

Cross-coupling reactions of organoborons with organic halides

Pro Gradu Thesis

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Abstract

In the literature section the overview of the Suzuki coupling with boronic derivatives is presented and concentrated on the properties and design of boronic derivatives. The articles used were located by using on-line databases (SciFinder, National Electronic Library Interface, NELLI, Web of Science, WOS) and downloaded from the libraries of Jyväskylä University and Tampere University of Technology.

The experimental section presents the attempted syntheses for organic molecules, namely arylbenzothiazole derivatives which can be potentially used in organic solar cells. Dr. Alexander Efimov designed the target molecules and the synthesis route via five stages.

Due to the limited time available and potential suitability for tempted use, only syntheses of molecules **229** and **232** were attempted.

Target molecule **229**:

The synthesis of the molecule **229** failed.

Target molecule **232**:

The syntheses of arylboronic pinacol ester **220** and 5-bromo-2-(benzyloxy)-benzothiazole **226** were successful and molecule **232** was successfully synthesized.

Foreword

The articles studied were located by the on-line resources using the SciFinder Scholar program and NELLI (National Electronic Library Interface) portal and downloaded from the libraries of Jyväskylä University and Tampere University of Technology.

The experimental section was carried out in the spring-summer 2011 at Tampere University of Technology, Department of Chemistry and Bioengineering. The counselors and supervisors for the thesis were Academy Professor Kari Rissanen (Department of Chemistry, Section of Organic Chemistry at Jyväskylä University) and Dr. Alexander Efimov (Department of Chemistry and Bioengineering at Tampere University of Technology).

First of all I thank Academy Professor Kari Rissanen and Professor Helge Lemmetyinen for giving me the opportunity to work in the Department of Chemistry and Bioengineering. I'd also like to thank my supervisor Dr. Alexander Efimov for help both in theoretical and practical issues as well as all the staff at the department.

I am thankful for my family and friends for encouragement and support during my studies. Risto, my fiancé, I am grateful for your support and loving me as I am.

Tampere, 1.9.2011

Petra Lindholm

Table of Contents

ABSTRACT	I
FOREWORD	II
TABLE OF CONTENTS	III
ABBREVIATIONS	VI
<u>LITERATURE SECTION</u>	
1 PREFACE	1
2 SUZUKI COUPLING.....	2
2.1 Overview	2
2.2 Reactions with aryl halides.....	3
2.3 Reactions with triflates.....	4
2.4 Types of boronic derivatives	6
2.5 N-, O-, S-arylation.....	7
3 BORONIC ACID DERIVATIVES FOR CROSS-COUPLING REACTIONS.....	9
3.1 Properties of boronic acids.....	9
3.2 Preparation of boronic acids and their esters.....	11
3.3 Reaction conditions	15
3.3.1 Base.....	16
3.3.2 Solvents.....	20
3.3.3 Functional groups.....	20
3.3.4 Stability	21
3.4 Ketone synthesis.....	22
3.5 Cross-coupling of chiral boronic esters.....	24
3.6 Green cross-coupling chemistry.....	25
3.7 Microwave-assisted reactions.....	27
4 REACTION MECHANISM OF ORGANOBORONS.....	29
4.1 Catalytic cycle	29
4.2 Catalysts	31
4.2.1 Palladium catalysts with phosphate ligands.....	32
4.2.2 Palladium catalysts without phosphate ligands.....	34
4.2.3 Platinum catalysts	36

4.2.4 Nickel catalysts	37
4.2.5 Titanium catalysts	38
4.3 Ligands	40
4.3.1 Amine-based ligands.....	46
4.3.2 Porphyrin ligands	47
5 SIDE REACTIONS.....	49
5.1 Overview	49
5.2 Homocoupling induced by oxygen.....	51
5.3 Dehalogenation.....	53
5.4 <i>ipso</i> -Coupling	54
6 SUMMARY.....	55
<u>EXPERIMENTAL SECTION</u>	
7 THE PLAN FOR SYNTHESIS	57
8 REAGENTS AND EQUIPMENT	59
8.1 Reagents and solvents	59
8.1.1 Drying of potassium acetate.....	59
8.1.2 Recrystallation of palladium catalyst.....	60
8.2 Equipment	60
9 SYNTHETIC MECHANISMS.....	61
9.1 Borylation	61
9.2 Preparation of benzothiazole	62
9.3 Benzyl protection	63
9.4 Suzuki coupling	64
9.5 Deprotection by Pd/C reduction	66
10 THE SYNTHESSES.....	67
10.1 N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	67
10.2 N,N-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline.....	68
10.3 2-(1,3-Benzothiazol-2-yl)-4-bromophenol.....	70
10.4 2-[2-(Benzyloxy)-5-bromophenyl]-1,3-benzothiazole	71
10.5 3'-(Benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-dimethyl-[1,1'-biphenyl]-4-amine	73
10.6 3'-(Benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine	74

11 SUMMARY	80
12 SYNTHESIZED MOLECULES	82

REFERENCES

APPENDICES

Abbreviations

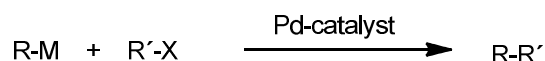
acac	acetylacetone
Bn	benzyl
dba	dibenzylideneacetone
bpy	2,2'-bipyridine
BuPA ₂	di-1-adamantyl- <i>n</i> -butylphosphin
Cp	pentamethylcyclopentadienyl
Cy	cyclohexyl
dppb	1,4-bis(diphenylphosphinyl)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphinyl)propane
DCM	dicloromethane
DMA	dimethylacetamide
DME	dimethyl ether
DMSO	dimethyl sulfoxide
Et ₃ N	triethylamine
HBpin	pinacolborane
KOAc	potassium acetate
LDA	lithium diisopropylamide
MS	mass spectrum
MSCl	mesylchloride
NMR	nuclear magnetic resonance
OTf	triflate
PdCl ₂ (dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PPA	polyphosphoric acid
ppm	parts per million
r.t.	room temperature
SDS	sodium dodecyl sulfonate
<i>t</i> -BuOK	potassium <i>tert</i> -butoxide
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAA	tetra- <i>n</i> -butylammonium acetate

TMEDA	tetramethylethylenediamine
THF	tetrahydrofuran
Å	Ångström, 10^{-10} m

1 Preface

The aim of the literature section of the thesis was to investigate the palladium-catalyzed cross-coupling reaction of organoboron compounds with aryl halides. The review was to focus on the mechanism of cross-coupling reaction, the reaction conditions and the novel applications of organoboronic derivatives with aryl halides and other coupling partners. Reactions catalyzed by the palladium catalysts and their ligands were the main focus but an overview of the more uncommon catalysts was studied too.

Palladium-catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates is a general and efficient method for the formation of carbon-carbon bonds.^{1,2} The reaction is called Suzuki coupling or Suzuki-Miyaura coupling after the scientists who first found this versatile reaction. The cross-coupling reaction proceeds via general mechanism shown in scheme 1.



Scheme 1. The general mechanism of the Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. M=boron derivative, X=halide, R=e.g. aryl or alkenyl.²

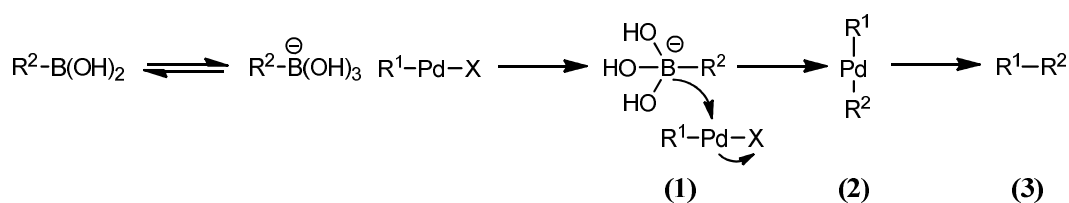
The Suzuki-Miyaura cross-coupling has several advantages since mild reaction conditions can be used.^{1,2} The reagents for the reaction are easily available and the reaction proceeds in the presence of wide variety of functional groups. Several organometallic reagents are used for analogous cross-coupling reactions but organoboron compounds are interesting reagents because they are thermally stable, inert to water and oxygen and thus easy to handle. In addition, inorganic by-products are non-toxic which makes the coupling reaction suitable also for industrial processes.

2 Suzuki coupling

2.1 Overview

Suzuki-Miyaura reaction is one of the most popular reactions in modern organic chemistry.³ Generally, it is a palladium-catalyzed process of cross-coupling of an organoboron compound with an organic halide which produces a bis-aryl via direct C-C bond formation. The reaction has plenty of applications in organic syntheses, material and medicinal chemistry and it is still an area of intense research. The reaction mechanism has been largely studied and reviewed but the organic partners involved in the reaction have had much less attention. One common group of substrates of Suzuki-Miyaura cross-coupling reactions are boronic acids and esters.

The general palladium-catalyzed reaction mechanism involves (1) an oxidative addition of the halogenated species to the palladium catalyst, (2) transmetallation step where the organic group of the activated boron species is transferred to the metal, and (3) the reductive elimination step that yields the coupling product and regenerates the catalyst (scheme 2).⁴ The boron atom must be activated with a base in the transmetallation step to increase its nucleophilicity and give a clean reaction. Even though the reaction's catalytic cycle is known, the role of the base in the mechanism is not fully understood.



Scheme 2. Mechanism of palladium-catalyzed cross-coupling reaction with oxidative addition, transmetallation and reductive elimination steps.⁵

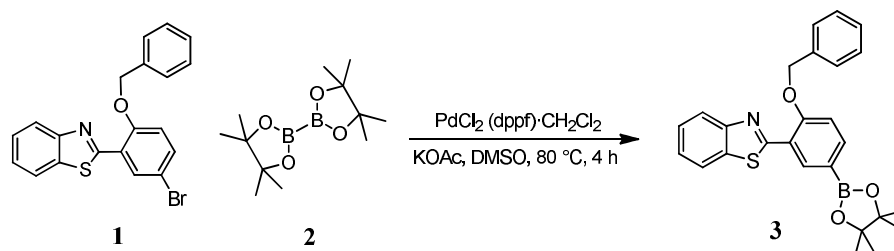
Organoboron compounds are highly electrophilic but the organic groups on boron are weakly nucleophilic.² This limits their use of reagents for the ionic reactions. The negatively charged base activates the boron atom, increases its nucleophilicity and enables it to transfer the organic group on boron to the adjacent positive center. Organoboron com-

pounds are reactive enough for the transmetalation to other metals, even though intermolecular transfer reaction, such as Grignard-like reaction, is fairly rare.

2.2 Reactions with aryl halides

Even though catalytic species have a great effect on the catalytic reaction, also the nucleophilic coupling partner is important.^{3,6} A wide variety of organometallic reagents have been explored^{2,7} but organic halides and pseudohalides, such as triflates, are the most useful electrophilic counterparts.

Aryl halides used in Suzuki reactions are often bromides and iodides. Also aryl triflates are often used.^{1,8} For example, substituted benzothiazoles can be prepared by Suzuki-Miyaura coupling reaction of an arylboronic derivative and a bromoaryl as shown in scheme 3. Aryl chlorides do not participate in coupling reactions unless they are in conjunction with electron-deficient groups.



Scheme 3. Suzuki-Miyaura cross-coupling reaction of bromobenzothiazole and bis(pinacolato)diboron $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (5 mol %) as catalyst KOAc (2 equiv.) as base and DMSO as solvent at $80\text{ }^\circ\text{C}$ for 4 hours.⁸

The nature of the substituents in the aromatic ring determines which components should be used in Suzuki-Miyaura cross-coupling reaction.⁸ For example, pinacolborane derivatives with electron-withdrawing aryl are difficult to synthesize and not commercially available.

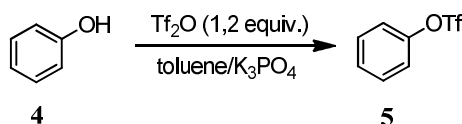
The cross-coupling reaction of bromobenzothiazole **1** and bis(pinacolato)di-boron **2** as reactant, gives borylated product **3** and only a small amount of dimer (scheme 3).⁸ Long

reaction times are often recommended but with suitable amount and variation of catalyst, solvents and bases only few hours of reaction time may be enough. To avoid dimerization, a solvent with high polarity, such as DMSO, 1,4-dioxane or THF, and a weak base (Et₃N, KOAc) need to be chosen.

2.3 Reactions with triflates

Aryl triflates are widely used as synthetic precursors in cross-coupling reactions and are more stable to air and moisture than boronic acids.^{9,10} Conventional preparation of triflates involves treatment of the corresponding phenol with triflic anhydride in the presence of a base, such as pyridine or triethylamine.

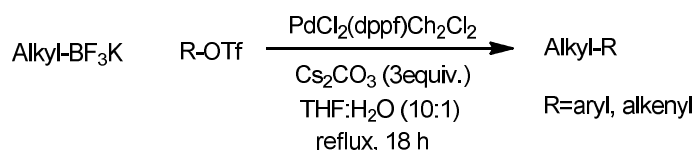
Because the residual ammonium salts interfere the catalytic process, another method has been developed, as presented in scheme 4.⁹ Phenol **4** is triflated **5** in good yield in biphasic mixture of toluene and 30 % aqueous K₃PO₄. Reaction proceeds with wide variety of phenol substituents. In most cases the reactions are instantaneous and can be performed in an open-air flask.



Scheme 4. Formation of triflate. Reaction is conducted at 0 °C, Tf₂O (1,2 equiv.) added slowly to biphasic mixture of toluene/K₃PO₄ (3 equiv.).⁹

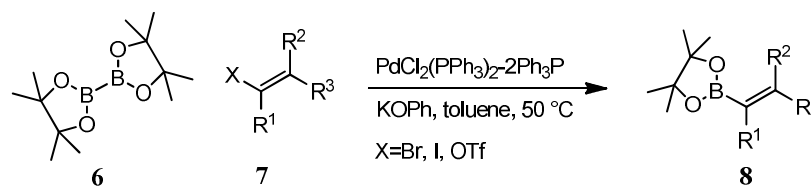
Aryl triflates couple with arylborates under neutral conditions in the presence of a palladium(0) catalyst and form a new bond between carbon atoms.¹¹ The reaction proceeds in the presence of variety of functional groups on the aryl triflates, such as alcohol, ester, nitro, acetal, ketone and aldehyde groups.

Triflates are base sensitive and thermally labile and therefore cross-coupling reactions of arylboronic acids with triflates are possible in mild reaction conditions.^{1,12} A catalyst, such as PdCl₂(dppf), weak, nonaqueous basic conditions, such as powdered K₃PO₄ and polar solvents, such as THF or dioxane, provide suitable conditions for cross-coupling reaction with triflates. For example, cross-coupling reactions of substituted potassium alkyltrifluoroborates and aryl halides or triflates proceed readily with palladium catalyst (scheme 5).



Scheme 5. Cross-coupling reaction of potassium alkyltrifluoroborates with aryl or alkenyl triflates, using PdCl₂(dppf)·CH₂Cl₂ (9 mol %) as a catalyst in the presence of base, Cs₂CO₃ or Et₃N. Alkyl: NC(CH₂)₅, Br(CH₂)₆, MeCO(CH₂)₄, BzO(CH₂)₇, Ph(CH₂)_{n(1-3)}, R=aryl or alkenyl.¹²

For triflates conjugated to a carbonyl group a suitable base is K₂CO₃ suspended in dioxane but for unconjugated triflates or bromides the best results are gained with KOPh suspended in toluene.¹³ As an example, coupling reaction of bis(pinacolato)diboron **6** with 1-alkenyl halides or triflates **7** is a one-step synthesis of 1-alkenyboronic esters **8** (scheme 6).

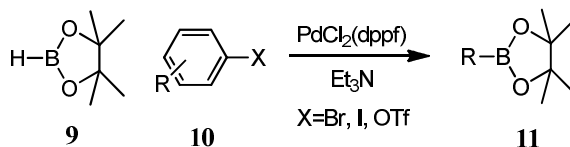


Scheme 6. Palladium-catalyzed coupling reaction of bis(pinacolato)diboron, pin₂B₂, with 1-alkenyl halides or triflates was performed in toluene at 50 °C in the presence of KOPh (1.5 equiv) and PdCl₂(PPh₃)₂·2PPh₃ (3 mol %) for 2-5 h. R=aryl or alkenyl.¹³

2.4 Types of boronic derivatives

Classical Suzuki-Miyaura cross-coupling reaction is done with arylboronic acids, $\text{ArB}(\text{OH})_2$.¹⁴ Other derivatives are used as well, such as aryl boronic esters $\text{ArB}(\text{OR})_2$, for example, $\text{ArB}(\text{OMe})_2$ and $\text{ArB}(\text{OEt})_2$. Aryl boronic acid pinacol esters and pinacolboranes, HBpin, are also commonly used boronic ester derivatives in cross-coupling reactions.

Pinacolborane is an economical boron nucleophile for the borylation of aryl and 1-alkenyl halides or triflates.¹⁴ An example of palladium-catalyzed cross-coupling reaction of pinacolborane **9** with aryl halide or triflate **10** for preparing arylboronic esters **11** is shown in scheme 7 below.

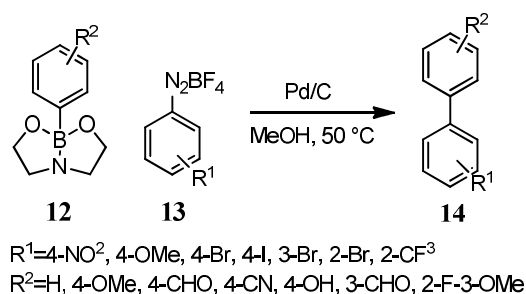


Scheme 7. Palladium-catalyzed coupling reaction of pinacolborane (1,5 mmol) and aryl halide or triflates (1 mmol) with Pd-catalyst and Et_3N (3 mol %) at 80 °C for 2 hours in DMF or dioxane (4 ml). $\text{X} = \text{Br}, \text{I}, \text{OTf}$.¹⁴

The proposed mechanism goes via displacement of Pd-X with a nucleophilic boryl anion ($\text{Et}_3\text{NH}^+\text{Bpin}^-$) or metathesis between H-Pd-Bpin and Ar-X and leads to formation of an Ar-Pd-Bpin intermediate.¹⁴ The amine Et_3N prevents the production of Ar-H and takes part in the B-C bond formation. Various reducible functional groups remain intact during the reaction at 80 °C even though some undesirable dehalogenation products are formed (Ar-H , 10-20 %).

Dioxazaborocanes are boronic esters prepared from diethanolamine and boronic acids or esters.³ Dioxazaborocanes are able to couple with diazonium salts without external activation of the boronic acid. They are solid, stable and easy to purify and handle. Dioxazaborocanes **12** can be used in palladium-catalyzed cross-coupling reactions, for example, with tetrafluoroborate diazonium salts **13**, as shown in scheme 8. They do not require the use of a large excess of the boron partner which is a significant advantage. Only 1,2 equiv. of bo-

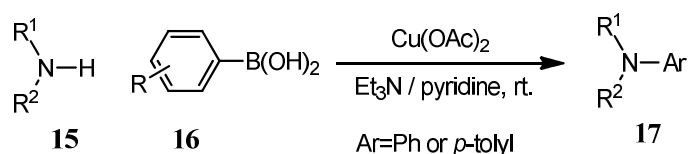
ronic partner is required compared to common 1,5-2 equiv. A good yield can be achieved in biaryl **14** synthesis with electron-rich and electron-poor dioxazaborocanes when reacting with electron poor bromoarenes. Coupling with more electron-rich bromides occurs less efficiently. However, the use of dioxazaborocanes in Suzuki-Miyaura reaction with aryl halides is quite rare and limited to the coupling of pyridyl dioxazaborocanes.



Scheme 8. Palladium-catalyzed cross-coupling reactions with tetrafluoroborate diazonium salts without base.³

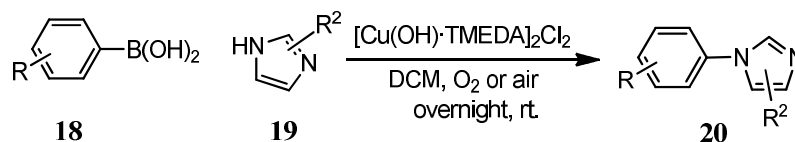
2.5 N-, O-, S-arylation

N-aryl compounds are required in the pharmaceutical and material sciences.¹⁵ C-N bond cross-coupling reactions of NH-containing substrates **15**, such as imidazoles **19** with arylboronic acids **16** give N-aryls **17**, such as N-arylimidazole **20**. The reaction can be performed at mild reaction conditions in the presence of oxygen, $\text{Cu}(\text{OAc})_2$ catalyst and an amine base, such as Et_3N or pyridine (schemes 9 and 10).



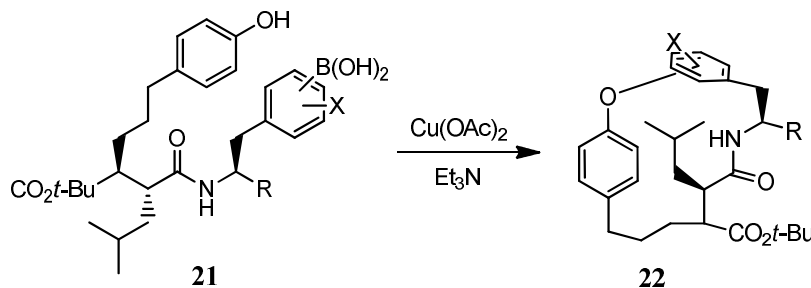
Scheme 9. N-arylation of arylboronic acid (2 equiv.) and NH-substrate (1 equiv.) in DCM or 1,4-dioxane at room temperature overnight with amine base, such as Et_3N or pyridine (2-5 equiv.), $\text{Cu}(\text{OAc})_2$ as catalyst (1,5 equiv.) and 4 Å molecular sieves.¹⁶

The reaction mechanism goes via formation of $[\text{Cu}(\text{II})\text{OAc}(\text{NR}_2)]$, transmetalation of arylboronic acid to $[\text{Cu}(\text{II})\text{Ar}(\text{NR}_2)]$, oxidation of $\text{Cu}(\text{II})$ species to $[\text{Cu}(\text{III})\text{Ar}(\text{NR}_2)]$ by air and reductive elimination to yield $\text{Cu}(\text{I})$ and ArNR_2 .¹⁶



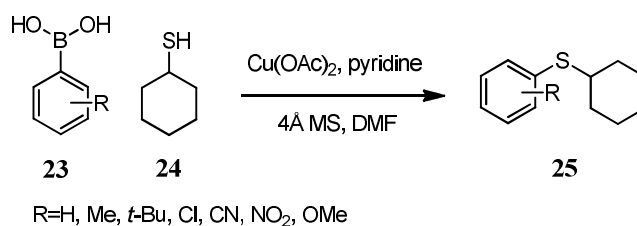
Scheme 10. Diamine-copper complex, $[\text{Cu}(\text{OH})\cdot\text{TMEDA}]_2\text{Cl}_2$ -catalyzed coupling reaction of arylboronic acids with imidazoles in DCM at room temperature.¹⁶

Under similar conditions as those used for N-arylation, arylboronic acids undergo O-arylation of phenols, such as phenylboronic acid pseudopeptides **21** to prepare macrocyclic biphenyl ether hydroxamic acids **22** (scheme 11).¹⁷ Only mild conditions are required to give amino acids without racemization with a weak base at room temperature.



Scheme 11. Intramolecular O-arylation of phenols with phenylboronic acid catalyzed by copper acetate.¹⁷

In contrast to previous reactions, the reaction of alkylthiols at temperature lower than $70\text{ }^\circ\text{C}$ is very slow, up to 1-2 days.¹⁸ That is probably caused by the inert gas atmosphere in order to prevent air-oxidation of thiols to dithianes. As presented in scheme 12, the cross-coupling reaction of aryl boronic acid **23** and cyclohexanethiol **24** to prepare aryl alkyl sulfides **25** can be carried out by heating at reflux in DMF.

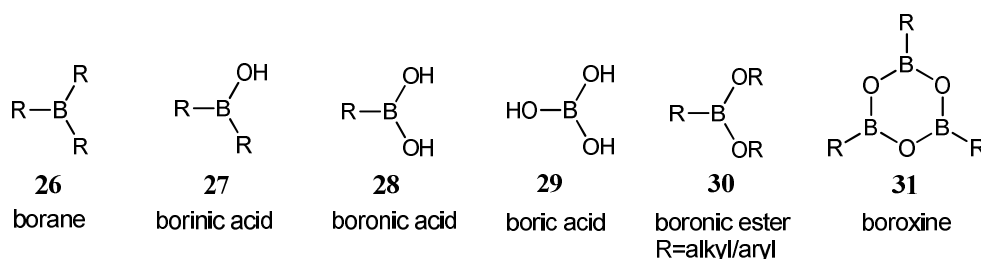


Scheme 12. Cross-coupling of aryl boronic acid (2 equiv.) and cyclohexanethiol (1 equiv.) by heating at reflux in DMF under argon atmosphere with Cu(OAc)₂ (1,5 equiv.), pyridine (3 equiv.) and 75 wt % of 4 Å molecular sieves.¹⁸

3 Boronic acid derivatives for cross-coupling reactions

3.1 Properties of boronic acids

Boronic acids are classified in subtypes as alkyl-, alkenyl-, alkynyl- and arylboronic acids.^{19a} The reactivity of boronic acids depends on the nature of the substituent directly bonded to boron. The crystals of alkyl or aryl boronic acids are orthorhombic and the asymmetric units of two distinct molecules are bound through a pair of O-H \cdots O hydrogen bonds. Structurally, boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent and two hydroxyl groups to fill the valences of the boron atom. Oxygenated organoboron compounds **26-31** are presented in scheme 13 below.

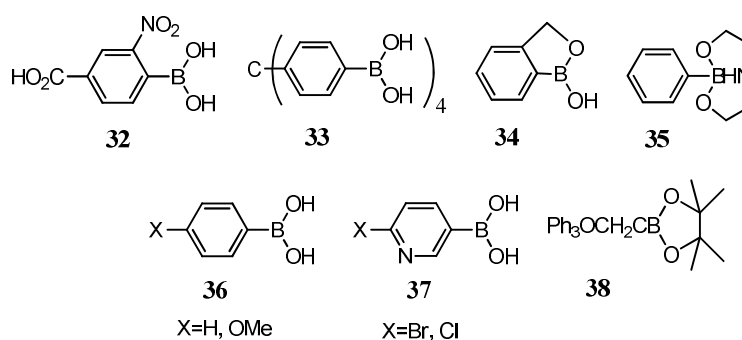


Scheme 13. Examples of oxygenated organoboron compounds.^{19a}

The dimeric ensemble is linked with hydrogen bonds to four similar units.^{19a} The geometry of boronic acid group is trigonal and fairly coplanar with an aryl group but it can be almost

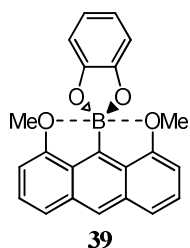
perpendicular to the aryl ring if there is steric strain caused by an *ortho*-substituent. The C-B bond of boronic acids and esters is slightly longer (1,55-1,59 Å) than typical C-C single bonds. The average bond energy (323 kJ/mol) is also slightly lower than that of C-C bonds (358 kJ/mol). The B-O distances of tricoordinate boronic acids are fairly short, about 1,35-1,38 Å and slightly larger than those of boronic esters.

Boronic acids and their esters may also coordinate basic molecules to complete borons octet and form stable tetracoordinated adducts.^{19a} Examples of boronic acid derivatives **32-38** are shown in scheme 14. When tetracoordinated, the B-O bond of boronic esters increases to about 1,43-1,47 Å and the bond becomes comparable to normal C-O ether linkages (~1,43 Å).



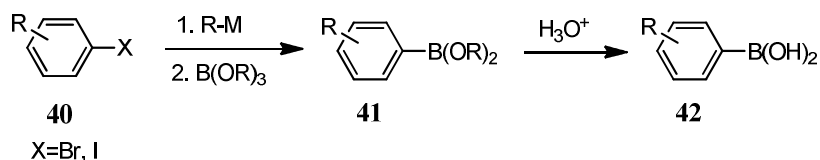
Scheme 14. Boronic acid derivatives.^{19a}

The bond strength is caused by conjugation between the lone electron pairs on the oxygen's and boron's vacant orbital and this explains a partial double bond character to the B-O linkage.^{19a} In rare cases boronic acid derivatives may be hypervalent. For example, in case of catechol ester **39**, the boron atom is pentacoordinated (scheme 15). Each ether group donates lone pair of electrons to both lobes of the vacant p-orbital of boron.

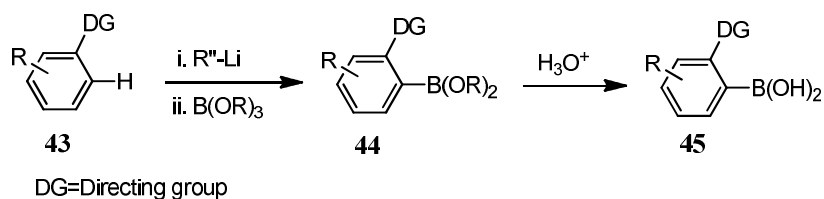
Scheme 15. Catechol ester.^{19a}

3.2 Preparation of boronic acids and their esters

Aryl boronic acids are the most popular class of boronic acids because of their role as cross-coupling partners for synthesis of biaryl units.^{19b} There are several methods available for the synthesis of arylboronic acids. The cheapest and the most common synthesis route to arylboronic acids **42** consist of the reaction of an organic halide **40**, an organometallic intermediate, such as R-Li or M-Mg and borate ester **41** at low temperature as shown in figure 16 below. The corresponding zinc and cadmium species can be used too but they are much less effective.

Scheme 16. Preparation of arylboronic acids where the organometallic intermediate M=Li or Mg.^{19b}

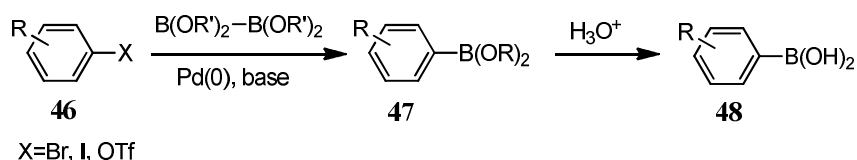
Aryls with an *ortho*-directing group **43** gives with organolithium reagents and electrophilic trialkylboronic esters arylboronic esters **44** and acids **45** via *ortho*-metallation intermediates as shown in scheme 17.^{19b}



Scheme 17. Reaction of borate and arylmetal intermediates by directed *ortho*-metallation.

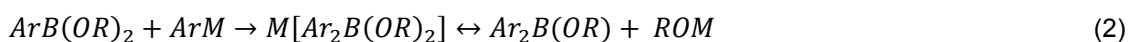
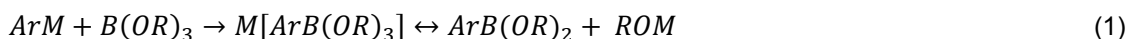
DG=*ortho*-directing group, such as ether, ester, amine, anilide or amide.^{19b}

Arylboronic esters **47** and acids **48** can be synthesized by coupling reaction of aryl halides or triflates **46** with diboron reagents catalyzed by transition metal catalyst (scheme 18).^{19b}



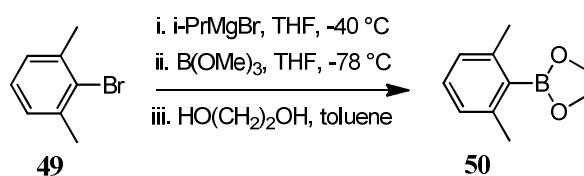
Scheme 18. Synthesis of arylboronic esters by coupling reaction between aryl halides or triflates and diboron reagents with a palladium catalyst.^{19b}

To minimize the amount of by-products, such as boronic acid, R_2BOH , and borane, BH_3 , phenyl magnesium bromide can be added to a solution of tri-*n*-butylborate at $-70\text{ }^\circ\text{C}$ when magnesium trialkoxyphenylborate salt is precipitated.^{19b} Instead of borates also boron trifluoride can be employed. The free boronic acid is obtained by work-up to hydrolyze the boronic ester substituents. Isolation of boronic acids by using aqueous work-up may give low yields because especially small or polar boronic acids tend to be water-soluble. Therefore, it is often better to isolate the product as an ester. The reaction between borates and arylmetal intermediates, Ar-Li and Ar-Mg, follows the following equilibria (equations 1 and 2).



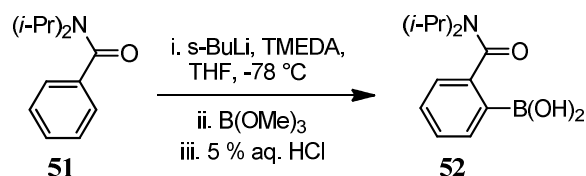
To minimize the formation of boronic acids and boranes by multiple displacements, organolithium can be added slowly to a solution of triisopropylborate in diethyl ether at $-78\text{ }^{\circ}\text{C}$.^{19b} Acid chlorides can be used to breakdown the lithium isopropylboronate salt and avoid the generation of free isopropanol and lithium chloride.

Arylboronic esters **50** can be synthesized also from aryl halide, such as 2-bromo-1,3-dimethylbenzene **49**, Grignard reagents and trimethylborate (scheme 19).^{19b} The method involves a nonaqueous workup procedure in which an aryl dimethoxyboronate evaporates to eliminate the excess of $\text{B}(\text{OMe})_3$. The residual solid is heated at reflux in solution of diol in toluene overnight. Also the pinacol ester can be obtained by electrophilic quenching of aryllithium intermediate with a pinacol borate ester.



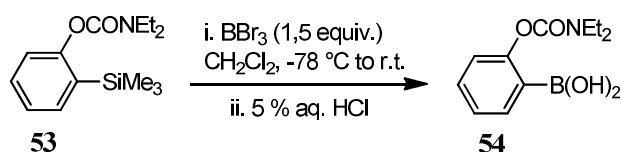
Scheme 19. An example of a preparative method to synthesize arylboronic ester by coupling of an aryl halide and a trimethylborate with Grignard reagent.^{19b}

Arylmetal intermediates can be prepared by metallation of the arenes functionalized with coordinating *ortho*-directing groups, such as amines, esters, anilides, esters and amides.^{19b} An example is shown in scheme 20 where an arene **51** with *ortho*-directing amide-group reacts first with *s*-BuLi. The resulting *ortho*-lithiated intermediates react with trimethyl borate and produce arylboronic acid **52** after acidic workup.



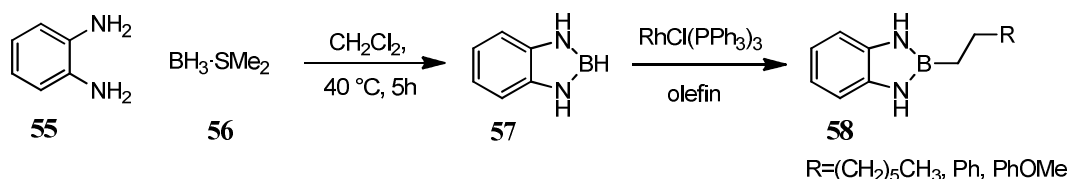
Scheme 20. N,N-bis(propan-2-yl)benzamide with *ortho*-directing amide-group yields *ortho*-arylboronic acid with trimethyl borate.^{19b}

Another method for preparing aromatic boronic acids involves a reaction between diaryl mercury compounds and boron trichloride.^{19b} However, for safety and environmental reasons, this method has remained unpopular. On the other hand, less dangerous trialkylsilanes **53** and stannanes can be transmetalated efficiently with a boron halide, such as boron tribromide. Upon acidic hydrolysis work up the aryl boron dibromides thus prepared can be converted into arylboronic acids **54** (scheme 21).



Scheme 21. Preparation of arylboronic acids from trialkylsilanes, such as 2-(trimethylsilyl)phenyl N,N-diethylcarbamate with boron tribromide.^{19b}

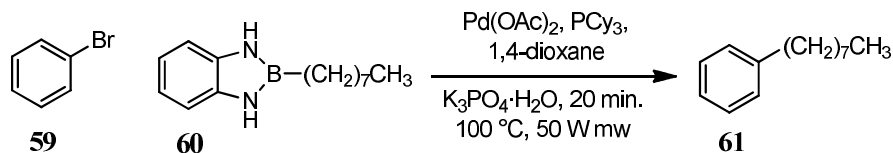
In cross-coupling reactions boronic acids and boronate esters are used almost exclusively and, for example, nitrogen-based organoboranes are not been investigated in Suzuki-Miyaura cross-coupling chemistry.²⁰ However, nitrogen-based organoboranes can be synthesized via rhodium-catalyzed hydroboration. The synthesis is performed in two steps as shown in scheme 22. First benzo-1,3,2-diazaborolane **57** is prepared from *o*-phenylenediamine **55** and borane-methyl sulfide complex **56**. The benzo-1,3,2-diazaborolane is easy to handle since it is not sensitive to air or moisture. Reaction with a suitable olefin in the presence of rhodium-catalyst gives the nitrogen-based organoborane product **58**.



Scheme 22. Synthesis of nitrogen-based organoboranes catalyzed by $\text{RhCl}(\text{PPh}_3)_3$.²⁰

Suzuki-Miyaura cross-coupling reactions with nitrogen-based diazaborolane compounds proceed easily with different aryl halides and with a variety of functional groups.²⁰ For ex-

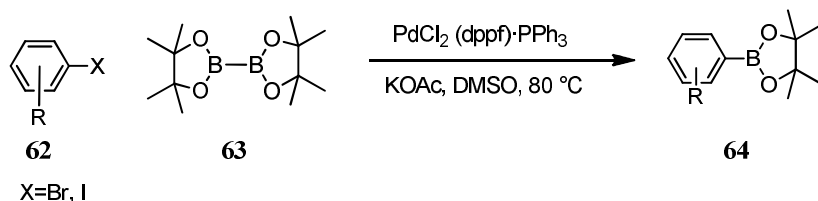
ample, a palladium-catalyzed cross-coupling reaction of bromobenzene **59** with 2-octylbenzo-1,3,2-diazaborolane **60** to prepare octylbenzene **61** is presented in scheme 23.



Scheme 23. A palladium-catalyzed cross-coupling reaction of bromobenzene (1 equiv.) with diazaborolane (1 equiv.) with Pd(OAc)₂ (4 mol %) and PCy₃ (8 mol %) catalyst. The reaction proceeds in closed vessel in 1,4-dioxane, K₃PO₄·H₂O (3 equiv.) as base, 50 W microwave irradiation at 100 °C for 20 minutes.²⁰

3.3 Reaction conditions

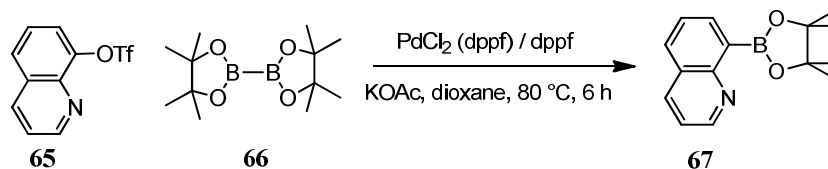
Suitable reaction conditions are highly dependent on the reactants and their properties.^{21,22} For example, arylboronic esters **64** can be prepared by palladium catalyzed cross-coupling reaction of the bis(pinacolato)diboron [(Me₄C₂O₂)BB(O₂C₂Me₄)] **63** with haloarenes **62**, as shown in scheme 24 below. PdCl₂(dppf)PPh₃ (3 mol %) is a suitable catalyst in the presence of KOAc (3 equiv.) in DMSO. An optimum reaction temperature is 80 °C.



Scheme 24. Coupling reaction of aryl halides (1 equiv.) with bis(pinacolato)diboron (1,1 equiv.) at 80 °C in DMSO with PdCl₂(dppf) (3 mol %) and KOAc (3 equiv.).²¹

The cross-coupling reaction of haloarenes with electron-donating substituents, such as NMe₂ or OMe is slow when bromides are involved and even 24 hours of reaction time is required.^{21,22} With iodides reaction proceeds faster and 2-6 hours of reaction time is suitable. However, electron-withdrawing substituents enhance the rate of coupling reaction and both aryl bromides and iodides react in 1-2 hours. Aryl triflates with electron-withdrawing

or -donating substituents, such as nitro, cyano, ester and carbonyl groups, react with diboron compounds readily. Reactions of more complex aryltriflates, such as 8-quinolyl triflates **65**, with bis(pinacolato)diboron **66** may require up to 39 hours of reaction time to prepare the borylated product **67**, as shown in scheme 25.



Scheme 25. Synthesis of 8-(tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline by coupling reaction of aryl triflates (1 equiv.) with bis(pinacolato)diborons (1,1 equiv.) at 80 °C in dioxane with PdCl₂(dppf) (3 mol %) dppf (3 mol %) and KOAc (3 mmol).²²

3.3.1 Base

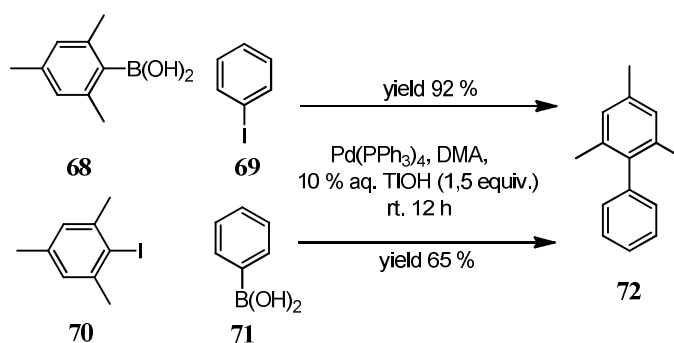
In the cross-coupling reactions of diboronic acids a suitable base is essential in order to achieve a successful reaction.²¹ The right base ensures high selectivity and high yield of the target product. Milder base, such as KOAc is preferable, since the stronger bases, such as K₃PO₄, K₂CO₃, promote further reactions of arylboronic esters with haloarenes and formation of high amounts of dimers.

In the catalytic cycle of the cross-coupling reaction, the transmetallation process is highly dependent on the organometallics and the conditions used in the reaction.²¹ Even though the transmetallation is not that well understood as oxidative addition and reductive elimination, it is thought that the base accelerates the transmetallation rate. The negatively charged base coordinates to the boron atom thus increasing its nucleophilicity for transmetallation to the palladium halide.

On the other hand, the base displaces the palladium halide to give an alkoxy-, hydroxyl- or acetoxopalladium(II) species in solution which transmetallate with organoboron compounds under neutral conditions.²¹ According to ¹B NMR analysis, it is clear that the latter

mechanism is predominant for acetopalladium(II) species. The high reactivity of oxopalladium complexes towards transmetallation with organoboron compounds is caused by the high reactivity of the Pd-O bond which consists of a mild acid and a strong base combination and the high oxophilicity of the boron center. In the transmetallation process first the coordination of the alkoxy ligand to the boron atom takes place and is followed by the transfer of the organic group from boron to the palladium atom.

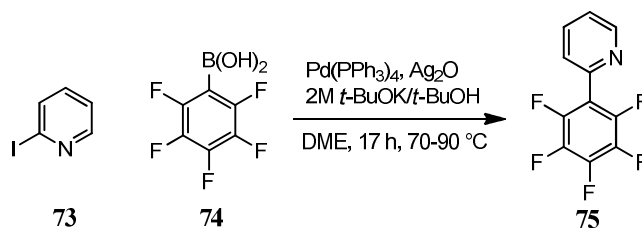
A negatively charged base, such as a solution of sodium or potassium carbonate, phosphate or hydroxide is needed in cross-coupling reactions of organoboronic acids with organic halides or triflates.²³ Na₂CO₃ is a mild base and is suitable for different kinds of coupling reactions of arylboronic acids. However, it is inefficient for sterically hindered reactants with several *ortho*-substituents. In the reactions of mesityl boronic acid **68** with iodobenzene **69** (scheme 26) the base has an effect on the order of reactivity: TlOH > Ba(OH)₂, Tl₂CO₃ > NaOH > Cs₂CO₃, K₃PO₄ > Na₂CO₃ > NaHCO₃. Ba(OH)₂ is usually used in syntheses of sterically hindered tri-*ortho*-substituted biaryls because of the poisonousness of the thallium bases. In addition, the more sterically hindered boronic acid gives better yield than the reaction with sterically hindered arylhalide, such as mesityl iodide **70** with phenyl boronic acid **71** to produce 1,3,5-trimethyl-2-phenylbenzene **72**.



Scheme 26. Cross-coupling reactions of mesityl boronic acid with iodobenzene and mesityl iodide with phenyl boronic acid with Pd(PPh₃)₄ (2 mol %) and 10 % aq. TlOH in DMA at room temperature for 12 hours.²³

Cesium bases, such as Cs₂CO₃ and CsOH, have a greater accelerating effect than sodium or potassium salts.²⁴ A combination of silver(I) salt and an inorganic base is advantageous too.

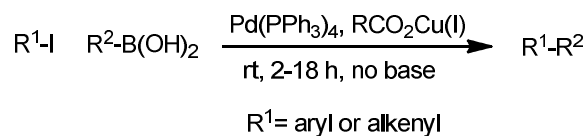
As an example, 2-(pentafluorophenyl)pyridine **75** is prepared by a cross-coupling reaction of 2-iodopyridine **73** and (pentafluorophenyl)boronic acid **74** (scheme 27). Ag₂O accelerates the coupling reaction over *ipso*-substitution.



Scheme 27. Synthesis of 2-(pentafluorophenyl)pyridine prepared via Suzuki-coupling by using Ag₂O to accelerate the rate of the reaction.²⁴

The effects of the bases can be roughly estimated by the basic strength and affinity of counter ions for halide ions.²⁵ Because the transmetalation involves nucleophilic displacement, the reaction can be fast for counter ions with a high stability constant for halide ions (Ag⁺>Tl⁺>>Ba²⁺>Cs⁺>K⁺). Hydroxyborate anion [R²B(OH)₃]M in alkaline solution is in equilibrium with a free organoboronic acid and its concentration increases as the basic strength increases (OH⁻>MPO₄⁻>MCO₃⁻>HCO₃⁻). The counter cation may have an effect on the solubility of [R²B(OH)₃]M in organic solvents.

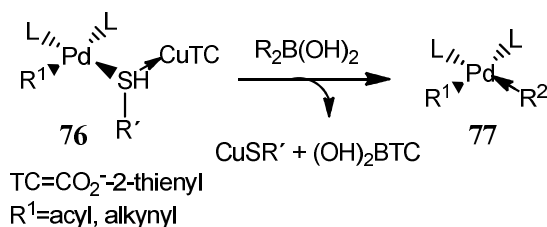
The cross-coupling reaction can be performed also under almost neutral conditions.²⁶ This is possible with copper carboxylate which mediates the cross-coupling reactions of organic sulfides and iodides at room temperature (scheme 28).



Scheme 28. Cross-coupling reaction of aryl or alkenyl iodide and boronic acid at room temperature mediated with copper carboxylate. No base is required.²⁶

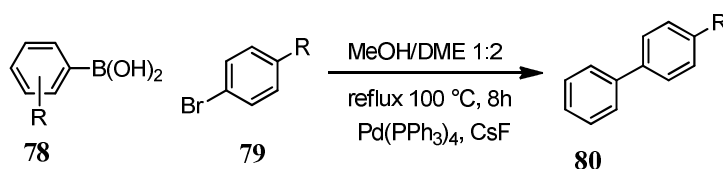
Since the reaction occurs in the absence of a base and at room temperature, it is a useful method for the construction of substrates bearing base-sensitive and thermally sensitive

moieties.²⁶ The reaction mechanism goes via chemoselective, copper carboxylate-mediated transmetallation from the boronic acid to the organopalladium thiolate intermediate **76** and transmetallation intermediate **77** (scheme 29).



Scheme 29. CuTC-mediated transmetallation of boron to palladium.²⁶

Cross-coupling reactions of 1-alkenylboronic acids with 1-halo-1-alkenes need a stronger base than reactions of arylboronic acids and the efficiency increases in the order of $\text{K}_2\text{CO}_3 < \text{K}_3\text{PO}_4 < \text{KOH} < \text{Ag}_2\text{O} < \text{TlOH}$.^{26,27} Aqueous TlOH has a strong accelerating effect even at room temperature. Mild fluoride salts can be used for base-sensitive reactants, such as Bu_4NF , Bu_4NHF_2 and CsF as in the reaction of aryl boronic acid **78** and aryl bromide **79** to yield biphenyl **80**, as shown in scheme 30.



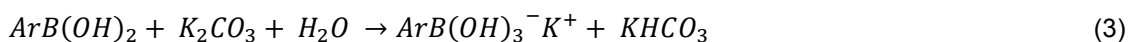
Scheme 30. Synthesis of methyl 4-phenylphenylacetate by using weakly basic fluoride salt, CsF (2 equiv.).²⁷

The reaction with sterically hindered halides or boronic acids is slow but proceeds in the presence of variety of functional groups.^{28,29} A combination of arylboronic esters and fluoride salts under anhydrous conditions is advantageous for boronic acids that are sensitive to hydrolytic B-C cleavage. Amines, such as Et_3N , are generally not as efficient as inorganic bases, but they can be used as well, typically at 100°C in DMF.

3.3.2 Solvents

The cross-coupling reactions of organoboronic acids with organic halides or triflates are often carried out in a two-phase system of organic and basic aqueous solutions and therefore phase transfer catalysts must be used.³⁰ In basic solutions esters may saponify, optically active compounds racemize and aldol condensations of carbonyl compounds may occur. These difficulties can be overcome by using bases in heterogeneous phase systems. For example, in a two-phase system of aqueous K_2CO_3 and toluene, esters remain intact and anhydrous K_2CO_3 suspended in toluene does not cause racemization of optically pure compounds.

Even though anhydrous inorganic bases are used with organic solvents, the presence of water may be preferred.³¹ Water accelerates the cross-coupling reactions of arylboronic acid with bromoarenes since the anion $ArB(OH)_3^-$ is 10^6 times more reactive than the neutral boronic acid in electrophilic reactions. In the cross-coupling reactions 1 mol of water and 1 mol of carbonate are required to activate the boronic acid. Another mol of each is used to neutralize boric acid, the coupling reaction by-product, as shown in equations 3 and 4.



The rate of the cross-coupling depends on solvent, since polar solvents increase the reaction rate.^{14,21} Reaction is accelerated in the order of toluene < dioxane < DMF < DMSO. However, DMF causes low yield and low selectivity because it induces decomposition of dialkoxyboranes to diborane, B_2H_6 .

3.3.3 Functional groups

The borylation reaction of haloarenes with electron-donating groups is slow for aryl bromides (24 hours) but notably faster for aryl iodides (2-6 hours).²¹ Electron-withdrawing

groups enhance the rate of cross-coupling with bis(pinacolato)diboron, and also aryl bromides can be used with shorter reaction times. Sterically hindered halides and heteroaromatic halides can be used as well for preparing arylboronates in high yields. Functional groups of the starting material, such as CO₂Et, COMe, CN and NHAc, among various other functional groups, do not disturb the reaction. Cross-coupling reaction is performed in mild conditions, thus several functional groups remain intact, unlike reactions using Grignard or lithium reagents which require protection of functional groups sensitive to these reagents.

Generally aryl iodides exhibit higher reactivity than aryl bromides or fluoroalkane sulfonates.¹⁴ However, the use of aryl fluoroalkane sulfonates, such as aryl triflates and nonaflates, in syntheses has some advantages due to their easy access from phenols. If aryl iodides or triflates have an electron-donating group, such as -Me or -OMe, the reaction goes smoothly at 80 °C. Borylation of aryl triflates with electron-withdrawing groups requires higher temperature (100 °C). The reactivity of bromides is lower. The borylation of aryl bromides with electron-donating groups goes smoothly at 100 °C but for the compounds with electron-withdrawing substituents the yield decreases remarkably. Strong electron-withdrawing groups, such as NO₂, cause reductive halogenations of aryl halides.

Under optimum conditions a wide variety of aryl triflates with electron-withdrawing or electron-donating groups can participate in the cross-coupling reaction.²² Functional groups, such as nitro, cyano, ester and carbonyl groups, are suitable as substituents for aryl triflates. *Ortho*-monosubstituted aryl triflates are suitable for the reaction but mesityl triflates are not. If the borylated carbon has a heteroatom next to it, increases the rate of the C-B bond formation.

3.3.4 Stability

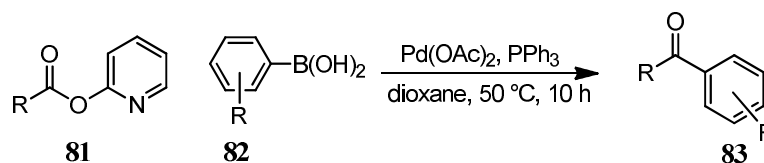
Since boronic acids and esters are often used as substrates in Suzuki-Miyaura cross-coupling reactions³, their properties must be taken into account.^{12,32} The advantages of the Suzuki-Miyaura coupling are the stability to water and oxygen, nontoxic properties of or-

ganoboronic acids and esters and the fact that reactions proceed in the presence of variety of functional groups. Compared to other alkyl-metal cross-coupling reactions, organoboronic acids and esters are readily available, nontransferable boron ligands are easily attached to them and they are easily separated from the inorganic by-products.

Trialkylboranes, R_3B , have been used extensively in the Suzuki cross-coupling reactions.^{12,14} However, coupling reactions of these organoboron compounds have characteristic problems, such as air sensitivity, lack of economy and side-reactions with some functional groups e.g. ketones. Instead of trialkylboranes, alkylborinate esters, R_2BOR , boronic esters, $RB(OR)_2$, and alkylboronic acids, $RB(OH)_2$, can be used as coupling partners. For example, cross-coupling reactions of pinacolboranes and pinacolboronates with aryl halides proceed in the presence of various functional groups. The reaction products are insensitive to air, moisture and chromatography. Various functional groups can be attached to them without intramolecular reactions.

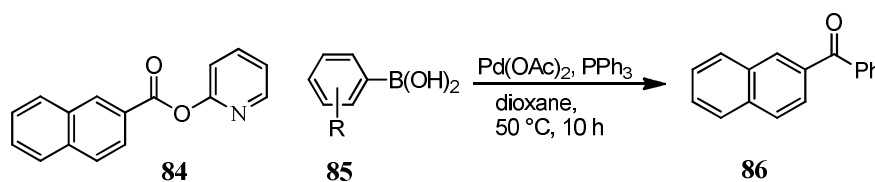
3.4 Ketone synthesis

Palladium-catalyzed cross-coupling reactions are one of the most reliable methods for C-C bond formation and complex molecules are often constructed via coupling reactions.³³ The carbonylative Miyaura-Suzuki reaction can be used to produce ketones in the presence of carbon monoxide. Instead of carbonylative coupling reactions of halides, ketones can be prepared from carboxylic acid derivatives. Carboxylic acids can be used directly as starting material by converting them to acid anhydrides *in situ*. Thioesters are also suitable substrates for coupling reactions. Among various combinations of catalysts and esters derived from alcohols with heteroatoms, the reaction of 2-pyridyl ester **81** with phenylboronic acid **82** proceeds in the presence of a catalytic amount of a palladium complex to produce the ketone product **83** (scheme 31).



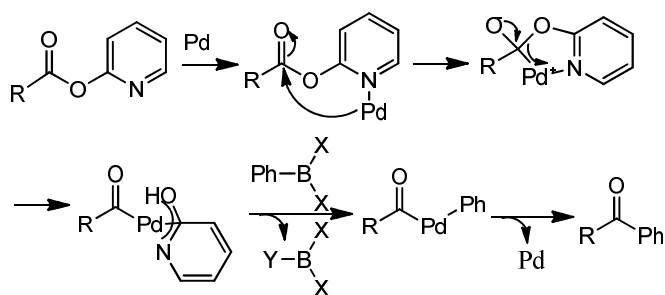
Scheme 31. Palladium-catalyzed coupling reaction of 2-pyridyl ester (1 mmol) with phenyl boronic acid (2 mmol) with (Pd(OAc)₂ (0,03 mmol), PPh₃ (0,09 mmol) in 1,4-dioxane (2 ml) at 50 °C for 10 hours.³³

2-Pyridyl esters are useful substrates for ketone and peptide synthesis because of their high reactivity towards nucleophiles.³³ The high reactivity of pyridyl esters is caused by the fact that 2-pyridyloxy group is a good leaving group and functions also as a directing group. The reaction gives no by-products, such as decarbonylated product. For example, preparation of 2-naphthalenylphenyl methanone **86** from 2-pyridinol-2-naphthoate **84** and phenylboronic acid **85** proceeds as shown in scheme 32.



Scheme 32. Formation of 2-naphthalenylphenyl methanone by treating 2-pyridinol-2-naphthoate (1 mmol) with phenylboronic acid (2 mmol), (Pd(OAc)₂ (0,03 mmol) and PPh₃ (0,09 mmol) in dioxane (2 ml) at 50 °C for 10 hours.³³

The palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds is compatible with various functional groups and can be performed under mild reaction conditions.³³ An efficient reaction is achieved via coordination of the nitrogen atom to palladium as a key step. The proposed mechanism is described in scheme 33.



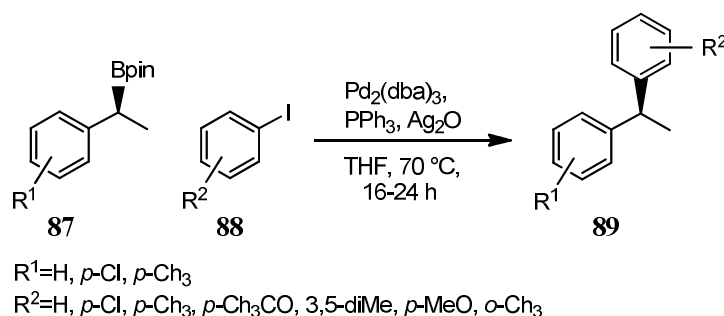
Scheme 33. Reaction mechanism of palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds.³³

The ketone synthesis by the palladium-catalyzed coupling reaction is compatible with various functional groups and can be performed under mild conditions.³³ Benzylboron compounds are suitable nucleophiles in this case, though they are rarely used in other coupling reactions of carbonyl compounds. Coordination of the nitrogen atom to the catalyst is essential and the reaction involves the catalytic generation of acylpalladium intermediates from esters.

3.5 Cross-coupling of chiral boronic esters

Chiral organometallic species, such as organoboranes, can be prepared by enantioselective additions of alkenes and organometallic compounds.³⁴ The reaction gives a route to a class of chiral compounds. Cyclopropyl boronic acids and esters and their derivatives are immune to β -hydride elimination reaction and participate in Suzuki-Miyaura coupling reactions in high yield, without loss of stereochemistry. Also cyclopentyl boronic acid can undergo cross-coupling reaction with aryl chlorides in high yields. In addition, cyclopentyl fluoroborate-type nucleophiles are possible as well when bulky, electron-rich phosphines are present. However, β -hydride elimination or addition occurs as a side reaction of these substrates and leads to linear products when starting with branched boronate ester. The β -hydride elimination can be minimized by optimization of reaction conditions but it leads to racemization of enantiomerically enriched substrates.

For example, the unsymmetrically substituted 1,1-diarylethanes **89** are difficult to prepare by other methods but they can be prepared by the cross-coupling reaction of chiral, secondary benzylic boronic ester **87** and aryl iodide **88**, as shown in scheme 34.³⁴ The reaction gives the desired coupling product when palladium catalyst and phosphine ligands are used. Silver oxide is used as base since it accelerates the slow transmetallation step. The reaction gives the highest yields when PPh₃ is used as ligand. The ratio of Pd₂(dba)₃/PPh₃ needs to be 1:4 in order to reach the highest possible yield.



Scheme 34. Coupling reaction of chiral secondary boronic ester (0,15 mmol) and aryl iodide (0,1 mmol) in the presence of Pd-catalyst Pd(dba)₃ (8 %), PPh₃ (8-12) equiv./Pd, Ag₂O (0,15 mmol), THF, at 70 °C and N₂ atmosphere for 16-24 h.³⁴

The reaction gives under optimized conditions optical purity of over 90 % and retains its configuration.³⁴ Functional groups can be introduced via either the aryl iodide or the boronic ester. This example shows that cross-coupling reactions of secondary boronic esters proceed without loss of regiochemistry and with high retention of enantioselectivity.

3.6 Green cross-coupling chemistry

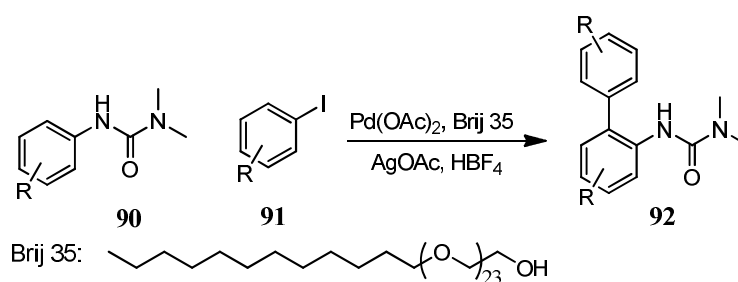
Cross-coupling reactions are traditionally based on reactive electrophile into which a transition metal catalyst inserts and a reductive nucleophile transfers an organic fragment to the transition metal center.^{4,21,35} Finally, reductive elimination gives the product. The method usually requires high temperatures, potentially toxic organic solvents, highly reactive organometallic reagents and super-stoichiometric levels of additives. The more reactive nucleophile used in cross-coupling reaction the more precautions has to be taken to avoid mois-

ture. The reaction has to be handled in an inert atmosphere to minimize oxidation. Low functional group tolerance often requires protecting group chemistry adding steps thus reducing overall yields.

Recently, milder and more selective conditions for cross-coupling reactions have been developed.³⁵ Few methods were proposed to perform palladium catalyzed cross-coupling reactions in water and/or at room temperature. They involve *in situ* activation of carbon-halogen or C-H bonds by cationic palladium. Palladium catalysts have ligands with wide structural variation, such as phosphines, phosphoramidites and diamines.

Both alkyl-aryl and benzyl-aryl couplings can be performed at room temperature.³⁵ Under low temperatures fewer side reactions occur which lower the amount of impurities. The reactions are simple to run because the reactants are just added in a vessel containing surfactant or water and stirred.

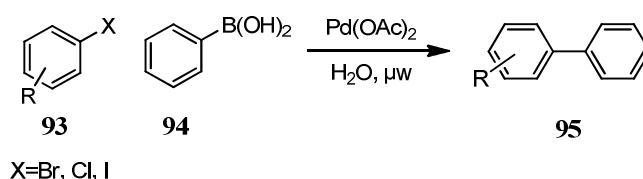
In comparison with other cross-coupling reactions, transition metal-catalyzed aryl C-H bond activation reactions are a good method to functionalize aromatic rings.³⁵ In order to control regioselectivity and enhance reactivity of C-H bonds in arenes, various *ortho*-directing groups are used, such as anilide derivatives. Their drawback is the harsh conditions needed to achieve the activation of a stable aryl C-H bond. However, C-H arylations of aryl ureas can be performed under milder conditions with highly reactive cationic palladium catalysts. For example, palladium-catalyzed arylation of aryl urea **90** with aryl iodide **91** can be performed at room temperature to produce 3,3-dimethyl-1-(2-phenylphenyl)urea **92** (scheme 35).



Scheme 35. Arylation of 3,3-dimethyl-1-phenylurea with aryl iodide in the presence of Pd(OAc)₂ (10 %), Brij 35 (2 %), AgOAc (2 equiv.) and HBF₄ (5 equiv.) at room temperature.³⁵

3.7 Microwave-assisted reactions

Many metal-catalyzed reactions are completed in a few minutes by using microwave irradiation.^{36,37,38} Since polar solvents absorb microwaves, reactions can be carried out in water, ethylene glycol or DMF. Microwave irradiation significantly increases the efficiency of ligandless palladium acetate, and can be utilized both for homogeneous and solid-phase coupling reactions of arylboronic acids. For example, the cross-coupling reactions of aryl boronic acids **94** and aryl bromides, iodides and activated chlorides **93** in water are carried out in five minutes by using microwave irradiation to yield phenylbenzene **95**, as shown in scheme 36 below.

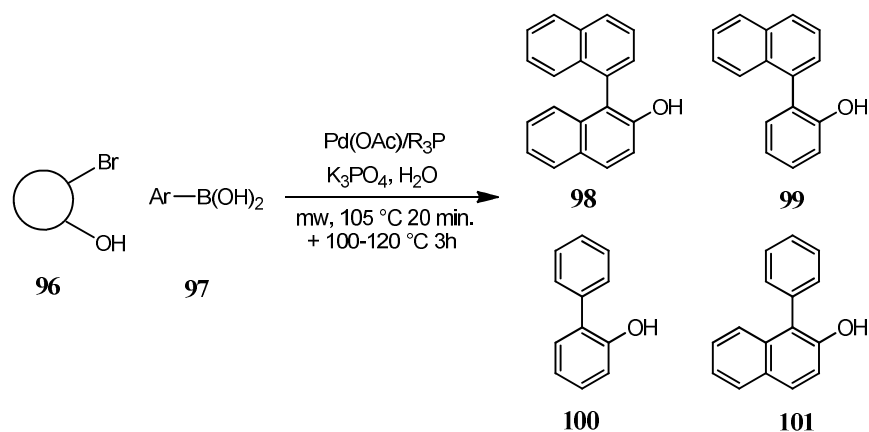


Scheme 36. Suzuki-Miyaura cross-coupling reactions of boronic acids and aryl iodides, bromides and activated chlorides with low palladium loading (0,4 mol %) and reaction time of 5-10 min by using microwave irradiation.³⁸

Microwave irradiation suits well for solid-phase coupling reactions too.^{39,40,41} Reactions at high temperature may suffer from competitive saponification of the ester group because the main reaction is slow, but this side process is suppressed by using the microwave irradiation.

tion method and reaction time less than five minutes. The cross-coupling reaction of aryl- or 1-alkenylboronic acids can be performed at 100 °C without solvents when alumina and palladium catalysts are used as solid-phase system. Microwave irradiation has also enabled arylation of bromoarenes without metal catalysts. Heating at 150 °C is efficient for activated bromides but microwave irradiation enables reactions of both activated and deactivated bromoarenes to be completed in five minutes.

For example, Suzuki-Miyaura coupling of arylboronic acids and *o*-bromophenols can also be performed by microwave heating.³² Unprotected 2-hydroxyaryl bromides **96** or *o*-chlorophenol react with arylboronic acids **97** to produce naphthalen-2-ols **98**, **101** and 2-phenols **99**, **100**. The reaction proceeds in moist K₃PO₄/toluene or moist CsF/dioxane with phosphine/Pd(OAc)₂ catalyst under microwave heating first at 105 °C for 20 minutes and then at 100-120 °C for 3 hours (scheme 37). Tris(*o*-tolyl) phosphine is a suitable phosphine ligand because it gives as good yields as the commonly used ligand *t*-Bu₃P but with higher air stability. Good yields are gained by this method under relatively mild conditions. The method is suitable also for more substituted aryl halides.



Scheme 37. Suzuki-Miyaura coupling of 2-hydroxyaryl bromides (1 equiv.) and arylboronic acid (2 equiv.), with Pd(OAc)₂ (2,5 mol %), *o*-Tol₃P (5 mol %) in water 50 mg/g K₃PO₄ (2 equiv.), heated by microwave irradiation for 20 min at 105 °C, 3 h at 100-120 °C.³²

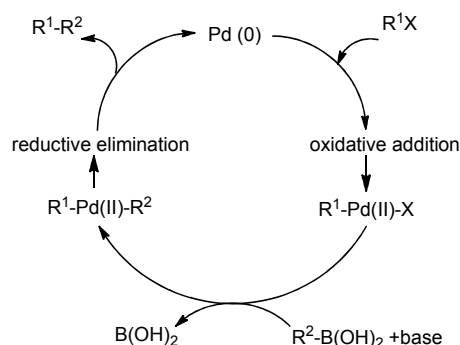
4 Reaction mechanism of organoborons

Cross-coupling reactions of organoboron compounds involving transmetallation to palladium(II) halides is a general reaction for a wide range of selective carbon-carbon bond formations and related coupling reactions of organomagnesiums, -zincs, -silicones and -stannanes.^{11,42,43} Organoboron reagents are used for cross-coupling reactions in laboratory and also in industrial scale. They are convenient reagents since they are generally thermally stable and inert to water and oxygen and can be handled without special precautions.

Arylboronic acids and esters are useful in organic syntheses due to their high reactivity, ease of access and great variety of reactions they are capable of.²¹ Usually the syntheses of boronic acids are based on the reaction of trialkyl borates with Grignard or lithium reagents. The transition-metal -catalyzed cross-coupling reaction of boron nucleophiles and aryl electrophiles is a convenient route to boronic acids and esters but the lack of suitable boron nucleophiles has limited this method. Alkoxydiborons are thermally stable and easily handled in air and useful as boron nucleophiles for the cross-coupling reaction with organic halides. By this method palladium-catalyzed coupling reaction of the pinacol ester of diboron and aryl halides is a one-step procedure for preparing arylboronic esters from aryl halides.

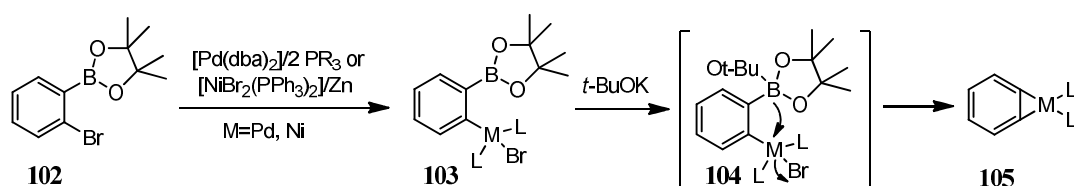
4.1 Catalytic cycle

The cross-coupling reaction proceeds according to a catalytic cycle that involves the oxidative addition of haloarenes or other electrophiles to the palladium(0) complex yielding Ar-Pd(II)-X, transmetallation between pinacol ester of diboronic acid and Ar-Pd(II)-X with the aid of base to gain Ar-Pd(II)-B(OR)₂ intermediate.²¹ Reductive elimination of arylboronic ester regenerates the palladium(0) complex. The catalytic cycle is shown in scheme 38. The mechanism involving a palladium(IV) intermediate formed by double-oxidative additions of pinacol ester of diboronic acid and aryl halides to the palladium(0) complex can be excluded since the oxidative addition of pinacol ester of diboronic acid to Pd(PPh₃)₄ does not proceed under given conditions.



Scheme 38. Catalytic cycle, the mechanism of the cross-coupling reaction.^{44,45}

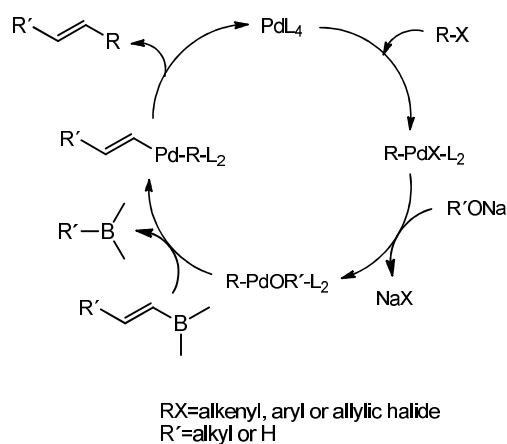
The steps of oxidative addition and reductive elimination are quite well understood but the transmetalation process is not that well known.^{46,47} There are several processes involved in transferring the organic group onto R^1 -Pd-X. Sodium hydroxide and other bases accelerate the transmetalation between R^1 -Pd-X and trialkylboranes or organoboronic acids. However, the transmetalation in the catalytic cycle is not the rate-determining step. Organoboron compounds do not react with R^1 -Pd-X (X =halogen, OTf) but complexes, such as $(RBBu_3)Li$, Ph_4BNa and $(R_3BOMe)Na$, directly undergo a palladium- or nickel-catalyzed coupling reaction. For example, a bromoarene substituted in the *ortho*-position by a boronic ester **102** form *ortho*-substituted arylnickel(II) or -palladium(II) complexes **103** which react with the boronic ester group in the presence of *t*-BuOK **104**. Corresponding benzyne complex **105** is formed at room temperature as shown in scheme 39.



Scheme 39. Intramolecular transition metal-boron transmetalation assisted by a base yields a benzyne complex at room temperature.⁴⁷

An alternative process is a transmetalation of an alkoxy-, acetoxo-, hydroxyl- or (acetyla-ceto)palladium(II) complex formed by the ligand exchange between R^1 -Pd-X and a base (RO^-) .⁴⁸ The RO -Pd(II) complexes undergo transmetalation of organoboronic acids without the aid of base. Methoxo-, hydroxo- and (acetoxo)palladium(II) complexes react with

1-alkenyl- and arylboronic acids or bis(pinacolato) diboron and give the corresponding coupling products. The mechanism of the reaction is presented in catalytic cycle shown in scheme 40.



Scheme 40. Mechanism of cross-coupling reaction of haloalkynes or haloalkenes with alkenylboranes.⁴⁸

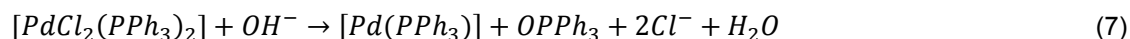
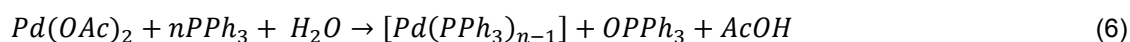
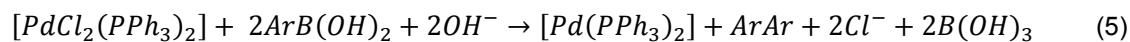
As a result of complex formation, the organic group from boron is transferred to palladium.⁴⁸ The strong reactivity of RO-Pd complexes has an effect on the high basicity of Pd-O and the high oxophilicity of the boron center. Thus, there are two transmetalation processes depending on the reactants and reaction conditions in an alkaline solution.

Transmetalation step is significantly accelerated by the presence of electron donor substituents in the *para*-position of the phenyl boronic acids.⁴ The nucleophilicity of the boronate species has a strong effect on the reaction yield and selectivity. Electron donor substituents in the boronic acids improve the reaction course in contrast to electron-withdrawing substituents.

4.2 Catalysts

The combination of catalysts, bases and solvents has a great effect on the yields and selectivity of the cross-coupling reaction products.⁴⁵ The most common catalyst is $\text{Pd}(\text{PPh}_3)_4$ but

$\text{Pd}(\text{OAc})_2$ and $\text{PdCl}_2/\text{phosphines}$ are good precursors, too and can be reduced to corresponding $\text{Pd}(0)$ complexes *in situ*, as shown in equations 5-7.



Reduced palladium complexes are commonly abbreviated as $\text{Pd}(0)\text{Ln}$.⁴⁵ Reduction of palladium catalyst leads to formation of anionic palladium(0) species, such as $\text{Pd}(0)\text{L}_2\text{Cl}^-$ and $\text{Pd}(0)\text{L}_2(\text{OAc})^-$. The anionic ligand of catalyst precursors has an effect on the rate of oxidative addition of catalysts.

4.2.1 Palladium catalysts with phosphate ligands

Organoboron compounds can be synthesized by cross-coupling reactions of tetra-(alkoxo)diborons catalyzed by transition-metals.¹⁴ Palladium catalysts with bulky, electron-donating alkylphosphines are recognized to be excellent catalysts in cross-coupling reactions of haloarenes. $\text{PdCl}_2(\text{dppf})$ is the most suitable catalyst for borylation of haloarenes having both an electron-withdrawing and -donating group, even for chloroarenes.

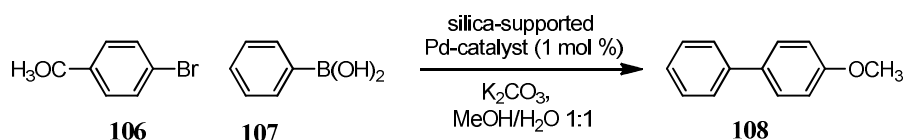
Palladium-catalyzed cross-coupling reactions of aryl halides with arylboronic acids are one of the most important ways of making symmetric and nonsymmetric biaryls.⁴⁹ A variety of homogenous catalysts have been used but they are difficult to recover and reuse and they could not be used in large-scale synthesis because of environmental and economic reasons and therefore a reusable and recoverable heterogeneous catalyst is needed.

In large-scale industrial processes it is advantageous to use aqueous media because of the simplicity of the catalyst separation, economy and safety.²² However, complete conversion

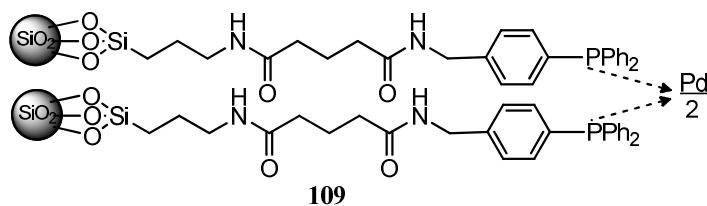
of the catalyst is not always possible especially in slow reactions of electron-rich and sterically hindered substrates even though rapid coupling reaction in aqueous media do occur.

Supported palladium-phosphines have been suitable catalysts in coupling reactions of arylboronic acids.^{49,50} Silica supported palladium-phosphine complex is an efficient catalyst for cross-coupling reactions under mild conditions and it can be reused at least 10 times without loss of catalytic activity. Various organic and inorganic supports have been explored, such as polymers, ionic liquid, charcoal, hydroxyapatite, sepiolite or other clays, mesoporous silica and magnetic nanoparticles. Palladium-phosphine catalyst anchored to active silica shows catalytic activity and is also insensitive to oxygen, thermally stable and recyclable. These properties make the catalyst valuable from the synthetic and environmental point of view.

For example, a cross-coupling reaction of 4-bromoanisole **106** with phenylboronic acid **107** can be performed with a silica supported palladium catalyst to yield 1-methoxy-4-phenylbenzene **108** as shown in scheme 41.⁴⁹ The silica supported palladium-phosphine catalyst **109** is shown in scheme 42.



Scheme 41. A cross-coupling reaction of phenylboronic acid (0,6 mmol) with 4-bromoanisole (0,5 mmol) yields 1-methoxy-4-phenylbenzene with a silica-supported palladium catalyst (Pd 0,005 mmol), K₂CO₃ (1 mmol) for 4 hours. The most suitable solvent is a 1:1 mixture of MeOH/H₂O (2 ml).⁴⁹



Scheme 42. Palladium-phosphine catalyst anchored to active silica.⁴⁹

Just 1 mol % of the catalyst is enough to complete the in a Suzuki-Miyaura reaction at room temperature in 4 hours.^{49,50} A suitable solvent with the catalyst in such reaction can be non-aqueous, such as MeOH, EtOH and *i*-PrOH. Water gives also quite good yield but aprotic solvents produce only moderate yields. The best yield can be gained in MeOH/H₂O (1:1). K₂CO₃ is an excellent base but Na₂CO₃, Cs₂CO₃ and KOAc are suitable too.

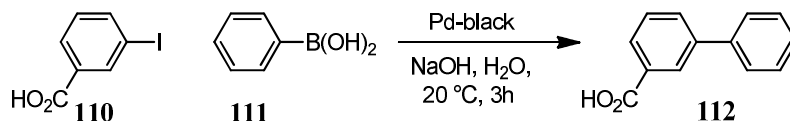
Clay stabilized palladium particles give better yields than unsupported particles.⁵⁰ The reaction can take place on the surface of the particles and the catalyst can be recycled without the loss of its activity. The supported palladium complexes, such as palladium-phosphine complexes, have been designed to combine the advantages of the homogeneous and heterogeneous catalysts. For example, a good polymer catalyst for reactions of 1-alkenyl- and arylboronic acids with organic halides or triflates is a palladium-phosphine complex on polystyrene resin.

4.2.2 Palladium catalysts without phosphate ligands

The cross-coupling reactions of organoborons and organic halides are often carried out in a mixture of an organic solvent and an aqueous solution of base in the presence of palladium phosphine complex catalysts.⁵¹ However, the cross-coupling of organoboron compounds can be performed also in the presence of ligandless palladium catalyst in water or in water/acetone mixture at room temperature. Unfortunately, the catalyst cannot be recovered. For that reason a lot of efforts have been applied to develop a catalyst that can be reused multiple times.

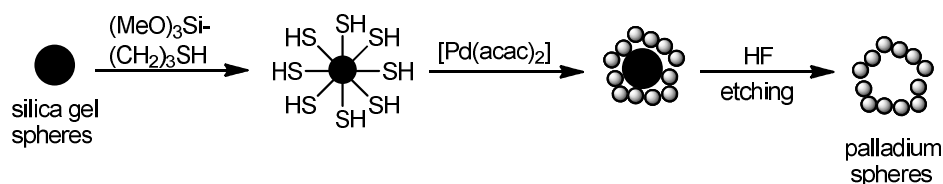
As an example, heterogeneous catalysts PdCl₂/C and Pd(0)/C and crystalline palladium black have been tested in a reaction of [Ph₄B]Na and *m*-bromobenzoic acid.⁵¹ When reused, the activity of the catalysts decreases but by increasing the reaction time or temperature, cross-coupling occurs in good yields. The purification and isolation of the end products is the easiest when Pd(0)/C and Pd-black are used as catalysts, thus only cross-coupled products are obtained, such as in the reaction of 3-iodobenzoic acid **110** and phenyl boronic acid

111 to produce 3-phenylbenzoic acid **112** (scheme 43). With PdCl₂/C (1 mol % Pd) a small amount of corresponding diaryl is formed due to the reduction of PdCl₂ to Pd(0).



Scheme 43. Cross-coupling reaction of *m*-iodobenzoic acid and phenyl boronic acid can be performed in room temperature, under argon atmosphere and in the presence of an effective Pd-black catalyst.⁵¹

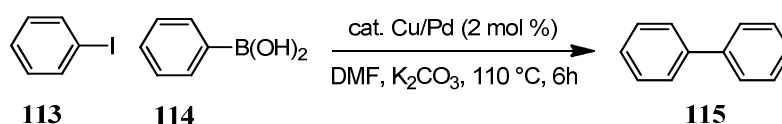
The mechanism of cross-coupling reaction goes via catalytic cycle with oxidative addition, transmetallation and reductive elimination steps.^{52,53} However, it has been shown that there is another possible reaction pathway where the active moieties are nanosized palladium colloids or hollow palladium spheres. Hollow palladium spheres are catalysts composed of an empty core with 15 nm nanoparticles. They are prepared by absorbing [Pd(acac)₂] onto uniform silica gel spheres and functionalized by mercaptopropyltrimethoxysilane, (MeO)₃Si(CH₂)₃SH. Thermolysis at 250 °C yields palladium metal -coated spheres which are treated with aqueous HF to remove the silica gel (scheme 44). The size of the catalyst can be controlled by the size of the silica gel spheres and the catalyst remains highly active even after seven recyclings.



Scheme 44. Preparation of hollow palladium sphere catalysts.⁵³

Palladium nanoparticles generated from Pd(OAc)₂ are an excellent catalyst in biaryl coupling reactions in water or in aqueous organic solvents.⁵⁴ Their advantage is that the catalyst eliminates phosphine-related side reactions, such as phosphonium salt formation, is catalytically highly efficient and needs shorter reaction times.

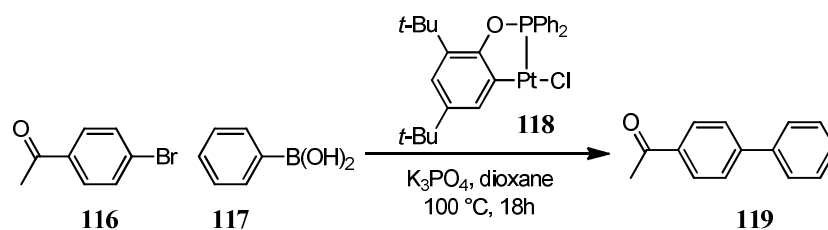
In order to search for alternative catalysts for cross-coupling reaction, copper-based colloids are attractive because they are much cheaper and less environmentally harmful than noble metals.⁵² In the reaction of iodobenzene **113** and phenylboronic acid **114**, copper and copper-based nanocolloids can catalyze the coupling reaction to yield phenylbenzene **115** with moderate yields. When mixture of copper and palladium is used as catalyst, even excellent yields can be achieved (scheme 45).



Scheme 45. The coupling reaction of phenylboronic acid (0,75 mmol) and iodobenzene (0,5 mmol) with K₂CO₃ (1,5 mmol) copper and palladium nanocolloids (2 mol %) as catalysts in DMF and N₂ atmosphere at 110 °C for 6 hours.⁵²

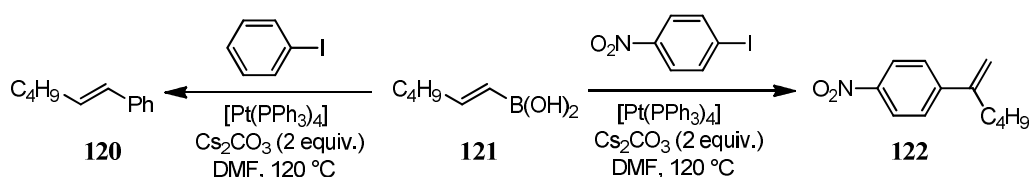
4.2.3 Platinum catalysts

Platinum catalysts have been used for cross-coupling reactions of organoboronic acids to a limited degree.⁵⁵ The main reason is that both oxidative addition and reductive elimination are slower than with palladium complexes. However, platinum(II) complexes of a *o*-metalated triarylphosphite **118** catalyses the reaction of bromoarene **116** and aryl boronic acids **117** with a lower catalyst loading than palladium catalysts, excluding the reactions with iodoarenes at 120 °C catalyzed by Pt(PPh₃)₄. An example of cross-coupling reaction catalyzed by platinum(II) complex yields 1-(4-phenylphenyl)ethan-1-one **119**, as shown in scheme 46 below.



Scheme 46. Cross-coupling reaction of aryl halide (10 mmol), $PhB(OH)_2$ (15 mmol), Pt-catalyst (0,0001 mol %), K_3PO_4 (20 mmol) in 1,4-dioxane (30 ml) at 100 °C for 18 hours.⁵⁵

The selectivities of platinum- and palladium-catalyzed reactions are almost alike.⁵⁵ However, the reactions of [(1E)-hex-1-en-1-yl]boronic acid **121** and iodobenzene gives (1E)-hex-1-en-1-ylbenzene **120** but 4-nitroiodobenzene gives *ipso*-coupling product **122** when platinum-catalyst is used, as shown in scheme 47.

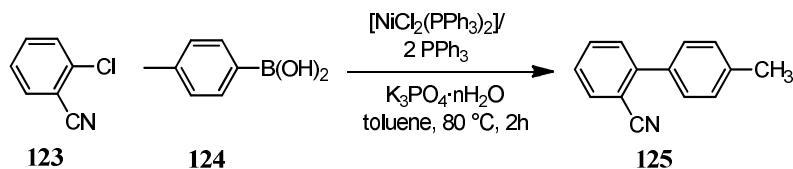


Scheme 47. Cross-coupling reaction of alkene and NO_2 -substituted aryl iodide with platinum catalyst induces *ipso*-coupling reaction.⁵⁵

4.2.4 Nickel catalysts

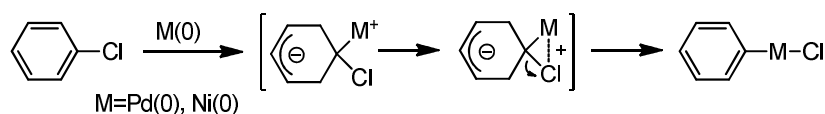
Nickel (0) catalysts are highly active towards aryl chlorides and mesylates unlike palladium complexes.⁵⁶ Nickel catalysts are cheap so recycling of the catalysts is not necessarily required. Nickel(II) complexes form catalytically inactive nickel hydroxides and oxides in the presence of aqueous base, thus the reduction of nickel(II) complexes with zinc powder, DIBAL-H or BuLi is required for preparation of air-sensitive nickel(0). Nickel (II) complexes can be reduced *in situ* if dry arylboronic acid and K_3PO_4 are used in toluene. For example, the cross-coupling reaction of 2-chlorobenzonitrile **123** with tolylboronic acid **124**

proceeds readily with nickel catalyst and gives 2-(4-methylphenyl)benzotrile **125** (scheme 48).



Scheme 48. Cross-coupling reaction of 2-chlorobenzonitrile (1.0 mmol) and tolylboronic acid (1,3 equiv.) and with $\text{K}_3\text{PO}_4 \cdot n\text{H}_2\text{O}$ (2,6 equiv.) catalyzed by nickel(II) complex $\text{NiCl}_2(\text{PPh}_3)_2/2 \text{ PPh}_3$ (3 mol %) in toluene (3 ml) at 80°C .⁵⁶

Triphenyl phosphine complex is more suitable than a 1,1'-bis(diphenylphosphino)ferrocene complex in toluene.^{56,57} Reactions with iodo- or bromoalkenes, aryl mesylates and allyl acetates proceed smoothly at room temperature. Oxidative addition is often the rate-determining step in the catalytic cycle, especially in the reactions of bromo- and chloroarenes. The reactivity usually decreases in the order of $\text{I} > \text{Br} > \text{OTf} > \text{Cl}$ for aryl electrophiles but the order can be reversed depending on phosphine ligands. $\text{Ni}(\text{PPh}_3)_4$ complex makes the reactivity increase linearly if there are electron-withdrawing groups on the arylhalide but is insensitive to electron-donating substituents. By contrast, palladium(0) complex shows a linear correlation for donating and withdrawing groups. The mechanism of oxidative addition of chloroarenes is shown in scheme 49 below.

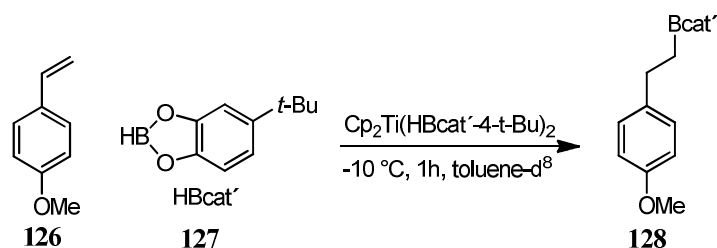


Scheme 49. Oxidative addition of chloroarenes to Pd(0) and Ni(0) complexes.⁵⁶

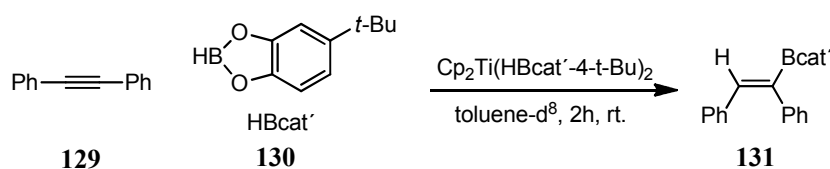
4.2.5 Titanium catalysts

Addition of catecholborane, $\text{HBO}_2\text{C}_6\text{H}_4$, to alkenes and alkynes can be catalyzed by transition metal complexes, such as rhodium, lanthanide and titanium complexes.^{57,58} The addi-

tion of boranes to alkenes and alkynes through the metal catalyzed chemistry can produce alkyl boronate esters **128** and vinylboronate esters **131** that are useful reagents in Suzuki cross-coupling reactions. Titanocene complexes catalyze hydroboration of alkenes and alkynes efficiently. For the hydroboration of vinylarenes **126** and arylalkynes **129** the bis(borane) complex $\text{Cp}_2\text{Ti}(\text{HBcat}')_2$ ($\text{HBcat}' = \text{HBO}_2\text{C}_6\text{H}_4\text{-4-}t\text{-Bu}$) **127**, **130** is a highly active catalyst. The catecholborane serves as a substrate and a ligand in the reaction. Examples of the reactions with alkenes and alkynes are shown in schemes 50 and 51.

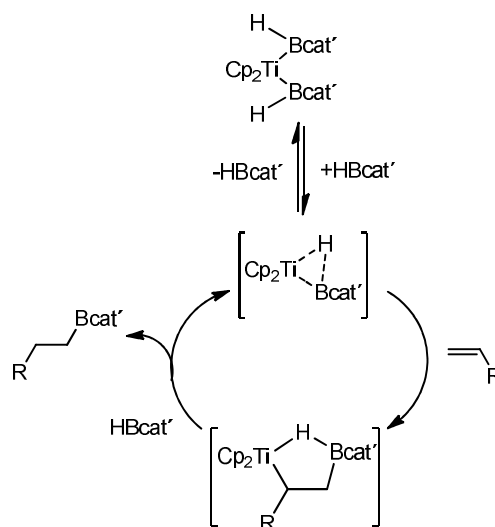


Scheme 50. Hydroboration of alkene (*p*-methoxystyrene) at $-10\text{ }^\circ\text{C}$ in toluene-d^8 for 1 hour, catalyzed by $\text{Cp}_2\text{Ti}(\text{HBcat}')_2$ complex (10 mol %), (HBcat' 5 equiv.), Cp =pentamethylcyclopentadienyl, $\text{HBcat}' = \text{HBO}_2\text{C}_6\text{H}_4\text{-4-}t\text{-Bu}$.⁵⁸



Scheme 51. Hydroboration of alkyne (diphenylacetylene) and borane reagent at room temperature, toluene-d^8 as solvent and catalyzed by $\text{Cp}_2\text{Ti}(\text{HBcat}')_2$ complex (10 mol %), HBcat' (5 equiv.) Cp =pentamethylcyclopentadienyl, $\text{HBcat}' = \text{HBO}_2\text{C}_6\text{H}_4\text{-4-}t\text{-Bu}$.⁵⁸

During the hydroboration of alkenes bis(borane) complex $\text{Cp}_2\text{Ti}(\text{HBcat}')_2$ dissociates the coordinated borane to generate a monoborane intermediate.⁵⁸ The intermediate coordinates an alkene to give a complex that is a resonance hybrid between an alkene borane complex and a β -borylalkyl hydride. The hydroboration of alkynes involves a similar complex and forms a resonance hybrid between an alkyne borane complex and a β -borylvinyl hydride. The reaction gives an alkylborinate ester and regenerates the monoborane intermediate. The reaction mechanism is shown in scheme 52.



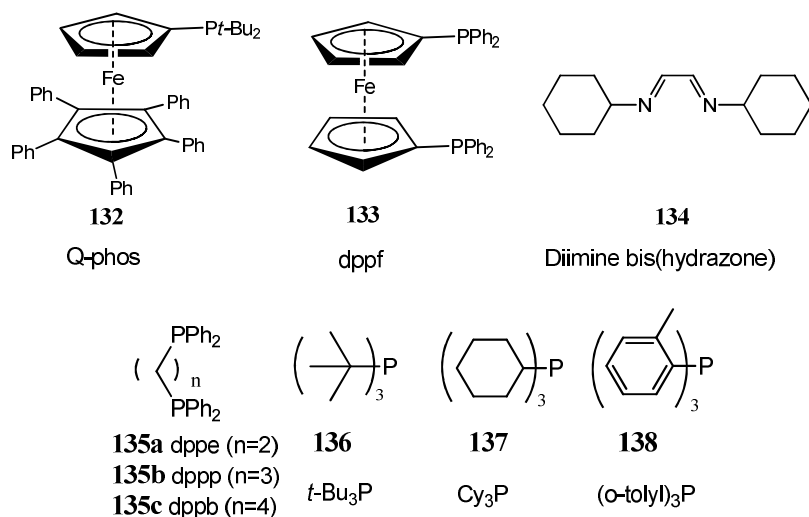
Scheme 52. A reaction mechanism of an alkene hydroboration catalyzed by $\text{Cp}_2\text{Ti}(\text{HBcat}')_2$ complex, Cp= pentamethylcyclopentadienyl, $\text{HBcat}' = \text{HBO}_2\text{C}_6\text{H}_4\text{-4-}t\text{-Bu}$.⁵⁸

4.3 Ligands

There is a wide variety of ligands available which give high catalyst efficiency and selectivity.⁵² Phosphine ligands are effective in stabilizing the palladium(0) species but the bulkiness, stoichiometry of phosphine to palladium or donating ability of phosphine ligands makes the catalyst more susceptible towards oxidative addition, reductive elimination and transmetalation. Depending upon the bulkiness of the ligands phosphine complexes are in equilibrium with coordinatively unsaturated compounds. Either monophosphine $\text{Pd}(0)\text{L}$ or biphosphine $\text{Pd}(0)\text{L}_2$ complex is responsible for the oxidative addition of organic halides. Palladium complexes with less than four phosphine ligands or weakly coordinating ligands, such as AsPh_3 , are highly reactive catalysts because of the easy formation of coordinatively unsaturated species.

The ligand donates an electron to the palladium(0) metal center.^{57,60} Triarylphosphines are effective ligands for coupling reaction of organic iodides, bromides, triflates and activated chlorides because of their air-stability. However, they do not catalyze reactions of electron-rich chlorides. Bulky and easily donating ligands, such as $\text{P}(t\text{-Bu})_3$, function as highly ac-

tive catalysts even at room temperature. These ligands have an ability to donate electrons to the metal center which assures their accelerating effect on the reaction. Common ligands **132-138** used in palladium catalysts are shown in scheme 53 below.

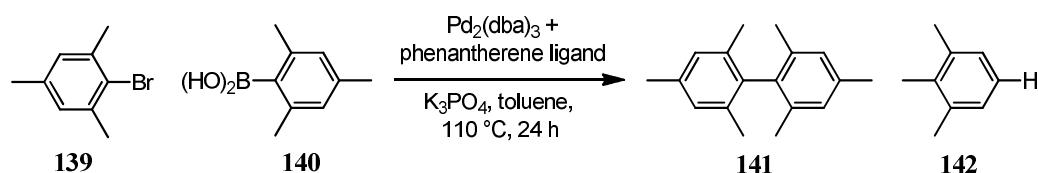


Scheme 53. Common ligands for palladium catalysts.⁶⁰

Less bulky phosphines are suitable for slow reactions of functionalized substrates because they yield thermally stable complexes.⁶¹ For example, (*t*-Bu)₂POH and N-heterocyclic carbines are suitable for the reactions at high temperatures. Bisphosphines, such as 1,3-bis(diphenylphosphinyl)propane, dppp, 1,4-bis(diphenylphosphinyl)butane, dppb, and 1,1'-bis(diphenylphosphino)ferrocene, dppf, have a large P-M-P angle and accelerate the reductive elimination in the coupling reaction of alkylmetals. In addition, the ligand dppf works well for coupling reactions of 1-alkenyl- and arylboronic acids. Palladacycles derived from tris(*o*-tolyl)phosphine, triarylphosphite, benzoxime and bis(phosphinite) are air-stable catalysts with high catalytical efficiency in coupling reactions of arylboronic acids and bromoarenes or activated chloroarenes.

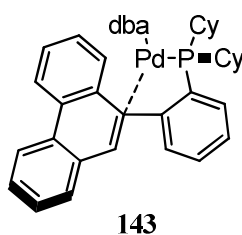
Because the best catalyst for coupling reactions of arylboronic acids with haloarenes is dependent on reaction conditions, reactants and solvents, it is often chosen by screening.⁶² Alkylphosphines, such as *t*-Bu₃P and BuP(Ad)₂, are suitable ligands for chloroarenes and for slow reactions of electron-rich bromoarenes.

Specific methods are needed for synthesis of di-*ortho*-substituted biaryls.⁶³ A phenanthrene ligand-based catalyst allows the synthesis of sterically hindered biaryls where the reactants have two *ortho*-substituents. As an example of cross-coupling reaction of hindered substrates, 2,4,6-trimethylphenyl bromide **139** reacts with 2,4,6-trimethylphenyl boronic acid **140** and gives 1,3,5-trimethyl-2-(2,4,6-trimethylphenyl)benzene **141** (scheme 54). 1,2,3-Trimethylbenzene **142** is formed as by-product.



Scheme 54. Cross-coupling reaction of 2,4,6-trimethylphenyl bromide (1 equiv.), 2,4,6-trimethylphenyl boronic acid (1,4 equiv.) with K_3PO_4 (3,0 equiv.), $\text{Pd}_2(\text{dba})_3$ (2 mol %) phenanthrene ligand (8 mol %), toluene, 110°C for 17-24 h.⁶³

Only the phenanthrene **143** ligand-based catalyst allows the synthesis of sterically hindered biaryls with two *ortho*-substituents (scheme 55).⁶³ The corresponding naphthyl- and bi-phenyl-based ligands give significantly lower yields and low conversions. The mechanism of the phenanthrene ligand action is based on a highly stabilized monophosphine-palladium(0) in phenanthrene/ $\text{Pd}(\text{dba})_2$ complex with an unusual π -coordination of a phenanthrene moiety to a palladium metal center.

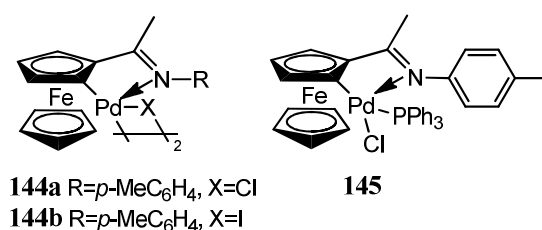


Scheme 55. A phenanthrene ligand.⁶³

The traditional catalysts in palladium-catalyzed C-C and C-heteroatom bond forming reactions are simple Pd(0) species and Pd(II) salts, such as $\text{Pd}(\text{PPh}_3)$, $\text{Pd}_2(\text{dppf})_3$ and $\text{PdCl}_2(\text{PPh}_3)_2$.⁶⁴ However, they have some drawbacks, such as sensitivity to air and moisture and the need of large loading, 5 mol % or more. In contrast, cyclopalladated ferroceny-

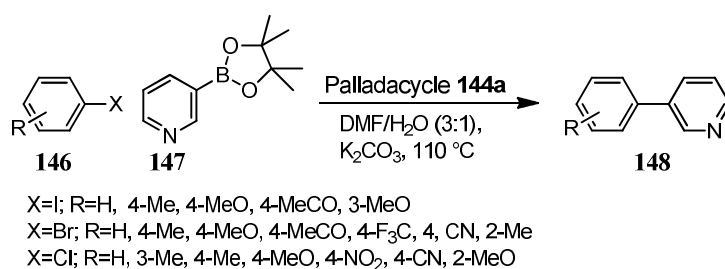
limines are air-stable and efficient palladium catalyst precursors which are easy to handle. They can be applied to wide variety of reactions, such as Suzuki, Heck and Buchwald-Hardwig couplings and reactions of arylboronic acids.

A variety of palladacycles are suitable catalyst precursors for the Suzuki-Miyaura reaction of organoboron compounds with aryl halides in organic solvent or water.⁶⁴ For example, palladacycle **144a** (scheme 56) is effective in reactions of aryl iodides, aryl bromides and electron-poor aryl chlorides.



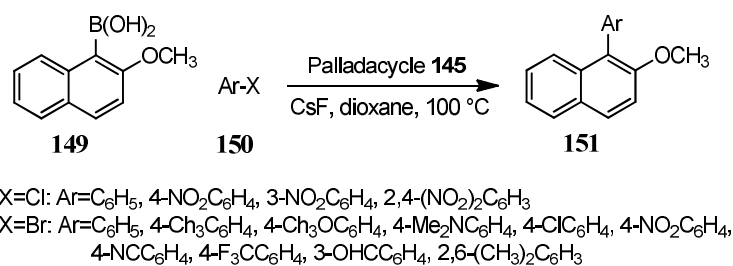
Scheme 56. Cyclopalladated ferrocenylimine adducts.⁶⁴

As shown in scheme 57, palladacycle **144a** can be used in Suzuki-Miyaura reaction of 3-pyridylboronic ester **147** with aryl halides **146** under two-phase conditions.⁶⁴ For palladacycles **144a** and **144b** the catalytic efficiency increases in water under ultrasonic conditions and the reaction time can be shortened from 10-24 hours to 0,5-8 hours to give 3-phenylpyridine **148**.



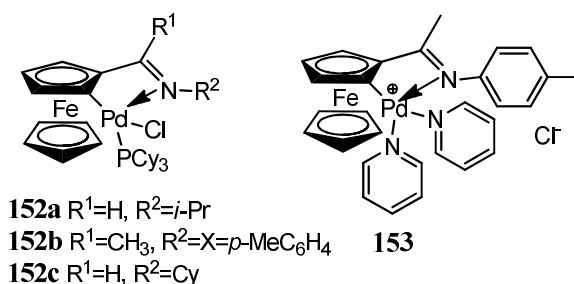
Scheme 57. Suzuki-Miyaura cross-coupling reaction of 3-pyridylboronic esters with aryl halides under the two-phase conditions. The reaction proceeds with functional groups of the aryl halide listed above.⁶⁴

The triphenylphosphane adduct of cyclopalladated ferrocenylimine **145** is a suitable catalyst for synthesis of *o*-substituted biaryls **149** with aryl halides **150** to prepare 2-methoxy-1-arylnaphthalene **151**.⁶⁴ The reaction proceeds via Suzuki-Miyaura cross-coupling reaction as presented in scheme 58 below. The catalytic system is suitable for substrates with various functional groups and substituents, such as CH₃O, CHO, CH₃CO, NMe₂, CF₃, NO₂, CN and Cl.



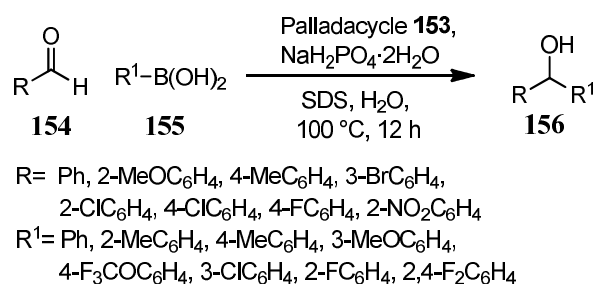
Scheme 58. Reaction conditions of *ortho*-substituted biaryl synthesis. The reaction proceeds with functional groups of the aryl halide listed above.⁶⁴

Tricyclohexylphosphine adducts of cyclopalladated ferrocenylimines **152a-c** can act as the catalyst precursor for Suzuki-Miyaura reaction of the deactivated aryl chlorides due to their bulky, sterically hindered alkylphosphine ligands (scheme 59).⁶⁴ Good yields can be gained even with low catalyst loading (0,1 mol %).



Scheme 59. Tricyclohexylphosphine adducts of cyclopalladated ferrocenylimines and 2,2'-bipyridine adducts of cyclopalladated ferrocenylimine.⁶⁴

2,2-Bipyridine adduct of palladacycle **153** is an effective catalyst in reactions of aldehydes **154** and arylboronic acids **155** and gives secondary alcohols **156** (scheme 59).⁶⁴ The reaction is performed in aqueous media with SDS and a weak acid NaH₂PO₄·2H₂O, as shown in scheme 60.



Scheme 60. Reaction of arylboronic acids and aldehydes with 2,2'-bipyridine adducts of cyclopalladated ferrocenylimine catalyst in aqueous media with SDS and a weak acid NaH₂PO₄·2 H₂O.⁶⁴

Palladacycles with phosphine or carbene ligand enhance the catalyst activity which leads to activation of C-Cl bond.⁶⁴ Palladacycles with 2,2'-bipyridine ligand can act as catalyst for various reactions of arylboronic acids and can be used in water. The greatest advantage of palladacycles is its low catalyst loading of 0,1-1 % or lower, the possibility to perform the reactions under mild conditions and suitability for a wide variety of functional groups.

The mechanism of the catalytic cycle consists of oxidative addition, transmetallation and reductive elimination.⁶¹ The modification of the ligand affects the catalytic cycle but the effect is not always straightforward. For example, for monodentate phosphines the presence of labile ligands, such as dibenzylideneacetone, halide ligands and acetate, can change the kinetics of the reaction by coordination to the low-valent palladium intermediates.

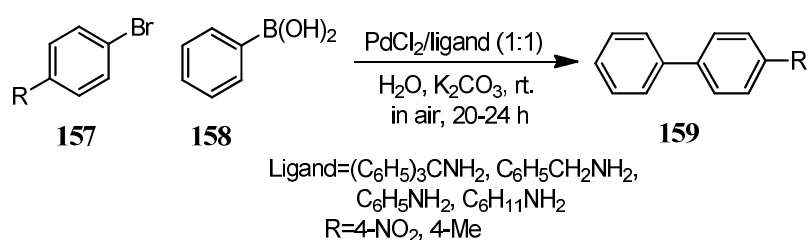
Because reductive elimination is the reverse reaction of oxidative addition, ligand effects are often opposite.⁶¹ As the bite angle of the multiple-dentate ligand increases, both oxidative addition and reductive elimination reactions become faster. The optimum angle of P-Pd-P varies between 85-111° depending on ligand.

4.3.1 Amine-based ligands

Phosphine-based ligands, such as tertiary phosphines, hemilabile-type phosphines, sterically crowded biphenyl-type phosphines and other electron-rich phosphines are capable of forming palladacycles.⁶⁵ Complexes containing those ligands show excellent activities but often are commercially unavailable, very expensive or difficult to synthesize.

Most of the ligands are insoluble in water which restricts their use.⁶⁵ Water is an eligible solvent in the Suzuki-Miyaura reactions because it is cheap, readily available and non-toxic. Unfortunately, only rarely water is used successfully as solvent and even then additives, such as TBAB, are needed. However, with a PdCl₂ and primary amine ligands Suzuki-Miyaura reactions can be performed in aqueous media under mild conditions.

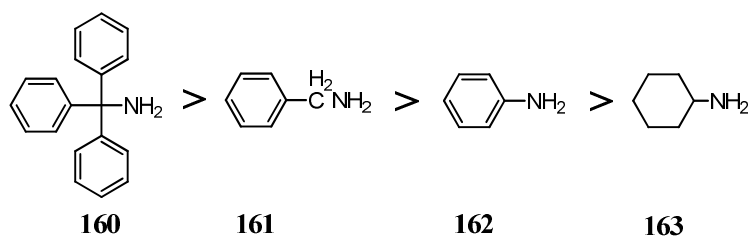
Amines are often used as bases in palladium-mediated cross-coupling reactions but rarely as ligands.⁶⁵ On the other hand, especially secondary and tertiary amines are highly efficient and have an ability to form five- or six-membered palladacycles. For example, Suzuki-Miyaura reaction between the arylbromide **157** and phenylboronic acid **158** proceeds with K₂CO₃ as base in water at room temperature (scheme 61). The catalyst can be generated *in situ* from PdCl₂ in ratio 1:1 and gives the substituted phenylbenzene **159** in good yields.



Scheme 61. Suzuki-Miyaura cross-coupling reaction of arylbromide (0,5 mmol) and phenylboronic acid (0,55 mmol) with K₂CO₃ base (1,5 mmol), in H₂O (6 ml) catalyzed by PdCl₂ (1–4 mol %) with an amine-based ligand (1–4 mol %).⁶⁵

It is known that primary amines undergo amination reactions with aryl halides and form secondary amines in the presence of Pd-catalysts.⁶⁵ However, in this case such side reaction

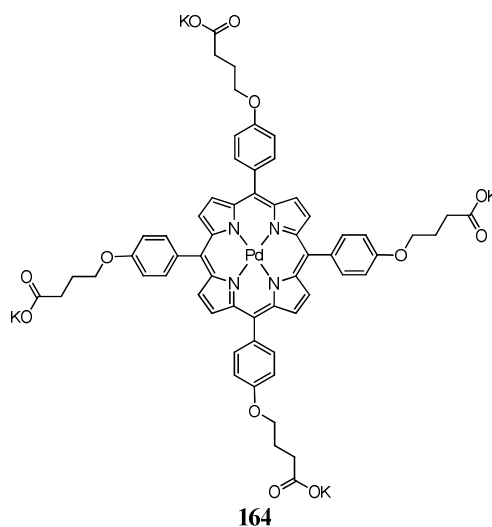
does not occur. The efficiencies of the ligands **160-163** follow the order: $(\text{C}_6\text{H}_5)_3\text{CNH}_2 > \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 > \text{C}_6\text{H}_5\text{NH}_2 > \text{C}_6\text{H}_{11}\text{NH}_2$, as shown also in scheme 62 below. It is consistent with the palladacycle-forming capacity of the ligands. If PdCl_2 is changed to $\text{Pd}(\text{OAc})_2$, with the ligand $(\text{C}_6\text{H}_5)_3\text{CNH}_2$ it catalyzes even the reaction of the less reactive aryl chlorides.



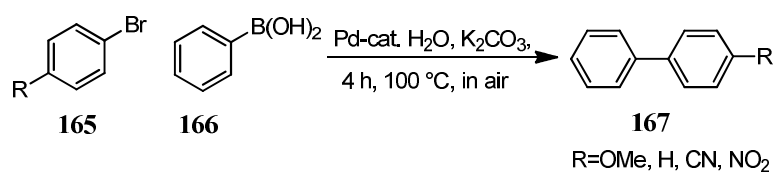
Scheme 62. Primary amine-based ligands suitable for the Suzuki-Miyaura reactions.⁶⁵

4.3.2 Porphyrin ligands

Palladium porphyrins traditionally have applications as oxygen sensors, photo-induced protein cross-linking agents and luminescent markers.⁶⁵ However, palladium complex with a porphyrin ligand **164** is a rare but suitable catalyst precursor for cross-coupling reactions (scheme 63). For example, palladium-porphyrin catalyzed Suzuki-Miyaura reaction of aryl bromides **165** and phenyl boronic acid **166** gives high yields of phenylbenzene **167** coupling product (scheme 64). The reaction is performed in water at 100 °C under aerobic conditions for 4 hours and K_2CO_3 is used as base. As expected, the electron-withdrawing groups of the aryl ring increase the reaction rate. A suitable molar ratio of substrate and catalyst is 1000:1. The catalyst can be recycled for further use but it loses some of its activity.

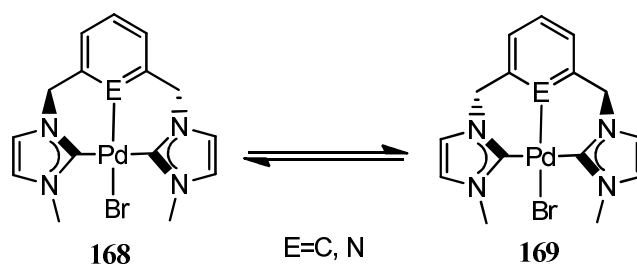


Scheme 63. Water-soluble palladium porphyrin ligand.⁶⁶



Scheme 64. Suzuki-Miyaura cross-coupling reaction of phenylboronic acid (1,5 mmol) and aryl bromides (1 mmol) with Pd-catalyst (0,1 mol %) under aerobic conditions at 100 °C, in water, K₂CO₃ (2 mmol). The molar ratio of substrate to catalyst is 1000:1.⁶⁶

The use of water instead of organic solvents in Suzuki-Miyaura coupling reaction allows separation and reuse of the catalyst.⁶⁶ Therefore the reaction is often performed either in aqueous, biphasic solvent mixture or in neat water. Water-soluble phosphines are traditionally used as ligands in aqueous media but phosphine-free porphyrin-like systems, such as CNC-pincer palladium complexes, are also efficient catalysts (scheme 65).

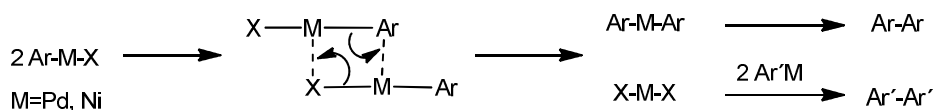


Scheme 65. Air and thermally stable palladium(II) complexes of CNC and CCC bis-carbene pincer ligands have a twisted conformation.⁶⁷

5 Side reactions

5.1 Overview

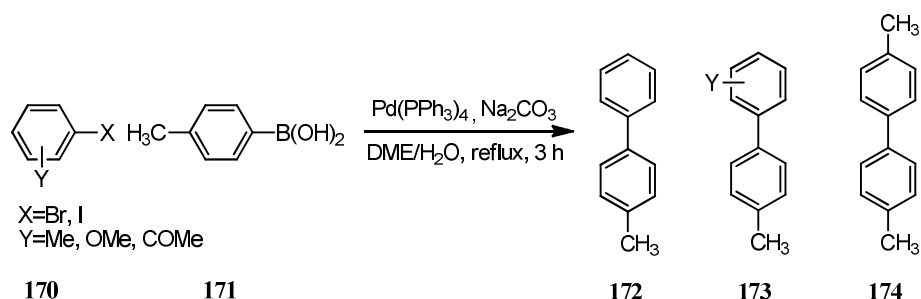
The most common side reactions are undesirable homocoupling products.⁶⁸ Palladium-catalyzed reaction mechanism is presented in scheme 66. The metathesis of R-M-X to MX_2 and R_2M ($\text{M}=\text{Ni}, \text{Pd}$) gives dimers of electrophiles and organometallics. However, the side reactions do not often disturb the coupling reactions of organoboronic acids when palladium or nickel catalysts are used.



Scheme 66. The mechanism of Pd-catalyzed homocoupling reactions.⁶⁸

Triarylphosphines are good ligands to stabilize the palladium species.^{69,70} However, there is a reaction between palladium- and phosphine-bound aryls that can lead to an undesirable side reaction. A phenyl-coupling product of triphenylphosphine and an electron-rich haloarene gives a 1-methyl-4-phenylbenzene by-product **172**, as shown in scheme 67. Compound **173** is the target product and compound **174** is another by-product. With electron-deficient haloarenes the by-product forms only in small amounts and *ortho*-substituted haloarenes reduce the yield of the by-product. Bromoarenes demonstrate better selectivity

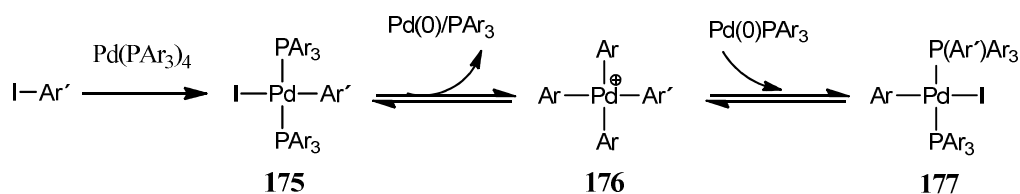
than corresponding iodides even though iodoarenes are highly reactive towards palladium(0) complexes.



Scheme 67. Cross-coupling reaction of haloarene (**170**) and *p*-tolyl boronic acid (**171**) with Pd-catalyst (3 mol %) and Na₂CO₃ (2 equiv.). A phenyl-coupling product (**172**) is formed as by-product.⁶⁹

Electronic and steric effects and the presence of electron-donating group in the haloarenes and phosphine ligands have a great influence on aryl-aryl interchange.^{70,71} Electron-withdrawing groups and steric hindrance of an *ortho*-substituent slow down the interchange reaction but electron-donating group in phosphine or haloarene increases the rate of side reactions.

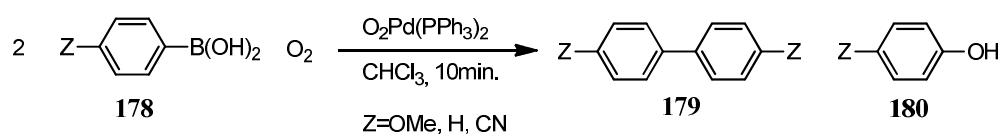
Slow transmetallation caused by steric and electronic effects increases the activity of phosphine-bound aryls and therefore aryl exchange occurs before transmetallation.^{70,72} Electron-rich haloarenes slow down the transmetallation but strong bases accelerate it relative to aryl-aryl interchange. The amount of phenyl coupling product decreases according to the base strength Na₂CO₃>K₃PO₄>NaOH. The haloarene should be chosen to minimize side reactions because the rate of transmetallation to R-Pd-X is dependent on the type of halogen (X=Cl>Br>I). As shown in scheme 68, the interchange of **175** to **177** proceeds via phosphonium salt formation **176**. The rate is decreased by steric hindrance but accelerated by the stabilizing electron-rich aryls.



Scheme 68. Mechanism of aryl interchange catalyzed by $\text{Pd(PAr}_3)_4$.⁷⁰

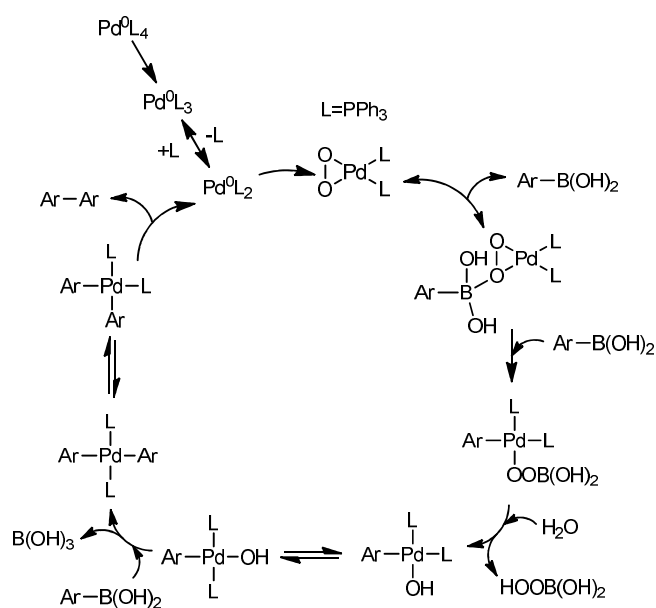
5.2 Homocoupling induced by oxygen

The palladium-catalyzed homocoupling may compete with Suzuki-Miyaura cross-coupling reaction if the reaction does not proceed in inert atmosphere and is exposed to air.^{73,74} Dimerization may also take place during work-up if unreacted arylboronic acid remains in the reaction mixture. An example of oxygen induced homocoupling reaction is shown in scheme 69 below. The rate of reaction is slow under neutral conditions, but is very fast in the presence of aqueous base.



Scheme 69. Homocoupling of arylboronic acids **178** yields homocoupling product **179** and another by-product **180** in the presence of $\text{Pd(PPh}_3)_4$ complex which is known to react with O_2 and generate the peroxo complex $\text{O}_2\text{Pd(PPh}_3)_2$.⁴²

Oxidative homocoupling of arylboronic acids produces symmetrical biaryls by the mechanism shown in scheme 70.^{73,74} The mechanism involves double transmetalation to PdX_2 followed by reductive elimination of biaryl and formation of palladium(0) species which is oxidized in the presence of arylboronic acid. Suitable oxidants are e.g. 4-MeC₆H₄SO₂Cl, PhCH(Br)CH(Br)CO₂Et, PhCH(Br)CO₂Me and O_2 .



Scheme 70. Suggested mechanism for oxygen induced homocoupling of arylboronic acids.⁴²

As a result, hydrogen peroxide is generated which oxidizes some of the arylboronic acids to phenols, as shown in equations 8 and 9.^{20,73} The occurrence of homocoupling side reactions can be dramatically reduced when boronic esters are used in DMSO. Common conditions and reagents inducing homocoupling products are presented in table 1.

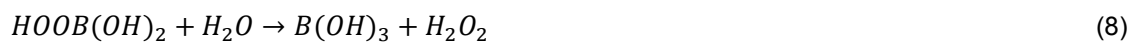
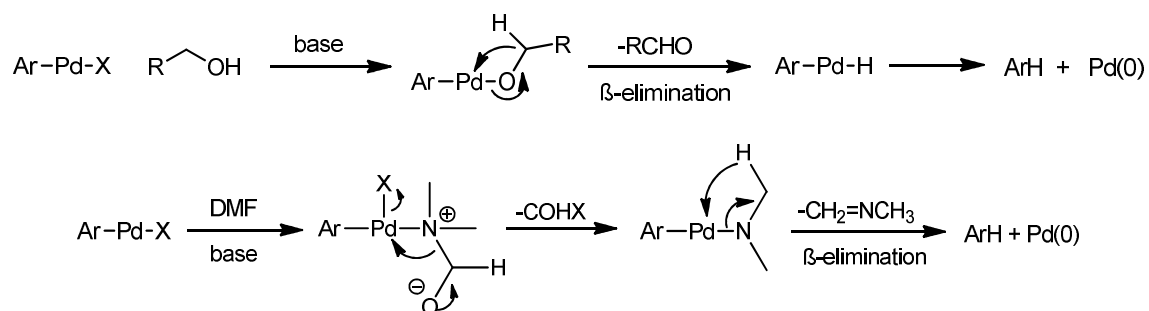


Table 1. Conditions and reagents for synthesizing symmetrical biaryls^{73,74}

Catalyst	Reoxidant	Base/ Solvent/ Temp.
[PdCl ₂ (dppb)]	PhCH(Br)CH(Br)CO ₂ Et	K ₂ CO ₃ / THF-H ₂ O/ 70 °C
PdCl ₂ / BINAP	PhCH(Br)CO ₂ Me	KF/ dioxane-H ₂ O/ 100 °C
PdCl ₂	4-MeC ₆ H ₄ SO ₂ Cl	Na ₂ CO ₃ / MeOH-H ₂ O/ r.t.
Pd(OAc) ₂	O ₂	Na ₂ CO ₃ / EtOH-H ₂ O/ r.t.
Pd(OAc) ₂	O ₂	NaOAc-R ₄ NX/ H ₂ O/ r.t.
Pd(OAc) ₂ / dppp	O ₂	DMSO/ 80 °C

5.3 Dehalogenation

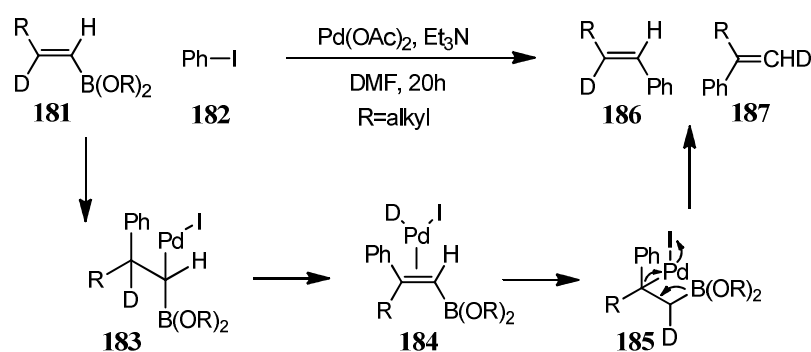
Organic halides are often dehalogenated during cross-coupling reactions, especially if alcohols are used as solvents.⁴³ The hydride is often derived from β -hydride elimination yielding RCHO and Ar-Pd-H, as shown in scheme 71. DMF can also act as hydride ion donor in the presence of base, thus dehalogenation can be avoided by replacement of DMF with DMA.



Scheme 71. Dehalogenation mechanism of organic halides.⁴³

5.4 *ipso*-Coupling

ipso-Coupling reactions are possible between 1-alkenylboronic acids **181** or esters and haloarenes **182** in the presence of a ligandless palladium catalysts and a weak base, such as Et₃N, NaOEt or NaOH.⁷⁵ The *ipso*-coupling proceeds by the mechanism of the Heck reaction **183-185** for alkenyl compounds and yields alkene **186** and an unsymmetrical alkene **187**, as shown in scheme 72.



Scheme 72. Mechanism of *ipso*-coupling. The reaction proceeds with a Pd-catalyst; Pd(PPh₃)₄, PdCl₂(PPh₃)₂ or Pd-black (3 mol %) in DMF or benzene at 80 °C for 20 hours, PhI (1 equiv.) and 1-alkenylboronic acid (1,1 equiv.).⁷⁵

6 Summary

Suzuki-Miyaura reaction is one of the most popular reactions in modern organic chemistry.^{3,4} An organoboron compound reacts with an organic halide in the presence of a palladium catalyst and produces a bis-aryl via direct C-C bond formation. The reaction proceeds via catalytic cycle that involves the oxidative addition of the halogenated species to the palladium catalyst, transmetalation step where the organic groups of activated boron species are transferred to the metal and the reductive elimination step that gives the coupling product and regenerates the catalyst. The boron atom is activated by a base in the transmetalation step to increase its nucleophilicity and give a clean reaction.

There are a lot of applications of the Suzuki-Miyaura reaction in organic synthesis, material and medicinal chemistry.^{3,15} The reaction can be performed with a variety of organometallic reagents, among which organic halides and triflates are the most useful ones. Also compounds containing heteroatoms, such as nitrogen, oxygen and sulfur, are useful in cross-coupling reactions but used less commonly. The present work is concentrated on the cross-coupling reactions of organoborons and organic halides.

Suzuki-Miyaura cross-coupling reaction is usually performed with arylboronic acids which are the most often used partners for synthesis of biaryl units, but other derivatives, such as aryl boronic esters, arylboronic pinacol esters and pinacolboranes, are used as well.^{14,19} The most common synthesis route to arylboronic acids involves a reaction of an organic halide, organometallic intermediate, such as R-Li or M-Mg and borate ester at low temperature.

Cross-coupling reaction is mild, thus several functional groups remain intact.^{8,14,21,23,26,30,38} Electron-withdrawing groups enhance the rate of cross-coupling. Sterically hindered and heteroaromatic halides can be used as well for preparing arylboronates. In order to achieve a clean cross-coupling reaction, the reaction conditions must be selected correctly. For example, the right base ensures high selectivity and good yield of the target product, and mild bases, such as KOAc and Na₂CO₃, are often suitable. The cross-coupling reaction can be performed also under almost neutral conditions which is possible with copper carboxylate

at room temperature. The cross-coupling reactions are often carried out in a two-phase system of organic and basic aqueous solutions. For example, a two-phase system of aqueous K_2CO_3 and toluene is a common solvent combination. The cross-coupling reactions of boric acids and aryl halides are usually performed at 80-100 °C with reaction time of 4-24 hours. However, by using microwave irradiation the reaction time can be reduced to 5-10 minutes.

Even though in cross-coupling reactions the most commonly used catalysts are palladium-based, other transition metal complex catalysts, such as platinum, nickel and titanium, have been used as well.^{14,49,55,65} A variety of palladium catalysts are available with and without ligands and even catalyst anchored to active silica has been developed which makes the catalyst recyclable. There is a wide variety of different ligands but the palladium catalysts with bulky, electron-donating alkylphosphines are the most suitable in reactions of organoborons and haloarenes. Porphyrin and amine-based ligands have also been used successfully.

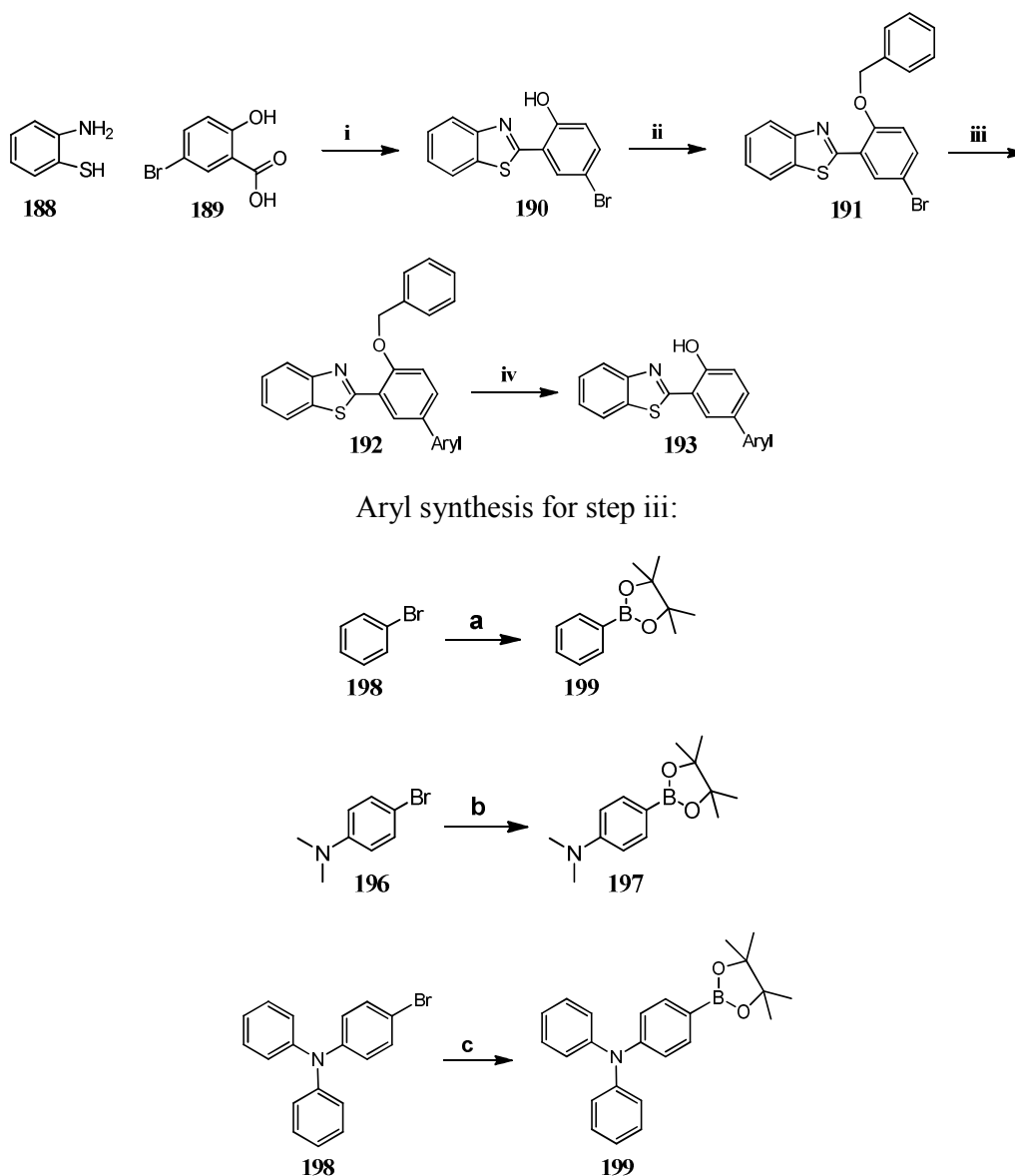
In addition to desirable cross-coupling products, homocoupling, *ipso*-coupling or dehalogenation by-products may be formed during the reaction.^{35,70,72} Electronic and steric effects, strong bases and electron-donating group in the haloarenes or phosphine ligands increase the amount of homocoupling by-products. Usually the reaction is performed in an inert atmosphere to minimize the amount of oxidation by-products. By carefully selecting the reaction conditions, the amount of by-products can be kept at minimum.

Cross-coupling reaction mechanism usually requires high temperatures, potentially toxic organic solvents, highly reactive organometallic reagents and super-stoichiometric levels of additives.³⁵ Recently, milder and more selective conditions for cross-coupling reactions have been developed. By *in situ* activation of carbon-halogen or carbon-hydrogen bonds by cationic palladium, the cross-coupling reactions can be performed in water and/or at room temperature.

EXPERIMENTAL SECTION

7 The plan for synthesis

The aim of the experimental work was to synthesize phenylamine derivative of benzothiazole **193a-c**, which can be potentially used as a material for organic solar cells. The target molecules and the synthesis route (scheme 73) were designed by Dr. Alexander Efimov.



Scheme 73. Synthesis route of boroaryl derivatives and the target molecules.

The synthetic plan comprises five steps: preparation of benzothiazole (1); protection of benzothiazole with benzyl group (2); borylation of bromoaryl (3); Suzuki coupling of protected benzothiazole and boroaryl derivatives (4); and deprotection of the coupled product to produce the target compound (5).

First, the plan was to test the reactions with small amounts of starting materials. When satisfactory yields were achieved, the amounts of starting materials could be raised and larger amounts of intermediate molecules synthesized in order to prepare the target molecules.

8 Reagents and equipment

8.1 Reagents and solvents

The reagents and solvents used in the syntheses are listed in table 2.

Table 2. The reagents and solvents, supplier and purity

Reagent	Supplier	Purity
Acetone	Sigma-Aldrich	99,0 %
Chloroform	Sigma-Aldrich	99,0-99,4 %
Dichloromethane	Sigma-Aldrich	99,8 %
Ethyl acetate	Sigma-Aldrich	≥99,5 %
Hexane	Sigma-Aldrich	≥97,0 %
KOAc	Sigma-Aldrich	
Polyphosphoric acid	Sigma-Aldrich	115,0 %
Toluene	Sigma-Aldrich	99,9 %
2-Aminothiophenol	Sigma-Aldrich	99,0 %
4-Bromo-N,N-dimethylanilin	Sigma-Aldrich	97,0 %
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane	Sigma-Aldrich	
NaCl	VWR prolabo	99,9 %
Tetrabutylammonium chloride	Fluka	≥99,0 %
Bis(pinacolato)diboron	TCI Europe	>97,0 %
4-Bromotriphenylamine	TCI Europe	>95,0 %
Benzoyl bromide	Merck	98,0 %
Dimethyl sulfoxide	Merck	
Deuteriochloroform	Merck	min. 99,8 %
K ₂ CO ₃	Merck	≥99,0 %
NaOH	Merck	≥99,0 %
Na ₂ SO ₄	Merck	≥99,9 %

8.1.1 Drying of potassium acetate

Since the reactions performed were moisture sensitive, the base, KOAc, was dried before use. The potassium acetate powder was placed evenly in a large beaker and kept at 200 °C

for about 12 hours in order to remove any residual moisture. Then the base was cooled down *in vacuo* in an exsiccator and placed in a properly sealed jar.

8.1.2 Recrystallation of palladium catalyst

Palladium catalyst $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (2 g) was recrystallized by heating at reflux in 50 ml of CH_2Cl_2 for 20 minutes. The solution was red with some red, solid particles. The hot solution was filtered through paper filter and the liquid was collected. Then it was diluted with hexane (100 ml). Red needle-like precipitate started to grow. The mixture was kept in a fridge over night to help the precipitation since almost all solids are less soluble in a cold solvent. The precipitate was filtered, washed with hexane and acetone and dried. Yield is 1,2 g.

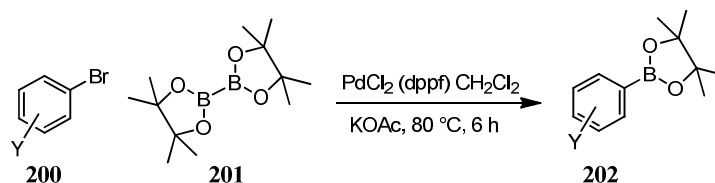
8.2 Equipment

The equipment used for purifying and analyzing the products of the syntheses:

- Rotor evaporator: Rotavapor R3000, Büchi
- Liquid chromatography: CombiFlash liquid chromatography, Teledyne Isco
- NMR spectrometer: Varian Mercury 300 MHz NMR Spectrometer
- HR ESI-TOF mass spectrometer: Waters LCT Premier XE

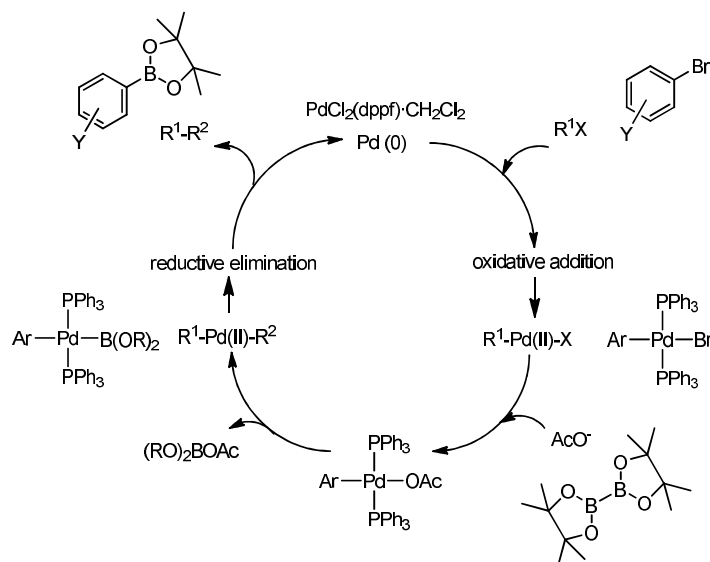
9 Synthetic mechanisms

9.1 Borylation



Scheme 74. Borylation of organohalides via cross-coupling mechanism.

The borylation of organohalides proceeds via cross-coupling mechanism.²¹ The cross-coupling reaction of bromoaryl **200** and bis(pinacolato)diboron **201** proceeds via a catalytic cycle (scheme 74). It involves the oxidative addition of bromoarene, the electrophile, to the palladium(0) complex yielding Ar-Pd(II)-Br. The transmetalation between pinacol ester of diboronic acid and Ar-Pd(II)-Br with the aid of base gives Ar-Pd(II)-B(OR)₂ intermediate. Reductive elimination of arylboronic ester **202** regenerates the palladium(0) complex. The catalytic cycle is shown in scheme 75 below.

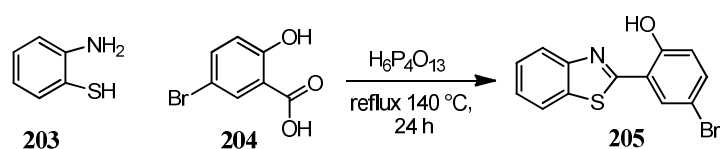


Scheme 75. The catalytic cycle of the cross-coupling mechanism when borylated compounds are synthesized from arylbromides and bis(pinacolato)diboron.²¹

The steps of oxidative addition and reductive elimination are quite well understood.⁴⁶ However, the transmetallation process is not that well known since there are several processes involved in transferring the organic group onto R^1 -Pd-X. Sodium hydroxide and other bases accelerate the transmetallation between R^1 -Pd-X and trialkylboranes or organoboronic acids.

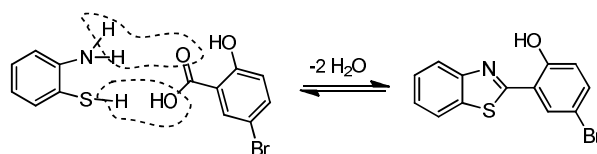
9.2 Preparation of benzothiazole

Benzothiazole is a compound with bicyclic ring containing heteroatoms.⁷⁶ Benzothiazoles have multiple applications, mostly in medicinal and bioorganic chemistry. Combination of 2-aminobenzothiazoles with other heterocycles is a common approach in the field of drug designing chemistry. However, recently benzothiazoles gained considerable attention in the field of organic electronics and light emitting devices. In the present work the benzothiazole derivatives were prepared for potential application in organic solar cells. 5-Bromo-2-hydroxy-benzothiazole **205** was synthesized by heating 2-aminothiophenol **203** and 5-bromosalicylic acid **204** at reflux in polyphosphoric acid for 24 hours, as shown in scheme 76.



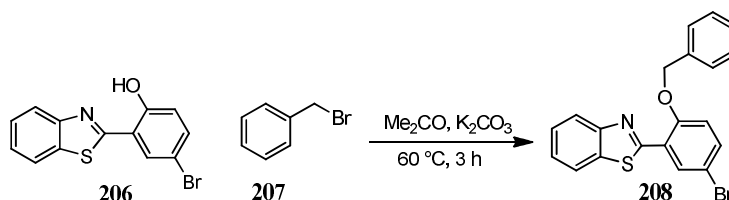
Scheme 76. Reaction conditions in the synthesis of 5-bromo-2-hydroxy-benzothiazole.

In strongly acidic reaction conditions 5-bromosalicylic acid and 2-aminothiophenol react while water is removed, as described in scheme 77.⁷⁷ Polyphosphoric acid binds the formed water molecules.



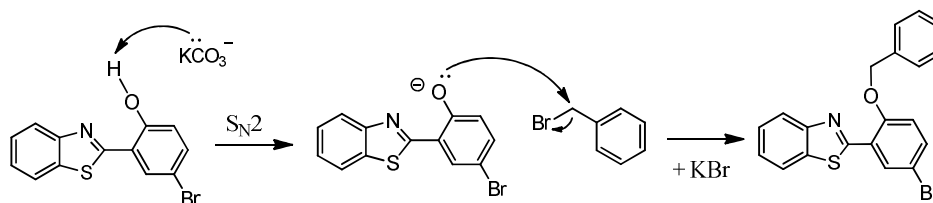
Scheme 77. Water molecules are removed during the reaction of 2-aminothiophenol and 5-bromosalicylic acid to synthesize 5-bromo-2-hydroxy benzothiazole.⁷⁷

9.3 Benzyl protection



Scheme 78. The reaction conditions for the synthesis of 5-bromo-2-(benzyloxy)-benzothiazole.

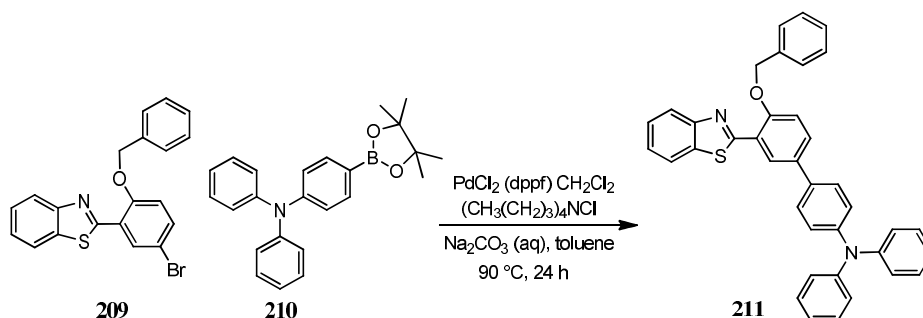
In order to make the desirable product by cross-coupling reaction, the hydroxyl group of the benzothiazole must be protected. In this case, benzyl protection was chosen, as shown in scheme 78. The reaction of benzothiazole **206** and benzyl bromide **207** proceeds via S_N2 mechanism and yields the 5-bromo-2-(benzyloxy)-benzothiazole **208**. Since the phenolic hydroxyl of benzothiazole is a weak acid, a weak base is enough to remove the proton and start the reaction, as shown in scheme 79 below.



Scheme 79. Benzyl protection of benzothiazole proceeds via S_N2 mechanism.

9.4 Suzuki coupling

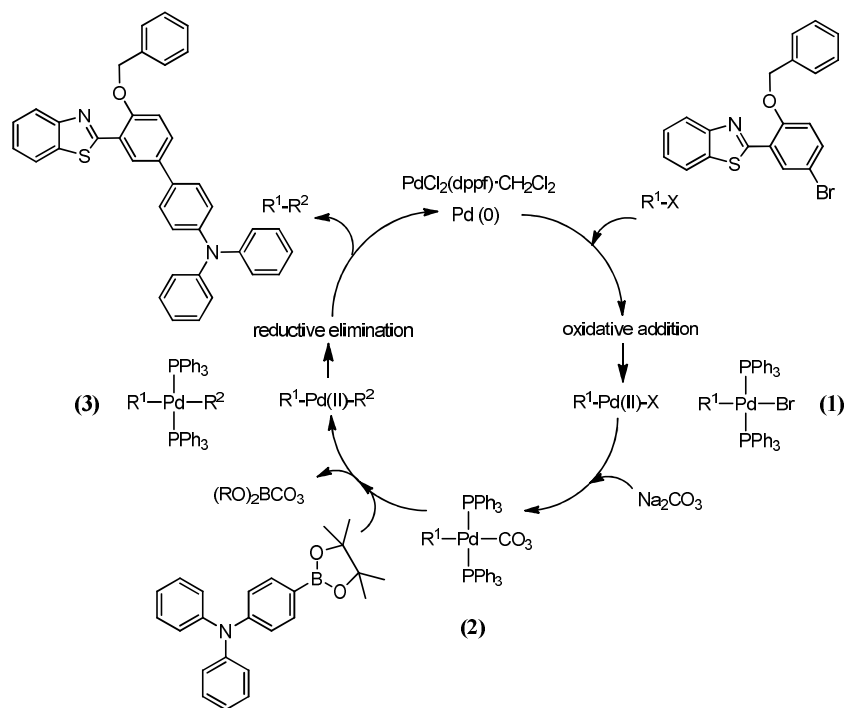
The 2-(benzyloxy)-5-aryl-benzothiazole **211** was synthesized via Suzuki-Miyaura cross-coupling reaction of 5-bromo-2-(benzyloxy)-benzothiazole **209** and pinacol ester of arylboronic acid **210**, as shown in scheme 80.



Scheme 80. Suzuki-Miyaura cross-coupling reaction for synthesis of 2-(benzyloxy)-5-aryl-benzothiazole.

The Suzuki-Miyaura cross-coupling reaction proceeds via catalytic cycle that involves the oxidative addition (1) of 5-bromo-2-(benzyloxy)-benzothiazole to the palladium(0) complex yielding aryl-palladium(II)-halogen complex, $\text{R}^1\text{-Pd(II)-X}$ (scheme 81).²¹ The next step involves transmetalation (2) between pinacol ester of arylboronic acid and $\text{R}^1\text{-Pd(II)-X}$ with the aid of base to gain $\text{R}^1\text{-Pd(II)-R}^2$ intermediate.

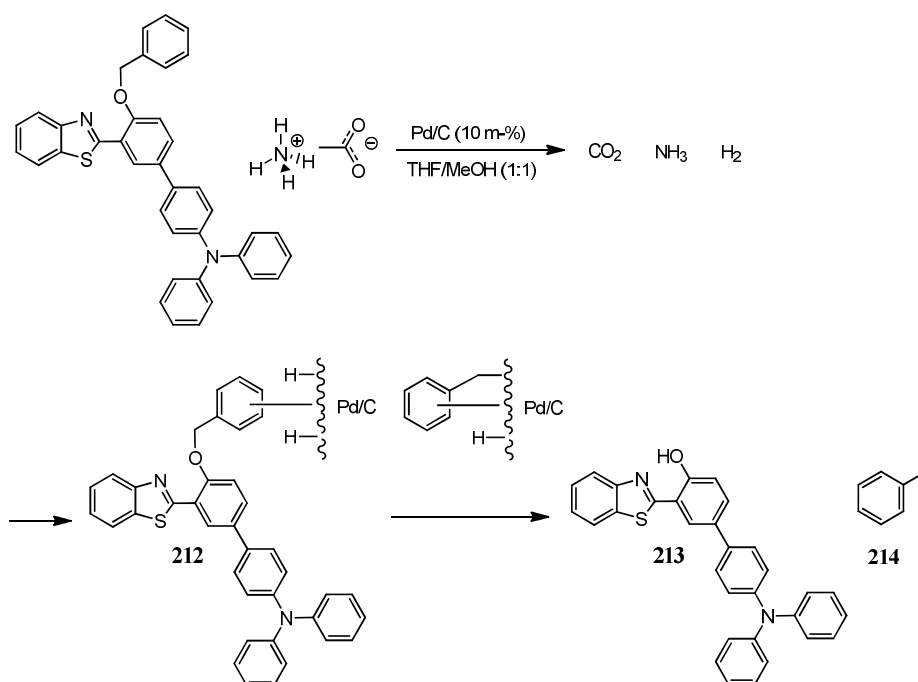
In this reaction sodium carbonate was used as base, and tetrabutylammonium chloride served as phase-transfer agent.^{21,46} Bases, such as Na_2CO_3 , accelerate the transmetalation between $\text{R}^1\text{-Pd-X}$ and organoboronic acids and esters. Reductive elimination (3) of arylboronic ester regenerates the palladium(0) complex and gives the cross-coupling product, 2-(benzyloxy)-5-aryl-benzothiazole.



Scheme 81. The catalytic cycle of the Suzuki-Miyaura cross-coupling reaction when 2-(benzyloxy)-5-aryl-benzothiazole is synthesized from arylboronic acid pinacol ester and 5-bromo-2-(benzyloxy)-benzothiazole.²¹

9.5 Deprotection by Pd/C reduction

The benzyl protection can be removed by hydrogenolysis. The bond between oxygen and carbon atoms is cleaved and hydrogen added. 2-(2-Hydroxy-5-aryl) benzothiazole **213** is synthesized by the hydrogenolysis reaction of 2-(benzyloxy-5-aryl)benzothiazole **212** and ethylbenzene **214** is formed as by-product. The general mechanism of the hydrogenolysis is presented in scheme 82 below.

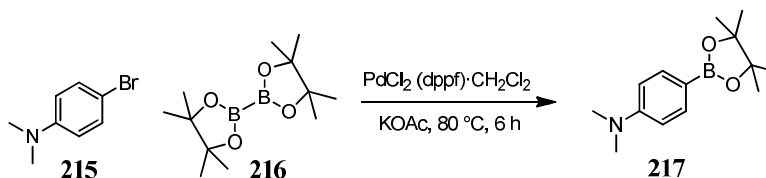


Scheme 82. Mechanism of hydrogenolysis of 2-(benzyloxy-5-aryl)benzothiazole to 2-(2-hydroxy-5-aryl) benzothiazole.

First ammonium formate decomposes in the presence of Pd/C to carbon dioxide, ammonia and hydrogen. The hydrogen gas is absorbed onto the surface of palladium metal. Then benzyloxy group coordinates to the metal catalyst via the aromatic ring. The benzyl gets close to palladium-bound hydrogen atoms and reduces. By this method only benzylic or allylic C-X bonds can be reduced because of the need for initial coordination. In addition to alcohols, amines can be reduced by the same method.

10 The Syntheses

10.1 N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



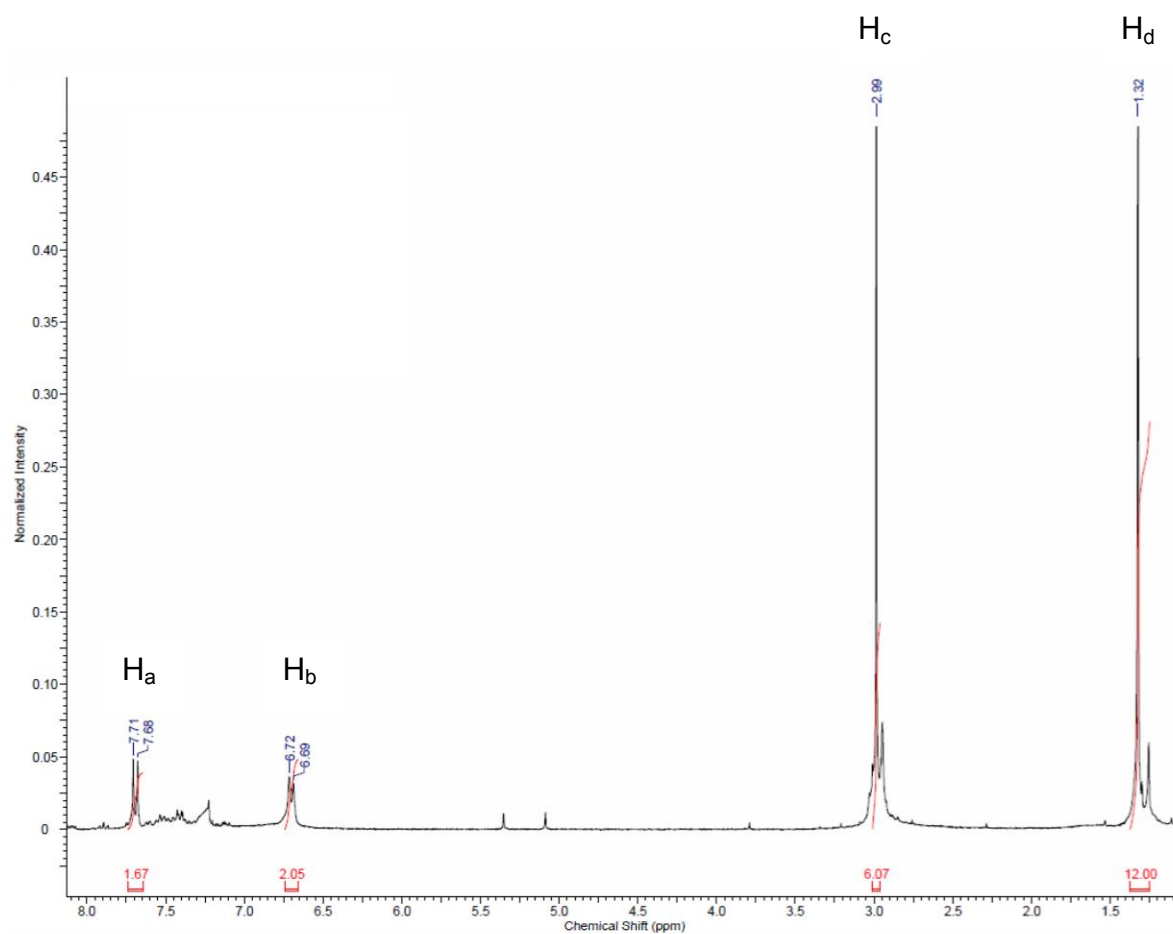
Scheme 83. The reaction conditions for the synthesis of arylboronic acid pinacol ester **217**.

A screw cap vial was loaded with 4-bromo-N,N-dimethylaniline (0,100 g, 0,50 mmol), potassium acetate (0,147 g, 1,41 mmol), PdCl₂(dppf)·CH₂Cl₂ (0,020 g, 0,025 mmol), bis(pinacolato)diboron (0,152 g, 0,60 mmol) and dry DMSO (5 ml). The solution was stirred at 80 °C for 6 hours and purged with argon for the first 15 minutes (scheme 83). After cooling down, the solution was poured into a beaker with cold water (80 ml) and extracted with DCM (4·20 ml). The organic phase was separated and washed with water (2·50 ml). The organic phases were combined, dried over anhydrous sodium sulfate and evaporated by a rotary evaporator. The purification was done by silica gel column chromatography (DCM/hexane, 1:3). A high amount of starting material was recovered from the reaction. The yield of N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline is 0,0075 g (0,03 mmol) as brown powder.

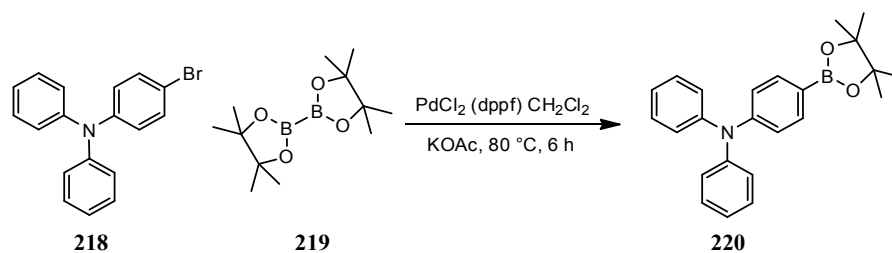
M(C₁₄H₂₂O₂NB)= 247.14 g/mol

¹H NMR(CDCl₃): δ= 7,70 (d, J=8,5 Hz, 2H), 6,71 (d, J=8,5 Hz, 2H), 3,0 (s, 6H), 1,32 (s, 12H) ppm.

MS(ESI/TOF) m/z 248,18 [M+H]⁺



10.2 N,N-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



Scheme 84. The reaction conditions for the synthesis of arylboronic acid pinacol ester **220**.

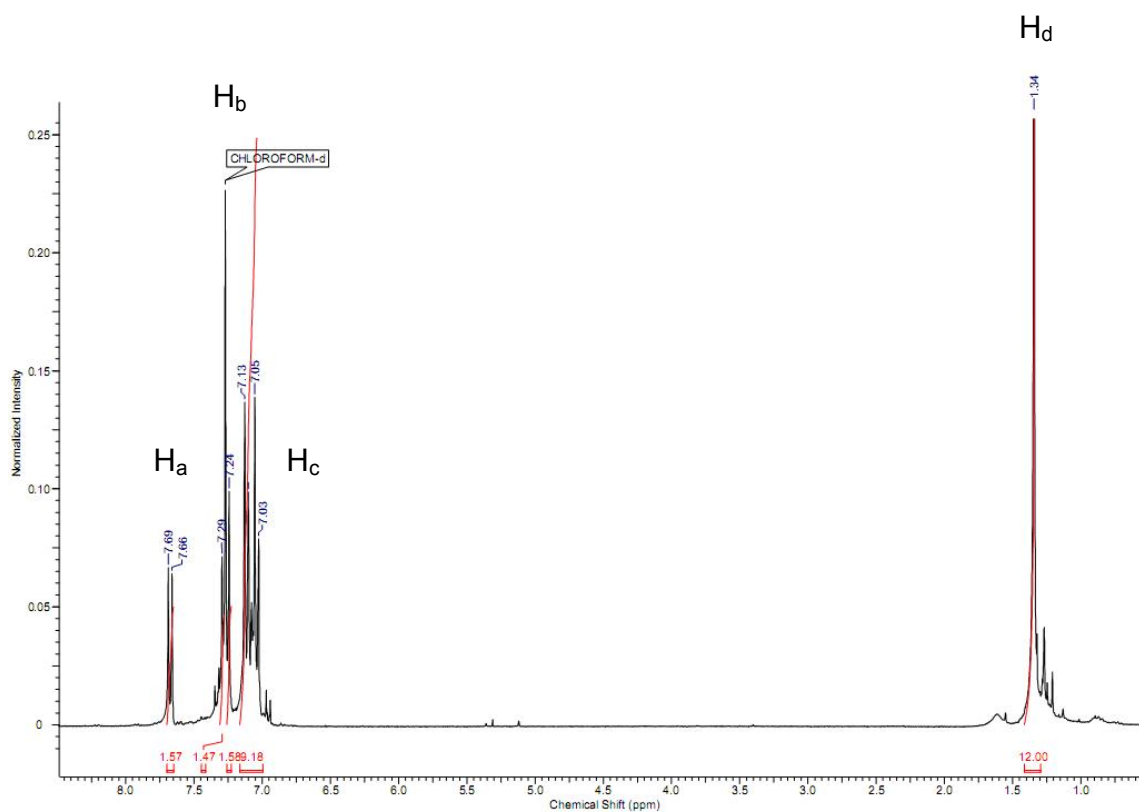
A screw cap vial was loaded with 4-bromo-N,N-diphenylaniline (0,100 g, 0,31 mmol), potassium acetate (0,091 g, 0,92 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0,013 g, 0,015 mmol) and bis(pinacolato)diboron (0,094 g, 0,37 mmol) and dry DMSO (5 ml). The solution was

purged with argon for the first 15 minutes and stirred at 80 °C for 6 hours (scheme 84). After cooling down, the solution was poured into cold water (80 ml) and extracted with DCM (4·20 ml). The organic phase was separated and washed with water (2·50 ml). The organic phases were combined, dried over anhydrous sodium sulfate and evaporated on rotary evaporator. The purification was done by silica gel column chromatography (DCM/hexane, 1:3). The yield of N,N-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline is 0,080 g (0,22 mmol).

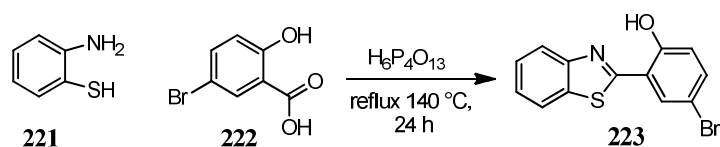
$M(C_{24}H_{26}O_2NB)=371.28$ g/mol

1H NMR ($CDCl_3$): $\delta=7,68$ (d, $J=8,08$ Hz, 2H), 7,27 (m, 3H), 7,08 (m, 9H), 1,34 (s, 12H) ppm.

MS(ESI/TOF) m/z 372,21 $[M+H]^+$



10.3 2-(1,3-Benzothiazol-2-yl)-4-bromophenol



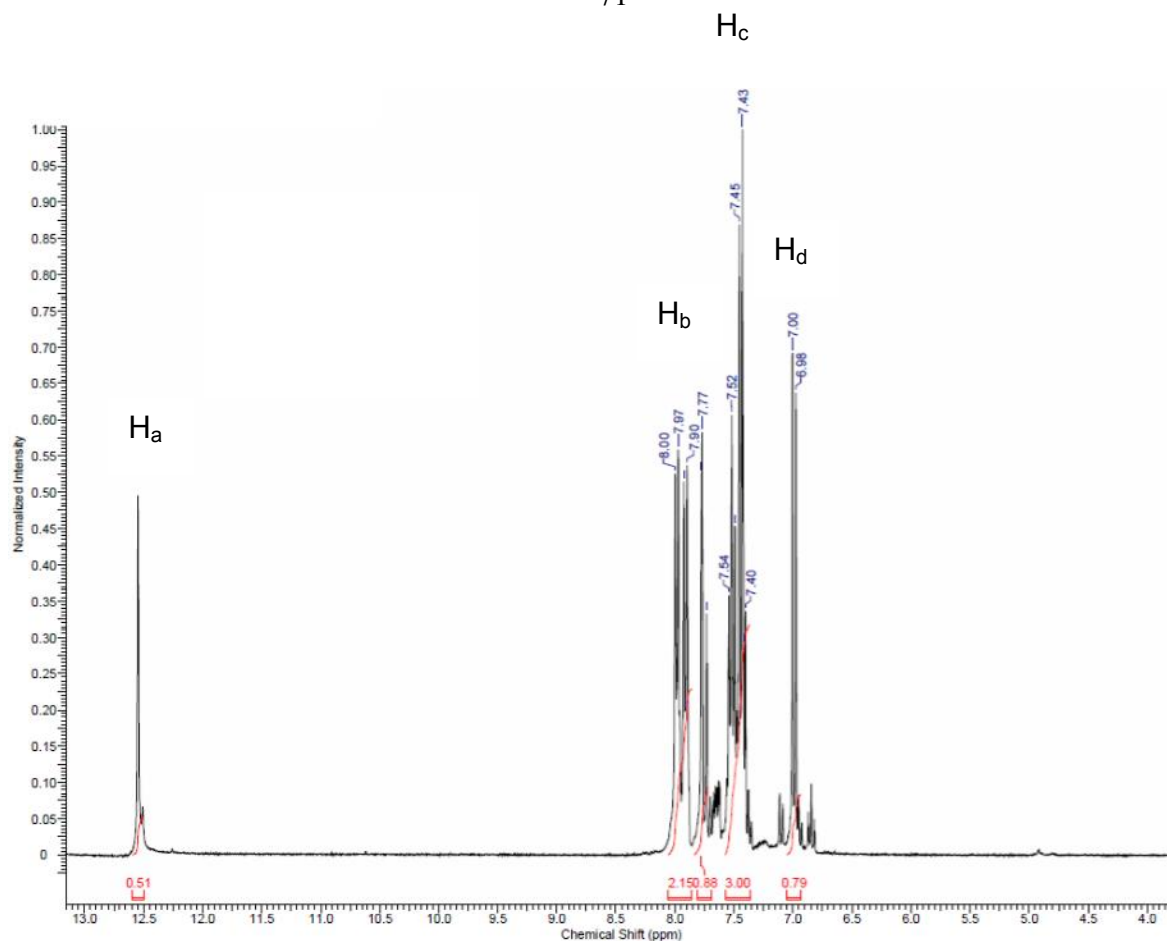
Scheme 85. The reaction conditions for the synthesis of 5-bromo-2-hydroxy benzothiazole **223**.

2-Aminothiophenol (0,500 g, 4 mmol), 5-bromosalicylic acid (0,868 g, 4 mmol) were added in a vial with 10 g of polyphosphoric acid, heated to 140 °C and stirred intensively for 24 hours (scheme 85). The mixture was cooled down, poured into ice water (~ 200 ml) and the pH was adjusted from 0 to 5 with 2M NaOH (aq.), after which the green flakes started to precipitate. The mixture was kept in an ice bath over night to maximize the precipitation. The suspension was filtered on a Büchner funnel. The solid residue was dried *in vacuo* over KOH. The solid crude product was dissolved in ethyl acetate and the solution was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by silica gel column chromatography (CHCl₃/hexane, 1:2). The yield of 2-(1,3-benzothiazol-2-yl)-4-bromophenol is 0,49 g (1,60 mmol).

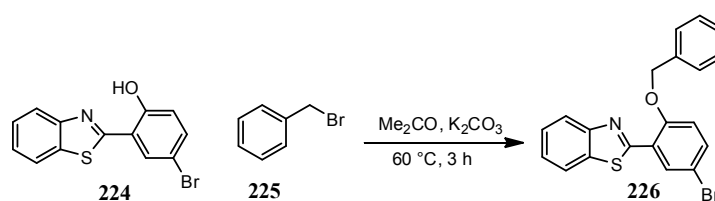
M(C₁₃H₈ONSBr)=306.18 g/mol

¹H NMR (CDCl₃): δ=12,6-12,5 (s, 1H), 8,0-7,9 (dd, J=8,05 Hz, 2H), 7,8-7,7 (dd, 1H), 7,5-7,4 (m, 3H), 7,0-6,9 (d, 1H) ppm.

MS(ESI/TOF) m/z 305,96 [M+H]⁺



10.4 2-[2-(Benzyloxy)-5-bromophenyl]-1,3-benzothiazole



Scheme 86. The reaction conditions for the synthesis of 5-bromo-2-(benzyloxy)-benzothiazole **226**.

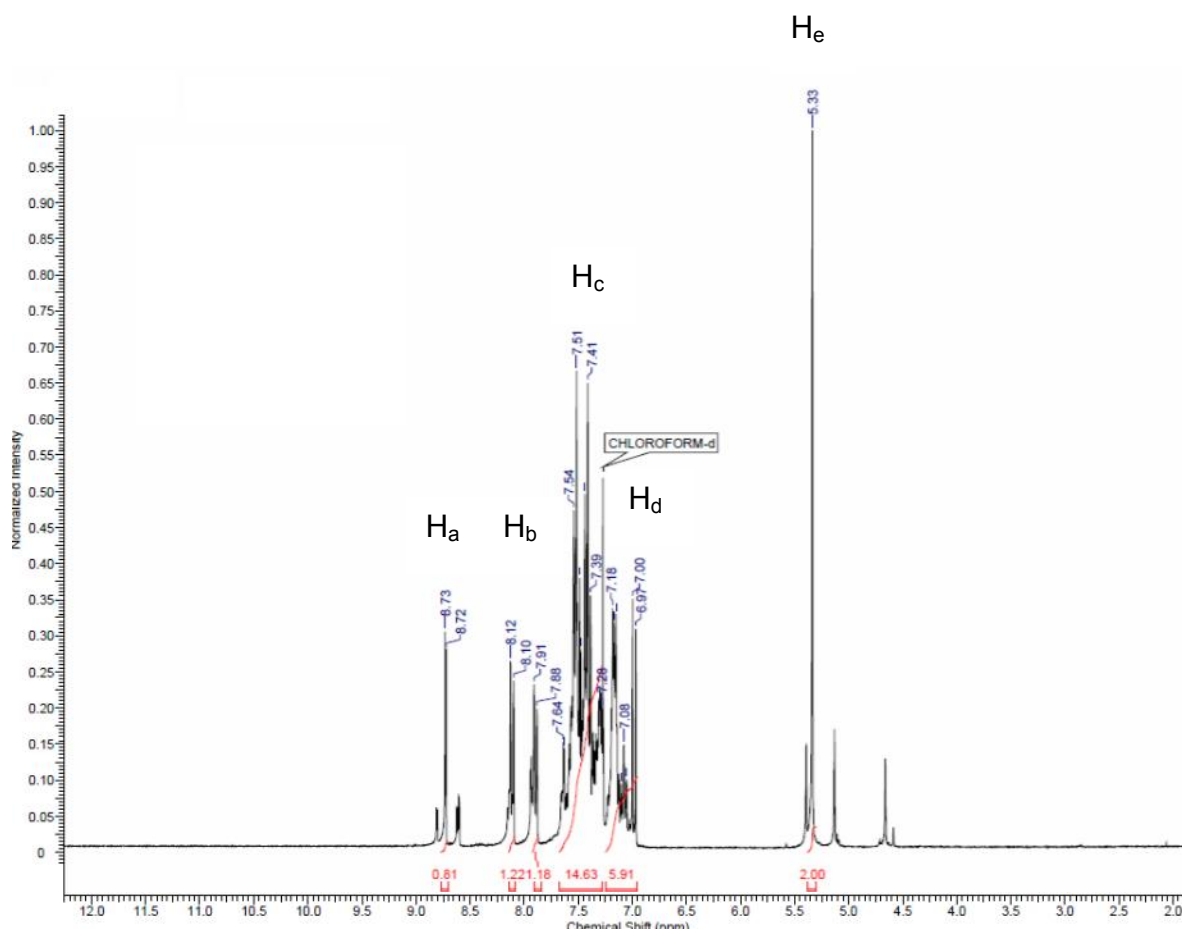
2-(1,3-Benzothiazol-2-yl)-4-bromophenol (0,200 g, 0,65 mmol) was dissolved in acetone, then benzyl bromide (0,122 g, 0,72 mmol) and potassium carbonate (0,225 g, 1,63 mmol) were added (scheme 86). The reaction mixture was stirred intensively in a vial at $60\text{ }^\circ\text{C}$ for 3 hours. After cooling down the solution was filtered to remove the solids and the filtrate

was evaporated to dryness. The crude product was purified by silica gel column chromatography (CHCl₃/hexane, 1:4). The yield of 2-[2-(benzyloxy)-5-bromophenyl]-1,3-benzothiazole is 0,21 g (0,53 mmol).

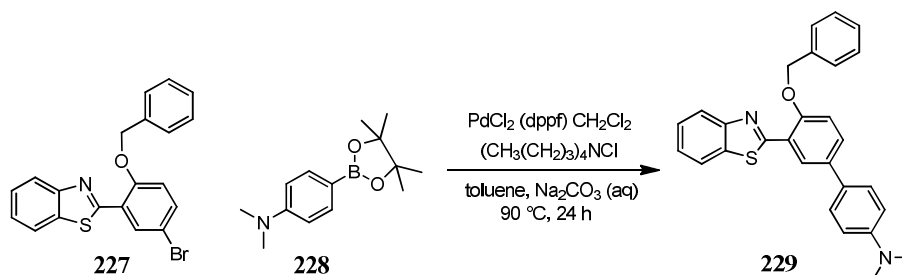
M(C₂₀H₁₄ONSBr) = 396,30 g/mol

¹H NMR (CDCl₃): δ= 8,71-8,70 (d, 1H), 8,10-7,87 (dd, J=63,4 Hz, 2 H), 7,52-7,35 (m, 8H), 6,98-6,95 (d, 1H), 5,32, (s, 2H) ppm.

MS(ESI/TOF) m/z 397,96 [M+H]⁺



10.5 3'-(Benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-dimethyl-[1,1'-biphenyl]-4-amine

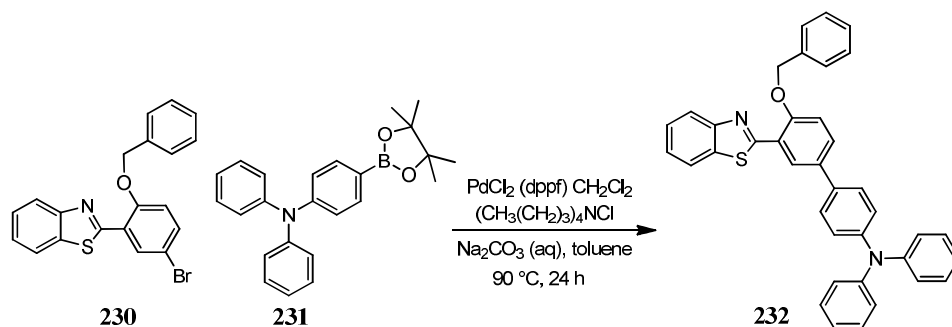


Scheme 87. The reaction conditions for the synthesis of 2-(benzyloxy)-5-aryl benzothiazole **229**.

2-[2-(Benzyloxy)-5-bromophenyl]-1,3-benzothiazole (0,072 g, 0,18 mmol), N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0,045 g, 0,81 mmol), tetrabutylammonium chloride (0,005 g, 0,002 mmol) and PdCl₂ (dppf)·CH₂Cl₂ (0,007 g, 0,001 mmol) were added to two-phase mixture of toluene (8 ml) and 1M K₂CO₃ (aq) solution (8 ml). The reaction mixture was heated in a vial at 90 °C and stirred intensively for 24 hours (scheme 87). The organic layer was separated and the aqueous phase was extracted with toluene (3·20 ml). The organic layers were combined, washed with water (2·20 ml), dried over anhydrous sodium sulfate and filtrated. The solvent was evaporated. The crude product was purified by Combi Flash liquid chromatography with 12 g Silica gel 60 column (EtOAc/toluene, 1:7). The eluent composition was according to the gradient shown in appendix 8. No desired product is obtained from the column.

M(C₂₈H₂₄ON₂S)= 436.57 g/mol

10.6 3'-(Benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine



Scheme 88. The reaction conditions for the synthesis of 2-(benzyloxy)-5-aryl benzothiazole **232**.

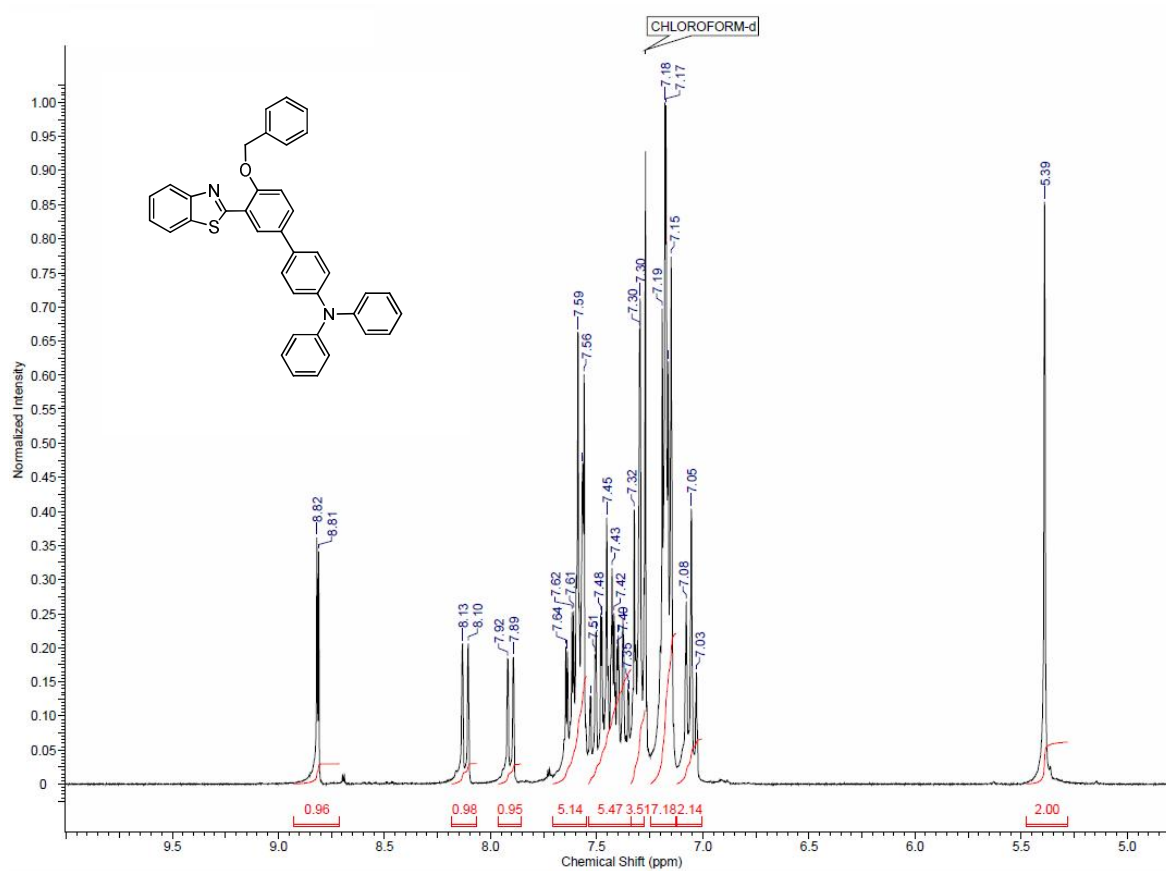
2-[2-(Benzyloxy)-5-bromophenyl]-1,3-benzothiazole (0,315 g, 0,80 mmol), N,N-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0,296 g, 0,80 mmol), tetrabutylammonium chloride (0,022 g, 0,08 mmol) and $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0,033 g, 0,04 mmol) were added to two-phase mixture of toluene (20 ml) and 1M K_2CO_3 (aq) solution (20 ml). The reaction mixture was heated on oil bath at 90 °C and stirred intensively for 24 hours (scheme 88). The organic layer was separated and the aqueous phase was extracted with toluene (3·20 ml). The organic layers were combined, washed with water (2·20 ml), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated. The crude product was purified by Combi Flash liquid chromatography with 12 g Silica gel 60 column (EtOAc/hexane, 1:10). The eluent composition was according to the gradient shown in appendix 9. The yield of 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine is 0,33 g (0,59 mmol).

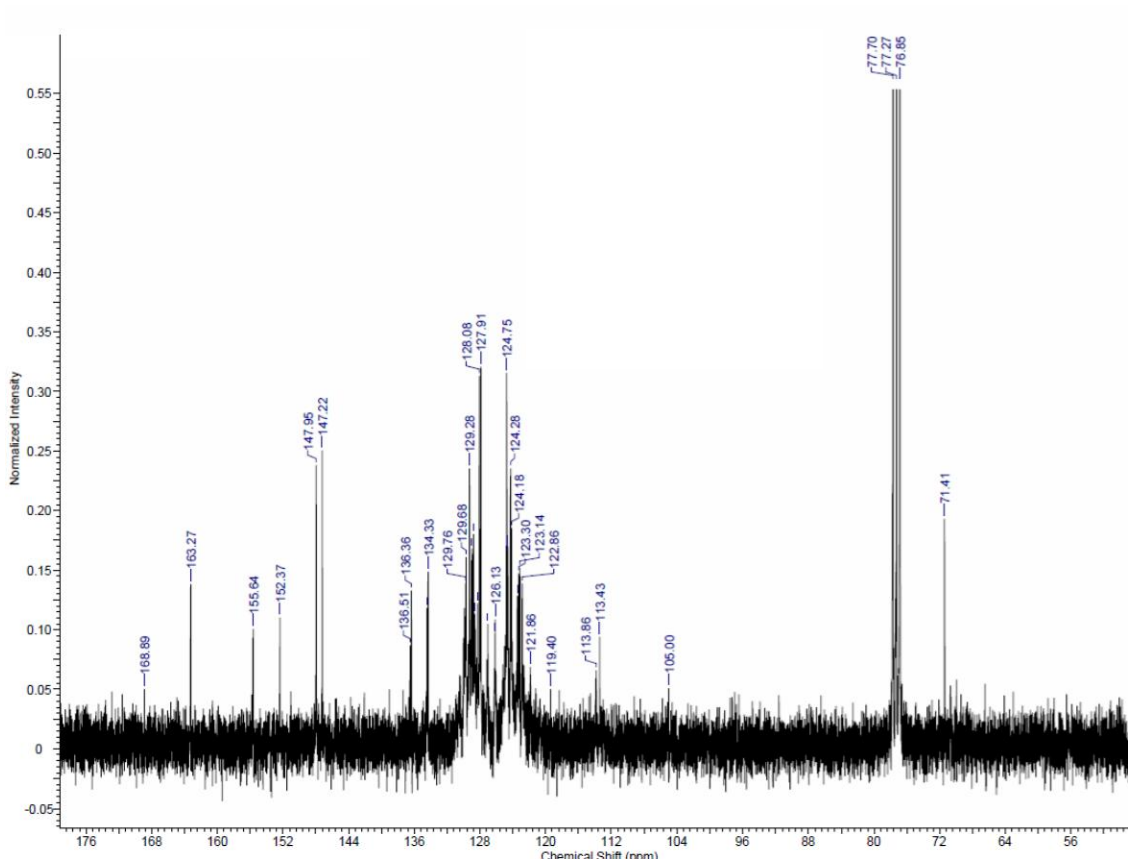
$M(\text{C}_{38}\text{H}_{28}\text{ON}_2\text{S})=560,71 \text{ g/mol}$

$^1\text{H NMR}(\text{CDCl}_3)$: $\delta= 8.80$ (d, $J=2,34$ Hz, 1 H), 8.11 (d, $J=8,2$ Hz, 1 H), 7.91 (d, 8.2 Hz, 1H), 7.60 (dd, $J_1=2,34$ Hz, $J_2=8,49$ Hz, 1H), 7.58 - 7.56 (m, 4H), 7.52 - 7.34 (m, 5H), 7.32 - 7.27 (m, 4H), 7.19 - 7.15 (m, 7H), 7.05 (t, 2H), $5,39$ (s, 2H) ppm.

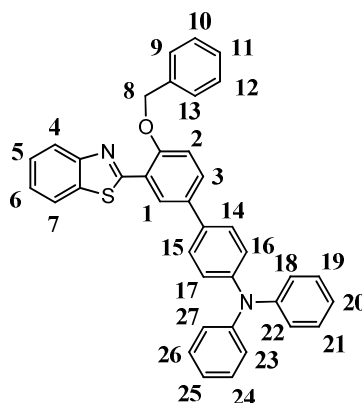
^{13}C NMR (CDCl_3): $\delta = 163.27, 155.64, 152.37, 147.95, 147.22, 135.59, 134.33, 129.97, 129.68, 128.82, 128.08, 127.91, 126.13, 124.75, 124.67, 124.61, 123.46, 123.14, 122.86, 121.86, 71.41$ ppm.

MS(ESI/TOF) m/z 561,20 $[\text{M}+\text{H}]^+$





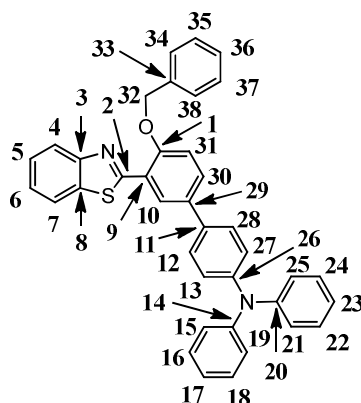
From ^1H NMR spectrum of the 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine can be seen that the sample contains only the wanted product. In addition, the ^{13}C NMR, ^1H COSY (Appendix 1) and gHSQC (Appendix 2) measurements were performed. According to the results, a more accurate assignment of the chemical shifts can be done. The results are shown in scheme 89 (^1H) and table 3 as well as scheme 90 (^{13}C) and table 4.



Scheme 89. The protons of the 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine numbered in order to assign the signals in ^1H NMR-spectra.

Table 3. δ -values [ppm] of each proton of the 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine numbered according to scheme 89

Proton(s) #	δ [ppm]	Proton(s) #	δ [ppm]	Proton(s) #	δ [ppm]	Proton(s) #	δ [ppm]
1	8,80	8	5,39	15	7,58	22	7,16
2	7,16	9	7,58	16	7,17	23	7,16
3	7,60	10	7,44	17	7,17	24	7,28
4	7,91	11	7,44	18	7,16	25	7,05
5	7,38	12	7,44	19	7,28	26	7,28
6	7,49	13	7,58	20	7,05	27	7,16
7	8,11	14	7,58	21	7,28		



Scheme 90. The carbon atoms of the 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine numbered in order to assign the signals in ^{13}C NMR-spectra.

Table 4. δ -values [ppm] of each carbon atom of the 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine numbered according to scheme 90

Carbon #	δ [ppm]	Carbon #	δ [ppm]	Carbon #	δ [ppm]	Carbon #	δ [ppm]
1	155,64	11	135,59	21	124,67	31	129,97
2	163,27	12	127,91	22	129,68	32	71,41
3	152,37	13	124,61	23	123,46	33	136,51
4	121,86	14	147,95	24	129,68	34	128,08
5	124,75	15	124,67	25	124,67	35	128,82
6	126,13	16	129,68	26	147,22	36	128,82
7	123,14	17	123,46	27	124,61	37	128,82
8	152,37	18	129,68	28	127,91	38	128,08
9	122,86	19	124,67	29	134,33		
10	128,08	20	147,95	30	129,97		

The purification with Combi Flash low-pressure liquid chromatograph was performed multiple times subsequently since the target product was hard to separate from by-products due to their very similar mobilities. The mobility of the starting material, 2-benzyloxy-5-aryl benzothiazole, and a dimer of 4-bromo-N,N-diphenylaniline which is the starting material of arylboronic pinacol ester, is higher than the mobility of the product. Mobility of the dimer of 5-bromo-2-hydroxy benzothiazole is marginally lower which allowed removing this by-product during the first purification.

In appendix 8 is shown spectra taken by HR ESI-TOF mass spectrometry of three purified fractions. The mass spectra of the 2-[2-(benzyloxy)-5-bromophenyl]-1,3-benzothiazole by-product **226**, the target product 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine **232** and the mixture of both are presented. In addition, the mass spectra of the intermediate compounds **217-226** and the target product **232** are presented in appendices 3-7.

11 Summary

The aim of the experimental work was to synthesize three different phenylamine derivatives of benzothiazole **193a-c**, which can be potentially used as material for organic solar cells.

The syntheses of N,N-diphenyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **220**, 2-(1,3-benzothiazol-2-yl)-4-bromophenol **223** and 2-[2-(benzyloxy)-5-bromophenyl]-1,3-benzothiazole **226** were successful with moderate or good yields and the synthesis of the target product could be attempted. The synthesis of 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-diphenyl-[1,1'-biphenyl]-4-amine **232** was successful with moderate yield.

In addition to the desired product, there was starting material **226** left after the reaction time, as shown in the MS spectrum in appendix 8. The yields of the dimers were low and the unwanted substance was mostly starting material. Since the mobilities of the starting material **226** and the desired product **232** were quite similar, several purifications were needed. However, pure product was gained.

The synthesis of N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **217** gave very low yield even though the reaction mechanism was similar to the successful reaction of **220**. Perhaps the solubilities of the reagents in the synthesis of **217** were different from those in the synthesis of **220** which may have caused the difference. Since this reaction has been made before, it must be possible to perform successfully.

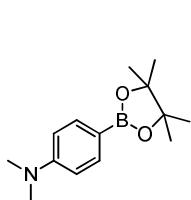
The synthesis of 3'-(benzo[d]thiazol-2-yl)-4'-(benzyloxy)-N,N-dimethyl-[1,1'-biphenyl]-4-amine **229** failed and no target product was detected.

Because of the limited time available, the synthesis of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane **199** or 2-[2-(benzyloxy)-5-phenylphenyl]-1,3-benzothiazole **193a** was not attempted.

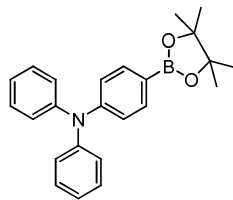
Since the target product **232** had not been prepared before, it was the primary target molecule. Because of the difficulties encountered during the syntheses, a lot of time and effort was needed before the wanted product was gained. It was noticed that the base must be absolutely dry and dried right before use. Also the recrystallation of the catalyst improves its efficiency and increases the yields.

Within the limits of this study, the last step of the synthesis route, the removal of the benzyl group, was not attempted nor the suitability of the synthesized material in organic solar cells. However, it may have potential in organic solar cell technology and might be worth studying.

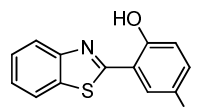
12 Synthesized molecules



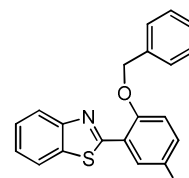
217



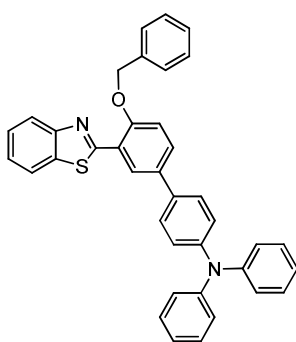
220



223



226



232

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Appendices

Appendix 1: ^1H COSY spectrum for **232**.

Appendix 2: gHSQC spectrum for **232**.

Appendix 3: MS spectrum for **217**.

Appendix 4: MS spectrum for **220**.

Appendix 5: MS spectrum for **223**.

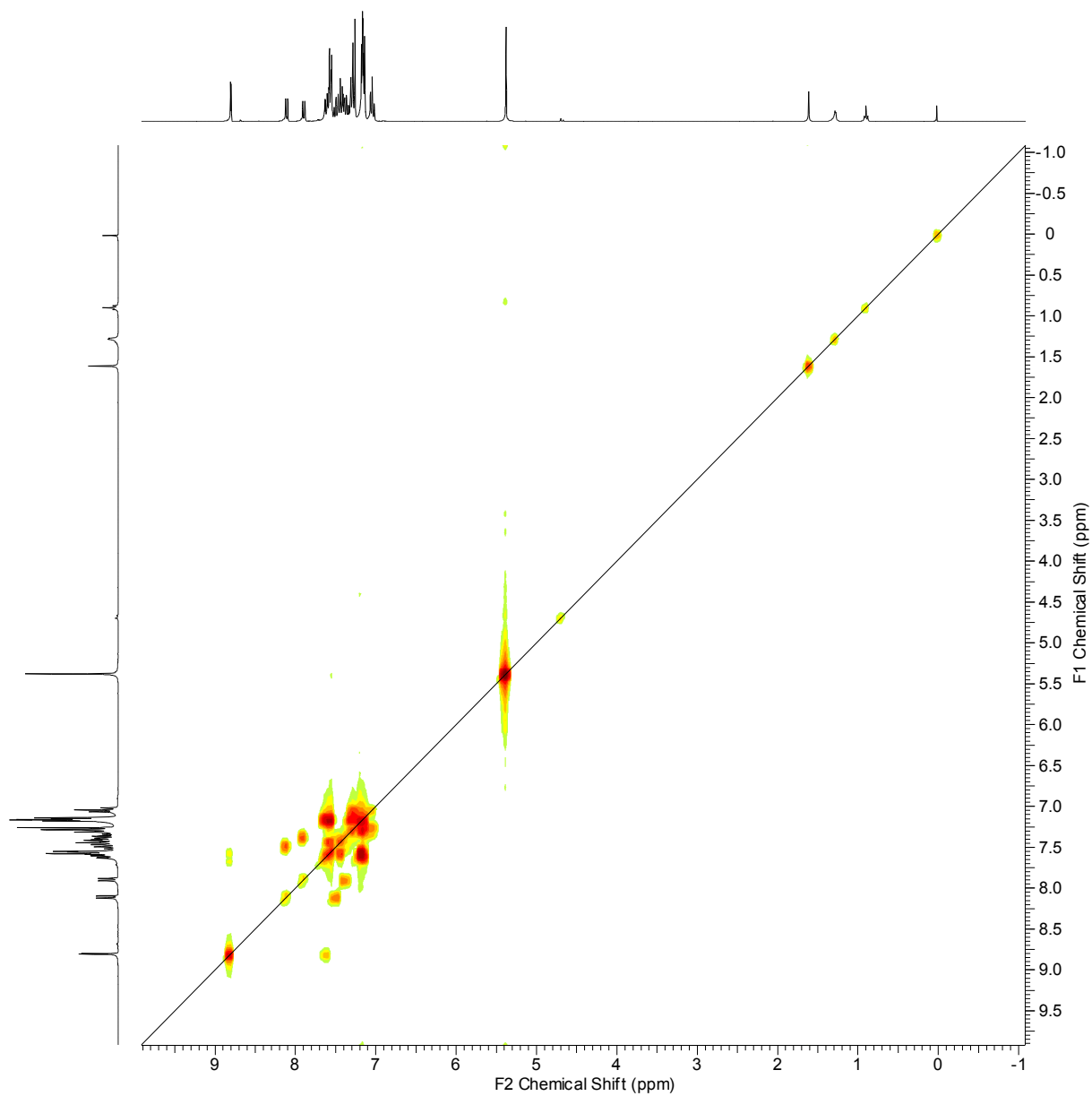
Appendix 6: MS spectrum for **226**.

Appendix 7: MS spectrum for **232**.

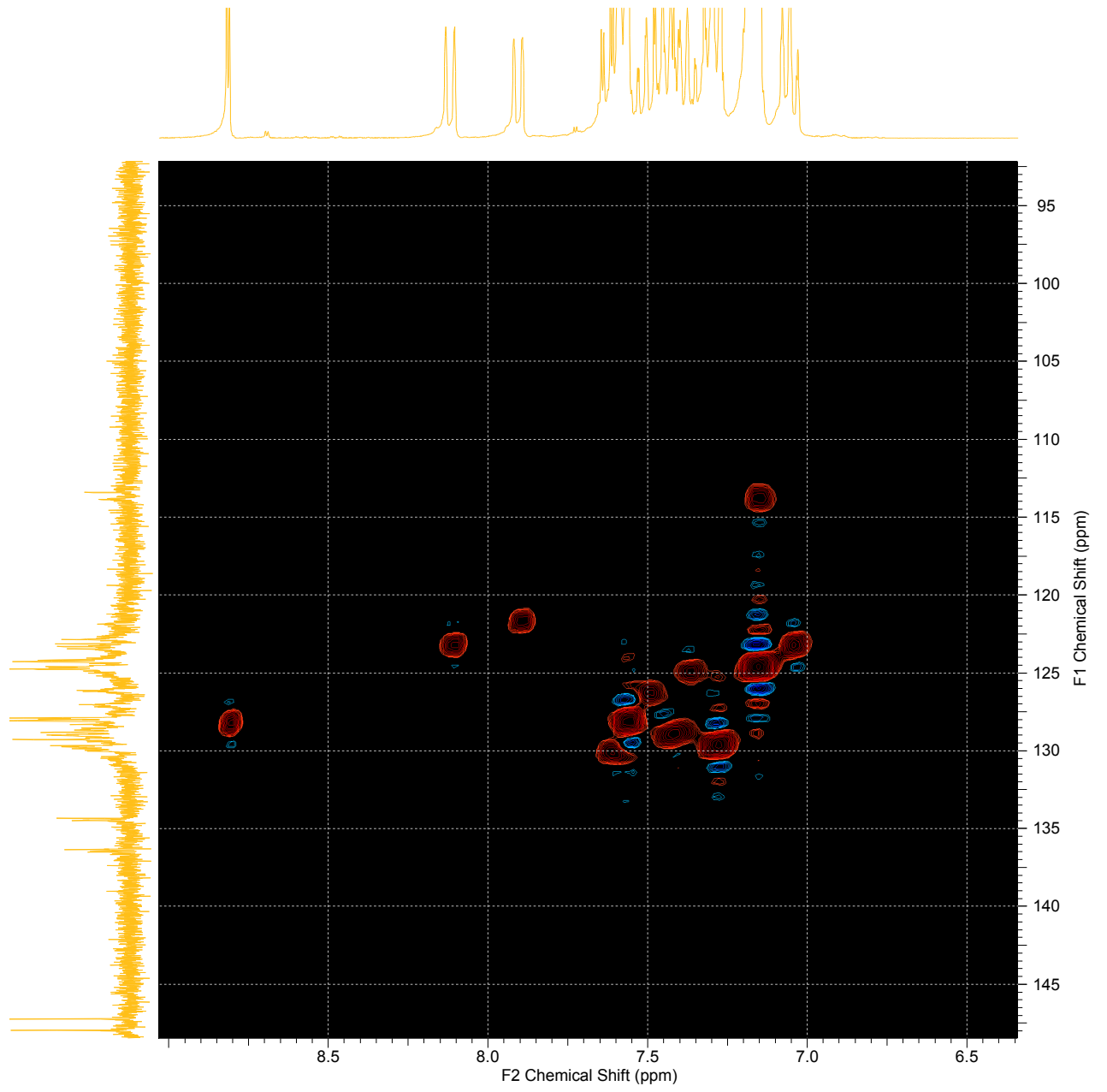
Appendix 8: MS spectra for **232**, the mixture of **226** and **232** and the starting material **226**.

Appendix 9: Combi Flash run for **232**.

APPENDIX 1: ^1H COSY spectrum for **232**.



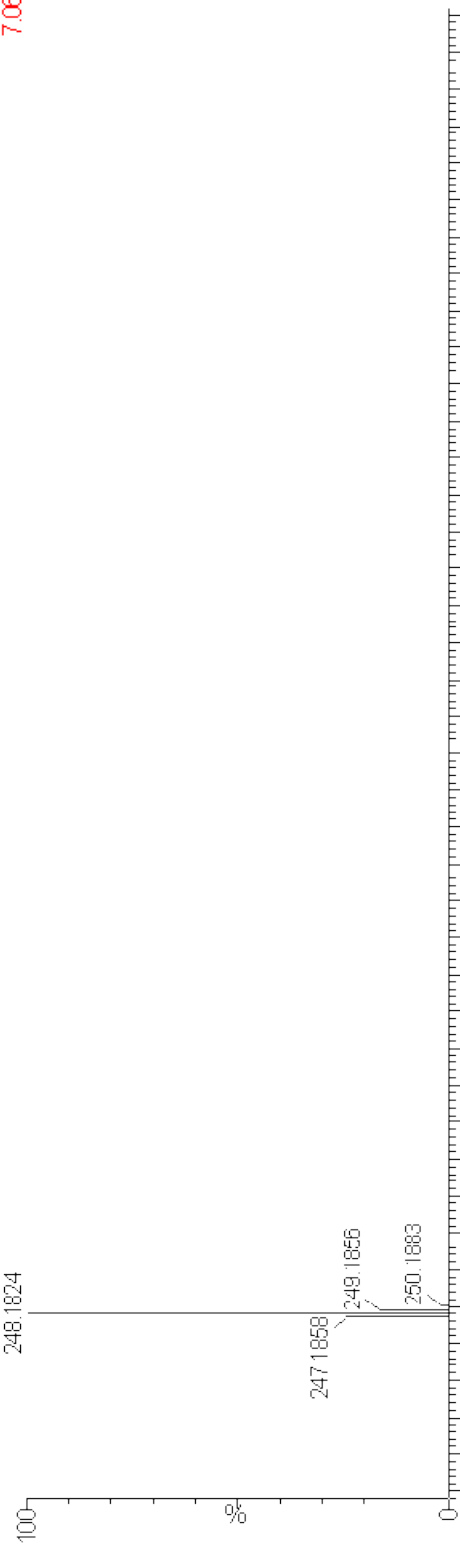
APPENDIX 2: gHSQC spectrum for **232**.



APPENDIX 3: MS spectrum for 217.

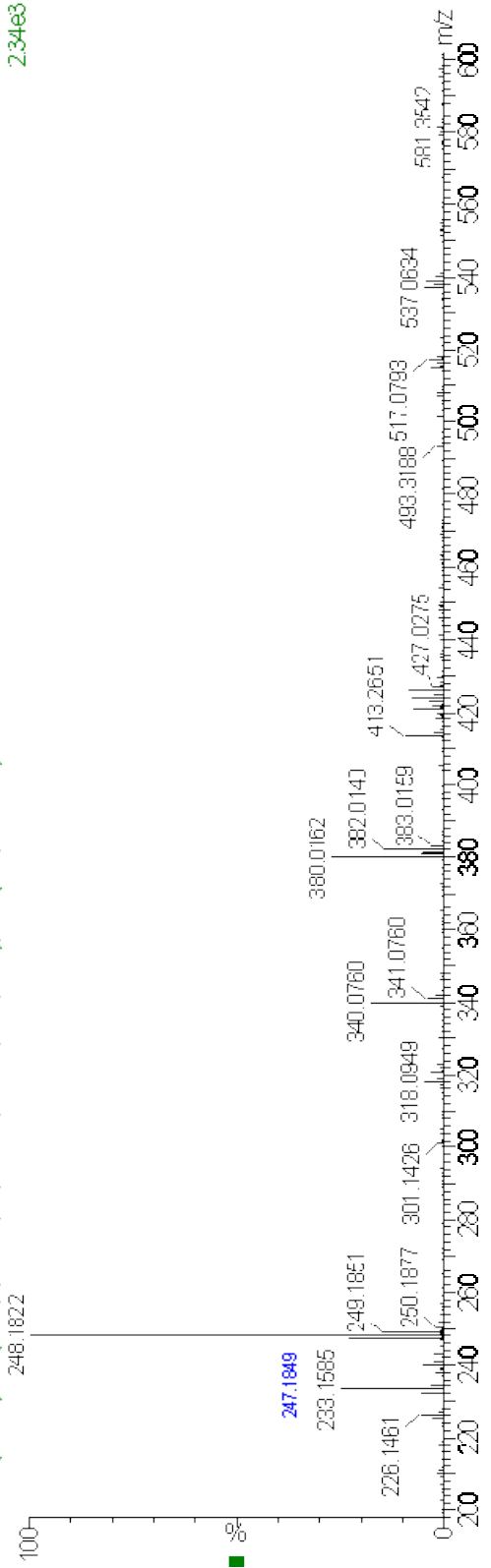
1: TOF MSES+
7.06e12

PL 13-30 (0.036) Is (1.00;1.00) C14H22BNO2



1: TOF MSES+
2.34e3

PL 13-30 1 (C.036) AM (Cen4, 80.00, Ar,8000.0,556.28,1.00,LS 5); Str (SG, 2x10.00)

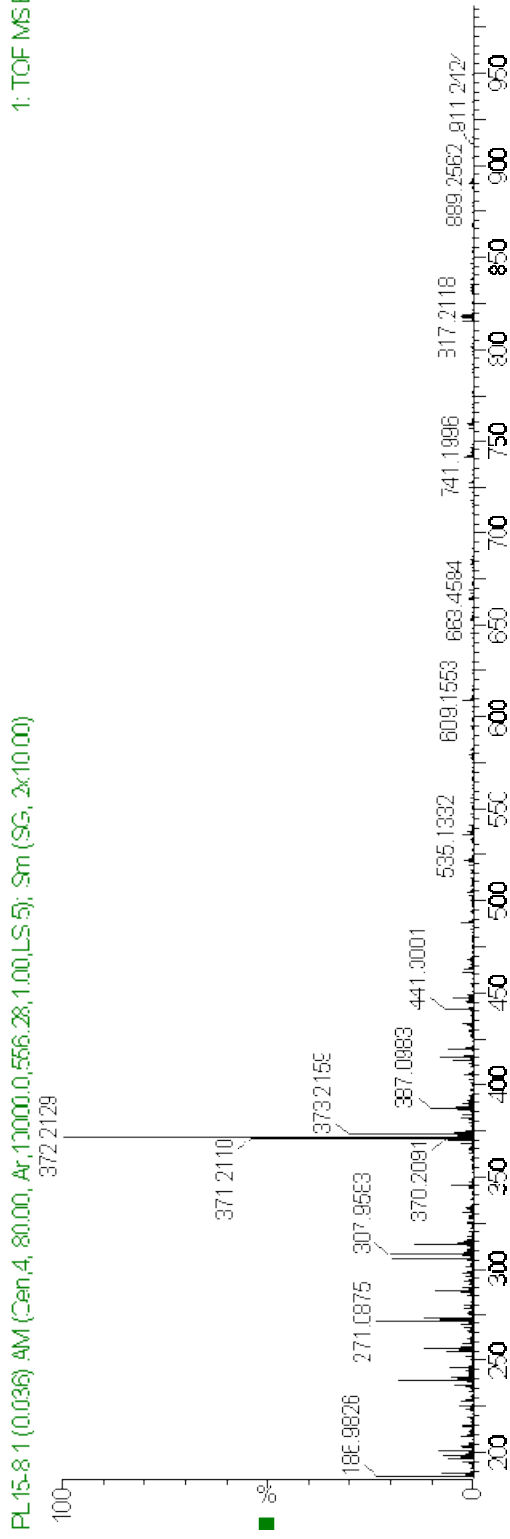


APPENDIX 4: MS spectrum for 220.

1. TOF MS/ES-
6.48e12

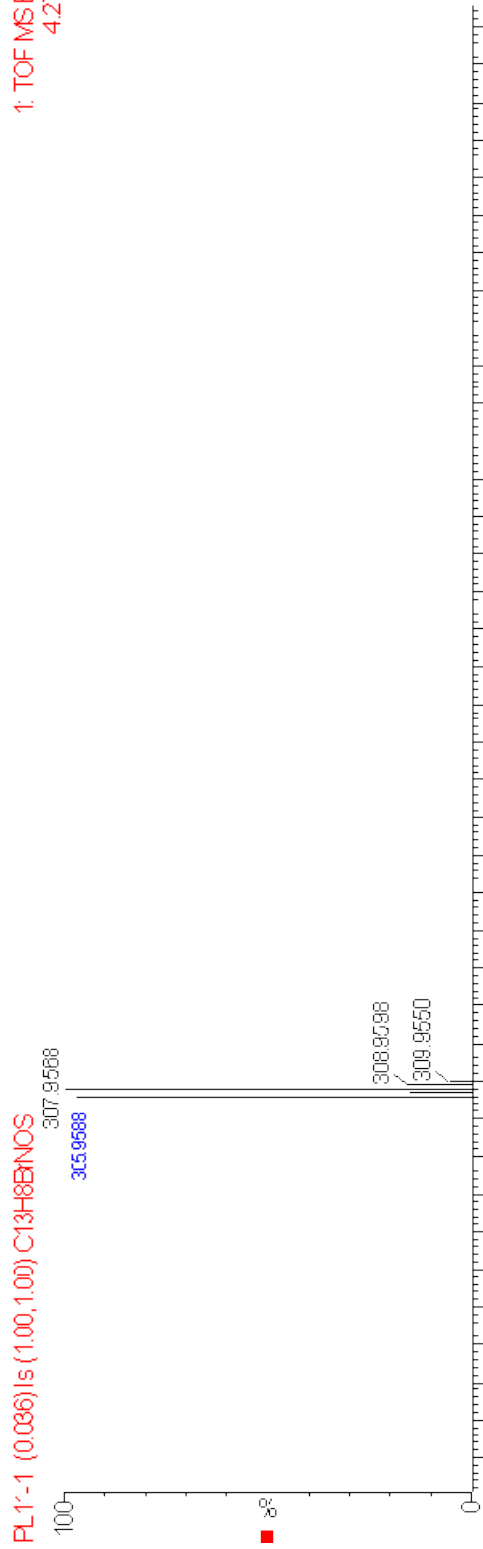


1. TOF MS/ES-
563

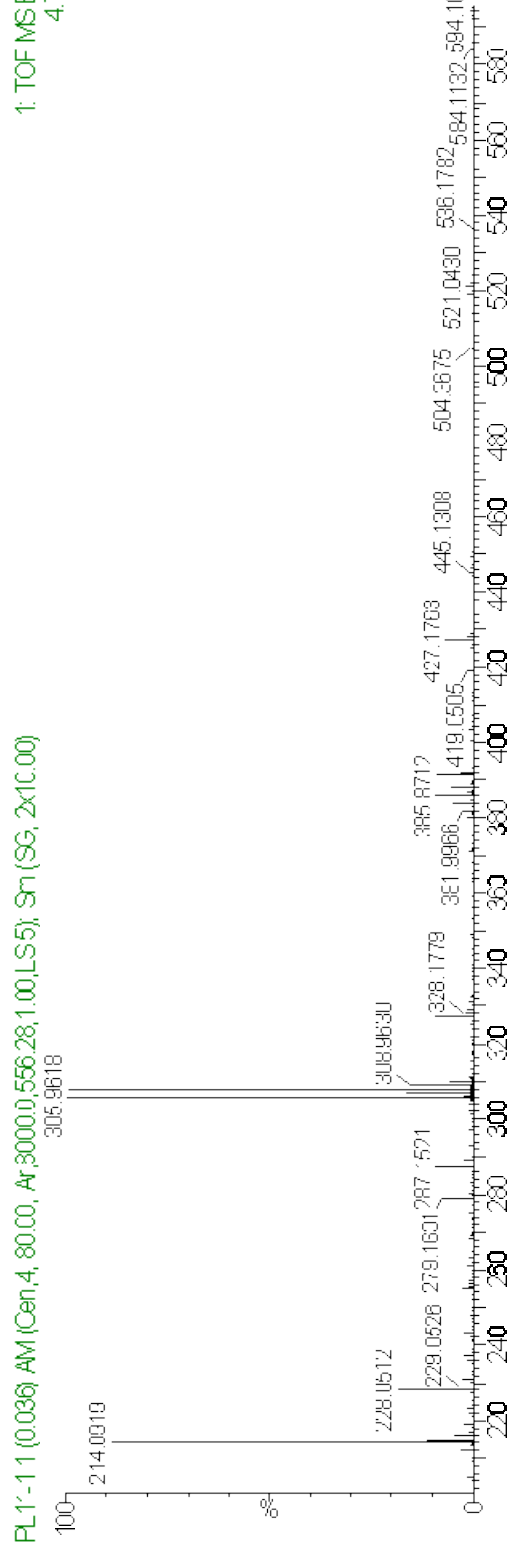


APPENDIX 5: MS spectrum for 223.

1: TOF MS ES+
4.27e12



1: TOF MS ES+
4.77e3



APPENDIX 6: MS spectrum for 226.

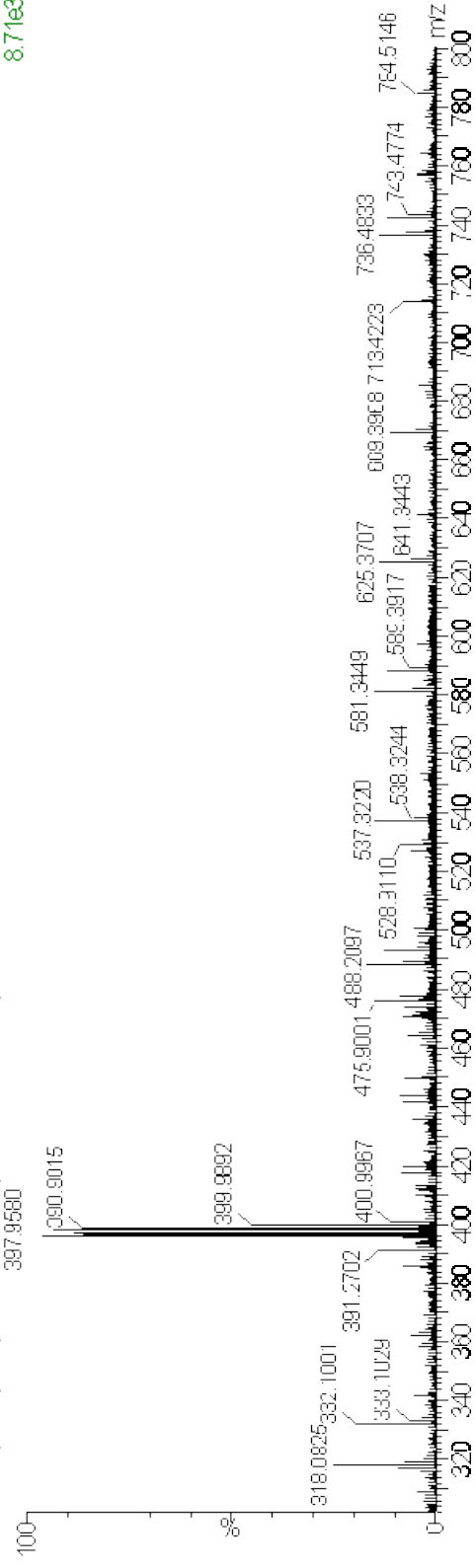
1: IOF-MS-ES+
4.00e12

-L13-28 (0.035) s (1.00, 1.00) C20H14BrNOS

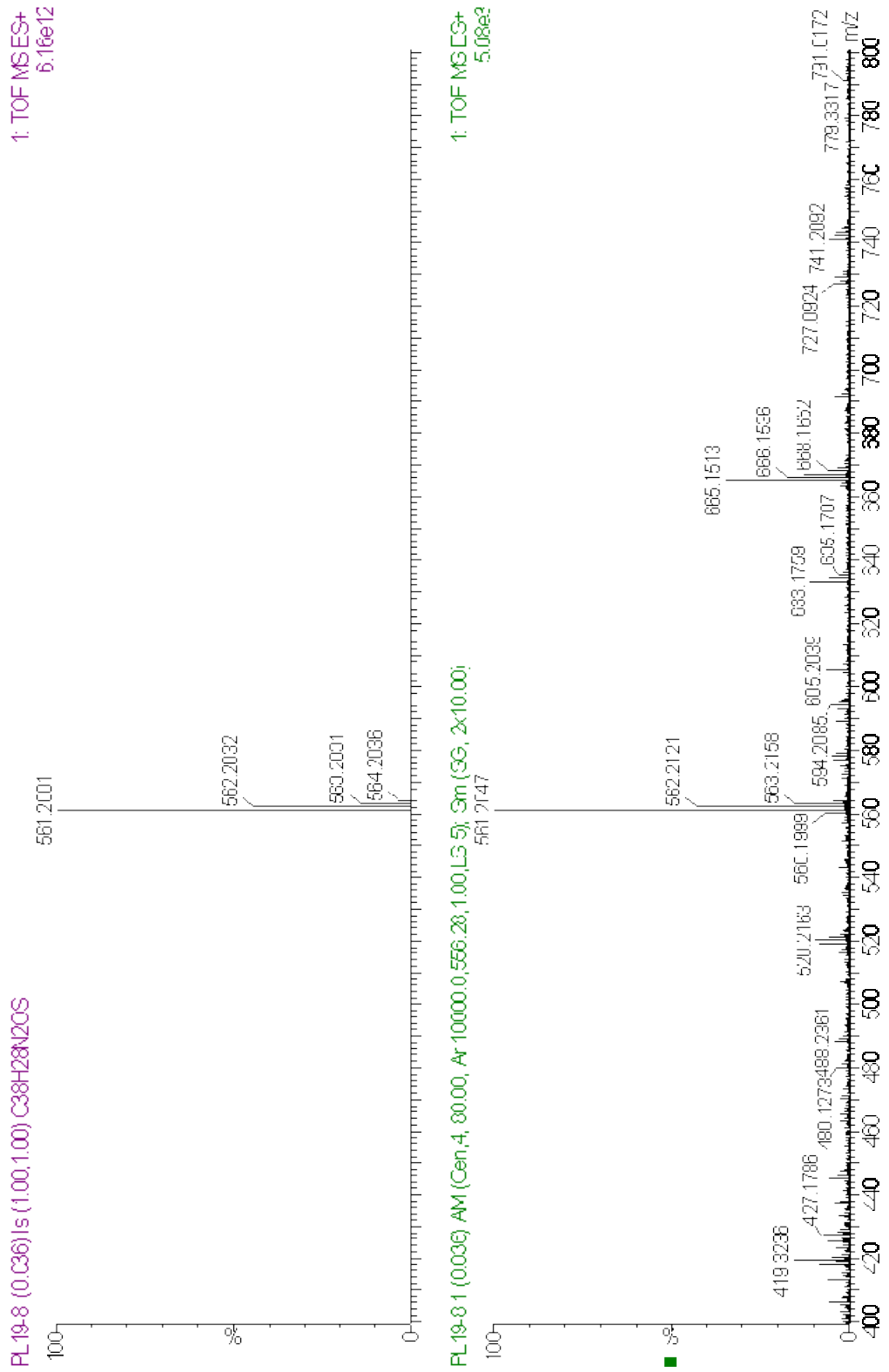


1: TOF MS-ES+
8.71e3

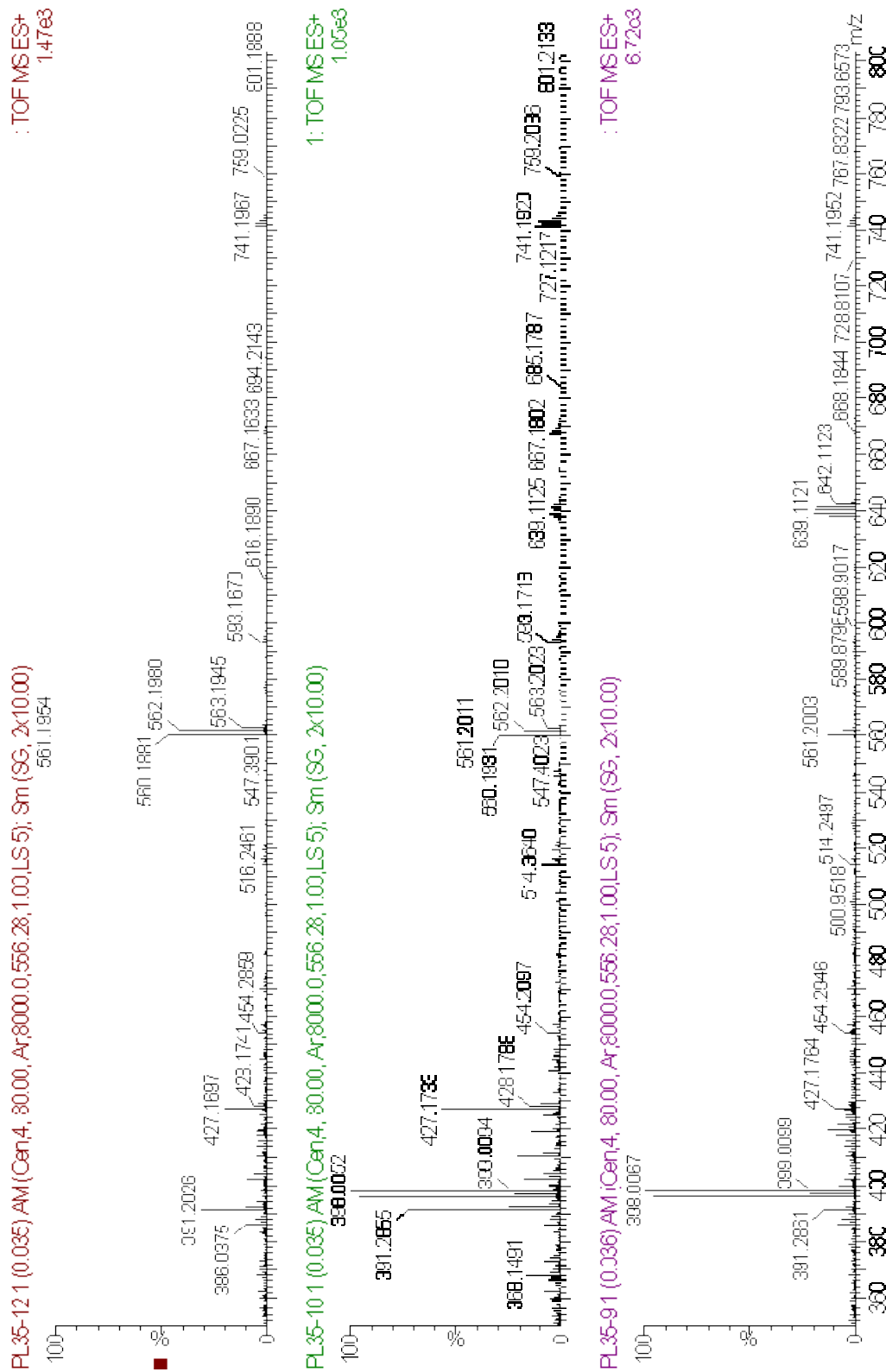
-L13-28 1 (0.035) On (Cen-4, 80.00, Ar), Sm (SG, 2x10.00)



APPENDIX 7: MS spectrum for 232.



APPENDIX 8: MS spectra for **232** (top), the mixture of starting material **226** and the target product **232** (middle) and the starting material **226** (below).



APPENDIX 9: The eluent composition of Combi Flash run for purification of **232**.

