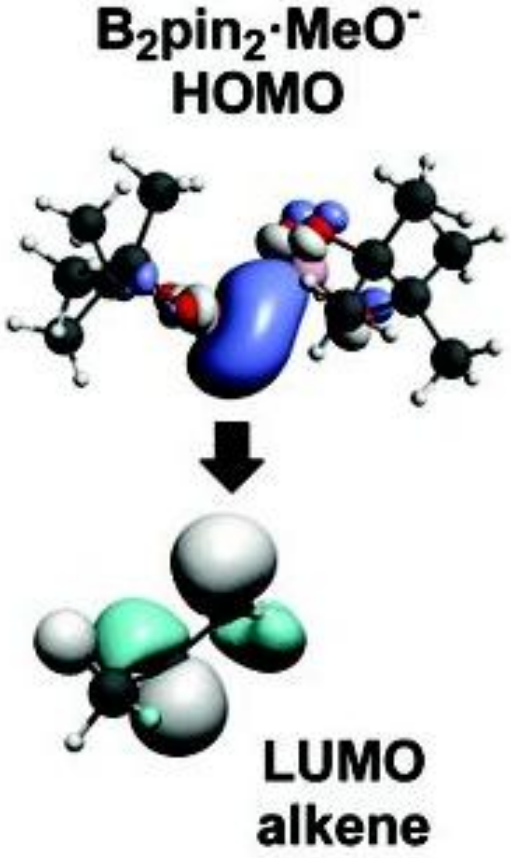
CATALYTIC ACTIVATION OF DIBORON REAGENTS TOWARDS THEIR ADDITION TO ALKENES: EXPERIMENTAL AND THEORETICAL APPROACH

Cristina Pubill Ulldemolins

Dipòsit Legal: T. 52-2013

Catalytic activation of diboron reagents towards their addition to alkenes: experimental and theoretical approach



Cristina Pubill Ulldemolins

Doctoral Thesis

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"Catalytic activation of diboron reagents towards their addition to alkenes: experimental and theoretical approach"

DOCTORAL THESIS

Supervised by

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UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2012

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FAIG CONSTAR:

Que el present treball, titulat "Catalytic activation of diboron reagents towards their addition to alkenes: experimental and theoretical approach", que presenta la Sra. Cristina Pubill Ulldemolins per a l'obtenció del títol de Doctor en Química, ha estat realitzat sota la meva direcció i la co-direcció de la Dr. Elena Fernández del Departament de Química Física i Química Inorgànica de la Universitat Rovira i Virgili, a l' Institut Català d'Investigació Química i compleix els requisits per a optar a la Menció Europea.

Tarragona, setembre 2012

Dr. Carles Bo Jané Dr. Elena Fernández Gutiérrez

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El present treball ha estat desenvolupat amb una beca ICIQ finançada per l' Institut Català d'Investigació Química. El treball que descriu la següent tesi ha estat finançat pels següents projectes:

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Agraïments

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Durant aquests quatre anys he tingut moltíssims companys, més dels que em podria haver imaginat! Crec que és una de les coses bones que té la recerca. A tots, gràcies per formar part d'aquest camí: Luca Bellarosa, Piotr Blonski, Giuliano Carchini, Fernando Castro, Gemma Christian, Silvia Diez, Steven Donald, Laura Estévez, Torstein Fjermestad, Monica García, Mickael Gicquel, Adrià Gil, Charles Goehry, Jaime Gómez, Alexander Hamilton, Jesús Jover, David Karhánek, Chunhui Liu, Laura Mateus, Maxime Mercyó, Ainara Nova, Gerard Novell, Chamil Sameera, Crisa Vargas, Abel Locati, David Balcells, Simon Pierrefixe, Neyvis Almora, Carina Backtorp, Olivier Jacquet, Nico Fleury-Brégeot, Cyril Godad, Aitor Gual (*el tio de la bara!!*), Carolina Blanco, Verònica de la Fuente, Ali Aghmiz, Jessica Llop, Eli Mercadé, Angelica Balanta, Jorge Alonso, Jamin Krinsky, Bernabé Fernández, Doris Ruiz, Dagoberto, Tatiana, Ariadna Campos, Marta , Siahm, Isabel, Dolores González, Javier Mazuela, Eva Raluy, Mercè Coll (la mami!), Sabina Alegre, Lourdes, (els del màster) Isidoro López, Núria Huguet, Miriam Díaz de los Bernardos, Moira Ciardi, Carlo Di Giovanni (gracias por tu ayuda en el último sprint!) i molts més companys de la URV i de l'ICIQ!

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"La nostra recompensa es troba en l'esforç i no en el resultat. Un esforç total és una victòria completa"

Mahatma Gandhi

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Chapter 1: General introduction and objectives

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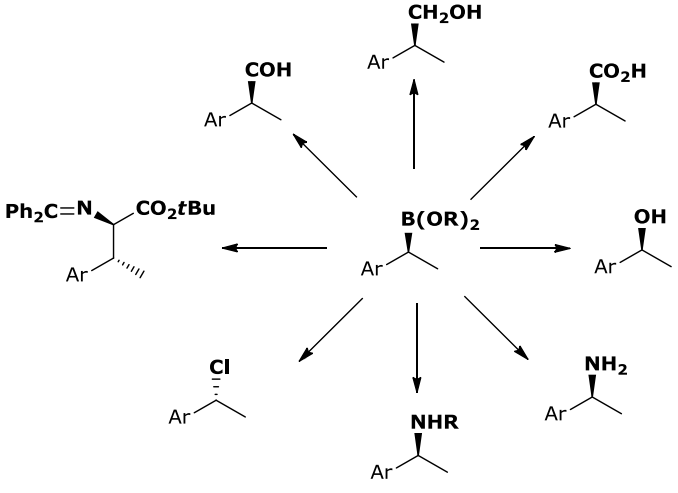
Chapter 1

1.1 General overview on organoboron chemistry

Organoboron compounds are considered one of the most important class of compounds because they can be utilized as functional molecules,[1–6] functional polymers,[7–9] ^{10}B carriers for neutron capture therapy,[10,11] and biologically active compounds.[12,13] In addition, the C-B bond can be transformed into C-O, C-N and C-C bond, through well defined protocols.[14–19]



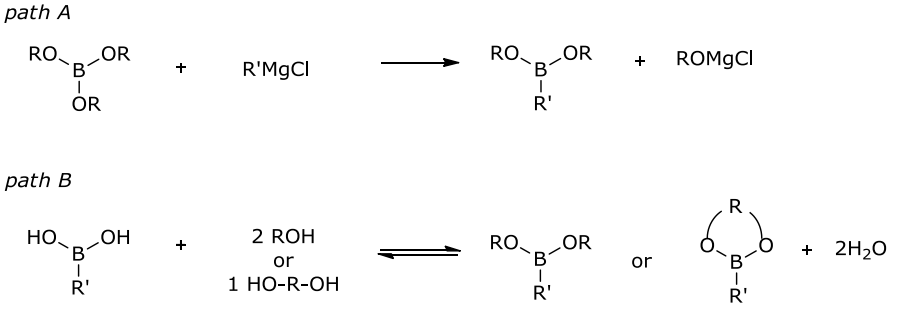
Scheme 1.1 Examples of transformations of C-B bond

Among the organoborane compounds, the most frequently used in synthesis are the organoboronic esters. This is due to three reasons:

a) The superior stability of organoboronic esters to the air, water and silica gel chromatography. This is related to the partial donation of the lone pair of electrons of the oxygen atoms into the empty *p*-orbital of the boron. However, the degree of stability depends on the nature of the organoboronic ester. Thus, bulky, aliphatic and cyclic organoboronic ester compounds are, in general, easy to purify, to store and to handle.[20]

b) Secondly, we can find a large scope of organoboronic esters readily commercially available or easy to synthesize. There are two general synthetic routes towards the synthesis of organoboronic esters. The first one is the transmetallation of the corresponding trialkoxyborane (Scheme 1.2, *path A*)

with organolithium or organomagnesium compound.[21,22] The second one (Scheme 1.2, *path B*) is the esterification of organoboronic acid with the corresponding alcohol.[23–25]



Scheme 1.2 General synthesis of organoboronic esters

These synthetic routes allow the modification of the backbone of the boryl moiety. The nature of the substituent in the borane reagents changes their Lewis acidity and consequently their stability and reactivity (Figure 1.1).

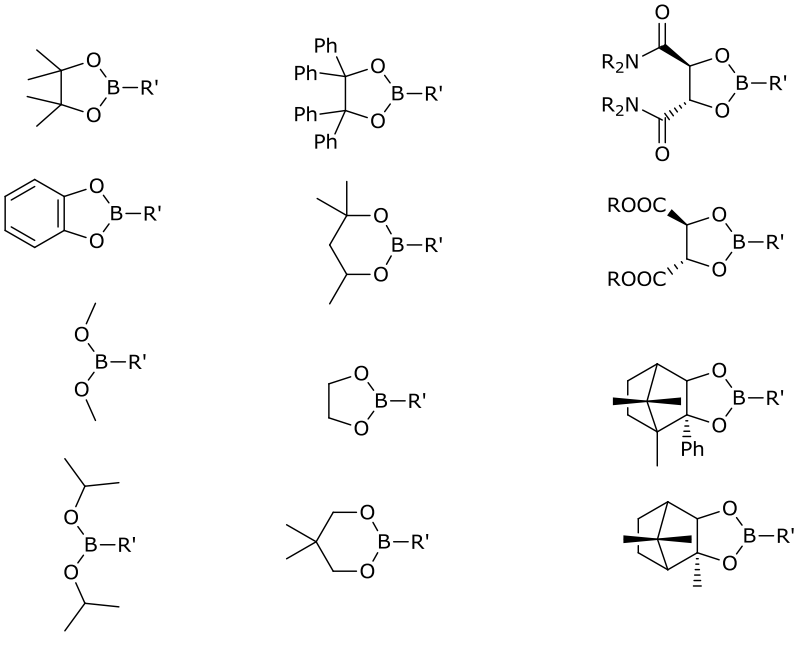
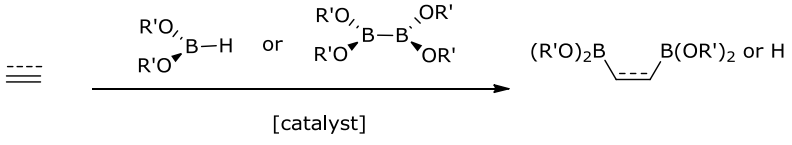


Figure 1.1 Palette of organoboronic esters

c) The addition of organoboronic esters to unsaturated carbon-carbon bonds provides an alternative synthetic methodology to obtain organoboron compounds (Scheme 1.3).

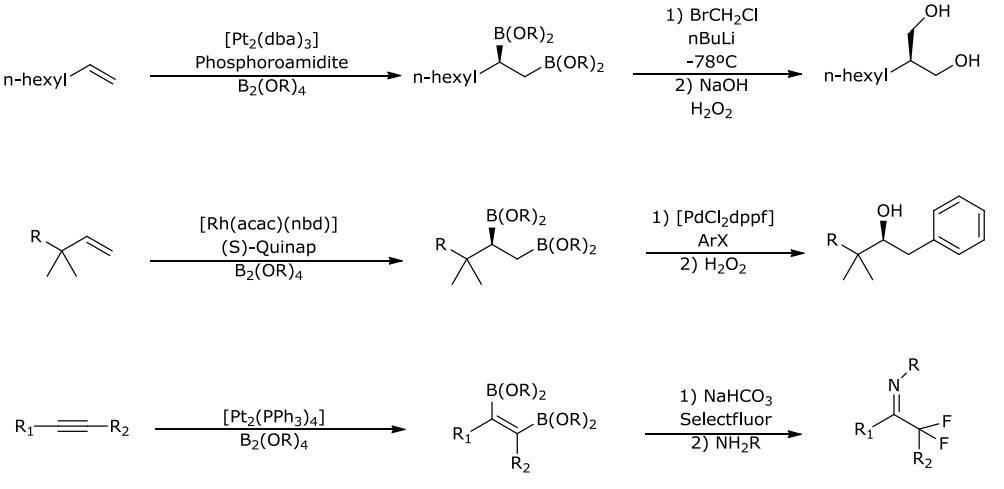


Scheme 1.3 Alternative route to the synthesis of organoboron compounds by addition of the boron reagent to an unsaturated substrate

Taking into consideration the last point, the addition of borane reagent to C=C or C≡C can be divided into two main groups depending on the nature of the borane reagent: hydroboranes ($HB(OR)_2$) and diboranes ($B_2(OR)_4$). In this thesis we focus our efforts on exploring the reactivity of the diboron reagents.

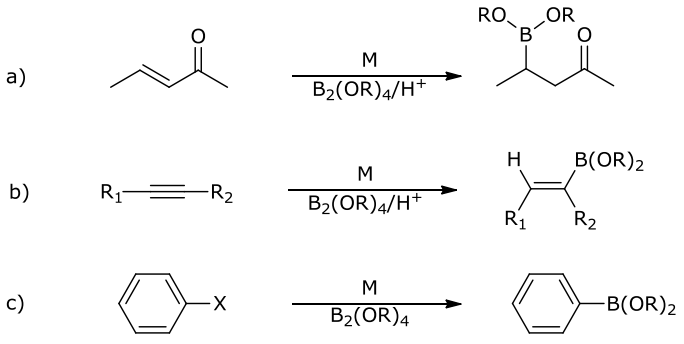
1.2 Reactivity of diboron reagents

Diboron compounds are generally used to introduce simultaneously two boryl units in the substrate. The addition to unsaturated carbon-carbon bond proceeds in *syn* fashion. The diboration reaction is an atom economical and very versatile procedure because both boryl units can be transformed independently into different functional groups (Scheme 1.4).[26–28]



Scheme 1.4 Examples of catalytic diboration reaction and the independent transformations of the C-B bonds

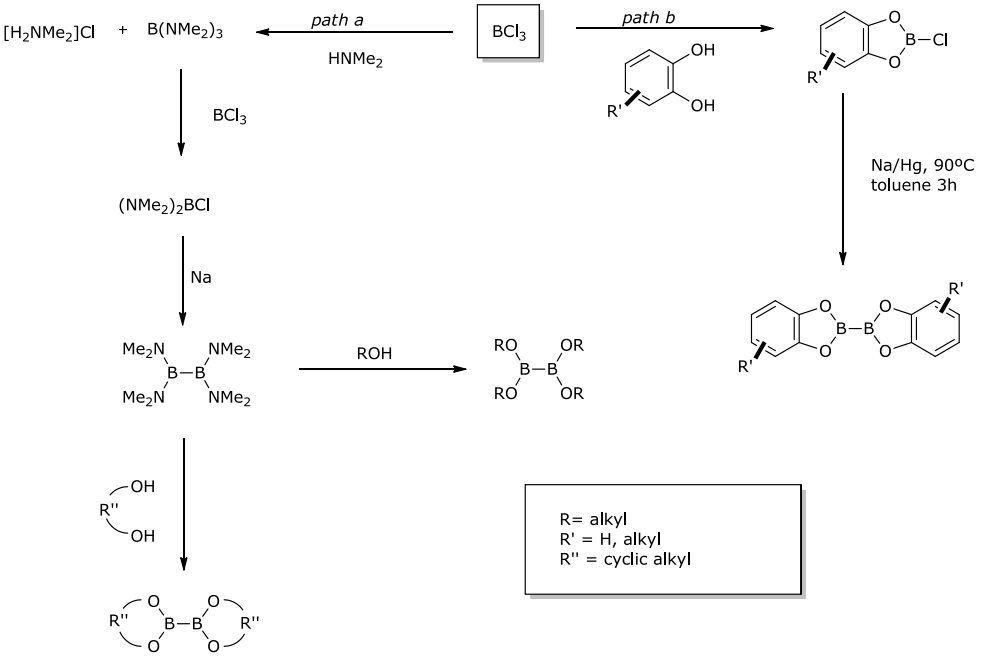
Nowadays, diboron reagents are not only used in diboration reactions. Other reactions utilize them with less atom economy such us *β*-boration, hydroboration and borylation of unsaturated compounds (Scheme 1.5).



Scheme 1.5 Less atom economical reactions with diboron reagents: *β*-boration (a), hydroboration (b) and borylation (c)

Diboron tetrahalides (B_2X_4, X=Cl^-,F^-, Br^-) can react with alkenes and alkynes in the absence of a catalyst. However, the diboron tetrahalides are rather difficult to prepare and handle and are unstable towards disproportionation.[29–31] In contrast, the tetraalkoxydiboron compounds, $B_2(OR)_4$, are relatively easy to prepare and are quite stable and easy to handle.

The synthesis of diboranes can involve multiple-step synthesis. One of the best established methods involves the formation of tris(alkylamino)borane as an intermediate (Scheme 1.6, *path a*). This synthesis was developed by Noth[32] and improved by Marder[33–35] and Srebnik.[36] Hartwig and coworkers reported an alternative synthesis from homocoupling of the halocatecholboranes[37] (Scheme 1.6, *path b*), failing in the synthesis of tetraalkoxydiboron reagents.



Scheme 1.6 Synthetic routes towards the synthesis of diborane compounds

Following the described methodologies, a large scope of stable diboron reagents can be synthesized (Figure 1.2). Among the most common diboron reagents, bis(pinacolato)diboron (B_2pin_2) and bis(catecholato)diboron (B_2cat_2) are the most used ones because of its commercial availability. This type of $B_2(OR)_4$ compounds contain a 8-π-electron 6-atom system. The B-B bond distance depends on the alkyl or aryl nature of the substituents. Therefore, for bis(catecholato)diboron the B-B distance (1.678(3) Å) is somewhat shorter than for bis(pinacolato)diboron (1.711(6) Å) or bis(neopentylglycolato)diboron (2.029(10) Å), within a comparative dihedral angle of 180º for the three structures.[34]

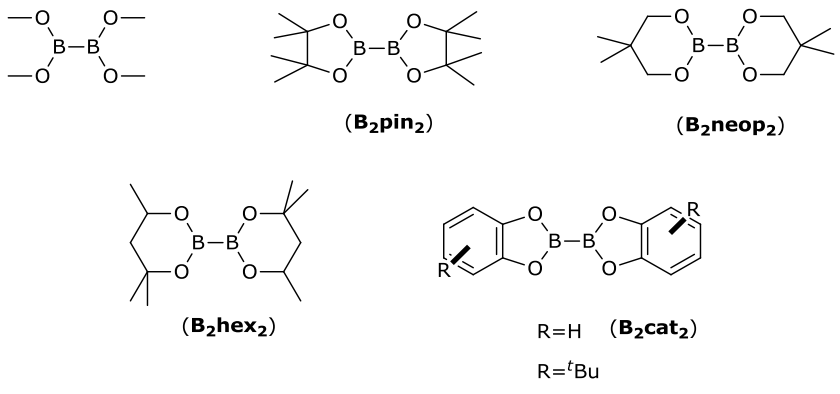


Figure 1.2 Most common diboron reagents

The high B-B bond energy (104 kcal mol^{-1})[32] might justify the lack of success on the direct addition of diboron reagents to C-C multiple bonds.[38] For this reason, unlike tetrahalide diborons, the tetralkoxydiborons need to be activated to promote the reaction with unsaturated substrates. The most widely extended method to activate diboron reagents is mainly performed by transition metal catalyst *via* homolytic oxidative addition or *via* σ-bond metathesis (heterolytic cleavage of the B-B bond).

1.2.1 Activation of diboron reagents by transition metal catalysts. Applications

1.2.1.1 *Via* oxidative addition

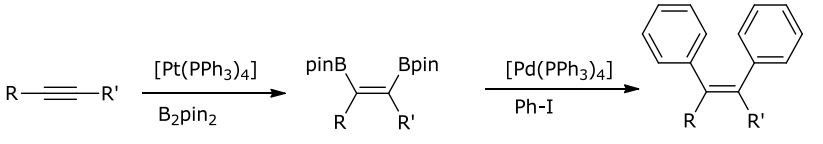
The advantage of diborons is that they can be oxidatively added to low-valent transition metals through the B-B bond cleavage, thus allowing the catalytic transfer of the diboron reagent to the unsaturated organic substrates,[39] due to the kinetic lability of the resulting boryl-metal complexes. When these two factors are combined, the use of transition metal complexes guarantees, first, the activation of tetraalkoxy- and tetraaryloxydiborons by oxidative addition, and second, the reductive elimination towards the diboron products in a catalytic cycle.[40]

The use of suitable transition metal complexes has other advantages, such as the ability to control chemo- and regioselectively in the formation of the new C-

B bonds. Finally, the possibilities of modifying the catalyst precursor with chiral ligands provide an opportunity for the enantioselective formation of new C-B bonds.

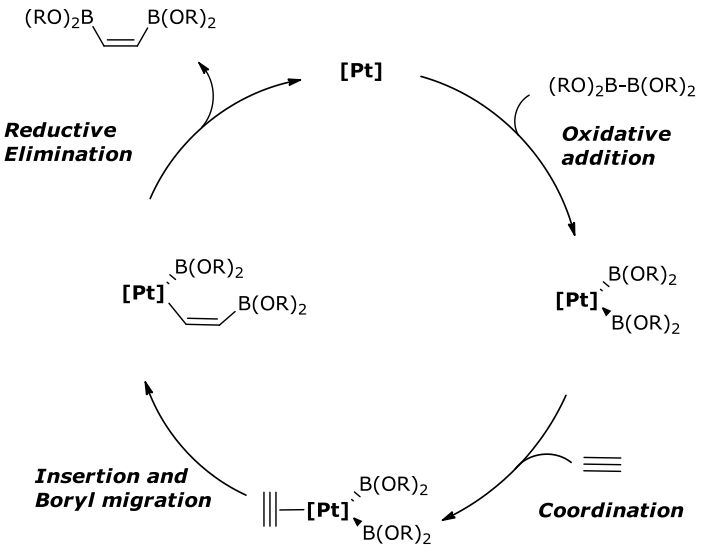
The boryl-metal complexes are the key species of a catalytic cycle in which several consecutive steps transform unsaturated molecules into organomono- and organodiboron compounds.[41]

The advantages of metal-promoted 1,2-diboration over the uncatalyzed reaction justifies that researchers have been searching for suitable catalytic systems ever since Miyaura and coworkers's first report.[42] They were pioneers in the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors. In their report, they showed that tetrakis(triphenylphosphine)platinum(0), [$Pt(PPh_3)_4$], catalyzed the clean addition of bis(pinacolato)diboron to both terminal and internal alkynes, resulting in the formation of *cis*-alkene bis-boronate esters. The two C-B bonds obtained in this reaction were transformed into two C-C bonds through a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 1.7).[42]



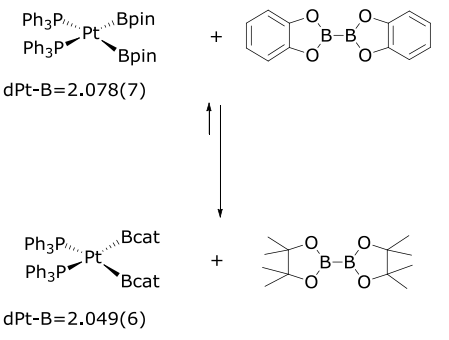
Scheme 1.7 First Pt-catalyzed diboration of alkynes reported by Miyaura and Suzuki and their derivatization through cross coupling reaction

Miyaura and coworkers also reported spectroscopic evidences for the formation of the *cis*-bis(boryl)metal complex *cis*-[$Pt(PPh_3)_2(Bpin)_2$], which was isolated and structurally characterized by single-crystal X-ray diffraction confirming that the diboron reagent was added to the metal center *via* oxidative addition. Taking into account this information the authors proposed the following catalytic cycle (Scheme 1.8). The oxidative addition of diboron reagents to the metal center 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. Subsequent experimental[43–45] and theoretical studies were in accordance with this proposal.[46–49]



Scheme 1.8 General catalytic cycle of the platinum mediated diboration reaction first proposed by Miyaura and coworkers

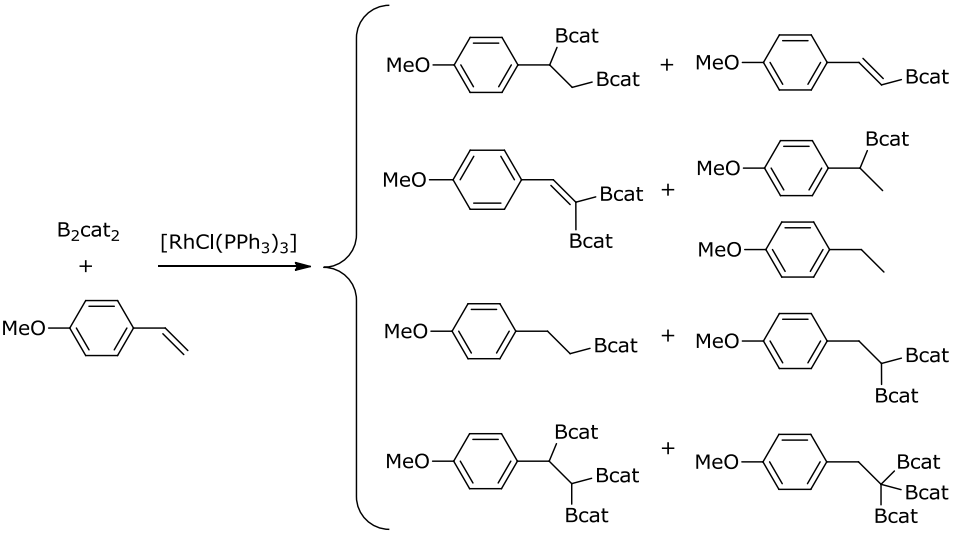
Importantly, the nature of the diboron reagent was found to be critical in the relative stability of the resulting bisboryl-Pt(II). $[Pt(Bpin)_2(PPh_3)_2]$ with B_2cat_2 gave $[Pt(Bcat)_2(PPh_3)_2]$ and B_2pin_2, suggesting stronger Pt-B bonding interactions in Pt-Bcat rather than in Pt-Bpin, (Scheme 1.9).[50] The presence of sp^2 carbons, and the aromatic ring capability of removal electron density from the oxygens, causes the B-O bonds in Bcat to be weaker than those in Bpin. The pair of electrons in the σ bond with the metal center is less electron releasing for M-Bcat than M-Bpin, therefore Bcat exert a weaker *trans* influence than Bpin.[41,51,52] Thus, formation of $[Pt(Bcat)_2(PPh_3)_2]$ and B_2pin_2 is thermodynamically favoured over $[Pt(Bpin)_2(PPh_3)_2]$ and B_2cat_2.



Scheme 1.9 Relative stability of platinum diboryl species. Stronger Pt-B bonding interactions with B=Bcat than with B=B_2pin_2. Pt-B distances are given in Å.

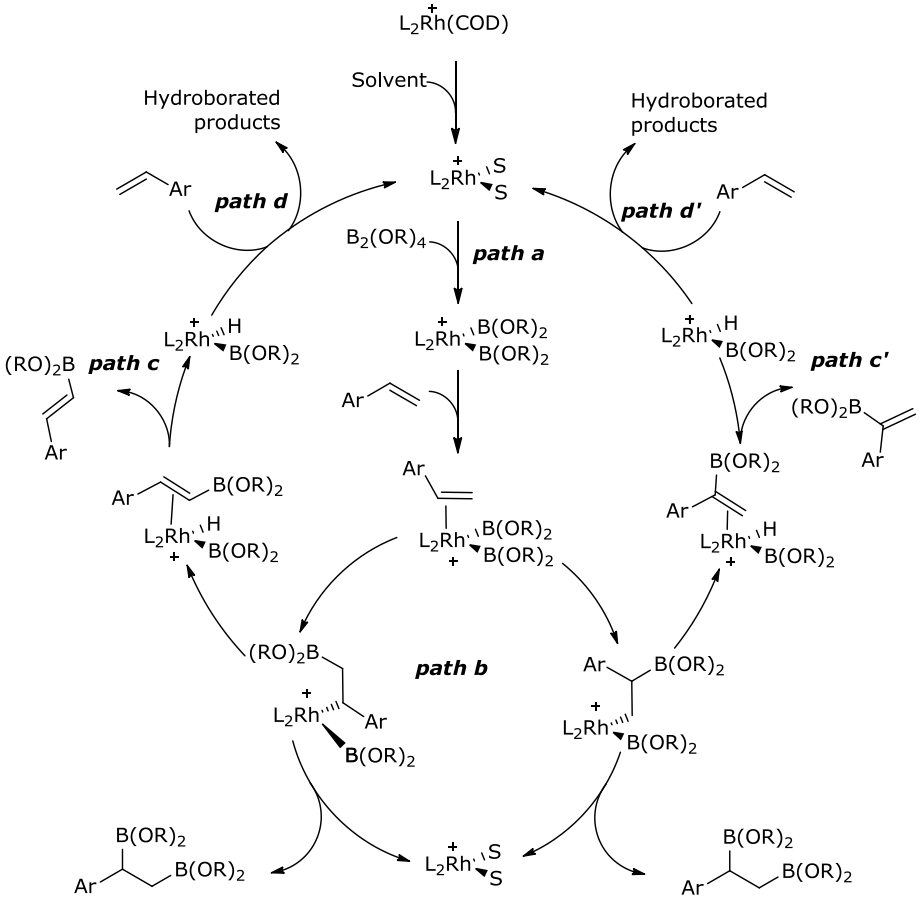
Along with Pt complexes, Rh(I) complexes were also explored in the activation of the diboron reagents towards the diboration reaction.

The nature of the catalytic system in diboration reaction is crucial. Both transition metal complexes modified with phosphorous ligands and also phosphine-free metal complexes have been tested,[43–45] but in all these approaches the catalytic diboration of alkenes gave a complex mixture of organoboron products (Scheme 1.10).[53]



Scheme 1.10 Product distribution observed in Rh(I)-catalyzed diboration of 4-vinylanisole

A plausible explanation, from a mechanistic point of view, suggests that the first step is likely to be an oxidative addition of the B-B bond of the diboron reagent to the metal, leading to a metal-diboryl complex (Scheme 1.11, *path a*). The desired 1,2-bis(boronate)ester seems to arise from alkene insertion into a M-B bond (Scheme 1.11 *path b*) followed by B-C reductive elimination involving the second boryl ligand (moiety). However, the alkenyl and alkenylboronate esters can be formed by a competitive *β*-hydride elimination (Scheme 1.11, *paths c-c'*). Monoborated products could also be formed from hydroboration competitive pathways (Scheme 1.11, *paths d-d'*).



Scheme 1.11 Postulated catalytic cycle of the diboration and some of the side reactions

An important aspect of the selective diboration reaction is the nature of the boryl moiety and its influence on the chemoselectivity. The use of

bis(pinacolato)diboron (B_2pin_2) or bis(neopentylglycolato)diboron (B_2neop_2) favors the *β*-H-elimination versus reductive elimination when the catalyst precursor is *trans*-[Rh(Cl)(CO)(PPh_3)$_2$].[54] Alternatively, the activation of B_2cat_3 (Figure 1.3) by [Rh(acac)L_2] provides a zwitterionic complex, which facilitates the reductive elimination towards the diborated product, disfavoring the *β*-H-elimination step.[55]

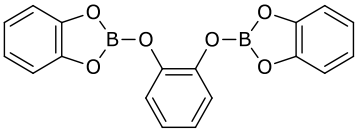
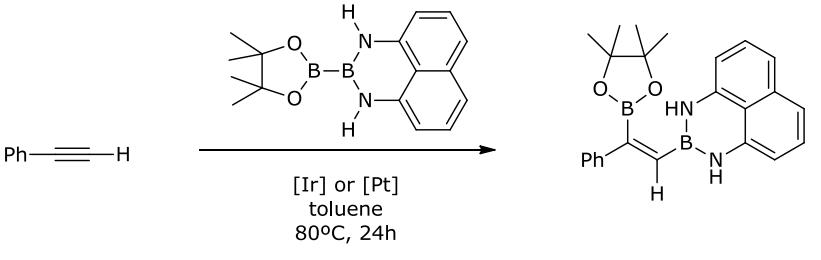


Figure 1.3 Tris(catecholato)diboron (B_2cat_3)

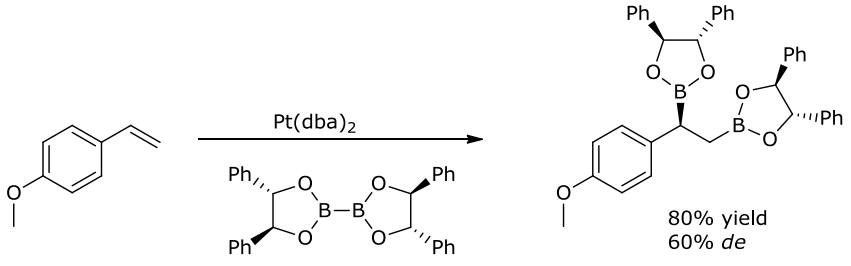
Alternative strategies with different catalytic systems have lead to high chemoselectivities in the formation of organodiboronic esters from C=C, C=N and C=S substrates.[56–58]

Recently, it has been demonstrated that an unsymmetrical diboron reagent can regioselectively be added to terminal alkynes in the presence of Ir or Pt catalyst, leading to the formation of 1-alkene-1,2-diboron derivatives, in which the internal boryl moiety (Bpin) is more reactive towards further functionalization (Scheme 1.12).[59]



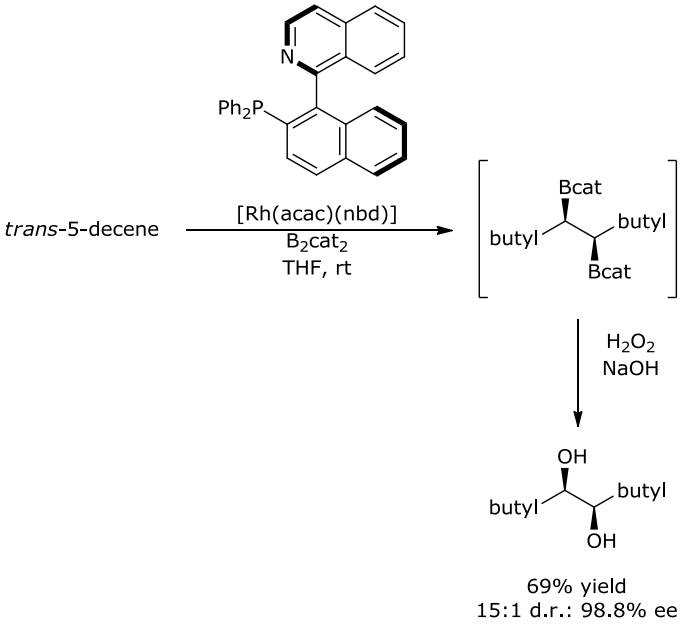
Scheme 1.12 Example of diboration of alkynes with unsymmetrical diboron reagents

The asymmetric catalytic diboration reaction was first carried out using chiral diboron reagents. Marder and coworkers[60] studied the platinum mediated addition of enantiomerically pure chiral diboron compounds to vinylarenes. The reaction was very slow and after 3 days of reaction time at 4ºC, 80% of diboron product was obtained with a diastereomeric excess (*de*) of 60% (Scheme 1.13).



Scheme 1.13 Initial attempts towards asymmetric diboration

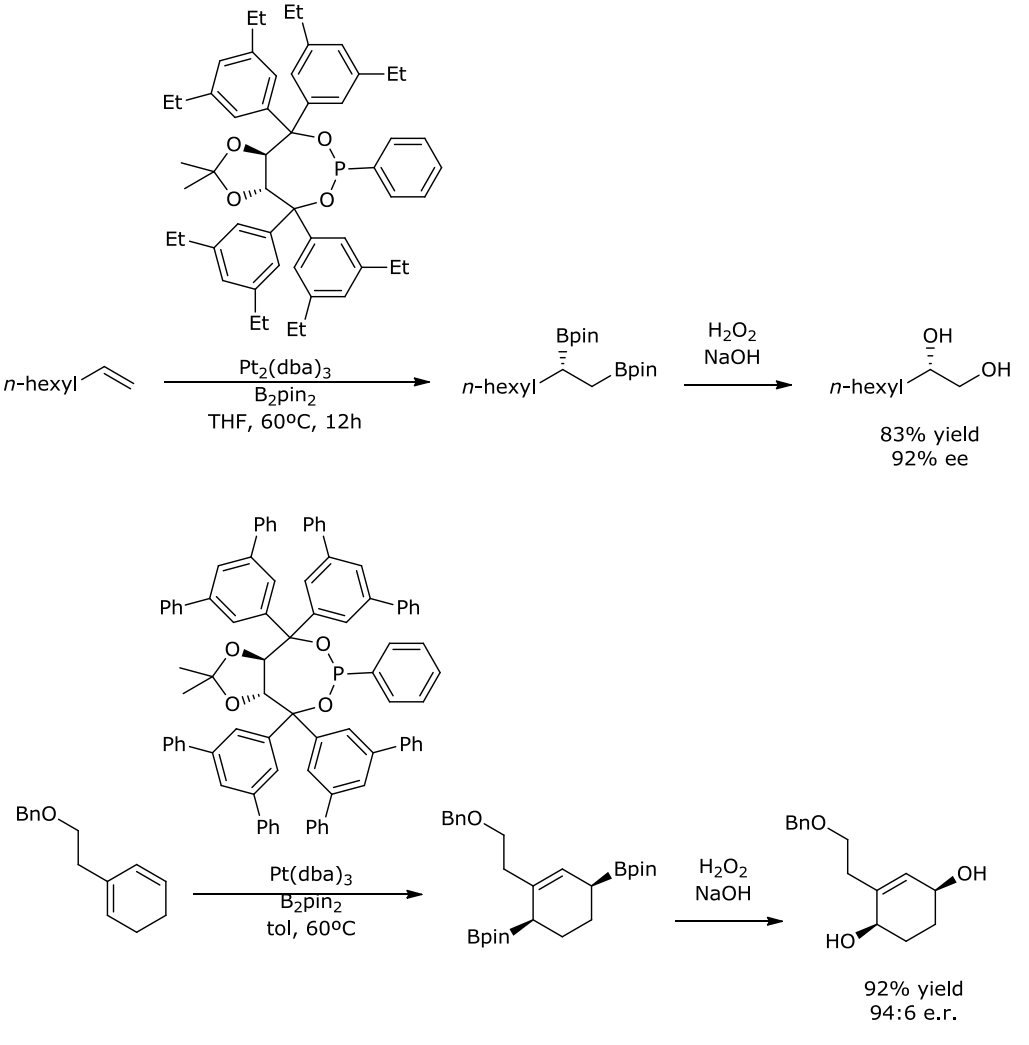
However, the modification of transition metal complexes with chiral ligands opened new doors for asymmetric induction. Morken and coworkers were pioneers in the field of enantioselective diboration reaction of alkenes, by modification of rhodium complexes with the P,N-ligand (R)-QUINAP (Scheme 1.14).[61–63]



Scheme 1.14 An example of enantioselective diboration of simple alkenes carried out with Rh-(R)-QUINAP system and B_2cat_2

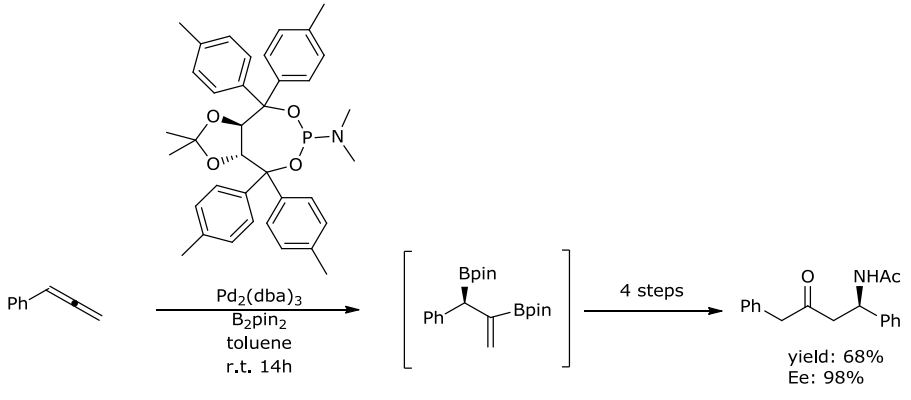
Recently, Morken and coworkes have described a very active and selective Pt catalytic system modified with chiral phosphonites (with TADDOL backbone) achieving enantioselectives up to 92% for a large scope of terminal alkenes.[28]

Analogous catalytic systems have been recently applied in enantioselective diboration of cyclic dienes.[64,65] In contrast to the Rh/(R)-QUINAP system that activated bis(catecholato)diboron, the platinum/phosphonite is the first catalytic system providing high enantioselectivity using bis(pinacolato)diboron as the diboron source (Scheme 1.15)



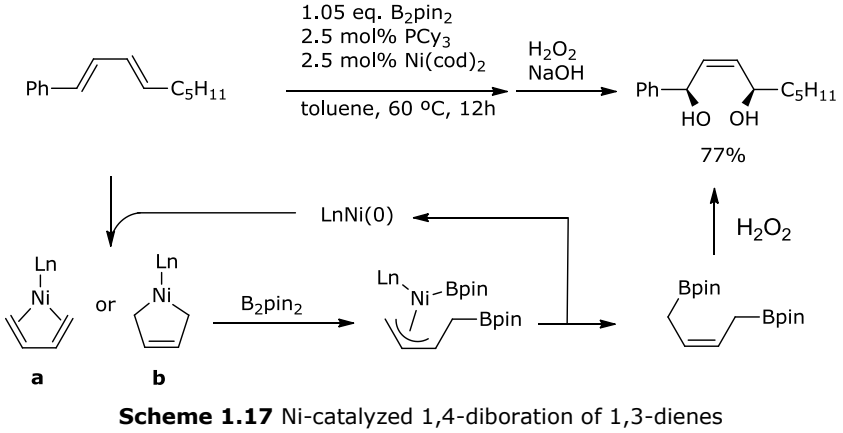
Scheme 1.15 Examples of enantioselective diboration of simple alkenes and cyclic dienes, carried out with Pt-phosphonite system and B_2pin_2

Alternative strategies with different catalytic systems using other metals, such as Pd, and phosphoramidites as chiral ligands have allowed to increase the substrate scope of the enantioselective diboration of allenes (Scheme 1.16).[66,67]



Scheme 1.16 Enantioselective diboration of allenes with the Pd-phosphoramidite catalytic system

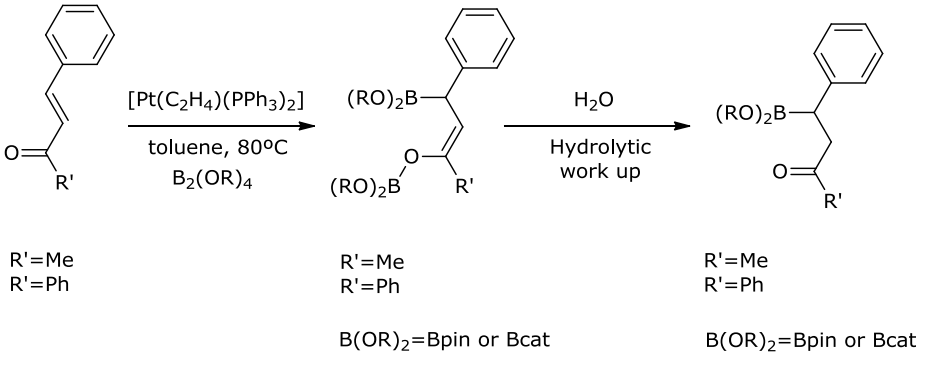
The substrate scope and selective diboration of new substrates have been always a challenge. Interestingly, the 1,4-diboration of 1,3-dienes with B_2pin_2 has efficiently been performed in the presence of $Ni(cod)_2/PCy_3$ (Scheme 1.17).[68] The diboration occurred selectively at 1,4-position of the diene moiety and no formation of 1,2-diboration products was observed for various 1,3-dienes, including 1-, 1,2-, 1,3-, or 1,4-substituted derivatives. It has been suggested that the reaction involves initial association of Ni(0) with 1,3-diene to form diene-Ni(0) complex **a** or nickelacyclopentene **b** and subsequent reaction with B_2pin_2.



Scheme 1.17 Ni-catalyzed 1,4-diboration of 1,3-dienes

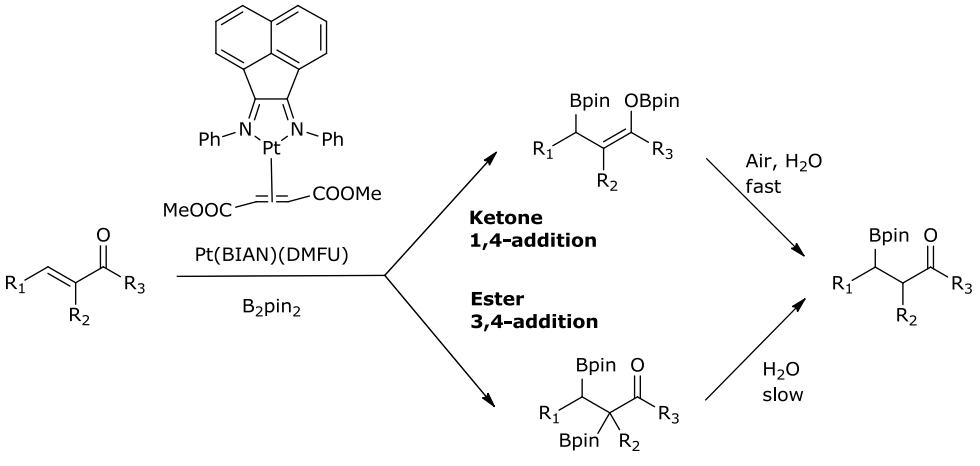
Among activated olefins, α,β-unsaturated carbonyl compounds are challenging substrates because the carbonyl functional group has a direct electronic influence on the double bond. The use of hydroboranes directly reduces the carbonyl group; however the use of diboron compounds allows the 1,4-diboration reaction.

The first 1,4-diboration of α,β-unsatured carbonyl compounds was carried out by Marder and coworkers[69] with platinum complexes. They described the reaction as a 1,4-diboration, which generated the corresponding β-borated product after the hydrolytic work up (Scheme 1.18). The β-boration reaction has a poor atom economy because only one boryl unit from the diboron reagent is incorporated into the final product.



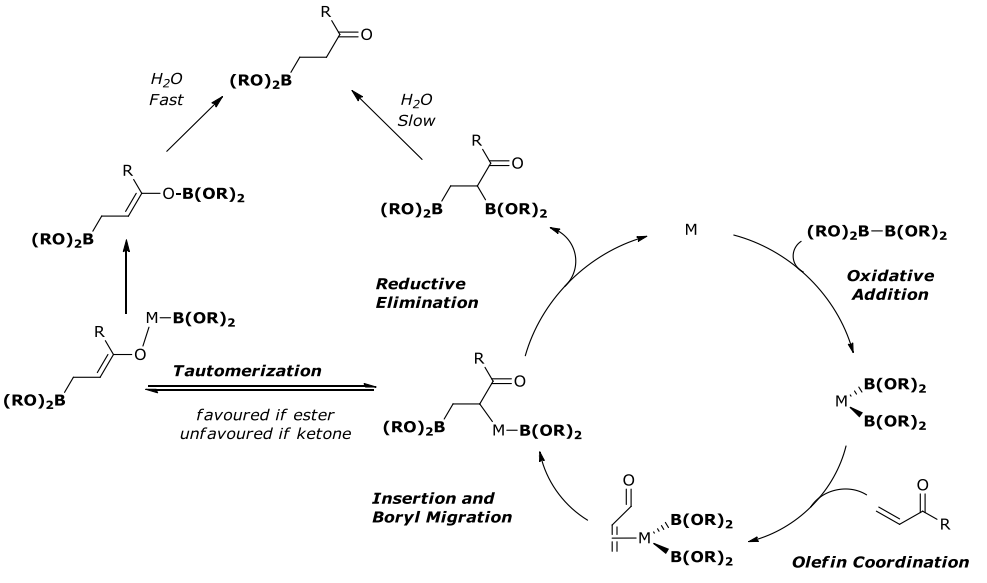
Scheme 1.18 First catalytic β-boration reaction of α,β-unsaturated ketones

Marder and coworkers[70] focused their efforts on the observation and isolation of diborated intermediates, consequently contributing to the understanding of the mechanisms of the metal catalyzed β-boration reaction. They observed that the second generation of Pt(0) catalyst (Scheme 1.19) displayed different reactivity between α,β-unsaturated ketones and esters. The activated ketones gave the expected 1,4-diboration and the activated esters formed the unprecedented 3,4-diborated products.



Scheme 1.19 *β*-boration of *α,β*-unsaturated ketones and esters with second generation of Pt(0) catalysts

Kabalka and coworkers reported in 2002 the catalytic *β*-boration of a large scope of *α,β*-unsaturated carbonyl compounds (cyclic and acyclic ketones, esters, aldehydes and nitriles) using Wilkinson catalyst.[71] From the mechanistic point of view, it has been reported that diboron reagents can be added to Rh(I) and Pt(0) *via* oxidative addition, and the substrate could be coordinated to the metal center, to promote further insertion and consequent boryl migration to the *β* position (Scheme 1.20). From that point, two possible pathways could complete the catalytic cycle, depending on the nature of the substrate: direct reductive elimination to give the 3,4-diborated product, or tautomerization followed by the reductive elimination to give the 1,4-diborated product (Scheme 1.20).



Scheme 1.20 Catalytic cycle of *β*-boration reaction

More recently Marder and coworkers, have corroborated this proposal by means of DFT calculations.[72]

1.2.1.2 *Via* σ-bond metathesis

Usually, metals with lower *d* orbital energies fail in the activation of diboron reagents *via* oxidative addition, but some transition metal complexes react with tetralkoxydiboranes without changing the formal oxidation state of the metal. The activation of the diboron reagent can be considered as σ-bond metathesis between the diboron reagent and the M-X unit (X=anionic ligand, alkoxide preferentially).

The first copper mediated diboration reaction was previously developed by our group.[73] It was found that Cu(I) complexes modified with NHC (N-heterocyclic carbene) ligands activated bis(catecholato)diboron and promoted a selective addition to alkenes and alkynes with B_2cat_2. The B_2pin_2 reagent was found to be less efficient in this reaction.[73]

Theoretical Density Functional Theory (DFT) calculations were carried out in order to clarify the nature of the interaction between Cu/NHC complexes and

B_2cat_2. The results were conclusive in favor of the formation of a sigma complex, and excluded the possibility of the oxidative addition due to the fact that its activation energy was 69.2 kcal·mol^{-1} higher than the sigma complex formation (Figure 1.4).[73] The [Cu(I)(NHC)(σ-B_2cat_2)]$^+$ could further undergo a σ-bond metathesis to deliver the active Cu-Boryl species (Figure 1.4).

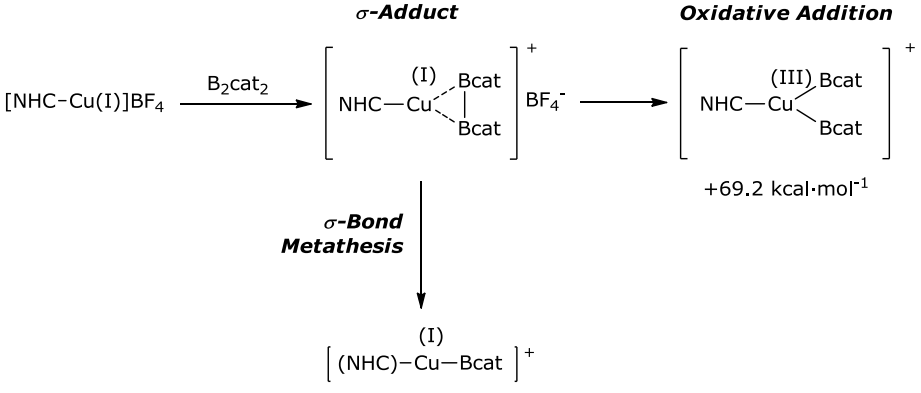


Figure 1.4 Activation of B_2cat_2 with Cu(I)-NHC complexes by σ-bond metathesis

Further DFT calculations reported by Marder and Lin pointed out the differences in reactivity between the two diboron reagents , B_2cat_2 an B_2pin_2.[74] Both metathesis reactions have similar and very small energy barriers (Figure 1.5). However, the nature of the diboron reagent is again important in the activation pathway, as binding of B_2cat_2 seems to be more favourable than for B_2pin_2, as a matter of the enhanced Lewis acid properties of the B_2cat_2 (Figure 1.5).

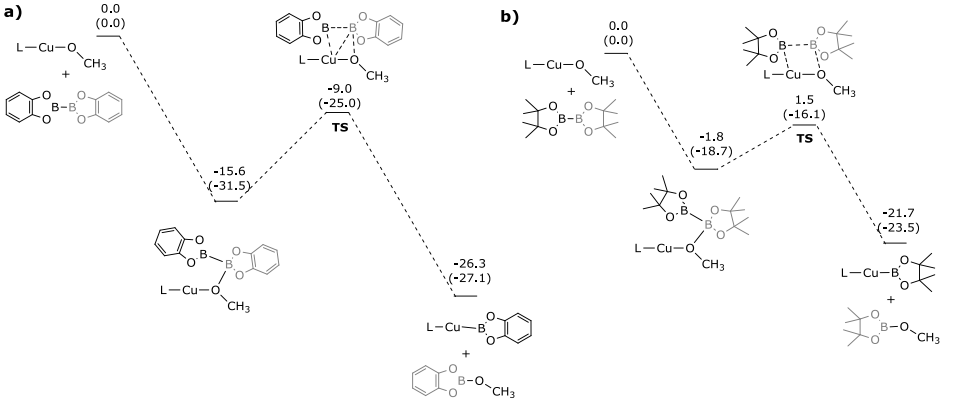
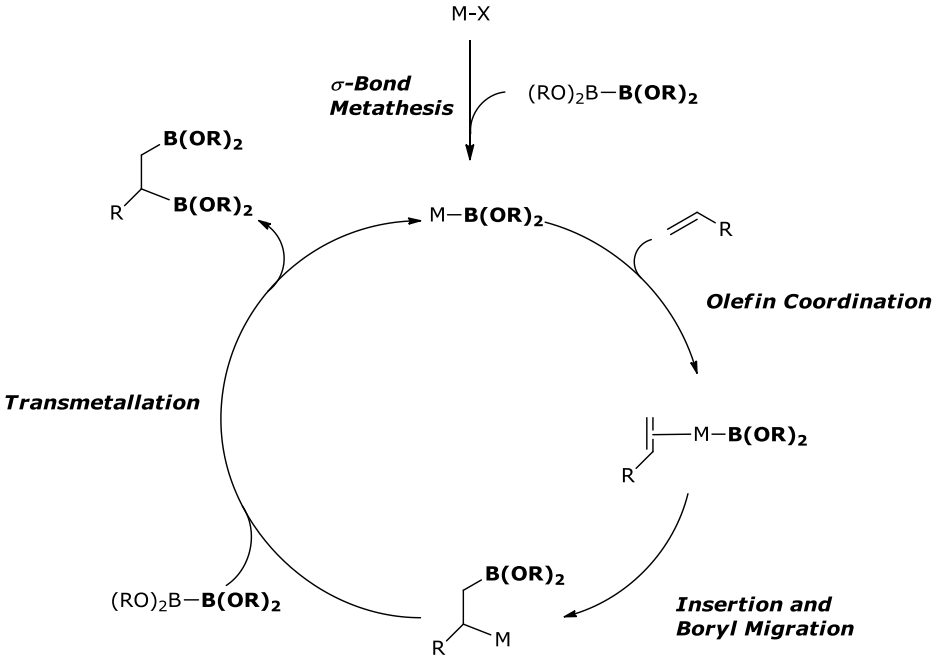


Figure 1.5 Energy profile calculated by Lin et al.[74] for the metathesis reaction of the model complex (NHC)Cu(OMe) with: (a) B_2cat_2 and (b) B_2pin_2. The calculated relative free energies and electronic energies (in parentheses) are given in kcal.mol^{-1}

Catalytic diboration of alkenes with transition metal complexes based on coinage metals was first explored by Marder and coworkers.[53] The catalytic system tested was [Au(PEt_3)Cl]/1,2-bis(dicyclohexylphosphino)ethane, because the gold system, as an example of metal with lower *d* orbital energy, disfavors the *β*-hydride elimination pathway. The authors found that terminal alkenes could be chemoselectively transformed into the 1,2-diborated products, although high temperatures (80 ºC) and long reaction times (84 hours) were required.

The reaction mechanism might involve the heterolytic cleavage of the diboron reagent by σ-bond metathesis, leading to the formation of the boryl complex, subsequent alkene coordination, insertion and transmetallation with diboron reagent provided the desirable product and regenerated the active species. The generation of the metal-boryl species was required to start the catalytic cycle (Scheme 1.21).



Scheme 1.21 Plausible catalytic cycles for diboration reaction through σ-bond metathesis

Our group was able to demonstrate that gold(0) nanoparticles stabilized with diphosphines were responsible for the diboration of alkenes, providing complete chemoselectivity towards the 1,2-bis(boronate)esters.[75] Of particular importance are the mild reaction conditions, the low catalyst loading and the substrate scope (Figure 1.6)

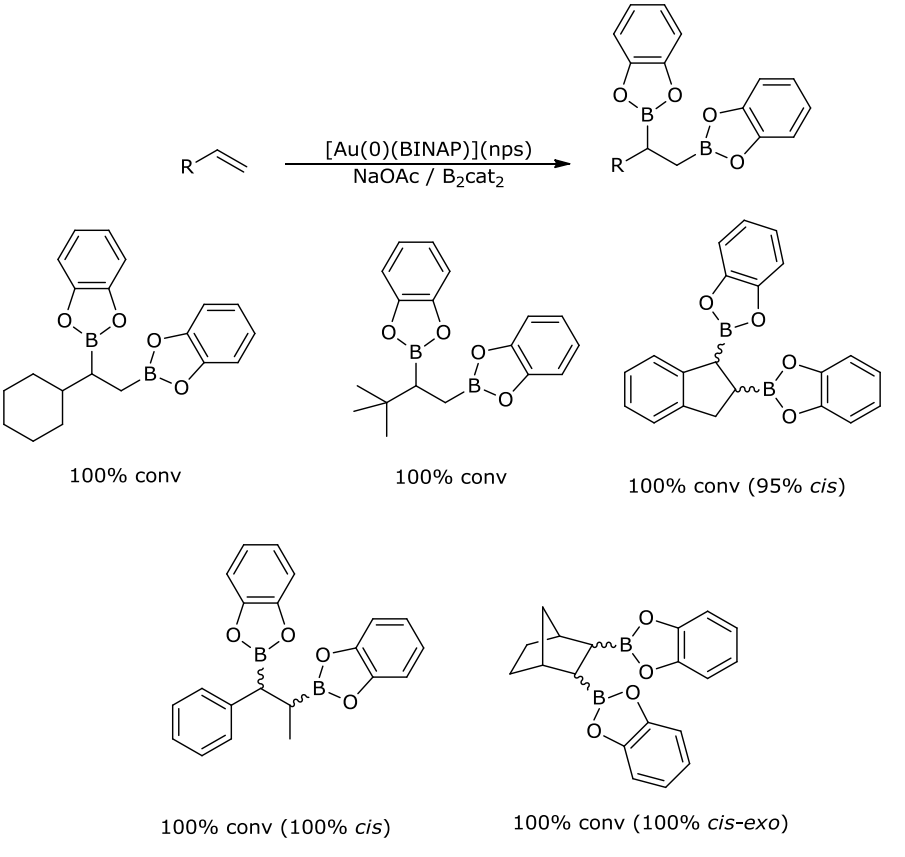
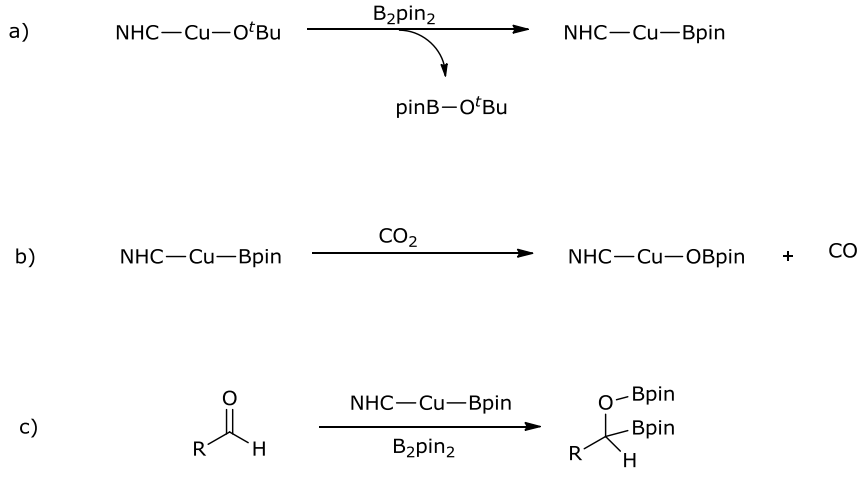


Figure 1.6 Au(0) nanoparticles catalyzed diboration of alkenes with B_2cat_2

Alternative catalytic systems based on silver complexes modified with N-heterocyclic carbene ligands have also been found to promote the chemoselective diboration of alkenes.[76,77]

Focusing on the transition metal complexes of group 11, the copper complexes were the preferred ones to explore new approaches towards diboration reaction. In this context, Sadighi and coworkers[78,79] reported the activation of diborons with Cu(I) salts, and the application of copper-boryl systems in boron addition reactions. The early approach by Sadighi and coworkers was the isolation of LCu-Bpin species (whereby L= N-heterocyclic carbene ligand) from LCu-O^{t}Bu and B_2pin_2 through σ-bond metathesis (Scheme 1.22, *path a*).[78] Another, important discovery by Sadighi's team involved the use of NHC-Cu-Bpin species

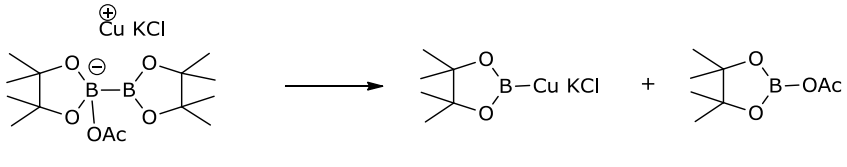
in the reduction of CO_2 to CO (Scheme 1.22, *path b*), and the diboration of aldehydes (Scheme 1.22, *path c*).[79]



Scheme 1.22 Sadighi and coworkers approaches towards copper-boryl synthesis and applications

The activation of diboron reagent with copper salts allowed the application of copper salts in β-boration of α,β-unsaturated carbonyl substrates. Miyaura and coworkers,[80,81] and Hosomi and coworkers,[82] at the same time but independently, reported that Cu(I) salts, in the presence of the appropriate additives, catalyzed the β-boration of α,β-unsaturated ketones and esters. In both cases the products were obtained after the aqueous work-up, and the possible primary 1,4- or 3,4-diborated products were not observed.

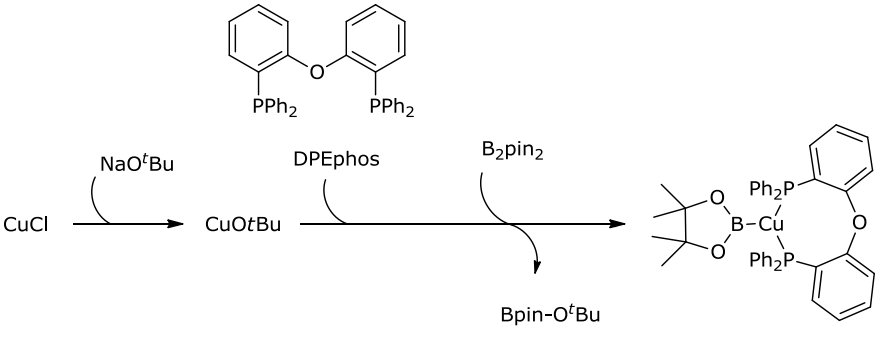
Miyaura and coworkers used copper chloride as precursor and KOAc as additive. The authors were able to study that the base assisted the transmetallation between the CuCl and the B_2pin_2 by ^{1}H NMR (Scheme 1.23)



Scheme 1.23 Base assisted transmetallation between B_2pin_2 and CuCl

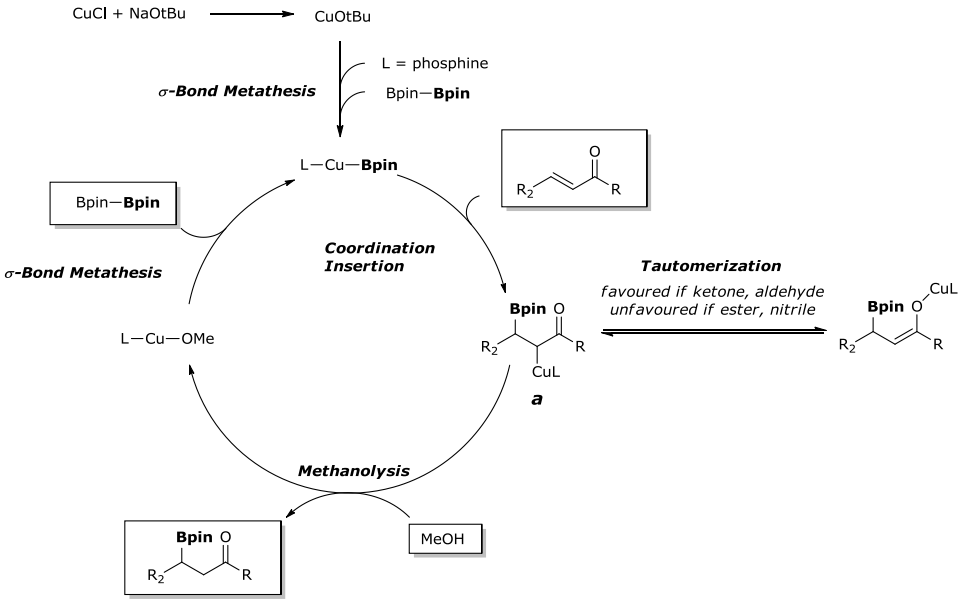
Both systems were fairly efficient in the β-boration of α,β-unsaturated carbonyl compounds, although long reaction times were required in order to obtain good yields. This drawback was circumvented only few years ago, when Yun and coworkers optimized the reaction conditions introducing MeOH as an additive to facilitate the recovery of the catalytically active species and provide a H^+ source for the formation of the desired β-borated product.[83] Apart from MeOH, other alcohols were also tested in order to accelerate the reaction and achieve complete conversions with alkenes[83] and alkynes,[84] at room temperature within short reaction times. The catalytic system consists on inexpensive copper chloride and phosphine ligand, catalytic amount of base (usually sodium *tert*-butoxide), diboron reagent (B_2pin_2) and methanol.

The authors postulated a mechanism whereby the base activated the CuCl by substitution of the chloride ligand with $^tBuO^-$, and σ-bond metathesis between the copper-alcoholate and the diboron reagent, B_2pin_2, lead to the catalytically active Cu-Bpin species (Scheme 1.24).



Scheme 1.24 *In situ* formation of L-Cu-Boryl by Yun and coworkers[83]

Coordination of the substrate and Michael type migratory insertion of the Bpin moiety provided the 4-Bpin-3-copper-alkyl (Scheme 1.25, ***a***) intermediate, which could form the copper-enolate intermediate by tautomerization. Methanolysis of both species provided the product and copper(I)-methoxide, which interacted with B_2pin_2 to regenerate the catalytically active species (Scheme 1.25).



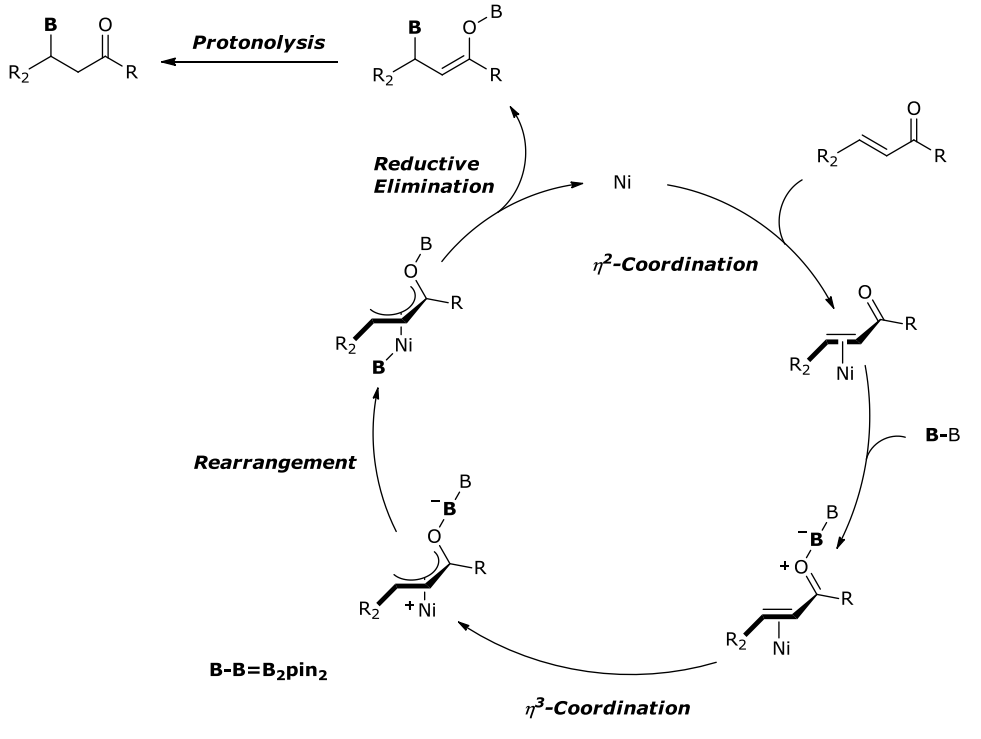
Scheme 1.25 Postulated catalytic cycle of the Cu-catalyzed β-boration reaction of α,β-unsaturated olefins

Lin, Marder and coworkers have carried out a comparative DFT study on the copper catalyzed β-boration of acrolein and methylacrylate.[85] They have shown that the model substrate, α,β-unsaturated aldehyde and ester, reacted with copper-boryl complexes through C=C insertion into the Cu-B bond, forming the corresponding Michael addition product. The aldehyde undergoes keto-enol tautomerization and forms the corresponding Cu-enolate, while in the case of the ester the tautomerization did not occur due to the inertness of the ester group.[74]

Recently, Santos and coworkers have contributed to the field of copper mediated β-boration with a Cu(II) system, that is not oxygen sensitive and allows the β-boration in water.[86]

Oshima and coworkers have found that Ni(0) complexes also catalyzed the β-boration of α,β-unsaturated carbonyl compounds.[87] The system, similarly to the Cu(I) catalysts, required the addition of base and alcohol. The authors have proposed a reaction mechanism whereby, as the first step, the substrate

coordinated to the Ni(0) precursor *via* the C=C double bond. After the formation of the η^2-nickel complex, the coordinated substrate activated the diboron reagent *via* a Lewis acid-base interaction between the carbonyl functional group and the empty p-orbital of one of the boron atoms (Scheme 1.26)



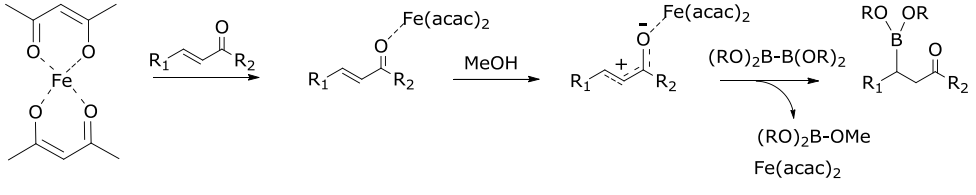
Scheme 1.26 Postulated catalytic cycle of *β*-boration of *α,β*-unsaturated carbonyl compounds with Ni complexes

The authors suggested that the Lewis acidity of the boron promoted a shift in the conjugated π electron system of the substrate, and therefore the coordination mode changed from η^2 to η^3, and the allylic ligand formally oxidized the central atom. The activated diboron reagent transferred the boryl ligand into the coordination sphere of nickel, and the 1,4-addition products was formed by elimination.

Despite the increased efforts devoted to the catalytic *β*-boration reaction, the first enantioselective approach was developed in 2006 by Yun and coworkers,[83]

using a chiral diphosphine that modified the copper-boryl catalytic systems. After further optimization, the authors reported in 2008 that ferrocenyl type chiral diphosphines were very efficient to promote high values of enantioselectivity in the β-boration of α,β-unsaturated esters and nitriles (up to 94%).[88]

Also, in our group it has been found that iron (II) and (III) complexes can promote the β-boration reaction of a wide range of α,β-unsaturated carbonyl compounds.[89] In this case, a preactivation of the substrate by the Lewis acidic Fe(II) and Fe(III) salts seems to have a beneficial influence on the reaction outcome (Scheme 1.27).

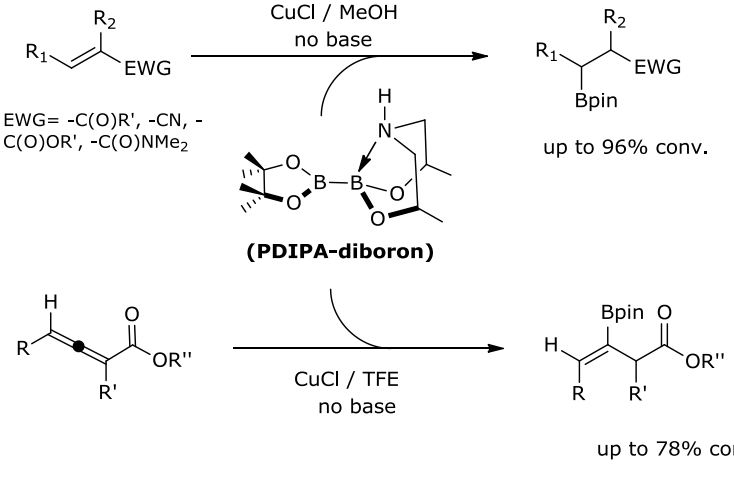


Scheme 1.27 Activation mode proposal for iron complexes in the β-boration reaction

1.2.2 Activation of diboron reagents by organocatalytic approaches. Applications

The activation of diboron reagents had generally been attributed to a direct interaction between the reagent and transition metal complexes, until Miyaura and coworkers observed that AcO^-activated diborons by Lewis acid–base interactions.[81] The resulting [B_2pin_2·AcO^-] adduct (see Scheme 1.23) facilitated the heterolytic cleavage of the B–B bond and the transference of one boryl moiety to a copper(I) salt.

Recently, intramolecular Lewis acid-base interaction has been reported between the secondary amine and one of the boron atoms in pinacolato(diisopropanolaminato)diboron (PDIPA-diboron). This intramolecular activation of the mixed diboron reagent, facilitated the σ-bond metathesis with the CuCl salts. This methodology has been applied for the copper-catalyzed borylation of α,β-unsaturated[90,91] substrates and β-borylation of allenoates (Scheme 1.28).[92]

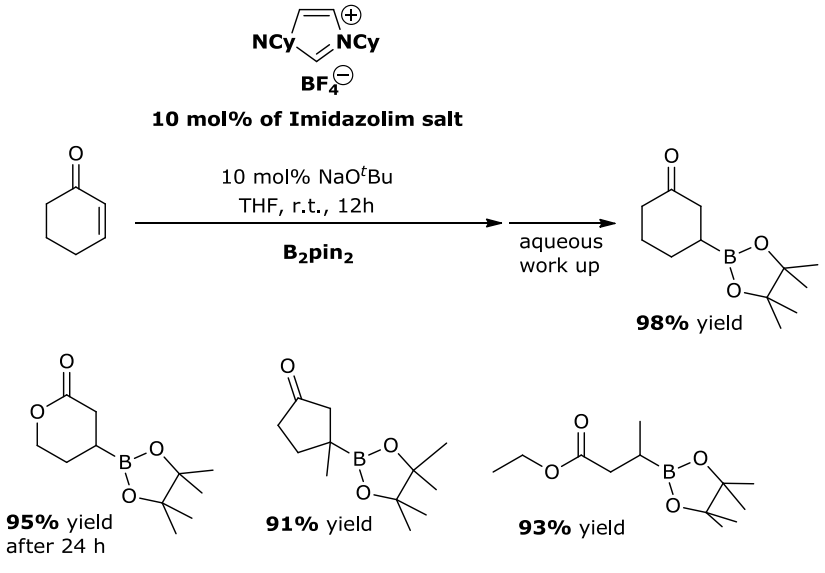


Scheme 1.28 General reaction conditions for Cu(I) catalyzed β-boration with the PDIPA-diboron and β-borylation of alleonates

It was not until 2009 when Hoveyda and co-workers reported the first metal free system to activate tetraalkoxydiborons towards the efficient C-B bond

formation using 10 mol% of an imidazolium salt and equimolar amouts of sodium *tert*-butoxide (Scheme 1.29) .[93] The authors postulated that the *in situ* generated nucleophilic N-heterocyclic carbene could associate with the Lewis acidic boron atoms of B_2pin_2 to activate it.[93,94] Under this reaction conditions (Scheme 1.29), cyclic and acyclic α,β-unsaturated ketones or esters were β-borated in up to >98% yield. They also illustrated that boron conjugate addition under metal-free conditions delivered reactivity and site-selectivity levels not attainable through the use of a Cu-catalyzed variant.

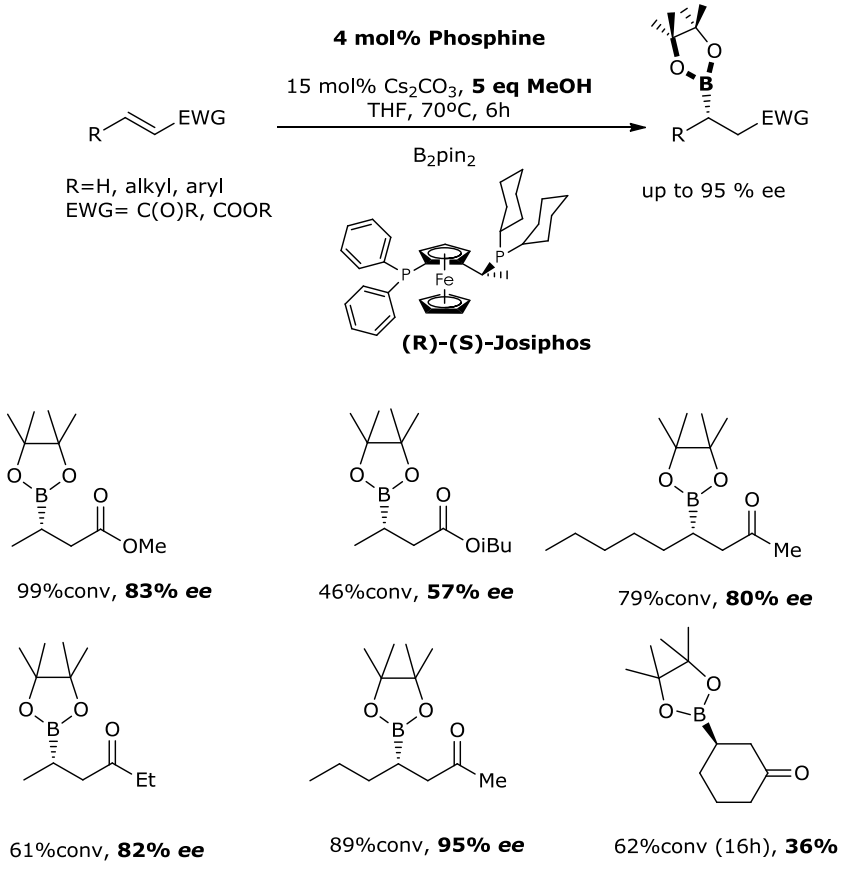
Importantly, by means of spectroscopic and DFT studies, Marder *et al.* have recently demonstrated the existence of a neutral Lewis acid-base adduct of B_2pin_2 and an N-heterocyclic carbene both in solution and in the solid state.[95]



Scheme 1.29 Representative scheme of the reaction conditions for the metal free β-boration reaction reported by Hoveyda *et al*.[93] and selected examples of borylated substrates under this conditions

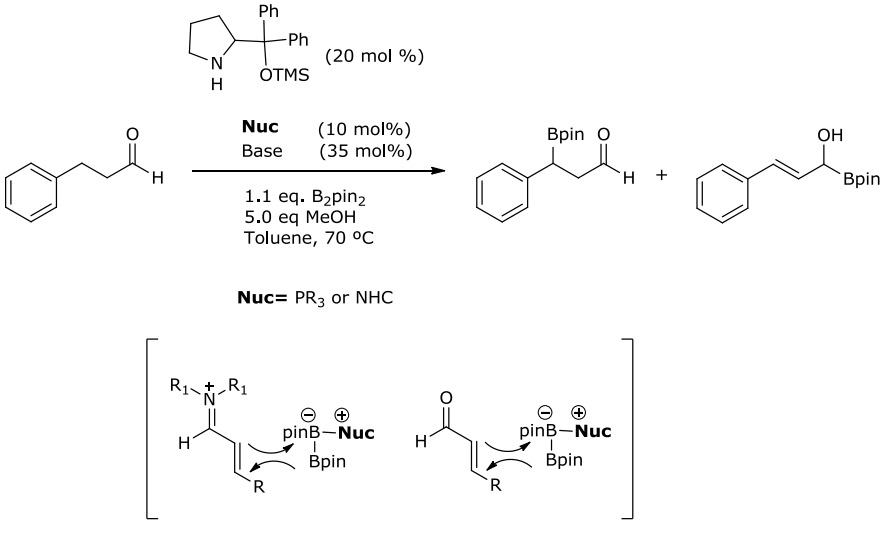
In this context some members of our group developed the first asymmetric organocatalytic β-boration reaction based on the use of Brönsted base, methanol and chiral phosphines in the presence of B_2pin_2.[96] Using the adequate phosphine, high conversions and high levels of enantiomeric excess (*ee*) could

be obtained with a wide range of α,β-unsaturated carbonyl compounds (Scheme 1.30).[96]



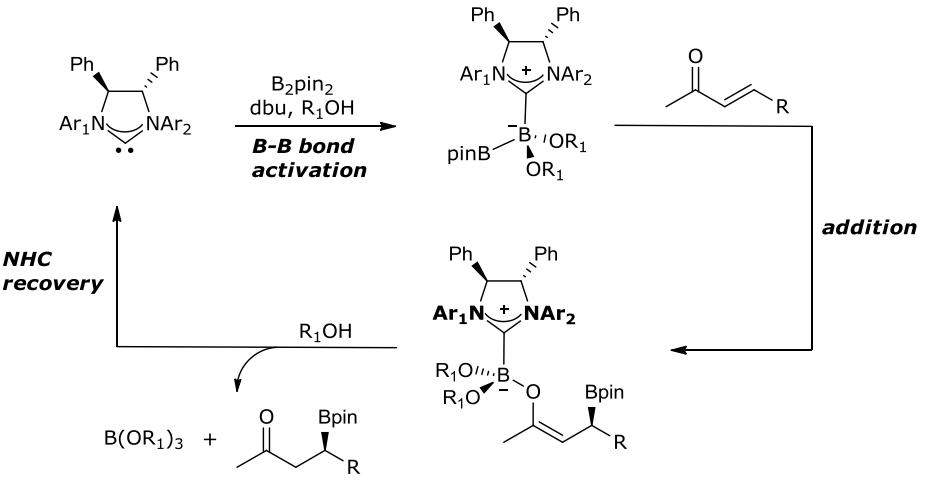
Scheme 1.30 General scheme of the reaction conditions for the first asymmetric metal-free β-boration reaction and selected examples of β-borated substrates with (R)-(S)-Josiphos

Early this year, Córdova *et al.*,[97] reported the organocatalytic β-boration with the *in situ* iminium formation (Scheme 1.31).



Scheme 1.31 Organocatalytic β-boration by means of iminium intermediates

More recently, Hoveyda *et al.* have reported the asymmetric version of the organocatalytic β-boration with chiral NHC.[98] Towards this end the authors used, 7.5 mol% imidazolium salt , 30 mol% dbu (1,8-Diazabicyclo[5.4.0]undec-7-ene.) , 60 eq MeOH to perform the β-boration of a series of α,β-unsaturated compounds with relatively high levels of enantioinduction in a range of 22ºC-50ºC. Although MeOH was crucial for an active system, the authors suggested that the NHC activates the diboron reagent by a Lewis acid-base adduct (Scheme 1.32).



Scheme 1.32 Mechanistic proposal for the NHC mediated enantioselective organocatalytic *β*-boration reaction[98]

1.3 Theoretical studies on the activation of diboron reagents

Computational chemistry[99] has become a very important tool in modern chemistry for understanding the structure, properties and reactivity of chemicals.

Experimental studies on the diboration reaction rapidly attracted the interest of theoretical chemists.[100,101] The addition of B_2H_4 to ethylene[102] was examined theoretically as a model for the uncatalyzed addition of B_2X_4 to alkenes, some years before the discovery of the catalyzed version of the diboration with tetraalkoxydiborons. The key findings in that two semiempirical MNDO (Modified Neglect of Differential Overlap) studies were that the reaction was exothermic and proceed in two steps via a 3-centred π-system serving as a donor to one of the two boron centers in the intermediate complex preceding the B-B bond cleavage. The activation energy for the uncatalyzed diboration of ethylene was slightly higher than for acetylene.

The oxidative addition of model compounds B_2H_4 and $B_2(OH)_4$ to $M(PH_3)$ (M= Pd, Pt) has been examined by ab initio computational techniques.[48,103,104] The study by Sakaki *et al*. suggested that the unoccupied B-B π- and π-*-orbitals, in addition to the B-B σ*-orbital, can be involved in the charge transfer interaction with Pt σ- and π-symmetry d-orbitals responsible for B-B oxidative addition.

Morokuma and co-workers examined the mechanism of the catalyzed addition of model diborane $B_2(OH)_4$ to ethylene and acetylene with $[Pt(PH_3)_2]$ by DFT (Density Functional Theory) techniques.[105] Their work confirmed the importance of phosphine dissociation leading to a mono-phosphine complex before B-B bond oxidative addition, and also showed that the activation energy for the insertion of ethylene into the Pt-B bond was higher than that for the analogous acetylene insertion reaction, which is consistent with the fact that the phosphine-based platinum systems catalyze the diboration of alkynes but not of alkenes.

In a parallel study, Morokuma *et al*.[46,105] reported a theoretical study with DFT-based methods of the mechanism of the Pd(0)-catalyzed alkyne diboration reaction and compared it with the Pt(0)-catalyzed one. They found that the mechanism involved the same steps: (i) coordination of diborane $R_2B\text{-}BR_2$ to the Pd(0) complex, (ii) oxidative addition of the B-B bond to Pd, (iii) dissociation of

one phosphine ligand, (iv) coordination of acetylene, (v) insertion of acetylene into one of the Pd-B bonds, (vi) isomerization of the resulting complex accompanied by recoordination of the phosphine ligand, an (vii) reductive elimination of the alkenyl-diboron products. However, experimentally, Pd(0) cannot catalyze this reaction. The main reason for the difference in the catalytic activities of Pd(0) and Pt(0) is the oxidative addition process of the B-B bond to $M(PH_3)_2$. The process occurs for M=Pt with a 14.0 kcal.mol^{-1} activation barrier and is endothermic by 7.2 kcal.mol^{-1}. Although the process for M=Pd has a lower barrier (8.6 kcal.mol^{-1}), it is 8.5 kcal.mol^{-1} endothermic, and the reverse barrier is only 0.1 kcal.mol^{-1}. Because of this low reverse barrier, B-B oxidative addition to $Pd(PH_3)_2$ cannot take place. In 2007, Morken *et al*.[106] have demonstrated using DFT methods, that the mechanism of the Pd-catalyzed allene diboration proceeds through an oxidative addition of the diboron to the metal center. The authors proposed that electron-donating ligands, like phosphoroamidites, stabilize high oxidation state of palladium-diboryl, L-Pd-$(B(OR)_2)_2$, intermediates, thus making the oxidative addition possible and facilitating Pd catalysis.

In summary, a variety of theoretical methods allowed an in–depth understanding of the activation mode of the diboron reagents and the reaction mechanisms of its addition to unsaturated substrates. Notably, DFT methods have gained importance during the past of the years, and nowadays, are the most used computational method to study the catalytic boron addition reactions.

A remarkable DFT study on tricoordinate boron compounds has recently been published highlighting the donor and acceptor properties of boryl.[107]

1.3.1 Density Functional Theory-based methods

Density Functional Theory (DFT) of electronic structure has made an unparalleled impact on the application of quantum mechanics to interesting and challenging problems in chemistry. As evidenced by some recent reviews,[108–117] the number of applications is growing rapidly by the year and some of the latest and most significant studies include from the understanding of catalytic processes (including enzymes and zeolites) to solar energy harvesting and conversion, drug design in medicine, as well as many other problems in science and technology.

Density Functional Theory (DFT) provides a good and time-economic way to handle many electron systems. Such methods were developed based on the Thomas-Fermi-Dirac model (1920's) and on the work of Slater in quantum chemistry (1950's). DFT methods are then similar to *ab initio* methods at a much less computational cost: they require roughly the same amount of computation resources as Hartree-Fock theory, the least expensive *ab initio* method.

Density Functional Theory methods rely on the electron density rather than the wave function. This simplification is possible thanks to the development of the Hohenberg & Kohn theorem,[118] which demonstrate that the energy of a system can be expressed as a functional of the electron density. A functional is described as a function of a function, but the theorem does not provide the form of such functional. The most common implementation is the Kohn-Sham formalism[119] that obtains the electron density from a set of orbitals.

Compared to Hartree-Fock based methods, less computational resources are needed because it is not necessary to calculate the many electron wavefunction. Moreover, DFT calculations include electron correlation. This term, referring to instantaneous repulsive interactions, is absent in Hartree-Fock theory. In the Hartree-Fock framework, electron correlation has to be introduced through computationally demanding schemes as configuration interaction or perturbation-methods.

The accuracy of a DFT calculation depends on the quality of the exchange correlation functional. As the exact expression of this functional is not known, some approximations are therefore needed. The quest for more accurate DFT functional is variations and improvements on how to address this term.

The first approximation was the Local Density Approximation (LDA) where the functional depends only on the value of the electron density. Local spin-density approximation (LSDA) also includes electron spin. These functionals were good for solid state physics, but failed when calculating chemical properties. The following major improvement was the consideration of the gradient of the density. The Generalized Gradient Approximation (GGA) method takes into account the fact that the electron density varies through the space, and as such, the approximation is more complex than that of the LDA method. Functionals following the GGA formalism typically estimate the energy of the

systems with a reasonable accuracy, improving the results obtained with LDA functionals. Their performance is however limited in a number of cases, for example when accurate descriptions of van der Waals interactions is needed.[120] Among the numerous functionals following the GGA approximation, BP86,[121,122] and BLYP are widely used.[121,123] The accuracy of this functional can be improved by using meta-GGA approaches, in which the gradient of the density and its Laplacian (second derivative) are included too.

A very popular class of functionals is the hybrid-GGA, which combine the exchange-correlation term of the GGA approximation with a part of the Hartree-Fock exchange. These functionals are now widely used because of the significant improvement obtained for the description of a wide range of molecular properties. The most popular hybrid functional is B3LYP.[124]

More Recently, Truhlar and coworkers have developed a suite of meta-hybrid density functionals including M06, M06HF, M062X, M05, and M052X.[125] Meta-hybrid-GGA functionals are now increasingly used in chemical modeling, since some of them appear to describe accurately molecular systems containing weak interactions (such as van der Waals interactions).

The more complex functionals (developed through more complex approximation,) describe more precisely the electron density, and by extension provide more accurate descriptions of the molecular properties as it is represented by the Jacob's ladder of exchange-correlation functionals.[126]

The choice of a particular method compromises the quality of the results and the time spend for the calculation.

In this PhD thesis, various functional have been used, namely, GGA BP86, meta-hybrid M06 and occasionally hybrid B3LYP.

1.4 Hypothesis of work and objectives

The formation of new C-B bonds is of high interest since the organoboranes are key intermediates in fine chemical and pharmaceutical industry.

This thesis focuses on the development of novel methodologies for boron addition to olefins, with particular attention to the understanding of the mechanism of these processes. For this purpose, experimental studies and theoretical calculations have been carried out.

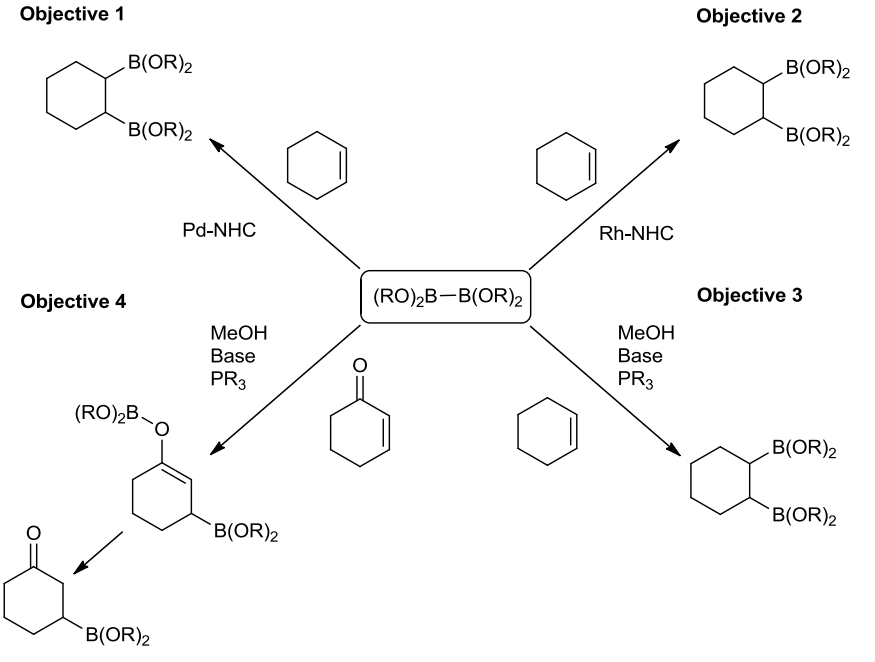
The hypothesis of work for this thesis are:

1. Since palladium is involved in catalytic diboration reaction, can we perform the palladium diboration of endocyclic alkenes? Do NHC ligands play a special influence? How is the mechanism expected to proceed?

2. Since rhodium complexes are believed to catalyze diboration reaction with relative selectivity, we postulate that rhodium complexes modified with NHC ligands can exert a positive influence improving the chemoselectivity. Is the mechanistic study supporting this idea?

3. Innovation in diboration reaction involves new approaches. Towards this end an organocatalytic diboration is proposed with a comprehensive study of the activation of the diboron reagent.

4. The new concept of organocatalytic 1,2-diboration reaction, could it be extended to 1,4-diboration of α,β-unsaturated carbonyl compounds? Is it possible to understand the role of additives to suggest a mechanism and design alternative organocatalytic approaches, even in the asymmetric version?



Objective 5. The understanding of the activation mode of the diboron reagent, $B_2(OR)_4$ and the mechanism of the diboration reactions.

Objective 6. Compare our results with previous and contemporary studies reported by other groups to be able to think in a constructive way and create knowledge.

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1.5 References

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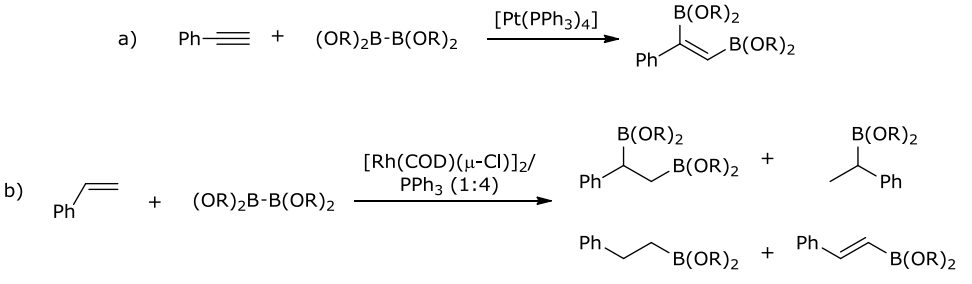
Chapter 2: (NHC)Palladium catalyzed selective diboration of endocyclic alkenes

Table of contents

2.1 Introduction

The simultaneous introduction of the two boryl units of diboron compounds in an unsaturated carbon-carbon bond is an efficient synthetic route towards organoboron compounds which are useful intermediates in organic synthesis.[1,2] When both C-B bonds are formed, they can be functionalized independently to produce homodifunctionalized or heterodifunctionalized compounds.[3–5]

The first transition metals used in the catalytic diboration reaction of alkynes and alkenes using tetraalkoxydiboranes were Pt and Rh.[6–11] In these cases the diboron reagent was oxidatively added to the metal center generating diboryl-metal species.[12] Reaction of these B-M-B species with unsaturated compounds provided monoborated or diborated products depending on the nature of the metal and the substrate. Monophosphine platinum-containing catalysts mediated the selective diboration of alkynes providing 1,2-alkene(bisboronate)esters through the *syn* addition of the B-B bond.[8,13,14] However, the related catalytic alkene diboration seems to be not selective due to the *β*-hydride elimination side reaction (Scheme 2.1).[7]



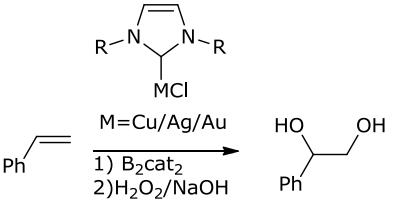
Scheme 2.1 Metal catalyzed addition of diboron reagents to unsaturated C-C bonds: a) phenylacetylene diboration; b) styrene diboration, showing the different products that can be formed

The availability of a very selective catalyst for selective diboration of alkenes is extremely desirable. In order to avoid the formation of byproducts, different strategies have been designed based on the use of transition metals in which the formation of M-H bond is disfavored, most of them based on transition metals with lower d orbital energies. These include the zwitterionic rhodium complex [Rh-(dppm)(η^6-catBcat)] (dppm=$Ph_2P(CH_2)PPh_2$ and cat=1,2-$O_2C_6H_4$) prepared in situ,[15] and the phosphine-free Pt-catalyst precursors.[16–18]

In addition to Rh and Pt, diphosphine-Au(I) complexes have been reported to selectively catalyze the addition of diborons to alkenes, although in moderate yields.[7] Our group has also demonstrated that gold nanoparticles efficiently catalyze the diboration of alkenes with total chemoselectivities.[19]

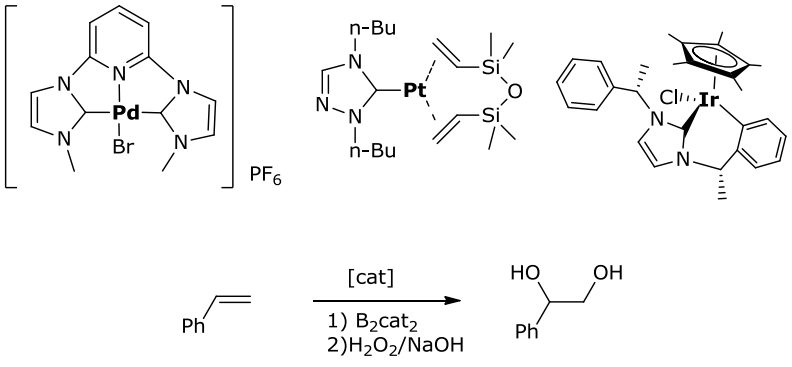
Selection of the appropriate transition metal is very important but also its modification by convenient ligands is critical for guarantee the selectivity of the reaction.

Concerning the nature of the ligands in transition metal complexes, N-heterocyclic carbenes (NHC) have already demonstrated to be a promising family of ligands to modify transition metal based catalytic systems.[20–26] The benefits of the use of N-heterocyclic carbenes as ligands in boron additions to alkenes have been widely demonstrated by our group. It is remarkably the study on the use of coinage metals: copper,[27] silver and gold[28,29] in the selective catalytic diboration of alkenes (Scheme 2.2).



Scheme 2.2 (NHC)-coinage metal mediated selective diboration of styrene

Also, our group extended the efficiency of N-heterocyclic carbene ligands to Pd(II),[30] Pt(0)[31] and Ir(III)[32] metal catalysts. The use of these systems provided excellent levels of chemoselectivity towards the diborated product, mainly of aliphatic and aromatic terminal and internal alkenes (Scheme 2.3).



Scheme 2.3 Selected expamles of Pd(II)-NHC, Pt(0)-NHC and Ir(III)-NHC complexes that mediated selective diboration of styrene

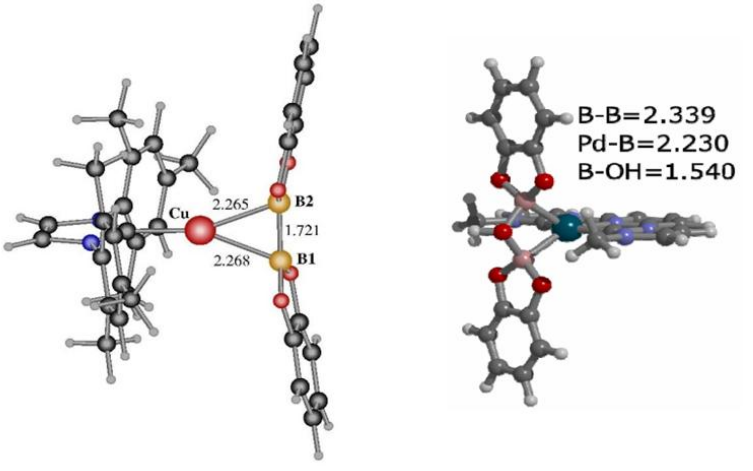
It is noteworthy to mention that until that moment, Pd complexes were ineffective in the B-B addition reaction to unsaturated compounds, although they were shown to be efficient in diboration of allenes[33,34] and borylative cyclization of 1,6-enynes.[35] The new Pd(II)-NHC complexes turned out to be very efficient precursor of catalysts for the 1,2-diboration of alkenes being the first examples of Pd-catalysts capable of mediating the B-B addition to C=C bond.

Metal diboryl species from the reaction of Pt(0) and Rh(I) complexes with diboron reagents have been experimentally isolated and characterized,[12] but the corresponding Pd-diboryl complexes have not ever been detected.

Previous theoretical studies by Morokuma,[36] and Sakaki and coworkers,[37,38] on Pd(0) phosphine model complexes discarded the oxidative addition of B-B bond to the metal centre since the reaction was endothermic and has an extremely low reverse barrier. Based on these precedents, the fact that Pd(II)-NHC catalytic systems mediated the reaction, might suggest a new activation mode of the diboron reagent.

Theoretical calculations were carried out to propose a plausible interaction of Pd(II)-NHC complexes with B_2cat_2. This study can be comparative to the observed interaction of B_2cat_2 and Cu(I)-NHC after demonstrating the efficiency of these copper catalytic systems in the diboration of alkenes. The group of Prof. Maseras *et al*. carried out a DFT study suggesting that the oxidative addition of B_2cat_2 to afford the Cu(III)-NHC-diboryl complex would be highly endothermic. Instead, formation of a [Cu(I)-NHC-(σ-B_2cat_2)]$^+$ intermediate

would be more favorable (Figure 2.1).[27] Some of us showed that palladium complexes interacted with B_2cat_2 to provide the relatively stable σ-adduct.[30] In contrast to the case of $[Cu(I)\text{-}NHC\text{-}(\sigma\text{-}B_2cat_2)]^+$ system, the oxidative addition of B_2cat_2 to $[Pd(NHC)\sigma\text{-}(B_2cat_2)]^+$ was found to be only slightly endothermic by 9.6 kcal.mol^{-1} with a moderate energy barrier (σ-adduct formation -32.9 kcal.mol^{-1}, oxidative addition -23.3 kcal.mol^{-1}).[30]



$[Cu(I)\text{-}NHC\text{-}(\sigma\text{-}B_2cat_2)]^+$ **$[Pd(II)\text{-}NHC\text{-}B_2cat_2\text{-}OH]^+$**

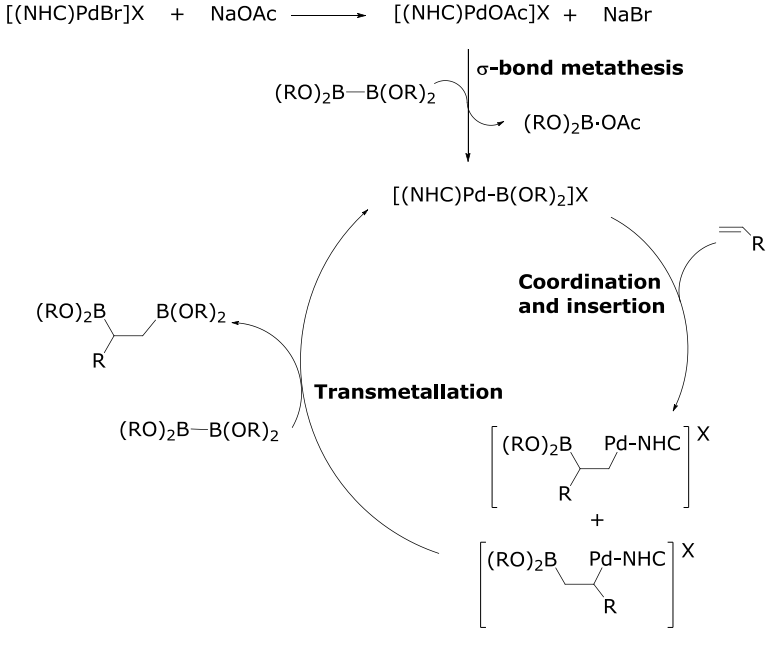
Figure 2.1 Molecular structures for the $[Cu(I)\text{-}NHC\text{-}(\sigma\text{-}B_2cat_2)]^+$ species and for the $[Pd(II)\text{-}NHC\text{-}B_2cat_2\text{-}OH]^+$ intermediate. Selected distances are given in Å

In view of these results, the possibility that Pd(IV) species participated in the mechanism, probably stabilized by the strong sigma donor NHC ligand could not be ruled out. In this regard, when weaker donor ligands were used the reaction did not proceed.

However a switch of the mechanism towards σ-bond metathesis was suggested since the addition of a base to the media (NaOH, NaOAc) and an excess of diboron reagent[30] increased substantially the conversion of alkenes towards very selective diborated products.

It has been accepted that the role of the base is related to accelerate the rate of the transmetallation, as it does in the cross-coupling reaction of organoboron compounds.[39–41] Some of us showed that the formation of the $[Pd(NHC)(B_2cat_2)(OH)]^+$ intermediate by σ-bond metathesis (Figure 2.1) is more favorable from the precursor $[Pd(NHC)(OH)]^+$ than $[Pd(NHC)X]$ (by -39.7

kcal.mol^{-1}).[30] Consequently, the role of the base could be related with the displacement of the halide substituent from palladium complexes promoting the σ-bond metathesis pathway with the diboron reagent (Scheme 2.4). Once the Pd-boryl complex is formed, insertion of the alkene might result in the formation of the corresponding [Pd(NHC)(alkyl)]$^+$ intermediate that interacts with another diboron reagent to regenerate the [Pd(NHC)B(OR)$_2$]$^+$ species and generate the 1,2-diborated product (Scheme 2.4).[30]

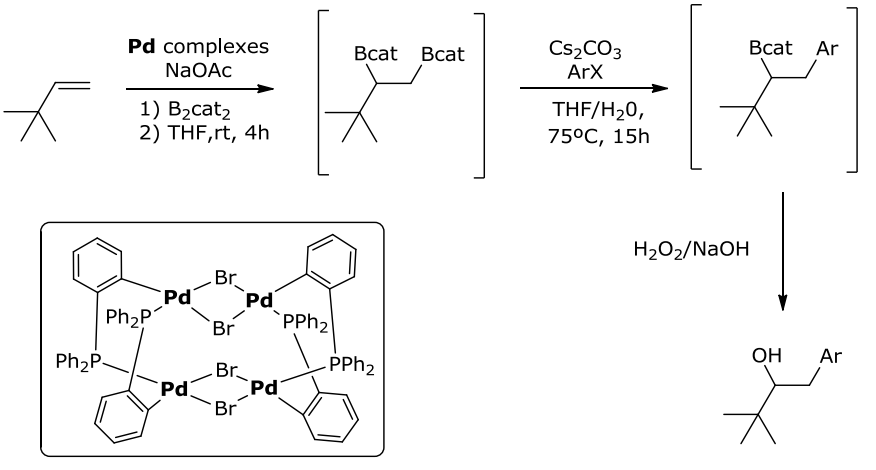


Scheme 2.4 Plausible mechanism for Pd(II)-NHC diboration *via* σ-bond metathesis

Marder and Lin reached a similar conclusion when they studied from a theoretical point of view, the alkene insertion into [Cu(NHC)B(OR)$_2$] species.[42] Importantly, they also showed the higher reactivity of B_2cat_2 versus B_2pin_2 in the course of the diboration of alkenes.[43]

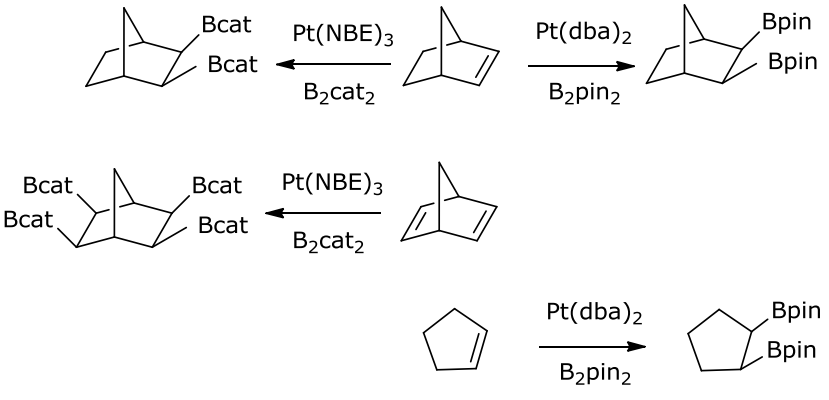
The remarkable advantages of palladium-catalyzed diboration reaction open perspectives towards a number of sequential reactions under the same catalytic system for assembling targeted organic compounds, such as C-C bond formation through cross-coupling reaction[44,45] or borylative cyclization of enynes and enediynes.[35,46]

Once it was demonstrated that Pd(II)-NHC/base catalytic system could activate diboron reagents, our group was able to prove that Pd(II)-PR_3 catalyst could mediate sequentially the diboration/arylation (Scheme 2.5).[47] In this case the catalytic precursor Pd(II) was *in situ* reduced to Pd(0) nanoparticles.[47]



Scheme 2.5 Example of Pd catalyzed consecutive diboration/arylation reaction

Regarding the type of alkenes used in metal mediated diboration, aliphatic and aromatic terminal alkenes have been the most studied substrates. Although, the first report of diboration of alkenes with Pt(0)[16] complexes already included a cyclic substrate: norbornene (NBE), there are only a few reports of diboration on cyclic alkenes that have an internal strain. These includes the earliest experiment by Smith[16] in which [$Pt(NBE)_3$] reacted stoichiometrically with bis(catecholato)diboron reagent (B_2cat_2) to generate *cis, exo*-bis(catecholboryl)norbornane (Scheme 2.6).[16] Also, [$Pt(NBE)_3$] was able to diborate norbornene and norbornadiene with B_2cat_2 by formation of a single stereoisomer because the B-B bond was preferentially added to the exo-olefin face.



Scheme 2.6 Earliest examples of Pt catalyzing diboration of endocyclic alkenes

Alternatively, Miyaura *et al*.,[18] demonstrated that $Pt(dba)_2$ could efficiently diborate norbornene, cyclopentene, and to a lesser extent cyclooctene with bis(pinacolato)diboron reagent. However all attempts to diborate cyclohexene were unsuccessful. Another system used for the diboration of indene was based on Rh(I)-Quinap (Quinap=1,2-diphenylphosphino-1-naphthyl)isoquinoline), but the selectivity towards the diborated product was not complete.[48]

2.2 Motivation

The remarkable advantages of palladium-catalyzed diboration reaction open perspectives towards a number of sequential reactions. The idea of forming C-B bonds by means of Pd complexes may be useful for assembling targeted organic compounds, such as C-C bond formation through Suzuki-Miyaura cross-coupling reaction.

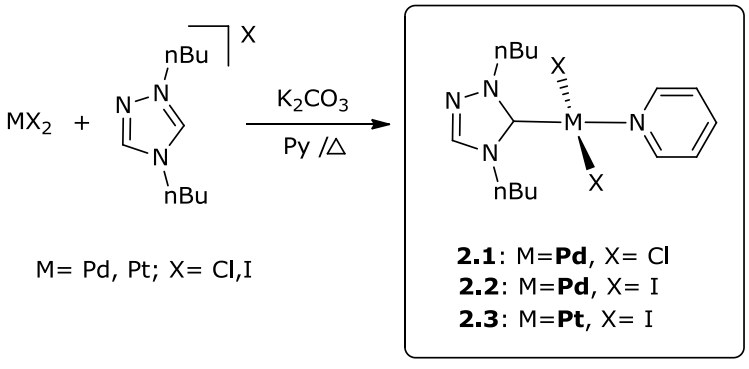
In order to expand and design new palladium catalytic systems and taking into account the success of N-heterocyclic carbene ligands (NHC) in M-NHC systems, we became interested in exploring the catalytic activity of new Pd(II) and Pt(II) complexes modified with NHC and pyridyl (py) ligands in the diboration reaction to determine their efficiency in selective C-B bond formation.

Due to the fact that endocyclic alkenes were much less studied than open chain alkenes, we focused our study on cyclic substrates.

Considering previous mechanistic studies on Pd(II)-NHC complexes, we found of great interest to study the formation of the diborated products by suggesting a plausible mechanism.

2.3 Results and Discussion

In collaboration with Dr. Jose A. Mata from the University of Jaume I of Castellón, it was prepared and fully characterized new neutral Pd(II) and Pt(II) complexes modified with monodentate triazole-based NHC ligands and pyridyl ligands. The reaction of 1,4-bis(n-butyl)triazolium salt with the corresponding metal halide within refluxing pyridine (Py) in the presence of K_2CO_3, afforded the metal complexes **2.1**, **2.2** and **2.3** in high yield (ca. 80%), as shown in Scheme 2.7. Analysis of single crystal of complex **2.3** shows that the coordination is square planar at the platinum (II) centre with *trans* configuration.



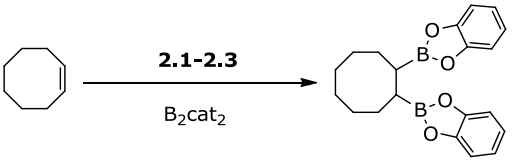
Scheme 2.7 Synthetic route for the neutral N-heterocyclic carbene pyridyl Pd(II) and Pt(II) complexes

The efficiency of metal heterocyclic carbene-pyridyl mixed ligand complexes was previously demonstrated in different catalytic processes such as cross-coupling reactions,[49–51] alkenylation,[52] alkylations,[53] aryl aminations,[54,55] and the Kumada-Tamao-Corriu reaction.[56] However, unlike metal-NHC catalytic systems, M-(NHC)(Py) complexes have never been used in boron addition reactions.

In the first series of experiments, we explored the catalytic diboration of cyclooctene as a model substrate. Upon mixing 2.0 mol% of **2.1** with cyclooctene and 1.0 equivalent of B_2cat_2, formation of the diborated product was not observed at 100ºC (Table 2.1, entry 1). This result suggests that the reaction did not proceed by oxidative addition of the B_2cat_2 to the [Pd(NHC)pyCl_2] complex. This is in contrast with previous experimental and

theoretical studies on Pd(II)-NHC model complexes[30] that concluded that oxidative addition of B-B is only slightly endothermic by 9.6mol^{-1} with a moderate energy barrier. And also it is opposite to the work of Morken *et al*.[57] that demonstrated that the mechanism of the Pd-catalyzed allene diboration proceeds through an oxidative addition of the diboron to the metal center. Several authors proposed that electron-donating ligands, like N-heterocyclic carbenes and phosphoroamidites, stabilize high oxidation state diboration intermediates, thus making the oxidative addition possible and facilitating Pd catalysis.[58] According to this, the NHC-pyridyl ligands of our tested system might not be basic enough to stabilize the possible Pd(IV) species and thus, activation of the diboron reagent by oxidative addition did not take place.

Table 2.1 Pd(II)-NHC and Pt(II)-NHC catalyzed the diboration of cyclooctene with B_2cat_2.[a]



Entry	Catalytic system	B_2cat_2	Base	T (ºC)	Conv. (%)[b]
1	[Pd(NHC)pyCl_2] (**2.1**)	1 eq	---	100	---
2	„	2 eq	NaOAc	25	83
3	„	2 eq	NaOAc	100	90(70) [c]
4	[Pd(NHC)pyI_2] (**2.2**)	2 eq	NaOAc	25	91
5	„	2 eq	NaOAc	100	93
6	„	2eq	NaO^{t}Bu	25	97
7	„	2eq	NaOH	25	90
8	„	2 eq	Cs_2CO_3	25	46
9	„	2 eq	CsF	25	25
10	[Pt(NHC)pyI_2] (**2.3**)	2 eq	NaOAc	25	99

[a]Standard conditions: Substrate / Pd or Pt = 1/0.02. B_2cat_2 = 2.0 eq., base = 1 eq., Solvent: CH_2Cl_2 (1mL). T = 25ºC, or 100ºC. t = 16h. [b] Determined by ^{1}H NMR spectroscopy and GC-MS. [c]Isolated yield as the corresponding 1,2-diol.

As our group demonstrated in previous studies,[30] Pd(II)-NHC complexes became catalytic active systems for diboration of terminal alkenes when a base is present in the reaction media and an excess of diboron reagent is used.

The [substrate]/[B_2cat_2] ratio seemed to be critical too. As it was shown by our group,[27] equimolar ratio (1:1) or an excess of diboron reagent with respect to the substrate provided the diborated product selectively. On the contrary, a ratio of 3:1 seems to favours the *β*-hydride elimination reaction since only monoborated product was obtained. This important effect has also been reported in a recent work by Szabo *et al*.,[59] in which a Pd(II) pincer complex catalyzed the C-H borylation of endocyclic alkenes towards monoborated products in neat or an excess of alkene.

Based on these precedents, increasing the equivalents of B_2cat_2 up to 2.0 and adding 1.0 equivalent of a mild base to the precursor of catalyst [Pd(NHC)pyCl_2] it was possible to form the diborated product in very high conversion, both at 25 and 100ºC (Table 2.1, entries 2 and 3). A slight improvement in the conversion towards *cis*-bis(catecholboryl)cyclooctane was detected when iodide was the counterion in complex **2.2** (Table 2.1, entry 4 and 5).

It is noteworthy to mention that the base seemed to have a crucial influence since the reaction conversion diminished significantly when NaOAc was substituted with other bases such as Cs_2CO_3 or CsF (Table 2.1, entries 6-9).

Finally, when the platinum-based complex **2.3** was involved in the reaction, quantitative formation of the desired 1,2-diborated product was observed (Table 2.1, entry 10).

More importantly, when we carried out the same reaction using $Pd(OAc)_2$ or $Pd_2(dba)_3$ catalyst, even in the presence of a base and excess of diboron, there was no conversion to the desired product (Table 2.2, entires 1 and 3). Modifying the catalytic system with a basic phosphine such as PCy_3 (Cy=cyclohexyl) did not change the inactive tendency (Table 2.2, entires 2 and 4). This is in agreement with previous experimental results of our group in which $Pd(OAc)_2$ and the dimer $Pd_2(dba)_3$ as catalytic precursors did not promote the diboration of internal and terminal linear alkenes even in the presence of base or/and modification with phosphine ligands.[30] Also, it was in accordance with the early results reported by Miyaura *et al*.[60]

Table 2.2 Catalytic test of $Pd(OAc)_2$ and $Pd_2(dba)_3$ complexes in the diboration of cyclooctene with B_2cat_2[a]

Entry	Catalytic system	B_2cat_2	Base	T (ºC)	Conv. (%)[b]
1	$Pd(OAc)_2$	2 eq	NaOAc	100	---
2	$Pd(OAc)_2/PCy_3$	2 eq	NaOAc	100	---
3	$Pd_2(dba)_3$	2 eq	NaOAc	100	---
4	$Pd_2(dba)_3/PCy_3$	2 eq	NaOAc	100	---

[a]Standard conditions: Substrate / Pd = 1/0.02 , Pd/PCy_3=1/2 B_2cat_2 = 2.0 eq., base = 1.0 eq., Solvent: CH_2Cl_2 (1 mL). T = 100ºC. t = 16h. [b] Determined by ^1H NMR spectroscopy and GC-MS.

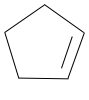
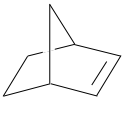
Therefore, the collected data clearly shows that N-heterolytic carbene-pyridyl mixed ligands modifies Pd complexes to become efficient catalytic systems towards catalytic diboration of cyclooctene. Notably, these ligands also enhances the reactivity of Pt complexes since conversions with $[Pt(dba)_2]$ and B_2pin_2[18] in the diboration of cyclooctene were very low. Remarkably, these systems are selective for the formation of the diborated product since no monoborated byproducts derived from the *β*-H-elimination were observed.

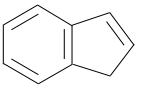
The fact that other catalytic systems based on Pd complexes were inactive in the catalytic diboration of cycloalkenes may suggest that the basic ligands in complexes **2.1**, **2.2** and **2.3** have a positive influence.

In order to determine the scope of the reaction we next explored the catalytic diboration of cyclohexene, cyclopentene and norbornene with complexes **2.1**, **2.2** and **2.3**. Table 2.3 shows the efficiency of all these catalytic systems, particularly when $[Pt(NHC)pyI_2]$ is involved even at room temperature. These new reactions conditions improved the previously reported diboration with $Pt(dba)_2$ (3 mol%) at 50ºC, where yields were based on consumption of diboron with an excess of alkenes (cyclopentene and norbornene)[18] and B_2pin_2 (3.0 eq.). It is noteworthy to mention that this is the first example of catalytic diboration of cyclohexene, and quantitative conversion could be achieved with Pd-NHC and Pt-NHC iodide systems, at room temperature, (Table 2, entries 3, 5). Also complex **2.3** favoured complete diboration of cyclopentene and norbornene, (Table 2.3, entries 10, 12). The cyclic vinylarene, indene, was also selectively converted to the diborated product, (Table 2.3, entry 12) in contrast to the unique attempt of diboration/oxidation with Rh(I)-Quinap complexes

previously reported, where 68% of 1,2-diol was formed in addition to 17% of 1-indanol.[48] Also in the first Pd-(II)-NHC diboration of alkenes, indene was one of the substrates. The catalytic system was also effective but in this case 3.0 eq.of the B_2cat_2 were necessary to complete conversion after 4h.[30]

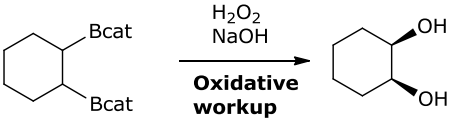
Table 2.3 Catalytic diboration of cycloalkenes with B_2cat_2.[a]

Entry	Substrate	Catalytic system	T (ºC)	Conv. (%)[b]
1		[Pd(NHC)pyCl$_2$]	25	96
2		„	80	99
3		[Pd(NHC)pyI$_2$]	25	99
4		„	80	99
5		[Pt(NHC)pyI$_2$]	25	99
6		[Pd(NHC)pyCl$_2$]	25	86
7		„	50	99
8		[Pd(NHC)pyI$_2$]	25	95
9		„	50	99
10		[Pt(NHC)pyI$_2$]	25	99
11		[Pd(NHC)pyI$_2$]	25	99
12		[Pt(NHC)pyI$_2$]	25	99

13		$[Pd(NHC)pyI_2]$	25	77

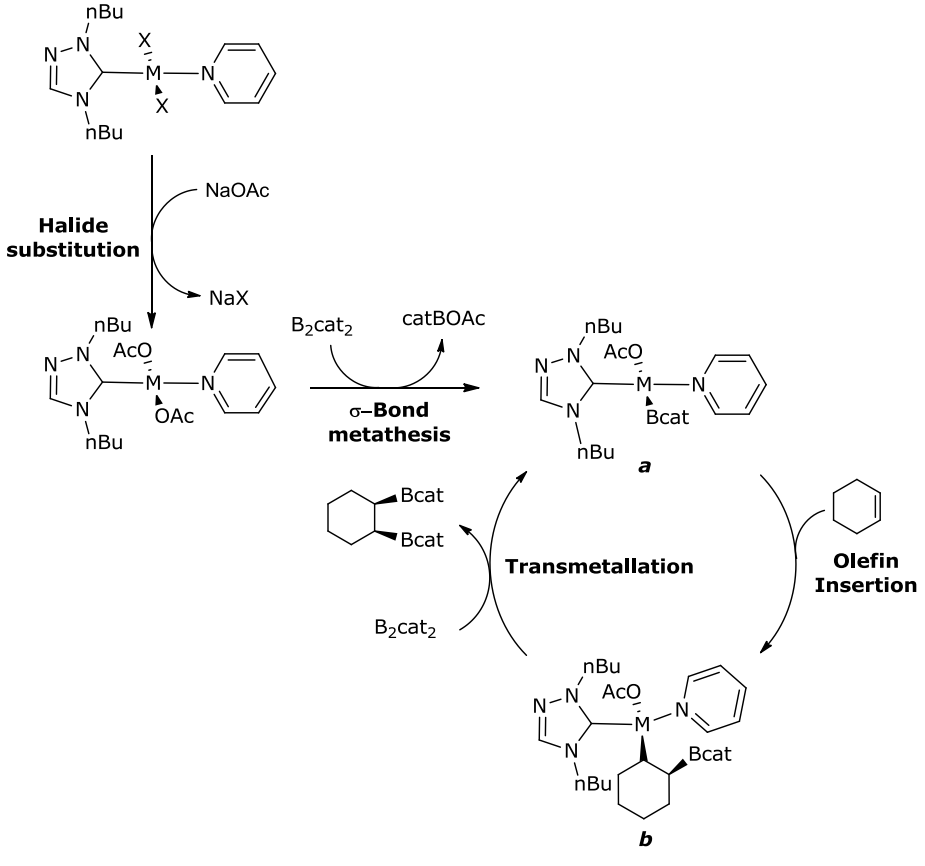
[a]Standard conditions: Substrate / Pd or Pt = 1/0.02. B_2cat_2 = 2.1 eq., base (NaOAc) = 1.0 eq., Solvent: CH_2Cl_2 (1mL). t = 16h. [b] Determined by ^1H NMR spectroscopy and GC-MS.

Posterior oxidative work up of the 1,2-diborated product confirmed the *cis*-1,2-diol formation, in all the cases (Scheme 2.8).



Scheme 2.8 An example of the oxidative workup for the 1,2-diborated product

Taking into account that the Pd-mediated diboration of alkenes might be conducted through σ-bond metathesis as a key step,[30] we have suggested a similar mechanistic approach with the cyclic alkenes (Scheme 2.9).



Scheme 2.9 Mechanistic proposal for the [M(NHC)(py)] (M=Pt or Pd) diboration of cyclohexene as a model substrate with B_2cat_2

In the first step, the base might displace the halide from the catalytic system. The fact that the complexes **2.1** and **2.3** modified with iodides are more active could be related to the easier displacement of I^- from the metal centre. The heterolytic cleavage of B_2cat_2 by $[M(NHC)py(OAc)_2]$ could promote the formation of the metal-boryl intermediate ***a***, which would interact with the cyclic alkene to insert the double bond. Next step is defined by the reaction of intermediate ***b*** with another molecule of B_2cat_2 to afford the organodiboron product and thereby releasing and regenerating the metal-boryl species.
Although *β* hydride elimination is a potential secondary reaction that results from intermediate ***b***, such elimination seemed to be inhibited under these reaction conditions because of the absence of allyl boronate products.

2.4 Conclusions

We have developed an efficient methodology for the selective catalytic diboration reaction of hindered cyclic alkenes based on Pd(II) complexes. High conversions to the desired 1,2-diborated product were obtained even at room temperature after relatively short reaction times (16h).

Importantly, we have demonstrated the positive influence of the N-heterocyclic carbene-pyridyl mixed ligands in activating Pd (II) and Pt (II) since traditional Pd precursor complexes did not convert the substrate into the desired product even after modification with phosphine ligands.

Also, based on previous theoretical and experimental work, we have proposed a plausible mechanism in which the presence of a base seems to be crucial in assisting the heterolytic cleavage of the diboron *via* the σ-bond metathesis.

The fact that Pd was involved in that double C-B bond formation reaction, opens new perspectives towards a potential difunctionalization through Suzuki-Miyaura cross coupling reaction.

2.5 References

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Chapter 3: (NHC)Rhodium mediated diboration versus dehydrogenative borylation

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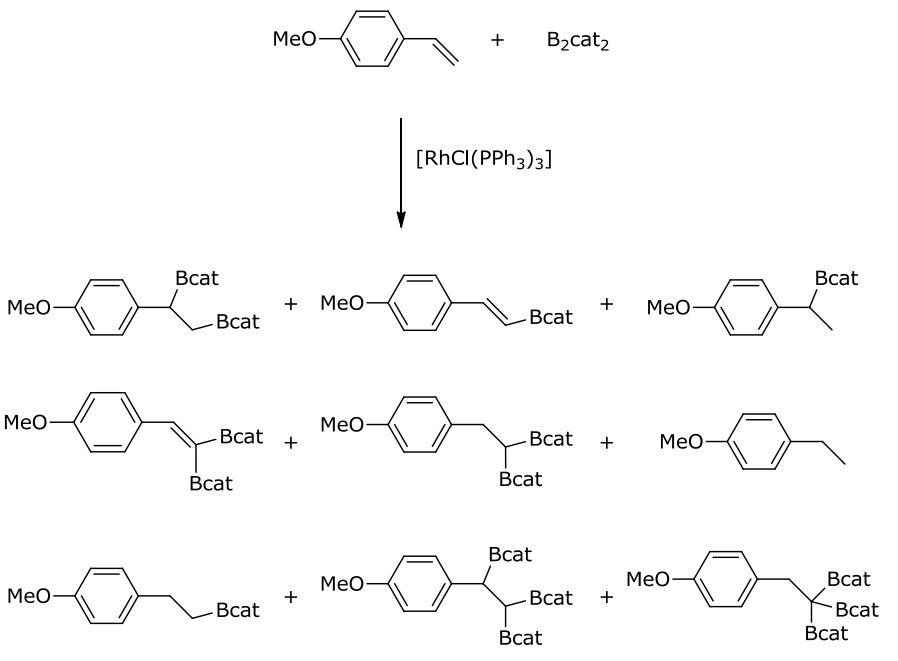
3.1 Introduction

One of the first transition metals used in the catalytic diboration reaction of alkynes and alkenes, using tetraalkoxydiboranes, was Rh together with Pt.[1–6]

Activation of the diboron reagent by oxidative addition to the rhodium (I) center has been demonstrated experimentally.[7–9] Single crystals of the rhodium (III) diboryl species were isolated and characterized by X-ray crystallography.[9] Also, theoretical calculations carried out by Morokuma *et al*. showed that activation of a model diboron reagent by Rh(I) neutral complexes modified with phosphines proceed throughout homolytic cleavage of the B-B bond.[10] Reactivity of the resulting bisboryl rhodium species was widely studied in the catalytic diboration of alkenes together with Pt complexes.[4–6,11–16] The main drawback with rhodium catalyzed diboration reaction is the competitive *β*-hydride elimination.[17]

It has been observed that the typical rhodium hydroborating catalyst such as $[RhCl(PPh_3)_3]$ activated bis(catecholato)diboron, B_2cat_2, to promote the diboration of electron rich alkenes, such as 4-vinylanisole, but the 1,2-diborated product was formed along with products from the *β*-hydride elimination (Scheme 3.1).[17] Further attempts to circumvent this problem, suggested that the zwitterionic complex [Rh(DPPB)(η^6-catBcat)] (DPPB=1,4-bis(diphenylphosphino)butane) (Figure 3.1) could control the chemoselectivity yielding 44% of the 1,2-diborated product.[17]



Scheme 3.1 Different products observed in the Rh(I)-catalyzed diboration of 4-vinylanisole

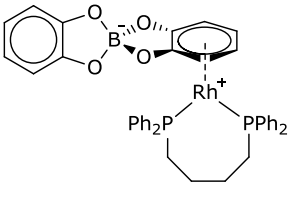


Figure 3.1 [Rh(DPPB)(η^6-catBcat)]

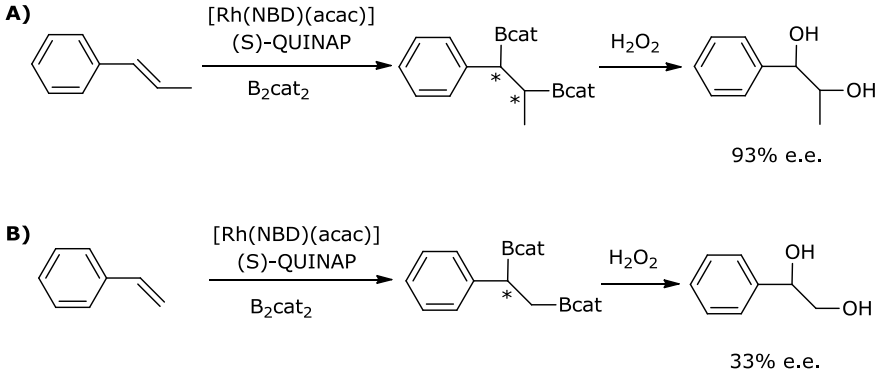
As it was discussed in Chapter 2, one of the strategies to reduce the products from the *β*-hydride elimination involved the use of other metals. Metals with lower d-orbital energies (on the right of the periodic table) are likely to inhibit π-backbonding to alkenes and thus destabilize the alkene-hydride metal complex (formed after the *β*-hydride elimination) with respect to the alkyl metal complex. Thus, high chemoselectivity towards the diborated product were achieved with complexes based on phosphine-free Pt-catalyst precursors[18–20] and phosphine-gold species.[17,21]

Also, the modification of the metal centre by convenient ligands was found to be crucial to selectively perform the diboration of alkenes. Remarkably, the beneficial influence of N-heterocyclic carbenes, as ligands, in the catalytic diboration of olefins has been previously demonstrated with Pd,[22] Pt,[23] Ir,[24] Ag[25] and Au[26] complexes, with complete chemoselectivity towards the 1,2-diborated product.

A relevant example that illustrates the critical role of the nature of the ligand is the modification of the ligand in Rh catalyzed diboration[27] from DPPB to DPPM (DPPM=bis(diphenylphosphino)methane). Complex [Rh(DPPM)(η^6-catBcat)], which was characterized by X-ray diffraction, was applied in the diboration of vinylarenes, internal alkenes, *cis*- and *trans*-stylbene and *trans*-*β*-methylstyrene. It was the most active and chemoselective Rh(I) catalyst system found, yielding in some cases full conversion to the 1,2-diborated product.[27]

Marder and coworkers showed that the nature of the boryl moiety of the diboron reagent has also an influence on the chemoselectivity of the diboration reaction. The use of bis(pinacolato)diboron (B_2pin_2) or bis(neopentylglycolato)diboron (B_2neop_2) favors the *β*-H-elimination versus reductive elimination when the catalyst precursor was *trans*-[Rh(Cl)(CO)(PPh_3)$_2$].[28] Also, in this work, they pointed out that selectivity was influenced by the nature of the solvent too. Reactions conducted in THF, toluene, and 1,4-dioxane yielded complex mixtures of vinyl boronic esters (VBEs), hydroborated products, hydrogenated products, vinyl bis(boronate esters) (VBBEs), and saturated bis(boronate ester)s (BBEs) when 4-vinylanisole was the substrate. In contrast, reactions conducted in neat CH_3CN selectively formed VBEs, but these reactions were slow.[28]

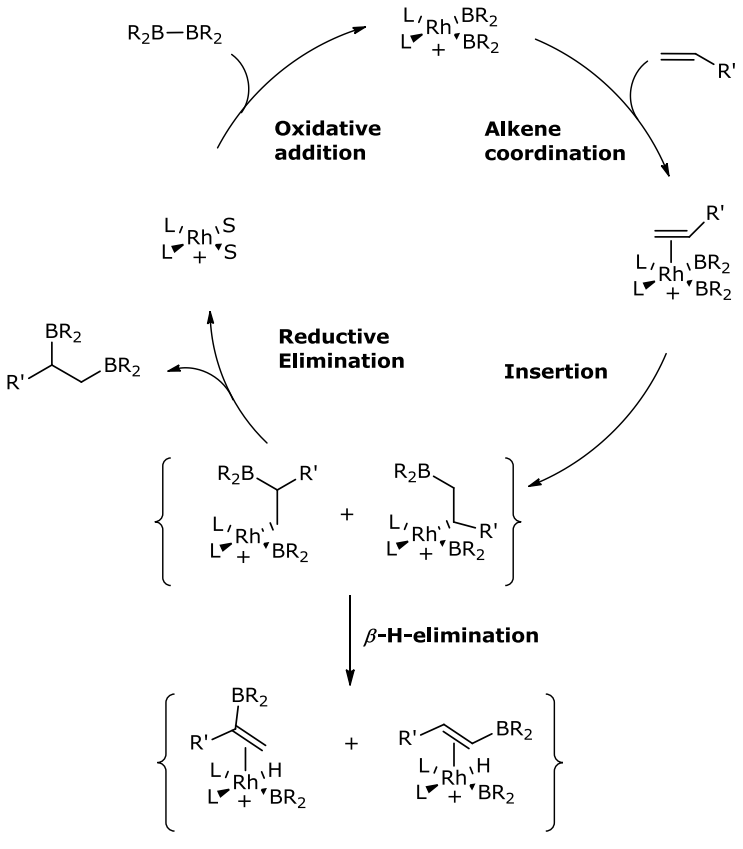
Although alternative chemoselective catalytic systems have been discovered, the interest of the rhodium mediated diboration of alkenes relies on the possibility to introduce asymmetry.[4,11,29,30] Morken and coworkers were pioneers in the field of enantioselective diboration reaction of alkenes by modification of [Rh(NBD)(acac)] (where acac= acetylacetonate) with the P,N-ligand (*S*)-QUINAP (Scheme 3.2).[29]



Scheme 3.2 An example of enantioselective diboration of alkenes carried out with Rh-QUINAP system A) *tans*-alkenes, B) terminal alkenes[29]

A contemporary study by Fernandez and coworkers compared the Rh mediated asymmetric diboration with the double enantioselective hydroboration, showing the benefits of the first versus the second. Also, the influene of the nature of the diboron reagent in the chemoselectivity was also pointed out.[31]

The most widely accepted mechanism for the alkene diboration reaction based on experimental and DFT studies[10,32] suggested that the first step is likely to be an oxidative addition of the B-B bond of the diboron reagent to the metal, leading to a metal-diboryl complex[9] (Scheme 3.3). The desired 1,2-bis(boronate)ester seems to arise form alkene insertion into a M-B bond[33] followed by B-C reductive elimination involving the second boryl ligand.[34] Formation of alkyl and alkenylboronate esters is due to competitive *β*-hydride elimination (Scheme 3.3).



Scheme 3.3 Proposed catalytic cycle for the Rh(I) catalyzed diboration of alkenes

While some authors have focused on the development of new strategies towards the selective diboration, some others took advantage of this *β*-hydride elimination side reaction to selectively form useful vinyl boronate esters.[35]

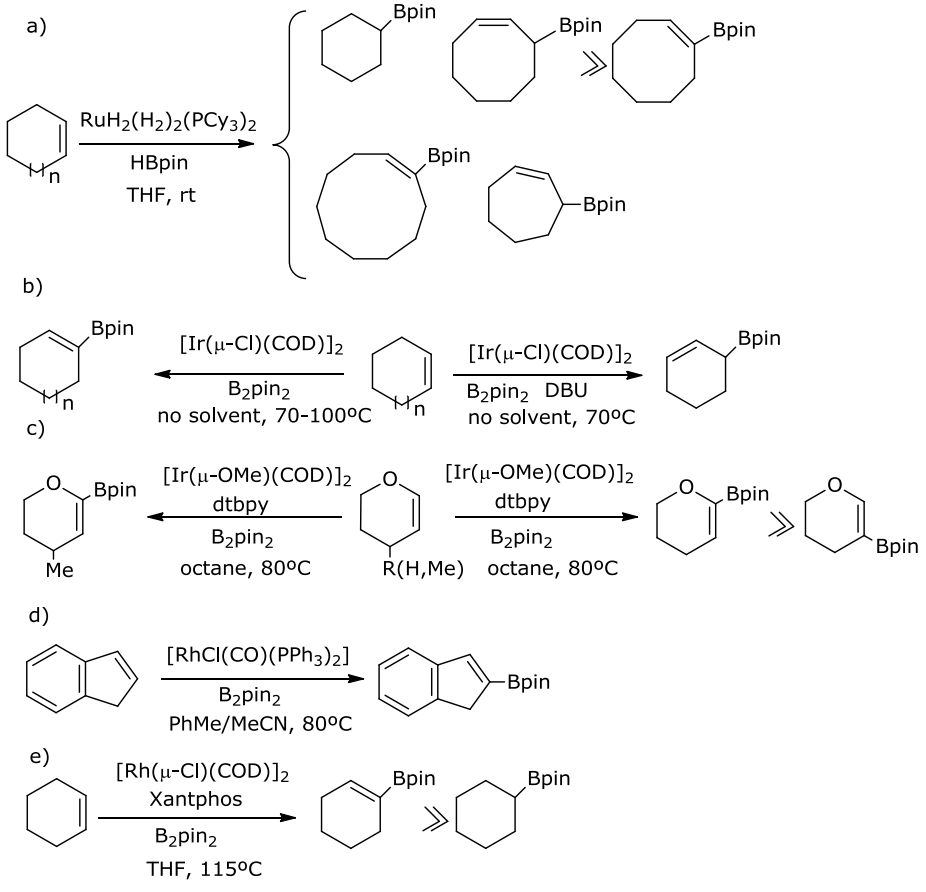
In fact, alkenyl boronate esters, can be synthetized by a variety of methods including hydroboration of alkynes,[36] palladium catalyzed borylation of alkenyl halides,[37] hydrogenation of 1-boryl alkynes[38] among others.[35] Dehydrogenative borylation of olefins, in which a vinylic C-H bond is replaced with a C-B bond, is a very efficient alternative widely applied for vinylarenes.[35]

However, the extension of the metal mediated dehydrogenative borylation of cyclic olefins has been much less explored and can be differentiated by the nature of the reagent (HBpin or B_2pin_2) or the transition metal complex involved in the activation of the borane reagent. Scheme 3.4 summarizes the limited examples of cyclic olefins that underwent dehydrogenative borylation,

illustrating the reaction conditions and the selectivity of the reaction products.

When Sabo-Etienne and co-workers activated pinacolborane by means of $RuH_2(H_2)_2(PCy_3)_2$,[39] the hydroboration of cyclohexene seemed to be highly favored, whereas for cyclodecene, vinylboronate ester was produced with only traces of allylboronate ester. Cyclooctene provided the vinyl- and allylboronate ester in a 1:3 ratio, whereas only allylboronate ester is obtained from cycloheptene (Scheme 3.4, a).

Szabó and co-workers were the first to use B_2pin_2 in the dehydrogenative borylation of cyclic olefins and towards the activation of the diboron reagent, the iridium precursor $[Ir(\mu\text{-}Cl)(COD)]_2$ was selected.[40] Heating at 70ºC, cyclohexene gave a 1:1 ratio of allylic and vinylic borylated products while addition of 0.5 eq. of 1,8-diazabicyclo[5.4.0]undecane (DBU) led to an increase in the ratio of allylic to vinylic products although the proportion of the vinylic product increased with prolonged heating (Scheme 3.4 b).



Scheme 3.4 Updated strategies on metal mediated dehydrogenative borylation reaction of cyclic alkenes

Miyaura and coworkers further reported the borylation of vinyl C-H bonds in cyclic vinyl ethers with B_2pin_2 catalyzed by $[Ir(\mu\text{-OMe})(COD)]_2$ and dtbpy (4,4'-di-*tert*-butylbipyridine).[41] Borylation of 1,4-dioxene with 0.5 eq of B_2pin_2 provided the vinylboronate ester product in 81% yield. Substrates containing substituents at the *γ*-position in dihydropyrans reacted with higher regioselectivity where borylation occurred solely at the α-position (Scheme 3.4, c).

In subsequent work, Marder and coworkers explored the dehydrogenative borylation catalyzed by *trans*-$[RhCl(CO)(PPh_3)_2]$ and the borylation of indene with B_2pin_2.[42] They observed the selective formation of the vinylboronate ester with borylation occurring at the 2-position, however only 19% conversion was

achieved after 6 days at 80 °C (Scheme 3.4, d).[42] Finally, Jamison and co-workers have reported the benefits of Xantphos as ligand on the rhodium precursor $[Rh(\mu\text{-}Cl)(COD)]_2$ towards the dehydrogenative borylation of cyclic alkenes with B_2pin_2, forming the corresponding cyclic 1-alkenylboronic acid pinacol esters (Scheme 3.4, e).[43]

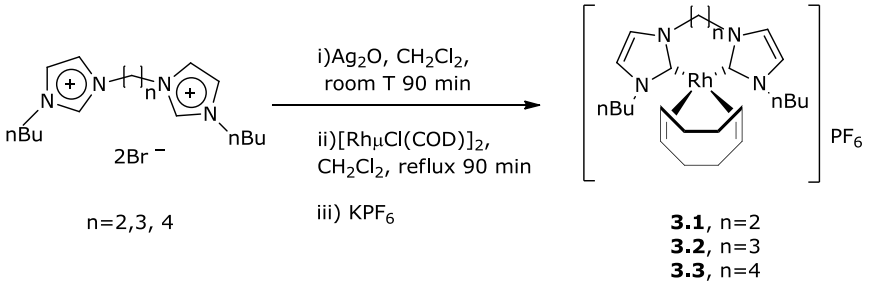
3.2 Motivation

We became surprised by the fact that in all the examples where B_2pin_2 was the boron reagent used, the 1,2-diborated product was not observed, even in the presence of rhodium complexes modified with phoshines.[4,5,11,13,14] We also noticed that apart from phosphines and amines,[44] no other ligands have been studied to modify the catalytic systems in order to promote the dehydrogenative borylation reactions. In that context, we planned to focus our efforts on exploring the catalytic activity of rhodium complexes modified with N-heterocyclic carbenes (NHC), towards the borylation of cyclic olefins in the presence of B_2pin_2. But also, in view of the lack of detailed studies concerning the mechanism of rhodium-mediated borylation of cyclic alkenes, we became interested to rationalize the experimental data with theoretical data and propose a plausible mechanism based on the reaction energy profile.

3.3 Results and Discussion

3.3.1 Experimental study

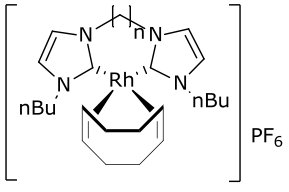
NHC-based rhodium complexes **3.1**-**3.3** are well known complexes, first reported by Crabtree *et al*.[45] In collaboration with Dr. Macarena Poyatos from the Universitat Jaume I in Castellón, NHC-based rhodium complexes **3.1**-**3.3** were prepared by transmetallation from the corresponding silver carbene derivatives by a two step procedure described in the literature.[45] The first step involves the deprotonation of the corresponding chelating bis(imidazolium) salt with Ag_2O. The so generated Ag(I)-NHC complexes were reacted *in situ* with $[Rh(\mu\text{-}Cl)(COD)]_2$ giving the desired chelating complexes in moderate yields (Scheme 3.5).[45]



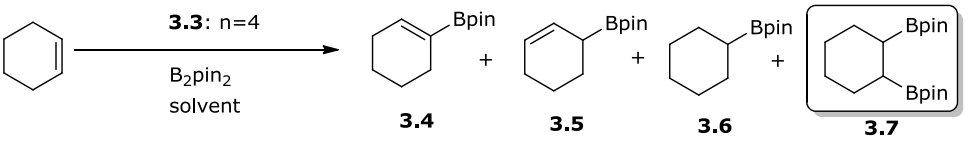
Scheme 3.5 General synthetic route for the complexes **3.1**-**3.3** of general formula $[Rh(COD)(NHC)]PF_6$

We selected cyclohexene as the model substrate to undergo the borylation reaction with the synthesized Rh(I)-(NHC) catalyst under different reaction conditions. The borylation of cyclohexene in THF, when the rhodium complex **3.1** was used, provided moderate conversions of a mixture of borylated products where the vinyl boronate ester **3.4** was the major one (49%), (Table 3.1, entry 1). In addition, certain amounts of allyl boronate ester and hydroborated product were also observed, but the diborated product **3.7** was not identified among the mixture of products. Similar results were observed using complexes **3.2** and **3.3** (Table 3.1, entries 2 and 3), but to our surprise, complex **3.2** allowed to achieve the 1,2-diborated product in a modest percentage (25%), as the *cis*-1,2-diborated product.

Table 3.1 Rhodium complexes modified with NHC ligands catalyzed the borylation of cyclohexene[a]



3.1: n=2
3.2: n=3
3.3: n=4



3.4 **3.5** **3.6** **3.7**

Entry	Rh complex	Solvent	Conv (%)[b]	3.4/3.5/3.6/3.7 (%)[b]
1	**3.1**	THF	30	49/29/23/--
2	**3.2**	"	9	17/40/18/25
3	**3.3**	"	18	30/30/40/--
4	**3.2**	cyclooctane	27	30/8/17/45
5	**3.2**	pentane	64	1/--/--/99
6	**3.2**	hexane	54	1/--/--99
7	**3.2**	cyclohexane	68	1/--/--99
8[c]	**3.2**	cyclohexane	89	1/--/--99
9	**3.1**	cyclohexane	52	14/--/--/86
10	**3.3**	cyclohexane	68	28/3/3/66
11[d]	$[Rh(\mu\text{-}Cl)(COD)]_2$	cyclohexane	17	78/6/4/13
12[d]	$[Rh(\mu\text{-}Cl)(COD)]_2$ PPh_3 (1:2)	cyclohexane	24	61/17/14/8
13[d]	$[Rh(\mu\text{-}Cl)(COD)]_2$ PPh_3 (1:4)	cyclohexane	33	62/14/9/14

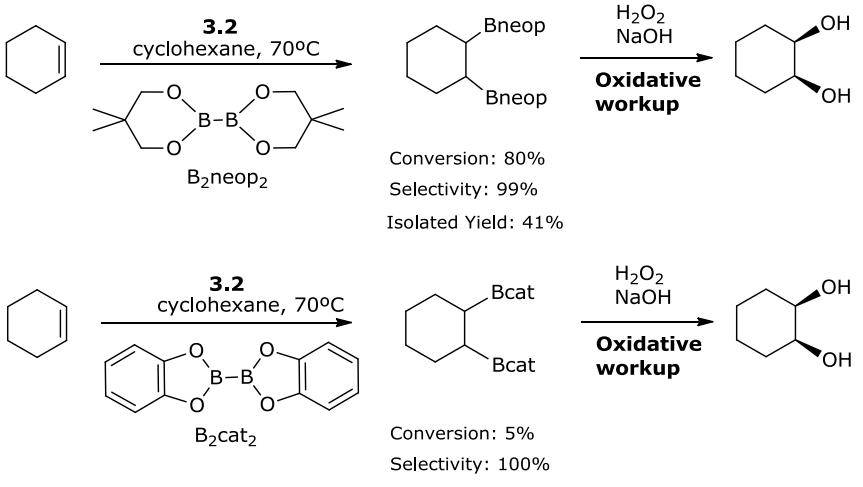
[a]Standard conditions: Rh-NHC complex (4 mol%), substrate (0.2 mmol), B_2pin_2 (1 eq.), 70ºC, 16 h. [b]Conversion and selectivity calculated using ^1H NMR spectroscopy and GC. [c]T: 120ºC. [d]Rh complex (2 mol%), phosphine (4 or 8 mol%), substrate (0.2 mmol), B_2pin_2 (1.0 eq.), 70ºC, 16 h.

Exploring in detail the catalytic behaviour of complex **3.2** in less polar solvents like cyclooctane, we found that despite the fact that the conversion was still low, the percentage of diborated product increased significantly, becoming the

major product (45%) (Table 3.1, entry 4). The beneficial influence of this type of solvents was enhanced when the borylation of cyclohexene took place in pentane, hexane and cyclohexane, obtaining better conversions and quantitative formation of the 1,2-diborated product (Table 3.1, entries 5-7). Interestingly, under the same reaction conditions but using a non-polar and coordinating solvent, 1,4-dioxane, the formation of diborated neither monoborated products were not observed.

Increasing the temperature from 70ºC to 120ºC, improved the conversion of the reaction (89%) keeping constant the quantitative formation of the diborated product **3.7** (Table 3.1, entry 8). Rhodium complexes **3.1** and **3.3** resulted less selective (Table 3.1, entries 9 and 10) towards the diborated product in basis to the partial formation of the vinyl boronate ester **3.4**. A direct comparison with an unmodified Rh complex $[Rh(\mu\text{-}Cl)(COD)]_2$ and modified Rh complexes with phosphines, confirmed the previously observed experimental trend by Jamison and co-workers[43] where dehydrogenative borylation of the cyclic olefins is the major process (Table 3.1, entries 11-13). However, under our reaction conditions, and using cyclohexane as the solvent of choice, a representative amount of 1,2-diborated product could be observed.

At this point and with all these data in mind we concluded that the synergy between the catalyst **3.2** and the solvent cyclohexane favoured the diboration process versus the dehydrogenative borylation of cyclic olefins, in the presence of B_2pin_2. To generalize the methodology, we explored alternative tetraalkoxydiboron reagents such as bis(catecholato)diboron (B_2cat_2) and bis(neopentylglycolato)diboron (B_2neop_2) to borylate cyclohexene with complex **3.2**, using cyclohexane as solvent. In both cases, after 16h at 70ºC, the catalytic 1,2-diboration was the preferred borylation process with quantitative formation of the corresponding 1,2-diborated product, despite the fact that conversion values were significantly different depending on the diboron reagent used (Scheme 3.6).



Scheme 3.6 1,2-Diboration of cyclohexene with bis(catecholato)diboron and bis(neopentylglycolato)diboron and posterior general oxidative workup

When B_2neop_2 was involved, the conversion reached 80%. The oxidative work up of the 1,2-diborated product confirmed the *cis*-1,2-cyclohexanediol formation, in all the cases (Scheme 3.6).

The nature of the bidentate ligand NHC is of crucial importance because when the borylation of cyclohexene was performed with the analogue cationic rhodium system [Rh(COD)(BINAP)]BF_4 under the same reaction conditions as with precursor of catalyst **3.2** (Table 3.1, entry 7), less than 20% of conversion was observed and only 57% of selectivity towards the diborated product was obtained.

In a comparative study, we used the analogous iridium(I) complex of **3.2** ([Ir(COD)(NHC)]PF_6), synthesized by the group of Eduardo Peris in the University of Castellon.[46] Under the same reaction conditions for selective diboration (Table 3.1, entry 7), Ir(I)-NHC complex did not promote the selective diboration of cyclohexene. This is in well agreement with the reported literature since there is only one example of Ir catalyzing selective diboration reported by our group.[24] The complex used was an Ir(III) modified with a N-heterocyclic carbene ligand and 3.0 eq of the diboron reagent B_2cat_2 and the presence of a base were required to obtain selectively the diborated product of vinylarenes and terminal linear alkenes in relatively high conversions.

The scope of the Rh(I)-NHC mediated diboration of cyclic alkenes was also explored. In all the studied cases, exclusive formation of the 1,2-diborated product could be observed, with high conversion in the case of cyclopentene even at 50ºC (Table 3.2, entries 1 and 2).

Table 3.2 Substrate scope of Rh-NHC mediated 1,2-diboration reaction with B_2pin_2.[a]

Entry	Substrate	Product	T (ºC)	Conv (%)[b]	1,2-Diborated (%)[c]	Isolated Yield (%)
1			70	99	100	89
2	"	"	50	95	100	77
3			70	70	100	62
4			70	68	100	61
5			70	63	100	57
6			70	68	99	65

[a]Standard conditions: Rh-NHC complex (4 mol%), substrate (0.2 mmol), B_2pin_2 (1.0 eq.), 16 h. [b]Conversion and selectivity were calculated using ^{1}H NMR spectroscopy and GC-MS.

Rh(I)-NHC catalyzed diboration of cyclooctene was also selective towards the diborated product reaching up to 68% of conversion (Table 3.2, entry 4), much higher than the only attempt of metal mediated diboration of this substrate with [Pt(dba)$_2$] as catalytic system reported by Miyaura *et al*.[18]

Importantly, in the case of cycloheptene and 3,4-dehydropyrane the corresponding diborated product was formed selectively with relatively high conversions, being this, the first attempt of metal mediated diboration of this cyclic substrates (Table 3.2, entries 3 and 5).

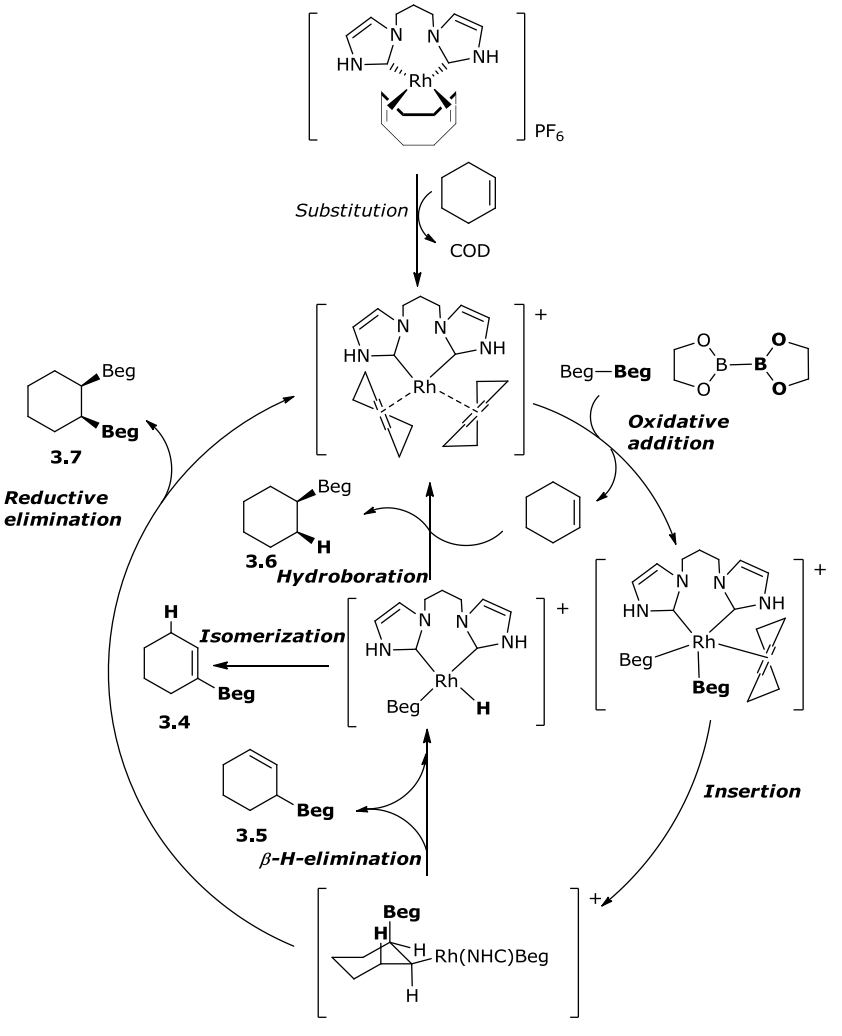
The beneficial influence of N-heterocyclic carbenes as ligands in the catalytic diboration of olefins has been previously demonstrated with Pd,[22] Pt,[23] Ir,[24] Ag[25] and Au[26] complexes, with complete chemoselectivity towards the 1,2-diborated product. However, in this case where NHC ligands modify rhodium complexes, it

has an added value because the dehydrogenative borylation of olefins was usually favoured in the presence of rhodium complexes modified with phosphines.[17,28,33,47–53]

In this particular case, we became interested to know more detail about the mechanism of the Rh(I)-NHC mediated boron addition reaction in order to identify the elements that could favour the 1,2-diboration versus the dehydrogenative borylation.

3.3.2 DFT study

The main goal of the present theoretical approach is to determine the reaction energy profile for the formation of the diborated product **3.7** and the allyl boronate ester **3.5** when catalyst **3.2**, [Rh(COD)(NHC)]PF_6 is used. Scheme 3.7 shows the general mechanistic pathways that we have considered performing the theoretical study. This proposed mechanism resembles the mechanism previously suggested by Sazbó[40] and Jamison,[43] where the conformational flexibility of a model cyclic alkene was already considered.



Scheme 3.7 General proposed catalytic pathways for the formation of products **3.4-3.7**

3.3.2.1 Computational details and modeling strategy.

In this present theoretical approach, molecular structures for all the species were optimized without constraints by using Density Functional Theory (DFT) based methods as implemented in the Amsterdam Density Functional (ADF v2007.01) package.[54,55]

A triple-ζ plus polarization (TZP) Slater basis set was used on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[56]

For geometry optimizations we used the local VWN correlation potential[57] together with the Becke's exchange[58] and the Perdew's correlation[59,60] (BP86) generalized gradient corrections.

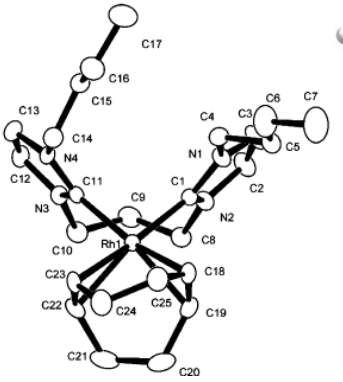
Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequencies calculations.

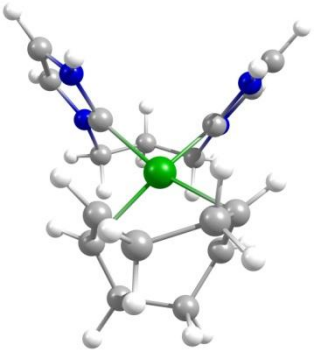
Standard corrections to Gibbs free energy at 298 K were evaluated too. Solvent effects were introduced by using the continuous solvent model COSMO.[61]

To reduce the computational cost, in our DFT calculations we used Beg (eg= ethylenglicolato = OCH_2CH_2O) as a suitable model for the Bpin boryl moiety[62] and $[Rh(COD)(NHC)]^+$ as the metal **3.2** complex simplifying the n-Buthyl groups of the NHC ligand by hydrogen atoms. Cyclohexene was selected as the model cyclic olefin.

It is worthy to note, that the geometry of our model catalyst, optimized with the chosen DFT method, precisely coincided with the parameters of the crystal structure of Rh(I)-NHC complex **3.2**.[45] The geometry at rhodium (Table 3.3) is square planar, with the two imidazole rings of the chelating ligand (Table 3.3, experimental value for the bite angle 87.60° and the calculated 83.5º). The Rh-C(carbene) bond lengths of 2.038 and 2.029 Å are almost equal to the calculated ones, 2.037 and 2.030 Å respectively. The C-C distances in the imidazole units are short (1.342 and 1.346 Å experimentally and 1.355 and 1.356 in the computed structure), as always observed for NHCs. In both cases, the crystal structure and the computed model, the cod ligand adopts a slightly twisted conformation.

Table 3.3 Selected bond lengths (Å) and angles (deg) for the crystal structure of complex **3.2** and our computational model.





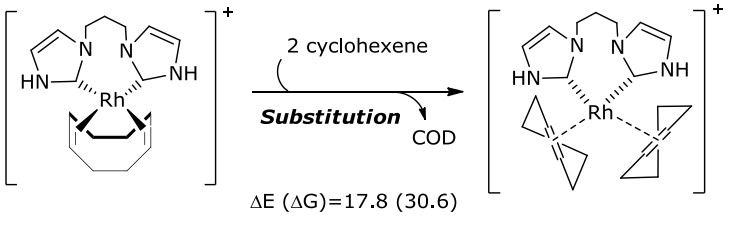
	Rh(I)-NHC **3.2**	Rh(I)-NHC **DFT model**
Rh-C(carbene)		
Rh(1)-C(1)	2.038	2.037
Rh(1)-C(11)	2.029	2.030
C(imidazolim)-C(imidazolium)		
C(2)-C(3)	1.342	1.355
C(12)-C(13)	1.346	1.356
Bite Angle (C-Rh-C)		
C(1)-Rh(1)-C(11)	87.6	83.5

The good agreement between experimental and theoretical results using this DFT method, was pointed out in previous studies on the Rh mediated hydroboration of styrene in our group.[63,64]

3.3.2.2 Energy profile: diborated and allyl boronate esters

First we focused our study on the formation of the diborated product. The most accepted mechanism for the alkene diboration reaction involves oxidative addition of the diboron reagent to the metal centre, followed by insertion of the alkene and reductive elimination to generate the *syn*-organodiboron product.

Generation of the cationic metal species $[Rh(cyclohexene)_2(NHC)]^+$ is an endothermic process (ΔE=17.8 kcal.mol^{-1}) that takes place by substitution of the labile 1,5-cyclooctadiene (COD) by two molecules of cyclohexene (Scheme 3.8).

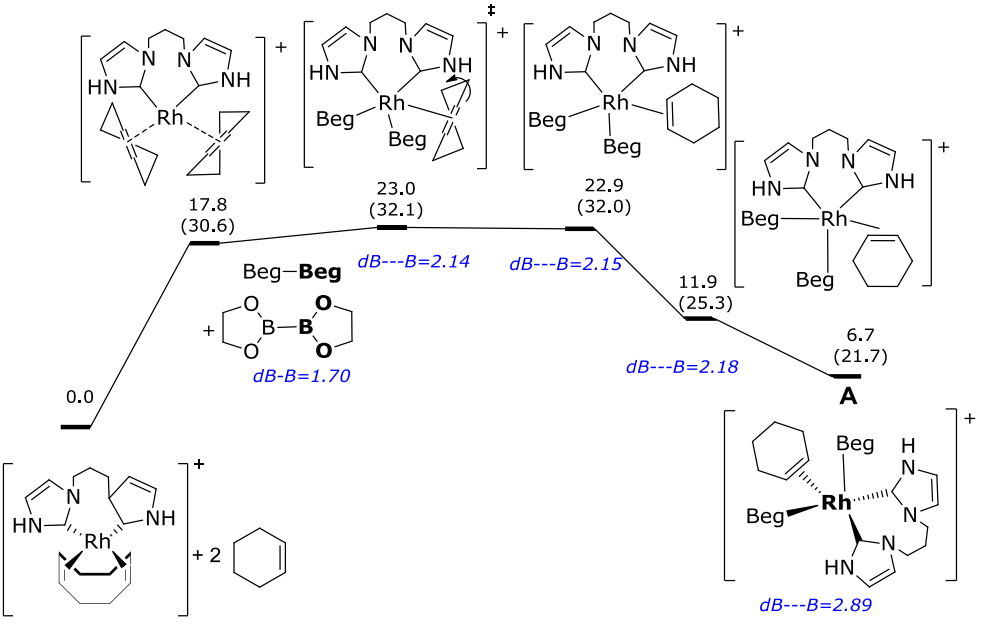


Scheme 3.8 Computed relative electronic energy (ΔE) and Gibbs free energy (ΔG in parenthesis, both in kcal.mol^{-1}) for the COD substitution by two molecules of cyclohexene as a model substrate

Concerning the oxidative addition pathway, it has experimentally been demonstrated that diboron reagents such as B_2cat_2 and B_2pin_2 can be activated by late transition metal complexes[7–9,65] promoting the homolytic cleavage of the B-B bond. The resulting bisboryl Rh(III) complexes have been completely characterized and in the case of Bcat moieties the crystal structure has also been determined.[9] Also, oxidative addition of the model $B_2(O_2C_2H_2)_2$ diboron reagent to neutral Rh(I) complexes modified with phosphines has been studied by means of computational studies.[10] However to the best of our knowledge, the oxidative addition of diboron reagents to cationic Rh(I) complexes modified with NHC ligands has not been previously reported.

Despite of employing different theoretical methods, we were not able to locate a transition state for the oxidative addition step of B_2eg_2 to $[Rh(cyclohexene)_2(NHC)]^+$. However, as it is shown in Scheme 3.9, we found a transition state for the rotation of the cyclohexene in the $[Rh(cyclohexene)(NHC)(Beg)(Beg)]^+$ (ΔE=21.7 kcal.mol^{-1}). While the B-B bond

length in B_2eg_2 is 1.70 Å, the distance between the two boron atoms in the located transition state is 2.14 Å. Taking into account the original length of the diboron reagent B_2eg_2 (1.70 Å) it seems that homolytic cleavage of the B-B bond has already taken place at this stage. It is also worthy to mention that the longer the distance is between the two boron atoms, the more stable seems to be the bisboryl Rh(III) complex (Scheme 3.9).



Scheme 3.9 Energy profile for the formation of cationic bisboryl Rh(III)-NHC complex **A**. Electronic and Gibbs free energy (in parenthesis) as kcal.mol^{-1} calculated at BP86 level. Distances between the two boron atoms are given in Å

This study is comparative to a previous DFT study on Pd(II)-NHC catalyzing diboration of alkenes.[22] The corresponding transition state for the oxidative addition of B_2cat_2 to cationic Pd(II) complexes modified with N-heterocyclic carbene ligands was also not located. Instead, the energy barrier of this process was evaluated by means of a linear transit procedure between the reactant $[Pd(NHC)(\sigma\text{-}B_2cat_2)]^+$ complex and the product.[22]

Nevertheless, we were able to characterize the structure for the resulting species of the oxidative addition of B_2eg_2 to the cationic $[Rh(cyclohexene)_2(NHC)]^+$.

After a conformational study of the resulting Rh(III) diboryl species $[Rh(Beg)_2(cyclohexene)(NHC)]^+$, we found that the most stable conformation was characterized as a distorted square planar pyramidal structure with one boryl moiety occupying the apical site and the other boryl moiety in the basal site (Figure 3.1). The bond angles about the rhodium centre support the description of the mentioned distorted square planar pyramidal geometry since the C(1)-Rh-B(1) is 166.47ºC and C(2)-Rh-C(3) is 168.61, both values are similar and reasonably close to linear. Remarkably, angles between the basal B(1) and the apical B(2) are 84.87 ºC, thus the two boryl moieties adopt a mutually perpendicular relative orientation, as it was found in some Rh(III) bisboryl species with B_2cat_2.[9] Also, the B(1)-Rh-B(2) angle results in a B···B separation of 2.89 Å which differs in 1.19 Å respect to the B-B distance in B_2eg_2 (1.70 Å). Consequently, any residual B···B interaction, if it still exists, must be weak.

As it is shown in Scheme 3.9, although the resulting Rh(III) species is stabilized by a strongly σ-donor chelate N-heterocyclic carbene ligand formation of the cationic bisboryl Rh(III)-NHC complex **A** is an endothermic process (ΔG=21.7 kcal.mol^{-1} above reactives in free form) as Morokuma *et al*. also calculated for a rhodium complex modified with phosphines.[10]

This new characterized rhodium(III) complex, $[Rh(Beg)_2(cyclohexene)(NHC)]^+$, has been chosen as the origin of energies in our reaction energy profile (Scheme 3.10).

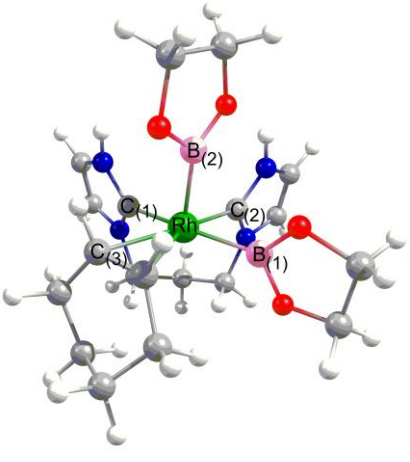
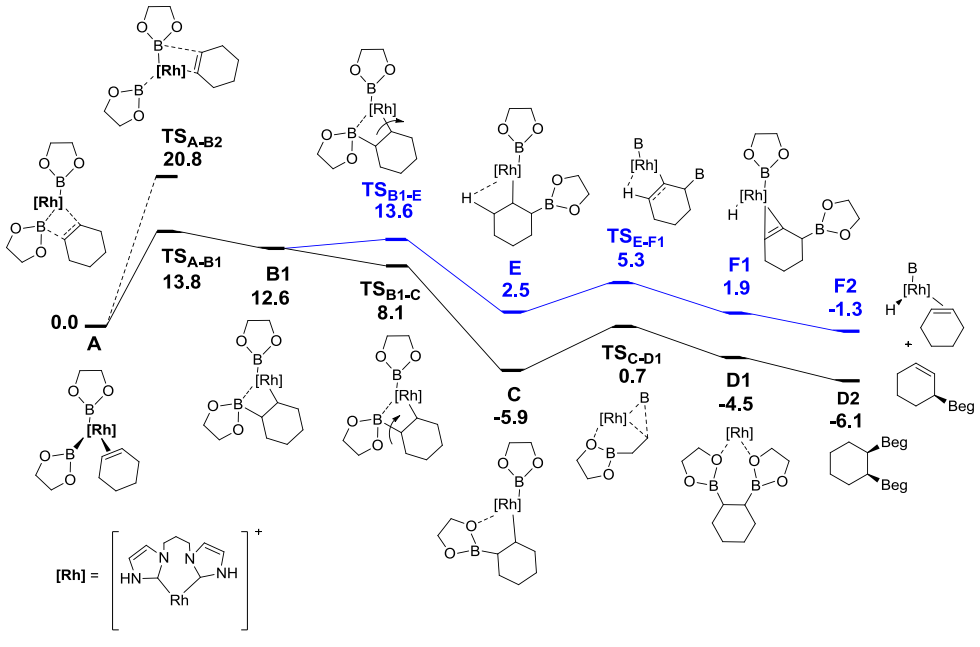


Figure 3.1 Model structure for the cationic bisboryl Rh(III)-NHC species $[Rh(Beg)_2(cyclohexene)(NHC)]^+$ (**A**)

As it has been depicted in Scheme 3.7, once the oxidative addition has taken place, the second step is defined as the insertion of the alkene into the Rh-B bond.

The insertion of an alkene into a Cu-B bond in copper (I) boryl complexes was studied by means of DFT calculations and was also demonstrated in stoichiometric studies.[32]

In this study, two plausible mechanisms for the insertion pathway can be considered (Scheme 3.10): apical insertion when the alkene binds the apical boryl (**TS_{A-B2}**) and basal insertion when the reaction occurs in the basal plane of the distorted square-based pyramid (**TS_{A-B1}**). According to our DFT results, it is clear that basal insertion is less energetically demanding (ΔG=7.0 kcal.mol^{-1} lower than the apical one). The resulting **B1** species can further undergo a rearrangement in order to occupy the vacancy generated in the coordination sphere of the metal. This process involves the rotation of the B(1)-$C_{cyclohexene}$ bond to afford a more stable species **C**, in which an interaction of the oxygen of the boryl unit with the metal centre has been established. Note, that this process is barrierless (**TS_{B1-C}**=-4.5 kcal.mol^{-1}). In the following step, reductive elimination takes place recovering a Rh(I) **D1** species in which the diborated product is coordinated through the oxygen atom of the Beg moiety to the metal centre (**D1** species). Dissociation of the diborated product is characterized as an exothermic process (ΔG= -6.1 kcal.mol^{-1}). Next, we evaluated the energy profile for the formation of the allyl boronate ester (Scheme 3.10, blue line). Once the **B1** intermediate was formed, an alternative rearrangement could take place through rotation of the Rh-$C_{cyclohexene}$ bond. Although the energy barrier for this rotation was found to be very low (ΔG=1.0 kcal.mol^{-1}), it was less favoured than the B(1)-$C_{cyclohexene}$ rotation. The resulting **E** species could favour an agostic interaction between the Rh centre and the ortho hydrogen of the cyclohexene, promoting the *β*-hydride-elimination towards the Rh-allylboronate complex (**F1**). Further dissociation of the allylboronate provides a Rh-hydride species, which is a key intermediate to obtain the rest of the observed organoborated byproducts (vinylic and hydroborated compunds). It is noteworthy to mention the overall formation process is only slightly exothermic (ΔG=-1.3 kcal.mol^{-1}) for the allyl boronated ester product and much more exothermic for the diborated one (ΔG=-6.1 kcal.mol^{-1}). Both experimental and theoretical calculations seem to be in agreement with the favoured formation of the diborated product over the *β*-borated one.



Scheme 3.10 Comparative energy profiles for the formation of the diborated and allyl boronate ester compounds computed at BP86 level. Gibbs free energy is given in kcal.mol^{-1}.

Differences between the two reaction pathways are not very large, thus subtle changes in the solvent and in the ligands can switch reactivity. Indeed, polarity and coordination ability of the solvent are key factors to explain the differences observed in selectivity (Table 3.1).

We further evaluated the solvent effect on the energy profile considering first the polarity of the solvent. For this purpose, we performed single point calculations in THF and cyclohexane modelled as a continuous solvation model (conductor-like screening model, COSMO).[61]

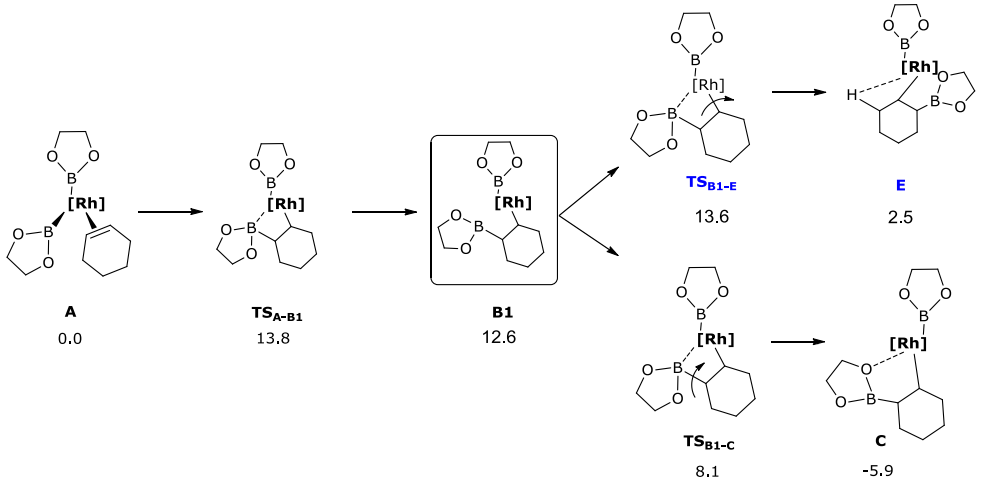
As it is collected in Table 3.4 differences in energy using THF or cyclohexane as a solvent are very small. Comparing the two computed Gibbs free energies in solution, it seems that polarity of the solvent (cyclohexane dielectric constant =2.02, THF=7.6) could not be as important as the coordination availability of the solvent in the energetic differentiation between the two pathways.

Table 3.4 Computed Gibbs Free energy in gas phase (ΔG_{gas}) and in solution (ΔG_{THF} and $\Delta G_{cyclohexane}$) for all molecular species involved in the formation of diborated and the allylic product. In parenthesis and in blue calculated energy barriers from its immediate intermediate

Species	**ΔG_{gas}**	**$\Delta G_{cyclohexane}$**	**ΔG_{THF}**
A	0.0	0.0	0.0
TS_{A-B2}	20.8	21.6	22.2
(apical insertion)			
TS_{A-B1}	13.8	14.2	14.5
(basal insertion)			
B1	12.6	12.8	12.9
(product basal insertion)			
TS_{B1-C}	8.1	8.0	7.6
(rotation C-B bond)	(-4.5)	(-4.8)	(-5.3)
C	-5.9	-6.0	-6.3
(rotation C-B bond product)			
TS_{C-D1}	0.7	0.4	-0.3
(reductive elimination)	(6.6)	(6.4)	(6.6)
D1	-4.5	-6.1	-8.3
(reductive elimination complex)			
D2	-6.1	-7.3	-7.9
(diborated product)			
TS_{B1-E}	13.6	13.9	13.9
(rotation C-Rh bond)	(1.0)	(1.1)	(1.0)
E	2.5	2.3	2.0
(rotation C-Rh bond product)			
TS_{E-F1}	5.3	5.1	4.7
(β-hydride elimination)	(2.8)	(2.8)	(2.7)
F1	1.9	1.8	1.4
(β-hydride elimination product)			
F2	-1.3	-3.4	-5.4
(allylic product)			

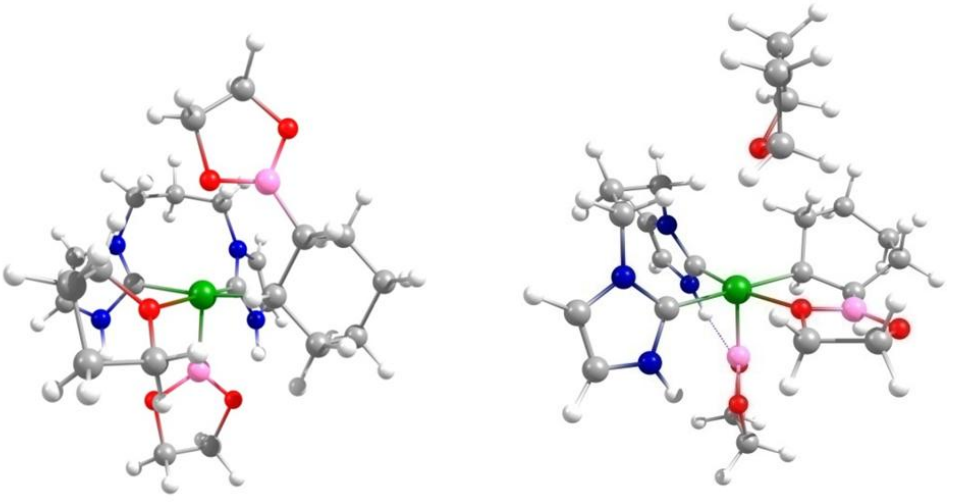
Since polarity of the solvent did not differentiate energetically the diboration pathway versus the allylic product path, changes on the selectivity upon using THF might be attributed to its ability of coordination. Concretely, after the basal

insertion has taken place a vacancy in the coordination sphere of the metal centre is generated (**B1** species). In order to occupy the vacancy generated in the coordination sphere of the metal centre, in concordance with the already commeted data in this chapter, a rearrangement must take place. Scheme 3.11 schematically shows these two possible rearrangements.



Scheme 3.11 Alkene insertion and rearrangement. Relative Gibbs free energies given in kcal.mol^{-1}

Tetrahydrofuran could coordinate to the resulting complex from the basal insertion, **B1**, blocking the rotation that leads to the most stable **C** species that can further undergo reductive elimination to form the diborated product. If this position is blocked, the alternative pathway could be more favoured, and thus formation of the allylic product could be seen when THF is used (Figure 3.2, **B1_THF** molecular structure). Also, coordination of the THF in Rh(III) species, such as **C** (Figure 3.2, **C_THF**) result in a less stable octahedral complex ($\Delta E_{gas}(\Delta G_{gas})$=1.5 (14.6) kcal.mol^{-1} respect to **C** plus THF).



B1_THF **C_THF**

Figure 3.2 Selected structures of the possible coordination of THF in singular Rh(III) species

Also coordination of solvent might compete with the coordination of the substrate (cyclohexene), thus, we could also explain the low conversions achieved when THF is used (9% after 16h, Table 3.1, entry 2). Notably, this is also in well agreement with the observed inactivity of the system when the coordinating solvent dioxane was used.

3.4 Conclusions

Despite it has been well established that rhodium complexes modified with phosphines favoured the dehydrogenative borylation reaction in borylation of cyclic olefins, we have found that Rh(I) cationic complexes modified with bidentate N-heterocyclic carbene ligands selectively promotes the diboration reaction. The use of non polar, non coordinating solvents, such as pentane, hexane or cyclohexane is also of crucial importance to guarantee the selective 1,2-diboronated ester formation. Theoretical calculations carried out to determine the key factors that might favour the diboration mechanism versus the dehydrogenative borylation mechanism have demonstrated that *β*-H-elimination pathway is more energetically demanding than the reductive elimination step in the catalytic cycle. Also, evaluation of solvent effects by computational means revealed that coordination ability of the solvents seems to be more influential than polarity on the activity and selectivity of the catalytic system.

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Chapter 4: Organocatalytic approach to diboration of alkenes

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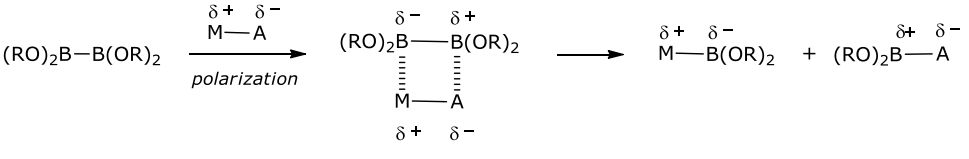
4.1 Introduction

Modern organic chemistry relies on the possibility to incorporate a manifold of different functionalities into the organic framework to produce target compounds of high added value. In this regard, the boryl group combines easy accessibility and versatility.[1,2]

In this context, diboration is one of the most efficient boron addition reactions because simultaneously introduces two boryl units in the unsaturated molecule with total atom economy from commercially available diboron reagents (i.e. B_2cat_2, B_2pin_2). When both C-B bonds are formed, they can be independently functionalized towards target compounds.[3,4,5]

Due to the high B-B bond energy (104 kcal.mol^{-1})[6] of the tetraalkoxydiboron compounds, their activation has been always associated with the use of transition metal catalysts. As mentioned in Chapters 2 and 3, depending on the metal centre $B_2(OR)_4$ activation occurs by homolytic oxidative addition to metals such as Pt(0) and Rh(I),[7]or heterolyctic cleavage *via* σ-bond metathesis with Cu(I),[8] Pd(II)[9] and Ir(III).[10] Particularly, our group has contributed experimentally and theoretically to gain more insights into the Cu(I)-boryl and Pd(II)-boryl formation.[8,9] It was shown that the presence of a base was critical towards the *in situ* generation of the active species for selective diboration of alkenes (Scheme 4.1).



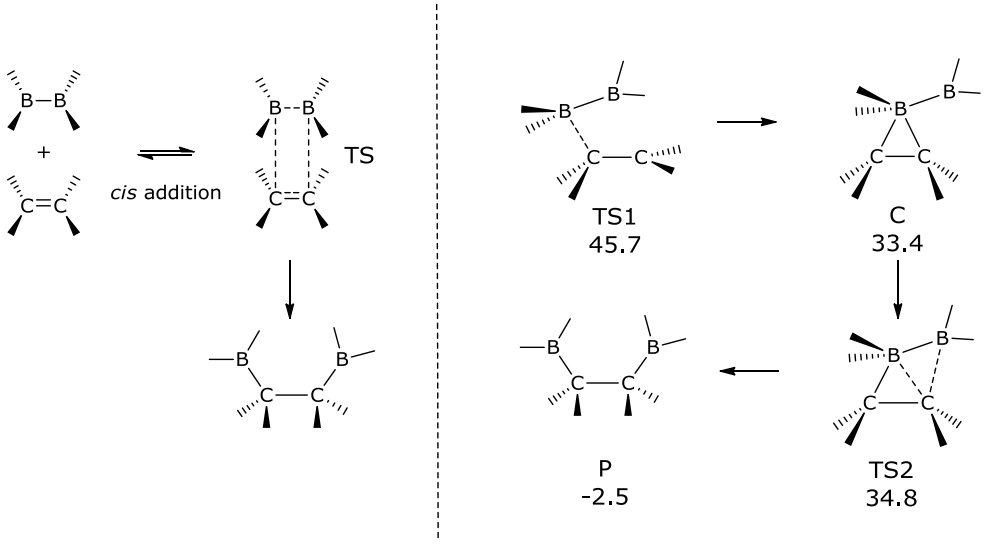
Scheme 4.1 σ-Bond metathesis between $(RO)_2B$-$B(OR)_2$ and M-A, (A= anionic ligand)

Although these metals have been demonstrated to be effective for the selective diboration of alkenes, the requirement of a transition-metal catalyst is still one major drawback, due to the added cost of the metals and the associated cost to separate the metal from the product.

Direct addition of diboron reagent to alkenes and alkynes[11,12] was only achieved with the highly reactive diborontetrahalides B_2X_4 (B-B bond energy 79.0 kcal.mol^{-1} for B_2Cl_4[13]). The first example of such metal-free diboration was published in 1954, describing the addition of B_2Cl_4 to ethylene in the absence of

any additive.[11] First mechanistic proposals by Holliday *et al*.[14,15] involved an initial π donation from the unsaturated linkage to the two vacant p-type orbitals of the adjacent boron atoms in B_2Cl_4 followed by subsequent B-B cleavage resulting in *cis* addition (Scheme 4.2, TS).

The unique computational study up to date with B_2H_4 as a model diboron reagent,[16] revealed that the metal-free uncatalyzed addition of B_2X_4 to alkenes is an exothermic process that occurs by a two step reaction involving the formation of a 3-center π-complex (Scheme 4.2, C) rather than 4-centre TS as it was previously suggested.[17]



Scheme 4.2 Suggested 4-centre TS mechanism versus the MNDO calculated mechanism through 3-π centre intermediate (electronic energies in kcal.mol^{-1})[16]

Despite the interesting metal-free addition of B_2Cl_4 to alkenes, diborontetrahalides are rather difficult to handle and are unstable.[18,19] For this reason, the development of a metal-free catalytic diboration with the more stable tetraalkoxydiboron reagents, $B_2(OR)_4$, is critical for modern chemical synthesis, particularly if selectivity issues can also be controlled as in metal mediated diboration protocols. Towards this end, the activation of diboron reagents by other species different than transition metal complexes is the first challenge. The second one is to generate an electronic polarization in the activated diboron reagent to promote the boryl addition reaction to olefins.

Boryl moieties in tetraalkoxydiborons do not have nucleophilic character, instead their electrophilicity is due to the empty *p*-orbitals of the boron atoms, which can be diminished by the electron donation from the non-bonding pairs of the oxygen atoms. Within the last few decades, it has been possible to identify Lewis acid-base interactions of diboron reagents with C,[20–22] N[23–28] and O[9,29–31] bases.

Initially, Marder and Norman studied the reactivity of B_2cat_2 and $B_2(1,2\text{-}S_2C_6H_4)$ towards nitrogen and phosphorus donors to afford the corresponding mono- and bis- adducts $B_2(1,2\text{-}E_2C_6H_4)\cdot L$ (E=O,S; L=4-picoline, PMe_2Ph, PEt_3, Figure 4.1, **A** and **B** respectively).[23,24] Remarkably, evidences of phosphines coordinating to the diboron reagent were only observed with the more acidic sulphur diboron.
Interestingly, Braunschweig *et al.* have recently showed novel asymmetric sp^2-sp^3 diborane from the more reactive halide-substiuted diboranes, ($X_2B\text{-}BMes_2$ (X=Cl, Br) and N-heterocyclic carbenes (Figure 4.1, **C**).[32] Also, analogous sp^2-sp^3 adducts have been observed with phosphines interacting with $Cl_2B\text{-}BMes_2$ (Figure 4.1, **D**).[33]

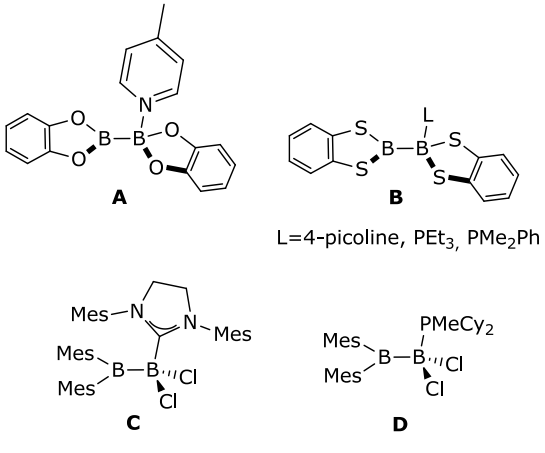


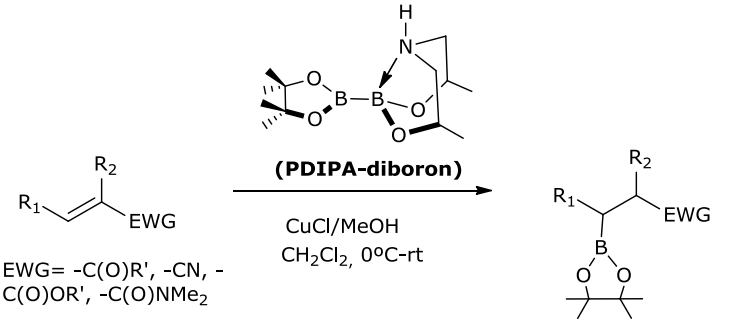
Figure 4.1 Known sp^2-sp^3 activated diboron adducts by Lewis acid-base interactions (Cy=cyclohexyl, Mes=mesityl)

More recently, intramolecular Lewis acid-base interaction has been reported between the secondary amine and one of the boron atoms in pinacolato(diisopropanolaminato)diboron (PDIPA-diboron, Scheme 4.3, **a**), which was shown to be highly useful sp^2-sp^3 diboron reagent in the copper-

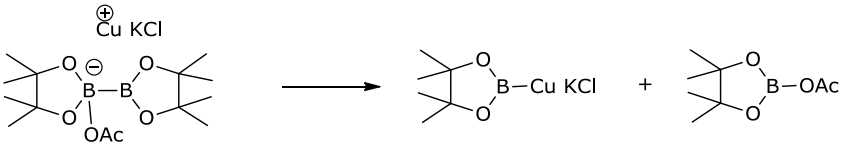
catalyzed borylation of α,β–unsaturated[26,28] substrates (Scheme 4.3, **a**) and β-borylation of allenoates.[27]

This activated diboron reagent was developed from an original idea of Miyaura and coworkers,[29] who suggested that AcO^- activated the B_2pin_2 (bis(pinacolato)diboron) by a Lewis acid-base interaction prior the boryl transfer to the copper center (Scheme 4.3, **b**).

a)



b)

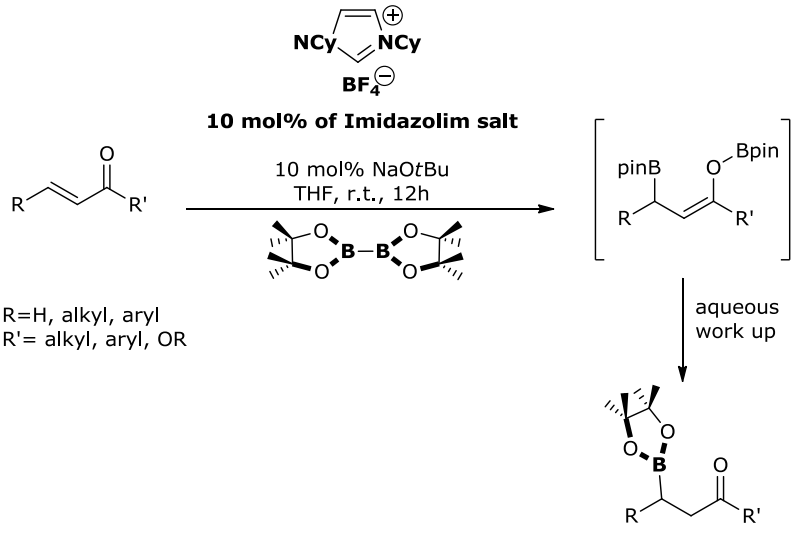


Scheme 4.3 a) General reaction conditions for Cu(I) catalyzed β-boration with the PDIPA-diboron, b) First example of diboron activation with a base by Miyaura and co-workers

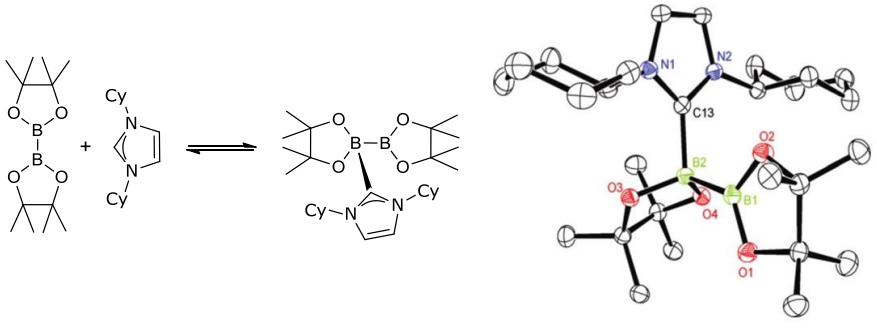
The first metal free catalytic activation of tetraalkoydiboron reagents was reported by Hoveyda *et al.* in 2009.[20] The combination of equimolar amounts of a base and an imidazolium salt, in the presence of B_2pin_2 allowed the borylation of a wide range of α,β-unsaturated compounds in high conversions (Scheme 4.4, **a**). An *in situ* formed neutral adduct B_2pin_2·NHC was suggested as the plausible catalytically active species responsible of borylation of α,β-unsaturated carbonyl compounds.[20,21]

Further spectroscopic and theoretical studies by Marder *et al*.[22] eventually verified the existence of the neutral Lewis acid-base adduct of B_2pin_2 and the NHC (1,3-is(cyclohexyl)imidazol-2-ylidene) both in solution and in the solid state (Scheme 4.4, **b**).

a)

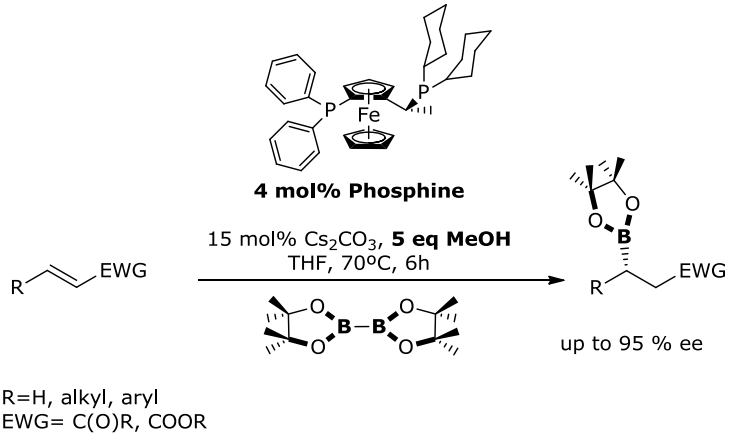


b)



Scheme 4.4 Representative scheme of the reaction conditions for the metal-free 1,4-diboration reaction reported by Hoveyda *et al*.[20] and the crystal structure of an B_2pin_2·NHC adduct isolated by Marder *et al*.[22]

In this context and simultaneously with Hoveyda's first report,[20] some members of our group developed a new organocatalytic methodology based on the use of Brönsted base, methanol and phosphines.[34] Application of this methodology towards the borylation of α,β-unsaturated carbonyl compounds resulted in high conversions towards the β-borated product. More importantly, high levels of enantioinduction were achieved with the use of chiral phosphines (Scheme 4.5).[34]



Scheme 4.5 General scheme of the reaction conditions for the first asymmetric metal-free *β*-boration reaction

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4.2 Motivation

Encouraged by the novelty and importance of this new metal-free methodology developed in our group, we planned to carry out a mechanistic study with two clear goals: 1) elucidate how the diboron reagent could be activated under this reaction conditions, Brönsted base/MeOH/phosphine system and 2) explore the reactivity of this novel organocatalytic methodology with the more challenging non activated alkenes.

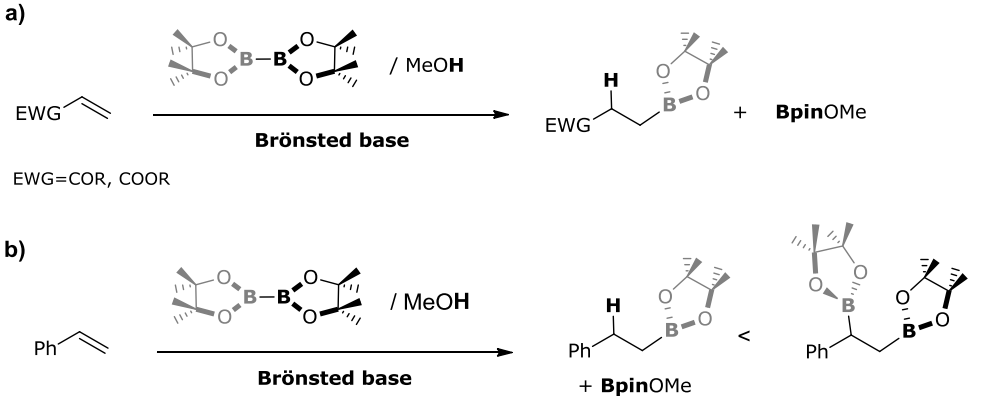
To get more insights into the activation of B_2pin_2 within the catalytic Brönsted bases/MeOH/phosphine system, we conducted NMR spectroscopic studies along with theoretical calculations aimed at suggesting a suitable mechanism for the application of the activated diboron reagent with non-activated olefins.

4.3 Results and Discussion

4.3.1 Experimental study

As it was previously demonstrated in our group,[34] the combination of B_2pin_2 with MeOH/Brönsted bases and phosphine promoted the borylation of a wide range of α,β-unsaturated carbonyl substrates. Interestingly, we pointed out that phosphines were not crucial for an active system, since the sole use of MeOH and Brönsted Bases promoted the B-B bond cleavage and its addition to the unsaturated substrate (Scheme 4.6, **a**)).

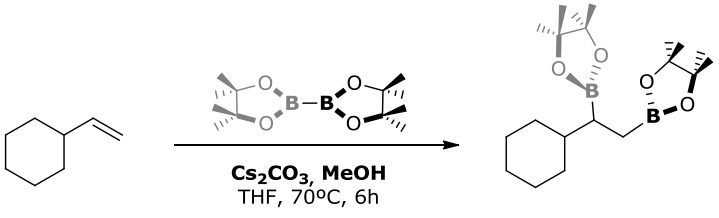
When non activated olefins were studied, and considering the presence of methanol as a crucial additive for an active system, hydroborated products were expected too. However, when styrene was the model substrate, only small amounts of hydroborated product was formed and instead the diborated olefin was the major product (Scheme 4 .6, **b**)).



Scheme 4.6 Metal free diboration of activated olefins with B_2pin_2, meditated with Brönsted base/MeOH as catalytic system

The formation of the later product was completely unexpected. In order to get more information, the same reaction was tested changing the substrate from styrene to vinyl cyclohexane. To our surprise, and satisfaction, only the diborated product was observed by ^1H NMR and GC (Scheme 4.7). This is the first case, in which both boryl moieties of the tetraalkoxydiborane reagent could be added to an olefin without the mediation of transition metal catalysts. Being

aware of the interest in this discovery, Dr. Amadeu Bonet optimized the reaction conditions.



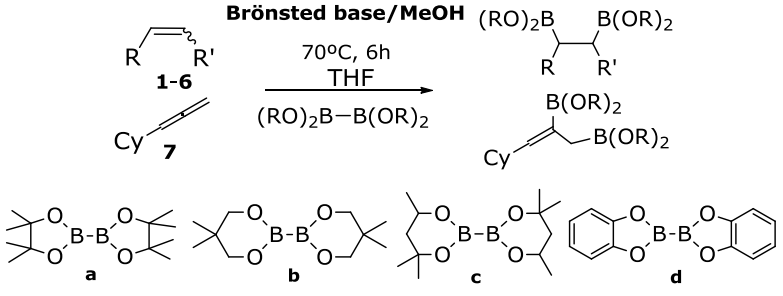
Scheme 4.7 Metal-free diboration of non-activated olefins with B_2pin_2, mediated with Brönsted base/MeOH as catalytic system

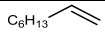
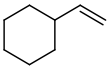
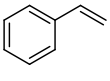
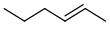
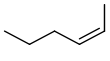
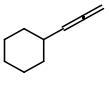
After screening a series of bases and alcohols we concluded that, in THF solutions, a combination of Cs_2CO_3 and MeOH provided synthetically useful conversions and chemoselectivities on the diborated product. It is worth noting that various other bases, such as alkali methoxides (Li^+, Na^+, K^+), or NaO^tBu provided comparable results. Despite the fact that for optimal activities the MeOH is added in excess with respect to the substrate, the formation of the "hydroborated" by-product rarely exceeds 5 mol%. This simple catalytic system is capable of mediating the addition of different diboron reagents to various non-activated unsaturated substrates. For instance, in a THF solution, at 70°C oil bath temperature, bis(pinacolato)diboron (**a**) could be added quantitatively to 1-octene in the presence of 15 mol% Cs_2CO_3 and 5 eq. of MeOH, within 6 hours (Table 4.1, entry 1). Only traces of the "hydroborated" by-product could be observed by GC analysis. Changing the *n*-hexyl substituent to cyclohexyl did not influence the reactivity of the C=C double bond significantly, 92% of the vinylcyclohexane was converted, with close to complete chemoselectivity into the desired diborated product (Table 4.1, entry 2).

Diboron reagents (**b**, **c**, **d**) formed from methyl substituted 1,3-diols and catechol are less reactive than bis(pinacolato)diboron (**a**) (Table 4.1, entries 2-5). The diboration of styrene required milder reaction conditions than that of the aliphatic alkenes, for high activity and selectivity (Table 4.2, entry 6). Diboration of *trans*-hex-2-ene (Table 4.2, entry 7) gives the diborated product in a 3:97 syn:anti ratio, while *cis*-hex-2-ene (Table 4.2, entry 8) forms the corresponding diborated product in 95:5 syn:anti ratio. Similarly, the diboration of cyclohexene exclusively gives the *cis* diborated product (Table 4.1, entry 9). Another interesting finding is that diboration of a terminal allene favors the formation of the 1,2-diborated product (Table 4.2, entry 10). This selectivity is

in contrast to most transition metal catalyzed diborations of allenes, which usually provided the 2,3-diborated isomers as primary products.[35–37]

Table 4.1 Transition metal-free diboration reaction of alkenes and allenes



Entry	Substrate	$B_2(OR)_4$	Base	Conv	Sel [b]	Yield[c] (IY)[d]
1		**a**	Cs_2CO_3	98	99	97(71)
2		**a**	Cs_2CO_3	92	97	89(71)
3	"	**b**	Cs_2CO_3	73	99	72(59)
4	"	**c**	Cs_2CO_3	60	99	59(56)
5	"	**d**	Cs_2CO_3	85[e]	99	84[e](82)[f]
6[g]		**a**	NaO^{t}Bu	82	99	81(74)
7		**a**	Cs_2CO_3	74	96 [syn: anti 3:97]	69(57)
8		**a**	Cs_2CO_3	92	95 [syn: anti 95:5]	83(69)
9[h]		**a**	NaO^{t}Bu	84	99	83(65)
10[i]		**a**	NaO^{t}Bu	95	92 [1,2-dibor.87%]	76

[a] General conditions: substrate (0.5 mmol), diboron reagent (0.55 mmol), base (15 mol%), MeOH (2.5 mmol), THF (2 mL), T= 70ºC, t= 6h. [b]Beside the "hydroborated" by-product (<5%), in certain cases traces of vinyl-boronic esters (<1%) could be identified by GC-MS. [c] GC yield of the diborated product. [d] Isolated yield of the diborated product. [e] Based on internal standard. [f] Isolated as the corresponding diol. [g] T= 45ºC, t= 15h. [h] T= 70ºC, t= 16h. [i] T= 45ºC, t= 20h.

4.3.2 NMR study

Once we knew that methanol and Brönsted bases were crucial for the activation of the B_2pin_2, we planned to perform stoichiometric NMR experiments to obtain a deeper insight into a possible adduct formation. For these experiments we selected a very strong organic base, the Verkade base ($pka_{(DMSO)=}26.8$), that was completely soluble in THF and allowed us to monitor the experiments by ^{31}P NMR too.

The reaction between the Verkade base and MeOH was studied in the absence and in the presence of B_2pin_2. $^{31}P\{^1H\}$ NMR studies showed that, when an excess of methanol was in the system (4.0 eq respect to the base), the Verkade base was totally protonated ($^{31}P\{^1H\}$ NMR δ=-13.1 ppm, Figure 4.2) in the absence of B_2pin_2 and, consequently, 1.0 equivalent of methoxide anion with respect to the amount of base was generated.

The equilibrium between Verkade's base and MeOH was further confirmed by addition of deuterated methanol to the previous solution since both species, [H^+-Verkade] and [D^+-Verkade] could be seen by $^{31}P\{^1H\}$ NMR spectrum in a ratio of $D_{Verkade}$ / $H_{Verkade}$ =33:67 (Figure 4.2).

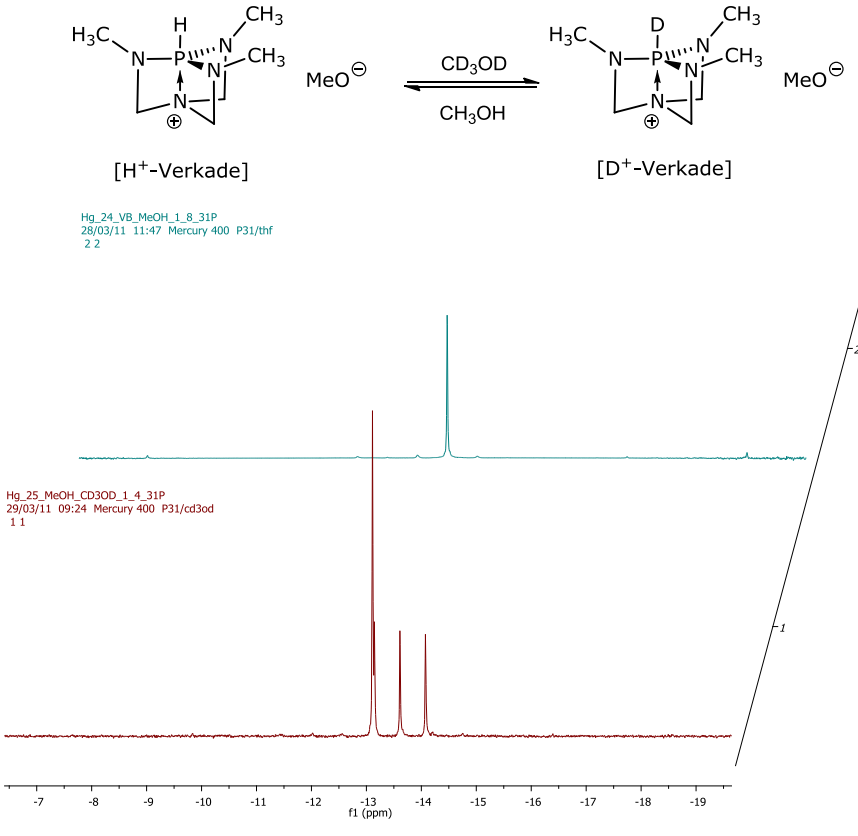
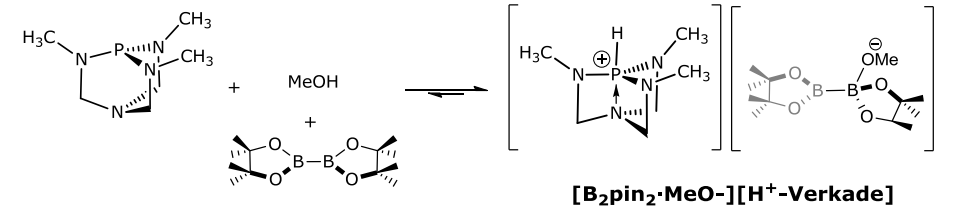


Figure 4.2 The spectrum colored blue illustrates the $^{31}P\{^{1}H\}$ NMR for Verkade base totally protonated. Red, shows a mixture between protonated Verkade and partially deuterated Verkade base

Next, we evaluated this interaction in the presence of the diboron reagent, B_2pin_2. Under argon, the Verkade base (0.5 mmol) and bis(pinacolato)diboron (0.5 mmol) were dissolved in THF (1 mL), and the solution was transferred into a quartz NMR tube, supplied with a capillary containing $Et_2O{\cdot}BF_3$, sealed with a rubber septum. $^{11}B\{^{1}H\}$ NMR experiments showed that the signals due to bis(pinacolato)diboron (30.5 ppm) did not change by the addition of Verkade's base in the absence of methanol, indicating the lack of interaction between the base and the diboron reagent. When MeOH (0.5 mmol) was added to the solution, the $^{31}P\{^{1}H\}$ NMR spectrum of the solution showed that 95% of the Verkade base became protonated upon the interaction with the MeOH, in the presence of B_2pin_2. Thus, comparing with the previous Verkade+MeOH study, the presence of the B_2pin_2 shifted the equilibrium favouring the deprotonation of

MeOH. More importantly, in the $^{11}B\{^1H\}$ NMR, the original signal of B_2pin_2 (30.5 ppm) was splitted into two new signals: a broad signal at 35.0 ppm and a less broad signal at 5.9 ppm (Figure 4.3) indicating a very distinct nature of the two diboron atoms. These new signals were assigned to the Lewis acid-base adduct $[B_2pin_2{\cdot}MeO^-][H^+\text{-Verkade}]$.



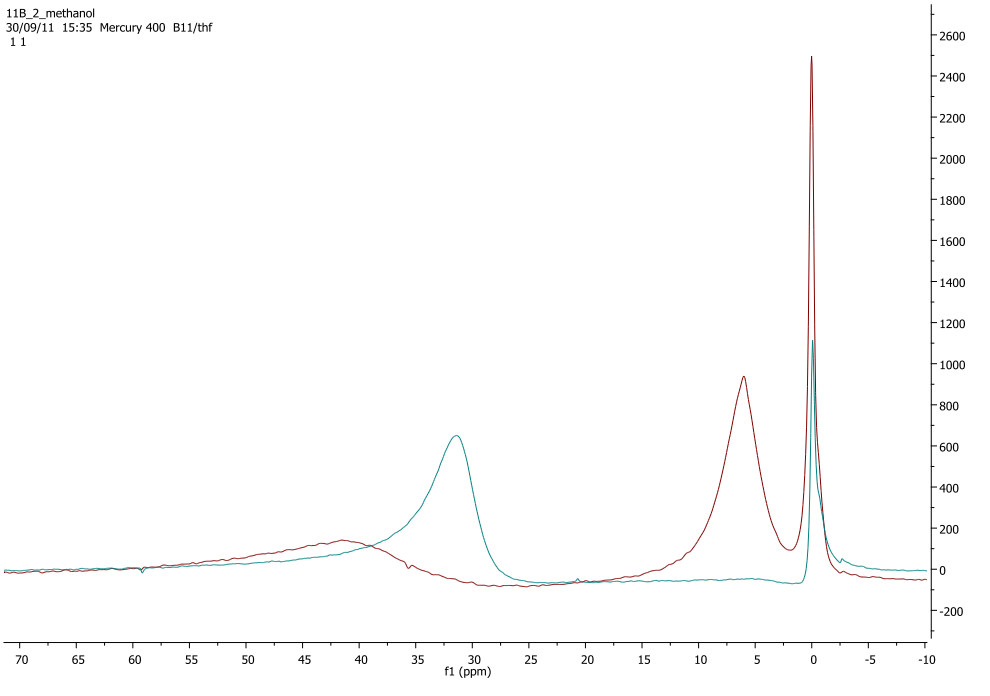


Figure 4.3 Blue, $^{11}B\{^1H\}$ NMR spectrum for B_2pin_2. Red, $^{11B}\{^1H\}$ NMR spectrum for $[B_2pin_2{\cdot}MeO^-][H^+\text{-Verkade}]$. $Et_2O{\cdot}BF_3$ is used as a reference

4.3.3 DFT study

4.3.3.1 Computational details

In this present theoretical approach, molecular structures for all the species were optimized without constraints by using Density Functional Theory (DFT) based methods as implemented in the Amsterdam Density Functional (ADF v2009.01) package.[38,39]

A triple-ζ plus polarization (TZP) Slater basis set was used on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[40] For geometry optimizations we used the local exchange VWN correlation potential[41] together with the Becke's exchange[42] and the Perdew's correlation[43,44] (BP86) generalized gradient corrections. Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequencies calculations.

Nuclear Magnetic Resonance chemical shifts were computed at the same level of theory by running single point calculations with all electron basis sets.

Standard corrections to Gibbs free energy at 298 K were evaluated too. Solvent effects were introduced by using the continuous solvent model COSMO.[45] Single point energy at the metahybrid M06[46] level were performed self-consistently.

4.3.3.2 Diboron adduct: novel activation mode

In order to properly assign the observed NMR signals, we further investigated computationally the possible species suggested from the NMR study and also other boron species already characterized by $^{11}B\{^1H\}$ NMR. As it is collected in Table 4.2, the calculated ^{11}B chemical shifts in THF perfectly reproduce the measured values for B_2pin_2, both for a B_2pin_2-N-heterocyclic carbene adduct reported by Hoveyda[21] and for the monoboryl (pin)B-O^{t}Bu species reported by Marder.[47] The adduct [B_2pin_2·MeO^-][H^+-Verkade] is observed as a broad signal at 5.9 ppm, and a very broad signal at around 35.0 ppm, which precisely coincides with the computed values for the sp^3 boron atom (5.4) and sp^2 boron (35.9). Furthermore, in an ESI-MS experiment, the peak of the [B_2pin_2·MeO^-] adduct, m/z=285.1 was detected. Also, a similar adduct formed from B_2pin_2 and KO^{t}Bu has been reported by Marder and coworkers.[47]

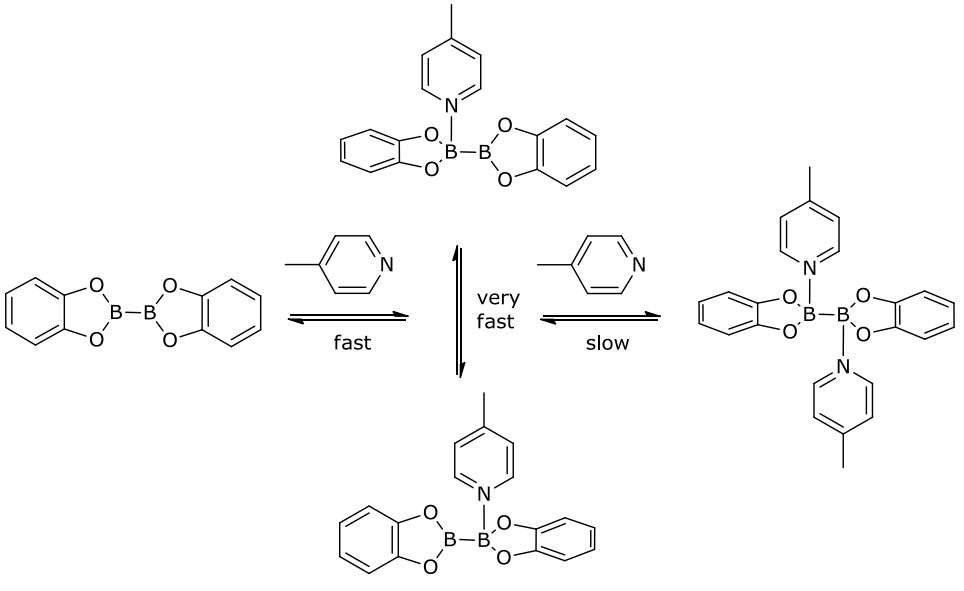
Table 4.2 Experimental and computed ^{11}B NMR chemical shifts values in solution (THF) for different boron species.[a]

Species	Experimental ^{11}B NMR	Computed ^{11}B NMR
B_2pin_2	30.5	30.5
B_2pin_2·NHC[21]	1.8 (sp^3) 36.2 (sp^2)	-0.6 (sp^3) 31.8 (sp^2)
(pin)BO^{t}Bu	21.5	18.7
[B_2pin_2·MeO^-][H^+-Verkade]	5.9 (sp^3) 35.0 (sp^2)	5.4 (sp^3) 35.9 (sp^2)
B_2pin_2·MeO^-		-17.9 (sp^3) 28.3 (sp^2)

[a] ^{11}B NMR values are given in ppm. Boron trifluoride etherate is taken as a reference

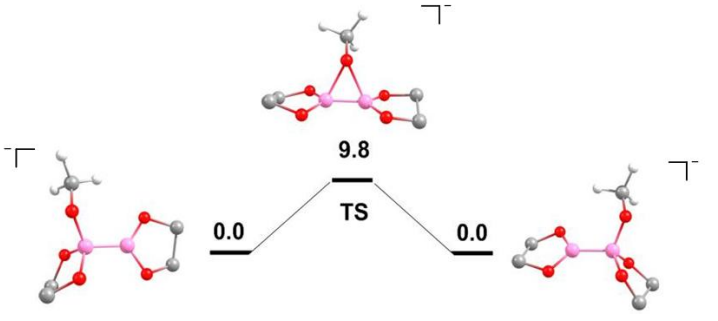
As it can be observed in Figure 4.3, signals of the [B_2pin_2·MeO^-][H^+-Verkade] adduct are very broad. Typically boron NMR signals are quite broad. This phenomena occurs because the quadrupolar nature of the ^{11}B nucleus is subject to quadrupolar coupling, and the quadrupolar relaxation pathways typically results in very short transverse relaxation times (T2), and hence broad line widths. Interestingly, in the case of the [B_2pin_2·MeO^-][H^+-Verkade] the signals are even broader. This broadening of the signals are probably due to the fast inter- and intramolecular exchange of the methoxide anion between the two

boron atoms. Such type of equilibrium were previously observed by Marder and coworkers,[23,24] with similar Lewis acid-base adducts based on B_2cat_2 and $B_2(1,2\text{-}S_2C_6H_4)$. In this previous work, multinuclear NMR studies for solutions containing B_2cat_2 and mpy (4-methylpiridine), $B_2(1,2\text{-}S_2C_6H_4)_2$ and mpy and $B_2(1,2\text{-}S_2C_6H_4)_2$ and PEt_3 indicated that intermolecular exchange of the base between the parent compound, the mono- and the bis-adducts occurs in solution together with intramolecular exchange between the two boron centres in the monoadducts (Scheme 4.8). Notably, phosphine-diboron interaction was only seen in the case of the more Lewis-acidic sulphur- based diborane.



Scheme 4.8 Possible inter- and intramolecular exchange in a solution of B_2cat_2 with mpy observed by Marder *et al*.[23,24]

In our case, we were able to locate the transition state for the intramolecular equilibrium in [B_2pin_2·MeO^-] species in THF. The energy barrier is relatively low (9.8 kcal.mol^{-1} above the adduct, Scheme 4.9). Thus, the broadening could also be seen at room temperature.



Scheme 4.9 Relative Gibbs free energy in THF (kcal.mol^{-1}) for the transition state (**TS**) for the intramolecular exchange of MeO^- between the two boron atoms in the [B_2pin_2·MeO^-] adduct calculated at BP86 level

Similarly, such a process has recently been seen by Braunschweig *et al*.[33] in the novel sp^2-sp^3 adduct formed by X_2B-$BMes_2$ (X=Cl, Br) and phosphines. The coordination of simple phosphines to this Lewis-acidic diborane Br_2B-BMe_2 results in the formation of two constitutional isomers of Br_2B-$BMes_2$·PEt_3 (major isomer **a1** and minor **a2**, Figure 4.5). Those authors were able to locate the transition state for the interconversion of the two isomeric species initiated by a 1,2-shift of one mesityl ligand (Figure 4.5, $TS_{a1\text{-}a2}$). In this case, the activation barriers for the interconversion of the two constitutional isomers are high (ΔE=94.24 kJ.mol^{-1}(22.57 kcal.mol^{-1}).

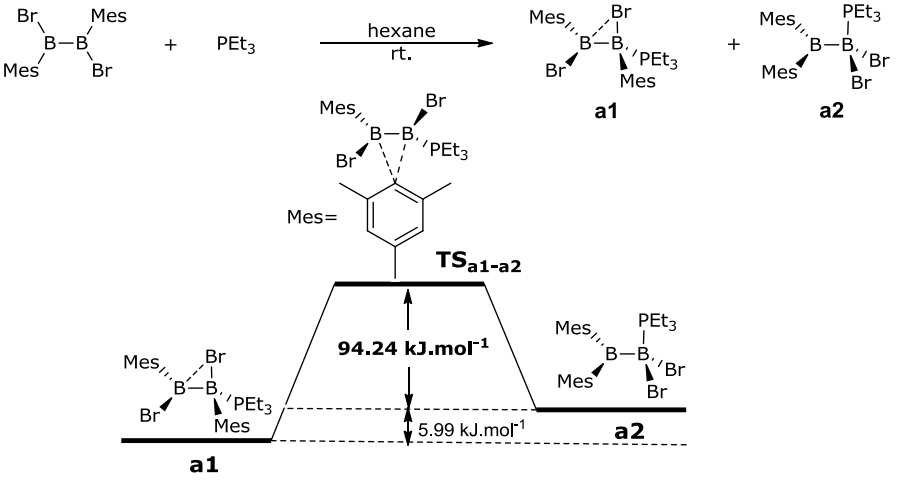
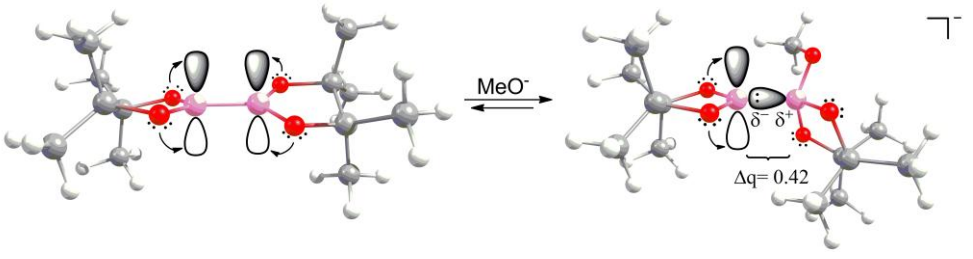


Figure 4.5 Synthetic route for the formation of the two isomeric species and calculated energetic parameters for the interconversion of constitutional isomers major **a1** and minor **a2** of Br_2B-$BMes_2$·PEt_3 adduct[33]

Remarkably, Marder and coworkers showed that in the case of the neutral Lewis acid-base adduct formed from B_2pin_2 and the N-heterocyclic carbene ligand (1,3-is(cyclohexyl)imidazol-2-ylidene), the binding must be weak in solution. NMR spectroscopy revealed a rapid exchange of the NHC between the two boron centers. In contrast to our study, DFT calculations revealed that the exchange involved dissociation and reassociation of NHC rather than an intramolecular process.[22]

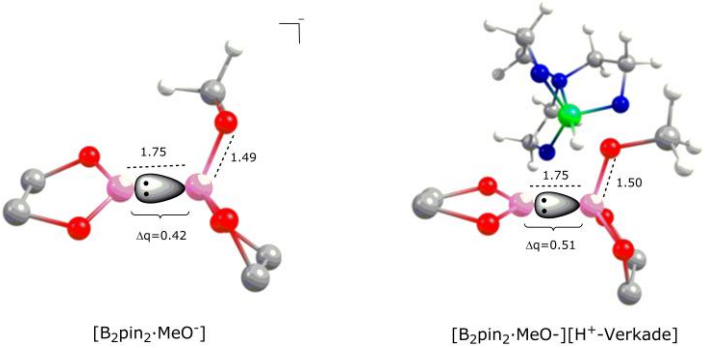
After having identified and characterized the novel Lewis-acid base adduct [B_2pin_2·MeO^-][H^+-Verkade] by NMR spectroscopy, we studied in more detail its nature by computational methods. Considering the Lewis structure of typical Lewis-acid base adducts, one would expect an increased negative charge density on the rehybridized, formally sp^3 boron atom. According to our DFT calculations carried out on bis(pinacolato)diboron, and on its Lewis acid-base adduct with MeO^- anion, the sp^3 boron atom *loses* electron density upon charge transfer from the Lewis base, while the virtually intact sp^2 boron atom unambiguously gains electron density with respect to its partial charge in the intact bis(pinacolato)diboron (Figure 4.6, Mulliken partial charge q_i Bsp^2 in the [B_2pin_2·MeO^-]=0.56 and q_i Bsp^2 in B_2pin_2=0.67, difference between the two sp^2 Boron atoms Δq=-0.11). The loss of electron density on the sp^3 boron atom (Figure 4.6, Mulliken partial charge q(Bsp^3) in the [B_2pin_2·MeO^-]=0.98 and q(Bsp^2) in B_2pin_2=0.67, difference between the two Boron atoms Δq=0.31), despite the direct charge transfer from the Lewis base, can be rationalized considering the fact that upon rehybridization the boron atom loses the π-electron donation from the oxygen atoms of the pinacolate moiety. The net result of these structural changes is that in the [B_2pin_2·MeO^-] adduct, the B-B bond becomes considerably polarized (Figure 4.6 difference between the Mulliken charges of the two boron atoms in [B_2pin_2·MeO^-], Δq=0.42), and the sp^2 boron atom acquires strong nucleophilic character. This suggests that a carbene type boryl nucleophile is formed.



B-B lenght (Å)	1.70		1.75	
Charge on Boron (qi)	0.67	0.67	0.56	0.98
			-0.11	**0.31**

Figure 4.6 Polarization of the B-B bond in the Lewis acid-base adduct, [B_2pin_2·MeO^-]. Δq: difference between the Mulliken charges of the boron atoms of the adduct

Notably, the most relevant features of the molecular structure of the [B_2pin_2·MeO^-] adduct are very similar to the neutral [B_2pin_2·MeO^-][H^+-Verkade]: the polarization of the B-B bond (Figure 4.7, Δq=0.42 for the anionic and Δq=0.51 for the neutral adduct), the intramolecular distance between the two boron atoms (Figure 4.7, 1.75 Å for both considered adducts) and the length of the sp^3 boron and the oxygen atom of the methoxide group (Figure 4.7, 1.49 Å and 1.50 Å for the anionic and neutral adduct respectively). In order to save computational time, from now on, all the calculations were performed considering the anionic [B_2pin_2·MeO^-] adduct.

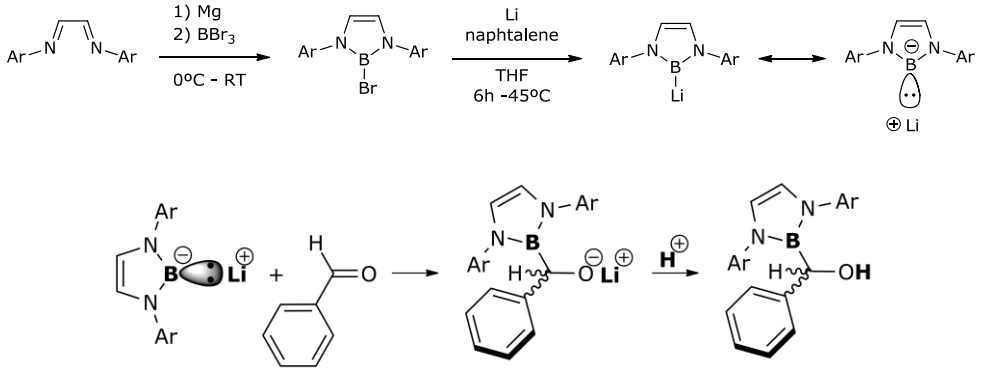


[B_2pin_2·MeO^-] [B_2pin_2·MeO-][H^+-Verkade]

Figure 4.7 Molecular structure of the anionic model [B_2pin_2·MeO^-] adduct and the [B_2pin_2·MeO^-][H^+-Verkade] adduct. Distances are given in Å and Δq: difference between the Mulliken charges of the boron atoms of the adduct. Methyl groups of the B_2pin_2 are omitted for clarity

Diboron reagents are expected to behave as electrophiles. However, on the basis of our study, the sp^2 boryl moiety of the *in situ* formed Lewis-acid base adduct has a strong nucleophilic character.

Prior to our study, only three examples were reported by Kraus,[48] Williams[49] and Weber[50] asserting the existence of alkali metal salts of anionic organoboron compounds as reactive intermediates in 1952. But spectroscopic characterization and isolation of the sp^2 boryl anions was not reported until 2006 by Nozaki *et al*. (Scheme 4.10).[51,52]



Scheme 4.10 Synthetic route for the preparation of the first isolated anionic sp^2 boryl nucleophile and its addition to benzaldehyde as an example of synthetic application

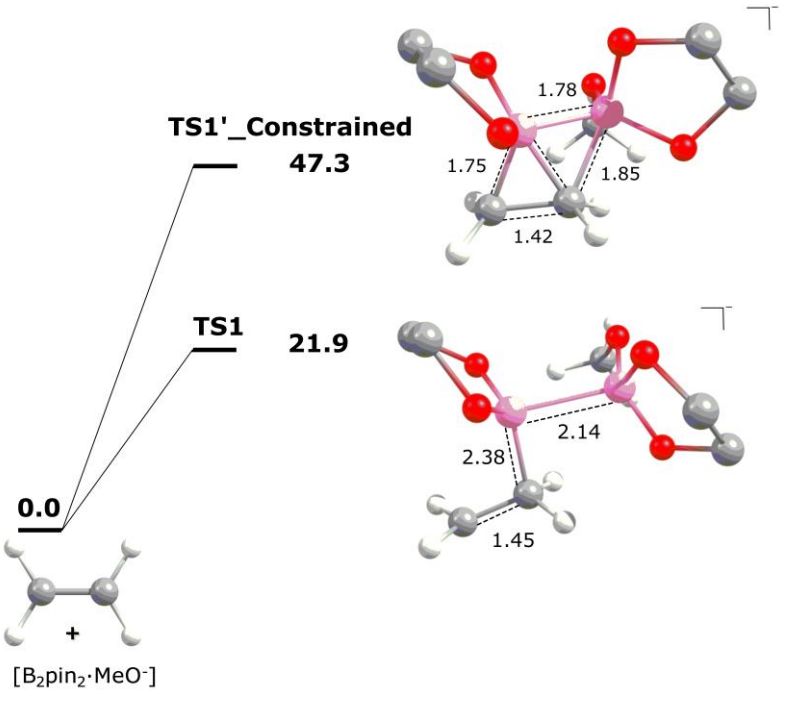
The nucleophilicity of boryl moieties is an important issue in modern chemistry, and we expect that it will open unprecedented synthetic pathways in the near future. Thus, the *in situ* generated nucleophilic Lewis acid-base adduct, [B_2pin_2·MeO^-], is an important contribution to this field mainly because the simplicity of the synthetic procedure involved.

4.3.3.3 Unprecedented mechanistic proposal

Once we identified the activation of B_2pin_2 by interaction with the methoxide anion, generated *in situ* from deprotonation of MeOH with a Brönsted base, the next challenge was to propose a mechanism that could explain its unprecedented reactivity towards the diboration of unactivated alkenes.

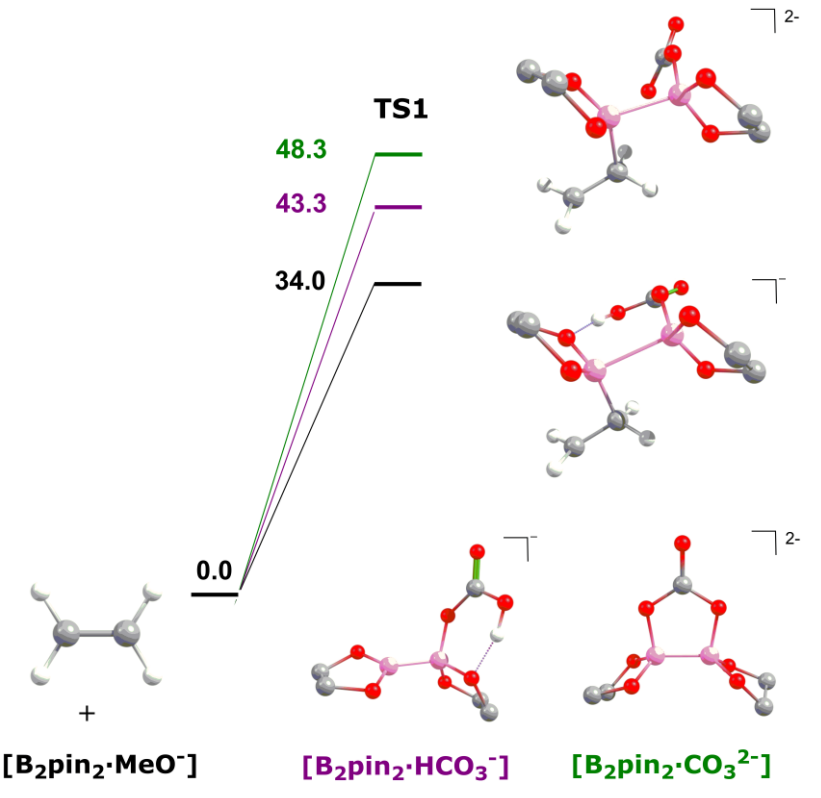
We have envisioned a mechanism for the organocatalytic diboration of olefins in which the first step is defined by the activation of the diboron reagent with the methoxide anion. In order to find evidences for the subsequent steps of the catalytic cycle, we have studied the possible interactions between model substrates, ethylene and propylene, and the [B_2pin_2·MeO^-] adduct using the DFT methods described in the computational details section in this chapter (section 4.3.3.1).[38,39]

Unequivocally, the switch from electrophile (B_2pin_2 in free form) to nucleophile character ([B_2pin_2·MeO^-] adduct) might suggest an unconventional mechanism for the formation of the two new C-B bonds. Nevertheless, and based on the mechanistic suggestions for the unique metal-free diboration of alkenes with B_2X_4, we first tried to locate an hypothetical 4-centre TS that involves the two different boron atoms of the [B_2pin_2·MeO^-] and the two carbons of the C—C double bond (TS1', Scheme 4.11). Location of such a concerted transition state, TS1', was not possible. The energy of this hypothetical concerted 4-centre TS1'was estimated from a constrained geometric optimization (TS1'_Constrained, Scheme 4.11) in which the B-B length, and the two B-$C_{ethylene}$ distances are fixed (1.78 Å, and 1.75, 1.85 Å respectively). Instead, a 3-centre TS transition state was located (TS1, Scheme 4.11). In comparison with the constrained structure of the hypothetical concerted 4-centre TS1', the difference in energy was ΔE=25.4 kcal.mol^{-1} favouring the 3-centre TS1. Thus, direct formation of the diborated product by addition of the [B_2pin_2·MeO^-] adduct towards the alkene could be ruled out.



Scheme 4.11 Relative electronic energy for different considered TS at BP86 level. Selected distances are given in Å. Methyl groups of the B_2pin_2 are omitted for clarity

Alternatively, we also evaluated the corresponding transition states for possible adducts between B_2pin_2 and CO_3^{2-} and HCO_3^- (potentially formed after deprotonation of methanol by the carbonate base). Notably, coordination of CO_3^{2-} with the B_2pin_2 resulted in a very stable symmetric adduct, like it was seen by Marder *et al*. when bispyridil ligands were added to $B_2(1,2\text{-}X_2C_6H_4)_4$ (X=O,S).[25] Such stable species might not be active towards diboration. Nevertheless, we were able to locate the corresponding transition state (Scheme 4.12, green energy profile), and also for the hypothetical $[B_2pin_2{\cdot}HCO_3^-]$ adduct (Scheme 4.12, purple energy profile). Both transition state structures were much more energetically demanding than the one computed for the $[B_2pin_2{\cdot}MeO^-]$ adduct (ΔG=9.0 and 14.3 kcal.mol^{-1} lower than the transition state for $[B_2pin_2{\cdot}HCO_3^-]$ and $[B_2pin_2{\cdot}CO_3^{2-}]$ respectively). These results are in well agreement with the catalytic experiments since formation of the *β*-borated product was not observed in the absence of MeOH. Consequently, as we observed in our NMR studies, the *in situ* generated methoxide from deprotonation of MeOH with a Börnsted base is the responsible for the activation of B_2pin_2.



Scheme 4.12 Relative Gibbs free energy (kcal.mol^{-1}) for some transition states of B_2pin_2·base adducts, at BP86 level. Methyl groups of the B_2pin_2 are omitted for clarity

We next focused on the characterization of the transition state, **TS1**, with propylene as a model substrate. In the most stable conformation for **TS1** with propylene, the sp^2 boron atom of the activated diboron reagent interacts with the unsubstituted carbon atom (C_1) of the C=C double bond, while the B-B bond weakens (0.49 Å longer respect to the B-B bond distance in the [B_2pin_2·MeO$^-$] adduct (1.75 Å)), and the charge density on the C_2 carbon increases (Figure 4.8, $\Delta q(C_2)$=-0.22 Mulliken increment of charge respect to C_2 in propylene as a reactive). Importantly, we have found that the interaction leading to **TS1** is the overlap between the strongly polarized B-B σ-bond (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the olefin (Figure 4.8).

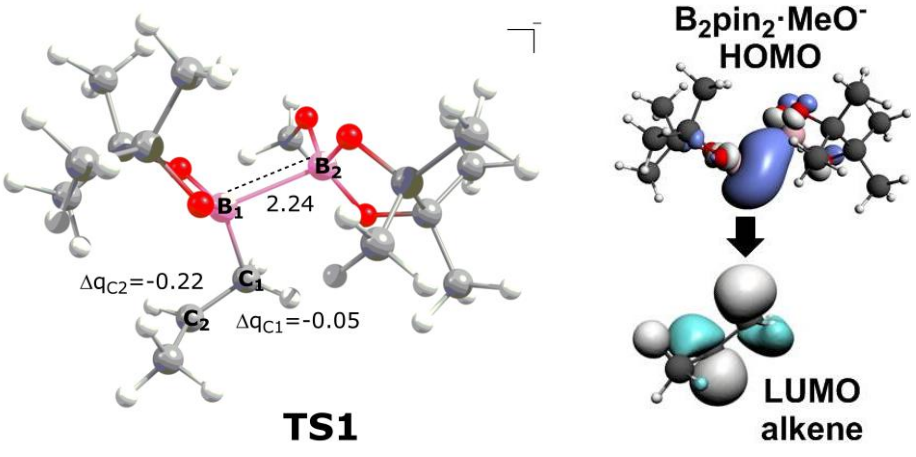


Figure 4.8 Most stable molecular structure for **TS1** of propylene as a model substrate and the interaction of its frontier orbitals. B-B bond length is given in Å and difference of Mulliken charges in C_2 and C_1 are calculated respect to the partial charges on the propylene in free form

Hence, the reactivity between the reaction partners clearly is a nucleophilic attack of the reagent, [B_2pin_2·MeO^-], towards the substrate, propylene. The increased charge density on C_2 in **TS1** results in a considerable kinetic lability, due to the positive inductive effect of the alkyl substituent. The negatively charged C_2 (ΔqC_2=-0.22 relative to the partial charge of C_2 in propylene in free form) should be prone to attack any electrophilic site, and the closest one in **TS1** is the attacking boron B1 atom (Figure 4.8, B1 in **TS1**) which is losing the B-B bond due to the nucleophilic attack. The distribution of the charge density among C_1, C_2 and the B1 boron atom, might explain the connection between **TS1** and the intermediate **I1** together with the BpinOMe byproduct (Figure 4.9).

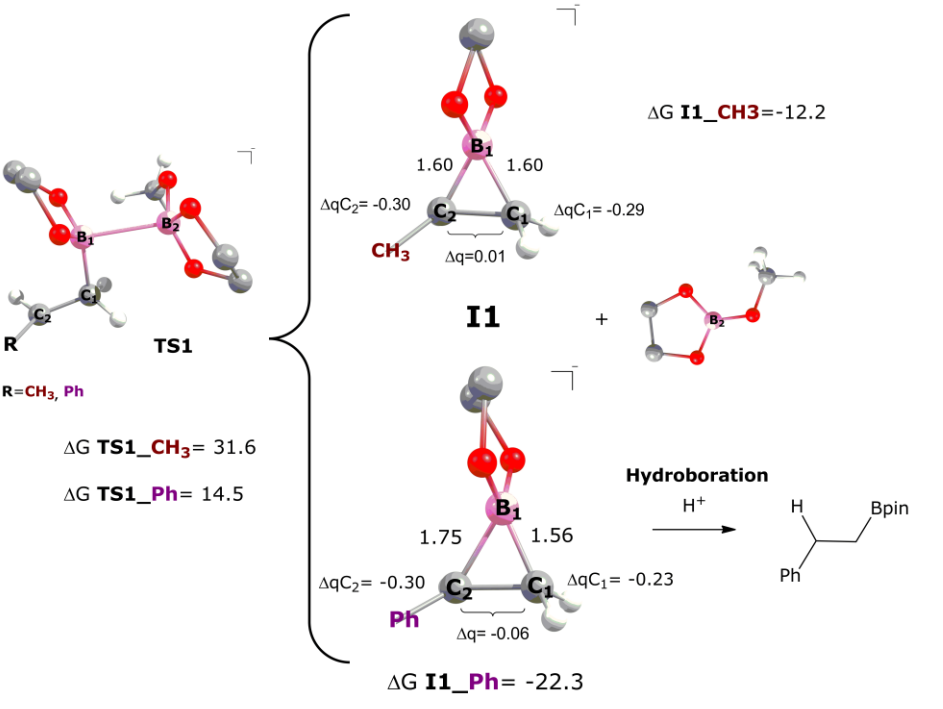


Figure 4.9 Connection of **TS1** and **I1** for propylene and styrene as selected substrates. Differences in Mulliken charges in C_1 and C_2 of the substrate (Δqi) are calculated relative to the partial charge of the substrate. Selected distances are given in Å. Relative Gibbs free energy at M06 level are given in kcal.mol^{-1}

Importantly, when electronic effects stabilize **TS1**, its kinetic stability increase, hence its lifetime, and therefore the "hydroboration" side reaction becomes competitive to the diboration reaction by protonation of **I1** intermediate. This is the case when styrene is the substrate, whereby the phenyl ring can stabilize the increased negative charge on the C_2 carbon (Figure 4.9, **I1** with Phenyl group). In contrast to the **I1** with propylene, the charge distribution between the two carbons is not symmetric, as it is also reflected in the different distances of the B1 to C1 and C2 (1.56 and 1.75 Å respectively). The intermediate **I1** with styrene is -10.1 kcal.mol^{-1} more stable than **I1** with propylene. The electronic stabilizing effect is even more pronounced in the case of α,β-unsaturated carbonyl compounds as substrates, where the "hydroborated" (β-borated) substrate is the only product of the reaction (In the next Chapter 5, a comparative study between the different molecular structures of **I1** depending on the substituent in C2 will be discussed in detail).

Importantly, in addition to **I1**, we found that **TS1** can be also connected with the formation of the structure of a second transition state. Upon the nucleophilic attack, the overlap between the strongly polarized B-B σ orbital and the C-C π* orbital, the BpinOMe moiety becomes electrophilic, capable of interacting with the negatively charged olefin-Bpin fragment. This interaction can be described with the second transition state structure, **TS2** (Figure 4.10).

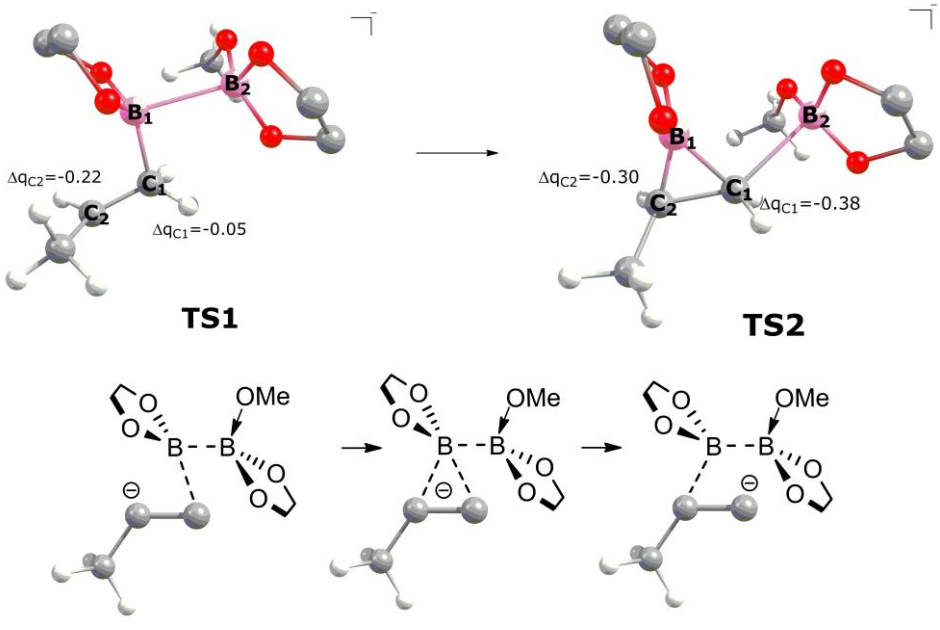
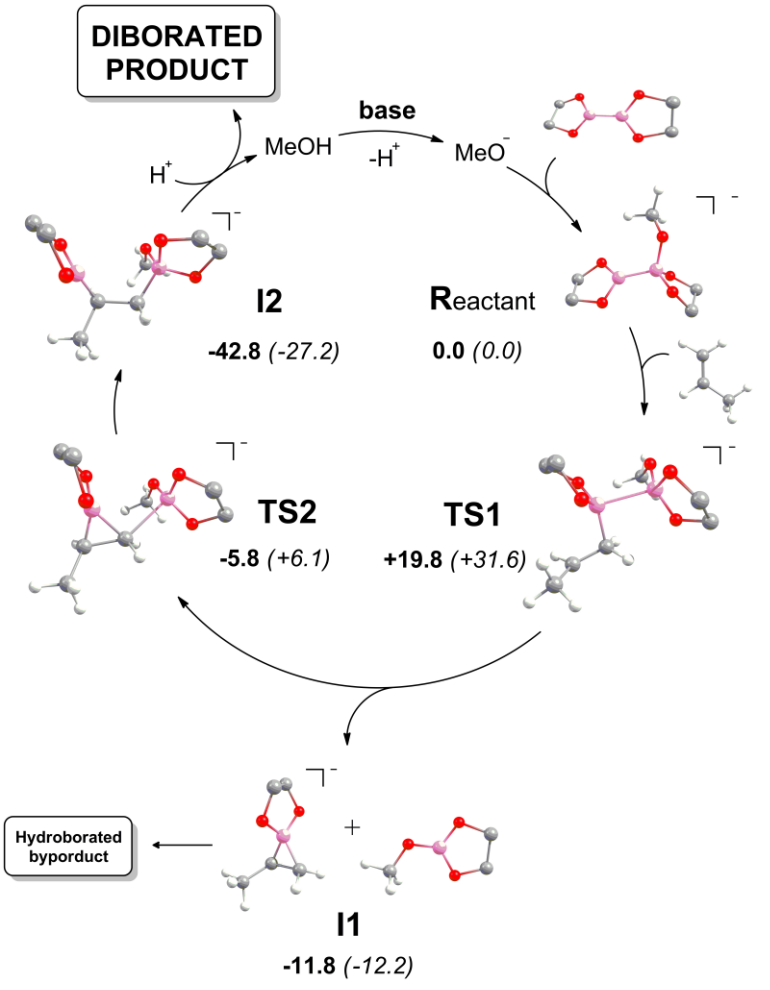


Figure 4.10 Connection of **TS1** with the **TS2** and a schematic illustration of the charge distribution between C1 and C2 in propylene from **TS1** to **TS2**. Mulliken charges are calculated respect to the partial charge of the substrate

TS2 directly leads to the methoxide adduct of the diborated main product (**I2**) rendering the overall process strongly exothermic (ΔG = -27.2 kcal·mol^{-1}, Scheme 4.12). The mechanism shown in Scheme 4.12 includes the energy barriers for **TS1** and **TS2** together with the relative stability of **I1** and **I2** intermediates (relative to the [B_2pin_2·MeO^-] adduct plus propylene) involved in the organocatalytic formation of the diborated product and the hydroborated byproduct.



Scheme 4.12 Suggested catalytic cycle for organocatalytic diboration reaction. Electronic energy (kcal.mol^{-1}) and Gibbs free energy (kcal.mol^{-1} ; in parenthesis) computed at the M06 level, relative to [B_2pin_2.MeO^-] adduct plus propylene

An interesting feature of the mechanism is that although the nucleophilic boron atom attacks at carbon C_1, in the product it will be bonded to C_2. Actually, this sort of reaction sequence (**R**-**TS1**-**TS2**-**I1**, **I2**), which connects one transition sate directly to a second one lower in energy (ΔG=25.5 kcal.mol^{-1} lower than **TS1**) and two products, resembles what Houk and coworkers[53] called a bifurcation (Figure 4.11).

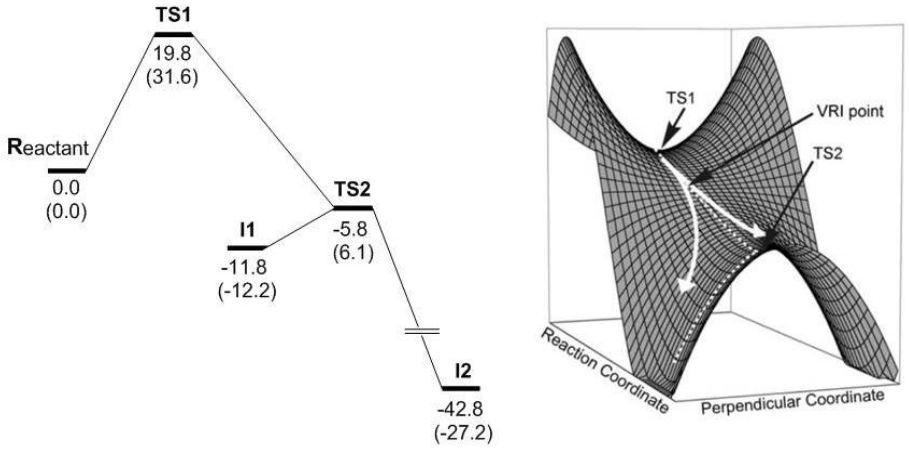


Figure 4.11

4.4 Conclusions

In this Chapter 4, it has been demonstrated that diboron reagents, such as B_2pin_2, can be activated by the sole use of base and methanol as catalytic system. Upon interaction of a Brönsted base with methanol, methoxide is generated, which interacts with the diboron reagent and forms a Lewis acid-base adduct. The nature of this resulting adduct has been studied in detail revealing a polarized B-B bond. This simple adduct [$B_2pin_2 \cdot MeO^-$] is prone to attack unactivated alkenes, *via* the nucleophilic character of the B sp^2 moiety.

The new organocatalytic diboration reaction, has several significant aspects: (i) First of all, the product is formed *via* a reaction between a nucleophilic substrate and a reagent which also has a pronounced nucleophilic character, representing an almost unknown reactivity. (ii) Secondly, unlike in the case of conjugate additions (like in the *β*-boration), both boryl units of the reagent are introduced in the substrate, resulting in an atom-economic addition reaction of outstanding practical importance. (iii) Finally, up to date, the only method to add tetralkoxydiborons to non-activated alkenes has been known to be the application of transition metal complexes as catalysts. Since the preparation of organoboranes is very important in organic synthesis and biomedical applications, the transition metal-free approach described here might be a very appealing alternative.

NMR spectroscopic studies and DFT calculations support the experimental evidences and become essential to understand the mechanism of this unprecedented organocatalytic diboration.

4.5 References

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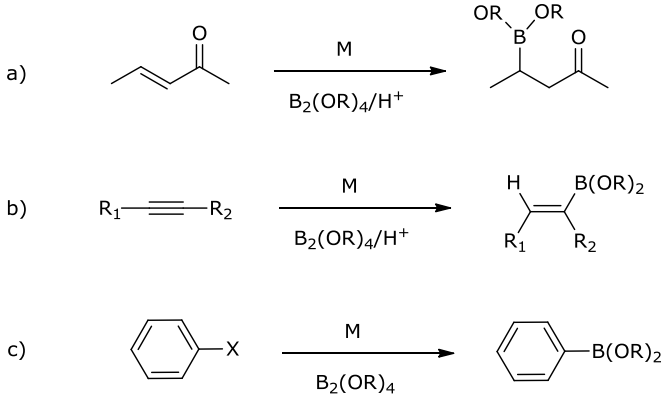
Chapter 5: Transition metal free *β*-boration reaction

Table of contents

5.1 Introduction

Nowadays, diboron reagents are not only used in diboration reactions. Other boron addition reactions utilize them with less atom economy such us β-boration, hydroboration and borylation reactions (Scheme 5.1).

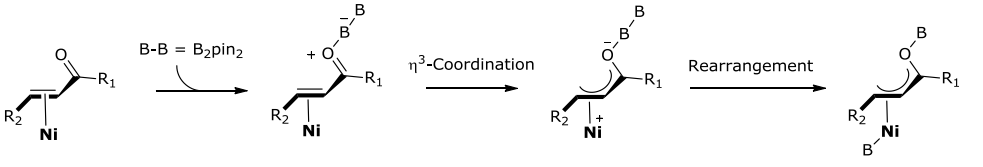


Scheme 5.1 Less atom economical reactions with diboron reagents: a) β-boration b) hydroboration c) borylation

Catalytic β-boration of activated olefins has gained an important recognition in synthetic chemistry since Norman, Marder and co-workers discovered the first Pt mediated 1,4-diboration of α,β–unsaturated ketones.[1] Together with Pt(0) complexes, the use of Rh(I) catalytic systems has also been explored in the β-boration reaction of activated olefins.[2] The use of copper was first introduced in 2000.[3–6] It has been suggested that the activation of diboron reagents by copper occurs *via* σ-bond metathesis[5] while platinum[7] and rhodium might involve an oxidative addition.[8] Importantly, DFT calculations on Cu(I)[9] and Pt(0)[7] systems carried by Marder and Lin *et al*. demonstrated the validity of the suggested activation mode for both studied systems. A recent example of Rh(III) mediated the β-boration of activated olefins suggest the transmetallation as an alternative activation pathway.[10]

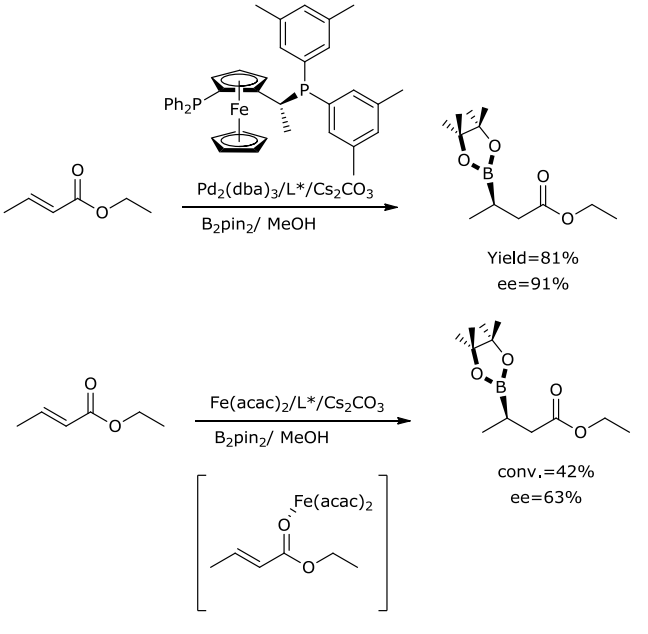
Oshima and coworkers, developed an alternative nickel based catalytic system for the β-boration of α,β-unsaturated carbonyl compounds.[11] From the mechanistic point of view, the authors suggested that the diboron reagent could interact with the carbonyl functional group, in agreement with the Lewis acid properties of the diboronate esters. As a consequence the coordination of the

substrate to Ni shifted from η^2 to η^3, and allowed the transmetallation step *via* the heterolytic cleavage of the B-B bond, (Scheme 5.2).



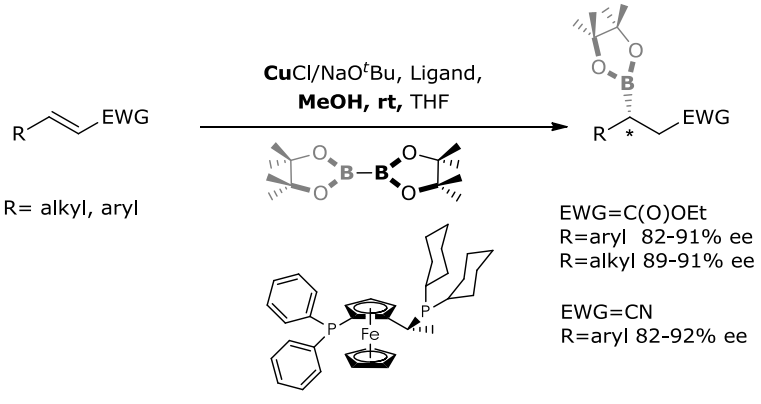
Scheme 5.2 Suggested activation of diboron by Ni(0) catalyst

Our group has recently studied the metal-mediated conjugate borylation reactions, specially focused on the asymmetric version of the reaction, in the presence of copper,[12,13] palladium,[14] nickel,[14] and iron complexes[15] that were modified with either chiral phosphine or chiral N-heterocyclic carbene ligands. Interestingly, in the case of the iron, a preactivation of the substrate by the Lewis acidic Fe(II) and Fe(III) salts seems to have a beneficial influence on the reaction outcome (Scheme 5.3).



Scheme 5.3 Palladium(0) and iron(II) mediated enantioselective *β*-boration of *α,β*-unsaturated carbonyl compounds

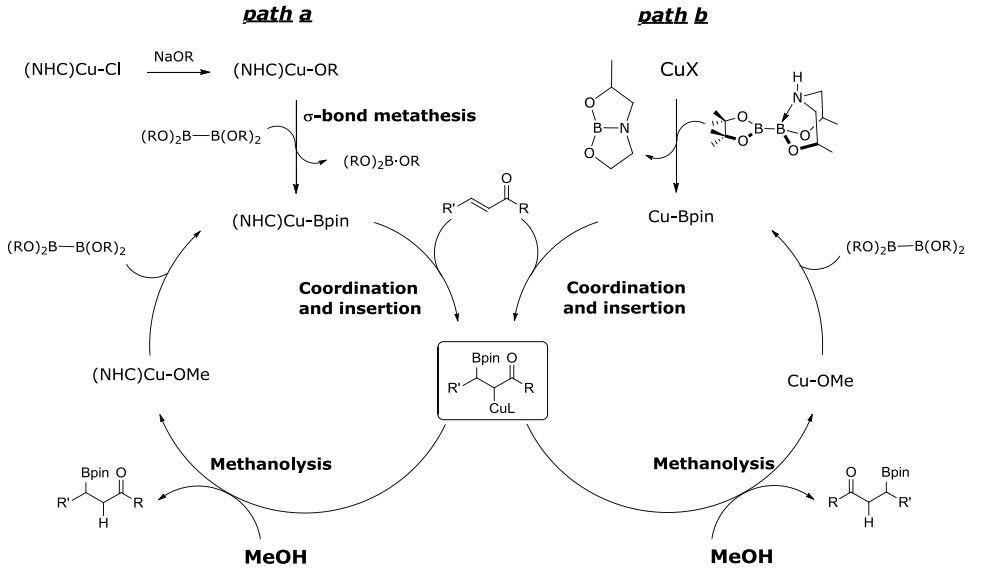
The first asymmetric β-boration reaction was reported with Cu(I) salts modified with chiral diphosphine ligands, by Yun *et al.* (Scheme 5.3).[16,17]



Scheme 5.3 Representative reaction conditions for the first asymmetric β-boration reaction

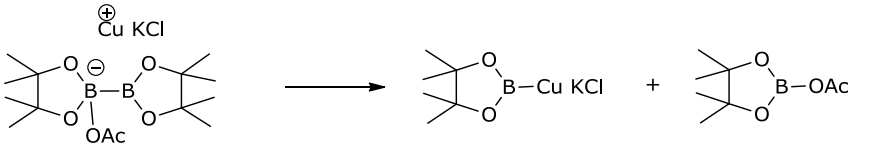
Remarkably, the presence of a base in the metal catalytic β-boration of activated olefins seems to be essential[18] to *in situ* generate metal-alkoxide complexes, in order to facilitate the σ-bond metathesis with diboron reagents[3,5,9,11–13,15,16,18–23] (Scheme 5.4, *path a*). This is consistent with the fact that isolated transition metal-alkoxides, such as [(NHC)CuOR] (NHC=N-heterocyclic carbene, OR= OMe, O^{t}Bu), can catalyze the reaction in the absence of base.[24]

However other exceptions to the required use of base in the boron conjugate addition reactions,[4] might attribute other important roles to the base. For instance Santos and co-workers have shown that the pinacolboryl unit of a mixed sp^2-sp^3 diboron reagent can be selectively added to the β-carbon of α,β-unsaturated carbonyl compounds and allenoates, using phosphine free Cu(I) complexes as catalysts, in the absence of base (Scheme 5.4, *path b*).[25–27]



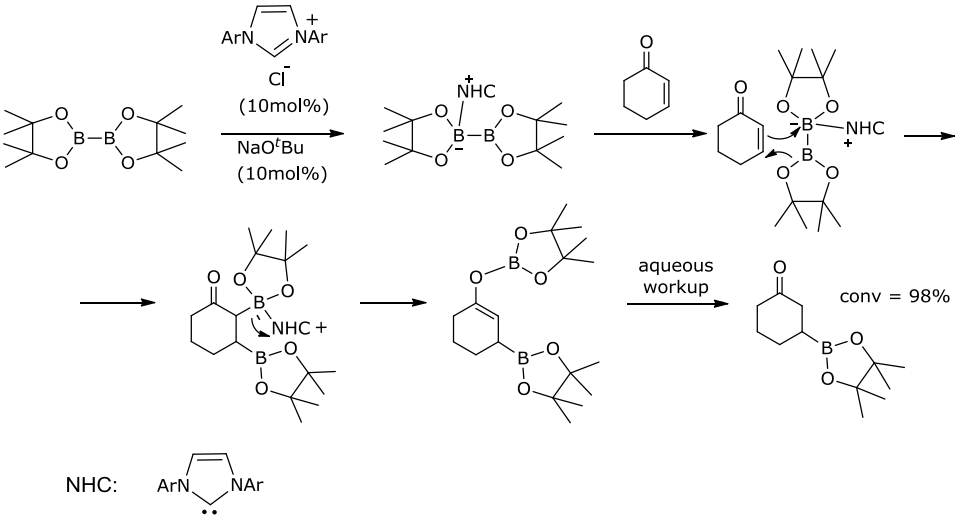
Scheme 5.4 Cycle a: catalytic cycle where base promotes the σ-bond metathesis pathway; Cycle b: catalytic cycle where the activation of the diboron reagent takes place intramolecularly

As commented in Chapter 4, the activation of the mixed diboron reagent was developed from the original idea of Miyaura and coworkers,[5] who suggested that AcO^- activated bis(pinacolato)diboron (B_2pin_2), by a Lewis acid–base interaction, prior to the boryl transfer to the copper center (Scheme 5.5).



Scheme 5.5 Bis(pinacolato)diboron activation suggested by Miyaura and coworkers

Base was also essential in the metal-free *β*-boration of cyclic and acyclic *α,β*-unsaturated carbonyl compounds promoted by N-heterocyclic carbenes (NHC-s) reported by Hoveyda *et al.*,[28] (Scheme 5.6). The role of the base was assumed to be the deprotonation of the corresponding imidazolium salt. By using a combination of 10 mol% of imidazolium salt and 10 mol% of NaO^tBu, cyclohexenone could be quantitatively converted to the corresponding *β*-borated product, at room temperature.[28]



Scheme 5.6 Mechansitic proposal for the NHC mediated β-boration of a cyclic ketone

5.2 Motivation

Since we discovered that MeOH and a Brönsted base was the simplest method to activate the diboron reagent through the formation of a Lewis acid-base adduct, [B_2pin_2·MeO^-], we became interested in exploring the role and the potential of the bases in the *β*-boration reaction.

Disclose the role of phosphines in this scenario, was also one of our main challenges. New *β*-boration reactions in the absence of Brönsted bases were also our target.

For this purpose, we performed mechanistic studies through DFT calculations along with experimental NMR spectroscopic studies to obtain a deeper insight into the reaction and postulate a plausible mechanism.

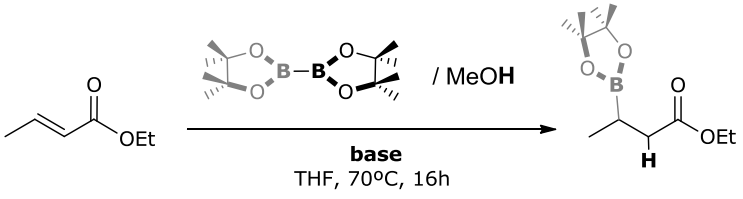
5.3 Results and Discussion

5.3.1 Brönsted base/MeOH system

5.3.1.1 Experimental study

In our group, it was first conducted a systematic study to convert ethlycrotonate into the β-borated product in the presence of a series of bases. Table 5.1 shows that alkoxides and inorganic bases allowed low to moderate conversion, at 70 ºC in 6h, using MeOH as additive (Table 5.1, entries 1-7).

Table 5.1 Base-mediated catalytic β-boration of ethylcrotonate with B_2pin_2[a]

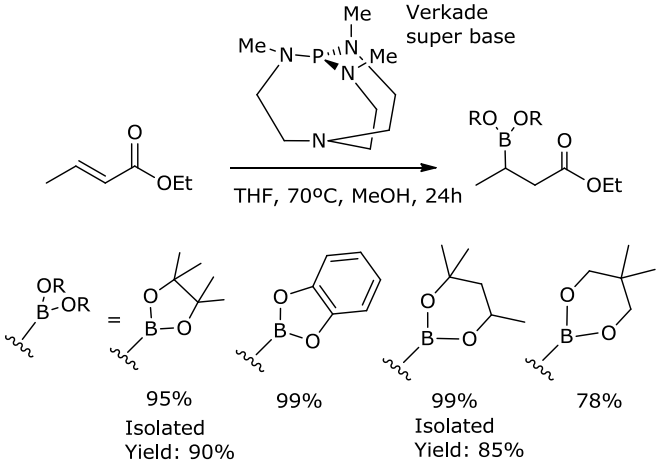


Entry	Base [b]	Solvent	Additive [b]	Conv(%)[c]
1	NaOMe	THF	MeOH	27
2	KOMe	″	″	24
3	LiOMe	″	″	23
4	NaO^{t}Bu	″	″	40
5	Cs_2CO_3	″	″	45
6	K_2CO_3		″	28
7	CsF	″	″	29
8	Cs_2CO_3	toluene	″	33
9	Cs_2CO_3	THF	^{t}BuOH	8
10	Cs_2CO_3	″	^{i}PrOH	13
11	Cs_2CO_3	″	BuOH	41
12	Verkade base	″	MeOH	69(90)[d]

[a] Standard conditions: substrate (0.5 mmol), diboron reagent: B_2pin_2 (bis(pinacolato)diboron), 1.1 eq., base (15 mol%), alcohol (2.5 mmol), solvent (2 mL), 70 ºC, 6h. [b] pKa-s (in water): MeOH =15.2, BuOH =16.0, iPrOH = 17.1, ^{t}BuOH =18.0, HCO_3^- = 10.4, Verkade =26.2. [c] Conversion calculated by GC analysis and confirmed by 'H NMR spectroscopy. [d] 16 h.

The benefit of the use of THF versus toluene as solvent is in accordance with the higher solubility of the bases in the former (Table 5.1, entries 5 and 8). The structure of the alcohol additive also had a considerable influence on the catalytic activity. Primary alcohols (MeOH and BuOH) provided significantly higher conversions (Table 5.1, entries 5 and 11) than secondary (^{i}PrOH) and tertiary (^{t}BuOH) alcohols (Table 5.1, entries 9, 10). The role of the alcohol additive could be divided into two parts: protonation of the β-borated enolate intermediate and the source of the corresponding alkoxide ion which will interact with the diboron reagent. Since the protonation step to generate the desired β-borated product is guaranteed with all the alcohols tested under the reaction conditions, the plausible Lewis acid-base interaction of the alkoxide ion with the boron reagent might be more crucial and therefore will be a matter of discussion throughout the mechanistic proposal. Selecting MeOH as a suitable additive, we also tested several organic bases in the β-boration reaction of ethylcrotonate, but only the Verkade base conducted the reaction to conversions up to 90% in 16h, (Table 1, entry 12). In Chapter 4, we used this very strong base to elucidate the formation of the Lewis acid-base [B_2pin_2·MeO^-] adduct by NMR. A solution of Verkade's base in THF with stoichiometric amounts of B_2pin_2 and MeOH, results in the quantitative formation of the Lewis acid-base [B_2pin_2·MeO^-] adduct. Moreover, the ability of this base to act as a catalyst has been widely explored in a broad range of base-catalyzed reactions.[29–32]

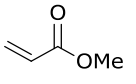
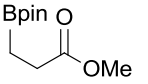
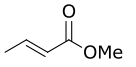
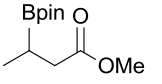
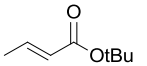
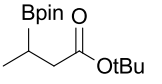
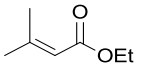
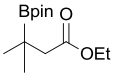
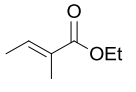
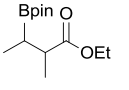
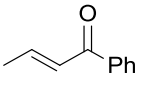
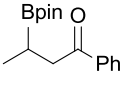
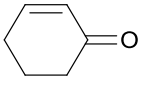
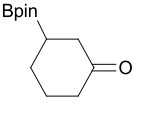
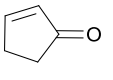
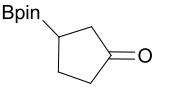
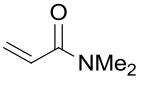
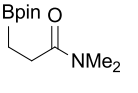
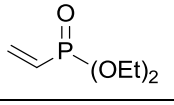
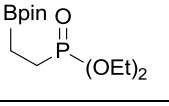
Since the nature of the diboron reagent has a direct impact on the reaction outcome, we explored different boron sources for the β-boration of ethylcrotonate under the optimized reaction conditions. Within 24h almost quantitative conversion was observed for bis(pinacolato)diboron (B_2pin_2), bis(cathecolato)diboron (B_2cat_2) and bis(hexyleneglycolato)diboron (B_2hex_2), but only moderate conversion has been achieved with bis(neopenthylglycolato)diboron (B_2neop_2) (Scheme 5.7). B_2pin_2 was selected for further studies due to its accessibility and chemical stability.



Scheme 5.7 Verkade base mediates the β-boration of ethycrotonate with different diboron reagents

To survey the general scope of the Verkade base mediated β-boration reaction, we carefully selected a series of activated olefins, with diverse structural features. α,β-Unsaturated esters were quantitatively β-borated, regardless of the steric bulk of the ester moiety (Table 5.2, entries 1-3). The nucleophilic attack at the beta position of the substrate is less favoured in the case of β,β-dimethyl substituted α,β-unsaturated ester or α,β-dimethyl substituted substrate (Table 5.2, entries 4, 5), probably due to steric factors. Open-chain and cyclic α,β-unsaturated ketones were quantitatively converted into the corresponding organoboranes (Table 5.2, entries 6-8). The analogous α,β-unsaturated amide and phosphonate were also efficiently converted into the desired β-borated products, (Table 5.2, entries 9, 10).

Table 5.2 Verkade-mediated catalytic β-boration of ethylcrotonate with B_2pin_2[a]

Entry	Substrate	Product	Conv(%)[b] [Yield(%)][c]
1			99
2			99 [88]
3			94 [85]
4			40
5			65
6			90 [81]
7			99 [82]
8			99
9			99
10			97

[a] Standard conditions: substrate (0.5 mmol), diboron: B_2pin_2 (bis(pinacolato)diboron), 1.1 eq., Verkade base (15 mol%), MeOH (2.5 mmol), THF (2 mL), 70ºC, 24h. [b] Conversion calculated by GC analysis and confirmed by 'H NMR spectroscopy. [c] Isolated yield.

5.3.1.2 DFT study

5.3.1.2.1 Computational details

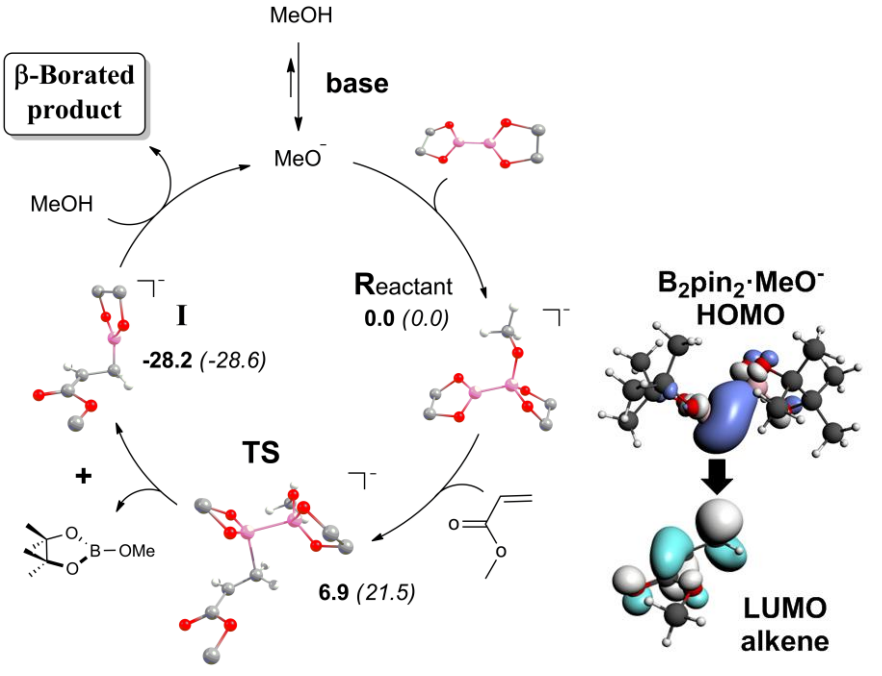
In this present theoretical approach, molecular structures for all the species were optimized without constraints by using Density Functional Theory (DFT) based methods as implemented in the Amsterdam Density Functional (ADF v2009.01) package.[33,34]
A triple-ζ plus polarization (TZP) Slater basis set was used on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[35] For geometry optimizations we used the local exchange VWN correlation potential[36] together with the Becke's exchange[37] and the Perdew's correlation[38,39] (BP86) generalized gradient corrections. Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequencies calculations.

Nuclear Magnetic Resonance chemical shifts were computed at the same level of theory by running single point calculations with all electron basis sets.

Standard corrections to Gibbs free energy at 298 K were evaluated too. Solvent effects were introduced by using the continuous solvent model COSMO.[40] Single point energy at the metahybrid M06[41] level were performed self-consistently.

5.3.1.2.2 Mechanistic proposal

The mechanism that we propose for the base-mediated β-boration of activated olefin is depicted in Scheme 5.8. The scheme shows the elementary steps of the reaction between methyl acrylate and bis(pinacolato)diboron. The methoxide anion, generated from MeOH in the presence of base, forms a Lewis acid-base adduct with the diboron reagent, which we chose as the origin of energies. In the next step, a transition state (TS) was fully characterized, and it corresponds to the nucleophilic attack of the sp^2 boron reagent at the non-susbstituted carbon C1 of the alkene. This interaction was identified as the overlap between the strongly polarized σ B-B bond (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the alkene.



Scheme 5.8 Reaction pathway. Electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level, relative to [B_2pin_2·MeO^-] adduct plus methyl acrylate. Methyl groups of the pinacol moieties are omitted for clarity. All values in $kcal.mol^{-1}$

The structural features of the TS shows the cleavage of the B-B bond (from 1.701 Å in the B_2pin_2 to 1.754 Å in the [B_2pin_2·MeO^-] to 1.956 Å in the TS) and the formation of the new B-C bond (2.208 Å). The TS structure releases the pinBOMe by-product and directly leads to the formation of the anionic **I** intermediate, which will be further protonated in the presence of the excess of MeOH to provide the *β*-boration product, and to generate another MeO^- anion. Regarding **I**, as we have seen in Chapter 4 for propylene and styrene (called I1 in Chapter 4), different structures can be found depending on the substituent in C2. We obtained two types of structures (Figure 5.2), which clearly reflect the role of the substituent in C2 in the stabilization of the negative charge developed on C2. Indeed, substrates with esters, ketones and aldehydes, which allow charge delocalization, form more stable intermediates (**IB**) than the non activated olefins such a propylene, in which the charge delocalization is not so evident (**IA**). In the case of the structure **IA** the negative charge is stabilized by an interaction between C2 and the Lewis acidic pinacolboryl unit.

Note that in the case of styrene the distribution of the negative charge density between the C2 carbon and the phenyl group is not as effective as in the case of the carbonyl group, giving also the **IA** type of structure.

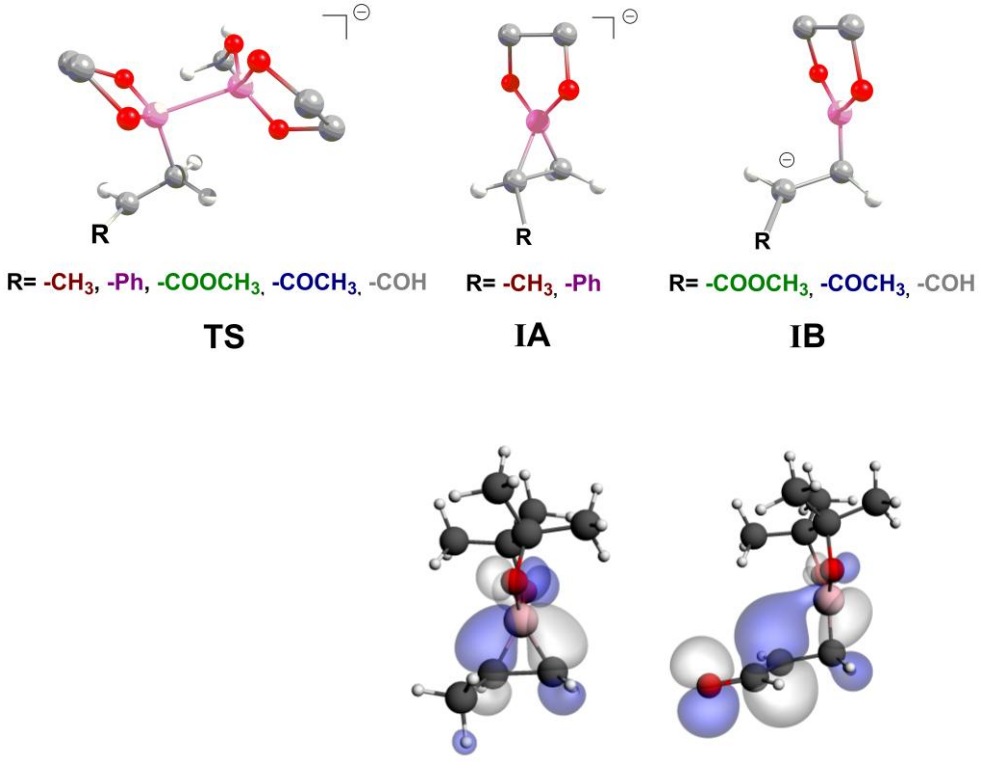


Figure 5.2 Molecular structures for a model transition state and the two different intermediates. Illustration of the charge delocalization with the HOMO for I1 of propylene and acrylaldehyde as a representative substrates

Importantly, the thermodynamic stability of **I** intermediate is also reflected in the reactivity of the corresponding substrate, thus, a dramatic decrease of the energy barrier is observed when electronic effects stabilize the TS (Figure 5.3). The largest difference of 22.0 kcal.mol^{-1} was found for the activation of propylene respect to acrylaldehyde.

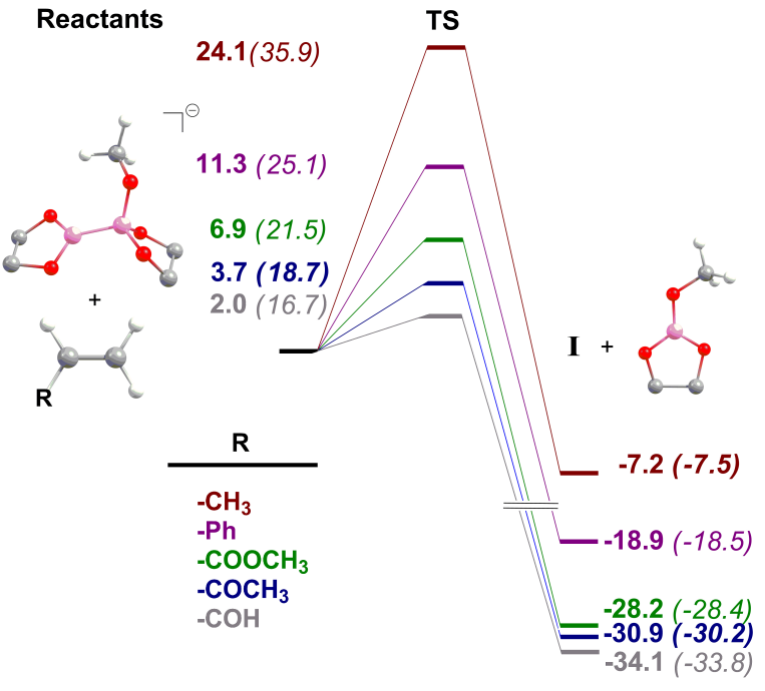
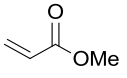
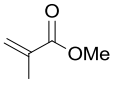
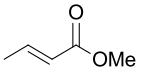
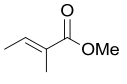
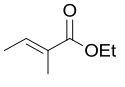
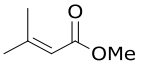


Figure 5.3 Energy profile for several monosubstituted alkenes. Energy barrier and reaction energy values are given as electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level, relative to [B_2pin_2·MeO^-] adduct plus the respective alkene. All values in kcal.mol^{-1}

We also evaluated the effect of different substituents on the energy barrier to explain the reactivities summarized in Table 5.3. Considering esters as model substrates, we observed that the energy barrier significantly increases when there are methyl groups in *β* position (Table 5.3, entries A, C and F), in agreement with the lower conversion observed in the corresponding experimental results. The influence of a methyl group in *α*-position is not as pronounced as in the *β*- position. Only a slight increase, *ca.* 3.0 kcal.mol^{-1}, in the activation energy was found (Table 5.3 entries A and B, as well as C and D). The replacement of a methyl for an ethyl group in the ester moiety (Table 5.3, entries D and E) results only in 1.0 kcal.mol^{-1} difference, in accordance with the similar reactivities of different esters of crotonic acid, observed experimentally (Table 5.2, entry 2).

Table 5.3 Relative electronic energy (kcal.mol^{-1}) and Gibbs energy (kcal.mol^{-1}) for the activation of different α,β-unsaturated esters[a]

Entry	Entry in Table 5.2	Substrate	$\Delta E^{\neq}$	ΔEr	$\Delta G^{\neq}$	ΔGr
A	1		6.9 (5.9)	-28.2 (-33.2)	21.5 (20.5)	-28.4 (-31.4)
B			10.2 (6.3)	-25.6 (-28.9)	26.0 (22.1)	-25.7 (-29.1)
C	2		14.0 (10.0)	-24.4 (-27.6)	29.3 (25.0)	-24.2 (-27.4)
D			16.3 (10.7)	-21.3 (-25.8)	32.2 (26.6)	-20.7 (-25.2)
E	5		17.1 (10.8)	-21.3 (-26.0)	33.1 (26.8)	-19.5 (-24.2)
F			23.0 (17.1)	-21.3 (-27.0)	39.6 (33.7)	-20.2 (-25.1)

[a] Molecular geometries for all the species were optimized using BP86 as a functional. Single point energies at the metahybrid M06 level are in parenthesis.

The next step was to study the influence of the nature of the alcohol additive (Table 5.1, entries 5, 9-11). The dramatic decrease in activity when ^{t}BuOH is used instead of MeOH can be explained by three facts: i) the ^{t}BuOH is less acidic than MeOH, thus, the generation of the alkoxide by the base would be less favoured (initial step in the suggested reaction pathway, Scheme 5.8) ii) the alkoxide-diboron adduct is thermodynamically more stable for the MeO^{-} (-0.5 kcal.mol^{-1} with respect to the energy of the B_2pin_2 and MeO^{-} before complexation) than for the ^{t}BuO^{-} (3.4 kcal.mol^{-1} over the reagents in free form) in THF (Figure 5.4) iii) in the case of acrylaldehyde as model substrate, the relative energy for the TS with [B_2pin_2.^{t}BuO^{-}] as nucelophile is 4 kcal.mol^{-1} higher than with the [B_2pin_2.MeO^{-}] . Consequently, under the same reaction conditions, the reaction is much more slower for ^{t}BuOH (Table 5.1, entry 9, conv. 8% of the β-borated product) than for MeOH (Table 5.1, entry 5, conv. 45% of the β-borated product).

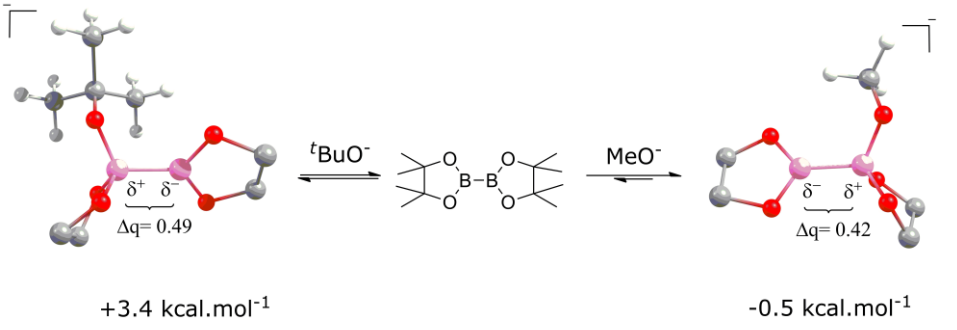
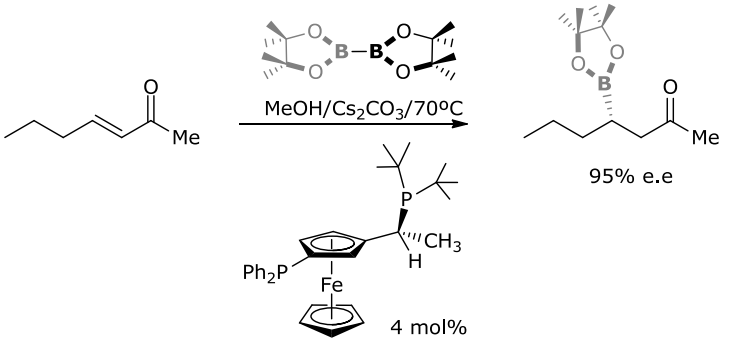


Figure 5.4 Computed relative Gibbs free energies in THF (kcal·mol^{-1}) for the [B_2pin_2·MeO$^-$] versus [B_2pin_2·^{t}BuO$^-$]

5.3.2 Role of the phosphine

We have demonstrated the convenience of using the Lewis acid-base adduct [$B_2pin_2 \cdot MeO^-$], to attack activated and non activated olefins. By adding phosphines as additives to the alcohol/base system, we found a beneficial influence in the reaction rate for the β-boration reaction. But more interestingly, high values of enantioselectivity were induced when chiral phosphines together with an alcohol and base were used (Scheme 5.9).[42]



Scheme 5.9

5.3.2.1 NMR and DFT study

5.3.2.1.1 Computational Details

All calculations presented in this section have been obtained using the same methodology described in this Chapter 5 in section 5.3.1.2.1.

PKa values were obtained based on the Born-Haber cycle[43] using the known solvation energy of the proton.[44]

In this particular case, molecular structures of I1-PR_3 , protonated ones ($^+$HI1-PR_3) and Verkade's base and the respective protonated species ($^+$HVerkade) were calculated without constraints using Gaussian 09,[45] Revision A.02, with the hybrid B3LYP[46] functional and 6-31+G(d)[47] as a basis set. Solvent effects (dimethylsulphoxide, DMSO) were introduced by using the Polarizable Continuum Model (PCM).[48]

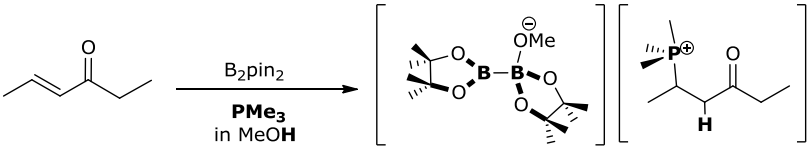
5.3.2.1.2 Mechanistic proposal

Aimed at unravelling the role of the phosphine, the first target was to establish unequivocally whether phosphines could activate the diboron reagent B_2pin_2, like alkoxides do. Characterization of the hypothesized adduct $[B_2pin_2 \cdot PR_3]$ (R=Me, Cy, Ph) was not possible neither theoretically nor by NMR experiments. No change in the B_2pin_2 signal (30.5 ppm, singlet (s)) in $^{11}B\{H\}$ NMR could be observed when PR_3 was added to a solution of the diboron compound. This simple experiment clearly showed that, unlike the methoxide anion, phosphines do not form any stable adduct with B_2pin_2, independently of the nucleophilic character of the phosphine. This is in well agreement with Marder and co-workers' observations[49] since a more acidic diboron compound, such $[B(1,2\text{-}S_2C_6H_4)_2]_2$, is required to afford mono and bis-phosphine adducts, with both PMe_2Ph and PEt_3. A subtle balance dictates these weak B-P interactions: bis(catecholato)diboron (B_2cat_2) does not form any adduct and B_2pin_2 neither. In a more recent example,[50] acidity on the boron was achieved by introducing halogen atoms directly bonded to one boron moiety.

Among the possible interactions between the phosphine and MeOH, the phosphine acting as a Brönsted base is unlikely. Previous experimental and theoretical studies demonstrated that strongly basic trialkyl phosphines do not deprotonate MeOH.[51]

In our previous NMR study (Chapter 4) we showed that even the Verkade base ($pK_{a,\ protonated\ Verkade\ base,(DMSO)}$ = 26.8) could not deprotonate MeOH quantitatively in THF, an excess of MeOH was necessary. However, in the presence of B_2pin_2 the deprotonation became virtually complete (1 mL THF, [Verkade base] = 1 M, [MeOH] = 0.5 M, $[B_2pin_2]$ = 0.5 M extent of deprotonation: >90%), and the MeO^- established the expected Lewis acid-base interaction with the diboron. Thus, the diboron reagent increases the Brönsted acidity of the MeOH, presumably because the conjugate base, MeO^-, is stabilized *via* the formation of the $[B_2pin_2 \cdot MeO^-]$ adduct. This also explains that in the Brönsted base-catalyzed boron conjugate addition (Base/MeOH system) relatively weak bases, such as Cs_2CO_3, can also be used to initiate the reaction. Nevertheless, when a strongly phosphine like PMe_3, PBu_3 or PCy_3 and B_2pin_2 were dissolved in MeOH (0.5 mL, $[PR_3]$ = 1 M, $[B_2pin_2]$ = 1 M) both the phosphine and the diboron reagent remained intact ($^{31}P\{^1H\}$- and $^{11}B\{^1H\}$-NMR spectroscopy). So, deprotonation of MeOH does not occur even in the presence of B_2pin_2.

Next we focused on possible interactions between the phosphine and the substrate, since it is known that trivalent phosphines react as nucleophiles with some α,β-unsaturated compounds to form phosphonium enolates.[52] A series of stoichiometric experiments were conducted to explore the formation of new species upon mixing stoichiometrically PMe_3, (*E*)-hex-4-en-3-one and B_2pin_2 in MeOH (Scheme 5.10, Figure 5.5). Quantitative formation of a new species was observed: complete disappearance of the PMe_3 signal at -62.0 ppm in the $^{31}P\{^1H\}$-NMR spectrum, and appearance of a new signal at 30.4 ppm. In the $^{11}B\{^1H\}$-NMR, the signal of B_2pin_2 (broad s, 30.5 ppm) completely disappeared, and two new broad peaks at +35.0 ppm and +1.3 ppm were detected, as it is shown in Figure 5.5 and Table 5.4. These two new boron signals correspond to the sp^2 and sp^3 boron atoms of our well known $[B_2pin_2{\cdot}MeO^-]$ anionic adduct (Chapter 4, NMR study). Thus, NMR data suggest the formation of a new ion-pair species, in which the anion is the $[B_2pin_2{\cdot}MeO^-]$ adduct, and the cationic counterpart is the $[\alpha\text{-(H)},\beta\text{-}(PR_3)\text{-hexanone}]^+$. Further ESI-MS experiments confirmed the mass for the cation (Mass=301.2659). Consequently, the new peak at 30.4 ppm in the $^{31}P\{^1H\}$-NMR spectrum corresponds to a phosphonium salt, which should derive from the nucleophilic attack of the phosphine at the β-carbon of the substrate, followed by the protonation of the zwitterionic phosphonium enolate by MeOH. It is important to remark that quantitative formation of this phosphonium species requires the presence of the diboron reagent.



Scheme 5.10 Ion pair ($[\alpha\text{-H},\beta\text{-}PR_3\text{-3-hexanone}]^+[B_2pin_2{\cdot}MeO]^-$ formation at stoichiometric level

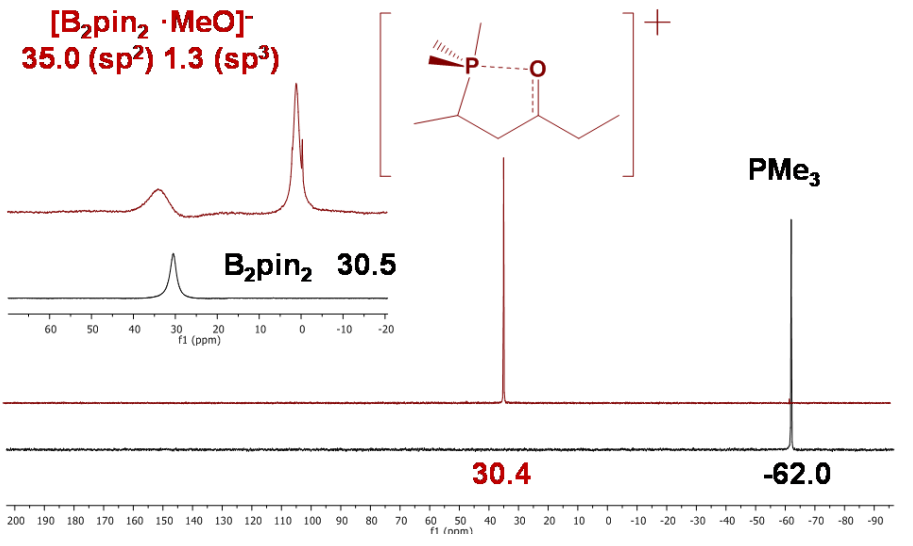


Figure 5.5. ^{11}B-{^{1}H}-NMR and ^{31}P-{^{1}H} for: *red*) the interaction of PMe_3 and (*E*)-hex-4-en-3-one in MeOH, in the presence of B_2pin_2 (1 mL, [PMe_3] = 0.5 M, [(*E*)-hex-4-en-3-one] = 0.5 M) ; *black*) same mixture of PMe_3, B_2pin_2 in MeOH without the substrate (1 mL, [PMe_3] = 0.5 M, [B_2pin_2] = 0.5 M)

The molecular structure of the ion-pair ([α-H,β-PR_3-3-hexanone]$^+$[B_2pin_2·MeO]$^-$), is shown in Figure 5.6. This structure was fully characterized computationally as a global minimum in the potential energy surface, taking into account its conformational flexibility. The computed NMR chemical shifts for this structure precisely coincide with the measured NMR shifts in both ^{11}B and ^{31}P NMR (Table 5.4).

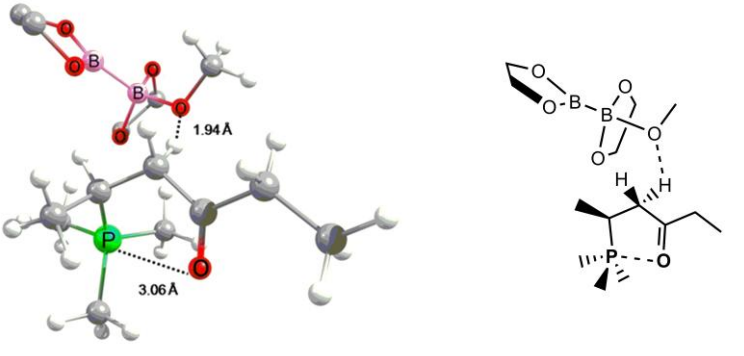
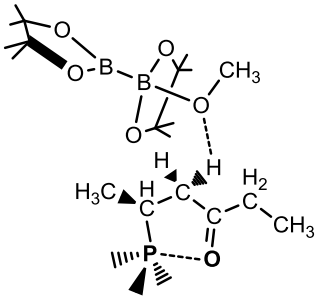


Figure 5.6 DFT derived molecular structure of ion-pair: [α-H,β-PMe_3-3-hexanone]$^+$[B_2pin_2·MeO]$^-$. Methyl groups of the B_2pin_2 are omitted for clarity

Table 5.4 Computed and experimental ^{11}B and ^{31}P NMR chemical shifts (in ppm) for several species.[a]

Species	NMR Chemical Shifts (ppm)			
	Computed		Experimental	
	^{11}B	^{31}P	^{11}B	^{31}P
B_2pin_2	30.5		30.5	
PMe_3		-63.0		-62.0
	1.5(sp^3)-33.0(sp^2)	31.4	1.3(sp^3)-35.0(sp^2)	30.4

[a] $^{11}B\{^1H\}$ NMR and $^{31}P\{^1H\}$ NMR values are given in ppm. Boron trifluoride etherate and phosphoric acid are taken as a reference.

The study of the formation of ion-pair species has revealed interesting features. Figure 5.7 shows the computed reaction energy profile for the formation of **I2** from acrylaldehyde. Values for energy activation barriers are rather reasonable and reflect distinct behaviour for each phosphine. Actually, formation of **I2** is exothermic for PMe_3 only, which is precisely the phosphine that enabled quantitative formation of **I2** in the NMR experiments. For PCy_3, the reaction is thermoneutral whereas for PPh_3 is slightly endothermic. These values reflect well the equilibrium between free phosphine and **I2** observed in NMR (See additional information, CD). Using a metahybrid exchange-correlation potential that includes dispersion corrections, such as M06, the general picture does not change although the reaction is exothermic for all the three phosphines (Table 5.5).

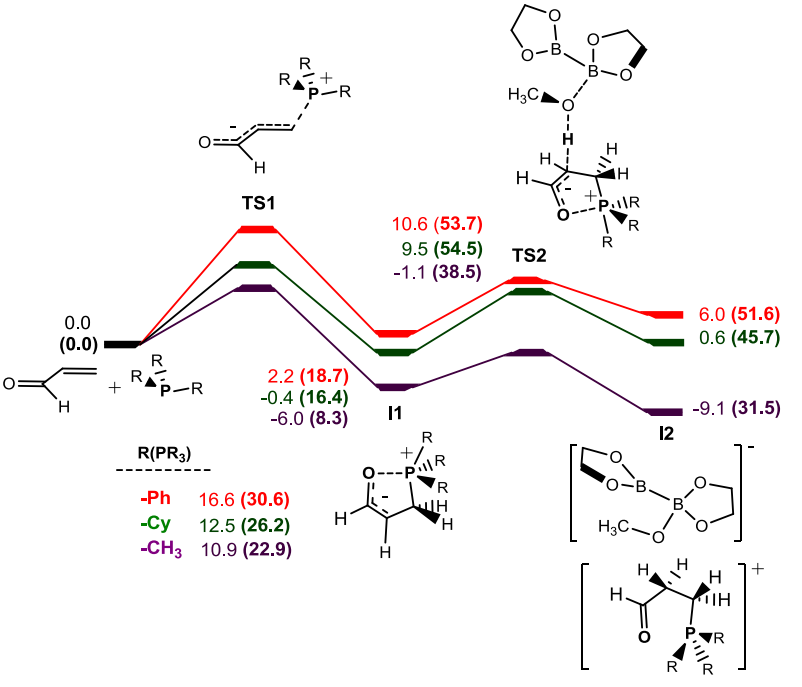


Figure 5.7 Reaction energy profile for the formation of ([α-H,β-PR_3-propionaldehyde]$^+$[B_2pin_2·MeO]$^-$). Purple: PMe_3; Green: PCy_3; Red: PPh_3. Electronic and Gibbs free energy (in parenthesis) computed at BP86 are given in kcal.mol^{-1}

Table 5.5 Computed relative energies for the species involved in the formation of I2 species at M06 level of theory (single points).[a]

Phosphine	TS1	I1	TS2	I2
PMe_3	12.7(24.7)	-6.9(7.4)	-10.6(28.9)	-28.3(12.3)
PPh_3	17.6 (31.6)	-0.9 (15.7)	-2.9 (40.5)	-14.4 (31.3)
PCy_3	12.1(25.8)	-3.2(13.6)	-3.2 (41.9)	-19.9(25.2)

[a] Reactives in free form are considered as the zero in energy.

We must point out that the assembly of four molecular entities implies an entropic cost, which is apparently huge as ΔG values reflect. Note the exaggerated accumulated value for **TS2**, for instance. Solvent effects introduced through continuous solvent models does not take into account the entropy gain/loss due to solvent reorganization, a component that can partly compensate the entropy loss of merging two species. We evaluated an average value of 12 units in Gibbs free energy per encounter, so roughly 36 kcal.mol^{-1} in

excess are accumulated in **TS2** and **I2**. Formation of the final β-borated product, in the next reaction steps, largely overcomes the costs of forming **I2**.

Reaction energy profiles exhibit a clear trend (PMe_3< PCy_3< PPh_3) that does not coincide neither with Brönsted basicity[53,54] nor with the Tolman angle.[55] The most nucleophilic PCy_3 phosphine also display the largest bulkiness, so a combination of stereo-electronic effects determines this reactivity.

The structure of **I1** intermediate in Figure 5.8 corresponds to the most stable conformation of the zwitterionic phosphonium enolate species, in which a dative bond between the oxygen and the formally positively charged pentavalent phosphine is formed. Topological analysis of electronic charge density revealed the existence of a P–O bond critical point.[56] The Laplacian of the charge density indicated that the P–O bond is mainly dative (Figure 5.8).

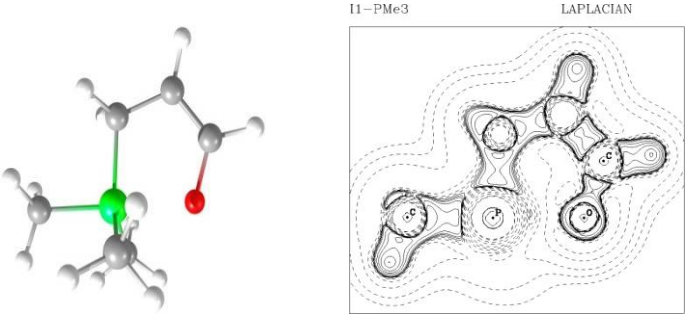


Figure 5.8 Molecular structure for **I1-PMe$_3$** and illustration of its Laplacian study

A similar system was studied previously with MP2 based methods[57] in the context of the phosphine-catalyzed hydroalkoxylation of enones and α,β-unsaturated substrates,[18] although the cyclic most stable form was not considered in that study. The pentavalent phosphorus atom adopts a trigonal bipyramid coordination, thus favouring the localization of the negative charge in C_α. The highest coefficient of C_α in the HOMO can be clearly visualized in Figure 5.9. The P-C bond length between the phosphorus atom and the carbon in axial position is slightly longer than the other two (Table 5.6, P-C_{ax} =1.90 Å with respect to P-C_1=1.84 and P-C_2=1.84). We also observed that the P-O bond length slightly changes with the type of substituent in the phosphorus centre. The shortest P-O bond length for PPh_3 can be rationalized by the fact that the phenyl groups have higher electron density than the alkyl groups. Since the two tested trialkyl phosphines present almost equal P-O distances, electronic effects

rather than sterics might control the establishment of this P-O bond.

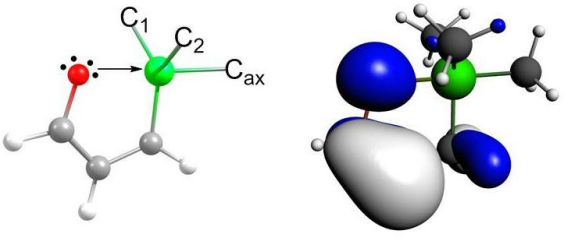


Figure 5.9 Molecular structure and plot of the HOMO of the zwitterionic phosphonium enolate, **I1**.

At this point we wondered how basic **I1** species are, and how is their reactivity compared to that of a very strong organic base, such as Verkade's. In the alcohol/base system, Verkade's superbase showed the best performance for deprotonating methanol. C_α position is by far the most basic spot in these zwiterionic species, and hence will be the atom that becomes protonated. By using the computational protocol described in the Computational Details section, we computed pKa values for some **I1** species as well as for the Verkade's base (Table 5.6). According to the pKa values, the zwitterionic species **I1** are very strong bases, as strong or even stronger than Verkade base. The trend clearly identifies the most basic phosphine and the highest pKa value.

Data collected up to this point clearly showed that the phosphine could interact with the substrate through a nucleophilic attack at the *β*-carbon of the activated olefin. Then, the very strong base formed *in situ*, i.e., the zwitterionic phosphonium enolate species **I1**, deprotonates MeOH assisted by B_2pin_2, forming the ion-pair **I2**. This conclusion is crucial, since it suggests that catalytic amounts of phosphine are enough to guarantee the formation of methoxy ions, which eventually activate the diboron reagent. This is clearly important as we found that phosphines can replace the standard bases used in the previous work presented in this Chapter 5, section 5.3.1 (Cs_2CO_3, NaO^{t}Bu, NaOMe, Verkade, etc…).

Table 5.6 Computed pKa values in dimethylsulphoxide (DMSO) and bond distances for some **I1** species. All distances are given in Å.

Species	pKa_{DMSO}	d(P-O)	d(P-Cax)	$d(P-C_1)$	$d(P-C_2)$
I1-PCy_3	29.0	2.07	1.96	1.91	1.89
I1-PMe_3	27.6	2.02	1.90	1.84	1.84
I1-PPh_3	25.8	1.98	1.92	1.85	1.83
Verkade	23.4	exp. value: 26.8			

Stoichiometric experiments in Schlenck and in NMR tube, and monitoring the reaction by ^{11}B NMR, ^{31}P NMR, and GC-MS led to new discoveries. As we mentioned before, when mixing 1.0 eq of PMe_3 with 1.0 eq of B_2pin_2 and 1.0 eq of (*E*)-hex-4-en-3-one in 1 mL of MeOH ([Reactives]=0.25 M), we observed complete formation of **I2** ion-pair by ^{1}H NMR, ^{31}P NMR, ^{1}H -^{31}P correlation NMR and ^{11}B NMR. Upon increasing the temperature to 70ºC, no conversion to the desired *β*-borated product was observed even after heating overnight. However, addition of an excess of substrate facilitated the formation of the *β*-borated product. After 1h at 70ºC, with 3.0 eq. of substrate, 1.0 eq of PMe_3 and 1.0 eq of B_2pin_2 in 1 mL of MeOH ([reactants]= 0.25M, except for [(*E*)-hex-4-en-3-one]=0.75 M) complete conversion was observed by ^{11}B NMR (Figure 5.10) and GC. More importantly, the ^{31}P NMR does not change the signal of the phosphonium salt remains unalterated.

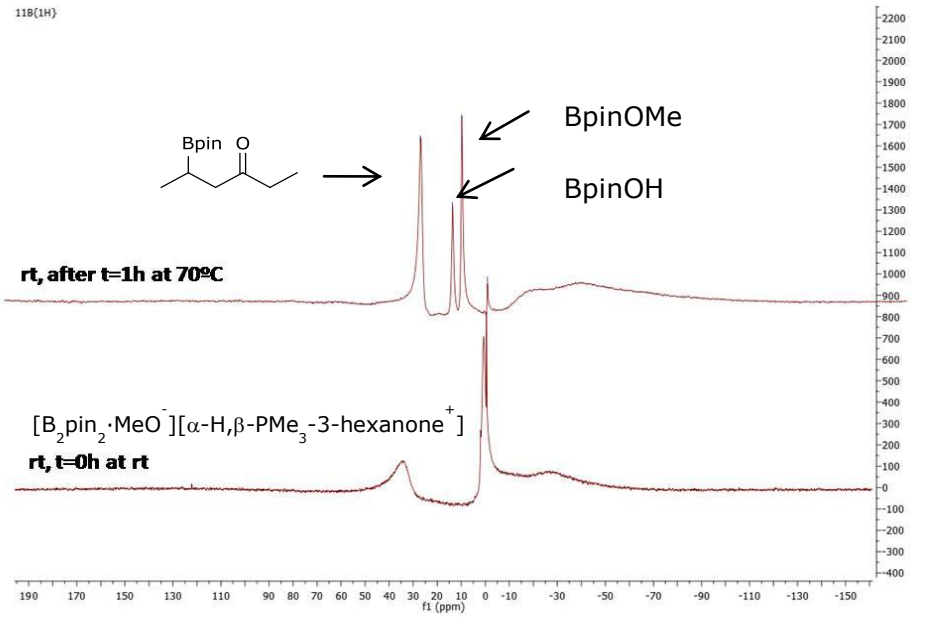


Figure 5.10 $^{11}B\{^1H\}$ -NMR spectra of a solution of PMe_3 (0.25 mmol) + (*E*)-hex-4-en-3-one (0.75 mmol) + B_2pin_2 (0.25 mmol) in 1.0 mL MeOH, measured at rt after heating at 70ºC during *t* time

Experiments above demonstrated that: i) **I2** species does not evolve to the *β*-borated product directly and ii) the reaction proceeds from **I2** with additional substrate. All these experiments might indicate that 1.0 eq of substrate with respect to the amount of phosphine is sacrificed to promote formation of the nucleophilic sp^2 B and consequently the nucleophilic boron attack. This idea derives in a new methodology for *β*-borating -unsaturated carbonyl compounds replacing the required Brönsted bases, thus using only phosphine/methanol.

With all this information in hand, following the energy profile from Figure 5.7, we completed the mechanism which started with the attack of a phosphine to *β*-position of the α,β-unsaturated carbonyl compound (**TS1**, Figure 5.11).

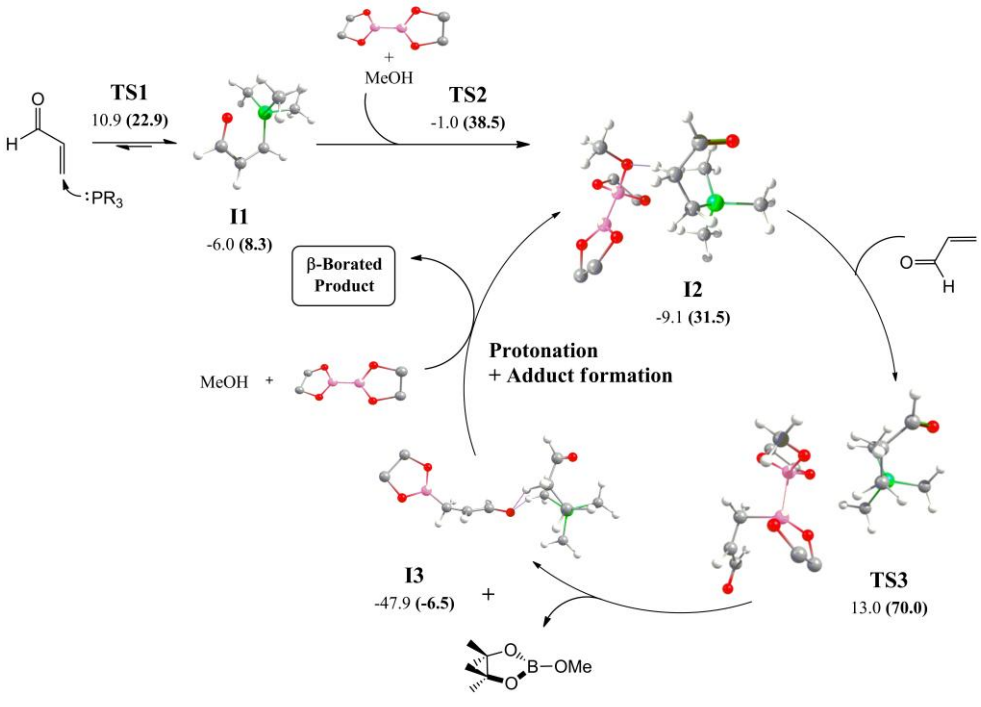


Figure 5.11 Suggested catalytic cycle for the new base-free organocatalytic *β*-boration reaction. Electronic energy (kcal.mol^{-1}) and Gibbs free energy (kcal.mol^{-1}; in parenthesis) computed at BP86 level relative to two molecules of acryladehyde, MeOH, B_2pin_2 plus PMe_3. Methyl groups of the B_2pin_2 are omitted for clarity

Attack of the trivalent phosphorus nucleophile to the most electrophilic carbon of the *α,β*-unsaturated compound results in the formation of the phosphonium enolate (**I1,** Figure 5.11), like it occurs in the first step in the Morita Baylis Hillman reaction.[58] This species can further deprotonate MeOH. On the basis of our NMR studies described before in this Chatper 5, this process is favoured by the presence of B_2pin_2 that stabilizes the MeO^- anion forming the [B_2pin_2·MeO^-] adduct. Therefore, the second transition state (**TS2,** Figure 5.11 and Figure 5.7) of our mechanistic proposal involves the protonation of **I1** in a concerted manner with the interaction of the MeO^- with the B_2pin_2 to provide a phosphonium intermediate type with the nucleophilic [B_2pin_2·MeO^-] adduct as a counter-ion, (**I2** ion-pair). In the next step (**TS3,** Figure 5.11), the sp^2 boryl unit of the activated diboron reagent in the *in situ* formed ion-pair (**I2**) attacks the C_β of another molecule of substrate. From **TS3**, it releases the pinBOMe byproduct and leads directly to the formation of an enolate ion-pair **I3** (Figure 5.11). Protonation of the enolate partner in **I3** results in the formation of the *β*-

borated product and regeneration of **I2**, since the protonation is assisted by another molecule of B_2pin_2 that stabilizes the generated MeO^-. Note, that the overall process is strongly exothermic (ΔE=-47.9 kcal.mol^{-1}) and exergonic (ΔG=-6.5 kcal.mol^{-1}), being **TS3** the most energetically demanding transition state in the catalytic cycle (22.1 kcal.mol^{-1} respect to **I2**). The mechanism in Figure 5.11 resembles that proposed by Toste *et al*. for the phosphine-assisted alkoxylation of activated olefins.[52]

We also computed two alternative reaction pathways: the intramolecular attack of the nucleophylic sp^2 boryl unit of the adduct [B_2pin_2·MeO^-] towards the C_β of the phosphonium salt by an nucleophilic substitution, SN_2 type of reaction (**TS-*SN*$_2$**), and although there were neither theoretical nor experimental evidences for the formation of stable phosphine-B_2pin_2 adducts, we were able to locate a transition state for the direct addition of the nucleophylic boryl unit to the alkene, assisted by the phosphine (**TS-PR$_3$**) (Figure 5.12). The computed energy barriers for the alternative mechanisms demonstrated that the reaction pathways through **TS-*SN*$_2$** or **TS-PR$_3$** are more energetically demanding than the intermolecular attack *via* **TS3** (Table 5.7).

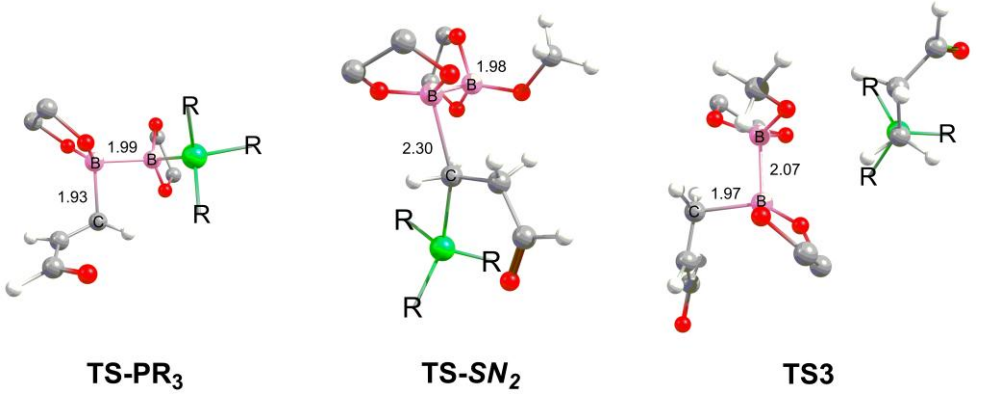


Figure 5.12 Transition state structures for alternative C–B bond forming steps. Selected interatomic distances in Å

Table 5.7 Comparison of the energy barriers for TS-PR_3, TS-SN_2 and the TS3 transition states. Electronic energies and Gibbs free energies (parenthesis) in kcal.mol^{-1} evaluated at BP86 and M06 level of theory respect to its immediate intermediate.

Phosphines	**TS-PR_3**		**TS-SN_2**		**TS3**	
	BP86 $\Delta E^{\neq}$ ($\Delta G^{\neq}$)	**M06** $\Delta E^{\neq}$ ($\Delta G^{\neq}$)	**BP86** $\Delta E^{\neq}$ ($\Delta G^{\neq}$)	**M06** $\Delta E^{\neq}$ ($\Delta G^{\neq}$)	**BP86** $\Delta E^{\neq}$ ($\Delta G^{\neq}$)	**M06** $\Delta E^{\neq}$ ($\Delta G^{\neq}$)
PMe_3	28.4 (57.3)	21.7 (50.6)	40.8 (40.2)	50.0 (49.4)	22.0 (38.2)	18.6 (34.7)
PPh_3	38.5 (69.6)	25.8 (56.9)	27.6 (25.5)	35.4 (33.1)	19.4 (34.8)	17.0 (32.4)
PCy_3	41.7 (73.2)	29.6 (61.0)	36.8 (35.3)	43.5 (42.1)	19.0 (32.9)	10.4 (24.3)

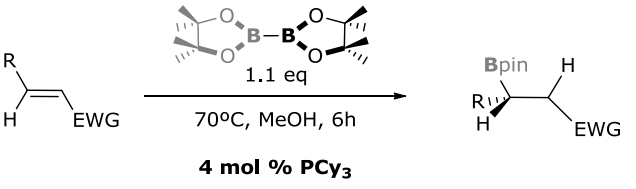
Independently of the functional used, BP86 or M06, TS3 is the less energetically demanding transition state for the three phosphines evaluated. Notably, TS3 for PCy_3 is the less energetically demanding TS among the other phosphines with both density functionals tested.

5.3.2.2 Phosphine/MeOH system: catalytic results

The benefits of phosphine in the reaction media towards the organocatalytic conjugate boron addition to α,β-unsaturated substrates was already proved by our group.[42] Not surprisingly, the nature of the phosphine is crucial for undergoing the β-boration reaction towards completion. For 4-hexen-3-one, we found that addition of 4% of PCy_3 allowed complete conversion within 6h in MeOH at 70ºC, whereas PMe_3 and PPh_3 gave worst results. On one hand, and according to the calculated energy barriers for the rate-determining step, PCy_3 showed the lowest value. On the other hand, although PPh_3 would potentially be as fast as PCy_3, solubility troubles were found.

Therefore, in order to prove the viability of the new phosphine assisted base-free β-boration reaction, we chose a series of α,β-unsaturated substrates, with

PCy_3 as the phosphine, in the absence of base and using methanol as the unique solvent. Within 6h, at 70ºC (Scheme 5.11), all the substrates tested were quantitatively converted, except those with α– or β-substituents (Figure 5.13).



Scheme 5.11. General reaction conditions for the novel PCy_3 promoted β-boration reaction

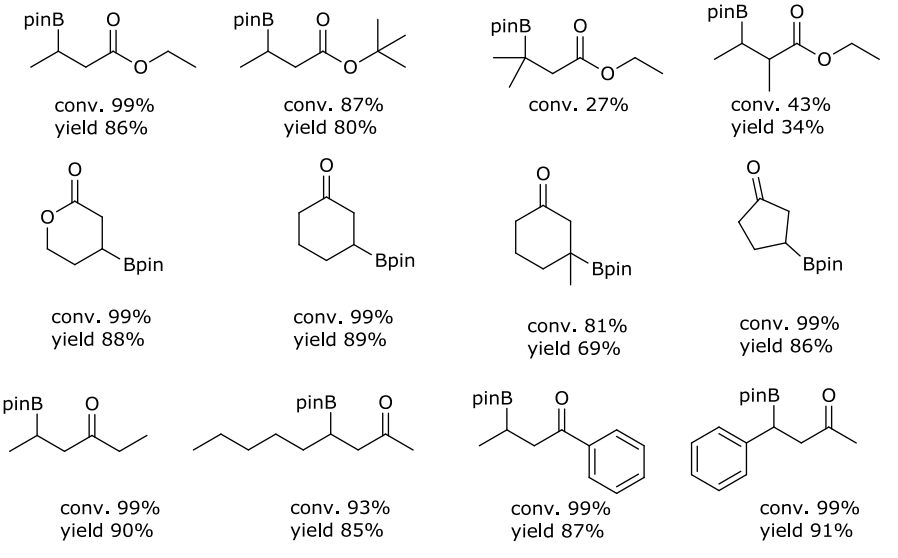
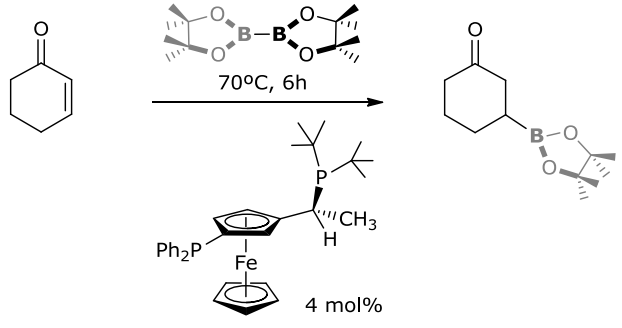


Figure 5.13 Substrate scope on the base free organocatalytic β-boration of α,β-unsaturated substrates assisted with PCy_3

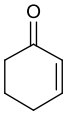
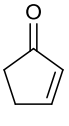
With this knowledge in hands, we postulated that the absence of base could have some effect on the enantioselectivity of the organocatalytic β-boration of α,β-unsaturated substrates. To prove this, we planned three parallel experiments with a Josiphos type chiral diphosphine. The experiments involved: 1) the Josiphos assisted base-free organocatalytic β-boration (Scheme 5.12), 2) the Josiphos-base assisted organocatalytic β-boration, and 3) the copper-Josiphos mediated β-boration with base. The substrate selected was

cyclohexenone and the mixture of solvents was MeOH/THF = 0.75/0.25 to guarantee the total solubility of the reagents. Results collected in Table 5.8 revealed a striking feature: the reaction without base and copper salt was the most enantioselective, although lower amount of substrate was converted for the same reaction time (Table 5.8).



Scheme 5.12 Enantioselective base-free β-boration with Josiphos.

Table 5.8 Asymmetric β-boration of cyclohexenone and cyclopentenone with Josiphos[a]

Entry	Substrate	CuCl/ Cs_2CO_3	Conv.[b]	Ee[c]
1		---/---	27	49
2	"	--- / 15 mol%	99	25
3	"	2 mol% /15 mol%	99	28
4		---/---	93	78

[a]Substrate: 0.5 mmol, Josiphos (4 mol%), solvent: THF (0.5 mL), methanol (1.5 mL), T= 70ºC, t=6h.[b] Conversion determined by GC. [C] *ee* determined by GC-MS.

These results indicate that when base and phosphine are present, two reaction mechanisms could operate simultaneously: the base-promoted achiral reaction, and the new phosphine promoted chiral β-boration. Enantiomeric excess decreases when the base-promoted mechanism is operating (Table 5.8, entry 2 respect to entry 1), but it is not totally cancelled. Consequently, the only chiral species in the reaction media that can induce chirality must be the

phosphonium cationic salt, **I2**. Remarkably, within this preliminary study, it was possible to achieve high levels of enantioselectivity (up to 78%) with Josiphos/MeOH system when cyclopentenone was the substrate (Table 5.8, entry 4).

5.4 Conclusions

In summary the role of the base in the organocatalytic conjugate boron addition reaction has been determined by experimental and theoretical methods. A plausible mechanism has been proposed in which the role of the base is crucial to provide the activated diboron reagent. The diboron adduct, $[B_2pin_2 \cdot MeO^-]$, is prone to attack activated olefins. The nucleophilic attack forms the borylated carbanionic intermediate, which is protonated in the protic medium, forming the *β*-borated product, and generating another methoxy anion. The rate of the formation of the carboanionic intermediate, as well as its thermodynamic stability, is mainly controlled by the functional group of the activated olefin. We believe that the sole use of base/alcohol as catalytic system is an important achievement in the emerging area of organocatalytic conjugate boron addition reactions.

Moreover, novel reaction conditions for the organocatalytic *β*-boration reaction of *α,β*-unsaturated carbonyl compounds using only phosphine and alcohol are presented here for the first time. The development of this novel transformation is based on convergent spectroscopic, stoichiometric and theoretical evidences about *in situ* formed reactive species, and the reaction mechanism. The sole use of catalytic amounts of phosphine catalyzes the *β*-boration reaction. No Brönsted base is required to activate the diboron reagent bis(pinacolato)diboron, B_2pin_2. The scope of the reaction is demonstrated, and includes esters, acyclic and cyclic ketones.

The phosphine directly attacks the most electrophilic carbon of the *α,β*-unsaturated carbonyl compound resulting in the formation of a strongly basic zwiterionic phosphonium enolate species. This base is further protonated by the excess of MeOH and particularly favoured by the presence of bis(pinacolato)diboron that stabilizes the MeO^- anion, thus forming the Lewis acid-base $[B_2pin_2 \cdot MeO^-]$ adduct.

When a base is present in the reaction media, the novel mechanism for the base-free *β*-boration reaction could operate simultaneously with the mechanism based on alcohol/base. The two mechanisms principally differ on which species deprotonate the alcohol, either the Brönsted base or the phosphonium enolate intermediate. A synergic effect is thus expected, as the activity of the

phosphine/alcohol/base system is higher than when the two mechanisms operate independently.

The asymmetric induction achieved with chiral phosphines must be attributed to the *in situ* formed chiral cation **I2**. The relative proximity between the phosphonium cation and the activated diboron reagent in the ion-pair might explain the origin of the enantioselectivity. This opens new possibilities for exploring similar transformations with other nucleophiles and other substrates.

The interest of this organocatalytic transformation is justified by the simplicity of the methodology. The results presented here give a turn of nut since *β*-boration can be performed even selectively by the unique presence of catalytic amounts of phosphine in MeOH. The simplicity of the system and the understanding of the role of the phosphine open now an unlimited palette of possibilities.

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Chapter 6: Conclusions

6.1 Chapter 2: (NHC)Palladium catalyzed selective diboration of endocyclic alkenes.

Our current understanding of Pd(II)-NHC mediated diboration of endocyclic olefins suggests that in the absence of base the precursor of catalyst [Pd(NHC)pyX_2] (X=Cl, I) could not activate the bis(catecholato)diboron *via* homolytic cleavage of the B-B bond. We found that the presence of a base is crucial in favouring the heterolytic cleavage of the diboron, and thus promoting the σ-bond metathesis.

The use of NHC-s as ligands in Pd(II) mediated diboration of cyclic olefins guaranteed high conversions of the substrate into the desired 1,2-diborated product selectively, in the presence of a mild base and an excess of B_2cat_2.

Also, based on previous theoretical and experimental work, a comprehensive understanding of the mechanism of this NHC-Pd(II) mediated selective diboration of endocyclic alkenes has been reached. A suitable mechanistic proposal has been suggested to rationalize the experimental results.

An advantage of the palladium-catalyzed diboration reaction leading to the formation of two C-B bonds is that it is possible to use the resulting organoborate intermediate to conduct a subsequent palladium-mediated reaction.

6.2 Chapter 3: (NHC)Rhodium mediated diboration versus dehydrogenative borylation

A selective rhodium mediated diboration of alkenes has been pursued since the first application of such complexes in diboration. It is well known that rhodium complexes modified with phosphines favoured the dehydrogenative borylation reaction in borylation of cyclic olefins, obtaining vinylboronate esters even selectively under the appropriate reaction conditions.

In our study, we have found that Rh(I) complexes modified with bidentate N-heterocyclic carbene ligands favour the formation of the desired 1,2-diborated product in combination with the use of non polar and non coordinating solvents such as pentane, hexane or cyclohexane. Although the good chemoselectivity of

the reaction, the conversions were not quantitative under the conditions reported.

By means of DFT calculations we have elucidated the reason why the mechanism of the diboration versus the corresponding of the dehydrogenative borylation might be favoured in this novel Rh(I)-NHC methodology. On the basis of our theoretical results, it is clear that the reductive elimination pathway is less energetically demanding than the one for the H-*β*-hydride elimination. Also, we found that the coordination ability of the solvents seems to be more important than polarity on the activity and selectivity of the catalytic system.

With this better understanding in hand, a more detailed study on evaluating the influence of similar ligands and solvents from a theoretical and experimental point of view could be further performed in the near future. And what is more important, expansion of the methodology for non cyclic substrates could be also interesting.

6.3 ***Chapter 4*****:** Organocatalytic approach to diboration reaction

Organocatalytic diboration represents a great advance in the methodology of metal free borylation reactions. For the first time this reaction could be carried out without metal using tetraalkoxydiboranes, in mild conditions and short reaction times for a broad scope of alkenes.

More importantly, DFT calculations and NMR studies revealed that the diboron reagent, such as B_2pin_2, can be activated by the sole use of base and methanol as catalytic system. Upon an interaction of a base with methanol an alkoxide is generated, which interacts with the diboron reagent, forming a Lewis acid-base adduct [$B_2pin_2 \cdot MeO^-$]. The nature of this resulting adduct has been studied in detail revealing an unexpected nucleophilic character in the Bpin sp^2 moiety.

Moreover, we have been able to propose a plausible mechanism to rationalize this unprecedented reactivity. This novel mechanistic suggestion describes a nucleophlic attack of a strongly nuchleophilic Lewis-acid base adduct towards an also nucleophilic substrate, the alkene. The subsequent steps can be explained as an intramolecular process to generate the *cis*-1,2-diborated product. Indeed, the features of this novel mechanistic proposal resemble a type of mechanism called bifurcation.

6.4 ***Chapter 5*****:** Transition metal-free β-boration of activated olefins

We have developed a new methodology for the organocatalytic β-boration reaction based on the sole use of Brönsted bases/alcohol. The in situ generated nucleophilic Lewis acid-base adduct, [B_2pin_2·MeO^-] could be added to a large scope of α,β-unsaturated carbonyl compounds.

In contrast with Hoveyda's methodology, our system does not need a N-heterocyclic carbene to activate the diboron reagent; the alkoxide is enough to promote the reaction. However, our methodology requires higher temperatures to obtain good yields.

This organocatalytic system is less active than the metal-mediated β-boration reaction and sterically hindered substrates became more difficult to β-borate.

Once again, by NMR studies and mainly DFT calculations a suitable mechanism was proposed to rationalize the experimental data. Remarkably, the 1,4-diborated product was not involved in this novel mechanistic proposal.

In this scenario, we have also demonstrated that the use of a Brönsted base is not strictly necessary to activate of the B_2pin_2. Nucleophilic attack of a phosphine to an α,β-unsaturated substrate in methanol generates methoxide anions that unpon interaction with the B_2pin_2 provides the activated diboron adduct, [B_2pin_2·MeO^-]. Consequently, the β-boration of a wide range of α,β-unsaturated substrates could be performed with a phosphine/MeOH system. However, under this novel conditions, only basic phosphines were effective towards the borylation of the α,β-unsaturated compounds and the conversions were lower than the corresponding with the Brönsted base/MeOH system in THF.

Moreover, using chiral phosphines, moderate levels of enantioinduction were achieved. At this early stage, and according to our mechanistic proposal based on DFT calculations, we could attribute the enantiodifferentiation to the *in situ* chiral cation of the ion pair I2 (i.e. [α-H,β-PR_3-3-hexenone]$^+$[B_2pin_2·$MeO]^-$). However, further optimization of the reaction conditions and mechanistic studies are needed to validate our hypothesis.

Chapter 7: Experimental part

7.1 General considerations

All reactions and manipulations were carried out under an argon atmosphere by using Schlenk-type techniques. The solvents were distilled over dehydrating reagents and were deoxygenated before use. Bis(pinacolato)diboron was provided from Allychem. Substrates, bases and other diboron reagents were used as purchased from Sigma-Aldrich and Alfa Aesar. Rh(I)-NHC complexes (**3.1**-**3.3**)[1] and Pt/Pd(II)-NHC (**2.1**-**2.3**) complexes were prepared following the literature protocol.[2] NMR spectra were obtained on a Varian Mercury 400 spectrometer. ^{1}H NMR and ^{13}C $\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to the chemical shifts of tetramethylsilane or residual solvent resonances. ^{11}B $\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to $BF_3(CH_3)_2O$. Gas Chromatography was equipped with HP-5 column with FID or MS detector.

7.1.1 Typical procedure for the (NHC)Pd(II) catalyzed selective diboration of endocyclic alkenes.

Bis(catecholato)diboron (2.0 eq, 1.0 mmol) was added to a solution of the catalyst (2.0 mol%, 0.01 mmol) and base (1.0 eq, 0.5 mmol) in CH_2Cl_2 (1 mL) under argon. The solution was stirred for 5 minutes and the substrate (0.5 mmol) was then added. The mixture was stirred for 16 hours at room temperature. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the degree of conversion and the nature of the reaction products.

Posterior oxidative workup of the products allowed to determine the *cis* conformation of the product and isolation of the corresponding *cis*-1,2-diol (see section 7.3).

7.1.2 Typical procedure for the (NHC)Rh(I) mediated diboration of endocyclic alkenes

Rh complexes (**3.1**-**3.3**) (4 mol% 0.008 mmol), or $[Rh(\mu\text{-}Cl)(COD)]_2$ (2 mol%, 0.004 mmol)/phosphine (4-8 mol%), and bis(pinacolato)diboron (1.0 eq, 51.0 mg, 0.2 mmol) were transferred into an oven-dried Schlenk tube under argon. Dried and deoxygenated solvent (2 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the diboron reagent completely. Cyclohexene (0.2 mmol) was added, and the reaction mixture was stirred at 70

°C oil bath temperature for 16 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC/GC-MS to determine conversion. After the GC analysis, the aliquot was analysed by ^{1}H-NMR to confirm the conversion previously observed by gas chromatography. The analytical samples were combined with the rest of the reaction mixture, all the volatiles were removed in vacuum, and the crude product was purified by column chromatography.

7.1.2.1 Typical procedure for the Rh catalyzed diboration/oxidation with B_2cat_2

Rhodium complex **3.2** (4 mol%, 1.0 mg, 0.008 mmol) and bis(catecholato)diboron (1.0 eq, 0.2 mmol) were transferred into an oven-dried Schlenk tube under argon. Dried and deoxygenated cyclohexane (2 mL) was added. The mixture was stirred for 10 minutes at room temperature. The substrate cyclohexene (21 µL, 0.2 mmol) was added, and the reaction mixture was stirred at 70 °C oil bath temperature for 16 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by NMR to determine conversion of the reaction. The aliquot was returned to the reaction mixture and the solvent was removed under vacuum. 1 mL of THF was added and it was cooled at 0ºC. NaOH (2 mL, 3.0M) and H_2O_2 (1mL, 33%) were added to the reaction mixture and the entire sample was stirred from 0ºC to room temperature, overnight. Then, saturated solution of $Na_2S_2O_3$ was added to the mixture and the product was extracted with ethyl acetate (3x25ml). A combination of the organic phases was gently concentrated on a rotary evaporator and chemoselectivity of the alcohol products was determined by ^{1}H NMR in comparison with reported data.

7.1.3 Typical procedure for the organocatalytic diboration of alkenes

Base (15mol%, 0.075 mmol) and bis(pinacolato)diboron (140 mg, 0.55 mmol) were transferred into an oven-dried Schlenk tube, provided with stir bar, under argon. THF (2 mL) was added to dissolve the mixture. After that, substrate (0.5 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at determinate temperature in an oil bath temperature for 6 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was

taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC and GC-MS to determine conversion and products of the reaction. The aliquot was added to the reaction mixture and the entire sample was gently concentrated on a rotary evaporator, after all the volatiles were evaporated, the sample was purified by column chromatography.

7.1.4 Typical procedure for the transition metal-free *β*-boration of activated olefins: Verkade/MeOH system

General Procedure for the *β*-boration of α,β–unsaturated carbonyl compounds, and other activated olefines: base, Verkade's base2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, (8.4 mg, 0.075 mmol, 15mol%) and bis(pinacolato)diboron (140 mg, 0.55 mmol) were transferred into an oven-dried Schlenk tube under argon. THF (2 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the diboron reagent completely. The substrate (0.5 mmol) and MeOH (100 μl, 2.5 mmol) were added, and the reaction mixture was stirred at 70 °C oil bath temperature for 24 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC/GC-MS to determine conversion, and confirm selectivity. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to confirm the conversion, and chemoselectivity previously observed by gas chromatography. In each case, both methods indicated that one single product was formed from the substrate. The differences in the conversions obtained with the two methods are within 5% in most cases. In each case, the conversion determined by GC

7.1.5 Typical procedure for the phosphine assisted organocatalytic transition metal free *β*-boration

Achiral version

The phosphine, trycyclohexylphosphine (5.6 mg, 0.02 mmol) and bis(pinacolato)diboron (140 mg, 0.55mmol) were transferred into an oven-dried Schlenk tube under nitrogen. Methanol (2 mL) was added. The substrate (0.5 mmol) was added, and the reaction mixture was stirred at 70 °C oil bath temperature for 6 hours. The reaction mixture was cooled to room temperature.

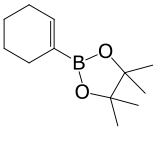
An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC to determine conversion. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at room T, and analyzed by ^{1}H-NMR to confirm the conversion previously observed by gas chromatography. In each case, both methods indicated that one single product was formed from the substrate. The differences in the conversions obtained with the two methods are within 5% in most cases. In each case, the conversion determined by GC

Chiral version

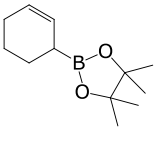
Chiral phosphorous compound (0.01 mmol) and bis(pinacolato)diboron (70 mg, 0.225mmol) were transferred into an oven-dried Schlenk tube under argon. Methanol (0.75 ml) and THF (0.25 mL) were added. The substrate (0.25 mmol) was added, and the reaction mixture was stirred at 70 °C oil bath temperature for 16 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC to determine conversion. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at room T, and analyzed by ^{1}H-NMR to confirm the conversion previously observed by gas chromatography. In each case, both methods indicated that one single product was formed from the substrate. The differences in the conversions obtained with the two methods are within 5% in most cases. In each case, the conversion determined by GC is given in the tables of the paper.

The sample was prepared to determine the enantiomeric excess via GC-Ms or HPLC-MS.

7.2. Characterization of organoboranes:

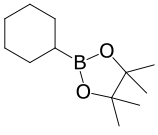


1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexene (3.4): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (s, 12H,) 1.59 (tt, 4H, J= 3.0 and 3.0 Hz), 2.05-2.15 (m, 4H), 6.57 (t, 1H, J=1.7 Hz). These spectroscopic data are in agreement with the previously reported.[3]

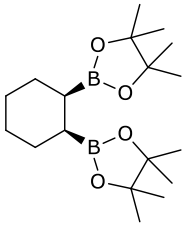


2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexene (3.5):
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 12H), 1.56–1.78 (m, 5H), 1.97–2.00 (m, 2H), 5.64–5.73 (m, 2H). These spectroscopic

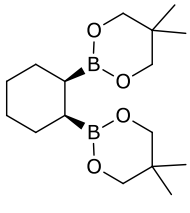
data are in agreement with the previously reported.[4]



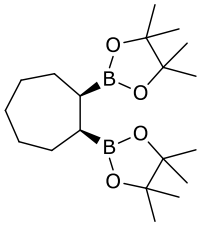
1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)clycloheхane (3.6): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93-1.00 (m, 1H), 1.23 (s, 12H), 1.54-1.70 (m, 8H). These spectroscopic data are in agreement with the previously reported.[5]



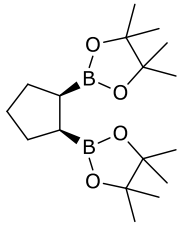
1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-cyclohexane (3.7): The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). White solid. Yield: (65%). Rf = 0.3 (silica TLC, petroleum ether : EtOAc, 15:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.67-1.50 (m, 5H), 1.48-1.34 (m, 5H), 1.23 (s, 12H, B(pin)), 1.22 (s, 12H, B(pin)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.96, 28.29, 27.07, 25.12, 25.04. ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.35. HRMS (ESI^+) m/z $C_{18}H_{34}B_2O_4$ $[M+H]^+$ = 337.2713.



1,2-bis(5,5-dimethyl-1,3,2-dioxaborolan-2-yl)cyclohexane: The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). White solid. Yield: (65%). Rf = 0.2 (silica TLC, petroleum ether : EtOAc, 15:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (s, 12H), 1.26-1.14 (m, 2H) 1.40-1.34 (m, 4H), 1.60-1.50 (m, 4H), 3.56 (s, 8H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 72.11, 31.76, 27.7, 27.06, 22.14, ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.9. HRMS (ESI^+) m/z for $C_{16}H_{30}B_2O_4$ $[M+H]^+$ = 309.236.



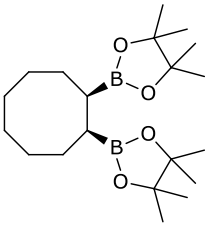
1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-cycloheptane: The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). Yellow pail solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76-1.70 (m, 2H), 1.65-1.50 (m, 3H), 1.52-1.43 (m, 5H), 1.40-1.31 (m, 2H),1.22 (s, 24H, B(pin)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.4, 30.45, 28.25, 27.61, 24.89; ^{11}B NMR ($CDCl_3$, MHz): δ 34.6 **;** HRMS (ESI^+) for $[C_{19}H_{36}B_2O_4 + H^+]$: 351.288



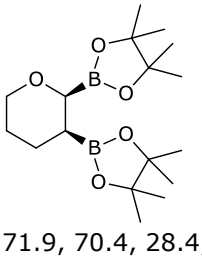
1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-cyclopentane: The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). White solid. Yield: (89%). ^{1}H NMR ($CDCl_3$, 400 MHz):

1.70-1.90 (m, 2H), 1.60-1.52 (4H, m), 1.48-1.40 (2H, m), 1.21 (s, 12H), 1.20 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): 88.8, 29.3, 32.0, 27.5, 24.7, 22.1 ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.0.

These spectroscopic data are in agreement with the previously reported NMR data.[6]

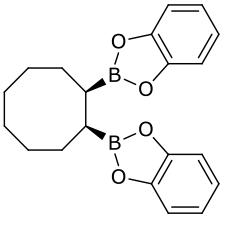


1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-cyclooctane: The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). White solid. (Yield: 72%) ^1H NMR ($CDCl_3$, 400 MHz): 1.72-1.68 (m, 2H), 1.58-1.40 (m, 10H), 1.39-1.37 (m, 2H), 1.22 (s, 24H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.84, 28.21, 27.70, 26.58, 24.88, 24.79; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.9. HRMS (ESI^+) m/z calculated for $C_{20}H_{38}B_2O_4$ $[M+H]^+$ = 365.304.

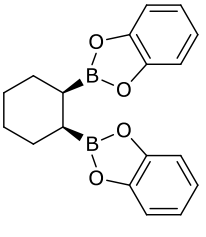


1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)tetrahydro-2H-pyran: The product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). Colorless oil. (Yield 57%) ^1H NMR ($CDCl_3$, 400 MHz): 1.20 (s, 12H), 1.24 (s, 12H), 1.38-1.50 (m, 2H), 1.53-1.72 (m, 3H), 3.5-3.7 (m, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): 88.8, 71.9, 70.4, 28.4, 26.3, 24.7, 17.5, ^{11}B NMR ($CDCl_3$, 128 MHz): δ 36.2

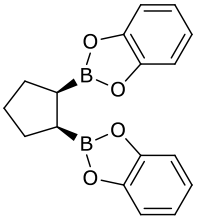
The following NMR data had been extracted from the reaction crude because of the instability of the product:



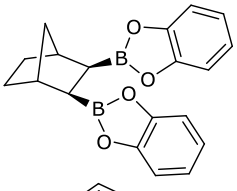
2-(Benzo[1,3,2]diocarborol-2-cyclooctyl)benzol-[1,3,2]dioxaborol: ^1H NMR ($CDCl_3$, 400 MHz): 1.60-1.80 (m, 8H), 1.89-1.95 (m, 4H), 2.01-2.20 (m, 2H), 7.01-7.05(m, 4H), 7.12-7.15 (m, 4H) ppm



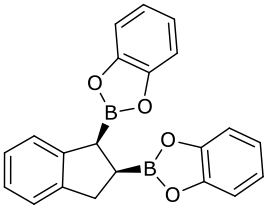
2-(Benzo[1,3,2]diocarborol-2-cyclohexenyl)benzol-[1,3,2]dioxaborol: ^1H NMR ($CDCl_3$, 400 MHz): 1.81-1.83 (m, 4H), 1.85-1.90 (m, 4H), 1.90-2.00 (m, 2H), 7.02-7.03(m, 4H), 7.11-7.14 (m, 4H) ppm



2-(Benzo[1,3,2]diocarborol-2-cyclopentyl)benzol-[1,3,2]dioxaborol: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.77-1.99 (m, 2H), 2.05-2.12 (m, 4H), 2.1-2.2 (m, 2H), 6.97-7.05 (m, 8H) ppm

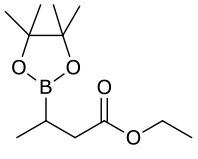


***exo,exo*-2,2'-Bicyclo[2.2.1]heptanes-2,3-di(bis-1,3,2-benzodioxaborol):** ^{1}H NMR ($CDCl_3$, 400 MHz): 1.44 (m, 2H), 1.73 (m, 2H), 1.83 (s, 4H), 2.65 (s, 2H), 6.93 (s, 8H). ppm These spectroscopic data are in agreement with the previously reported NMR data.[7]

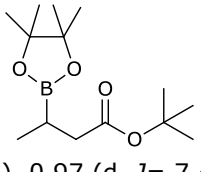


2,2'-(1-Phenylpropane-1,2-diyl)dibenzeno(1,3,2-dioxaborol): ^{1}H NMR ($CDCl_3$, 400 MHz): 2.77 (m, 1H), 3.47 (m, 1H), 3.67 (m, 1H), 7.00-7.50 (m, 12H) ppm These spectroscopic data are in agreement with the previously reported.[8]

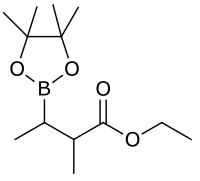
All the spectroscopic data of the following products have been reported previously[9–15]



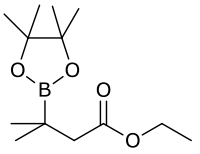
Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate: ^{1}H NMR(400 MHz, $CDCl_3$) = δ 4.12 (q, *J* = 7.2 Hz, 2H), 2.43 (dd, *J* = 16.3, 7.6 Hz, 1H), 2.36 (dd, *J*1= 16.3, *J*2=6.6 Hz, 1H), 1.41−1.34 (m, 1H), 1.27(s, 6H), 1.25 (CH_3 overlapped, 3H), 1.22 (s, 6H), 1.00 (d, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) = 173.9, 83.4, 60.4, 38.0, 25.1, 25.0, 15.5, 14.7, 13.8.



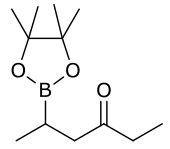
Tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (dd, *J1*= 16.6, *J2*= 8.7 Hz, 1 H), 2.27 (dd, *J1*= 16.6, *J2*= 7.8 Hz, 1 H), 1.36-1.25 (m, obs., 1 H), 1.25 (s, 12 H), 1.22 (s, 9 H), 0.97 (d, *J*= 7.44 Hz, 3 H).



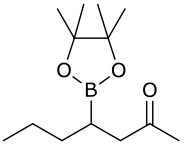
Ethyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.1 (q, *J*= 7.2 Hz, 2H), 2.6 (m, 1H), 2.5 (m,1H), 1.3 (m, 15H), 1.2 (d, *J*= 7.23 Hz, H), 1.1 (d, 3H), 0.9 (m, 3H).



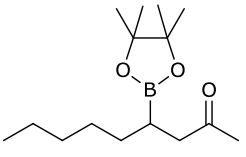
Ethyl 3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H NMR (400 MHz, $CDCl_3$): δ =4.16 (q, *J*=8.2 Hz, 2H), 2.33 (t, *J*=8.2 Hz, 2H), 2.18 (s, 3H), 1.25 (s, 12H), 1.90 (s, 3H), 1.00 (s, 3H)



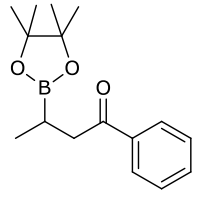
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (broad d, *J* = 6.9 Hz, 2H, CH_2), 2.38 (dq, *J1*= 7.4, *J2*= 2.2 Hz, 2H, CH_2), 1.28-1.24 (m, 1H, CH), 1.23 (s, 6H, pinacolate 2 CH_3), 1.21 (s, 6H, pinacolate 2 CH_3), 1.03 (t, *J*= 7.3, 3H, CH_3), 0.94 ppm (d, *J*= 7.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ = 211.7, 82.9, 46.2, 35.6, 25.00 24.7, 24.6, 15.0, 7.9. ^{11}B NMR: ($CDCl_3$, 128.3 MHz) δ = 34.08.



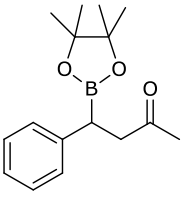
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (d, *J*= 7.0 Hz, 2H, CH_2), 2.08 (s, 3H, CH_3), 1.40-1.22 (m, 5H, 2 CH_2, CH), 1.21 (s, 6H, pinacolate 2 CH_3), 1.18 (s, 6H, pinacolate 2 CH_3), 0.84 (t, *J*= 6.8 Hz, 3H, CH_3) $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ = 209.3, 83.0, 45.8, 32.7, 29.8, 25.1, 24.9, 24.8, 22.2, 14.42. ^{11}B NMR: ($CDCl_3$, 128.3 MHz): δ = 33.9.



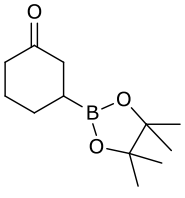
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (d, *J* = 7.2 Hz, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.28-1.21 (m, 9H, 4 CH_2, CH), 1.20 (s, 6H, pinacolate 2 CH_3), 1.80 (s, 6H, pinacolate 2 CH_3), 0.84 (t, *J*= 6.8 Hz, 3H, CH_3) $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ = 209.2, 82.9, 45.8, 31.9, 30.3, 29.6, 28.5, 24.9, 24.7, 24.6, 22.5, 14.00. ^{11}B NMR: ($CDCl_3$, 128.3 MHz): δ = 38.7.



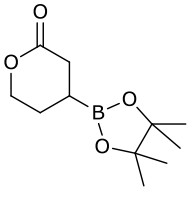
1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J*= 6.9 Hz, 1H), 7.42 (t, *J*= 6.9 Hz, 2H), 3.12 (d, *J*= 6.9 Hz, 2H), 1.40 (m, 1H), 1.26 (s, 6H), 1.25 (s, 6H), 1.06 (d, *J*= 7.5 Hz, 3H).



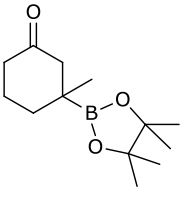
4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (dd, *J1*= 6, *J2*= 4 Hz, 2H), 7.25-7.21 (m, 3H), 3.05 (dd, *J1*= 20, *J2*= 12Hz, 1H), 2.85 (dd, *J1*= 20, *J2*= 4 Hz, 1H), 2.71 (dd, *J1*=12, *J2*=4Hz, 1H), 1.94 (s, 3H), 1.29-1.19 (m, 12H)



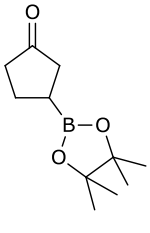
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone:^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38-2.24 (m,4H), 2.08-2.01 (m,1H), 1.88-1.83 (m,1H), 1.78-1.68 (m,1H), 1.66-1.56 (m,1H), 1.48-1.38 (m,1H), 1.22 (s, 12H, pinacolate 2 CH_3).



4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)tetrahydropyran-2-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50–4.20 (m, 2H), 2.64 (dd, J = 17.8, 6.9 Hz, 1H), 2.51 (dd, J = 17.8, 10.1 Hz, 1H), 2.14–1.90 (m, 1H), 1.90–1.74 (m, 1H), 1.66–1.44 (m, 1H), 1.25 (s, 12H); ^{13}C{^{1}H} NMR(75.4 MHz, CDCl3): δ 171.8, 84.0, 70.1, 31.0, 24.9, 24.8, 24.1, 17.7 (C–B)



3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone :. ^{1}H NMR (400MHz, $CDCl_3$): δ 2.51 (dt, *J* = 13.8, 1.3 Hz, 1H), 2.40–2.14 (m, 2H), 2.10–1.89 (m, 3H), 1.87–1.66 (m, 1H), 1.52–1.36 (m, 1H), 1.21 (s, 12H), 1.03 (s, 3H); ^{13}C{^{1}H} NMR (75.4 MHz, CDCl3): δ 212.2, 83.6, 50.8, 41.3, 34.3, 24.8, 24.7, 24.3, 24.0.

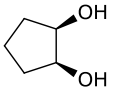


3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentanone: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42–2.02 (m, 5H), 1.94–1.76 (m, 1H), 1.74–1.56 (m, 1H), 1.26 (s, 12H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 221.4, 83.7, 40.4, 39.1, 25.4, 24.9.

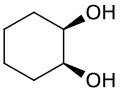
7.3. NMR date for the diol derivatives:

General oxidation protocol: 1,2-diborated product was treated with 2 mL of an aqueous solution of 3.0M NaOH and 1 mL of a solution of 33% H_2O_2. The mixture was stirred for 4 hours. After this time, it was quenched with saturated solution of $Na_2S_2O_3$ and then extracted with AcOEt (3 x 20 mL). The organic phase was dried over $MgSO_4$. The $MgSO_4$ was filtered off, and all the volatiles were removed in vacuum.

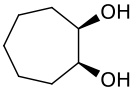
All the spectroscopic data of the follow products have been reported previously[16–19]



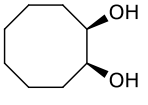
***cis*-cyclopentane-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39-1.45 (m, 4H), 1.5-1.72 (m, 4 H), 2.0 (bm, 2H), 3.25 (m, 2H).



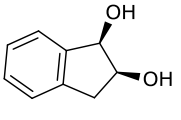
***cis*-cyclohexane-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33-1.52 (m, 4H), 1.6-1.7 (m, 4 H), 2.3 (bm, 2H), 3.29-3.4 (m, 2H).



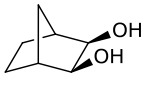
***cis*-cycloheptane-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35-1.54 (m, 4H), 1.57-1.72 (m, 4 H), 2.2 (bm, 2H), 3.29-3.4 (m, 2H).



***cis*-cyclooctane-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30-1.43 (m, 8H), 1.47-1.57 (m, 4 H), 2.4 (bm,2H), 3.29-3.4 (m, 2H).



***cis*-indan-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (dd, J=16.4 Hz, 4.4 Hz, 1H), 312 (dd, J=16.4 Hz, 5.6 Hz, 1H) 4.51 (m ample, 1H), 5.00 (dd, J=5.6 Hz, 5.6Hz), 7.2-7.3 (m, 3H), 7.4 (m, 1H).



***cis*-exo,exo2,2'-bicyclo[2.2.1]heptan-1,2-diol :** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 2.63-2.48 (m, 2H), 1.53-1.20 (m, 2H), 0.92 (t, J=7.6, 3H)

7.4. Computational Details: general strategy

Molecular structures for all the species were optimized without constraints by using Density Functional Theory (DFT) based methods as implemented in the Amsterdam Density Functional (ADF v2007.01 or 09.01) package.[20,21]
A triple-ζ plus polarization (TZP) Slater basis set was used on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[22] For geometry optimizations we used the local exchange VWN correlation potential[23] together with the Becke's exchange[24] and the Perdew's correlation[25,26] (BP86) generalized gradient corrections. Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequencies calculations. Nuclear Magnetic Resonance chemical shifts were computed at the same level of theory by running single point calculations with all electron basis sets.
Standard corrections to Gibbs free energy at 298 K were evaluated too. Solvent effects were introduced by using the continuous solvent model COSMO.[27] Single point energy at the metahybrid M06[28] level were performed self-consistently.

PKa values were obtained based on the Born-Haber cycle[29]using the known solvation energy of the proton.[30] In this particular case, molecular structures were calculated without constraints using Gaussian 09,[31] Revision A.02, with the hybrid B3LYP[32] functional and 6-31+G(d)[33] as a basis set. Solvent effects (dimethylsulphoxide, DMSO) were introduced by using the Polarizable Continuum Model (PCM).[34]

7.5. References

(1) Mata, J. A.; Chianese, A. R.; Miecznikowski, J. R.; Poyatos, M.; Peris, E.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2004**, *23*, 1253–1263.
(2) Pubill-Ulldemolins, C.; Bo, C.; Mata, J. a; Fernández, E. *Chem. Asian J.* **2010**, *5*, 261–264.
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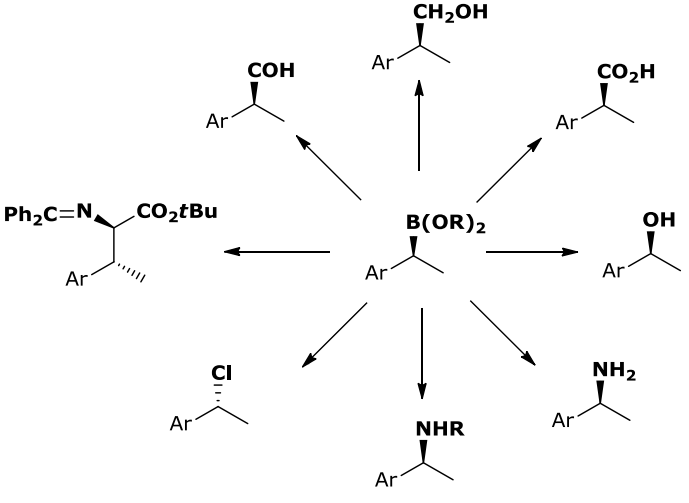
Chapter 8: Summary/Resum

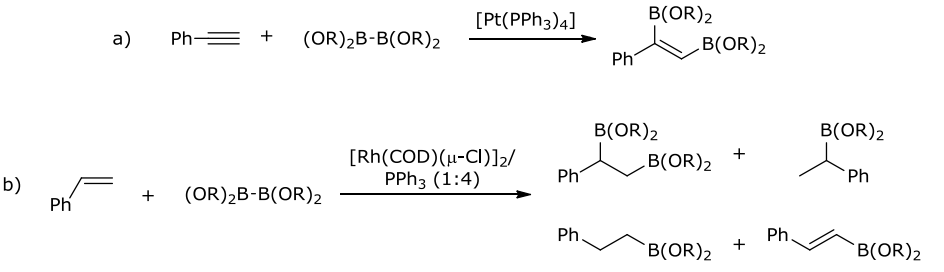
The organoborane products are highly used in a broad number of fields, from their use in medicine as a ^{10}B carrier for neutron capture therapy, or other molecules with biological activity, to their use as functional molecules such as polymers. Importantly, organoboranes are a very versatile and powerful intermediates in the synthesis of high value products (Scheme 1.8).[1,2]



Scheme 1.8 General derivatization of the C-B

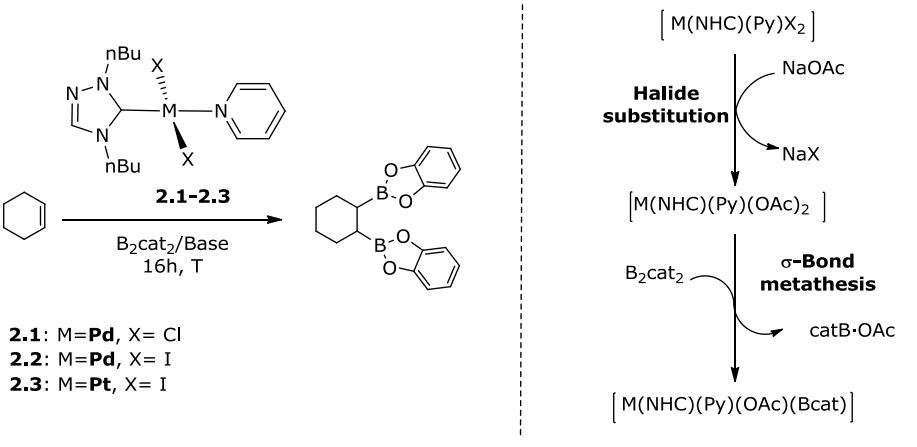
This thesis focuses on the development of novel methodologies for catalytic boron addition to alkenes, with particular attention to the understanding of the activation mode of the diboron reagent and the mechanism of their addition to olefins. For this purpose NMR studies together with DFT calculations are carried out.

The simultaneous introduction of the two boryl units of diboron compounds in an unsaturated carbon-carbon bond is an efficient synthetic route towards organoboron compounds. The first transition metals used in the catalytic diboration reaction of alkynes and alkenes using tetraalkoxydiboranes were Pt and Rh.[3–8] In this cases the diboron reagent was oxidatively added to the metal center generating diboryl-metal species.[9] Reaction of these B-M-B species with unsaturated compounds provided monoborated or/and diborated products depending on the nature of the metal and the substrate. Monophosphine platinum-containing catalyst mediated the selective diboration of alkynes providing 1,2-alkene(bisboronate)esters through the *syn* addition of the B-B bond.[5,10,11] However, the related catalytic alkene diboration seems to be not selective due to the *β*-hydride elimination side reaction (Scheme 8.2).[4]



Scheme 8.2 Metal catalyzed addition of diboron reagents to unsaturated C-C bonds: a) phenylacetylene diboration; b) styrene diboration, showing the different products that can be formed

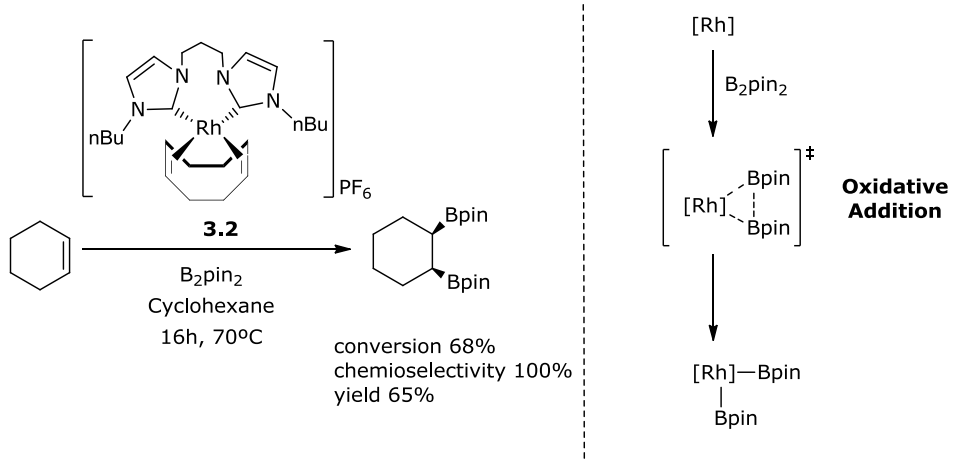
With the aim of selective formation of the 1,2-diborated product, we have developed an efficient methodology for the selective catalytic diboration reaction of hindered cyclic alkenes based on Pd complexes modified with N-heterocyclic carbenes as ligands. High conversions to the desired 1,2-diborated product were obtained even at room temperature after relatively short reaction times (16h) with B_2cat_2 (Scheme 8.3). Also, based on previous theoretical and experimental work, we have suggested a plausible mechanism in which the presence of a base seems to be crucial in assisting the heterolytic cleavage of the diboron *via* the σ-bond metathesis (Scheme 8.3).



Scheme 8.3 Example of Pd(II)-NHC and Pt(II)-NHC catalyzed the diboration of cyclohexene with B_2cat_2 and its activation mode

In this context, we also focused our efforts on exploring the catalytic activity of rhodium complexes modified with N-heterocyclic carbenes (NHC), towards the borylation of cyclic olefins in the presence of B_2pin_2.

After screening different Rh(I) catalysts and solvents, we found that Rh(I)-NHC complex **3.2** performed selectively the diboration reaction in non polar solvents, such as cyclohexane, with a series of endocyclic olefins (Scheme 8.4). In this case, the activation of B_2pin_2 occurs *via* homolytic cleavage of the B-B bond.



Scheme 8.4 Rhodium complexes modified with NHC ligands catalyzed the borylation of cyclohexene, as a model substrate, with B_2pin_2. Representative scheme of the activation of B_2pin_2

In view of the lack of detailed studies concerning the mechanism of rhodium-mediated borylation of cyclic alkenes, we became interested to know in more detail about the mechanism of the Rh(I)-NHC mediated boron addition reaction. Based on our theoretical results, the *β*-H-elimination pathway seems to be more energetically demanding than the reductive elimination step.

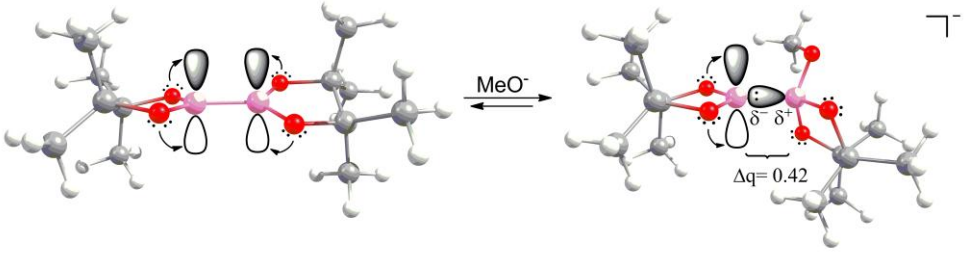
There are no great energetic differences between the two reaction pathways, thus subtle changes in the solvent and in the ligands can switch reactivity. Indeed, polarity and coordination ability of the solvent are key factors to explain the differences observed in selectivity, but the nature of the bidentate ligand NHC is of crucial importance.

Apart from the metal mediated diboration reaction, we also focused on novel methodologies to activate tetraalkoxydiborons towards the addition to alkenes without the need of a transition metal.

The first metal free catalytic activation of tetraalokydiboron reagents was reported by Hoveyda et al in 2009.[12] An *in situ* formed neutral 1:1 NHC adduct of B_2pin_2 was proposed as the catalytically active species capable to be added to α,β-unsaturated compounds.[12,13]

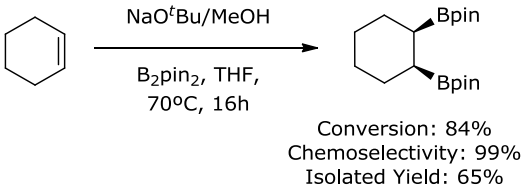
In this context and simultaneously with Hoveyda's first report,[12] some members of our group developed a new organocatalytic methodology based on the use of Brönsted base, methanol and phosphines.[14]

By means of NMR spectroscopy and DFT calculations, we have demonstrated that diboron reagent such as B_2pin_2, can be activated by the sole use of base and methanol as catalytic system. Upon an interaction of a base with methanol it generates alkoxides, which interact with the diboron reagent, forming a Lewis acid-base adduct. The nature of this resulting adduct has been studied in detail revealing a nucleophilic nature (Scheme 8.5).



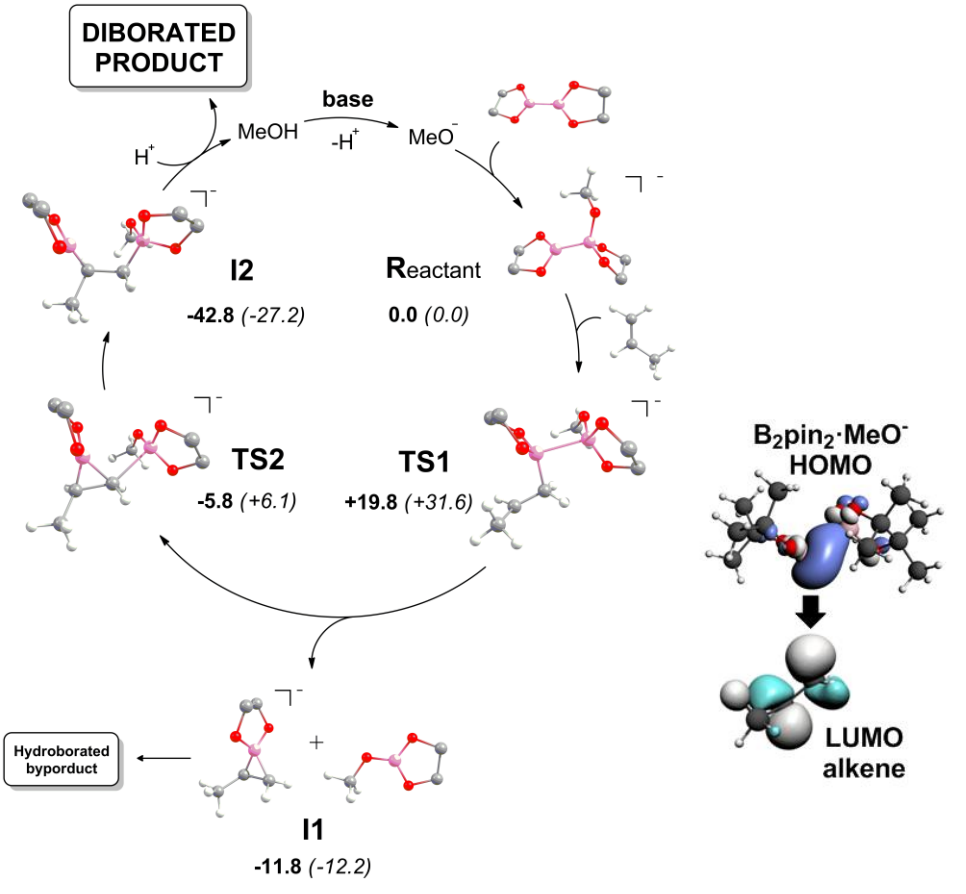
Scheme 8.5 Formation of the nucelophilic Lewis acid-base adduct and its polarization

More importantly, we have found that the adduct [B_2pin_2·MeO^-] is capable of adding the nucleophilic Bpin moiety to non-activated olefins. Surprisingly, in addition to the hydroborated product, the diborated one was also observed with styrene as substrate. Even more surprisingly, when simple and non-activated olefins were tested, complete and selective formation of the 1,2-diborated product was observed (Scheme 8.6). In contrast with the usual metal mediated diboration reaction, the organocatalytic approach is easy, selective and cheap, and could be extended to the most common non-activated alkenes.



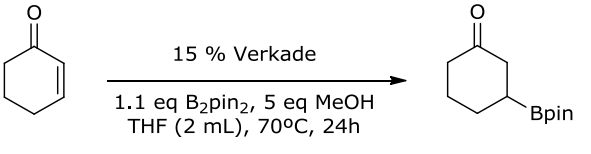
Scheme 8.6 General scheme for the organocatalytic diboration reaction of cyclohexene as an example

According to our DFT calculations, two transition states could explain the formation of the diborated product and the hydroborated byproduct. Hence the reaction between the reaction partners seems to start by the nucleophilic attack of the B(sp^2) moiety to the less hindered carbon of the olefin providing the first transition state (TS1, Scheme 8.7). Upon the nucleophilic attack, while the B(sp^2)-C_1 bond is being formed, the B-B bond is weaking, and the electron density is increasing on C_2. Nucleophilic attack from C_2 towards the Bpin moiety can conduct to the formation of I1 and TS2 (Scheme 8.7). If the electronic and steric effects stabilize the C_1-B(sp)^2 interaction, the I1 is formed towards the hydroborated byproduct. On the other hand, if C_1 attacks to the Bpin(OMe) moiety, TS2 will be formed towards the formation of the diborated product (Scheme 8.7).



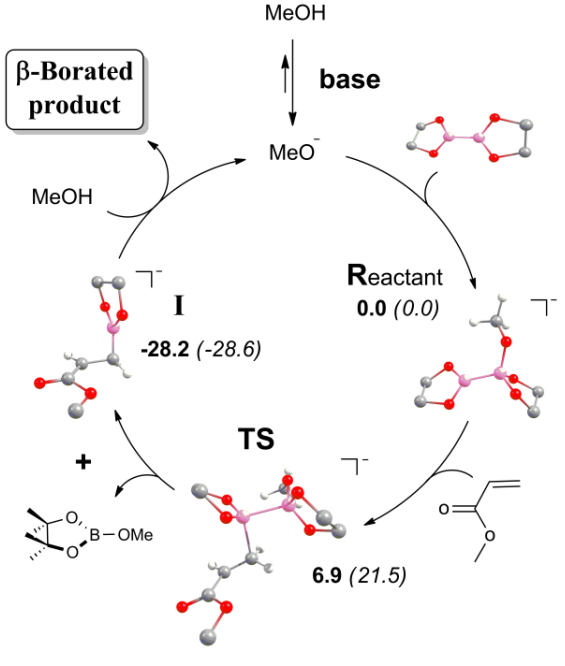
Scheme 8.7 Suggested catalytic cycle. Electronic energy (kcal.mol^{-1}) and Gibbs free energy (kcal.mol^{-1}; in parenthesis) computed at the M06 level, relative to B_2pin_2.MeO$^-$ adduct plus propylene. And illustration of the frontier orbitals in TS1

Also, application of this novel Brönsted base/MeOH methodology allowed the β-boration of a wide range of α,β-unsaturated compounds. The superiority of the "classic" Verkade superbase as mediator of the reaction is also pointed out (Scheme 8.8).



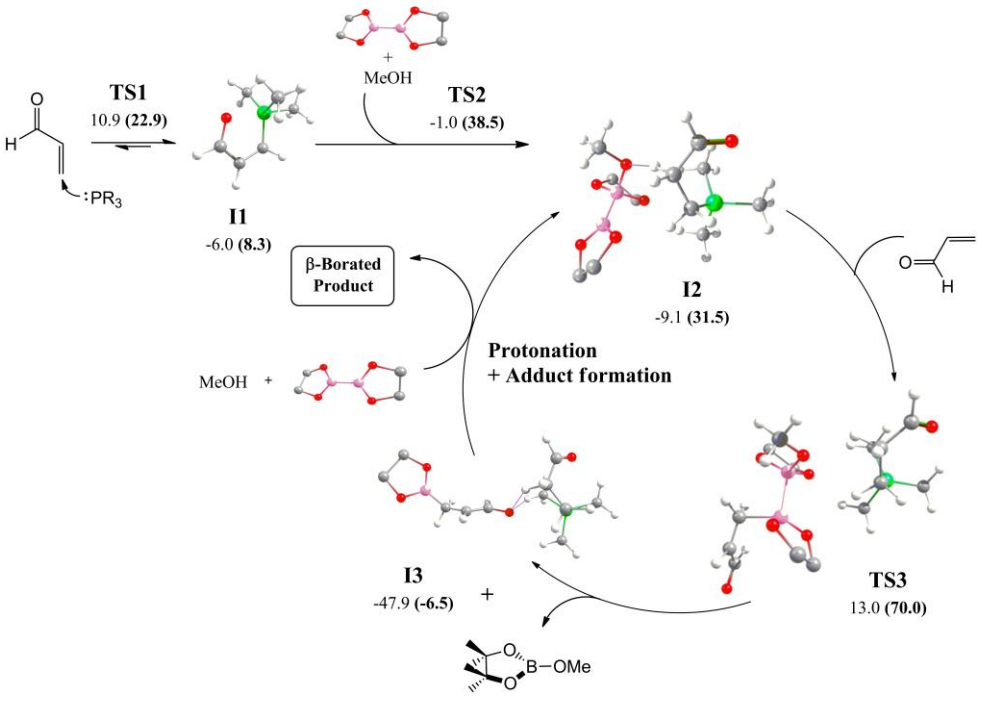
Scheme 8.8 An example of the Bönsted Base/MeOH β-boration reaction

The suggested mechanism for the base-mediated *β*-boration of activated olefin is depicted in Scheme 8.9. The methoxide ion, generated from MeOH in the presence of base, forms a Lewis acid-base adduct with the diboron reagent, which we chose as the origin of energies. In the next step, a transition state (TS) was fully characterized, and it corresponds to the nucleophilic attack of the sp^2 boron reagent at the non-substituted carbon C1 of the alkene. This TS1 leads directly to the formation of an anionic intermediate I which after protonation by methanol generate the desired *β*-borated product and another molecule of methoxide (Scheme 8.9).



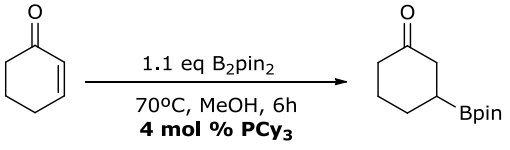
Scheme 8.9 Reaction pathway. Electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level, relative to $B_2pin_2 \cdot MeO^-$ adduct plus methyl acrylate. Methyl groups of the pinacol moieties are omitted for clarity. All values in $kcal.mol^{-1}$

Aimed at unravelling the role of the phosphine, we performed NMR studies and DFT calculations, and we found that the phosphine directly attacks the most electrophilic carbon of the *α,β*-unsaturated carbonyl compound resulting in the formation of a strongly basic zwiterionic phosphonium enolate species. This basic sepecies is further protonated by the excess of MeOH and particularly favoured by the presence of bis(pinacolato)diboron that stabilizes the MeO^- anion, thus forming the Lewis acid-base $[B_2pin_2 \cdot MeO]^-$adduct (Scheme 8.10).



Scheme 8.10 Suggested catalytic cycle for the new base-free organocatalytic *β*-boration reaction. Electronic energy (kcal.mol^{-1}) and Gibbs free energy (kcal.mol^{-1}; in parenthesis) computed at BP86 level relative to two molecules of acryladehyde, MeOH, B_2pin_2 plus PMe_3. Methyl groups of the B_2pin_2 are omitted for clarity

Importantly, novel reaction conditions for the organocatalytic *β*-boration reaction of *α,β*-unsaturated carbonyl compounds using only phosphine and alcohol were obtained here for the first time. No Brönsted base was required to promote the *β*-boration in such conditions (Scheme 8.11).



Scheme 8.11 Example of the organocatalytic *β*-boration reaction with Phosphine/MeOH as catalytic system

Also a certain degree of *ee* was achieved when chiral phosphines were used.

The interest of this organocatalytic transformation is justified by the simplicity of the methodology. The results presented here give a turn of nut since *β*-boration can be performed even selectively by the unique presence of catalytic amounts of phosphine in MeOH. The simplicity of the system and the understanding of the role of the phosphine open now an unlimited palette of possibilities.

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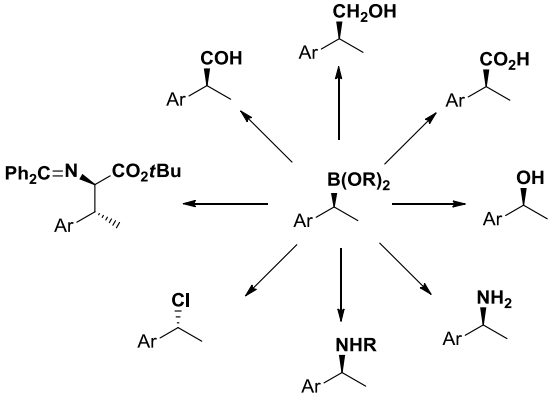
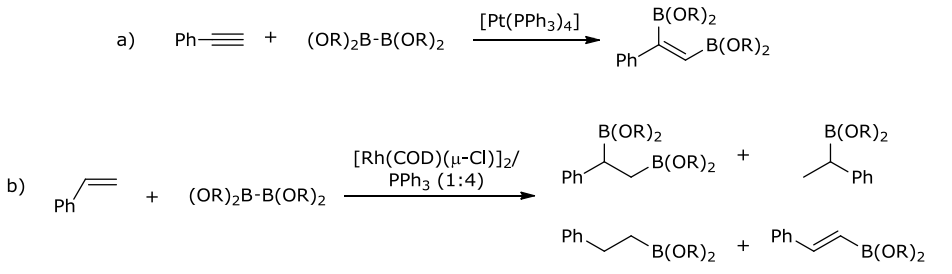
Els compostos organoborats són potencialment utilitzats en un extens nombre de camps, des de la medicina, en la teràpia de captura neutrònica amb bor o altres molècules amb activitat biològica, fins a l'ús de molècules funcionals com els polímers. A més a més, els compostos organoborats són curcials com a intermedis de síntesis per a productes d'alt valor afegit (Esquema 1.8).[1,2]



Esquema 1.8 Derivatitzacions generals de l'enllaç C-B.

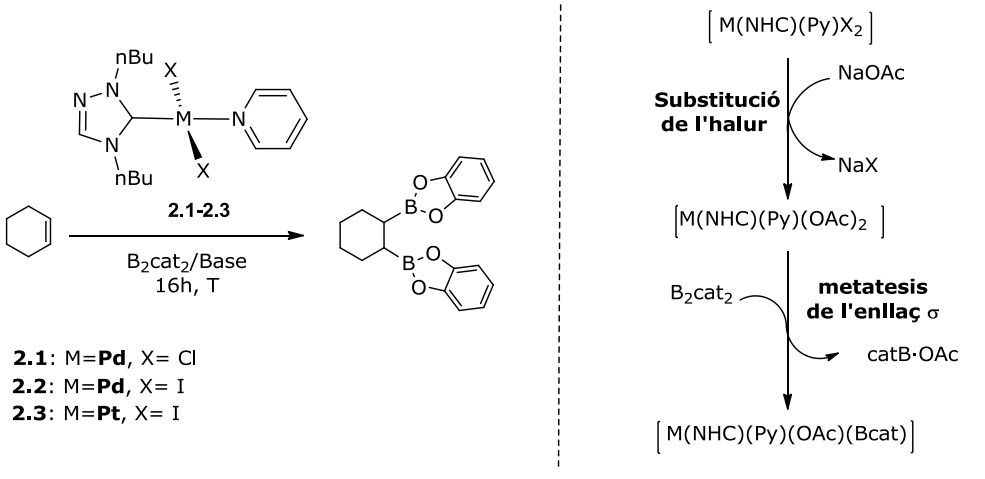
El tema principal d'aquesta tesi és el desenvolupament de noves metodologies sintètiques per a l'obtenció de compostos organoborats de manera eficient. Ens hem centrat en entendre els diferents modes d'activació d'agents diborans i el mecanisme dels processos d'addició de diborans a alquens. Amb aquest propòsit, en aquesta tesi s'han dut a terme estudis d'RMN juntament amb càlculs teòrics basats en la teoria del funcional de la densitat (DFT).

La introducció simultània de dos grups boryl a enllaços carboni-carboni insaturats és una ruta sintètica d'organoborans molt eficient. Pt i Rh varen ser els primers metalls de transició usats en la diboració catalítica d'alquins i alquens amb tetraalcoxidiborans.[3–8] En aquests casos, l'activació de l'agent diborà ocorre homolíticament a través de l'addició oxidant al metall de transició generant l'espècie diboril-metall.[9] La reacció d'aquestes especies B-M-B amb compostos insaturats produeix productes mono i/o diborats depenent de la naturalesa del metall i del substrat. Els catalitzadors de platí modificats amb monofosfines donen la reacció de diboració d'alquins selectivament a través de l'addició syn de l'enllaç B-B.[5,10,11] No obstant això, la corresponent diboració catalítica amb alquens no és tan selectiva com a conseqüència de la reacció competitiva de la β-H-eliminació (Esquema 8.2).[4]



Esquema 8.2 Addició catalítica d'agents diborans a enllaços C-C insaturats. a) diboració del fenilacetilè amb un complexe de platí; b) diboració de l'estirè amb rodi amb els productes que poden ser formats.

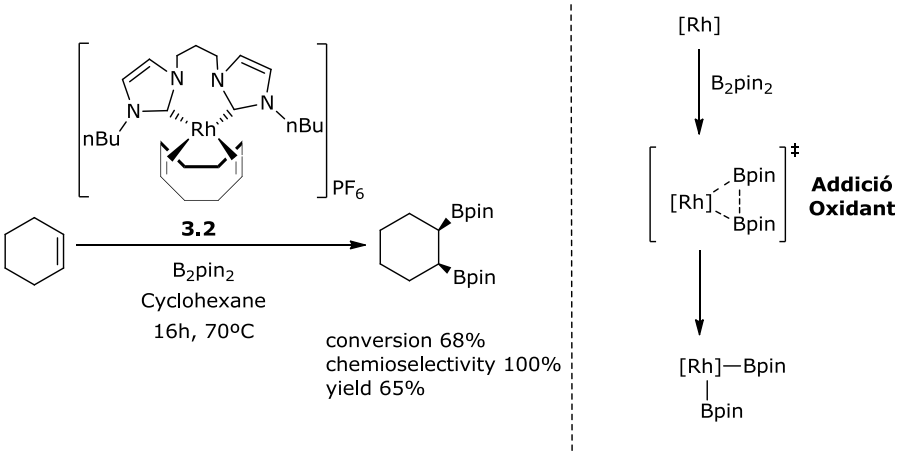
Amb l'obejctiu de la formació selectiva del producte 1,2-diborate, nosaltres hem desenvolupat una metodologia eficient per a la diboració selectiva d'olefines endocícliques basada en complexos de pal.ladi modificats amb carbens N-heterocíclics juntament amb lligands piridina. Amb aquest sistema catalític es varen obtenir conversions elevades del producte diborat desitjat inclús a temperatura ambient en temps de reacció curts (16h) amb l'agent diborà B_2cat_2 (Esquema. 8.3). Basats en estudis experimentals i computacionals, també hem proposat un mecanisme verosímil en el qual la presència d'una base sembla ser crucial per a l'activació de l'agent diborà *via* heterolítica a través de la metàtesis de l'enllaç σ (Esquema 8.3).



Esquema 8.3 Example de la diboració catalítica i selectiva del ciclohexè amb complexos de Pd i Pt modificats amb lligands carbens N-heterocíclics. També s'especifica com s'activa el B_2cat_2

En aquest context, també ens hem centrat en explorar l'activitat catalítica de complexos de rodi modificats amb carbens N-heterocíclics (NHC), en la boril.lació d'olefines endocícliques en presència de l'agent diborà B_2pin_2.

Després d'haver provat diferents catalitzadors de Rh(I) i varis dissolvents, vam observar que el complex **3.2**, (NHC)Rh(I), permetia la diboració selectiva d'olefines endocícliques en dissolvents no polars, com el ciclohexà (Esquema 8.4). En aquest cas, l'activació de l'agent diborà B_2pin_2, procedeix homolíticament a través de l'addició oxidant.



Esquema 8.4 Esquema de la diboració catalítica del ciclohexè amb el complex de rodi (I) modificat amb lligands carbens N-heterocíclics (**3.2**). També es mostra un esquema general de l'activació de l'agent diborà B_2pin_2

Considerant que no hi ha estudis detallats sobre el mecanisme de la boril.lació amb complexos de rodi, nosaltres vam dur a terme un estudi teòric amb el catalitzador **3.2.** Segons els nostres càlculs teòrics, el camí de la reacció competitva de la *β*-H-eliminació és energeticament més costosa que l' eliminació reductora. Per tant, el producte diborat està afavorit amb aquest sistema, tal i com es veu experimentalment.

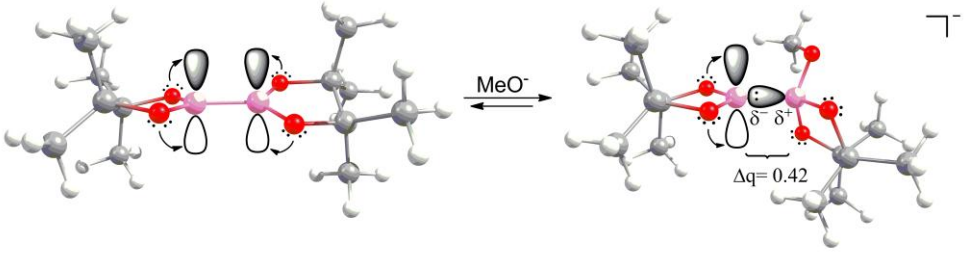
Tot i així, vam trobar que les diferències energètiques entre els dos camins de reacció no eren molt grans, per tant, el canvi de solvent i lligands podrien exercir un canvi en la reactivitat del sistema. L'habilitat per a coordinar del solvent és un factor determninant de la quimioselectivitat del sistema, però la naturalesa del lligand NHC és també molt important.

A part dels sistemes de diboració basats en metall, també ens hem centrat en l'obtenció de noves metodologies sense l'ús de metalls de transició per a activar els agents diborans i aplicar-los en l'addició a alquens.

La primera activació organocatalítica dels tetraalcoxidiborans va ser presentada pel grup de Hoveyda l'any 2009.[12] Es proposà que l'activació del B_2pin_2 ocorre per interacció amb carbens NHC per donar l'adducte neutre B_2pin_2·NHC. Aquest era capaç d'addicionar-se a compostos α,β-insaturats.[12,13]

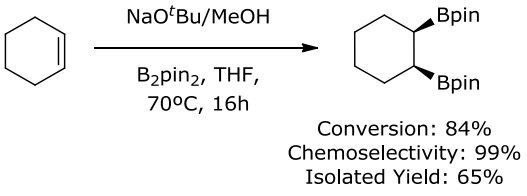
Simultàniament al treball del Hoveyda,[12] el nostre gurp va desenvolupar una nova metodologia organocatalítica basada en l'ús d'una base de Brönsted, metanol i fosfines.[14]

Els estudis d' RMN i els càlculs teòrics van permetre concloure que la barreja de solament la base i l'alcohol permet la formació de l'alcòxid i aquest és capaç d'interaccionar amb el diborà, formant un adducte àcid-base de Lewis i polaritzar així l'enllaç B-B (Esquema 8.5).



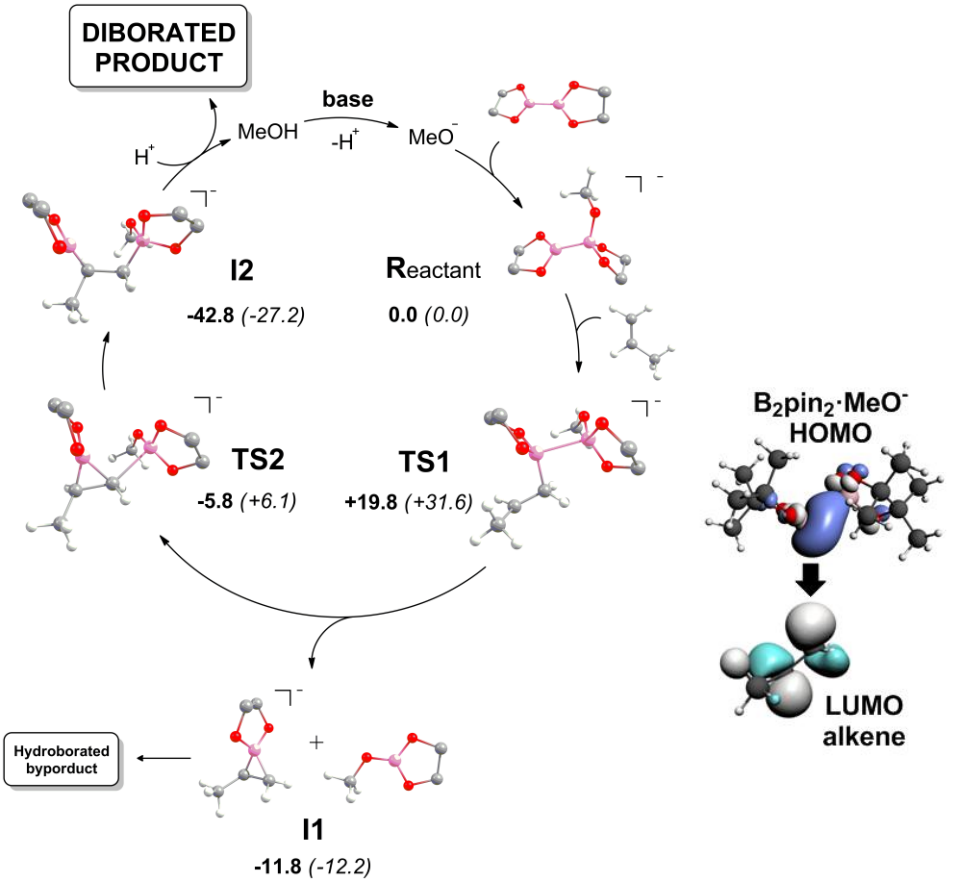
Esquema 8.5 Formació de l'adducte àcid-base de Lewis i la seva polarització d'enllaç

Sorprenentment, vam torbar que aquest adducte [B_2pin_2·MeO^-] pot transmetre el Bpin nucleofílic a les olefines no activades. Diferents substrats no activats van ser diborats de forma selectiva amb el sistema base de Brönsted/MeOH (Esquema 8.6). A diferència de la reacció de diboració mitjançant els metalls de transició, l'enfocament organocatalític és simple, selectiu, econòmic i pot ser estès a alquens més comuns i simples.



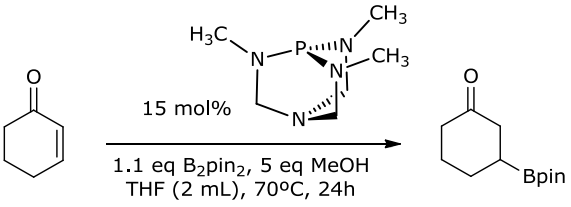
Esquema 8.6. Esquema general de les condicions de diboració organocatalítiques del cyclohexè com a substrat model

Des del punt de vista mecanístic, dos estats de transició poden explicar la formació del producte de diboració i del subproducte d'hidroboració. La reactivitat entre els reactius sembla que comença amb un atac del boril sp^2 de l'adducte sobre el carboni menys impedit del doble enllaç, donant el primer estat de transició (TS1). Després d'això, l'alta densitat electrònica concentrada en el carboni intern permet un atac nucleòfil d'aquest al boril més proper. Immediatament després, el C1 del substrat realitza un atac nucleòfil sobre el metoxi-boryl electrofílic, donant el segon estat de transició (TS2) que acaba donant el producte de diboració. Si, els efectes electrònics o estèrics fan que el TS1 s'estabilitzi, s'afavoreix l'aparició de l'intermedi 1 (I1) que acaba donant el subproducte de diboració (Esquema 8.7).



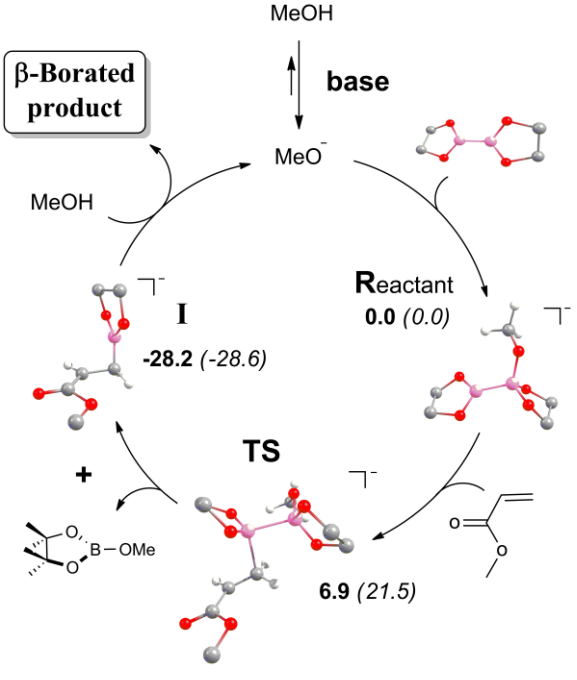
Esquema 8.7 Cicle catalític suggerit per a la diboració organocatalítcia amb l'ús de base de Brönsted i metanol. També es mostra l'energia relativa (kcal.mol^{-1}) dels intermedis i dels estats de transició involucrats. També s'inclou una il.lustració dels orbinatls HOMO i LUMO del TS1. Els metils del B_2pin_2 han estat omesos

Amb aquest nou sistema, varem β-borar un ampli ventall de substrats α,β-insaturats sent la superbase Verkade la que reportà millors resultats (Esquema 8.8)



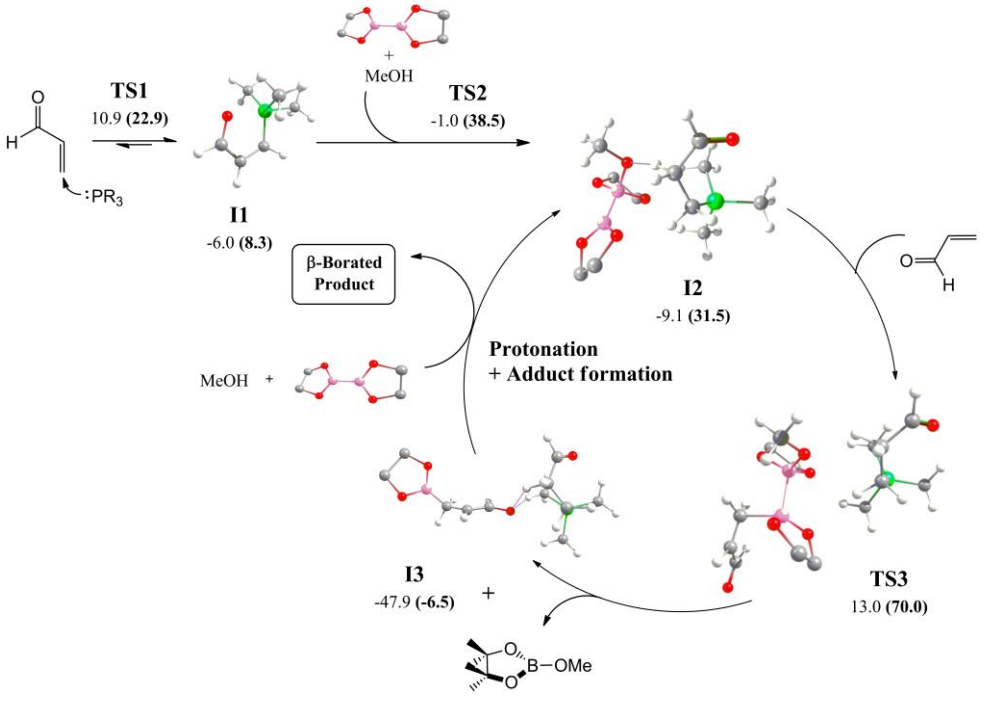
Esquema 8.8 Exemple de les condicions de reacció per a la *β*-boració organocatalítica d'una cetona cíclica amb el sistema Verkade's base/MeOH

Els càlculs teòrics van elucidar el cicle catalític i van concloure que l'espècie sp^2 de l'adducte $B_2pin_2 \cdot MeO^-$ té un caràcter nucleòfil i pot atacar l'olefina activada per a formar el producte de *β*-boració (Esquema 8.9).



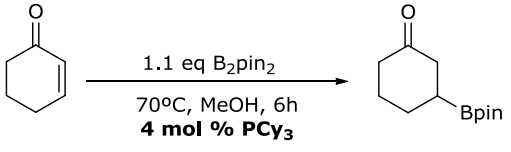
Esquema 8.9 Camí de reacció per a la *β*-boració organocatalitica basada en base de Brönsted i MeOH amb l'energia relativa per als intermedis i TS implicats (energia electronica i energia lliure de Gibbs (parentesis) estan expressades en $kcal.mol^{-1}$.Els grups metil del B_2pin_2 han estat omesos

Seguint en el context de la *β*-boració, a través d'estudis teòrics i d'RMN vam posar de manifest el paper de la fosfina en aquest sistema organocatalític. La fosfina pot addicionar-se directament al carboni més electrofílic del substrat *α,β*-insaturat donant com a resultaten la formació d'una espècie zwitteriònica amb un fort caràter nucleofílic. Aquesta espècie és capaç de desprotonar el metanol per a generar anions metòxid que interaccionen amb el B_2pin_2 present en el medi donant pas a la formació de l'espècie activa l'adducte àcid-base de Lewis [B_2pin_2·MeO^-] (Esquema 8.10).



Esquema 8.10 Cicle catalític suggerit per a la nova metodologia organocatalítica per a la *β*-boració basada en l'ús de fosfina i metanol. També es mostra l'energia relativa (kcal.mol^{-1}) dels intermedis i estats de transició involucrats en el sistema. Els metils del B_2pin_2 han estat omesos

Basats en aquest nou descobriment, vam desenvolupar una nova metodologia organocatalítica per a la β-boració basada en l'ús de fosfina i metanol que permeté la boril.lació d'un ampli ventall de substrats α,β-insaturats (Esquema 8.11).



Esquema 8.11 Exemple de β-boració amb el sistema Phosphine/MeOH com a sistema catalític

Finalment, l'última troballa d'aquesta tesi fou que la enantiodiferenciació fou possible amb l'ús de quantitats catalítiques de phosphines quirals. Tot i que es tracta d'un treball molt preliminar, valors d'enantioselectivitat s'ha pogut arribar ja a valors d'enantioselectivitat del 78%.

La simplicitat d'aquest sistema i saber el paper de la fosfina obra una nova perspectiva en la β-boració d'olefines en la versió aquiral.

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(13) Lee, K.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc. Additions & Corrections* **2010**, *132*, 12766–12766.
(14) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130–5134.

Chapter 9: Appendix

9.1 Publications within this thesis

"Essential role of phosphines in organocatalytic *β*-boration reaction"; Cristina Pubill-Ulldemolins, Amadeu Bonet, Carles Bo, Henrik Gulyás, Elena Fernández, *Org. Biomol. Chem., accepted*

"Rhodium-NHC complexes mediate diboration versus dehydrogenative borylation of cyclic olefins: a theoretical explanation"; Cristina Pubill-Ulldemolins, Macarena Poyatos, Carles Bo, Elena Fernández, *Dalton Transactions,* accepted

"**Nucleophilic boron strikes back"**; Henrik Gulyás, Amadeu Bonet, Cristina Pubill-Ulldemolins, Cristina Solé, Jessica Cid, and Elena Fernández**,** *Pure Appl. Chem*., ASAP Article

"Activation of Diboron Reagents with Brønsted Bases and Alcohols: An Experimental and Theoretical Perspective of the Organocatalytic Boron Conjugate Addition Reaction" ; Cristina Pubill-Ulldemolins, Amadeu Bonet, Carles Bo, Henrik Gulyás, Elena Fernández, *Chem. Eur. J.,* **2012**, 18, 1121

"Transition-Metal-Free Diboration Reaction by Activation of Diborons with Simple Lewis Bases" ; Amadeu Bonet, Cristina Pubill-Ulldemolins, Carles Bo, Henrik Gulyás, Elena Fernández, *Angew. Chem. Int. Ed*., **2011**, 50, 7158 **(VIP)**

"A new context for palladium mediated B-addition reaction: an open door to consecutive functionalization" ; Cristina Pubill-Ulldemolins, Amadeu Bonet, Carles Bo, Henrik Gulyás, Elena Fernandez, *Org. Biomol. Chem.,* **2010**, 8(12), 2667

"Perceptible Influence of Pd and Pt Heterocyclic Carbene-Pyridyl Complexes in Catalytic Diboration of Cyclic Alkenes" ; Cristina Pubill-Ulldemolins, Carles Bo, Jose A. Mata, Elena Fernandez, *Chem. Asian J.*, **2010**, 5, 261

9.2 Presentations and posters

Oral Communications

"Unravelling the mechanism of metal-free catalytic *β*-borations"
Cristina Pubill-Ulldemolins, Carles Bo, Elena Fernández
Nobel Campus, Chemistry for life, Port Aventura, 01-03/07/12

"Unraveling the mechanism of unprecedented metal-free catalytic borations"
Cristina Pubill-Ulldemolins, Carles Bo, Elena Fernández
ICIQ Young seminar, ICIQ, 16/12/2011

"Catalytic diboration of endocyclic alkenes: mechanistic insights" (*flash-poster presentation*)
Cristina Pubill-Ulldemolins, Carles Bo, Jose A. Mata, Elena Fernández
Euroboron V, Edinburgh, 29/08-02/09/2010

"Influència dels lligands carbens N-heterocíclics en l'adició catalítica de borans a olefines cícliques"
Cristina Pubill-Ulldemolins, Carles Bo, Jose A. Mata, Elena Fernández
Sisena trobada de Joves Investigadors dels Països Catalans, València, 1-2/02/2010

Posters

"On the Mechanism of PR_3-Assisted Organocatalytic *β*-Boration reaction: Origin of the enantioinduction "
Cristina Pubill-Ulldemolins, Amadeu Bonet, Henrik Gulyás, Elena Fernández, Carles Bo
18th International Symposium in Homogeneous Catalysis, Tolouse, França, 9-13/07/12

"On the Mechanism of PR_3-Assisted Organocatalytic *β*-Boration reaction: Origin of the enantioinduction "
Cristina Pubill-Ulldemolins, Amadeu Bonet, Henrik Gulyás, Elena Fernández, Carles Bo
Nobel Campus, Chemistry for life, Port Aventura, 01-03/07/12

"Transition metal-free *β*-boration: the role of the base"
Cristina Pubill-Ulldemolins, Amadeu Bonet, Carles Bo, Henrik Gulyás, Elena Fernández
IME Boron conference, Niagara Falls, 11-15/09/2011
Poster prize *in the XXXIII Reunión Bienal de la Real Sociedad Española de Química, 25-28/211*

"Catalytic diboration of endocyclic alkenes: mechanistic insights"
Cristina Pubill-Ulldemolins, Carles Bo, Jose A. Mata, Elena Fernández
17th International Symposium on Homogeneous Catalysis, Poland, 9-11/07/2010

"Diboración catalítica de alquenos endocíclicos: estudio mecanístico"
Cristina Pubill-Ulldemolins, Carles Bo, Jose A. Mata, Elena Fernández
XXVII Reunión el Grupo especializado en Química Organometálica, Huelva, 7-10/09/2010

"Catalytic Borylation of vinylic C-H bonds as a matter of regioselectivity"
Cristina Pubill-Ulldemolins, Macarena Poyatos, Carles Bo, Elena Fernández
Organometallic Chemistry directed towards Organic Synthesis (OMCOS), Glasgow, UK, 26-3/07/2009

9.3 Research Abroad

- Hydroboration of non activated olefins, Queen's University, Canada, Ontario, 05-10/2011
  Prof. Cathleen Crudden's group
  Manuscript in preparation

- Borylative cyclization of isocyanates with diboron reagents, Durham University, UK , 07-09/2009
  Prof. Todd Marder's group