Transition Metal-Catalyzed Borylation of Aromatics

By

Hafiza Tayyaba Shahzadi

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Syed Babar Ali School of Science and Engineering (SBASSE), Lahore
University of Management Sciences (LUMS), Lahore
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Hafiza Tayyaba Shahzadi
To my beloved Son
Author’s Declaration

I, Hafiza Tayyaba Shahzadi, hereby declare that my PhD thesis titled: “Transition Metal-Catalyzed Borylation of Aromatics” has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree from the Lahore University of Management Sciences (LUMS) or anywhere else in the country/world. The experimental work is almost entirely my own work; the collaborative contributions have been indicated clearly and acknowledged. Due references have been provided on all supporting literatures and resources.

At any time if my statement is found to be incorrect even after my graduation, the university has the right to withdraw my PhD degree.

Hafiza Tayyaba Shahzadi

Date: 15th May 15, 2019
Abstract
Selective functionalization of hydrocarbons represents a long-standing challenge in the synthetic world. Transition metal-catalyzed reactions, such as transformation of C–H/ C–X bond to C–B bond has emerged as potent tool towards this goal during the last few decades. Especially the Ir-catalyzed aromatic C–H activation/borylation provides unique selectivity which is complementary to those found in the traditional synthetic routes. Sterically governed regioselective control in this new synthetic tool allows the synthesis of (hetero)aromatic compounds which are difficult to access by the conventional routes. In the current work, we have utilized this methodology to gain facile access to new aromatic building blocks with better atom & step economy. One study presents the synthesis of hydroxybenzoates. Hydroxybenzoates are widely used as preservatives and antiseptics in the food and pharmaceutical industry. However, strategies focusing on the direct synthesis of 2,6- and 2,3-disubstituted hydroxybenzoates are lacking in literature. Herein we report an efficient protocol employing iridium-catalyzed C–H borylation/oxidation of commercially available benzoic acid/ester substrates. This route provides facile access to halogen decorated para-/meta-hydroxybenzoates as the synthesis of akin compounds is laborious by traditional approaches.

Second project targets the synthesis of boscalid analogs. Boscalid is an extensively used fungicide for crop protection. Traditional routes of boscalid synthesis involve precursors that need pre-functionalization of arenes, which affects the step economy and overall efficiency. The aim of this study is to develop boscalid analogues from readily available hydrocarbon feedstock without pre-functionalization. Sequential Ir-catalyzed C–H borylation of arenes and Suzuki coupling provide biphenyl amines which on amidation produce boscalid analogues in good yield. Synthesized compounds are further evaluated by molecular docking to gain insight into the binding pocket of protein. The In-vitro studies of the analogs are carried out against Fusarium moniliforme and few of the synthesized compounds provided superior inhibition on potato dextrose agar (PDA) plates.

Next, Ir-catalyzed C–H borylation of CF₃ substituted pyridines is reported. The versatility of the methodology is demonstrated by the use of various substitution patterns in the substrate molecule. Based on the steric evaluation, selective positions of CF₃ substituted pyridines are functionalized. Several functional groups like halo, ester, methoxy and amino are compatible with this methodology.
Chiral boronic esters are indispensable building blocks owing to their versatile transformations and immense applications in medicinal and material chemistry. Herein, we also disclose Pd-catalyzed chiral borylation of aryl halides, whereby numerous substrates bearing broad range of functional groups are found to be compatible for the developed approach. Aryl/hetero aryl chiral boronic esters are obtained in moderate to excellent yield. The resulting chiral boronic esters can serve as significant precursors in asymmetric synthesis.
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<tr>
<td>Ar</td>
<td>aryl</td>
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<tr>
<td>BPin</td>
<td>pinacolatoboryl</td>
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<tr>
<td>B2Pin2</td>
<td>bis-pinacolato-di-boron</td>
</tr>
<tr>
<td>Bpy</td>
<td>bi-pyridyl</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celsius</td>
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<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>d'bpy</td>
<td>di-tert-butyl bipyridyl</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
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<tr>
<td>GC-MS</td>
<td>gas chromatography-mass spectroscopy</td>
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<tr>
<td>h</td>
<td>hour</td>
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<tr>
<td>HBPin</td>
<td>pinacolborane</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>$m$</td>
<td>meta</td>
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<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>$p$</td>
<td>para</td>
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<tr>
<td>Pd</td>
<td>Palladium</td>
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<td>Ph</td>
<td>Phenyl</td>
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<td>q</td>
<td>quartet</td>
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<td>singlet</td>
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<tr>
<td>t</td>
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<td>$\mu$L</td>
<td>microliter</td>
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Publication

- Facile synthesis of halogen decorated para-/meta-hydroxybenzoates by iridium-catalyzed borylation and oxidation.

Tayyaba Shahzadi, Rahman S. Z. Saleem, Ghayoor A. Chotana*

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Chapter 1

Introduction
1. Introduction

The replacement of unreactive C–H bond with C–B bond has emerged as a potent tool in organic chemistry. During the last few decades, C–H borylation has proven to be one of the most convenient and versatile methods to functionalize specific positions in the molecule. The extensive use of organoboron compounds is attributed to their eco-friendly and benign nature. Moreover, the versatility of organoboron compounds can be seen from their numerous transformations to useful organic reagents, pharmaceuticals, agrochemicals, functional molecules, $^{10}$B carriers for neutron capture therapy and biologically active substrates.$^{1-6}$

The utility of organoboron compounds evoked the scientific community to develop new methodologies for the introduction of boryl group to organic molecule. One of such methodologies is C–H borylation that is considered as an attractive tool for organic chemists during the past decades. The driving force for the selection of C–H functionalization is its abundance in nature. Unfortunately, the inertness of C–H bond towards many organic transformations makes its functionalization a challenging task.$^{7,8}$

Traditionally aryl boron compounds are synthesized by their corresponding aryl halides via Grignard or lithiate intermediates formation and subsequent reaction with borate ester. Resulting organoboron compounds are hydrolyzed to yield boronic acids (Scheme 1.1). However, this protocol is incompatible with base sensitive, electrophilic and protic functional groups.

![Scheme 1.1: Traditional method for preparing organoboron compounds](image-url)
Miyaura et al reported Pd-catalyzed borylation using aryl halide and borylating agents.\(^9\) Miyaura borylation takes advantage of former organometallic pathway, as it provides direct route towards organoboronic acid with good functional group compatibility (Scheme 1.2). This methodology along with organometallic pathway have suffered from the availability of the starting material (aryl halide). Therefore, the quest for the more applicable methods than the previous methods has not stopped here. Scientists have moved forward towards the activation of inert bonds like C–H bonds.

Replacing the C–H bond with C–B bond is an attractive approach to synthesize organoboron compounds. Transition metal catalyzed C–H borylation can be classified into the following categories.\(^10\)

- Undirected C–H borylation of (hetero)arenes
- Directed C–H borylation of (hetero)arenes

1.1 Undirected C–H borylation of (hetero)arenes

Undirected C–H borylation of (hetero)arenes is mainly governed by sterics. In 1995, first undirected borylation of C–H bonds of alkane was reported by Hartwig et al.\(^11\) They used photochemical activation of rhenium catalyst. Currently, iridium-catalyzed borylation is considered superior than other metal catalyzed reactions.

1.1.1 Ir-catalyzed C–H borylation

Smith et al first reported the aromatic C–H borylation with Ir complex. Discoveries after discoveries provided efficient catalytic system with mechanistic details. The catalytic reaction was described by Smith and coworkers.\(^13\) They demonstrated the combination of
Cp*Ir with alkyl phosphine ligands for borylation. Marder and coworkers also reported the aromatic C–H borylation with Ir complex. Currently, iridium-catalyst with electron donating ligands like 2,2’-bipyridine (bpy) or (d'bpy) is considered as most the efficient system of borylation reported by Hartwig’s group.

Regioselectivity of Ir-catalyzed C–H borylation of arenes is mainly governed by steric effects. Borylation of arenes specifically takes place at the least hindered site while in case of heteroarenes it is controlled by electronic effects. For instance, 1,3-disubstituted arene produces 5 borylated product while five-membered ring heterocycles undergo borylation at α position to the heteroatom (Scheme 1.3).

![Scheme 1.3: Ir-catalyzed C–H borylation of (hetero)arenes](image)

1.1.2 Applications of Ir-catalyzed borylation

Utility of Ir-catalyzed C–H borylation can be seen from its tremendous functionalization. Selected examples include the conversion of arene to biaryl, aryl nitrile, phenol, biaryl ether, diphenyl amine and aryl halide (Scheme 1.4).
1.1.3 Recent approaches in tandem one pot transformations

Hartwig and coworkers described the one pot meta cyanation of arenes by Ir-catalyzed borylation and Cu mediated cyanation of the resulting arylboronic ester (Scheme 1.5). This strategy further utilized the conversion of cyano group to other useful functional groups (aldehyde, keto, amide etc) as well.\textsuperscript{19}

In 2010, Marder group reported synthesis of β-aryl substituted ketone or alcohols through microwave-assisted, one pot Ir-catalyzed borylation and Rh-catalyzed addition reaction of enones (Scheme 1.6).\textsuperscript{23} Reducing and non-reducing conditions were tried to access β-aryl substituted ketones or corresponding alcohols in good yield.
Hartwig et al developed an efficient system for the trifluoromethylation of arenes. They introduced the tandem C–H borylation/Cu-mediated perfluoroalkylation of arenes. They tried disubstituted, trisubstituted arenes and observed borylation and perfluoroalkylation at meta position (Scheme 1.7).²⁴

Robbins and coworkers established the site selective alkylation of various hetero(arenes) through Ir-catalyzed C–H borylation. They used Ni, or Pd-catalyzed system for the coupling of a range of allylic, benzylic and alkyl substrates (Scheme 1.8).²⁵ Moreover, site selectivity complementary to Friedel Craft alkylation was achieved.

An efficient method for the iodination of arenes is described by B. M. Partridge. They introduced Ir-catalyzed borylation followed by Cu-catalyzed iodination. Regioselectivity is controlled by the first step (Scheme 1.9). This methodology has potential for radiolabeled aryl iodides.²⁶
C–H borylation of pentafluorosulfanyl arenes was carried out by Carreira group. Pentafluorosulfanyl group was found to be compatible with Ir-catalyzed borylation reaction conditions (Scheme 1.10). Resulting boronic esters were converted into corresponding trifluoroborates, which were further utilized in Suzuki Miyaura coupling to form a series of disubstituted pentasulfanyl substrates.27

One-pot Ir-catalyzed C–H borylation/Pd-catalyzed dehalogenation methodology was developed to gain access to fluoroarene substrates resulting in borylation at ortho position. Bulkiness of chloro and bromo group allowed borylation to occur at ortho to fluoro group (Scheme 1.11).28

Ding et al demonstrated an efficient protocol that used other boryl group B(MIDA) and provided MIDA boronates (MIDA= N-methyliminodiacetic acid) (Scheme 1.12). A comparative study of Bpin and B(MIDA) was carried out in Suzuki Miyaura coupling and it was found that only Bpin under went coupling reaction while B(MIDA) remained intact
to the substrate. B(MIDA) group could be utilized in Suzuki Miyaura coupling by modification of the reaction conditions. This finding provided a novel route to synthesize functionalized compounds.²⁹

Recently, our group reported Ir-catalyzed C–H borylation of fluoroalkoxy substituted arenes (Scheme 1.13). Regioselectivity was governed by steric and borylation was observed at the least hindered site. Fluoroalkoxy group was found to be compatible in the reaction conditions.³⁰

1.2 Other metal-catalyzed borylation reactions of (hetero)arenes

1.2.1 Fe-catalyzed C–H borylation

Tasumi et al developed iron methyl complex supported with N-heterocyclic carbene ligand. This complex efficiently borylated furan and thiophene with pinacolborane as the borylating specie (Scheme 1.14). Moreover, they observed that site-selectivity with Fe-complex was similar with Ir-catalyzed C–H borylation.³¹
Dombary developed an efficient method of Fe-catalyzed borylation. They observed dehydrogenative C–H borylation of arenes and heteroarenes by using iron bis(diphosphine) complex under UV irradiation (Scheme 1.15). Mononuclear iron catalyst was used for borylation without any additives at room temperature.\(^{32}\)

![Scheme 1.15: Photochemical borylation with Fe-complex](image-url)

1.2.2 Co-catalyzed C–H borylation

Chirik group evaluated pincer-ligated cobalt (I) complexes for borylation (Scheme 1.16). They carried out borylation of arenes and heteroarenes with Co-complex and found that borylation of heteroarenes was more efficient with the reported ligand. Regioselectivity trend is similar to Ir-catalyzed borylation.\(^{33}\)

![Scheme 1.16: PNP pincer ligand supported Co-complex catalyzed borylation](image-url)

1.2.3 Ni-catalyzed C–H borylation

In 2015, Chatani and coworkers elaborated Ni-catalyzed borylation of (hetero)arenes (Scheme 1.17). They utilized N-heterocyclic carbenes for the transformation. The site-selectivity was mainly controlled by steric effects so meta- and para- borylated products predominated ortho-product. However, borylation of anisole provided a mixture of isomers with ortho-product as major isomer.\(^{34}\)
1.2.4 Zn-catalyzed C–H borylation

Marder group disclosed an interesting borylation methodology using Zn-catalyst. They combined C–X and C–H diboration. C–H bond next to C–X bond was borylated in the given reaction conditions (Scheme 1.18). If the ortho- bond was not free, then meta- position would be borylated. Ligand selection played important role for this transformation.\(^{35}\)

\[
\text{Scheme 1.18: Zn-catalyzed dual C–X and C–H borylation of aryl halides}
\]

1.3 Metal free borylation of (hetero)arenes

During the last decade, C–H borylation has emerged as a cutting edge research approach. A number of useful and efficient metal catalyzed reactions are known in literature. Scientific community still pursues metal free and cost effective methodologies. The utility of a metal free system induced Ingleson group to develop metal free borylation. They put forward a catalytic electrophilic borylation route for the synthesis of boronic esters via the cleavage of C–H bond. Cationic Lewis acid was used to initiate the reaction.\(^{36}\)

Fontain group developed an efficient protocol for metal free borylation. They used intramolecular frustrated Lewis pair compound as catalyst for dehydrogenative borylation of C–H bond of (hetero)arenes.\(^{37}\) They observed that site selectivity was complementary with the most metal catalyzed reactions.
1.4 Directed C–H borylation of (hetero)arenes

1.4.1 Ir-catalyzed ortho directed borylation

Ir-catalyzed C–H borylation is mainly controlled by steric effects and this aspect could be problematic if the desired compound’s regioselectivity is different. To overcome this issue, a bunch of functional groups have been used that direct the borylation to a selective site.

Ishiyama et al designed an Ir-catalyzed ortho C–H borylation of aldimines (Scheme 1.19). Moreover, they claimed that high regioselectivity was achieved by using 2-norborene, [Ir(COD)(OMe)]$_2$ pre-catalyst and P(C$_6$F$_5$)$_3$ ligand. A number of functional groups were compatible with the reaction conditions.$^{38}$

![Scheme 1.19: Ir-catalyzed ortho borylation of aldimines](image)

Ito and coworkers developed ligand controlled regiodivergent C–H borylation of functionalized substrates. Site selectivity were reversed by the combination of [Ir(COD)(OMe)]$_2$ and AsPh$_3$. (Scheme 1.20).$^{39}$

![Scheme 1.20: Regiodivergent synthesis of heteroarenes](image)
Smith group proposed an efficient protocol for *ortho* borylation of arenes. They used P or N containing silanes as ligand in combination with Ir-catalyst. They observed that ester, amido, and methoxy were feasible *ortho* directing groups. (Scheme 1.21).  

![Scheme 1.21: Ortho directed borylation using silane ligands](image)

Recently, Suginome group proposed *ortho* directed Ir-catalyzed C–H borylation of pyrazolylaniline modified boronic acid. (Scheme 1.22).

![Scheme 1.22: Directed Ir-catalyzed borylation of pyrazolylaniline modified boronic acid](image)

1.4.2 Ir-catalyzed meta directed borylation

Chattopadhyay group showed Ir-catalyzed meta directed C–H borylation occurred with assistance of imines as directing group. (Scheme 1.23). They also reported that differentially modified aryldiboronic acids underwent functionalization at selective positions e.g. oxidation and biaryl synthesis.

![Scheme 1.23: Ir-catalyzed ortho directed borylation of arenes](image)
Phippes group demonstrated Ir-catalyzed meta directed C–H borylation. They focused on ion pair interaction to control the regioselectivity of the substrates.\textsuperscript{43}

1.4.3 Ir-catalyzed para-directed borylation

Itami introduced a bulky diphosphine ligand for borylation. The characteristic of the newly designed ligand included para-directed borylation. (Scheme 1.24).\textsuperscript{44} Regioselectivity was controlled by the steric repulsion between catalyst and substrate. This methodology allowed them to synthesis Caramiphen, a drug used to treat Parkinson’s disease.

\[ R\text{--}H \xrightarrow{[\text{Ir(cod)OH}]_2 \text{Xyl-MeO-BIPHEP} \text{B}_2\text{pin}_2} R\text{--}\text{Bpin} \]

Scheme 1.24: Ir-catalyzed para directed borylation

Inspired from the tremendous applications of Ir-catalyzed borylation, we decided to contribute our humble efforts to this field. In the second chapter, we disclose facile synthesis of halogen decorated para-/meta-hydroxybenzoates by iridium-catalyzed borylation and oxidation. Third chapter of this dissertation emphasises design, synthesis, molecular docking and biological evaluation of novel boscalid analogues as potential antifungal agents.

Fourth chapter focuses on iridium-catalyzed C-H borylation of CF\textsubscript{3}-substituted pyridines.

In the fifth chapter, we introduce the synthesis of aryl/heteroaryl chiral boronic esters.
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Chapter 2: Facile Synthesis of Halogen Decorated para-/meta-Hydroxybenzoates by Iridium-Catalyzed Borylation and Oxidation
2. Facile Synthesis of Halogen Decorated para-/meta-Hydroxybenzoates by Iridium-Catalyzed Borylation and Oxidation

2.1 Abstract: Hydroxybenzoates are widely used as preservatives and antiseptics in food and pharmaceuticals. Selective C–H borylation of benzoates would be an attractive approach in synthetic domain as strategies focusing on the direct functionalization of 2,6-, 2,5- and 2,3-disubstituted alkyl benzoates are lacking. Herein we describe a general protocol employing iridium-catalyzed C–H borylation/oxidation of commercially available arene substrates. This methodology gained facile access to disubstituted hydroxybenzoates bearing either ortho-/para- or meta-directing groups, as synthesis of akin compounds proved to be laborious by traditional approaches.

Key words: Iridium-catalyzed C–H borylation, oxidation, hydroxybenzoates.

2.2 Introduction

Phenols are considered as key synthetic precursors to many drugs, polymers, herbicides and antioxidants. The importance of phenolic compounds like 4-hydroxybenzoates (parabens), 3-hydroxybenzoates and 2-hydroxybenzoate has been well reviewed. Parabens are widely used as antimicrobial preservatives in food, pharmaceuticals and cosmetics. 3-Hydroxybenzoates have also shown excellent antifungal properties while 2-hydroxybenzoate like methyl salicylate are active ingredient of many antiseptics. Due to their immense utility in pharmaceutical and food chemistry, methods to access hydroxybenzoates, especially in the presence of other functional groups are of considerable interest.

Classical approaches to such compounds include esterification of hydroxybenzoic acid using catalytic amount of concentrated sulfuric acid or PTSA. Traditionally hydroxybenzoic acids have been synthesized either using Kolbe-Schmitt process by
heating potassium phenoxide in a stream of carbon dioxide or by heating \( p \)-cresol with various metallic oxides.\textsuperscript{4} Unfortunately, harsh reaction conditions make these methods incompatible in the presence of other functional groups.

![Methyl paraben, Aspirin, Methyl salicylate, 3-Hydroxybenzoate](image)

Figure 2.1: Selected example of hydroxybenzoates of commercial importance
Some other existing protocols for the synthesis of phenolic compounds include nucleophilic substitution of aryl halides,\(^5\) Cu-catalyzed conversion of diazoarene to phenol,\(^6\) Cu-mediated reactions of aryl halide,\(^7\)\(^8\) and Pd-catalyzed\(^9\) transformation of aryl halid using phosphine ligands and conversion of pre-functionalized substrates\(^10\)\(^11\) to phenol.
Recently, aryl boronic ester and its derivatives have emerged as potential synthon for a variety of organic conversions. Several useful methods have been reported for the conversion of aryl boronic esters into their corresponding phenols. Hydrogen peroxide, hydroxylamine and oxone are commonly employed oxidants for such transformation. The first two oxidizing agents require long reaction time and gives moderate yield while oxone provides extremely rapid and efficient conversion.

Despite numerous long route syntheses of hydroxybenzoate, straightforward routes to 2,6-disubstituted or 2,3-disubstituted hydroxybenzoates bearing ortho-/para-, or meta-directing groups are lacking. To the best of our knowledge, only one direct method for synthesis of meta-substituted (mono-substituted) hydroxybenzoate is addressed by Smith and co-workers. This finding promoted us to develop a general, efficient, mild and convenient method for the synthesis of di-substituted hydroxybenzoates of biological significance.

2.2.1 Challenges
Conventional methods for the synthesis of substituted hydroxybenzoates have limited substrate scope as the precursors require either pre-functionalization or harsh reaction conditions. Harsh reaction conditions make these traditional methods incompatible to the labile functional groups. Therefore development of protocol with good functional group tolerance in mild reaction condition is desirable to provide synthetic short-cuts.

2.2.2 Aims and Objectives
The main objective of this project is to synthesize halogen decorated para-meta-Hydroxybenzoates from readily available hydrocarbon feedstock. Herein, we hypothesized that iridium-catalyzed C–H borylation/oxidation of substituted benzoates would constitute the direct route to di-substituted hydroxybenzoates. Our study started
with C–H borylation of alkyl benzoates which were prepared by Fischer esterification of commercially available benzoic acids. To access the research scheme scope, various substrates were examined. Methyl, ethyl and propyl esters were synthesized by refluxing the mixture of benzoic acid substrate in alcohol using catalytic amount of conc. sulfuric acid.

2.3 Results and Discussion

As a convenient borylation protocol developed by Smith, Miyura and hartwig, the precatalyst [Ir(OMe)(COD)]2 and d'bpy ligand were weighed and added into air free Schlenk flask under nitrogen atmosphere. Pinacol borane (HBpin) and benzoate substrates were also added in the flask. Reaction mixture was allowed to heat at 80 °C. We observed that borylation of 2,6 and 2,5-disubstituted benzoates selectively takes place at the least hindered 4-position and the resulting boronate esters were isolated in good yield (Scheme 2.1). In most cases, functional group tolerance of Cl, Br, F, Me, OMe and COOR were observed and regioselectivity for C–H borylation on 4-position was >98-99%. For entry 2.1c, 2.1d and 2.1f, formation of small amounts (1-2%) of monoborylated isomer was also detected by GC-MS.
All the synthesized boronate esters were then converted into hydroxybenzoates. Protocol, developed by Smith, using 1 equivalent oxone at room temperature and open air was found ideal for this transformation. The desired hydroxyl benzoates were isolated simply by aqueous workup and purified by column chromatography and gave excellent yield. Deborylation (<1%) for 2.2b and 2.2f was observed by GC-MS. The yield of 2.2f was low due to deborylation and incomplete conversion of the reactant into the product. Scheme 2.2 summarizes synthesis of 2,6 and 2,5-disubstituted hydroxybenzoates.
Next, attention was turned to synthesize 2,3-disubstituted hydroxybenzoates. Previously used borylation conditions worked well for these substrates as well. In most cases, borylation specifically at 5-position was observed with >98-99% regioselectivity (Scheme 2.3). For entry 2.3a, chloro borylated product (∼1%) was detected by GC-MS. Dechlorination (<1%) for entry 2.3b, 2.3c, 2.3d, 2.3e and 2.3f was also observed. For entry 2.3f, ethyl borylated product was also detected by GC-MS.
Synthesized boronic esters were subjected to oxidation by employing typical oxidation protocol used hitherto. For entry 2.4b, minor isomer (<1%) was detected. In case of 2.4a, chloro hydroxybenzoate was detected by GC-MS. Methyl 2,3-dichloro-5-hydroxybenzoate (entry 2.4d) was observed. Scheme 2.4 summarizes synthesis of 2,3-disubstituted hydroxybenzoates.
In summary, iridium-catalyzed borylation/oxidation of alkyl benzoates is an efficient protocol for synthesis of substituted hydroxybenzoates. This method is particularly attractive for the preparation of 2,6-, 2,5- and 2,3-disubstituted hydroxybenzoates bearing either ortho-/para- or meta-directing groups, as synthesis of such compounds is quite arduous by traditional methods.

2.4 Experimental Section

All reactions were carried out under N₂ atmosphere, without the use of glovebox or Schlenk line. All commercially available chemicals and reagents were used without further purification unless otherwise noted. EtOAc, hexanes, and CH₂Cl₂ were distilled before use. Reactions were carried out in air-free 25-mL Schlenk flask (0–4 mm Valve, 175-mm OAH). Analytical TLC was carried out using 250-μm thick SiliaPlate™ TLC Plates. Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was carried out using SiliaFlash® (particle size: 40–63 μm, 230–400
mesh). All reported yields are for isolated materials. Reaction times and yields are not optimized. HBPin = pinacolborane.

Infrared spectra were recorded as neat using a Bruker Alpha-P IR instrument in the ATR geometry with a diamond ATR unit. Melting points were taken on Electrothermal IA9100 melting point apparatus. Reactions were monitored by a GC-MS operating in EI mode. $^1$H NMR spectra were recorded at 500 MHz and $^{13}$C NMR spectra were recorded at 125 MHz at ambient temperatures. The chemical shifts in $^1$H NMR spectra are reported using TMS as internal standard and were referenced with the residual proton resonances of the corresponding deuterated solvent (DMSO: $\delta = 2.50$). The chemical shifts in the $^{13}$C NMR spectra are reported relative to TMS ($\delta = 0$) or the central peak of DMSO ($\delta = 39.52$) for calibration.

The abbreviations used for the chemical shifts are as; s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), and m (unresolved multiplet). All coupling constants are apparent $J$ values measured at the indicated field strengths. In $^{13}$C NMR spectra of arylboronic esters, the carbon atom attached to the boron atom of BPin group is typically not observed due to broadening from and coupling with boron. Regiochemistry of the borylated product isomers, where present, was assigned by NMR spectroscopy ($^1$H & $^{13}$C NMR).

Procedures

2.4.1. General procedure for borylation

In a fume hood, an oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere [Ir(OMe)(COD)]$_2$ (13.26 mg, 0.02 mmol, 2 mol%), 4,4-di-tert-butyl bipyridine (10.74 mg, 0.04 mmol, 4 mol%), and pinacolborane (HBPin) (436 µL, 384 mg, 3 mmol, 1.5 equiv) were added. Arene substrate (1 mmol, 1 equiv) was added via micropipette under
nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath. The color of the reaction mixture changed from light yellow to dark brown. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed under reduced pressure using rotary evaporator. The crude yield was determined. The crude product was purified by column chromatography (silica gel).

**Compound 2.1a: Methyl 2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to methyl 2-bromo-6-methoxybenzoate (488 mg, 2 mmol, 1 equiv) for 40 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.44) furnished the product as white solid (730 mg, 99 %); m.p: 117-118 °C; FT-IR (ATR):2979, 1739, 1387, 1350, 1264, 1249, 1122, 851 cm⁻¹;¹H NMR (500 MHz, DMSO): δ = 7.42 (s, 1 H), 7.25 (s, 1 H), 3.85 (s, 6 H, 2 CH₃), 1.31 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 165.6 (C), 165.3 (C), 129.4 (CH), 127.8 (C), 118.5 (C), 115.3 (CH), 84.5 (2 C), 56.3 (CH₃), 52.7 (CH₃), 24.6 (4 CH₃ of Bpin); GC-MS (EI): m/z (%) = 370 (M⁺, 62), 341 (50), 339 (58), 241 (89), 239 (100), 59 (61).

**Compound 2.1b: Methyl 2-bromo-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to 2-bromo-6-chlorobenzoate (375 mg, 1.5 mmol, 1 equiv) for 18 hr. Column chromatography (DCM/n-Hex 1:1, Rf ) furnished the product as white solid (614 mg, 82%); m.p: 84 °C; FT-IR (ATR): 2974, 1736, 1530, 1469, 1278, 1193, 1056 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 7.80 (d, J = 1 Hz, 1 H), 7.70 (d, J = 0.5 Hz, 1 H), 3.92 (s, 3 H, 1CH₃), 1.30 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 165.1 (C), 137.1 (C), 136.2 (CH), 133.5 (CH), 130.3
(C), 119.1 (C), 84.8 (2 C), 53.3 (CH₃), 24.6 (4 CH₃ of Bpin); GC-MS (EI): m/z (%) = 376 (M⁺, 17), 374 (14), 361 (19), 290 (100), 288 (81), 245 (25), 59 (32).

**Compound 2.1c: Methyl 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to methyl 2-methyl-6-chlorobenzoate (368 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.23) furnished the product as white solid (447 mg, 72 %); m.p: 72 °C. IR (ATR): 2977, 1732, 1354, 1269, 1124, 1080, 848 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 7.54 (s, 1 H), 7.51 (s, 1 H), 3.89 (s, 3 H, 1 CH₃), 2.27 (s, 3 H, CH₃), 1.30 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H) (125 MHz, DMSO)): δ = 166.7 (C), 136.3 (C), 135.7 (C), 134.5 (CH), 131.7 (CH), 129.1 (C), 84.3 (2 C), 24.6 (4 CH₃ of Bpin), 18.7 (CH₃); GC-MS (EI): m/z (%) = 310 (M⁺, 8), 295 (9), 279 (9), 226 (31), 224 (100), 193 (15).

**Compound 2.1d: Methyl 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to methyl 2,6-dichlorobenzoate (412 mg, 2 mmol, 1 equiv) for 20 hr. Column chromatography DCM/ n-hexane 1:1, Rf 0.52) furnished the product as white solid; m.p: 76 °C; IR (ATR): 2983, 1609, 1359, 1170, 1100 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 7.67 (s, 2 H), 3.93 (s, 3 H, CH₃), 1.31 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H) (125 MHz, DMSO)): δ = 164.3 (C), 134.9 (C), 133.1 (2 CH), 130.5 (2 C), 84.8 (2C), 53.3 (CH₃), 24.6 (4 CH₃ of Bpin); GC-MS (EI): m/z (%) = 330 (M⁺, 7), 315 (12), 244 (100), 213 (29), 199 (18), 85 (22).
Compound 2.1e: Methyl 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The general borylation procedure was applied to methyl 2,6-dimethylbenzoate (164 mg, 1 mmol, 1 equiv) for 36 hr. Column chromatography DCM/ n-hexane 1:1, Rf 0.52) furnished the product as white solid; m.p: 78°C (223 mg, 77 %); IR (ATR): 2980, 1732, 1365, 1321, 1260, 1126, 1077 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = δ 7.38 (s, 2 H), 3.85 (s, CH₃), 2.22 (s, 6 H, 2 CH₃), 1.29 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H) (125 MHz, DMSO)): δ = 169.4 (C), 136.4 (C), 133.5 (C), 133.4 (2 CH), 83.8 (2 C), 52.0 (1 CH₃), 24.6 (4 CH₃ of Bpin), 18.8 (2 CH₃); GC-MS (EI): m/z (%) = 290 (M⁺,52), 275 (42), 259 (47), 258 (50), 204 (100), 191 (84), 158 (68), 105 (23).

Compound 2.1f: Methyl 2-bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The general borylation procedure was applied to methyl 2-bromo-5-fluorobenzoate (464 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/ n-hexane 1:1, Rf 0.3) furnished the product as white solid (634 mg, 88 %). mp 95°C; FT-IR (ATR): 2972, 2930, 1482, 1447, 1371, 1245, 1143, 1079 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 7.84 (d, J = 5 Hz, 1 H), 7.60 (d, J = 9 Hz, 1 H), 3.87 (s, 3 H, CH₃), 1.31 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H) (125 MHz, DMSO)): δ = 164.9 (d, ¹JC-F = 1.62 Hz, C), 164.7 (d, ¹JC-F = 250.5 Hz, C), 140.9 (d, ²JC-F = 8.2 Hz, CH), 136.7 (d, ³JC-F = 8.1 Hz, C), 117.9 (d, ²JC-F = 27.5 Hz, CH), 114.3 (d, ³JC-F = 3.5 Hz, C), 84.5 (2 C), 52.9 (CH₃), 24.5 (4 CH₃ of Bpin); GC-MS (EI): m/z (%) = 358 (M⁺), 318 (48), 316 (54), 300 (27), 296 (81), 254 (76), 267 (58).
**Compound 2.3a: Methyl 2-bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to methyl 2-bromo-3-methylbenzoate (456 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex, Rf 0.3) furnished the product as white solid; m.p: 75°C; FT-IR (ATR): 2965, 1724, 1275, 1120, 827 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO): \(\delta = \delta 7.82\) (m, 1 H, CH), 7.78 (m, 1 H, CH), 3.85 (s, 3 H, CH\(_3\)), 2.42 (s, 3 H, CH\(_3\)), 1.30 (s, 12 H, 4 CH\(_3\) of Bpin); \(^{13}\)C NMR (\{\(^1\)H\} (125 MHz, DMSO)): \(\delta = 166.5\) (C), 138.9 (C), 138.7 (CH), 133.7 (C), 133.1 (CH), 125.5 (C), 84.2 (2 C), 52.6 (CH\(_3\)), 24.6 (4 CH\(_3\) of Bpin), 22.90 (CH\(_3\)); GC-MS (EI): \(m/z\) (%) = 354 (M\(^+\)), 313 (95), 311 (100), 281 (56), 225 (69), 223 (74), 143 (67).

**Compound 2.3b: Methyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to methyl 2,3-dichlorobenzoate (408 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.4) furnished the product as white solid; m.p: 96-97°C (541 mg, 82 %); FT-IR (ATR): 2977, 1727, 1692, 1351, 1268, 1242, 1138, 851 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO): \(\delta = 7.94\) (d, \(J = 1.5\) Hz, 1 H), 7.92 (d, \(J = 1.5\) Hz, 1 H), 3.88 (s, 3 H, CH\(_3\)), 1.31 (s, 12 H, 4 CH\(_3\) of Bpin); \(^{13}\)C NMR (\{\(^1\)H\} (125 MHz, DMSO)): \(\delta = 164.7\) (C), 138.1 (CH), 134.5 (CH), 133.2 (C), 132.7 (C), 132.4 (C), 84.7 (2C), 52.9 (CH\(_3\)), 24.6 (4 CH\(_3\) of Bpin); GC-MS (EI): \(m/z\) (%) = 330 (M\(^+\)), 315 (19), 299 (13), 295 (100), 253 (90), 232 (19), 199 (32).
**Compound 2.3c: Methyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate**

The general borylation procedure was applied to methyl 2-chloro-3-(trifluoromethyl)benzoate (476 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/ n-Hex 1:1, Rf 0.4) furnished the product as white solid; m.p: 77°C (531 mg, 73 %); FT-IR (ATR): 2980, 1723, 1601, 1299, 1271, 1130, 847 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 8.22 (d, J = 1.5 Hz, 1 H), 8.08 (d, J = 1.5 Hz, 1 H), 3.90 (s, 3 H, CH₃), 1.32 (s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 164.7 (C), 139.6 (CH), 134.8 (q, ³J_C-F = 4.8 Hz, CH), 133.3 (C), 132.4 (C), 127.8 (q, ²J_C-F = 30.5 Hz, C), 122.5 (q, ¹J_C-F = 271.7 Hz, CF₃), 84.8 (2 C), 53.1 (CH₃), 24.6 (4 CH₃ of Bpin); GC-MS (EI): m/z (%) = 364 (M⁺), 349 (12), 323 (31), 320 (100), 289 (36), 233 (49), 205 (37), 85 (60).

**Compound 2.3d: Ethyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate**

The general borylation procedure was applied to ethyl 2,3-dichlorobenzoate (436 mg, 2 mmol, 1 equiv) for 18 hr. Column chromatography DCM/ n-hexane 1:1, Rf 0.4) furnished the product as white solid; m.p: 67°C (502 mg, 73 %); FT-IR (ATR): 2983, 1609, 1359, 1170, 1100 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 7.91 (d, J = 1.5 Hz, 1 H), 7.896 (d, J = 7 Hz, 2 H, CH₂), 4.52 (q, J = 7 Hz, 2 H, CH₂), 1.34 (s, 12 H, 4 CH₃ of Bpin), 1.32 (t, J = 7 Hz, 3 H, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 164.41 (C), 137.9 (CH), 134.1 (C), 133.1 (C), 132.9 (C), 132.6 (C), 84.7 (2 C), 61.9 (CH₂), 24.9 (4 CH₃ of Bpin); 13.9 (CH₃); GC-MS (EI): m/z (%) = 344 (M⁺, 18), 301 (93), 273 (100), 255 (36), 217 (26), 199 (47), 85 (19).
Compound 2.3e: Ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate

The general borylation procedure was applied to ethyl 2-chloro-3-(trifluoromethyl)benzoate (504 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.4) furnished the product as white solid; m.p: 65 °C (629 mg, 83%); FT-IR (ATR): 2981, 1735, 1279, 1135, 848 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 8.17 (d, J = 1.5 Hz, 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 4.37 (q, J = 7 Hz, 2 H, CH₂), 1.33 (m, 15 H, 1 CH₃, 4 CH₃ of Bpin); ¹³C NMR (¹H) (125 MHz, DMSO): δ = 164.3 (C), 139.2 (CH), 134.7 (q, 3J₇Cₖ= 5.1 Hz, CH), 133.7 (C), 132.2 (C), 127.7 (q, ²J₇Cₖ= 30.3 Hz, C), 122.5 (q, ¹J₇Cₖ= 271.6 Hz, C), 84.8 (C), 67.4 (CH₂), 24.5 (4 CH₃ of Bpin), 21.4 (CH₃), 12.2 (CH₃); GC-MS (EI): m/z (%) = 378 (M⁺), 363 (18), 335 (100), 309 (100), 289 (36), 251 (42), 205 (27).

Compound 2.3f: Propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate

The general borylation procedure was applied to propyl 2-chloro-3-(trifluoromethyl)benzoate (532 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.4) furnished the product as colorless oil (629 mg, 83%); FT-IR (ATR): 2978, 1736, 1374, 1297, 1279, 1136, 848 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 8.16 (d, J = 1.5 Hz, 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 4.29 (t, J = 6.5 Hz, 2 H, CH₂), 1.73 (sext, J = 7.5 Hz, 2 H, CH₂), 1.31 (s, 12 H, 4 CH₃ of Bpin), 0.95 (t, J = 7 Hz, 3 H, CH₃); ¹³C NMR (¹H) (125 MHz, DMSO): δ = 164.5 (C), 139.2 (CH), 134.7 (q, ³J₇Cₖ= 4.9 Hz, C), 133.8 (CH), 132.1 (C), 127.7 (q, ²J₇Cₖ= 30.1 Hz, C), 122.5 (q, ¹J₇Cₖ= 272.1 Hz, CF₃), 84.8 (2 C), 67.4 (CH₂), 24.5 (4 CH₃ of Bpin), 21.4 (CH₃), 10.3 (CH₃); GC-MS (EI): m/z (%) = 392 (M⁺), 377 (20), 333 (23), 306 (100), 289 (21), 251 (23).
2.4.2. General procedure for oxidation

In an oven dried round bottom flask, boronic ester substrate (1 mmol) along with
3 mL acetone was added. Stirring produced homogenous solution, an aqueous solution of
oxone (6.15 mg, 1 mmol, 1 equiv. in 3 mL water) was added dropwise over 2-4 min. upon
complete addition, the reaction mixture was vigorously stirred for 10-20 min. After the
completion of the reaction, aqueous solution of NaHSO3 (1 mL) was added. Reaction
mixture was extracted with DCM (15 mL x 3). The combined organics were washed with
brine. Organic layer was separated and dried using anhydrous sodium sulphate (2 g) then
filtered. Volatiles were removed under reduced pressure using rotary evaporator. The
 crude yield was determined. The crude product was purified by column chromatography
(silica gel).

Compound 2.2a: Methyl 2-bromo-6-methoxy-4-hydroxybenzoate

The general oxidation procedure was applied to methyl methyl 2-chloro-6-
methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) (370 mg, 1mmol, 1 equiv) for
20 min. Column chromatography (DCM, Rf 0.2) furnished the product as white solid; m.p:
85°C (251 mg, 96 %). FT-IR (ATR): 3235, 1692, 1598, 1452, 1426, 1293, 1236, 1155,
1106, 1035 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.32 (s, 1 H, OH), 6.60 (d, J = 2 Hz,
1 H), 6.48 (d, J = 2 Hz, 1 H), 3.76 (s, 3 H, CH₃), 3.73 (s, 3 H, CH₃); ¹³C NMR (¹H) (125
MHz, DMSO)): δ = 166.2 (C), 160.1 (C), 158.1 (C), 119.1 (C), 116.5 (C), 110.6 (CH),
98.7 (CH), 55.9 (CH₃), 52.3 (CH₃); GC-MS (EI): m/z (%): 260 (M⁺, 18), 231 (95), 229
(100), 69 (41), 51 (19).

Compound 2.2b: Methyl 2-bromo-6-chloro-4-hydroxybenzoate

The general oxidation procedure was applied to methyl 2-chloro-6-bromo-4-
(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (188 mg, 0.5 mmol, 1 equiv) for
25 min. Column chromatography (DCM, Rf 0.2) furnished the product as white solid; m.p: 115-118°C (129 mg, 97 %); FT-IR (ATR): 3202, 2953, 1686, 1599, 1562, 1424, 1275, 1241 1134 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.81 (s, 1 H, OH), 7.05 (d, J = 2 Hz, 1 H), 6.94 (d, J = 2.5 Hz, 1 H), 3.85 (s, 3 H, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 165.6 (C), 159.5 (C), 131.1 (C), 125.7 (C), 119.6 (C), 118.2 (CH), 115.5 (CH), 52.9 (CH₃); GC-MS (EI): m/z (%) = 266 (M⁺, 25), 235 (25), 97 (24), 79 (23), 62 (100), 59 (45).

**Compound 2.2c: Methyl 2-chloro-4-hydroxy-6-methylbenzoate**

The general oxidation procedure was applied to methyl 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (310 mg, 1mmol, 1 equiv) for 30 min. Column chromatography (Ethyl acetate: n-Hexane 1:1, Rf 0.7) furnished the product as pale yellow semi solid; (186 mg, 93 %); FT-IR (ATR): 3409, 2386, 1712, 1270, 1130 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.23 (s, 1 H, OH), 6.70 (dd, J = 2 Hz, J = 0.5 Hz, 1 H), 6.64 (dd, J = 2.5 Hz, J = 1 Hz, 1 H), 3.81 (s, 3 H, CH₃), 2.18 (s, 3 H, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 167.0 (C), 158.7 (C), 138.3 (C), 130.4 (C), 124.1 (C), 115.8 (CH), 113.4 (CH), 52.2 (CH₃), 19.4 (CH₃); GC-MS (EI): m/z (%) = 200 (M⁺, 42), 169 (100), 141 (24), 77 (36).

**Compound 2.2d: Methyl 2,6-dichloro-4-hydroxybenzoate**

The general oxidation procedure was applied to methyl 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (161 mg, 0.5mmol, 1 equiv) for 25 min. Column chromatography (Ethyl acetate: n-hexane, 1:1 Rf 0.5) furnished the product as white solid; m.p: 108°C (166 mg, 75 %); FT-IR (ATR): 3385, 2980, 1729, 1434, 1352, 1136 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.85 (s, 1 H, OH), 6.91 (s, 2 H, 2 CH), 3.85 (s, 3 H, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 164.9 (C), 159.5 (C), 131.3 (2C), 123.6 (C), 115.2 (2 CH), 52.9 (CH₃); GC-MS (EI): m/z (%) = 220 (M⁺, 33), 189 (110), 133 (17), 97 (3).
**Compound 2.2e: Methyl 2,6-dimethyl-4-hydroxybenzoate**

The general oxidation procedure was applied to methyl 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (145 mg, 0.5 mmol, 1 equiv) for 30 min. Column chromatography (Ethyl acetate: n-hexane, 1:1, Rf 0.52) furnished the product as white solid; m.p: 111-113°C (87 mg, 97%); $^1$H NMR (500 MHz, DMSO): $\delta = 9.64$ (s, 1 H, OH), 6.46 (s, 2 H, 2 CH), 3.77 (s, 3 H, CH$_3$), 2.16 (s, 6 H, 2 CH$_3$); $^{13}$C NMR ($^1$H (125 MHz, DMSO)): $\delta = 169.5$ (C), 157.9 (C), 136.9 (2 C), 124.3 (C), 114.4 (2 CH), 51.5 (CH$_3$), 19.8 (2 CH$_3$); GC-MS (EI): $m/z$ (%) = 180 (M$^+$, 54), 149 (100), 121 (25), 103 (3), 91 (16).

**Compound 2.2f: Methyl 2-bromo-5-fluoro-4-hydroxybenzoate**

The general oxidation procedure was applied to methyl 2-bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (358 mg, 1 mmol, 1 equiv) for 25 min. Column chromatography (Ethyl acetate: n-Hexane, 1:1, Rf 0.6) furnished the product as white solid; m.p: 152-155°C (238 mg, 96%); FT-IR (ATR): 3360, 3086, 2979, 1712, 1436, 1327, 1141 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO): $\delta = 11.25$ (s, 1 H, OH), 7.68 (d, $J = 11.5$ Hz, 1 H), 7.26 (s, $J = 8$ Hz, 1 H), 3.80 (s, 1 H, CH$_3$); $^{13}$C NMR ($^1$H (125 MHz, DMSO)): $\delta = 164.3$ (d, 4$J_{C-F} = 1.5$ Hz, C), 149.5 (d, 4$J_{C-F} = 242.2$ Hz, C), 149.2 (d, 2$J_{C-F} = 12.7$ Hz, C), 122.7 (d, 3$J_{C-F} = 3.1$ Hz, CH), 121.3 (d, 3$J_{C-F} = 5.7$ Hz, C), 119.2 (d, 2$J_{C-F} = 21.1$ Hz, CH), 116.3 (d, 4$J_{C-F} = 3.1$ Hz, C), 52.3 (s, CH$_3$); GC-MS (EI): $m/z$ (%) = 248 (M$^+$, 30), 246 (23), 217 (95), 215 (100), 187 (26).

**Compound 2.4a: Methyl 2-bromo-5-hydroxy-3-methylbenzoate**

The general procedure was applied to methyl 2-bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (177 mg, 0.5 mmol, 1 equiv) for 30 min. Column chromatography (Ethyl acetate: n-Hexane, Rf 0.7) furnished the product as semi solid; (118 mg, 97%); FT-IR (ATR): 3368, 2979, 1712, 1436, 1327, 1141 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO): $\delta = 9.97$ (s, 1 H, OH), 6.91 (dd, $J = 3$ Hz, $J = 0.5$ Hz 1 H), 6.85 (dd, $J$ 34
=2.5 Hz, \( J = 0.5 \text{ Hz} \) 1 H), 3.82 (s, 3 H , CH\(_3\)), 2.31 (s, 3 H , CH\(_3\)); \(^{13}\)C NMR (\(\{^1\text{H}\}\) (125 MHz, DMSO)): \(\delta = 167.1\) (C), 156.3 (C), 139.9 (C), 134.7 (C), 120.2 (CH), 114.3 (CH), 110.0 (C), 52.5 CH\(_3\)), 23.1 (CH\(_3\)); GC-MS (EI): \(m/z\) (%) = 244 (M\(^+\),51), 215 (92), 213 (100), 185 (25), 78 (16).

**Compound 2.4b: Methyl 2,3-dichloro-5-hydroxybenzoate**

The general procedure was applied to methyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (330 mg, 1 mmol, 1 equiv) for 30 min. Column chromatography (Ethyl acetate: n-Hexane, R\(_f\) 0.7) furnished the product as white colored solid; m.p: 147-148°C (202 mg, 92 %); FT-IR (ATR): 3304, 1704, 1413, 1311, 1241, 778 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO): \(\delta = 10.55\) (s, 1 H, OH), 7.18 (d, \( J =3 \text{ Hz}\) , CH), 7.10 (d, \( J =3 \text{ Hz}\) , CH), 3.85 (s, 3 H, CH\(_3\)).

\(^{13}\)C NMR (\(\{^1\text{H}\}\) (125 MHz, DMSO)): \(\delta = 165.1\) (C), 156.6 (C), 133.2 (C), 133.2 (C), 119.8 (CH), 118.7 (C), 116.2 (CH), 52.8 (CH\(_3\)); GC-MS (EI): \(m/z\) (%) = 220 (M\(^+\), 64), 189 (100), 163 (11), 161 (16), 133 (10).

**Compound 2.4c: Methyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate**

The general procedure was applied to methyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (364 mg, 1 mmol, 1 equiv) for 20 min. Column chromatography (ethyl acetate: n-hexane, 1:1 R\(_f\) 0.6) furnished the product as white semi solid (240 mg, 94 %); FT-IR (ATR): 3385, 2980, 1729, 1434, 1352, 1136 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO): \(\delta = 10.78\) (s, 1 H, OH), 7.34 (s, 2 H, 2 CH), 3.87 (s, 3 H, CH\(_3\)); \(^{13}\)C NMR (\(\{^1\text{H}\}\) (125 MHz, DMSO)): \(\delta = 165.0\) (C), 153.4 (C), 134.8 (CH), 128.8 (q, \(2J_{C-F} = 30.5\) Hz, C), 122.4 (q, \(1J_{C-F} = 271.6\) Hz, C\(_F\)), 120.2 (CH), 117.5 (C), 117.1 (q, \(3J_{C-F} = 5.4\) Hz, C), 52.9 (CH\(_3\)); GC-MS (EI): \(m/z\) (%) = 254 (M\(^+\), 22), 225 (8), 223 (100), 195 (35), 132 (13).
Compound 2.4d: Ethyl 2,3-dichloro-5-hydroxybenzoate

The general procedure was applied to ethyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (344 mg, 1 mmol, 1 equiv) for 20 min. Column chromatography (Ethyl acetate: n-Hexane, Rf 0.7) furnished the product as white solid; m.p: 105-107ºC (215 mg, 92%); FT-IR (ATR): 3388, 1702, 1606, 1568, 1434, 1368, 1284, 1220 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.54 (s, 1 H, OH), 7.18 (d, J = 3 Hz, CH), 7.09 (d, J = 3 Hz, CH), 4.31 (q, J = 7 Hz, 2 H, CH₂), 1.30 (t, J = 7 Hz, 3 H, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 164.7 (C), 156.6 (C), 133.5 (C), 133.2 (C), 119.7 (CH), 118.6 (C), 116.1 (CH), 61.7 (CH₂), 13.1 (CH₃); GC-MS (EI): m/z (%) = 234 (M⁺, 57), 221 (4), 208 (35), 191 (59), 189 (100), 161 (17).

Compound 2.4e: Ethyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate

The general oxidation procedure was applied to ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl) benzoate (378 mg, 1 mmol, 1 equiv) for 30 min. Column chromatography (Ethyl acetate: n-hexane, 1:1 Rf 0.6) furnished the product as white solid; m.p: 113-114ºC (233 mg, 87%); FT-IR (ATR): 3389, 2986, 1700, 1438, 1257, 1136, 888 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.78 (s, 1 H, OH), 7.34 (d, J = 3 Hz, CH), 7.33 (d, J = 3 Hz, CH), 4.34 (q, J = 7.5 Hz, CH₂), 1.31 (t, J = 7.5 Hz, CH₃); ¹³C NMR (¹H (125 MHz, DMSO)): δ = 171.5 (C), 164.6 (C), 135.1 (C), 128.7 (q, ²J_C–F = 31 Hz, C), 122.4 (q, ¹J_C–F = 271.7 Hz, C), 120.1 (CH), 117.4 (C), 116.9 (q, ³J_C–F = 5.4 Hz, CH), 61.9 (CH₂), 13.9 (CH₃); GC-MS (EI): m/z (%) = 268 (M⁺, 36), 241 (11), 223 (100), 195 (23).
Compound 2.4f: Propyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate

The general oxidation procedure was applied to propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (392 mg, 1 mmol, 1 equiv) for 20 min. Column chromatography (Ethyl acetate: n-hexane, 1:1 Rf 0.6) furnished the product as white semi solid; (231 mg, 82 %); FT-IR (ATR): 3383, 2979, 1702, 1590, 1439, 1231, 1190, 1144 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ = 10.79 (s, 1 H, OH), 7.34 (s, 1 H, CH), 7.34 (s, 1 H, CH), 4.26 (t, J =6.5 Hz, CH₂), 1.71 (sxp, J =6.5 Hz, CH₂), 0.96 (t, J =7 Hz, CH₃); ¹³C NMR (¹H) (125 MHz, DMSO)): δ = 164.6 (C), 156.4 (C), 135.1 (C), 128.6 (C), 120.1 (CH), 117.4 (C), 117.1 (q, J_C-F= 5.5 Hz, CH), 67.3 (CH₂), 21.4 (CH₂), 10.3 (CH₃); GC-MS (EI): m/z (%) = 282 (M⁺, 18), 242 (25), 240 (58), 225 (31), 223 (100), 195 (44), 132 (36).
2.5 References


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Chapter 3: Design, Synthesis, Molecular Docking and Biological Evaluation of Novel Boscalid Analogues as Potential Antifungal Agents
3. Design, Synthesis, Molecular Docking and Biological Evaluation of Novel Boscalid Analogues as Potential Antifungal Agents

3.1 Abstract: Boscalid (a succinate dehydrogenase inhibitor) is widely used fungicide for crop protection. Traditional routes of boscalid synthesis involve pre-functionalization of arenes precursor, which affects the step economy and overall efficiency. We present synthesis of boscalid analogs from readily available hydrocarbon feedstock without pre-functionalization. The sequential Ir-catalyzed C–H borylation of arenes and Suzuki coupling provided biphenyl amines (key intermediate) which on amidation produced boscalid analogues in good yields. The molecular docking gave insight into the binding interaction of these compounds. The In-vitro studies of the analogs were carried out against Fusarium moniliforme and we found that compound 3j and 3g provided superior inhibition on potato dextrose agar (PDA) plates.

Keywords: Nicotinamide, borylation, Suzuki coupling, succinate dehydrogenase inhibitors, molecular docking.

3.2 Introduction
Agricultural sector, a vital component of the economy of a country, faces the challenge of fungal pathogens that can reduce impact production of major food crops in various countries (US, China, Pakistan and India) by 20%.1,2 Carboxamide, such as boxin, boscalid (BASF), bixafen (Bayer), isopyrazam (Syngenta), fluxapyroxad (BASF), tiadinil (Nihon Nohyaku), is an important class of agrochemicals, have been extensively used to control these pathogens and act as succinate dehydrogenase (SDH) inhibitors disrupting the mitochondrial tricarboxylic acid cycle of pathogen.2,3 Boscalid has emerged as one of the most commonly used fungicide throughout the world. The nuts and bolts of the boscalid synthesis lie in the construction of biaryl unit.4 Various approaches have been developed to access the biaryl structural moiety. These routes are commonly metal mediated. Ullman coupling, known as first coupling method for the biaryl synthesis, utilizes stoichiometric amount of copper at high temperature (100-300 °C).5 Directed ortho-metalation also provides a general way to biaryl synthesis but with narrow substrate scope. Another method called Gomberg Backmann reaction focuses on the arylation of anilines using aryl diazoates.6 Aforementioned traditional methods either suffer from harsh reaction conditions or known to have erratic yield. Catalytic cross
coupling using organozinc,\textsuperscript{7} -tin,\textsuperscript{8} -copper,\textsuperscript{9} -boron\textsuperscript{10} or -magnesium\textsuperscript{11} compounds represent most widely used class of reactions. Among them, Suzuki Miyaura coupling of aryl boronic ester with aryl halide has earned enormous attention being the most convenient tool to access biaryls both on laboratory and industrial scale.

![Chemical structures](image)

**Figure 3.1:** Selected examples of drug molecules containing the biaryl core

Industrial synthesis of boscalid involved Suzuki coupling of 4-chlorophenylboronic acid with 2-nitrobenzene (Figure 3.2). 4-Chlorophenylboronic acid in turn is synthesized from 1,4-dichlorobenzene through Grignard reaction. Goossen \textit{et. al}\textsuperscript{12} developed Cu/Pd mediated decarboxylative cross-coupling of arenecarboxylates with aryl halide to form 2-nitro-4'-chlorobiphenyl, a key intermediate in boscalid synthesis. Another approach introduced by Fagnou K. and co-workers employed palladium catalyst for the direct arylation of nitro-substituted arenes with aryl halides.\textsuperscript{13} Zakri C. highlighted the applications of palladium on charcoal catalyst employing aryl diazonium salt and boronic acid to form boscalid.\textsuperscript{14} Heinrich \textit{et. al.}\textsuperscript{15} exploited the metal free approach by using aryl diazoates and substituted anilines in aqueous medium. Recently, Mandal K. has reported the coupling of 4-chlorophenylboronic acid and 2-idoaniline using palladium nanoparticles on graphite oxide for the synthesis of boscalid.\textsuperscript{16} Though, useful strategies
yet need pre-functionalization of arenes which affects the step economy and reduces overall efficiency towards the target compound.

### 3.3.1. Challenges

Traditionally used method for the synthesis of Boscalid involves Suzuki coupling of 4-chlorophenylboronic acid with 2-nitrobenzene. 4-Chlorophenylboronic acid itself is synthesized from 1,4-dichlorobenzene through Grignard reaction. Reduction of nitro-substituted biaryl provides biarylamine which upon amidation gives Boscalid. Traditional synthesis consists of overall six steps. Although, it is a useful strategies yet need pre-functionalization of arenes which affects the step economy and reduces overall efficiency towards the target compound.

### 3.3.2. Aims and Objectives

In the previous decades, resistance to boscalid was observed, so that’s why there is a need to develop more effective boscalid analogs. The main objective of this project is to develop a methodology which will gain access to more effective boscalid analogs. Inspired from immense utility of selective C–H bond functionalization, we aim to develop a highly efficient protocol employing C–H borylation, cross coupling and amidation (three steps) for the synthesis of boscalid analogues from readily available hydrocarbon feedstock without pre-functionalization (Figure: 3.3). Ir-catalyzed C–H activation/borylation bypasses the need of pre-functionalization and imparts chemical versatility in the molecule.
Smith, Miyaura and Hartwig have developed efficient Ir-catalyzed C–H borylation method and this transformation has widespread applications in synthesis. In this study, a series of novel boscalid analogs with different substituents containing active skeleton (nicotinamide), have been synthesized. The docking studies were performed to evaluate binding of these compounds to SDH (pdb code: 2FBW)(Table 3.1). On the basis of binding score, it is revealed that electron withdrawing groups at R2 and R4 are more suitable than other positions. Therefore, we focused on the synthesis of boscalid analogs with different functional groups at R2 and R4 to verify our virtual screening. We then evaluated these compounds against Fusarium moniliforme through In-vitro inhibition of mycelial growth and report the analogs with superior activity that can act as hits for further structure optimization studies.

Table 3.1: Docking score for virtual screening in synthesis design

<table>
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<tr>
<th>Compounds</th>
<th>- Docking Score (kcal/mol)</th>
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<tr>
<td>R1 R2 R3 R4 R5 R6 R7 R8 R9</td>
<td></td>
</tr>
<tr>
<td>H CF3 H CF3 H H CF3 H H</td>
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<tr>
<td>H CF3 H Cl H H H H H</td>
<td>9.3</td>
</tr>
<tr>
<td>OCF3 H H CF3 H H H H H</td>
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<tr>
<td>H H NO2 H H H H H</td>
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<tr>
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<tr>
<td>H H OCF3CF3H OCF3CF3H H H H H H H</td>
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</tr>
<tr>
<td>H CF3 H CN H H H H H H</td>
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3.2.3. Molecular Docking: Docking was performed with Vina AutoDock. The molecular structures were energetically minimized using Avogadro-1.2.0n. The Gasteiger-Huckel charges of ligands were assigned. All bound water and ligand were removed from the protein. Polar hydrogen atoms and Kollman-united charges were added to the protein.

3.3 Results and Discussion

3.3.1. Chemical Synthesis: The synthetic route to the target compound is shown in Figure 3.4: General scheme for synthesis of boscalid.

C–H borylation of 1,3-disubstituted arene was carried out by using convenient borylation protocol developed by Smith, Miyaura and Hartwig. Precatalyst [Ir(OMe)(COD)]₂ and d'bpy ligand were weighed and added into air free Schlenk flask under nitrogen atmosphere. Pinacol borane and arene substrates were added in the flask. Reaction mixture was allowed to heat at 80 °C. (Scheme 3.1)
We observed that borylation of 1,3-disubstituted arenes selectively takes place at the least hindered 5-position as reported in literature and the resulting boronate esters were isolated in good yield. Functional group tolerance of Cl, OCH₃, CF₃, OCF₃, OCF₂CF₂H, CN and COOR was also observed. In all cases, regioselectivity for C–H borylation on 5-position was <99%. In some cases 3.1e and 3.1g, complete conversion of reactant into product was not observed, which led to the lesser yield as compared to the other compound. All the synthesized boronate esters were then subjected to Suzuki coupling reaction. Pd(PPh₃)₄, 2-bromoaniline, boronic ester substrate and K₃PO₄ were weighed and added into air free Schlenk flask under nitrogen atmosphere. Reaction mixture was allowed to heat at 80 °C and the progress of the reaction was monitored by TLC and GC-MS. (Scheme 3.2)
Suzuki coupling of 1,3-disubstituted arenes with 2-bromoaniline lead to the formation of biphenyl amines in reasonable yields regardless of the various functional groups present. The main side reactions observed were deborylation and in some cases (3.2c, 3.2f) homocoupling of the boronic ester. All the synthesized biphenyl amines were then reacted with 2-chloronicotinoyl chloride in the presence of triethyl amine at room temperature. Progress of the reaction was monitored by TLC and GC-MS (Scheme 3.3).
Coupling of biphenyl amines with 2-chloronicotinoyl chloride resulted in the formation of amide bond. To our delight, novel boscalid analogs were obtained in good yield.

We have also elaborated the reaction scheme by introducing another new route to boscalid analogs. Traceless borylation of substituted aniline was carried out and the resulting boronic ester was coupled with aryl halide to form biphenylamine that on amidation with nicotinoyl chloride yielded desired compound (Scheme 3.4).
3.3.2. Molecular Docking

In an effort to elucidate the possible mechanism of these synthesized compounds, the docking of these compounds into the binding pocket of SDH (pdb code: 2FBW) was performed. Docking of boscalid was also carried out as the same time as a reference. The docking scores are provided in
Table 3.2. All the analogs (3.3a, 3.3b, 3.3c, 3.3i and 3.3k) exhibited better scores as compared to Boscalid. 3-D schematic diagrams clearly explained the possible optimal combination between ligands and receptor protein. Ligands were well bound to the active site with amino hydrogen towards the carbonyl oxygen of TRP173 as shown in Figure 3.5. 2-D diagrams (Figure 3.6) also indicates that all amino acid residues TYR58, ARG43, HIS216, ILE40, TRP173, PRO169, and TRP173 interacted with ligand through van der Waals and polar interactions. Beside these, additional hydrogen bonds were formed between the electronegative atoms (e.g. fluorine) at position R₁ & R₃ and TYR58 & ARG43. Thus, a stable complex between ligands and active site was formed based on these interactions. This binding model indicates that introduction of electronegative atom at position R₁ and R₃ allowed the ligand to interact more easily with receptor protein.
Table 3.2: Docking Score of the ligands and Boscalid

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<th>Entry</th>
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<tr>
<td>3.3f</td>
<td>8.9</td>
<td>Boscalid</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Figure 3.5: Cannolly surface of complex II with 3.3a (left) and boscalid (right) shown as stick model.

Figure 3.6: Interaction of 3.3a (left) and boscalid (right) with amino acid residues in active site (3-D diagram).
Seven synthesized boscalid derivatives inhibited the growth of *Fusarium moniliforme* on PDA plates, however their inhibitory activities to *F. oxysporum*, *F. solani*, *Rhizopus* sp., *Curvularia* sp., and *C. falcatum* were negligible. Commercial agricultural fungicide boscalid exhibited the 10% inhibition of *F. moniliforme*. Maximum inhibition (15%) was shown by the compound 3.3j followed by the compound 3.3g, that showed significant inhibition (12.5%) of tested *F. moniliforme*. Compounds 3.3f and 3.3b exhibited moderate inhibition (7.5%) whereas 5% inhibition of *F. moniliforme* fungal mat was observed by compound 3.3c and 3.3i.
3.4 Conclusion

In summary, we have developed an efficient protocol for the synthesis of novel boscalid analogs. The synthesized compounds were evaluated by molecular docking studies. Moreover In-vitro studies against *Fusarium moniliforme* furnished good results. We anticipated that, this methodology could be of interest for many agrochemical processing.

3.5 Experimental Section

3.5.1. General procedure for borylation

In a fume hood, an oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere \([\text{Ir(OMe)(COD)}]_2\) (19.88 mg, 0.01 mmol, 1 mol%), bipyridine (9.37 mg, 0.02 mmol, 2 mol%), and bis(pinacolato)diboron (B$_2$pin$_2$) (571.5 mg, 2.25 mmol, 0.75 equiv) were added. Arene substrate (3 mmol, 1 equiv) was added via micropipette under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 60 °C in an oil bath. The color of the reaction mixture changed from light yellow to dark brown. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed under reduced pressure using rotary evaporator. The crude yield was determined. The crude product was purified by column chromatography (silica gel).

**Compound 3.1a: 2-(3,5-Bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol ane**

The general borylation procedure was applied to 3,5-bis(trifluoromethyl)benzene (642 mg, 3mmol, 1 equiv) for 15 h. Column chromatography (n-hex, R$_f$ 0.29) furnished the product as white solid (1010 mg, 99 %); m.p: 70 °C; $^1$H NMR (700 MHz, CDCl$_3$) ð;
FT-IR (neat) ν: 2984, 2921, 1310, 1168, 1130, 899, 844, 703 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 340 (M$^+$), 325 (100), 321 (13), 260 (6), 254 (24), 221 (11), 185 (5), 165 (14), 85 (7).

**Compound 3.1b:** 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) benzo nitrile

The general borylation procedure was applied to 3-(trifluoromethyl)benzonitrile (513 mg, 3mmol, 1 equiv) for 17 hr. Column chromatography (DCM/n-Hex 1:2, R$_f$ 0.33) furnished the product as colorless liquid (848 mg, 95%); $^1$H NMR (700 MHz, CDCl$_3$) δ; FT-IR (neat) ν: 3083, 2992, 2235, 1604, 1386, 1342, 1298, 1174, 1134, 966, 908, 843, 703 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 297 (M$^+$, 11), 282 (100), 254 (11), 211 (45), 198 (17), 178 (7), 85 (5).

**Compound 3.1c:** 2-(3-Chloro-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxa borolane

The general borylation procedure was applied to 3-chloro-5-(trifluoromethyl)benzene (540 mg, 3mmol, 1 equiv) for 16 h. Column chromatography (DCM/n-Hex 1:1, R$_f$ 0.29) furnished the product as colorless liquid (868 mg, 95%); $^1$H NMR (700 MHz, CDCl$_3$) δ; FT-IR (neat) ν: 2981, 2933, 1609, 1363, 1291, 1169, 1128, 964, 875, 703 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 306 (M$^+$, 18), 291 (100), 287 (9), 220 (83), 207 (37), 206 (17), 185 (10), 85 (7).

**Compound 3.1d:** Methyl 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

The general borylation procedure was applied to methyl 3-methoxybenzoate (498 mg, 3mmol, 1 equiv) for 16 hr. Column chromatography (DCM/n-Hex 1:1, R$_f$ 0.29) furnished the product as colorless liquid (740 mg, 84%); $^1$H NMR (700 MHz, CDCl$_3$) δ; FT-IR (neat) ν: 2974, 1715, 1560, 1455, 1371, 1264, 1141, 1053, 850, 773, 701 cm$^{-1}$; GC-MS
(EI) m/z (% relative intensity) 292 (M+, 49), 277 (18), 249 (100), 222 (25), 217 (60), 192 (45), 161 (37), 133 (23).

Compound 3.1e: 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethoxy)benzonitrile

The general borylation procedure was applied to 3-(trifluoromethoxy)benzonitrile (561 mg, 3mmol, 1 equiv) for 12 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.26) furnished the product as colorless liquid (789 mg, 84 %); ¹H NMR (700 MHz, CDCl₃) δ; FT-IR (neat) ν: 2978, 2298, 1350, 1198, 1141, 965, 852, 694 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 313 (M⁺, 8), 298 (60), 270 (8), 227 (100), 214 (19), 142 (18), 85 (20).

Compound 3.1f: 3-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

The general borylation procedure was applied to 3-chlorobenzonitrile (411 mg, 3mmol, 1 equiv) for 12 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.29) furnished the product as white solid (705 mg, 89 %); m.p: 68-70 °C; ¹H NMR (700 MHz, CDCl₃) δ; FT-IR (neat) ν: 2979, 2931, 2213, 1589, 1350, 1198, 1140, 965, 852 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 263 (M⁺, 9), 248 (29), 177 (100), 163 (56), 142 (19), 101 (47), 85 (19), 57 (27).

Compound 3.1g: 2-(3-Methoxy-5-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

The general borylation procedure was applied to 1-methoxy-3-(trifluoromethoxy)benzene (576 mg, 3mmol, 1 equiv) for 12 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.24) furnished the product as colorless liquid (822 mg, 86 %); ¹H NMR (700 MHz, CDCl₃) δ; FT-IR (neat) ν: 2980, 2939, 1585, 1422, 1361, 1247, 1214, 1139, 1054, 964, 849 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 318 (M⁺, 14), 259 (13), 232 (100), 218 (41), 188 (10), 147 (8).
Compound 3.1h: 2-(3-Chloro-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

The general borylation procedure was applied to 1-chloro-3-methoxyphenyl (426 mg, 3mmol, 1 equiv) for 18 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.39) furnished the product as colorless liquid (798 mg, 99 %); 1H NMR (700 MHz, CDCl3) δ; FT-IR (neat) v: 2978, 2935, 1566, 1449, 1409, 1346, 1141, 1047, 701 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 268 (M⁺, 100), 253 (43), 252 (19), 211 (8), 182 (96), 168 (41), 147 (12).

Compound 3.1i: 2-(3,5-Bis(1,1,2,2-tetrafluoroethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxa borolane

The general borylation procedure was applied to 3,5-bis(trifluoromethyl)benzene (930 mg, 3mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:2, Rf 0.24) furnished the product as white solid (1291 mg, 99 %); m.p: 65-67°C; 1H NMR (700 MHz, CDCl3) δ; FT-IR (neat) v: 2991, 2935, 1612, 1586, 1352, 1094, 963, 842, 777 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 436 (M⁺, 9), 421 (25), 350 (100), 337 (30), 319 (17), 279 (11), 233 (64), 219 (39), 145 (12), 85 (27).

Compound 3.1j: Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) benzoate

The general borylation procedure was applied to ethyl 3-(trifluoromethyl)benzoate (654 mg, 3mmol, 1 equiv) for 24 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.29) furnished the product as white solid (950 mg, 92 %); m.p: 77-81°C; 1H NMR (700 MHz, CDCl3) δ; FT-IR (neat) v: 2987, 1714, 1295, 1250, 1132, 1017, 703, 683 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 344 (M⁺, 4), 329 (27), 301 (98), 273 (100), 217 (36), 199 (19), 171 (17), 85 (15).
Compound 3.1k: 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,6-bis(trifluoromethyl) pyridine

The general borylation procedure was applied to 2,6-bis(trifluoromethyl)pyridine (645 mg, 3 mmol, 1 equiv) for 5 hr. Column chromatography (DCM/n-Hex 1:1, Rf 0.32) furnished the product as white solid (831 mg, 81%); m.p: 82-84 °C; 1H NMR (700 MHz, CDCl3) δ; FT-IR (neat) v: 2983, 2930, 1311, 1273, 1140, 964, 845, 691 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 341 (M⁺, 6), 326 (100), 299 (17), 256 (11), 222 (12), 166 (21), 69 (10), 57 (14).

3.5.2. General procedure for Suzuki Coupling reaction

Oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere Pd(PPh₃)₄ (69 mg, 0.03 mmol, 3 mol%), boronic ester substrate (2.2 mmol, 1.1 equiv) and K₃PO₄ (637 mg, 3 mmol, 1.5 equiv.) were added under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 60 °C in an oil bath. The color of the reaction mixture changed from light yellow to dark brown. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed under reduced pressure using rotary evaporator. Water (5 mL) was added in the crude reaction mixture and product was extracted using ethyl acetate (10 mL x3). Organic layer was separated and dried using anhydrous sodium sulphate (2 g) then filtered. Volatiles were removed under reduced pressure using rotary evaporator. The crude product was purified by column chromatography (silica gel).

Compound 3.2a: 3′,5′-Bis(trifluoromethyl)-[1,1′-biphenyl]-2-amine

The general Suzuki coupling procedure was applied to 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (748 mg, 2.2 mmol, 1.1 equiv) for 18 hr. Column
chromatography (ethyl acetate/n-hexane 1:4, Rf 0.68) furnished the product as dark brown liquid (551 mg, 90 %); $^1$H NMR (500 MHz, DMSO) δ 8.03 (m, 3 H, 3 CH), 7.12 (m, 1 H, CH), 7.08 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 1 H, CH), 6.80 (dd, $J = 8$ Hz, $J = 1$ Hz, 1 H, CH), 6.68 (m, 1 H, CH), 5.07 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 145.52 (C), 142.42 (C), 130.56 (q, $^2$J$_{C-F}$ = 32.6 Hz, 2 C), 130.38 (CH), 129.52 (CH), 129.35 (d, $J = 2.8$ Hz, 2 CH), 123.43 (q, $J = 271.3$ Hz, 2 CF$_3$), 120.29 (distorted q, CH), 116.99 (CH), 115.89 (CH); FT-IR (neat) ν: 3369, 3342, 3031, 2932, 1619, 1465, 1379, 1276, 899, 751, 680 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 305 (M$^+$, 100), 284 (40), 264 (17), 235 (21), 216 (66), 214 (4), 167 (7).

**Compound 3.2b: 2'-Amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile**

The general Suzuki coupling procedure was applied to 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzonitrile (653.4 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:4, Rf 0.46) furnished the product as light brown liquid (316 mg, 60 %); $^1$H NMR (500 MHz, DMSO) δ 8.27 (m, 1 H, CH), 8.17 (distorted t, 1 H, CH), 8.03 (t, $J = 1$ Hz, 1 H, CH), 7.12 (m, 1 H, CH), 7.06 (dd, $J = 1.5$ Hz, 1 H, CH), 6.79 (dd, $J = 1$ Hz, 1 H, CH), 6.66 (m, 1 H, CH), 5.11 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 145.53 (C), 142.23 (C), 136.40 (CH), 130.60 (q, $^2$J$_{C-F}$ = 32.6 Hz, C), 130.35 (CH), 129.91 (q, $^3$J$_{C-F}$ = 3.6 Hz, CH), 129.59 (CH), 127.29 (q, $^3$J$_{C-F}$ = 2.9 Hz, CH), 123.21 (q, $^1$J$_{C-F}$ = 271.4 Hz, CF$_3$), 122.09 (C), 117.70 (C), 116.89 (CH), 115.83 (CH), 113.14 (C); FT-IR (neat) ν: 3460, 3375, 3072, 3029, 2233, 1621, 1350, 1259, 1126, 750, 701 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 262 (M$^+$, 100), 241 (50), 193 (41), 192 (77), 164 (23), 139 (13), 113 (7), 69 (26).
**Compound 3.2c: 3’-Chloro-5’-(trifluoromethyl)-[1,1’-biphenyl]-2-amine**

The general Suzuki coupling procedure was applied to 2-(3-chloro-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (673.2 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:4, Rf 0.53) furnished the product as brown liquid (316 mg, 60 %). 1H NMR (500 MHz, DMSO) δ 7.79 (m, 1 H, CH), 7.77 (t, J = 1.5 Hz, 1 H, CH), 7.68 (m, 1 H, CH), 7.10 (m, 1 H, CH), 7.04 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H, CH), 6.78 (m, 1 H, CH), 6.65 (m, 1 H, CH), 5.03 (s, 2 H, NH$_2$); 13C NMR (125 MHz, DMSO) δ 145.41 (C), 143.03 (C), 134.26 (C), 132.57 (CH), 130.21 (CH), 129.34 (CH), 124.47 (C), 124.08 (dist q, $^3$J$_{C-F}$ = 5 Hz, CH), 123.34 (dist q, $^3$J$_{C-F}$ = 3.9 Hz, CH), 122.70 (C), 116.85 (CH), 115.76 (CH); FT-IR (neat) ν: 3471, 3384, 3071, 3028, 1618, 1590, 1331, 1223, 748, 697 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 271 (M$^+$, 100), 250 (16), 216 (58), 201 (16), 167 (87), 166 (32), 139 (25), 69 (13).

**Compound 3.2d: Methyl 2’-amino-5-methoxy-[1,1’-biphenyl]-3-carboxylate**

The general Suzuki coupling procedure was applied to methyl 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (642.4 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, Rf 0.57) furnished the product as yellowish brown solid (396 mg, 77 %); m.p: 106-107 ºC; 1H NMR (500 MHz, DMSO) δ 7.57 (t, J = 1.5 Hz, 1 H, CH), 7.40 (m, 1 H, CH), 7.22 (m, 1 H, CH), 7.07 (m, 1 H, CH), 7.01 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H, CH), 6.76 (dd, J = 8 Hz, J = 1 Hz, 1 H, CH), 6.63 (dt, J = 7.5 Hz, J = 1 Hz, 1 H, CH), 4.87 (s, 2 H, NH$_2$), 3.86 (s, 3 H, CH$_3$), 3.85 (s, 3 H, CH$_3$); 13C NMR (125 MHz, DMSO) δ 166.06 (C), 159.56, 144.11, 141.55 (C), 131.22 (C), 129.91 (CH), 128.62 (CH), 124.37 (C), 121.77 (CH), 119.24 (CH), 116.66 (CH), 115.37 (CH), 112.37 (CH), 55.40 (CH$_3$), 52.26 (CH$_3$); FT-IR (neat) ν: 3463, 3379, 1706, 1590,
1338, 1244, 1046, 768, 505 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 257 (M$^+$, 100), 224 (45), 197 (71), 182 (68), 154 (34), 127 (8).

**Compound 3.2e: 2'-Amino-5-(trifluoromethoxy)-[1,1'-biphenyl]-3-carbonitrile**

The general Suzuki coupling procedure was applied to methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)-5-(trifluoromethoxy)benzonitrile (688.6 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, R$_f$ 0.51) furnished the product as yellowish brown liquid (387 mg, 70 %); $^1$H NMR (500 MHz, DMSO) $\delta$ 7.95 (m, 1 H, CH), 7.93 (t, $J = 1.5$ Hz, 1 H, CH), 7.72 (m, 1 H, CH), 7.11 (m, 1 H, CH), 7.03 (dd, $J = 1.5$ Hz, 1 H, CH), 7.77 (dd, $J = 1$ Hz, 1 H, CH), 6.65 (m, 1 H, CH), 5.11 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) $\delta$ 148.51 (C), 145.45 (C), 143.49 (C), 131.82 (CH), 130.25 (CH), 129.56 (CH), 126.37 (CH), 122.88 (CH), 121.99 (C), 119.90 (d, $^{1}J_{C-F} = 256.3$ Hz, OCF$_3$), 117.58 (C), 116.86 (CH), 115.86 (CH), 113.48 (C), 117.70 (CH), 116.75 (CH), 115.72 (C); FT-IR (neat) $\nu$: 3452, 3374, 3076, 2236, 1620, 1164, 750, 690 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 278 (M$^+$, 100), 209 (8), 192 (93), 165 (16), 154 (9), 127 (5).

**Compound 3.2f: 2'-Amino-5-chloro-[1,1'-biphenyl]-3-carbonitrile**

The general Suzuki coupling procedure was applied to 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)benzonitrile (578.6 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, R$_f$ 0.59) furnished the product as yellowish brown (248 mg, 54 %); m.p: 96-100 ºC; $^1$H NMR (500 MHz, DMSO) $\delta$ 7.97 (m, 1 H, CH), 7.83 (t, $J = 1.5$ Hz, 1 H, CH), 7.78 (m, 1 H, CH), 7.09 (m, 1 H, CH), 7.03 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 1 H, CH), 6.67 (m, 1 H, CH), 6.63 (m, 1 H, CH), 5.08 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) $\delta$ 145.44 (C), 142.97 (C), 134.96 (C), 133.54 (CH), 131.29 (CH), 130.19 (CH), 129.78 (CH), 129.43 (CH), 122.18 (C), 117.70 (CH), 116.75 (CH), 115.72 (C), 113.46 (C); FT-IR (neat) $\nu$: 3438, 3350, 2924, 2851, 2234, 1655, 1562, 1288, 863,
747, 545 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 228 (M\(^+\), 100), 192 (67), 164 (17), 139 (17), 100 (17), 89 (23), 75 (27), 63 (17).

**Compound 3.2g: 3'-Methoxy-5'-(trifluoromethoxy)-[1,1'-biphenyl]-2-amine**

The general Suzuki coupling procedure was applied to 2-(3-methoxy-5-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (699.6 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, \(R_f\) 0.54) furnished the product as brown liquid (515 mg, 90 %); \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 7.08 (m, 1 H, CH), 7.01 (m, 2 H, 2 CH), 6.92 (m, 1 H, CH), 6.89 (m, 1 H, CH), 6.76 (dd, \(J = 8\) Hz, \(J = 1\) Hz), 6.63 (dt, \(J = 7\) Hz, \(J = 1\) Hz, 1 H, CH), 4.92 (s, 2 H, NH\(_2\)), 3.83 (s, 3 H, OCH\(_3\)); \(^{13}\)C NMR (125 MHz, DMSO) \(\delta\) 160.53 (C), 149.37 (d, \(^{3}J_{C-F} = 1.3\) Hz, C), 145.08 (C), 142.57 (C), 129.92 (CH), 128.81 (CH), 123.96 (C), 120.09 (d, \(^{1}J_{C-F} = 254.9\) Hz, OCF\(_3\)), 116.68 (CH), 115.51 (CH), 113.19 (CH), 112.89 (CH), 105.61 (CH), 55.66 (CH\(_3\)); FT-IR (neat) \(\nu\): 3474, 3378, 3012, 2964, 1606, 1420, 1208, 1180, 1051, 849, 748 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 283 (M\(^+\), 100), 268 (15), 252 (16), 198 (24), 182 (44), 154 (42), 127 (10).

**Compound 3.2h: 3'-Chloro-5'-methoxy-[1,1'-biphenyl]-2-amine**

The general Suzuki coupling procedure was applied to 2-(3-chloro-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (589.6 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, \(R_f\) 0.5) furnished the product as yellowish brown (293 mg, 63 %); m.p: 107-109 °C; \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 7.05 (m, 1 H, CH), 6.99 (m, 3 H, 3 CH), 6.91 (m, 1 H, CH), 6.75 (dd, \(J = 8\) Hz, \(J = 1\) Hz, 1 H, CH), 6.62 (dt, \(J = 7.5\) Hz, \(J = 1\) Hz, 1 H, CH), 4.89 (s, 2 H, NH\(_2\)), 3.81 (s, 3 H, OCH\(_3\)); \(^{13}\)C NMR (125 MHz, DMSO) \(\delta\) 160.30 (C), 149.34 (d, \(^{3}J_{C-F} = 1.3\) Hz, C), 145.08 (C), 142.58 (C), 133.90 (C), 129.87 (CH), 128.69 (CH), 124.11 (C), 120.62 (CH), 116.60 (CH), 115.40 (CH), 113.25 (CH), 112.48...
Compound 3.2i: 3',5'-Bis(1,1,2,2-tetrafluoroethoxy)-[1,1'-biphenyl]-2-amine

The general Suzuki coupling procedure was applied to 2-(3,5-bis(1,1,2,2-tetrafluoroethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (642.4 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1;3, Rf 0.6) furnished the product as yellowish brown liquid (666 mg, 83 %); 1H NMR (500 MHz, DMSO) δ 7.33 (d, J = 2 Hz, 2 H, 2 CH), 7.16 (t, J = 2 Hz, 1 H, CH), 7.10 (m, 1 H, CH) 7.04 (dd, J = 8 Hz, J = 1.5 Hz, 1 H, CH), 6.85 (tt, J = 51.5 Hz, J = 3 Hz, 2 H), 6.79 (dd, J = 8.5 Hz, J = 1 Hz, 1 H, CH), 6.66 (dt, J = 7.5 Hz, J = 1 Hz, 1 H, CH), 5.02 (s, 2 H, NH₂); 13C NMR (125 MHz, DMSO) δ 148.01 (C), 145.22 (C), 143.25 (C), 130.08 (CH), 129.32 (2 CH), 122.75 (C), 120.19 (CH), 117.01 (CH), 115.91 (CH), 113.34 (CH), 107.71 (tt, 1JCF = 247.9 Hz, 2JCF = 39.8 Hz, 2 CH) ; FT-IR (neat) ν: 3483, 3381, 3047, 3011, 1617, 1426, 1297, 1098, 996, 842, 750, 695 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 401 (M⁺, 23), 284 (13), 198 (9), 182 (100), 154 (77), 127 (14), 115 (6).

Compound 3.2j: Ethyl 2’-amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate

The general Suzuki coupling procedure was applied to ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzoate (756.8 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1;3, Rf 0.46) furnished the product as yellowish liquid (351 mg, 57 %); 1H NMR (500 MHz, DMSO) δ 8.24 (m, 1 H, CH), 8.11 (m, 1 H, CH), 7.98 (m, 1 H, CH), 7.11 (m, 1 H, CH), 7.05 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H, CH), 6.79 (dd, J = 8 Hz, J = 1 Hz, 1 H, CH), 6.67 (dt, J = 7.5 Hz, J = 1 Hz, 1 H, CH), 5.02 (s, 2H, NH₂), 4.38 (q, J = 7 Hz, 2 H, CH₂), 1.35 (t, J = 7 Hz, 3 H, CH₃); 13C NMR
(125 MHz, DMSO) δ 164 (C), 145.41 (C), 141.73 (C), 133.21 (CH), 131.39 (C), 130.17 (CH), 129.67 (d, $^3J_{C-F} = 2.9$ Hz, CH), 129.32 (CH), 123.55 (CH), 122.98 (C), 116.90 (CH), 115.70 (CH), 61.42 (CH$_2$), 14.06 (CH$_3$); FT-IR (neat) ν: 2983, 2930, 1311, 1273, 1140, 964, 845, 691 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 309 (M$^+$, 100), 281 (21), 262 (70), 235 (81), 216 (59), 167 (29).

**Compound 3.2k: 2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)aniline**

The general Suzuki coupling procedure was applied to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,6-bis(trifluoromethyl)pyridine (750.2 mg, 2.2 mmol, 1.1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:3, $R_f$ 0.62) furnished the product as light brown liquid (372 mg, 61 %); $^1$H NMR (500 MHz, DMSO) δ 8.24 (s, 1 H, CH), 7.19 (m, 2 H, 2 CH), 6.82 (dd, $J = 8$ Hz, $J = 1$ Hz, 1 H, CH), 6.70 (dt, $J = 7.5$ Hz, $J = 1$ Hz, 1 H, CH), 5.40 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 152.74 (C), 147.42 (d, $^2J_{C-F} = 38.3$ Hz, 2 C), 146.00 (C), 130.81 (CH), 130.50 (CH), 123.71 (d, $^3J_{C-F} = 1.4$ Hz, 2 CH), 121.03 (d, $^1J_{C-F} = 1273$ Hz, 2 CF$_3$), 120.20 (C), 117.07 (CH), 116.29 (CH); FT-IR (neat) ν: 3479, 3373, 1611, 1392, 1188, 1122, 851, 761, 694 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 306 (M$^+$, 100), 285 (30), 236 (10), 217 (77), 197 (12), 140 (11).

**Compound 3.4a: 5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine**

The general Suzuki coupling procedure was applied to 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethoxy)aniline (606 mg, 2 mmol, 1 equiv) for 24 hr. Column chromatography (ethyl acetate/n-hexane 1:1, $R_f$ 0.76) furnished the product as light brown liquid (583 mg, 75 %); $^1$H NMR (500 MHz, DMSO) δ 8.06 (m, 3 H, 3 CH), 7.13 (m, 2 H, 2 CH), 6.85 (m, 1 H, CH), 5.31 (s, 2 H, NH$_2$); $^{13}$C NMR (125 MHz, DMSO) δ 145.11 (CH), 140.73 (C), 139.01 (d, $^4J_{C-F} = 1.6$ Hz, C), 130.70 (q, $^2J_{C-F} = 32.3$ Hz, 2 C),
129.54 (d, $^3J_{C\text{-}F} = 2.9$ Hz, 2 CH), 123.32 (q, $^1J_{C\text{-}F} = 271.1$ Hz, 2 CF$_3$), 123.21 (CH), 122.81 (C), 122.56 (C), 120.90 (q, $^3J_{C\text{-}F} = 3.5$ Hz, CH), 120.32 (q, $^1J_{C\text{-}F} = 252.7$ Hz, OCF$_3$), 116.37 (CH).

3.5.3. General procedure for amidation

In an oven dried round bottom flask containing distilled chloroform (5 mL), biphenyl amine substrate (1 mmol, 1 equiv) and 2-chloronicotinoyl chloride (1.6 mmol, 1.6 equiv) were added, followed by drop wise addition of triethylamine (2 mmol, 2 equiv). Reaction mixture was stirred at room temperature for 2-5 hr. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, solvent was evaporated and residues were dissolved in ethyl acetate (10 mL). Organic layer was washed with water (2 mL) and organic layer was separated and dried with anhydrous sodium sulphate (1 g). Solvent was removed under reduced pressure using rotary evaporator. The crude yield was determined. The crude product was purified by column chromatography (silica gel).

**Compound 3.3a: N-(3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2-chloronicotinamide**

The general amidation procedure was applied to 3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine (305 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, R$_f$ 0.18) furnished the product as white solid (376 mg, 85 %); m.p: 172-175 °C; $^1$H NMR (500 MHz, DMSO) $\delta$ 10.31 (s, 1 H, NH), 8.48 (d, $J = 2$ Hz, 1 H, CH), 8.10 (s, 1 H, CH), 8.07 (s, 2 H, 2 CH), 7.80 (m, 1 H, CH), 7.68 (m, 1 H, CH), 7.53 (m, 3 H, 3 CH), 7.45 (m, 1 H, CH); $^{13}$C NMR ($^1$H) (125 MHz, DMSO) $\delta$ 163.94 (C), 150.53 (CH), 146.32 (C), 141.58 (C), 137.65 (CH), 134.43 (C), 134.12 (C), 132.53 (C), 130.66 (CH), 130.29 (q, $^2J_{C\text{-}F}$ 32.6 Hz, 2 C), 129.58 (d, $^3J_{C\text{-}F} = 2.6$ Hz, 2 CH), 129.40 (CH), 127.05 (CH), 126.94 (CH), 123.33 (q, $^1J_{C\text{-}F} = 271.1$ Hz, 2 CF$_3$), 122.90 (CH), 121.02 (q, $^3J_{C\text{-}F} = 3.6$ Hz, 1 CH); FT-
IR (neat) ν: 3379, 2984, 2693, 1655, 1475, 1718, 1123, 1034 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 444 (M⁺, 26), 283 (18), 215 (9), 142 (29), 140 (100), 112 (25).

**Compound 3.3b: 2-Chloro-N-(3'-cyano-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide**

The general amidation procedure was applied to 2'-amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile (262 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.22) furnished the product as white solid (340 mg, 83 %); m.p: 148-151°C; ¹H NMR (500 MHz, DMSO) δ 10.29 (s, 1 H, NH), 8.49 (dd, J = 5 Hz, J = 1.5 Hz, 1 H, CH), 8.35 (s, 1 H, CH), 8.22 (s, 1 H, CH), 8.07 (s, 1 H, CH), 7.86 (dd, J = 7.5 Hz, J = 2 Hz, 1 H, CH), 7.67 (dd, J = 8 Hz, J = 1 Hz, 1 H, CH), 7.54 (m, 3 H, 3 CH), 7.44 (dt, J = 7.5 Hz, J = 1 Hz, 1 H, CH); ¹³C NMR (125 MHz, DMSO) δ 163.92 (C), 150.53 (CH), 146.27 (C), 141.40 (CH), 137.81 (CH), 136.60 (C), 134.10 (C), 134.02 (C), 132.62 (C), 130.57 (CH), 130.31 (q, J_C-F = 32.6 Hz C), 130.00 (q, J_C-F = 3.5 Hz, CH), 129.46 (CH), 128.04 (q, J_C-F = 3.5 Hz, CH), 127.02 (CH), 126.95 (CH), 123.12 (q, J_C-F = 271.1 Hz, CF₃), 122.97 (CH), 117.43 (C), 112.82 (C); FT-IR (neat) ν: 3220, 1658, 1579, 1521, 1406, 1165, 1127, 1069 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 401 (M⁺, 7), 260 (13), 241 (20), 192 (16), 140 (100), 112 (58), 76 (13).

**Compound 3.3c: 2-Chloro-N-(3'-chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide**

The general amidation procedure was applied to 3'-Chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine (271 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.26) furnished the product as white solid (336 mg, 82 %); m.p: 127-130 °C; ¹H NMR (500 MHz, DMSO) δ 10.29 (s, 1 H, NH), 8.49 (dd, J = 5 Hz, J = 2 Hz, 1 H, CH), 7.86 (s, 1 H, CH), 7.83 (dd, J = 7.5 Hz, J = 2 Hz, 1 H, CH), 7.80 (s, 1 H, CH), 7.71 (s, 1 H, CH),
7.65 (dd, $J = 8$ Hz, $J = 1$ Hz, 1 H, CH), 7.53 (m, 2 H, 2 CH), 7.48 (m, 1 H, CH), 7.42 (dt, $J = 7.5$ Hz, $J = 1$ Hz, 1 H); $^{13}$C NMR (125 MHz, DMSO) $\delta$ 164.01 (C), 150.50 (CH), 146.33 (CH), 142.10 (CH), 137.71 (CH), 134.62 (C), 134.04 (C), 133.96 (C), 132.81 (C), 132.68 (C), 130.82 (q, $^2 J_{C-F} = 32.4$ Hz C), 130.49 (CH), 129.21 (CH), 127.12 (CH), 127.01 (CH), 124.25 (q, $^3 J_{C-F} = 3.6$ Hz CH), 124.00 (q, $^3 J_{C-F} = 3.6$ Hz, CH), 123.30 (d, $^1 J_{C-F} = 271.3$ Hz CF$_3$); FT-IR (neat) $\nu$: 3214, 1660, 1562, 1312, 1125, 760 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 410 (M$^+$, 10), 269 (7), 235 (11), 166 (5), 140 (100), 112 (40), 76 (10).

**Compound 3.3d: Methyl 2'-(2-chloronicotinamido)-5-methoxy-[1,1'-biphenyl]-3-carboxylate**

The general amidation procedure was applied to methyl 2'-amino-5-methoxy-[1,1'-biphenyl]-3-carboxylate (257 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, R$_f$ 0.28) furnished the product as white solid (323 mg, 82%); m.p: 124-126 °C; $^1$H NMR (500 MHz, DMSO) $\delta$ 10.21 (s, 1 H, NH), 8.47 (dd, $J = 5$ Hz, $J = 2$ Hz, 1 H, CH), 7.60 (m, 1 H, CH), 7.60 (s, 1 H, CH), 7.48 (m, 3 H, 3 CH), 7.43 (m, 2 H, 2 CH), 7.40 (m, 1 H, CH), 10.87 (m, 1 H, CH), 3.87 (s, 3 H, CH$_3$), 3.84 (s, 3 H, CH$_3$); $^{13}$C NMR {$^1$H} (125 MHz, DMSO) $\delta$ 166.01 (C), 164.04 (C), 159.32 (C), 153.36 (CH), 146.40 (C), 140.69 (C), 137.63 (CH), 136.32 (C), 133.98 (C), 132.89 (C), 130.83 (C), 130.30 (CH), 128.50 (CH), 127.28 (CH), 126.93 (CH), 122.90 (CH), 122.08 (CH), 119.86 (CH), 112.55 (CH), 55.52 (OCH$_3$), 55.31 (CH$_3$); FT-IR (neat) $\nu$: 3387, 3060, 3005, 1720, 1671, 1578, 1524, 1477, 1235, 1051, 767, 748 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 396 (M$^+$, 23), 329 (9), 301 (7), 255 (36), 224 (100), 197 (12), 140 (29), 112 (19).
Compound 3.3e: 2-Chloro-N-(3'-cyano-5'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)nicotinamide

The general amidation procedure was applied to 2'-Amino-5-(trifluoromethoxy)-[1,1'-biphenyl]-3-carbonitrile (278 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.26) furnished the product as white solid (334 mg, 61%); m.p: 153°C; $^1$H NMR (500 MHz, DMSO) δ 10.29 (s, 1 H, NH), 8.49 (dd, $J = 5$ Hz, $J = 2$ Hz, 1 H, CH), 8.03 (m, 1 H, CH), 7.97 (m, 1 H, CH), 7.90 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 1 H, CH), 7.77 (s, 1 H, CH), 7.66 (d, $J = 7.5$ Hz, 1 H, CH), 7.54 (m, 2 H, 2 CH), 7.48 (m, 1 H, CH), 7.43 (m, 1 H, CH); $^{13}$C NMR {$^1$H} (125 MHz, DMSO) δ 164.02 (C), 150.52 (CH), 146.26 (C), 142.56 (C), 137.89 (CH), 134.02 (C), 133.99 (C), 132.64 (CH), 132.12 (C), 130.50 (CH), 129.42 (CH), 127.15 (CH), 127.05 (CH), 126.71 (CH), 123.66 (CH), 123.12 (C), 122.99 (CH), 117.32 (C), 113.12 (C); FT-IR (neat) ν: 3239, 2236, 1652, 1579, 1518, 1262, 1212, 1064, 760 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 417 (M$^+$, 16), 277 (5), 207 (7), 192 (9), 164 (10), 140 (100), 112 (44), 76 (12).

Compound 3.3f: 2-Chloro-N-(3'-chloro-5'-cyano-[1,1'-biphenyl]-2-yl)nicotinamide

The general amidation procedure was applied to 2'-amino-5-chloro-[1,1'-biphenyl]-3-carbonitrile (750.2 mg, 0.5 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.29) furnished the product as white solid (143 mg, 78%); m.p: 144-145°C; $^1$H NMR (500 MHz, DMSO) δ 10.27 (s, 1 H, NH), 8.49 (dd, $J = 5$ Hz, $J = 2$ Hz, 1 H, CH), 8.04 (t, $J = 2$ Hz, 1 H, CH), 7.90 (dd, $J = 7.5$ Hz, $J = 2$ Hz, 1 H, CH), 7.88 (t, $J = 1.5$ Hz, 1 H, CH), 7.83 (t, $J = 2$ Hz, 1 H, CH), 7.65 (m, 1 H, CH), 7.48 (m, 4 H, 4 CH); $^{13}$C NMR {$^1$H} (125 MHz, DMSO) δ 163.98 (C), 150.50 (CH), 146.23 (C), 142.01 (C), 137.88 (CH), 134.15 (C), 134.02 (C), 133.86 (C), 133.63 (CH), 132.77 (C), 131.47 (CH), 130.47 (CH), 130.41 (CH), 129.30 (CH), 127.09 (CH), 126.99 (CH), 123.02 (CH), 117.46 (C), 113.12 (C); FT-
IR (neat) ν: 2983, 2930, 1311, 1273, 1140, 964, 845, 691 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 367 (M⁺, 25), 226 (11), 192 (18), 140 (100), 112 (53), 76 (14).

**Compound 3.3g: 2-Chloro-N-(3′-methoxy-5′-(trifluoromethoxy)-[1,1′-biphenyl]-2-yl)nicotinamide**

The general amidation procedure was applied to 3′-methoxy-5′-(trifluoromethoxy)-[1,1′-biphenyl]-2-amine (283 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.36) furnished the product as yellowish white solid (308 mg, 73 %); m.p: 152-156 °C; ¹H NMR (500 MHz, DMSO) δ 10.20 (s, 1 H, NH), 8.48 (dd, J = 5 Hz, J = 2 Hz, 1 H, CH), 7.80 (dd, J = 7.5 Hz, J = 2 Hz, 1 H, CH), 7.62 (m, 1 H, CH), 7.50 (m, 2 H, 2 CH), 7.41 (m, 2 H, 2 CH), 7.01 (m 1 H, 1 CH), 6.96 (m, 1 H, 1 CH), 6.94 (m, 1 H, 1 CH), 3.82 (s, 3 H, CH₃); ¹³C NMR {¹H} (125 MHz, DMSO) δ 164.18 (C), 160.24 (C), 150.41 (CH), 148.96 (C), 146.44 (C), 141.60 (C), 137.72 (CH), 136.08 (C), 133.95 (C), 132.78 (C), 130.35 (CH), 128.64 (CH), 127.43 (CH), 126.96 (CH), 122.90 (CH), 120.03 (d, J_C-F = 254 Hz, OCF₃), 113.98 (CH), 113.39 (CH), 105.96 (CH), 55.80 (OCH₃); FT-IR (neat) ν: 3370, 3071, 2841, 1668, 1580, 1523,1312, 1151, 749, 669 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 422 (M⁺, 24), 310 (18), 282 (43), 266 (6), 196 (6), 154 (8), 140 (100), 112 (39), 76 (8).

**Compound 3.3h: 2-Chloro-N-(3′-chloro-5′-methoxy-[1,1′-biphenyl]-2-yl)nicotinamide**

The general amidation procedure was applied to 3′-Chloro-5′-methoxy-[1,1′-biphenyl]-2-amine (116.5 mg, 0.5 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, Rf 0.33) furnished the product as off-white solid (122 mg, 66 %); m.p: 129-131°C; ¹H NMR (500 MHz, DMSO) δ 10.15 (s, 1 H, NH), 8.48 (m, 1 H, CH), 7.81 (dd, J = 7.5 Hz, J = 2 Hz, 1 H, CH), 7.60 (d, J = 8 Hz, 1 H, CH), 7.52 (m, 1 H, CH), 7.47 (m, 1 H, CH), 7.40 (m, 1 H,
Compound 3.3i: \( N-(3',5'-\text{Bis}(1,1,2,2\text{-tetrafluoroethoxy})-1,1'\text{-biphenyl})-2\text{-yl})\)-2-chloronicotin amide

The general amidation procedure was applied to \( 3',5'-\text{Bis}(1,1,2,2\text{-tetrafluoroethoxy})-1,1'\text{-biphenyl})-2\text{-amine} \) (401 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, \( R_f \ 0.44 \)) furnished the product as white solid (388 mg, 72 %); m.p: 168-170°C; \( ^1H \) NMR (500 MHz, DMSO) \( \delta \) 10.31 (s, 1 H, NH), 8.49 (dd, \( J = 5 \) Hz, \( J = 2 \) Hz, 1 H, CH), 7.84 (m, 1 H, CH), 7.61 (d, \( J = 7.5 \) Hz, 1 H, CH), 7.48 (m, 4 H, CH), 7.33 (d, \( J = 2.5 \) Hz, 2 H, 2 CH), 7.23 (s, 1 H, CH), 6.84 (tt, \( J = 52 \) Hz, \( J = 2.5 \) Hz, 2 H); \( ^{13}\text{C} \) NMR \( \{^1H\} \) (125 MHz, DMSO) \( \delta \) 164.21 (C), 150.49 (CH), 148.33 (C), 146.43 (C), 142.36 (C), 137.74 (CH), 134.93 (C), 133.92 (C), 132.65 (C), 130.42 (CH), 129.16 (CH), 127.58 (CH), 127.18 (2 CH), 122.85 (CH), 120.65 (CH), 113.96 (CH), 107.67 (t, \( ^1J_{C,F} = 247.5 \) Hz, 2 CH); FT-IR (neat) \( v \): 3252, 3044, 3002, 1641, 1530, 1179, 1104, 842, 754 cm\(^{-1}\); GC-MS (EI) \( m/z \) (% relative intensity) 540 (M\(^+\), 18), 270 (4), 154 (5), 142 (33), 140 (100), 112 (24), 76 (4).

Compound 3.3j: Ethyl 2'-(2-chloronicotinamido)-5-( trifluoromethyl)-1,1'\text{-biphenyl})-3-carboxylate

The general amidation procedure was applied to Ethyl 2'-amino-5-(trifluoromethyl)-1,1'\text{-biphenyl})-3-carboxylate (309 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography
Compound 3k: \( N\)-(2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)phenyl)-2-chloronicotinamide

The general amidation procedure was applied to 2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)aniline (306 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, \( R_f \) 0.3) furnished the product as white solid (312 mg, 70 %); m.p: 163-168 °C; \(^1\)H NMR (500 MHz, DMSO) \( \delta \) 10.41 (s, 1 H, NH), 8.49 (m, 1 H, CH), 8.29 (s, 2 H, 2 CH), 7.92 (m, 1 H, CH), 7.76 (m, 1 H, CH), 7.62 (m, 2 H, 2 CH), 7.54 (m, 1 H, CH), 7.48 (m, 1 H, CH); \(^{13}\)C NMR \( \{^1\} \) (125 MHz, DMSO) \( \delta \) 169.05 (C), 157.34 (C), 155.98 (CH), 155.80 (CH), 139.43 (C), 137.69 (C), 137.09 (C), 135.80 (distorted peak, CH), 132.15 (distorted peak, CH), 131.58 (distorted peak, CH), 129.47 (d, \(^{1}J_{C-F} = 3.9, 2\) CH), 128.30 (CH), 128.18 (CH), 126.17 (q, \(^{1}J_{C-F} = 272.6\) Hz, 2 CF\(_3\) Hz); FT-IR (neat) v: 3204, 2924, 2853, 1652, 1394, 1193, 1133, 758 cm\(^{-1}\); GC-MS (EI) \( m/z \) (% relative intensity) 445 (M\(^+\), 9), 262 (8), 234 (12), 140 (100), 112 (27), 76 (6); HRMS: \( m/z \) 445.04166 [(M\(^+\)]; calcd for C\(_{19}\)H\(_{10}\)ClF\(_6\)N\(_3\)O: 445.04166]
**Compound 3.4b: 2-chloro-N-(5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl] -2-yl)nicotinamide**

The general amidation procedure was applied to 5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine (389 mg, 1 mmol, 1 equiv) for 2 hr. Column chromatography (DCM, R_f 0.3) furnished the product as white solid (262 mg, 50 %); $^1$H NMR (500 MHz, DMSO) $\delta$ 10.40 (s, 1 H, NH), 8.48 (m, 1 H, CH), 8.13 (s, 2 H, 3 CH), 7.83 (m, 2 H, 2 CH), 7.59 (m, 2 H, 2 CH), 7.52 (m, 1 H, CH); $^{13}$C NMR {$^1$H} (125 MHz, DMSO) $\delta$ 164.00 (C), 150.65 (CH), 146.29 (CH), 146.25 (d, $^4 J_{C-F} = 1.1$ Hz, C), 139.88 (CH), 137.72 (CH), 135.95 (CH), 133.46 (CH), 132.29 (C), 130.39 (q, $^2 J_{C-F} = 27.3$ Hz, 2 C), 129.83 (C), 128.55 (CH), 123.47 (C), 123.26 (q, $^1 J_{C-F} = 271.1$ Hz, 2 CF$_3$), 122.91 (CH), 121.88 (C), 121.65 (q, $^3 J_{C-F} = 3.7$ Hz, 2 CH), 120.06 (d, $^1 J_{C-F} = 255.2$ Hz, OCF$_3$).

**In-vitro inhibition of mycelial growth**

Agar well diffusion assay was used to determine the antagonistic activity of synthetic boscalid derivatives against fungal phytopathogens.$^{18}$ A 100 µL aliquot ($1 \times 10^9$ cells/mL) of each fungal pathogen (Fusarium moniliforme, Fusarium oxysporum, Fusarium solani, Rhizopus sp., Curvualria sp., and Colletotrichum falcatus) was separately spread on potato dextrose agar (PDA) plates. Using a sterile cork borer, a central well was made in each PDA plate and filled with 100 µL (1 mg/mL) of test boscalid derivative. Plates were sealed with parafilm and incubated at 26 °C for 3-5 days. Results were expressed as percentage inhibition zones by antagonizing synthetic boscalid derivatives to suppress the growth of fungal mats. Plates with sterile DMSO (dimethyl sulfoxide) and boscalid in agar-wells were used as negative and positive controls, respectively.

Each experiment was performed in triplicate and percentage inhibition was calculated as: $I = (C-T/C) \times 100$: where $I =$ % inhibition, $C =$ fungal diameter in test plate, $T =$ fungal diameter in control plate.
3.6 References


Chapter 4

Iridium-catalyzed C-H Borylation of CF$_3$-Substituted Pyridines
4. Iridium-catalyzed C-H Borylation of CF₃-Substituted Pyridines

4.1 Abstract
Ir-catalyzed C-H borylation of CF₃-substituted pyridines is reported. The approach focuses on the regioselective borylation considering unique substitution pattern of the substrate. Based on the steric evaluation, selective positions of CF₃-substituted pyridines are functionalized. Numerous functional groups like halo, ester, methoxy, amino are found to be compatible with this methodology. Moreover, heteroaryl boronic esters derived from CF₃-substituted pyridines can serve as useful precursors in synthetic regime.

4.2 Introduction
Pyridine and its derivatives are one of the most prevalent heterocyclic moiety in organic chemistry. In addition to dominant structural unit in pharmaceuticals and agrochemicals, they are also used as biological probes, drug candidates, clinically used drugs, functionalized materials and ligands preparation.²⁻⁶ Substitution of various functional groups on pyridine core can have a huge impact on its properties. Nowadays, introduction of fluorinated group is more common, as it enhances the stability and functional group compatibility.⁷⁻⁸ Among other fluorine containing groups, CF₃ exhibits enhanced binding selectivity, lipophilicity, chemical and metabolic stability.⁹⁻¹³

Figure 4.1: Representative of biologically active pyridines
In this regard, synthetic amalgamation of pyridine derivatives and \( \text{CF}_3 \) in a substrate would be of great synthetic value. Numerous protocols are available for the trifluoromethylation of pyridine.\(^{14,15}\) Other useful approaches include functionalization of pyridine backbone. Clapham \textit{et al} has reported the synthesis of trifluoromethyl substituted-pyridylboronic acid derivatives via lithiation and boronation protocol.\(^{16}\) Beside the usefulness, aforementioned method is affected by the availability of halopyridines and harsh reaction condition. Metal-catalyzed reactions provide a solution to such predicament. Apart from traditional functionalization, \( \text{C}–\text{X} \), and \( \text{C}–\text{H} \) functionalization of pyridine have gained numerous attention. Among them, Ir-catalyzed \( \text{C}–\text{H} \) borylation reported by Smith, Maleczka, Ishiyama, Miyaura and Hartwig has become the most preferred method for the \( \text{C}–\text{H} \) activation. As the method requires mild reaction conditions, low catalyst loading and the resulting boronic esters are highly versatile and can easily undergo various transformations.\(^{17-19}\) Beauty of Ir-catalyzed \( \text{C}–\text{H} \) borylation is the sterics dictating the regiochemistry in the molecule, allowing those positions to be easily functionalized that are not accessible by traditional chemistry.

Ir-catalyzed \( \text{C}–\text{H} \) borylation of pyridine has been extensively studied. Steel \textit{et al} first reported the borylation of pyridines including only two examples of \( \text{CF}_3 \)-substituted pyridines that were not isolated and used for coupling reaction.\(^{20}\) Recently, GAC has reported the borylation of 2,6-bis(trifluoromethyl)pyridine.\(^{21}\) Substituted trifluoromethylpyridines were focused in previous studies while there is still a room available for the functionalization of specific positions with unique substitution pattern that are not accessible by traditional methods. We, therefore became interested in the Ir-catalyzed borylation of trifluoromethylated pyridines with different substitution pattern.

\textbf{4.3 Results and discussion}

Previous studies involved the borylation of \( \text{CF}_3 \)-substituted halopyridines via lithiation-boronation method.\(^{16}\) These methodologies counted on the availability of respective heteroaryl halides and harsh reaction conditions. In the present study, we became interested to solve the previous issues by introducing regioselective Ir-catalyzed \( \text{C}–\text{H} \) borylation of \( \text{CF}_3 \)-substituted pyridines. We anticipated that justified choice of substitution pattern can afford site-selective borylation of \( \text{CF}_3 \)-substituted pyridines. Initially 2,3-disubstituted pyridines were evaluated. Combination of different functional groups like fluoro, chloro, bromo, methoxy, amino along with trifluoromethyl were examined. Bulkiness of trifluoromethyl group at 3 position directed borylation specifically
at 5 position and heteroaryl boronic esters were obtained in good yields (4.1a-e). Switching the position of trifluoromethyl group to 2 and bromo group at 3 position also provided complementary result (4.1d). (Scheme 4.1)

Next, we turned our attention towards the borylation of 2,4-disubstituted pyridines (Scheme 4.2). Sterics of trifluoromethyl and chloro group didn’t allow borylation at 3 position (4.2a). Mixture of isomer in 68:32 ratio were observed (NMR analysis). Small size of chloro group as compared to trifluoromethyl group directed borylation at 6 (major isomer) and 5 (minor isomer) position (4.2a). On the other hand traceless borylation resulted borylation only at 5 position (4.2b). Borylation of substrates (4.2c-2e) having either electron donating or weakly electron withdrawing group at 2-position, was not observed (4.2d-e).
2,5-Disubstitution pattern also proved to be another unique combination for the borylation of CF₃ containing pyridines (Scheme 4.3). In this scenario, position 4 and 6 were hindered by the bulkiness of trifluoromethyl group, leaving behind only 3 position for the borylation. Fluoro, chloro and methoxy functional groups were tolerated (4.3a, 4.3b, 4.3c). 20% GC-MS conversion of (4.3d) was observed but after column it got decomposed. Borylation of 4.3e and 4.3f was not observed.
Usefulness of 2,5-disubstitution pattern triggered us to investigate this pattern further. We decided to alter the position of the substituents. To our delight, borylation was observed only at 4 position that was the least hindered position (Scheme 4.4). Functional group tolerance of fluoro, chloro, bromo and methoxy was also observed (\textbf{4.4a}, \textbf{4.4b}, \textbf{4.4c}, and \textbf{4.4d}). Moreover, borylation of \textbf{4.4f} was not observed.
Pyridines with substituents at 2 and 6 positions led to the formation of products 4.5a-4.5c. Trifluoromethyl group at 2 position and iodo/ester/amino group at 6 position directed borylation at 4 position (Scheme 4.5).

\[
\begin{align*}
\text{Scheme 4.4: Borylation of 2,5-disubstituted pyridine} \\
\text{Scheme 4.5: Borylation of 2,6-disubstituted pyridine}
\end{align*}
\]
Synthetic utility of the synthesized boronic esters were demonstrated by employing oxidation and Suzuki coupling reaction (Scheme 4.6 & Scheme 4.7).

Scheme 4.6: Oxidation of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)-pyridine

Scheme 4.7: Suzuki coupling of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(tri-fluoromethyl)pyridine

4.4 Conclusion
In conclusion, Ir-catalyzed C–H borylation of trifluoromethyl substituted pyridines were successfully carried out. Various substitution patterns were evaluated and excellent regioselectivities were obtained. Resulting boronic esters can potentially be very useful synthetic intermediates.

4.5 Experimental Section
4.5.1 General procedure for borylation
In a fume hood, an oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere [Ir(OMe)(COD)]₂ (6.6 mg, 0.01 mmol, 1 mol%), 4,4-di-tert-butyl bipyridine (5.4 mg, 0.02 mmol, 2 mol%), and pinacolborane (HBPin) (218 µL, 192 mg, 1.5 mmol, 1.5 equiv) were added. Arene substrate (1 mmol, 1 equiv) was added under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath. The color of the reaction mixture changed from light yellow to dark brown. The progress of reaction was monitored.
by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed using rotary evaporator. The crude yield was determined. The crude product was purified by column chromatography (silica gel).

**Experimental Details:**

**Compound 4.1a: 2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine**

The general borylation procedure was applied to 2-fluoro-3-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h. GC-MS of the crude reaction mixture showed formation of 7% of minor monoborylated isomer besides the major isomer. Column chromatography (DCM, Rf 0.8) furnished the product as colorless liquid (241 mg, 83 %); 1H NMR (600 MHz, CDCl3) δ 8.37 (s, 1 H), 8.39 (d, J = 9.7 Hz, 1 H), 1.36 (br s, 12 H, 4 CH3 of Bpin); 13C NMR (151 MHz, CDCl3) δ: 161.6 (d, 1J_C–F = 248.8 Hz, C), 157.7 (d, 3J_C–F = 15.1 Hz, CH), 144.5 (apparent quintet, CH), 121.9 (dq, 1J_C–F = 272.2, 3J_C–F = 6.4 Hz CF3), 113.0 (dq, 2J_C–F = 34.9, 2J_C–F = 26.8 Hz C), 84.9 (2 C), 24.8 (4 CH3 of Bpin); FT-IR (neat) ν: 2977, 2925, 1589, 1365, 1303, 1134, 1062, 963, 851, 776, 676 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 291 (M⁺), 191 (40), 172 (41), 146 (26), 126 (32), 114 (21), 85 (50), 69 (85), 57 (100).

**Compound 4.1b: 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin**

The general borylation procedure was applied to 2-chloro-3-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 2 h. GC-MS of the crude reaction mixture showed formation of X% of minor monoborylated isomer besides the major isomer. Column chromatography (DCM, Rf 0.68) furnished the product as pale yellow liquid (161 mg, 52 %); 1H NMR (600 MHz, CDCl3) δ; 8.84 (s, 1 H), 8.35 (s, 1 H), 1.35
(br s, 12 H, 4 CH₃ of Bpin); $^{13}$C NMR (151 MHz, CDCl₃) $\delta$: 157.9 (CH), 151.5 (C), 142.5 (q, $^3$J_{C-F} = 4.5 Hz, CH), 124.8 (q, $^2$J_{C-F} = 33.4 Hz, C), 122.3 (q, $^1$J_{C-F} = 272.8 Hz, C), 85.0 (2 C), 24.8 (4 CH₃ of Bpin); FT-IR (neat) ν: 2981, 1593, 1556, 1363, 1291, 1236, 1131, 1046, 963, 847, 759, 723 cm⁻¹; GC-MS (EI) m/z (% relative intensity): 307 (M⁺, 8), 294 (31), 293 (21), 292 (100), 291 (36), 275 (23), 251 (14), 250 (73), 249 (24), 223 (13), 222 (26), 221 (38), 210 (10), 208 (28), 207 (8), 85 (26).

**Compound 4.1c: 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(tri fluoromethyl)pyridine**

The general borylation procedure was applied to 2-methoxy-3-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h. Column chromatography (DCM, Rf 0.91) furnished the product as pale yellow liquid (296 mg, 98 %); $^1$H NMR (600 MHz, CDCl₃) $\delta$: 8.65 (s, 1 H), 8.19 (s, 1 H), 4.06 (s, 3 H, OCH₃), 1.34 (br s, 12 H, 4 CH₃ of Bpin); $^{13}$C NMR (151 MHz, CDCl₃) $\delta$: 162.7 (C), 157.2 (C, CH), 142.2 (q, $^3$J_{C-F} = 4.4 Hz, CH), 123.1 (q, $^1$J_{C-F} = 271.6 Hz, CF₃), 112.7 (q, $^2$J_{C-F} = 32.8 Hz, C), 84.3 (CH₃), 54.2 (CH₃), 24.8 (4 CH₃ of Bpin); FT-IR (neat) ν: 2986, 2953, 1608, 1573, 1495, 1370, 1311, 1124, 1055, 1007, 946, 848, 788, 672, 606 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 303 (M⁺, 84), 288 (65), 274 (24), 246 (29), 245 (10), 204 (100), 203 (43).

**Compound 4.1d: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(triflu oromethyl)pyridine**

The general borylation procedure was applied to 2,3-bis(trifluoromethyl)pyridine (107.5 mg, 0.5 mmol, 1 equiv) with B₂Pin₂ (95.3 mg, 0.37 mmol, 0.75 equiv) and bipyridine (1.6 mg, 0.02 mmol, 2 mol%) for 16 h. Column chromatography (CH₂Cl₂, Rf 0.3) furnished the product as colorless liquid (139 mg, 82 %); $^1$H NMR (600 MHz, CDCl₃) $\delta$: 9.15 (s, 1 H), 8.53 (s, 1 H), 1.38 (br s, 12 H, 4 CH₃ of Bpin); $^{13}$C NMR (151 MHz, CDCl₃) $\delta$: 156.9 (CH), 146.9 (q, $^2$J_{C-F} = 37.4 Hz, C), 142.3 (q, $^3$J_{C-F} = 5.4 Hz, CH), 124.4 (q, $^2$J_{C-F} = 34.7 Hz, C), 122.3 (q, $^1$J_{C-F} = 270.0 Hz, CF₃), 120.6 (q, $^1$J_{C-F} = 275.1 Hz, CF₃),
85.3 (2 C), 24.8 (4 CH₃ of Bpin); ¹⁹F {¹H} NMR (376 MHz, CDCl₃) δ: -59.7 (q, ²J_F-F = 12.0 Hz, CF₃), -64.7 (q, ²J_F-F = 12.0 Hz, CF₃); ¹¹B NMR (192 MHz, CDCl₃) δ: 30.0; FT-IR (neat) ν: 2984, 2936, 1605, 1372, 1318, 1293, 1257, 1227, 1140, 1043, 963, 848, 796, 688, 652 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 341 (M⁺), 326 (100), 284 (31), 242 (15), 222 (19), 172 (38), 113 (12), 85 (14), 69 (48).

**Compound 4.1e: 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine**

The general borylation procedure was applied to 3-bromo-2-(trifluoromethyl)pyridine (255 mg, 1 mmol, 1 equiv) 2 h. Column chromatography (DCM, Rf 0.34) furnished the product as colorless liquid (309 mg, 88 %); ¹H NMR (600 MHz, CDCl₃) δ; 8.87 (s, 1 H), 8.39 (s, 1 H), 1.35 (br s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (151 MHz, CDCl₃) δ: 152.4 (CH), 148.9 (CH), 147.5 (q, ²J_C-F = 34.1 Hz, C), 121.1 (q, ¹J_C-F = 275.4 Hz, CF₃), 117.8 (C), 85.1 (2 C), 24.8 (4 CH₃ of Bpin); FT-IR (neat) ν: 2978, 2901, 1457, 1359, 1316, 1209, 1167, 1119, 1035, 862, 924, 845, 770 cm⁻¹; GC-MS (EI) m/z (% relative intensity): 351 (M⁺, 11), 338 (59), 337 (25), 336 (62), 335 (22), 294 (51), 293 (17), 268 (29), 267 (91), 266 (38), 264 (100), 254 (24), 254 (24), 253 (11), 252 (31), 232 (11), 85 (26), 57 (16).

**Compound 4.2a: 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine and 4-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine**

The general borylation procedure was applied to 4-chloro-2-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 3 h. Column chromatography (DCM, Rf 0.36) furnished the product as pale yellow liquid (257 mg, 84 %) mixture of 2 isomers in 3:1 ratio by ¹H NMR. The major isomer is highly susceptible to deborylation upon standing. Regioisomeric assignment is based on NMR spectroscopy; ¹H NMR (600
MHz, CDCl$_3$) isomer A $\delta$: 7.99 (d, $J = 1.8$ Hz, 1 H), 7.69 (d, $J = 1.8$ Hz, 1 H), 1.38 (s, 12 H, 4 CH$_3$ of Bpin); Isomer B $\delta$: 8.90 (s, 1 H), 7.65 (s, H), 1.38 (s, 12 H, 4 CH$_3$ of Bpin); $^{13}$C NMR (151 MHz, CDCl$_3$) isomer A $\delta$: 150.1 (q, $^2$J$_{C-F} = 35.0$ Hz, C), 144.9 (C), 133.2 (CH), 122.1 (q, $^3$J$_{C-F} = 3.0$ Hz, CH), 121.0 (q, $^1$J$_{C-F} = 274.8$ Hz, C), 85.3 (2 C), 24.8 (4 CH$_3$ of Bpin); Isomer B $\delta$: 156.9 (CH), 151.3 (C), 150.5 (q, $^2$J$_{C-F} = 35.0$ Hz, C), 121.5 (q, $^3$J$_{C-F} = 2.4$ Hz, C), 120.9 (q, $^1$J$_{C-F} = 274.8$ Hz, C), 85.0 (2 C), 24.8 (4 CH$_3$ of Bpin); (FT-IR (neat) $\nu$: 2983, 2924, 1306, 1256, 1127, 1096, 964, 915, 872, 845, 720 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) (a isomer): 307 (M$^+$, 3), 294 (11), 293 (8), 292 (36), 291 (8), 273 (10), 272 (78), 271 (28), 250 (41), 231 (10), 230 (100), 229 (34), 223 (14), 222 (10), 210 (15), 208 (19); (b isomer): 307 (7), 292 (13), 288 (7), 253 (32), 252 (27), 251 (100), 210 (24), 208 (69), 207 (18), 190 (10), 188 (26), 85 (21), 82 (54).

**Compound 4.2b:** 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridin-4-amine

The general traceless borylation procedure was applied to 2-(trifluoromethyl)pyridin-4-amine (162 mg, 1 mmol, 1 equiv) using 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (4.7 mg, 0.02 mmol, 2 mol %) and 3 equiv of pinacol borane for 2 hr. Column chromatography (DCM, R$_f$ 0.21) furnished the product as yellowish liquid (239 mg, 83 %); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.59 (s, 1 H), 6.83 (s, 1 H), 5.72 (s, 2 H, NH$_2$), 1.34 (br s, 12 H, 4 CH$_3$ of Bpin); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 159.9 (C), 157.1 (CH), 149.7 (q, $^2$J$_{C-F} = 34.0$ Hz, C), 121.5 (q, $^1$J$_{C-F} = 274.2$ Hz, CF$_3$), 105.9 (q, $^3$J$_{C-F} = 3.7$, CH), 85.4 (2 C), 24.8 (4 CH$_3$ of Bpin); GC-MS (EI) m/z (% relative intensity): 288 (18), 287 (6), 273 (11), 272 (4), 269 (3), 244 (3), 232 (9), 231 (100), 230 (36), 215 (10), 214 (3), 202 (8), 201 (3), 189 (16), 188 (13), 187 (5).
Compound 4.3a: 2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine

The general borylation procedure was applied to 2-fluoro-5-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h. Column chromatography (DCM, Rf 0.4) furnished the product as brown liquid (236 mg, 81 %); 1H NMR (600 MHz, CDCl3) δ: 8.58 (d, J = 2.0 Hz, 1 H), 8.40 (dd, J = 7.3 Hz, J = 2.5 Hz, 1 H), 1.37 (br s, 12 H, 4 CH3 of Bpin); 13C NMR (151 MHz, CDCl3) δ: 167.3 (d, 1J_C-F = 250.0 Hz, C), 147.3 (qd, 3J_C-F = 17.3 Hz, 3J_C-F = 3.9 Hz, CH), 144.8 (dq, 3J_C-F = 8.7 Hz, 3J_C-F = 3.0 Hz, CH), 123.7 (qd, 2J_C-F = 33.7 Hz, 4J_C-F = 4.6 Hz, C), 122.2 (q, 1J_C-F = 272.7 Hz, CF3), FT-IR (neat) ν: 2982, 2935, 1608, 1447, 1340, 1298, 1130, 1075, 850, 780, 674, 630 cm–1; GC-MS (EI) m/z (% relative intensity) 291 (M+), 276 (39), 232 (52), 218 (54), 191 (46), 172 (65), 146 (54), 126 (43), 99 (25), 75 (36), 69 (100).

Compound 4.3b: 2-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine

The general borylation procedure was applied to 2-chloro-5-(trifluoromethyl)pyridine (543 mg, 3 mmol, 1 equiv) with [Ir(OMe)(COD)]2 (39.7 mg, 0.02 mmol, 2 mol%), 4,4-di-tert-butyl bipyridine (32.2 mg, 0.04 mmol, 4 mol%), for 24 h. Column chromatography (DCM, Rf 0.2) furnished the product as yellowish liquid (59 mg, 6 %); recovered reactant (438 mg), yield based upon the recovered starting material 99 %; 1H NMR (600 MHz, CDCl3) δ: 8.67 (d, J = 2.4 Hz, 1 H), 8.23 (d, J = 2.4 Hz, 1 H), 1.38 (br s, 12 H, 4 CH3 of Bpin); 13C NMR (151 MHz, CDCl3) δ: 159.3 (C), 148.2 (q, 3J_C-F = 3.6 Hz, CH), 142.7 (q, 3J_C-F = 3.0 Hz, CH), 125.1 (q, 3J_C-F = 33.4 Hz, C), 123.3 (q, 1J_C-F = 272.7 Hz, C), 85. 2 (2 C), 24.8 (4 CH3 of Bpin); FT-IR (neat) ν: 2980, 2930, 1600, 1563, 1336, 1294, 1131, 1087, 1054, 963, 849, 760, cm–1; GC-MS (EI) m/z (% relative intensity) 307 (M+), 292
(33), 272 (30), 230 (100), 208 (41), 172 (51), 145 (43), 126 (38), 99 (43), 85 (59), 69 (78), 57 (83).

**Compound 4.3c: 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(tri fluoromethyl)pyridine**

The general borylation procedure was applied to 2-methoxy-5-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h. $^1$H NMR of isolated product showed the presence of two isomers in 10:1 ratio. Regioisomeric assignment is tentatively assigned based on generally observed sterically controlled selectivity. The chemical shift of the quaternary carbon attached to the CF3 group is deshielded in the minor isomer by the presence of adjacent BPin group and is moved to 121.0 ppm instead of 119.6 ppm which was observed in case of major isomer. Column chromatography (DCM, Rf 0.60) furnished the product as white solid (258 mg, 85 %); m.p: 79-80 °C; $^1$H NMR (600 MHz, CDCl$_3$) major isomer $\delta$: 8.48 (d, $J = 2.4$ Hz, 1 H), 8.16 (d, $J = 2.4$ Hz, 1 H), 4.01 (s, 3 H), 1.35 (br s, 12 H, 4 CH$_3$ of BPin); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 169.1 (C), 147.3 (q, $^3$J$_{C-F} = 4.1$ Hz, CH), 143.4 (q, $^3$J$_{C-F} = 3.1$ Hz, CH), 124.1 (q, $^1$J$_{C-F} = 271.0$ Hz, C), 119.6 (q, $^2$J$_{C-F} = 33.2$ Hz, C), 84.3 (2 C), 54.4 (OCH$_3$), 24.8 (4 CH$_3$ of BPin); FT-IR (neat) v: 2981, 2946, 1608, 1581, 1484, 1329, 1292, 1143, 1110, 1071, 1014, 965, 930, 899, 852, 786, 675, 597 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 303 (M$^+$, 39), 288 (64), 245 (48), 217 (100), 202 (83), 174 (92), 160 (47).

**Compound 4.4a: 5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoro methyl)pyridine**

The general borylation procedure was applied to 5-fluoro-2-(trifluoromethyl)pyridine (165 mg, 1 mmol, 1 equiv) for 2 h. Besides a single monoborylated product, small amount (1-2%) of a diborylated product was also observed by GC-MS at the end of reaction. Column chromatography (DCM, Rf 0.31) furnished the
product as pale yellow liquid (255 mg, 88 %); $^1$H NMR (600 MHz, CDCl$_3$) δ 8.54 (s, 1 H), 8.00 (d, $J = 4.2$ Hz, 1 H), 1.38 (br s, 12 H, 4 CH$_3$ of Bpin);$^{13}$C NMR (151 MHz, CDCl$_3$) δ: 164.0 (d, $^1$J$_{C-F} = 265.9$ Hz, C), 143.6 (qd, $^4$J$_{C-F} = 4.2$ Hz, $^2$J$_{C-F} = 35.3$ C), 138.8 (d, $^2$J$_{C-F} = 28.7$ Hz, CH), 127.4 (dq, $^3$J$_{C-F} = 6.0$ Hz, $^3$J$_{C-F} = 3.0$ Hz, CH), 121.4 (q, $^1$J$_{C-F} = 273.4$ Hz, CF$_3$), 85.3 (2 C), 24.8 (4 CH$_3$ of Bpin); FT-IR (neat) ν: 2983, 2936, 1423, 1352, 1308, 1268, 1212, 1135, 1101, 1072, 963, 913, 888, 848, 701, 674, 633, 602 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 291 (M$^+$), 276 (100), 232 (95), 208 (26), 188 (14), 138 (14), 85 (22), 57 (26).

**Compound 4.4b:** 5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

The general borylation procedure was applied to 5-chloro-2-(trifluoromethyl)pyridine (181 mg, 1 mmol, 1 equiv) for 14 h. Besides a single monoborylated product, small amount of (1%) of diborylated product was also observed by GC-MS at the end of the reaction. Column chromatography (DCM, R$_f$ 0.3) furnished the product as white solid (256 mg, 83 %); m.p: 79-80 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.66 (s, 1 H), 7.92 (s, 1 H), 1.39 (br s, 12 H, 4 CH$_3$ of Bpin);$^{13}$C NMR (151 MHz, CDCl$_3$) δ: 149.4 (CH), 145.4 (q, $^2$J$_{C-F} = 35.3$ Hz, C), 139.8 (C), 126.6 (q, $^3$J$_{C-F} = 2.5$ Hz, CH), 121.5 (q, $^1$J$_{C-F} = 274.5$ Hz, C), 85.4 (2 C), 24.8 (4 CH$_3$ of Bpin); FT-IR (neat) ν: 2984, 1351, 1307, 1257, 1139, 1097, 964, 872, 845, 698, 671 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 307 (M$^+$), 292 (29), 272 (100), 230 (95), 208 (26), 188 (14), 138 (14), 85 (22), 57 (26).

**Compound 4.4c:** 5-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

The general traceless borylation procedure was applied to 5-bromo-2-(trifluoromethyl)pyridine (225 mg, 1 mmol, 1 equiv) for 4 hr. Column chromatography
(DCM, R_f 0.3) furnished the product as white solid (68 mg, 19 %); m.p: 75 °C; ^1^H NMR (600 MHz, CDCl\textsubscript{3}) δ 8.80 (s, 1 H), 7.85 (s, 1 H), 1.39 (br s, 12 H, 4 CH\textsubscript{3} of Bpin); ^1^C NMR (151 MHz, CDCl\textsubscript{3}) δ: 151.9 (CH), 145.8 (q, \(^2\)J\textsubscript{C-F} = 35.1 Hz, C), 129.1 (C), 126.8 (q, \(^3\)J\textsubscript{C-F} = 2.2 Hz, CH), 121.5 (q, \(^1\)J\textsubscript{C-F} = 274.5 Hz, CF\textsubscript{3}), 85.8 (2 C), 24.8 (2 CH\textsubscript{3} of Bpin); FT-IR (neat) ν: 2983, 2923, 1306, 1256, 1167, 1134, 1094, 1026, 964, 914, 867, 843, 710, 696, 672 cm\textsuperscript{-1}; GC-MS (EI) m/z (% relative intensity) 351 (M^+\textsuperscript{+}, 4), 337 (6), 273 (7), 272 (66), 271 (18), 251 (5), 250 (5), 230 (100), 229 (43), 210 (17), 209 (10), 172 (3), 166 (3), 85 (4), 77 (3).

**Compound 4.4d: 5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine**

The general borylation procedure was applied to 5-methoxy-2-(trifluoromethyl)pyridine (177 mg, 1 mmol, 1 equiv) for 2 h. Column chromatography (DCM, R_f 0.5) furnished the product as light yellow solid (246 mg, 81 %); m.p: 73-75 °C; ^1^H NMR (600 MHz, CDCl\textsubscript{3}) δ 8.35 (s, 1 H), 7.88 (s, 1 H), 3.99 (s, 3 H), 1.36 (br s, 12 H, 4 CH\textsubscript{3} of Bpin); ^1^C NMR (151 MHz, CDCl\textsubscript{3}) δ: 160.7 (C), 140.3 (q, \(^2\)J\textsubscript{C-F} = 34.8 Hz, C), 133.4 (CH), 126.8 (q, \(^3\)J\textsubscript{C-F} = 2.5 Hz, CH), 121.9 (q, \(^1\)J\textsubscript{C-F} = 273.0 Hz, CF\textsubscript{3}), 84.7 (CH\textsubscript{3}), 56.7 (2 C), 24.8 (4 CH\textsubscript{3} of Bpin); FT-IR (neat) ν: 2982, 2948, 2849, 1549, 1464, 1335, 1274, 1120, 1018, 963, 903, 882, 848, 698, 674, 614 cm\textsuperscript{-1}; GC-MS (EI) m/z (% relative intensity) 303 (M^+, 45), 288 (61), 284 (12), 246 (28), 230 (23), 202 (100), 174 (20), 160 (17).

**Compound 4.4e: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-3-amine**

The general traceless borylation procedure was applied to 6-(trifluoromethyl)pyridin-3-amine (162 mg, 1 mmol, 1 equiv) using 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (4.7 mg, 0.02 mmol, 2 mol%) and 3 equiv pinacol borane for 0.5 hr. Column chromatography (DCM, R_f 0.35) furnished the product as white solid (265 mg, 92 %);
m.p: 149 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.07 (s, 1 H), 7.77 (s, 1 H), 4.47 (s, 2 H, NH\(_2\)), 1.36 (br s, 12 H, 4 CH\(_3\) of Bpin); \(^1\)C NMR (151 MHz, CDCl\(_3\)) δ: 150.6 (C), 137.2 (CH), 135.6 (distorted q, C), 126.9 (CH), 122.4 (q, \(^1\)J\(_{C-F}\) = 272.2 Hz, CF\(_3\)); FT-IR (neat) ν: 3459, 3330, 3224, 2983, 1619, 1548, 1373, 1300, 1273, 1247, 1163, 1115, 964, 892, 850, 679, 638 cm\(^{-1}\); GC-MS (EI) m/z (% relative intensity) 288 (M\(^+\), 26), 173 (4), 231 (100), 215 (8), 188 (13), 169 (5), 83 (2), 165 (14), 85 (7).

**Compound 4.5a:** 2-Iodo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl) pyridine

The general borylation procedure was applied to 2-iodo-6-(trifluoromethyl)pyridine (273 mg, 1 mmol, 1 equiv) for 1 h. Column chromatography (DCM, R\(_f\) 0.5) furnished the product as pale yellow liquid (98 mg, 25 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.23 (s, 1 H), 7.94 (s, 1 H), 1.35 (br s, 12 H, 4 CH\(_3\) of Bpin); \(^1\)C NMR (151 MHz, CDCl\(_3\)) δ: 148.7 (q, \(^2\)J\(_{C-F}\) = 35.0 Hz, C), 143.1 (CH), 124.3 (distorted q, CH), 120.7 (q, \(^1\)J\(_{C-F}\) = 274.9 Hz, C), 117.8 (C), 85.4 (2 C), 24.8 (4 CH\(_3\) of Bpin); GC-MS (EI) m/z (% relative intensity): 399 (M\(^+\), 6), 384 (6), 313 (6), 300 (4), 273 (12), 272 (100), 271 (31), 230 (12), 190 (23), 186 (17), 166 (7), 146 (4).

**Compound 4.5b:** Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoro- methyl)picolinate

The general borylation procedure was applied to methyl 6-(trifluoromethyl)picolinate (205 mg, 1 mmol, 1 equiv) for 1 h. Column chromatography (DCM, R\(_f\) 0.4) furnished the product as pale yellow liquid (279 mg, 84 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.62 (d, \(J = 2.4\) Hz, 1 H), 8.18 (d, \(J = 2.4\) Hz, 1 H), 4.01 (s, 3 H), 1.38 (s, 12 H, 4 CH\(_3\) of Bpin); \(^1\)C NMR (151 MHz, CDCl\(_3\)) δ: 164.8 (CO), 147.9 (q, \(^2\)J\(_{C-F}\) = 34.7 Hz, C), 147.8 (C), 132.7 (CH), 128.5 (CH), 121.2 (q, \(^1\)J\(_{C-F}\) = 272.7 Hz, CF\(_3\)), 85.4 (2 C), 51.2 (CH\(_3\)), 24.9 (4 CH\(_3\) of Bpin); FT-IR (neat) ν: 2988, 2955, 1752, 1388, 1298, 1253,
1136, 980, 913, 858, 841, 788, 710 cm⁻¹; GC-MS (EI) m/z (% relative intensity): 331 (M⁺, 8), 316 (19), 288 (43), 287 (15), 273 (100), 272 (89), 271 (24), 256 (17), 246 (32), 245 (11), 232 (41), 231 (18), 230 (33), 229 (20), 200 (23), 191 (10), 190 (10).

**Compound 4.5c: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl) pyridin-2-amine**

The general traceless borylation procedure was applied to 6-(trifluoromethyl)pyridin-2-amine (162 mg, 1 mmol, 1 equiv) for 1 h. The ratio of major to minor monoborylated isomer was 96:4 by GC-MS. Column chromatography (DCM, Rf 0.3) furnished the product as pale yellow liquid (257 mg, 89 %); ¹H NMR (600 MHz, CDCl₃) major isomer δ 7.97 (d, J = 7.4 Hz, 1 H), 6.89 (d, J = 7.4 Hz, 1 H), 4.86 (s, 2 H, NH₂), 1.33 (br s, 12 H, 4 CH₃ of Bpin); ¹³C NMR (151 MHz, CDCl₃) δ major isomer: 158.1 (C), 145.7 (q, ²J_C–F = 33.8 Hz, C), 121.7 (q, ¹J_C–F = 273.9 Hz, C), 117.9 (CH), 114.4 (distorted q, CH), 84.7 (2 C), 24.8 (4 CH₃ of Bpin); FT-IR (neat) ν: 3322, 3206, 2981, 1640, 1553, 1436, 1317, 1277, 1191, 1129, 966, 862, 845 cm⁻¹; GC-MS (EI) m/z (% relative intensity): 288 (M⁺, 33), 287 (12), 231 (100), 230 (32), 215 (19), 211 (10), 189 (12), 188 (12), 187 (5), 169 (9), 168 (4).

**4.5.2. Procedure for oxidation**

**Compound 4.6a: 5,6-Bis(trifluoromethyl)pyridin-3-ol**

In an oven dried round bottom flask, 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine (1 mmol) along with 3 mL acetone was added. Stirring produced homogenous solution, an aqueous solution of oxone (615 mg, 1 mmol, 1 equiv. in 3 mL water) was added dropwise over 2-4 min. upon complete addition, the reaction mixture was vigorously stirred for 30 min. After the completion of the reaction, aqueous solution of NaHSO₃ (1 mL) was added. Reaction mixture was extracted with DCM (15 mL × 3). The combined organics were washed with brine. Organic layer was separated and
dried using anhydrous sodium sulphate (2 g) then filtered. Volatiles were removed under reduced pressure using rotary evaporator. Column chromatography (ethyl acetate: hexanes 1:1, Rf 0.4) furnished the product as white solid (211 mg, 91 %); ¹H NMR (600 MHz, CDCl₃) δ: 8.44 (d, J = 2.4 Hz, 1 H), 7.63 (d, J = 2.4 Hz, 1 H), 2.43 (br s, 1 H, OH); ¹³C NMR (151 MHz, CDCl₃) δ: 154.7 (C), 139.4 (CH), 136.9 (distorted q, C), 126.6 (distorted q, C), 122.5 (distorted q, CH), 120.8 (distorted q, 2 CF₃); GC-MS (EI) m/z (% relative intensity): 231 (100), 230 (7), 229 (3), 213 (4), 212 (30), 183 (2), 182 (5), 181 (45), 163 (4), 162 (60), 160 (2), 114 (11), 106 (3), 69 (3).

4.5.3. Procedure for Suzuki Coupling

Compound 4.7a: 2,3-bis(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)pyridine

Oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere Pd(OAc)₂ (2.2 mg, 0.01 mmol, 1 mol%), Sphos (8.2 mg, 0.02 mmol, 2 mol%), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine (1 mmol, 1 equiv) and K₃PO₄ (318 mg, 1.5 mmol, 1.5 equiv.) and 1-bromo-4-(trifluoromethyl)benzene (29 mg, 1.2 mmol, 1.2 equiv.) were added under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath. The color of the reaction mixture changed from light yellow to dark brown. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed under reduced pressure using rotary evaporator. Water (5 mL) was added in the crude reaction mixture and product was extracted using ethyl acetate (10 mL ×3). Organic layer was separated and dried using anhydrous sodium sulphate (2 g) then filtered. Volatiles were removed under reduced pressure using rotary evaporator. Column chromatography (DCM: n-hexanes 1:2, Rf 0.4) furnished the product as colorless.
liquid (296 mg, 82 %); $^1$H NMR (600 MHz, CDCl$_3$) δ: 9.10 (d, $J = 1.8$ Hz, 1 H), 8.35 (d, $J = 1.2$ Hz, 1 H), 7.83 (d, $J = 8.4$ Hz, 1 H), 7.76 (d, $J = 7.8$ Hz, 1 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ: 149.8 (CH), 144.6 (q, $^{2}J_{C-F} = 37.1$ Hz C), 138.3 (C), 138.2 (C), 134.6 (q, $^{3}J_{C-F} = 5.4$ Hz, CH), 131.9 (q, $^{2}J_{C-F} = 32.9$ Hz, C), 127.9 (2 CH), 126.6 (q, $^{3}J_{C-F} = 5.4$ Hz, 2 CH), 125.6 (q, $^{2}J_{C-F} = 35.1$ Hz, C), 123.7 (q, $^{1}J_{C-F} = 272.4$ Hz, CF$_3$), 122.0 (q, $^{1}J_{C-F} = 274.0$ Hz, CF$_3$), 120.6 (q, $^{1}J_{C-F} = 275.1$ Hz, C), 119.7 (C); FT-IR (neat) ν: 2974, 2901, 1317, 1254, 1138, 1109, 1074, 1034, 930, 845, 790, 762, 728, 657 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity): 359 (M*, 100), 340 (35), 309 (59), 291 (23), 290 (96), 290 (96), 271 (15), 270 (52), 269 (49), 243 (30), 240 (11), 221 (26), 220 (68), 202 (14), 201 (27), 200 (20), 194 (11), 193 (12).
4.6 References


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Chapter 5

Synthesis of Aryl/heteroaryl Chiral Boronic Esters
5. Synthesis of Aryl/heteroaryl Chiral Boronic Esters

5.1 Abstract: Chiral boronic esters are considered as indispensable building blocks due to their versatile transformations and immense applications in medicinal and material chemistry. Herein, we describe Pd-catalyzed chiral borylation of aryl/heteroaryl halides, whereby numerous substrates bearing broad range of functional groups are found to be compatible for the developed approach. Aryl/heteroaryl chiral boronic esters are obtained in moderate to excellent yield. Moreover, resulting chiral boronic esters can serve as significant precursors in asymmetric synthesis.

\[
\begin{align*}
\text{Aryl/hetero aryl-X} & \quad 0.75 \text{ equiv (Bpnd)}_2 \\
& \quad 0.5 \text{ mol}\% \text{ Pd(OAc)}_2 \\
& \quad 1 \text{ mol}\% \text{ X-Phos} \\
& \quad 1.5 \text{ equiv Et}_3\text{N} \\
& \quad 1 \text{ mL toluene} \\
& \quad 110 \ ^\circ\text{C}, 24 \text{ H} \\
\rightarrow & \quad \text{Aryl/hetero aryl-Bpnd}
\end{align*}
\]

X = Cl, Br, I

42 examples up to 99% yield

Keywords: Palladium-catalyzed C–X borylation, asymmetric synthesis.

5.2 Introduction

Chiral organoboronates have attracted substantial interest in asymmetric synthesis due to the versatile nature of C–B bond that can be easily transformed into a diverse array of enantioenriched compounds.\textsuperscript{1-4} Not only chiral boronic esters and derivatives have exhibited noteworthy characteristics but enormous chiral compounds derived from them have demonstrated bundle of synthetic significance.\textsuperscript{5,7} Use of \(\alpha\)-amino organoboronic acid derivatives as protease inhibitors and fluorescent sensor have been well documented.\textsuperscript{8,9} Chiral phenolic compounds possessing benzylic stereo centers are found in many commercially available drugs and agrochemicals (Figure 1).\textsuperscript{10,11}
Chiral boronic ester preparation is one of the cutting edge topic in asymmetric synthesis. Bunch of research has been carried out to either generate chiral boronic species or its further transformation. Tang and coworkers put forward a sophisticated method showing the rhodium-catalyzed enantioselective synthesis of tertiary $\alpha$-aminoboronic esters. Shibasaki and coworkers focused on the asymmetric conjugate addition of B$_2$pin$_2$ to unsaturated esters, thioesters and ketones. In the last decade, $S_N2'$ substitution of allylic carbonates by B$_2$pin$_2$ using copper catalyst have been reported. Considerable efforts have been dedicated by Aggarwal group, they presented comprehensive methodologies focusing on enantioselective lithiation followed by addition of boronic ester and subsequent rearrangement to design chiral boronic ester having benzyl, allyl, propargyl and alkyl groups. More recently, Hartwig and coworkers turned the research direction towards the enantioselective borylation of aromatic C–H bonds. They developed an efficient protocol based on iridium-catalyst and chiral quinolyl oxazoline ligands. Beauty of chiral boronic esters’ chemistry is in their manipulation and subsequent stereospecific transformation. Stereocontrolled homologation of these substrates can create enantiopure compounds having applications in pharmaceutical, agrochemical and material chemistry.

In general, two broad methodologies exist in literature for the stereo-controlled homologation of boronic esters.
1. Reagent controlled method utilizes the chirality in the reagent to control the stereochemistry.

2. Substrate controlled method emphasizes on the chirality of diol to control the stereochemistry.

Matteson homologation is based on substrate controlled method. It is proved to be a potent tool for the construction of several stereogenic centers in a complex chiral molecule. Matteson has first time reported the homologation of pinanediol boronic esters that has been remarkably explored for the synthesis of many complex structures.

Inspired from the outstanding work of Matteson and Hartwig on homologation of pinanediol boronic esters and metal catalyzed enantioselective borylation of aromatic substrates respectively, we turned our research gear towards the functionalization of C–H bonds of aromatic compounds using chiral borane. We anticipated that Matteson homologation can be applied on the resulting aryl chiral boronic esters to construct chiral compounds of medicinal and biological importance. A handful of examples are present in literature, focusing on the metal catalyzed synthesis of pinanediol boronic esters. Herein, we describe the Pd-catalyzed borylation of aryl/heteroaryl halides using bis[(+)-pinanediolato]diboron and bis[(-)-pinanediolato]diboron.

5.3 Results and discussion

In the course of our research project aiming at the Pd-catalyzed C–B bond formation using chiral borane source, Miyaura borylation of 5.1a was firstly conducted to screen out the optimal reaction conditions. Initial study was carried out by examining 1-bromo-3-(trifluoromethyl)benzene under given conditions (Table 5.1, entry 1). The desired product 5.3a was obtained in 85 % yield without any side reaction in GC-MS. Encouraged by this preliminary result various alterations in the reaction protocol were carried out to find out the best condition. Finally, optimized reaction conditions were
determined as the combination of 0.5 mol% Pd(OAc)$_2$, 1 mol% X-Phos, 1.5 equiv. Et$_3$N at 110 °C in toluene (entry 8).

![Image of chemical reaction]

**Table 5.1: Optimization of reaction condition for Pd-catalyzed chiral borylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (1 mmol)</td>
<td>X-phos (4 mmol)</td>
<td>80</td>
<td>DME</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (1 mmol)</td>
<td>X-phos (4 mmol)</td>
<td>120</td>
<td>Octane</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (1 mmol)</td>
<td>X-phos (4 mmol)</td>
<td>110</td>
<td>Toluene</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (1 mmol)</td>
<td>X-phos (4 mmol)</td>
<td>80</td>
<td>Et$_3$N</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (1 mmol)</td>
<td>X-phos (2 mmol)</td>
<td>110</td>
<td>Toluene</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (0.5 mmol)</td>
<td>X-phos (1 mmol)</td>
<td>110</td>
<td>Toluene</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$ (1 mmol)</td>
<td>X-phos (2 mmol)</td>
<td>110</td>
<td>Toluene</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$ (0.5 mmol)</td>
<td>X-phos (1 mmol)</td>
<td>110</td>
<td>Toluene</td>
<td>99 ($^c$)</td>
</tr>
</tbody>
</table>

$^a$Reaction condition: 1a (0.2 mmol), 2a (0.15 mmol, 0.75 equiv), catalyst (0.5-1 mol%), ligand 1-4 mol%), base (1.5 equiv.), solvent (1 mL), 15 h. $^b$GC-MS yields. $^c$Isolated yield.

With the optimized conditions in hand, the substrate scope of the reaction was explored. Array of functional groups, electron withdrawing to electron rich, were examined. Trifluoromethly, meta- to bromo group furnished excellent yield (98%, 5.1a, Scheme 5.1). Keto- and sulphone groups were also tolerated in the given reaction conditions (5.1b and 5.1c). It is noteworthy that some reducible functional groups like cyano and aldehyde were also unaffected by the reaction conditions. Disubstituted aniline gave moderate yield in the given protocol (5.1l). Some fused rings were also subjected to
this chiral borylation methodology and to our delight, exhibited good to moderate yields (5.1q-t). However, sterics could be the reason for low yield of 5.1s.

We were pleased to find that our developed protocol of chiral borylation worked well for heterocyclic compounds as well. Heterocyclic compounds bearing different
functional groups were examined and chirality was successfully introduced. Moreover, fused heterocyclic compounds provided the desired product in moderate yield (5.2h–i).

Scheme 5.2: Pd-catalyzed chiral borylation of heteroaryl bromide using (+)(Bpnd)$_2$

\[ \text{Heteroaryl-Br} \xrightarrow{0.75 \text{ equiv } (+)(Bpnd)$_2$} \xrightarrow{0.5 \text{ mol\% Pd(OAc)$_2$}} \xrightarrow{1 \text{ mol\% X-Phos}} \text{Heteroaryl-Bpnd} \]

1.5 equiv Et$_3$N  
1 mL toluene  
110 °C, 24 H  

5.2a 77%$^b$  
5.2b 7%  
5.2c 82%  
5.2d 79%  
5.2e 64%  
5.2f 87%  
5.2g 54%  
5.2h 68%  

5.2i 51%$^b$

$^b$1 mol\% Pd(OAc)$_2$ and 2 mol\% X-phos

To check the versatility of the scheme, this transformation was successfully extended to aryl chloride substrates. Selected substrates were examined and gave good yield (5.3a – e). Nitro, keto, cyano groups were also tolerated in the reaction.
A comparative study was conducted to examine the reactivities of bromo- and chloro-functional groups within a substrate and to our surprise, chloro group remained intact in the reaction while bromo- underwent the desired conversion (5.4a-c). Diborylation was not observed.

Scheme 5.4: Comparative study of bromo and chloro groups’ reactivity in chiral borylation
Substrate scope was further elaborated by introducing aryl iodides instead of aryl bromides and aryl chlorides. Two substrates were subjected under chiral borylation and good yields were observed.

![Scheme 5.5: Pd-catalyzed chiral borylation of aryl iodide using (+)(Bpnd)$_2$](image)

Next we paid our attention towards the use of other isomer, bis(−)-pinanediolato)diboron, abbreviated as (−)(Bpnd)$_2$. Selected examples demonstrated good yield (5.6a-c).

![Scheme 5.6: Pd-catalyzed chiral borylation of aryl bromide using (−)(Bpnd)$_2$](image)

However, few aryl/heteroaryl bromides and ary/heteroaryl chlorides were observed to be unreactive in this methodology.
In conclusion, we have successfully introduced a general method for chiral borylation of aryl halides. Two chiral boron sources, bis((+)-pinanediolato)diboron and bis((−)-pinanediolato)diboron were utilized. Various aryl/heteroaryl chlorides, bromides and iodides were examined in the developed scheme. Broad substrate scope with excellent function group tolerance was observed. Of particular note are the findings of chloro and bromo group comparative reactivities within a substrate. This methodology will likely find broad utility for the synthesis of complex chiral compounds. Further transformations of the strategy are ongoing in our lab.

Scheme 5.7: Unreactive substrates in Pd-catalyzed chiral borylation

5.3 Conclusion
5.4 Experimental Section

General procedure of Miyaura Borylation

In a fume hood, an oven dried Schlenk flask equipped with magnetic stirring bar was filled with nitrogen and evacuated (three cycles). Under nitrogen atmosphere Pd(OAc)$_2$ (1.1 mg, 0.005 mmol, 0.5 mol%), X-phos (4.8 mg, 0.01 mmol, 1 mol%), and bis[(+)-pinanediolato]diboron or bis[(-)-pinanediolato]diboron (Bpnd)$_2$ (268 mg, 0.75 mmol, 0.75 equiv) were added. Aryl halid substrate (1 mmol, 1 equiv) along with 1 mL toluene was added under nitrogen atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 110 °C in an oil bath. The color of the reaction mixture changed from light yellow to brown. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to room temperature and exposed to air. The reaction mixture was taken out by dissolving in dichloromethane and the volatiles were removed using rotary evaporator. The crude yield was determined. The crude product was purified by column chromatography (silica gel).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1a)

The general Miyaura borylation procedure was applied to 1-bromo-3-(trifluoromethyl)benzene (224 mg, 1 mmol, 1 equiv) for 15 hr. Column chromatography (DCM/hexanes 1:1, R$_f$ 0.50) furnished the product as pale yellow liquid (317 mg, 98 %); $^1$H NMR (600 MHz, CDCl$_3$) δ 8.08 (s, 1 H), 7.99 (d, $J$ = 7.8 Hz, 1 H), 7.70 (d, $J$ = 7.8 Hz, 1 H), 7.49 (t, $J$ = 7.8 Hz 1 H), 4.48 (dd, $J$ = 9 Hz, $J$ = 1.8 Hz, 1 H), 2.43 (m, 1 H), 2.26 (m, 1 H), 2.17 (t, $J$ = 5.4 Hz, 1 H), 1.98 (m, 2 H ), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.20 (d, $J$ = 11.4 Hz, 3 H).
Hz, 1 H), 0.90 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 138.1 (CH), 131.4 (q, \(^3J_{C-F} = 3\) Hz, CH), 130.1 (q, \(^2J_{C-F} = 32\) Hz, C), 128.1 (CH), 127.7 (q, \(^3J_{C-F} = 4\) Hz, CH), 124.3 (q, \(^1J_{C-F} = 272\) Hz, C), 86.8 (C), 78.6 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH\(_2\)), 28.7 (CH\(_3\)), 27.1 (CH\(_3\)), 26.5 (CH\(_2\)), 24.0 (CH\(_3\)); FT-IR (neat) \(\nu\): 2927, 2874, 1614, 1371, 1162, 1068, 988, 885, 753 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 324 (M\(^+\), 22), 309 (27), 282 (11), 280 (12), 268 (24), 255 (77), 254 (34), 241 (33), 228 (100), 227(43), 226 (10), 173 (12), 134 (13).

1-(3-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)ethanone (5.1b)

The general Miyaura borylation procedure was applied to 1-(3-bromophenyl)ethanone (198 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, \(R_f\) 0.18) furnished the product as pale yellow liquid (203 mg, 68 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.37 (s, 1 H), 8.06 (d, \(J = 7.8\) Hz, 1 H), 8.00 (d, \(J = 7.8\) Hz, 1 H), 7.48 (t, \(J = 7.8\) Hz, 1 H), 4.46 (m, 1 H), 2.40 (m, 1 H), 2.63 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.17 (t, \(J = 5.4\) Hz, 1 H), 1.98 (m, 2H ), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.20 (d, \(J = 10.8\) Hz, 1 H), 0.90 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 198.4 (C), 139.5 (CH), 136.6 (C), 134.9 (CH), 130.7 (CH), 128.1 (CH), 86.6 (C), 78.5 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH\(_2\)), 28.7 (CH\(_3\)), 27.1 (CH\(_3\)), 26.7 (CH\(_3\)), 26.5 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) \(\nu\): 2918, 2871, 1685, 1601, 1363, 1274, 1250, 1121, 1076, 1021, 936, 887, 805, 744 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 351 (M\(^+\)), 298 (25), 283 (30), 255 (20), 254 (24), 242 (25), 241 (18), 229 (100), 228 (47), 215 (40), 203 (16), 202 (47), 201 (18), 187 (31), 134 (17), 111 (15).
(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3-(methylsulfonyl)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1c)

The general Miyaura borylation procedure was applied to 1-bromo-3-(methylsulfonyl)benzene (234 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, Rf 0.50) furnished the product as pale yellow solid (144 mg, 43%); m.p 90-92 ºC (144 mg, 43 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.38 (s, 1 H), 8.06 (d, \(J = 7.8\) Hz, 1 H), 8.03 (d, \(J = 7.8\) Hz, 1 H), 7.57 (t, \(J = 7.8\) Hz, 1 H), 4.48 (dd, \(J = 8.4\) Hz, \(J = 1.2\) Hz, 1 H), 3.06 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, \(J = 5.4\) Hz, 1 H), 1.97 (m, 2H ), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.16 (d, \(J = 10.8\) Hz, 1 H), 0.89 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 140.1 (C), 139.8 (CH), 133.5 (CH), 129.7 (CH), 128.7 (CH), 86.9 (C), 78.6 (CH), 51.3 (CH), 44.5 (CH\(_3\)), 39.5 (CH), 38.2 (C), 35.4 (CH\(_2\)), 28.6 (CH\(_3\)), 27.1 (CH\(_3\)), 26.5 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) \(\nu\): 2924, 2871, 1599, 1345, 1297, 1238, 1148, 1076, 1021, 958, 886, 836, 767 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 334 (M\(^+\), 61), 319 (47), 292 (32), 291 (51), 278 (43), 265 (100), 251 (34), 238 (48), 237 (53), 134 (42), 97 (63), 83 (69), 82 (32), 67 (30).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3-(methylthio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1d)
The general Miyaura borylation procedure was applied to (3-bromophenyl)(methyl)sulfane (202 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:4, Rf 0.27) furnished the product as pale yellow liquid (198 mg, 66 %); ¹H NMR (600 MHz, CDCl₃) δ 7.72 (s, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 7.23 (t, J = 7.8 Hz, 1 H), 4.45 (dd, J = 8.4 Hz, J = 1.2 Hz, 1 H), 2.50 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.16 (t, J = 5.4 Hz, 1 H), 1.97 (m, 2H ), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.16 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ 137.9 (C), 132.8 (CH), 131.5 (CH), 129.5 (CH), 128.3 (CH), 86.4 (C), 78.4 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.6 (CH₂), 28.7 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.1 (CH₃), 15.9 (CH₃); FT-IR (neat) ν: 2918, 2869, 1592, 1342, 1280, 1235, 1122, 1076, 1026, 988, 888, 789 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 302 (M⁺,100), 233 (37), 232 (52), 206 (37), 205 (44), 151 (32), 150 (69), 149 (42), 135 (17), 109 (18), 91 (17), 83 (37).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(m-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1e)

The general Miyaura borylation procedure was applied to 1-bromo-3-methylbenzene (170 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:3, Rf 0.18) furnished the product as yellowish solid (251 mg, 93 %); m.p 78-80 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.89 (s, 1 H), 7.86 (t, J = 4.2 Hz, 1 H), 7.52 (d, J = 4.8 Hz, 1 H), 7.50 (s, 1 H), 4.48 (d, J = 9 Hz, 1 H), 2.66 (m, 1 H), 2.60 (s, 3 H), 2.47 (m, 1 H), 2.40 (t, J = 5.4 Hz, 1 H), 2.20 (m, 2 H ), 1.72 (s, 3 H), 1.56 (s, 3 H), 1.46 (d, J = 10.8 Hz, 1 H), 1.14 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ 137.2 (C), 135.4 (CH), 132.0 (CH), 131.8 (CH), 127.7 (CH), 86.2 (C), 78.2 (CH), 51.4 (CH), 39.6 (CH), 38.2 (C), 35.6 (CH₂), 28.7 (CH₃), 27.1
4-(3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-
methanobenzo[d][1,3,2]dioxaborol-2-yl)benzonitrile (5.1f)

The general Miyaura borylation procedure was applied to 4-bromobenzonitrile (181 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.16) furnished the product as white solid (317 mg, 98%); m.p 100-101 °C; 1H NMR (600 MHz, CDCl₃) δ 7.82 (d, J = 7.8 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 4.46 (dd, J = 9 Hz, J = 1.2 Hz, 1 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.15 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl₃) δ 135.2 (2 CH), 131.2 (2 CH), 132118.9 (C), 114.4 (C), 86.9 (C), 78.7 (CH), 51.2 (CH), 39.4 (CH), 38.2 (C), 35.4 (CH₂), 28.6 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.0 (CH₃); FT-IR (neat) v: 2925, 2869, 2225, 1398, 1361, 1272, 1237, 1122, 1090, 1018, 922, 880, 832, 737 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 281 (M⁺), 212 (39), 211 (44), 185 (38), 184 (49), 134 (42), 130 (100), 129 (80), 103 (27), 96 (72), 95 (29), 91 (32), 83 (84), 82 (48), 81 (64), 79 (34), 77 (36), 67 (62).
4-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzaldehyde (5.1g)

The general Miyaura borylation procedure was applied to 4-bromobenzaldehyde (184 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, R_f 0.19) furnished the product as white solid (139 mg, 49 %); m.p 60 °C; 1H NMR (600 MHz, CDCl_3) δ 10.05 (s, 1 H), 7.97 (d, J = 7.8 Hz, 2 H), 7.87 (d, J = 7.8 Hz, 2 H), 4.48 (d, J = 9 Hz, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 H), 2.16 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, J = 11.4 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl_3) δ 192.6 (d, J = 1.6 Hz, C), 138.1 (C), 135.3 (2 CH), 128.7 (2 CH), 86.7 (C), 78.6 (CH), 51.3 (CH), 39.5 (CH), 38.2 (C), 35.4 (CH_2), 28.7 (CH_3), 27.1 (CH_3), 26.5 (CH_2), 24.0 (CH_3); FT-IR (neat) ν: 2917, 2870, 2823, 2729, 1700, 1508, 1362, 1273, 1237, 1203, 1121, 1087, 1018, 923, 884, 825, 797 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 284 (M⁺, 24), 269 (29), 242 (17), 241 (22), 240 (25), 228 (34), 227 (25), 215 (100), 201 (37), 188 (50), 133 (17), 111 (20), 83 (54), 82 (18).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(4-((trifluoromethyl)thio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1h)

The general Miyaura borylation procedure was applied to (4-bromophenyl)(trifluoromethyl)sulfane (256 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:3, R_f 0.58) furnished the product as pale yellow solid (242 mg, 68 %);
m.p 54-56 °C; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.85 (d, \(J = 7.8\) Hz, 2 H), 7.65 (d, \(J = 7.8\) Hz, 2 H), 4.47 (dd, \(J = 8.4\) Hz, \(J = 1.2\) Hz, 1 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, \(J = 5.4\) Hz, 1 H), 1.97 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.17 (d, \(J = 10.8\) Hz, 1 H), 0.89 (s, 3 H); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta\) 135.7 (2 CH), 135.2 (2 CH), 129.6 (q, \(\textsuperscript{1}J_{C-F} = 308\) Hz, C), 127.4 (C), 86.7 (C), 78.5 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH\textsubscript{2}), 28.7 (CH\textsubscript{3}), 27.1 (CH\textsubscript{3}), 26.5 (CH\textsubscript{2}), 24.0 (CH\textsubscript{3}); FT-IR (neat) \(\nu\): 2971, 2920, 1598, 1396, 1361, 1237, 1166, 1090, 1018, 883, 831, 755 cm\(^{-1}\); GC-MS (EI) m/z (% relative intensity) 356 (M\textsuperscript{+}), 312 (25), 300 (38), 287 (60), 286 (27), 273 (34), 260 (91), 205 (36), 204 (29), 191 (23), 159 (20), 137 (17), 135 (28), 134 (53), 111 (26), 109 (18), 83 (100), 82 (26).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(p-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1i)

The general Miyaura borylation procedure was applied to 1-bromo-4-methylbenzene (170 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:3, \(R_f\) 0.21) furnished the product as white solid (178 mg, 70 %); m.p 60-61 °C; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.72 (d, \(J = 7.8\) Hz, 2 H), 7.20 (d, \(J = 7.2\) Hz, 2 H), 4.44 (d, \(J = 8.4\) Hz, 1 H), 3.06 (s, 3 H), 2.41 (m, 1 H), 2.38 (CH\textsubscript{3}), 2.22 (m, 1 H), 2.16 (t, \(J = 5.4\) Hz, 1 H), 1.96 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.22 (d, \(J = 10.8\) Hz, 1 H), 0.89 (s, 3 H); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta\) 141.3 (C), 134.8 (2 CH), 128.6 (2 CH), 86.1 (C), 78.2 (CH), 51.5 (CH), 39.5 (CH), 38.2 (C), 35.6 (CH\textsubscript{2}), 28.7 (CH\textsubscript{3}), 27.1 (CH\textsubscript{3}), 26.5 (CH\textsubscript{2}), 24.1 (CH\textsubscript{3}), 21.7 (CH\textsubscript{3}); FT-IR (neat) \(\nu\): 2922, 2866, 1612, 1399, 1360, 1287, 1235, 1122, 1089, 1021, 886, 813, 754 cm\(^{-1}\); GC-MS (EI) m/z (% relative intensity) 270 (M\textsuperscript{+}), 255 (39), 229 (29), 214
The general Miyaura borylation procedure was applied to 1-bromo-3,5-bis(trifluoromethyl)benzene (292 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.32) furnished the product as pale yellow solid (317 mg, 98%); m.p 68-71 °C; 1H NMR (600 MHz, CDCl3) δ 8.25 (s, 2 H), 7.95 (s, 1 H), 4.51 (d, J = 8.4 Hz, 1 H), 2.44 (m, 1 H), 2.27 (m, 1 H), 2.17 (t, J = 5.4 Hz, 1 H), 1.97 (m, 2 H), 1.51 (s, 3 H), 1.33 (s, 3 H), 1.16 (d, J = 10.8 Hz, 1 H), 0.90 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 134.7 (d, 3J_C-F = 2 Hz, 2 CH), 130.9 (q, 2J_C-F = 32 Hz, 2 C), 124.7 (q, 3J_C-F = 4 Hz, CH), 123.5 (q, 1J_C-F = 273 Hz, 2 C), 87.3 (C), 78.9 (CH), 51.3 (CH), 39.5 (CH), 38.2 (C), 35.3 (CH2), 28.6 (CH3), 27.0 (CH3), 26.5 (CH2), 24.0 (CH3); FT-IR (neat) ν 2917, 1618, 1377, 1276, 1168, 1127, 1022, 902, 843, 705 : cm⁻¹; GC-MS (EI) m/z (% relative intensity) 392 (M⁺), 323 (30), 322 (22), 309 (34), 241 (41), 221 (127), 195 (26), 134 (36), 95 (21), 94 (19), 83 (100), 82 (54), 81 (59), 67 (37).

(3aS,4S,6S,7aR)-2-(3,5-bis(trifluoromethyl)phenyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1j)

(3aS,4S,6S,7aR)-2-(3,5-dimethylphenyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborole (5.1k)
The general Miyaura borylation procedure was applied to 1-bromo-3,5-dimethylbenzene (184 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.51) furnished the product as pale yellow liquid (207 mg, 73 %); m.p 80-82 °C; 1H NMR (600 MHz, CDCl₃) δ 7.46 (s, 2 H), 7.12 (s, 1 H), 4.45 (d, J = 8.4 Hz, 1 H), 2.42 (m, 1 H), 2.33 (s, 6 H), 2.25 (m, 1 H), 2.17 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2 H), 1.49 (m, 3 H), 1.32 (s, 3 H), 1.23 (d, J = 10.8 Hz, 1 H), 0.90 (s, 3 H); 13C NMR (151 MHz, CDCl₃) δ 137.2 (2 C), 132.9 (CH), 132.5 (2 CH), 86.2 (C), 78.2 (CH), 51.5 (CH), 39.6 (CH), 38.2 (C), 35.6 (CH₂), 28.7 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.1 (CH₃); FT-IR (neat) ν: 2991, 2965, 2909, 2867, 1385, 1363, 1282, 1227, 1120, 1080, 1030, 938, 857, 740 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 284 (M⁺, 38), 269 (22), 243 (14), 228 (21), 216 (13), 215 (100), 188 (36), 134 (13), 133 (11).

2-methyl-6-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)aniline (5.11)

The general Miyaura borylation procedure was applied to 2-bromo-6-methylaniline (185 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 2:1, Rf 0.60) furnished the product as pale yellow liquid (153 mg, 54 %); m.p 55-58 °C; 1H NMR (600 MHz, CDCl₃) δ 7.55 (d, J = 7.2 Hz, 1 H), 7.15 (d, J = 7.2 Hz, 1 H), 6.66 (t, J = 7.2 Hz, 1 H), 4.46 (m, 1 H, NH₂), 2.43 (m, 1 H), 2.23 (m, 1 H), 2.16 (m, 4 H), 1.97 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.25 (d, J = 10.8 Hz, 1 H), 0.90 (s, 3 H); 13C NMR (151 MHz, CDCl₃) δ 1151.7 (C), 134.8 (CH), 133.7 (CH), 121.5 (C), 117.0 (CH), 86.0 (C), 77.8 (CH), 51.5 (CH), 39.6 (CH), 38.2 (C), 35.7 (CH₂), 28.8 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.1 (CH₃), 17.6 (CH₃); FT-IR (neat) ν: 3495, 3391, 2923, 2865, 1615, 1596, 1431, 1397, 1364,
1305, 1234, 1078, 1030, 986, 838, 751 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 285 (M$^+$, 100), 284 (32), 175 (11), 162 (22), 161 (13), 151 (12), 133 (42), 132 (32).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3,4,5-trifluorophenyl)hexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborole (5.1m)

The general Miyaura borylation procedure was applied to 5-bromo-1,2,3-trifluorobenzene (210 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:3, R$_f$ 0.50) furnished the product as pale yellow liquid (244 mg, 78 %); $^1$H NMR (600 MHz, CDCl$_3$) δ 7.39 (t, $J_{F-H}$ = 7.2 Hz, 2 CH) 4.46 (dd, $J$ = 8.4 Hz, $J$ = 1.2 Hz, 1 H), 2.40 (m, 1 H), 2.24 (m, 1 H), 2.13 (t, $J$ = 5.4 Hz, 1 H), 1.94 (m, 2 H), 1.47 (s, 3 H), 1.32 (s, 3 H), 1.13 (d, $J$ = 10.8 Hz, 1 H), 0.88 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 118.4 (dd, $^2J_{C-F}$ = 15 Hz, $^4J_{C-F}$ = 4 Hz, 2 CH), 87.0 (C), 78.7 (CH), 51.3 (CH), 39.4 (CH), 38.2 (C), 35.3 (CH$_2$), 28.6 (CH$_3$), 27.0 (CH$_3$), 26.4 (CH$_2$), 24.0 (CH$_3$); FT-IR (neat) ν: 2922, 2873, 1612, 1531, 1420, 1388, 1277, 1223, 1122, 1037, 990, 941, 871, 716 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 310 (M$^+$), 295 (30), 267 (30), 241 (94), 240 (53), 239 (26), 236 (31), 227 (68), 214 (84), 213 (58), 159 (26), 134 (44), 119 (27), 111 (37), 83 (100), 82 (50), 81 (37).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3,4,5-trimethoxyphenyl)hexahydro-4,6-methanobenzo [d][1,3,2]dioxaborole (5.1n)
The general Miyaura borylation procedure was applied to 5-bromo-1,2,3-trimethoxybenzene (246 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, Rf 0.37) furnished the product as pale yellow solid (166 mg, 48 %); m.p 142-143 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.04 (s, 2 CH) 4.45 (dd, J = 8.4 Hz, J = 1.2 Hz, 1 H), 3.90 (s, 6 H), 3.87 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2 H ), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.22 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ 152.9 (C), 140.8 (C), 111.3 (2 CH), 86.4 (C), 78.3 (CH), 60.8 (CH₃), 56.1 (2 CH₃), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH₂), 28.7 (CH₃), 27.0 (CH₃), 26.5 (CH₂), 24.0 (CH₃); FT-IR (neat) v: 2988, 2926, 1578, 1450, 1399, 1372, 1233, 1183, 1120, 1077, 1014, 937, 719 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 346 (M⁺, 100), 345 (32), 277 (56), 276 (20), 249 (11), 235 (13), 231 (18), 195 (13), 194 (20), 179 (15), 150 (27), 136 (10).

(3S,4S,6S,7aR)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1o)

The general Miyaura borylation procedure was applied to 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (236 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:4, Rf 0.23) furnished the product as pale yellow solid (204 mg, 61 %); m.p 51 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.56 (d, J = 7.8 Hz, 1 H), 7.48 (s, 1 H), 7.06 (d, J = 7.8 Hz, 1 H), 4.45 (d, J = 9 Hz, 1 H), 2.41 (m, 1 H), 2.24 (m, 1 H), 2.14 (t, J = 5.4 Hz, 1 H), 1.95 (m, 2 H ), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.16 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ 146.0 (C), 143.6 (C), 131.4 (t, ¹JC-F = 255 Hz, C), 131.0 (CH), 115.1 (CH), 109.1 (CH), 86.6 (C), 78.5 (CH), 51.4 (CH), 39.5
The general Miyaura borylation procedure was applied to 2-bromo-4-fluoro-1-methoxybenzene (204 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, R<sub>f</sub> 0.29) furnished the product as pale yellow solid (174 mg, 57 %); m.p 69-70 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.37 (dd, <i>J</i> = 3.0 Hz, <i>J</i> = 9.0 Hz, 1 H), 7.06 (dt, <i>J</i> = 3.0 Hz, <i>J</i> = 8.4 Hz, 1 H), 6.79 (dd, <i>J</i> = 4.2 Hz, <i>J</i> = 9.0 Hz, 1 H), 4.48 (dd, <i>J</i> = 8.4 Hz, 1 H), 3.81 (s, 3 H), 2.40 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, <i>J</i> = 5.4 Hz, 1 H), 1.97 (m, 2 H), 1.48 (s, 3 H), 1.30 (s, 3 H), 1.25 (d, <i>J</i> = 10.8 Hz, 1 H), 0.89 (s, 3 H); <sup>1</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 160.2 (C), 156.9 (C), 122.6 (d, <i>J</i><sub>C-F</sub> = 15 Hz, CH), 118.4 (d, <i>J</i><sub>C-F</sub> = 23 Hz, CH), 111.7 (d, <i>J</i><sub>C-F</sub> = 7 Hz, CH), 85.6 (C), 78.5 (CH), 56.5 (CH<sub>3</sub>), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.6 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>), 26.5 (CH<sub>3</sub>), 24.0 (CH<sub>3</sub>); FT-IR (neat) v: 2987, 2942, 2910, 2840, 1614, 1492, 1419, 1336, 1274, 1252, 1190, 1174, 1121, 1061, 1025, 943, 918, 898, 809, 734 cm<sup>-1</sup>; GC-MS (EI) m/z (% relative intensity) 304 (M+, 100), 303 (32), 289 (35), 235 (49), 234 (69), 221 (14), 220 (15), 208 (48), 152 (21), 151 (16), 134 (21), 109 (17).
The general Miyaura borylation procedure was applied to 1-bromonaphthalene (206 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, Rf 0.61) furnished the product as pale yellow solid (195 mg, 64 %); m.p 63 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.77 (d, \(J = 8.4\) Hz, 1 H), 8.11 (d, \(J = 6.0\) Hz, 1 H), 7.95 (d, \(J = 8.4\) Hz, 1 H), 7.85 (d, \(J = 8.4\) Hz, 1 H), 7.55 (m, 1 H), 7.49 (m, 2 H), 4.57 (d, \(J = 9\) Hz, 1 H), 2.49 (m, 1 H), 2.27 (m, 1 H), 2.09 (m, 1 H), 1.99 (m, 2 H), 1.58 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 1 H), 0.95 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 136.9 (C), 135.7 (CH), 133.3 (C), 131.6 (CH), 128.5 (CH), 128.4 (CH), 126.4(CH), 125.5 (CH), 125.0 (CH), 86.2 (C), 78.2 (CH), 51.6 (CH), 39.6 (CH), 38.2 (C), 35.7 (CH\(_2\)), 28.8 (CH\(_3\)), 27.2 (CH\(_3\)), 26.6 (CH\(_2\)), 24.1(CH\(_3\)); FT-IR (neat) \(\nu\): 3042, 2987, 2924, 1575, 1508, 1462, 1371, 1321, 1279, 1236, 1204, 1135, 1076, 1059, 1030, 888, 841, 802, 776 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 306 (M\(^+\), 100), 305 (35), 291 (13), 237 (37), 236 (18), 210 (36), 209 (18), 155 (15), 154 (40), 153 (21).

(3aS,4S,6S,7aR)-2-(6-methoxynaphthalen-2-yl)-3a,5,5-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole (5.1r)
The general Miyaura borylation procedure was applied to 2-bromo-6-methylnaphthalene (236 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, Rf 0.57) furnished the product as pale yellow solid (232 mg, 69 %); m.p 147 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.31 (s, 1 H); 7.82 (d, \(J = 7.8\) Hz, 1 H), 7.78 (d, \(J = 8.4\) Hz, 1 H), 7.73 (d, \(J = 8.4\) Hz, 1 H), 7.13 (m, 2 H), 4.50 (dd, \(J = 9\) Hz, \(J = 1.8\) Hz, 1 H), 3.93 (s, 3 H), 2.45 (m, 1 H), 2.25 (m, 1 H), 2.20 (t, \(J = 5.4\) Hz, 1 H), 1.99 (m, 2 H), 1.53 (s, 3 H), 1.33 (s, 3 H), 1.28 (d, \(J = 10.8\) Hz, 1 H), 0.92 (s, 3 H); \(^1\)C NMR (151 MHz, CDCl\(_3\)) δ 158.5 (C), 136.4 (C), 136.0 (CH), 131.1 (CH), 130.2 (CH), 128.4, 125.9 (CH), 118.7 (CH), 105.6 (CH), 86.3 (C), 78.3 (CH), 55.3 (CH\(_3\)), 51.5 (CH), 39.6 (CH), 38.2 (C), 35.6 (CH\(_2\)), 28.8 (CH\(_3\)), 27.1 (CH\(_3\)), 26.5 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) ν: 2966, 2919, 2866, 1626, 1484, 1367, 1338, 1276, 1232, 1206, 1120, 1082, 1028, 926, 862, 821, 702 cm\(^{-1}\); GC-MS (EI) m/z (% relative intensity) 336 (M\(^+\), 100), 335 (24), 267 (16), 266 (11), 240 (13), 239 (6), 184 (36), 141 (16), 140 (9).

\((3aS,4S,6S,7aR)-2-(anthracen-9-yl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.1s)\)

The general Miyaura borylation procedure was applied to 9-bromoanthracene (256 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, Rf 0.52) furnished the product as brown solid (55 mg, 15 %); m.p 101-105 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.53 (d, \(J = 8.4\) Hz, 2 H), 8.50 (s, 1 H), 8.00 (d, \(J = 8.4\) Hz, 2 H), 7.50 (t, \(J = 6.6\) Hz, 2 H); 7.45 (t, \(J = 8.4\) Hz, 2 H), 4.74 (d, \(J = 9\) Hz, 1 H), 2.56 (m, 1 H), 2.44 (m, 1 H), 2.33 (t, \(J = 5.4\) Hz, 1 H), 2.16 (m, 2 H), 1.73 (s, 3 H), 1.66 (d, \(J = 10.8\) Hz, 1 H), 1.40 (s, 3 H),
0.99 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$; FT-IR (neat) $\nu$: 2921, 2868, 1719, 1676, 1590, 1513, 1415, 1373, 1280, 1211, 1120, 1055, 1018, 885, 842, 787 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 356 (M$^+$, 94), 355 (28), 205 (21), 204 (100), 203 (27), 202 (18), 176 (9).

(3aS,4S,6S,7aR)-2-(3a1,5a1-dihydropyren-4-yl)-3a,5,5-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole (5.1t)

The general Miyaura borylation procedure was applied to 6-bromo-1,9-dihydropyrene (282 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, $R_f$ 0.42) furnished the product as pale yellow solid (129 mg, 34 %); m.p 136-138 °C; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 9.10 (m, 1 H), 8.58 (m, 1 H), 8.16 (m, 6 H), 8.02 (t, $J$ = 7.8 Hz, 1 H), 4.66 (d, $J$ = 9 Hz, 1 H), 2.55 (m, 1 H), 2.33 (m, 1 H), 2.18 (d, $J$ = 15 Hz, 1 H), 2.03 (m, 2 H ), 1.66 (s, 3 H), 1.44 (m, 1 H), 1.38 (s, 3 H), 0.98 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 136.5 (C), 133.9 (CH), 133.5 (C), 131.2 (C), 130.8 (C), 128.6 (CH), 128.1 (C), 127.8(CH), 127.5 (CH), 125.7 (CH), 125.4 (CH), 125.2 (CH), 124.7 (C), 124.5 (C), 124.2 (CH), 86.4 (C), 78.4 (CH), 51.6 (CH), 39.7 (CH), 38.3 (C), 35.8 (CH$_2$), 28.9 (CH$_3$), 27.2 (CH$_3$), 26.7 (CH$_2$), 24.2 (CH$_3$); FT-IR (neat) $\nu$: 2966, 2908, 2866, 1599, 1510, 1362, 1337, 1301, 1272, 1224, 1203, 1141, 1121, 1083, 1040, 1020, 885, 852, 829, 755 cm$^{-1}$; GC-MS (EI) $m/z$ (% relative intensity) 380 (M$^+$, 72), 379 (25), 284 (12), 229 (23), 228 (100), 227 (39), 226 (24), 202 (11), 201 (15), 200 (10).
Methyl 5-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxabor-2-yl)furan-2-carboxylate (5.2a)

\[ H_5COOC_\text{\textit{B}}O \]

The general Miyaura borylation procedure was applied to methyl 5-bromofuran-2-carboxylate (204 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, \( R_f \) 0.33) furnished the product as pale yellow liquid (234 mg, 77 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.18 (d, \( J = 3.6 \) Hz, 1 H), 7.07 (d, \( J = 3.6 \) Hz, 1 H), 4.45 (dd, \( J = 9 \) Hz, \( J = 1.8 \) Hz, 1 H), 3.89 (s, 3 H), 2.39 (m, 1 H), 2.24 (m, 1 H), 2.14 (t, \( J = 5.4 \) Hz, 1 H), 1.97 (m, 2 H), 1.48 (s, 3 H), 1.30 (s, 3 H), 1.17 (d, \( J = 10.8 \) Hz, 1 H), 0.86 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 159.1 (C), 148.40 (C), 124.01 (CH), 117.94 (CH), 87.3 (C), 78.7 (CH), 51.9 (CH\(_3\)), 51.2 (CH), 39.4 (CH), 38.2 (C), 35.2 (CH\(_2\)), 28.5 (CH\(_3\)), 27.0 (CH\(_3\)), 26.5 (CH\(_2\)), 24.0 (CH\(_3\)); FT-IR (neat) \( \nu \): 3124, 2972, 2927, 2871, 1703, 1579, 1528, 1439, 1329, 1285, 1243, 1209, 1139, 1111, 1077, 1019, 990, 923, 875, 765 cm\(^{-1}\); GC-MS (EI) \( m/z \) (% relative intensity) 304 (M\(^+\), 38), 303 (13), 289 (22), 263 (23), 262 (22), 248 (34), 247 (18), 235 (100), 234 (50), 208 (34), 207 (18), 134 (16), 121 (16), 83 (24).

Methyl 4-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxabor-2-yl)-1H-pyrrole-2-carboxylate (5.2b)

\[ H_5COOC_\text{\textit{B}}O \]

The general Miyaura borylation procedure was applied to methyl 4-bromo-1H-pyrrole-2-carboxylate (203 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, \( R_f \) 0.15) furnished the product as pale yellow liquid (21 mg, 7 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \)
9.39 (s, 1 H, NH), 7.34 (d, J = 1.2 Hz, 1 H), 7.24 (s, 1 H), 4.38 (d, J = 9 Hz, 1 H), 3.81 (s, 3 H), 2.39 (m, 1 H), 2.22 (m, 1 H), 2.12 (t, J = 5.4 Hz, 1 H), 1.94 (m, 2 H), 1.45 (s, 3 H), 1.30 (s, 3 H), 1.20 (d, J = 10.8 Hz, 1 H), 0.88 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 161.6 (C), 130.9 (CH), 123.9 (C), 121.3 (CH), 85.8 (C), 77.8 (CH), 51.5 (CH$_3$), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.6 (CH$_2$), 28.7 (CH$_3$), 27.1 (CH$_3$), 26.5 (CH$_2$), 24.1 (CH$_3$); FT-IR (neat) v: 3436, 3124, 2973, 2928, 2871, 1703, 1579, 1439, 1329, 1285, 1242, 1210, 1139, 1111, 1077, 1020, 989, 923, 875, 801, 765 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 303 (M$^+$, 80), 288 (29), 234 (100), 207 (65), 206 (68), 202 (53), 201 (36), 175 (43), 174 (39), 152 (61), 151 (31), 134 (26), 120 (46), 119 (43).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(thiophen-2-yl)hexahydro-4,6-methanobenzo[d][1,3,2] dioxaborole (5.2c)

The general Miyaura borylation procedure was applied to 2-bromothiophene (162 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, R$_f$ 0.64) furnished the product as light grayish solid (215 mg, 82%); m.p 86 °C; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.66 (d, J = 2 Hz, 1 H), 7.64 (d, J = 4.8 Hz, 1 H), 7.20 (t, J = 4.2 Hz, 1 H), 4.45 (d, J = 9 Hz, 1 H), 2.41 (m, 1 H), 2.25 (m, 1 H), 2.16 (t, J = 5.4 Hz, 1 H), 1.98 (m, 2 H), 1.49 (s, 3 H), 1.31 (s, 3 H), 1.23 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 137.2 (CH), 132.3 (CH), 128.3 (CH), 86.6 (C), 78.4 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH$_2$), 28.6 (CH$_3$), 27.1 (CH$_3$), 26.5 (CH$_2$), 24.1 (CH$_3$); FT-IR (neat) v: 3113, 2995, 1904, 1519, 1427, 1365, 1305, 1279, 1239, 1210, 1122, 1059, 1033, 875, 780 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 262 (M$^+$, 77), 247 (54), 221 (48), 220 (24), 219
4-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carbonitrile (5.2d)

The general Miyaura borylation procedure was applied to 4-bromothiophene-2-carbonitrile (189 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.15) furnished the product as white solid (227 mg, 79 %); m.p 74 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.09 (s, 1 H), 7.90 (s, 1 H), 4.43 (d, $J$ = 8.4 Hz, 1 H), 2.40 (m, 1 H), 2.24 (m, 1 H), 2.12 (t, $J$ = 5.4 Hz, 1 H), 1.94 (m, 2 H ), 1.47 (s, 3 H), 1.31 (s, 3 H), 1.13 (d, $J$ = 10.8 Hz, 1 H), 0.88 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 142.8 (CH), 142.3 (CH), 114.2 (C), 110.2 (C), 86.8 (C), 78.5 (CH), 51.3 (CH), 39.5 (CH), 38.2 (C), 35.3 (CH$_2$), 28.6 (CH$_3$), 27.1 (CH$_3$), 26.5 (CH$_2$), 24.1 (CH$_3$); FT-IR (neat) v: 3100, 2979, 2921, 2869, 2221, 1531, 1436, 1394, 1277, 1020, 982, 809, 748 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 287 (M$^+$, 51), 286 (15), 272 (39), 246 (32), 245 (26), 244 (20), 231 (42), 230 (23), 218 (100), 217 (27), 216 (17), 204 (36), 191 (36), 134 (19), 96 (20), 83 (31), 82 (19).

2-fluoro-6-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)pyridine (5.2e)
The general Miyaura borylation procedure was applied to 2-bromo-6-fluoropyridine (175 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, Rf 0.20) furnished the product as pale yellow solid (176 mg, 64 %); m.p 69-70 ºC; 1H NMR (600 MHz, CDCl3) δ 7.77 (q, J = 8.4 Hz, 1 H), 7.69 (m, 1 H), 6.97 (d, J = 8.4 Hz, 1 H), 4.50 (d, J = 9 Hz, 1 H), 2.40 (m, 1 H), 2.23 (m, 1 H), 2.18 (t, J = 5.4 Hz, 1 H), 1.99 (m, 2 H), 1.50 (s, 3 H), 1.31 (s, 3 H), 1.21 (d, J = 10.8 Hz, 1 H), 0.88 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 163.6 (d, 1J_{C-F} = 240 Hz, C), 140.1 (d, 2J_{C-F} = 8 Hz, CH), 128.4 (d, 3J_{C-F} = 3 Hz, CH), 111.9 (CH), 111.7 (C), 87.3 (C), 78.9 (CH), 51.2 (CH), 39.5 (CH), 38.2 (C), 35.2 (CH2), 28.6 (CH3), 27.1 (CH3), 26.5 (CH2), 24.0 (CH3); FT-IR (neat) ν: 2980, 2915, 2871, 1567, 1472, 1423, 1337, 1283, 1241, 1162, 1134, 1075, 1059, 1031, 988, 914, 871, 821, 783 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 275 (M⁺, 44), 206 (50), 205 (40), 195 (29), 193 (58), 192 (31), 180 (50), 179 (55), 178 (52), 177 (37), 176 (35), 142 (48), 134 (100), 124 (72), 123 (43), 119 (94).

The general Miyaura borylation procedure was applied to 5-bromo-2-(trifluoromethyl)pyridine (225 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, Rf 0.29) furnished the product as pale yellow solid (283 mg, 87 %); m.p 119-121 ºC; 1H NMR (600 MHz, CDCl3) δ 9.05 (s, 1 H), 8.24 (d, J = 7.8 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 1 H), 4.49 (d, J = 7.8 Hz, 1 H), 2.43 (m, 1 H), 2.26 (m, 1 H), 2.16 (t, J = 5.4 Hz, 1 H), 1.97 (m, 2 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.14 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 155.5 (C), 150.0 (q, 2J_{C-F} = 35 Hz, C), 143.9 (CH), 128.9 (C), 128.4 (C), 111.9 (C), 111.7 (C), 84.0 (C), 78.9 (CH), 51.2 (CH), 39.5 (CH), 38.2 (C), 35.2 (CH2), 28.6 (CH3), 27.1 (CH3), 26.4 (CH2), 24.0 (CH3).
121.5 (q, $^1J_{C-F} = 274$ Hz, C), 119.6 (q, $^3J_{C-F} = 2$ Hz, CH), 87.2 (C), 78.8 (CH), 51.2 (CH), 39.5 (CH), 38.2 (C), 35.3 (CH$_2$), 28.6 (CH$_3$), 27.0 (CH$_3$), 26.4 (CH$_2$), 24.0 (CH$_3$); FT-IR (neat) ν: 3048, 2982, 2923, 1599, 1374, 1333, 1237, 1173, 1130, 1105, 1022, 880, 861, 821, 751 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 325 (M$^+$, 39), 310 (36), 284 (32), 283 (26), 270 (26), 269 (50), 268 (31), 256 (100), 242 (58), 241 (23), 230 (89), 229 (77), 228 (45), 192 (49), 191 (26), 174 (24).

2-methyl-3-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)pyridine (5.2g)

![Chemical structure](image)

The general Miyaura borylation procedure was applied to 3-bromo-2-methylpyridine (171 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, $R_f$ 0.46) furnished the product as pale yellow liquid (146 mg, 54 %); $^1$H NMR (600 MHz, CDCl$_3$) δ 8.52 (d, $J = 3.6$ Hz, 1 H), 8.04 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz 1 H), 7.10 (m, 1 H), 4.46 (m, 1 H), 2.75 (s, 3 H), 2.42 (m, 1 H), 2.26 (m, 1 H), 2.15 (t, $J = 5.4$ Hz, 1 H), 1.96 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, $J = 10.8$ Hz, 1 H), 0.89 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 164.0 (C), 150.5 (CH), 144.2 (CH), 120.3 (CH), 86.4 (C), 78.3 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH$_2$), 28.7 (CH$_3$), 27.1 (CH$_3$), 26.5 (CH$_2$), 24.9 (CH$_3$), 24.0 (CH$_3$); FT-IR (neat) ν: 2918, 2871, 1581, 1400, 1336, 1279, 1235, 1123, 1079, 1059, 1021, 936, 886, 844, 783 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 271 (M$^+$, 74), 256 (67), 230 (39), 215 (52), 214 (31), 202 (100), 200 (24), 188 (30), 176 (40), 175 (62), 138 (37), 137 (27), 120 (30), 119 (21).
7-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)-1H-indole (5.2h)

The general Miyaura borylation procedure was applied to 7-bromo-1H-indole (195 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, R_f 0.43) furnished the product as white solid (201 mg, 68 %); m.p 97-100 °C; ^1H NMR (600 MHz, CDCl_3) δ 9.23 (s, NH), 7.79 (d, J = 7.8 Hz, CH), 7.68 (d, J = 7.2 Hz, CH), 7.21 (s, 1 H), 7.16 (t, J = 7.2 Hz, CH), 6.57 (s, 1 H), 4.53 (d, J = 9 Hz, 1 H), 2.48 (m, 1 H), 2.24 (m, 2 H), 2.02 (m, 2 H), 1.55 (s, 3 H), 1.35 (s, 3 H), 1.28 (d, J = 10.8 Hz, 1 H), 0.94 (s, 3 H); ^13C NMR (151 MHz, CDCl_3) δ 141.0 (C), 129.3 (CH), 126.8 (C), 124.2 (CH), 124.1 (CH), 119.3 (CH), 102.0 (CH), 86.3 (C), 78.1 (CH), 51.5 (CH), 39.6 (CH), 38.2 (C), 35.7 (CH_2), 28.9 (CH_3), 27.1 (CH_3), 26.5 (CH_2), 24.1 (CH_3); FT-IR (neat) ν: 3436, 2969, 2917, 2867, 1591, 1428, 1363, 1316, 1274, 1186, 1130, 1055, 1030, 988, 873, 838, 799 cm^{-1}; GC-MS (EI) m/z (% relative intensity) 296 (M^+, 17), 295 (100), 294 (29), 185 (17), 172 (29), 171 (18), 161 (15), 143 (44), 142 (29), 118 (12), 116 (9).

5-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)quinoline (5.2i)

The general Miyaura borylation procedure was applied to 5-bromoquinoline (207 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, R_f 0.27) furnished
the product as brown solid (157 mg, 51%); m.p 100-102 °C; \( ^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 9.10 (d, \( J = 8.4 \) Hz, 1 H), 8.90 (d, \( J = 4.2 \) Hz, 1 H), 8.21 (d, \( J = 8.4 \) Hz, 1 H), 8.15 (d, \( J = 7.2 \) Hz, 1 H), 7.71 (t, \( J = 7.8 \) Hz, 1 H), 7.43 (m, 1 H), 4.53 (d, \( J = 9 \) Hz, 1 H), 2.46 (m, 1 H), 2.24 (m, 1 H), 2.22 (t, \( J = 5.4 \) Hz, 1 H), 1.97 (m, 2 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 1.21 (t, \( J = 5.4 \) Hz, 1 H), 0.91 (s, 3 H); \( ^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 149.9 (CH), 147.9 (C), 137.0 (CH), 136.2 (CH), 132.7 (CH), 132.1 (C), 128.7 (CH), 121.3 (CH), 86.4 (C), 78.2 (CH), 51.4 (CH), 38.2 (C), 35.6 (CH\(_2\)), 28.8 (CH\(_3\)), 27.1 (CH\(_3\)), 26.6 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) \( \nu \): 2917, 2868, 1570, 1499, 1460, 1366, 1278, 1196, 1039, 991, 805, 752 cm\(^{-1}\); GC-MS (EI) \( m/z \) (% relative intensity) 307 (M\(^+\), 77), 306 (28), 251 (29), 238 (91), 237 (29), 230 (25), 224 (28), 212 (27), 211 (100), 156 (45), 155 (48), 83 (26).

(3aS,4S,6S,7aR)-3a,5,5-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.3a)

The general Miyaura borylation procedure was applied to 1-chloro-3-(trifluoromethyl)benzene (180 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, R\(_f\) 0.57) furnished the product as pale yellow liquid (298 mg, 92%); \( ^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 8.07 (s, 1 H), 7.98 (d, \( J = 7.8 \) Hz, 1 H), 7.70 (d, \( J = 7.8 \) Hz, 1 H), 7.49 (t, \( J = 7.8 \) Hz, 1 H), 4.47 (dd, \( J = 9 \) Hz, \( J = 1.8 \) Hz, 1 H), 2.43 (m, 1 H), 2.25 (m, 1 H), 2.16 (t, \( J = 5.4 \) Hz, 1 H), 1.96 (m, 2 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, \( J = 11.4 \) Hz, 1 H), 0.90 (s, 3 H); \( ^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 138.0 (CH), 131.4 (q, \( ^3\)J\(_{C-F} = 4 \) Hz, CH), 130.1 (q, \( ^2\)J\(_{C-F} = 32 \) Hz, C), 128.1 (CH), 127.7 (q, \( ^3\)J\(_{C-F} = 4 \) Hz, CH), 124.3 (q, \( ^1\)J\(_{C-F} = 273 \) Hz, C), 86.7 (C), 78.5 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.4 (CH\(_2\)), 28.7
(CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.1 (CH₃); FT-IR (neat) v: 2981, 2927, 2874, 1614, 1371, 1305, 1163, 1117, 1068, 1021, 988, 936, 885, 908, 753 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 324 (M⁺, 33), 309 (42), 284 (26), 282 (18), 281 (19), 268 (35), 267 (24), 255 (100), 254 (49), 241 (48), 240 (20), 228 (99), 173 (16), 134 (22), 83 (45), 82 (20).

\((3aS,4S,6S,7aR)-3a,5,5\text{-trimethyl-2-(3-nitrophenyl)}\text{hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.3b)}\)

\[
\text{O}_2\text{N}
\]

The general Miyaura borylation procedure was applied to 1-chloro-3-nitrobenzene (157 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.26) furnished the product as pale yellow solid (220 mg, 73 %); m.p 70-73 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.79 (s, 1 H), 7.67 (d, \(J = 7.2 \text{ Hz}\), 1 H), 7.42 (d, \(J = 8.4 \text{ Hz}\), 1 H), 7.31 (t, \(J = 7.2 \text{ Hz}\), 1 H), 4.45 (d, \(J = 9 \text{ Hz}\), 1 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, \(J = 5.4 \text{ Hz}\), 1 H), 1.96 (m, 2 H ), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.18 (d, \(J = 11.4 \text{ Hz}\), 1 H), 0.89 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ ; FT-IR (neat) v: 2949, 2919, 2871, 1616, 1524, 1484, 1365, 1284, 1121, 1074, 1020, 616, 866, 740 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 301 (M⁺) 286 (32), 260 (32), 245 (41), 232 (65), 231 (75), 205 (38), 204 (47), 134 (54), 107 (32), 103 (40), 96 (51), 95 (68), 83 (100), 82 (55), 81 (59), 77 (33), 67 (54).

\((3aS,4S,6S,7aR)-2-(3\text{-methoxyphenyl})\text{-3a,5,5\text{-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.3c)}\)

\[
\text{H}_3\text{CO}
\]
The general Miyaura borylation procedure was applied to 1-chloro-3-methoxybenzene (142 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.46) furnished the product as white solid (211 mg, 74%); m.p 58-60 °C; 1H NMR (600 MHz, CDCl3) δ 7.41 (s, 1 H), 7.34 (s, 1 H), 7.31 (t, J = 8.4 Hz, 1 H), 7.02 (dd, J = 7.8 Hz, J = 2.4 Hz, 1 H), 4.45 (d, J = 9 Hz, 1 H), 3.84 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.16 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.22 (d, J = 11.4 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 159.1 (C), 129.0 (CH), 127.2 (CH), 118.7 (CH), 117.8 (CH), 86.3 (C), 78.3 (CH), 55.2 (CH3), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.6 (CH2), 28.7 (CH3), 27.1 (CH3), 26.5 (CH2), 24.1 (CH3); FT-IR (neat) ν: 2994, 2970, 2915, 2869, 1579, 1456, 1419, 1358, 1314, 1281, 1181, 1104, 1068, 10411026, 985, 933, 875, 800, 773, 753 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 285 (M⁺, 100), 271 (26), 245 (15), 230 (26), 217 (92), 216 (26), 203 (26), 198 (27), 190 (60), 135 (15), 134 (27).

Methyl 4-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzoate (5.3d)

The general Miyaura borylation procedure was applied to methyl 4-chlorobenzoate (170 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.42) furnished the product as white solid (51 mg, 16%); m.p 100-102 °C; 1H NMR (600 MHz, CDCl3) δ 8.02 (d, J = 7.2 Hz, 2 H), 7.87 (d, J = 7.8 Hz, 2 H), 4.47 (d, J = 9 Hz, 1 H), 3.92 (s, 3 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (m, 1 H), 1.97 (m, 2 H), 1.49 (s, 3 H), 1.31 (s, 3 H), 1.20 (d, J = 11.4 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 167.1 (C), 134.7 (2 CH), 132.2 (C), 128.6 (2 CH), 86.6 (C), 78.5 (CH), 52.2 (CH3), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.4 (CH2), 28.7 (CH3), 27.1 (CH3), 26.5 (CH2), 24.1 (CH3); FT-IR (neat)
v:2976, 2923, 1717, 1400, 1368, 1268, 1055, 887, 776 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 314 (M⁺), 245 (49), 244 (58), 218 (66), 163 (45), 134 (49), 131 (88), 130 (36), 119 (30), 105 (73), 103 (56), 96 (34), 91 (33), 83 (100), 82 (41), 81 (40), 79 (30), 77 (36), 67 (80).

2-(3-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)acetonitrile (5.3e)

The general Miyaura borylation procedure was applied to 3-(3-chlorophenyl)acetonitrile (151 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, Rf 0.25) furnished the product as white solid (180 mg, 61%); m.p 85-86 °C; ¹H NMR (600 MHz, CDCl₃) 7.77 (d, J = 7.2 Hz, 1 H), 7.75 (s, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 1 H), 4.45 (d, J = 9 Hz, 1 H), 3.74 (s, 2 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, J = 5.4 Hz, 1 H), 1.95 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.18 (d, J = 11.4 Hz, 1 H), 0.89 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ 134.4 (CH), 134.3 (CH), 130.6 (CH), 129.2 (C), 128.6 (CH), 117.9 (C), 86.5 (C), 78.4 (CH), 52.4 (CH₃), 39.5 (CH), 38.2 (C), 35.5 (CH₂), 28.7 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 24.1 (CH₃), 23.5 (CH₂); FT-IR (neat) v: 2972, 2922, 2869, 2280, 1432, 1376, 1358, 1281, 1236, 1185, 1101, 1077, 1019, 923.857, 789 cm⁻¹; GC-MS (EI) m/z (% relative intensity) 295 (M⁺, 30), 280 (39), 279 (35), 254 (28), 253 (27), 252 (30), 251 (30), 226 (100), 225 (100), 224 (33), 199 (94), 198 (78), 197 (25), 134 (18), 83 (35).
The general Miyaura borylation procedure was applied to 1-bromo-3-chlorobenzene (190 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:1, R_f 0.67) furnished the product as pale yellow liquid (272 mg, 94 %); ^1^H NMR (600 MHz, CDCl$_3$) δ 7.79 (d, J = 1.8 Hz, 1 H), 7.67 (m, 1 H), 7.42 (m, 1 H), 7.31 (t, J = 7.2 Hz, 1 H), 4.46 (dd, J = 8.4 Hz, J = 1.8 Hz, 1 H), 2.40 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, J = 5.4 Hz, 1 H), 1.96 (m, 2H ), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, J = 10.8 Hz, 1 H), 0.89 (s, 3 H); ^13^C NMR (151 MHz, CDCl$_3$) δ 134.6 (CH), 134.1 (C), 132.7 (CH), 131.2 (CH), 129.2 (CH), 86.6 (C), 78.4 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH$_2$), 28.7 (CH$_3$), 27.1 (CH$_3$), 26.5 (CH$_2$), 24.0 (CH$_3$); FT-IR (neat) ν: 2919, 1412, 1344, 1282, 1237, 1122, 1076, 1026, 887, 790 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 290(M$^+$, 59), 275 (47), 223 (25), 222 (32), 221 (88), 220 (54), 207 (35), 206 (28), 196 (36), 195 (35), 194 (100), 192 (26), 139 (27), 134 (30), 83 (39).

The general Miyaura borylation procedure was applied to 1-bromo-3-chloro-5-(trifluoromethyl)benzene (258 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, R_f 0.67) furnished the product as pale yellow liquid (240 mg, 67 %);
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.94 (d, 2 H), 7.68 (s, 1 H), 4.48 (d, $J = 8.4$ Hz, 1 H), 2.42 (m, 1 H), 2.25 (m, 1 H), 2.15 (t, $J = 5.4$ Hz, 1 H), 1.96 (m, 2 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.15 (d, $J = 10.8$ Hz, 1 H), 0.89 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 137.9 (CH), 134.6 (C), 131.8 (q, $^2J_{C-F} = 33$ Hz, C), 129.4 (q, $^3J_{C-F} = 4$ Hz, CH), 127.9 (q, $^3J_{C-F} = 4$ Hz, CH), 123.4 (q, $^1J_{C-F} = 273$ Hz, C), 87.1 (C), 78.7 (CH), 51.3 (CH), 39.5 (CH), 38.2 (C), 35.3 (CH$_2$), 28.6 (CH$_3$), 27.0 (CH$_3$), 26.5 (CH$_2$), 24.0 (CH$_3$); FT-IR (neat) v: 2921, 2873, 1609, 1367, 1292, 1238, 1170, 1128, 1077, 1027, 988, 886, 823, 727 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 358 (M$^+$), 343 (34), 302 (49), 289 (93), 288 (49), 275 (60), 264 (28), 263 (27), 262 (77), 261 (48), 207 (51), 111 (31), 96 (29), 83 (100), 82(49).

**2-chloro-4-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)pyridine (5.4c)**

The general Miyaura borylation procedure was applied to 4-bromo-2-chloropyridine (191 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM, R$_f$ 0.25) furnished the product as pale yellow solid (119 mg, 41 %); m.p 94-96 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.40 (d, $J = 4.8$ Hz, 1 H), 7.68 (s, 1 H), 7.53 (d, $J =4.8$ Hz, 1 H), 4.47 (m, 1 H), 2.41 (m, 1 H), 2.24 (m, 1 H), 2.14 (t, $J = 5.4$ Hz, 1 H), 1.95 (m, 2 H), 1.47 (s, 3 H), 1.31 (s, 3 H), 1.11 (d, $J = 10.8$ Hz, 1 H), 0.87 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 151.5 (C), 149.3 (CH), 129.6 (CH), 127.2 (CH), 87.3 (C), 78.8 (CH), 51.2 (CH), 39.4 (CH), 38.2 (C), 35.2 (CH$_2$), 28.5 (CH$_3$), 27.0 (CH$_3$), 26.4 (CH$_2$), 24.0 (CH$_3$); FT-IR (neat) v: 2983, 2921, 2865, 1525, 1462, 1391, 1339, 1285, 1243, 1133, 1097, 1080, 1031, 986, 883, 857, 740 cm$^{-1}$; GC-MS (EI) m/z (% relative intensity) 291 (M$^+$, 43), 250 (40), 236 (31), 235...
(44), 234 (37), 224 (37), 222 (100), 221 (55), 208 (41), 196 (60), 195 (70), 194 (29), 140 (36), 134 (28), 83 (54), 81 (32).

\((3aS,4S,6S,7aR)-3a,5,5\text{-trimethyl-2-(3-(trifluoromethoxy)phenyl)hexahydro-4,6-methano benzo}[d][1,3,2]\text{dioxaborole (5.5a)}\)

The general Miyaura borylation procedure was applied to 1-iodo-3-(trifluoromethoxy)benzene (288 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, \(R_f\) 0.57) furnished the product as pale yellow liquid (269 mg, 79%); \(^1\)H NMR (600 MHz, CDCl\(_3\)) 7.73 (d, \(J = 7.2\) Hz, 1 H), 7.65 (s, 1 H), 7.40 (t, \(J = 7.2\) Hz, 1 H), 7.30 (d, \(J = 8.4\) Hz, 1 H), 4.46 (d, \(J = 9\) Hz, 1 H), 2.42 (m, 1 H), 2.25 (m, 1 H), 2.15 (t, \(J = 5.4\) Hz, 1 H), 1.96 (m, 2 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, \(J = 11.4\) Hz, 1 H), 0.89 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 149.0 (C), 131.1 (CH), 129.3 (CH), 126.9 (CH), 123.7 (CH), 120.5 (q, \(^{1}J_{C-F} = 257\) Hz, C), 86.7 (C), 78.5 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.4 (CH\(_2\)), 28.7 (CH\(_3\)), 27.1 (CH\(_3\)), 26.5 (CH\(_2\)), 24.0 (CH\(_3\)); FT-IR (neat) v: 2921, 2873, 1612, 1578, 1430, 1361, 1250, 1156, 1076, 952, 884, 785 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 340 (M\(^+\), 26), 325 (26), 299 (18), 296 (12), 284 (30), 283 (17), 271 (77), 270 (26), 257 (33), 244 (100), 243 (28), 83 (32).

\((3\text{-}(\text{trifluoromethyl}-4-((3aS,4S,6S,7aR)-3a,5,5\text{-trimethylhexahydro-4,6-methanobenzo}[d] [1,3,2]\text{dioxaborol-2-yl})benzonitrile (5.5b)}\)
The general Miyaura borylation procedure was applied to 4-iodo-3-(trifluoromethyl)benzonitrile (297 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.39) furnished the product as pale yellow solid (108 mg, 31 %); m.p 100-104 °C; 1H NMR (600 MHz, CDCl3) δ 7.94 (s, 1 H), 7.90 (d, J = 7.8 Hz, 1 H), 7.80 (d, J = 7.2 Hz, 1 H), 4.52 (d, J = 9 Hz, 1 H), 2.43 (m, 1 H), 2.29 (m, 1 H), 2.15 (t, J = 5.4 Hz, 1 H), 1.98 (m, 2 H ), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.20 (d, J = 11.4 Hz, 1 H), 0.89 (s, 3 H); 13C NMR (151 MHz, CDCl3) δ 135.9 (CH), 135.3 (q, 2J_C-F = 33 Hz, C), 133.9 (CH), 128.7 (q, 3J_C-F = 6 Hz, CH), 123.2 (q, 1J_C-F = 274 Hz, C), 117.5 (C), 114.2 (C), 87.4 (C), 79.2 (CH), 51.2 (CH), 39.4 (CH), 38.3 (C), 35.2 (CH2), 28.4 (CH3), 27.0 (CH3), 26.4 (CH2), 24.0 (CH3); FT-IR (neat) v: 2926, 2872, 2252, 1611, 1399, 1271, 1121, 1089, 987, 880, 737 cm\(^{-1}\); GC-MS (EI) m/z (% relative intensity) 349 (M\(^+\)), 198 (52), 185 (61), 178 (71), 137 (66), 135 (33), 134 (100), 119 (54), 109 (59), 83 (77), 82 (27), 81 (59), 67 (48).

Borylation using (-)-(Bpnd)\(^2\)

\(3aR,4R,6R,7aS\)-3a,5,5-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (5.6a)

The general Miyaura borylation procedure was applied to 1-bromo-3-(trifluoromethyl)benzene (224 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.34) furnished the product as colorless liquid (220 mg, 68 %); 1H NMR (600 MHz, CDCl3) δ 8.08 (s, 1 H), 7.98 (d, J = 7.2 Hz, 1 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 1 H), 4.47 (d, J = 9 Hz, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 H), 2.17 (t, J = 5.4 Hz, 1 H), 1.97 (m, 2 H ), 1.50 (s, 3 H), 1.32 (s, 3 H), 1.19 (d, J = 11.4 Hz, 1 H),
\[ \text{Cl} \quad \text{O} \quad \text{H} \]

The general Miyaura borylation procedure was applied to 1-bromo-3-chlorobenzene (190 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.32) furnished the product as pale yellow liquid (234 mg, 82 %); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.79 (s, 1 H), 7.67 (d, \(J = 7.2\) Hz, 1 H), 7.42 (d, \(J = 7.8\) Hz, 1 H), 7.32 (t, \(J = 7.8\) Hz, 1 H), 4.45 (d, \(J = 9\) Hz, 1 H), 2.42 (m, 1 H), 2.24 (m, 1 H), 2.15 (t, \(J = 5.4\) Hz, 1 H), 1.96 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H), 1.18 (d, \(J = 11.4\) Hz, 1 H), 0.89 (s, 3 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 134.6 (CH), 134.1 (C), 132.7 (CH), 131.2 (CH), 129.2 (CH), 86.6 (C), 78.5 (CH), 51.4 (CH), 39.5 (CH), 38.2 (C), 35.5 (CH\(_2\)), 28.7 (CH\(_3\)), 27.1 (CH\(_3\)), 26.5 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) \(\nu\) 2970, 2918, 2870, 1597, 1497, 1382, 1209, 755 \(\text{cm}^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 290 (M\(^+\)), 275 (24), 248 (22), 234 (25), 223 (31), 221 (55), 220 (63), 207 (40), 194 (63), 193 (35), 134 (40), 83 (100), 82 (27).
(3aR,4R,6R,7aS)-3a,5,5-trimethyl-2-(naphthalen-1-yl)hexahydro-4,6-methanobenzo [d][1,3,2]dioxaborole (5.6c)

The general Miyaura borylation procedure was applied to 1-bromonaphthalene (206 mg, 1 mmol, 1 equiv) for 24 hr. Column chromatography (DCM/hexanes 1:2, Rf 0.29) furnished the product as light brown solid (217 mg, 71 %); m.p 58-60 °C; \(^1^H\) NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.77 (d, \(J = 8.4\) Hz, 1 H), 8.12 (d, \(J = 6.6\) Hz, 1 H), 7.95 (d, \(J = 7.8\) Hz, 1 H), 7.85 (d, \(J = 8.4\) Hz, 1 H), 7.55 (t, \(J = 7.8\) Hz, 1 H), 7.49 (m, 2 H), 4.46 (d, \(J = 9\) Hz, 1 H), 2.49 (m, 1 H), 2.27 (m, 1 H), 2.26 (t, \(J = 5.4\) Hz, 1 H), 2.04 (m, 2 H ), 1.58 (s, 3 H), 1.33 (m, 4 H), 0.94 (s, 3 H); \(^1^C\) NMR (151 MHz, CDCl\(_3\)) \(\delta\) 136.9 (C), 135.7 (CH), 133.3 (C), 131.6 (CH), 128.5 (CH), 128.4 (CH), 126.4 (CH), 125.5 (CH), 125.0 (CH), 86.2 (C), 78.2 (CH), 51.6 (CH), 39.6 (CH), 38.2 (C), 35.7 (CH\(_2\)), 28.9 (CH\(_3\)), 27.2 (CH\(_3\)), 26.6 (CH\(_2\)), 24.1 (CH\(_3\)); FT-IR (neat) v: 3041, 2986, 2924, 2865, 1575, 1461, 1312, 1279, 1255, 1135, 1031, 994, 841, 680 cm\(^{-1}\); GC-MS (EI) \(m/z\) (% relative intensity) 306 (M\(^+\), 26), 305 (41), 250 (19), 237 (84), 236 (30), 223 (44), 210 (100), 208 (21), 154 (62), 152 (33), 134 (48), 83 (67).
5.5 References

(1) Sandford, C.; Aggarwal, V. K. *Chemical Communications* **2017**, *53*, 5481.


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6. Conclusion and Outlook

Step economical methodologies were introduced to gain facile access for novel aromatic substrates. The second chapter of this dissertation focuses on the synthesis of hydroxybenzoates. We have reported an efficient protocol employing iridium-catalyzed C–H borylation/oxidation of commercially available arene substrates. This route provided halogen decorated para-/meta-hydroxybenzoates, as synthesis of such compounds has proven to be laborious by traditional approaches. Third chapter targets the synthesis of boscalid analogs. We have successfully synthesized boscalid analogs from readily available hydrocarbon feedstock without pre-functionalization. Sequential Ir-catalyzed C–H borylation of arenes and Suzuki coupling provided biphenyl amines which on amidation produced boscalid analogs in good yield. Synthesized compounds were further evaluated by molecular docking to gain insight into the binding pocket of protein. The in-vitro studies of the analogs were carried out against *Fusarium moniliforme* and few of the compounds provided superior inhibition on PDA plates. Ir-catalyzed C-H borylation of CF₃ substituted pyridines is reported in the fourth chapter. The methodology focuses on the various substitution patterns in the molecule. Based on the steric evaluation, selective positions of CF₃ substituted pyridines were functionalized. Numerous functional groups like halo, ester, methoxy, amino were found compatible with this methodology. In the fifth chapter, we disclosed Pd-catalyzed chiral borylation of aryl halides. We evaluated numerous substrates bearing broad range of functional groups. Aryl/hetero aryl chiral boronic esters were obtained in moderate to excellent yield. Resulting chiral boronic esters can serve as significant precursors in asymmetric synthesis.

In future, analogs of various drugs, insecticides, pesticides and fungicides consisting of biaryl ring can be synthesized using iridium-catalyzed borylation and Suzuki coupling. Moreover, effect of different ligands (chiral and achiral) can be examined to increase the selectivity of the reaction. New boron resources with their applications can also be introduced.
Spectroscopic Data
**1H NMR & 13C NMR Spectra**

Compound 2.1a: 1H NMR spectrum of methyl 2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1a: 13C NMR spectrum of methyl 2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.1b: $^1$H NMR spectrum of methyl 2-bromo-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1b: $^{13}$C NMR spectrum of methyl 2-bromo-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.1c: $^1$H NMR spectrum of methyl 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1c: $^{13}$C NMR spectrum of methyl 2-chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.1d: $^1$H NMR spectrum of methyl 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1d: $^{13}$C NMR spectrum of methyl 2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.1e: $^1$H NMR spectrum of methyl 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1e: $^{13}$C NMR spectrum of methyl 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.1f: $^1$H NMR spectrum of methyl 2-bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.1f: $^{13}$C NMR spectrum of methyl 2-bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.3a: $^1$H NMR spectrum of methyl 2-bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.3a: $^{13}$C NMR spectrum of methyl 2-bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.3b: $^1$H NMR spectrum of methyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.3b: $^{13}$C NMR spectrum of methyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.3c: $^1$H NMR spectrum of methyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate

Compound 2.3c: $^{13}$C NMR spectrum of methyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate
Compound 2.3d: $^1$H NMR spectrum of ethyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Compound 2.3d: $^{13}$C NMR spectrum of ethyl 2,3-dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Compound 2.3e: $^1$H NMR spectrum of ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate

Compound 2.3e: $^{13}$C NMR spectrum of ethyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate
Compound 2.3f: 1H NMR spectrum of propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate:

Compound 2.3f: 13C NMR spectrum of propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate:
Compound 2.2a: $^1$H NMR spectrum of methyl 2-bromo-6-methoxy-4-hydroxybenzoate

Compound 2.2a: $^{13}$C NMR spectrum of methyl 2-bromo-6-methoxy-4-hydroxybenzoate
Compound 2.2b: $^1$H NMR spectrum of methyl 2-bromo-6-chloro-4-hydroxybenzoate

Compound 2.2b: $^{13}$C NMR spectrum of methyl 2-bromo-6-chloro-4-hydroxybenzoate
Compound 2.2c: $^1$H NMR spectrum of methyl 2-chloro-4-hydroxy-6-methylbenzoate

Compound 2.2c: $^{13}$C NMR spectrum of methyl 2-chloro-4-hydroxy-6-methylbenzoate
Compound 2.2d: $^1$H NMR spectrum of methyl 2,6-dichloro-4-hydroxybenzoate

Compound 2.2d: $^{13}$C NMR spectrum of methyl 2,6-dichloro-4-hydroxybenzoate
Compound 2.2e: $^1$H NMR spectrum of methyl 2,6-dimethyl-4-hydroxybenzoate

Compound 2.2e: $^{13}$C NMR spectrum of methyl 2,6-dimethyl-4-hydroxybenzoate
Compound 2.2f: $^1$H NMR spectrum of methyl 2-bromo-5-fluoro-4-hydroxybenzoate

Compound 2.2f: $^{13}$C NMR spectrum of methyl 2-bromo-5-fluoro-4-hydroxybenzoate
Compound 2.4a: $^1$H NMR spectrum of methyl 2-bromo-5-hydroxy-3-methylbenzoate

Compound 2.4a: $^{13}$C NMR spectrum of methyl 2-bromo-5-hydroxy-3-methylbenzoate
Compound 2.4b: $^1$H NMR spectrum of methyl 2,3-dichloro-5-hydroxybenzoate

Compound 2.4b: $^{13}$C NMR spectrum of methyl 2,3-dichloro-5-hydroxybenzoate
Compound 2.4c: $^1$H NMR spectrum of methyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate

Compound 2.4c: $^{13}$C NMR spectrum of methyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate
Compound 2.4d: $^1$H NMR spectrum of ethyl 2,3-dichloro-5-hydroxybenzoate

Compound 2.4d: $^{13}$C NMR spectrum of ethyl 2,3-dichloro-5-hydroxybenzoate
Compound 2.4e: $^1$H NMR spectrum of ethyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate

Compound 2.4e: $^{13}$C NMR spectrum of ethyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate
Compound 2.4f: $^1$H NMR spectrum of propyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate

Compound 2.4f: $^{13}$C NMR spectrum of propyl 2-chloro-3-(trifloromethyl)-5-hydroxybenzoate
Compound 3.2a: $^1$H NMR spectrum of 3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine

Compound 3.2a: $^{13}$C NMR spectrum of 3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine
Compound 3.2b: $^1$H NMR spectrum of 2'-Amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile

Compound 3.2b: $^{13}$C NMR spectrum of 2'-Amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile
Compound 3.2c: $^1$H NMR spectrum of 3'-Chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine

Compound 3.2c: $^{13}$C NMR spectrum of 3'-Chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine
Compound 3.2d: $^1$H NMR spectrum of Methyl 2'-amino-5-methoxy-[1,1'-biphenyl]-3-carboxylate

Compound 3.2d: $^{13}$C NMR spectrum of Methyl 2'-amino-5-methoxy-[1,1'-biphenyl]-3-carboxylate
Compound 3.2e: ¹H NMR spectrum of 2'-Amino-5-(trifluoromethoxy)-[1,1'-biphenyl]-3-carbonitrile

Compound 3.2e: ¹³C NMR spectrum of 2'-Amino-5-(trifluoromethoxy)-[1,1'-biphenyl]-3-carbonitrile
Compound 3.2f: $^1$H NMR spectrum of 2'-Amino-5-chloro-[1,1'-biphenyl]-3-carbonitrile

Compound 3.2f: $^{13}$C NMR spectrum of 2'-Amino-5-chloro-[1,1'-biphenyl]-3-carbonitrile
Compound 3.2g: $^1$H NMR spectrum of 3'-Methoxy-5'-(trifluoromethoxy)-[1,1'-biphenyl]-2-amine

Compound 3.2g: $^{13}$C NMR spectrum of 3'-Methoxy-5'-(trifluoromethoxy)-[1,1'-biphenyl]-2-amine
Compound 3.2h: $^1$H NMR spectrum of 3'-Chloro-5'-methoxy-[1,1'-biphenyl]-2-amine

Compound 3.2h: $^{13}$C NMR spectrum of 3'-Chloro-5'-methoxy-[1,1'-biphenyl]-2-amine
Compound 3.2i: $^1$H NMR spectrum of 3',5'-Bis(1,1,2,2-tetrafluoroethoxy)-[1,1'-biphenyl]-2-amine

Compound 3.2i: $^{13}$C NMR spectrum of 3',5'-Bis(1,1,2,2-tetrafluoroethoxy)-[1,1'-biphenyl]-2-amine
Compound 3.2j: $^1$H NMR spectrum of Ethyl 2'-amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate

Compound 3.2j: $^{13}$C NMR spectrum of Ethyl 2'-amino-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate
Compound 3.2k: $^1$H NMR spectrum of 2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)aniline

Compound 3.2k: $^{13}$C NMR spectrum of 2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)aniline
Compound 3.2l: $^1$H NMR spectrum of 5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine

Compound 3.2l: $^{13}$C NMR spectrum of 5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-amine
Compound 3.3a: $^1$H NMR spectrum of $N$-(3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2-chloronicotinamide

Compound 3.3a: $^{13}$C NMR spectrum of $N$-(3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2-chloronicotinamide
Compound 3.3b: $^1$H NMR spectrum of: 2-Chloro-$N$-(3'-cyano-5'-((trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide

Compound 3.3b: $^{13}$C NMR spectrum of: 2-Chloro-$N$-(3'-cyano-5'-((trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide
Compound 3.3c: $^1$H NMR spectrum of 2-Chloro-$N$-(3'-chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide

Compound 3.3c: $^{13}$C NMR spectrum of 2-Chloro-$N$-(3'-chloro-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide
Compound 3.3d: $^1$H NMR spectrum of Methyl 2'- (2-chloronicotinamido)-5-methoxy-[1,1'-biphenyl]-3-carboxylate

Compound 3.3d: $^{13}$C NMR spectrum of Methyl 2'- (2-chloronicotinamido)-5-methoxy-[1,1'-biphenyl]-3-carboxylate
Compound 3.3e: $^1$H NMR spectrum of 2-Chloro-$N$-(3′-cyano-5′-(trifluoromethoxy)-[1,1′-biphenyl]-2-yl)nicotinamide

Compound 3.3e: $^{13}$C NMR spectrum of 2-Chloro-$N$-(3′-cyano-5′-(trifluoromethoxy)-[1,1′-biphenyl]-2-yl)nicotinamide
Compound 3.3f: $^1$H NMR spectrum of 2-Chloro-N-(3'-chloro-5'-cyano-[1,1'-biphenyl]-2-yl)nicotinamide

Compound 3.3f: $^{13}$C NMR spectrum of 2-Chloro-N-(3'-chloro-5'-cyano-[1,1'-biphenyl]-2-yl)nicotinamide
Compound 3.3g: $^1$H NMR spectrum of 2-Chloro-$N$-(3'-methoxy-5'-(trifluoromethoxy)-\[1,1'$\text{-biphenyl}]$2$-yl$nicotinamide

Compound 3.3g: $^{13}$C NMR spectrum of 2-Chloro-$N$-(3'-methoxy-5'-(trifluoromethoxy)-\[1,1'$\text{-biphenyl}]$2$-yl$nicotinamide
Compound 3.3h: $^1$H NMR spectrum of 2-Chloro-$N$-(3'-chloro-5'-methoxy-[1,1'-biphenyl]-2-yl)nicotinamide

Compound 3.3h: $^{13}$C NMR spectrum of 2-Chloro-$N$-(3'-chloro-5'-methoxy-[1,1'-biphenyl]-2-yl)nicotinamide
Compound 3.3i: $^1$H NMR spectrum of $N$-(3',5'-Bis(1,1,2,2-tetrafluoroethoxy)-[1,1'-biphenyl]-2-yl)-2-chloronicotinamide

Compound 3.3i: $^{13}$C NMR spectrum of $N$-(3',5'-Bis(1,1,2,2-tetrafluoroethoxy)-[1,1'-biphenyl]-2-yl)-2-chloronicotinamide
Compound 3.3j: $^1$H NMR spectrum of Ethyl 2'-(2-chloronicotinamido)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate

Compound 3.3j: $^{13}$C NMR spectrum of Ethyl 2'-(2-chloronicotinamido)-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylate
Compound 3.3k: $^1$H NMR spectrum of $N$-(2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)phenyl)-2-chloronicotinamide

Compound 3.3k: $^{13}$C NMR spectrum of $N$-(2-(2,6-Bis(trifluoromethyl)pyridin-4-yl)phenyl)-2-chloronicotinamide
Compound 3.3l: $^1$H NMR spectrum of 2-chloro-N-(5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide

Compound 3.3l: $^{13}$C NMR spectrum of 2-chloro-N-(5-(trifluoromethoxy)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)nicotinamide
Compound 4.1a: $^1$H NMR spectrum of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine

Compound 4.1a: $^{13}$C NMR spectrum of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine
Compound 4.1b: $^1$H NMR spectrum of 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine

Compound 4.1b: $^{13}$C NMR spectrum of 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine
Compound 4.1c: $^1$H NMR spectrum of 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine

Compound 4.1c: $^{13}$C NMR spectrum of 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine
Compound 4.1d: $^1$H NMR spectrum of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine

Compound 4.1d: $^{13}$C NMR spectrum of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-bis(trifluoromethyl)pyridine
Compound 4.1e: $^1$H NMR spectrum of 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

Compound 4.1e: $^{13}$C NMR spectrum of 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine
Compound 4.2a: $^1$H NMR spectrum of 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoro-methyl)pyridine

Compound 4.2a: $^{13}$C NMR spectrum of 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoro-methyl)pyridine
Compound 4.2b: $^1$H NMR spectrum of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoro methyl)pyridin-4-amine

Compound 4.2b: $^{13}$C NMR spectrum of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoro methyl)pyridin-4-amine
Compound 4.3a: $^1$H NMR spectrum of 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine

Compound 4.3a: $^{13}$C NMR spectrum of 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine
Compound 4.3b: $^1$H NMR spectrum of 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine

Compound 4.3b: $^{13}$C NMR spectrum of 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridine
Compound 4.3c: $^1$H NMR spectrum of 2-methoxy-3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trfluoromethyl)pyridine

Compound 4.3c: $^{13}$C NMR spectrum of 2-methoxy-3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trfluoromethyl)pyridine
Compound 4.4a: $^1$H NMR spectrum of 5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

Compound 4.4a: $^{13}$C NMR spectrum of 5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine
Compound 4.4b: $^1$H NMR spectrum of 5-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

Compound 4.4b: $^{13}$C NMR spectrum of 5-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine
Compound 4.4c: $^1$H NMR spectrum of 5-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

Compound 4.4c: $^{13}$C NMR spectrum of 5-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine
Compound 4.4d: $^1$H NMR spectrum of 5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine

Compound 4.4d: $^{13}$C NMR spectrum of 5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine
Compound 4.4f: $^1$H NMR spectrum of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-3-amine

Compound 4.4f: $^{13}$C NMR spectrum of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-3-amine
Compound 4.5a: $^1$H NMR spectrum of 2-iodo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine

Compound 4.5a: $^{13}$C NMR spectrum of 2-iodo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine
Compound 4.5b: $^1$H NMR spectrum of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)picolinate

Compound 4.5b: $^{13}$C NMR spectrum of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)picolinate
Compound 4.5c: $^1$H NMR spectrum of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-2-amine

Compound 4.5c: $^{13}$C NMR spectrum of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-2-amine
Compound 4.6a: $^1$H NMR spectrum of 5,6-Bis(trifluoromethyl)pyridin-3-ol

Compound 4.6a: $^{13}$C NMR spectrum of 5,6-Bis(trifluoromethyl)pyridin-3-ol
Compound 4.7a: $^1$H NMR spectrum of 2,3-bis(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)pyridine

Compound 4.7a: $^{13}$C NMR spectrum of 2,3-bis(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)pyridine
Compound 5.1a: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1a: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1b: $^1$H NMR spectrum of 1-(3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)ethanone

Compound 5.1b: $^{13}$C NMR spectrum of 1-(3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)ethanone
Compound 5.1c: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(methylsulfonyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1c: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(methylsulfonyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1d: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(methylthio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1d: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(methylthio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1e: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(m-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1e: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(m-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1f: $^1$H NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzonitrile

Compound 5.1f: $^{13}$C NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzonitrile
Compound 5.1g: $^1$H NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzaldehyde

Compound 5.1g: $^{13}$C NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzaldehyde
Compound 5.1h: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(4-((trifluoromethyl)thio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1h: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(4-((trifluoromethyl)thio)phenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1i: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(p-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1i: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(p-tolyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1j: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(3,5-bis(trifluoromethyl)phenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1j: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(3,5-bis(trifluoromethyl)phenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1k: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(3,5-dimethylphenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1k $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(3,5-dimethylphenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1l: $^1$H NMR spectrum of 2-Methyl-6-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)aniline

Compound 5.1l: $^{13}$C NMR spectrum of 2-Methyl-6-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)aniline
Compound 5.1m: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3,4,5-trifluorophenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1m $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3,4,5-trifluorophenyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1n: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3,4,5-trimethoxyphenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1n $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3,4,5-trimethoxyphenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1o: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1o: $^{13}$C NMR spectrum of 3aS,4R,6R,7aR)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1p: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(4-fluoro-2-methoxyphenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1p: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(4-fluoro-2-methoxyphenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1q: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(naphthalen-1-yl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.1q: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(naphthalen-1-yl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.1r: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(6-methoxynaphthalen-2-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.1r: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(6-methoxynaphthalen-2-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.1s: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(anthracen-9-yl)-5,5,7a-trimethyl hexahydro-4,6-methanobenzo[d][1,3, 2]dioxaborole (5.1s)

Compound 5.1s: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(anthracen-9-yl)-5,5,7a-trimethyl hexahydro-4,6-methanobenzo[d][1,3, 2]dioxaborole (5.1s)
Compound 5.1t: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(4,6-dihydropyren-1-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborole

Compound 5.1t: $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(4,6-dihydropyren-1-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborole
Compound 5.2a: $^1$H NMR spectrum of 4-((3S,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carbonitrile

Compound 5.2a: $^{13}$C NMR spectrum of 4-((3S,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carbonitrile
Compound 5.2b: $^1$H NMR spectrum of Methyl 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carboxylate

Compound 5.2b: $^{13}$C NMR spectrum of Methyl 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carboxylate
Compound 5.2c: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(thiophen-2-yl)hexahydro-4,6-methanobenzo[d][1,3,2] dioxaborole

Compound 5.2c $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(thiophen-2-yl)hexahydro-4,6-methanobenzo[d][1,3,2] dioxaborole
Compound 5.2d: $^1$H NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carbonitrile

Compound 5.2d $^{13}$C NMR spectrum of 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)thiophene-2-carbonitrile
Compound 5.2e: $^1$H NMR spectrum of 2-fluoro-6-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxa borol-2-yl)pyridine

Compound 5.2e $^{13}$C NMR spectrum of 2-fluoro-6-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxa borol-2-yl)pyridine
Compound 5.2f: $^1$H NMR spectrum of 2-(Trifluoromethyl)-5-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborol-2-yl)pyridine

Compound 5.2f $^{13}$C NMR spectrum of 2-(Trifluoromethyl)-5-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborol-2-yl)pyridine
Compound 5.2g $^1$H NMR spectrum of 2-Methyl-3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2] dioxaborol-2-yl)pyridine

Compound 5.2g $^{13}$C NMR spectrum of 2-Methyl-3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2] dioxaborol-2-yl)pyridine
Compound 5.2h: ¹H NMR spectrum of 7-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)-1H-indole

Compound 5.2h ¹³C NMR spectrum of 7-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)-1H-indole
Compound 5.2i: $^1$H NMR spectrum of 5-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)quinolone

Compound 5.2i $^{13}$C NMR spectrum of 5-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)quinolone
Compound 5.3a: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.3a $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.3b $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-nitrophenyl)hexahydro-4,6-methanobenzo[d][1,3,2] dioxaborole

Compound 5.3b $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-nitrophenyl)hexahydro-4,6-methanobenzo[d][1,3,2] dioxaborole
Compound 5.3c $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(3-methoxyphenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborole

Compound 5.3c $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(3-methoxyphenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborole
Compound 5.3d: $^1$H NMR spectrum of Methyl 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxa borol-2-yl)benzoate

Compound 5.3d $^{13}$C NMR spectrum of Methyl 4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxa borol-2-yl)benzoate
Compound 5.3e: $^1$H NMR spectrum of 3-(3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)acetonitrile

Compound 5.3e $^{13}$C NMR spectrum of 3-(3-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)phenyl)acetonitrile
Compound 5.4a: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(3-chlorophenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.4a $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(3-chlorophenyl)-5,5,7a-trimethylhexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.4b: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-2-(3-chloro-5-(trifluoromethyl)phenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.4b $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-2-(3-chloro-5-(trifluoromethyl)phenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.4c $^1$H NMR spectrum of 2-Chloro-4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methano[1,3,2]dioxaborol-2-yl)pyridine

Compound 5.4c $^{13}$C NMR spectrum of 2-Chloro-4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methano[1,3,2]dioxaborol-2-yl)pyridine
Compound 5.5a: $^1$H NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethoxy)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.5a $^{13}$C NMR spectrum of (3aS,4R,6R,7aR)-5,5,7a-trimethyl-2-(3-(trifluoromethoxy)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.5b: $^1$H NMR spectrum of 3-(Trifluoromethyl)-4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborol-2-yl)benzonitrile

Compound 5.5b: $^{13}$C NMR spectrum of 3-(Trifluoromethyl)-4-((3aS,4R,6R,7aR)-5,5,7a-trimethylhexahydro-4,6-methanobenzo [d][1,3,2]dioxaborol-2-yl)benzonitrile
Compound 5.6a: $^1$H NMR spectrum of (3aR,4R,6R,7aS)-3a,5,5-Trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole

Compound 5.6a $^{13}$C NMR spectrum of (3aR,4R,6R,7aS)-3a,5,5-Trimethyl-2-(3-(trifluoromethyl)phenyl)hexahydro-4,6-methano benzo[d][1,3,2]dioxaborole
Compound 5.6b $^1$H NMR spectrum of (3aR,4R,6R,7aS)-2-(3-Chlorophenyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole

Compound 5.6b $^{13}$C NMR spectrum of (3aR,4R,6R,7aS)-2-(3-Chlorophenyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole
Compound 5.6c: $^1$H NMR spectrum of (3aR,4R,6R,7aS)-3a,5,5-Trimethyl-2-(naphthalen-1-yl)hexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborole

Compound 5.6c $^{13}$C NMR spectrum of (3aR,4R,6R,7aS)-3a,5,5-Trimethyl-2-(naphthalen-1-yl)hexahydro-4,6-methanobenzo[d] [1,3,2]dioxaborole
Facile Synthesis of Halogen Decorated para-/meta-Hydroxybenzoates by Iridium-Catalyzed Borylation and Oxidation

Tayyaba Shahzadi
Rahman S. Z. Saleem
Ghayoor A. Chotana*

Department of Chemistry & Chemical Engineering,
Syed Babar Ali School of Science & Engineering, Lahore
University of Management Sciences, Lahore 54792,
Pakistan
ghayoor.abbas@lums.edu.pk

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Abstract
Hydroxybenzoates are an important class of phenols that are widely used as preservatives and antiseptics in the food and pharmaceutical industries. In this report, we describe a facile preparation of 2,6- and 2,3-disubstituted 4/5-hydroxybenzoates by iridium-catalyzed borylation of respective disubstituted benzoate esters followed by oxidation. This synthetic route allows for the incorporation of halogens in the final hydroxybenzoates with substitution patterns not readily accessible by the traditional routes of aromatic functionalization.

Key words
iridium-catalyzed C–H borylation, oxidation, Oxone®, hydroxybenzoates, parabens, preservatives, halogen, trifluoromethyl

Hydroxybenzoates are important synthetic precursors to many drugs, polymers, herbicides, and antioxidants.1–4 4-Hydroxybenzoates, also known as parabens, are widely used as antimicrobial preservatives in food, pharmaceuticals, and cosmetics.5–7 Approximately 8000 tons of parabens are consumed annually around the globe.8 This scaffold is also found in many natural products and molecules of biological relevance (Figure 1). Recently, 3,5-dihalogen-substituted 4-hydroxybenzoates have been reported to possess enhanced antimicrobial properties along with reduced risk of breast cancer as compared to the parent paraben.9 3-Hydroxybenzoates have shown excellent antifungal properties10 and 2-hydroxybenzoates such as methyl salicylate are active ingredient of many analgesics.11 The harsh reaction conditions used in these traditional approaches result in limited functional group tolerance. These classical routes also rely on early incorporation of the hydroxyl functional group, which limits the subsequent derivatizations ortho to the hydroxyl group.

Classical approaches to access hydroxybenzoates include esterification of hydroxybenzoic acids using sulfuric acid, p-toluensulfonic acid, or cation-exchange resins as catalyst.11 The starting hydroxybenzoic acids used for esterification are in turn synthesized either using Kolbe–Schmitt process by heating potassium phenoxide in a stream of carbon dioxide, or by heating p-cresol with various metallic oxides.12 The harsh reaction conditions used in these traditional approaches result in limited functional group tolerance. These classical routes also rely on early incorporation of the hydroxyl functional group, which limits the subsequent derivatizations ortho to the hydroxyl group.

Keeping in view of their immense utility in pharmaceutical, cosmetic, and food industries, there is need to develop new green synthetic methodologies to access novel hydroxybenzoates with additional useful functional groups to find next generation compounds with better activities and reduced side effects.9,13–16 In this direction, development of methodologies that allow introduction of a hydroxyl group later in the synthetic route is an ideal approach for obtaining new and unique substitution patterns not accessible through the traditional routes.
During the last two decades, several new methodologies have been developed to synthesize substituted phenols under mild reaction conditions and with improved functional group compatibilities. Among these, the most convenient route is through the oxidation of arylboronic acids and esters. Various oxidizing agents utilized for this purpose include Oxone®, hydrogen peroxide, hydrazine derivatives, sodium ascorbate, photocatalysts, and electrocatalysts, etc. In addition, alternative synthetic routes recently reported for the preparation of phenols include nucleophilic aromatic substitutions, transition-metal-catalyzed hydroxylation of aryl halides, and hydroxylation of arylsilanes. However, all these methods need pre-functionalization of the aromatic ring in the form of halogen or nitro groups, which are ultimately converted to the hydroxyl group. Since incorporation of halogens often results in improved bioactivities, it is desirable to develop methods for the preparation of halogenated hydroxybenzoates with new substitution patterns not readily accessible through the traditional aromatic functionalization routes.

The group of Smith and Maleczka has reported iridium-catalyzed aromatic C–H borylation/oxidation route for the synthesis of meta-substituted phenols directly from the hydrocarbon feedstock. This transition-metal-catalyzed reaction is highly selective for aromatic C–H activation in the presence of other functional groups and thus allows for the incorporation of various substituents including halogens into the final phenol products. Moreover, sterically governed regioselectivity observed in this C–H functionalization reaction is complementary to that obtained through the traditional electrophilic aromatic substitution and directed ortho-metalation approaches. Building on the foundations of Smith and Maleczka methodology for the preparation of halogenated phenols, we explored the application of this route to the borylation/oxidation of 2,6- and 2,3-disubstituted benzoic esters to prepare the corresponding 4- and 5-hydroxybenzoate esters.

We started with the iridium-catalyzed borylation of 2,6-disubstituted benzoate esters. Using the standard borylation protocol, precatalyst [Ir(OMe)(COD)]2 and dtbbpy ligand were weighed in air and transferred to a Schlenk flask under nitrogen atmosphere. Pinacolborane (HBpin) and benzoate ester substrate were subsequently added to the flask and the mixture was heated at 80 °C using an oil bath. The progress of reaction was monitored by GC-MS. Since regioselectivity in iridium-catalyzed C–H borylation is governed by sterics, catalytic borylation selectively took place at the least hindered site, that is, the 4-position (Scheme 1, entries 1a–e). In the case of 2-bromo-5-fluoro-substituted benzoate ester, the small size of fluorine allowed borylation ortho to itself (Scheme 1, entry 1f). The resulting arylboronate esters were isolated in good to excellent yields.

Catalytic borylation of 2,3-disubstituted benzoate esters also took place on the least sterically hindered 5-position (Scheme 2). Halogenated and trifluoromethyl-substituted benzoic esters were examined. Since it has been known that the antimicrobial activity of the parabens increases with increasing the alkyl chain length of benzoic ester, the ethyl and n-propyl esters were also included in this study (Scheme 2, entries 2c, 2e, and 2f).

The synthesized boronic esters were then subjected to oxidation using Oxone® (Scheme 3). The desired hydroxyl benzoates were isolated in good to excellent yields. In the case of 3b and 3f, small amounts (<1%) of protodeborylation was detected by GC-MS. This synthetic route allowed the ready preparation of 2,6- and 2,5-halo-substituted 4-hydroxybenzoates. It is interesting to note that the closely related isomeric 3,5-disubstituted 4-hydroxybenzoate esters have recently been reported to exhibit improved antimicrobial activities together with diminished side effects commonly associated with unsubstituted parabens.
Similarly, 2,3-disubstituted 5-borylated benzoate esters were oxidized to the corresponding 5-hydroxy benzoates (Scheme 4). Although ortho-substituted phenols are readily available by traditional electrophilic aromatic substitution, however, access to meta-substituted phenols is more challenging and requires long synthetic routes. The current synthetic route provides ready access to these difficult to prepare meta-halogenated phenols.

In summary, iridium-catalyzed borylation and subsequent oxidation of benzoate esters is an efficient protocol for synthesis of various substituted hydroxybenzoates. This method is particularly attractive for the preparation of halogenated hydroxybenzoates where the halogen substituent is present meta to the ortho/para directing hydroxyl group.

All reactions were carried out under N₂ atmosphere. All commercially available chemicals and reagents were used without further purification unless otherwise noted. EtOAc, hexanes, and CH₂Cl₂ were distilled before use. Carboxylic esters, if not readily commercially available, were prepared by acid-catalyzed esterification of the corresponding carboxylic acid. Iridium-catalyzed borylation reactions were carried out in air-free 25 mL Schlenk flask (0–4 mm valve, 175 mm OAH). Analytical TLC was carried out using 250 μm thick SiliaPlate™ TLC Plates. Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was carried out using SiliaFlash® (particle size: 40–63 μm, 230–400 mesh). All reported yields are for isolated materials. Reaction times and yields are not optimized. HBPin: pinacolborane; dtbbpy: 4,4′-di-tert-butylylidene-2,2′-bipyridyl.

IR spectra were recorded as neat using a Bruker Alpha-P IR instrument in the ATR geometry with a diamond ATR unit. Melting points were taken on Electrothermal IA9100 melting point apparatus. Reactions were monitored by a GC-MS operating in EI mode. 1H NMR spectra were recorded at 500 MHz, and 13C NMR spectra were recorded at 125 MHz at ambient temperature. The chemical shifts in 1H NMR spectra are reported using TMS as internal standard and were referenced with the residual proton resonances of the corresponding deuterated solvent (DMSO-d₆: δ = 2.50). The chemical shifts in the 13C NMR spectra are reported relative to TMS (δ = 0) or the central peak of DMSO-d₆ (δ = 39.5) for calibration. Standard abbreviations were used for denoting the multiplicities. All coupling constants are apparent J values measured at the indicated field strengths. In 13C NMR spectra of aryloboric esters, the carbon atom attached to the boron atom of BPin group is typically not observed due to broadening from and coupling with boron. Regiochemistry of the borylated products was assigned by NMR spectroscopy (1H and 13C NMR).

Borylation of Arenes; General Procedure

In a fume hood, an oven dried Schlenk flask equipped with a magnetic stirring bar was filled with N₂ and evacuated (three cycles). Under N₂ atmosphere [Ir(OMe)(COD)₂] (13.3 mg, 0.01 mmol, 1 mol%), 4,4′-di-tert-butyl-2,2′-bipyridyl (10.7 mg, 0.02 mmol, 2 mol%), and pinacolborane (HBPin) (436 μL, 384 mg, 3 mmol, 1.5 equiv) were added. The appropriate arene substrate (2 mmol, 1 equiv) was added via micropipette under N₂ atmosphere. The Schlenk flask was closed and the reaction mixture was heated at 80 °C in an oil bath. The progress of reaction was monitored by GC-MS and TLC. Upon completion of reaction, Schlenk flask was cooled to r.t. and exposed to air. The contents of the flask were dissolved in CH₂Cl₂ (3–5 mL) and taken out in a round-bottomed flask. The volatile organic compounds were removed under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography (silica gel, hexanes–CH₂Cl₂: 1:1).

Methyl 2-Chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)benzoate (1a)

General borylation procedure was applied to methyl 2-methyl-6-chlorobenzoate (368 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 447 mg (72%); mp 73–74 °C; Rₚ = 0.3 (hexanes–CH₂Cl₂: 1:1).

FT-IR (ATR): 2977, 1732, 1550, 1442, 1354, 1269, 1124, 1080, 958, 886, 848, 860, 813, 686 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): δ = 7.54 (s, 1 H), 7.51 (s, 1 H), 3.89 (s, 3 H, CH₃), 2.27 (s, 3 H, CH₃), 1.30 (s, 12 H, 4 × CH₃ of BPin).

13C NMR {1H} (125 MHz, DMSO-d₆): δ = 166.8 (C=O), 136.3 (C), 135.7 (C), 134.5 (CH), 131.7 (CH), 129.0 (C), 84.3 (2 C), 52.7 (CH₃), 24.6 (4 × CH₃ of BPin), 18.7 (CH₃).

GC-MS (EI): m/z (%) = 310 [M⁺], 295 (16), 279 (26), 275 (17), 243 (100), 233 (89), 211 (54), 201 (26), 179 (21), 175 (18).
Methyl 2-Bromo-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1b)

General borylation procedure was applied to 2-bromo-6-chlorobenzoate (500 mg, 2 mmol, 1 equiv) for 18 h; colorless solid; yield: 614 mg (82%); mp 83–84 °C; Rf = 0.5 (hexanes–CH2Cl2 1:1).

FT-IR (ATR): 2983, 2951, 1745, 1610, 1589, 1341, 1271, 1160, 1071, 979 cm−1.

1H NMR (500 MHz, DMSO-d6): δ = 7.80 (d, J = 1.0 Hz, 1 H), 7.70 (d, J = 0.5 Hz, 1 H), 3.92 (s, 3 H, CH3), 1.30 (s, 12 H, 4 × CH3 of BPin).

13C NMR {1H} (125 MHz, DMSO-d6): δ = 135.0 (C), 133.1 (2 × CH), 130.5 (2 C), 84.8 (2 C), 53.3 (CH3), 24.6 (4 × CH3 of BPin).

GC-MS (EI): m/z (%) = 332 [10, (M + 2)⁺], 330 [17, (M⁺)], 315 (28), 299 (21), 244 (100), 231 (25), 213 (17), 199 (24).

Methyl 2-Bromo-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1f)

General borylation procedure was applied to methyl 2-bromo-5-fluorobenzoate (464 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 634 mg (88%); mp 95 °C; Rf = 0.3 (hexanes–CH2Cl2 1:1).


1H NMR (500 MHz, DMSO-d6): δ = 7.84 (d, J = 1.0 Hz, 1 H), 7.60 (d, J = 1.5 Hz, 1 H), 3.87 (s, 3 H, CH3), 1.31 (s, 12 H, 4 × CH3 of BPin).

13C NMR {1H} (125 MHz, DMSO-d6): δ = 143.4 (d, JCF = 8.2 Hz, C=O), 136.7 (d, JCF = 8.1 Hz, C), 117.9 (d, JCF = 27.5 Hz, CH), 114.3 (d, JCF = 3.5 Hz, C), 84.2 (C), 52.9 (CH3), 24.5 (4 × CH3 of BPin).

GC-MS (EI): m/z (%) = 358 [40, (M⁺)], 343 (36), 316 (80), 300 (27), 298 (95), 259 (58), 254 (100), 227 (85).

Methyl 2-Bromo-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2a)

General borylation procedure was applied to methyl 2-methylbenzoate (456 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 502 mg (71%); mp 75–76 °C; Rf = 0.4 (hexanes–CH2Cl2 1:1).


1H NMR (500 MHz, DMSO-d6): δ = 7.75–7.74 (m, 1 H), 7.71–7.70 (m, 1 H), 3.85 (s, 3 H, CH3), 2.34 (s, 3 H, CH3), 1.30 (s, 12 H, 4 × CH3 of BPin).

13C NMR {1H} (125 MHz, DMSO-d6): δ = 166.7 (d, JCF = 250.5 Hz, C=O), 138.9 (C), 138.7 (CH), 133.7 (C), 133.1 (CH), 125.5 (C), 84.2 (C), 52.6 (CH3), 24.6 (4 × CH3 of BPin).

GC-MS (EI): m/z (%) = 354 [38, (M⁺)], 339 (18), 311 (100), 279 (19), 255 (29), 223 (30), 143 (41).

Methyl 2,3-Dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2b)

General borylation procedure was applied to methyl 2,3-dichlorobenzoate (408 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 541 mg (82%); mp 89–91 °C; Rf = 0.4 (hexanes–CH2Cl2 1:1).

FT-IR (ATR): 2977, 2727, 1592, 1439, 1351, 1268, 1242, 1025, 1047, 984, 963, 904, 851 cm−1.

1H NMR (500 MHz, DMSO-d6): δ = 7.94 (d, J = 1.5 Hz, 1 H), 7.92 (d, J = 1.5 Hz, 1 H), 3.88 (s, 3 H, CH3), 1.31 (s, 12 H, 4 × CH3 of BPin).

13C NMR {1H} (125 MHz, DMSO-d6): δ = 164.7 (C=O), 138.1 (CH), 134.5 (CH), 133.2 (C), 132.8 (C), 132.4 (C), 84.7 (C), 52.9 (CH3), 24.6 (4 × CH3 of BPin).

GC-MS (EI): m/z (%) = 332 [12, (M + 2)⁺], 330 [17, (M⁺)], 315 (17), 299 (23), 287 (100), 255 (38), 231 (52), 199 (43).

Ethyl 2,3-Dichloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2c)

General borylation procedure was applied to ethyl 2,3-dichlorobenzoate (436 mg, 2 mmol, 1 equiv) for 18 h; colorless solid; yield: 502 mg (73%); mp 66–67 °C; Rf = 0.4 (hexanes–CH2Cl2 1:1).

FT-IR (ATR): 2979, 1730, 1590, 1470, 1353, 1239, 1127, 1030, 968, 904, 847, 777, 748, 704 cm−1.
1H NMR (500 MHz, DMSO-d6): δ = 7.91 (d, J = 1.5 Hz, 1 H), 7.89 (d, J = 1.5 Hz, 1 H), 4.35 (q, J = 7.0 Hz, 2 H, CH3), 1.34 (s, 12 H, 4 × CH3 of BPin), 1.32 (t, J = 7.0 Hz, 3 H, CH3).

13C NMR (125 MHz, DMSO-d6): δ = 164.4 (C=O), 137.9 (CH), 134.1 (CH), 133.1 (C), 132.9 (C), 126.2 (C), 84.7 (2 C), 61.9 (CH3), 24.9 (4 × CH3 of BPin), 13.9 (CH3).

GC-MS (EI): m/z (%) = 392 [M+], 377 (20), 333 (23), 307 (100), 289 (21), 251 (36), 233 (43), 205 (37).

Oxidation Boronic Esters 1 and 2; General Procedure
An oven-dried round-bottomed flask equipped with a magnetic stirring bar was charged with the respective boronic ester substrate 1 or 2 (1 mmol, 1 equiv) and acetonitrile (3 mL). The mixture was stirred to generate a homogeneous solution. An aqueous solution of Ozone (1 equiv in 3 mL/mmol H2O) was added dropwise over 2–4 min. The reaction mixture was vigorously stirred for 20–30 min. After the completion of reaction, an aq solution of NaHSO3 (1 mL) was added to quench the reaction. The mixture was extracted with CH3Cl (3 × 15 mL) and the combined organics were washed with brine. The organic layer was separated, dried (anhyd Na2SO4, 2 g), and filtered. Volatile organics were removed using rotary evaporator. The crude product was purified by column chromatography (silica gel, hexanes–EtOAC 1:1).

Methyl 2-Chloro-4-hydroxy-6-methylbenzoate (3a)
General oxidation procedure was applied to methyl 2-chloro-6-methylbenzoate (3a) (100), 255 (36), 245 (31), 217 (40), 199 (47).

Ethyl 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2e)
General borylation procedure was applied to methyl 2-chloro-3-(trifluoromethyl)benzoate (476 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 531 mg (73%); mp 125–126 °C.

GC-MS (EI): m/z (%) = 346 [11, (M)+], 344 [17, (M)+], 301 (95), 273 (100), 255 (36), 245 (31), 217 (40), 199 (47).

GC-MS (EI): m/z (%) = 392 [M+], 377 (20), 333 (23), 307 (100), 289 (21), 251 (36), 233 (43), 205 (37).

Oxidation Boronic Esters 1 and 2; General Procedure
An oven-dried round-bottomed flask equipped with a magnetic stirring bar was charged with the respective boronic ester substrate 1 or 2 (1 mmol, 1 equiv) and acetonitrile (3 mL). The mixture was stirred to generate a homogeneous solution. An aqueous solution of Ozone (1 equiv in 3 mL/mmol H2O) was added dropwise over 2–4 min. The reaction mixture was vigorously stirred for 20–30 min. After the completion of reaction, an aq solution of NaHSO3 (1 mL) was added to quench the reaction. The mixture was extracted with CH3Cl (3 × 15 mL) and the combined organics were washed with brine. The organic layer was separated, dried (anhyd Na2SO4, 2 g), and filtered. Volatile organics were removed using rotary evaporator. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc 1:1).

Methyl 2-Chloro-4-hydroxy-6-methylbenzoate (3a)
General oxidation procedure was applied to methyl 2-chloro-6-methylbenzoate (3a) (100), 255 (36), 245 (31), 217 (40), 199 (47).

Ethyl 2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2e)
General borylation procedure was applied to methyl 2-chloro-3-(trifluoromethyl)benzoate (476 mg, 2 mmol, 1 equiv) for 24 h; colorless solid; yield: 531 mg (73%); mp 125–126 °C.

GC-MS (EI): m/z (%) = 346 [11, (M)+], 344 [17, (M)+], 301 (95), 273 (100), 255 (36), 245 (31), 217 (40), 199 (47).
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**GC-MS (EI):** $m/z (\%) = 262 \ [18, \ (M + 2^{+})], 260 \ [(M^{+})], 231 \ (95), 229 \ (100), 214 \ (6), 186 \ (11), 158 \ (4), 150 \ (5)$.

**Methyl 2,6-Dimethyl-4-hydroxybenzoate (3d)**
General oxidation procedure was applied to methyl 2,6-dimethyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate ($1d$; 145 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 238 mg (96%); mp 111–113 °C; $R_f = 0.5$ (hexanes–EtOAc 1:1).


**1H NMR (500 MHz, DMSO-$_d_6$):** $\delta = 6.94$ (br s, 1 H, OH), 6.46 (s, 2 H, 2 × CH), 4.17 (s, 3 H, CH$_3$), 3.85 (s, 3 H, CH$_3$).

**1C NMR {1H} (125 MHz, DMSO-$_d_6$):** $\delta = 149.5$ (d, 1 CH, 84.9, C), 136.9 (CH), 124.3 (C), 114.4 (2 CH), 51.5 (CH$_3$), 19.8 (2 × CH$_3$).

**GC-MS (EI):** $m/z (%) = 180 \ [54, (M^{+})], 149 \ (100), 121 \ (25), 103 \ (3), 91 \ (16).$

**Methyl 2,6-Dichloro-4-hydroxybenzoate (3e)**
General oxidation procedure was applied to methyl 2,6-dichloro-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate ($1e$; 161 mg, 0.5 mmol, 1 equiv) for 0.5 h; colorless solid; yield: 118 mg (97%); mp 145–147 °C; $R_f = 0.7$ (hexanes–EtOAc 1:1).


**1H NMR (500 MHz, DMSO-$_d_6$):** $\delta = 7.68$ (d, $J = 11.5$ Hz, 1 H), 7.26 (s, $J = 8.0$ Hz, 1 H), 3.86 (s, 3 H, CH$_3$).

**1C NMR {1H} (125 MHz, DMSO-$_d_6$):** $\delta = 149.5$ (d, 1 CH, 84.9, C), 133.17 (C), 119.8 (CH), 118.7 (C), 116.2 (CH), 52.8 (CH$_3$).

**GC-MS (EI):** $m/z (%) = 236 \ [34, (M + 2^{+})], 234 \ [56, (M)^{+}], 219 \ (8), 208 \ (35), 191 \ (11), 189 \ (100), 161 \ (17).$

**Ethyl 2,3-Dichloro-5-hydroxybenzoate (4c)**
General oxidation procedure was applied to ethyl 2,3-dichloro-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate ($2c$; 345 mg, 1 mmol, 1 equiv) for 20 min; colorless solid; yield: 215 mg (92%); mp 109–111 °C; $R_f = 0.7$ (hexanes–EtOAc 1:1).


**1H NMR (500 MHz, DMSO-$_d_6$):** $\delta = 10.54$ (br s, 1 H, OH), 7.18 (d, $J = 3.0$ Hz, CH$_2$), 7.09 (d, $J = 3.0$ Hz, CH$_2$), 4.31 (q, $J = 7.0$ Hz, 2 H, CH$_2$), 1.30 (t, $J = 7.0$ Hz, 3 H, CH$_3$).

**1C NMR {1H} (125 MHz, DMSO-$_d_6$):** $\delta = 164.7$ (C=O), 156.6 (C), 133.5 (C), 133.2 (C), 119.7 (CH), 118.6 (C), 116.1 (CH), 61.7 (CH$_2$), 13.1 (CH$_3$).

**GC-MS (EI):** $m/z (%) = 256 \ [54, (M + 2^{+})], 254 \ [22, (M^{+})], 225 \ [32], 223 \ [100], 195 \ (35), 132 \ (13).$

**Ethyl 2-Chloro-3-(trifluoromethyl)-5-hydroxybenzoate (4f)**
General oxidation procedure was applied to ethyl 2-chloro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate ($2f$; 365 mg, 1 mmol, 1 equiv) for 20 min; colorless semi-solid; yield: 240 mg (94%); $R_f = 0.6$ (hexanes–EtOAc 1:1).

FT-IR (ATR): 3385, 2980, 1729, 1434, 1352, 1136 cm–1.

**1H NMR (500 MHz, DMSO-$_d_6$):** $\delta = 10.78$ (br s, 1 H, OH), 7.74 (s, 2 H, 2 × CH), 3.87 (s, 3 H, CH$_3$).

**1C NMR {1H} (125 MHz, DMSO-$_d_6$):** $\delta = 165.1$ (C=O), 153.4 (C), 134.8 (CH), 128.8 (q, $J_{CF} = 30.5$ Hz, C), 122.4 (q, $J_{CF} = 271.6$ Hz, CF$_3$), 120.2 (CH), 117.5 (C), 117.1 (q, $J_{CF} = 5.4$ Hz, CF$_3$).

**GC-MS (EI):** $m/z (%) = 256 \ [11, (M + 2^{+})], 254 \ [22, (M^{+})], 225 \ [32], 223 \ [100], 195 \ (35), 132 \ (13).$
13C NMR (1H) (151 MHz, CDCl3): δ = 166.1 (C=O), 154.2 (C), 134.6 (C), 130.9 (q, 3C, CH3), 122.2 (q, 3C, CH3), 121.9 (C), 120.3 (CH), 117.8 (q, 3C, CH3), 62.7 (CH2), 14.1 (CH3).

GC-MS (EI): m/z (%) = 270 [8, (M + 2)⁺], 268 [24, (M⁺)²], 240 (37), 223 (100), 195 (23).

**Propyl 2-Chloro-3-(trifluoromethyl)-5-hydroxybenzoate (4f)**

General oxidation procedure was applied to propyl 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzoate (2f; 392 mg, 1 mmol, 1 equiv) for 20 min; colorless solid; yield: 231 mg (82%); mp 102–104 °C.

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**Supporting Information**

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