Universitat Rovira i Virgil

NUCLEOPHILIC VERSUS ELECTROPHILIC BORYL MOIETIES: ACTIVATION AND APPLICATION IN CATALYSIS

Jessica Cid Torta

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Jessica Cid Torta

Nucleophilic *versus* electrophilic boryl moieties: Activation and application in catalysis

PhD Thesis

Supervised by Dra.Maria Elena Fernández Gutiérrez and Dr. Jorge J. Carbó Martín

Departament de Química Física i Inorgànica

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UNIVERSITAT
ROVIRA I VIRGILI

Departament de Química Física i Inorgànica

Dra. Maria Elena Fernández, professora titular del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i Dr. Jorge J. Carbó, professor agregat del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili,

FEM CONSTAR que la present memòria, titulada:

“Nucleophilic *versus* electrophilic boryl moieties: Activation and application in catalysis”

ha estat realitzada sota la nostra direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili per Jessica Cid Torta per a l’obtenció del títol de Doctor i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, 20 de desembre de 2013

Els directors de la tesis doctoral

Dra. Maria Elena Fernández Dr. Jorge J. Carbó

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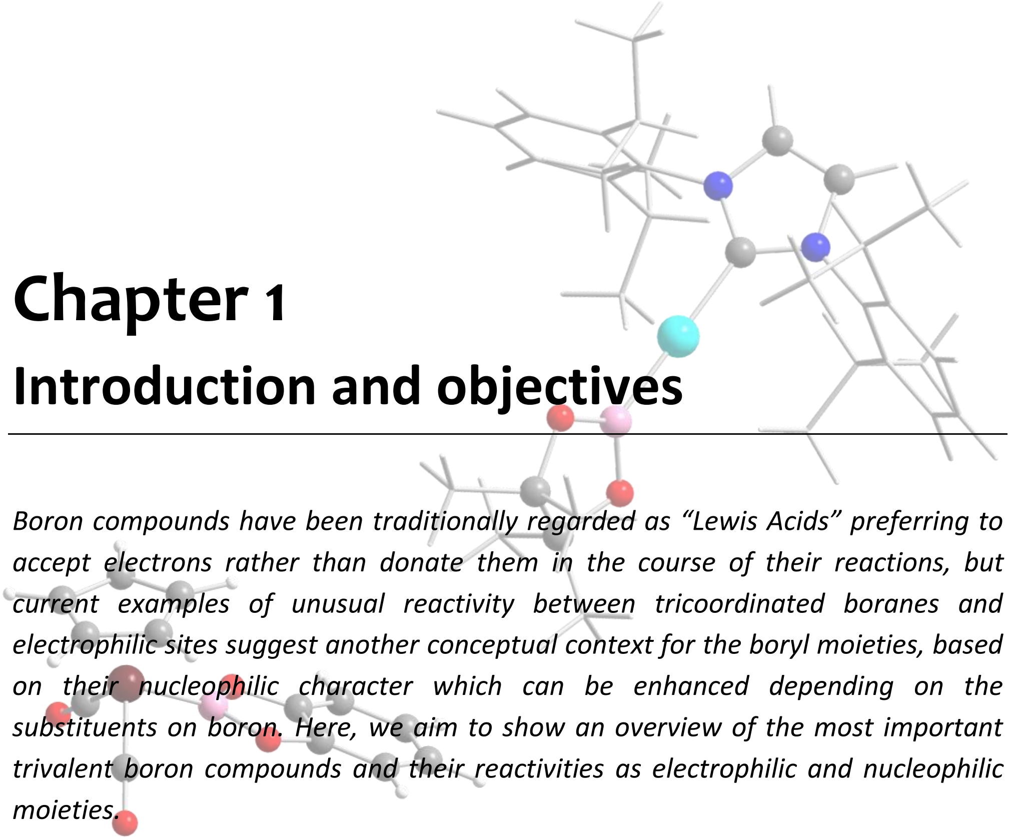
Chapter 1

Introduction and objectives

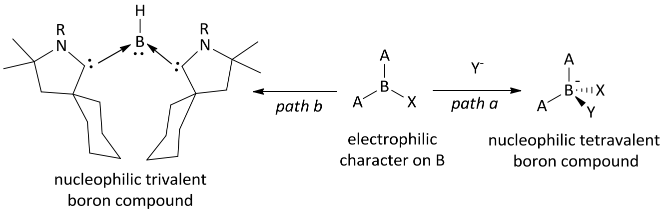


Boron compounds have been traditionally regarded as "Lewis Acids" preferring to accept electrons rather than donate them in the course of their reactions, but current examples of unusual reactivity between tricoordinated boranes and electrophilic sites suggest another conceptual context for the boryl moieties, based on their nucleophilic character which can be enhanced depending on the substituents on boron. Here, we aim to show an overview of the most important trivalent boron compounds and their reactivities as electrophilic and nucleophilic moieties.

1.1. Tunable reactivity of boryl moieties

Most trivalent boron reagents are electrophiles, due to the vacancy for two electrons to fill the outer orbital of boron, and their reactivity relies on an electron deficient boryl fragment that interacts with electron rich organic molecules. An additional bond to trivalent boron reagents generates anionic tetravalent boron compounds that might behave as nucleophiles (Scheme 1.1, path a). But it is also interesting when trivalent boron compounds switch their electrophilic character to nucleophilic character upon changing only the nature of the substituents on boron.

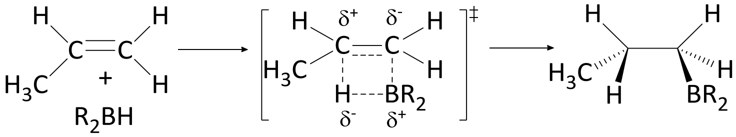
To focus the discussion it is important to note that subtle changes on the boron substituents can promote a tremendous impact on the boron electronic properties. This is the case of the new neutral tricoordinate organoboron generated by replacement of two substituents that donate only one electron for two substituents that each gives two electrons to boron. This unprecedented neutral tricoordinate boron derivative has recently been synthesised by Bertrand and co-workers.[1] The picture shows eight electrons around the boron, with a lone pair available for reacting (Scheme 1.1, path b). Although such boron compounds could be expected to be very unstable, the nature of the new substituents (cyclic(alkyl)(amino)-carbenes) ensured a perfect balance of electron donation and withdrawal that sufficiently stabilised the electron-rich boron centre. Although nucleophilicity was limited by the steric demand of the boron substituents, when the borane reacted with an equimolar amount of trifluoromethane sulfonic acid, the conjugate acid was obtained in quantitative yield. It could be considered the first example of such a tunable reactivity on boron tricoordinate compounds, but in fact this is one of the latest example of nucleophilic trivalent boron compounds. We became interested in exploring in this thesis the most important electronic and structural properties of the borane reagents and exemplify their reactivity towards different nucleophiles and electrophiles.



Scheme 1.1 Singular approaches to tetravalent and trivalent nucleophilic boron centers.

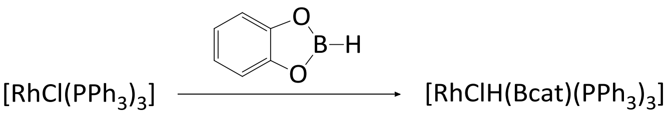
1.2. Reactivity of trivalent boron electrophiles

The history of the trivalent boron compounds started when Brown and co-workers developed the first hydroboration of alkenes using HBR_2 as a boron source.[2] This reaction is characterized by a high anti-Markovnikov regioselectivity and a pronounced chemoselectivity, that is, the reaction occurs preferentially at C=O rather than C=C bonds, with addition of the boron atom to the oxygen atom. The formation of the anti-Markovnikov products requires the approach of a formal hydride to the most substituted carbon atom of the organic substrate, since the latter stabilizes the partial positive charge occurring during the concerted transition state of this reaction (Scheme 1.2). Hence, this selectivity associated with the non-metal catalyzed hydroboration provides conclusive proof for a $B^{\delta+}$-$H^{\delta-}$ polarization of the boron-hydrogen bond in boranes and the electrophilic character of the boron center.



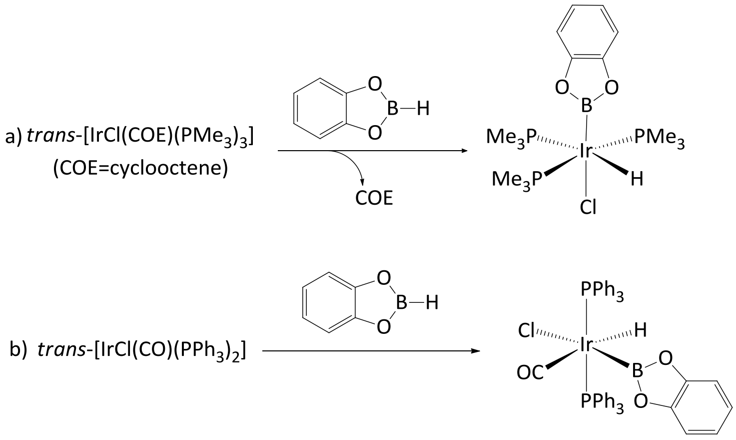
Scheme 1.2 Reported mechanism for the non-catalyzed hydroboration reaction.

When Kono and co-workers[3] demonstrated that catecholborane (HBcat) could be oxidatively added to Rh(I) in $[RhCl(PPh_3)_3]$ with the formation of the Rh (III) complex $[RhClH(Bcat)(PPh_3)_3]$ (Scheme 1.3), a new perspective was opened towards the activation of dialkoxyboranes by transition metal complexes. Since then, many metal-catalyzed reaction and complexes have been developed in order to take advantage of this electrophile character of B in M-$B(OR)_2$ fragments.[4]



Scheme 1.3 Reactivity of catecholborane with Rh complexes.

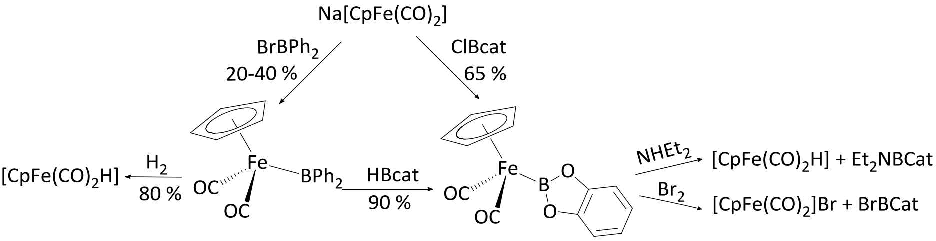
The synthesis of the analogous boryliridium complex [$IrClH(Bcat)(PMe_3)_3$], by the reaction of catecholborane and [$IrCl(COE)(PMe_3)_3$] (COE= cyclooctene), was reported by Merola and co-workers (Scheme 1.4a).[5] The iridium (III) complex showed a distorted octahedral geometry around the Ir (III) center, with a meridional arrangement of the PMe_3 ligands. A tendency towards the formation of dπ-pπ backbonding from metal to boron depended on the substituents bonded to the boron and the relative position of the boryl ligand in the metal complex. The presence of CO ligands has been reported to facilitate the oxidative addition of HBcat to the metal center. For instance, the saturated iridium boryl complex *trans*-[$IrClH(Bcat)(CO)(PPh_3)_2$] has been prepared in high yield by reaction of HBcat with Vaska's complex *trans*-[$IrCl(CO)(PPh_3)_2$] (Scheme 1.4b). This was the first example of a metal-carbonyl boryl complex characterized by crystal X-ray diffraction.



Scheme 1.4 Reactivity of Ir complexes with catecholborane.

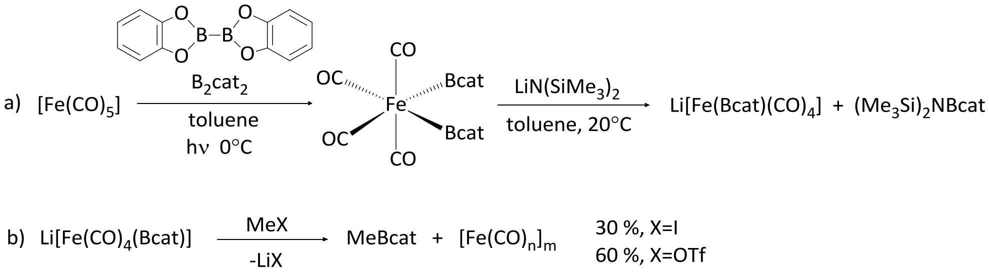
If we focus on the nature of the metal and the metal-boron bond, although the transition metals are often less electronegative that boron, detailed computational studies on boryl metal complexes have revealed that the metal-boron bond is polarized towards the metal ($Mt^{\delta-}-B^{\delta+}$, Mt=transition metals such as Fe, Rh, Os). The intrinsic nature of the Mt-BR_2 bond is described as a two-electron, two-center σ-bond, which can be additionally stabilized by a π donation from Mt to the BR_2. The boron atom may also become electronically stabilized by π-donation from the R substituents having a lone-pair to the vacant p orbital of boron.[6]

Starting from group 8, Hartwig and co-workers were the first to isolate boryl iron complexes,[6d] of molecular formula [Fe(Cp)(BR$_2$)(CO)$_2$] (R = OC$_6$H$_4$O or R = Ph). Detailed studies indicated that the π-donation from the metal to the boron in these compounds exists but is weak, resulting in a very reactive metal-boron linkage. The reactivity studies of these complexes are summarized in Scheme 1.5. They observed a rapid and quantitative reactivity of complex with amine N-H bonds to provide de [Fe(Cp)(CO)$_2$H][7] and the corresponding aminoborane. Also they described that [Fe(Cp)(BPh$_2$)(CO)$_2$] reacted with bromine to provide [Fe(Cp)(CO)$_2$Br] and bromocatecholborane. Complex [Fe(Cp)(BOC$_6$H$_4$O)(CO)$_2$] displayed a wider range of chemistry. It reacted with hydrogen (2 atm) over the course of 30 min at ambient temperature to provide [Fe(Cp)(CO)$_2$H] and catecholborane (1-10 equiv) complex 60-90 % yield, depending on the concentration of catecholborane.



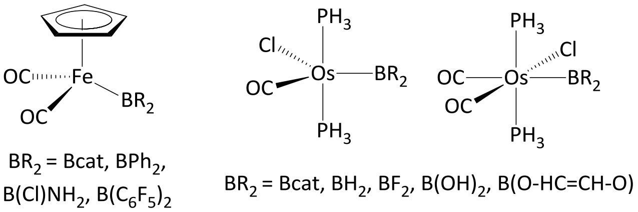
Scheme 1.5 Reactivity of the boryliron complexes reported by Hartwig and co-workers.

Hartwig and co-workers were also the first to report the synthesis of bis(boryl) iron complexes (Scheme 1.6, path a).[8] The synthesis consist of a photochemically induced oxidative addition of tetraaryloxydiboranes to [Fe(CO)$_5$], resulting a *cis*-bis(boryl) iron(II) complexes. The reactivity of the *cis*-bis(boryl) iron(II) with an aminolithium salt provided the ionic specie Li[Fe(Bcat)(CO)$_4$]. Interestingly, when the latter specie reacted with MeI and MeOTf generated methylcatecholborane in 30 % and 60 % respectively (Scheme 1.6, path b). The authors pointed out that it was unlikely that this reaction involved free catecholboryl anion and further studies of the reaction could not distinguish between one pathway in which the organic electrophile (Me) suffer a nucleophilic attack by the Bcat moiety or another pathway along which the metal center attacks the electrophilic Me group, and the resulting neutral alkyl boryl compound undergoes B-C bond-forming reductive elimination.[8]



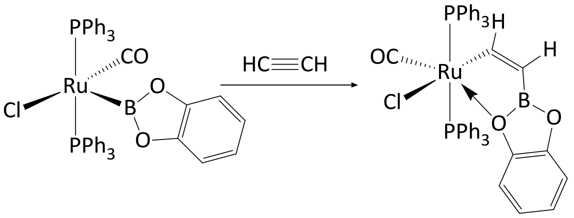
Scheme 1.6 Synthesis of neutral and ionic Fe-Bcat (cat=$O_2C_6H_4$) species.

Parallel studies on detailed DFT studies (to quantify the relative contribution to the metal boryl linkage from ionic and covalent interactions) on specific boryl complexes revealed that Fe-B[9] and Os-B bonds are polarized towards the metal (i.e. $M^{\delta-}$-$B^{\delta+}$).



Scheme 1.7 Some iron and osmium complexes studied by Aldridge and Frenking and co-workers, respectively.

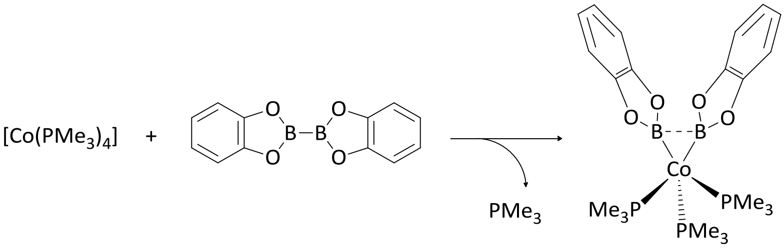
Another interesting M-B complexes are the borylruthenium species, which the polarization towards the Ru metal center has been established. Wright and co-workers reported the synthesis and characterization of the first example of a stable metalated vinyl boronate ester derived from the formal insertion of ethyne into the Ru-B bond of $[RuCl(Bcat)(CO)(PPh_3)_2]$ (Scheme 1.8).[10] Actually, it was the first example of formal insertion of an unsaturated molecule into a M-B bond. The geometry about the double bond of the vinylboronate ligand is Z with an oxygen of the catecholboryl group interacting weakly with the metal. The obtention of this product indicates that it is feasible that such a process could also occur in some metal-catalyzed hydroboration reactions of alkynes and, by inference, alkenes.



Scheme 1.8 Ru specie formed by a formal insertion of ethyne into the Ru-B bond.

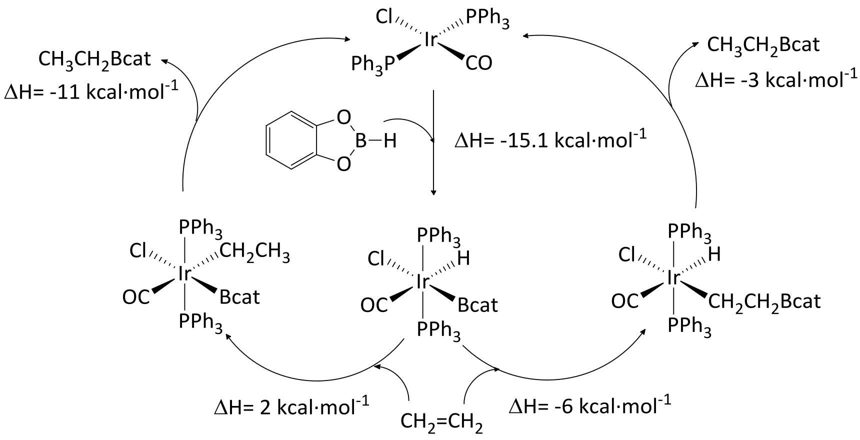
Sabo-Etienne and co-workers reported that in the ruthenium-catalyzed hydroboration of linear and cyclic alkenes, the nature of the olefin controls the selectivity of the reaction, obtaining in some cases the product of the dehydrogenative borylation instead of the hydroborated product.[11]

Moving to group 9, it can be found that borylcobalt compounds, formed through the activation of B_2cat_2 by oxidative addition to $[Co(PMe_3)_4]$, generating the formally Co(II) 17-electron complex $[Co(Bcat)_2(PMe_3)_3]$ where the B-B distance in the complex of only 0.507 Å longer than the B-B distance in B_2cat_2 (1.678(3)Å), suggested the possibility of some remaining B-B interaction (Scheme 1.9).[12]



Scheme 1.9 Co-mediated oxidative addition of bis(catecholato)diboron.

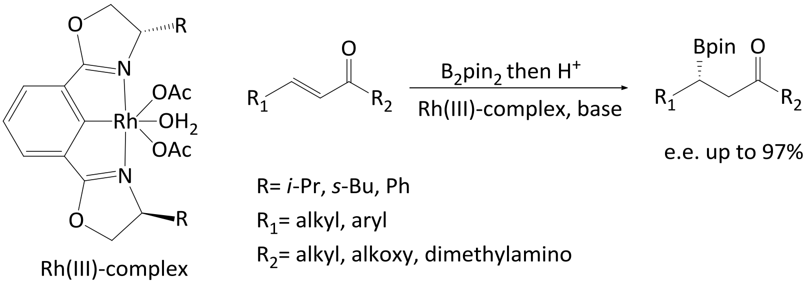
The electrophilic properties of the boryl moieties in the $M\text{-}BR_2$ fragments described above, were investigated in the mechanistic pathways of their catalytic performance. Mannig and Nöth reported the first hydroboration of olefins with $[RhCl(PPh_3)_3]$ and catecholborane as the boron source.[13] They proposed a mechanism which involves the oxidative addition of a B-H bond to the coordinatively unsaturated metal center, followed by alkene coordination, alkene insertion by hydride migration to the coordinated alkene and subsequent reductive elimination to form the B-C bond. Hartwig and co-workers determined computationally the strength of the metal-boron bond in various steps in the catalytic cycle of the corresponding iridium mediated hydroboration reaction (Scheme 1.10).[6e] Alkene insertion into the Ir-H bond is slightly less favorable thermodynamically than Ir-B bond. However, the similarity of the two ΔH values is consistent with the apparent competition between the two insertion processes and kinetic factors that might dominate the selectivity between these two catalytic pathways. Importantly, boron-carbon reductive elimination of the metal-alkyl species, after alkene insertion into the Ir-H bond is clearly exothermic.



Scheme 1.10 Catalytic cycle for iridium-mediated hydroboration of alkenes.

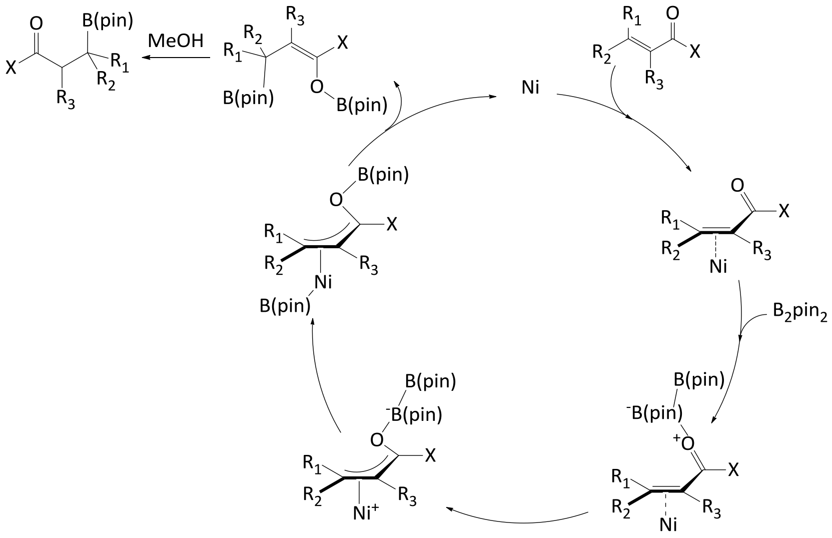
Kabalka and co-workers reported the first example of a rhodium catalyzed β-boration reaction.[14] The Wilkinson catalyst, $Rh(PPh_3)_3Cl$ successfully catalyzed the β-boration of cyclic and acyclic enones, α,β-unsaturated esters, aldehydes and nitrils. At 10 mol% catalyst loading, 80 °C, 10-14 hours of reaction time, the β-borated products could be isolated in 62-78 % yield. The authors suggested that the rhodium (I) catalyst activates the diboron reagent, B_2pin_2 and B_2neop_2 (neop= $OCH_2CMe_2CH_2O$), by oxidative addition, and that the primary products are formed by 1,4-addition of the reagents to the substrate. Due to the immediate aqueous work-up in their experimental procedure, the intermediates are not observed experimentally. Alternatively, Rh(III)-monoboryl complexes formed by σ-bond methatesis, can also be active catalysts for β-boration of α,β-unsaturated carbonyl compounds, as it has recently been suggested by Nishiyama and co-workers (Scheme 1.11).[15] Chiral Rh(III)-bisoxazoline acetate complexes catalyzed the 1,4-

conjugate addition of B_2pin_2 to α,β-unsaturated esters, ketones and an amide, providing enantioselectivities up to 97%. The addition of catalytic amount of base as co-catalyst substantially increased the catalytic activity, but, interestingly, the addition of alcohols was rather counterproductive, resulting in the undesirable conjugate reduction of the substrate. In that particular case, the Rh-Bpin fragment was not studied to determine the electronic properties of the boryl system.



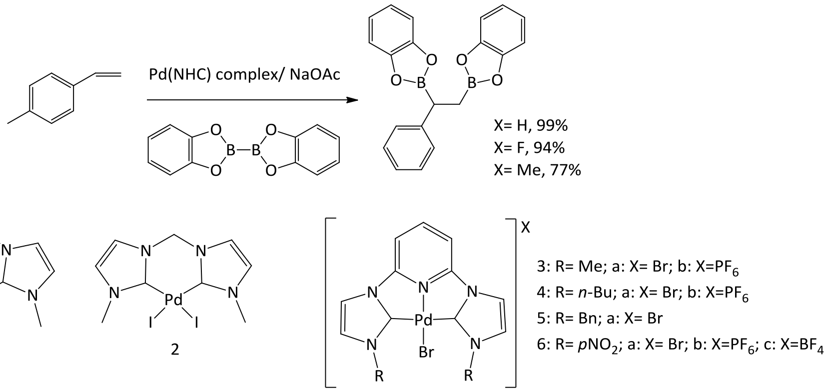
Scheme 1.11 Rh(III)-complex as catalyst precursor for β-boration of α,β-unsaturated carbonyl compounds.

Moving to group 10, Oshima and co-workers have recently found that Ni (0) complexes also catalyze β-boration of α,β-unsaturated carbonyl compounds.[16] The authors have proposed a reaction mechanism whereby, as the first step, the substrate coordinates to the Ni (0) precursor via the C=C double bond. After the formation of the η^2-nickel complex, the coordinated substrate activates 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 1.12). The authors suggested that the Lewis acidity of the boron promotes shift in the conjugated π-electron system of the substrate, its coordination mode changes from η^2 to η^3, and the allylic ligand formally oxidizes the central atom. The activated diboron reagent transfers a boryl ligand into the coordination sphere of the nickel, and the 1,4-addition product is formed by reductive elimination. It is worth noting that if we considered that the formal oxidation state of the central atom does not change when the coordination mode of the substrate switches from η^2 to η^3, the mechanism still remains plausible. In this case the formation of the product by elimation of the anionic boryl and cationic allylic ligand should not be labeled as reductive elimination. In either case, alcoholysis of the boryl enolate with MeOH leads to the formation of the β-borated product. The authors also suggested that the base, Cs_2CO_3, might assist the transmetallation step through its coordination to boron centre.



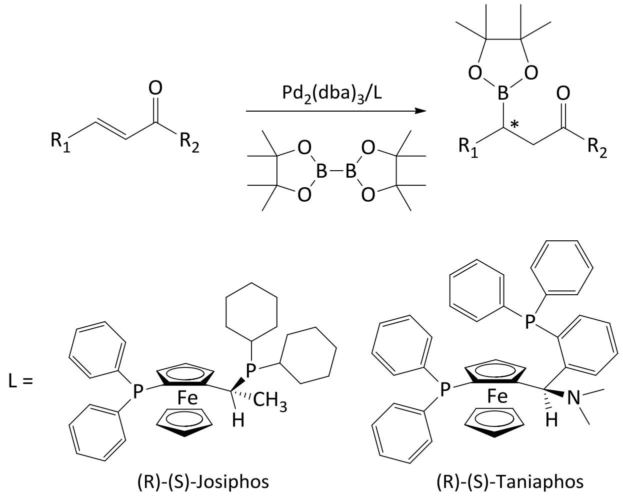
Scheme 1.12 Proposed catalytic cycle for the Ni-mediated β-boration of electron deficient olefins.

Another set of interesting M-B bonds came from Pd-boryl species. Their synthesis has been considered by σ-bond metathesis between Pd-X and diboron reagents.[17] Therefore, palladium(II)-NHC complexes (NHC= N-heterocyclic carbene ligands, Scheme 1.13) turned out to be very efficient catalysts for the 1,2-diboration of alkenes, and were the first examples of Pd-catalysts capable of mediating this B-B addition.[17] The reaction is completely chemoselective in the presence of a mild base (NaOAc) and excess of diboron reagent. The scope of the catalytic reaction is quite broad, as it has been demonstrated that both terminal and internal alkenes can be functionalized. Several changes in the palladium catalytic system lead our group to increase the scope of substrates and perform the reaction enantioselectively.[18]



Scheme 1.13 Pd(II)-mediated diboration of alkenes with NHC-ligands.

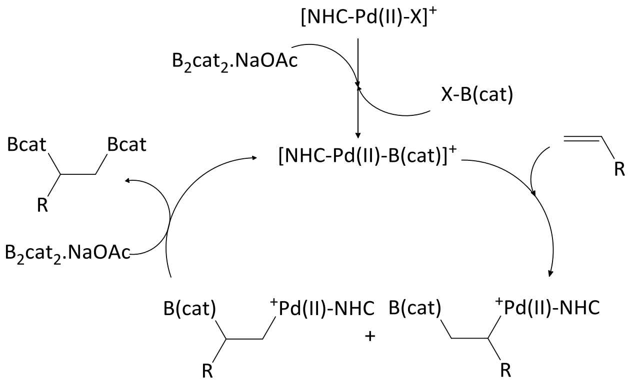
Also in our experimental group it has been developed the first β-boration on α,β-unsaturated esters. We observed that the catalyst precursor [$Pd_2(dba)_3L$] (L= (*R*)-(*S*)-Taniaphos, (*R*)-(*S*)-Josiphos) mediated the B_2pin_2 activation and delivered the Bpin moiety addition to electron deficient olefins. The enantioselectivities strongly depended on the ester moiety of the substrate (Scheme 1.14).



Scheme 1.14 Pd-mediated β-boration of α,β-unsaturated esters.

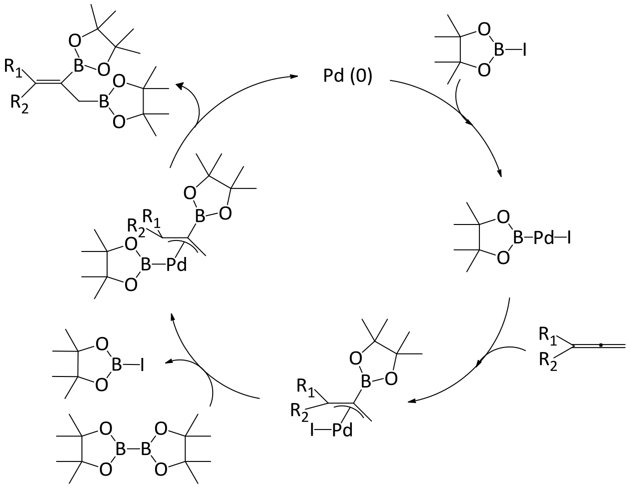
Based on experimental observations and computational studies,[17, 18b] the catalytic cycle proposed for Pd(II) species is the following: first, a base assisted σ-bond metathesis step which activates the diboron; second, alkene insertion into the Pd-

B bond; and third, a new σ-bond metathesis with B_2cat_2 provides the diborated final product and regenerates the active specie (Scheme 1.15).



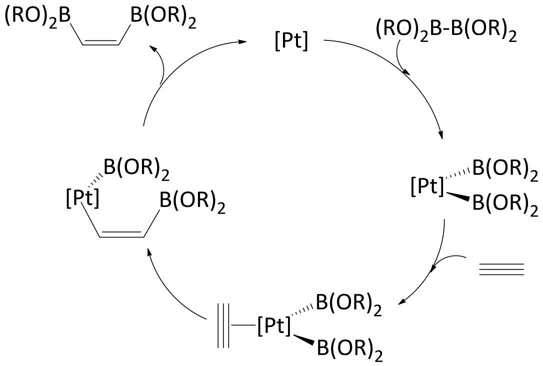
Scheme 1.15 Proposed catalytic cycle for the diboration with Pd(II)-NHC complexes.

Cheng and co-workers[19] have also suggested a mechanism for the Pd mediated diboration of allenes, where the σ-bond metathesis is the key step. This is important since oxidative addition of B_2pin_2 to Pd(0) was discarded from theoretical point of view (Scheme 1.16).[20]



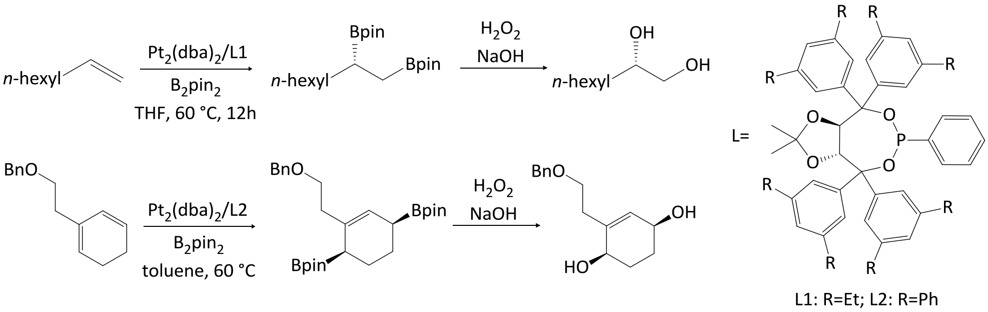
Scheme 1.16 Proposed catalytic cycle for the Pd-mediated diboration of allenes.

Looking into the platinum chemistry, Miyaura and co-workers were the first to explore the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors.[21] In their report, they showed that tetrakis-(trisphenylphosphine)platinum (0) catalyzed the clean addition of B_2pin_2 to both terminal and internal alkynes, resulting the formation of *cis*-alkene bis-boronate esters. They also reported spectroscopic evidences for the formation of the *cis*-bis(boryl) 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 catalytic cycle displayed in Scheme 1.17. The oxidative addition of diboron reagents to the metal center is followed by coordination of the substrate, insertion into the M-B bond, finishing with the reductive elimination that regenerates the active species and provides the diborated product.



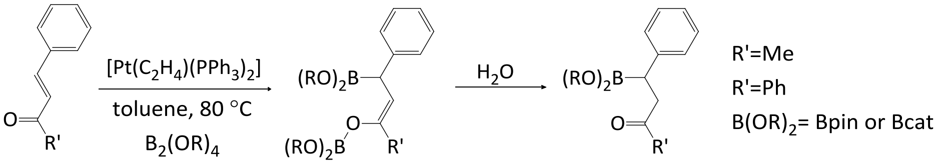
Scheme 1.17 Proposed catalytic cycle for the Pt-mediated diboration of alkynes.

Recently, Morken and co-workers have described a very active and selective Pt catalytic system modified with chiral phosphonites (with TADDOL backbone) achieving enantioselectivities up to 92 % for a large scope o terminal alkenes.[22] Analogous Pt catalytic systems have been recently applied in enantioselective diboration of cyclic dienes.[23] These catalytic systems have provided the highest enantioselectivity using B_2pin_2 as a boron source (Scheme 1.18).



Scheme 1.18 Examples of enantioselective diboration of alkenes and cyclic dienes with Pt-phosphonite sytem and B_2pin_2.

Another important feature with borylplatinum complexes, was the first β-boration of α,β-unsaturated carbonyl compounds that was reported by Marder and co-workers.[24] They described the reaction as a 1,4-diboration reaction, which generated the corresponding β-borated product after the hydrolytic work up (Scheme 1.19).

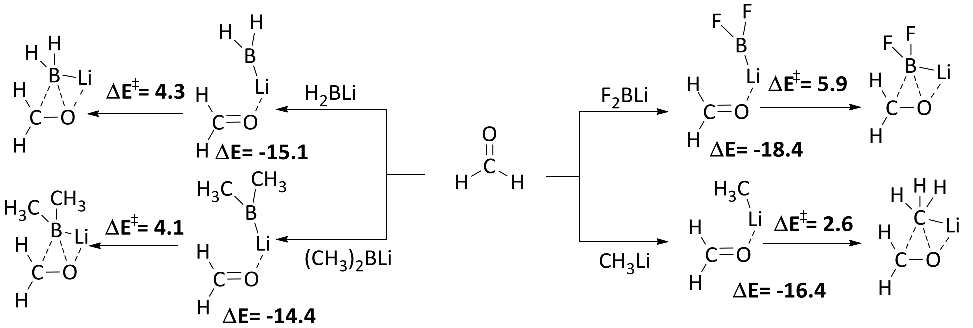


Scheme 1.19 First β-boration reaction of α,β-unsaturated ketones.

1.3. Reactivity of trivalent boron nucleophiles

The reactivity of trivalent boron is dominated by compounds in which the B element adopts the +3 oxidation state and acts as a potent electron pair acceptor. But this trend can be changed when the boron is surrounded by substituents that electronically enrich the boron center. It is a question of a balance between the intrinsic Lewis acidity of the boron, due to its empty p orbital perpendicular to the molecular plane, and the accumulated electron density in the polarized σ bonds.

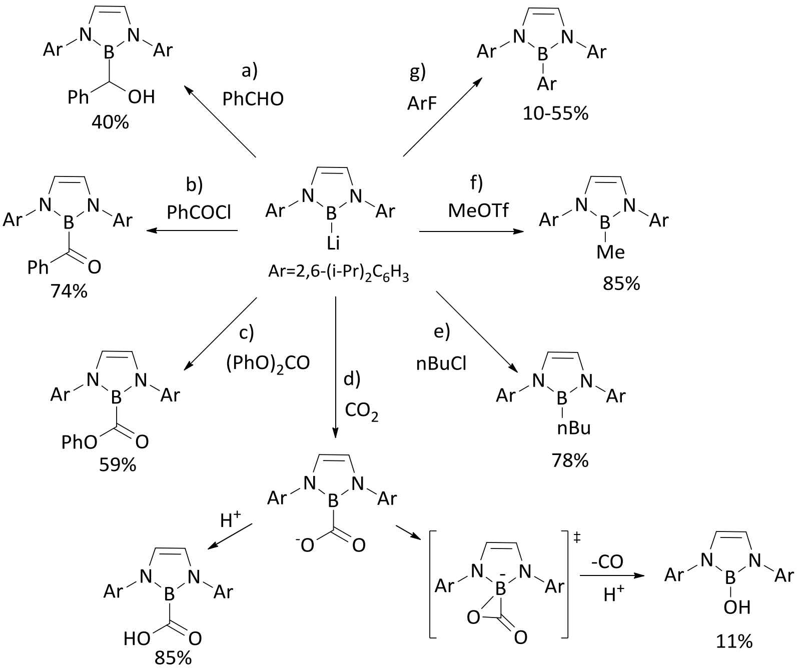
A starting point is the case of the lithioboranes $LiBR_2$, which combine a formal negative charge located on the boryl moiety with a vacant p orbital on boron, generating an unusual reactivity of these boron reagents. The first studies of the reactivity of these compounds, performed by Schleyer and co-workers, were theoretical ones due to the difficulty in isolating these species.[25] The addition reaction of lithioboranes to formaldehyde has been computed, proceeding similarly to the addition of methyllithium (Scheme 1.20). The first stage consisted of the formation of a precursor complex, in which the carbonyl oxygen was coordinated side-on to lithium. The alternative coordination of the carbonyl oxygen to boron could not be characterized as a minimum, and the optimization attempts yielded lithium coordinated complexes. For all lithioboranes, the reaction has low energy barriers (<6 kcal·mol^{-1}) and is largely exothermic (by more of -58 kcal·mol^{-1}), showing the products an interesting three-membered B-C-O ring structure, with a dative boron-oxygen bond. Thus, despite no umpolung on boron occurs and considering that the boron atoms bear a positive charge (with the exception of the parent compound H_2BLi), the predicted reactivity proceeds via nucleophilic attack of the boryl anion moiety. The computed activation barriers are 4.1, 4.3 and 5.9 kcal·mol^{-1} for $(CH_3)_2BLi$, H_2BLi and F_2BLi, respectively, indicating that the nucleophilicity trend of boryl fragments follows the order: $(CH_3)_2B > H_2B > F_2B$.



Scheme 1.20 Calculation on a typical model nucleophilic reaction, the addition of lithioboranes and methyllithium to formaldehyde. Reaction energies and activation barriers ΔE≠ in kcal·mol^{-1}.

The first diamino-substituted boryllithium compound isolated by Segawa, Yamashita and Nozaki was shown to react with a variety of organic electrophiles (Scheme 1.21).[26] In general the reactivity with carbonyl groups gave the corresponding products in the same way as carbanions react. For instance, the boryl moiety attacked the carbonyl group of benzaldehyde to afford, upon subsequent protonation, the corresponding adduct α-borylbenzyl alcohol (Scheme 1.21a). The reaction of the diamino-substituted boryllithium with benzoyl chloride gave the substituted product benzoylborane (Scheme 1.21b), while the reaction with anhydrous carbonates afforded the corresponding borylcarboxylate ester product (Scheme 1.21c). Interestingly, the reaction with carbon dioxide followed by protonation provided a borylcarboxylic acid in high yields with a small amount of hydroxyborane as a by-product (Scheme 1.21d). A plausible mechanism for the formation of the hydroxyborane was explained on the basis of intramolecular cyclization, followed by CO elimination from a borylcarboxylate anion to afford the corresponding boronate, which was protonated to give the hydroxyborane. The reaction of the diamino-substituted boryllithium with 1-chlorobutane in THF gave n-butylborane (Scheme 1.21e), while its reaction with methyl trifluoromethane-sulfonate provided methylborane (Scheme 1.21f). Remarkably, the reaction of this diamino-substituted boryllithium with ArF (Ar = Ph) yielded phenylborane, although in a low yield because the reaction is slower than the decomposition of boryllithium (reaction time 12 h). The reactivity could be improved when Ar= C_6F_5 in ArF reagent, affording the pentafluorophenylborane in a moderate yield within shorter reaction times (Scheme 1.21g). These experiments demonstrated that the boryllithium compounds do behave as nucleophiles, and react with organic electrophiles via a wide range of mechanisms such as nucleophilic substitution

(S_N2-type), nucleophilic addition, nucleophilic addition/elimination, and nucleophilic aromatic substitution (S_NAr-type).[26]

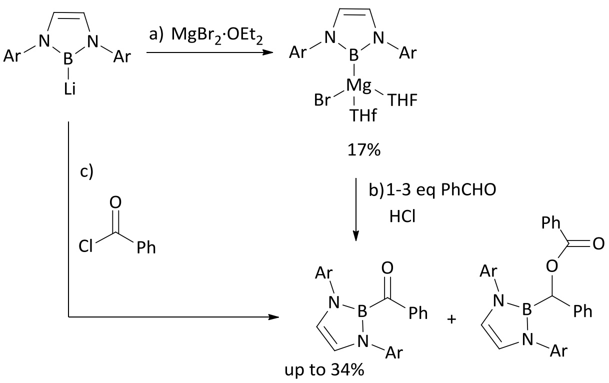


Scheme 1.21 Reactivity of the diamino-substituted boryllithium compound with various organic electrophiles.

With regard to the reactivity of boryllithium compounds with organohalides, Lin and Marder have recently computationally studied how different organohalides affect the outcome of reactions with boryl anions.[27] The calculations indicated that the boryl anion in the boryllithium can form the S_N2 substitution product and/or the halogen-abstraction product, depending on the electronic nature of the organohalide.

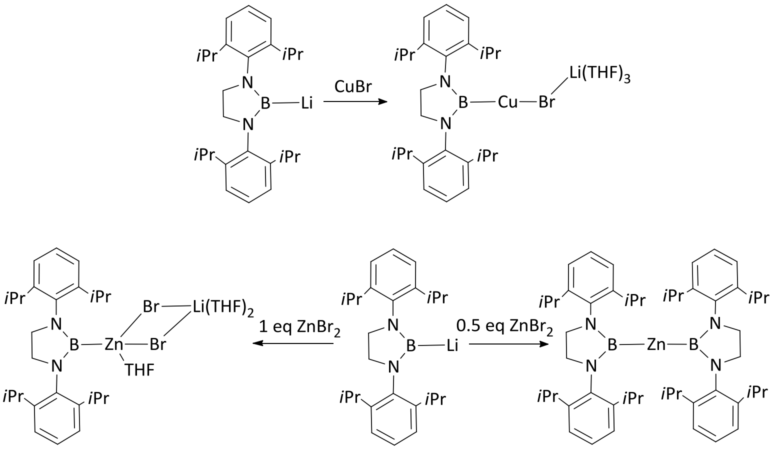
The advantageous nucleophilic character of the boryl anion was also applied to introduce boryl ligands *via* nucleophilic attack to alkaline-earth metal halides. Therefore, borylmagnesium compounds were prepared by the transmetallation between boryllithium and $MgBr_2 \cdot OEt_2$ in THF at room temperature, by Nozaki and co-workers (Scheme 1.22a).[28] Interestingly, changing the counterion of the boryl anion, its reactivity considerably changes towards the electrophile reagents.

In contrast to the reactivity of boryllithium with benzaldehyde giving the α-borylbenzyl alcohol in high yield, the reaction of borylmagnesium bromide with 1–3 equivalents of benzaldehyde afforded a mixture of products, whereby unexpectedly benzoylborane was the main product instead of the α-borylbenzyl alcohol (Scheme 1.22b). With regard to the effect of the counter cation on the reactivity of anionic nucleophiles, it should be noted that a similar difference has been observed in the reactivity of magnesium and lithium alkoxides.[29] Nevertheless, the new benzoylborane was the first example of a fully characterised acylborane and, as described in the same work, it was also possible to increase the yield via the reaction of boryllithium with benzoyl chloride (Scheme 1.22c).

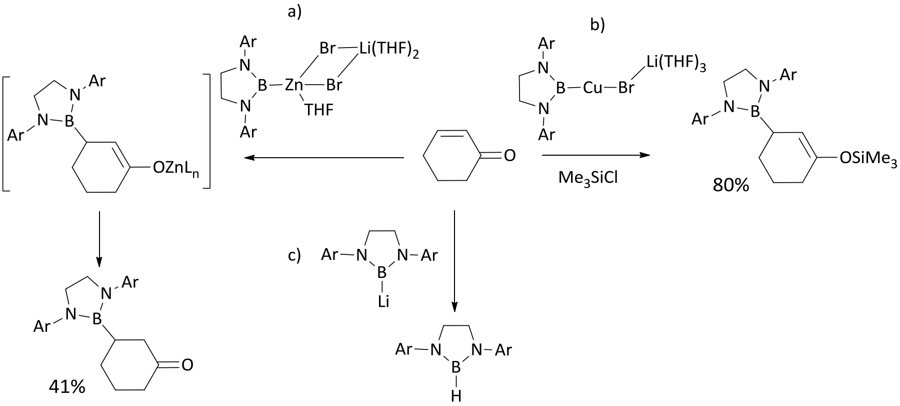


Scheme 1.22 Reactivity of the diamino-substituted boryllithium and borylmagnesium compounds.

As it is shown the boryllithium compounds were also very useful for the nucleophilic substitution on transition metal chlorides of group 11 to form the corresponding boryl-coinage metal complexes.[30] Reactivity of boryllithium with one equivalent of CuBr and ZnBr$_2$, respectively, allowed the isolation of lithium borylbromocuprate and lithium boryldibromozincate, respectively (Scheme 1.23).[31] These boryl compounds were allowed to react with α,β-unsaturated ketones to confirm the nucleophilicity of the boryl moieties. Therefore the reaction of lithium boryldibromozincate with 2-cyclohexen-1-one gave the corresponding conjugate addition product, 3-borylcyclohexan-1-one after hydrolysis (Scheme 1.24a). Alternatively, trapping the copper enolate intermediate, generated from lithium borylbromocuprate and 2-cyclohexen-1-one, with Me$_3$SiCl afforded the γ-siloxyallylborane (Scheme 1.24b). In contrast, the reaction of the boryllithium with 2-cyclohexen-1-one led only to protonation of the borylanion, forming the corresponding hydroborane [HB(NArCH$_2$)$_2$], instead of the expected 1,2- or 1,4-addition product (Scheme 1.24c). [32]

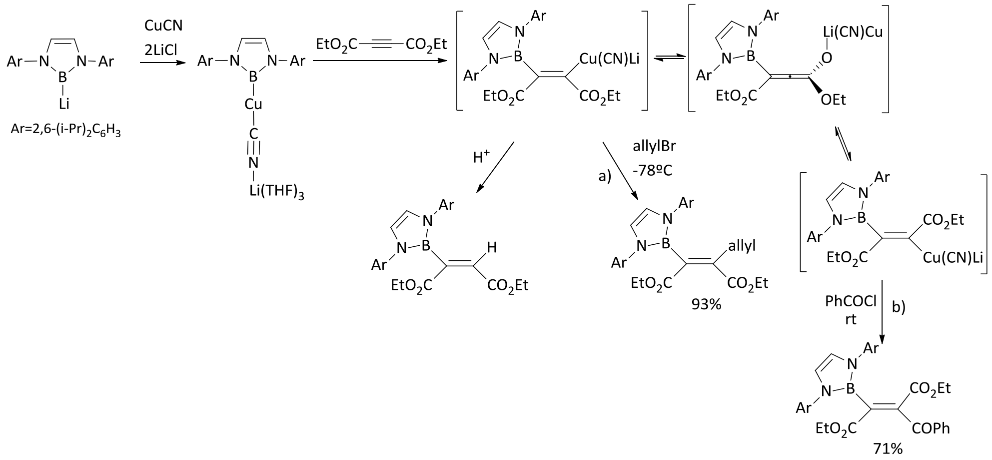


Scheme 1.23 Reactivity of boryllithuim with one equivalent of CuBr and ZnBr$_2$.



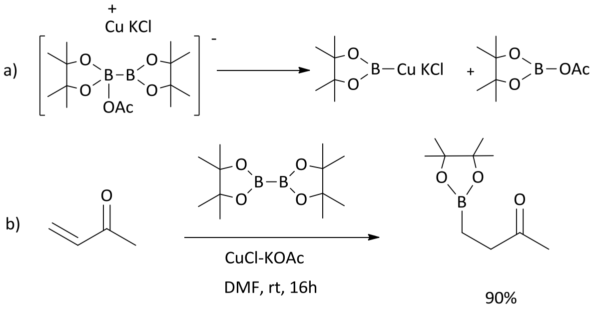
Scheme 1.24 Reactivity of 2-cyclohexen-1-one with (a) lithium boryldribromozincate, (b) lithium boryl bromocuprate and Me$_3$SiCl and (c) borylithium.

A similar compound, borylcyanocuprate, has also been synthesized to study its addition to an ynoate. The borylcupration was followed by reactions with carbon electrophiles to achieve a one-pot carboboration of alkynes (Scheme 1.25).[33] In fact the goal of these experiments was to prove the formation of the β-borylalkenylcopper species by trapping them with benzoyl chloride or allyl bromide, forming the carboboration products. At low temperature (-78 °C) the reaction of borylcyanocuprate with allylbromide provided the *syn* adduct almost exclusively (Scheme 1.25a), but at room temperature the β-borylalkenylcopper intermediate reacted with benzoyl chloride to afford the *anti*-isomer (Scheme 1.25b). The formation of *anti*-adducts has been explained by the isomerisation of the *syn*-borylalkenylcuprates, via an allenolate intermediate, into the *trans*-isomer which would give *trans*-products with organic electrophiles. It is worth noting that other electrophiles, such as MeOTf or PhCHO, were not suitable as trapping reagents. The kinetic and thermodynamic properties with regard to the C *versus* O enolates with Cu, B and Si have been extensively studied by Lin and Marder. [34]



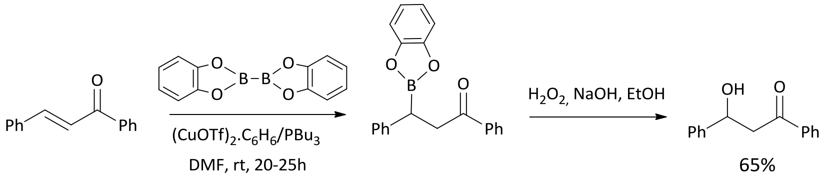
Scheme 1.25 Sequential reaction of borylcyanocuprate with diethyl acetylenedicarboxylate and organic electrophiles.

But originally, the reactivity of borylcopper species was initiated by Miyaura and co-workers in the XXI century,[35] when copper salts activated the heterolytic cleavage of B-B in diboron reagents, by the aid of AcO^- forming a Lewis acid-base interaction prior to transfer to the copper center (Scheme 1.26a). These borylcopper species efficiently promoted the selective conjugate boron addition to α,β-unsaturated carbonyl compounds (Scheme 1.26b). An evidence of a related adduct formed between B_2pin_2 and KO*t*Bu has recently been disclosed by Kleeberg and Marder. [32]



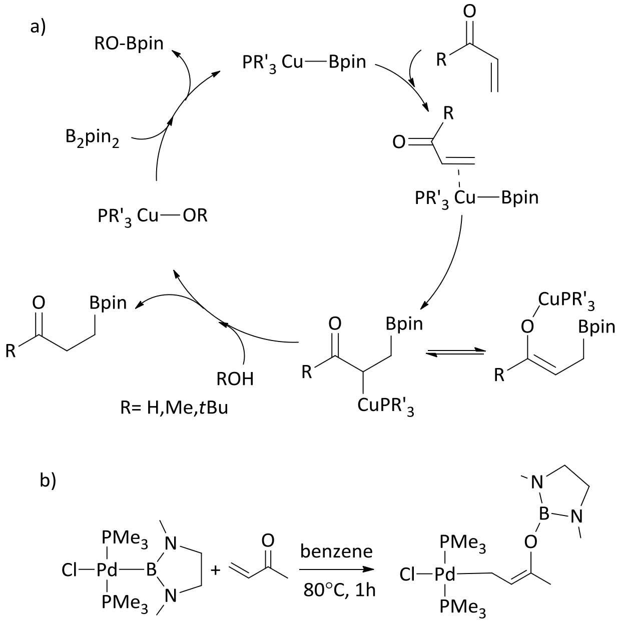
Scheme 1.26 (a) First example od “in situ” borylcopper formation and (b) borylcopper mediated β-boration reaction with bis(pinacolato)diboron.

Simultaneously, Hosomi and co-workers postulated that Cu(I) salt itself did not consume bis(catecholato)diboron (B_2cat_2) in the absence of α,β-enones, and that the coordination of a basic phosphine ligand to Cu(I) might enhance the reaction pathway preventing undesired aggregation of the metal salt (Scheme 1.27).[36]



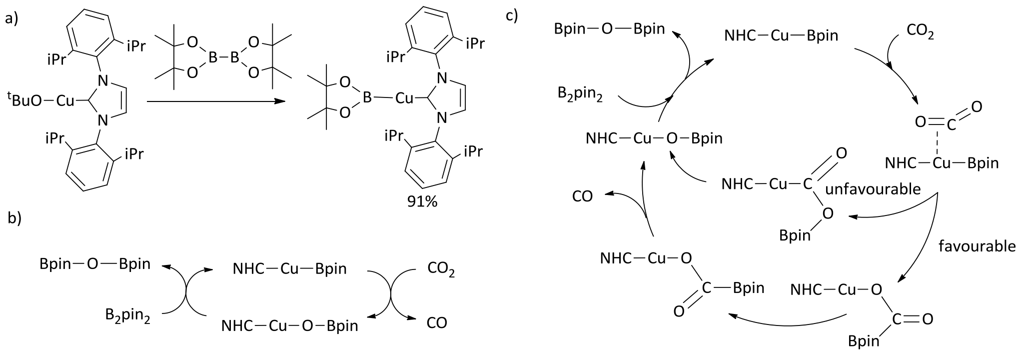
Scheme 1.27 Borylcopper modified with phosphines mediated β-boration reaction with bis(catecholato)diboron.

Theoretical studies have revealed the nature of the interaction between phosphine borylcopper complexes and α,β-unsaturated carbonyl compounds (Scheme 1.28a). It has been found that the mechanism of the boron conjugate addition to acrolein and to methylacrylate substrates is closely related to the relative thermodynamic and kinetic stability of the C- and O-enolate intermediates involved.[34, 37] However, the most relevant result of this study is the clear evidence that the boryl moiety acts as a nucleophile and attacks at the beta carbon of the substrate promoting the formation of the β-boryl carbonyl compounds and imines.[38] In contrast, the analogous stoichiometric reaction of *trans*-[Pd(B(MeN-CH_2CH_2-NMe))(Cl)(PMe_2)$_2$] with an α,β-unsaturated ketone indicated that the insertion of the substrate into the Pd-B bond takes place with reversed regioselectivity, providing the 1,4-addition product wherein the Pd is bonded to the β-carbon and the boryl unit to the oxygen (Scheme 1.28b).[39]



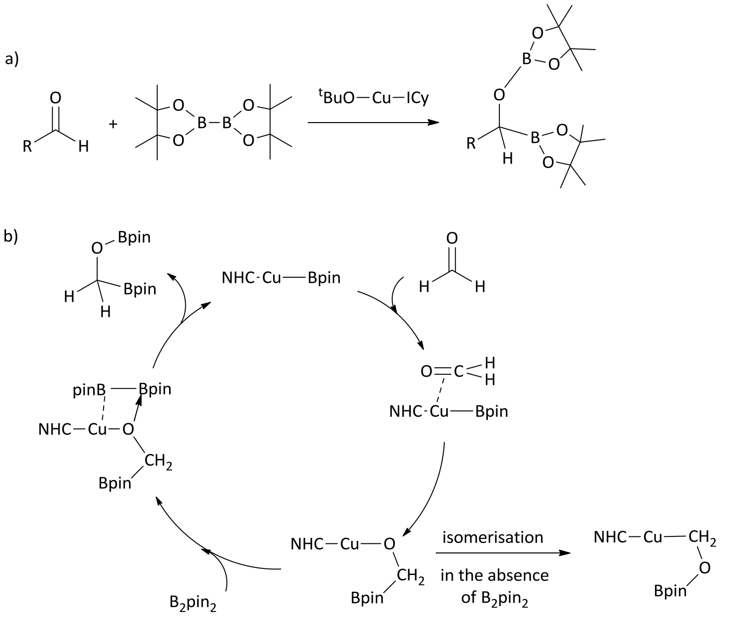
Scheme 1.28 Reactivity of α,β-unsaturated carbonyl compounds with (a) a borylcopper complex modified with phosphines and (b) a borylpalladium modified with phosphines.

The early examples initiated a broad range of applications of borylcopper complexes, providing further evidences of their nucleophilic reactivity. Experimental[40] and theoretical[34] studies were carried out on the reaction between the isolated [Cu(Bpin)(NHC)] complex (Scheme 1.29a) and CO_2 (Scheme 1.29b). The complex catalysed the reduction of CO_2 to CO with B_2pin_2. Computational studies have demonstrated that reduction occurs through CO_2 insertion into a Cu-B bond to give a Cu-O-C-B linkage, in accordance with a nucleophilic attack of the boryl ligand at the C=O carbon. Boryl migration from C to O, followed by a σ-bond metathesis between B_2pin_2 and [Cu(OBpin)(NHC)] regenerated the active borylcopper species (Scheme 1.29c).[41] The ''electron-richness'' of the Cu-B bond, with a polarization towards the B, gives rise to a small CO_2 insertion barrier.[34] It is the nucleophilicity not the oxophilicity of the Bpin ligand that determines the direction of the CO_2 insertion.



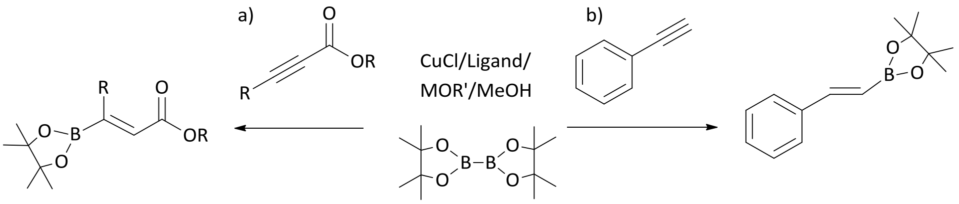
Scheme 1.29 Borylcopper modified with NHC ligand (NHC= IPr= 1,3-bis(2,6-diisopropyl)phenyl imidazole-2-ylidene) mediated CO_2 reduction to CO.

Similar observations have been made, both experimentally[42] and theoretically,[43] in the case of 1,2-addition of bis(pinacolato)diboron to aldehydes catalyzed by the [Cu(Bpin)(NHC)] complex (Scheme 1.30a). The computational studies showed that the diboration occurred through the insertion of the C=O into the Cu-B bond to give a Cu-O-C-B linkage, followed by a σ-bond metathesis with the diboron reagent. Again, the polarity of the Cu-B bond towards the B gives rise to a small insertion barrier and determines the direction of insertion (Scheme 1.30b). In the absence of a diboron reagent, the insertion intermediate having a Cu-O-C-B linkage isomerized into the thermodynamically preferred Cu-C-O-B isomer *via* a boryl migration to the metal-bonded oxygen through a S_E2-like transition state. In these reactions, the nucleophilicity of the boryl ligand was explained from the high-lying Cu-B σ-bonding molecular orbital, which is mainly boryl in character.



Scheme 1.30 Borylcopper modified with NHC ligand (NHC= IPr= 1,3-bis(2,6-diisopropyl)phenyl imidazole-2-ylidene) mediated diboration of aldehydes.

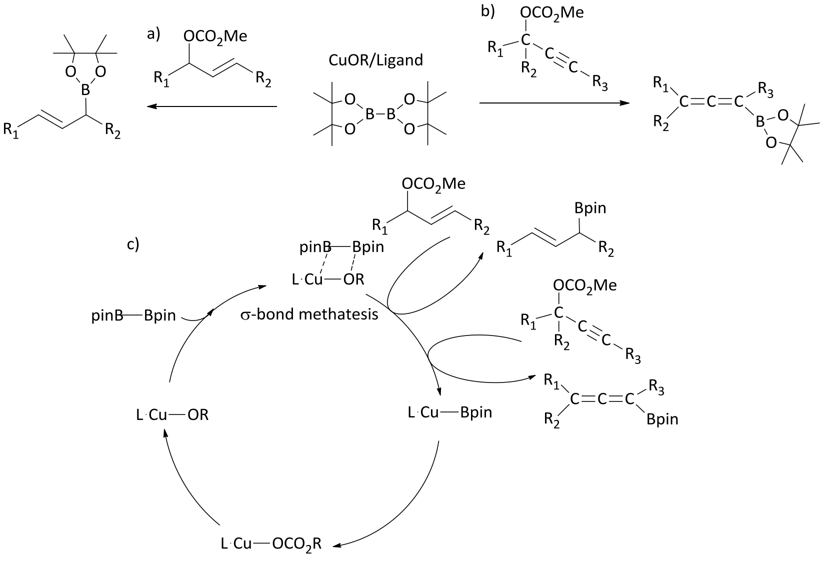
The borylcopper species modified with phosphine ligand have been used as nucleophilic boryl synthons in the efficient synthesis of β-boryl-α,β-ethylenic esters as well as alkenylboranes (Scheme 1.31). The conjugate addition of bis(pinacolato)diboronto α,β-acetylenic esters by means of copper phosphine catalysts was very stereoselective. The product of *syn* addition to the triple bond was almost exclusively formed except for the *tert*-butyl substituted esters where a mixture of (*E*)- and (*Z*)-isomers were observed (Scheme 1.31a).[44] Interestingly, in the same work, it was examined whether the electron withdrawing group was a requisite for the conjugate boron addition reaction. It was found that when phenylacetylene and 1-octyne were the substrates, only the phenylacetyene was transformed into the borylated product (Scheme 1.31b).[44]



Scheme 1.31 Borylcopper modified with phosphines mediated boron addition reaction to conjugated alkynes.

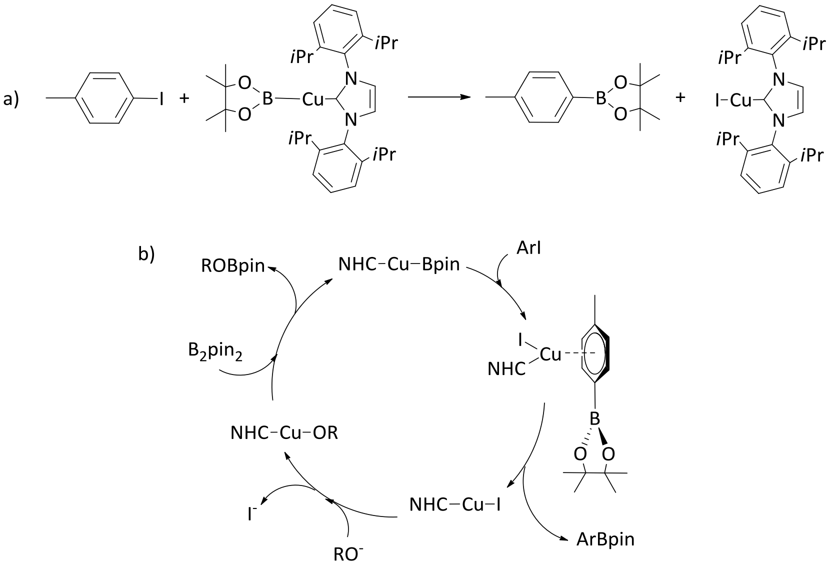
Borylmetal complexes of group 11 have been described to interact with diboranes (B_2cat_2= bis(catecholato)diboron and B_2pin_2= bis(pinacolato)diboron), to catalyze the diboration as well as the hydroboration of alkenes and alkynes.[45]

In the presence of B_2pin_2, the in situ formed borylcopper complexes could also catalyse S_N2' borylation of allylic and propargylic substrates (Scheme 1.32).[46] The reaction of Cu-Bpin species with allylic carbonates has allowed the γ-selective formation of allylboron or allenylboron compounds, along with a copper carbonate intermediate that undergoes decarboxylation to regenerate the Cu-OR species, which is transformed into the catalytically active Cu-Bpin complex via σ-bond metathesis.



Scheme 1.32 Borylcopper species mediated S_N2' borylation of allylic and propargylic substrates.

The application of the nucleophilic boryl complexes in the borylation of aryl halides has also been described (Scheme 1.33).[32] The treatment of the boryl complex [Cu(Bpin)(NHC)], prepared in situ from [Cu(O*t*Bu)(NHC)] and B_2pin_2, with 4-MeC_6H_4I led to the formation of 4-MeC_6H_4Bpin. The reaction was made catalytic by the addition of the base, because the Cu-I intermediate reacted with the alkoxide forming the Cu-OR species, which eventually transmetallated with the diborane reagent affording the active borylcopper complex. It is worth noting that electron-rich and sterically hindered bromides could also be transformed under mild conditions and phosphine copper boryl complexes were found to be even more active species than borylcopper complexes modified with NHCs.

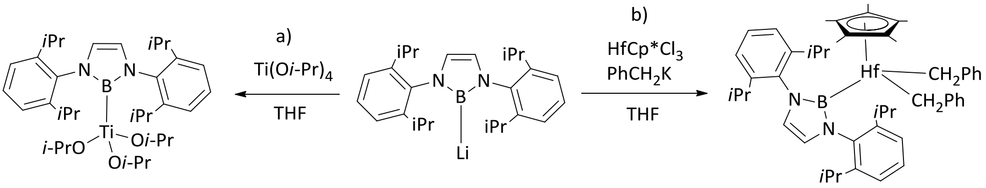


Scheme 1.33 Borylcopper modified with NHC (NHC= IPr= 1,3-bis(2,6-diisopropyl)phenyl imidazole-2-ylidene) mediated the borylation of aryl halides.

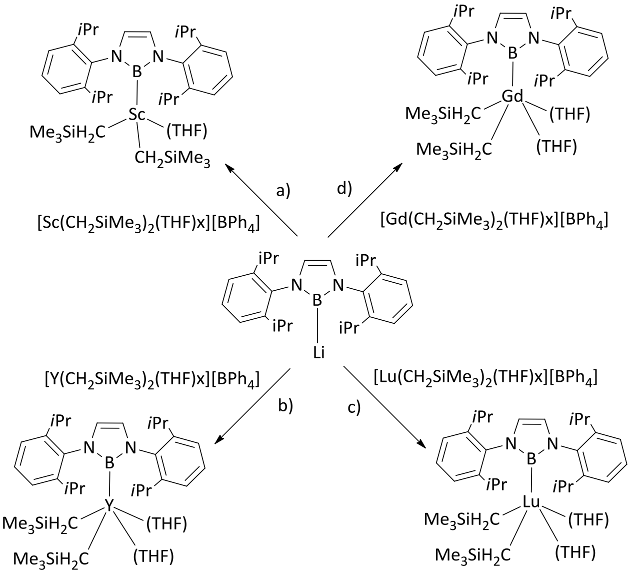
An unprecedented copper-catalyzed cross-coupling reaction of inactivated alkyl halides and pseudohalides with diboronreagents has been recently developed by Steel, Marder and Liu.[47]

The message of the well documented reactivity of borylcopper complexes is that these complexes readily behave as nucleophilic boryl synthons against electrophilic substrates, and can, thus, be the base of efficient synthetic routes towards organoborane compounds.

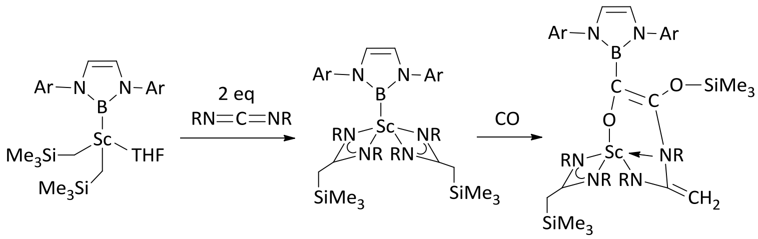
Do the boryl moieties coordinated to early transition metals and rare earth metals provide the same type of nucleophilic boryl synthon? The complexes boryltitanium and borylhafnium have been synthesized *via* nucleophilic borylation using the diamino-substituted boryllithium (Scheme 1.34).[48] The Hf complex has shown an activity for polymerization of ethylene and hex-1-ene, but it does not reflect a clear nucleophilic reactivity.[48] Also rare earth metal boryl dialkyl complexes can be easily obtained by reaction of a lithium boryl salt with dialkyl rare earth tetraphenylborate ion-pair compounds (Scheme 1.35).[49] Preliminary reactivity studies have shown that the Sc-B bonds can undergo insertion reactions with carbodiimide and carbon monoxide to give new boron containing rare earth metal complexes (Scheme 1.36), where the boron is bonded to the C after the CO insertion.[49a]



Scheme 1.34 Synthesis of boryltitanium and borylhafnium from boryllithium.

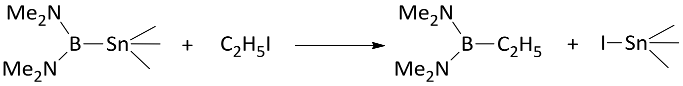


Scheme 1.35 Synthesis of group 3 and lanthanide boryl complexes.



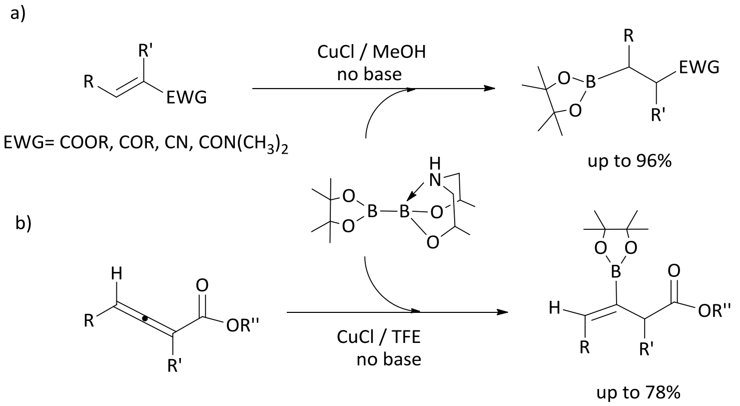
Scheme 1.36 Reactions of scandium boryl complexes with carbodiimide and carbon monoxide.

Considering the p block elements, a still unpublished work gives a very nice example of the reactivity of stannylated boranes, wherein the boryl moiety reacted with an alkylhalide, resulting in the alkylation of the boron as nucleophile (Scheme 1.37).[50]



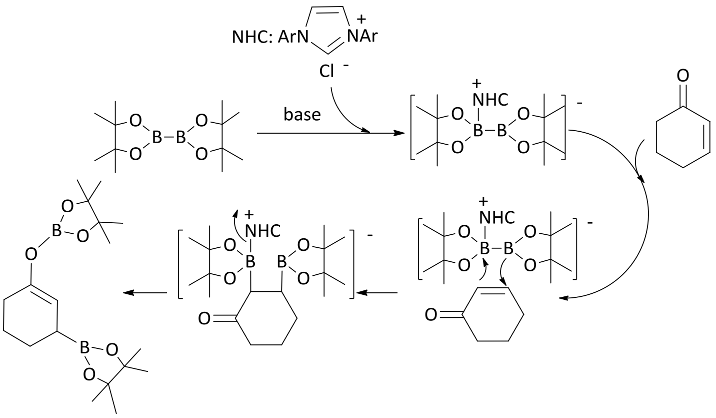
Scheme 1.37 Reactivity of stannylated boranes with methyliodides.

It is important to note that organoboranes containing B-B bond can also show nucleophilic behaviour under appropriate conditions. Nowadays, it has been demonstrated that it is possible to activate diboron reagents in the absence of metals, by the sole addition of electron donor reagents, such as amines, N-heterocyclic carbenes and alkoxides. This preactivation increases the reactivity of the reagent towards both inorganic and organic electrophiles. For instance, it can assist the transmetallation of the diboron reagent with transition metals or promote its reactivity towards electron deficient olefins. An important example of such a B-B bond activation is the unsymmetrical mixed sp^2-sp^3 diboron compound, pinacolato diisopropanolaminato diboron first prepared by Santos,[51] in which the amino group of the molecule interacts intramolecularly with one boron moiety. This interaction polarizes the B-B bond, and facilitates the heterolytic cleavage of the B-B towards transmetallation with Cu-OR moieties, thus, assisting the Cu-B bond formation. This activation process is of great importance because in the application of this type of unsymmetrical diboron to the β-boration of α,β-unsaturated carbonyl compounds (Scheme 1.38a) and allenoates (Scheme 1.38b), bases or phosphine ligands are not required. However, the described intramolecular N→B interaction was not sufficient to promote the addition of the nucelophilic boron synthon to organic electrophiles, therefore when copper was not present in the medium none of the two conjugate boron addition reactions took place.



Scheme 1.38 Copper catalyzed β-boration of α,β-unsaturated conjugated compounds with sp^2-sp^3 hybridized mixed diboron.

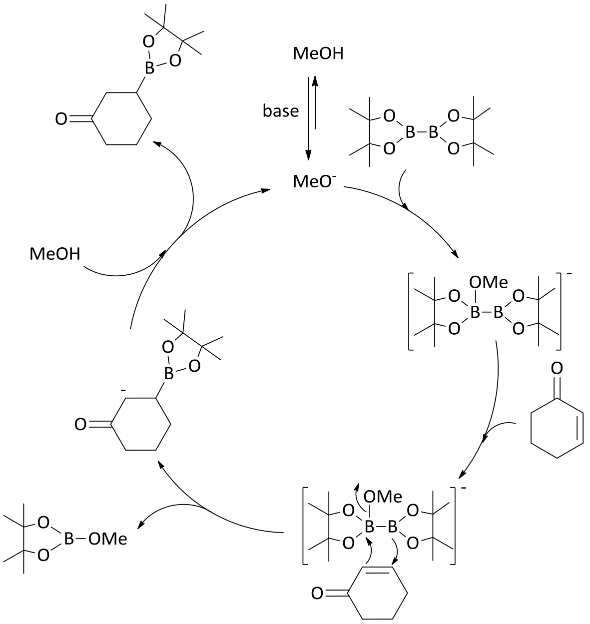
Intermolecular activation of symmetrical diborons such as bis(pinacolato)diboron can create a significant nucleophilic boryl synthon, which in the absence of any transition metal complexes can efficiently be added to the C_β of α,β-unsaturated carbonyl compounds. This methodology represents the very first metal free approach towards the application of trivalent nucleophilic boron atoms. For instance, N-heterocyclic carbenes generated in situ by deprotonation of imidazolium salts with Brönsted bases activated the bis(pinacolato)diboron reagent *via* Lewis acid–base interaction and catalyzed the β-boration of electron deficient olefins (Scheme 1.39).[52]



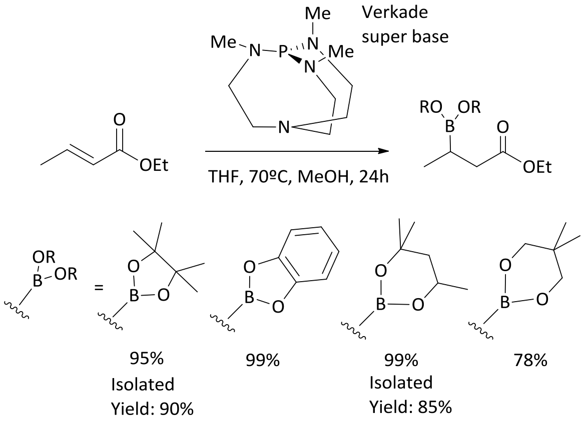
Scheme 1.39 NHC-mediated the catalytic β-boration of α,β-unsaturated conjugated compounds with bis(pinacolato)diboron.

A spectroscopic and structural characterization of the adduct formed by N-heterocyclic carbenes and bis(pinacolato)diboron has recently been described.[53] Hodgkinson, Lin and Marder have observed that in solution the binding was weak and NMR spectroscopy revealed a rapid exchange of the N-heterocyclic carbenes between the two boron centers. DFT calculations demonstrated that the exchange involved dissociation and reassociation of N-heterocyclic carbenes rather than an intramolecular process.

Our experimental group have simplified this concept even more, as it was demonstrated that the sole use of MeOH and base can efficiently transform acyclic and cyclic activated olefins into the corresponding β-borated products in the presence of a series of diborons.[54] Both inorganic and organic bases deprotonated MeOH and the resulting methoxide formed a Lewis acid-base adduct with the diboron reagents. Similar adducts have been reported by Kleeberg and Marder.[32] The sp^2 boron of the MeO^-→bis(pinacolato)diboron adduct gained a pronounced nucleophilic character and attacked the electron deficient olefins. The frontier orbitals that are involved in the attack that leads to the transition state are the polarized σ-B-B bond and the $\pi^*_{C=C}$ of the activated olefin. From the transition state the anionic organic intermediate is formed directly *via* the heterolytic cleavage of the Bsp^2–Bsp^3 bond and the formation of the new C-B bond. Protonation of the anionic intermediate with MeOH provided the product and generated another methoxide anion, converting the reaction into a catalytic process (Scheme 1.40). The efficiency of the catalytic system has been found to depend on the nature of the base that is used to deprotonate the MeOH. It has been observed that the organic Verkade base is able to promote quantitatively the MeO^- formation to consequently activate diborons such as bis(pinacolato)borane (B_2pin_2), bis(catecholato)borane (B_2cat_2), bis(hexyleneglycolato)diboron (B_2hex_2), and bis(neopentylglycolato)diboron (B_2neop_2) (Scheme 1.41).[54]



Scheme 1.40 Methoxide-mediated the catalytic β-boration of α,β-unsaturated compounds with bis(pinacolato)diboron.



Scheme 1.41 Verkade base deprotonated MeOH to generate MeO$^-$ that promoted the β-boration of ethylcrotonate with different diboron reagents.

The activation energies of the boryl nucleophilic attack and thermodynamic stabilities of the anionic intermediate have been calculated for a wide range of substrates. The lowest activation energy and greatest thermodynamic stability of the intermediate have been observed in the case of acrylaldehyde, followed by the ketone and the ester. Interestingly, the borylnucleophilic attack seemed to be feasible even against non-activated olefins, such as styrene and propylene, as shown experimentally and theoretically in the diboration of non-activated olefins (Table 1.1).[54]

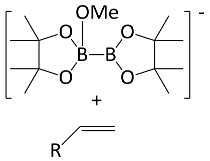
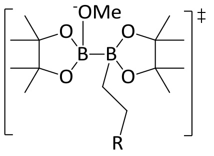
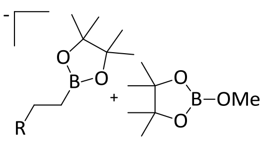
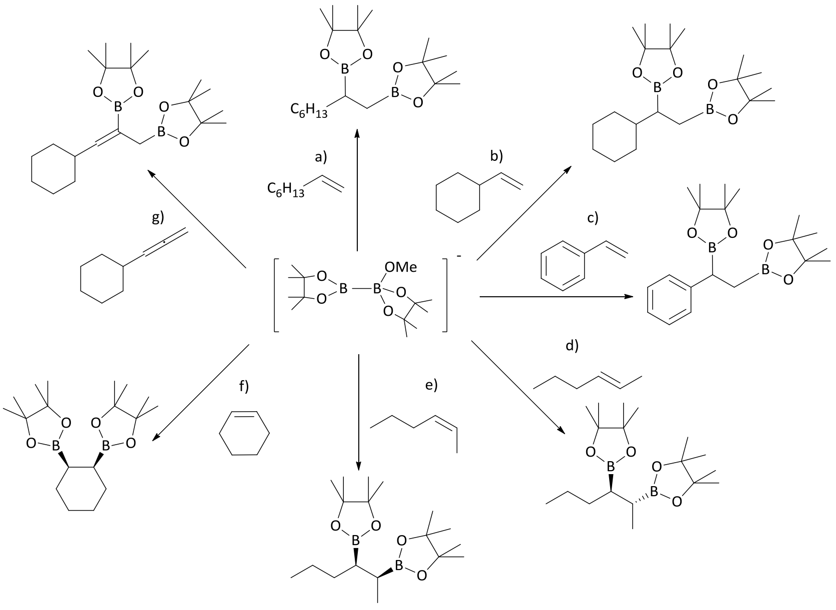
		
R: -CHO	2.0 (16.7)	-34.1 (-33.8)
R: -$COCH_3$	3.7 (18.7)	-30.9 (-30.2)
R: -$COOCH_3$	6.9 (21.5)	-28.2 (-28.4)
R: -Ph	11.3 (25.1)	-18.9 (-18.5)
R: -CH_3	24.1 (35.9)	-7.2 (-7.5)

Table 1.1 Energies of several monosubstituted alkenes and their transition state. 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}.

All these precedents have proved that trivalent boron can act as nucelophilic synthons in an organocatalytic context, but now the question is: what the scope of this nucleophilic boryl synthon is? Our group explored the addition of the MeO^- →bis(pinacolato)diboron adduct to non-activated olefins.[55] For instance, bis(pinacolato)diboron could be added quantitatively to 1-octene in the presence of 15 mol% Cs_2CO_3 and 5 eq. of MeOH, within 6 hours (Scheme 1.42a). The chemoselectivity of the reaction changed because the electrophilic counterpart of the nucleophilic boryl synthon also derives from the diboron reagent. That is, despite the presence of the MeOH, the main product of the reaction is the diborated olefin. Only traces of the ‘‘hydroborated’’ product could be observed. Changing the *n*-hexyl substituent to cyclohexyl did not influence the reactivity of the C=C double bond significantly with quantitative conversion of vinylcyclohexane close to complete chemoselectivity into the desired diborated product (Scheme 1.42b). The diboration of styrene required milder reaction conditions than that of the aliphatic alkenes to obtain high selectivity (Scheme 1.42c). The diboration of internal alkenes provided crucial information on the mechanism of the reaction. Unlike many of the classic electrophilic additions such as halogenation of alkenes, the nucleophilic diboration of non-activated olefins always occurs in a *syn*-fashion.



Scheme 1.42 Scope of organocatalytic diboration of alkenes mediated by MeO^-→ bis(pinacolato)diboron.

Thus, diboration of *trans*-hex-2-ene gave the diborated product in a 3:97 *syn*:*anti* ratio (Scheme 1.42d), while *cis*-hex-2-ene formed the corresponding diborated product in a 95:5 *syn*:*anti* ratio (Scheme 1.42e). Similarly, the diboration of cyclohexene exclusively gives the *cis* diborated product (Scheme 1.42f). Another interesting finding is that nucleophilic diboration of allenes favoured the formation of the 1,2-diborated product (Scheme 1.42g), in contrast to most transition metal catalyzed diborations of allenes which usually provide the 2,3-diborated isomers as primary products.[56] The generality of the methodology has been proved by the successful use of different diborons, which all have been efficiently activated by the MeOH/base system (base= Cs_2CO_3) providing a similarly powerful boryl nucleophilic boryl synthons (Figure 1.1).[55]

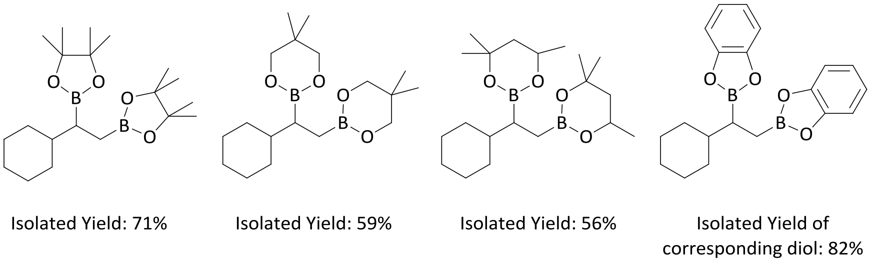
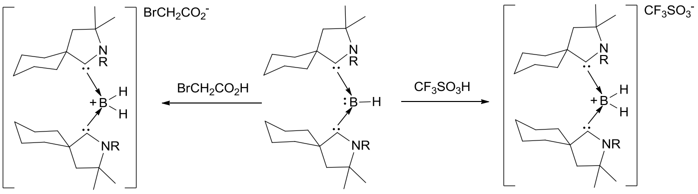


Figure 1.1 Organocatalytic diboration of vinylcyclohexane with bis(pinacolato)borane (B_2pin_2), bis(hexyleneglycolato)diboron (B_2hex_2), bis(neopentylglycolato)diboron (B_2neop_2) and bis(catecholato)borane (B_2cat_2) activated by MeO^-.

This new reaction has a significant importance, because the diborated products are formed in a reaction between a nucleophilic boryl reagent and a substrate which also has a pronounced nucleophilic character, representing an almost unknown reactivity. Furthermore, it is probably even more important that unlike in the case of conjugate additions, both boryl units of the reagent are introduced to the substrate, resulting in an atom-economic addition reaction of great practical importance, which up to date has only been accomplished by transition metal mediation.[57]

The latest example of tricoordinated boron that behaves as a nucleophile is the recently isolated bis(carbene)BH adduct. The boron, in this compound, is in the formal oxidation state +1 and is clearly electron-rich due to two features: (1) although the boron is three valent its valence shell is filled, formally it holds a non-bonding pair, (2) the carbene→BH donation that occurs from the σ lone pairs of carbene ligands into the empty in-plane molecular orbitals of the boron affords two low-lying bonding orbitals. The presence of a lone pair of electrons at the boron of the bis(carbene)BH adduct renders it nucleophilic and it can be expected to have the potential to react with electrophiles. Indeed it has been reported that the bis(carbene)BH adduct reacted with an equimolecular amount of trifluoromethane sulfonic acid at room temperature, and after the work up the conjugate acid was isolated in 89% yield (Scheme 1.43).[1] The solid state structure confirmed the formation of a tetracoordinateboron compound, with two hydrogen atoms directly bonded to boron generating a boronium cation. Similar reactivity has been observed with $BrCH_2CO_2H$ (Scheme 1.43).



Scheme 1.43 Reactivity of bis(carbine)BH adduct.

1.4. Computational tools for catalysis

During last years, computational methods have become a powerful tool to understand many chemical processes. Actually, catalysis is one of the areas that computational chemistry has achieved most success. Nowadays, computational methods in catalysis are very important because they allow us to determine reaction mechanism with sufficient accuracy in a reasonable time, and therefore understand the behavior of a catalyst and propose changes to alter its function. The main objectives of any modeling technique are to reproduce the experimental values and to identify and rationalize the catalytic process in order to obtain a mechanistic comprehension. The ultimate goal is to predict the behavior of the catalysts and establish rules for the design of new catalysts. In this regard, it is interesting to note that the 2013 Nobel Prize in Chemistry was awarded to Martin Karplus, Michael Levitt and Arieh Warshel *for their contribution in the development of multiscale models for complex chemical systems*.

The homogeneous catalysis occurs through a sequence of reactions which constitutes a catalytic cycle. To understand its mechanism, the computational strategy frequently used, is based in determining the key transition states (TS) using electronic structure methods, and it is frequently referred to *TS-based* approach. This approach requires the determination of the geometries and the energies of the reactants, products and all relevant intermediates and transition states. In other words, it is concerned with the localization of the stationary points of the *potential energy surface* (PES) and their energy evaluation. Optimization of the geometries is usually done through gradient techniques. In the procedure, all degrees of freedom are varied simultaneously until the gradient (first derivatives) of the energy is zero. The characterization of the stationary points involves the differentiation between the local minima (intermediates, reactants and products) and saddle points (transition states), by computing the matrix of the second derivatives of the energy with respect to molecular coordinates (Hessian matrix). In the case of local minima all the eigenvalues or the Hessian matrix are positive, whereas in the saddle points, there is one and only one negative eigenvalue. Based on this information, it is possible to identify the activity- and the selectivity-determining step of the catalytic cycle by evaluating the different relative energies and the energy barriers.

Another type of computational strategy is the so-called *Structure-Activity Relationship* (SAR) method.[58] This approach tries to evaluate the reactivity from ground-state structure properties and not from TS in order to look for qualitative or quantitative relationships with the activity or selectivity. Calculations on ground state structures are simpler, and in principle, permit screening large data sets. The ultimate goal of this strategy is to predict their reactivity in different scenarios. In chapter 2 we have analyzed the electronic properties of a set of boryl complexes in order to identify some trends, building a tendency map that allows us to anticipate the reactivity of boryl synthons as nucleophilic or electrophilic reagents. The map includes unprecedented boryl complexes “virtual systems”, and for some of them there is a reasonable theoretical support to attempt the experimental identification. In chapter 4, we use the tendency map to anticipate the reactivity character of mixed Bpin-Bdan reagent.

But how do we have access to the TS and minima? The most popular and common method used nowadays are Density Functional Theory (DFT) method.[59] They have become the standard choice for the study for transition-metal reactivity and homogeneous catalysis.[60] In the DFT method, the energy is expressed as a functional of the electron density. In other words, the interacting system is described via its electron density and not via its wave function. This simplification is possible thanks to the development of the Hohenberg & Kohn theorem,[61] which states that all-ground state properties of a system are functions of the electron density. A functional is described as function of a function, but the theorem does not provide the form of such functional. The most common implementation is the Kohn-Sham formalism,[62] which allows optimizing the energy by solving a set of one-electron equations, the so-called Kohn-Sham equations. The derived one-electron functions, the Kohn-Sham orbitals, can be also expressed as linear combination of atomic orbitals. One of the main advantages of DFT methods is that they included electron correlation with a little computational cost compared to wavefunction-based methods. This term, *electron correlation*, referring to instantaneous repulsive interactions, is absent in Hartree-Fock theory. In the framework of wavefunction-based methods, 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 consists of variations and improvements on how to address this term.

The first DFT approximation was the local density approximation (LDA) where the functional depends only on the value of the electron density. It assumes that the charge varies slowly throughout the molecule so that the density can be treated as an uniform electron gas. The LDA approximation generally gives good results for the determination of structural features of the system, as well as for vibrational frequencies and dipole moments. However, it usually overestimates the binding energies. This can be significantly improved by adding gradient corrections to the exchange correlation functional, through terms that involve the gradient of the density. It has been proposed several functionals belonging to this class of methods, generalized gradient approximation (GGA). 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. Functional 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 description of van der Waals interactions is needed.[63] Among the numerous functionals following the GGA approximation, BP86,[64] and BLYP[64a, 65] have been widely used. 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. Another 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. Probably, the most popular hybrid is the B3LYP scheme.[65-66] It owes its origins to a proposal by Becke for a parameterized hybrid approximation involving the Perdew correlation functional, which lately was substituted by the LYP correlation functional. More recently, Truhlar and co-workers have developed a suit of meta-hybrid density functionals including M06, M06-HF, M06-2X, M05 and M05-2X.[67] Meta-hybrid-GGA functionals are known increasingly used in chemical modeling, since some of them appear to describe accurately molecular systems containing weak interactions (such as van der Waals interactions). A good alternative is the use of DFT methods with dispersion correction (DFT-D) such as B97D.[68]In this PhD thesis, we have used mainly the hybrid B3LYP functional since it has been successfully used in boron chemistry.[37, 45b]

Using DFT methods is possible to obtain reliable structure and energies for medium-sized molecular systems with low computational cost. Larger systems are amenable to hybrid quantum mechanics/molecular mechanics (QM/MM) methods.[69] The QM/MM method divides the system into two regions. The active site region is described by the QM method and the flexible bulky regions are described classically by the less computationally demanding MM method. The most popular implementations of QM/MM treatment for organometallic-type catalysts are the IMOMM[69d] method and its extension ONIOM method.[69e] Within this partition, there is no charge transfer from the MM part, thereby resulting in ligands with symmetric electronic properties, but its steric properties are accounted for. Also ONIOM calculations might provide a better description of molecular structures with critical intramolecular non-covalent interactions than full calculations with conventional DFT methods.[70] Furthermore, the combination of QM/MM and DFT methods can be used as a tool for analysis allowing separating straightforwardly the steric and the electronic effects.[69a, 71] In chapter 3, we have used QM/MM methods, in order to understand the origin of selectivity induced by bulky ligands, in the non-conventional hydroboration catalyzed by Rh complexes.

The last decades have not only witnessed progress in computational chemistry methods for calculating measurable properties of molecules, but also theoretical methods have been developed to analyze the calculated electronic structure. One of these tools for analyzing the electronic structure, which is based on orbitals, is the natural bond orbital (NBO) method.[72] This partitioning scheme concerns with the distribution of electrons into atomic and molecular orbitals, and thereby with the derivation of atomic charges and molecular bonds. Two analysis derive from NBO method; the NBO analysis for the assignment of molecular bonds and the natural population analysis (NPA) for assignment of atomic charges. The NBO method merged as an alternative to the extensively used Mulliken population analysis.[73] On the one hand, the NBO method is quite robust toward changing the basis set. On the other hand, it shares some of the most appealing features of the Mulliken method, like the low computer cost and the general applicability to any wavefunction. In chapter 2, we have used the NBO method to derive several electronic parameters related to the nucleophilic character of a set of boryl systems.

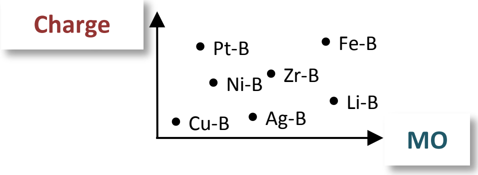
1.5. Objectives

The trivalent boron compounds have definitely tunable electronic properties, depending on the elements bonded directly to the boron atom. A deeper knowledge of the electronic properties of trivalent boron compounds and their reactivity will be **principal objective** of our study.

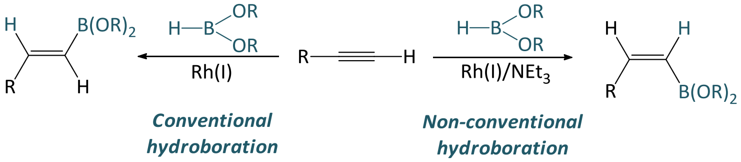
The **specific objectives** of the thesis are:

1. Study of boryl moieties with electrophilic and nucleophilic properties.

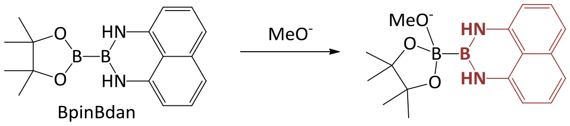
2. Provide a map of trends on electronic properties of M-B systems and Lewis acid-base adducts [RO→B-B]⁻, [NHC→B-B] and [NR_3→B-B].



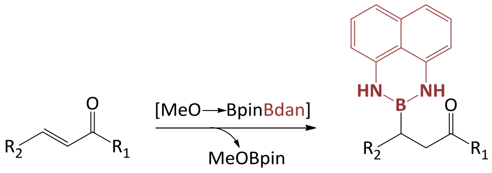
3. Perform and fully understand a non-conventional hydroboration of alkynes.



4. Develop the first approach on organocatalytic activation of mixed diboron reagents.



5. Conduct a selective β-boration with Bdan systems and comprehension of the mechanism.



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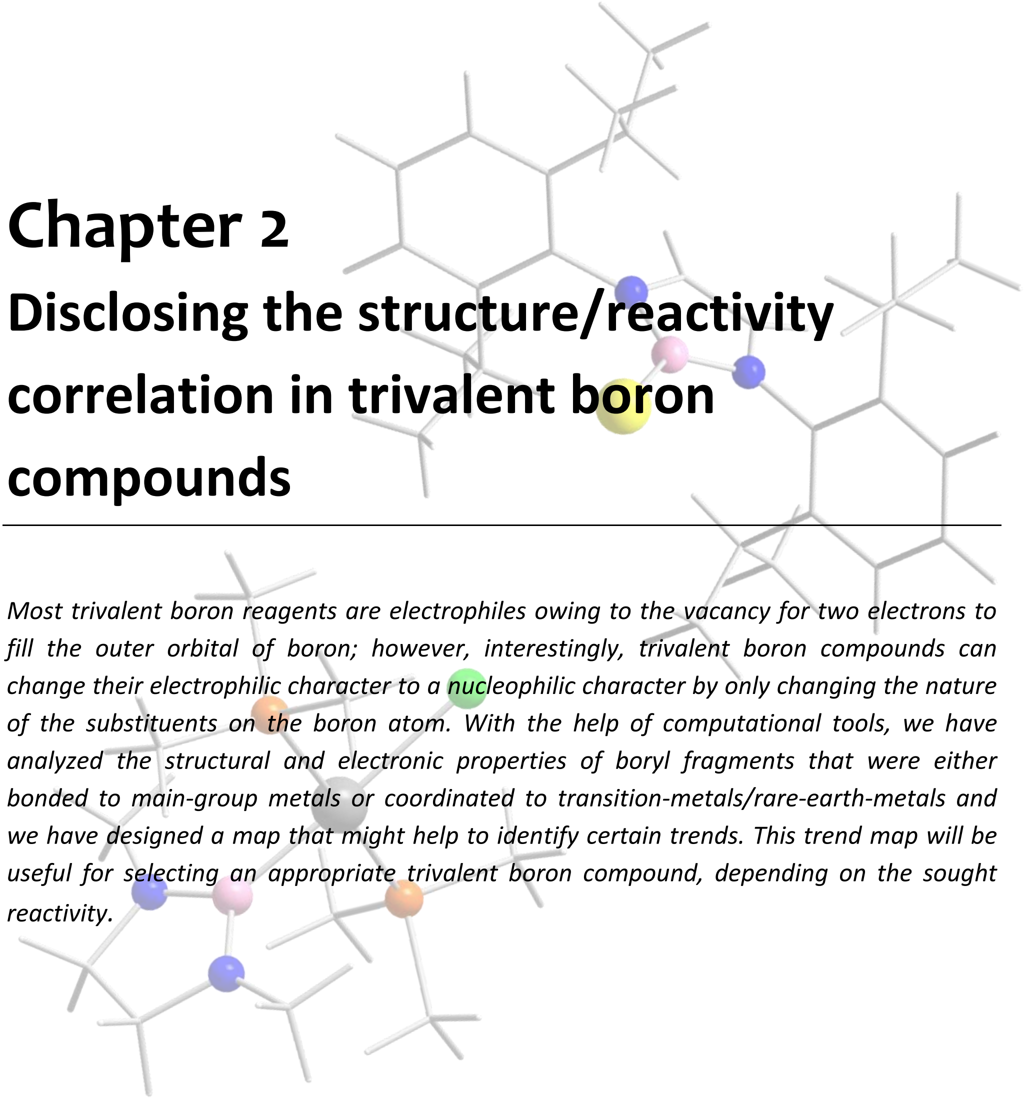

Chapter 2

Disclosing the structure/reactivity correlation in trivalent boron compounds

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Most trivalent boron reagents are electrophiles owing to the vacancy for two electrons to fill the outer orbital of boron; however, interestingly, trivalent boron compounds can change their electrophilic character to a nucleophilic character by only changing the nature of the substituents on the boron atom. With the help of computational tools, we have analyzed the structural and electronic properties of boryl fragments that were either bonded to main-group metals or coordinated to transition-metals/rare-earth-metals and we have designed a map that might help to identify certain trends. This trend map will be useful for selecting an appropriate trivalent boron compound, depending on the sought reactivity.

2.1. Introduction

In trivalent boron compounds, every type of boryl unit has distinctive electronic and structural properties that can be exploited in a plethora of useful applications through various electrophilic- or nucleophilic interactions (Figure 2.1).[1] This tunable reactivity of boron compounds has emerged over the last ten years and, nowadays, many stable trivalent boron nucleophiles that have been synthesized, show potential application in organic synthesis. [2]

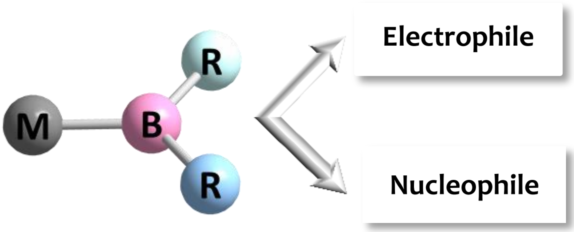


Figure 2.1 Tunable reactivity of trivalent boron compounds.

The nucleophilic or electrophilic character of trivalent boryl units depends on the nature of the substituents on the boron atom. In an early work, Schmid[3] concluded that “covalent bonds between boron and metals and boron and nonmetals are similar in character”. Several theoretical studies have revealed that boron–alkali-metal bonds have a significant covalent character and can be moderately polar.[4] The boron atom may also become electronically stabilized by π-donation from substituents (OR) that contain a lone-pair (Figure 2.2a).

Moving from s-block metals (M) to d-block transition metals (Mt), the nature of the Mt-BR_2 bond is described as a two-center two-electron σ-bond, which can be further stabilized by π-donation from Mt to BR_2, in a process that competes with the π-donation from the OR substituents on the B atom (Figure 2.2b). It is now generally well-accepted that the π-component of the Mt–boryl bond is relatively weak, but it is even weaker in Mt-BR_2 systems in which π-interaction between the B center and its substituents seems to be dominant.[5] However, when BH_2 is the boryl unit, theoretical NBO analysis has shown that the p(π) orbital of boron is populated by π-donation from Mt.[6] Thus, the question is how can the electronic character of the boryl fragment be influenced by the nature of the bonded metal?

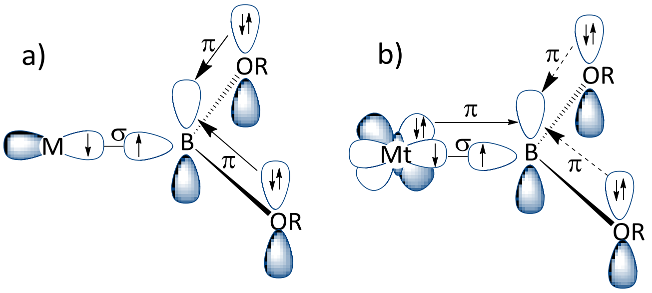


Figure 2.2 Boron-metal-bonding considerations: a) M-B(OR)$_2$; b) Mt-B(OR)$_2$.

Herein, we have constructed a map to trace some of the important trends when boron is 1) bonded to main-group metals; 2) bonded to transition metals and rare-earth metals; and 3) bonded to sp^3-hybridized boryl units. The map can help to identify the electronic character at certain B centers and can be useful for selecting the appropriate trivalent boron compound for a desired application. Towards this end, we carried out DFT calculations (B3LYP functional) on a large and varied set of trivalent boron compounds. Then, the map was constructed from computational electronic descriptors that were derived from NBO analysis in vacuum. The advantage of these descriptors is that they measure the intrinsic properties of the boryl fragments without the influence of additional factors, such as the solvent or the type of counterion.

2.2. Results and Discussion

2.2.1. Trivalent boranes with boron-alkali-metal- and boron-alkaline-earth-metal bonds

The potential of lithioboranes as nucleophilic reagents was first suggested by Schleyer and co-workers on the basis of theoretical calculations (Figure 2.3 A).[4] According to theoretical calculations,[4, 7] lithiation at the boron center increases the charge density on the boron atom. The addition of lithioboranes to formaldehyde has been computed[4] and it proceeded in a similar manner to the addition of methyllithium (Scheme 2.1). Despite the fact that the boron atom bears a positive charge in $LiBF_2$ and $LiB(CH_3)_2$, the predicted reactivity proceeds through nucleophilic attack of the boryl anion.

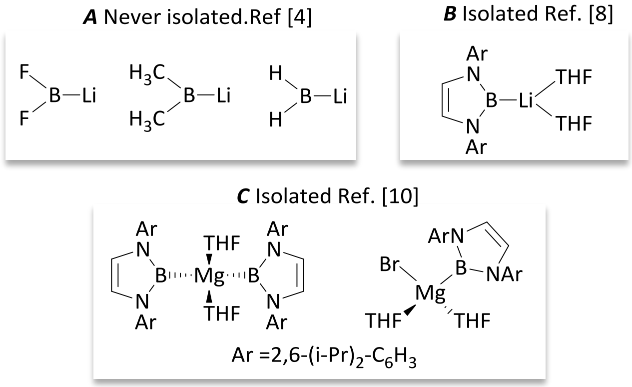
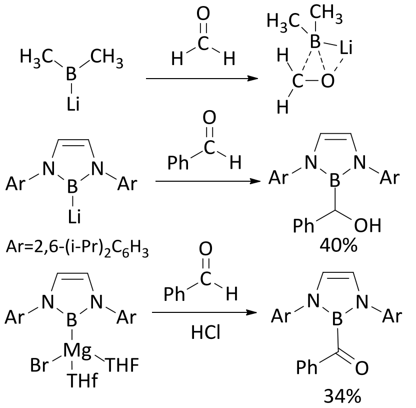


Figure 2.3 Representative trivalent boranes with boron-alkali and boron-alkaline-earth-metals.

More recently, the first isolated diamino-substituted boryllithium compound (Figure 2.3 B) was shown to react with a variety of organic electrophiles[8] and the reactions with carbonyl groups gave their corresponding products in the same way that carbanions react. For instance, the boryl moiety attacked the carbonyl group of benzaldehyde to afford, upon subseqüent protonation, the corresponding α-borylbenzyl alcohol adduct (Scheme 2.1).



Scheme 2.1 Reactivity of boryllithium and borylmagnesium compounds with organic electrophiles.

Moving from alkali metals to alkaline-earth metals, the elaboration of a reliable synthetic route to stable boryllithium compounds has also allowed the synthesis and characterization of borylmagnesium compounds (Figure 2.3 C), including the first example of a B-Mg single bond[9] (excluding compounds such as superconductor MgB_2).

Interestingly, changing the counterion of the boryl anion from Li to Mg caused its reactivity towards the electrophile reagents to change considerably. In contrast to the reactivity of boryllithium with benzaldehyde, which gave the α-borylbenzyl alcohol in high yield, the reaction of borylmagnesium bromide (Figure 2.3 C) with 1–3 equivalents of benzaldehyde afforded a mixture of products, of which, unexpectedly, benzoylborane was formed as the main product (Scheme 2.1).[9]

To understand the origin of the different reactivities of trivalent boranes with boron–alkali- and boron–alkaline-earth metals, we performed DFT calculations that reproduced the main structural features of isolated boryllithium- and borylmagnesium compounds. The calculated B-Li and B-Mg distances (2.27 and 2.30 Å) are comparable and are close to the experimentally obtained values (2.28 and 2.28 Å, respectively).[8a, 9] Table 2.1 shows the main electronic parameters, as obtained by natural bond orbital (NBO) analysis. As previously shown, with the exception of $LiBH_2$, the boron atom remains positively charged and the partial negative charge on the boryl anion moiety is located on the boron substituents.[4] However, the charge that is supported by the overall boryl fragment is negative. In agreement with their relative reactivity, the charge on the diamino-substituted boryl fragment is more negative for the boryllithium compounds than for the borylmagnesium compounds. Moreover, the occupancy of the perpendicular boron p orbital (p_z) is significantly larger for the diamino-substituted boryl compounds than for $LiBF_2$, $LiB(CH_3)_2$, and $LiBH_2$. Thus, we expect a larger stability of these former boryl compounds through π-donation of the N substituents on the boron center, which explains why only diamino-substituted boryllithium compounds have been isolated.

Table 2.1 Selected electronic properties that were derived from NBO analysis of $LiBR_2$ and $MgBR_2$ compounds (Figure 2.3). Charges and occupancies are in the atomic units. [a]

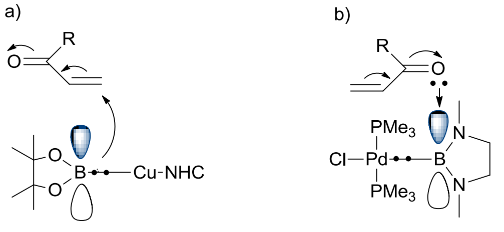
Compound	Charge			B-M bond	
	qB	q[B]	p_z occ.	M %	B p/s ratio
(ArNCH=CHNAr)B-Li	0.10	-0.63	0.47	14	1.5
(ArNCH=CHNAr)B-MgBr	0.38	-0.46	0.53	23	1.5
$(CH_3)_2B$-Li	0.24	-0.47	0.10	27	2.7
H_2B-Li	-0.31	-0.54	0.00	23	2.1
F_2B-Li	0.51	-0.54	0.24	19	1.4

[a] Charges on the boron aton (qB) and on the boryl fragment (q[B]); occupancy of the perpendicular boron p orbital (p_z occ.); and the M % contribution and boron p/s-population ratio in the M-B σ-bond. Ar = 2,6-(*i*Pr)$_2$-C_6H_3.

In the case of the virtual lithioborane compounds ($LiBF_2$, $LiB(CH_3)_2$, $LiBH_2$), their addition to formaldehyde has been computed as a measure of the nucleophilicity of the boryl group, with very low energy barriers (<6 kcal·mol^{-1}).[4] Their relative nucleophilicity followed the order: $(CH_3)_2BLi$ > H_2BLi > F_2BLi and their computed activation energies were 4.1, 4.3, and 5.9 kcal·mol^{-1}, respectively. Although the differences in the energy barriers are small, the reactivity does not correlate with the charge on the boryl fragment or with the charge on the boron atom (Table 2.1). Structural data, such as X-B-X angles, can reflect the rehybridization on B. The p/s ratio of the B atom of the B-M sigma bond can also be an indicator of the intrinsic nucleophilicity of the boryl moiety. Therefore, for M-BX_2 (M = alkali- or alkaline-earth metals), we observed in this present study that the larger the amount of p character, the more reactive as a nucleophile the boryl fragment can be. From a frontier molecular orbital perspective, we expected that the orbital energy of a hybrid sp orbital would increase with its p character because p orbitals are higher in energy than s orbitals. As a consequence, the higher in energy the sp orbital is, the larger degree of nucleophilic character is expected. Accordingly, the p/s ratio on the B atom for $(CH_3)_2BLi$, H_2BLi, and F_2BLi (2.7, 2.1, and 1.4, respectively) correlates with the calculated nucleophilic reactivity of the boryl moiety (activation barriers).

2.2.2. Trivalent boranes with boron-transition-metal bonds

Since Nöth and Schmid reported the first complexes in which a boryl group (BR_2) was directly bonded to a transition metal through a boron atom,[10] more than hundred examples have been reported, many of which have been structurally characterized by X-ray diffraction methods.[11] The reactivity of boryl–transition-metal complexes switches depending on the nature of the transition metal. For example, borylcopper complexes seem to react in a complementary manner to borylpalladium complexes with α,β-unsaturated carbonyl ketones (Scheme 2.2). The copper-mediated β-boration to α,β-unsaturated carbonyl compounds was first developed by Miyaura and co-workers[12] and by Hosomi and co-workers.[13] From a theoretical point of view, Lin, Marder, and co-workers provided evidence that the boryl moiety could act as a nucleophile and could attack at the beta carbon of the substrate, thereby promoting the formation of β-boryl carbonyl compounds (Scheme 2.2a).[14] In contrast, the analogous reaction of *trans*-[Pd(B(NMe-CH_2-CH_2-NMe))(Cl)(PMe_3)$_2$]with an α,β-unsaturated ketone was reported by Onozawa and Tanaka, which suggested that the insertion of the substrate into the Pd-B bond took place with reversed regioselectivity, thereby providing the 1,4-addition product in which the Pd was bonded to the beta-carbon atom and the boryl unit was bonded to the oxygen atom (Scheme 2.2b).[15]



The Cu-B bonding pair initiates the reaction

The "empty" p orbital initiates the reaction

Scheme 2.2 Reactivity of α,β-unsaturated carbonyl compounds with a) a borylcopper complex that was modified with N-heterocyclic carbenes and b) a borylpalladium complex that was modified with phosphines.

Since Lin, Marder, and co-workers showed how the substituents on the boryl moieties can influence the nature of the Mt-B σ-bonding interactions,[16] we assume that this effect may also have implications on the reactivity of the boryl moiety. For instance, in the case of *trans*-[Pt(BX_2)(Cl)(PMe_3)$_2$] complexes, they observed a nice correlation between the boron p/s-population ratio and the percentage contribution of Pt to the Pt-B σ-bond, thus suggesting that a boryl ligand that has more boron p character releases more electron density to the metal, thereby strengthening the covalent interaction between the Pt and B atoms. Conversely, the greater the s character in the Pt-B σ-bond, the more polarized the bond becomes towards the B atom.[16] To examine how the nature of the transition metal influences the nature of the Mt-B bond and to assess whether it can be used to gauge the reactivity of the boryl moieties, we decided to carry out similar computational studies for late-, middle-, and early-transition-metal complexes.

Initially, we analyzed the striking cases of Cu and Pd complexes (see above, Scheme 2.2). The Cu-B σ-bond in the isolated complex [Cu(Bpin)(NHC)][17] (NHC = N-heterocyclic carbene 1,3-bis(2,6-diisopropyl)phenyl imidazol-2-ylidene) was more polarized towards the B atom (B% = 68.6), in contrast to the palladium complex in which the Pd-B σ-bond was computed to be less polarized towards the B atom (B% = 53.2, Figure 2.4). Moreover, the s character in the Cu-B σ-bond is significantly greater (p/s ratio = 0.94) than in the Pd-B σ-bond (p/s ratio = 1.63, Figure 2.4). These differences might justify the nucleophilic addition of pinacolboryl from the copper complex to the α,β-unsaturated ketone. Interestingly, the influence of the p/s ratio in Mt-B bonds on the reactivity shows the opposite trend that in boron–alkali-metal and boron–alkaline-earth-metal bonds. This type of analysis was useful for examining both the nature of the Mt-B bond and the plausible nucleophilic behavior of the boryl moiety.

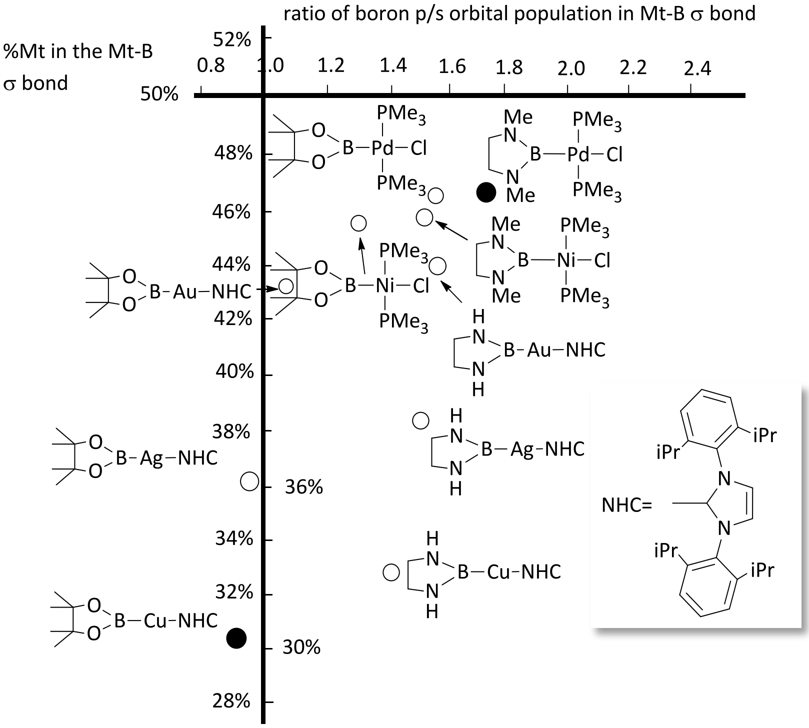


Figure 2.4 Representation of Mt % versus boron p/s-population ratios in the Pd-B, Ni-B, Ag-B, and Au-B σ-bonds of isolated- (●) and virtual complexes (○).

Figure 2.4 also shows a plot of Mt % versus boron p/s-population ratios in related complexes of Group 10 metals, which we consider to be "virtual" because they have not been synthesized yet. When the pinacolboryl moiety (Bpin) is present in an analogous virtual Pd complex *trans*-[Pd(Bpin)(Cl)$(PMe_3)_2$], we found that the boron p/s ratio diminishes slightly, as in the case of Pt complexes.[16] Calculations on the analogous virtual nickel complexes, *trans*-[Ni(B(NMe-CH_2-CH_2-NMe))(Cl)-$(PMe_3)_2$] and *trans*-[Ni(Bpin)(Cl)$(PMe_3)_2$], showed similar values, that is, the Ni-Bpin bond was more polarized towards the boron atom (B% = 54.3) with the lowest boron p/s-population ratio (1.33, Figure 2.4). In this case, the polarization of the Mt-B bond towards the boron atom seems to increase in the order Pt < Pd < Ni. In addition, the boryl ligand B(NMe-CH_2-CH_2-NMe) seems to have a greater σ-donating ability than Bpin and uses a hybrid orbital that has more p character to form the σ-bond with Pd or Ni. We observed that the less-electronegative substituents on the B atom diminished the Mt % in the Mt-B bond, thereby resulting in a less-polarized Mt-B bond.

Next, we examined the nature of the Mt-B bond in similar -but virtual- borylcopper complexes (Figure 2.4). Our calculations highlighted the strong polarization of the Cu-B bond towards the boryl moiety (Cu: 33.2%, B: 66.8%) with a boron p/s ratio of 1.4 in [Cu(B(NHCH$_2$-CH$_2$NH))(NHC)] (NHC = N-heterocyclic carbene 1,3-bis(2,6-diisopropyl)-phenyl imidazol-2-ylidene; Figure 2.4). However, its plausible nucleophilic character is less than the pinacolboryl moiety in the analogous isolated complex [Cu(Bpin)(NHC)] (NHC = 1,3-bis(2,6-diisopropyl)phenyl imidazol-2-ylidene). At this point, a question naturally arises: what can we expect with the corresponding borylsilver and borylgold complexes? Therefore, we performed similar theoretical calculations on virtual complexes [Mt(B(NHCH$_2$-CH$_2$NH))(NHC)] and [Mt(Bpin)(NHC)], where Mt = Ag and Au (NHC = 1,3-bis(2,6-diisopropyl)phenyl imidazol-2-ylidene). In accordance with the trend that we found for the Group 10 transition metals, the more we move down Group 11, the lower the contribution of B to the Mt-B bond and the more enhanced the boron p/s-population ratio becomes (Figure 2.4). Interestingly, the replacement of B(NHCH$_2$-CH$_2$NH) with Bpin moieties equally favored a slight enhancement in the B% and in the s character of the hybrid boron orbital for each complex. These results clearly show that the polarity of the Mt-B bond in Group 11 complexes increases in the order $\mathrm{Au^I} < \mathrm{Ag^I} < \mathrm{Cu^I}$ and can be further enhanced when pinacolboryl moieties are involved. To date, the reactivity of the analogous [Ag(Bpin)(NHC)] and [Au(Bpin)(NHC)] complexes in the conjugate addition reaction of boron to α,β-unsaturated carbonyl compounds has not been described, presumably owing to the fact that the pinacolboryl moieties in these complexes have a lower nucleophilic character. In this case, the combination of both the efficiency and low cost of the borylcopper complexes[18] justifies the generalized use of the in situ formed nucleophilic boryl synthons over electrophilic substrates as the basis of efficient synthetic routes towards organoborane compounds.[2]

After examining the structural and electronic properties of the boryl–transition-metal complexes of Group 10 and 11 metals, we became interested in exploring the nature of the Mt-B σ-bonds in complexes of Group 12 transition metals. To the best of our knowledge, two different types of Zn-B complexes have been synthesized: lithium boryldibromozincate and its corresponding diborylzinc species.[19] The nucleophilic behavior of the former compound has been associated with its reactivity with 2-cyclohexen-1-one, thereby giving the corresponding conjugate-boron-addition product, although with a slightly lower yield (41%) than with the analogous borylcopper compound.[19] When the polarization of the Zn-B bond in the boryldibromozincate and diborylzinc species was calculated, we observed that the contribution of boron to the B-Zn bonds was 66.4% and 68.2%, with boron p/s ratio of 1.68 and 1.54 respectively (Figure 2.5), which were comparable to those in the copper [Cu(B(NHCH$_2$-CH$_2$NH))-(NHC)] complexes (Figure 2.4).

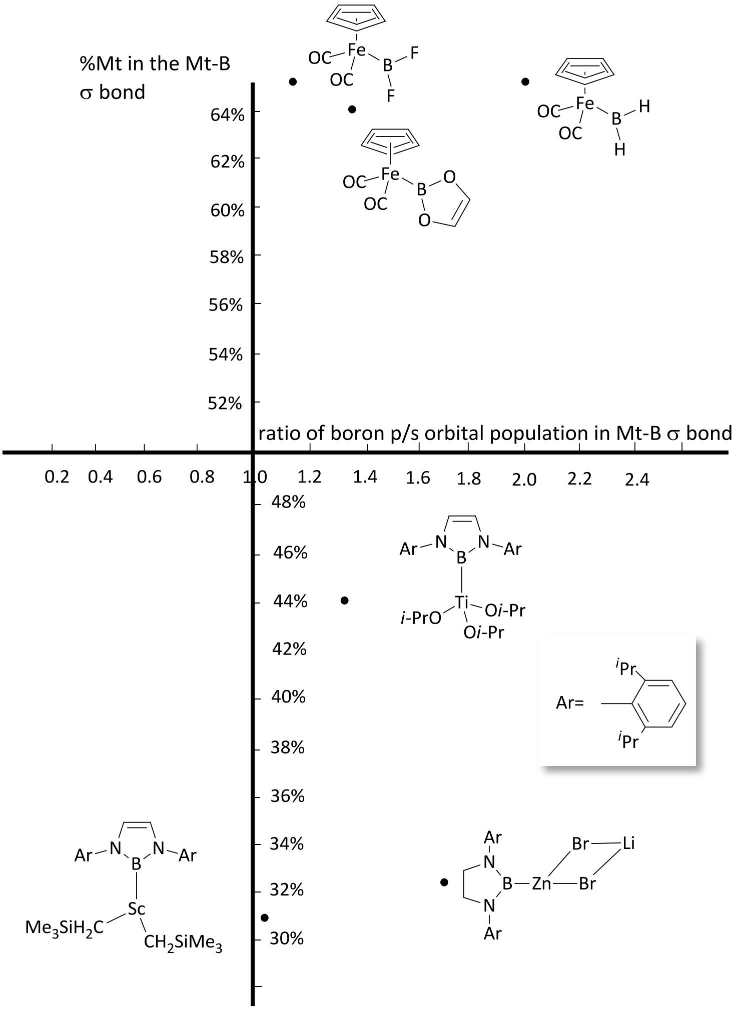


Figure 2.5 Representation of Mt % versus boron p/s ratio in the Zn-B, Fe-B, Ti-B, and Sc-B σ-bonds for the synthesized complexes.

The next question that we wanted to address was what would be expected to happen for the boryl–middle-transition-metal- and boryl–early-transition-metal complexes? To answer this question, we selected isolated complexes that were based on the coordination of boryl moieties to Fe and Ti. An analysis of the metal–boron interactions in complexes of molecular formula $[Fe(BL_2)Cp(CO)_2]$ has been already performed by Aldridge and co-workers,[20] who used NBO methods to reveal that the Fe-B bond was markedly polarized toward the iron center. We recalculated these complexes at our selected computational level and, for the model complex $[FeB(OCHCHO)Cp(CO)_2]$, the contribution of iron to the bond orbital was 65% (Figure 2.5). Of particular note is the significant increase in p character at the boron end of the Fe-B bond in $[Fe(BH_2)Cp(CO)_2]$, as well as the significantly lower p character at the boron atom in $[Fe(BF_2)Cp(CO)_2]$ as a consequence of the more-electronegative substituents on the B atom.

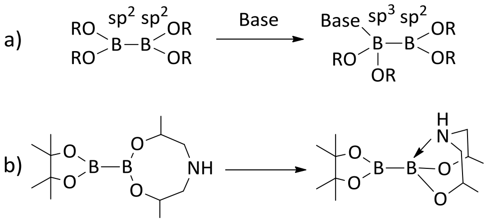
Examples of boryl–transition-metal complexes of Group 4 are very rare, but the reaction of boryllithium with $Ti(O\textit{i}Pr)_4$ has allowed the isolation and solid-state X-ray characterization of boryltitanium triisopropoxide.[21] A previous theoretical calculation on a related model molecule revealed that the boron–metal bond had a covalent character.[21] Our analysis on the isolated boryltitanium triisopropoxide confirmed the slight polarization of the Ti-B bond towards the B center (Ti % = 44 %) and the relatively low boron p/s ratio (1.31, Figure 2.5).

For the sake of completeness, we also studied boryl–transition-metal complexes of Group 3 metals, as well as metals in the f block. Recently, some new mixed boryl–dialkyl complexes of rare-earth metals have been synthesized from boryllithium compounds.[22] Atoms-in-molecules (AIM) data for the Ln-B bond critical points (bcp) have indicated that the Ln-B bond is predominantly ionic, albeit with a highly polarized covalent contribution to the interaction. From these data, it has also been suggested that the boryl–scandium complex contains the least-ionic Ln-B bond whilst the related boryl–yttrium complex contains the most-ionic bond. Herein, we also examined the polarization of the Sc-B bond and the boron p/s ratios. We observed that the polarization of the Sc-B bond towards the B atom is one of the highest among the complexes that we have studied (B % = 69.3, Sc % = 30.7), with a boron p/s ratio of 1.03 (Figure 2.5). Does the boryl-scandium complex provide the same type of nucleophilic boryl synthons? Preliminary reactivity studies have shown that the Sc-B bonds can undergo insertion reactions with carbodiimide and carbon monoxide to give new boron-containing rare-earth-metal complexes in which the boron atom is bonded to the C center after CO-insertion.[22b] With all of these data in mind, we conclude that boryl moieties that are coordinated to Cu, Zn, or Sc show the highest polarization of the Mt-B bond towards the boryl moiety.

2.2.3. Trivalent boranes with B(sp^2)-B(sp^3) bonds

We also became interested to study interelement compounds, that is, compounds that contain B-B, B-Si, B-Ge, and B-Sn bonds.[23] For silylboranes,[24] germanylboranes, and stannylboranes, their reactivity indicates that the boron moiety is acting as the electrophilic counterpart, owing to its higher Lewis acid character than that of Si, Ge, and Sn, respectively. However, probably the most-interesting question is what is the nature of B-B bonds and how are expected to behave.

The symmetric homoelement–element linkage should be principally covalent. However, appropriate Lewis bases can interact with one of the boron moieties to form Lewis acid–base adducts and the resulting species would contain a rehybridized B(sp^2)-B(sp^3) system (Scheme 2.3a).[25] These adducts can be derived from both intermolecular and intramolecular interactions with the Lewis base. An example of the latter is the pinacolato diisopropanolaminato diboron,[26] in which the N atom intramolecularly interacts with one of the boron moieties, thereby resulting in a distorted tetrahedral geometry around the boron acceptor (Scheme 2.3b). As a consequence, the B-B bond length increases and the new tetravalent boron center loses any O-B π bonding.



Scheme 2.3 Formation of a Lewis acid-base adduct and rehybridization of the boron atom.

The intermolecular activation of symmetrical diboron compounds, such as bis(pinacolato)diboron, can create a significant nucleophilic boryl B(sp^2) synthon, which, in the absence of any transition-metal complexes, can be efficiently added to the C_β atoms of α,β-unsaturated carbonyl compounds.[27] In a previous contribution, the addition of the MeO$^-$→bis(pinacolato)diboron adduct to non-activated olefins was explored, fouding that the nucleophilic B(sp^2) boryl moiety can attack non-activated C=C double bonds.[28] Computational studies identified the interaction as an overlap between the strongly polarized B-B σ-bond (HOMO) and the antibonding π^* orbital (LUMO) of the C=C bond, thus confirming the nucleophilic character of the boryl moiety.[28]

Previous DFT studies have demonstrated that, in the new unsymmetrical mixed B(sp^2)-B(sp^3) diboron compounds, which are formed by the addition of MeO$^-$[27c, 27d, 28] or N-heretocyclic carbenes,[27a, 27b, 27e] the B-B bond is polarized towards the B(sp^2) atom and the difference between the atomic charges of the boron atoms is higher in the case of the MeO$^-$ adducts than in the N-heterocyclic carbene adducts.

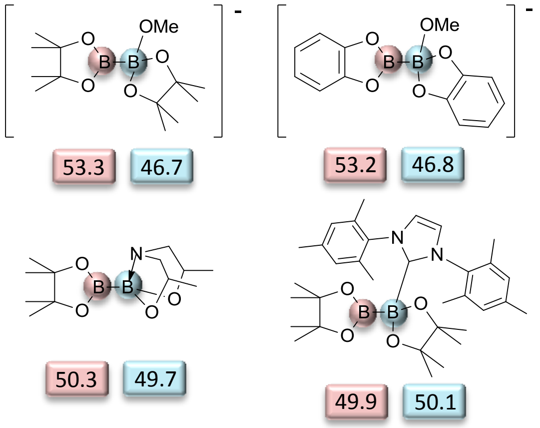


Figure 2.6 NBO analysis of B % in B(sp^2)-B(sp^3) σ-bond for Lewis acid-base adducts.

To compare the nature of the B(sp^2)-B(sp^3) σ-bond, we also carried out NBO calculations for the Lewis acid-base adducts. The highest polarization towards the B(sp^2) moiety was found in the MeO$^-$→bis(pinacolato)diboron and MeO$^-$ →bis(catecholato)diboron adducts, (Bpin(sp^2) = 53.3%, Bcat(sp^2) = 53.2%). Finally, an insignificant polarized B(sp^2)-B(sp^3) linkage was found for the NHC→bis(pinacolato)diboron adduct, B(sp^2) (49.9%)-B(sp^3) (50.1%, Figure 2.6).

In general, the polarization towards the B atom (< 55%) is not too large compared with that in the Cu-B or Zn-B bonds (> 65%). However, the p/s ratio of the B(sp^2) atom (in the range 1.05–1.19 for pinacolboryl moieties) diminishes significantly with respect to the Bpin fragment of the Pd complex (p/s = 1.47). Within the examples that were analyzed, the p/s ratio follows the order MeO^-→Bcat < MeO^-→Bpin < NHC→Bpin ≈ N(intramolecular)→Bpin. It seems that the addition of a Lewis base to diboron reagents not only polarizes the B-B bond but it also increases the polarizability of the B(sp^2) moiety and, hence, its propensity to react with soft electrophiles.

2.2.4. Trend map

Next, we considered that it would be interesting to conclude this study by designing a map that correlates the charge on the boryl fragment in each case with the boron p/s-population ratio in the M-B or B(sp^3)-B(sp^2) σ bond (Figure 2.7). Although these factors are not independent and are not the only ones that determine the nucleophilicity of the boryl moiety, a map can help to identify certain trends and can be useful for the synthetic chemist to select the appropriate trivalent boron compound, depending on the sought reactivity. The overall charge on the boryl fragments provides an indication of the nucleophilic character that is induced by its counterpart, whereas the boron p/s ratio gives a measure of the intrinsic nucleophilicity of the boryl fragment and, at the same time, reflects the polarization in the M-B or B(sp^3)-B(sp^2) σ-bond. The negative charge on the boryl fragments correlates with the polarization towards the B moiety on the Mt-B σ-bond and it is also a valid indicator for gauging the polarity of the σ-bond between the main-group elements and the B atom.

The map includes all three types of boryl moieties that we have discussed above: 1) bonded to main-group metals; 2) coordinated to transition metals and rare-earth metals; and 3) bonded to an sp^3 boryl unit. In the bottom part of the map the [Li(B(NAr-CH_2-CH_2-NAr)] compound can be found, in which the boryl fragment bears the highest negative charge (about -0.63). The [Cu(Bpin)NHC] complex is located in the bottom-left part of the map. The charge on the boryl fragment is also highly negative (about -0.41) and the boron p/s-population ratio (about 0.9) is one of those with the greatest s character. Interestingly, although there is a very similar charge on the boryl fragments in [Cu-(Bpin)NHC] and [Cu(B(NAr-CH_2-CH_2-NAr)NHC], the boron p/s ratio in the second complex is significantly higher, thus indicating that the order of magnitude of the p/s ratio is mainly determined by the nature of the substituents on the B atom in the boryl ligand.

Among the transition metals that were studied, the boryl fragments that were coordinated to zinc showed the highest negative charge (about -0.5). In fact, the boryl fragments that were coordinated to transition metals of Groups 11 and 12 showed a trend: the negative charge density on the boryl fragments increased depending on the transition metal in the order [$AuBX_2L$] < [$AgBX_2L$] < [$CuBX_2L$] < [$ZnBX_2L$]. The nature of the ligands that modify these complexes is also very influential on both parameters. For example, in the case of [AuB(NAr-CH_2-CH_2-NAr)(NHC)] and [AuB(NAr-CH_2-CH_2-NAr)PPh_3], the complex that was modified with N-heterocyclic carbene ligands was the one that generated the larger charge on the boryl fragment with a lower boron p/s-population ratio. The boryl ligand in the scandium complex has a similar negative charge to that in Ag-Bpin and Au-Bpin complexes, but the p/s-population ratio (about 1.0) is significantly lower than for the other N substituted boryl ligands showed in the map. In the titanium complex, the boryl charge decreases significantly (about -0.1) and the p/s-population ratio increases to about 1.3.

In an intermediate group are the diboron reagents that are activated with Lewis bases, in which the negative charge on the B(sp^2) fragment is modest but the boron p/s-population ratios are very low. Their position on the map indicates that the B(sp^3)-B(sp^2) σ-bond is weakly polarized. The MeO^- ion clearly induces greater polarization than the nitrogen- or carbon-donor Lewis bases. Therefore, the B(sp^2) fragment in the MeO^-→bis(pinacolato)diboron and MeO^-→bis(catecholato)-diboron adducts has a slight more negative charge than the boryl fragment in the N→B- and NHC→B adducts. This result could suggest that the Bpin-(sp^2) fragment in the MeO^-→bis(pinacolato)diboron adduct acts as a nucleophile in the absence of metals but that the Bpin from pinacolato diisopropanolaminato diboron only transmetalates with Cu-X species.

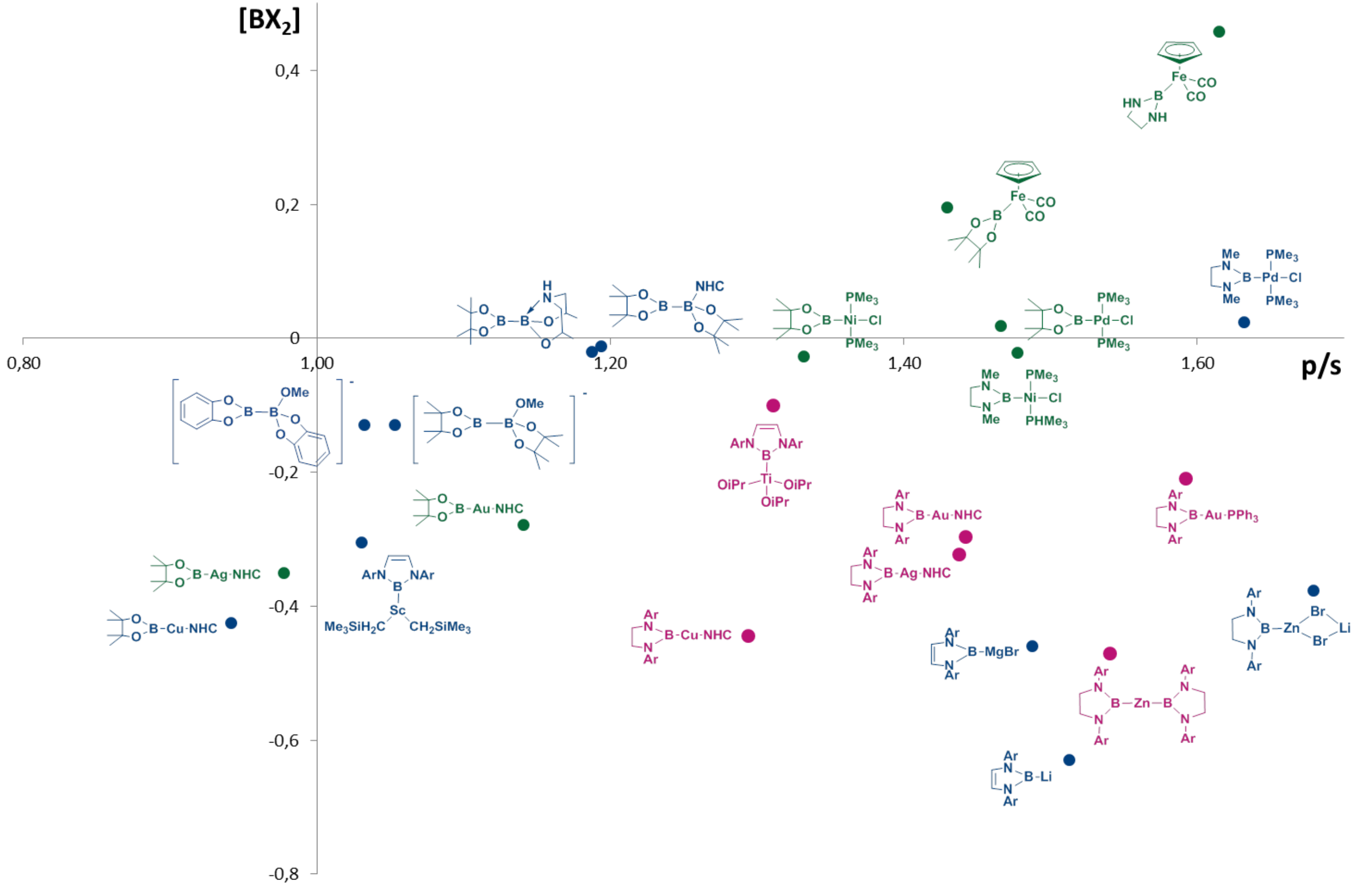


Figure 2.7 Correlation between the charge on the [BX$_2$] fragment and the boron p/s-population ratio for synthetized and reactivity tested system (blue); synthetized systems (pink) and for virtual system (green).

The last group represents boryl moieties that are coordinated to transition-metal complexes of Group 10 metals and iron. In all of these complexes, the charge on the boryl fragment is close to zero or is even positive (the atoms that are coordinated to Fe are the most-positively charged). The values for the boron p/s-population ratio are dependent on the metal, in the order [$PdBX_2L_3$] > [$NiBX_2L_3$] > [$FeBX_2L_3$], and, in particular, on the nature of the substituents on the boryl moiety: [$MtB(NMe\text{-}CH_2\text{-}CH_2\text{-}NMe)L_3$] > [$Mt(Bpin)L_3$] (Mt = Pd, Ni, Fe). The results for these boryl–transition-metal complexes are in complete agreement with the lack of examples in which the boryl moiety is acting as a nucleophilic synthon.

To establish a gradient in the nucleophilic character of the trivalent boron moieties that were considered in this study, we need to summarize a few ideas: 1) For the same type of boryl moiety, the higher the negative charge on the boryl fragment, the better as nucleophile the boryl synthon can be. 2) Taking into consideration the boron p/s ratio in the M-B σ-bond, it seems that, within the given body of examples, it can also be an indicator of the nucleophilicity of the boryl moiety. Decreasing the boron p/s ratio increases the polarity of the M-B bond and, hence, it favors the generation of the boron nucleophile through heterolytic cleavage. However, we should note that, in the case of strongly polar M-B bonds, this trend might change; that is, the more s character, the more-stable the anion and the more p character, the more reactive the boryl fragment is as a nucleophile.

The map only represents species in which the substituents on the B atoms are N or O because they provide boryl species with a lower Lewis acidity on the boron center and, consequently, they are easier to handle experimentally.[29] The selection of the nucleophilic trivalent boron compound will depend on the type of electrophile it reacts with, but, even more important, is the availability of the reagent. For example, the boryllithium compounds are certainly great nucleophiles, but they are difficult to synthesize and handle. On the other hand, the [Cu(Bpin)L] system seems to provide a singular nucleophilic trivalent boryl unit to react with a large number of electrophiles[2] and it is even easy to prepare in situ from CuCl/NaO*t*Bu/Bpin-Bpin. Another advantage of the [Cu(Bpin)L] system is that, with the introduction of a chiral ligand (L; both phosphines and N-heterocyclic carbenes), the complexes can be used in asymmetric synthesis.

Finally, unlike the application of boryl–alkali metal species, the borylcopper complexes are involved in very efficient catalytic processes, thus making their application possible on a large scale. The organocatalytic scenario is another alternative because, although the nucleophilic character of the B(sp^2) fragment of MeO$^-$→bis(pinacolato)diboron adduct is lower than that in the borylcopper systems, the simplicity of the system can be considered to be a great advantage (for example, Bpin-Bpin/base/MeOH).

2.3. Conclusions

In this chapter, we have systematically studied several types of boryl moieties that were either bonded to main group metals, coordinated to transition metals, coordinated to rare-earth metals, or bonded to sp^3-hybridized boryl units. By taking into consideration the charge on the boryl fragment and the boron p/s-population ratio, we were able to establish a gradient of nucleophilic character for the trivalent boron moieties that were considered in this study.

We constructed a map and we identified several groups of trivalent boron compounds that could act as nucleophiles or electrophiles. The versatile electronic properties of trivalent boron compounds depend on the nature of the metal or element that is bonded to it, but also on the substituents on the boron moiety.

In general, the trend that was observed for all of the trivalent boron compounds that were studied herein correlates well with their reported reactivity. We hope that this map can open up new perspectives on the preparation and use of trivalent boron compounds with the desired nucleophilic character.

2.4. Computational Methods

All calculations were performed by using the Gaussian09 series of programs.[30] Full quantum mechanical calculations on model systems were performed within the framework of density functional theory (DFT)[31] by using the B3LYP functional.[32] A quasi-relativistic effective core-potential operator was used to represent the innermost electrons of the transition-metal atoms, as well as the innermost electrons of the P atoms.[33] The basis set for transition-metal- and P atoms was that associated with the pseudopotential,[33] with a standard double-ξ LANL2DZ contraction,[30] and, in the case of P, the basis set was supplemented by a d shell (exponent = 0.387).[34] The rest of the atoms were represented by means of the 6-31G(d,p) basis set.[35] All geometry-optimizations were full, with no restrictions. The bonding situation of the molecules, as well as the fragment charges, was analyzed by using the NBO method.[36]

2.5. Appendix chapter 2.

Appendix 2.1 Selected electronic properties derived from NBO analysis. Charges in a.u. [a]

						Charges NBO		
	%M(or B sp^3)	%B	s(B)	p(B)	p/s B	q(B)	q(M or B sp^3)	q[B]
$LiB(B(NAr)_2(CH)_2)$	14,3	85,7	39,8	60,2	1,51	0,1	0,63	-0,63
$Li(BF_2)$	19,23	80,8	42,3	57,6	1,36	0,51	0,54	-0,54
$Li(BH_2)$	22,8	77,2	32,5	67,5	2,08	-0,31	0,54	-0,54
$Zn(B(NAr)_2(CH_2)_2)_2$	31,8	68,2	39,4	60,6	1,54	0,22	0,95	-0,47
$Li(B(CH_3)_2)$	26,6	73,4	26,7	73,3	2,74	0,24	0,48	-0,47
$Mg(B(NAr)_2(CH)_2)Br$	22,6	77,4	40,2	59,8	1,49	0,38	0,14	-0,46
$Cu(B(NAr)_2(CH_2)_2NHC$	29,2	70,8	43,6	56,4	1,29	0,32	0,27	-0,44
Cu(Bpin)NHC	31,5	68,6	51,5	48,5	0,94	0,51	0,25	-0,43
$Cu(B(NH)_2(CH_2)_2)NHC$	33,2	66,8	41,7	58,3	1,40	0,32	0,24	-0,39
$Zn(B(NAr)_2(CH_2)_2)Br_2Li$	33,6	66,4	37,3	62,7	1,68	0,29	0,94	-0,38
Ag(Bpin)NHC	36,0	64,0	50,5	49,4	0,98	0,58	0,16	-0,35
$Ag(B(NH)_2(CH_2)_2)NHC$	37,9	62,1	39,3	60,8	1,55	0,40	0,14	-0,33
$Ag(B(NAr)_2(CH_2)_2)$ NHC	34,2	65,8	41,0	59,0	1,44	0,40	0,17	-0,32
$Sc(B(NAr)_2(CH)_2)_2(CH_2SiMe_3)_2$	30,7	69,3	49,3	50,8	1,03	0,30	1,25	-0,31
$Au(B(NAr)_2(CH_2)_2)NHC$	41,0	59,0	40,9	59,0	1,44	0,45	0,06	-0,30
Au(Bpin)NHC	42,6	57,4	46,7	53,3	1,14	0,63	0,06	-0,28
$Au(B(NH)_2(CH_2)_2)NHC$	43,7	56,3	39,4	60,6	1,54	0,43	0,06	-0,26
$Au(B(NAr)_2(CH_2)_2)PPh_3$	45,0	55,0	38,6	61,4	1,59	0,50	-0,01	-0,21
$B_2cat_2\text{-}OMe^-$	46,8	53,2	49,2	50,8	1,03	0,88	0,81	-0,13
$B_2pin_2\text{-}OMe^-$	46,7	53,3	48,7	51,3	1,05	0,87	0,80	-0,13
$Ti(B(NAr)_2(CH)_2)(O\textit{i}Pr)_3$	44,0	56,0	43,3	56,7	1,31	0,51	1,13	-0,10
$Ni(Bpin)(PMe_3)_2Cl$	45,7	54,3	42,9	57,1	1,33	0,89	-0,31	-0,03
$Ni(B(NMe)_2(CH_2)_2)Cl(PMe_3)_2$	46,0	54,0	40,4	59,6	1,48	0,73	-0,33	-0,02
PDIPA diboron	49,7	50,3	45,7	54,3	1,19	0,87	0,77	-0,02
$B_2pin_2\text{-}NHC$	50,1	49,9	45,6	54,4	1,19	0,90	0,55	-0,01

						Charges NBO		
	%M(or B sp^3)	%B	s(B)	p(B)	p/s B	q(B)	q(M or B sp^3)	q[B]
Pd(Bpin)Cl(PMe$_3$)$_2$	47,1	52,9	40,5	59,4	1,47	0,93	-0,32	0,02
Pd(B(NMe)$_2$(CH$_2$)$_2$)Cl (PMe$_3$)$_2$	46,8	53,2	38,0	62,0	1,63	0,75	-0,31	0,02
Fe(Bpin)Cp(CO)$_2$	65,2	34,9	41,2	58,9	1,43	1,09	-1,14	0,20
Fe(BH$_2$)Cp(CO)$_2$	67,7	32,3	32,8	67,1	2,05	0,35	-1,16	0,21
Fe(BO$_2$(CH)$_2$)Cp(CO)$_2$	64,7	35,3	43,3	56,6	1,31	1,08	-1,16	0,26
Fe(BF$_2$)Cp(CO)$_2$	67,6	32,4	46,5	53,3	1,15	1,25	-1,23	0,27
Fe(B(NH)$_2$(CH$_2$)$_2$)Cp (CO)$_2$	66,2	33,8	38,2	61,7	1,62	0,91	-1,12	0,46

[a] Contribution of the %M(or B sp^3) and %B in the M-B σ-bond, boron p/s population, charges at the boron atom (q(B)), at the metal or B(sp^3) atom (q(M or B sp^3)) and at the boryl fragment (q[B]).

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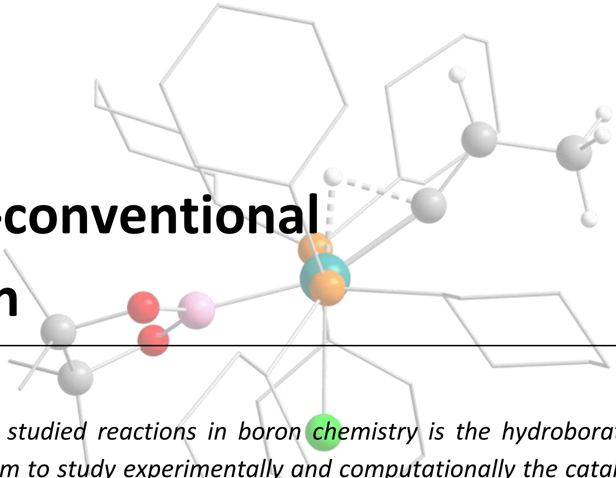
Chapter 3

Catalytic non-conventional hydroboration



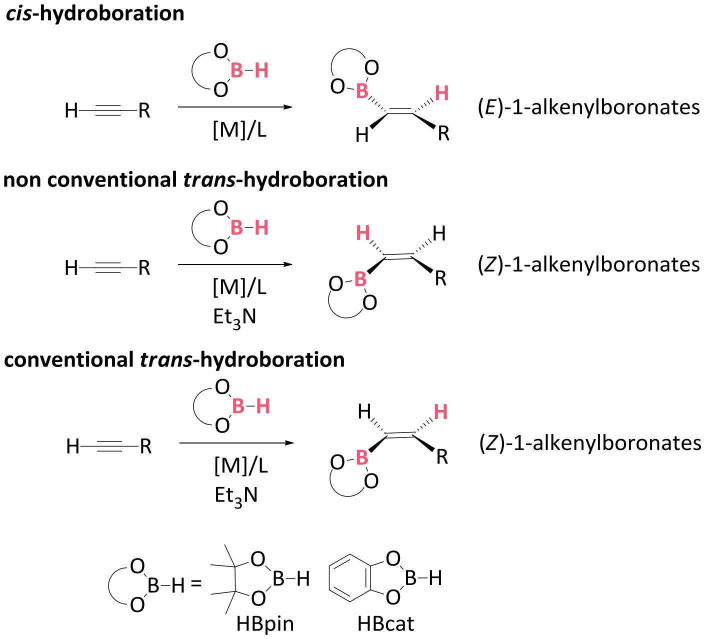
One of the most famous and studied reactions in boron chemistry is the hydroboration reaction. In this chapter, we aim to study experimentally and computationally the catalytic non-conventional hydroboration of alkynes, which shows an unseen selectivity. This reaction will allow us to explore the electrophilic character of the boryl moiety when is coordinated to rhodium and iridium complexes as well as its reactivity with unsaturated substrates with nucleophilic character.

3.1. Introduction

The hydroboration of alkynes is a useful method for the synthesis of 1-alkenylboronate compounds, which are versatile intermediates in organic synthesis.[1] The conventional *cis*-hydroboration reaction of alkynes with pinacolborane (HBpin),[2] catecholborane (HBcat),[3] and 4,4,6-trimethyl-1,3,2-dioxaborinane[4] to yield (*E*)-1-alkenylboronates was first studied through stoichiometric syn-addition approaches (Scheme 3.1). The activation of dialkoxyboranes by transition-metal complexes opened up a new perspective on hydroboration reactions when Kono and co-workers[5] demonstrated that catecholborane could be oxidatively added to the rhodium(I) center in $[RhCl(PPh_3)_3]$ to form the rhodium(III) complex $[RhClH(Bcat)(PPh_3)_3]$.

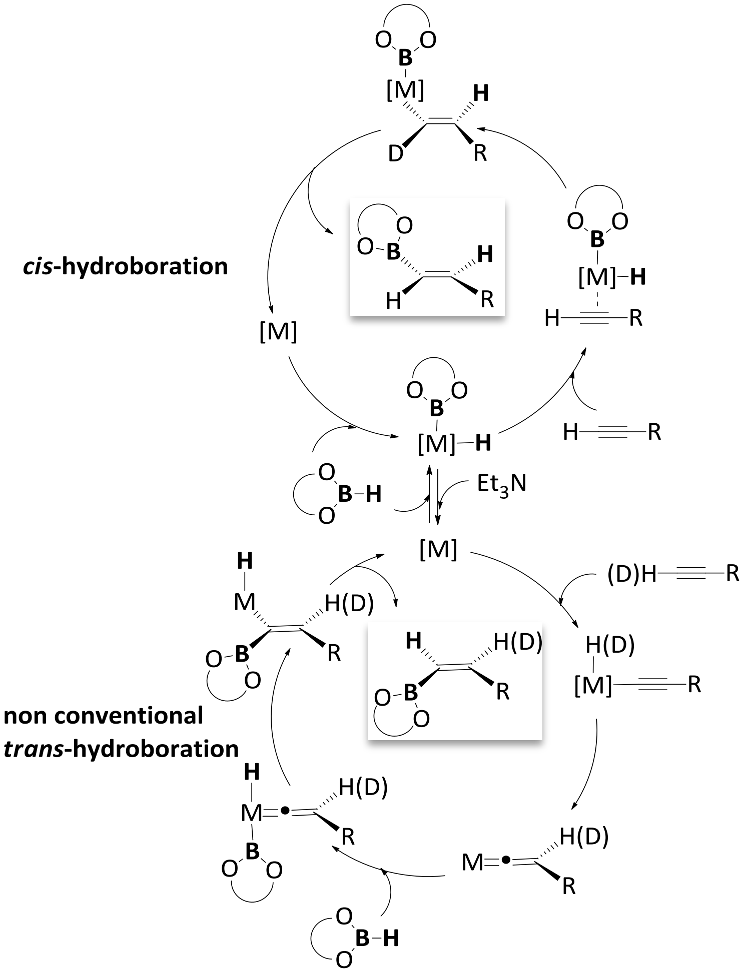
Since then, transition-metal catalyzed hydroboration has been shown to alter the chemo-, regio-, and diastereoselectivity of the stoichiometric hydroboration reactions, but always with the formation of *cis*-hydroborated products.[6] However, Miyaura and co-workers reported the first rhodium- and iridium-catalyzed non-conventional *trans*-hydroboration reaction to yield (*Z*)-1-alkenylboronates.[7] (Scheme 3.1) They postulated that at least two dominant factors could reverse the conventional *cis*-hydroboration to prefer the *trans*-hydroboration: 1) the presence of Et_3N as an additive and 2) the use of an excess of the alkyne over the borane reagent.

The first catalytic *cis*-hydroboration reaction was observed on alkenes by Mannig and Nöth.[6a] They proposed a mechanism for the rhodium-catalyzed hydroboration reaction that involved the oxidative addition of a B-H bond to the coordinatively unsaturated metal center followed by alkene coordination, insertion, and hydride migration onto the coordinated alkene, with subsequent reductive elimination to form the B-C bond. Scheme 3.2 (top) has adapted the catalytic cycle of the alkene *cis*-hydroboration reaction to the reaction with alkynes. Elucidation by quantum mechanical methods complemented the mechanistic studies on the rhodium-mediated *cis*-hydroboration reaction, although, to the best of our knowledge, the theoretical studies reported so far have only considered alkene substrates.[6d, 8]



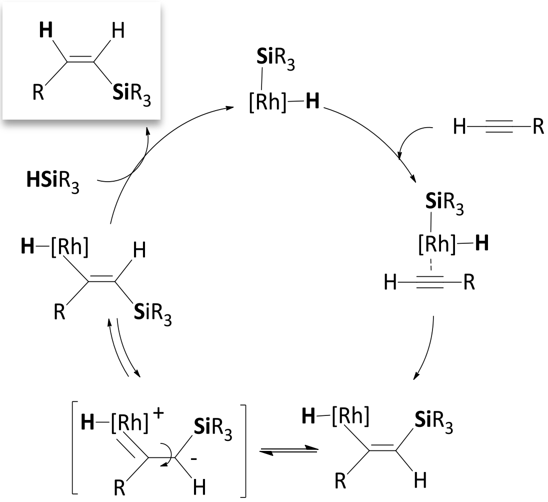
Scheme 3.1 Transition-metal-catalyzed *cis*- and *trans*-hydroboration reactions.

When Miyaura and co-workers developed the first *trans*-hydroboration reaction of alkynes, they observed that the β-hydrogen atom in the (*Z*)-1-alkenylboronate unexpectedly did not derive from the borane reagent, thus representing an example of non-conventional *trans*-hydroboration. By means of a rhodium mediated hydroboration of [1-D]-1-octyne, they observed that the deuterium-labeled terminal-carbon atom selectively shifted onto the β-carbon atom. On the basis of this interesting observation, the authors suggested a plausible mechanism for both the acetylenic hydrogen migration and the gem-addition of the B-H bond. A rhodium complex modified with an electron-donating ligand could favor the oxidative addition of the terminal C-H bond on the substrate and the resulting stable vinylidene complex (carbene-type metal species) might be the key intermediate. This process would be followed by the oxidative addition of the borane and 1,2-migration of the boryl group onto the α-carbon atom, thus providing the (*Z*)-1-alkenylboronate via reductive elimination (Scheme 3.2, on bottom). The presence of Et_3N might suppress the *cis*-hydroboration of the borane because a parallel experiment demonstrated that the treatment of $[RhClH(Bcat)(P\textit{i}Pr_3)_2]$ with Et_3N led to the complete reductive elimination of catecholborane.[7]

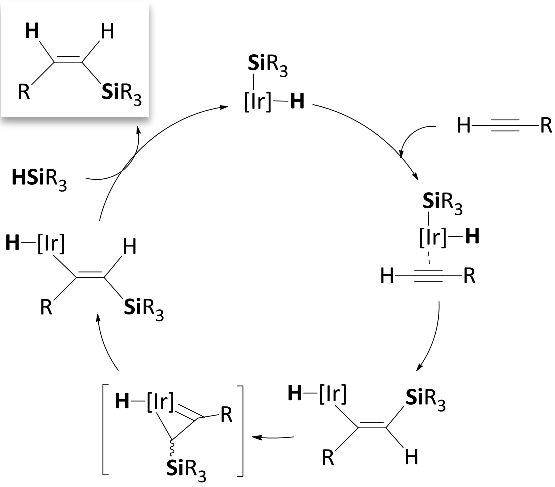


Scheme 3.2 Suggested mechanistic cycles for *cis*-hydroboration and the non-conventional *trans*-hydroboration reaction. [M = Rh (I), Ir(I)]

Conventional *trans*-hydrosilylation of alkynes has been explained by the formation of carbene-type metal species as the key intermediates.[9] To justify the observed unique stereoselectivity, Ojima and co-workers[9a] postulated a silicon shift onto the acetylenic bond and a zwitterionic carbene–rhodium complex that undergoes isomerization (Scheme 3.3), whereas Tanke and Crabtree[9b, 9c] proposed that the key intermediate is actually the closely related η^2-vinyl iridium complex (Scheme 3.4). To the best of our knowledge, only one example of the conventional *trans*-hydroboration of alkynes has been reported after this work with a ruthenium pincer complex[10].

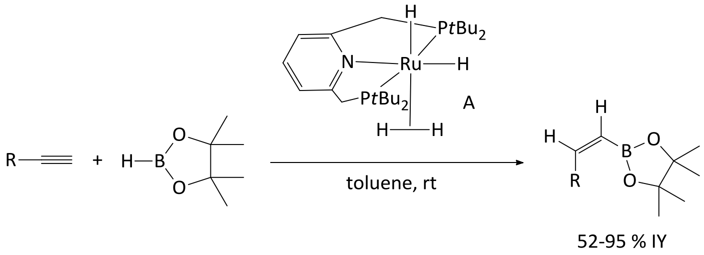


Scheme 3.3 Suggested catalytic cycle for the conventional rhodium-catalyzed *trans*-hydrosilylation reaction.



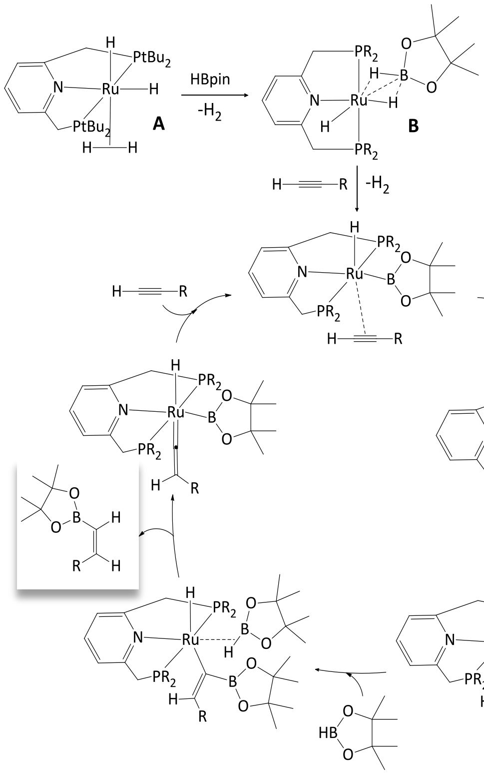
Scheme 3.4 Suggested catalytic cycle for the conventional iridium-catalyzed trans-hydrosilylation.

On the basis of these ruthenium catalyzed hydrosilylation reaction mechanism, Leitner and co-workers[10] have developed the hydroboration of terminal alkynes to give selectively *Z*-vinylboronates in high yields, with ruthenium pincer complexes, **A**, bearing a non-classical hydride (Scheme 3.5).



Scheme 3.5 Z-Selective borylation of terminal alkynes with HBpin using a ruthenium pincer complex.

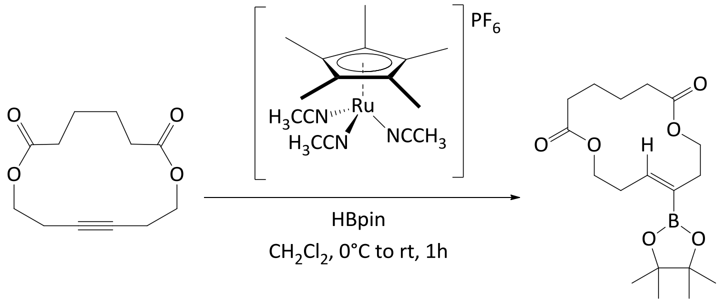
The proposed mechanism is depicted in Scheme 3.6 in which the formation of the Ru-borane intermediate **B** plays an important role.



Scheme 3.6 Proposed mechanism for non-conventional *trans*-hydroboration of terminal alkynes with a ruthenium pincer complex.

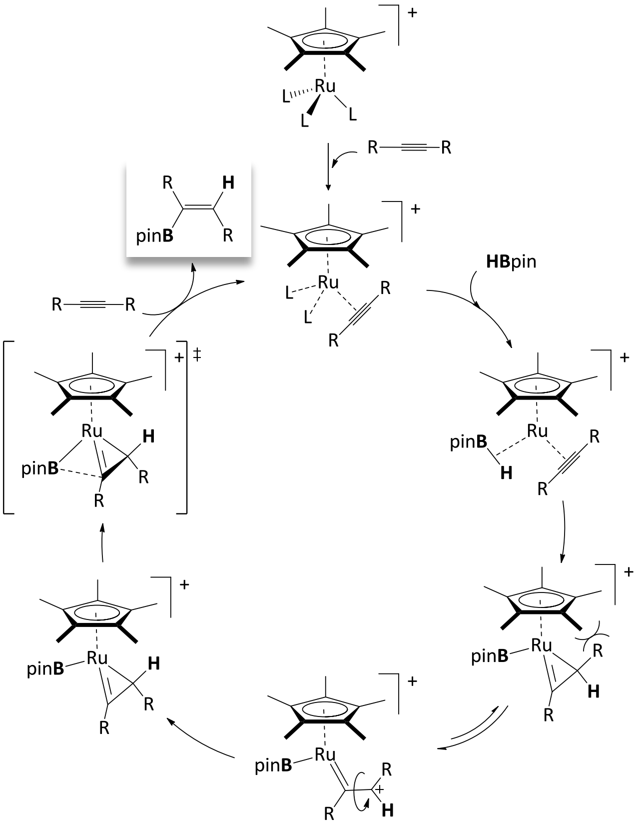
The reaction with deuterium labeled terminal alkyne demonstrated that the *Z*-vinylboronate proceeds from the HBpin addition to the terminal carbon, as in the case of the non-conventional *trans*-hydroboration of Miyaura.[7]

More recently, a great input in the search of catalyzed *trans*-hydroboration come from the group of Fürstner and co-workers.[11] They have discovered that a simple ruthenium catalysts $[RuCp^*(MeCN)_3]PF_6$, which is commercially available, provides the *trans*-selective hydroboration of alkynes towards *E*-configured alkenylboron derivatives (Scheme 3.7).



Scheme 3.7 Model reaction for the study of the *trans*-hydroboration of internal alkynes.

The mechanism that has been postulated is based on the coordination of an alkyne to Ru complex followed by the borane. From that intermediate, the acetylene moiety is supposed to function as a four-electron donor, facilitating an inner-sphere delivery of the hydride with formation of the η^2-vinyl complex without previous generation of the Ru-H bonds (Scheme 3.8).



Scheme 3.8 Proposed mechanism for the *trans*-hydroboration.

Despite the fact that the Fürstner method is the conventional *trans*-hydroboration, still there are some limitations, as far as substrate scope is concerned, because alkenes doesn’t work under the same reaction conditions and terminal alkynes are also elusive to provide the *E*-vinylboronate.

The unexpected selectivity observed in the non-conventional *trans*-hydroboration reaction by Miyaura[7] prompted us to study its mechanism from an experimental and a theoretical point of view in order to establish the basis of the desired selectivity in the *trans*-hydroboration reaction. Thus, we explored the influence of the ligand in modifying the metal species and the influence of reaction conditions in order to make general the methodology. Furthermore, we performed mechanistic studies through density functional theory (DFT) calculations of the mechanism proposed by Miyaura and co-workers,[7] which focused on the origin of the non-conentional *trans*-selectivity.

3.2. Results and discussion

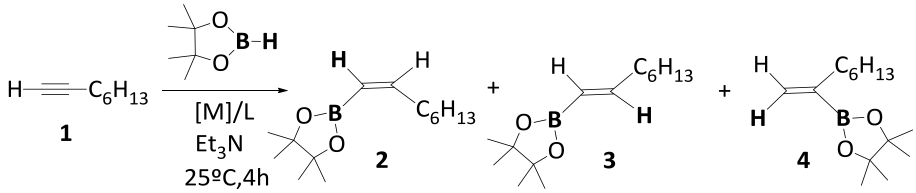
3.2.1. Experimental catalysis results

To gain more insight into the dominant mechanism in the *cis*- and non-conventional *trans*-hydroboration reactions, we performed a series of rhodium and iridium-mediated hydroboration reactions of alkynes. A catalytic system formed in situ from [{RhCl(cod)}$_2$]/PCy$_3$ (cod = 1,5-cyclooctadiene, Cy = cyclohexyl) transformed the model substrate 1-octyne (**1**) into a mixture of alkenylboronate isomers **2**–**4**, (Table 3.1) depending on the substrate/borane ratio. Isomer **2** was expected to be formed via the non-conventional *trans*-hydroboration pathway, whilst isomers **3** and **4** are the two regioisomers formed from the *cis*-hydroboration reaction.

The alkyne/borane ratio seems to play a role in determining the regioselectivity for isomer **2** (Table 3.1, entries 1–3). In this case, the optimal result was obtained when the pinacolborane reagent was present in slight excess. Apart from tetrahydrofuran, other solvents like cyclohexane and dichloromethane were explored without any significant improvement in the regioselectivity towards product **2**, (Table 3.1, entries 4–6).

When the analogous catalytic system [{IrCl(cod)}$_2$]/PCy$_3$ was used instead, a lower percentage of isomer **2** was achieved, to the benefit of the *cis*-hydroborated products (Table 3.1, entries 7 and 8). Next, we examined the influence of the phosphine ligands at a fixed substrate/borane ratio of 1:1.2 in tetrahydrofuran. Under these reaction conditions, several monophosphines, such as P(*n*Bu)$_3$, PMe$_3$, and PPh$_3$, and diphosphines 1,4-bis(diphenylphosphino)butane (dppb) and 1,1’-bis(diphenylphosphino)ferrocene (dppf) favored the formation of *cis*-hydroborated products **3** and **4** more-strongly than monophosphine PCy$_3$, with isomer **3** being the major product (Table 3.1, entries 9–13).

Table 3.1 Base-assisted metal-catalyzed hydroboration of 1-octyne.[a]



Entry	Catalytic system	Solvent	Substrate/ borane	Conv. [%][b]	**2**[c]	**3**[c]	**4**[c]
1	[{RhCl(cod)}$_2$]/PCy$_3$	THF	1.2:1	47	38	47	15
2	[{RhCl(cod)}$_2$]/PCy$_3$	THF	1:1	87	60	34	6
3	[{RhCl(cod)}$_2$]/PCy$_3$	THF	1:1.2	73	66	30	4
4	[{RhCl(cod)}$_2$]/PCy$_3$	C_6H_{12}	1:1	99	48	46	6
5	[{RhCl(cod)}$_2$]/PCy$_3$	C_6H_{12}	1:1.2	88	65	28	7
6	[{RhCl(cod)}$_2$]/PCy$_3$	CH_2Cl_2	1:1	71	58	34	8
7	[{IrCl(cod)}$_2$]/PCy$_3$	THF	1:1	98	53	37	9
8	[{IrCl(cod)}$_2$]/PCy$_3$	THF	1:1.2	63	58	33	9
9	[{RhCl(cod)}$_2$]/PPh$_3$	THF	1:1.2	87	30	47	23
10	[{RhCl(cod)}$_2$]/P(nBu)$_3$	THF	1:1.2	98	18	56	26
11	[{RhCl(cod)}$_2$]/PMe$_3$	THF	1:1.2	89	9	62	29
12	[{RhCl(cod)}$_2$]/dppb	THF	1:1.2	64	21	57	22
13	[{RhCl(cod)}$_2$]/dppf	THF	1:1.2	39	33	47	20

[a] Standard conditions: [{MCl(cod)}$_2$]/L (M = Rh or Ir, 0.015 mmol), monophophine (0.06 mmol), diphosphine (0.03 mmol), Et$_3$N (5 mmol), pinacolborane (1.2 mmol), 1-octyne (1 mmol) for substrate/borane ratio = 1:1.2. Solvent (3 mL), 25 °C, 4 h. [b] Conversion determined by GC analysis of the consumption of 1-octyne. [c] Percentage of isomeric ratio, determined by GC analysis.

When diphosphines were used in the catalytic system, the activity was also lower, particularly when dppf was used as the bidentate ligand (Table 3.1, entry 13). Because the modification of the rhodium complex with monophosphine PCy$_3$ provided the highest regioselectivity towards isomer **2** (Table 3.1, entry 3), we explored the influence of the Rh/PCy$_3$ ratio and temperature on the reaction outcome. Figure 3.1 illustrates the inverse relationship between activity and regioselectivity towards isomer 2 when the ratio of Rh/PCy$_3$ changed from 1:1 to 1:2 to 1:4. The highest percentage of product achieved for the non-conventional *trans*-hydroboration reaction was obtained at a Rh/PCy$_3$ ratio of 1:4 and was independently formed at 0°C, 25°C, and 70°C.

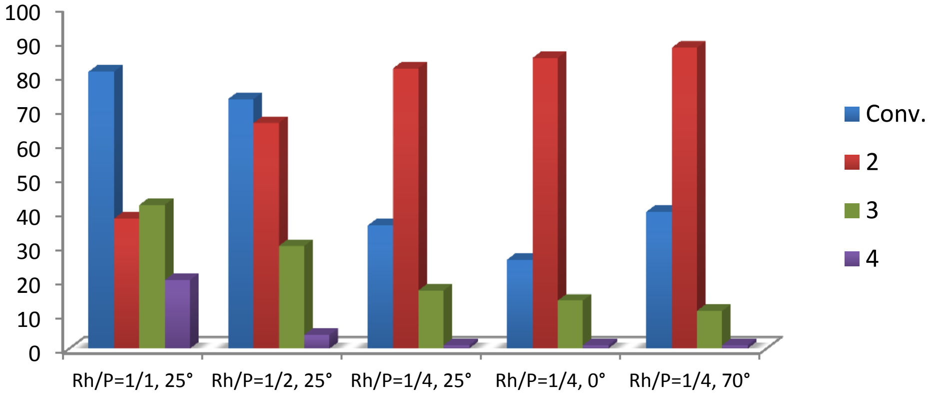
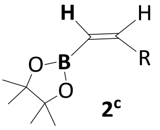
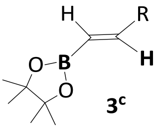
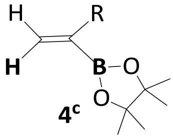
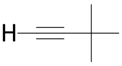
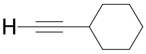
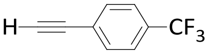
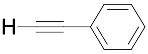
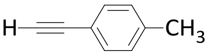
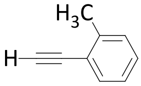
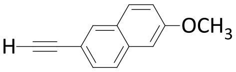


Figure 3.1 Influence of the Rh/PCy$_3$ ratio and temperature on the catalytic hydroboration of 1-octyne with pinacolborane.

With all these data in mind, we performed a study of the scope of the substrates, taking into consideration different steric and electronic properties. We first extrapolated the best reaction conditions to promote the non-conventional *trans*-hydroboration reaction with similar aliphatic alkynes such as 1-heptyne and 1-pentyne. In both cases, although the catalytic activity was improved, the regioselectivity of isomer **2** decreased slightly (Table 3.2, entries 1 and 2). Steric demands on the alkyne substituent favored the formation of the desired product in the case of *tert*-butyl acetylene but not in the case of cyclohexyl acetylene (Table 3.2, entries 3 and 4).

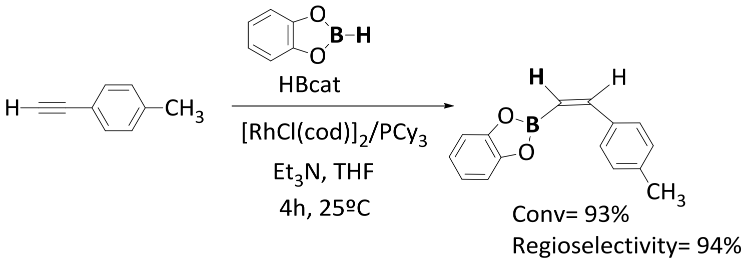
Table 3.2 Rhodium-catalyzed hydroboration of alkynes with pinacolborane.[a]

Entry	Substrate	Conv. [%]	 **2**[c]	 **3**[c]	 **4**[c]
1	$H-\equiv-C_5H_{11}$	80	65	33	2
2	$H-\equiv-C_3H_7$	65	67	31	2
3		84	74	26	0
4		88	51	49	0
5		95	48	32	18
6		75	90	10	0
7		76	94	6	0
8		72	77	23	0
9		44	78	22	0

[a] Standard conditions: [{RhCl(cod)}$_2$]/L (0.015 mmol), PCy$_3$ (0.12 mmol), Et$_3$N (5 mmol), pinacolborane (1.2 mmol), alkyne (1 mmol) for substrate/borane ratio = 1:1.2, THF (3 mL), 25 °C, 4 h. [b] Conversion determined by GC analysis of the consumption of 1-alkyne. [c] Percentage of isomeric ratio, determined by GC analysis.

The influence of electronic effects on the rhodium-catalyzed hydroboration reaction was principally observed when electron-withdrawing and electron-donating phenyl acetylenes were transformed into the alkenylboronate products. Regioselectivities of up to 94% for isomer **2** were achieved when electron-rich alkynes were involved (Table 3.2, entries 6–7). On the contrary, despite being electron poor, *para*-trifluoromethyl-phenylacetylene was converted into the product in almost quantitative yield, but the *cis*-hydroboration was very competitive (Table 3.2, entry 5). Other electron-rich alkynes with high steric demand were also mainly converted into isomer **2** (Table 3.2, entries 8 and 9).

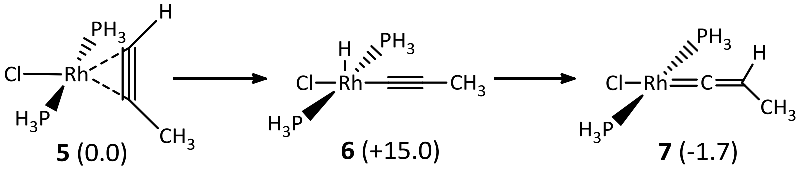
It is important to note that despite the successful hydroboration of the *para*-trifluoromethyl-phenylacetylene, all of the other substrates provided negligible or no formation of isomer **4**, owing to the constrained addition of the boryl moiety onto the most-hindered carbon in the *cis*-hydroboration reaction. Interestingly enough, when the rhodium-mediated hydroboration of *para*-methyl-phenyl acetylene was carried out with catecholborane as the borane reagent, the regioselectivity towards isomer **2** remained very high whilst the conversion increased significantly (Scheme 3.9). It is known that borane reagents derived from catechol units are more reactive owing to their enhanced Lewis acid properties.[12]



Scheme 3.9 Optimized *trans*-hydroboration reaction of alkynes with catecholborane.

3.2.2. Theoretical analysis of the reaction mechanism

In order to gain a greater insight into the mechanistic details of the non-conventional *trans*-hydroboration reaction, a detailed theoretical study of the rhodium-mediated reaction of alkynes was performed. In our first approach to the mechanism, we used simplified model systems: PH_3 for phosphine ligands, $HB(O_2C_2H_4)$ for the pinacolborane reagent, and the simplest alkyne substrate, $HC\equiv CMe$. We also considered the results from real systems in order to assess several key variables, such as ligand and substrate structure. We assumed that the two phosphine ligands are coordinated *trans* to each other, as observed in the X-ray structure of the key vinylidene complex [RhCl(=C=CHMe)*trans*-(P*i*Pr)$_2$].[13] Initially, we examined the mechanism proposed by Miyaura and co-workers (Scheme 3.2, bottom); the first step studied involved the isomerization of the terminal alkyne group into the vinylidene in the coordination sphere of rhodium complex. This process has been observed previously[13-14] and extensively studied by computational methods.[15] The precise mechanism of isomerization had been the subject of some controversy, but in the end all evidence pointed toward an unimolecular process involving the formation of an alkynyl hydride intermediate (Scheme 3.10).

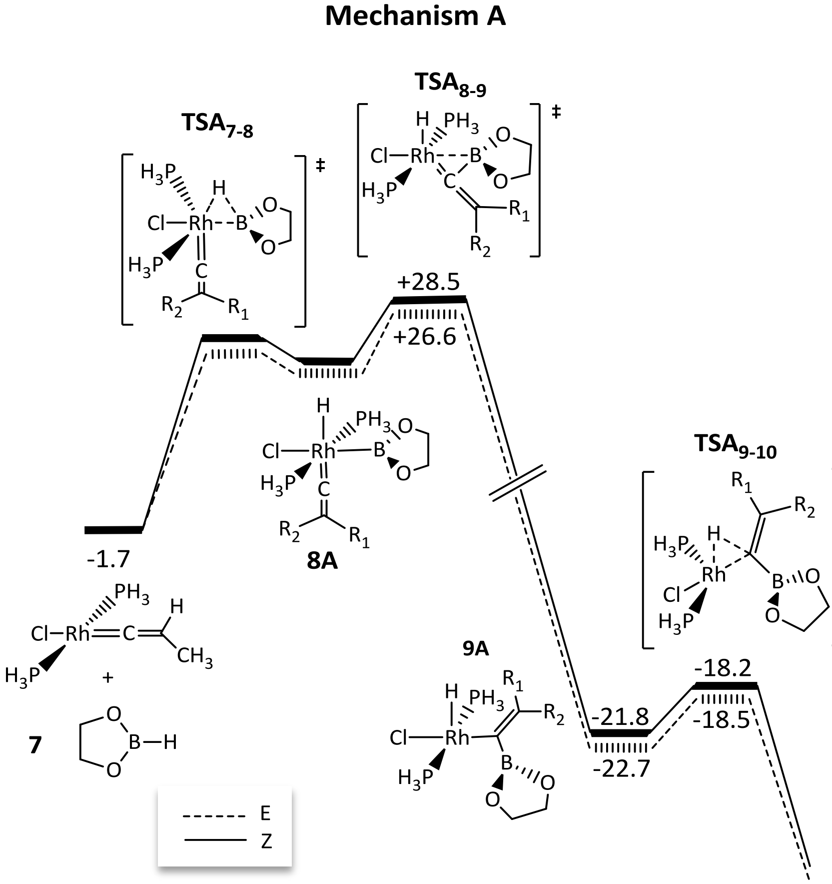


Scheme 3.10 Mechanism for alkyne-vinylidene isomerization in electron-rich metal (e.g., rhodium) centers. Relative energies shown are in kcal·mol^{-1}.

The second step studied in the catalytic cycle, 1,3-hydrogen shift to yield the vinylidene, was postulated to be the rate-limiting step.[16] Angelis and co-workers[15c] and Grotjahn and co-workers[15d] have demonstrated that electron-donating ligands favor the formation of both hydrido-alkynyl and vinylidene species. This trend was also proposed in other transition metal complexes,[17] adding that the steric hindrance of bulky ligands has an influence through the destabilization of the alkyne.[17a] We noted that the non-conventional *trans*-hydroboration was principally observed for bulky and strongly electron-donating ligands, such as PCy_3 and P*i*Pr_3. Thus, in this first part of the discussion, we assume that isomerization takes place and we focus on the addition of borane to the Rh-vinylidene complex.

Scheme 3.11 shows the computed energy profile for the *Z*- and *E*-pathways of the borane addition to the vinylidene group, starting with boryl migration (mechanism **A**). The Rh-vinylidene complex (**7**) was calculated to be 1.7 kcal·mol^{-1} lower in energy than the Rh-alkyne complex $[RhCl(PH_3)_2(HCCMe)]$ (**5**). However, at a similar computational level, the preference for the specie **7** was reported to increase to up to approximately 13 kcal·mol^{-1} using real P*i*Pr_3 instead of model PH_3 phosphines.[15b] This result further supports the postulation that the process is thermodynamically favorable and essentially irreversible, as demonstrated in previous experimental studies.[15a] This process should be followed by oxidative addition of the borane agent to compound **7** to yield a hydrido-boryl intermediate (**8A**) with the boryl group *cis* to the vinylidene ligand. Despite all of our efforts, we could not locate either species **8A** or the transition state for oxidative addition.

Following the previous discussion about the effect of strongly donating ligands,[15b, 15c, 17] it is reasonable to think that the species **8A** would be stabilized by basic PCy_3 phosphine groups and that the same effect cannot be achieved by simplified PH_3 ligands. A similar situation was faced in previous theoretical studies on the hydroboration of alkenes using a $[RhCl(PH_3)_2]$ complex, in which not all of the conceivable hydrido-boryl species and none of the transition states for oxidative addition were located.[8]

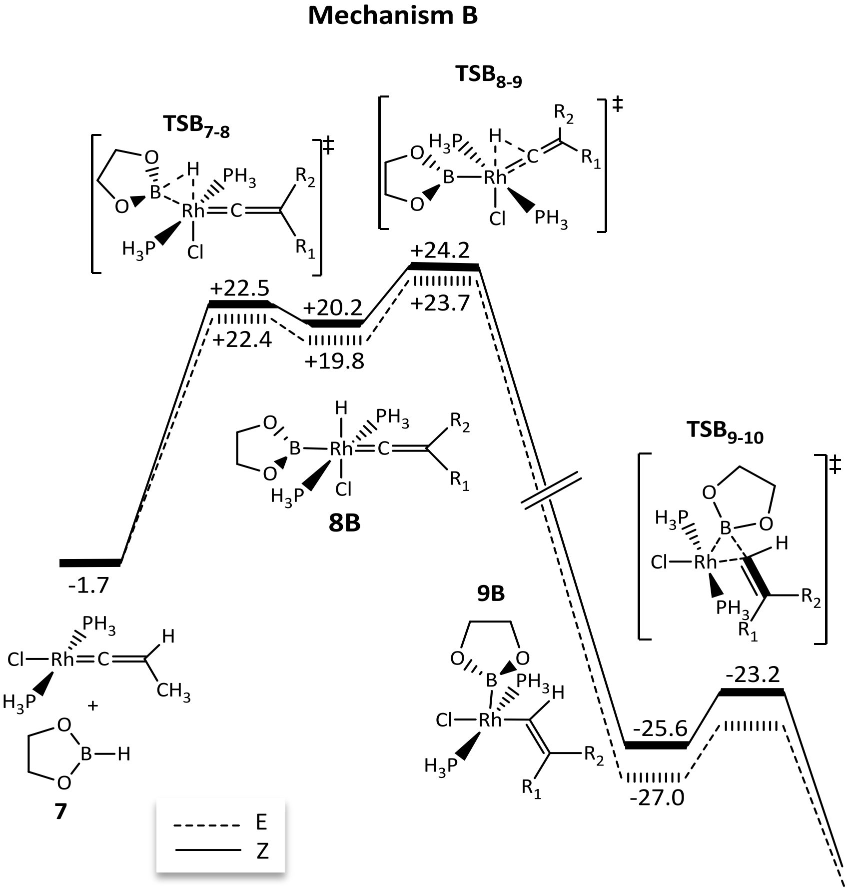


Scheme 3.11 Calculated potential-energy profile (kcal·mol^{-1}) for the mechanism suggested by Miyaura and co-workers involving an initial isomerization of the alkyne to the vinylidene (mechanism **A**). Hydroboration of propyne with $HB(O_2C_2H_4)$ catalyzed by a $[RhCl(PH_3)_2]$ complex. Solid lines correspond to the Z path (R_1 = Me), dashed lines correspond to the E path (R_2 = Me).

We located the transition state connecting intermediates **8A** to vinyl complexes **9A** (**TSA$_{8\text{–}9}$**), which corresponded to the 1,2-boryl migration onto the α-carbon atom of the vinylidene group. This migration occurs within the vinylidene molecular plane, and the distance of the B-C forming bond is 1.89 Å at the pro-*Z* transition state. The distance between the boron atom and the hydride moiety is relatively long (2.58 Å), thereby showing that the B-H bond is cleaved when boryl migration takes place rather than the concerted addition of borane to the vinylidene fragment. The key geometric parameters at the corresponding pro-*E* transition state only differ by less than 0.01 Å. Accordingly, we found that the two transition states for the *Z*- and *E*- pathways lay 30.2 and 28.3 kcal·mol^{-1} above complex **7**, respectively. These overall energy barriers seem somewhat high for a process occurring at room temperature. The product of boron migration (**9A**) is 21 kcal·mol^{-1} more stable than complex **7**. Subsequent reductive elimination with concomitant C-H bond-formation leads to the borylated-alkene product via transition state **TSA$_{9\text{–}10}$** with low energy barriers (ca. 4 kcal·mol^{-1}). For this last part of the mechanism, the energy differences between the *Z* and *E* paths are within 1 kcal·mol^{-1}.

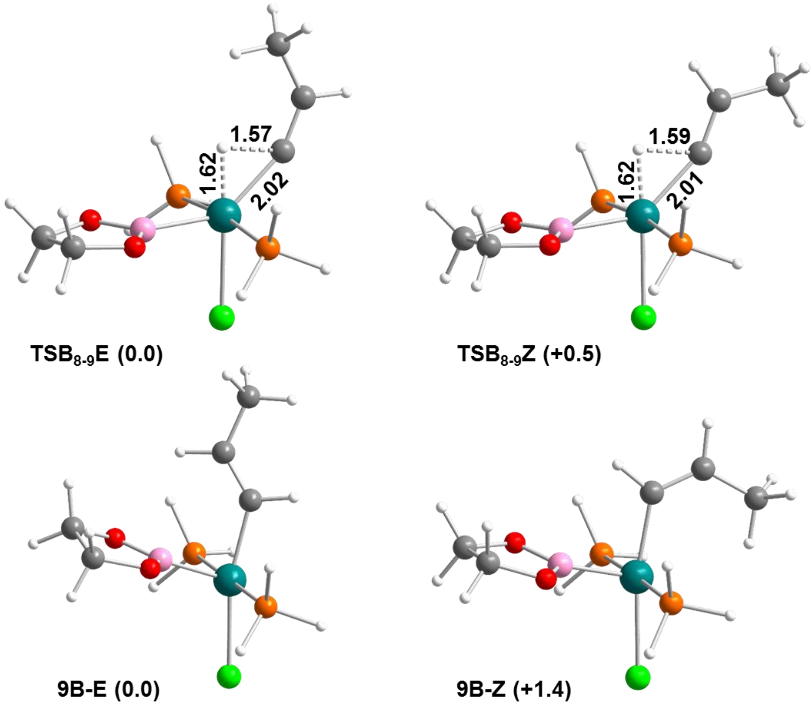
Alternatively, the sequence of the reaction could be inversed, that is, hydride migration followed by reductive elimination of the C-B bond (mechanism **B**). Scheme 3.12 shows the computed energy profile for both the *Z* and *E* pathways, and Figure 3.2 shows the structures and main geometric parameters of selected intermediates and transition states. In this case, it was possible to locate the two hydrido-boryl intermediates (**8B**) and the transition states for the oxidative addition of the B-H bond to the rhodium center (**TSB$_{7\text{–}8}$**). The formation of complexes **8B** is endothermic by 20 kcal·mol^{-1} and proceeds via transition-state structures that have similar energies, leading to very-low reverse energy barriers (<3 kcal·mol^{-1}). From intermediates **8B**, the forward energy barriers for hydride migration via **TSB$_{8\text{–}9}$** are also very low (ca. 4 kcal·mol^{-1}). These low energy barriers mean that the existence of intermediate **8** may depend on the specific conditions. Among them, having a chloride atom *trans* to the hydride (**8B**) instead of *trans* to the boryl ligand (**8A**) stabilizes the intermediate. Nevertheless, the important fact is that the reaction goes uphill from compound **7** to reach the transition state for hydride migration (**TSB$_{8\text{–}9}$**), and the calculated overall barriers are 25.9 and 25.4 kcal·mol^{-1} for the *Z* and *E* pathways, respectively.

Interestingly, these values are significantly lower than those corresponding to mechanism **A**. In the **TSB$_{8\text{–}9}$** structures (Figure 3.2), the vinylidene ligand bends away from its position in the reactants (**8B**) to approach the hydride group (Cl-Rh-C$_\alpha$) bond angle changes from 113° in **8B** to 133° in **TSB$_{8\text{–}9}$** for both the *Z* and *E* pathways), thereby ending up *trans* to the chloride atom in the products (**9B**). In this migratory insertion, the formation of the C-H bond is co-planar with the vinylidene moiety. Once the transition state for migratory insertion is reached, the reaction drops significantly in energy (ca. 50 kcal·mol^{-1}) to give the rhodium/vinyl intermediates (**9B**), which are 24–25 kcal·mol^{-1} lower in energy than compound **7**.



Scheme 3.12 Calculated potential-energy profile (kcal·mol^{-1}) for a variant on the mechanism suggested by Miyaura, in which hydride migration onto the vinylidene carbon atom occurs first (mechanism **B**). Hydroboration of propyne with $HB(O_2C_2H_4)$ catalyzed by a $[RhCl(PH_3)_2]$ complex. Solid lines correspond to the Z path (R_1 = Me), dashed lines correspond to the E path (R_2 = Me).

The pro-*E* intermediate **9B**, which contains the alkyne substituent and the rhodium fragment *trans* one to each other, is 1.4 kcal·mol^{-1} thermodynamically more stable than the pro *Z* intermediate. Notably, the difference in energy between the *E* and *Z* paths has increased on going from **TSB$_{8\text{–}9}$** to **9B** in favor of the *E* path. However, the high reverse barriers for intermediates **9B** prevent stereospecific product formation from being achieved thermodynamically, since the two intermediates **9B** do not interconvert (Figure 3.2, see below). Finally, the reaction proceeds by reductive elimination of the C-B bond to give the product via **TSB$_{9\text{–}10}$**. Again, the barrier for the termination step was calculated to be very low, only 2.4 kcal·mol^{-1} for the *Z* pathway. Despite our efforts, we were unable to locate the transition state **TSB$_{9\text{-}10}$** for the *E* path. We expect a very low energy barrier as for the other three calculated transition states in the reductive elimination step, and consequently, only a small influence in determining the selectivity and activity of the reaction.

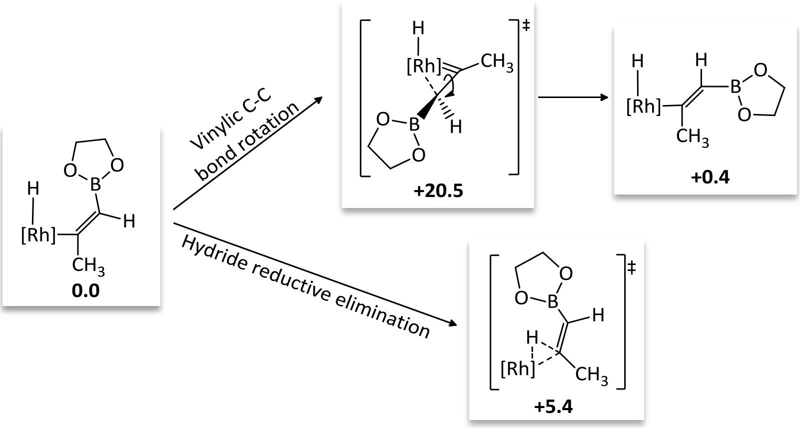


TSB$_{8\text{-}9}$E (0.0) **TSB$_{8\text{-}9}$Z (+0.5)**

9B-E (0.0) **9B-Z (+1.4)**

Figure 3.2 Molecular structures and main geometric parameters of transition state **TSB$_{8\text{-}9}$** and intermediate **9B** in the pro-*E* and pro-*Z* propyne-hydroboration pathways using PH_3 ligands. Distances in Å and relative energies in kcal·mol^{-1}.

By analogy with the proposed mechanisms for *trans*-hydrosilylation, we explored a new mechanism that was consistent with the observed *trans*-hydroboration products. The reaction could proceed via migratory insertion of the alkyne into the Rh-B bond leading to a complex in which the boryl and alkyl substituents of the vinyl ligand were *trans* one to each other. Then, prior to the reductive C-H coupling step, the pro-*Z* intermediate could be formed via vinylic C-C rotation (Scheme 3.13). In addition, these calculations will evaluate the feasibility of interconversion between the *Z* and *E* isomers in intermediate **9B**.



Scheme 3.13 Schematic representation of an alternative *trans*-hydroboration reaction through vinylic C-C bond-rotation; this mechanism is analogous to those proposed for *trans*-hydrosilylation reaction. The transition state involves a η^2 interaction of the vinylic fragment with the rhodium center. The hydride reductive-elimination *cis* mechanism is shown for comparison. Energies shown are in kcal·mol^{-1}.

The attempts to obtain the zwitterionic carbene/rhodium complex separately, as proposed by Ojima and co-workers[9a] (Scheme 3.3), and the related η^2-vinyl complex proposed by Crabtree and co-workers[9b-e] (Scheme 3.4) ended up with the same structure, which resembles the proposal by Crabtree and co-workers (Scheme 3.13). This species was characterized as a transition state by a single imaginary frequency, which normal mode corresponds to the rotation of the vinylic C-C carbon bond. The computed energy barrier was not very high (20.5 kcal·mol^{-1}), but it was significantly higher (ca. 5 kcal·mol^{-1}) than of the reductive elimination of the C-H bond. Obviously, these results do not necessarily preclude the proposed mechanism for the hydrosilylation of alkynes, but they discard the C-C rotation in the *trans*-hydroboration reaction catalyzed by phosphine-modified rhodium complexes. Moreover, they indicate that the *Z* and *E* isomers of intermediates **9B** would not readily interconvert into one to another, leading to the thermodynamically more stable *E* species. With all of these results in hand, we can consider which could be the most plausible determining step for the selectivity. Although the energy profiles might be tuned by the inclusion of real ligands, some features are already clear.

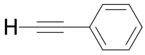
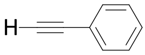
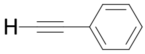
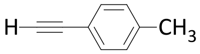
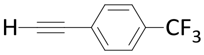
Comparing mechanism **A** and **B**, we observed the same energetic pattern: the reaction goes uphill in energy until the boryl- and hydride-migration transition states, respectively. The resulting rhodium/vinyl complex is low in energy, and has a very high reverse barrier and a low barrier to give the product. This pattern indicates that both boryl and hydride migration are irreversible steps to give the product as defined *Z* and *E* stereoisomers. Because we have shown that the *Z* and *E* isomers do not interconvert easily, we can state the either the boryl or hydride migration might be the determining step for the selectivity. As a consequence, the selectivity of the process is determined by kinetic control and can be described by applying transition-state theory (TST). The hydride migration in mechanism **B** has the lowest energy barrier, and consequently, it is the most likely. Moreover, as we will discuss below, mechanism **B** is fully consistent with the expected selectivity. Thus, we focused on analyzing this mechanism by determining the transition states for hydride migration to the vinylidene group.

3.2.3. Origin of selectivity. Ligand and substrate effects

To assess the effect of the real ligands and experimental selectivity, we performed hybrid quantum mechanics/molecular mechanics (ONIOM) calculations on the key **TSB$_{8\text{–}9}$** transition states. The MM region included the phosphine substituents and methyl groups of pinacolborane in order to take into account the steric effects of them. We used ONIOM calculations because they allowed us to screen several ligands and substrates.[18] Moreover, we felt that non-bonding ligand–substrate interactions are key factors governing selectivity. In these cases, DFT/MM methods can give superior results to pure DFT calculations because dispersion forces are not properly described for standard gradient-corrected density functional approaches.[18b]

Table 3.3 compares the relative energies of the key pro-*Z* and pro-*E* transition states for different ligands and substrates with the experimentally observed selectivity. For propyne and monophosphine ligands PH_3 and PMe_3 (Table 3.3, entries 1 and 2), the calculated energy difference between the *Z* and *E* transition states is low, with the *E* isomer slightly favored. Upon introduction of the steric effects of the bulky PCy_3 and $PiPr_3$ phosphine groups, the trend inverts and the *Z* path becomes more favorable by 1.6 and 0.5 kcal·mol^{-1}, respectively (Table 3.3, entries 3 and 4). These results are fully consistent with the observed major products in our work and the work of Miyaura and co-workers,[7] thus supporting mechanism **B** for non-conventional *trans* hydroboration reactions.

Table 3.3 Calculated relative energies of pro-*E* and pro-*Z* transition states for different type of phosphines. Comparison with the experimental results.

Entry	Sustrate	Phosphine	**TSB$_{8-9}$** pro-*Z* [kcal·mol^{-1}]	pro-*E* [kcal·mol^{-1}]	*Z/E*^{c}
1	$H-\equiv-CH_3$	PH_3	+0.5	0.0	-
2	$H-\equiv-CH_3$	PMe_3	+0.6	0.0	9:62^{a}
3	$H-\equiv-CH_3$	PCy_3	0.0	+1.6	66:30^{a}
4	$H-\equiv-CH_3$	$PiPr_3$	0.0	+0.5	91:7^{a,b}
5		PH_3	0.0	+0.2	-
6		PCy_3	0.0	+2.7	90:10
7		$PiPr_3$	0.0	+1.1	97:2^{b}
8		PH_3	0.0	+0.1	-
9		PH_3	0.0	+0.4	-

^{a} Results for 1-octyne; ^{b} Values taken from the paper by Miyaura and co-workers, see Ref 7. ^{c} Ratio determined experimentally

If we take a closer look at the geometry of the pro-*E* transition state with PCy_3 (Figure 3.3), we can observe that the alkyne substituent is pointing towards the metal center, thereby establishing a repulsive steric interaction with the auxiliary ligands. On the other hand, the alkyne substituent in the corresponding pro-*Z* transition state, points away from the metal center. Thus, it is reasonable to think that increasing the bulk of the phosphine or alkyne substituent will increase the preference for the *Z* isomer by destabilizing the *E* path.

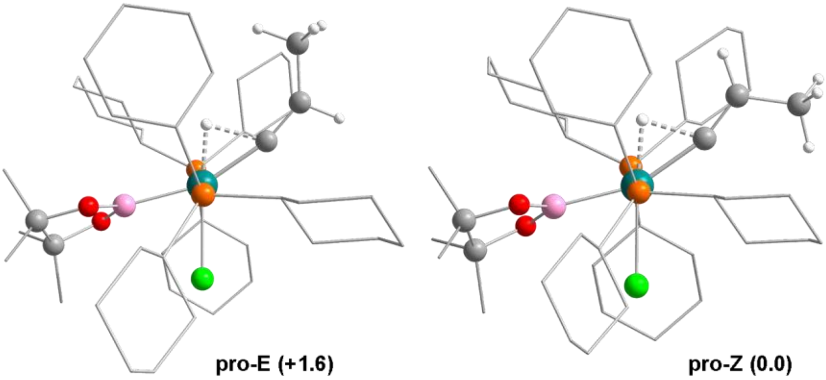


Figure 3.3 Molecular structures of the selectivity-determining pro-*E* and pro-*Z* transition states for vinylidene insertion into Rh-H bond during propyne hydroboration using PCy_3 ligands at the B3LYP:UFF level. Hydrogen atoms from the phosphine groups and the borane agent are omitted for clarity. The atoms in the MM part are represented by sticks. Relative energies shown are in kcal·mol^{-1}.

Next, we analyzed the origin of substrate effects on the reaction outcome. To understand the higher selectivity observed for aryl alkynes compared with aliphatic alkynes, we considered three different aspects: 1) the intrinsic preference of the alkyne substituents in the *Z* or *E* pathways, 2) the higher sensitivity to the steric hindrance of the phosphine groups, and 3) the preference of the vinylidene path (non-conventional *trans*) over the classical path (*cis*) that involves direct addition of the borane group to the alkyne.

In the absence of steric effects with the PH_3 ligand, we observed a clear difference on going from methyl- to phenylacetylene. The relative energies of the pro-*Z* and pro-*E* transition states invert, with the *Z* isomer becoming preferred (Table 3.3, entries 1 and 5). Nevertheless, the energy difference between the *Z* and *E* isomers for phenylacetylene is also small (ca. 0.2 kcal·mol^{-1}), and consequently subtle effects are expected to be responsible for them. Figure 3.4 collects the structures of the pro-*Z* and pro-*E* transition states for the phenylacetylene substrate.

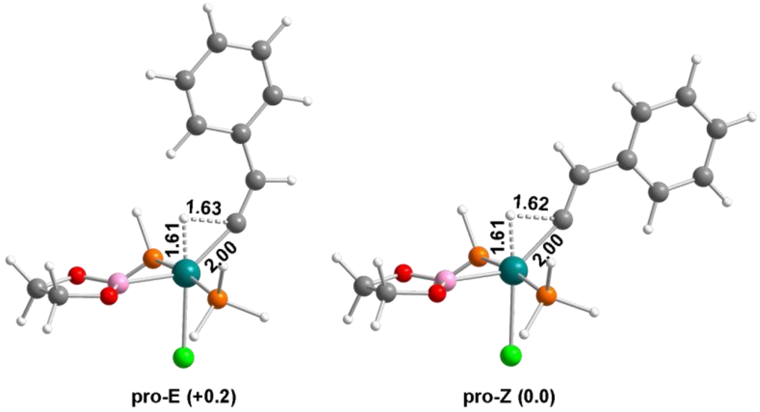


Figure 3.4 Molecular structures and main geometric parameters of the selectivity-determining pro-*E* and pro-*Z* transition states for vinylidene insertion into Rh-H bond during phenylacetylene hydroboration with PH_3 ligands. Distances in Å and relatives energies shown are in kcal·mol^{-1}.

When comparing the two isomers for each substrate type, we observed very similar geometric and electronic parameters (Figure 3.2, Figure 3.4). The inverse trend should be related to the balance between the *cis* and *trans* disposition of the alkyne substituents and between the *cis* and *trans* stabilization of the developing negative charge at the vinylidene α-carbon atom. Other aryl-substituted alkyne substrates show similar relative energies of the transition states for PH_3 ligand (Table 3.3, entries 8 and 9). Thus, the intrinsic electronic properties of phenyl acetylene have a positive influence on the selectivity towards the *Z* product as compared with alkyl acetylenes.

For phenylacetylene, addition of the steric hindrance of PCy_3 ligand causes the energetic preference of the *Z* isomer to increase by 2.5 kcal·mol^{-1} (Table 3.3, entries 5 and 6). The latter value is similar to that observed for methyl-acetylene (+2.1 kcal·mol^{-1}), thus showing that both types of substrates have similar sensitivities to the steric effect exerted by the phosphine ligands. The last aspect that we considered was whether the vinylidene formation becomes more favored than the *cis*-hydroboration channel for phenylacetylene. Thus, assuming that the 1,3-shift of the hydrogen onto the alkynyl ligand is the rate-determining step in vinylidene formation,[16] we first calculated the energy barriers for different substrates with the PH_3 ligand. The overall energy barriers from the vinylidene complex for HC≡CR (R = $C_6H_4CF_3$, Me, Ph, and $C_6H_4CH_3$) were 30.1, 29.1, 28.5, and 28.0 kcal·mol^{-1}, respectively, which nicely correlated with the percentages of obtained *Z* isomer: 48%, 66%, 90%, and 94%, respectively. The lower the energy barrier, the more favored the non-conventional *trans* reaction channel is, and consequently, the higher the selectivity towards the *Z*-alkene isomer. We identified a linear relationship between the observed selectivity for the *Z* isomer and the overall energy barriers for vinylidene formation (Figure 3.5).

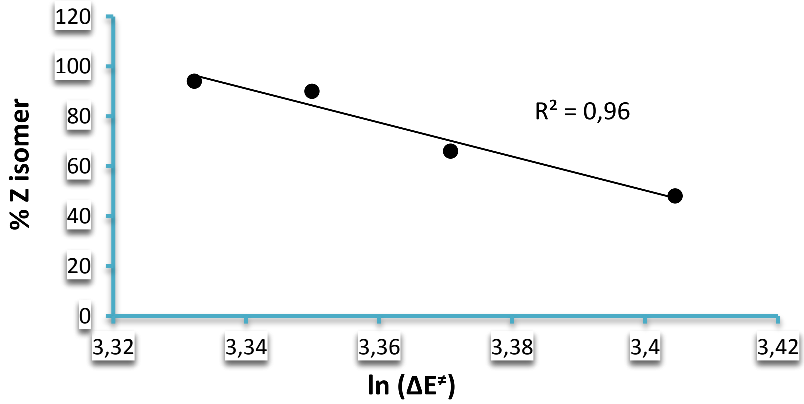


Figure 3.5 Correlation between the observed Z isomer (%) and the overall activation barriers for vinylidene formation.

Lynam and co-workers[15a] have determined the rate constants for the isomerization of the two-step process for *n*-butyl- and phenyl-substituted alkynes. They obtained values for the 1,3-hydrogen shift that were somewhat lower (22.8 and 22.1 kcal·mol^{-1} for R = *n*Bu and Ph, respectively) than ours (29.1 and 28.5 kcal·mol^{-1} for R = CH_3 and Ph, respectively) owing to our use of the simplified less-basic PH_3 ligands. However, the trend in substituent effects observed by the same authors was reflected in the calculations on our model systems, that is, that isomerization is easier for aryl than for alkyl substituents. These results also support the idea that the higher selectivity for the *Z* isomer in aryl-substituted alkynes is also related to the predominance of vinylidene over the *cis*-hydroboration reaction channel. We note that the rigorous analysis of this aspect would require full characterization of both reaction channels, thereby accounting for the electronic effects of PR_3 ligand and the role of the base.

3.3. Conclusions

We can conclude that the catalytic system based on the in situ mixture of [{RhCl(cod)}$_2$] and basic and bulky phosphine groups, such as PCy_3, favored the non-conventional *trans*-hydroboration over the *cis*-hydroboration in the presence of Et_3N. The optimized reaction conditions for the hydroboration of 1-octyne showed that the most-successful substrate/borane ratio was 1:1.2, and tetrahydrofuran seemed to be the solvent of choice. The highest percentage of non-conventional *trans*-hydroborated product was achieved with a ratio of [Rh]/PCy_3 = 1:4 and was successfully formed at 0°C, 25°C, and 70°C. Subtle changes in the nature of the substrate indicated that electron-rich alkynes with high steric demands were mainly converted into the desired organoboron isomers.

We have computationally characterized a plausible reaction mechanism for the non-conventional *trans*-hydroboration reaction through an initial alkyne to vinylidene isomerization, following the suggestion of Miyaura and co-workers based on their deuterium-labeled experiment. Unlike their mechanism, we propose a sequence of vinylidene insertion into the Rh-H bond followed by reductive elimination of the C-B bond. Thus, the mechanism can be divided into four stages: 1) oxidative addition of alkyne to metal and isomerization from alkyl ligand to vinylidene ligand to yield a Rh-vinylidene complex, 2) oxidative addition of the borane reagent, 3) vinylidene insertion into the Rh-H bond, and finally 4) reductive elimination of the C-B bond to yield the 1-alkenylboronate.

Calculations indicated that the insertion of vinylidene into the Rh-H bond is the selectivity-determining step. Introducing the steric effects of real ligands, we were able to reproduce the experimental outcome, thus supporting the consistency of the proposed mechanism. Our calculations also indicated that bulky ligands are required to selectively obtain (*Z*)-1-alkenylboronates and that increasing the steric hindrance of the ligands causes an increase in selectivity of the *Z* isomer (PCy_3 > P*i*Pr_3 > PMe_3 > PH_3). The higher selectivity observed for aryl alkynes compared with aliphatic alkynes can be explained by the analysis of different factors. The intrinsic electronic properties of aryl substituents are more favorable for the *Z* pathway than alkyl substituents. For electron-donating substituents, the formation of the Rh-vinylidene complex is favored, which seems to facilitate the occurrence of the vinylidene reaction channel over the classical *cis*-hydroboration pathway.

3.4. Computational methods

In this present theoretical approach, all calculations were performed using the Gaussian09 series of programs.[19] Full quantum mechanical calculations on model systems were performed within the framework of density functional theory (DFT)[20] using the B3LYP functional.[21]

A quasi-relativistic effective-core potential operator was used to represent the 28 innermost electrons of the Rh atom, as well as the 10 innermost electrons of the P atoms.[22] The basis set for Rh and P atoms was that associated with the pseudopotential,[22] with a standard double-ξ LANL2DZ contraction,[19] and, in the case of P atoms, supplemented by a d shell.[23] The C, H, O, Cl and B atoms were represented by means of the 6–31G(d,p) basis set.[24]

All geometry optimizations were full, with no restrictions. Stationary points located in the potential-energy hypersurface were characterized as true minima through vibrational analysis. Transition states located in the potential-energy hypersurface were characterized through vibrational analysis, having one and only one imaginary frequency, whose normal mode corresponded to the expected motion.

For the hybrid quantum mechanics/molecular mechanics (QM/MM) calculations, we applied the ONIOM method as implemented in the Gaussian 09 package.[25] The QM region included the [RhCl(PH_3)$_2$] complex, the methyl- and aryl acetylene substrates, and the HB($O_2C_2H_4$) reagent. The MM region constituted of the methyl substituents of borane and the substituents (Me, *i*Pr, and Cy_3) of the phosphines. The QM level was the same as mentioned above. UFF force field[26] was used as implemented in Gaussian 09 to describe the atoms included in the MM part.

3.5. References chapter 3

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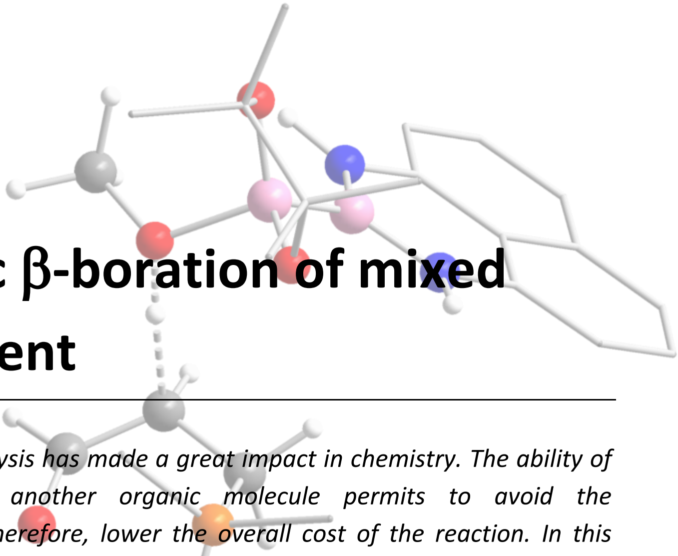


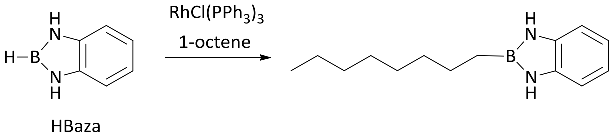
Chapter 4

Organocatalytic β-boration of mixed Bpin-Bdan reagent

In the past few years, organocatalysis has made a great impact in chemistry. The ability of activating reagents only with another organic molecule permits to avoid the organometallics complexes and therefore, lower the overall cost of the reaction. In this chapter we aim to study the organocatalytic β-boration reaction with a mixed diboron reagent. In our group, it was reported that the methoxide was able to activate diboron [B(sp^2)-B(sp^2)] reagents, providing [MeO$^-$→B(sp^3)-B(sp^2)] adducts with enhanced nucleophilic character on B(sp^2). Thus, we wanted to explore which of the different boryl units will gain more nucleophilicity when a mixed diboron is used in the reaction and study its reactivity with α,β-unsaturated carbonyl compounds.

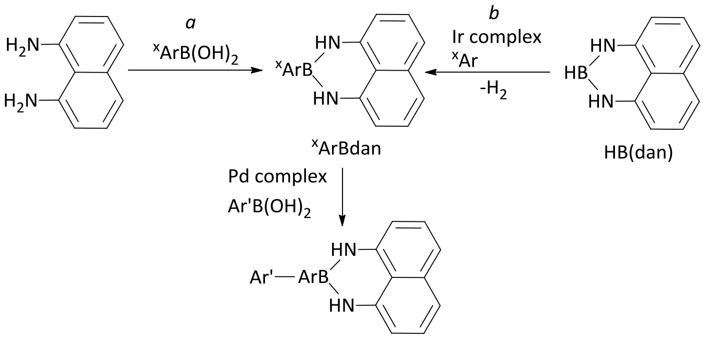
4.1. Introduction

The Lewis acidity of the boron atom is the key factor governing the reactivity of organoboron compounds. The vacant p-orbital of the boron atom can be partially filled with lone pair of electrons from adjacent atoms, tuning the Lewis acid property. Nitrogen atoms donate their lone pair of electrons thus lowering the acidity significantly in comparison with that of the corresponding boronic acids and their esters.[1] Diamines, which form cyclic diaminoboranes, increase the overall stability on the boryl species reducing the reactivity. 1,2-Diaminobenzene reacts with borane-dimethyl sulfide complex to generate 1,3,2-benzodiazaborolane, HBaza (Scheme 4.1), which became very stable against disproportionation and therefore more efficient than catecholborane in metal mediated hydroboration reactions.[2]



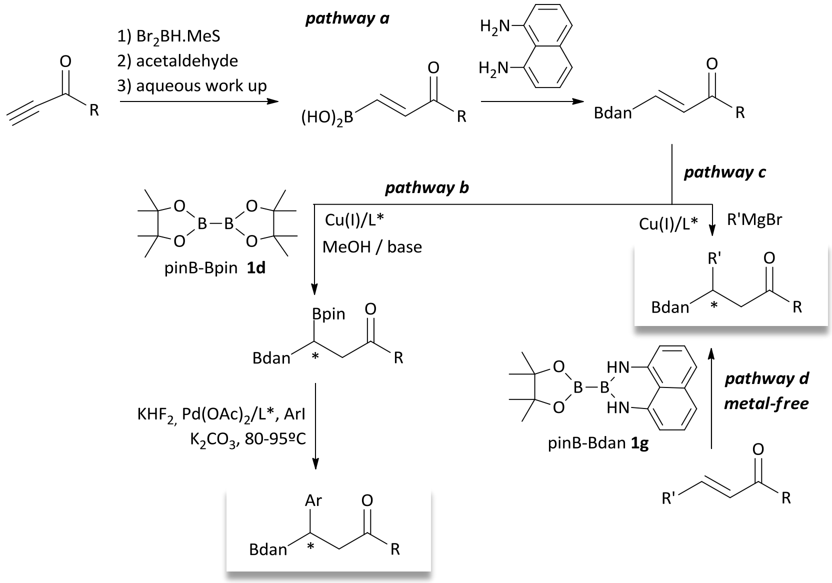
Scheme 4.1 Rh-mediated hydroboration of 1-octene with 1,3,2-benzodiazaborolone.

1,8-Diaminonaphthalene (dan) treated with haloarylboronic acids afforded the corresponding naphthalene-1,8-diamido derivatives ^{X}ArB(dan) (Scheme 4.2a), which were subjected to Suzuki-Miyaura coupling with arylboronic acids $ArB(OH)_2$ in the presence of palladium complexes. The 1,8-diaminonaphthalene group acted as a masking group on B along the reaction to avoid undesirable coupling and eventually it could be easily unmasked by simple treatment with aqueous acid.[3] Similarly, the masked haloareneboron compounds, ^{X}ArB(dan), could be prepared by Ir-catalyzed C-H borylation of the haloarene with 1,8-naphthalenediaminatoborane HB(dan) (Scheme 4.2b).[4] On the basis of the boron-masking strategy, new divalent cross-coupling modules have been designed for the efficient synthesis of boron substituted oligoarenes.[5]

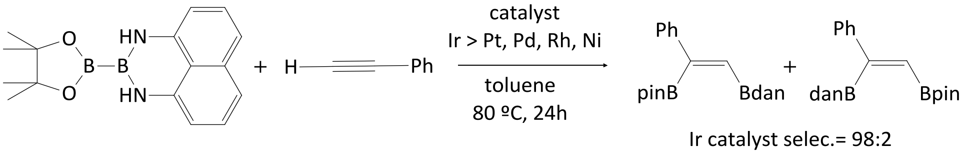


Scheme 4.2 Synthesis of Bdan moieties and application as masked groups in cross coupling reactions.

So far Bpin moieties have been exclusively transferred from symmetric B_2pin_2 reagent to unsaturated substrates, but the pinacol substituent on B does not mask the B atom towards further interactions. In that context, the interest of generating C_β-Bdan enoates were justified because they have served as intermediates towards the copper mediated asymmetric conjugate borylation (Scheme 4.3 pathway b) to deliver the desired chiral 1,1-diboronyl ester, with high enantioselectivity, that conducted a subsequent chemoselective Suzuki-Miyaura coupling (Scheme 4.3 pathway b).[6] C_β-Bdan enoates also served as precursor for Cu(I)-catalyzed addition of EtMgBr towards chiral alkylboronate derivatives (Scheme 4.3 pathway c).[7] However, nowadays the synthesis of C_β-Bdan enoates was achieved from the corresponding boronic acid, following a multistep synthesis methodology (Scheme 4.3 pathway a).[8] We became interested in developing a method to access directly to chiral alkylboronate derivatives containing the Bdan moiety, from commercially accessible α,β-unsaturated esters and ketones following a catalytic β-boration (Scheme 4.3 pathway d).[9] Towards this new strategy we envisaged the activation of the mixed diboron reagent Bpin-Bdan, with an alkoxide.[10] To the best of our knowledge there is only one example in the literature in which Bpin-Bdan has been used to diborate alkynes in a regioselective manner, and it was required the activation of the diboron by transition metal complexes (Scheme 4.4).[11]



Scheme 4.3 Synthesis of 1,8-diaminonaphtalenyl (dan) 3-boronyl enoates and their application in asymmetric organic synthesis.



Scheme 4.4 Diboration reaction with Bpin-Bdan developed by Miyaura and co-workers.

Before embarking in the experimental effort of performing the β-boration reaction, in an organocatalytic context, we evaluated whether the alkoxide should interact with the Bpin moiety to release the Bdan as a nucleophile, or viceversa. To answer this important question we conducted a theoretical study on the relative stability and reactivity of the MeO^{-}→Bpin-Bdan and MeO^{-}→Bdan-Bpin adducts.

4.2. Results and discussion

4.2.1. Theoretical evaluation of the potential reactivity of Bpin-Bdan

Initially, we computationally explored the potential reactivity of the Bpin-Bdan reagent. Previous DFT studies by Bo et al. have already demonstrated the nucleophilic character of $B(sp^2)$ moiety of $MeO^-\rightarrow$Bpin-Bpin adducts.[10b, 12] In chapter 2, a tendency map was constructed based on DFT calculations and NBO analysis of ground-state structures in order to establish a gradient in the nucleophilic character of trivalent boron moieties.[13] Structure-Activity Relantionships (SAR) approaches can be used to screen large and varied datasets of compounds in homogeneous catalysis.[14] The boron p/s ratio in the M-B σ-bond was considered an indicator of the intrinsic nucleophilicity of the boryl fragment, based on a previous work of Lin and Marder.[15] For diboron reagents that are activated with Lewis bases, the p/s ratio of the $B(sp^2)$ atom is relatively low with respect to the corresponding fragment bonded to Pd (Figure 4.1).[13] This indicated the greater polarizability of the $B(sp^2)$ moiety in the B-B bond, and consequently, its propensity to react with soft electrophiles. Moreover, the MeO^- ion induced greater polarization of the B-B bond than the nitrogen- and carbon-donor Lewis bases.[13] Thus, we initially calculated the p/s ratio of B atom from the $Bdan(sp^2)$ moiety, in the $MeO^-\rightarrow$Bpin-Bdan adduct in other to evaluate it as a potential nucleophilic boryl moiety. The computed p/s value, 1.15, is within the range (1.03 - 1.19) of other tested diboron compounds activated with Lewis bases (Figure 4.1).[13]

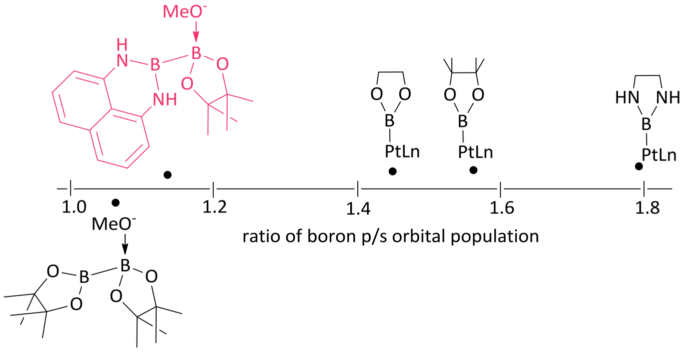


Figure 4.1 Relative distribution of p/s ratio of the orbital population of *B* in *B*-$Pt(PMe_3)_2Cl$ moieties and $MeO^-\rightarrow$Bpin-*B*dan, $MeO^-\rightarrow$Bpin-*B*pin adducts.

Although the tendency map identifies Bdan as a potential nucleophilic boryl moiety,[13] its semi-quantitative nature does not allow discerning whether the Bdan moiety is more or less reactive than the Bpin moiety. Therefore, we performed a more detailed DFT study in order to compare the reactivity of both adducts (Figure 4.2). Using the CH_2CHCOH substrate as the simplest model of α,β-unsaturated ketones, we located the transition states (TSs) corresponding to the nucleophilic attack of the Bpin(sp^2) and Bdan(sp^2) moieties at the β-carbon of the olefinic group. The computed energy barrier for the Bdan group (+12.0 $kcal.mol^{-1}$) is higher than for the Bpin moiety, +4.2 $kcal.mol^{-1}$, indicating that the Bdan (sp^2) has a lower nucleophilic character than Bpin (sp^2). However, due to the π-donation from nitrogen lone pair to boron empty orbital, the acidity of boron is weakened and has less tendency to add the alkoxide. The $MeO^- \rightarrow$Bpin-Bdan adduct is 7.6 $kcal.mol^{-1}$ lower in energy than $MeO^- \rightarrow$Bdan-Bpin. Thus, we cannot discard that the activation of the mixed diboron reagent Bpin-Bdan with alkoxyde would lead selectively to the formation of a C-B bond. In this scenario, the 1,8-diaminonaphtalene group might protect the boron from Lewis base attack forming preferentially the $MeO^- \rightarrow$Bpin-Bdan reagent, which only needs to overcome a modest energy barrier to release Bdan as a nucleophile.

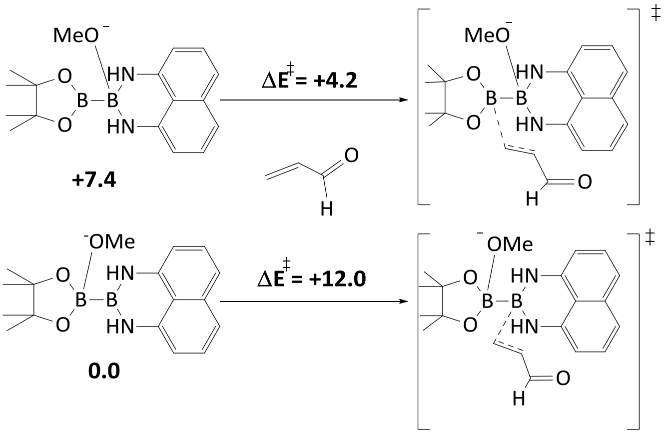


Figure 4.2 Relative $MeO^- \rightarrow$Bpin-Bdan and $MeO^- \rightarrow$Bdan-Bpin adduct formation and relative reactivity with CH_2CHCHO. Electronic energies in $kcal{\cdot}mol^{-1}$.

4.2.2. Experimental catalysis results

These results prompted us to synthesize the Bpin-Bdan reagent and use it in the organocatalyic β-boration reation of α,β-unsaturated carbonyl compounds. We adapted the synthetic protocol from Suginome's method,[11] by mixing tetrakis(dimethylamino)diboron, $B_2(NMe_2)_4$, with 1,8-diaminonaphthalene and pinacol in a 1:1:1 ratio. However, since we prepared $B_2(Me_2N)_4$ from B_2cat_2,[16] instead of $BCl_3.SMe_2$, the global isolated yield of Bpin-Bdan resulted slightly higher (up to 75%) (Figure 4.3).

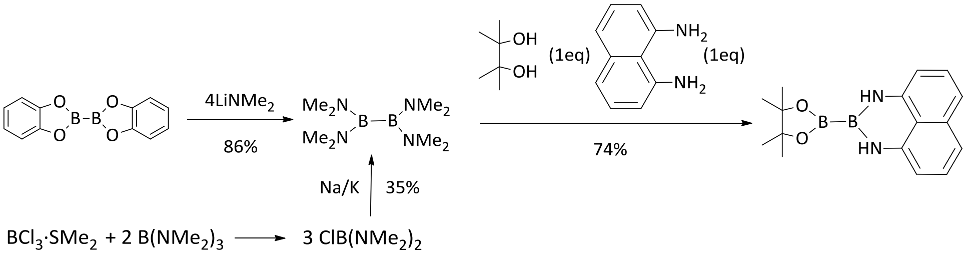
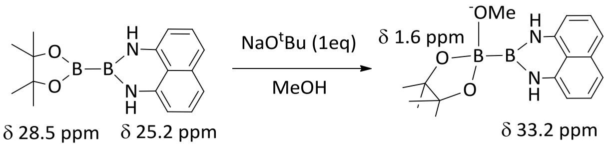


Figure 4.3 Optimized synthesis of Bpin-Bdan from B_2cat_2.

In the presence of a base and MeOH, some spectroscopic evidences have demonstrated the formation of the Lewis acid-base adduct [RO^-→Bpin-Bdan]. The original ^{11}B NMR spectra of the mixed diboron reagent Bpin-Bdan**,** in MeOH as solvent, shows signals at 28.5 ppm and 25.2 ppm due to the sp^2 Bpin and sp^2 Bdan fragment, respectively. After the addition of 1 eq of NaO*t*Bu, one of the signals completely shifted to higher fields (1.6 ppm), with one signal remaining at low field (33.2 ppm) (Scheme 4.5). The new signal might correspond to the sp^3 Bpin moiety of the adduct [RO^-→Bpin-Bdan] in agreement with previous spectroscopic evidences of [RO^-→Bpin-Bpin].[10] This finding is also in agreement with the DFT calculations that suggested the preferred formation of the Lewis acid-base adduct [RO^-→Bpin-Bdan].

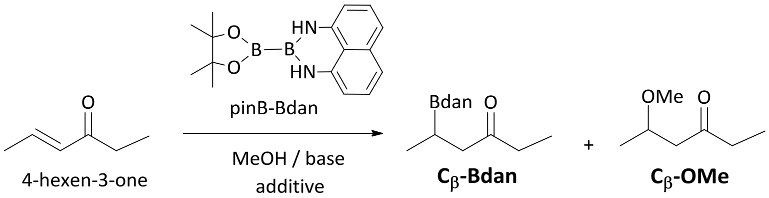


Scheme 4.5 In situ ^{11}B NMR of the suggested [MeO$^-$→Bpin-Bdan] adducts.

With the aim of activating organocatalytically Bpin-Bdan and selectively transfer the Bdan moiety to activated olefins, we first attempted to find the optimal conditions for the β-boration of 4-hexen-3-one with Bpin-Bdan (Table 4.1). When the reaction was carried out in MeOH as solvent at 70ºC, no β-borated product was observed. The sole addition of 9 mol% of NaO*t*Bu favoured the formation of 5-methoxy-hexan-3-one (C_β-OMe) as the only product, with a conversion of 72% (Table 4.1, entry 1). It seemed that the MeOH-base interaction provided the methoxy group that attacked directly to the substrate instead of activating Bpin-Bdan. However, when no base was present in the reaction media and PCy_3 was added as additive (6 mol%), the substrate was totally transformed into the β-borated product with exclusive formation of the C_β-Bdan bond, (Table 4.1, entry 2). The use of phosphines to assist the organocatalytic β-boration reaction of α,β-unsaturated carbonyl compounds has been demonstrated with a selected number of substrates.[17] We previously observed that the new method eludes the use of Brönsted bases to promote the catalytic active species and PR_3 becomes essential to interact with α,β-unsaturated ketones resulting in the formation of a zwitterionic phosphonium enolate. This species can further deprotonate MeOH when the diborane B_2pin_2 is present forming eventually the ion pair [α-(H),β-(PR_3)-ketone]$^+$-[B_2pin_2·MeO]$^-$ that is responsible for the C_β-B(pin) formation.[17] Therefore, our finding on the efficient assistance of PCy_3 in the selective C_β-B(dan) formation is in agreement with previous observations.[10a, 17]

The presence of base and phosphine as additive resulted beneficial (Table 4.1, entry 3), and the reaction was observed even at 25°C (Table 4.1, entry 4). The nature of the phosphine is also important. When PPh_3 was involved in the reaction together with NaO*t*Bu as base, selectivity towards the β-borated product decreased to 60% with the generation of 5-methoxy-hexan-3-one (C_β-OMe) as byproduct (Table 4.1, entry 5). But once again, when no base was present and PPh_3 assisted the reaction, the β-borated product was exclusively formed, but with lower conversion (Table 4.1, entry 6). Importantly, the activation of Bpin-Bdan with the alkoxide exclusively renders C_β-Bdan formation as no C_β-Bpin product has been detected.

Table 4.1 Optimization of reaction conditions fot the β-boration of 4-hexen-3-one with Bpin-Bdan.



Entry	Additive (6 mol%)	Base (9 mol%)	Conv. (%)[b]	C_β-Bdan (%)[c]	C_β-OMe (%)[c]
1	---	---	---	---	---
2	---	NaO*t*Bu	72	---	99
3	PCy_3	---	99	99	---
4	PCy_3	NaO*t*Bu	99	99	---
5[d]	PCy_3	NaO*t*Bu	23	99	---
6	PPh_3	NaO*t*Bu	99	60	40
7	PPh_3	---	70	99	---

[a] Reaction condition: 4-hexen-3-one (0.25 mmol), Bpin-Bdan (0.275 mmol), base (9 mol%), PR_3 (6 mol%), MeOH (2 mL), 70 °C, 16 h. [b] Conversion calculated by ^{1}H NMR from an average of two reactions. [c] Selectivity calculated by ^{1}H NMR. [d] 25 °C.

The scope of substrates was also a subject of study. Under optimized reaction conditions, we were able to generalize the selective transfer of the Bdan moiety from the adduct [$RO^- \rightarrow$Bpin-Bdan] to a variety of α,β-unsaturated ketones and esters (Figure 4.3).

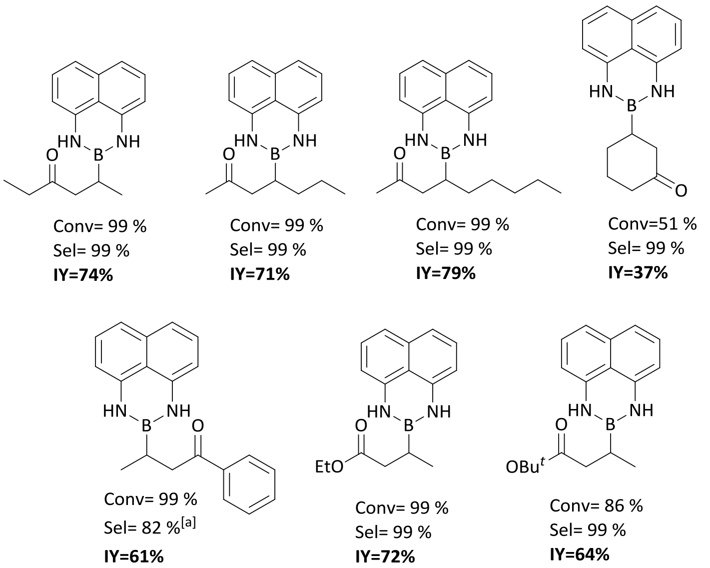
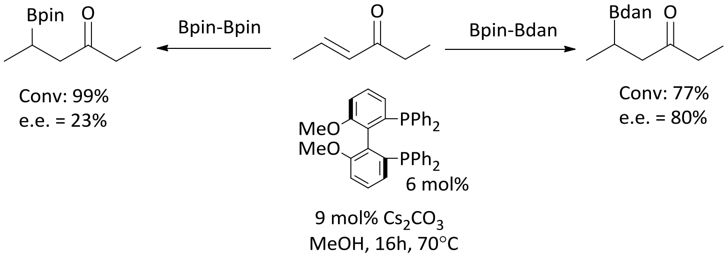


Figure 4.4 Substrate scope of selective organocatalytic β-boration of α,β-unsaturated carbonyl compounds with Bpin-Bdan. Conditions: substrate (0.25 mmol), Bpin-Bdan (0.275 mmol), NaO*t*Bu (9 mol%), PCy_3 (6 mol%), MeOH (2 mL), 70 °C, 16 h. Determined by NMR spectroscopy. [a] 18 % of β-methoxi byproduct was observed.

Our research group recently pointed out that chiral phosphines can assist the asymmetric organocatalytic β-boration of α,β-unsaturated carbonyl compounds with B_2pin_2.[10a] In the present study, we explored this possibility and conducted a parallel β-boration of model substrate 4-hexen-3-one, with B_2pin_2 and Bpin-Bdan in the presence of (*R*)-(+)-MeO-BIPHEP diphosphine (*R*)-(+)-(6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine). Scheme 4.6 shows that the asymmetric induction in the organocatalytic C_β-Bdan formation is much higher (e.e = 80%) than that observed in the formation of the C_β-Bpin bond (e.e = 23%).



Scheme 4.6 Comparative asymmetric β-boration of 4-hexen-3-one with B_2pin_2 and Bpin-Bdan assisted by (R)-(+)-MeO-BIPHEP diphosphine.

4.2.3. Theoretical analysis of the mechanism

To get more insight into the selective addition of Bdan moiety in the presence of phosphines as additive, we performed a systematic DFT study using PMe_3 and $CH_2C(H)C(H)O$ as model phosphine and substrate. First of all, DFT studies related to the plausible interaction of PMe_3 with Bpin-Bdan, demonstrated the lack of stability of the corresponding [PMe_3→Bpin-Bdan] adduct.[17] Similar conclusion was observed from the spectroscopic studies carried out in ^{11}B NMR and ^{31}P NMR by mixing Bpin-Bdan and PMe_3. Recently, Bo and co-workers had computationally characterized the role of the phosphine in the organocatalytic β-boration of α,β-unsaturated ketones and esters with Bpin-Bpin reagent.[17] In that previous study, the role of the phosphine was associated with the preactivation of the substrate, by forming a phosphonium salt. Following previous proposal,[17] we suggest a catalytic cycle that starts with the plausible phosphine attack to the electrophilic carbon of the α,β–unsaturated carbonyl compound yielding the zwitterionic phosphonium enolate, species **B** in Figure 4.5. This intermediate might act as a Brönsted base deprotonating the MeOH, and in the presence of an excess of MeOH, it is reasonable to assume the formation of the adduct C (Figure 4.5), where MeOH molecule is H-bonded to the α-carbon of the phosphonium enolate. From **C**, two ion pair can be formed by the interaction with Bpin-Bdan: the [α-H,β-PMe_3-propionaldehyde]$^+$[MeO^-→Bdan-Bpin], **Da**, (Figure 4.5, *mechanism a*) and the formation of [α-H,β-PMe_3-propionaldehyde]$^+$ [MeO^-→Bpin-Bdan], **Db**, (Figure 4.5, *mechanism b*). The corresponding energies associated to the formation of the ion-pair **Da** (5.6 kcal·mol^{-1}) and **Db** (-7.5 kcal·mol^{-1}), clearly shows the favored formation of the ion-pair **Db**, in which Bpin moiety acts as the preferred Lewis acid. Moreover, the energy barrier to reach the ion pair **Db** is significantly lower than that calculated to reach the ion pair **Da**, 4.0 and 13.9 kcal.mol^{-1}, respectively. These results are coherent with previous experimental findings in which quantitative formation of phosphonium species, required the presence of the Bpin-Bpin reagent,[17-18] and indicates that the Bdan moiety in Bpin-Bdan diboron reagent is not as good Lewis acid as Bpin moiety.

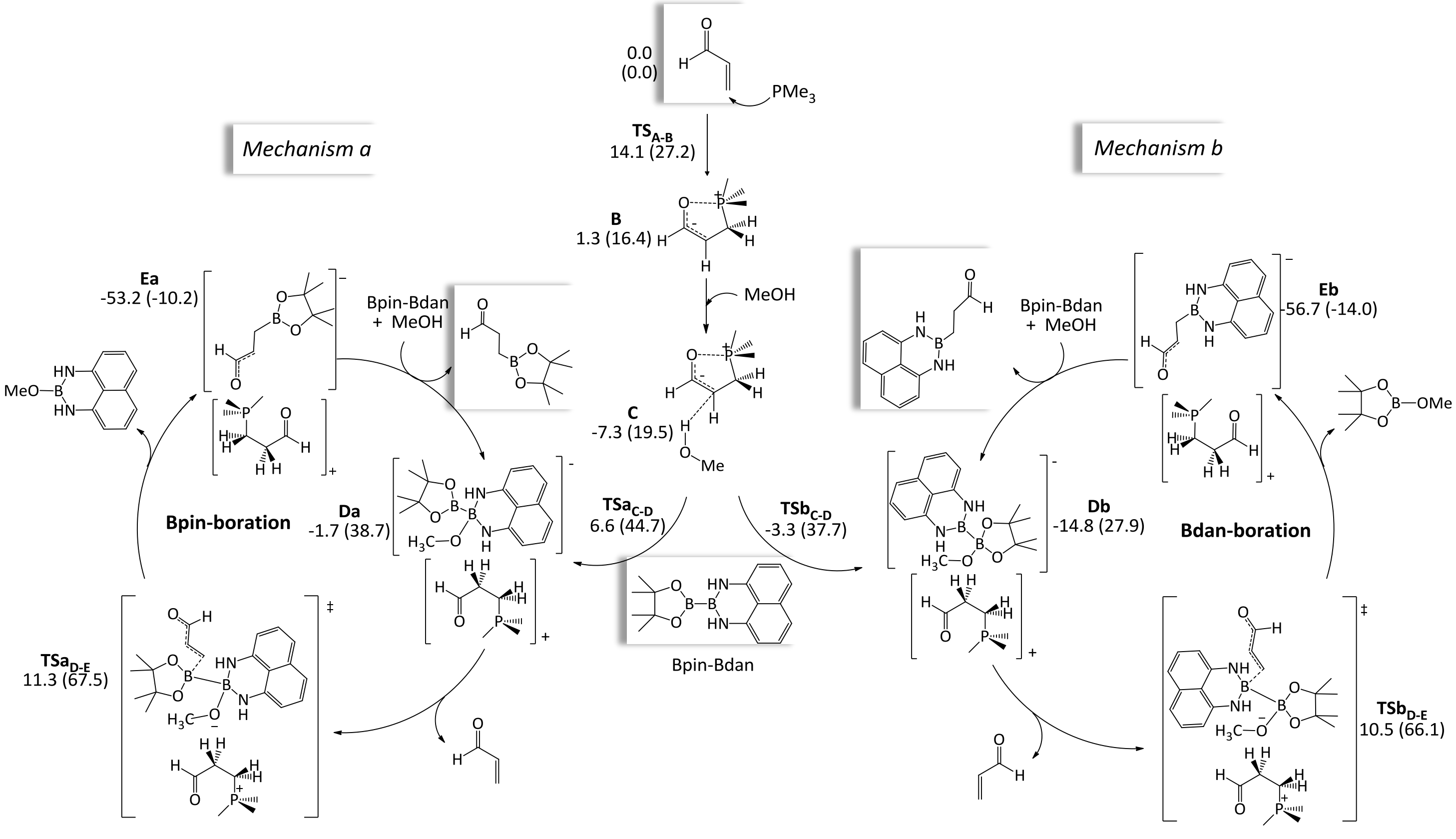


Figure 4.5 Suggested catalytic cycle for β-boration of acryladehyde with Bpin-Bdan diboron reagent in the presence of MeOH and PMe_3. Mechanism a depicts the C_β-Bpin formation and mechanism b illustrates the C_β-dan formation. Electronic energies and Gibbs free energies (in parenthesis) in kcal·mol^{-1}.

In the next step, it has been suggested that the enhanced nucleophilic sp^2 boryl unit in the ion-pairs **Da** and **Db** might transfer the Bpin moiety or the Bdan moiety, respectively, to the β-carbon of another molecule of substrate through the transition state **TS$_{D-E}$**. For both types of boryl units the process is strongly exothermic, -51.5 kcal·mol^{-1} for Bpin release in *mechanism a* and -41.9 kcal·mol^{-1} for Bdan release in *mechanism b*. As it was found for the free anionic adducts depicted in the Figure 4.2, the activated Bpin(sp^2) moiety is more reactive than the Bdan(sp^2) one ($\Delta E^{\neq}$ = 13.0 and 25.3 kcal·mol^{-1}, respectively). However, if we look at the overall catalytic cycle, the transition state **TS$_{D-E}$** is the most energetically demanding, and this is higher in energy for Bpin release (**TSa$_{D-E}$**) than for Bdan release (**TSb$_{D-E}$**) by ~1 kcal·mol^{-1}. Thus, the computed overall catalytic cycle explains the observed selectivity from both the thermodynamic and the kinetic point of view. Thermodynamically, the deprotontation of methanol requires the enhanced Lewis acidity of Bpin moiety in Bpin-Bdan by forming the [MeO^-→Bpin-Bdan] adduct. Kinetically, the overall energy barrier to transfer Bdan moiety from the suggested ion pair to acrylaldehyde is somewhat lower than that for the Bpin transfer to acrylaldehyde. Finally, we must note that the assembly of four molecular entities implies an entropic cost, which could be seen in in the ΔG values of the Figure 4.5. For example, note the exaggerated accumulated values of structures **Da** and **Db**. 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. Nevertheless, formation of the final β-borated product largely overcomes the costs of the formation of these species.

4.3. Conclusions

We have been able to demonstrate a new activation of Bpin-Bdan in the absence of any metal complex. With the assistance of DFT calculations and spectroscopic studies it was possible to postulate the exclusive formation of the Lewis acid-base adduct [RO^-→Bpin-Bdan]. This activated intermediate reacts with α,β-unsaturated carbonyl compounds to give exclusively the C_β-Bdan carbonyl compound with high yields. In addition to the unprecedented conjugate Bdan addition to α,β-unsaturated ketones and esters, the presence of chiral diphosphine as additive assisted the asymmetric induction in a more efficient way than the analogue borylation with B_2pin_2 to form the corresponding enantioselective C_β-Bpin bond. The new synthetic platform opens a non existing methodology to prepare selectively C_β-Bdan carbonyl compounds in a selective straightforward pathway.

4.4. Computational methods

All calculations were performed using the Gaussian09 series of programs.[19] Calculations were performed within the framework of density functional theory (DFT)[20] using the B3LYP functional.[21] All the atoms were represented by means of the 6-31G(d,p) basis set.[22] All geometry optimizations were full, with no restrictions. All stationary points located in the potential energy hypersurface were characterized as minima or transition states by vibrational analysis. Transition states had one and only one imaginary frequency, whose normal mode corresponded to the expected motion.

4.5. References chapter 4

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Chapter 5

Concluding remarks

In chapter 2, we have systematically analyzed the electronic properties of several types of boryl moieties that were either bonded to main group metals, coordinated to transition metals, coordinated to rare-earth metals, or bonded to sp^3-hybridized boryl units by the so-called *Structure-Activity Relantionship* (SAR) appoach. We were able to establish a gradient of nucleophilic character for the trivalent boron moieties that were considered in this study by taking into consideration the charge on the boryl moiety and the boron p/s-population ratio.

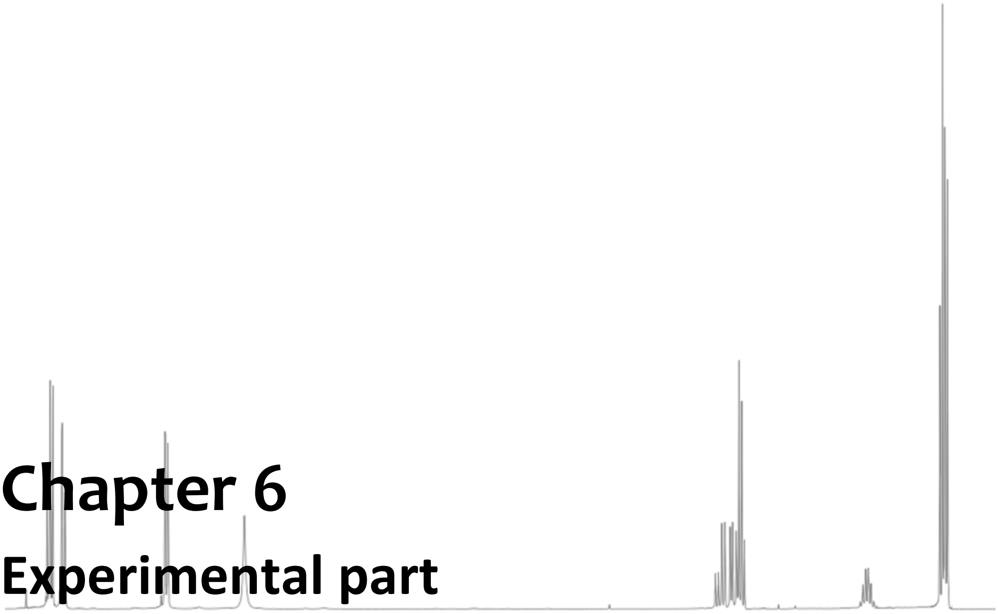
We constructed a map and we identified several groups of trivalent boron compounds that could act as nucleophiles or electrophiles. The versatile electronic properties of trivalent boron compounds depend on the nature of the metal or element that is bonded to it but also on the substituents on the boron moiety. The map also includes unprecedented boryl complexes “virtual systems”, and for some of them there is a reasonable theoretical support to attempt the experimental identification. In general, the trend that was observed for all of the trivalent boron compounds that were studied herein correlates well with their reported reactivity.

In chapter 3, we can conclude that the catalytic system based on the in situ mixture of $[\{RhCl(cod)\}_2]$ and basic and bulky phosphine groups, such as PCy_3, favored the non-conventional *trans*-hydroboration over the *cis*-hydroboration in the presence of Et_3N. We also optimized the reaction conditions for the hydroboration of 1-octyne and extended the methodology to other substrates. Subtle changes in the nature of the substrate indicated that electron-rich alkynes with high steric demands were mainly converted into the desired organoboron isomers.

We have computationally characterized a plausible reaction mechanism for the non-conventional *trans*-hydroboration reaction through isomerization of the alkyne to vinylidene, following the suggestion of Miyaura and co-workers based on their deuterium-labeled experiment. Unlike their mechanism, we propose a sequence of vinylidene insertion into the Rh-H bond followed by reductive elimination of the C-B bond. Thus, the mechanism can be divided into four stages: 1) oxidative addition of alkyne to metal and isomerization to yield a Rh-vinylidene complex, 2) oxidative addition of the borane reagent, 3) vinylidene insertion into the Rh-H bond, and finally 4) reductive elimination of the C-B bond to yield the *Z*-1-alkenylboronate.

We identified the selectivity-determining step as the insertion of vinylidene into the Rh-H bond. By means of QM/MM methods, we introduced the steric effects of real ligands and we were able to reproduce the experimental outcome, thus supporting the consistency of the proposed mechanism. Our calculations also indicated that bulky ligands are required to selectively obtain (*Z*)-1-alkenylboronates and that increasing the steric hindrance of the ligands causes an increase in selectivity of the *Z* isomer (PCy_3 > $P\textit{i}Pr_3$ > PMe_3 > PH_3). The higher selectivity observed for aryl alkynes compared with aliphatic alkynes can be explained by the analysis of different factors. The intrinsic electronic properties of aryl substituents are more favorable for the *Z* pathway than alkyl substituents. For electron-donating substituents, the formation of the Rh-vinylidene complex is favored, which seems to facilitate the occurrence of the vinylidene reaction channel over the classical *cis*-hydroboration pathway.

In chapter 4, we were able to activate a mixed diboron reagent Bpin-Bdan in the absence of any metal complex by a simple Lewis base. With the assistance of DFT calculations and spectroscopic studies it was possible to postulate the exclusive formation of the Lewis acid-base adduct [$RO^{-}\rightarrow$Bpin-Bdan]. This activated intermediate reacts with the phosphine activated α,β-unsaturated carbonyl compounds to give exclusively the C_β-Bdan carbonyl compound with high yields. In addition to the unprecedented conjugate Bdan addition to α,β-unsaturated ketones and esters, the presence of chiral diphosphine, as additive, assisted the asymmetric induction in a more efficient way than the analogue borylation with B_2pin_2 to form the corresponding enantioselective C_β-Bpin bond. We also characterized a plausible mechanism according to the previous work of Bo and co-workers and explained the observed selectivity from both the thermodynamic and the kinetic point of view. The new synthetic platform opens a non existing methodology to prepare selectively C_β-Bdan carbonyl compounds in a selective straightforward pathway.



Chapter 6

Experimental part

6.1. General considerations

All reactions and manipulations were carried out under a nitrogen atmosphere by using Schlenk-type techniques. The solvents were distilled over dehydrating reagents and were deoxygenated before use. Bis(pinacolato)diboron and bis(catecholato)diboron were used as purchased from Allychem. Bpin-Bdan was synthetized as previously reported.[1] Phosphines were used as purchased from STREM. Substrates and $[\{RhCl(cod)\}_2]$, $[\{IrCl(cod)\}_2]$ were used as purchased from Alfa Aesar or Sigma-Aldrich. All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise.

Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements. NMR spectra were obtained on either a Varian Gemini 300 or a Varian Mercury 400 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane, references to the chemical shifts of residual solvent resonances. ^{11}B NMR chemical shifts are reported in ppm (δ) relative to $BF_3(CH_3)_2O$. Coupling constants (*J*) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

GC analyses of the solutions were performed on an Agilent Technologies 6850 apparatus with a flame ionization detector equipped with an achiral column HP-5 (30m, 0.25mm i. d., 0.25µm thickness) using H_2 as the carrier gas.

HPLC-TOF was equipped with chiral column Chiracel OD-H. Electron impact (EI) (70 Ev) and chemical ionization (CI) were recorded with a Kratos MS50 or a Finnigan MAT 95S spectrometer. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer.

6.2. Experimental procedure for the rhodium-catalyzed non-conventional *trans*-hydroboration of terminal alkynes

Catalyst precursor ([{RhCl(cod)}$_2$]or [{IrCl(cod)}$_2$] = 0.015 mmol) and the ligand (0.06 mmol) were introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in 3 ml of THF and NEt$_3$ (5 mmol). The mixture was stirred for 5 minutes to reach complete dissolution and formation of the catalytic complex *in situ*. Next, freshly distilled catecholborane (1.2 mmol) or pinacolborane (1.2 mmol) was added to the solution of catalyst followed by the addition of the substrate (1 mmol). The mixture obtained was stirred at room temperature and stopped after 4 hours. The products were characterized by ^{1}H NMR spectroscopy and by GC to determine the degree of conversion and the selectivity obtained.

6.3. Experimental procedure for the organocatalytic β-boration of α,β-unsaturated compounds

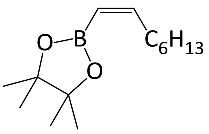
6.3.1. General procedure for the β-boration of α,β-unsaturated carbonyl compounds

The phosphine, (0.015 mmol), sodium tert-butoxide (2.2 mg, 0.023 mmols) and BpinBdan (81 mg, 0.275 mmol) were transferred into an oven-dried Schlenk tube under nitrogen. MeOH (2 mL) was 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 gently concentrated on a rotary evaporator at room temperature and analyzed by ^{1}H-NMR to determine the conversion. The sample was combined with the rest of the reaction mixture, all the volatiles were removed in vacuum and the crude product was purified by column chromatography.

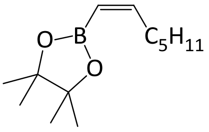
6.3.2. General procedure for the chiral β-boration of α,β-unsaturated carbonyl compounds

The chiral phosphine, (0.015 mmol), cesium carbonate (7.3 mg, 0.023 mmols) and BpinBdan (81 mg, 0.275 mmol) were transferred into an oven-dried Schlenk tube under nitrogen. THF (2 mL) and MeOH (51 µl, 1.25mmol) were added. The mixture was stirred 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. 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 gently concentrated on a rotary evaporator at room temperature and analyzed by ^{1}H-NMR to determine the conversion. The sample was combined with the rest of the reaction mixture, all the volatiles were removed in vacuum and the crude product was purified by column chromatography.

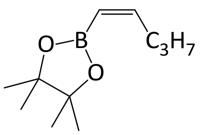
6.4. Characterization of organoboranes



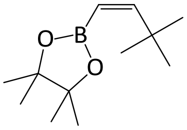
(*Z*)-4,4,5,5-tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 80:1) as a yellow oil. ^{1}H NMR (400 MHz,CDCl$_3$): δ 6.42 (dt, *J*=13.2, 7.2 Hz, 1H), 5.32 (dt, *J*=13.4, 1.5 Hz, 1H), 2.39 (dtd, *J*=7.2, 7.2, 1.2 Hz, 2H), 1.29-1.39(m, 8H), 1.28 (s, 12H), 0.87 (t, *J*=7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$): δ 155.3, 82.7, 32.2, 31.6, 29.4, 28.7, 24.8, 22.6, 14.1. ^{11}B NMR (128.3 MHz, CDCl$_3$): δ 29.79. The spectroscopic data are in agreement with the previously reported.[2]



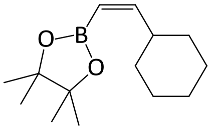
(*Z*)-2-(hept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 40:1) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.43 (dt, *J*=13.2, 6,4 Hz, 1H), 5.31 (dt, *J*=13.2, 1.2 Hz, 1H), 2.38 (dtd, *J*=7.2, 7.2, 1.2, 2H), 1.40 (m, 2H), 1.32-1.28 (m, 4H), 1.25 (s, 12 H), 1.08 (t, *J*=7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$): δ 155.3, 82.7, 32.1, 31.2, 29.7, 29.1, 24.8, 22,4, 14.0. ^{11}B NMR (128.3 MHz, CDCl$_3$): δ 29,90.



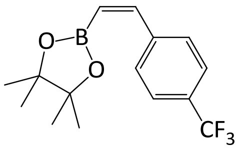
(*Z*)-4,4,5,5-tetramethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 40:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (dt, *J*=13.2, 7.6 Hz, 1H), 5.33 (dt, *J*=13.2, 1.6 Hz, 1H), 2.34 (dtd, *J*=7.6, 7.2, 1.6 Hz, 2H), 1.38 (m, 2H), 1.26 (s, 12H), 0.88 (t, *J*=7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 154.9, 82.7, 34.2, 29.8, 24.8, 22.6, 13.5. ^{11}B NMR (128.3 MHz, $CDCl_3$): δ 29.80.



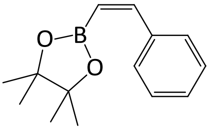
(*Z*)-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 40:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (d, *J*=15.1 Hz, 1H), 5.17 (d, *J*=15.1 Hz, 1H), 1.28 (s, 12H), 1.09 (s, 9H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 159.7, 83.3, 29.9, 24.8, 22.6. ^{11}B NMR (128.3 MHz, $CDCl_3$): 30.61. The spectroscopic data are in agreement with the previously reported.[2]



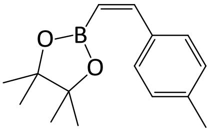
(*Z*)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 19:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (dd, *J*=13.6 Hz, 1H), 5.22 (d, *J*=13.6 Hz, 1H), 2.74-2.66 (m, 1H), 1.73-1.60 (m, 4H), 1.35-1.01 (m, 18H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 160.6, 82.7, 40.6, 33.3, 26.0, 25.7, 24.8. ^{11}B NMR (128.3 MHz, $CDCl_3$): δ 29.79. The spectroscopic data are in agreement with the previously reported.[3]



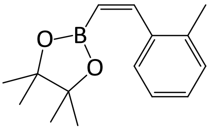
(*Z*)-4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)styryl)-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc =20:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=8 Hz, 2H), 7.53 (d, *J*=8 Hz, 2H), 7.21 (d, J=14.8 Hz, 1H), 5.73 (d, J=14.8 Hz, 1H), 1.28 (s, 12H).). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): 24.8, 83.7, 124.2, 124.8, 128.8, 129.7, 141.8, 146.6. ^{11}B NMR (128 MHz, $CDCl_3$) δ 22.49. The spectroscopic data are in agreement with the previously reported.[4]



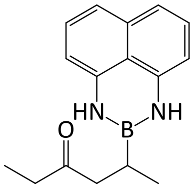
(*Z*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 80:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=6.8 Hz, 2H), 7.26-7.33 (m, 3H), 7.22 (d, *J*=14.9 Hz, 1H) 5.58 (d, *J*=14.8 Hz, 1H), 1.29 (s, 12H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 148.1, 138.4, 128.6, 128.0, 127.9, 83.5, 24.8. ^{11}B NMR (128.3 MHz, $CDCl_3$): δ 30.15. The spectroscopic data are in agreement with the previously reported.[2-4]



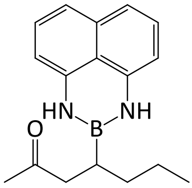
(*Z*)-4,4,5,5-tetramethyl-2-(4-methylstyryl)-1,3,2-dioxaborolane: The chromatography over silica gel (petroleum ether/EtOAc = 20:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8 Hz, 2H), 7.18 (d, *J*=14.8 Hz, 1H), 7.11 (d, *J*=8 Hz, 2H), 5.52 (d, *J*=14.8 Hz, 1H), 2.34 (s, 3H), 1.29 (s, 12H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): 146.9, 137.9, 135.9, 128.6, 83.3, 24.6, 22.6, 21.3. ^{11}B NMR (128.3 MHz, $CDCl_3$): δ 30.36. The spectroscopic data are in agreement with the previously reported.[4]



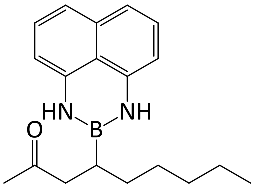
(*Z*)-4,4,5,5-tetramethyl-2-(2-methylstyryl)-1,3,2-dioxaborolane: The product was purified by flash column chromatography (petroleum ether/EtOAc = 20:1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J*=7.6 Hz, 2H), 7.34 (d, *J*=14.4 Hz, 1H), 7.19-7,09 (m, 3H), 5.65 (d, *J*=14.4 Hz, 1H), 2.31 (s, 3H), 1.23 (s, 12H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): 146.9, 137.9, 135.9, 129.6, 128.6, 127.9, 125.1, 83.4, 24.7, 22.6, 19.8. ^{11}B NMR (128.3 MHz, $CDCl_3$): δ 30.32.



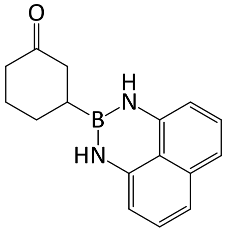
5-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hexan-3-one: The product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) as a yellow oil (74 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J*=8.0, 7.6 Hz, 2H), 7.00 (dd, *J*=8, 1.2 Hz, 2H), 6.30 (dd, *J*=7.2, 1.2 Hz, 2H), 5.74 (br s, 2H), 2.57 (d, *J*=6.8 Hz, 1H), 2.47 (dd, *J*=16, 7.2 Hz, 1H), 2.43 (q, *J*=7.6 Hz, 2H), 1.57 (m, 1H), 1.06 (t, *J*=7.2 Hz, 3H), 1.04 (d, *J*=7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 212.6, 141.4, 136.5, 127.8, 119.9, 117.7, 105.9, 47.1, 36.5, 16.6, 8.1; ^{11}B NMR (128.3 MHz, $CDCl_3$) δ 32.5; MS (70 eV) *m/z* : 267.16 [M^+]



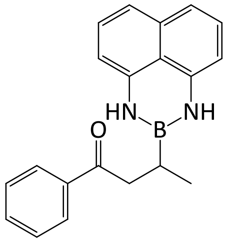
4-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)heptan-2-one: The product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) as a yellow oil (71 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J*=8.4, 7.2 Hz, 2H), 7.00 (dd, *J*=7.2, 1.2 Hz, 2H), 6.31 (dd, *J*=6.8, 1.2 Hz, 2H), 5.73 (br s, 2H), 2.57 (d, *J*=6.8 Hz, 2H), 2.15 (s, 3H), 1.40-1.24 (m, 5H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 209.6, 141.3, 136.5, 127.7, 119.8, 117.6, 105.8, 46.6, 34.2, 30.4, 25.3, 22.4, 14.5; ^{11}B NMR (128.3 MHz, $CDCl_3$) δ 32.6 ; MS (70 eV) *m/z* : 281.18 [M^+].



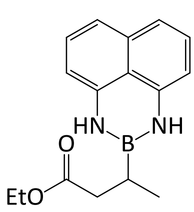
4-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)nonan-2-one: The product was purified by flash column chromatography (petroleum ether/EtOAc = 8:1) as a yellow oil (79 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J*=7.6, 7.2 Hz, 2H), 6.99 (d, *J*=8 Hz, 2H), 6.31 (d, *J*=7.6 Hz, 2H), 5.72 (br s, 2H), 2.57 (d, *J*=6.4 Hz, 2H), 2.15 (s, 3H), 1.45-1.27 (m, 9H), 0.87 (t, *J*=6.4 Hz, 3H); ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 209.6, 141.3, 136.4, 127.7, 119.8, 117.6, 105.8, 46.6, 32.2, 31.9, 30.4, 28.9, 22.7, 14,3; ^{11}B NMR (128.3 MHz, $CDCl_3$) δ 32.5; MS (70 eV) *m/z* : 309.21 [M^+].



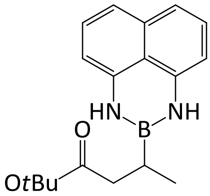
3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)cyclohexanone: The product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) as a yellow oil (37 % yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08 (dd, *J*=8.4, 7.2 Hz, 2H), 6.99 (d, *J*=8 Hz, 2H), 6.30 (d, *J*=7.2 Hz, 2H), 5.68 (br s, 2H), 2.44-2.24 (m, 4H), 2.11-2.06 (m, 1H), 1.92-1.87 (m, 1H), 1.80-1.76 (m, 1H), 1.64-1.59 8m, 1H), 1.50-1.46 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 212.6, 140.8, 127.7, 119.8, 117.9, 106.0, 43.7, 42.1, 28.6, 27.6; ^{11}B NMR (128.3 MHz, CDCl$_3$) 31.7 δ ; MS (70 eV) *m/z* : 265.15 [M$^+$].



3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-1-phenylbutan-1-one: The product was purified by flash column chromatography (petroleum ether/EtOAc = 8:1) as a yellow oil (61 % yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J*=7.2 Hz, 2H), 7.56 (t, *J*=7.6 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 7.08 (dd, *J*=8.4, 7.2 Hz, 2H), 6.98 (d, *J*=8.4 Hz, 2H), 6.31 (d, *J*=7.2 Hz, 2H), 5.80 (br s, 2H), 3.16 (dd, *J*=17.6, 8 Hz, 1H), 3.08 (dd, *J*=17.6, 6 Hz, 1H), 1.76 (m, 1H), ,1.14 (d, *J*=7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 200.7, 141.3, 137.1, 136.5, 133.3, 128.8, 128.2, 127.7, 119.8, 117.6, 105.9, 43.4, 25.3, 16.8; ^{11}B NMR (128.3 MHz, CDCl$_3$) δ 32.3; MS (70 eV) *m/z* : 275.18 [M$^+$].



ethyl 3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-butanoate: The product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) as a yellow oil (72 % yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.10 (dd, *J*=8.0, 7.6 Hz, 2H), 7.01 (dd, *J*=8, 1.2 Hz, 2H), 6.31 (dd, *J*=7.6, 1.2 Hz, 2H), 5.80 (br s, 2H), 4.15 (q, J=7.2 Hz, 2H), 2.46 (dd, *J*=15.6, 7.6 Hz, 1H), 2.37 (dd, *J*=15.6, 6.8 Hz, 1H), 1.57 (m, 1H), 1.26 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 174.1, 141.2, 136.4, 127.7, 119.8, 117.7, 105.9, 60.7, 38.7, 25.3, 16.5, 14.4 ; ^{11}B NMR (128.3 MHz, CDCl$_3$) δ 32.6; MS (70 eV) *m/z* : 283.16 [M$^+$].



tert-butyl 3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)butanoate: The product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) as a yellow oil (64 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J*=8.0, 7.2 Hz, 2H), 7.01 (d, *J*=8 Hz, 2H), 6.31 (d, *J*=7.6 Hz, 2H), 5.80 (br s, 2H), 2.37 (dd, *J*=15.6, 8 Hz, 1H), 2.30 (dd, *J*=15.6, 7.2 Hz, 1H), 1.57 (m, 1H), 1.46 (s, 9H), 1.09 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5, 141.3, 136.4, 127.7, 119.8, 117.6, 105.8, 80.7, 39.9, 28.3, 16.4; ^{11}B NMR (128.3 MHz, $CDCl_3$) δ 35.5; MS (70 eV) *m/z* : 293.19 [M^+].

6.5. References chapter 6

[1] a) N. Iwadate, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 2548; b) J. T. Patton, S. G. Feng, K. A. Abboud, *Organometallics* **2001**, *20*, 3399.
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Chapter 7

Resum en català

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7.1. Resum en català

Els compostos de bor s'han considerat tradicionalment com a àcids de Lewis, preferint acceptar electrons més que donar-los en el curs de les reaccions, però darrerament han sorgit exemples a la bibliografia on el compost trivalent de bor presenta una reactivitat insòlita vers posicions electrofíliques. Aquest fet ens suggereix un nou context nucleofílic per als sintons boril, que pot ser augmentat depenent dels substituents als quals estigui unit el bor (Figura 7.1). En aquesta tesi, volem mostrar una visió de les reactivitats oposades mitjançant l'estudi teòric de diferents compostos de bor. A més a més també ens hem centrat en l'estudi de dues reaccions, la hidroboració *trans* no convencional on el grup boril actua com a electròfil i la β-boració organocatalítica amb un diborà mixt on el grup boril actua com a nucleòfil.

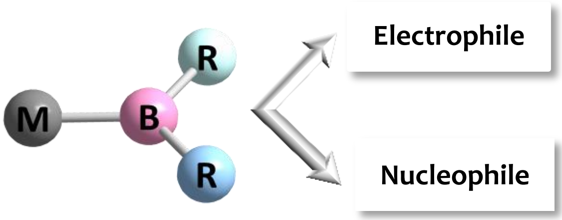


Figura 7.1 Reactivitat observada en els compostos de bor trivalent.

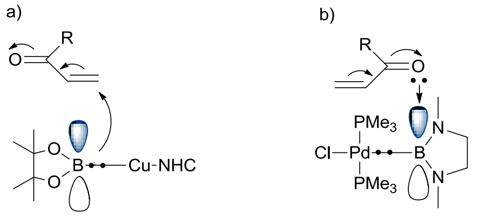
El primer capítol es un compendi dels estudis previs a aquesta tesi, descrivint els compostos de bor trivalent sintetitzats segons la seva nucleofilia o electrofilia. L'exemple més clar d'electrofilia el trobem en els inicis de la química del bor quan Brown i col·laboradors van publicar la primera hidroboració.[1] L'obtenció d'un producte anti-Markovnikov en aquesta reacció requereix de l'apropament d'un hidrur formal a l'àtom de carboni més substituït del substrat orgànic, donant així proves conclusives de la polarització $B^{\delta+}$-$H^{\delta-}$ de l'enllaç bor-hidrogen. Un dels exemples més importants en el cas dels borils nucleòfils, és el primer compost de boril-liti amb substituents diamino aïllat per Segawa, Yamashita i Nozaki.[2] Aquests compostos reaccionen amb una gran varietat d'electròfils i en general la seva reactivitat es semblant als carbanions.

Com ja hem dit, la majoria de reactius de bor són electròfils, això es degut a que hi ha una vacant de dos electrons per emplenar l'orbital p del bor. En el segon capítol amb l'ajuda de eines computacionals, hem analitzat sistemàticament les propietats electròniques i estructurals de diferents fragments de bor que estan enllaçats a metalls del grup principal o coordinats a metalls de transició/metalls de les terres rares.

Quan els fragments de bor es troben enllaçats a metalls del grup principal podem observar que la relació p/s (entre les contribucions dels orbitals p i s del bor) en l'enllaç sigma B-M pot ser un indicador de la nucleofilia del sintó boril. És a dir, com més caràcter p tingui l'enllaç, més reactiu podrà ser el boril com a nucleòfil. Des de la perspectiva dels orbitals moleculars frontera, s'espera que l'energia de l'orbital híbrid sp augmenti amb el caràcter p perquè els orbitals p són més alts en energia que els orbitals s. Com a conseqüència, com més alta l'energia del orbital sp, més gran serà el grau de caràcter nucleofílic esperat.

Si ens movem al bloc de metalls de transició/metalls de les terres rares, el exemple més clar que mostra la diferència de comportament dels compostos de bor es troba en la β-boració catalitzada per coure de compostos α,β-insaturats desenvolupada per Miyaura i Hosomi[3] i la reacció anàloga catalitzada per pal·ladi reportada per Onozawa i Tanaka[4] (Esquema 7.1).

En el primer cas, el sintó boril pot actuar com a nucleòfil i pot atacar al carboni beta del substrat, obtenint la formació del compost β-borat. En canvi, en el segon cas, es va suggerir la inserció del substrat en l'enllaç Pd-B, amb la qual cosa s'obté la regioselectivitat oposada, on el Pd esta enllaçat a l'àtom de carboni beta i la unitat boril esta enllaçada a l'àtom d'oxigen. Un cop analitzades les seves propietats electròniques i estructurals, podem veure que la influencia de la relació p/s en els enllaços Mt-B mostra una tendència oposada als metall alcalins. També podem concloure que per tots els compostos analitzats els borils que estan coordinats a Cu, Zn, or Sc mostren la polarització més alta de l'enllaç Mt-B cap a la unitat boril.



El parell enllaçant de Cu-B inicia la reacció

L'orbital p "buit" inicia la reacció

Esquema 7.1 Reactivitat dels compostos carbonil α,β-insaturats amb a) un complex de coure modificat amb N-heterociclic carbens i b) un complex de pal·ladi modificat amb fosfines.

L'últim grup de compostos de bor estudiats són aquells on el bor trivalent, que és sp^2, es troba enllaçat a un altre B que té una hibridació sp^3. Aquests compostos es formen quan una base de Lewis forma un adducte àcid-base de Lewis amb el diborà present en el medi. Els resultats obtinguts ens mostren que aquesta base de Lewis no només polaritza l'enllaç B-B, sinó que a més a més augmenta la polaritzabilitat del la unitat de B(sp^2) i per tant, la seva tendència a reaccionar amb electròfils tous. Amb tota la informació obtinguda hem construït un mapa de tendències que pot ésser útil per a seleccionar un compost de bor trivalent apropiat, depenent de la reactivitat desitjada (Figura 7.2).

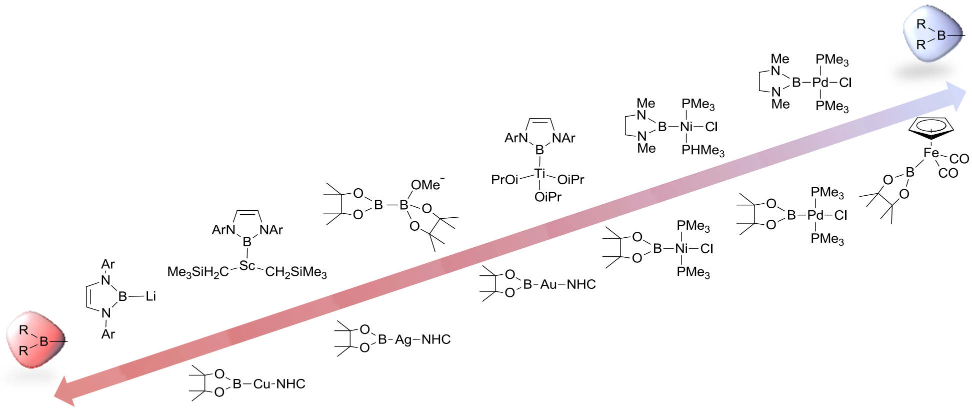
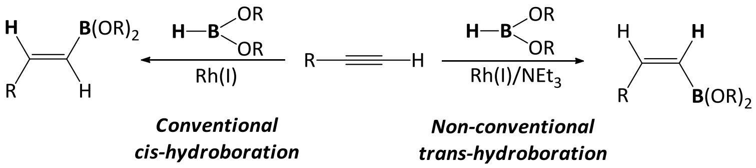


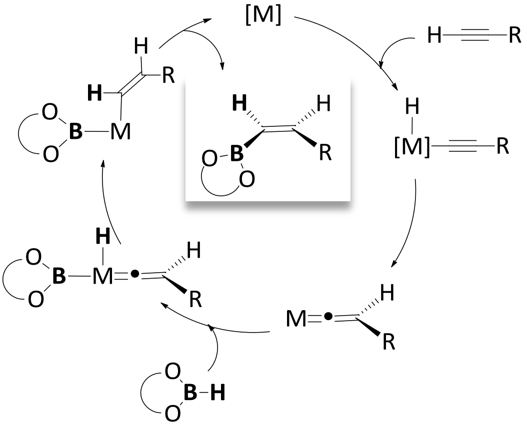
Figura 7.2 Representació esquemàtica de diferents compostos estudiats, essent roig més nucleòfils i blau més electròfils.

Per tal d'estudiar en un cas concret una reacció on el bor es comporta com a electròfil, en el capítol 3 s'estudia la reacció de hidroboració *trans* no convencional. La hidroboració d'alquins és un mètode útil per a la síntesi de èsters alquenilborònics, els quals són intermedis versàtils en síntesi orgànica ja que l'enllaç C-B pot ser transformat fàcilment en enllaços C-O, C-N i C-C. Els mètodes catalítics per obtenir aquests compostos estan basats principalment amb reaccions catalitzades per metalls de transició on es produeix una addició en *syn* de l'agent de hidroboració H-B(OR)$_2$ sobre el triple enllaç. Recentment, Miyaura i col·laboradors han descrit la hidroboració *trans* (no convencional) catalitzada per rodi i base on s'obtenen (*Z*)-1-alquenilborònic èsters, a diferència de la hidroboració convencional *cis* que genera (*E*)-1-alquenilborònic èsters (Esquema 7.2).[5]



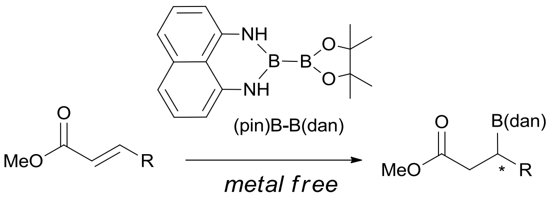
Esquema 7.2. Reacció de hidroboració convencional i no convencional.

Els nostres estudis experimentals realitzats ens mostren que aquesta reacció esta afavorida per la presencia d'un excés de lligand i d'agent hidroborà i que els alquins rics en electrons i amb impediment estèric afavoreixen la formació dels isòmers desitjats. Pel que fa a l'estudi teòric, hem caracteritzat un mecanisme de reacció plausible que es pot dividir en quatre etapes: 1) addició oxidant de l'alquí al metall i isomerització per formar el complex vinilidè, 2) addició oxidant del reactiu de bor, 3) inserció del vinilidè al l'enllaç Rh-H i finalment 4) eliminació reductora de l'enllaç C-B per a donar l'alquenilborònic èster (Esquema 7.3). A més a més els càlculs ens revelen que l'etapa determinant de la selectivitat és la inserció del vinilidè al l'enllaç Rh-H i que quan hi afegim lligands i substrats reals al model, som capaços de reproduir els resultats experimentals obtinguts.



Esquema 7.3 Cicle catalític proposat per la reacció de hidroboració no convencional.

Finalment, ens hem centrat en una reacció que recentment s'ha descobert en el nostre grup, on el boril pot actua com a nucleòfil. Aquesta reacció es la β-boració organocatalítica amb B_2pin_2.[6] Aquest diborà en presencia de metoxi forma un adducte on el boril el qual no està unit el metoxi guanya caràcter nucleofilic. Per anar un pas més enllà, ens vam interessar en l'activació d'un diborà mixt, el Bpin-Bdan, sintetitzat per Suginome i col·laboradors,[7] ja que volíem explorar quina de les dues unitats boril seria la que augmentaria la nucleofilia en interacció amb un grup metoxi. Amb l'assistència d'estudis computacionals i espectroscòpics, hem estat capaços de postular la formació exclusiva de l'adducte àcid-base de Lewis [MeO^-→Bpin-Bdan]. I també aconseguir la formació exclusiva del compost carbonil C_β-Bdan quan hem estudiat experimentalment aquesta reacció (Esquema 7.4). La presència de fosfines quirals en la reacció ens ha permès obtenir inducció asimètrica d'una manera més eficient que l'anàloga borilació amb B_2pin_2. Aquesta síntesi obre una nova metodologia per preparar selectivament compostos carbonil C_β-Bdan.



Esquema 7.4 β-boració organocatalítica de substrats α,β-insaturats.

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Chapter 8

List of publications, contributions to conferences and research stays

.

List of publications

J. Cid, J. J. Carbó and E. Fernández. "Catalytic non-conventional trans-hydroboration: a theoretical and experimental perspective" *Chem. Eur J.* **2012**, *18*, 1512.

J. Cid, H. Gulyás, J. J. Carbó and E. Fernández. "Trivalent boron nucleophile as a new tool in organic synthesis: reactivity and asymmetric induction" *Chem. Soc. Rev.* **2012**, *41*, 3558.

H. Gulyás, A. Bonet, C. Pubill-Ulldemolins, C. Solé, J. Cid and E. Fernández. "Nucleophilic boron strikes back" *Pure Appl. Chem.* **2012**, *84*, 2219.

J. Cid, J. J. Carbó and E. Fernández. "Disclosing the structure-activity correlation in trivalent boron compounds: a tendency map" *Chem. Eur. J.* **2012**, *18*, 12794.

J. Cid, J. J. Carbó and E. Fernández. "A clear-cut example of selective Bpin-Bdan activation and precise Bdan transfer on boron conjugate addition" **2013**, *submitted*.

A. D. J. Calow, J. Cid, E. Fernández, J. J. Carbó, A. Whiting. "Making α,β-unsaturated imines through simple condensation. An investigation using in situ IR spectroscopy and DFT" *in preparation*.

Non indexed journals, divulgation

A. Bonet, M. Soriano, C. Pubill-Ulldemolins, C. Solé, J. Cid, H. Gulyás and E. Fernández "L'edat del bor: Reacció de β-boració catalítica" *Revista de la Societat Catalana de Química* **2011**, *10*, 11.

Posters and presentations

Euroboron 5, Edinburgh, United Kingdom, September 2010 - Poster and flash presentation.

XXVIII Meeting of GEQO Punta Umbría, Huelva, Spain, September 2010 - Poster contribution.

XXXIII Biennial Meeting of Real Sociedad Española de Química, Valencia, Spain, July 2011 - Poster and flash presentation.

IME Boron XIV Conference, Niagara Falls, Canada, September 2011 - Poster and flash presentation.

7th Meeting of Young Researchers of the Catalan Countries, Mallorca, Spain, February 2012 - Oral presentation

18th International Symposium on Homogeneous catalysis International, Toulouse, France, July 2012 - Poster presentation.

96th Canadian Chemistry Conference and Exhibition, Québec, May 2013 - Poster Presentation.

Euroboron 6, Radziejowice, Poland, September 2013 - Poster and flash Presentation.

Research abroad

Project: Vinyl boronate synthesis using catechol based borenium cations.
Center: University of Manchester, United Kingdom.
Supervisor: Dr. Michael J. Ingleson
Period: April-June 2012