BORON HETROCYCLES AS COUPLING COUNTERPARTS EN-ROUTE TO PHARMACUETICALLY RELEVANT BENZOSULTAMS

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by

Emil STEINWENDTNER

Supervisor: PJ Persichini, III, Associate Prof..

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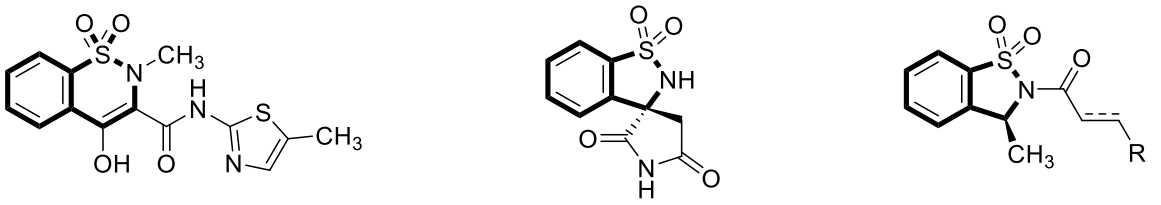
DoM	Directed ortho-metalation
DMG	Directing metalation group
NMR	Nuclear Magnetic Resonance
HIV	Human Immunodeficiency Virus
n-BuLi	n-Butyllithium
COX	Cyclooxygenase
FT	Fourier Transform
THF	Tetrahydrofuran
*i*Pro	*iso*-Propyl
FLP	Frustrated Lewis Pairs
OLED	organic optical light-emitting device

1 Introduction

Benzosultams are heterocyclic aryl sulfonamides. They offer a broad profile of biological applications. The benzosultam functionality consist of an aryl moiety and a 5-, 6-, or 7-membered heterocycle containing a sulfone and a nitrogen (Figure 1). Compounds with benzosultam functionality are reported to exhibit several properties of interest in drug discovery. These include antibacterial, anti-inflammatory, anti-cancer, HIV-1 inhibitory and anti-diabetic properties.



1 Meloxicam, COX-2 inhibitor

2 aldose reductase inhibitor

3 chiral auxillaries

Figure 1 - Highlighted: the benzosultam cores of 3 selected compounds

This, combined with the fact that they do not occur as natural products and can only be obtained synthetically, makes them attractive targets for organic synthesis. As a result, there is a continued demand for the development of new and more efficient methods for synthesizing benzosultams.

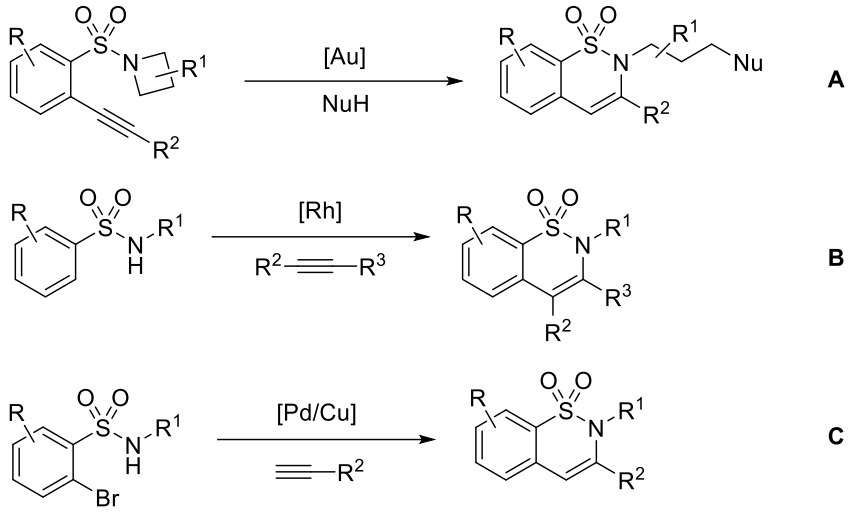
Especially for drug discovery benzosultams possess a lot of very interesting and promising properties. The hydrogen bond accepting and donating capabilities are comparable if not identical with their corresponding sulfonamide, while retaining the steric complexity and rigidity of a heterocyclic molecule. This might allow access to binding pockets, that sulfonamides can not access. The sterically hindered bulk could also protect the molecule from being metabolized in an inconvenient place.

In addition to their applications as pharmaceuticals benzosultams are also used in asymmetric synthesis as chiral auxiliaries. Outside of that, agricultural agents, that contain the benzosultam functionality, mainly in the form of fungicides, are used.[1–4]

Overall, benzosultams are an important class of compounds that have a wide range of applications in various fields, including pharmacology, chemical synthesis, and chemical research. Their unique properties and the fact that they are not found

naturally make them valuable tools and targets for a variety of scientific and technological purposes.

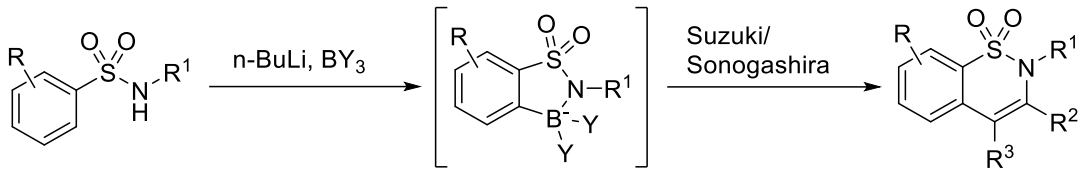
Previous work:



Scheme 1 - Previous Work: **A**: Pertschi, 2019; **B**: Cramer, 2012; **C**: Mondal, 2015

Currently, most reported routes to benzosultam involve the intramolecular cyclization of complex precursors using specialized catalysts[5]. Existing intermolecular routes come with strong limitations. Known paths start out with ortho-functionalized sulfonamides[6] or benzothiatriazine derivatives[7], require strongly modified directing groups to facilitate the ortho carbon-hydrogen cleavage[8], require lesser explored catalyst systems[9], and lack flexibility (Scheme 1). A simplified, more general approach utilizing boron heterocycles in order to directly access a widely available technology like intermolecular palladium cross-coupling and subsequent intramolecular cyclization in the synthesis of benzosultams from unaltered sulfonamides would undoubtedly be a welcome addition to the available routes. Moreover, the intermolecular methodology allows for additional functionalization and flexibility as outlined in Scheme 2.

This work:



4 **5** **6**

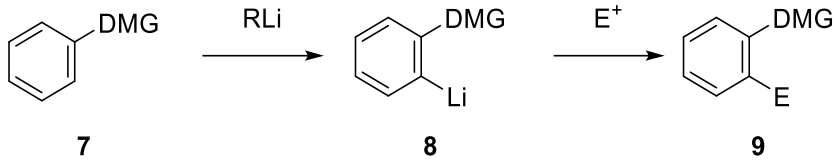
Scheme 2 - Schematic outline of this work, Y = F, O-Alkyl

In this work, the previously underexplored DoM of *N*-hydrogen-bearing aryl sulfonamides is investigated in its ability to form a boron heterocycle, which will subsequently be studied and its compatibility to act as a palladium coupling counterpart in a concerted reaction to form a carbon-carbon bond and a carbon-nitrogen bond will be tested. The DoM methodology provides an elegant, efficient and direct path to the boron heterocycles that are novel compounds and might have interesting properties for a wide variety of fields in chemistry, biology and medicine.

One of the main factors contributing to the wide success and prevalence of Suzuki coupling reactions and other similar methods to this day is the innate ability of organoboron compounds to be compatible with a wide range of functional groups and that many organoboron compounds are commercially available.

The concerted reaction consists in one part of the installation of an alkene-containing moiety via a Suzuki reaction of an alkyl-bearing moiety via a modified Sonogashira coupling protocol. The second part is the ring closure and formation of the carbon-nitrogen bond. This part of the synthesis route is based on the Larock indole synthesis reaction.

1.1 Directed ortho-Metalation



7 **8** **9**

Scheme 3 - The general directed ortho-metalation reaction

The selective ortho-deprotonation of anisole was first reported in the years 1939 and 1940, as an independent discovery by Gilman and Bebb and Wittig and Fuhrman.[10,11] Since then, it has been expanded extensively, most notably by Hauser and more recently Snieckus, who eventually developed DoM to be an established way to regiospecifically assemble substituted aromatic compounds and heterocyclic molecules.[12]

Directed ortho-metalation is a chemical reaction in which metal atom, usually lithium from an alkyllithium base, coordinates to a directing metalation group (DMG) of a substituted aromatic compound. The base subsequently deprotonates the ortho-position selectively and the hydrogen atom gets exchanged for a metal cation. The ortho-metalized species is then subjected to attack by an electrophile that replaces the metal cation.[12,13]

Directing metalation groups guide the deprotonating species to the ortho position. An integral part of the directing group is a heteroatom, since it must serve as a good coordination site for the base and at the same time be only slightly susceptible to its electrophilic attack. Steric hindrance and charge deactivation may be incorporated into the structure of the directing group.

In most cases, the deprotonation step requires the application of potent organolithium bases to successfully displace the proton and thereby upsetting the molecules aromaticity. The resulting species is extremely reactive and is easily reprotonated, which makes the use of aprotic solvents a necessity.

The DoM reaction, in short, is a valuable tool in organic synthesis that enables the precise functionalization of aromatic compounds and the synthesis of a range of derivatives. It has played a significant role in the development of many important chemicals and remains an active area of research in chemistry.[12]

1.2 Frustrated Lewis Pairs

Transition metals are capable of both accepting electrons from a substrate and donating them by back-bonding to the anti-bonding orbitals. These properties lead to the observed reactivity of transition metals, which has made them a pillar of modern organic synthesis.[14]

The electron pair acceptor capabilities of group III species are classic examples of Lewis acids, while the electron-donating nature of derivatives of group V elements are typically used as examples to illustrate Lewis basicity. This means that they exhibit analogues properties in regard to reactivity. Small molecules like H_2, CO_2 and olefines among others, can be activated by employing a Lewis base and a Lewis acid synergistically. A mixture containing both, a sterically hindered Lewis acid and a sterically hindered Lewis base, or a species containing both in a way they're prohibited from forming a classical Lewis acid-base adduct. This puts them in a position where they're able to accept and donate electron density respectively, causing, for example the heterolytic cleavage of the covalent bond in H_2. The necessary presence of sterically demanding substituents also enables stereoselective methodologies. Most frustrated Lewis pair systems employ boron in the role of a Lewis acid and nitrogen or phosphorous as a Lewis base. [15,16]

While the chemistry of and around frustrated Lewis pairs has rapidly evolved over the last years, there is still a lot of work necessary to fully understand and utilize the methodology's extensive synthetic capabilities.[14,17]

1.2.1 Hydrogenation

The frustrated Lewis pair methodology offers an alternative in the metal-free reduction of organic substrates. The activation of H_2 as a heterolytic cleavage prompts sequential proton and hydride supply. Thus, polar substrates can be

effectively hydrolyzed by utilizing FPAs. By changing the temperature, hydrogen source and adjusting solvent systems the scope and limitations of the hydrogenation of polar substrates were expanded from initially only being able to reduce imines, enamines and silyl enol ethers, to eventually being able to reduce ketones and aldehydes to their corresponding alcohols.[14]

Via the contribution of a weak donor molecule as the base portion in the FLP to activate H_2 the highly acidic conjugate acid is generated. This conjugate acid only exists for a brief moment but is acidic enough to protonate 1,1-disubstituted alkenes. The hydride, captured by the Lewis acidic part of the FLP is then able to interact with the formed carbocation. This interaction results in the saturated species, while at the same time regenerating the FLP. This makes this process catalytic. This concept was further used to reduce alkynes, polyaromatic and heterocyclic aromatic systems.[14]

Frustrated Lewis pairs also find application as catalysts in the asymmetric reduction of carbon and nitrogen centers. The stereoselectivity is thought to be the product of a, briefly by van der Waals forces stabilized, species that is held in place while the H_2 cleavage is taking place. [18]

1.2.2 Activation of olefines and alkynes

Simple olefines react with frustrated Lewis pairs to afford the addition product, a zwitterionic phosphonium borate compound. In a similar fashion, pendant olefinic substituents of aniline derivatives can be activated to initiate a cyclization reaction that leads to a zwitterionic nitrogen heterocycle. This methodology is able to generate polycyclic pyridine and quinoline products.[14,16]

Alkynes react in an analogous manner and afford zwitterionic addition products. The formation of addition products between substrate and FLPs makes the application of carbon-based nucleophiles very attractive, as this opens up a possibility to make carbon-carbon bonds. In this context pyrrole derivative FPAs were probed against alkynes and showed the ability to generate fused adducts with a newly formed carbon-carbon bond. Alkyne addition reactions with frustrated Lewis pairs have also been found to undergo intramolecular cyclization. This can be exploited to quickly

assemble larger heterocyclic structures. By employing boron and nitrogen based FLPs, alkynes can be reduced and converted to enamines. A positively charged intermediate, in which the nitrogen bears a positive charge is formed, to which the borate species acts as the counterion. This reaction can be performed in tandem with the further reduction of the enamine to afford the corresponding amine.[14,16]

While alkenes are thought to be activated by the formation of π complexes, alkynes seem to be stronger bound with the highly Lewis acidic boranes in σ complexed intermediates. This stronger association allows for a wider utilization of FLPs in the activation of alkynes. One of the most powerful applications of boranes in alkyne activation is in the development of stoichiometric reactions with enamines and pyrrole that create a new bond between two carbons. Another important application of boranes in alkyne activation is in catalytic alkyne hydroboration. This transformation involves the use of boranes to activate alkynes and react them with boron-containing compounds, forming carbon boron bonds. These reactions involve the use of highly Lewis acidic boranes to activate alkynes and react them with enamines or pyrrole, forming carbon-carbon bonds between the two molecules. [14,16,17]

Boranes have also been used in catalytic alkyne hydroamination, a transformation that involves the activation of alkynes and the reaction with amines, forming carbon nitrogen bonds. There exist numerous transition metal catalyzed reactions that follow a very similar mechanism.[17]

Another important application of boranes in alkyne activation is in catalytic alkyne hydroboration. This transformation involves the use of boranes to activate alkynes and react them with boron-containing compounds, affording new carbon boron bonds.[17]

Boranes in FLPs have also been utilized in alkyne-silane dehydrocoupling, a reaction that involves the use of boranes to activate alkynes and react them with silanes, forming silicon-containing compounds and carbon-carbon bonds. This reaction has been extensively studied and has been used in the synthesis of a range of important organosilicon compounds.[14,17]

1.2.3 Capture and reduction of CO_2

Carbon capture systems have become a topic of interest and new methods are highly sought after. Often carbon capture systems are described as an important tool in the future fight against climate change.

Many frustrated Lewis pairs, both intermolecular and intramolecular, have been reported to bind and capture CO_2 in a thermally reversible way. [14]

FLPs can also be used to reduce CO_2 molecules. The initially in the capture formed species reacts readily with NH_3BH_3 and upon workup, this route affords methanol. In this methodology and others, the FLPs have to be used stoichiometrically to afford formate,acetal and methoxy- derivatives.[14,19]

There are however also catalytic approaches towards the reduction of CO_2 both with and without the additional use of metals.[14]

1.2.4 Capture and reactions with N_2O, NO and SO_2

FLPs exhibit analogous capturing properties for other small molecules such as N_2O, NO and SO_2. The binding of these small molecules occurs via the formation of a complexed species with the FLP. Depending on the particular small molecule and the FLPs used, the bound species is able to undergo a wide variety of subsequential reactions.[14]

1.3 Boron heterocycles

Just like boronic acids and boronic ester derivatives, boron heterocycles are able to undergo palladium cross coupling reactions. In those reactions the boron is replaced and substituted to usually facilitate the formation of a carbon-carbon bond.[20]

But the utility of boron in heterocycles goes far beyond being replaced. The topic of boron containing heterocycles is an extremely vast and diverse one. The applications of heterocyclic organoborons span over a multitude of areas in chemistry and medicine. Especially the emergence of frustrated Lewis pairs (FLPs) and the rising interest in metallomimetic main group molecules that can be used to replace transition metals for some applications. [21]

The synthesis of isoelectric analogs of aromatic alongside with the exploration of their commonalities and differences has been another point of interest, due to the similarity between the carbon-carbon double bond and the nitrogen-boron bond. [22]

Boron heterocycles are also very useful in the detection of natural biopolymers, in particular the detection of sugars.[23]

In the rapidly evolving field of photochemistry paths towards highly conjugated, boron containing systems are explored. These highly delocalized electron systems frequently show remarkable optical properties and are of great interest in the research for new organic optical light emitting devices (OLEDs).[21,24]

Other boron heterocycles have been explored for their direct application and there is a number of drugs on the market that contain boron heterocycle moieties.[25]

1.3.1 Aromatic boron containing heterocycles

Aromatic hydrocarbons have been studied extensively due to their unique electronic properties and potential applications in materials science, catalysis, and medicinal chemistry. Incorporating heteroatoms into the aromatic ring system can lead to the formation of new types of aromatic compounds with similar but unique properties. In particular, the incorporation of boron into the ring system has led to the development of a range of boron-containing heterocycles, including boroles and borazines.

The synthesis of cyclic aromatic hydrocarbons containing boron can occur through a wide variety of routes. For example, boron-containing aryl lithium or magnesium reagents can be used in the reaction with halogenated aromatic compounds to form boron-containing aryl compounds. The boron atom can also be introduced through the use of boron-containing coupling agents, such as BBr_3 or B_2pin_2.[26]

Cyclic aromatic hydrocarbons containing boron can also be synthesized through cyclization reactions. For example, boron-containing precursors can be cyclized using transition metal catalysts to form boroles or borazines. Borylene transfer reactions have been extensively studied as a method for the functionalization of organic molecules with boron-containing groups. These reactions can be induced by either photochemical or thermal means and have been found to be highly efficient and selective for the transfer of borylene groups.[26,27]

Photochemical borylene transfer reactions typically involve the use of a photoactive borylene precursor, which can be activated by exposure to light of a certain wavelength. Upon irradiation, the borylene precursor undergoes homolytic cleavage to generate a borylene species, which can then undergo transfer to an organic substrate. The use of photochemical borylene transfer reactions has been found to be highly effective for the synthesis of boron-containing compounds with high regio- and stereo-selectivity.[28]

Thermally induced borylene transfer reactions, on the other hand, involve the use of a thermally stable borylene precursor, which can be activated by heating to a certain temperature. Upon heating, the borylene precursor undergoes homolytic cleavage to generate a borylene species, which can then undergo transfer to an organic substrate. Thermally induced borylene transfer reactions have been found to be highly efficient and selective for the transfer of borylene groups and have been used for the synthesis of a range of boron-containing compounds. The use of transition metal catalysts can help to control the regioselectivity of the cyclization reaction and improve the yield of the desired product.[26,29]

Cyclic aromatic hydrocarbons containing boron exhibit unique electronic properties compared to conventional aromatic hydrocarbons. The boron atom in the ring system acts as an electron-deficient center, which can influence the aromaticity and

electronic properties of the molecule. Boroles, which are five-membered rings containing one boron atom and four carbon atoms, have been found to exhibit highly distorted geometries due to the electronic repulsion between the boron atom and the adjacent carbon atoms.[21,25,26]

Borazines, which are six-membered rings containing alternating boron and nitrogen atoms, have been found to exhibit high thermal stability and strong Lewis acidity due to the presence of the boron atom. The boron atom in borazines can also act as a center for the coordination of transition metal ions, making them potential ligands for catalytic applications.[26,29,30]

In addition to five- and six-membered boron-containing heterocycles, cyclic aromatic hydrocarbons containing boron with three, four, and seven-membered rings have also been synthesized and studied. These heterocycles have unique electronic and chemical properties due to the presence of the boron atom in the ring system. [21,31]

Three membered boron heterocycles constitute the smallest possible heterocycles and they can be subdivided into three different substructures. The borirene motif is made of two carbon atoms and one boron atom and is the unsaturated counterpart of borirane. They are isoelectric with the cyclopropenylium cation which has aromatic character due to its 2π electrons which satisfies Hückel's rule. Borirenes form Lewis acid-base adducts when they react with a Lewis base. This reaction is reversible as the base can be removed by adding $B(C_6F_5)_3$. This means that the aromaticity of these systems can be turned on and off by attaching and detaching a Lewis Base.[26]

The interest in the borirenes is high due to their potential use in molecular electronics and photonics.[27]

Azadiboriridines and triboracyclopropenyl ions are other examples for three membered boron containing ring systems.[26]

1.3.2 Boron-Containing heterocycles in drug discovery

Boron-containing heterocycles have gained significant attention in drug discovery and development due to their unique properties, such as their ability to form various

bonds with biological targets, broad spectrum of pharmacological activities, and metallomimetic properties. Boron-based compounds are effective isosteres, highly specific in eliciting potent pharmacological activities, and typically non-toxic. In addition, these compounds are less complex than their carbon counterparts, and can be produced more easily and cost-effectively in the pharmaceutical industry.[25]

Recent studies have explored the therapeutic potential of boron-containing heterocycles, including diazaborines, azaborines, oxadiazaboroles, oxazaborilidines, boronate esters, and benzoxaboroles. These compounds have demonstrated significant antibacterial and antiprotozoal activity, as well as activity against other biological targets. Additionally, boron-based drugs such as bortezomib and ixazomib have been developed for the treatment of multiple myeloma and mantle cell lymphoma, demonstrating potent bioactivity with various molecular mechanisms.[21,25,27,31]

The possibilities for the use of boron containing heterocycles in drug discovery seem to be everything but exhausted. The use of boron based compounds for the treatment of neurodegenerative diseases has been severely underexplored, even though they show promising properties for combatting certain aspects of Alzheimer's disease, while also being able to easily cross the blood brain barrier.[25]

1.3.3 Boron containing heterocycles for the use in biosensors

The selective recognition of complex carbohydrates in physiological conditions is challenging due to the competition between the multiple hydroxyl groups on the carbohydrates and the overwhelming ones from the bulk solvent, water. Synthetic receptors for the recognition of complex carbohydrates in organic solvents have been described, but it is notoriously difficult to achieve the same success under physiological conditions. [25]

Benzoboroxoles have emerged as an interesting class of compounds for the recognition of sugars in water due to their unique binding properties. In contrast to normal boronic acids, benzoboroxole has the capability of complexing glycopyranosides efficiently in neutral water, which means that they can be active under physiological conditions. The measurement of association constants with a

panel of model hexopyranosides indicates that the preferred mode of binding is through a cis-3,4-diol, such as that found in galactopyranosides, and mass spectrometric studies support a 1:1 binding stoichiometry. The complexation of glucopyranosides is weaker, and they are bound through their 4,6-diol unit. The relatively high Lewis acidity of benzoboroxoles is a likely contributing factor to their exceptional affinity for binding carbohydrates, along with subtle factors such as intramolecular hydrogen bonds with other hydroxyl groups in the resulting anionic complex. The unique binding properties of boron and specifically benzoboroxoles offer a big potential applications in chemical biology and medicine. The development of a selective and noninvasive molecular sensor for monitoring blood glucose has long been sought as a key component of insulin-releasing implants for diabetes patients. With further development of the benzoboroxoles this might soon become reality. The selective recognition of glucose in water by benzoboroxoles is another attractive avenue, especially for bioanalytical chemists. Other potential applications include the sensing, transport, and purification of complex carbohydrates, as well as the targeting of biologically relevant cell-surface oligosaccharides using oligomeric benzoboroxole receptors. The potential that benzoboroxoles have as biosensors, markers and transporters of biomolecules is definitely underappreciated and underexplored[23,32,33]

1.3.4 Optical properties

Boron heterocycles exhibit several interesting photophysical properties, including fluorescence, phosphorescence, and photothermal conversion. The fluorescence of boron heterocycles arises from the excited state of the boron atom, which can be populated by absorbing light. The fluorescence emission of these compounds is typically in the blue to green region of the spectrum, making them useful for applications in organic light-emitting diodes (OLEDs) and fluorescence imaging.[34–36]

Phosphorescence, on the other hand, arises from the triplet state of the boron atom, which can also be populated by absorbing light. The phosphorescence emission of boron heterocycles is typically in the red to near-infrared region of the spectrum,

making them useful for applications in phosphorescence imaging and as triplet sensitizers in triplet-triplet annihilation-based conversion.[37,38]

Boron heterocycles also exhibit photothermal conversion properties, where the absorbed light is converted into heat. This property has been used in photothermal therapy for cancer treatment.[39]

1.3.5 Semiconductors

Boron containing compounds are a staple of the field of semiconductor research as boron semiconductors were shown to display ambipolar mobility. Ambipolar means that they are capable of rapidly conducting both holes as well as electrons. A high ambipolar mobility means that little energy is lost to heat, which in turn means that the system is less likely to lose conductivity due to increased heat. Other promising boron compounds for the field of semiconductor research include a boron fullerene analogue. These B_{40} borospherenes represent crystalline boron quantum dots (BQDs) that can be injected into synthetic polymers to create semi conducting polymers. Boron doped nanoribbons represent powerful semiconductive polymers that form boron heterocycles.[40–43]

Others boron heterocycles that came into the focus of study in the search for new semiconductors are oxazaborinines. These BON containing heterocycles are air stable and have among a plethora of other attractive attributes interesting characteristics for semiconductors.[44]

Bigger conjugated diazaborate systems have been found to also have great semiconducting qualities. They, however, have been of particular interest in the research concerning itself with OLEDs and infrared light harvesting. This opened up the development of novel photoelectric dyes for the application in photovoltaics. Nowadays these 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes and their derivatives tend to be highly absorbing in the UV range as well.[22,40,45]

5,5′-bis(dimesitylboryl)-2,2′-bithiophene (BMB-2T) and 5,5″-bis-(dimesitylboryl)-2,2′:5′,2″-terthiophene (BMB-3T) are another boron containing heterocyclic system that exhibits promising electron transferring properties. For the charge carrier

transport, the presence of a π-electron system is essential. BMB-2T and BMB-3T analogously undergo reversible cathodic reductions.[46,47]

1.4 Palladium-catalyzed cross-coupling of organoboron compounds

Organoboron compounds are important reagents in organic chemistry and have been widely used in various coupling reactions. These reactions are a powerful tool for the formation of a new carbon-carbon bond between two organic molecules, resulting in the synthesis of a more complex molecule. The creation of a new carbon-carbon bond is a key step in the synthesis of many important chemicals and pharmaceuticals and essential to the mission of synthetic organic chemistry.

While Heck initially observed that boronic acids were able to undergo coupling when stoichiometric amounts of palladium were employed, it was Negishi and coworkers who were the first to identify alkenylborons as possible coupling counterparts for palladium-catalyzed cross-coupling reactions. This was further expanded by Suzuki and Miyaura who recognized and realized the coupling capabilities of organoboron compounds.[48]

One important factor for the way an organoboron compound behaves in coupling reactions is the hybridization state of boron, as it determines the three-dimensional structure of a given molecule.[49]

The sp^2 hybridization results in a planar geometry, the sp^3 hybridization results in a tetrahedral geometry, and the sp^3d hybridization results in a trigonal bipyramidal geometry. The presence of suitable ligands, such as alkoxy groups, amines, and alkyl groups, can influence the hybridization state of boron and the reactivity and stability of the resulting compound. Whenever sp^2 hybridized boron reagents like boronic acids are employed, the use of an activating species is required, usually in form of a base. The activation increases the previously weak nucleophilic character of the organic moiety, which allows for the migration reaction to the adjacent positive center.[50]

One of the most common types of coupling reactions involving organoboron compounds is the previously mentioned Suzuki coupling. This reaction involves the

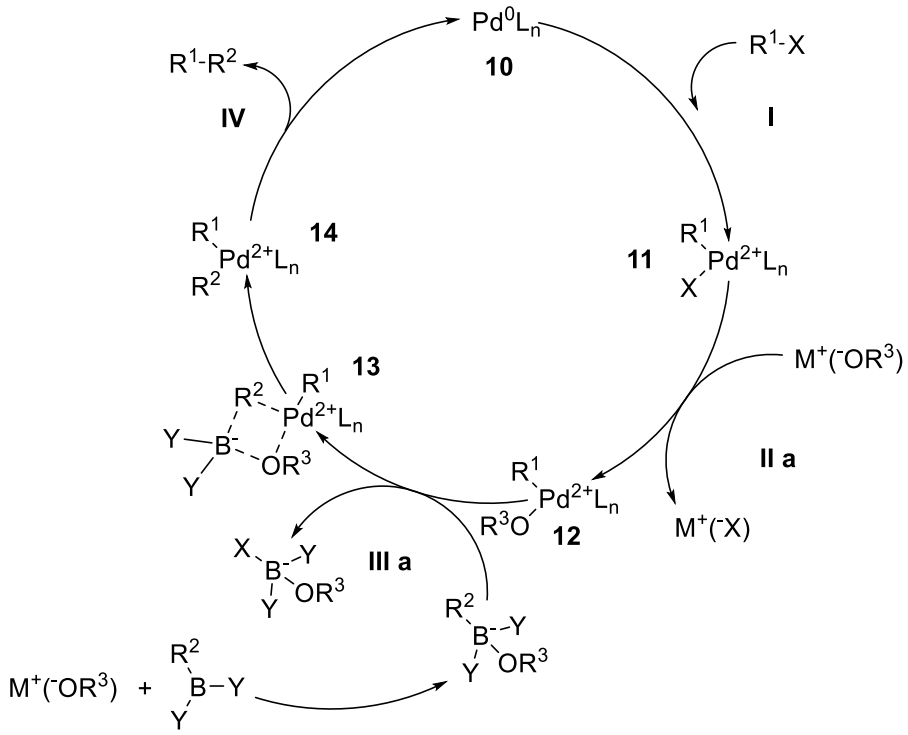
coupling of an organoboron compound with an aryl or alkyl halide using a palladium catalyst. The resulting product is an aryl or alkyl-substituted organoboron compound. The Suzuki coupling is a highly efficient and widely used synthetic method that employs organoboron compounds. It is exceptionally useful in the synthesis of elaborate targets.[50]

Another common type of coupling reaction in which organoboron compounds find application is a modified Sonogashira coupling. This version of the reaction involves the coupling of an organoboron compound with an aryl or alkyl acetylene using a palladium catalyst. The resulting product is an aryl or alkyl-substituted compound. The Sonogashira coupling is a highly efficient and widely used method for the synthesis of a wide array of compounds and is particularly useful for the synthesis of complex molecules.[51]

Other coupling reactions in which organoboron compounds can be used include the Negishi coupling, the Hiyama coupling, and the Buchwald-Hartwig amination. These reactions are also highly efficient and widely used methods for the creation of carbon-carbon bonds and are particularly useful for the synthesis of complex molecules.[48]

1.4.1 Suzuki coupling

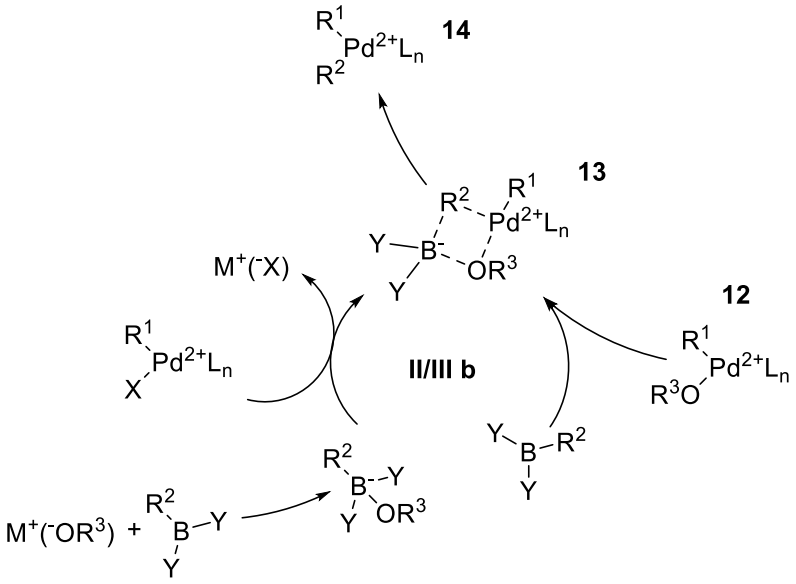
Suzuki coupling is a widely used chemical reaction that allows for the synthesis of carbon-carbon bonds between two aryl or alkenyl halides and an organoboron compound. The method was first published in 1981 by Suzuki and Miyaura. It is named after the former, Akira Suzuki, who was awarded the Nobel Prize in Chemistry in 2010, alongside of Heck and Negishi, for his contributions to the development of this reaction.[48,52]



Scheme 4 - general scheme of a Suzuki coupling reaction

To this day there remain a few mysteries regarding the exact mechanism and intermediates of the reaction. However, the general mechanism of the coupling process can be described in four steps as described in Scheme 4, with the first being the oxidative addition of an organohalide to a Pd^0 complex **10**. This step is labeled step **I** in the scheme above. During this stage the bond between the carbon and the halogen atom of the organohalide is broken and transferred to the palladium, which leads to formation of the palladium complex **11**. The palladium is oxidized in this process, changing its oxidation state from Pd(0) to Pd(II).

A sigma-bond metathesis constitutes the second step **II** of the cross coupling, although it is sometimes combined with step **III**. At this stage of the reaction, a hydroxide or alkoxide displaces a halide or pseudo halide and attaches to the palladium to give the intermediate **12**. The exact sequence of this step and the one that follows are disputed and might differ according to the organoboron that's used. An alternative is presented as **II/III b**.



Scheme 5 - alternative proposed routes for the metathesis and transmetalation steps

Step three is the transmetalation between an organoboron reagent and a Pd(II) complex and is described in more detail in Scheme 5. There are multiple paths that lead to the intermediate species **13** active during the transmetalation depending on the reacting species and even specific reaction conditions. This intermediate sets the organoboron compound and the palladium catalyst up to undergo another sigma-bond metathesis to afford the diorganopalladium complex **14**.

The reductive elimination **IV** concludes the coupling cycle and generates the desired carbon-carbon bond and regenerates the Pd catalyst as the Pd(II) complex **14** gets reduced back to its original Pd(0) state **10**.[53]

In summary, the Suzuki reaction is typically performed in the presence of a palladium catalyst and a base, such as sodium carbonate or sodium hydroxide. The palladium catalyst activates the aryl or alkenyl halide and the organoboron compound, facilitating the coupling reaction. The base acts to activate the

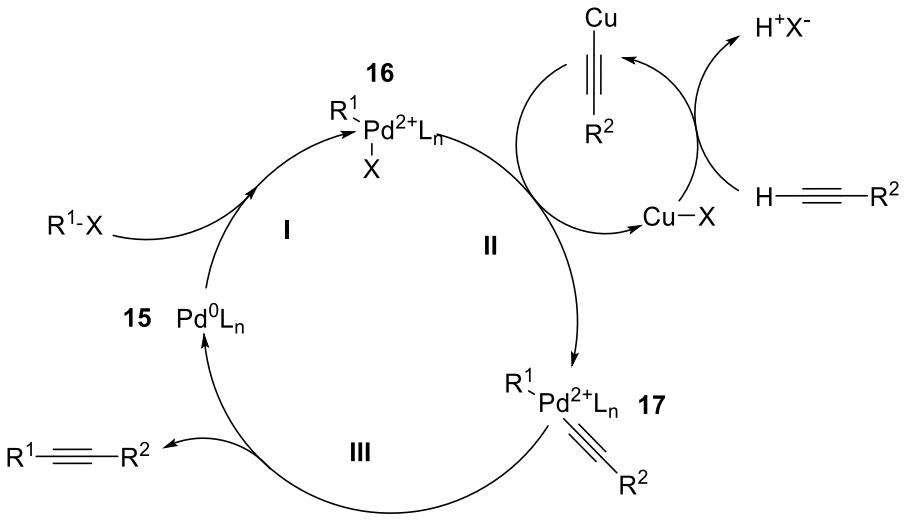
organoboron compound and facilitate the transfer of the aryl or alkenyl group to the palladium catalyst.

One of the main advantages of Suzuki coupling is its high efficiency and versatility, as it can be used to synthesize a wide range of aryl and alkenyl compounds with good yields. It is also highly regioselective, meaning that it typically favors the formation of a single isomer over other possible isomers.

There are several variations of the Suzuki coupling reaction, including the use of different palladium catalysts, bases, and solvents. In addition, the reaction can be performed in the presence of various functional groups, such as esters, amides, and ketones, without significant loss of yield or selectivity.[48]

1.4.2 Sonogashira Coupling

The Sonogashira coupling reaction was introduced in 1975 by Kenkichi Sonogashira and typically involves the use of a palladium catalyst, such as palladium acetate or palladium(II)chloride, in combination with a copper salt, such as copper(I)iodide. Cassar as well as Heck also independently reported coupling reactions with aryl or vinyl halides with terminal acetylenes in 1975, their reactions however did not include the Cu(I) cocatalyst and thus required considerably harsher conditions. The reaction is typically carried out in the presence of a base, such as potassium carbonate, and is usually performed in an inert solvent, such as toluene, tetrahydrofuran, or dimethylformamide.[54]



Scheme 6 - general Sonogashira coupling cycle

The Sonogashira coupling reaction follows the same general oxidative addition – reductive elimination cycle as the Suzuki cross-coupling. Another similarity is that some details of the reaction remain unknown. Particularly the precise role of the copper species is not yet fully understood. The general mechanism is illustrated in Scheme 6.

Step **I** is the previously described oxidative addition of an sp^2-carbon containing halide. The organohalide is couples electrophilically to the Pd(0) complex **15**. During

this process, both the organic moiety and the halide bind to the Pd center and the bond connecting them is broken, giving the Pd(II) complex **16**.

Step **II** may be considered to involve a second sub-cycle, which is suspected of providing a transient copper acetylene species from the reaction of a terminal alkyne with a copper halide. The copper alkyne species reacts with the Pd(II) complex **16** to afford the complex **17** and remove the X-ligand in a transmetalation reaction.

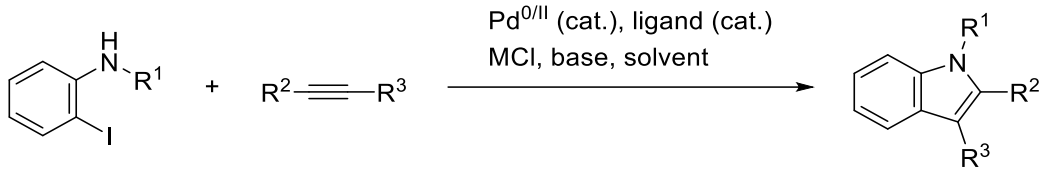
In step **III**, the two organic groups are reductively eliminated to form the final coupled product and the Pd(II) complex **17** is reduced to the initial Pd(0) species **15**.

One of the key advantages of the Sonogashira coupling reaction is its ability to form carbon-carbon bonds under mild conditions, which makes it a useful method for the synthesis of a wide range of organic compounds. Additionally, the reaction can be easily performed on a large scale, making it a practical and efficient method for the synthesis of complex molecules in large scale production. Modifications of the Sonogashira reaction include the use of organoboron compounds as coupling partners, the inverse Sonogashira reaction and the direct alkynation.[51]

The Sonogashira coupling reaction has been used in the synthesis of a variety of important organic compounds, including natural products, pharmaceuticals, and other functional materials. For example, the reaction has been used in the synthesis of the anti-cancer drug Eniluracil and the antifungal drug Lamisil.[55] In addition, the reaction has been used in the synthesis of polymers, dyes, and other materials with important industrial applications.

1.4.3 Larock heteroannulation

The ring closure and carbon-nitrogen bond formation, that follows the initial carbon-carbon bond formation at the ortho-position in this work, was designed based on the Larock indole synthesis, also known as the Larock heteroannulation. The Larock heteroannulation reaction is an organic synthesis method that allows for the formation of heterocyclic compounds from acyclic, nitrogen-bearing precursors. This reaction, which was first reported by Richard C. Larock in 1980, has become a widely used method for the synthesis of various heterocyclic compounds, including those with important pharmaceutical applications.[48]



Scheme 7 - generic Larock cyclization reaction

The Larock heteroannulation reaction typically involves the use of a metal catalyst, such as palladium or copper, in combination with a base, such as sodium hydroxide. The reaction typically involves the formation of a carbon-carbon bond between two functional groups on the acyclic precursor, usually with an iodine on the ortho-position, that functions as a bulky leaving group, making the ortho-position available for the formation of a new bond. It constitutes a powerful method to build heterocyclic molecules by the intramolecular creation of a bond between a carbon and a nitrogen that sit on the same molecule.

One of the key advantages of the Larock cyclization reaction is its ability to form complex cyclic structures from simple precursors. This makes it a useful method for the synthesis of heterocyclic compounds, which are often found in natural products and pharmaceuticals. Additionally, the reaction can be easily performed on a large scale, making it a practical and efficient method for the synthesis of complex molecules, even on the level of industrial manufacturing.[52]

The Larock cyclization reaction has been used in the synthesis of a variety of important organic compounds, including natural products, pharmaceuticals, and other functional materials. For example, the reaction has been used in the synthesis of the anti-inflammatory drug celecoxib and the anti-cancer drug irinotecan. The reaction has also been utilized in the synthesis of dyes and other materials that have significant industrial uses.[56]

2 Objectives

This research project will primarily focus on preparing heterocyclic benzoborosulfonamides with the general structure **(5)** via Directed ortho-Metalation chemistry developed by Snieckus and utilized in the Allegheny College Chemistry Department's lab for the synthesis of a selection of boron heterocycles. These heterocyclic benzoborosulfonamides contain either sp^2 or sp^3 hybridized boron and are stable under standard conditions. The characterization via NMR spectroscopy of these compounds will take a central role in this research.

Once protocols for the synthesis of these boron heterocycles have been established and investigated, their suitability as palladium-catalyzed coupling counterparts en route to benzosultams will be tested according to the highlighted bonds in Figure 2.

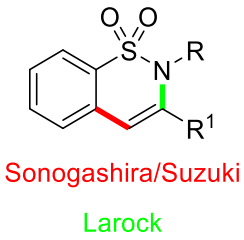
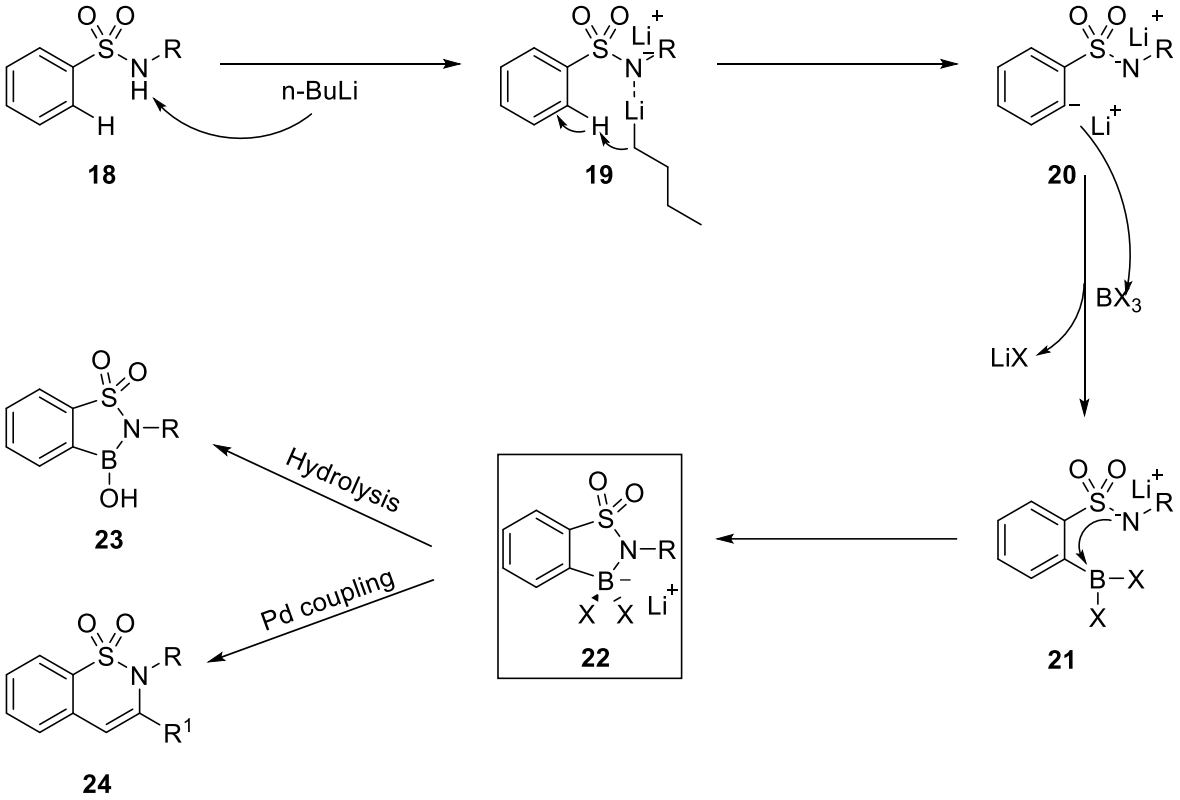


Figure 2 – A general structure of a benzosultam with the newly established bonds highlighted and labeled

Furthermore, an effort will be made towards establishing suitable monitoring and analysis protocols.

3 Results and Discussion

The primary focus of this work was the preparation of novel boron heterocycles.



Scheme 8 - Directed ortho-Metalation of a Sulfonamide with general structure **10**; X … F, OR (R ≠ H)

The directed ortho-metalation method developed by Victor Snieckus is utilized in this reaction to generate the ortho-deprotonated dianion **(20)**. To prepare the dianion, an aryl sulfonamide **(18)** is treated with an alkyllithium base. At least 2 molar equivalents of the base are necessary. First, the proton on the nitrogen gets cleaved off, as it is more acidic than the proton in the ortho-position **(19)**, which becomes accessible only after the first equivalent base reacted. The formation of the dianion is complete when the second equivalent of the base has reacted to perform the ortho-deprotonation.

The dianion exists as a highly reactive species, as the loss of the ortho-proton and resulting additional p-electron upsets the compounds aromaticity. This reactive dianion undergoes a Lewis acid-base reaction with the boron first being attacked by

the carbon in the ortho-position, that now bears a negative charge. The regioselective formation of this boron-carbon bond reinstates the compounds aromaticity and results in an sp^2 hybridized boron containing moiety. This boron atom is susceptible to a nucleophilic attack by the nitrogen atom, carrying a negative charge. This intramolecular cyclization reaction results in the formation of the heterocyclic boronate intermediate **(22)**. The negative charge, previously situated on the nitrogen atom is now located on the boron, which changes its hybridization state to sp^3, leading to tetrahedral bond angles. The formation of this ate complex was easily observable by the use of ^{11}B NMR spectroscopy. This change in hybridization is a key feature of the intermediate and is essential for the successful completion of the reaction. The resulting hydrolyzed boron heterocycle **(23)** was isolated and characterized, allowing for further analysis and study of this important compound.

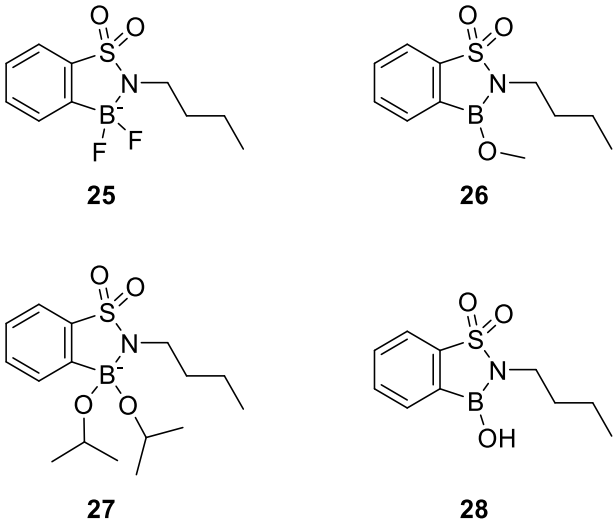


Figure 3 - boron heterocycles prepared over the course of this work

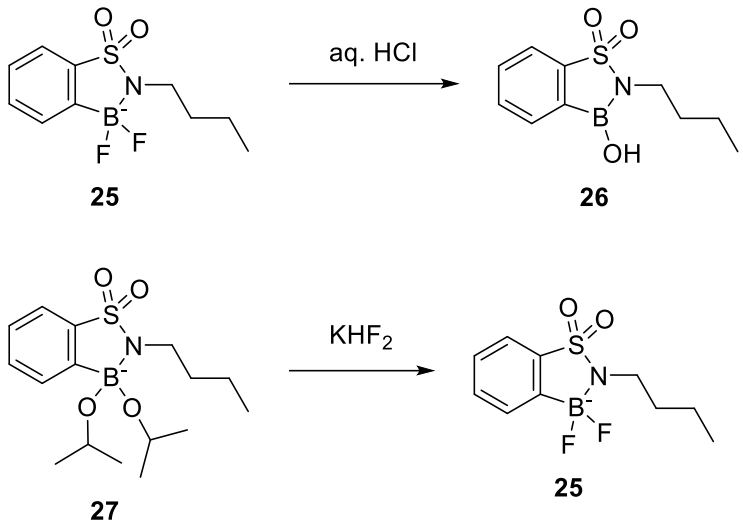


Figure 4 - transformation reactions of prepared boron heterocycles

This figure outlines transformations of two heterocycles **(25)** and **(27)**. The aim of these transformations was to showcase and explore the utility and versatility of these novel heterocycles. All of them were stable under standard temperature and even more importantly, not susceptible to oxygen and moisture. The compounds were entirely present as clear crystalline products.

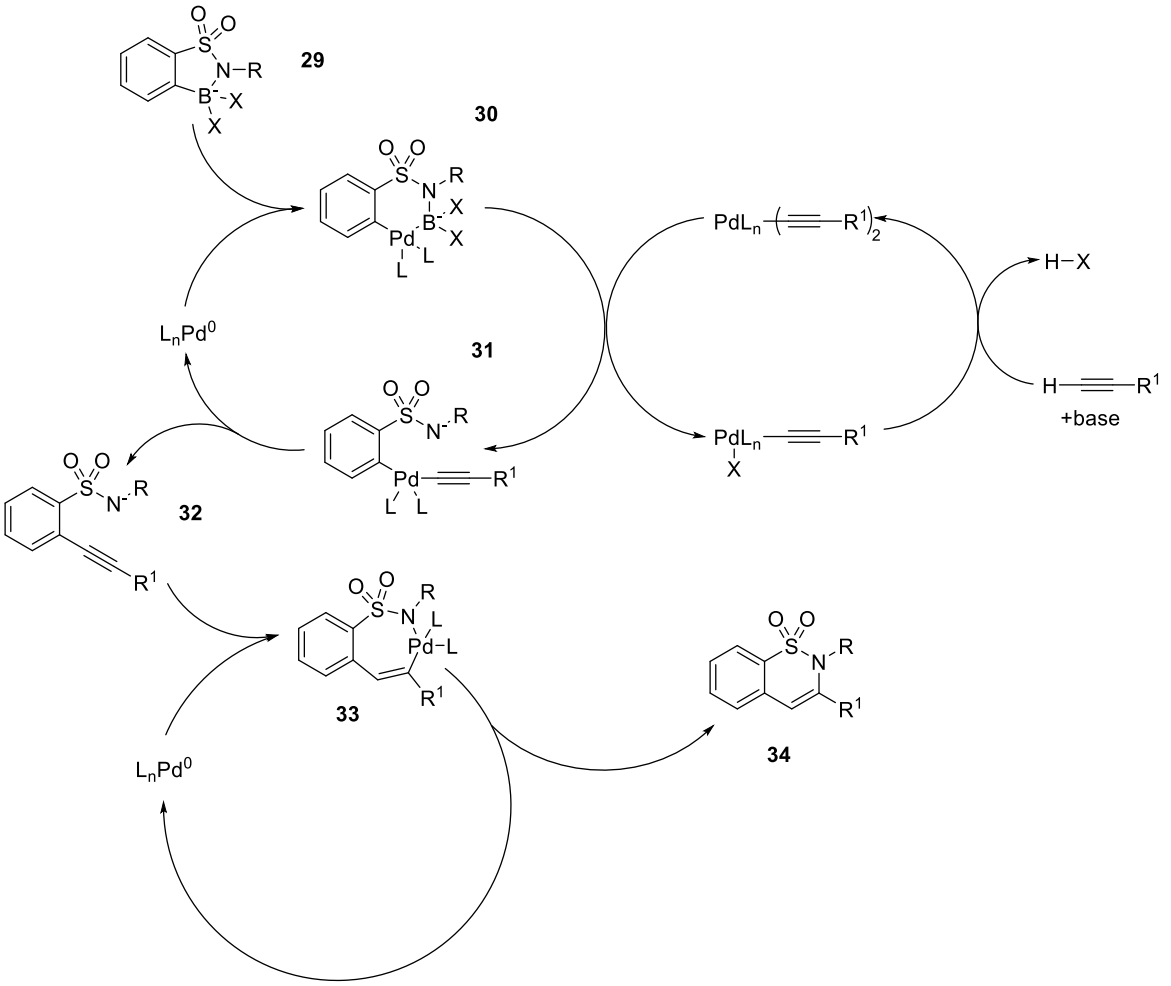
The methodology developed in this work opens up an avenue to synthesize complex substituted boron heterocycles. These heterocycles are of interest for various applications in different fields of chemistry. In organic synthesis, the heterocycles might be used as building blocks for the synthesis of more complex molecules. A number boron-containing heterocycles have been used to synthesize drugs and other bioactive compounds. In the field of materials science, boron-containing heterocycles have been used as building blocks for the synthesis of new materials with interesting properties. Boron-containing polymers have been developed for use in electronic and optical devices.

But maybe most enticing are the possibilities for the field of catalysis. boron-containing heterocycles have been used as Lewis acid catalysts in various chemical reactions. The steric rigidity of the heterocycle and bulkiness of the aryl moiety of the prepared heterocycles are promising attributes for the use in FLP chemistry and asymmetric synthesis.

The prepared heterocycles were subjected to coupling conditions, with the aim to achieve a tandem coupling reaction as outlined in scheme 9.

Several coupled species were synthesized in this manner, but the final benzosultam was not isolated and purified. This is only a matter of optimized coupling conditions, however and should be further investigated as there was evidence of coupling. This would further cement the importance of these molecules and contribute greatly to the field of organic synthesis. A possible reaction mechanism postulated can be seen in Scheme 9.

All in all it can be said that these novel boron containing heterocycles are very promising for a wide array of fields and the elegant methodology that comes with it allows for the necessary flexibility in the modification and substitution of the heterocycles. This flexibility makes them exciting candidates for the application as Lewis acids, as drug candidates in medicinal and pharmaceutical chemistry, in organic synthesis as a potential activator for small molecules in conjunction with a weak Lewis base, in photochemistry and as a potential part of new semiconductor technology. Due to the built in rigidity and steric complexity of heterocyclic boron containing compounds, they will most likely find some utilization in the evermore important field of asymmetric synthesis. The complexity of the π-system created by the unique nature of the bond between nitrogen and boron only adds to the fascinating nature of these novel heterocycles.



Scheme 9 – Possible mechanism of a concerted Sonogashira coupling and Larock-type cyclization

4 Experimental

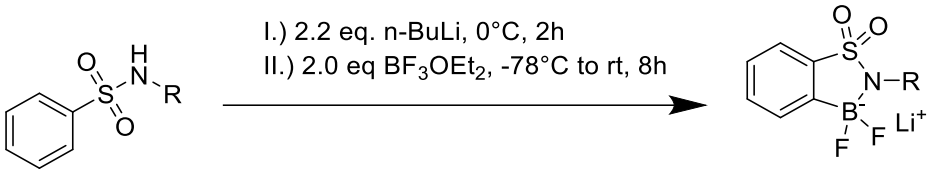
General

Reagents, purchased from Sigma Aldrich were used throughout without further purification unless otherwise noted. Reactions were routinely carried out under Nitrogen atmosphere using oven-dried glassware. A JEOL JNM-ECP 400 FT-NMR spectrometer was used to obtain ^{1}H-NMR (400MHz), ^{11}B-NMR (126.4MHz), ^{13}C-NMR (100MHz) and ^{19}F-NMR (376MHz). For monowave reactions, the Anton Paar Microwave Synthesis Reactor Monowave 400 (Type), P/N:163523 S/N:83937941 was utilized.

Reaction of N-butylbenzensulfonamide with triisopropyl borate

A dry 25 ml round bottom flask was flushed with nitrogen and charged with N-butylbenzenesulfonamide (3 mmol) and 15 ml tetrahydrofuran. This mixture was stirred and cooled to 0°C in an ice/brine bath. After the reaction was allowed to cool down, 2.2 equivalents of n-BuLi (2.5 M in Hexane; 6.6 mmol) were added dropwise with a syringe. The resulting mixture was left to stir for 2 hours. Next, the reaction was cooled to -78°C in a dry-ice/acetone bath. Under maintained temperature and nitrogen atmosphere, 3 equivalents of triisopropyl borate (9 mmol) was added dropwise via syringe. The temperature was left to stir at -78°C for 2 hours. After the 2 hours passed, the reaction was removed from the dry-ice bath and allowed to slowly warm up to room temperature, while stirring. The mixture was left stirring for 8 hours. The solution first quenched with 5 ml of saturated ammonium chloride solution and then, using aqueous HCl, brought to a pH of ~5. This was monitored using pH paper. The acidified solution was extracted 3 times with 10 ml of ethyl acetate and washed with 3 times with 10 ml of water and 3 times with 10 ml brine. The organic layers were dried over $MgSO_4$, and excess solvent was removed under reduced pressure.

1H NMR (400 MHz, METHANOL-D4) δ 7.66 (d, J = 6.8 Hz, 1H), 7.39 (h, J = 6.4 Hz, 2H), 7.19 – 7.13 (m, 1H), 2.92 (p, J = 7.9 Hz, 2H), 1.46 (h, J = 7.0 Hz, 1H), 1.15 (h, J = 7.1 Hz, 2H), 0.72 (t, J = 7.4 Hz, 3H).



Scheme 10 - Synthesis of the heterocyclic benzenesulfonamide boron-ate complex

Reaction of N-butylbenzenesulfonamide with boron trifluoride diethyl etherate

A 25 ml round bottom flask was charged with N-butylbenzenesulfonamide (3 mmol) and 15 ml tetrahydrofuran. This mixture was stirred and cooled to 0°C in an ice/brine bath. After the reaction was allowed to cool, 2.2 equivalents of *n*-BuLi (2.5 M in hexane; 6.6 mmol) were added dropwise with a syringe. The resulting mixture was left to stir for 2 hours. Next, the reaction was cooled to -78 °C in a dry-ice/acetone bath. Under maintained temperature and nitrogen atmosphere, 3 equivalents of boron trifluoride diethyl etherate (9 mmol) was added dropwise via syringe. The temperature was left to stir at -78 °C for 2 hours. After the 2 hours passed, the reaction was removed from the dry-ice bath and allowed to slowly warm up to room temperature, while stirring. The mixture was left stirring for 8 hours. The resulting solution was extracted with ethyl acetate and washed 3 times with 10 ml of water and 3 times with 10 ml of brine. The organic layer was dried over $MgSO_4$ and excess solvent was removed under reduced pressure.

1H NMR (400 MHz, METHANOL-D4) δ 7.66 (d, J = 6.8 Hz, 1H), 7.39 (h, J = 6.4 Hz, 2H), 7.19 – 7.13 (m, 1H), 2.92 (p, J = 7.9 Hz, 2H), 1.46 (h, J = 7.0 Hz, 1H), 1.15 (h, J = 7.1 Hz, 2H), 0.72 (t, J = 7.4 Hz, 3H).

Reaction of N-butylbenzenesulfonamide with trimethyl boroxine

A 50 ml round bottom flask was charged with N-butylbenzenesulfonamide (5 mmol) and 25 ml tetrahydrofuran. This mixture was stirred and cooled to 0°C in an ice/brine bath. After the reaction was allowed to cool down, 2.2 equivalents of n-BuLi (2.5 M in Hexane; 11 mmol) were added dropwise with a syringe. The resulting mixture was left to stir for 2 hours. Next, the reaction was cooled to -78°C in a dry-ice/acetone bath. Under maintained temperature and nitrogen atmosphere, 1.4

equivalents of trimethoxy boroxine (7 mmol) was added dropwise via syringe. The reaction was left to stir at -78°C for 2 hours. After the 2 hours passed, the reaction was removed from the dry-ice bath and allowed to slowly warm up to room temperature, while stirring. The mixture was left stirring for 8 hours. The resulting solution was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. It was subsequently washed 3 times with 20 ml of water and 3 times with 15 ml of brine. The organic layer was dried over $MgSO_4$ and excess solvent was removed under reduced pressure.

1H NMR (400 MHz, METHANOL-D4) δ 7.66 (d, J = 6.8 Hz, 1H), 7.39 (h, J = 6.4 Hz, 2H), 7.19 – 7.13 (m, 1H), 2.92 (p, J = 7.9 Hz, 2H), 1.46 (h, J = 7.0 Hz, 1H), 1.15 (h, J = 7.1 Hz, 2H), 0.72 (t, J = 7.4 Hz, 3H).

Coupling of boron heterocycle (25) with Tetrakis(triphenylphosphine)palladium(0) and phenylacetylene

A dry 15 ml round bottom flask was with 200.0 mg (0.75 mmol) of compound **(25)**, that were dissolved in 3 ml of dry THF. A separate dry 15ml round bottom flask was loaded with $[Pd(PPh_3)_4]$ (22.0 mg; 2.3 mol%), PPh_3 (10.4mg; 5.0 mol%) and phenylacetylene (0.11 ml; 1.0 mmol). Catalyst, ligand and phenylacetylene were stirred for 10 minutes under nitrogen. The dissolved heterocycle **(25)** was added to the reaction flask via cannula. The reaction was stirred at room temperature over the course of 48 hours.

Coupling of boron heterocycle (25) with Tetrakis(triphenylphosphine)palladium(0) and allyl bromide

A 25 ml round bottom flask was charged with N-butylbenzenesulfonamide (3 mmol) and 15 ml tetrahydrofuran. This mixture was stirred and cooled to 0°C in an ice/brine bath. After the reaction was allowed to cool down, 2.2 equivalents of n-BuLi (2.5 M in Hexane; 6.6 mmol) were added dropwise with a syringe. The resulting mixture was left to stir for 2 hours. Next, the reaction was cooled to -78°C in a dry-ice/acetone bath. Under maintained temperature and nitrogen atmosphere, 3 equivalents of boron trifluoride diethyl etherate (9 mmol) was added dropwise via syringe. The temperature was left to stir at -78°C for 2 hours. After the 2 hours

passed, the reaction was removed from the dry-ice bath and allowed to slowly warm up to room temperature, while stirring. The mixture was left stirring for 8 hours. To the reaction flask, which was considered to contain 5 mmol of compound **(25)**, a suspension of $[Pd(PPh_3)_4]$ (288.9 mg; 5.0 mol%), PPh_3 (1382.1 mg; 10.0 mol%) and allyl bromide (0.52 ml; 6.0 mmol) in THF was added via cannula. The reaction was stirred at room temperature over the course of 48 hours and the resulting mixture separated via column chromatography.

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