Towards nickel boride catalyzed C-C coupling reactions

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Abstract
This thesis focuses on the study of nickel boride as a catalyst in various coupling reactions. The nickel boride catalyst was investigated in three different coupling reactions, the experiments aimed at understanding the activity and catalytic properties of nickel boride.

We successfully synthesized the nickel boride catalyst, alongside with the cobalt and iron boride. Different methods of preparation were compared and we concluded, that the differences in the preparation, such as solvent and atmosphere, influence the activity of the catalyst in coupling reactions. We found that the most suitable solvent for preparing nickel boride is anhydrous methanol, thus we proceeded our research with this catalyst.
In the case of the Sonogashira cross-coupling we found that the homocoupling of the acetylene starting material is a side reaction we could not exclude. However, with the proper solvent it is possible to shift the reaction towards homocoupling, without the formation of the heterocoupling product. Thus, we decided to investigate the Glaser homocoupling between acetylenes. In the case of the Sonogashira coupling only TLC was used to examine the reaction mixture. However, in the case of Glaser coupling, after pre-investigations we developed a gas chromatography method for analyzing the reaction mixtures. We learned, that the homocoupling only results in trace amounts (2-4%) of product. Previous investigations in our research group showed, that the nickel boride could catalyze Suzuki-Miyaura-type couplings. Examining this reaction all three metal borides were tested; however the reactions only led to the desired product with nickel boride. Analyzing the reaction with gas chromatography we learned that the choice of solvent influences the stability of the starting materials and the formation of side products. Reactions with different starting materials, in different solvents, with different bases were analyzed. The effect of microwave irradiation was also examined. Based on the results we concluded, that with nickel boride it is not possible to achieve high yields in coupling reactions.

Keywords
nickel catalysis, coupling reactions, cross-coupling, homocoupling
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name</th>
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<td>Ni(CO)₄</td>
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</tr>
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</tr>
<tr>
<td>Ni(PPh₃)₄</td>
<td>Tetrakis(triphenylphosphate)palladium(0)</td>
</tr>
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<td>Nickel chloride</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>Sodium borohydride</td>
</tr>
<tr>
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<td>X-ray diffraction</td>
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<tr>
<td>XPS</td>
<td>X-ray photoelectron spectroscopy</td>
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<tr>
<td>HRTEM</td>
<td>High-resolution transmission electron microscopy</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission electron microscopy</td>
</tr>
<tr>
<td>DDT</td>
<td>1,1'-(2,2,2-Trichloroethane-1,1-diyl)bis(4-chlorobenzene)</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>Methanol</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>CuI</td>
<td>Copper(I) iodide</td>
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<td>Sodium tetrachloroplatinate</td>
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<td>Poly(styrene)</td>
</tr>
<tr>
<td>PEG</td>
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<tr>
<td>DMF</td>
<td>Dimethyl formamide</td>
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<tr>
<td>CoBr₂</td>
<td>Cobalt(II) bromide</td>
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<tr>
<td>[bmim]OH</td>
<td>1-Butyl-3-methylimidazolium hydroxide</td>
</tr>
<tr>
<td>OTf</td>
<td>Triflate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>CsF</td>
<td>Ceasium fluoride</td>
</tr>
<tr>
<td>PPh₃</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>Potassium carbonate</td>
</tr>
<tr>
<td>TLC</td>
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</tr>
<tr>
<td>NMR</td>
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</tr>
<tr>
<td>DMAc</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>DEE</td>
<td>Diethyl ether</td>
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<tr>
<td>KOᵗBu</td>
<td>Potassium tert-butoxide</td>
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<tr>
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</tr>
<tr>
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<td>Tripotassium phosphate</td>
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<td>Gas chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>FeCl₃</td>
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1 Introduction

Over the years, societies have become aware of the damaging effects of some chemical practices and the need to protect the environment. In the past, few were aware of the negative effects our lifestyle might have on the environment, and rather saw only the positive potential for creating new, useful materials and products. The term chemical pollution contains the damages caused by the agriculture (such as pesticides and fertilizers) and household chemicals; however, the major part of chemical pollution is caused by the industries and factories in the form of hazardous waste, metals and solvents. As the 12 principles of Green Chemistry state, it is better to prevent waste than to treat or clean up waste after it has been created. Therefore, wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment. In addition, starting materials from renewable sources are preferred. Green chemistry searches for alternative, environmentally friendly reaction media. Alcohols and esters are considered as recommended solvents; however, in the case of the widely applied dipolar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide substitution is requested. The pollution and waste produced by the environmentally harmful chemicals that were used in stoichiometric amount has become a serious issue; therefore, catalytic reagents became superior to stoichiometric reagents. Green chemistry also aims to increase reaction rates and lower reaction temperatures. Catalytic reactions allow milder reaction conditions, such as lower temperature and pressure, resulting in a better selectivity.

1.1 Catalysis

The term "catalyst" was first introduced in 1835 by Berzelius who stated in his yearly report that "it is then shown that several simple and compound bodies, soluble and insoluble, have the property of exercising on other bodies and action very different from chemical affinity. The body effecting the changes does not take part in the reaction and remains unaltered through the reaction. [...] I will therefore call it
the "Catalytic Force" and I will call "Catalysis" the decomposition of bodies by this force." [1] In 1894, Ostwald gave the first modern definition: "Catalysis is the acceleration of a chemical reaction, which proceeds slowly, by the presence of a foreign substance" [2]. For his work on catalysis, Ostwald was awarded the 1909 Nobel Prize in Chemistry. Later studies proved that catalysts lower the activation barrier and thereby increase the rate of the reaction without themselves undergoing any permanent chemical change. In the 20th century, a wide range of applications were discovered, such as the hydrogenation of ethylene over nickel and cobalt catalysts by Sabatier [3], and the synthesis of ammonia from the elements by Haber [4].

1.1.1 Classification

Catalysts are often divided into groups called homogenous catalysts and heterogeneous catalysts. A homogenous catalyst (e.g. metal salts of organic acids, organometallic complexes, and carbonyls of cobalt, iron, and rhodium) resides in the same phase as the reactants. Heterogeneous catalysts are often inorganic solids such as metals, oxides, sulfides, and metal salts, but they may also be organic materials such as ion exchangers and enzymes and reside in different phase from the reagents, often being insoluble solids [5]. Each class has its own advantages and disadvantages; however, the use of heterogeneous catalyst are more common due to their low cost, ease of separation from products, high stability, and an ability to be recycled. A specific advantage of the heterogeneous catalyst is that it can be used in a continuous process operation, instead of in a batch-type process where it must be separated in an individual step from the reaction product. At the same time, heterogeneous catalyst can only react with reagents at the interface of the two phases, which result in slower rates because of the low effective concentration. Throughout the years, heterogeneous catalysis is used in more than 80% of current bulk chemical processes in the chemical and petrochemical industries [6].
1.1.2 Heterogeneous catalysts

The most important group of catalysts consists of the solid catalysts and these materials are used in important industrial large-scale processes, such as conversion of chemicals, fuels and pollutants [7]. The group of solid catalysts can be divided into several families such as: unsupported (bulk) catalysts (metal oxides, simple binary oxides, complex multicomponent oxides, metals and metal alloys, ion-exchange resins, metal salts); supported catalysts (support: silica, carbon, silicon carbide); confined catalysts (ship-in-a-bottle catalyst: metal complexes in zeolite cages), hybrid catalysts, polymerization catalysts, and several others [8].

1.1.3 Transition metal catalysts

Historically, non-catalytic routes were used for syntheses of fine chemicals; however, because of environmental and economic considerations such as low price, high quality and availability of materials the use of catalytic routes are preferred. With transition metals (Pd, Pt, Rh, Fe, Co, Ru, Ni) a great variety of chemical reactions can be carried out, for example: hydrogenation, isomerization, dehydrogenation, asymmetric synthesis, oxidation, C-C coupling [9]. Considering the chemo-, regio- and stereoselective properties of these catalysts, transition metals make it possible to synthetize asymmetric molecules selectively.

1.1.4 Nickel as catalyst

The first report of organonickel chemistry dates back to 1890, when Mond et al. first isolated nickel tetracarbonyl [10]. Nickel got more attention in 1940 with the discovery of the Reppe catalysts and from the 1960s the number of publications in this field seems to rise [11]. Compared to other transition metals, the advantage of using nickel as a catalyst is its low cost; moreover, the difference between the prices in the past 10 years got more significant (Table 1). However, certain disadvantages of nickel and its derivatives are associated with toxicity, human carcinogenesis, and skin allergies [12].
Table 1: Price comparison of Ni, Pd and Pt and their dichlorides (Aldrich Catalog) [12]

<table>
<thead>
<tr>
<th></th>
<th>Ni  (99.99)(^a)</th>
<th>Pd (99.95)(^ab)</th>
<th>Pt (99.99)(^ab)</th>
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<tr>
<td>2004</td>
<td>5.4</td>
<td>62.9</td>
<td>83.1</td>
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<tr>
<td>(EUR/g(^{-1}))</td>
<td>[11.5]</td>
<td>[15.4]</td>
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<tr>
<td>2017</td>
<td>1.43</td>
<td>81.9</td>
<td>142.1</td>
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<tr>
<td>(EUR/g(^{-1}))</td>
<td>[57.3]</td>
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<td>[99.4]</td>
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<table>
<thead>
<tr>
<th></th>
<th>NiCl(_2) (99.99)</th>
<th>PdCl(_2) (99.999)</th>
<th>PtCl(_2) (99.9)</th>
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<td>26</td>
<td>120.0</td>
<td>250.8</td>
</tr>
<tr>
<td>(EUR/g(^{-1}))</td>
<td>[4.6]</td>
<td>[9.6]</td>
<td></td>
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<tr>
<td>2017</td>
<td>35.4</td>
<td>125.0</td>
<td>311.0</td>
</tr>
<tr>
<td>(EUR/g(^{-1}))</td>
<td>[3.5]</td>
<td></td>
<td>[8.8]</td>
</tr>
</tbody>
</table>

\(^a\) Figures in parenthesis refer to the purity in %.

\(^b\) Figures in square brackets refer to price rates relative to nickel compounds.

It has been well documented, that organonickel complexes are suitable for organic transformations in catalytic as well as stoichiometric systems, especially for carbon-carbon formation [11], [13]. Nickel can possess two stable oxidation states, the +2 and the zerovalent state, both states are suitable to develop active organonickel complexes.

Nickel(0) complexes [Ni(CO)\(_4\) (1), Ni(cod)\(_2\) (2), Ni(PPh\(_3\))\(_4\) (3), Ni(bipy)Et\(_2\) (4), Ni(dppe)Et\(_2\), (5)] (Figure 1) have been utilized as stoichiometric reagents for homocoupling of organic halides (Figure 2) [14] and they promote the intramolecular coupling of organic halides with enolates and enones [15]. Other application is the catalytic co-oligomerization of unsaturated hydrocarbons [11].
Dialkynickel(II) complexes have the formula of NiR₂L₂, for example NiCl₂(dppp) (6) and NiCl₂(PPh₃)₂ (7) (Figure 3), and can be used for catalytic cross-coupling reactions [16]. Using chiral phosphine ligands (8) gives the possibility of asymmetric synthesis (Figure 4) [17].
Figure 4: Dialkylnickel(II) complexes and their reactions

(π-allyl)nickel(II) complexes are derived from allyl halides and have been utilized a stoichiometric reagents for allylation of organic halides [18] and ketons [19]. Nickelacycle complexes can be used for cyclization of unsaturated organic molecules [20].

1.1.5 Nickel boride

In 1945, Schlesinger observed that although the alkali borohydrides reduced a certain number of salts to the metallic state (silver, mercury, bismuth salts, etc.), but they only gave the corresponding borides with nickel or cobalt salts [21]. Schlesinger and co-workers compared the prepared black precipitate with Raney nickel and found that the new catalyst is neither ferromagnetic nor pyrophoric and decomposes slower in hydrochloric acid. With analytical investigations, they determined the formula of the catalyst: the boron to nickel ratio is virtually constant and always corresponds to the presence of one boron atom for two nickel atoms. Therefore, the authors concluded that the catalyst is nickel boride (Ni$_2$B). In 1952, Paul et al. examined the reactivity of nickel boride in different hydrogenation reactions with safrole, furfural and benzonitrile [22]. They found that the nickel boride catalyst has the activity at least equal to and often superior to that of Raney nickel. Given the low cost, abundance, corrosion resistance, high efficiency and ease of fabrication, nickel boride
is one of the best alternatives to noble metal hydrogen evolution catalysts. The industrial synthesis of borides usually involves reduction of metal oxides using a mixture of boron carbide and carbon; electrolysis; or direct reaction of the elements.

$$4 \text{NaBH}_4 + 2 \text{NiCl}_2 + 9 \text{H}_2\text{O} \rightarrow \text{Ni}_2\text{B} + 3 \text{H}_3\text{BO}_3 + 4 \text{NaCl} + 12.5 \text{H}_2\text{O}$$

Schlesinger discovered that the catalyst can be generated easily by using nickel(II) salts (mainly NiCl$_2$) with aqueous sodium borohydride [23].

1.1.5.1 Structure

Investigations using different solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, diglyme, alcoholic or ether solvents showed that small variations in the method of preparations can significantly affect the activity, selectivity, physical and chemical properties of nickel boride. The unusual structure of the nickel boride catalyst gained more attention which resulted in detailed studies. Maybury, Mitchell, and Hawthorne analyzed nickel boride prepared in ethanol under nitrogen atmosphere using excess NaBH$_4$, and concluded that Ni$_2$B inadequately represents its composition [24]. Glavee et al. compared the product of the reaction using inert atmosphere (diglyme) and open air (water). With XRD and X-ray power diffraction analysis they concluded that the resulting product in the case of water solvent is noncrystalline Ni$_2$B with small quantities of metallic Ni and Ni$_3$B while in the case of the dyglime the product is a mixture of the above listed three components [25]. Legrand et al. synthetized the catalyst with the help of reverse micelles. After the formation of nickel metal nanoparticles with the addition of sodium borohydride nickel boride nanoparticles were obtained. As XPS is nondestructive, it allowed the investigation of the nanoparticles. From the XPS, they concluded that nanoparticles made under nitrogen are Ni$_2$B while the catalyst made on open air is a mixture of Ni metal and Ni-B with an undetermined stoichiometry. The analysis proved that regardless the chemical process, the nanoparticles contain boron bound nickel and also borate [26]. In 2002 Geng et al. examined the nanostructure of the nickel boride catalyst with HRTEM and observed an ultra-fine crystalline structure; the material consists of
very small nickel single crystals from clusters as host that hold guest boron species captive with their interstitial sites. This allows the extremely small size and very high surface area [27]. Zeng and co-workers synthetized the nickel boride catalyst by electroless plating technique and the TEM image revealed that the Ni-B particles were amorphous with flower inner structure which formed during the preparation process and they confirmed with HRTEM that there are no small crystallites in the big particles, contradicting Geng’s findings [28].

1.1.5.2 Nickel boride promoted organic reactions

The literature only presents examples that use nickel boride as a reducing agent; however, a wide range of substrates can be used and it gives a remarkable variety of products depending on the reaction conditions [29].

Brown et al. observed, that nickel boride can act as a more reactive catalyst than Raney Ni towards less reactive alkenes (e.g. cyclopentene, cyclohexene and cyclooctene) [30], [31]. Belisle et al. reported a method for hydrogenation of α,β-unsaturated ketones and aldehydes using ex situ generated nickel boride (Figure 5) [32].

\[
\text{CHO} \xrightarrow{\text{Ni}_2\text{B}, \text{H}_2, \text{MeOH}} \text{CHO} 
\]

Figure 5: Hydrogenation of α,β-unsaturated aldehyde

With in situ formed nickel boride in methanol, several quinolines, isoquinolines and quinoxalines were converted to their tetrahydro-derivatives at room temperature (Figure 6) [33]. In order to get good to excellent yields (83-94%), high excess of sodium borohydride is necessary; however, using quinolines as starting materials requires only sub-stoichiometric amounts of nickel chloride (0.35 eq.). Kudo et al. also reported mechanistic investigations which revealed that in these cases complexes between the nickel chloride and heterocyclic compounds were reduced by sodium borohydride.
Sodium borohydride itself is not able to reduce unactivated alkyl halides. However, Dennis and Copper reported the reductive force of the combination of NiCl$_2$ and NaBH$_4$ in alcohol. The disposal of organochlorine pesticides, such as DDT (9) and 2,4-DB[4-(2,4-dichlorophenoxy)butanoic acid] (10) is difficult, but with the use of nickel boride both compounds can be extensively dechlorinated (Figure 7) [34].

Figure 6: Reduction of heterocycles

Figure 7: Toxic polychlorinated hydrocarbon pesticides and their reductions

Pharmaceutically active compounds often bear amino groups and the reduction of aromatic nitro compounds to amines is an important synthetic reaction. Kudo and Nose reported a method using NiCl$_2$ with NaBH$_4$ in methanol to reduce nitroarenes
to anilines in good yield [35]. Osby and Ganem found that the same system rapidly reduces a variety of nitro compounds at room temperature (Figure 8) [36].

\[
\begin{align*}
R-\text{NO}_2 & \xrightarrow{\text{NiCl}_2/\text{NaBH}_4/\text{MeOH}} \text{R-NH}_2 \\
R & = \text{aryl, alkyl, allyl}
\end{align*}
\]

Figure 8: Reduction of nitroarenes and nitroalkanes

Other nitrogenous functional groups, such as nitroso (11), azoxy (12), azo (13), hydrazo (14) and hydroxylamines (15) (Figure 9) also can be reduced using the nickel boride catalyst. Aromatic compounds bearing these groups can be transformed to anilines in acidic or basic media [35].

![Nitrogenous functional groups](image)

Figure 9: Nitrogenous functional groups

The NiCl₂/NaBH₄/CH₃OH system can be used for the reductive removal of allylic, propargylic and benzylic groups from acetate esters (Figure 10). Comparing nickel boride with Raney nickel, the former proved to be superior for reductive removal while the latter was more efficient in deoxygenations [37]. Russel et al. reported that in unsaturated aldehydes both the carbonyl and the olefinic group can be hydrogenated [38].

![Example of ester reduction](image)

Figure 10: Example of ester reduction
Truce and Perry reduced thioketals and thioacetals with the same catalyst system and successfully desulfurized the organic structures [39]. The reductive desulfurization of thioethers is also a possibility with nickel boride; Euerby and Waigh reported the selective reduction of alkylthio derivatives of benzaldehyde and benzyl alcohol to give good yields of benzyl alcohol, while with Raney nickel the main product is toluene (Figure 11) [40].

In 1984, Back reported a convenient method for selective reductive deselenization of alkyl, allyl and alkenyl selenides with the NiCl$_2$/NaBH$_4$/CH$_3$OH/ THF system. Under these conditions no alkene reduction was observed; moreover, sulfones ketones and acetates also remained untouched (Figure 12) [41], [42].

As the different type of reductions indicate, nickel boride behaves differently under different reaction conditions. The influencing factors are:

1. the NiCl$_2$/NaBH$_4$ molar ratio,
2. the preparation of the catalyst, the type of the nickel salt,
3. the solvent or solvent mixture,
4. the temperature.
These findings indicate that the range of application could be widened and other type reactions could also be conducted with this type of catalytic system.

1.2 Coupling reactions

A coupling reaction is a general term for a variety of reactions where two organic fragments are coupled in the presence of a metal catalyst. In most cases the C-C single bond is formed by the reaction of an organometallic (R-M) and an organic halide (R’-X) \[43\].

\[
R-M + R'-X \xrightarrow{\text{catalyst}} R-R' + M-X
\]

Based on the reagents, coupling reactions can be divided into two groups. In the case of heterocoupling two different fragments are coupled. Grignard published the first so called cross-coupling reaction in 1900 and was awarded the 1912 Nobel Prize in Chemistry for this work \[44\]. Several other cross-couplings have been reported since, such as the Kumada, Sonogashira, Negishi, Stille, Suzuki and Hiyama coupling. In 1994, Buchwald and Hartwig reported a new kind of cross-coupling, in which case a new N-C single bond is formed (Figure 13) \[45\], \[46\]. In 2010, for developing palladium catalyzed cross coupling reactions Richard F. Heck, Ei-ichi Negishi and Akira Suzuki were awarded the Nobel Prize in Chemistry \[47\]. Homocoupling couples two identical partners, which narrows down the possible outcomes of a reaction; consequently, this group was reported earlier. In 1855, Wurtz published the reaction of two halides in the presence of Na as reducing agent (Figure 13) \[48\].
1.2.1 Sonogashira reaction

The Sonogashira reaction is the most widely used method for synthesis of substituted alkynes (Figure 14) and reflects typical properties of Pd-catalyzed cross-coupling reactions, due to the availability of starting materials, mild coupling conditions, and the ability to tolerate a large variety of functional groups. The reaction requires catalytic amounts of palladium as catalyst and copper(I)-iodide as co-catalyst. The use of copper makes it possible to use milder conditions as the ones earlier reported by Heck and Cassar [49].
1.2.1.1 Mechanism

The mechanism of the Sonogashira reaction has not yet been established clearly, there has been evidence from recent studies of cross-coupling reactions that suggest a more complex mechanism [50]. Nonetheless, the general outline of the mechanism involves a sequence of oxidative addition, transmetalation, and reductive elimination, which are common to palladium-catalyzed cross-coupling reactions. However, the precise role of the copper co-catalyst and the structure of the catalytically active species remain uncertain. The mechanism displayed in Figure 15 includes the catalytic cycle itself, the preactivation step and the copper mediated transfer of acetylide to the Pd complex and is based on proposals already made in the early publications of Sonogashira [51].

The most commonly used palladium source is (PPh₃)₂PdCl₂ (1), which was originally employed by Sonogashira himself. Pd(OAc)₂, (CH₃CN)₂PdCl₂, or Na₂PdCl₄ with at least two equivalents of a tertiary phosphine can also be used to form the catalytically active species in situ. The active catalytic complex is still the subject of some debate, but is classically thought be the coordinatively unsaturated 14-electron Pd(0)L₂ (4) [51]. With all Pd(II) salts the initial step leading to the catalytically active species is preactivation of the catalyst, i.e. reduction of Pd(II) to Pd(0). As a side reaction reductive elimination from the cis-diacetylide (2) can result in the respective butadiyne (3). Alternatively, generation of 4 from Pd(II) proceeds via reductive elimination of 6. From 4 oxidative addition of aryl or vinyl halides results in a Pd(II) intermediate (5); this is considered as the rate-determining step. The copper-supported alkynylation leads to the alkynylpalladium(II) derivative (6),
Figure 15: Mechanism of the Sonogashira reaction for Pd/Cu-catalyzed cross-coupling which regenerates the catalytic species (4) by reductive elimination of the coupled products (7).

There are many variables that dictate the overall efficiency of the catalytic cycle, including ligand(s), amine base, copper salt, solvent, other 'additives', and the electronic and steric characteristics of the organic electrophile and alkyne.

1.2.1.2 Recent advances and developments

Recently microwave heating proved to be able to accelerate chemical reactions frequently delivering high yields in just a few minutes as opposed to hours with conventional heating. A microwave-enhanced Sonogashira reaction in the presence of (PPh₃)₂PdCl₂ and CuI was presented by Erdelyi and Gogoll and applied to the cou-
pling of aryl iodides, bromides, triflates, and activated aryl chlorides with trimethylsilylacetylene (Figure 16) [52].

\[
\text{Ar-X} + \text{H-SiMe}_3 \xrightarrow{\text{Pd(Ph}_3)_2\text{Cl}_2, \text{CuI, Et}_2\text{NH, DMF}} \text{Ar-SiMe}_3 \\
t = 5-25 \text{ min} \quad 80-99\%
\]

Figure 16: Microwave-assisted Sonogashira reaction

Heterogeneous polymer-supported catalysts have also attracted considerable interest: Merrifield resin (Figure 17 A) [53] and PS-PEG resin (Figure 17 B) [54] have both shown to be applicable as support for the cross-coupling of iodoarenes with alkynes at moderate temperatures.

Based mainly on economic considerations, different attempts have been made to replace the expensive noble metal palladium by using a cheaper metal [55]. Research on the use of different copper-based catalysts has been rather frequent in recent years [56]. CuI and triphenylphosphane (Figure 17 C) [57]; simple copper(II) acetate (Figure 17 D) [58]; and some copper complexes (Figure 17 E) [59] have also been used in Sonogashira reactions. Colacino et al. reported ligand-free procedures involving copper salts as catalysts (Figure 17 F) [60]. Iron also has been used as catalyst in the cross-coupling reaction; however, the influence of palladium impurities in the coupling process is still a question (Figure 17 G) [61]. Other catalysts based on cobalt (Figure 17 H) [62] and gold (Figure 17 I) [63] have been reported to catalyze Sonogashira reactions, too. Vechorkin et al. reported Ni-catalyzed Sonogashira coupling of non-activated, \(\beta\)-H-containing alkyl halides. The coupling is tolerant to a wide range of functional groups, including ether, ester, amide, nitrile, keto, heterocycle, acetal, and aryl halide, in both coupling partners (Figure 17 J) [64].
1.2.2 Glaser reaction

Homocoupling of terminal acetylenes first described by Glaser in 1869 [65] occurs in presence of a base, a copper(I) salt (usually CuCl) and oxygen (Figure 18). Natural products often consist of di- and polyacetylenic structures, such as the polyacetylenes from *Chrysanthemum leucanthemum*, *Bidens aurea* and *Artemesia capillaris* [66]. Therefore, there is a rapidly growing interest of material sciences in conjugated oligo- and polyacetylenes [67]. Whereas Glaser-type oxidative coupling opens efficient syn-
thetic pathways toward symmetrical diynes, its performance in heterocoupling is poor.

$$2 \text{R} \equiv \text{H} \xrightarrow{\text{CuCl, O}_2, \text{base}} \text{R} \equiv \text{R}$$

Figure 18: General Glaser reaction

1.2.2.1 Mechanism

Although acetylenic homo- and heterocouplings have been widely used in different fields of organic synthesis, their exact mechanism is still obscure. Because of the difficulty of kinetic studies, owing to the rapid reaction rates observed for the bromoalkynes commonly employed, several mechanistic hypotheses have been postulated [67]. Studies have shown the strong dependency of the mechanism on the experimental setup, suggesting highly complex coherences and interactions. All currently known mechanisms of oxidative acetylenic homocouplings are very specific to single reaction conditions, e.g. pH or oxidation state of the used copper salt.

Studies by different research groups indicate that both Cu$^+$ and Cu$^{2+}$ ions are involved in the coupling process [67]. Whereas copper(II) serves as the direct oxidizing agent, the role of copper(I) seems more versatile. Hay and co-workers found that the copper(II) carboxylates are the only copper(II) salts that are catalysts for the reaction, but they proved to be far inferior in catalytic activity to copper(I) salts [68].

A very reasonable role of copper(I) in the coupling process seems to be intermediate formation of non-reactive copper-$\pi$-complexes (1) (Figure 19). Coordination of cuprous ions activates the corresponding alkyne units toward deprotonation. Bohlmann and co-workers assumed that this activation process can be the initial step in the formation of dinuclear copper(II) acetylde complexes (4) [69]. Stepwise displaces the negatively charged counter ions of copper(II) salt dimers (2). The dinuclear copper(II) acetylde complex which finally results (4) collapses to the coupled product (5) under reductive elimination of copper(I).
However, the current mechanistic understanding of copper-mediated oxidative acetylenic couplings is unsatisfactory, the mechanistic idea of Bohlmann et al. described above still provides the most accepted picture for Glaser-type oxidative acetylenic homocouplings.

1.2.2.2 Recent advances and developments

Glaser-type homocouplings have been applied to the synthesis of numerous aliphatic and aromatic diynes, because of the tolerance of a large variety of functional groups. Their synthetic capacity has been impressively demonstrated in the synthesis of the conjugated organic oligomers and polymers [49] in polymer and supramolecular chemistry. Complex molecular architectures, such as: conjugated macrocycles (dehydrobenzoannulenes, graphdiyne subunits, π expanded radialene macrocycles); macrocyclic oligothiophenes; pyridine containing macrocycles; macrocyclic and dendrimeric
polyynes; shape persistent macrocycles; rotaxanes and catenanes; cyclophanes; ferrocenophanes; fullerol derivatives; molecular cages are formed from simple building blocks [70].

![Diagram](https://example.com/diagram.png)

**Figure 20: Glaser reaction developments**

Efforts have been made to develop new methods with milder conditions. Jia et al. developed a facile and simple CuI/iodine-mediated pathway (Figure 20 A) for the homocoupling reaction and proposed a mechanism that involves the formation of alkynylcopper intermediate, which undergoes oxidative dimerisation with iodine [71].

Jiang et al. investigated the use of CuAl-LDH (copper(II) in the host layers of layered double hydroxide or hydrotalcites) (Figure 20 B) [72]. Zeolites modified with cuprous ions in DMF offer another alternative catalyst; a large number of alkynes, including those containing carbohydrate moieties could be coupled (Figure 20 C) [73]. Instead of copper salts, copper immobilised on a functionalised silica support also serves as an efficient heterogeneous catalyst (Figure 20 D) [74]. Glaser-type coupling of terminal alkynes was also attempted with cobalt catalysts: with a suspension of CoBr₂, Zn powder and nitrobenzene which can be used as a stoichiometric oxidant. In contrast to the classical Glaser coupling reaction, the cobalt-catalysed reaction was performed under reductive conditions (zinc powder) (Figure 20 E) [75].

Efforts have been made to replace the traditional solvents with green solvents such as supercritical fluids, ionic liquids, water, etc. and even solvent free conditions would...
be attractive. Zhang et al. reported that polyethyleneglycol could be an alternative as the reaction system could be readily recycled more than five times (Figure 20 F) [76]. Ionic liquids allow the recycling and reuse of this catalytic system with simple procedures, and thus pave the path for green synthesis. Ionic liquid, such as [bmim]OH has also been tried as a solvent under atmospheric conditions for the homocoupling of acetylenes (Figure 20 G) [77].

Microwave irradiation can also be applied for better efficiency in macrocyclisation. Bedard and co-workers managed to reduce the reaction time from 48 hours to 1-6 hours (Figure 20 H) [78].

1.2.3 Suzuki-Miyaura reaction

The cross-coupling of organoboron reagents with organic electrophiles in the presence of a base and a Pd catalyst is commonly referred to as the Suzuki-Miyaura reaction (Figure 21) and has proved to be one of the most popular cross-coupling methodologies. The original version, first reported in 1979, was the palladium(0)-catalysed coupling of a vinyl boronate with an aromatic iodide or bromide [79].

$$B(OH)_2 + X \rightarrow R \quad \text{Pd cat.} \quad \text{base} \quad \rightarrow \quad R$$

Figure 21: General Suzuki-Miyaura reaction

Organoboron coupling partners show a number of advantageous properties over other organometals: organoborons have a much lower toxicity than organostannane reagents, they are stable to water and air, which makes their isolation and storage possible. Many organoboron building blocks are nowadays commercially available and they have remarkable tolerance against various functional groups along with their insensitivity to steric effects. Alkynylboron and aromatic boron compounds both can be used as reagents, making the synthesis of conjugated alkadienes and biaryls possible. Suzuki and co-workers also discovered that the reaction provides the expected coupled products regio- and stereoselectively in high yields [80, 81].

Boronic acids are one of the most readily available kinds of boron reagent for the
Suzuki coupling. They are; however, complicated by the fact that they are often in equilibrium with their anhydrides, the boroxines. In addition, the boronic acids can have a tendency to undergo protio-deboration, resulting in the decomposition of the starting material and the need to employ excess boronic acid in the coupling reaction. Esters of boronic acids, especially the pinacol esters, are widely used and can be easily prepared from the boronic acid [43]. Alkynylboranes are valuable intermediates; however, owing to their pronounced Lewis acidity, alkynylboranes can easily hydrolyze under basic aqueous conditions, which severely complicated their early application in coupling reactions [82].

1.2.3.1 Mechanism

The general catalytic cycle for Suzuki cross-coupling involves the three fundamental steps: oxidative addition, transmetalation, and reductive elimination as demonstrated in Figure 22 [83].

In most cases the oxidative addition is the rate determining step of the catalytic cycle; the relative reactivity decreases in the order of I > OTf > Br > Cl. During this step, the palladium catalyst is oxidized from palladium(0) to palladium(II). The palladium catalyst (1) is coupled with the aryl halide (2) to yield an organopalladium complex (3). The reaction with the base gives intermediate 4 which undergoes transmetalation with the previously activated organoboron compound (5). The base that was added in the prior step is exchanged with the substituent on the organoboron species to give the new palladium(II) complex (6). The organoboron compounds do not undergo transmetalation in the absence of base; and therefore, the role of the base is believed to be the activation of the organoboron compound as well as facilitate the formation of 4 from 3 [84]. The final step is the reductive elimination step where the palladium(II) complex (6) eliminates the product (7) and regenerates the palladium(0) catalyst (1).
1.2.3.2 Recent advances and developments

Typically, cross coupling reactions are run in organic solvents. However, Suzuki couplings can be performed in heterogeneous or purely aqueous conditions as organoboranes are water soluble and compatible with water soluble, inorganically supported, ligand-free Pd-catalysts; making the reaction milder and greener [80]. Pd(OAc)$_2$ in a mixture of water and poly(ethylene glycol) is shown to be an extremely active catalyst for the Suzuki reaction of aryl iodides and bromides. The reaction can be conducted under mild conditions without the use of phosphine ligand in high yields, and the Pd(OAc)$_2$-PEG can be reused without significant loss in activity [85].

Suzuki couplings have been used in the synthesis of complex molecules. For exam-
ple, coupling of two large fragments of the epothilone A structure was accomplished in this way (Figure 23). The advantage of this type of reaction is that the desired intermediate was successfully obtained in the presence of numerous stereocenters and functional groups, because of the stereoselectivity [86].

![Figure 23: Suzuki reaction in the synthesis of epothilone A](image)

Various catalysts have been developed for metals other than palladium, especially nickel. The use of nickel catalysts has allowed for electrophiles that proved challenging for the original Suzuki coupling using palladium, including substrates such as phenols, aryl ethers, esters, phosphates, and fluorides [87].

Wu et al. reported that dendritic phosphine-stabilized nickel nanoparticles were found to be a highly active and recyclable catalyst for Suzuki coupling reactions, especially those extended to aryl chloride substrates, affording the biaryls in moderate to good yields (Figure 24 A) [88]. Copper-catalysts’ attractive features are being earth-abundant and inexpensive. Gurung and co-workers reported on a versatile Cu-catalyzed cross-coupling of aryl- and heteroarylboronate esters with aryl- and heteroaryl iodides that affords biaryl products in good to excellent yields. The reaction proceeds under ligand-free conditions, with the assistance of CuI, CsF and o-(di-tert-butylphosphino)-N,N-dimethylaniline (Figure 24 B) [89]. Han et al. found that with the aid of sodium hydroxide gold nanoparticles can catalyze the synthesis of biaryls in high yields. The reaction media is chosen as water instead of organic
solvent in consideration of the green-chemistry processes and low cost. Furthermore, the catalyst could be reused without decreasing the yield (Figure 24 C) [90].

\[ \text{R-B(OR)}_2 + \text{R-X} \rightarrow \text{R-R} \]

Figure 24: Suzuki reaction recent developments

Microwave reactions have gained ground in the past decades because of their ability to shorten reaction times. Nun and co-workers developed a solvent-free, microwave-assisted Suzuki reaction with the aid of potassium carbonate and a new palladium N-heterocyclic carbene catalyst (Figure 24 D) [91]. The use of supported catalysts makes both the purification process and the recycling easier. Yang et al. developed al Merrifield resin immobilized phenanthroline-palladium(II) complex which was found to be an efficient catalyst for Suzuki-Miyaura cross-coupling reaction between arylboronic acids and a range of aryl halides under mild reaction conditions. The catalyst exhibited both high catalytic activity and stability; furthermore, the catalyst could be recycled at least 10 times without a sig-
significant loss of catalytic activity (Figure 24 E) [92]. Wei and co-workers reported a silica-immobilized system in an ionic liquid brush in water as solvent for coupling aryl iodides and bromides with phenylboronic acid (Figure 24 F) [93].

1.3 The aim of this thesis

Transition metal-catalyzed cross-coupling reactions represent an important segment of organic chemistry, since in these reactions new carbon-carbon bonds can be formed allowing a simple way to build up molecules. This thesis is focused on the nickel boride catalyst, and concerns with the possibility to widen the scope of reactions in which nickel boride can be applied successfully. The aim is to investigate named catalyst’s activity in three different coupling reactions, Sonogashira cross-coupling, Glaser homocoupling and Suzuki-Miyaura cross-coupling.

2 Experimental work

2.1 Synthesis of nickel boride catalyst

Besides nickel boride, cobalt boride and iron boride have also been prepared, investigated and used in different reductions [96]. Based on this reports our group also considered using these catalysts in the coupling reactions. Although all metal borides have been prepared, in this work we only investigated thoroughly the behavior and activity of the nickel boride.

2.1.1 Preparation of metal borides

The metal boride catalysts can be prepared in aqueous and non-aqueous media [25]. In different solvents, the composition of the catalyst can vary. Nickel, cobalt and iron boride had been prepared in anhydrous methanol and in water (Appendix A.2). In all cases, the catalysts were forming with good yields; however, the difficulty of collecting the magnetic particles resulted in some loss of material (Table 2).
Table 2: Preparation of metal borides

<table>
<thead>
<tr>
<th>Metal</th>
<th>Prepared in</th>
<th>Magnetic properties</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>methanol</td>
<td>non-magnetic</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>non-magnetic</td>
<td>91%</td>
</tr>
<tr>
<td>Cobalt</td>
<td>methanol</td>
<td>non-magnetic</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>magnetic</td>
<td>75%</td>
</tr>
<tr>
<td>Iron</td>
<td>methanol</td>
<td>magnetic</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>magnetic</td>
<td>67%</td>
</tr>
</tbody>
</table>

2.1.2 Nickel boride applications

To explore the catalytic activity of the nickel boride, different preparations have been utilized in the reactions. In most reaction previously prepared (Appendix A.2.1) catalyst has been used. In this case, we observed that by storing the catalyst, with time the activity decreases until the nickel boride loses all catalytic activity. It is also possible to buy nickel boride from Sigma-Aldrich; however, the commercially available and the pre-prepared nickel boride have different appearances. While the commercially available appeares metallic, the pre-prepared catalyst consists of black particles. To prevent the degradation of the nickel boride, before starting the reactions, the catalyst was freshly prepared on filtering paper (Appendix A.2.3).

In the case of alcoholic solvents it is possible to use *in situ* prepared catalyst; however, the solubility of nickel chloride hexahydrate decreases when using bulkier alcohols.

2.2 Sonogashira coupling

As stated previously, there are a number of publications reporting successful Sonogashira couplings with the aid of nickel catalyst [64], and even ligand-free copper-catalyzed procedures have been developed [60]. Our aim was to investigate, if nickel
boride can catalyze the Sonogashira reaction between an alkyne and an aryl halide. Okuro and co-workers reported that the treatment of iodobenzene with phenylacetylene in DMF in the presence of catalytical amount of CuI, PPh$_3$ and K$_2$CO$_3$ at 120 °C for 16 hours gave diphenylacetylene almost quantitatively [94]. We chose this reaction as starting point for our research (Figure 25).

Two parallel reactions were set up in DMF (Table 3, Entry 1-2). To the first vial, only CuI as catalyst together with sodium borohydride, to the second vial also pre-prepared nickel boride was added. Analyzing the reaction mixtures with TLC (eluent: hexane), in both cases two new spots appeared, really close to each other. After column chromatography (eluent: hexane), the unknown components were analyzed via $^1$H-NMR and one of the components proved to be the expected product (Appendix A.3.1). The structure of the other component could not be determined due to impurities. However, both the product and the side product the could only be obtained in trace amounts.

Based on the publication of Yi et al. [95], DMF was exchanged with a mixture of DMAc and DEE (Table 3, Entry 3-4). To exclude the possibility of dehalogenation, the activities of two starting materials (1-iodohexane and 4-iodotoluene) were compared. Analyzing the reaction mixtures with TLC (eluent: hexane), in both cases the yet unidentified new spot appeared and the spot of the cross-coupled product could not be detected. The 1-iodotoluene stayed intact in the reaction mixture. After column chromatography (eluent: hexane), the purified unknown component (white chrystals) was analyzed via $^1$H-NMR and proved to be the homocoupled product of phenylacetylene (Appendix A.3.2).

To determine, if nickel boride or copper iodide catalyzes the reaction, three reactions were set up (Table 3, Entry 5-7). To the first vial only nickel boride catalyst,
Table 3: Sonogashira coupling investigations

\[ \text{aryl iodide} + \text{phenylacetylene} \xrightarrow{\text{Ni}_2\text{B}, \text{CuI}, \text{K}_2\text{CO}_3, \text{DMF}} \text{aryl acetylene} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product\textsuperscript{a}</th>
<th>Side product\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>120 °C, 16 h</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>Ni\textsubscript{2}B/CuI</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>120 °C, 16 h</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>3</td>
<td>Ni\textsubscript{2}B/CuI</td>
<td>KO\textsuperscript{t}Bu</td>
<td>DEE/DMAc\textsuperscript{b}</td>
<td>rt, 24 h</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>4\textsuperscript{c}</td>
<td>Ni\textsubscript{2}B/CuI</td>
<td>KO\textsuperscript{t}Bu</td>
<td>DEE/DMAc\textsuperscript{b}</td>
<td>rt, 24 h</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ni\textsubscript{2}B</td>
<td>KO\textsuperscript{t}Bu</td>
<td>DEE/DMAc\textsuperscript{b}</td>
<td>rt, 24 h</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>KO\textsuperscript{t}Bu</td>
<td>DEE/DMAc\textsuperscript{b}</td>
<td>rt, 24 h</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>KO\textsuperscript{t}Bu</td>
<td>DEE/DMAc\textsuperscript{b}</td>
<td>rt, 24 h</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} determined with TLC.

\textsuperscript{b} DEE/DMAc (2 ml, 9:1).

\textsuperscript{c} 1-Iodohexane starting material.

**Reaction conditions**: 4-Iodotoluene (1 mmol), phenylacetylene (1 mmol), solvent (2 ml), CuI (0.05 mmol, 0.05 eq.), Ni\textsubscript{2}B (0.12 mmol, 0.12 eq.) and K\textsubscript{2}CO\textsubscript{3} (1.5 mmol, 1.5 eq.).

to the second vial only CuI catalyst were added as catalysts and to the third vial no additional chemicals were added. Analyzing the reaction mixtures with TLC, in the third case, without any metal no reaction occurred. In the other two cases, only the homocoupling product could be detected, which suggests that copper alone also catalyzes the homocoupling without the nickel catalyst, which is expected from previous literature.

In conclusion, we found that both the cross-coupling and the homocoupling reactions proceed in DMF, and with appropriate solvents it is possible to shift this balance towards the homocoupling product (Figure 26). Based on the results we decided to exclude the aryl halide from the reaction mixtures and continue the work with Glaser-type couplings.
2.3 Glaser coupling

Our aim was to achieve the homocoupling of phenylacetylene with the aid of nickel boride (Figure 27). In the case of the initial screening reactions only TLC analysis was used to detect the product.

![Glaser homocoupling model reaction](image)

Figure 27: Glaser homocoupling model reaction

2.3.1 Solvent screening

To optimize the reaction, the effect of different solvents was investigated. The solvents were chosen based on the literature and the principles of green chemistry were also considered. The reaction was set up with seven different solvents (Table 4, Appendix A.4.1).
Table 4: Glaser coupling solvent screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>DEE/DMAc$^b$</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>methanol</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>3</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>ethanol</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>4</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>butanol</td>
<td>rt, 24 h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>water</td>
<td>rt, 24 h</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>7</td>
<td>$\text{Ni}_2\text{B}$</td>
<td>KO$^t\text{Bu}$</td>
<td>DMF</td>
<td>rt, 24 h</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ determined with TLC.

$^b$ DEE/DMAc (1 ml, 9:1).

**Reaction conditions**: 4-Iodotoluene (0.25 mmol), phenylacetylene (0.25 mmol), solvent (1 ml), Ni$_2$B (0.03 mmol, 0.12 eq.) and KO$^t\text{Bu}$ (0.5 mmol, 2.0 eq.).

In the cases of water, butanol and DMF no product was detected. Using alcohols as solvents also resulted in trace amounts of the product. Based on the relative intensity of the product spot compared to the phenylacetylene’s spot, the previously tested DEE-DMAc and acetonitrile solvents proved to be the optimal conditions. However, the TLC of the reaction mixture with the solvent DEE-DMAc showed more side products. In conclusion, we chose acetonitrile for further reactions.

### 2.3.2 Base screening

Literature revealed that weaker bases can also be sufficient in Glaser couplings [71]. Therefore, other inorganic bases (sodium carbonate and tripotassium phosphate) were also tried as possible replacements for potassium tert-butoxide (Table 5).
Table 5: Glaser coupling base screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni$_2$B</td>
<td>KO'Bu</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>Ni$_2$B</td>
<td>Na$_2$CO$_3$</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ni$_2$B</td>
<td>K$_3$PO$_4$</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>x</td>
</tr>
</tbody>
</table>

* a determined with TLC.

**Reaction conditions**: phenylacetylene (0.25 mmol), acetonitrile (1 ml), Ni$_2$B (0.03 mmol, 0.12 eq.) and base (0.5 mmol, 2.0 eq.).

Based on TLC analysis, in the case of sodium carbonate no reaction occurred, while tripotassium phosphate proved to be a better option than potassium tert-butoxide, since the reaction mixture contained less components, side products. With a weaker base the possibility of side reactions is lower, thus we decided to continue the research with tripotassium phosphate.

### 2.3.3 Analysis with gas chromatography

Gas chromatography is a common type of chromatography used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition. This method makes it possible to determine the concentration of different components without the need of column chromatography or other time-consuming workup. Out of these reasons, we chose GC to analyze our reaction mixtures.

As the first step, the starting material, and the product were injected on the GC in order to develop a suitable method for the separation. As can be seen in Appendix A.4.3, after the intense solvent peak, the starting material can be detected at 3.782 min. The peak of the product appears at 14.720 min; however, the high boiling point (200-210°C) made it difficult to reduce the retention time. Anisole was used as internal standard, with the retention time of 4.195 min. Because of the potential
overlap of the starting material’s and the standard’s peak, no further shortening of
the GC method was possible (Figure 28, Appendix A.4.2).

![Figure 28: Calibration chromatogram (point 4)](image)

In both cases a five-point calibration curve was made. The five samples contained
different amount of starting material and product, while the amount of standard was
kept constant. In the case of the starting material, the ratio of the phenylacetylene’s
peak area ($A_s$) and the anisole’s peak area ($A_a$) was calculated (Table 6).
Table 6: Calibration of phenyacetylene (s) with anisole (a) as standard

<table>
<thead>
<tr>
<th>Entry</th>
<th>n_s/n_a</th>
<th>Concentration</th>
<th>A_s/A_a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.95</td>
<td>56.8</td>
<td>1.09</td>
</tr>
<tr>
<td>2</td>
<td>0.70</td>
<td>41.8</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>0.52</td>
<td>31.4</td>
<td>0.63</td>
</tr>
<tr>
<td>4</td>
<td>0.29</td>
<td>17.2</td>
<td>0.33</td>
</tr>
<tr>
<td>5</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

\[ y = 0.8631x - 0.0044 \]
\[ R^2 = 0.9995 \]

Figure 29: Phenylacetylene calibration curve with anisole as standard

The diagram in Figure 29 represents the correlation between the \( A_s/A_a \) values and the \( n_s/n_a \) values. If the molar amount of standard is equal to the starting material when starting the reaction, conversion can be directly calculated by using the equation.
The same calibration was made for the product. The ratio of the product’s peak area \( A_p \) and the standard’s peak area \( A_a \) was calculated (Appendix A.4.4). The coupling reaction of two mols of starting material theoretically results in one mol of product (Figure 27), thus multiplying the calculated \( n_p/n_a \) values with 2 gives the GC yield of the product.

### 2.3.4 Reactions

With the new GC method, the previously reactions were repeated in order to more accurately determine yields of the homocoupling product (Table 7, Entry 1). On TLC an intense spot of the product appeared; however, with the GC method only 4% of product was detected. This suggests that there is a large discrepancy between the intensity of the product’s spot compared to the spot of the starting material and the yield of the product.

#### Table 7: Glaser coupling reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni(_2)B</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pre-prepared</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>70 °C, 24 h</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>pre-prepared</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>in situ formed</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>commercial</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NiCl(_4) hexahydrate</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>rt, 24 h</td>
<td>-</td>
</tr>
<tr>
<td>6(^b)</td>
<td>pre-prepared</td>
<td>K(_3)PO(_4)</td>
<td>acetonitrile</td>
<td>60 °C, 2 h + 2 h</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) determined with GC.

\(^b\) microwave reaction.

**Reaction conditions**: phenylacetylene (0.5 mmol), acetonitrile (2 ml), Ni\(_2\)B (0.06 mmol, 0.12 eq.), K\(_3\)PO\(_4\) (1.0 mmol, 2.0 eq.) and anisole (0.5 mmol).
The effect of the catalyst and the possibility to increase the GC yield were investigated with four parallel reactions (Table 7, Entry 2-5). In the case of catalyst-formation in situ, NiCl$_2$ hexahydrate did not dissolve in acetonitrile. However, with the addition of NaBH$_4$ black particles and gas evolution could be observed. On TLC (eluent: hexane), in the first three cases the product’s spot appeared, while with GC the product only in the case of the pre-prepared catalyst (GC yield: 2%) could be observed.

With a microwave reactor it is possible to shorten the reaction times by microwave irradiation and heating. Therefore, we performed several reactions using microwave irradiation (Table 7, Entry 6). After 2 hours of stirring at 60 °C, the product was only detected with TLC (eluent: hexane); and after an additional 2 hours of heating, only trace amounts of product could be detected with GC.

Based on the consequently low GC yields, we concluded, that using TLC for monitoring the reaction is misleading, because of the strong conjugation in the molecule (two benzene rings and triple bonds) leads to high UV intensity. As a result of the developed GC method we can state, that the homocoupling product could be detected only in trace amounts. Furthermore, the question also arises: is it really the Ni$_2$B, that is catalyzing the coupling, or other metal impurities cause the 2-4% product formation?

2.4 Suzuki-Miyaura coupling

2.4.1 Catalyst investigations

2.4.1.1 Initial reactions with contaminated chemicals

As model reaction, the Suzuki-Miyaura coupling of phenylboronic acid and 3-iodotol-uene was chosen, in the presence of potassium tert-butoxide (Figure 30, Appendix A.5.1). In the initial screening reactions, the conversion of the reactions was only monitored with TLC.
Using nickel boride prepared in anhydrous methanol (Table 8, Entry 1), the reaction mixture was analysed with TLC (eluent: hexane) after 24 hours. The 3-iodotoluene’s spot disappeared from the mixture and the product’s spot appeared. The reaction mixture was filtered through Celite and then evaporated. The crude reaction mixture was purified with column chromatography using hexane as eluent yielding 69% product. The purity was proved via $^1$H-NMR (Appendix A.5.2).

The reaction was repeated with all three metal borides prepared in water (Table 8, Entry 2-4). Based on TLC (eluent: hexane), the starting material disappeared in all three cases. This extremely positive result generated the question if it is indeed the catalyst driving the reaction, or maybe it is not needed. To examine this, two reactions were set up (Table 8, Entry 5-6): in the case of the first one reagent ratios were not altered and in the second one the 3-iodotoluene was used in excess. In both cases the iodo-compound disappeared, and product was forming.
Table 8: Initial reactions with contaminated chemicals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni$_2$B$^b$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>69% $^b$</td>
</tr>
<tr>
<td>2</td>
<td>Ni$_2$B$^d$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>3</td>
<td>Co$_2$B$^d$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>4</td>
<td>Fe$_2$B$^d$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>5</td>
<td>Ni$_2$B$^b$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>x</td>
</tr>
<tr>
<td>6$^f$</td>
<td>Ni$_2$B$^b$</td>
<td>KO$^t$Bu</td>
<td>ethanol</td>
<td>110 °C, 24 h</td>
<td>x</td>
</tr>
</tbody>
</table>

$^a$ determined with TLC.

$^b$ prepared in anhydrous methanol.

$^c$ isolated yield.

$^d$ prepared in water.

$^f$ 3-iodotoluene (1.5 mmol, 1.5 eq.), phenylboronic acid (1.0 mmol), ethanol (1 ml), Ni$_2$B (0.12 mmol, 0.12 eq.) and KO$^t$Bu (3.0 mmol, 3.0 eq.).

Reaction conditions: 3-iodotoluene (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 eq.), ethanol (1 ml), Me$_2$B (0.12 mmol, 0.12 eq.) and KO$^t$Bu (3.0 mmol, 3.0 eq.).

The literature reports metal-free biaryl coupling reactions with potassium tert-butoxide as base [97] and direct C-H arylations of arenes promoted by mixed potassium alkoxides [98]. There are reactions with radical mechanism in which cases where the electron is the catalyst [99]. To investigate if the mechanism is radical of the present model reaction, TEMPO and anthracene were added to the reaction mixture (Table 9, Entry 1-2). The role of the radical scavenger TEMPO is to catch radicals so the product cannot form. Alternatively, the aryl-halide could be deprotonated to form a reactive benzyne. Therefore, anthracene can react with the aryl-halide in a Diels-Alder reaction. As a result, in both cases the iodo-compound did not disappear.
from the reaction mixture and the conversion decreased. These results supported the theory of a radical mechanism.

To prove the mechanism, the product of the TEMPO and the radicals present in the reaction mixture needed to be isolated. The reactions were repeated without adding the phenylboronic acid (Table 9, Entry 3-4). In the case of TEMPO according to the TLC only a really small new spot appeared, which could not be separated. Using anthracene no reaction occurred. In the reaction of 3-iodotoluene with KOtBu no homocoupling occurred. The radical mechanism could not be proved.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additional reagent</th>
<th>3-Iodotoluene</th>
<th>Product(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>TEMPO present</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2(^b)</td>
<td>anthracene present</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>3(^c)</td>
<td>TEMPO present</td>
<td>traces</td>
<td></td>
</tr>
<tr>
<td>3(^c)</td>
<td>anthracene present</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) determined with TLC.

\(^b\) 3-iodotoluene (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 eq.), ethanol (1 ml), Ni\(_2\)B (0.12 mmol, 0.12 eq.) and KOtBu (3.0 mmol, 3.0 eq.), 110 °C, 24 h.

\(^c\) 3-iodotoluene (1.0 mmol), ethanol (1 ml), Ni\(_2\)B (0.12 mmol, 0.12 eq.) and KOtBu (3.0 mmol, 3.0 eq.), 110 °C, 24 h.

Coupling reactions without transition metals could be really sensitive towards contaminations, since trace amounts of these metals can catalyze the reactions [100]. It is important, to make sure that all materials used are contamination-free, thus we decided to examine the starting materials used in the previous reactions. Comparing the newly purchased (purity: 99.99%) and the old KOtBu (purity: ≥
97%), the reaction mixtures bear a different colour. In the case of the new one the mixture turned yellow; however, in the case of the old one the mixture turned brown with time. We decided to use freshly ordered base to avoid unnecessary contaminations.

For the reactions three different bottles of phenylboronic acid were available: two bottles from Fluka (an old one and a later ordered one) and one bottle from Sigma-Aldrich (freshly ordered). In order to test the quality, in all three cases the model reaction was executed with and without catalyst, too (Table 10).

Table 10: Phenylboronic acid investigations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Distributor</th>
<th>Catalyst present</th>
<th>GC yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sigma-Aldrich</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Sigma-Aldrich</td>
<td>x</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>Fluka</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>Fluka</td>
<td>x</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>Fluka</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Fluka</td>
<td>x</td>
<td>9%</td>
</tr>
</tbody>
</table>

a self-developed GC method, explained later.
b older bottle.

**Reaction conditions**: 3-iodotoluene (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 eq.), ethanol (1 ml), Ni$_2$B (0.12 mmol, 0.12 eq.) and KO'Bu (3.0 mmol, 3.0 eq.), 110 °C; 24 h.

Using the phenylboronic acid, which was purchased earlier from Fluka, in both cases comparable conversions were observed. In the cases of the other two bottles, without catalyst no reaction occurred. The starting material, which gave reactions without the presence of the catalyst, was used in the previous reactions. This results might explain why all the catalysts gave the product in the model reaction; it is
possible that the old bottle contains palladium traces that are driving the reaction. To avoid confusion, for further experiments only recently ordered starting material, purchased from Sigma-Aldrich, was used.

This findings made it necessary to repeat the model reactions with the different metal borides. Both catalysts prepared in anhydrous methanol and in water were used to explore the activities (Table 11).

Table 11: Repeated model reaction with metal borides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Prepared in</th>
<th>GC yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni$_2$B</td>
<td>methanol</td>
<td>23%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>water</td>
<td>6%</td>
</tr>
<tr>
<td>3</td>
<td>Co$_2$B</td>
<td>methanol</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>water</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Fe$_2$B</td>
<td>methanol</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>water</td>
<td>0%</td>
</tr>
</tbody>
</table>

$^a$ self-developed GC method, explained later.

**Reaction conditions:** 3-iodotoluene (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 eq.), ethanol (1 ml), Me$_2$B (0.12 mmol, 0.12 eq.), KO$_t$Bu (3.0 mmol, 3.0 eq.) and dodecane (1.0 mmol), 110 °C, 24 h.

As can be seen in Table 11, only in the case of nickel boride product detected was detected. The catalyst prepared in methanol gave a higher yield then the catalyst prepared in water. This indicated the decision to only use nickel boride prepared in methanol for further reactions.
2.4.2 Gas chromatography method

To be able to quantitatively analyze the reaction mixture and to determine the yield and conversion, a GC method was developed (Appendix A.5.3). As internal standard dodecane was chosen ($R_t = 12.186$ min) due to its assumed inactivity in the model reaction. The starting material’s peak appears at 13.339 min, and the coupled product’s retention time was 21.123 min (Appendix A.5.4). The calibration curve for the starting material and the product was calculated with the same method that was used for the Glaser coupling (2.3.3). The calibration point molar ratios and the calibration curves can be seen in Appendix A.5.5. For the analysis of the reaction mixture filtration was not enough, because not only the solid components, but also the phenylboronic acid needed to be eliminated to not to cause any harm to the column in the gas chromatograph. Therefore, silica plug was used with hexan-diethyl ether (1:1) eluent. When checking the method, corrections were needed, because the regression was not precise enough. The corrected calibration curve contained three new points, each with of 60% theoretical yield. With this regression line the expected yields were calculated (Appendix A.5.4, Figure A.3). Examining the chromatograms, in most of the cases an unidentified peak at 19.739 min was detected. The biphenyl was produced and injected to the GC and the results confirmed that the homocoupling occurred as side reaction. To determine the amount of the side product a calibration was done (Appendix A.5.6).

2.4.3 Solvent screening

In the model reaction ethanol was used as solvent. However, the literature reports on several other methods with different solvents that bear different properties (polar, apolar, protic and aprotic). Ten solvents were screened to see if higher conversion could be obtained with these conditions (Table 12). For this screening a method for a smaller scale was developed, where 2 ml sample holders with plastic caps were used (Appendix A.5.7). The problem with this method was, that the evaporating solvents could easily escape since the caps could not be sealed properly. This questions the accuracy of the GC results.
As can be seen in Table 12, in only one of these reactions was a higher product yield than 50% observed. The main reason for the low yields is that there is a competing dehalogenation reaction, which results in the decomposition of the iodocompound. This effect is extremely dominant in the case of THF and ethanol. The findings also indicate that using tert-amyl alcohol, dioxane, and acetonitrile enhances the generation of the biphenyl side product. In the case of acetonitrile, the GC chromatogram confirms that the reaction led to a mixture containing different kinds of undesired side products. Using the listed solvents in Entry 1-4 did not lead to the desired prod-
uct. However, the calculations for the remaining starting material show that using biphasic reactions (e.g. PEG) makes calculations more difficult considering that the distribution of the internal standard in these two phases is unknown. Using DMF lead to the highest conversion, although the reaction mixture was biphasic. Comparing the different alcohols confirms our theory that the solvent choice has a larger effect on the outcome of this reaction. With methanol no product was observed, but using n-butanol or ethanol led to the desired product. The difference in these two cases is the decomposition of the starting material. Analyzing the chromatogram of n-butanol shows that the starting material is more resistant towards dehalogenation in this solvent. To summarize our results, we found that the most suitable solvent for further optimizations is n-butanol.

2.4.4 Base screening

In several Suzuki-Miyaura reactions, potassium tert-butoxide is replaced with weaker bases, such as potassium carbonate or potassium triphosphate. These two bases were tested in four different solvents (based on the solvent screening in 2.4.3) (Table 13).

As can be seen in Table 13, only in two of the cases the cross-coupling reaction was observed. Although dioxane gave 9% yield, the undesirable homocoupling occurred in a higher degree. Using n-butanol as solvent also shows that the less basic potassium phosphate also gave almost 20% yield of the product, while no homocoupling product was detected.
Table 13: Base screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Product</th>
<th>Biphenyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetonitrile</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>dioxane</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>n-butanol</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>acetonitrile</td>
<td>0%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>K₃PO₄</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>dioxane</td>
<td>9%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>n-butanol</td>
<td>19%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

*inconclusive results.

**Reaction conditions:** 3-iodotoluene (0.10 mmol), phenylboronic acid (0.15 mmol, 1.5 eq.), solvent (400 µl), Ni₂B (0.012 mmol, 0.12 eq.), base (0.3 mmol, 3.0 eq.) and dodecane (0.1 mmol), 110 °C, 24 h.

2.4.5 Alternative starting materials

2.4.5.1 Reaction with different halides

Chloro-, bromo- and iodotoluene have different reactivities based on the different characteristics of the halogen substituents, where iodotoluene is more reactive than chlorotoluene. The model reaction was set up with the three different starting materials, to investigate their behaviour in the coupling reaction (Table 14).
Table 14: Reaction with different halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product GC yield</th>
<th>Biphenyl GC yield</th>
<th>Starting material GC yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-iodotoluene</td>
<td>4%</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>3-bromotoluene</td>
<td>4%</td>
<td>0%</td>
<td>-a</td>
</tr>
<tr>
<td>3</td>
<td>3-chlorotoluene</td>
<td>0%</td>
<td>0%</td>
<td>-a</td>
</tr>
</tbody>
</table>

*a* starting material calibration would be needed.

**Reaction conditions:** 3-halogenotoluene (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 eq.), ethanol (1 ml), Ni$_2$B (0.12 mmol, 0.12 eq.), KOtBu (3.0 mmol, 3.0 eq.) and dodecane (1.0 mmol), 110 °C, 24 h.

With 3-chlorotoluene no reaction occurred, but 3-bromotoluene seems to have the same reactivity as 3-iodotoluene. The problem using ethanol is that in the case of 3-iodotoluene the starting material decomposes, which could be avoided by using less reactive halides. In this case, the reactivity of 3-iodotoluene in the coupling reaction is needed due to the low yields. In the other two cases calibration is needed to determine the amount of starting materials.

### 2.4.5.2 Reaction with phenylboronic acid pinacol ester

Protodeboronation is a well-known undesired side reaction, and frequently associated with metal-catalysed coupling reactions that utilise boronic acids, like the Suzuki-Miyaura coupling [101]. In this reaction the boronic acid undergoes protonolysis in which a carbon-boron bond is broken and replaced with a carbon-hydrogen bond (Figure 31).
Replacing the free hydroxy groups in the phenylboronic acid is a possible solution to avoid the protodeboronation side reaction. However, using protection groups also alters the reactivity of said compounds. Our aim was to examine the reaction using phenylboronic acid pinacol ester (Appendix A.5.8) to see if it has a positive effect on the outcome of the reaction.

Four reactions were set up with using ethanol and butanol as solvents, KO\textsubscript{t}Bu and K\textsubscript{3}PO\textsubscript{4} as bases (Table 15). Repleacing the phenylboronic acid with the pinacol ester also allowed us to track the amount of both starting materials present in the reaction mixture; the phenylboronic acid pinacol ester could be detected at 17.980 min.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Product</th>
<th>Biphenyl</th>
<th>3-Iodotoluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ethanol</td>
<td>KO\textsubscript{t}Bu</td>
<td>7%</td>
<td>0%</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>butanol</td>
<td>KO\textsubscript{t}Bu</td>
<td>0%</td>
<td>0%</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>ethanol</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>0%</td>
<td>0%</td>
<td>113%</td>
</tr>
<tr>
<td>4</td>
<td>butanol</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>0%</td>
<td>0%</td>
<td>108%</td>
</tr>
</tbody>
</table>

**Reaction conditions:** 3-iodotoluene (1.0 mmol), phenylboronic acid pinacol ester (1.5 mmol, 1.5 eq.), ethanol (1 ml), Ni\textsubscript{2}B (0.12 mmol, 0.12 eq.) and KO\textsubscript{t}Bu (3.0 mmol, 3.0 eq.), 110 °C, 24 h.

According to the chromatograms, only in the case of ethanol and using KO\textsubscript{t}Bu...
can be the product detected. The 3-iodotoluene did not decompose in this case and the other starting material also stayed intact. These results question if there is any correlation between the protodeboronation and the dehalogenation side reactions.

2.4.6 Temperature studies

Literature reports of coupling reactions at different temperatures; since it effects the stability of the starting materials. Also considering green chemistry it is also desired to develop methods at as low temperatures as possible. Therefore, the reaction was tested at higher (150 °C) and lower (80 °C) temperatures. Decreasing the temperature to 80 °C gave no product, even though the starting material stayed intact in the reaction mixture.

Table 16: Reaction at 150°C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Product</th>
<th>Biphenyl</th>
<th>3-Iodotoluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>ethanol</td>
<td>KO’Bu</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>butanol</td>
<td>3-PO4</td>
<td>5%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>3a</td>
<td>ethanol</td>
<td>3-PO4</td>
<td>6%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>butanol</td>
<td>3-PO4</td>
<td>27%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*a* evaporated solvent.

**Reaction conditions:** 3-iodotoluene (0.10 mmol), phenylboronic acid (0.15 mmol, 1.5 eq.), solvent (400 µl), Ni2B (0.012 mmol, 0.12 eq.), base (0.3 mmol, 3.0 eq.) and dodecane (0.1 mmol), 150 °C, 24 h.

The model reaction was set up at 150 °C in ethanol and butanol with potassium tert-butoxide and potassium triphosphate as bases (Table 16). Based on the result butanol appears to be a better choice for solvent, because even at 110 °C ethanol
evaporates from the vials; therefore, these results are not reliable. In the case of butanol it is interesting to notice that using potassium triphosphate led to 27% product. Using ethanol as solvent gave similar results. Repeating the reactions in a larger scale (1.0 M) gave the same results. Using the phenylboronic acid pinacol ester did not lead to product in any case.

2.4.7 Microwave reactions

As stated earlier, microwave irradiation can enhance the reaction and shorten the reaction time. Using the same reaction conditions as in previous studies, reactions were set up at 180 °C using phenylboronic acid and phenylboronic acid pinacol ester in butanol (Table 17).

The reaction using phenylboronic acid pinacol ester resulted in less product (5%), while with the phenylboronic acid 17% product could be obtained, with a minimal amount of side product. In Entry 3 the catalyst was prepared before starting the reaction and led to higher yield. However, no 3-iodotoluene could be detected with the GC and therefore the yield could not be increased any further. It is important to note, that working at elevated temperature (above the boiling point of the solvents) the risk of explosion arises, since the vapour pressure can be significant inside the microwave vials. During our work multiple reaction mixtures exploded at 180 °C; therefore, we decided to lower the temperature.
Table 17: Microwave reactions

\[
\begin{align*}
\textbf{Entry} & \quad \textbf{Starting material} & \quad \textbf{Base} & \quad \textbf{Time} & \quad \textbf{Product} & \quad \textbf{GC yield} & \quad \textbf{Biphenyl GC yield} \\
1 & \text{phenylboronic acid} & \text{K}_3\text{PO}_4 & 1\text{h} & 9\% & 15\% \\
2 & \text{phenylboronic acid} & \text{K}_3\text{PO}_4 & 2\text{h} & 12\% & 0\% \\
3^a & \text{phenylboronic acid} & \text{K}O'Bu & 2\text{h} & 17\% & 1\% \\
4 & \text{phenylboronic acid pinacol ester} & \text{K}O'Bu & 3.5\text{h} & 5\% & 0\% \\
\end{align*}
\]

\[^a\text{with freshly made catalyst.}\]

**Reaction conditions**: 3-iodotoluene (0.1 mmol), phenylboronic acid or phenylboronic acid pinacol ester (0.15 mmol, 1.5 eq.), butanol (400 µl), Ni$_2$B (0.012 mmol, 0.12 eq.), base (0.3 mmol, 3.0 eq.) and dodecane (0.1 mmol).

### 3 Conclusion and outlook

Based on the results presented in this work the conclusion can be made, that nickel boride in general is an appropriate catalyst for various reductions; however, for coupling reactions it is not suitable, exactly because of the reductive properties. In all three cases, side reactions connected to reduction (such as alkyne to alkene reduction and dehalogenation) could be observed. These side reactions appeared to be faster than the coupling reactions, making it impossible to increase the yield. The highest yield (52%) was obtained in the case of the Suzuki-Miyaura coupling reactions. Nevertheless, the nature and activity of the nickel boride could be examined with the more sensitive Suzuki-Miyaura reaction. We found, that exposing the catalyst to
air and oxygen significantly shortens the lifetime of nickel boride; this should be considered while using the catalyst for different reactions. As an alternative, nickel boride might be an efficient catalyst in reductive coupling reactions, but this theory needs further investigations.
4 References


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of Alkyl Iodides, Bromides, and Chlorides’ *Journal of the American Chemical Society* 131(34): 12078-12079.


A Appendix

A.1 General methods and chemicals

All chemicals were purchased from commercial suppliers with the highest available purity. Solvents for workup and flash column chromatography were of analytical grade and used as supplied. Microwave reactions were carried out using Biotage Initiator Classic reactor. All reactions were set up in Biotage Microwave Reaction Vials (if not stated otherwise). Thin layer chromatography was carried out using pre-coated Merck silica gel 60 F254 aluminium-backed plates (0.25 mm), and visualized by UV light ($\lambda = 254$ nm). Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm). NMR spectroscopy was carried out using Bruker Ascend 400 spectrometer (400 MHz). Gas chromatography was carried out with Agilent Technologies 6850A gas chromatograph and a 6850 automatic sampler.

A.2 Preparations of metal borides

A.2.1 Method A

Metal chloride hexa- or tetra hydrate (2.0 mmol) was dissolved in anhydrous methanol (100 ml) in inert atmosphere. The solution was stirred and degassed. Sodium borohydride (4.0 mmol, 2 eq.) was added, while instantaneous gas evolution was observed with the precipitation of the black powder. The suspension was stirred, the gas evolution ceased in a few minutes. The suspension was filtered, washed with prepurged water and acetone, and dried in vacuum.

A.2.2 Method B

Metal chloride hexa- or tetra hydrate (2.0 mmol) was dissolved in prepurged water (100 ml) in inert atmosphere. The solution was stirred and degassed. Sodium borohydride (4.0 mmol, 2 eq.) was added, while instantaneous gas evolution was observed with the precipitation of the black powder. The suspension was stirred, the gas evo-
lution ceased in a few minutes. The suspension was filtered, washed with acetone and methanol and dried in vacuum.

A.2.3 Preparation of nickel boride on filtering paper

Nickel chloride hexahydrate (0.2 mmol) was dissolved in methanol (0.5 ml) and injected onto a 0.5 x 0.5 cm filtering paper, and the paper was dried on air. Sodium borohydride (4.0 mmol, 2 eq.) was dissolved in methanol (0.5 ml) and injected on the dried paper, while instantaneous gas evolution was observed and the surface of the paper was covered with the black catalyst.

A.3 Sonogashira coupling

A.3.1 Characterisation of 4-methylbiphenyl

$^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm): 7.53 (d, 2H), 7.51 (d, 2H), 7.44-7.42 (t, 2H), 7.34-7.33 (m, 3H), 2.37 (s, 3H).

A.3.2 Characterisation of 1,4-diphenylbutadiyne

$^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm): 7.40-7.32 (m, 6H), 7.55-7.53 (m, 4H).

A.4 Glaser coupling

A.4.1 Solvent screening method

In solvent (1 ml), phenylacetylene (0.25 mmol) was dissolved in a microwave vial, potassium tert-butoxide (0.5 mmol, 2.0 eq.) and pre-prepared nickel boride (3.75 mg, 0.03 mmol, 0.12 eq.) were added to the solution. After 24 hours of stirring at room temperature, the mixtures were analyzed with TLC (eluent: hexane).
A.4.2 GC method

Table A.1: GC method for the Glaser coupling

<table>
<thead>
<tr>
<th>Oven Ramp</th>
<th>°C/min</th>
<th>Next °C</th>
<th>Hold min</th>
<th>Run Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>80</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Ramp 1</td>
<td>20.00</td>
<td>120</td>
<td>3.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Ramp 2</td>
<td>40.00</td>
<td>250</td>
<td>8.00</td>
<td>16.25</td>
</tr>
<tr>
<td>Post Run</td>
<td>50</td>
<td>0.00</td>
<td>16.25</td>
<td>16.25</td>
</tr>
</tbody>
</table>

A.4.3 GC chromatograms of the reaction components

Phenylacetylene (Starting material)
1,4-diphenylbutadiyne (Product)

Anisole (standard)
A.4.4 GC calibration curve for 1,4-diphenylbutadiyne (product)

Table A.2: Calibration of 1,4-diphenylbutadiyne (p) with anisole (a) as standard

<table>
<thead>
<tr>
<th>Entry</th>
<th>np/na</th>
<th>Concentration</th>
<th>Ap/Aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00</td>
<td>0.00 g/dm³</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>30.2 g/dm³</td>
<td>0.68</td>
</tr>
<tr>
<td>3</td>
<td>1.01</td>
<td>60.4 g/dm³</td>
<td>1.31</td>
</tr>
<tr>
<td>4</td>
<td>1.48</td>
<td>89.0 g/dm³</td>
<td>1.93</td>
</tr>
<tr>
<td>5</td>
<td>1.99</td>
<td>119.2 g/dm³</td>
<td>2.51</td>
</tr>
</tbody>
</table>

\[ y = 0.7886x - 0.0177 \]
\[ R^2 = 0.9993 \]

Figure A.1: 1,4-Diphenylbutadiyne calibration curve with anisole as standard
A.5  Suzuki-Miyaura coupling

A.5.1  Method for the catalytic investigations of metal borides

Metal boride (15 mg, 0.12 mmol, 0.12 eq.), phenylboronic acid (1.5 mmol, 1.5 eq.) and potassium tert-butoxide (3.0 mmol, 3.0 eq.) were added to a microwave vial. Ethanol (1 ml) was added and the phenylboronic acid dissolved. 3-Iodotoluene (1.0 mmol) was added with a Hamilton-syringe. An oil bath was heated to 110 °C. The reaction was carried out for 24 hours. The reaction mixture then was analyzed with TLC (eluent: hexane) and was filtered through celite than evaporated. Flash column chromatography (eluent: hexane) was used to purify the product.

A.5.2  Characterisation of 3-methylbiphenyl

$^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm): 7.69-7.67 (d, 2H), 7.54-7.48 (d, 2H), 7.44-7.40 (t, 2H), 7.26-7.25 (m, 3H), 2.51 (s, 3H).

A.5.3  GC method

<table>
<thead>
<tr>
<th>Oven Ramp</th>
<th>°C/min</th>
<th>Next °C</th>
<th>Hold min</th>
<th>Run Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>100</td>
<td>5.00</td>
<td>5.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Ramp 1</td>
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<td>150</td>
<td>0.00</td>
<td>15.00</td>
</tr>
<tr>
<td>Ramp 2</td>
<td>10.00</td>
<td>220</td>
<td>5.00</td>
<td>27.00</td>
</tr>
<tr>
<td>Post Run</td>
<td>50</td>
<td>0.00</td>
<td>27.00</td>
<td>27.00</td>
</tr>
</tbody>
</table>
A.5.4 GC chromatograms of the reaction components

3-Iodotoluene (starting material)

3-Methylbiphenyl (product)
### A.5.5 GC calibration curves

Table A.4: Calibration of the 3-iodotoluene (s) and the 3-methylbiphenyl (p) with dodecane (d) as standard

<table>
<thead>
<tr>
<th>Entry</th>
<th>n_s/n_d</th>
<th>n_p/n_d</th>
<th>A_s/A_d</th>
<th>A_p/A_d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
<td>1.29</td>
</tr>
<tr>
<td>2</td>
<td>0.30</td>
<td>0.70</td>
<td>0.19</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>0.50</td>
<td>0.29</td>
<td>0.71</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0.60</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0.60</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>0.60</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>7</td>
<td>0.70</td>
<td>0.30</td>
<td>0.41</td>
<td>0.35</td>
</tr>
<tr>
<td>8</td>
<td>1.00</td>
<td>0.00</td>
<td>0.59</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Figure A.2: 3-iodotoluene calibration curve

Figure A.3: 3-methylbiphenyl calibration curve
A.5.6 Biphenyl GC calibration

Table A.5: Calibration of the biphenyl (b) with dodecane (d) as standard

<table>
<thead>
<tr>
<th>Entry</th>
<th>n_p/n_a</th>
<th>A_b/A_d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.005</td>
<td>0.0094</td>
</tr>
<tr>
<td>2</td>
<td>0.010</td>
<td>0.0171</td>
</tr>
<tr>
<td>3</td>
<td>0.015</td>
<td>0.0249</td>
</tr>
<tr>
<td>4</td>
<td>0.030</td>
<td>0.0465</td>
</tr>
<tr>
<td>5</td>
<td>0.040</td>
<td>0.0599</td>
</tr>
<tr>
<td>6</td>
<td>0.050</td>
<td>0.0734</td>
</tr>
</tbody>
</table>
The coupling reaction of two equivalents of phenylboronic acid theoretically results in one mol of biphenyl thus multiplying the calculated nb/nd values with 2 and dividing the number by 1.5 (the initial ratio of the phenylboronic acid and the standard is 1.5:1.0) gives the GC yield of the homocoupling side reaction.

A.5.7 Solvent screening method

Nickel boride (1.5 mg, 0.012 mmol, 0.12 eq.), phenylboronic acid (0.15 mmol, 1.5 eq.) and potassium tert-butoxide (0.30 mmol, 3.0 eq.) were added to a 2 ml sample vial with plastic cap. Solvent (400 µl) was added and the phenylboronic acid dissolved. 3-Iodotoluene (0.10 mmol) was added with a Hamilton-syringe. A heating block was heated to 110 °C. The reaction was carried out for 24 hours. The reaction mixture was passed through a silica plug and analyzed with GC.

A.5.8 Preparation of the phenylboronic acod pinacol ester

To a solution of phenylboronic acid (1 mmol) in acetonitrile (4 ml) was added a solution of FeCl₃ (0.05 mmol, 0.05 eq.) in water (1 ml), imidazole (3 mmol, 3 eq.)
and pinacol (1 mmol, 1 eq.). The resulting cloudy orange mixture was stirred at room temperature for 30 minutes. The reaction was then diluted with water (5 ml) and extracted with diethyl ether (3 x 8 ml). The combined organic extracts were dried (sodium sulphate) and concentrated in vacuum. The resulting oil was then purified by flash column chromatography (eluent: hexane), affording the pure product. 

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 7.80-7.78 (d, 2 H,), 7.45-7.42 (m, 1 H), 7.36-7.33 (m, 2 H), 1.32 (s, 12 H).

### A.5.9 Method for microwave reactions

Nickel boride (1.5 mg, 0.012 mmol, 0.12 eq.) and potassium tert-butoxide (0.30 mmol, 3.0 eq.) were added to a microwave vial. Phenylboronic acid (0.15 mmol, 1.5 eq.) or phenylboronic acid pinacol ester (0.15 mmol, 1.5 eq.) was added to the solvent (400 µl, ethanol or butanol). 3-Iodotoluene (0.10 mmol) and dodecane (0.10 mmol) was added with a Hamilton-syringe. The reaction mixture was passed through a silica plug and analyzed with GC.