The Manganese-Catalyzed Cross-Coupling Reaction

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Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

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PhD Thesis – November 2017

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“*The good thing about science is that it's true whether or not you believe in it.*”

Neil deGrasse Tyson

Acknowledgements

It is a pleasure to thank the many people who made this thesis possible.

First and foremost, I would like to express my profound gratitude to my supervisor Prof. Robert Madsen, for all the advices, support, and especially his understanding along the way. It has been a great opportunity for me to do my PhD in his group.

Thanks to all the members of the Madsen group, present and former colleagues, for the support and the friendship you gave me right away. In particular thanks to Clotilde, Carola, Andrea, Fabrizio Jr and Fabrizio Sr. Thanks to Andreas for all the chats and for making our lab a happier place.

Thanks to Enzo, Andrea, Carola, Fabbro, Luca, Fabrizio, Ylenia and Ludo for the friendship and affection that made my time in Denmark enjoyable.

My sincere gratitude goes to the technical staff of the chemistry department. Thanks to Anne Hector, Lars Egede Bruhn, Brian Dideriksen, Brian Ekman-Gregersen, and Charlie Johansen for their great help.

Thanks to Fabrizio Bottaro for proofreading along the way, and to Daniel Lupp for the final reading.

Thanks to all my family members for their love and support, in particular to my father, always there for every difficulty and for always answering my calls for help. Thanks to Francesca and Lynell for the nights spent on my thesis looking for the many mistakes.

Thanks to all my friends, old and new, for the support and the special moments spent with me. Thanks to Domenico to be the friend I can always trust, always there to help and never demanding.
Thanks to Rosa, to be by my side, making my days brighter. Thanks for all the patience, the sweetness and the smiles that you donate to me every day.

Giuseppe Antonacci
November 2017

Ringraziamenti

Questa tesi descrive il lavoro condotto durante il mio Phd. Il dottorato è stato svolto presso il DTU in Danimarca, sotto la supervione del professor Robert Madsen, da novembre 2013 a marzo 2017.

Prima di tutto, vorrei esprimere la mia profonda gratitudine nei confronti del mio supervisor professor Rober Madsen. È stata una grande opportunità per me poter lavorare nel suo gruppo. Grazie per i buoni consigli, il supporto e la comprensione mostrata.

Grazie a tutti i membri del Madsen Group, colleghi presenti e passati. In particolar modo un ringraziamento a Andrea, Carola, Clotilde, Enzo, Fabrizio jr and Fabrizio sr. Un ringraziamento anche ad Andreas per tutte i bei discorsi affrontati in laboratorio, e per aver reso lo stesso un posto più allegro.

Grazie a Enzo, Andrea, Carola, Fabbro, Luca, Fabrizio sr., Ylenia e Ludo per l'amicizia e l'affetto che mi avete dimostrato. Avete reso il tempo passato in Danimarca memorabile!

La mia sincera gratitudine va anche allo staff tecnico del dipartimento di chimica; Anne Hector, Lars Egede Bruhn, Brian Dideriksen, Brian Ekman-Gregersen, Charlie Johansen. Grazie per l'aiuto.

Mille grazie a Fabrizio Bottaro per le correzioni durante la stesura, e grazie a Daniel per la lettura finale.

Un ringraziamento a tutta la mia famiglia per il loro amore e supporto. In particolare un ringraziamento a mio padre per essermi sempre di conforto, e di rispondere

sempre con prontezza a ogni richiesta d'aiuto. Grazie a Francesca e Lynell per le notti passate a correggere i vari capitoli in cerca di errori.

Grazie a tutti i miei amici, i nuovi e i vecchi, per tutte le volte che avete reso le mie giornate migliori. Grazie in particolare a Domenico, per essere un amico fidato e un aiuto su cui contare.

Grazie a Rosa, per rendere i miei giorni più luminosi, per la pazienza che mi dimostri, la dolcezza con cui mi tratti e i sorrisi che mi regali ogni giorno.

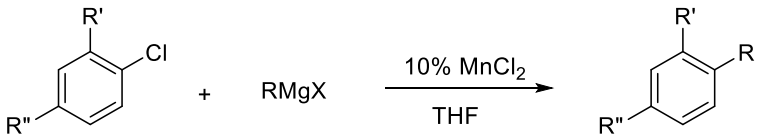
Giuseppe Antonacci
Novembre 2017

Table of Contents

Abstract

Manganese-catalyzed cross-coupling reactions

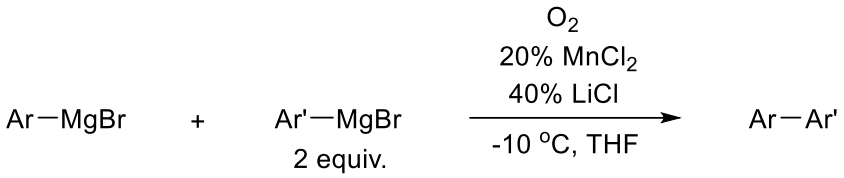
Herein it is presented the $MnCl_2$-catalyzed cross-coupling reaction between aryl halides and Grignard reagents. Aryl chlorides containing a cyano or an ester group in the *para* or *ortho* position react smoothly and in good yield. A variety of alkyl- and arylmagnesium chlorides can be used in this cross-coupling reaction. The mechanism of the cross-coupling is believed to proceed by a $S_{RN}1$ mechanism and radical clock experiments were performed in order to elucidate this pathway. A triorganomanganate complex is believed to be formed by the reaction between the organomagnesium halide and manganese chloride, and it serves both as the nucleophile and the single electron donor. Other mechanistic hypotheses were excluded on the basis of the results of the performed experiments.



General reaction for Mn-catalyzed crross-coupling reactions

An improved protocol has been developed for the manganese catalyzed cross-coupling of two arylmagnesium bromides under an atmosphere of dioxygen. The reaction is performed with a 2:1 ratio between the Grignard

reagents and 20% of $MnCl_2$. When the limiting Grignard regent undergoes little homo-coupling under the reaction conditions, very good yields of the hetero-coupling product can be achieved. Arylmagnesium bromides with 4-methoxy, 4-dimethylamino, 4-fluoro and 4-chloro substituents give high yields in the cross-coupling while heterocyclic Grignard reagents turned out to be poor substrates for the reaction.

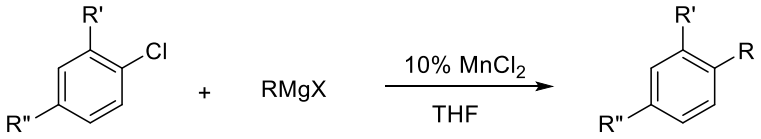


Mn-catalyzed oxidative cross-coupling reaction

Resume

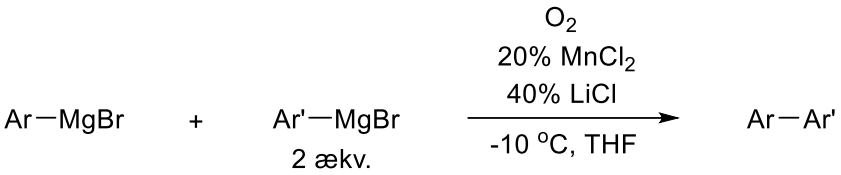
Mangankatalyseret krydskoblingsreaktion

I denne afhandling præsenteres den $MnCl_2$-katalyserede krydskobling mellem arylhalider og Grignard reagenser. Arylchlorider indeholdende en cyano eller en ester gruppe i para eller ortho positionen reagerer nemt og i godt udbytte. En række alkyl- og arylmagnesium chlorider kan anvendes i denne krydskoblingsreaktion. Mekanismen for krydskoblingen formodes at forløbe via en $S_{RN}1$ mekanisme, og radikalklokke eksperimenter blev gennemført for at afklare denne reaktionsvej. Et triorganomanganat kompleks formodes at blive dannet ved reaktionen mellem organomagnesium halidet og manganchlorid, og denne fungerer både som nukleofil og enkelt elektron donor. Andre mekanistiske hypoteser blev afvist baseret på resultaterne i de gennemførte eksperimenter.



Generel reaktion for Mn-katalyserede krydskoblingsreaktioner

En forbedret metode er blevet udviklet til den mangankatalyserede krydskobling af to arylmagnesium bromider under en oxygen atmosfære. Reaktionen blev gennemført med et 2:1 forhold mellem Grignard reagenserne og 20% af $MnCl_2$. Meget gode udbytter kunne opnås af heterokoblingsproduktet, når det begrænsende Grignard reagens reagerede meget lidt i en homokobling under reaktionsbetingelserne. Arylbromider med 4-methoxy, 4-dimethylamino, 4-fluor og 4-chlor substituenter giver høje udbytter i krydskoblingen, mens heterocykliske Grignard reagenser viste sig at være dårlige substrater for reaktionen.



Mn-katalyseret oxidativ krydskobling

List of abbreviations

Ar	Aromatic
Bu	Butyl
Cy	Cyclohexyl
DFT	Density functional theory
DMA	*N*,*N*-Dimethylacetamide
Et	Ethyl
ET	Electron transfer
EWG	Electron withdrawing group
GC-MS	Gas chromatography / mass spectrometry
HRMS	High resolution mass spectrometry
^{i}Pr	*iso*-Propyl
m	Meta
Me	Methyl
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
Ph	Phenyl
ppm	Parts per million
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilc substitution
rt	Room temperature
*t*Bu	*tert*-Butyl
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
THF	Tetrahydrofuran
TS	Transition state

Chapter 1

Introduction to catalysis

1.1 Fundamental principles

Catalysis (from Greek καταλύειν) is a phenomenon that changes the rate of a chemical reaction due to the action of an agent called a catalyst.

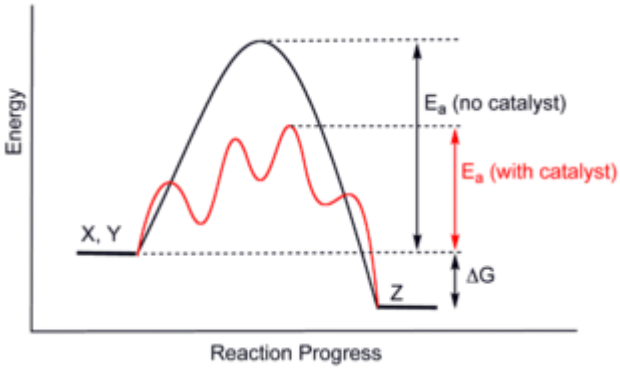


Figure 1.1: Effect of the catalyst on the energetic profile of a standard reaction.

The catalysis field is a branch of chemistry that is specialized in the synthesis, design and characterization of compounds intended to be catalysts for a large variety of reactions.

The catalyst can act in two different ways: it can modify the mechanism of the reaction, or it can reduce the energy of the rate-determining step without changing the overall Gibbs energy of the reaction.[1] This will lead to the completion of reactions that could be immensely slow or impossible to achieve without a significant temperature increase.

By definition the catalyst is not consumed during the reaction, and usually it is added in sub-stoichiometric amounts, i.e. catalytic quantities. As a matter of fact, the catalyst often loses its activity after a certain number of interactions, where this number is called the turnover number (TON) and represents the productivity of a catalyst. Another parameter that needs to be taken into consideration is the turnover frequency (TOF) that is the TON per unit of time.

The detailed description of how a catalyst interacts with a molecule to obtain the product is called the catalytic cycle. The catalytic cycle gives information about the oxidation state of the metal, the orientation of its ligands and every information that is important to understand what occurs during the catalytic process.

A further differentiation between catalysts comes from the phase they are in. If the catalyst is dissolved in the same phase as the reagents it is called a homogeneous process, and if not it is a heterogeneous procedure.

The concept of catalysis is well known in nature. In fact, every kind of living being is provided with a huge number of enzymes that help them to complete reactions that would be impossible to achieve without any catalytic agent.

The use of a catalyst provides important benefits, since it is possible to perform reactions, in a very efficient way, that would otherwise be impossible or expensive and only by using small amounts of reagents and energy.

1.2 Catalysis in the past

Since the birth of civilization the human kind started to use the power of catalysis in several different applications. For example, the simple process of making bread involves the use of enzymes present in yeast, and the wine production uses the anaerobic fermentation.

The first documented examples of catalysis applied to chemistry are reported in the early 1800s where Kirchhoff reported the acid catalyzed AMIDO hydrolysis.[2]

The term catalysis itself was introduced by Bèrzelius in 1835, but it was adjusted in the work of Ostwald in 1885, claiming that the catalysts are substances that can modify the speed without changing the energy factors of a reaction. Ostwald's precious work was awarded with the Nobel prize in Chemistry in 1909.[3]

The first experiments on metal reagents such as nickel, platinum, iron and others showed that they were suitable to conduct a redox reaction as, for example, the way to obtain chlorine from hydrochloric acid[4] promoted by copper, or water splitting promoted by platinum.[5]

Probably, the first attempt to apply metal catalysis to organic compounds was performed in the early 1900s by Wilhelm Normann who discovered the oleic acid reduction to stearic acid in the presence of nickel powder.

Other two major discoveries were the Haber process[6] (*scheme 1.1)* for the production of ammonia (awarded with the Nobel prize in 1918), and the Fischer-Tropsch process (1926, *scheme 1.2*) that allows the synthesis of hydrocarbons from hydrogen and carbon monoxide.

$$N_2(g) \rightleftarrows 2\ N_{ads}$$

$$H_2(g) \rightleftarrows 2\ H_{ads}$$

$$N_{ads} + H_{ads} \rightleftarrows NH_{ads}$$

$$NH_{ads} + H_{ads} \rightleftarrows NH_{2ads}$$

$$NH_{2ads} + H_{ads} \rightleftarrows NH_{3ads}$$

$$NH_{3ads} \rightleftarrows NH_3(g)$$

Scheme 1.1: Description of the Haber process: It allows the production of ammonia on large scale from nitrogen and hydrogen in the presence of an iron heterogeneous catalyst.

$$nCO+(2n+1)H_2 \rightarrow C_nH_{2n+2} + nH_2O$$

Scheme 1.2: General chemical equation that describes the Fischer-Tropsch process for the synthesis of alkanes.

The evolution of catalysis continued incessantly during the ’50 and the ’60 and the first International Conference on Catalysis (ICC) was organized in 1950. Finally, in 1962 the first issue of “Journal of Catalysis” was published.

During these years an interesting topic was about the synthesis of the polymers, and as a result the Nobel Prize in 1963 was given to Ziegler and Natta for their work about polymerization using TiO_2 based catalysts.[7]

The ’70 brought the energy crisis on the desk of the major chemists of that time, and consequently they tried to obtain gasoline and other chemicals from raw materials other than oil. Furthermore, the necessity to improve the sustainability of the chemical processes by producing less waste, and

optimizing the already existing methods, led to a further development in the catalysis field.

During this period the area of palladium cross-coupling catalysis saw the light with the work of Mizoroki, Heck, Sonogashira, Kumada and many others. This led to the Nobel Prize awarded in 2010 to Heck, Suzuki and Negishi for their contribution to one of the most versatile ways of forming C-C bonds in organic chemistry (*scheme 1.3*).

General reaction scheme of cross-coupling reactions:

$$\text{R'-M} + \text{R''-X} \xrightarrow{\text{cat.}} \text{R'-R''} + \text{M-X}$$

cat.: transition metal catalyst, e. g. Ni(0) or Pd(0)-complex
R', R'': organic substituents
M: non-noble metal based substituent, e. g. BR_2 (Suzuki coupling)
SnR_3 (Stille coupling), ZnX (Negishi coupling), MgX (Kumada coupling)
X: leaving group, e. g. Cl, Br, I, OTf.

Scheme 1.3: General scheme of cross-coupling reaction.

In 1990 the area of research that addresses the challenges of environmental pollution and the public demand to do something about it, was named "green chemistry". This branch of chemistry aims to replace the most harmful processes for the environment with more sustainable transformations.

Again catalysis is viewed as one of the most important tools to achieve this goal, since it by definition mediates a process in a more efficient way.

At the beginning of the 21st century the political agenda is focused on climate change, and the search for sustainable energy and more efficient synthetic methods. Moreover, the pharmaceutical industry needed more and cheaper ways to synthetize compounds. All of these are topics where the catalysis field finds itself fully involved.

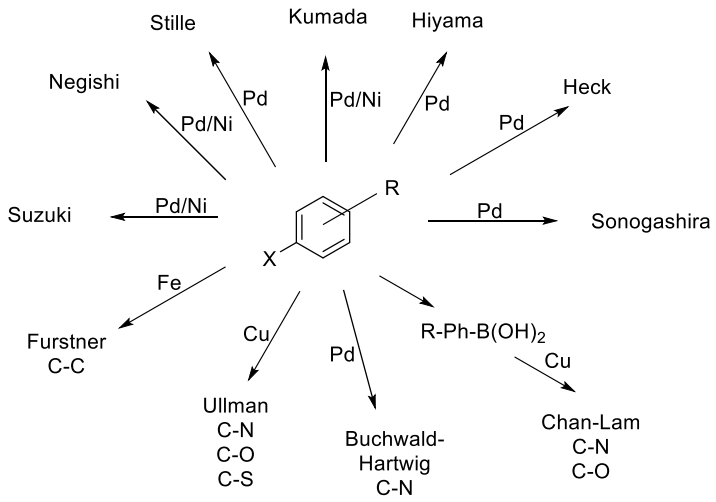
1.3 Overview of cross-coupling reactions

One of the first things that comes into mind of a chemist when talking about catalysis are the cross-coupling reactions. This kind of process involves the fusion of two fragments by the creation of a C-C bond (sometimes a C-N bond). It usually involves a metal (palladium, nickel, iron, etc.) that acts as a catalyst (*scheme 1.4*).

The family of the cross-coupling reactions is divided in two types:

- The hetero-coupling, where the two fragments are different, as for example the Kumada-Corriu coupling and the Heck reaction;
- The homo-coupling, where the two fragments are identical, as for example the Glaser coupling reaction.

It is commonly accepted that the first reaction of this kind was accomplished by Wurtz in 1855.[8] Since then the number of scientists that have put their focus on this topic has steadily reached the pinnacle with the Nobel Prize assigned in 2010 to Heck, Suzuki and Negishi for their work on the palladium-catalyzed carbon carbon bond formation.

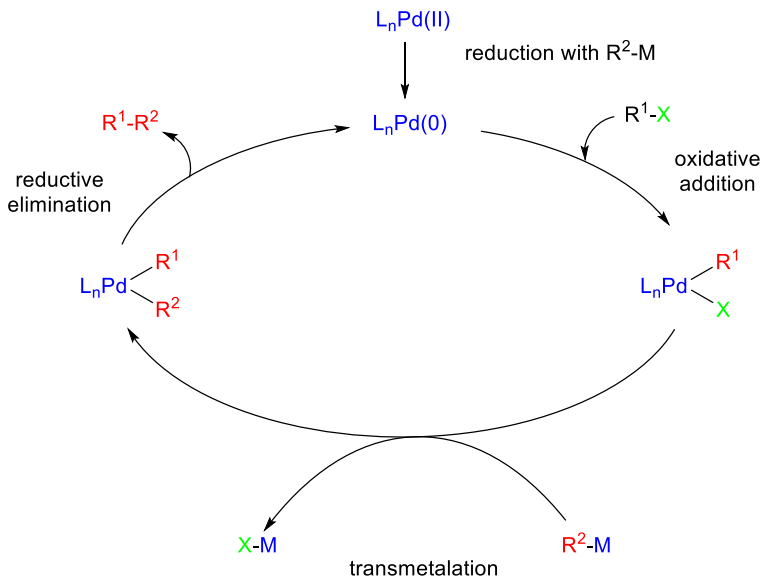


Scheme 1.4: Examples of the most well-known name cross-coupling reactions.

This discovery has been of paramount importance, and it has been introduced in every field of organic synthesis.

Palladium is a very versatile catalyst for most of the cross-coupling reactions discovered so far, and was the metal of choice in the early development of the transformation. But palladium has also some flaws, since is a very expensive and a toxic metal. As a result, the attention in these days is directed towards finding good substitutes for palladium.

A short overview about the most renowned cross-coupling reactions will follow, with particular focus on the Kumada coupling that is the most relevant reaction for this project.

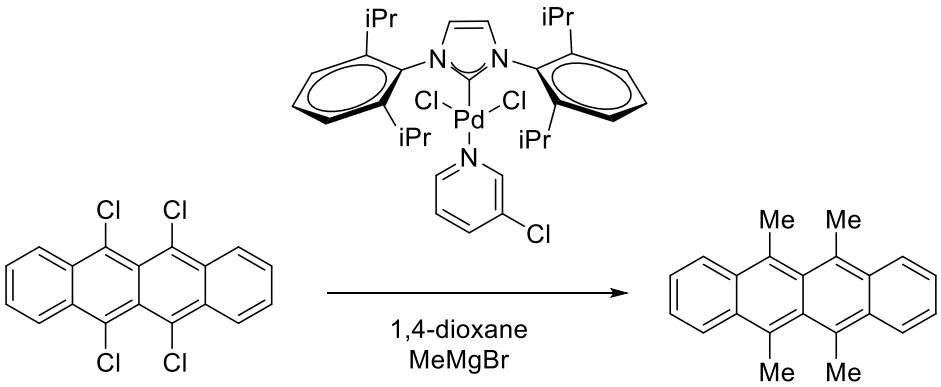


Scheme 1.5: General mechanism of a palladium catalyzed cross-coupling reaction.

1.3.1 Kumada coupling

The Kumada coupling is a cross-coupling reaction used to make carbon-carbon bonds starting from a Grignard reagent and an organic halide.

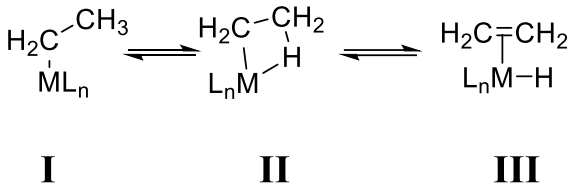
It was reported independently in 1972 from the research groups of Robert Corriu[9] and Makoto Kumada.[10]
Despite being discovered almost 50 years ago it is still used in several industrial applications, such as the synthesis of drugs and electronic components like the polythiophenes (*scheme 1.6*).



Scheme 1.6: Synthesis of derivatives of acene used as semiconductor.[11]

It was the first palladium or nickel catalyzed cross-coupling reaction to be presented. The scope of the reaction is very broad, since a large variety of Grignard reagents can be used. Moreover, it is relatively easy to synthesize Grignard reagents from the corresponding halides. Pseudohalides can be used as well, and the coupling also works effectively with tosylates[12] and triflates[13] under various conditions.

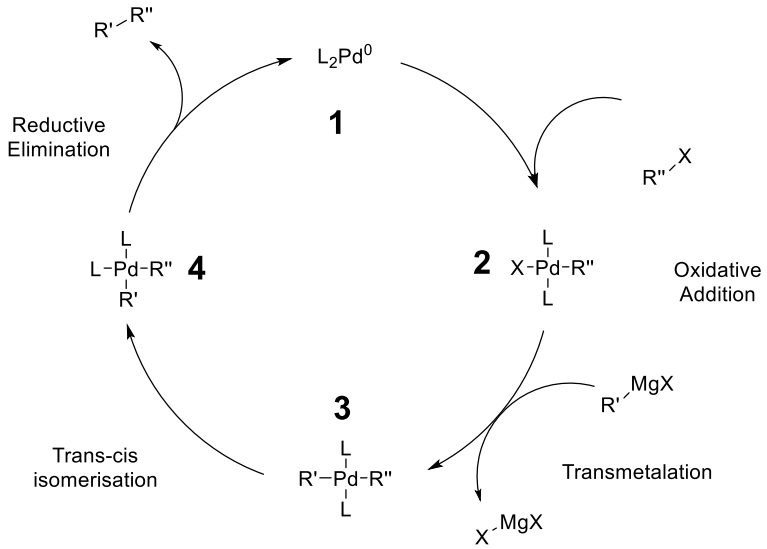
The limitations of this reaction come from the reactivity of Pd(0) with air and from the limited tolerance to functional groups, since the Grignard reagents are generally strong bases and strong nucleophiles. Another problem comes from the reaction of ß-hydride elimination that can occur when the Grignard reagent is an alkylmagnesium halide (*scheme 1.7*).



Scheme 1.7: Mechanism of β-hydride elimination.

Unfortunately, palladium catalysts are easily oxidized by air. This problem can be solved by using phosphine ligands. They slow the oxidation process making the use of palladium less complex.

The accepted mechanism of the Kumada coupling usually involves four steps (*scheme 1.8*).



Scheme 1.8: Accepted catalytic cycle for palladium catalyzed Kumada coupling reaction.[14]

After the active form of the catalyst is formed, the organohalide reacts with the metal in an oxidative addition, where the oxidation number of the metal increases by two. Then, a transmetalation between magnesium and the metal occurs. The third step is a trans-cis isomerization of the complex that finally expels the two organic fragments with a reductive elimination that brings the metal to its initial oxidation state.

This reaction can also be enantioselective by using chiral ligands.[15]

After understanding how important this reaction is, scientists have tried to introduce other metals instead of nickel or palladium.[16,17,18]

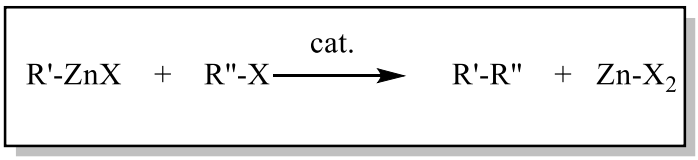
1.3.2 Negishi coupling

Published in 1977 the Negishi coupling was the first reaction that allowed the synthesis of unsymmetrical biaryls with a good yield. The scope is not limited to the synthesis of the biaryls, but is in fact very broad.[19]

The protocol consists of a reaction of an organozinc compound with a halide or a triflate (*scheme 1.9*), in the presence of a palladium or nickel catalyst, that usually needs to be reduced in situ.

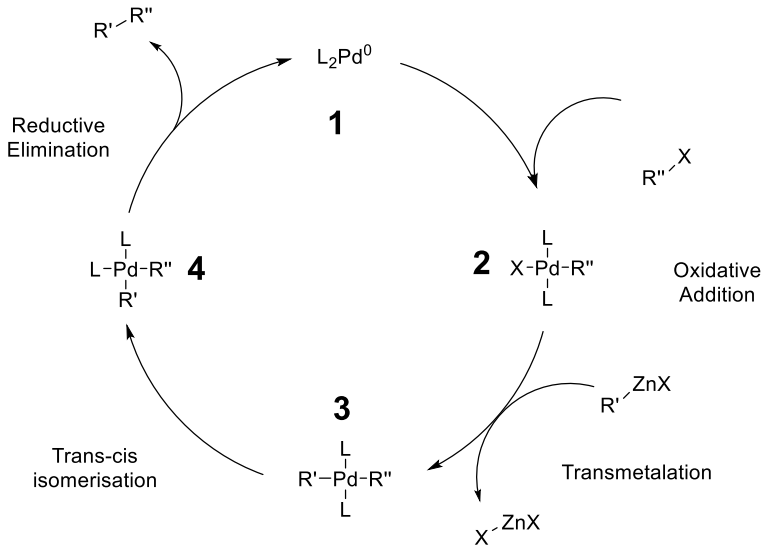
Organozinc compounds can be prepared by the insertion of iodine-activated zinc metal into alkyl bromides in DMA.[20]

General reaction scheme of cross-couling reactions:



cat.: Ni(0) or Pd(0)-complex
R': alkenyl, aryl, allyl, benzyl, propargyl
R": alkenyl, aryl, alkynyl, alkyl, allyl, benzyl.

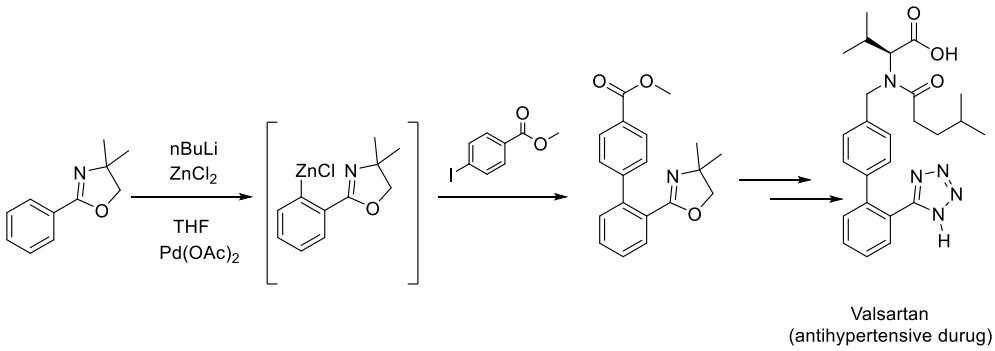
Scheme 1.9: Negishi coupling general scheme.



Scheme 1.10: Negishi coupling mechanism.

The catalytic cycle starts with the active form of the catalyst (often generated in situ) and then the halide reacts with the metal in an oxidative addition, where the oxidation number of the metal increases by two. Then, a transmetalation between zinc and the metal occurs. The third step is a trans-cis isomerization of the complex that finally expels the two organic fragments in a reductive elimination that brings the metal to its initial oxidation state (*scheme 1.10*).

The Negishi coupling is widely used in industry to produce drugs (*scheme 1.11*), and is often used in the field of total synthesis since it allows the

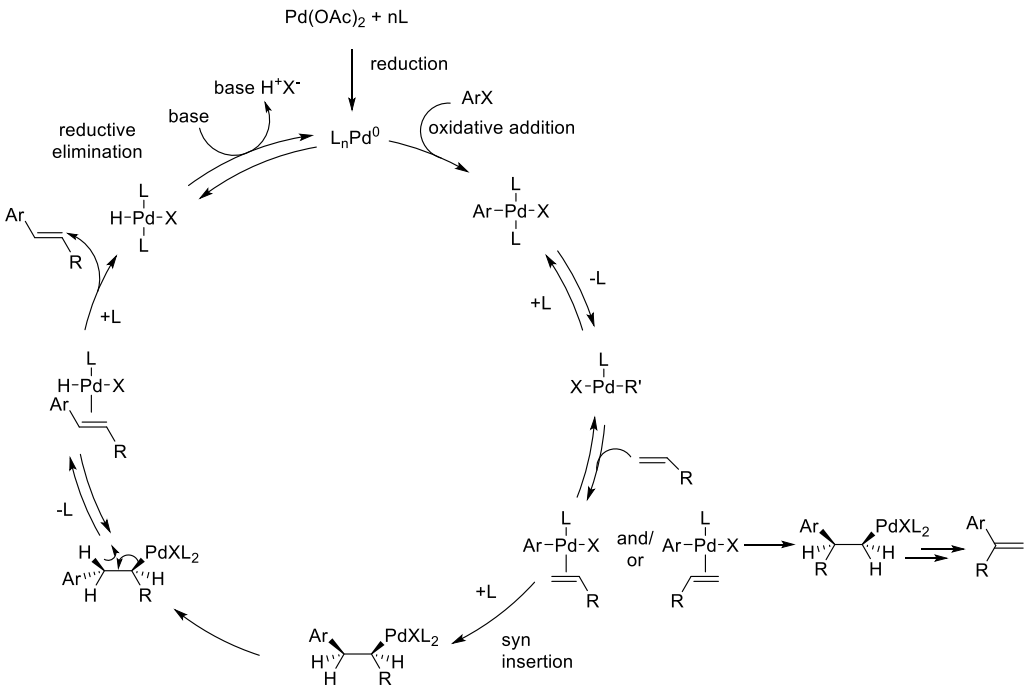


Scheme 1.11: Synthesis of Valsartan using the Negishi coupling.[21]

coupling of sp^3 and sp^2 carbons – a peculiar feature among the palladium catalyzed coupling reactions.[21]

1.3.3 Heck coupling

The Heck reaction was discovered in 1972 by Richard F. Heck. It is a chemical reaction that occurs between an unsatured halide (or triflate) and an alkene in presence of a base and a palladium catalyst to form a substituted alkene (*scheme 1.12*).[22]

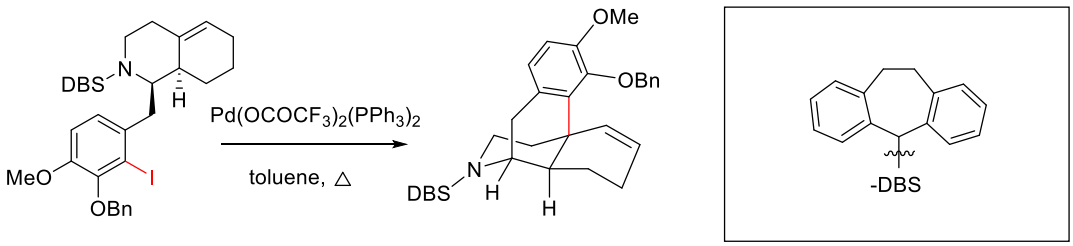


Scheme 1.12: Heck coupling catalytic cycle.

This reaction is extremely versatile, and the used alkenes can be mono-substituted and di-substituted, and the required base as mild as Na_2CO_3. The Heck coupling is also trans-selective. Unfortunately, as all the reactions based on the use of Pd(0), it is very oxygen and water sensitive.

Recently, developments have extended the scope of the reaction, making it one of the most popular cross-coupling reactions known (*scheme 1.13*).

The mechanism goes through an oxidative addition followed by coordination of the alkene to form a π complex with palladium. Then, the alkene inserts into the Pd-C bond in a syn addition step. A cis-trans isomerization occurs and then, after a ß-elimination of a hydride, a new π complex is again formed. This complex releases the newly formed alkene and the catalyst is regenerated with a reductive elimination of HX that is quenched immediately by the base.

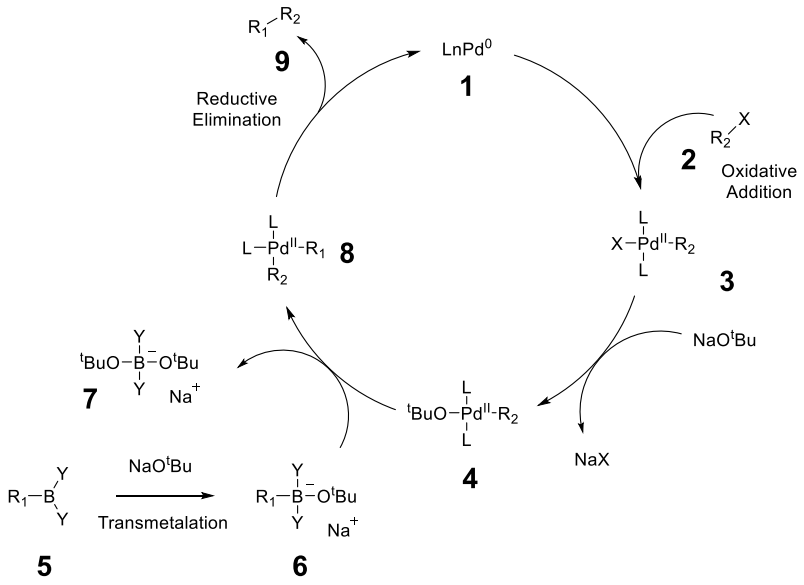


Scheme 1.13: Application of the Heck reaction on (-)-Morphine synthesis.[23]

1.3.4 Suzuki reaction

In 1979 Suzuki and Miyaura reported that organoboranes, in the presence of a base, could be used as efficient nucleophiles in palladium catalyzed cross-coupling reactions (*scheme 1.14*).[24]

This important procedure was improved even more when it was discovered that also the boronic acid and the easily produced boronic ester could be used as nucleophiles in this type of coupling.



Scheme 1.14: Suzuki reaction mechanism.

The mechanism follows the guideline of a classic palladium catalyzed cross-coupling reaction. The first step is an oxidative addition of the organohalide to the catalyst. Then, the complex reacts with the base to produce an intermediate that through a transmetalation with the boronate complex forms the organopalladium species. A reductive elimination restores the catalyst and generates the desired product.

The power of this reaction comes from the less toxic nature of the boronate (compared to stannanes and organozinc reagents), the mild conditions that is employed, and the easy availability of the reagents.

1.3.5 Stille coupling

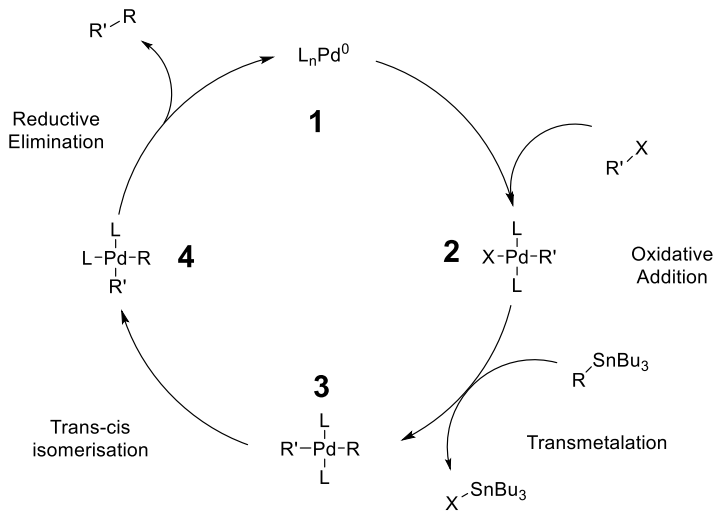
The Stille coupling is a palladium catalyzed cross-coupling reaction where an organic halide reacts with a stannane[25] (*scheme 1.15*).

The group attached to tin is usually sp^2 hybridized, but some examples of sp^3 hybridized carbons have been reported. The counterpart is usually a halide, a pseudohalide, or a phosphonate.[26,27]

The stannanes are very stable to air and moisture, but they are more toxic than the equivalent organometallic complex used in the other palladium cross-coupling reactions.

The mechanism of this reaction is one of the most studied.[28] In broad terms it follows the common palladium catalyzed cross-coupling reaction mechanism, but it is more complex because several reaction pathways can occur. After obtaining the active form of palladium it goes through an oxidative addition, and then an isomerization occurs. It has been investigated that the isomerization could follow several pathways, some of them self-catalyzed and some that require the interaction of the solvent.

Usually the isomerization is favored because of the bulky ligands that are often used in this kind of reactions. Then, the transmetalation proceeds followed by the reductive elimination that regenerates the catalyst.



Scheme 1.15: Stille reaction mechanism.

One of the most frequent side reactions that could significantly decrease the yield is the homo-coupling between two stannanes.

This reaction is used in the synthesis of a large variety of polymers[29], and in general in the synthesis of organic compounds.

1.3 Manganese

The aim of all the projects related to this thesis are linked to the use of manganese in organic chemistry, and therefore a short summary about this metal will be provided here (*figure 1.2,1.3*).

Figure 1.2: Manganese.

Manganese is a metal with atomic number 25, and appears as a grey-white metal similar to iron. It has seven oxidation states althought the most common are +2,+3,+4,+6,+7. It is usually not found as the free metal in nature, but in combination with iron.[30]

It is usually used for the production of steel and other metallic alloys, paint and for the decolorization of glass. Potassium permanganate is used in chemistry as an oxidant and also in medicine as a disinfectant.[31]

Manganese salts have been used as pigments since prehistory, and over the years for several uses by the Egyptians and the Romans.

The Spartans were the first to discover the enhanching property of manganese in the production of steel. They realized the superior hardness of the iron alloy with manganese, which they used to make weapons.

The isolation of manganese as an element was performed the first time in 1774 by Johan Gottlieb Gahn by treathing manganese with carbon.

In biology manganese is an oligo mineral present in all forms of life, and many enzymes also have manganese as cofactors.

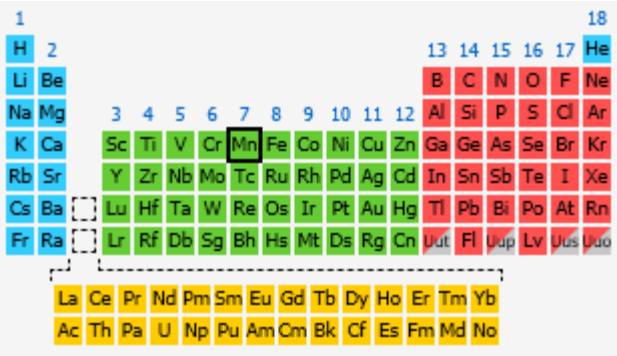


Figure 1.3: Manganese in the periodic table

An excess of exposure to manganese could lead to neurodegenerative disorders with symptoms similar to Parkinson's disease.

Manganese has great potential in redox reactions due to the several possible oxidation states. The most stable oxidation state is +2.

1.4.1 Organo manganese complexes

In recent years, the attention of organic chemists has focused on the use of many different organometallic complexes, where often the previous choice was either palladium, nickel, rhodium or ruthenium. The interest is now shifted towards cheaper and more benign metals. With regards to this, the goal of this thesis has been to investigate the catalytic property of manganese (II) salts.

Manganese (II) complexes have been studied for the most part by Cahiez and his group who in the last forty years have focused their work on this topic.[32]

The complexes in question are more stable if compared to the other transition metal complexes, and they often can be used at room temperature.

The most common way to prepare them is through transmetalation from the corresponding organomagnesium and organolithium reagents.[33,35,36,37,38,39,40,41] Recently there have been some attempts to obtain organomanganese compounds via oxidative addition, which is straightforward and cheaper and allows the preparation of functionalized organomanganese compounds in a more convenient way.[42]

Through a transmetalation mechanism, the addition of organolithium or organomanganese reagents can lead to different organomanganese compounds (*scheme 1.16*).

Organomanganese halides

$RM + MnX_2 \longrightarrow RMnX$ (+ LiX or MgXX')

(M= Li, MgX')

Diorganomanganese compounds

$2\ RM + MnX_2 \longrightarrow R_2Mn$ (+ 2 LiX or 2 MgXX')

(M= Li, MgX')

Organomanganates (ate complexes)

$3\ RM + MnX_2 \longrightarrow R_3MnM$ (+ 2 LiX or 2 MgXX')

(M= Li, MgX')

$4\ RM + MnX_2 \longrightarrow R_4MnM_2$ (+ 2 LiX or 2 MgXX')

(M= Li, MgX')

Scheme 1.16: Organomanganese compounds obtained through transmetalation.

Organomanganese complexes are highly reactive and are not compatible with solvents containing acidic moieties or electrophilic functional groups. Usually, the salts of manganese complexes are the corresponding chloride or bromide.

As previously mentioned, the organometallic derivatives from manganese are more stable than those derived from the first or second group metals. In this particular case the stability follows the order: R_4MnLi_2 (or $(MgX)_2$) ≈ R_3MnLi (or MgX) > RMnX » R_2Mn.

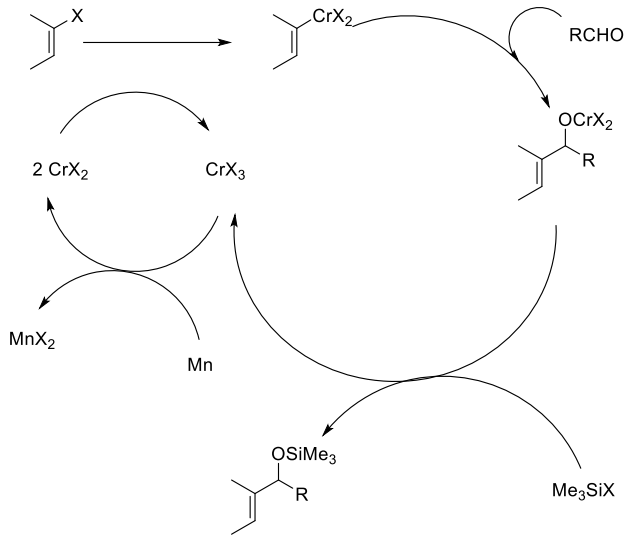
A paramount factor regarding the stability of these compounds is the nature of the R group, since like many other transition metal derivatives they may decompose via a ß-hydride elimination.

The common reactivity of organomanganese is similar to the one of Grignard reagents,[43,44] but they do not attack esters, nitriles or amides. However, the reaction between organomanganese and α,ß-unsaturated compounds has not been of synthetic interest, since it leads to a mixture of products.

1.4.2 Use of manganese in organic synthesis

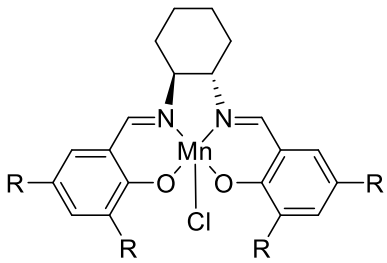
In organic chemistry manganese has been used in several ways.[45,46,47]

In many other studies metallic manganese has been used in cross-coupling reactions to reduce the catalyst back to the active form, as in the nickel or cobalt catalyzed cross-coupling reactions[48] or in other reactions, where the active state of the metal is oxidized and needs to be regenerated (*scheme 1.17*).



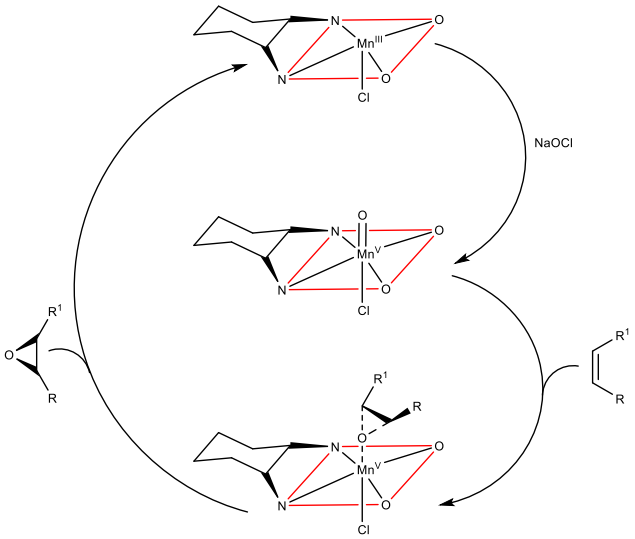
Scheme 1.17: Example of the use of manganese in Nozaki-Hiyama-Kishi coupling.

Another name reaction that uses Mn as catalyst is the Jacobsen epoxidation,[49] where a manganese salen complex (*scheme 1.18*) is used as catalyst.



Scheme 1.18: Manganese salen complex.

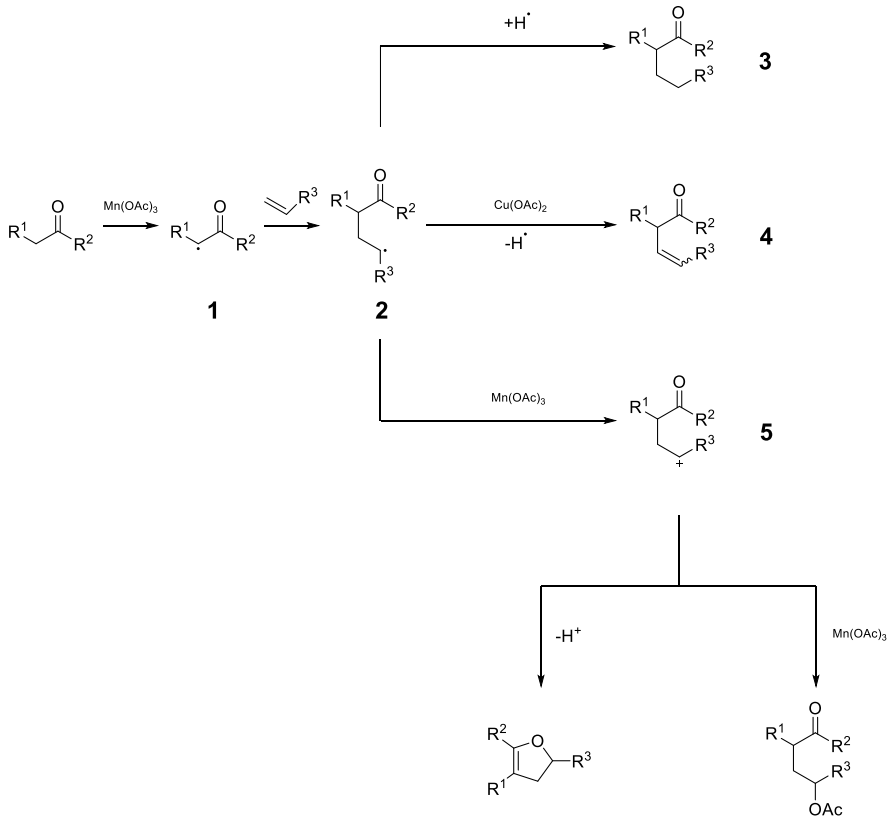
The mechanism of this reaction is not fully understood yet, but the most accepted mechanism is the concerted pathway reported below (*scheme 1.19*).



Scheme 1.19: Jacobsen epoxidation proposed mechanism.

Manganese is also known to participate in a mechanistically different class of manganese-mediated coupling reactions. Those are typically radical coupling reactions between enolizable carbonyl compounds and unsaturated compounds. Usually they are initiated by manganese and sometimes also copper is used as co-oxidant to oxidize the intermediate radical.[50]

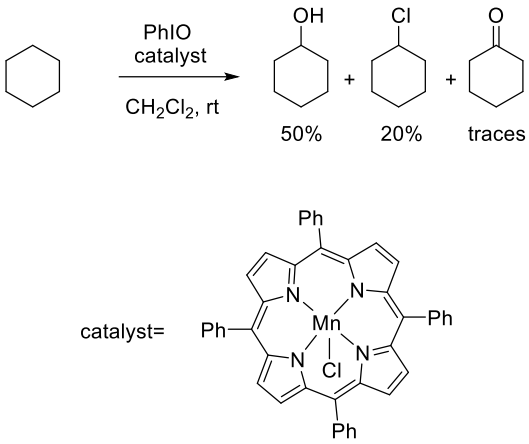
The mechanism (*scheme 1.20*) of this reaction goes through the production of an enol-radical on the carbonyl compound (**1**), and then the radical couples with an unsaturated compound to produce the intermediate **2**, that will react following one of the pathways illustrated in the picture, considering the reagents present in the reaction mixture.



Scheme 1.20: Manganese mediated coupling reaction general scheme.

Another field where the use of manganese has been explored is C-H activation.

With C-H activation is intended the functionalization of a carbon hydrogen bond, without the necessity of a pre-functionalization. The challenge is the selectivity of the chosen catalyst. In 1980 Groves, already reported a biomimetic approach to this challenge using a manganese porphyrin complex[51] (*scheme 1.21*).



Scheme 1.21: C-H activation of cyclohexane.

1.4.3 Literature overview on manganese catalyzed cross-coupling reactions

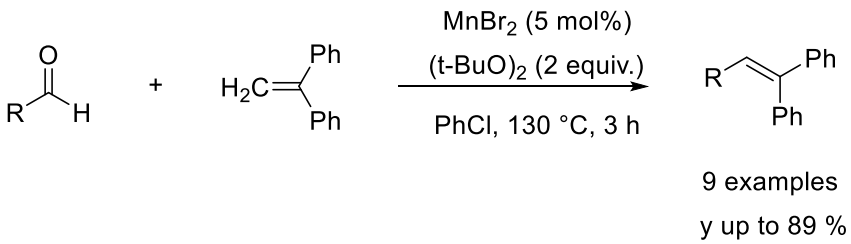
The use of manganese in cross-coupling reactions has been investigated by several research groups.

The Suzuki-type coupling has been reported in one paper where manganese(II) acetate catalyst on a heterogeneous support was employed in aqueous dimethylformamide at reflux to give the coupling products in moderate yields.[52] The Stille-type coupling has been reported in one paper where 10% of manganese(II) bromide was used in *N*-methylpyrrolidinone at 100 °C, but the reaction was limited to aryl iodide substrates.[53]

The Heck-type coupling can be achieved with a heterogeneous manganese catalyst, but the structure of the catalyst as well as the yield of the reaction have not been described in detail.[54]

Examples of Buchwald-Hartwig-type coupling performed with 5 – 10% of manganese(II) chloride in dimethylsulfoxide (or water) at 130 °C, is described by Teo and co-workers. The reaction is mainly limited to iodide substrates.[55,56]

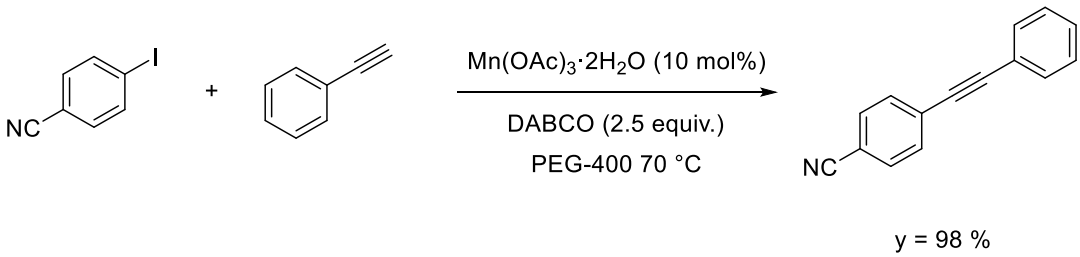
Recently, Li and co-workers developed a radical alkyl-Heck-type reaction of different aliphatic aldehydes via a decarbonylation, where $MnBr_2$ is used as the catalyst (*scheme 1.22*).[57] It is known that the aryl or alkenyl-Heck reactions have a wide spectrum of available and well-functioning substrates, while the alkyl-Heck coupling suffers from oxidative addition to sp^3-hybridized electrophiles and ß-hydrogen elimination. The employment of compounds containing a carbonyl group as alkyl donors such as aldehydes, which are inexpensive and easily available, allows the extent of the substrates scope for the alkyl-Heck coupling to be extended.[57]



Scheme 1.22: Mn-catalyzed alkyl-Heck type reaction via oxidative decarbonylation of aldehydes.

A manganese-catalyzed Sonogashira reaction was reported by Wu and co-workers in 2016.[58] The procedure described by the authors uses mild and green conditions: the coupling between aryl iodides and aryl acetylenes is

supported by $Mn(OAc)_3 \cdot 2H_2O$ as catalyst, DABCO as additive and polyethylene glycols (PEGs) as solvent. This reaction is tolerant to moisture and air. Several functionalized diphenylacetylenes are synthesized through this strategy in moderate to good yields (*scheme 1.23*).

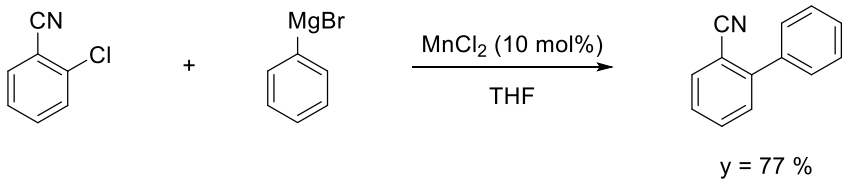


Scheme 1.23: Manganese catalyzed Sonogashira coupling of 4-iodobenzonitrile and phenylacetylene.

1.4.4 The Kumada coupling under manganese catalysis

Probably the most documented manganese cross-coupling reaction is the Kumada reaction. This is probably due to the reactivity of Grignard reagents towards manganese to form organomanganese species. In fact, the transmetalation Mg/Mn constitutes the first step in all of the reactions involving organomagnesium halides catalyzed by manganese and takes place very quickly.[59] Several examples for the cross-coupling reactions under manganese catalysis with the involvement of Grignard reagents have been reported in the last few years. In particular, Cahiez and co-workers deeply investigated this topic. He was able to obtain biaryl compounds from the coupling between *ortho*- or *para*-activated aryl chlorides and phenylmagnesium bromide in the presence of 10 mol% of $MnCl_2$ as catalyst and THF as solvent. This method has been extended to

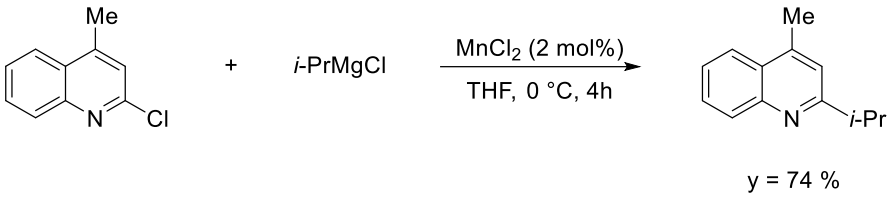
alkyl Grignard reagents with success and is performed under mild conditions, producing good to excellent yields of the cross-coupling products (s*cheme 1.24*).[60]



Scheme 1.24: $MnCl_2$ catalyzed Kumada couplings by Cahiez and co-workers.

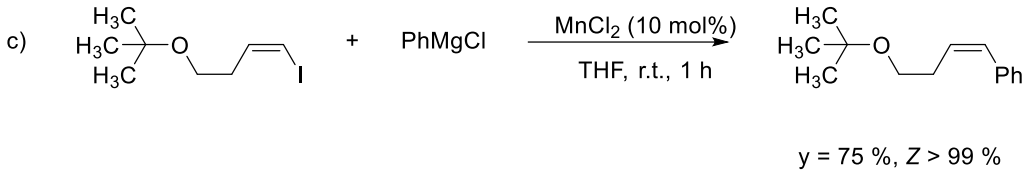
Further research carried out by Cahiez and co-workers has led to the discovery of a chemoselective reaction between *ortho*-acylated aryl chlorides and phenylmagnesium chloride catalyzed by 10 mol% of $MnCl_2$. This method was limited by the side reactions that occur between the Grignard reagent and the electrophilic groups when present on the halide partner. To overcome this issue, the authors employed a stoichiometric amount of the organomanganese reagents which were prepared *in situ* from $MnCl_2$ and the related organomagnesium halide reagent. This gave high chemoselectivity and excellent yields of the desired products.[61]

Until 2017, the scope of the manganese catalyzed Kumada coupling was limited to the aryl compounds containing electron-withdrawing groups. In this year Rueping and coworkers developed a cross-coupling reaction of various chloro-heterocycles with aryl or alkyl magnesium halides catalyzed by $MnCl_2$ (2-5 mol%).[62]



Scheme 1.25: $MnCl_2$ catalyzed Kumada couplings by Rueping and co-workers.

Additionally, a procedure for coupling of aryl Grignard reagents with nonactivated alkenyl halides by the employment of $MnCl_2$ 10 mol% was established (*scheme 1.26*).[63] Alkenyl bromides and iodides were suitable substrates for this reaction while the corresponding chlorides led to poor yields.



Scheme 1.26: $MnCl_2$ catalyzed Kumada couplings.

1.5 Principle of radical chemistry

As will be explained in the following chapters of this thesis, radical chemistry has been of paramount importance for these projects.

A radical by definition[64] is an atom, molecule, or ion that has an unpaired valence electron. This condition makes the radicals extremely reactive, with themselves or with other molecules. There are very few exceptions to this rule, and often they are observed by keeping the compound in vacuum or in a low concentration.

The first time the word radical was used was by Lavoisier,[65] but he intended a completely different concept from the one we use nowadays. Only later it was used to describe substituents in organic chemistry.

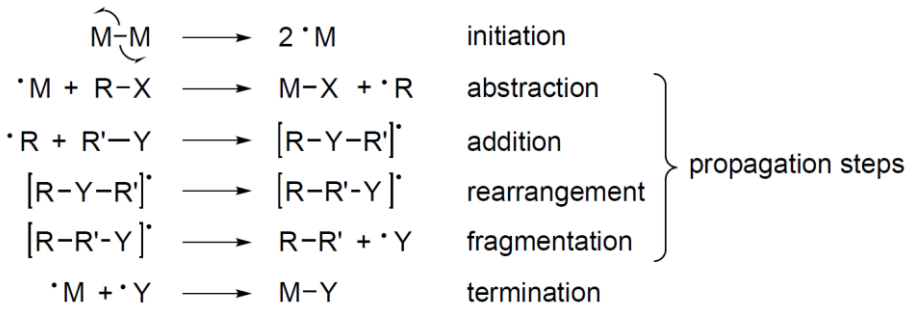
Radicals are made in several ways: breakup of larger molecules, heat, electrolysis, photolysis and by some chemical reactions. Surprisingly there are a lot of reactions that comprehend a radical intermediate.

The formation of a radical needs a large amount of energy, because it involves the cleavage of a covalent bond through homolysis. This amount of energy is known as the bond dissociation energy and abbreviated with $\Delta H°$.

The first radical to be discovered was the triphenylmethyl radical, by Gomberg in 1900.[66]

Until 1970 the use of radicals was strictly related to the synthesis of polymers. It was the arrival of more advanced analytical techniques such as ESR (electron spin resonance) that allowed a deeper understanding of radical processes and thus the ability to use them to design synthetic procedures.

The pathway of a radical reaction can be summarized into three steps: initiation, propagation and termination (*scheme 1.27*). After the radical is formed (initiation) through homolysis or a single electron transfer mechanism, it can proceed through abstraction, addition, rearrangement or fragmentation, as shown in the scheme. Finally, the radical will couple with another radical terminating the reaction.



Scheme 1.27: Common radical reaction pathways.

The carbon centered radical can have either a planar or a pyramidal shape, depending in which orbital the unpaired electron is situated, in an sp^3 or in a p orbital, the size and electronic density of the other R group. If the substituents are bulky the radical will tend to the planar in shape, that allows less repulsive interactions between the groups.

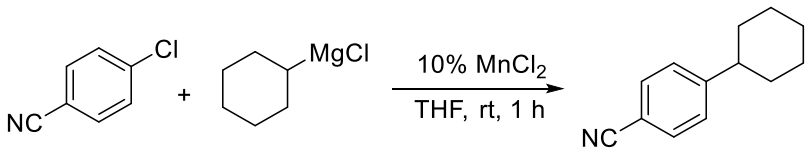
The stability of a radical is ruled by the same conditions that stabilize a carbocation including resonance stabilization. The stability of a radical has paramount importance for the selectivity of the transformation. A more stable radical will also be more selective and thus allowing chemists to use it as a reagent in organic synthesis, especially for the preparation of small molecules. An important factor to obtain a radical is the ease required to break a bond, as for example halogens are relatively easy to extract, and as said above the stability of the radical obtained is also fundamental.

Chapter 2

Manganese-catalyzed cross-coupling reactions

As mentioned in the introduction, the palladium-catalyzed cross-coupling reactions were among the major discoveries in chemistry over the last 50 years. Unfortunately, the metal palladium is considered toxic,[67] expensive and it also has a low rate production.

The use of nickel complexes as catalysts has been investigated thoroughly but it has the same problems as palladium. The investigations then went through the use of different metal catalysts as copper,[68] iron[69] and cobalt.[70] Although they are able to achieve the coupling reactions, these catalysts generally require a high loading and some are toxic.



Scheme 2.1: Mn catalyzed cross-coupling reaction.

Since manganese is one of the cheapest transition metals and it does not have an elevated toxicity, the aim of this thesis is to explore its catalytic possibilities and eventually the mechanism involved in the transformations.

The formation of 4-cyclohexylbenzonitrile by the reaction of 4-chlorobenzonitrile with cyclohexylmagnesium chloride in the presence of $MnCl_2$, shown in *scheme 2.1*, was discovered while attempting to perform a manganese-catalyzed Kumada coupling. The current section describes the screening of the reaction conditions as well as the exploration of the scope and limitations of the method, and the investigation of the mechanism involved.

2.1 Reaction optimization

The first attempt to perform a manganese catalyzed Kumada coupling was to obtain the cross-coupling reaction between bromobenzene and 4-tolylmagnesium bromide in the presence of $MnCl_2$.

The reactions were performed using the protocol developed by Cahiez *et al.*.[71] The procedure consists of adding $MnCl_2$ to degassed THF, then the halide is added to the reaction mixture, followed by the Grignard reagent in a ratio of 1:2. All the operations were performed under inert atmosphere.

The first parameter that was screened was the temperature. Experiments were performed in the temperature range between -78 ºC and 66 ºC with THF, 1,4-dioxane or Et_2O as the solvents (*table 2.1*).

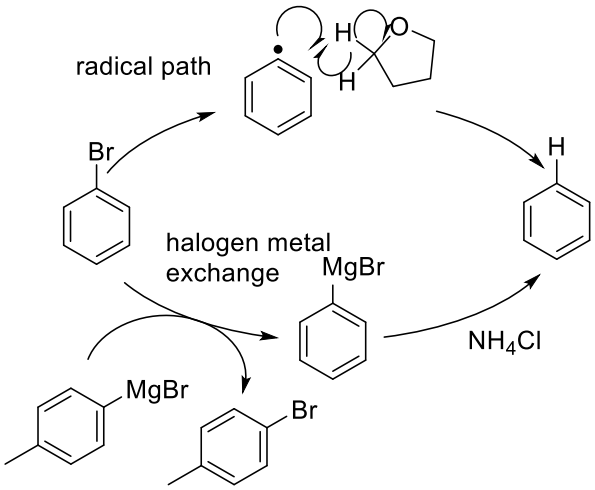
The Grignard reagent has been previously titrated to ensure that the stoichiometry is accurate and the solvent has been degassed through the "freeze thaw pump" technique.

Table 2.1: Attempted cross-coupling between bromobenzene and tolylmagnesium bromide.

Entry	**$MnCl_2$ Loading**	**Solvent**	**T [ºC]**	**Cross-coupling yield[%]**	**Homo-coupling yield[%]**
1	10%	THF	-78	-	-
2	10%	THF	-30	-	-
3	10%	THF	0	-	-
4	10%	THF	rt	Traces	Traces
5	10%	THF	45	-	-
6	10%	THF	50	-	-
7	10%	THF	Mild reflux	-	-
8	20%	THF	rt	-	-
9	10%	1,4-Dioxane	rt	-	-
10	10%	1,4-Dioxane	Mild reflux	-	-
11	10%	Et_2O	rt	-	-
12	10%	Et_2O	Mild reflux	-	-

The first reactions in THF (*entry 1-8*) did not give any product and the conversion of the starting material was about 10%. After performing the analysis on GC-MS a small amount of the dehalogenated product was detected.

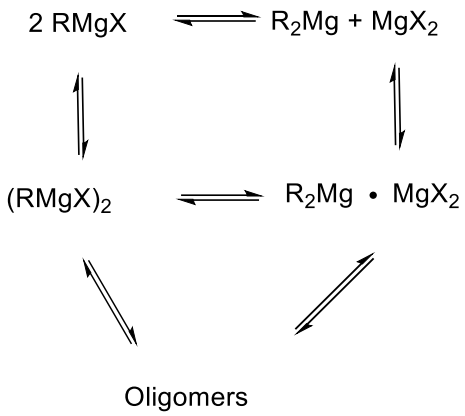
For this kind of transformation, the dehalogenation is a common side reaction. In particular, in this case it can be due to two different mechanisms: a halogen-metal exchange or a quenching of a radical intermediate (*scheme 2.2*).



Scheme 2.2: Aryl halide dehalogenation reaction paths.

The halogen-metal exchange can occur between the aryl halide and one molecule of the Grignard reagent.[72] This newly formed arylmagnesium halide will persist in the reaction mixture until the final quenching with ammonium chloride. The second path involves the interaction of the aryl halide with the catalyst, resulting in the formation of an aryl radical that will react with the solvent to produce the dehalogenated compound.

Another parameter that should be considered, when using Grignard reagents, is their basic composition in a polar solvent. An adequate description of the behavior of the organomagnesium halides in solution is the Schlenk equilibrium.[73]



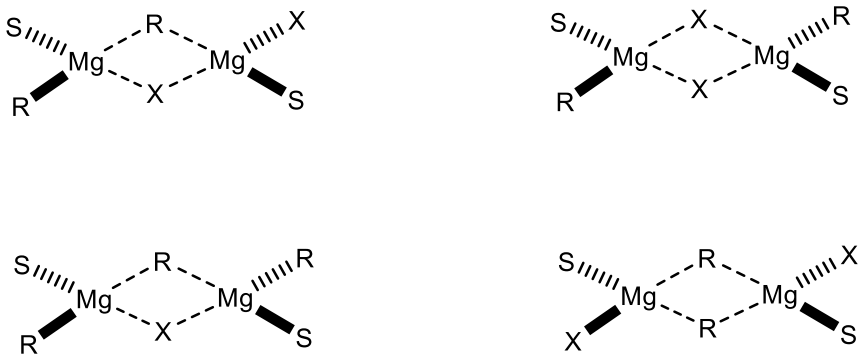
Scheme 2.3: Generalized Schlenk equilibrium.

The Schlenk equilibrium illustrates how, depending on a few parameters, the aggregation of the Grignard reagents can shift from a monomeric to a dimeric form (*scheme 2.3*). The factors that influence the Schlenk equilibrium are the temperature, the solvent, the nature of the Grignard reagent itself, the presence of salts and the presence of oxygen.

Despite the use of Grignard reagents in synthesis is very common, their molecular structure in solution is still elusive.[74] It is conceivable to think that the monomeric state prevails at higher temperature, since the intramolecular force should be more labile due to the entropy contribution.

The solvent has a paramount importance since it influences the equilibrium in at least two ways: with the solvation of the organomagnesium halide complex and with the solubility of the magnesium salts. It is reported that in THF the Grignard reagents are mostly in their monomeric form. In Et_2O, on the other hand, the alkylmagnesium halides are mostly in their dimeric form, because the MgX_2 salts developed by the dimerization are insoluble in this media. This moves the equilibrium to the right side. With regard to the aryl Grignard the situation is more complicated since the aggregation state depends also on its concentration. In fact, in Et_2O the monomeric form prevails if the

concentration stays under 0.1 mol/L. At higher concentration, the dimeric form is the more stable, and some oligomers (*scheme 2.4*) can be formed[74].



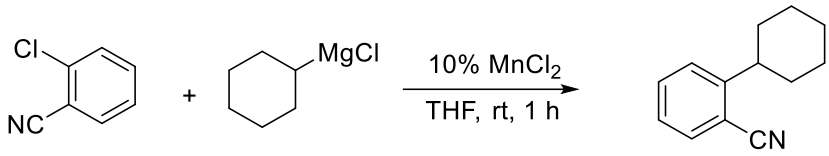
Scheme 2.4: Possible oligomer structures of Grignard reagents.

In order to understand if a perturbation of the Schlenk equilibrium could lead to a better reactivity, a set of experiments were performed using 1,4-dioxane (*table 2.1*, *entry 9-10*) followed by diethyl ether (*entry 11-12*). The magnesium salts developed by dimerization of the Grignard reagents are not soluble in these two solvents and they make the Schlenk equilibrium shift to the right side.

Only traces of the expected cross-coupling product and the homo-coupling counterpart were observed (<5% GC-MS yield) (*entry 4*). The presence of the homo-coupling product could be explained by the previously reported reactions which describe how salts of manganese (II) in the presence of oxygen and of Grignard reagents give homo-coupling with a high yield.[75] However, also in these experiments the conversion was never higher than 15%, and the only side product detectable by GC-MS was the dehalogenated aryl halide.

2.2 Substrate screening

Due to the failure of the experiments reported in table 2.1, a previously reported manganese cross-coupling reaction was chosen as a control experiment.[71] (*scheme 2.5*).



Scheme 2.5: Mn catalyzed cross coupling reaction between 2-chlorobenzonitrile and cyclohexyl magnesium chloride.

This reaction was performed following the same protocol as described by Cahiez *et al.*[71] that had already been used for the experiments reported in the previous paragraph.

At room temperature the yield of 2-cyclohexylbenzonitrile was comparable to the one reported (85-90%) by Cahiez. There are, however, a few observations that can be done. The $MnCl_2$ is insoluble in THF but it disappears immediately when the Grignard reagent is added dropwise. This is probably due to the manganate complexes that are formed. Although the Grignard reagent was added in an ice bath, the temperature rose immediately, reaching the boiling point of the solvent. This behavior was observed also when the Grignard addition was spread over a longer period. The attempts to keep the reaction cold only led to an increase in the side products. It is worth to be noted that when the reaction does occur it is possible to observe a color transition from a cloudy white to a dark brown color during the reaction, and giving finally a yellowish solution in most of the cases.

4-Chlorobenzonitrile was tested under the same conditions (*scheme 2.6*) and the reaction succeeded with 90% GC-MS yield and full conversion.

Benzonitrile and chlorophenyl(cyclohexyl)methanone were the only side products detected by GC-MS. Cyclohexyl(phenyl)methanone is originated by the addition of the Grignard reagent to the cyano group and the following quenching with NH_4Cl. 3-Chlorobenzonitrile, on the other hand, did not react at all (*table 2.2*).

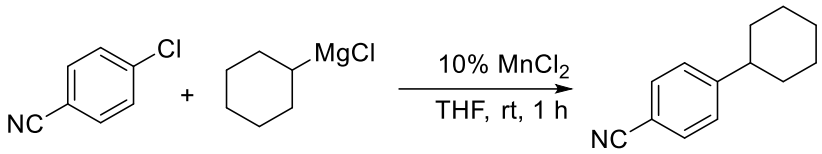


Table 2.2: Mn-catalyzed cross-coupling reaction between chlorobenzonitriles and cyclohexyl magnesium chloride.

Entry	Reagent	Grignard reagent	Yield [%][a]
1	4-Chlorobenzonitrile	Cyclohexylmagnesium chloride	85-90
2	2-Chlorobenzonitrile	Cyclohexylmagnesium chloride	85-90
3	3-Chlorobenzonitrile	Cyclohexylmagnesium chloride	-

[a] Yield calculated by GC-MS

The first substrate screening was performed on different aryl halides. A broad spectrum of substituents was chosen in order to achieve an overview of the reactivity. A variety of aryl substrates with electron donating

groups, electron withdrawing substituents and radical stabilizers were tested (*table 2.3*).

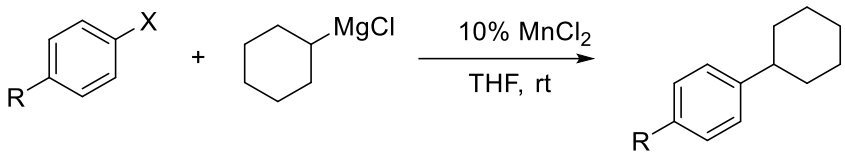
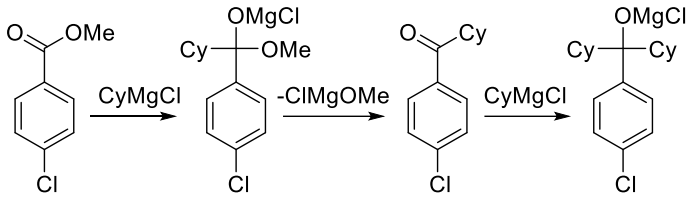


Table 2.3: List of substrates tested against cyclohexylmagnesium chloride in the presence of $MnCl_2$.

Entry	R	X	Yield [%][a]
1	CN	Cl	90[a]
2	COOMe	Cl	65[b]
3	CHO	Cl	-
4	COMe	Cl	-
5	$CONMe_2$	Br	-
6	NO_2	Cl	-
7	H	F	
8	H	Cl	-
9	H	Br	-
10	H	I	-
11	OMe	Cl	-
12	Br	Cl	-
13	Br	Br	-
14	SMe	Cl	-
15	SO_2Me	Cl	-
16	Me	Cl	-
17	CF_3	Cl	-
18	Ph	Cl	-

[a] Isolated yield, [b] NMR calculated yield

The first entry was previously discussed. Methyl 4-chlorobenzoate gave a positive outcome (*entry 2*), and afforded 48% yield in the first attempt. Side reactions, although, limited the amount of the desired product. The methyl ester group is attacked by the Grignard reagent producing the corresponding ketone and a tertiary alcohol (*scheme 2.6*). After several attempts to reduce the impact of this side reaction it was managed to increase the yield up to 65% (those attempts will be described in detail in the following pages).

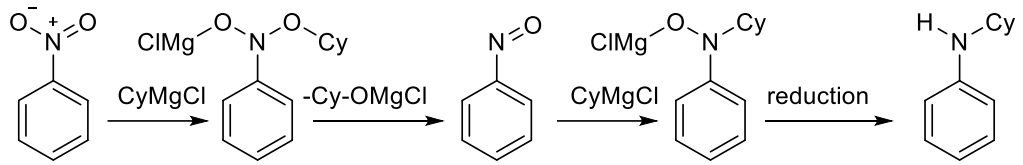


Scheme 2.6: Side reaction for methyl 4-chlorobenzoate.

It was first hypothesized that the conjugative effect of the cyano group could be a factor that allows the cross-coupling to proceed and therefore other groups with similar properties were tested. A nucleophilic addition occurred when the protocol was applied to 4-chlorobenzaldehyde (*entry 3*) and to 1-(4-chlorophenyl)ethan-1-one. Both of the substrates underwent the nucleophilic attack on the carbonyl group by the Grignard reagent. In order to diminish or prevent the impact of this side reaction the transformations were run at -78 ºC, and the Grignard reagent addition rate was drastically slowed down. Neither of these experiments had an effect, and still no cross-coupling product was obtained.

The reaction with 1-chloro-4-nitrobenzene (*entry 6*) gave no trace of product, but a GC-MS analysis of the crude of reaction showed the formation of a reduced amine coupling product. This kind of reaction is already described in the literature[76] and it has been reported for nitrobenzene *(scheme 2.7*). The Grignard reagent reacts with the nitro group, and then this adduct eliminates a molecule of the oxidized Grignard

reagent. The nitrosobenzene is then attacked by another molecule of the organomagnesium halide, and this compound undergoes a reduction resulting in the reduced amine.



Scheme 2.7: Reaction between nitrobenzene and cyclohexylmagnesium chloride.

The experiment was repeated with 1-bromo-4-nitrobenzene and 1-iodo-4-nitrobenzene but only the side product described earlier was observed. A screening of the halobenzenes followed. Fluorobenzene, chlorobenzene, bromobenzene and iodobenzene were tested but did not afford the desired coupling product. However, they showed an interesting tendency: Fluorobenzene (*entry 7*) did not react at all, with 0% conversion, chlorobenzene (entry 8) showed only 5% conversion, and a very small amount of the dehalogenated product was detected from GC-MS analysis. Bromobenzene (*entry 9*) showed 13% conversion and almost 10% of benzene was produced. Iodobenzene (*entry 10*) showed almost 40% conversion and about the same amount of the dehalogenated product. All the halobenzenes gave no cross-coupling with this protocol, while they showed an increasing tendency to dehalogenate with the size of the halogen.

1-Chloro-4-methoxybenzene (*entry 11*) showed no conversion. 1-Bromo-4-chlorobenzene and 1,4-dibromobenzene were also tested (*entry12-13*). As the other halobenzenes they showed no cross-coupling products when reacted with cyclohexylmagnesium chloride, but as the halobenzenes they suffered a dehalogenation side reaction.

(4-Chlorophenyl)(methyl)sulfane (*entry 14*), 1-chloro-4-(methylsulfonyl)benzene (*entry 15*), and 4-chlorotoluene (*entry 16*) did not produce any cross-coupling. While (4-chlorophenyl)(methyl)sulfane and 4-chlorotoluene did not give any conversion, 1-chloro-4-(methylsulfonyl)benzene produced a number of different side products, that were detected on GC-MS but not further characterized.

1-Chloro-4-(trifluoromethyl)benzene (*entry 17*) showed almost 15% conversion. Part of the starting material underwent the dehalogenation process, and traces of other side products were detected but not characterized.

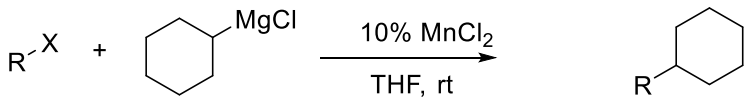
4-Chlorobiphenyl did not show any conversion.

2.3 Substrate scope

Six substrates were chosen to test the substrate scope in the Grignard reagent: 4-chlorobenzonitrile, 1-chloro-4-methoxybenzene, bromobenzene, 1-bromo-4-chlorobenzene, 1-chloro-4-(trifluoromethyl)benzene and benzyl bromide. 4-Chlorobenzonitrile was used as a control, since it already showed good performance with the protocol described in *paragraph 2.2*. 1-Chloro-4-methoxybenzene is an aryl halide with an electron donating group. When it was tested with cyclohexylmagnesium chloride it did not produce any cross-coupling product. Bromobenzene was chosen because it can show if the reaction eventually can work on a halide with no substituents. 1-Chloro-4-(trifluoromethyl)benzene has an electron withdrawing substituent, as 4-chlorobenzonitrile. Finally, benzyl bromide has been selected to check if the reaction is applicable to substrates different than an aryl halide.

2.3.1 Grignard reagent screening

First, a screening of six different Grignard reagents was performed.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

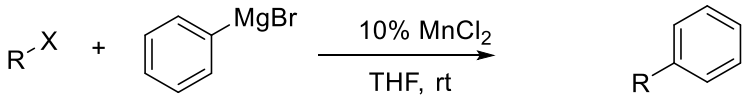
Table 2.4: Reactions of different halides with cyclohexylmagnesium chloride.

Reagent	Yield [%][a]
4-Chlorobenzonitrile	90
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	61

[a] Isolated yield

Most of the reactions described in this table have already been described in detail in the previous paragraph. The reaction between benzyl bromide and cyclohexylmagnesium chloride afforded 61% (*table 2.4*). To optimize this result, the reaction was repeated several times by modifying the temperature and the organomagnesium halide rate addition.

Unfortunately, when a control reaction in the absence of manganese was performed the desired products were still detected in a similar amount. This is probably due to a simple S_N2 due to the Grignard reagent.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

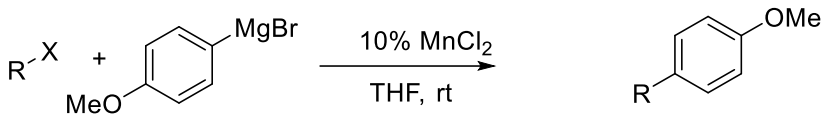
Table 2.5: Reactions of different halides with phenylmagnesium bromide.

Reagent	**Yield [%]**[a]
4-Chlorobenzonitrile	93%
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Isolated yield

When 4-chlorobenzonitrile reacted with phenylmagnesium bromide, it gave 93% yield. The only side product that was possible to detect was from the addition of the Grignard reagent to the cyano group. 1-Chloro-4-methoxybenzene did not show any conversion. 1-Chloro-4-(trifluoromethyl)benzene showed 8% conversion, and the only side product observed was the dehalogenated arene. Bromobenzene did not show any cross-coupling product, but produced almost 10% of the dehalogenated product. Almost the same result was achieved by 1-bromo-4-chlorobenzene that yielded 15% of chlorobenzene. Neither 1-chloro-4-

(trifluoromethyl)benzene nor benzyl bromide gave any cross-coupling, but the latter produced some toluene.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

Table 2.6: Reactions of different halides with 4-methoxyphenylmagnesium bromide.

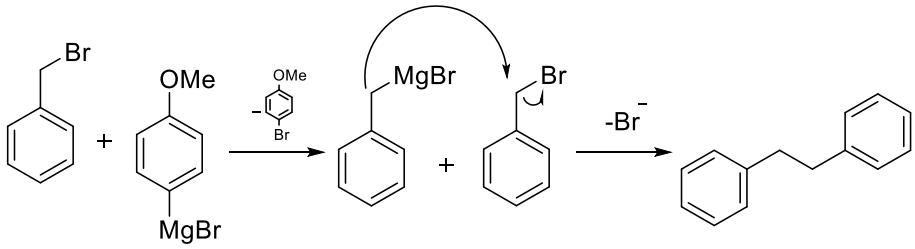
Reagent	Yield [%][a]
4-Chlorobenzonitrile	83%
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Isolated yield

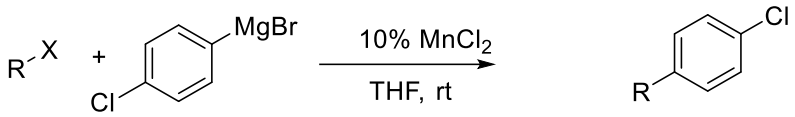
The first time 4-chlorobenzonitrile was reacted with 4-methoxyphenylmagnesium bromide, the yield was below 20%. In fact, a significant side product from the addition of the Grignard reagent to the cyano group was detected. The reaction was then optimized. The first attempts consisted on reducing the temperature. The reaction was performed several times, with a range of temperatures between -78 ºC and

0 ºC. After that the Grignard reagent addition rate was explored. Experiments were performed by adjusting the addition from 0.1 mL/h to a one single addition. The condition that allowed to obtain the best result was adding the Grignard reagent in 120 minutes (2 mL/h) at 0 ºC.

The reaction with 1-chloro-4-methoxybenzene did not lead to any conversion. Bromobenzene produced 18% of benzene, but without any trace of the cross-coupling product. 1-Bromo-4-chlorobenzene produced 29% of chlorobenzene. 1-Chloro-4-(trifluoromethyl)benzene did not show any cross-coupling product but it gave 6% of the dehalogenated product. Benzyl bromide gave 100% of conversion, and an almost quantitative yield of the homo-coupling product. This could be the result of a metal-halogen exchange[72] between the Grignard reagent and benzyl bromide, followed by a S_N2 reaction between the newly formed organomagnesium halide and the benzyl bromide (*scheme 2.8*). GC-MS data, in fact, show the presence of 1-bromo-4-methoxybenzene.



Scheme 2.8: Hypothesis about the benzyl bromide homo-coupling mechanism.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

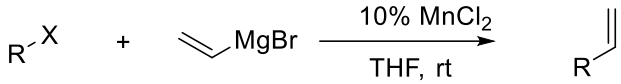
Table 2.7: Reactions of different halides with 4-chlorophenylmagnesium bromide.

Reagent	Yield [%][a]
4-Chlorobenzonitrile	79%
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Isolated yield

4-Chlorobenzonitrile gave 79% yield when reacted with 4-chlorophenylmagnesium bromide. The homo-coupling of the Grignard reagent limits the yield of this reaction. This side product is formed despite the attempt to completely remove oxygen from the reaction mixture in order to reduce the oxidative cross-coupling side reaction. 1-Chloro-4-methoxybenzene and 1-chloro-4-(trifluoromethyl)benzene did not show any conversion. Bromobenzene produced less than 5% of the dehalogenated product. 1-Bromo-4-chlorobenzene yielded 12% of

chlorobenzene. Benzyl bromide showed no conversion at all. This difference, compared to the situation described in *scheme 2.8*, is due to the difference in nucleophilicity between 4-methoxyphenylmagnesium bromide and 4-chlorophenylmagnesium bromide. The first is more nucleophilic than the latter, and this influences the metal-halogen exchange.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

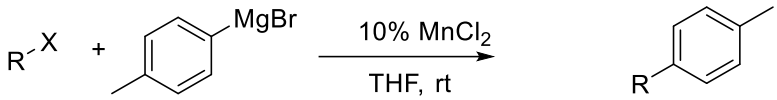
Table 2.8: Reactions of different halides with vinylmagnesium bromide.

Reagent	**Yield [%]**[a]
4-Chlorobenzonitrile	-
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Yield calculated by GC-MS

When 4-chlorobenzonitrile was reacted with vinylmagnesium bromide it did not produce any cross-coupling product, and after one hour it showed 0% conversion. The homo-coupling product is always present in the experiments with other Grignard reagents, even though in small amounts,

but it was not detected in this case. 1-Chloro-4-methoxybenzene and 1-chloro-4-(trifluoromethyl)benzene did not show any conversion. Bromobenzene gave only traces of the dehalogenated product, and the same result was achieved by 1-bromo-4-chlorobenzene. 1-Chloro-4-(trifluoromethyl)benzene did not show any conversion. Likewise, no conversion was detected for benzyl bromide.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

Table 2.9: Reactions of different halides with 4-tolylmagnesium bromide.

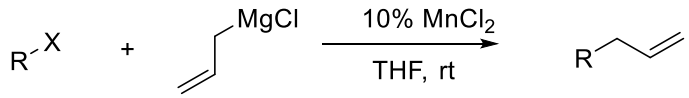
Reagent	Yield [%][a]
4-Chlorobenzonitrile	77%
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Isolated yield

4-Chlorobenzonitrile reacted with 4-tolylmagnesium bromide producing 77% yield of the cross-coupling product. Although in the beginning this reaction was afflicted by side reactions as the nucleophilic addition from the Grignard reagent to the cyano group. This side reaction limited the

reaction efficacy to a mere 24% of yield. The condition that allowed to obtain the best result was by adding the Grignard reagent over 120 minutes (2 mL/h) at 0 ºC. In this way the yield obtained was the one reported in the table (77%). 1-Chloro-4-methoxybenzene and 1-chloro-4-(trifluoromethyl)benzene did not show any conversion.

Bromobenzene produced 20% of benzene, while 1-bromo-4-chlorobenzene produced 16% of chlorobenzene and benzyl bromide gave 53% of conversion. In the latter case, the homo-coupling product was detected as in the reaction with (4-methoxyphenyl)magnesium bromide.



X=Cl, Br
R=4-cyanophenyl, 4-methoxyphenyl-, phenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl-, benzyl-

Table 2.10: Reactions of different halides with allylmagnesium chloride.

Reagent	**Yield [%][a]**
4-Chlorobenzonitrile	-
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Yield calculated by GC-MS

In the reaction with allylmagnesium chloride, 4-chlorobenzonitrile produced no yield. There was no conversion observed with this substrate, and this time the homo-coupling product was not detected with the method used for the GC-MS analysis. 1-Chloro-4-(trifluoromethyl)benzene did not show any conversion, 1-chloro-4-(trifluoromethyl)benzene showed 5% conversion and traces of the dehalogenated product. Bromobenzene produced 8% of benzene, while 1-bromo-4-chlorobenzene yielded 11% of chlorobenzene, and benzyl bromide produced some homo-coupling product.

Among the different halides tested, only 4-chlorobenzonitrile showed a good affinity with the protocol (*tables 2.4 to 2.10*), while the other aryl halides tested showed a tendency to dehalogenate and did not afford the desired cross-coupling product. Benzyl bromide proved to be not suitable for this reaction for its tendency to react with the Grignard reagent, through a metal-halogen exchange mechanism, resulting in a homo-coupling.

2.3.2 Effect of the solvent

The second parameter explored was the effect of the solvent. The same six substrates of the previous screening were reacted using toluene and MeCN as the solvents and cyclohexyl magnesium chloride as the Grignard reagent.

Toluene inhibits the reaction. This effect is probably due to the poor stability of the Grignard reagents in non-coordinating solvents. In fact, 4-chlorobenzonitrile showed no trace of the cross-coupling product, or the homo-coupling counterpart. The reaction performed in toluene appeared different from the outside: there was no change in colors, but a white precipitate (probably magnesium salts) appeared in conjunction with the addition of the Grignard reagent. The other substrates showed no conversion and also the dehalogenation did not occur.

1,4-Dioxane, diethyl ether, and DME have the ability to move the Schlenk equilibrium to the right, because the magnesium salts are less soluble compared to THF. Therefore, a set of reactions was run in these solvents. The six substrates were reacted with cyclohexylmagnesium chloride. The results confirmed the trend that was shown and described in the previous chapters, but the yield of the desired product was always lower. It was decided to continue with THF for the further experiments.

In order to clarify if MeCN could be a ligand for Mn, the same set of reactions was performed in acetonitrile. However, the Grignard reagent now reacted with the solvent and this was the main reaction that occurred in all six cases (*table 2.11*). Only 4-chlorobenzonitrile showed a yield of 30%, but unlike the other experiments no sign of the homo-coupling product was detected.

Table 2.11: Exploration of the effect of the solvent: MeCN.

Reagent	**Yield [%]**[a]
4-Chlorobenzonitrile	30%
1-Chloro-4-methoxybenzene	-
Bromobenzene	-
1-Bromo-4-chlorobenzene	-
1-Chloro-4-(trifluoromethyl)benzene	-
Benzyl bromide	-

[a] Isolated yield

2.3.3 Presence of ligands or salts

Both the solvents and salts can interfere with the Schlenk equilibrium and with the coordination sphere of the manganese in solution. They interfere with the Schlenk equilibrium because of the peculiar solubility of the magnesium salts in all the solvents. Moreover, the different solvents coordinate to manganese and magnesium in different ways depending on the structure and the chemical property of the species.

The use of salts as additives can move the Schlenk equilibrium to the left in favor of the monomer instead the dimer or the oligomers (in case of the aryl Grignard).

The effect of two of the most common ligands, triphenylphosphine (PPh_3) and triethylamine (TEA), was also explored (*table 2.12*).

Table 2.12: Exploration on the effect of ligands and salts.

Reagent	**Yield (PPh_3) [%][a]**	**Yield (TEA) [%][a]**	**Yield (LiCl) [%][a]**	**Yield ($MgBr_2$) [%][a]**
4-Chlorobenzonitrile	65%	26%	87%	83%
1-Chloro-4-methoxybenzene	-	-	-	-
Bromobenzene	-	-	-	-
1-Bromo-4-chlorobenzene	-	-	-	-
1-Chloro-4-(trifluoromethyl)benzene	-	-	-	-
Benzyl bromide	-	-	-	-

[a] Yield calculated by GC-MS

The six substrates described in *paragraph 2.3* were reacted with cyclohexylmagnesium chloride in presence of 30% of triphenylphosphine. When 4-chlorobenzonitrile was reacted with cyclomagnesium chloride, it gave 65% yield in the presence of triphenylphosphine and it showed a quantitative conversion. Under these conditions 4-chlorobenzonitrile seemed to be more vulnerable to the nucleophilic addition of the Grignard reagent to the cyano group. In fact, almost 30% of the nucleophilic addition to the cyano group was obtained. 1-Chloro-4-methoxybenzene did not show any conversion. 1-Chloro-4-(trifluoromethyl)benzene showed almost no conversion, and produced traces of the dehalogenated arene, in the presence of PPh_3. Bromobenzene did not show any cross-coupling product, but produced 4% of the dehalogenated product. Almost the same result was achieved with 1-bromo-4-chlorobenzene that yielded 17% of chlorobenzene. Benzyl bromide did not react either in the desired way, but it produced some dehalogenated product.

The same experiments were reproduced in presence of triethylamine (TEA). 4-Chlorobenzonitrile reacted with cyclohexylmagnesium chloride producing 26% yield of 4-cyclohexylbenzonitrile, and the major byproduct was (4-chlorophenyl)(cyclohexyl)methanone derived from the nucleophilic addition of the Grignard reagent to the cyano group. The reactions with the other substrates listed did not show any improvements in the presence of TEA, proving that this additive is not beneficial for the reaction.

Two different salts were also tested: LiCl and $MgBr_2$. Their presence did not cause any improvement but a small decrease in the yield for 4-chlorobenzonitrile, that decreased from 90% in the absence of any salts to 87% in the presence of LiCl and 83% in the presence of $MgBr_2$. The other substrates tested in the presence of LiCl and $MgBr_2$ did not produce any cross-coupling product.

2.3.4 Source of manganese

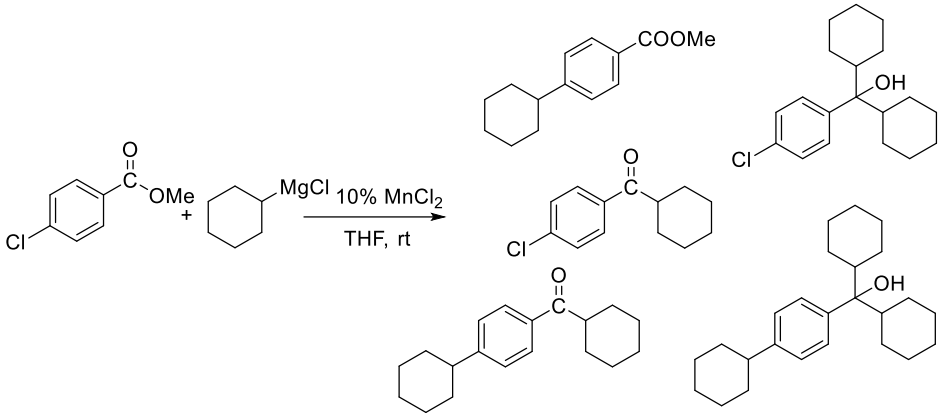
All the experiments have been performed using 98% pure $MnCl_2$ bought from Sigma-Aldrich. It was necessary to check if the catalysis was due to manganese or to some trace metal.[77] For this reason, ultra-pure manganese chloride (99.9999% pure) was used as a catalyst in the reaction between 4-chlorobenzonitrile and cyclohexylmagnesium chloride. The reaction gave the same outcome as with the less pure manganese chloride. Trace metal analysis was also commissioned showing the presence of 2 ppb of palladium and 1 ppb of nickel in the ultra-pure manganese.

Since only $MnCl_2$ was used so far also other manganese salts such as $MnBr_2$, MnI_2 and MnF_2 needed to be tested.

$MnCl_2$ proved to be the best catalyst, inasmuch the other salts did not catalyze the reactions except for $MnBr_2$ that decreased the yield to 60%.

2.4 Methyl 4-chlorobenzoate

When methyl 4-chlorobenzoate was reacted with cyclohexylmagnesium chloride, the main product was the desired cross-coupling product. However, side products were detected, from the nucleophilic addition of the Grignard reagent to the electrophilic ester group carbon. The different side products are reported in *scheme 2.9*. The amount of each one of them was not quantified.

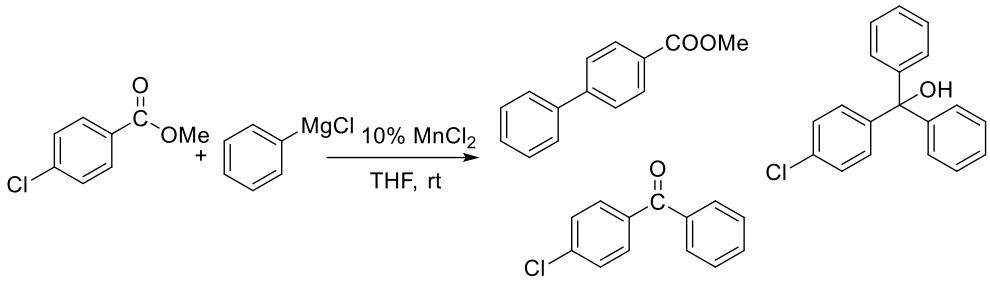


Scheme 2.9: Reaction between methyl 4-chlorobenzoate and cyclohexylmagnesium chloride.

To avoid the formation of these side products, the Grignard reagent was added over 120 minutes (2 mL/h) at 0 ºC. Unfortunately, it did not improve the yield of the reaction, leading to the synthesis of 55% of the cross-coupling product.

In order to understand if this substrate also could be a suitable partner for other Grignard reagents additional experiments were performed.

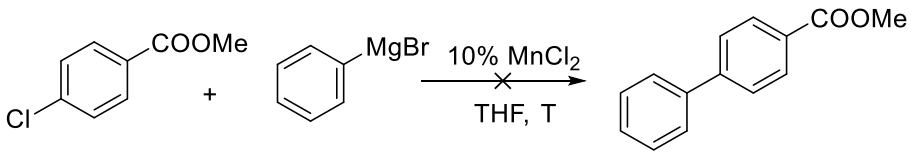
The first attempts using a different Grignard reagent failed because it reacted with the ester moiety (*scheme 2.10*): phenylmagnesium bromide reacted with methyl 4-chlorobenzoate producing an almost quantitative yield of the products deriving from the nucleophilic addition of the Grignard reagent to the ester group. In fact, it was possible to detect by GC-MS only the presence of (4-chlorophenyl)(phenyl)methanone and (4-chlorophenyl)diphenylmethanol *(scheme 2.10*).



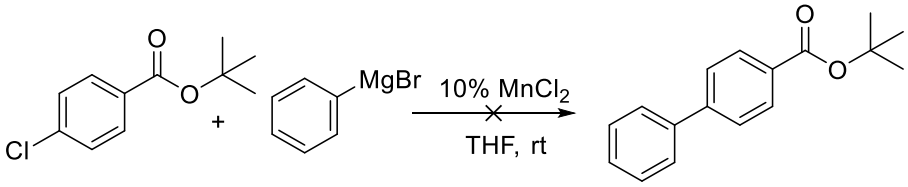
Scheme 2.10: Reaction between methyl 4-chlorobenzoate and phenylmagnesium chloride.

Also in this case, in order to avoid these side reactions, some precautions were taken. The first approach was to perform the same reaction (*scheme 2.11*) at different temperatures. Several attempts were done, first at 0 ºC, then -30 ºC and finally at -78 ºC, without producing the cross-coupling product. Then, the addition time of the Grignard reagents was slowed down from 5 mL/h to 0.5 mL/h going through intermediate speeds. The reaction again proceeded without producing any cross-coupling product. The only change was the ratio between the side products. With a slower addition of the Grignard reagent the ketone was favored as compared to the tertiary alcohol.

Tert-Butyl 4-chlorobenzoate (*scheme 2.12*) was the synthesized and used since the nucleophilic addition is hampered by the bulky ester group. Unfortunately, the only reaction observable was again the addition to the ester group by the phenylmagnesium bromide.



Scheme 2.11: Cross-coupling experiment between methyl 4-chlorobenzoate and phenylmagnesium bromide.



Scheme 2.12: Attempted reaction between tert-butyl 4-chlorobenzoate and phenylmagnesium bromide.

2.5 The role of the cyano group

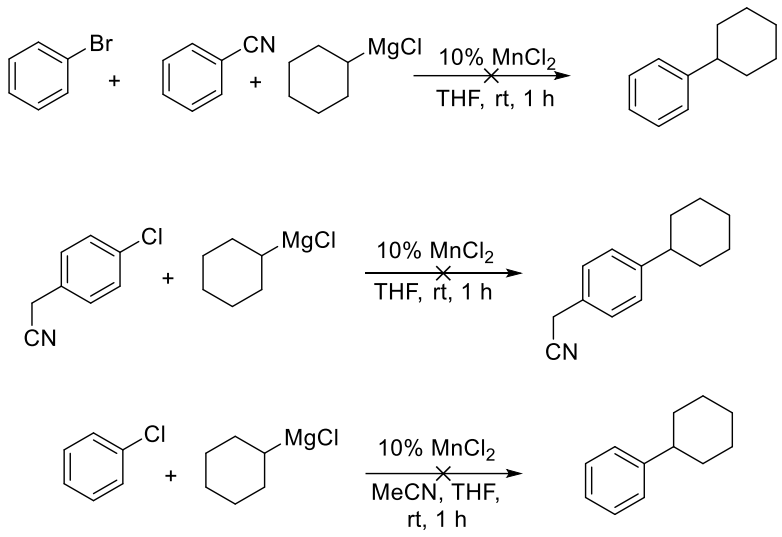
After these experiments, a step backwards was necessary to clarify the role of the cyano group in this type of reaction.

It was first hypothesized that the cyano group could either work as a ligand for manganese, stabilizing an intermediate or it could be necessary as a substituent on the aromatic ring because of its property as a radical stabilizer.

In order to understand if the benzonitrile could be a ligand for manganese, cyclohexylmagnesium chloride was added to a solution of bromobenzene and benzonitrile. In this way, if the benzonitrile worked as ligand the reaction would succeed (*scheme 2.13*).

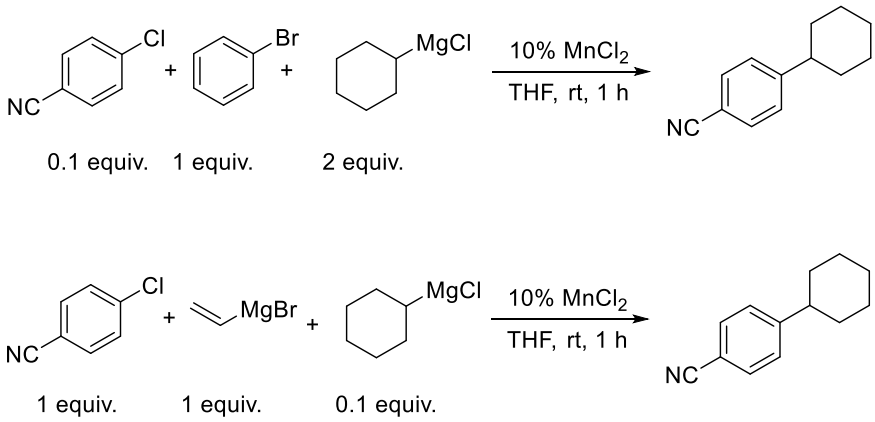
The second attempt was to move the cyano group to a benzylic position to check if the conjugative effect could be necessary for the reaction.

The third attempt was to add 30% of MeCN to the reaction. In this way it should be possible to understand if only the presence of acetonitrile could favor the process outcome.



Scheme 2.13: Attempts to understand the role of the cyano group

The reaction with bromobenzene and cyclohexylmagnesium chloride in presence of benzonitrile produced only 23% of benzene and the product from the nucleophilic addition to the benzonitrile. 2-(4-Chlorophenyl)acetonitrile afforded 42% of 2-(4-chlorophenyl)-1-cyclohexylethan-1-one, but no cross-coupling product. The reaction between chlorobenzene and cyclohexylmagnesium chloride in the presence of acetonitrile did not show any conversion. However, from the outcome of this reaction it is possible to extrapolate some conclusions. The cyano group has an active role in the catalysis. It is necessary that it is connected to the substrate in a position that allows for conjugation.

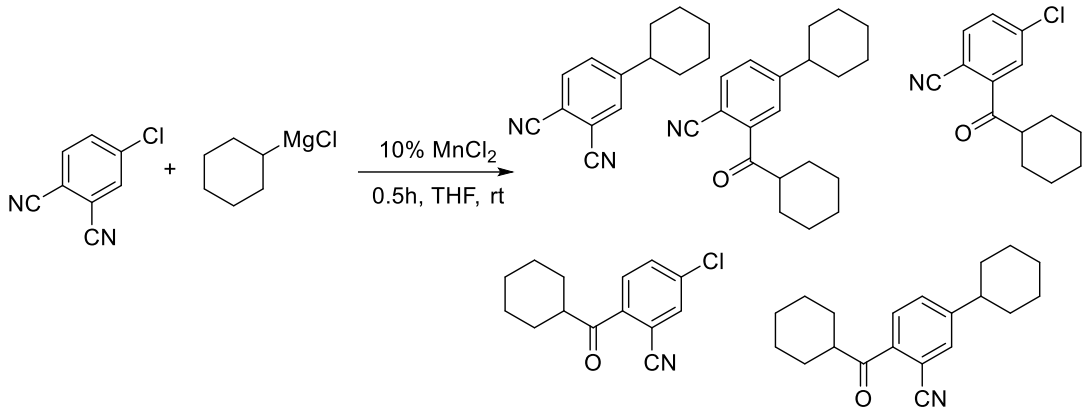


Scheme 2.14: Competitive experiments with cyclohexylmagnesium chloride.

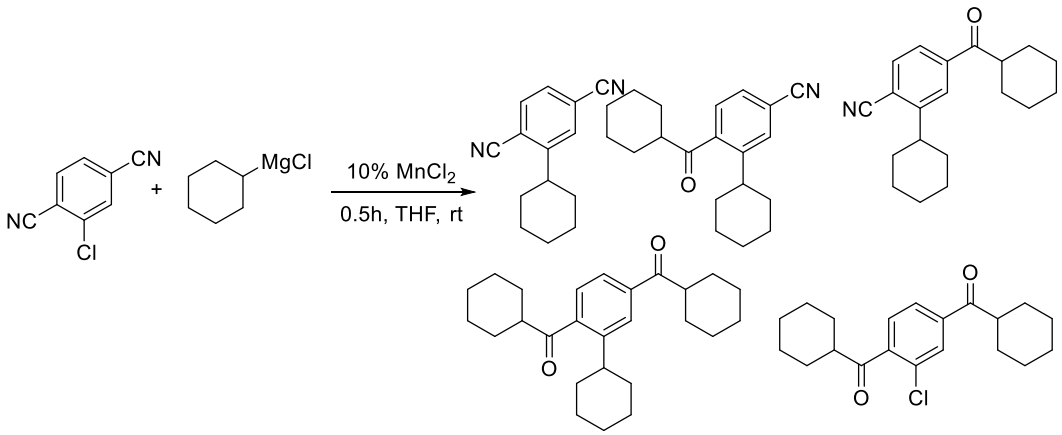
At this point the possibility that an activated compound could be formed during the reaction between 4-chlorobenzonitrile and cyclohexylmagnesium chloride needed to be tested. At first one equivalent of bromobenzene was added to the standard reaction with the hope that the system, once activated, could lead to cyclohexylbenzene (*scheme 2.14*).

Then, 4-chlorobenzonitrile was mixed with vinylmagnesium bromide (a reaction already proven unsuccessful) followed by dropwise addition of cyclohexylmagnesium chloride.

In both cases the only product detectable by GC-MS was 4-cyclohexylbenzonitrile.



Scheme 2.15: Side products obtained from the reaction with 4-chloro-2-cyanobenzonitrile.



Scheme 2.16: Side products obtained from the reaction with 2-chloroterephthalonitrile.

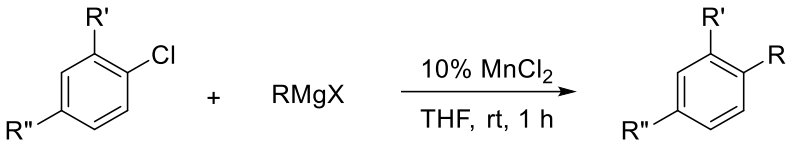
Moreover, some other aryl halides with more than one cyano group were tested.

4-Chloro-2-cyanobenzonitrile and 2-chloroterephthalonitrile were reacted with cyclohexylmagnesium chloride. It was possible to detect the cross-coupling product by GC-MS. Unfortunately, already after a few minutes, a large number of byproducts were observed (*shown in scheme 2.15 and*

2.16). This complex mixture made the quantification of the cross-coupling product impossible with the used technique.

2.6 Ortho- and para-chlorobenzonitriles

Ortho- and *para*-chlorobenzonitriles and other Grignard reagents were used in order to further investigate the scope and the limitations (*scheme 2.17*) (*table 2.13*).



Scheme 2.17: General reaction for chlorobenzonitrile substrate screening.

Table 2.13: Substrate screening of ortho- and para-chlorobenzonitriles.

Entry	R'	R"	R	X	Yield [%]
1	H	CN	C_6H_5	Br	93[a] [b]
2	H	CN	4-$MeOC_6H_4$	Br	83[a] [b]
3	H	CN	4-ClC_6H_4	Br	79[a] [b]
4	H	CN	4-MeC_6H_4	Br	77[a] [b]
5	H	CN	$CH_3(CH_2)_3$	Cl	68[b]
6	H	CN	$(CH_3)_2CHCH_2$	Cl	63[c]
7	H	CN	$(CH_3)_2CH$	Br	58[b]
8	CN	H	Cyclohexyl	Cl	91[b]
9	CN	H	C_6H_5	Br	90[b]
10	CN	H	4-$MeOC_6H_4$	Br	80[b]
11	CN	H	4-ClC_6H_4	Br	79[b]
12	CN	H	4-MeC_6H_4	Br	78[b]

[a] Result previously reported, [b] Isolated yield, [c] Yield calculated by NMR

Table 2.13 summarizes the experiments described earlier with 4-chlorobenzonitrile and different aryl Grignard reagents. The same experiments were reproduced with 2-chlorobenzonitrile to study the influence of the cyano group in the *ortho* position. No changes were observed: the behavior of 2-chlorobenzonitrile is very similar to 4-chlorobenzonitrile, except for a slightly lower yield that is possible to attribute to the steric hindrance of the cyano group in the *ortho* position.

4-Chlorobenzonitrile was also reacted with several alkyl organomagnesium halides: *n*-butylmagnesium chloride (*entry 5*), isobutylmagnesium chloride (*entry 6*), and isopropylmagnesium bromide (*entry 7*). None of the organomagnesium halides gave any homo-coupling product detectable with the analysis method used, but they were affected from the *β-elimination* (*scheme 1.7*).

The reaction with butylmagnesium chloride gave 68% yield and the ketone was the only detectable side product, due to the nucleophilic addition of the Grignard reagent to the nitrile group. A similar result was achieved when 4-chlorobenzonitrile was reacted with isobutylmagnesium chloride giving a 63% yield. With isopropylmagnesium bromide a further deterioration was observed. The yield in this case reached 58% probably because of the steric hindrance of the isopropyl substituent. The side product from the nucleophilic addition of the Grignard reagent was also detected but not quantified.

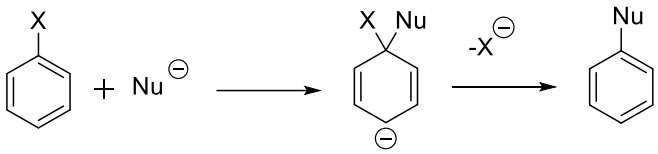
2.7 The role of the halogen

4-Chlorobenzonitrile was tested with the optimized conditions described in *paragraph 2.1*. In order to obtain a better picture, the same reaction was performed with the other halogens instead of chloride. Thus, 4-bromobenzonitrile, 4-iodobenzonitrile and 4-fluorobenzonitrile were also reacted with cyclohexylmagnesium chloride. 4-Fluorobenzonitrile did not show any conversion while 4-bromobenzonitrile yielded 43% of the desired product. The yield was low because of the competition between the cross-coupling reaction and the dehalogenation reaction. 4-Iodobenzonitrile suffered too from the dehalogenation reaction and benzonitrile was the only product to be detected.

In order to clarify the mechanism, it was important to check if the pathway could be a S_NAr (*scheme 2.18*). The nucleophilic aromatic substitution is a

reaction mechanism that requires the presence of electron withdrawing groups. It is known that the presence of fluorine at the *ipso* position, favors the reaction. In this way, the carbon to be attacked is more electropositive and susceptible toward the incoming nucleophile. The electron withdrawing groups on the ring help to stabilize the negative charge developing in the aromatic ring.

In case of 4-chlorobenzonitrile the electron withdrawing group is the cyano substituent. If S_NAr occurs, the reaction would still happen in the presence of fluoride instead of chloride and this did not happen. Therefore, the S_NAr pathway can be excluded in the search for the reaction mechanism.



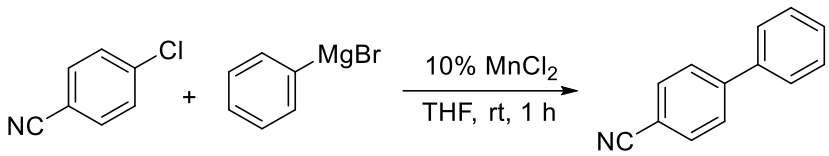
Scheme 2.18: Mechanism of a S_NAr.

2.8 Time studies and competitive experiments

To get more evidence about the mechanism of this transformation, time study experiments were conducted (*scheme 2.19*). The conditions of these experiments were modified: the organomagnesium halide was added all at the same time. This change caused the amount of the side products from the nucleophilic addition to the cyano group to rise.

Since the reaction is extremely fast at room temperature, it was decided to explore lower temperatures. When it was performed at 6 ºC the process is still very fast showing 80% conversion after one minute. Unfortunately, under 0 ºC the cross-coupling reaction did not occur and after one hour the conversion reached only 10% and the only product detected was the

nucleophilic addition to the cyano group. In the following chart are reported the amounts (in percentage) of the starting material and the product (*chart 2.1*).



Scheme 2.19: Reaction tested in the time study

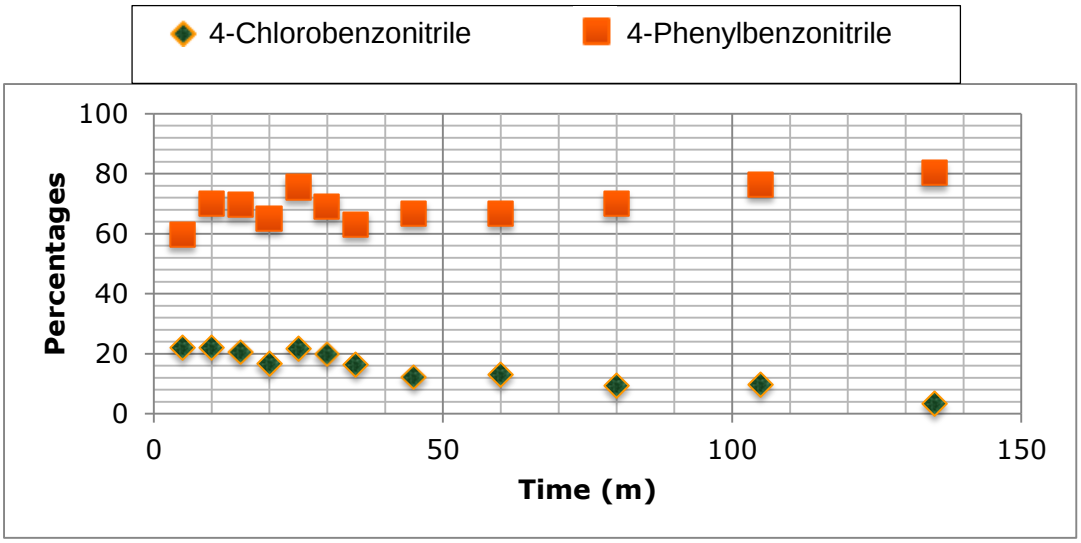
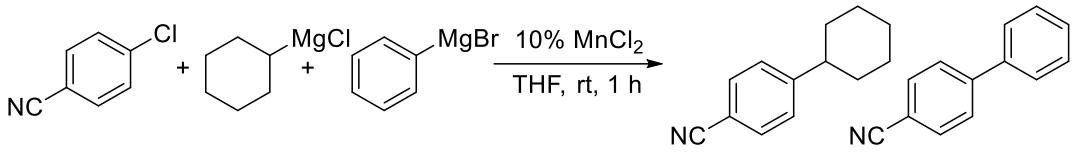


Chart 2.1: Reaction between 4-chlorobenzonitrile and phenylmagnesium bromide monitored over time.

4-Chlorobenzonitrile reacts in high yield with both cyclohexylmagnesium chloride and phenylmagnesium bromide. A competitive experiment was therefore performed to observe which Grignard reagent reacted faster (*scheme 2.20*).

In the following chart are displayed the amounts in percentage of the different compounds: blue for 4-chlorobenzonitrile, red for 4-phenylbenzonitrile, and green for 4-cyclohexylbenzonitrile (*chart 2.2*).



Scheme 2.20: Reaction tested in the competitive time study.

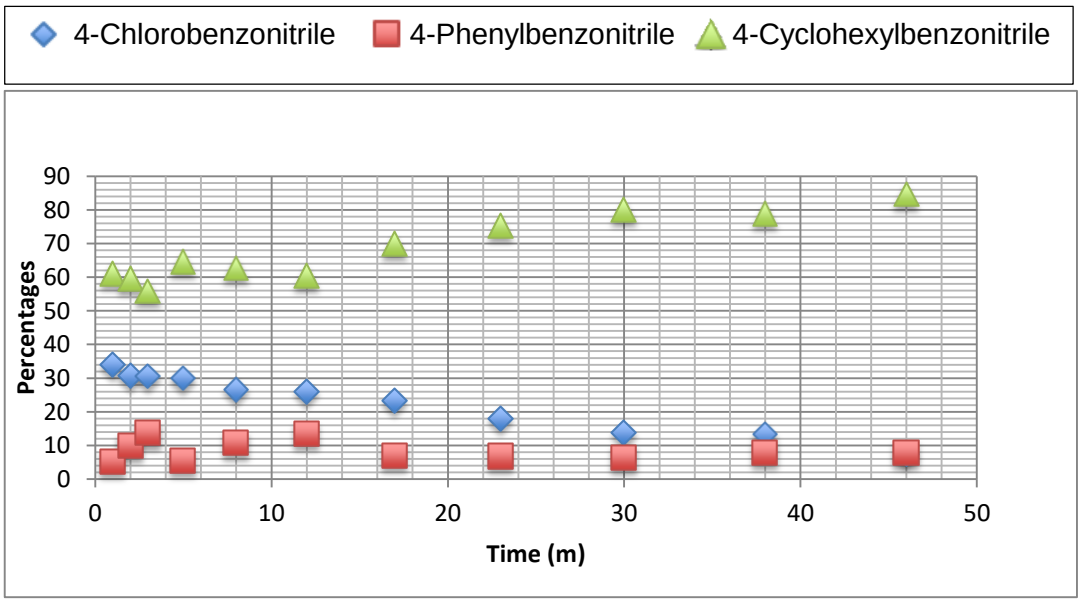


Chart 2.2: Competitive time study for reaction between 4-chlorobenzonitrile and two Grignard reagents.

The result of this experiment shows the immediate formation of 4-cyclohexylbenzonitrile and very little of 4-phenylbenzonitrile. This suggests that the most nucleophilic Grignard reagent gives a higher reaction rate.

In another competition experiment cyclohexylmagnesium chloride was reacted with a mixture of 4-chlorobenzonitrile and methyl 4-chlorobenzoate. In this case, the two substitution products were formed in equal amounts and the 4-cyano and the 4-methyl ester substituents therefore display a similar influence on the reactivity of the aryl halide.

2.9 Consideration

After this preliminary study it is clear that the reaction works with good yield only on para and ortho chlorobenzonitriles. With other substrates the reaction does either not occur, or the presence of a carbonyl group leads to a reduced yield or complete carbonyl addition with the Grignard reagent.

Another interesting aspect is the presence of some homo-coupling products from the Grignard reagents. This could be the result of the reaction between oxygen, manganese and the Grignard reagent as reported in the literature.[75]

Homo-coupling of the chlorobenzonitriles, however, was never observed in any of the experiments.

2.10 Mechanism investigation

Due to the limited substrate scope, the investigation into the manganese catalyzed cross-coupling reactions moved towards the understanding of the mechanism involved.

The study of the scope and limitations gave some results that needed to be further explored.

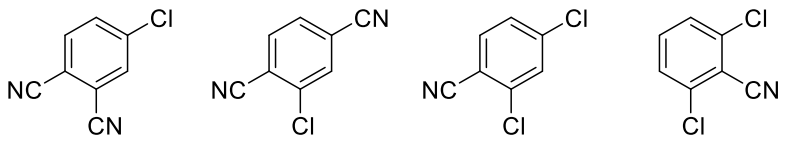
The chloro-substituted substrates react well with the Grignard reagents, and the aryl fluorides are unreactive. This shows that the transformation

does not proceed by a S_NAr mechanism, through an intermediate Meisenheimer adduct, with the addition of the nucleophile as the rate-determining step.

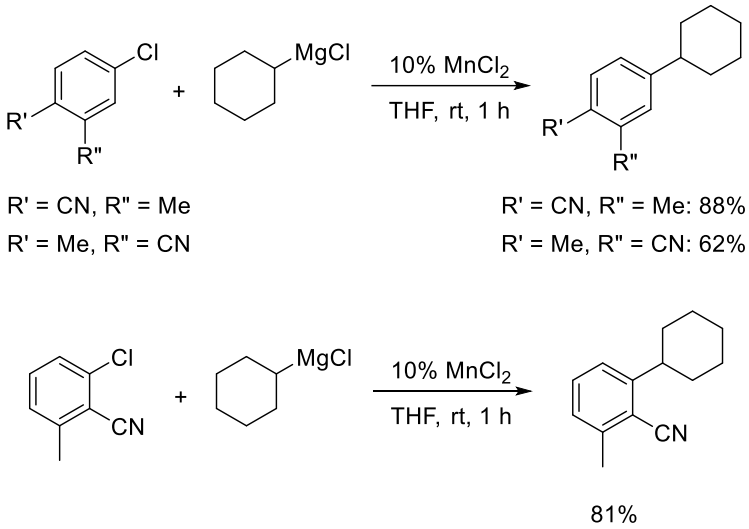
An oxidative addition of the aryl chloride, as known for the corresponding palladium- and nickel-catalyzed reaction, could also be excluded based on the substrate study. 4-Chlorobenzonitrile gave complete conversion while 1-chloro-4-(trifluoromethyl)benzene showed no reactivity. Since the cyano and trifluoromethyl substituent are both electron withdrawing groups with similar Hammett constant σ_{para} of about 0.6[78] a similar reactivity would be expected if the reaction proceeded by an oxidative addition.

2.10.1 Hammett study

A useful method to gain more information about the mechanism of a chemical reaction is to perform a Hammett study. In this prospective investigation more than one substrate was selected for the kinetic study (*scheme 2.21* and *scheme 2.22*).



Scheme 2.21 Substrates chosen for the Hammett study.



Scheme 2.22: Substrates chosen for the Hammet study.

Unfortunately, as previously mentioned, some compounds (*scheme 2.15 and 2.16*) gave a mixture of products, that were difficult to characterize. In fact, 4-chloro-2-cyanobenzonitrile and 2-chloroterephthalonitrile produced a great number of byproducts, due to the nucleophilic attack of the Grignard reagent to the cyano group. The same was observed with 2,4- and 2,6-dichlorobenzonitrile (*scheme 2.21*). Good results, however, were obtained with 4-chloro-2-methylbenzonitrile that showed an 88% yield (*scheme 2.22*). 5-Chloro-2-methylbenzonitrile also reacted producing 62% yield. This result is surprising, since it is the first time that a substrate with a characteristic CN in the meta position reacts with this protocol. In fact, the previous successful experiments proved the necessity to have a cyano or an ester moiety in *para* or *ortho* position. In addition, 2-chloro-6-methylbenzonitrile was reacted with cyclohexylmagnesium chloride affording 81% of the desired cross-coupling product (*scheme 2.22*).

2.10.2 Radical clock experiment

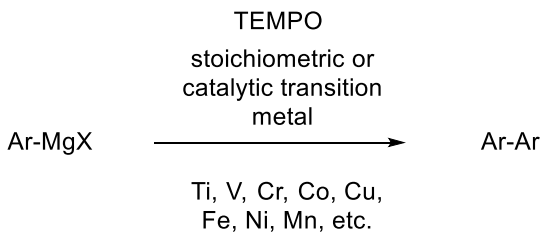
This part of the research was done in collaboration with fellow PhD student Andreas Ahlburg.

As shown in the experiments previously described, the transformation is fast, mostly limited to *ortho*- and *para*-substituted aryl halides, and it occurs only with temperatures higher than 0 °C.

From experimental data, the reaction does not seem to proceed through a S_NAr or through an oxidative addition – reductive elimination as the classical palladium- or nickel-catalyzed cross-coupling reactions.

After these considerations the idea that the reaction proceeds through a radical pathway began to develop.

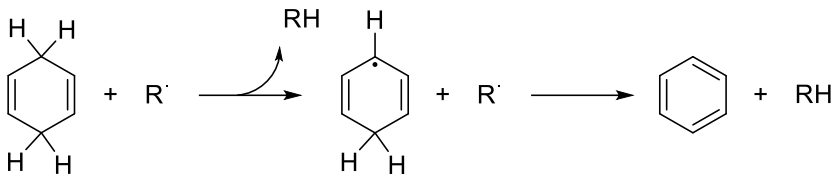
To prove this hypothesis, it was first attempted to trap the radical with a radical scavenger. The first reagent was TEMPO (*2,2,6,6-tetramethyl-1-piperidinyloxy*), but unfortunately, as previously reported[79] it interacts with the aryl Grignard reagents leading to a homo-coupling reaction (*scheme 2.23*).



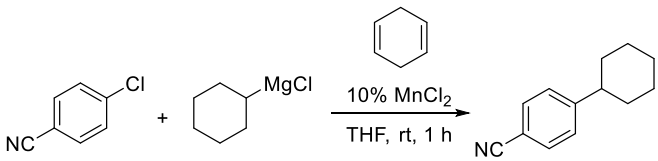
Scheme 2.23: Homo-coupling reaction of a Grignard reagent in the presence of TEMPO and a transition metal.

Subsequently, a reaction between cyclohexylmagnesium chloride and 4-chlorobenzonitrile was performed in the presence of cyclohexa-1,4-diene with the aim to dehalogenate the aryl chloride (*scheme 2.25*).

Cyclohexa-1,4-diene is well known as a two hydrogen atom donor.[80] In fact, the reaction between a radical species R· and cyclohexa-1,4-diene results in benzene and the hydrogenated RH (*scheme 2.24*).



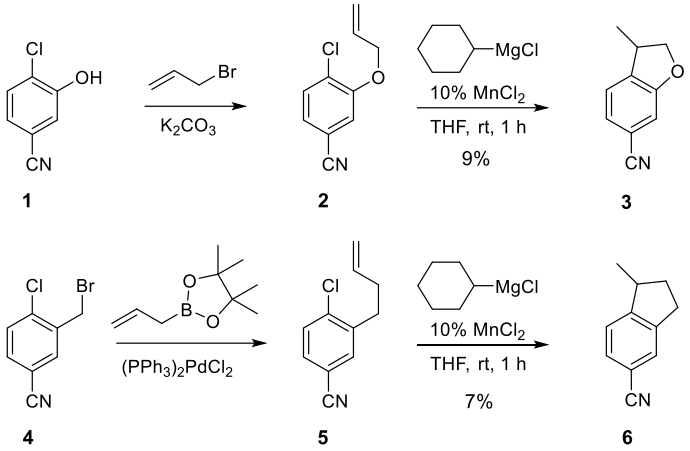
Scheme 2.24: Schematic reaction of radical trapping by cyclohexa-1,4-diene.



Scheme 2.25: Reaction between cyclohexylmagnesium chloride and 4-chlorobenzonitrile was performed in the presence of cyclohexa-1,4-diene.

Despite the addition of cyclohexa-1,4-diene the reaction proceeded smoothly without showing any dehalogenation. The same reaction was performed several times with an amount of cyclohexa-1,4-diene from 1 equivalent to 20, releasing only traces (less than 5% yield) of the dehalogenated product. In addition, this small amount of the dehalogenated product may not be caused by the use of cyclohexa-1,4-diene, since it is possible to detect benzonitrile also without the use of the radical scavenger.

However, the possibility that a $S_{RN}1$ mechanism[81] was involved was not excluded. In fact, it is reported in the literature that alkali metal enolates and a few other carbanions are able to react with halobenzenes through a $S_{RN}1$ pathway, even though this behavior is not reported for Grignard reagents.[82]



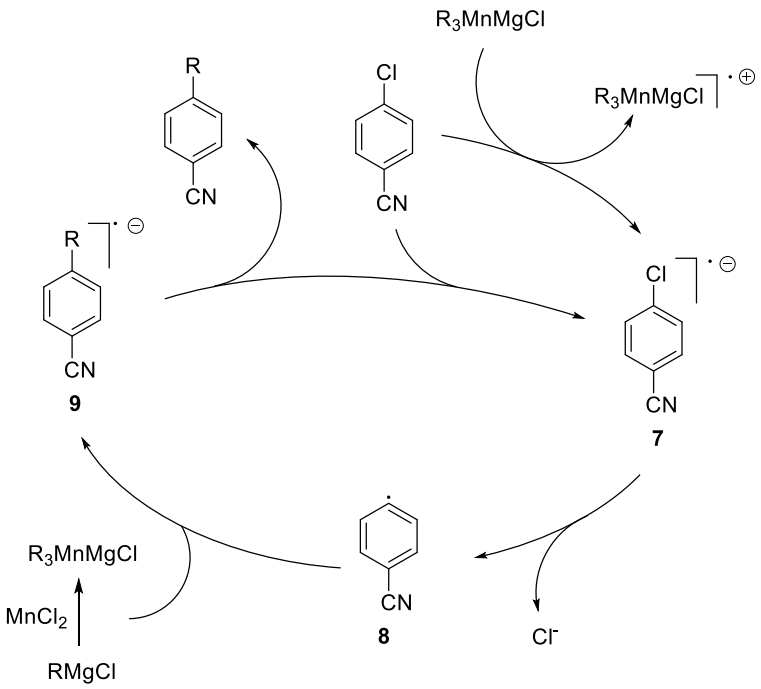
Scheme 2.26: Radical clock experiments.[83]

Then, two radical clock experiments were designed (*scheme 2.26*) which required the synthesis of new substrates that could fit the experiment.

To synthesize compound **2** and **5** an allylation reaction was performed on compounds **1** and **4**. We obtained a pure compound **2**, but compound **5** presented 30% of an impurity due to a byproduct where the double bond has migrated.

The optimized protocol was utilized on both products **2** and **5**. Reacting with cyclohexylmagnesium chloride gave in both cases a mixture of compounds. The cyclization product was detected in both cases with a yield of 9% and 7%, respectively. For both cases a small amount of the direct cross-coupling was also detected from GC-MS but it could not be quantified.

This result was a major lead in the hypothesis that a $S_{RN}1$ mechanism was involved.



Scheme 2.27: Proposed mechanism.

It is unlikely that the Grignard reagent serves as one-electron donor at 0 °C, considering that the reaction also requires the presence of $MnCl_2$. The initiator is probably the corresponding triorganomanganate complex, that is formed by the addition of three organic residues that come from the Grignard reagent. This complex is known for mediating radical reactions[84] and it can also be produced from organomagnesium halides.

The loss of chloride from 4-chlorobenzonitrile is three times faster than the same reaction from the corresponding meta compound[85] and this fact can justify the lack of reactivity of *3*-chlorobenzonitrile.

The mechanism proposed (*scheme 2.27*) proceeds through a SET from the triorganomanganate complex to 4-chlorobenzonitrile. This leads to the benzonitrile radical, that is electrophilic and is most likely attacked by the

triorganomanganate, that is a softer nucleophile compared to a Grignard reagent.[32] It should be noted in this context that the reaction also gives a high yield and fast conversion with one equivalent of $MnCl_2$ and under these conditions, there is no free Grignard reagent present. The cycle is closed with a SET from **9** to another molecule of 4-chlorobenzonitrile.

This pathway could also explain why the reaction has a narrow scope, since the presence of the cyano group in the *para* or *ortho* position stabilizes the radical that is created.

Usually if the reaction goes through a single electron transfer mechanism, the reactivity order on the aryl halides should be iodides > bromides > chlorides, in contrast with the result obtained. However, it has already been explained that with the present conditions the cross-coupling reaction is in competition with side reactions such as the dehalogenation of the aryl halide and the nucleophilic attack on the cyano group from the Grignard reagent. When bromobenzonitrile was tested, it showed 43% yield of the cross-coupling product and the presence of the dehalogenated coumpound. 4-Iodobenzonitrile did not produce any cross-coupling although the conversion was over 80%. From GC-MS it was only possible to detect the presence of benzonitrile and the nucleophilic addition product.

2.11 Conclusion

In summary, the manganese-catalyzed cross-coupling reaction at room temperature was explored. The scope and limitations of the reaction was extended to a short number of nitriles and to methyl 4-chlorobenzoate. The present method was used to produce biaryls and some substituted benzonitriles since the method allows the use of different Grignard reagents.

A plausible reaction mechanism through a $S_{RN}1$ pathway is hereby proposed for the manganese-catalyzed coupling between aryl halides and Grignard reagents. The $S_{RN}1$ pathway explains why the scope of the reaction is narrow since only the aryl halides that allow a single electron

reduction, followed by a facile halide dissociation are able to succeed under these conditions.

The proposed intermediate has been trapped by a radical clock substituent, where the cyclization reaction is preferred over the intermolecular coupling with the Grignard reagent. On the contrary, the intermolecular coupling is favored over bimolecular reactions with base-stable radical trapping reagents like cyclohexadiene.

Substrates which react directly with the Grignard reagents are not suitable for this reaction. On the other side, there are several organomagnesium halides that are suitable coupling partners for this cross-coupling reaction.

Experimental section

General methods

Decane was used as the internal standard and GC yields were determined with the following equation i).

i) $y(\%) = \left(\frac{A_p}{A_0} \cdot \frac{m_0}{MW_0} \cdot \frac{MW_s}{m_s} \cdot k \cdot 100\right)$

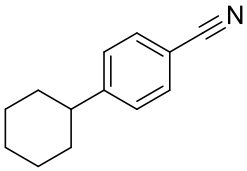
Where A_p = product peak's area, A_0 = standard peak's area, m_0 = mass (mg) of the internal standard in the reaction mixture, MW_0 = molecular weight of the internal standard, m_s = mass (mg) of the initial substrate, MW_s = molecular weight of the initial substrate, k = value extrapolated by the product's calibration curve. All chemicals were purchased from Sigma-Aldrich and ABCR and used without further purifications. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck 25, 20 × 20 cm, 60 F_{254}). The plates were visualized under UV-light.

Flash column chromatography was performed on silica gel 60 (40 – 63 µm) with specified solvents given as volume ratio. NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_c = 77.16 ppm). Multiplicity are reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, ddt = double double triplet, s = sextet, m = multiplet, br. s = broad singlet, while coupling constants are shown in Hz.

All Grignard reagents were obtained from commercial suppliers and titrated with a 0.06 M solution of I_2 in Et_2O to determine the concentration: cyclohexylmagnesium chloride (1.6 M in Et_2O), phenylmagnesium bromide (0.9 M in THF), 4-methoxyphenylmagnesium bromide (0.3 M in THF), 4-chlorophenylmagnesium bromide (0.5 M in

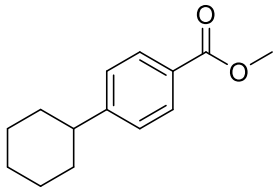
Et_2O), 4-tolylmagnesium bromide (0.9 M in THF), *n*-butylmagnesium chloride (1.6 M in THF), isobutylmagnesium chloride (1.8 M in THF) and isopropylmagnesium bromide (0.8 M in THF).

General Procedure for Cross-Coupling: A dry three-neck Schlenk tube was equipped with a stir bar and a nitrogen inlet. The flask was flushed with nitrogen and charged with $MnCl_2$ (25 mg, 0.2 mmol) and dry THF (6 mL). The mixture was stirred for about 10 min to completely dissolve $MnCl_2$ followed by addition of the aryl halide (2 mmol) and cooling to 0 °C in an ice bath. A solution of the Grignard reagent (4 mmol) was added dropwise over 5 min and the ice bath was removed. The mixture was stirred for 1 h at ambient temperature. Decane (0.4 mL, 2 mmol) was injected as an internal standard for determining the yield by GC and the reaction was quenched with saturated ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (4 × 10 mL) and the combined organic layers were concentrated and the residue purified by flash column chromatography (70/30 pentane/CH_2Cl_2).



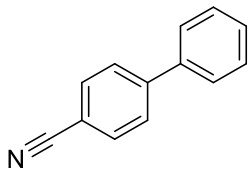
4-Cyclohexylbenzonitrile: Isolated as a colorless oil in 94% yield (347 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.52 (m, 2H), 7.33–7.26 (m, 2H), 2.55 (tt, J = 9.1, 2.6 Hz, 1H), 1.90–1.83 (m, 4H), 1.82–1.76 (m, 1H), 1.44–1.36 (m, 4H), 1.33–1.17 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 132.3, 127.8, 119.4, 109.7, 44.9, 34.1, 26.8, 26.1 ppm. MS (EI): m/z = 185 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[86]



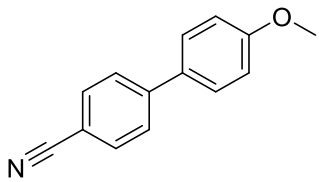
Methyl 4-cyclohexylbenzoate: Isolated as a white solid (430 mg) containing about 25% of cyclohexyl 4-cyclohexylphenyl ketone which could not be separated. Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 2H), 7.30–7.21 (m, 2H), 3.87 (s, 3H), 2.60–2.41 (m, 1H), 2.01–1.61 (m, 5H), 1.54–0.73 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 153.6, 129.8, 127.8, 127.0, 52.0, 44.8, 34.6, 27.1, 26.4 ppm. MS (EI): m/z = 218 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[86]



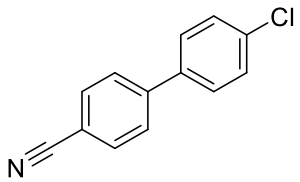
[1,1'-Biphenyl]-4-carbonitrile: Isolated as a yellowish solid in 93% yield (334 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.65 (m, 4H), 7.63–7.55 (m, 2H), 7.53–7.44 (m, 2H), 7.47–7.38 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 139.3, 132.7, 129.2, 128.8, 127.9, 127.4, 119.1, 111.1 ppm. MS (EI): m/z = 179 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[87]



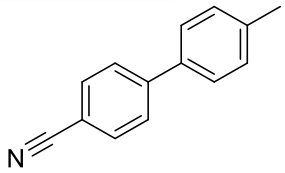
4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile: Prepared according to the general procedure where the Grignard reagent was added over 120 min at 0 °C to prevent a competing addition to the cyano group. Isolated as a white solid in 83% yield (341 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 2H), 7.66–7.62 (m, 2H), 7.57–7.50 (m, 2H), 7.04–6.97 (m, 2H), 3.87 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 145.3, 132.7, 131.6, 128.5, 127.2, 119.2, 114.7, 110.2, 55.5 ppm. MS (EI): m/z = 209 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[87]



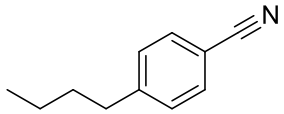
4'-Chloro-[1,1'-biphenyl]-4-carbonitrile: Prepared according to the general procedure where the reaction mixture was stirred for 2 h at 60 °C in an oil bath to ensure complete conversion of 4-chlorobenzonitrile. Isolated as a white solid in 79% yield (335 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 137.7, 135.1, 132.9, 129.5, 128.6, 127.7, 118.9, 111.4 ppm. MS (EI): m/z = 213 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[88]



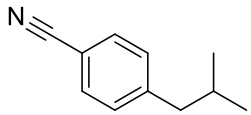
4'-Methyl-[1,1'-biphenyl]-4-carbonitrile: Prepared according to the general procedure where the Grignard reagent was added over 120 min at 0 °C to prevent a competing addition to the cyano group. Isolated as a white solid in 77% yield (296 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.43–7.39 (m, 2H), 7.21 (d, J = 7.9 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 138.9, 136.4, 132.7, 130.0, 127.6, 127.2, 119.2, 110.7, 21.3 ppm. MS (EI): m/z = 193 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[89]



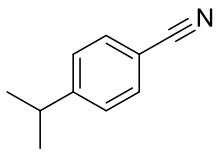
4-Butylbenzonitrile: Isolated as a colorless oil in 68% yield (217 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 1.67–1.51 (p, J = 7.5 Hz, 2H), 1.33 (q, J = 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 132.0, 129.2, 119.1, 109.4, 35.8, 33.1, 22.2, 13.8 ppm. MS (EI): m/z = 159 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[90]



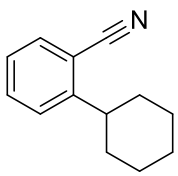
4-Isobutylbenzonitrile: Isolated as a colorless oil (290 mg) which could not be obtained completely pure. Yield 63% as estimated from the NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 2H), 7.12–7.08 (m, 2H), 2.38 (d, J = 7.3 Hz, 2H), 1.74 (dt, J = 13.6, 6.8 Hz, 1H), 0.76 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 131.9, 129.8, 129.7, 119.1, 109.5, 45.4, 30.0, 22.2 ppm. MS (EI): m/z = 159 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[91]



4-Isopropylbenzonitrile: Isolated as a yellowish oil in 58% yield (168 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.45 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 2.88 (d, J = 6.9 Hz, 1H), 1.19 (d, J = 7.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 132.2, 127.3, 119.2, 109.6, 34.4, 23.5 ppm. MS (EI): m/z = 145 $[M]^+$.

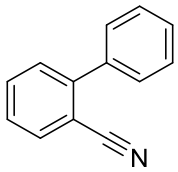
The observed chemical shifts are in accordance with the literature values.[92]



2-Cyclohexylbenzonitrile: Isolated as a colorless oil in 91% yield (337 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.36 (m, 2H), 7.25 (dd, J = 8.0, 1.1 Hz, 1H), 7.14 (td, J = 7.6, 1.2 Hz, 1H), 2.93–2.77 (m, 1H), 1.83–1.60 (m,

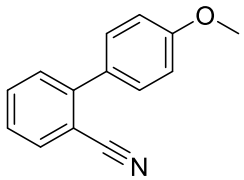
5H), 1.42–1.25 (m, 4H), 1.22–1.02 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 132.8, 132.7, 126.4, 126.2, 118.1, 111.7, 42.7, 33.5, 26.5, 25.8 ppm. MS (EI): m/z = 185 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[93]



[1,1'-Biphenyl]-2-carbonitrile: Isolated a as white solid in 90% yield (321 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (td, J = 6.3, 1.5 Hz, 1H), 7.63 (td, J = 7.8, 1.5 Hz, 1H), 7.57–7.40 (m, 7H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 138.3, 133.9, 132.9, 130.2, 127.7, 118.9, 111.4 ppm. MS (EI): m/z = 179 $[M]^+$.

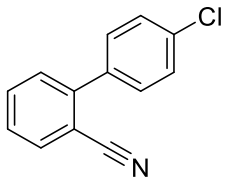
The observed chemical shifts are in accordance with the literature values.[94]



4'-Methoxy-[1,1'-biphenyl]-2-carbonitrile: Prepared according to the general procedure where the Grignard reagent was added over 120 min at 0 °C to prevent a competing addition to the cyano group. Isolated as a white solid in 80% yield (336 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.61 (td, J = 7.7, 1.4 Hz, 1H), 7.54–7.47 (m, 3H), 7.39 (td, J = 7.6, 1.2 Hz, 1H), 7.05–6.99 (m, 2H), 3.86 (s, 3H) ppm. ^{13}C NMR

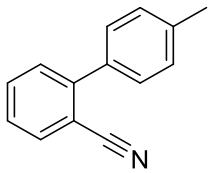
(100 MHz, $CDCl_3$): δ = 160.2, 145.3, 133.8, 132.9, 130.0, 127.1, 119.1, 114.3, 111.1, 55.5 ppm. MS (EI): m/z = 209 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[94]



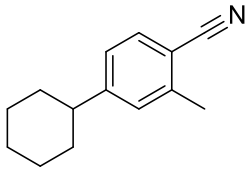
4′-Chloro-[1,1'-biphenyl]-2-carbonitrile: Prepared according to the general procedure where the reaction mixture was stirred for 2 h at 60 °C in an oil bath to ensure complete conversion of 4-chlorobenzonitrile. Isolated as a white solid in 79% yield (335 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, J = 7.7, 1.3 Hz, 1H), 7.65 (td, J = 7.5, 1.3 Hz, 2H), 7.52–7.44 (m, 7H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 136.7, 135.2, 133.9, 133.1, 130.2, 128.0, 118.6, 111.4 ppm. MS (EI): m/z = 213 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[94]



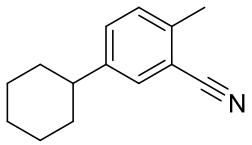
4'-Methyl-[1,1'-biphenyl]-2-carbonitrile: Prepared according to the general procedure where the Grignard reagent was added over 120 min at 0 °C to prevent a competing addition to the cyano group. Isolated as a white solid in 78% yield (302 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (dd, J = 7.8, 1.3 Hz, 1H), 7.57 (td, J = 7.7, 1.4 Hz, 1H), 7.47–7.39 (m, 3H), 7.36 (td, J = 7.6, 1.3 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 138.7, 135.3, 133.7, 132.8, 130.0, 129.5, 128.6, 127.3, 111.2, 21.4 ppm. MS (EI): m/z = 193 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[95]

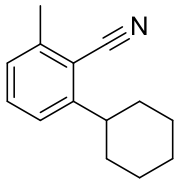


4-Cyclohexyl-2-methylbenzonitrile: Isolated as a colorless oil (384 mg) which could not be obtained completely pure. Yield 88% as estimated from the NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.54 (m, 1H), 7.46–7.31 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 2.80–2.35 (m, 4H), 2.02–1.75 (m, 5H), 1.71–1.15 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 141.9, 133.7, 132.6, 130.6, 129.0, 126.9, 125.0, 110.1, 44.8, 34.1, 26.8, 26.1, 20.6 ppm. MS (EI): m/z = 199 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[93]

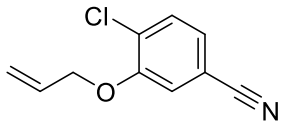


5-Cyclohexyl-2-methylbenzonitrile: Isolated as a colorless oil in 62% yield (246 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.0 Hz, 1H), 7.29–7.15 (m, 2H), 2.66–2.60 (m, 4H), 2.10–1.75 (m, 5H), 1.63–1.26 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 132.5, 128.9, 124.9, 118.6, 110.0, 44.8, 34.0, 26.7, 26.0, 20.6 ppm. HRMS: calcd for $C_{14}H_{18}N$ 200.1434 $[M + H]^+$, found: 200.1436.

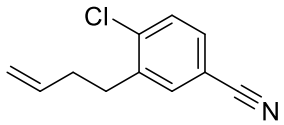


2-Cyclohexyl-6-methylbenzonitrile: Isolated as a white solid in 81% yield (322 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 2.98 (tt, J = 11.3, 3.1 Hz, 1H), 2.53 (s, 3H), 1.95–1.72 (m, 5H), 1.57–1.35 (m, 4H), 1.34–1.17 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 142.3, 132.4, 127.5, 123.7, 117.3, 112.5, 43.1, 33.9, 26.8, 26.1, 21.1 ppm. MS (EI): m/z = 199 $[M]^+$.

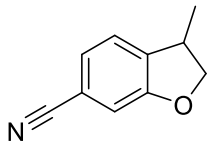
The observed chemical shifts are in accordance with the literature values.[93]



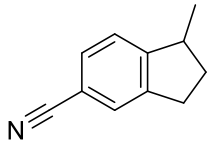
3-(Allyloxy)-4-chlorobenzonitrile: A mixture of 4-chloro-3-hydroxybenzonitrile (1 g, 6.5 mmol), allyl bromide (0.6 mL, 7.1 mmol) and K_2CO_3 (1 g, 7.2 mmol) in acetone (50 mL) was stirred under reflux. The reaction was monitored by TLC and additional allyl bromide (0.6 mL, 7.1 mmol) and K_2CO_3 (1 g, 7.2 mmol) were added after 20 min. After two hours, the reaction was diluted with water and extracted with diethyl ether. The organic layers were concentrated to give 1.2 g (95%) of a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 6.04 (ddd, J = 15.8, 10.5, 5.2 Hz, 1H), 5.48 (d, J = 15.8 Hz, 1H), 5.37 (d, J = 10.5 Hz, 1H), 4.64 (d, J = 5.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 131.6, 131.3, 129.0, 125.3, 118.9, 118.2, 116.4, 111.5, 70.1 ppm. HRMS: calcd for $C_{10}H_8ClNNaO$ 216.0186 $[M + Na]^+$, found: 216.0188.



3-(But-3-en-1-yl)-4-chlorobenzonitrile: A mixture of 3-(bromomethyl)-4-chlorobenzonitrile (2.4 g, 10 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.75 g, 1 mmol), tri(*2*-tolyl)phosphine (325 mg, 10 mmol), allylboronic acid pinacol ester (1.97 g, 12 mmol) and Na_2CO_3 (2.15 g, 20 mmol) in aqueous acetonitrile (1/10 H_2O/MeCN, 100 mL) was stirred at reflux for 2 h. Water was added and the mixture was extracted with Et_2O. The organic layers were concentrated and the residue purified by column chromatography (4/1 pentate/CH_2Cl_2) to give 439.5 mg (22%) of the product as a brown oil, which contained about 30% of a byproduct where the olefin had migrated. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 1.7 Hz, 1H), 7.40–7.38 (m, 2H), 5.78 (ddt, J = 16.9, 10.3, 6.5 Hz, 1H), 5.02–4.98 (m, 1H), 4.98–4.95 (m, 1H), 2.80 (dd, J = 8.7, 6.7 Hz, 2H), 2.37–2.29 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 139.3, 136.7, 133.9, 130.8, 130.5, 118.2, 116.1, 110.8, 33.1, 32.8 ppm. HRMS: calculated for $C_{11}H_{11}ClNNa$ 214.0394 $[M+Na]^+$, found: 214.0401.



3-Methyl-2,3-dihydrobenzofuran-6-carbonitrile: 3-(Allyloxy)-4-chlorobenzonitrile (386 mg, 2 mmol) was reacted with cyclohexylmagnesium chloride and $MnCl_2$ as described above in the general procedure to give 30.1 mg (9%) of the product as a brown oily solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 7.7 Hz, 1H), 7.17 (dd, J = 7.7, 1.3 Hz, 1H), 6.99 (d, J = 1.2 Hz, 1H), 4.74 (t, J = 9.0 Hz, 1H), 4.14 (dd, J = 8.8, 7.4 Hz, 1H), 3.65–3.50 (m, 1H), 1.34 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 138.5, 125.3, 124.7, 119.2, 112.7, 111.6, 79.1, 36.6, 19.1 ppm. HRMS: calcd for $C_{10}H_9NNaO$ 182.0576 $[M + Na]^+$, found: 182.0577.



1-Methyl-2,3-dihydro-1H-indene-5-carbonitrile: 3-(But-3-en-1-yl)-4-chlorobenzonitrile (382 mg, 2 mmol, including 30% of the olefin isomer) was reacted with cyclohexylmagnesium chloride and $MnCl_2$ as described above in the general procedure to give 21.7 mg (7%) of the product as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 7.1 Hz, 1H), 3.27–3.17 (m, 1H), 2.94 (ddd, J = 16.2, 8.7, 4.0 Hz, 1H), 2.86 (dt, J = 16.4, 8.5 Hz, 1H), 2.35 (dtt, J = 11.4, 7.4, 3.7 Hz, 1H), 1.65 (dq, J = 12.6, 8.7 Hz, 1H), 1.30 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 145.2, 130.7, 128.1, 124.1, 119.8, 109.9, 39.9, 34.5, 31.3, 19.5 ppm. HRMS: calcd for $C_{11}H_{12}N$ 158.0964 $[M + H]^+$, found: 158.0964.

Chapter 3

Further development of the manganese catalyzed cross-coupling reaction

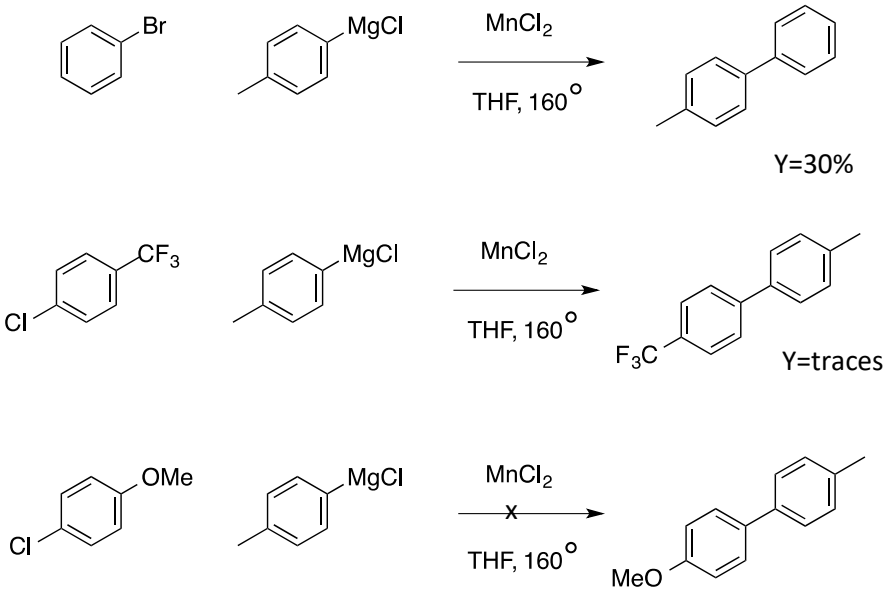
3.1 Preliminary studies

The manganese-catalyzed cross-coupling reaction performed at room temperature showed significant limitations. This procedure is limited to aryl chlorides with cyano or ester groups in the *para* or *ortho* position.

Several attempts were performed to extend the scope of this protocol at room temperature, but they were unsuccessful.

In order to make the reaction kinetically more favorable, it was decided to explore higher temperatures. For this reason, the reaction was repeated at the reflux temperature of the solvent, but no cross-coupling product was detected although the amount of the dehalogenated product increased.

A further optimization experiment was to perform the reaction in a closed system by applying a temperature higher than the boiling point of the solvent (*scheme 3.1*).



Scheme 3.1: Reaction between bromobenzene and 4-tolylmagnesium bromide in the presence of $MnCl_2$

With this protocol The reaction between bromobenzene and tolylmagnesium chloride produced almost 30% yield of the desired cross-coupling product. The homo-coupling product of the Grignard reagent and the dehalogenated arene were detected as byproducts. 1-Chloro-4-(trifluoromethyl)benzene was also reacted with tolylmagnesium chloride and afforded traces of 4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl, and surprisingly, a product of nucleophilic substitution between the fluoride and the organomagnesium halide were observed. The cross-coupling reaction did not occur between 1-chloro-4-methoxybenzene and tolylmagnesium chloride. The only side product detected was the homo-coupling of the Grignard reagent. With regards to the interesting results shown, it was possible to continue the optimization process that will be described in the next paragraphs.

3.2 Results and discussion

3.2.1 Temperature screening

After the preliminary studies by the author two PhD students, Carola Santilli and Somayyeh Sarvi Beigbaghlou continued the study toward the optimization of the reaction and performed the following experiments. As a result, all the yields and compound characterization data reported in this paragraph were obtained by Carola Santilli and Somayyeh Sarvi Beigbaghlou.

It was decided to try to perform these reactions in a microwave oven. In this way the heating would be more homogeneous and the procedure more reproducible.

The system bromobenzene and 4-tolylmagnesium bromide in THF was selected as a model reaction (*table 3.1*) for the temperature screening.

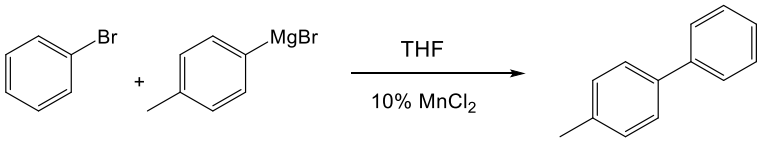


Table 3.1: Temperature screening for the reaction between bromobenzene and 4-tolylmagnesium bromide in the presence of $MnCl_2$[a]

Entry	T [°C]	t [h]	Yield [%][b]
1	180	2	40
2	200	1	29
3	160	2	33
4	140	2	34
5	120	14	21

[a] Conditions: aryl halide (2 mmol), 4-tolylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), decane (1 mmol, internal standard) and solvent (8 mL, i.e. Grignard concentration 0.5 M) in a closed vial with microwave heating. [b] GC yield.

The best result was obtained when the reaction was performed at 180 ˚C in the microwave oven for two hours yielding 40% of 4-phenyltoluene (*entry 1*). Increasing the temperature to 200 ˚C, the time necessary to obtain full conversion was reduced to 1 h, but the yield of the hetero-coupling product dropped to 29% (*entry 2*) due the competing dehalogenation reaction. Decreasing the temperature to 160 ˚C and 140 ˚C did not improve the reaction yield and 4-phenyltoluene was obtained in 33% and 34% yields, respectively (*entry 3-4*). Furthermore, products deriving from the organomagnesium bromide homo-coupling reaction and the aryl halide dehalogenation were detected. Performing the experiment at 120 ˚C gave a slightly lower yield (21%) and 14 h were needed to obtain the full conversion of the substrate (*entry 5*).

3.2.2 Solvent effect

The major drawback of the reaction performed so far is the dehalogenation process that involves the aryl halide. This reaction is supposed to follow one of the two possible pathways (*scheme 2.2*): a radical pathway, or a metal-halogen exchange. If the reaction between bromobenzene and 4-tolylmagnesium bromide is assumed to proceed by a radical pathway it should go through the formation of a benzene radical. The dehalogenation can be also explained by considering the metal-halogen exchange between bromobenzene and 4-tolylmagnesium bromide under the reaction conditions. The presence of an electron-donating group in the *para* position of the Grignard reagent allows a transmetallation with bromobenzene. Phenyl magnesium bromide is generated from the reaction. In both cases the quenching made with ammonium chloride will create the dehalogenated arene.

In order to avoid the dehalogenation side reaction[96] due to the halogen metal exchange, two new substrates were chosen. This time the same

protocol described in paragraph 3.2.1, was applied to 4-tolyl bromide and phenylmagnesium bromide.

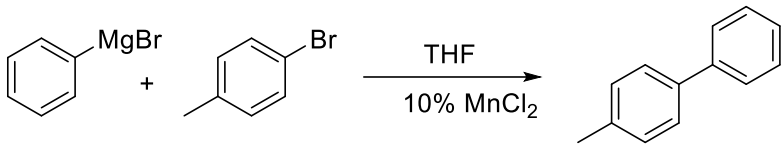


Table 3.2: Temperature screening for the reaction between 4-tolylbromide and phenylmagnesium bromide in the presence of $MnCl_2$[a]

Entry	X	Solvent	T [˚C]	t [h]	yield [%][b]
1	Br	THF	160	2	7
2[c]	Br	THF	160	2	15
3[c]	Br	Et_2O	160	1	23
4	Br	Et_2O	160	1	60
5	Br	Et_2O	140	2	57
6	Br	Et_2O	120	5	70
7	Br	Et_2O	100	12	69
8	Br	2-MeTHF	160	2	65
9	I	Et_2O	120	5	75
10	Cl	Et_2O	120	5	33

[a] Conditions: 4-bromotoluene (2 mmol), phenylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), decane (1 mmol, internal standard) and 1.3 mL solvent (Grignard concentration 3 M) in a closed vial with microwave heating. [b] GC yield. [c] 4 mL solvent (Grignard concentration 1 M).

For the reason described before, it was decided to switch the functionality for the cross-coupling reaction. It was chosen to use 4-bromotoluene as the aryl halide, and phenyl magnesium bromide as the Grignard reagent. When the reaction was run with these substrates at 160 ˚C in THF (Grignard concentration 0.5 M), only 7% of 4-methylbiphenyl was observed (*entry 1*). The reaction gave a better yield when the concentration of the organomagnesium bromide was increased to 1 M (entry 2) and Et_2O was

used as solvent (entry 3). When the Grignard reagent concentration was raised from 1 M to 3 M, the reaction provided yields between 60 - 70% depending on the temperature and the reaction time (entries 4-7). The reaction in *entry 6* was also performed by heating the reaction flask with an oil bath overnight and 4-methylbiphenyl was obtained with 62% yield. While the first reactions (*table 3.2, entry 1,2*) gave a poor yield, the others (*entry 3 to 7*) showed an interesting formation of the product. Under these conditions the reaction exhibited an improvement when Et_2O was used instead of THF as solvent. Since the solvent plays a major role influencing the Schlenk equilibrium (*scheme 2.3*), it was hypothesized that this variation could have a positive influence for this reaction.

3.2.3 Amount of Grignard reagent

One of the mechanisms that can lead to halide dehalogenation is the metal halogen exchange that can occur between the halide and the Grignard reagent.
In order to limit the dehalogenation side reaction, the influence was tested of the amount of the organomagnesium halide necessary to perform the cross-coupling reaction.
The results of this study are reported in the following table:

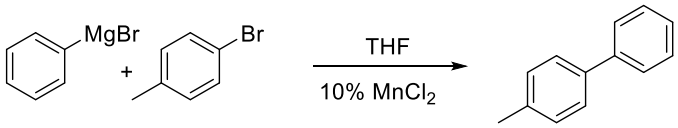


Table 3.3: Investigation about the amount of Grignard reagent required[a]

Entry	n (4-bromotol.)	n (phenylMgBr)	4-methylbiphenyl y [%][b]	toluene y [%][b]
1	2	4	70	26
2	2	2	22	24
3	4	2	traces	traces
4	2	8	66	32

[a] Conditions: 4-bromotoluene (n mmol), phenylmagnesium bromide (n mmol), $MnCl_2$ (0.2 mmol), decane (1 mmol, internal standard) and 1.3 mL solvent (Grignard concentration 3 M) in a closed vial with microwave heating. [b] GC yield.

When a 1:1 ratio of the two substrates was used, the yield of the heterocoupling product dropped to 22%, and 24% of toluene was produced, while the remaining portion was unreacted 4-bromotoluene (*entry 2*). The worst result was obtained with a 2:1 ratio of 4-bromotoluene to phenylmagnesium bromide where only traces of 4-methylbiphenyl and toluene were generated (*entry 3*). Differently, when 4-bromotoluene and phenylmagnesium bromide were used in a 1:4 ratio, the reaction produced 4-methylbiphenyl and toluene in 66% and 32% yields, respectively. In this case the ratio between the two main products is comparable to the one reported in *entry 1*.

3.2.4 Source of manganese

Another factor that was examined during this optimization is the source of the manganese. For this purpose, four different manganese salts were selected: $MnCl_2$, $MnBr_2$, MnI_2, and MnF_2.
The four reactions were performed under these conditions: 4 mL of solvent (THF), ratio 2:1 between the Grignard reagent and the halide, and 10% of the manganese salt.

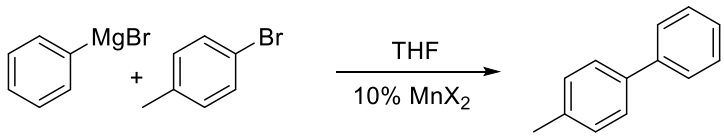


Table 3.4: Manganese salts screening.

Entry	X	cat.	T [°C]	t [h]	yield [%][b]
1	Cl	$MnCl_2$	160	2	30
2	F	MnF_2	160	2	10
3	Br	$MnBr_2$	160	2	29
4	I	MnI_2	160	2	28

[a] Conditions: aryl halide (2 mmol), 4-tolylmagnesium bromide (4 mmol), MnX_2 (0.2 mmol), decane (1 mmol, internal standard) and solvent (8 mL, i.e. Grignard concentration 0.5 M) in a closed vial with microwave heating. [b] GC yield.

As shown in *table 3.4*, the reactivity of the manganese salts are similar except for manganese fluoride, that appears to be three times less reactive.

3.2.5 Use of additives

The standard reaction was tested in the presence of LiCl, LiBr, and $MgBr_2$. The salts did not have any influence on the reaction outcome, except for $MgBr_2$, which made the reaction less efficient.
A major drawback of this protocol is the amount of the homo-coupling product that decreases the overall reaction yield. Some years ago Nakamura *et al.*[97] reported that the presence of NHC ligands in iron-catalyzed cross-coupling reactions to form biaryls can suppress the homo-coupling process.
Therefore, it was decided to perform the reaction between tolylbromide and phenylmagnesium bromide, in the presence of two different imidazolium salts (*table 3.5)*.

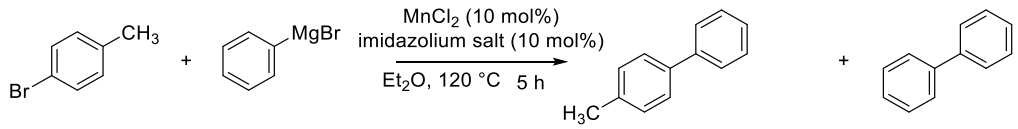
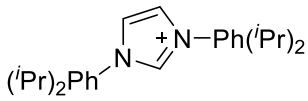
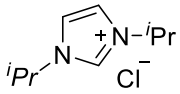


Table 3.5: Investigation about the influence of imidazolium salts to suppress the homo-coupling product [a]

Entry	Imidazolium salt	Yield [%][b] 4-Methylbiphenyl	Yield [%][c] biphenyl
1	-	70	33
2		36	17
3		63	29

[a] Conditions: 4-bromotoluene (2 mmol), phenylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), decane (1 mmol, internal standard) and 1.3 mL solvent (Grignard concentration

3 M) in a closed vial with microwave heating. [b] GC yield. [c] GC yield based on the amount of phenylmagnesium bromide.

Unfortunately, as shown in *table 3.5* (*entry 2-3*) the imidazolium salts do not improve the reaction yield.

3.2.6 Substrate screening

Another interesting aspect that can be extrapolated from *table 3.2* is how the reaction is sensitive to the concentration of the Grignard reagent. A more concentrated Grignard reagent produces a better yield.
Considering the good yield reported with 4-tolyl iodide (*table 3.6, entry 1)*, it was hypothesized that this protocol could show a good affinity with the iodine substrates. For this reason, a new set of experiments based on aryl iodides were performed.
These reactions were conducted under the optimized conditions: an aryl iodide (2 mmol) was mixed with phenylmagnesium bromide (4 mmol, Grignard concentration 3 M) in the presence of $MnCl_2$ (10 mol%) at 120 ˚C in the microwave oven (*table 3.6*).

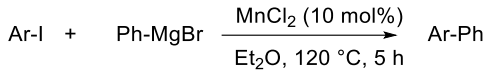
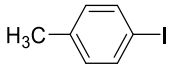
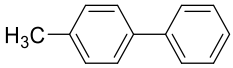
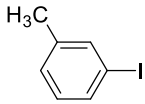
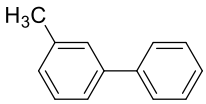
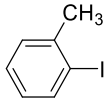
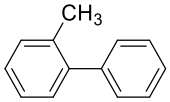
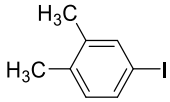
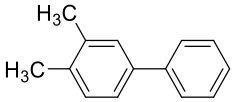
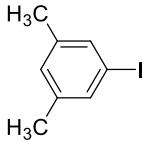
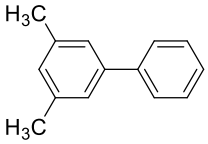
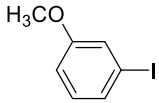
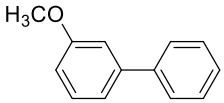
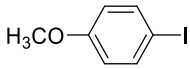
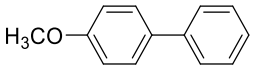
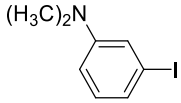
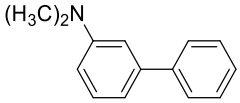
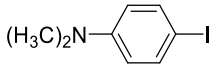
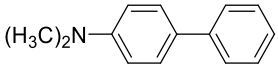
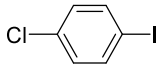
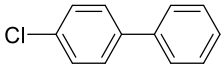
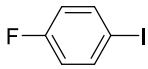
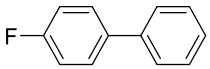


Table 3.6: Manganese catalyzed cross-coupling reaction of aryl iodides.

Entry	Ar-X	Ar-Ph	Yield [%][b]
1			66[c]
2			50[c]
3			34[c]
4			77
5			62[c]
6			26
7			23
8			33
9			28
10			13
11			6

[a] Conditions: aryl iodide (2 mmol), phenylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), and 1.3 mL solvent (Grignard concentration 3 M) in a closed vial with microwave heating. [b] Isolated yield. [c] Yield based on NMR since isolated product was not completely pure.

The first example reported in *table 3.6*, involving 4-iodotoluene as the substrate, shows that this reaction has a higher yield when performed on iodine substrate as compared to the bromine counterpart (*entry 1*). The product was afforded in 66% yield and only in 47% for bromobenzene (result no shown). In the reaction between 3-iodotoluene and phenylmagnesium bromide, 3-methylbiphenyl was obtained in 50% yield (*entry 2*). A lower yield was achieved with *3*-bromotoluene. In fact, only 20% of the heterocoupling product was obtained from the reaction (result not shown). 2-Iodotoluene yielded the corresponding coupling product in 34% yield (*entry 4*). This result can be explained by considering the steric effect exercised by the methyl group in the *ortho* position. Dimethyliodobenzenes perform well with this protocol. In fact, 4-iodo-1,2-dimethylbenzene and 1-iodo-3,5-dimethylbenzene yielded 77% and 62% of the corresponding biphenyl product (*entries 4-5*). Aryl iodides bearing a methoxy group in the *para* or *meta* position were tested as well. Poor yields were observed in both cases: 3-methoxybiphenyl was achieved in 26% yield while 4-methoxybiphenyl was produced in 23% yield (*entry 6-7*). When a dimethylamino group was used instead, the corresponding coupling product was obtained in a slightly better yield (*entries 8-9*). 4-Chloroiodo- and 4-fluoroiodo-benzene were also tested and the reaction resulted in only 13% and 6% yield (*entry 10-11*).
No cross-coupling was observed when 4-phenyliodobenzene or 3-phenyliodobenzene reacted with phenylmagnesium bromide.

3.3 Consideration

After investigating a Mn-catalyzed cross-coupling reaction at room temperature, as described in the previous chapter, new conditions were examined in order to extend the substrate scope.

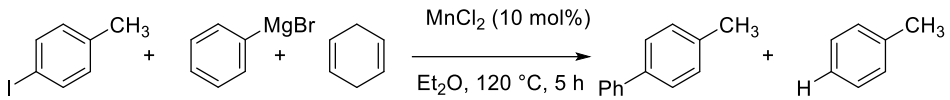
The room temperature cross-coupling reaction showed some limitations in the substrate scope. It is applicable only to 2- and 4-chlorobenzonitriles

and to methyl 4-chlorobenzoate. This high temperature cross-coupling has a broader application that includes alkyl substituted halides, while other substrates give a low yield.

3.4 Investigation on the reaction mechanism

We hypothesized that the reaction mechanism could be an $S_{RN}1$ as for the room temperature Mn-catalyzed cross-coupling.

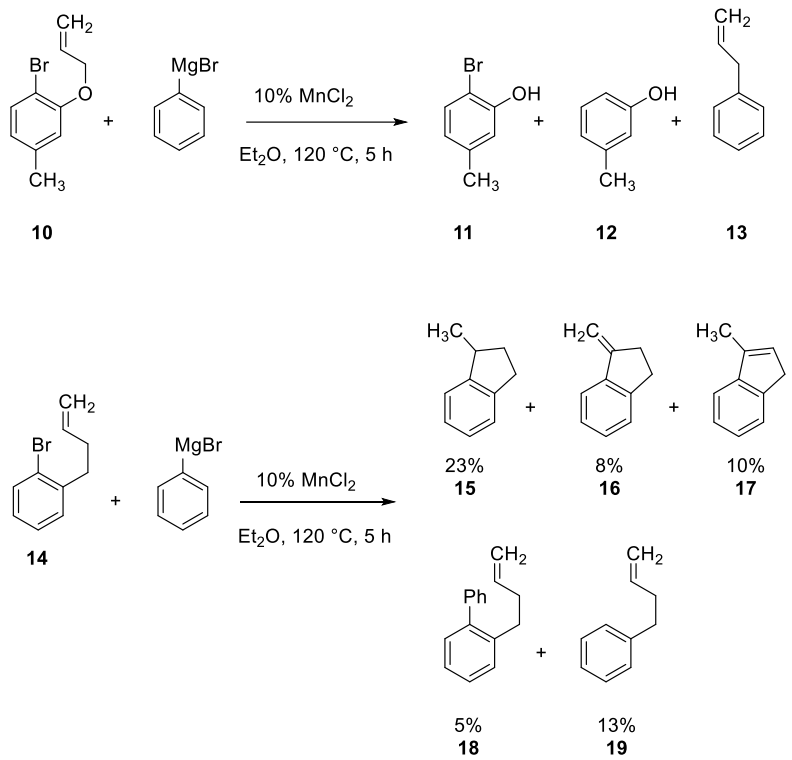
At first an attempt was made to obtain the dehalogenated halide performing the reaction in the presence of 1,4-cyclohexadiene. As explained earlier, cyclohexa-1,4-diene is a two hydrogen atom[80] donor and it should be able to produce the dehalogenated halide (*scheme 3.2*).



Scheme 3.2: Reaction between 4-tolyl iodide and phenylmagnesium bromide in the presence of 1,4-cyclohexadiene

The reaction was performed with 10 equivalents of 1,4-cyclohexadiene and produced 56% yield of toluene against only 7% of the cross-coupling product. This result suggests that a radical pathway is probably involved.

Another attempt to prove the $S_{RN}1$ mechanism was performed through a radical clock experiment (*scheme 3.3*). It was decided to test two different compounds (2-(allyloxy)-1-bromo-4-methylbenzene and 4-(2-bromophenyl)-but-1-ene).

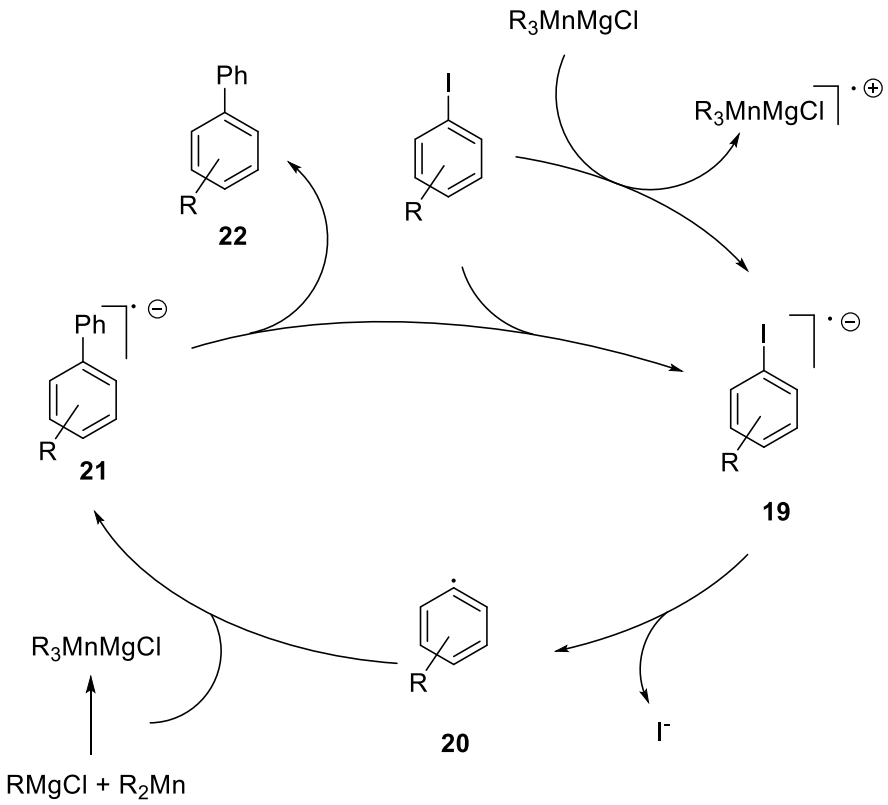


Scheme 3.3: Radical clock experiments.

When the reaction was performed with 2-(allyloxy)-1-bromo-4-methylbenzene (**10**), it produced a mixture of products **11** and **13**, caused by the decomposition of the substrate and by a S_N2 side reaction that occurs between the compound and the Grignard reagent.

The reaction performed on 4-(2-bromophenyl)-but-1-ene was more effective, and it was possible to obtain 23% of the cyclization product **15**.

A $S_{RN}1$ mechanism was proposed as for the room temperature Mn-catalyzed cross-coupling reaction (*scheme 3.4*).



Scheme 3.4: $S_{RN}1$ mechanism proposed.

The proposed mechanism is shown in *scheme 3.4*. The triphenylmanganate complex works as a radical initiator, and performs a SET to the aryl halide resulting in the radical anion **19**. This generates the aryl radical **20**, which reacts with triphenylmanganate complex thus producing a biphenyl radical anion **21**. Triphenylmanganate complex is a softer nucleophile than a Grignard reagent and according to the reaction mechanism previously suggested in *scheme 2.27*, it is most likely the only nucleophile which can act in this mechanism.

The following electron transfer, from the biphenyl radical anion **21** to the aryl halide, leads to the heterocoupling product **22** and closes the catalytic cycle.

3.5 Conclusions

The scope of this project was to improve the applicability of the Mn-catalyzed cross-coupling reaction described in the previous chapter. This aim was achieved by developing a method that involves the use of a microwave oven and a more concentrated solution of the Grignard reagent. The scope was extended to a variety of substituted aryl halides, obtaining products from low to good yields. In general, methyl substituted aryl halides gave the best yields demonstrating that the reaction is limited to these substrates.

The major drawback of this procedure are the dehalogenation and the homo-coupling reaction.

The reaction mechanism was investigated, suggesting that an $S_{RN}1$ pathway is involved.

Experimental section

General methods

All the reactions were performed in Biotage microwave reactor and monitored by gas chromatography on a Shimadzu GCMS-QP2012S instrument equipped with an Equity-5, 30 m × 0.25mm × 0.25µm column. Decane was used as the internal standard and GC yields were determined with the following equation i).

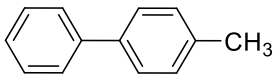
i) $y(\%) = \left(\frac{A_p}{A_0} \cdot \frac{m_0}{MW_0} \cdot \frac{MW_s}{m_s} \cdot k \cdot 100\right)$

Where A_p = product peak's area, A_0 = standard peak's area, m_0 = mass (mg) of the internal standard in the reaction mixture, MW_0 = molecular weight of the internal standard, m_s = mass (mg) of the initial substrate, MW_s = molecular weight of the initial substrate, k = value extrapolated by the product's calibration curve. All chemicals were purchased from Sigma-Aldrich and ABCR and used without further purifications. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck 25, 20 × 20 cm, 60 F_{254}). The plates were visualized under UV-light.

Flash column chromatography was performed on silica gel 60 (40 – 63 µm) with specified solvents given as volume ratio. NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_c = 77.16 ppm). Multiplicity are reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, ddt = double double triplet, s = sextet, m = multiplet, br. s = broad singlet, while coupling constants are shown in Hz.

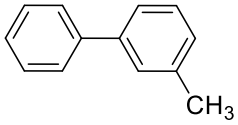
General procedure for cross-coupling catalyzed by $MnCl_2$

$MnCl_2$ (25 mg, 0.2 mmol) was placed in a predried microwave vial (with a liquid volume allowance between 0.5 mL and 2 mL) equipped with a magnetic stirrer and then sealed with a rubber septum. The vial was evacuated and refilled three times with nitrogen through a syringe. The aryl halide (2 mmol) and decane (1 mmol, internal standard) were placed in the vial followed by addition of 3 M phenylmagnesium bromide (4 mmol) in diethyl ether under a flow of nitrogen. The reaction vial was sealed with a cap and placed in the microwave reactor at 120 °C for 5 h. The mixture was quenched with a saturated solution of ammonium chloride. The phases were separated and the aqueous phase extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude product, which were purified by flash chromatography eluting with pentane or pentane containing 0.5 – 10% EtOAc.



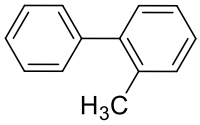
4-Methyl-1,1'-biphenyl: Prepared from 4-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 4-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H-NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.49 (m, 2H), 7.42-7.32 (m, 4H), 7.28-7.21 (m, 1 H), 7.18-7.14 (m, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl3): δ = 141.3, 138.5, 137.1, 129.6, 128.8, 127.1, 127.1, 21.2 ppm. MS (m/z) 168.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[98]



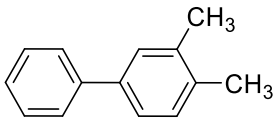
3-Methyl-1,1'-biphenyl: Prepared from 3-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 3-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H-NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62-7.59 (m, 2 H), 7.48-7.33 (m, 6 H), 7.19-7.17 (m, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 141.4, 138.5, 128.8, 128.8, 128.1, 127.3, 124.4, 21.7 ppm. MS (m/z) 168.05 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[98]



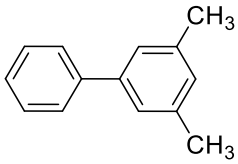
2-Methyl-1,1'-biphenyl: Prepared from 2-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 2-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H-NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.40 (m, 2 H), 7.37-7.32 (m, 3 H), 7.28-7.23 (m, 4 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 142.1, 135.5, 130.4, 129.9, 129.3, 128.2, 127.3, 126.9, 125.9, 20.69 ppm. MS m/z 168.05 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[99]



3,4-Dimethyl-1,1'-biphenyl: Prepared from 4-iodo-1,2-dimethylbenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield the desired product as a colorless oil (75%).

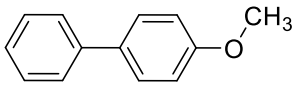
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.58 (m, 2 H), 7.45-7.39 (m, 3 H), 7.36-7.31 (m, 2 H), 7.22 (d, J= 7.7 Hz 1H), 2.35 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 139.0, 137.0, 135.8, 130.2, 128.8, 128.6, 127.1, 127.0, 124.6, 20.1, 19.6 ppm. MS m/z 182.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[100]



3,5-Dimethyl-1,1'-biphenyl: Prepared from 1-iodo-3,5-dimethylbenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 3,5-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H-NMR spectrum.

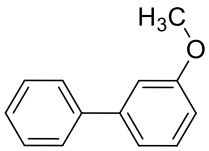
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63-7.59 (m, 2 H), 7.49-7.43 (m, 2 H), 7.39-7.33 (m, 2 H), 7.24 (br s, 1 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 141.4, 138.4, 129.0, 128.8, 127.3, 127.2, 125.2, 21.6 ppm. MS m/z 182.00 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[98]



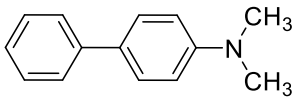
4-Methoxy-1,1'-biphenyl: Prepared from 4-iodoanisole and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/ ethyl acetate (10:0.05 *v*/*v*) to yield the desired product as a white solid (23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.52 (m, 4 H), 7.44-7.40 (m, 2 H), 7.33-7.28 (m, 1 H), 7.00-6.97 (m, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.3, 55.5 ppm. MS m/z 184.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[98]



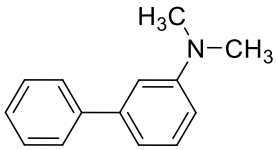
3-Methoxy-1,1'-biphenyl: Prepared from 3-iodoanisole and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/ ethyl acetate (10:0.05 *v*/*v*) to yield the desired product as a white solid (26%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61-7.58 (m, 2 H), 7.46-7.42 (m, 2 H), 7.38-7.33 (m, 2 H), 7.20-7.18 (m, 1 H), 7.14-7.13 (m, 1 H), 6.92-6.89 (m, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 142.9, 141.3, 128.9, 128.9, 127.6, 127.3, 119.8, 113.0, 112.8, 55.5 ppm. MS m/z 184.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[99]



***N*,*N*-Dimethyl[1,1'-biphenyl]-4-amine:** Prepared from 4-bromo-*N*,*N*-dimethylaniline and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/ ethyl acetate (10:1 *v*/*v*) to yield the desired product as a white solid (28%).

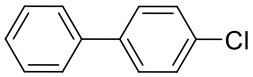
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.52 (m, 4 H), 7.43-7.39 (m, 2 H), 7.29-7.25 (m, 1 H), 6.84-6.82 (m, 2 H), 3.01 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 141.3, 128.8, 127.9, 126.4, 126.1, 113.0, 40.8 ppm. MS m/z 197.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[102]



***N*,*N*-Dimethyl[1,1'-biphenyl]-3-amine:** Prepared from 3-bromo-*N*,*N*-dimethylaniline and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/ ethyl acetate (10:1 *v*/*v*) to yield the desired product as a colorless oil (33%).

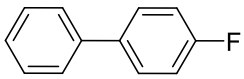
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.61 (m, 2 H), 7.47-7.44 (m, 2 H), 7.38-7.32 (m, 2 H), 7.00-6.97 (m, 2 H), 6.80-6.77 (m, 1 H), 3.03 (s, 6 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 142.4, 142.4, 129.5, 128.7, 127.5, 127.2, 116.1, 111.8, 111.8, 40.9. MS m/z 197.05 $[M]^+$.

The observed chemical shifts are in accordance with the literature values.[101]



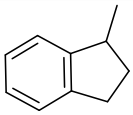
4-Chloro-1,1'-biphenyl: Prepared from 1-chloro-4-iodobenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield the desired product as a white solid (13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.51 (m, 4 H), 7.48-7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1, 139.8, 133.5, 129.0, 129.0, 128.5, 127.7, 127.1 ppm. MS m/z 187.90 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[103]

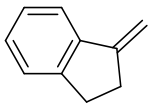


4-Fluoro-1,1'-biphenyl: Prepared from 1-fluoro-4-iodobenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography, eluting with pentane to yield the desired product as a white solid (6%).

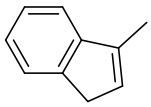
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 4 H), 7.47-7.43 (m, 2 H), 7.38-7.34 (m, 1 H), 7.17-7.11 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.60 (d, J= 246.2 Hz), 140.39, 137.47 (d, J= 3.3 Hz), 128.95, 128.82 (d, J= 8.1 Hz), 127.39, 127.16, 115.85 (d, J= 21.3 Hz) ppm. MS m/z 172.05 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[98]



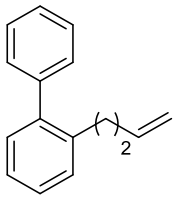
1-Methylindan: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 3.20 (sextet, J = 7.2 Hz, 1 H), 3.02–2.79 (m, 2 H), 2.36–2.28 (m, 1 H), 1.66–1.57 (m, 1 H), 1.31 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 144.0, 128.4, 126.2, 124.5, 123.3, 39.6, 34.9, 31.6, 20.0 ppm. MS: m/z = 132.05 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[104]



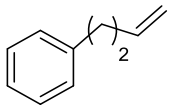
1-Methyleneindan: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 5.47 (t, J = 2.6 Hz, 1 H), 5.09–5.08 (m, 1 H), 3.02–2.98 (m, 2 H), 2.93–2.79 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 146.9, 141.2, 128.4, 126.5, 125.5, 120.7, 102.6, 31.3, 30.2 ppm. The observed chemical shifts are in accordance with the literature values.[105]



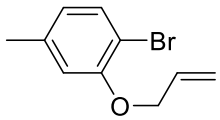
3-Methyl-1*H*-indene: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 6.22–6.21 (m, 1 H), 3.34–3.33 (m, 2 H), 2.20–2.18 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 144.5, 140.1, 128.9, 126.2, 124.6, 123.7, 119.0, 37.8, 13.2 ppm. The observed chemical shifts are in accordance with the literature values.[105]



2-(But-3-en-1-yl)-1,1'-biphenyl: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.24 (m, 9 H), 5.73 (ddt, J = 16.9,10.2, 6.6 Hz, 1 H), 4.94 (q, J = 1.7 Hz, 1 H), 4.91–4.89 (m, 1 H), 2.72–2.68 (m, 2 H), 2.26–2.20 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 142.0, 139.4, 138.3, 130.2, 129.3, 128.2, 127.5, 126.9, 125.9, 114.8, 35.3, 32.7 ppm. MS: m/z = 208.00 $[M]^+$. The observed chemical shifts are in accordance with the literature values.[106]



4-Phenyl-1-butene: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 5 H), 5.88 (ddt, J = 16.9,10.2, 6.6 Hz, 1 H), 5.05–5.04 (m, 1 H), 5.00 (dd, J = 10.2, 1.6 Hz, 1 H), 2.75–2.71 (m, 2 H), 2.42–2.37 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 138.2, 128.6, 126.2, 125.9, 115.0, 35.7, 35.5 ppm. MS: m/z = 132.05 $[M]^+$.The observed chemical shifts are in accordance with the literature values.[107]



2-(Allyloxy)-1-bromo-4-methylbenzene: Prepared from 2-bromo-5-methylphenol and allyl bromide, according to the procedure found in the literature.[108] The residue was purified by flash column chromatography,

eluting with hexane/ ethyl acetate (35:1 *v*/*v*) to yield the desired product as a colorless oil (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J*= 8.0 Hz, 1 H), 6.72-6.71 (m, 1 H), 6.67-6.65 (m, 1 H), 6.08 (ddt, *J*= 17.2, 10.3, 5.0 Hz, 1 H), 5.50 (dq, *J*= 17.2, 1.7 Hz, 1 H), 5.32 (dq, *J*= 10.6, 1.5 Hz, 1 H), 4.59 (dt, *J*= 5.0, 1.7 Hz, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 138.7, 133.0, 132.8, 122.9, 117.7, 114.7, 109.0, 69.7, 21.5 ppm. MS: m/z = 225.85 $[M]^+$. HRMS calcd. for $C_{10}H_{12}BrO$ $[MH^+]$: 227.0066, found: 227.0034.

Chapter 4

Manganese-catalyzed aerobic heterocoupling of aryl Grignard reagents

4.1 Introduction

The aryl-aryl bond formation has been one of the most interesting challenges of this century.[109] This type of bonds is often found in natural products, pharmaceuticals, agrochemicals and conducting materials (*figure 4.1)*. For these reasons the synthesis of biaryls represent a relevant topic for the organic chemists.

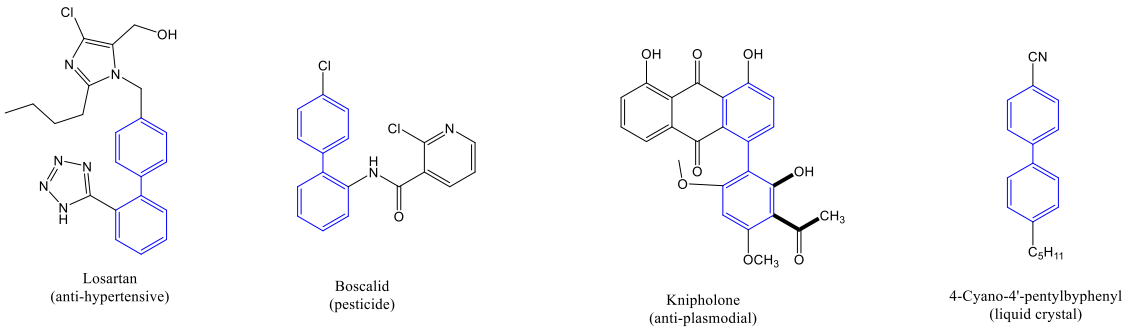


Figure 4.1: Example of chemical compounds containing a biaryl motif.

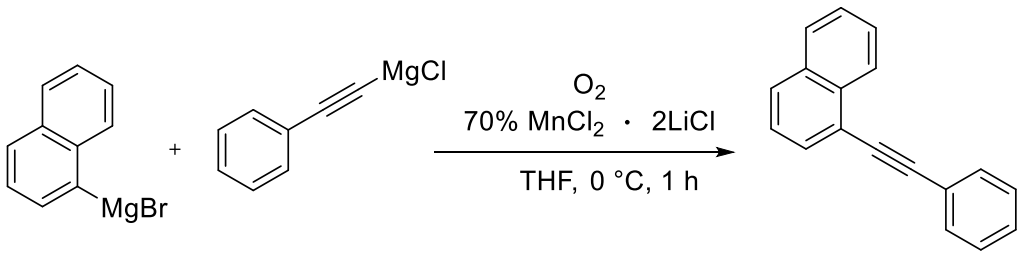
Their importance results in a large variety of reactions developed to produce aryl-aryl bonds. Usually, the synthesis of these bonds is made by metal-catalyzed cross-coupling reactions[110] like the palladium-catalyzed Stille and Suzuki coupling. However, there is not a method that allows for the synthesis of all the different aryl-aryl bonds and, in fact, often the use of several procedures are required.

In some cases, oxidative methods are proven to be effective as well as the reactions with radical chemical intermediates.[111]

The oxidative homo-coupling of organomagnesium halides has been thoroughly investigated. Several different transition metals, like iron,[112] copper,[113] cobalt,[114] manganese,[115] nickel[116] and ruthenium[117] are proven to be suitable catalysts for this transformation.

However, the corresponding cross-coupling between two different Grignard reagents leaves space for further investigations. A previous study showed how it is possible to obtain a statistical mixture of products, reacting the substrates with a mixture of two different types of Grignard reagents[118].

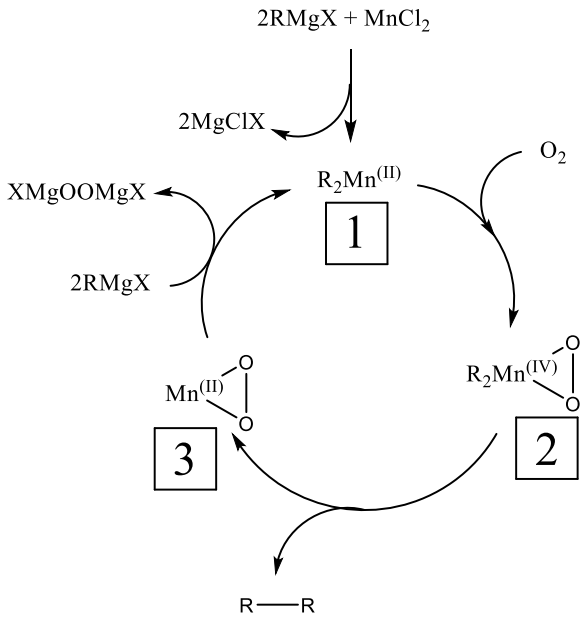
In 2009 Cahiez *et al.*[115] achieved a yield of 70% (based on the limiting agent) using a 2.5:1 ratio between the two Grignard reagents (*scheme 4.1*).



Scheme 4.1: Example of Mn-catalyzed oxidative cross-coupling.

The electron-rich Grignard reagents react faster than the other species. This factor can be used to influence the selectivity.

After the discovery of the effectiveness of the manganese catalyzed oxidative coupling,[115] the mechanism of this reaction has been investigated through DFT calculations.[119]



Scheme 4.2: Mn-catalyzed oxidative cross-coupling proposed by Bottoni et al.[119]

The mechanism proposed, through DFT studies, by Bottoni *et al.* is shown in *scheme 4.2*. The catalytic specie is formed by transmetalation, where the chlorine atoms bonded to manganese are substituted by the R group from the Grignard reagent. This reaction is favored because the "soft" carbon of the organomagnesium halide should have a preference to move to the "soft" manganese. Then an oxidative addition will follow, creating a η^2 oxo complex (***2***). A fast reductive elimination will follow, and the catalyst

will be reformed by reaction with two more molecules of the Grignard reagent.

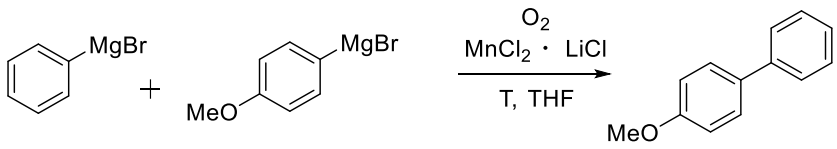
It was speculated that the Mn-catalyzed oxidative cross-coupling could be extended to other substrates, and optimized with regard to the catalyst load.

4.2 Results and discussion

4.2.1 Preliminary studies

Following the procedure illustrated by Cahiez *et al.*[115] it was decided to try to extend the substrate scope and limitation of this reaction.

4-Methoxyphenylmagnesium bromide was reacted with phenylmagnesium bromide in a *ratio* of 1:2.5. The two aryl halides are added one at the time at -15 ˚C in a THF solution containing $MnCl_2$ and LiCl. When the addition is complete a flux of oxygen is gurgled into the solution (*scheme 4.3*). The yield achieved was about 65%. This experiment showed one important aspect. The coupling partner 4-methoxyphenylmagnesium bromide did not undergo any homo-coupling. The major drawback seemed to be the homo-coupling reaction of phenylmagnesium bromide.



Scheme 4.3: Mn-catalyzed oxidative cross-coupling reaction.

4-Methoxyphenylmagnesium bromide was reacted with 4-chlorophenylmagnesium bromide following the same procedure. The yield obtained was about 40% and it was still impossible to detect the homo-coupling of 4-methoxyphenylmagnesium bromide.

When tolylmagnesium bromide was reacted with phenylmagnesium bromide the yield obtained was only the statistical one. Unfortunately, both of the organomagnesium halides underwent the homo-coupling in this case.

4.2.2 Solvent choice

The procedure used until this point involved the use of THF as the solvent. This choice has been influenced by two factors: the stability of the Grignard reagents in coordinating aprotic solvents,[82] and the solubility of manganese in the presence of LiCl.

$MnCl_2$ is insoluble in Et_2O, resulting in a very slow transmetalation of the organomagnesium halides.[32] Later on, after the substrate scope was done (description in the following chapters) 4-methoxyphenylmagnesium bromide was reacted with 4-chlorophenylmagnesium bromide in ethyl ether. Surprisingly, the yield of the reaction dropped to 30% and under these conditions it was possible to identify, by GC-MS, also the homo-coupling product deriving from 4-methoxyphenylmagnesium bromide.

4.2.3 Optimizing conditions

The experiments reported in this paragraph were performed by Hajar Golshadi Ghalehshahi, a visiting PhD student. The contribution of the author of this thesis consisted in the discovery of the reaction and in the data analysis.

The Mn-catalyzed oxidative cross-coupling reaction protocol developed by Cahiez *et al.* consists of mixing the compounds at -5 ˚C, then stirring the mixture for 5 minutes before adding dioxygen to the mixture.

Again, phenylmagnesium bromide was reacted with 4-methoxyphenylmagnesium bromide (*table 4.1*). Performing the reaction with the mentioned conditions gave only 67% yield (GC yield). This was a poor result compared to the paper where 80% was reported.[115]

In order to try an optimization of the protocol, it was first tested with the corresponding chloride of the Grignard reagents, and then the reaction was performed using dry air instead of dioxygen. The first test did not produce any improvement, while the second resulted in a slightly lower yield.

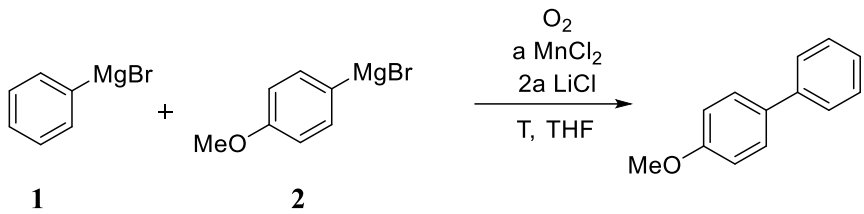


Table 4.1: Mn-catalyzed oxidative cross-coupling reaction optimization

Entry	1:2	Mixing time of 1 and 2 [min]	a [%]	*T* [°C]	Yield [%][a]
1	2.5:1	5	70	-5	67
2	2.5:1	5	20	-5	40
3	2.5:1	10	70	-5	86
4	2.5:1	20	70	-5	88
5	2.5:1	20	70	-15	96
6	2:1	20	70	-10	96
7	2:1	20	50	-10	96
8	2:1	20	30	-10	95
9	2:1	20	20	-10	95
10	2:1	20	10	-10	57

[a] GC yield.

E*ntry 1* (*table 4.1*) shows the results obtained by performing the reaction between 4-methoxyphenylmagnesium bromide and phenylmagnesium bromide, using the procedure described by Cahiez *et al.* When the reaction was performed using 20% of the catalyst the yield of the desired product dropped to 40% producing more biphenyl as side product.

Increasing the time for mixing the reactants resulted in an improvement of the yield (*entry 3 to 10*). In fact, using the same amount of catalyst and reagents as in *entry 1*, and stirring the reaction mixture for 10 minutes (*entry 2*), the yield raised to 86%. Further increasing the stirring time to 20 minutes resulted in a yield of 88% (*entry 4*). Diminishing the temperature gave an improvement of the yield. The original protocol for this reaction suggests a temperature of -5 ˚C (*entry 1*). The same reaction was performed at -15 ˚C (*entry 5*) and -10 ˚C (*entry 6*) with a yield of 96%. It was therefore decided to perform the rest of the reactions at -10 ˚C.

The amount of catalyst necessary to obtain the best yield was determined. Starting from the amount described in the protocol (*entry 6*), the quantity was lowered to 50% (entry 7), 30% (entry 8) and finally 20% (entry 9). The results obtained from these experiments were similar, in fact they all yielded about 95% of the desired cross-coupling product. Lowering the catalyst loading to 10% made the reaction yield drop to 57% (*entry 10*). Another improvement that was applied during the described experiment (*entry 6-10*) was to modify the ratio between the two Grignard reagents, from 2.5:1 to 2:1.

When the components are mixed together, before adding dioxygen, the color of the mixture is generally yellow. After stirring the color slowly turns green. This behavior is probably due to the formation of the active complex. In fact, it is possible that the active manganese specie that catalyzes the homo-coupling is formed faster than the active complex that leads to the cross-coupling. Stirring the reaction mixture for a longer time may therefore give sufficient time for an active complex that catalyzes the formation of the cross-coupling product to form. When dioxygen starts to flow, the reaction mixture turns almost immediately black. This time the color change is probably due to the formation of the oxo-complex that will lead to the desired reaction, and to the formation of some higher valent and inactive manganese species. This could explain why a 20% load of manganese catalyst is needed, which could not be further optimized.

A pure statistical mixture of products would result in only 67% of the desired cross-coupling product. By monitoring the reaction (*figure 4.2*) it

is possible to observe that 4-methoxyphenylmagnesium bromide undergoes very little homo-coupling product, while biphenyl and 4-methoxybyphenyl are produced with approximately the same rate. Using the Grignard reagent which is less prone to homo-couple as the limiting reagent it is possible to obtain the cross-coupling product in high yield.

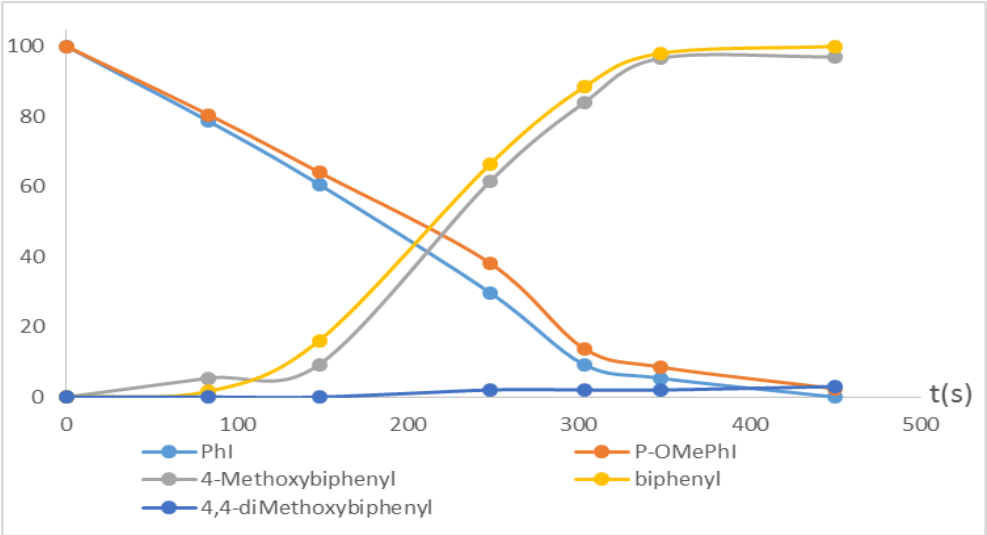
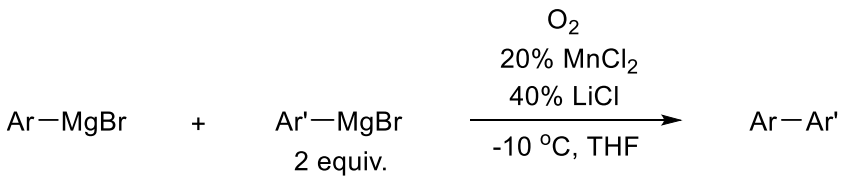


Figure 4.2: Mn-catalyzed oxidative cross-coupling reaction time study

However, when the stirring time is below 20 minutes, a lower amount of the desired cross-coupling product is obtained.

4.2.3 Substrate screening

Using the optimized conditions, it was possible to expand this method even more (*scheme 4.4 and table 4.2*).

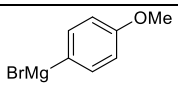
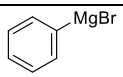
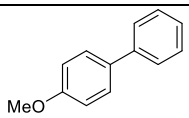
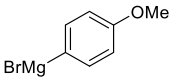
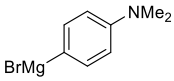
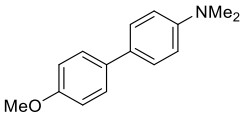
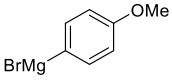
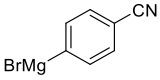
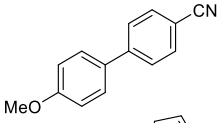
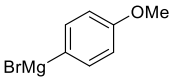
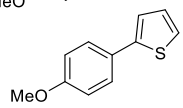
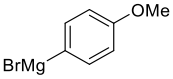
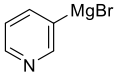
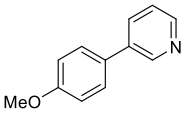
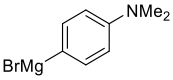
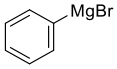
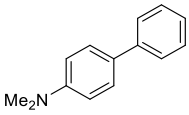
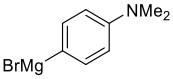
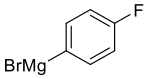
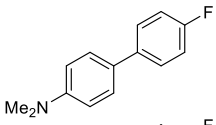
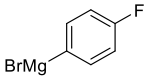
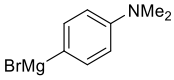
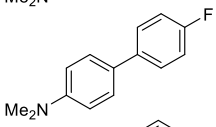
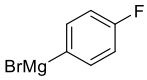
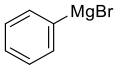
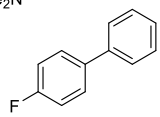
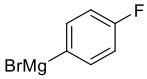
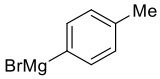
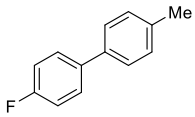
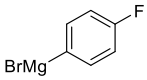
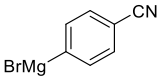
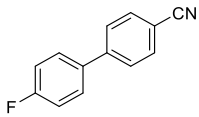


Scheme 4.4: Mn-catalyzed oxidative cross-coupling reaction

When 4-methoxyphenylmagnesium bromide was reacted with 4-dimethylaminophenyl- and 4-cyanophenylmagnesium bromide (*entries 2-3*) a yield of 91% and 89%, respectively, was obtained. The coupling with 2-thienyl- and 3-pyridylmagnesium bromide, on the other hand, gave lower yields (*entries 4 – 5*), due to the very fast homo-coupling of these two heterocyclic Grignard reagents. Since also 4-dimethylaminophenylmagnesium bromide does not tend to homocouple, it was also reacted phenylmagnesium bromide (*entry 6*) and 4-fluorophenylmagnesium bromide (*entry 7*). In both cases the yield is almost quantitative (99% and 98%). If 4-fluorophenylmagnesium bromide, used as the limiting reagent, is reacted with 4-dimethylaminophenylmagnesium bromide the efficacy of the reaction drops, leading to a yield of 90% (*entry 8*) and 98% when the ratio is inverted. Since 4-fluorophenylmagnesium bromide has also a slow tendency to homocouple it was tested with 4-phenyl-, 4-tolyl-, 4-cyano- and 4-chlorophenylmagnesium bromide. The reactions produced similar results, yielding all between 80 and 85% (*entries 9 – 12*). 4-Chlorophenylmagnesium bromide has the same tendency to react slower in the homo-coupling (*entry 13*). In fact, when tested against phenylmagnesium bromide it produced 4-chlorobiphenyl in 81% yield (*entry 14*). 4-Chlorophenylmagnesium bromide was also reacted with 4-methoxyphenylmagnesium bromide yielding 87% (entry 15).

4-Fluorophenylmagnesium bromide was tested with 2-thienyl-, 3-pyridyl, 2-furanylmagnesium bromide. A low yield was obtained in the first two cases (*entry 16-17*), while for the third it was slightly better (*entry 18*).

Table 4.2: Aerobic cross-coupling of different Grignard reagents.

Entry	***Ar–MgBr***	***Ar'–MgBr***	***Ar–Ar'***	***Yield [%][a]***
1				91
2				91
3				89
4				65
5				56
6				99
7				98[b]
8				90
9				83[c]
10				82[c]
11				81

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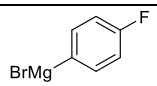
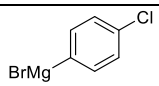
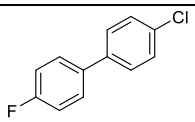
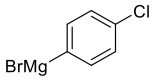
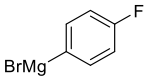
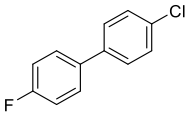
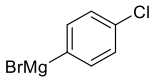
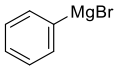
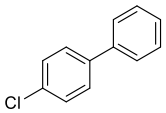
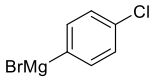
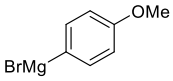
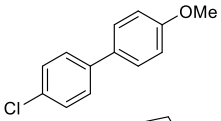
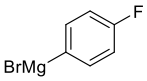
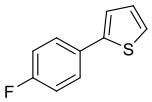
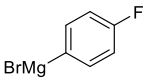
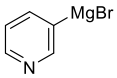
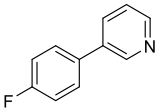
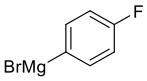
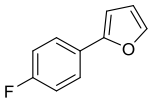
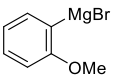
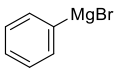
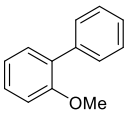
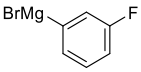
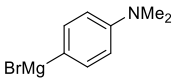
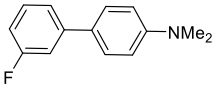
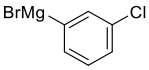
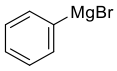
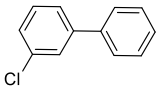
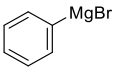
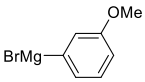
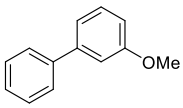
2				84[c]
13				79[c]
14				81
15				87
16				51
17				50
18				70[c]
19				70
20				85
21				64
22				76

[a] Isolated yield. [b] GC yield. [c] Yield based on NMR since isolated product not completely pure.

Other experiments where performed with ortho and meta substituents (*entry 19-22*). 2-Methoxyphenylmagnesium bromide produced 70% of 2-methoxy-1,1'-biphenyl when reacted with phenylmagnesium bromide (*entry 19*). The difference in yield with the para substituted counterpart can be attributed to the hindrance that the methoxyl group in *ortho* position creates. The reaction between 3-fluorophenylmagnesium bromide and (4-(dimethylamino)phenyl)magnesium bromide yielded 85% (*entry 20*), a result that is comparable with 4-fluorophenylmagnesium bromide (90% yield). 3-Chlorophenylmagnesium produced 64% of 3-chloro-1,1'-biphenyl, when reacted with phenyl magnesium bromide (*entry 21*). The yield is lower than the one observed when 4-chlorophenylmagnesium bromide was reacted with phenylmagnesium bromide. Probably the absence of conjugation in 3-chlorophenylmagnesium bromide has a negative effect on the active complex rate formation. 3-Methoxyphenylmagnesium bromide gave 76% of 3-methoxy-1,1'-biphenyl when reacted with phenylmagnesium bromide (*entry 22*).

4.3 Conclusions

An improved protocol for the $MnCl_2$-catalyzed aerobic cross-coupling of arylmagnesium halides was developed. A previously reported procedure was implemented, and the substrate scope and limitation was expanded.

It was discovered that is was important to allow the two Grignard reagents to react with $MnCl_2$ before the addition of dioxygen since the subsequent oxidative coupling is a very fast reaction. Under these conditions high yields could be obtained in a number of cases with a 2:1 ratio between the Grignard reagents and 20% of $MnCl_2$. The most successful cross-coupling experiments were achieved when the limiting aryl magnesium halide showed only little inclination to undergo a competing self-coupling. Very little homo-coupling was observed with 4-methoxy- and 4-dimethylaminophenylmagnesium bromide, while relatively little homo-coupling occurred with 4-fluoro- and 4-chlorophenylmagnesium bromide. The successful coupling of Grignard reagents with electron-withdrawing substituents constitutes a new development for this transformation. Heterocyclic Grignard reagents, on the other hand, were not good coupling partners since the self-coupling with these reagents is a fast reaction.

Experimental section

General methods

Gas chromatography was performed on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30 m × 0.25 mm × 0.25 µm column. HRMS measurements were made using ESI with TOF detection. Decane was used as the internal standard and GC yields were determined with the following equation i).

i) $y(\%) = \left(\frac{A_p}{A_0} \cdot \frac{m_0}{MW_0} \cdot \frac{MW_s}{m_s} \cdot k \cdot 100\right)$

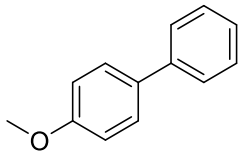
Where A_p = product peak's area, A_0 = standard peak's area, m_0 = mass (mg) of the internal standard in the reaction mixture, MW_0 = molecular weight of the internal standard, m_s = mass (mg) of the initial substrate, MW_s = molecular weight of the initial substrate, k = value extrapolated by the product's calibration curve. All chemicals were purchased from Sigma-Aldrich and ABCR and used without further purifications. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck 25, 20 × 20 cm, 60 F_{254}). The plates were visualized under UV-light.

Flash column chromatography was performed on silica gel 60 (40 – 63 µm) with specified solvents given as volume ratio. NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_c = 77.16 ppm). Multiplicity are reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, ddt = double double triplet, s = sextet, m = multiplet, br. s = broad singlet, while coupling constants are shown in Hz.

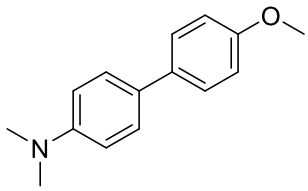
Grignard reagents: The heterocyclic Grignard reagents and 4-cyanophenylmagnesium bromide were prepared from the corresponding bromides and magnesium in THF while the remaining reagents were purchased from commercial suppliers. All Grignard reagents were titrated with a 0.06 M solution of I_2 in Et_2O to determine the concentration: phenylmagnesium bromide (1.5 M in 2-methyltetrahydrofuran), 4-methoxyphenylmagnesium bromide (0.6 M in THF), 4-dimethylaminophenylmagnesium bromide (0.3 M in THF), 4-cyanophenylmagnesium bromide (0.5 M in THF), 2-thienylmagnesium bromide (1.2 M in THF), 3-pyridylmagnesium bromide (0.5 M in THF), 4-fluorophenylmagnesium bromide (0.5 M in THF), 4-tolylmagnesium bromide (0.3 M in Et_2O), 4-chlorophenylmagnesium bromide (0.5 M in Et_2O), 2-furylmagnesium bromide (0.2 M in THF), 2-methoxyphenylmagnesium bromide (0.6 M in THF), 3-fluorophenylmagnesium bromide (0.6 M in THF), 3-chlorophenylmagnesium bromide (0.3 M in THF), and 3-methoxyphenylmagnesium bromide (0.6 M in THF),

General procedure for aerobic heterocoupling of two Grignard reagents: A dry three-neck round-bottom flask was equipped with a stir bar, a thermometer and a nitrogen inlet. The flask was flushed with nitrogen and charged with $MnCl_2$ (51 mg, 0.405 mmol), LiCl (37 mg, 0.873 mmol) and dry THF (3 mL). The mixture was stirred for about 10 min to completely dissolve $MnCl_2$ and LiCl followed by cooling to -10 °C. A solution of the Grignard reagent in excess (4 mmol) was added dropwise over 4 min and the mixture was then stirred for an additional 2 min before dropwise addition of the limiting Grignard reagent (2 mmol) over 4 min. The mixture was stirred for 20 – 30 min after which time the nitrogen flow was stopped and a balloon of dioxygen was connected through a septum with a needle. A continuous flow of dioxygen was allowed into the reaction flask for 10 min which caused the temperature to rise to +10 – +20 °C and the color to change to black. Decane (0.4 mL, 2 mmol) was then injected as an internal standard for determining the yield by GC and the reaction was quenched with saturated ammonium chloride solution (10 mL). The

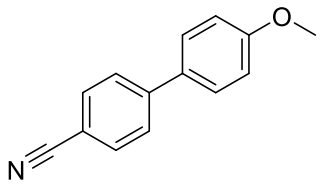
mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were concentrated and the residue purified by flash column chromatography.



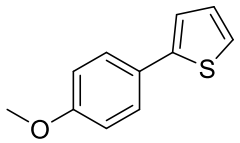
4-Methoxy-1,1'-biphenyl: Purified by flash chromatography (heptane/EtOAc, 99:1) to afford a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2 H), 7.31 (t, J = 7.8 Hz, 1 H), 7.42 (dd, J = 8.5, 6.9 Hz, 2 H), 7.55 (t, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 114.0, 126.5, 128.0, 128.5, 133.6, 140.7, 159.0 ppm. MS: m/z = 184.10 [M^+]. The observed chemical shifts are in accordance with the literature values.[115]



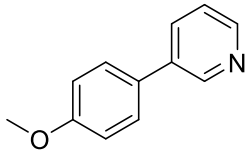
4'-Methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-4-amine: Purified by flash chromatography (heptane/EtOAc, 10:1) to afford a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99 (s, 6 H), 3.85 (s, 3 H), 6.83 (d, J = 8.3 Hz, 2 H), 6.96 (d, J = 8.3 Hz, 2 H), 7.48 (t, J = 9.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.7, 55.2, 113.0, 113.9, 127.2, 127.2, 133.7, 149.1, 158.1 ppm. MS: m/z = 227.00 [M^+]. The observed chemical shifts are in accordance with the literature values.[121]



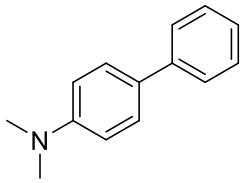
4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile: Purified by flash chromatography (heptane/EtOAc, 98:2) to yield a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.54 (d, J = 8.8 Hz, 2 H), 7.74–7.61 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 110.5, 115.0, 119.5, 127.5, 128.8, 131.9, 133.0, 145.6, 160.6 ppm. MS: m/z = 209.00 [M^+]. The observed chemical shifts are in accordance with the literature values.[122]



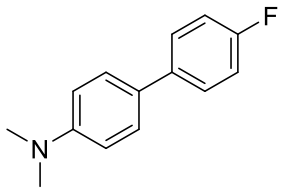
2-(4-Methoxyphenyl)thiophene: Purified by flash chromatography (pentane) to give a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.06 (dd, J = 5.1, 3.6 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.54 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 114.7, 122.5, 124.3, 127.7, 128.4, 144.8, 159.6 ppm. MS: m/z = 189.95 [M^+]. The observed chemical shifts are in accordance with the literature values.[115]



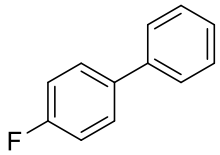
3-(4-Methoxyphenyl)pyridine: Purified by flash chromatography (heptane/EtOAc, 3:1) to afford a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.02 (d, J = 8.8 Hz, 2 H), 7.37 (dd, J = 8.0, 4.8 Hz, 1 H), 7.52 (d, J = 8.8 Hz, 2 H), 7.73–7.97 (m, 1 H), 8.54 (dd, J = 5.0, 1.5 Hz, 1 H), 8.82 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 115.1, 124.2, 128.7, 130.4, 134.8, 137.0, 147.8, 160.3 ppm. MS: m/z = 185.00 [M^+]. The observed chemical shifts are in accordance with the literature values.[123]



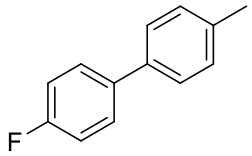
***N*,*N*-Dimethyl-[1,1'-biphenyl]-4-amine:**. Purified by flash chromatography (heptane/EtOAc, 10:1) to furnish a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (s, 6 H), 6.87 (d, J = 8.3 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 113.3, 126.4, 126.7, 128.2, 129.1, 129.8, 141.6, 150.3 ppm. MS: m/z = 197.15 [M^+]. The observed chemical shifts are in accordance with the literature values.[121]



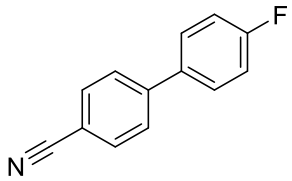
4'-Fluoro-*N*,*N*-dimethyl-[1,1'-biphenyl]-4-amine: Purified by flash chromatography (heptane/EtOAc, 3:1) to yield a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01 (s, 6 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.09 (t, J = 8.7 Hz, 2 H), 7.55–7.42 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.2, 113.5, 115.9 (d, J = 21 Hz), 128.2 (d, J = 7 Hz), 128.2, 137.8 (d, J = 3 Hz), 150.2, 160.8, 162.1 (d, J = 244 Hz) ppm. HRMS: calcd. for $C_{14}H_{15}FN$ $[M + H]^+$ 216.1188, found 216.1183.



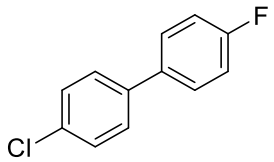
4-Fluoro-1,1'-biphenyl: Purified by flash chromatography (pentane) to furnish a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (td, J = 8.7, 4.1 Hz, 2 H), 7.42 (td, J = 7.1, 1.7 Hz, 1 H), 7.57–7.47 (m, 2 H), 7.61 (td, J = 5.8, 1.8 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =115.4 (d, J = 21 Hz), 127.6 (d, J = 7 Hz), 127.6, 129.2, 129.3, 137.7, 140.7, 161.6 (d, J = 245 Hz) ppm. MS: m/z = 172.10 $[M^+]$. The observed chemical shifts are in accordance with the literature values.[124]



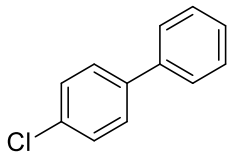
4-Fluoro-4'-methyl-1,1'-biphenyl: Purified by flash chromatography (pentane) to give a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 6.94 (td, J = 8.7, 2.9 Hz, 2 H), 7.07 (dd, J = 8.2, 1.9 Hz, 2 H), 7.21–7.43 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 116.0 (d, J = 21 Hz), 127.3, 128.9 (d, J = 9.0 Hz), 130.0, 137.5, 137.7 (d, J = 2.0 Hz), 137.8, 162.7 (d, J = 244 Hz) ppm. MS: m/z = 185.95 [M$^+$]. The observed chemical shifts are in accordance with the literature values.[125]



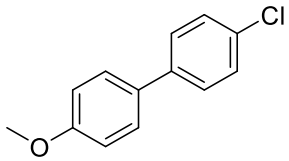
4'-Fluoro-[1,1'-biphenyl]-4-carbonitrile: Purified by flash chromatography (heptane/EtOAc, 98:2) to give a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 8.6 Hz, 2 H), 7.56 (dd, J = 8.8, 5.2 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.1, 116.3 (d, J = 21 Hz), 119.0, 127.7, 129.1 (d, J = 8 Hz), 132.8, 135.4, 144.8, 163.4 (d, J = 247 Hz) ppm. MS: m/z = 196.95 [M$^+$]. The observed chemical shifts are in accordance with the literature values.[125]



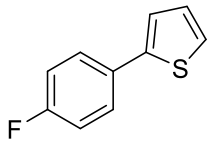
4-Chloro-4'-fluoro-1,1'-biphenyl: Purified by flash chromatography (pentane) to afford a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (td, J = 8.8, 2.7 Hz, 2 H), 7.35–7.53 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.2 (d, J = 22 Hz), 128.7, 129.0 (d, J = 8 Hz), 129.4, 133.9, 136.6 (d, J = 4 Hz), 139.1, 163.1 (d, J = 245 Hz) ppm. MS: m/z = 206.10 [M^+]. The observed chemical shifts are in accordance with the literature values.[124]



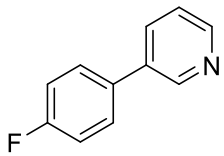
4-Chloro-1,1'-biphenyl: Purified by flash chromatography (pentane) to give a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.48 (m, 4 H), 7.48–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.5, 128.5, 128.9, 129.3, 133.8, 140.1, 140.5 ppm. MS: m/z = 188.05 [M^+]. The observed chemical shifts are in accordance with the literature values.[126]



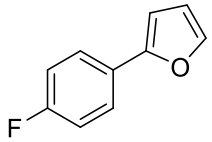
4-Chloro-4'-methoxy-1,1'-biphenyl: Purified by flash chromatography (heptane/EtOAc, 98:2) to afford a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.44–7.55 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 114.8, 128.4, 128.5, 129.3, 132.9, 133.1, 139.7, 159.8 ppm. MS: m/z = 218.05 [M^+]. The observed chemical shifts are in accordance with the literature values.[126]



2-(4-Fluorophenyl)thiophene: Purified by flash chromatography (pentane) to yield a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–7.17 (m, 2 H), 7.24–7.31 (m, 2 H), 7.47–7.54 (m, 2 H), 7.59 (dd, J = 8.8, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.5 (d, J = 21 Hz), 122.9, 124.6, 127.9, 128.4 (d, J = 9.0 Hz), 136.2, 143.1, 162.2 (d, J = 258 Hz) ppm. MS: m/z = 165.95 [M^+]. The observed chemical shifts are in accordance with the literature values.[126]

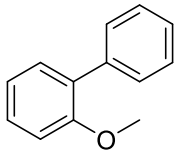


3-(4-Fluorophenyl)pyridine: Purified by flash chromatography (heptane/EtOAc, 4:1) to yield a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, J = 8.7 Hz, 2 H), 7.34 (ddd, J = 7.9, 4.8, 0.8 Hz, 1 H), 7.51 (dd, J = 8.9, 5.2 Hz, 2 H), 7.81 (ddd, J = 7.9, 2.4, 1.6 Hz, 1 H), 8.56 (dd, J = 4.8, 1.6 Hz, 1 H), 8.78 (dd, J = 2.4, 0.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.2 (d, J = 21 Hz), 123.7, 128.9 (d, J = 8 Hz), 134.0 (d, J = 3 Hz), 134.4, 135.8, 148.1, 148.5, 163.0 (d, J = 248 Hz) ppm. MS: m/z = 173.0 [M^+]. The observed chemical shifts are in accordance with the literature values.[123]

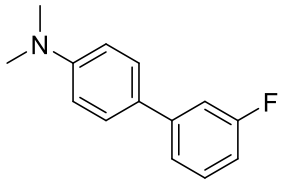


2-(4-Fluorophenyl)furan: Purified by flash chromatography (pentane) to furnish a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41–6.69 (m, 1 H), 6.96–7.21 (m, 2 H), 7.49 (dd, J = 8.8, 5.2 Hz, 2 H), 7.64 (dd, J = 8.9, 5.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.8, 111.8, 115.8 (d, J = 22 Hz), 128.7 (d, J = 8 Hz), 136.6, 142.2, 153.3, 162.6 (d, J = 245 Hz) ppm.

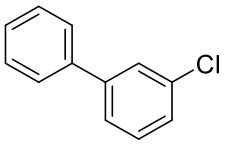
MS: m/z = 162.05 [M$^+$]. The observed chemical shifts are in accordance with the literature values.[125]



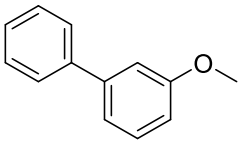
2-Methoxy-1,1'-biphenyl: Purified by flash chromatography (heptane/EtOAc, 99:1) to yield a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 7.14 (dd, J = 8.8, 3.4 Hz, 1 H), 7.21 (ddt, J = 10.3, 5.9, 2.0 Hz, 1 H), 7.51 (tdd, J = 9.6, 4.8, 2.0 Hz, 3 H), 7.57–7.62 (m, 2 H), 7.70–7.77 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 111.0, 120.6, 126.6, 127.7, 128.4, 129.3, 130.5, 130.6, 138.3, 156.2 ppm. MS: m/z = 184.10 [M$^+$]. The observed chemical shifts are in accordance with the literature values.[127]



3'-Fluoro-*N*,*N*-dimethyl-[1,1'-biphenyl]-4-amine: Purified by flash chromatography (heptane/EtOAc, 20:1) to afford a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 6 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.57 (d, J = 10.2 Hz, 1 H), 7.66 (s, 2 H), 7.73–7.93 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.4, 112.6 (d, J = 21 Hz), 112.6 (d, J = 21 Hz), 121.6 (d, J = 2 Hz), 127.5, 127.7, 129.0, 129.8 (d, J = 9 Hz), 143.3 (d, J = 8 Hz), 163.1 (d, J = 244.8 Hz) ppm. HRMS: calcd. for $C_{14}H_{15}FN$ [M + H]$^+$ 216.1188, found 216.1183.



3-Chloro-1,1'-biphenyl: Purified by flash chromatography (heptane/EtOAc, 99:1) to give a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.45 (m, 3 H), 7.46–7.53 (m, 3 H), 7.56–7.69 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.1, 126.9, 127.1, 127.7, 128.7, 129.8, 134.4, 139.6, 142.9 ppm. MS: m/z = 188.05 [M^+]. The observed chemical shifts are in accordance with the literature values.[128] 20



3-Methoxy-1,1'-biphenyl: Purified by flash chromatography (heptane/EtOAc, 99:1) to afford a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 7.08 (dd, J = 8.2, 1.1 Hz, 1 H), 7.31–7.43 (m, 2 H), 7.52 (tt, J = 6.5, 1.2 Hz, 2 H), 7.57–7.67 (m, 2 H), 7.74–7.84 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 113.0, 113.3, 120.0, 127.5, 127.8, 129.1, 130.1, 141.4, 143.1, 160.3 ppm. MS: m/z = 184.09 [M^+]. The observed chemical shifts are in accordance with the literature values.[124]

Publications

- Hajar Golshadi Ghaleshahi, Giuseppe Antonacci, and Robert Madsen. Manganese-Catalyzed Aerobic Heterocoupling of Aryl Grignard Reagents. *European Journal of Organic Chemistry*, **2017**, 1331-1336.

- Giuseppe Antonacci, Andreas Ahlburg, Peter Fristrup, Per-Ola Norrby, and Robert Madsen. Manganese-Catalyzed Cross Coupling of Aryl Halides and Grignard Reagents by a Radical Mechanism. *European Journal of Organic Chemistry*, **2017**, 4758-4764.

- Carola Santilli, Somayyeh Sarvi Beigbaghlou, Andreas Ahlburg, Giuseppe Antonacci, Peter Fristrup, Per-Ola Norrby, and Robert Madsen. The Manganese-Catalyzed Cross-Coupling Reaction and the Influence of Trace Metals. *European Journal of Organic Chemistry*, **2017**, 5269-5274.

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