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Memòria presentada per

Jesús Ramírez Artero

Tarragona, Desembre de 2007

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La doctora MARÍA ELENA FERNÁNDEZ GUTIERREZ, del departament de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili, i el doctor CARLES BO I JANÉ, de l'Institut Català d'Investigació Química

FAN CONSTAR:

Que la memòria titulada "CATALYTIC DIBORATION REACTION TOWARDS THE ORGANIC FUNCTIONALIZATION", que presenta en Jesús Ramírez Artero per tal d'obtenir el grau de Doctor en Química, ha estat realitzada sota la seva direcció en el Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili.

Tarragona, Desembre de 2007

Dra. María Elena Fernández Dr. Carles Bo

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Agraïments

En primer lloc voldria agrair a l'Elena tota la confiança que ha dipositat en mi des del primer dia, sense conèixer-me. Gràcies per donar-me l'oportunitat de realitzar aquesta tesi, per obrir-me tantes portes, pel teu recolzament i dedicació, per tot el que m'has ensenyat i per la familiaritat amb la que sempre m'has tractat. Espero no haver-te defraudat.

En segon lloc, voldria agrair al Dr. Carles Bo la seva dedicació en introduir-me a la química teòrica i computacional, sabent que estava bastant verd en el tema. Gràcies per la confiança dipositada en el meu treball, per totes les lliçons particulars de química quàntica i per solucionar tots els típics problemes de principiant que han anat sorgint.

M'agradaria també donar les gràcies a la Prof. Carmen Claver per la oportunitat que em va donar per a incorporar-me al seu grup i l'amabilitat amb la que em va presentar totes les línies d'investigació i investigadors d'aquest. Sense la seva ajuda encara estaría coent perovskites a Barcelona. I també, com no, per tots aquests sopars a casa seva, i per ajudar-me en tot moment en què ho he necessitat.

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Aitor i Eduardo, dos companys i amics amb els que he compartit bromes y riallades. A Ali i Cyril, dos grans doctors que sempre han estat disposats a discutir de química o de futbol. A Vanesa, la meva companya d'equip, per tots els problemes químics que junts hem intentat resoldre. I a Isabel i Olga, les heterogènies. A tots, per totes les bones estones que hem passat junts, tots els sopars i els congressos. Os trobaré a faltar.

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La ciència ens ha fet déus
abans que mereixèssim ser homes

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Chapter 1

Introduction

***Chapter 1*. Introduction**

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Chapter 1

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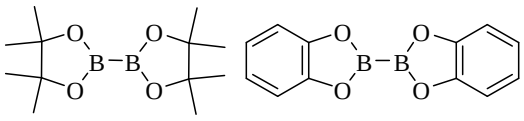
1.1. General overview

Organoboron compounds are some of the most useful reagents in organic synthesis. The carbon-boron bond, once formed, can be cleaved in a variety of ways, with or without homologation, leading to a wide range of useful functional groups.[1] The traditional methods for their synthesis are the alkylation of trialkylborates or haloborons with organomagnesium or organolythium reagents (transmetallation) [1d,1g,2] or the addition of hydroborons to unsaturated hydrocarbons (hydroboration).[1a]

The diboron tetrahalides B_2X_4 (X= F, Cl, Br) can be added across C=C and C≡C in the absence of catalysts.[3] However, the diboron tetrahalides are rather difficult to prepare and handle and are unstable to disproportionation. In contrast, the tetraalkoxydiboron compounds, such as bis(pinacolato)diboron (B_2pin_2 - **1**) and bis(catecholato)diboron (B_2cat_2 - **2**) (Figure 1),[4] are relatively easy to prepare from $B_2(NMe_2)_4$ and are quite stable. However, they fail to add to alkenes or alkynes under conventional reaction conditions,[5] because of the high B-B bond energy (104 kcal.mol^{-1}).



B_2pin_2 (**1**) B_2cat_2 (**2**)

Figure 1. Bis(pinacolato) diboron (1) and bis(catecholato) diboron (2)

The advantage of this sort of reagents is that they are oxidatively added to a low-valent transition metal to favour the B-B bond cleavage, thus allowing the catalyzed transfer of the diboron reagent to unsaturated organic substrates[6] because of the kinetic lability of the resulting bis(boryl) complexes.[7] When these two factors are combined the use of transition metal complexes guarantees first the activation of tetraalkoxy- and tetraaryloxydiborons by oxidative

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addition, and second the B-C reductive elimination to afford organo-1,2-diboron compounds.[8]

The use of suitable transition-metal complexes has other advantages over non-catalyzed boron-boron addition: for example, the ability to orientate the new C-B bonds chemo- and regioselectively. Finally, the possibility of modifying the catalyst precursor with chiral ligands provide a new route towards the formation of new C-B bonds in a stereoselective manner, using optically active material limited to the relatively small amount of catalyst required.

The decisive role of the boryl-metal complexes is that they are part of a catalytic cycle in which several consecutive steps transform unsaturated molecules into organomono- and organodiboron compounds. However, the appropriate selection of the metal and ligands guarantees the success of the overall transformation, especially in those cases in which side reactions and metal or borane decomposition can occur. Theoretical studies in this field have also made a cosiderable contribution to the understanding of bonding in boryl-metal complexes[9] and helped to clarify the mechanisms involved in transition-metal-catalyzed boron-element additions.[10]

The advantages of metal-promoted 1,2-diboration over the uncatalyzed reaction[3] has meant that researchers have been searching for a suitable catalytic system ever since Miyaura et al.'s first report.[11] Some studies have focused on metal-phosphine complexes, while others have focused on base-free metal complexes.[12]

1.2. Catalyzed diboration of alkynes

Miyaura and Suzuki explored the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors. In their first report,[11] they showed that [$Pt(PPh_3)_4$] catalyzed the clean addition of **1** to both terminal and

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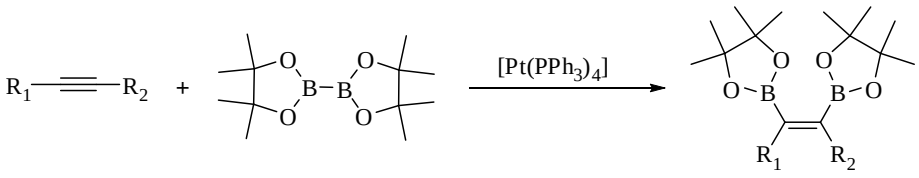
internal alkynes, over a period of 24h hours in DMF at 80ºC, resulting in the formation of *cis*-alkene bis-boronate esters (Scheme 1). The products obtained in this reaction were transformed through a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. Miyaura also reported spectroscopic evidences for the formation of the *cis*-bis(boryl) complex *cis*-[$Pt(PPh_3)_2(Bpin)_2$], which was isolated and structurally caracterized by single-crystal X-ray diffraction.[13] This single crystal consisted of a distorted square-planar coordination geometry for the Pt atom. In the study of the catalytic reaction, several solvents, catalyst precursors and substrates were tested. It is interesting to note that all attempts at the diboration of alkenes with platinum complexes were unsuccessfull. They also found that [$Rh(PPh_3)_3Cl$] in DMF at 80ºC was ineffective at adding of **1** to alkynes such as oct-1-yne, with only 1% of the desired product being formed within 24h. Other ineffective catalysts under these conditions were [$Pd(PPh_3)_4$] (8% yield), [$Pd(OAc)_2$]/15 eq. ^tBuNC (1% yield), [$Ni(PPh_3)_4$], [$Pt(PPh_3)_2(Cl)_2$], [$Co(PPh_3)_3Cl$] and [CuCN] (no yield). Other diboron compounds were tested in the diboration of alkynes. $B_2(OMe)_4$ was shown to add to oct-1-yne (89% yield), yet the very hindered $B_2(NMe_2)_4$ gave only a yield of about 7% diboron product even at 120ºC.



Scheme 1. Catalyzed diboration of alkynes

Another Pt(0) catalytic precursor, [$Pt(PPh_3)_2(\eta\text{-}C_2H_4)$], was developed simultaneously by Smith et al.[14] and Marder et al.[15] They both managed to structurally caracterize the intermediate *cis*-[$Pt(PPh_3)_2(Bcat)_2$], and Marder obtained the single-crystal structures of related bis(boryl) complexes containing 4-^{t}Bu-catecholate groups and those containing chelating bidentate phosphine

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ligands dppe (1,2-bis(diphenylphosphino)ethane) and dppb (1,4-bis(diphenylphosphino)butane).

Smith et al.[14] showed that *cis*-[Pt(PPh_3)$_2$(Bcat)$_2$] reacts stoichiometrically with oct-1-yne in the presence of 1.5 eq. of **2** to give the corresponding diboron product. They also found that the metallacyclopentane complex [Pt(PPh_3)$_2$((CH_2)$_4$)] reacted with **2**, presumably by a metathetical pathway, giving catB(CH_2)$_4$Bcat. Finally, they found that tris(norbornene)platinum reacted with **2** to give the alkene diboration product bis(boryl)bicyclo[2.2.1]heptane as the major diboron derivative. This was the first example of alkene diboration reaction assisted by a platinum(0) system.

Marder et al.[15] found that the bis(phosphine) complexes [Pt(PPh_3)$_2$(η^2-C_2H_4)], *cis*-[Pt(PPh_3)$_2$(Bcat)$_2$] and *cis*-[Pt(PPh_3)$_2$(B-4-^{t}Bu-cat)$_2$] are more active catalyst precursors than [Pt(PPh_3)$_4$] and require shorter reaction times because, as was observed in the single-crystal structure, there are only two phosphines on the platinum centre. He also found that complexes containing a chelating phosphine ligand exhibited extremely low activity or none at all, and that the addition of PPh_3 to bis(phosphine)platinum systems considerably decreased their activity. All this indicated that the active catalyst could contain only one single bound phosphine ligand. So, the basic mechanism of the platinum-catalyzed alkyne diboration reaction was suggested (see Scheme 2). Toluene was an excellent solvent for these catalysts, so there was no need to use DMF.

Marder et al.[15] reported that a donor group in the *para* position of the phenyl ring in either mono- or diphenylacetylenes enhanced the reaction rate, whereas acceptors reduced it. Meanwhile, Smith stated the opposite.[14] In addition, Marder found that **2** reacted faster than **1**, probably because the platinum bis(boryl) complex was less stable with Bpin groups than with Bcat groups. The use of buta-1,3-diyne as substrate shows the difference in the reactivity of the two diboron compounds: using 1 molar equiv. of **1** Marder

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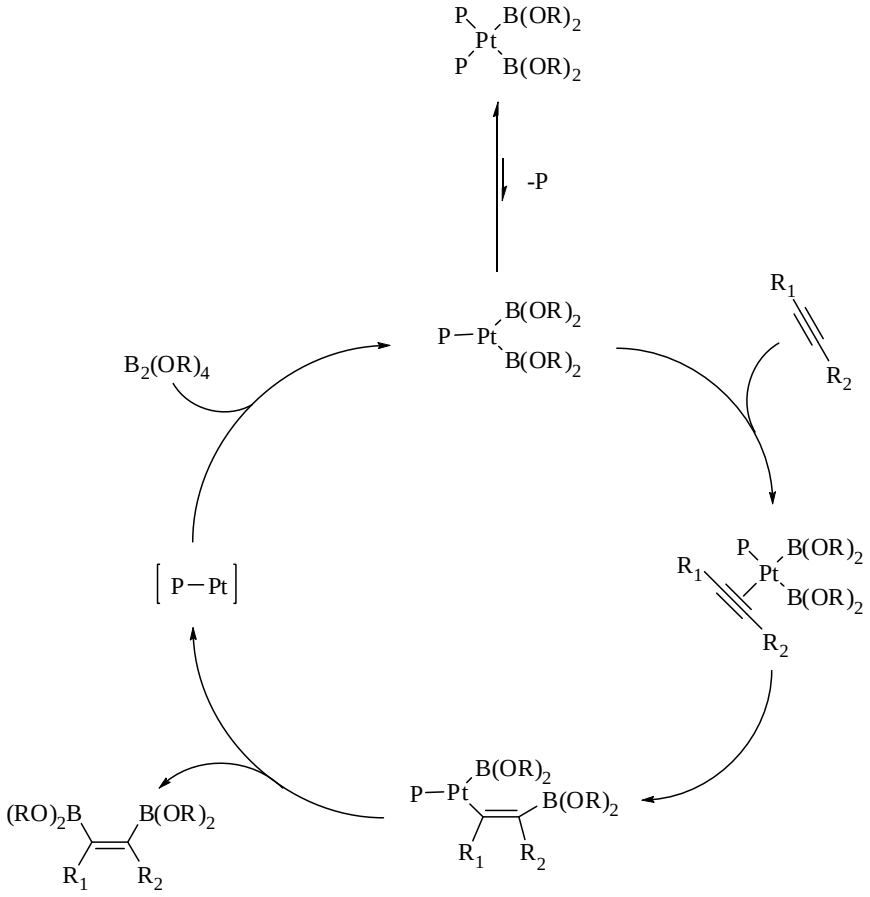
observed clean 1,2-diboration whereas with **2** he observed mixtures of unreacted, 1,2-diboron and 1,2,3,4-tetraboron products which indicated that the second diboration reaction proceeded at a rate similar to that of the first. The 1,2,3,4-tetraborated products were obtained using two equiv. of **1** (with extended reaction times) or **2** (Scheme 3).



Scheme 2. Suggested mechanism for the platinum-catalyzed alkyne diboration reaction

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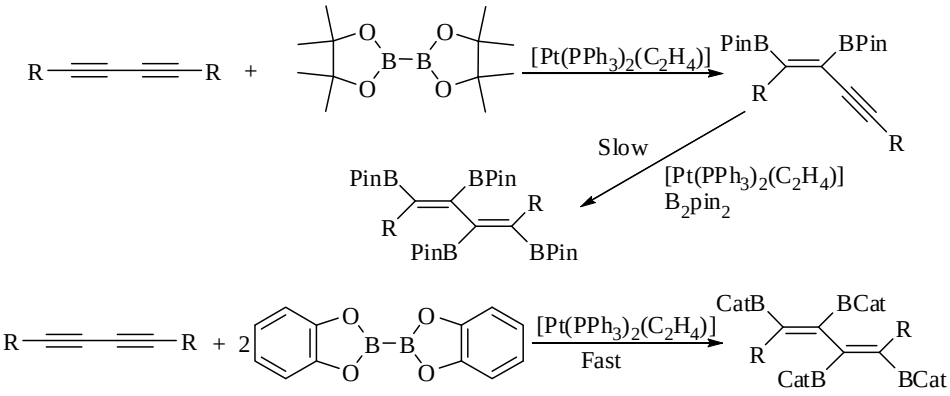
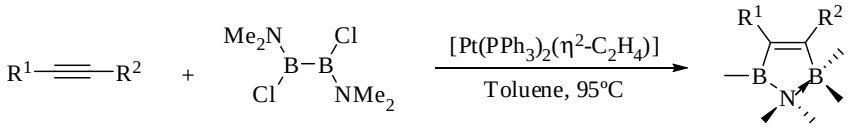


Scheme 3. Diboration reaction of alkadiynes

X-ray diffraction studies of the diboron products[15] confirmed that the addition of the two borons occurred on the same face of the C≡C bond. In the resulting alkene-1,2-bis(boronate) product, the borons were in *cis*-positions.

Norman et al.[16] reported the use of $B_2Cl_2(NMe_2)_2$ as a diborating reagent in the diboration of alkynes catalyzed by $[Pt(PPh_3)_2(\eta^2\text{-}C_2H_4)]$. It afforded high yields of cyclic 1-azonia-2-borata-5-borole compounds, which were the result of the redistribution of B-Cl and B-NMe_2 bonds (Scheme 4).



Scheme 4

Marder et al. found that a highly unsaturated monophosphine platinum(0) complex prepared from equimolar amounts of Pt(norbornene)$_2$ and P(2-MeC_6H_4)Ph_2 or PCy_3 was highly active for carrying out the reaction at room temperature.[17] They also reported that the best Pt:PR_3 ratio is 1:1, and that it is better to use a phosphine free Pt(0) catalytic system than a Pt:PR_3 ratio of 1:2.

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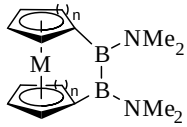
Recently, Braunschweig et al.[18] reported the first example of a heterogenized catalytic diboration of an unsaturated organic substrate, an alkyne. They used finely dispersed palladium or platinum metals, being this last one the most active. They also used a new class of diboron reagents, the [2]borametalloarenophanes (Figure 2).



1: n=1, M=Fe

2: n=2, M=Cr

Figure 2. [2]borametalloarenophanes

1.3. Catalyzed diboration of alkenes

If alkenes are used as substrates in the catalyzed diboration reaction, the problem of the β-hydride elimination from boryl-metal alkyl complexes can arise. When several Rh(I) catalysts where used, with **2** as diboron reagent, and 4-vinylanisole as substrate, Marder et al. observed the formation not only of the desired 1,2-diborated product, but also hydrogenated and hydroborated products.[19] [Rh(DPPB)(η^6-catBcat)] (Figure 3) was the most chemoselective catalytic system used in this previous study, yielding a 44% of the 1,2-diboron product (Scheme 5).

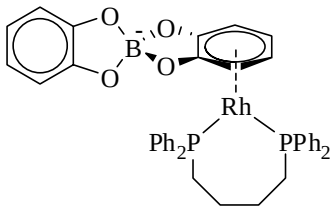


Figure 3. [Rh(DPPB)(η^6-catBcat)]

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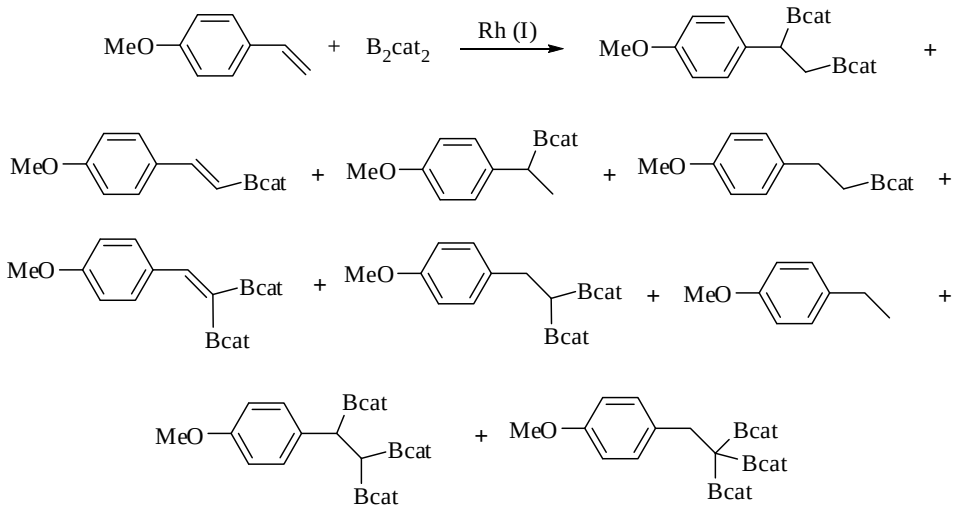

Scheme 5. Different products observed in the Rh(I)-catalyzed diboration of 4-vinylanisole

This problem was solved by using other metals. Metals with lower d-orbital energies (the right part of the periodic table) are likely to inhibit π-backbonding to alkenes and thus destabilize the alkene-hydride metal complex with respect to the alkyl metal complex. It is important to consider that while less electron rich metal centers should show less β-hydride elimination, the metal center should be electron rich enough to support the oxidative addition of the B-B bond to start the catalytic process. Marder et al. chose a gold(I) catalytic system,[19] because of the lack of known gold-hydride complexes. The system tested, [Au(PEt_3)Cl]+1,2-bis(dicyclohexylphosphino)ethane, led to the exclusive formation of the desired 1,2-bis(boronate) ester, with no presence of the β-hydride elimination products. However, 8 mol% of the catalyst, temperatures about 80ºC for 48 hours and 1.5 equiv. of **2** were required.

A base-free platinum complex, [Pt($dba)_2$], was reported by Miyaura to be a good catalytic system for the clean diboration of terminal alkenes and strained cyclic alkenes with **1**, but the system failed to diborate simple internal alkenes.[20]

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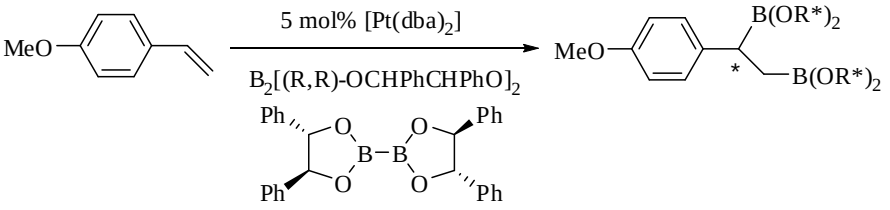
Similarly, Smith reported that [Pt(NBE)$_3$] and [Pt(COD)$_2$] (NBE=norbornene, COD=cycloocta-1,5-diene) catalyze the addition of B_2cat_2 to terminal alkenes and the strained norbornene and norbornadiene.[21] Apparently, this system also suffers from β-hydride elimination problems, but only with unstrained internal alkenes. Baker et al.[22] obtained good yields and chemoselectivities in the diboration of terminal alkenes and alkynes using a Pt(II) commercially available catalytic system, [Pt(COD)Cl_2], also active in the 1,2-diboration of aldimines.

The modification of the ligand in Rh catalyzed diboration[23] to DPPM (DPPM= bis(diphenylphosphino)methane) allowed the isolation of [Rh(DPPM)(η^6-catBcat)], which was characterized by X-ray diffraction and applied in the diboration of vinylarenes, including the internal alkenes *cis*- and *trans*-stylbene and *trans*-β-methylstyrene. It was the most active and chemoselective Rh(I) catalyst system found, yielding in some cases full conversion to the 1,2-diboron product.

The asymmetric catalytic diboration reaction was first carried out using chiral diboranes. Marder et al.[24] studied the addition of enantiomerically pure chiral diboron compounds such as B_2[(R,R)-OCHPhCHPhO]$_2$ to vinylarenes in the presence of [Pt(dba)$_2$]. After 3 days of reaction at 4ºC, about 80% of diboron product was obtained with a diastereomeric excess of 60% (Scheme 6). One of the drawbacks of this first example of asymmetric diboration was that it used stoichiometric amounts of chiral diboron reagent.



Scheme 6

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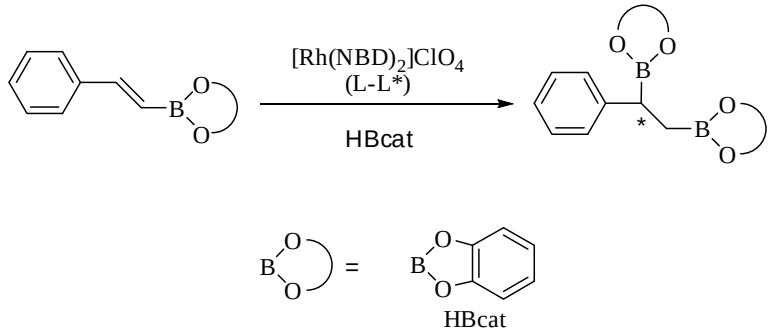
Therefore, another interesting approach at that time was the asymmetric version of the catalyzed regioselective hydroboration of preformed vinylboronate esters (Scheme 7).[25] When the catalytic system involved was $[Rh(NBD)_2]ClO_4$ / (S,S-CHIRAPHOS) (Figure 4), enantiomeric excesses of up to 73% were obtained at -20ºC, although the yield of the corresponding diboron/oxidated product was only about 13%. When the chiral diphosphine ligand (R,R)-DIOP (Figure 4) modified the precursor $[Rh(COD)_2]BF_4$ at -60ºC, the yield of the diol product increased to 87%, although the asymmetric induction was no higher than 11% of enantiomeric excess. Using $[Rh(COD)_2]BF_4$ and (R)-BINAP (Figure 4) at -60ºC, a yield of 49% and an enantiomeric excess of 72% were obtained.



Scheme 7

More recently, a new strategy has been developed to induce asymmetry in diboron products by the asymmetric diboration of alkenes using a chiral phosphine-rhodium complex. Morken et al.[26] transformed *trans*-alkenes into 1,2-bis(catechol)diboron ester intermediates that were eventually oxidized to the corresponding diols with moderate yield and high enantioselectivity (Scheme 8 (a)). The catalytic system used was [(NBD)Rh(acac)] / (S)-QUINAP at room temperature for 24h. However, the catalytic diboration of *cis*-alkenes does not appear to be as general as with the *trans*-substrate geometry. The authors also

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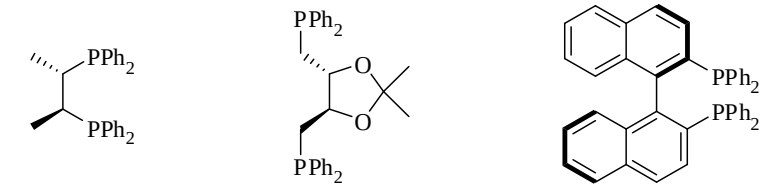
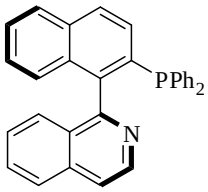
suggested that monosubstituted and 1,1-disubstituted alkenes will probably require new chiral ancillary ligand structures for effective enantiocontrol (Scheme 8 (b)).

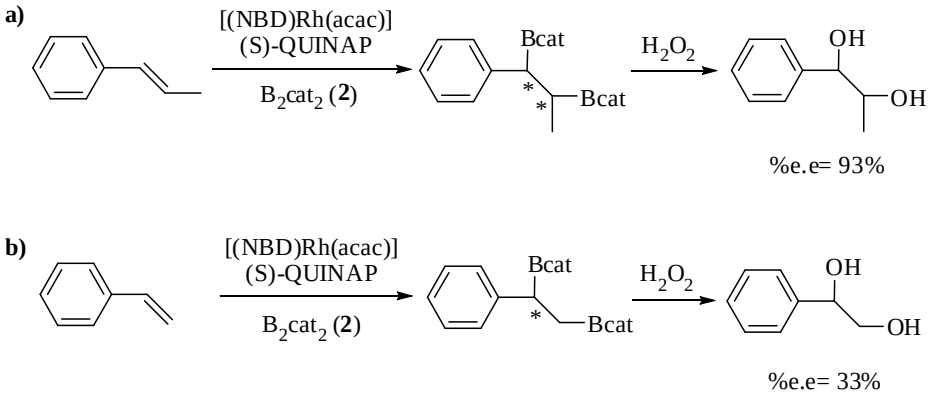


(S,S)-CHIRAPHOS (R,R)-DIOP (R)-BINAP

Figure 4



(S)-QUINAP



Scheme 8

An alternate approach to enantiomerically enriched alkyl 1,2-bis(boronate) ester formation, however, is the catalytic asymmetric

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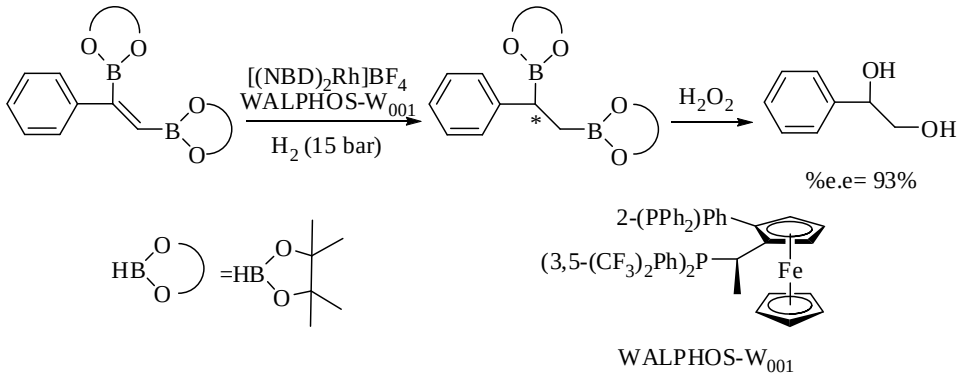
hydrogenation of vinyl 1,2-bis(boronate) esters. Morken et al.[27] developed a single-pot diboration of alkynes with [$Pt(PPh_3)_2$(ethylene)] followed by hydrogenation of the resulting 1,2-bis(boryl)alkenes with the Rh(I)/chiral phosphine complex. The oxidative work-up protocol duly delivers 1,2-diols with high yield and high enantioselectivity (Scheme 9) with the family of WALPHOS ligands as the chiral ligands of choice. However, the high level of asymmetric induction seems to be a matter of combined facts: an excess of ligand with regard to catalyst was required (Rh/ligand=1/2), and toluene seems to be the most convenient solvent.



Scheme 9

To improve stereoselection with monosubstituted alkenes, Morken et al.[28] examined alternate diboron reagents using more hindered substituted bis(catecholato)diboron, (Scheme 10). However, it seems that the substitution was too far from the metal center to have a significant impact on selectivity.

The most widely accepted mechanism for the alkene diboration reaction is thought to occur through a catalytic cycle that involves oxidative addition of the diboron reagent to the metal,[29,14a] insertion of the alkene,[30] and then reductive elimination of the organodiboron product (Scheme 11).[31] Significant reaction side products are often observed, due to β-hydride elimination of the intermediate organometallic complex.

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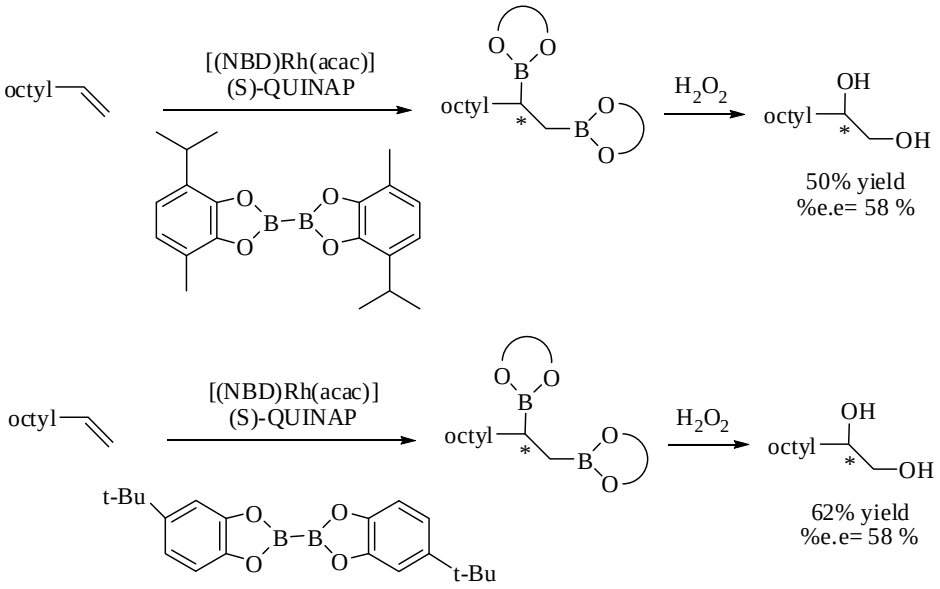
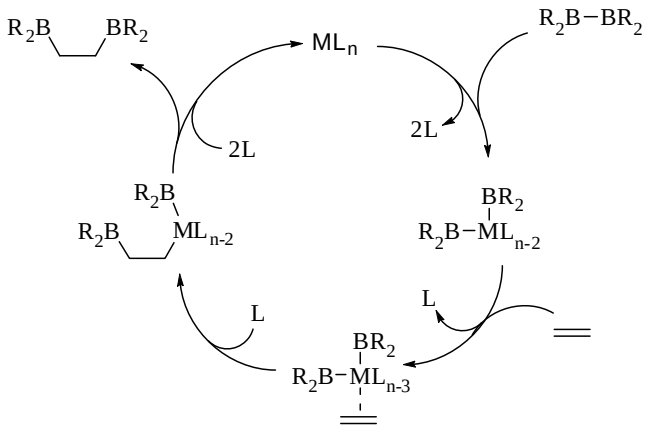


Scheme 10



Scheme 11. Proposed mechanism for the metal-catalyzed alkene diboration reaction

Recently, an interesting new route to obtain chemoselectively 1,2-diboron compounds was developed by our group,[32] using a palladium(II)-NHC complex as catalytic precursor, in the presence of a mild base (NaOAc) and an excess of the diboron reagent. DFT calculations suggested the possibility that the

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mechanism for this chemoselective diboration process involved a heterolytic cleavage of the B-B bond to the metal. The mechanism for this transmetalation process is thought to consist of a sigma interaction of bis(catecholato)diboron (**2**) with the metal complex $[Pd(II)(NHC)Br]^+$, followed by elimination of a B(cat)Br adduct, which would produce a $[Pd(II)(NHC)(Bcat)]^+$ cationic complex intermediate. The subsequent alkene insertion into the Pd-B bond would form the Pd-alkylboronate species. Next, transmetalation between **2** and the Pd-alkylboronate species would generate the diborated product. The base is thought to accelerate the transmetalation rate, as in the related cross-coupling reaction or organoboron compounds.[33]

At this point, it is important to note the significant implication of the various transition metal complexes in the catalytic diboration of alkenes. An interesting application is the Pt(0)-catalyzed diboration of alka-1,3-dienes with bis(pinacolato)diboron (**1**).[34] This process, carried out in toluene at 80ºC, requieres $[Pt(PPh_3)_4]$ as the catalytic system, providing Z-bis(allyl)boronates with up to a 90% yield and more than 99% of Z-stereoselectivity. Using an excess (3 equiv.) of the diene with the phosphine-free catalyst precursor $[Pt(dba)_2]$ in toluene at room temperature provided the diene dimerization product in a 94% yield and with more than 99% E,E-stereoselectivity (Scheme 12). Norman et al.[35] applied the use of chiral diboranes in the Pt(0)-catalyzed 1,4-diboration of 1,3-dienes, with no significant asymmetric induction (up to 20% d.e.).

Another noteworthy application is the platinum-catalyzed 1,4-diboration of α,β-unsaturated ketones. Marder et al.[36] reported that, with $[Pt(PPh_3)_2(\eta^2\text{-}C_2H_4)]$ as the catalytic system in toluene at 80ºC, it was possible to diborate α,β-unsaturated ketones in a 1,4-manner to provide boronated boron enolates with either **1** or **2**. The products from **2** are more susceptible to hydrolysis than those from **1**, so it is only possible to isolate the β-boronated ketone when **2** is

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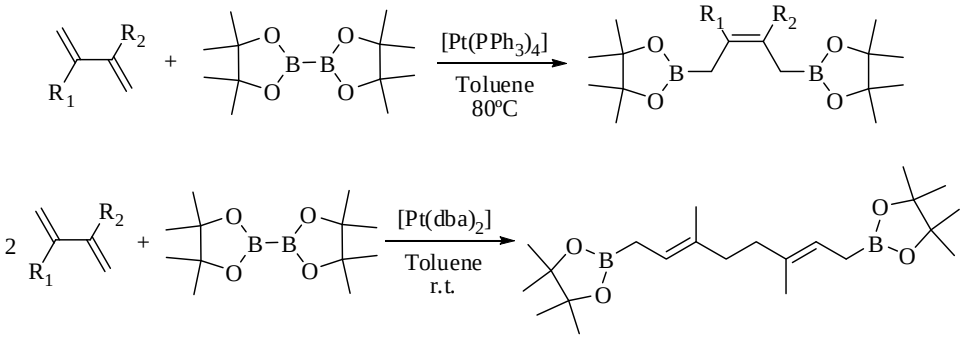
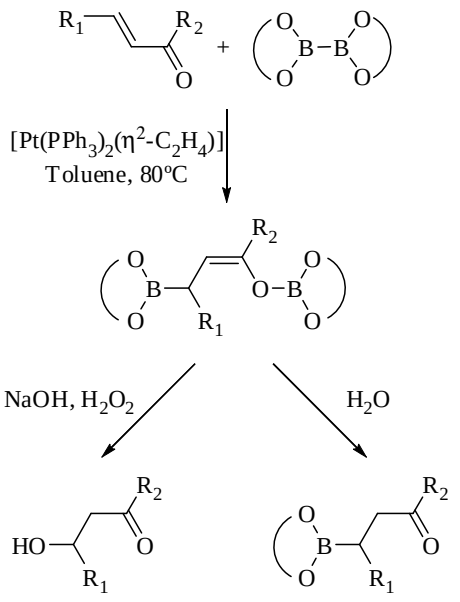
involved (Scheme 13). More recently, Marder et al.[37] found that for the same reaction, with [Pt(BIAN)(DMFU)] (Figure 5) as catalytic system and **1** as diboron reagent, it was possible to obtain not only the 1,4-diboron product, but also the 3,4-diboron product, in ratios that depended on the substrate.



Scheme 12



Scheme 13

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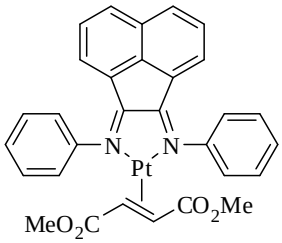
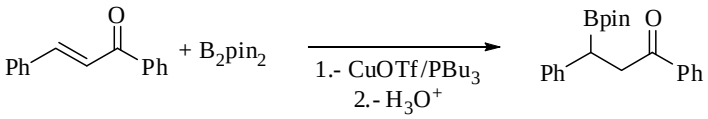
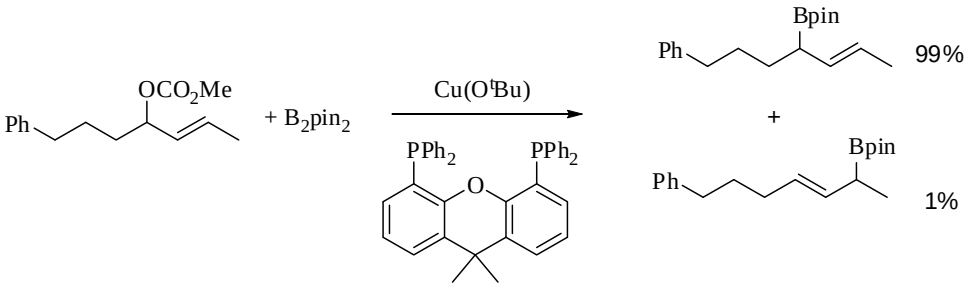


Figure 5.- [Pt(BIAN)(DMFU)]

New reactions have been developed using Cu(I) catalytic systems. Hosomi et al.[38] described the Cu(I) salt catalyzed boration of an α,β-enone using a diboron, with cleavage of the B-B bond (Scheme 14). More recently, Sawamura et al.[39] reported the γ-selective and stereospecific copper-catalyzed substitution of allylic carbonates with a diboron reagent, which is a convenient method for the synthesis of allylboronates (Scheme 15).



Scheme 14



Scheme 15

In 2006, Sadighi et al.[40] described the first example of the 1,2-diboration of carbonyl substrates. A Cu(I)-(NHC) complex (NHC= N-heterocyclic carbene) (Figure 6) is used as the catalytic system for aldehyde diboration, with

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1 as diboron reagent. In this case, no oxidative addition was produced. These complexes are thought to catalyze diboration through a mechanism that involves the insertion of an aldehyde carbonyl group into a metal-boron bond, leading to metal-carbon σ-bond formation. Subsequent reaction with a diboron reagent results in carbon-boron bond formation and catalytic turnover.

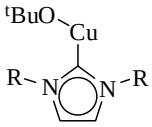
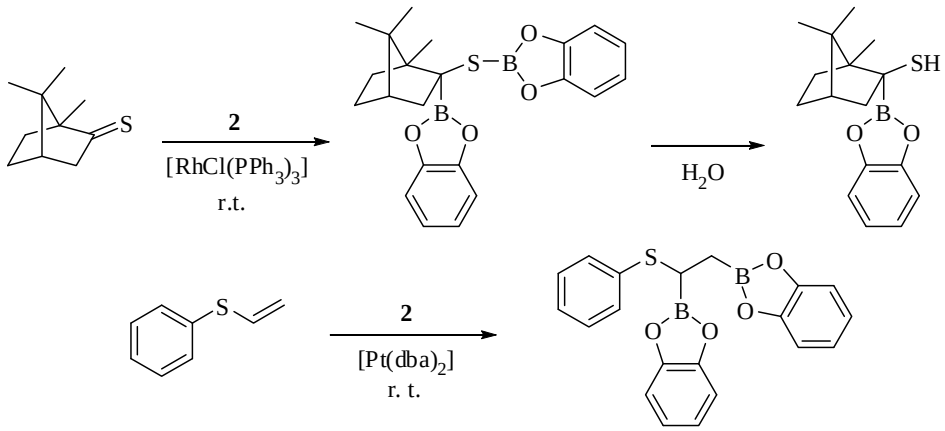


Figure 6

Considerable catalytic diboration of heteroatom-containing substrates was reported by Westcott et al.[41] In this paper, thiocarbonyl compounds were 1,2-diborated with Wilkinson's catalytic system, and vinyl sulfides with the phosphine-free $Pt(dba)_2$ catalytic system (Scheme 16).



Scheme 16

The diboration of allenes has also been reported.[42] Therefore the diboration of allenes yields allylboron compounds that have a boryl group at the vinyl carbon. For terminal allenes, the addition has a strong tendency to occur at the internal double bond. Nevertheless, steric hindrance in both allenes and

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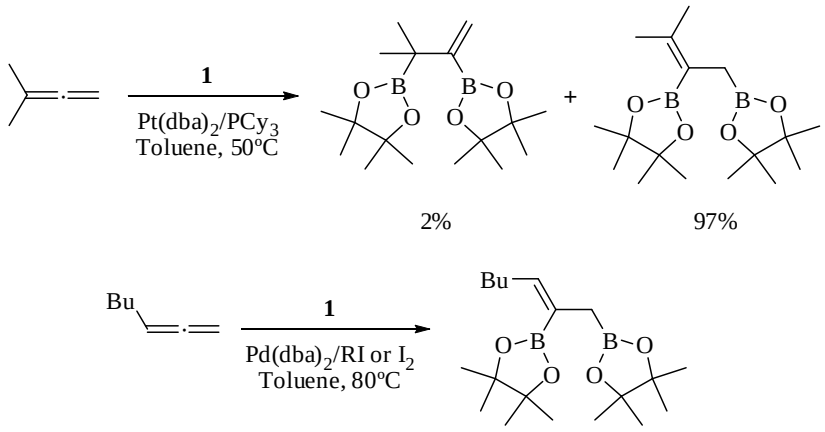
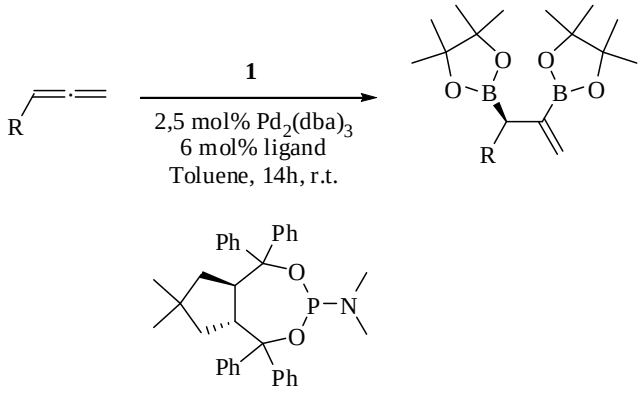
phosphine ligands forces the addition towards the terminal double bond. A highly selective diboration of the terminal double bond can be obtained using a palladium catalytic system in the presence of a cocatalyst such as I_2, iodoalkenes or iodoarenes. The role of the cocatalyst is attributed to the *in situ* formation of an I-Bpin intermediate, which undergoes oxidative addition and insertion, leading to a 2-boryl-π-allylpalladium intermediate (Scheme 17).

More recently, Morken et al.[43] reported the first asymmetric diboration of prochiral allenes using a Pd(0) catalyst modified by a phosphoramidite. Yields were over 70%, and enantiomeric excesses over 85% (Scheme 18).



Scheme 17



Scheme 18

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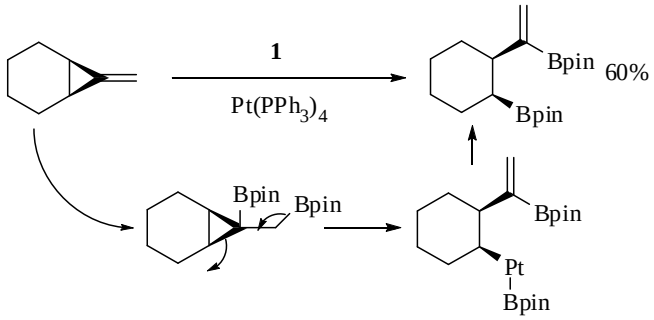
In 2007, Morken et al.[44] improved this system by modifying the ligand, and values of 98% ee were obtained. They studied the mechanism of the catalytic allene diboration, and demonstrated that the reaction proceeds by a mechanism that involves rate-determining oxidative addition of the diboron to Pd(0) followed by transfer of both boron groups to the unsaturated substrate, through the insertion of the more accessible double bond of the allene substrate and then reductive elimination. This insertion reaction is most likely the enantiomer-determining step of the allene diboration process.

Also noteworthy is the catalyzed diboration of methylencyclopropane and its derivatives,[45] which are interesting substrates because their strained structure makes them highly reactive. The platinum-catalyzed diboration of this sort of compounds causes the cyclopropane ring to break. The catalytic cycle involves the regioselective insertion of the methylene-cyclopropane into a Pt-B bond, followed by a rearrangement of the structure to a homoallylplatinum(II) species, which causes the ring opening (Scheme 19).



Scheme 19

Taking advantage of the β-hydride elimination, Marder et al.[46] reported the rhodium-catalyzed dehydrogenative borylation. Therefore, when they used alkenes as the starting material, they prepared vinylboronate esters, which are very useful synthetic intermediates. This new method is important because it

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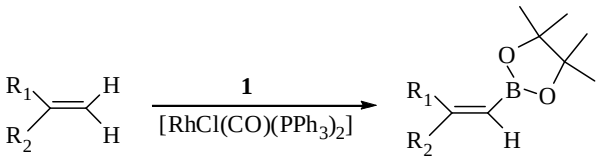
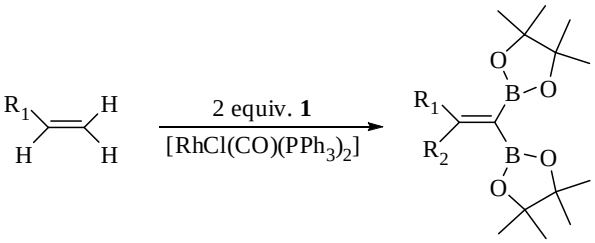
makes it possible to prepare 1,1-disubstituted vinylboronate esters, which cannot be prepared through an alkyne hydroboration. The effective catalyst system for this reaction was found to be [RhCl(CO)(PPh_3)$_2$], and the diboron reagent used was **1** (Scheme 20). Marder also found that by using 2 equiv. of the diboron reagent it was possible to isolate the vinyl(bis)boronate ester with good selectivity (up to 85%) (Scheme 21).



Scheme 20



Scheme 21

1.4. Theoretical studies

Experimental studies on the diboration reaction rapidly attracted the interest of theoretical chemists.[12,47] The addition of B_2H_4 to ethylene[48] and acetylene[49] was examined theoretically as a model for the uncatalyzed addition of B_2X_4 to alkenes, some years before the discovery of the catalyzed version of the diboration with tetraalkoxodiborons. The key findings in the two MNDO-computational studies were that the reactions were exothermic and proceed in two steps via a 3-centred π-complex between the C=C or C≡C bond and the diboron reagent. Thus, the carbon-carbon π-system serves as a donor to one of the two boron centers in the intermediate complex preceding B-B bond rupture.

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The activation energy for the uncatalyzed diboration of ethylene was slightly higher than for acetylene.

The oxidative addition of model compounds B_2H_4 and $B_2(OH)_4$ to $M(PH_3)_2$ (M= Pd, Pt) has been examined by *ab initio* computational techniques.[50] The study by Sakaki et al. suggested that the unoccupied B-B π- and π*-orbitals, in addition to the B-B σ*-orbital, can be involved in the charge transfer interaction with Pt σ- and π-symmetry d-orbitals responsible for B-B oxidative addition.

Morokuma and co-workers examined the mechanism of the catalyzed addition of model diborane $B_2(OH)_4$ to ethylene and acetylene with $[Pt(PH_3)_2]$ by DFT (density functional theory) techniques.[10c] Their work confirmed the importance of phosphine dissociation leading to a mono-phosphine complex before the B-B bond oxidative addition, and also showed that the activation energy for the insertion of ethylene into the Pt-B bond was higher than that for the analogous acetylene insertion reaction, which is consistent with the fact that the phosphine-based platinum systems catalyze the diboration of alkynes but not alkenes.

In another paper, Morokuma et al.[10d] made a theoretical study of the mechanism of the Pd(0)-catalyzed alkyne diboration reaction and compared it with the Pt(0)-catalyzed one. They found that the mechanism involved the same steps: (i) coordination of diborane $R_2B\text{-}BR_2$ to the Pd(0) complex, (ii) oxidative addition of the B-B bond to Pd, (iii) dissociation of one phosphine ligand, (iv) coordination of acetylene, (v) insertion of acetylene into one of the Pd-B bonds, (vi) isomerization of the resulting complex accompanied by recoordination of a phosphine ligand, and (vii) reductive elimination of the alkenyl-diboron products. However, experimentally, Pd(0) cannot catalyze this reaction. The main reason for the difference in the catalytic activities of Pd(0) and Pt(0) is the oxidative addition process of the B-B bond to $M(PH_3)_2$. The process occurs for

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M = Pt with a 14.0 kcal.mol^{-1} activation barrier and is exothermic by 7.2 kcal.mol^{-1}. Although the process for M = Pd has a lower barrier (8.6 kcal.mol^{-1}), it is 8.5 kcal.mol^{-1} endothermic, and the reverse barrier is only 0.1 kcal.mol^{-1}. Because of this low reverse barrier, B-B oxidative addition to $Pd(PH_3)_2$ cannot take place. Recently, Morken et al.[44] have demonstrated that the mechanism of the Pd-catalyzed allene diboration proceeds through an oxidative addition of the diboron to the metal center. The authors proposed that electron-donating ligands, like phosphoramidites, stabilize high oxidation state diboration intermediates, thus making the oxidative addition possible and facilitating Pd catalysis.[51]

1.5. Functionalization of organoboron compounds

Some of the significant advantages of using organoboranes as intermediates for synthetic organic purposes[1] are their stability, relatively low toxicity and easily accessibility. In particular, the catalytic B-B addition across unsaturated C-C bonds can be considered to be a platform for introducing functionality with special emphasis on the selective control of the C-B formation and the retention of configuration in the functionalization process from the organoborane intermediates towards the targeted products.[12] Some of these functionalization protocols have been efficiently carried out by means of oxidation,[52] amination[53] or homologation[54] tandem reactions (Scheme 22).

The access to allene diboration products provides new opportunities for synthesis through tandem reaction sequences such as allylation/functionalization. The products arising from allylboration processes contain versatile alkene functionality that renders by functionalization-oxidation to the homoallylic alcohol as an important building block for organic synthesis, in particular in the asymmetric version for asymmetric purposes. The sequential catalytic enantioselective diboration of prochiral allenes with Pd(0)-

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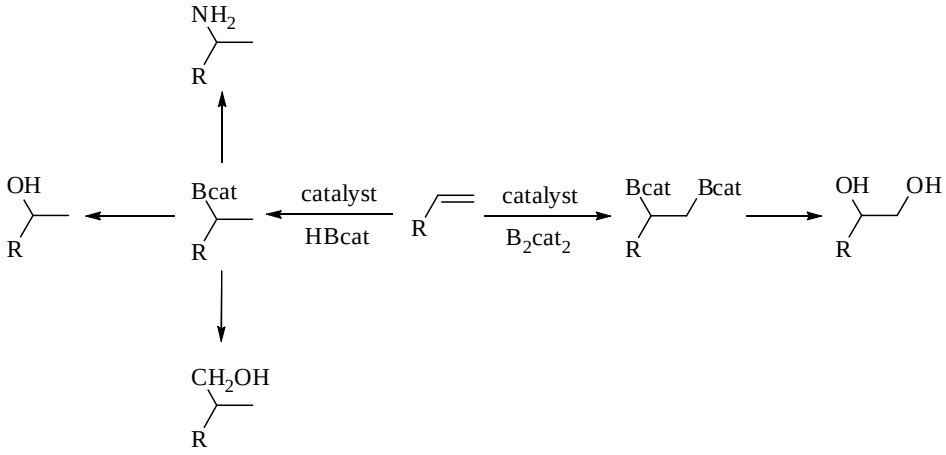
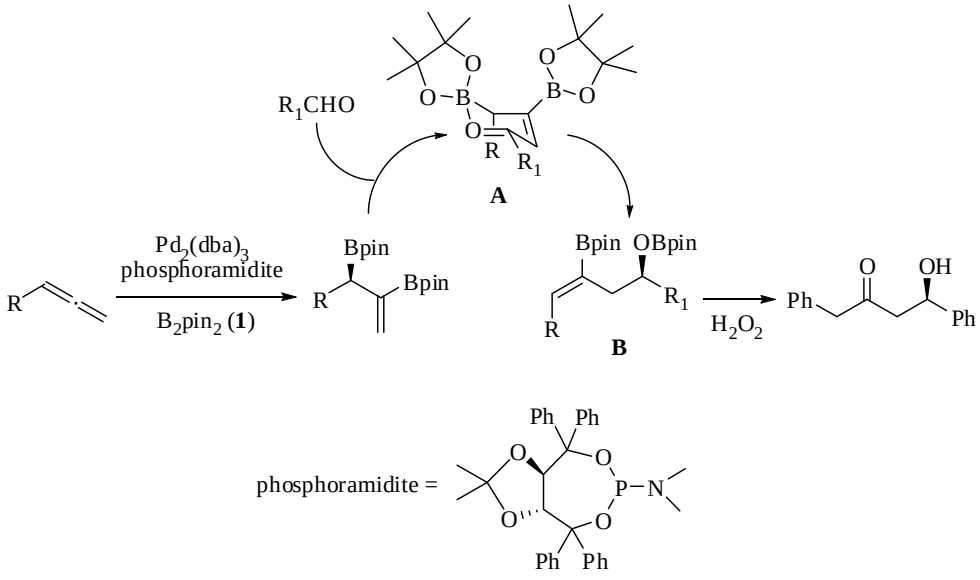
phosphoramidite followed by the addition of benzaldehyde and hydrogen peroxide results in the formation of β-hydroxiketones[43] (Scheme 23).



Scheme 22



Scheme 23

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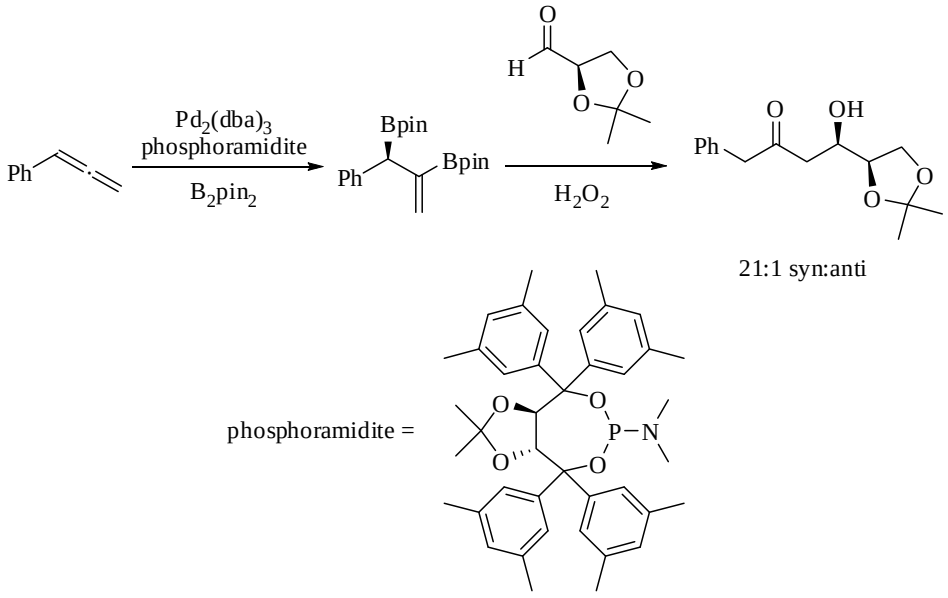
Initial studies suggested that carbonyl allylation reactions proceed through transition structure **A** to give vinylboronate **B** in an enantioenriched fashion, although the level of chirality transfer in the allylation pathway is not perfect (i.e., 88% ee **A** to 82% ee **B**). However, recent advances have demonstrated that the incorporation of TADDOL-derived phosphoramidite ligands, with modifications in the aryl rings, have a significant positive impact on asymmetric induction.[55] The process could be extended to the use of chiral aldehydes, but only high levels of asymmetric induction occur if a stereocenter is placed adjacent to the reacting carbonyl (Scheme 24).



Scheme 24

Further transformations might be achieved by alternate transformations of the vinylboronic ester present in the allylation product, such as functionalization towards vinyl iodide derivatives, coupling reactions and *Z*-olefin formation. In Scheme 25, *path a* shows the formation of *E*-configured vinyl iodide in a 48% yield by filtration of the allylboration reaction mixture through a short plug of

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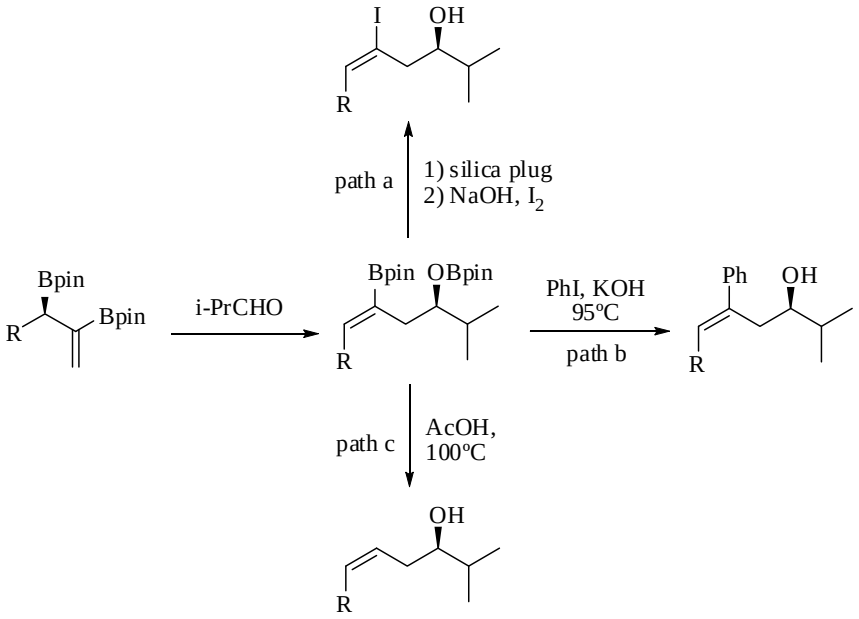
silica followed by treatment with aqueous NaOH and I_2.[55, 56] Alternatively, the Suzuki-Miyaura coupling reaction can also terminate a single-pot cascade reaction sequence by the simple addition of iodobenzene and KOH to the diboration/allylboration mixture to afford the coupling product in a 79% yield after 6h at 95ºC. (Scheme 25, *path b*). The palladium catalyst that affects the allene diboration is also competent for the Suzuki-Miyaura coupling and is not destroyed during the allylation reaction.[55] Finally, simply heating the crude diboration/allylation reaction mixture with acetic acid provided access to the *Z*-olefin in 80% yield (Scheme 25, *path c*).[57] None of the above mentioned functionalized tandem protocols involve erosion of enantiomeric excess from the asymmetric allene diboration/allylboration process.



Scheme 25

Morken et al.[58] have recently developed the tandem allene diboration/imine allylation process, by performing allene diboration followed

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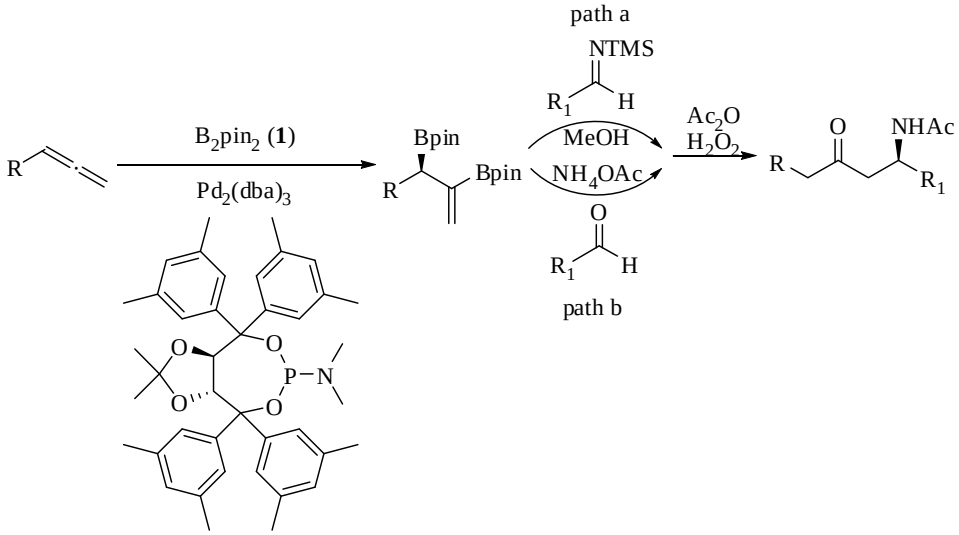
by the addition of silylimine in methanol (Scheme 26, *path a*). Alternatively, upon executing the allene diboration, the authors mixed the reaction mixture with a methanolic solution of an aldehyde and solid amonium acetate (Scheme 26, *path b*). In any case, the β-amidoketone product was isolated after protection with Ac_2O and oxidation with H_2O_2, in good yield and enantioselectivity.



Scheme 26

In addition to preparing the β-amidoketone products, the allylation intermediate could be subjected to non-oxidative conditions. In Scheme 27, *path a* shows how the vinylboronate could be protonated to afford the homoallylic product in good yields. It is notable that only the *Z*-configured allylation adduct was obtained, which was not formed directly by any other methodology. As an alternative transformation, the allylation product could be subjected to Boc protection conditions, and the vinylboronate could be then treated with iodobenzene under Suzuki-Miyaura cross-coupling conditions (Scheme 27, *path b*).

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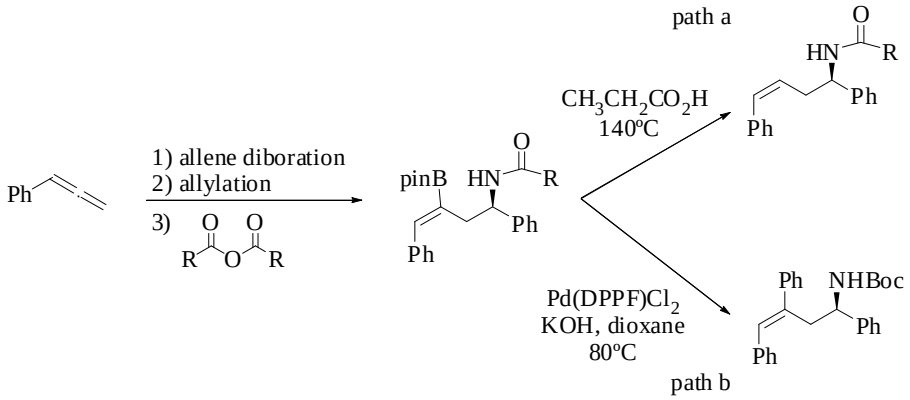

Scheme 27

The same authors have described a single-pot tandem catalytic diene diboration/carbonyl allylation reaction using a comercially available chiral diboron reagent.[59] The main advantage of the method is that the chirality of the intermediate diboronation adduct is transferred to the product in the carbonyl allylation reaction, with total retention of the configuration, thus providing access to enantioenriched quaternary stereocenters (Scheme 28). First, the catalytic diboration of 1,3-dienes generated the allyl(bis)metal species which can engage in a carbonyl addition reaction, which eventually reacts with an electrophile. Yields are high for the three-step procedure regardless of the substrate structure, although the enantiomeric ratio is strongly substrate dependent. Therefore aliphatic aldehydes provide the highest enantioselectivities whereas aromatic and α,β-unsaturated aldehydes provide the lowest.

A new protocol for the sequential allylic transfer reaction of a diene with two aldehydes in the construction of cyclic systems containing four stereogenic centers has recently been achieved in a one-pot operation (Scheme 29).[60] The use of Ni(0) complexes led to the best results in terms of reactivity and stereoselectivity, but also an excess of ligand with respect to the Ni substantially

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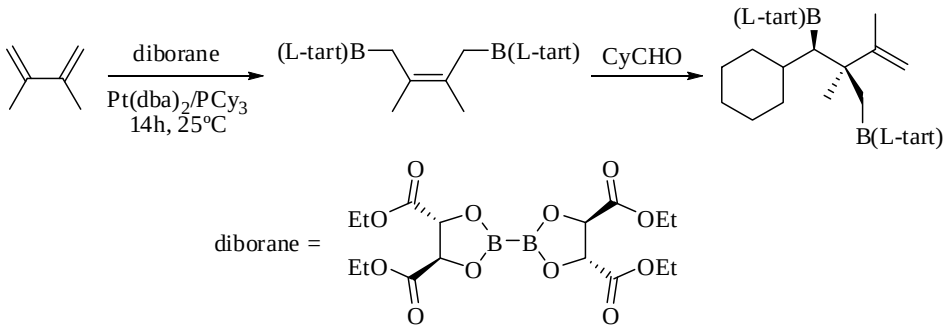
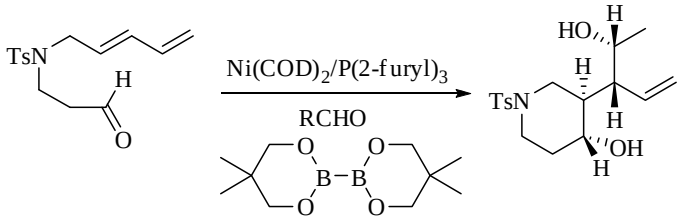
improved the catalytic activity. The stereochemical outcomes of this transformation depend on the reaction conditions.



Scheme 28



Scheme 29

Another interesting application is the transition-metal catalyzed functionalization through C-C bond forming. The palladium-catalyzed cross-coupling reaction has often been succesfully carried out starting from the transmetalation pathway between organoborane derivatives and palladium catalytic systems. Therefore, the carbon-carbon bond forming reactions through the Suzuki-Miyaura protocols have found a wide range of applications in both industrial processes and laboratory transformations,[61] because they have the advantages of being largely unaffected by the presence of water, tolerating a wide range of functional groups and proceeding generally in a regio- and stereoselective way. Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction mixture.

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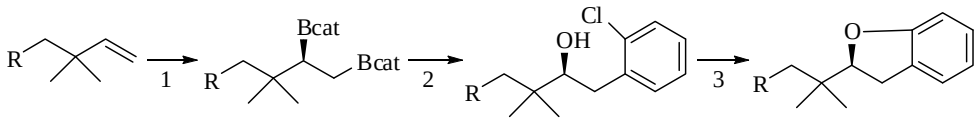
An interesting catalytic carbohydroxylation of alkenes by a tandem diboration/Suzuki-Miyaura cross-coupling/oxidation reaction has been developed in an asymmetric version.[62] Aliphatic alkenes can undergo efficient diboration in a highly selective fashion and provide unsymmetrical 1,2-bis(boronates) which can be subjected to in situ cross-coupling with arylhalides (Scheme 30). In this process, the more accessible C-B bond reacts faster leaving the secondary C-B unreactive towards the C-C bond formation, but available for alternative transformations such as oxidation. Finally, catalytic intramolecular etherification provides the benzofuran derivative, preserving the chiral configuration up to 87% ee.



1.- B_2cat_2, [Rh(nbd)(acac)]/S-QUINAP, THF, rt, 6h.
2.- 1-bromo-2-chlorobenzene, H_2O_2, Pd(dppf)Cl_2, Cs_2O_3, THF, 80ºC 16h.
3.- Pd$(OAc)_2$/P(^{t}Bu)$_2$(2-biphenyl), Cs_2CO_3, THF, 80ºC, 28h.

Scheme 30

Alternatively, chiral allyl vinyl boronates generated by catalytic enantioselective diboration of prochiral allenes can be reacted in situ with a hydroborating reagent to form a novel triboron intermediate which can be used in a cross-coupling reaction (Scheme 31). However, only the primary boronate ester is transformed into the new C-C bond, while the remaining C-B bonds can be oxidyzed in the reaction work up to provide internal chiral diols in a concise single-pot fashion.[63]

A double functionalization of a 1,2-bis(boronate) ester derivative was developed by Suzuki and Miyaura in a tandem alkyne catalytic diboration-cross coupling reaction.[11,13] To this end, terminal and internal alkynes were first

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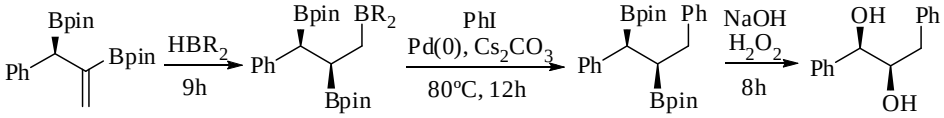
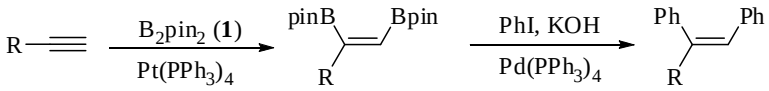
subjected to catalytic diboration with bis(pinacolato)diboron (**1**) in the presence of the catalytic system $Pt(PPh_3)_4$, providing the *cis*-bis(boryl)alkene product in excellent yields. The potential ability of these intermediates for use in the boron cross-coupling reaction was confirmed when they reacted with two equivalents of iodobenzene at 90ºC in dioxane in the presence of $Pd(PPh_3)_4$ and aqueous 3M KOH (Scheme 32). The reaction provided the (*Z*)-1,2-diphenyl-1-alkene as the sole product, the stereochemistry of which was consistent with that of the *cis*-bis(boryl)alkene intermediate. More recently, Miyaura et al. have reported that the *cis*-bis(boryl)alkene derivative obtained from the catalytic diboration of terminal alkynes, regioselectively cross-couples with 1 eq. of aryl, 1-alkenyl, benzyl and allyl halides in the presence of a palladium catalyst and a base to give the corresponding product where only a new C-C bond is formed in the terminal position.[64]



Scheme 31



Scheme 32

Another application related to C-C bond forming from bis(boronate) esters has been developed by Armstrong et al.,[65] who synthesize tetrasubstituted ethylenes in which all four substituents can be modified. This provides an interesting route towards the synthesis of antiestrogenic triphenylethylene derivatives.[66] They based their study on the fact that a *cis*-bis(boryl)alkene derivative can be differentiated to introduce two additional substituents through

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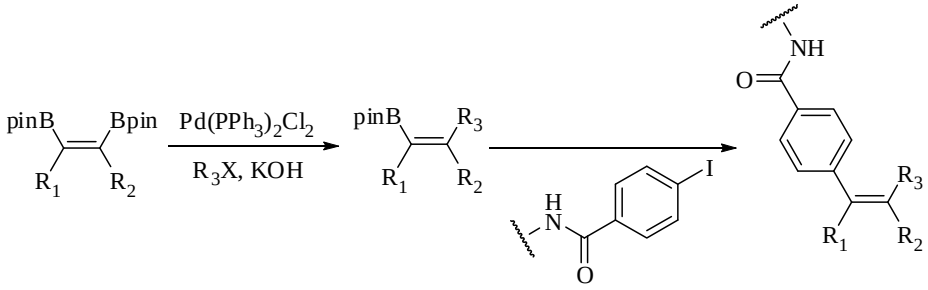
the Suzuki-Miyaura cross-coupling reaction. First, the bis(boronate) ester can be monoalkylated with alkyl or aryl halides, and a second Suzuki reaction with a resin-bound aryl halide can result in the synthesis of substituted ethylenes involving three distinct components in a single-pot transformation (Scheme 33). The study was also extended to symmetrical aryl-aryl and alkyl-alkyl boronates and the methodology efficiently provided sterically hindered tetraphenylethylenes in high yields.



Scheme 33

1.6. Microwave techniques

High-speed reactivity with microwaves has attracted a considerable amount of attention in recent years.[67] The uptake of the technology was initially slow because of its lack of controllability and reproducibility, coupled with a general lack of understanding of the basis of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and improve reproducibility.

Microwave irradiation is an electromagnetic field in the frequency range of 0.3 to 300 GHz. All dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz. The energy of the microwave photon in this

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frequency region (0.0016 eV) is too low to break chemical bonds and is also lower than the energy of Brownian motion. It is therefore clear that microwaves cannot induce chemical reactions.[68]

Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. The heating characteristics of a particular material under microwave irradiation conditions are dependent on its dielectric properties. Alcohols, water, acetonitrile and chloroform all have good heating characteristics. Other common solvents without a permanent dipole moment such as carbon tetrachloride, benzene and dioxane are more or less microwave transparent. This does not preclude a solvent from being used in a microwave-heated reaction. Since the substrates, some of the reagents or the catalyst are likely to be polar, the overall dielectric properties of the reaction medium will in most cases allow sufficient heating by microwaves. Furthermore, polar additives such as ionic liquids can be added to low-absorbing reaction mixtures to increase the absorbance level of the medium. Microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixture. The very efficient internal heat transfer minimizes the wall effects caused by inverted temperature gradients, which may lead to so-called specific microwave effects, for example, in the context of diminished catalyst deactivation.

Today most scientists agree that in the majority of cases rate enhancements are the result of a purely thermal/kinetic effect: that is, they are the consequence of the high reaction temperatures that can rapidly be attained when polar materials are irradiated in a microwave field. Temperatures over the boiling point of the solvents can be reached when the reaction is carried out in a sealed vessel.

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1.7. Scope and objectives

As described above, organoboron derivatives are important synthetic intermediates and biologically active compounds. The catalytic diboration reaction is a very interesting method for synthesizing chemo-, regio- and stereoselectively organodiboron compounds. The significant advantages of using organoboranes as intermediates in organic synthesis are their stability, relatively low toxicity and easily accessibility. One of the important properties of this sort of intermediates is that they retain their configuration in the functionalization process from the organoborane intermediates to the targeted products.

In that context, our first objective involves the search of new catalytic systems which improve the activity, chemoselectivity and enantioselectivity of previously reported catalysts in the catalytic diboration reaction. To this end, we test new metal centres and new ligand families (*Chapter 2*).

We are also interested in making an in-depth study of the mechanism of the catalytic alkene diboration reaction. This study is described in *Chapter 3*. Towards this end we explore NMR techniques in an attempt to characterize the intermediates of the reaction pathway, and DFT calculations to fully characterize the reaction pathway.

Organoborons are important intermediates for synthetic organic purposes. In *Chapter 4* we describe our attempts to find a new route to fluorofunctionalize alkenyl 1,2-bis(boronate) esters through an electrophilic fluorination process.

Finally, *Chapter 5* attempts to develop a new method for the enantioselective α-fluorination of α-nitroesters, as a part of a predoctoral stay in Prof. Togni's group, in the Swiss Federal Institute of Technology.

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Chapter 2

Selective catalytic diboration

Chapter 2. **Selective catalytic diboration**

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2.1. Introduction

The most convenient methodology for organodiboron preparation involves the metal-mediated addition of a diboron reagent to an unsaturated carbon–carbon bond.[1] The catalytic diboration of alkynes provides the syn addition of the B-B bond to afford 1,2-diborylalkene products by a well established protocol based on monophosphane platinum-containing catalysts.[2] However, the related catalytic alkene diboration seems to be more complex, judging from the mixtures of products commonly observed when alkenes and diborons react in the presence of the appropriate transition-metal catalyst. The availability of a very selective catalyst for the exclusive diboration of alkenes, thus avoiding the drawback of low selectivity, is extremely desirable, particularly for the subsequent development of chiral systems to induce enantiomeric excesses. Much work has been done mainly on phosphane-containing Rh(I) and Pt(0) catalyst precursors, but only a few examples of selective conversion into the diborated product have been reported to date. These include the zwitterionic rhodium complex [Rh-(dppm)(η^6-catBcat)] (dppm= $Ph_2P(CH_2)PPh_2$ (1,2-bis(diphenyl-phosphino)ethane), cat=1,2-$O_2C_6H_4$) prepared in situ,[3] and the phosphane-free Pt-catalyst precursors.[4] In addition to rhodium and platinum, diphosphane–Au(I) complexes have been reported to selectively catalyze the addition of diborons to alkenes, although in moderate yields.[5] With the goal of developing both active and selective catalysts for this transformation, we studied the activity, the chemo- and the enantioselectivity of several complexes containing different transition metals, including Rh, Pt, Au, Ag and Cu, and P-N, P-P or N-heterocyclic carbenes (NHC) as ligands.

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2.2. Rhodium-catalyzed alkene diboration

A certain level of enantioenrichment (ee=33%) has been described in the asymmetric diboration of styrene with bis(catecholato)diboron (**2**) by means of the catalytic system [Rh(NBD)acac]/(S)-QUINAP.[6] Moreover, the isolated yield of purified material reported was moderate (68%), and the remaining mass balance was described as unconverted starting material. When we reproduced this reaction under identical conditions, we found that the enantioselectivity was roughly as reported, but that the conversion of the substrate was almost complete and the formation of hydroborated products became significant (Table 1, entry 1). These findings are in agreement with the well-known studies by Marder et al.[1a,5] in which, depending on the rhodium(I) catalytic system used, a range of products from mono-, bis- and tris-boronated derivatives were observed. A plausible explanation, from a mechanistic point of view, suggests that the first step is likely to be an oxidative addition of B-B in the diboron reagent to the metal, leading to a metal-diboryl complex (Scheme 1, path a). The desired 1,2-bis(boronate)ester seems to arise from alkene insertion into an M-B bond (Scheme 1, paths b-b') followed by B-C reductive elimination involving the second boryl ligand. However, the alkenyl and alkylboronate esters were produced by a competitive β-hydride elimination (Scheme 1, paths c-c', d-d'). Even the addition of achiral monophosphine to block any vacant coordination sites around the rhodium, involving an unfavourable β-hydride elimination step, did not improve selectivity (Table 1, entry 2). Interestingly, the asymmetry induced on the formation of **4** is lower as a byproduct in catalytic diboration than as the main product in catalytic hydroboration,[7] probably because a different chiral metal-(β-borylalkyl) species is involved in the catalytic cycle.

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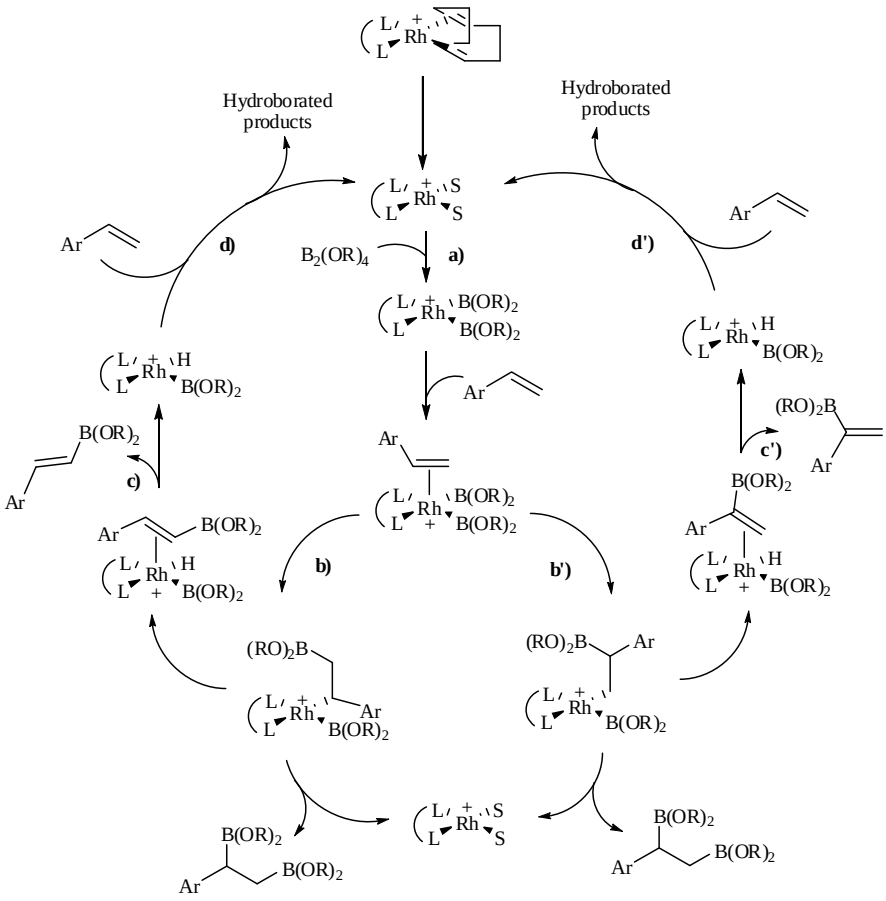

Scheme 1

To analyze to what extent the relative rates of B-C reductive elimination versus β-hydride elimination are sensitive functions of the chiral ligand, new catalytic 1,2-diborations of styrene were performed with [Rh(NBD)(acac)] modified with (R)-BINAP, (S,S)-BDPP (Figure 1) and DPPM. Selectivity on the 1,2-bis(boronate)ester was significantly reduced with the ligand (R)-BINAP, which chelates with rhodium to form a seven-membered ring, one more than with (S)-QUINAP (Table 1, entry 3). The same ligand influence was observed with the use of DPPM (Table 1, entry 5), which forms a four-membered ring,

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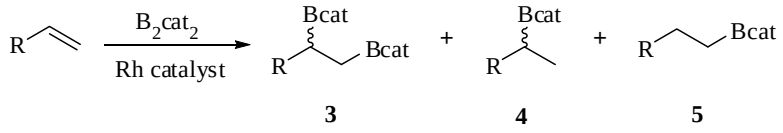
unlike (S,S)-BDPP (Table 1, entry 4), which has the same sort of backbond, but which forms a six-membered ring. We observed a similar trend to that reported by Marder et al. with the bidentate ligand DPPB in the [Rh(L-L)acac]/B_2cat_3-catalyzed diboration of alkenes.[3] However, not only is it the size of the bite angle that seems to influence selectivity: the use of (S,S)-BDPP, which as (S)-QUINAP also forms a six-membered ring with metal, provided poor selectivities towards the 1,2-diboron product.



3 **4** **5**

Table 1. Rh-catalyzed asymmetric 1,2-diboration of styrene with B_2cat_2 (2)[a]

Entry	Catalytic system	Conversion[b] (%)	% **3**[b] (%ee)[c]	% **4**[b] (%ee)[c]	% **5**[b]
1	[Rh(NBD)acac]/(S)-QUINAP	90	76 (35R)	24 (34S)	-
2[d]	[Rh(NBD)acac]/(S)-QUINAP	78	70 (37R)	27 (33S)	3
3	[Rh(NBD)acac]/(R)-BINAP	99	21 (21R)	69 (3S)	10
4	[Rh(NBD)acac]/(S,S)-BDPP	95	17 (16R)	68 (2S)	14
5[e]	[Rh(NBD)acac]/DPPM	90	71	20	9
6	$[Rh(NBD)_2]$/(S)-QUINAP	95	55 (35R)	40 (47S)	5
7	$[Rh(COD)_2]$/(S)-QUINAP	89	66 (36R)	34 (41S)	-
8	$[Rh(\mu\text{-Cl})(NBD)]_2BF_4$/(S)-QUINAP	92	68 (35R)	25 (40S)	7

[a] Standard conditions: substrate/B_2cat_2/Rh complex/ligand = 1/1.1/0.05/0.05; THF; *T*: 25ºC; *t*: 15h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derived alcohols for **4**, and derived acetal for **3**. [d] Addition of 5 mol% of PPh_3. [e] *t*: 3h.

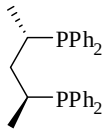


Figure 1. (S,S)-BDPP

Asymmetry induced by both the P,P-bidentate ligands, (R)-BINAP and (S,S)-BDPP, diminishes slightly in the diboron product and significantly in the 1-phenylethylboronate ester byproduct. We should point out that the 1,2-diboron product obtained from both chiral complexes modified with (S)-

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QUINAP and (R)-BINAP mainly provided the same (R)-enantiomer. This contrasts substantially with the trend observed in the hydroboration/oxidation of styrene, when the Rh/(S)-QUINAP catalytic system provided the (S)-1-phenylethanol,[7] while the Rh/(R)-BINAP catalytic system favoured the (R)-enantiomer.[8]

We demonstrated the generality of the asymmetric diboration reaction by carrying out the 1,2-addition of bis(catecholato)diboron (**2**) on styrene, with cationic and neutral precursors of rhodium catalyst modified with (S)-QUINAP (Table 1, entries 6-8). The results were similar to those obtained with [Rh(NBD)acac]/(S)-QUINAP, although the selectivity on the diboron product seemed to be somewhat sensitive to the nature of the precursor.

The electronic factors in the substrate usually alter as much as the steric factors of the catalyst, so we studied how different the aryl substituents would affect chemo- and enantioselectivity (Table 2). The electron-rich and electron deficient vinylarenes, *p*-methoxystyrene and *p*-fluorostyrene, respectively, produced similar but low enantioselectivities (Table 2, entries 2 and 3). The chemoselectivity towards the 1,2-diboron product was the most satisfactory (82%) when the electron-releasing aryl substituent was used on the styrene substrate. During the alkene insertion into the Rh-boryl complex, the chemo- and enantioselection were dependent on alkene electronics, so we reasoned that aliphatic 1-alkenes might exhibit different selectivity patterns from those of aromatic olefins. Table 2, entry 4 shows that vinylcyclohexane was mainly converted into the desired 1,2-bis(boronate)ester with moderate enantiomeric excess (54%). However, the percentage of terminal hydroborated product was twice that of the branched hydroborated product.

Various strategies, mainly related to the nature of the catalyst,[3,5] and less related to the nature of the diboron reagent, have been used to inhibit the competitive β-hydride elimination process. Miyaura and co-workers [4a] reported

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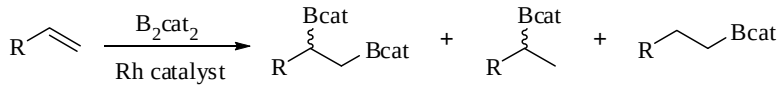
the addition of bis(pinacolato)diboron (**1**) to terminal alkenes using a catalytic amount of $Pt(dba)_2$ at 50ºC, but although the 1,2-diboration addition was cleaner, the base-free Pt-system could not be modified by chiral ligands.



3 **4** **5**

Table 2. Catalytic asymmetric diboration reaction with [Rh(NBD)acac]/(S)-QUINAP[a]

Entry	Substrate	Conversion[b] (%)	% **3**[b] (%ee)[c]	% **4**[b] (%ee)[c]	% **5**[b]
1	Styrene	90	76 (35R)	24 (34S)	-
2	Vinylanisole	77	82 (26R)	11 (-)	7
3	*p*-Fluorostyrene	58	58 (20R)	36 (45S)	6
4	Vinylcyclohexane[d]	100	78 (54R)	7 (ND)	15

[a] Standard conditions: substrate/B_2cat_2/Rh complex/ligand = 1/1.1/0.05/0.05; THF; *T*: 25ºC; *t*: 15h. [b] Conversion and selectivity calculated by ^1H NMR. [c] ee determined by GC with chiral columns, as derived alcohols for **4**, and derived acetal for **3**. [d] Chemoselectivity measured as derived diol and alcohol.

Bearing this in mind, we studied how tetraalkoxodiboranes other than bis(catecholato)diboron (**2**) (Figure 2) influence the 1,2-diboration addition to styrene using the catalytic system [Rh(NBD)(acac)]/(S)-QUINAP. Table 3 shows that chemoselectivity towards the desired 1,2-bis(boronate)ester was low and that enantioselectivity was null when bis(pinacolato)diboron (**1**), bis(neopentylglycolato)diboron (**6**) and bis(hexyleneglycolato)diboron (**7**) were used as diboron reagents (Table 3, entries 1-3). All of these reagents favoured the formation of the branched hydroborated by-product, but asymmetric induction was also null.

In an attempt to increase enantioselectivity during this model reaction, we performed a double asymmetric induction using the chiral catalytic system [Rh(NBD)(acac)]/(S)-QUINAP and chiral diboron reagents. As Table 3 shows, when bis(diethyl-D-tartrateglycolato)diboron (**8**) and bis(diisopropyl-D-tartrate-glycolato)diboron (**9**) were involved in the reaction, enantiomeric excesses were only 17% and 14% respectively (Table 3, entries 4 and 5). Note that in these

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cases the enantioenriched mixture was on the (S)-enantiomer rather than on the favoured (R)-enantiomer formed with bis(catecholato)diboron. The change in the main enantiomer must be due to the chiral diboron reagent, as can be seen by the reactivity when the catalytic system was not modified with the (S)-QUINAP (Table 3, entry 6).

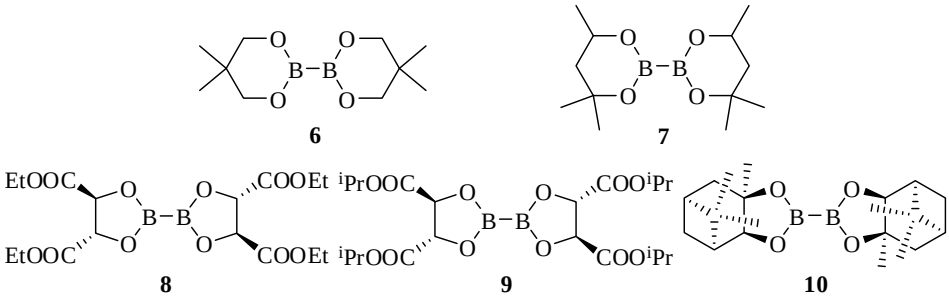

Figure 2

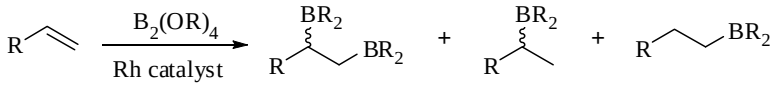

Table 3. Catalytic asymmetric 1,2-diboration reaction of vinylarenes

Entry	Substrate	Diboron	Conversion[c] (%)	% **3**[c] (%ee)[d]	% **4**[c] (%ee)[d]	% **5**[c]
1[a]	Styrene	**1**	100	20 (-)	75 (ND)	5
2[a]	Styrene	**6**	95	39 (-)	61 (-)	-
3[a]	Styrene	**7**	36	22 (-)	78 (5S)	-
4[a]	Styrene	**8**	60	17 (17S)	83 (-)	-
5[a]	Styrene	**9**	100	20 (14S)	80 (-)	-
6[b]	Styrene	**9**	50	12 (23S)	88 (-)	-
7[a]	Vinylanisole	**10**	80	36 (14S)	64 (-)	-
8[b]	Vinylanisole	**10**	100	25 (15S)	75 (ND)	-
9[a]	Vinylcyclohexane	**10**	100	32 (50S)	3 (-)	65

[a]Reaction conditions: substrate/diboron/[Rh(NBD)acac]/(S)-QUINAP = 1/1.1/0.05/0.05; THF; *T*: 25ºC; *t*: 15h. [b] Reaction conditions: substrate/diboron/[Rh(NBD)acac]= 1/1.1/0.05; THF; *T*: 25ºC; *t*: 15h. [c] Conversion and selectivity calculated by ^{1}H NMR as derived alcohols. [d] ee determined by GC with chiral columns, as derived alcohols for **4**, and derived acetal for **3**.

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As far as enantioselectivity is concerned, the chiral diboron reagent bis((+)-pinanediolato)diboron (**10**) behaved like the other chiral diborons on the 1,2-diboration of vinylanisole and vinylcyclohexane (Table 3, entries 7-9). These results are comparable to those of the platinum catalyzed diboration of terminal alkenes with other chiral diborons,[9] although isolated yields of the 1,2-diboron product were higher with platinum as the metal center of the catalytic system than with rhodium.

We felt that it would be interesting to introduce a new class of ligands to electronically enrich the metal center, in order to increase the activity and improve the chemoselectivity. In collaboration with Prof. E. Peris's group from the Jaume I University (Spain), we studied the activity and the chemoselectivity of a Rh(I) complex containing an NHC ligand (NHC = N-heterocyclic carbene), [(mentimid)RhCl(COD)] (Figure 3) in the catalytic 1,2-diboration reaction of alkenes using the most chemoselective diboron reagent, bis(catecholato)diboron (**2**) (Table 4). N-heterocyclic carbenes have emerged as a promising family of ligands that can be used to design efficient homogeneous catalysts.[10]

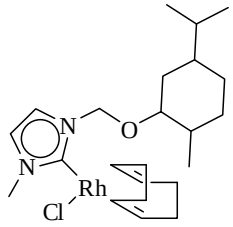

Figure 3. [(mentimid)RhCl(COD)]

As it is shown in Table 4, the chemoselectivity towards the diboron product obtained was very poor for the diboration of styrene (entry 1), and null for the diboration of vinylcyclohexane and the 3,3-dimethylbutene (entries 2 and 3). However, the most interesting observation was that the activity of the

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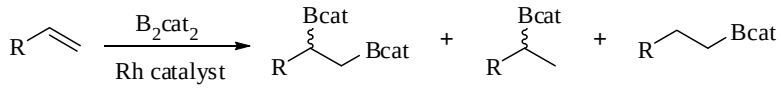
rhodium catalyst was high, and full conversions took only 3 hours. Encouraged by this result, we decided to try complexes of other transition metals modified with NHC ligands, which were supposed to diminish the β-hydride elimination, such as those on the right-hand side of the periodic table.



3 **4** **5**

Table 4. Catalytic 1,2-diboration reaction with a Rh-(NHC) complex[a]

Entry	Substrate	Conversion[b] (%)	% **3**[b]	% **4**[b]	% **5**[b]
1	Styrene	100	23	64,5	12,5
2	Vinylcyclohexane[c]	100	0	0	100
3	3,3-Dimethylbutene[c]	100	0	0	100

[a] Standard conditions: substrate/B_2cat_2/Rh complex = 1/1.1/0.05; THF; *T*: 25ºC; *t*: 3h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] Selectivity determined as derivated alcohols

2.3. Silver-catalyzed alkene diboration

Although cationic rhodium(I) complexes with chiral P,N- or P,P-bidentate ligands make the enantioselective addition of bis(catecholato)diboron to alkenes possible,[6] chemoselectivity is low because of the inherent competitive β-hydride elimination, which provides alkyl- and alkenylboronate esters. We believed that cationic silver (I) could be used to prevent this side reaction and selected N-heterocyclic carbene ligands to modify the electronic and steric properties of the Ag(I) complex. These complexes combine enough electron richness to guarantee B-B cleavage of the diboron, with low energy *d*-orbitals that minimize π-backbonding and thus β-hydride elimination.

The structural diversity of silver (I) N-heterocyclic carbenes has been studied in depth,[11] and they have been widely used as carbene transferring agents for easy access to various important metal-(NHC) complexes.[11b,12] However, despite the high number of silver-(NHC) complexes that have been described in the literature, to date few applications have been reported in

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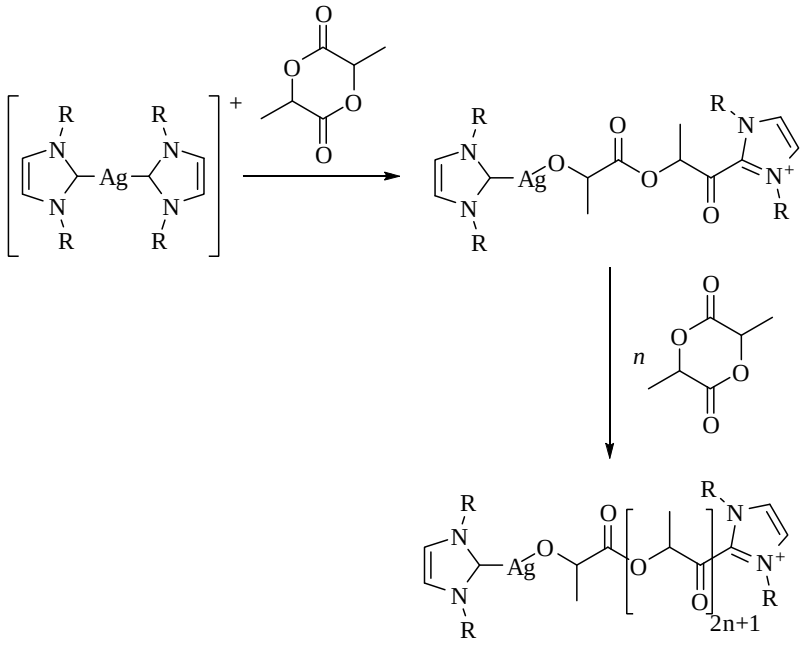
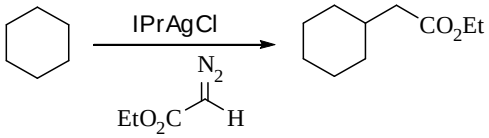
catalytic processes. Jin et al.[13] reported the moderate activity of a silver N-heterocyclic carbene complex precatalyst in the polymerization of ethylene. In addition, silver N-heterocyclic carbenes were also used as precatalysts in the ring opening polymerization of lactides (Scheme 2).[14] Finally, Perez et al.[10g] reported the silver-(NHC) catalyzed insertion of ethyl diazoacetate into C-H bonds (Scheme 3).



Scheme 2



Scheme 3

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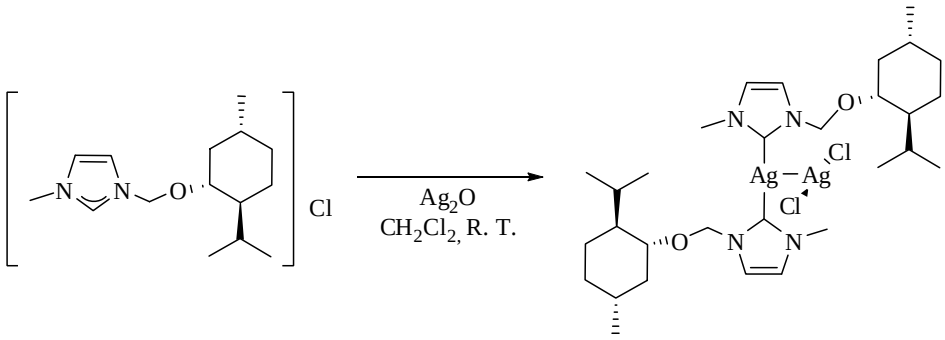
In collaboration with Prof. E. Peris's group and on the basis of their previous experience in the synthesis of transition metal N-heterocyclic carbenes, a series of silver (I) (NHC)-complexes were prepared and applied to the catalyzed 1,2-diboration reaction of alkenes. In an attempt to obtain a sterically hindered complex that could make the diboration reaction highly stereoselective, it was decided to use 1-methyl-3-(+)-methylmenthoxide imidazolium chloride (**11**) as the precursor of the N-heterocyclic carbene. In Prof. E. Peris's group, $[(mentimid)_2Ag]AgCl_2$ (**12**) was prepared by the addition of chiral imidazolium chloride to a suspension of an excess of Ag_2O in dichloromethane, affording the isolation of the expected complex (Scheme 4).



11 **12**

Scheme 4

Bis(catecholato)diboron (**2**) was added to internal and terminal alkenes in the presence of the catalytic precursor **12** (5 mol%), under optimized reaction conditions (room temperature, in THF). Among the terminal alkenes, we observed that the diboration of styrene provided the single product 1,2-bis(boronate)ester (**3**) with 76% conversion (Table 5, entry 1). Isolated compound **12** had a much higher catalytic activity than when it was prepared in situ from Ag_2O and the imidazolium chloride, which showed only conversions of about 5%. When the reaction was carried out at 70ºC we observed an unusually slow transformation towards the desired product, probably due to the

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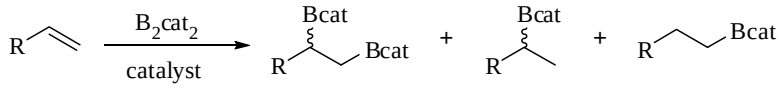
decomposition of the catalytic system under these conditions, although β-hydride elimination was not competitive even under these reaction conditions (Table 5, entry 2). The electron-accepting substituted vinylarenes proved to be less reactive than styrene (Table 5, entries 3-5). On the other hand, the more electron-rich vinylcyclohexane was by far the most active substrate in terms of conversion into the corresponding 1,2-bis(boronate)ester (**3**) (Table 5, entry 6). A similar trend has been reported in the diboration of *para*-substituted terminal phenylacetylenes with Pt(0) catalytic complexes where electron withdrawing substituents diminish the reaction rates.[2c] Remarkably, the hindered internal alkene indene was cleanly transformed into the desired product, although the conversion was low (Table 5, entry 7).



3 **4** **5**

Table 5. [(mentimid)$_2$Ag]AgCl$_2$ catalyzed diboration of alkenes with bis(catecholato)diboron[a]

Entry	Substrate	Conversion[b] (%)	% **3**[b] (%ee)[c]	% **4**[b]	% **5**[b]
1	Styrene	76	100 (-)	0	0
2[d]	Styrene	32	100 (-)	0	0
3	*p*-Fluorostyrene	12	100 (-)	0	0
4	*p*-Chlorostyrene	14	100 (-)	0	0
5	*p*-Trifluoromethylstyrene	10	100 (-)	0	0
6	Vinylcyclohexane	90	100 (-)	0	0
7	Indene	20	100 (-)	0	0

[a] Standard conditions: substrate/B_2cat_2/Ag complex = 0.5/0.55/0.025; THF; *T*: 25ºC; *t*: 60h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derived acetal. [d] Reflux at 70ºC, 20h.

Despite the use of the chiral imidazolydene ligand we observed no asymmetric induction on the reaction products, presumably because the chiral center is at some considerable distance from the metal. In addition, the lability of the Ag-$C_{carbene}$ bond may favour some equilibrium between [(mentimid)$_2$Ag]AgCl$_2$ (**12**) and [(mentimid)AgCl],[11a] thus making it difficult to establish what the real catalytic especies is. Alternatively, the use of chiral

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diboron reagents[9,15] such as bis(diethyl-D-tartrateglycolato)diboron (**8**), bis(di-isopropyl-D-tartrateglycolato)diboron (**9**) and bis((+)-pinanediolato)diboron (**10**) led to a total inhibition of the diboration reaction, making bis(catecholato)diboron the specific diboron reagent for this reaction with $[(mentimid)_2Ag]AgCl_2$ (**12**).

It should be pointed out that we performed the same reaction with analogous Ag(I) complexes modified with phosphines and diphosphines, such as $[\{(R)\text{-BINAP}\}_2Ag]OTf$, $[\{(R)\text{-BINAP}\}Ag]OAc$, $[\{(R)\text{-BINAP}\}Ag_2]OTf_2$ and [{(S)-QUINAP}Ag]OAc,[16] but they did not lead to the conversion of the alkenes towards the desired diborated products, under the same reaction conditions. Even $AgNO_3$ was tested in this reaction to study the possible participation of the Ag^+ ion as the catalytic species, but no reactivity was monitored.

In order to improve the activity and/or the enantioselectivity of the reaction, other Ag(I)-NHC complexes were tested (Figure 4). These complexes were prepared by Prof. E. Peris's group. Complex **13** was synthesized analogously to **12**, using 1,3-di-*n*-butyl-4,5-dichloroimidazolium iodide as the carbene precursor. Complexes **14**, **15** and **16** were synthesized as previously described.[17]

As can be seen in Table 6, the introduction of electron attracting atoms into the carbene partly deactivates the catalyst (for the sake of comparison, see Table 5, entry 1 and Table 6, entry 1). We would expect that diminishing the electrodonating character of the ligand would imply a reduction of the catalytic performance, so the results are in agreement with previously reported ones.[5]

When the chiral NHC-Ag-Cl complexes **14**, **15** and **16** were tested in the catalytic diboration reaction, the diboron product was still the major product, although the conversion was lower, probably because the catalytic system was more sterically hindered. Interestingly, complex **15** was able to induce,

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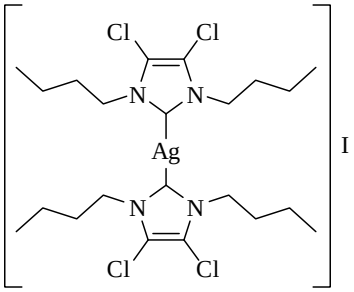
modestly, some enantioselectivity, with ee values between 4% and 9%. We believe that this result may be due to the steric crowding of the metal in **15** being higher than in the other chiral catalysts. We are aware that this ee values are very low, but they must be compared to the maximum values (35%) achieved by the Rh(I)/(S)-QUINAP complex. So we believe that chiral [Ag(I)-(NHC)]Cl complexes may be a useful alternative for the clean asymmetric catalytic diboration of alkenes. Compound **15** was also tested in the diboration of vinylcyclohexane (Table 6, entry 5). Conversion was quantitative, but asymmetric induction was negligible. The diboration of *p*-fluorostyrene and *p*-vinylanisole (Table 6, entries 6 and 7) showed that the more electron attracting the substituents are, the higher the conversion to the diboron species is. When the Rh(I)/(S)-QUINAP catalytic system is used, the behaviour is just the opposite.



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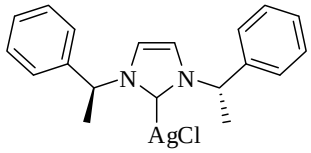

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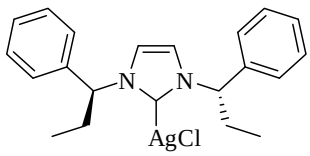

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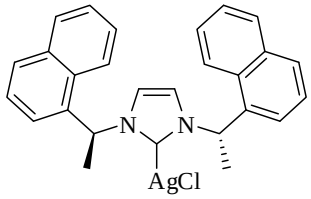

16

Figure 4

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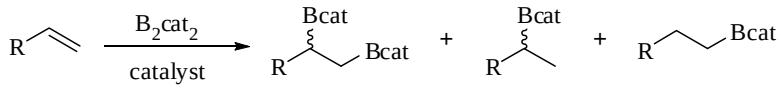

3 **4** **5**

Table 6. Catalytic diboration reaction of alkenes with Ag-NHC complexes and bis(catecholato)diboron (2)[a]

Entry	Catalytic system	Substrate	*t* (h)	*T* (ºC)	Conversion[b] (%)	% **3**[b] (%ee)[c]
1	**13**	Styrene	60	25	46	100
2	**14**	Styrene	60	25	40	100 (-)
3	**15**	Styrene	60	25	13	91 (9R)
4	**15**	Styrene	24	70	42	100 (4R)
5	**15**	Vinylcyclohexane	24	70	100	100 (-)
6	**15**	*p*-fluorostyrene	24	70	51	100 (-)
7	**15**	Vinylanisole	24	70	13	100 (-)
8	**16**	Styrene	60	25	10	93 (-)

[a] Standard conditions: substrate/B_2cat_2/Ag complex = 0.5/0.55/0.025; THF. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derived acetal.

2.4. Gold-catalyzed alkene diboration

Encouraged by the results obtained using the Ag(I)-(NHC) catalytic systems, we decided to continue exploring the 11th group metals. Westcott, Marder and Baker[5] studied the activity of the gold catalytic system [Au(PEt_3)Cl] modified with a bidentate diphosphine ligand on the basis of unknown mononuclear neutral gold-hydride complexes.[18] The desired 1,2-bis(boronate)ester was mainly attained from styrene and bis(catecholato)di-boron (**2**), as a model reaction, although catalytic activity and stability were lower than desired.

We decided to explore the effect of the NHC ligands, expecting them to be as successful as the Ag(I)-NHC catalytic system. The gold(I) complexes used were obtained in high yields by members of Prof. E. Peris's group (ca. 90%) by in situ generation of the free carbenes from 1-methyl-3-(+)-methylmenthoxide imidazolium chloride or 1,3-di-*n*-butyl-4,5-dichloro-imidazolium iodide in THF at -78ºC with ^{t}BuLi, and then addition of Au(PEt_3)Cl, yielding complexes **17** and **18**, respectively (Figure 5). Alternatively, complexes **17** and **18** were

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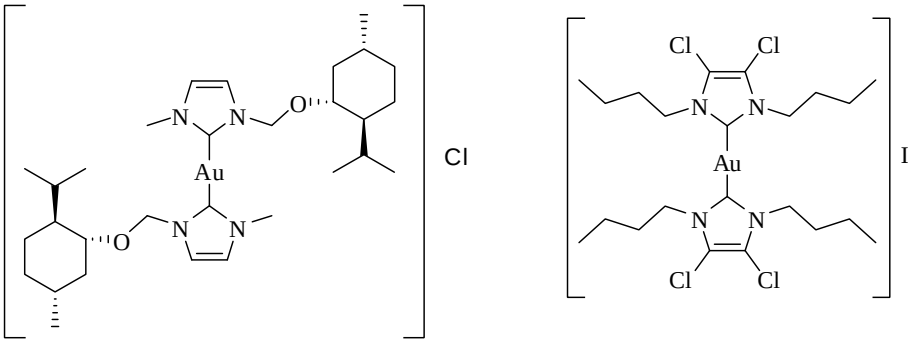
obtained by transmetallation of the corresponding carbenes from the silver complexes **12** and **13** to Au(PEt_3)Cl, although yields were lower (ca. 50%) than those obtained by direct coordination of the free carbene to Au.



17 **18**

Figure 5

The catalytic activity provided by compounds [NHC-Au(I)-NHC]X was examined. Modifying gold(I) with an NHC ligand clearly enhances the catalytic performances, in agreement with Baker et al.,[5] which suggests that arylphosphine gold(I) complexes are not sufficiently electron rich to serve as competent alkene diboration catalysts. We were able to get 100% selectivity for the diboron product in the catalyzed diboration of styrene when using **17** and **18**, with up to 94% conversion (Table 7).

The activity of complex **18** may be different from that of its silver(I) analogues, **13** (Figure 4) because of the lability of the Ag-$C_{carbene}$ bond, which could favour an equilibrium between mono- and bis-carbene species in solution.[19] In fact, while we have assigned a bis-NHC structure for both silver(I) complexes **12** (Scheme 4) and **13** (Figure 4), we believe that the species present in solution have a mono-NHC structure, according to data reported in the literature for similar complexes.[19b]

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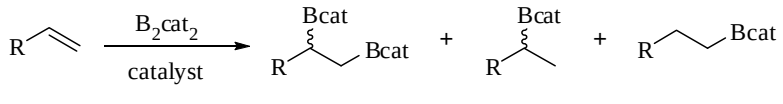

3 **4** **5**

Table 7. Catalytic diboration reaction of alkenes with Au-NHC complexes and bis(catecholato)diboron (2)[a]

Entry	Catalytic system	Substrate	*t* (h)	*T* (ºC)	Conv.[b] (%)	% **3**[b] (%ee)[c]
1	**17**	Styrene	60	25	69	100 (-)
2	**17**	Styrene	20	70	86	100 (-)
3	**17**	Vinylcyclohexane	60	25	40	100 (-)
4	**18**	Styrene	60	25	94	100 (-)

[a] Standard conditions: substrate/B_2cat_2/Ag complex = 0.5/0.55/0.025; THF. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derivated acetal.

On the other hand, Au-NHC are known to have stronger Au-$C_{carbene}$ bonds,[20] which allow well defined molecular arrangements in both solid state and in solution. This may somehow justify the differences in the catalytic behaviour upon introduction of the chloro substituents into the imidazolylidene rings of the silver and gold complexes. In the case of gold complexes, the introduction of the electron attracting atoms improves the catalyst activity (Table 7, entries 1 and 4), just the opposite effect observed in the case of silver(I) complexes. We do not have a satisfactory explanation for this observation, but the structural versatility of the Ag-NHC complexes may also play a role, implying that the catalytic Ag(I) and Au(I) species have a different structural nature in solution. Thus, the behaviour of gold(I)-NHC complexes is the opposite of that previously reported.[5] For chiral complex **17**, total chemoselectivity for the diborated product was observed, and conversions were high when the reaction was carried out at 70ºC. However, no asymmetric induction was observed in the corresponding diols, after the oxidation procedure.

Inspired by these preliminary results and in an attempt to achieve clean alkene diboration, we focussed on finding new gold catalytic systems that not only performed as clean diborating catalysts, but also were able to induce

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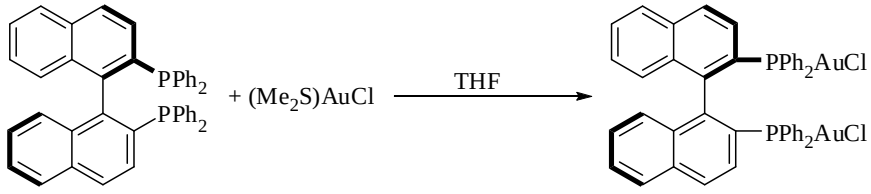
asymmetry in the organodiboron products. The lack of any attempted synthesis of 1,2-bis(boronate)esters with catalytic chiral systems based on gold(I) complexes prompted us to synthesize a chiral diphosphine gold(I) complex, using (R)-BINAP as the ligand. The desired complex was obtained by the direct reaction of $(Me_2S)AuCl$ (2 equivalents) and (R)-BINAP (1 equivalent) in THF.[21] The complex obtained, $[\{(R)\text{-BINAP}\}Au_2Cl_2]$ (**19**), was converted to $[\{(R)\text{-BINAP}\}Au_2I_2]$ (**20**) by ionic exchange with an excess of KI in THF (Scheme 5).[22]



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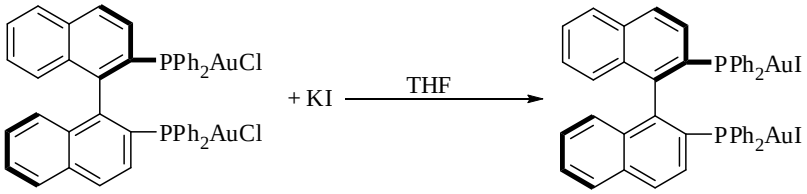

19 **20**

Scheme 5

Crystals of $[\{(R)\text{-BINAP}\}Au_2I_2]$ (**20**) suitable for X-ray diffraction were obtained by precipitation with hexane of a concentrated dichloromethane solution. Crystallographic data confirmed the structure proposed. Figure 6 shows the ORTEP diagram of $[\{(R)\text{-BINAP}\}Au_2I_2]$ (**20**). In the structure we can observe that each gold atom coordinates only one of the phosphine units of (R)-BINAP, thus obtaining a dimetallic complex with no interactions between the two metal units. Comparing the ^1H NMR spectra of the two complexes with the spectra of free (R)-BINAP, we can observe that the protons of the ligand in

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the complexes are more unshielded than those of the free ligand (Figure 7). The ^{31}P NMR spectra of the two complexes show a lonely singlet corresponding to the equivalent P atoms, because of the simmetry of the complex and the lack of couplings (Figure 8). The phosphorous atoms of **20** are more unshielded than those in **19**.

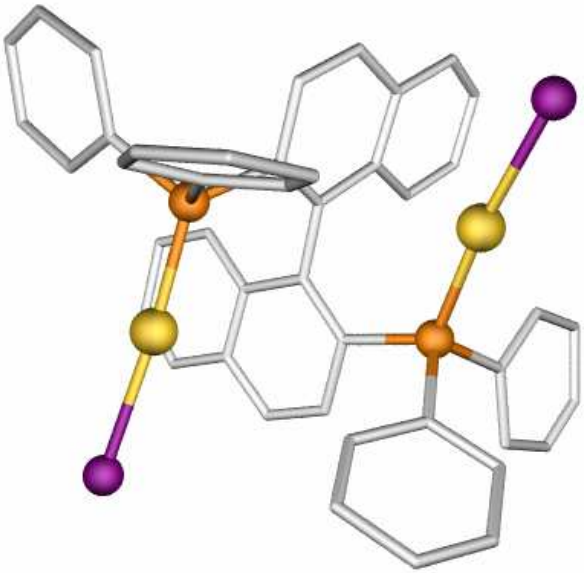

Figure 6. X-ray crystal structure of [{(R)-BINAP}Au_2I_2] (20). Selected bond distances (Å) and angles (deg): Au-P: 2.257; Au-I: 2.549; P-Au-I: 172.20

We can compare the crystal structure of [{(R)-BINAP}Au_2I_2] with that of [{(R)-TolBINAP}Au_2Cl_2] reported by Echavarren et al.[23] The main difference between the two structures is the length of the bond between the metal center and the halide. It is 0.26 Å longer in [{(R)-BINAP}Au_2I_2] than in [{(R)-TolBINAP}Au_2Cl_2]. However, the Au-P distance is almost the same in the two complexes: it is only 0.022 Å longer in [{(R)-BINAP}Au_2I_2]. Echavarren et al.[23] used these sort of complexes in the enantioselective cyclization of enynes.

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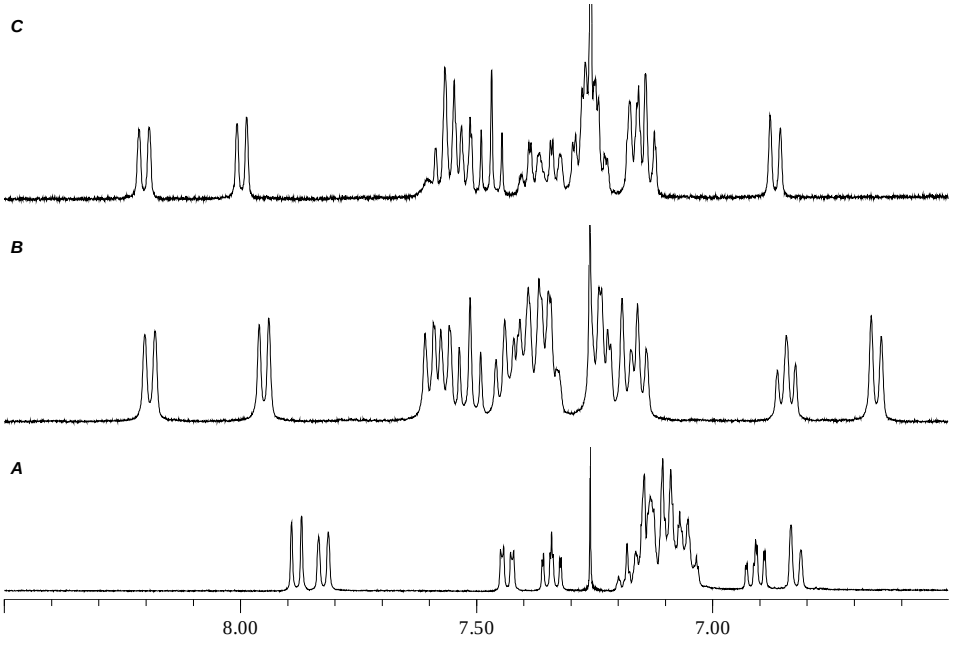

Figure 7. ^{1}H NMR spectra of the compounds: A) R-BINAP; B) [{(R)-BINAP}Au_2Cl_2] (19); C)) [{(R)-BINAP}Au_2I_2] (20).

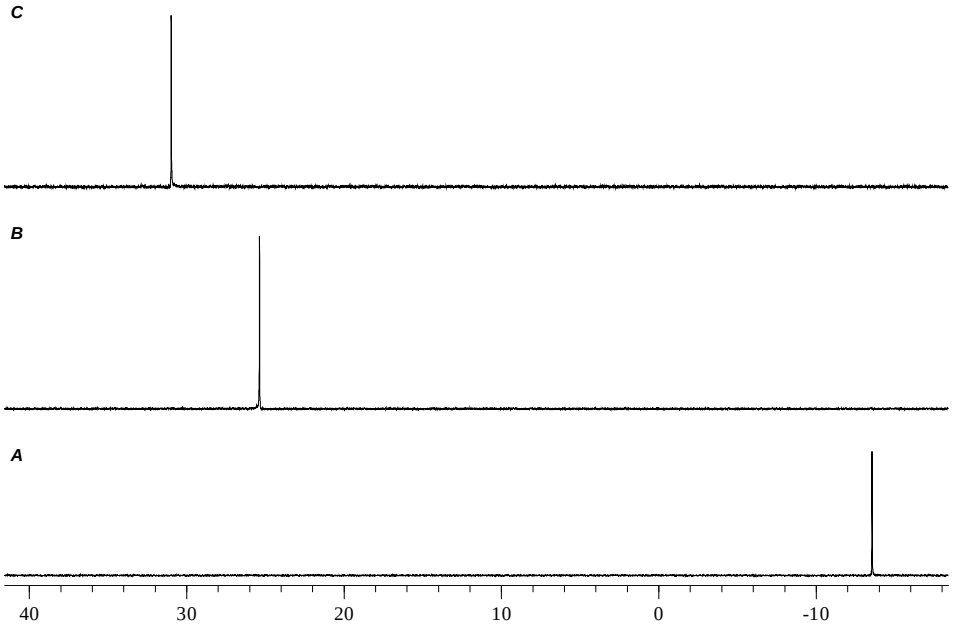

Figure 8. ^{31}P NMR spectra of the compounds: A) R-BINAP; B) [{(R)-BINAP}Au_2Cl_2] (19); C)) [{(R)-BINAP}Au_2I_2] (20).

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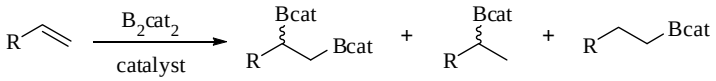
The two gold(I) complexes synthesized, [{(R)-BINAP}Au_2Cl_2] (**19**) and [{(R)-BINAP}Au_2I_2] (**20**), were used as the catalytic system in a room temperature diboration reaction of styrene in THF, but after 72 hours no product formation was detected (Table 8, entries 1 and 2). In order to activate the catalytic system, [{(R)-BINAP}Au_2Cl_2] was used in a refluxing diboration reaction. Only a 6% of conversion on the diboron product was obtained, but the chemoselectivity was 100% (Table 8, entry 3). Unfortunately, there was no enantioenrichment in the diboron product. In an attempt to improve the activity of the catalyst, a new experiment was designed: $AgBF_4$ was added to the solution of [{(R)-BINAP}Au_2Cl_2] to remove the chloride, but no yield was obtained after 72h.

Using an excess of diboron **2** and adding a mild base (NaOAc) we were able to substantially increase the conversion keeping a total chemoselectivity. The catalyitic system formed from **20** was more active than that formed from **19**, and conversion was complete in 2 hours (Table 8, entries 4 and 5). This may be due to the higher lability of the Au-I bond in **20** with respect to Au-Cl in **19**. Taking into account these results, we continued to use **20** as the catalytic system.



3 **4** **5**

Table 8. Catalytic diboration of styrene with gold[a]

Entry	Catalytic system	Base	Eq. B_2cat_2 (**2**)	*t* (h)	Conv.[b] (%)	% **3**[b] (%ee)[c]
1	**19**	-	1.1	72	0	0
2	**20**	-	1.1	72	0	0
3[d]	**19**	-	1.1	72	6	100 (0)
4	**19**	NaOAc	3	15	75	99 (0)
5	**20**	NaOAc	3	2	100	99 (0)
6	**20**	NaOAc	2	2	89	99 (0)
7	**20**	NaOAc	1.1	2	13	99 (0)
8	**20**	NaOH	3	2	100	84 (-)
9	**20**	$CsCO_3$	3	2	100	65 (-)

[a] Standard conditions: substrate/base/Au complex = 1/1/0.125; THF; room temperature. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derived acetal. [d] Reflux.

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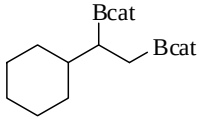
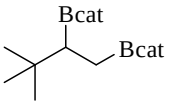
The optimal quantity of diboron was also tested. Although using 2 equivalents of the diboron **2** had little effect on the conversion (Table 8, entry 6), using 1 equivalent of diboron **2** had a dramatic effect, obtaining only 13% (Table 8, entry 7). However, chemoselectivity was not affected. The use of the base was found to be necessary, because the lack of the base inhibited the conversion. Other bases were tested (NaOH, $CsCO_3$), obtaining also good conversions, but worse chemoselectivities (Table 8, entries 8 and 9).

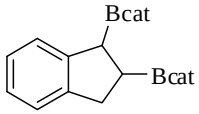
The efficiency of this system was extended to aliphatic alkenes like vinylcyclohexane and 3,3-dimethylbutene, and the conversions and chemoselectivities (Figure 9) were the same, but unfortunately, no enantiomeric excess was obtained.



100% conv.

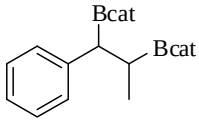


100% conv.



100% conv. (100% cis)

100% conv. (100% exo)



100% conv. (95% cis)

Figure 9

The diboration of internal alkenes showed the ability of this catalytic system to diborate internal double bonds with high diastereoselectivity (Figure 9). The development of this protocol for selective formation of *cis*-bis(boryl) cyclic molecules is important, because few succesful examples have been described in the literature. Diboration of norbornene has been reported using base-free Pt(0) complexes[4a,b] or Rh(I) complexes[3], with good yields and chemoselectivities, but longer reaction times or higher temperatures. However,

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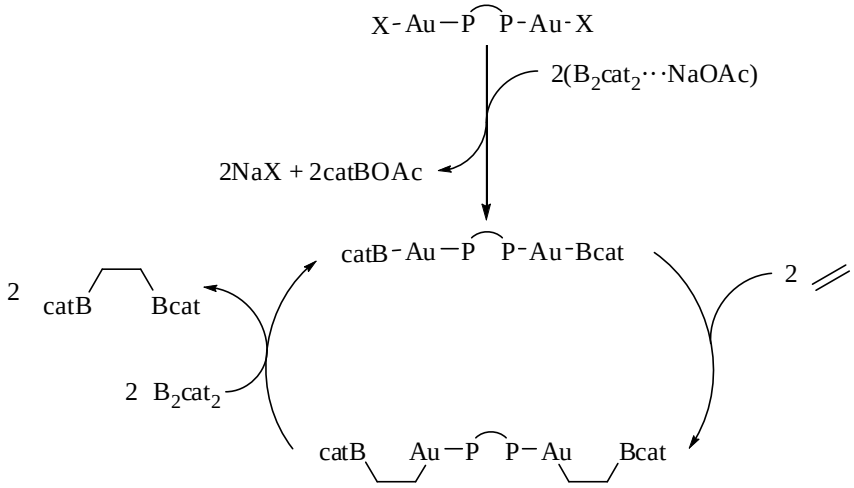
the diboration of indene has only been reported once.[6] It required longer reaction times and gave lower chemoselectivity (68%).

The high chemoselectivity described above suggests that the precursor of catalyst [{(R)-BINAP}Au_2X_2] (X= Cl, I) is involved in a base-mediated heterolytic cleavage of the diboron reagent and, therefore, transmetallation becomes the key step in the mechanism instead of oxidative addition. Similar mechanism has recently been postulated for the first catalytic diboration of alkenes with palladium complexes.[24]



Scheme 6. Proposed mechanism for the gold catalyzed base mediated diboration reaction of alkenes

2.5. Copper-catalyzed alkene and alkyne diboration

With the goal of developing both active and selective catalysts for the alkene diboration reaction, we have turned our attention to copper, the remaining group 11 metal still not known to catalyze the diboration of alkenes.[25] In collaboration with the groups of Prof. P. J. Pérez (Huelva University) and Prof. F. Maseras (ICIQ), and because of the success of such compounds in other

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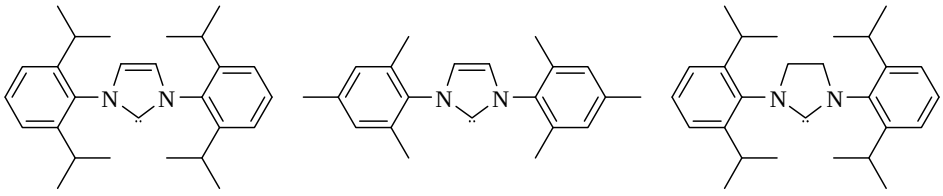
catalytic processes.[26] we investigated the potential of several complexes containing the Cu-(NHC) core as the catalyst for this reaction.

In the first screening, the previosly described[26c-e] Cu(I)-(NHC) compounds **21-26** (Figure 10) were tested as catalytic precursors in the reaction of diboration of styrene with bis(catecholato)diboron (**2**). The latter was added to a solution of the catalyst precursor in tetrahydrofuran under nitrogen and stirred for 5 minutes before styrene was added. The mixture was stirred for 4 hours at room temperature or solvent refluxing temperature.



IPr
21: [CuCl(IPr)]
22: [Cu(IPr)($NCCH_3$)]BF_4

IMes
23: [CuCl(IMes)]
24: [Cu(IMes)($NCCH_3$)]BF_4

SIPr
25: [CuCl(SIPr)]
26: [Cu(SIPr)($NCCH_3$)]BF_4

Figure 10

In the first series of experiments, the IPr ligand (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) was used in four different catalytic precursors: the neutral complex [CuCl(IPr)] (**21**), the isolated cationic species [Cu(IPr)($NCCH_3$)]BF_4 (**22**), and mixtures of **21** with NaBAr'$_4$ [27] (Bar'$_4$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) or $AgBF_4$ for the in-situ generation of the cationic species.

The neutral complex **21** did not induce the transformation at room temperature (Table 9, entry 1): the conversions were very low in refluxing THF (Table 9, entry 2). Addition of NaBAr'$_4$ as the halide scavenger was not effective (Table 9, entry 3), but moderate conversions (53%) were observed when $AgBF_4$ was used instead (Table 9, entry 4). The nature of the salt seems to play an important role in the in situ formation of the cationic complexes.

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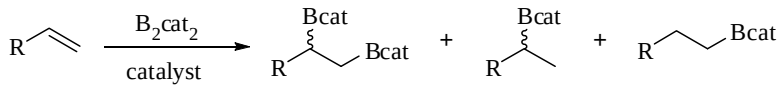
However, when the well defined, previously isolated complex **22** was used as the catalytic precursor, moderate conversion (50%) was obtained at room temperature, and nearly quantitative conversion (94%) was achieved at refluxing THF temperature (Table 9, entries 5 and 6, respectively). The previous literature on the use of Cu(I) catalysts for alkene diboration did not report any transformation; only the monoboration of α,β-unsaturated ketones was succesful with this metal.[28]



3 **4** **5**

Table 9. Catalytic diboration of styrene with Cu(I)-(NHC)

Entry	Catalyst prec.	Solvent	*T*	Conv.[b] (%)	% **3**[b]	% **5**[b]
1	**21**	THF	22ºC	0	0	0
2	**21**	THF	reflux	11	100	0
3	**21**/$NaBAr'_4$	THF	reflux	5	100	0
4	**21**/$AgBF_4$	THF	reflux	53	63	37
5	**22**	THF	22ºC	50	80	20
6	**22**	THF	reflux	94	89	11
7	**22**	CH_3CN	reflux	12	99	0
8	**22**	Toluene	reflux	59	22	54[c]
9[d]	**22**	THF	reflux	74	20	80
10[e]	**22**	THF	reflux	43	0	99
11	**23**	THF	reflux	25	59	41
12	**24**	THF	reflux	53	42	58
13[f]	**25**	THF	reflux	100	99	0
14	**26**	THF	reflux	41	58	42

[a] Standard conditions: substrate/B_2cat_2/Cu complex = 0.5/0.55/0.025; THF. Reaction time: 4h. [b] Conversion and selectivity calculated by ^1H NMR. [c] Branched alcohol observed (24%). [d] Diboron = B_2pin_2 (**1**). [e] [styrene]/[B_2cat_2] = 3:1 [f] *t* = 10h.

The reaction conditions can induce effects on both activity and selectivity. For instance, the selection of the solvent is important because, as shown in entries 6,7 and 8 in Table 9, it affected the conversion as well as the distribution of products. In the case of toluene, the monoalcohol was the major

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product, and some branched isomer is observed (24%). The nature of the diboron reagent also has an effect: the use of bis(pinacolato)diboron (**1**) instead of bis(catecholato)diboron (**2**) reduces the yield of the reaction and gives the linear monoalcohol as the main product (80%) (Table 9, entry 9). Perhaps the most intriguing result was obtained when the [styrene]/[B_2cat_2] ratio was varied. The above results were obtained with a slight excess of bis(catecholato)diboron (**2**) (10%) with respect to styrene; however, when a [styrene]/[B_2cat_2] ratio of 3:1 was used, only the linear monoalcohol, and no other borated product, was observed at the end of the reaction (Table 9, entry 10). This result suggests that the chemoselectivity of the reaction can be controlled merely just by modifying this ratio. Use of the inverse ratio ([styrene]: [B_2cat_2] = 1:3) provided the same selectivity as the nearly equimolar one.

These copper-based catalysts make it possible to readily modify the nature of the groups bonded to the nitrogen atoms of the NHC ligand as well as that of the backbone. Thus, use of mesityl instead of 2,6-diisopropylphenyl groups as the N substituents seems to increase the amount of the linear monoalcohol (Table 9, entries 11 and 12). Another variable is the saturation of the backbone, which also influences the course of the reaction. When the ligand SIPr was employed in the neutral precatalyst **25**, 68% conversion was observed after the standard 4 hours of reaction time. This is substantially higher than that found with complex **21** (11%) (Table 9, entry 2), and was completed by prolonging the reaction time to 10 hours (Table 9, entry 13). Only the diboron product was observed at the end of the reaction, in a quantitative and selective transformation. However, cationic analogue **26** did not provide such complete selectivity.

These results are worth commemting since both activity and selectivity values are, at least, comparable with previously reported data. Exclusive formation of the difunctionalized product has only been reached with Au(I)-

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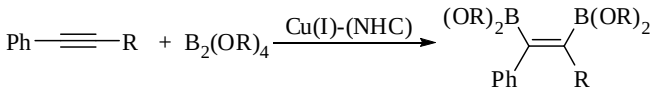
(NHC) and Ag(I)-(NHC) catalyst precursors, but in the case of Cu(I)-(NHC), the catalytic system **25** was more active because of the shorter reaction times required for total conversion. Only the very active [Rh(dppb)(η^6-catBcat)],[3] the monophosphine Pt(0) complexes,[2c] the base-free platinum catalyst precursors [Pt(dba)$_2$],[4a] [Pt(nbe)$_3$] [4b] and [Pt(cod)$_2$],[4b] and [Pt(cod)Cl$_2$] [4c] seem to be comparable with this Cu(I)-(NHC) system. However, this system has two advantages: the metal is inexpensive and the tunability of the ligand allows the asymmetric version of the catalytic reaction to be developed.

To broaden the scope of diboration by Cu(I)-(NHC), alkynes were also transformed into the corresponding 1,2-bis(boronate)esters. Both phenylacetylene and diphenylacetylene were diborated with bis(catecholato)di-boron (**2**) in THF at refluxing temperature for 4 hours, with conversions between 90 and 95% when complexes **22** and **24** were used as the catalytic precursor. Selectivity on the diboron product was completely towards the *cis* isomer (Scheme 7). Reaction with bis(pinacolato)diboron (**1**) resulted in very low conversions (less than 5%).



27 **28**

Scheme 7

In colaboration with Prof. P. J. Perez and Prof. F. Maseras groups, we also investigated the mechanism of this reaction. Complex **22** and styrene were dissolved in deuterated tetrahydrofuran, with no change in the ^{1}H-NMR of complex **22**. However, when bis(catecholato)diboron (**2**) was added to a solution of complex **22** in deuterated tetrahydrofuran, the colour immediately changed from colourless to brownish, and there was also a slight change in the ^{1}H-NMR signals of complex **22** and bis(catecholato)diboron (**2**). Unfortunately, the resulting product was not isolated or identified. When styrene was added to

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the mixture, diboration started immediately, even at room temperature, with a low rate that was accelerated when the temperature was raised to 50ºC. Only one Cu(I)-(NHC) species was detected during catalysis, with identical ^{1}H-NMR signals to those observed when complex **22** and bis(catecholato)diboron were mixed. There was no evidence of styrene coordination. Interestingly, when the same set of experiments were carried out in deuterated acetonitrile, no reaction was observed, probably due to the necessity of a dissociation preequilibrium of the CH_3CN ligand of complex **22** required to generate an unsaturated species which is reactive towards bis(catecholato)diboron (**2**). That dissociation takes place readily in tetrahydrofuran, but not in acetonitrile.

Mechanisms proposed for the Rh(I)- and Pt(I)-catalyzed diboration involve an oxidative addition of the B-B bond to the metal center.[1,29,30] Subsequent insertion of the olefin into one M-B bond and reductive elimination would afford the final diboron product. In this case, it seems clear that the reaction is initiated by an interaction between the Cu(I) center and the bis(catecholato)diboron (**2**), though we have no evidence of the oxidative addition product. The broadening of the ^{11}B NMR spectra of bis(catecholato)diboron (**2**) when it is mixed with complex **22** seems to indicate that there is equilibria among several species.

To obtain more information about the nature of the interaction between the unsaturated $[Cu(NHC)]^+$ complex and bis(catecholato)diboron (**2**), A. A. C. Braga and Prof. F. Maseras carried out a theoretical DFT study with the B3LYP functional. The results excluded an oxidative addition process, as Marder et al.[31] showed in the study of the reduction mechanism of CO_2 to CO catalyzed by Cu(I) boryl complexes, using bis(pinacolato)diboron (**1**) reducting reagent. Instead, Maseras et al. were conclusively in favor of a $[Cu(NHC)(\sigma\text{-catB-Bcat})]^+$ description, in which the unbroken B-B bond coordinates Cu as a B-B σ adduct. Although all attempts to optimize the expected diboryl complex failed,

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its energy was estimated from a constrained geometric optimization in which the B-Cu-B and C-Cu-B angles were frozen at 120º. The energy for this oxidative addition state was 69.2 kcal.mol^{-1} above that of the σ adduct. An additional attempt in which the C-Cu-B angle was constrained to 90º and the B-Cu-B angle to 180º, gave a higher energy (85.6 kcal.mol^{-1}). These data suggest that the existence of the Cu(III)-diboryl species is very unlikely. Thus, the above experimental and calculated data indicate that the products due to the oxidative addition of the diboron reagent are more unstable in terms of energy than the related σ-borane complex.

With the above information, we proposed a mechanism for the diboration reaction (Scheme 8). The first step consists of an equilibrium between the cationic catalytic precursor [Cu(NHC)(NCMe)]BF_4 and the adduct [Cu(NHC)(σ-catB-Bcat)]$^+$. This is not based on the oxidative addition pathway commonly used for Rh- and Pt- catalysts already mentioned, and assumes a new approach to this type of transformation. Westcott et al.[32] reported the use of Cu-, Ag- and Au-based catalysts for the hydroboration of imines in a process in which no oxidative addition of the HBcat was observed, which supports this explanation. In addition, Hosomi et al. later reported a similar result during the copper catalyzed boration of α,β-enones, in which no reaction of the borane and the metal center was found.[33]

The interaction of the σ adduct with the Lewis base BF_4^- would lead to the formation of a neutral copper-boryl species [Cu(NHC)(Bcat)] with one equivalent of catB·BF_4. This heterolytic cleavage has a precedent in previous work by Miyaura et al.,[34] in which a copper-boryl species was generated in situ from bis(pinacolato)diboron (**1**) and copper acetate. More recently, Sadighi et al.[35] reported the synthesis of a related complex [Cu(IPr)(Bpin)] through direct reaction of [Cu(IPr)(O^{t}Bu)] and bis(pinacolato)diboron (**1**).

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The [Cu(NHC)(Bcat)] species in Scheme 8 would then react with styrene to give Cu(I)-alkyl intermediates which undergo further interaction with another diboron molecule to afford the desired diboron product through transmetallation and to regenerate the real catalytic species, [Cu(NHC)(Bcat)]. Sadighi et al. described the reactivity of a (NHC)Cu(I)-boryl complex toward styrene, demonstrating the clean insertion of styrene into the Cu-B bond to give a β-boroalkyl intermediate, which can be converted into the α-derivative upon heating. It has been proposed that this step proceeds through a β-hydride elimination/reinsertion sequence.[36]

The above explanation, represented by cycle A in Scheme 8, would only explains the formation of the diboron product, which is the major product in most of the experiments shown in Table 9. However, the formation of the hydroboration products cannot be explained by cycle A. The reversible β-elimination reactions observed by Sadighi in [Cu(IPr){(Bpin)H-CH_2Ph}] can be invoked to account for the appearance of these byproducts.[36] Such elimination from the alkyl intermediates in Cycle A would lead to M-hydridoalkene compounds that can undergo olefin dissociation to generate an unsaturated hydridocopper(I) species. The interaction of this [CuH(NHC)] intermediate with styrene and further transmetallation with a diboron molecule would provide the monoborated byproducts before the [Cu(NHC)(Bcat)] catalytic species is regenerated, thus closing this Cycle B. It has been proposed that neutral catalytic precursors may undergo halide exchange in the presence of donor substrates.[26c]

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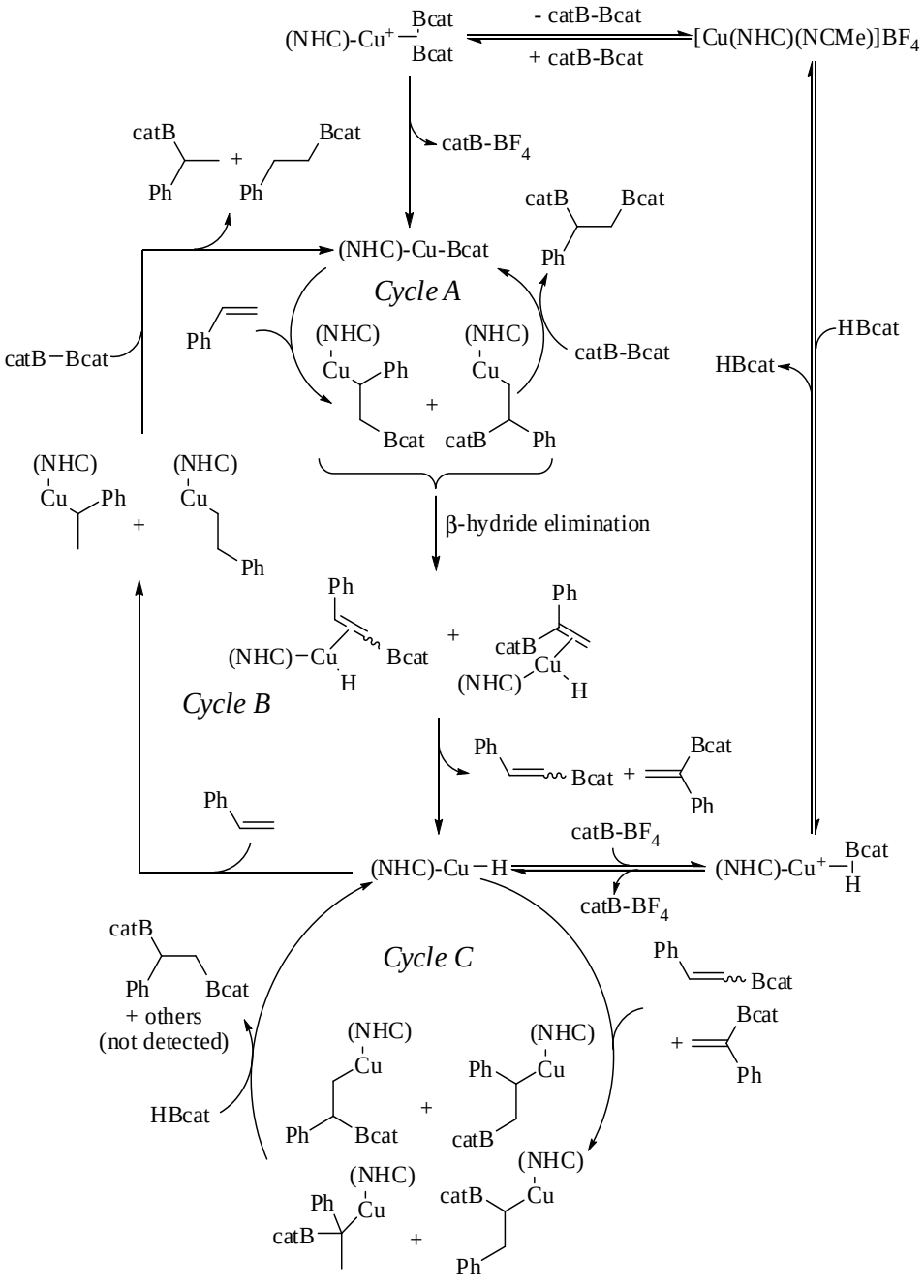

Scheme 8. Proposed mechanism for the copper-catalyzed diboration of styrene.

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The formation of the CuH species also promotes the appearance of two different alkenylboron compounds that we have not detected in any of the in-situ NMR monitoring of the catalytic experiments. Our group designed an experiment to demonstrate that these species are consumed when they are formed during the catalytic cycle. In this experiment, PhCH=CH(Bcat), a feasible intermediate in our reaction scheme, was used as the substrate in a catalyzed diboration reaction with catalytic precursor **22** and bis(catecholato)diboron. The only product formed was PhCH(Bcat)-CH_2(Bcat). To account for this behaviour, we propose a third cycle (Cycle C), consisting of the insertion of the alkenyl boron molecule into the Cu-H bond, followed by interaction of the Cu-alkyl intermediates with HBcat. This catecholborane could appear as a consequence of an equilibrium between the Cu-H species and the catB-BF_4 formed at the beginning of the reaction, which would lead to the formation of the σ-adduct, and subsequent decoordination. This proposed mechanism also ensures the mass balance, since the hydrogen source for the monoborated product is the styrene. No incorporation of deuterium was observed when the reactions were carried out in deuterated solvents, even when D_2O was present (Scheme 9). All the products obtained contained H atoms exclusively, within the NMR detection scale. A new experiment was designed to ensure which is the hydrogen source, using deuterated styrene as the substrate, and **24** as catalyst precursor. The only hydroborated product detected by GC/MS after oxidation workup was $(C_6D_5)CD_2CD_2OH$, confirming styrene as the hydrogen source (Scheme 9).

The results in Table 9 indicate that the ligand, the precatalyst charge and the solvent exert a perceptible influence on activity and selectivity. Therefore, in some cases not all the cycles or intermediates exist. For example, using complex **25** mainly involves Cycle A.

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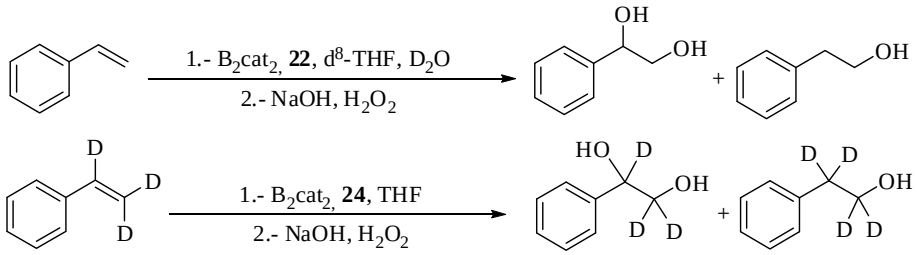
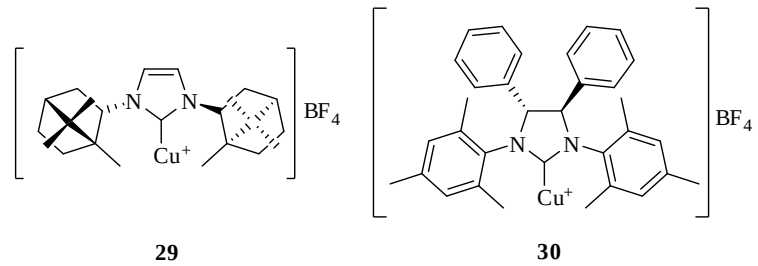
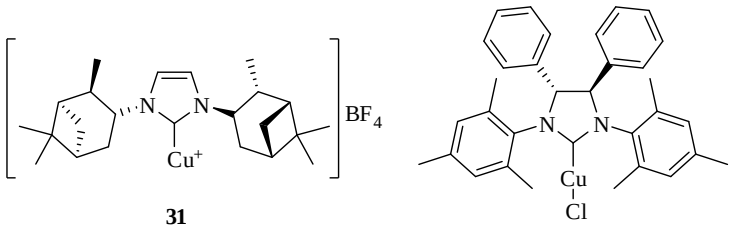
In colaboration with Prof. P. J. Pérez's group, we tried to obtain the diboron product enantioselectively, by testing some Cu complexes modified with chiral carbenes in the catalytic diboration of styrene (Figure 11). The first series of experiments used the methodology applied in the preceding Cu(I)-(NHC) catalyzed diboration of styrene.



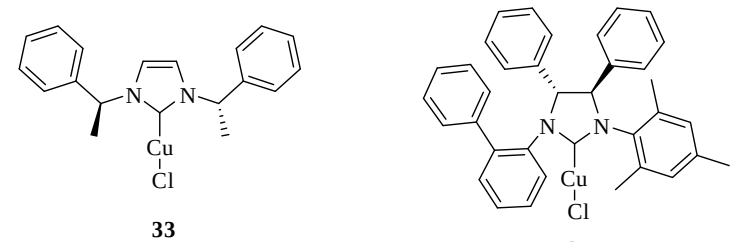
Scheme 9



29 **30**



31 **32**



33 **34**

Figure 11

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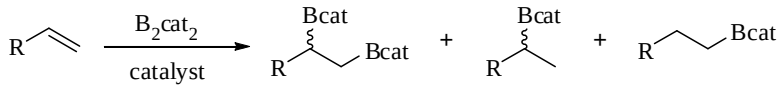
Although when cationic catalytic precursors **29** and **31** were used the chemoselectivity towards the diboron product was very low, there was no enantiomeric excess, with catalytic precursor **30** the only two products obtained were **3** and **5**, and there was a moderate enantiomeric excess in **3** (28%, Table 10, entry 1). Neutral complexes proved to be inactive under these reaction conditions.

In order to improve the activity and the chemoselecticity of these catalysts, and taking into account the precedents of the the catalytic diboration in presence of a base with Pd[24] and Au complexes, we decided to add an excess of bis(catecholato)diboron (**2**) (3 equiv.) and a salt (NaOAc) to the reaction media. When these catalytic precursors were tested under these conditions at a reflux temperature, they all proved to be active, and the chemoselectivity towards the diborated product improved (Table 10, entries 2-7). Unfortunately, the only catalytic precursor which induced asymmetry was **30**, but the enantioselectivity was lower than in the absence of the base.



3 **4** **5**

Table 10. Catalytic diboration of styrene using chiral Cu(I)-(NHC) catalytic precursors.[a]

Entry	Catalytic system	Base	Equiv. **2**	*T*	Conv.[b] (%)	% **3**[b] (%ee)[c]	% **5**[b]
1	**30**	-	1.1	reflux	88	14 (28S)	86
2	**29**	NaOAc	3	reflux	55	100 (-)	0
3	**30**	NaOAc	3	reflux	60	74 (19S)	26
4	**31**	NaOAc	3	reflux	22	100 (-)	0
5	**32**	NaOAc	3	reflux	24	85 (-)	15
6	**33**	NaOAc	3	reflux	40	100 (-)	0
7	**34**	NaOAc	3	reflux	20	95 (-)	5

[a] Standard conditions: substrate/Cu complex = 0.5/0.025; THF. Reaction time: 4h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] ee determined by GC with chiral columns, as derived acetal.

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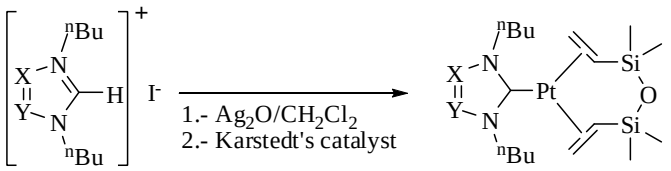
2.6. Platinum-catalyzed alkene and alkyne diboration.

In order to improve the activity and selectivity of the catalytic precursors, and in colaboration with Prof. E. Peris's group, we turned our attention to the promising Pt(0)-NHC complexes and their ability to catalyze the diboration of alkenes and alkynes.

The NHC-platinum compounds **35-37** were synthesized in the group of Prof. E. Peris by transmetallation from the corresponding silver carbenes (see Scheme 10). The three complexes were obtained to study how the electronic nature of the NHC ligand affects the catalytic performances.

The Pt(0)-NHC complex **36** was initially tested in the diboration of alkynes using diphenylacetylene and phenylacetylene as model substrates for internal and terminal alkynes, respectively. As shown in Table 11, THF was the most suitable solvent for conducting at room temperature the clean addition of **1** to alkynes with the formation of the *cis*-alkene bis(boronate) esters (entries 1-3). However, conversion depended on the electronic properties of the NHC-ligand, and the electron releasing triazolylidene carbene ligand in complex **36** was the most suitable, as expected, because of the higher electronic density on the metal (entries 3-5). Thus, we selected complex **36** for further studies, and the use of the most reactive diboron **2** allowed quantitative conversions of diphenylacetylene in 5 hours (entry 6).



35 - X= Y= C-Cl
36 - X= N; Y= C-H
37 - X= Y= C-H

Scheme 10

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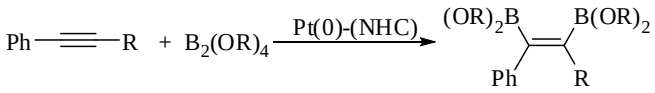
When the significance of the electronic parameters in this process was reinforced, we observed that the less electron rich the diarylalkyne was, the higher the product yield (Table 11, entries 7-9). This is in agreement with Marder's observations.[2c] Remarkably, complex **36** performed a total conversion on diboron product, with the less reactive substrate, phenylacetylene, tolerating even electron-donating and electron-withdrawing moieties in the substrate (Table 11, entries 10-14). Conversions were calculated on the basis of the ^{1}H-NMR. However, to test whether the substrate could be pumped off during the sample preparation, we carried out the same catalytic reaction under d_8-THF, and no changes in the conversion were detected.



27 **28**

Table 11. 1,2-Diboration of alkynes with Pt(0)-(NHC)[a]

Entry	Substrate	Catalytic system	Diboron	*t* (h)	Conv.[b] (%)
1[c]	Ph-C≡C-Ph	**36**	**1**	24	4
2[d]	Ph-C≡C-Ph	**36**	**1**	24	39
3	Ph-C≡C-Ph	**36**	**1**	24	60
4	Ph-C≡C-Ph	**35**	**1**	24	41
5	Ph-C≡C-Ph	**37**	**1**	24	19
6	Ph-C≡C-Ph	**36**	**2**	5	>95
7	(*p* -CF_3-Ph)-C≡C-(p-CF3-Ph)	**36**	**2**	5	>95
8	(*p* -MeO-Ph)-C≡C-(p-CF3-Ph)	**36**	**2**	5	50
9	(*p* -MeO-Ph)-C≡C-Ph	**36**	**2**	5	57
10	Ph-C≡C-H	**36**	**1**	24	3
11	Ph-C≡C-H	**36**	**2**	8	99
12	(*p* -CF_3-Ph)-C≡C-H	**36**	**2**	8	99
13	(*p* -Cl-Ph)-C≡C-H	**36**	**2**	8	99
14	(*p* -MeO-Ph)-C≡C-H	**36**	**2**	8	99

[a] Standard conditions: substrate/diboron/Pt complex = 1/1.5/0.05; THF; room temperature. [b] Conversion calculated by ^{1}H NMR. [c] Solvent: CH_3CN. [d] Solvent: Toluene.

To broaden the scope of the catalytic performance of our Pt(0)-NHC complexes, we went on to study alkenes. Complex **36** was found to be an excellent catalyst precursor that allowed styrene to be diborated at room temperature within 4 hours, with THF as the solvent of choice (Table 12, entries

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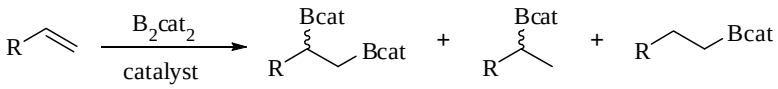
1-5). However, other alkylborane byproducts were observed, probably arising from β-hydride elimination pathways that compete with the diboration catalytic cycle. Electron-poor and electron-rich vinylarenes showed comparable conversions and selectivities in bis(boryl)alkane formation (entries 6 and 7). Extension to aliphatic alkenes was also possible, but greater percentages of byproducts were formed (entries 8 and 9). Thus, Pt(0)-NHC catalyzed diboration improves the B-B addition with $Pt(PPh_3)_4$[37] and $[Pt(PPh_3)_2(\eta^2\text{-}C_2H_4)]$[2a,38] and is an alternative to the more classical base-free platinum[4] and monophosphine platinum complexes,[2c,39] although the latter performed slightly faster.



3 **4** **5**

Table 12. 1,2-Diboration of alkenes with Pt(0)-NHC and 2[a]

Entry	Substrate	Catalytic system	Solvent	Conversion[b] (%)	% **3**[b]
1	Styrene	**35**	THF	88	42
2	Styrene	**36**	THF	97	66
3	Styrene	**37**	THF	94	54
4	Styrene	**36**	Toluene	85	58
5	Styrene	**36**	Acetonitrile	0	-
6	*p*-Fluorostyrene	**36**	THF	91	67
7	Vinylanisole	**36**	THF	85	62
8	Vinylcyclohexane[c]	**36**	THF	100	21
9	3,3-dimethylbutene[c]	**36**	THF	100	11

[a] Standard conditions: substrate/diboron/Pt complex = 1/1.1/0.05; THF; room temperature; *t*= 4h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] Selectivity measured as derived alcohols and diols.

In colaboration with Prof. E. Peris, we tried to induce enantioselectivity by testing the chiral carbene complexes showed in Figure 12 as catalysts precursors in the catalytic diboration reaction of styrene. Unfortunately, no enantiomeric excess was obtained. Surprisingly, the best results in conversions and chemoselectivities were obtained using the more hindered complex **39**

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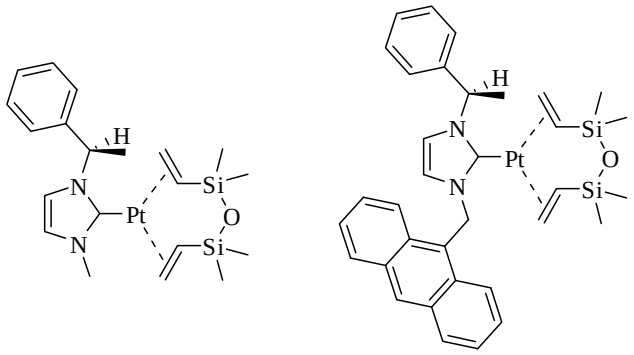
(90% conversion, 73% diboron with **39**, versus 70% conversion, 46% diboron with **38**).



38 **39**

Figure 12

In collaboration with Prof. O. Kappe (University of Graz, Austria), we tried to reduce reaction times and improve reaction economy. We decided to apply the commercially available catalyst $Pt(PPh_3)_4$ in the microwave-assisted alkyne diboration reaction. In a typical experiment of the $Pt(PPh_3)_4$ catalyzed alkyne diboration reaction, the alkyne was added to a *N,N*-dimethylformamide solution of the catalyst precursor (3 mol%) and an equimolar amount of the diboron reagent bis(pinacolato)diboron (**1**). A yield of up to 79% was obtained in the diboration of phenylacetylene and diphenylacetylene, at 80ºC and 120ºC, respectively.[37a]

Moving to sealed vessel controlled microwave reaction, times for the catalytic diboration were substantially reduced. Using acetonitrile as the solvent, we found that clean diboration could be achieved within 20 minutes or less at 120-150ºC using 3 mol% of the platinum catalyst as monitored by HPLC and ^{1}H-NMR analysis (Table 13). Increasing the reaction temperature to 180ºC allowed us to reduce the required reaction time to only 2 minutes (entry 3). It was also possible to reduce the catalyst loading to 1 mol%, but at a expense of a somewhat longer reaction time (entry 1). As it was observed by Miyaura et

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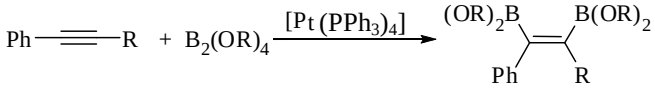
al.,[37a] diphenylacetylene is more reactive than phenylacetylene (entries 2 and 7). In general, it is more difficult to diborate terminal or internal alkynes with electronwithdrawing substituents than with electrondonating ones (compare entries 4, 5 and 6, and entries 8 and 9). Another benefit of applying high-speed sealed vessel microwave technology is that an inert atmosphere and degassed solvents proved to be unnecessary.



27 **28**

Table 13. Microwave-assisted Pt-catalyzed diboration of terminal and internal alkynes.[a]

Entry	Substrate	$Pt(PPh_3)_4$ (mol%)	T (ºC)	*t (min)*
1	phenylacetylene	1	180	10
2	phenylacetylene	3	120	20
3	phenylacetylene	3	180	2
4	(*p*-methoxyphenyl)acetylene	3	120	10
5	(*p*-chlorophenyl)acetylene	3	140	20
6	(*p*-trifluoromethylphenyl)acetylene	3	150	20
7	diphenylacetylene	3	120	15
8	di(*p*-methoxyphenyl)acetylene	3	120	15
9	di(*p*-trifluoromethylphenyl)acetylene	3	140	15
10	1-methoxy-4-(phenylethynyl)benzene	3	120	15
11	1-methoxy-4-(*p*-trifluoromethyl-phenylethynyl)benzene	3	120	20

[a] Standard conditions: 0.25 mmol alkyne, 1.1 equiv. bis(pinacolato)diboron (**1**), acetonitrile (2 mL). Full conversion was confirmed by the dissappearance of the corresponding alkyne signals in the ^{1}H NMR.

2.7. Conclusions.

It has been shown that chemoselectivity in catalytic diboration is sensitive to the nature of the catalyst and to the electronics of the substrate. The utilization of ligands with low bite angles diminishes the β-hydride elimination in the rhodium catalyzed diboration of alkenes, and increases the chemoselectivity towards the 1,2-bis(boronate)esters. Asymetry induced by both ligands BINAP and QUINAP provided the same (R)-enantiomer.

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However, the double asymmetric induction using chiral diboron reagents and Rh/(S)-QUINAP favoured the (S)-enantiomer. The scope of the Rh-mediated diboration reaction involved aryl and alyphatic alkenes.

We performed the first study of diboration reaction catalyzed by transition metal complexes modified with N-heterocyclic carbene ligands (NHC). An increased catalytic activity was observed for Pt and group 11 metals. Internal and terminal alkenes were diborated with coinage metal NHC complexes, leading to 1,2-bis(boronate)esters as single intermediates, but without asymetric induction, except for the copper mediated B-B addition. The Ag(I)-NHC catalytic system represented the first attempt in the literature to diborate unsaturated substrates.

An excess of diboron in presence of NaOAc for the Au(I)-BINAP catalyzed diboration of alkenes provided the first complete conversion and selectivity towards the desired product at room temperature. An alternative mechanistic pathway has been postulated where a base mediated heterolytic cleavage of the diboron can generate metal-boryl species that eventually insert the alkene and transmetallate with the diboron reagent.

In addition, DFT calculations suggested that the Cu-NHC complexes do not include the oxidative addition of the diboron reagents, but heterolytic diboron cleavage as the first mechanistic pathway. In that case, all the metal species involved in the catalytic cycle could remain as Cu(I) complexes.

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Chapter 3

Mechanistic insights

***Chapter 3*. Mechanistic insights**

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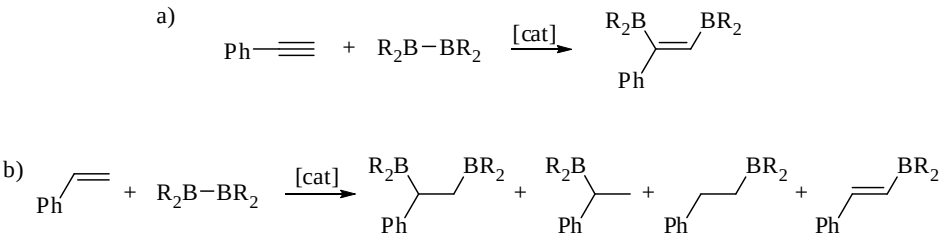
3.1. Introduction

The catalytic diboration of alkynes provides the *syn* addition of the B-B bond to generate the 1,2-alkene(bisboronate)esters by a well established protocol mainly based on platinum-containing catalysts.[1] However, the related alkene diboration seems to be more complex, because a mixture of products is commonly observed when alkenes and diborons react in the presence of the appropprate transition metal catalyst (Scheme 1).[2]



Scheme 1. Metal-catalyzed addition of boranes to unsaturated C-C bonds. a) phenylacetylene diboration; b) styrene diboration, showing the different products that can be formed

The most widely studied catalytic systems for the alkene diboration are based on rhodium precursors. The problem with this sort of catalysts are the side reactions produced due to the competitive β-hydride elimination. Very few examples of high chemoselectivity towards the diboron product have been reported so far: the ones that have involved phosphine-free Pt-catalyst precursors,[3] phosphine-gold complexes,[4] and the zwitterionic rhodium complex [Rh(DPPM)(η-catBcat)] prepared in situ,[5] in addition to the M-(NHC) complexes reported here, and a new strategy that uses the influence of a base on the palladium-[6] and gold-catalyzed diboration reaction.

The most accepted mechanism for the alkene diboration reaction is thought to occur through a catalytic cycle that involves oxidative addition of the diboron reagent to the metal, followed by the insertion of the alkene, and the

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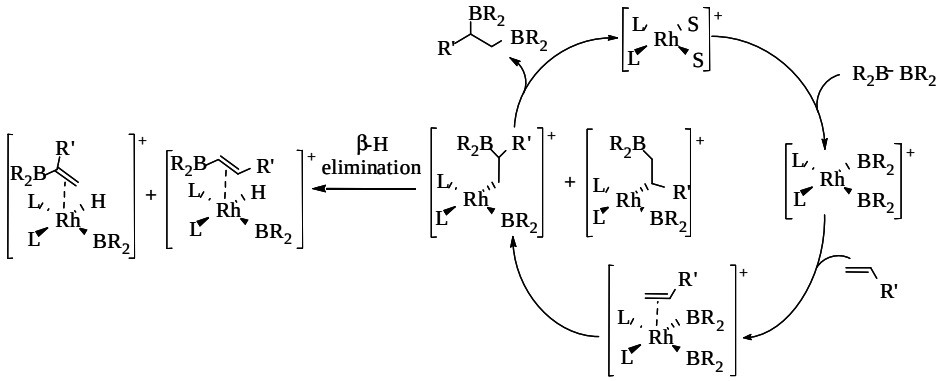
reductive elimination of the organodiboron product. Significant reaction side products are often observed, due to β-hydride elimination of the interemediate organometallic complex (Scheme 2).[4,5,7]



Scheme 2. Proposed mechanism for the alkene catalyzed diboration reaction

For the rhodium-catalyzed diboration reaction, the oxidative addition of the diboron reagent to the metallic center has been demonstrated experimentally in some cases, in which diboron reagents are oxidatively added to rhodium (I) centers.[8] Single crystals of the rhodium (III) diboryl species were isolated and characterized by X-ray crystallography,[8c] showing a five-coordinate rhodium center in a distorted square-based pyramidal environment with one of the boryl groups occupying the apical site, and the other one in a basal site. The acute B-Rh-B angle results in a long B-B separation, so any residual B-B interaction is necessarily very weak. Moreover, the relative orientation of the two boryl ligands is close to orthogonal.

Nevertheless, the theoretical calculations mentioned in chapter 2 on the copper-catalyzed diboration reaction have justified the absence of the oxidative addition of the borane reagent and the presence of σ-borane adducts instead, therefore suggesting a transmetallation step in the diboration mechanism. This was also supported by the observation of Miyaura et al.,[9] in which a copper

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boryl species was generated in situ from bis(pinacolato)diboron (**1**) and copper acetate. Recently, the insertion of an alkene into a Cu-B bond in copper (I) boryl complexes was studied by means of DFT calculations and was demonstrated in stoichiometric studies by Lin et al.[10]

Although other more chemoselective catalytic systems have been discovered, the importance of the rhodium catalytic systems is that they are the only systems that can induce asymmetry.[2,11] In an attempt to further our knowledge of the mechanism for the rhodium-catalyzed diboration reaction, we took advantage of our experience in the study of this reaction to characterize the catalytic cycle for the rhodium-catalyzed diboration reaction of alkenes through a combination of NMR spectroscopy and DFT based calculations. Moreover, the origin of the chemoselectivity towards mono- or diborated products in the presence of different chelating ligands (QUINAP or BINAP) is discussed.

3.2. NMR study

In a typical rhodium-catalyzed styrene diboration experiment, with [Rh(acac)(NBD)] as catalyst precursor and (S)-QUINAP as ligand, styrene is 90% converted, but the selectivity towards the desired diboron product is only 76%, due to the intrinsic competitive β-hydride elimination that provides alkyl- and alkenylboronate esters. When (S)-BINAP was used as ligand, the chemoselectivity towards the β-hydride elimination products was increased, and only 21% of the diboron product was obtained. The use of such different Rh(I) precursors as $[Rh(COD)_2]BF_4$ and $[Rh(\mu\text{-}Cl)(NBD)]_2$ does not result in a dramatic change in chemoselectivity.

We performed an NMR spectroscopic study of the addition of bis(catecholato)diboron (**2**) and styrene to the precursor of catalyst $[Rh(COD)(L\text{-}L)]BF_4$, where L-L= (S)-BINAP or (S)-QUINAP. The five-coordinate system was more informative for L-L=(S)-BINAP due to the

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coupling of the P atoms, which do not appear when (S)-QUINAP is used as ligand. It provides important information about the symmetry of the complex obtained. As can be observed in Figure 1, two new sets of double doublets appeared in the ^{31}P NMR when **2** was added to a solution of [Rh(COD){(S)-BINAP}]BF_4 and styrene in CD_3CN. On the strength of these new signals, we suggest that there are two non-equivalent phosphorous nuclei in the complex formed. The non-equivalence of the phosphorous nuclei could be due to the fact that while one P is *trans* to a catecholboryl unit, the other is *trans* to the 1-alkene (Figure 1). The other catecholboryl unit is in the apical position of the square based pyramid. The initial doublet centered at δ 45.8 ppm ($J_{P\text{-}Rh}$= 174.5 Hz) corresponding to [Rh(COD){(S)-BINAP}]BF_4 shifted to two new double doublets centered at δ 38.5 ppm and δ 47.3 ppm ($J_{P\text{-}Rh}$= 124.5 Hz, $J_{P\text{-}P}$= 32.9 Hz) for [Rh(sty){(S)-BINAP}$(Bcat)_2$]BF_4.

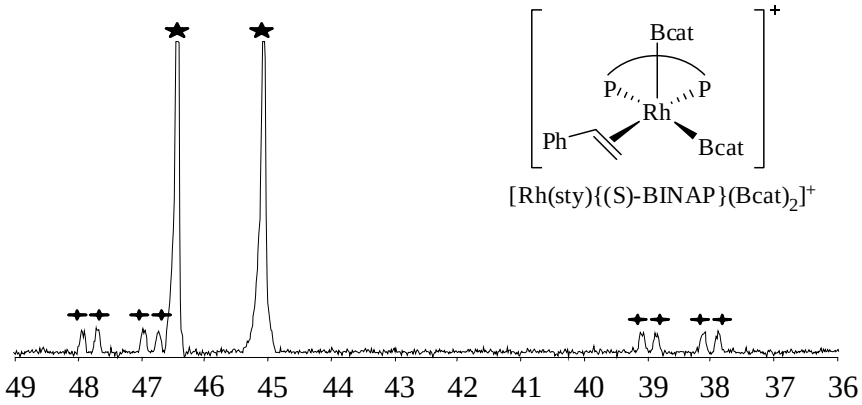

Figure 1. ^{31}P NMR spectrum: ☆ [Rh(COD){(S)-BINAP}]BF_4; ✦ [Rh(sty){(S)-BINAP}$(Bcat)_2$]BF_4

These results are in agreement with those of Marder et al.,[8c] who isolated some single crystals resulting from the oxidative addition of **2** to the rhodium (I) complex [$RhCl(PPh)_3$], to obtain the neutral complex [$RhCl(Bcat)_2(PPh_3)_2$]. One of the catecholboryl was units in the apical site and the other was in a basal site of a square based pyramid, *trans* to the chloride. The two phosphine units were

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in a *trans* position. Therefore, the new NMR results presented here suggest that the same conformation of the catecholboryl units is obtained in solution when a chelating diphosphine is used.

3.3. Theoretical study

On the basis of the NMR results showed above, [Rh(sty){(S)-BINAP}$(Bcat)_2$]BF_4 will be considered as the starting point for the study of other plausible intermediates participating in the rhodium-catalyzed diboration reaction mechanism. As our group did in related previous studies,[12] we first made a systematic investigation into the structure of all possible isomers. In general, the stability of the penta-coordinate intermediates involved in the catalytic cycle is largely determined by the distribution of the ligands around the metal atom, but fine tuned by the steric interactions between ligands and between the alkene substituents and the catalyst.

In this first stage, to reduce the computational cost, we chose ethene as a model for the alkene, and following the study of Cundary et al.,[13] $B_2(O_2C_2H_2)_2$ as a model for bis(catecholato)diboron (**2**). The models used for the ligands (S)-QUINAP and (S)-BINAP are represented in Figure 2. Below, we present the results obtained using a DFT based method in the various steps of the mechanism of the rhodium-catalyzed diboration reaction, namely oxidative addition, alkene insertion and reductive elimination.

3.3.1. Oxidative addition

As mentioned above (Scheme 2), the first step in the reaction mechanism is the oxidative addition of the diboron to the metal center. Taking into account recent theoretical studies on the related metal catalyzed diboration reaction using Cu-(NHC) (Chapter 2) and Pd-(NHC) [6] catalyst precursors, we start by

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proposing two different initial geometries in which the diboron unit is coordinated to the metal center through a sigma interaction, either with the alkene *trans* to the N-atom of (S)-QUINAP (**1n**), or with the alkene *trans* to the P-atom of (S)-QUINAP (**1p**) (see Scheme 3). The latter (**1p**) is 8.0 kcal/mol more stable than **1n**. In both complexes, the B-B bond coordinates in a sigma fashion while the B atoms acquire a non-negligible degree of pyramidalization. Indeed, unlike the sigma adduct reported for [Cu(NHC)(B_2cat_2)], the angle formed by the two Bcat rings is 104.2º for **1n** and 88.1º for **1p**. When the two Bcat rings are bent, a distorted B-B σ^* orbital becomes the LUMO of the diboron moiety, which is the empty orbital best suited to receiving the metal back donation. In **1n**, the B-B bond distance is 0.2 Å longer than in the free $B_2(O_2C_2H_2)_2$ species, a clear manifestation of the charge transfer from the metal to the antibonding B-B orbital. Meanwhile, B-B bond distance in **1p** is almost 0.4 Å longer than that in the free diboron species. Both the angle formed by the two Bcat rings and the B-B bond distance, indicate that the diboron is more activated in **1p** than in **1n**.

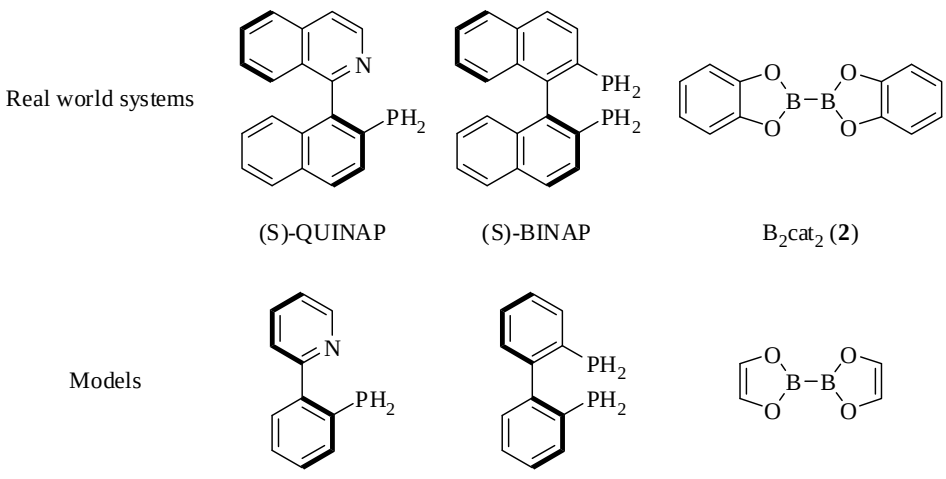

Figure 2. Models for the ligands and for the diboron used in the DFT study

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In the oxidative addition product, the two boryl units adopted a mutually perpendicular relative orientation, as was found by X-ray crystallography in some rhodium (III) diboryl species.[8] Therefore, a search was made for all possible rhodium (III) diboryl species considering **1p** and **1n** diboryl as starting points. In path *n*, two different structures for the oxidative addition product were found (Scheme 3): **2na**, in which the alkene is oriented perpendicular to the plane of the square based pyramid, the apical boryl unit is oriented towards the alkene, and the basal boryl unit is parallel to the plane of the pyramid, and the B-B distance is 2.798 Å, 0.91 Å longer than in the sigma complex; and **2nb**, in which the alkene is parallel to the plane of the square-based pyramid, the basal boryl unit is perpendicular to this plane and oriented towards the alkene, the apical boryl unit is perpendicular to the basal boryl unit, and the B-B distance is 2.878 Å, almost 1 Å longer than in the sigma complex. Note that while **2nb** is almost isoenergetic to **1n**, **2na** is 5.4 kcal.mol^{-1} less stable than the sigma adduct. In spite of several attempts, only one transition state structure was located, namely **ts1-2nb**, in which the B-B bond is 2.184 Å, 0.3 Å longer than in the sigma complex. In this case, the energy barrier for the oxidative addition is calculated to be quite low, only 2.5 kcal.mol^{-1}.

In path *p*, only one structure was found for the oxidative addition product, **2pb**, in which the alkene is parallel to the plane of the square based pyramid, the basal boryl unit is not perfectly perpendicular to the basal plane while the apical boryl unit is perpendicular to the alkene. The B-B distance is 2.604 Å, 0.53 Å longer than in the sigma complex. The other possible structure, **2pa**, was found to be unstable and reverted to the sigma complex during the optimization process. The energy surface is so flat that no transition state structures could be located in this path. Species with two boryl units in the basal plane were not considered because they are not compatible with the NMR results obtained above or with the crystallographic data reported.[8]

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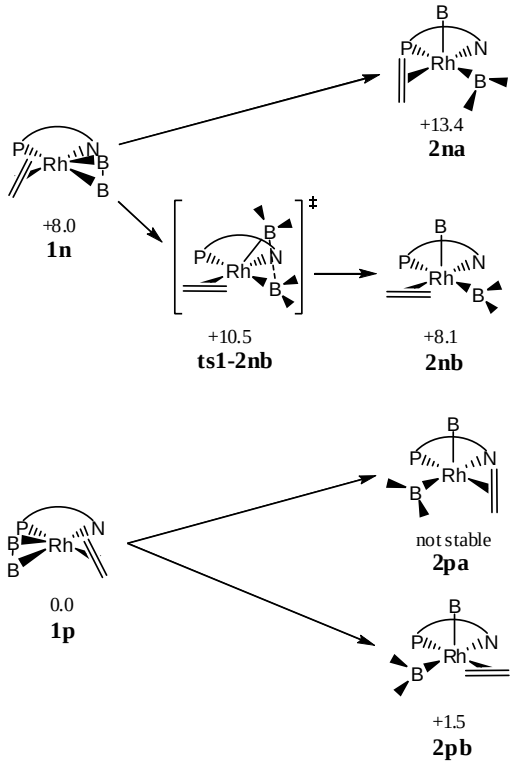
The oxidative addition of the diborane has been found to be only slightly endothermic compared to the Cu-catalyzed diboration reaction, in which the energy difference between the sigma adduct and the oxidative addition product is about 60 kcal.mol^{-1}, and the Pd-catalyzed diboration reaction, in which the difference is 9.6 kcal.mol^{-1}.[6]



Scheme 3. Oxidative addition. Relative energies in kcal.mol^{-1}

Taking these results into account it is very likely that the signals obtained in the NMR experiments correspond to the sigma complex, which is more stable than the oxidative addition product. Since the experiment was recorded using (S)-BINAP, the relative stability of the sigma complex and the oxidative addition product was calculated using a model of the (S)-BINAP (Figure 2). The corresponding sigma complex turned out to be 0.2 kcal.mol^{-1} more stable

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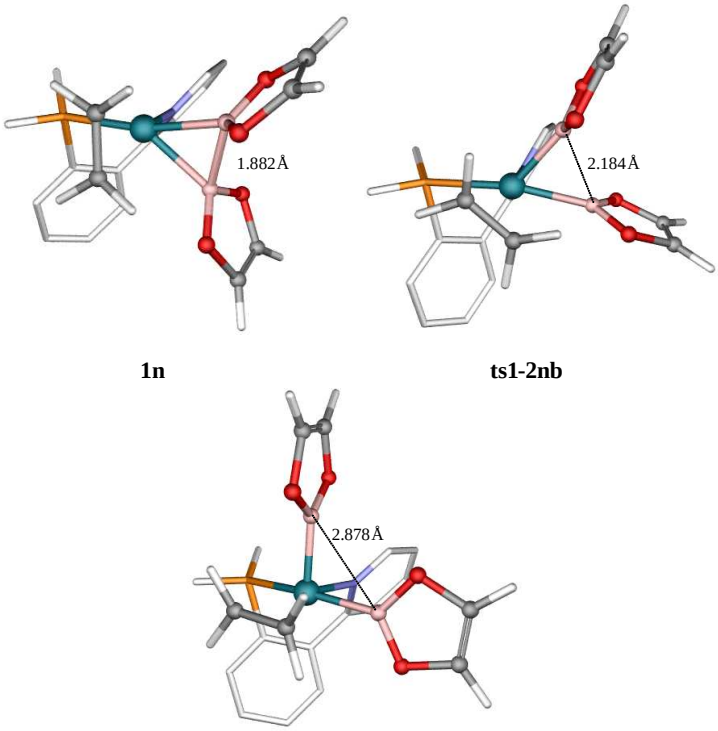
than the corresponding oxidative addition product. Note that introducing the electronic effects of real world phosphine ligands causes a relative stabilization of the highest oxidation states such as Rh(III).[14] In any case, the two species are compatible with the ^{31}P NMR signals obtained, and due to the low barriers, a quick equilibrium between the two species can be expected.



1n **ts1-2nb** **2nb**

Figure 3. Selected structures

3.3.2. Alkene insertion

The next step in the catalytic cycle is the insertion of the alkene into the Rh-B bond. Four different mechanisms of insertion can be defined depending on the nature of the four different intermediates (**2na**, **2nb**, **2pa** and **2pb**), namely the apical insertion when the alkene binds the apical boryl (**2na**, **2pa**), and the basal insertion when the reaction takes place on the basal plane of the

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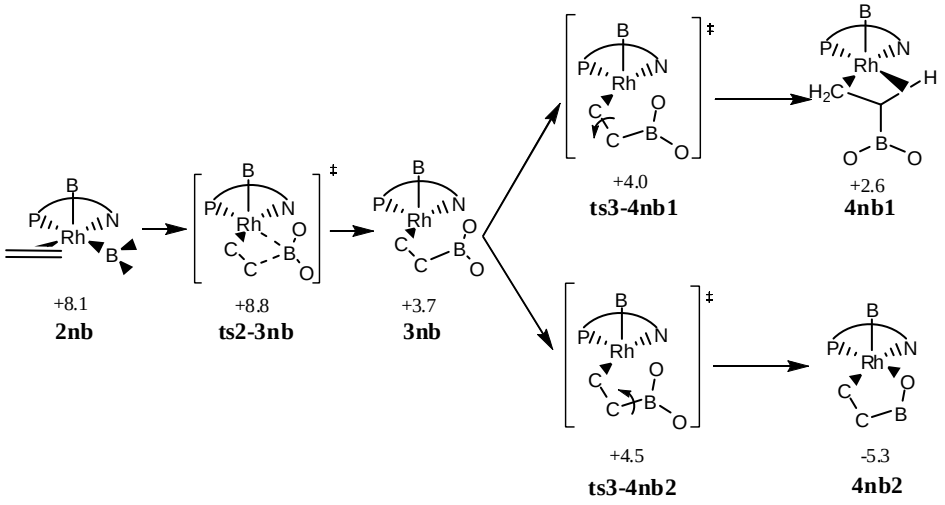
square-based pyramid (**2nb**, **2pb**). The insertion that started from **2na** was not studied, because of the high energy of the initial intermediate. The other three possible insertions were studied. The one starting from **2nb** was the most stable product, **3nb** in Scheme 4. After the insertion has taken place, and in order to occupy the vacancy generated in the coordination sphere of the metal center, a rearrangement must take place. Scheme 4 schematically shows the structures and energies obtained for path *nb*. As can be observed, the transition state **ts2-3nb** involves a four-membered ring formed by the metal, the alkene and the basal boryl unit. In this transition state, the C-B distance has been reduced by about 0.35 Å, the C-C bond is 0.03 Å longer and the Rh-B bond is 0.035 Å longer than in **2nb**. The energy barrier is extremely low, and was calculated to be 0.7 kcal.mol^{-1}.



Scheme 4. Alkene insertion and rearrangement for path *nb*. Relative energies in kcal.mol^{-1}

The product of this step (i. e., the alkene insertion product **3nb**) presents a vacancy in the metal coordination sphere *cis* to the newly formed Rh-C bond. In this case, the C-B, C-C and Rh-B distances are 0.8 Å shorter (1.61 Å), 0.12 Å longer (1.533 Å) and 0.52 Å longer (2.59 Å) than in **2nb**, respectively. It is

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important to note that while in **2nb** the dihedral Rh-C-C-B is near to 0º, in **3nb** the same dihedral is near -36º, because the basal boryl unit is displaced out of the plane of the square-based pyramid. In order to occupy the vacancy created in the metal coordination sphere, two different internal rearrangements are possible, the only difference being the bond that rotates. If the C-C single bond rotates, an agostic interaction between the Rh and the C-H bond is formed, leading to **4nb1**, where the dihedral Rh-C-C-B is about 120º, and the C-H bond involved in the agostic interaction is 1.172 Å, 0.07 Å longer than in **3nb**. For this rotation, a transition state was characterized (**ts3-4nb1**), which has a very low energy barrier (only 0.3 kcal.mol^{-1}).

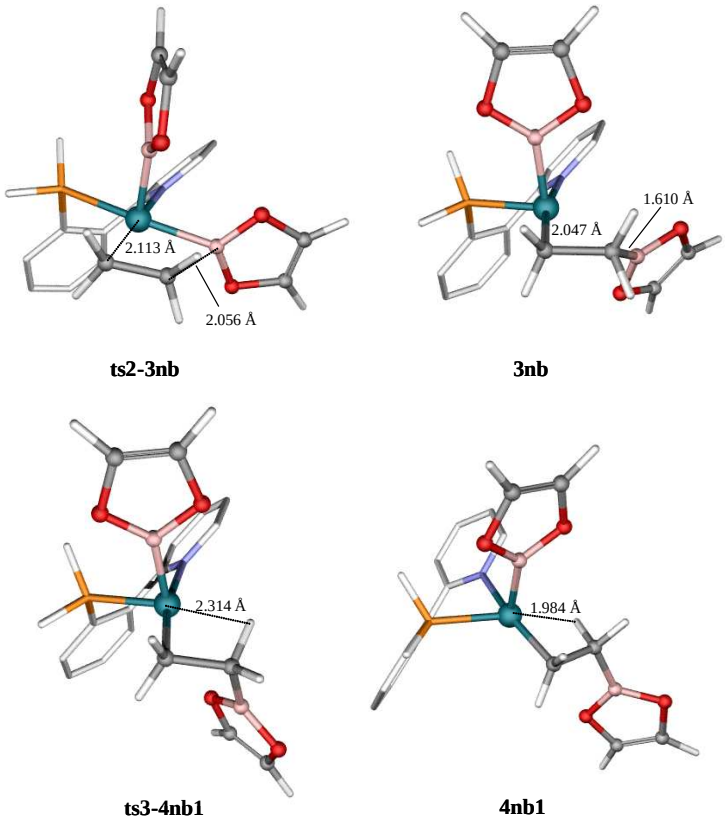

Figure 4. Selected structures

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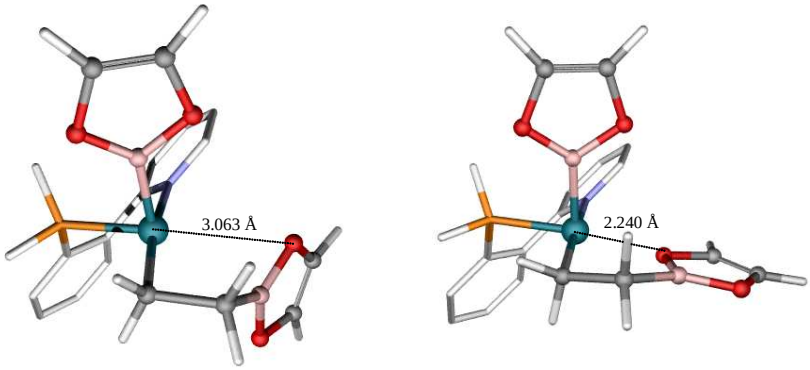
The second possible rearrangement involves the rotation of the C-B bond, which gives rise to an interaction between one oxygen atom of the boryl unit and the rhodium. This evolves towards the stable complex **4nb2**, in which the dihedral Rh-C-C-B is about 30º, and the distance between the rhodium and the oxygen involved in the interaction is 2.24 Å. In this case, the C-C bond leaves the plane of the square based pyramid. The transition state for this rotation was also characterized (**ts3-4nb2**), and the rotation energy calculated to be also very low (0.8 kcal.mol^{-1}). Note that the energy of the intermediate **2na** is even higher than the transition structures involved in the path *nb*. Therefore, and based on the intrinsic low stability of **2na**, the alkene insertion into the apical boryl starting from **2na** is improbable.



ts3-4nb2 **4nb2**

Figure 5. Selected structures

As far as path *p* is concerned (Scheme 5), we found only the transition state for the insertion of the alkene into the Rh-B bond corresponding to path *pa*, **ts2-3pa**, because there were enormous difficulties in determinining stable geometries that evolved directly to products during the optimization processes. The structure of **ts2-3pa** is more similar to a trigonal bipyramid than to a square-based pyramid, with the alkene, the apical borane and the phosphorous in the equatorial plane. In this structure, the C-B, C-C and Rh-B distances are

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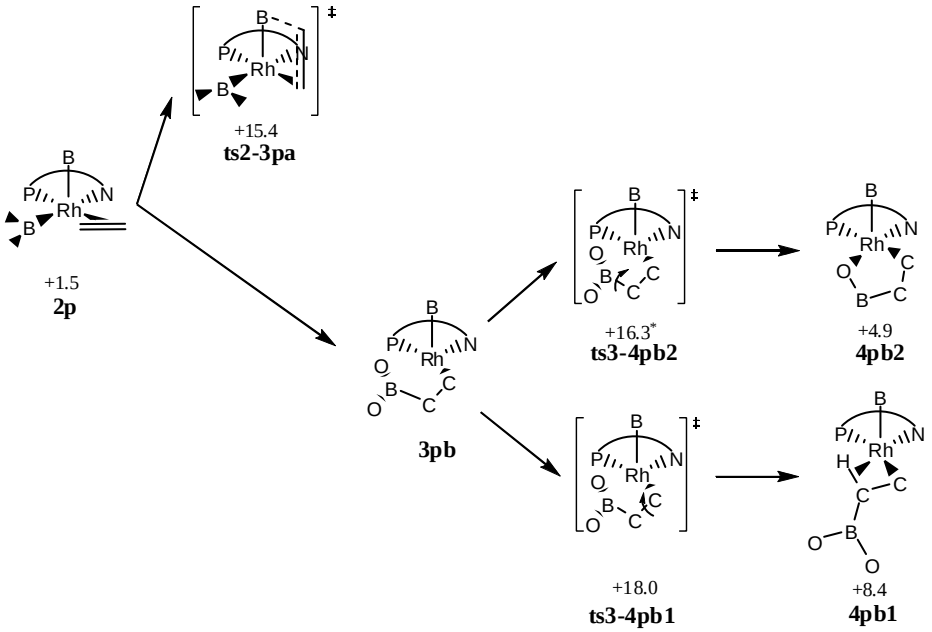
0.57 Å shorter (2.027 Å), 0.05 Å longer (1.444 Å) and 0.01 Å shorter (2.053 Å) than in **2p**, respectively. The energy barrier corresponding to this apical mechanism is calculated to be 13.9 kcal.mol^{-1}. Because of the high energy of this reaction path and the difficulties of finding stable geometries for the subsequent intermediates, it was rejected.



Scheme 5. Alkene insertion and rearrangement for path *p*. Relative energies in kcal.mol^{-1}. * Estimated energy

With regard to path *pb*, no transition state was found either for the alkene insertion or for the C-B bond rotation, even when different strategies where used in the transition state search. A relaxed scan of a distinguished coordinate, namely the C-B distance, allowed us to estimate the overall barrier (14.8 kcal.mol^{-1}) for the combined process C-B formation and C-B rotation (Figure 6). The process leads to **4pb2**, corresponding to the molecular structure in which the vacancy in the coordination sphere of the metal center has been

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occupied by one oxygen atom of the boryl group. In this case, and in contrast to **4nb2**, the alkene insertion-reorganization process is endothermic. The dihedral Rh-C-C-B, which is close to 0º in **2pb**, is about 25º. The boryl unit remains in the plane and the C-C bond leaves the plane of the square-based pyramid, as it does in **4nb2**. In this complex, the C-C bond is 0.15 Å longer (1.545 Å) and the C-B distance is over 1 Å shorter (1.56 Å) than in **2pb**.

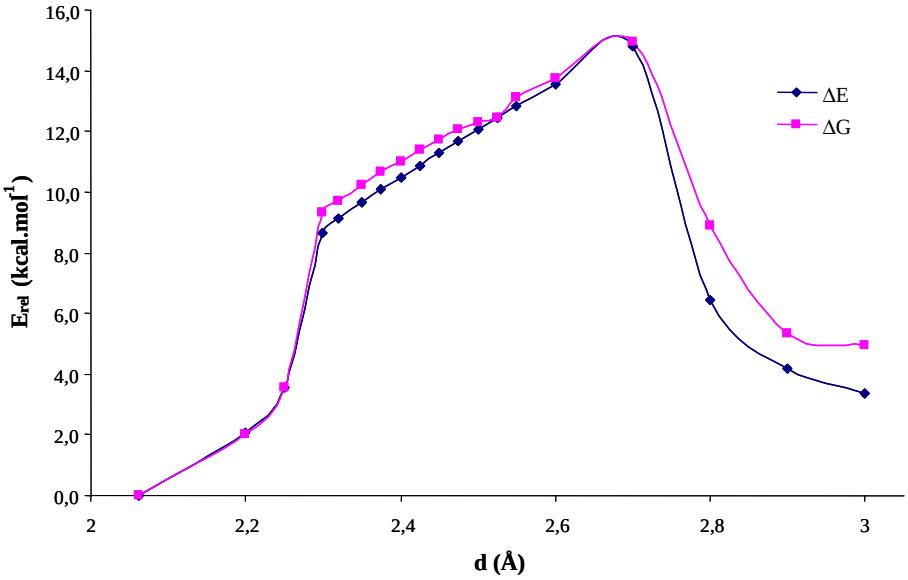

Figure 6. Relaxed scan of C-B distance for path *pb*

The only transition state that we were able to characterize for the insertion-rearrangement process was **ts3-4pb1**, corresponding to the rotation of boryl around the C-C bond. In this case, the rotation barrier was calculated to be quite high, 16.5 kcal.mol^{-1} above **2pb**, leading to **4pb1**, in which the vacancy generated during the alkene insertion is already occupied by an agostic interaction between the rhodium and a C-H bond of the hydrocarbon. Note that this process is quite endothermic. In this case, the dihedral Rh-C-C-B is over 112º. The C-H bond involved in the agostic interaction is 0.18 Å longer (1.281 Å), the C-C bond is 0.09 Å longer (1.479 Å), and the C-B distance is about 1 Å

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shorter (1.58 Å) than in **2pb**. Therefore, at this point it can be concluded that the basal insertion is more favored than the apical in all cases, and leads to lower activation barriers, probably due to the energetic cost needed to rotate the alkene 90º. So, for this process we need to have the alkene in the plane rather than perperdincular to it. For more substituted systems or bulky ligands, steric effects can force the alkene coordinate in the plane and not perpendicular, as it has been recently shown by Galindo et al.[15]

3.3.3. Reductive elimination versus β-hydride elimination

The final step in the rhodium catalyzed diboration reaction is thought to be the reductive elimination of the diborated alkane by the formation of the second C-B bond. In path *n* (Scheme 6) we found two transition states for the reductive elimination, **ts4-6nb1** and **ts4-6nb2**, corresponding to the intermediates found previously, **4nb1** and **4nb2**. Their energy barriers were very similar and calculated to be 4 and 4.1 kcal.mol^{-1}, respectively. Interestingly, we also located the transition state for the β-hydride elimination reaction (**ts4-5nb1**) when starting from the complex **4nb1**. In the transition state, the C-H bond is 0.5 Å longer (1.676 Å) than in **4nb1**. The β-hydride elimination barrier is calculated to be 8.4 kcal.mol^{-1}. This process generates a hydride-boryl-rhodium (III) species **5nb1**, which is the key intermediate in the hydroboration reaction of vinyl arenes.[12,16] Hence, this species is the origin of the hydroborated side products obtained in the rhodium catalyzed alkene diboration reaction.

Analogously to path *nb*, in path *pb* (Scheme 7), we also found two transition states for the reductive elimination, **ts4-6pb1** and **ts4-6pb2**, with higher energy barriers that were calculated to be +7.8 and +13.3 kcal.mol^{-1}, respectively. Moreover, the transition state that leads to the β-hydride elimination product (**ts4-5pb1**) and the rhodium hydride (**5pb1**) were also

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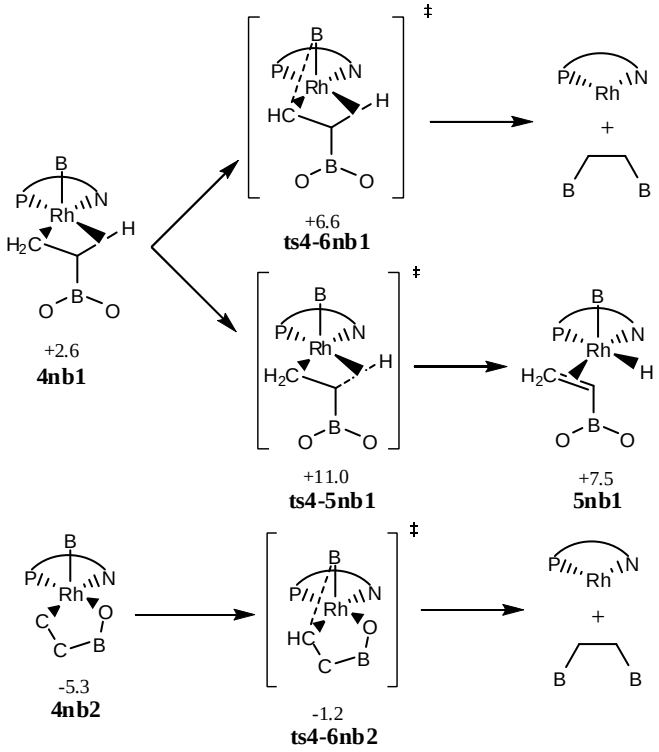
found. In this case, the β-hydride elimination barrier is calculated to be only 0.6 kcal.mol^{-1}. The C-H bond involved in the agostic interaction is 0.15 Å longer in the transition state than in **4pb1**.



Scheme 6. Reductive elimination and β-hydride elimination for path *n*. Relative energies in kcal.mol^{-1}

Taking into account these results, in path *nb* the reductive elimination is more favored than the β-hydride elimination, as in the experimental results. Contrary, for path *pb*, the β-hydride elimination is energetically lower than the corresponding path for the formation of the diborated alkane, which, unlike experimental observations, would favour the hydroboration side reaction. Thus, two different paths starting from completely different starting structures give different compounds, diborated or monoborated products. This clearly indicate that the path *nb* is more likely to be operative.

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Jesús Ramírez Artero
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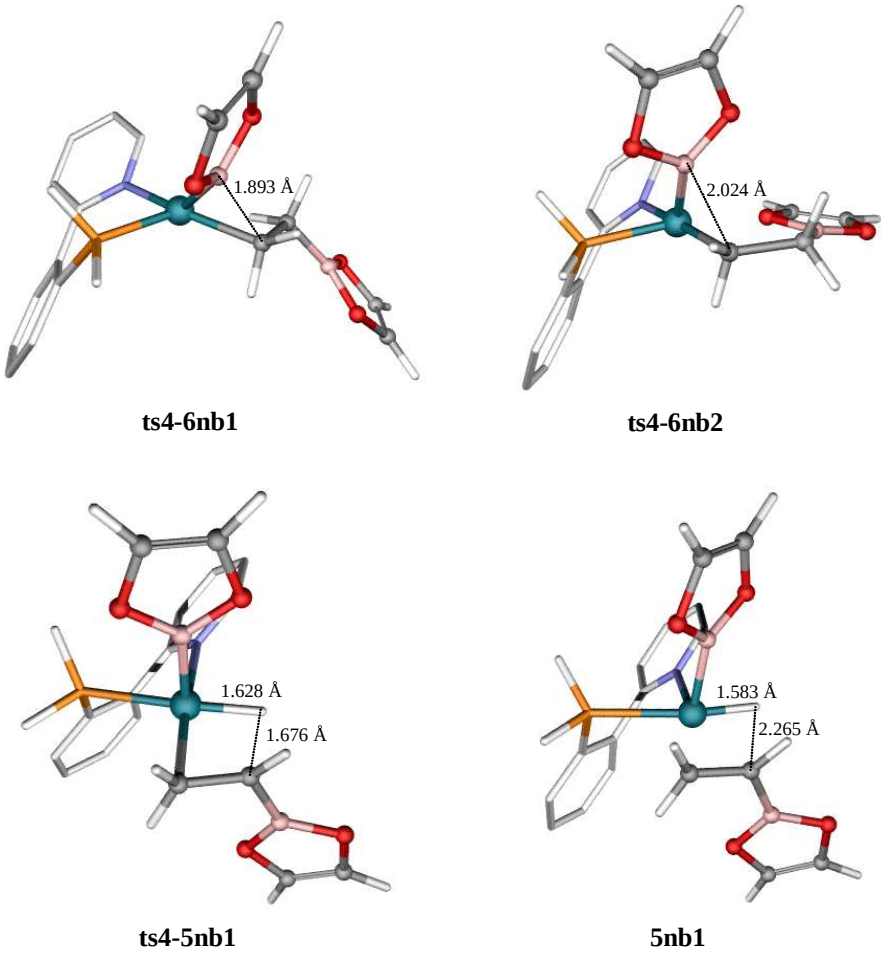

ts4-6nb1 **ts4-6nb2**

ts4-5nb1 **5nb1**

Figure 7. Selected structures

Finally, we studied the reductive elimination and β-hydride elimination steps with a model of (S)-BINAP ligand. As we mentioned above, when BINAP is used as ligand in the rhodium catalyzed diboration reaction, the chemoselectivity towards the β-hydride elimination products is increased, diminishing the quantity of diboron product (only 21%). For the diphosphine BINAP ligand, both the paths *nb* and *np* can be considered equivalent.

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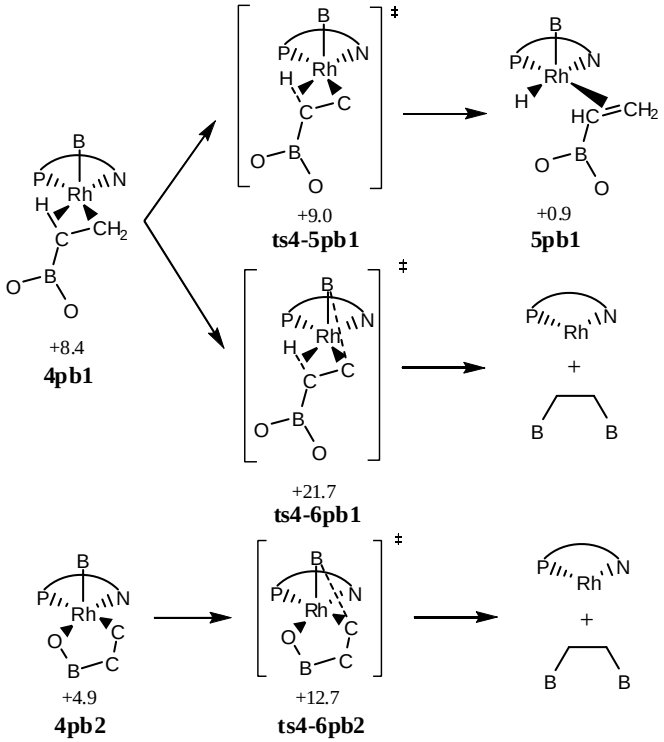

Scheme 7. Reductive elimination and β-hidride elimination for path *p*. Relative energies in kcal.mol^{-1}

We carachterized the structures of the two key intermediates, **4binap1** and **4binap2**, which are the result of alkene insertion and subsequent reorganization, as shown in Scheme 8. In the same way as we found for QUINAP, **4binap1** can undergo either reductive elimination or β-hydride elimination, while **4binap2** produces only diborated products. Thus, three transition state structures were charachterized as well. Intermediate **4binap2** is the most stable, but here the difference between both intermediates (5.2 kcal.mol^{-1}) is smaller than the difference between **4nb1** and **4nb2** in QUINAP (7.9 kcal.mol^{-1}). Nevertheless, and as the values included in Scheme 8 indicate, the relative stability of the three distinct **ts4** transition states differs substantially of the order that we obtained for QUINAP. The key transition state for

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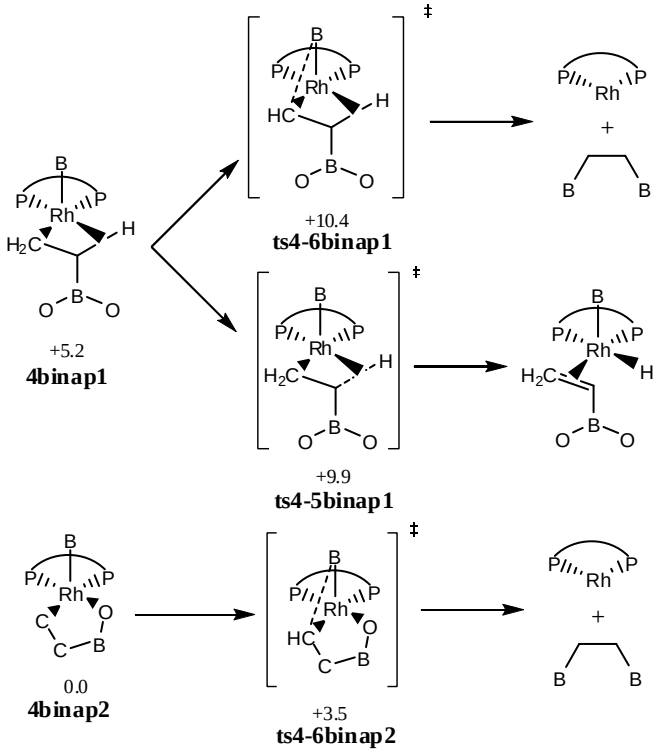
determining selectivity, **ts4-5binap1**, is now more stable than what **ts4-5nb1** was in QUINAP. Clearly, β-hydride elimination is more competitive in the case of BINAP than with QUINAP. A pure electronic effect induced by the ligand is driving the reaction towards hydroborated products. These results fully agrees with experimental.



Scheme 8. Reductive elimination and β-hydride elimination using (S)-BINAP as ligand. Relative energies in kcal.mol^{-1}

3.3.4. Overall mechanism

Collecting all the results obtained above, we can draw an overall picture of the reaction mechanism. Despite the sigma complex **1p** is 8.0 kcal.mol^{-1} more stable than sigma complex **1n**, the path *p* (alkene trans to the P atom)

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exhibits species that lies at higher energies. These are the transition states for boryl rearrangement through basal alkene insertion path *pb* (**ts3-4pb2** and **ts3-4pb1**) and the transition state for alkene insertion into apical boryl (**ts2-3pa**, path *pa*). Moreover, for path *p*, the lowest energy transition state leading to diborated product (**ts4-6pb2**) is 3.7 kcal.mol^{-1} higher than the transition state for β-hydride elimination (**ts4-5pb1**). This is unlike the chemoselectivity observed for Rh-QUINAP catalysts, for which the diborated species are the major product. Thus, our results indicate that a reaction mechanism occurring through path *p* is less favoured than through path *nb*. However, the energy differences between the two paths are rather small, and therefore small changes could invert their relative energetic preference. The reaction energy profile for path *nb* is schematically represented in Figure 8, where all energies are referred to the intermediate **1p**. The barriers for all the steps are quite low, being the transition state for the oxidative addition of the diborane (**ts1-2nb**) the highest energy species. After this first step occurs, the energy barriers for alkene insertion-rearrangement that we obtained are very small, thus these processes takes place quite fast. The least energetically demanding process proceeds via intermediate **4nb1** and it produces the diborated alkane irreversibly. The intermediate **4nb2** is also accessible from **3nb**, being the reaction barrier only 0.5 kcal.mol^{-1} higher than that yielding to **4nb1**. In both cases, the reductive elimination barriers to obtain the diborated alkane are low 4.0 and 3.9 kcal.mol^{-1} from **4nb1** and **4nb2**, respectively. From **4nb1** there is a competitive process, which lead to β-hydride elimination products, although in minor amounts. This result is in complete agreement with experimental findings. Nevertheless, we should bear in mind that the present study is based on model systems and that additional effects introduced by the ligand and the substrates could modify this energy profile. Note that subtle changes may promote the reaction towards path *pb*, where β-hydride elimination products are mainly obtained. In the case of (S)-BINAP, the

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transition state that leads to β-hydride elimination experiences a strong stabilization, making this process more competitive than in the case of (S)-QUINAP. Again this is consistent with our experimental observations.

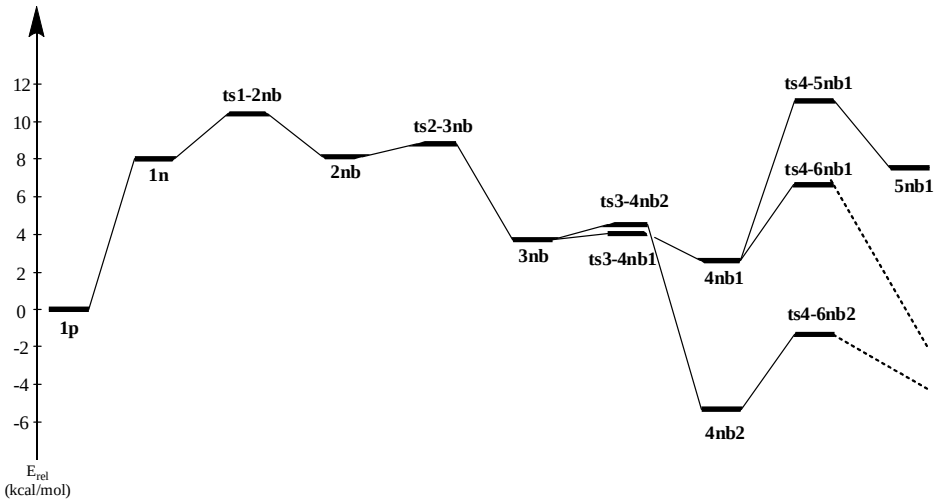

Figure 8. Potential energy profile for path nb

3.4. Conclusions

By using NMR spectroscopy, a cationic intermediate involved in the rhodium-catalyzed diboration of alkenes has been characterized for the first time. Its structure, suggested by NMR, has been fully characterized by means of DFT-based calculations. Moreover, the computational study enabled to propose a preferred reaction path for the reaction.

Path *nb* (alkene *trans* to the N-atom of (S)-QUINAP; insertion in the basal plane) is found to be more favourable than the other possible paths and proceeds via the following steps: (a) coordination of the diborane to the rhodium complex through a sigma interaction; (b) oxidative addition of the B-B bond to the metal center; (c) insertion of the alkene into a Rh-B bond; (d)

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rearrangement to occupy the vacancy created; (e) reductive elimination of the product.

The higher chemoselectivity towards diborated products obtained when (S)-QUINAP is used in comparision with BINAP, can now be explained in a rational way. Two intermediates are observed in which either a B–O or a C–H bond is used to stabilize the empty coordination site on Rh. In the latter case, the species with the agostic interaction can evolve either into a diborated product or to a rhodium hydride species, which then leads to hydroborated products. The relative energetics of these processes are then responsible for the observation of the two pathways.

When a BINAP analog was considered, both the agostic-stabilized intermediate and the β-hydride elimination transition state are of lower energy when compared with the QUINAP model. Consequently, the β-hydride elimination and generation of hydroboration products becomes more competitive, leading to more side products. This is in direct agreement with experimental observations where a lower chemoselectivity is obtained with BINAP as compared to QUINAP.

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Chapter 4

Functionalization of organodiboron compounds

***Chapter 4*. Functionalization of organodiboron compounds**

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4.1. Introduction

Organoboron compounds are considered to be useful intermediates in organic synthesis.[1] One interesting transformation of the *cis*-1,2-bis(boryl)alkenes involves the palladium-catalyzed cross-coupling reaction with aryl, alkenyl, benzyl and allyl halides to allow di- and monosubstitution to occur selectively influenced by the nature of the base.[2] However, to the best of our knowledge, no other reaction has been described that can transform the boryl units in the *cis*-1,2-bis(boryl)alkenes into interesting functional groups, such as fluorines. In view of the unique features of fluorine-containing compounds,[3] interest in novel and practical synthetic methods for preparing fluorinated molecules has been increasing.[4]

One approach that rapidly became one of the most important is electrophilic fluorination. In this approach, fluorine acts as an electrophile (F^+) rather than as a nucleophile (F^-) or a radical ($F^{\cdot}$). A variety of electrophilic fluorinating reagents have been developed over the last 50 years: for example, perchloryl fluoride ($FClO_3$),[5] xenon difluoride (XeF_2),[6] fluoroxy compounds (such as acyl hypofluorites, CF_3OF or $CsSO_4F$),[7] and fluoronitrogen compounds (R_2N-F or R_3N^+-F).[8] In the presence of highly polar protic solvents and modifiers such as Lewis acids, dilute solutions of elemental fluorine (F_2) have been used as a source of elemental fluorine at low temperatures.[9] All of these reagents have been used extensively to prepare of organofluorine compounds and exhibit traditional electrophilic reactivity patterns.

One of the most important developments in the field of electrophilic fluorination has been the invention of a variety of N-F electrophilic fluorinating agents.[8] Unlike many other types of electrophilic fluorinating agents, these reagents are usually stable and easy to handle. They are prepared from relatively inexpensive starting materials (usually prepared by reacting the corresponding

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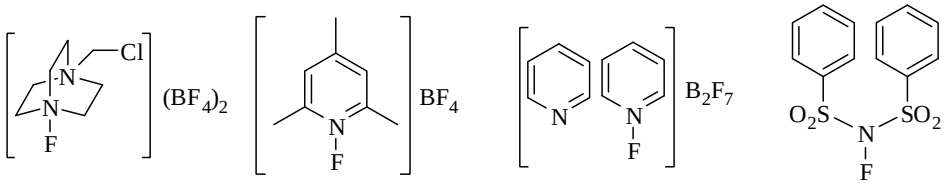
N-H compound with F_2). Some of them, such as 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (Selectfluor®, **40**), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**41**), 1-fluoropyridinium pyridine heptafluorodiborate (**42**) or *N*-fluorobenzenesulfonimide (NFSI, **43**) are comercially available (Figure 1).



40 **41** **42** **43**

Figure 1

Until recently, only organolithium, Grignard reagents, organothallium and organomercury derivatives were succesfully reacted in the presence of electrophilic sources of fluorine for the preparation of simple fluorinated compounds with the fluorine atom attached to an sp^3-hybridized carbon (Scheme 1).[10] The lack of a halide is an advantage that organolithium compounds have over Grignard reagents, because an oxidation of the halogen ion can occur as a competitive process. But some of the electrophilic sources of fluorine decompose under the strong basic conditions produced by the organolithium. Milder organolead, tin, mercury and thallium species have been examined very little because of the high toxicity of their derivatives.

Olah et al.[11] reported the convenient synthesis of alkenyl fluorides as well as difluoromethylsubstituted alcohols and amides through an electrophilic fluorination of alkenylboronic acids and trifluoroborates (Scheme 2). This is the only report published to date about the electrophilic fluorofunctionalization of an organoboron compound.

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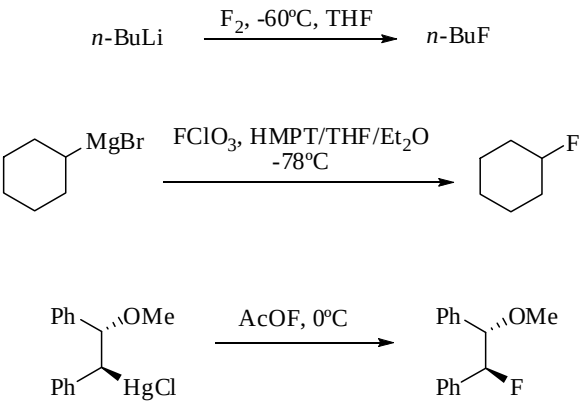

Scheme 1

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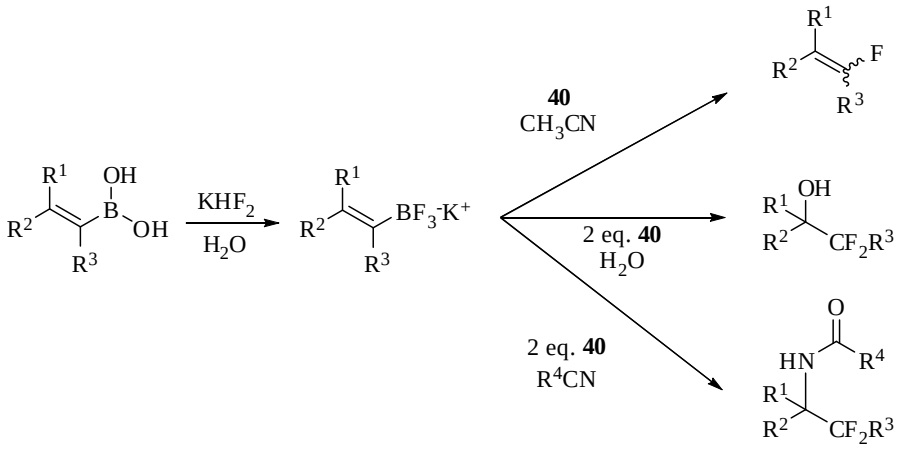

Scheme 2

One of the reactions that is closest to the fluorofunctionalization of organoboranes is the fluorofunctionalization of organosilanes.[12] Organosilanes have the advantage of being safe to handle. In this sort of reaction, the sylil group enhances the reactivity of the π-nucleophile to which it is attached, and controls the sense of regiochemistry when the electrophilic source of the fluorine is added. The β effect of a silicon center (stabilization of the atom placed in the β-position due to an hyperconjugation) plays an important role.

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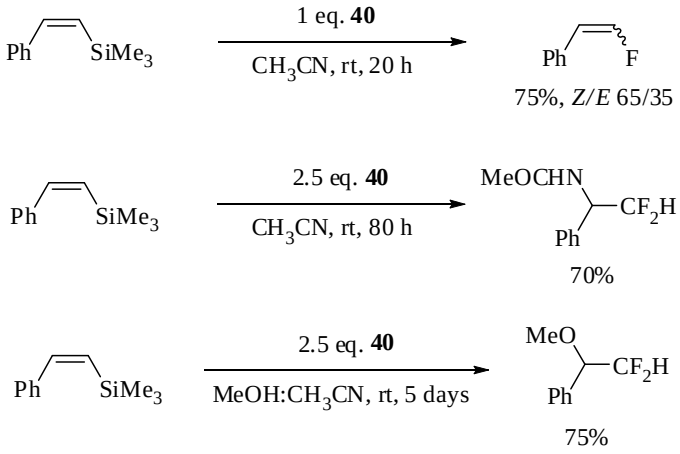
The *ipso*-substitution of arylsilanes for the formation of aryl fluorides was only achieved by using relatively strong fluorinating agents such as F_2, AcOF, caesium fluoroxysulfate and XeF_2.[13] N-F reagents are not suitable for this sort of reactions. This is probably because the ring loses aromaticity when the β-silyl cation is formed.

Recent studies, however, have demonstrated that vinylsilanes can be converted to fluoroalkenes when they are treated with Selectfluor in acetonitrile at room temperature (Scheme 3).[14] This reactivity is very similar to that reported by Olah et al.[11] for the organotrifluoroborates, and it is also possible to obtain difluoromethylsubstituted alcohols, ethers and amides. The formation of a mixture of stereoisomers and the faster reaction with the more nucleophilic vinylsilanes are consistent with an addition-elimination mechanistic pathway via a carbocationic intermediate followed by the loss of the silyl group to restore neutrality.



Scheme 3

Probably the most useful type of nucleophilic organosilanes are allylsilanes, which are typically more reactive than vinyl- or arylsilanes,

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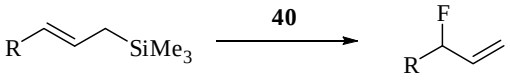
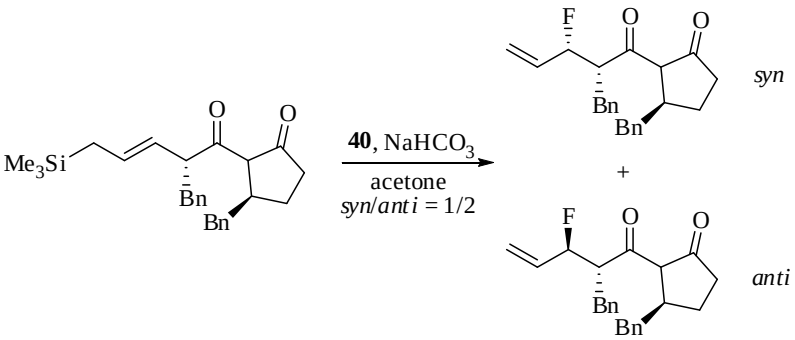
because they are extremely reactive to a wide variety of electrophiles (Scheme 4).[15] Gouverneur et al. have reported the enantioselective synthesis of allylic fluorides with two different strategies: (i) the use of non-racemic chiral allylsilanes, to obtain a mixture of diastereomers (with enantiomeric excesses that depend on the substrate) that can be cleanly separated by column chromatography (Scheme 5);[16] (ii) the use of chiral non-racemic *N*-fluorocinchona alkaloid derivatives generated in situ as fluorinating reagents (Figure 2).[17]



Scheme 4



Scheme 5

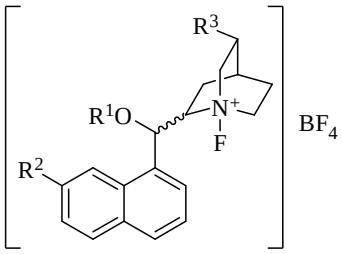


Figure 2.- *N*-fluorocinchona alkaloid

Gouverneur et al.[18] have also reported the fluorination of allenylmethylsilanes with Selectfluor® (**40**) with yields up to 99%, depending

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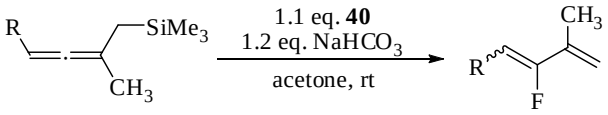
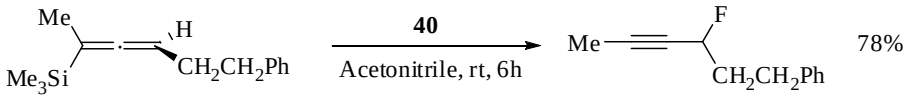
on the substituents of the subtrates (ability of the substituents to reinforce the β-effect of the trimethylsylil group) (Scheme 6). It is essential that the reaction takes place in the presence of $NaHCO_3$ to prevent the formation of non-fluorinated dienes.



Scheme 6

More recently, Gouverneur has also reported the electrophilic fluorination of allenylsilanes to yield propargylic fluorides, with yields up to 78% (Scheme 7).[19]



Scheme 7

4.2. Synthesis of α,α-difluorinated carbonyl compounds from alkynes through a tandem catalytic diboration/fluorination reaction

The interest in the synthesis of *gem*-difluorinated compounds is based in the potential biological properties of these molecules.[20] Many selectively fluorinated analogues of biologically important compounds have had their biological activity dramatically enhanced.[21] Electrophilic carbonyl derivatives, such as α,α-difluoroketones, are compounds of great interest because they can form hydrates and hemiketals.[22] This property is believed to allow some fluorinated ketones to mimic the transition states involved in the hydrolytic action of proteases and esterases as well as many other enzymes.[23] A series of

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α,α-difluoroketones have also shown interesting activities as HIV-1 proteases inhibitors.[23a,24] The introduction of fluorine atoms adjacent to the carbonyl functionality increases the electrophilicity of the carbonyl carbon atom and consequently facilitates the addition of nucleophiles. It is worth mentioning that it has been suggested that the nucleophilic addition of enzyme active sites to the carbonyl group of α-fluoroketones is responsible for inhibiting a variety of enzymes.[21] To date α-fluoroketones have been synthesized from well established routes: fluoride ion displacement of a halide from α-halocarbonyls,[21] the reaction of diazo derivatives with HF,[21] and electrophilic fluorination of enolates.[25,8b] However, in all these synthetic routes the carbonyl functional group has already been formed.

We decided to explore the possibility of synthesizing α,α-difluoroketones from alkynes. We first tried to isolate stereodefined *cis*-1,2-bis(boryl)alkenes (**28**) by adding diboron reagents to internal and terminal alkynes, in the presence of Pt(0) complexes. We selected $Pt(PPh_3)_4$[26] as the catalyst precursor because of its commercial accesibility, despite the fact that other Pt(0) derivatives such as $Pt(PPh_3)_2(\mu\text{-}C_2H_4)$,[26a,27] mono(phosphine)platinum complexes,[26b,28] Pt(0)-(NHC) complexes (Chapter 2) and base-free platinum complexes[29] have significantly improved the activity and selectivity of the diborated product. Tetraalkoxydiboranes, such as bis(pinacolato)diboron (**1**), bis(catecholato)diboron (**2**) and bis(neopentylglycolato)diboron (**6**) were chosen to be added to the alkynes. However, following the methodologies described previously in the literature[30] we were only able to isolate the *cis*-1,2-bis(boryl)alkenes (**28**) quantitatively when diboron reagents **1** and **2** were used.

Next, we explored the possibility of performing electrophilic fluorination on the *cis*-1,2-bis(boryl)alkene (**28**) (Scheme 8), in the presence of commercially available electrophilic reagents, such as Selectfluor® (**40**), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**41**), 1-fluoropyridinium

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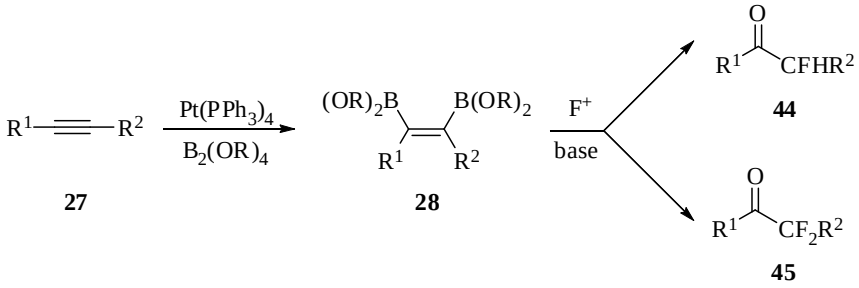
pyridine heptafluorodiborate (**42**) or NFSI (**43**). The solvents used in the fluorination reaction were toluene, THF, MeOH or acetonitrile. Different bases were also used. Combining all these factors we observed that: (i) the only 1,2-bis(boryl)alkene (**28**) which could be derivatized to a fluorinated species was the one obtained in the diboration with **1**; (ii) of all the electrophilic fluorinating reagents studied, only **40** proved to be active; (iii) the approppriate solvent for the electrophilic fluorination step was acetonitrile; (iv) the most effective base was $NaHCO_3$.



27 **28** **44** **45**

Scheme 8

The addition of one equivalent of **40** to a solution of the *cis*-1,2-bis(boryl)alkene in acetonitrile at room temperature provided a quasi equal mixture of the α-fluorinated and the α,α-difluorinated carbonyl compounds (Figure 3). The addition of two and three equivalents of the electrophilic fluorinating reagent favored the formation of the α,α-difluorinated product carbonyl derivatives with chemoselectivities of about 95%. This is of particular importance because we found in the literature that 2,2-difluoroderivatives could only be obtained by the electrophilic fluorination of very reactive β-dicarbonyl compounds under neutral conditions via their metal enolates.[31] We extended this method to different terminal and internal alkynes (Table 1).A more related reaction was described more recently,[32] in which 1-phenylsubstituted acetylenes were directly transformed into their corresponding α,α-difluoroketones, in the presence of **40**. Some substrates, however, proved not to be very reactive.

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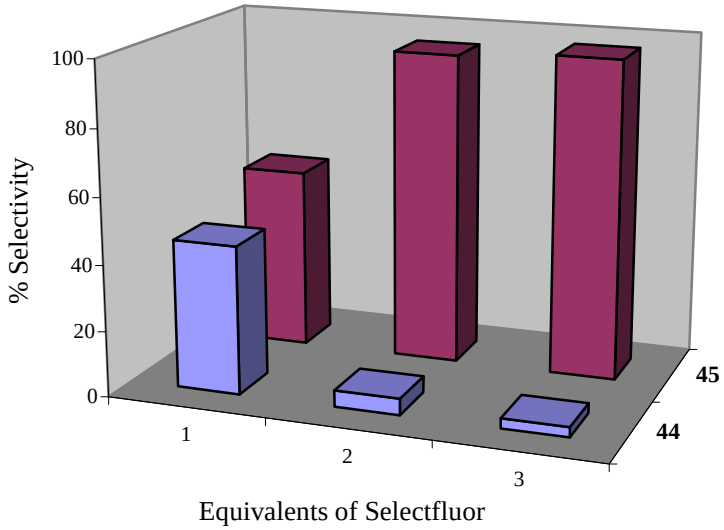

Figure 3

Table 1. Tandem Catalytic diboration/fluorination of alkynes[a]

Entry	R^1	R^2	% **45** [b]
1	Ph	H	33
2	*p*-(OMe)-Ph	H	40
3	*p*-(CF_3)-Ph	H	26
4	Ph	Ph	50
5	*p*-(CF_3)-Ph	*p*-(CF_3)-Ph	21

[a] Standard conditions: *for catalytic diboration*: substrate/Pt catalyst/**1** = 1/0.03/1; CH_3CN; reflux; *t*= 15h; *for fluorination reaction*: substrate/**40**/ $NaHCO_3$ = 1/2/2.2; CH_3CN; rt; *t*= 15h. [b] The reaction was monitored by ^1H NMR and ^{19}F NMR, in the presence of perfluoronaphthalene as internal standard.

Our current mechanistic understanding of the transformation suggests that Selectfluor® (**40**) can react with the *cis*-1,2-bis(boryl)alkene intermediate through an electrophilic attack. To confirm this hypothesis, we investigated to what extent the electronic nature of the *cis*-1,2-bis(boryl)alkene intermediate can affect the fluorination process. The electronic properties of the substituents in the *para* position of phenylacetylene seem to influence the electronic fluorination pathway. Apparently, the more electron rich the *cis*-1,2-

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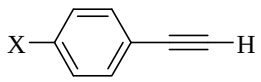
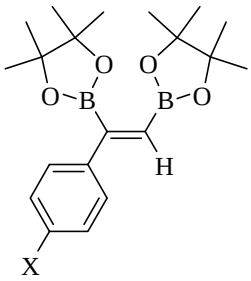
bis(boryl)alkene is, the more reactive towards the electrophilic fluorination it will be (Table 1). This is in agreement with the indirect measurement of the chemical shift in the ^{1}H NMR of the *cis*-1,2-bis(boryl)alkene formed in situ during the catalytic diboration of the *para*-substituted phenylacetylenes. The ^{1}H NMR values for the alkenyl moiety increase from 6.21 ppm in *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*p*-methoxystyrene to 6.34 ppm in *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*p*-trifluoromethylstyrene (Figure 4). The differences in the chemical shift values could be due to the inductive effects of the *para*-substituents. In addition, the substituted *cis*-1,2-bis(boryl)alkenes seem to react more efficiently than the corresponding substituted phenylacetylenes towards the electrophilic N-F fluorinating reagent **40**.[32] The ^{1}H NMR is also consistent with the fact that the terminal vinyldiborons are more nucleophilic than the aryl acetylenes.





X= OMe	δ= 3.00 ppm	X= OMe	δ= 6.21 ppm
X= H	δ= 3.08 ppm	X= H	δ= 6.29 ppm
X= CF_3	δ= 3.20 ppm	X= CF_3	δ= 6.34 ppm

Figure 4

These results provide some insight into the mechanism of the fluorination process, especially when some authors have reported radical mechanisms in related fluorination processes.[33] A plausible mechanism for fluorination process is shown in Scheme 9. We suggest a concerted mechanism in which the

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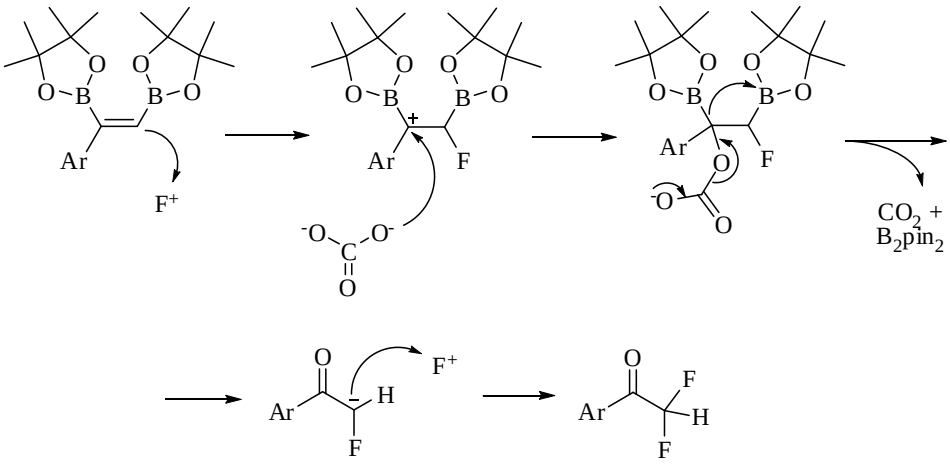
electrophilic attack of F^+ occurs at the most electronegative C-B bond in the *cis*-1,2-bis(boryl)alkenes, followed by a nucleophilic attack of the carbonate base, ultimately leading to the formation of carbon dioxide and the regeneration of bis(pinacolato)diboron (**1**), with concominant formation of the second C-F bond at the terminal position. However, deprotonation of the fluorinated cation by the carbonate to deliver a fluorinated olefin which could eventually be fluorinated again can also be considered as an alternative pathway for the fluorination step. The regioselective electrophilic attack on the terminal alkenyl boryl unit might be related both to electronic (more nucleophilic) and steric factors (less hindered).



Scheme 9. Proposed mechanism for the fluorodeboronation process

Two factors support this mechanism: (i) no fluorination is observed in the absence of a base, and (ii) the formation of regenerated bis(pinacolato)diboron (**1**) was confirmed by GC-MS analysis of the crude reaction mixture. A close oxidation protocol has recently been described to transform (fluoroalkenyl)boranes into α-fluoroketones.[34] Although we have no evidence for the participation of a radical mechanism, it cannot be discarded.

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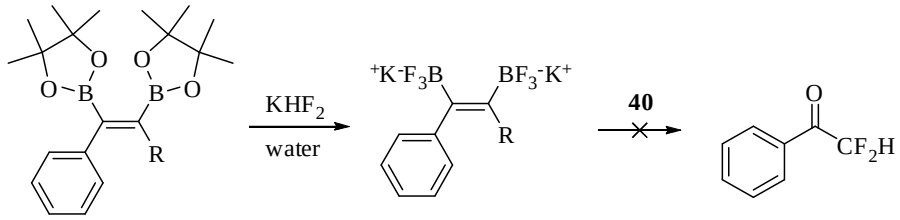
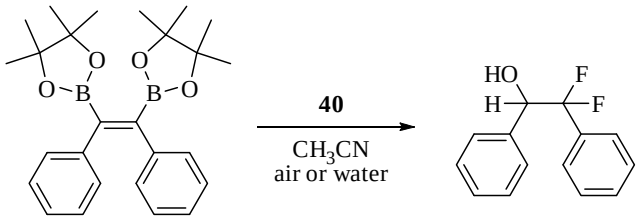
Attempts to improve the fluorination pathway were unsuccesful, even when *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styrene was treated with an aqueous solution of KHF_2 to obtain the alkenyl bis(trifluoroborate), which is more reactive towards electrophilic fluorination (Scheme 10).[11]



Scheme 10

We decided to conduct the same electrophilic reaction with Selectfluor® (**40**) on the alkenyl diboronate ester *cis*-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexene. To our surprise, this aliphatic diboron intermediate did not provide any fluorinated compounds. This is in agreement with the tendency observed by Olah et al.,[11] where the fluorination of alkenyl boronic acids and trifluoroboronates worked well only with compounds leading to benzylic carbocations. When the electrophilic fluorination was carried out in the presence of traces of water or under air atmosphere, the product obtained was mainly the difluoromethyl alcohol (Scheme 11).



Scheme 11

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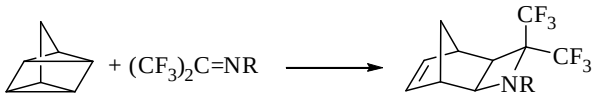
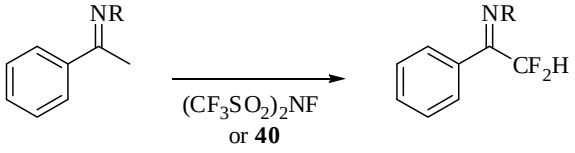
4.3. Synthesis of α,α-difluorimines from alkynes through a tandem catalytic diboration/fluorination/imination reaction

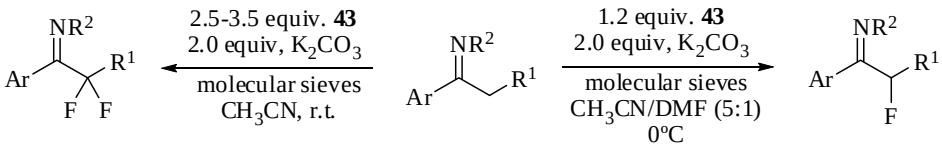
During our continous study of the tandem diboration/functionalization reaction, we became interested in direct fluorination for the synthesis of α,α-difluoroimines, as these compounds are considered to be interesting synthetic intermediates to fluorinated azaheterocyclic and β-fluorinated amines (Scheme 12).[35] To the best of our knowledge, only two previous reports have described the direct electrophilic fluorination of imines (Scheme 13).[36] More recently, a milder and more efficient procedure has been reported for synthesizing and isolating both α-fluoroimines and α,α-difluoroimines via the direct electrophilic fluorination of ketimines using NFSI (**43**) (Scheme 14).[37] However, all these attempts have the imine functionality as a part of the substrate, and ketone derivatives from hydrolysis cannot be avoided. In this context, we aimed to explore an alternative synthetic method, in which the imine functionality was formed simultaneously to the C-F formation.



Scheme 12



Scheme 13



Scheme 14

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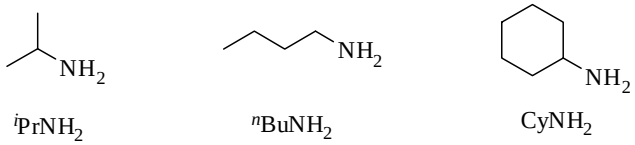
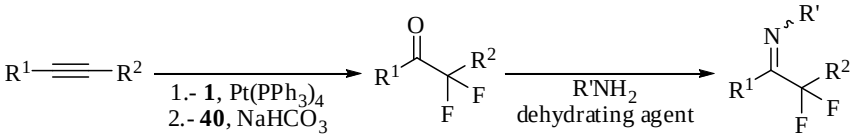
Taking into account the results obtained in the tandem catalytic diboration/fluorination reaction, we tried to perform a tandem approach for difluorofunctionalizing imines from alkyne substrates in a one-pot reaction. The addition of R'NH_2 (Figure 5) and a dehydrating reagent (Montmorillonite K-10 or $TiCl_4$) to the reaction mixture obtained after the fluorofunctionalization of a *cis*-1,2-bis(boryl)alkene (**28**) led to the formation of α,α-difluoroimine, after 15h of reaction (Scheme 15).



$^{i}PrNH_2$ $^{n}BuNH_2$ $CyNH_2$

Figure 5. Amines used in the tandem catalytic diboration/fluorination/imination reaction



27 **45** **46**

Scheme 15. Tandem catalytic diboration/fluorination/amination reaction

The direct formation of *gem*-difluorinated imines in this one-pot reaction protocol is particularly atractive, since it opens up the possibility of in situ synthesis of the imine functionality when a primary amine is present in the reaction media, thus avoiding any hydrolysis byproducts.

The dehydrating capability of Montmorillonite K-10 (MK-10)[38] was particularly shown for terminal α,α-difluoroimine formation (Table 2, entries 1-5). However, for internal α,α-difluoroimines, the use of MK-10 did not completely convert the α,α-difluoroketones into α,α-difluoroimines, even under refluxing conditions (Table 2, entries 6 and 7). Therefore, $TiCl_4$[39] was required for total imine transformation (Table 2, entries 8-10). The percentage

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of internal α,α-difluoroimine formation is greater than that of the terminal α,α-difluoroimines, which is in agreement with the fact that terminal alkenyldiboraonate intermediates proved to be less reactive than internal alkenyldiboronates towards the electrophilic fluorination step.

Table 2. Tandem catalytic diboration/fluorination/imination of alkynes[a]

Entry	R^1	R^2	$R'NH_2$	Dehydrating agent	% **45** [b]	% **46** [b]
1	Ph	H	$^{i}PrNH_2$	MK-10	1	27
2	Ph	H	$^{n}BuNH_2$	MK-10	-	33
3	*p*-(CF_3)-Ph	H	$^{n}BuNH_2$	MK-10	-	26
4	*p*-(OMe)-Ph	H	$^{n}BuNH_2$	MK-10	-	40
5	Ph	H	$CyNH_2$	MK-10	-	19
6	Ph	Ph	$^{n}BuNH_2$	MK-10	18	27
7[c]	Ph	Ph	$^{n}BuNH_2$	MK-10	8	37
8	Ph	Ph	$^{n}BuNH_2$	$TiCl_4$	-	45
9	Ph	Ph	$^{i}PrNH_2$	$TiCl_4$	-	43
10	Ph	Ph	$CyNH_2$	$TiCl_4$	-	42

[a] Standard conditions: *for catalytic diboration*: substrate/Pt catalyst/**1** = 1/0.03/1; CH_3CN; reflux; *t*= 15h; *for fluorination reaction*: substrate/**40**/ $NaHCO_3$ = 1/2/2.2; CH_3CN; rt; *t*= 15h; *for imination reaction*: $R'NH_2$/substrate = 4/1; dehydrating reagent: 100 mg MK-10 or 0.6 equiv. of $TiCl_4$; CH_3CN; rt; *t*= 15h. [b] The reaction was monitored by ^1H NMR and ^{19}F NMR, in the presence of perfluoronaphthalene as internal standard. [c] Temperature for the imination step: 82ºC.

The tendency observed in the tandem catalytic diboration/fluorination/imination reaction is the same as that reported by De Kimpe et al.[37] The yields were best when the amine used was $^{n}BuNH_2$, and worst when the amine was $CyNH_2$. This is probably due to the steric hinderence of the backbone. Although the yields obtained by De Kimpe are slightly better than ours, our method has the advantage that it is a one-pot methodology, which uses the same solvent for the whole process, while De Kimpe's process uses diethylether in the imination step, and acetonitrile in the fluorination step.

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4.4. Conclusions

As we have demonstrated, *cis*-1,2-bis(boryl)alkenes can be easily fluorofunctionalized towards α,α-difluoroketones under mild conditions through an electrophilic fluorination process. Bis(pinacolato)diboron (**1**) derivatives are the only cis-1,2-bis(boryl)alkenes that can be fluorofunctionalized towards α,α-difluoroketones.

Internal alkynes are more active in the tandem diboration/fluorination process than terminal alkynes. Aliphatic alkynes cannot be fluorinated, probably because of the instability of the carbocation intermediate, which can be stabilized by the presence of a contiguous aromatic ring.

α,α-Difluoroimines can be synthesized directly from alkynes through a tandem catalytic diboration/fluorination/imination process, the efficiency of which depends on the electronic factors on the substrate.

One of the most important issues that our work has adressed is the conversion of the two C-B bonds into the functionalized C=N and C-F bonds, simultaneously. Therefore it was possible to provide a direct methodology that transforms arylacetylenes into α,α-difluoroimines.

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Chapter 5

Asymmetric Electrophilic Fluorination of α-Nitro Esters

This work was carried out in the Swiss Federal Institute of Technology (ETH) of Zurich, under the supervision of Prof. Antonio Togni.

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Chapter 5

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5.1. Introduction

The discovery of efficient methods for asymmetric fluorination is one of the most important aspects of organofluorine chemistry.[1] Molecules containing a fluorinated stereogenic center are potentially of great interest in biological and medicinal applications.[2] Several routes to chiral fluoroorganic compounds have been developed,[3] including procedures for the diastereoselective fluorination of chiral organic compounds,[4] enantioselective alkylation of monofluorinated derivatives[5] and also enantioselective fluorination of achiral carbanions.

An important route for the enantioselective introduction of fluorine into organic molecules is the reaction of enolizable substrates with chiral nonracemic electrophilic fluorinating agents.[6] A major development in the area of asymmetric fluorination was the introduction of quaternary *N*-fluoro ammonium salts based on cinchona akaloids as electrophilic fluorinating agents.[7] The advantage of cinchona alkaloids is their ready availability in both (pseudo)enantiomeric forms and the fact that their quinuclidine moiety can be fluorinated under mild conditions via fluorine transfer from commercially available fluorinating reagents.[8]

Nitro compounds are valuable precursors for azo dyes and explosives, but their ready availability and their facile transformation into a variety of other functionalized molecules also makes them important intermediates for organic synthesis.[9] Furthermore, halogenated nitro compounds have shown pronounced antimicrobial and insecticidal activity.[10] However, although halogenations of nitroalkanes are well known,[11] there are few satisfactory methods for introducing fluorine or fluorine-containing groups into nitro compounds.[12] In addition, α-nitro esters have previously been fluorinated using reagents such as F_2 or $FClO_3$.[13] Only recently, Shreeve reported a new, mild method for

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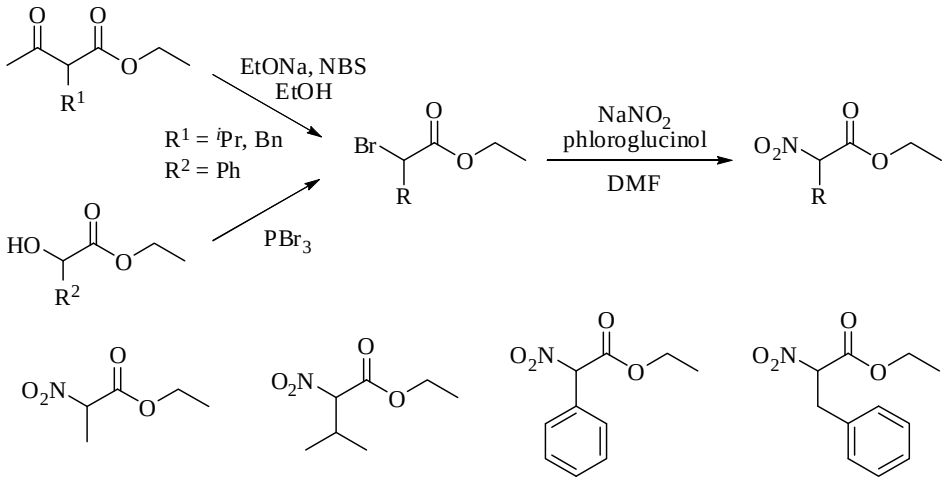
introducing fluorine into nitro compounds using Selectfluor® as the fluorinating agent.[14]

Recently, Prof. A. Togni's group developed a new, mild method for the trifluoromethylation of α-nitro esters based on the use of new hypervalent trifluoromethyliodine reagents.[15] Taking into account this group's experience in handling α-nitro esters and fluorination reactions, we decided to develop a new method for the enantioselective α-fluorination of α-nitro esters with Selectfluor® using cinchona alkaloid derivatives as chiral auxiliaries.

5.2. Asymmetric electrophilic fluorination of α-nitro esters

The α-nitro esters used in the present study were prepared in accordance with procedures found in the literature,[16] from either the corresponding β-keto ester or α-hydroxy ester (see Scheme 1).



47a **47b** **47c** **47d**

Scheme 1

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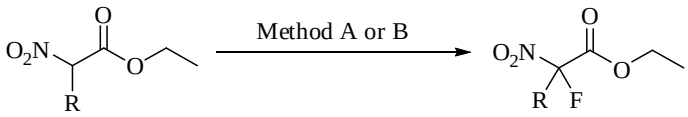
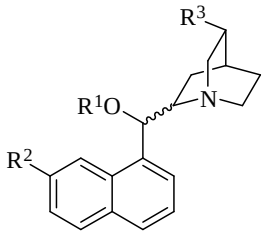
Our study started with the comercially available ethyl 2-nitropropanoate (**47a**). Our first attempts to obtain the corresponding α-fluoro-α-nitro ester were focused on the transition metal-catalyzed enantioselective electrophilic fluorination.[1] Several copper and titanium catalysts were tested. However, much to our surprise and disappointment, none of them showed any activity. Therefore, Shreeve's non catalytic method was adopted, in which the substrate is first deprotonated by KOH in CH_3CN-H_2O and then fluorinated using Selectfluor® in the presence of a chiral auxiliary (Scheme 2, method A). We thereby relied on five compounds (Figure 1): cinchonidine (CD), quinine (QN), hydroquinidine 4-chlorobenzoate (HQCB), acetyl cinchonidine (AcCD) and acetyl quinine (AcQN). The first three of these are commercially available whereas the latter two were synthesized using reported procedures.[17]



47 **48**

Scheme 2. Asymmetric electrophilic fluorination of α-nitro esters
Method A: (i) 0.5 M KOH solution, CH_3CN-H_2O = 1:1, stirring 2h; (ii) fluorinating reagent solution in CH_3CN, stirring overnight. Method B: (i) NaH, THF, stirring 30min under N_2; (ii) fluorinating reagent solution in CH_3CN, stirring overnight.



CD: R^1= H, R^2= H, R^3= vinyl
QN: R^1= H, R^2= MeO, R^3= vinyl
HQCB: R^1= *p*-ClBz, R^2= OMe, R^3= Et
AcCD: R^1= Ac, R^2= H, R^3= vinyl
AcQN: R^1= Ac, R^2= MeO, R^3= vinyl

Figure 1. Cinchona alkaloids used

When substrate **47a** was fluorinated following method A, an enantiomeric excess of up to 40% and yields up to 82% were obtained (Table

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1). Using either an isolated or an in-situ prepared fluorinating agent did not affect yield and enantioselectivity to any significant extent.(Table 1, entries 1 and 2). Lowering the temperature to 0ºC prevented unidentified side products from forming and therefore resulted in higher yields (Table 1, entries 3-8). However, the enantiomeric excess was not influenced by the lower reaction temperature of 0ºC (Table 1, entries 2 and 3). Under these conditions acetyl quinine (AcQN) gave the highest enantioselectivity so far of 40% ee (Table 1, entry 7).

Table 1. Fluorination of substrate 47a under the conditions of Method A

Entry	Fluorinating reagent	*T* (ºC)	Yield (%)[a]	ee (%)[b]
1	isolated F-CD-BF_4	25	42	23
2	in situ F-CD-BF_4	25	37	25
3	isolated F-CD-BF_4	0	59	25
4	in situ F-CD-BF_4	0	68	26
5	in situ F-QN-BF_4	0	65	40
6	in situ F-AcCD-BF_4	0	78	31
7	in situ F-AcQN-BF_4	0	68	40
8	in situ F-HQCB-BF_4	0	82	7

[a] The reaction was monitored by ^{19}F NMR, in the presence of perfluoronaphthalene as internal standard. [b] Enantiomeric excess determined by GC.

In an attempt to further improve the enantioselectivity, the fluorination was carried out at even lower temperatures. For this purpose, the reaction conditions had to be changed. THF was used as the main solvent, NaH as the base, and CH_3CN to solubilize the fluorinating reagent before being added to the reaction mixture (Scheme 2, method B[8]). Like the results obtained when using method A, the isolated or in situ nature of the fluorinating reagent did not lead to altered ee (Table 2, entries 1 and 2). Although the yields were quite satisfactory in all the experiments, the enantioselectivity did not exceed 30% ee (Table 2, entries 3-6). While acetylquinine (AcQN) gave best results for method A, quinine itself (QN) proved to be better under the conditions of Method B.

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Table 2. Fluorination of substrate 47a under the conditions of Method B

Entry	Fluorinating reagent	*T* (ºC)	Yield (%)[a]	ee (%)[b]
1	isolated F-CD-BF_4	25	80	9
2	in situ F-CD-BF_4	25	81	9
3	in situ F-CD-BF_4	-15	71	16
4	in situ F-CD-BF_4	-40	71	19
5	in situ F-QN-BF_4	-40	73	30
6	in situ F-AcCD-BF_4	-40	78	7

[a] The reaction was monitored by ^{19}F NMR, in the presence of perfluoronaphthalene as internal standard. [b] Enantiomeric excess determined by GC.

As the next step in this study, α-nitro esters that had sterically more hindered substituents at the α-position than the methyl group of ethyl 2-nitropropanoate were fluorinated. As is apparent from the data in Table 3, none of the three new substrates **47b-d** (bearing an isopropyl, a phenyl or a benzyl group, respectively) gave any improved enantiomeric excesses with respect to the enantioselectivity observed for compound **47a**. Furthermore, lowering the reaction temperature or varying the chiral fluorinating agent for the new substrates had only a marginal influence on the stereoselectivity.

Table 3. Fluorination of substrates 47b-d

Entry	Substrate	Method	Fluorinating reagent	*T* (ºC)	Yield (%)[a]	ee (%)[b]
1	**47b**	A	in situ F-AcCD-BF_4	0	78	23
2	**47b**	A	in situ F-AcQN-BF_4	0	72	21
3	**47c**	A	in situ F-AcCD-BF_4	0	9	21
4	**47c**	A	in situ F-AcQN-BF_4	0	8	27
5	**47c**	B	in situ F-AcCD-BF_4	-40	85	31
6	**47c**	B	in situ F-AcQN-BF_4	-40	82	6
7	**47d**	A	in situ F-CD-BF_4	0	75	13
8	**47d**	A	in situ F-QN-BF_4	0	83	18
9	**47d**	A	in situ F-AcCD-BF_4	0	78	15
10	**47d**	A	in situ F-AcQN-BF_4	0	78	24
11	**47d**	A	in situ F-HQCB-BF_4	0	91	8
12	**47d**	B	in situ F-AcCD-BF_4	-40	91	18
13	**47d**	B	in situ F-AcQN-BF_4	-40	84	16

[a] The reaction was monitored by ^{19}F NMR, in the presence of perfluoronaphthalene as internal standard. [b] Enantiomeric excess determined by GC or HPLC.

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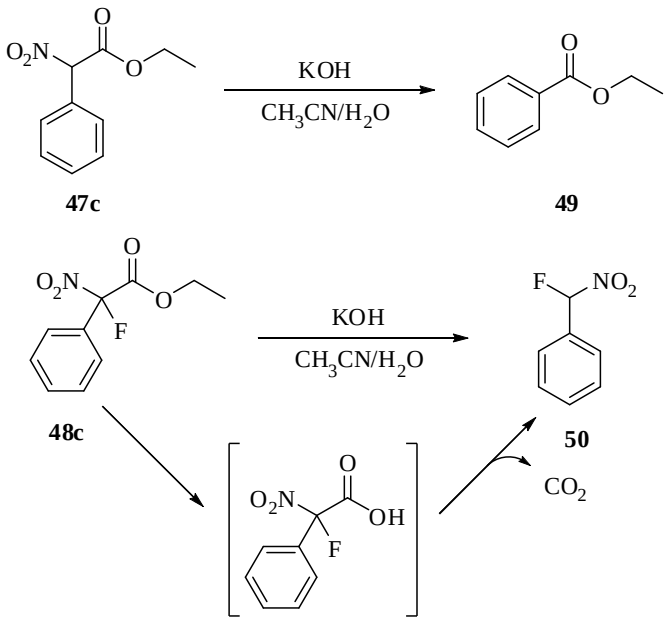
Surprisingly, when **47c** was fluorinated under the conditions of method A, the starting material was fully converted but the yields of the desired fluorinated product **48c** were low (Table 3, entries 3 and 4). By NMR and GC-MS analyses of the crude reaction mixture, it was found that the major product formed was ethyl benzoate (**49**). Application of the method B conditions yielded the desired fluorinated product and no ethyl benzoate was detected. When ethyl 2-nitro-2-phenylacetate (**47c**) was subjected to a basic CH_3CN/H_2O medium (Method A), ethyl benzoate was obtained in high yield (Scheme 3). On the other hand, when the fluorinated product **48c** was treated under the same conditions, it decomposed quantitatively to [fluoro(nitro)methyl]benzene (**50**), as expected for a saponification-decarboxylation sequence, and as analogous β-keto esters do.[18]



Scheme 3

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The known compound **50** was identified by comparing its ^{1}H NMR and ^{19}F NMR spectroscopic parameters with reported data.[14] From these experiments we conclude that the peculiar transformation of the nitro compound **47c** to ethyl benzoate (**49**) occurs prior to any fluorination reaction under basic conditions.

5.3. Conclusions.

This study established suitable reaction conditions for the preparation of enantiomerically enriched α-fluoro-α-nitro esters starting from racemic α-nitro esters. The products were generally obtained in high yield (up to 91%) but with relatively low enantioselectivities (up to 40%) when various cinchona alkaloids were used as chiral fluorinating agents in combination with Selectfluor®.

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Experimental Section

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1. General Considerations

All reactions and manipulations were carried out under a nitrogen atmosphere by using Schlenk-type techniques, unless otherwise stated. The solvents were distilled over dehydrating reagents (toluene and THF were distilled over Na using benzophenone as dryness indicator, CH_3CN was distilled over CaH_2) and were deoxygenated before use. Bis(pinacolato)diboron (**1**) was used as purchased from Lancaster. (S)-QUINAP and vinylcyclohexane were provided by Across. $RhCl_3 \cdot H_2O$ was used as purchased by Johnson Matthey. The rest of the reagents were provided by Sigma-Aldrich.

GC/MS analyses of the solutions were performed on a Hewlett Packard 5890 Serier II apparatus equipped with a Supelco β-DEX 120 capillary column (30 m, 0,25 mm i. d., 0,25 μm film thickness) using H_2 as the carrier gas.

Deuterated solvents for routine NMR measurements were used as purchased from SDS. 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, referenced to the chemical shift of residual solvents ressonances. ^{19}F NMR chemical shifts are reported in ppm (δ) relative to $CFCl_3$, referenced to the chemical shift of perfluoronaphthalene. ^{31}P NMR chemical shifts are reported in ppm (δ) relative to H_3PO_4.

2. Synthesis of the catalyst precursors

2.1. $[Rh(\mu\text{-}Cl)(COD)]_2$

This complex was prepared according to the literature.[1] Under nitrogen atmosphere, 2 g of $RhCl_3 \cdot H_2O$ (8.8 mmol) are introduced in a schlenk, and dissolved in ethanol. Next, 4 ml of COD (*cis*,*cis*-1,5-cyclooctadiene) were

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added. The solution obtained was stirred under reflux during 3 hours. Once the solution was at room temperature, cold and degassed diethylether was added in order to precipitate the product. Finally, the product was isolated by filtration, washed with cold and degassed diethylether and dried in vacuum, to yield 1,65 g of a yellow powder (76% yield). ^{1}H NMR ($CDCl_3$): 4.3 (m, 8H), 1.7-2.6 (m, 16H)

2.2. $[Rh(\mu\text{-}Cl)(NBD)]_2$

This metal complex was prepared following the procedure for the synthesis of $[Rh(\mu\text{-}Cl)(COD)]_2$,[1] using NBD (norbornadiene) instead of COD. This compound was obtained with a 51% yield (1,041 g). ^{1}H NMR ($CDCl_3$): 3.95 (m, 4H); 3.85 (m, 2H); 1.2 (m, 2H).

2.3. $[Rh(COD)_2]BF_4$

This compound was prepared following a procedure previously reported.[2] Under nitrogen atmosphere, 0,71 mmol of $[Rh(\mu\text{-}Cl)(COD)]_2$ (350 mg) were introduced in a schlenk and dissolved in the minimum quantity of dry and degassed dichloromethane. Next, 1 ml of COD and 2,13 mmol of $AgBF_4$ (415 mg) were added. Quickly, the mixture obtained turned brown. The mixture was stirred under nitrogen and protected from the light during 1 hour. Passed this time, a white precipitate corresponding to AgCl was formed. The mixture obtained was filtered through celite. The brown solution obtained was concentrated in a rotatory evaporator until a brown precipitate was formed. The product was isolated by means of filtration, yielding 220 mg of a brown powder (76% yield). ^{1}H NMR ($CDCl_3$): 5.1 (m, 8H), 2.4-2.6 (m, 16H)

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2.4. $[Rh(NBD)_2]BF_4$

This rhodium (I) complex was prepared following the same procedure as $[Rh(COD)_2]BF_4$,[2] but starting from $[Rh(\mu\text{-}Cl)(NBD)]_2$ and using NBD instead of COD. This compound was obtained with a 70% yield (186 mg). ^{1}H NMR ($CDCl_3$): 5.66 (m, 4H); 4.29 (m, 2H); 1.62 (m, 2H).

2.5. [Rh(acac)(NBD)]

This complex was prepared following a reported procedure.[3] 200 mg (0,434 mmol) of $[Rh(\mu\text{-}Cl)(NBD)]_2$ were introduced in a schlenk under nitrogen atmosphere. 3 ml of acetone were added, without complete dissolution of the solid. Consecutively, 90 µl of 2,4-pentanedionate and 49 mg of KOH were added, and the mixture obtained was stirred for one hour. Passed this time, the formation of a white precipitate was observed, which was filtered through celite. The clear solution obtained was evaporated to dryness, obtaining a solid, which was dried in vacuum, yielding 121 mg of the desired product (48% yield). ^{1}H NMR ($CDCl_3$): 5.31 (s, 1H), 3.95 (m, 4H) 3.83 (m, 2H), 1.92 (s, 6H), 1.23 (m, 2H).

2.6. [(mentimid)RhCl(COD)]

This complex was prepared by the group of Prof. Eduardo Peris.[4]

2.7. $[(mentimid)_2Ag]AgCl_2$ (12)

This complex was prepared by the group of Prof. Eduardo Peris.[5]

2.8. Bis(1,3-di-n-butyl-4,5-dichloroimidazolium)silver iodide (13)

This complex was prepared by the group of Prof. Eduardo Peris.[6]

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2.9. 1,3-Bis-(1-(*S*)-1-phenyl-ethyl)-imidazolin-2-ylidene silver (I) chloride (14)

This complex was prepared by the group of Prof. Eduardo Peris.[6,7]

2.10. 1,3-Bis-(1-(*S*)-phenyl-propyl)-imidazolin-2-ylidene silver (I) chloride (15)

This complex was prepared by the group of Prof. Eduardo Peris.[6,7]

2.11. 1,3-Bis-(1-(*S*)-1-naphthyl-ethyl)-imidazolin-2-ylidene silver (I) chloride (16)

This complex was prepared by the group of Prof. Eduardo Peris.[6,7]

2.12. $[(mentimid)_2Au]Cl$ (17)

This complex was prepared by the group of Prof. Eduardo Peris.[6]

2.13. Bis(1,3-di-n-butyl-4,5-dichloroimidazolium) gold iodide (18)

This complex was prepared by the group of Prof. Eduardo Peris.[6]

2.14. $[\{(R)\text{-BINAP}\}Au_2Cl_2]$ (19)

This complex was synthesized following a reported procedure.[8] 200 mg of $(Me_2S)AuCl$ (0,68 mmol) were dissolved in 10 ml of THF. Next, 221,4 mg of R-BINAP (0,34 mmol) were added, and the mixture obtained was stirred for half an hour. Once this time was passed, the solvent was removed, and the residue was dissolved in dichloromethane. The desired product was precipitated with pentane, and isolated after filtration, yielding 370 mg (50% yield). ^1H NMR ($CDCl_3$): 8.2 (d, J=8.7 Hz, 2H), 7.96 (d, J= 8.1 Hz, 2H), 7.36-7.32 (m, 17H), 7.31-7.28 (m, 7H), 6.87 (t, J= 7.9 Hz, 2H), 6.67 (d, J= 8.5 Hz, 2H). ^{31}P NMR ($CDCl_3$): 25.8.

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2.15. [{(R)-BINAP}Au_2I_2] (20)

This complex was prepared through a ionic exchange procedure.[9] 150 mg of [{(R)-BINAP}Au_2Cl_2] (**19**) (0,138 mmol) were introduced in a schlenk under nitrogen atmosphere, and were dissolved in 40 ml of dry THF. 1 g of KI was added, and the mixture was stirred for 6 hours. Once this time passed, the mixture was filtered to remove the salts, and the solvent was evaporated. The residue obtained was dissolved in dichloromethane, and the desired product was precipitated with pentane, yielding 140 mg (80% yield). ^{1}H NMR ($CDCl_3$): 8.21 (d, J=8.4 Hz, 2H), 8.0 (d, J= 8.0 Hz, 2H), 7.60-7.45 (m, 9H), 7.42-7.34 (m, 3H), 7.33-7.25 (m, 8H), 7.18-7.12 (m, 6H), 6.87 (d, J= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 135.01 (d, J(C-P)=6.9 Hz), 133.61 (d, J(C-P)=6.8 Hz), 131.43 (d, J(C-P)=5.7 Hz), 130.65 (d, J(C-P)=4.2 Hz), 130.40 (d, J(C-P)=2.1 Hz), 129.48, 129.36, 129.26, 129.14, 129.02, 127.6, 127.03. ^{31}P NMR ($CDCl_3$): 31.5.

Suitable crystals of this complex were obtained by diffusion of hexane in a saturated dichloromethane solution. The single crystal was mounted on a glass fiber in a random orientation. Data collection was performed at 0ºC on a Siemens Smart CCD diffractometer using graphit-monochromated Mo Kα radiation (λ = 0.71073 Å) with a nominal crystal to detector distance of 4.0 cm. The structures were solved by direct methods with the aid of successive difference Fourier maps and were refined using the SHELTXTL 6.1 software package.[10] All non-hydrogen atoms were refined anisotropically.

Table 1. Crystalographic data for 18

Empirical Formula	$C_{44}H_{32}Au_2I_2P_2$
Formula Weight	1270.41
Temperature	273(2) K
Wave Length	0.71073 Å
Crystal System	Monoclynic
Space Group	C2

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A	19.5301(14) Å
B	9.0292(7) Å
C	14.5043(10) Å
α	90º
β	123.3750(10)º
γ	90º
Volume	2135.9(3)Å^3
Z	2
Calculated Density	2.025 Mg/m^3
Absortion Coefficient	8.415 mm^{-1}
F (000)	1212
Theta Range for Data Collection	2.50 to 30.50º
Index ranges	-27≤h≤12 -12≤k≤12 -20≤l≤20
Reflections collected / unique	8650 / 6081 [R(int)= 0.0557]
Data/restraints/parameters	6081/1/236
GOF F^2	0.999
Final R indices [I>2sigma(I)]	R1= 0.0720, wR2= 0.1837
R indices (all data)	R1= 0.1363, wR2= 0.2347
Largest diff. Peak and hole	1.505 and -1.761 e·Å^{-3}

Table 2. Cartesian coordinates for 18

	x	y	z
Au	3.0782	5.3719	9.5792
I	5.4640	4.6311	9.0754
P	0.8770	5.7800	9.8670
C	-0.2000	3.6600	11.3300
C	1.1200	9.2700	13.9800
C	-0.9400	9.9400	15.0400
C	-1.6600	9.0500	14.3000
C	0.5300	10.0200	14.9320
C	0.3900	8.3520	13.1390
C	-1.0300	8.3160	13.2930
C	1.0500	7.5290	12.1380

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C	0.2500	6.7900	11.2970
C	-1.7900	7.4850	12.3780
C	-1.2000	6.7810	11.3970
C	-0.2400	3.4500	8.9300
C	0.0500	4.1810	10.0420
C	-0.9700	1.6100	10.3700
C	-0.6900	2.4100	11.5300
C	-0.7500	2.0900	9.1900
C	-1.2200	6.3800	8.0400
C	0.1700	6.5730	8.3960
C	1.0400	7.4400	7.7000
C	0.5600	8.2900	6.6400
C	-0.9000	8.0700	6.3500
C	-1.6100	7.3100	6.9400
Au	0.4938	5.3719	14.6450
I	-1.8920	4.6311	15.1490
P	2.6950	5.7800	14.3580
C	3.7700	3.6600	12.9000
C	2.4500	9.2700	10.2400
C	4.5100	9.9400	9.1800
C	5.2400	9.0500	9.9200
C	3.0400	10.0200	9.2930
C	3.1800	8.3520	11.0850
C	4.6100	8.3160	10.9310
C	2.5300	7.5290	12.0870
C	3.3300	6.7900	12.9280
C	5.3600	7.4850	11.8470
C	4.7700	6.7810	12.8280
C	3.8100	3.4500	15.3000
C	3.5200	4.1810	14.1820
C	4.5400	1.6100	13.8600
C	4.2600	2.4100	12.6900
C	4.3300	2.0900	15.0300
C	4.7900	6.3800	16.1900
C	3.4000	6.5730	15.8280
C	2.5300	7.4400	16.5200
C	3.0100	8.2900	17.5900
C	4.4700	8.0700	17.8800
C	5.1900	7.3100	17.2800

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2.16. [CuCl(IPr)] (21)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.17. [Cu(IPr)(NCCH$_3$)]BF$_4$ (22)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.18. [CuCl(IMes)] (23)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.19. [Cu(IMes)(NCCH$_3$)]BF$_4$ (24)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.20. [CuCl(SIPr)] (25)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.21. [Cu(SIPr)(NCCH$_3$)]BF$_4$ (26)

This complex was prepared by the group of Prof. Pedro J. Pérez.[11]

2.22. Chiral NHC-Cu compound 29

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.23. Chiral NHC-Cu compound 30

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.24. Chiral NHC-Cu compound 31

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

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2.25. Chiral NHC-Cu compound 31

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.26. Chiral NHC-Cu compound 32

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.27. Chiral NHC-Cu compound 33

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.28. Chiral NHC-Cu compound 34

This complex was prepared by the group of Prof. Pedro J. Pérez.[12]

2.29. NHC-Pt compound 35

This complex was prepared by the group of Prof. Eduardo Peris.[13]

2.30. NHC-Pt compound 36

This complex was prepared by the group of Prof. Eduardo Peris.[13]

2.31. NHC-Pt compound 37

This complex was prepared by the group of Prof. Eduardo Peris.[13]

2.32. Chiral NHC-Pt compound 38

This complex was prepared by the group of Prof. Eduardo Peris.[14]

2.33. Chiral NHC-Pt compound 39

This complex was prepared by the group of Prof. Eduardo Peris.[14]

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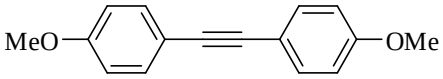
3.1. Synthesis of the internal alkynes

This synthesis was performed following a previously reported proceeding.[15] To a mixture of $[Pd(PPh_3)_2Cl_2]$ (0,05 mmol) and CuI (0,05 mmol) in triethylamine (75 ml) were added 4-XC_6H_4I (5 mmol) and 4-$YC_6H_4C{\equiv}CH$ (5,5 mmol). Formation of a solid deposit began immediately, and vigorous stirring at room temperature was required for 1 hour. After filtration through silica, the solvent was removed from the dark solution under reduced pressure. The oily solid produced was dissolved in Et_2O (25 ml) and washed with dilute aqueous HCl (0,2M, 3x50ml). The ether was removed from the residue under reduced pressure.

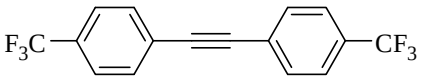
3.2. Selected NMR data

Di(*p*-methoxyphenyl)acetylene (27f)[16]



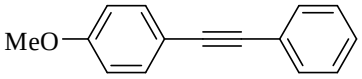
Yield: 29%. ^{1}H NMR ($CDCl_3$): 3.82 (s, 6H), 6.86 (d, J= 8.8 Hz, 4H), 7.44 (d, J= 8.8 Hz, 4H).

Di(*p*-trifluoromethylphenyl)acetylene (27g)[15]



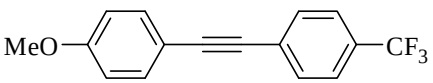
Yield: 87%. ^{1}H NMR ($CDCl_3$): 7.64 (m, 8H). ^{19}F NMR ($CDCl_3$): -63.03 (s, 6F).

1-Methoxy-4-(phenylethynyl)benzene (27h)[16]



Yield: 85%. ^{1}H NMR ($CDCl_3$): 3.83 (s, 3H), 6.88 (m, 2H), 7.33 (m, 3H), 7.51 (m, 4H).

1-Methoxy-4-(*p*-trifluoromethylphenylethynyl)benzene (27i)[17]



Yield: 94%. ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H), 6.89 (d, J= 8.7 Hz, 2H), 7.49 (d, J= 8.7 Hz, 2H), 7.59 (m, 4H). ^{19}F NMR ($CDCl_3$): -62.85 (s, 3F).

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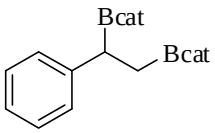
4.1. Typical catalytic diboration reaction

Catalyst precursor (and ligand when necessary) were introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in the corresponding solvent (tetrahydrofuran, toluene or acetonitrile – 2 ml when the reaction was carried out at room temperature, and 4 ml when at reflux conditions) and the mixture was stirred for 5 minutes to reach complete dissolution (and formation of the complex *in situ*, when ligand was used). Next, diboron reagent was added. The solution was stirred for 5 minutes, and then the substrate (alkene or alkyne) was added. The mixture obtained was then stirred the corresponding time at the corresponding temperature to complete the addition of the diboron into the insaturated bond. When the mild base NaOAc was used, it was added just after the diboron reagent.

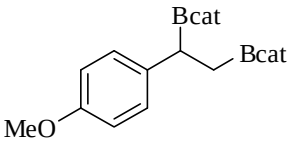
4.2. Selected NMR data for alkyldiboronate esters[18]

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



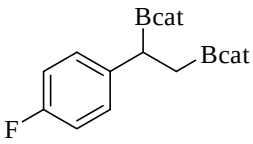
^{1}H NMR ($CDCl_3$): 1.93 (dd, J= 10 Hz, 17 Hz, 1H), 2.19 (dd, J= 10 Hz, 17 Hz, 1H), 3.36 (m, 1H), 7.00-7.45 (m, 13H).

2,2'-(1-(4-methoxyphenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3b)



^{1}H NMR ($CDCl_3$): 1.88 (dd, J= 10 Hz, 17 Hz, 1H), 2.12 (dd, J= 10 Hz, 17 Hz, 1H), 3.28 (m, 1H), 3.76 (s, 3H), 6.85 (m, 2H), 7.00-7.35 (m, 10H).

2,2'-(1-(4-fluorophenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3c)



^{1}H NMR ($CDCl_3$): 1.90 (dd, J= 9.8 Hz, 17.1 Hz, 1H), 2.15 (dd, J= 9.8 Hz, 17.1 Hz, 1H), 3.33 (m, 1H), 6.90-7.40 (m, 12H).

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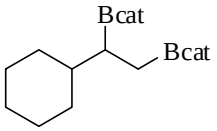
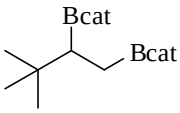
Experimental Section

2,2'-(1-cyclohexylethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3d)



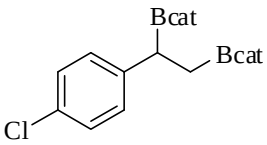
^{1}H NMR ($CDCl_3$): 1-1.95 (m, 14H), 7.00-7.45 (m, 8H).

2,2'-(3,3-dimethylbutane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3e)



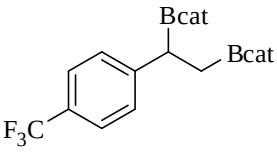
^{1}H NMR ($CDCl_3$): 1.08 (s, 9H), 1.62 (d, J= 11 Hz, 2H), 1.85 (t, J= 11 Hz, 1H), 7.00-7.45 (m, 8H).

2,2'-(1-(4-chlorophenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3f)



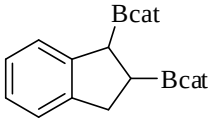
^{1}H NMR ($CDCl_3$): 1.88 (dd, J= 17 Hz, 9.9 Hz, 1H), 2.15 (dd, J= 17 Hz, 9.9 Hz, 1H), 3.31 (m, 1H), 7.00-7.50 (m, 12H).

2,2'-(1-(4-trifluoromethylphenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3g)



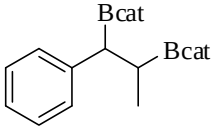
^{1}H NMR ($CDCl_3$): 1.95 (dd, J= 16.7 Hz, 9.3 Hz, 1H), 2.21 (dd, J= 16.7 Hz, 9.3 1H), 3.45 (m, 1H), 7.00-7.50 (m, 12H).

2,2'-(1-phenylpropane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3h)



^{1}H NMR ($CDCl_3$): 2.77 (m, 1H), 3.35 (m, 1H), 3.47 (m, 1H), 3.67 (m, 1H), 7.00-7.50 (m, 12H).

2,2'-(1-phenylpropane-1,2-diyl)dibenzo[1,3,2]dioxaborole (3i)



^{1}H NMR ($CDCl_3$): 1.13 (d, J= 7.6 Hz, 3H), 2.34 (m, 1H), 3.02 (d, J= 11.6 Hz, 1H), 7.00-7.50 (m, 13H).

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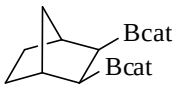
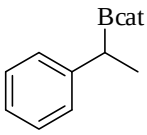
exo,exo-2,2'-bicyclo[2.2.1]heptan-2,3-diylbis-1,3,2-benzodioxaborole (3j)



^{1}H NMR ($CDCl_3$): 1.44 (m, 2H), 1.73 (m, 2H), 1.83 (s, 4H), 2.65 (s, 2H), 6.93 (s, 8H).

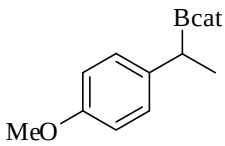
4.3. Selected NMR data for alkylboronate esters[19]

2-(1-phenylethyl)benzo[1,3,2]dioxaborole (4a)



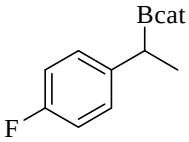
^{1}H NMR ($CDCl_3$): 1.70 (d, J= 7.7 Hz, 3H), 3.04 (q, J= 7.7 Hz, 1H), 7.00-7.50 (m, J= 9H).

2-(1-(4-methoxyphenyl)ethyl)benzo[1,3,2]dioxaborole (4b)



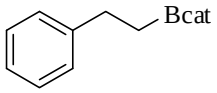
^{1}H NMR ($CDCl_3$): 1.68 (d, J= 7.4 Hz, 3H), 3.03 (q, J= 7.4 Hz, 1H), 3.86 (s, 3H), 6.98 (d, J= 8.6 Hz, 2H), 7.09 (m, 2H), 7.30 (m, 2H), 7.35 (d, J= 8.6 Hz, 2H).

2-(1-(4-fluorophenyl)ethyl)benzo[1,3,2]dioxaborole (4c)



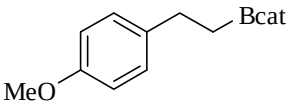
^{1}H NMR ($CDCl_3$): 1.63 (d, J= 7.6 Hz, 3H), 3.02 (q, J= 7.6 Hz, 1H), 7.1-7.4 (m, 8H).

2-phenethylbenzo[1,3,2]dioxaborole (5a)



^{1}H NMR ($CDCl_3$): 1.67 (t, J= 8.2 Hz, 2H), 2.99 (t, J= 8.2 Hz, 2H), 7.00-7.20 (m, 9H).

2-(4-methoxyphenethyl)benzo[1,3,2]dioxaborole (5b)



^{1}H NMR ($CDCl_3$): 1.55 (t, J= 8 Hz, 2H), 2.90 (t, J= 8 Hz, 2H), 3.65 (3H, s), 6.73-7.17 (m, 8H).

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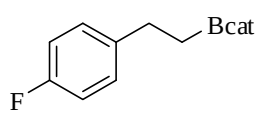
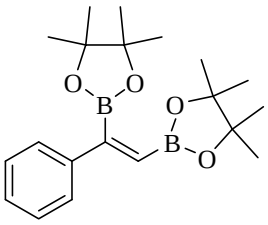
2-(4-fluorophenethyl)benzo[1,3,2]dioxaborole (5c)



^{1}H NMR ($CDCl_3$): 1.59 (t, J= 8.1 Hz, 2H), 2.92 (t, J= 8.1 Hz, 2H), 6.90-7.40 (m, 8H).

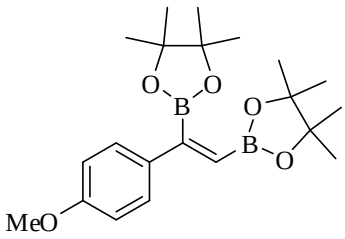
4.3. Selected NMR data for alkenyldiboronate esters[20]

(E)-Phenyl-1,2-ethylenediboronic acid bis(pinacol) ester (28a1)



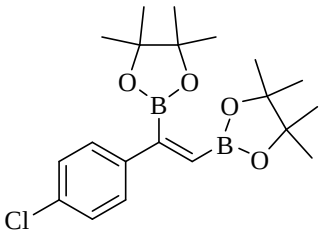
^{1}H NMR ($CDCl_3$): 1.30 (s, 12H), 1.37 (s, 12H), 6.28 (s, 1H), 7.28 (m, 3H), 7.43 (m, 2H)

(E)-(4-Methoxyphenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28b1)



^{1}H NMR ($CDCl_3$): 1.29 (s, 12H), 1.37 (s, 12H), 3.78 (s, 3H), 6.20 (s, 1H), 6.83 (d, J= 8.8 Hz, 2H), 7.38 (d, J= 8.8 Hz, 2H).

(E)-(4-Chlorophenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28c1)



^{1}H NMR ($CDCl_3$): 1.31 (s, 12H), 1.38 (s, 12H), 6.28 (s, 1H), 7.27 (d, J= 8.7 Hz, 2H), 7.36 (d, J= 8.7 Hz, 2H).

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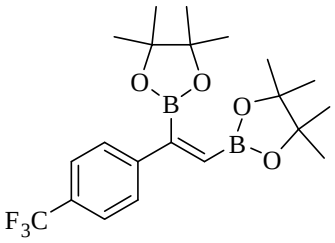
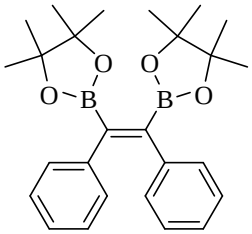
(E)-(4-trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28d1)



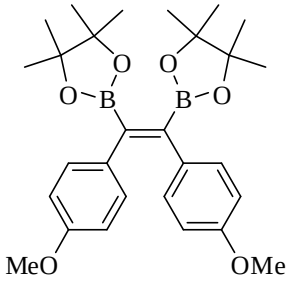
^{1}H NMR ($CDCl_3$): 1.32 (s, 12H), 1.37 (s, 12H), 6.34 (s, 1H), 7.50 (d, J= 8Hz, 2H), 7.55 (d, J= 8Hz, 2H). ^{19}F NMR ($CDCl_3$): -62.6 (s, 3F).

(Z)-1,2-diphenyl-1,2-ethylenediboronic acid bis(pinacol) ester (28e1)



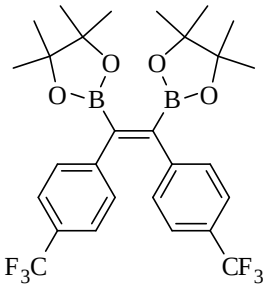
^{1}H NMR ($CDCl_3$): 1.32 (s, 24H), 6.94 (m, 4H), 7.05 (m, 6H).

(Z)-1,2-di(4-methoxyphenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28f1)



^{1}H NMR ($CDCl_3$): 1.32 (s, 24H), 3.71 (s, 6H), 6.63 (d, J= 8.8 Hz, 4H), 6.88 (d, J= 8.8 Hz, 4H).

(Z)-1,2-di(4-trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28g1)



^{1}H NMR ($CDCl_3$): 1.32 (s, 24H), 7.03 (d, J= 8.1 Hz, 4H), 7.34 (d, J= 8.1 Hz, 4H). ^{19}F NMR ($CDCl_3$): -62.6 (s, 6F).

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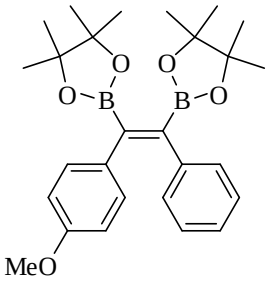
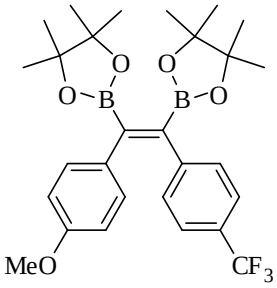
(Z)-1-(4-methoxyphenyl)-2-phenyl-1,2-ethylenediboronic acid bis(pinacol) ester (28h1)



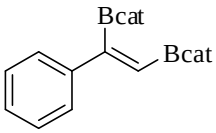
^{1}H NMR ($CDCl_3$): 1.31 (s, 12H), 1.32 (s, 12H), 3.70 (s, 3H), 6.61 (d, J= 8.7 Hz, 2H), 6.87 (d, J= 8.7 Hz, 2H), 6.95 (m, 2H), 7.06 (m, 3H).

(Z)-1-(4-methoxyphenyl)-2-(4-trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(pinacol) ester (28i1)



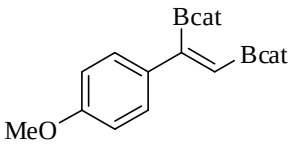
^{1}H NMR ($CDCl_3$): 1.31 (s, 12H), 1.33 (s, 12H), 3.71 (s, 3H), 6.62 (d, J= 9.3 Hz, 2H), 6.85 (d, J= 9.3 Hz, 2H), 7.06 (d, J= 8.7 Hz, 2H), 7.33 (d, J=8,7 Hz, 2H).

(E)-Phenyl-1,2-ethylenediboronic acid bis(catechol) ester (28a2)



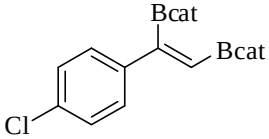
^{1}H NMR ($CDCl_3$): 6.98 (s, 1H), 7.01 (s, 4H), 7.10 (m, 2H), 7.25 (m, 2H), 7.30 (m, 3H), 7.54 (m, 2H).

(E)-(4-Methoxyphenyl)-1,2-ethylenediboronic acid bis(catechol) ester(28b2)



^{1}H NMR ($CDCl_3$): 3.81 (s, 3H), 6.87 (s, 1H), 6.90 (d, J= 8.8 Hz, 2H), 6.98 (s, 4H), 7.16 (m, 2H), 7.30 (m, 2H), 7.52 (d, J= 8.8 Hz, 2H).

(E)-(4-Chlorophenyl)-1,2-ethylenediboronic acid bis(catechol) ester (28c2)



^{1}H NMR ($CDCl_3$): 6.94 (s, 1H), 7.02 (s, 4H), 7.15 (m, 2H), 7.27 (m, 2H), 7.36 (d, J= 8.9 Hz, 2H), 7.50 (d, J= 8.9 Hz, 2H).

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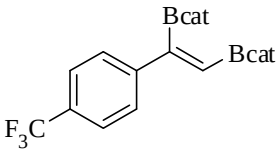
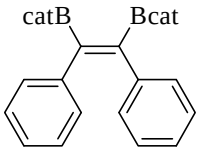
(E)-(4-Trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(catechol) ester (28d2)



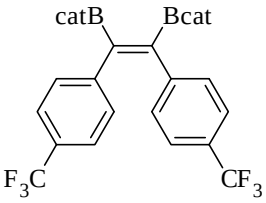
^{1}H NMR ($CDCl_3$): 7.01-7.09 (m, 7H), 7.15 (m, 2H), 7.26 (m, 2H), 7.67 (m, 2H). ^{19}F NMR ($CDCl_3$): -63.1 (s, 3F).

(Z)-1,2-diphenyl-1,2-ethylenediboronic acid bis(catechol) ester (28e2)



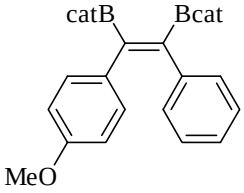
^{1}H NMR ($CDCl_3$): 7.00 (m, 4H), 7.05 (m, 4H), 7.18 (m, 10H).

(Z)-1,2-di(4-trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(catechol) ester (28g2)



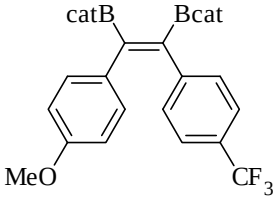
^{1}H NMR ($CDCl_3$): 7.09 (s, 4H), 7.19 (m, 2H), 7.29 (m, 4H) 7.39 (m, 2H), 7.49 (m, 4H). ^{19}F NMR ($CDCl_3$): -63.04 (s, 6F).

(Z)-1-(4-methoxyphenyl)-2-phenyl-1,2-ethylenediboronic acid bis(catechol) ester (28h2)



^{1}H NMR ($CDCl_3$): 6.74 (d, J= 8.6 Hz, 2H), 6.92 (d, J= 8.6 Hz, 2H), 7.0-7.4 (m, 13H).

(Z)-1-(4-methoxyphenyl)-2-(4-trifluoromethylphenyl)-1,2-ethylenediboronic acid bis(catechol) ester (28i2)



^{1}H NMR ($CDCl_3$): 3.76 (s, 3H), 6.9-7.5 (m, 16H). ^{19}F NMR ($CDCl_3$): -63.14 (s, 3H).

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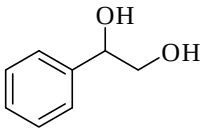
5.1. Typical oxidative work up

Oxidation of the borylated products derivated from alkenes was done to obtain the percentages of product formation. It must be carried out carefully owing to the risk of explosion when using peroxides with THF. NaOH (3M, 1 mL) and H_2O_2 (1 mL) were added successively to the borylated mixture and then it was stirred for 3 hours. After this time, 1 mL of saturated $Na_2S_2O_3$ was added to remove the excess of H_2O_2, followed by 10 mL of NaOH (1M). The reaction mixture was extracted into AcOEt (3x25 mL), washed with brine and dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent.

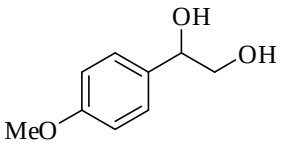
5.2. Selected NMR data for the alcoholic derivatives[21]

Phenylethane-1,2-diol



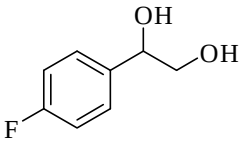
^{1}H NMR ($CDCl_3$): 3.65 (dd, J= 10.8 Hz, 8.0 Hz, 1H), 3.75 (dd, J= 10.8 Hz, 3.6 Hz, 1H), 4.81 (dd, J= 8.0 Hz, 3.6 Hz, 1H), 7.41-7.26 (m, 5H).

(4-methoxyphenyl)ethane-1,2-diol



^{1}H NMR ($CDCl_3$): 3.60-3.72 (m, 2H), 3.78 (s, 3H), 3.75 (dd, J= 3.8 Hz, 8.1 Hz, 1H), 6.82-7.31 (m, 4H).

(4-fluorophenyl)ethane-1,2-diol



^{1}H NMR ($CDCl_3$): 3.64 (br, 1H), 3.76 (br, 1H), 4.82 (br, 1H), 7.06 (t, J=8.4 Hz, 2H), 7.34 (dd, J=8.1 Hz, 5.5 Hz, 2H).

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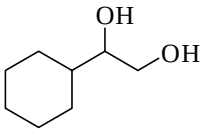
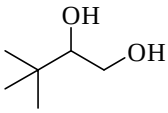
Cyclohexylethane-1,2-diol



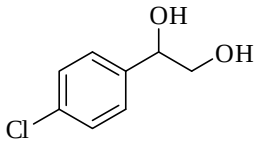
^{1}H NMR ($CDCl_3$): 0.9-1.5 (m, 6H), 1.63 (m, 2H), 1.73 (m, 2H), 1.84 (d, J = 12.4 Hz, 1H), 3.42 (m, 1H), 3.51 (m, 1H), 3.68 (d, J = 9.6 Hz, 1H).

3,3-dimethylbutane-1,2-diol



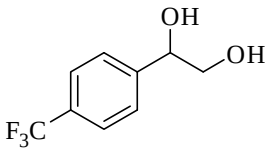
^{1}H NMR ($CDCl_3$): 0.91 (s, 9H), 3.37 (dd, J= 9.2 Hz, 2.8 Hz, 1H), 3.47 (dd, J= 10.8 Hz, 9.2 Hz, 1H), 3.73 (dd, J= 10.8 Hz, 2.8 Hz, 1H).

(4-chlorophenyl)ethane-1,2-diol



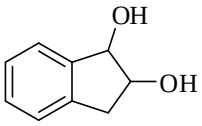
^{1}H NMR ($CDCl_3$): 3.56-3.73 (m, 2H), 4.77 (dd, J= 3.4 Hz, 8.3 Hz, 1H), 7.26-7.32 (m, 4H).

(4-trifluoromethylphenyl)ethane-1,2-diol



^{1}H NMR ($CDCl_3$): 3.65 (ddd, J= 11.3 Hz, 8.0 Hz, 5.0 Hz, 1H), 3.82 (ddd, J= 11.1 Hz, 6.9 Hz, 3.4 Hz, 1H), 4.90 (m, 1H), 7.51 (d, J= 8.0, 2H), 7.63 (d, J= 8.2, 2H).

***cis*-indan-1,2-diol**



^{1}H NMR ($CDCl_3$): 2.95 (dd, J= 16.4 Hz, 4.4 Hz, 1H), 3.12 (dd, J= 16.4 Hz, 5.6 Hz, 1H), 4.51 (br m, 1H), 5.00 (dd, J= 5.6 Hz, 5.6 Hz, 1H), 7.2-7.3 (m, 3H), 7.4 (m, 1H).

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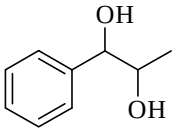
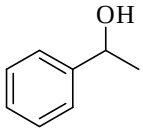
cis-phenylpropan-1,2-diol



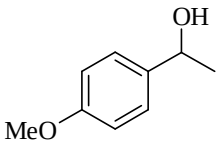
^{1}H NMR: 1.05 (d, J = 6.4 Hz, 3H), 3.85 (qd, J = 7.2 Hz, 6.4 Hz, 1H), 4.36 (d, J= 7.6 Hz , 1H), 7.25-7.42 (m, 5H).

1-Phenylethanol



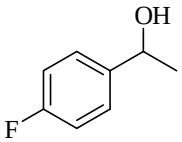
^{1}H NMR ($CDCl_3$): 1.50 (d, J= 6.6 Hz, 3H), 4.55 (q, J= 6.6 Hz, 1H), 7.20-7.50 (m, 5H).

1-(4-methoxyphenyl)ethanol



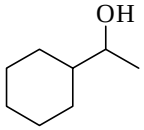
^{1}H NMR ($CDCl_3$): 1.48 (d, J= 6.5 Hz, 3H), 3.82 (s, 3H), 4.87 (q, J= 6.5 Hz, 1H), 6.9 (d, J= 8.2 Hz, 2H), 7.31 (d, J= 8.2 Hz, 2H).

1-(4-fluorophenyl)ethanol



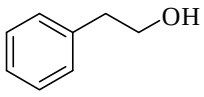
^{1}H NMR ($CDCl_3$): 1.48 (d, J= 6.4 Hz, 3H), 4.86 (q, J= 6.4 Hz, 1H), 7.10-7.40 (m, 4H).

1-Cyclohexylethanol



^{1}H NMR (CDCl3): 0.84-1.25 (m, 7H), 1.09 (d, J= 6.4 Hz, 3H) 1.56-1.80 (m, 5H), 3.48 (dq, J= 6.4 Hz, 6.4 Hz, 1H).

2-Phenylethanol



^{1}H NMR ($CDCl_3$): 2.88 (t, J= 6.6 Hz, 2H), 3.85 (t, J= 6.6 Hz, 2H), 7.22-7.37 (m, 5H).

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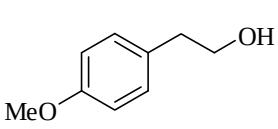
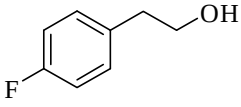
2-(4-methoxyphenyl)ethanol



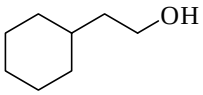
^{1}H NMR ($CDCl_3$): 2.81 (t, J= 6.5 Hz, 2H), 3.79 (s, 3H), 3.82 (t, J= 6.5 Hz, 2H), 6.86 (d, J= 8.5 Hz, 2H), 7.15 (d, J= 8.5 Hz, 2H).

2-(4-fluorophenyl)ethanol



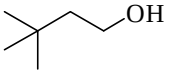
^{1}H NMR ($CDCl_3$): 2.84 (t, J= 6.6 Hz, 2H), 3.84 (t, J= 6.6 Hz, 2H), 7.00 (t, J= 8.6 Hz, 2H), 7.16-7.26 (m, 2H).

2-Cyclohexylethanol



^{1}H NMR ($CDCl_3$): 0.75-1.00 (m, 2H), 1.00-1.35 (m, 4H), 1.50- 1.85 (m, 5H), 3.6 (t, J= 5Hz, 2H).

3,3-dimethylbutanol



^{1}H NMR ($CDCl_3$): 0.92 (s, 9H), 1.51 (t, J= 7.8 Hz, 2H), 3.57 (t, J= 7.8 Hz, 2H).

6. Typical diol derivatization

The diols obtained are too polar to be resolved by means of gas cromatography in order to determine the enantiomeric excess. Therefore, the diols were derivatized into the corresponding cetals (Figure 1). To carry out this derivatization, the phenylethane-1,2-diol was dissolved in acetone, and Montmorillonite K-10 (MK-10) was added to the solution. MK-10 provides the acidic media necessary to carry out the derivatization, and also absorbs the water formed. The product obtained was characterized by ^{1}H NMR and ^{13}C NMR, and the conversion was calculated to be quantitative. During this

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derivatization, the enantioselectivity was comproved to be constant, comparing the results obtained with those reported in the literature.[21a] This method was extended to the rest of diols.

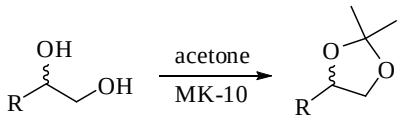
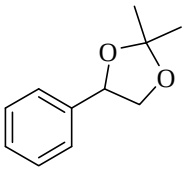


Figure 1

2,2-Dimethyl-4-phenyl-1,3-dioxolane[22]



^{1}H NMR ($CDCl_3$): 1.50 (s, 3H), 1.57 (s, 3H), 3.72 (t, J= 8.1 Hz, 1H), 4.32 (dd, J= 8.1 Hz, 6 Hz, 1H), 5.08 (dd, J= 8.1 Hz, 6 Hz, 1H), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): 26.43, 27.05, 72.15, 78.41, 110.17, 126.68, 128.51, 128.99, 139.39.

7.1. Typical tandem catalytic alkyne diboration/fluorination reaction

Pt(0) catalyst was introduced in a previously purged schlenk, and it was dissolved in acetonitrile under nitrogen atmosphere. The alkyne was then added to the solution, followed by the diborating reagent bis(pinacolato)diboron (**1**). After the mixture was stirred at reflux temperature (82ºC) for 15h, 2 equiv of Selectfluor and 2.2 equiv of $NaHCO_3$ base were added to the crude preparation of the diborated product. After an additional 15h stirring at room temperature, an NMR spectrum of an aliquot showed the formation of the expected 2,2-difluorocetone, with complete conversion of the substrate. The products obtained were characterized by ^{1}H NMR and ^{19}F NMR. Yield was calculated using perfluoronaphthalene as an internal standard.

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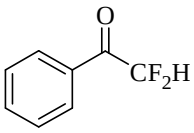
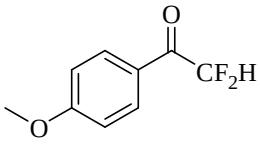
7.2. Selected NMR data.[23]

2,2-difluoro-1-phenylethanone (45a)



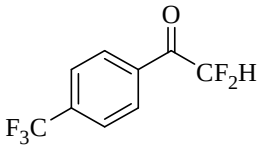
^{1}H NMR ($CDCl_3$): 6.30 (t, J= 54 Hz, 1H), 7.53 (m, 2H), 7.66 (m, 1H), 8.07 (m, 2H). ^{19}F NMR ($CDCl_3$): -122.5 (d, J= 54 Hz, 2F).

2,2-difluoro-1-(4-methoxyphenyl)ethanone (45b)



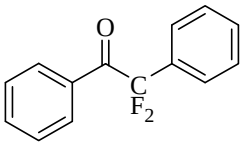
^{1}H NMR ($CDCl_3$): 3.86 (s, 3H), 6.23 (t, J= 53.5 Hz, 1H), 6.94 (d, J= 9.2 Hz, 2H), 8.01 (d, J= 9.2 Hz, 2H). ^{19}F NMR ($CDCl_3$): -121.7 (d, J= 53.5 Hz, 2F).

2,2-difluoro-1-(4-trifluoromethylphenyl)ethanone (45c)



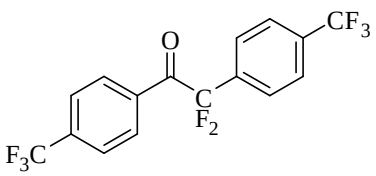
^{1}H NMR ($CDCl_3$): 6.27 (t, J= 53.2 Hz, 1H), 7.78 (d, J= 8.2 Hz, 2H), 8.18 (d, J= 8.2 Hz, 2H). ^{19}F NMR ($CDCl_3$): -122.2 (d, J= 53.5 Hz, 2F), -63.65 (s, 3F). GC/MS: 205.

2,2-difluoro-1,2-diphenylethanone (45d)



^{1}H NMR ($CDCl_3$): 7.3-8.1 (m, 10H). ^{19}F NMR ($CDCl_3$): -97.7 (s, 2F).

2,2-difluoro-1,2-bis(4-trifluoromethylphenyl)ethanone (45e)



^{1}H NMR ($CDCl_3$): 7.1-8.2 (m, 8H). ^{19}F NMR ($CDCl_3$): -63.28 (s, 3F), -63.68 (s, 3F), -98.54 (s, 2F).

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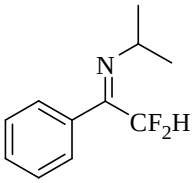
8.1. Typical tandem catalytic alkyne diboration/fluorination/imination reaction

Following the same procedure as in the catalytic alkyne diboration/fluorination reaction, once the fluorinated cetone has been obtained, in situ addition of 4 equiv of the amine and Montmorillonite K-10 (MK-10) or $TiCl_4$ as dehydrating agent, allowed the α,α-difluoroimine formation, after 15h of stirring. Products obtained were characterized by ^{1}H NMR and ^{19}F NMR. Yield was calculated using perfluoronaphthalene as an internal standard.

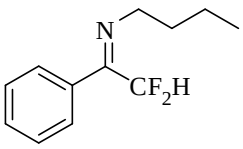
8.2. Selected NMR data[24]

***N*-(2,2-difluoro-1-phenylethylidene)propan-2-amine (46a)**



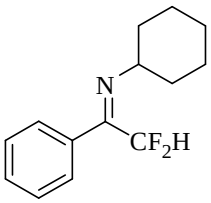
^{1}H NMR ($CDCl_3$): 1.12 (d, J= 6.2 Hz, 6H), 3.59 (sept, J= 6.2 Hz, 1H), 6.13 (t, J= 55.4 Hz, 1H), 7.23 (m, 2H), 7.44 (m, 3H). ^{19}F NMR ($CDCl_3$): -117.8 (d, J= 55.4 Hz, 2F).

***N*-(2,2-difluoro-1-phenylethylidene)butan-1-amine (46b)**



^{1}H NMR ($CDCl_3$): 0.86 (t, J= 6.9 Hz, 3H), 1.26 (m, 2H), 1.58 (m, 2H), 3.34 (m, 2H), 6.15 (t, J= 55.5 Hz, 1H), 7.23 (m, 2H), 7.45 (m, 3H). ^{19}F NMR ($CDCl_3$): -117.8 (d, J= 55.5 Hz, 2F). ^{13}C NMR ($CDCl_3$): 14.0, 20.6, 32.8, 53.0, 115.6 (t, J=242 Hz), 128.1, 128.7, 129.6. GC/MS: 210.

***N*-(2,2-difluoro-1-phenylethylidene)cyclohexanamine (46c)**



^{1}H NMR ($CDCl_3$): 0.8-1.8 (m, 10H), 3.23 (m, 1H), 6.12 (t, J= 55 Hz, 1H), 7.48 (m, 2H), 7.60 (m, 1H), 7.80 (m, 2H). ^{19}F NMR ($CDCl_3$): -118.11 (d, J= 55 Hz, 2F). ^{13}C NMR ($CDCl_3$): 14.3, 24.3, 25.6, 33.5, 115.6 (t, J= 244 Hz), 128.0, 128.5, 129.5. GC/MS: 235.

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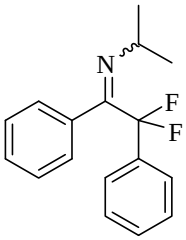
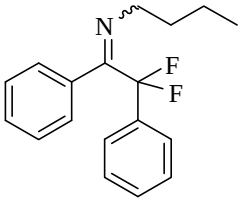
_N_-(2,2-difluoro-1,2-diphenylethylidene)propan-2-amine (46d)



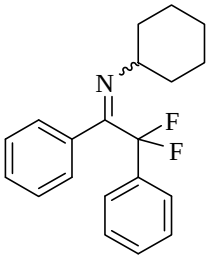
This product was obtained as a mixture of isomers (E/Z = 11/4). ^{1}H NMR ($CDCl_3$): 1.06 (d, J= 6 Hz ,6H, E), 1.11 (d, J= 6 Hz , 6H, Z), 3.42 (m, 1H, E), 3.57 (m, 1H, Z), 6.88-7.84 (m, 10H, E and Z). ^{19}F NMR ($CDCl_3$): -100.00 (s, 2F). GC/MS: 272.

_N_-(2,2-difluoro-1,2-diphenylethylidene)butan-1-amine (46e)



This product was obtained as a mixture of isomers (E/Z = 8/3). ^{1}H NMR ($CDCl_3$): 0.82 (t, J= 7.2 Hz, 3H, E), 0.88 (t, J= 7.2 Hz, 3H, E), 1.27 (m, 2H, E), 1.37 (m, 2H, Z), 1.57 (m, 2H, E), 1.66 (m, 2H, Z), 3.26 (tt, J= 1.6 Hz, 7.6 Hz, 2H, E), 3.33 (t, J= 7.6 Hz, 2H, Z), 6.92-7.74 (m, 10H, E and Z). ^{19}F NMR ($CDCl_3$): -99.37 (s, 2F). GC/MS: 286.

_N_-(2,2-difluoro-1,2-diphenylethylidene)cyclohexanamine (46f)



This product was obtained as a mixture of isomers (E/Z = 5/2). ^{1}H NMR ($CDCl_3$): 0.80-1.90 (m, 10H, E and Z), 3.05 (m, 1H, E), 3.22 (m, 1H, Z), 6.82-7.84 (m, 10H, E and Z). ^{19}F NMR ($CDCl_3$): -99.70 (s, 2F). GC/MS: 312.

9.1. Asymmetric electrophilic fluorination of α-nitro esters

Method A: 0.375 mmol of α-nitro ester were introduced in a schlenk and dissolved in 6 ml of a 1 to 1 mixture of CH_3CN and water. After that, 0.8 ml of a 0.5M KOH solution were added, and the mixture was stirred for 2 hours.

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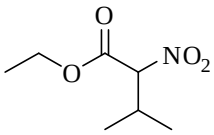
Next, a CH_3CN solution of the fluorinating reagent (1 equiv.) was added, and the mixture obtained was stirred overnight.

Method B: 0.375 mmol of α-nitro ester were introduced in a previously purged schlenk and were dissolved in 5 ml of dry THF. Then, 1 equiv. of NaH in mineral oil was added, and the mixture was stirred for half an hour. Passed this time, a CH_3CN solution of the fluorinating reagent (1 equiv.) was added, and the mixture obtained was stirred overnight.

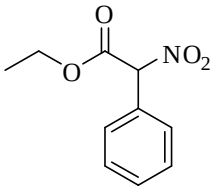
9.2. Selected NMR data

Ethyl 3-methyl-2-nitrobutanoate (47b)



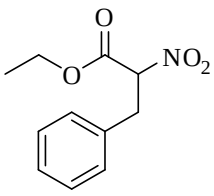
^{1}H NMR ($CDCl_3$): 1.10 (dd, J= 2.1 Hz, 6.6 Hz, 6H), 1.33 (t, J= 7.2 Hz, 3H), 2.68 (m, J= 6.6 Hz, 1H), 4.31 (q, J= 7.2 Hz, 2H), 4.89 (d, J= 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 18.4, 18.8, 30.1, 62.7, 93.6, 163.8.

Ethyl 2-nitro-2-phenylacetate (47c)



^{1}H NMR ($CDCl_3$): 1.33 (t, J= 6.9 Hz, 3H), 4.35 (m, 2H), 6.18 (s, 1H), 7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.9, 63.3, 90.9, 129.0, 129.1, 129.9, 130.8, 163.9.

Ethyl 2-nitro-3-phenylpropanoate (47d)



^{1}H NMR ($CDCl_3$): 1.27 (t, J= 7.1 Hz, 3H), 3.48-3.55 (m, 2H), 4.27 (q, J= 7.1 Hz, 2H), 5.29-5.37 (m, 1H), 7.18-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): 13.8, 36.1, 56.9, 89.1, 127.7, 127.9, 128.9, 129.5, 129.7, 134.0, 164.0.

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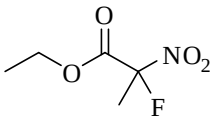
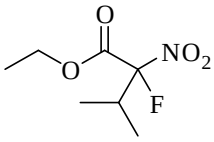
Ethyl 2-fluoro-2-nitropropanoate (48a)



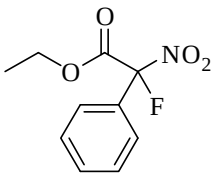
^{1}H NMR ($CDCl_3$): 1.37 (t, J= 7.0 Hz, 3H), 2.12 (d, J= 20.2 Hz, 3H), 4.38 (q, J= 7 Hz, 2H). ^{19}F NMR ($CDCl_3$): -120.3 (q, J= 20.2 Hz). ^{13}C NMR ($CDCl_3$): 13.7, 20 (d, J= 22 Hz), 64.2, 112.5 (d, J= 248 Hz), 161.5 (d, J= 27 Hz).

Ethyl 2-fluoro-3-methyl-2-nitrobutanoate (48b)



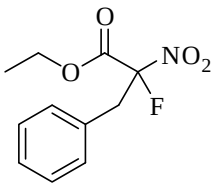
^{1}H NMR ($CDCl_3$): 1.12 (t, J= 7.00 Hz, 6H), 1.37 (t, J= 7.25, 3H), 3.04 (dsp, J= 26.0 Hz, 7.0 Hz, 1H), 4.38 (q, J= 7.25 Hz, 2H). ^{19}F NMR ($CDCl_3$): -140.9 (d, J= 26.0 Hz). ^{13}C NMR ($CDCl_3$): 13.7, 15.0 (d, J= 3.0 Hz), 15.9 (d, J= 3.0 Hz), 33.2 (d, J= 20.2 Hz), 63.9, 116.9 (d, J= 254 Hz), 160.9 (d, J= 27.8 Hz).

Ethyl 2-fluoro-2-nitro-2-phenylacetate (48c)



^{1}H NMR ($CDCl_3$): 1.40 (t, J= 7.2 Hz, 3H), 4.47 (q, J= 7.2 Hz, 2H), 7.47-7.60 (m, 3H), 7.72-7.78 (m, 2H). ^{19}F NMR ($CDCl_3$): -125.85 (s). ^{13}C NMR ($CDCl_3$): 13.7, 64.5, 112.5 (d, J= 251 Hz), 126.4, 126.5, 128.6, 131.7, 161.2 (d, J= 27 Hz).

Ethyl 2-fluoro-2-nitro-3-phenylpropanoate (48d)



^{1}H NMR ($CDCl_3$): 1.33 (t, J= 6.9 Hz, 3H), 3.76 (d, J= 22.8 Hz, 2H), 4.36 (q, J= 6.9 Hz, 2H), 7.24-7.29 (m, 2H), 7.32-7.36 (m, 3H). ^{19}F NMR ($CDCl_3$): -127.4 (t, J= 22.8 Hz). ^{13}C NMR ($CDCl_3$): 13.7, 39.9 (d, J= 22 Hz), 64.2, 113.7 (d, J= 251 Hz), 128.5, 128.8, 129.6, 130.3, 161.0 (d, J= 27 Hz).

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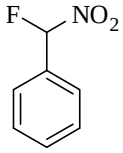
[Fluoro(nitro)methyl]benzene (50)[25]



^{1}H NMR ($CDCl_3$): 6.65 (d, J= 49 Hz, 1H), 7.45-7.68 (m, 5H). ^{19}F NMR ($CDCl_3$): -139.9 (d, J= 49.0 Hz).

10.- Computational details

Calculations were performed using the Gaussian03 series of programs.[26] Density functional theory (DFT) was applied with the BP86/DFT functional. Rhodium atoms were described using an effective core potential (LANL2DZ) for the inner electrons, and also P atoms were, but using an additional d polarization shell. The O, N and C atoms were represented by means of the 6-31G(d) basis set, and also the C atoms of the alkene. H atoms of the alkene were represented by means of the 6-31G(d,p) basis set, whereas the 6-31G basis set was employed for the rest of the C and H atoms. 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 negative frequency.

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Resum

Els compostos organoborats són intermedis de reacció molt valuosos en síntesi orgànica, degut a que l'enllaç carboni-bor pot ser derivatitzat de múltiples maneres. La diboració catalitzada d'alquins i alquens ha estat ampliament estudiada en els darrers quinze anys, essent la diboració catalitzada d'alquins un procés en el que s'han obtingut elevats rendiments i activitats. No obstant això, en la diboració catalitzada d'alquens la presència de la reacció secundaria de β-eliminació de H sempre s'ha presentat com un seriós inconvenient, impedint un bon compromís entre activitat catalítica i quimioselectivitat.

En el primer capítol de la present tesi es recull l'evolució a través de la bibliografia de les reaccions de diboració d'alquens i alquins, els diferents metalls i lligands utilitzats en la reacció catalítica de diboració i els estudis mecanístics que s'han realitzat fins a data d'avui. Tanmateix, s'han posat de manifest les diferents derivatitzacions que s'han dut a terme a partir d'intermitjos organoborats. També es descriu breument la tècnica de les microones. Com a punt final del capítol, s'introdueixen els objectius de la tesi, incloent-hi el desenvolupament de nous sistemes catalítics que millorin l'activitat, quimioselectivitat i enantioselectivitat dels catalitzadors reportats prèviament en la reacció de diboració catalítica, l'estudi del mecanisme de la reacció de diboració d'alquens catalitzada per rodi, i la busqueda de nous mètodes de fluorofuncionalització d'esters vinil(bisboronics).

En el segon capítol es descriu l'activitat, quimioselectivitat i enantioselectivitat de diferents precursors catalítics en la diboració catalitzada d'alquens i alquins. En el primer apartat es porta a terme un estudi en profunditat de la diboració d'alquens catalitzada per compostos de Rh(I), observant-se que en aquest cas els efectes estèrics en el diborà tenen un efecte dramàtic en la quimioselectivitat de la reacció. També s'observa que el lligand

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que ofereix una major quimioselectivitat es el DPPM (bis(difenilfosfino)metà), mostrant una influència del *bite angle* del lligand, mentre que el lligand QUINAP (1-(2-difenilfosfino-1-naftil)isoquinolina) és el que ofereix una major enantioselectivitat. En els següents apartats es descriu la utilització de diferents complexos d'or, argent, coure i platí modificats amb lligands carbens, els quals augmenten la quimioselectivitat de la reacció, reduïnt la producció de subproductes de β-eliminació de H. Malgrat que s'han utilitzat diferents carbens quirals, només en un cas s'ha aconseguit induir asimetria, utilitzant un complex de Cu(I) modificat amb un lligand carbé quiral, però comprometent la quimioselectivitat. També es descriu l'aplicació de carbens de platí i coure a la diboració catalitzada d'alquins, obtenint-se bons resultats d'activitat i quimioselectivitat. La utilització d'unes noves condicions de reacció, en les que es requereix un excés de diborà (2 eq.) i l'addició d'una base (NaOAc), fa que precursors catalítics en principi inactius, com complexos d'Au(I) modificats amb lligands difosfina tipus BINAP (2,2'-bis(difenilfosfino)-1,1'-binaftil), donin bons resultats d'activitat i quimioselectivitat, encara que malauradament no indueixen asimetria. Per últim, es descriu l'aplicació de les tècniques de microones com a mitjà d'acceleració en la diboració d'alquins catalitzada per Pt(0), disminuint-se espectacularment els temps de reacció.

En el tercer capítol de la tesi es porta a terme un estudi mecanístic de la reacció de diboració d'alquens catalitzada per Rh(I)-QUINAP. En primer lloc es porta a terme un estudi de RMN (Ressonància Magnètica Nuclear) per a detectar les possibles espècies metàl·liques implicades. A partir d'aquí, es realitza un estudi computacional DFT (*Density Functional Theory*) del mecanisme de reacció, observant-se que després de l'addició oxidant es produeix la inserció de l'alqué en un enllaç Rh-B, seguida d'un reordenament per a ocupar la posició vacant creada, finalitzant amb la eliminació reductora del producte, essent el camí més favorable aquell en el qual l'alquè queda

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coordinat *trans* al nitrogen del lligand QUINAP. L'estudi de la reacció secundària de β-eliminació de H demostra que la utilització de BINAP com a lligand l'afavoreix, en comparació amb la utilització del lligand QUINAP.

En el quart capítol es descriu la flurofuncionalització d'ésters vinil(bisborònics), la qual dóna lloc a la formació de cetones α,α-difluorades a través d'un procés de fluoració electròfila. Primer de tot, es fa una petita introducció als processos de fluoració electròfila, amb especial interès en la fluoració electròfila de compostos organosilats, els quals estan força relacionats amb els compostos organoborats. La reacció es duu a terme a partir dels alquins, a través d'un procés *tandem* de diboració catalítica/fluoració electròfila. Només els esters vinil(bisborònics) derivats del bis(pinacolato)diborà són susceptibles d'ésser derivatitzats d'aquesta manera. Els alquins interns són més actius que els alquins terminals. També es descriu la síntesi d'α,α-difluoroimines directament a partir d'alquins mitjançant un procés *tandem* de diboració catalítica/fluoració electròfila/iminació, l'eficiència del qual depen de les propietats electròniques del sustrat.

Per últim, en el capítol 5 es descriu la fluoració electròfila asimètrica d'α-nitroésters, la qual es porta a terme mitjançant la utilització d'auxiliars quirals derivats d'alcaloids de cincona, obtenint-se excessos enantiomèrics de fins a un 40%.

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Summary

Organoboron compounds are very useful intermediates in organic synthesis, because the carbon-boron bond can be cleaved in a variety of ways leading to the formation of useful functional groups. The catalyzed diboration of alkenes and alkynes has been widely studied in the last 15 years, obtaining high yields and activities in the alkyne catalyzed diboration reaction. However, when alkenes are used as substrates in the catalyzed diboration reaction, the problem of β-hydride elimination could arise, preventing a good agreement between catalytic activity and chemoselectivity.

In the first chapter of this thesys an overview of the precedents of the diboration reactions of alkenes and alkynes is presented, including the different metals and ligands used in this reactions and the mechanistic studies published to date. Moreover, there has been collected the different derivatizations of organoboron intermediates carried out. The microwave technique is also described briefly. Finally, the scope of this thesys is explained, including the development of new catalytic systems which improve the activity, chemoselectivity and enantioselectivity of the catalytic systems previously reported, the study of the mechanism of the rhodium catalyzed alkene diboration reaction, and the search of new routes for the fluorofunctionalization of organoboron compounds.

In the second chapter, the activity, chemoselectivity and enantioselectivity of different catalytic precursors in the alkene and alkyne catalytic diboration reaction is described. In the first part, a deep study on the rhodium catalyzed alkene diboration reaction is carried out, finding in this case that the steric effects on the diborating reagent have a dramatic effect on the chemoselectivity of the reaction. It is also observed that the DPPM (bis(diphenylphosphino)methane) is the ligand which provide a better

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chemoselectivity, showing an important bite angle influence on the ligand, while QUINAP (1-(2-diphenilphosphino-1-naphthyl)isoquinoline) is the ligand which offers a higher enantioselectivity. In the next parts it is described the utilization of different gold, silver, copper and platinum complexes as catalyst precursors, which improve the chemoselectivity of the reaction, reducing the β-hydride elimination side reaction. Despite several chiral carbene modified complexes have been used, only in one case some enantioselectivity was induced, using a carbene modified copper complex, but reducing chemoselectivity. It is also described the application of carbene modified copper and platinum complexes as catalyst precursors in the alkyne diboration reaction, obtaining good results in activity and chemoselectivity. The utilization of new reaction conditions, in which an excess of the diborating reagent (2 eq.) and the addition of a base (NaOAc) is required, improve the activity of catalytic systems like BINAP (2,2'-bis(difenilfosfino)-1,1'-binaphthyl) modified gold complexes, whose activity was very low under the typical conditions; unfortunately, no enantioselectivity was obtained in this case. Finally, it is described the application of microwave techniques to the platinum catalyzed alkyne diboration reaction, in order to reduce the reaction times.

In the third chapter, an in-depth study of the mechanism of the Rh(I)-catalyzed alkene diboration reaction is described. First of all, an NMR (Nuclear Magnetic Ressonance) study was carried out in order to identify plausible intermediates. Next, a DFT (Density Functional Theory) study of the reaction mechanism was carried out, finding that after the oxidative addition of the diborane, an insertion of the alkene into a Rh-B bond is produced, followed by an internal rearrangement in order to ocupy the vacant position created, and, finally, reductive elimination of the product is produced, being the most favourable path that in which the alkene is placed trans to the nitrogen of the QUINAP ligand. The study of the β-hydride elimination side reaction shows

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that the utilization of BINAP as ligand favours it, with respect to the utilization of QUINAP.

In the fourth chapter, the fluorofunctionalization of *cis*-1,2-bis(boryl)alkenes is described, leading to the formation of α,α-difluorinated ketones through an eletrophilic fluorination process. First of all, a little introduction to the electrophilic fluorination processes is made, with special interest to the electrophilic fluorination of organosilanes, which are quite similar to the organoboron compounds. The reaction is carried out starting from alkynes, through a tandem catalytic diboration/electrophilic fluorination process process. Only the *cis*-1,2-bis(boryl)alkenes derived from bis(pinacolato)diboron are susceptible to the fluorination process. Internal alkynes are more reactive than terminal ones. It is also described the synthesis of α,α-difluoroimines directly from alkynes through a tandem catalytic diboration/electrophilic fluorination/imination process, the efficiency of which depends on the electronic properties of the substrate.

Finally, in the fifth chapter, the asymmetric electrophilic fluorination of α-nitro esters is described. This process was carried out using cinchona derivatives chiral auxiliaries, obtaining enantiomeric excesses up to 40%.

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