric Heck reactions of unsaturated triflates, or halides in the presence of Ag(I) or Tl(I) additives; it is illustrated in Scheme 5.10. for the palladium-diphosphine-catalyzed intramolecular Heck cyclization of an unsaturated aromatic substrate. Oxidative addition of the Pd(0) catalyst is followed by either a triflate dissociation or a halide abstraction by Ag(I) or Tl(I) salts to vacate a coordination site on the Pd(II) complex, thus permitting coordination of the pendant alkene. In the cationic manifold, both phosphorus atoms of the chiral diphosphine ligand remain coordinated to the palladium center throughout the alkene coordination and migratory insertion steps. Either of these steps could be the enantiodifferentiating step of the asymmetric carbon-carbon bond formation. Partial dissociation of the chiral ligand would diminish rigidity of the ligand and could lead to erosion of enantioselectivity. Thus, the cationic mechanism is consistent with the enhanced enantioselectivity typically achieved in the asymmetric Heck reactions of unsaturated halides by the addition of Ag(I) or Tl(I) salts [134].



Scheme 5.10. The coordination-insertion process following the cationic pathway.

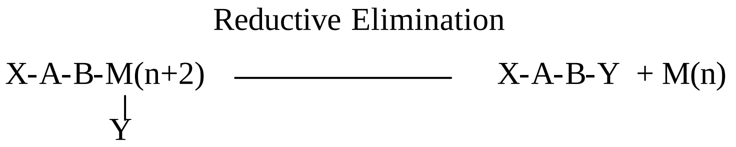
E. b **-Elimination:** Another common reaction encountered in organometallic chemistry is β-hydride elimination. β-hydride elimination is the transfer of a hydride from the β-position of the ligand to metal center. The mechanism involves a four-centered transition state in which the hydride transferred to the metal (Scheme 5.11.)



Scheme 5.11. Mechanism of β-hydride elimination

The β-hydride elimination is the step yielding the final product of the Heck-reaction. For this process to occur, through stereoselective elimination, the alkyl palladium species **43** has to undergo an internal rotation to align the β-hydride syn to the palladium centre **44** (Scheme 5.12.). The elimination will then result in a reconstituted alkene **35** and **36** and a Palladium hydride species **37**. The β-hydride elimination step is reversible, favoring the thermodynamically more stable isomer [93]. Furthermore, if the dissociation of the olefin to the Pd (II)-hydride complex **45** is slow, re-addition to the double bond might occur, resulting in the formation of a double-bond isomer [137,138].

F. Pd(0) Regeneration: Pd(0) regeneration process can also be called as the reductive elimination process since Pd(II) species is reduced to Pd(0). Similar to "oxidative" the term "reductive" used in organometallic chemistry has a meaning different from reduction in organic chemistry. Reductive elimination is a unimolecular decomposition pathway and the reverse of oxidative addition. Reductive elimination involves the loss of two ligands from the metal centre, which is shown in Eq. 5.4.

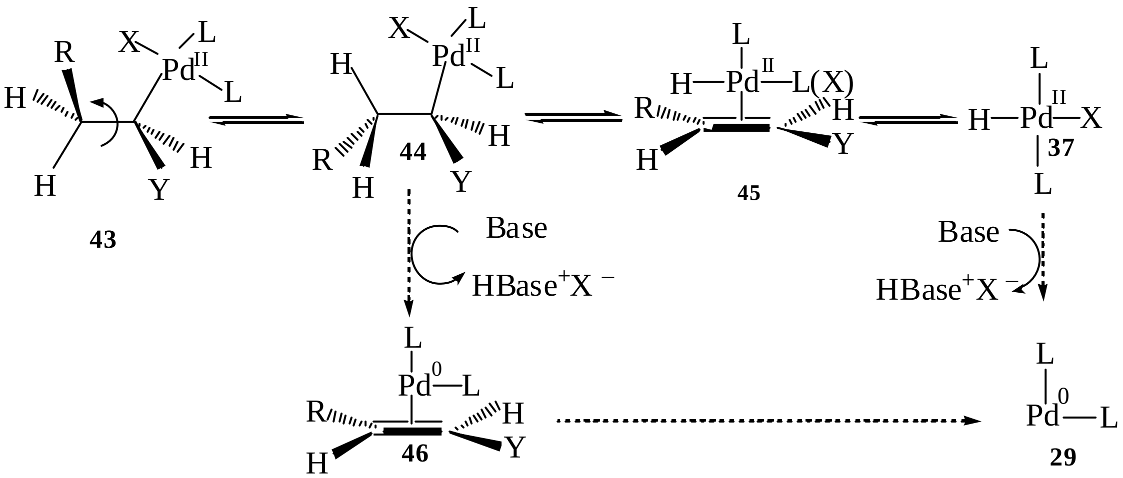


$$X\text{-}A\text{-}B\text{-}\underset{\displaystyle Y}{\underset{|}{M}}(n+2) \xrightarrow{\text{Reductive Elimination}} X\text{-}A\text{-}B\text{-}Y + M(n)$$

(5.4.)

By reductive elimination, both the coordination number and the formal oxidation state of the metal M(n+2) are reduced by two units to generate M(n) [39].

In the Pd(0) regeneration process, the presence of base will scavenge the readdition by removing HX from the palladium(II)-complex **37**, producing the reduced Pd(0)L$_2$-species **29**. The re-formed active Pd(0) catalyst can then activate another R-X and initiate the next catalytic cycle.



Scheme 5.12. The base promoted vs. the classical elimination mechanism

There is today no precise knowledge of how Pd(II) is reduced to Pd(0). Recently density calculations by Brown have suggested an alternative mechanism that supports a more energetically favored base-promoted reduction of Pd(II) to Pd(0) **46** over a mechanism where β-elimination produces the $HPdXL_2$ complex **37** without the assistance of the base (Scheme 5.12) [139].

5. 2. Limitations of the Heck Reaction

5.2.1 C-X Bond Strength

The oxidative addition of Ar-X to palladium(0) species, has been the most well studied step of the Heck reaction as it is a common initiation stage for many palladium-catalyzed reactions involving aryl halide substrates [100]. The strength of the carbon-halogen bond depends on the electronegativity of the halogen. Since halogen atoms are more electronegative than the carbon, the carbon-halogen bond of aryl halides is polarized (Figure 5.2.). As a result of this the carbon atom bears a partial positive charge and the halogen atom bears a partial negative charge.

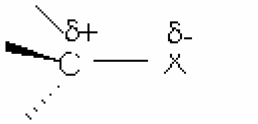


Figure 5.2. Representation of a polarized carbon-halogen bond

The size of the halogen atom increases as we go down the periodic table. Fluorine atom is the smallest and iodine atom is the largest. The carbon-halogen bond length also increases as we go down the periodic table [140]. So, in Heck reactions, when palladium is used as catalyst, oxidative addition of palladium into a carbon–halogen bond occurs mainly on the strength of the carbon-halogen bond. The order of bond strengths for aryl halides is ArCl > Ar-Br > Ar-I, which corresponds to the experimentally found bond dissociation energies of 96, 81 and 65 kcal/mol, respectively. F is unreactive with any of the known catalysts. This trend is also reflected in the ability of aryl halides to undergo oxidative addition with palladium(0) complexes: ArCl <Ar-Br << Ar-I. Electron-donating substituents on the aryl group also make the oxidative addition more difficult and, as a result, electron-poor aryl halides are often referred to as “activated”, and electron-rich aryl groups as “deactivated”.

With these factors in mind, it is perhaps, not surprising that the Heck reaction has evolved such that the conditions developed have mainly focused on using aryl iodides as substrates. There are, however, a number of advantages in developing procedures to efficiently utilize aryl bromides and the synthetically more challenging aryl chlorides: (a) aryl iodides are often more expensive than either aryl bromides or chlorides and are less desirable in terms of atom economy. The reactive iodides need low activation energy and no added ligands are required to undergo oxidative addition; however, they are labile, les common and expensive as starting materials in comparison to bromides and chlorides. They are also more suitable for the traditional neutral route because of the large trans effect of the iodine atom; (b) aryl chlorides are more widely available; and (c) aryl chlorides are inherently more robust and can tolerate a wider range of reaction protocols. One of the biggest challenges for Heck chemistry is the development of an efficient system that can achieve high turnovers for deactivated aryl halides such as 4-chloroanisole [100].

5.2.2 P-C Bond Cleavage and Catalyst Decomposition

Aryl bromides and chlorides are often unreactive towards oxidative addition under mild conditions, and reaction will only occur, if at all, at much higher temperatures as compared with the iodides. Triarylphospine ligands have traditionally been used in the Heck reaction to promote the lifetime of the catalyst, at temperatures 120°C, however, often lead to competitive degradation of the palladium catalyst and the formation of the unwanted by-products through thermally-activated P-C bond cleavage of a coordinated phosphine ligand.

P-C bond cleavage was first observed to occur at 60°C in $(Ph_3P)_2Pd(Ph)(I)$ and was subsequently observed for both activated and deactivated bromides and chlorides at higher temperatures. P-C bond cleavage was also seen as a contributing factor to the decomposition of the catalytic species by creating unstable subcoordinated palladium complexes that eventually precipitated out of the solution as palladium black [93].

5.3. Experimental Conditions

The development of efficient, enantioselective Heck reaction conditions for a particular substrate generally requires optimization of a variety of reaction parameters [136]. Evidently, it is difficult to analyze the precise importance of every ingredient of a reaction and the Heck reaction has proven to be a tough nut to crack, as has been noted not without humor in a recent review by Beletskaya [93], where it is amply demonstrated that even small variations in the reaction conditions can have considerable effects on the overall performance of the system. Heck reactions, which typically employ phosphine ligands, must be conducted under an inert atmosphere (nitrogen or argon) using degassed solvents, because phosphines are readily oxidized to phosphine oxides in the presence of oxygen and palladium. Standard laboratory glassware can be used; however, as a convenient alternative, sealable Schlenk tubes are frequently used for heating reaction mixtures to elevated temperatures for prolonged reaction times with rigorous exclusion of oxygen [134]. Some of the components of the Heck reaction are reviewed below.

5.3.1 Precatalysts

There is at present an abundance of different complexes available. It is difficult to predict how a certain catalytic system will work under given reaction conditions and it is not uncommon to test several different catalyst/ligand pairs when a new reaction is to be optimized. However, mechanistic investigations have suggested a role for the $^{-}$OAc anion in the catalytic cycle [105, 107] and the relatively moisture insensitive $Pd(OAc)_2$ catalyst is perhaps the first choice today.

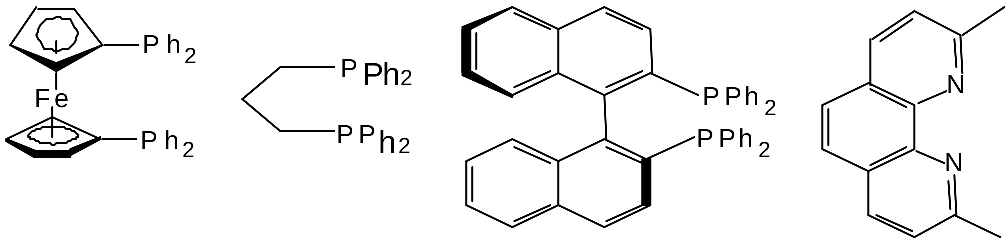
Moreover today a variety of Pd(II) and Pd(0) complexes serve as effective precatalysts, or precursors to the active Pd-(0) catalyst. Except for $Pd(OAc)_2$, the most commonly used precatalysts in Heck chemistry are, $Pd_2(dba)_3$, and $Pd_2(dba)_3.CHCl_3$, all of which are commercially available and air stable. Recent studies by Amatore and Jutand have demonstrated that 2.0 equiv of diphosphine ligand is required per equivalent of Pd when $Pd(OAc)_2$ is used as a precatalyst, because 1 equiv of ligand is consumed in the reduction of the Pd(II) precatalyst to the Pd(0) catalyst species.

Although most mechanisms written for the Heck reaction indicate the active Pd(0) diphosphine catalyst in a generic representation and omit altogether the ligands derived from the palladium precatalyst, these “spectator” ligands can play a significant role in the Heck reaction. Dibenzylidene acetone (dba) can also play a role. For example, Amatore and Jutand have shown that mixtures of Pd(dba)$_2$ and BINAP (2,2’-bis(diphenylphosphino)-1,1’-binaphthyl) afford Pd(dba)(BINAP), which is sluggish in oxidative addition reactions with PhI. Likewise, Pregosin and co-workers have shown that Pd(dba)(MeO-BIPHEP) undergoes oxidative addition to aryl triflates and halides more sluggishly than the Pd(0) catalyst generated by reduction of PdCl$_2$(MeOBIPHEP) with NaBH$_4$[93].

5.3.2. Ligands

The choice of the ligand can have a considerable effect on the outcome and the selectivity of the Heck coupling [93]. Ligands usually influence all steps in the Heck cycle and the optimal ligand for the reactivity of the oxidative addition step can have the reverse effect in the insertion step. To form the desired linear product, monodentate phosphine such as PPh$_3$ or P(o-tol)$_3$ are generally used in the active catalytic complex [93, 98, 141]. Phosphine ligands are regularly used as they stabilize reactive intermediates and influence the reactivity and the selectivity through electronic and steric effects [141, 142]. Generally, the presence of phosphine ligands can reduce the rate of readdition, and increase the rate of dissociation, of the hydridopalladium to the double bond in a Pd-olefin π-complex intermediate [131]. This would tend to decrease double-bond migration and the formation of unwanted β-elimination products.

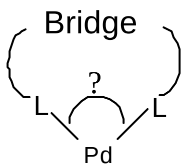
One of the most commonly used bidentate ligands is 1,1’-bis(diphenylphosphino)-ferrocene (dppf) **47** [143]. Dppf is a sandwich-complex and is known to be flexible in three-dimensional space, [144] probably more so than other most ordinarily used bidentate ligands, such as dppp (1,3-bis(diphenylphosphino)propane **48** and BINAP **49**. The chiral binap **49,** developed by the 2001 Nobel-prize winner Noyori, has also been used in palladium(0)-mediated reactions, especially in asymmetric intramolecular Heck reactions [145, 146]. Investigations with bidentate (N-N) ligands, especially the 2,9-dimethyphenantroline **50** (Figure 5.3.), showed similar results to those using dppp but slightly higher selectivity was achieved and milder reaction conditions were required. This observation might be due to the flat nature and the coordination ability of the phenanthroline derivatives. Notably, the reaction rate decreased with an electron-withdrawing group on the aryl triflates and the a-selectivity dropped. Applying the same conditions with dppp did not affect the regioselectivity. This phenomenon may be explained by the ability of the nitrogens to increase the charge density on the metal [98, 147].



47 **48** **49** **50**

Figure 5.3. Common bidentate ligands: dppf **47,** dppp **48**, (S)-binap **49** and 2,9-dimethyl-1,10-phenanthroline **50**.

Several studies support the idea that ligands with a large bite angle [141, 148] (Scheme 5.13.) can increase the rate of palladium elimination, as the large bite angle induces as stress in the structure of the intermediate complex that will be released by the elimination [112, 141, 149].



Scheme 5.13. Representation of the bite angle ? of a bidentate ligand.

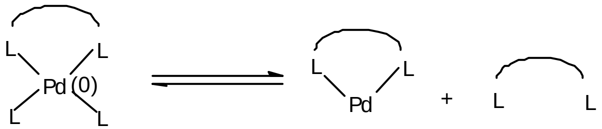
Analogues of dppf that have an even larger bite angle e.g. (diisopropylphosphino)-ferrocenes (disoppf), are known to give very high regioselectivities. Too large bite angles, on the other hand, are known to be deleterious for the Heck reaction [141]. Bite angles of some of the ligands are represented in Table 5.1.

If dppf is added in more than two equivalents to the amounts of palladium can the complex **51** be formed (Scheme 5.14.). It was previously assumed that a dissociation of one of the pairs of the bidentate ligands was necessary in order for a Heck reaction to

Table 5.1. Bite angles of some of the ligands

LIGAND	BITE ANGLE
Dppp	91.0°
BINAP	92.7°
Dppf	99.1°
Disoppf	103.4°

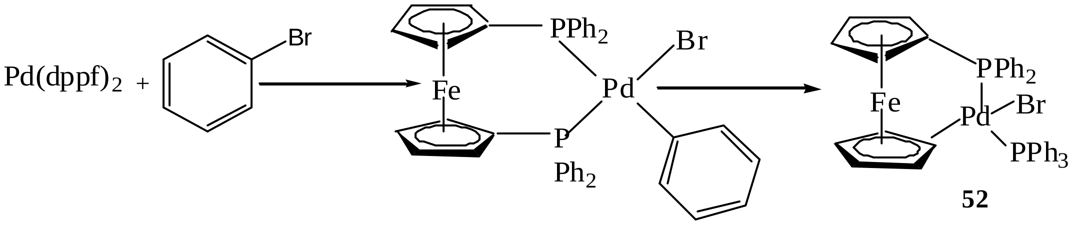
take place [149] but recent results, where the complex **51** was found to have catalytic activity with aryl halides [150], put doubt on this suggestion. Instead, it has been suggested that **50** might be the dominating resting state of the active catalyst in the reaction medium [150, 41].



51

Scheme 5.14. The Equilibrium of PdL_4 and PdL_2 with Bidentate Ligands.

Another explanation for the success of bidentate ligands in catalysis might be formation of the palladacyclic intermediate **52**, which was identified after 6 h at 100 °C in DMA (Scheme 5.15.) [150].

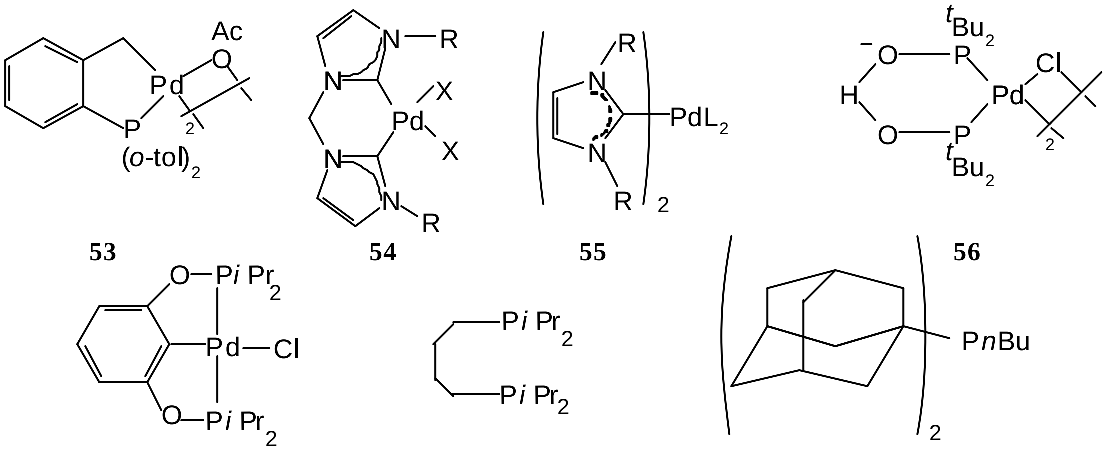


52

Scheme 5.15. Formation of Palladacycle intermediates with Pd-dppf Complexes.

The importance of palladacyclic complexes in palladium catalyzed reactions with bidentate ligands is at present poorly understood but palladacycles are known for their stability [151] and the formation of **52** could protect the catalytic system from decomposition at high reaction temperatures and during prolonged reactions.

New types of ligands: The high cost of palladium, Heck-precursors and ligands has spurred much research aimed at the development of more active (high TOF) and stable (high TON) palladium catalysts. The quest to overcome the low reactivity of the aryl chlorides, especially the nonactivated aryls, has promoted generation of new types of ligands over the last ten years [152]. The most popular ligands used for terminal arylations are the air and temperature-stable Hermann's palladacycle [151] **53,** carbene palladacycles **54** [152], the palladium carbenes [61] **55**, the air stable POP(I) [153] **56**, the phosphite PCP-complex [154] **57**, the electron rich dippb [155] **58**, the alkyl phosphane *n*BuP(1-Ad)$_2$ [156] **59**, (Figure 5.4.) and the very active but air sensitive P(*t*-Bu)$_3$ [157]. The last four ligands have even overcome the low reactivity of the nonactivated anisole chloride and furnished fair to excellent yields in the Heck reaction. However, Fu et al. elegantly replaced the air-sensitive P(*t*-Bu)$_3$ with the corresponding phosphonium salt [(*t*-Bu)$_3$PH]BF$_4$ (acting as a convenient trialkylphosphine precursor) [158].



53 **54** **55** **56** **57** **58** **59**

Figure 5.4 New types of ligands and palladium complexes: Hermann's palladacycle **53**, carbene palladacycles **54**, palladium carbenes **55**, POPd(I) **56**, PCP-complex **57**, dippb **58** and *n*BuP(1-Ad)$_2$ **59**.

Herrmann et al. were the first to demonstrate that palladacycles **53** can catalyze Heck couplings of activated aryl chlorides. To obtain high conversions, *n*Bu$_4$NBr was employed as a co-catalyst. These conditions were not effective for electron-neutral or electron-rich aryl chlorides. Subsequently, both nitrogen- and sulfur-containing palladacycles have also been shown to be reasonably efficient catalysts for Heck reactions of activated aryl chlorides.

Another class of cyclometallated Pd(II) complexes **54** was derived from stable N-heterocyclic carbenes (NHC) which Hermann et. al. had experience in the preparation of [153]. Palladium di(monocarbene) complexes which efficiently catalyze the Heck reaction with aryl bromides and activated aryl chlorides. Taking these results into account, it was to be expected that complexes of chelating dicarbene ligands should also exhibit catalytic activity. Experiments confirmed this and showed that the catalytic activity of chelating dicarbene and di(monocarbene) Pd(II) complexes are comparable. With activated 4-bromoacetophenone and n-butyl acrylate TONs of 1000 were obtained applying defined Pd(II) carbene complexes like **54**. Using $Pd_2(dba)_3{\cdot}dba$ and two equivalents of free monocarbene ligand in situ resulted even in TONs as high as 3.3×10^5. Table 5.2 shows the results obtained with complex **54** [102].

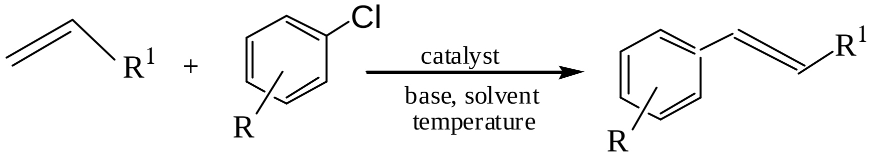
Herrmann et al. pioneered not only the use of palladacycles, but also of palladium carbenes **55** as catalysts for Heck couplings of activated aryl chlorides. Recently, additional palladium-carbene adducts have been shown to be active, but, as with the original catalyst, only electron-poor chlorides are suitable substrates, and elevated temperatures are required (Table 5.2., entry 3).

In addition, Li et al. have demonstrated that commercially available, air-stable Pd (II) complexes that bear phosphinous acid ligands **56** are useful for the Heck reaction of an electron-poor aryl chloride (Table 5.2., entry 4).

Jensen and co-workers have determined that a phosphite PCP-pincer complex **57**, which can be prepared in two steps, is an effective catalyst for Heck reactions of a range of aryl chlorides, including hindered and electron-rich substrates (Table 5.2., entry 5). A disadvantage of this system is that a very high temperature (180 °C, 24 hours) or a prolonged reaction time (120 °C, 5 days) is required

Milstein and co-workers subsequently revealed several important findings regarding Heck reactions of aryl chlorides. They determined that use of a bulky, electron-rich, chelating phosphane ligand **58** (1,4-bis(diisopropylphosphanyl)butane; dippb) furnishes a palladium catalyst that can efficiently couple electron-poor and electron-neutral aryl chlorides. Unfortunately, the catalyst affords low yields for reactions of electron-rich chlorides (Table 5.2., entry 6).

Table 5.2. Heck cross-coupling reaction using new types of ligands.



Entry	R	R^1	Catalyst	Conditions	Yield [%]	Ref.
1[a]	4-CHO, CN,COMe	Ph, CO_2nBu	**53**	NaOAc,DMA,130°C	31-81	[151]
2[b]	4-CF_3,-OCH_3,- NO_2,-H,4-OCH_3	Ph	**54**	NaOAc,DMF,130-160°C	38-97	[152]
3[a]	4-CHO,NO_2	CO_2nBu	**55**	NaOAc, DMA, 130°C	99	[61]
4[a]	4-COMe	CO_2tBu	**56**	NaOAc, DMF, 135°C	66	[153]
5	4-CHO, COMe, -H,OMe,2-Me	Ph	**57**	CsOAc,diox,120,180°C	81-99	[154]
6	4-NO_2,4-CHO, 4-CH_3	Ph	**58**	NaOAc, DMF, 150°C	55-95	[155]
7	-H,4-Me, -OMe, 2-Me	Ph, $CO_2C_8H_{17}$	**59**	K_3PO_4, diox, 120°C	33-98	[156]

[a] $n$$Bu_4$Br was used as cocatalyst [b] PPh4Cl was used as cocatalyst

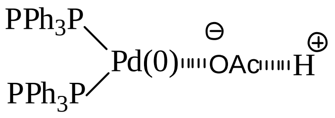
Remarkably, other bulky, electron-rich chelating phosphanes, such as dippp and dippe, as well as monodentate phosphanes such as $P(iPr)_3$, provide essentially inactive catalysts. Beller and co-workers have established that di(1-adamantyl)-n-butylphosphane is a highly effective ligand for Heck couplings of unactivated aryl chlorides, although hindered aryl chlorides furnish modest yields. An array of bulky, electron-rich dialkylaryl- and trialkyphosphanes were screened for the palladium-catalyzed coupling of 4-chlorotoluene and styrene, and it was determined that di(1-adamantyl)-n-butylphosphane and $P(tBu)_3$ afford the highest yields and turnover numbers **59** (Table 5.2, entry 7)[157].

5.3.3. Additives

Additives play a critical role in many asymmetric Heck reactions. Silver(I) additives which have been used to increase the reaction rates in Heck reactions of unsaturated halides, prevent deactivation of the palladium catalyst, minimize alkene isomerization of the Heck products, and dramatically enhance enantioselectivity. Most of these changes are likely due to the fact that silver salts serve as efficient halide scavengers, facilitating the formation of 16-electron, cationic palladium intermediates, thus diverting the Heck reaction from a neutral to a cationic pathway (vide supra). Although a variety of silver salts have been used as additives in Heck reactions of Halide precursors, the most common and effective reagents are Ag_2CO_3, Ag_3PO_4, and silver-exchanged zeolite. Thallium salts (Tl_2CO_3, TlOAc, and $TlNO_3$) have also been used as halide scavengers in Heck reactions, but the high toxicity associated with these reagents makes them a less attractive alternative to silver salts. Recent reports suggest that the use of aqueous DMF-K_2CO_3 as a reaction medium for the Heck reactions of aryl bromides may provide an inexpensive and “green” alternative to the use of Ag and Th additives. As part of a probe of the cationic and neutral reaction manifolds, Overman and Poon examined the use of halides as additives in the asymmetric Heck cyclizations of aryl triflates. Their experiments demonstrated that addition of halide salts to the intramolecular Heck reactions of some unsaturated triflates directs the reactions of aryl triflates from the cationic to the neutral pathway, just as halide scavengers in the Heck reactions of vinyl and aryl halide substrates direct the reactions into the cationic manifold. Shibasaki and co-workers have reported that the addition of tertiary alcohols such as pinacol or *tert*-butyl alcohol accelerated the Heck cyclizations of vinyl triflates in 1,2-dichloroethane (DCE); potassium acetate produced similar rate enhancements. PNMR studies suggest that these additives prevent the DCE-promoted oxidation of the catalytically active Pd(0) species to a Pd(II) species [134].

5.3.4. Bases

The role of the base in the Heck coupling has been debated and although some clarity has been added, it is nonetheless safe to say that knowledge of the details of the functions of bases in the reaction medium is unsatisfactory. It was suggested from an early point that bases were needed to deprotonate the hydridopalladium complex formed at the β-elimination step in order to regenerate Pd(0) (Scheme 5.16.). This mechanism has been corroborated recently [158]. Jutand has suggested that nitrogen bases may be involved in the abstraction of protons that otherwise would interact with the $^-$OAc anion in complex $Pd(PPh_3)_2OAc^-$ (Scheme 5.7) and produce the proton coordinated complex **60** (Scheme 5.16). Complex **60**, where the acetate is more weakly coordinated to the palladium than $Pd(PPh_3)_2OAc^-$ would result in a more naked and reactive palladium species [103]. The proton abstraction would occur less readily when bases are added and bases may thus slow the oxidative addition.

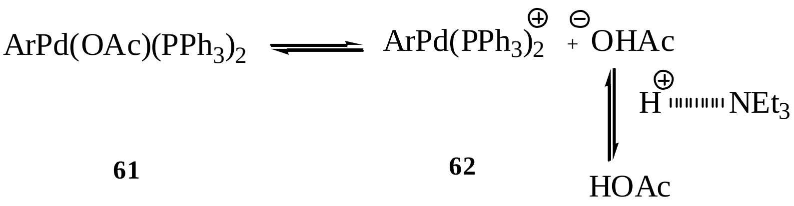


60

Scheme 5.16. Abstraction of palladium ligand acetate by protons in the reaction medium.

In most of the studies, inorganic bases have been used successfully in couplings where a lower degree of reduction of the aryl precursors was needed [135]. This could be explained, when aryl bromides are used, by the neutralization of the HBr formed during the reaction [159]. Nitrogen bases have also been suggested to act as a source of hydrides in the deoxygenation of triflates, which would explain the low degree of deoxygenation when inorganic bases are used in favor of organic [135, 160].

The base can also affect an equilibrium that influences the concentration of the key reactive species of the insertion, $ArPd(II)(OAc)(PPh_3)_2$ **61**, as illustrated in Scheme 5.19. The abstraction of hydrogens is thought to shift the equilibrium to favor the reactive **61** over the less reactive cationic complex $ArPd(II)(PPh_3)_2{}^+$ **62** [103]. The base has thus at least two roles; one that impedes the fast oxidative addition (Scheme 5.16) and one that speeds the slow π-coordination and insertion (Scheme 1.17).



Scheme 5.17. Equilibrium Shift due to abstraction of hydrides by a base.

This is suggested to be beneficial for the catalytic cycle as the oxidation addition and insertion steps then can take place with comparable rates [103].

A stoichiometric amount of base is needed, but in practice, 1-2 molar equivalents are often used. A variety of inorganic bases have been used in Heck reactions, with K_2CO_3 $NaHCO_3$, NaOAc and $CsCO_3$ reported most frequently [135]. Tertiary amine bases such as Et_3N, *i*-Pr_2NEt, Proton Sponge, and 1,2,2,6,6-pentamethylpiperidine (PMP) are also commonly employed. Among these, the extremely hindered base PMP has become a favorite choice for asymmetric Heck cyclizations.

5.3.5. Solvents, Temperature

Solvent polarity has been shown to affect enantioselectivity in many Heck reactions. [134]. Although a wide range of solvents have been used for Heck coupling reactions, the polar aprotic solvents such as the standard solvent DMF, the more thermostable DMA and NMP, and the relatively low boiling point MeCN and THF, are the most useful. These have the ability to stabilize the palladium complex by weak coordination. The search for alternative media for Heck chemistry is targeted at the development of highly productive, environmentally safe, recyclable techniques which can be promoted to large-scale applications. Molten salts (the so-called nonaqueous ionic liquids) are used for this purpose. The use of molten salts as media allows for both easy recycling of catalytic system (e.g., due to temperature-dependent miscibility with nonpolar solvents and water) and possible activation of catalyst. Molten salts are highly polar, thus facilitating the cationic mechanism of Heck reactions, and can contribute to the stabilization of underligated Pd(0) species by forming anionic complexes with halide ions. The following molten salts were used: *n*-Bu_4-NBr, Ph_3MePCl, Ph_3MePBr, *n*-Bu_3-*n*-$C_{16}H_{33}NBr$, and 1-methyl-3-propylimidazolium bromide. The simplest salt of the series *n*-Bu_4NBr performed the best and thus was recommended as a basic choice for such media. Better stability of underligated palladium complexes is revealed by enhanced reactivity of PhCl [93]. The possible effects of trace amount of water in the reaction medium have also been discussed, with varying conclusions. Brown indicated that just traces of water could alter the composition of the palladium complexes [158], while Overmann found no noticeable effect of up to 5% (v/v) water in coupling with

Pd/BINAP systems [161]. Poorly degassed reaction solutions were on the other hand clearly shown to have a negative effect on the stereoselectivity due to oxidation of phosphine ligands to phosphine oxides by oxygen [161]. Jutand has noted that the presence of water does not affect the rate of reduction of Pd(II) to Pd(0) [106]. Crisp suggested that water might be a source for hydroxide ligands that in reactions with aryl chlorides temporarily can replace the halogen and produce a more reactive species [162]. Traces of water may also increase the degree of aryl scrambling (especially when reactions are run with relatively unpolar solvents) by making the reaction medium more polar [163]. Reaction temperatures range from room temperature to over 100 °C [134].

5.3.6. Effects of Pressure and Microwave Heating

Additional improvement of Heck procedures can be sought in ultra fast heating and pressure effects. Very fast heating by means of microwaves leads to shortening of the reaction time, while the yields and selectivity do not greatly differ from the same reactions carried out using conventional heating. The effect can be observed for simple arylation reactions of both Michael-type and donor olefins by aryl iodides, bromides, and triflates in phosphine assisted or phosphine-free processes.

No specific effects belonging to any particular type of reaction were noted. Most probably the influence of microwave heating is associated with direct and uniform input of energy to the reaction media. Heck reactions are very well-known to run better at higher temperatures, naturally if reagents, products, and catalyst can survive such a harsh treatment. In conventional heating the energy is transferred by heat transfer through the walls of the reaction vessel and further on through convection causing nonuniform distribution of heat. Local overheating at the walls leads to decomposition of catalyst. Uniform deployment of heat directly to the reacting molecules by means of absorption of microwave energy by a polar solvent effectively affords higher temperatures than those achievable through conventional heating.

High pressure can also have a beneficial effect on Heck reactions. The key steps of the Heck cycles oxidative addition and migratory insertions have a negative activation volume and thus are likely to be accelerated by pressure. On the other hand, PdH elimination can be retarded by high pressure, which may lead to a change of the product distribution. The increase of oxidative addition with pressure rate makes it possible to perform reactions with substrates, practically unreactive under normal pressure, e.g., to perform differential Heck reaction by substituting a better leaving group (nonaflate) at normal pressure and poorer leaving group (chlorine) at high pressure as well as to use bromoderivatives in place of iododerivatives [93].

5.4. Heterogeneous Heck Reactions

The increasing demand of environmentally benign processes has led in the last decade to a great development in both preparation and use of heterogeneous catalysts in organic chemistry. The most extensive efforts to find heterogeneous versions for Pd-catalyzed C–C coupling reactions have been made for the Heck reaction. In principle, heterogeneous catalysis could help in solving some of the problems which have prevented the technical applications of the Heck reaction so far. First of all, the catalyst could be easily recovered from the reaction mixture. Secondly, the heterogeneous catalyst could be recycled, provided it does not deactivate too quickly under duty. Third, palladium would be already present as metal crystallites dispersed onto the solid support, so that the precipitation of Palladium black should not occur, unless it is not released in the liquid phase in soluble forms (HR takes place in liquid phase, hence any heterogeneous catalysis is bound to operate under solid–liquid conditions). As shown below, the question of metal losses is of the utmost importance in heterogeneous Heck reaction (HETHR). More generally, metal leaching is potentially a major problem in every reaction where solid–liquid heterogeneous catalysis is employed [94]. Although the industrial use of heterogeneous catalysts is more desirable owing to the ease of catalyst separation and recycling, there are only very few reports of heterogeneous-reusable catalysts for the Heck reaction [93].

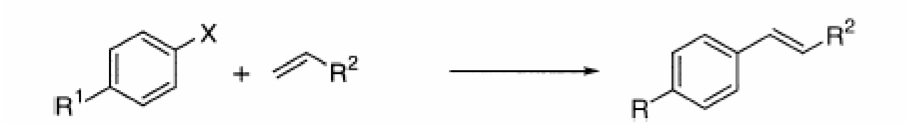
In general, commercially available supported palladium catalysts on supports like charcoal, SiO_2, Al_2O_3, MgO, $BaSO_4$, $CaCO_3$, or TiO_2 have been used. Besides these classical catalysts, colloidal Pd, Pd clusters, Pd nanoparticles, as such or stabilized by poly(vinylpyrrolidone), block copolymer micelles of polystyrene-*b*-poly-4-vinylpyridine, propylene carbonate, Pd-modified zeolites and clays, palladium on porous glass, and palladium grafted onto molecular sieves were also shown to be suitable. Mesoporous MCM-41, and silica supported poly-?-mercaptopropylsiloxane, exhibit higher catalytic activity in the Heck olefination of bromo- and iodoarenes because of the larger surface areas [94].

In efforts to develop a heterogeneous system with the catalysts such as Pd/SiO_2, Pd/C, Pd complexes grafted on SiO_2, Pd complexes intercalated in montmorillonite, Pd/Al_2O_3, Pd/resin, and Pd-modified zeolites, a desired option for commercial realization affords poor to moderate conversions and selectivities in the Heck olefination of chloroarenes. The use of basic support, for example, Pd/MgO, in the Heck olefination resulted in high conversions albeit poor selectivity [94]. Kaneda found that Pd/MgO could catalyze the coupling of chlorobenzene and styrene in moderate yield (Table 5.3; entry 1) [164]. Increasingly, the classic hydrogenation catalyst Pd/C was also capable of stilbenes formation, although the yield was low (Table 5.3; entry 2). The differences in yield between Pd/MgO and Pd/C could be due to the intrinsic character of the solid support. The basic Mg/O support can donate electrons to the palladium particles creating an electron-rich environment, which is favourable during the oxidative addition of the aryl halide. Pd/C is more acidic and its electron-donating character is therefore minimized [100].

Zeolites, which have specific properties (ion exchange capability, crystalline structure with regular pores of molecular size) were utilized to prepare heterogeneous systems containing highly dispersed metals**.** Djakovitch and Köhler have studied a series of palladium catalysts obtained by ion-exchanging Na- or H-zeolites (Mordenite, Y) with $[Pd(NH_3)_4]Cl_2$. The exchanged materials were calcined in O_2 at 500 °C and then used as such or after reduction of Pd(II) to Pd(0) under H_2 at 350 °C. The performances of the reduced and unreduced catalysts in terms of yields and product distribution were similar for the Heck reaction of styrene with 4-substituted bromobenzenes (nitro, acetyl and fluoro derivatives). These catalysts, however, were not particularly active: reaction times exceeding 24 h were required for complete reaction (Table 5.3; entries 8, 9 and 10). The catalysts generally showed reduced effectiveness upon recycling. However, in the second run over Pd(0)/H-Mor, the yield of the coupling of bromobenzene was roughly twice larger than in the first cycle. Palladium complexes entrapped in zeolite NaY were also tested as catalyst for Heck arylation [165]. Of the four complexes of palladium, the smallest $(Pd(NH_3)_4Cl_2)$ gave the most active supported catalyst. $Pd(OAc)_2$ and $[Pd\text{-}(C_3H_5)Cl]_2$ were moderately active, while Herrmann palladacycle apparently choked the zeolite pores to show only marginal activity (Table 5.3,entry 3-

7). A zeolite-supported Pd-$(NH_3)_4Cl_2$ complex showed considerable activity in the reactions of bromoarenes with styrene and methyl acrylate comparable to that of the same catalyst in the homogeneous reaction. The catalyst could be recycled twice with

Table 5.3. Heck reactions of aryl bromides and chlorides using insoluble catalysts

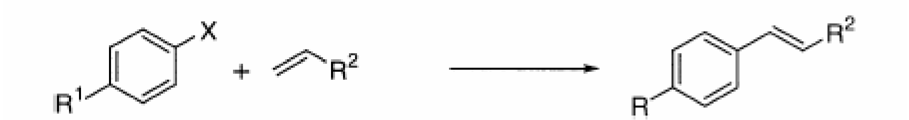


Entry	R^1	X	R^2	Catalyst	Conditions	Yield [%][a]	Ref.
1	H	Cl	Ph	Pd/MgO	0.25 wt % Pd, 150 °C, 5h	42	[164]
2	H	Cl	Ph	Pd/C	0.5wt%Pd, 150°°C, 5h	19	[164]
3	F	Br	Ph	$[Pd(NH_3)_4]^{2+}$NaY	1mol%Pd, 40-100°°C 20h	93-95	[13c]
4	F	Br	Ph	Palladacycle[b] NaY	0.1 mol % Pd, 140 °C, 20h	3	[13c]
5	OMe	Br	Ph	$[Pd(NH_3)_4]^{2+}$ NaY	0.1 mol % Pd, 140 °C, 20h	81	[13c]
6	COPh	Cl	Ph	$[Pd(NH_3)_4]^{2+}$ NaY	0.1 mol % Pd, 170 °C, 20h	44	[13c]
7	COPh	Cl	Ph	$[Pd(NH_3)_4]^{2+}$ NaY[c]	0.1 mol %Pd, 170°C, 20h	59	[13c]
8	NO_2,COMe	Br,H	Ph	Pd(0)NaMor	0.2 mol %Pd, 140°C, 20h	96,86,32	[166]
9	NO_2,COMe,H	Br	Ph	Pd(II)NaMor	0.2 mol %Pd, 140°C, 20h	94,86,72	[166]
10	F	Br	Ph	Pd(II)HY/Mor	0.2 mol %Pd, 140°C, 20h	93,91	[166]

[a] Yield of *trans* isomer given only [b] Pd[P(*o*-Tol)$_2$($PhCH_2$)]$^+$ [c] Bu_4NCl added.

negligible degrease in the activity. All data showed that the entrapped catalyst behaved almost exactly same as catalyst in homogeneous solution but is more stable. It was interesting that the catalyst prepared by the calcination of $Pd(NH_3)_4Cl_2$-modified zeolite, both in Pd(II) or Pd(0) (prereduced by hydrogen), showed poorer activity and increased leaching compared to the original complex.

Table 5.4. Heck reactions using Mesoporous silica MCM-41



Entry	R^1	X	R^2	Catalyst	Conditions	Con.	Ref
1	COMe	Br	$CO_2{}^n Bu$	Pd-TSM11	0.02mol%Pd, 120 °C,1h	100	[167]
2	H	Br	$CO_2{}^n Bu$	Pd-TSM11	0.1mol%Pd, 170 °C,48h	67	[167]
3	H	Cl	$CO_2{}^n Bu$	Pd-TSM11	0.1mol%Pd, 170 °C, 32h	16	[167]
4	H	I	CO_2Me	MCM41-bc-dcnPd(0)	0.156mol%Pd 70°C, 8h	100	[168]
5	H, OMe	I	CO_2H,Ph	MCM41 NH_2.Pd(0)	0.3mol%Pd, 70°C, 2h, 4h	100	[169]

Mesoporous molecular sieves that are crystalline materials structurally related to zeolites are also used in heterogeneous reactions. The first report on the use of siliceous MCM-41 grafted with palladium for Heck arylation was recently published [167]. Pd was deposited onto the niobium modified mesoporous material by chemical deposition of [Pd(?-C_3H_5)(?^{3}-C_3H_5)], followed by reduction with H_2. This, as well as the surface silanized material (Pd-TMS11), was tested for its ability to couple aryl halides with either styrene or n-butyl acrylate. Very good conversions were obtained for activated aryl bromides where TONs of 5000 were achieved (Table 5.4; entry 1). Harsh conditions (170 °C, 48 h) were necessary to convert bromobenzene to cinnamic ester (Table 5.4; entry 2). Even at 170 °C, however, chlorobenzene remained essentially inactive (entry 3). No data were reported on catalyst recycling, but it was found that about 5% of the metal was lost and that some carbon deposited onto the catalyst [94]. It shows higher catalytic activity when compared with Pd/Al_2O_3 or Pd/C. However, in the Heck reaction of bromobenzene with styrene, $Pd(NH_3)_4^{2+}$ /Y seems much more active at lower temperatures than the Pd-TMS-11 catalyst.

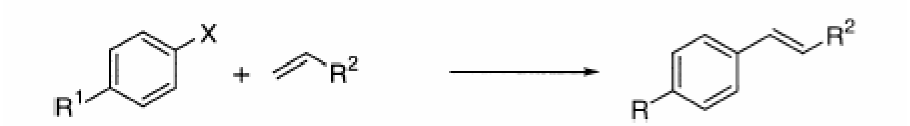
Currently, the development of the palladium complexes immobilized on supports via spacers as heterogeneous catalysts for the Heck reaction receives much attention. Zhang et al. anchored the palladium complexes onto the dicyano-functionalized mesoporous molecular sieve MCM-41, which was firstly synthesized via two-step surface modification of MCM-41 [168]. The resulting anchored-palladium complexes as new heterogeneous catalysts for the Heck reaction showed good activity (Table 5.4; entry 4) and reusability. The developed catalysts based on the dicyano-functionalized MCM-41 had high activity, which remained almost constant through four recycles, considering all the reactions were finished in ca. 3-4 h Pd leaching of the dicyano-functionalized supported catalysts was very little after four recycles.

In a recent report, an aminopropylated MCM-41 was used as a support for Pd, but the resulting catalyst (MCM–NH_2.Pd(0)) was only applied in a relatively easy reaction with an aryl iodide. Two recycles were carried out for the arylation of acrylic acid with iodobenzene (Table 5.4; entry 5), and it was found that the yield of trans-cinnamic acid deceased only by 1–3% in each recycle but there was no indication about the Pd leach [169].

Zhao et al. also followed a similar strategy for the preparation of series of polymeric amine–palladium(0) complex but this time fumed silica was used as the support. All the catalysts were stereoselective for Heck arylation of deactivated aryl iodides as before (Table 5.5.,entry 1) and two recycles were carried out for the reaction of iodobenzene with acrylic acid. It was found that the activity of the catalysts decreased very slightly after two recycles, which gave > 91% yield in the first recycle, and > 89% yield in the second recycle [170].

Comparison with supported palladium catalysts, silica supported poly-?-aminopropylsilane Ni^{2+}, Cu^{2+}, Co^{2+} complexes, that are much less expensive, were also tested for Heck vinylation of aryl iodides (Table 5.5; entry 3-4). All catalysts were treated with KBH_4/C_2H_5OH before they were used. The functional groups on benzene ring have influence on the activity of aryl iodides markedly. Longer reaction time was required in the reaction of 4-iodobenzoic acid with alkenes (48 h for all three), and no reaction was observed with 4-iodonitrobenzene catalyzed by these catalysts. Two recycling was carried out for the supported transition metal (Ni^{2+}, Cu^{2+}, Co^{2+}) complexes without treatment with KBH_4 and it was tested for the vinylation of iodobenzene with acrylic acid. It could be reused without loss in activity. It was interesting that an induction period of more than 2 h has been observed in the first run reactions for these catalysts [171].

Table 5.5. Heck reactions using immobilized catalysts



Entry	**R^1**	**X**	**R^2**	**Catalyst**	**Conditions**	**Con Yield***	**Ref.**
1	OMe, COOH	I	Ph	“Si”NH_2.Pd(0)	0.1175mol%Pd, 90°C, 12h	98.9, 97.8	[170]
2	H	I	CO_2Me	“Si”Schiffbase Pd(II)	0.21 mol % Pd, 82°C, 24h	82*	[18a]
3	H	I	Ph	“Si”NH_2Ni,Cu, $Co(0Ac)_2$	0.68 mol%Pd, 150°C,15-48-48h	98,40 39*	[171]
4	OMe	I	Ph	“Si”NH_2Ni,Cu, $Co(0Ac)_2$	0.68mol%Pd, 130°C, 15-24-24h	96,92 91*	[171]
5	H	I	Ph	SILPY.Pd	0.3mol%Pd, 110°C, 2 h	100	[172]
6	OMe COMe	I,Br	Ph	IMEO-Pd-MSN	1.5 mol %Pd , 100 °C, 4h	89, 87*	[18c]
7	H	Br	Ph	Pd-HT	20 wt % Pd, 150 °C, 12 h	67*	[16a]
8	H, OMe	Br	$CO_2{}^{n}Bu$	Si.Pd(PCP)	0.8 mol % Pd, 140°C, 24 h	86*, 90*	[18d]
9	COMe,OMe	Br	$CO_2{}^{n}Bu$	ResinPd(NHC)	0.02 mol % Pd, 160 °C, 12, 60 h	99* 45*	[11a]

An efficient method for the formation of a silica-immobilized tridentate diphosphinoaryl ligand (PCP-type) palladium(II) complex was successfully used as a catalyst for the Heck reaction. It (Si.Pd(PCP)) showed high catalytic activity in the Heck reaction of aryl iodides, and aryl bromides with butyl or methyl acrylate at 140 °C in the presence of Na_2CO_3. Lower reactivity was observed when changing the substrate from butyl acrylate (TON=3030) (6h, 99 % yield) to styrene (TON = 1320) (30 h, 85 % yield). The catalyst was not only thermally stable but also stable towards oxygen and moisture. In addition, it could be recycled and reused with moderate loss of activity. Recyclability tests were performed both for iodo- and bromo-benzene and also for *para*-substituted bromobenzenes using methyl and butyl acrylate as the substrate. However chlorobenzene was found to react poorly with the acrylate (TON =16) under drastic reaction conditions (high temperature, no solvent or reacting solvent such as MeOH). It was also found that a *para*-substituent on the benzene ring had no significant effect on the reaction, in other words all performed reactions resulted quantitatively at the same reaction time (within 24 h) [18d].

Clark et al. developed a range of heterogeneous Palladium catalysts based on chemically modified mesoporous silica gel, which was either commercially available or prepared via sol-gel technology [18a]. The hybrid Palladium catalyst was prepared by reaction of sol-gel processed aminopropyl-modified micelle-templated silica (3-aminopropyl-MTS) with pyridinecarbaldehyde, followed by complexation with palladium acetate. The activity of catalyst was investigated in the Heck reaction of aryl iodides with olefins in an acetonitrile suspension (Table 5.5; entry 2). In the first 6 h the conversion rate was ~4% h^{-1} after an induction period of ~1 h. Supposedly the decrease of the activity after 6 h to 2% h^{-1} is due to the congestion of the gel pores by the products. By decanting the liquid from the reactor the active polymer could be recycled and was further applied without any conditioning and regeneration. Only after five additional runs (corresponding to a turnover number of >2000) was a significant drop in activity observed. There was no induction period on repeated uses. Analysis by atomic absorption spectroscopy corroborated that no detectable amounts of palladium (< 0.1 ppm Pd by AAS) leached during the reaction. No conversion was observed in the hot filtrate, which further implied that the transition metal species did not dissociate from the support during the reaction. The same polymer was also successful in the Heck reaction of aryl iodides with allylic alcohols to give carbonyl compounds. The catalyst was reusable without noticeable loss of activity.

Pd-complexes of silica anchored secondary amines that were formed by the reduction of the Schiff bases were also studied. Palladium anchored on pyridine–amine functionalized silica exhibited high activity and selectivity in the arylation reactions of ethyl acrylate to ethyl cinnamate and styrene to stilbene using iodobenzene (Table 5.5.; entry 5). These heterogenised palladium catalysts were reusable many times without deactivation by leaching of palladium. Fourteen reaction cycles for ethyl cinnamate (TON = 4100 mmol ethyl cinnamate/mmol Pd) and 10 for styrene (TON=2000 mmol styrene/mmol Pd) were performed [172].

Özdemir et al. have developed a convenient synthetic route to heterogenize catalytically active imidazoline complex by hydrolyzing and condensation of $–Si(OEt)_3$ group attached through $–(CH_2)_3–$ spacer to a nitrogen atom of the imidazoline via hydroxyl bonding on mesoporous silica nanotube (MSN) particles [118c]. In our study, the same strategy was also used for the heterogenation of the homogeneous catalyst. The catalyst showed high activity for Heck reactions of a wide array of iodides or bromides (85-94%, 0.5-4h). However there was no result for the olefination of aryl chlorides. The heterogenised catalysts were reusable in the olefination of iodoanisole and bromoacetophenone (activated bromoarene) without leaching of palladium (Table 5.5; entry 6). This novel catalyst had the same activity even after five cycles in the Heck reaction.

Sivasanker et al. used Pd(II) supported hydrotalcite for the first time. It was an efficient and reusable (2 cycles) catalyst for heterogeneous Heck reactions between substituted iodobenzene and methylacrylate. Stilbene derivatives were isolated in moderate to good yields (48–87%) at 140 and 150 °C. The results showed that good yields of the products can be obtained with allyl iodides (highest TON achieved was around 1000) at 140 °C. Under similar experimental conditions aryl bromides did not appear to be much reactive. Hence the temperature was raised to 150 °C and NMP was used as a solvent (Table 5.5; entry 7). Stilbenes were isolated in good yields (48-67 %). The catalyst, however, was not effective with the less reactive aryl chlorides. Chlorobenzene failed to react with methyl acrylate. The activated aryl chlorides like p-nitrochlorobenzene also gave low yields [16a].

Particles >10 nm in diameter are generally described as colloids and those <10 nm in diameter as clusters. Colloids and clusters differ from insoluble heterogeneous catalysts in that, while catalysis takes place on the surface of the dispersed metal particles, the colloid or cluster can be soluble. Pd sols are usually prepared either by chemical reduction of a palladium salt or electrochemical dispersion of palladium metal in the presence of a stabilizer. The stabilizer, e.g. a polymer, tetraalkylammonium salt or surfactant, forms a protective shell around the metal particles, preventing agglomeration and formation of an insoluble precipitate, i.e. palladium black.

Table 5.6. Heck reactions of aryl bromides and chlorides using Pd sols.

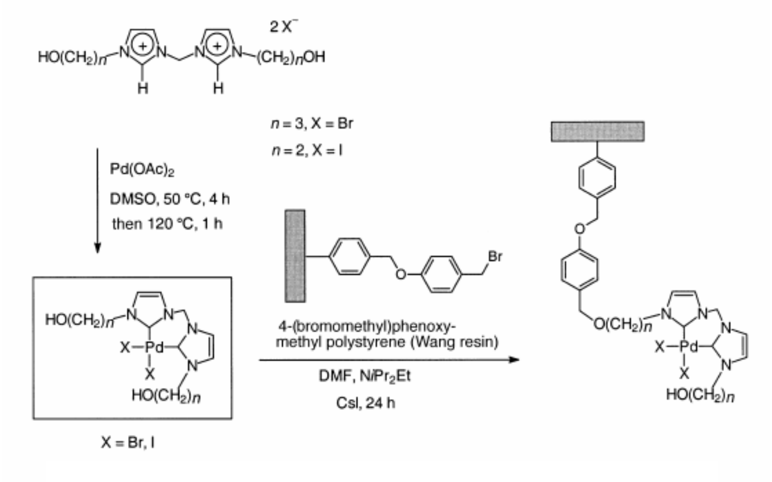
Entry	**R^1**	**X**	**R^2**	**Stabiliser**	**Conditions**	**Conv. [%]**	**Ref**
1	NO_2	Br	Ph	Propyl.carbonate[a]	3.5mol%Pd,130 °C, 5h	100	[173]
2	H	Cl	Ph	Propyl.carbonate[a]	3.5mol% Pd,155°C,65h	55	[173]
3	COMe	Br	$CO_2{}^n Bu$	$(C_8H_{17})_4NBr$[b]	0.05 mol % Pd, 140 °C	97	[174]
4	COMe	Cl	Ph	$(C_8H_{17})_4NBr$[b]	1 mol % Pd, 140 °C	<5	[174]
5	NO_2	Br	Ph	PS-*b*-P4VP[b]	0.05 mol % Pd, 140 °C, 24h	92	[174]
6	Me	Br	Ph	PS-*b*-P4VP[b]	0.05mol %Pd,140°C, 72h	7	[175]
7	COMe	Cl	Ph	PS-*b*-P4VP[b]	0.05 mol % Pd,40°C,72h	0	[175]

[a] =Electrochemical reduction; [b]=Chemical reduction; PS-*b*-P4VP= block copolymer, polystyrene-*b*-poly-4-vinylpyridine.

In recent years, considerable efforts have been directed towards the synthesis and application of colloids and clusters in the Heck reaction with some degree of success. Representative examples of aryl bromides and chlorides that have been successfully transformed are given in Table 5.6. Excellent conversions can be achieved with activated aryl bromides using three types of stabilizers shown (Table 5.6; entries 1, 3 and 5). The propylene carbonate stabilized Pd sols could activate chlorobenzene, giving a reasonable conversion of 55% (Table 5.6; entry 2), but the block copolymer micelle system and tetraoctylammonium bromide stabilized sol could not convert electron rich aryl bromides or activated aryl chlorides (Table 5.6; entries 4, 6 and 7).

The preparation of the stabilized colloids involves invariably difficult protocols using exotic reagents. Choudary et al. stabilized palladium particles on Mg-Al layered double hydroxides and Merrifield resin for the first time [22a]. Supported nanopalladium(0) catalysts were prepared by an exchange of $PdCl_4^{2-}$ followed by reduction. The ligand-free heterogeneous layered double hydroxide supported nanopalladium (LDH-Pd(0)) catalyst indeed exhibited higher activity and selectivity in the Heck olefination of electron poor and electron-rich chloroarenes in nonaqueous ionic liquids(NAIL) over the homogeneous $PdCl_2$ system. Using microwave irradiation, the rate of the Heck olefination reaction was accelerated, manifold with the highest turnover frequency ever recorded in the case of both electron-poor and electron-rich chloroarenes. The basic LDH-Pd(0) showed a superior activity over a range of supported catalysts, from acidic to weakly basic Pd/C, Pd/SiO_2, Pd/Al_2O_3, and resin-$PdCl_4^{2-}$ in the Heck olefination of deactivated electron-rich 4-chloroanisole. The catalyst was reused for a number of cycles with almost consistent activity in all the coupling reactions.

Recently, transition metal complexes of N-heterocyclic carbenes have been the focus of considerable attention since they can act as catalysts or catalyst precursors to important transformations. In contrast to the widely used phosphine complexes, they have been shown to be remarkably stable towards heat, oxygen and moisture. The metal–carbon bonds in the carbene complexes are much stronger than the metal–phosphorus bond of typical phosphine complexes [90]. The only representative example of a heterogeneous NHC Heck catalyst was reported by Hermann et al. [11a]. Good results in the Heck coupling reactions were achieved with polymers on the basis of the Wang resin (4- bromomethyl)phenoxymethylpolystyrene (Scheme 5.18). The catalyst was used 15 times without detectable loss of activity in the coupling of bromoacetophenone and styrene within 15 h at 150 °C in the presence of 0.15 mol % Pd. When butylacrylate was used as the substrate in the presence of 0.02 % Pd at 160 °C, the catalyst can be recycled six times before the conversion slowly drops down to 80% in the 7th run (TON=35500). On the other hand, noticeable deactivation is dis played in the case of less reactive bromobenzene. Hardly any catalyst leaching was observed, which supported earlier proposals that the NHCs are strongly bound to the catalyst metal center. It is noted that it was not possible to convert chlorobenzenes even under harsh reaction conditions (0.15 mol % Pd, 170°C, 50h).



Scheme 5.18. Immobilization of a NHC palladium catalyst according to Hermann et al.

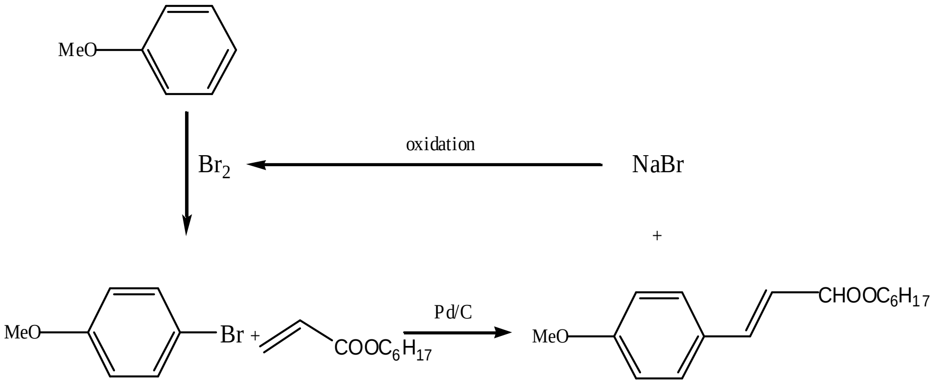
On comparison, all of the heterogeneous catalysts described here could convert aryl iodides. Some of them can convert activated aryl bromides in almost quantitative yields. Reasonable conversions can be achieved for bromobenzene using Pd-TMS11 (Table 5.4; entry 2), palladium(II) containing hydrotalcite (Table 5.5; entry 7), Si.Pd(PCP) (Table 5.5; entry 8), resin bonded Pd(NHC) complex (Table 5.5; entry 9) and zeolites (Table 5.3; entry 8 and 9) but only the zeolite-based catalyst, resin bonded Pd(NHC) complex and Si.Pd(PCP) can convert electron rich aryl bromides. The main difference of these, as a catalyst, is the number of recycles that can be performed variety of types of aryl halides that can be recycled and prolonged reaction times.

Aryl chlorides, that are commercially more attractive but less reactive have again proved to be problematic. Only zeolite in the presence of Bu_4NBr,catalyst, Pd-MgO and propylene carbonate-stabilized sol gave reasonable yields, 59 %, 42%, 55% respectively. No examples of electron rich aryl chlorides were given except for the catalysts LDH-Pd(0) which is by far the most active catalyst ever reported for both activated and deactivated aryl chlorides. However which showed very low activity in organic solvents.

5.5. Contribution to Fine Chemical Manufacture via Heck Coupling

Some technical applications using heterogeneous strategies have already been developed. Eisenstadt and coworkers mention a multi-ton scale process for octyl *p*-methoxy cinnamate [29], the most common UV-B sunscreen, with an estimated world consumption of ca 5000 tons year^{-1}. The production of this compound is an example of the novel chemistry and economical attractiveness of the Heck reaction on an industrial scale.

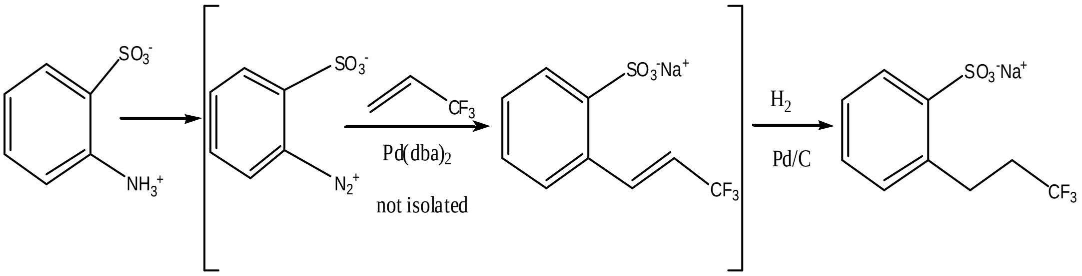
The production process involves two main chemical transformations (Scheme 5.19.) bromination of commercial anisole produces p-bromoanisole (> 97%), and heterogeneous Heck coupling between p-bromoanisole and commercially available octyl acrylate, in the presence of a Pd\C catalyst, with Na_2CO_3 as HBr sponge, and NMP as the solvent furnishes octyl p-methoxycinnamate) [176]



Scheme 5.19. Production process for octyl methoxy cinnamate

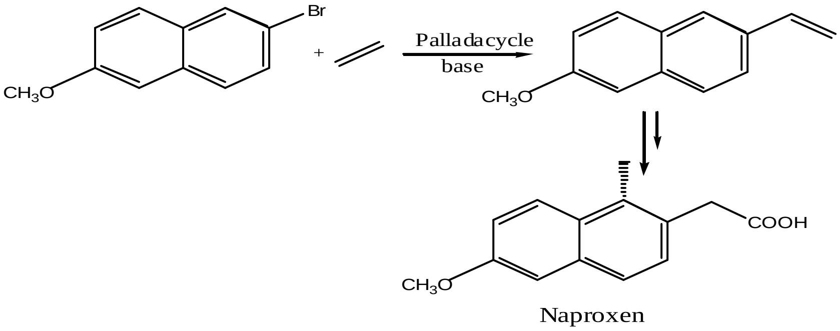
Because of the high cost of bromoanisole, this synthesis is only commercially competitive if the recycling of the bromine and the bromination of anisol are part of this overall process. A potential UVA+B filter reagent ODMAC (octyl dimethylaminocinnamate) was also synthesized by using Heck coupling [29].

An interesting combination of a homogeneous and heterogeneous approach is the production process developed for an intermediate of the Prosulfuron® sulfonylurea herbicide of Ciba-Geigy (now Novartis) /Syngenta, as shown in Scheme 5.20. While the Matsuda Heck reaction of an aryl diazonium salt with trifluoropropene is catalyzed by a homogeneous Pd catalyst on ton-scale, the subsequent hydrogenation is carried out in the same reactor with Pd/C catalysts prepared in situ by adding active carbon to the reaction mixture. The overall yield is around 93%, but the catalyst activity and productivity are relatively low.



Scheme 5.20. Production process for an intermediate of the Parasulfon® herbicide.

Apart from the synthetic elegance the Heck reaction still suffers from serious limitations which have precluded widespread industrial use so far. Other examples of Heck reactions which have been used industrially on pilot plant-scale include the coupling of ethylene with 2-bromo-6-methoxynaphthalene and with 2-bromotoluene. The former reaction was applied as a key step by Hoechst AG for the synthesis of Naproxen (Scheme 5.21). The latter coupling process has been used by Dow to make high-purity 2- and 4-vinyltoluenes, which are of interest as comonomers in styrene polymers [177].



Scheme 5.21. Synthesis of Naproxen synthesis by Hoechst

The use of Heck couplings in the synthesis of a variety of compounds is well documented. This includes many other examples of lilial (fragrance), developed by Givaudan, metoprolol (*b*-blocker), nobumetone (a non-steroidal anti inflammatory drug, or NSAID) and stilbenes [177]. Although stilbene itself (1,2-diphenylethene) is not a natural product, a large number of its derivatives have been isolated from various plant species. Among these naturally occurring stilbenoid compounds, polyhydroxystilbenes and their glucosides are currently attracting considerable attention, because of their wide range of biological activities and potential therapeutic value.

These molecules are found mainly among members of the vegetable kingdom classified as spermatophytes, but also in bryophytes and pteridophytes. Numerous structural variations have been identified, depending on the configuration of the carbon–carbon double bond, the number of hydroxyl functionalities, and the extent to which the phenol groups are substituted with sugars, methoxy, or other alkoxy groups. To cite but a few recent results in the field of styrene synthesis, the Heck reaction provided a ready access to oligomeric styrylpyrroles, oligo(phenylenevinylene) derivatives, stilbenoid dendrimers, and new non linear optical electron donor–acceptor substituted stilbene derivatives. It also served as the key step in the synthesis of various polyhydroxylated stilbenes, including resveratrol and related highly oxygenated stilbenoid dimers [178].

CHAPTER 6

EXPERIMENTAL STUDY

6.1. Synthesis of Amorphous Silica

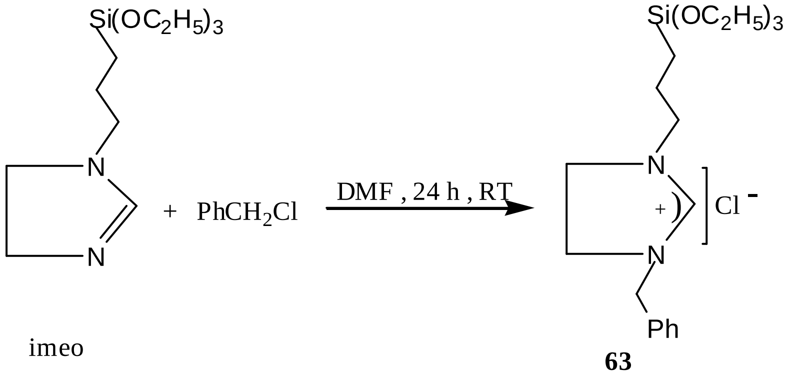
The Amorphous Silica was donated by Prof. Devrim Balköse, who is a faculty of chemical engineering department of Izmir Institute of Technology. Their method of synthesis is given elsewhere. The gelation process was performed at pH 3.65 [179].

6.2. Synthesis of Palladium N-Heterocyclic Carbene Complex

Synthesis of bis[1-benzyl-3-(propyltriethoxysilane)imidazolidin-2-ylidine]dichloropalladium II complex **64** and 1-benzyl-3-(propyltriethoxysilane)imidazolidinium chloride salt **63** was performed in Prof. Dr. Bekir Çetinkaya' s laboratories of the chemical department Ege University. All the materials were used directly without further purification. 1-(3-triethoxysilylpropyl)-2-imidazoline (imeo) was obtained from Fluka. Diethyl ether (J. T. Baker) was distilled under nitrogen from sodium benzophenone ketyl just before use. DMF (J. T. Baker) was dried over molecular sieve 4A. All synthesis of the 1,3-dialkylimidazolidininum salt **63**, and the Pd(NHC) complex **64** (Scheme 6.1. and 6.2.) were performed under a nitrogen atmosphere with the use of standard Schlenk techniques.

6.2.1. Synthesis of 1-benzyl-3-(propyltriethoxysilane)imidazolidinium chloride (63)

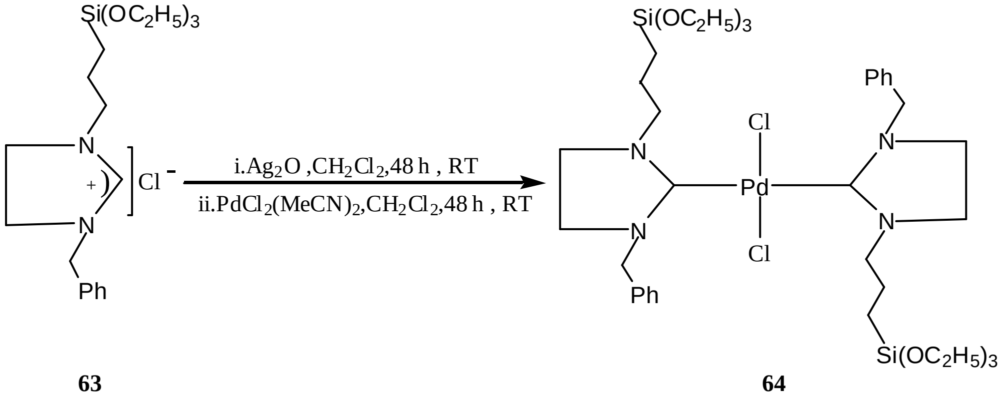
To a DMF solution (5 mL) of imeo (3.99 g, 14.78 mmol) was added 1.87 g, 14.79 mmol of benzyl chloride at 25 °C and the resulting mixture was stirred at RT for 24 h. Diethyl ether (20 mL) was added to obtain a white crystalline solid which was washed with Et_2O (2 × 15 mL) and dried under vacuum.



Scheme 6.1. Synthesis of imidazolidinium salt **63**

6.2.2. Synthesis of Palladium N-Heterocyclic Carbene Complex Pd(NHC) (64)

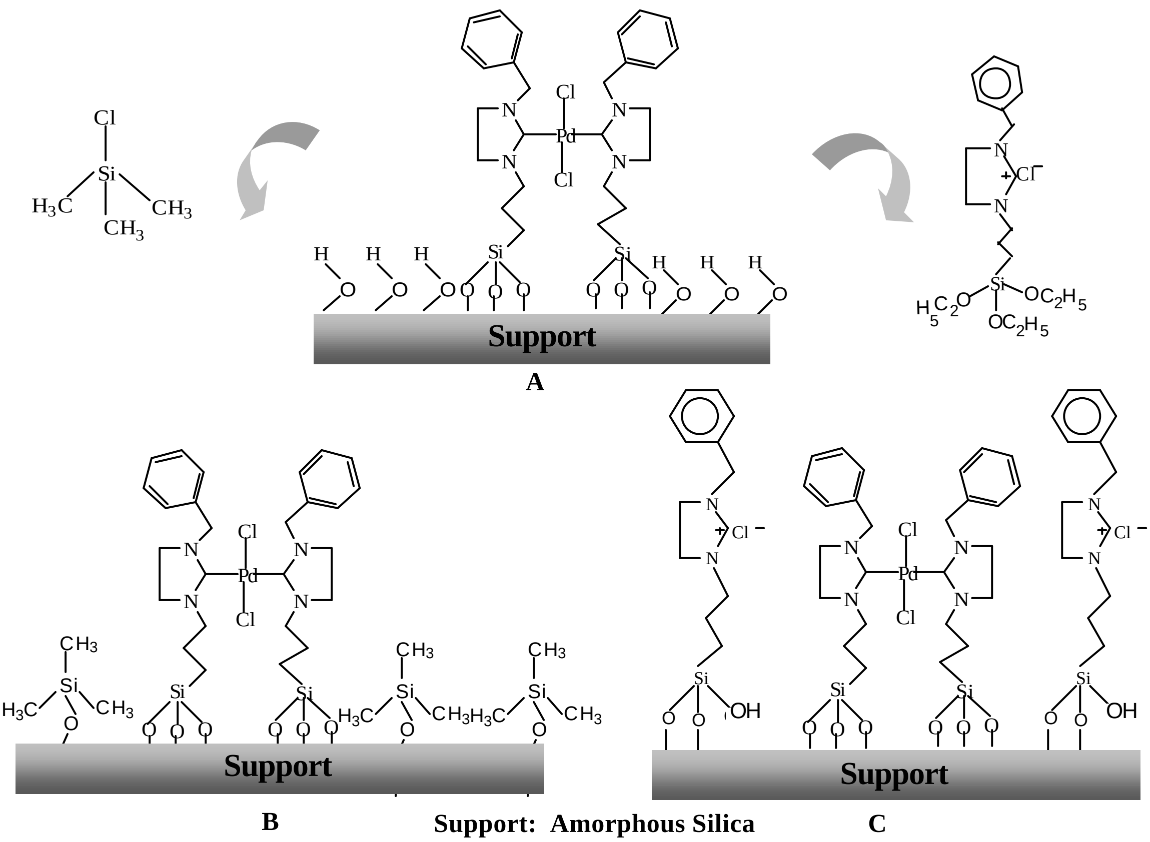
A suspension of imidazolidinium salt synthesized (0.29 g, 1.07 mmol) and Ag_2O 0.36 g (1.5 mmol) in CH_2Cl_2 (20 mL) was stirred for 48 h at RT. After 24 h of stirring $PdCl_2(CH_3CN)_2$ (0.13 g, 0.53 mmol) was added and it was further stirred 24 h at RT. Upon cooling to room temperature, pale yellow crystals were filtered off, washed with hexane (2 × 15 mL) and dried under vacuum. Bis[1-(benzyl)-3-(propyltriethoxysilane)imidazolidin-2-ylidene]dichloropalladium-(II) complex **64** was recrystallized from CH_2Cl_2-Et_2O at room temperature.



Scheme 6.2. Synthesis of Pd(NHC) complex **64**

6.3. Heterogenization of the Homogeneous Catalyst

We have considered three strategies for heterogenisation (**A**, **B** and **C**) (Scheme 6.3.), which reserve as much possible as the coordination sphere of the metal. This was achieved by mainly direct anchoring of the homogeneous catalyst to an inorganic support, amorphous silica, (**A**) and followed by modification of the free silanol groups (**B** and **C**). We also prepared pure silica modified salt **63**, to understand the effect of presence of the immobilized salt **63** to the reaction.



Scheme 6.3. Heterogenization of Homogeneous Catalyst.

6.3.1. Anchoring of Pd(NHC)complex (A)

Direct anchoring to an inorganic support (Amorphous Silica) is achieved via covalent bonds between the solid (silanol groups -Si-OH) and Pd(NHC) complex that has appropriate groups ($-Si(OEt)_3$) at a position remote to the metal center.

Preparation of heterogenized materials of complexes bearing a triethoxysilylpropyl group were carried out, by controlled hydrolysis of Si-OEt bonds and reaction with the free silanol (Si-OH) on the surface of Amorphous Silica (Scheme 6.3).

In a typical experiment, 1 g of Amorphous Silica was treated with 0.01 M CH_3COOH (Riedel-de Haën, extra pure) (3 g / 50 mL) and the suspension was shaked under vacuum in ultrasonic bath for 1 h. The resulting suspension was filtered and washed with ultra pure water until filtrate reaches the neutral pH. The acid treated silica was evacuated overnight at 120 °C prior to heterogenisation. Reaction was carried out in a three-necked round-bottomed flask equipped with a reflux condenser and a dropping funnel under Ar. A solution support of a slightly yellow Pd(NHC) complex (1 % Pd / 100 g silica) was prepared by adding 20 mL dry $CHCl_3$ (Riedel-de Haën, extra pure) (refluxed over $CaCl_2$) into a dropping funnel. Then it was drop wise added to the inorganic support and the resulting suspension was refluxed in a preheated oil bath while being magnetically stirred. The mixture was stirred for 24 h to give a yellow solid. After filtration, it was treated in a soxhlet apparatus with CH_2Cl_2 (Merck, 99 %) for 24 h. Both of the final products were evacuated at 100 °C for overnight. The heterogenised sample is denoted as **A**.

6.3.2. Synthesis of Trimethylchlorosilane Modified Pd(NHC)-Silica (B)

For the synthesis of trimethylchlorosilane Modified Pd(NHC)-Silica (B) the free silanol groups of (A) was modified by silylation of the as-synthesized samples using trimethylchlorosilane (Scheme 6.1.). In an effort to significantly block the -OH groups of the material while maintaining a uniform Pd distribution, A was used as the support material. Prior to silylation, the as-synthesized **A** sample was evacuated overnight at 100 °C. Silylation of the samples was performed under reflux in dried $CHCl_3$ while being stirred in an oil bath. 2.5 mmol of trimethylchlorosilane (Aldrich, 98 %) in 40 mL chloroform was used per 1 g of the dried amorphous silica. The dried sample was refluxed in the TMCS/Chloroform solution for 24 h. The silylated sample was then filtered off and washed with $CHCl_3$. Finally, to rinse away any residual TMCS, a 24 h

Soxhlet extraction with CH_2Cl_2 was performed. The final product (light orange) was evacuated at 100 °C for overnight (**B**).

6.3.3. Synthesis of Imidazolidinium Salt Modified Pd(NHC)-Silica (C)

Modification of free silanol groups was also performed by using imidazolidinium salt 63 (Scheme 4). The reaction was carried out in a 3-necked round bottomed flask equipped with a condenser and a dropping funnel under Ar. A suspension of 1.5 mmol of imidazolidinium salt (white) **63** in 40 mL dried $CHCl_3$, was drop wise added per 1 g of **A** that was evacuated at 100 °C before modification. The suspension was placed in a preheated oil bath at reflux with magnetic stirring for 24 h. The resulting solid (**C**) was obtained by filtration, extracted with CH_2Cl_2 in soxhlet apparatus, and finally dried at 100 °C under vacuum for 24 h.

6.3.4. Synthesis of Imidazolidinium Salt (63) Modified Silica

The reaction was carried out in a 3-necked round bottomed flask equipped with a condenser and a dropping funnel under Ar. A suspension of 1 mmol of imidazolidinium salt (white) **63** in 40 mL dried $CHCl_3$, was drop wise added to 1 g of acid treated inorganic support that was evacuated at 100 °C before modification. The suspension was placed in a preheated oil bath and refluxed with magnetic stirring for 24 h. The resulting solid was obtained by filtration, extracted with CH_2Cl_2 in soxhlet apparatus, and dried at 100 °C under vacuum for 24 h. The Salt modified pure silica sample will be denoted as Silica-Salt.

6.4. Catalyst Characterization

Catalysts were characterized by use of several routine methods: IR, AAS, Elemental Analysis, BET Analysis and ^1H and ^{13}C NMR.

6.4.1. IR Spectrum of the Catalysts

DRIFTS experiments were carried out using Nicolet Magna 550 FTIR spectrometer equipped with Spectra-Tech Collector II model 0030-0XX diffuse reflectance accessory. The spectra were collected at an 8 cm^{-1} resolution (4 cm^{-1} data spacing) and averaged over 32 scans. Samples were prepared with KBr, 1 mg of sample was mixed and completely dispersed in 10 mg KBr.

6.4.2. Determination of Pd Content

The palladium content of the catalyst was determined by atomic absorption spectroscopy (Solaar AA Spectrometer Thermo Elemental). The dissolved samples were prepared according to the microwave digestion method, which is summarized below.

A mixture of 3 mL concentrated HNO_3 (Merck, 65%), 2 mL concentrated HF (Merck, 40 %), and 1 mL $HClO_4$ (Riedel-de Haën, 65 %) were added over 100 mg of a catalyst and these mixtures were heated in the Ethos Plus Microwave Labstation furnace according to the following heating program:

Step	Time (min)	Temperature (^oC)	Microwave Power(W)
1	4	120	500
2	4	150	550
3	5	180	550
4	17	180	600

At the end of this program, the digested samples were diluted to 50 mL. Standard solutions (1, 2, 3, 4, 5 ppm) were prepared from standard stock solution (0.5 mol/L) of 1000 ppm palladium(II)nitrate (Merck) in nitric acid for AAS analysis.

6.4.3. Elemental Analysis

Elemental analyses were performed by the TUBITAK ATAL Laboratories by using LECO CHNS-932 instrument. Samples were prepared by drying at 100 °C in an oil bath under vacuum for 2 days.

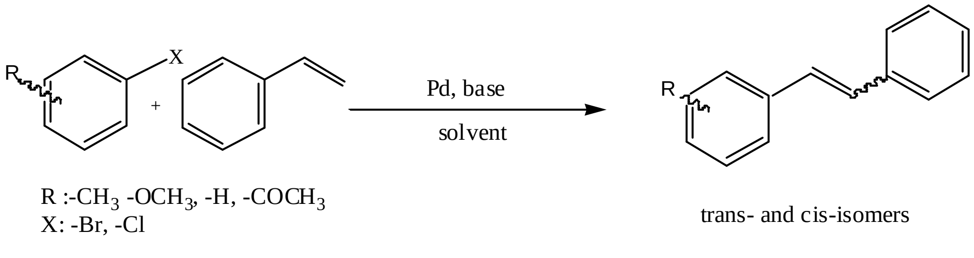
6.4.4. BET Analysis

Specific surface areas of the catalysts and the pure support material were measured using a static process by means of a Micromeritics ASAP 2010 instrument using nitrogen at 77 K. The specific surface area was calculated by the BET method and average pore diameters and pore size distributions were calculated from the adsorption branch of the isotherm using the Barrett, Joyner and Helenda (BJH) method. All samples were degassed overnight at 423 K.

6.4.5. NMR

^{1}H and ^{13}C NMR spectra of **64** were recorded on a Varian AS Mercury + 400 MHz spectrometer. *J* values are given in Hz.

6.5. General Procedure for the Heck Reactions



Scheme 6.4. Reaction conditions: 4 mmol aryl halide, 4.8 mmol styrene, 6 mmol base, 2.5 mmol of hexadecane, 0.5 or 1.5 mol % Pd, 10 mL DMF or DMAc, 140 °C.

Prior to use, the heterogenized catalyst was dried under vacuum for 1 day at 100 °C. For the Heck reactions (Scheme 6.4.), 4 mmol of aryl halide, 4.8 mmol of styrene (Fluka, >99 %) (alkene), 6 mmol of base (NaOAc.3H_2O, Carlo Erba, %99-101), 2.5 mmol of hexadecane (Merck, > 99%) (internal standard) and 10 mL of solvent DMF (Lachema) were introduced into a 3-necked round bottomed flask containing 0.5 mol % Pd (as heterogeneous catalysts) which was equipped with a condenser and a septum. The reactor was then placed in a preheated oil bath at 140 °C with vigorous stirring. Small amount of samples were periodically withdrawn by syringe during the reaction, diluted in CH_2Cl_2 and analyzed by GC. The conversions were calculated based on hexadecane as internal standard. The course of the reaction was followed until no further increase on the conversion is observed. After cooling to the room temperature the catalyst was recovered by filtering through a membrane filter with 0.2 μm porosity. In order to remove adsorbed organic substrates and bases, it was first washed with CH_2Cl_2 and then with CH_3OH (Riedel-de Haën, 99.7 %). A small sample of the reaction mixture was collected for GC analysis and the remaining reaction mixture was taken for Pd analysis. For the recycling studies, a catalyst issue, dried at 100 °C for 2 h, from a first run was used without any further treatment.

6.6. Leaching Test

The heterogeneity of the catalysts was evaluated by digesting the filtrate after each reaction completion. The filtrate was digested in Teflon beakers by addition of 20 mL H_2O, 1 mL H_2O_2 (Merck, 99 %) and 2 mL of HNO_3 after all the organic solvent was completely evaporated. The Pd content in the digested residue was determined by using AAS as described before.

6.7. GC Method

The samples were analyzed by GC/MS (Varian Star 3400 CX gas chromatograph and Varian Saturn 2000 GC/MS/MS, DB5, 30 m, 0.25 mm column with 0.25 μm film thickness) and GC (Shimadzu GC-17A on a 30 m, 0.25 mm capillary column (5 % Dimethylsiloxane, 95 % phenyldimethylsiloxane) with a 0.25 µm film thickness and a FID detector).

The GC and GC/MS programs applied throughout the analysis was as follows: the column temperature was 40 ºC at the beginning of the program and it was heated with a rate of 10 ºC / min up to 250 ºC, then it was kept at this temperature for 3 min. Throughout the analysis the injector and detector temperatures were kept constant at 280 ºC and 300 ºC, respectively. The analysis was performed on a split mode with a split ratio of 1/50. A sample of GC and GC\MS chromatogram of a reaction taken at this temperature program is given in Figure 6.1.

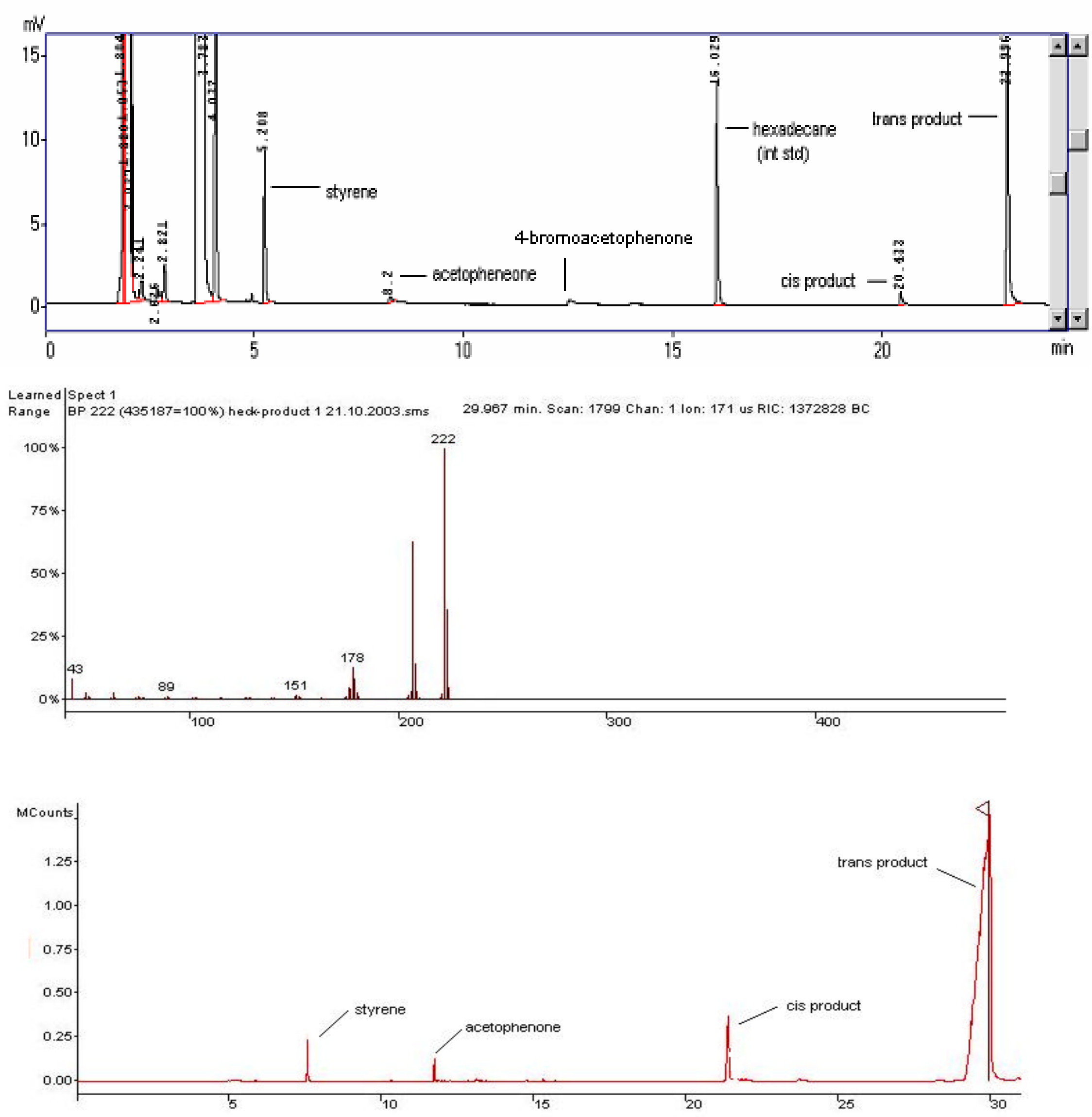


Figure 6.1. GC and GC/MS chromatogram of a selected Heck Reaction (styrene and p-bromoacetophenone)

6.7.1. Calculation of Reactant and Product Amount on GC

For the calculation of amount of reactant and products, initially response factor of each reactant and product for the set temperature program of GC was determined. Hexadecane was used as an internal standard. The amount of internal standard does not change throughout the reaction, so the response factor of each compound was determined according to the amounts and areas under the peaks of internal standard and standard compound of interest. For the determination of the response factor of a compound, a known amount of standard compound together with a known amount of internal standard dissolved in the reaction solvent and diluted with dichloromethane is injected to GC. After the analysis is completed according to the set temperature program, equation (6.1) is used for the determination of response factor. Since we did not have the standard compounds of cis and 1,1-diethene derivatives, R.F. of the trans product was used for the calculation of the amount of them.

$$\text{R.F.} = \left(\frac{\text{internal standard area}}{\text{compound area}}\right) \times \left(\frac{\text{compound amount}}{\text{internal standard amount}}\right) \qquad (6.1.)$$

In order to calculate the amount of both reactant and products at any time of reaction, aliquots of reaction sample were taken from the reaction flask at that time were injected to GC. At the end of GC analysis, taking the amount of hexadecane and the area under the hexadecane peak into account, equation (6.2) was used in order to calculate the amount of the reactant and products at that time.

$$\text{amount of compound} = \left(\frac{\text{internal standard amount}}{\text{internal standard area}}\right) \times \text{R.F.} \times \text{compound area} \qquad (6.2.)$$

6.7.2. Calculation of Reactant Conversion, Product Yield and Recovery

Reactant conversion at any time is calculated using equation 6.3:

$$(\text{Reactant Conversion})_t\ \% = \frac{\left((\text{Reactant})_i - (\text{Reactant})_t\right)}{(\text{Reactant})_i} \times 100 \qquad (6.3.)$$

where $(\text{reactant})_i$ is the weight of reactant at the beginning of the reaction and $(\text{reactant})_t$ is the weight of reactant at time t.

Product yield of a molecule was calculated according to the following equation (6.4):

$$\text{Product Yield} = \frac{\text{moles of product}_t}{\text{initial moles of reactant}} \qquad (6.4.)$$

Product recovery at any time of reaction is calculated according to the following equation (6.5):

$$\text{Product Recovery} = \frac{(\text{Total of Product yield})}{(\text{Reactant Conversion})_t\,\%}\, x\, 100 \qquad (6.5)$$

6.8. PURIFICATION OF THE PRODUCTS

Various types of products were purified by using column chromatography or crystallization techniques in this study.

The reaction mixture, which contained styrene derivatives were separated from catalyst by filtration. Then the catalyst was washed with dichloromethane and water, aqueous phase was extracted. The organic phase was dried over sodium sulphate and solvent was removed by using evaporator. The product was purified by using column chromatography (diameter of column 1.5 cm) on silica gel (Merck, Silica Gel 60) (6-8 g) using hexane-dichloromethane (10:1) or only hexane as an eluent.

CHAPTER 7

RESULTS AND DISCUSSIONS

Palladium complexes of N-heterocyclic carbene ligands (NHCs), in particular have proved to be excellent catalysts for C-C coupling reactions especially the Heck reaction. The NHC complexes are cost efficient to prepare, insensitive to air and moisture and are thermally stable in both the solid state and in solution; the carbenes are non-dissociative ligands. However, the development of new ligands or the application of existing ligands in these reactions, particularly those involving aryl chlorides as substrates, is still of considerable importance. Although the nature of the NHC ligand on complexes has a tremendous influence on the rate of catalyzed reactions, the use of saturated NHC ligands especially in heterogeneous systems in coupling reactions is a neglected area. Recently, a saturated carbene complex of palladium was immobilized into inorganic oxide particles and successfully applied in the Suzuki reaction of chloroarenes [92].

In this study, we synthesized three types of catalysts, which were Pd(NHC) Silica (**A**) and Pd(NHC) Silica-TMCS (**B**) and Pd(NHC) Silica-Salt (**C**) and tested their activity in the Heck coupling reaction. The Heck coupling reactions were carried out in the presence of different aryl halides. Recycling studies were performed as well.

7.1. Synthesis of Palladium N-heterocyclic Carbene Pd(NHC) complex, 64

The preparation of the salt **63** was readily accomplished by quarternization of imeo with the appropriate benzyl chloride as described by Çetinkaya et al [91]. We chose 1-(3-triethoxysilylpropyl)-2- imidazoline (imeo) as starting material for two reasons: (i) it is commercially available and (ii) it has a ‘sticky end’, $–Si(OEt)_3$, which can be linked to the surface of the inorganic matrix. The salt **63** is colorless, hygroscopic and freely soluble in $CHCl_3$, but insoluble in hexane or diethyl ether.

The reaction of 1-(benzyl)-3-(propyltriethoxysilane)imidazolidinium chloride, **63**, with the Ag_2O and after with $PdCl_2(CH_3CN)_2$ complex proceeded smoothly in

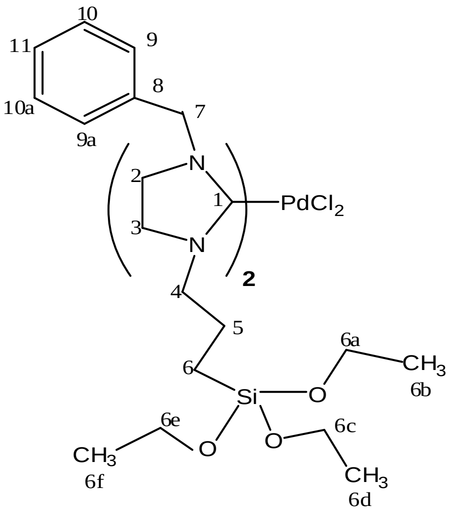
CH_2Cl_2 to give the bis[1-(benzyl)-3-(propyltriethoxysilane)imidazolidin-2-ylidene]dichloropalladium-(II) complex **64** as a pale yellow solid in 62 % yield (Scheme 6.1.).

The calculated % of C and N of Pd(NHC) complex **64** was 50.36 and 6.19 respectively. When the elemental analysis results (Table 7.2) were compared with the theoretical values, a slight difference could be revealed. However the C/N ratios were almost the same 8.13 and 8.03 for the calculated and elemental analysis values respectively. Thus a contamination might have occurred during sampling.

7.2. NMR

Salt **63**, was also characterized by spectroscopic techniques. The NMR spectrum of the salt was also in agreement with the results indicated earlier by Çetinkaya et al [91]. The ^{13}C NMR spectra provided a useful diagnostic for metal carbene complexes, showed that the carbene carbon was substantially deshielded (δ, 199.67 ppm) (Table 7.1). This new complex exhibited the typical spectroscopic signatures that were reported for other 1,3-dialkylimidazolin-2-ylidene-metal complexes [92]. The reason some of the unexpected shifts may be due to the different unexpected crystal structure of the complex **64**. This can be overwhelmed by preparing the single crystal of the catalyst **64** and having its single crystal X-ray and being fully informed of its crystal structure.

Table 7.1. ^{13}C and ^{1}H NMR spectra of bis[1-(benzyl)-3-(propyltriethoxysilane)imidazolidin-2-ylidene]dichloropalladium-(II) complex (100 and 400 MHz, $CDCl_3$)



	DEPT	$^{?}$C	dH	**gCOSY** $_{H-H}$
z	C, q	199.67	…..	…..
8	C, q	135.22;135.09 J=13 Hz	…..	…..
9, 9a	CH, d	127.76;127.67 J=9Hz	7.60;7.48 (2H, d, J=6.8 Hz; d J=1.6 Hz)	H10(H10a),H7
10, 10a	CH, d	127.67;127.53 J=14 Hz	7.36;7.20 (2H, t, J=6.8 Hz;7.6 Hz;ma))	H9(H9a),H11
11	CH, d	126.76;126.63 J=13 Hz	7.20 (1H, m)[a)]	H10(H10a)
6a,6c;6e	CH_2, t	57.43;57.31 J=12 Hz	3.86;3.73 (2H, q, J=6.8, 7.2, 7.2Hz;4H, q, J=6.8, 7.2, 7.2 Hz)	6b;6d;6f
7	CH_2, t	53.08;53.02 J=6 Hz	5.27;5.17 (2H, s)	H9(H9a)
4	CH_2, t	51.55;51.41 J=14 Hz	4.40;3.98 (2H, t, J=7.6,7.6 Hz; t, J=7.6,7.6Hz)	H5
2	CH_2, t	47.67;47.58 J=9 Hz	3.55 (2H, m)	H3
3	CH_2, t	46.77;46.72 J=5 Hz	3.36(2H, m)	H2
5	CH_2, t	20.73	1.97;1.80 (2H, m)	H4;H6
6b;6d;6f	CH_3, s	17.34;17.28 J=6Hz	1.24;1.16 (3H, t, J=6.8 , 7.2 Hz; 6H, t, J=6.8, 7.2Hz)	6a,6c;6e
6	CH_2, t	6.80;6.49 J=31Hz	0.80;0.53 (2H, m)	H5

a) Overlapping

7.3. Determination of Pd Content

The immobilization of **64** by refluxing with silica particles in a ratio of 0.01 g Pd per 1 gram of silica for 24 h gave the modified silica product Pd(NHC)Silica shown in Scheme 6.3. Palladium analysis was performed on this sample and showed a palladium loading of 0.88 ± 0.02 mmol g^{-1}, indicating that 88±2 % of the complex had been immobilized.

As stated earlier, the silanol groups, which are the reactive sites for silylation reaction on the silica surface, play an important role in the surface modification process. In order to understand the effect of free silanol groups in the course of the reaction two main routes are followed for the modification. In order to block these groups, TMCS and the salt **63** was used for the silylation. Modification with TMCS is a well known and a common process. It is well recognized that silylation of silica takes place through the reaction between TMCS and SiOH groups as follows [180].

$$\text{Si-OH} + \text{Cl-Si(CH}_3)_3 \ ? \ \text{Si-O-Si(CH}_3)_3 + \text{HCl}$$

A monolayer of trimethylsilyl (TMS) groups is thus covalently attached to the pore surface of silica. The fractional capping of the reactive hydroxy groups with an inert silane fragment reduced the susceptibility of the support surface to electrophilic attack, providing a convenient method for synthesizing Pd-grafted materials with a 0.48± 0.02 % Pd.

As a second route, a novel approach for the modification of the support was progressed by using imidazolidinium salt **63**. The AAS gave a 0.55 ± 0.04 wt % of Pd.

7.4. Elemental Analysis

Elemental analyses revealed the presence of C and N for all the modified and unmodified materials Table 7.2.

Table 7.2. Elemental analysis results of synthesized materials.

Material	**C % (w/w)**	**N % (w/w)**
A	2.54	0.46
B	4.67	0.38
C	6.91	1.14
Silica modified with **63**	10.23/6.47	1.83/1.12
Pd(NHC) complex **64**	48.75	6.07

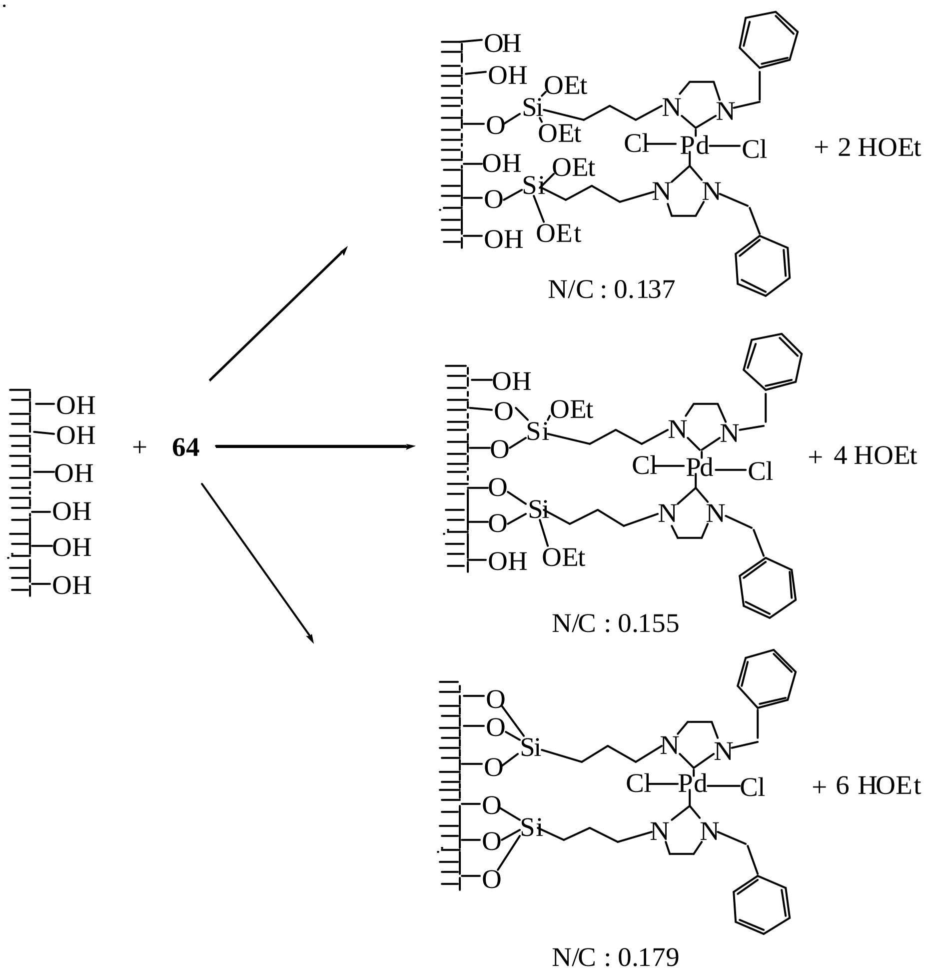
The amount of **64** anchored to Silica, catalyst **A**, can be calculated using the date in Table 7.2 as in Equation (7.1);

$$\frac{0.46\ \text{g N}}{100\ \text{g Silica}} \times \frac{1000\ \text{mg N}}{1\text{g N}} \times \frac{1\ \text{mmol N}}{14\ \text{mg N}} \times \frac{1\text{mmol}\ \mathbf{64}}{4\ \text{mmol N}} = \frac{0.082\ \text{mmol}\ \mathbf{64}}{1\ \text{g Silica}} \qquad (7.1)$$

0.082 mmol **64** containing 1 g of Silica also contains 0.082 mmol of Pd. This result was in accordance with the Pd analysis performed with AAS. Equation (7.2)

$$\frac{0.88\ \text{g Pd}}{100\ \text{g Silica}} \times \frac{1\ \text{mol Pd}}{106.4\ \text{g Pd}} \times \frac{1000\ \text{mmol Pd}}{1\ \text{mol Pd}} = \frac{0.083\ \text{mmol Pd}}{1\ \text{g Silica}} \qquad (7.2)$$

The silanol groups on the silica which are the reactive sites for silylation play an important role in the modification process. Under anhydrous conditions, three possible reactions can occur for the catalysts **A**:



(7.3)

(7.4)

(7.5)

There was no nitrogen and carbon associated with the starting silica gel particles, but after modification with **64** it contained 2.54 and 0.46 % C and N respectively. The calculated N/C ratio for catalyst **A** was 0.18 (0.46/2.54) which was same with the Equation 7.5. Thus, a complete grafting of –OEt groups was observed for **64**. The same calculation method was used for the rest of the materials.

The C and N % of **B** was 4.67 and 0.38 respectively (Table 7.2). When C % was considered (including the ones in the structure of **64**), approximately 0.59 mmol of TMCS was successfully anchored to 1 g of silica.

The C and N % of **C** is 6.91 and 1.14 respectively (Table 7.2). It was calculated that 1 g of the catalyst contain 0.56 mmol and 0.48 mmol salt **63** (including the ones in the structure of Pd(NHC) complex) with respect to C and N %. The calculated N/C ratio 0.155 (0.68/4.37), same with the theoretical value, showed that one –OEt group of **63** remained unattached.

Two samples of pure silica modified with **63** were prepared. The C and N % of Silica modified with **63** was 10.23/6.47 and 1.83/1.12 respectively that corresponded to 0.65-0.4 mmol of **63** per 1 g of silica.

7.5. BET Analysis

N_2 sorption isotherm is an efficient way for providing information about the pore system of materials. The isotherms had gradual changes at each stage of modification as expected because the organic fragments or metal complexes entered the channels. All the catalytic materials gave similar adsorption–desorption isotherms. The pore volume and size reduced apparently after modification (illustrated in Table 7.2.), also indicated that the organic groups or the metal complexes were successfully introduced into the inner channels (0.73 to 0.49 cm^3/g). The pore distribution of modified catalysts was around 56 Å. The results were summarized in detail in Table 7.3.

Table 7.3. Textural parameters and elemental content of the catalytic materials

Materials	Surface Area[a] (m^2/g)	Pore Volume[b] (cm^3/g)	Diameter[c] (Å)
Silica	335.0148	0.73	71.2757
Pd(NHC)Silica	271.3082	0.49	55.5167
Pd(NHC)Silica-TMCS	265.1488	0.50	55.9048
Pd(NHC)Silica-Salt	292.5260	0.54	56.9399

[a] BET surface area

[b] Single point total pore volume

[c] Pore diameter according to the maximum of the BJH pore size distribution

7.6. IR Spectrum of the Materials

The FT-IR spectrum of the pure silica and the palladium-modified silica samples (Figure. 7.1.) also supported the successful anchoring.

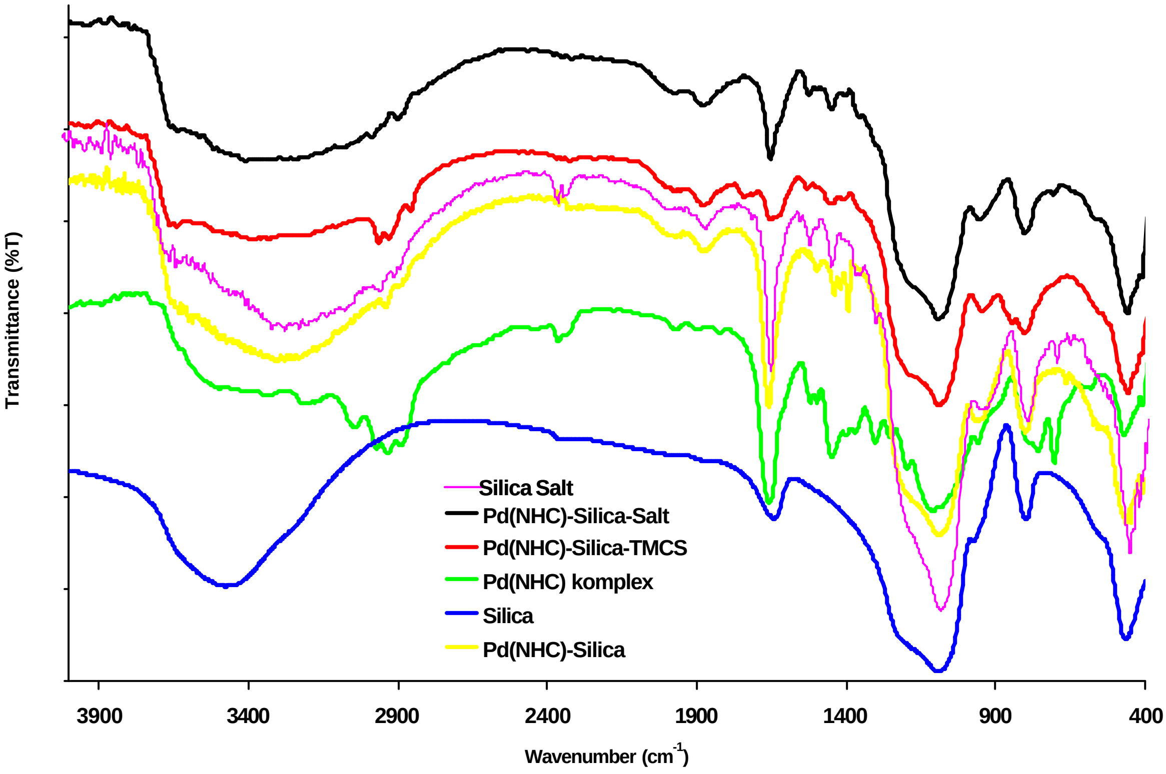


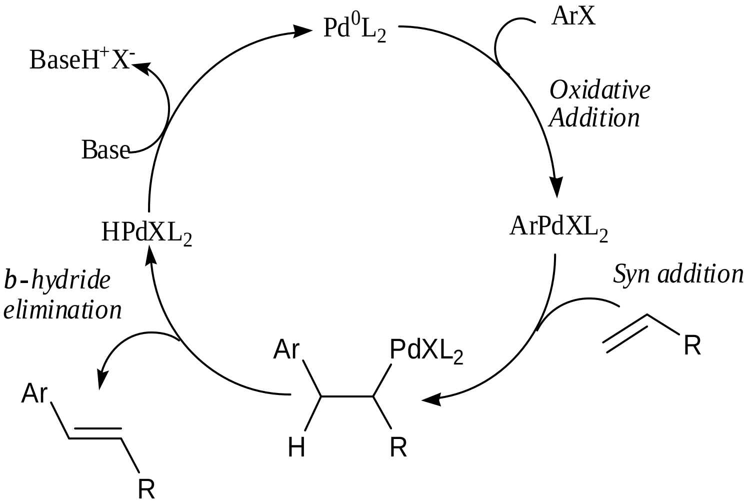
Figure 7.1. FTIR spectra of the catalysts and the support

It is assumed that the Soxhlet extraction process removed all of the physisorbed **64** or salt **63** and TMCS on the silica. IR confirmed the fact that structures of the starting complexes were maintained when attached to the surface and show only minor frequency shifts from those of the corresponding complex. The palladium complex exhibited a characteristic NCN stretching vibration at 1511 cm^{-1}. The spectrum of all the modified catalysts displayed absorption at 3430 cm^{-1}, which indicated the presence of physisorbed H_2O. In addition, there were NCN stretching bands at 1450 and 1620 cm^{-1}, an imide ring stretching vibration at 1381–1396 cm^{-1}, as well as a strong asymmetric Si-O–Si stretching vibration at 1230–1111 cm^{-1}. Moreover, a characteristic SiO_4 tetrahedron ring was observed at 806 cm^{-1} and O-Si-O deformation was observed at 471 cm^{-1} and a symmetric CH_2 stretching band appeared at 2894 cm^{-1}. Due to its hygroscopic character the FTIR spectra of the salt **63** could not be recorded.

7.7. Heck Coupling Reactions

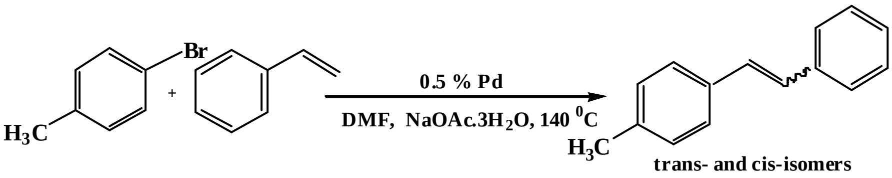
The catalytic activity of saturated Palladium N-heterocyclic dicarbene complex **64** immobilized catalyst (**A**), and all its modified counterparts Pd(NHC)Silica-TMCS (**B**) and Pd(NHC)Silica-Salt (**C)** were studied in the arylation reaction of an olefin. The catalytic activity of these materials was investigated in detail with activated (electron poor), non- and deactivated (electron neutral and electron rich) aryl halides, and styrene (electron poor olefin) as the vinylic substrate. In this study, 0.5-1.5 mol % Pd was used for all aryl bromides and aryl chlorides respectively. Reusability studies were also performed for all catalysts.

At the beginning of our study the catalytic activity of all catalysts were tested with 5 aryl halides that have different activities. The reactivity order decreases in the order of 4-iodoanisole > 4-bromoacetophenone > 4-bromonitrobenzene > bromobenzene > 4-bromotoluene > 4-bromoanisole > 4-chloroacetophenone. Since the strength of the sp^2-carbon-halogen bond mainly determines the reactivity difference in carbon-carbon bond formation reactions, the rate determining step in Scheme 7.1. is the oxidative addition of palladium into a carbon–halogen bond.



Scheme 7.1. Reaction mechanism of Heck reaction.

Table 7.4. Heck Reactions with p-bromotoluene and styrene[a]



Entry	Catalyst	Recycle	Time(h)	Conversion[b] %	Yield %	
					-trans	-cis
1	**A**	1	28	100	90	7
2	**A**	2	25	43	31	7
3	**B**	1	26.5	100	89	7
4	**B**	2	14	20	12	4
5	**C**	1-7	22.5	100	89[81][c]	8

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (4 mmol): styrene: NaOAc.3H$_2$O, DMF(10 mL) was used as the solvent, [b]Conversion of the aryl halide using hexadecane as internal standard.[C] isolated yield

First of all, Heck reaction of bromotoluene (a deactivating aryl bromide) (Fluka, >98 %) with styrene was performed. Although all catalysts showed 100 % conversion in their first run, only salt **63** modified catalyst (**C**) could be recycled without any loss in the activity at least for 7 uses (Table 7.4). **A** and **B** displayed gradual decrease even in the second run (43 and 20 % respectively). No induction period was observed for all the catalysts even after recycling (Figure 7.2.).

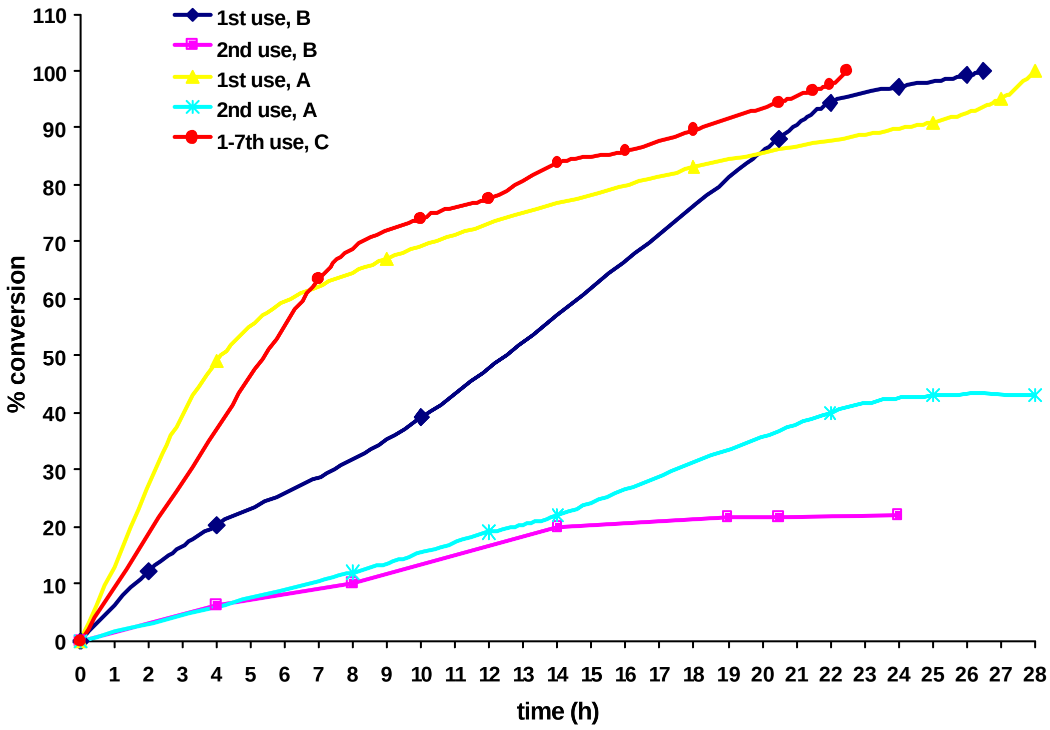
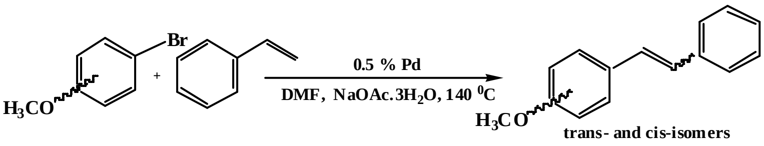


Figure 7.2. Comparison of activities of the three types of catalysts in the Heck reaction of bromotoluene and styrene.

When changing the aryl halide to bromoanisole (Merck, >98%), the influence of the catalyst type was more apparent. In the presence of a more deactivated bromobenzene derivatives bearing electron-donating ether groups, the Heck reaction with **B** surprisingly leaded to complete debromination. 89 % dehalogenation product, anisole was produced. When the same reaction was carried out in the same condition with only the change of solvent to DMAc, the expected Heck product with 78 % yield was obtained. In this case, the side product dropped down to 17 %. This fact guided us to the conclusion that dehalogenation reaction occurs at such a rate that was comparable to the overall C-C forming reaction rate at elevated solvents in the presence of **B**. When compared to thermodynamically more stable DMAc, DMF might be the source of hydride at high temperatures. In contrast to **B** (Table 7.5, entry 6), **C** gave only Heck product in 27.5 hours. The catalyst **C** demonstrated again a high catalytic activity and reusability even after seven recycles without having an induction period (Table 7.5. entry 8). When we used *ortho*-substituted aryl bromide such as 2-bromoanisole, the conversion was only 22 %. 10 % dehalogenation product was also formed. No further conversion was obtained after 8 hours (Table 7.5, entry 9). Thus, steric effect played a significant role in the reaction.

Table 7.5. Heck Reactions with p-bromoanisole and styrene[a]

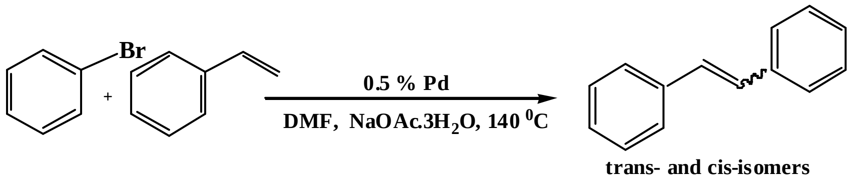


Entry	Catalyst	Recycle	Time(h)	Conversion[b] %	Yield % -trans	Yield % -cis
6	**B**	1	35.5	100	0	0
7	**B**	1	56	100	72[c]	2
8	**C**	1-7	22.5	100	89	7
9	**C**	1	8	22	12[d] [10][e]	-

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (4 mmol): styrene: NaOAc.3H_2O, DMF(10 mL) was used as the solvent, [b] Conversion of the aryl halide using hexadecane as internal standard. [c] DMA (10 mL) used [d] 2-bromoanisole was used as aryl halide [e] isolated yield

In the case of bromobenzene (Merck, 99 %), a non-activated bromoarene derivative, all types of catalysts could be converted with high yields in the range of 88-90 % in the first run (Table 7.6. entry 10, 14 and 16). The longer reaction times were necessary for > 98 % conversion for **B** and **A** (22 and 21 h, 90 % and 88 % yield respectively) when compared with **C** (15.5 h, 90 % yield). After separation and washing, the heterogeneous catalysts **A** and **B** were tested for their reuse under the same conditions as for the initial run without any regeneration. Noticeable deactivation was displayed in the case of **B**, the conversion dropping down to 52 % in the second run. When **A** was used, the activity dropped significantly after 4th run (33 %). Low yields, as low as < 4 % of 1,1- diphenylethene was formed in the presence of **C**.

Table 7.6. Heck Reactions with bromobenzene and styrene[a]



Entry	Catalyst	Recycle	Time(h)	Conversion[b] %	Yield % -trans	Yield % -cis
10	**A**	1	21	100	88	8
11	**A**	2	22	100	85	8
12	**A**	3	28	90	84	4
13	**A**	4	23	33	28	4
14	**B**	1	22	100	90	6
15	**B**	2	29	52	44	6
16	**C**	1	15.5	100	90	8

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (4 mmol): styrene: NaOAc.3H$_2$O, DMF(10 mL) was used as the solvent, [b] Conversion of the aryl halide using hexadecane as internal standard.

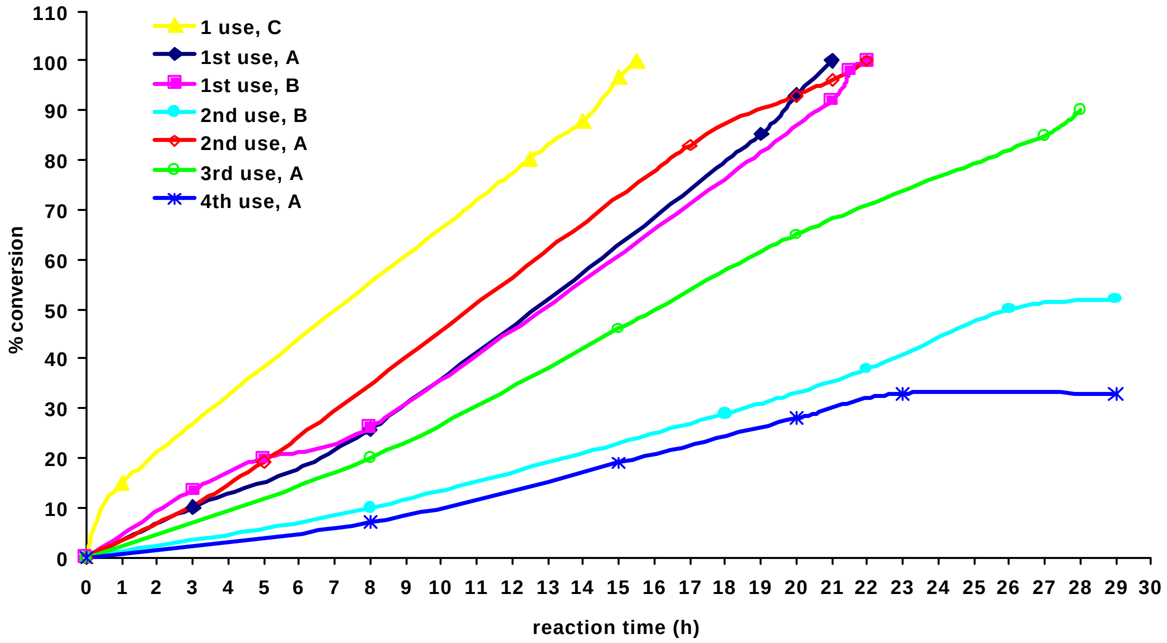
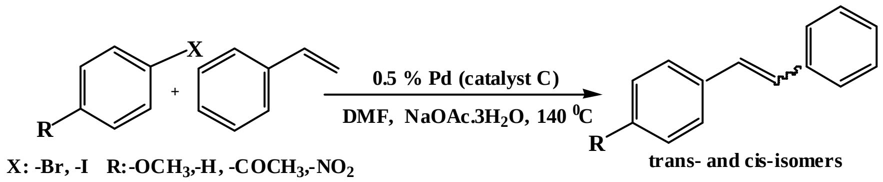


Figure 7.3. Comparison of activities of the three types of catalysts in the Heck reaction of bromobenzene and styrene.

Table 7.7. Heck Reactions with different arylhalides and styrene[a]



Entry	Arylhalide	Recycle	Time (h)	Conversion[b] %	Yield %	
					-trans	-cis
17	4-iodoanisole	1-7	1	98	89	5
18	4-bromoacetophenone	1-7	1	98	90	4
19	4-bromonitrobenzene	1	2.5	90	84 [77][c]	4
6	4-bromobenzene	1	15.5	100	90	8
5	4-bromotoluene	1-7	22.5	100	89 [81][c]	8
8	4-bromoanisole	1-7	27.5	100	87	7
20	3-bromopyridine	1	2.5	89	77 [71][c]	7
21	3-bromothiophene	1	13	24[d]	0	-

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (4 mmol): styrene: $NaOAc.3H_2O$, DMF(10 mL) was used as the solvent, [b] Conversion of the aryl halide using hexadecane as internal standard. [c] isolated yield [d] no further conversion was observed

Full conversions were obtained for the coupling of p-bromoacetophenone (Merck, > 98 %) with styrene after 1.25 hours with 0.5 mol % of **C** (Table 7.7. entry 18). This was reused again at least 7 times without any decrease in the activity. C-I bond is the weakest bond among the other C-halide bonds. So, carbon-iodine bond is easily broken and the oxidative addition of palladium to carbon easily occurs. When iodoanisole (Merck, >98%) was used in the same conditions with the same catalyst, the reaction occurred readily, and gave 89 % yield in 1 hour (Table 7.7. entry 17) as expected. Only < 2.1 % side product was formed. 7 successive recycles were also performed for iodoanisole. In the case of p-bromonitrobenzene (Merck, > 99 %), an electron poor aryl bromide, the same catalyst showed 90 % conversion in 2.5 hours. Conversion graphs of the aryl bromides mentioned above was represented in Figure 7.4.

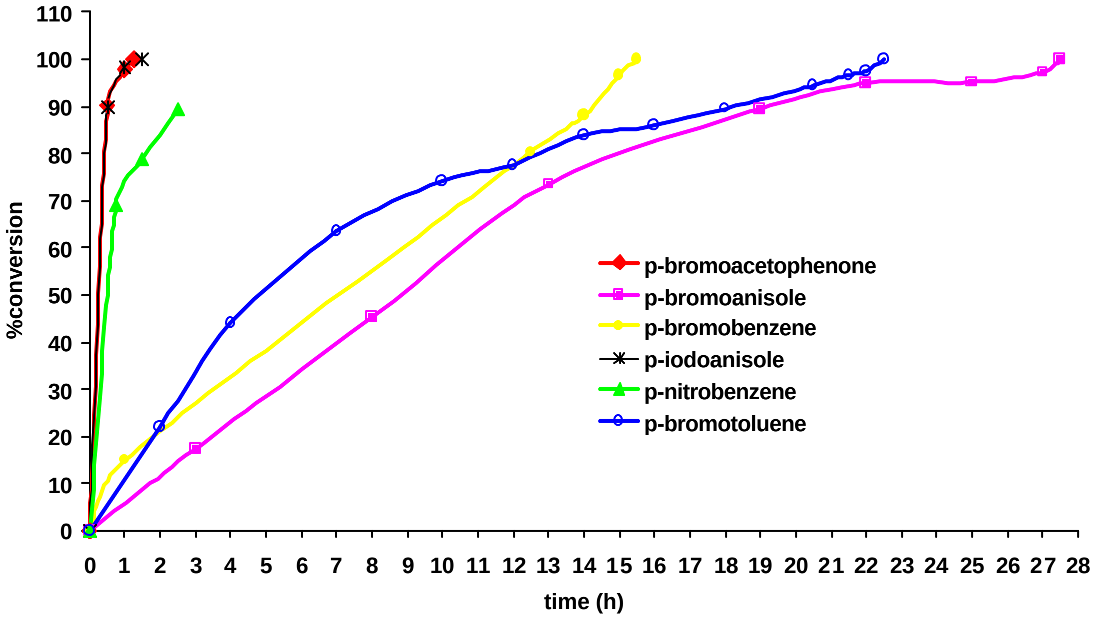
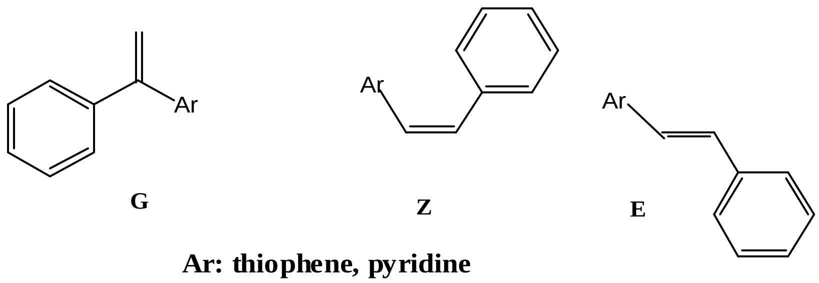


Figure 7.4. Heck reactions with different aryl bromides with **C**.

Heteroaryl compounds have important biological properties. The palladium-catalysed Heck reaction between heteroaryl halides and alkenes provides a very efficient method for the preparation of several heteroaryl derivatives [186]. A few ligands have been successfully used for the reaction in the presence of these substrates. The most popular ones are triphenylphosphine or tri-*ortho*tolylphosphine. In most cases, fast decomposition of the catalysts occurs, and 1–10 % of these catalysts must be used. Finally, we tried to determine the efficiency of **C** in the presence of heteroaromatic substrates such as 3-bromopyridine and 3-bromothiophene.

Due to the electronegativity of the nitrogen atom, the a and ? positions of halo pyridines should be the most susceptible to the oxidative addition to Pd(0) [186]. Albeit, we observed high reaction rates for the coupling with the β- substituted bromopyridine. Pyridines are p-electron deficient heterocycles. The regioselectivity of the addition to p-electron deficient heterocycles should be in favor of the linear isomers *Z* and *E* (Equation 7.6).

(7.6)



Ar: thiophene, pyridine

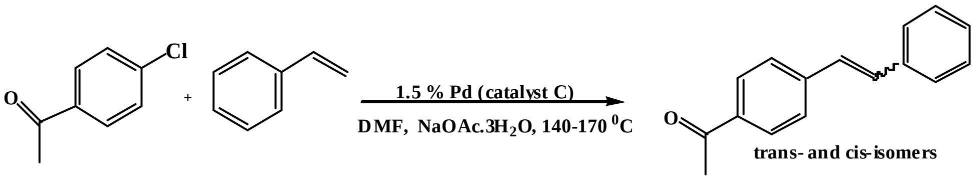
Thiophenes are p-electron excessive [186]. With these heterocycles, the regioselectivity of the reaction should be in favor of the branched isomer *G* (Equation 7.6). We observed the formation of mixtures of linear products. As expected, in the presence of halo pyridines the regioselectivity was generally in favor of the linear isomers. In the case of 3-bromopyridine 77 % yield (71 % isolated yield) was obtained within 2.5 hours (Table 7.7, entry 20). The low yield could be ascribed to the formation of self coupling product. When compared with 3-bromopyridine, 3-bromothiophene showed lower conversion (24 % in 13 hours) forming only the 19 % self coupling byproduct (17 % isolated yield).

Another important issue concerning the heterogeneous Heck reaction is the possibility to activate the economically more interesting aryl chlorides. To examine this possibility, we studied the reaction between 4-chloroacetophenone (Merck, > 99 %) and styrene using **C** as heterogeneous catalyst that showed superior activity among the others. As expected, the results reported in Table 7.8 show that the activation of aryl chlorides required a higher temperature than did the activation of the bromo derivatives. This result paralleled the halogen-carbon bond energy, which was calculated for bromoacetophenone (ca. 80.5 kcal/mol) and chloroacetophenone (ca. 96 kcal/mol) [185]. However, one should also consider that the Pd-Cl bond is stronger in the resulting Pd complex, and this stronger bond makes the thermodynamics for activation of aryl chlorides more favorable.

The reaction between p-chloroacetophenone and styrene at 140 °C with **C** gave a 13 % yield. A 24-hour induction period was observed (Figure 7.5.). On the other hand when the reaction was performed at 170 °C, the yield increased to 64 %. When this catalyst was used for the second time, no further conversion (50 %) was observed after

4 hours (Figure 7.5.). Unfortunately, the catalyst showed no activity at all in the third run (Table 7.7 entry 25).

Table 7.8. Heck Reactions with p-chloroacetophenone and styrene[a]



Entry	Recycle	Temperature (°C)	Time (h)	Conversion[b] %	Yield %	
					-trans	-cis
22	1	140	28	13	5	-
23	1	170	21	64	56	-
24	2	170	4	50	45	-
25	3	170	24	0	0	-
26c	1	170	21	88	81	2
27c	2	170	4	33	24	1

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (2 mmol): styrene: NaOAc.3H_2O, DMF(10 mL) was used as the solvent, [b] Conversion of the aryl halide using hexadecane as internal standard.[c] addition of immobilized salt

As a novel strategy, we added saturated NHC salt **63** immobilized pure silica to the reaction mixture (Table 7.8, entry 26). The addition of immobilized salt (containing 0.52 mmol salt) noticeably increased the activity to 88 %. Although this catalyst **C**-immobilized salt mixture showed higher activity when compared with the reaction with only catalyst **C** in the first run (Figure 7.5.), in contrast to the first run, the activity of it was lower in the second run 50 % and 33 % respectively (Table 7.8.entry 24 and 27). Further studies will be performed for the optimization of amount of salt to improve the recycling. As a result, the increase of immobilized salt in the reaction media increases the yield.

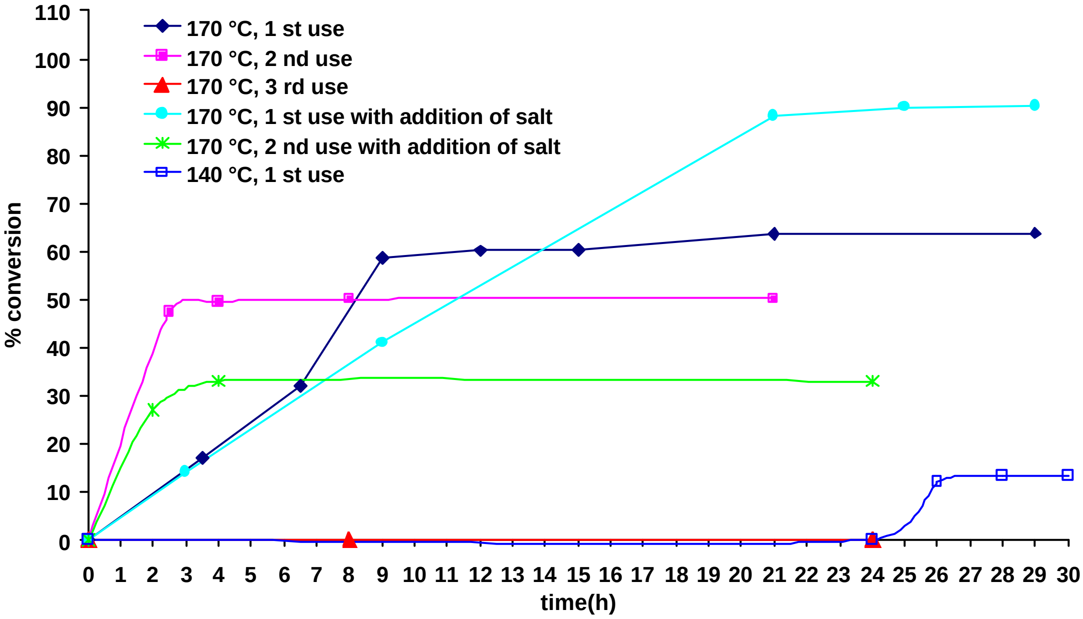


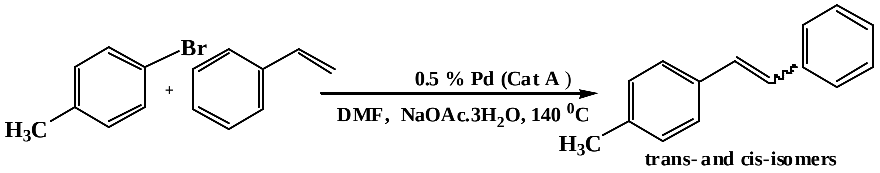
Figure 7.5. Effect of temperature and additive to the Heck reaction of chloroacetophenone and styrene.

In the last few years, 1,3-dialkylimidazolinium salts (such as **63**), that are conventional NHC precursors attract increasing attention in in-situ carbon-carbon coupling reactions, especially the Heck reaction. The effect of the presence of different types of saturated 1,3-dialkylimidazolinium salts in the homogeneous Heck coupling reaction is well documented [181]. To introduce these into the heterogeneous systems, salt **63** was immobilized to the pure support.

On the basis of the results, catalyst **C** showed superior activity when compared with the others. The reason of the superior activity of catalyst **C** might be attributed to the immobilized salt **63** or its nature. Thus, we performed a reaction similar to homogeneous in-situ reactions. The Heck reaction of 2 mmol p-bromotoluene with 1.2 mmol styrene was performed in the presence of 10 % immobilized salt **63** and $Pd(OAc)_2$ (0.5 % Pd) at 140 °C in 10 mL DMF. Even after 72 hours only 33 % of conversion was obtained.

Another test experiment that was carried out was performed at the standard reaction conditions in entry 24 but this time salt immobilized pure silica that contained the same amount of immobilized salt that catalyst **C** contained was added to the catalyst **A** (Figure 7.6). As seen in Figure 7.6 the catalyst showed high activity in the first run. A complete conversion was obtained within 21 hours. However, at the second use, for a complete conversion prolonged reaction time (28 hours) was required. No significant change in the reaction time was observed for a complete conversion in the 3rd, 4th and 5th use (27 hours). However the catalytic activity dropped significantly after the 5th run. Again no induction period was observed for all the runs.

Table 7.9. Effect of Additives to the Heck Reaction of p-bromotoluene and styrene in the presence of catalyst **A**[a]



Entry	Recycle	Time (h)	Conversion[b] %	Yield %	
				-trans	-cis
28[c]	1	21	100	87	8
29[c]	2	28	100	89	9
30[c]	3	27	100	88	9
31[c]	4	27	100	89	7
32[c]	5	27	100	89	8
33[c]	6	27	43	32	7
34[d]	1	24	100	88	8
35[d]	2	24	100	87	8
36[d]	3	24	41	34	7

[a] Typical reaction conditions: A molar ratio of 1:1.2:1.5 was used for the aryl bromide (4 mmol): styrene: NaOAc.3H_2O, DMF(10 mL) was used as the solvent, [b] Conversion of the aryl halide using hexadecane as internal standard. [c] addition of immobilized salt [d] addition of *n*-Bu_4NBr

As already mentioned in the literature, the effect of different additives is well documented [93]. An interesting salt effect was observed with *n*-Bu_4NBr [182-184]. Addition of this salt gave increased activity for this reaction, but this increased activity was accompanied by a dehalogenation reaction leading to the formation of dehalogenation by-product in 8.3 % yield.

Thus, we also performed the reaction in entry 26 but this time we added *n*-Bu_4NBr instead of immobilized salt (entry 32). The reaction took 24 hours in the first and the second run but in the third run again the conversion dropped down to 41 %.

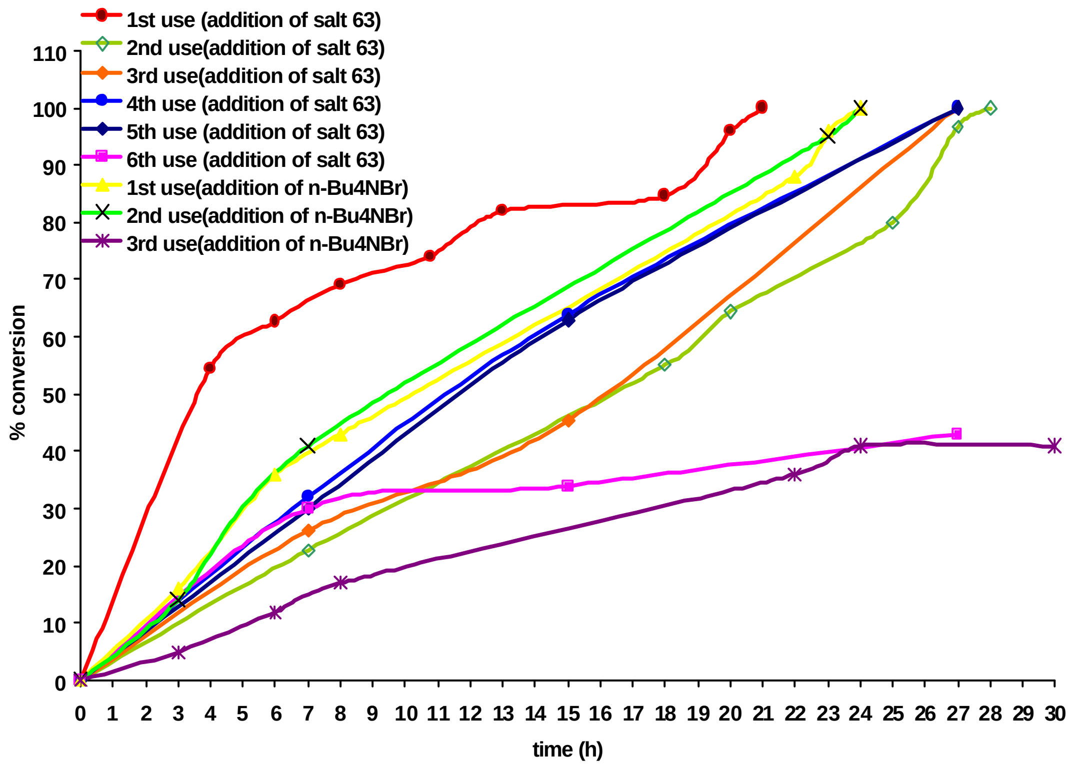


Figure 7.6. The effect of additives to the catalyst **A** in the Heck reaction of bromotoluene and styrene.

As a result of these experiments, we can surely conclude that for a high yield and a reusable catalytic system, the combination of immobilized salt **63** with the immobilized Pd(NHC) complex **64** or the direct use of **C** was an asset. The first test experiment showed that immobilized salt **63** was not the only reason of high activity besides the immobilized Pd(NHC) complex **64** played a complementary role in the Heck reaction. In addition *n*-Bu_4NBr had no positive effect on the continuous activity and reusability.

7.8. Heterogeneity Test

The leaching of active species from heterogeneous catalysts into solution is a crucial question in order to identify whether the active centers are immobilized to the inorganic support or whether they are dissolved palladium complexes in the homogeneous solution. In related precedents, it has been found [93] that the use of polar solvents and particularly DMF causes the partial leaching of Pd metal from the solid to the solution.

We have addressed the leaching by performing the experiment in a similar manner as the general procedure for Heck reactions, with the exception that the catalyst (**C**) was isolated from the reaction mixture by hot filtration via cannular to a three necked round bottomed flask containing equal amounts of base and the resulting filtrate under identical reaction conditions was allowed to react for a further 23 hours. No further reaction was noted after the catalyst removal (Figure 7.7.).

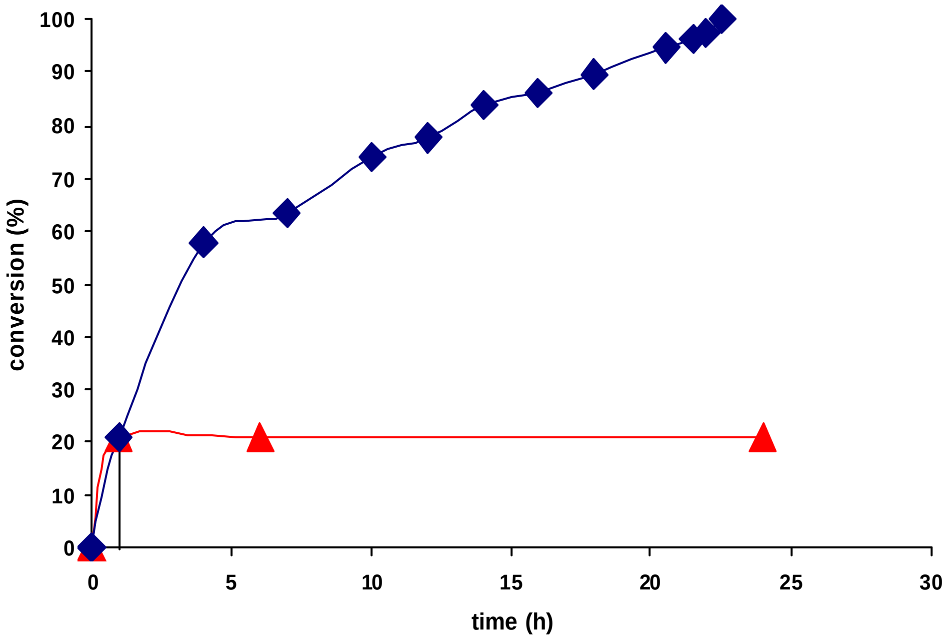


Figure 7.7. Time conversion plot for the Heck reaction of p-bromotoluene (1 mmol), styrene (1.2 mmol) and $NaOAc.3H_2O$ (1.5 mmol), 0.625 mmol hexadecane, in DMF (5 mL) at 140 °C: ◆ in the presence of **C** (% 0.5 mmol Pd); ▲ initiating the reaction as before in the presence of **C** (% 0.5 mmol Pd) and filtrating the solid in hot at the time indicated in the arrow and allowing the clear solution to continue the reaction.

The resulting solution was also analyzed by AAS. The same digestion procedure was carried out that was described before for the analysis of the resulting filtrate. The AAS analysis gave no detectable amount of palladium. Further, the recovered catalyst was tested in 7 successive cycles in the same conditions; the catalytic activity remains essentially undiminished (Table 7.4, entry 5). Thus no active species leached in the course of the reaction which meant that the reaction was truly heterogeneous. It could also be concluded that the reaction media was a right choice for this heterogeneous system. In addition to this, we have also tested the Pd amount of each reaction by digesting the reaction mixture (both the CH_2Cl_2 and MeOH phases). AAS analysis showed no detectable amount of Pd for the digested solutions of the first run experiment. Digestions for the rest of the experiments are being performed.

CHAPTER 8

CONCLUSION

As far as we are concerned, this study is the first representative example of Silica supported saturated Pd(NHC) complex used for the recyclable Heck Reaction. The yields were good to excellent (81-93 %) for all catalysts for the first run. In all reactions *trans* isomer selectivity is very high. Generally, no formation of 1,1-diarylethene was observed. This is in agreement with the fact that bis-carbene complexes are capable of *cis*-*trans*-isomerism [93]. Among the three catalysts, the salt modified one showed the highest activity and reusability. Unfortunately, the reusability of the other catalysts is not satisfactory to be an appropriate heterogeneous catalyst for the Heck reaction.

The effect of presence of free Si-OH groups in the course of reaction was studied by the modification method. By the help of modification the reactive hydroxy groups reduce the susceptibility of the support surface to electrophilic attack and also change the polar surface to apolar one. If blocking of the Si-OH groups have played a positive effect, Pd(NHC)Silica-TMCS should also have higher yields when compared with unmodified catalyst as seen in the case of the salt modified one. Thus the salt immobilized into the silica surface has played a direct role in the maintenance of the catalyst activity. The excellent cross-coupling activity furnished by the saturated NHC precursor modified catalyst may be attributable to the increase of electron-rich environment of the catalyst.

Results show that, a para-substituent on benzene ring has a significant effect on the reaction activity of all 3 types of catalysts. The trend was as expected, lower reaction times for 4-iodoanisole and higher for 4-bromoanisole. No induction period was observed for none of the catalysts. In addition, we found that replacing DMF by DMAc as solvent would disfavor the formation of anisole, one of the main side products of the reaction (Table 7.5, entry 6).

An important point concerning the use of heterogeneous catalysts is its lifetime, particularly for industrial and pharmaceutical applications of the Heck reaction. The Salt modified catalyst (**C**) has not only showed high activity and stereoselectivity for the

Heck reaction but also offers practical advantages. The possibility of carrying out the reactions without exclusion of air and moisture and using nondried solvents were of particular interest for practical applications. In addition, separation of the catalyst by filtration was easy and possible within a short time. After separation and washing, the heterogeneous catalyst was used at least 7 times under the same conditions as for the initial run of the catalyst without any regeneration and loss in the activity for various activated, nonactivated and deactivated aryl bromides. The cumulated turn over number (TON) for the reactions being 1358-1400 as calculated. It should be noted that the catalyst has potential to offer even much higher TONs provided it preserves its activity in many more recycles [187]. We also report a direct activation of aryl chlorides using a heterogeneous catalyst under standard reaction conditions. No undesired reactions (i.e., strong dehalogenation of the aryl chlorides, self coupling derivatives, or reacting solvent) were observed. It was found the catalyst also showed moderate activity towards 3-bromopyridine. Leaching tests revealed the heterogeneity of the system.

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