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AMINES CATALYSE ORGANOBORONE REACTIONS

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Tarragona
2016

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1. Abstract

The versatility of carbon-boron bond as a platform for chemical transformations has attracted the attention of many researchers aiming to develop new methodologies to have access to new organoboron compounds. Recently, organocatalytic methodologies have raised as real alternative to the transition metal methodologies. The goal of this project is to expand the current organocatalytic methodologies and develop a new and milder organocatalytic methodologies towards the synthesis of diboron compounds whit a broader functional group compatibility. During this study a novel methodology for the organocatalytic activation of diboron compounds have been discovered and we have explored their use towards a selective diboration of alkenes.

2. Objectives

The formation of new C-B bonds have a higher interest since the organoboranes are key intermediates in fine chemical and pharmaceutical industry. This project emphasizes the development of new transition metal free methodologies for boron addition to olefins.

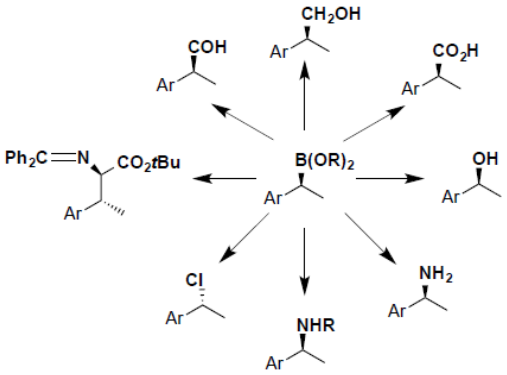
The aim of this study is:

- Develop of a novel methodology for the amine catalayse diboration reaction of alkenes.
- Explorer the scope of this new methodology
- The mechanistic study of the reaction.

3. Introduction

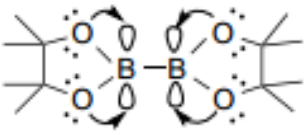
3.1. General introduction

Organoboron derivatives are recognized as a crucial class of compounds and it have an extended use as synthetic intermediates [1], functional molecules [2], functional polymers[3], ^{10}B carriers for neutron capture therapy [4], and biologically active agents [5]. Thus, organoboron derivatives are a versatile tool in organic synthesis because, once the C-B bond is formed, it can be transformed to new C-O, C-N, C-C and C-X bonds (Scheme 1).



Scheme 1: Possible transformations of C-B bond

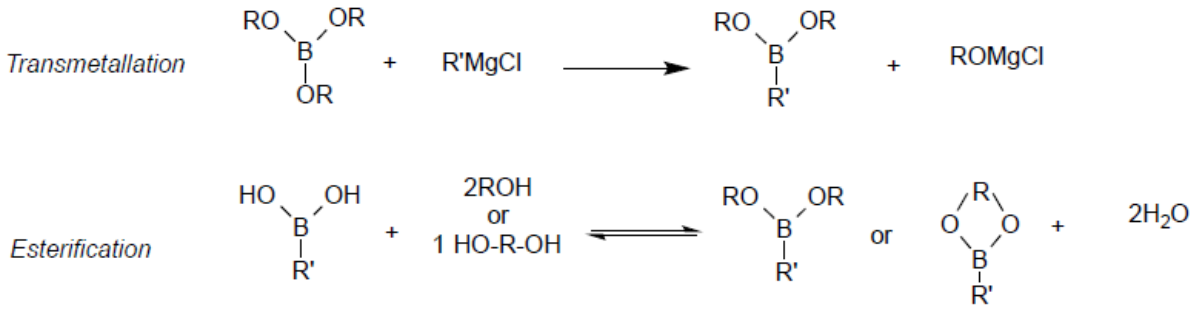
Among all organoborane compounds, organoboronic esters are usually the most utilized in synthesis. This preference is a result of its stability, availability and it's functional applicability in synthetic methods, against boranes, which are unstable to air and moisture and can't be purified by silica gel chromatography. The higher stability of boronic esters in contrast of the boranes is due to the lone pair of the oxygen atoms that partially fill the empty *p*-orbital of the boron (Scheme 2).



Scheme 2: Lone pair of oxygen stabilizing the empty p-orbitals of the boron

Regarding the stability, the nature of the organoboronic esters has an influence on it. For instance, bulky, aliphatic and cyclic organoboronic ester derivatives are, frequently, more stable. However, unhindered, aromatic and acyclic compounds are less stable by presenting sensitivity to the air, water, and silica gel [6].

Furthermore, a wide range of organoboronic esters is commercially available or can be obtained by an easy process of synthesis. Commonly, there are two paths to synthesize boranes compounds: by transmetallation or esterification of organoboronic derivatives (Scheme 3).

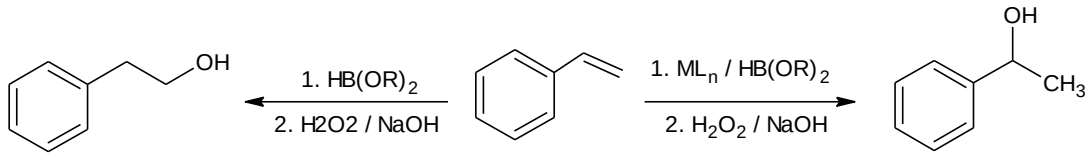


Scheme 3: Transmetallation and esterification of organoboronic derivatives

Hydroboranes and diboranes are the main categories of borane reagents that can be inserted in unsaturated two compounds. However, in this literature review we will mostly focus on the diboranes due to the importance for this research project.

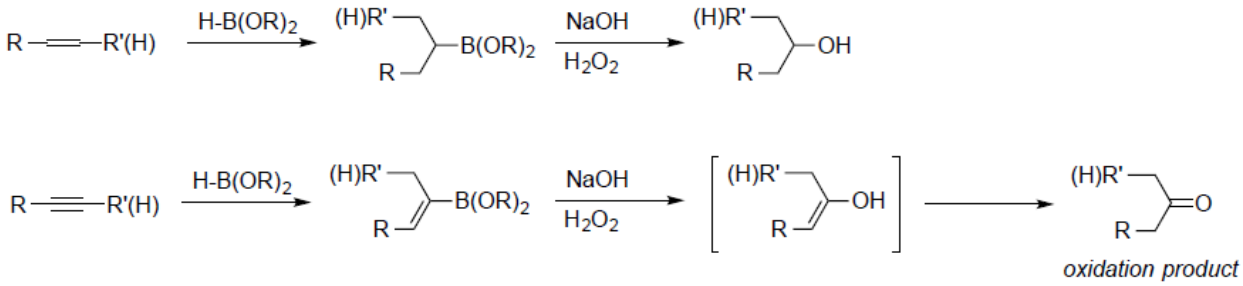
3.2. Hydroboranes

The preferred reagent to do the addition of one boryl moiety and a hydride into an unsaturated molecule is hydroborane. In hydroboration reaction, the hydride undergoes to a syn fashion addition with the boryl group. Generally, hydroboration follows an anti-Markovinikov selectivity but this can be modified with the use oftransition metals catalyst (Scheme 4).



Scheme 4: Regioselectivity of hidroboranes

Regarding alkenes and alkynes, hydroboration afford a convenient synthesis path towards alcohols, ketones and aldehydes (Scheme 5).



Scheme 5: Hydroboration of unsaturated compounds

The most commonly used dialkoxiborane (Figure 1) reagents are catecholborane and pinacolborane. Through a borane reaction, is possible to prepare easily these boranes and also the correspondent alcohol.

In comparison, catecholborane is more Lewis acidic, more reactive and more sensitive to hydrolysis than pinacolborane. Thus, the positive resonance effect of the phenolic oxygens in the direction of the benzene ring is there as on that decreases the π-donation from the oxygen atom to the boron atom.

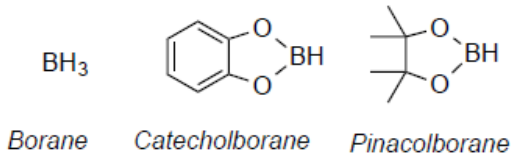
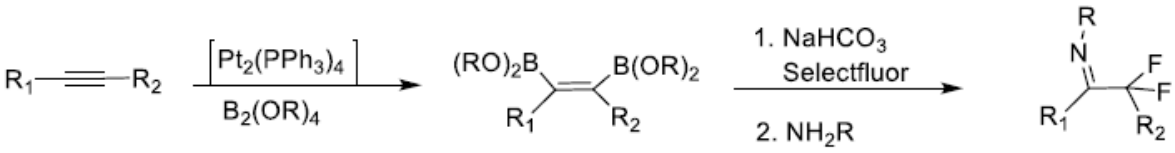


Figure 1: The most used types of boranes

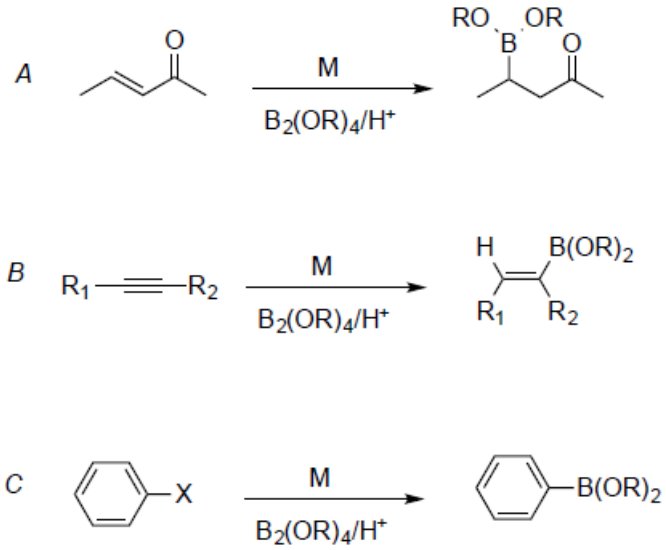
3.3. Diboranes

Diboranes are used in order to introduce two boryl units to an unsaturation. This reaction is called diboration and the addition follow a *syn* stereochemistry. Once the boryl units are introduced in the substrate, it can be further functionalized independently one of the other [7] (Scheme 6).



Scheme 6: Boron units from diboranes reacting independently

The use of diboron reagents is wide spread into various reactions, not only for diboration reactions, but also for β-boration, hydroboration and borylation(Scheme 7).



Scheme 7: Reactions regarding diboron compounds: β-boration (A), hydroboration (B) and borylation (C)

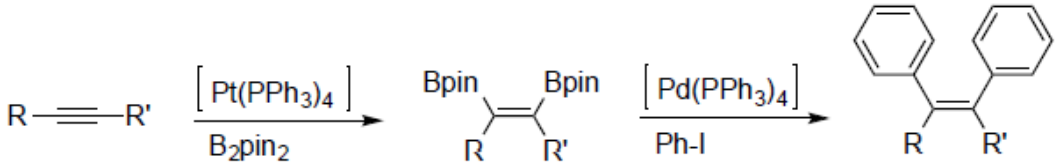
To introduce the diboronic esters moieties is necessary the activation of the unsaturated compound [8]. The B-B bond energy is high, fact that difficult the addition intramolecular and consequently, activation of diboron reagents is required in order to promote the reaction with unsaturated substrates. Among the possibilities for activation, there are three principally methodologies via oxidative addition, transmetallation or organocatalysis.

3.3.1.Activation of diboron reagents with transition metalcatalysts via oxidative addition

The catalytic transference of the diboron reagent to unsaturated organic substrates is allowed due to their favorable kinetic in the oxidation process when it is added to low-valent transition metals by the B-B bond cleavage [9], resulting in boryl-metal complexes. Moreover, it is possible to control chemo- and regioselectively the creation of the new C-B bond by choosing the correct combination of transition metal complexes and a substrate. Modifying the chirality of the catalyst precursor can also provide the enantioselectivity of the new C-B bond.

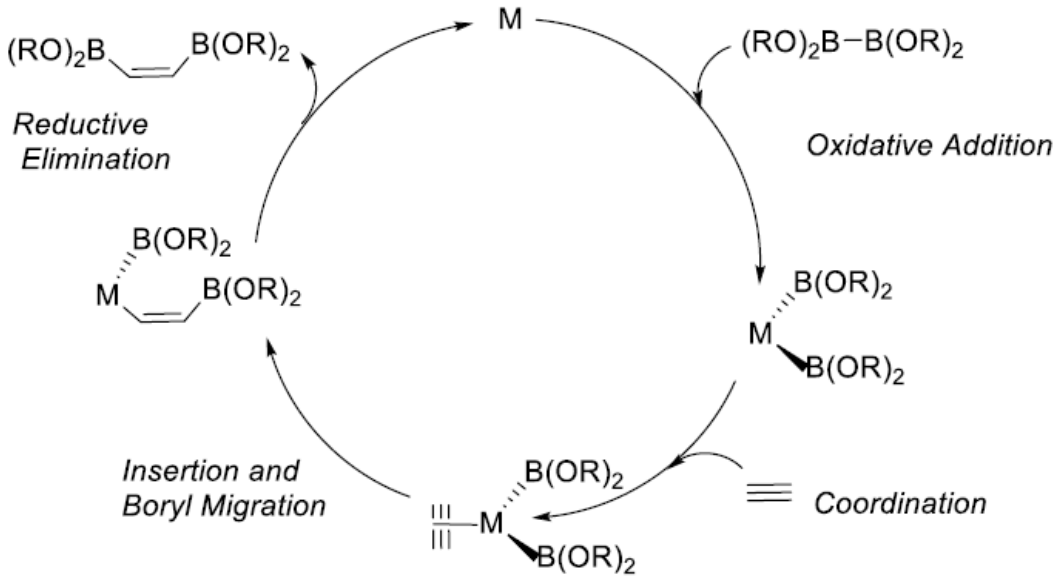
Boryl-metal complexes are able to transform unsaturated molecules into organomono- and organo diboron compounds in a catalytic cycle through few steps. Concerning the effectiveness of the overall transformation, the combination of reagents is crucially important due to possible side reactions and catalys to borane decomposition. Miyaura and co-workers [10] reported for first time, the advantages of metal-catalyzed 1,2-diboration and suggested the importance over uncatalyzed reactions.

They exposed the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors. The products obtained in this reaction were transformed through a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 8).



Scheme 8: Suzuki-Miyaura cross-coupling reaction

They established by using spectrometric methods that the process was carried out through the oxidative addition and the regioselectivity of the products. Regarding this work, they proposed a catalytic cycle (Scheme 9).



Scheme 9: Catalytic cycle for oxidative addition.

The oxidative addition of diboron reagents to the metalcentre is followed by coordination of the substrate, insertion into the M-B bond and boryl migration, finishing with the reductive elimination that regenerates the active species and provides the diborated product.

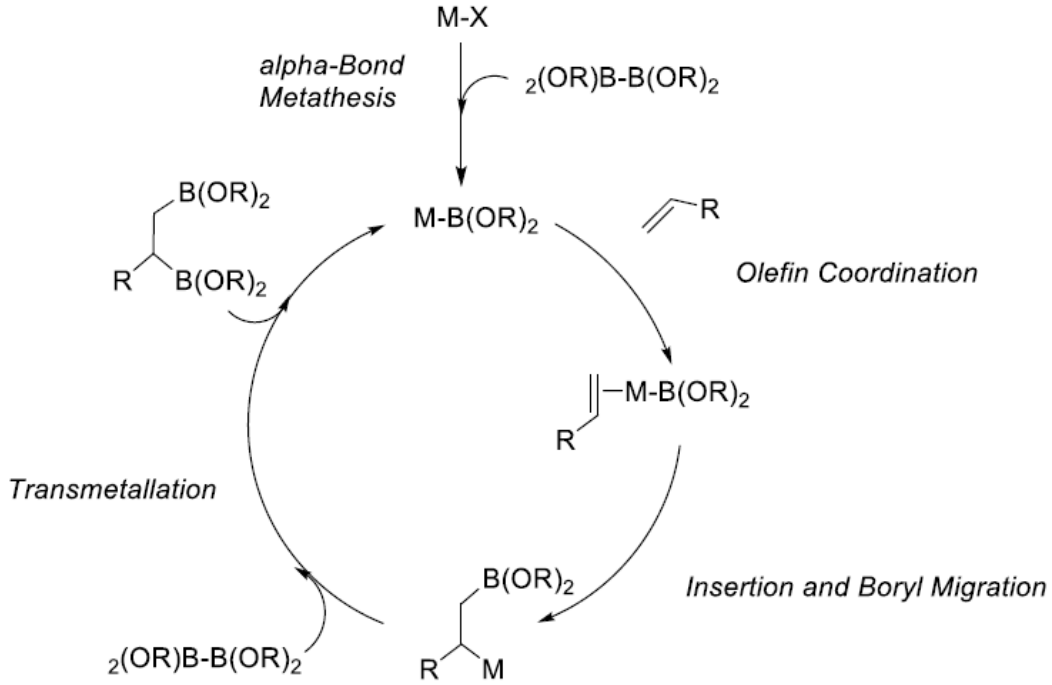
Other researches followed this line of development in this area and until current days it is strongly researched aiming to improve the diboration and the enantioselective approach leading reactions via oxidative addition.

The activation of the diboron reagents via oxidative addition is mostly restricted to low valence transition metals of group 9 and 10.

3.3.2. Activation of diboronreagents with transition metal catalysts via σ-bond metathesis

A metal that presents lower *d* orbital energies cannot be activated via oxidative addition. However, some transition metal complexes react with tetralkoxi diboranes preserving the oxidation state of the metal.

The activation of diboron reagent can be considerate as σ-bond metathesis between the diboron reagent and the metal-halogen unit. Fernández and co-workers [11] were the first group to mediate copper-catalyzed diboration reaction in order to confirm the mechanism through σ-bond metathesis. Marder and co-workers proposed later a plausible catalytic cycle for diboration reaction [12] (Scheme 10).

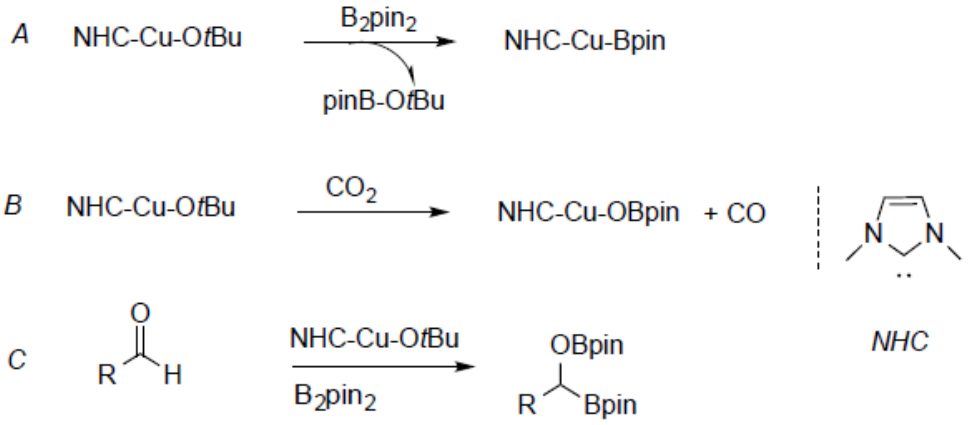


Scheme 10: Catalytic cycle for transmetallation

The provided mechanism described the formation of boryl complexes as leaded by the heterolytic cleavage of the diboron reagent through bond metathesis, followed by the alkene coordination, insertion and transmetallation with diboron reagent, generating product and recuperating the activated species.

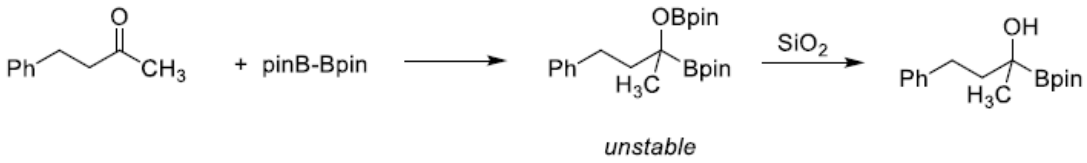
Sadighi and co-workers demonstrated that transition metal complexes of group 11, specifically copper complexes, were favoured to explore new approaches related to diboration reaction. They activated diborons with Cu(I) salts and they utilized these nucleophilic copper-boryl systems in boron addition reactions. In early context, they isolated NHC-Cu-Bipin(NHC-heterocyclic carbene ligand) departing from NHC-Cu-OtBu and B_2pin_2 via σ-bond metathesis [13].

In addition of their discoveries, they showed that the use of NHC-Cu-Bpin species reduces CO_2 to CO [13]. The first introduction of a metal-boron bond reducing an aldehyde carbonyl group generating a metal-carbon σ-bond were reported by the min2006 [14]. In the presence of an excess of aldehyde, this metal-carbon σ-bond was lead to further reaction formatting a carbon- boron bond, characterizing the diboration of aldehydes (Scheme 11 A, B and C, respectively).



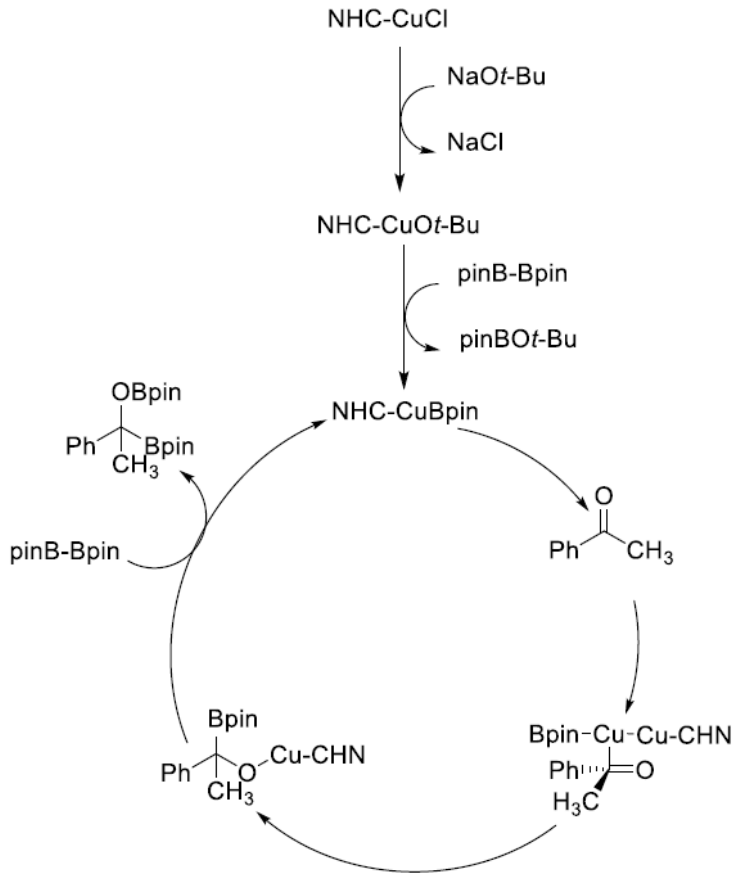
Scheme 11: Discoveries of Sadighi and co-workers

In 2010, Clark and co-workers [15] used a similar methodology towards the diboration of ketones providing access to tertiary α-hydroxy boronate esters (Scheme 12).



Scheme 12: Diboration of ketone with a copper catalyst performed by Clark and co-workers

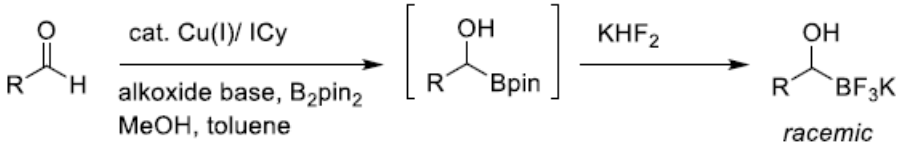
The postulated mechanism started with the ligand exchange between the NHC-CuCl catalyst and the base to for the alkoxide analogue. Once this is formed σ bond metathesis occurs to generate the nucleophilic Cu-B specie, followed by coordination of the ketone. The coordinated ketone can undergo migratory insertion to for the copper alkoxide intermediate which will react with the B_2pin_2 via σ bond metathesis to regenerate the active copper-boryl specie (Scheme 13).



Scheme 13: Catalytic cycle proposed to diboration of ketones in the presence of a base.

These diboration products (either diborated, aldehydes and ketones) tend to decompose when exposed to silica gel. The decomposition is explained with studies of Sadighi that show similar decomposition of diborates benzaldehyde product. Sadighi associated this decomposition to a process mediated by oxygen.

In the direction of isolation and purification of these unstable compounds, many researchers started to work with different options of *insitu* derivatization. Derivatization is a chemical technique utilized in order to transform one molecule in a similarly structured molecule. In 2012, Molander and co-workers [16] synthesized, via copper catalysis diboration of aldehydes, a derivatization methodology generating the α-hydroxy trifluoroborate salts (Scheme 14).

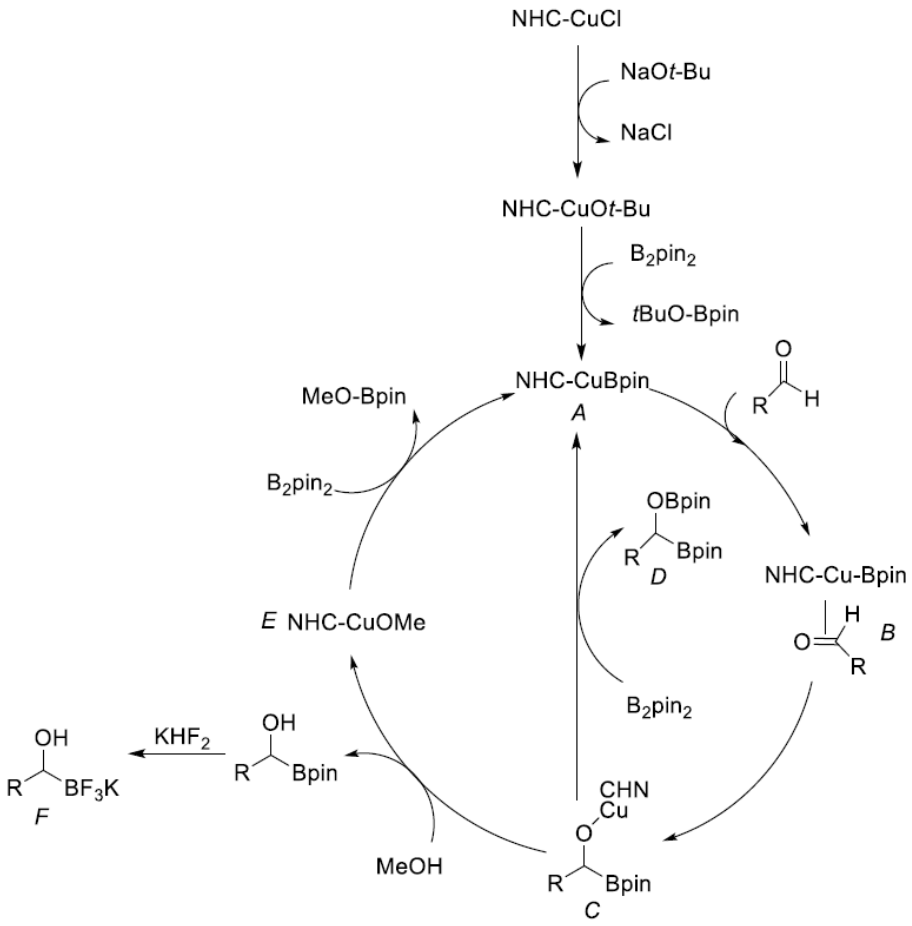


Scheme 14: Derivatization to organotrifluoroborates proposed by Molander and co-workers

Besides the transformation of pinacolborate to the related trifluoroborate, this reaction also cleave the borate O-B bond, modifying the diboron compounds to the correlated 1-(hydroxy)alkylfluoroborate salt allowing the new compound to be handled without special conditions making possible its purification.

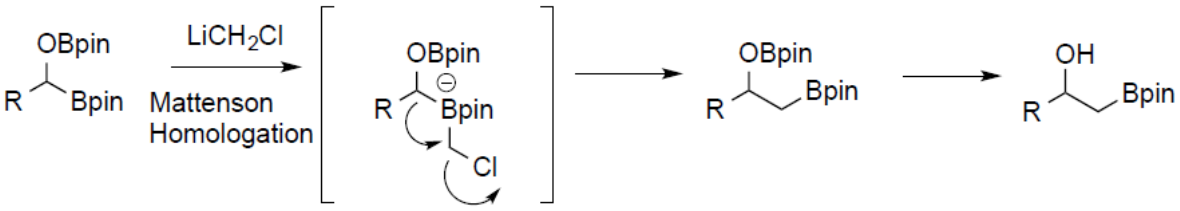
They proposed a catalytic cycle where they could analyze the presence and the absence of methanol in the reaction. Methanol has been shown to facilitate protolytic turnover of the catalyst in other diboration reactions [16].

The catalytic cycle performed (Scheme 15) activated the copper catalyst complexes in the beginning, which was generated by subsequent transmetalation with NaOt-Bu and B_2pin_2. The coordination of the carbonyl of the aldehyde to copper causes the formation of the compound *A*, consequently the boron proceeds being added to the aldehyde to afford the intermediate *B*. Protonation of compound *C* leads to compound *E*. There generation of the activated catalyst goes through transmetalation with another molecule of B_2pin_2. Finally; after all, the catalytic cycle is completed. This side procedure, starting from aldehydes, provided access to the desired products.



Scheme 15: Catalytic cycle proposed by Molander in order to analyze the presence of methanol

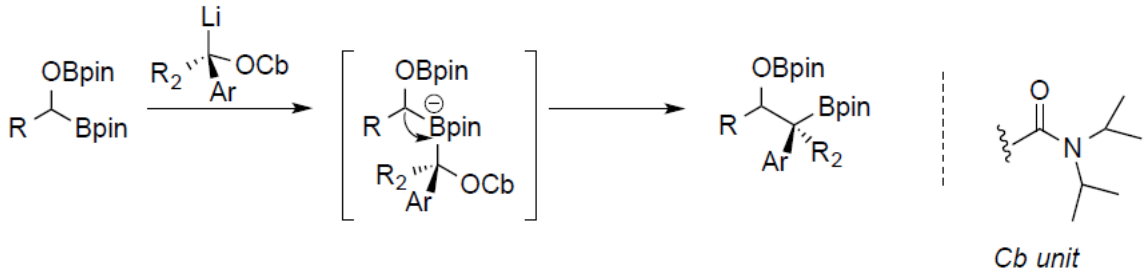
Clark and co-workers reported an alternative methodology to the BF_3K in order to be able to isolate a synthetic useful intermediate. They reported the copper-catalyzed diboration of aldehydes followed by the Matteson homologation, resulting in the efficient synthesis of β-hydroxy boronate esters, which are more stable (Scheme 16) than the α-hydroxy analogues. They could observe that the oxygen-bond boronate ester played a key role in theme diation of the homologation reaction, which was compared to the α-hydroxy boronate ester [17] (isolated hydrolysis product).



Scheme 16: Mattenson Homologation performed by Clark and co-workers

They noticed that the Tander diboration/homologation sequence do not need of isolation or protection of the α-hydroboronate esters intermediates. Oxygen-boron bond, from the aldehyde diboration, served as a plausible protecting group while the homologation was carried out. They stated that the boronate keep bonded to the oxygen during the step.

This transformation open doors to the use ofthese intermediates for more challenging homologations, like Aggarwal homologation [18] (Scheme 17),which will allow the incorporation of a more complex side chain.

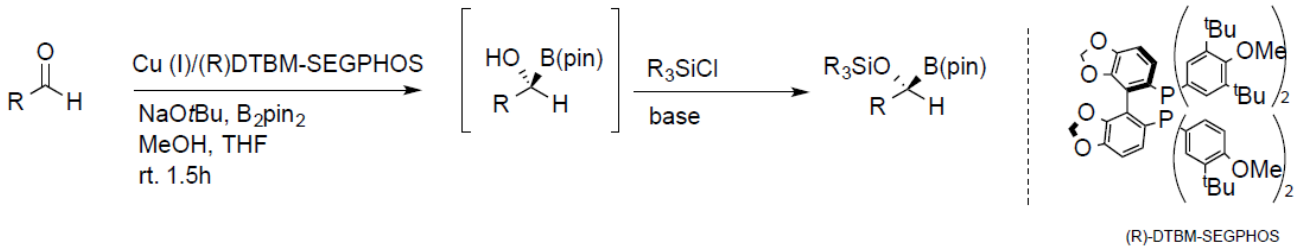


Scheme 17: Aggarwal homologation

Early this year, Ito and co-workers were able to develop the first enantioselective borylation of aldehydes with diboron compounds [19]. The catalyst cycle is similar of the one postulated by Sadighi, Molander and Clark.

In order to evaluate the enantioselectivity of the reaction and due to the instability of the α-hydroxiboronate, the authors decided to protect the alcohol intermediate. Among all the possibilities, silicon protecting group was the only one that could be done in a synthetic useful yield. However, this derivatives are also sensitive to silica gel and it's purification have to be done quickly in order to remain the minimum time on the silica.

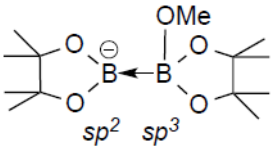
A wide substrate scope was examined and this new reaction showed an excellent enantioselectivity, up to 99% using (R)-DTBM-SEGPHOS as a ligand (Scheme 18).



Scheme 18: Enantioselective diboration with copper catalysis

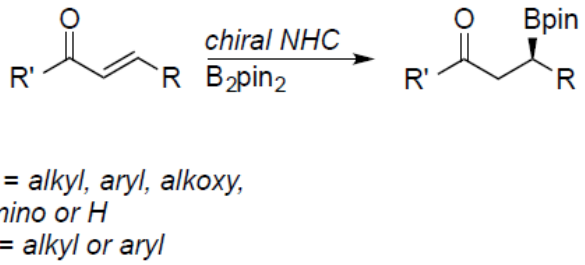
3.3.3 Organocatalysis activation

Recently, several groups have been studying the addition of organoboronic esters in the absence of a transition metal complex. This methodology required the activation of the diboronic ester with a Lewis base resulting in the hybridization of the diboron reagent into a sp^2-sp^3 diboron complex. The sp^2 moiety has nucleophilic behavior and can react with some electrophiles (Scheme 19).



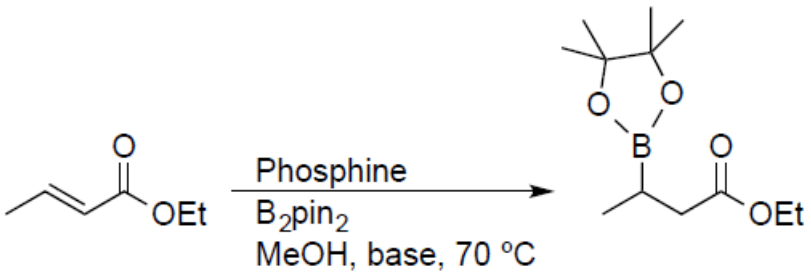
Scheme 19: Nucleophilic behaviour of sp^2-sp^3 boron moieties

Hoveyda and co-workers , in 2009, proposed that the diboron reagent B_2pin_2 was activated by a free NHC, in the absence of a transition metal, to facilitate the borylation reaction at ambient temperature [20]. They also noticed that in the simply presence of the base, the reaction did not work. In 2012, Hoveyda reported an enantiomeric synthesis of boron conjugates (Scheme 20).



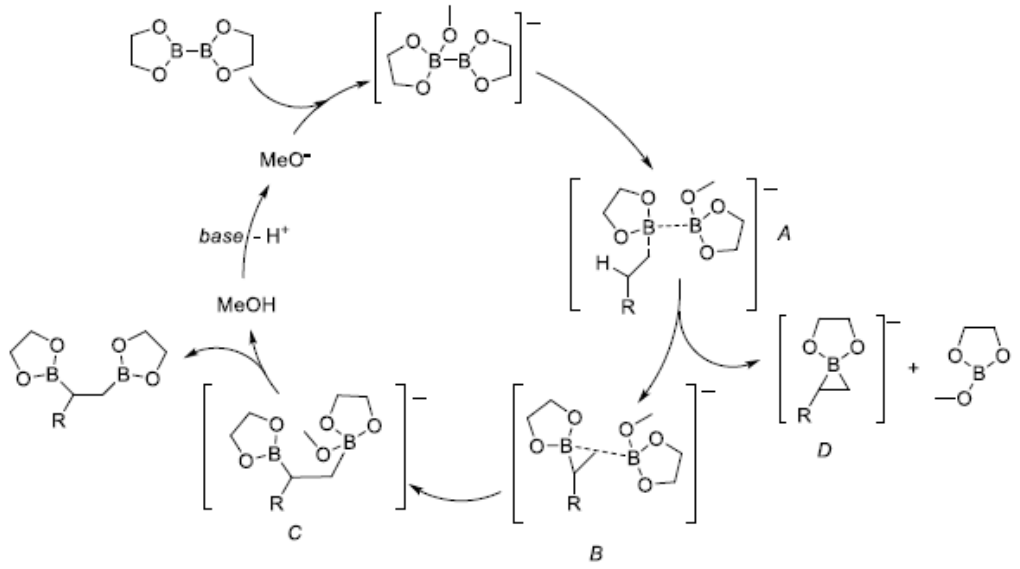
Scheme 20: Enantiomeric synthesis of boron conjugates performed by Hoveyda

Fernándezand co-workers [21] proposed a different asymmetric β-borylation without the presence of transition metal in the reaction (Scheme 12). The system used catalytic amounts of chiral phosphine with enantioselectivities up to 95%. In contrast with the example of Hoveyda, the chiral phosphine reacts with the substrate generating a phosphonium enolate intermediate which further interact with MeOH and B_2pin_2. This method have been successfully extended to the unsymmetrical.



Scheme 21: Phosphine-mediated catalytic β-boration of ethylcrotonate with B_2pin_2

Anionic Lewis base have also showed as substances that can activate diboron compounds directly. Fernández and co-workers showed that alkoxides could promote the transition-metal-free diboration of unsatured compounds. Following this methodology, a wide range of substrates was investigated providing good yields. Fernández and co-workers proposed the follow catalytic cycle for the diboration of alkenes (Scheme 22).



Scheme 22: Catalytic cycle proposed by Fernández and co-workers with activation through alkoxide anion.

Methanol is deprotonated in the beginning of the reaction by organic or inorganic base, sequentially transformed in a methoxide anion to react with B_2pin_2 to generate in situ the complex $[B_2pin_2OMe]^-$ [24]. Then, this adduct reacts with the substrate via transition state A that either rearranges directly to a second transition state B or an intermediated D with MeOBpin as a side product and consequently, the protonation of D or C providing the formation of both, hydroborated or diborate product, respectively.

4. Experimental Part

4.1. General considerations

All air- and water-sensitive reactions were carried out in oven-dried glassware under argon atmosphere using standard Schlenk manifold technique. Anhydrous solvents (THF, Toluene) were obtained from distillation over Na/Benzophenone and stored subsequently in a Strauss flask over 3Å molecular sieves. The THF was degassed using Freeze-Pump-Thaw degassing techniques Other dry solvents were purchased from Across. Diboron reagent were purchased from Allychem and used as arrived. Amines were purchased in Sigma- Aldrich and Alfa Aesar and were destilled and degassed using Freeze-Pump-Thaw degassing techniques before were used. Styrene was purchased in Alfa Aesar and was filtrated through silica gel before use to remove the stabilizer.

Deuterated solvents for routine NMR measurements were purchased fromEURISO-TOP. NMR spectrums were obtained on a Jeol 400 MHz.^{1}H NMR and^{13}C{1H} NMR chemical shifts are reported in ppm relative to the reference to the chemical shifts of residual solvent resonances. ^{11}B{1H} NMR chemical shifts are reported in ppm relative to BF_3-OEt_2 used as internal standard.

4.2 Procedure for transition metal free diboration of alkenes

At first, bis(catecholato)diboron (37 mg, 0,3 eq) was added in anoven drySchlenk under inert atmosphere. The diboron reagent were dissolvent n dry tetrahydrofuran (2mL) and the solution was stirred until the solid was dissolved. Subsequently, the substrate (57 uL, 0,5mmols) was added followed by the amine (2,5 uL, 5%) and let the mixture to warm up at 70ºC for 2,5h. After this time, was added another batch of B_2cat_2 (148 mg, 1,25 equivalents) followed by the amine (10 uL, 20%) to the reaction mixture and let at 70ºC another 2,5h .

After this time, the reaction is let to cold down and 1,3,5-trimethoxybenzene (28 mg, 0,17 mmols) was added to the reaction mixture as NMR internal standard. 0,5mL of the reaction mixture was evaporated and the solid was redisolved with 0,5mL of $CDCl_3$ under argon atmosphere. The resulting mixture was analyse by NMR.

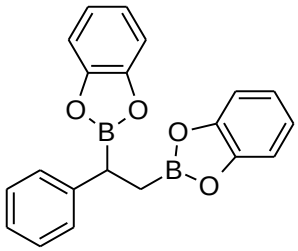
4.3 Procedure for the mechanistic experiments

At first, bis(catecholato)diboron (37 mg, 0.155 mmols) was placed in a dry NMR tube under argon atmosphere which contain an 11B NMR internal standard (BF_3-OEt_2)The mixture was dissolved with dry THF (0,5mL) shaking carefully the NMR tube under inert atmosphere. Once the sample is completely dissolved, the sample is analyse by $^{11}B\{H\}$NMR. Then, the amine (x equivalents) was added into the tube in argon atmosphere, the sample was carefully shacked and immediately analyse by $^{11}B\{H\}$ NMR. The procedure is repited until the experiment is finished.

4.4 NMR of the product

2,2'-(1-phenylethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (Figure 3)

Figure 3: Structure 2,2'-(1-phenylethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



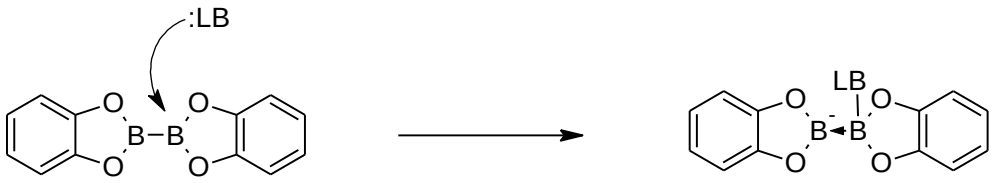
^{1}H NMR (CDCl3): 1.93 (dd, J= 10 Hz, 17 Hz, 1H), 2.19 (dd, J= 10 Hz, 17 Hz, 1H), 3.36 (m, 1H), 7.00-7.45 (m, 13H).

5. Results and Discusion

5.1 Diboration of alkenes

In order to develop a catalytic transition metal free diboration of alkenes. The aim was to develop a mild method for the activation of diboron compounds because the actual method's are not conceivable with some functional groups. In this context, NHC react with aldehydes and alkoxydes can deprotect esters and acetates.

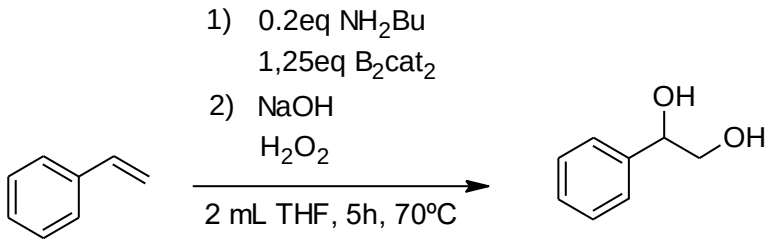
Hybridization of diboron compounds has been described using a large variety of Lewis bases such as amines, phosphines, lithium salts, carbenes and alkoxydes. However, not all the diboron reagents interact with all the Lewis bases (Scheme 16).



Scheme 16. Activation of the bis(catecholato)diboron

Amines cannot hybridize B_2pin_2 and consequently cannot activate it in order to produce organic transformation. On the other hand, it is described that B_2cat_2 interact with amines (such as picoline or DNB) forming the sp^2-sp^3 adduct, but this adduct have not been used so far in any organic transformations. With this in main, the aim of this work was the develop of a method for the activation of diboron reagents using catalytic amount of amines and their use in organic transformations such as diboration reaction.

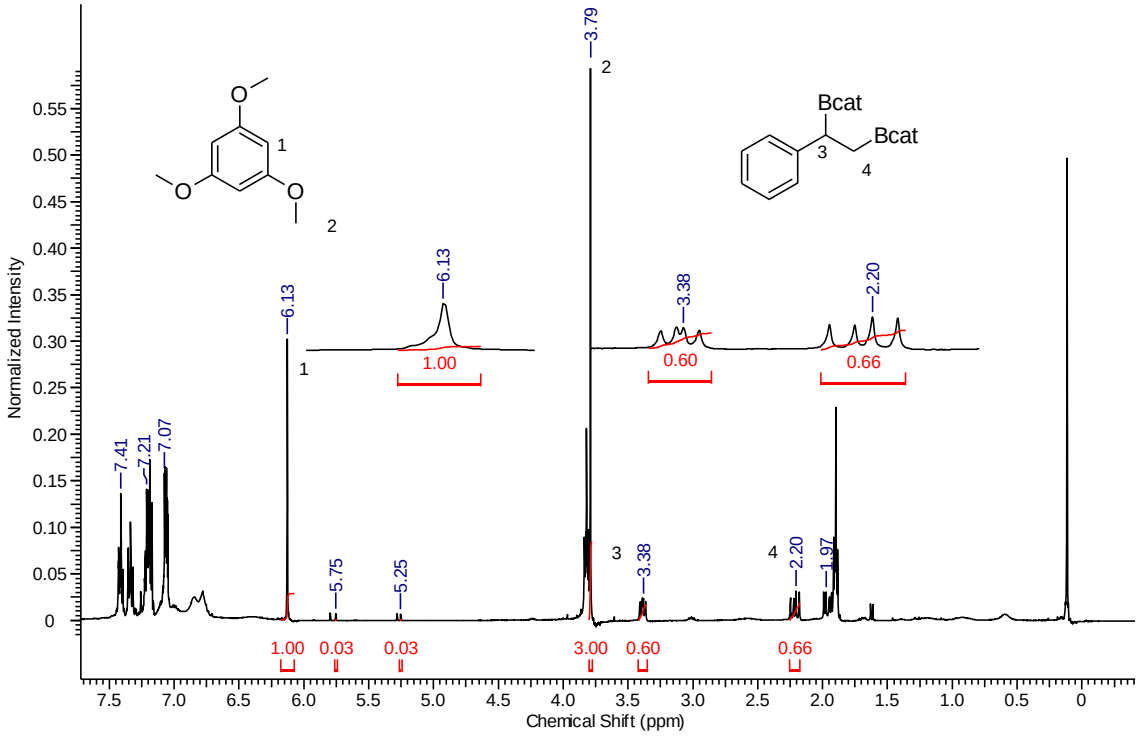
Kaline Soarez, is a Brazilian undergraduate, which started this project. Actually, she was working on the same reaction. My first aim was to reproduce the reaction which was done under nitrogen atmosphere and she obtained a 69% of isolated yield. In the next Scheme is showed the Kaline's conditions (Scheme 17).



Scheme 24: Kaline's reaction conditions

Inspired by Kaline's work, it was tested the same reaction to achieve the same results, the reaction was done under argon atmosphere, but unfortunately was only got a 20 % of yield. The NMR yield was calculated related to the internal standard 1,3,5-methoxybenzene, which was 1/3 of substrate mol % (Figure 2).

Figure 2: ^{1}H NMR spectrum of the reaction mixture



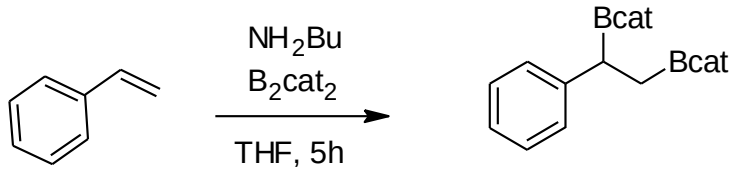
The reaction gave a lower yield with the same conditions, so it was decided to examine all the starting materials in order to find why the reaction was not reproducible. The amine and the THF was distilled and degassed. The B_2cat_2 dried and store under argon.

Purity of all the reagents where confirm by H NMR unfortunately no improvement was achieved. Alternative reaction conditions which include, change of amine, temperature, solvent was tested trying, unsuccessfully, to reproduce previous Kaline's results.

In our desire of understanding why the reaction was not working in our hands we decided to test to add a second batch of diboron reagent and amine under the same reaction conditions giving a hopeful 63% of NMR yield.

This reaction conditions where not ideal due to the large excess of B_2cat_2 (2.5eq overall) and 40% of amine only obtaining 63% of product. However this was our starting point in order to optimize the reaction conditions. Our priority was to reduce the amount of amine and diboron reagent used for that reason we slowly reduce the amounts in the first batch of the reaction in order to spend as little as possible of the reagents and getting the highest NMR yield as possible (Table 1).

Table 1: Screening of the amount of the 1st batch

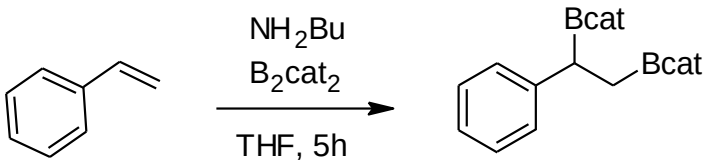


Entry	1st NH_2Bu (equiv)	1st B_2Cat_2 (equiv)	1st THF (mL)	2nd NH_2Bu (equiv)	2nd B_2Cat_2 (equiv)	2nd THF (mL)	NMR Yield %
1	0.2	1.25	2	0.2	1.25	2	63
2	0.1	0.6	2	0.2	1.25	2	74
3	0.05	0.3	2	0.2	1.25	2	64
4	0.025	0.15	2	0.2	1.25	2	43

Reaction conditions: 0.5 mmols Styrene, 70C, 2.5h 1st bacth and 2nd batch 70c, 2.5h.

As can be observed, the NMR yield of the reactions is now very similar as Kaline's work (69%).The best reaction conditions to obtain highest NMR yield is using 0.1 eq of amine and 0.6eq of B_2cat_2 in the first batch but due to our aiming of use as little as possible of amine and diboron reagent we continue our optimization using entry 3 conditions. Different temperatures was tested to check the effect that have on the reaction (Table 2).

Table 2: Screening of the temperature:



T	NMR Yield %
70	68
45	25
20	10

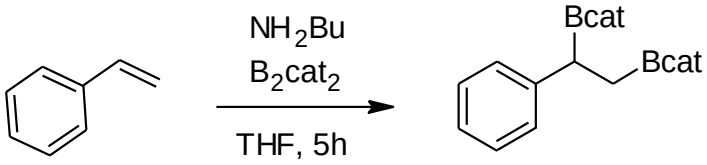
Reaction conditions: 0.05 eq of Butylamine (0.025mmols), 0.3 eq of B_2cat_2 (0.15mmols), 2mL THF 0.5mmol Styrene, 2.5h, 0.2 eq of Butylamine (0.1mmols), 1.25 eq of B_2cat_2 (0.625mmol), 2mL THF, 2.5h.

As can be seen in Table 2, at higher temperatures the reaction gave a better yield. This correlate with alkoxydes methodologies showing that, even the interaction of the Lewis base with the diboron reagent take place at room temperature, the reaction needs some energy to obtain product.

5.1.1 Solvent Effects

The solvent it's an important fact on the reactions, for that, was done a screening of solvents to find the best one to get the best NMR yield (Table 3).

Table 3: Screening of Solvents.



Solvent	NMR Yield %
THF	68
CHCL3	55
Dioxane/THF	22
ACN/THF	47
Dioxane	40
ACN	30
Toluene	15
CPME	29

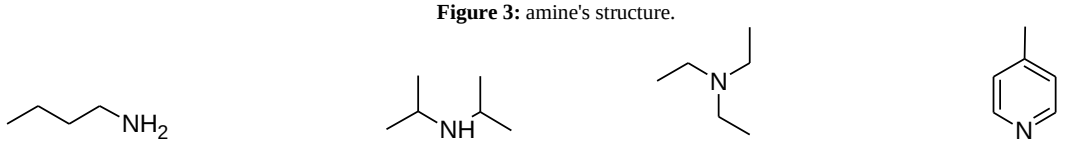
Reaction conditions: 0.05 eq of Butylamine (0.025mmols), 0.3 eq of B_2cat_2 (0.15mmols), 2mL solvent 0.5mmol Styrene, 2.5h, 0.2 eq of Butylamine (0.1mmols), 1.25 eq of B_2cat_2 (0.625mmol), 2mL solvent, 2.5h.

As can been observed, the most polar solvents as THF and $CHCl_3$ had better yield than apolar solvents in the reaction as indicated in Figure 9. The solubility of the diboron and the stability of ionic intermediates should be the reason that polar solvents show better NMR yields..

5.1.2 Amine Effects

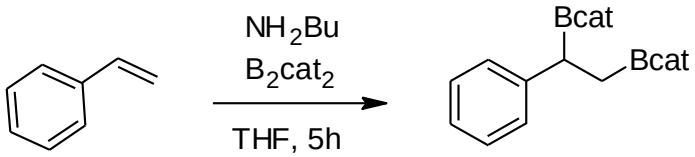
Here we notice that the reaction have a lack of reproducibility due to the small amount of amine that we were using. For that reason we decide to use 0.1eq in the first batch of the reaction. After exploring temperature and solvents we decide to explore the nature of the amines(Figure 3). Exploring how the nature of the amine effects to the activation of the diboron compound and further affects to the reaction (Table 4).

Figure 3: amine's structure.



n-Butyl amine | Diisopropylamine | Triethylamine | Picoline

Table 4: Screening of the amines on the different batches



BATCH	SECOND				
F	Amines	Butylamine	Disioprop.	Triethyl.	Picoline
I	Butylamine	74(78 O/N)	62	47	Traces
R	Diisopropyl.	45	35 (54 O/N)	30	Traces
S	Triethylamine	62	43	39(62 O/N)	Traces
T	Picoline	54	29	Traces	Traces

Reaction conditions: 0.1 eq of amine (0.05mmols), 0.6 eq of B_2cat_2 (0.3mmols), 2mL THF 0.5mmol Styrene, 2.5h, 0.2 eq of amine (0.1mmols), 1.25 eq of B_2cat_2 (0.625mmol), 2mL THF, 2.5h.

The table show that the nature of the amine is extremely important for the success of the reaction. Primary amines give higher NMR yields than secondary, tertiary and aromatic. Order of reactivity follows almost the order of Lewis basicity of the amines.

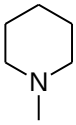
Only secondary amine don't follow the trend and lower yield than the tertiary amine. We believe that is due to the sterics of the isopropyl groups which can decrease their Lewis basicity ability. Less steric hinderate secondary amines needs to be tested to confirm the impact of the steric effects in the reaction.

As shown, the use of different amines in the different batches have an effect in the reaction. As we expected, amine in the second bath have a higher impact in the overall of the reaction. For example, the use of butylamine in the first batch and picoline in the second provide only traces of product but if we reverse the order we obtain a notably 54%. In general, the reaction that are left overnight increase their NMR yield up to 78%.

5.1.3 Steric effects of the amines

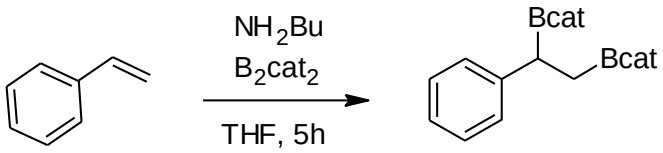
We perform the reaction using trimethylamineand N-Methylpiperidine (Figure 4) in order to study the sterics effects in the tertiary amine, which will be more important than in the secondary and primary amines. N-Methylpiperidine is a cyclic tertiary amine which reduce notably the steric effects in contrast with the Triethylamine (Table 5).

Figure 4: Tertiary amine



N-Methylpiperidine

Table 5: Screening different amines



Amines	NMR Yield%
N-MethylPiperidine	52
Triethylamine	39

Reaction conditions: 0.1 eq of amine (0.05mmols), 0.6 eq of B_2cat_2 (0.3mmols), 2mL THF 0.5mmol Styrene, 2.5h, 0.2 eq of amine (0.1mmols), 1.25 eq of B_2cat_2 (0.625mmol), 2mL THF, 2.5h.

The table show a considerable effect, more than 10% NMR yield difference between using a less steric hindered amine. This aspect should take in account in order to increase the yield, mostly if secondary and tertiary amines wants to be used for the reaction.

5.2 Mechanistic Experiments

We believe that the mechanistic will be an analogue that the one described by Fernandez and co-workers using alkoxydes. The reaction should involve the coordination of the amine into the empty *p* orbital of the B_2cat_2 which polarize the B-B generating a sp^2-sp^3 complex. The sp^j boron moiety have a nucleophilic character which can be added to alkenes generating the diboron product (Scheme)

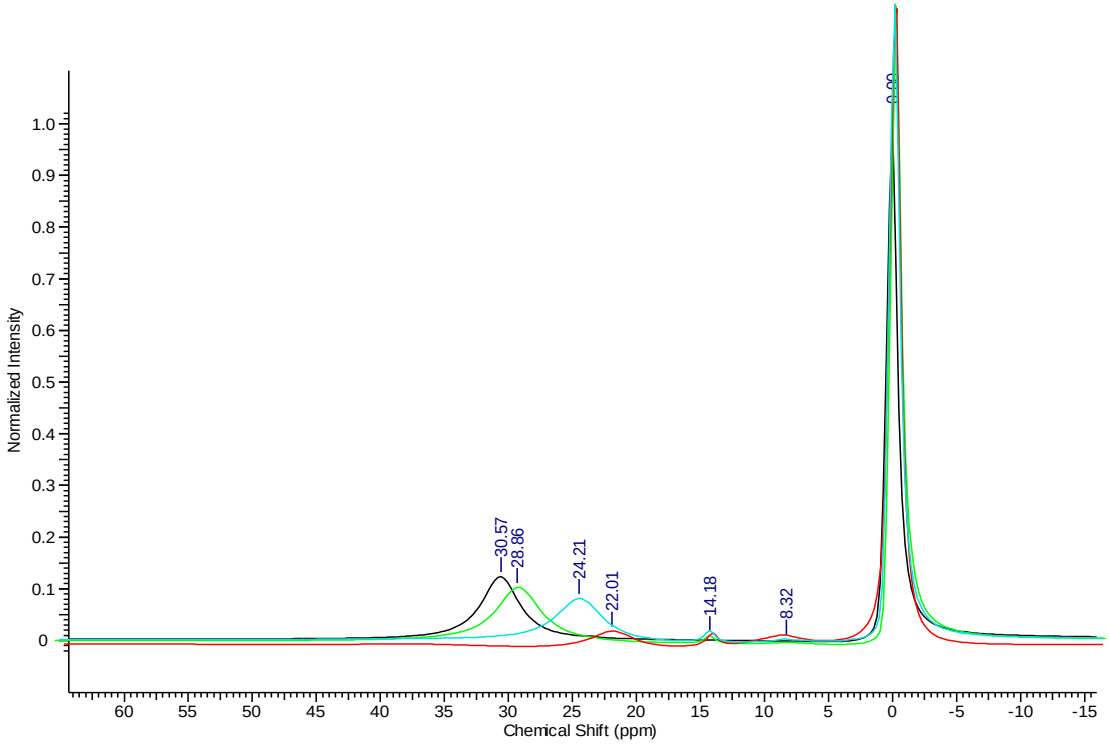
Marder and co-workers and Ingleson and co-workers [27] have described that the coordination of the amine to the diboron reagent is in constant equilibrium between the free form and the two borons of the same diboron reagent instead of the case of the alkoxydes which have a more stable bond. This is probably because alkoxydes are more nucleophilic than amines. The generation of a bond which is in equilibrium between the two boron generate a ^{11}B NMR signal which is a mixture of the two signals and the free diboron reagent. The ^{11}B NMR signal will shift up field when the equilibrium between the free form and the adduct is majoritary for the adduct form.amine in contrast of diboron reagent. This type of complexation is not observed in the alkoxyde methodology.

Ingleson and co-workers reported that the B_2cat_2 in the presence of amines like DBU could rearrange the diboron reagent generating the 1,2-isomer which would be unreactive as well. The isomerization is highly dependent of the amine and the solvent (Table 6).

Table 6: Mechanistic Experiments

Amina	Eq	Peak1	%	Peak2	%	Peak3	%.
Butylamine	0	30.57	0.59	-	-	-	-
	0.5	29.833	0.45	14.184	0.04	8.32	0.01
	1	22.493	0.26	14.184	0.04	8.32	0.02
	2	14.524	0.14	14.184	0.08	8.32	0.07
Diethylamine	0	30.57	0.46	-	-	-	-
	0.5	28.86	0.33	14.184	0.008	8.32	-
	1	24.21	0.286	14.184	0.01	8.32	0.005
	2	22.01	0.06	14.184	0.02	8.32	0.005
Triethylamine	0	30.57	0.44	-		-	-
	0.5	29.592	0.36	14.428	0.03	8.32	-
	1	28.369	0.35	14.428	0.03	8.32	0.01
	2	26.657	0.33	14.428	0.04	8.32	0.02
Picoline	0	30.57	0.83	-	-	-	-
	0.5	26.168	0.8	14.184	0.04	-	-
	1	22.255	0.7	14.184	0.04	8.32	0.02
	2	19.565	0.16	14.184	0.04	0	0.14

Figure 6: Overlay of mechanistic spectra from the diethylamine



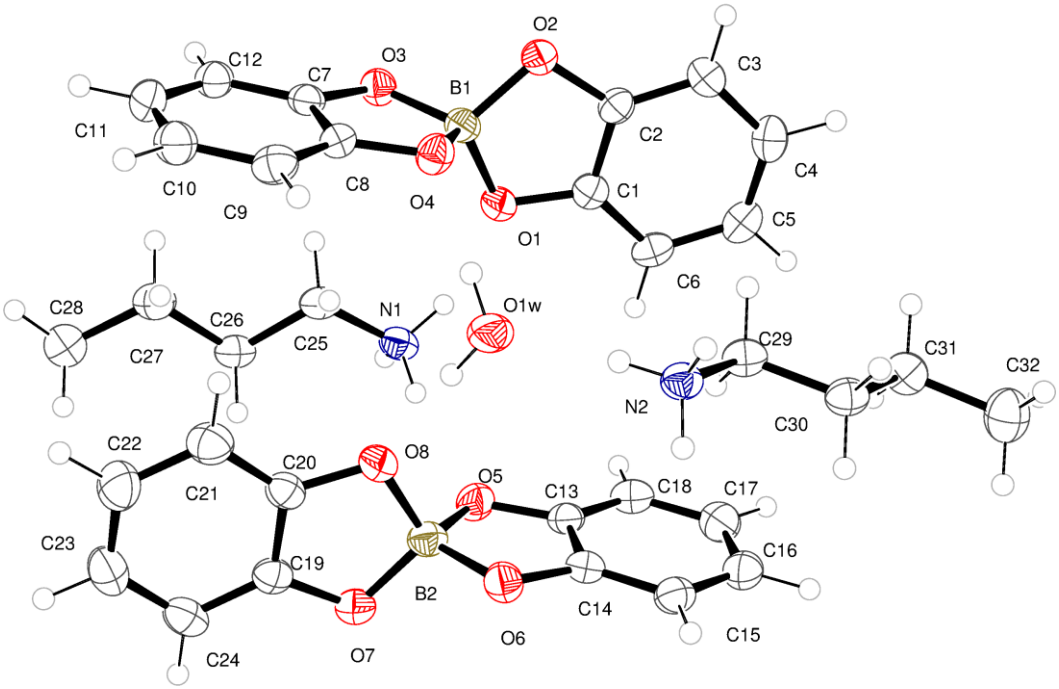
In general, in all the cases we can observe that after the addition of the amine over the solution of B_2cat_2 we generate three different peaks. The Peak 1 is constantly going up-field when the amount of amine is increasing as can be seen on the figure. This is due to the polarization of the B_2cat_2 which is in equilibrium with the free form and the two different B_2cat_2 adducts. If there is more adduct, it goes up-field. As well if the bond is more polarize the signal go up-field as well.

We can observe a nice trend between primary, secondary and tertiary where, with the same number of equivalent, the primary amine polarize more the B-B than secondary and tertiary which match with the synthetic experiments. Aromatic amine polarize, incredibly, the B-B, much more than the primary amine but this don't correlate to the activity in catalysis. Theorical calculations are carried out trying to understand this phenomena. The % of the peak is decreasing over the time due to the formation of other species in solution.

In order to get a better understanding of the polarization of the bonds, we are planning to do solid NMR which will show the pure chemical shifts of the reaction.

Second peak is reported to be an spiro compound (B_2cat_2). This specie is form in all the cases and increase when more amine is present. In order to confirm the presence of this specie we could isolate it and crystallized (Figure 5).

Figure 5: Sturcture of the Spiro



During our experiments we could confirm that the formation of the spiro compound is dependent of the solvent, looking that THF is the one that we found less prone to the formation of this byproduct. As well, looks like air and moisture could promote the formation of this byproduct.

The formation of the spiro compound could be a reasonable explanation of why we had some problems of reproducibility and as well why we can't get yields higher than 78%. The formation of the spiro compounds compromise the amine. making unable to continue the reaction even if there is an excess of B_2cat_2.

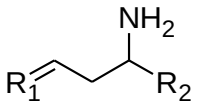
The question that we had is why we need to proceed in this two step batch procedure in order to get synthetic useful yields and the formation of the spyro compound can be an answer. Hypothetically, the formation of this compound is key, helping as contraion to lower the energy barriers in some steps of the mechanism. The role of the spiro compounds is still under study.

Finally, the 3rd peak is the formation of the sp3-sp3 adduct and we notice that this peak is easily to form when higher amount of amine is present but never is the most important spiece in the reaction mixture. The formation of this adduct, if is unreactive, can contribute lower the yield of the reaction.

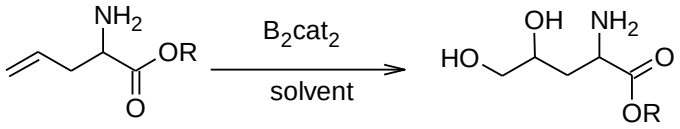
6. Future Work

Future work would be consistent in further screening of reaction conditions trying to obtain higher yield. Once this has been obtained, we will do the oxidation and the substrate scope. Specially, interested in the compounds that contain amines which could self-catalyse the reaction (Figure 6).

Figure 6: Example compounds which could self-catalyse



Self-catalyse reaction could be really interesting for the pharmaceutical industry due the mild reaction conditions, the easy synthesis of complex compounds and the compatibility with others functional groups e.g. Z-Allylglicine (Scheme 25).



Scheme 25: Typical aplication of Self-catalyse

7. Conclusion

We explored the use of the amine in order to activate diboron reagents and using it in diboration reaction. To the best of our knowledge, here was performed for the first time the diboration reaction of alkenes using only amines as catalyst in good yields but using two batches. Higher temperatures and polar solvents perform higher reaction yield.

Regarding the nature of the amines, primaries amines gave higher yield than tertiary and secondary as can be expected and the aromatic weren't reactive. The steric effects are strong in tertiary amines and we have to explore more in the secondary ones.

We saw on the mechanistic experiments that other species are formed on the reaction. The formation of the spiro compound could be a reasonable explanation of why we had some problems of reproducibility and as well why we can’t get yields higher than 78%.

The question that we had is why we need to proceed in this two step batch procedure in order to get synthetic useful yields and the formation of the spyro compound can be an answer. Hypothetically, the formation of this compound is key, helping as contraion to lower the energy barriers in some steps of the mechanism. The role of the spiro compounds is still under study.

8. Summary

This report explored methodologies for transition metal free diboration of alkenes activated by nucleophilic amines. We were able to develop a new and milder methodology to activate diboron reagents and applied in the diboration of alkenes In the best of our knowledge, here was performed for the first time the screening of conditions regarding the analysis of nucleophilicity in different amines toward the activation of bis(catecholato)diboron aiming the reaction with styrene.

Regarding the nature of the amines, primaries amines gave higher yield by NMR than tertiaries and secondary and the aromatic amines weren't reactive. The variation in temperature showed that higher temperatures gave better yield. Moreover, solvents were tested from more polar to apolar and showed better effectiveness in polar environment.

Primary amines are higher yielding than the others and we postulated that is because have higher Lewis basicity and nucleophilicity . Exceptionally, secondary amines weren’t succeeded while tertiary followed the trend of primaries, affording lower yield.

Our methodology showed to be efficient and useful for diboration of alkenes.The reactions are simple to be reproduced and innovative. Also, it is an environmental friendly process and contributes to the development of green Chemistry. Not with standing, due to the short period of time available to the project wasn’t possible to track all the wide area regarding amines as activation agents. It would be beneficial to the area of chemistry that studies carbon-boron transformations. This area is well known, but it still has much to develop.

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