Catalytic Cross Coupling Reactions

Dissertation

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DEDICATIONS

To

Candles of my life, my Mother, Soul of my Father,
My Brothers, Sisters
, and Friends
With Love

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List of Abbreviations

M	Metal
PPh_3	Triphenylphosphine
OAc	Acetate
dppp	1,3-Bis(diphenylphosphino)propane
dppe	1,2-Bis(diphenylphosphino)ethane
dppm	1,1-Bis(diphenylphosphino)methane
dmpf	1,1-Bis(methylphosphino)ferrocene
dippb	1,4-bis(diisopropylphosphino)-butane
S_N2	Bimolecular Nucleophilic Substitution
TMEDA	Tetramethylethylenediamine
MeNN2	Amidobis- (amine) ligand
MeCN	Acetonitrile
Mw	Molecular Weight
THF	Tetrahydrofuran
HRMS	High Resolution Mass Spectrometry
Mmu	Milli mass unit
δ	Chemical shift
j	Coupling constant (NMR)
NMR	Nuclear magnetic resonance
dd	Doublet of doublets (^{1}H NMR)
Hz	Herz

$CDCl_3$	Deuterated chloroform
Cy	Cyclohexyl
Dippe	Diisopropylphosphino-ethane
NMP	N-Methylpyrrolidone

1. Introduction

Cross coupling reactions of organic compounds catalyzed by various transition metals are an important method of generating carbon – carbon bonds. In the past three decades, carbon-carbon bond formation has allowed chemists to produce complex molecular structures of various interests including total synthesis of natural products, medicinal chemistry, and industrial process development [1]. Thus, different nucleophiles with various transition metals, such as magnesium, lithium, boron and zinc bonded to carbon were improved to couple with different electrophilic substrates. Substantial advances and researches were achieved in this field over the last decade that have made cross-coupling reactions to be even effective between alkyl groups by using either a nickel or palladium catalyst [2]. Non-activated alkyl halides are difficult substrates for metal catalyzed C-C coupling reactions because of their reluctance to undergo oxidative addition, and because metal alkyl intermediates are prone to undesired β-hydride eliminations [3].

There has been intensive interest in the development of iron catalysts for C-C bond formation. This is in part due to the push towards the development of inexpensive and environmentally friendly iron complexes as catalysts in cross coupling reactions [4].

1.1 Cross Coupling Reactions.

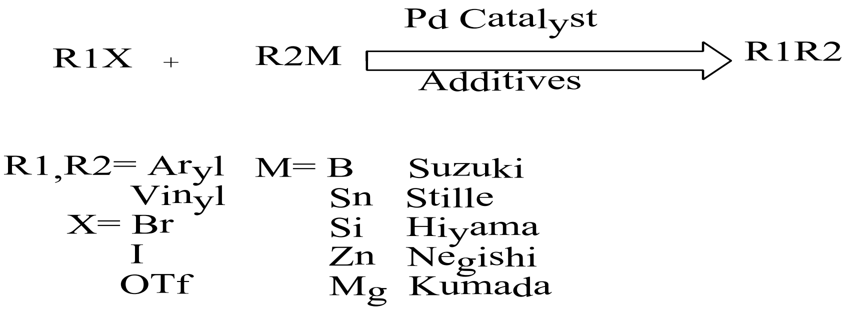


Figure 1.1. General Cross Coupling Reactions

There is an increasing demand for different chemicals with special chemical and physical properties. Humanity wants new and effective medicines that can cure cancer. The electronics and electrical industry are seeking products that can release light or have unique characteristics to emit high quality liquid crystal displays, and the agricultural industry wants substances that can protect and enhance crops. So, the cross coupling reactions play a very important role in preparing a lot of chemical compounds. Tow or more organic moieties are coupled with the aid of a metal catalyst this called cross coupling reactions. Cross coupling reactions characteristically depend on the types of nuceophiles, electrophiles and metal catalysts used.

1.1.1 Suzuki reaction

The Suzuki reaction of aryl and vinyl halides or triflates with aryl or vinyl boronic acids by employing palladium as catalyst is emerging as a favorite, and it has been applied industrially to the production of compounds such as losartan, a Merck antihypertensive drug, this popularity is attributable to a variety of factors, such as commercial availability and easy to synthesize as well as their nontoxic nature and stability to heat and moisture. Furthermore, the boron-containing by-product of the Suzuki cross-coupling can be easily separated from the desired cross coupled compounds [5].

$PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ plus PPh_3 or other phosphine ligands are also effective in cross coupling reactions since they are stable to moisture and readily reduced to palladium(0) to be catalytically active complexes with organometallics or phosphines used for the cross coupling. Palladium complexes that contain bulky phosphines such as tris(2,4,6-tri-methoxypheny1)phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinatively unsaturated palladium species [6,7,8]. One major disadvantage of the Suzuki cross coupling reaction is that stoichiometric amounts of a base, such as sodium ethoxide in ethanol, are required.

To avoid the high cost of the Suzuki reaction and reducing the influence of moisture on the reaction some Suzuki reactions are prepared by using non-coordinated palladium catalysts. However, nickel and iron catalysts are investigated in Suzuki reactions the iron–pyridine complex e.g. can serve as an excellent catalyst for Suzuki–Miyaura coupling reactions [9].

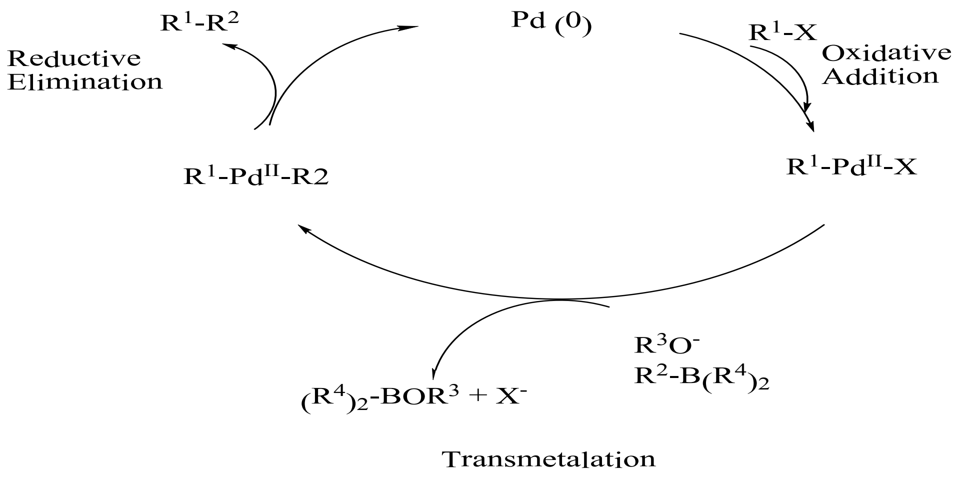


Figure 1.2. Suzuki Reaction

1.1.2 Heck reaction

C-C coupling between aryl or vinyl halides and activated alkenes in the presence of palladium catalysts and a base is referred as the Heck Reaction and is, arguably, one of the most significant carbon - carbon bond-construction processes in synthetic organic chemistry [5,10,11]. A great advantage of the Heck reaction is that the substrate can be a simple olefin that should not be restricted to activated alkene. Moreover, there are many benefits associated with Pd-mediated reactions,[4] particularly ease of scale-up and tolerance to water and/or other functional groups, such as ketones, esters, amides, ethers, or heterocyclic rings, which supply polyfunctional molecules. Thus, it has been applied to a variety of complex natural product syntheses [12]. Palladium is always selected as a catalyst for Heck reaction, but nickel appears to be most promising among the inexpensive transition metals for the replacement of palladium. Nickel is known to be active for Heck reactions and about 500 times cheaper than palladium, but Heck vinylation was reported with Ni catalyst only by a few researchers up to now. $NiCl_2(PPh_3)_2$ is known to catalyze the reaction of aryl halides with olefins [13].

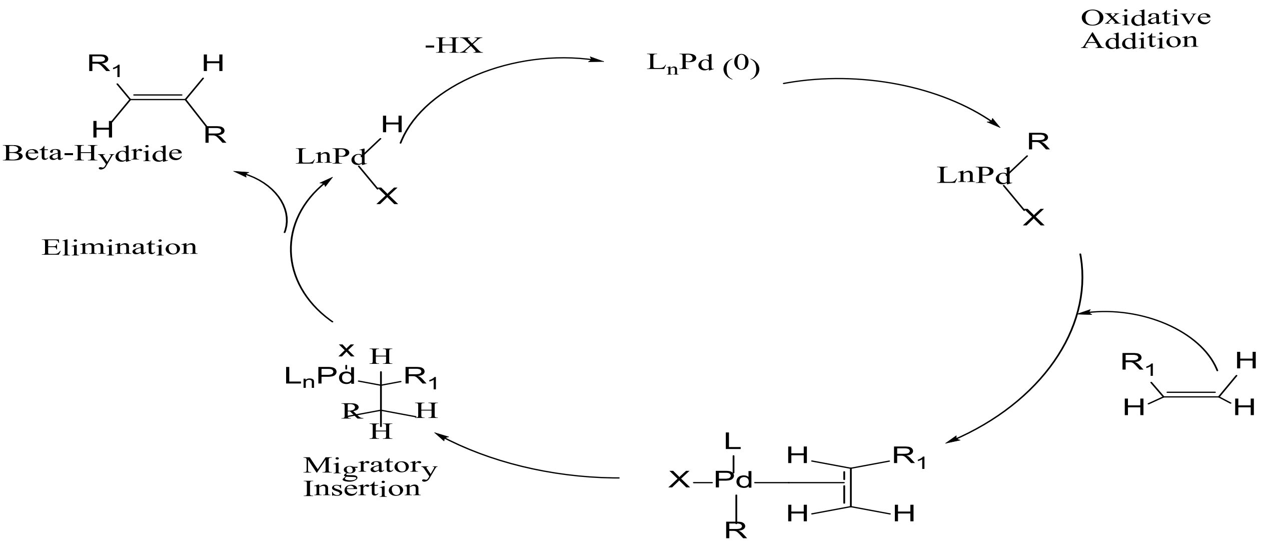


Figure 1.3. Heck Reaction

1.2.3 Hiyama coupling

Palladium-catalyzed C-C bond formation between aryl, alkenyl, or alkyl halides and organosilanes are known as the Hiyama cross coupling reaction. Organosilicon compounds have recently appeared as attractive organometallic donors because of their high stability, nontoxicity and ease of handling as well as their commercial availability. Their inherent resistance to undergo cross-coupling, as a result of the absence of a significant dipole associated with C-Si bond, has been successfully overcome and a variety of heteroatom containing silicon species (halosilanes, siloxanes, polysiloxanes, and silanols) have been shown to couple efficiently to organic electrophiles upon treatment with an appropriate palladium catalyst and a nucleophilic promoter (the Hiyama reaction) [15]. Biaryls play an important role in many functional organic molecules from pharmaceuticals to optoelectronic materials. Nickel catalysed aryl–aryl cross-coupling reactions using arylsilanes with inexpensive aryl chlorides and tosylates have also been reported [16, 17].

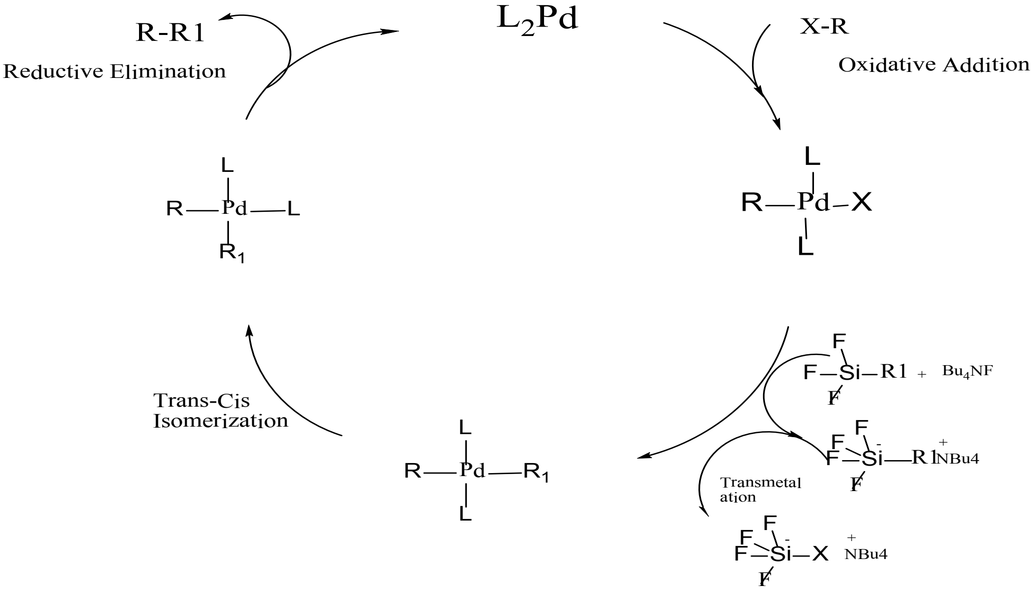


Figure 1.4. Hiyama Reaction

1.2.4 Negishi coupling

Organozinc nucleophiles react with alkyl, aryl and alkenyl halide substrates to affoard significant compounds. The so-called Negishi cross-coupling of organozinc reagents is an important tool for the formation of C–C bonds in the, although this reaction is catalysed by Ni or Pd complexes, the latter have been much more developed, nevertheless, Ni derivatives have become more important in recent years, especially concerning their activity in the formation of alkyl–alkyl bonds [18,19]. Negishi cross coupling reactions are employed to prepare biaryl, alkyl-alkyl and aryl-alkyl compounds. The coupling of heterocyclic organometallic reagents with aryl halides is a used by many in the chemical community to produce coupled products utilized in pharmaceuticals, ligands, and materials [20].

A selective iron-catalyzed cross-coupling of alkyl halides with alkenylzinc reagents is described; primary and secondary alkyl chlorides, bromides, and iodides take part in the Negishi cross coupling reaction to afford the olefins in good to excellent yields in a stereospecific manner [21].

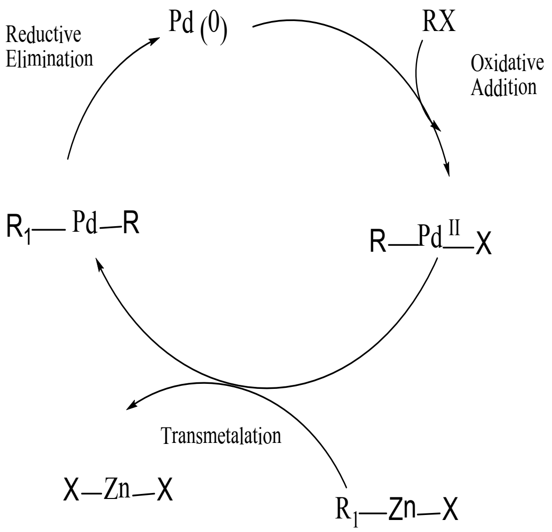


Figure 1.5. Negishi Reaction

1.2.5 Sonogashira Coupling

The Sonogashira cross-coupling of aryl halides and terminal alkynes or arylenes is a key step for the synthesis of Csp^3- Csp^2 bonds. Functionalized alkynes are important building blocks for the formation of biologically active molecules and, surprisingly, are common structural features of natural products that extracted from plants and marine organisms [22]. Therefore, the Sonogashira reaction is frequently used as a valuable tool in the synthesis of pharmaceuticals such as the enediyne antibiotics or the contraceptive pill [23].

Sonogashira coupling is also employed for producing liquid crystals, polymers, and materials with particular optical and electronic properties [22]. The reaction generally takes place in organic solvents such as benzene, toluene and THF. A base is required, which is usually an amine such as triethylamine, diethylamine or diisopropylethylamine. The most widely used catalysts are $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ in conjunction with copper(I) iodide [22,24,25]. The enhancement of improved procedures in which low cost and more sustainable catalysts are used has remained an urgent target. In this respect, iron catalysts attract attention of chemists as valuable alternatives to those transition metals used in Sonogashira coupling reactions [26, 27].

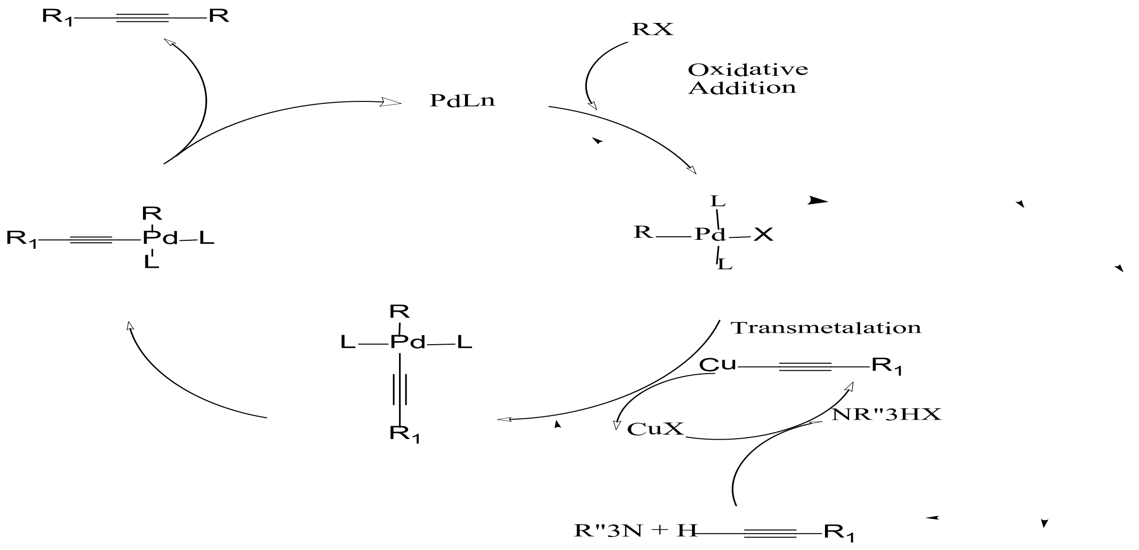


Figure 1.6. Sonogashira Reaction

1.1.6 The Kumada-Corriu-Tamao Coupling

The reaction of an organic electrophile substrate being coupled to a Grignard nucleophile under an inert atmosphere was discovered at the very early stage of modern cross-coupling chemistry [28]. Grignard reagents remain desirable coupling partners owing to the ease of their preparation and many of them are commercially available. Furthermore, many other organometallic coupling nucleophiles are synthesized from the corresponding Grignard reagents [29,30] .

The catalytic activity of nickel complexes depends strongly upon the nature of the ligands. Generally speaking, bidentate phosphines as ligands show much higher catalytic activity than monodentate ones; the performance of the bidentate phosphine ligands in cross coupling reactions decreases roughly in the sequence dppp > dmpf > dppe > dppm [31]. Progress has been made during the last several years on the coupling of aryl and alkyl halides with sp^3 carbon nucleophiles. Fürstner et al. developed an iron catalyzed Kumada coupling of aryl chlorides and activated aryl and heteroaryl tosylates with alkylmagnesium chlorides, similar processes based on cobalt and an iron-catalyzed coupling of aryl Grignard reagents with vinyl halides were published by Knochel and coworkers [32,33,34].

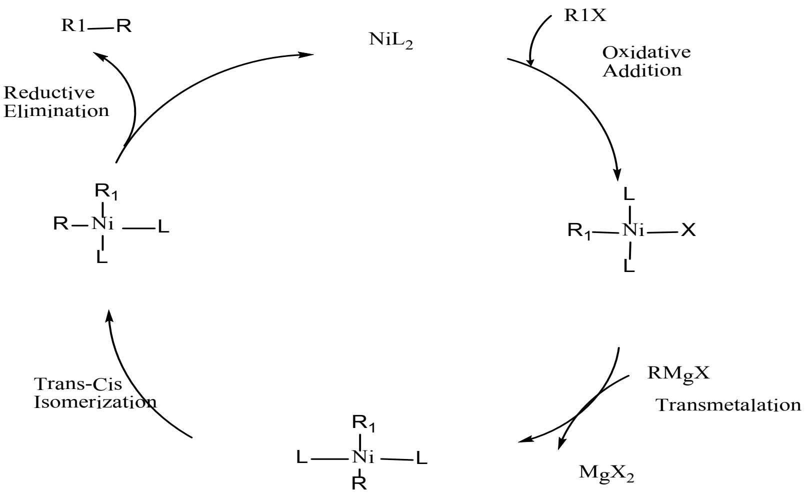


Figure 1.7. The Kumada-Corriu-Tamao Reaction

1.2 General Aspects of Cross Coupling Mechanisms

Palladium, nickel and iron catalyzed cross coupling reactions are generally described as a combination of two organic groups from an organometallic nucleophile such as e.g. a Grignard reagent, and elctrophiles such as alkyl halides. Catalytic cycles consist of three main steps: oxidative addition of C-X to the metal center, transmetalation to produce diorganometal intermediates and finally reductive elimination to afford the coupled product and to regenerate the catalytically active species.

1.2.1 Oxidative Addition

A number of factors determine the capability of transition metals to undergo oxidative addition, the transition metal must be reduced to a low valent state, behaving either as a nucleophile or a reducing agent in which electrons are removed from the electron-rich metal center, unlike the group 1 and 2 metals that react in bulk, group 8 and 10 transition metals must be in the atomic state, usually by the formation of complexes by ligands, generally, the reactivity of group 8 and 10 metals toward oxidative addition increases in going from right to left in the periodic table, in going down a given group in the table, and in decreasing the initial oxidation number, the coordination number of the metal and the nature of ligands play an important role in oxidative addition processes, in order for oxidative addition to occur, producing a vacant site to give a coordinatively unsaturated species may be favourable (dissociative mechanism) [35].

Palladium complexes are effective catalysts for a large number C-C coupling reactions, such as nucleophilic aromatic and vinylic substitutions, arylation of olefins, etc. All these catalytic reactions are considered to proceed via chain cycles, these cycles are initiated by oxidative addition of zerovalent palladium complex by an organic halide substrate or pseudo halide (noted RX in the following), zerovalent palladium may be formed *in situ* by spontaneous endergonic ligand dissociation from stable zerovalent complex precursors or by reduction of a stable divalent palladium complex, if the reductive pathway is used the reducing agent in these cases usually is an organometallic species such as a Grignard reagent or an organometallic compound in general, like the nucleophile itself, or a phosphine when is an oxygen containing ligand such as acetate, the reduction can also be performed electrochemically [36-42].

Ligands L having strong electron donating abilities and organo halides having an R–X bond that can be considered as ‘‘electron-poor’’ generally promote oxidative addition reactions, the concerted and S_N2 mechanisms are used to explain the oxidative addition process during cross coupling reaction, both mechanisms consider palladium(0) as a nucleophile and the organohalide as an electrophile, $C(sp^3)$–X bonds are normally much less reactive than $C(sp^2)$–X bonds in oxidative addition reactions [43-44].

1.2.2 Transmetallation

Concerning transmetallation reactions, it is assumed that the *trans*-configuration of the starting complex is preserved to give a *trans*-$[PdR_1R_2L_2]$ intermediate, since the reductive elimination of R_1-R_2 is well established to occur on *cis* derivatives, a rapid isomerization of *trans*- to *cis*-$[PdR_1R_2L_2]$ needs to be postulated. An important additional problem with mechanisms based on ligand dissociation is that this type of substitution is rare for Pd(II), the observed dependence on the ligand concentration has recently been described within the framework of an associative mechanism. Importantly, transmetallation process includes an associative L-for-R_2 substitution, through transition state, to afford a bridged intermediate which directly produces an intermediate with a *cis*-R^1/R^2 arrangement. So this reaction sequence seems to be more likely compared to a rearrangement of *trans*- to *cis*-$[PdR^1R^2L_2]$, in both cases the resulting complex *cis*-$[PdR^1R^2L_2]$ will immediately eliminate the organic product R^1-R^2 [45].

1.2.3 Reductive Elemination

Reductive elimination is the reverse of oxidative addition. It is a very important process that is often the last step in catalytic cycles involving the combination of two organic moieties together by the formation of the new C-C bond as well as the regeneration of the catalytically active species.

The coupling reaction of organic compounds catalyzed by transition metals is a valuable method of assembling carbon- carbon bonds, the final step of which requires the elimination of the organic partners from the transition metal, reductive elimination can take one or more paths, categorized according to the mechanism (and products), including heterolytic as well as homolytic or concerted a–elimination, β–elimination, 1,l-reductive elimination, and dinuclear elimination, in the 1,l reductive elimination reaction, the formal oxidation state and the coordination number of the metal are reduced by two; bond breaking is accompanied by bond making, the reductive elimination reaction frequently follows an oxidative addition reaction, and this combination, oxidative addition-reductive elimination is responsible for both stoichiometric and catalytic coupling reactions via transition metals, particularly those of group 8 [46].

1.3 Nickel and Palladium Catalyzed Cross Coupling Reactions

The parallel synthesis of key precursor components and then linking them together at a late stage in the process is a widely used approach in modern synthetic chemistry. This has only been possible due to the advances in coupling chemistry, many of them related to the use of palladium catalysis. The father of palladium-catalysed coupling chemistry is generally considered to be Professor Richard Heck, although other reports on organometallic coupling reactions had already been published before. Nevertheless, it was through his work that the Pd-catalysed reactions became widely known and applied [47].

Since Corriu and Kumada reported in 1972 that the cross coupling of Grignard reagents with aryl and alkenyl halides could be catalyzed by nickel-phosphine complexes, a wide variety of such coupling reactions have been improved and some of them have achieved great success in synthetic chemistry, the cross-coupling reaction has been extended to involvement of aryl and alkenyl ethers, sulfides, selenides, and phosphates [48,50]. Palladium and nickel complexes, in particular, boast high catalytic activity for a wide range of alkyl and aryl halide substrates and high functional-group tolerance. Chelating phosphine ligands sometimes impart great effects on homogeneously performed reactions catalyzed by transition metals in general and on palladium catalyzed reactions in particular, tentative explanations have been given, although definite answers for this important effect are generally not available. For example, the complex Pd(dippp)$_2$, [dippp = l,3-bis(diisopropy1phosphino)propane is an excellent catalyst for the carbonylation, formylation and reduction of aryl chlorides, whereas complexes of monodentate phosphines are much less reactive under similar conditions [51]. Moreover, the chelate ring size has a dramatic effect on reactivity. Thus, reducing or increasing the size of the chelating ligand by one carbon, i.e. utilizing the complexes Pd(dippe)$_2$ and Pd(dippb)$_2$ [dippe = 1,2-bis(diisopropy1phosphino)-ethane; dippb = 1,4-bis(diisopropylphosphino)-butane], results in a substantial reduction of catalytic activity, also, complexes of chelating phosphines of the same chelate size as dippp but of lower basicity are much less reactive [52-53].

Palladium and nickel complexes containing phosphine ligands are among the most successful and widely used catalyst precursors for the coupling of sp^2 carbons. Bulky, electron-rich tertiary alkyl phosphines are particularly effective in this respect. Their success is explained by reference to the catalytic cycle. The increased electron density imparted to the metal centre by the electron-donating phosphine assists in the cleavage of an Ar-X bond in the oxidative addition elementary step, while the steric bulk of the ligand promotes the reductive elimination of the Ar-Ar' coupling product following transmetallation with M-Ar'. While the Heck reaction, the catalytic amination and the CuI-free Sonogashira reaction do not, strictly speaking, involve a transmetallation step, they are generally included in discussions of cross-coupling chemistry since their catalytic cycles possess essentially the same features [54-55].

1.4 Iron Catalyzed Cross Coupling Reactions

The iron-catalyzed sp^3-sp^2 cross-coupling between an alkyl Grignard reagents and alkenyl bromides was described in 1971 by KOCHI. Cross-coupling reactions catalysed by iron complexes are one of the promising research areas for the formation of C-C bonds, because of the cheapness of iron and it's more nature friendly properties compared to palladium or nickel [56-58].

Typical reaction partners are Grignard reagents, though organomanganese, -copper, and -zinc derivatives have also been employed in certain cases. Such iron-catalyzed processes occur very rapidly even at low temperature and therefore are distinguished by broad functional group compatibility. Recent developments in carbon-heteroatom bond construction and studies relevant to the catalytically activity of the catalyst in situ generated and structurally defined “low-valent” iron catalysts are presented [59].

$FeCl_2$ reacts with 4 equiv of R-MgX to produce a new species of the formal composition $[Fe(MgX)_2]$, an “inorganic Grignard reagent”, which is highly soluble in ethereal solvents such as THF. The available information suggests that $[Fe(MgX)_2]$ consists of small clusters incorporating magnesium and iron centers that are connected via fairly covalent intermetallic bonds. Fe(0), is formed but leads to species bearing a *formally negative charge at iron*, such highly nucleophilic entities lacking any stabilizing ligands are able to oxidatively add to aryl halides. The resulting organometallic iron compounds (formally Fe(0) are again alkylated by the excess of the Grignard reagent in analogy to the case of the elementary steps passed through during the initial formation of $[Fe(MgX)_2]$ from $FeCl_2$ and RMgX. Subsequent reductive coupling of the organic ligands should then form the desired product and regenerate the propagating Fe(-II) species [60-63].

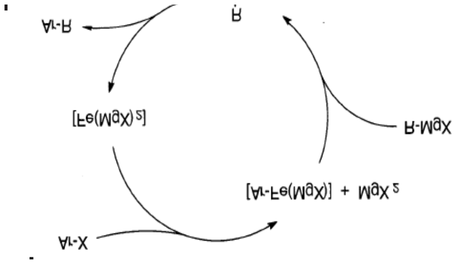


Figure 1.8 Iron Catalyzed Cross Coupling Mechanism (Ref. 60)

1.5 sp^3-sp^2 Kumada-Corriu-Tamao Coupling

To carry out sp^3- sp^2 coupling in terms of a Kumada-Corriu-Tamao coupling reaction, unique and particular conditions are required e.g. additives such as TMEDA and a catalyst exhibiting pincer ligands. The stable and easy to handle Ni(II) complex [(MeNN$_2$)Ni-Cl] ((MeNN2 is an amidobis- (amine) ligand)) efficiently catalyzes the sp^3-sp^2 Kumada-Corriu-Tamao coupling of nonactivated and β-H containing alkyl halides with aryl and heteroaryl Grignard reagents [64]. Nevertheless, the protocol optimized for alkyl-alkyl Kumada-Corriu-Tamao coupling was inefficient for alkyl-aryl coupling. Amine ligands and additives such as TMEDA were widely used to promote alkyl-aryl Kumada-Corriu-Tamao coupling [65-67], especially in Fe-catalyzed systems.

The high reactivity of Grignard reagents, however, results in poor compatibility with functional groups. Subsequently, alternative coupling protocols employing less reactive organometallic reagents such as Zn, B, Sn, and Si nucleophiles were developed [68].

Grignard nucleophiles are seldom used for the coupling of functionalized organic halides. Even so, Grignard reagents remain desirable coupling partners because they are economical and easy to synthesize, and many of them are commercially available. Thus, the Kumada-Corriu-Tamao coupling provides more direct access to the same desired products [69]. Improvements of functional group compatibility with Grignard reagents in the Kumada-Corriu-Tamao coupling will encourage the employing of this atom-economic coupling reaction in synthesis [70].

1.6 Fluorinated Liquid Crystals

The investigation of liquid crystals started in 1888 when an Austrian botanist, Friedrich Reinitzer observed two characteristic melting points in the compound cholesteryl benzoate. A German physicist, Otto Lehmann later emphasized this discovery and coined the name liquid crystal. Liquid crystals are known as the fourth state of matter and exhibit phases, which flow like a liquid but also have properties of crystalline solids. The molecules in crystals are ordered (positional and orientational) whereas in the liquid they are not [71-72].

In crystals the molecules are held in particular positions by intermolecular forces that need not be the same in all directions, the molecules vibrated by heating to overcome the weaker organizing forces first but they remain bound by the stronger forces and lose some or all of their positional order, but orientational order is existing, the molecular axes of the individual molecules remain relatively aligned and parallel to each other leading to a preferred direction in space, liquid crystals are usually anisotropic materials and the physical properties of the bulk system change with the average alignment of the director in which large alignment tends towards anisotropic materials while small alignment tends towards isotropic materials [73]. In the case of liquid crystals, the transition from the isotropic liquid phase to a crystal phase is not a single step but occurs by one or more intermediary steps [74].

The use of organofluorine compounds has afforded much research effort. The replacement of hydrogen atoms by fluorine confers to the resulting material unusual and peculiar properties which allow their use as good precursors with many applications: surface coating, fire retardants and biomedicine, the introduction and the choice of the fluorine atom position within liquid crystal systems allow formation of materials which present a considerable technological interest for display or non-display applications: the nematics and smectics [75, 76]. The involvement in the nematogenic devices is generally obtained from the introduction of fluorine on to the rigid core so-called fluoro-substituents [77]. In fact, the properties required are those for materials employed in the electronic industry: physical and chemical stability, wide mesomorphic temperature range, low melting point, low viscosity and low conductivity. Fluorinated systems have become a more attractive because of having low conductivities and viscosities. Furthermore, the controlled choice of the position of fluoro-substituents allows tailoring of appropriate dielectric anisotropies for commercial applications [78]. The use of fluorine within liquid crystal materials can prove useful as short term prospects as good alternatives to overcome defaults or instabilities asserted in hydrocarbon series, in fact the wide temperature range of mesomorphism is crucial point for use as liquid crystal, with enantiotropy and reproductibility during the phase transition phenomena, the perfluorinated species are chemically stable [79].

1.7 Thiophenes

Thiophenes are common in natural products and constitute attractive targets in pharmaceutical and fine chemistry because of their potential biological activity [80]. Organic molecules bearing heteroaromatic moieties have attracted great attention recently as potential advanced materials. In particular, oligothiophenes have been a major concern of excellent conductivity and electroluminescent behaviors [81].

In the field of polyconjugated organic materials, polythiophenes (poly(3-cyclohexylthiophene) have received increasing attention for their comparatively large chemical and physical stability, variable optical properties and their electrical conductivity in the oxidized state[82-83] or deviations from coplanarity [84], however reduce the conjugation length, thus increasing the band gap and decreasing the nonlinear optical susceptibility. The major drawbacks in the handling of the unsubstituted polyheterocycles, insolubility and infusibility, have been overcome by the polymerization of 3-alkyl-substituted monomers via Grignard coupling [85], chemical oxidation with $FeCl_3$ [86], or electrochemical oxidation, the resulting polymers being soluble in common organic solvents (e. g. chloroform or toluene), the substituent may limit the amount of β-coupling by blocking the 3- (and partially the 4-) position, but induces additional steric interaction between adjacent subunits and may force the thiophene rings out of a coplanar conformation [87].

2. Experimental

Preparation of Palladium and Nickel Complexes by Employing Dppm, Dppe, and Dppp Ligands.

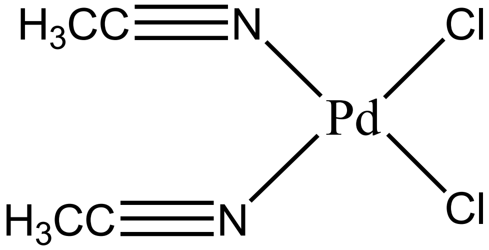
There are several methods to prepare bis-diphenylphosphino alkane palladium(II) and nickel(II) Complexes. An improved method for the preparation of nickel and palladium complexes containing the ligands diphenylphosphino methane, diphenylphosphino ethane and diphenylphosphino propane, based on the interaction between solid $[MCl_2(MeCN)_2]$ and a solution of the appropriate ligand in CH_2Cl_2, has been developed.

General Method for the Preparation of $PdCl_2(MeCN)_2$ and $NiCl_2(MeCN)_2$.

General remarks

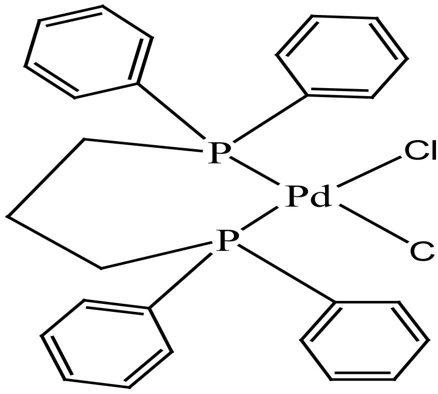
CH_2Cl_2 and light petroleum (b.p. 40-60°C) were purified by distillation in an argon atmosphere. Glass ware was cleaned well and dried in an oven. All nickel and palladium complexes were kept in tightly closed Schlenk tubes under argon.

2.1.1 Preparation of $PdCl_2(MeCN)_2$.



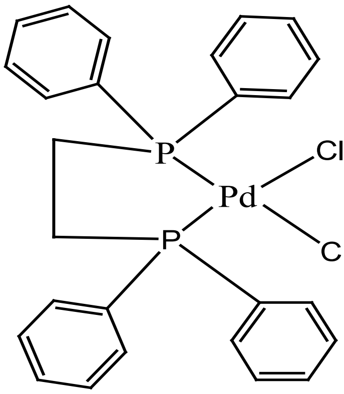
Well-powdered $PdCl_2$ (2 g), in a mortar, was mixed with MeCN (10 cm^3) and stirred slowly for 24 hours in a closed Schlenk tube. The mixture was refluxed for another 24 hours under argon, cooled down to room temperature and the excess of acetonitrile removed under reduced pressure. The yellow pellets formed were crushed and dried *in vacuo* Schlenk. The percentage yield exceeded 98%. *Physical Data of* $PdC_4H_6Cl_2N_2$. Elemental analysis ($PdCl_2C_4H_6N_2$, Mw = 259.43) [%]: Calcd.: C 18.53, H 2.33, N10.80; Found: C 18.56, H 2.26, N10.76.

2.1.2. Preparation of $PdCl_2$(dppp)



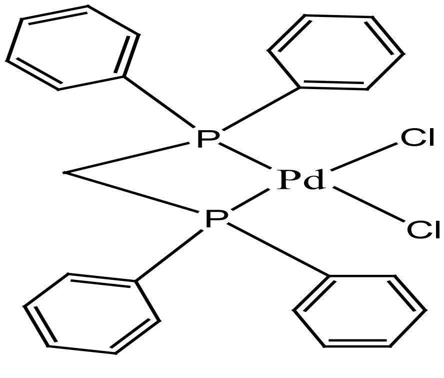
One mmol of diphenylphosphino propane (412 mg) was dissolved in 25ml CH_2Cl_2 under an argon environment by stirring for 15 minutes. 1.2 mmol of well powdered solid [$PdCl_2(MeCN)_2$] (311mg) was added to this suspension and stirring was continued for 20 min. The white product partly precipitated. After addition of light light petroleumand stirring for another 20 min, the sediment formed was filtered, washed with light light petroleum and left to dry under reduced pressure for 40 min. The percentage yield reached 96%. *Physical data of of $PdCl_2$(dppp):* MS (EI): 555 $[M - Cl]^+$, 519 $[M – 2Cl]^+$, 412 $[M – PdCl_2]^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: $\delta = 14.99$. Elemental analysis ($PdC_{27}H_{26}Cl_2P_2$, Mw = 589) [%]: Calcd : C 55.00, H 4.44; Found: C 56.36 , H 4.33.

2.1.3. Preparation of $PdCl_2$(dppe)



1 mmol of diphenylphosphino ethane (398 mg) was dissolved in 25ml CH_2Cl_2 under argon by stirring for 15 minutes. 1.2 mmol of well powdered solid [$PdCl_2(MeCN)_2$] (311 mg) was added to this suspension and stirring was continued for 20 min. The product partly precipitated. After addition of light petroleum and stirring for another 20 min, the light yellow suspension formed was filtered, washed with light petroleumand left to dry under reduced pressure for 40 min (yield: 95%. *Physical data of of $PdCl_2$(dppe):* MS (EI) : 575 $[M - Cl]^+$, 539 $[M - Cl]^+$, 519 $[M – 2Cl]^+$, 398 $[M – PdCl_2]^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: $\delta = 67.34$. Elemental analysis ($PdC_{26}H_{24}Cl_2P_2$, Mw = 575) [%]: Calcd : C 55.00, H 4.44; Found : C 49.99, H 3.66.

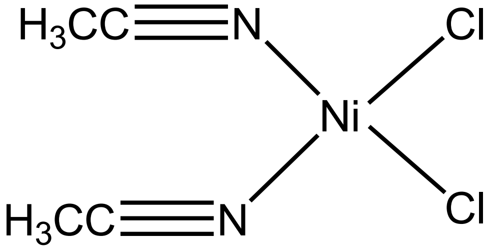
2.1.4. Preparation of $PdCl_2$(dppm)



1 mmol of diphenylphosphino methane (384 mg) was dissolved in 25ml CH_2Cl_2 under argon in a Schlenk tube by stirring for 15 min. 1.2 mmol of well powdered solid [$PdCl_2(MeCN)_2$] (311mg) was added to this suspension and stirring was continued for 20 min. The yellow product partly precipitated. After addition of light light petroleum and stirring for

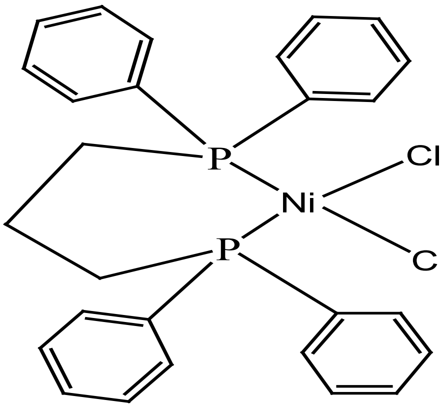
another 20 min, the precipitate formed was filtered, washed with 20 ml of light light petroleumand left to dry under reduced pressure for 40 min (yield: 96%). *Physical data of $PdCl_2(dppm)$:* MS (EI) : 526 [M - Cl]$^+$, 449 [M – (Cl + phenyl)]$^+$, 384 [M – $PdCl_2$]$^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: δ = - 50.76. Elemental analysis ($PdC_{25}H_{22}Cl_2P_2$, Mw = 561) [%]: Calcd: C 53.46, H 3.95; Found: C 50.57, H 3.43.

2.1.5. Preparation of $NiCl_2(MeCN)_2$.



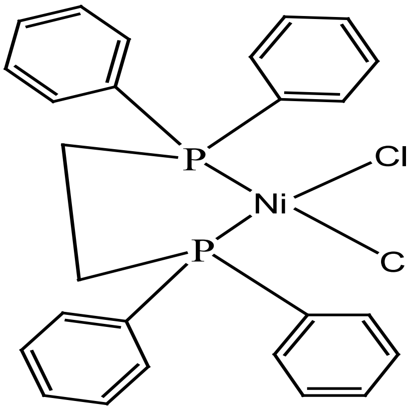
Well-powdered $NiCl_2$ (2 g), in a mortar, was mixed with MeCN (10 cm^3) and left under argon in a Schlenk tube for 24 h. The mixture was periodically stirred. Afterwards the solution was refluxed for additional 24 hours under argon, cooled down to room temperature, filtered from the excess of acetonitrile and dried under reduced pressure. The light green pellets formed were crushedand dried *in vacuo*(yield: >98%). *Physical data of $NiCl_2(CH_3CN)_2$.* MS (EI) : 198 [M – CH_3]$^+$, 128 [M – $(CH_3CN)_2$]$^+$, 41 [M – $NiCl_2$]$^+$. Elemental analysis ($NiC_4H_6Cl_2N_2$, Mw = 211) [%]: Calcd.: C 21.9, H 2.86; Found: C 19.49, H 2.50.

2.1.6. Preparation of NiCl$_2$(dppp)



1 mmol of diphenylphosphino propane (412 mg) was dissolved in 25ml CH_2Cl_2 under argon by stirring for 15 minutes. 1.2 mmol of well powdered solid [NiCl$_2$(MeCN)$_2$] (211mg) was added to this suspension and stirring was continued for 20 min. After addition of light light petroleumand stirring for 20 min, the light orange precipitate formed was filtered, washed with light light petroleum and left to dry under reduced pressure for 40 min(yield: 94%). *Physical data of NiCl$_2$(dppp):* MS (EI): 542 $[M]^+$, 505 $[M - Cl]^+$, 430 $[M - Phenyl + Cl]^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: δ= 35.99. Elemental analysis ($NiC_{27}H_{26}Cl_2P_2$, Mw = 542) [%]: Calcd.: C 58.83, H 4.58; Found: C 58.25, H 4.16.

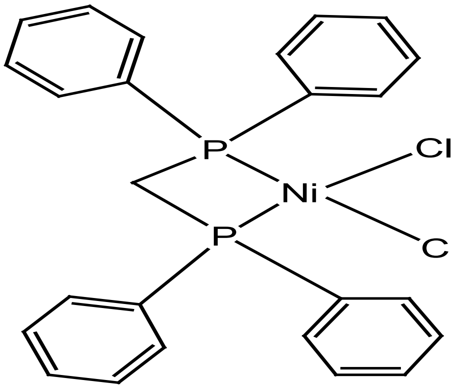
2.1.7. Preparation of NiCl$_2$(dppe)



1 mmol of diphenylphosphino ethane (398 mg) was dissolved in 25ml CH_2Cl_2 under argon by stirring for 15 minutes. 1.2 mmol of well powdered solid [NiCl$_2$(MeCN)$_2$] (211mg) was added to this suspension and stirring was continued for 20 min. After addition of light

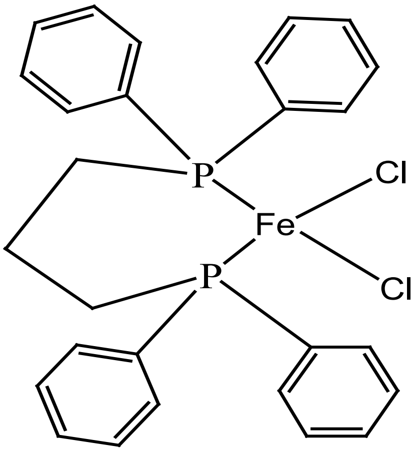
petroleum and stirring for 20 min, the orange precipitate formed was filtered, washed with light petroleum and left to dry under reduced pressure for 40 min (yield: 94%). *Physical data of NiCl$_2$(dppe):* MS (EI): 528 $[M]^+$, 493 $[M - Cl]^+$, 384 $[M - PdCl_2]^+$. ^{31}P NMR (200.13, CDCl$_3$) [ppm]: $\delta = 60.93$. Elemental analysis ($NiC_{26}H_{24}Cl_2P_2$, Mw = 528) [%]: Calcd.: C 59.14, H 4.58; Found: C 58.25, H 4.16

2.1.8. Preparation of NiCl$_2$(Dppm)



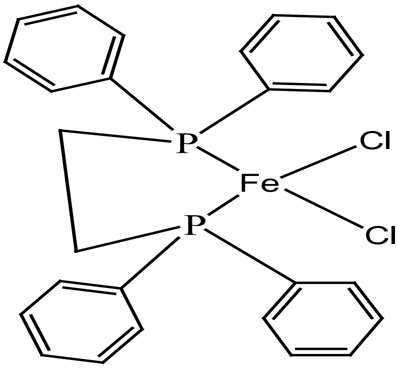
1 mmol of diphenylphosphino methane (384 mg) was dissolved in 25ml CH_2Cl_2 under argon by stirring for 15 minutes. 1.2 mmol of well powdered solid $[NiCl_2(MeCN)_2]$ (211mg) was added to this suspension and stirring was continued for 20 min. After addition of light petroleum and stirring for 20 min, the red precipitate formed was filtered, washed with light petroleum and left to dry under reduced pressure for 40 min (yield: 94%). *Physical data of NiCl$_2$(dppm):* ^{31}P NMR (200.13, CDCl$_3$) [ppm]: $\delta = -42.92$. Elemental analysis ($NiC_{25}H_{22}Cl_2P_2$, Mw = 514) [%]: Calcd.: C 58.42, H 4.31; Found: C 56.35, H 3.97.

2.1.9. Preparation of $FeCl_2$(dppp)



To a suspension of $FeC1_2$ (500 mg ,3.9 mmol) in toluene (50 mL) was added dppp (1648 mg, 4 mmol). After the suspension was stirred for 4 h to dissolve $FeCl_2$ and dppp in toluene completely, the solution was refluxed for 24 hours. The pale off white microcrystalline solid was filtered off, washed with toluene and dried under vaccum. *Physical data of $FeCl_2$(dppp):* MS (EI): 538 $[M]^+$, 503 $[M -Cl]^+$, 412 $[M - PdCl_2]^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: δ = 35.62. Elemental analysis ($FeC_{27}H_{26}Cl_2P_2$, Mw = 539) [%]: Calcd.: C 60.14, H 4.86; Found: C 55.48, H 4.24.

2.1.10. Preparation of $FeCl_2$(dppe)



To a suspension of $FeC1_2$ (500 mg, 3.9 mmol) in toluene (50 mL) was added dppe (1592 mg, 4 mmol). After the suspension was stirred for 4 h to dissolve $FeCl_2$ and dppe in toluene completely, the solution was refluxed for 24 hours. The pale off white microcrystalline solid was filtered off, washed with toluene and dried under vaccum. *Physical data of $FeCl_2(dppe)$:* MS (EI): 524 $[M]^+$, 489 $[M - Cl]^+$, 398 $[M - PdCl_2]^+$. ^{31}P NMR (200.13, $CDCl_3$) [ppm]: δ = 37.01. Elemental analysis ($FeC_{26}H_{24}Cl_2P_2$, Mw = 525) [%]: Calcd.: C 59.46, H 4.61; Found: C 58.25, H 4.16.

2.2. Cross Coupling Reactions

General remarks

All reactions were carried out in an argon atmosphere using standard Schlenk techniques. Solvents were dried according to common procedures and distilled under argon.

2.2.1. Synthesis of Cyclohexyl Magnesium Bromide

225 mg (9.3 mmol) of Mg were suspended in 40 ml of anhydrous THF. A solution of cyclohexyl bromide (1304 mg , 8 mmol) in anhydrous THF was dropwise added to the suspension of magnesium in THF. Refluxing of the reaction mixture was continued for one hour to finish the reaction. During the reaction the colour changed from colourless to grey. After cooling down to room temperature the Grignard solution was filtered under argon to give a clear light green solution and was kept in a Schlenk tube under argon for further use.

2.2.2. Synthesis of Cyclohexyl Magnesium Bromide LiCl adduct

225 mg (9.3 mmol) of Mg were suspended in 40 ml of anhydrous THF together with 380 mg (9mmol) of anhydrous LiCl. Stirring was continued until the entire amount of LiCl was dissolved. A solution of cyclohexyl bromide (1304 mg , 8 mmol) in 10 ml of anhydrous THF was dropwise added to the suspension containing magnesium and LiCl. Refluxing of the reaction mixture for one hour was continued to finish the reaction. During the reaction its colour changed from colourless to grey. After cooling down to room temperature, the Grignard solution was filtered and kept in a Schlenk tube under argon for further use.

2.2.3. Synthesis of Cyclohexyl Magnesium Bromide LiBr adduct

225 mg (9.3 mmol) of Mg were suspended in 40 ml of anhydrous THF together with 780 mg (9mmol) of LiBr. After LiBr was completely dissolved a solution of cyclohexyl bromide (1304 mg , 8 mmol) in 10 ml of THF was dropwise added to the resulting suspension. Refluxing of the reaction mixture is continued for one hour to finish the reaction. The colour of the reaction mixture changed from colourless to grey . After cooling down to room temperature, the Grignard solution was filtered and kept in a Schlenk tube under argon for further use.

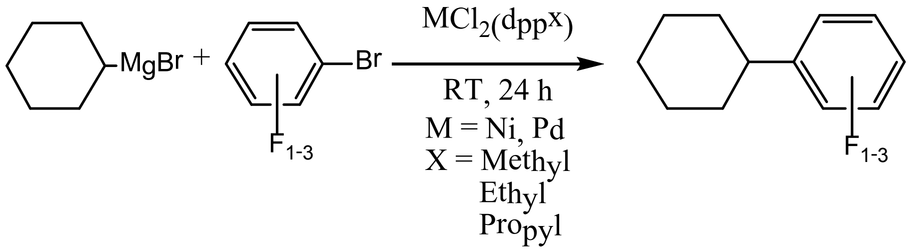
2.2.4. Titration of Grignard Solution.

Prepared Grignard reagents were titrated by back titration before being employed in cross coupling reactions. This was carried out by using sodium hydroxide (1M) and sulphuric acid (0.06M) with methyl red as an indicator. Firstly 1M NaOH was prepared carefully, which then was employed to titrate the sulphuric acid solution to exactly determine its concentration. Then 10 ml of H_2SO_4 was added to 1 ml of Grignard reagent. This solution was then stirred at 40°C for 15 min. The resulting solution then is titrated with NaOH to determine the concentration of the Grignard reagent. There are differences in molarity among various batches of prepared Grignard reagents, however, most of the determined molarities lie in a range between 0.20 - 0.25 $molL^{-1}$.

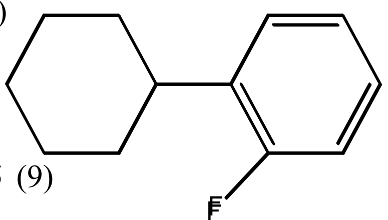
2.3. Cross Coupling Reactions

All manipulations were carried out under an argon atmosphere using standard Schlenk techniques. Tetrahydrofuran was dried by refluxing it over sodium for 48 hours. The catalysts used to prepare the cross coupled products are $NiCl_2$(dppm), $NiCl_2$(dppe), $NiCl_2$(dppp), $PdCl_2$(dppm), $PdCl_2$(dppe) and $PdCl_2$(dppp).

2.3.1. Synthetic procedure for the cross coupling of cyclohexyl magnesium bromide with fluorinated bromobenzene derivatives



In a typical experiment a dry and argon-flushed 50-mLSchlenk tube, equipped with a magnetic stirring bar, was charged with the respective fluorinated bromobenzene derivative (0.5 mmol, 88 mg for monosubstituted, 97 mg for disubstituted and 105 mg for trisubstituted derivatives) and 3mol% of the respective catalyst dissolved in 15 ml of THF ($NiCl_2$(dppm): 7.7 mg, $NiCl_2$(dppe): 7.9 mg, $NiCl_2$(dppp): 8.1 mg, $PdCl_2$(dppm): 8.4 mg, $PdCl_2$(dppe): 8.6 mg, $PdCl_2$(dppp): 8.8 mg). The solution was stirred for 5 min, then cyclohexyl magnesium bromide or the respective LiCl or LiBr adduct (0.8 mmol, 4 ml of a 0.2M Grignard reagent) was quickly added to the reaction mixture and stirring vigorously at room temperature was continued for 24 hour. After hydrolysis with diluted hydrochloric acid, the organic layer and ether extracts from the aqueous layer were combined, washed with water, saturated NaCl solution, dried over $MgSO_4$ and filtrated through a pad of silica. Concentration under reduced pressure followed by column chromatography (hexane : diethyl ether, *v/v* = 100 : 1) afforded the respective coupling products as light yellow oily compounds. All coupling products were then characterized by GC-MS, HRMS, 1H-, 13C- and 19F-NMR spectroscopy as well as by elemental analysis.



Spectroscopical data of 1-cyclohexyl-2-fluoro-benzene,: MS (EI) [(m/z, %)]: 178 (3) [M^+], 160 (100) [MH^+-F], 131 (12) [$C_{10}H_{11}^+$], 128 (13) [$C_{10}H_8^+$], 117 (69) [$C_9H_9^+$], 104 (99) [$C_8H_8^+$], 91 (60) [$C_7H_7^+$], 83 (6) [$C_6H_{11}^+$], 77 (19) [$C_6H_5^+$], 65 (9) [$C_5H_5^+$], 55 (5) [$C_4H_7^+$], 41 (23) [$C_3H_5^+$] . HRMS $C_{12}H_{15}F$ (178.11578): 178.11551, Δ= 0.27 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$): δ = 0.83 – 1.88 (m, 10H, CH_2), 2.39 – 2.50 (m, 1H, CH), 7.04 – 7.39 (m, 4H, CH_{ar}). ^{13}C NMR (100.62 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.2 (CH_2), 26.9 (CH_2), 34.5 (CH_2) , 44.6 (CH), 115.2 (C_{ar}H, d, *J* = 22 Hz), 123.9 (C_{ar}H, d, *J* = 4 Hz), 127.0 (C_{ar}H, d, *J* = 8 Hz), 127.6 (C_{ar}H, d, *J* = 6 Hz), 134.5 (C_{ar}, d, *J* = 15 Hz), 160.6

(C_{ar}, d, J = 244 Hz). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -120.1. Elemental analysis ($C_{12}H_{15}F$, M = 178.25 g mol^{-1}) [%]: Calcd: C 80.86, H 8.48; Found: C 79.12, H 9.12.

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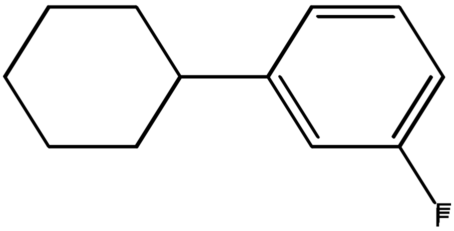
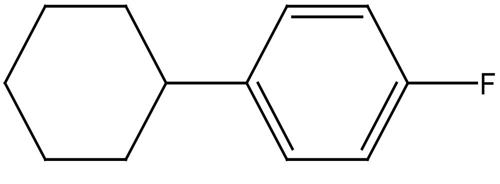
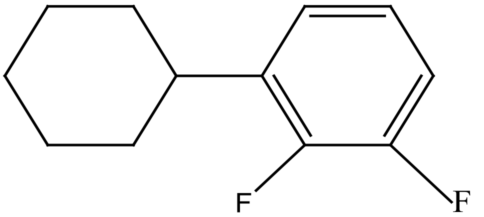


Spectroscopical data of 1-cyclohexyl-3-fluoro-benzene, MS (EI) [(m/z, %)]: 178 (100) [M^+], 160 (21) [MH^+-F], 135 (52) [$C_{10}H_{15}^+$], 122 (98) [$C_9H_{14}^+$], 109 (52) [$C_8H_{13}^+$], 104 (13) [$C_8H_8^+$], 96 (12) [$C_7H_{12}^+$], 83 (16) [$C_6H_{11}^+$], 65 (9) [$C_5H_9^+$], 55 (5) [$C_4H_7^+$], 41 (13 [$C_3H_5^+$]. HRMS $C_{12}H_{15}F$ (178.11578): 178.11577, Δ = 0.01 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 1.08 – 1.96 (m, 10 H, CH_2), 2.38 – 2.59 (m, 1H, CH), 6.80 – 7.04 (m, 3H, CH_{ar}), 7.17 – 7.28 (m, 2H, CH_{ar}). ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 26.1 (CH_2), 26.8 (CH_2), 34.3 (CH_2) , 44.3(CH), 112.5 (C_{ar}H, d, J= 21 Hz), 113.6 (C_{ar}H, d, J = 21 Hz), 122.5 (C_{ar}H, d, J = 3 Hz), 129.6 (C_{ar}H, d, J= 9 Hz), 150.74 (C_{ar}, d, J = 7 Hz), 163.0 (C_{ar}, d, J = 245 Hz), ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -114.4. Elemental analysis ($C_{12}H_{15}F$, M = 178.25 g mol^{-1}) [%]: Calcd: C 80.86, H 8.48; Found: C 79.27, H 8.52.



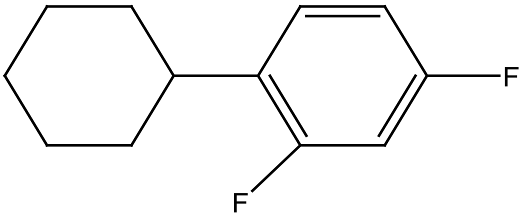
Physical data of* 1*-cyclohexyl-4-fluoro-benzene: MS (EI) [(m/z, %)]: 178 (20) [M^+], 160 (1) [MH^+-F], 135 (52) [$C_{10}H_{15}^+$], 122 (98) [$C_9H_{14}^+$], 109 (52) [$C_8H_{13}^+$], 104 (13) [$C_8H_8^+$], 96 (68) [$C_7H_{12}^+$], 83 (100) [$C_6H_{11}^+$], 65 (9) [$C_5H_9^+$], 55 (5) [$C_4H_7^+$], 41 (13 [$C_3H_5^+$]. HRMS $C_{12}H_{15}F$ (178.11578): 178.11577, Δ = 0.01 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 95 – 1.81 (m, 10 H, CH_2), 2.23 – 2.45 (m, 1H, CH), 6.80 – 7.10 (m, 3H, CH_{ar}), 7.17 – 7.32 (m, 2H, CH_{ar}). ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 26.3 (CH_2), 26.7 (CH_2), 35.3 (CH_2) , 44.55(CH), 115.4 (C_{ar}H, d, J= 21 Hz), 116.9 (C_{ar}H, d, J = 21 Hz), 128.5 (C_{ar}H, d, J = 7.0 Hz), 129.6 (C_{ar}H, d, J= 9 Hz), 144.5 (C_{ar}, d, J = 7 Hz), 162.11(C_{ar}, d, J = 242 Hz), ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -121.46Elemental analysis ($C_{12}H_{15}F$, M = 178.25 g mol^{-1}) [%]: Calcd: C 80.86, H 8.48; Found: C 79.60, H 8.48.

Physical data of* 1*-cyclohexyl-2,3-difluoro-benzene:

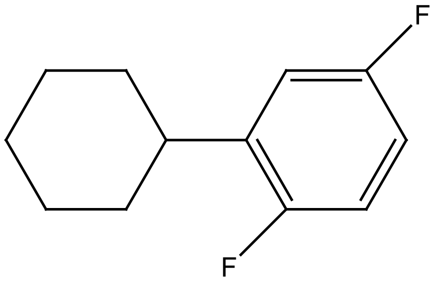


MS (EI) [(m/z, %)]: 196 (68) [M^+], 178 (56) [MH^+ - F], 160 (100) [MH_2^+ - 2 F], 140 (98) [$C_{11}H_8^+$], 127 (44) [$C_{10}H_8^+$], 122 (39) [$C_9H_{14}^+$], 117 (60) [$C_9H_9^+$], 109 (26) [$C_8H_{13}^+$], 104 (84) [$C_8H_8^+$], 91 (44) [$C_7H_7^+$], 83 (14) [$C_6H_{11}^+$], 77 (12) [$C_6H_5^+$], 67 (16) [$C_5H_7^+$], 55 (11) [$C_4H_7^+$], 41 (40) [$C_3H_5^+$]. HRMS $C_{12}H_{14}F_2$ (196.10636): 196.10644, Δ = 0.06 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.83 – 1.51 (m, 10 H, CH_2), 1.71 – 1.85 (m, 1H, CH), 6.87 – 7.32 (m, 3H, CH_{ar}). ^{13}C NMR (100.61 MHz, 298 K, $CDCl_3$) [ppm] : δ = 26.0 (CH_2), 26.7 (CH_2), 33.0 (CH_2), 37.2 (CH), 114.2 (C_{ar}H, d, *J*= 18 Hz), 122.3 (C_{ar}H, t, J = 4 Hz), 123.7 (C_{ar}H, dd, *J* = 9 Hz, *J* = 5 Hz), 137.0 (C_{ar}, d, *J* = 11 Hz), 148.5 (C_{ar}, dd, J = 245 Hz, *J* = 11 Hz), 150.6 (C_{ar}, dd, *J* = 245 Hz, *J* = 13 Hz). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -139.6 (d, *J*= 20.7 Hz), -145.6 (d, *J* = 20.7 Hz). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd: C 73.45, H 7.19; Found: C 73.98, H 8.15.

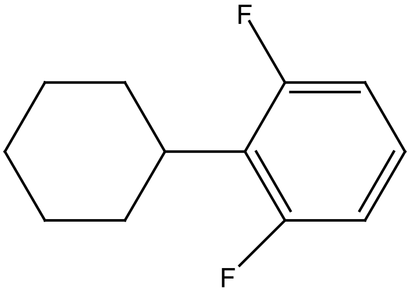
Physical data of* 1*-cyclohexyl-2,4-difluoro-benzene:



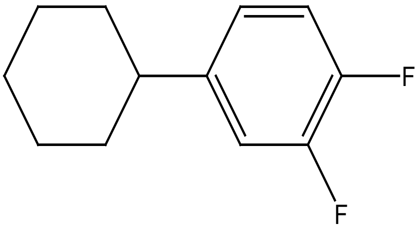
MS (EI) [(m/z, %)]: 196 (99) [M^+], 178(18) [M^+ - F], 165 (10) [$C_{11}H_{12}F^+$], 153 (91) [$C_{12}H_9^+$], 140 (100) [$C_{11}H_8^+$], 127 (95) [$C_{10}H_7^+$], 122 (23) [$C_8H_7F^+$], 109 (17) [$C_7H_6F^+$], 101 (18) [$C_8H_5^+$], 83 (19) [$C_6H_{11}^+$], 69 (18) [$C_5H_9^+$], 55 (13) [$C_4H_7^+$], 41 (36) [$C_3H_5^+$]. HRMS $C_{12}H_{14}F_2$ (196.10636): 196.10475, Δ = 1.61 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 1.05 – 1.93 (m, 10H, CH_2), 2.67 – 2.92 (m, 1H, CH), 6.63 – 6.88 (m, 2H, CH_{ar}), 7.05 – 7.23 (m, 1H, CH_{ar}). ^{13}C NMR (50.32 MHz, 298 K, $CDCl_3$) [ppm] : δ = 26.1 (CH_2), 26.8 (CH_2), 33.1 (CH_2), 36.8 (CH), 103.5 (dd, *J*= 27 Hz, *J* = 25 Hz, C_{ar}H), 110.8 (dd, *J*= 21 Hz, *J*= 4 Hz, C_{ar}H), 128.2 (dd, *J* = 10 Hz, *J* = 7 Hz, C_{ar}H), 130.1 (dd, *J* = 45 Hz, *J* = 4 Hz, C_{ar}), 155.4 (dd, *J* = 251 Hz, *J* = 12 Hz, C_{ar}), 160.7 (dd, *J* = 205 Hz, *J* = 12 Hz, C_{ar}). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -116.1 (d, *J* = 7 Hz), -115.2 (d, *J* = 7 Hz). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd: C 73.45, H 7.19; Found: C 74.46, H 7.58.



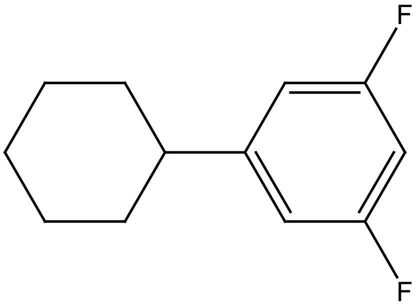
Physical data of* 1*-cyclohexyl-2,5-difluoro-benzene: MS (EI) [(m/z, %)]: 196 (100) $[M^+]$, 178 (77) $[M^+ - F]$, 153 (36) $[C_{12}H_9^+]$, 140 (100) $[C_{11}H_8^+]$, 135 (40) $[C_9H_8F^+]$, 127 (33) $[C_{10}H_7^+]$, 122 (36) $[C_9H_{14}^+]$, 109 (16) $[C_8H_{13}^+]$. HRMS $C_{12}H_{14}F_2$ (196.10636): 196.10213, Δ = 4.23 mmu. ^{1}H NMR (400.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.86 – 1.95 (m, 10H, CH_2), 2.35 – 2.59 (m, 0.5H, CH), 2.73 – 2.94 (m, 0.5H, CH), 6.75 – 7.02 (m, 2H, CH_{ar}), 7.12 – 7.18 (m, 1H, CH_{ar}). ^{13}C NMR (100.62 MHz, 298 K, $CDCl_3$) [ppm]: δ = 25.9 (CH_2), 26.6 (CH_2), 32.8 (CH_2), 40.0 (CH), 113.0 (dd, J = 9 Hz, J = 24 Hz, C_{ar}H), 114.0 (dd, J = 5 Hz, J = 24 Hz, C_{ar}H), 115.9 (dd, J = 9 Hz, J = 25 Hz, C_{ar}H), 136.2 (dd, J = 8 Hz, J = 17 Hz, C_{ar}), 156.4 (d, J = 245 Hz, C_{ar}), 158.8 (d, J = 247 Hz, C_{ar}). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -126.2 (d, J = 9 Hz), -119.9 (d, J = 9 Hz). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd: C 73.45, H 7.19; Found: C 75.00, H 7.41.



Physical data of* 1*-cyclohexyl-2,6-difluoro-benzene: MS (EI) [(m/z, %)]: 196 (71) $[M^+]$, 153 (28) $[C_{12}H_9^+]$, 140 (100) $[C_{11}H_8^+]$, 127 (43) $[C_{10}H_7^+]$, 97 (21) $[C_7H_{13}^+]$, 81 (21) $[C_6H_9^+]$, 69 (18) $[C_5H_9^+]$, 67 (19) $[C_5H_7^+]$, 55 (25) $[C_5H_7^+]$. HRMS $C_{12}H_{14}F_2$ (196.10636): 196.10529, Δ = 1.07 mmu. ^{1}H NMR (400.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.79 – 1.75 (m, 11H, CH_2, CH), 6.85 – 7.50 (m, 3H, CH_{ar}). ^{13}C NMR (100.62 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.9 (CH_2), 30.2 (CH_2), 43.5 (CH), 111.4 (dd, J = 6 Hz, J = 20 Hz, C_{ar}H), 127.2 (t, J = 7 Hz, C_{ar}), 130.8 (t, J = 10 Hz, C_{ar}H), 160.6 (d, J = 249 Hz, br). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -111.0 (s). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd : C 73.45, H 7.19; Found: C 74.67, H 7.53.

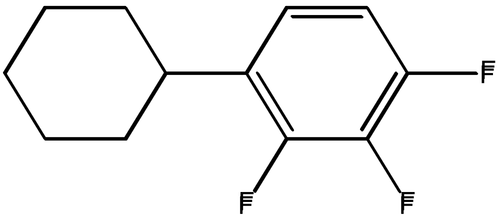


Physical data of* 1-*cyclohexyl-3,4-difluoro-benzene: MS (EI) [(m/z, %)]: 196 (100) [M^+], 178 (9) [MH^+ - F], 166 (64) [$C_{11}H_{15}F^+$], 153 (84) [$C_{12}H_9^+$], 140 (100) [$C_{11}H_8^+$], 127 (72) [$C_{10}H_7^+$], 83 (56) [$C_6H_{11}^+$], 82 (84) [$C_6H_{10}^+$], 67 (60) [$C_5H_7^+$], 55 (44) [$C_4H_8^+$], 41 (34) [$C_3H_5^+$]. HRMS $C_{12}H_{14}F_2$ (196.10636): 196.10575, Δ = 0.61 mmu. ^{1}H NMR (400.13 MHz, 298 K, CD_2Cl_2) [ppm]: δ = 0.87 – 1.91 (m, 10H, CH_2), 2.43 – 2.55 (m, 1H, CH), 6.92 – 7.13 (m, 3H, CH_{ar}). ^{13}C NMR (50.32 MHz, 298 K, CD_2Cl_2) [ppm][60]: δ = 26.4 (CH_2), 27.1 (CH_2), 27.3 (CH_2), 30.6 (CH_2), 34.8 (CH_2), 43.9 (CH), 44.2 (CH), 115.7 (C_{ar}H, d, J = 16 Hz), 117.0 (C_{ar}H, d, J = 17 Hz), 119.0 (C_{ar}H, d, J = 18 Hz), 121.3 (C_{ar}H, d, J = 20 Hz), 123.1 (C_{ar}H, dd, J = 6 Hz, J = 4 Hz), 128.3(C_{ar}H, d, J = 6 Hz), 145.8 (C_{ar}, t, J = 4 Hz), 148.8 (C_{ar}, dd, J = 244 Hz, J = 13 Hz), 150.5 (C_{ar}, dd, J = 246 Hz, J = 13 Hz). ^{19}F NMR (188.29 MHz, 298 K, CD_2Cl_2) [ppm]: δ = -144.1 (d, J = 21 Hz), -140.5 (d, J = 21 Hz), -140.2 (d, J = 21 Hz), -135.9 (d, J = 21 Hz). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd: C 73.45, H 7.19; Found: C 73.49, H 7.65.

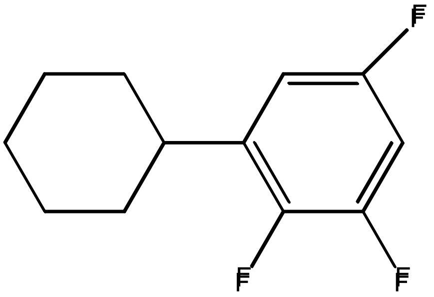


Physical data of* 1-*cyclohexyl-3,5-difluoro-benzene: . MS (EI) [(m/z, %)]: 196 (100) [M^+], 178 (5) [MH^+ - F], 164 (40) [$C_{11}H_{13}F^+$], 153 (60) [$C_{12}H_9^+$], 140 (92) [$C_{11}H_8^+$], 128 (73) [$C_{10}H_8^+$], 114 (22) [$C_9H_6^+$], 101 (20), [$C_8H_5^+$], 83 (16) [$C_6H_{11}^+$], 81 (24) [$C_6H_9^+$], 69 (36) [$C_5H_9^+$], 55 (22) [$C_4H_7^+$], 41 (45) [$C_3H_5^+$]. HRMS $C_{12}H_{14}F$ (196.10636): 196.10604, Δ = 0.32 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.82 – 1.96 (m, 10H, CH_2), 2.41 – 2.58 (m, 1H, CH), 6.48 – 6.78 (m, 3H, CH_{ar}). ^{13}C NMR (50.32 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.0 (CH_2), 26.6 (CH_2), 34.1 (CH_2), 44.4 (CH), 101.1 (C_{ar}H, t, J = 26 Hz), 109.5 (C_{ar}H, d, J = 24 Hz), 152.1 (C_{ar}, t, J = 9 Hz), 163.0 (C_{ar}, dd, J = 248 Hz, J = 13 Hz). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -109.3 (s). Elemental analysis ($C_{12}H_{14}F_2$, M = 196.24 g mol^{-1}) [%]: Calcd: C 73.45, H 7.19; Found: C 74.49, H 7.64.

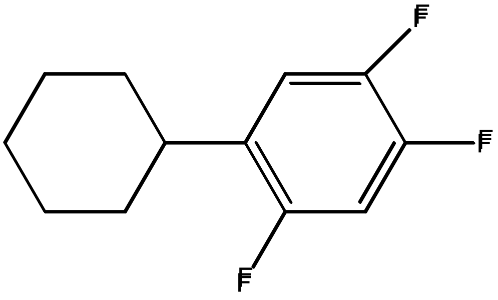
Physical data of 1-_cyclohexyl-2,3,4-trifluoro-benzene:_ MS (EI) [(m/z, %)]: 214 (8) [M^+], 196 (26) [$C_{12}H_{14}F_2^+$], 178 (52) [$C_{12}H_{15}F^+$], 160 (100) [$C_{12}H_{16}^+$], 153 (15) [$C_{12}H_9^+$], 140 (53) [$C_{11}H_8^+$], 135 (35) [$C_9H_8F^+$], 127 (30) [$C_{10}H_7^+$], 122 (65) [$C_9H_{14}^+$], 117 (45) [$C_9H_9^+$], 109 (33) [$C_8H_{13}^+$], 104 (69) [$C_8H_{10}^+$], 91 (40) [$C_7H_7^+$], 77 (13) [$C_6H_5^+$], 67 (12) [$C_5H_7^+$], 55 (10) [$C_4H_7^+$], 41 (31) [$C_3H_5^+$]. HRMS $C_{12}H_{13}F_3$ (214.09694): 214.09717, Δ = 0.23 mmu. ^1H NMR (200 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.98 – 1.88 (m, 10H, CH_2), 2.76 – 2.91 (m, 1H, CH), 6.75 – 7, 11 (m, 2H, CH_{ar}). ^{13}C NMR (100.62 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.1 (CH_2), 26.2 (CH_2), 26.8 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 34.4 (CH_2) , 34.5 (CH_2), 44.6 (CH), 44.7 (CH), 111.7 (dd, *J* = 20 Hz, *J* = 172 Hz, CH_{ar}), 115.0 (dd, *J* = 20 Hz, *J* = 246 Hz, C_{ar}), 121.8 (d, *J* = 128 Hz, C_{ar}), 123.5 (dd, *J* = 7 Hz, *J* = 119 Hz, C_{ar}), 128.8 (dd, *J* = 7 Hz, *J* = 151 Hz, CH_{ar}), 150.5 (dd, *J* = 7 Hz, *J* = 46 Hz, C_{ar}). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -159.7 (t, *J* = 21 Hz), -135.0 (dd, *J* = 9 Hz), -133.5 (dd, *J* = 8 Hz, *J* = 21 Hz). Elemental analysis ($C_{12}H_{13}F_3$, M = 214.23 g mol^{-1}) [%]: Calcd: C 67.28, H 6.12; Found: C 68.99, H 6.82.



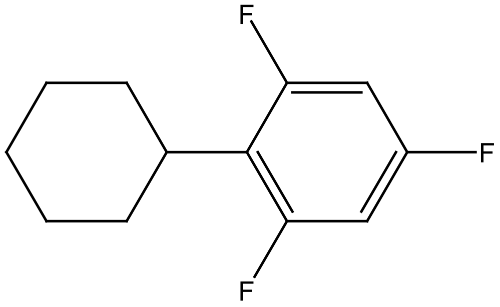
Physical data of 1-_cyclohexyl-2,3,5-trifluoro-benzene:_ MS (EI) [(m/z, %)]: 214 (16) [M^+], 196 (41) [$C_{12}H_{14}F_2^+$], 178 (100) [$C_{12}H_{15}F^+$], 160 (31) [$C_{12}H_{16}^+$], 158 (38) [$C_{11}H_7F^+$], 153 (21) [$C_{12}H_9^+$], 147 (34) [$C_{10}H_8F^+$], 140 (68) [$C_{11}H_8^+$], 135 (89) [$C_9H_8F^+$], 127 (43) [$C_{10}H_7^+$], 122 (100) [$C_9H_{14}^+$], 116 (32) [$C_9H_8^+$], 109 (82) [$C_8H_{13}^+$], 104 (23) [$C_8H_{10}^+$], 101 (20) [$C_8H_5^+$], 96 (19) [$C_6H_5F^+$], 91 (20) [$C_7H_7^+$], 83 (16) [$C_6H_{11}^+$], 67 (18) [$C_5H_7^+$], 55 (14) [$C_4H_7^+$], 41 (34) [$C_3H_5^+$]. HRMS $C_{12}H_{13}F_3$ (214.09694): 214.09692,Δ = 0.02 mmu. ^1H NMR (298 K, $CDCl_3$) [ppm]: δ = 0.83 – 2.49 (m, 11H, CH_2, CH), 6.66 – 7,26 (m, 2H, CH_{ar}). ^{13}C NMR (150.9 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.2 (CH_2), 26.9 (CH_2), 34.5 (CH_2), 44.6 (CH), 112.5 (dd, *J* = 5 Hz, *J* = 17 Hz, $C_{ar}H$), 123.2 (ddd, *J* = 6 Hz, *J* = 8 Hz, *J* = 9 Hz, $C_{ar}H$), 140.1 (dt, *J* = 15 Hz, *J* = 252 Hz, C_{ar}), 148.0 (s, C_{ar}), 151.6 (dd, *J* = 3 Hz, *J* = 249 Hz, C_{ar}), 151.5 (dd, *J* = 6 Hz, *J* = 250 Hz). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -150.2 (dd, *J* = 15 Hz, *J* = 21 Hz), -134.9 (dd, *J* = 2 Hz, *J* = 23 Hz), -116.6 (dd, *J* =



2 Hz, *J* = 23 Hz). Elemental analysis ($C_{12}H_{13}F_3$, M = 214.23 g mol^{-1}) [%]: Calcd: C 67.28, H 6.12; Found: C 67.34, H 6.30.

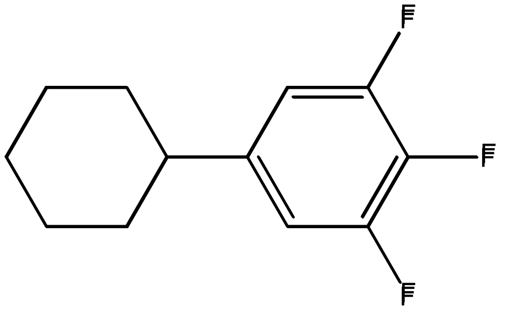


Physical data of* 1-*cyclohexyl-2,4,5-trifluoro-benzene. MS (EI) [(m/z, %)]: 214 (66) [M^+], 196 (40) [$C_{12}H_{14}F_2^+$], 178 (9) [$C_{12}H_{15}F^+$], 171 (34) [$C_{12}H_8F^+$], 166 (48) [$C_{13}H_{10}^+$], 158 (70) [$C_{11}H_7F^+$], 145 (48) [$C_{10}H_6F^+$], 140 (40) [$C_{11}H_8^+$], 127 (22) [$C_{10}H_7^+$], 109 (15) [$C_8H_{13}^+$], 96 (12) [$C_6H_5F^+$], 82 (100) [$C_6H_{10}^+$], 67 (62) [$C_5H_7^+$], 55 (57) [$C_4H_7^+$], 41 (55) [$C_3H_5^+$]. HRMS $C_{12}H_{13}F_3$ (214.09694): 214.09697, Δ = 0.03 mmu. ^{1}H NMR (200 MHz, 298 K, $CDCl_3$) [ppm]: δ = 0.79 – 2.10 (m, 10H, CH_2), 2.68 – 2.97 (m, 1H, CH), 6.73 – 7.13 (m, 2H, CH_{ar}). ^{13}C NMR (150.9 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.2 (CH_2), 26.9 (CH_2), 34.5 (CH_2), 44.6 (CH), 103.4 (ddd, J = 5 Hz, J = 9 Hz, J = 20 Hz, CarH), 114.8 (dd, J = 3 Hz, J = 23 Hz, CarH), 140.1 (dddd, J = 2 Hz, J = 12 Hz, J = 2 Hz, J = 12 Hz, J = 15 Hz, J = 255 Hz, Car), 141.3 (dddd, J = 5 Hz, J = 12 Hz, J = 17 Hz, J = 257 Hz, Car), . ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -144.0 (dd, *J* = 15 Hz, *J* = 21 Hz), -138.7 (d, *J* = 23 Hz), -121.9 (d, *J* = 15 Hz). Elemental analysis ($C_{12}H_{13}F_3$, M = 214.23 g mol^{-1}) [%]: Calcd: C 67.28, H 6.12; Found: C 67.44, H 7.02.



Physical data of* 1-*cyclohexyl-2,4,6-trifluoro-benzene: MS (EI) [(m/z, %)]: 214 (45) [M^+], 196 (28) [$C_{12}H_{14}F_2^+$], 178 (22) [$C_{12}H_{15}F^+$], 171 (23) [$C_{12}H_8F^+$], 158 (100) [$C_{11}H_7F^+$], 145 (35) [$C_{10}H_6F^+$], 140 (41) [$C_{11}H_8^+$], 135 (14) [$C_9H_8F^+$], 127 (19) [$C_{10}H_7^+$], 122 (20) [$C_9H_{14}^+$], 109 (13) [$C_8H_{13}^+$], 91 (7) [$C_7H_7^+$], 81 (10) [$C_6H_9^+$], 69 (9) [$C_5H_9^+$], 55 (6) [$C_4H_7^+$], 41 (14) [$C_3H_5^+$]. HRMS $C_{12}H_{13}F_3$ (214.09694): 214.09681, Δ = 0.13 mmu. ^{1}H NMR (200 MHz, 298 K, $CDCl_3$) [ppm]: δ = 1.15 – 1.92 (m, 10H, CH_2), 2.35 – 2.48 (m, 1H; CH), 6.68 – 6.84 (m, 2H, CH_{ar}). ^{13}C NMR (100.62 MHz, 298 K, $CDCl_3$) [ppm]: δ = 26.1 (CH_2), 26.3 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 34.3 (CH_2), 34.6 (CH_2), 44.5 (CH), 44.8 (CH), 110.8 (d, *J*= 21 Hz, C_{ar}H), 121.2 (d, *J*= 2 Hz, C_{ar}), 124.7 (d, *J*= 108 Hz, C_{ar}), 150.3 (d, *J* = 7 Hz, C_{ar}), 163.0 (d, *J* = 245 Hz, C_{ar}). ^{19}F NMR (188.29 MHz, 298 K,

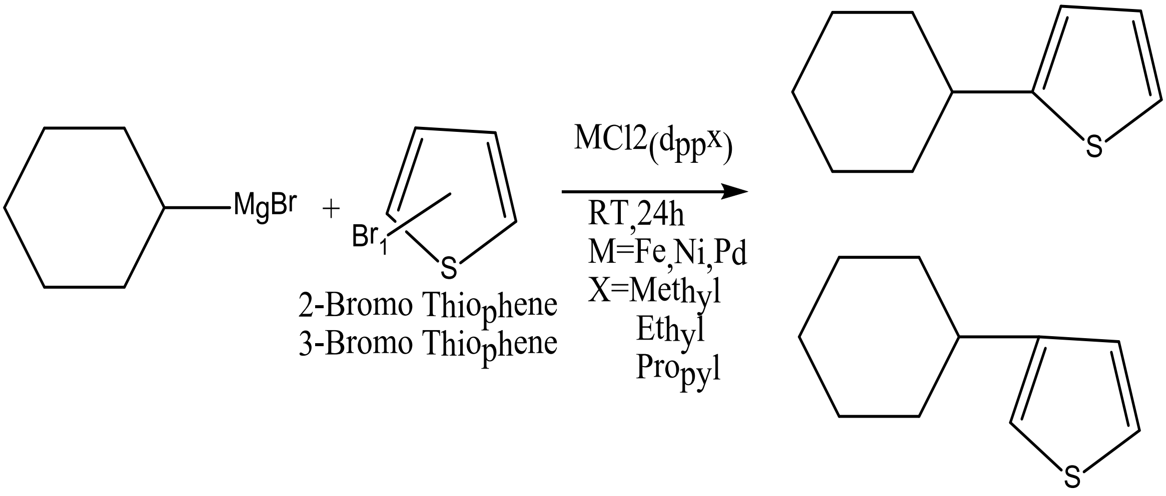
$CDCl_3$) [ppm]: δ = -107.8 (dd, *J* = 2 Hz, *J* = 8 Hz), -106.5 (t, J = 8 Hz). Elemental analysis ($C_{12}H_{13}F_3$, M = 214.23 g mol^{-1}) [%]: Calcd: C 67.28, H 6.12; Found: C 66.77, H 6.80..



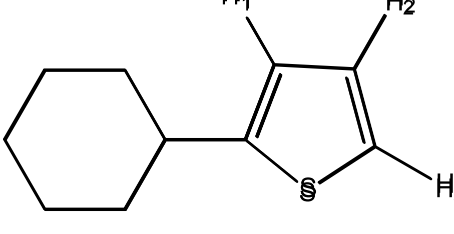
Physical data of **1-*cyclohexyl-3,4,5-trifluoro-benzene:*** MS (EI) [(m/z, %)]: 214 (68) [M^+], 196 (35) [MH^+ - F], 178 (20) [MH_2^+ - 2F], 158 (100) [$C_{12}H_{14}^+$], 140 (53) [$C_{11}H_8^+$], 127 (25) [$C_{10}H_9^+$], 123 (23) [$C_9H_{15}^+$], 109 (11) [$C_8H_{13}^+$], 91 (6) [$C_7H_7^+$], 82 (8) [$C_6H_{10}^+$], 69 (17) [$C_5H_9^+$], 55 (5) [$C_4H_7^+$], 41 (16) [$C_3H_5^+$]. HRMS $C_{12}H_{13}F_3$ (214.09694): 214.09717, Δ = 0.23 mmu. ^{1}H NMR (200.13 MHz, 298 K, $CDCl_3$) [ppm]: δ = 1.15 – 1.89 (m, 10H, CH_2), 2.37 – 2.45 (m, 1H, CH), 6.78 (dd, *J* = 10 Hz, *J* = 8 Hz, 2H, CH_{ar}). ^{13}C NMR (50.32 MHz, 298 K, $CDCl_3$) [ppm] : δ = 25.9 (CH_2), 26.5 (CH_2), 34.2 (CH_2) , 43.9 (CH), 110.51 (dd, *J* = 20 Hz, *J* = 6 Hz, C_{ar}H), 137.8 (dd, *J* = 264 Hz, *J* = 16 Hz, C_{ar}), 144.2 (dt, *J* = 5 Hz, *J* = 4 Hz, C_{ar}), 151.0 (ddd, *J* = 248 Hz, *J* = 10 Hz, *J* = 4 Hz, C_{ar}). ^{19}F NMR (188.29 MHz, 298 K, $CDCl_3$) [ppm]: δ = -165.4 (t, *J* = 21 Hz), -135.9 (d, *J* = 21 Hz). Elemental analysis ($C_{12}H_{13}F_3$, M = 214.23 g mol^{-1}) [%]: Calcd: C 67.28, H 6.12; Found: C 68.16, H 6.73.

2.3.2. Synthetic procedure for the cross coupling of cyclohexyl magnesium bromide with Thiophene derivatives.

2.3.2.1. Mono Bromo-Thiophene



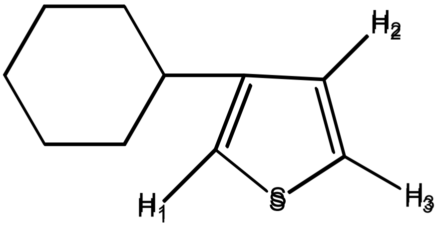
In a typical experiment a dry and argon-flushed 50-mLSchlenk tube, equipped with a magnetic stirring bar, was charged with the respective fluorinated bromobenzene derivative (0.5 mmol, 81 mg for Bromo-Thiophene and 3mol% of the respective catalyst dissolved in 15 ml of THF ($NiCl_2$(dppm): 7.7 mg, $NiCl_2$(dppe): 7.9 mg, $NiCl_2$(dppp): 8.1 mg, $PdCl_2$(dppm): 8.4 mg, $PdCl_2$(dppe): 8.6 mg, $PdCl_2$(dppp): 8.8 mg). The solution was stirred for 5 min, then cyclohexyl magnesium bromide or the respective LiCl or LiBr adduct (0.8 mmol, 4 ml of a 0.2M Grignard reagent) was quickly added to the reaction mixture and stirring vigorously at room temperature was continued for 24 hour. After hydrolysis with diluted hydrochloric acid, the organic layer and ether extracts from the aqueous layer were combined, washed with water, saturated NaCl solution, dried over $MgSO_4$ and filtrated through a pad of silica. Concentration under reduced pressure followed by column chromatography (n-heptane) afforded the respective coupling products as yellow oily compounds.



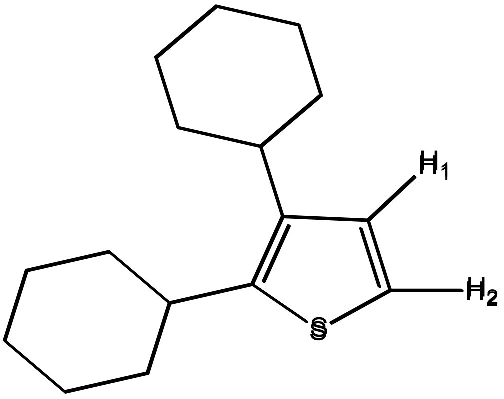
Physical data of 2-cyclohexyl Thiophene: MS (EI)[(m/z, %] : 166 (88) [M^+,] 151 (33) [M –CH_3]$^+$, 137 (56) [M – CH_2CH_3]$^+$, 123 (90) [M – $CH_2CH_2CH_3$]$^+$, 110 (100) [M – $CH_2CH_2CH_2CH_3$]$^+$, 100. 98 (90) [M – $CH_2CH_2CH_2CH_2CH_3$]$^+$, 84 (25) [M

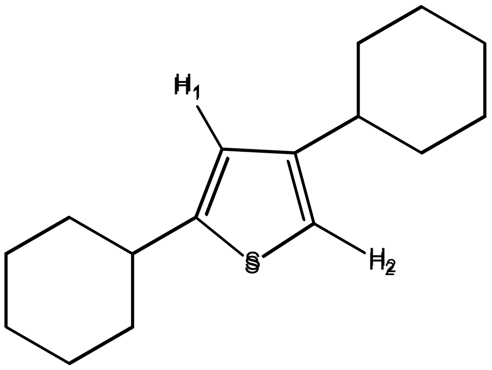
– Cyclohexyl]$^+$. ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.84 – 2.85) Cyclohexyl, 6.78 (Thiophene H_1, dd, ^{3}J= 2 Hz, ^{4}J= 1 Hz) , 6.91(Thiophene H_2, dd, ^{3}J= 8 Hz, ^{3}J= 7 Hz) , 7.09 (Thiophene H_3, dd, ^{3}J= 6 Hz, ^{4}J= 4 Hz) . ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 25.97 (CH_2), 26.48 (CH_2) , 35.51 (CH_2), 39.37 (CH), 121.69 ($C_{thio}H$), 122.10 ($C_{thio}H$), 126.40 ($C_{thio}H$), 152.36 (C_{thio}).

***Physical data of* 3-*cyclohexyl Thiophene*:** MS (EI)[(m/z, %)] : 166 (100) [M^+], 151 (7) ([M –CH_3]$^+$, 137 (18) [M – CH_2CH_3]$^+$, 123 (85) [M – $CH_2CH_2CH_3$]$^+$, 110 (30) [M – $CH_2CH_2CH_2CH_3$]$^+$, 98 (88) [M – $CH_2CH_2CH_2CH_2CH_3$]$^+$, 84 (10) [M – Cyclohexyl]$^+$. ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.81 – 2.75) Cyclohexyl, 6.96 (Thiophene H_1, dd, ^{3}J= 1.5 Hz, ^{4}J= 0.5) , 7.01(Thiophene H_2, d, ^{4}J= 2 Hz) , 7.26 (Thiophene H_3, dd, ^{3}J= 4 Hz, ^{4}J= 2Hz) . ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 26.15(CH_2), 26.90 (CH_2) , 34.21 (CH_2), 39.50 (CH), 118.22($C_{thio}H$), 124.85 ($C_{thio}H$), 126.97 ($C_{thio}H$), 149.01 (C_{thio}).

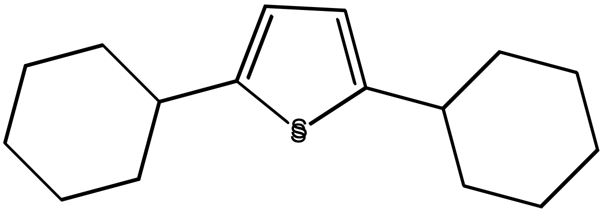


Physical data of* 2.3-Di*cyclohexyl Thiophene: MS (EI)[(m/z, %)] : 248 (100) [M^+] , 233 (10) [M – CH_3]$^+$, 219 (12) [M – CH_2CH_3]$^+$, 205 (19) [M – $CH_2CH_2CH_3$]$^+$, 166 (20) [M – Cyclohexyl]$^+$, 83 (10) ([M – 2 Cyclohexyl]$^+$, ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.84 – 2.79) Cyclohexyl, 7.00 (Thiophene H_1, dd, ^{3}J= 5.4 Hz) , 7.18 (Thiophene H_2, dd, ^{3}J= 5.4 Hz) . ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 25.6(CH_2), 26.23 (CH_2), 26.53 (CH_2), 33.50 (CH_2), 37.10 (CH), 38.08 (CH), 119.66($C_{thio}H$), 122.00 ($C_{thio}H$), 135.60 (Cthio), 139.16 (Cthio). . HRMS (EI, 70 eV): Calcd for $C_{16}H_{24}S$ [M^+]: 248.15987, found 248.15974.

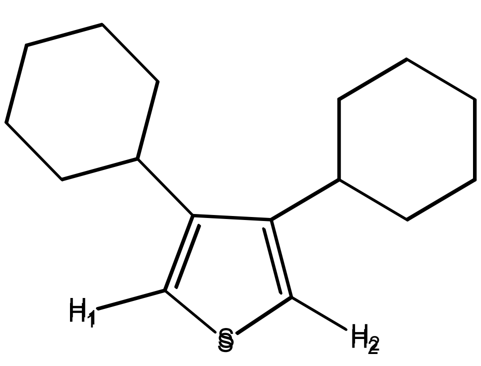




Physical data of 2.4-Di_cyclohexyl Thiophene_: MS (EI)[(m/z, %)] : 248 (75) [M$^+$], 219 (15) [M – CH_2CH_3]$^+$, 205 (100) [M – $CH_2CH_2CH_3$]$^+$, 166 (25) [M – Cyclohexyl]$^+$, 83 (57) [M – 2 Cyclohexyl]$^+$, ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.84 – 2.50) Cyclohexyl, 7.01 (Thiophene H_1, dd, ^4J= 1.0 Hz, ^4J= 1.2 Hz) , 7.03 (Thiophene H_2, dd, ^4J= 1.0 Hz, ^4J= 1.0 Hz) . ^{13}C NMR (50.32 MHz, CDCl3) [ppm] δ = 25.13 (CH_2), 25.54 (CH_2), 26.53 (CH_2), 33.04 (CH_2), 33.09 (CH_2), 38.78 (CH), 38.75 (CH) 116.30(C_{thio}H), 118.30(C_{thio}H), 135.02 (Cthio), 137.09 (Cthio). HRMS (EI, 70 eV): Calcd for $C_{16}H_{24}S$ [M$^+$]: 248.15987, found 248.15974.



Physical data of 2.5-Di_cyclohexyl Thiophene:_ MS (EI)[(m/z, %)] : 248 (90) [M$^+$], 219 (25) [M – CH_2CH_3]$^+$, 205 (100) [M – $CH_2CH_2CH_3$]$^+$, 166 (30) [M – Cyclohexyl]$^+$, 83 (80) [M – 2 Cyclohexyl]$^+$, ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.81 – 2.44) Cyclohexyl, 7.00 (Thiophene $H_{1 and 2}$, S) . ^{13}C NMR (50.32 MHz, CDCl3) [ppm] : δ = 25.25(CH), 26.89 (CH_2) , 33.00 (CH_2), 40.7 (CH), (C_{thio}H), 122.10 (C_{thio}H), 127.17 (C_{thio}H), 131.05 (C_{thio}). HRMS (EI, 70 eV): Calcd for $C_{16}H_{24}S$ [M$^+$]: 248.15987, found 248.16014.



Physical data of 3.4-Di_cyclohexyl Thiophene:_ MS (EI)[(m/z, %)] : 248 (100) [M$^+$], 219 (8) [M – CH_2CH_3]$^+$, 205 (15) [M – $CH_2CH_2CH_3$]$^+$, 166 (15) [M – Cyclohexyl]$^+$, 83 (30) [M – 2 Cyclohexyl]$^+$, ^{1}H NMR (200.13 MHz, $CDCl_3$)[ppm]: δ = (0.82 – 2.57) Cyclohexyl, 6.89 (Thiophene $H_{1 and 2}$, S), ^{13}C NMR (50.32 MHz, $CDCl_3$) [ppm] : δ = 25.6(CH_2), 26.23 (CH_2), 26.53 (CH_2), 33.50 (CH_2), 38.08 (CH), 119.66(C_{thio}H), 127.00 (C_{thio}H), 135.60 (Cthio). HRMS (EI, 70 eV): Calcd for $C_{16}H_{24}S$ [M$^+$]: 248.15987, found 248.16011.

3. Results and Discussion

The aim of the present study was to develop procedures for using palladium, nickel and iron catalysts for the cross coupling reactions of various fluorinated bromobenzene electrophiles with cyclohexyl Grignard nucleophiles. The products are commonly used as liquid crystalline compounds or in mixtures exhibiting liquid crystalline properties. The catalytic activities of Pd(II) and Nickel(II) complexes, [$PdCl_{2(}$dppp)], [$PdCl_2$(dppe)], [$PdCl_2$(dppm)], [$NiCl_2$(dppp)], [$NiCl_2$(dppe)] and [$NiCl_2$(dppm)] were compared to quantify the effect of various bis-(diphenylphosphino) alkane ligands on the efficiency of the catalyst in cross coupling reactions. Another aim was to find protocols for the use of the iron complexes [$FeCl_2$(dppp)], [$FeCl_2$(dppe)] and [$FeCl_2$(dppm)] as precatalysts for cross coupling reactions. So the primary focus was on the development of synthetic methods for the preparation of the respective Grignard reagents.

Four coordinate complexes of the first transition series are particularly intriguing, given the choice between square planar and tetrahedral ground states. The tetrahedral geometry is sterically preferred and occurs with large ligands and small metal ions whereas square planar coordination, in general is sterically disfavoured [86]. For d^8 metal ions, the factors that govern the choice between square planar and tetrahedral geometry are fairly well understood [87]. For larger second and third row metals such as Pd(II), Pt(II), and Au(III), the LFSE dominates and square planar geometries are almost exclusively observed.

The lighter Ni(II) complexes offer both limiting structural types. When ligands with a weak ligand field such as halides or arylated phosphines are present, as is the case with $[NiCl_4]^{2-}$ and $[(Ph_3P)_2NiCl_2]$, a tetrahedral coordination sphere is observed, whereas compounds exhibiting ligands with a strong field or alkylated phosphines such as $[Ni(CN)_4]^{2-}$ and $[(Cy_3P)_2NiCl_2]$ prefer a square planar geometry. Interestingly, complexes supported by mixed alkyl/aryl phosphines such as $\{[(PhCH_2)Ph_2P]_2NiBr_2\}$ contain both tetrahedral and square planar geometries in the same crystal lattice [88,89,90,91]. Ferrous halides react with 1, 2-bis-(diisopropylphosphino)ethane (dippe) to give tetrahedral, high-spin adducts [FeX_2(dippe)] (X =C1, Br, I) [92]. Therefore, palladium and nickel precatalysts with bis-

(diphenylphosphino)alkane ligands that are employed in this research are considered to be square planar and that this geometry is pertained throughout the catalytic cycle of the cross coupling reactions.

Grignard reagents are very important coupling partners because of being economical and easy to synthesize. Moreover, a substantial number of Grignard reagents are commercially available [29]. The advantage of this reaction is that Grignard reagents are used directly thus avoiding additional reaction steps such as the conversion to zinc compounds for the starting materials required in Negishi coupling. A drawback in the use of Grignard reagents is that homocoupling and β-H elimination were observed with both nickel and palladium catalysts [93]. β-H elimination is a reaction in which an alkyl group bonded to a metal centre is converted into the corresponding metal-bonded hydride and an alkene.

3.1. Palladium and Nickel Catalyzed C(sp^2)-C(sp^3) Cross Coupling Reactions

Dichloro [bis(diphenylphosphino)methane] palladium(II),
Dichloro [1,2-bis(dipheny1phosphino)ethane] palladium(II)
Dichloro [1,3-bis(diphenylphosphino)propane] palladium(I1)

Palladium complexes play a very important role in cross coupling reactions. To investigate the impact of different ligands on palladium catalyzed cross coupling reactions, especially the Kumada cross coupling reaction, three types of palladium complexes with bis-(Diphenylphosphino)alkane ligands were prepared (*cf.* experimental part), characterized and finally kept in closed Schlenk tubes under argon until they were used in several cross coupling reactions. The effect of the natural bite angle of diphosphane ligands on catalyst selectivity and activity in palladium catalyzed cross-coupling reactions of cyclohexyl magnesium bromide with fluorinated benzene substrate was investigated., In addition, the influence of some additives such as lithium chloride and lithium bromide on the catalytic activity under ambient circumstances was studied. Dichloro[bis(diphenylphosphino)methane]palladium(II) (Pddppm), Dichloro[1,2-bis(diphenylphosphino)ethane]palladium(II) (Pddppe) and Dichloro[1,3-bis(diphenylphosphino)propane]palladium(II) (Pddppp) are square planer complexes and their bite angles increasess from Pddppm (72.7°), Pddppe (85.9°) to Pddppp (90.6°) [94].

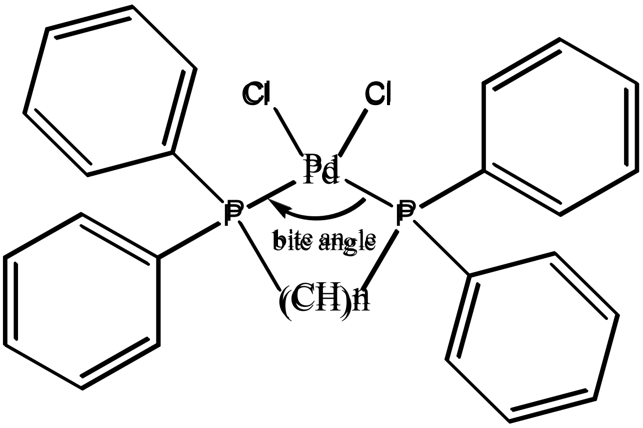


Figure 3.1. Bite Angle in Palladium Complexes

3.2. Palladium and Nickel Catalyzed Cross Coupling Reactions of Cyclohexyl Grignard Reagents with Fluorinated Bromobenzenes

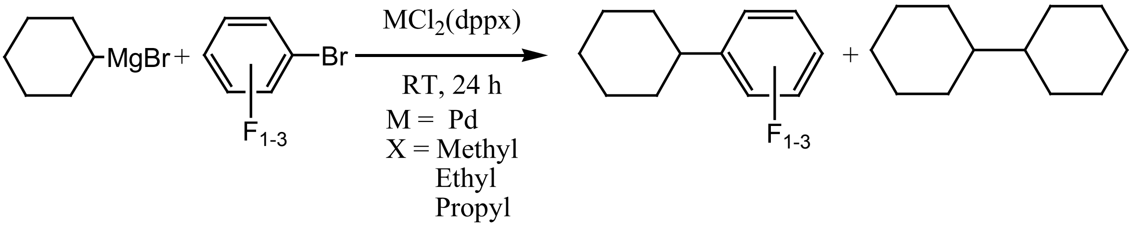


Figure 3.2. Cross Coupling Reactions

Coupling reactions between cyclohexyl magnesium bromide and fluorinated bromobenzene substrates by employing palladium complexes with bis-(diphenylphosphino)alkane ligands at room temperature for 24 hours led to the corresponding coupling products (Figure 3.2). But this reactions are always accompanied by the formation bicyclohexane (homocoupling product) that already arises during the preparation of the Grignard reagent and is additionally formed during the cross coupling reactions. Palladium precatalysts are reduced by first reacting with two equivalents of the respective Grignard reagent (cyclohexyl magnesium bromide). Then the reductive elimination of the homocoupling product (bicyclohexyl, Figure 3.3) yield the catalytically active Pd^0 compound

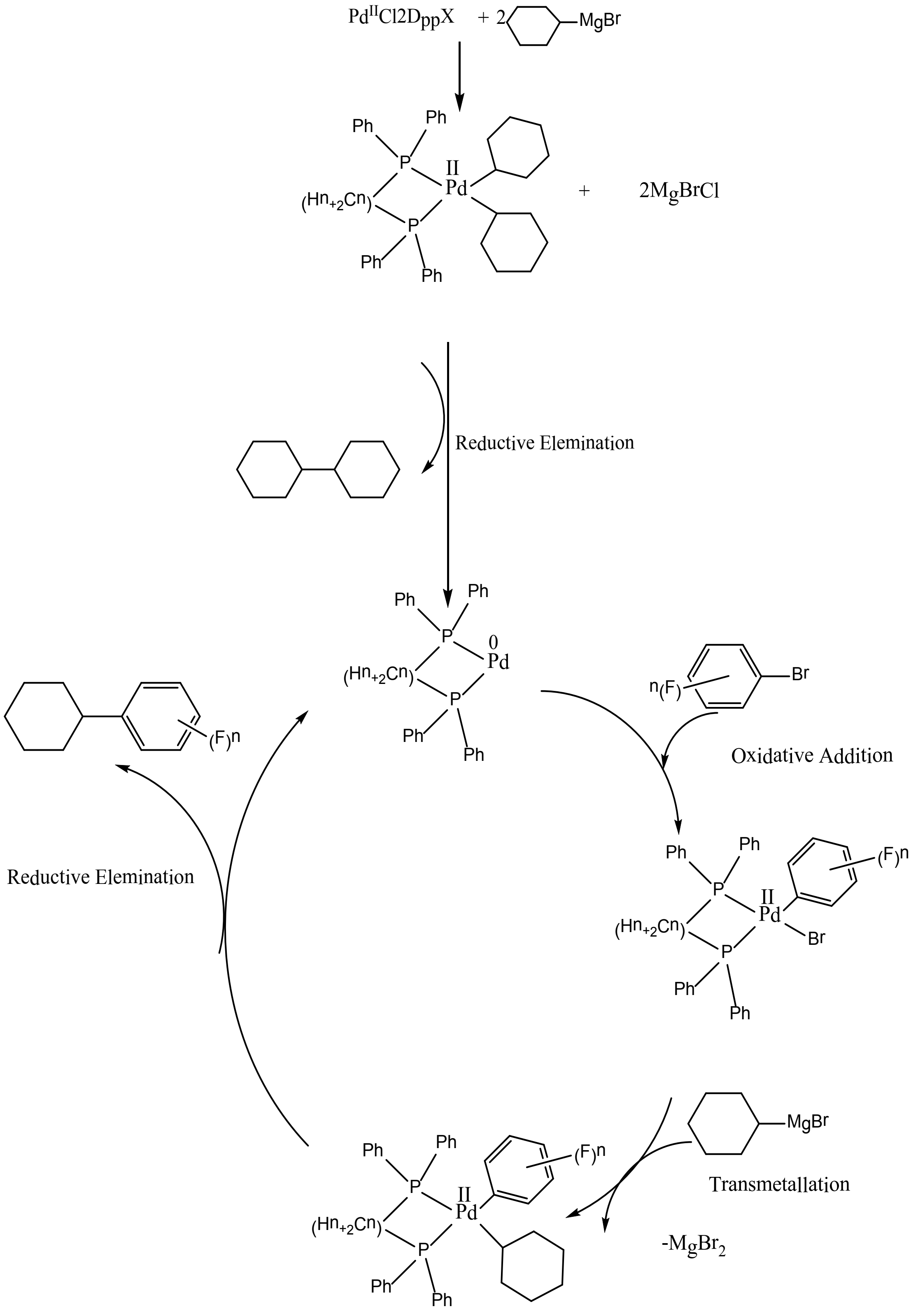


Figure 3.3 Mechanism of Cross Coupling

After reducing palladium to Pd(0) this species immediately reacts with the organohalide (fluorinated bromobenzene) in a so-called oxidative addition process. In this reaction the oxidation state of palladium is increased to Pd (II) with the formation of an organopalladium compound. The most critical step in these catalytic processes often is the oxidative addition of the organic halide RX. Breaking this bond gets easier in the order R–Cl < R–Br < R–I as the bond energy is the lowest for the C–I bond [95]. As the C(sp^3)-X bond in alkyl halides is more electron rich than the C(sp^2)-X bond in aryl and vinyl halides, the reluctance of alkyl halides to undergo oxidative addition to a low-valent transition-metal complex (i.e. formal reduction of C(sp^3)-X) is much lower than that of aryl and vinyl halides. The resulting alkyl–metal complex is highly reactive owing to the absence of stabilizing electronic interactions with the metal d orbitals. The fast and thermodynamically favored β-hydride elimination leads to the formation of olefinic by-products with most catalyst systems. The relatively slow reductive elimination of the cross-coupling product from the catalyst (aryl–aryl > aryl–alkyl > alkyl–alkyl) makes side reactions even more likely [96].

The second elementary reaction in the catalytic cycle is transmetallation by reaction with the Grignard reagent (cyclohexyl magnesium bromide) to form a diorganopalladium complex (Figure 3.4). . In connection with this intermediate there are some hypotheses to interpret the observation of homocoupling from the transmetallation stage, which also illustrate the difficulty of sp^2-sp^3 coupling in general.

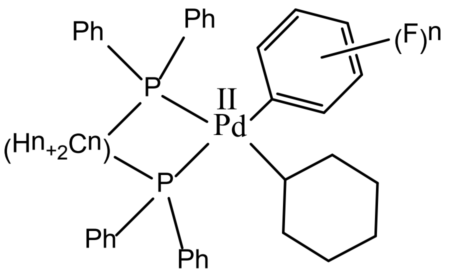


Figure 3.4. Intermediate after transmetallation

There is an explanation put forward in the literature that undesired homocoupled products occur during the transmetallation process on the basis of the exchange of organic groups between the palladium complex formed by the oxidative addition step and the intermediate after transmetallation. The exchange of organic groups between both intermediates leads to a mixture of two mono-organopalladium(II) complexes and two di-organopalladium(II) species, which can combine in four different ways leading to the formation of either cross-coupled or homocoupled products [97]. In our reaction, the reaction of [Pd(dppx)Br($C_6H_{5-n}F_n$)] with cyclohexyl magnesium bromide may replace the fluorinated phenyl with a cyclohexyl moiety. After transmetallation processes three different intermediates may be formed which after reductive elimination give two types of homocoupling compounds (bicyclohexyl and fluorinated biphenyl). The amount of the Grignard homocoupling product in our reactions always is significantly higher than the product from organo halide homocoupling, The different ratios of products could be attributed to a subtle interplay between thermodynamic and kinetic factors.

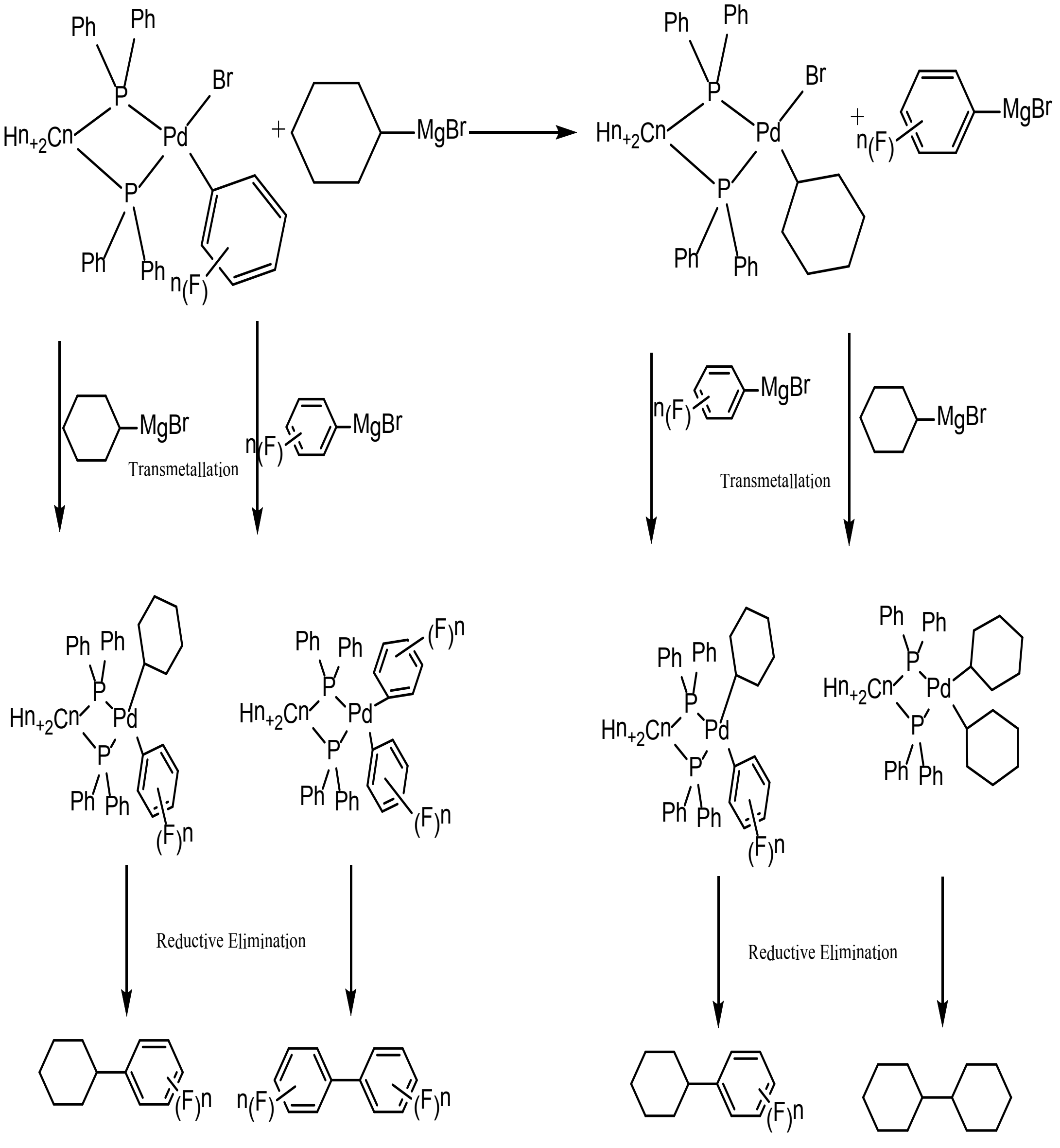


Figure 3.5. Mechansim of the Formation of Homocoupling Products

The exchange of organic groups between organotransition metal complexes and a transmetallating reagent is not restricted to palladium complexes to produce the homocoupling products but has also been observed in nickel and iron catalyzed cross coupling reactions. Studies on palladium-phosphine-catalyzed coupling reactions and studies on the mechanism of reductive elimination reactions from organopalladium(II) complexes have revealed several mechanisms, which also must be taken into account for the explanation of homocoupled products in cross-coupling reactions. These mechanisms include halogen-metal exchange between the organic halide and the Grignard reagent (eq **3.1),** as has been observed in some reactions of organic halides with transmetalating-reagents. This mechanism is often used to elucidate the formation of homocoupled products in palladium-phosphine-catalyzed reactions [97, 98].

$$RX + R^1M_gX^1 \rightleftharpoons RM_gX^1 + R^1X$$

Eq 3.1 Halogen Metal Exchange

Another possibility to interpret the formation of homocoupled products can be concluded from the fact that a reductive elimination may occur after the transmetallation step. Studies on the reductive elimination from diorgano-bis(phosphine)palladium(II) complexes suggested two mechanismsthat may play an important role in catalytic cross-coupling reactions. After the transmetalation, either the diorgano-Pd (II) species formed undergoes a further oxidative addition process to give a triorgano- Pd(IV) or the diorgano-Pd (II) complex reacts with an organo-Pd (II) halide, giving a dinuclear species. Both intermediates might then react *via* a reductive elimination to produce homocoupling products [97, 99, 100].

So as illustrated above, there are a lot of mechanisms proposed in the literature that may occur *in situ* to explain the formation of both types of homocoupled products during the cross coupling reactions. Moreover, Grignard homocoupling also occurs obviously as side product during a preparation of the Grignard reagent itself. In the presence of oxygen and a trace amount of a metal complex another mechanism may play a role in the formation of homocoupled Grignard reagents already during and after the preparation of Grignard reagents.

A mechanism is shown in Figure 3.6 for this metal catalyzed reaction. The critical step of this catalytic cycle is the conversion of the stable diorganometal(II) complex **1** to a metal(IV)-peroxo complex **2**. The latter may undergo a rapid reductive elimination to afford the homocoupling product and a metal-(II)-peroxo complex **3** which would upon reaction with the Grignard reagent close the catyltic cycle. With manganese and iron the formation of peroxo complexes as catalytic intermediates is very well established for various manganese- and iron-catalyzed oxidation reactions [101]. So in case of a small amount of oxygen present during the cross coupling reactions, this mechanism might lead to the formation of homocoupled Grignard compound as a minor product.

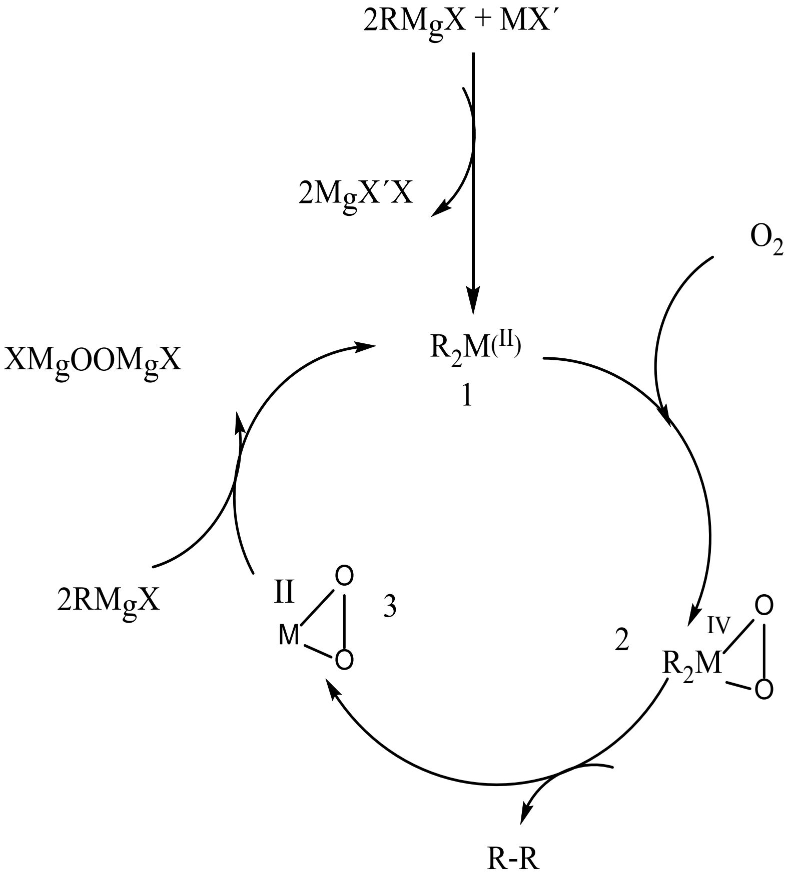


Figure 3.6. Metal catalyzed homocoupling induced by O_2

In general, the period between transmetallation and reductive elimination has great influence on the mechanism of cross coupling reaction and nature of the products, especially the ratio of cross coupled products relative to homocoupled products. If this period of the catalytic cycle works at low reaction rates, the amount of side products formed by β-H elimination and homocoupling increase. This problem always gets more pronounced when C(sp^3) alkyl or cycloalkyl are used as electrophile or nucleophile in cross coupling reactions.

The higher electronegativity of C(sp^2) centers compared to C(sp^3) atoms promotes the reductive elimination, but also the presence of adjacent double bonds which are able to remove *d* electron density from palladium or nickel by transfer to the respective π* orbitals may be responsible for fast cross-coupling reactions in these cases. Reductive elimination including C(sp^3) atoms is especially difficult due to the high electron-donor ability of a C(sp^3) center, which provides an electron-rich organometallic intermediate less prone to reductive elimination [102]. So this fosters the exchange of R groups with subsequent formation homcoupled products.

	Precatalyst					
	[$PdCl_2$(dppm)]	[$PdCl_2$(dppe)]	[$PdCl_2$(dppp)]	[$NiCl_2$(dppm)]	[$NiCl_2$(dppe)]	[$NiCl_2$(dppp)]
2-F	30	53	55	10	40	60
3-F	50	65	75	30	53	80
4-F	55	70	85	45	52	60
2,3-F_2	25	45	55	15	30	40
2,4-F_2	50	55	60	27	35	50
2,5-F_2	40	66	75	40	50	60
2,6-F_2	20	35	40	10	30	35
3,4-F_2	60	75	80	55	60	70
3,5-F_2	91	94	97	70	78	89
2,3,4-F_3	33	45	50	20	25	60
2,3,5-F_3	40	60	75	20	55	73
2,4,5-F_3	35	50	75	25	50	68
2,4,6-F_3	25	30	45	15	30	40
3,4,5-F_3	48	75	80	50	66	65

Table 3.1. Yields of the Respective Cross Coupling Products using Palladium and Nickel Catalysts, Cyclohexyl Magnesium Bromide as Grignard Reagent and Fluorinated Benzene Substrates.

The cross coupling reactions depicted in Figure 3.2 has been performed with various ligands and nucleophiles to be able to illustrate the effect of ligands (bite angle) and additives to the Grignard reagents (LiCl and LiBr) on cross coupled and homocoupled products. The results shown in table 3.1 show that the yields of cross coupled products gradually improve when going from [MCl_2(dppp)] > [MCl_2(dppe)] > MCl_2(dppm)] (M = Pd, Ni). This behaviour is attributed to the effect of the bite angle which plays an important role in the reductive elimination stage.

Increasing the chelate ring size leads to widened bite angles, an increased flexibility of the backbone chain and the steric size in general. All these effects lead to the expectation of a more effective reductive elimination step in the present case. These factors favor both a mechanism involving an intact chelate ring (where the PMP angle is ideally larger in the transition state than in the square planar starting material) or a mechanism involving a preequilibrium chelate ring opening. Increasing the diphosphine bite angle and sterics compresses the angle CPdC that Pd encloses with the two organic moieties, forcing the two carbon atoms closer together. This would also be expected to accelerate C-C bond formation and subsequent elimination [103]. However, a reductive elimination will not take place easily when sp^3 carbon atoms are involved in the cross coupling reactions.

In general, cross coupling reactions work extremely well if two sp^2 carbon atoms are to be coupled. The increased s character of the sp^2 hybrids causes this orbital to be less directional than the sp^3 hybrids. Therefore, the sp^2 hybrid can realize multicentered bonding in the transition state, leading to lower activation energies for CH_3-CH=CHPh, CH_3-Ph, and Ph-Ph coupling [104]. Moreover, transition state requires a planar arrangement of the ligands to achieve an effective reductive elimination. Ananikov et al. have shown by theoretical methods in the case of a sp^2-sp^3 coupling (CH_3-Ph) that the presence of methyl groups leads to nonplanar transition states (figure 3.7) and that the degree of the nonplanarity is correlated with the number of Me ligands involved. The authors propose that the reason for this is the weaker M-C bond for bound methyl groups, the increased directionality of the M-Me bond and other non-specified steric factors [105].

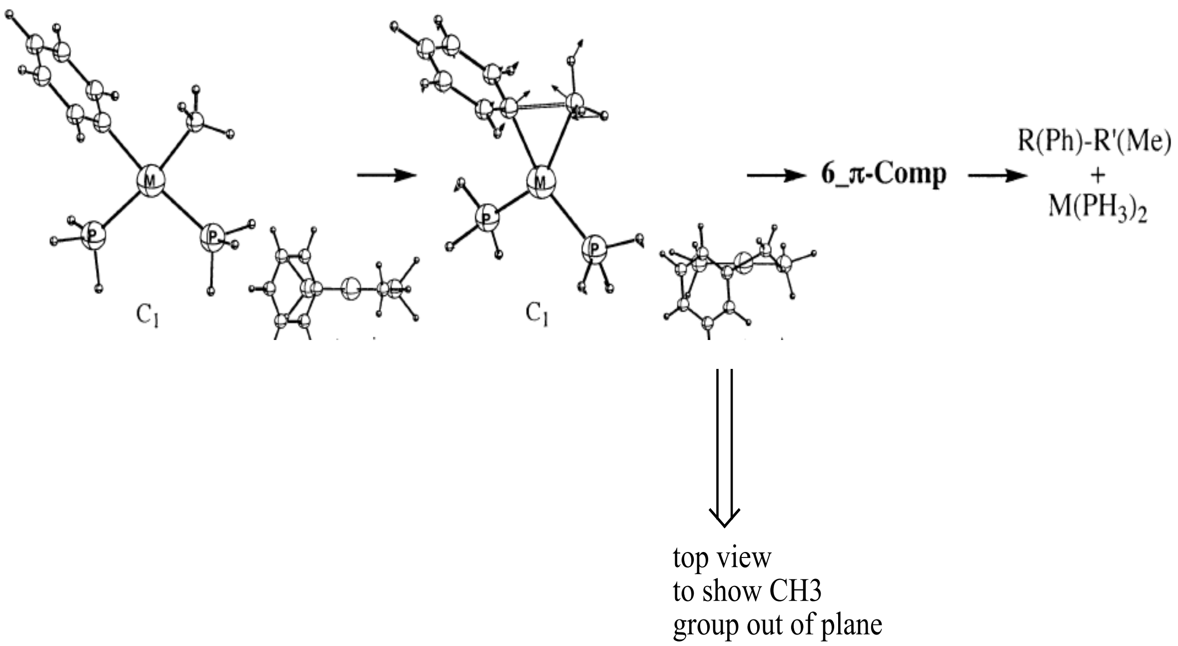


Figure 3.7. Transition state of coupling methyl with phenyl (reference 105)

As there should be a suitable orientation of orbitals to perform the required overlap that is needed to establish the new bond, the use of CH_3 as a ligand in coupling reactions with another phenyl group this will create nonplanarity of a transition state (Figure 3.7 and 3.8) which backwards the reductive elimination step. Therefore, the probability of homocupling and β-elimination formation during the reaction becomes higher leading to a lower amount of cross coupled products. If as in our reactions methyl is replaced by cyclohexyl, we would expect the same influence with an induced nonplanarity of the transition state. Moreover, the steric factor will be increased due to its size. Altogether these facts show that the development of catalytic systems that allow the coupliong of cycohexyl with fluorophenyl groups is a challenging task as we would expect an increased amount of homocoupled and an increased activation energy of the reductive elimination step due to the nonplanarity of the transition state.

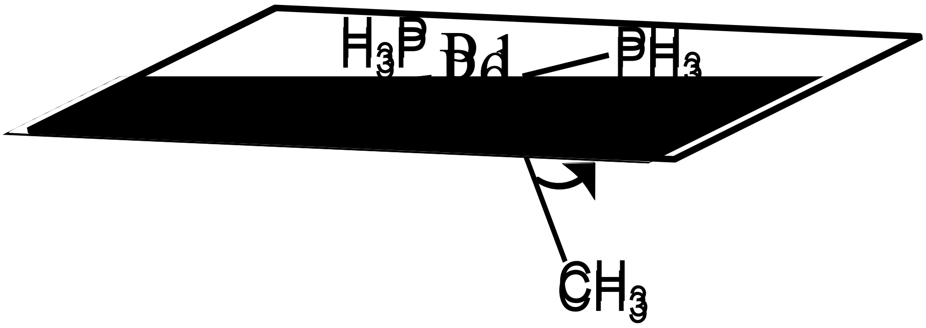


Figure 3.8. Nonplanarity of the methyl group with respect to the other ligands

In a typical example the coupling of cyclohexyl with monofluoro-phenyl (entries 1-3, Table 3.1) shows the effect of the ligand and the position of the substituents at the phenyl ring on the yield of cross coupling reactions. In general, the yield obviously increases when going from dppm to dppp. This is attributed to an increased bite angle in the phosphine ligand. Also, palladium catalysts in almost all cases give better results than the corresponding nickel precatalysts.

The reaction of cyclohexyl magnesium bromide with 4– fluorobenzene (entry 3) gives the coupling product in higher yield compared to the analogous reaction of 3–fluorobenzene and 2–fluorobenzene. This might be attributed to steric considerations (figure 3.8) which have an effect both in the oxidative addition and the reductive elimination step. This steric effect is observed whenever a fluoro substituent was present in the *ortho*-position of the phenyl ring.

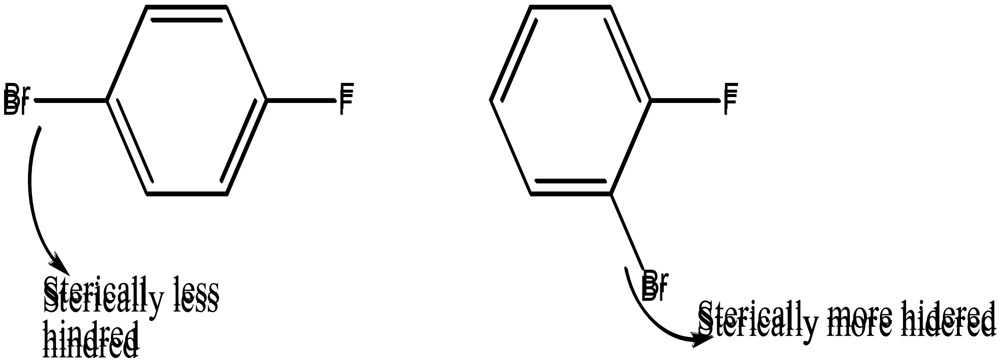


Figure 3.9. Steric effect of the position of fluorine at the phenyl ring

Di- and tri-fluoro-bromobenzene substrates react with cyclohexyl Grignard reagent to afford the corresponding coupling compounds with some differences in yield, which reflect the nature of the fluorobenzene substrates, especially electronic and steric factors. The yields of cross coupled products increase when going from mono to di then tri–fluoroinated substrates and this could be interpreted because of existing a withdrawing group (fluoro) which may be facilitate oxidative addition process by increasing the electrophilicity of aryl halide. .

3.3 Iron Catalyzed C(sp^2)-C(sp3) Coupling Reactions

Iron complexes as catalysts in cross coupling reactions have attracted much attention due to economical and toxicological reasons. Therefore, [$FeCl_2$(dppp)], [$FeCl_2$(dppe)] and

$[FeCl_2(dppm)]$ were prepared to employ them in the coupling reaction of cyclohexyl magnesium bromide with fluorinated bromobenzene substrates under the same conditions that were used in palladium and nickel catalyzed cross coupling reactions.

Substrate	$[FeCl_2(dppe)]$	$[FeCl_2(dppp)]$
2-F	35	50
3-F	40	65
4-F	55	65
2,3-F_2	30	35
2,4-F_2	25	45
2,5-F_2	30	55
2,6-F_2	20	30
3,4-F_2	55	60
3,5-F_2	75	85
2,3,4-F_3	30	65
2,3,5-F_3	50	65
2,4,5-F_3	40	63
2,4,6-F_3	35	45
3,4,5-F_3	70	80

Table 3.2. Yields of the Respective Cross Coupling Products Using Iron Precatalysts, Cyclohexyl Magnesium Bromide as Grignard Reagent and Fluorinated Benzene Substrates.

Unfortunately, $[FeCl_2(dppm)]$ was not an effecient precatalyst in cross coupling reactions and was therefore discarded in this research. All attention was concentrated on $[FeCl_2(dppp)]$ and $[FeCl_2(dppe)]$ which gave good yields of coupling products and their catalytic activity was very close to palladium and nickel to couple the two organic moieties. Again, the precatalyst system with the bigger bite angle induced by the ligand backbone ($[FeCl_2(dppp)]$) afforded higher yields of the coupling products than $[FeCl_2(dppe)]$.

In other words, iron complexes have advantages making them suitable for some coupling reactions. E.g. complexes have been developed for the cross-coupling reaction of Grignard reagents with primary or secondary alkyl halides bearing β-hydrogens. These precatalysts work very well mostly due to their ability to efficiently suppress the undesired β-hydrogen elimination as well as their potential from a mechanistic point of view [106].

The optimized reaction conditions to couple cyclohexyl magnesium bromide and fluorinated bromobenzenes were determined to be 3 mol% $[FeCl_2(dppx)]$ at room temperature for 24 hours to obtain cross coupled products besides various amounts of the homocoupled product (bicyclohexyl).

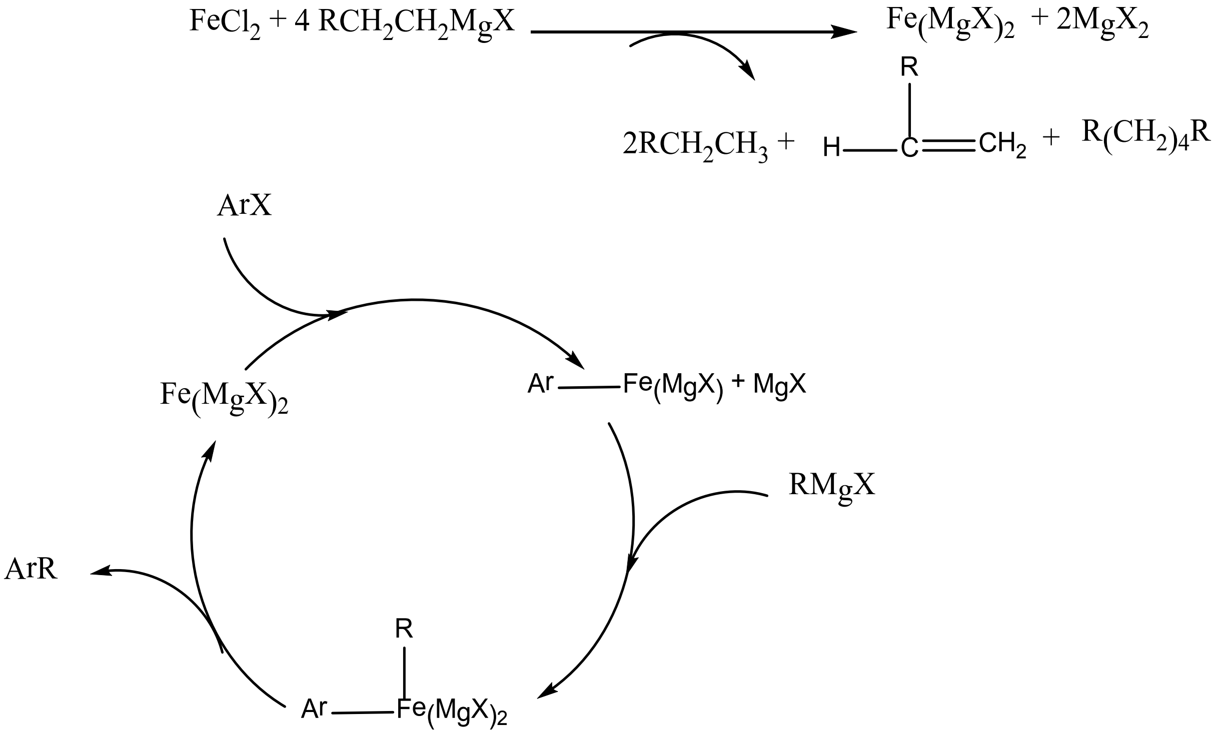


Figure 3.10. Iron catalyzed cross coupling mechanism

According to figure (3.10) the mode of action of iron based precatalysts in the presence of Grignard reagents differs from that of nickel and palladium. First of all, the iron precatalyst ($FeCl_2$ in the example shown in Figure 3.10) reacts with 4 equiv of the Grignard reagent (RMgX) to afford $[Fe(MgX)_2]$, which are highly nucleophilic species with a negative formal charge at iron. The highly nucleophilic iron species acts as the catalytically active species and oxidatively adds to aryl halides. The resulting organometallic iron compounds (formally Fe(0)) are transmetallated by the reaction with another equivalent of the Grignard reagent in analogy to the elementary steps passed through during the initial formation of $[Fe(MgX)_2]$ from $FeCl_2$ and RMgX. Subsequent reductive coupling of the organic ligands then forms the desired product and regenerates the Fe(-II) species [107].

Competitive homocoupling reactions are common in iron catalyzed cross coupling reactions and are caused by oxidation with organic halides or iron-catalyzed halogen-metal exchange. So for example, iron-catalyzed aryl-aryl cross-coupling reactions were performed using a $FeCl_3$/KF mixture that also afforded catalytically active species and suppressed the homocoupling. This may be attributed to the fluoride anion coordinating to the iron center therefore hampering the formation of ferrate complexes that possess excess aryl groups (such as $Ar^1Ar^2_2Fe$ and $Ar^1Ar^2_3Fe$) as well as the resulting nonselective reductive elimination (formation of Ar^1-Ar^2 and Ar^2-Ar^2). The fluoride effect is also observed in cobalt- and nickel-catalyzed cross-coupling reactions to suppress homocoupling [108, 109, 110].

One of the most important goals of this research has been to improve the catalytic activity of iron complexes in cross coupling reactions. Although a number of research papers that are interested in iron catalysts especially for C(sp^2)-C(sp^3) coupling were published, most of them utilized particular complexes such as e.g. $FeCl_3$, $Fe(acac)_3$ or $FeCl_2$. Moreover, this required certain conditions and additives such as TMEDA and NMP. Therefore, we synthesized iron complexes with bis-phosphine ligands and employed them directly to cross coupling reactions at ambient conditions without additives to investigate the effect of the ligands on the reaction and for comparison with the results achieved using palladium and nickel catalysts.

It is interesting to note, that the nature of the alkyl chain between the two phosphorus atoms of the ligand is also crucial in improving the desired cross-coupling reactions, as shown in table 3.2. The best results are obtained using [$FeCl_2$(dppp)] together with fluorinated bromobenzenes without ortho-substituents such as bromo-4-flourobenzene, bromo-3,5–difluorobenzene and bromo-3,4,5–trifluorobenzene. These substrates afforded very good yields, whereas the same reactions in the presence of [$FeCl_2$(dppe)] gave lower yields.

It was strange in this respect that [$FeCl_2$(dppm)] was ineffective in all cross coupling reactions. Yields of the cross coupled products was less than 5% with every substrate used. Although we tried to optimize the reaction conditions by refluxing the reaction mixture, increasing the amount of the precatalyst or applying extended reaction timesno progress could be achieved.

3.4 LiCl and LiBr Adducts of Cyclohexyl Grignard reagents in Palladium and Nickel Catalyzed Cross Coupling Reactions with Fluorinated Bromobenzene Substrates.

Since optimization of cross coupling reactions is a major subject in this thesis, a lot of efforts were exerted to enhance the yield of desired cross coupled products by employing additives to the Grignard reagents that play a significant role in oxidative addition, transmetallation and reductive elimination steps. Nevertheless, it should also be kept in mind, that the adjustment of cross coupling reaction condition such as temperatures, the reaction time and pressure will also have an impact on the efficiency of the reaction.

	[$NiCl_2$(dppm)]	[$NiCl_2$(dppe)]	[$NiCl_2$(dppp)]	[$PdCl_2$(dppm)]	[$PdCl_2$(dppe)]	[$PdCl_2$(dppp)]
2-F	35	45	60	55	57	65
3-F	40	65	85	55	76	85
4-F	67	71	85	80	85	90
2,3-F_2	27	45	55	40	55	60
2,4-F_2	30	45	67	65	70	80
2,5-F_2	45	50	65	50	70	85
2,6-F_2	15	40	50	30	43	55
3,4-F_2	60	67	75	70	78	85
3,5-F_2	88	93	96	95	98	99
2,3,4-F_3	30	45	65	50	70	75
2,3,5-F_3	30	60	75	50	65	80
2,4,5-F_3	35	55	75	45	60	80
2,4,6-F_3	20	40	45	35	45	55
3,4,5-F_3	60	65	73	65	80	90

Table 3.3. Yields of the Respective Cross Coupling Products Using Palladium and Nickel Catalysts, Cyclohexyl Magnesium Bromide LiCl Adduct and Fluorinated Bromobenzene Substrates.

If LiCl was added to the Grignard reagent and then the cross coupling reaction was carried out under the same conditions as described above, the yield improved greatly. Some experiments afforded excellent yields that reached up to 99% (Table 3.3). So obviously the addition of LiCl highly increased the efficiency of the cross coupling reactions.

As it was mentioned previously, there is a competitive reaction leading to the formation of homocupling products therefore lowering the percentage yield of cross coupled products. One of the major sources of this side-reaction is the reaction of Grignard reagents. However, Grignard reagents in solution are always inherent to aggregation processes forming dimeric or oligomeric magnesium reagents. This aggregation processes might well be responsible for the acceleration of homocoupling formation from Grignard reagents.

Employing the stoichiometric complex RMgCl·LiCl by addition of LiCl inhibits the formation of polymeric aggregates of RMgCl and affords a more reactive complex. The magnesiate character of $[RMgCl2^{-}Li^{+}]$ is responsible for the improved nucleophilicity of this reagent which in turn leads to a higher reactivity towards electrophiles [111, 112]. These highly reactive Grignard reagents with an enhanced nucleophilicity are expected to facilitate oxidative addition during the cross coupling reaction. This will increase the yield of the desired cross coupling products whereas a slow oxidative addition may be leading to an increased amount of homocoupled product, because then trace of impurities in the employed catalyst or oxygen might get a chance to efficiently compete with the catalytic cycle.

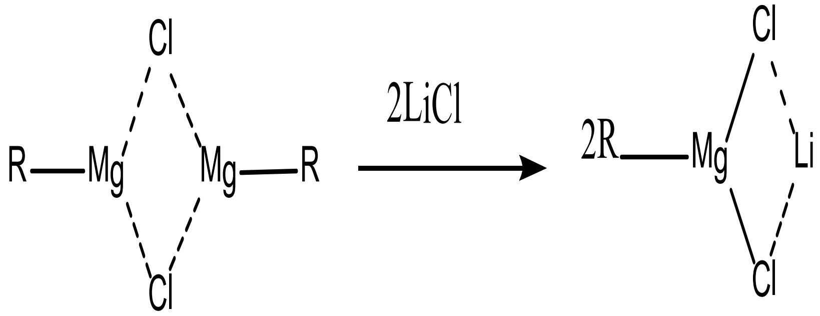


Figure 3.11. Breaking of Dimeric Grignard Reagents by LiCl

When using LiCl during Grignard formulation, it was noticed that the percentage yield of the homocoupling product (bicyclohexyl) became lower compared to reactions without adding LiCl. Even the induction time to initiate the Grignard reaction and the reaction time were obviously decreased. This has also been reported by Knochel *et al.* as a method to prepare functionalized Grignard reagents from aryl halides with the aid of LiCl, which eases the insertion of magnesium into the carbon halogen bond at room temperature to afford the high percentage of Grignard [28]. In addition, LiCl enhances the catalytic activity of a catalyst because of its efficiency to prevent catalyst aggregation during the reaction by forming a salt of high solubility and by inhibiting catalyst degradation [113].

	[$NiCl_2$(dppm)]	[$NiCl_2$(dppe)]	[$NiCl_2$(dppp)]	[$PdCl_2$(dppm)]	[$PdCl_2$(dppe)]	[$PdCl_2$(dppp)]
2-F	40	52	70	65	70	73
3-F	55	75	88	70	90	95
4-F	89	94	98	88	95	100
2,3-F_2	40	60	75	50	66	80
2,4-F_2	40	65	75	70	77	85
2,5-F_2	50	75	90	60	80	95
2,6-F_2	30	45	65	45	65	75
3,4-F_2	65	75	80	75	88	97
3,5-F_2	90	97	100	95	99	100
2,3,4-F_3	45	75	80	50	80	85
2,3,5-F_3	50	65	75	60	85	95
2,4,5-F_3	45	58	80	50	80	90
2,4,6-F_3	30	40	50	35	50	65
3,4,5-F_3	65	80	88	70	90	98

Table 3.4. Yields of the Respective Cross Coupling Products Using Palladium and Nickel Catalysts, Cyclohexyl Magnesium Bromide LiBr Adduct and Fluorinated Bromobenzene Substrates.

It is surprising that the addition of lithium bromide to the Grignard reagent improves the percentage yield of cross coupling reactions greatly, with some experiments showing a complete conversion of the substrates (100% yield of cross coupling product, Table 3.4). This indicates that the influence of LiBr is even more pronounced than the effect of LiCl on cross coupling reactions. Corresponding to the dramatically increased yields of cross coupled products the fraction of homocoupled products is diminished. LiBr seem to have the same chemical and physical influences on the reaction mechanism as LiCl. In general, these salts play a significant role in the efficient preparation of Grignard reagents and also have a positive effect on the oxidative addition and reductive elimination steps in the catalytic cycle that afford the desired products.

3.5 LiCl and LiBr Adducts of Cyclohexyl Grignard Reagents in Iron Catalyzed Cross Coupling Reactions with Fluorinated Bromobenzene Substrates.

	[FeCl$_2$(dppe)]	[FeCl$_2$(dppp)]
2-F	40	55
3-F	65	80
4-F	75	85
2,3-F$_2$	50	60
2,4-F$_2$	40	65
2,5-F$_2$	50	70
2,6-F$_2$	45	50
3,4-F$_2$	70	80
3,5-F$_2$	80	90
2,3,4-F$_3$	50	65
2,3,5-F3	40	55
2,4,5-F$_3$	65	80
2,4,6-F$_3$	75	85
3,4,5-F$_3$	50	60

Table 3.5. Yields of the Respective Cross Coupling Products Using Iron Catalysts, Cyclohexyl Magnesium Bromide LiCl Adduct and Fluorinated Bromobenzene Substrates.

As pointed out above the use of iron precatalysts is triggered by the interest in the optimization of inexpensive, non-toxic, commercially available, and environmentally benign catalytic systems to be employed in cross coupling reactions. In conjunction with our experiences in nickel and palladium catalyzed reactions the addition of lithium salts might also increase the activity of iron precatalysts under mild conditions. Table 3.5 shows the ability of LiCl to improve the yields of the desired product when using iron precatalysts. However, the catalytic activity of iron bis-(diphenylphosphino)alkyl compounds affords percentage yields 90% maximum.

	$[FeCl_2(dppe)]$	$[FeCl_2(dppp)]$
2-F	45	60
3-F	80	90
4-F	90	95
2,3-F_2	55	65
2,4-F_2	70	75
2,5-F_2	75	85
2,6-F_2	50	70
3,4-F_2	75	85
3,5-F_2	90	95
2,3,4-F_3	70	75
2,3,5-F_3	60	70
2,4,5-F_3	65	75
2,4,6-F_3	50	66
3,4,5-F_3	80	90

Table 3.6. Yields of the Respective Cross Coupling Products Using Iron Catalysts, Cyclohexyl Magnesium Bromide LiBr Adduct and Fluorinated Bromobenzene Substrates.

As depicted in Table 3.6 the addition of LiBr produced a high positive impact on the catalytic activity of iron catalysts with percentage yields of cross coupled products up to 95% in some experiments employing $[FeCl_2(dppp)]$. So the reaction conditions applied to get the results shown in Table 3.6 describe an iron based catalytic system that well compares to palladium catalysts under comparable reaction conditions.

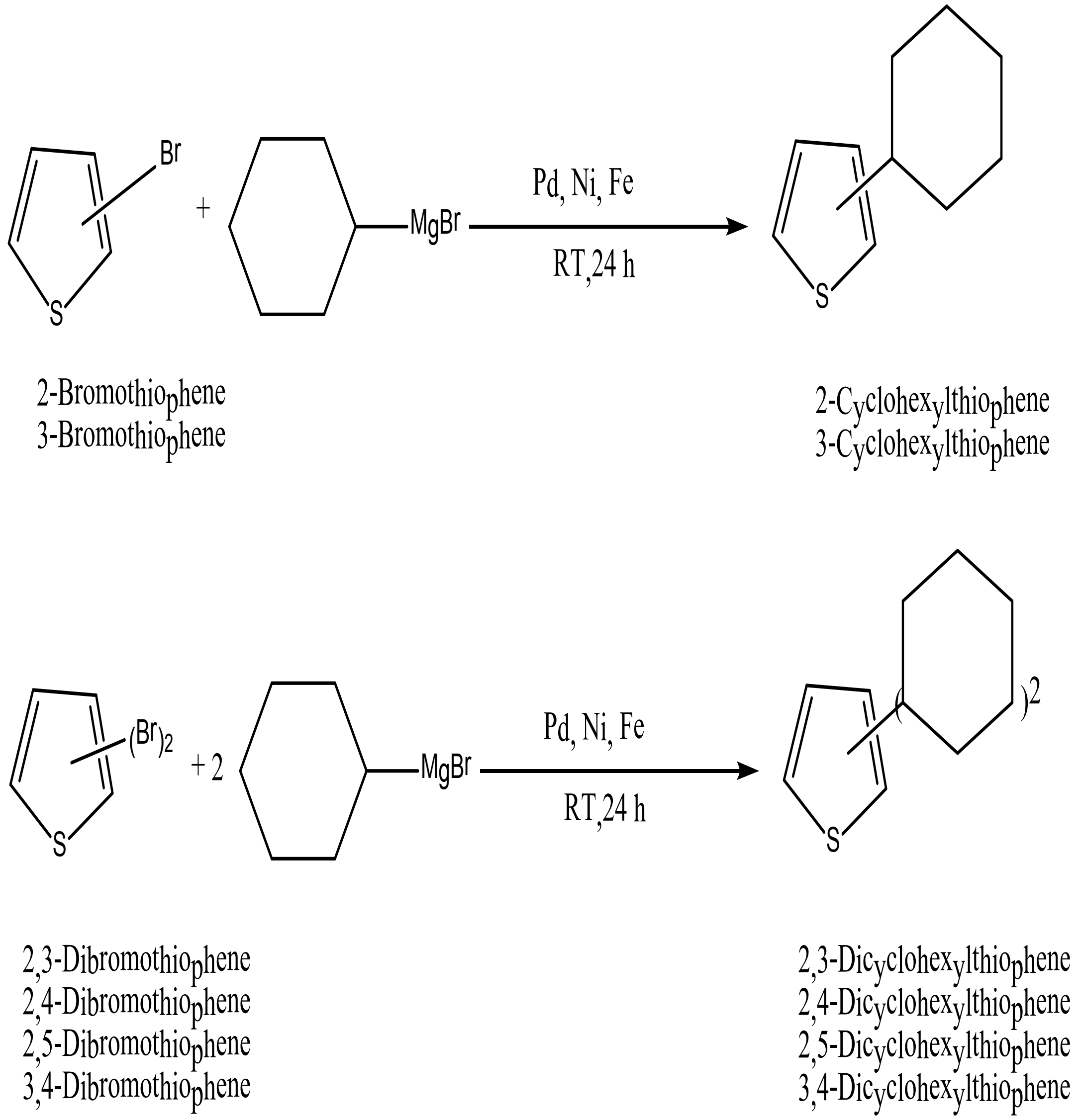


Figure 3.12 Catalytic Cross Coupling Reactions of Cyclohexyl Grignard Reagents with Bromothiophenes.

3.6 Palladium, Nickel and Iron Catalyzed Cross Coupling Reactions of Cyclohexyl Grignard Reagents or their LiCl and LiBr Adducts with Bromothiophene Substrates.

The same catalysts and reaction conditions were applied to carry out the coupling between cyclohexyl magnesium bromide and thiophene derivatives. Table 3.7 presents the results for reactions where just the Grignard reagent without the addition of lithium salts was used. The results show gradually improving yields of cross coupled products when going from [MCl_2(dppp)] > [MCl_2(dppe)] > [MCl_2(dppm)] (M = Pd, Ni and Fe) which is again mainly attributed to the effect of the variation of the bite angle. In general, the reactions took place smoothly and gave the coupling products in reasonable yields.

	$FeCl_2$(dppe)	$FeCl_2$(dppp)	$NiCl_2$(dppm)	$NiCl_2$(dppe)	$NiCl_2$(dppp)	$PdCl_2$(dppm)	$PdCl_2$(dppe)	$PdCl_2$(dppp)
2	30	50	20	40	55	30	50	70
3	40	50	40	47	60	40	55	80
2,3	50	60	30	55	70	50	65	75
2,4	50	65	40	60	75	45	70	85
2,5	30	45	30	40	55	30	60	70
3,4	45	60	40	65	70	50	70	70

Table 3.7 Yields of the Respective Cross Coupling Products Using Pd, Ni and Fe Catalysts, Cyclohexyl Magnesium Bromide as Grignard Reagent and Bromothiophene substrates.

	$FeCl_2$(dppe)	$FeCl_2$(dppp)	$NiCl_2$(dppm)	$NiCl_2$(dppe)	$NiCl_2$(dppp)	$PdCl_2$(dppm)	$PdCl_2$(dppe)	$PdCl_2$(dppp)
2	40	70	30	60	75	50	60	90
3	50	75	40	65	75	55	75	90
2,3	66	70	25	70	80	50	75	88
2,4	70	80	55	70	85	55	75	90
2,5	50	60	35	60	75	40	80	85
3,4	65	75	50	80	85	50	90	90

Table 3.8 Yields of the Respective Cross Coupling Products Using Pd, Ni and Fe Catalysts, Cyclohexyl Magnesium Bromide LiCl adduct and Bromothiophene substrates.

	FeCl$_2$(dppe)	FeCl$_2$(dppp	NiCl$_2$(dppm)	NiCl$_2$(dppe)	NiCl$_2$(dppp)	PdCl$_2$(dppm)	PdCl$_2$(dppe)	PdCl$_2$(dppp)
2	50	90	40	70	80	50	75	95
3	70	95	45	75	85	60	85	95
2,3	75	80	30	80	95	60	90	99
2,4	80	90	60	80	90	60	85	95
2,5	65	80	50	75	85	55	80	90
3,4	75	90	60	90	95	50	99	99

Table 3.9 Yields of the Respective Cross Coupling Products Using Pd, Ni and Fe Catalysts, Cyclohexyl Magnesium Bromide LiBr adduct and Bromothiophene substrates.

The effieciency of this coupling protocol for alkyl-heteroaryl coupling may even be optimized if lithium halogenides are added to the solution of Grignard reagents. When LiCl is employes to the Grignard reagent and then the cross coupling reaction was carried out under the same reaction conditions as before , yields improved improved significantly, affording very good results (Table 3.8). Percentage yields were even more enhanced giving excellent results by employing lithium bromide in the cross coupling reactions of bromothiophenes with cyclohexyl Grignard reagent LiBr aducct. The highest catalytic activity was achieved using [PdCl$_2$(dppp)] as the precatalyst giving almost quantitative yields for all compounds. Nevertheless, it should be pointed out that the addition of LiBr again leads to enhanced catalytic activity of iron complexes which therefore are compatible with nickel and palladium precatalysts for C(sp^2)-C(sp^3) coupling reactions with different substrates. In general, the impact of LiCl and LiBr on the coupling of bromothiophene derivatives with cyclohexyl Grignard reagents can be interpreted in the same way that has been elucidated in conjunction with the fluorinated bromobenzene coupling with cyclohexyl nucleophiles.

The formation of cyclohexyl thiophene as an undesired side product when using dibromothiophene could be attributed to metallation of one of the carbon atoms once being bound to bromine. This may be achieved either via a metal halogen exchange or by a direct insertion of a magnesium atom generating the grignard part in the dibromothiophene compound. Subsequent hydrolysis took place to afford cyclohexyl thiophene that caused diffculties in the separation of pure dicyclohexyl thiophene. In Figure (3.13) an example of this side reaction to illustrate the formation mono cyclohexyl thiophene is depicted.

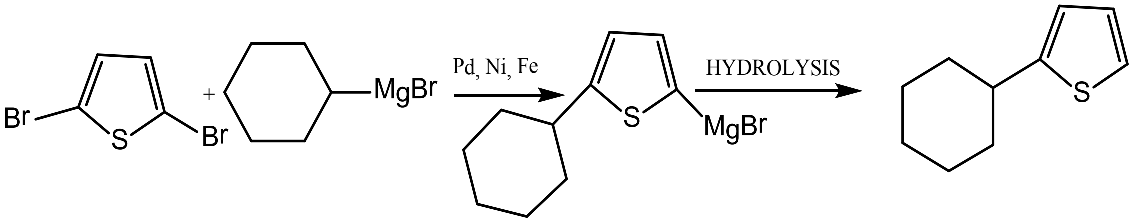


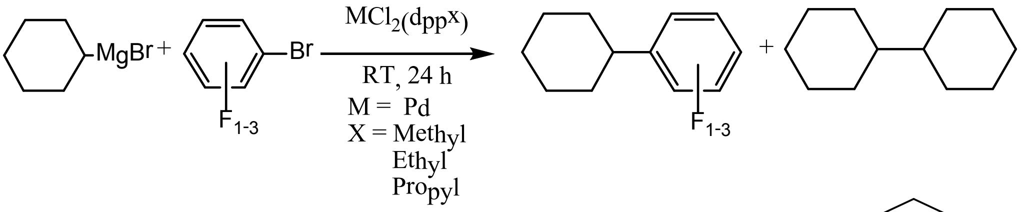
Figure 3.13 . Formation mono cylohexyl thiophene when use dibromothiophene as a substrate

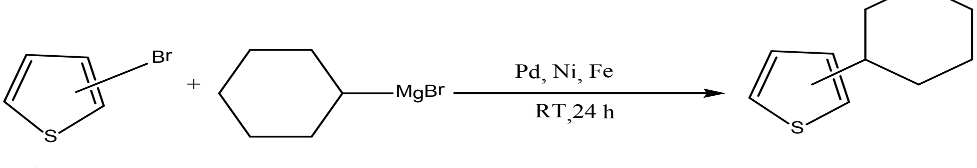
4. Summary

In this work, in general, our efforts were concentrated on improving the catalytic activity of nickel and iron complexes comparing them with catalytically active palladium complexes that typically are utilized in cross coupling reactions. As we know cross-coupling reactions catalysed by iron complexes are one of the promising research areas for the construction of C-C bonds, because of iron is cheap and more environmentally friendly than palladium or nickel. The second goal of this research was to find a general procedure for the coupling of Csp^3 with Csp^2 under ambient conditions such as room temperature, normal pressure and reasonable reaction times. In addition, effects of ligand bite angles and addition of lithium salts on the efficiency of catalysts was investigated.

In contrast to most of the published reactions we chose the coupling of an alkyl Grignard component with an aromatic electrophile while these reactions are normally performed the other way round. Cyclohexyl magnesium bromide as Csp^3 nucleophile reacted with various fluorinated bromobenzene substrates (Csp^2), as well as bromo-thiophene derivatives to afford the desired cross coupled products that are e.g. used as precursors for liquid crystalline materials according to the equations below:

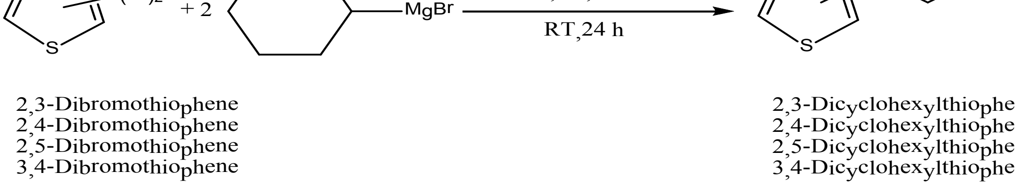
To achieve optimized reaction circumstances, LiCl and LiBr were employed as additives





2-Bromothiophene
3-Bromothiophene

2-Cyclohexylthiophene
3-Cyclohexylthiophene



2,3-Dibromothiophene
2,4-Dibromothiophene
2,5-Dibromothiophene
3,4-Dibromothiophene

2,3-Dicyclohexylthiophene
2,4-Dicyclohexylthiophene
2,5-Dicyclohexylthiophene
3,4-Dicyclohexylthiophene

in the preparation of Grignard reagents, which were then introduced to the reaction mixtures under inert conditions to afford the desired (Csp^3-Csp^2) coupled products in significantly enhanced yields. Especially the use of LiBr highly improved the catalytic activity for all catalysts, even the performance of iron complexes in cross coupling reactions was enhanced greatly to sometimes give results equal to palladium at the same conditions.

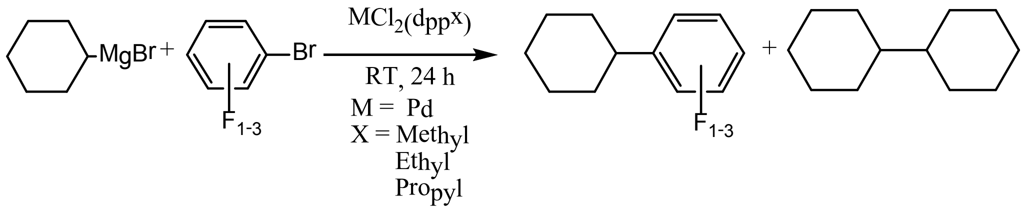
We noted that the bite angle of the used bisphosphine ligands played a crucial role to the percentage yield through impact on cross coupling stages during the reactions. Yields of cross coupled products gradually improved when going from [MCl_2(dppp)] > [MCl_2(dppe)] > [MCl_2(dppm)] (M = Pd, Ni, Fe). This behaviour is attributed to the effect of widening the bite angle therefore facilitating and accelerating the reductive elimination elementary step leading to a reduced amount of homocoupling products . The formation of homocoupling products under certain reaction conditions turned out to be one of the major drawbacks of the Kumada coupling procedure because extensive purification procedures were necessary to obtain pure compounds.

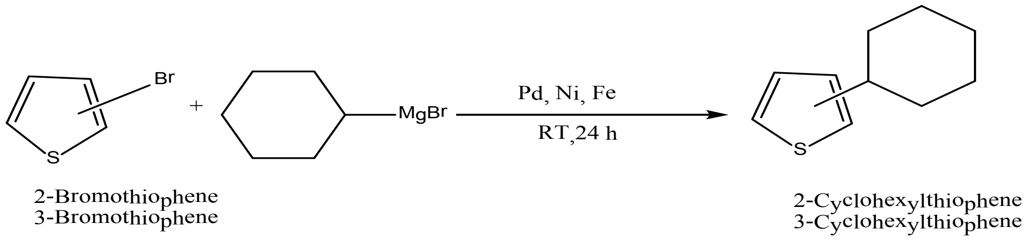
5. Zusammenfassung

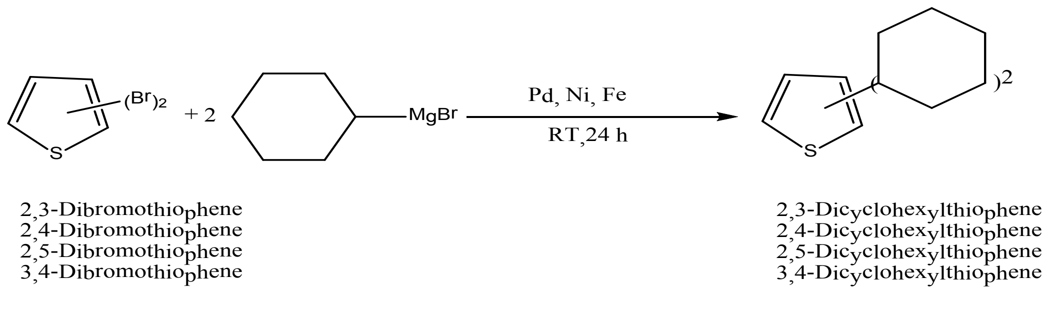
Das Hauptanliegen der Arbeit war die Verbesserung der katalytischen Aktivität von Nickel- und Eisenkomplexen und der Vergleich mit den in Kreuzkopplungsreaktionen typischerweise verwendeten Palladiumkomplexen. Dabei war uns bewusst, dass eisenkatalysierte Kreuzkopplungsreaktionen zu den vielversprechenden Ansätzen zum Aufbau von C-C Bindungen gehören, da Eisen zum einen billig und zum anderen in seinen Auswirkungen auf die Umwelt weniger problematisch ist als Palladium oder Nickel.

Das zweitre Ziel der Untersuchungen war, eine generalisierbare Verfahrensweise zur Kopplung von Csp^3 und Csp^2 Atomen unter gemäßigten Bedingungen wie Raumtemperatur, Normaldruck und vernünftige Reaktionszeiten zu finden. Außerdem wurden die Effekte des Bisswinkels der verwendeten Co-Liganden und die Auswirkungen der Addition von Lithiumsalzen auf die Katalysatoreffizienz untersucht.

Im Gegensatz zu den meisten bisher publizierten Untersuchungen wählten wir die Kopplung von Alkyl Grignard Komponenten mit einem aromatischen Elektrophil, während vergleichbare Reaktionen normalerweise genau umgekehrt realisiert werden. Cyclohexyl-magnesium-bromid als Csp3 Nukleophil wurde mit verschiedenen fluorierten Bromobenzen-Derivaten sowie







bromierten Thiophenen zur Reaktion gebracht, um die gewünschten Kreuzkopplungsprodukte zu erhalten, wie sie in den Abbildungen unten gezeigt sind.

Um optimierte Reaktionsbedingungen zu erreichen, wurden LiCl und LiBr als Additive in der Bereitung der Grignard Reagenzien zugesetzt, die dann unter Inertbedingungen in die Reaktionsmischungen eingebracht waren und die Ausbeuten an (Csp^3-Csp^2) gekoppelten Produkten signifikant erhöhten. Vor allem die Verwendung von LiBr verbesserte die katalytische Aktivität aller Katalysatoren deutlich, wobei vor allem die Eigenschaften der Eisenkomplexe in besonderem Ausmaß erhöht wurde, sodass diese Reaultate ergaben, die mit denen von Palladiumkomplexen unter denselben Reaktionsbedingungen vergleichbar sind.

Wir stellten außerdem fest, dass der Bisswinkel der verwendeten Bisphosphane eine wichtige Rolle in Bezug auf die prozentuale Ausbeute an Kreuzkopplungsprodukten im Verlauf der Reaktionen spielt. Die Ausbeuten der Kreuzkopplungsprodukte erhöhte sich dabei gleichmäßig beim Gang von [MCl_2(dppm)] über [MCl_2(dppe)] zu [MCl_2(dppp)] (M = Pd, Ni, Fe). Dieses Verhalten beruht auf der Weitung des Bisswinkels, wodurch der Elementarschritt der reduktiven Eliminierung erleichtert und beschleunigt wird, was gleichzeitig zu einer geringeren Ausbeute an Homokopplungsprodukten führt. Die Bildung dieser Homokopplungsprodukte stellte sich als einer der wesentlichen Schwierigkeiten der Kumada-Kopplung heraus, da sich daraus die Notwendigkeit aufwändiger Aufarbeitungsschritte zum Erhalt reiner Verbindungen ergab.

6. References

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Declaration of Originality

I certify that the work presented here is, to the best of my knowledge and belief, original and the result of my own investigations, except as acknowledged, and has not been submitted, either in part or whole, for a degree at this or any other university.

Ich erkläre, dass ich die vorliegende Arbeit selbstständig und nur unter Verwendung der angegebenen Hilfsmittel, persönlichen Mitteilungen und Quellen angefertigt habe und dass ich nicht die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung bei einer anderen Hochschule als Dissertation eingereicht habe.

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DFT calculations on catalysis products

	aromatic axial		aromatic equatorial		half-chair (TS)		
Subst.	HF [a.u.]	NImag	HF [a.u.]	NImag	HF [a.u.]	NImag	□$H^{\#}$ [$kJmol^{-1}$]
2	-566.101661	0	-566.108370	0	-566.089274	1	35.52 50.14
3	-566.101277	1	-566.108012	0	-566.089673	1	30.47 48.15
4	-566.100788	0	-566.107780	0	-566.089908	1	28.57 46.92
2,3	-665.368426	0	-665.375170	0	-665.356469	1	31.39 49.10
2,4	-665.374538	0	-665.381486	0	-665.362198	1	48.09 50.64
2,5	-665.374264	0	-665.381299	0	-665.362229	1	31.60 50.07
2,6	-665.371522	0	-665.381093	0	-665.363466	1	21.15 46.28
3,4	-665.367670	0	-665.374312	0	-665.355909	1	30.88 48.31
3,5	-665.374628	0	-665.381892	0	-665.362773	1	31.13 50.20
2,3,4	-764.633743	0	-764.640457	0	-764.622522	1	31.07 47.09
2,3,5	-764.640241	0	-764.647261	0	-764.627575	1	33.25 51.69
2,3,6	-764.636769	0	-764.646199	0	-764.629113	1	20.10 47.65
2,4,5	-764.639735	0	-764.646652	0	-764.627901	1	31.07 49.23
2,4,6	-764.642986	0	-764.652681	0	-764.635432	1	19.83 45.29
3,4,5	-764.633500	0	-764.640804	0	-764.621276	1	32.09 51.27

Element	Einheit	wasserfreies $FeCl_2$
Li	mgkg	<1
Be	mgkg	<3
B	mgkg	<10
Na	mgkg	4
Mg	mgkg	1
Al	mgkg	<3
Si	mgkg	<50
P	mgkg	<20
S	mgkg	<5
K	mgkg	<2
Ca	mgkg	35
Sc	mgkg	<2
Ti	mgkg	<1
V	mgkg	<5
Cr	mgkg	8
Mn	mgkg	20
Fe	mgkg	Matrix
Co	mgkg	12
Ni	mgkg	5
Cu	mgkg	<10
Zn	mgkg	<10
Ga	mgkg	<3
Ge	mgkg	<3
As	mgkg	<10
Se	mgkg	<10
Rb	mgkg	<1
Sr	mgkg	<1
Y	mgkg	<1
Zr	mgkg	<2
Nb	mgkg	<1
Mo	mgkg	<5
Ru	mgkg	<2
Rh	mgkg	<1
Pd	mgkg	<5
Ag	mgkg	<2
Cd	mgkg	<5
In	mgkg	<20