NOVEL MOLECULAR AND COLLOIDAL CATALYSTS FOR C-C BOND FORMATION PROCESSES

Angelica Balanta Castillo

Dipòsit Legal: T. 157-2012

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Doctoral Thesis

Angelica Balanta Castillo

"Novel molecular and colloidal catalysts for C-C bond formation processes"

DOCTORAL THESIS

Supervised by

Prof. Dra. Carmen Claver Cabrero and Dr. Cyril Godard

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2011

Universitat
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Departament de Química
Física i Inorgánica

Prof. Dra. Carmen Claver Cabrero, catedràtica del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili,

Faig constar:

Que el present treball, titulat “Novel molecular and colloidal catalysts for C-C bond formation processes”, que presenta Angelica Balanta Castillo per a l´obtenció del títol de Doctor, ha estat realitzat sota la meva direcció i la co-direcció del Dr. Cyril Godard, al Departament de Química Física i Inorgànica i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, 16 de desembre de 2011

Prof. Dra. Carmen Claver Cabrero Dr. Cyril Godard

UNIVERSITAT ROVIRA I VIRGILI
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El presente trabajo ha sido desarrollado con una beca FI financiada por la Generalitat de Catalunya. Los siguientes proyectos han financiado el trabajo que se describe en esta tesis:

Ministerio de Educación y Ciencia (CTQ2008-62288/BQU, Consolider Ingenio 2011, CSD2006-0003), SGR (2009 SGR 116), Consolider (CSD2006-0003)

Agraïments/ Agradecimientos/ Acknowledgements/ Remerciements

Agosto del 2005, acababa de llegar a Cali después de hacer una estancia en Brasil y me preparaba para recibir mi grado en Química. Mi director de trabajo de grado, el profesor Alberto Bolaños me habló de la posibilidad de hacer un posgrado en España bajo la supervisión de la Prof. Carmen Claver con una beca Alban. Profe Bolaños le agradezco su fe, dedicación, confianza y el haber sido para mí una persona crucial y de gran ayuda!!!

En cuanto le escribí a Carmen, sin vacilaciones acepto ser mi supervisora en el proyecto de tesis para dicha beca. Que luego en el otoño del 2006 se materializaría en una tarde de octubre al aeropuerto de Barcelona donde me esperaban, para aquel entonces (el que se convertiría en pocos meses en mí otro supervisor de tesis) el Dr. Cyril Godard y en aquella época, el doctorando Eduardo García. Y así comenzó esta aventura que ya termina… mi tesis doctoral.

Fueron años llenos de muchas cosas, especialmente buenas, en los cuales siempre conté con la ayuda de la Prof. Carmen Claver; a quien le tengo mucho aprecio; la que en ningún momento dejó de creer en mí y quien siempre me ha dicho la frase correcta en el momento preciso: un no dudes en llamarme o un no dudes en preguntarme. Carmen, eres una persona con una vitalidad, energías, fuerza y optimismo extraordinariamente contagioso. Fuiste un gran apoyo durante este tiempo, muchísimas gracias, por ayudarme, guiarme y sobre todo por entenderme.

También agradezco al Doctor Cyril Godard, de quien soy la primera doctoranda y aunque el camino fue difícil… no debió haber de haber estado tan mal porque ya tienes otros futuros doctores bajo tu cargo, jejeje. Te deseo muchos éxitos. Gracias por la orientación, las 1000 y una reuniones para ver las mismas tablas y tratar de encontrarles sentido, por ayudarme siempre que lo he necesitado, por moldear, pulir, lijar y lustrar esta tesis hasta que tuviera forma, y por no desfallecer, gracias.

También quiero agradecer a la Profesora Montserrat Gomez, quien en los pocos meses de estancia en Toulouse, me enseñó muchísimo; Quien siempre tenía tiempo para una discusión de química a pesar de sus múltiples

ocupaciones y siempre se pasaba para un *hola! como va todo?*. Muchas gracias por seguir siendo tan especial conmigo aun después de acabar la estancia.

I would like to thank to Prof. Dieter Vogt for giving the opportunity to work in his group. I specially want to thank to the Dr. Christian Muller for the great help offered not only as a supervisor but also as colleague during my stay in Eindhoven.

Agradecer también muy especialmente a la profesora Yolanda Cesteros, fue una de las primeras personas que conocí aquí. Quien siempre ha tenido muy buena disposición para todo. A los profesores Sergio Castillón, María Aurora Ruiz, Pilar Salagre, Montserrat Diéguez, Osca Pàmies, muchas gracias. A la profesora Anna María Masdeu por su buen humor y fortaleza le considero una persona excepcional. A la doctora Elena Fernández por sus frases de ánimos, las invitaciones a cenar y por el cariño he ha mostrado hacia mí, muchas gracias Elena.

También quiero agradecer a Ramón Guerrero de RMN; Además de las innumerables veces que me ayudó a hacer los experimentos, le agradezco por siempre tener una sonrisa y la capacidad de hacerme ver que cada día es un milagro. A Rosa Ras por hacer mucho más que su trabajo, por el trafico de muestras, los trapicheos para colar un masas, por sacar un pedacito de aquí y colocar otro pedacito allá para que esa pinchada tan urgente estuviera lista el día de la reunión, por ser una conciliadora y una excelente persona, gracias Rosa.

A Maria Jose Romero por suminístrame de esos 2.000.000 de lápices que fueron necesarios para hacer esta tesis, muchas gracias ;). A Arantxa Orejón que ahora no está con nosotros pero que dejo una huella imborrable en nuestros corazones. A Raquel Rivas muchas gracias por ser, con diferencia, una persona muy eficiente que siempre está dispuesta ayudar con una sonrisa y a ofrecer una buena charla en el pasillo, jejeje. Jordi gracias por las xuxets!!! A Marisol por toda la ayuda que me ofreció durante estos años y por ser tan amable te deseo lo mejor!!

En estos años como en la vida misma, han pasado por mi camino un número tan grande de personas, que jamás me hubiera imaginado. Años llenos de momentos buenos, malos, regulares, inmejorables o incalificables,

y lo único que queda es esa huella que cada persona deja. Muchos aun están por estos lado, otros se han ido.… jejeje pero a todos mi más sinceros agradecimientos.

Comenzaré en orden de aparición más o menos…. en mis inicios una persona de la que recibí gran apoyo fue Martha con H, gracias por las tardes de una que otra cerveza. A la doctora Eva Raluy muchas gracias por la colaboración y la ayuda que siempre me brindaste, por enseñarme técnicas antiestress como el lanzamiento de corcho!!!. Muchas gracias Comanche!!.

A la doctora Carolina Blanco, parce se le agradece en el alma, las tantas y tanta veces que me decías "parce no se preocupe" jejeje funcionaba!!! Las tardes de cafecitos, los bailes en el labo, las idas de shoppinnnn pa'hablar paja, y por ser más que una compañera chévere de labo, una buena amiga con la que aun sigo compartiendo muchas cosas y espero compartir más. Otra doctora, la de la Fuente!! Vero, muchacha muchas gracias por las cosas que aquí escribo y por muchas más que tu sabes, muchas gracias por el apoyo, por siempre estar allí con ganas de ayudar, porque a pesar de estar hasta el cuello de trabajo íbamos a tomar agüita para tocar temas más banales, por las bravas de vez en cuando. Amiguita muchas gracias por ser un ejemplo como profesional, en todo el sentido de la palabra, y por ser mi amiga. Ali, maestro y sobre todo gran amigo, muchas gracias por las muchas veces que me ayudaste en el labo, por los consejos sobre la vida, por la paciencia y por ser siempre la persona más correcta en todo lo que hace,. Te echaré mucho de menos. ☹

Al señor acetato de etilo (Javi Mazuela), no puedo calcular la cantidad de carcajadas que me echado contigo, eres una persona llena de sorpresas buenas y confiable. Gracias a ti tengo en mi mente un repertorio insólito de series, canciones y todo tipo de material que te dejan con cara de  !!!. Jessica Llop, personaje!! Te esperan años de pequeños puntitos negros en tu tesis, hazles bien el TEM!!! Jejeje futura veterana…que miedo, muchas gracias por ser una buena compañera y estar siempre pendiente de todo y cuando digo de todo es de todo, jejeje. Jessi, en estos últimos tiempos de pretésica, me has ayudado en muchas cositas y esté donde esté ya sabes que cuentas conmigo, gracias!!

Eli, habias heredado mi vitrina mis reactivos espero no heredes mi problemita de los lunes en la mañana jajaja muchos éxitos!! Ánimos que lo mejor del camino es disfrutar del trayecto.

Mama Merce, la mama de grupo, tu eres de las personas más organizadas que conozco cuando sea grande quiero ser como tú, jijiiji. Merce (no coloco el acento porque nunca he dicho bien tu nombre) agradecerte ante todo el siempre ser la misma y esa actitud de siempre sacarle a la vida el mejor partido. Estos meses de pretésicas juntas han estado geniales, la carga aunque pesada se ha hecho mucho más llevadera y te digo que de no haber sido por ti, más de un papel se me hubiera olvidado, gracias!!! Manuel, otro pretésico, muchas gracias por compartir tu experiencia con nosotros y demostrar que se puede ser buen padre, buen esposo, buena persona y eficiente a la vez.

Doctora Dolores y doctora Ariadna, estos años han pasado volando, les deseo muchos éxitos en el camino que comienzan y sé que serán una excelentes profesionales!!. Cristinas, Jessica Cid, grupo boro, fue un placer contar con personas como ustedes en el labo, sigan así!!!

Pajarito, no sé si agradecerte o maldecirte…aun me lo estoy pensando…jejejeje, Oriol, que todo marche muy bien en todas las cosas que te has propuesto y que tengas muchos éxitos!!!

A los ex veteranos Isa, Clara, Bianca, Jesús, Vanesa, Aitor, Eduardo muchas gracias por la ayuda recibida.

A Isabelle Favier muchas gracias por hacer de mi estancia en Toulouse una de las mejores cosas que me han pasado, por ser una excelente persona y por las discusiones sobre nanos, chacalas y chantales, sobre todo por tu amistad, gracias!. I want to thank to Olivier, Leen, Delfine, Atila, Jerôme, Alberto, Sabrine for making the stays a very good time.

Los de orgánica Isidro, Ismael, Miriam, Pep gracias por dejarme uno que otro reactivo de vez en cuando y muchos éxitos!! A los nuevos y no tan nuevos, Sabina, Laia, Jessica III, Gerard, Xavi, Siam, Jamin, Jorge Alonso, Marc, Rafael paciencia y muchos éxitos. A las chicas de Green Cat Tati y Elena muchos éxitos!! .Doctora Tati, te deseo la mejor de las suertes por el camino que desees tomar, que nos volvamos a ver en Cali y que no perdamos el

contacto. A los que han pasado por aquí Gawaine, Cara, Lourdes, Doris, Nicolas, Benjamin, Vanesa, Oli, Matteo, Takahiro, Bernabé, Marta, Tati Brasil, Dagoberto, químicos somos y en camino probablemente nos encontraremos!! Muchos éxitos!!

A la familia Bonet por las navidades, fiestas, reuniones, los cafés y por convertirse en mi familia aquí. A Judith por su alegría, las fiestas, las vacaciones geniales en Mallorca y su fortaleza, a los Amadeus padres por las palabras de ánimos!!. A la yaya, por los poemas y a Helena por las muchas risas.

A Aida, profe, amiga gracias por las largas horas de dedicación, por las risas, los cuentos y por decir mal las cosas para que yo las pronuncie bien!!. Isa, mi peque, señorita Castro, que sepa que le echo mucho de menos que siempre te tengo presente, muchas gracias por tu amistad.

Agradezco a mi madre por ser un gran ejemplo de lucha y entrega, por quien mi vida y las cosas que hago tiene sentido, por enseñarme a luchar y no desfallecer, por enseñarme a levantarme después de cada derrotar, a sonreír aun estando triste, a no llorar por las causas perdidas y a quien extraño y amo tanto. A mi hermanita Carolina, a mi familia querida en Colombia y a Dios.

Por último pero no por eso menos importante a Cali y Ganxet por los ronroneos sobre mis pies, por la compañía en los días de sombría escritura, muaks mis gaticos. Y por supuesto a ti Amadeu, mi chiki, a ti que me has tenido que soportar en esta fase tan crítica, a ti que te has ganado mi corazón, a ti que me apoyas, a ti que me comprendes, que eres mi soporte. No sabes cuánto de agradezco por las discusiones de química, por ayudarme a desenredar estos nudos existenciales. Gracias por crear tantos y tantos momentos felices, por escucharme y siempre arrancarme una sonrisa, por estar ahí, y sobre todo por estar en mi vida.

Gracias a todos/Thanks/Gràcies/Merci beaucoup

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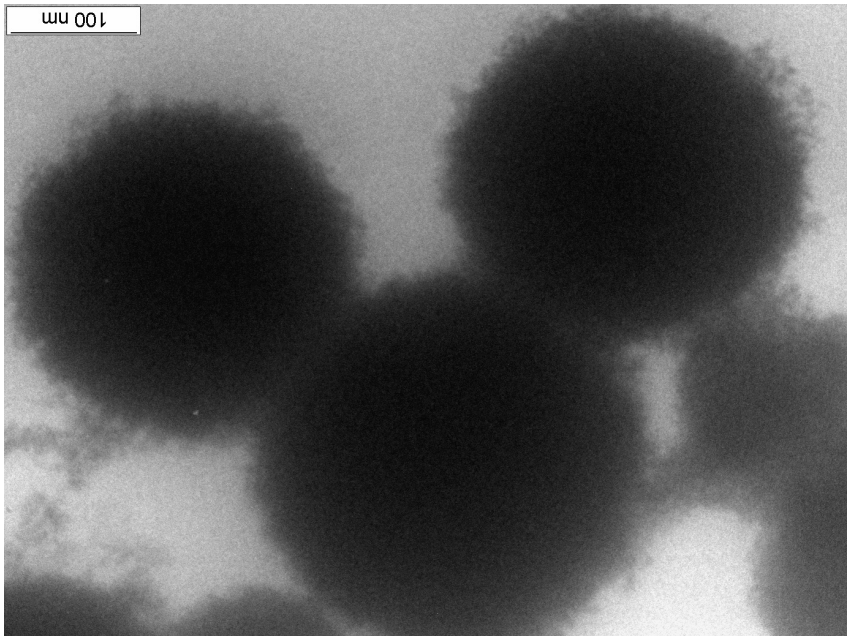
"I have learned more from my mistakes than from my successes"

Humphry Davy

Contents

Chapter 1.

General Introduction and Objectives



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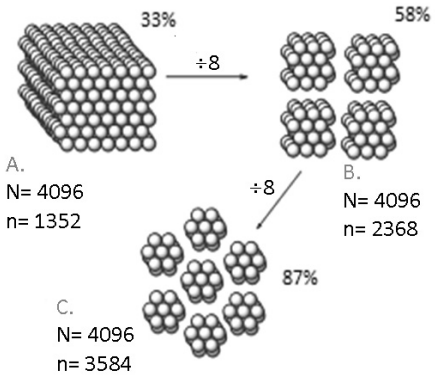
1.1 Nanoparticles: Background

This chapter is divided in two parts. The first part describes the synthetic methods and usual techniques of characterization for metal nanoparticles (NPs). The second part of this introduction is devoted to the applications of metallic NPs as catalysts in asymmetric reactions.

NPs are defined as clusters of metallic atoms with a size comprised between 1 and 100 nm. The synthesis of these colloids entities can be carried out by aggregation or dispersion methods.[1] A wide range of methods have been reported for the synthesis of metal NPs and can be separated into two main groups: the physical methods (dispersion of metallic aggregates) and the chemical methods (nucleation of metallic atoms).[1] Metal NPs have interesting chemical and physical properties, which differ from those of their bulk and molecular counterparts. One of these features is that as particles get smaller, their surface area to volume ratio increases. For a very large particle, the number of atoms at the surface is very small compared to the number of internal atoms; in contrast, very small particles contain the majority of their atoms at the surface (Scheme 1.1).[2]



Scheme 1.1 Dependence of the percentage of atoms at the surface (n) to total atoms (N) as a function of the NP size.

As shown in Scheme 1.1, the surface area per unit weight increases exponentially as the size decreases. Thus, the percentage of the surface atoms that are available is higher for smaller NPs C. (87%) >B. (58%) >A (33%). Several methods for the syntheses of NPs have been reported.[1] Metal NPs have been obtained either by the so-called "top down methods", *i.e*. by the mechanical grinding of bulk metals, or via "bottom-up methods" which rely on the wet chemical reduction of metal salts or, alternatively, the controlled decomposition of organometallic compounds such as metal carbonyls. The reported "bottom-up" approaches to generate metal NPs are the following:[3]

1. Chemical reduction of a metal salt.
2. Thermal, photochemical, sonochemical decomposition of a metal (0) complex.
3. Hydrogenation of coordinated oleofinic ligand.
4. Vapor phase decomposition.
5. Electrochemical reduction of higher valent species of the metal.

Independently of the route chosen, a key issue in their synthesis is their stabilization by a protective agent to avoid the formation of bulk metal. Two types of stabilization can be achieved (Figure 1.1) depending on the nature of the protecting agents: a) electrostatic stabilization can be obtained using ionic compounds as protecting agents; b) steric stabilization can be achieved by the use of neutral molecules such as polymers or other bulky molecules. While the electrostatic stabilization is mainly used in aqueous media, the steric protection can be used in both organic and aqueous solvents. [1]

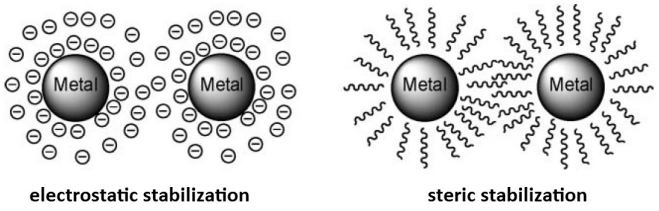
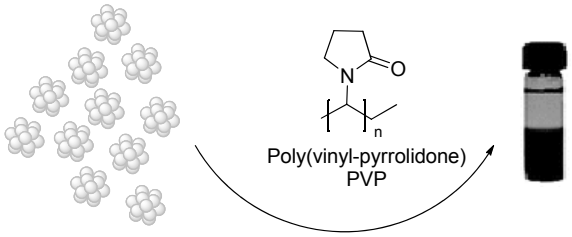


Figure 1.1. Schematic representation of electrostatic and steric stabilization of metal particles.

The electrostatic stabilization of NPs (Figure 1.1) can be performed by ionic compounds such as carboxylates or polyoxoanions in solution (generally aqueous solution). The presence of these compounds and the related counteranions surrounding the metal surface generate a coulombic repulsion between the NPs, which form an electrical double layer hampering the aggregation.[1]



Scheme 1.2. Poly(vinyl-pyrrolidone) stabilised metal NPs.

The steric stabilization (Figure 1.1) involves the use of compounds that contain coordinating groups in its molecular structure and that prevent particle agglomeration by providing a protective layer. Polymers are very often used in the synthesis of NPs and the most commonly used polymer for NPs stabilization is PVP. Polyvinyl pyrrolidone (PVP) is a cheap, commercially available stabilizer that is widely used in the preparation of nanoparticles in organic or inorganic solvents (Scheme 1.2).[4]

1.2 Synthesis of metal NPs.

As previously mentioned, the most common methods for the synthesis of NPs are: chemical reduction of metal salts, thermal, photochemical or sonochemical decomposition, metal vapour synthesis, electrochemical method and decomposition of organometallic precursors.[1]

The reduction of metal salts is the most common method for synthesizing metal NPs. The reducing agents used are hydrides or salts such as sodium borohydride, or oxidable agents such as alcohols.

The metal vapour synthesis is a method for the formation of metal NPs that consists in evaporating volatile metals at reduced pressure and subsequent co-condensing at low temperatures with the vapour of organic solvents. The

colloidal particles nucleate and grow as the frozen mixture warms up to melting point. [1]

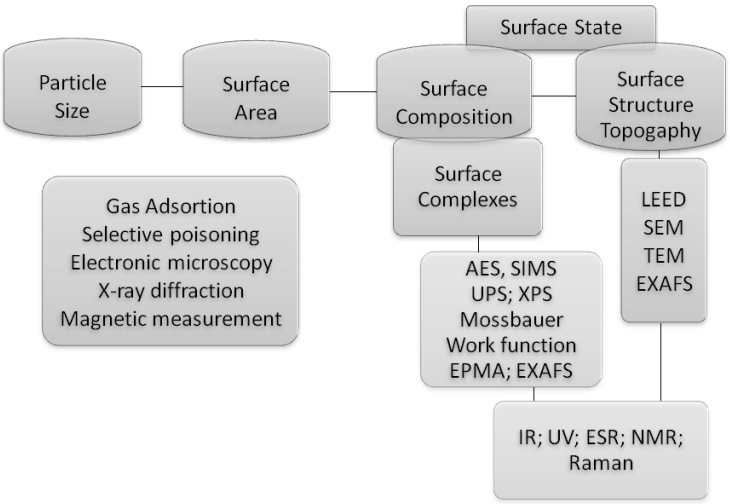
The electrochemical method was developed by Reetz. [5] This method consists in the reduction of a metal solution (anode) in the presence of ammonium salts, which are both electrolyte (cathode) and stabilising agent.

Using these methods, some impurities generated during the synthesis such as salts or water can adsorb at the surface and modify the properties of the NPs.

The displacement from organometallic compounds consists in the decomposition of an organometallic precursor, mainly zerovalent organometallic complexes, in an organic solvent.[1] This method makes possible the synthesis of NPs exhibiting a "clean surface" since no salts are formed during the synthesis.

1.3 Characterization techniques of NPs

Part of NPs characterization is to establish their particle size and the in overall composition. Surface composition is sometimes also probed, but this is a more complicate task. Several methods are nowadays available and complementary for the characterization of metal NPs. The Scheme 1.3 provides a general picture of the most used techniques to characterize NPs.[6] These techniques include transmission electron microscopy (TEM), UV–Visible spectroscopy (UV–Vis.), nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), elemental analysis, and energy dispersive spectroscopy (EDS). To a lesser extent, the analytical ultracentrifugation–sedimentation, extended X-ray absorption fine structure (EXAFS), scanning tunneling microscopy (STM), atomic force microscopy (AFM), high performance liquid chromatography (HPLC), light scattering, time-of-flight mass spectrometry, magnetic susceptibility, and electrophoresis or ion-exchange chromatography are also used.



Scheme 1.3. Common methods available for the characterisation of metal NPs.[6]

The most important techniques in nanocluster characterization and the structural or compositional information gained from them are discussed in the next section. Although X-ray crystallography would be the ideal method of characterizing such molecules, nanoclusters generally do not crystallize.

Transition electronic microscopy (TEM) is the most commonly used technique with the Scattering Electronic Spectroscopy (SEM) and provides direct visual information on their size, shape, dispersity, structure and morphology (Figure 1.2). TEM allows the visualization of thin slices of material with nanometre resolution. Top of the line instruments have sub-nanometer resolution, and can almost resolve the electron density of individual atoms.[7]

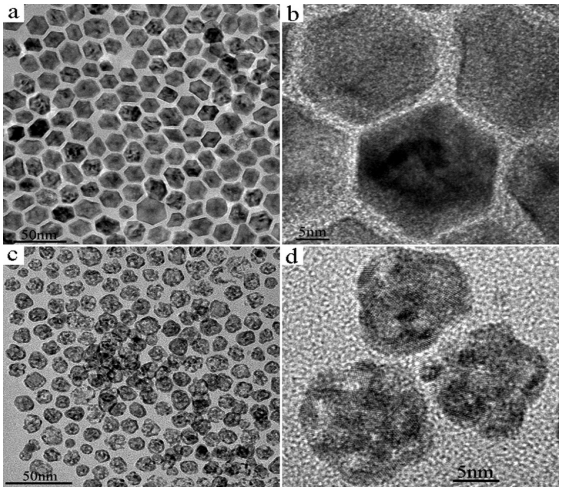


Figure 1.2. TEM image of Pt-Ni NPs. (b) HRTEM image of Pt-Ni NPs. (c) TEM image of nanoporous Pt-Ni alloys. (d) HRTEM image of nanoporous Pt-Ni alloys.

Scanning Electron Microscopy (SEM) generates a lower-resolution image, but allows the direct mapping of surface features, and can even be used for elemental analysis.

X-Ray Diffraction (XRD) is a non-destructive technique that can identify the crystal phase for particles larger than 3 nm. When the NPs are smaller, the acquisition of structural information is more difficult.[8] EXAFS (Extended X-ray Absorption Fine Structure) is a more sophisticated technique to determine the atomic number, distance and coordination number of the atoms surrounding the metal center whose absorption edge is being examined.

Infrared spectroscopy (IR) provides information on organic groups surrounding the metallic atom and has been used as a surface probe in NPs systems. This technique is commonly used to determine the adsorption of carbon monoxide onto the surface of the metal NPs. Carbon monoxide is an ideal ligand because it readily adsorbs to metal surfaces, and it has characteristic vibrational frequencies around 1800-2100 cm^{-1} once adsorbed or coordinated to the metal surface. Baker and co-workers reported studies of ATR-IR to determine the adsorption geometry of (rac)-BINAP, **1** on Pd NPs surface (Figure 1.3).

the ATR-IR investigation of **Pd1** NPs stabilised with (rac)-BINAP, **1**, revealed clear differences between the spectra of powdered **1**, **1** dissolved in ethylbenzene, and **1** adsorbed on a Pd surface.[9]

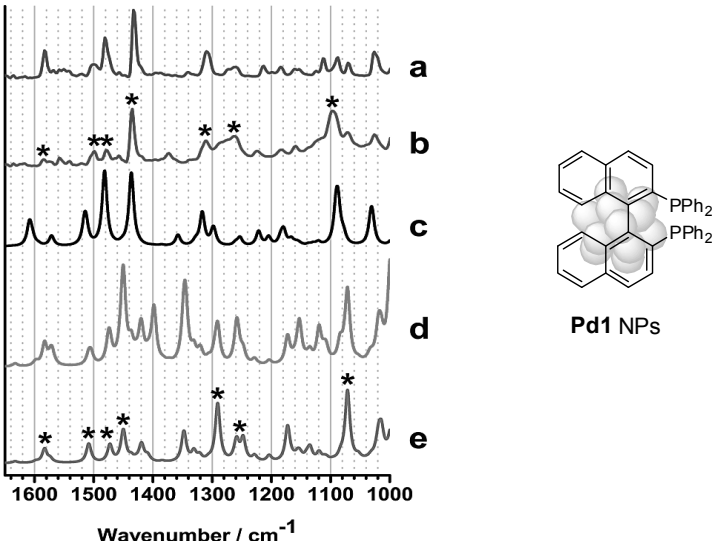
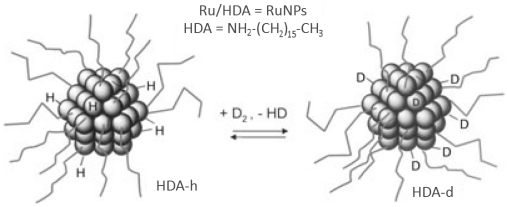


Figure 1.3. Experimental ATR-IR spectra of (a) **1** powder and (b) **1** adsorbed on PdNPs as well as the calculated spectra of (c) **1** and **1** adsorbed on PdNPs (d) without and (e) with the surface selection rule consideration. The band that changes considerably upon **1** adsorption on Pd are marked with asterisks.

UV-Vis spectroscopy is a technique used to quantify the light absorbed and scattered by a sample. This spectroscopic technique is particularly effective for characterizing semiconductor-type NPs or metal particles whose plasmon resonance lies in the visible range (such as Cu, Ag and Au).[10] The UV–Vis has been used to determine both particle size and the degree of cluster aggregation in the sample.[11]

NMR spectroscopy provides information on the molecules that surround the metal core of the NPs. Recently, the first direct NMR evidence for the presence of mobile and reactive hydride ligands coordinated to a ruthenium NPs was reported by Chaudret *et al.* using gas phase NMR.[12] They studied the hydrogen–deuterium exchange between the surface of the **RuHDA** NPs and ligand sites (Scheme 1.4). These studies extended the works that previously

evidenced the coordination of ancillary ligands such as amines or thiols at the NPs surface.[13,14] The reactivity of the hydrogen detected on the nanoparticles was demonstrated by the finding of hydrogen–deuterium exchange between surface and ligand sites (Scheme 1.4).



Scheme 1.4. RuHDA NPs showing hydrogen–deuterium exchange between surface and gas phase.[13]

Other interesting studies were reported by Chaudret and co-workers about of the coordination of CO at the surface of very small ruthenium nanoparticles by IR and solid state NMR spectroscopies. Two sets of ruthenium nanoparticles stabilized either by a polymer (polyvinylpyrrolidone; PVP) or a ligand (bisdiphenylphosphinobutane; dppb) were studied in order to evidence any influence of the stabilizer on the location and dynamics of CO molecules at the particles surface. It was found that CO groups are mobile on the surface of the nanoparticles even in the solid state and that bulky ancillary ligands such as dppb may slow down the fluxionality of CO and prevent exchange at certain positions.

Scanning Tunneling Microscopy (STM) and *Atomic Force Microscopy (AFM)* Scanning Tunneling Microscopy makes possible the determination of the total diameter of the NPs, including the stabilizing ligand shell.[7]

X-ray photoelectron spectroscopy (XPS) has become an increasingly available and powerful tool for understanding the nature of many different types of surfaces.[15] Characterization of nanostructures using XPS is not new. From the earliest days, XPS or ESCA (electron spectroscopy for chemical analysis) was widely used to study many aspects of NPs.[16]

XPS is routinely used to determine what elements and the quantity of those elements that are present within the top 1-12 nm of the sample surface,

what contamination, if any, exists in the surface or the bulk of the sample, empirical formula of a material that is free of excessive surface contamination, the chemical state identification of one or more of the elements in the sample, the binding energy of one or more electronic states, the thickness of one or more thin layers (1–8 nm) of different materials within the top 12 nm of the surface. Despite such advances, determining the structure and composition of metal NPs, and in particular, the nature of the interactions between the metal surface and the stabilizing agents, is still a very complex task.

1.4 Transition-metal NPs in Catalysis

Transition metal NPs have been applied in a number of fields due to their unique properties.[17] They are particularly interesting as catalysts due to their exceptional combination of reactivity, stability and selectivity besides their large surface.[18] The first metal-NPs (Ag) were reported in the middle of the 19th century in photography by Faraday to study the optical properties of metals.[19] Since the 1970's, transition-metal NPs have been more frequently used in catalysis.[20]

Highly dispersed mono- and bimetallic NPs have been used as catalyst precursors in many processes. These NPs can be used directly in colloidal solutions or immobilized onto a support. The chemical reactions catalysed using transition metal nanocatalysts in colloidal solution include cross-couplings, electron transfers, hydrogenations, oxidations, etc....[21] Besides their applications in powder technology, material science and chemical catalysis, recent studies have examined the great potential of NPs as fuel cell catalysts.[22] Due to their special properties they have even been considered as revolutionary catalysts.[23] For instance, their much larger surface-to-volume ratio compared to that of their bulk counterparts has attracted a great deal of attention for catalytic applications.[24]

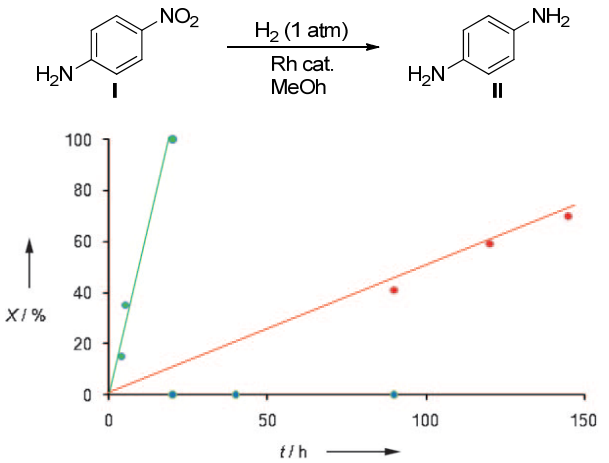


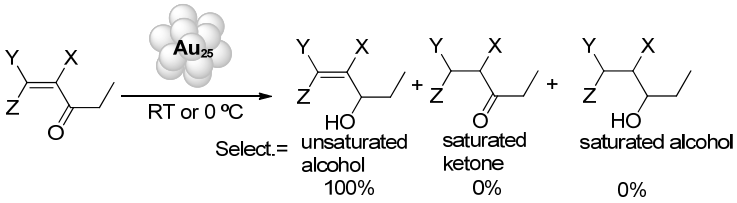
Figure 1.4 Dependence of conversion (X) as a function of the reaction time (t) in the rhodium-catalysed hydrogenation of 4-nitroaniline. Wilkinson's catalyst [$RhCl(PPh_3)_3$] (blue), Rh_{60}@TPP-DPA G4 (red), and $Rh_{32}Fe_{28}$@TPPDPA G4 (green).

Over the last decade, the number of publications on the use of NPs has been growing exponentially in several research fields from chemistry to physics[25] and from laboratories to large industrial processes.[26]

Hydrogenation reactions have been widely studied using metal NPs as catalysts. [27] Several types of soluble nanocatalysts have been successfully applied in the hydrogenation of arenes and stabilizers such as poly(vinylpyrrolidone), surfactants and ionic liquids have proved to be especially suitable for the production of highly active catalysts.[28]

Lately, although new metal nanocatalysts based on Co, Pd, Ni and Fe have shown promising results in hydrogenation reactions, Ru, Rh, Pt and Ir are still currently the metals of choice for arene hydrogenation nanocatalysts.[29] Recent studies by Nishihara and co-workers described efficient Ru/Fe bimetallic NPs stabilized by fourth-generation (G4) phenylazomethine dendrimers (TPP-DPAG4). These NPs were used as catalysts for the hydrogenation of olefins and nitroarenes under relatively mild conditions (Figure 1.4).[30] The figure 1.4 shows that $Rh_{32}Fe_{28}$@TPPDPA G4 Nps resulted more active than the monometallic NPs Rh_{60}@TPP-DPA G4 and Wilkinson's catalyst [$RhCl(PPh_3)_3$].

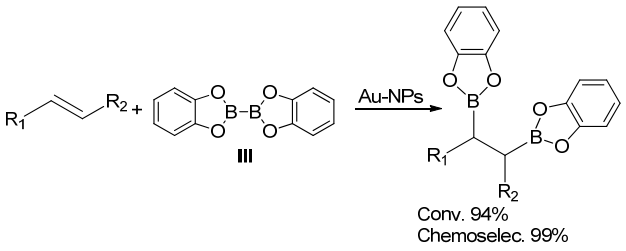
These catalysts are usually very active. Furthermore, highly selective reactions were also achieved using these types of systems. For instance, the well defined thiolate-stabilized gold NPs $Au_{25}(SR)_{18}$ were shown to catalyse the chemoselective hydrogenation of α,β-unsaturated ketones and aldehydes to unsaturated alcohols with complete (100%) selectivity to the unsaturated alcohol.[31] These studies determined that the core–shell structure of the $Au_{25}(SR)_{18}$ particles (*i.e*. Au_{13} core/Au_{12} shell) and their unique electronic properties (*i.e*. electron-rich Au_{13} core and low-coordinate (N=3) surface gold atoms) is responsible for the observed catalytic performances (Scheme 1.5).



Scheme 1.5. $Au_{25}(SR)_{18}$-catalysed hydrogenation of a range of substituted α,β-unsaturated ketones and aldehydes.

Over the last decade, the hydrogenation of arenes catalysed by soluble nanoparticles has attracted much interest from both academic and industrial research groups due to the milder conditions and the interesting selectivities achieved when compared to those obtained with classical heterogeneous catalysts.[32] These mild conditions also present potential in order to overcome selectivity issues such as chemoselectivity when several functional groups are present in the substrates and stereoselectivity for substituted arenes.[27]

Fernandez and co-workers reported the use of Au NPs as very selective catalysts in the diboration of terminal and internal alkenes. [33] They reported a new gold-mediated diboration reaction, in which Binap-stabilized AuNPs are responsible for the conversion of alkenes with complete chemoselectivity to the 1,2-bis(boronate)esters.[32]



Scheme 1.6 Au-NPs catalysed diboration of terminal and internal alkenes.

The intrinsic size–activity relationship and the particle shape are important features of the NPs that have to be taken into account.[34] This effect was reported by Somorjai *et al*.[35] which showed that hexagonal Pt(111) surfaces are between 3 and 7 times more active for aromatization reactions than cubic Pt(100) surfaces.[35] Another interesting study was published by El-Sayed and co-workers, who established that cuboctahedra particles are composed of numerous (100) and (111) facets, while the tetrahedral NPS only contain the more reactive (111) facets.[36] The tetrahedrical NPs are thus more active in catalysis. Controlling the particle morphology is therefore crucial to tune their activity and selectivity.[37]

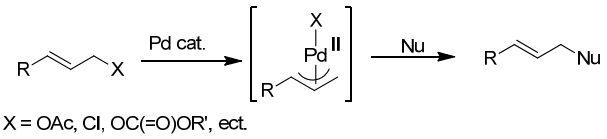
The other group of reactions that frequently used metal NPs as catalysts is the Pd-catalysed C-C bond formation reactions.[38,36,18]

In the next sections, representative results reported in Pd-catalysed asymmetric allylic substitutions, asymmetric Suzuki couplings and 1,4 conjugate addition reaction, which are the reactions studied in this thesis, will be described.

1.4.1 Pd-catalysed allylic substitution reactions

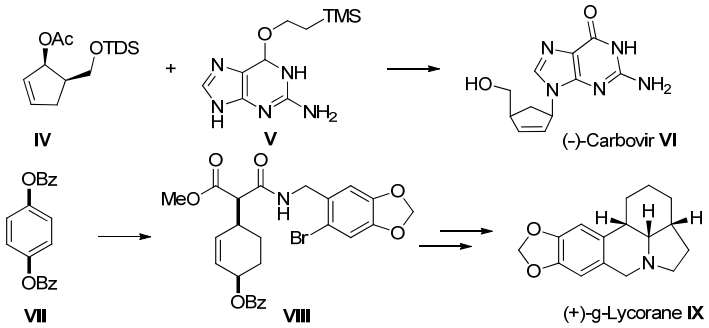
Giants of the synthesis such as the pharmaceutical and food industries are very influenced by the development of stereoselective approaches in organic synthesis.[39] The stereoselective reactions that lead to the formation of new C-C or C-heteroatom bonds are the most required. In this context, the Pd catalysed asymmetric allylic alkylation provides an efficient and versatile method to obtain such products.[40] The Pd-catalysed asymmetric allylic substitutions consist in the reaction of a nucleophile with a racemic substrate

containing a leaving group (LG) in an allylic position (Scheme 1.7). The nucleophile can include a carbon, nitrogen, and oxygen or phosphorus donor species.[40] The leaving group usually used is halide or acetate. A base is required for the *in-situ* generation of the nucleophile.[40]



Scheme 1.7. Pd-catalysed allylic substitution reactions

Biologically active molecules such as Carbovir (**VI**) and Lycorane (**IX**) can be obtained by Pd-catalysed asymmetric allylic alkylation reactions (Scheme 1.8). The compound **VI** is a carbocyclic nucleoside, which has potent in vitro activity against the human immunodeficiency virus, and the compound **IX** is an alkaloid isolated from the *Amaryllidacae* family that present an interesting biological activity. [41,42]



Scheme 1.8. Example of molecules with biological activity that can be obtained by Pd-catalysed allylic substitution reactions.[43]

The most common substrates used in Pd-catalysed allylic substitution are shown in the Figure 1.5. The benchmark substrates in the Pd-allylic alkylation are the compounds **X** and **XII**.

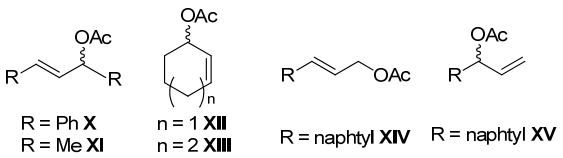
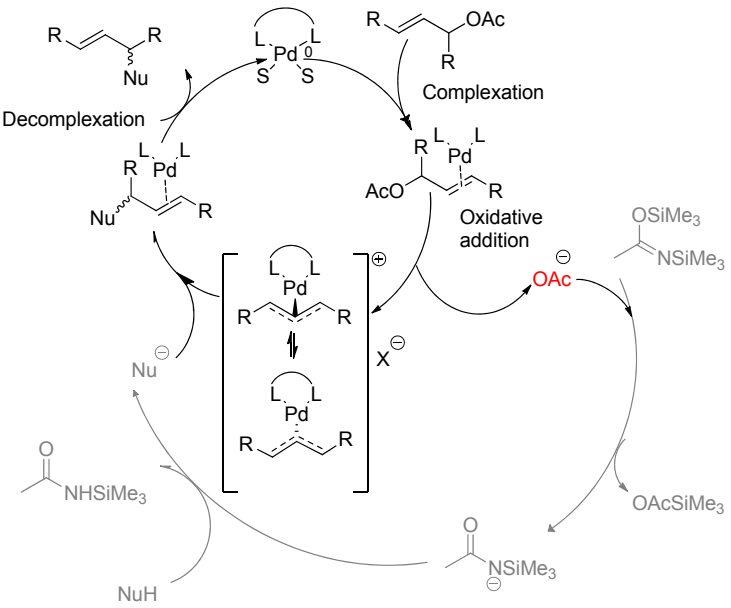


Figure 1.5. Substrates used in enantioselective Pd-catalysed allylic alkylation

1.4.1.1 Mechanism

The accepted mechanism of the Pd-asymmetric allylic substitution reaction is depicted in Scheme 1.9.[40a,41b,44,45] The catalytic cycle consists in four main steps. The first step is the complexation of the substrate followed by oxidative addition to form the cationic complex **XVII** or the neutral complex **XIX**. The equilibrium between these two species is dependent on the properties of the anion, the solvent and the ligand. With bidentate ligands, which are the most common, the cationic complex usually dominates.[46] For several Pd/L systems, the oxidative addition and expulsion of the leaving group LG is considered as the rate-determining step of the reaction.[47] The product of the oxidative addition has two susceptible positions where to receive a nucleophilic attack: the C-1 and C-3 positions (see green rectangle, Scheme 1.9). From the nucleophilic attack, an unstable Pd(0)-oleofinic complex is produced, which releases the final product and regenerates the initial Pd(0) species. When the reaction is to be carried out in an enantioselective manner, the structure of the ligand, usually bidentate, is crucial to efficiently induce stereoselectivity.



Scheme 1.9 Accepted catalytic cycle for Pd-catalysed allylic substitution reactions**.**

The enantioselectivity of this reaction is determined by the external nucleophilic attack at the most electrophilic allylic carbon terminus of the π-allyl intermediate **XVIII**. This intermediate was isolated and studied in the absence of nucleophile, showing that several isomers can coexist in solution (Figure 1.6).[40]

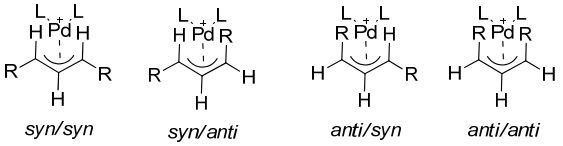


Figure 1.6 Possible isomers of the Pd-allyl intermediate.

The most commonly used nucleophiles are carbanions or amines.[41b] In early reports, sodium salts were used but they were not soluble in conventional organic solvents. This problem was solved by the use of *N,O*-bis(trimethylsilyl)acetamide (BSA) and catalytic amounts of potassium acetate (see gray part of Scheme 1.9).[48] In this case, a carbanion is formed by the transfer of a silyl group from the BSA to the acetate anion producing the

N-(trimethylsilyl)acetamide anion, which abstracts the acidic proton of the dimethyl malonate (Scheme 1.9).

1.4.1.2 Pd-catalysed allylic alkylation

The enantioselective allylic alkylation of symmetrical substrates with identical substituents in the 1,3 positions such as **X**, has been carried out using dimethyl malonate as benchmark nucleophile.

The ligands used in this reaction are often classified into two groups, depending on whether they present C1- or C2-symmetry. [40] In the following sections, a selection of C1- and C2-symmetry ligands reported in Pd-catalysed asymmetric allylic substitutions is described.

C1-symmetry ligands

In the case of C1-symmetry ligands, two isomeric *syn/syn* complexes, designated *endo* and *exo*, can be formed. These species usually undergo fast interconversion via π-σ-π rearrangement (Figure 1.7).

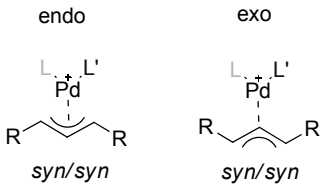


Figure 1.7 Possible isomers of the Pd-allyl intermediate using C_1-symmetric ligands.

Gilberson *et al*. introduced a combinatorial approach by building peptides from the phosphine-containing amino acids **2** and up to 81% ee was achieved for cyclic substrate **VIII**.[49]

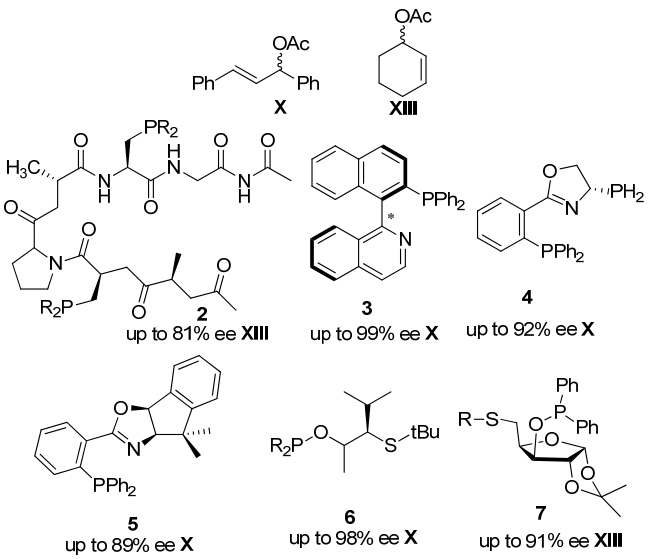


Figure 1.8. C1 symmetric ligands used in enantioselective allylic alkylation.

Several phosphine ligands with axial chirality have been used in Pd-catalysed asymmetric allylic alkylation.[50] Mechanistic and synthetic studies in the Pd-catalysed allylic alkylation of **X** using the Pd/**3** (Figure 1.8) catalytic system were reported and excellent enantioinduction was achieved (ee up to 99%).[51] These reactions have been extensively explored using PHOX ligands (P,N ligands).[52,] The phosphino-oxazoline ligand **4** was successfully applied in the Pd-catalysed allylic substitution of **X**, with 95% ee (Figure 1.8). This type of ligands is very efficient for this transformation and as a result, a wide number of P,N ligands were synthesised and used in this reaction.[53] Extensive mechanistic investigations led to the development of very bulky ligands such as **5**, which induces excellent enantioselectivities (up to 89%) in the Pd-catalysed asymmetric allylic alkylation of **X** (Figure 1.8).[54]

P,S ligands are also interesting for these processes ligands such as **6** have been reported to be highly enantioselective in the Pd-catalysed asymmetric allylic alkylation of the substrate **X** with ee's up to 98%.[55] Moreover, furanoside thioether-phosphite and phosphinite ligands have also been tested in this reaction with several acyclic and cyclic substrates.[56] The results indicated that the enantioselectivity of the products strongly depends on the steric and electronic properties of the substituents at the thioether moiety

and on the substrate structure. By carefully selecting the ligand parameters, good enantioselectivities were obtained for unhindered cyclic substrates **XIII** (ee.'s up to 91%, Figure 1.8).

C2-Symmetric ligands

Since Trost and co-workers discovered the application of diphosphine ligands in Pd-catalysed allylic alkylation reactions, many bidentate ligands have been designed and probed in this reaction. When C2-symmetric ligands are used, three possible π-allyl intermediates can be formed: syn/syn, syn/anti, and anti/anti as shown in Figure 1.6.

In this section, the best results obtained in enantioselective allylic substitution reactions using Pd systems based on C2-symmetric ligands will be summarised.

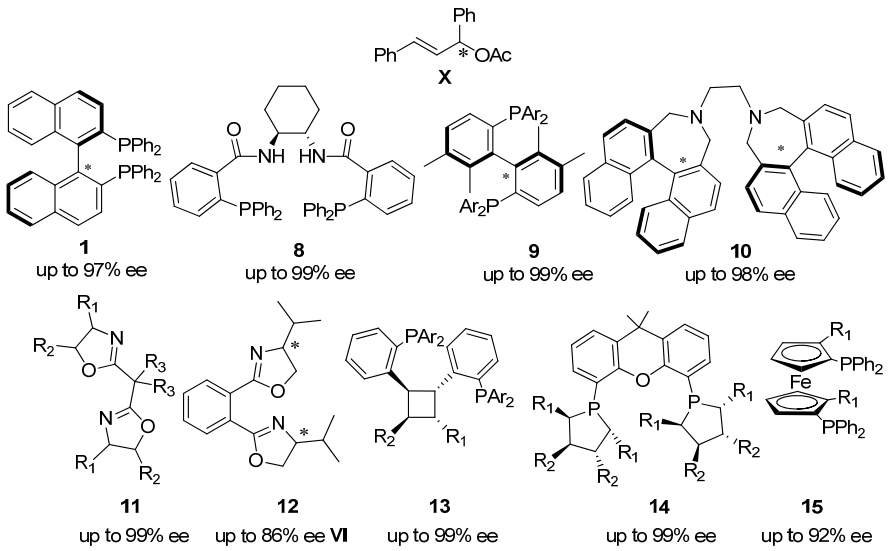


Figure 1.9 C2-symmetry ligands used in enantioselective allylic alkylation reactions.

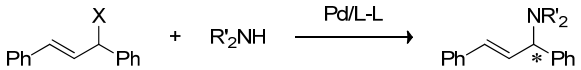
Trost developed the diphosphine **8** and derivates (Figure 1.9), and achieved high chiral discrimination in these processes.[40] The use of axially chiral phosphines such as BINAP **1**,[57] or **9** [58] resulted in excellent asymmetric induction, particularly in the Pd-catalysed allylic alkylation of **X** (ee's up to

97% and 99%, respectively). Other ligands such as the optically active C2-symmetric diamine ligand **10**[59] and the bisoxazoline ligand **11**[60], were reported in this reaction with excellent enantioselectivity (*ee* up to 98% and 99%, respectively). Moreover, catalytic systems bearing C2-symmetry bis(oxazolines) such as **12** (Figure 1.9) showed low activity, but good asymmetric inductions, affording enantiomeric excesses up to 86% in the asymmetric allylic alkylation of **X**.[61] Bidentate phosphorus ligands with a cyclobutane backbone **13**[62] and the bis phospholane **14**[63] ligands(Figure 1.9) also yielded high enantioselectivities (*ee* up to 99%) in the Pd-catalysed asymmetric allylic alkylation of **X**. Another important class of ligands with central chirality consists in the P-chiral diphosphine ligands based on a ferrocenyl backbone.[64] In the allylic alkylation of **X** at room temperature, the use of this type of ligands gave up to 80% yield of the product. The steric hindrance induced by the aryl substituents in the ligand **15** leads to large variations in the enantiodiscrimination.

Nowadays, the Pd-catalysed allylic amination reaction can also be performed with a high degree of efficiency and selectivity, and has become an established procedure in organic synthesis.[65]

1.4.1.3 Pd-catalysed asymmetric allylic amination

The Pd-catalysed asymmetric allylic amination consists in the reaction of an amine nucleophile with a racemic substrate containing a leaving group (LG) in an allylic position to form allylamines (Scheme 1.10), which are fundamental building blocks in organic chemistry and important industrial precursors.[66]

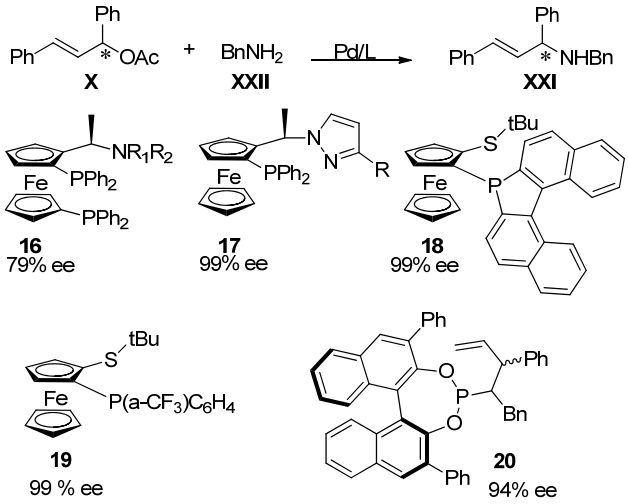


Scheme 1.10. General representation of the Pd-catalysed asymmetric allylic amination reaction.

Several types of nucleophiles can be used in this reaction such as primary and secondary alkyl and aromatic amines. However, ammonia does not react. As a consequence, many ammonia synthons have been developed, and protected primary allylamines are now readily available through the use

of azide, sulfonamide, phthalimide, di-*tert*-butyl iminocarbonate ($(Boc)_2NNa$), and dialkyl N-(*tert*-butoxycarbonyl)-phosphoramide anions as nucleophiles.[67,68] The substrates are usually allyl acetates, carbonates, phosphates, and in some cases, even the un-reactive chlorides have been used.[69]

In Scheme 1.11, a selection of chiral ligands used in Pd-catalysed allylic amination of **X** using benzylamine **XXII** as nucleophile is shown. The allylic amination reaction using Pd catalysts bearing the ferrocenyl ligands **16** was the first example of a successful system in this reaction with ee's up to 79%.[70] Togni *et al*. reported high enantioselectivities (up to 99%) using Pd-complexes containing the chiral ferrocenyl pyrazole ligands **17**.[71] The sulfenylferrocene ligands **18** and **19**, which exclusively possess planar chirality, afforded 99% of enantioselectivity using benzylamine as nucleophile.[71, 72]



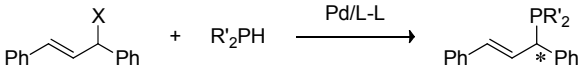
Scheme 1.11. Selected ligands used in enantioselective allylic amination.

Recently, the novel BINOL-based ligands **20** were reported to be effective in this reaction for a large number of amine nucleophiles. Significantly, the terminal olefin moieties proved to be essential for the observed high activity and selectivity.[73]

Nucleophiles such as activated amides, isocyanates, carbodiimides, azides, sulphonamides, imides, heterocycles, oxygen nucleophiles and sulfur nucleophiles were successfully used in these reactions.[74] Preliminary results have been published on the use of silicon[75] and phosphine nucleophiles,[76] however, these have not yet been developed into general systems.

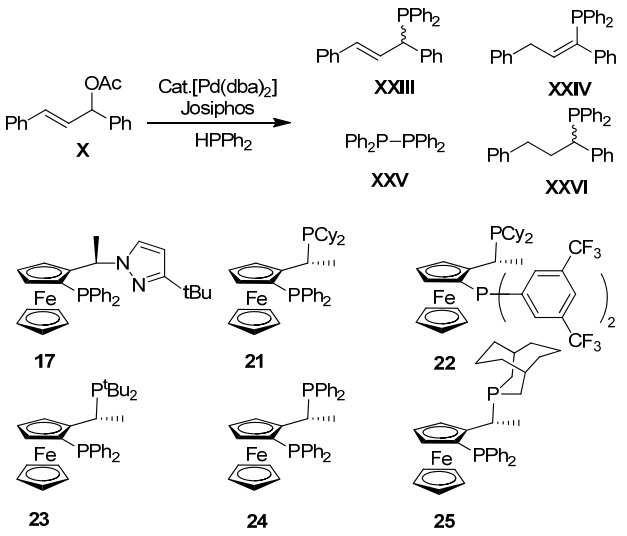
1.4.1.4 Pd-catalysed asymmetric allylic phosphination

The Pd-catalysed asymmetric allylic phosphination involves the nucleophilic reaction of phosphine ligands to form allylphosphines (Scheme 1.12).This type of reaction is of high interest for the synthesis of enantiomerically pure phosphines.[77]



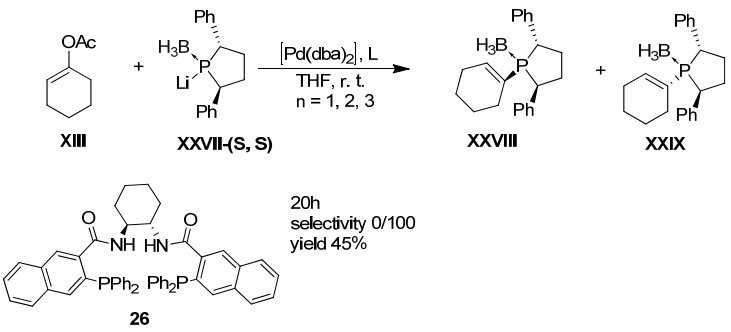
Scheme 1.12. General representation of Pd-catalysed asymmetric allylic phosphination reaction.

Togni recently reported the first enantioselective Pd-catalysed asymmetric allylic phosphination of **X** with diphenylphosphine as nucleophile in the presence of the Josiphos ligands **17** and **21**-**25** and achieved ee's up to 96%.[77] However, the regio- and chemoselectivity of the reaction was low (Scheme 1.13), giving the allylic phosphine product **XXIV**, the product formed by dehydrocoupling of the secondary phosphine, **XXV** and a small amount of the vinyl isomer **XXVI** resulting from a 1,3-hydrogen shift (Scheme 1.13).



Scheme 1.13. First Pd-catalysed asymmetric allylic phosphination reaction reported by Togni and co-workers.

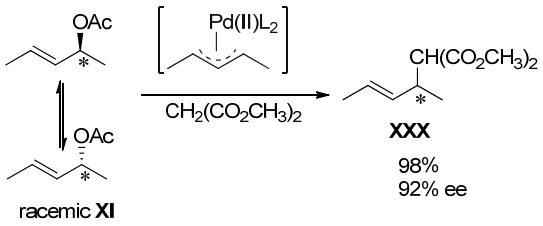
Secondary phosphine-boranes were also used as nucleophiles in Pd-catalysed asymmetric allylic phosphination reactions (Scheme 1.14). In this case, an enantiopure secondary phosphine-borane was used as nucleophile to produce allylic phosphines containing two chiral centres. The enantiopure phosphine-borane anion was shown to partially orientate the stereoselectivity of the reaction.[78] Using a Pd catalyst bearing the chiral ligand DACH-naphtyl **26**, total selectivity was observed for the cyclic substrate **XIII** .



Scheme 1.14. Allylic phosphination catalysed by chiral palladium complexes with enantiopure phospholane.[78]

As a summary, catalytic systems bearing bidentate ligands provide excellent ee's in the Pd-allylic alkylation reaction. Usually, the catalytic systems have been tested with the benchmark substrate **X** and dimethyl malonate as nucleophile. Compared to carbon nucleophiles, the use of heteroatom nucleophiles in Pd-catalysed allylic substitution reactions is more challenging. To date, many efforts have been made in investigating the type of heteroatom nucleophiles that can be used in these transformations.[40]

Finally, it is important to note that several reports on Pd-catalysed allylic substitution reactions describe a kinetic resolution of the substrate during the reactions.[40] In a kinetic resolution, two enantiomers react at distinct reaction rates in a chemical reaction, thereby creating an excess of the less reactive enantiomer. This excess goes through a maximum and disappears on full conversion of the most active enantiomer. Ideally, the maximum conversion is thus 50% of the initial racemic mixture. In allylic substitution reactions, the dynamic kinetic resolution (DKR) is more common.[79] In DKR the starting substrate racemises under the reaction conditions. Thus, when the most active enantiomer reacts, an equilibrium between both enantiomers re-establishes the racemic mixture. The conversion can therefore reach 100%. In Scheme 1.15, an example of such process is described where 98% conversion is obtained with 92% ee.[79]



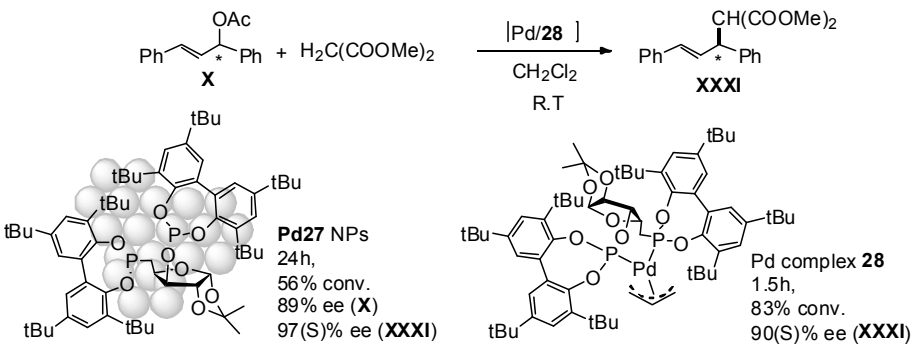
Scheme 1.15. Example of Pd-catalysed asymmetric allylic alkylation through palladium-allyl complex with Dynamic Kinetic Resolution.

Only few studies have been reported about the use of PdNPs applied to Pd-catalysed allylic substitution reactions. In the next section, the most important results obtained in these reactions using Pd NPs as catalysts will be described.

1.4.2 Pd NPs as catalysts in allylic substitution reaction

While the use of NPs in catalysis is increasing by leaps and bounds, the eternal debate persists about whether the catalysis is intrinsically heterogeneous, if occurs via reactant adsorption on the surface of NPs, or whether atoms leaching from the NPs promote the traditional homogeneous path.

In 2004, PdNPs stabilized by the chiral xylofuranoside diphosphite **27** (Scheme 1.16), were used in the Pd-catalysed allylic alkylation of **X** with dimethyl malonate, and experiments aiming at distinguishing these observations from classical molecular catalysis were reported.[80] They reported the successful reaction of **X** with dimethyl malonate under standard conditions using as catalyst either **Pd27** NPs or the molecular complex **28** generated in situ by reaction of $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and **27** (Scheme 1.16).



Scheme 1.16. Pd-catalysed asymmetric allylic alkylation of **X** with dimethyl malonate as nucleophile and **Pd27** or the complex **28** as catalyst.

The enantiomeric excess obtained using the molecular catalyst matched the published data,[81] whereas that found using the colloid catalyst was slightly higher (*ca.* 97% (S) ee). However, these catalytic systems displayed some important differences:

- When **Pd27** NPs were used as catalyst, only ca. 55% product (**XXXI**) was obtained after 24 h, and this value did not change after 168 h. In contrast, using the molecular complex $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{27})]PF_6$, **28** as catalyst, quasi total conversion of the substrate was observed after 1.5 h.

- When **Pd27** NPs were used as catalyst, kinetic resolution[82] of the substrate was observed and 89% ee was measured for the remaining substrate. With the molecular catalyst, no kinetic resolution was observed.

The main difference between the colloidal and the molecular systems lay in the relative rates of alkylation of the two enantiomers of the substrate. They reported the apparent absence of reaction of one enantiomer using a sample enriched in the (S) substrate for the colloidal catalyst. This apparent lack of reactivity observed at 58-60% conversion was not due to catalyst deactivation, as demonstrated by further addition of substrate, which led to its alkylation at the same rate and with the same selectivity. At the end of the reaction, both nearly enantiomerically pure substrate and product were

obtained. The origin of this selectivity could be due to a particular combination between the metallic surface, the substrate and the ligand.[82]

No differences in the NPs size could be observed when the TEM images were recorded after catalysis. Later, further comparative studies were reported using colloidal and molecular catalytic systems containing three diphosphite ligands (Figure 1.10) and employing different types of allylic substrates. [83]

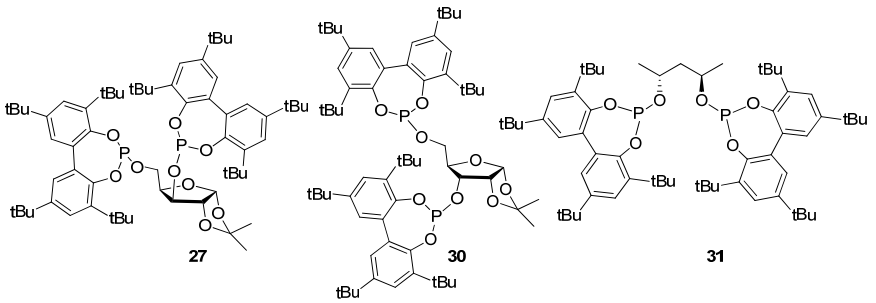


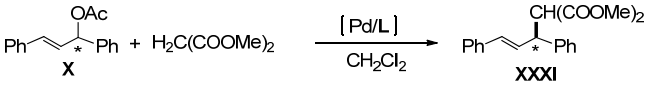
Figure 1.10. Pd-catalysed asymmetric allylic alkylation using molecular complex and NPs systems.

The chiral diphosphites **27** and **30**, which only differ by their C-3 configuration of the carbohydrate backbone, gave significant differences in catalytic behaviour. While the molecular system bearing the ligand **27** is highly enantioselective (ee=90% for the allylic alkylation of **X**), the analogous system with ligand **30** does not induce any enantioselectivity for the same reaction (Table 1.1). In addition, palladium NPs stabilized with these ligands (**Pd27** and **Pd30**) show a remarkable difference in stability. Under catalytic conditions using **X**, **Pd30** NPs decompose into molecular species, whereas **Pd27** does not (Table 1.1).[83] When **Pd30** NPs were used, an "induction period" revealed to be necessary in order to observe conversion. During this period, the leaching of molecular species was expected to take place. The catalytic results obtained after this period were identical to those obtained with molecular catalysts, thus confirming the leaching of homogeneous catalysts from the NPs.

When the molecular catalytic system bearing the flexible ligand **31** was used, high activity and excellent enantioselectivity were observed in the allylic alkylation of **X** with dimethyl malonate as nucleophile. The **Pd31** NPs

constitute a highly active and selective system for the allylic alkylation of **X,** similarly to the analogous molecular catalytic system. In summary, these studies evidenced that the use of Pd NPs may be very effective in these reactions in terms of enantioselectivity (Table 1.1).

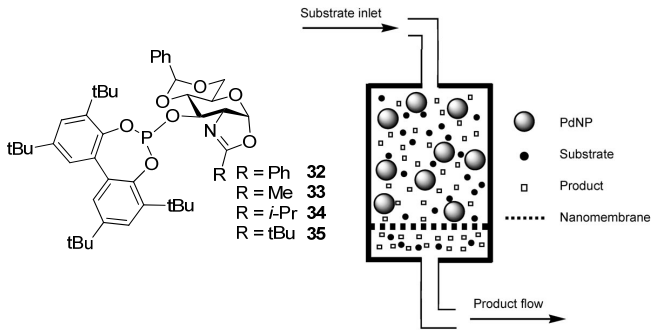
Table 1.1. Pd-catalysed allylic alkylation of **X** using dimethylmalonate as nucleophile.[a]



	Molecular			NPs		
L	**Conv. (%)**	**ee X (%)**	**ee XXXI (%)**	**Conv. (%)**	**ee X (%)**	**ee XXXI(%)**
27	83	0	90 (*S*)	56	89 (*S*)	97 (*S*)
30	80	0	0	0	-	-
31	100	-	94 (*S*)	88	>99 (*S*)	90 (*S*)

a. For the experimental conditions, see ref.[79]. **b**. Based on the substrate and determined by ^{1}H NMR spectroscopy. **c**. Catalytic precursor generated in situ from $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand. **d**. Preformed palladium NPs used as catalytic precursor.

Interesting mechanistic insights were later reported using Pd NPs stabilised by the chiral ligands **32-35** as catalysts for this reaction**.** [84] In this case, the Pd-catalysed asymmetric allylic alkylation of **X** was carried out using a continuous-flow membrane reactor, CFMR (Scheme 1.17). Using this method, the authors established that the behaviour of the Pd NPs depends on the stability of the Pd/ligand system. The **Pd32** NPs were found to be more resistant to leaching of molecular species than the **Pd33** under the same catalytic conditions**.**



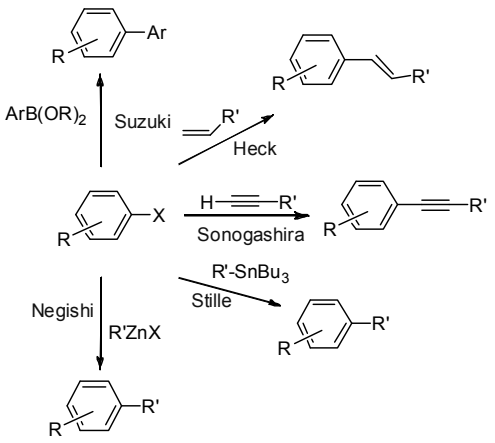
Scheme 1.17. Schematic representation of the oxazolinyl-phosphite ligands **32-35** and membrane reactor used by van Leeuwen and co-workers.[84]

In the case of allylic amination, only one case has been reported using Pd NPs as catalysts. [85] This reaction was carried out using Pd NPs generated in situ from palladium (II) chloride. A wide range of amines (cyclic, open chain, aromatic) and allyl acetates were used.

In the next section, general aspects of the Suzuki-Miyaura coupling reaction will be introduced with particular emphasis on the use of Pd NPs as catalysts in this process.

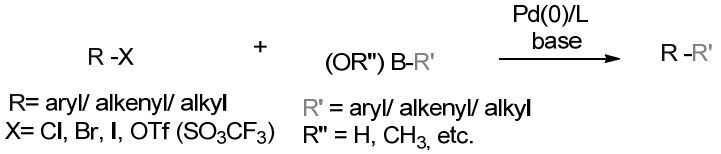
1.4.3 Pd-catalysed Suzuki-Miyaura coupling reactions

The Pd-catalysed C-C bond coupling reactions constitutes one of the most important tools in organic synthesis. In 1901, the first case of cross coupling reaction was reported by Ullman and Bielecki. [86] This reaction involved the obtention of symmetric biaryls via copper-catalysed coupling. Subsequently, new cross-coupling reactions appeared with Pd as the metal center and using other organometallic partners such as Kumada (Mg), Stille (Sn), Hiyama (Si), Neguishi (Zn) and Suzuki (B), among others.[87] (Scheme 1.18).



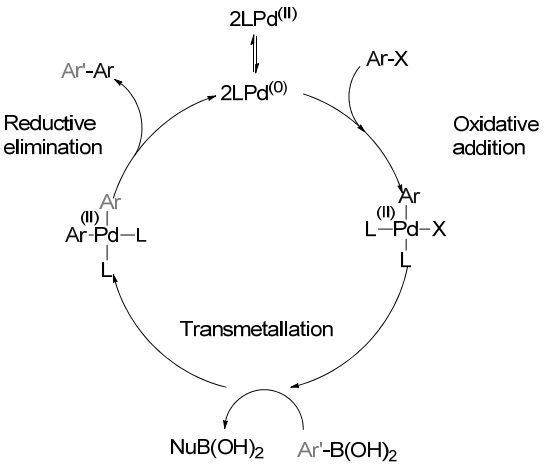
Scheme 1.18. Pd-NPs catalysed C-C bond coupling reactions.

The Suzuki-Miyaura coupling reaction is an important approach for the synthesis of biaryls compounds of industrial importance. This catalytic reaction involves an organoboron reagent, an organic halide or triflate (aryl/alkenyl halides as electrophilic cross-coupling partners) in the presence of a base and a metallic catalyst (Scheme 1.19). In cross-coupling reactions, new carbon-carbon bonds are formed, which is of high interest in organic transformations.



Scheme 1.19. General representation of the Pd-catalysed Suzuki-Miyaura reaction.

For this reaction, the reagents are readily available, nontoxic, and usually air and water stable. Furthermore, the reaction is usually carried out under mild conditions and aqueous solvents, supercritical fluids or supported catalysts can be used.[88] The mechanism of the Suzuki reaction has been widely studied by different methods such as NMR,[89] DFT,[90] and kinetics studies.[91,92,93] The mechanism can be described as three elemental steps: oxidative addition, transmetallation and reductive elimination (Scheme 1.20).



Scheme 1.20. Proposed catalytic cycle for the Suzuki cross coupling reaction

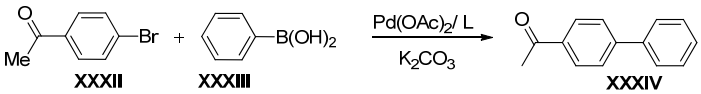
Initially, a coordinatively unsaturated 14-electron species is formed and this step depends on the nature of the palladium precursor. In the precursor, the metal can be in the oxidation state 0 or II. Although the latter requires reduction prior to enter the catalytic cycle, it is usually preferred due to its greater stability. In this reaction, the oxidative addition of the electrophiles to a Pd(0) intermediate has been often described as the rate-limiting step.[94]

In the oxidative addition, an organic halide adds to the metal complex and as a result, the R-X bond is broken and two new bonds are formed, Pd-X and Pd-R. The oxidative addition of alkyl halides can proceed in different ways, although the result is usually a *trans* species, independently of the mechanism. Thus, the electron-rich metal nucleophile attacks the carbon atom of the alkyl halide, the halide being the leaving group. With alkenyl halides, this reaction proceeds with complete retention of configuration and with inversion for allylic and benzylic halides.[95] Aryl and 1-alkenyl halides can be activated by the presence of electron-withdrawing groups that decreases the electronic density. Thefore the organic halides, can be non-activated (electron-neutral), deactivated (electron-rich) or activated (electron-deficient). Senn and Ziegler[96] reported a DFT (Density-Functional Theory) study of the oxidative addition of phenyl halides to palladium (0) complexes bearing bidentate phosphanes and concluded that, in agreement with other results:

a. Ligand dissociation from $Pd(PPh_3)_4$ to form the active species is the first step for oxidative addition and in several cases may even be rate-limiting.[97]
b. The available kinetic data do not allow one to exclude the formation of a pre-reaction complex [(L)Pd (η^2-ArX)].[98]
c. Oxidative addition takes place at the coordinatively unsaturated palladium complex.[99]

The oxidative addition step is therefore of crucial importance in cross coupling reactions and is strongly influenced by the electron density and the nature of the halide reagents. The transmetallation step involves the catalytic intermediate R-$PdXL_2$ and the organoborane to yield a palladium diaryl complex. In this step, the formal oxidation state of the palladium species remains the same. The boron reagents have an important role, as unhindered electron-rich organoboranes together with the electron-deficient vinyl or aryl halides or triflates are the most reactive partners for the reaction. The coordination of a negatively charged base to the boron atom has been documented to be an efficient method of increasing its nucleophile capacity to transfer the organic group from boron to the metal center (1,2-migration reaction).

The reductive elimination is the last step of the catalytic cycle and provides the organic product from a Pd(II)-diaryl species and regenerates the Pd(0) species. Punji reported the influence of the solvents in the coupling between 4-bromoacetophenone **XXXI** and phenylboronic acid **XXXII**, using a wide range of systems (Scheme 1.21).[100] The more polar solvent (methanol) provided high conversion due to the high solubility of the base ($CaCO_3$). Non-polar solvents such as toluene were shown to lead to slower reactions.



XXXII XXXIII XXXIV

Scheme 1.21. Suzuki cross-coupling reaction between 4-bromoacetophenone and phenylboronic acid.

The solvent was also shown to have an important role for the reductive elimination step.[101] When a biaryl phosphine is used in Suzuki-Miyaura coupling, an aryl-aryl interchange phenomenon can arise. Solvents such as THF reduce the formation of by-products when these phosphines are used as ligands. Less hydrophilic solvents such as methylene chloride (CH_2Cl_2) increase the formation of these by-products.[101] The selection of the base in Suzuki coupling is also crucial since it reacts with the organoboron reagent to form a boronate anion, which later acts as nucleophile in the transmetallation step.

It was observed that stronger bases such as NaOH, TlOH, and NaOMe performed well in THF/H_2O solvent systems, whereas weaker bases such as K_2CO_3 and K_3PO_4 were more successful in DMF. [102] The nature of the base has a dramatic effect on the efficiency of the coupling, as reported by Cheng and co-workers.[103] In the coupling reaction of *p*-iodoanisole and phenylboronic acid, the use of bases such as K_2CO_3, Cs_2CO_3, or Na_2CO_3 improved the yield of the desired product, but side products were also produced in substantial amounts. However, the use of CsF led to the formation of the product with essentially no side products. A large number of ligands have been used in Suzuki coupling reactions. A selection of these ligands is shown in Figure 1.11. It was demonstrated that both the rate and the selectivity of this reaction are strongly influenced by the steric and electronic properties of the ligands.[101] They concluded that the active Pd complexes were stabilized by only one bulky monodentate electron-rich ligand.

In the case of bidentate ligands, it is often supposed that in the catalytically active palladium species, the metal atom is coordinated through both donor atoms.[94] Catalytic systems with high σ-basicity ligands have been reported to be very active in the cross-coupling of aryl chlorides.[104] In general, it is considered that the electronic properties of the ligands mainly influence the oxidative addition step whereas their steric bulk is an important parameter during the reductive elimination step.[98] For instance, Pd-complexes that contain bulky phosphines such as the tris(2,4,6-trimethoxyphenyl)phosphine **36** are highly reactive for the oxidative addition (Figure 1.11). Both mono- and bidentate phosphorus-based ligands were reported in this reaction and small structural differences within the ligands were shown to have strong

effects on the outcome of the reaction. For instance, catalysts bearing PCy_3 were found to be very effective in the Suzuki coupling of alkyl chloride although their tricyclopentyl- and triisopropylphosphine analogues revealed to only be poorly active (Figure 1.11).[92]

Buchwald and co-workers reported the use of the SPhos ligands and derivatives **37** and **38** in Suzuki reactions of aryl chlorides at room temperature (Figure 1.11).[105] The performance of these systems strongly depended on the Pd/P ratio and the nature of the palladium source. Others bulky monophosphines such as **39**-**43** have been used in order to study the stabilization that these ligands confer to the catalytic system (Figure 1.11).[106]

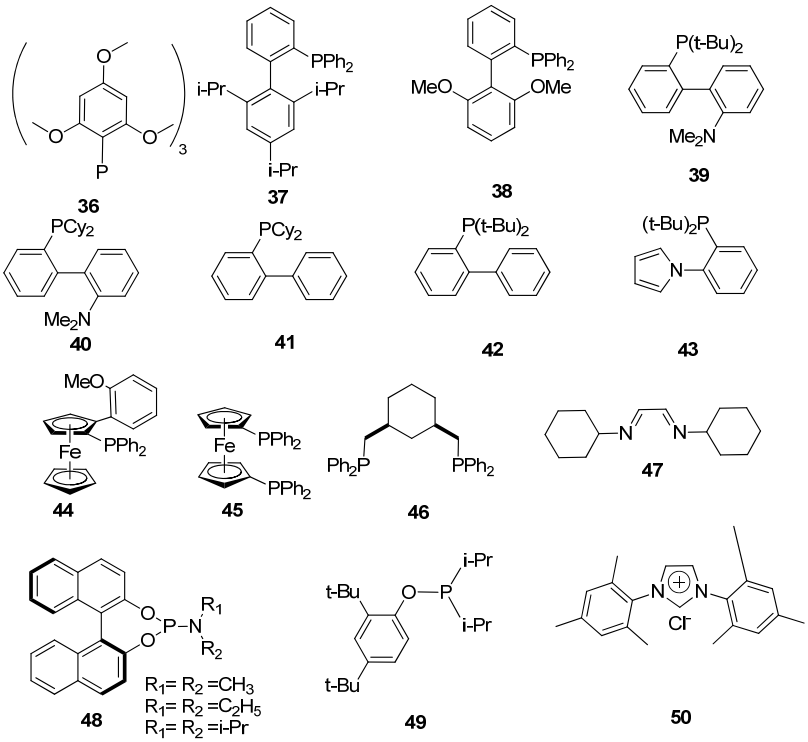


Figure 1.11. Selection of ligands used in Suzuki cross coupling reactions

The influence of the bite angle of bidentate ligands on the catalytic reaction was reported by van Leeuwen and co-workers, who showed that ligands with large bite angles accelerate the rate of reductive elimination.[107] The cross-

coupling of alkylboronates involving iodoalkenyl or aryl halides proceeds in moderate yields in the presence of Tl_2CO_3 and $PdCl_2$(**45**).[107]

Xiao reported ferrocenyl monophosphine ligands synthetised by palladium-catalysed Suzuki- Miyaura coupling. [108] The modular procedure creates a rapid synthesis of phosphines with diverse properties. Electron-rich phosphines such as **44**, have been successfully applied to the Suzuki-Miyaura coupling of activated and deactivated aryl chlorides, with low catalyst loading.

Andersson also reported the use of the bidentate phosphine ligand **46** that gives stable palladium catalysts for Suzuki couplings, as no palladium black formation was observed in the reactions of iodoarenes and bromoarenes. [109] Nolan et al. reported interesting results for the coupling reaction of various aryl bromides and activated aryl chlorides with arylboronic acid using palladium (II) complexes bearing the bidentade diazabutadiene (DAB) ligand **47**.[110] The $Pd(OAc)_2$/DAB-R system was very efficient in the Suzuki-Miyaura cross-coupling reaction of aryl bromides with aryl boronic acids in terms of reactivity, reaction conditions. This system represents unprecedented reactivity for a bis(nitrogen) ligand system with regard to reactivity with unactivated and sterically encumbered substrates, as well as activated aryl chlorides.[110]

Pd complexes bearing monodentate phosphoramidite ligands were reported to catalyze the Suzuki coupling at room temperature in high yields.[111] Wan reported a highly efficient palladium catalysed Suzuki coupling of aryl bromides with arylboronic acids using the phosphoramidite ligand **48**.[111] Other ligands such as palladacycles based on phosphinite ligands such as **49** have also been used in Suzuki coupling of phenylboronic acid with aryl bromides and chlorides.[112] These systems were extremely active for the Suzuki coupling of aryl bromides but not particularly useful for the coupling of aryl chlorides, probably due to the π-acidic properties of the phosphinite ligand.

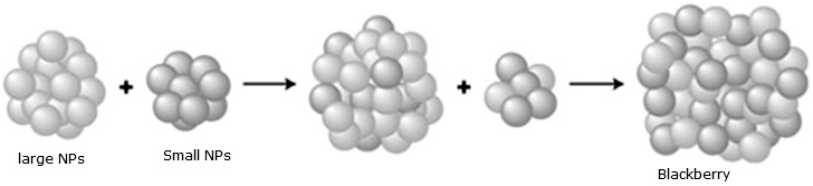
Recently, Pd catalysts bearing N-heterocyclic carbenes (NHCs) have also been successfully reported in the Suzuki-Miyaura reaction. These ligands combine

strong σ-donating properties with a shielding steric pattern that allows both stabilization of the metal center and enhancement of its catalytic activity.[113] For instance, Nolan reported the highly active Pd-catalysed Suzuki-Miyaura reaction of aryl chlorides with phenylboronic acid derivatives using the NHC ligand **50** (yield up to 99%).[114]

1.4.3.1 Pd-NPS as catalysts in Suzuki-Miyaura coupling reactions

Among metallic NPs, the Pd NPs are the most frequently utilised to catalyze the Suzuki coupling reaction.[115] However Ru,[116-117] Cu,[117] Au,[118] and bimetallic NPs have also been used to a lesser extent. In 1996, the first use of Pd NPs as catalysts in C-C coupling reactions was report by Beller and Reetz.[119] So far, several mechanistic approaches to the *modus operandi* of the NPs have been reported.[120] Parameters such as the size, the nature of the stabilizing agent, substrate, etc influence the catalytic activity of the Pd NPs.

Liu reported the Suzuki cross coupling between bromobenzene and phenylboronic acid.[121] In this study, the authors reported the recycling of the nanocatalyst and looked at the "aging" effect on the size of these particles. In the recycling process, small NPs were dissolved to form larger crystalline NPs. This process is called the "Oswald ripening" and has often been observed during NPs recycling (Scheme 1.22). The addition of PVP stabilizers to the reaction mixture diminishes the process but also the catalytic activity due to the lower adsorption of substrates at the metallic atoms.[122]



Scheme 1.22 Representation of the Oswald ripening.

El-Sayed and co-workers have reported a study on the influence of these parameters.[115] For instance, Pd NPs stabilised by PVP with several sizes (3.0, 3.9, 5.2 and 6.6 nm) presented changes in the turn over frequencies (TOFs) by more than a factor of two in this size range. They indicated that when the

NPs are smaller the catalytic activity is lower due to the absorption of the substrates at the NPs surface.

The nature of the stabilizing agents has an important role during the Suzuki coupling reaction. In the case of **PdPVP** NPs (Figure 1.12), their size was found to increase after each recycling.[115b] However, when **PdPAMAM** NPs (PAMA = Poly(amido amine)) were used, aggregation and precipitation of NPs out the solution was observed but TEM analysis showed that smaller NPs were present in solution.[115c]

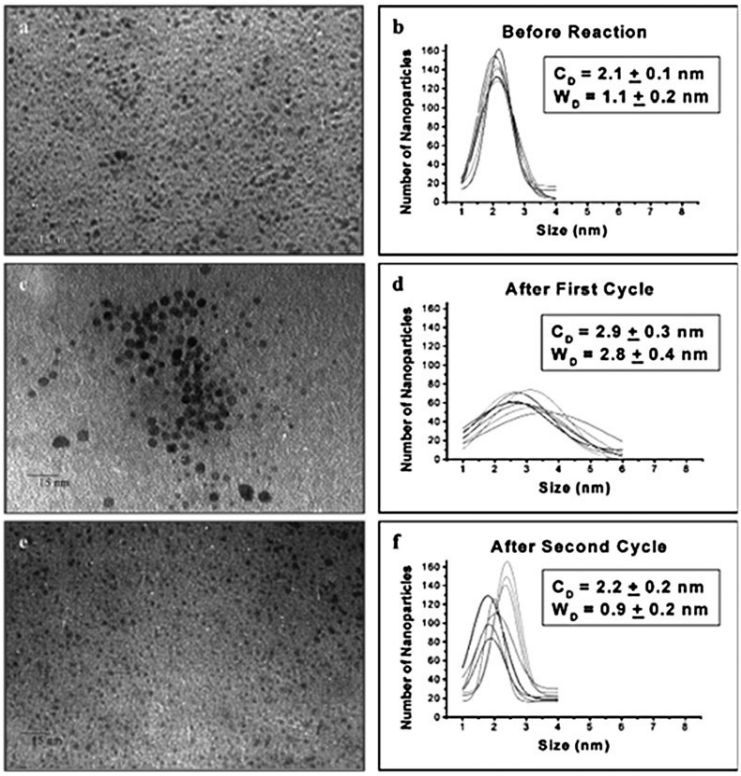
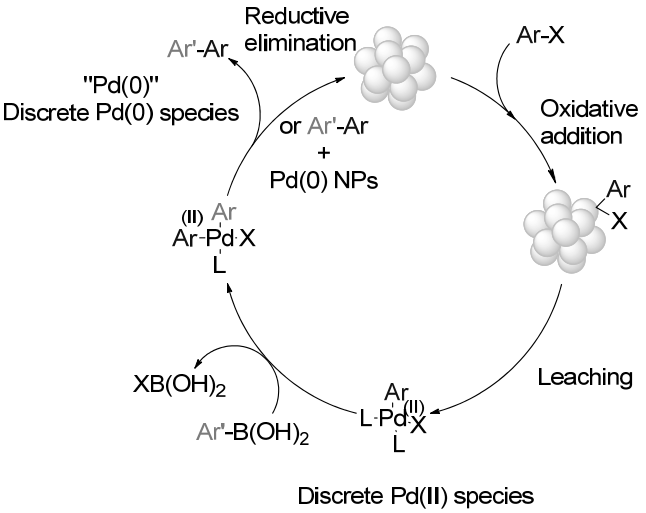


Figure 1.12. TEM images and Gaussian fits of the size distributions of PVP–Pd NPs before the Suzuki reaction (a, b), after the first cycle of the reaction (c, d), and after the second cycle of the reaction (e, f).

This growth process was not observed when the NPs were only placed in presence of iodobenzene. However, in the presence of both iodobenzene and phenyl boronic acid, the NPs increased in size.

The results obtained from the FTIR studies showed that the phenylboronate anion does indeed bind to the nanoparticle surface through both B-O-groups. Because no interaction was observed between iodobenzene and the nanoparticle surface, the mechanism was proposed involve the phenylboronic acid binding the nanoparticle surface in the form of phenylboronate anion followed by its reaction with the iodobenzene present in solution.[123] Then, it is proposed that the mechanism of the Suzuki coupling involves phenylboronic acid binding to the nanoparticle surface and reacting with the iodobenzene in solution.[115b,c]

The thorough study of the recycling and reuse of the catalysts monitored by TEM gave support for important changes in nanoparticle size and shape during the reaction. This observation, together with the lack of homocoupling side reaction using the solid precatalysts, prompted the authors to hypothesize that the active species in catalysis was a discrete soluble Pd(II) species in solution. Following the elimination of the coupled product from the discrete Pd(II) species, the resulting Pd(0) species could oxidatively add another aryl halide to re-enter the catalytic cycle or could cluster to reform Pd NPs or palladium black.[124]



Scheme 1.23. Proposed catalytic cycle using NPs as catalysts in Suzuki coupling reaction

The proposed mechanism (Scheme 1.23) is similar to those described by DuPont[125] for nanoparticle catalysts in ionic liquids and by de Vries[126] for catalysis by homoeopathic, "naked" palladium, although the intermediate species are likely to be more accurately represented as anionic entities.

Gómez et al studied the effect of the metallic precursors used in the synthesis of the NPs.[127] They observed that Pd(II) precursors could not lead to the formation of well-defined NPs, even for ligands containing N-donor groups which should favour their coordination to the metallic surface. In this study they observed that using NPs as catalysts, higher conversion was obtained in the Suzuki-Miyaura coupling reaction of the deactives bromoanisole than for the activated 4-bromobenzotrifluoride, which is in contrast with the results reported for homogeneous catalyst. The authors concluded that the oxidative addition step was favoured with bromoanisole due to the interactions between the donor group of this substrate and the organometallic surface (Figure 1.13).

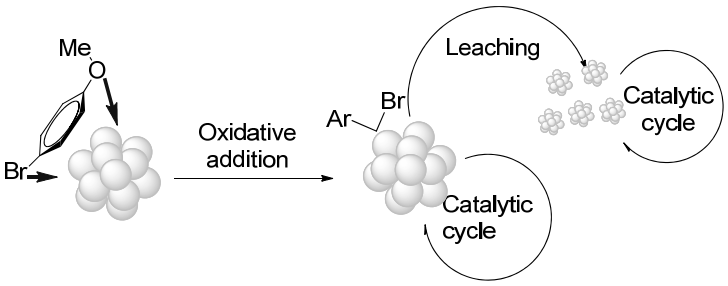
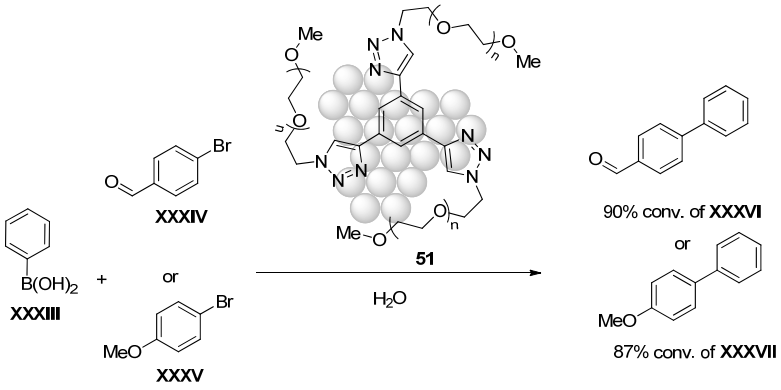


Figure 1.13. Activation of 4-bromoanisole promoted by the metallic surface of palladium NPs.[127]

Recently, new water soluble Pd-poly(ethylene glycol) stabilised NPs displayed good activity as catalysts in the Suzuki coupling of aryl iodides, and of the more challenging bromides and chlorides in aqueous media. These NPs provided good to excellent yields in the coupling of a range of aryl and heteroaryl substrates. The use of water proved to be optimal for the coupling of the **XXXIV** and for deactivated anisole derivatives **XXV**.



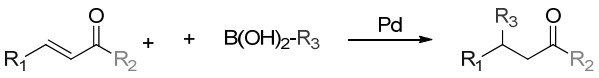
Scheme 1.24. Water-soluble PdNPs as catalysts in Suzuki cross coupling reactions in aqueous media.[128]

In this system, the recyclability of the NPs for aryl iodides and bromides was also established (up to five cycles) giving rise to good isolated yields in successive runs (Scheme 1.24).[128]

Another important C-C bond formation reaction is the conjugate addition to unsaturated substrates. In the next section, the conjugate addition of boronic acids to unsaturated α-β ketones will be introduced.

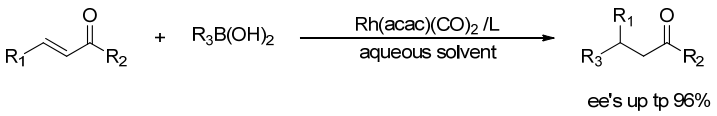
1.4.4 Asymmetric conjugate addition of arylboronic acids to α, β–unsaturated ketones.

The catalytic enantioselective construction of quaternary stereocenters remains a difficult problem in synthetic chemistry.[129] Over the last decades, reliable approach towards this challenge has been the asymmetric conjugate addition of carbon-based nucleophiles to suitable α,β-unsaturated carbonyl acceptors. For the asymmetric version of this reaction, interesting results were achieved using Pd based catalysts.[130] The Pd-catalysed asymmetric conjugate addition of arylboronic acids to α,β-unsaturated ketones involves the nucleophilic attack on an electrodeficient C=C alkene (Scheme 1.25).



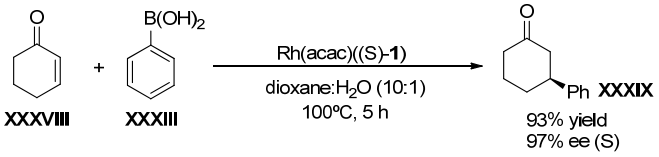
Scheme 1.25. General representation of the Pd-catalysed asymmetric conjugate 1,4-addition reaction with boronic acids

Initially, the majority of asymmetric conjugate additions for the synthesis of quaternary carbon centers involved the use of highly reactive organometallic reagents (e.g., diorganozinc,[131] triorganoaluminum,[132] and organomagnesium reagents[133]) to a variety of unsaturated electrophiles in the presence of copper catalysts.[134] In most of cases, the organometallic reagents were air and moisture sensitive and extremely anhydrous reaction conditions were required. As an alternative, Hayashi and Miyaura reported the first example of air stable chiral rhodium catalysts together with easily handled nucleophilic organoboron reagents with excellent yields and ee's (Scheme 1.26).[135]



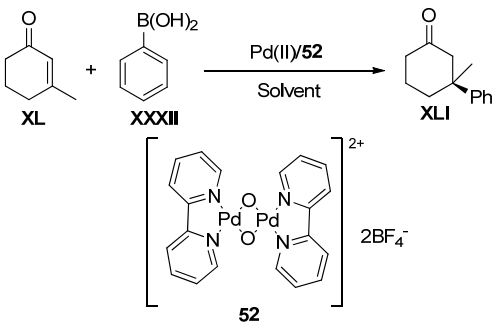
Scheme 1.26. 1,4-addition of α,β-unsaturated ketones using $Rh(acac)(CO)_2$ and several ligands.

The rhodium-catalysed 1,4-addition of organic boronic acids has several advantages over other 1,4-additions: *a)* the organoboronic acids used are relatively stable to oxygen and moisture compared with other organometallic reagents, therefore allowing the reaction to be performed in protic media or even in aqueous solution. *b)* The organoboronic acids are much less reactive toward enones in the absence of a rhodium catalyst than organometallic reagents such as organolithium reagents. *c)* Aryl and alkenyl groups can be introduced at the β-position. Hayashi and co-workers reported the characterization of the complex $RhPh(PPh_3)$(binap), which is a key intermediate in the rhodium-catalysed 1,4-addition.[136] The reaction of phenylboronic acid with 2-cyclohexen-1-one catalysed by Rh/binap is shown in Scheme 1.27.



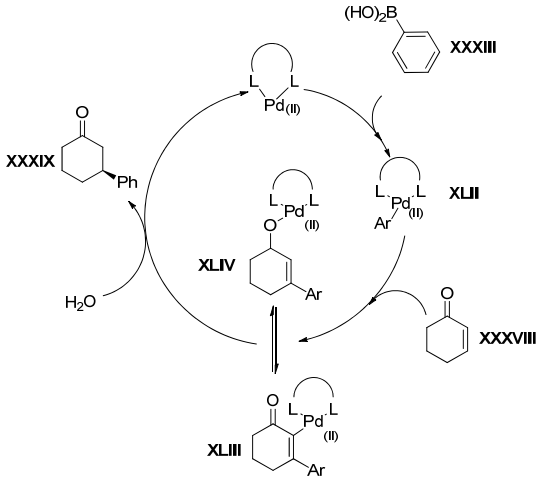
Scheme 1.27. 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one catalysed by the Rh/binap system

The conjugate addition of arylboronic acids and derivatives to enones with palladium catalysis has been investigated for some time and resulted in the development of addition reactions that produce enantioenriched tertiary β-substituted ketones. In 2010, Lu reported the use of dicationic bipyridine derived Pd catalysts for additions to β-substituted enones that yield products containing a quaternary carbon center in high yield (Scheme 1.27).[137,138]



Scheme 1.28 Pd(II)/bpy-catalysed conjugate addition of phenylboronic acid to 3-methylcyclohex-2-enone reported by Lu.[139]

A plausible mechanism for the palladium catalysed conjugate addition was reported and is described in Scheme 1.29.[139] The authors suggested that the transmetallation step yields the aryl Pd species **XLII**. Insertion of the olefin into the carbon–palladium bond gives the palladium enolate **XLIII** or **XLIV**. β-H elimination of the C–Pd bond in **XLIII** is suppressed in the presence of the ligand and protonolysis in water gives the corresponding conjugate addition product **XXXIX** with the regeneration of initial palladium species.



Scheme 1.29. Mechanism of the Pd(II) catalysed conjugate addition reaction.

The enantioselective Pd-catalyzed construction of all-carbon quaternary stereocenters via 1,4-addition of arylboronic acids to β-substituted cyclic

enones was reported by Stoltz and co-workers.[140] In this case, reaction of a wide range of arylboronic acids and cyclic enones using a catalyst prepared from $Pd(OCOCF_3)_2$ and a chiral pyridinooxazoline ligand yields enantioenriched products bearing benzylic stereocenters. Notably, this transformation was tolerant to air and moisture, providing a practical and operationally simple method of synthesizing enantioenriched all-carbon quaternary stereocenters.[140]

Tabatabaeian *et al*., reported the first work in the double conjugate 1,4-addition of indoles to dibenzylacetones in one-pot with good yields using a Ru(III) catalyst.[141] This catalytic system presents the advantage of using methanol instead of non-environment-friendly solvents such as acetonitrile, chlorinated solvents or toluene, which are usually used in this reaction.

Bedford *et al*. reported the 1,4-addition of phenylboronic acid to chalcone catalysed by a platinocycle generated by ortho-platination of tri(2,4-di-*tert*-butylphenyl)phosphate, showing a moderate activity.[142] Hu and co-workers also reported the successful use of orthoplatinated triarylphosphites as catalysts in the addition of aryl boronic acids to aldehydes.[143]

1.5 Objectives

The enantioselective formation of carbon-carbon bonds through catalysis is of high interest for the synthesis of key molecules in fine chemicals and pharmaceutical industry. This thesis focuses on the study of several C-C bond formation reactions using new molecular complexes and NPs as catalytic systems.

The objective of this study includes the synthesis and characterization of new families of metal NPs stabilized by chiral phosphorus-based ligands and their application in the following processes:

1. Pd-catalysed asymmetric allylic substitutions
2. Pd-catalysed asymmetric cross-coupling Suzuki-Miyaura reactions
3. Ni-catalysed Suzuki-Miyaura reactions.
4. Pt-catalysed conjugate 1,4 addition of boronics acids to α,β–unsaturated ketones.

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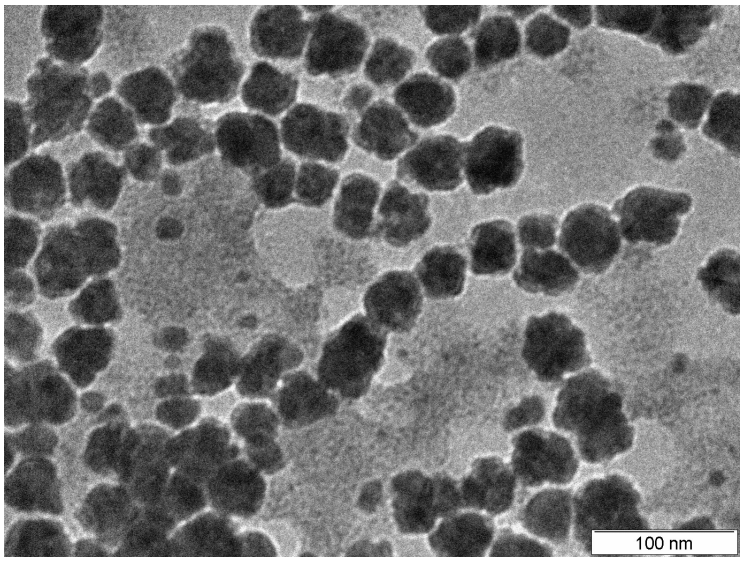
Chapter 2.

Pd-catalyzed asymmetric allylic substitution reactions



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2.1. Background

2.1.1. Phosphite ligands in Pd-catalysed allylic substitution reactions

Catalytic systems bearing chiral phosphorus compounds such as phosphine ligands have been widely studied because of their efficient stereo-discrimination in asymmetric reactions.[1] Chiral diphosphite ligands have also been successfully applied in metal-catalysed asymmetric reactions such as allylic alkylation,[2] asymmetric hydrogenation,[3] asymmetric hydroformylation,[4] etc.

Over the last years, catalytic systems containing chiral diphosphite ligands derived from carbohydrates have emerged as interesting and efficient systems for Pd-catalysed asymmetric allylic substitution reactions.[4] Sugar derived ligands have numerous advantages because they are readily available, highly functionalised, and can be systematically modified. For instance, the carbohydrate backbone can be modulated by varying the diphosphite substituents in order to twice their steric and electronic properties.[4]

Pd/Phosphite systems have been reported to be efficient in allylic substitution reactions of several substrates. Figure 2.1 summarises the most representative substrates used in these reactions.

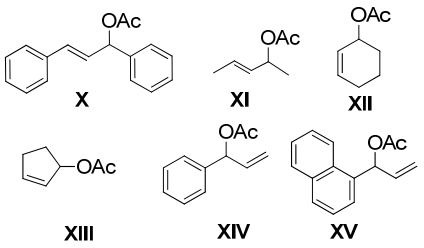
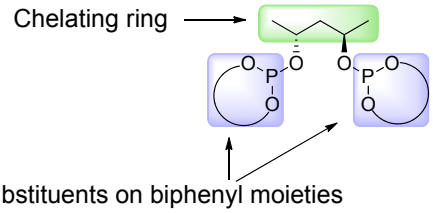


Figure 2.1. Common substrates in Pd-catalysed asymmetric allylic substitution reactions.

Dieguez and co-workers reported the design of a series of diphosphite ligands varying the backbone, size of the chelating ring and the substituents of the biphenyl moieties as shown in Scheme 2.1.[5]

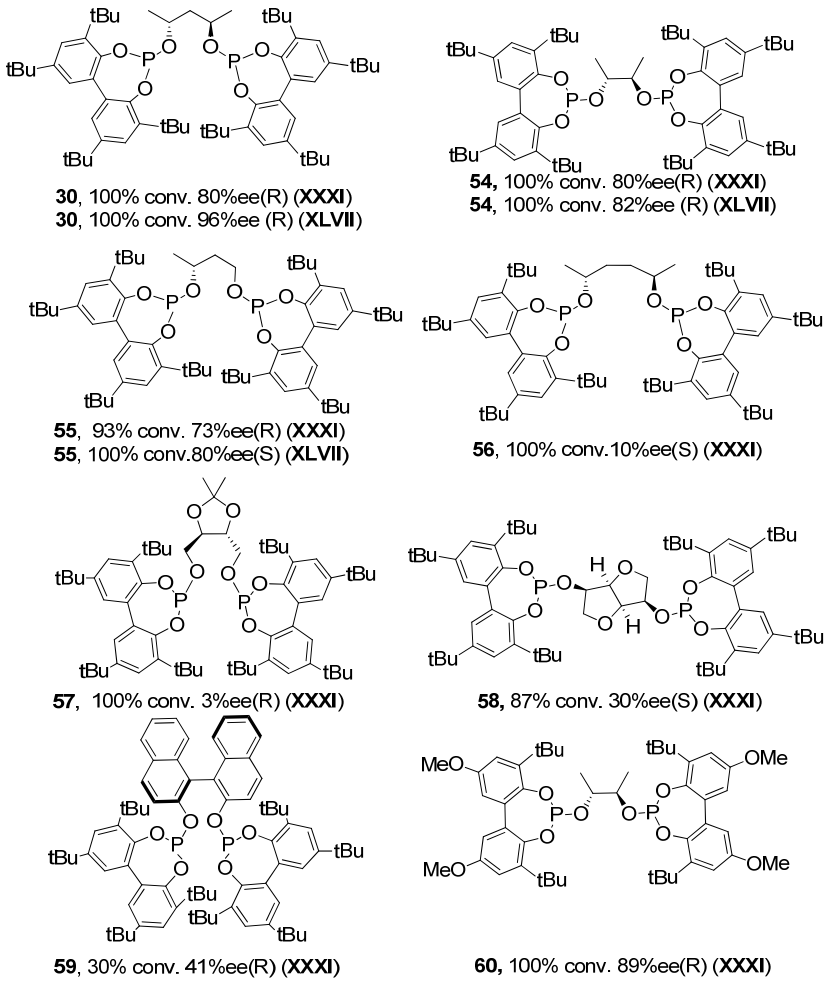


Scheme 2.1. Modular diphosphite ligands (Figure taken from ref. 5).

They studied the scope of this type of ligand in the Pd-catalyzed asymmetric allylic substitution reaction of several model substrates.[5] Good activity (TOF > 200 mol × (mol × h)$^{-1}$) and enantioselectivity (80% (R) ee) were reported in the Pd-catalyzed asymmetric allylic alkylation of **X** using the ligand **30** (Scheme 1.2). This latter ligand **30**, which only differs from ligand **54** by a -CH_2 group in its backbone than ligand **54** (Scheme 2.2), provided the highest activity (TOF > 1200 mol × (mol × h)$^{-1}$) and enantioselectivity (94% (R)).

The results obtained with the ligand **55** indicated that the presence of the two stereocenters in the backbone is necessary to obtain high enantioselectivity (73 % of ee **XLVII**, Scheme 2.2). The catalysts bearing the ligands **56**-**59**, which form a nine-membered chelate ring with the metal, were less active and enantioselective than ligands **30** and **55**, which form an eight-membered chelate ring (Scheme 2.2). In general, ligands containing a more rigid backbone produced higher ee values.

The effect of the different substituents in *ortho* and *para* positions indicated that both activities and enantioselectivities are higher when bulky *tert*-butyl substituents are present at both *ortho* and *para* positions of the biphenyl phosphite moieties (ligands **54** and **60**, Scheme 2.2). In Pd-catalysed allylic amination reactions, similar trends were observed using the ligands **54**-**60**.



Scheme 2.2. Chiral diphosphite ligands used in Pd-catalysed asymmetric allylic substitution reactions.

In 2001, the first family of chiral diphosphite ligands derived from carbohydrates was reported in Pd-catalyzed asymmetric allylic substitution reactions.[6] The C1 symmetry backbone of these ligands can be modulated due to the easy inversion of the configuration at C-3 and C-5 positions and the possibility to introduce an R function at the C-5 carbon (Figure 2.2). Later, a new family of modular furanoside diphosphite ligands was successfully applied in the Pd-catalyzed asymmetric allylic substitution of several substrates.[7]

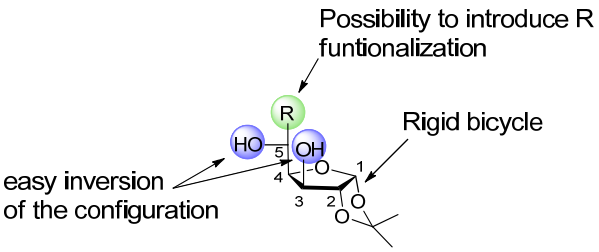
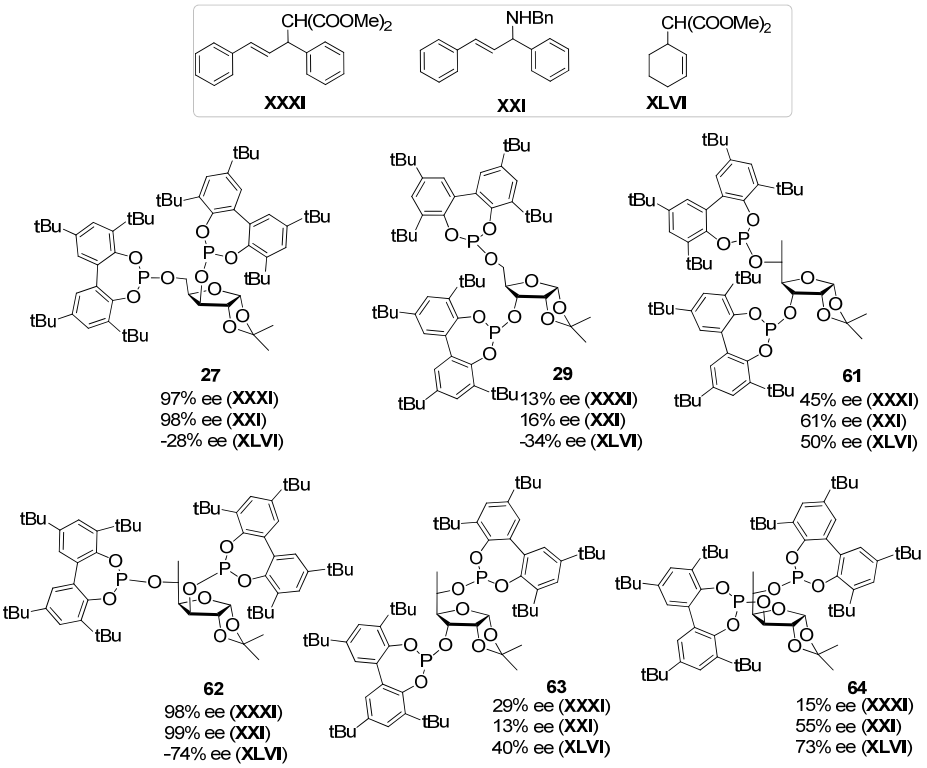


Figure 2.2. The diol carbohydrate in the furanose backbone.

Scheme 2.3 displays the results obtained with chiral diphosphite furanoside derivative ligands applied in the Pd-catalyzed asymmetric allylic substitution of several substrates. In the Pd-catalysed allylic alkylation reaction of **X** to obtain **XXXI**, the enantioselectivities were affected by the substituent at C-5 and the phosphite moiety. Furthermore, they were also affected by the configuration at C-3 and C-5 and at the biaryl moieties. Moreover, the enantioselectivities were best (ee's up to 98%) with the xylo- (**27**) and gluco-furanoside (**62**) ligands containing bulky substituents at the ortho positions of the biaryl moieties. Moreover, a cooperative effect between C-3 and C-5 was observed (Scheme 2.3).[7]

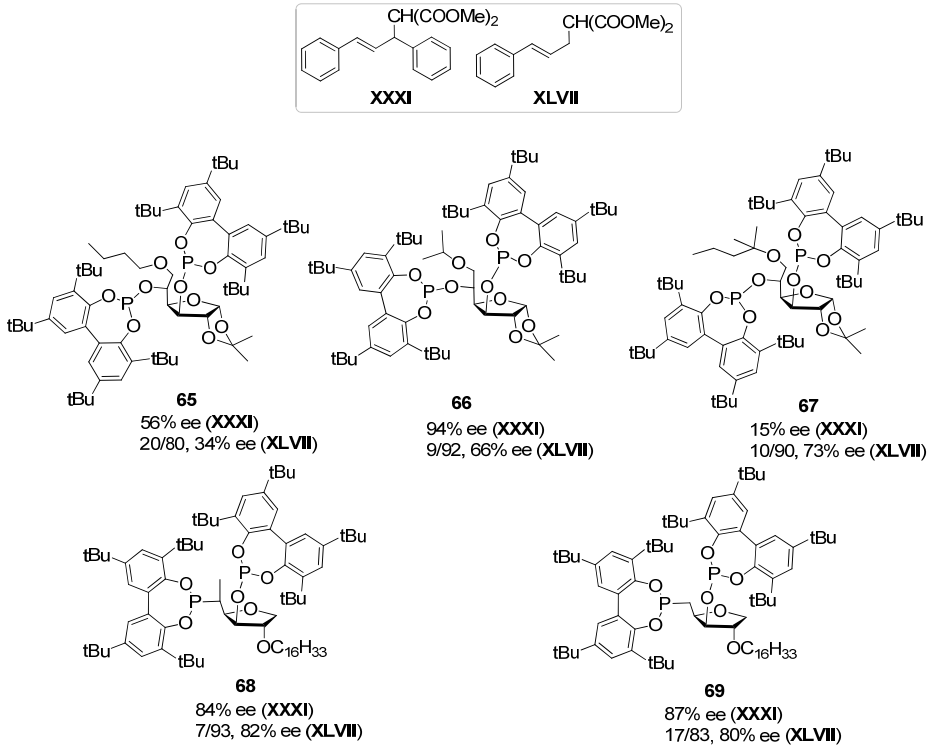
In the Pd-catalysed asymmetric allylic amination of **X** to obtain **XXI,** the enantiomeric excesses were higher (ee's up to 99% at room temperature) with ligands **62** (-74% ee) and **64** (73% ee). Therefore, to obtain high enantioselectivities, the ligand must contain a substituent at C-5. These results also indicated that the configuration at C-5 controls the enantioselectivity (Scheme 2.3).[7]



Scheme 2.3. Furanoside diphosphite ligands used in Pd-catalysed asymmetric allylic alkylation and amination reactions.

Recently, a new series of C1-symmetrical 1,3-diphosphite ligands with a furanoside backbone, **65**-**69** was reported and used in the Pd-catalysed asymmetric allylic alkylation of mono- and disubstituted linear substrates (Scheme 2.4).[8] The backbones of these diphosphite ligands were selectively modified to study the effect of the ligand structure on the catalytic performances.[8] Using the ligand **65,** the product **XXXI** was formed with 53% conversion and 95% ee. Furthermore, the enantiopure substrate **X** was recovered (99.9% ee) (Scheme 2.4). High regioselectivities (up to 9/92% linear/branched) and up to 94% ee was obtained with the catalytic system containing the ligands **66**, **68** and **69**. The study of the 1,3-diphenyl Pd-π-allyl intermediates by NMR spectroscopy indicated that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety at the C-5 position of the carbohydrate backbone.

However, the difference in enantioselectivity observed cannot be explained by the reactivity of the nucleophile versus the different π-allyl intermediates.



Scheme 2.4. C1-symmetriy diphosphite ligands used in Pd-catalysed asymmetric allylic alkylation and amination reactions.

It is usually assumed that although a symmetric ligand is no guarantee of high enantioselection, the number of possible diastereomeric intermediates or transition states in a catalytic process could be likely reduced, and thereby increases the probability of a highly selective process. A bidentate C2-symmetric ligand in a tetrahedral or square planar geometry (Figure 2.3) renders the two remaining coordination sites equivalent (homotopic).[9]

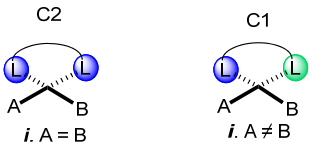


Figure 2.3 Geometry differences between C2- and C1-symmetry ligands.

Chiral carbohydrate diphosphite ligands with C2-symmetry have been used with success in the Rh-catalysed asymmetric hydroformylation of vinylarenes[10,11] with high enantioselectivities.

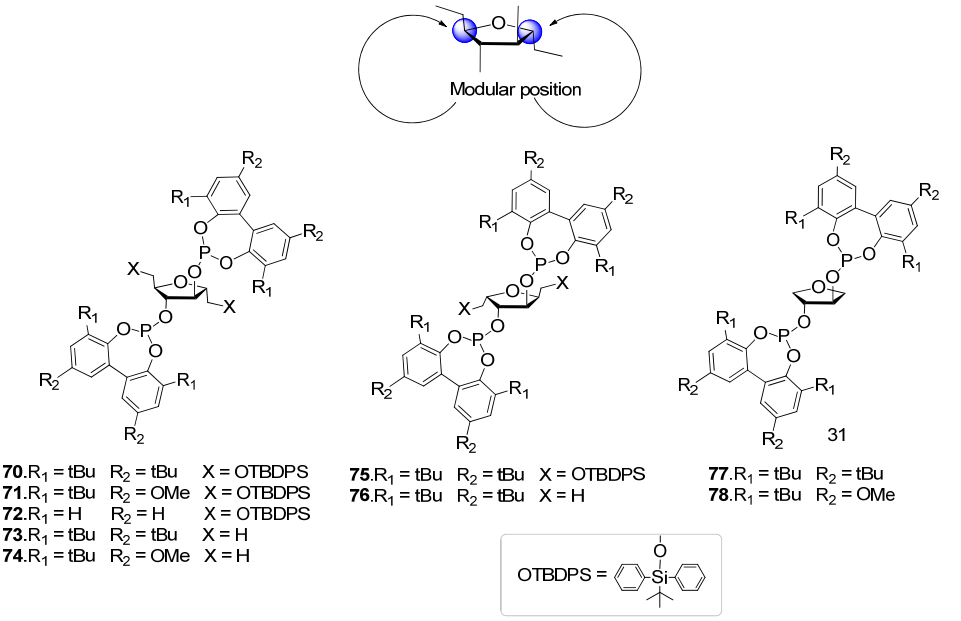


Figure 2.4. Modular chiral diphosphite ligands derived from carbohydrate with C2-symmetry used in Rh-catalysed asymmetric hydroformylation of vinylarenes.[10]

Nevertheless, C2-symmetry chiral carbohydrate diphosphite ligands had not been reported in the Pd-catalysed asymmetric allylic alkylation reactions. In this chapter, we present the studies of the catalytic activity of the Pd systems bearing C2-symmetry diphosphite ligands in the asymmetric allylic substitution of **X** and **XXI** substrates using several nucleophiles. In addition, parallel studies using NPs stabilised with these ligands will be presented. NPs catalysts stabilised by C1-symmetry diphosphites were reported and used in

the Pd-catalysed asymmetric allylic substitution of **X**, achieving high conversion and enantiomeric excess (up to 97%) (Chapter 1).[14, 15]

2.2. Results and Discussion

As previously mentioned, the catalysts containing C1-symmetry diphosphite ligands reported by Diéguez[5] were shown to be efficient in Pd-catalysed asymmetric allylic alkylation and allylic amination reactions.[11] In this chapter, our results in Pd-catalysed asymmetric allylic substitutions using the C2-symmetry chiral diphosphite ligands **70** and **75** are presented.

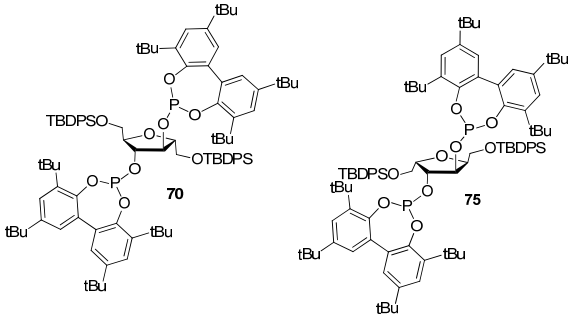
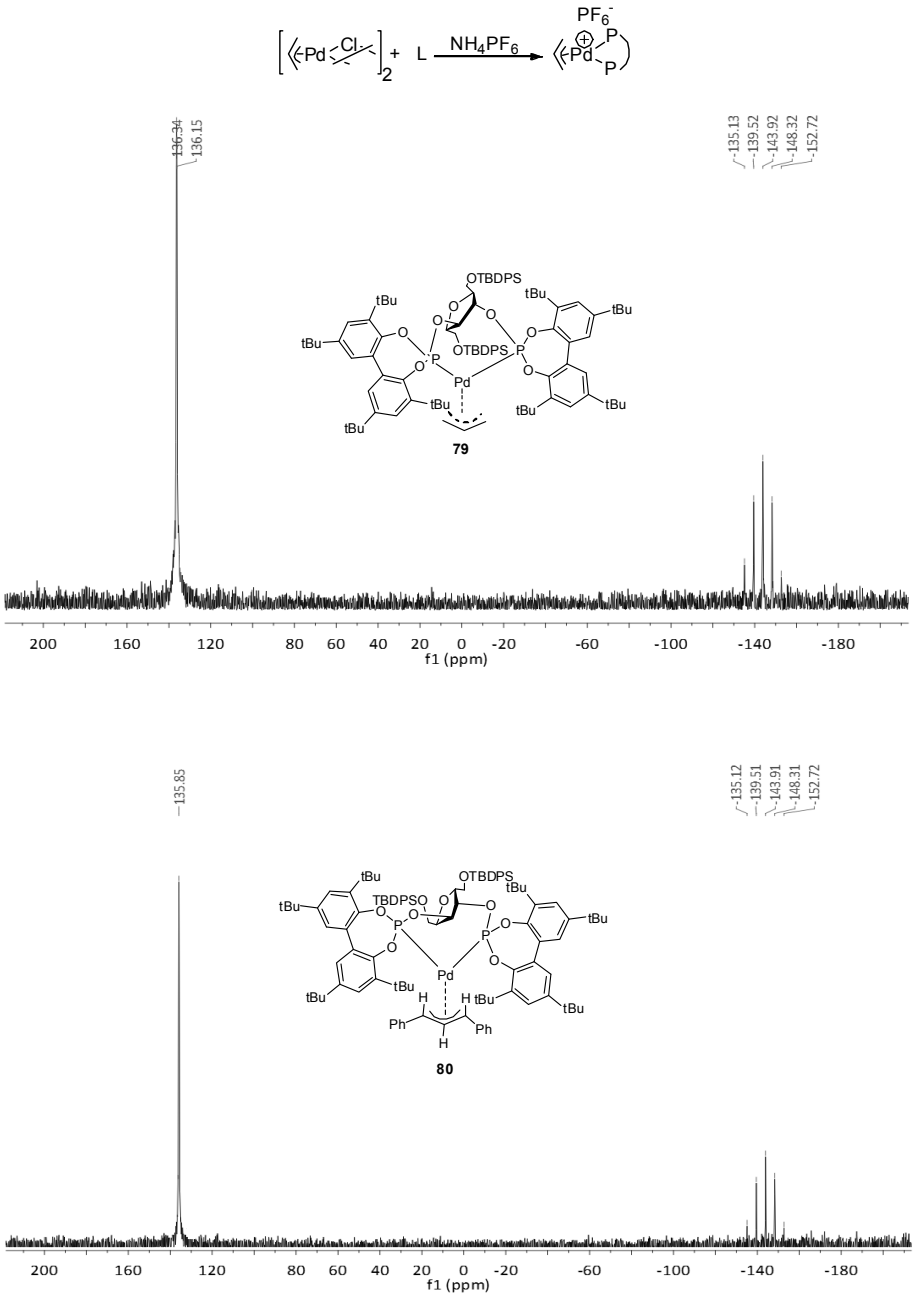


Figure 2.5. Structure of the carbohydrate derived chiral diphosphite ligands **70** and **75**.

Initially the ligands **70** and **75** and the corresponding cationic complexes were synthesized following reported methods.[10,12]

2.2.1. Synthesis of palladium precursors

The cationic palladium complexes, $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{70})]PF_6$, **79**, and $[Pd(\eta^3\text{-}C_3H_5)(\mathbf{75})]PF_6$, **80**, were prepared from the palladium dimer $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)_2]_2$ with the ligands **70** and **75**, respectively, and in the presence of ammonium hexafluorophosphate (Scheme 2.5), following the methodology previously described.[12] These complexes were characterized by NMR spectroscopy and mass spectrometry (see experimental section). ^1H and $^{31}P\{^1H\}$ NMR spectra showed the presence of only one species in both cases (Scheme 2.5).



Scheme 2.5. $^{31}P\{^{1}H\}$ spectra of the palladium complexes **79** and **80** in CD_2Cl_2.

Due to difficulties to obtain crystals suitable for X-ray characterisation of the Pd complexes **79** and **80**, the analogue Pt complex containing the ligand **70**,

[$PtCl_2$(**70**)], **81** was synthesised and monocrystals suitable for X-ray diffraction were obtained by slow diffusion of OEt_2 into a CH_2Cl_2 solution of the complex. The X-ray analysis show the presence of one diethyl ether molecule (OEt_2) per complex molecule, thus the complex should be formulated $C_{94}H_{126}Cl_2O_9P_2PtSi_2.C_4H_{10}O_2$. The complex is located on a crystallographic two-fold axis passing through the metal and the tetrahydrofuranyl oxygen O4.

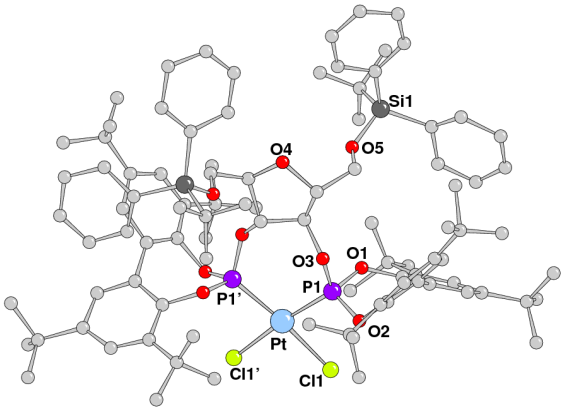


Figure 2.6 Molecular structure of the complex **81**.

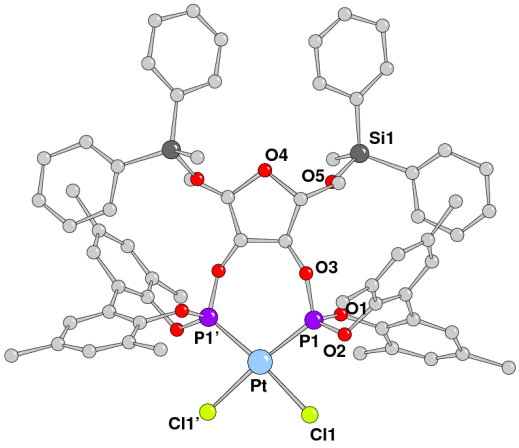


Figure 2.7 Other view of the molecular structure of the complex **81**.

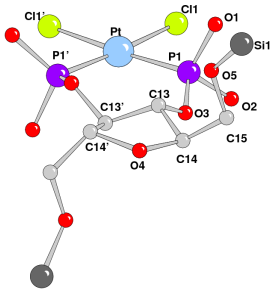


Figure 2.8 Simplified picture (methyl groups are omitted for clarity) of the molecular structure of the **81** complex.

The metal presents a square planar geometry with coplanar donor atoms. The Pt-P bond lengths (2.201(5) Å) are slightly shorter than the Pt-Cl ones (2.336(5) Å). It is worth noting the difference between the Cl(1)-Pt-Cl(1') and the P(1')-Pt-P(1) bond angle, likely induced by steric factors and the geometry of the chelating ligand. The rings of the biphenyl moiety are tilted by *ca*. 50°.

Table 2.1. Experimental X-ray diffraction parameters and crystal data for **81**.

Empirical formula	$C_{98}H_{136}Cl_2O_{10}P_2PtSi_2$
Formula weight	1858.18
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system space group	Monoclinic, C2
Unit cell dimensions	a = 21.970(2) A alpha = 90 deg. b = 19.724(2) A beta = 104.120(11) deg. c = 13.1980(12) A gamma = 90 deg.
Volume (Å)	5546.4(10)
Z, Calculated density (Mg/m^3)	2, 1.113
Absorption coefficient (mm^{-1})	3.661
F(000)	1948
Theta range for data collection	3.05 to 46.16 deg
Reflections collected / unique	11510 / 4217 [R(int) = 0.0480]
Data>2sigma(I)/restraints/parameters	3875 / 55 / 522
Goodness-of-fit on F^2	1.114
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.1416
Absolute structure parameter	0.021(14)
Largest diff. peak and hole ($e/Å^3$)	0.872 and -0.696

Table 2.2 Selected bond lengths (Å) and angles (°) for complex **81**.

Bond lengths (Å)		Bond angles (°)	
Pt-P(1)	2.201(5)	Cl(1)-Pt-Cl(1')	90.2(3)
Pt-Cl(1)	2.336(5)	P(1')-Pt-P(1)	101.9(2)
P(1)-O(1)	1.583(10)	P(1')-Pt-Cl(1)	174.2(2)
P(1)-O(2)	1.580(9)	P(1)-Pt-Cl(1)	83.95(14)
P(1)-O(3)	1.579(9)		

These data can be compared with the analogue Rh complex [Rh(**70**)(COD)]BF_4, **82** reported by Castillón *et al*. (Figure 2.10). [10] The compound **82** crystallises with two independent cations in the elementary cell (Figure 2.9 and Figure 2.10). The monocritaline structure indicates that the independent cations detected in the crystal cell differ in their conformation. In molecule A, the five-membered ring has a twisted conformation and in molecule B this ring has an envelope conformation.

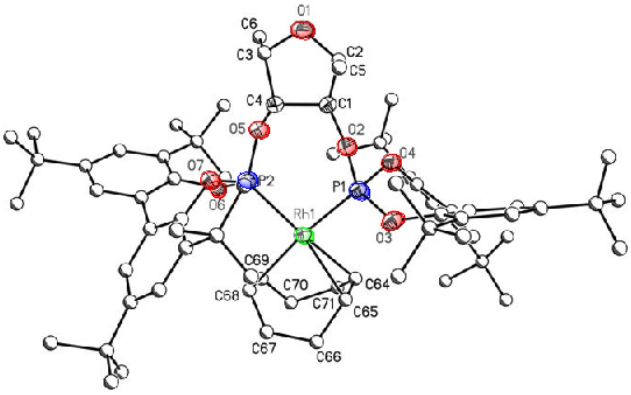


Figure 2.9 ORTEP diagram (ellipsoids at 50% probability level) of [Rh(**70**)(COD)]BF_4 (**82**), molecule A. Counterions, solvates and hydrogen atoms have been omitted for the sake of clarity.

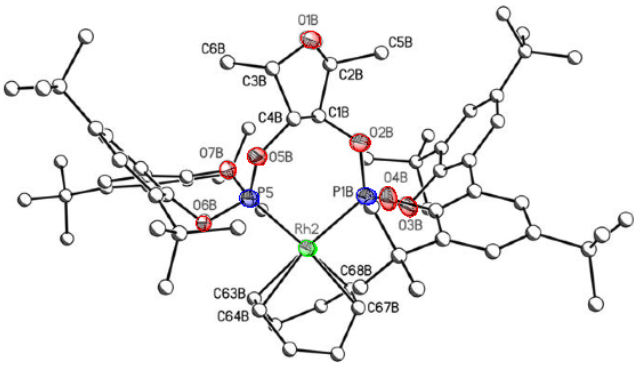


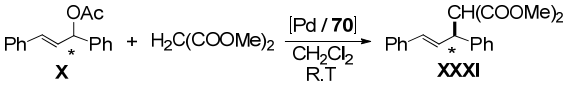
Figure 2.10 ORTEP diagram (ellipsoids at 50% probability level) of [Rh(**70**)(COD)]BF_4 (**82**), molecule B. Counter-ions, solvates and hydrogen atoms have been omitted for the sake of clarity.

The bond distances and angles measured for the Pt **81** complex were similar to those of the reported Rh **82** complex.

2.2.2. Pd-catalysed asymmetric allylic alkylation of X using catalytic systems bearing the chiral diphosphite ligands 70 and 75.

The results obtained in the Pd-catalysed asymmetric allylic alkylation of **X** using the Pd complex containing the ligand **70** are shown in Table 2.3. The reaction was carried out in dichloromethane as solvent at room temperature, using N,O-bis-(trimethylsilyl) acetamide (BSA) and dimethyl malonate as nucleophile and a catalytic amount of potassium acetate. When the reaction was performed with 2 mol % of catalyst, total conversion was reached in 10 minutes with 98% ee (entry 1, Table 2.3). Similar results were achieved using the isolated complex **80** as catalytic precursor after 30 minutes, 98% ee (entry 2). When the **X**/Pd ratio was increased to 5000, 34% conversion was obtained after 5 min of reaction (entry 3, TOF = 20,400); after 1 h, 89% conversion was achieved (entry 4). In both cases, excellent asymmetric induction was reached (ee ≥ 96%). To the best of our knowledge, this is the highest TOF value reported for Pd catalyzed asymmetric allylic alkylation reaction at this level of enantioselectivity.

Table 2.3 Pd-catalysed asymmetric allylic alkylation of **X** using the chiral diphosphite Pd/**70** system as catalyst and dimethyl malonate as nucleophile.[a]



Entry	Pd/70/X	Time (min)	Conv. (%)[b]	Ee(X) (%)[c]	Ee(XXXI) (%)[c]
1	1/1.25/50	10	100	-	98 (*S*)
2[d]	1/1.25/100	30	100	-	98 (*S*)
3	1/1.25/5000	5	34	nd	96 (*S*)
4	1/1.25/5000	60	89	nd	96 (*S*)
5	1/1.25/10000	15	55	99 (*S*)	98 (*S*)
6	1/1.25/10000	30	55	99 (*S*)	98 (*S*)
7	1/1.25/10000	120	55	99 (*S*)	98 (*S*)
8[e]	1/1.25/10000	15	0	>98 (*S*)	>98 (*S*)
9[e]	1/1.25/10000	1440	20	>98 (*S*)	>98 (*S*)

a. Reaction conditions: 1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of N,O-bis(trimethylsilyl)acetamide (BSA); Pd/**70** = 0.5 $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ + 1.25 eq. of **70**, a pinch of KOAc in 4 mL of CH_2Cl_2 at room temperature. **b.** Conversion determined by ^1H NMR analysis. **c.** Enantiomeric excess determined by HPLC on a Chiracel-OJ column. Absolute configuration, between brackets, determined by optical rotation. **d**. Catalyst precursor = **79**. **e.** Mixture of **X** and **XXXI** obtained from entry 7 used as substrate.

Interestingly, using a substrate to palladium ratio of 10,000, a maximum conversion of 55% (entries 5-7) was reached with a TOF = 22,000 h^{-1} after 15 minutes of reaction. These results are significantly higher than those previously reported with other systems. For instance, very active Pd-catalyst bearing modular chiral diphosphite derived from L-tartaric acid **83** and **84**, were used with the same substrate **X** and afforded 7200 h^{-1} of conversion rates and ee's up to 68% (Figure 2.11).[13]

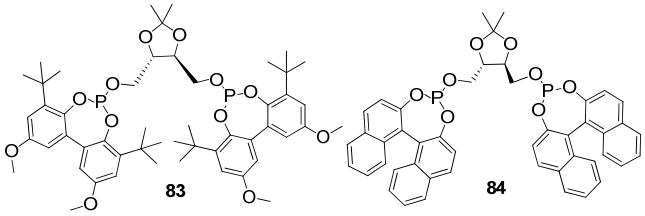


Figure 2.11. Modular chiral diphosphite derived from L-tartaric acid

The remaining substrate (S) was used to measure the differences of reaction rates for both enantiomers. The resulting reaction mixture containing the

enantiopure (S)-**X**, (S)-**XXXI**, was re-used as substrate under the same catalytic conditions (entries 8 and 9). After 24h of reaction, only 20% of conversion was observed. This fact evidences that the reaction rate for the transformation of the (S)-**X** is more than 100 times slower than that of the corresponding (R)-**X** enantiomer.

The Pd-catalysed asymmetric allylic alkylation of **X** was carried out with the Pd catalyst system containing the chiral ligand **75** and using dimethyl malonate as nucleophile under the conditions described in Table 2.3. However, poor reproducibility and very low conversions were obtained. By comparison with the catalytic system bearing the ligand **70,** it can be concluded that the different spatial disposition of the substituents at C2 and C5 of the tetrahydrofuran backbone of the ligands have a strong influence on the activity of the system. Such a remarkable remote effect was previously reported for Rh catalysts bearing the ligands **70** and **75** and their diphosphinite analogues (**85** and **86**) in other catalytic processes.[10] The increased steric hindrance induced by the ligand **75** at the metal centre could explain these observations.

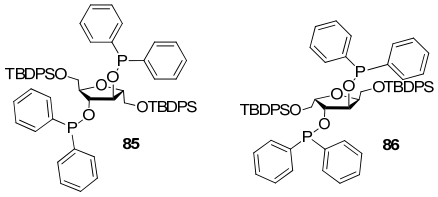


Figure 2.12. Chiral carbohydrate diphosphinite ligands **85** and **86** with C2-symmetry**.**

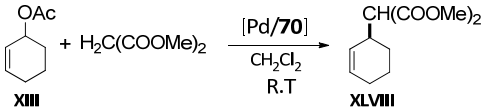
Next, the Pd-catalysed asymmetric allylic alkylation of the more challenging cyclic substrate **XIII** was performed.

2.2.3. Pd-catalysed asymmetric allylic alkylation of the cyclic substrate XIII using catalyst bearing the chiral diphosphite ligand 70.

The results of the Pd-catalysed asymmetric allylic alkylation of **XIII** with the chiral ligand **70** and using dimethyl malonate as nucleophile are summarised in Table 2.4. Moderate conversion (up to 27%) and ee (up to 42%) were achieved after 5 min of reaction time with the catalytic system Pd/**70** (entry

1). However, total conversion was afforded after 90 min with 52% ee (entry 3). The unreacted substrate was found to be a racemic mixture, indicating that both enantiomers had reacted at similar rates. At lower catalyst concentration (Pd/**XIII** = 1/5000) the conversion dropped to 21% after 24h although the ee increased to 66% (entry 4) under the same reaction conditions.

Table 2.4. Pd-catalysed asymmetric allylic alkylation of rac-**XIII** with chiral ligand **72** using dimethyl malonate as nucleophile.[a]



Entry	Pd/70/XIII	Time (min)	Conv. (%).[b]	Ee(XIII) (%)[c]	Ee(XLVIII) (%)[c]
1	1/1.25/50	5	27	0	42 (*S*)
2	1/1.25/50	15	59	0	50 (*S*)
3	1/1.25/50	90	100	0	52 (*S*)
4	1/1.25/5000	1440	21	nd	66 (*S*)

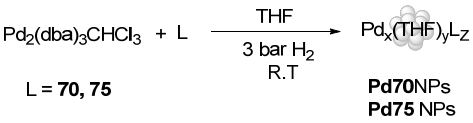
a. Reaction conditions: 1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of N,O-bis(trimethylsilyl)acetamide (BSA); [Pd/**70**]= 0.5 $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ + 1.25 eq. of **70**, neither presented any representative conversion KOAc in 4 mL of CH_2Cl_2 at room temperature; **b**. Conversion determined by ^1H NMR analysis; **c.** enantiomeric excess determined by HPLC on a Chiracel-OD column. Absolute configuration, between parentheses, determined by optical rotation.

The analogous catalytic system bearing the ligand **75** was not active in the Pd-catalyzed allylic alkylation of this substrate. This could be due to the increased steric hindrance induced by the ligand **75**.

To conclude, the catalytic system containing the diphosphite ligand **70** was tested in the Pd-catalyzed allylic alkylation of **X** and was highly active and enantioselective. The highest turnover frequency reported to date for this reaction was obtained (TOF = 22,000 h^{-1}) with excellent ee (up to >99%). Surprisingly, the results obtained with the ligand **75** clearly demonstrate that small changes in the ligand structure can significantly affect the catalytic activity. The differences in reactivity of both enantiomers of the substrate allow the isolation of both the pure product **XXXI** (ee 99%) and the unreacted substrate **X-**(S) (ee 99%).

2.2.4. Synthesis of Pd-NPs stabilized by the ligands 70 and 75.

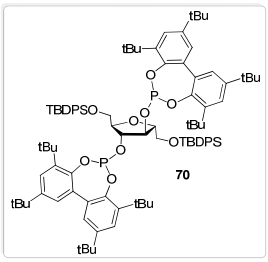
The **Pd70** and **Pd75** NPs were synthesized from $[Pd_2(dba)_3{\cdot}CHCl_3]$ and the appropriate chiral diphosphite ligand, using the methodology reported by Chaudret and co-workers (Scheme 2.6)[14]



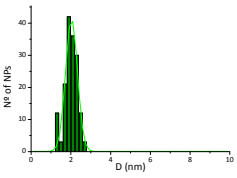
Scheme 2.6. Synthesis of the Pd NPs **Pd70** and **Pd75**.

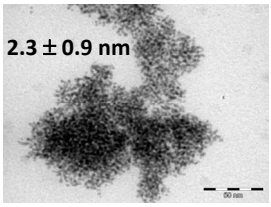
As a standard procedure, the decomposition of $[Pd_2(dba)_3{\cdot}CHCl_3]$ was carried out in a Fischer-Porter bottle under 3 bar of H_2 at room temperature and in the presence of sub-stoichiometric amounts of the appropriate chiral ligand in THF (Scheme 2.6). During the course of the synthesis, the initial purple solution turned black, confirming the decomposition of the precursor.

Finally, the Pd NPs were isolated as black powders after precipitation with pentane. The NPs were characterized by transmission electron microscopy (TEM) and elemental analysis. The Figure 2.13 describes the results obtained with the chiral ligand **70** using L/Pd ratios of 0.2, 0.4 and 0.6. In all cases, the TEM revealed the presence of small spherical NPs.

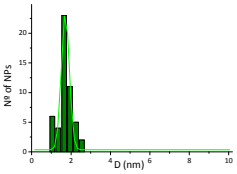


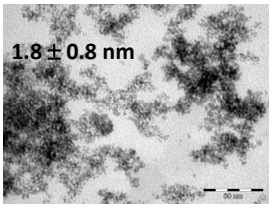
[Pd/**70**]=1/0.2
Pd70 NPs



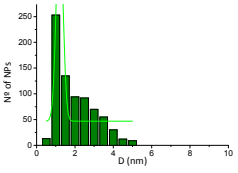


[Pd/**70**]=1/0.4
Pd70$_{(0.4)}$ NPs





[Pd/**70**]=1/0.6
Pd70$_{(0.6)}$ NPs



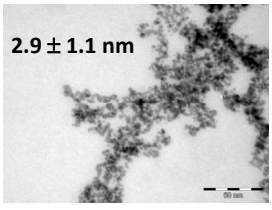
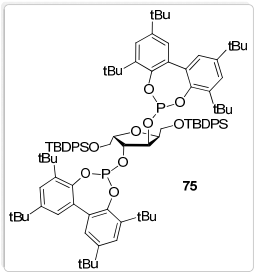


Figure 2.13. TEM micrographs and size histograms for Pd-NPs stabilized by ligand **70**.

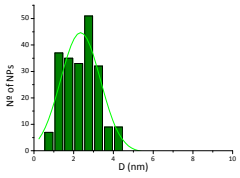
The stabilization of the PdNPs using the ligand **70** was performed using different Pd/P ratio to determine the effect of the ligand concentration on the shape, size and activity of these colloidal entities. As shown in Figure 2.13, small NPs were obtained using different Pd/L ratio (1/0.2, 1/0.4 and 1/0.6). The mean diameter using Pd/**70** = 1/0.2 was 2.3 ± 0.9 nm. At higher Pd/P ratios **Pd70**$_{(0.4)}$ NPs and **Pd70**$_{(0.6)}$ NPs had a mean diameter of 1.8 ± 0.8 nm and 2.9 ± 1.1 nm, respectively.

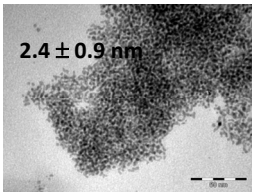
As described in Figure 2.14, NPs were prepared using the ligand **75** as stabiliser at different Pd/P ratios (**Pd75** NPs, **Pd75**$_{(0.4)}$ NPs and **Pd75**$_{(0.6)}$ NPs).

In this case, the **Pd75** NPs exhibited a mean diameter of 2.4 ± 0.9 nm. The **Pd70$_{(0.4)}$** NPs and **Pd70$_{(0.6)}$** NPs presented a mean diameter of 3.1 ± 0.8 nm 1.3 ± 1.1 nm respectively.

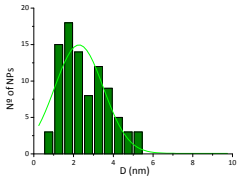


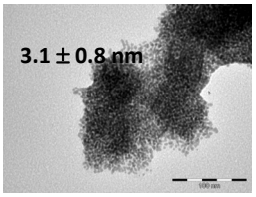
[Pd/**75**]=1/0.2
Pd75 NPs



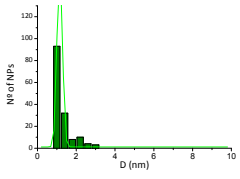


[Pd/**75**]=1/0.4
Pd75$_{(0.4)}$ NPs





[Pd/**75**]=1/0.6
Pd75$_{(0.6)}$ NPs



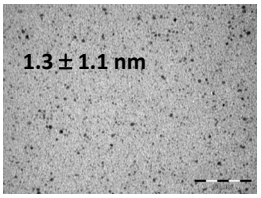


Figure 2.14. TEM micrographs and size histograms for Pd-NPs stabilized by ligand **75**.

It is important to note that **Pd75$_{(0.4)}$** were larger than **Pd75** and that **Pd75$_{(0.6)}$** were smaller than **Pd75**. This is the opposite effect to that observed with the NPs stabilized by the ligand **70** since **Pd70$_{(0.4)}$** were smaller than **Pd70** and that **Pd70$_{(0.6)}$** were larger than **Pd70**. No clear trend could thus be deduced for these results.

Next, the Pd NPs stabilized by the diphosphite ligands **70** and **75** were used as catalytic precursors in the Pd-catalysed asymmetric allylic alkylation of **X**.

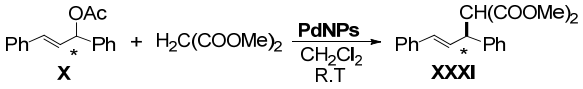
2.2.5. Pd-catalysed asymmetric allylic alkylation of X in the presence of Pd70 and Pd75 NPs.

Table 2.5 collects the results obtained in the Pd-catalysed asymmetric allylic alkylation of **X** with dimethyl malonate as nucleophile in dichloromethane using the preformed **Pd70** and **Pd75** NPs as catalyst precursors. When the reaction was carried out in the presence of **Pd70**, no conversion was observed (entry 1). However, after addition of 1.05 equivalent of the corresponding ligand **70**, 23% of conversion with 96% of ee was obtained (entry 2). These results are in agreement with those reported by our group using **Pd27** NPs, where the presence of extra ligand was required to obtain catalytic activity.[7] After 3, 5 and 9 hours (entries 3, 4 and 5) moderate to high conversions were obtained (48%, 56% and 89%) with ee's up to 98%.

The robustness stability of **Pd70** under catalytic conditions was studied by the addition of more substrate. After 5 hours of reaction, 45% of the substrate **X** was consumed and 77% of enantioselectivity was obtained. At this moment, 1 mmol of substrate was again added to the catalytic mixture and after 24 hours, 70% of conversion was achieved with 83% enantioselectivity (entry 7).

When the reaction was performed with **Pd70$_{(0.4)}$** /**70** as catalytic system, 58% of conversion was achieved after 6 hours with 92% ee. In this case, the substrate was found to be enantiopure (entry 10).

Table 2.5. Pd-catalysed asymmetric allylic alkylation of **X** using the **Pd70** and **Pd75** NPs.[a]



Entry	[Pd/L]	Time (h)	Conv.(%)[b]	Ee(X) (%)[c]	Ee(XXXI)(%)[c]
1	**Pd70** /-	24	0	-	-
2		1	23	13(*S*)	-
3	**Pd70**/**70**	3	48	69(*S*)	96(*S*)
4		5	56	89(*S*)	96(*S*)
5		9	73	>98(*S*)	>98(*S*)
6	**Pd70**/**70**	5	45	75 (*S*)	77 (*S*)
7[d]		24	39 (70 total)	99 (*S*)	83 (*S*)
8		1	20	9 (S)	95(S)
9	**Pd70$_{(0.4)}$** /**70**	3	49	99(S)	98(S)
10		6	58	100 (S)	92(S)

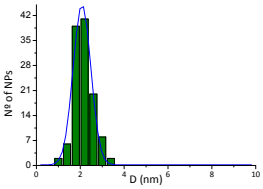
a. Reaction conditions: 1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of N,O-bis(trimethylsilyl)acetamide (BSA), Pd/**X**= 1/100, a pinch of KOAc in 4 mL of CH_2Cl_2 at room temperature. **b**. Conversion determined by ^{1}H NMR analysis. **c.** Enantiomeric excess determined by HPLC on a Chiracel-OJ column. Absolute configuration, between brackets, determined by optical rotation. **d.** After 5h of reaction, addition of 1 mmol of substrate.

The use of Pd/**70** as molecular catalytic precursor in the Pd-catalysed allylic alkylation of **X** afforded high ee (up to 98%). In the case of **Pd70** NPs at 9 h of reaction high conversion and ee, 73% and 98% respectively, were afforded (entry 5, Table 2.5) while with the molecular system bearing ligand **70**, only 10 minutes were necessary to reach total conversion 98% (entry 1,Table 2.3). The use of **Pd70$_{(0.4)}$** NPs provided a remarkable difference in the activity of both enantiomer of the substrate, **X**. Similar behaviour was observed with the molecular precursor at low concentrations of Pd catalyst (Pd/**X**=1/10.000) in which (S)-**X** substrate remained unreacted. When the **Pd75** was used as catalyst low conversion and poor enantioselectivity were obtained. Morover, low reproducibility was observed.

The post-catalysis TEM micrograph of **Pd70** showed small and spherical and well dispersed NPs with a mean diameter of 2.1 $\pm$ 0.4 nm (Figure **2.15**). Thus, the mean diameter of **Pd70** remained similar before and after the catalytic

process (2.3 ± 0.9 nm before and 2.1 ± 0.4 nm after. Surprisingly, the width of the size distribution of these NPs was narrower after catalysis.

TEM Post catalysis
Pd70
2.1 ± 0.4 nm.



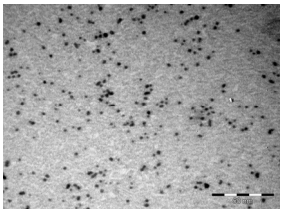


Figure 2.15. TEM micrographs and size histograms for **Pd70** NPs after catalysis.

It should be noted that when the cyclic racemic substrate **XIII** was used in the Pd-catalysed asymmetric allylic alkylation using these NPs as catalysts, no conversion was observed.

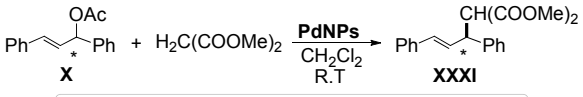
2.2.6. "Cross-system" experiments

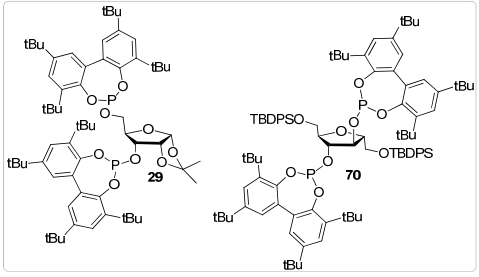
In order to corroborate the robustness of the colloid **Pd70** under catalytic conditions, the nature of the system was studied through the use of cross-system experiments. This method was reported by first time by Gomez and co-workers. It consists in the use of two catalytic systems. The first one, **L1** is should be active and highly enantioselective with both molecular and colloidal systems. The second one, **L2**, is highly active but not enantioselective in molecular system and it is inactive in the colloidal system. The active and enantioselective nanoparticles **PdL1** are used with an additional amount of the ligand **L2** in the catalytic reaction. If the system is not active, it can be concluded that the **PdL1** NPs no produce leaching of active molecular species and thus, the NPs system is stable and robust.

In these experiments, the free ligand **29** (and no **70**) was added to the catalytic reaction mixture (ratio **Pd70** + **29** 1.05 equiv.).[15] The results obtained of these experiments are shown in the Table 2.6. The molecular system Pd/**70** is active and enantioselective in the Pd-catalysed asymmetric allylic alkylation of **X** with dimethyl malonate. However, the molecular system Pd/**29** is active but not enantioselective (entries 1, 2, Table 2.6). The catalytic systems using **Pd29** and **Pd70** NPs were inactive (entries 3, 4, Table 2.6). However, the catalyst **Pd70** became active and enantioselective after

the addition of 1 equivalent of extra ligand (**70** or **29**) to the catalytic reaction mixture (entries 5 and 6, Table 2.6). This fact can be related to the presence of free ligand in solution, which prevents nanoparticles agglomeration, favours their stabilization and/or leaching of molecular palladium species. When the addition of 1 equiv of ligand **29** to the system **Pd29** was carried out (entry 6, Table 2.6), the catalytic mixture was active but only after long reaction time, indicating that leaching of molecular species from the NPs had occurred. When free ligand **29** was added to the catalytic system **Pd70**, no conversion was obtained (entry 7, Table 2.6). One hypothesis to explain this result is that ligand **29** does not interact with **Pd70** NPs. However, the absence of catalytic activity also suggests that the **Pd70** NPs do not leach molecular species.

Table 2.6. Cross-system experiment in Pd-catalysed asymmetric allylic alkylation of **X** in presence of **Pd70** NPs *versus* **Pd29** NPs.[a]





Entry	Catalytic system	Active?	ee?	Conclusion
1	Pd/**70**	Yes	Yes	Molecular precursor Pd/**70** is active and enantioselective
2	Pd/**29**	Yes	No	Molecular precursor Pd/**29** is active but not enantioselective
3	**Pd70** NPs	No	No	Colloidal system **Pd70** is inactive
4	**Pd29** NPs	No	No	Colloidal system **Pd29** is inactive
5	[**Pd70**] NPs +**70**	Yes	Yes	Colloidal system **Pd70** with extra ligand **70** is active and enantioselective
6	[**Pd29**] NPs +**29**	Yes	No	Colloidal system **Pd29** with extra ligand **29** is active and not enantioselective
7	[**Pd70**] NPs +**29**	No	No	Colloidal system **Pd70** with extra ligand **29** is inactive.

In conclusion, these experiments indicate that stable nanoparticles were obtained using the ligand **70** as stabiliser and that no leaching of molecular species occur under catalytic conditions.

To summarise the sections 2.1.3-2.1.6, the molecular system Pd/**70** was highly active and enantioselective in the Pd-catalysed asymmetric allylic alkylation of the substrates **X.** As expected, lower ee's were achieved for the cyclic substrate **XIII**. Moreover, the **Pd70** NPs were also successfully used as catalyst in this reaction and afforded high conversion and enantioselectivity.

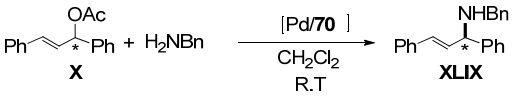
In view of the good results obtained in terms of conversion and enantioselectivity with both molecular and colloidal Pd systems bearing the ligand **70**, we decided to study the reaction using other nucleophiles such as amines and phosphines.

2.2.7. Pd-catalysed asymmetric allylic amination of X using the chiral diphosphite ligand 70.

The catalytic system Pd/**70** was evaluated in the Pd-catalysed allylic amination of **X** using benzylamine as nucleophile (Table 2.7). When the reaction was performed at Pd/substrate 1/50 ratio (entry 1), complete conversion was achieved within 1h with excellent ee (98%). When the Pd/substrate ratio was increased to 1/2500 and monitored until 24 h (entries 2-6), the conversion was 16% after 1h of reaction. Indeed, the ee of the product **XLIX** was constant throughout the reaction (≥99%) while that corresponding to the substrate **X** was increasing during the reaction (entry 2), to reach 93% after 24h with a substrate conversion of 60% (entry 6). The ratio of the reaction rates for the enantiomers (R)-**X** and (S)-**X** was found to vary between 13 and 26%. Concerning the activity, the turn over frequency of the reaction reached 400 h^{-1} at 16% conversion (entry 2) and *ca*. 250 h^{-1} for a substrate conversion of 40% (entry 4). To the best of our knowledge, this is the highest activity reported for the asymmetric allylic amination with such a high enantioselectivity.

However, when the reaction was repeated using the ligand **75,** very low conversions were obtained in the allylic alkylation of **X** (less than 5% conversion after 1 h of reaction using **X**/Pd = 50).

Table 2.7. Pd-catalysed asymmetric allylic amination of **X** using the ligand **70.**[a]



X **XLIX**

Entry	Pd/70/X	Time (h.)	Conv. (%)[b]	Ee(X) (%)[c]	Ee(XLIX)[c] (%)	k(*R*-X)/ k(*S*-X)[d]
1	1/1.25/50	1	100	-	98 (*R*)	-
2	1/1.25/2500	1	16	16 (*S*)	>99 (*R*)	13.4
3	1/1.25/2500	2	26	31 (*S*)	>99 (*R*)	21.6
4	1/1.25/2500	4	40	58 (*S*)	>99 (*R*)	25.8
5	1/1.25/2500	7	55	87 (*S*)	>99 (*R*)	16.4
6	1/1.25/2500	24	60	93 (*S*)	99 (*R*)	13.8

a Reaction conditions: 1 mmol of substrate, 1 mmol of benzylamine; Pd/**70** = 0.5 [Pd(μ-Cl)(η^3-C_3H_5)]$_2$ + 1.25 eq. of **70**, in 4 mL of CH_2Cl_2 at room temperature. **b**. Conversion determined by ^{1}H NMR analysis. **c**. Enantiomeric excess determined by HPLC on a Chiracel-OD column. Absolute configuration, between parentheses, determined by optical rotation. **d** .kR/kS= ln[(1-C/100)(1-ee/100)]/ln[(1-C/100)(1+ee/100)] with C and ee corresponding to rac-**I**.

In conclusion, these results in Pd-catalysed asymmetric allylic amination reactions using diphosphite ligand **70** allowed to obtain the highest turn-over frequency (TOF = 400 h^{-1}) in this processes with excellent ee values (99%)

In addition, the amount of nucleophile was observed to modify the rate of the reaction, as previously observed in allylic alkylation. When a large excess of dimethyl malonate in relation to the substrate (**X**/dimethyl malonate/BSA = 1/20/20) was used, the catalytic activity dropped significantly (9% conversion versus 89% obtained for **X**/dimethyl malonate/BSA = 1/3/3 (entry 4, Table 2.3)). This effect was even more remarkable for the allylic amination: a higher excess of benzylamine (**X**/benzylamine = 1/3) led to 15% conversion in comparison with the conversion (55%) obtained for **X**/benzylamine = 1/1 (entry 5, Table 2.7). This effect could be explained by the slow decomposition of ligand **70** in the presence of a large excess of nucleophile and base. To confirm this hypothesis, the reaction of the ligand **70** in the presence of 5 mmol of benzylamine was carried out and monitored by ^{31}P NMR spectroscopy (figure 2.6).

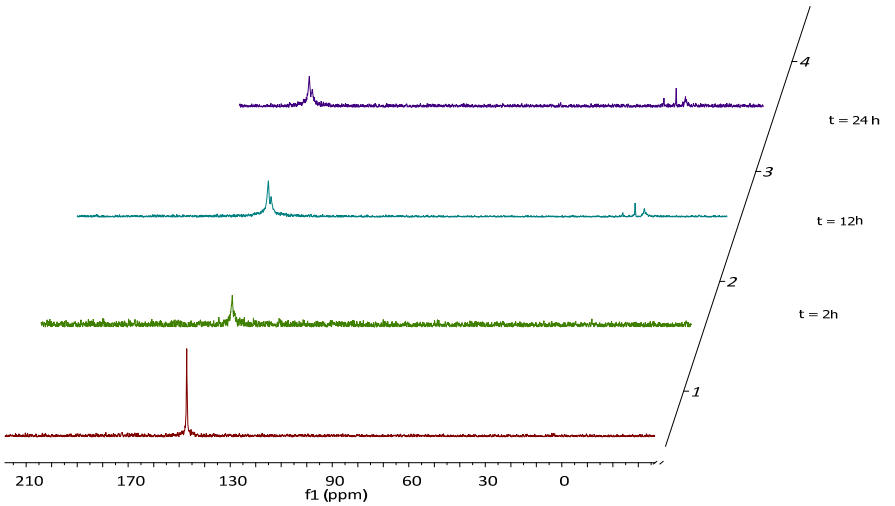


Figure 2.16. $^{31}P\{^{1}H\}$ NMR spectra of the ligand **70** in the presence of benzylamine at various reaction time.

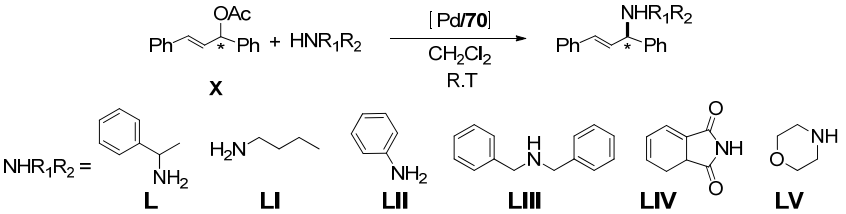
The presence of several new signals at δ 2.48, 2.35 and 5.98 ppm after 12 h of reaction indicated that indeed, the ligand **70** slowly decomposes in the presence of a large excess of amine nucleophile. This result could therefore explain the lower conversion obtained when a higher excess of nucleophile was used.

Interestingly, the significant difference in activity for both allylic substitution reactions using identical substrate to nucleophile ratio clearly indicates that the kinetics of the reaction highly depends on the nature of the nucleophile used. The nucleophile does not only participate in the selectivity-determining step, but could also be involved in the decomposition of the ligand.

To further investigate the effect of the nucleophile, several primary and secondary amines were used in Pd-catalysed asymmetric allylic amination of **X** using the ligand **70** in dichloromethane at room temperature. The results are summarised in Table 2.8. When the racemic α-methylbenzylamine, **L**, was used, 99% of conversion and for both diasteroisomers products 99% of ee were obtained (entry 1). Thus, the presence of a chiral centre in the nucleophile does not affect the enantioselectivity of the catalytic reaction.[16]. In addition, when butylamine **LI** was used, good conversion and ee (99%,

entry 2) were obtained. Using aniline **LII** as nucleophile, 86% of conversion and 70% of ee were achieved. When the secondary amine dibenzylamine **LIII** was used as nucleophile, 50% of conversion and 97% of ee were obtained (Entry 3).[17] However, when the reaction was carried out using the phthalimide **LIV** as nucleophile (entry 4), only 20% of the desired alkyl-amine was obtained. It is important to note that again both the amount and the nature of the nucleophile affected the rate of the allylic substitution. Nevertheless, the use of morpholine as nucleophile led to total conversion and 99% of ee under the same reaction conditions (entry 6).

Table 2.8. Pd-catalysed asymmetric allylic amination of **VI** using different amines as nucleophile.[a]



Entry	HNR_1R_2	Conv. (%)[b]	Ee(X) (%)[c]	Ee(L-LV) (%)[c]
1	**L**	92	-	≤99(≤99*)
2	**LI**	99	-	99
3	**LII**	84	nd	70
4	**LIII**	50	89	97
5	**LIV**	20	33	nd
6	**LV**	99	-	99

a Reaction conditions: 1 mmol of substrate, 1 mmol of amine; Pd/**70** = 0.5 $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ + 1.25 eq. of 1, in 4 mL of CH_2Cl_2 at room temperature. Pd/**70**/**X** = 1/1.25/50 **b** Conversion determined by ^1H NMR analysis. **c** enantiomeric excess determined by HPLC on a Chiracel-OD or AD-H column.

To conclude, the use of primary amines led to the production of alkylamines in good conversion and high enantioselectivity except in the case of the less nucleophile aniline. Secondary amines such as **LIII** and **LIV** resulted less reactive than primary amines in most cases due to their weaker nucleophile character. However, excellent ee was also achieved using these nucleophiles up to 99%, entry 6). In view of these results, it was concluded that the nucleophile must be involved in the rate determining step of the catalytic

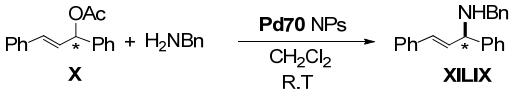
cycle, both the nature and concentration of the nucleophile affects the conversion in this process.

2.2.8. Pd-catalysed asymmetric allylic amination of the X using Pd70 Nps.

In this section, the results obtained in the Pd-catalysed asymmetric allylic amination of **X** using the **Pd70** NPs are described.

The reaction was carried out in dichloromethane during 48h (Table 2.9). After 7h of reaction (entry 1), only 17% of conversion were obtained but with high ee (98%). After 24 hours of reaction, 24% of the **X** substrate had been converted into the product **XLIX** (entry 2) with high ee (up to 98 %). Even after 48h the conversion was still moderate, 48% (entry 3). In all of cases, the enantioselectivities were 98%.

Table 2.9 Pd-catalysed asymmetric allylic amination of **X** using the **Pd70** NPs.[a]



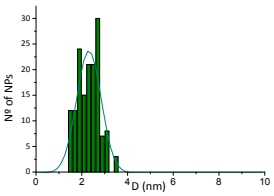
Entry	Pd70/70/X	Time (h.)	Conv. (%)[b]	Ee(X) (%)[c]	Ee(XLIX)[c] (%)
1		7	17	12	98 (*R*)
2	1/1.25/100	24	49	74	98 (*R*)
3		48	67	100	98 (*R*)

a Reaction conditions: 1 mmol of substrate, 1 mmol of amine, in 4 mL of CH_2Cl_2 at room temperature. **b** Conversion determined by ^1H NMR analysis. **c** enantiomeric excess determined by HPLC on a Chiracel-OD or AD-H column. Absolute configuration, between parentheses, determined by optical rotation.

The post-catalysis TEM micrograph of **Pd70** showed small and well dispersed NPs with a mean diameter of 2.3 ± 0.5 nm (Figure 2.17), which is very similar to that measured before the catalytic reaction (2.3 nm). This indicated that no relevant change in the NPs structure occurs during the catalytic reaction.

To conclude, the Pd-catalysed asymmetric allylic amination of **X** with benzylamine as nucleophile using colloidal **Pd70** NPs was slower than the analogous molecular system, although the enantioselectivities were similar.

TEM Post catalysis
Pd70 NPs
2.3 ± 0.5 nm.



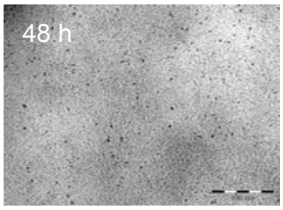


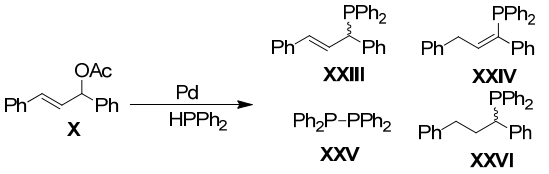
Figure 2.17 TEM micrographs and size histograms for **Pd70** NPs after Pd-catalysed asymmetric allylic amination of rac-**I.**

Next, the Pd/**70** system was used in Pd-catalysed asymmetric allylic phosphination reactions.

2.2.9. Pd-catalysed asymmetric allylic phosphination of X using molecular catalysts bearing the diphosphite ligands 27 and 70.

In this study, the chiral diphosphites **27** and **70** were used. The diphosphite **27** was previously used with success in Pd-catalysed allylic alkylation reactions.[7] Table 2.10 summarises the results obtained in the Pd-catalysed asymmetric allylic phosphination of **X** using the Pd/**70** and Pd/**27** catalytic systems. Initially, the reaction was carried out in toluene with a **X**/Nu/L/Pd=20/20/1.25/1 ratio, diphenylphosphine as nucleophile at 40º C and $[Pd_2(dba)_3]$/**70** as catalytic precursor. After 18 h of reaction, 19% of conversion and no ee were obtained (entry 1). When the reaction was carried out in dichloromethane as solvent, the conversion decreased to 12%, but the ee increased to 15% (entry 2). At room temperature poor conversion was afforded (entry 3). When $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** was used as catalytic precursor the conversion was increased to 50% and 10% of ee was obtained. Using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**27** at 40º C no conversion was observed**.** Nevertheless, $[Pd(OAc)_2]$/**27** catalytic system at 80º C afforded moderate conversion (25%, entry 5) and ee (-23% entry 6). In this case, the use of $[Pd(OAc)_2]$ afforded the opposite enantiomer.

Table 2.10. Pd-catalysed asymmetric allylic phosphination of **X** using the ligands **27** and **70.**[a]



Entry	L	Solvent	Precursor	Time (h)	T (°C)	Conv.(XXIII) (%)[b]	ee.(XXIII) (%)[c]
1	**70**	Toluene	$[Pd_2(dba)_3]$	18	40	19	-
2	**70**	CH_2Cl_2	$[Pd_2(dba)_3]$	18	40	12	15
3	**70**	CH_2Cl_2	$[Pd_2(dba)_3]$	18	25	8	-
4	**70**	CH_2Cl_2	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	6	25	50	10
5	**27**	Toluene	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	1	-	-	-
6	**27**	Toluene	$Pd(OAc)_2$	24	80	25	-23

a Results from duplicated reactions. Reaction conditions: **X**/Nu/L/Pd = 20/20/1.25/1. **b** Determined by ^{1}H NMR. **c**. Determined by chiral SFC.

It is important to note that in the presence of BSA and/or potassium acetate no conversion was observed, which is in contrast with the results previously obtained in allylic alkylation (see Section 2.1.3).

Interestingly, comparing the results obtained in allylic alkylation and allylic phosphination, the significant difference in conversion for these substitution reactions using identical substrate to nucleophile ratio indicates a dependence on the nature of the nucleophile used. This behaviour shows a strong influence of the nucleophilic in the activity and suggests the nucleophilic attack as the rate limiting step.

2.2.10. Pd-catalysed asymmetric allylic substitution of X in ionic liquids using molecular Pd catalysts bearing the diphosphite ligands 27 and 70.

One of the remaining challenges in Pd-catalysed asymmetric allylic substitution is the efficient recycling of the catalyst. In this context, the use of a new reaction medium such as ionic liquids (IL) is an interesting approach. To date, only a few studies on Pd-catalysed allylic substitutions in ILs have been reported.[18] Furthermore, most of these reports did not include the use of chiral ligands and did not explore the possibility of reusing the catalyst.[19]

The use of ionic liquids provide advantages due to their physical properties such as low vapour pressure, low toxicity, immiscibility with some organic solvents and their ability to dissolve metal catalysts and organic compounds that make them interesting as solvents. Due to the good results achieved with the Pd/**70** catalytic system in Pd-catalysed asymmetric allylic substitutions in organic solvents, we decided to study the Pd-catalysed allylic alkylation using ionic liquids as solvents and in a second stage, to recycle the catalytic system.

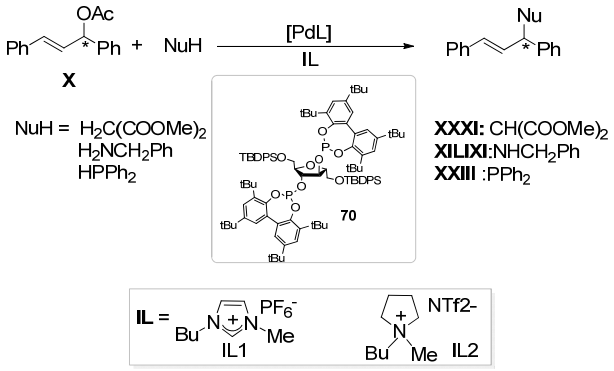
It is now well established that imidazolium cations and their associated anions form hydrogen bonds in solution, which can considerably slow down allylic alkylation reactions. Furthermore, in dialkylimidazolium ionic liquids, the anions are not efficient bases and thus, do not deprotonate the nucleophile reagent, thus decreasing the rate of nucleophilic attack.[20]

First, the ligands **70** and **27** derived from carbohydrates were used in the Pd-catalysed asymmetric allylic alkylation, amination and phosphination reactions of **X** in neat imidazolium- and pyrrolidinium-based ionic liquids. The two catalytic systems bearing the ligands **70** and **27** were generated in situ from $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ in the presence of the appropriate ligand (L/Pd = 1.25/1). The Pd-catalysed asymmetric allylic alkylation and amination of **X** were evaluated in 1-butyl-3-methyl imidazolium hexafluorophosphate (IL1) and N-butyl-N-methyl pyrrolidinium bis(trifluoromethylsulfonylamide) (IL2) using Pd bearing the ligand **70** as catalyst (Table 2.11).

Initially, the Pd-catalysed asymmetric allylic alkylation reaction was carried out using IL1 as solvent, **X**/Nu/BSA=1/3/3 ratio, dimethylmalonate as nucleophile at room temperature and $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** as catalytic precursor. After 90 min of reaction, total conversion and 95% ee was obtained (entry 1). When the reaction was carried out in IL2 as solvent, total conversion and 92% ee was afforded (entry 2). Then, the Pd catalysed asymmetric allylic amination was carried out using the X/Nu=1/1 ratio in IL1 under the same catalytic conditions. In this case, 69% of conversion and 91% of ee were obtained (entry 3). When the IL2 was used, the conversion increased to 69% but the ee decreased to 82% (entry 4). When

dichloromethane was used as solvent, 83% of conversion and 90% of ee and 63% of conversion and 99% of ee in the amination reaction was afforded.

Table 2.11 Pd-catalysed asymmetric allylic alkylation and amination of **X** using the ligand **70** in ILs.[a]



Entry	Solvent	NuH	Conv. (%) [b]	Ee (%)[c]
1[d,e]	IL1	$CH(COOMe)_2$	100[e]	95(*S*)
2[d,e]	IL2	$CH(COOMe)_2$	100[e]	92(*S*)
3[f]	IL1	$NHCH_2Ph$	69	91(*R*)
4[f]	IL2	$NHCH_2Ph$	87	82(*R*)
5[g]	CH_2Cl_2	$CH(COOMe)_2$	83	90(*S*)
6	CH_2Cl_2	$NHCH_2Ph$	63	>99(*R*)

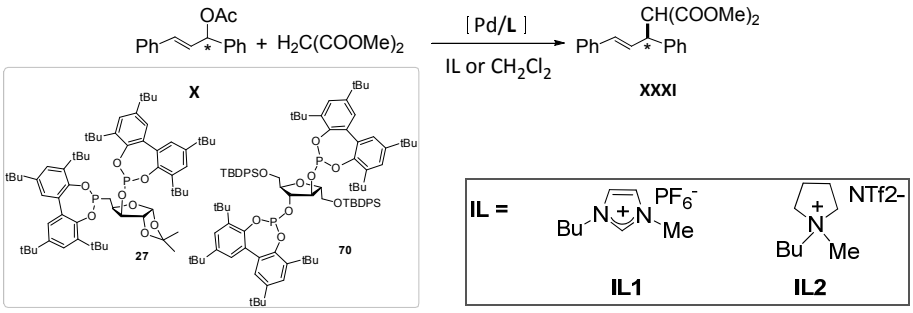
a Results from duplicated reactions. Reaction conditions: **X**/Pd = 100, 30 min at 40 °C. **b** Determined by ^{1}H NMR. **c** Determined by HPLC. **d** **X** /BSA/Nu = 1/3/3 with addition of a pinch of KOAc; BSA. **e** Reaction time = 5 minutes. **f** **X**/Nu = 1/1. **g** From reference [21]: reaction time = 90 min; **X** /Pd = 50.

Concerning the allylic alkylation, no remarkable differences were observed in both ionic liquids (Table 2.11, entries 1 and 2). In the amination reaction, higher activity was obtained in IL2 than IL1 (Table 2.11, entries 3 and 4). In this case, the formation of hydrogen bonds between the imidazolium cation and benzylamine could decrease its nucleophilic behaviour and thus explain these results.[22] However, more surprisingly, both allylic alkylation and amination were more active in IL2 than in CH_2Cl_2 (Table 2.11, entries 5 and 6).

To evaluate the catalytic activity of the systems bearing the ligands **27** and **70**, allylic substitutions were performed in IL2 with different **X** /Pd molar

ratios (Table 2.12). Only the pyrrolidinium-based ionic liquid IL2 was used in the subsequent experiments due to the potential formation of carbene species by activation of the C(2)-H bond of the imidazolium cation of IL1 in basic medium.[23] The Pd-catalysed asymmetric allylic alkylation of **X** was carried out in IL2, with a **X**/Nu/BSA=1/3/3 ratio, Pd/**X**=1/1000 ratio, dimethylmalonate as nucleophile at 40º C and using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**27** as catalytic precursor. In 30 min of reaction, 96% of conversion and 83% ee were obtained (entry 1). When the reaction was carried out using the ligand **70**, total conversion and 92% ee was afforded (entry 2). Then, the Pd/**X** was increased to 1/10000, and in 15 minutes, 21% of conversion and 96% of ee was obtained (entry 3). When the reaction was repeated in dichloromethane at room temperature the conversion increased to 99% and 98% ee was achieved (entry 4).

Table 2.12. Pd-catalysed asymmetric allylic alkylation of **X** using the ligands **27** and **70** in IL2 and CH_2Cl_2.[a]



Entry	L	X/Pd	Solvent	Conv.(%)[b]	Ee(X)(%)	Ee(XXXI)(%)[c]	TOF(h^{-1})
1	**27**	1000	IL2	96	-	83(*S*)	-
2	**70**	1000	IL2	100	-	92(*S*)	-
3	**70**	10000	IL2	21	20(*S*)	96(*S*)	8400
4[d]	**70**	10000	CH_2Cl_2	55	99(*S*)	98(*S*)	22000

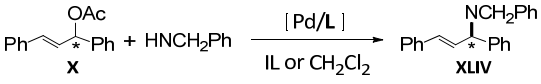
a. Reaction conditions: **X**/BSA/ dimethyl malonate = 1/3/3 with addition of a pinch of KOAc at 40 °C. Reaction time for entries 1 and 2: 30 min and for entries 3 and 4: 15 min. **b**. Determined by ^{1}H NMR. **c**. Determined by HPLC. **d**. Temperature reaction = 25 °C.

To conclude, the $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** catalyst showed higher activity and enantioselectivity in IL2 than the $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**27** catalytic system (entries 1 and 2, Table 2.12). However, at high **X** /Pd ratio, the conversion was lower than that achieved in dichloromethane (entry 3 vs. 4, Table 2.12).

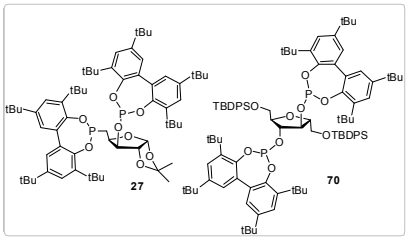
Actually, this fact can be related to the different reactivity of both enantiomers of **X** in these solvents. The relative rate of *(R)*-**X** and *(S)*-**X** in IL2 was similar, in contrast to that observed in dichloromethane (in IL2: k(*R*)/k(*S*) = 8.6, data from entry 3 in Table 2.12; in CH_2Cl_2, k*(R)*/k*(S)* = 49, data from entry 4 in Table 2.12).[24]

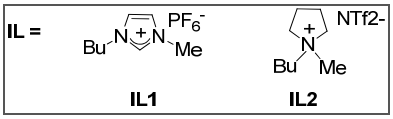
The results obtained in the Pd-catalysed asymmetric allylic amination of **X** are summarised in the Table 2.13. The reaction was carried out in IL2, using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** as catalytic precursor, **X**/Nu=1/1 ratio, Pd/**X**=1/500 ratio, benzylamine as nucleophile at 40º C. After 1h of reaction, 72% of conversion and 88% ee were obtained (entry 1). When the reaction was carried out using the ligand **27**, 75% of conversion and 91% ee were afforded (entry 2). Using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** in dichloromethane at room temperature, 55% of conversion and 99% of ee were obtained in 15 minutes (entry 3).

Table 2.13. Pd-catalysed asymmetric allylic amination of **X** using the ligands **27** and **70** in IL2 and CH_2Cl_2.[a]



X **XLIV**





Entry	L	X/Pd	Solvent	Time (min)	Conv.(%)[b,d]	Ee(XLIV)(%)[c]	TOF(h^{-1})[d]
1	**70**	500	IL2	60	72(62)[d]	88(*R*)	3720[e]
2	**27**	500	IL2	60	75(53)[d]	91(*R*)	3180[e]
3[f]	**70**	100	CH_2Cl_2	15	55	>99(*R*)	220

a. Reaction conditions: rac-**I**/ benzylamine = 1/1 at 40 °C. **b.** Determined by ^{1}H NMR. **c.** Determined by HPLC. **d.** In brackets, conversion at 5 min. **e.** Determined at 5 min. **f.** Temperature reaction = 25 °C.

For amination reactions in IL2, both systems exhibited high activity (entries 1 and 2, Table 2.13).

In contrast with the results obtained in allylic alkylation reactions, the catalytic systems bearing the ligand **70** was more active in IL2 than in dichloromethane (entries 1 *vs.* 3, Table 2.13). However, the enantioselectivities were slightly lower in IL2, which is in agreement with those observed for the allylic alkylation (Table 2.12).

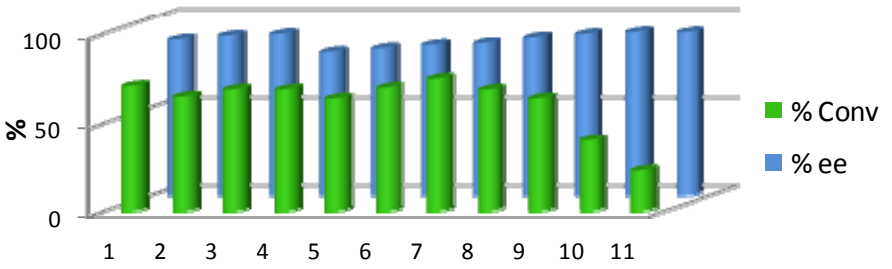


Figure 2.18 Catalyst recycling experiments in the Pd-catalysed asymmetric allylic amination of **X** using the ligand **70** in IL2

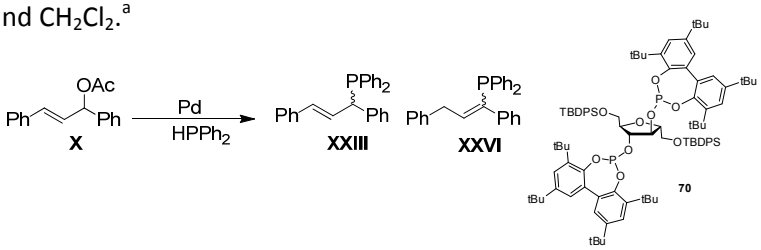
In the Pd-catalysed asymmetric allylic amination of **X**, the catalytic system $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70** could be recycled up to nine times without activity loss, preserving the enantioselectivity up to eleven times (Figure 2.18). The product was quantitatively extracted with pentane after each run. It is important to note that the palladium content in the extracted organic product was less than 0.1 ppm (determined by ICP-MS) for the first two runs and no palladium was detected for the next runs. The activity loss after the ninth run is attributed to the catalyst deactivation.

The Pd-catalysed asymmetric allylic phosphination of **X** using diphenylphosphine as nucleophile was also studied. $[Pd_2(dba)_3]$, $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ and $[Pd(OAc)_2]$ were used as catalytic precursors in the presence of ligand **70** (Table 2.14).

Initially, $[Pd_2(dba)_3]$ was used as precursor with the **X**/diphenylphosphine/**70**/Pd= 20/20/1.25/1 ratio, diphenylphosphine as nucleophile at 40º C. After 24h of reaction, 65% of conversion and 5% ee was obtained (entry 1). When the reaction was carried out using $[Pd(OAc)_2]$/**70** as

catalytic precursor, 95% of conversion without ee was afforded (entry 2). Then, using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$/**70**, total conversion and no ee was obtained (entry 3). When the **X**/diphenylphosphine/**70**/Pd = 200/200/2. 5/1 ratio was used at room temperature 55% of conversion and 155 ee was obtained (entry 4). The use of dichloromethane as solvent afforded 50% of conversion and 10% ee (entry5). Remarkably, low chemoselectivities to the desired phosphination product were obtained (≤ 60% in all cases). This is one of the most commonly problems in this allylic phosphination reaction

Table 2.14. Pd-catalysed asymmetric allylic phosphination of X using the ligand **70** in IL2 and CH_2Cl_2.[a]



Entry	Solvent	Pd	Time(h)	T(°C)	Conv(%)[b]	ee (XXIII)(%)[c]
1	IL2	$[Pd_2(dba)_3]$	24	40	65[d]	5
2	IL2	$[Pd(OAc)_2]$	24	40	95	0
3	IL2	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	24	40	100	0
4[e]	IL2	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	6	25	100	13
5[e]	IL2	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	6	25	55	15
6[e]	CH_2Cl_2	$[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$	6	25	50	10

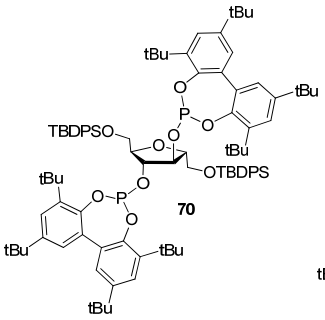
a. Reaction conditions: **X**/diphenylphosphine/**70**/Pd = 20/20/1.25/1. **b.** Determined by ^{1}H NMR. **c.** Determined by chiral SFC. **d. XXIII**/**XXVI** = 70/30. **e. X**/ diphenylphosphine /**70**/Pd = 200/200/2.5/1.

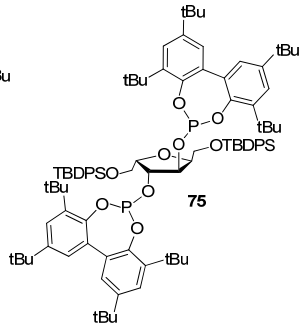
In IL2 at 40 °C, the desired allylic phosphine **XLIX** was exclusively obtained using palladium acetate and $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ as catalytic precursors (entries 2 and 3). However using $[Pd_2(dba)_3]$, the formation of 1,3-diphenylpropyl)diphenylphosphine was again observed (entry 1). Unfortunately, no enantioselectivity was induced in any case. At lower temperature and shorter reaction time, the enantioselectivity increased up to 13% (entry 4). The enantioselectivity remained unchanged even at lower conversion using lower Pd loading (0.5 mol%) (Entries 5 vs. 4,

Table **2.14**). Interestingly, the catalytic results in dichloromethane were similar to those observed in IL2 (entries 5 and 6).

The low asymmetric induction obtained could be explained the competition between phosphines involved in the allylic phosphination, and the diphosphite **75**, in contrast to the robust catalytic system containing Josiphos-type ligands reported by Togni.[25]

2.3. Conclusions





The catalytic system containing ligand **70** is highly active in the Pd-catalysed asymmetric allylic substitution reactions, reaching the highest turnover frequency values reported for asymmetric allylic alkylation (TOF = 22,000 h^{-1}) and allylic amination (TOF = 400 h^{-1}) reaction of the substrate **X** with excellent ee values (up to >98%). Moreover, the effect of the substrate/nucleophile ratio in the activity of these reactions indicates a poisoning effect of the nucleophiles. Furthermore, the results obtained with ligand **70** and **75** clearly show that small changes in the ligand structure can drastically affect the catalytic activity.

The use of several nucleophilies (malonate, amines and phosphines) showed a direct dependence of the activity of the catalytic system on the nature and concentration of nucleophile. It can be concluded that the nucleophile is involved in the rate limited step of the allylic substitution reaction of the substrate X using Pd catalytic system bearing the ligand **70**.

Palladium NPs were successfully synthesised in the presence of carbohydrate derivative ligands (**70** and **75**) and the shape, size and dispersion of the nanoparticles were shown to depend on the structure and amounts of the stabiliser used.

Pd NPs bearing the ligands **70** and **75** were stabilized using different palladium/ligand ratios and used as catalytic precursors in allylic substitution reactions. Pd-asymmetric allylic alkylation using preformed NPs bearing the

ligands **70** and **75** showed similar behaviour to that observed with the corresponding molecular systems.

Pd70 and **Pd75** NPs showed a remarkable difference in reactivity. Under catalytic conditions using **X** or **XIII** as substrates, **Pd70** was more active than **Pd75**. It is also remarkable the excellent kinetic resolution shows by **Pd70** in the allylic alkylation of **X**, which has not been observed using **Pd75**. This fact points to a key-lock matching between substrate and catalyst.

The reaction rate for the transformation of the (S)-**X** is more than 100 times slower than that of the corresponding (R)-**X** enantiomer, showing a kinetic resolution under these conditions.

In pyrrolidinium-based ionic liquid, the chiral palladium catalytic system containing the diphosphite ligand **70** is highly active and induces high enantioselectivities in the allylic alkylation and amination reactions. Its activity even increases in relation to that obtained in dichloromethane for the amination. Furthermore, using this medium, the Pd system bearing the ligand **70** could be recycled for the first time up to nine times without activity loss, preserving the enantioselectivity. The preliminary results obtained for the allylic phosphination are very promising in terms of chemoselectivity, and encourage us to look for suitable catalytic systems to induce enantioselectivity.

2.4. Experimental part

2.4.1. General

All compounds were prepared under nitrogen atmosphere using standard Schlenk and vacuum-line techniques. The organic solvents were purified on solvent purification system – 800 series or distilled over drying reagents and were deoxygenated before use. Chemicals were purchased from Aldrich Chemical Co and Fluka.

Ionic liquids IL1 (1-butyl-3-methyl-imidazolium hexafluorophosphate) and IL2 (N-butyl-N-methyl pyrrolidinium bis-trifluoromethylsulfonylamide) were supplied by Solvionic and were treated under vacuum at 60º C overnight prior to use. Other chemicals were used as purchased. The deuterated solvents for NMR measurements were dried over molecular sieves.

^{1}H, ^{13}C $\{^{1}H\}$, and ^{31}P $\{^{1}H\}$ NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer. Chemical shifts were calibrate relative to SiMe4 (^{1}H and ^{13}C NMR) as internal standard or 85% H_3PO_4 as external standard (^{31}P NMR). Assignments in NMR spectra of the complex were determined by COSY and HSQC spectra. Coupling constants, J, are given in Hz. Multiplicities of peaks in ^{1}H and ^{13}C NMR are given as: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), m (multiplet), and b (broad).

Enantiomeric excess were determined by HPLC at 25º C on a Waters Alliance 2695 HPLC separation module with a Waters 996 PDA Detector for allylic alkylation, amination and phosphination.

Enantiomeric excesses were determined for allylic phosphination on PIC solution Supercritical fluid chromatography SFC with a UV PDA detector at 35º C. ICP-MS were done by an independent analytical laboratory (Antellis) from Toulouse (France).

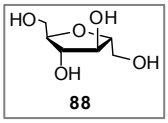
TEM measurements were realized on a Zeiss 10 Å electron microscope at 100 kW with a resolution of 3Å; Pd NPs samples were prepared under Argon atmosphere. A drop of the solution was placed on a carbon covered Cu grid. Final drying of the sample was performed under vacuum for 12 hours. Elemental analyses of carbon, hydrogen and phosphorus were realized on a

Carlo Erba EA 1108 instrument. The NPs size and distribution were determined by counting approximately 800 NPs from 4 enlarged TEM images (approximately 200 NPs from each TEM image). The size distribution plots were fit using a Gaussian model with Microcal Origin 6.1 graphing software to determine the widths and centers of the size distributions.[26]

Merck silica gel 60 (0.040-0.063 mm) was employed on flash chromatography. The conversion of the reaction was measured by GC on a Hewlett-Packard HP 5890 A instrument (split/splitless injector, J&W scientific, HP5, 25 m column, internal diameter 0,25 mm, film thickness 0.33 mm, carrier gas: 150 kPa He, F.I.D. detector) equipped with a Hewlett-Packard eHP3396 series II integrator.

2.4.2. Synthesis of ligands

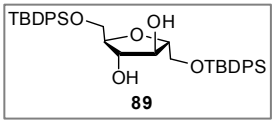
The synthesis of ligands was carried out following reported literature procedures.



88

*2,5-anhydro-D-mannitol (**88**)* 2-amino-2-deoxy-D-glucose (20 g, 0.11 mol) was added to a 140 ml of distilled water. The solution was stirred for 24 h at room temperature. The solution was cooled to -5º C and sodium nitrite was slowly added (11.50 g, 0.167 mol). A solution of HCl (0.92 ml, 3.2 M) was dropwise added at 0º C (1 hour). Later, 11.32 ml of HCl 3.2 M were added to the solution and the mixture was stirred 3 hours at 0º C. The excess of nitrite acid was eliminated by mean of nitrogen flow at room temperature. The pH of the solution was regulated at pH ~ 6 using the resin poly(4-vinylpiridine). The mixture was filtered and the solution was evaporated to give brown oil. This oil was triturated with acetone (200 ml x 3) and methanol (15 ml). The solution was decanted and cooled at 0º C in order to precipitate residual salts in solution. The salts were filtered and the resulting solution left Amberlite IRN-150 (H+, OH-) resin stirring 2 hours. The mixture was filtered and the filtered was concentrated to dryness to afford 10.6 g of the aldehyde A solution of the aldehide (8.34 g, 0.05 mol) in 100 ml of distilled water was cooled at 0º C. $NaBH_4$ was slowly added (1.93 g, 0.05 mol). The mixture was stirred for 7 hours and neutralized with Amberlite IR-120 (H+) resin. The resin was filtered off and the filtrate was concentrated to dryness. The crude

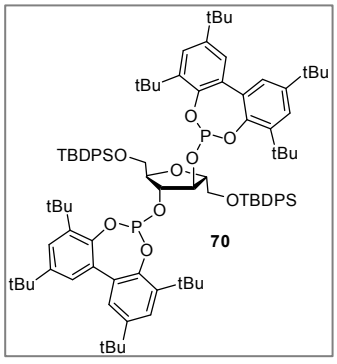
product was dissolved in methanol and dried (this procedure was repeated 3 times). The residue was dissolved in methanol and Amberlite IRN-150 (H+, OH-) resin was added. The resin was filtered off through a Celite pad, and the filtrate was concentrated to dryness. The alcohol **88** was obtained as black oil (6.7 g, 63.6%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 3.96 (m, 2H, H_3), 3.82 (m, 2H, H_2), 4.05 (dd, 2H, $J_{1,1'}$ = 11.1 Hz, $J_{1,2}$ = 3.71 Hz, H_1), 3.75 (dd, 2H, $J_{1',1}$ = 11.1 Hz, $J_{1',2}$ = 3.62 Hz, H_1) ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 85.14 (C_2), 78.80 (C_3), 63.67 (C_1).



89

*1,6-Di-O-(tert-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (**89**)*[27] tert-Butyldiphenylsilyl chloride (3 mL, 11.66 mmol) was added dropwise to a solution of **86** (0.87 g, 5.3 mmol) and imidazole (1.5 g, 22.28 mmol) in 12 ml of dry DMF at 0 °C. The reaction mixture was left to warm to room temperature and stirred for 24 h. The solvent was then removed in vacuum, and the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate, 4:1) to afford 1.48 g (45%) of **89** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.85 – 7,27 (m, 20H, Ph), 4.36 (m, 2H, H_3), 4.24 (m, 2H, H_2), 4.10 (d, 2H, $J_{OH,3}$ = 8.9 Hz, O<u>H</u>), 4.05 (dd, 2H, $J_{1,1'}$ = 11.1 Hz, $J_{1,2}$ = 3.6 Hz, H_1), 3.75 (dd, 2H, $J_{1',1}$ = 11.1 Hz, $J_{1',2}$ = 2.4 Hz, H_1), 1.06 (s, 18H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.8-128-5 (Ph), 86.99 (C_2), 79.70 (C_3), 65.34 (C_1), 26.72 (<u>C</u>H_3), 19.02 (<u>C</u>$(CH_2)_3$).

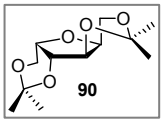
*3,4-Bis-O-(diphenylphosphino)-1,6-di-O-(tert-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (**70**)* The alcohol **89** was azeotropically dried with toluene (3x1 ml). Then,0.32 g (0.5 mmol) of **89** was dissolved in dry and degassed toluene (5 ml) dry pyridine (0.2 ml, 2.4 mmol) was added. After the mixture was cooled to 0 °C, a solution of phosphorochloridite (2.2 mmol), synthesized in situ by standard procedure, in dry and degassed toluene (6 ml) and dry pyridine (0.7 ml, 2.0 mmol). The mixture was stirred overnight at room temperature. The mixture was filtered to eliminate the



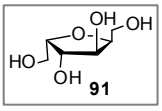
70

pyridine salts, and the filtered was concentrated to dryness. The white foam was purified by flash column chromatography with toluene as eluent and 0.15 g of the diphosphite **70** was afforded as a white solid (17%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.65 – 7.09 (m, 28H, Ph), 5.29 (br s,2H, H_3), 3.98 (br s, 2H, H_2), 3.68 (m, 2H, H_1), 3.40 (m, 2H, $H_{1'}$), 1.41 (s, 18H, o-C(C$\underline{H}_3$)$_3$) 1.33 (s, 18H, *p*-C(C$\underline{H}_3$)$_{3'}$), 1.35 (s, 18H, p-C(C$\underline{H}_3$)$_3$), 1.23 (s, 18H, *o*-C(C$\underline{H}_3$)$_{3'}$), 0.99 (s, 18H, C(C$\underline{H}_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 147.02-124.7 (C_{Ar}), 82.39 (C_2), 79.5 (broad, C_3), 63.70 (C_1), 35.4 (o-$\underline{C}$(CH$_3$)$_3$), 34.6 (*p*-$\underline{C}$(CH$_3$)$_{3'}$), 34.4 (p-$\underline{C}$(CH$_3$)$_3$), 31.7 (*o*-$\underline{C}$(CH$_3$)$_3$), 31.4 (*o*-C($\underline{C}$H$_3$)$_3$) 31.2 (*p*-C($\underline{C}$H$_3$)$_{3'}$) 31.0 (*o*-$\underline{C}$(CH$_3$)$_{3'}$), 26.3 (C($\underline{C}$H$_3$)$_3$), 19.3 ($\underline{C}$(CH$_2$)$_3$). ^{31}P{^{1}H} NMR ($CDCl_3$, 161.97 MHz) δ in ppm: 114.95 (s)

*2,5-anhydro-1,3:4,6-di-O-isopropyliden-L-iditol (***90***)* *p*-Toluene sulfonic acid (0.3 g) was added to the solution of D-glucitol (103 g) in xilene (520 ml). In a Dean Stark distillator, the solution was refluxed 2 hours in order to give up the water formed in the reaction (11 ml). Afterwards, the solution was left to cool to room temperature and the solvent was decanted eliminating the dianhydro-hexytols that are soluble in xilene. The residue was dissolved in anhydrous acetone (41 ml) and 1 ml of sulfuric acid was added, the color changed from brown to orange. The solution was stirred for 24 hours and then a solution of $KHCO_3$ (8 g en 100 ml de H_2O) was added, the color of the solution change from orange to green. The mixture was filtered and the solvent evaporated to obtain yellow syrup. This syrup was dissolved in hexane (11 ml) and the solution was extracted in continuous with hexane/H_2O (7:3) overnight. Then, the solvent was evaporated and the residue was recrystallized in hexane (50 ml) to afford a white solid 9.5 g (12 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 4.30 (d, 2H, $J_{3,2}$ = 2.3 Hz, H_3), 4.16 (m, 2H, H_2), 4.01 (dd, 2H, $J_{1,1'}$ = 13.1 Hz, $J_{1',2}$ = 2.8 Hz, H_1), 3.98 (dd, 2H, $J_{1',1}$ = 13.1 Hz, $J_{1',2}$ = 2.4 Hz, H_1), 1.42 (s, 6H, C$\underline{H}_3$), 1.34 (s, 6H, C$\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 96.9 (C_{acetal}), 77.13 (C_2), 72.5 (broad, C_3), 62.72 (C_1), 29.00 ($\underline{C}$H$_3$), 19.04 ($\underline{C}$H$_3$).

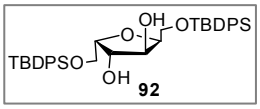


*2,5-anhydro-L-iditol (***91***)* 8.6 g of **90** was dissolved in 200 ml of THF/H_2O (2:1) and then, IR-120 (H^+) resin (17 g) was added. The mixture was stirred for 24 hours and the resin was



filtered off; the filtered was washed with THF and evaporated to dryness. The alcohol **90** was obtained as syrup (4.3 g, 84%). NMR ^{1}H ($CDCl_3$, 400 MHz) δ in ppm: 4.99 (s, 4H, O<u>H</u>), 4.20 (m, 2H, H_2), 4.17 (m, 2H, H_3), 3.80 (dd, 2H, $J_{1,1'}$ = 11.1 Hz, , $J_{1',2}$ = 4.4 Hz, H_1), 3.75 (dd, 2H, $J_{1',1}$ = 11.1 Hz, , $J_{1',2}$ = 7.4 Hz, $H_{1'}$). NMR ^{13}C ($CDCl_3$, 100.6 MHz) δ in ppm: 82.1 (C_2), 79.0 (C_3), 62.2 (C_1).

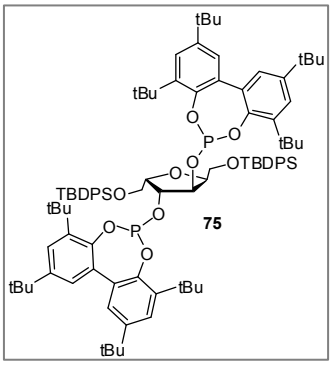
*<u>2,5-anhydro-1,6-di-O-[(t-butyldophenyl)silyl]-L-iditol (**92**)</u>* The diol **91** (0.45 g, 2.74 mmol) was dissolved in anhydrous DMF (6.5 ml) at 0º C and imidazole (0.8 g, 11.75 mmol) was added under nitrogen atmosphere.



92

Then, the tert-butylsilyl chloride (1.6 ml, 6.15 mmol) was slowly added to the solution. The mixture was stirred at room temperature during 48 hours. The solvent was then evaporated under vacuum; the residue was dissolved in CH_2Cl_2 and washed with H_20. The resulting mixture was extracted with CH_2Cl_2 and the organic phase was dried with $NaSO_4$. The residue was purified by flash chromatography (hexane/ethyl acetate 4:1) and drying under vacuum. **92** were obtained as white crystals.

*<u>3,4-Bis-O-[(3,3',5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-1,6-di-O-(tert-butyl-diphenylsilyl)-2,5-anhydro-L-iditol (**75**)</u>*



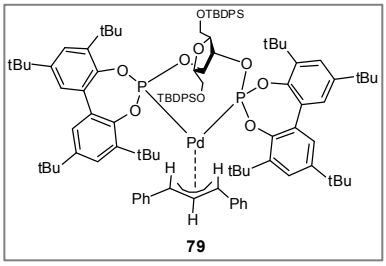
75

The synthesis of **75** was carried out according to reported procedure. To a solution of 0.30 g (2.28 mmol) of diol **92** in 20 ml of dry and a degassed toluene, 1 ml (10.4 mmol) of dry pyridine was added. This solution was slowly added to a solution of 9.2 mmol of corresponding phosphorochloridite formed in situ, dissolved in 24 ml of toluene and 1 ml (10.4 mmol) of pyridine. The mixture was stirred overnight, the salts were then filtered off and the white foam was purified by flash column chromatography in toluene to afford 0.93 g of 92 (53%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.15 – 7.64 (m, 28H, Ph), 5.10 (br sbr s,2H, H_3), 4.28 (br s, 2H, H_2), 3.78 (m, 2H, H_1), 3.67 (m, 2H, $H_{1'}$), 1.43 (s, 18H, o-C(C<u>H</u>$_3$)$_3$) 1.34 (s, 18H, *o*-C(C<u>H</u>$_3$)$_{3'}$), 1.32 (s, 18H, *p*-C(C<u>H</u>$_3$)$_3$), 1.25 (s, 18H, *p*-C(C<u>H</u>$_3$)$_{3'}$), 0.97 (s, 18H, C(C<u>H</u>$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 146.2-124.3 (C_{Ar}), 79.45 (C_2), 77.3 (broad, C_3), 62.50 (C_1), 35.3 (o-

C(CH_3)$_3$), 35.6 (*p*-C(CH_3)$_{3'}$), 34.5 (p-C(CH_3)$_3$), 34.7 (*o*-C(CH_3)$_3$), 31.2 (*o*-C(CH_3)$_3$) 31.0 (*p*-C(CH_3)$_{3'}$) 30.8 (*o*-C(CH_3)$_{3'}$), 26.5 (C(CH_3)$_3$), 19.8 (C(CH_2)$_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 161.97 MHz) δ in ppm: 148.2 (s)

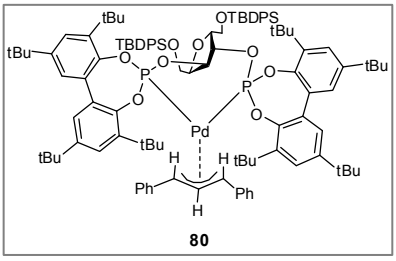
2.4.3. General procedure for the preparation of $[Pd(\eta^3\text{-}C_3H_5)(L)]PF_6$ complexes

In a purged Schlenk tube, 9 mg (0.025 mmol) of $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and 75 mg (0.05 mmol) of ligand were dissolved in 5 ml of distilled dichloromethane. The solution was stirred for 30 min at room temperature and 15 mg of NH_4PF_6 (0.09 mmol) dissolved in 1 ml of dichloromethane were then added. After 24h of stirring, washings were performed with degassed water (4 x 5 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered off and the solvent removed under reduced pressure. The pale yellow solid obtained was washed with diethyl ether (3 x 5 ml) and dried under reduced pressure.



79

Complex 79: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.0 – 7.6 (m, Ph) , 5.66 (t, 1H, CH) , 5.59 (t, 1H, CH), 5.26 (m, 1H, CH), 4.27 (br s,2H,), 3.98 (br s, 2H,), 3.71 (d, 2H), 3.33 (d, 2H), 1.45 (s, 18H) 1.40 (s, 18H), 1.32 (s, 18H), 1.25 (s, 18H), 0.95 (s, 18H); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 101.3 MHz, 728 K) 138.77 ppm (s), -150.9 ppm (PF_6). Yields: 83%. LC/ESI-TOF/MS: m/z (100%)= 1663.7945 ($[M\text{-}PF_6]^+$)



80

Complex 80: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.2 – 7.6 (m, Ph), 5.65 (br s, 1H, CH) , 5.53 (br s, 1H, CH), 5.02 (m, 1H, CH), 4,61 (br s,2H), 4.68 (br s, 2H), 3.79 (m, 2H), 3.76 (m, 2H), 1.46 (s, 18H) 1.37 (s, 18H), 1.33 (s, 18H), 1.26 (s, 18H), 0.95 (s, 18H);. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 101.3 MHz, 728 K) 140.32 ppm (s), -161.3 ppm (PF_6). Yields: 85%. LC/ESI-TOF/MS: m/z (100%)= 1663.7945 ($[M\text{-}PF_6]^+$)

2.4.4. General Procedure for the Synthesis of Pd Colloids

In a standard procedure, 160 mg of $[Pd_2(dba)_3]$ (0.175 mmol) were dissolved under argon at 110º C (ethanol/N_2 bath) and under vigorous magnetic stirring in a solution of 160 mL of THF containing 0.2 equiv./Pd of the chosen ligand in a Fischer–Porter bottle. The mixture was then pressurized under dihydrogen (3 bars) at room temperature. The colour of the solution turned from purple to black in a few minutes. The vigorous stirring and the dihydrogen pressure were maintained for 18 h at room temperature, leading to black and homogeneous colloidal solutions. After depressurization, a drop of each colloidal solution was deposited under argon on a holey carbon-covered copper grid for TEM analysis. The colloidal solution was then concentrated to ca. 5 mL. Addition of cold pentane allowed the precipitation of the particles as black solids that were washed with pentane (2x40 mL) and dried under vacuum. The colloids were characterized by TEM analysis, elemental analysis and XPS.

Colloid Pd70 was synthesized according to the standard procedure from 160 mg of $[Pd_2(dba)_3{\cdot}CHCl_3]$ (0.175 mmol) and 74.7 mg of diphosphite **70** (0.070 mmol). TEM: mean size 4.2 nm; elemental analysis: 72.72% Pd, 0.17% P, 14.68% C, 0.94% H.

Colloid Pd75 was synthesised according to the standard procedure from 160 mg of $[Pd_2(dba)_3{\cdot}CHCl_3]$ (0.175 mmol) and 74.7 mg of diphosphite **75** (0.070 mmol). TEM: mean size 4.2 nm; elemental analysis: 72.97% Pd, 0.37% P, 13.99% C, 0.38% H.

2.4.5. General Procedure for Pd-catalysed allylic alkylation reactions

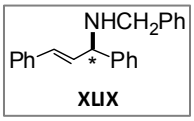
For molecular catalytic systems containing ligands **70** and **75**, the catalytic precursor was generated in situ from $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and the appropriate ligand (0.02 mmol of Pd and 0.025 mmol of chiral ligand) dissolved in 2 cm^3 of CH_2Cl_2 and stirred for 30 min before adding the substrate. For colloidal catalytic systems, 2.5 mg of preformed NPs, **Pd70** and **Pd75**, with 0.005 mmol of the appropriate ligand (for 1 and 2: 5.2 mg; for 3: 4.7 mg) were dissolved in 4 cm^3 of CH_2Cl_2 for 30 min before adding the substrate. (1 mmol), dissolved in CH_2Cl_2 (2 cm^3), was then added to the catalyst solution followed by dimethyl malonate (396 mg, 3 mmol), BSA (610

mg, 3 mmol), and a catalytic amount of KOAc. The mixture was stirred at room temperature until total conversion of substrate (monitored by TLC). Then, the solution was diluted with diethyl ether, filtered over celite, and washed with saturated ammonium chloride solution (4x10 cm^3) and water (4x10 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered off, and solvent removed under reduced pressure. Conversions were determined by ^1H NMR and enantiomeric excesses determined by HPLC.

2.4.6. General procedure for palladium-catalysed allylic amination reactions

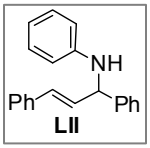
The catalytic precursor was generated in situ from $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and the appropriate ligand (for 1 mol% of catalyst: 0.01 mmol of Pd and 0.0125 mmol of the corresponding chiral ligand) dissolved in 1 cm^3 for 30 minutes before adding the substrate (1 mmol) and amine (1 mmol). The mixture was stirred at 40 °C. At the end of the reaction, the products were extracted with pentane and filtered over celite. Then the solvent removed under reduced pressure. Conversions were determined by ^1H NMR and enantiomeric excesses determined by HPLC

(R,E)-N-benzyl-1,3-diphenylprop-2-en-1-amine on a Chiralcel OJ-H chiral column, using (0.6 mL/min, n-hexane/isopropyl alcohol 99:1,254 nm): (R)-**XLIX** Rt=19.5 min, (S)- **XLIX** Rt=20.8 min.



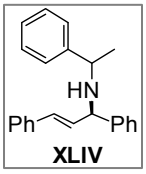
XLIX

(E)-N-(1,3-diphenylallyl)aniline Chiralpak IA column: n-hexane/i-PrOH: 99/1; flow rate: 0.55 ml/min; wavelength at 254 nm; Rt(major) = 26.44 min, Rt(minor) = 31.78 min.



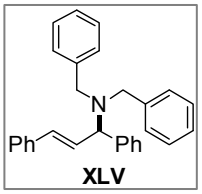
LII

(R,E)-1,3-diphenyl-N-(1-phenylethyl)prop-2-en-1-amine
Chiralcel OJ-H chiral column, using (0.6 mL/min, n-hexane/isopropyl alcohol 99:1,254 nm): (R)-isomer =25.4 min, (S)-isomer =29.0 min.



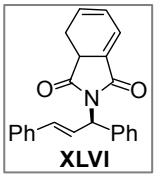
XLIV

(R,E)-N,N-dibenzyl-1,3-diphenylprop-2-en-1-amine
Chiralcel AD-H column, hexane/2-propanol = 70/30, 0.5 mL/min, 254 nm; 3% ee, (R)-isomer Rt = 6.7 min, (S)-isomer Rt = 7.0 min.



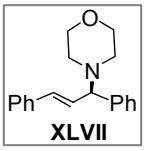
XLV

2-((R,E)-1,3-diphenylallyl)-3a,4-dihydro-1H-isoindole-1,3(2H)-dione The enantiomeric excess was determined by HPLC on an ODH column (0.5 mL/min, n-hexane/isopropyl alcohol 98:2, 254 nm): (S)-439 Rt=25.6 min, (R)-439 Rt=31.6 min



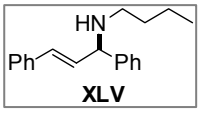
XLVI

(R,E)-4-(1,3-diphenylallyl)morpholine Chiralpak IA column: n-hexane/ i-PrOH: 99.5/0.5; flow rate: 0.8 ml/min; wave length at 254 nm; Rt(major) = 22.21 min, Rt(minor) = 24.37 min.



XLVII

(R,E)-N-(1,3-diphenylallyl)butan-1-amine Chiralpak AD-H, hexane/2-propanol = 9:1, 1.0 mL/min, 254 nm, (R)-isomer Rt = 10.5 min, (S)-isomer Rt = 14.1 min.

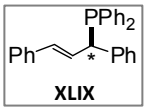


XLV

2.4.7. General procedure for palladium-catalysed allylic phosphination reactions

The catalytic precursor was generated in situ from $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and the appropriated ligand ($1.5x10^{-3}$ mmol of Pd and 3 $x10^{-3}$ mmol of the corresponding chiral ligand) dissolved in 1 cm^3 of **IL** or CH_2Cl_2 for 30 minutes before adding the substrate **VI** (63 mg, 0.25 mmol) and diphenylphosphine (45 µL, 0.25 mmol). The mixture was stirred at 25 °C. At the end of the reaction, diethylether and 10 mg of sulphur were added and stirred during 1 h. Then the organic phase was filtered over celite and the solvent removed under reduced pressure. Conversions were determined by ^1H NMR and chemoselectivity by ^{31}P NMR.

(R,E)-(1,3-diphenylallyl)diphenylphosphine Enantiomeric excesses were determined by SFC on a Chiralcel AD-H column, MeOH 15% as eluent, in a flow of 4 cm^3/min under 100 bar CO_2. The by-product coming from **XI** was isolated from the mixture by precipitation with diethyl ether.



XLIX

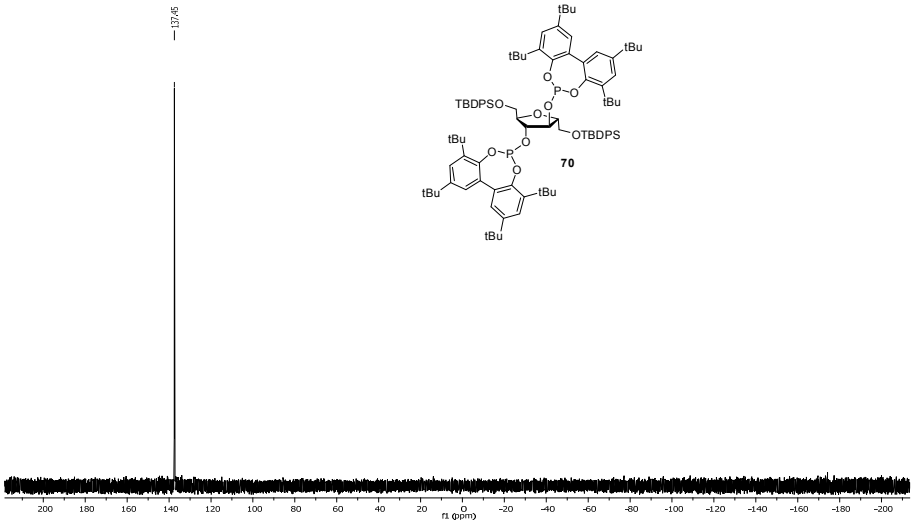
2.4.8. General procedure for the recycling

After each catalytic run (**X**/amine/Pd/L = 250/250/1/1.25, 1 cm^3 IL2, 1 h, 40 °C), the reaction mixture was cooled at room temperature and extractions were carried out with pentane (3x5 cm^3) in order to remove all the organic compounds (substrate, amination product and benzylamine) from the ionic liquid phase. Under these conditions, neither the ionic liquid nor catalyst (palladium species and ligand) was extracted (checked by NMR and ICP-MS analysis). Upon extractions, the catalytic ionic liquid phase was then treated under vacuum in order to remove the volatiles. The corresponding amounts of substrate (**X**) and nucleophile ($BnNH_2$) were then added for starting a new run.

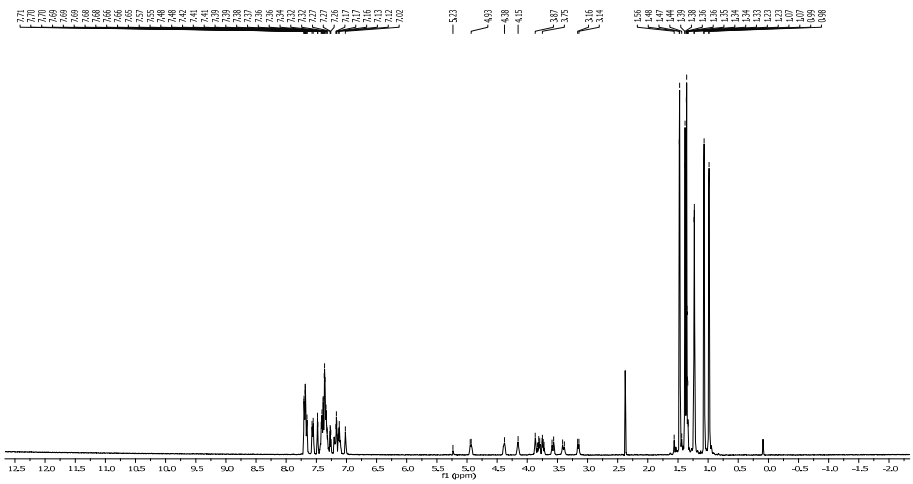
2.4.9. NMR spectra

3,4-Bis-O-(diphenylphosphino)-1,6-di-O-(tert-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (70)

^{31}P-NMR

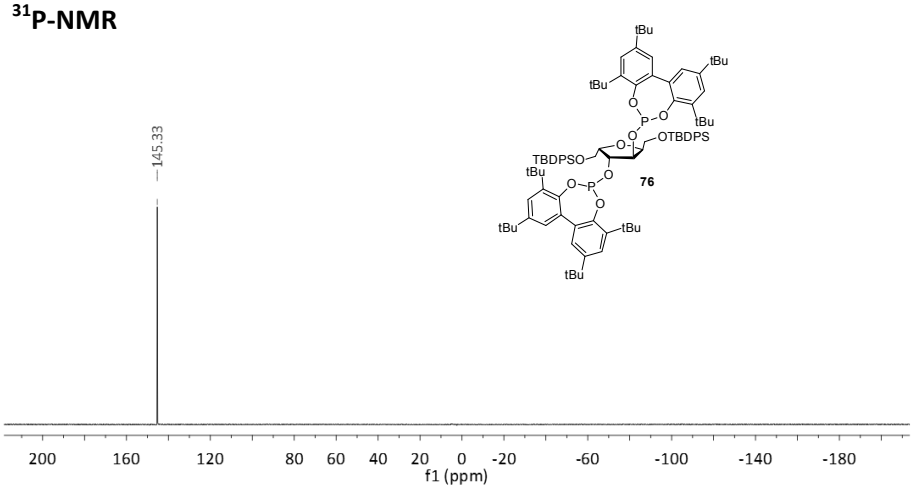


^{1}H-NMR

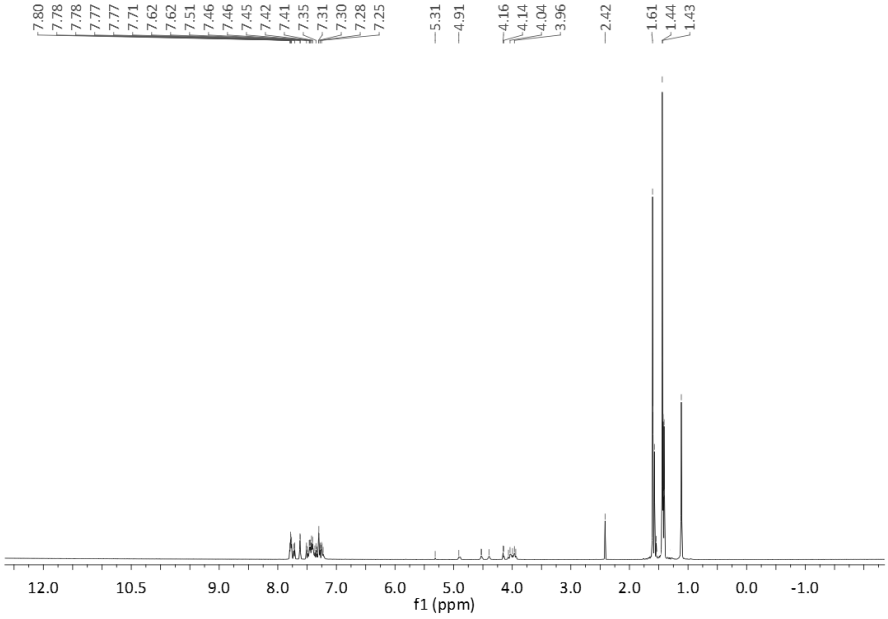


3,4-Bis-O-(3,3',5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl)phosphite-1,6-di-O-(tert-butyl-diphenylsilyl)-2,5-anhydro-L-iditol (75)

^{31}P-NMR

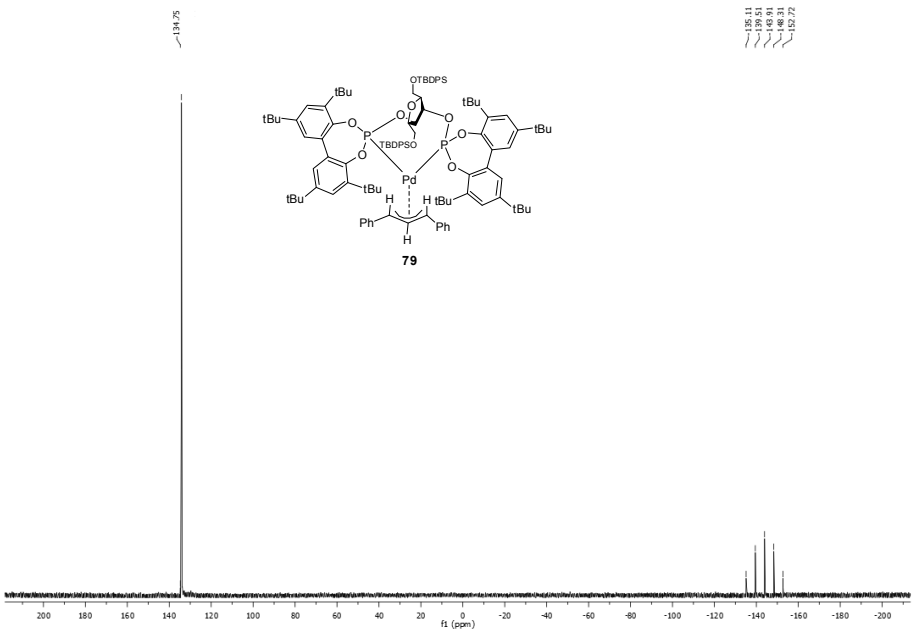


^{1}H-NMR



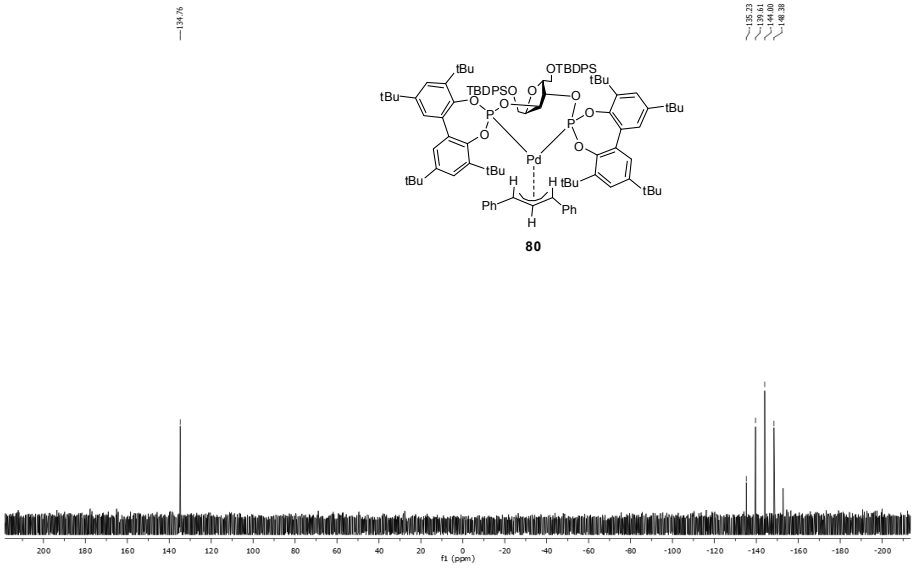
Complex 79

^{31}P-NMR

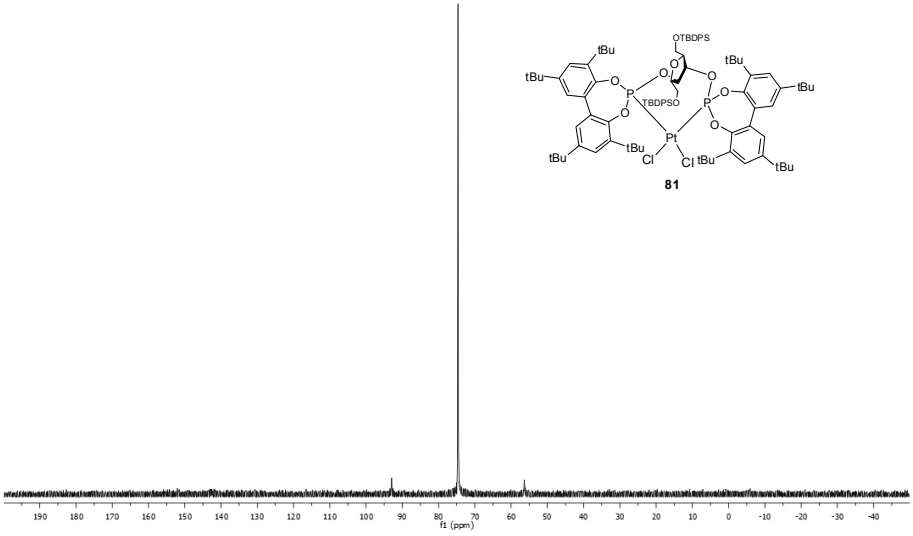


Complex 80

^{31}P-NMR



Complex 81



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[24] k(*R*)/k(*S*) = ln[(1-C/100)(1-ee/100)]/ln[(1-C/100)(1+ee/100)], where C = conversion and ee = enantiomeric excess of the substrate (**X**), see: C.-H. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.*, **1982**, *104*, 7294.

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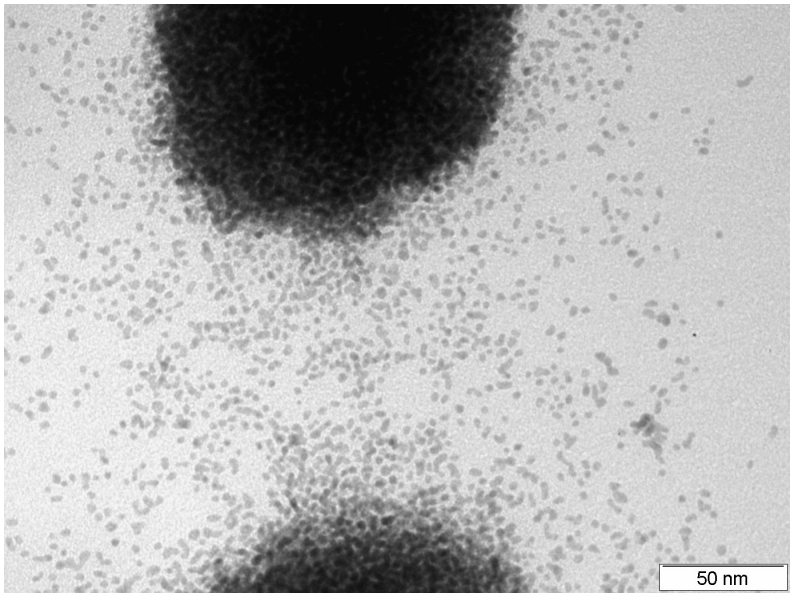
Chapter 3.

Pd-catalyzed asymmetric Suzuki-Miyaura reactions



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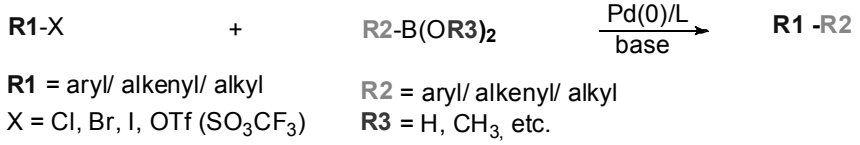
3.1 Background

The Suzuki-Miyaura reaction is the coupling of an aryl or vinyl halide or triflate with an alkyl, aryl or vinyl boronic acid using a palladium catalyst (Scheme 3.1). This powerful cross coupling method can be utilised for the synthesis of conjugated olefins, styrene, and biaryl compounds, which are an important class of organic compounds.[1,2,3,4]



Scheme 3.1. General representation for Pd-catalysed Suzuki cross coupling reaction

The Suzuki coupling reaction has many inherent advantages over other methods such as the tolerance of broad range of functional groups, non-toxic by-products, thermally stable organometallic partner (organoboronic acid derivative) that is inert to air and water and unreactive to many of the electrophilic functional groups.[5,6]

Axially chiral biaryls (Figure 3.1) are very important structural motifs in biologically active natural products or as ligands in homogeneous catalysis. The chirality of these compounds arises from the restricted rotation around the aryl-aryl bond. This type of chirality is called atropoisomerism.[7] The rotation is usually restricted by the presence of three ortho substituents (Figure 3.1) but in the case of binaphthalenes, only one ortho substituent is required to obtain this type of chirality since the steric hindrance induced by the fused aromatic rings also restricts the C-C rotation. The binaphthalenes are the most representative compounds of the atropisomerism phenomenon.

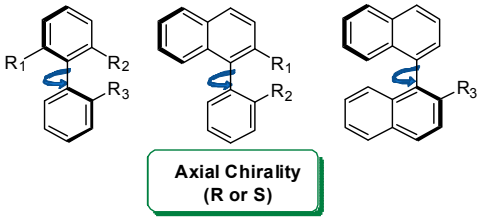
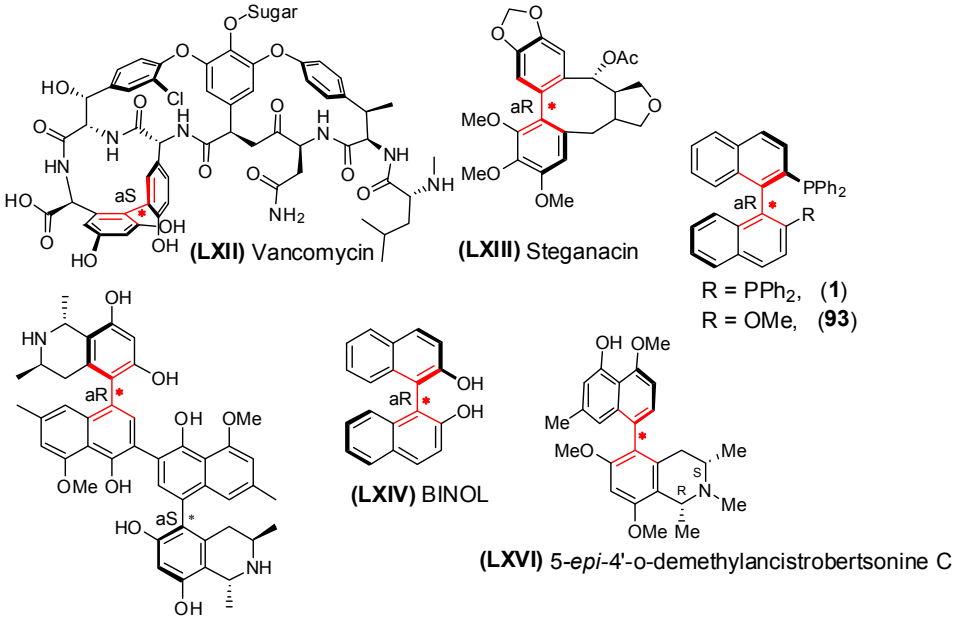


Figure 3.1. Structures exhibiting atropisomerism (or axial chirality).

Several natural products contain biaryl or binaphthyl units with axial chirality as central building blocks.[8] Figure 3.2 describes selected examples of such compounds: vancomycin (**LXII**), which is a clinically used glycopeptide antibiotic,[9] steganacin (**LXIII**), which is a cytotoxic tubulin-binding dibenzocyclooctadiene lignan,[10] michellamine B (**LXV**), which is a naphthylisoquinoline alkaloid anti-HIV [11] and the compound 5-epi-4'-o-demethylancistrobertsonine C **LXVI** that is use as an antimalarial

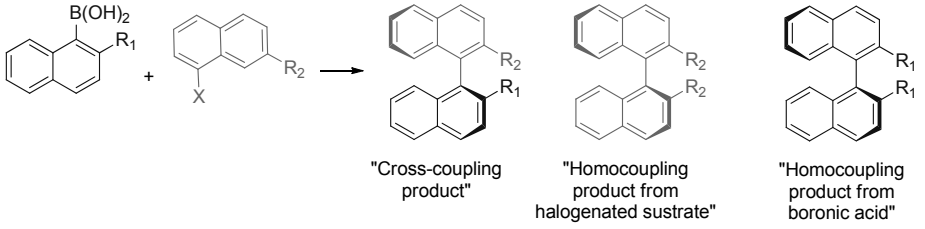


naphthylsiquinoline alkaloid.[12]

Figure 3.2. Examples of natural products containing a chiral biaryl unit.

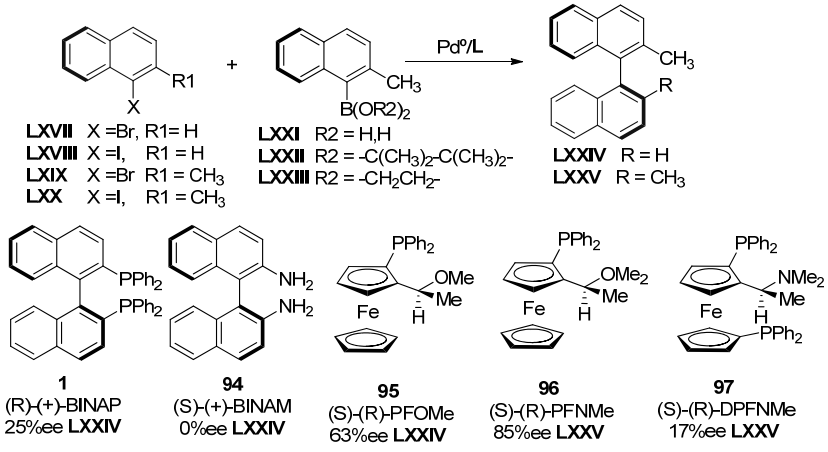
Other applications of biaryl compounds in materials[13] and supramolecular chemistry[14] are also of interest. Moreover, chiral biaryl units are the

structural base of many ligands such as BINAP (**1**),[15] MOP (**93**)[16] derived from the BINOL **LXIXV** (Figure 3.2)[17] which show remarkable enantioselectivities in a number of transition metal catalyzed processes.[10] In view of these applications, the synthesis of optically active 1, 1- binaphthalenes has received much attention. Nevertheless, the number of publications in asymmetric Suzuki-Miyaura coupling of naphthalenes moieties remains modest.[10,18-30] Another very important aspect in this reaction is the selectivity, as by-products can be produced by homocoupling reaction (Scheme 3.2).



Scheme 3.2. Coupling products that can be produced in Pd-catalysed Suzuki-Miyaura cross-couplings.

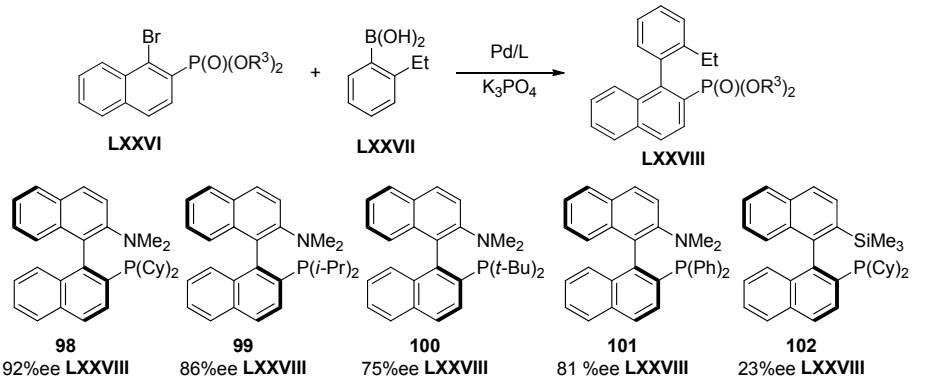
The first report on the synthesis of axially chiral biaryls through enantioselective Suzuki-Miyaura reactions was published independently by Buchwald[18] and Cammidge.[19]



Scheme 3.3. Selected ligands reported in Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.

Cammidge et al. reported the Pd-catalysed asymmetric Suzuki-Miyaura coupling of various naphthyl boronic partners and naphthyl halides. The catalytic system bearing the BINAP ligand **1**, yielded modest ee's of 25% (Scheme 3.3). It was observed that the use of different boronate esters improved the selectivity to the cross coupling product. Furthermore, this selectively was even further improved when monophosphine ligands **95** and **96** were employed (63% and 85% respectively, Scheme 3.3).

Buchwald reported the successful use of Pd catalytic systems containing the binaphthyl ligands **98-99** in asymmetric Suzuki-Miyaura couplings. The Pd/**98** catalyst was found to give the highest ee values for the reaction of **LXXVI** and *o*-tolylboronic acid **LXXVII** (Scheme 3.4). Replacing the cyclohexyl group of the ligand by an isopropyl, a phenyl or a *tert*-butyl group (ligands **99**-**101**, Scheme 3.4) had only a slight effect on the conversion and enantioselectivity of the resulting products (86%, 75% and 81% ee of **LXXVIII**). However, replacing the dimethylamino group with an *n*-butyl or trimethylsilyl group (ligand **102**, Scheme 3.4) resulted in a significant decrease in enantioselectivity.



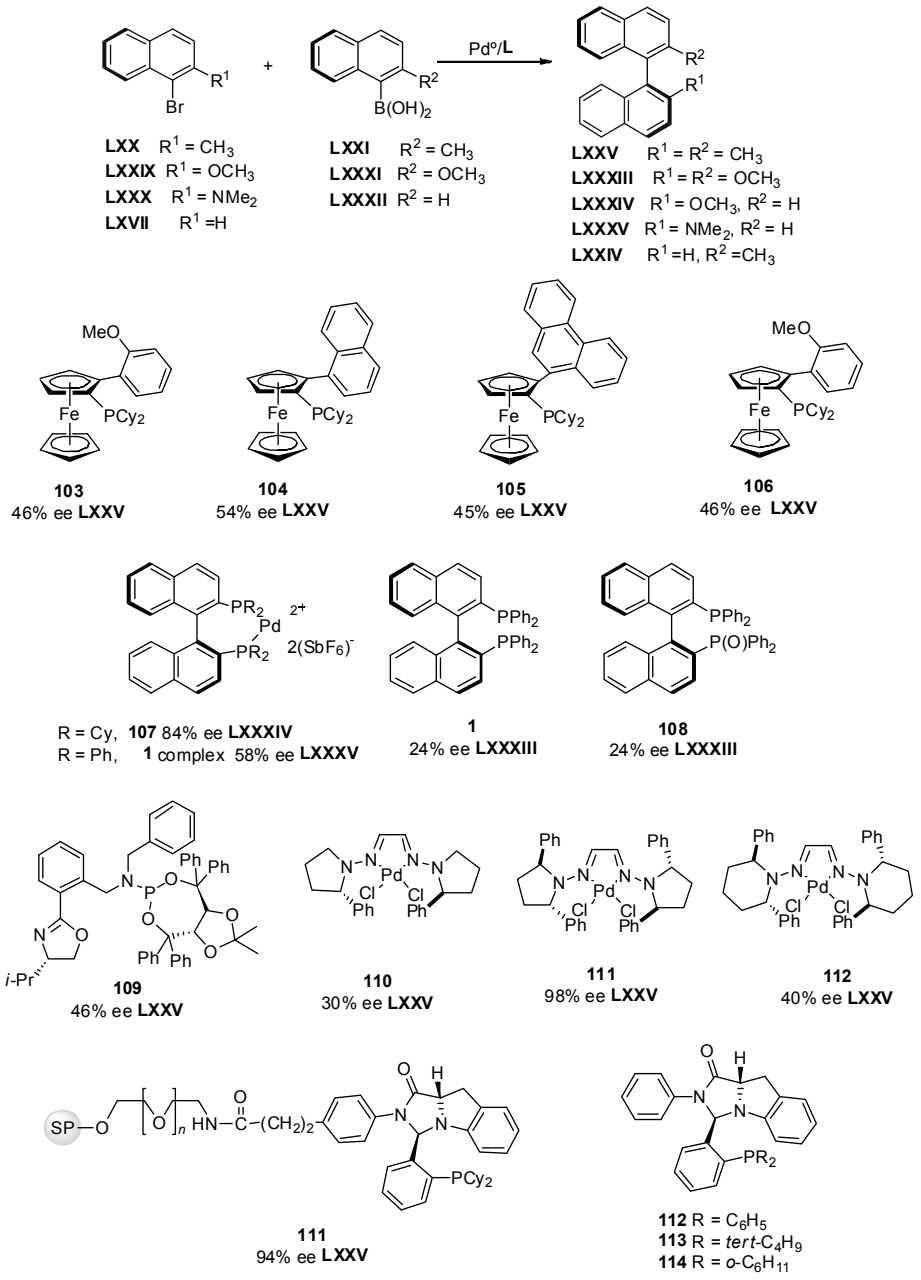
Scheme 3.4. Pd-catalysed asymmetric Suzuki coupling reaction reported by Buchwald.

In 2003, Johannsen and Jensen communicated the Pd-catalysed asymmetric coupling reaction between the aryl halide **LXVIII** and aryl boronate **LXX** using Pd catalysts bearing the dialkyl arylferrocenylphosphines ligands **103**-**105** (Scheme 3.5) and obtained moderate ee´s (46%, 54% and 45% respectively).[20]

Espinet and co-workers studied the microwave assisted Pd/**106**-catalysed asymmetric Suzuki-Miyaura reaction of the naphthyl bromide **LXVIII** and the boronic acid **LXX** and obtained reasonable to excellent yields (65–96%) and fair to good enantioselectivities (43–70% ee, Scheme 3.5).[21]

Mikami *et al* reported successful results in the Suzuki-Miyaura coupling reaction using the cationic chiral Pd complexes of the ligands **1** and **107**, which afford the coupling products in good yield and enantioselectivity (84% and 58% respectively).[22]

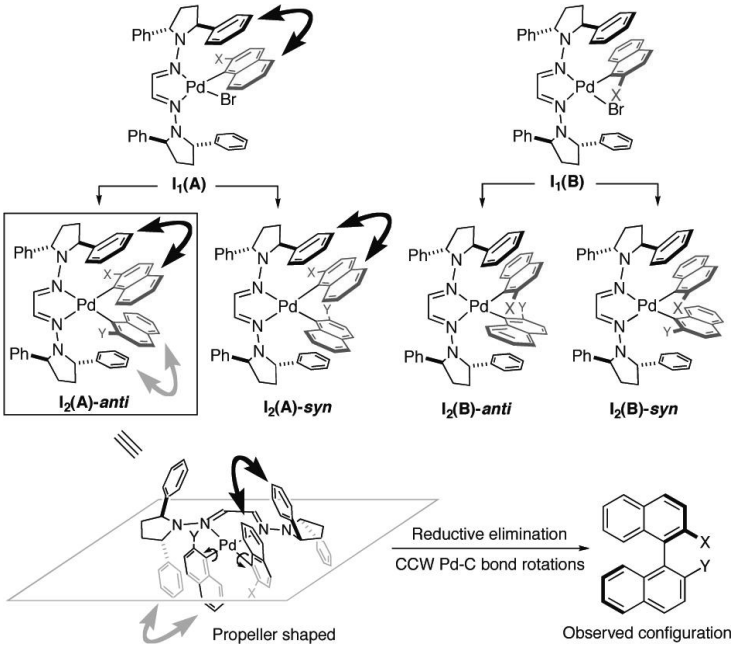
Colobert and co-workers reported the catalytic asymmetric reaction between 2-methoxy-1-naphthylboronic acid **LXXXI** and 1-bromo-2-methoxynaphthalene **LXXIX** in the presence of the Pd/**1** and Pd/**108** catalysts. Moderate conversions and ee's were obtained when these ligands were used in the catalytic system (24% both cases, Scheme 3.5). Optimizing the phosphine/Pd ratio, they observed that this parameter had an effect on the catalysis but that could not be rationalised.[23]



Scheme 3.5. Ligands and complexes reported in Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction.

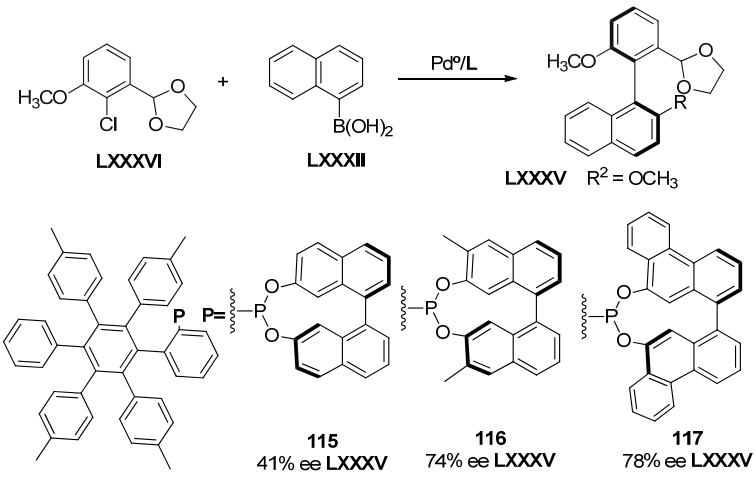
The Pd/phosphoramidite–oxazoline **109** system was tested by Guiry and Bronger in the asymmetric Suzuki-Miyaura coupling between 2-methylnaphthylboronic acid **LXXI** and 1-bromonaphthalene **LXXXI**, leading to a maximum of 46% ee and 54% isolated yield at room temperature (Scheme 3.5).[24]

In 2008, Lassaletta and co-workers utilized the novel C_2-symmetric nitrogen donor ligands **110-112** and obtained up to 98% of ee in the Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction although reaction was performed during 7 days.[25] The authors proposed a reaction path through several intermediates to explain the high enantioselection and the absolute configurations observed (Scheme 3.6). π-stacking interactions between the phenyl substituents of the ligands and the aromatic rings of the coupling partners are suggested to be crucial for the enantiodiscrimination.



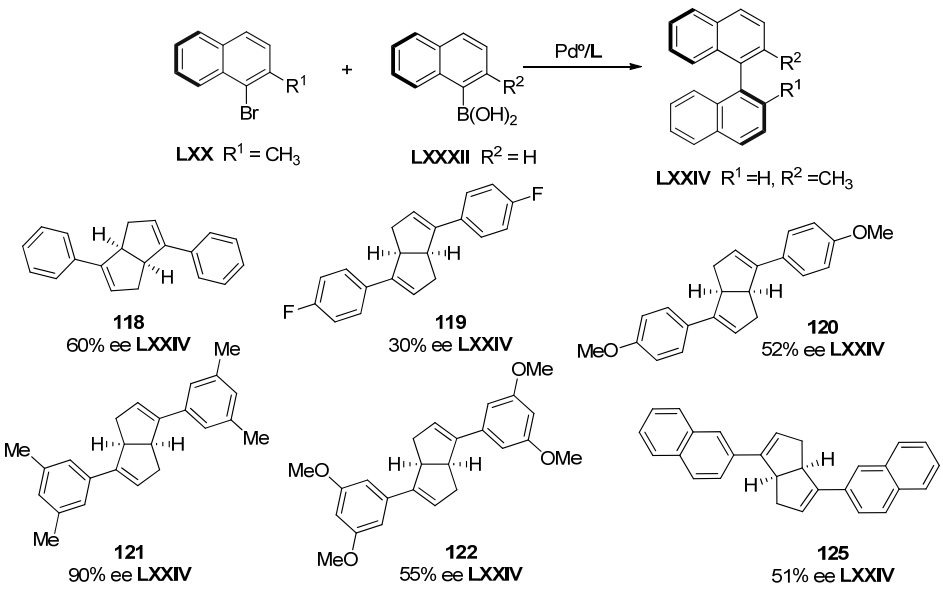
Scheme 3.6. Oxidative addition and transmetalation intermediates to binaphthyls. Arrows indicate π-stacking interactions (Scheme from reference 25).

Uozumi and co-workers developed the polymer-supported catalyst **111-114** (Scheme 3.7).[26] The Pd/**111** catalytic system was applied in the Pd-catalysed asymmetric Suzuki-Miyaura coupling of the naphthyl boronic acid **LXX** and the naphthyl halide **LXVII**, the catalyst was re-used 4 times and high conversions and ee were obtained (up to 94%,Scheme 3.5). In this context, the phosphonite ligands **115** - **117** promoted the asymmetric cross coupling of aryl chlorides with low catalyst loading and short reaction times and good ee were obtained (up to 78% ee , Scheme 3.7).[27]



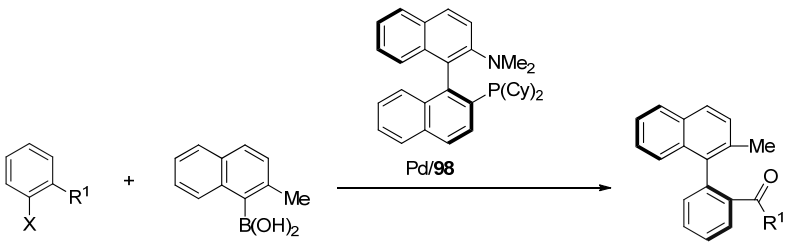
Scheme 3.7. Ligands reported in Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.

Recently, the first Pd-diene-catalyzed asymmetric Suzuki-Miyaura coupling reaction was achieved (Scheme 3.8). [28] Using catalytic systems bearing the ligands **118**-**125,** high yields, and moderate to high enantioselectivities were obtained (up to 90%). Interestingly, when 15 mol % of the ligand **121** was added to the Pd/**121** catalytic system, high ee was obtained and this system was successfully applied to obtain several functionalized biaryls.[28]



Scheme 3.8. Chiral dienes used as chiral ligands for the synthesis of axially chiral compounds via Pd-catalyzed Suzuki-Miyaura coupling reaction

Buchwald and co-workers reported the enantioselective synthesis of axially chiral biaryls including a large substrate scope and quantum mechanical investigations.[29] The efficient syntheses of axially chiral biaryl amides in yields ranging from 80-93%, and with enantioselectivity in the range 88-94% ee employing a Pd-catalysed asymmetric Suzuki-Miyaura process with $Pd(OAc)_2$ and the KenPhos ligand **98** was reported (Scheme 3.9). These studies demonstrate that electron-rich and electron-deficient o-halobenzamides can be efficiently coupled with the 2-methyl-1-naphthylboronic acid **LXX**. The yields and selectivities of the reactions are independent of the nature of the halide and of the N-based substituents of the substrate. Their investigations demonstrated that axially chiral heterocyclic and biphenyl compounds could also be synthesized with this methodology.

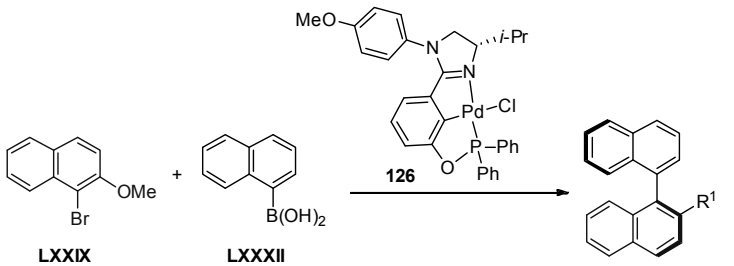


LXX

LXXXVI	$R^1 = NEt_2$, X = Br	**XCIV**	$R^1 = NEt_2$, 75% ee
LXXXVII	$R^1 = NEt_2$, X = I	**XCV**	$R^1 = NEt_2$, 73% ee
LXXXVIII	$R^1 = NEt_2$, X = OTf	**XCVI**	$R^1 = NEt_2$, 71% ee
LXXXIX	$R^1 = NiPr_2$, X = Br	**XCVII**	$R^1 = NiPr_2$, 82% ee
XC	$R^1 = N(Me)^tBu$, X = Br	**XCVIII**	$R^1 = N(Me)^tBu$, 75% ee
XCI	$R^1 = N(OMe)Me$, X = Br	**XCIX**	$R^1 = N(OMe)Me$, 80% ee
XCII	$R^1 = N(H)^tBu$, X = Br	**C**	$R^1 = N(H)^tBu$, 87% ee
XCIII	$R^1 = N(H)C(Me)_2Ph$, X = Br	**CI**	$R^1 = N(H)C(Me)_2Ph$, 93% ee

Scheme 3.9 Enantioselective synthesis of axially chiral biaryls by Pd-catalyzed Suzuki-Miyaura coupling.[29]

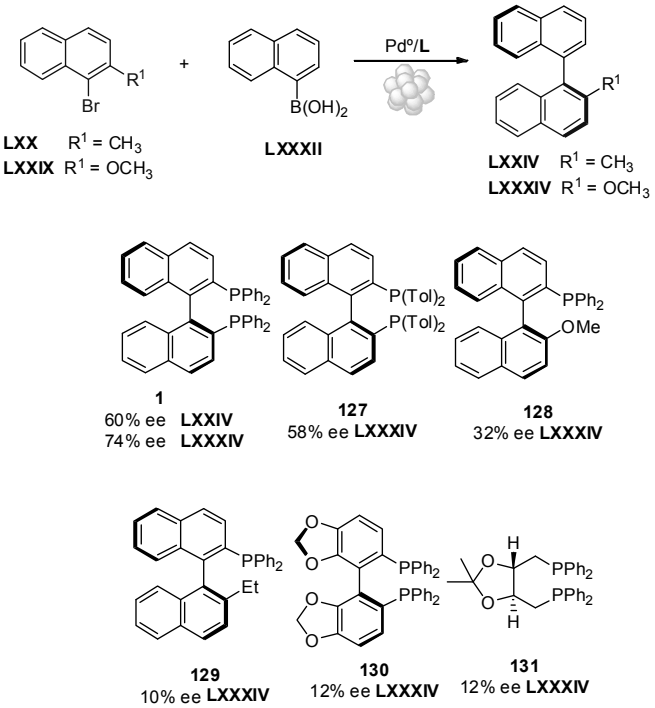
Buchwald and co-workers also performed computational studies to determine the origin of stereoselectivity during the selectivity-determining reductive elimination step of the related coupling of tolyl boronic acid with naphthylphosphonate bromide that was reported in a previous publication.[18] These studies indicate that the stereoselectivity arises from a combination of weak -(C)H--O interactions as well as steric interactions between the tolyl and naphthylphosphonate addends in the transition state for C-C coupling.[29] Recently, Song and Gong reported the use of the chiral PCN pincer Pd complex **126** in the asymmetric Suzuki- Miyaura reaction with moderate ee (~26%) (Scheme 3.10).[30]



LXXIX **LXXXII** **LXXXIV** R^1 = OMe, 26% ee

Scheme 3.10. Pd-catalysed asymmetric Suzuki-Miyaura reaction of 1-iodo-2-methoxynaphthalene with 1-naphthaleneboronic acid catalyzed by chiral the PCN pincer Pd complex **126**.

To date, only two examples of utilisation of chiral Pd-NPs as catalysts in the Pd-catalysed asymmetric Suzuki-Miyaura coupling can be found in the literature.[31-32] Fujihara et al. achieved the room temperature Suzuki–Miyaura cross-coupling reaction catalyzed by chiral phosphine-stabilized palladium NPs with good conversion and ee (up to 74%).[31] Although the chiral PdNPs have similar diameters of 1.2–1.7 nm, they showed very different catalytic activities and levels of enantioinduction. In this case, particularly, both activity and selectivity decreased in the order **1** > **127** > **128** > **129** ≥ **130** > **131.** Although no clear explanation for this behaviour was reported (Scheme 3.11).[32]



Scheme 3.11. Metal NPs stabilized by chiral ligands reported as catalysts in Suzuki–Miyaura cross-coupling reactions.

FePd NPs were synthesized via the thermal decomposition of iron carbonyl [$Fe(CO)_5$] and subsequent reduction of [$Pd(acac)_2$] in the presence of oleic acid and oleylamine to produce FexOy-rich core and Pd-rich shell. [33] These bimetallic NPs were modified with chiral ligand **1** through the simple ligand exchange procedure. These NPs were successfully used in Pd-catalysed asymetric Suzuki–Miyaura reaction of 1-bromo-2-methylnaphthylene and 1-naphthylboronic acid in DME/H_2O with 48% of ee (Figure 3.3). This catalytic system could be recycled once without further addition of chiral modifier (Figure 3.3).

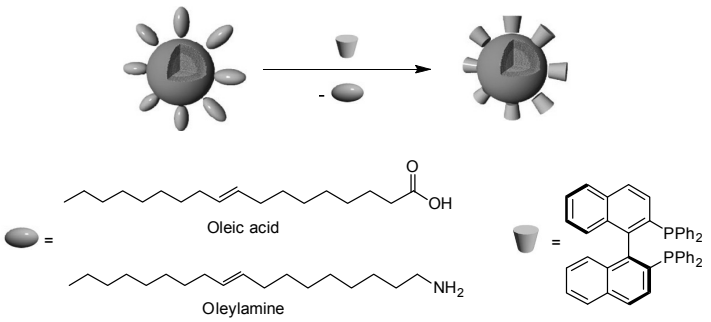


Figure 3.3. FePd NP using a ligand exchange procedure between oleic acid/ oleylamine and chiral BINAP, **1**.

Here, we report the study of novel catalytic systems containing chiral phosphorus donor ligands such as phosphines, phosphinines, phosphoramidites, phosphites and phosphonites in the Pd-catalysed Suzuki-Miyaura coupling of naphthyl halides and substituted naphthyl boronic acids. A comparative study using colloidal catalytic systems stabilised by the same phosphorus ligands is also described.

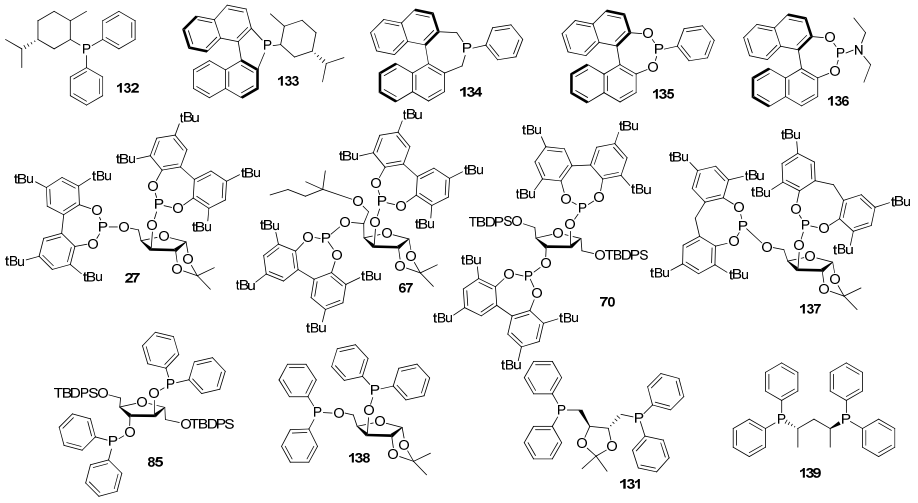


Figure 3.4. Chiral ligands used in this chapter.

3.2 Results and discussion

Aryl or biaryl phosphines are the most often used ligands in Pd-catalysed asymmetric Suzuki-Miyaura couplings. [34] Other types of ligands based on phosphorus such as phosphonite, phosphinite, phosphoramidate or phosphite were less studied. In this chapter, the results obtained with monodentate and bidentate ligands will be discussed. An overview of the ligands employed in the first part of this study is presented in Figure 3.5.

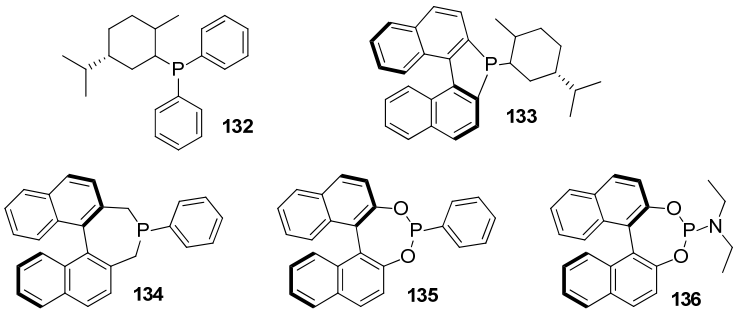


Figure 3.5. Chiral monodentate ligands used in asymmetric Suzuki-Miyaura coupling reaction

In the Suzuki-Miyaura coupling reaction, the influence of the parameters such as solvent, base, temperature and the amount and nature of the boron reagent have been widely studied to minimise the formation of homocoupling products.[35] In the next section, the results of the optimization reaction will be presented.

3.2.1 Synthesis of palladium precursors

The complex [$PdCl_2$(**132**)], **140** was synthesised according to reported methods and characterized by NMR spectroscopy. Due to the difficulties to obtain monocrystals of the complex **140**, the analogous Pt complex of this especies was prepared, complex [$PtCl_2$(**132**)], **141**. Monocrystals of **141** suitable for X-ray diffraction were obtained by slow diffusion of OEt_2 into a CH_2Cl_2 solution of the ligand. The X-ray diffraction analysis showed the presence of two half independent complexes in the unit cell, both located on a crystallographic two-fold axis. However, in the former the two-fold axis is oriented along the Cl1-Pt1-Cl2 vector, while in the other it is passing through the metal (Pt2) perpendicular to the P2Cl2 coordination plane. These

crystallographic features leads the cyclohexyl groups on different sides of the coordination plane in complex Pt1 and on the same side in complex Pt2 (see Figures). The different conformation induces a bending in the P-Pt2-P angle (167.40(15)°), that must be compared to the P-Pt1-P of 173.81(16)°, likely promoted by steric reasons. The metal is coplanar with the donor atoms in complex 1, while Pt2 is displaced by 0.176(2) Å from the mean coordination plane.

Table 3.1. Crystal data and details of refinement

Empirical formula	$C_{44}H_{58}Cl_2O_{10}P_2Pt$
Formula weight	914.83
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system space group	Orthorhombic, C2 2 21
Unit cell dimensions	a = 13.380(2) A alpha = 90 deg. b = 14.758(2) A beta = 90 deg. c = 42.479(4) A gamma = 90 deg.
Volume (Å)	8388(2) A^3
Z, Calculated density (Mg/m^3)	8, 1.449
Absorption coefficient (mm^{-1})	8.358
F(000)	3712
Theta range for data collection	2.08 to 63.37 deg
Reflections collected / unique	34952 / 6264 [R(int) = 0.0740]
Data>2sigma(I)/restraints/parameters	5115 / 0 / 450
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1268
Absolute structure parameter	-0.005(18)
Largest diff. peak and hole ($e/Å^3$)	0.873 and -1.064

Table 3.2 Selected coordination bond lengths (Å) and angles (°)

Pt(1)-Cl(1)	2.307(4)	Pt(2)-Cl(3)	2.306(2)
Pt(1)-Cl(2)	2.272(4)	Pt(2)-P(2)	2.318(2)
Pt(1)-P(1)	2.323(2)		
Cl(2)-Pt(1)-Cl(1)	180.00	Cl(3)-Pt(2)-Cl(3'')	175.16(17)
Cl(1)-Pt(1)-P(1)	86.90(8)	Cl(3)-Pt(2)-P(2'')	93.88(9)
Cl(2)-Pt(1)-P(1)	93.10(8)	Cl(3)-Pt(2)-P(2)	85.58(9)
P(1)-Pt(1)-P(1')	173.80(16)	P(2'')-Pt(2)-P(2)	167.36(15)

Symmetry codes : (') -x+2, y, -z+1/2; ('') #2 x ,-y+2, -z+1.

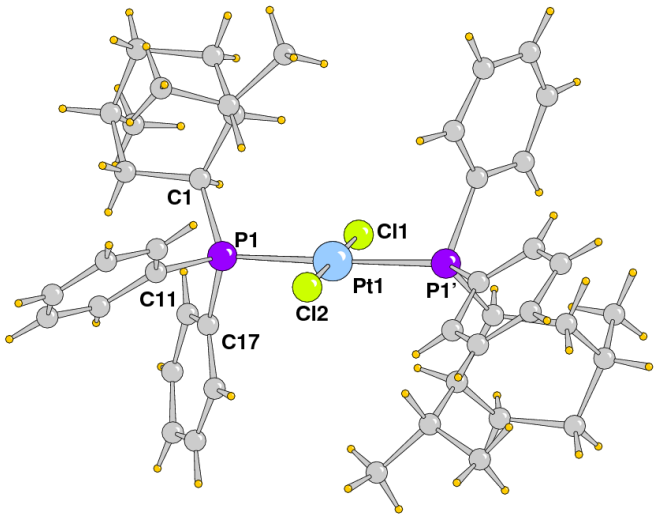


Figure 3.6. Structure of the independent complex Pt1 located on a two axis passing through the Cl-Pt-Cl atoms. P1' is referred by -x+2, y, -z+1/2.

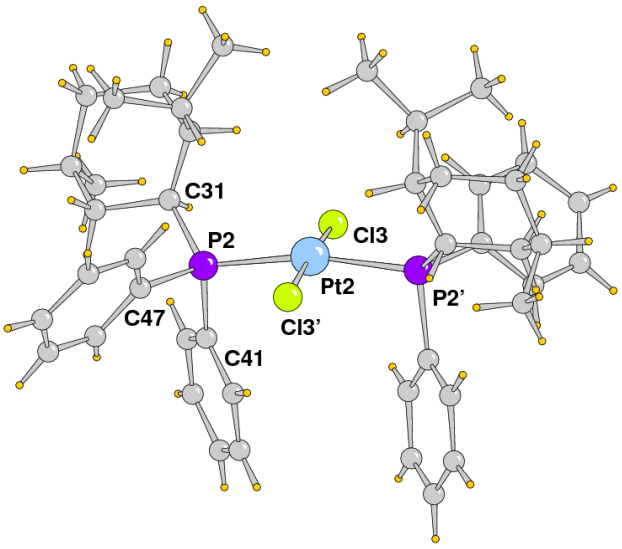
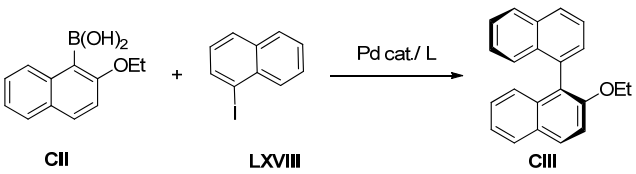


Figure 3.7. Structure of complex Pt2 located on a two axis perpendicular to the P2Cl2 coordination plane. Primed atoms at x, -y+2, -z+1.

3.2.2 Pd-catalysed asymmetric Suzuki-Miyaura coupling using Pd catalysts bearing monodentate chiral ligands

First, the catalytic system was optimised using Pd/**132** catalytic system in Pd-catalysed Suzuki-Miyaura reaction of 2-ethoxy-1-naphthylboronic acid **CII** and 1-iodonaphthalene **LXVIII** in presence of various Pd/L ratios, palladium precursors, bases and solvents (Scheme 3.12).



Scheme 3.12. Reaction conditions optimized in Suzuki-Miyaura reaction using monodentate ligands.

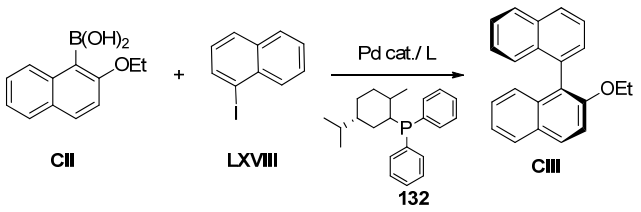
The results are summarised in Table 3.1. Initially, the reaction was carried out using $[PdCl_2(PhCN)_2]$ as catalytic precursor and CsF as the base, during 4 h at 70°C and in the absence of ligand. This system afforded 19% of conversion (entry 1, Table 3.1). Using L/Pd = 2 ratio 24% conversion and 14%

of ee was obtained (entry 2, Table 3.3). When the Pd/L ratio was decreased to L/Pd = 1.5, the activity increased to 66 %, but the ee remained unchanged (entry 3). Next, several Pd precursors were examined. Using [$PdCl_2$(COD)] and [$Pd(dba)_2$] as Pd sources, the conversions were 80% and 79%, respectively (entries 4-5, , Table 3.3). When the reaction was carried out with the [$Pd(OAc)_2$] as precursor, the conversion increased up to 89% (Entry 6, Table 3.3) The ee's were of *ca*. 15% in all cases. The preformed [$PdCl_2$(**132**)$_2$] complex afforded 78% of conversion which is quite similar to the other precursors (Entry 7, Table 3.3).

Next, several bases were tested. CsF and $Ba(OH)_2$ provided high conversions (up to 89%, entry 8, 9. Table 3.1). Other common bases such as K_2CO_3, KF, Na_3PO_4 only afforded moderate conversions (up to 57%) (Entry 10-12 Table 3.1). Surprisingly, when Cs_2CO_3 was used, the conversion dropped to 10% under the same conditions. These results demonstrated that the nature of the base used during the catalytic reaction strongly influences the rate of reaction. Noteworthy, the selectivity of the system was *ca*. 95% in all cases. The enantiomeric excess remained of *ca*. 15%. In view of these results, CsF was used as base in the subsequent experiments.

To summarise, the use of CsF as base, with a L/Pd ratio of 1.5 and [$Pd(dba)_2$] as catalytic precursor were the catalytic conditions that gave the best results in terms of conversion and were used in the subsequent experiments. Similar influence of the L/Pd ratio was previously reported by Fu and co-workers. [36] They described the use of the bulky trialkylphosphine P(t-Bu)$_3$ as ligand Suzuki-Miyaura coupling reactions. When the L/Pd ratio was superior to 1.5 they suggested that about half of the Pd contained no phosphine ligands and half contained two ligands. As the complex containing two ligands did not appear to be active under the reaction conditions, they observed the decrease of the conversion. The authors assumed that small amounts of the palladium-monophosphine adduct may represent the true catalytic species.

Table 3.3 Pd-catalysed asymmetric Suzuki-Miyaura coupling using Pd catalyst bearing monodentate chiral ligand **132**, optimization. [a]



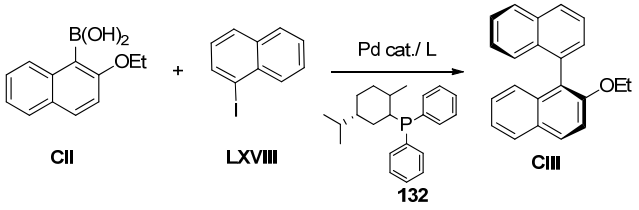
Entry	Precursor	Pd/L	base	Conv(%) [b]	Sel(%)[b]	ee(%)[c]
1[d]	$[PdCl_2(PhCN)_2]$	-	CsF	19	99	1
2	$[PdCl_2(PhCN)_2]$	1/2	CsF	24	97	14
3	$[PdCl_2(PhCN)_2]$	1/1.5	CsF	66	99	14
4	$[PdCl_2(COD)]$	1/1.5	CsF	80	98	16
5	$[Pd(dba)_2]$	1/1.5	CsF	79	97	15
6	$[Pd(OAc)_2]$	1/1.5	CsF	89	97	15
7	$[PdCl_2(\mathbf{132})_2]$	1/2	CsF	78	98	15
8	$[Pd(OAc)_2]$	1/1.5	$Ba(OH)_2$	85	97	15
9	$[Pd(OAc)_2]$	1/1.5	K_2CO_3	50	93	15
10	$[Pd(OAc)_2]$	1/1.5	KF	48	95	13
11	$[Pd(OAc)_2]$	1/1.5	Na_3PO_4	57	96	14
12	$[Pd(OAc)_2]$	1/1.5	Cs_2CO_3	10	98	12

a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 1.0 mol % Pd precursor, 1.5 mol% Ligand **132**, 3 ml of THF, t = 24h. **b**. Determined by GC. **c**. Determined by HPLC.

Next, the reaction was studied in various solvents and at various temperatures. The results are summarised in Table 3.4. The coupling reaction of 2-ethoxy-1-naphthylboronic acid **CII** and 1-iodonaphthalene, **LXVIII** was first performed in THF with 2.5 equiv. of CsF per mol of boronic acid and $Pd(OAc)_2$/**132** catalyst (Entry 1). Under these conditions, 89% conversion was achieved after 4 h at 70°C. In CH_2Cl_2, the conversion and the enantioselectivity dropped to 10 and 8%, respectively (Entry 2). Surprisingly, in the commonly used solvent system DME/H_2O, only 5% of the binaphthyl product was formed (entry 3). In view of these results, THF was used as solvent in the subsequent experiments. The reaction was therefore carried out at 50º, 30º and 10º C. Lowering the reaction temperature resulted in a decrease of the conversion from 88 to 32% and an increase in enantioselectivity from 13% to 26% (Table 3.2, entries 5-7). Surprisingly, the selectivity of the reaction also decreased from 98 to 92% when the

temperature was lowered. It is important to note that the system remained active even at 10º C.

Table 3.4 Pd-catalysed asymmetric Suzuki-Miyaura coupling using Pd catalyst bearing monodentate chiral ligand **132** in different solvents.



CII **LXVIII** **132** **CIII**

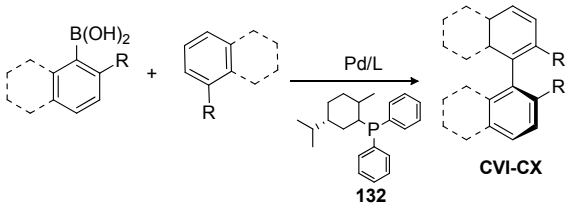
Entry	Solvent	Temp (ºC)	Conv(%) [b]	Sel(%)[b]	ee(%)[c]
1	THF	70	89	97	14
2	CH_2Cl_2	70	10	92	6
3	DME/H_2O	70	5	50	14
4	Toluene	70	60	98	14
5	THF	50	88	98	13
6	THF	30	71	97	15
7	THF	10	32	92	26

a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 1.0 mol % [$PdCl_2(PhCN)_2$], 1.5 mol% Ligand NMDPP, 3 ml of THF, t = 4h. **b**. Determined by GC. **c.** determined by HPLC.

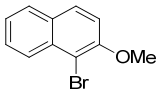
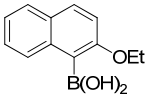
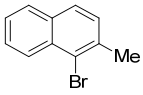
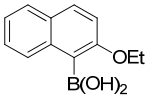
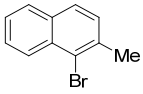
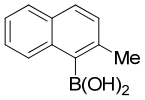
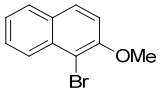
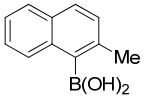
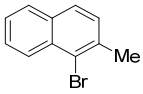
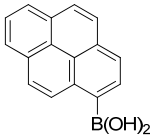
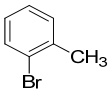
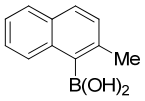
In the following experiments, several boronic acids and aryl halides bearing substituents in 2-position were tested using the Pd/**132** catalytic system. First, the asymmetric coupling of 1-bromo-2-methoxynaphthalene **LXXIX** and 2-ethoxynaphthalene-1-boronic acid **CII** was carried out using 10 mol %of Pd, THF as solvent at 70º C during 24 hours. In this case, 57% of conversion with 89 % of selectivity to the cross-coupling product was obtained (entry 1, Table 3.5) and 35% ee. The coupling reaction between 1-bromo-2-methylnaphthalene **LXX** and 2-ethoxynaphthalene-1-boronic acid **CII** afforded the coupling product in 48% conversion, 80% of selectivity and 28% of ee (entry 2, Table 3.5). When 1-bromo-2-methylnaphthalene **LXX** reacted with 2-mehtylnaphthalene-1-boronic acid **LXXI** the conversion was 53%, the selectivity 89% and 24% of ee (entry 3, Table 3.5). The coupling reaction between 1-bromo-2-methoxynaphthalene **LXXIX** and 2-methylnaphthalene-1-boronic acid **LXXI** afforded 65% of the coupling product. In this case, the selectivity dropped dramatically to 50% and only 12% of ee was obtained (entry 4, Table 3.5). The coupling reaction between 1-bromo-2-

methylnaphthalene **LXX** and pirene-1-boronic acid **CIV** afforded 67% of the coupling product with 99% of selectivity and 26% of ee (entry 5, Table 3.5). The coupling reaction between 1-bromo-2-methylbenzene **CV** and 2-methylnaphthalene-1-boronic acid **LXXI** afforded 65% of the coupling product with 87% of selectivity and 10% of ee (entry 6, Table 3.5).

Table 3.5. Pd-catalysed asymmetric Suzuki-Miyaura coupling of various substrates using Pd catalyst bearing monodentate chiral ligand **132**.



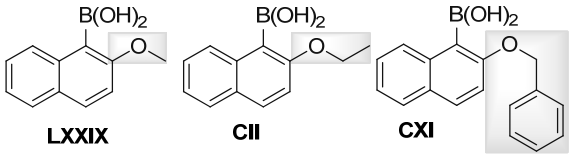
132 **CVI-CX**

Entry	-X	[-B(OH)$_2$]	Conv(%)[a]	Sel(%)[b]	ee(%)[c]
1	 **LXXVIII**	 **CI**	57	89	35
2	 **LXVIII**	 **CI**	48	80	28
3	 **LXVIII**	 **LXX**	53	89	24
4	 **LXXVIII**	 **LXX**	65	50	12
5	 **LXVIII**	 **CIII**	67	99	26
6	 **CIV**	 **LXX**	65	87	10

Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 10 mol % [Pd(PhCN)$_2$Cl$_2$], 15 mol% Ligand **132**, 3 ml of THF, t = 24h. **a**. Determined by GC. **b**. Selectivity to the cross-coupling product **c.** determined by HPLC.

To summarise, the Pd system bearing the ligand **132** was successfully used in asymmetric Suzuki-Miyaura coupling reaction of several halides and boronic acids. Conversions up to 67% and moderate ee's (up to 35%) were obtained. The highest ee was obtained when 2–OEt-naphthyl boronic acid was used as coupling partner (Entry 1 and 2, Table 3.5).

Next, the catalytic systems bearing the ligands **132-136** were evaluated in the Pd-catalysed asymmetric Suzuki-Miyaura reaction of bromo-naphthalene with naphthalene boronic acids bearing methoxy- (**LXXIX**), ethoxy- (**CII**) and benzyloxy (**CXI**) substituents in 2-position (Figure 3.8).



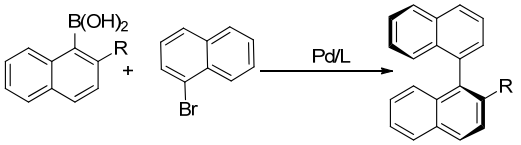
LXXIX **CII** **CXI**

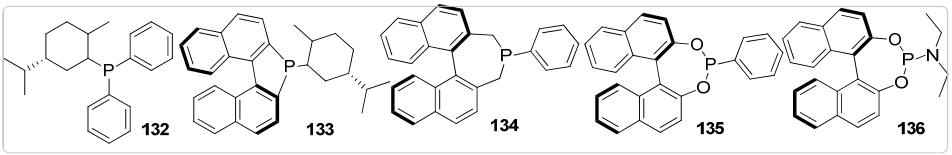
Figure 3.8. Boronic acids used in Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.

First, the catalytic system bearing the ligand **132** was evaluated in the coupling of bromonaphthalene **LXVII** with **LXXIX**, **CII** and **CXI** in the presence of CsF as a base at 70º C during 4 hours (Table 3.6). The reaction between 1-bromonaphthalene **LXVII** and the 2-methoxynaphthalene-1-boronic acid **LXXIX** afforded 76% of conversion and 10% of ee (Entry 1, Table 3.7). When 2-ethoxynaphthalene-1-boronic acid **CII** was used the conversion dropped to 56%, and 14% of ee was obtained (entry 2, Table 3.7). The use of 2-benzyloxynaphthalene-1-boronic acid **CXI** produced 80% of product, but a racemic mixture was obtained (entry 3). The coupling reactions using the catalytic system bearing the ligand **133** with the substrate **LXXIX** and **CII** afforded 76% and 49% of conversion and 10% and 9% ee, respectively (entries 4-5). Using the ligand **134**, 15% of conversion, and 24% of ee with 2-methoxynaphthalene-1-boronic acid **LXXIX** was obtained (entry 6, Table 3.7). Under the same catalytic conditions, 21% and 9% ee of the coupling product with 2-ethoxynaphthalene-1-boronic acid **CII** was achieved (entries 7, Table 3.7). The use of 2-benzyloxynaphthalene-1-boronic acid **CXI** produced 11% of product without any enantioinduction (entry 8). In the case of the catalytic system containing ligand **135**, 19%, 15% and 3% of conversion and ee up to

17% were obtained with the substrates **LXXIX**, **CII** and **CXI** respectively (entries 9-11, Table 3.7). Finally using the phosphoramidite ligand **136**, the reaction between 1-bromonaphthalene **LXVII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** afforded 23% of conversion and 10% of ee (entry 12, Table 3.7). When 2-ethoxynaphthalene-1-boronic acid **CII** was used 33% of conversion and 12% of ee was obtained (entry 13, Table 3.7). With 2-benzyloxynaphthalene-1-boronic **CXI** acid, 50% conversion was obtained but without enantioselectivity (Entry 3).

Table 3.6. Pd-catalysed asymmetric Suzuki-Miyaura coupling using Pd catalysts bearing monodentate chiral ligands with different substrates.[a]





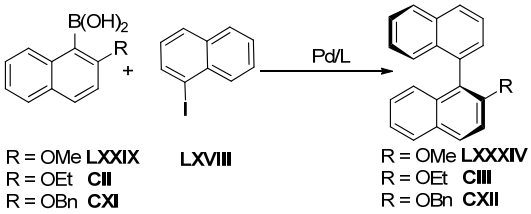
Entry	Ligand	-B(OH)$_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1		**LXXIX**	76	98	10
2	**132**	**CII**	56	98	14
3		**CXI**	80	99	<1
4	**133**	**LXXIX**	76	99	10
5		**CII**	49	99	9
6		**LXXIX**	15	94	24
7	**134**	**CII**	21	98	9
8		**CXI**	11	99	<1
9		**LXXIX**	19	98	7
10	**135**	**CII**	15	99	17
11		**CXI**	3	-	<1
12		**LXXIX**	23	97	10
13	**136**	**CII**	33	98	12
14		**CXI**	50	99	<1

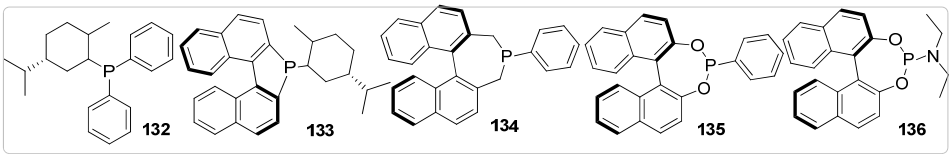
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 10 mol % Pd precursor, 1.5 mol% Ligand, 3 ml of THF, t = 24h. **b.** Determined by GC. **c**. determined by HPLC.

To summarise, the monodentate ligands **132-136** were successfully used in the Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions of bromonaphthalene and 2-substituted naphthalene boronic acids. Conversions up to 80% were obtained although only moderate lo low ee's could be achieved.

Next, these catalytic systems were evaluated in the Pd-catalysed asymmetric Suzuki-Miyaura reactions of iodonaphthalene with the boronic acids **LXXIX**, **CII** and **CXI** in the presence of CsF as a base at 70º C during 4 hours (Table 3.7). The reaction between 1-iodonaphthalene **LXVIII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** afforded 80% of conversion and 22% of ee (entry 1, Table 3.7). When 2-ethoxynaphthalene-1-boronic acid **CII** was used, the conversion dropped to 66%, and 14% of ee was obtained (entry 2, Table 3.7). The use of 2-benzyloxynaphthalene-1-boronic acid **CXI** produced 83% of product, but without enantioinduction (entry 3). The coupling reaction using the catalytic system bearing the ligand **133** with the substrate **LXXIX** and **CII** afforded 73% and 60% of conversion and 15% and 7% respectively (entries 4-5). Using the ligand **134**, 63% of conversion and 12% of ee were obtained in the coupling of 2-methoxynaphthalene-1-boronic acid **LXXIX** (entry 6, Table 3.7). With 2-ethoxynaphthalene-1-boronic acid (**CII**), 17% conversion and 9% ee was achieved (entries 7, Table 3.7). The use of 2-benzyloxynaphthalene-1-boronic acid (**CXI**) led to 73% conversion and 4% ee (entry 8). In the case of the catalytic system containing ligand **135**, 3%, 67% and 73% of conversion and ee up to 12% were obtained with the substrates **LXXIX**, **CII** and **CXI** respectively (entries 9-11, Table 3.7). Finally, using the phosphoramidite ligand **136**, the reaction between 1-iodonaphthalene **LXVIII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** afforded 64% conversion and 16% of ee (entry 12, Table 3.7). When 2-ethoxynaphthalene-1-boronic acid **CII** was used the conversion dropped to 54%, and 7% of ee was obtained (entry 13, Table 3.7). The use of 2-benzyloxynaphthalene-1-boronic acid **CXI** led to 40% conversion as a racemic mixture (entry 3).

Table 3.7. Pd-catalysed asymmetric Suzuki-Miyaura couplings using monodentate chiral ligands.[a]





Entry	Ligand	-$B(OH)_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1		**LXXX**	80	98	22
2	**132**	**CI**	66	99	14
3		**CXI**	83	99	1
4	**133**	**LXXX**	73	93	15
5		**CI**	60	96	7
6		**LXXX**	63	98	12
7	**134**	**CI**	17	99	9
8		**CXI**	73	99	4
9		**LXXX**	3	-	-
10	**135**	**CI**	67	98	14
11		**CXI**	73	99	3
12		**LXXX**	64	98	16
13	**136**	**CI**	54	99	7
14		**CXI**	40	99	2

a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 10 mol % Pd precursor, 1.5 mol% Ligand, 3 ml of THF, t = 4h. **b**. Determined by GC. **c**. Determined by HPLC.

As expected, the activity of these catalytic systems was higher with iodonaphthalene than for bromonaphthalene analogues. However, no significant differences in enantioselectivity were observed and in both cases, low to moderate ee's were obtained.

In view of the poor enantioinduction that was achieved with monodentate ligands, it was decided to probe the use of bidentate ligands and in the following section, our results in the asymmetric Suzuki-Miyaura coupling

using various bidentate ligands including diphosphine, diphosphinite and diphosphite ligands are described.

3.2.3 Pd-catalysed asymmetric Suzuki-Miyaura coupling using Pd catalysts bearing bidentate chiral ligands

The bidentate ligands used in this study are presented in Figure 3.9. As previously mentioned in Chapter 2, the ligands **27**, **70**, **137** and **139** were used in several asymmetrical transformations affording high enantioselectivities. [37]The phosphinite ligand, **85**, has the same backbone than the ligand **70**. This ligand was reported in the enantioselective Rh-and Ir-catalysed asymmetric hydrogenation of unsaturated substrates.[38]

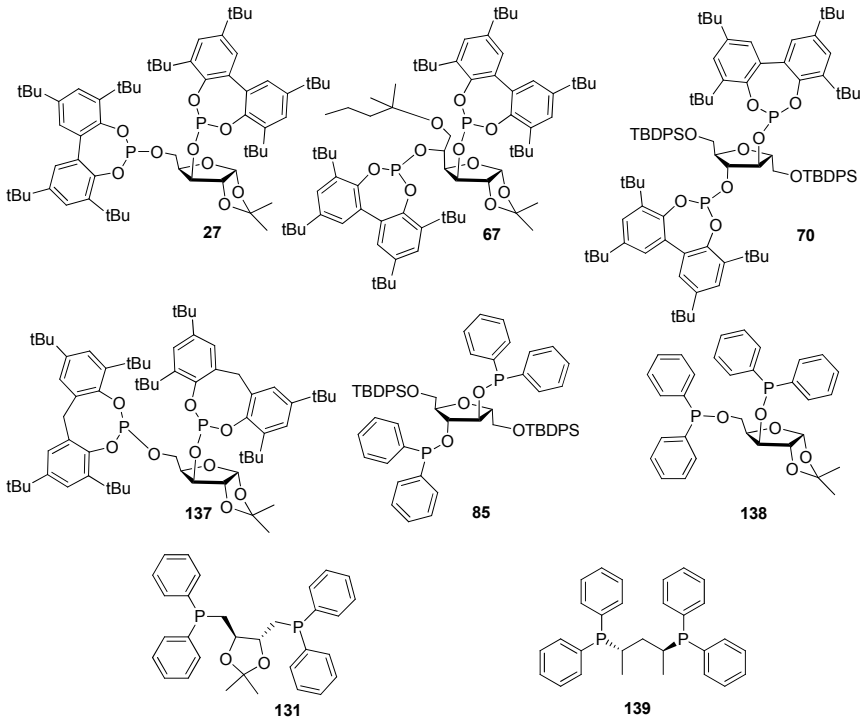
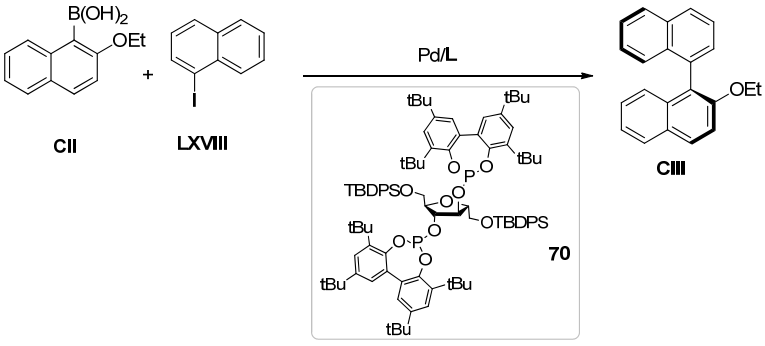


Figure 3.9. Chiral bidentate ligands used in Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.

A screening of Pd precursors at different L/Pd ratios was performed using the ligand **70** in the Pd-catalysed asymmetric Suzuki-Miyaura coupling of 1-iodonaphthalene **LXVIII** and 2-ethoxy-1-naphthyl boronic acid **CII** are shown in Table 3.8. All the systems were found to yield high chemoselectivity towards the desired cross coupling product (>97%). The coupling reaction between 1-iodonaphthalene **LXVIII** and 2-ethoxynaphthalene-1-boronic acid **CII** was carried out with a $[PdCl_2(PhCN)_2]$/**70** ratio of 1/1. After 4 h at 70 ° C, 52% conversion of the cross-coupling product was obtained without any enantioselectivity (entry 1, Table 3.8). When the Pd/L ratio was increased to 1/1.5 both the conversion and enantioselectivity increased to 65% and 11%, respectively (entries 2, Table 3.8). When the Pd/**70** ratio = 1/2, lower conversion and ee were obtained (entry 3, Table 3.8). However, when $[Pd(OAc)_2]$ was used, the enantioselectivity increased to 19% although the conversion decreased to 24% under the same reaction conditions (entry 4, Table 3.8). Therefore, higher conversions were obtained with $[PdCl_2(PhCN)_2]$ precursor although higher ee's was obtained with $[Pd(OAc)_2]$. The optimum Pd/L ratio was 1/1.5.

Table 3.8. Pd-catalysed asymmetric Suzuki-Miyaura coupling using the chiral ligand **70**.[a]



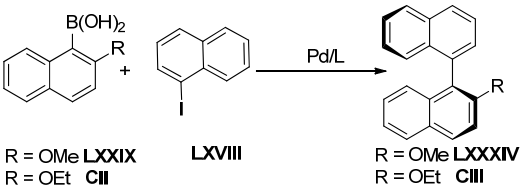
Entry	Pd	L/Pd	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1	$[PdCl_2(PhCN)_2]$	1	52	97	1
2	$[PdCl_2(PhCN)_2]$	1.5	65	98	11
3	$[PdCl_2(PhCN)_2]$	2	57	99	3
4	$[Pd(OAc)_2]$	1.5	24	98	19

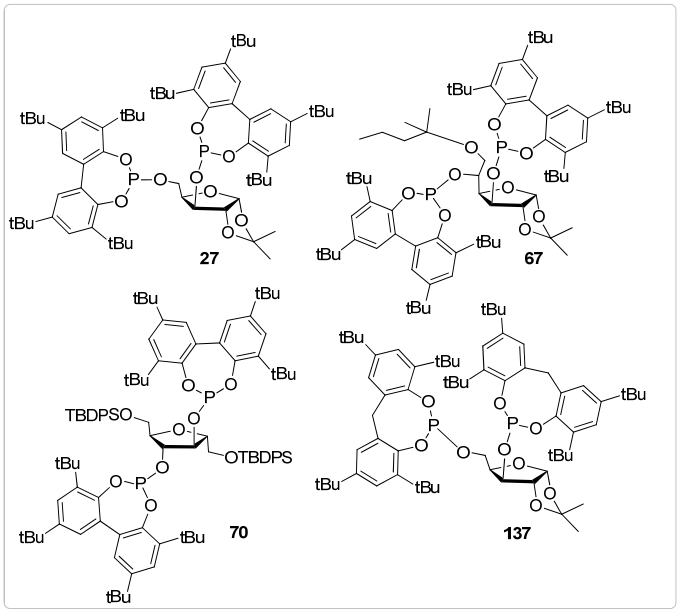
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 1.0 mol % Pd precursor, 1.5 mol% Ligand **70**, 3 ml of THF, t = 4 h. **b**. Determined by GC. **c**. Determined by HPLC.

Next, the ligands **27**, **67**, **70**, **85**, **131**, **137**, **138** and **139** were evaluated in the Suzuki-Miyaura reaction of iodonaphthalene with 2-methoxy and 2-ethoxy substituted naphthylboronic acids.

First, Pd-catalysts bearing the diphosphite ligands **27**, **67**, **70** and **137** were used in the Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction. Initially, the reaction between iodonaphthalene **LXIX** and 2-ethoxynaphthalene-1-boronic acid **CI** was carried out using the Pd/**60** catalytic system in presence of CsF as a base at 70º C during 4 hours. In this case, good conversion (90%) and 37% ee were obtained (entry 1, Table 3.9). The reaction between 1-iodonaphthalene **LXIX** and 2-methoxynaphthalene-1-boronic acid **LXXX** using the Pd / **68** system afforded 50% conversion and poor ee (entry 2, Table 3.9). When 2-ethoxynaphthalene-1-boronic acid **CI** was used, 48% of conversion and 19% of ee was obtained (entry 3, Table 3.9). Then, the coupling reaction using the catalytic system bearing the ligand **70** with the substrate **LXXX** and **CI** afforded 65% and 56% of conversion and 2% and 11% respectively (entries 4-5, Table 3.9). Using the ligand **137** and 2-methoxynaphthalene-1-boronic acid **LXXX** as substrate, 58% of conversion and 8% ee was obtained (entry 6, Table 3.9). Under the same catalytic conditions, 43% conversion and 12% ee was achieved with 2-ethoxynaphthalene-1-boronic acid **CI** (entries 7, Table 3.9). In all cases, high selectivity to the desired product was afforded (up to 99%).

Table 3.9 Pd-catalysed asymmetric Suzuki-Miyaura reaction using Pd/diphosphite ligands, **60**, **68**, **70** and **137**.[a]





Entry	Ligand	-B(OH)$_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[b]
1	**27**	**CII**	96	99	37
2	**67**	**LXXIX**	50	98	4
3		**CII**	48	99	19
4	**70**	**LXXIX**	65	98	2
5		**CII**	56	98	11
6	**137**	**LXXIX**	58	99	8
7		**CII**	43	98	12

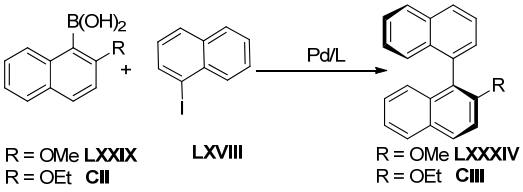
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 1.0 mol % [$PdCl_2(PhCN)_2$], 1.5 mol% Ligand, 3 ml of THF, t = 4 h. **b.** Determined by GC. **c**. determined by HPLC.

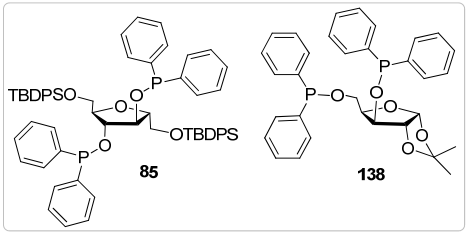
As a conclusion, several catalytic systems bearing diphosphite ligands were active in the Pd-catalysed asymmetric Suzuki-Miyaura. When the catalytic system bearing the ligand **27** was used, high conversion (up to 96%) and moderate ee (37%) were obtained (entry 1, Table 3.9) in the coupling of 1-

iodonaphthalene **LXXIX** and 2-ethoxy-1-naphthyl boronic acid **CII**. This is the first report on the use of chiral phosphite ligands in this asymmetric reaction.

Next, the chiral diphosphinite ligands **85** and **138** were tested in this reaction under the same catalytic conditions. The results are summarised in Table 3.8). The reaction between 1-iodonaphthalene **LXVIII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** using Pd catalyst bearing the ligand **85** afforded 36% of conversion and 22% ee (entry 1, Table 3.10). When 2-ethoxynaphthalene-1-boronic acid **CII** was used, 56% of conversion and 17% of ee was obtained (entry 2, Table 3.10). Then, the coupling reaction using the catalytic system bearing the ligand **138** with the substrate **LXXIX** and **CII** afforded 14% and 73% of conversion, respectively and 30% and 21% ee, respectively (entries 3-4, Table 3.10). In all cases, high selectivities to the desired product were obtained (up to 99%).

Table 3.10. Pd-catalysed asymmetric Suzuki-Miyaura reaction using Pd/diphosphinite ligands, **85** and **138.**[a]





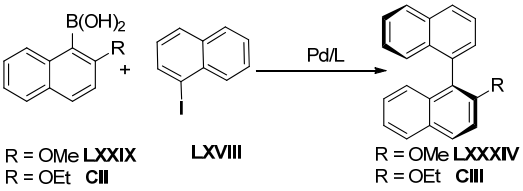
Entry	Ligand	-B(OH)$_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1	**85**	**LXXIX**	36	99	22
2		**CII**	56	97	17
3	**138**	**LXXIX**	14	98	30
4		**CII**	73	99	21

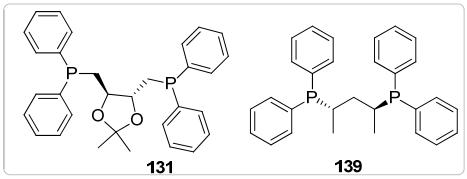
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 1.0 mol % [$PdCl_2(PhCN)_2$], 1.5 mol% Ligand, 3 ml of THF, t = 4 h. **b.** Determined by GC. **c**. determined by HPLC.

To conclude, these Pd catalysts bearing diphosphinite ligands were more active when the boronic acid **CII** was used although the ee's were slightly higher with **LXXIX** (Table 3.10). This is the first report on the use of chiral diphosphinite ligands in this asymmetric reaction.

Next, the diphosphine ligands **131** and **139** were used in this reaction under the same catalytic conditions. The reaction between 1-iodonaphthalene **LXVIII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** using Pd catalyst bearing the ligand **131** afforded 32% of conversion without ee (entry 1, Table 3.11). When 2-ethoxynaphthalene-1-boronic acid **CII** was used, 40% of conversion and 4% of ee was obtained (entry 2, Table 3.11). Then, the coupling reaction using the catalytic system bearing the ligand **139** afforded 50% and 31% of conversion and 17% and 3% respectively with the substrate **LXXIX** and **CII** (entries 3-4, Table 3.11). In all cases, high selectivities to the desired product were obtained (up to 99%).

Table 3.11. Pd-catalysed asymmetric Suzuki-Miyaura reaction using Pd/diphosphinite ligands, **131** and **139**.[a]





Entry	Ligand	-B(OH)$_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1	**131**	**LXXIX**	32	99	3
2		**CII**	40	99	4
3	**139**	**LXXIX**	50	97	17
4		**CII**	31	98	3

a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol CsF, 1.0 mol % [$PdCl_2(PhCN)_2$], 1.5 mol% Ligand, 3 ml of THF, t = 4 h. **b.** Determined by GC. **c**. determined by HPLC.

To conclude, the Pd catalysts containing the diphosphine ligands **131** and **139** were active in asymmetric Suzuki-Miyaura reaction but gave rather disappointing results both in terms of conversion and in terms of ee. In general, the catalytic systems bearing the diphosphite and diphosphinite ligands were more active and gave higher ee's than those containing the phosphine ligands.

The chiral ligands used in the Pd-catalysed asymmetric Suzuki-Miyaura coupling were also utilised in the stabilization of Pd NPs in order to study the use of these colloidal entities as catalysts in this reaction.

3.2.4 Synthesis of Pd-nanoparticles using chiral ligands

The PdNPs **Pd132**, **Pd133**, and **Pd134** were synthesized from $[Pd_2(dba)_3{\cdot}CHCl_3]$ in the presence of the chiral monophosphine ligands **132**-**134** using a previously reported method.[39] As a standard procedure, the decomposition of the palladium precursor was realized in THF in a Fischer–Porter bottle at room temperature under H_2 atmosphere (3 bars), in the presence of the selected ligand (P/Pd =0.2). These Pd nanoparticles were soluble in THF and were isolated as black powders after pentane precipitation. In the case of the the phosphoramidite ligand **136**, only the presence of Pd black was observed. It was therefore deduced that the properties of this ligand were not appropriate to stabilise PdNPs.

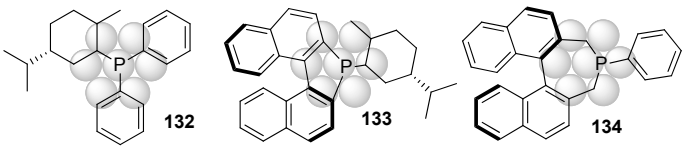


Figure 3.10. Chiral monodentate ligands used in PdNPs stabilization.

The transmission electron microscopy (TEM) images with the mean diameter and size distribution of the **Pd132, Pd133** and **Pd134** NPs are shown in Figure 3.11. Mean diameters of 3.4 ± 0.8, 3.0 ± 0.4 and 3.4 ± 0.5 nm were measured for the **Pd132, Pd133** and **Pd134** NPs, respectively. Thus, no strong effect of the structure of these ligands on the mean diameter and the size distribution of the resulting NPs were observed.

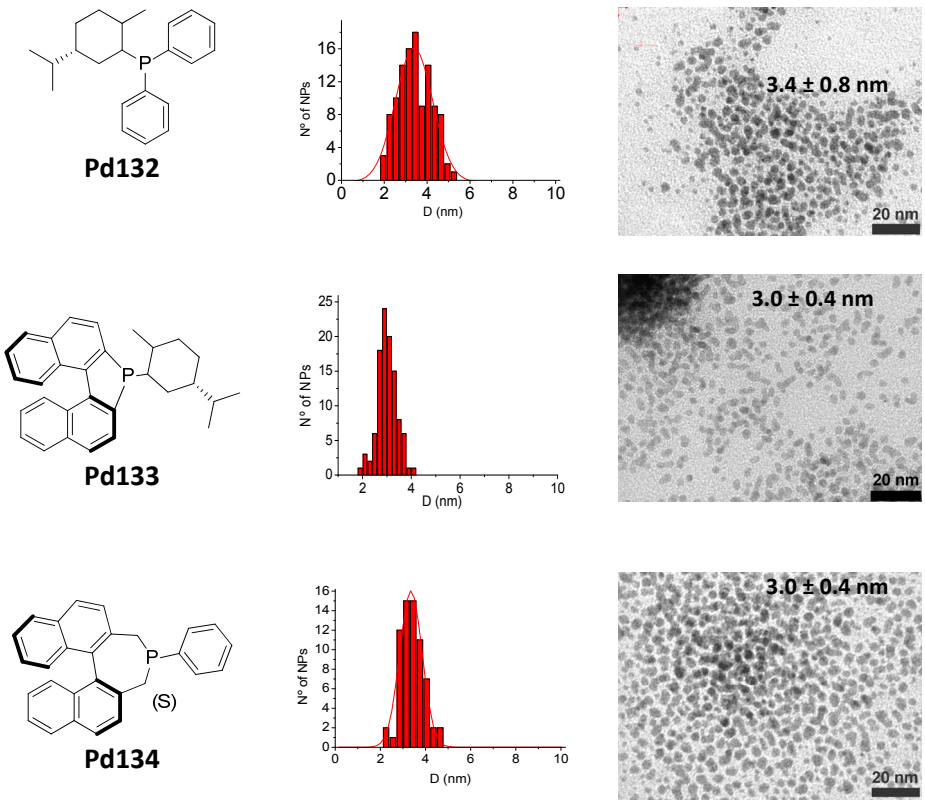


Figure 3.11. TEM images and size distributions of the Pd NPs stabilised by monodentate ligands **132**-**134.**

The NPs stabilised by bidentate ligands were synthesised by the method described in the section 3.2.4. The TEM micrograph, mean diameter, and size distribution of the **Pd137, Pd67, Pd138** and **Pd85** NPs are shown in Table 3.10. The TEM micrograph of **Pd137** revealed nanoparticles with a mean diameter of 4.3 ± 0.5 nm. The **Pd67** and **Pd138** were found to be colloids with a mean diameter of 3.8 ± 0.6 nm and 5.1 ± 0.6 nm. Agglomerates consisting of small groups of individual NPs were also observed in the TEM micrograph of **Pd67** and **Pd138** NPs. In the case of **Pd85**, well-dispersed NPs were observed, with a mean diameter of 4.3 ± 1.0 nm.

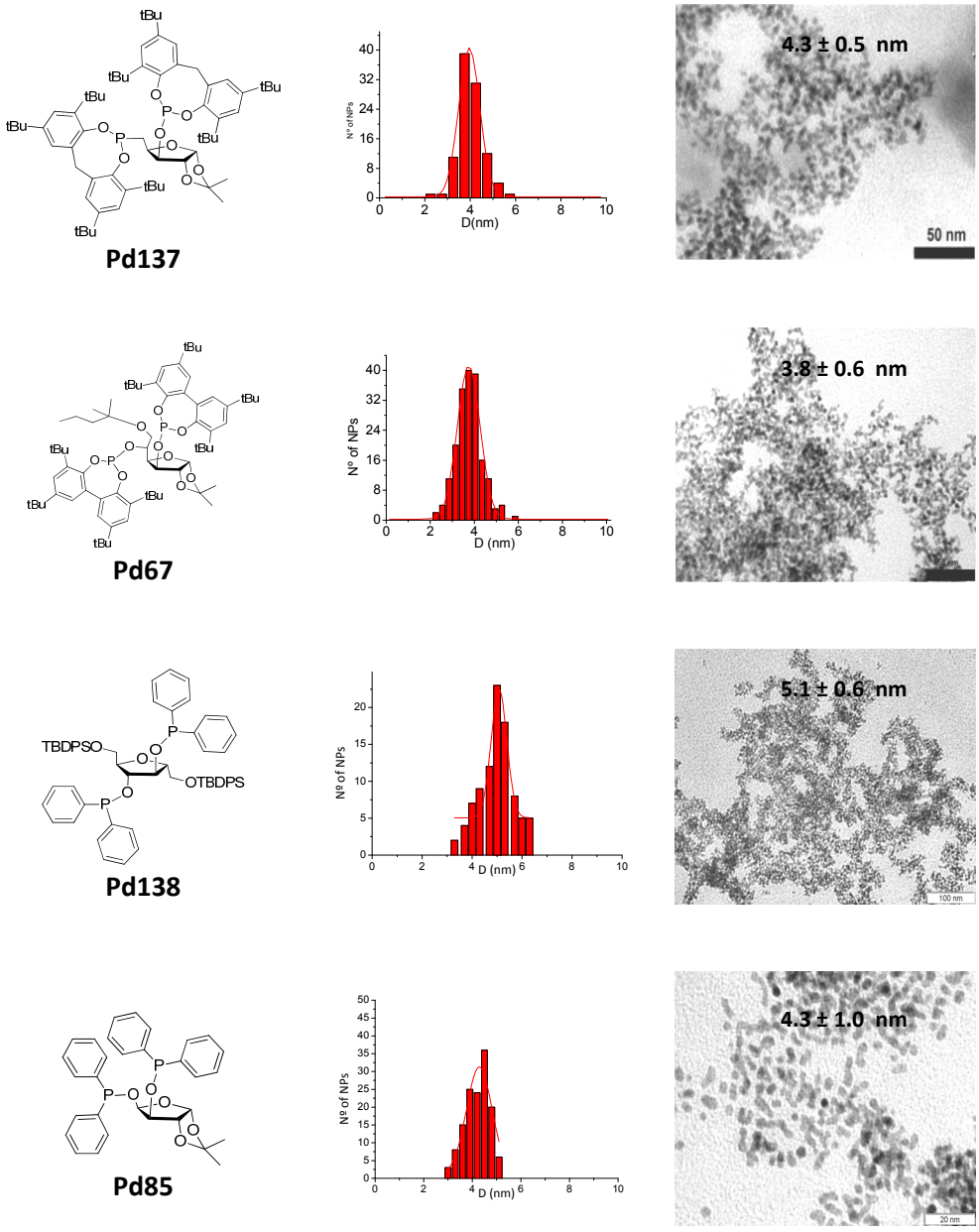


Figure 3.12 TEM micrographs and size distributions of the Pd NPs stabilised by diphosphite (**Pd137** and **Pd67**) and diphosphinite (**Pd138** and **Pd85**) ligands

The TEM micrograph, mean diameter and size distribution of **Pd131** and **Pd139** NPs stabilised by phosphine ligands **131** and **139** are shown in Figure

3.13. In the TEM micrograph of **Pd131** small and aggregated NPs were observed. The mean diameter of these NPs was 3.4 ± 0.5 nm. In the TEM micrograph of **Pd139**, an elevated degree of agglomeration was observed. The mean diameter of these NPs was 3.2 ± 0.4 nm.

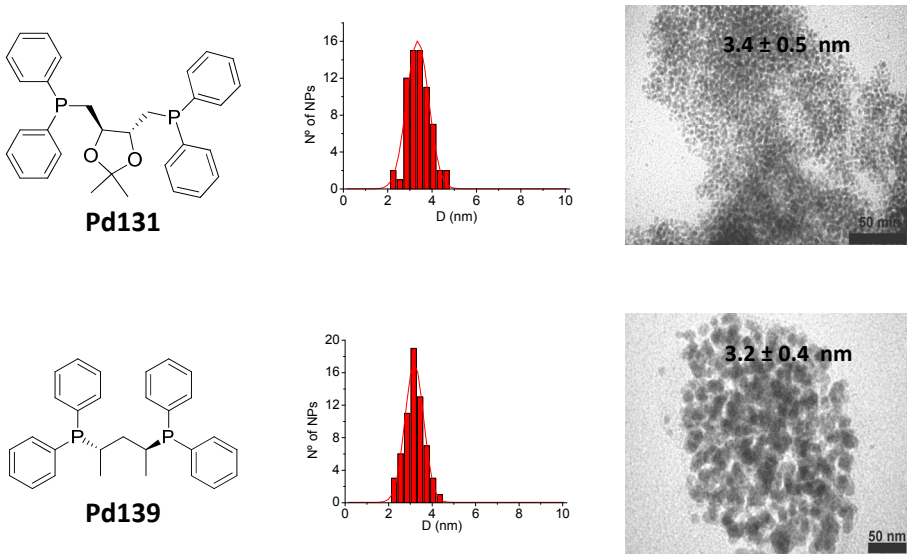


Figure 3.13. TEM micrographs and size distribution of the Pd NPs stabilised by phosphine ligands (**Pd131** and **Pd139**).

To conclude, the **Pd70** NPs stabilised with C2 symmetry diphosphite ligand **70** were smaller than the **Pd27**, **Pd67** and **Pd137** NPs stabilised by C1 symmetry diphosphite ligands. A subtle effect was observed in the mean diameter between **Pd27**, **Pd67** and **Pd137** NPs. The **Pd131** and **Pd139** stabilised by phosphine ligands were quite similar in diameter and size distribution. In terms of aggregation, the NPs stabilised by monophosphine ligands presented a lower level of aggregation than the NPs stabilised by the bidentate ligands.

Moreover, with monophosphines as stabilisers, the mean diameter was *ca*. 3.2 nm. In the case of NPs stabilised by diphosphite and diphosphinite ligands the mean diameter was superior to 3.8 nm and *ca.* 3.2 nm in the case of diphosphines.

In the next section, the **Pd132-134** NPs stabilised by monodentate ligands were used as catalysts in Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.

3.2.5 Pd-catalyzed asymmetric Suzuki-Miyaura coupling reaction using NPs stabilized by chiral monodentate ligands

First, preliminary optimization of the temperature, solvent and base were realized in the coupling of iodonaphthalene **LXVIII** with 2-ethoxynaphthalene-1-boronic acid **CII** using the preformed **Pd132** NPs as catalytic system.

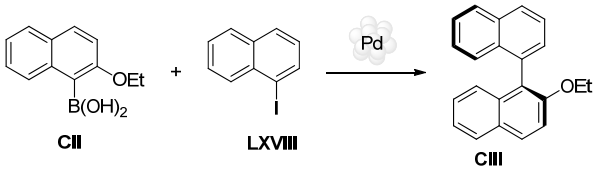
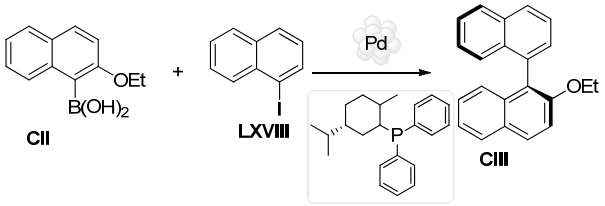


Figure 3.14. Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction using Pd NPs.

These catalytic systems afforded in all cases high chemoselectivity towards the desired cross coupling product (>94%) (Table 3.12). When the reaction was carried out at 70ºC, 86% of conversion but no ee was obtained. At room temperature, 62% of conversion was achieved in 24h with a slight increase in ee (10%) (Entry 2). At 0ªC, the conversion decreased to 42% and 12% of ee was afforded (entry 3). When the reaction was repeated at room temperature with $Ba(OH)_2$ as a base (entry 6), the conversion was found to be 60% and 10 % of ee was obtained. Using Cs_2CO_3, the conversion dropped to 28% and 8% of ee was obtained under the same reaction conditions (entry 8). Moreover, when the toluene and DME solvents were used for this reaction, the conversion dropped to 34% and 10 %, and the ee to 12% and 13%, respectively (entries 8 and 9).

Table 3.12. Pd-catalysed asymmetric Suzuki-Miyaura coupling using preformed **Pd132** NPs.[a]



Entry	solvent	base	Temp. (ºC)	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1[e]	THF	CsF	70	86	98	3
2	THF	CsF	rt	66	96	10
3	THF	CsF	0	42	93	12
6	THF	$Ba(OH)_2$	rt	60	98	10
7	THF	$CsCO_3$	rt	28	96	8
8	Toluene	CsF	rt	34	96	12
9	DME	CsF	rt	10	95	13

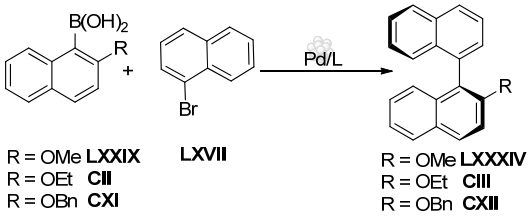
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 1.0 mol % PdNPs, 1.5 mol% Ligand **132**, 3 ml of THF, t = 24 h. **b**. determined by GC, **c**. Determined by HPLC.

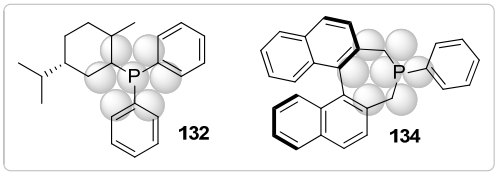
To conclude, the best results in the asymmetric Suzuki-Miyaura coupling catalysed by the Pd/**132** system were obtained in THF, with CsF as the base and at room temperature.

The results obtained in the asymmetric Suzuki-Miyaura coupling reaction catalysed by **Pd132**, **Pd133** and **Pd134** NPs under the previously optimised conditions are summarised in Table 3.13 and Table 3.14. The reactions of iodonaphthalene **LXVIII** and bromonaphthalene **LXVII** with the boronic acids **LXXIX**, **CII**, and **CXI** were carried out. First, the **Pd132** NPs were used in the coupling of bromonaphthalene **LXVII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** afforded 70% of conversion and 3% of ee (entry 1, Table 3.13). When 2-ethoxynaphthalene-1-boronic acid **CII** was used, the conversion dropped to 40%, and but an increase in ee to 15% was observed (entry 2, Table 3.13). The use of 2-benzyloxynaphthalene-1-boronic acid, **CXI**, produced 80% of product and 12% ee was obtained (entry 3). Using the **Pd134** NPs, the coupling reaction of bromonaphthalene **LXVII** with 2-methoxynaphthalene-1-boronic acid **LXXIX** and 2-ethoxynaphthalene-1-boronic acid **CII** afforded 21% and 25% of conversion, and 5% and 11% ee

respectively (entries 4-5). With 2-benzyloxynaphthalene-1-boronic acid, **CXI** 11% of conversion and 11% of ee was obtained (entry 6, Table 3.13).

Table 3.13. Pd-catalyzed asymmetric Suzuki-Miyaura coupling reactions catalysed by Pd **Pd132** and **Pd134** NPs.[a]





Entry	Catalyst	$B(OH)_2$	Conv(%) [b]	Sel(%)	ee(%)[d]
1	**Pd132**	**LXXIX**	70	98	3
2	**Pd132**	**CII**	40	95	15
3	**Pd132**	**CXI**	80	99	12
4	**Pd134**	**LXXIX**	21	99	8
5	**Pd134**	**CII**	25	93	5
6	**Pd134**	**CXI**	11	94	11

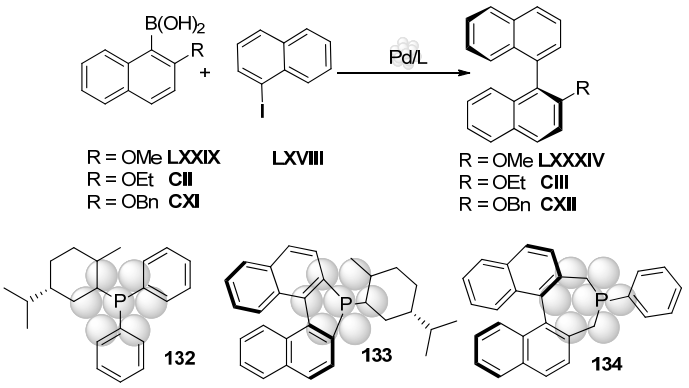
a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 1.0 mol % PdNPs, 3 ml of THF, t = 24 h, room temperature. **b**. determined by GC, **c**. Determined by HPLC.

As conclusion, the NPs stabilised by the monophosphine ligand **132** were very active at room temperature but low ee values were obtained.

Using the catalytic system **Pd132** NPs in the coupling of 1-iodonaphthalene **LXVIII** and 2-methoxynaphthalene-1-boronic acid **LXXIX** in THF at room temperature, 26% of conversion was obtained after 24h of reaction but no enantioinduction was achieved (entry 1, Table 3.14). When 2-ethoxynaphthalene-1-boronic acid **CII** was used, 66% of conversion and 10% of ee was obtained (entry 2,Table 3.14). The use of 2-2-benzyloxynaphthalene-1-boronic acid **CXI**, produced 38% of product and 16% ee (entry 3). When **Pd133** NPs were used as catalysts with 2-ethoxynaphthalene-1-boronic acid **CII** as substrate, 58% of conversion and

11% ee were obtained. The coupling reaction using the **Pd134** NPs with the 2-methoxynaphthalene-1-boronic acid **LXXIX** substrate and 2-ethoxynaphthalene-1-boronic acid **CII** afforded 24% and 62% of conversion and 3% and 6% ee respectively (entries 5-6). With **Pd134** NPs as catalyst in the coupling of 1-iodonaphthalene and 2-benzyloxynaphthalene-1-boronic acid, **CXI**, 49% conversion and 24% ee were obtained (entry 7, Table 3.14).

Table 3.14. Pd-catalyzed asymmetric Suzuki coupling reactions catalysed by **Pd132**-**Pd134** NPs.[a]



Entry	Catalyst	-$B(OH)_2$	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1	**Pd132**	**LXXIX**	26	96	3
2	**Pd132**	**CII**	66	92	10
3	**Pd132**	**CXI**	38	99	16
4	**Pd133**	**CII**	58	99	11
5	**Pd134**	**LXXIX**	24	93	3
6	**Pd134**	**CII**	62	90	6
7	**Pd134**	**CXI**	49	99	24

a. Reaction conditions: 1.0 mmol iodonaphthalene, 2.0 mmol naphthylboronic acid, 5 mmol base, 1.0 mol % Pd precursor, 1.5 mol% Ligand, 3 ml of THF, t = 24h. **b**. determined by GC, **c**. Determined by HPLC.

In terms of conversion, the results obtained were found to vary considerably depending on the substituent attached to the naphthyl moiety of the boronic acid. The highest conversion was obtained with the boronic acid containing an -OEt group in 2 position (66%, Table 3.13). The activities of the PdNPs were quite similar in all cases. Surprisingly in the case of **Pd132** NPs, the

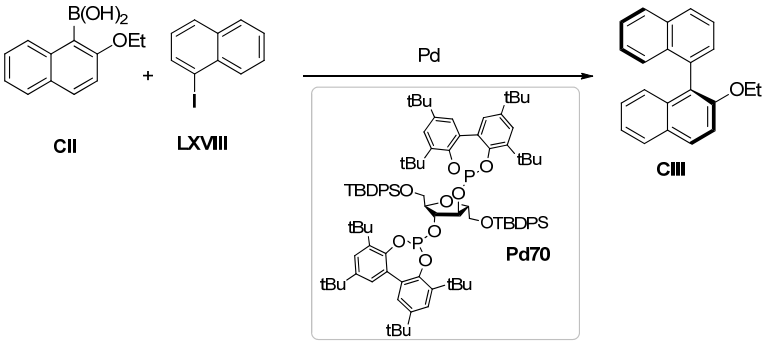
conversion of the bromonaphthalene **LXVII** substrate was higher than when iodonaphthalene, **LXVIII**, was the substrate.

Next, the **Pd27**, **Pd67**, **Pd70**, and **Pd137** NPs stabilised by bidentate ligands were also tested as catalysts in the asymmetric Suzuki-Miyaura coupling reaction of 2-ethoxynaphthalene-1-boronic acid **CII** and iodonaphthalene **LXVIII.**

3.2.6 Pd-catalyzed asymmetric Suzuki-Miyaura coupling reactions using NPs stabilized by chiral bidentate ligands

First, the coupling of iodonaphthalene **LXVIII** and 2-ethoxynaphthalene-1-boronic acid **CII** was performed in 24h. The results are shown in Table 3.15. When the preformed NPs **Pd70** were used in the presence of CsF as base at 70º C, high conversion (62%) but poor ee were obtained (entry 1, Table 3.15). At 50º C, 60% of conversion without ee was observed (Entry 2, Table 3.15). When the reaction was carried out at room temperature, 20% conversion but no ee was again obtained (entry 3). When only one equivalent of boronic acid was used, 23% of conversion and no ee were observed (Entry 4). With 5 equivalents of boronic acid, the conversion decreased to 21% (entry 5). When the reaction was repeated with two equivalents of boronic acid at room temperature but with $Ba(OH)_2$ as a base (entry 6), the conversion was 12%. Using Cs_2CO_3, the conversion increased to 32% under the same reaction conditions (entry 7).

Table 3.15 Pd-catalysed asymmetric Suzuki-Miyaura coupling using preformed **Pd70** NPs.[a]



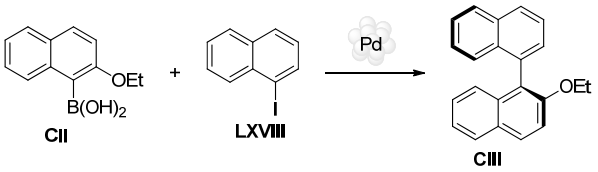
Entry	base	B(OH)2	Temp. (ºC)	Conv(%)[b]	Sel(%)[b]	ee(%)[c]
1	CsF	2	70	62	98	4
2	CsF	2	50	60	97	4
3	CsF	2	rt	20	94	1
4	CsF	1	rt	23	90	-2
5	CsF	5	rt	21	93	4
6	$Ba(OH)_2$	2	rt	12	96	2
7	Cs_2CO_3	2	rt	32	90	1

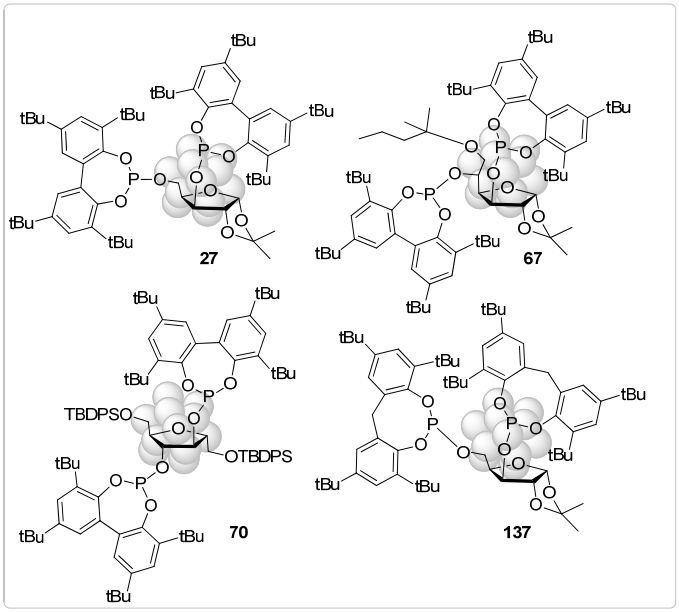
a. Conditions: 0,25 mmol iodonaphthalene, 2-ethoxynaphthylboronic acid, 1,25 mmol CsF, 1 mol% PdNPs, at room temperature, 5 ml THF as solvent, t = 24h. **b.** Determined by GC. **c.** Determined by HPLC.

Although distinct reaction conditions were tested in this reaction, using **Pd70** NPs as catalysts, only low to moderate conversions were obtained and no enantioinduction could be achieved.

Next, the coupling of 1-iodonaphthalene **LXVIII** and 2-ethoxynaphthalene-1-boronic acid **CII** using performed NPs stabilised by diphosphite ligands (the **Pd27**, **Pd67**, **Pd70**, and **Pd137** NPs) as catalysts at room temperature, with CsF as a base and two equivalents of boronic acid was carried out (Table 3.16). In all cases at room temperature, conversions of *ca.* 20% were obtained after 24h of reaction (Table 3.15). Although the selectivity was high (≥92%), no ee (≤4%) could again be obtained. When 1-bromonaphthalene **LXVII** was used as substrate, no conversion was obtained with these 4 catalytic systems.

Table 3.16. Pd-catalysed asymmetric Suzuki-Miyaura coupling using preformed NPs.[a]





Entry	Ligand	Conv.(%)[b]	Sel.(%)[b]	ee(%)[c]
1	**Pd27**	26	96	2
2	**Pd67**	22	92	0
3	**Pd70**	20	97	2
4	**Pd137**	20	98	2

a. Conditions: 0,25 mmol iodonaphthalene **LXVIII**, 2-ethoxynaphthylboronic acid, **CII** 1,25 mmol CsF, 1 mol% PdNPs, at room temperature, 5 ml THF as solvent 24h **b.** Determined by GC. **c.** Determined by HPLC.

To summarise, the PdNps stabilised by the diphosphite ligands derived from carbohydrate **27**, **67**, **70** and **137** presented a moderate activity and poor ee`s in the Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction of 1-iodonaphthalene with 2-ethoxy-1-naphthyl boronic acid **CII**.

3.2.7 Summary of the catalytic experiments in Pd-catalysed asymmetric Suzuki-Miyaura coupling

In terms of activity, the colloidal catalytic systems used in this study revealed more active than the molecular catalysts since at room temperature, higher conversion was achieved with NPs.

In terms of selectivity towards the cross coupling product, excellent results were obtained in all cases.

In terms of ee, although several catalytic conditions were tested, the results obtained in Pd-catalysed asymmetric Suzuki-Miyaura coupling reaction in both molecular and NPs systems were moderate to low. Interestingly, in the Pd-catalysed asymmetric Suzuki-Miyaura coupling of naphthyl halides with 2-R-1-naphthyl boronic acids, the ee's obtained with colloidal precursors were slightly higher than those achieved with molecular catalysts.

3.2.8 TEM studies of the nanoparticles along the reaction

The micrographs of these NPs were acquired after the catalytic reactions and compared to those before catalysis. The TEM micrograph of the **Pd132** before and after catalysis is presented in Figure 3.15. The **Pd132** NPs after catalysis presented a mean diameter of 3.8 ± 0.6 nm. This size was quite similar to their initial size (3.4 ± 1.74 nm) although they slightly increased in size and their size distribution became narrower.

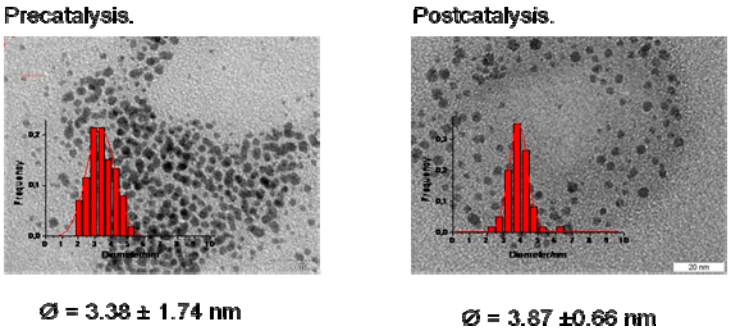


Figure 3.15. TEM images of **Pd132** NPs before and after the catalytic reaction.

It was therefore concluded that no aggregation or important structural changes had occurred to these nanocatalysts during the catalytic reaction.

Next, the influence of the substrates in the surface of the NPs was analysed by TEM micrograph. First, the preformed NPs stabilised by the ligand **132**, **Pd132**, were stirring during 4h in presence of 1-iodonaphthalene. The TEM micrograph shown small and disperse NPs (Figure 3.16). Then, to this solution was adding 2-ethoxy-1-naphthyl boronic acid and stirring during 4 h. TEM micrograph of this solution shown large nanospheres (Figure 3.16).

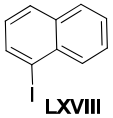
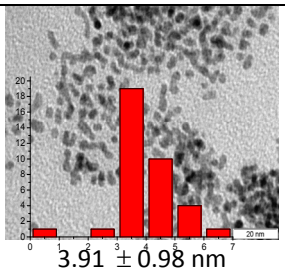
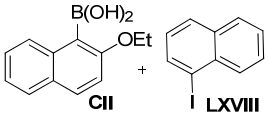
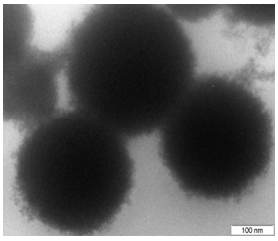
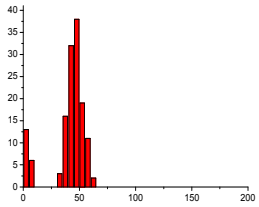
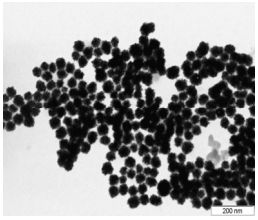
entry	Additives	TEM
1	 LXVIII	 3.91 ± 0.98 nm
2	 CII + LXVIII	 249 ± 61 nm

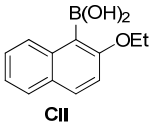
Figure 3.16 Influence of substrates over nanoparticle surface

To corroborate the effect of the boronic acid over the Pd surface, the synthesis of PdNPs stabilised by boronic acids **CII** and **LXXXII** was carried out. TEM images of **PdCII** and **PdLXXXII** revealed nanospheres with a diameter around to 40.8 ± 15.1 nm for and 92.7 ±20.0 nm respectively. NPs.

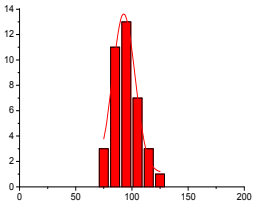


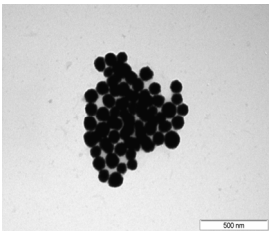


40.8 ± 15.1 nm

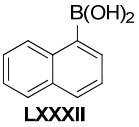


CII





92.7 ±20.0 nm



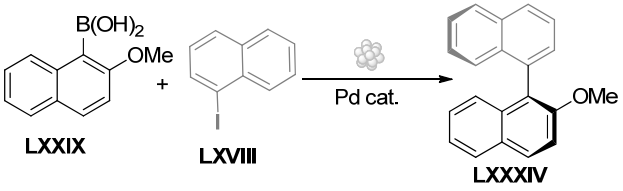
LXXXII

Figure 3.17. Nanoparticles stabilized by boronic acid reagent in absence of ligand.

Taking into account these results, it was to concluded that the nanospheres obtained below when the boronic acid was added to the system **Pd132/CII/LXVIII** were originated by the interaction of the boronic acid with the surface of the

Next, the **PdCII** and **PdLXXXII** NPs were used as catalyst in Pd-catalysed asymmetric Suzuki-Miyaura coupling. The reaction using boronic acid nanoparticles were carried out on optimized reaction conditions. The **PdCII** NPs system was not active in the reaction of the reaction of 1-iodonaphthalene **LXVIII** with 2-methoxy-1-boronic acid **LXXIX** at room temperature (entry 1, Table 3.17).

Table 3.17. Pd-catalysed Suzuki-Miyaura coupling using nanoparticles stabilised by boronic acids.[a]



LXXIX **LXVIII** **LXXXIV**

Entry	NPs	Conv(%) [b]	Sel(%)
1	**PdCII**	0	0
2	**PdLXXXII**	18	99

a.Conditions: 0,25 mmol iodonaphthalene, 2-ethoxynapthylboronic acid, 1,25 mmol CsF, 1 mol% Pd NPs, at room temperature, 5 ml THF as solvent. **b.** Determined by GC. **c.** Determined by HPLC.

Surprisingly, the reaction of these substrates in presence of preformed **PdLXXXII** NPs afforded 18% of conversion under the same reaction

conditions. Interestingly, the coupling product of 1-iodonaphthalene and **LXXXII** from the NPs surface was not detected.

3.3 Conclusions

Several molecular Pd catalytic systems bearing the monodentate ligands **132-136** were used in asymmetric Suzuki-Miyaura coupling reactions of iodo- and bromonaphthalene and several naphthalene boronic acids. The use of the neomenthyl phosphine ligand **132** in this reaction provided the highest activities (98%) with excellent selectivities to the cross coupling product (up to >99%) and moderate enantioselectivities (up to 35%). The bidentate ligands **27**, **67**, **70**, **85**, **131**, **137**, **138** and **139** were successfully used in the Pd-catalysed asymmetric Suzuki coupling reactions of the same substrates. Excellent conversions and good ee's were obtained using the Pd/**70** system (96% and 37% respectively).

The new well dispersed Pd NPs **Pd132, Pd133** and **Pd134** stabilised by monodentate ligands were successfully synthesised and characterised by TEM, XPS and elemental analysis. These NPs were used as catalysts in asymmetric Suzuki coupling and good activities were obtained at room temperature (62%) with excellent selectivities to the cross coupling product (up to >99%) and moderate enantioselectivities (ee up to 24%). The Pd NPs **Pd70**, **Pd27**, **Pd67** and **Pd137** stabilised by bidentate ligands were synthesised and characterised by TEM, XPS and elemental analysis. These NPs were poorly active at room temperature in the asymmetric Suzuki coupling. Interestingly, the enantioselectivity was found to be low with these systems and even lower than the obtained with PdNPs stabilised by chiral monodentate ligands.

To corroborate the hypothesis that the boronic acids used in catalysis could interact with the metallic surface of the NPs, the stabilization of new Pd NPs using boronic acids as stabiliser was carried out and the resulting nanospheres were characterised by TEM microscopy. The formation of these nanospheres evidenced that interactions of the boronic acid with the surface of the colloids occurs.

3.4 Experimental Part

3.4.1 General methods

All air- or water-sensitive reactions were performed using standard Schlenk techniques under a nitrogen atmosphere. Chemicals were purchased from Aldrich Chemical Co and Fluka. All solvents were distilled over drying reagents and were deoxygenated before use. The precursors $[PdCl_2(COD)]$[40] (COD=1,5-cyclooctadiene) and $[PdCl_2(PhCN)_2]$[41] were prepared following previously described methods. The nanoparticle syntheses were performed using a 200 ml Fisher-Porter bottle and pressurized using a high-pressure line.

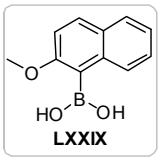
The deuterated solvents for NMR measurements were dried over molecular sieves prior to use. ^{1}H, $^{13}C\{1H\}$, and $^{31}P\{1H\}$ NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer. Chemical shifts were calibrated using $SiMe_4$ (^{1}H and ^{13}C NMR) as internal standard or 85% H_3PO_4 as external standard (^{31}P NMR). Assignments in NMR spectra of the complexes were determined by COSY and HSQC spectra. Coupling constants, J, are given in Hz. Multiplicities of peaks in ^{1}H and ^{13}C NMR are given as: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), m (multiplet), and b (broad).

TEM measurements were realized on a Zeiss 10 CA electron microscope at 100 kW with a resolution of 3Å; Pd nanoparticles samples were prepared under nitrogen atmosphere. A drop of the solution was placed onto a carbon covered Cu grid. Final drying of the sample was performed under vacuum for 12 hours. Elemental analyses of carbon, hydrogen and phosphorus were realized on a Carlo Erba EA 1108 instrument. The nanoparticles size and distribution were determined by counting approximately 800 nanoparticles from 4 enlarged TEM images (approximately 200 nanoparticles from each TEM image). The size distribution plots were fit using a Gaussian model with Microcal Origin 6.1 graphing software to determine the widths and centres of the size distributions.

Merck silica gel 60 (0.040-0.063 mm) was employed on flash chromatography. The conversion of the reaction was measured by GC on a Hewlett-Packard HP 5890 A instrument (split/splitless injector, J&W scientific, HP5, 25 m column, internal diameter 0,25 mm, film thickness 0.33

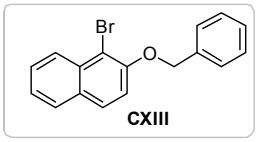
mm, carrier gas: 150 kPa He, F.I.D. detector) equipped with a Hewlett-Packard eHP3396 series II integrator.

3.4.2 Synthesis of naphthyl boronic acids



LXXIX

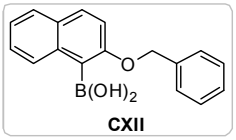
Synthesis of 2-Methoxy-1-naphthylboronic acid: Under argon, in a flame-dried vessel, a solution of 1-bromo-2-methoxynaphthalene (7.67 g, 32.36) in THF (50 ml) was added dropwise to the magnesium (0.905 g, 37.2 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 2 h then at 50°C for 1h. It was then cooled to -78°C and trimethylborate (11.4 ml, 101.7 mmol) was slowly added. After 2 h at -78°C, the mixture was allowed to warm to room temperature and stirred overnight. After addition of water (40 ml), THF was removed under reduced pressure. The mixture was extracted with dichloromethane; the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Recrystallization from dichloromethane gave the boronic acid as a white powder (80% yield). NMR ^1H (400.14 MHz, $CDCl_3$): d = 4.08 (s, 3H), 6.22 (s, 2 H), 7.28 (d, J = 9.1 Hz, 1H), 7.34–7.43 (m, 1H), 7.47–7.56 (m, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 8.86 ppm (d, J = 9.1 Hz, 1H); NMR $^{13}C\{^1H\}$ (75.47 MHz, $[D_6]$DMSO): d = 56.1, 113.7, 121.8, 122.7, 125.8, 127.4, 127.8, 128.5, 129.4, 135.6, 159.0



CXIII

Synthesis of 1-Bromo-2-(benzyloxy)naphthalene: To a suspension of 1-bromo-2-naphthol (15.0 g, 67.3 mmol) and K_2CO_3 (18.6 g, 135 mmol) in DMF (100 mL) was added benzyl bromide (9.6 mL, 81 mmol), and the mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the solvent was evaporated in vacuo and the residue, dissolved in a small amount of CH_2Cl_2, passed through a thin pad of flash silica. Fractions containing the product were evaporated in vacuo to give an off-white solid. Crystallization from CH_2Cl_2/petroleum ether gave the title compound 50 as a white crystalline solid (16.0 g, 76%). The mother liquor was concentrated and purified by flash chromatography (petroleum ether/CH_2Cl_2, 2/1) to give an additional amount of the product 50 (3.7 g, 17%; total yield: 93%). NMR ^1H (400.14 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.32 (d, J 9.0 Hz, 1H), 7.38-7.50 (m, 4H), 7.57-7.66 (m, 2H), 7.79-7.86 (m, 3H), and 8.31

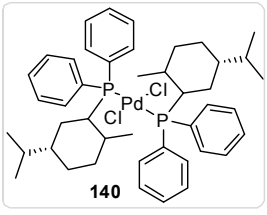
(d, J) 8.5 Hz, 1H). NMR $^{13}C\{^1H\}$ (63 MHz, $CDCl_3$) δ 1.81, 110.0, 115.6, 124.6, 126.3, 127.2, 127.8, 128.1 (2C), 128.7, 128.9, 130.1, 133.2, 136.7, and 153.0.



CXII

2-(Phenylmethoxy)-1-naphthaleneboronic Acid: To a suspension of aryl bromide 50 (6.26 g, 20.0 mmol) in Et_2O (75 mL) at -78 °C was added n-BuLi (8.0 mL, 2.5 M, 20 mmol) in hexanes, and the mixture was stirred at 0 °C for 1 h. After recooling to -78 °C, the mixture was treated with trimethyl borate (2.5 mL, 22 mmol) and allowed to warm to room temperature overnight. The resulting mixture was quenched with 1 M HCl (50 mL) and stirred at room temperature for 45 min. The phases were separated, and the extraction was completed with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuum to give the title compound 51 as a white powder (4.62 g, 83%), which was used in the next step without further purification. For analytical purposes, a small amount of the product was recrystallized from MeOH/H_2O: mp 133.0-135.0 °C. ^1H NMR (400.14 MHz, D4-MeOD) 5.20 (s, 2H), 7.28-7.60 (m, 9H), and 7.56-7.88 (m, 2H). $^{13}C\{^1H\}$ NMR (63 MHz, D4-MeOD) 71.95, 115.4, 124.8, 127.7 (2C), 128.4, 128.9, 129.5, 129.6, 130.7 (2C), 131.8, 137.2, 139.0, and 159.7.

3.4.3 Synthesis of Pd and Pt complexes

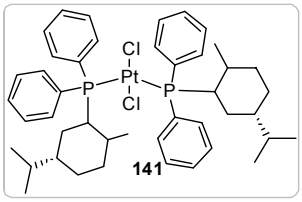


140

Synthesis of the complex [$PdCl_2$(132)$_2$] , 140: A solution of 0.053 g of [$PdCl_2$(COD)] (0.13 mmol) in toluene (10 ml) were added a solution of the ligand **132** (0.2 mmol) in toluene (5 ml). The clear solution was stirred at room temperature for approximately 3 h. The yellow solution was then concentrated under vacuum to 2 ml and hexane (20 ml) was added in order to precipitate the product as a yellow solid. The solid was washed with hexane (2x5 ml) and dried under vacuum at room temperature for 2 h (0.220 g, 75%). Yield: 85 mg (48%). ^1H NMR (CD_2Cl_2, 400.14 MHz, ppm): δ 0.7 (d, JHH= 8 Hz, CH_3), 1.04 (d, JHH= 8 Hz, CH_3), 1.21 (d, JHH= 8Hz, CH_3), 1.1 (m, CH_2), 1.3 (br s, CH_2), 1.4 (m, CH_2), 1.6 (m, CH_2), 1.9 (br s, CH), 2.70 (br s, CH), 2.78 (br s, CH), 3.60 (pseudo t, JHH= 12 Hz, CH), 7.36-7.78 (m, Ar). $^{13}C\{^1H\}$ NMR (THF-d8, 100.63 MHZ, ppm): δ 17.9 (m, CH_2), 20.46 (d, JPC= 12.1 Hz, CH_2), 20.9 (s, CH_3), 24.6 (s,

CH_3), 27.9 (d, JPC= 9.1 Hz, CH), 28.5 (s, CH_2), 29.7 (s, CH_2), 31.7 (d, JPC= 5.1 Hz, CH), 32.1 (br s, CH_2), 35.6 (br s, CH), 36.1 (br s, CH), 40.2 (br s, CH), 117.1 (s, Ar), 127.5 (d, JPC= 11.1 Hz, Ar), 128.7 (d, JPC= 12.1 Hz, Ar), 131,2 (m Ar), 131,5 (m Ar), 132. 7 (d, JPC= 9.1 Hz, Ar), 135.5 (d, JPC= 9.1 Hz, Ar). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 161.98 MHZ, ppm): δ 38.9 (s).

Synthesis of the complex [$PtCl_2(132)_2$] , 141 The synthesis of the isolated Pt complex was achieved according to reported to the reported method with some modifications.[42] $PtCl_2$(COD) previously synthesized (0.13 mmol) was dissolved in 8 ml of degassed CH_2Cl_2. Solid ligand (0.13 mmol) was added to the solution and the resulting pale yellow solution was stirred for 4 h at room temperature. The solution was brought to dryness in vacuum and the solid residue was thoroughly washed with stirring using a small volume of toluene. The solid was filtered via cannula and then, washed with hexane and ether and dried in vacuum. Complex **95:** ^{1}H NMR (CD_2Cl_2): δ in ppm 1.64-1.78 (m, 2H), 1.91-2.04 (m, 2H), 2.26-2.29 (m, 2H), 2.88-2.91 (m, 1H), 7.01-7.25 (m, 5H). ^{13}C-NMR (CD_2Cl_2): δ in ppm 26.11, 33.34, 41.61, 45.29, 49.37, 127.07, 127.13, 129.11, 145.24, 211.18. ^{31}P-NMR *δ* 16.25 ($^1J_{P-Pt}$ = 2460 Hz). Yields: 85%. LC/ESI-TOF/MS: m/z (100%) = 919,39 ([M-CH_3CN]$^+$Cl)

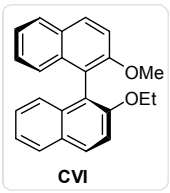


141

3.4.4 General procedure for asymmetric Suzuki-Miyaura coupling reaction

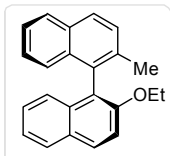
A Schlenk tube was charged with 0.25 mmol of naphthyl halide, 0.05 mmol of Pd precursor, 0.075 mmol of the appropriate chiral ligand, 0.5 mmol of boronic acid, and 1.25 mmol of base. Anhydrous solvent was added, the flask was sealed and the mixture was stirred and heated at the corresponding temperature. The conversion and selectivity was monitored by gas chromatography. To determine the ee, the reaction mixture was treated with 10 mL of distilled water, extracted with 3 x10 mL of CH_2Cl_2, dried over $MgSO_4$, and purified by flash chromatography to obtain the corresponding products. The ee values were determined by High Performance Liquid Chromatography using a Daicel AD-H column.

2-ethoxy-2'-methoxy-1,1'-binaphthalene: $[\alpha]^{20}_{D}$ +50.1 (c 0.9, $CHCl_3$)



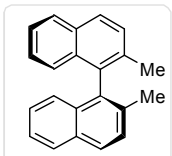
CVI

2-ethoxy-2'-methyl-1,1'-binaphthalene:$[\alpha]^{20}_{D}$ -5.4 (c 1.63, $CHCl_3$)



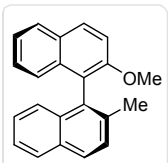
CVII

(S)-2,2'-dimethyl-1,1'-binaphthalene: Chiralpac AD-H column, eluent; *n*-hexane:i-PrOH = 100:1, flow rate; 0.5 mL/min, retention times; major isomer 65.4 min and minor 89.8 min.



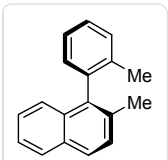
LXXV

(R)-2-methoxy-2'-methyl-1,1'-binaphthalene: Chiralpac AD-H, eluent column; n-hexane: *i*-PrOH = 95:5, flow rate; 0.5 mL/min, retention times; major isomer 42.3 min and minor 54.9 min.



CVIII

(R)-2-methyl-1-(o-tolyl)naphthalene: Daicel Chiralcel OJ-column, eluent; hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min, λ = 254 nm, retention times = 9.45 min (major) and 14.4 min (minor).



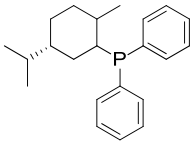
CIX

3.4.5 General procedure for the synthesis of chiral PdNPs

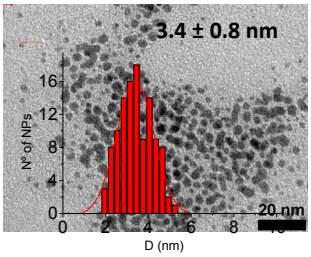
The synthesis of the Pd NPs used in this work was performed using the method previously described by Chaudret and co-workers.(ref) The solvent (THF) was freshly distilled over Na prior to use and degassed using the freeze-pump-thaw method. The corresponding monodentate ligand (0.2 mmol) and the palladium precursor $[Pd_2(dba)_3.CHCl_3]$ (1 mmol) were

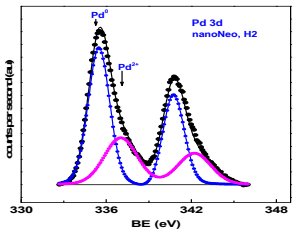
dissolved in THF (40 ml) in the Fisher Porter bottle. Then, the Fisher-Porter bottle was pressurized with H_2 (3 bar) and vigorously stirred during 18 hours and the initial purple solution rapidly became black. The hydrogen pressure was removed and the colloids were concentrated under vacuum and precipitated with pentane. After several washing with pentane, the NPs were dried under vacuum. The colloids were characterized by TEM, XPS and elemental analysis. In all cases, the yields were *ca*. 56%.

Monodentate ligands

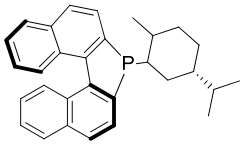


Pd132





Elementary analysis : 65,0 % Pd 1,4 P



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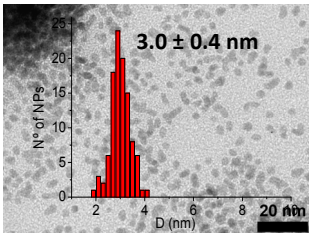
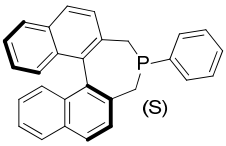


Elementary analysis : 65,0 % Pd 0,6 P



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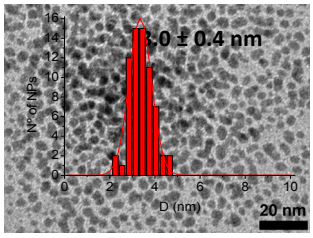
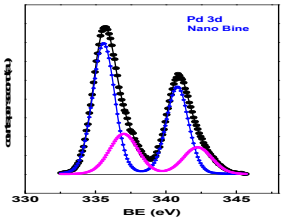
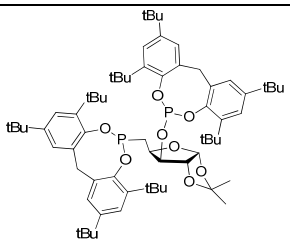


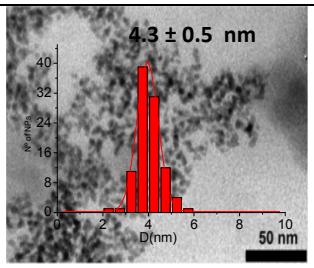


Elementary analysis : 64,8 % Pd 1,2 P

Bidentate ligands

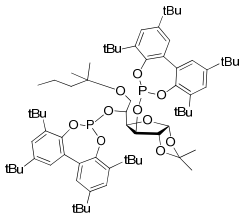


Pd137

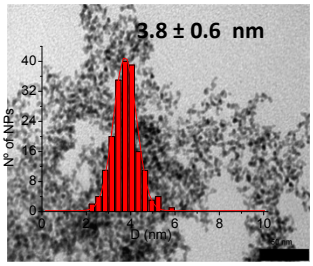


Elementary analysis
68,5 % Pd 0,7% P

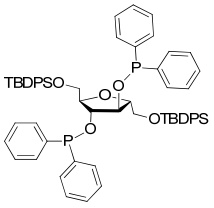
:



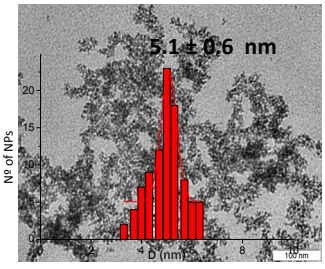
Pd67



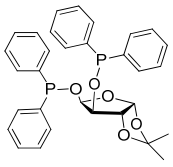
68,5 % Pd 0,7% P



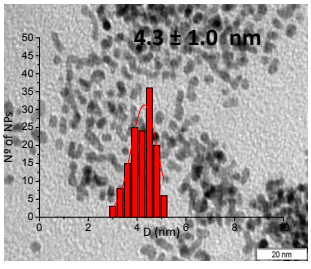
Pd137



78,1 %Pd 0,8 %P



Pd85



55,5 %Pd 2,2 %P

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Chapter 4.

Phosphinine ligands in Ni-catalyzed Suzuki-Miyaura coupling reaction

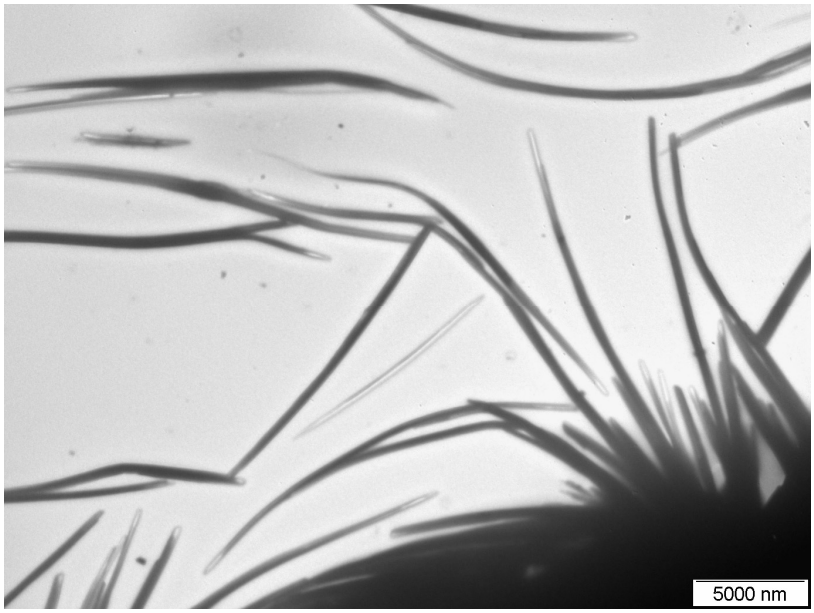
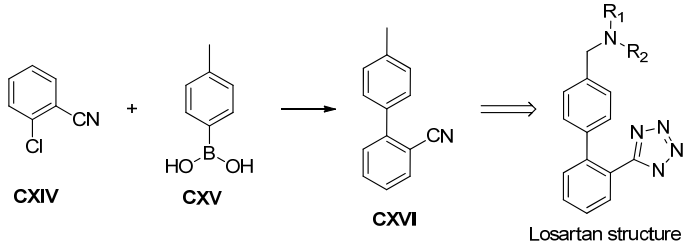


Table of contents

4.1 Background

4.1.1 Suzuki- Miyaura cross-coupling reactions using Ni based catalysts

In the 80's, the first cases of arylboron, alkenylboron and alkylboron reaction with aryl halides catalyzed by Pd were reported.[1] Since then, this reaction has become an important approach in the synthesis of novel organic compounds. For instance, at industrial scale, Clariant's synthesis produces the coupling product **CXVI** as starting material for the industrial production of Losartan (Scheme 4.1).[2]



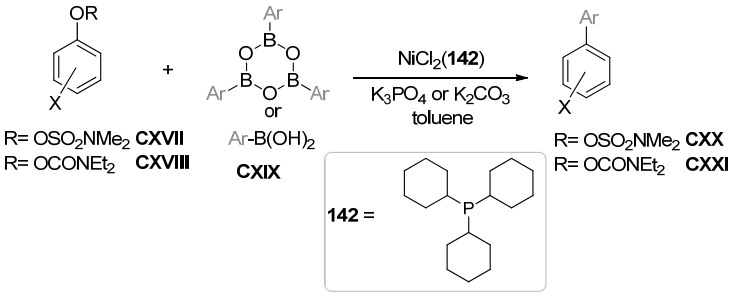
Scheme 4.1. Clariant's Suzuki approach for the production of losartans.

Pd catalysts bearing phosphine ligands are the most commonly studied catalytic system in Suzuki-Miyaura cross-coupling reaction.[3] Nevertheless, the replacement of Pd by cheaper metals such as Ni is of high interest. For instance, Ni catalysts are used for the homocoupling of aryl halides.[4]

In some cases, nickel catalysts have been shown to be more effective than their palladium analogues as Ni(0) is more reactive towards oxidation than the Pd(0) species.[5] In other words, Ni(0) is a stronger nucleophile than Pd(0). However, the Ni-catalyzed Suzuki cross-coupling reaction is rarely reported due to the difficulty of reducing Ni(II) to Ni(0) during the catalytic cycle. Usually, Zn or BuLi have been used as additives in Ni-catalysed C-C coupling reactions in order to reduce in situ the Ni(II) precursor to Ni(0).[5]

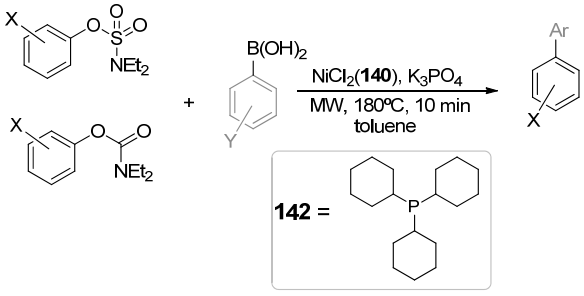
The use of phosphine ligands such as the tricyclohexylphosphine **142** (Scheme 4.2) has been reported by several authors in this reaction. For instance, the groups of Garg,[6] Snieckus,[7] and Shi[8] introduced independently the use of aryl carbamates and/or sulfamates as electrophilic coupling partners for Ni-catalyzed Suzuki-Miyaura cross-coupling reactions (Scheme

4.2). These coupling protocols are highly attractive from the synthetic point of view. In all three reports the commercially available and air/moisture stable [$NiCl_2$(**142**)$_2$] catalyst was employed.[6,7,8]



Scheme 4.2. Ni-catalyzed Suzuki-Miyaura cross-couplings of aryl carbamates and sulfamates with aryl boronic acids.

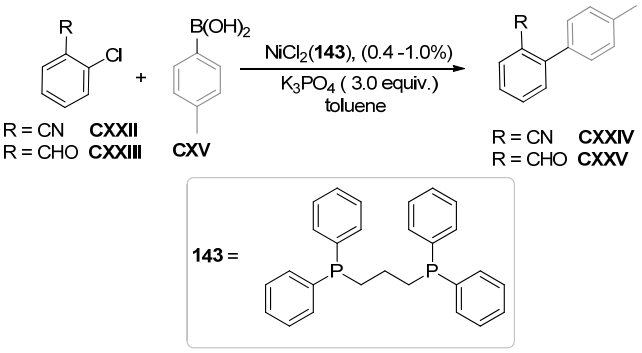
Kappe and co-workers developed a highly efficient microwave-assisted procedure using Ni/**142** catalyst in the Suzuki-Miyaura cross-coupling of aryl carbamates and sulfamates with boronic acids (Scheme 4.2).[9] Compared to the originally published methods,[6,7,8] this protocol features reaction times of only 10 min at low catalyst loading and boronic acid stoichiometry and high coupling efficiency (Scheme 4.3).[9]



Scheme 4.3. Ni-catalyzed Suzuki-Miyaura cross-couplings of aryl carbamates and sulfamates utilizing microwave.

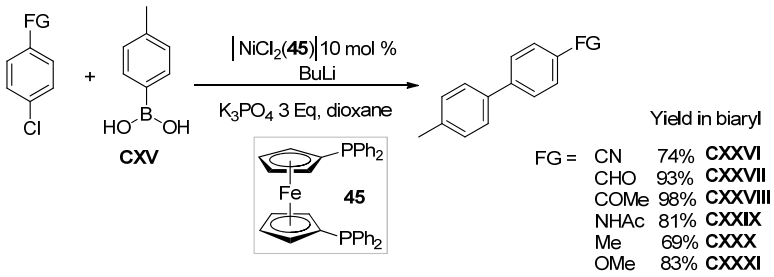
Diphosphine ligands have also been reported in Ni-catalyzed Suzuki-Miyaura cross-coupling reactions. Han and co-workers reported high conversions in this reaction using 1.0 mol% of a catalyst bearing the ligand **143** and without the need of extra supporting ligands (Scheme 4.4).[10] Moreover, this transformation tolerated a wide variety of aryl bromide and chloride

electrophiles, as well as boronic acid nucleophiles, including activated, non-activated, deactivated, heterocyclic and sterically hindered substrates. The potential application of this methodology was further demonstrated by the elaboration of two core motifs of commercialized sartan-type drugs and a fungicide in gram-scale operations such as Boscalid®.[11]



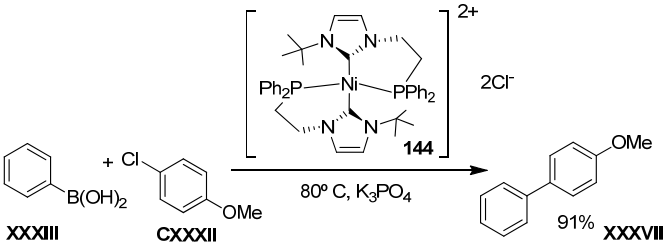
Scheme 4.4. Synthesis of biphenyls using Suzuki-Miyaura reaction with Ni/**143** as catalyst.

Miyaura and co-workers reported the first case of Ni(0)-catalyzed cross coupling of aryl chlorides with arylboronic acids using the dppf ligand **45** (Scheme 4.5).[12] In this report the reaction of phenylboronic acid with chloroarenes containing an electron-withdrawing or -donating group was described. When electron-deficient chloroarenes were used, the biaryl product was obtained in high yields. In the case of substrates containing electron-donating groups, even if the yields were slightly lower, they remained higher for the nickel catalyst than for the palladium ones.[12]



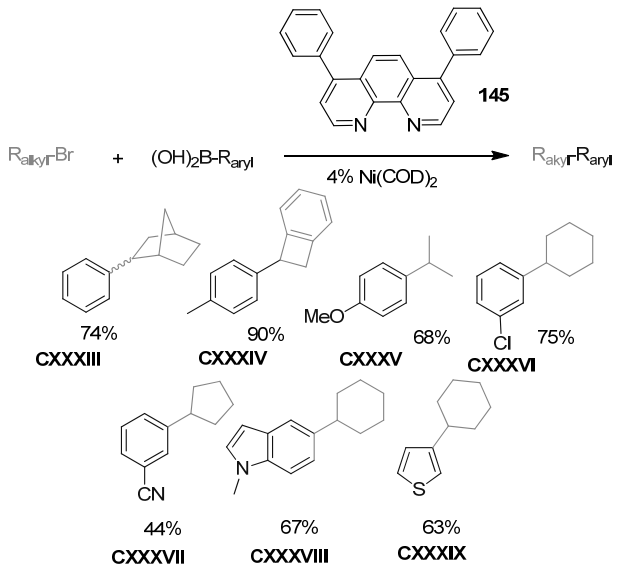
Scheme 4.5. Ni-catalyzed cross coupling of aryl chlorides with arylboronic acids using Ni/**45** as catalyst.

Other types of ligands such as carbenes or nitrogen based ligands have also been reported in this reaction. For instance, the Ni catalyst **144** bearing a NHC-phosphine ligand was reported as highly efficient catalysts for Suzuki coupling reactions of aryl chlorides and bromides under mild conditions (Scheme 4.6).[13]



Scheme 4.6. Nickel (II) complexes bearing bidentate N-heterocyclic carbeno-phosphine ligands in the Suzuki-Miyaura coupling of aryl chlorides**.**

In this reaction, the phenanthroline derivative **145** was used as ligand by Zhou and Fu, who described the efficient Ni-catalysed cross-coupling of non-activated secondary alkyl bromides and iodides with aryl boronic acids (Scheme 4.7).[14]



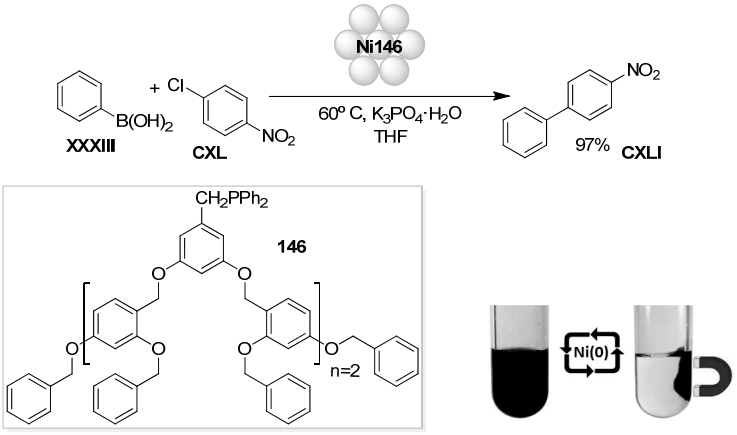
Scheme 4.7. Ni-catalyzed Suzuki coupling of secondary alkyl bromides using the ligand **145.**

NiI_2/*trans*-2-aminocyclohexanolin in isopropanol (IPA) was reported as active catalyst for Ni-catalysed Suzuki couplings of unactivated secondary alkyl bromides with arylboronic acids (Scheme 4.7).[15] The authors demonstrated that the Ni-catalysed Suzuki-Miyaura coupling reaction of unactivated primary and secondary alkyl halides (including challenging alkyl chlorides) can be accomplished through the use of nickel/amino alcohol-based catalysts.[15] Recently, various phenol derivatives such as aryl sulfonates,[16] ethers,[17] esters,[18] carbamates,[19] carbonates,[19] sulfamates,[19] phosphates,[20] phosphoramides,[21] and phosphonium salts were also used as substrate in Ni-catalysed Suzuki couplings.[22]

To summarise, the Ni-catalysed Suzuki-Miyaura reaction have been mainly studied using catalytic systems bearing phosphine ligands. However, the successful use of ligands such as bipyridine derivatives demonstrated that strong σ-donor ligands are not required for this process.

As was mentioned in the chapter 1, metallic NPs have emerged as a potential alternative as catalyst in several transformations. In the case of Ni-catalysed Suzuki-Miyaura coupling reaction, only a few studies have been reported.[23]

[24]NiNPs stabilised by dendritic phosphine ligands, **146** were reported as a highly active and recyclable catalysts. (Scheme 4.8)



Scheme 4.8 Ni-catalysed Suzuki-Miyaura coupling reaction of using **Ni146** NPs.

Moreover, these NPs are magnetically separable under N_2 and were recycled up to six times without loss of activity. Nevertheless, the authors conclude that the true catalytic species could be formed by leaching from the NPs. [23]

Pd-Ni nanoalloys catalysts with tuneable composition were reported to be active in Miyaura-Suzuki coupling reaction.[24] These catalysts showed better catalytic activity than that of palladium nanoparticles under the same reaction conditions.

NiNPs have been also reported as highly active catalysts in hydrogenation reactions and reductions of a variety of organic compounds,[25] highly selective in conjugate reduction of α,β-unsaturated carbonyl compounds[26] as well as in the stereoselective *cis* semihydrogenation of internal alkynes and the semihydrogenation of terminal alkynes under mild reaction conditions.[27]

4.1.2 Phosphinine ligands in catalysis

Phosphinines are planar, aromatic phosphorus heterocycles, which are more similar to their pyridine analogues than trivalent phosphines (Figure 4.1). In comparison to pyridines, they are much better π-acceptor, but less good σ-donor ligands. Moreover, they are relatively inert to electrophilic attack.[28 29]

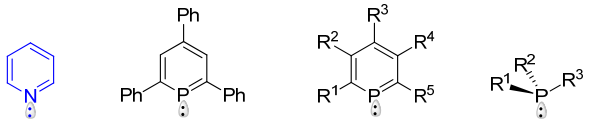
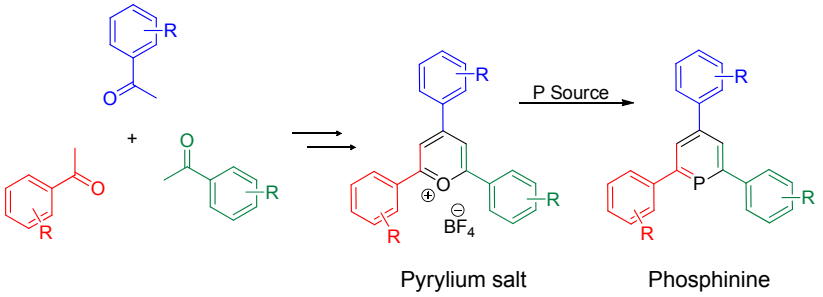


Figure 4.1. Pyridine, phosphinine and trivalent phosphorus based ligands.

The synthetic route of these ligands starts from substituted benzaldehydes and acetophenones. The key intermediate is the formation of the pyrylium salt, which is converted in the corresponding phosphinines by reaction with a highly nucleophilic phosphorus source, PH_3-analogues $P(CH_2OH)_3$ or $P(SiMe_3)_3$.[30]



Scheme 4.9. Modularity of the synthesis of phosphinines

Phosphinine ligands have two different coordination sites, the phosphorus lone pair and the aromatic system. The coordination through these coordination sites leads to different coordination modes, the most common ones are represented in Figure 4.2. Generally, the most commonly observed coordination mode is through the lone pair of the phosphorus atom (η^1 coordination), which is observed with late transition metals in low oxidation states (for example Rh(I))), due to the strong π-acceptor properties of the phosphinine ligand.

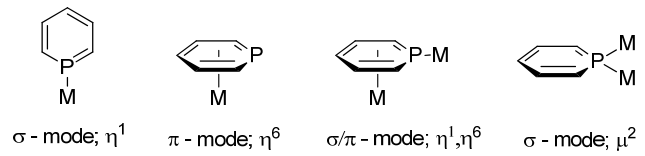


Figure 4.2. Common coordination modes of phosphinines

The interest in phosphinine-based ligands as alternative phosphorus source has been growing over the last years.[31]. Phosphinine based systems have been successfully applied in Fe-catalyzed cyclotrimerizations and cyclodimerizations,[32] Rh-catalyzed hydroformylation[33] and Rh- and Ir-catalyzed hydrogenation.[34]In view of their particular electronic and steric properties, they are expected to efficiently stabilize Pd(0) and Ni(0) species.

In 2004, the first NPs stabilized by sp^2-based phosphinine ligands with gold as metal centre were reported.[35,36] These NPs were synthesized and characterized using phosphinines **147** and **148** ligands (Figure 4.3). ^{31}P NMR studies of gold NPs stabilised by phosphinine ligands led to the observation of metal-bound phosphinine units as well several surface-bound species that are formed by chemical transformation of the original ligands. Other possible fact is that phosphinines can be oxidized more easily than pyridines and form in fact rather stable radical monocations.[37,38]

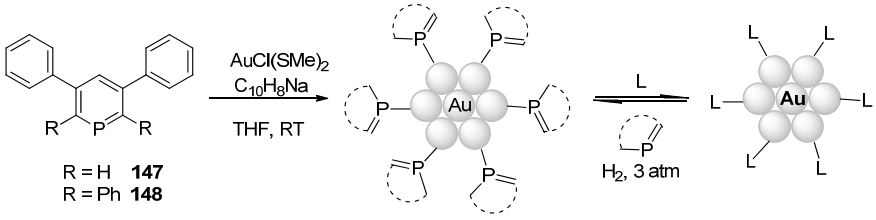


Figure 4.3. Synthesis of phosphinine-based Au nanoparticles

Here, in the framework of collaboration with Prof. Dieter Vogt group in TUE University preliminary studies on the synthesis and characterization of new phosphinine-based Ni and Pd catalysts are described. Both molecular and NPs precursors were applied as catalysts in the in Suzuki-Miyaura coupling reactions.

4.2 Results and discussion

The phosphinine ligands **149**, **150** were reported by Vogt and co-workers[39] phosphinine **151** and pyridine derivatives **152** and **153** were synthesised by Leen Broeckx in the TUE University (Figure 4.4).[40]

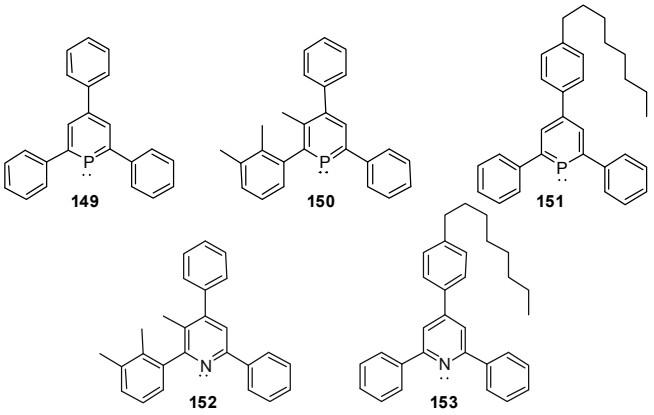


Figure 4.4. Phosphinine and pyridine derived ligands used in Suzuki-Miyaura coupling reaction.

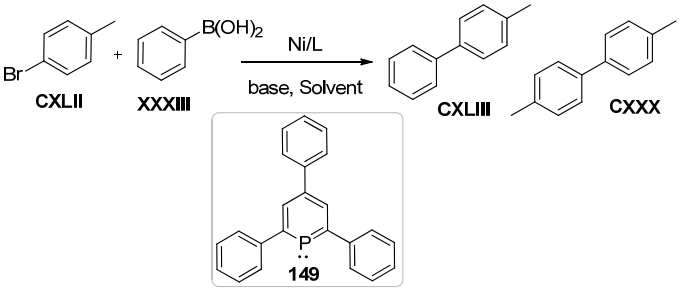
As mentioned in the last section, the use of less expensive Ni-based catalyst systems instead of the classical Pd catalysts could significantly decrease the costs of the cross-couplings reactions. Here we report the use of novel Ni catalysts bearing the ligands **149**-**153** in Suzuki-Miyaura coupling reactions.

4.2.1 Ni-catalysed Suzuki-Miyaura coupling: optimization of reaction conditions using the ligand 149.

The base plays a very important role in C-C coupling reactions, in particular in the transmetallation step. Here, various bases were used in the Suzuki-Miyaura coupling of 1-bromo-4-methylbenzene **CXLII** and phenylboronic acid **XXXIII** using [Ni(COD)$_2$]/**149** in order to optimize the reaction conditions. The results obtained are described in Table 4.1. Initially, the reaction was carried out in the presence of K_3PO_4 as base, toluene as solvent during 18 hours at 80°C and afforded 36% conversion (entry 1). When KOH was used as base under the same conditions, the conversion decreased to 23% (entry 2). When K_2CO_3 was used, the conversion dropped to 18 % (entry 3). Using Cs_2CO_3 the conversion decreased to 14% (entry 4). When CsF was used as base, the conversion was 23% (entry 5).The lowest conversion was observed

with NaOAc (2%, entry 6). The selectivity to the cross coupling product was 99% in all cases. Next, using K_3PO_4 as a base, various solvents were tested in this reaction. The presence of water in the solvent mixture increased the conversion to 53% (entry 7). When other solvents (DMF, DME and xylene) were used, the conversions were between 19% and 37% (entries 8, 9 and 10). Surprisingly, when the reaction was carried out without ligand only the homocoupling product from bromobenzene was observed (90% of conversion, entry 11)

Table 4.1 Suzuki-Miyaura coupling reaction using [Ni(COD)$_2$]/**149.** Study of the reaction conditions.[a]



Entry	Solvent	Base	Conv.(%)[b]	Sel(%)[b]
1	Toluene	K_3PO_4	36	99
2	Toluene	KOH	23	99
3	Toluene	K_2CO_3	18	99
4	Toluene	Cs_2CO_3	14	99
5	Toluene	CsF	23	99
6	Toluene	NaOAc	2	-
7	Toluene/H_2O	K_3PO_4	53	99
8	DMF	K_3PO_4	19	99
9	DME	K_3PO_4	37	99
10	Xylene	K_3PO_4	25	99
11[c]	Toluene	K_3PO_4	90[d]	0

a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol base,5 mol% Ni(COD)$_2$, 5 mol% Ligand **149**, T= 80ºC, 3 ml of solvent, t=18h. **b.** Determined by GC using internal standard. **c.** Reaction without ligand. **d.** Homocoupling product **CXXX.**

In summary, the best results using [Ni(COD)$_2$]/**149** as precursor were obtained in a toluene/H_2O mixture, with K_3PO_4 as the base at 80º C during 18

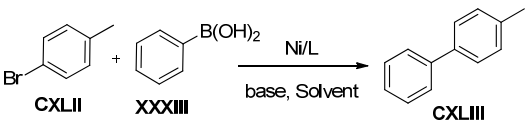
hours. The use of water in the solvent system increased significantly the conversion (entry 7).The increment of the activity when toluene/H_2O could be explained by the greater solubility of the base in the catalytic medium.

Next, the ligands **149**-**153** were evaluated in the Ni-catalysed Suzuki-Miyaura reaction.

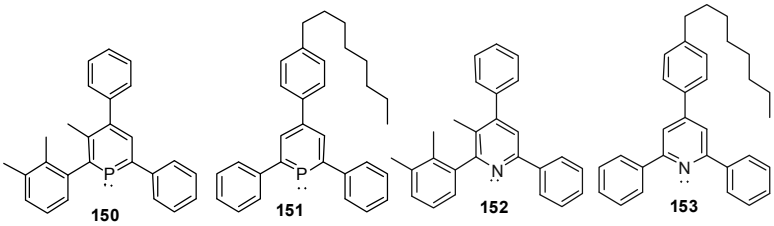
4.2.2 Ni-catalysed Suzuki-Miyaura reaction using the ligands 149-153

The reaction was carried out with 1-bromo-4-methylbenzene **CXLII** and phenylboronic acid **XXXIII** using the optimized conditions. The results are shown in Table 4.2. Initially, [Ni(COD)$_2$]/**150** as precursor, toluene/H_2O as solvents, K_3PO_4 as base at 80º C during 18 hours were used obtaining quasi total conversion (99%, entry 1). When the catalytic system [Ni(COD)$_2$]/**151** was used 73% conversion was obtained. When the catalytic system [Ni(COD)$_2$]/**152** bearing the pyridine derivate ligand was used, the conversion dropped dramatically to 2% (entry 3). In the case of [Ni(COD)$_2$]/**153**, only traces of the product was obtained (entry 4). The selectivity of this system to the desired product was 99% in all of cases.

Table 4.2. Ni-catalyse Suzuki-Miyaura using the ligands **150-153**.[a]



CXLII XXXIII CXLIII



150 151 152 153

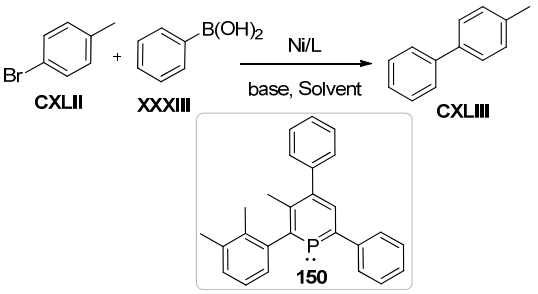
Entry	Ligand	Conv.(%)[b]	Sel(%)[b]
1	**150**	99	99
2	**151**	73	99
3	**152**	2	-
4	**153**	1	-

a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol K_3PO_4, 5 mol% Ni(COD)$_2$, 5 mol% Ligand, T= 80º C, 3 ml of toluene/H_2O=(2/1), t =18h **b.** Determined by GC using internal standard.

In summary, the catalytic systems containing phosphinine ligands exhibited excellent activity in this coupling reaction. The system bearing the ligand **150** and **151** gave moderate to high conversion. However, the catalytic system bearing pyridine ligands **152** and **153** were inactive.

Using the active system [Ni(COD)$_2$]/**150** as catalytic precursor various Ni/Br ratios were used (Table 4.3). When 5 mol% of catalyst was used, high conversion was afforded at only 1 hour of reaction (entry 1). Similar results were obtained when the amount of Ni catalyst was decreased to 2.5 mol% (entry 2). At lower concentrations, 1 mol%, decreased the conversion (40%) under the same reaction conditions (entry 3). When the ligand to Ni ratio was incremented from 1 to 2, the conversion increased to 88% (entry 1 *versus* entry 4).

Table 4.3 Study of the Ni-catalysed Suzuki-Miyaura reaction using the phosphinine ligand **150.**[a]

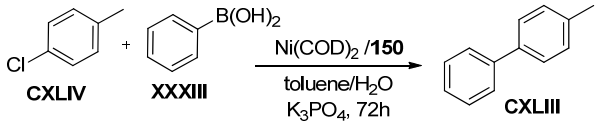


Entry	L/Ni	Ni/Br	Conv. (%)[b]			Selec. (%)[b]
			1h	2h	18h	
1	1	0.05	72	73	74	99
2	1	0.025	78	80	80	99
3	1	0.01	40	39	39	99
4	2	0.05	88	92	96	99

a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol K_3PO_4, [Ni(COD)$_2$], Ligand **150**, T= 80º C, toluene/H_2O **b.** Determined by GC using internal standard.

The [Ni(COD)$_2$]/**150** system exhibited higher activities in comparison to the other ligands **149** and **151-153**. Consequently, the catalytic behaviour of the [Ni(COD)$_2$]/**150** catalyst was further examined by performing the cross-coupling of aryl chlorides. These substrates are more appealing as coupling

partner that the analogous aryl bromides and iodides due to these lower cost and greater availability.[19c] However, the notoriously unreactive nature of aryl chlorides makes their coupling reactions considerably more challenging. The Suzuki–Miyaura cross-coupling of 1-chlorotoluene **CXLIV** with the arylboronic acid **XXXIII** afforded 34% of product after 72h of reaction.



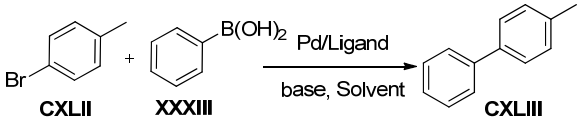
Scheme 4.10. Suzuki–Miyaura cross-coupling of 1-chlorotoluene with phenylboronic acid.

As conclusion the [$Ni(COD)_2$]/**150** catalyst is a promising system that can be used in Suzuki coupling reaction of several substrates, including aryl chlorides.

In the next section, we reported comparative studies of the use of phosphinines Pd-catalyzed Suzuki–Miyaura cross-coupling.

4.2.3 Pd-catalysed Suzuki-Miyaura coupling reaction using the ligands 149-153

In order to optimize the reaction conditions, 1-bromo-4-methylbenzene **CXLII** and phenylboronic acid **XXXIII** were used as substrates (Scheme 4.11).

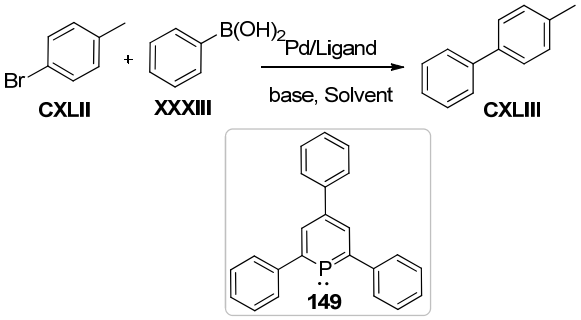


Scheme 4.11. Pd-catalysed Suzuki-Miyaura coupling reaction.

The influence of the base, ligand, solvent, Pd precursor was studied (Table 4.4.). The reaction was initially carried out in presence of [$Pd(OAc)_2$]/**149** as catalytic system, Na_2CO_3 as base, THF/H_2O as solvent during 7 h at 60°C. In this case the conversion was 39% (entry 1). When Cs_2CO_3 was used as base, the conversion decreased to 35% (entry 2, Table 4.4) under the same conditions. When CsF was used as base, the conversion dropped to 10 % (entry 3). Using Cs_2CO_3 as base and THF or toluene instead of THF/H_2O as solvent the conversion decreased to 20% and 22% respectively (entry 1

versus entry 4 and 6, Table 4.4). With Na_2CO_3 similar results were observed. The THF/H_2O solvent afforded better results (entry 2 versus entry 5 and 7, Table 4.4). This could be due to the low solubility of the base in organic solvents. When [$Pd_3(dba)_2$·$CHCl_3$] was used as Pd precursor the conversion was 40% (entry 1 versus entry 8, Table 4.4).

Table 4.4 Suzuki-Miyaura reaction using Pd/**149** catalysts.[a]



Entry	Base	Solvent	Conv.(%)[b]	Sel.(%)
1	Na_2CO_3	THF/H_2O	39	99
2	Cs_2CO_3	THF/H_2O	35	99
3	CsF	THF/H_2O	10	99
4	Na_2CO_3	THF	20	99
5	Cs_2CO_3	THF	18	99
6	Na_2CO_3	Toluene	22	99
7[c]	Cs_2CO_3	Toluene	15	99
8[d]	Na_2CO_3	THF/H_2O	40	99

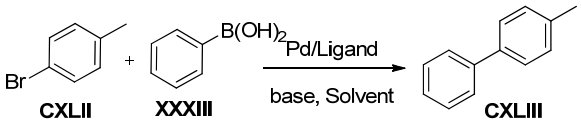
a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol base, 1 mol% [$Pd(OAc)_2$], 1 mol% Ligand **149**, 3 ml of solvent T= 60ºC or, t = 7h. **b.** Determined by GC using internal standard. **c.** 80º C, **d.** [$Pd_2(dba)_3$·$CHCl_3$] was used as precursor.

It is important to note that the selectivity of this system to the desired product was 99% in all of cases. In summary, low to medium conversions were obtained, the highest conversion was obtained using [$Pd(OAc)_2$]/**149** and **150** as catalytic precursors in the presence of Na_2CO_3 as base and THF/H_2O as solvent.

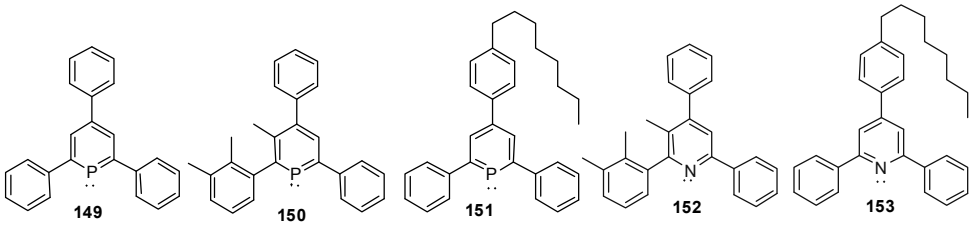
Next, the ligands **150-153** were utilized in the Suzuki coupling reaction of 1-bromo-4-methylbenzene **CXLII** and phenylboronic acid **XXXIII**. The results of this reaction are described in Table 4.5. When the catalytic system

[$Pd(OAc)_2$]/**150** was used (entry 2) the conversion was found to increase considerably (52%). When the reaction was repeated with the catalytic system [$Pd(OAc)_2$]/**151** bearing the pyridine derivate ligand (entry 3), the conversion was incremented to 69%. When catalytic systems containing the ligands **152** and **153** were used, the conversions were 35% and 54% respectively.

Table 4.5 Reaction conditions for optimized Suzuki-Miyaura reaction using different phosphinine and pyridine derivate ligands.[a]



CXLII XXXIII CXLIII



149 150 151 152 153

Entry	Ligand	% Conv. (%)[b]	Sel(%)[b]
1	**149**	39	99
2	**150**	52	99
3	**151**	69	99
4	**152**	35	99
5	**153**	54	99

a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol base, 1 mol% [$Pd(OAc)_2$], 1 mol% Ligand, 3 ml of solvent T= 60ºC t = 7h. **b**. Determined by GC using internal standard.

Therefore, under these conditions, the Pd catalytic system containing the pyridine derived ligands **150** and **153** were more active in Suzuki-Miyaura reaction than their phosphinine analogues. These results could be explained by the differences in the electronic properties of these ligands/metals.

4.3 Synthesis and characterization of Pd and Ni nanoparticles stabilized by ligands 149-153

Pd Nanoparticles

The PdNPs were generated from the decomposition of $[Pd_2(dba)_3 \cdot CHCl_3]$ in the presence of the phosphinine and pyridine ligands **149-153**.[41] It is important to note that no stabilization was obtained using the pyridine-based ligands **151** and **153.** In this case, only Pd black precipitation was observed (Figure 4.5). It was thus concluded that these ligands were not suitable for the stabilization of PdNPs and that therefore, the presence of the phosphorous atoms is crucial in this type of molecules in order to efficiently stabilize PdNPs.

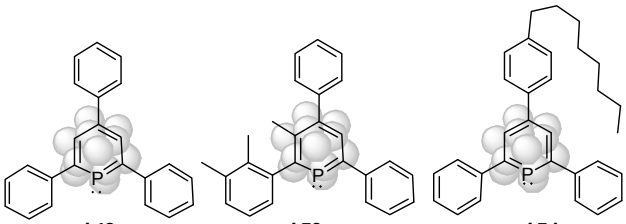


Figure 4.5. Stabilizations metal phosphinine NPs.

The transmission electron microscopy (TEM), mean diameter and size distribution of the **Pd151** and **Pd151** NPs are shown in Figure 4.6. The solutions resultin from the work-up of these syntheses were analysed by ^{1}H and ^{31}P NMR. The ^{1}H NMR showed the presence of dibenzylidenacetone (dba) and products corresponding to the partial reduction of dba.

TEM micrographs corresponding to **Pd151** and **Pd152** showed the formation of small NPs with mean diameters of 3.01 ± 0.4 and 1.92 ± 0.35 respectively.

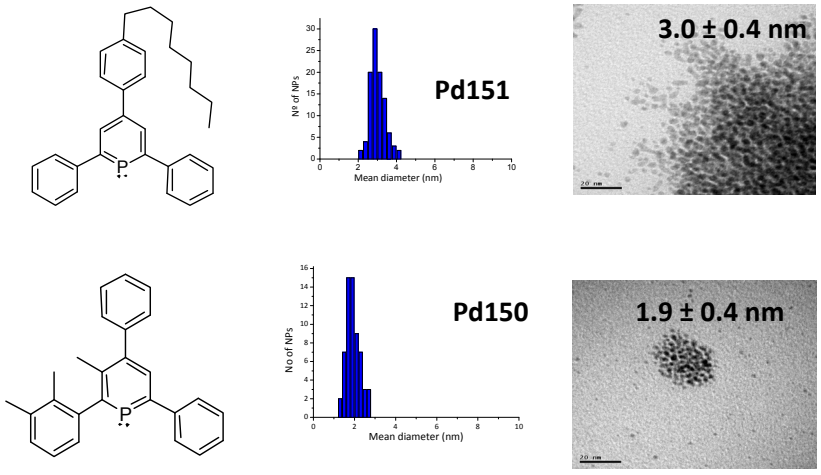
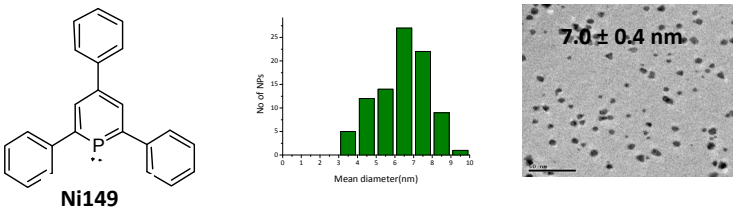
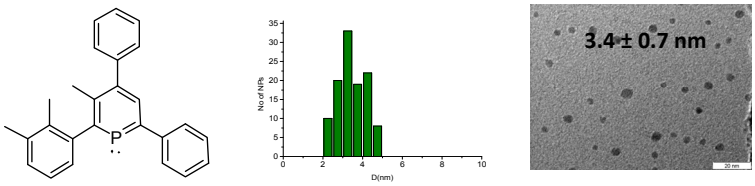


Figure 4.6. PdNPs stabilised by phosphinine ligands **151**, **150.**

Ni Nanoparticles

The NiNPs **Ni149** and **Ni150** were synthesized from [Ni(COD)$_2$] precursor with phosphinine ligand **149**, using the reported method.[42] The decomposition of the Ni precursor was carried out in CH_2Cl_2 at low temperature in N_2 bath under H_2 atmosphere (3 bars) using a Fischer–Porter bottle, in the presence of ligand (P/Pd=0.2). The black powder was obtained after pentane precipitation. The transmission electron micrograph (TEM), mean diameter and size distribution of the **Ni149** and **Ni150** NPs are shown in Figure 4.7. The mean diameter was measured to be 7.0 ± 0.4 nm and 3.4± 0.7 respectively. These NPs thus exhibit in a larger mean diameter than those of analogous PdNPs..





Ni150

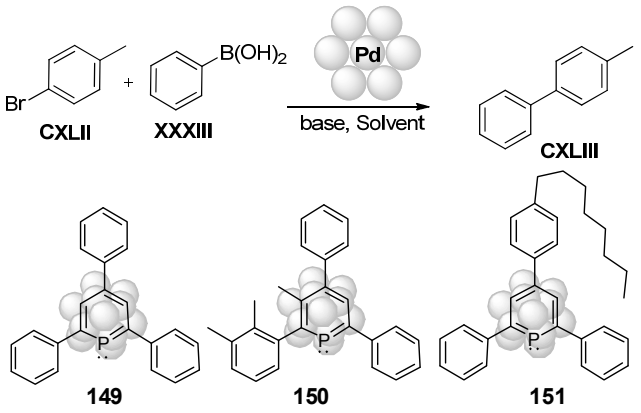
Figure 4.7. NiNPs stabilized by phosphinine ligand **149**.

Once synthesized and characterised the phosphinine PdNPs, the activity of these NPs were studied in Suzuki-Miyaura coupling reaction.

4.4 Suzuki-Miyaura coupling reaction in presence of PdNPs stabilized by ligands 149-151

The catalytic reaction between 1-bromo-4-methylbenzene **CXLII** and phenylboronic acid **XXXIII** was carried out in the presence of Na_2CO_3 as base, THF as solvent during 18h at 60°C. The results are summarized in Table 4.6. When the catalytic system was **Pd149**, the reaction afforded 21% of conversion after 18h (entry 1). When the reaction was repeated in the presence of **Pd150** NPs, the conversion was found to increase to 31%. However, when **Pd151** was used as catalytic precursor (entry 3) the conversion decreased to 18%. When THF/H_2O (2/1) and **Pd149** were used, the conversion increased to 71% (entry 4). However, lower conversion (26%), was obtained with THF/H_2O (2/0.5) (entry 5). This effect could be due to the incomplete dissolution of the base in water. When the reaction was carried out in DMF or EtOH/DMF, the conversion of the reaction decreased to 17% and 37% respectively (entries 6 and 7). In the case of **Pd149** NPs, the use of THF/H_2O (2/1) as solvent also had a positive effect (61% of conversion, entry 8). In all of cases the selectivity of this system to the desired product was 99%.

Table 4.6. Suzuki-Miyaura reaction using phosphinine NPs.[a]



Entry	NPs	Solvent	% Conv.(%)[b]		Sel.(%)[b]
			2h	18h	
1	**Pd149**	THF	3	21	99
2	**Pd150**	THF	4	31	99
3	**Pd151**	THF	3	18	99
4	**Pd149**	THF/H_2O (2/1)	12	71	99
5	**Pd149**	THF/H_2O (2/0.5)	11	26	99
6	**Pd149**	DMF	4	17	99
7	**Pd149**	EtOH/DMF	13	37	99
8	**Pd150**	THF/H_2O (2/1)	12	61	99

a. Reaction conditions: 1 mmol bromotoluene, 0,5 mmol phenyl boronic acid, 3 mmol Na_2CO_3, 0.01 mol% PdNPs (4 mg), T= 60ºC, 3 ml of solvent**. b.** Determined by GC using internal standard.

In terms of activity, the preformed **Pd149** NPs using the mixture of the THF/H_2O (2/1) as solvents afforded the best results in the Suzuki coupling reaction. When these PdNPs were used as catalyst using 1-chloro-4-methylbenzene **CLXIV** as substrate no conversion was obtained.

Ni- and Pd-catalyst bearing the ligands **149**-**153** resulted as efficient systems in the Suzuki coupling reaction of 1-bromo-4-methylbenzene **CXLI** and phenylboronic acid **XXXIII.** New Pd and NiNPs were synthesised and characterized using phosphinine ligands. Pyridine-derivate ligands does not stabilised PdNPs.

4.5 Conclusions

The Ni-catalysed Suzuki-Miyaura coupling of bromobenzene with aryl boronic acids was studied in the presence of the phosphinine and pyridine ligands **149-153**. The systems bearing the phosphinine ligands gave good to excellent conversions even at low catalyst loading while those bearing the analogous pyridine ligands were inactive under the conditions used. It is noteworthy that the Ni/**150** system was able to transform the inactive *p*-tolyl-chloride in the presence of phenyl boronic acid. The analogous Pd systems provided moderate to good activities using optimised conditions. Interestingly, the Pd/pyridine systems were also active in the Suzuki-Miyaura coupling of bromobenzene with phenyl boronic acid.

The ligands **149-151** were also used to successfully stabilise PdNPs, which were subsequently used in Pd-catalysed Suzuki-Miyaura coupling reactions of bromobenzene at room temperature and provided moderate to good conversions. Surprisingly, the analogous pyridine ligands did not provide stabilisation for PdNPs and only bulk metal was formed.

The ligands **139**-**150** were also used to stabilise NiNPs from decomposition of $[Ni(COD)_2]$ under H_2 pressure. These NPs were found to be magnetic and were characterised by TEM microscopy.

4.6 Experimental Part

4.6.1 General methods

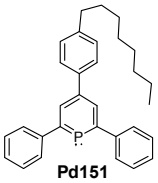
All air- or water-sensitive reactions were performed using standard Schlenk techniques under a nitrogen atmosphere. Chemicals were purchased from Aldrich Chemical Co and Fluka. All solvents were distilled over drying reagents and deoxygenated before use. Nanoparticles syntheses were performed using a 200 ml Fisher Porter and pressurized on a high pressure line.

The deuterated solvents for NMR measurements were dried over molecular sieves. ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer. Chemical shifts were calibrate relative to SiMe4 (^{1}H and ^{13}C NMR) as internal standard or 85% H_3PO_4 as external standard (^{31}P NMR). Assignments in NMR spectra of the complex were determined by COSY and HSQC spectra. Coupling constants, J, are given in Hz. Multiplicities of peaks in ^{1}H and ^{13}C NMR are given as: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), m (multiplet), and b (broad). TEM measurements were realized on a Zeiss 10 CA electron microscope at 100 kW with a resolution of 3Å; Pd nanoparticles samples were prepared under nitrogen atmosphere. A drop of the solution was placed on a carbon covered Cu grid. Final drying of the sample was performed under vacuum for 12 hours. Elemental analyses of carbon, hydrogen and phosphorus were realized on a Carlo Erba EA 1108 instrument. The nanoparticles size and distribution were determined by counting approximately 800 nanoparticles from 4 enlarged TEM images (approximately 200 nanoparticles from each TEM image). The size distribution plots were fitted using a Gaussian model with Microcal Origin 6.1 graphing software to determine the widths and centers of the size distributions.

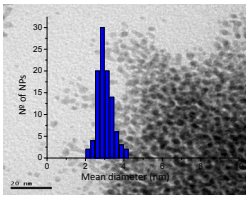
Merck silica gel 60 (0.040-0.063 mm) was employed a flash chromatography. The conversion of the reaction was measured by GC on a Hewlett-Packard HP 5890 A instrument (split/splitless injector, J&W scientific, HP5, 25 m column, internal diameter 0,25 mm, film thickness 0.33 mm, carrier gas: 150 kPa He, F.I.D. detector) equipped with a Hewlett-Packard eHP3396 series II integrator.

4.6.2 Synthesis of metal NPs:

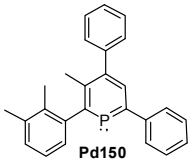
Synthesis of PdNPs: The systems of NPs were prepared using the method previously described by Chaudret and co-workers.[43] For these synthesis the solvent (THF) was freshly distilled over Na and degassed using the freeze-pump-thaw method. The corresponding ligand (0.2 mmol) and the palladium precursor $[Pd_2(dba)_3{\cdot}CHCl_3]$ (1 mmol) were dissolved in THF (40 ml) in the Fisher Porter bottle. Then, the Fisher-Porter bottle was pressurized with H_2 (3 bar) and vigorously stirred during 18 hours. The initial purple solution became black in few minutes. The hydrogen pressure was removed and the colloids were concentrated under vacuum and precipitated with pentane. After several washing with pentane, the NPs were dried under vacuum. The NPs were characterized by TEM, XPS and elemental analysis.



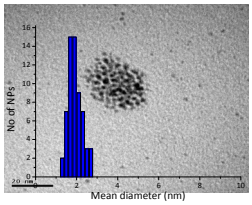
Pd151



Diameter: 3.0 ± 0.4 nm
83.0% Pd, 3.0% P

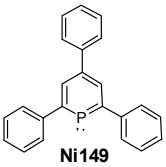


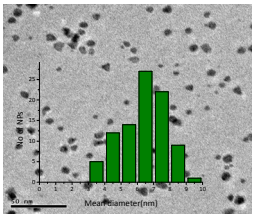
Pd150



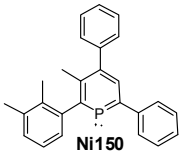
Diameter: 1.9± 0.4 nm
82.4% Pd, 5.7% P

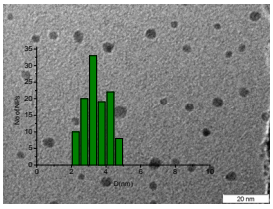
Synthesis of NiNPs: The corresponding phosphinine ligand (0.2 mmol) and the nickel precursor [Ni(COD)$_2$] (1 mmol) were dissolved in cooled CH_2Cl_2 (40 ml) in the Fisher Porter bottle. Then, the Fisher-Porter bottle was pressurized with H_2 (3 bar) and vigorously stirred (overnight) the initial yellow solution became black after few minutes. The hydrogen pressure was removed and the colloids were concentrated under vacuum and precipitated with pentane. After several washing with pentane, the NPs were dried under vacuum. The colloids were characterized by TEM microscopy.





Diameter: 7.0± 0.4 nm





Diameter: 3.4± 0.7 nm

4.6.3 General procedure for Suzuki coupling reaction

A Schlenk tube was charged with 1 mmol of bromotoluene, 0.05 mmol of Pd or Ni precursor, 0.05 mmol of ligand, 1.5 mmol of boronic acid, and 3 mmol of base. Anhydrous solvent was added, the flask was sealed and the mixture was stirred and heated at the corresponding temperature. The conversion was monitored by gas chromatography.

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Chapter 5.

Pt-catalysed asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one

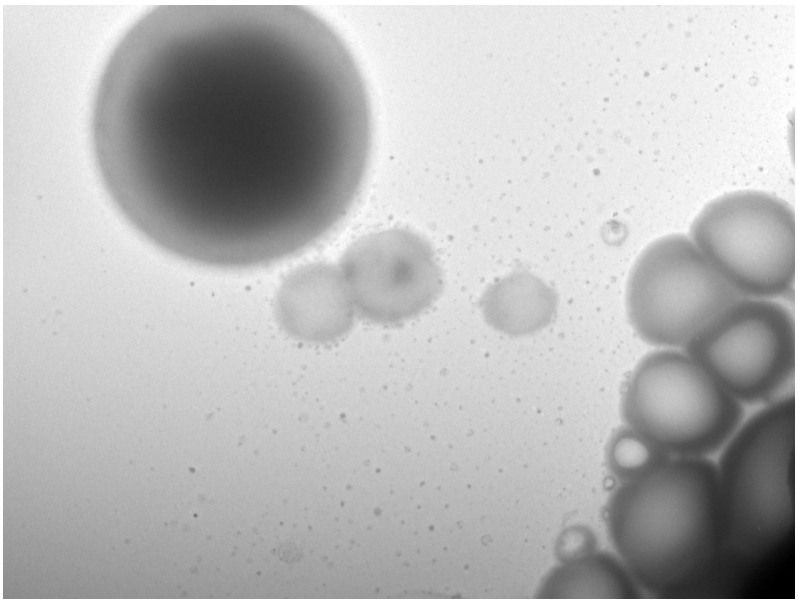
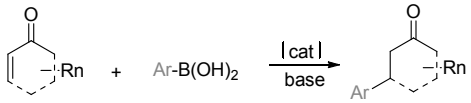


Table of contents

5.1 Background

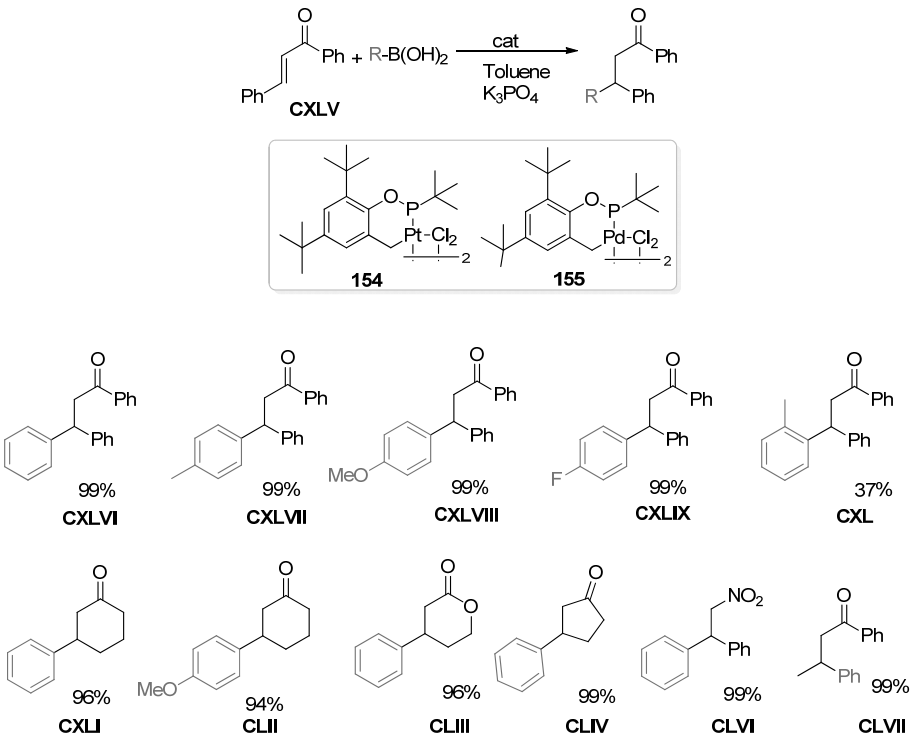
5.1.1 Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one

The conjugate addition is usually constituted by the nucleophilic addition of a carbanion or another nucleophile to a α,β unsaturated carbonyl compounds.[1] The 1,4-addition of arylboronic acids to enones (Scheme 5.1) and related substrates is a versatile method for the formation of new C-C bonds. To date, the enantioselective 1,4 addition of arylboronic acids to enones has been principally dominated by rhodium-based systems, reaching high levels of enantioselectivity (>99%) .[2]



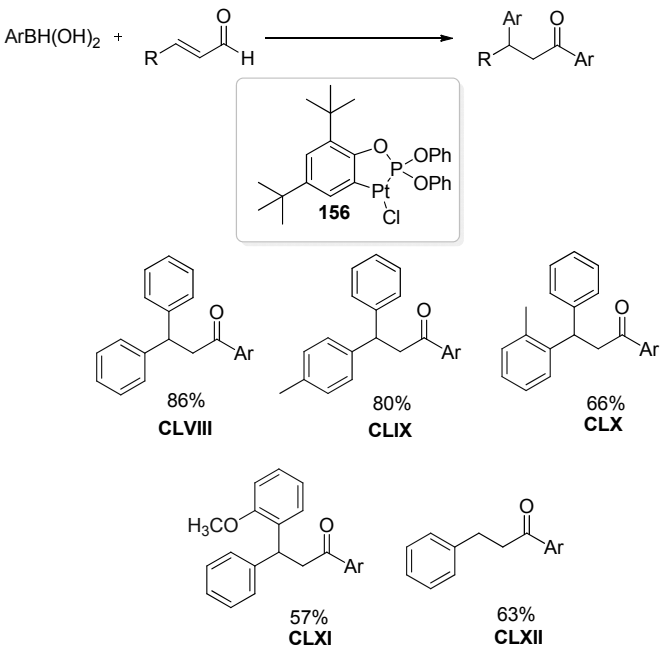
Scheme 5.1. 1,4-conjugate addition of arylboronic acids to enones.

However, only a few reports were published on the use of Pt catalysts for this process. Bedford et al.[3] reported a range of metals such as palladacyclic, platinacyclic, and pincer-based catalysts (Scheme 5.2) in 1,4-conjugate addition reactions.[3] The π-acidic palladacycles showed excellent activity at room temperature in the reaction of enones with arylboronic acids. Reasonable activity was also achieved when the arylboronic acids were replaced by arylsiloxanes. The authors compared the results obtained with palladacyclic and platinacyclic catalysts and observed that the palladacyclic catalyst was much active than its platinacyclic analogue. Furthermore, the use of palladacyclic **154** afforded high conversion (up to 99%, Scheme 5.2) in the Pd-catalysed conjugate addition of several boronic acids to chalcone whereas the use of platinacyclic **155** afforded poor conversions in this process.



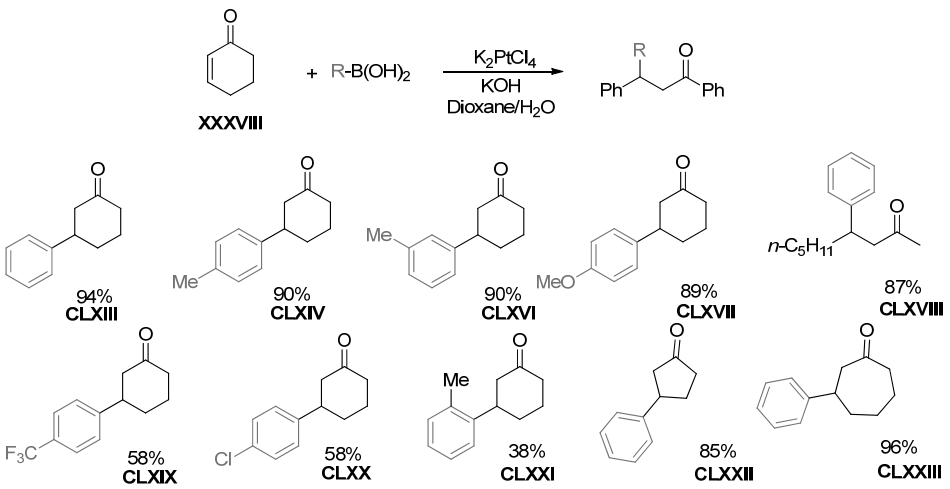
Scheme 5.2 Results from the use of Pd-metallacycles in the coupling of phenylboronic acid with chalcone.

Nevertheless, Hu and co-workers reported that the readily available air/moisture-stable orthoplatinated triarylphosphite **156** was a highly efficient catalyst for the addition reactions of arylboronic acids to aldehydes, even at low catalyst loading and obtained high activities (up to 86% conversion).[4]



Scheme 5.3. Conjugated adition of arylboronic acids to aldehides catalyzed by orthoplatinated triarylphosphite **90**.

Finally, Hayashi and Sasaki reported the Pt-catalysed 1,4-addition of arylboronic acids to α,β-unsaturated ketones using Pt salts such as $K_2[PtCl_4]$, $PtCl_2$, $[PtCl_2(COD)]$, $[PtCl_2(BINAP)]$,**157** and $[PtCl_2(PPh_3)_2]$, **158** under mild conditions.[5] The conditions of a standard 1,4-addition reaction of phenylboronic acid to 2-cyclohexen-1-one were: 1.0 equivalent of KOH, Pt (3mol%), dioxane/H_2O (10:1), 70ºC and 4 h.



Scheme 5.4. Platinum-catalyzed 1,4-addition of arylboronic acids to α-β unsaturated ketones.

The authors reported that K_2PtCl_4 is an efficient catalyst, and quantitative yield was obtained for 3-phenylcyclohexanone as the 1,4-addition product (>98%). The best results were obtained using the phosphine free salt $K_2[PtCl_4]$. When the reaction was performed using Pt species bearing phosphine ligands, no activity was obtained with bidentate ligands while 70% conversion was achieved with the monophosphine based complex $[PtCl_2(PPh_3)_2]$, **158**. The authors concluded that the lower conversion obtained with this latter catalyst when compared to that using $K_2[PtCl_4]$ was due to the presence of the ligand and that the real active specie was phosphine free. Furthermore, the formation of a black precipitate during the reaction suggested that NPs were formed and could play a role in the catalytic process.

The work presented in this chapter is based on this hypothesis, and deals with the synthesis and study of the catalytic activity of Pt NPs stabilised by phosphorus based ligands in this reaction in the context of a collaboration with the group of Prof. Hayashi (Japan).

PtNPs stabilised by several ligands were used as catalysts in several reactions such as ethylene hydrogenation,[6] hydrogenation of nitrobenzenes[7] and

electron-transfer reaction.[8] Moreover, PtNPs were recently used for the medical treatment of oxidative stress diseases.[9]

5.2 Results and discussion

To carry out the study, a series of PtNPs were synthesized and characterised by TEM microscopy. To probe the effect of the ligand structure on the size and the shape of the NPs, a series of chiral monodentade and bidentate phosphines, phosphite and phosphoramidite were used as stabilizers. For comparison purposes, the molecular Pt complexes $[PtCl_2L_2]$ bearing the same ligands were synthesised, characterised and tested in this reaction.

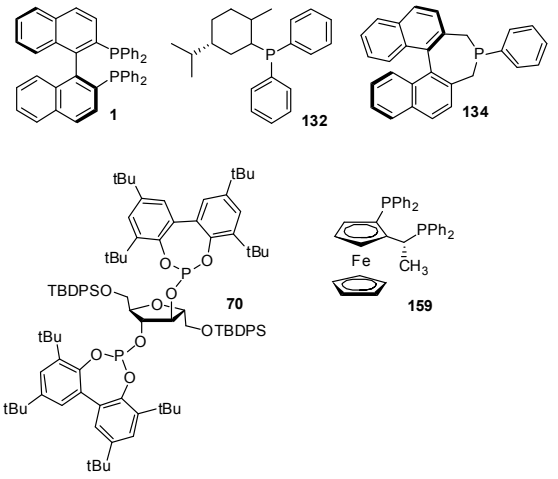


Figure 5.1. Chiral ligands used in the platinum-catalyzed 1,4-addition of arylboronic acids to cyclohexen-1-one.

5.2.1 Synthesis of Pt precursors

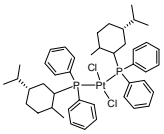
The platinum species $[PtCl_2(COD)]$[10] and $[Pt_2(dba)_3]$[11] were synthesised according to previously reported methods and used as precursors for the synthesis of complexes bearing phosphorus ligands and for the synthesis of Pt NPs, respectively.

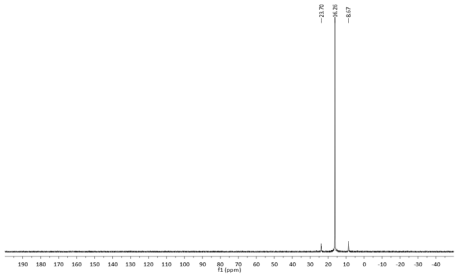
5.2.1.1 Synthesis of the Pt complexes

The platinum complexes $[PtCl_2(\mathbf{1})]$ **157**, $[PtCl_2(\mathbf{70})]$ **160,** $[PtCl_2(\mathbf{132})]$ **141,** $[PtCl_2(\mathbf{134})]$ **161,** and $[PtCl_2(\mathbf{159})]$ **162**, were prepared from $[Pt(COD)Cl_2]$, following a previously described methodology.[12] These complexes were characterized by ^1H and $^{31}P\{^1H\}$, ^{13}C, and ^1H NMR spectroscopy and mass

spectrometry (see experimental section). The $^{31}P\{^{1}H\}$ spectra of these species are show in the Figure 5.2.

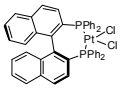
a.

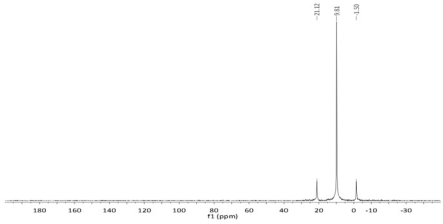




δ 16.25 ($^{1}J_{P-Pt}$ = 2460 Hz).

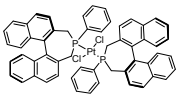
b.

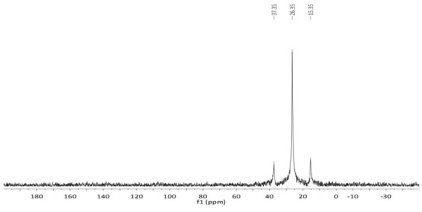




δ 9.81 ($^{1}J_{P-Pt}$ = 3178 Hz).

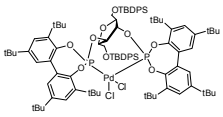
c.

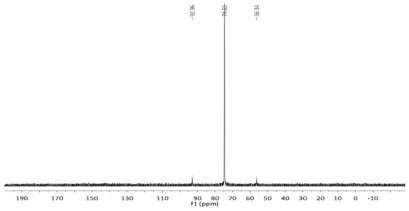




δ 26.35 ($^{1}J_{P-Pt}$ = 3563 Hz).

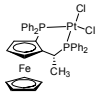
d.

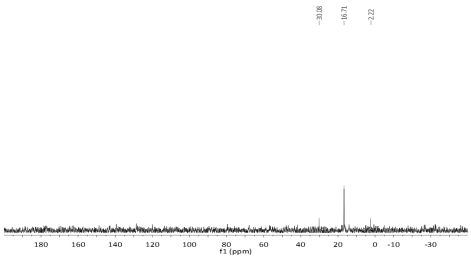




δ 74.60 ($^{1}J_{P-Pt}$ = 5948 Hz).

e.





δ 16.69 ($^{1}J_{P-Pt}$ = 4049 Hz).

Figure 5.2 $^{31}P\{^{1}H\}$ NMR spectra of the Pt complexes $[PtCl_2(\mathbf{L})_2]$ IN CD_2Cl_2.

As expected, the $^{31}P\{^{1}H\}$ spectra of the compounds exhibited a singlet as the only signal. The detection of Pt satellites confirmed the coordination of these ligands to the metal center and it was reported that the magnitude of ^{1}J(PtP) is indicative of the *cis/trans* geometry of the complexes: for the *cis* isomers, ^{1}J(RP) is typically greater than 3000 Hz while for the *trans* isomers ^{1}J(PtP) is usually less than 2500 Hz:[13,14,15]

As expected, the Pt complexes **157, 160** and **163** bearing bidentate ligands exhibited $^{1}J_{PtP}$ constants that clearly indicated a *cis* configuration (>3500 Hz). However, for the Pt complexes **141** and **162** containing two monodentate ligands, the values for the ^{1}J(PtP) constants were not as conclusive. In the case of complex **141**, the $^{1}J_{PtP}$ was low (2460 Hz), which suggest the expected *trans* arrangement that was observed in the molecular structure of this species obtained by X-ray crystallography (see Chapter 3). However, for complex **157**, the $^{1}J_{PtP}$ was 3178 Hz, which indicates a *cis* configuration. This result is surprising due to the high steric hindrance induced by this monodentate ligand, which should favour a *trans* arrangement.

5.2.1.2 Synthesis of PtNPs stabilized by the chiral ligands

The PtNPs were prepared from decomposition of $Pt_2(dba)_3$ under H_2 atmosphere according to the Chaudret's method.[16] $Pt_2(dba)_3$ and were synthesised following a published method.[17] The synthesis of the NPs was performed at room temperature in THF in the presence of the appropriate chiral ligand under 3 bar of H_2 for 18 hours (Figure 5.3)

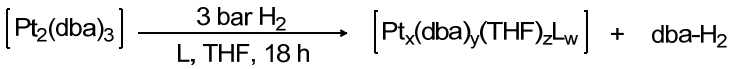
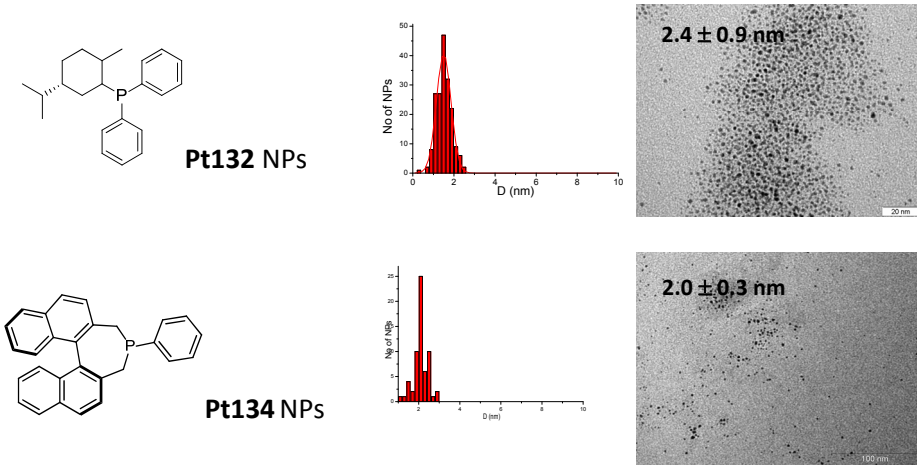


Figure 5.3. Synthesis of Pt nanoparticles.

The NPs were then dried overnight under vacuum and stored in a glove box under N_2 atmosphere. During the course of the synthesis, the initial purple solution was observed to turn black, confirming the decomposition of the precursor. Finally, the Pt NPs were isolated as black powders after precipitation with pentane. The NPs were characterized by transmission electron microscopy (TEM) and elemental analysis. The Figure 5.4 summarises the results obtained.

All these PtNPs were found to have a mean diameter inferior to 2.5 nm, with a spherical shape and narrow distribution. A few agglomerates consisting of small groups of individual nanoparticles were also observed. Mean diameters of 2.4 ± 0.9 nm, 2.0 ± 0.3 nm, 1.3 ± 1.1 nm, 2.1 ± 0.2 nm and 2.1 ± 0.4 nm were found for the **Pt1**, **Pt70**, **Pt9132**, **Pt134** and **Pt159**, respectively. Interestingly, the diameter of the NPs stabilised by the bidentate ligand **9** was smaller than the PtNPs stabilised by monodentate ligands.



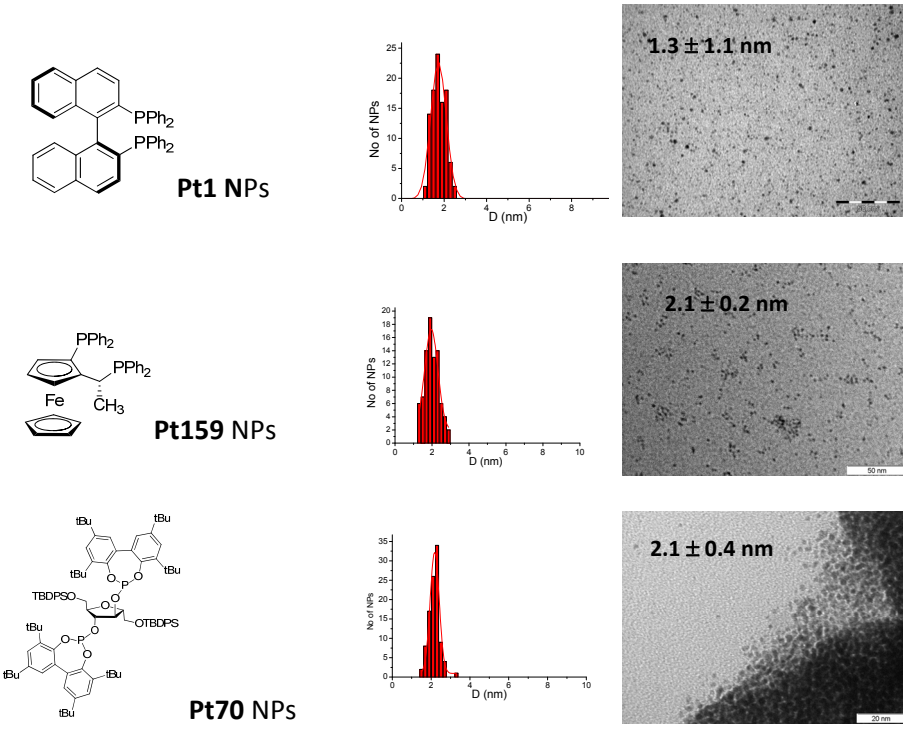


Figure 5.4 TEM micrographs and size histograms of the PtNPs stabilized by the chiral ligands**.**

The main objective of this study was to probe the catalytic activity and selectivity of these Pt NPs stabilised by chiral ligands in the enantioselective Pt-catalysed conjugated 1,4-addition reaction

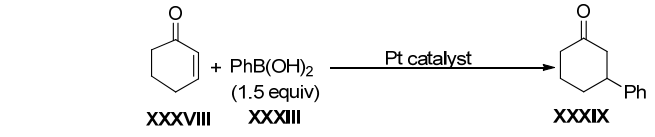
5.2.2 Conjugated 1,4-addition reactions

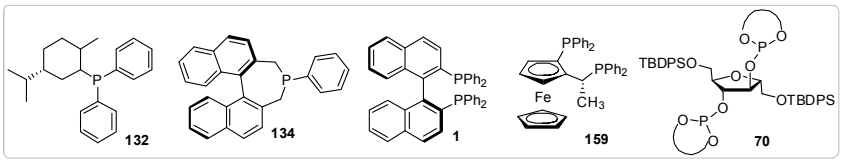
5.2.2.1 Molecular catalysts

In this section, the results obtained in the Pt-catalyzed conjugate 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using molecular precursors are presented. First, the catalytic reactions were performed using the conditions described by Hayashi and coworkers,[21] in order to reproduce the results and set up the experimental conditions in our lab. The reaction was also carried out using *in situ* molecular systems bearing the ligands **Pt1**, **Pt70**, **Pt9132**, **Pt134** and **Pt159**.

Initially, K_2PtCl_4 was used as catalytic precursor and the conversion was 74% (entry 1, Table 5.1), which is a bit lower than that reported by Hayashi and co-workers. When the reaction was performed in presence of Pt/**1**, Pt/**70**, Pt/**132**, Pt/**134** and Pt/**159** catalytic systems, no conversion was observed.

Table 5.1 Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using molecular systems.[a]



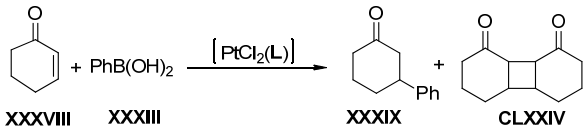


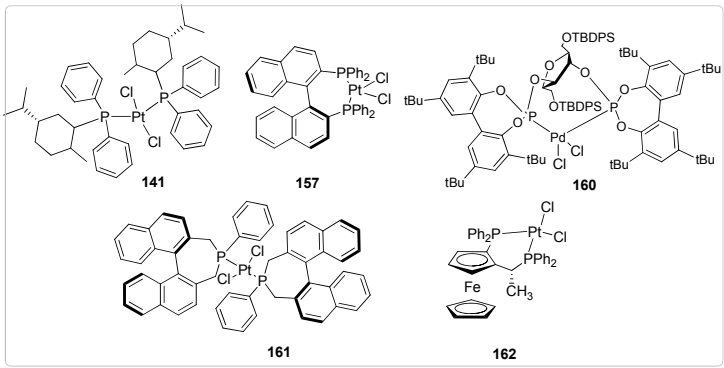
Entry	Precursor	Conv(%)[b]
1	K_2PtCl_4	74
2	Pt/**132**	0
3	Pt/**134**	0
4	Pt/**1**	0
5	Pt/**159**	0
6	Pt/**70**	0

a. Reaction conditions: 9 μmol $Pt_2(dba)_3$, 100μL KOH 3M, dioxane (1 mL), 0.30mmol 2-cyclohexen-1-one, 0.45mmol $PhB(OH)_2$, time = 4 h.T = 70º C **b.** Determined by GC.

These results are in agreement with those reported by Hayashi. The Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one in dioxane was also carried out using the preformed Pt complexes **141**, **157**, **160**, **161**, **162** as catalysts (Table 5.2). When the reaction was carried out in presence of the complex **141**, 15% of conversion was obtained (entry 1). However, the only product detected was **CLXX**. When the complex **157** was used as catalyst precursor, 49% of conversion was obtained. When the reaction was performed with **160** and **162** as catalytic system, all the substrate was converted (entry 3 and 5). Nevertheles, the use of the complex **161** as catalyst afforded only the homocoupling product. In all cases, no enantioselectivity was induced.

Table 5.2 Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using isolated Pt complexes system.[a]





Entry	Precursor	Conv(%) [b]	Selec.(%) [b]	ee(%) [c]
1	**141**	15	99	2
2	**157**	49	99	-
3	**160**	100	99	3
4	**161**	100*	0	0
5	**162**	100	99	0

a. Reaction conditions: 9 μmol $Pt_2(dba)_3$, 100μL KOH 3M, dioxane (1 mL), 0.30mmol 2-cyclohexen-1-one, 0.45 mmol $PhB(OH)_2$, time = 24 h. T = 70º C **b**. Determined by GC. * the only product was the byproduct **CLXXIV c.** Determined by HPLC.

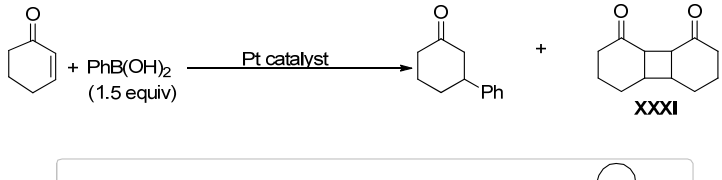
Therefore, the Pt complex **141**, **157**, **160**, and **162** were active in the Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one and afforded very high conversions but no enantioselectivity (ee ≤3) was induced under these conditions.

5.2.2.2 Colloidal catalysts

The Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using the preformed PtNPs as catalyst was performed in dioxane with a solution of KOH 3M during 24h at room temperature (Table 5.3). When the reaction was carried out in presence of **Pt132**, 56% of conversion was observed (entry 1). When the reaction was performed with **Pt134** as catalytic

system, the conversion decreased to 19%. The use of **Pt159** led to 59% conversion. Finally the **Pt70** NPs stabilised with the carbohydrate derivate ligand **70** afforded 36% of conversion. In all cases, no enantioselectivity was induced.

Table 5.3. Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using **Pt132, Pt1, Pt159** and **Pt70** system.[a]



Entry	Precursor	Conv(%) [b]	Selec.(%) [b]	ee(%)[c]
1	**Pt132**	56	99	0
2	**Pt1**	19	99	0
3	**Pt159**	59	99	2
4	**Pt70**	36	99	2

a. Reaction conditions: 9 μmol Pt, 100μL KOH 3M, dioxane (1 mL), 0.30 mmol 2-cyclohexen-1-one, 0.45mmol $PhB(OH)_2$, time = 24 h. Room temperature **b**. Determined by GC. **c.** Determined by HPLC.

The PtNPs stabilised by chiral ligands were thus active in the Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one giving moderate conversions. It should be noted that the PtNPs were active even at room temperature. Nevertheless, as for the molecular system, no enantioselectivities were obtained.

5.3 Conclusions

The complexes **141**, **157**, **160**, **161** and **162** bearing the ligands **1**, **70**, **132**, **134** and **159** were successfully synthesised and characterised by NMR spectroscopy and HR-MS. These ligands were also used as stabilisers in the synthesis of the corresponding Pt NPs. These colloids were characterised by TEM microscopy.

The study of the 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using molecular complexes provided very distinct results whether the reactions were carried out using "in situ" formed catalysts or with the preformed complexes **141**, **157**, **160**, **161** and **162**. Indeed, no conversion was obtained using the *in situ* systems while moderate to good activities were achieved with the isolated complexes. This behaviour indicates that phosphine containing Pt species are active catalysts in this transformation and that the active species is not formed when $Pt_2(dba)_3$ is used as precursor in the presence of the free ligand.

Using PtNPs as catalyst precursors, moderate conversions were achieved. However, with both molecular and colloidal systems, no enantioinduction could be obtained, suggesting that the active species did not contain the chiral ligand.

The platinum nanoparticles were found to be active in the 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one. To the best of our knowledge, there are no examples of the use of platinum nanoparticles as catalysts in this reaction.

5.4 Experimental part

5.4.1 General methods

All compounds were prepared under nitrogen atmosphere using standard Schlenk and vacuum-line techniques. The organic solvents were purified on solvent purification system – 800 series or distilled over drying reagents and were deoxygenated before use. Chemicals were purchased from Aldrich Chemical Co and Fluka.

^{1}H, ^{13}C $\{^{1}H\}$, and ^{31}P $\{^{1}H\}$ NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer. Chemical shifts were calibrated relative to $SiMe_4$ (^{1}H and ^{13}C NMR) as internal standard or 85% H_3PO_4 as external standard (^{31}P NMR). Assignments in NMR spectra were determined by COSY and HSQC spectra. Coupling constants, J, are given in Hz. Multiplicities of peaks in ^{1}H and ^{13}C NMR are given as: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), m (multiplet), and b (broad).

TEM measurements were realized on a Zeiss 10 CA electron microscope at 100 kW with a resolution of 3Å; Pt nanoparticles samples were prepared under nitrogen atmosphere. A drop of the diluted solution was placed on a carbon covered Cu grid. Final drying of the sample was performed under vacuum overnight. The nanoparticle size and distribution were determined by counting approximately 600 nanoparticles from four enlarged TEM imaged (*ca.* 150 nanoparticles from each TEM image). The size distribution plots were fitted using a Gaussian model with Origin 8.0 graphing software in order to determine the widths and centers of the size distributions.mm, carrier gas: 150 kPa He, F.I.D. detector) equipped with a Hewlett-Packard eHP3396 series II integrator.

GC-MS spectrums were achieved on a Hewlett-Packard HP 6890 Series GC System coupling to a 5973 Mass Selective Detector, with automatic injector Hewlett-Packard HP 7683 Series Injector. The chromatographic column: HP 5MS de 30 m, internal diameter 0.25 mm and film thickness 0.25μm.

The conversion of the reactions were measured by GC on a Hewlett-Packard HP 5890 A instrument (split/splitless injector), J&W scientific, HP%, 25 m. column, internal diameter 0.25 mm, film thickness 0.33 mm, F.I.D. detector) equipped with a Hewlett-Packard HP3396 series II integrator. Conditions in order to determine the conversions: temperatures from 70 to 180 ºC, rate 10ºC, detector and injector temperature: 250ºC.

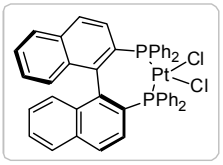
5.4.2 General procedure for the preparation of [$PtCl_2$(L)] complexes

Synthesis of [$PtCl_2$(COD)]

The synthesis of the isolated Pt complex was achieved according to reported methods.[58] K_2PtCl_4 (250 mg, 0.6 mmol) was dissolved in 4 ml of H_2O and 250μL (2 mmol) of 1,5-cyclooctadiene was added. Then, 6.0 ml of glacial acetic acid was added and the mixture heated at 90ºC. The solution turned yellow and a pale yellow solid was formed. The solution volume was reduced under vacuum. The solid was washed with H_2O, ethanol and ether and then dried to at 100ºC for 1 hour.

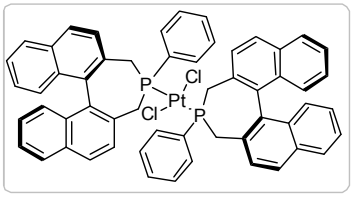
5.4.3 Synthesis of the Pt complexes.

The synthesis of the isolated Pt complex was achieved according to reported to the reported method with some modifications.[18] $PtCl_2$(COD) previously synthesized (0.13 mmol) was dissolved in 8 ml of degassed CH_2Cl_2. To the solution solid ligand (0.13 mmol) was added and the resulting pale yellow solution was stirred for 4 h at room temperature. The solution was brought to dryness in vacuum and the solid residue was thoroughly washed with stirring using a small volume of toluene. The solid was filtered via cannula and then, washed with hexane and ether and dried in vacuum. The cPt complex bearing the ligand 132 was described in the chapter 3.

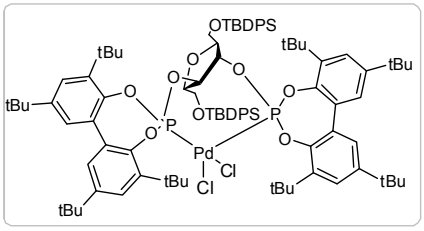


Complex **157:** ^{1}H NMR ($CDCl_3$): 7.80 (4H, m, H), 7.60 (4H, br, H), 7.56 (2H, m, H), 7.50 (2H, m, H), 7.40–7.44 (6H, m, H), 7.33–7.37 (4H, m), 7.11 (2H, m, H), 6.82 (2H, m, H), 6.74 (2m, H), 6.66 (4H, m, H) ppm; ^{13}C NMR ($CDCl_3$): 138.76 (C_2 or C_3), 135.59 (C_{12}), 134.82 (C_{12}′), 133.88 (C_2 or C_3), 133.06 (C_8), 130.43 (C_{14}′), 131.05 (C_{14}), 129.06 (C_9), 128.14 (C_5 or C_6), 128.05 (C_{10}), 127.71 (C_4 or C_7), 127.62 (C_4 or C_7), 127.54 (C_{13}), 127.31 (C_{13}′),

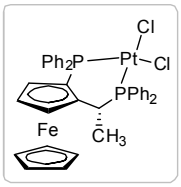
126.67 (C_5 or C_6), 122.41–121.69 (C_{11}, C_{11}', C_1) ppm; $^{31}P\{^1H\}$ NMR ($CDCl_3$): 9.81 ppm (satellite bands at −1.50 and 21.12ppm, $J_{P\text{-}Pt}$=3178 Hz) LC/ESI-TOF/MS (CH_3CN): 852.13 (88.88%), 853.13 (100%), 854.13 (58.70%), 855.13 (45.34%), 856.13 (16.99%) calcd for $C_{44}H_{32}ClP_2Pt$; Yields: 85%.



Complex **134:** ^1H NMR (400MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.90 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.32 (m, 3H), 7.28 – 6.98 (m, 8H), 6.87 (t, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 1H), 3.50 – 2.99 (m, 2H), 2.82 (d, *J* = 11.2 Hz, 1H). $_{13}C$ NMR (100.6MHz, $CDCl_3$): δ= 30.3 (d, *J* = 16.2 Hz, CH_2); 32.2, 124.8, 125.0, 125.8, 125.9, 126.6, 126.7; 127.4, 127.5; 128.0; 128.1–128.7; 131.6; 132.2; 131.9, 132.3, 132.7, 132.8; 133.5, 133.7; 134.3; 137.5. $^{31}P\{^1H\}$ NMR ($CDCl_3$): 26.35 ppm (satellite bands at 15.35 and 37.35 ppm, $J_{P\text{-}Pt}$=3563 Hz). LC/ESI-TOF/MS (CH_3CN): 1083.21 (100%), $C_{58}H_{45}Cl_2NP_2Pt$; Yield: 82%.



Complex **160:** ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.50 – 6.74 (m, Ph) , 5.68-5.37 (m, 1H, CH) , 5.59 (t, 1H, CH), 3.50 (s, 1H, CH), 3.37 (d, *J* = 9.9 Hz, 2H,), 2.72 (d s, 2H, d, *J* = 11.1 Hz), 2.62 (d, 2H), 2.20 (d, 2H *J* = 8.7 Hz), 1.57 (s, 18H) 1.47 (s, 18H), 1.34 (s, 18H), 1.05 (s, 18H), 0.95 (s, 18H); ^{31}C NMR (CDCl3, 100.6 MHz) δ in ppm: 146.8, 82.2, 77.4, 32.8, 35.0, 34.9, 3.9, 31,8, 30.2, 11.5 $^{31}P\{^1H\}$ NMR ($CDCl_3$, 101.3 MHz) 74.65 ppm (satellite bands at 56.35 and 92.95 ppm, $J_{P\text{-}Pt}$=5948 Hz)Yields: 83%. LC/ESI-TOF/MS: m/z (100%)= (CH_3CN): 1735.71 (98%), $C_{96}H_{129}Cl_2NO_9P_2PdSi_2$, Yield: 90%.



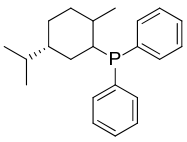
Complex **163:** ^1H NMR ($CDCl_3$): δ (ppm) 7.9–7.2 (m, 10H, $-C_6H_5$); 4.64 (br, s, 1H, C_5H_3), 4.31 (br, s, 1H, C_5H_3), 4.24 (br, s, 1H, C_5H_3), 4.23 (s, 5H, Cp), 3.47 (m, 1H, CHMe), 2.4–1.1 (m, 25H, C–CH_3 and –Cy). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 101.3 MHz) 26.78 ppm (satellite bands at 2.22 and 33.08 ppm, $J_{P\text{-}Pt}$=4049

Hz)Yields: 67%. LC/ESI-TOF/MS: m/z (100%)= (CH_3CN): 900.16 (100%), $C_{38}H_{47}Cl_2FeNP_2Pt$, Yield: 90%.

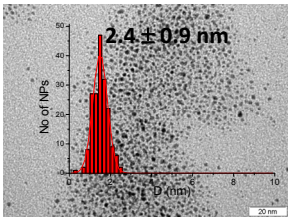
5.4.3.1 General Procedure for the Synthesis of Pt Colloids

Synthesis of [**$Pt_2(dba)_3$**] The synthesis of the Pt complex was achieved according to reported methods with some modifications. The platinum salt K_2PtCl_4 (1.11 g, 2.7mmol) was introduced in an inert schlenk tub and solubilised in previously degassed distilled water (2 ml). A limpid bright orange solution was obtained. In the meantime, dibencylidenacetonate (dba, 1.69 g, 7 mmol) and sodium acetate (CH_3COONa, 1.7 g, 20mmol) were introduced in a 250 ml schlenk and kept under vacuum for 45 min. Then, degassed ethanol (10 ml) is added. The two solutions were mixed and heated at 80 ºC for 2 hours under nitrogen. The previously orange reaction mixture turned black very quickly. After decantation, a black precipitate is retrieved by filtration, thoroughly washed with water and dried under vacuum for 10 hours, before being washed with pentane to remove dba. The obtained product is kept under nitrogen. Yield: 79%

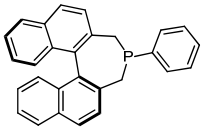
Synthesis of PtNPs In a standard procedure, 160 mg of [$Pt_2(dba)_3$] (0.175 mmol) were dissolved under argon at 110º C (ethanol/N_2 bath) and under vigorous magnetic stirring in a solution of 160 mL of THF containing 0.2 equiv./Pd of the chosen ligand in a Fischer–Porter bottle. The mixture was then pressurized under dihydrogen (3 bars) at room temperature. The colour of the solution turned from purple to black in a few minutes. The vigorous stirring and the dihydrogen pressure were maintained for 18 h at room temperature, leading to black and homogeneous colloidal solutions. After depressurization, a drop of each colloidal solution was deposited under argon on a holey carbon-covered copper grid for TEM analysis. The colloidal solution was then concentrated to ca. 5 mL. Addition of cold pentane allowed the precipitation of the particles as black solids that were washed with pentane (2x40 mL) and dried under vacuum. The colloids were characterized by TEM analysis, elemental analysis and XPS.



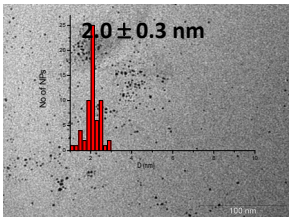
Pt132 NPs



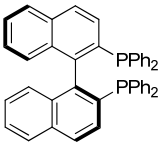
51.4% Pt, 0,19% P



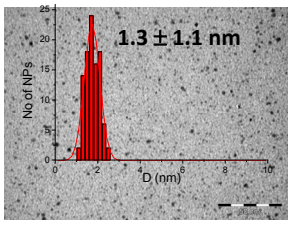
Pt134 NPs



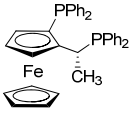
45.8% Pt, 0,19% P



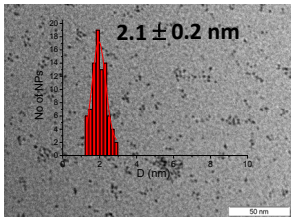
Pt1 NPs



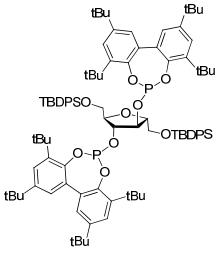
56.4% Pt, 0,19% P



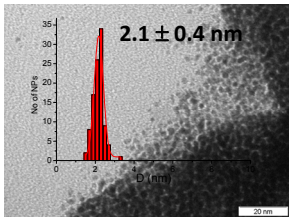
Pt159 NPs



47,1% Pt, 0,4% P



Pt70 NPs



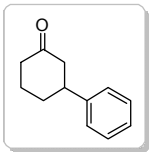
47,7% Pt, 0,3%

5.4.4 General procedure for 1,4-addition reaction

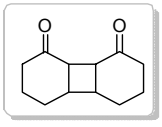
In-situ systems: To a solution of $PtCl_2(COD)$ (9 mmol), phenylboronic acid (54.9mg, 0.45mmol), phosphine ligand (9μmol for ratio Pt:ligand 1:1 and 18μmol for ratio Pt:ligand 1:2) and 1,4-dioxane (1.0ml) was added 100μL KOH 3M as additive, and 28.8 mg (0.30 mmol) of 2-cyclohexen-1-one. Then, the mixture was stirred at ambient temperature or 70ºC for 4 hours. The reaction mixture was passed though a celite pad with Et_2O. The conversion was determined by GC.

Colloidal systems: To a solution of colloid (4mg), phenylboronic acid (54.9 mg, 0.45 mmol) and of 1,4-dioxane (1.0 ml) was added100μL KOH 3M as additive, and 28.8 mg (0.30 mmol) of 2-cyclohexen-1-one. Then, the mixture was stirred at ambient temperature or 70ºC for 4 hours. The reaction mixture was passed though a celite pad with Et_2O. The conversion was determined by GC.

Attempts of separation and purification of the products detected by GC: After evaporation of the solvent of the reaction mixture, the residue was diluted with ethyl acetate. The solution was washed with a saturated solution of sodium bicarbonate (3 times) and dried over magnesium sulphate. Although the expected reaction product 3-phenylcyclohexanone was isolated by flash chromatography (eluent hexane: ethyl acetate 4:1), the second product could not be isolated and was obtained as a mixture of two products.



3-phenylcyclohexanone*:* Obtained as colorless oil. ^{1}H NMR (CH_2Cl_2): δ in ppm 1.64-1.78 (m, 2H), 1.91-2.04 (m, 2H), 2.26-2.29 (m, 2H), 2.88-2.91 (m, 1H), 7.01-7.25 (m, 5H). ^{13}C-NMR (CH_2Cl_2): δ in ppm 26.11, 33.34, 41.61, 45.29, 49.37, 127.07, 127.13, 129.11, 145.24, 211.18. *m/z*= 174(100.0%), 131(68.8%), 117(81.7%), 104(60.5%), 91 (27.5%), 78 (17.4%) and 42 (11.9%).



Di-cyclohexenone*: m/z*=192 (100.0%), 175 (11.0%), 164 (17.4%), 149 (23.9%), 136 (49.5%), 121 (30.3%), 108 (39.5%), 91 (28.4%), 79 (41.3%), 66 (15.6%), 55 (22.9%) and 41(16.5%)

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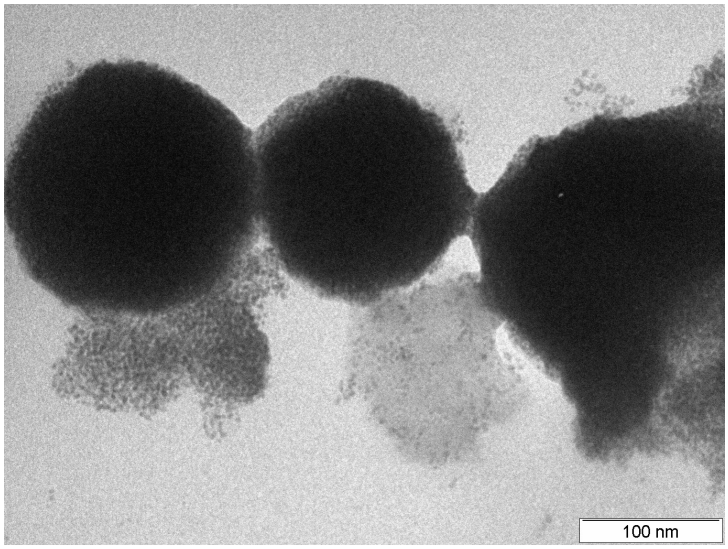
Chapter 6.

Conclusions



***Chapter. 2**. Pd-catalysed asymmetric allylic substitution reactions using C2-symmetry diphosphite carbohydrate derived ligands*

This work was carried out in the context of collaboration with the group of Prof. M. Gomez in Toulouse (France)

The synthesis of the chiral palladium complexes containing the C2-symmetric ligands **70** and **75** was successfully carried out and these species were fully characterised by NMR spectroscopy and HR-MS.

The palladium NPs **Pd70** and **Pd75** were also successfully synthesised using the chiral carbohydrate derived diphosphite ligands **70** and **75**. The shape, size and dispersion of the nanoparticles were observed to depend on the structure of the stabilising ligand used. Different palladium/ligand ratios were used to stabilise the Pd NPs with the ligands **70** and **75.**

In the Pd-catalysed asymmetric allylic substitution reactions of the substrate **X**, the catalytic system containing the ligand **70** was found to be highly active, showing the highest turnover frequency values reported for asymmetric allylic alkylation (TOF = 22,000 h-1) and allylic amination (TOF = 400 h-1) processes with excellent ee values (up to >98%). Moreover, the effect of the substrate/nucleophile ratio on the activity of these reactions indicates a poisoning effect of the nucleophiles. When the Pd system with the ligand **77** was probed, no reproducible results could be obtained. These results clearly show that small changes in the ligand structure can drastically affect the catalytic activity. The preliminary results obtained for the asymmetric Pd-catalysed allylic phosphination were moderate in terms of chemoselectivity and enantioselectivity.

The NPs **Pd70** and **Pd75** were tested as catalytic precursors in Pd-catalysed allylic substitution reactions and showed similar behaviour to that of the analogous molecular system. Under catalytic conditions using **X** as substrates, the **Pd70** were active and gave excellent results in terms of conversion and enantioselectivity (up to 99%). In contrast, the use of **Pd75** NPs as precursors did not provide reproducible results. It is noteworthy that **Pd70** was used in the allylic alkylation of the racemic substrate **VI**, a large difference in reactivity between the two enantiomers of **VI** was observed. This fact pointed to a key-lock matching between substrate and catalyst.

The catalytic performances of the chiral palladium catalytic system containing the diphosphite ligand **70** in pyrrolidinium-based ionic liquid were also studied. This system was highly active and induced high enantioselectivity in the allylic alkylation and amination reactions in this medium and was even more active than in dichloromethane for the amination. For the first time, the Pd system bearing the ligand **70** could be recycled up to nine times without activity loss and preserving the enantioselectivity. The preliminary results obtained for the asymmetric Pd-catalysed allylic phosphination are very promising in terms of chemoselectivity, although only moderate enantioselectivity was obtained in this reaction.

Chapter. 3. *Asymmetric Suzuki-Miyaura coupling reaction using Pd nanoparticules, parallel studies with the molecular system*

Several molecular Pd catalytic systems bearing the monodentate ligands **132-136** were used in asymmetric Suzuki-Miyaura coupling reactions of iodo- and bromonaphthalene and several naphthalene boronic acids. The use of the neomenthyl phosphine ligand **132** in this reaction provided the highest activities (98%) with excellent selectivities to the cross coupling product (up to >99%) and moderate enantioselectivities (up to 35%). The bidentate ligands **27**, **67**, **70**, **85**, **131**, **137**, **138** and **139** were successfully used in the Pd-catalysed asymmetric Suzuki coupling reactions of the same substrates. Excellent conversions and good ee's were obtained using the Pd/**44** system (96% and 37% respectively).

The new well dispersed Pd NPs **Pd132, Pd133** and **Pd134** stabilised by monodentate ligands were successfully synthesised and characterised by TEM, XPS and elemental analysis. These NPs were used as catalysts in asymmetric Suzuki coupling and good activities were obtained at room temperature (62%) with excellent selectivities to the cross coupling product (up to >99%) and moderate enantioselectivities (ee up to 24%). The Pd NPs **Pd70**, **Pd27**, **Pd67** and **Pd137** stabilised by bidentate ligands were synthesised and characterised by TEM, XPS and elemental analysis. These NPs were poorly active at room temperature in the asymmetric Suzuki coupling. Interestingly, the enantioselectivity was found to be low with these systems and even lower than those obtained with Pd NPs stabilised by chiral monodentate ligands.

To corroborate the hypothesis that the boronic acids used in catalysis could interact with the metallic surface of the NPs, the stabilization of new Pd NPs using boronic acids as stabiliser was carried out and the resulting nanospheres were characterised by TEM microscopy. The formation of these nanospheres evidenced that interactions of the boronic acid with the surface of the colloids occurs.

***Chapter 4**. Ni-Catalyzed Suzuki coupling reactions containing phosphinine ligands.*

This work was carried out in the context of collaboration with the group of Prof. D. Vogt, The Netherlands.

The Ni-catalysed Suzuki-Miyaura coupling of bromobenzene with aryl boronic acids was studied in the presence of the phosphinine and pyridine ligands **149-153**. The systems bearing the phosphinine ligands gave good to excellent conversions even at low catalyst loading while those bearing the analogous pyridine ligands were inactive under the conditions used. It is noteworthy that the Ni/**150** system was able to transform the inactive *p*-tolyl-chloride in the presence of phenyl boronic acid. The analogous Pd systems provided moderate to good activities using optimised conditions. Interestingly, the Pd/pyridine systems were also active in the Suzuki-Miyaura coupling of bromobenzene with phenyl boronic acid.

The ligands **149-151** were also used to successfully stabilise Pd NPs, which were subsequently used in Pd-catalysed Suzuki-Miyaura coupling reactions of bromobenzene at room temperature and provided moderate to good conversions. Surprisingly, the analogous pyridine ligands did not provide stabilisation for Pd NPs and only bulk metal was formed.

The ligands **139**-**150** were also used to stabilise Ni NPs from decomposition of $[Ni(COD)_2]$ under H_2 pressure. These NPs were found to be magnetic and were characterised by TEM microscopy.

***Chapter 5**. Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one*

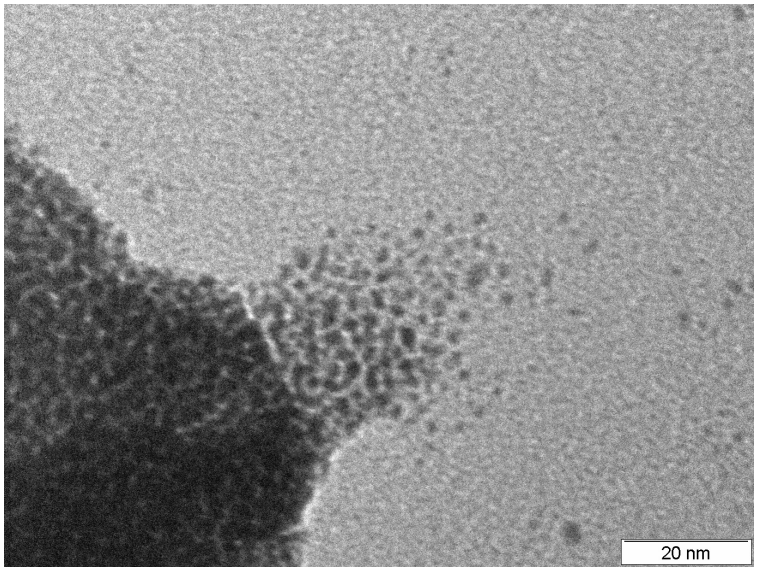
In this chapter, our preliminary results in the Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one are described. This work was carried out in the context of collaboration with the group of Prof. Hayashi, Japan.

The complexes bearing the ligands **1**, **70**, **132**, **134** and **159** were successfully synthesised and characterised by NMR spectroscopy and HR-MS. These ligands were also used as stabilisers in the synthesis of the corresponding Pt NPs **Pt1**, **Pt70**, **Pt9132**, **Pt134** and **Pt159**. These colloids were characterised by TEM microscopy, XPS and elemental analysis.

The study of the 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using molecular complexes provided very distinct results whether the reactions were carried out using "in situ" formed catalysts or with the preformed complexes [$PtCl_2$(**1**)] **157**, [$PtCl_2$(**70**)] **160,** [$PtCl_2$(**132**)] **161,** [$PtCl_2$(**134**)] **162,** and [$PtCl_2$(**159**)] **163**. Indeed, no conversion was obtained using the in situ systems while moderate to good activities were achieved with the isolated complexes. This behaviour indicates that phosphine containing Pt species are active catalysts in this transformation and that the active species is not formed when $Pt_2(dba)_3$ is used as precursor in the presence of the free ligand. Using Pt NPs as catalyst precursors, moderate conversions were achieved. However, with both molecular and colloidal systems, no enantioinduction could be obtained, suggesting that the active species did not contain the chiral ligand.

Chapter 7.

Summary/Resum



Besides the applications of NPs in powder technology, material science and as advantageous fuel cell catalysts, the use of metal NPs in catalysis has recently received a great deal of interest from both academic and industrial research groups.[1] Metallic nanoparticles (NPs) have special properties that allowed them to be considered a revolutionary catalyst.[2] The much larger surface-to-volume ratio of nanoparticles compared to their bulk counterparts has attracted a great deal of attention for catalytic applications.[3]

Highly dispersed mono- and bimetallic colloids can be used as precursors for a new type of catalyst that is at the frontier between homogeneous and heterogeneous catalyst. Several chemical reactions have been successfully catalyzed by transition metals in colloidal solution including cross-coupling, electron transfer, hydrogenation, and oxidation reactions.[4]

In organic synthesis, one of the most important challenge remains the stereoselective formation of C-C bonds through efficient catalysis. Therefore, asymmetric reactions such as the Pd- and Ni-catalysed Suzuki-Miyaura coupling, the Pd-catalysed allylic substitution and conjugate addition are of high interest.

In this context, this thesis focuses on the study of several transition metals catalysed C-C bond formation reactions using both molecular complexes and metallic NPs as catalyst precursors.

In this thesis, the following reactions were studied:

1. Pd-catalysed asymmetric allylic substitution reactions
2. Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions
3. Ni-catalysed Suzuki-Miyaura coupling reactions
4. *Pt-catalysed 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one*

For each reaction, the synthesis and characterization of metal complexes and NPs stabilized by several types of ligands were performed and both types of catalytic systems were tested in the appropriate reactions.

***Chapter. 2**. Pd-catalysed asymmetric allylic substitution reactions using C2-symmetry diphosphite carbohydrate derived ligands*

In this chapter, the diphosphite carbohydrate derived ligands **70** and **75** were used in Pd-catalysed asymmetric allylic alkylation, amination and phosphination reactions. These reactions were carried out using molecular complexes and colloidal NPs as catalytic precursors.

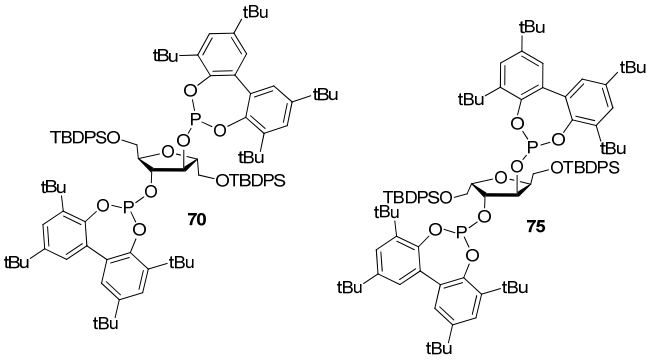


Figure 7.1. Ligands used in this work in Pd-catalysed asymmetric allylic substitution reactions.

The asymmetric allylic alkylation reaction using the molecular Pd/**70** system showed the highest turnover frequency values reported for asymmetric allylic alkylation (TOF = 22,000 h^{-1}) and allylic amination (TOF = 400 h^{-1}) processes with excellent ee values (up to >98%). Moreover, the effect of the substrate/nucleophile ratio on the activity of these reactions indicates a poisoning effect of the nucleophiles. When the Pd system with the ligand **75** was probed, no reproducible results could be obtained. The preliminary results obtained for the asymmetric Pd-catalysed allylic phosphination were moderate in terms of chemoselectivity and enantioselectivity.

Pd NPs were stabilized by the ligands **70** and **75** using various palladium/ligand ratios and were used as catalytic precursors in allylic substitution reactions. The NPs **Pd70** and **Pd 75** were tested as catalytic precursors in Pd-catalysed allylic substitution reactions and showed similar behaviour to that of the analogous molecular system. Under catalytic conditions using linear 1,3-diphenylallyl acetate and cyclic 2-cyclohexylen acetate substrates, the **Pd70** were active and gave excellent results in terms

of conversion and enantioselectivity (up to 99%). In contrast, the use of **Pd75** NPs as precursors did not provide reproducible results. It is noteworthy that **Pd70** was used in the allylic alkylation of the racemic substrate, a large difference in reactivity between the two enantiomers of 1,3-diphenylallyl acetate was observed.

To summarise, in the Pd-asymmetric allylic substitutions, similar behaviour was observed when preformed NPs stabilised by the ligands **70** and **75** and when the molecular systems Pd/**70** and Pd/**75** were used, suggesting that molecular species could be the real active catalysts in this process.

The use of the chiral molecular Pd/**70** catalysts was also studied in ionic liquids. This system was highly active and induces high enantioselectivities in the Pd-catalysed asymmetric allylic alkylation and amination reactions in pyrrolidinium-based ionic liquid. Its activity even increases in relation to that obtained in dichloromethane for the amination. For the first time, the Pd bearing the ligand **70** system could be recycled up to nine times without activity loss and preserving the enantioselectivity

Chapter. 3. "*Asymmetric Suzuki coupling reaction using Pd nanoparticules, parallel studies"* describes the use of novel Pd-catalysts bearing several types of chiral ligands in asymmetric Suzuki coupling reactions.

First, the use of the monodentate chiral ligands **132-136** (Figure 7.2) was probed in asymmetric Suzuki coupling reactions.

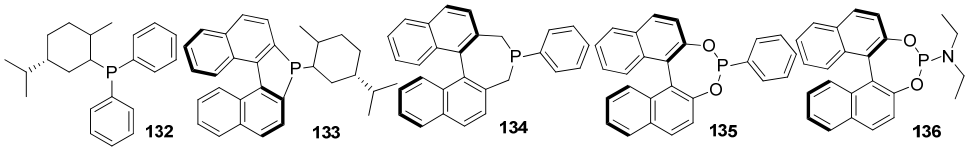


Figure 7.2. Monodentate ligands synthesised for the Pd- catalysed Asymmetric Suzuki coupling.

The catalytic system Pd/**132** in this reaction provided the highest activity with excellent selectivities to the cross coupling product (up to >99%) and moderate enantioselectivities (ee up to 35%).

New well dispersed **Pd132, Pd133** and **Pd134** NPs were successfully synthesised and characterised. These NPs were used as catalysts in asymmetric Suzuki coupling at room temperature and good activities with

excellent selectivities to the cross coupling product and moderate enantioselectivities were obtained.

Next, the bidentate ligands **27**, **67**, **70**, **85**, **131**, **137**, **138** and **139** (Figure 7.3) were used in asymmetric Suzuki couplings.

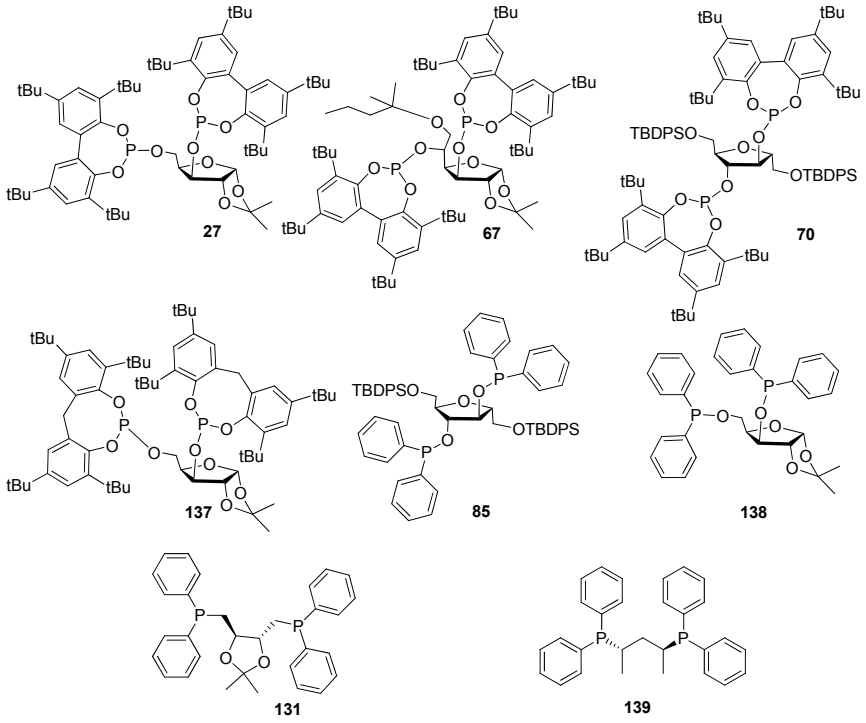


Figure 7.3. Bidentate ligands synthesised for the Pd- catalysed asymmetric Suzuki coupling.

Excellent conversions and good ee's were obtained with Pd/**70** as catalytic system.

The well dispersed **27**, **67**, **70**, **85**, **131**, **137**, **138** and **139** were synthesised and characterised using these bidentate ligands as stabilizers. Small and well dispersed NPs were obtained and observed by TEM microscopy. These NPs were active at room temperature in the asymmetric Suzuki coupling of aryl iodides. However, moderate conversions and low ee were obtained. The stabilization of new nanospheres stabilised by boronic acids evidence that these compounds are able to stabilise metallic surfaces and as such, can affect the activity of NPs during catalysis.

The **Chapter 4** *entitled "Ni-catalyzed Suzuki coupling reaction using phosphinine ligands"* describes the utilization of the phosphinine ligands and pyridine analogues **149**-**153** (Figure 7.4) in the Ni-catalyzed Suzuki coupling reaction of several aryl substrates. This work was completed in the context of a collaboration with the group of Prof. D. Vogt, The Netherlands.

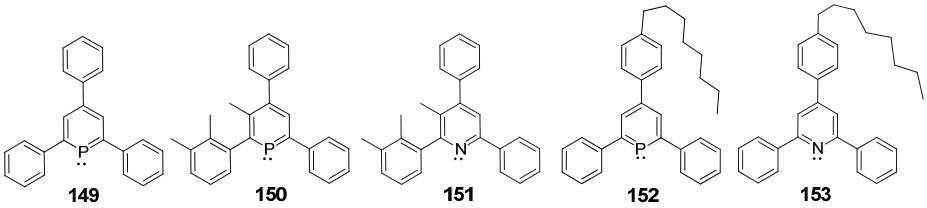


Figure 7.4. Phosphinine ligands used in Pd- catalysed Suzuki coupling reaction.

The systems bearing the phosphinine ligands gave good to excellent conversions even at low catalyst loading while those bearing the analogous pyridine ligands were inactive under the conditions used. It is noteworthy that the Ni/**150** system was able to transform the inactive *p*-tolyl-chloride in the presence of phenyl boronic acid. The analogous Pd systems provided moderate to good activities using optimised conditions. Interestingly, the Pd/pyridine system was also active in the Suzuki-Miyaura coupling of bromobenzene with phenyl boronic acid.

The ligands **149-151** were also used to successfully stabilise Pd NPs, which were subsequently used in Pd-catalysed Suzuki-Miyaura coupling reactions of bromobenzene at room temperature and provided moderate to good conversions. Surprisingly, the analogous pyridine ligands did not provide stabilisation for Pd NPs and only bulk metal was formed.

The ligands **149**-**150** were also used to stabilise Ni NPs from decomposition of $[Ni(COD)_2]$ under H_2 pressure. These NPs were found to be magnetic and were characterised by TEM microscopy.

The **Chapter 5** entitled *"Pt-catalysed asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one"*

describes our preliminary results in the Pt-catalysed asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one are described. This work was carried out in the context of collaboration with the group of Prof. Hayashi, Japan. The chiral ligands used in this study are described in Figure 7.5.

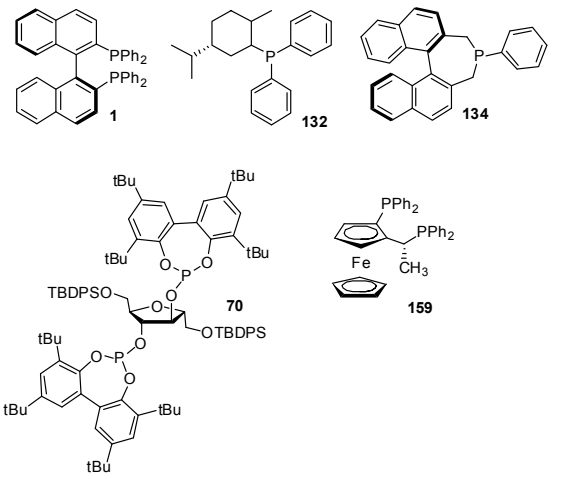


Figure 7.5. Chiral ligands used in the Pt-catalysed asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one

The complexes [$PtCl_2$(**1**)] **157**, [$PtCl_2$(**70**)] **160,** [$PtCl_2$(**132**)] **161,** [$PtCl_2$(**134**)] **162,** and [$PtCl_2$(**159**)] **163** bearing these ligands were successfully synthesised and characterised by NMR spectroscopy and HR-MS. These ligands were also used as stabilisers in the synthesis of the corresponding Pt NPs. These colloids were characterised by TEM microscopy, XPS and elemental analysis.

The study of the 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one using molecular complexes provided very distinct results whether the reactions were carried out using "in situ" formed catalysts or with the preformed complexes. Indeed, no conversion was obtained using the in situ systems while moderate to good activities were achieved with the isolated complexes. This behaviour indicates that phosphine containing Pt species are active catalysts in this transformation and that the active species is not formed when $Pt_2(dba)_3$ is used as precursor in the presence of the free ligand. Using Pt NPs as catalyst precursors, moderate conversions were

achieved. However, with both molecular and colloidal systems, no enantioinduction could be obtained, suggesting that the active species did not contain the chiral ligand.

7.1 References

[1] P. Sehkyu, Park, Yuyan Shao, Haiying Wan, Peter C. Rieke, Vilayanur V. Viswanathan, A. Silas, A. Towne, Laxmikant V. Saraf a, Jun Liu a, Yuehe Lin a, Yong Wang. *Electrochemistry Communications*, **201**1, *13*, 258.
[2] C.-J. Jia, F. Schüth *Phys. Chem. Chem. Phys*., **2011**, *13*, 2457.
[3] (a) P. L. Freund, M. Spiro, J. Phys. Chem., **1985**, *89*, 1077. (b) L. N. Lewis, *Chem. Rev*., **1993**, 93, 2693. (c) M. Moreno-Manas, R. Pleixats, *Acc. Chem. Res*., **2003**, *36*, 638. (d) R. Narayanan, M. A. El-Sayed, *J. Phys. Chem. B*, **2005**, *109*, 12663.
[4] (a) D. De Jesus, M. Spiro, *Langmuir*, **2000**, 16, 4896. (b) Y. Shiraishi, N. Toshima, *Colloids Surf. A*, **2000**, 169, 59. (c) Y. Shiraishi and N. Toshima, *J. Mol. Catal. A: Chem*., **1999**, 141, 187. (d) M. Comotti, C. D. Pina, R. Matarrese and M. Rossi, *Angew. Chem., Int. Ed.*, **2004**, *43*, 5812.

Entre les moltes aplicacions de les nanoparticules en la nanotecnologia, ciència dels materials i en cel·les de combustible, l'ús de nanoparticules en catàlisis ha estat un tema de gran interès tant en la recerca a nivell industrial com a nivell acadèmic.[1] Les nanoparticules metàl·liques tenen propietat especials i son considerades com uns catalitzadors revolucionaris.[2] La gran superfície activa de les nanoparticules en comparació a altres mètodes heterogenització ha centrat l'atenció en totes les seves possibles aplicacions industrials.[3]

Col·loides mono- o bimetalics d'alta dispersió poden ser utilitzats com a precursors de nous tipus de catalitzadors aplicables tant en catàlisis homogènia com heterogènia. Moltes reaccions químiques han pogut ser catalitzadors amb èxit amb l'ús de nanocatalitzadors en forma de solució col·loïdal incloent reaccions d'acoblament, de transferència d'electrons, d'hidrogenació i d'oxidacions entre altres.[4]

Dintre de la síntesis orgànica, un dels reptes més importants continua sent la formació esteroselectiva de enllaços C-C. Per exemple, reaccions asimètriques d'acoblament Suzuky-Miyaura catalitzades per pal·ladi i níquel, la substitució al·lílica o l'addició conjugada catalitzades per pal·ladi, son algunes de les reaccions que tenen gran interès.

Dintre d'aquest context, en aquesta tesis hem realitzat l'estudi de diverses reaccions catalitzades per metalls de transició per la formació de nous enllaços carboni-carboni utilitzant sistemes moleculars i sistemes de col·loïdals com a precursors dels catalitzadors.

En aquesta tesis, les següents reaccions son estudiades:

1. Alquilació al·lílica asimètrica catalitzada per pal·ladi
2. Reacció d'acoblament asimètric Suzuky-Miyaura catalitzada per pal·ladi
3. Reacció d'acoblament Suzuky-Miyaura catalitzades per níquel
4. Reacció d'addició 1,4 de l'àcid fenilboronic a 2-ciclohexen-ona

Per cada reacció, s'ha realitzat la síntesis de lligands i caracterització dels complexes metàl·lics i s'han estabilitzat les nanoparticules anàlogues

estabilitzades amb corresponents lligands. Els dos sistemes catalítics han estat provats en les reaccions corresponents.

***Capítol. 2**. Reacció de substitució al·lílica asimètrica catalitzada per pal·ladi utilitzant difosfits derivats de carbohidrats amb simetria C2*

En aquest capítol, els lligants difosfit derivats de carbohidrat amb **70** i **75** han estat utilitzat per les reaccions d'alquilació al·lilica, aminació i fosfinació asimètriques catalitzada per pal·ladi. En aquestes reaccions han estat utilitzats complexes molecular i sistema col·loïdals de nanoparticules com a precursors catalítics.

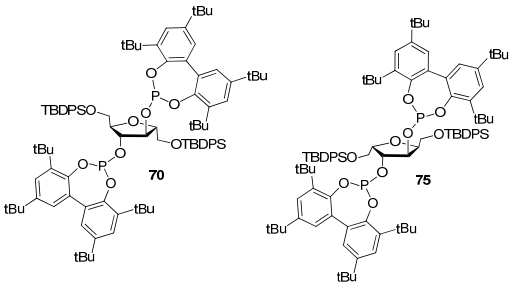


Figura 7.1. Lligants difosfits derivats de carbohidrat amb simetria C2 utilitzats amb alquilació al·lilica.

El sistema molecular Pd/**70** mostra el TOF mes alt publicat a dia d'avui per la reacció alquilació al·lílica (TOF = 22,000 h^{-1}) i per la reacció d'aminació al·lílica (TOF = 400 h^{-1}) amb excel·lents enantioselectivitats (superiors al 98%). D'altra banda, l'efecte de la relació substrat/nucleòfil amb l'activitat del catalitzador indica un efecte d'enverinament per part dels nucleòfils sobre el catalitzador. Quan el sistema de pal·ladi amb el lligand **75** va ser utilitzat es van obtenir resultants no reproduïbles. També s'ha estudiat la reacció fosfinació al·lílica asimètrica, els resultats en quan a selectivitat I enantioselectivitat son moderats.

Les nanoparticules de pal·ladi estabilitzades amb lligants **70** i **75** utilitzant diferents relacions de pal·ladi/lligant han estat utilitzades com a precursors catalítics en la reacció de alquilació al·lílica. Les NPs **Pd70** i **Pd 75** tenen un comportament molt similar al seus anàlegs moleculars. Sota les condicions catalítiques dels substrats **VI** i **VIII**, les **Pd70** son actives i donen resultants excel·lents en termes de conversió i enantioselectivitat (fins a

99%). Per altre banda, l'ús de **Pd75** NPs com a precursor donar una sèrie de resultants no reproduïbles. **Pd70** ha estat utilitzat en alquilació al·lílica del substrat racèmic **VI**, ja que s'ha observant una gran diferencia de reactivitat d'un enantiòmer a l'altre

En resum, en la substitució al·lílica asimètrica catalitzada per pal·ladi, ha estat observat un comportament similar en els sistemes molecular Pd/**70** i Pd/**75** i entre els sistemes col·loïdals **Pd70** i **Pd75**. Suggerint que les especies moleculars poden ser les especies catalítiques reals d'aquest procés.

L'ús del sistema catalític quiral Pd/**70** ha estat estudiat amb líquids iònics com ha solvent. Aquest sistema es molt actiu i indueix alta enantioselectivitat en les reaccions de alquilació al·lílica I aminació catalitzades per pal·ladi quan el líquid iònic format amb l'esquelet de l'anió pirrolidina. Per la reacció d'aminació, l'activitat pot arribar a ser superior que en els solvents convencionals com diclorometa. Per primera vegada, el sistema de pal·ladi modificat amb el lligant **70** pot ser reciclat fins a nou vegades sense perdre ni activitat ni enantioselectivitat.

Capítol 3 "*Reacció d'acoblament Suzuky-Miyaura utilizant nanoparticules de pal·ladi"* descriu l'ús de nous catalitzadors quirals de pal·ladi i la seva aplicació en la reacció d'acoblament de Suzuky.

Primer, els catalitzadors modificats amb els següents lligants quirals monodentats **132-136** (Figura 7.2) van ser provats en la reacció asimètrica d'acoblament Suzuky-Miyaura.

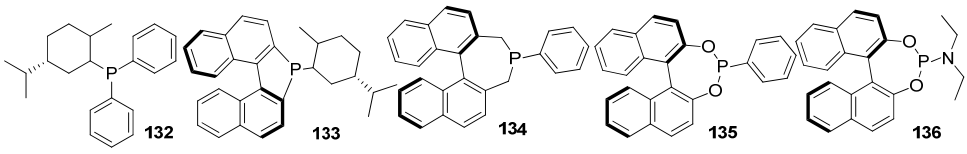


Figura 7.2. Lligands monodentat utilitzats en la reacció d'acoblament Suzuky

El sistema catalític Pd/**132** en aquesta reacció dona l'activitat més elevada i selectivitat excel·lents per el producte d'acoblament (superiors al 99%) però enantioselectivitats moderades (ee fins al 35%).

Noves nanoparticules **Pd132, Pd133** i **Pd134** amb els lligands quirals monodentats van ser sintetitzades i caracteritzades. Aquestes nanoparticules

van ser utilitzades com a catalitzadors en la reacció de Suzuky asimètrica a temperatura ambient amb bones activitats i selectivitats però novament nomes enantioselectivitats moderades van ser obtingudes.

Després, lligants bidentats **27**, **67**, **70**, **85**, **131**, **137**, **138** i **139** (Figura 7.3) van ser utilitzats en la reacció:

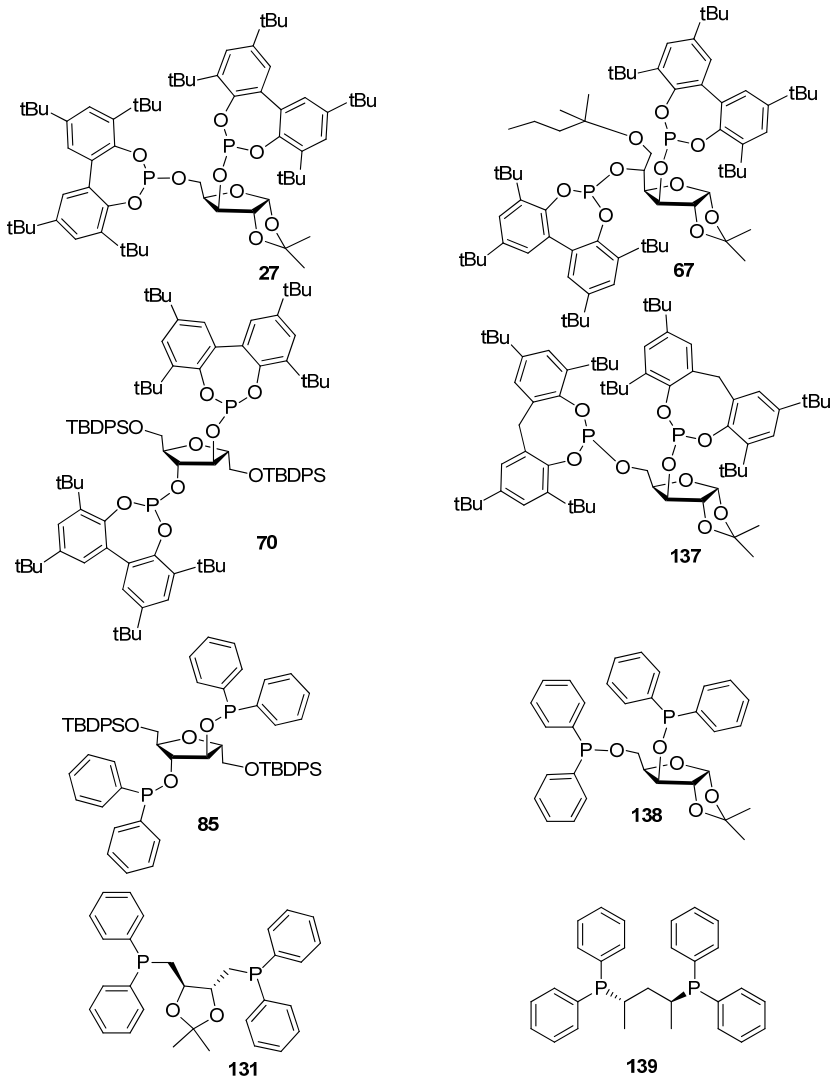


Figura 7.3. Lligands bidentats utilitzats en la reacció de Suzuky catalitzada amb pal·ladi.

Conversions excel·lents i bons excessos enantiomerics van ser obtinguts amb el sistema catalític Pd/**70**.

Nanoparticules formades amb els lligands bidentats **27**, **67**, **70**, **85**, **131**, **137**, **138** i **139** com a estabilitzants van ser sintetitzades i caracteritzades. Petites i ben disperses nanoparticules es van obtenir i observar amb el microscopi electrònic de transmissió (TEM). L'ús de nanoparticules en catàlisis es

tradueix en una activitat major a temperatura ambient de la reacció asimètrica d'acoblament amb iodurs d'aril. Malauradament, es van obtenir enantioselectivitats baixes. L'estabilització de noves nanoesferes per mitja dels àcids borònics evidencia que aquest compost es pot estabilitzar a la superfície metàl·lica, i conseqüentment pot afectar a l'activitat de les nanoparticules durant la catàlisis.

Capítol 4 *"Reacció d'acoblament Suzuky-Miyaura catalitzada per sistemes de níquel modificats per lligands fosfinines"* en aquest capítol es descriu la utilització dels sistemes de níquel modificats amb lligands fosfinina i anàlegs piridínics **149**-**153** (Figura 7.4). Aquest treball esta fet amb la col·laboració del grup del Prof. D. Vogt, Holanda.

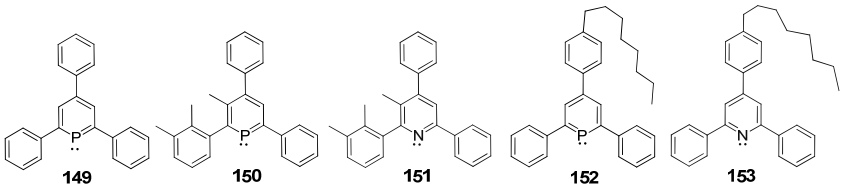


Figure 7.4. Lligands fosfinina i anàlegs utilitzats en la reacció d'acoblament Suzuky-Miyaura utilitzant níquel i pal·ladi com a metall de transició.

Els sistemes modificats amb lligants fosfinina donen excel·lents conversions fins i tot amb baixes concentracions de catalitzadors. Els anàlegs piridínics van ser inactius. El sistema Ni/**150** es capaç de transformar el inactiu *p*-clorur de tolil en la presencia del àcid fenilbornic. Els sistema anàleg de pal·ladi va donar bones activitats utilitzant les condicions optimitzades. Afortunadament el sistemes Pd/piridina son actius en la reacció d'acoblament creuat de Suzuky-Miyaura entre el bromobenzè i el àcid fenilboronic.

Els ligands **149-151** van ser exitosament utilitzats per la estabilització de les corresponents nanoparticules, que conseqüentment van ser utilitzades per l'acoblament creuat de Suzuki-Miyaura utilitzant bromobenze a temperatura ambient donant bones conversions. Sorprenentment, els derivats piridinimics no van ser capaços de estabilitzar les nanoparticules.

Els ligands **149**-**150** poden estabilitzar les nanoparticules de Ni a partir de la descomposició del [Ni(COD)$_2$] sota pressió de H_2. Aquestes nanoparticules son magnètiques i van ser caracteritzades mitjançant el microscopi TEM .

Capitol 5 *"Reacció d'addició 1,4 asimètrica de l'àcid fenilboronic a la 2-ciclohexen-1-ona catalitzada per Pt"* aquest capítol descriu els resultats preliminars de l'addició 1,4 asimètrica de l'àcid fenilboronic catalitzada per platí i utilitzant la 2-ciclohexen-1-ona com a substrat model. Aquest treball s'ha fet amb col·laboració del grop del Prof. Hayashi, Japan. Els lligands quirals utilitzats es mostren a la Figura 7.5.

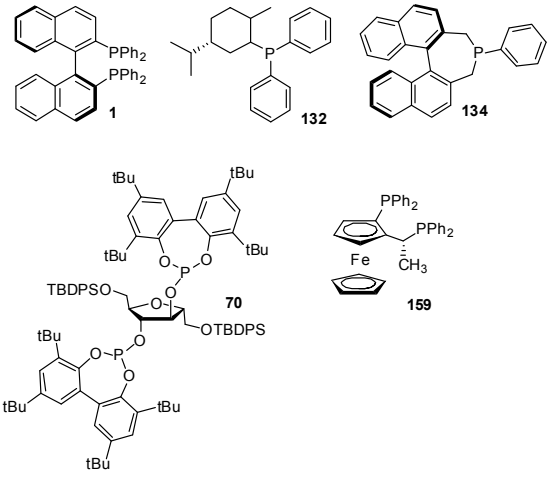


Figure 7.5. Lligands quirals utilitzats per la addicció 1,4 asimètrica catalitzada per Pt

Els complexos [$PtCl_2$(**1**)] **157**, [$PtCl_2$(**70**)] **160,** [$PtCl_2$(**132**)] **161,** [$PtCl_2$(**134**)] **162,** i [$PtCl_2$(**159**)] **163** van ser sintetitzats i caracteritzats amb èxit per NMR i HR-MS. A més a més, aquest ligands van ser capaços d'estabilitzar les corresponents NPs de platí. Aquestes van ser caracteritzades per TEM, XPS i anàlisis elemental.

L'estudi de la addició 1,4 del àcid fenilboronic a la cetona α,β-insaturada utilitzant sistemes molecular va donar resultants molt diferents segons si es sintetitzava el catalitzador "in situ" o es feia la catàlisis amb els complexos aïllats. No es va aconseguir transformar el substrat quan els catalitzadors es formaven "in situ", m'entres que els sistemes amb complexos aïllats donaven activitats moderades. Aquest comportament indica que les especies de platí modificades amb fosfina son les especies actives i que les especies de platí sense fosfina son inertes en el sistema catalític. Utilitzant nanoparticules de platí com a precursor, s'han obtingut conversions moderades. Malgrat tot,

independentment del sistema (col·loïdal o molecular) no s'ha pogut induir excés enantiomeric, suggerint que les especies actives no contenen lligand quiral o ve que la quiralitat en aquests sistemes es troba molt lluny del lloc on es produeix la enantiodescriminació.

7.1 References

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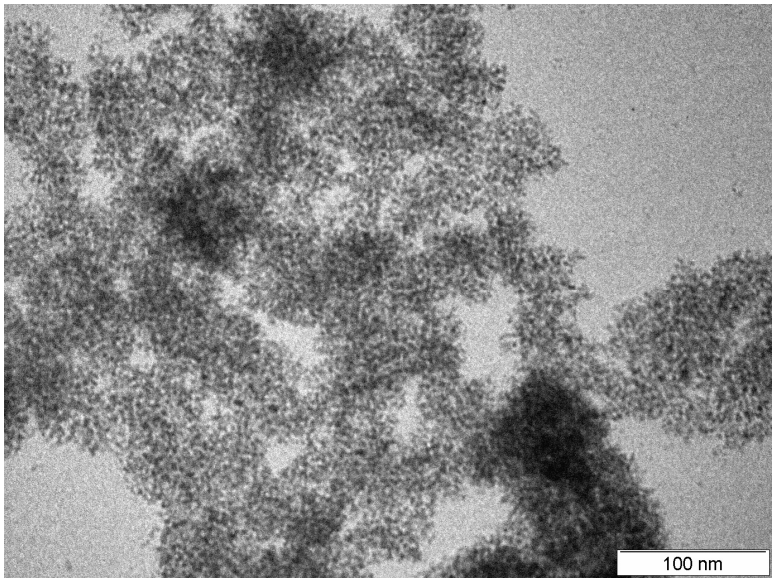
Chapter 8.

Appendix



8.1 Congresses and Scientific meetings

2008

Congress: 16th International Symposium on Homogeneous Catalysis **Place:** Florence, Italy **Year:** 2008 **Authors:** Angelica Balanta Castillo, I. Favier, C. Godard, E. Teuma, M. Gómez, C. Claver **Title:** *Chiral C2-Symmetry diphosphite ligands for the stabilization of Pd nanoparticles. Applications in enantioselective allylic substitution s* **Contribution:** Poster

2009

Congress: Symposium International Sur La Chimie Organometallique et la Catalyse/ (RENANCOM 2009) **Place:** Tétouan, Marocco **Year:** 2009 **Authors:** A. Balanta Castillo, C. Godard, C. Claver **Title:** *Synthesis of axially chiral binaphthyl products by Pd catalysed asymmetric Suzuki Coupling* **Contribution:** Poster.

Congress: XXXII Reunión Bienal de la RSEQ **Place:** Oviedo, Spain **Year:** 2009.**Authors:** A. Balanta Castillo, C. Godard, C. Claver **Title:** Uso de nanopartículas quirales de Pd altamente activas y selectivas en reacciones de Suzuki Asimétrica **Contribution:** Poster

2010

Congress: *17th International symposium on Homogeneous Catalysis. ISHC-17*, **Place:** Poznan, Poland Year**:** 2010 **Authors:** A. Balanta Castillo, Leen Broeckx, Christian Müller, Dieter Vogt, Cyril Godard, Carmen Claver **Title:** *Novel phosphinine-based ligands in Ni and Pd catalyzed Suzuki- Miyaura coupling reactions* **Contribution:** poster communication

Congress: Journée Catalyse 2010, **Place:** Toulouse, France **Year:** 2010 **Authors:** A. Balanta Castillo, C. Godard, C. Claver **Title:** *Pd Nanoparticles stabilized by chiral ligands as catalysts in Suzuki coupling reactions* **Contribution:** Oral communication

Congress: GEQO 2010, **Place:** Huelva, Spain **Year:** 2010 **Authors:** Angelica Balanta Castillo, Leen Broeckx, Christian Müller, Dieter Vogt, Cyril Godard, Carmen Claver **Title:** *Suzuki- Miyaura Coupling reactions using novel phosphinine-based ligands in Ni and Pd* **Contribution:** Poster

8.2 Publications based on the content of thesis

a. Angelica Balanta Castillo, Isabelle Favier, Emmanuelle Teuma, Sergio Castillón, Cyril Godard, Carmen Claver, and Montserrat Gómez. An outstanding palladium system containing C2-symmetrical phosphite ligand for enantioselective allylic substitution processes. *Chem. Commun.* (**2008**), 6197-6199.

b. Isabelle Favier, Angelica Balanta Castillo, Cyril Godard, Sergio Castillón, Carmen Claver, Montserrat Gómez and Emmanuelle Teuma. Efficient recycling of a chiral palladium catalytic system for asymmetric allylic substitutions in ionic liquid. *Chem. Commun*. (**2011**) 47, 7869-7871

c. Angelica Balanta Castillo, Cyril Godard, Carmen Claver. Pd nanoparticles for coupling reactions. *Chem. Soc. Rev*. (**2011**) *40*, 4973.

d. Angelica Balanta Castillo, Cyril Godard, Carmen Claver. Pd-catalyzed asymmetric allylic substitution reactions using colloidal and molecular system. *In preparation*.

e. Angelica Balanta Castillo, Cyril Godard, Carmen Claver. Pd-catalyzed asymmetric Suzuki-Miyaura reactions using colloidal and molecular system. *In preparation*.

f. Angelica Balanta Castillo, Cyril Godard, Carmen Claver, Christian Muller, Dieter Vogt. Phosphinine ligands in Ni-catalyzed Suzuki-Miyaura coupling reaction. *In preparation*.

g. Angelica Balanta Castillo, Cyril Godard, Carmen Claver, Noyori Hayasi, Pt-nanoparticles in asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one. *In preparation*.