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PhD Thesis

supervised by Dr Mª Elena Fernández

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona
2009

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MARÍA ELENA FERNÁNDEZ GUTIERREZ, profesora titulada del Departament de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili,

CERTIFICO:

Que la memoria titulada "TRANSITION METAL CATALYSED FUNCTIONALISATION OF C=C THROUGH BORON CHEMISTRY: A TANDEM APPROACH", que presenta Vanesa Lillo García para la obtención del título de Doctor en Química, ha sido realizado bajo mi supervisión en el Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili y que cumple los requisitos para poder optar a Mención Europea.

Tarragona, 4 de Mayo de 2009

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Lo maravilloso de aprender algo
es que nadie puede arrebatártelo

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A mis padres, hermanas y Raúl

Siempre habéis estado a mi lado.

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Chapter 1

Introduction

Chapter 1. **Introduction**

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Chapter 1

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Catalysis plays a key role in the industrial production of liquid fuels, bulk chemistry and, most recently fine chemistry. Homogeneous catalysis involves a catalytic system in which the substrates for a reaction and the catalyst components are brought together in one phase, most often the liquid phase, where the catalyst is usually a metal complex modified with ligands. Ligand effects, then, are extremely important in homogeneous catalysis by metal complexes. In enantioselective homogeneous metal catalysis the design of ligands is perhaps the most crucial step in achieving the highest levels of reactivity and selectivity.

Numerous reports on highly efficient systems have shown that phosphine ligands have positive effects on turnovers and selectivities applied to traditional industrial processes such as hydrogenation. However, the disadvantages of the high cost of producing tertiary (especially chiral) phosphines and their tendency to degrade to phosphine oxides have only now been addressed by the rich field of NHC ligands used in homogeneous catalysis.

The advantages of using N-heterocyclic carbenes as ancillary ligands are: 1) they are stronger σ-donors than phosphines and so provide favorable rates of metal-catalysed oxidative addition of aryl halides; 2) the strong metal-carbene bond of the NHC complex favors tight binding kinetics, and therefore diminishes ligand dissociation; 3) the presence of sterically encumbering groups bound to the N-atoms facilitate reductive elimination of the product from metal; and 4) the activity of NHC ligands can be modified by introducing electronic directing substituents remotely, as witnessed in the synthesis of benzimidazolidines that contain different electronic groups on the aromatic backbone.

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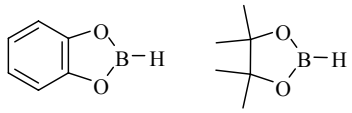
Chapter 1

1.1 General overview

Organoboron compounds are some of the most useful reagents in organic synthesis.[1] It is noteworthy that these compounds have also been used as ^{10}B carriers for neutron capture therapy[2] and biologically active compounds.[3] The traditional method for synthesising the C-B bond was the alkylation of trialkylborates or haloborons with organomagnesium or organolythium reagents through a transmetallation pathway[1d,g,4] However, probably the most common method of preparing organoboron compounds for large-scale preparations is the uncatalysed *syn* addition of a B-H bond across a C=C or C≡C bond by means of a hydroboration reaction,[1a-f] although when the boron atom is bonded to heteroatoms the electron density at boron is increased and elevated temperatures are needed for the B-H addition.[5] Männing and Nöth[6] reported the first effective catalytic hydroboration of alkenes and alkynes with catecholborane (HBcat, **1**) (Figure 1.1) catalysed by Wilkinson's catalyst [$RhCl(PPh_3)_3$]. Therefore, catalysed hydroboration of alkenes and alkynes with **1** or pinacolborane (HBpin, **2**) (Figure 1.1) [5a,7] has become a method for the asymmetric hydroboration of alkenes using a rhodium catalyst modified with chiral phosphine.[8]



HBcat **1** HBpin **2**

Figure 1.1. Catecholborane (1) and pinacolborane (2)

Similarly, the diboron tetrahalides B_2X_4 (X= F, Cl, Br) can also be added across C=C and C≡C in the absence of catalysts.[9] However, diboron tetrahalides are rather difficult to prepare and handle and are unstable to disproportionation.

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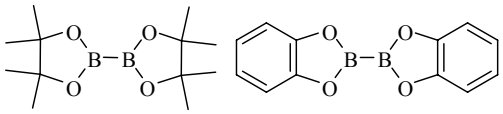
In contrast, the tetraalkoxydiboron compounds, such as bis(pinacolato)diboron (B_2pin_2, **3**) and bis(catecholato)diboron (B_2cat_2, **4**) (Figure 1.2),[10] are relatively easy to prepare from $B_2(NMe_2)_4$ and are quite stable. However, they fail to add to alkenes or alkynes under conventional reaction conditions,[11] because of the high B-B bond energy (104 kcal.mol^{-1}).



B_2pin_2 **3** B_2cat_2 **4**

Figure 1.2. Bis(pinacolato) diboron (1) and bis(catecholato) diboron (2)

The advantage of this sort of reagents is that they can be oxidatively added to a low-valent transition metal to favour the B-B bond cleavage, thus allowing the catalysed transfer of the diboron reagent to unsaturated organic substrates[5b,12] because of the kinetic lability of the resulting bis(boryl) complexes.[13] When these two factors are combined, the use of transition metal complexes guarantees first the activation of tetraalkoxy- and tetraaryloxydiborons by oxidative addition, and second the B-C reductive elimination to afford organo-1,2-diboron compounds.[14]

The advantages of metal-promoted 1,2-diboration over the uncatalysed reaction[9] mean that researchers have been searching for a suitable catalytic system ever since Miyaura et al.'s first report.[15] Some studies have focused on metal-phosphine complexes, while others have focused on base-free metal complexes.[16]

The use of suitable transition-metal complexes has other advantages over the non-catalysed boron addition: for example, the chemo- and regioselectively of the new C-B bonds can be orientated. Finally, the possibility of modifying

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the catalyst precursor with chiral ligands provides 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 boryl-metal complexes play a decisive role because 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 considerable contribution to the understanding of bonding in boryl-metal complexes[17] and helped to clarify the mechanisms involved in transition-metal-catalysed boron-element additions.[18]

On the other hand, the carbon-boron bond, once formed, can be functionalised in a variety of ways, leading to a wide range of useful functional groups[19] and are often subject, with or without homologation, to a consecutive carbon-oxygen,[20] carbon-carbon,[21] boron-carbon,[22] boron-chlorine[23] or carbon-nitrogen[24] bond-forming reaction (Figure 1.3). Remarkably, all these functionalisations occur with retention of stereochemistry.

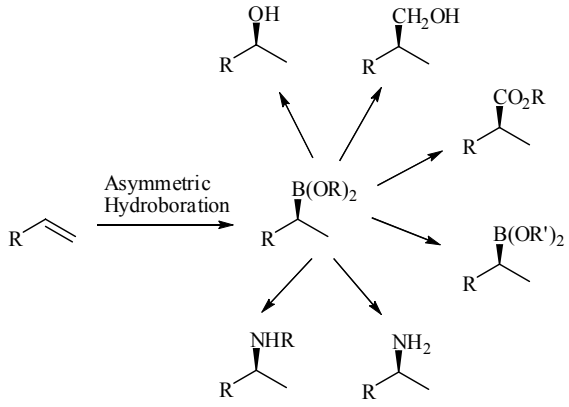

Figure 1.3. Transformations of the carbon-boron bond

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One particularly useful synthetic methodology for carbon-carbon bond formation uses the Suzuki-Miyaura palladium-catalysed cross-coupling reaction.[25,21i] Over the past two decades, the Suzuki−Miyaura cross-coupling reaction (SMC) has been considered one of the most efficient methods for constructing biaryl or compounds that contain substituted aromatic moieties as building blocks of polymers,[26] ligands,[27] a wide range of natural products such as alkaloids, and numerous biologically active pharmaceuticals.[28]

The key advantages of the SMC are the mild reaction conditions, the high tolerance of functional groups, the commercial availability of organoborates, the stability of boronic acids to heat, oxygen, and water, and the ease in which boron-containing byproducts can be handled and separated from the reaction mixtures.[29] These desirable features make the SMC an important tool in both medicinal chemistry and the large-scale synthesis of pharmaceuticals and fine chemicals.[30] In addition to aryl and heteroaryl boronic acids and esters, vinyl and alkyl derivatives are also commonly used in the SMC.

From a mechanistic point of view, the catalytic cycle of the palladium-catalysed SMC is thought to follow a sequence involving the oxidative addition of an aryl halide to a Pd(0) complex to form an arylpalladium(II) halide intermediate. Transmetallation with a boronic acid and reductive elimination from the resulting diarylpalladium complex affords the corresponding biaryl compound and regenerates the Pd(0) complex (Scheme 1.1).[31] The bases that are commonly used for these processes are K_3PO_4 and K_2CO_3. Others, including KOH or KF, have also been used. At present, however, the choice of base is still empirical, and no general rule for their selection has been established. The role of the base in these reactions is to facilitate the otherwise slow transmetallation of the boronic acid by forming a more reactive boronate species that can interact with the Pd center and transmetalate in an intramolecular fashion (Scheme 1.1, path A).[32] Alternatively, it has also been proposed that the base should replace

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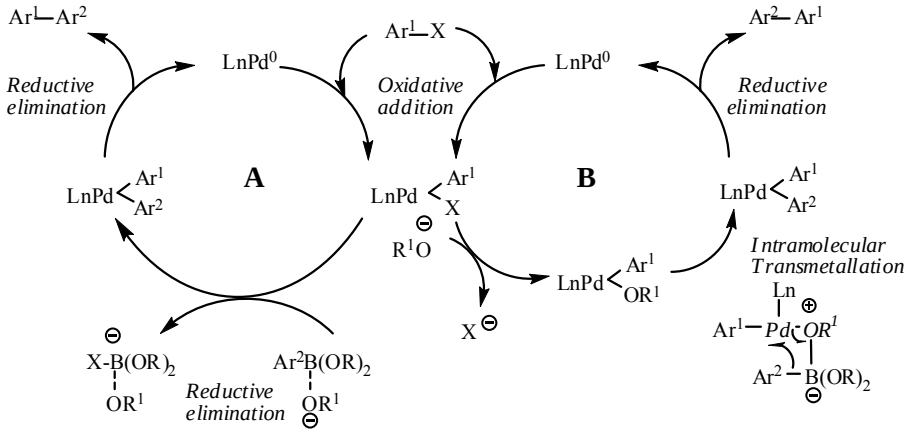
the halide in the coordination sphere of the palladium complex and facilitate an intramolecular transmetallation (Scheme 1.1, path B).[33] While in most cases the exact nature of the actual catalyst remains ambiguous, recent reports with bulky ligands have provided circumstantial evidence that the mechanism involves highly reactive monoligated L_1Pd species, where the L/Pd ratio can play an important role in the catalytic performance.[34]



Scheme 1.1. Proposed mechanism for the catalysed Suzuki-Miyaura cross-coupling reaction when base= OR^1

Most early work on the SMC was conducted using triarylphosphines as supporting ligands. During the last ten years, the application of new ligands has dramatically improved the efficiency and selectivity attainable in such cross-coupling reactions. In the ever-growing catalogue of available ligands for cross-coupling reactions, bulky dialkylbiaryl-[35] and trialkylphosphines[36] remain the most widely used, followed by *N*-heterocyclic carbenes (NHCs).[37]

The general beneficial effect of water as a reaction solvent in the SMC is well known, and some authors have turned out their attention to it.[38] Because of the favoured palladacycle complex formation,[39] Najera et al. used a variety of air- and water-stable oxime-derived palladacycles[40] (Figure 1.4) as precatalysts

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for cross-coupling boronic acids with different aryl and heteroaryl bromides and chlorides, and allyl and benzyl halides.

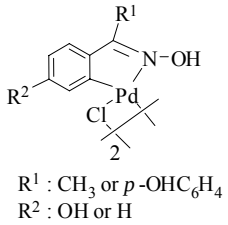
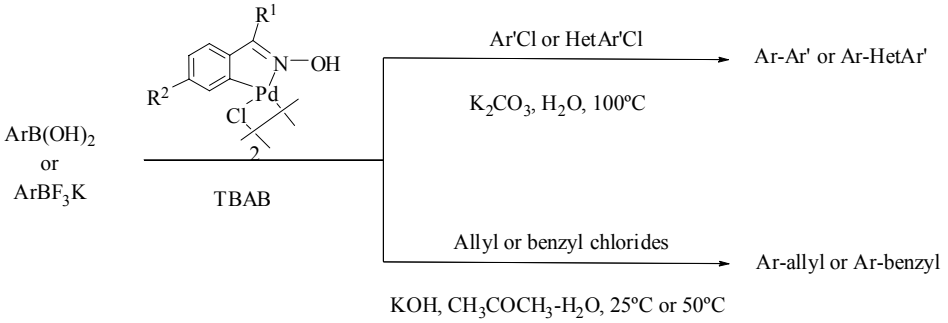


Figure 1.4. Oxime-derived palladacycle

These precatalysts were efficient in both water at 100ºC in the presence of tetrabutylammonium bromide (TBAB) as additive and K_2CO_3 as base and methanol-water (3:1) at room temperature in the presence of TBAB as additive and KOH under aerobic conditions (Scheme 1.2).[40c,d]



Scheme 1.2

Najera et al.[40e] also described that easily available and highly stable potassium aryltrifluoroborates can be used instead of arylboronic acids in these types of cross-coupling reactions (Scheme 1.2) using the same conditions mentioned above.

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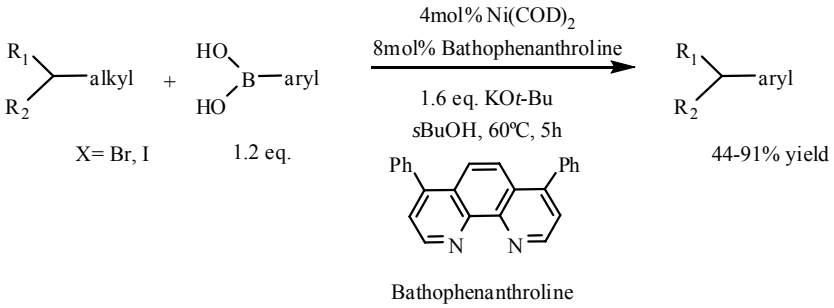
More recently, Zhou and Fu[41] reported an efficient system based on the $[Ni(COD)_2]$ catalyst modified with a bidentate pyridine ligand which mediates the first Suzuki coupling using unactivated secondary alkyl halides as alkyl electrophiles and with aryl boronic acids as carbon nucleophiles (Scheme 1.3)



Scheme 1.3

Saito and Fu[42] further extended the scope of nickel-catalysed Suzuki reactions to include alkyl boranes as coupling partners, which provided the cross-coupled product in excellent yield. They also carried out the first effective asymmetric cross-coupling of unactivated alkyl electrophiles in the presence of a nickel-based catalyst modified with chiral diamine ligand (Scheme 1.4).[43]

Asensio and co-workers[44] reported a Suzuki-coupling reaction catalysed by the $[Pd(PPh_3)_4]$ complex in which a mixture of diastereomeric bromo sulfoxides reacts with aryl boronic acids, but only the *cis* diasteroisomer inverts the configuration at the stereogenic center.

Nowadays, significant advances in transition-metal catalysed cross-coupling reactions of secondary alkyl halides with nickel, cobalt, iron and palladium have been reported to show excellent activity in this transformation.[45]

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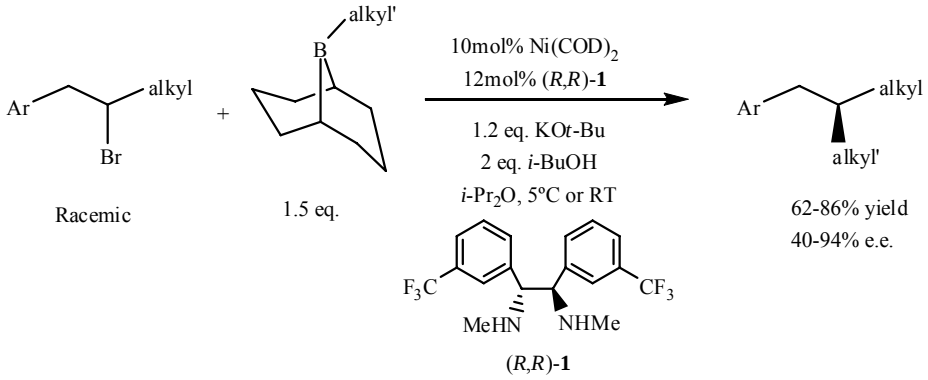

Scheme 1.4

Removing the catalytic system from the reaction is particularly important for industry and this led some authors to use a heterogeneous catalyst as an alternative to recover the catalytic system from the reaction. Arai and Kholer showed that the traditional heterogeneous Pd/C catalyst released small amounts of soluble Pd, which is deposited at the end of the reaction.[46] Crudden et al.[47] used a Pd foil as heterogeneous catalyst in an attempt to understand the redistribution of Pd during the SMC by using a reactor which could heat only a small area (reactive area). They used scanning electron microscopy (SEM) and X-ray photoelectron spectroscopy (XPS) to show that the change in the surface morphology took place only in the reactive zones when the reaction was carried out or when the Pd foil was treated with aryl halide. Moreover, Pd was redeposited on the cool edges of these reactive zones. These observations show that, with the Pd foil, the reaction might occur by dissolution of Pd and re-deposition, both of which can be thermally controlled.

In this context, this section attempts to provide the reader with a general overview of the principal concepts of the catalytic hydroboration, catalytic diboration and catalytic β-boration of α,β-unsaturated carbonyl compounds, as convenient synthetic protocols for organoboronate formation as useful synthons for the Suzuki-Miyaura cross-coupling reaction.

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1.2. Catalysed hydroboration of alkenes

Unsaturated vinylarenes, aliphatic terminal alkenes, perfluoroalkenes, alkynes, conjugate dienes, allenes and enynes have been shown to be suitable substrates for the catalytic hydroboration reaction. The hydroboration of vinylarenes has been extensively studied, and these are perhaps the best substrates to demonstrate the efficiency and selectivity of the catalyst. In this introduction we provide an overall picture of the catalysed hydroboration of unsaturated substrates (particularly vinylarenes).

In the hydroboration of vinylarenes, the preference for branched or terminal alkylboronate ester products depends on the catalytic system, the ligand and the borane reagent. Hayashi et al.[20a,48] showed that the regioselectivity was relatively insensitive to the electronic effects of substitution on the aryl ring, but was influenced by steric effects. Hayashi[48] suggested that the high internal selectivity of the catalytic hydroboration of vinylarenes on the branched products (99%) could be favoured by a contribution from the η^3-benzylrhodium complex (Figure 1.5) as a key intermediate.

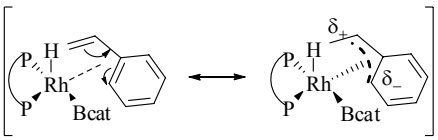

Figure 1.5. η^3-Benzylrhodium intermediate

However, substrates such as perfluoroalkenes,[49] α,β-unsaturated esters and amides,[50] or in general substrates which contain an electron-withdrawing group,[51] commonly have high internal selectivities in the hydroboration reaction catalysed with rhodium complexes and catecholborane (**1**).

Most studies of the catalysed hydroboration reaction have used the five-member ring heterocycle diorganyloxyborane catecholborane (**1**), because of its

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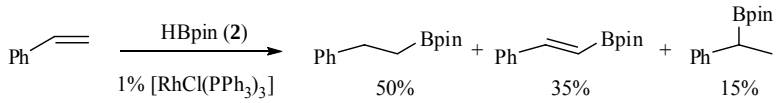
high degree of Lewis acidity and the favourable steric profile of the borane coordinated to the metal.[52] The steric effects of borane reagents also play an important role in this selectivity. There are numerous references in the literature to the fact that changes in the nature of the hydroboration reagent have effects on the regioselectivity of the hydroboration reaction.

Pereira and Srebnik[53] have shown that when pinacolborane (**2**) is used as hydroborating reagent instead of catecholborane (**1**) in the rhodium- or zirconium-catalysed hydroboration of vinylarenes (Scheme 1.5), the selectivity favoured terminal organoboronate because of its bulkiness, which was in sharp contrast to the addition of catecholborane according to the electronic effect of the vinylarene. Furthermore, the reaction produced undesired products such as alkenylboron compounds due to the 'dehydrogenative borylation' reaction.



Scheme 1.5

Several transition metals are used in the catalytic hydroboration/oxidation reaction with catecholborane as the borane reagent. Iridium (I)[5a,19,54] and ruthenium (II) or (III)[55] are some of the transition metals that have been studied. When they were modified with phosphines, their selectivity towards linear isomer was high. Other metals such as Ti, Sm, Zr modified with cyclopentadienyl ligands have proved to be excellent catalysts for the addition of boron to the terminal carbon of the substrate.[56,21j]

Dehydrogenative borylation of alkenes has been considered to be an interesting alternative for preparing intermediates for the Suzuki cross-coupling reaction.[57] In this context, Sabo-Etienne et al.[58] carried out the ruthenium-catalysed dehydrogenative borylation of cyclic alkenes in the presence of

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pinacolborane (**2**). They pointed out that the selectivity of the reaction depended on the size of the alkene cycle. Moreover, they characterised the $[RuH(Bpin)(C_2H_4)(PCy_3)_2]$ complex, which can be considered as the catalyst resting state and the cause of the above mentioned transformation.

The mechanism of rhodium-catalysed hydroboration is thought to depend on the nature of the substrate, the catalyst, the ligand and the reaction conditions.[59]

The original mechanism proposed by Männing and Nöth,[6] and later supported by Evans and Fu,[60] consisted of several different steps. They demonstrated that B-H activation by Wilkinson's catalyst provides the hydride-η-borylrhodium complex. As far as the catalytic mechanism is concerned, they proposed a dissociative pathway which involved oxidative addition of catecholborane to the rhodium complex with the hydride and boryl ligand in *trans*, followed by alkene coordination with simultaneous dissociation of one PPh_3 group (Scheme 1.6, Cycle A, intermediate **5**). Furthermore, migratory insertion of the alkene into the Rh-H bond, and reductive C-B bond coupling eventually provided the branched or linear alkylboronate ester, which regenerates the catalytic species (Scheme 1.6, Cycle A).

Intermediate **5** is the key species in the cycle, as the reaction may diverge from this intermediate. Burgess et al.[57a] proposed an alternative associative pathway which involves boron migration followed by β-H elimination as a competitive process in the catalytic hydroboration (Scheme 1.6, Cycle B). Mechanistic investigations by Burgess,[57a,61] and Marder and Baker[62] established that the catalytic cycle can be further complicated by the presence of degradation products of catecholborane (**1**). As a result, hydrogenation and uncatalysed hydroboration can compete with the metal-catalysed variant.[63]

Ziegler et al.[64] made extensive theoretical studies of the dissociative pathway in the hydroboration catalytic reaction with the rhodium catalyst

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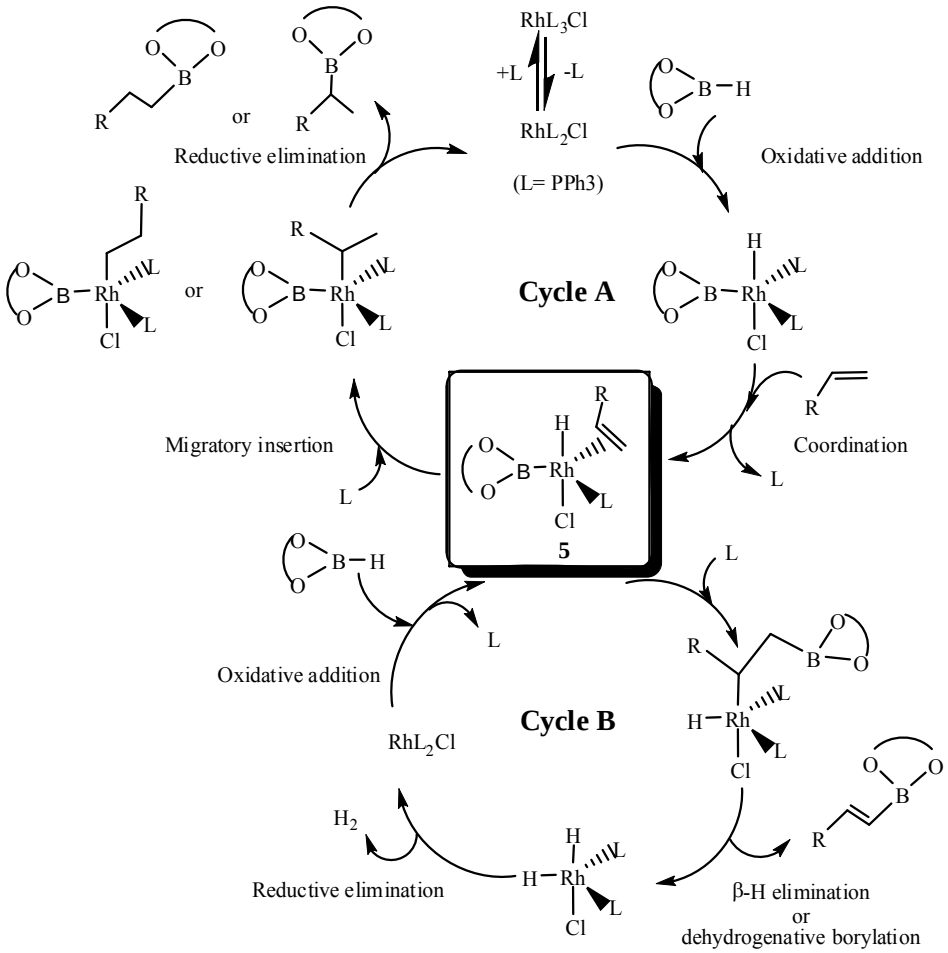
modified with phosphines. They found a dramatic kinetic difference between the two routes. Insertion into Rh-H bond occurs readily and with *virtually no barrier*, but it is followed by a difficult reductive elimination step with a high barrier of almost 15 Kcal·mol^{-1}. On the other hand, initial boryl migration has a barrier of 19 Kcal·mol^{-1} but is followed by a facile C-H reductive elimination step.



Scheme 1.6

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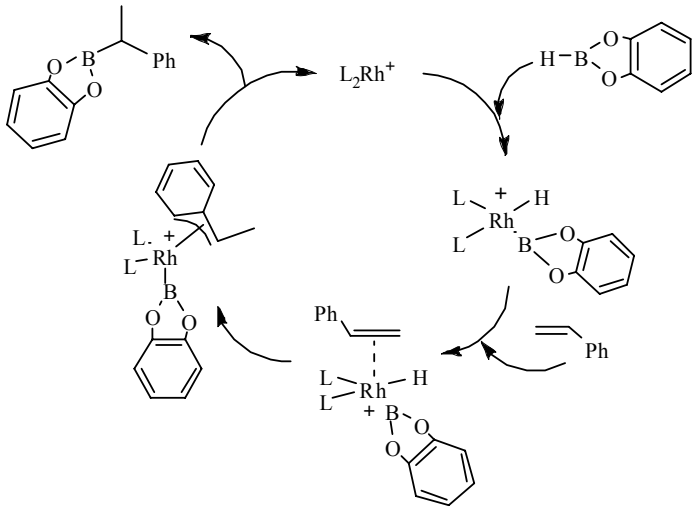
They concluded that the boryl migration may be preferred on the hydride path because of the initial rapid preequilibrium followed by the high activation barrier.

Hayashi et al.[20a,48] suggested that the η^3-benzylrhodium complex was a key intermediate in the catalytic cycle. They also proposed that the vacant coordination site in the cationic rhodium intermediate, instead of a neutral complex, favoured the formation of the intermediate because the reductive elimination step provided the branched borane regioselectively (Scheme 1.7).



Scheme 1.7

Hayashi et al.[20a,48] made a breakthrough in the enantioselective hydroboration of styrene catalysed by cationic rhodium complexes modified with chiral P,P ligand diphosphines with **1** as hydroborating reagent. They found that (*R*)-Binap (**6**) was the most effective chiral ligand and achieved values up to 96% e.e. at -78ºC (Scheme 1.8). Like Burgess,[65] Hayashi found that there was an inverse relationship between the asymmetry induced and the reaction temperature.

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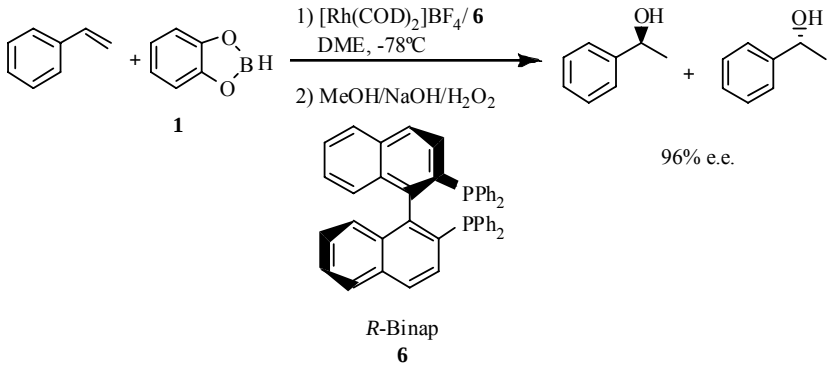
Burgess et al.[66] found that there was a slight correlation between chelate-ring size and enantioselectivity. Ligands that gave five-membered chelate rings were less enantioselective than those that gave six- or seven-membered rings.

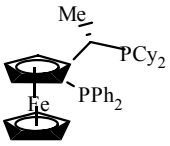


1

R-Binap
6

Scheme 1.8. Rhodium/(*R*)-Binap catalysed hydroboration of styrene

Togni et al.[67] found that the enantiocontrol in the hydroboration/oxidation of styrene was similar when they used $[Rh(NBD)_2]BF_4$ (where NBD= norbornadiene) complex modified with ferrocenyldiphosphine, Josiphos (**7**) (Figure 1.6).



(*S*,*R*)-Josiphos
7

Figure 1.6

However, the best results to date have been obtained by J. M. Brown et al.[68] in the catalytic hydroboration/oxidation reaction of vinylarenes using the

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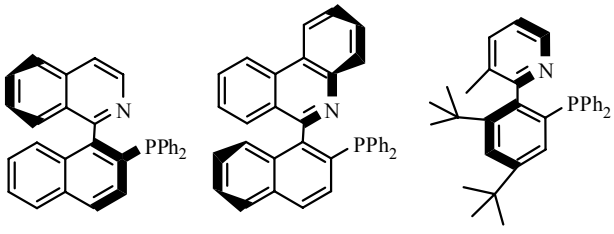
effective chiral P,N-type ligand Quinap (**8**) (Figure 1.7) coordinated to rhodium complexes. Substrates such as *p*-MeO-styrene have been transformed into their corresponding α-alcohol with 94% e.e at room temperature. The **8** is less bulky than Binap (**6**) in the region of the isoquinoline, which replaces one of the diphenylphosphinonaphthalene moieties and thus facilitates the oxidative addition of a sterically demanding secondary borane reagent. The structural modifications permitted by the synthetic route to phosphinoisoquinolines make it possible to synthesise analogous P,N ligands such as Phenap (**9**)[69] which have a related enantiomeric excess.



(**S**)-Quinap **8** (*R*)-Phenap **9** (*R*)-Phyphos **10**

Figure 1.7

J. M. Brown et al.[68c] suggested a simple trend related to the inductive electronic effect of the substituents for the rhodium catalyst complex modified with Quinap and other similar ligands with catecholborane as the hydroborating reagent. For electron-releasing *para*-substituents enantiodifferentiation is higher than for the electron-withdrawing *para*-substituents. Chan et al.[70] developed a new atropoisomeric P,N ligand called Pyphos (**10**) for the rhodium-calalysed asymmetric hydroboration (Figure 1.7). This ligand provided enantiomeric excesses similar to those of Rh/(*S*)-Quinap when the reaction was carried out at 0ºC. These results led Chan to suggest that transition-state models, based on the pentacoordinated Rh/H/Pyphos/catecholborane/vinylarene complexes, could

explain the electronic effect of modified substrates and/or ligands in asymmetric hydroboration. Thus, they proposed that vinylarenes with electron-releasing substituents coordinate more strongly to the rhodium center than vinylarenes with electron-withdrawing substituents. And they speculated that electron-rich substrates may be closer to the metal than their electron-poor analogues, thus improving stereochemical communication and providing higher enantioselectivity.

In collaboration with Prof. Bo and E. Daura, our group made a theoretical study of model systems from spectroscopically postulated Rh-Binap and Rh-Quinap intermediates in the catalytic cycle, and concluded that the origin of regio- and enantioselectivity in hydroboration reactions of vinylarenes is related to the coordination step of the alkene not the migratory insertion. In addition, an analysis of the intermolecular interactions revealed that the intermolecular π-π stacking interactions between the substrate and the ligand, the ligand and the hydroborating reagent, and the hydroborating reagent and the ligand could be the reason for the relative stability of the key intermediates.[18a,b]

In a parallel study, Crudden et al.[71] demonstrated that when iridium complexes modified with chiral diphosphines were the catalyst precursor in the catalytic hydroboration of vinylarenes, the selectivity was completely reversed. They suggested that the cause of the reversal selectivity was a change in the mechanism from Rh-H insertion to Ir-B insertion.[72] The same trend in the enantioselectivity was also observed when HBpin (**2**) was used instead of HBcat (**1**).

In a further attempt to attribute the π-benzyl interactions to the regioselectivity in the rhodium-catalysed hydroboration reaction of vinylarenes, recently, Crudden et al.[73] used deuterium labeling studies to demonstrate that mechanisms of metal hydride addition in the rhodium-catalysed hydroboration of styrene with HBpin (**2**) are different from those observed with HBcat (**1**).

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They also observed the presence of a minimum centered at the origin in the Hammett plot for styrene derivatives, which indicated that, depending on their electronic properties, styrene derivates have different mechanisms.

In an attempt to investigate how the steric demand of the ligand affects the degree of enantioselection, Guiry et al.[74] developed a series of axially chiral 2-substituted quinazoline-containing phosphinamine ligands called Quinazolinaps (Figure 1.8). Their asymmetry values were comparable to other atropoisomeric ligands such as Quinap (**8**) and Phyphos (**10**).

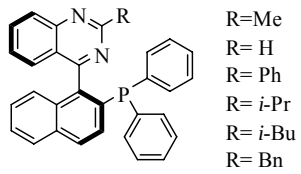
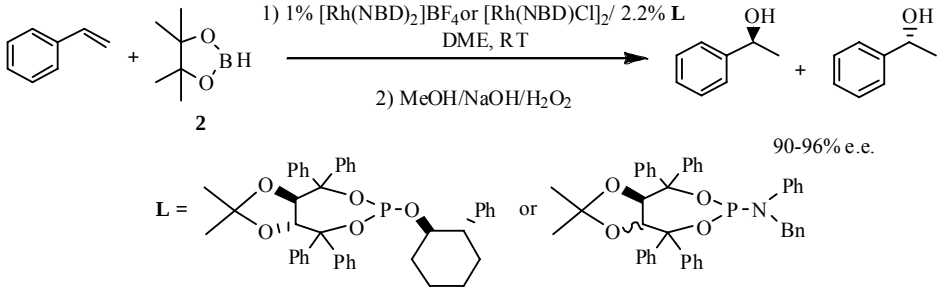


Figure 1.8. Quinazolinap ligands

Recently, Tackacs et al.[75] showed that the TADDOL-derived monodentate ligands such as (1*R*,2*S*)-2-phenylcyclohexanol-derived phosphite and the *N*,*N*-(phenylbenzyl)-phosphoramidite (Scheme 1.9) afforded enantioselectivities in the room-temperature rhodium-catalysed hydroboration of substituted vinylarenes that were comparable to those obtained with Quinap (**8**).



Scheme 1.9

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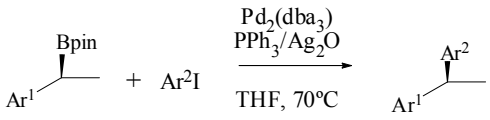
These ligands gave similar results with both neutral and cationic rhodium catalyst precursors, even though electron-realising and electron-withdrawing substrates were tolerated. Using these systems both catecholborane (**1**) and pinacolborane (**2**) gave the same sense of asymmetry induction and **2** provided better results than **1**, which contrasts substantially with the trend observed by Crudden et al.[71] and our group.[18a]

As an example of the usefulness of catalytic hydroboration for the efficient consecutive cross-coupling reaction, Crudden el al.[76] described the first example of cross-coupling chiral secondary boronic esters,[71] which proceeds with no loss in regiochemistry and with high retention of enantioselectivity (Scheme 1.10). They observed that Ag_2O is the most effective additive for this transformation, and an excess of phosphine was necessary to obtain the desired coupling product. Substituting the aryl halide on the phenyl moiety with hindrance groups decreased the yield of the reaction.



Scheme 1.10

Of particular note was the development by members of our group of a recyclable hydroboration process in which the ionic rhodium complexes were immobilised onto the clay montmorillonite K-10. The activity and selectivity of the immobilised ionic rhodium complex were comparable to those of the free catalyst. Most of the catalyst was recovered and reused with no loss in activity, selectivity or enantioselectivity on consecutive runs.[77]

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1.3. Catalysed diboration of alkenes

The transition-metal catalysed diboration of alkenes seems to be a more complex transformation probably due to the mixture of products commonly observed. When several Rh(I) catalysts were used and bis(catecholato)diboron (**4**) was the diboron reagent and 4-vinylanisole the substrate, Marder et al.[78] observed the formation not only of the desired 1,2-diborated product but also of hydrogenated and hydroborated products. [Rh(DPPB)(η^6-catBcat)] (Figure 1.9) was the most chemoselective catalytic system used in previous studies, yielding 44% of the 1,2-diborated product (Scheme 1.11).

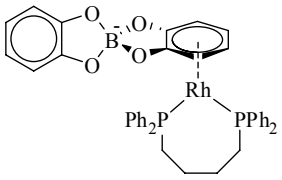
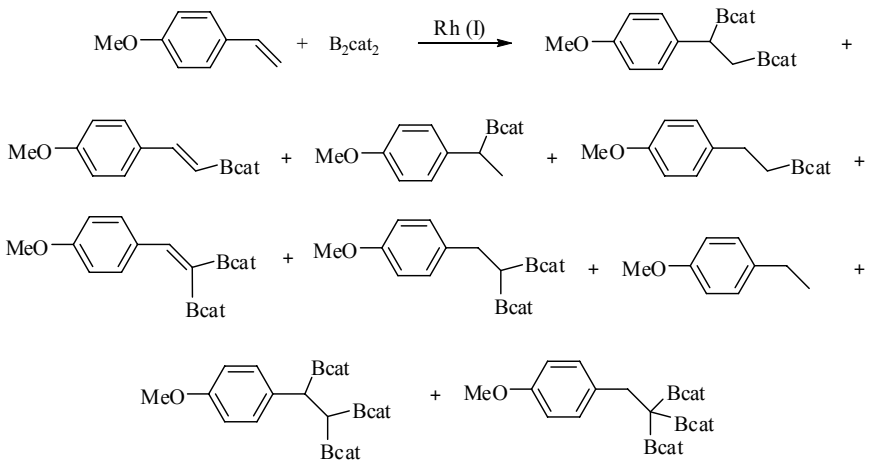


Figure 1.9. [Rh(DPPB)(η^6-catBcat)]



Scheme 1.11. Different products observed in the Rh(I)-catalysed diboration of 4-vinylanisole

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This problem was solved by using other metals. Metals with lower d-orbital energies (on the right of the periodic table) are likely to inhibit π-backbonding to alkenes and thus destabilise 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.[78] chose a gold(I) catalytic system, because of the lack of known gold-hydride complexes. The system tested, [$AuCl(PEt_3)$]+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, the conditions required were 8 mol% of the catalyst, temperatures of about 80ºC for 48 hours and 1.5 equiv. of **4**.

Miyaura[79] showed that a base-free platinum complex, [$Pt(dba)_2$], was a good catalytic system for the clean diboration of terminal alkenes and strained cyclic alkenes with bis(pinacolato)diboron (**3**), but the system failed to diborate simple internal alkenes. Similarly, Smith[80] reported that [$Pt(NBE)_3$] and [$Pt(COD)_2$] (where NBE=norbornene and COD=cycloocta-1,5-diene) catalysed the addition of B_2cat_2 to terminal alkenes and the strained norbornene and norbornadiene. Apparently, this system also suffers from β-hydride elimination problems, but only with unstrained internal alkenes. Baker et al.[81] obtained good yields and chemoselectivities in the diboration of terminal alkenes and alkynes using a Pt(II) commercially available catalytic system, [$PtCl_2(COD)$], also active in the 1,2-diboration of aldimines.

The modification of the ligand in Rh-catalysed diboration[82] to DPPM (where 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

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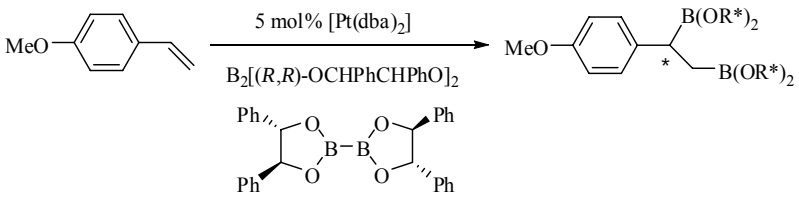
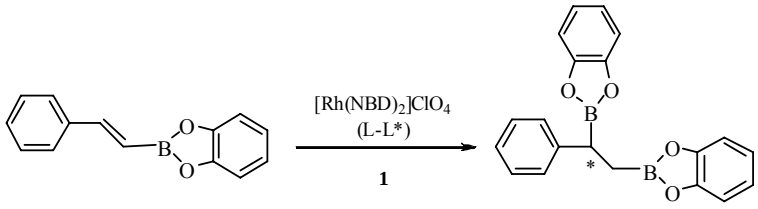
trans-stylbene and *trans*-β-methylstyrene. This was the most active and chemoselective Rh(I) catalyst system found, and in some cases yielded full conversion into the 1,2-diboron product.

The asymmetric catalytic diboration reaction was first carried out using chiral diboranes. Marder et al.[83] studied the addition of enantiomerically pure chiral diboron compounds such as $B_2[(R,R)\text{-OCHPhCHPhO}]_2$ 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 1.12). One of the drawbacks of this first example of asymmetric diboration was that it used stoichiometric amounts of chiral diboron reagent.



Scheme 1.12

Therefore, another interesting approach at that time was the asymmetric version of the catalysed regioselective hydroboration of preformed vinylboronate esters (Scheme 1.13) with catecholborane (**1**).[84]



Scheme 1.13

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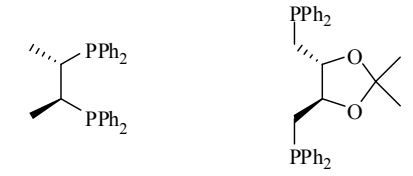
When the catalytic system was $[Rh(NBD)_2]ClO_4$ / (*S*,*S*-CHIRAPHOS) (Figure 1.10), enantiomeric excesses of up to 73% were obtained at -20ºC, although the yield of the corresponding diboron/oxidated product was only about 13%.



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

Figure 1.10

When the chiral diphosphine ligand (*R*,*R*)-DIOP (Figure 1.10) 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 (**6**) at -60ºC, a yield of 49% and an enantiomeric excess of 72% were obtained.

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.[85] transformed *trans*-alkenes into 1,2-bis(catechol)diboron ester intermediates that were eventually oxidised to the corresponding diols with moderate yield and high enantioselectivity (Scheme 1.14, A). The catalytic system used was [Rh(NBD)(acac)] / (*S*)-QUINAP (**8**) (where acac= acetylacetonate) 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 suggested that monosubstituted and 1,1-disubstituted alkenes will probably require new chiral ancillary ligand structures for effective enantiocontrol. Therefore, a certain level of enantioenrichment (ee=33%) was obtained in the asymmetric diboration of

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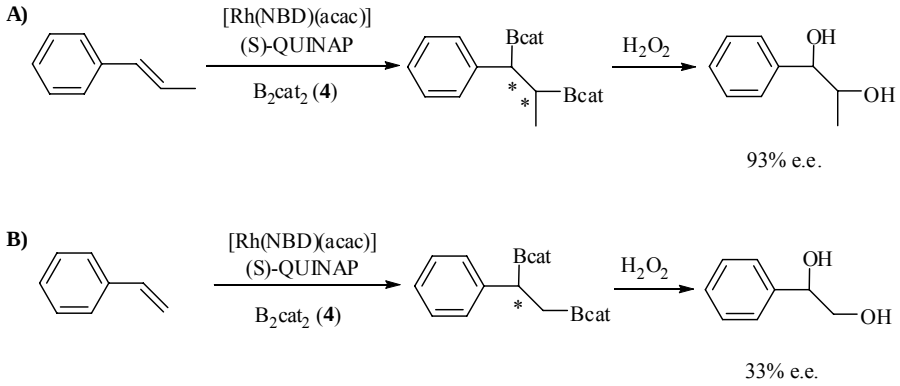
styrene with bis(catecholato)diboron (**2**) by means of the catalytic system [Rh(NBD)acac]/(S)-QUINAP (Scheme 1.14, B). Moreover, the isolated yield of purified material reported was moderate (68%), and the remaining mass balance was described as unconverted starting material.



Scheme 1.14

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,[86,87] leading to a metal-diboryl complex (Scheme 1.15, path a). The desired 1,2-bis(boronate)ester seems to arise from alkene insertion into a M-B bond[88] followed by B-C reductive elimination involving the second boryl ligand (Scheme 1.15, cycle A).[89] However, the alkenyl and alkylboronate esters were produced by a competitive β-hydride elimination (Scheme 1.15, paths b-b', c-c').

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.[90]

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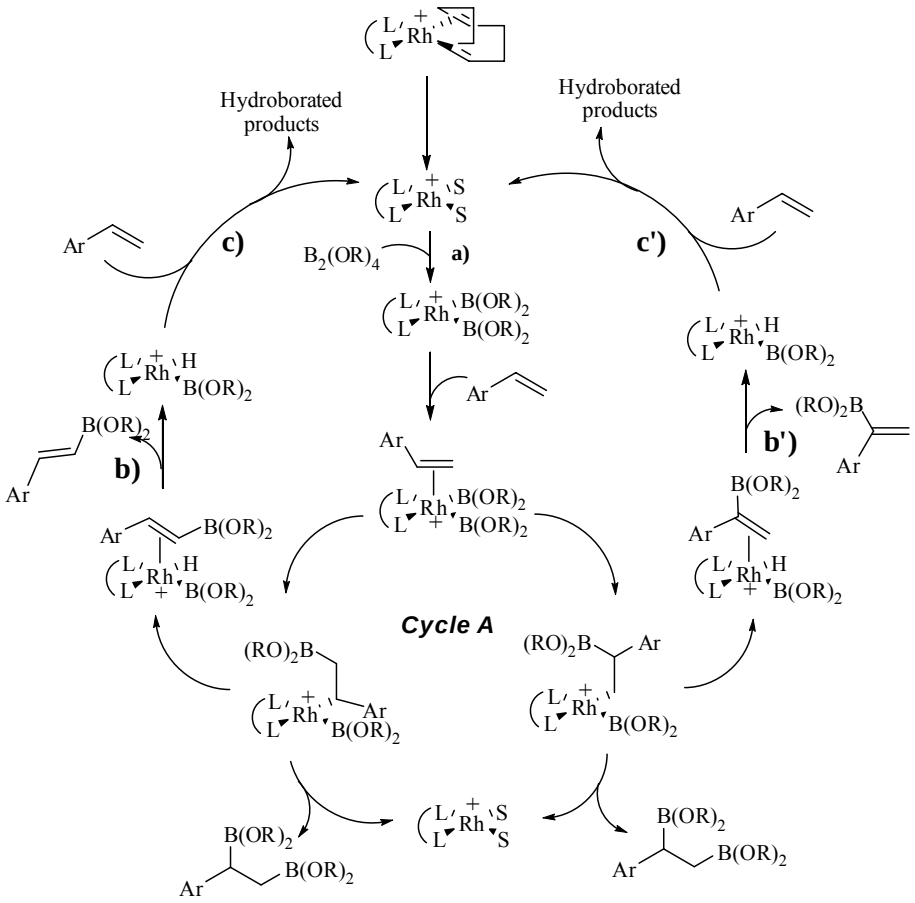

Scheme 1.15. Proposed mechanism for the metal-catalysed alkene diboration reaction

An alternative approach to enantiomerically enriched alkyl 1,2-bis(boronate) ester formation, nonetheless, is the catalytic asymmetric hydrogenation of vinyl 1,2-bis(boronate) esters. Morken et al.[91] 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 provides 1,2-diols in high yields and with high enantioselectivities (Scheme 1.16) with the family of

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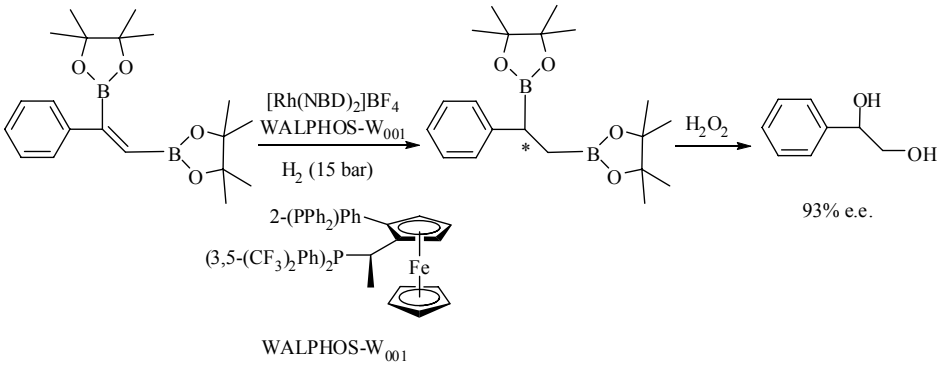
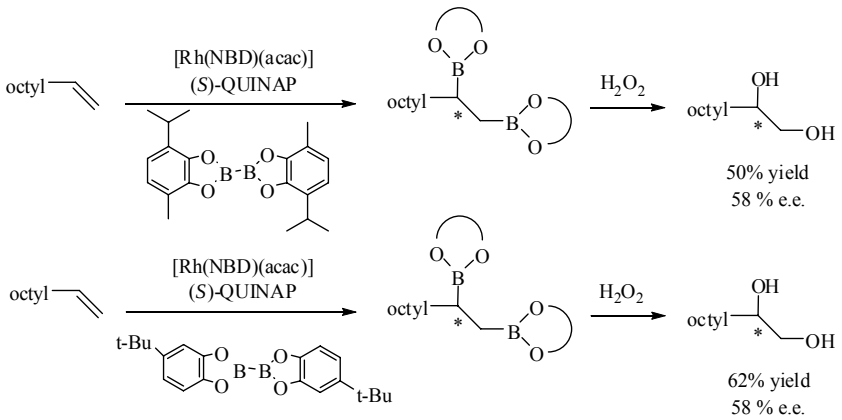
WALPHOS ligands as the chiral ligands of choice. However, the high level of asymmetric induction seems to be the result of a combination of facts: an excess of ligand with regard to catalyst was required (Rh/ligand=1/2), and toluene seems to be the most convenient solvent.



Scheme 1.16

To improve stereoselection with monosubstituted alkenes, Morken et al.[92] examined alternative diboron reagents that used more hindered substituted bis(catecholato)diboron, (Scheme 1.17).



Scheme 1.17

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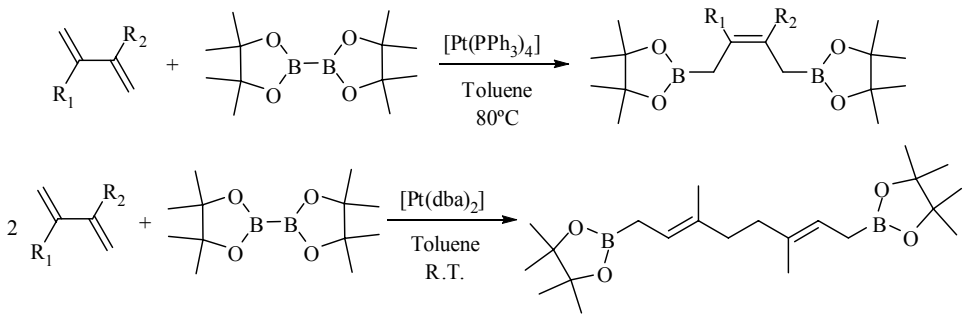
However, it seems that the substitution was too far from the metal center to have a significant impact on selectivity.

At this point, it should be mentioned that the various transition metal complexes have a significant involvement in the catalytic diboration of alkenes. One interesting application is the Pt(0)-catalysed diboration of alka-1,3-dienes with bis(pinacolato)diboron (**3**).[93] This process, carried out in toluene at 80ºC, requires [$Pt(PPh_3)_4$] as the catalytic system and providesg 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 1.18).

Norman et al.[94] applied chiral diboranes in the Pt(0)-catalyzed 1,4-diboration of 1,3-dienes, with no significant asymmetric induction (up to 20% d.e.).



Scheme 1.18

Westcott et al.[95] reported considerable catalytic diboration of heteroatom-containing substrates. In this paper, thiocarbonyl compounds were 1,2-diborated

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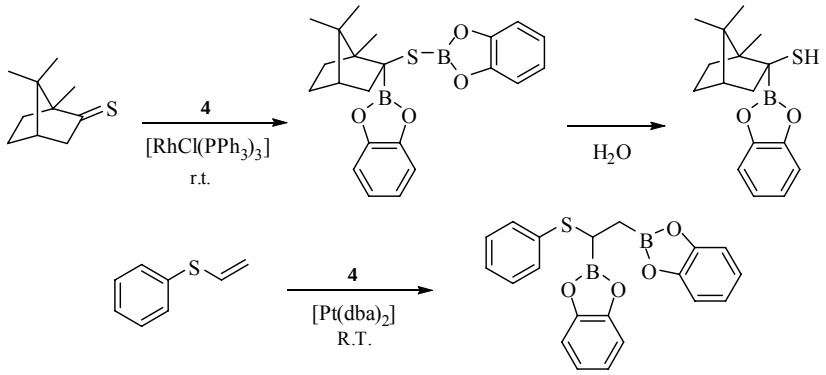
with Wilkinson's catalytic system, and vinyl sulfides with the phosphine-free $Pt(dba)_2$ catalytic system (Scheme 1.19).



Scheme 1.19

The diboration of allenes has also been reported[97] to yield 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 phosphine ligands forces the addition towards the terminal double bond. A highly selective diboration of the terminal double bond can be obtained by using a palladium catalytic system in the presence of a cocatalyst such as I_2, iodoalkenes or iodoarenes. The role of the cocatalyst is to form *in situ* an I-Bpin intermediate, which undergoes oxidative addition and insertion, leading to a 2-boryl-π-allylpalladium intermediate (Scheme 1.20).

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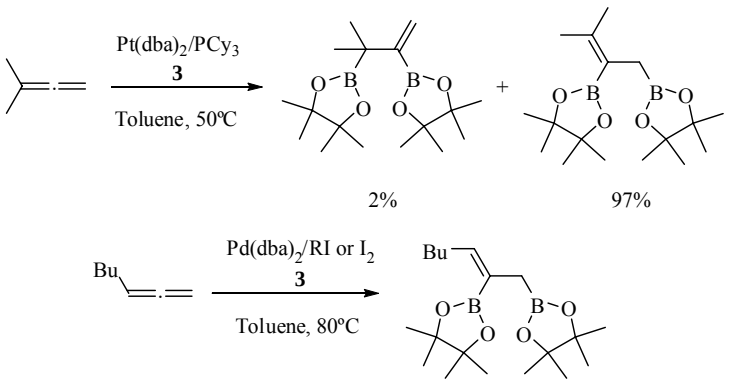
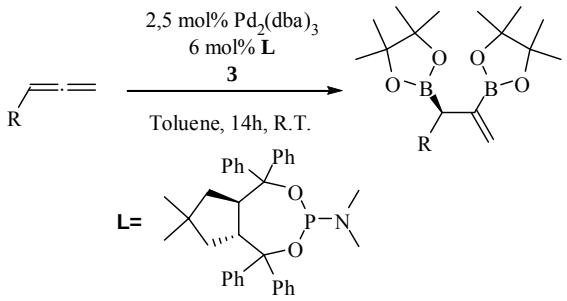


Scheme 1.20

More recently, Morken et al.[98] 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 1.21).



Scheme 1.21

In 2007, Morken et al.[99] improved this system by modifying the ligand. They obtained values of 98% e.e. They studied the mechanism of 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

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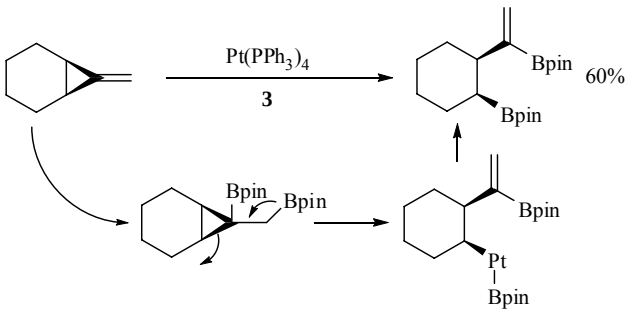
reductive elimination. This insertion reaction is most likely the enantiomer-determining step of the allene diboration process.

Also noteworthy is the catalysed diboration of methylencyclopropane and its derivatives,[100] which are interesting substrates because their strained structure makes them highly reactive. The platinum-catalysed 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 1.22).



Scheme 1.22

Using β-hydride elimination, Marder et al.[101] reported rhodium-catalysed dehydrogenative borylation. 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 makes it possible to prepare 1,1-disubstituted vinylboronate esters, which cannot be prepared with alkyne hydroboration. The effective catalyst system for this reaction was found to be $[RhCl(CO)(PPh_3)_2]$, and the diboron reagent used was **3** (Scheme 1.23). Marder also found that by using 2 equiv. of the diboron reagent the vinyl(bis)boronate ester could be isolated with good selectivity (up to 85%) (Scheme 1.24).

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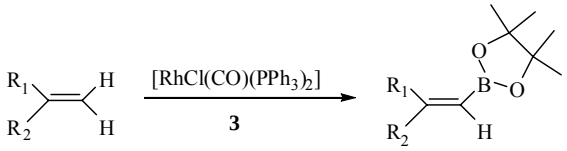
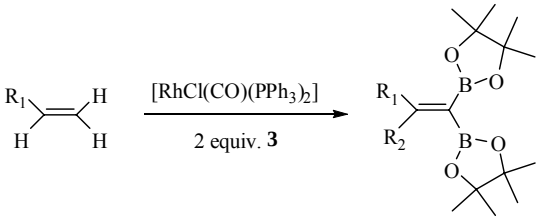


Scheme 1.23



Scheme 1.24

1.4. Catalysed β-boration of α,β-unsaturated carbonyl compounds

The addition of compounds with an M-M and M-M' bond (M,M'=Si, B, Sn Ge, S) to C-C multiple bonds catalysed by transition metal complexes has been extensively studied during the past decade.[16] Since Miyaura et al's work[93] demonstrating the catalytic 1,4-addition of a B-B bond to 1,3-dienes, a significant research effort culminated in Marder et al's first example[102] of B-addition to α,β-unsaturated ketones in a 1,4-manner to provide boronated boron enolates with either **3** or **4**. The products from **4** were more susceptible to hydrolysis than those from **3**, so it was only possible to isolate the β-boronated ketone when **4** was involved (Scheme 1.25). The catalysed β-boration of α,β-unsaturated carbonyl compounds is an interesting approach to the simultaneous incorporation of a boronate moiety at C_β and the formation of a hydrolytically sensitive boron enolate.

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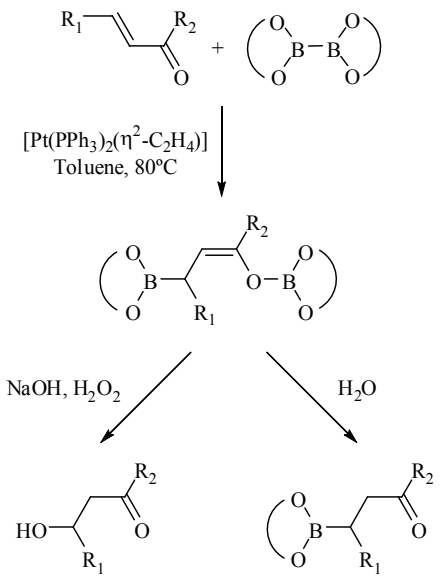
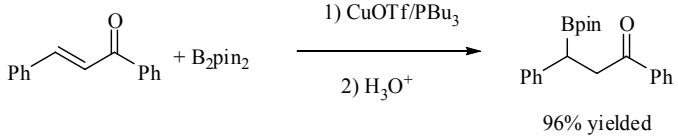


Scheme 1.25

Hosomi et al.[103] described the first Cu(I) salt catalysing the β-boration of a variety of α,β-unsaturated ketones with **3** and **4**. Interestingly, they found that the Cu(I) salt itself did not consume **3** in the absence of an α,β-unsaturated ketone. This contrasted with the similar reaction mediated by Pt complexes,[102] in which the oxidative addition of the boron to Pt metal was through the expected B-B bond cleavage.[15,87,104] They also consider that the coordination of a basic phosphine ligand to Cu(I) might increase the reaction pathway by reducing undesired aggregation of the Cu(I) salt in a solvent (Scheme 1.26).



Scheme 1.26

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Srebnik et al.[105] described how 5 mol% of [$Pt(PPh_3)_4$] efficiently promoted the β-boration to cyclic carbonyl enones, and α,β-unsaturated esters and aldehydes (Figure 1.11) with different levels of conversion.

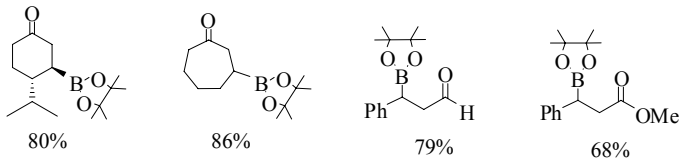

Figure 1.11

More recently, Marder et al.[106] found that for the same reaction, with [Pt(BIAN)(DMFU)] (Figure 1.12) as catalytic system and **3** 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.

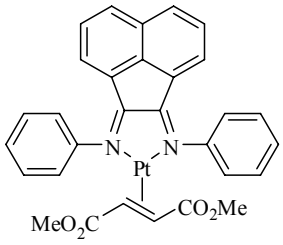

Figure 1.12. [Pt(BIAN)(DMFU)]

Kabalka et al.[107] described the 1,4-addition reaction which involved the addition of **3** and bis(neopentyl glycolato)diboron to electron-deficient alkenes such as α,β-unsaturated ketones, esters, nitriles and aldehydes in the presence of 5mol% of [$RhCl(PPh_3)_3$]. The oxidative addition of diboron to rhodium complexes had already been very well established as the early catalytic step of the alkenes.[88]

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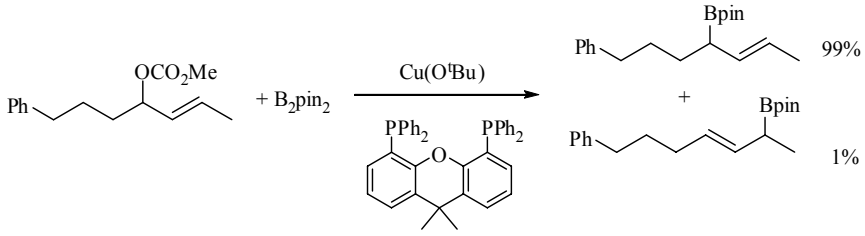
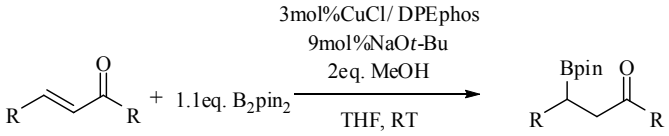
Simultaneously, Sawamura et al.[108] reported the γ-selective and stereospecific copper-catalysed substitution of allylic carbonates with a diboron reagent, which is a convenient method for the synthesis of allylboronates (Scheme 1.27).



Scheme 1.27

Yun et al.[109,110] recently reported that CuCl modified with DPEphos ligand (where DPEphos= (bis(2-diphenylphosphinophenyl)ether) in the presence of a base such as NaO*t*Bu, provided a highly efficient protocol for the conjugate addition of B_2pin_2 (**3**) to a wide range of α,β-unsaturated esters by adding MeOH as additive. The addition of the MeOH was essential for successful β-boration and enhancement of the scope (Scheme 1.28). In addition, the present catalytic system was tolerant of steric hindrance at the β-carbon position and reacted with sterically hindered β,β-disubstituted enone. Other α,β-unsaturated nitriles and phosphates were also suitable substrates for this transformation.



Scheme 1.28

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Encouraged by those results, Yun et al.[111] carried out the first catalytic asymmetric conjugate addition of boryl groups to acyclic α,β-unsaturated esters and nitriles with Cu(I) salt / chiral ligand as catalytic system. Yields were excellent and the enantiomeric excess high when the planar chiral ligands (*R*)-(*S*)-Josiphos and (*R*)-(*S*)-NMe_2-PPh_2-Mandyphos were used.

More recently, Yun et al.[112] also reported a catalytic asymmetric β-boration of various acyclic enones by using a copper-Josiphos complex. With various acyclic enones, enantioselectivities were excellent (up to 97% e.e.).

In an attempt to obtain evidence about the possible reaction pathway, they performed the β-boration of acyclic enone in the optimised conditions by the addition of MeOD as alcohol additive. The product contained a deuterium atom at the α-position. Bearing this in mind, they proposed that the reaction mechanism proceeded via an intermediate copper enolate followed by protolytic cleavage of an alcohol to form the protonated product and a copper alkoxide. Therefore, copper alkoxide reacted with diboron by transmetallation to regenerate the active boryl complex (Scheme 1.29).

In their theoretical studies on the diboration of aldehydes, Marder, Lin et al.[113] have shown that σ-bond metathesis between a Cu-O bond and a B-B bond is almost barrierless, while the metathesis between process Cu-C bond and a B-B bond has a higher barrier. This may mean that the addition of the alcohol to copper enolate speeds up the formation of Cu-OR bond in such a way that the rate of the overall transformation is accelerated.

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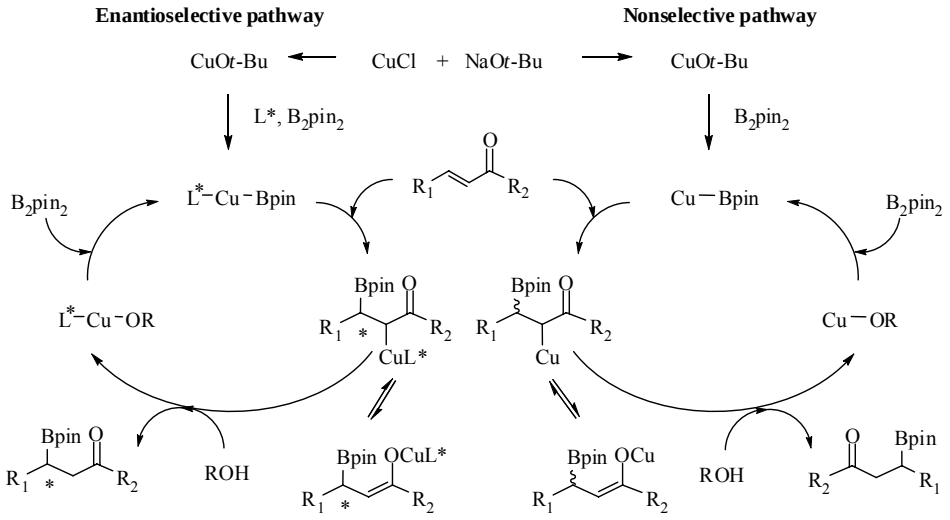
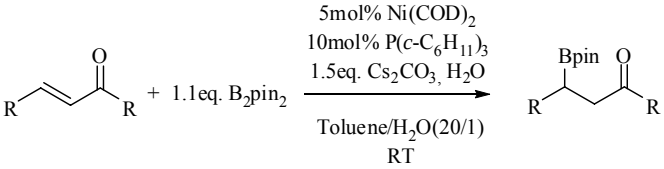


Scheme 1.29. Proposed mechanism of copper catalysed β-borylation of α,β-unsaturated substrates

Other metals such as palladium[114] and nickel[115] have been shown in the literature to be available to provide the desired 1,4-additon product in the metal-catalysed 1,4-addition of alkylmetal reagents to α,β-unsaturated carbonyl compounds.

Oshima et al.[116] developed an effective β-boration of α,β-unsaturated esters and amides with B_2pin_2 (**3**) by using the $Ni(COD)_2$ as catalytic precursor modified with monophosphine. The catalytic system was effective for di-, tri- and tetrasubstituted substrates in good yields. The addition of Cs_2CO_3 as base and, above all, the use of the toluene/MeOH cosolvent system were found to be essential for good reproducibly (Scheme 1.30).



Scheme 1.30

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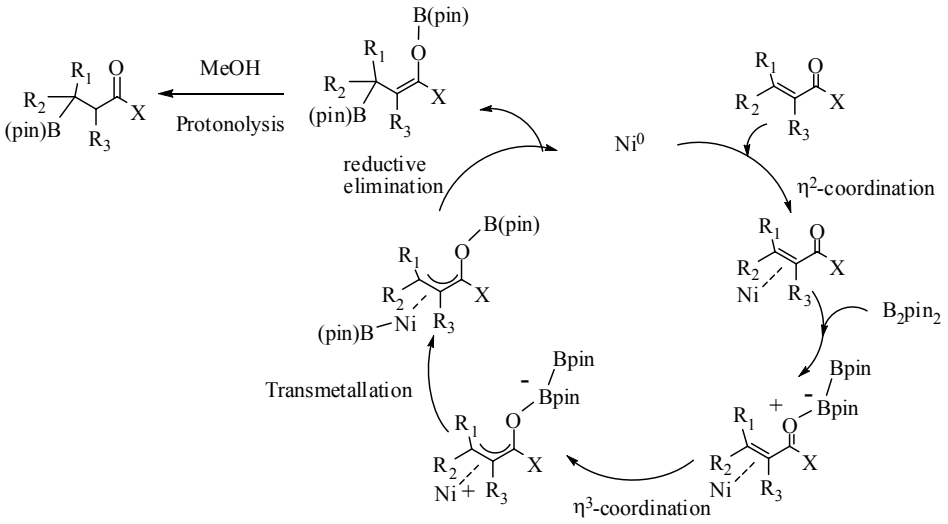
They also found that the amides, which have more electron rich carbonyl oxygen than esters, reacted with **3** faster than the corresponding esters probably because the amides have a stronger interaction with **3**.

They suggested a new mechanism (Scheme 1.31) in which a η^2-coordinate complex was formed by the addition of α,β-unsaturated substrate to the $Ni(COD)_2$ complex. The diboron is added to the carbonyl moiety of the η^2-coordinate complex to form a new η^3-coordinate complex followed by transmetallation of a boryl group to furnish the boryl nickel species. Finally, reductive elimination afforded the starting activity species.



Scheme 1.31. Proposed mechanism of nickel catalysed β-borylation of α,β-unsaturated substrates

Recently, Oshima et al.[117] developed a new $Ni(COD)_2$ catalysed borylation of aryl cyclopropyl ketones by using N-heterocyclic carbene IMes·HCl ligand and B_2pin_2 (**3**) as boron source (Scheme 1.32).

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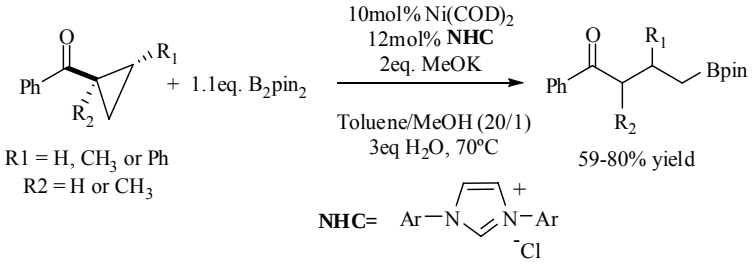
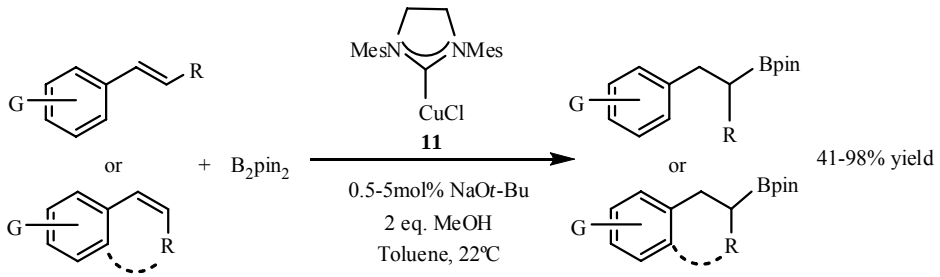


Scheme 1.32

Another recent example of borylation with N-heterocyclic carbene as ligand has been reported by Hoveyda et al.[118] They showed an effective catalysed boron addition to acyclic and cyclic β-substituted aryl olefins with [MesCuCl] as the catalytic system (**11**) (Scheme 1.33).



Scheme 1.33

Remarkably, they described the asymmetric version of this transformation using a bidentate imidazolinium salt (**12**) as ligand for acyclic β-substituted aryl arenes and the monodentate **13** for cyclic β-substituted aryl arenes (Scheme 1.34).

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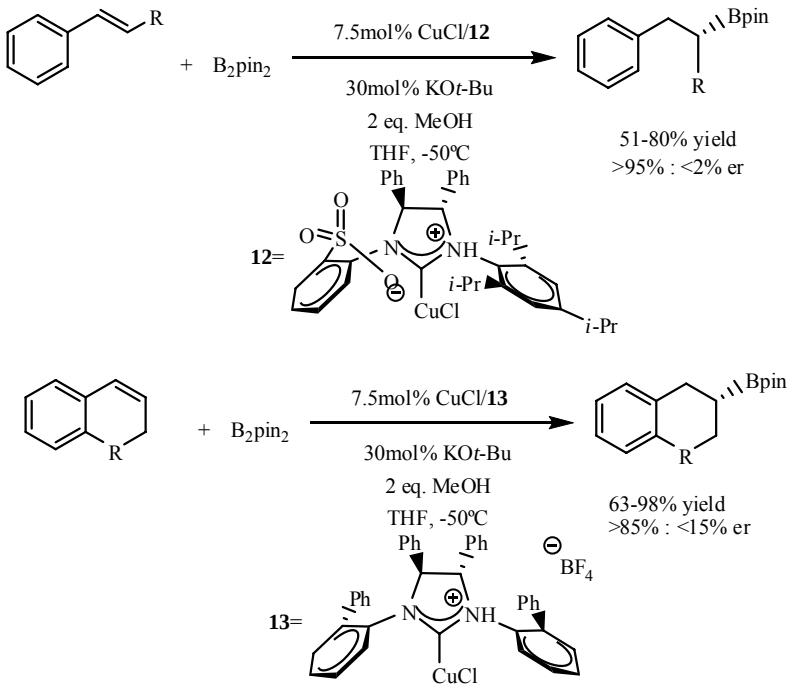

Scheme 1.34

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1.5. Scope and objectives

Organoboron derivates are important synthetic intermediates and biologically active compounds. The transition metal-catalysed addition of a mono- and diboron to unsaturated carbon-carbon bonds provides an efficient and convenient route for the preparation of mono- and diorganoboronates. These compounds are versatile intermediates for organic synthetic purposes. The catalytic control of the chemo-, regio- and diastereoselective C-B formation allows access to highly selective functionalised molecules by consecutive tandem sequences. The main advantages of the use of organoboranes as intermediates for synthetic organic purposes are their stability, relatively low toxicity and easy accessibility. A special emphasis on the selective control of the C-B formation is the retention of configuration in the functionalisation process from the organoboranes intermediates toward the targeted products.

We have focused in particular on developing an environmental and economic chemical transformation.

In this context, this thesis focuses on the synthesis of chiral organoboron (C-B bond) by using an innovative catalytic system and the subsequent *in situ* functionalisation to the C-C bond.

Chapter 2 discusses the effects of the electronic properties of the heteroatom-containing allyl substrates on the regio- and stereocontrol of the catalytic hydroboration. In addition, the catalytic system that was easily recovered from the products and could be reused in consecutive runs.

Chapter 3 discusses catalytic diboration and the use of new metal centers and new ligand families to improve the activity and chemoselectivity of previously reported catalysts.

Chapter 4 shows the successful synthesis of chiral boron enolates by using inexpensive metals such as copper and nickel. Chiral N-heterocyclic

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carbenes and modulated chiral commercially available diphosphines can induce asymmetry on the boron enolate.

In *Chapter* 5 we describe our attempts to develop an alternative strategy on functionalised organoboron compounds. Complexes containing transition metals such as platinium and palladium modified with N-heterocyclic carbenes and P,P respectively, perform the *in situ* tandem catalytic boron-addtion-Suzuki-Miyaura cross-coupling.

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Chapter 2

Heterofunctional control from substrates in metal-mediated B-addition reaction

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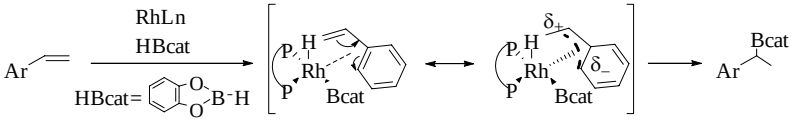
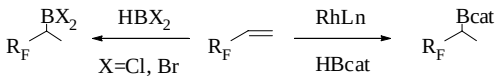
2.1. Introduction

The unusual secondary alcohol produced in the rhodium-catalysed hydroboration/oxidation of vinylarenes is believed to arise from metal-stabilisation of the benzylic intermediate during the catalytic cycle (Scheme 2.1).[1]



Scheme 2.1 η^3-Benzylrhodium intermediate

Both catalysed[2] and uncatalysed[3] hydroboration/oxidation reactions can also exhibit special control towards the formation of the branched alcohol on perfluoroalkene substrates, probably due to the combined electronic effects of the borane reagent and the substrate (Scheme 2.2).



Scheme 2.2

More remarkable is the regiocontrol provided by the electronic properties of heteroatom-containing substrates[4] such as phenyl vinyl sulfide, which regioselectively adds the boron unit from catecholborane at the 2-position of the alkene in the rhodium-catalysed hydroboration reaction (Scheme 2.3).[5] Furthermore, organosulfur compounds with boryl groups on both the α- and β-carbons were obtained by the platinum-catalysed diboration reaction (Scheme 2.3).

However, the directing effects, which revealed a trend in regioisomeric branched organoborane formation, seem to diminish substantially from vinylic

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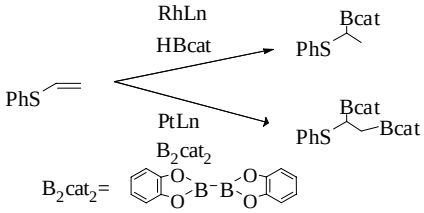
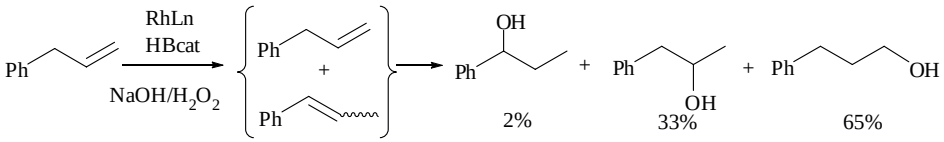
to allylic systems. Such is the case for the hydroboration/oxidation of 1-phenylprop-2-ene,[6] which provided mixtures of primary and secondary regioisomers (Scheme 2.4). In addition, this substrate, where the aromatic group is in the β-position to the alkene moiety, can undergo isomerisation of the double bond, which favours the formation of 1-arylpropanol.



Scheme 2.3



Scheme 2.4

Surprisingly, the metal-catalysed hydroboration of some heteroatom substituted allylic substrates has furnished the desired branched heteroorganoborate ester as a consequence of the nature of the catalyst. Thus, Wilkinson's catalyst precursor [$RhCl(PPh_3)_3$] favours the formation of the secondary boronate ester in the hydroboration of allyl sulfones[7] (Scheme 2.5, A) the selectivity of which was attributed to a directing effect of the sulfone oxygens, while [$RhH(PPh_3)_4$] carries out the same hydroboration of allyl sulfonamides[8] (Scheme 2.5, B) through a tandem isomerisation/hydroboration catalytic reaction.

The reversed regioselectivity from terminal B-H addition in aliphatic and unfunctionalised terminal alkenes to the branched manner in vinyl systems

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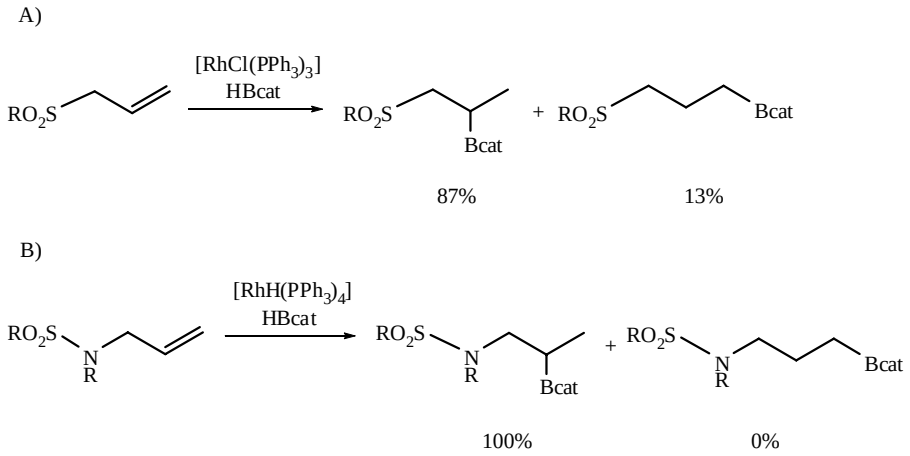
made it possible to study an asymmetric version of the catalysed hydroboration/oxidation of vinylarenes[9] and, more recently, our group explored the case of perfluoroalkenes.[10]



Scheme 2.5. A) Catalytic hydroboration of allyl sulfone. B) Catalytic hydroboration of allyl sulfonamide

However, to the best of our knowledge no work has been carried out in this respect on heteroatom-containing allylic substrates. In this context and due to the synthetic utility of chiral organosulfurboronate esters in biological applications,[11] we decided to examine the catalytic chiral hydroboration/oxidation of allyl sulfones, to determine whether it was possible to preferentially obtain one of the enantiomers of 1-(phenylsulfonyl)-2-propanol.

2.2. Rhodium-catalysed hydroboration of allylic systems

Hou and Dai's observations on the catalytic hydroboration of allyl sulfones[7] show that the neutral Rh(I) precursor of catalyst [$RhCl(PPh_3)_3$] favours

addition of the catecholboryl unit at the 2-position of the terminal alkene. When we re-examined this reactivity, we first found that the conversion of the substrate was total and that, as well as the branched and linear hydroborated/oxidated products, small percentages of hydrogenated derivatives could be obtained as a consequence of the partial formation of the metal complex $RhH_2Cl(PPh_3)_3$,[12] (Table 2.1, entries 1 and 2).

In the hydroboration/oxidation of phenyl allyl sulfone **14**, an excess of hydroborating reagent seemed to be necessary to guarantee high selectivity (Table 2.1, entry 3). Chemo- and regioselectivity towards the branched alcohol was low when the sterically hindered hydroborating reagent pinacolborane (**2**) was used instead of catecholborane (**1**) (Table 2.1, entry 4). Next, we decided to study how Rh-neutral and Rh-cationic catalytic systems affected the activity and selectivity of the hydroboration of organosulfur-substituted 1-alkenes. Like Wilkinson's catalyst precursor, a preferentially secondary insertion of the alkene into the metal complex formed from $[Rh(\mu\text{-}Cl)(COD)]_2$ /6 eq. PPh_3 and $[Rh(\mu\text{-}Cl)(NBD)]_2$ /6 eq. PPh_3, (Table 2.1, entries 5 and 6). These results differ from the preferential primary insertion of organofluoro-substituted 1-alkenes with neutral catalytic systems.[2]

In general, the catalytic hydroboration of phenyl allyl sulfones with neutral Rh complexes provides higher selectivity towards branched organosulfurboronate esters than cationic Rh complexes (Table 2.1, entry 7). The considerable neutralising influence of chlorine as counterion was confirmed in a new experiment in which the salt $BnMe_3NCl$ was added to the catalytic system formed from $[Rh(COD)_2]BF_4/PPh_3$ (Table 2.1, entry 8) because the products were distributed in a very similar way to when the system $[Rh(\mu\text{-}Cl)(COD)]_2$ /6 eq. PPh_3 was used.

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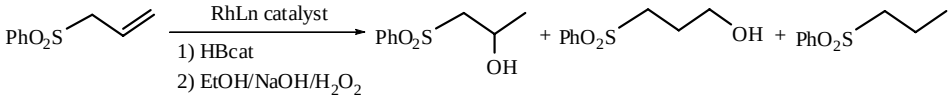

14 **15** **16** **17**

Table 2.1. Rhodium-catalysed hydroboration/oxidation of phenyl allyl sulfone (14) with catecholborane (1)[a]

Entry	Catalytic System	Conversion (%)[b]	**15** (%)[b]	**16** (%)[b]	**17** (%)[b]
1[c]	$[RhCl(PPh_3)_3]$	83	87	13	---
2	$[RhCl(PPh_3)_3]$	100	86.2	8.2	5.6
3[d]	$[RhCl(PPh_3)_3]$	100	37	43	20
4[e]	$[RhCl(PPh_3)_3]$	100	42.3	18	39.7
5	$[Rh(\mu\text{-}Cl)(COD)]_2$ + 6eq.PPh_3	100	84.2	10.1	5.7
6	$[Rh(\mu\text{-}Cl)(NBD)]_2$ + 6eq.PPh_3	100	84.3	9.7	6
7	$[Rh(COD)_2]BF_4$ + 2eq.PPh_3	100	54	32.8	13.2
8[f]	$[Rh(COD)_2]BF_4$ + 2eq.PPh_3	100	94	---	6

[a] Standard conditions: Phenyl allyl sulfone/ catecholborane/ Rh complex= 1/3/0.0075; Solvent: THF; T: 25ºC; 1 h. [b] Conversion and selectivity calculated on the alcohol derivate by ^1H NMR. [c] Ref. 7 [d] Catecholborane 1eq. [e] Hydroborating reagent: pinacolborane 3eq. [f] Addition of 3 eq. of $BnMe_3NCl$.

Taking into account all these preliminary experiments, we envisaged that the chiral bidentate phosphine ligands might lead to the desired branched boronate ester with some asymmetric induction. The ligands considered for this study were those described in Figure 2.1, which form five-, six- and seven-membered rings when chelated with rhodium.

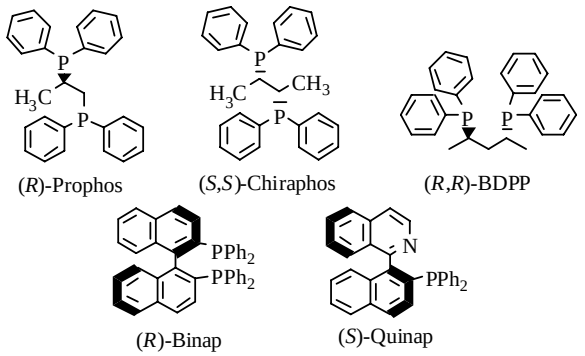

Figure 2.1

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To analyse the extent to which the relative activity, and regio- and enantioselectivity are sensitive to the chiral ligand, new catalytic hydroboration/oxidation reactions of phenyl allyl sulfone (**14**) were performed with cationic and neutral Rh complexes modified with (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP, (*R*)-Binap and (*S*)-Quinap. Conversion of the substrate was complete in 1h but selectivity for the secondary alcohol was significantly dependent on the nature of the Rh complex and the chiral ligands (Table 2.2). Small percentages of hydrogenated products were observed. For those ligands, which chelate with rhodium to form five- and six-membered rings, (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP, major regioselection was observed for the secondary alcohol with the cationic rhodium catalytic system (Table 2.2, entries 1-6). A certain level of enantioenrichment (e.e.=30-33.4%) was attained when ligand (*R*,*R*)-BDPP was involved (Table 2.2, entries 5 and 6). However, when the atropoisomeric chiral ligand (*R*)-Binap chelates with rhodium to form a seven-membered ring, a change in the independence of the electronic nature of the metal complex was detected. Major regioselectivity toward the secondary alcohol was associated with the neutral rhodium catalyst system, which was also responsible for the highest e.e. values obtained in this preliminary study (Table 2.2, entries 7-10). The use of other hydroborating reagents or lower reaction temperatures did not improve these results. In an attempt to combine the beneficial effects of the atropoisomeric ligand (*R*)-Binap and the ability to chelate with rhodium and form a six-membered ring by (*R*,*R*)-BDPP, we then focused on the atropoisomeric heterotopic chiral ligand (*S*)-Quinap, which chelates with rhodium to form a six-membered ring. However, despite the efficiency shown by this P,N ligand in several enantioselective syntheses,[13] we were disappointed to observe that while regioselectivity remained high, enantioselectivity decreased significantly.

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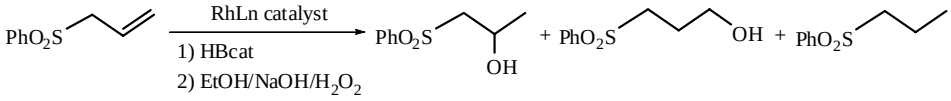

14 **15** **16** **17**

Table 2.2. Catalytic asymmetric hydroboration/oxidation of 14 with Rh complexes and catecholborane(1)[a]

Entry	Catalytic System	Conv. (%)[b]	**15** (%)[b]	e.e. (%)[c]
1	$[Rh(COD)_2]BF_4$ + (*R*)-Prophos	100	90.1	8 (S)
2	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*)-Prophos	100	54.4	3 (S)
3	$[Rh(COD)_2]BF_4$ + (*S*,*S*)-Chiraphos	100	88	17 (S)
4	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*S*,*S*)-Chiraphos	100	68.6	11 (S)
5	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	100	97.6	30 (S)
6	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*,*R*)-BDPP	100	77.2	33.4 (S)
7	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	100	74	22 (S)
8[d]	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	100	12	39 (S)
9	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*)-Binap	100	87	38 (S)
10[e]	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*)-Binap	100	86.8	37.9 (S)
11	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	100	85	12.4 (R)
12	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*S*)-Quinap	100	89	12 (R)

[a] Standard conditions: Phenyl allyl sulfone/ catecholborane/ Rh complex= 1/3/0.0075; Solvent: THF; T: 25ºC; 1 h. [b] Conversion and selectivity calculated on the alcohol derivate by ^{1}H NMR. [c] Determined on the alcohol product by G.C. with chiral column. Absolute configuration was assigned by comparison with Ref. 14. [d] Hydroborating reagent HBpin. [e] T=-20ºC.

At this point, we can infer two things from our initial asymmetric catalytic results. Firstly, regioselectivity for the secondary alcohol depends upon the electronic properties of the substrate, but also on the electronic properties of the metal complexes used as the catalyst. To highlight the importance of this point, we carried out two catalytic reactions with the analogous neutral complex $[Ir(\mu\text{-}Cl)(COD)]_2$ modified with (*R*)-Binap and (*S*)-Quinap. However, only 23% and 28% of the secondary alcohol was observed, respectively, with almost no e.e.'s. Secondly, enantioselectivity seemed to be favoured with chiral ligands that form major chelate rings with rhodium(I) complexes.

We demonstrated the generality of the regio- and enantioselective hydroboration/oxidation reaction of aryl allyl sulfones as a function of the electronic and steric propierties, by carrying out the catalytic reaction on electron-rich and electron-deficient substituted aryl allyl sulfones. Of the many

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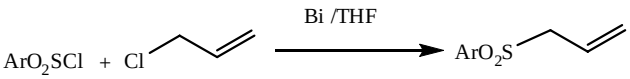
sulfone synthetic procedures described in the literature,[15] we prepared the *p*-methyl-phenyl allyl sulfone, **18**, and *p*-chlorophenyl allyl sulfone, **19**, with an efficient and inexpensive protocol, which uses the bismuth-catalysed coupling of allylic halides with the corresponding sulfonyl chloride, under mild conditions[16] (Scheme 2.6).



18 Ar = p-MePh
19 Ar = p-ClPh

Scheme 2.6. Synthesis of *p*-substituted aryl allyl sulfones

The results of the Rh-catalysed hydroboration/oxidation of **18** and **19** were similar to the phenyl allyl sulfone **14**. The data are summarised in Table 2.3. The regioselectivity for the secondary alcohol was almost complete when $[Rh(COD)_2]BF_4$/(*R*,*R*)-BDPP was used as a catalyst precursor (Table 2.3, entries 1 and 7) and e.e. values around 33% were determined from the ^{1}H NMR spectrum in the presence of the chiral shift reagent $Eu(TFC)_3$ (TFC= Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]). Contrary to the strong electronic influence of the aryl sulfonyl functional group on branched isomer formation, aryl substitution with electron-releasing groups was also seen to have a beneficial effect. The asymmetric induction was not affected by aryl substitution on the aryl allyl sulfone either.

Bearing all this in mind and in an attempt to improve the enantioselectivity, we decided to explore the effect of another kind of atropoisomeric heterotopic chiral ligand such as Quinazolinap ligands (Figure 2.2). In collaboration with Prof. P. J. Guiry's group (University College of Dublin), we synthesised the Quinazolinap ligands which have already been reported in the literature.[17]

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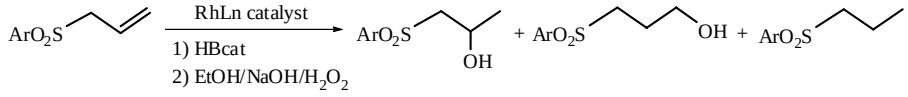


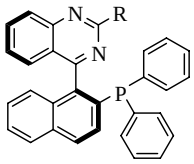
18 Ar = *p*-MePh
19 Ar = *p*-ClPh

20 **21** **22**

Table 2.3. Catalytic asymmetric hydroboration/oxidation of substituted aryl allyl sulfone with Rh complexes and 1[a]

Entry	Catalytic System	Substrate	**20** (%)[b]	e.e. (%)[c]
1	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**18**	98	33.6 (S)
2	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*,*R*)-BDPP	**18**	49.5	32.7 (S)
3	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	**18**	74	11.2 (S)
4	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*)-Binap	**18**	52	7.3 (S)
5	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**18**	70	16 (R)
6	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*S*)-Quinap	**18**	76	25 (R)
7	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**19**	95	33.3 (S)
8	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*,*R*)-BDPP	**19**	37	30 (S)
9	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	**19**	73	17 (S)
10	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*R*)-Binap	**19**	38	13 (S)
11	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**19**	50	6.7 (R)
12	$[Rh(\mu\text{-}Cl)(COD)]_2$ + (*S*)-Quinap	**19**	38	15.6 (R)

[a] Standard conditions: Substrate/ catecholborane/ Rh complex= 1/3/0.0075; Solvent: THF; T: 25ºC; 1 h. [b] Conversion (100% in all cases) and chemoselectivity calculated on the alcohol derivative by ^{1}H NMR. [c] Determined on the alcohol product by ^{1}H NMR in the presence of chiral shift reagent $Eu(TFC)_3$. Absolute configuration was assigned by comparison with Ref. 14



(*S*)-23 R= H
(*S*)-24 R= Me
(*S*)-25 R= *i*-Pr

Figure 2.2. Quinazolinap ligands

The catalytic hydroboration of phenyl allyl sulfone was performed with the neutral complex $[Rh(\mu\text{-}Cl)(COD)]_2$ modified with (*S*)-Diphenyl-[1-quinazolin-4-yl)(2-naphthyl)]phosphine (**(*S*)-23**), (*S*)-Diphenyl-[1-(2-methyl-quinazolin-4-yl)(2-naphthyl)]phosphine (**(*S*)-24**) and (*S*)-Diphenyl-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine (**(*S*)-25**), all of which were

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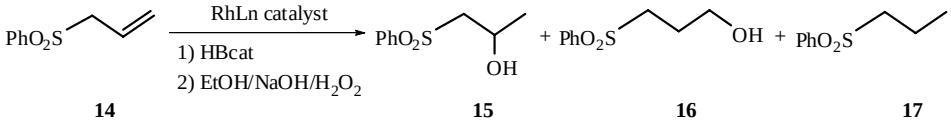
chelated with rhodium to form a six-membered ring. Although the conversion was total in the three cases, regioselectivity to the branched product was significantly reduced in all cases (Table 2.4, entries 1-3). The enantiomeric excess were similar to those obtained with (*R*)-Binap and (*R*,*R*)-BDPP. However, the use of cationic complexes $[Rh(COD)_2]BF_4$ modified with **(S)-25** afforded lower asymmetric induction than the neutral complex $[Rh(\mu\text{-}Cl)(COD)]_2$ modified with **(S)-25** (Table 2.4, entry 4).



14 **15** **16** **17**

Table 2.4. Catalytic asymmetric hydroboration/oxidation of phenyl allyl sulfone (14) with Rh complexes and catecholboane[a]

Entry	Catalytic System	Conv. (%)[b]	**15** (%)[b]	e.e. (%)[c]	**16** (%)[c]	**17** (%)[c]
1	$[Rh(\mu\text{-}Cl)(COD)]_2$ + **(*S*)-23**	100	53	34 (R)	28	19
2	$[Rh(\mu\text{-}Cl)(COD)]_2$ + **(*S*)-24**	100	42	42 (R)	46	12
3	$[Rh(\mu\text{-}Cl)(COD)]_2$ + **(*S*)-25**	100	39	47 (R)	47	14
4	$[Rh(COD)_2]BF_4$ + **(*S*)-25**	100	54	31 (R)	38	8

[a] Standard conditions: Phenyl allyl sulfone/ catecholborane/ Rh complex= 1/3/0.0075; Solvent: THF; T: 25ºC; 1 h. [b] Conversion and selectivity calculated by ^1H NMR. [c] Determined on the alcohol product by G.C. with chiral column. Absolute configuration was assigned by comparison with Ref. 14.

Inspired by these preliminary results, we focused our attention on the catalytic hydroboration/oxidation of a series of heterofunctional allylic substrates (Figure 2.3) in an attempt to establish how the electronic properties of the O, N and S heteroatoms influenced the regiocontrol and stereocontrol.

When the catalytic hydroboration/oxidation was performed using cationic Rh complexes modified with (*R*,*R*)-BDPP and an excess of HBcat (**1**) as a hydroborating reagent, we found that the conversion of these substrates was completed after 1h. (Table 2.5).

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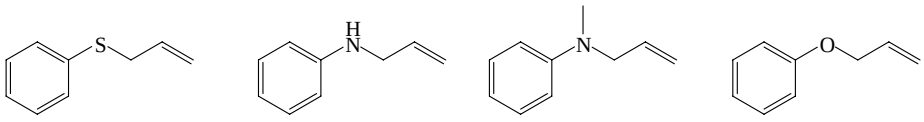

26 **27** **28** **29**

Figure 2.3. Heterofunctional aryl allylic substrates

The regiocontrol of the hydroboration/oxidation reaction seems to depend on the electronic influence of the heterofunctional group which plays a decisive role in obtaining the desired branched product. In general, we found that the sulfone group in substrates **14**, **18** and **19**, selectively induced the Markovnikov alcohol product as the majority isomer. However, when the sulfone group was replaced by a sulfide group, substrate **26**, the regiocontrol decreased to give a poor percentage of the secondary alcohol and a high percentage of linear and hydrogenated product instead (Table 2.5, entry 1). When the cationic rhodium-complex was modified with (*S*)-Quinap, the percentage of the branched organoboronated product improved slightly. In the cases of substrates *N*-allylaniline **27** and *N*-allyl-N-methylaniline **28**, with both cationic and neutral complexes, the regiocontrol was only moderate, although the hydrogenated byproduct was hardly observed (Table 2.5, entries 3-10). This is in contrast with Wescott's[8] observations on the catalytic hydroboration of allyl sulfonamides which show a competing isomerisation reaction as the main reason for the formation of branched isomers in high yields.

The activity and selectivity of the hydroboration/oxidation of phenyl allyl ether **29** with neutral and cationic rhodium complexes was similar to **28** (Table 2.5, entries 11-14). In both cases, we observed that the modification of rhodium complexes with (*S*)-Quinap provided higher percentages of the secondary alcohol than modification with (R,R)-BDPP.

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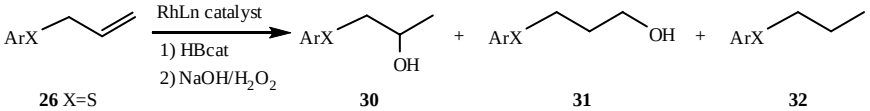

26 X=S
27 X=NH
28 X=NCH_3
29 X=O

30 **31** **32**

Table 2.5. Catalytic asymmetric hydroboration/oxidation of aryl allyl systems with Rh complexes and 1[a]

Entry	Catalytic System	Substrate	**30** (%)[b]	e.e. (%)	**31** (%)[b]	**32** (%)[b]
1	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**26**	7	---	67	24
2	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**26**	30	---	30	40
3	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**27**	67	23 (S)[c]	33	---
4	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*,*R*)-BDPP	**27**	62	12 (S)[c]	35	3
5	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**27**	60	20 (R)[c]	39	1
6	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*S*)-Quinap	**27**	74	23 (R)[c]	23	3
7	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**28**	41	22 (S)[c]	59	---
8	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*,*R*)-BDPP	**28**	22	23 (S)[c]	88	---
9	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**28**	51	26 (R)[c]	49	---
10	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*S*)-Quinap	**28**	57.5	22 (R)[c]	42.5	---
11	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	**29**	40	15 (S)[d]	60	---
12	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*,*R*)-BDPP	**29**	24	22 (S)[d]	76	---
13	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	**29**	61	23 (R)[d]	39	---
14	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*S*)-Quinap	**29**	68	25 (R)[d]	32	---

[a] Standard conditions: Substrate/ catecholborane/ Rh complex= 1/3/0.0075; Solvent: THF; T: 25ºC; 1 h. [b] Conversion (100% in all cases) and chemoselectivity on the alcohol derivate calculated by ^{1}H NMR. Characterisation was made in comparison with pure products, Ref. 18 and 19. [c] Determined on the alcohol product by ^{1}H NMR in the presence of chiral shift reagent $Eu(TFC)_3$. Absolute configuration was assigned by comparison with Ref. 14. [d] Determined on the alcohol product by GC with a chiral column. Absolute configuration was assigned by comparison with Ref. 14.

The enantioselectivity obtained was moderate and, as for aryl allyl sulfones, it was determined either from the ^{1}H NMR spectra in the presence of the chiral shift reagent $Eu(TFC)_3$ or by GC with a chiral column. Although the heterofunctional group affects branched isomer formation, it does not affect the enantioselectivity. The e.e. values were found to be between 22% and 32% for the secondary alcohol obtained from substrates **27**-**29** and were similar to those e.e. obtained for substrates **14**, **18** and **19**.

For **29**, the use of neutral and cationic complexes modified with (*S*)-Quinap afforded higher asymmetric induction than the cationic complex $[Rh(COD)_2]BF_4$, modified with (*R*,*R*)-BDPP (Table 2.5, entries 11 and 14).

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2.3. Rhodium-catalysed hydroboration of allylic systems in a heterogenised version

In the past the immobilisation of chiral rhodium-complexes onto clays provided clear advantages in the asymmetric hydroboration of vinylarenes[13d,e] (eg. greater stability of the metal species under air, easy separation from the reaction mixture by simple filtration and recycling for consecutive runs without any loss in activity, or regio- and stereoselectivity). Indeed, the catalyst is not often recovered in hydroboration reactions,[20] but even less on the recycling capability. The most recent study by Leitner et al.[21] using the biphasic IL/scCO_2 methodology is one of the few examples.

In the cases in which the catalytic system provides an efficient and selective route to the corresponding secondary organoboronate product, we decided to explore the recovery and recycling of the active metal species involved.

In order to perform the heterogenised version of the catalytic asymmetric hydroboration of the heterofunctional allylic system, we selected the Rh(I) catalytic system since it had previously been shown to have the highest activity and selectivity in the catalytic hydroboration of aryl allyl sulfones.

We tested the long-term stability of [Rh((*R*,*R*)-BDPP)(COD)]BF_4 and its recovery and reuse in consecutive runs by immobilizing it on the montmorillonite-smectite clay MK-10, previously treated at 100ºC for 24h. To immobilise the ionic rhodium complex onto the MK-10, the coloured solution of the metal compound had to be stirred into anhydrous dichloromethane with MK-10 for 24h at room temperature, under nitrogen, following a solvent-impregnation methodology.[13d,e,22] The high surface area of the montmorillonite allows immobilisation via adsorption of the cationic complex and thus enables the substrate to access the immobilised complex easily.

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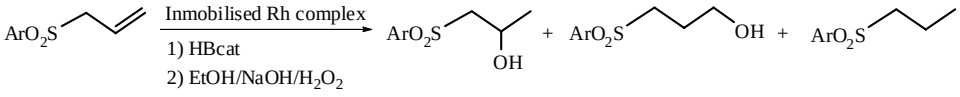
The experiments with the heterogenised rhodium catalytic system [Rh((*R*,*R*)-BDPP)(COD)]BF_4/MK-10 were carried out using the previously optimised conditions for the homogenous version in the hydroboration/oxidation of substrates **14** and **18** with HBcat. The results are shown in Table 2.6.



14 Ar = Ph
18 Ar = *p*-MePh

20 **21** **22**

Table 2.6. Heterogenised catalytic asymmetric hydroboration/oxidation of aryl allyl sulfone with Rh complexes and catecholborane[a]

Entry	Catalytic System	Substrate	Run	Conv. (%)[b]	**20** (%)[b]	e.e. (%)	**21** (%)[b]
1	[Rh((*R*,*R*)-BDPP)(COD)]BF_4/MK-10	**14**	1	100	93	32 (S)[c]	7
			2	100	98	34 (S)[c]	2
			3	100	94	36 (S)[c]	6
			4	89.5	97	29 (S)[c]	3
2	[Rh((*R*,*R*)-BDPP)(COD)]BF_4/MK-10	**18**	1	100	>99	30 (S)[d]	---
			2	100	>99	28 (S)[d]	---
			3	100	>99	25 (S)[d]	---

[a] Standard conditions: Substrate/ catecholborane=1/3; 1.5% of catalytic precursor immobilised in 250mg of MK-10; Solvent: THF.; T: 25ºC.; 2 h. [b] Conversion and selectivity calculated on the alcohol derivative by ^{1}H NMR. [c] Determined on the alcohol product by GC with a chiral column. Absolute configuration was assigned by comparison with Ref. 14. [d] Determined on the alcohol product by ^{1}H NMR in the presence of chiral shift reagent $Eu(TFC)_3$. Absolute configuration was assigned by comparison with Ref. 14.

The activities, selectivities and enantioselectivities were similar to those of the homogenous catalytic system from the first run and were maintained during four consecutive runs (Table 2.6). Leaching of the catalyst was not observed. These results show that the [Rh((*R*,*R*)-BDPP)(COD)]BF_4/MK-10 catalytic system can be recovered and reused in the asymmetric catalytic hydroboration/oxidation reaction of aryl allyl sulfone for more than four runs, in which the secondary alcohol is the major product and enantiomeric excess is moderate.

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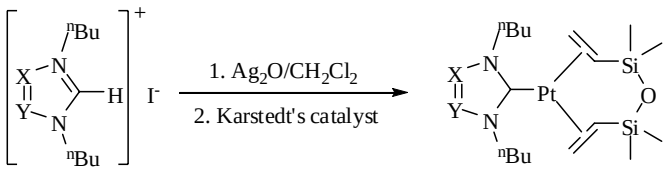
2.4. Platinum-catalysed aryl allyl sulfones diboration

Taking into account the experience of the group in the scope of the catalytic diboration reaction,[23] we turned our attention to the promising NHC-Pt(0) (NHC= N-heterocyclic carbene ligand) complexes and their ability to catalyse the diboration of aryl phenyl sulfones.

We worked in collaboration with Prof. E. Peris's group, who are experts on the synthesis of transition metal complexes modified with NHC ligands. Prof. E. Peris' group used transmetallation to synthesize the NHC-platinum compounds **33-35** from the corresponding silver carbene complexes (Scheme 2.7). The three complexes were obtained so that the effect of the electronic nature of the NHC ligand on catalytic performance could be studied.



33 - X= Y= C-Cl
34 - X= N; Y= C-H
35 - X= Y= C-H

Scheme 2.7. Synthesis of (NHC)-Pt(0) complexes

The NHC-Pt(0) complexes **33-35** were initially tested in the diboration of phenyl allyl sulfone **14** as model substrate. As shown in table 2.7, the three complexes allowed quantitative conversions towards the bis(boryl)alkyl sulfone (entries 1-3) when bis(pinacolato)diboron $B_2(pin)_2$ (**3**) was added.

Complex **33** proved to be the most suitable for this transformation (Table 2.7, entry 1). However, small percentages of monoalkylboranes were observed as a subsequent β-H elimination competitive pathway. Remarkably, an excess of 2eq of $B_2(pin)_2$ led to total conversion, even when electron-donating

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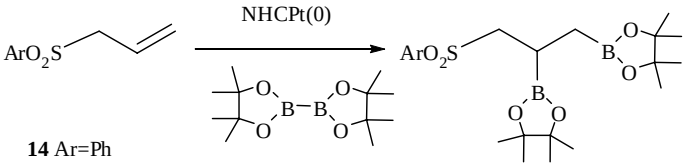
or electron-withdrawing moieties were present in the substrate (Table 2.7, entry 4-6).



14 Ar=Ph
18 Ar=*p*-MePh
19 Ar=*p*-ClPh

36: Bis(boryl)alkyl sulf one
36 a: Ar=Ph
36 b: Ar=*p*-MePh
36 c: Ar=*p*-ClPh

Table 2.7. Catalytic 1,2-diboration of aryl allyl sulfones with NHC-Pt(0) complexes and bis(pinacolato)diboron (3)[a]

Entry	NHC-Pt(0)	Substrate	Conversion (%)[b]	**36** (%)[b]
1	**33**	**14**	90	75
2	**34**	**14**	69	71
3	**35**	**14**	87	85
4	**33**	**14**[c]	100	90
5	**33**	**18**[c]	100	91
6	**33**	**19**[c]	100	94

[a] Standard conditions: Substrate/ bis(pinacolato)diboron = 1/1.1; 5mol% of NHC-Pt(0); Solvent: Toluene; T: 80ºC; 16 h. [b] Conversion and selectivity calculated by ^{1}H NMR. [c] Substrate/ bis(pinacolato)diboron = 1/2.

It seems that the electron-withdrawing terminal group in the allylic system facilitated the simultaneous B-B catalytic addition to the C=C bond without any undesired byproduct formation due to the isomerisation of the double bond.

It is interesting to note that the aryl allyl sulfones could not be diborated with metal-phosphine catalytic systems based on rhodium or platinum complexes such as $[RhCl(PPh_3)_3]$, $[Rh(COD)(PPh_3)_2]BF_4$ or $Pt(PPh_3)_4$.

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2.4. Conclusions

We have performed the first example of direct access to enantiomerically enriched mixtures of 1-phenylsulfonyl-2-propanol by varying the catalytic system throughout the hydroboration/oxidation of aryl allyl sulfones with catecholborane. These results could be used as a synthetic alternative due to the importance of sulfur-substituted 2-propanols as sulphur-containing chiral synthons in asymmetric organic synthesis.[24]

Three equivalents of catecholborane were required to obtain high selectivity towards the branched isomer. Nevertheless, the use of sterically hindered pinacolborane provided low chemio- and regioselection towards the branched isomer.

We have also shown that the regioselectivity toward the secondary heteroorganoboronate ester in the hydroboration of heterofunctional allylic substrates is controlled by the nature of the heteroatom, with the following order: SO_2>NH>N(CH_3)~O>>S. However, the enantioselectivity seems to be controlled by the chiral ligand and the nature of the complex which in all cases gave only moderate enantiomeric excesses. The cationic rhodium complex modified with (*R*,*R*)-BDPP was immobilised on MK-10 and used in the heterogenised hydroboration/oxidation reaction of aryl allyl sulfones. The recovery and reuse of the catalytic system were efficient and there was no loss of activity and selectivity.

We also made the first study of the diboration reaction of phenyl allyl sulfones catalysed by a platinum complex modified with N-heterocyclic carbene ligands (NHC). We observed total conversion into 1,2-bis(boryl)alkyl sulfones in situ which were transformed into 1,2-dihydroxy sulfones by oxidation with hydrogen peroxide in a basic medium. Both electron-donating and electron-withdrawing aryl allyl sulfones were diborated with NHC-Pt(0) complexes,

which afforded the difunctionalised compound as the major product in the form of a single intermediate.

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Chapter 3

Transition metal complexes in the catalytic diboration reaction

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3.1. Introduction

The most convenient methodology for organodiboron preparation involves the metal-mediated addition of a diboron reagent to an unsaturated carbon–carbon bond. A low valent transition metal catalyst is required to cleave the B-B bond from the diboron reagent to form the intermediate metal bis(boryl)complex, generally via oxidative addition.[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 monophosphine platinum-containing catalysts.[2] However, the related catalytic alkene diboration seems to be a more complex transformation, 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 phosphine-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)] (where 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 phosphine-free Pt-catalyst precursors.[4] In addition to rhodium and platinum, transition metal complexes on Au(I) have been shown to promote this transformation.[5] Diphosphine ligands seem to be necessary to selectively promote the addition of diborons to alkenes, although long reaction times are required for only moderate yields.

Our group has also demonstrated that gold nanoparticles efficiently catalyse the diboration of alkenes with total chemoselectivity (Figure 3.1).[6]

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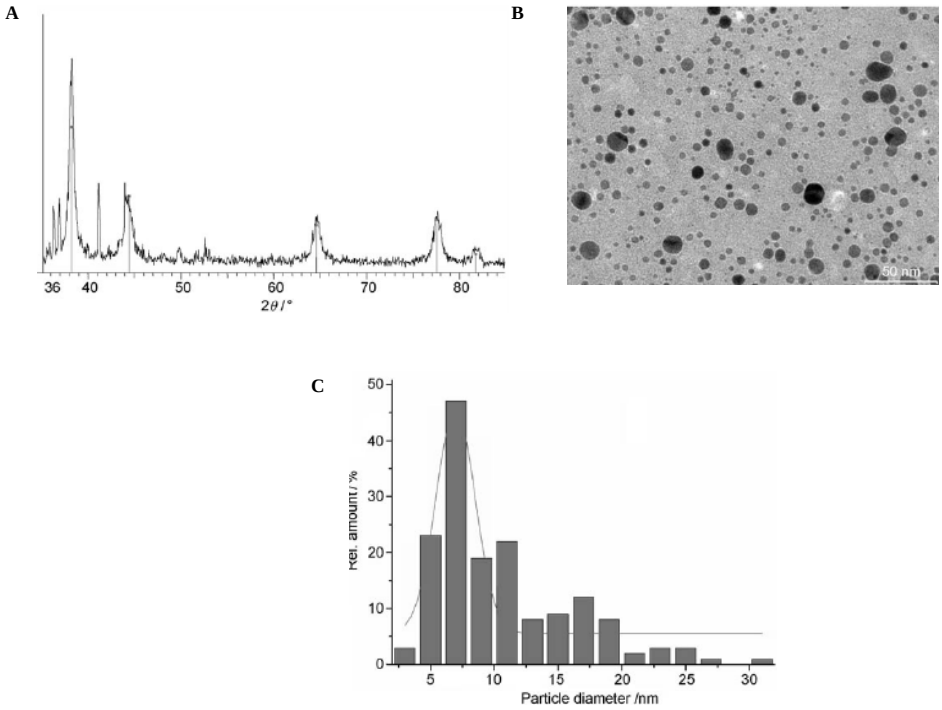

Figure 3.1. A) X-Ray diffractogram; B) TEM micrograph (500000 x enlargement); C) Core size distribution

Considering that the catalytic diboration reaction reported to date has been conducted by transition metal complexes modified with phosphine ligands, our group thought that it would be interesting to introduce an alternative type of ligand, such as an N-heterocyclic carbene ligand (NHC). NHCs are considered to be better electron donors than phosphines and therefore provide enough richness to the metal center to guarantee diboron B-B cleavage of the diboron. NHCs have also emerged as a promising family of ligands for designing efficient homogenous catalysts[7] because they make the metal complexes extremely stable.

The structural diversity of silver (I) N-heterocyclic carbenes has been studied in depth,[8] and they have been widely used as carbene transferring agents

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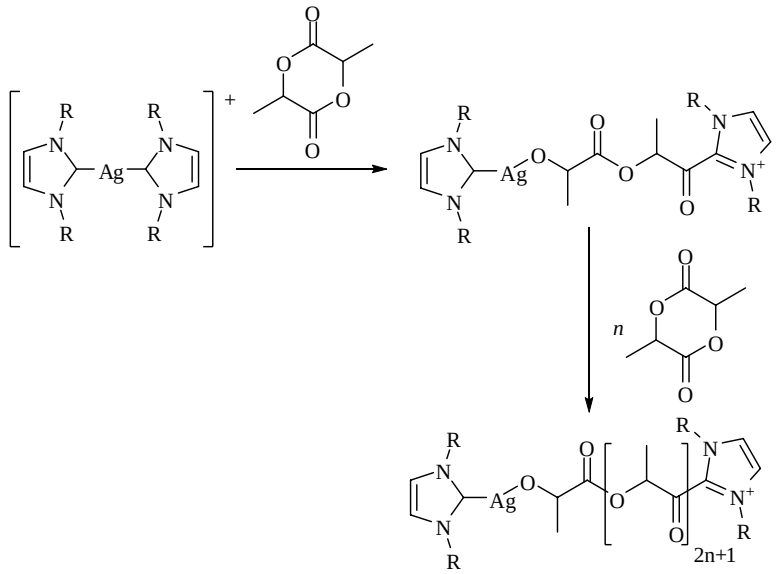
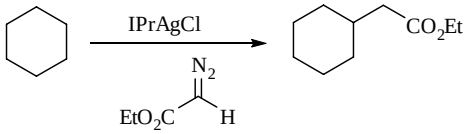
for easy access to various important (NHC)-metal complexes.[8b,9] However, despite the high number of (NHC)-silver complexes that have been described in the literature, few applications have been reported in catalytic processes. Jin et al.[10] reported the moderate activity of a silver N-heterocyclic carbene complex precatalyst in the polymerization of ethylene. Silver N-heterocyclic carbenes have also been used as precatalysts in the ring opening polymerization of lactides (Scheme 3.1).[11]



Scheme 3.1

Perez et al.[7g] reported the (NHC)-silver catalysed insertion of ethyl diazoacetate into C-H bonds (Scheme 3.2).



Scheme 3.2

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Bearing all this in mind and in the context of a collaboration with Prof. E. Peris from the Jaume I University (Castellón), our group planned to perform the first catalytic diboration of terminal alkenes with Ag(I) complex modified with NHC ligands.[12] The carbene complex $[(mentimid)_2Ag]AgCl_2$ (where mentimid= 1-methyl-3-(+)-methylmenthoxide imidazolium chloride) (Figure 3.2) was tested in the catalytic diboration of styrene as model substrate, providing a conversion of 76% of the single product 1-phenyl-1,2-ethanediol but non asymmetric induction was detected.

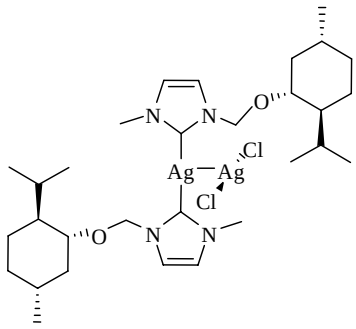

Figure 3.2

In an attempt to achieve asymmetric induction, we decided to examine the catalytic activity provided by a series of NHC-Ag(I) and NHC-Au(I) complexes where the chirality was introduced into the wingtip of the ligands (Figure 3.3).[13] These compounds were also tested in the diboration of a series of terminal olefins and although they both showed total selectivity on the diborated product, conversions were moderate (values between 40% and 60%) and asymmetric induction was not observed in any case.

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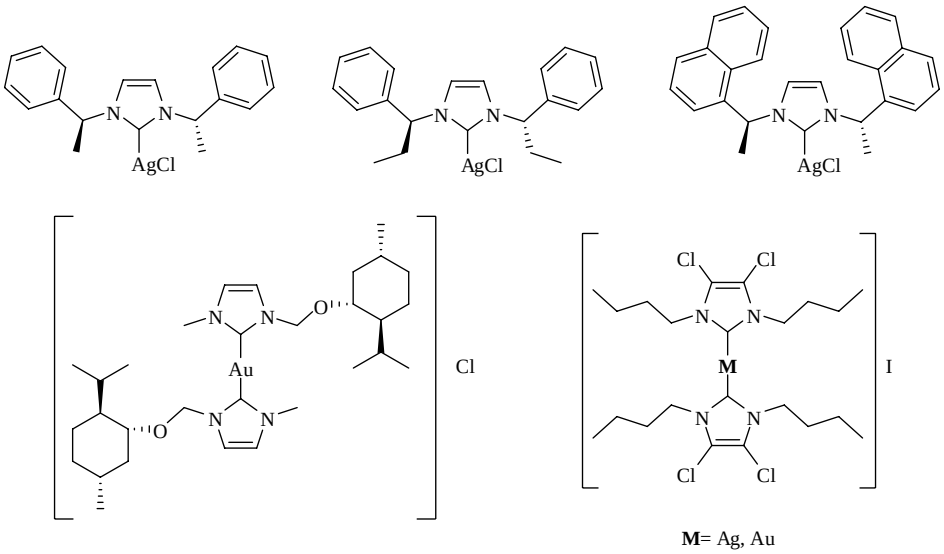

Figure 3.3

We also simultaneously showed that Pt(0)-containing NHC ligands provided a high degree of conversion (up to 80%) and moderate chemoselectivity (values between 40% and 60%) on the diborated product when bis(catecholato)diboron was the diboron source.[14] Similarly, the diboration of aryl allyl sulfones provided total conversion and selectivity on the diborated product when an excess of bis(pinacol)diboron was added (see chapter 2).

3.2. Cu/NHC-catalysed alkene diboration

In an attempt to develop both active and selective catalysts for the alkene diboration reaction, we turned our attention to copper, the only group 11 metal that is still not known to catalyse the diboration of alkenes.[15] In collaboration with the groups of Prof. P. J. Pérez (Huelva University) and Prof. F. Maseras (ICIQ), and taking into account the success of such compounds in other

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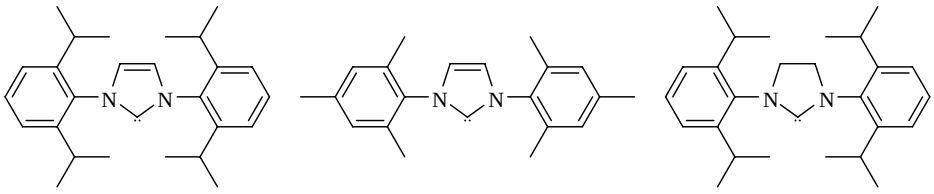
catalytic processes,[16] we investigated the potential of several complexes containing the (NHC)Cu(I) core as the catalyst for this reaction.

In the first screening, the previously described[16c-e] **37-42** (Figure 3.4) were tested as catalytic precursors in the diboration of styrene with bis(catecholato)diboron, B_2cat_2 (**4**). The diboron 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
37: [(IPr)CuCl]
38: [(IPr)Cu(NCCH$_3$)]BF$_4$

IMes
39: [(IMesCuCl]
40: [(IMes)Cu(NCCH$_3$)]BF$_4$

SIPr
41: [(SIPr)CuCl]
42: [(SIPr)Cu(NCCH$_3$)]BF$_4$

Figure 3.4

In the first series of experiments, the IPr ligand (where IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) was used in four different catalytic precursors: the neutral complex [(IPr)CuCl] (**37**), the isolated cationic species [(IPr)Cu(NCCH$_3$)]BF$_4$ (**38**), and mixtures of **37** with NaBAr'$_4$ [17] (where BAr'$_4$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) or $AgBF_4$ for the in situ generation of the cationic species.

The neutral complex **37** did not induce the transformation at room temperature (Table 3.1, entry 1) and when the transformation was performed at refluxing THF temperature the conversions were very low (Table 3.1, entry 2). Addition of NaBAr'$_4$ as the halide scavenger was not effective (Table 3.1, entry 3), but moderate conversions (53%) were observed when $AgBF_4$ was used instead (Table 3.1, entry 4). The nature of the salt seems to play a significant

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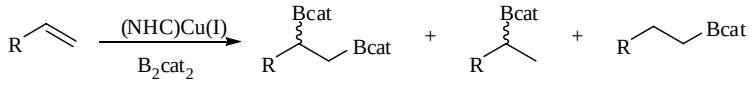
role in the in situ formation of the cationic complexes. However, when the well defined, previously isolated complex **38** was used as the catalytic precursor, moderate conversion (50%) was obtained at room temperature, and nearly quantitative conversion (94%) was achieved at refluxing THF temperature (Table 3.1, entries 5 and 6, respectively). The use of Cu(I) catalysts, which had previously only been reported for the monoboration of α,β-unsaturated ketones, was succesful with this metal.[18]



43 **44** **45**

Table 3.1. Catalytic diboration of styrene with (NHC)Cu(I) and B_2cat_2 (4)[a]

Entry	Catalytic System	Solvent	T (ºC)	Conv. (%)[b]	**43** (%)[b]	**45** (%)[b]
1	**37**	THF	22	---	---	---
2	**37**	THF	reflux	11	100	0
3	**37**/$NaBAr'_4$	THF	reflux	5	100	0
4	**37**/$AgBF_4$	THF	reflux	53	63	37
5	**38**	THF	22	50	80	20
6	**38**	THF	reflux	94	89	11
7	**38**	CH_3CN	reflux	12	100	0
8	**38**	Toluene	reflux	59	22	54[c]
9[d]	**38**	THF	reflux	74	20	80
10[e]	**38**	THF	reflux	43	0	100
11	**39**	THF	reflux	25	59	41
12	**40**	THF	reflux	53	42	58
13[f]	**41**	THF	reflux	100	100	0
14	**42**	THF	reflux	41	58	42

[a] Standard conditions: substrate/B_2cat_2/Cu complex = 0.5/0.55/0.025; Reaction time: 4h. [b] Conversion and selectivity calculated by ^1H NMR. [c] Branched organoboronate product **44** observed (24%). [d] Diboron reagent = B_2pin_2 (**3**). [e] [styrene]/[B_2cat_2] = 3:1 [f] *t* = 10h.

The reaction conditions can affect both the activity and selectivity. For instance, the selection of the solvent is important because, as shown in Table 3.1, entries 6, 7 and 8, it affects the conversion and the distribution of products. In the case of toluene, the monofunctionalised compound was the major product, and some branched isomer **44** was observed (24%). The nature of the

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diboron reagent also affects the conversion of the reaction; the use of bis(pinacolato)diboron (**3**) instead of bis(catecholato)diboron (**4**) reduces the yield of the reaction and gives the linear monoalcohol as the main product (80%) (Table 3.1, 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 **4** (10%) with respect to styrene; however, when a [styrene]/[B_2cat_2] ratio of 3:1 was used, only the linear monofunctionalised compound, and no other borated product, was observed at the end of the reaction (Table 3.1, entry 10). This result suggests that the selectivity of the reaction could be controlled 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 moiety as well as the backbone. Thus, use of mesityl instead of 2,6-diisopropylphenyl groups as the N substituents seems to increase the amount of the linear monoborated product (Table 3.1, 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 used in the neutral precatalyst **41**, 68% conversion was observed after the standard 4hours of reaction time. This value is substantially higher than that found with complex **37** (11%) (Table 3.1, entry 2), and conversion was completed by prolonging the reaction time to 10 h. (Table 3.1, entry 13). Only the diboron product was observed at the end of this reaction, in a quantitative and selective transformation (Table 3.1, entry 13). However, the cationic analogue **42** did not provide such complete selectivity (Table 3.1, entry 14).

These results are worth commenting since both activity and selectivity values are, at least, comparable with previously reported data. Exclusive

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formation of the difunctionalized product has been reported with (NHC)Au(I) and (NHC)Ag(I) catalyst precursors, but in the case of (NHC)Cu(I), the catalytic system **41** was more active because of the shorter reaction times required for total conversion (10h with 5mol% of **41**, instead of 48h with 8mol% of diphosphine-Au(I)[5] or 60h with 5mol% of [(mentimid)$_2$Ag]AgCl$_2$[12]). Only the very active [Rh(dppb)(η^6-catBcat)],[3] the monophosphine Pt(0) complexes,[2c] the base-free platinum catalyst precursors [Pt(dba)$_2$] (where dba= dibenzylideneacetone),[4a] [Pt(NBE)$_3$[4b] and [Pt(COD)$_2$],[4b] and [Pt(COD)Cl$_2$] [4c] seem to be comparable with this (NHC)Cu(I) 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.

As a consequence of the formation of the terminal monoborated product in the catalytic diboration, we also decided to study the capabilities of these (NHC)Cu(I) complexes in the alkene hydroboration reaction. Thus, when HBcat (**1**) was added to styrene in a solution of the complexes **37-42** in THF at room temperature, a smooth reaction took place. After 4h at room temperature, the linear monoborated product was predominantly obtained in all cases (Table 3.2). The branched isomer was obtained as the minor product, presumably as a result of the steric hindrance of the NHC ligands.

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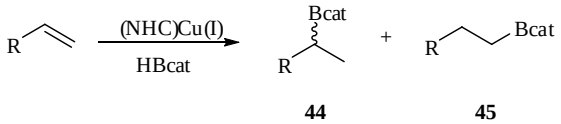

44 **45**

Table 3.2. Catalytic hydroboration of styrene with (NHC)Cu(I) and 1[a]

Entry	Catalytic System	Conv. (%)[b]	**44** (%)[b]	**45** (%)[b]
1	**37**	95	27	73
2	**38**	73	30	70
3	**39**	85	16	84
4	**40**	77	12	88
5	**41**	73	28	72
6	**42**	78	19	81

[a] Standard conditions: substrate/HBcat/Cu complex = 0.5/0.55/0.025; Sovent: THF; Reaction time: 4h.; T=25ºC. [b] Conversion and selectivity calculated by ^{1}H NMR.

In collaboration with Prof. P. J. Perez and Prof. F. Maseras, we also investigated the mechanism of this reaction. Complex **38** and styrene were dissolved in deuterated tetrahydrofuran, with no change in the ^{1}H NMR of complex **38** at either 22ºC or 50ºC. However, when bis(catecholato)diboron (**4**) was added to a solution of complex **38** 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 **38** and some broadening in the aromatic resonances of the catechol units from **4**. Unfortunately, the resulting product was not isolated or identified. In this case, when styrene was added to the mixture, diboration started immediately, even at room temperature, with a low rate that accelerated when the temperature was raised to 50ºC. Only one (NHC)Cu(I) species was detected during catalysis, with ^{1}H NMR signals that were identical to those observed when complex **38** and **4** were mixed. There was no evidence of styrene coordination. Interestingly, when the same set of experiments was carried out in deuterated acetonitrile, no reaction was observed, probably due because a dissociation preequilibrium of the CH_3CN ligand of complex **38** is required to generate an unsaturated species which is

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reactive towards B_2cat_2 (**4**). This dissociation takes place readily in tetrahydrofuran, but not in acetonitrile.

The mechanisms proposed for the Rh(I)- and Pt(I)-catalysed diboration involve an oxidative addition of the B-B bond to the metal center.[1,19,20] Subsequent insertion of the olefin into one M-B bond and reductive elimination would afford the final diboron product. In our case, it seems clear that the reaction is initiated by an interaction between the Cu(I) center and **4**, though we have no evidence of the oxidative addition product. The broadening of the ^{11}B NMR spectra of **4** when it is mixed with complex **38** seems to indicate that there is equilibrium among several species.

To obtain more information about the nature of the interaction between the unsaturated $[(NHC)Cu(I)]^+$ complex and **4**, Dr. 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.[21] showed in the study of the reduction mechanism of CO_2 to CO catalyzed by Cu(I) boryl complexes, using bis(pinacolato)diboron (**3**) as reducing reagent. Instead, Maseras et al. were conclusively in favour of a $[(NHC)Cu(\sigma\text{-catB-Bcat})]^+$ description, in which the unbroken B-B bond coordinates Cu as a B-B σ adduct. Although all attempts to optimise the expected diboryl complex failed, 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.

After these calculations and in collaboration with the groups of Prof. P. J. Perez and Prof. F. Maseras, we decided to do the same mechanistic study in the catalytic hydroboration reaction. Catecholborane (**1**) was added to a solution of

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complex **38** in deuterated THF. Although the solution's colour changed, the resulting product was not isolated or identified. As in the diboration reaction, when styrene was added to the mixture, hydroboration started immediately.

Dr. A. A. C. Braga and Prof. F. Maseras also carried out a theoretical DFT study on the stability of the $[(NHC)Cu(HBcat)]^+$ species containing a borane ligand with a coordinated H-B bond. In good accord with the previous results, they were again in favour of the $[(NHC)Cu(\sigma\text{-H-Bcat})]^+$ structure. The energy for this oxidative addition state was 86.5 $kcal.mol^{-1}$ above that of the σ adduct. This energy was estimated from a constrained geometric optimisation. These data suggest again that the existence of the Cu(III)-hydridoboryl species is very unlikely.

The above experimental and calculated data indicated that the products due to the oxidative addition of the diboron or hydroboron reagent were more unstable in terms of energy than the related σ-borane complex.

With this information, we proposed a mechanism for the diboration reaction (Scheme 3.3). The first step consists of an equilibrium between the cationic catalytic precursor $[(NHC)Cu(NCMe)]BF_4$ and the adduct $[(NHC)Cu(\sigma\text{-catB-Bcat})]^+$. This is not based on the oxidative addition pathway commonly used for Rh- and Pt- catalysts (see above); it assumes a new approach to this type of transformation. Westcott et al.[22] 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 (**1**) was observed, thus supporting our proposal. In addition, Hosomi et al.[23] later reported a similar result during the copper-catalysed boration of α,β-enones, in which no reaction of the borane and the metal center was found. However, some early metal-based catalysts for alkene hydroboration were also described as inducing this transformation without the oxidative addition step.[24]

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The interaction of the σ adduct with the Lewis base BF_4^- leads to the formation of a neutral copper-boryl species [(NHC)Cu(Bcat)] and one equivalent of catB·BF_4. This heterolytic cleavage has a precedent in previous work by Miyaura et al.,[25] in which a copper-boryl species was generated in situ from B_2pin_2 (**3**) and copper acetate. More recently, Sadighi et al.[26] reported the synthesis of a related complex [(IPr)Cu(Bpin)] through direct reaction of [(IPr)Cu(O^{t}Bu)] and **3**.

The [(NHC)Cu(Bcat)] species in Scheme 3.3 then reacts with styrene to give Cu(I)-alkyl intermediates which undergo further interaction with another diboron molecule to afford the desired diborated product through transmetallation and to regenerate the real catalytic species, [(NHC)Cu(Bcat)]. Sadighi et al. described the reactivity of a (NHC)Cu(I)-boryl complex toward styrene, and demonstrated 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.[27]

The above explanation, represented by cycle A in Scheme 3.3, only explains the formation of the diboration product, which is the major product in most of the experiments shown in Table 3.1. However, the formation of the hydroborated products cannot be explained by cycle A.

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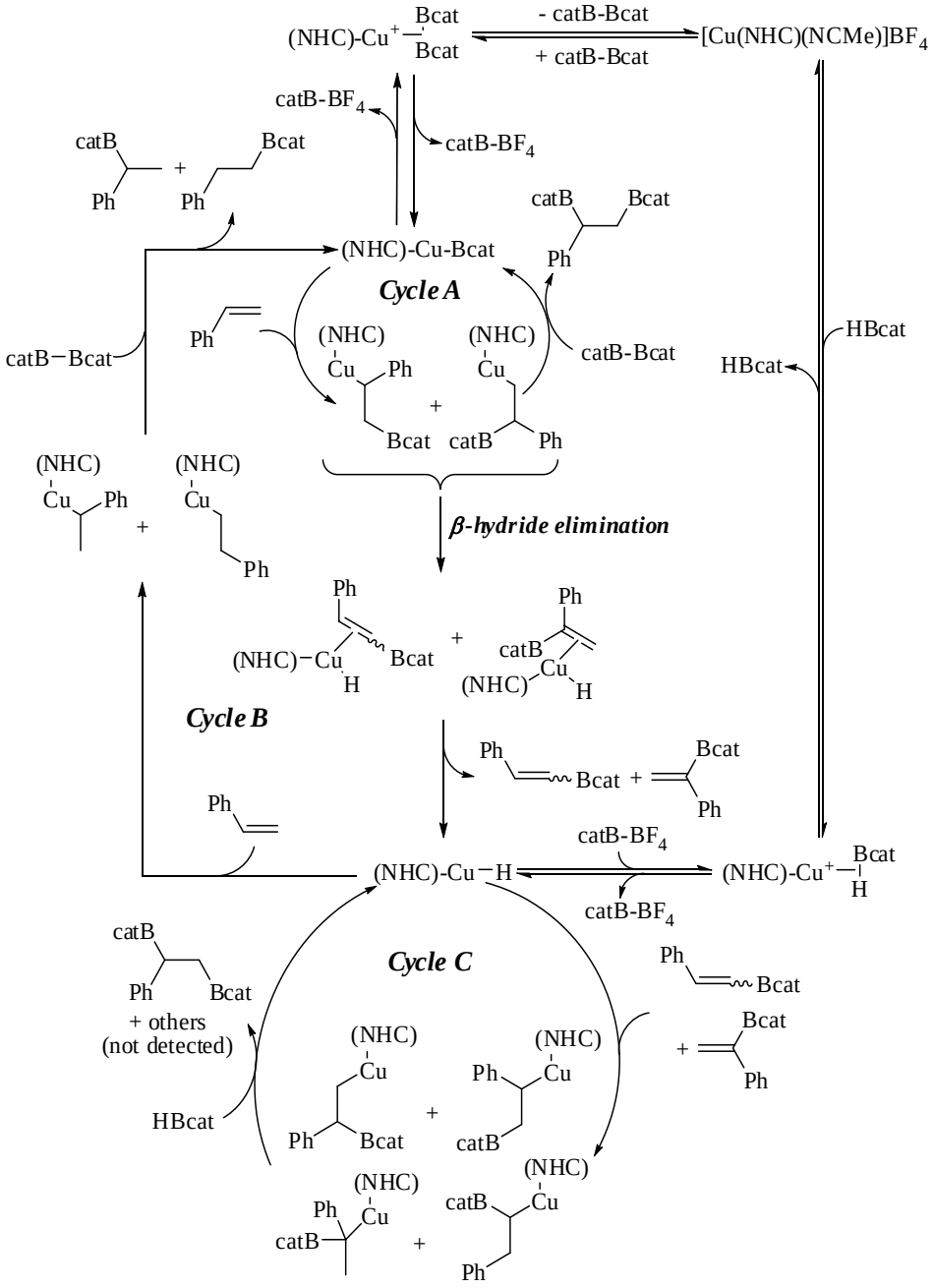

Scheme 3.3. Proposed mechanism for the copper-catalyzed diboration of styrene

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The reversible β-H-elimination reaction observed by Sadighi in [(IPr)Cu{(Bpin)H-CH_2Ph}] can be invoked to account for the appearance of these byproducts.[27] 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 [(NHC)CuH] intermediate with styrene and further transmetallation with a diboron molecule provide the monoborated byproducts before the [(NHC)Cu(Bcat)] catalytic species is regenerated, thus closing Cycle B. It has been proposed that neutral catalytic precursors may undergo halide exchange in the presence of donor substrates.[16c]

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 **38** and **4**. 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 3.4). All the products obtained exclusively contained H atoms, within the NMR

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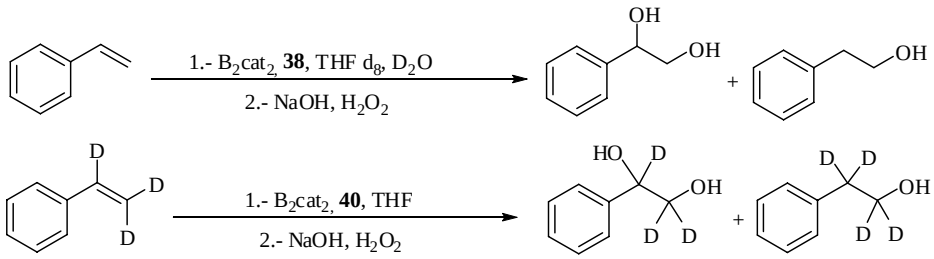
detection scale. A new experiment was designed to determine the hydrogen source, using deuterated styrene as the substrate, and **40** as the catalyst precursor. The only hydroborated product detected by GC/MS after oxidation workup was $(C_6D_5)CD_2CD_2OH$, confirming styrene as the hydrogen source (Scheme 3.4).



Scheme 3.4

The results in Table 3.1 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 **41** mainly involves Cycle A.

As remarked above, the (NHC)Cu complexes also catalyse the hydroboration of styrene. However, if we compare the results presented in Tables 3.1 and 3.2, the regioselectivities of the linear and branched organoborated products, clearly indicate that the formation of the monoborated compounds must take place by two different pathways. In the case of the diboration system, we have proposed that the monoborated products were formed through Cycle B in Scheme 3.3. Nevertheless, for the hydroboration of styrene with HBcat, the mechanism proposed is related to Cycle C and is shown in Scheme 3.5. The first step consists of an equilibrium between the cationic catalytic precursor $[(NHC)Cu(NCMe)]BF_4$ and the adduct [(NHC)Cu(σ-H-

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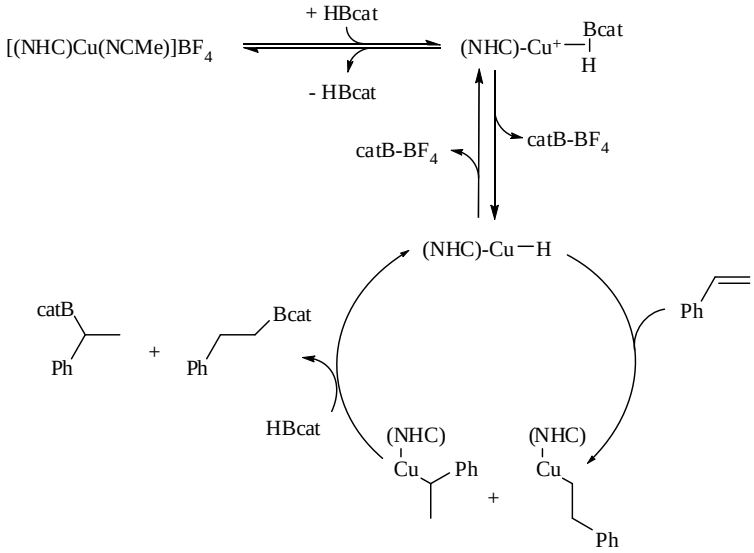
Bcat)]$^+$. The σ adduct would then interact with the Lewis base BF_4 to give catB-BF_4 and the neutral cooper-hydridoboryl catalyst [(NHC)CuH]

The [(NHC)CuH] species in Scheme 3.5 would then react with styrene to give Cu(I)-alkyl intermediates which, after transmetallation with HBcat, would afford the desired monoborated product, so the catalytic species [(NHC)CuH] would be regenerated and the cycle completed.



Scheme 3.5. Proposed mechanism for the copper-catalysed hydroboration of styrene

3.3. Pd/NHC-catalysed alkene diboration

Encouraged by the results obtained using the (NHC)Cu catalytic system, we decided to continue exploring the diboration reaction with (NHC)Pd in an attempt to increase the activity and selectivity of the reaction.

To the best of our knowledge, palladium complexes are ineffective in the catalytic diboration reaction, although they have proved to be efficient in the

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diboration of allenes[28] and the borylative cyclization of 1,6-enynes and enediynes.[29]

In their computational studies Morokuma[30] and Sakaki[31] have postulated that oxidative addition of B-B cannot take place in palladium complexes because it is an endothermic process with an extremely low reverse barrier. In fact, it is well known that oxidative adducts are produced by the reaction of Pt(0) and Rh(I) complexes with diboron reagents,[32] but the corresponding palladium complexes have not been detected.

Bearing all this in mind we first explored a series of standard Pd(0) and Pd(II) complexes in the catalytic diboration of styrene as a model reaction. The palladium (0) complex $Pd(PPh_3)_4$ was as ineffective as $Pd(dba)_2$, which was in accordance with the results reported by Miyaura et al.[33] Alternative palladium (II) complexes such as $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(COD)$, $PdCl_2(PhCN)_2$ and $PdCl_2(PPh_3)_2$ did not lead to the formation of any diboronate esters when bis(catecholato)diboron, (**4**), was added to a solution of the precursor of catalyst and styrene in THF under argon.

In this context and in collaboration with Prof. E. Peris (University of Castellón) and C. Bo (ICIQ) we turned our attention to (NHC)Pd(II) complexes. We expected them to be as successful as the (NHC)Cu(I). The (NHC)Pd(II) complexes **46**-**55** (Figure 3.5) were prepared by Prof. E. Peris's group [34] in an attempt to find a correlation between the nature of the counterion and the efficient catalytic activity. When these complexes were tested in the catalytic diboration reaction, only complexes **52-55** afforded the desired 1,2-bis(boronate)ester at room temperature (Table 3.3, entries 1-4). In addition to the diborated product, we also observed branched (**44**) and linear (**45**) monoborated byproducts in conjunction with the alkenylboronate derivative (**56**).

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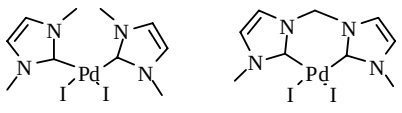
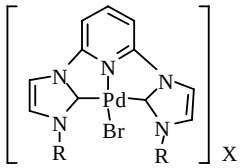
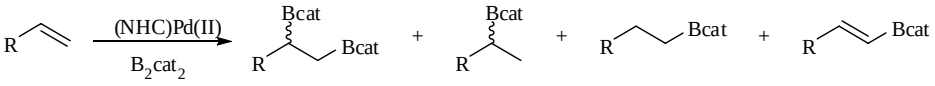


46 **47**



48: R = Me, X= Br; **49**: R= Me, X= PF_6
50: R= n-Bu, X= Br; **51**: R= n-Bu, X= PF_6
52: R= Bn, X= Br
53: R= *p* -NO_2-Bn, X= Br; **54**: R= *p* -NO_2-Bn, X= PF_6; **55**: R= *p* -NO_2-Bn, X= BF_4

Figure 3.5



43 **44** **45** **56**

Table 3.3. Catalytic diboration of styrene with (NHC)Pd(II) and B_2cat_2 (4)[a]

Entry	Catalytic System	B_2cat_2 (Eq.)	Base	Conv. (%)[b]	**43** (%)[b]
1	**52**	1.1	---	84	23
2	**53**	1.1	---	89	25
3	**54**	1.1	---	70	27
4	**55**	1.1	---	83	30
5	**54**	1.1	NaOAc	55	100
6	**54**	3	NaOAc	100	100
7	**54**	3	NEt_3	98	76
8	**54**	3	K_2CO_3	28	100
9	**46**	3	NaOAc	100	92
10	**47**	3	NaOAc	100	100
11	**48**	3	NaOAc	87	47
12	**49**	3	NaOAc	74	44
13	**50**	3	NaOAc	91	46
14	**51**	3	NaOAc	90	61
15	**52**	3	NaOAc	96	79
16	**53**	3	NaOAc	100	45
17	**55**	3	NaOAc	85	100

[a]Standard conditions: Substrate/ base/ Pd complex= 0.5/0.5/0.0255; THF; 4h; Room temperature.
[b]Conversion and selectivity calculated by ^1H NMR.

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Remarkably, the addition of a mild base improves the total chemoselectivity on the diborated product (Table 3.3, entry 5).

Using an excess of diboron (**4**) and adding the mild base (NaOAc) we were able to substantially increase the conversion and maintain total chemoselectivity (Table 3.3, entry 6). Other bases were tested (NaOH, NEt_3, K_2CO_3) with complex **54**, and chemoselectivities were also good, but conversions lower (Table 3.3, entries 7-8).

The catalytic system formed by **47** and **54** was the most active and selective of all the (NHC)Pd(II) complexes explored (Table 3.3, entries 6 and 10).

Taking these results into account, we could not establish whether neutral or cationic system had a specific influence on the activity and selectivity of the diboration reaction of styrene.

To broaden the scope of the catalytic diboration by (NHC)Pd(II), terminal and internal alkenes were also transformed into the corresponding 1,2-bis(boronate)esters. Because of the simplicity of the synthesis and the good results, we decided to explore this performance with precursor **54** which was synthetised by Prof. E. Peris's group. Remarkably, the reaction was completely chemoselective for the diborane product formation in all substrates (Table 3.4). Merely increasing the temperature improved the conversion of the more hindered products (Table 3.4, entries 3, 5, 7 and 10).

Taking into account the theoretical studies postulated by Morokuma[30] and Sakaki[31] and our results in the framework of the diboration of styrene with (NHC)Cu(I) that suggested a (NHC)-Cu(I)-(σ-B_2cat_2) intermediate was more favourable than a NHC-Cu(III)-diboryl intermediate, we wondered whether the observation that an excess of **4** is required for total conversion of alkenes (Table 3.3, entries 5 and 6) could suggest an alternative mechanism involving transmetallation rather than oxidative addition.

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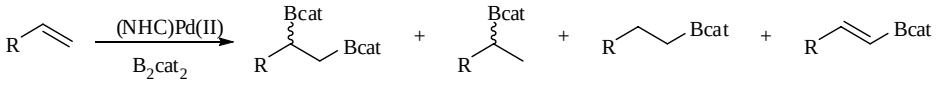

43 **44** **45** **56**

Table 3.4. Catalytic diboration of styrene with 54 and 4[a]

Entry	Substrate	Temp. (ºC)	Conv. (%)[b]	**43** (%)[b]
1	*p*-Fluorostyrene	25	94	100
2	*p*-Methylstyrene	25	77	100
3	*p*-Methylstyrene	80	94	100
4	Trans-β-methylstyrene	25	61	100
5	Trans-β-methylstyrene	80	100	100
6	Indene	25	73	100
7	Indene	80	96	100
8	1-Vinylnaphthalene	25	100	100
9	2-Vinylnaphthalene	25	20	100
10	2-Vinylnaphthalene	80	90	100

[a]Standard conditions: Substrate/ NaOAc/ B_2cat_2/ **54**= 0.5/0.5/1.5/0.0255; THF; 4h.
[b]Conversion and selectivity calculated by ^{1}H NMR.

To gain insight into the nature of the intermediates involved in the mechanism, Prof. C. Bo and co-workers carried out theoretical DFT studies with compound **48** to reduce conformational fluxionality. Firstly, the direct oxidative addition of **4** to cationic complex **48** was explored. The results obtained indicated that the formation of $[(NHC)\text{-}Pd(IV)\text{-}(B_2cat_2)Br]^+$ is an endothermic process with a energy value of 22.0 Kcal.mol^{-1} above the reactants, while the barrier of the reverse process is extremely low. These results are in agreement with the previously reported results.[30,31] It is worth mentioning that the $[(NHC)\text{-}Pd(IV)\text{-}(B_2cat_2)Br]^+$ is a saturated hexacoordinate Pd(IV) complex which requires a vacant site to be created if the reaction is to continue. The next step would be the decoordination of bromide followed by the coordination of the substrate, alkene insertion and reductive elimination.

However, as well as the "classical" reaction pathway mentioned above, the reductive elimination of a B(cat)Br adduct from the $[(NHC)\text{-}Pd(IV)\text{-}(B_2cat_2)Br]^+$ complex to produce the $[(NHC)\text{-}Pd(II)\text{-}(Bcat)]^+$ intermediate was explored. The energy data for this transformation was 3.4 Kcal.mol^{-1} above the

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reactants. The cationic complex intermediate $[(NHC)\text{-}Pd(II)\text{-}(Bcat)]^{+}$ was able to insert the alkene into the Pd-B bond to form the Pd-alkylboronate species.

Another possible active species can be formed in the first step of the pathway by decoordinating the bromide to give a dicationic $[NHC\text{-}Pd(II)]^{2+}$ complex. This intermediate can form a very stable σ-adduct with B_2cat_2 (**4**) forming the $[(NHC)\text{-}Pd(II)\text{-}(\sigma\text{-}B_2cat_2)]^{2+}$ complex. The energy data for this process was 32.9 Kcal.mol^{-1} below the two isolated reagents. The oxidative addition of bis(catecholborane)diboron to the $[NHC\text{-}Pd(II)]^{2+}$ would lead to the formation of the $[(NHC)\text{-}Pd(IV)\text{-}(Bcat)_2]^{2+}$ with a slight endothermic process by 9.6 Kcal.mol^{-1} above that of the σ-adduct, that is in a contradiction of the case of (NHC)Cu(I) where the oxidative addition was discarded because of the energy data was 69.2 Kcal.mol^{-1} above that of the σ-adduct, (Figure 3.6).

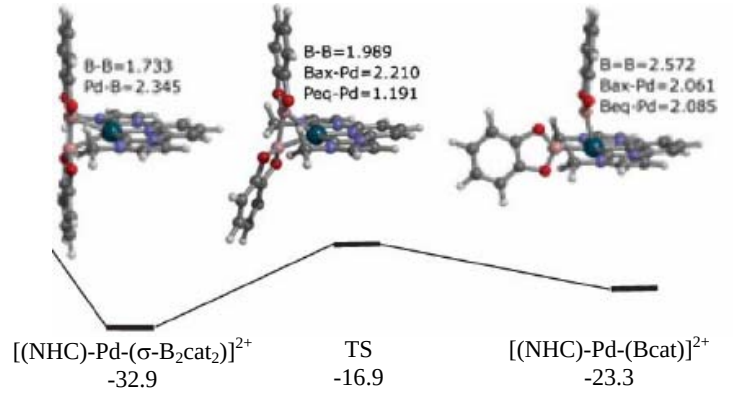

Figure 3.6. Molecular structures for direct oxidative addition processes

When the base is added, the mechanism may switch towards transmetallation, since this would explain not only the increase in selectivity, but also the total conversion obtained when an excess of **4** is added. The base is thought to accelerate the transmetallation rate, as it does in the related cross-

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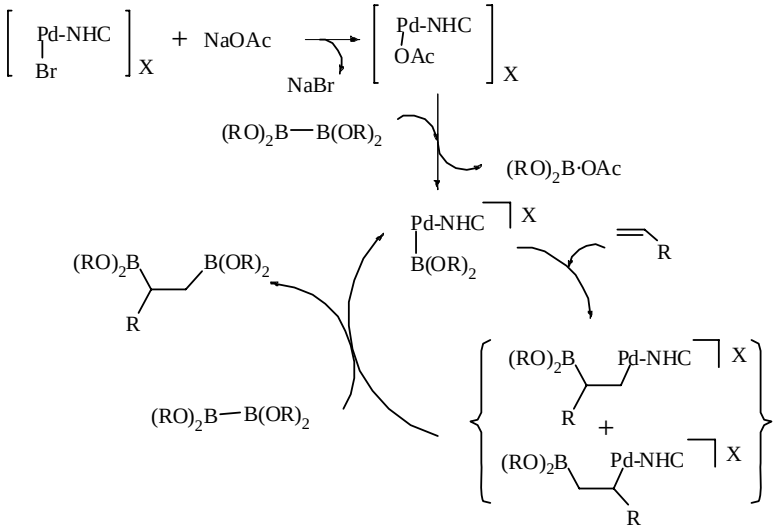
coupling reaction of organoboron compounds.[35] However, we cannot rule out the possibility that the base participates in the halide displacement at the palladium species favouring the transmetallation (Scheme 3.6).[36]



Scheme 3.6. Plausible mechanism for (NHC)Pd(II) catalyzed diboration of alkenes

In an attempt to understand the role of the base, we decided to mix complex **53** with NaOAc and B_2cat_2 (**4**) in THF-d_8 and to monitor with NMR. We observed that this treatment favours the formation of a new signal at 13.6 ppm in ^{11}B NMR from the original 28ppm of **4** and at 6.5 ppm and 6.7 ppm in the ^{1}H NMR. The shift of the ^{11}B and ^{1}H signal to higher fields from the original **4** may be explained by the increase in diboron nucleophilicity caused by interaction with NaOAc. This idea is also supported by the fact that when the catalytic diboration was carried out in the presence of **53** and bis(pinacolato)diboron, (**3**), no diboronate ester was observed. There were no new signals in ^{11}B and ^{1}H NMR of the mixture of **53** with NaOAc and **3**.

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A recent theoretical study on the role of the base in the closely related Suzuki-Miyaura cross coupling[37] suggested that the catalytic cycle starts with a direct reaction between the base and the organoboronic acid that mediates the transmetallation process.

Prof. C. Bo and co-workers also investigated the effect of the base when **4** is coordinated to the palladium dicationic complex. The approach of the OH^- base to the $[(NHC)\text{-}Pd(II)\text{-}(\sigma\text{-}B_2cat_2)]^{2+}$ complex was found to be highly dependent on the initial geometry, and led either to a new intermediate, or to the formation of the species BcatOH and the cationic complex $[(NHC)\text{-}Pd(II)\text{-}(Bcat)]^+$, which meant reconsidering the intermediates of the transmetallation process. In order to evaluate the thermodynamics of this transformation, B_2cat_2 and $[NHC\text{-}Pd(II)\text{-}OH]^+$ were considered as the starting point. The overall process is rather favourable with an energy data of 39.7 $kcal.mol^{-1}$ below the two isolated reagents. Note that this result contrasts with the bromide-mediated transmetallation that was computed to be slightly endothermic (3.4 $kcal.mol^{-1}$). Therefore, the interaction of the base with the diboron reagent together with the strong exothermicity of the transmetallation step in the presence of the base could be the driving force that completes the reaction.

3.4. Ir/NHC-catalysed alkene diboration

Encouraged by the successful results obtained with NHC-Pd(II) complexes and the approach to enantiomerically-enriched alkyl 1,2-bis(boronate)ester described by our group in the asymmetric diboration of alkenes with the NHC-based metal complex,[12,13] we decided to turn our attention to chiral (NHC)Ir(III) complexes because this metal has significantly improved the stability of metal intermediates[32,38] toward catalytic hydroboration[39] and C-H borylation.[1b]

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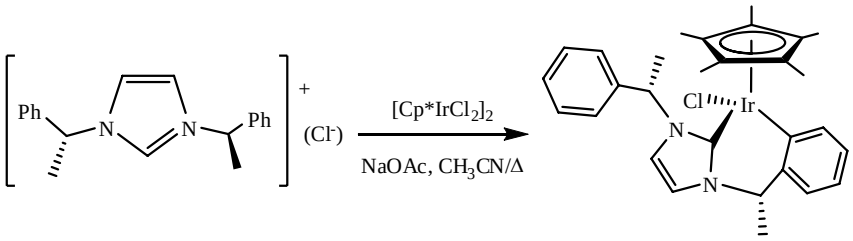
In collaboration with Prof. E. Peris's group and on the basis of their previous experience in the synthesis of transition metal N-heterocyclic carbenes, a series of (NHC)IrCp* (where Cp*= η^5-pentamethylcyclopentadienyl) complexes were prepared. These complexes had previously been used successfully in other processes such as C-H bond activation.[40]

The iridium(III) complex used was obtained in high yield (63%) by members of Prof. E. Peris's group by reacting (*S*,*S*)-1,3-di(methylbenzyl)imidazolium chloride with $[Cp^*IrCl_2]_2$ in acetonitrile in the presence of NaOAc yielding complex **57** (Scheme 3.7).



57

Scheme 3.7

In the first screening, compound (S_{Ir}, S_C, S_C)-**57** was tested in the diboration of styrene, but it did not afford any diboronate ester when bis(catecholato)diboron (**4**) was added (Table 3.5, entry 1). $AgBF_4$ was added to a solution of **57** for the *in situ* generation of cationic species, but the desired product was not achieved either (Table 3.5, entry 2). However, the addition of NaOAc and an excess of diboron reagent afforded an almost quantitative conversion of the styrene. The chemoselectivity on the 1,2-bis(boronate)ester was extraordinarily high, with values up to 99.2% (Table 3.5, entry 3).

It should be pointed out that we performed the same reaction with other neutral and cationic Ir(I) complexes modified with (*S*)-Quinap such as

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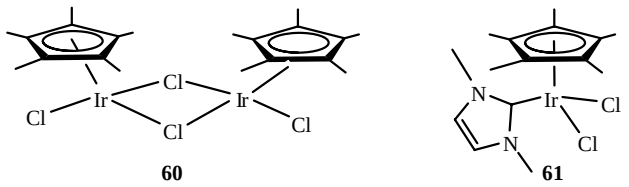
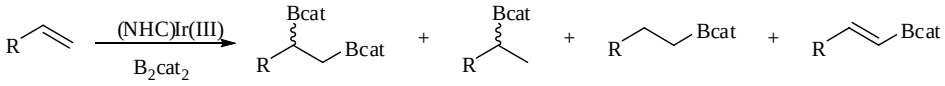
[Ir(COD)]BF_4/(*S*)-Quinap (**58**) and [Ir(μ-Cl)$_2$(COD)]/(*S*)-Quinap (**59**) but they were not active under such conditions (Table 3.5, entries 4 and 5), despite the effectiveness of their Rh analogue complexes.[41]

In collaboration with the group of Prof. E. Peris, we demonstrated the specific effectiveness of the NHC ligands toward the high chemoselectivities on the diboronate product in a comparative diboration reaction catalysed by [Cp*Ir(μ-Cl)Cl_2]$_2$ (**60**)[42] and [(IMe)-Ir(III)-Cp*Cl_2] (**61**)[43] (Figure 3.7) (where IMe = 1,3-dimethyl-imidazolydene). The results are shown in Table 3.5, entries 6 and 7.



60 **61**

Figure 3.7



43 **44** **45** **56**

Table 3.5. Catalytic diboration of styrene with (NHC)Ir(III) and B_2cat_2 (4)[a]

Entry	Catalytic system	Additive	Conv.(%)[b]	**43** (%)[b]	**44** (%)[b]	**45** (%)[b]	**56** (%)[b]
1[c]	**57**	---	60				100
2[c]	**57**/$AgBF_4$	---	---	---	---	---	---
3	**57**	NaOAc	91	99.2	0.8		
4	**58**	NaOAc	40			100	
5	**59**	NaOAc	100			100	
6	**60**	NaOAc	87	97			3
7	**61**	NaOAc	95	100			

[a]Standard conditions: Substrate/ NaOAc/ B_2cat_2/ Catalytic system= 0.5/0.5/1.5/0.0255; THF; 4h. [b]Conversion and selectivity calculated by ^{1}H NMR. [c] Substrate/ B_2cat_2/ Catalytic system= 0.5/0.55/0.0255.

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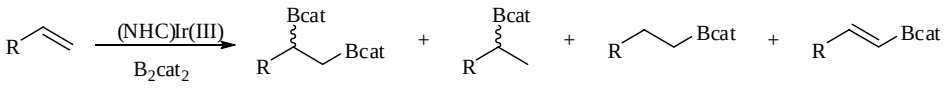
Chemoselectivities were also high for the diboration of *p*-fluorostyrene and *p*-methoxystyrene with complex **57** (Table 3.6, entries 1 and 2), although the conversions dropped significantly for these substituted vinylarenes.

The efficiency of this system was also extended to aliphatic alkenes such as vinylcyclohexane and 3,3-dimethyl-1-butene (Table 3.5, entries 3 and 4). In both cases the conversion was complete and the chemoselectivity was quantitative toward the 1,2-bis(boronate)ester product. Under these reaction conditions, we were unable to obtain any asymmetric induction.



43 **44** **45** **56**

Table 3.6. Catalytic diboration of alkenes with 57 and B_2cat_2 (4)[a]

Entry	Substrate	Conv.(%)[b]	**43** (%)[b]	**44** (%)[b]	**45** (%)[b]	**56** (%)[b]
1	*p*-Fluorostyrene	79	91	9		
2	p-Methoxystyrene	43	93	7		
3	Vinylcyclohexane	100	92	8		
4	3,3-Dimethyl-1-butene	100	100			
5[c]	styrene	100	82 (e.e.= 10%)[d]	11	7	

[a]Standard conditions: Substrate/ NaOAc/ B_2cat_2/ Catalytic system= 0.5/0.5/1.5/0.0255; THF; 4h. [b]Conversion and selectivity calculated by ^{1}H NMR. [c] Catalytic system= **57**/$AgBF_4$. [d] Enantiomeric excess determined on the derived acetal by GC with chiral column.

The neutral complex **57** did not induce enantioselectivity in this transformation. In order to improve the activity and enantioselectivity of the reaction we decided to add $AgBF_4$ to the reaction mixture to promote the removal of the halide from the Ir sphere. We found that the catalytic diboration was efficiently performed with total conversion and high chemoselectivity (Table 3.6, entry 5) in the presence of NaOAc. Remarkably, under these conditions, enantiomeric excess values were around 10%.

Taking into account the experimental and computational analysis previously obtained with NHC-Pd(II) we believe that the role of NaOAc may favor the heterolytic cleavage of B_2cat_2, thus justifying the formation of the Ir-B

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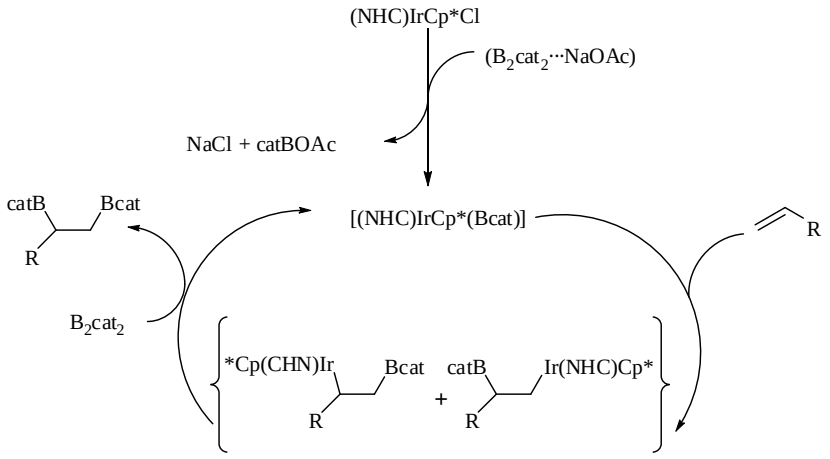
with no need for oxidative addition of the diborane to the Ir(III) complex. This means that the metal remains in the same oxidation state (III) throughout the reaction process. Subsequent alkene coordination and migratory insertion into the Ir-B bond may provide the Ir-alkylborate, which could finally transmetallate with another molecule of B_2cat_2 to generate the desired product 1,2-bis(boronate)ester (Scheme 3.8). Further investigations, however, will be needed.



Scheme 3.8. Proposed mechanism for the iridium-catalysed diboration reaction of alkenes

3.5. Conclusions

We have shown that Cu(I) modified with N-heterocyclic carbene ligands catalyses the diboration and hydroboration of styrene. Quantitative conversions toward 1,2-bis(boronate)ester as a single intermediate were achieved in moderate reaction times and mild conditions depending on the ligand selected. Remarkably, the modification of the [styrene]/[diboron] ratio led to very high yields of either diborated or monoborated product.

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Furthermore, theoretical calculations suggest that the (NHC)Cu(I) complexes do not include the oxidative addition of the diboron or hydroboron reagent, otherwise the formation of σ-borane adduct followed by heterolytic diboron or hydroboron cleavage could be the first mechanistic pathway. In such a way that all the metal species involved in the catalytic cycle could remain as Cu(I) complexes.

We performed the first attempt to catalyse the diboration reaction of alkenes with (NHC)Pd(II) and (NHC)-Ir(III)-Cp*. An excess of diboron reagent in the presence of NaOAc provided complete activity and selectivity toward the desired organodiboronate product at room temperature. Although theoretical studies on (NHC)Pd(II) do not discard oxidative addition, an alternative mechanism has been proposed in which a base-mediated heterolytic cleavage of the diboron would generate the metal-boryl species that would insert the alkene and transmetallate with the diboron reagent.

In the case of (NHC)Ir(III)Cp*Cl, $AgBF_4$ had to be added to produce a slight asymmetric induction (10% e.e.) on the diboration of styrene.

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Chapter 4

Asymmetric catalytic induction in the β-boration of α,β-unsaturated carbonyl compounds

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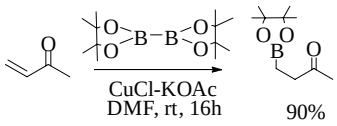
4.1. Introduction

The main goal of early reports on the catalytic borylation of α,β-unsaturated compounds was to use inexpensive metals.[1,2] Copper efficiently promoted the selective β-boron addition from diboron to α,β-ketones, esters, nitriles and terminal alkynes. Miyaura et al.[1] proposed that transmetallation from bis(pinacol)diboron (B_2pin_2) to Cu(I) salts, which generated a B-Cu species, was the key step in the reactions (Scheme 4.1).



Scheme 4.1

The preliminary work revealed a plausible different mechanism involving the Cu- and Pt-catalysed β-boration to α,β-unsaturated compounds. After Marder et al's first report on 1,4-bis(boronate) ester formation from α,β-unsaturated ketones with 5 mol% of $[Pt(C_2H_4)PPh_3)_2]$[3] further reports described changes in the Pt complexes so that their applications could be extended.

A platinum(0) diimine species Pt(BIAN)(DMFU) was postulated by Marder et al.[4] to be the catalyst precursor at 5 mol% loading for α,β-unsaturated ketones. Their observation that 3,4-diborated products were selectively obtained from α,β-unsaturated esters may justify a mechanism that functions through the oxidative addition of the diboron to Pt complexes (Scheme 4.2).

An ^1H NMR spectroscopic study of B-C_α and B-C_β demonstrated that while C-B_α bonds are stable when exposed to air but hydrolyse slowly upon addition of water, B-C_β bonds are stable to both air and moisture. The observed

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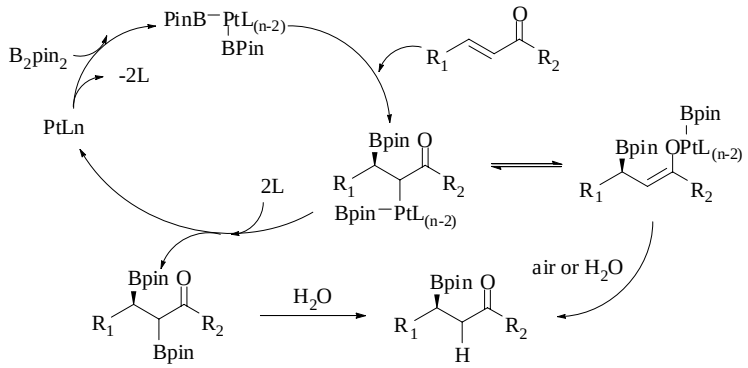
1,4-diborated products, however, hydrolysed rapidly when the reaction mixtures were exposed to air or moisture.



Scheme 4.2

With this protocol in mind, another reaction that can be compared to the platinum-catalysed β-boration to electron-deficient olefins is the rhodium reaction described by Kabalka el al.[5] The 1,4-addition of B_2pin_2 and bis(neopentylglycolato)diboron to α,β-unsaturated ketones, esters, nitriles and aldehydes was achieved in the presence of 5 mol% of [$RhCl(PPh_3)_3$]. The oxidative addition of diboron to rhodium complexes had already been very well established as the early catalytic step in the diboration of alkenes.[6]

In this context, Yun et al. recently postulated an alternative mechanism in which copper-diphosphine catalysts are responsible for the β-boration of α,β-unsaturated carbonyl compounds, and the reaction can be dramatically accelerated by adding alcohol derivates.[7] Their view is that a diphosphine ligated copper boryl complex is the key intermediate and its conjugate addition to α,β-unsaturated carbonyl compounds could take place. The resulting organocopper species reacts with methanol (MeOH) to yield the protonated product and a copper alkoxide which eventually regenerates the active catalyst by transmetallation with the diboron, (Scheme 4.3).

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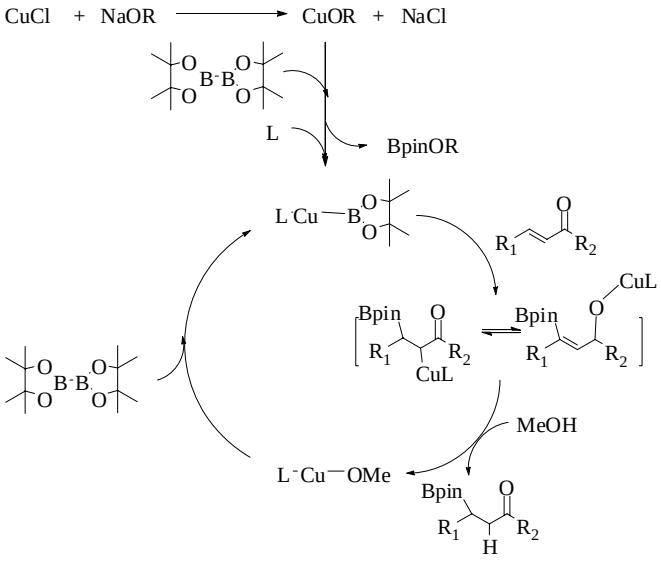
Yun et al.[7] initially postulated that diphosphines could enhance the nucleophilic reactivity of copper boryl species. However, only partial conversion of the substrates was observed before the addition of alcohol increased the overall conversion by effectively protonating the organocopper species.



Scheme 4.3

They also observed this beneficial effect on the conjugated addition of α,β-unsaturated nitriles.[8] This group also explored the copper-catalysed addition of diboron to α,β-acetylenic esters toward the efficient synthesis of β-boryl-α,β-ethylenic esters.[9] In the presence of a diphosphine (Xantphos), the CuCl salt promoted the first example of a catalytic and stereoselective preparation of the corresponding β-boryl-α,β-ethylenic esters, in the presence of MeOH. The addition reaction was shown to be highly stereoselective, affording almost exclusively the product of *syn* addition to the triple bond. One proposed

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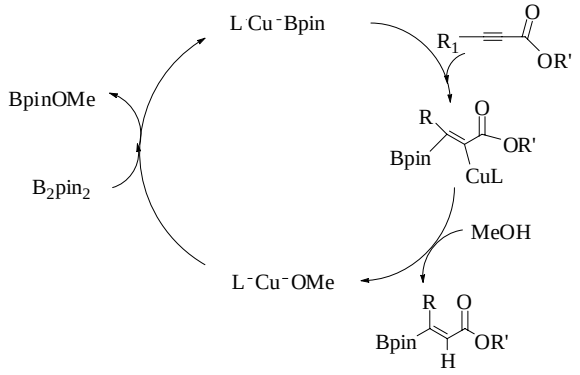
catalytic cycle (Scheme 4.4) involves a phosphine ligated copper boryl complex conjugatively added to the ester and the resulting copper enolate reacted with MeOH to yield the protonated product and a copper alkoxide, which regenerates the active catalyst with B_2pin_2.



Scheme 4.4

Like the Cu-catalytic cycle proposed by Yun et al., the catalytic cycle for the copper catalyzed γ-selective substitution reaction of allylic carbonates with diboron can be found. Ito and Sawamura[10] reported a formal S_N2' attack of the Cu-B species on an allylic carbonate leading to γ-selective formation of an allylboron compound along with a copper carbonate that undergoes decarbonxylation to regenerate the catalytic species (Scheme 4.5).

Transmetallation from B_2pin_2 to Cu(I) salts, which generates a B-Cu species, seems to be a common key step, as Miyaura et al.[1] suggested. As has been demonstrated in Chapter 3, our group made a theoretical DFT study with the B3LYP functional of the nature of the interaction between the cationic copper complex $[Cu(NHC)(NCMe)]^+$ and B_2cat_2 in order to clarify this issue.

The presence of a base seems to favour the heterolytic cleavage of the diboron in the $[Cu(NHC)(\sigma\text{-catB-Bcat})]^+$ species, to generate the catalytically active copper boryl complex (see Chapter 3). To date, Sadighi et al.[11] are the

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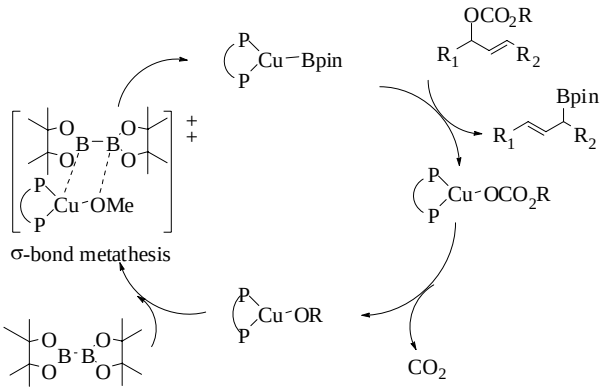
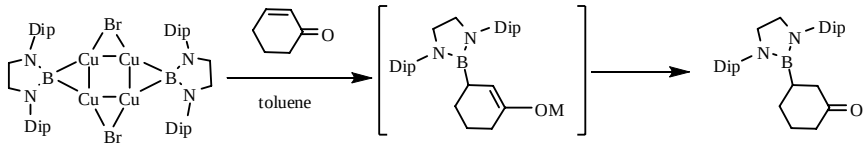
only ones to have isolated a copper boryl complex. The modified ligand was also an N-heterocyclic carbene ligand, and alkenes were inserted efficiently into the Cu-B bond.[12]



Scheme 4.5

To investigate the reactivity of the boryl compounds as boron nucleophiles, a tetranuclear boryl copper complex was reacted with α,β-unsaturated ketones to give the corresponding conjugate addition product[13] (Scheme 4.6). The regioselectivity of the addition was the same as the regioslectivities afforded with organocuprates by the copper-catalysed 1,4-addition of α,β-unsaturated ketones.



Scheme 4.6

A more detailed mechanism for the borylation of α,β-unsaturated carbonyl compounds was described by Lin et al.[14] with the aid of density

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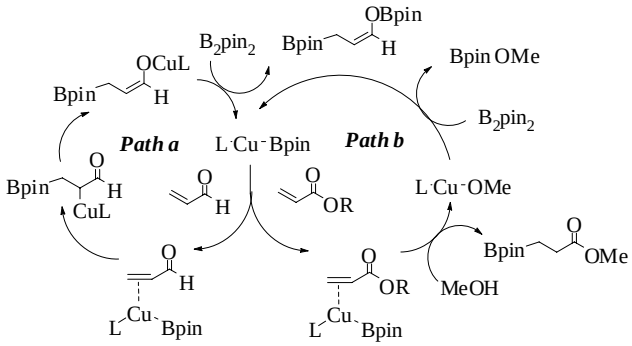
functional theory calculations. They showed that catalysed borylation occurs through C=C insertion into Cu-B to give a β-borylalkyl C-bound Cu(I) enolate intermediate. They compare the insertion reaction of acrolein and methylacrylate into a Cu-B bond, and support the notion that the insertion mainly involves a nucleophilic attack of the Cu-B σ bond at the coordinated unsaturated substrate. In the borylation of acrolein, the C-bound Cu(I) enolate undergoes a keto-to-enol isomerisation to give an O- bound enolate intermediate followed by a σ-bond metathesis with a diboron reagent (Scheme 4.7, path a). However, in the borylation of the methylacrylate, a keto-to-enol isomerisation does not occur due to the inertness of the ester group. Further hydrolysis is required to convert the C-bound Cu (I) enolate intermediate to the borylation product while Cu(I) alkoxide can eventually undergo σ-bound metathesis with a diboron reagent (Scheme 4.7, path b).



Scheme 4.7. Mechanism of the insertion reaction. Path a: acrolein; Path b: methylacrylate

The regioselectivity in this reaction seems to be related to how the M-B bond is added to the α,β-unsaturated carbonyl compounds. In this context, Tanaka et al.[15] proved that the insertion of an α,β-unsaturated ketone into the

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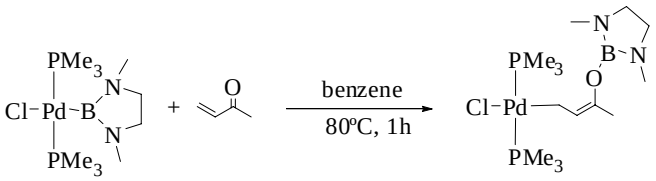
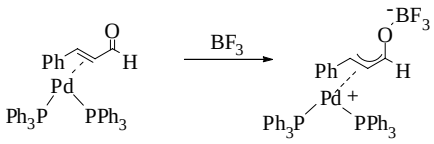
Pd-B bond gave the alternative 1,4-addition where the Pd complex is bonded to the β-carbon and the boryl unit at the oxygen (Scheme 4.8).



Scheme 4.8. Alternative 1,4-addition of α,β-unsaturated ketones

Ogoshi and Kurosawa[16] reported that η^2-coordinated palladium complexes with cinnamaldehyde were converted to η^3-coordinated complexes in the presence of the BF_3 thanks to the Lewis acidity of boron (Scheme 4.9). They also stated that the palladium-catalysed 1,4-addition of disilanes to α,β-unsaturated aldehydes and ketones initiated by Me_3SiOTf would proceed through η^3-coordinated intermediates although the oxidative addition of the Si-Si bond to the palladium complexes would not.[17]



Scheme 4.9

A more recent study by Oshima et al.[18] has opened up interesting new perspectives on the mechanistic insights of the first example of Ni-catalysed borylation of α,β-unsaturated esters and amides. They found that $Ni(COD)_2$, modified with monophosphine ligand enabled the boration of di-, tri- and tetrasubstituted substrates in good yield (Scheme 4.10).

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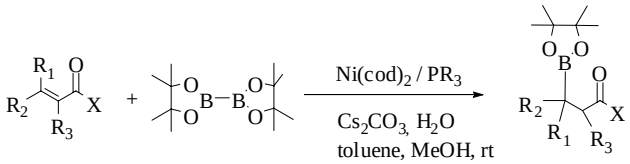
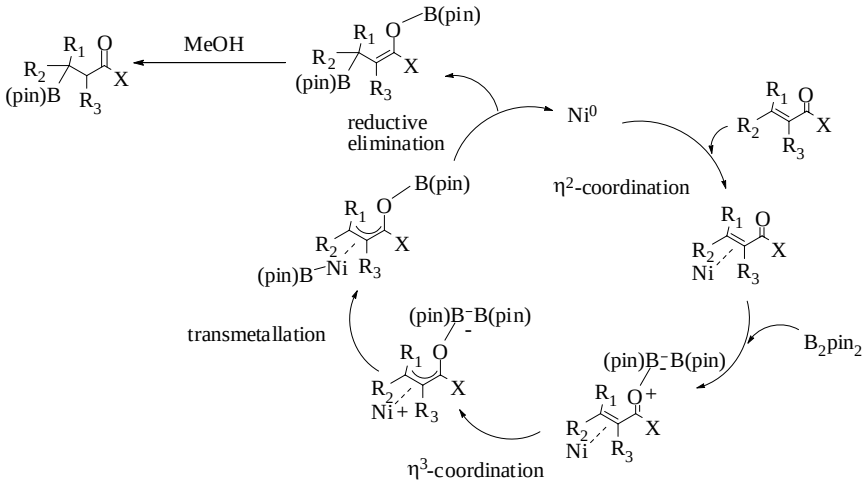


Scheme 4.10. First example of Ni-catalysed borylation

During their studies on the catalytic activity of nickel complexes, they tried to predict the reaction mechanism in which a Ni(0) species reacts with the substrate to generate a η^2-coordinated complex, followed by the carbonyl moiety coordinating to diboron (Scheme 4.11).



Scheme 4.11. Mechanism of the Ni(0)-catalysed borylation

They believe that the Lewis acidity of the boron promotes the formation of the η^3-coordinated nickel complex and then transmetallates the boryl group to furnish the boryl-nickel species. Finally, reductive elimination could provide the 1,4-addition product along with the starting nickel complex to complete the catalytic cycle. Further alcoholysis of boryl enolate with MeOH justified the formation of the β-borated product. The authors also suggest that the presence

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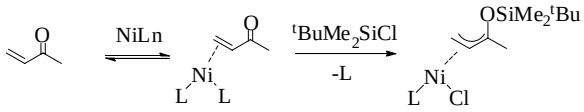
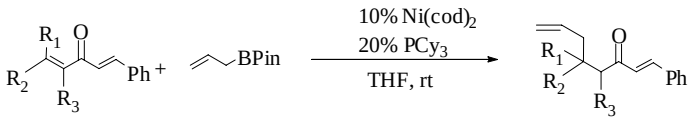
of the base Cs_2CO_3 could enhance the transmetallation step by coordinating to the boron centre, as we postulated in Chapter 3.

Previous work in which chlorotrialkylsilane promoted the transformation of η^2-coordinated nickel complexes with α,β-unsaturated aldehydes and ketones to the corresponding η^3-complexes also suggests that this is the reaction mechanism (Scheme 4.12).[19]



Scheme 4.12

However, in nickel-catalysed 1,4-addition of allylboronic acid pinacol ester to styryl ketones, the η^3-coordinate nickel complexes were also proposed as the key intermediate (Scheme 4.13).[20]



Scheme 4.13

The direction of the insertion found in their work on Pd and Ni seems to be opposite to that reported by Lin et al.[14] (who used Cu complexes) and the Ni and Pd fragments take on the role of the nucleophile. However, this may be because the metal centres, Cu and Pd or Ni, behave differently, the ligands modify the metals, the α,β-unsaturated substrates are of different kinds (ketones, aldehydes and esters), and the scales are not the same. Tanaka et al.[15] studied Pd on a stoichiometric scale, which favours the characterization of the

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most thermodynamic product of insertion, but studied Cu from a catalytic kinetic perspective.

Marder et al. also focused on the fact that nucleophilicity is the determining factor in the catalytic pathway with Cu, rather than the oxophilicity of boron units.[21] For the Cu-catalysed reduction of CO_2 to CO they found that the Cu-C(=O)-O-Bpin species is thermodynamically more stable than isomeric Cu-O-C(=O)-Bpin, the former being kinetically inaccessible.

To sum up, in the catalytic borylation of α,β-unsaturated compounds, Pt, Rh, Cu, Pd and Ni play significantly different roles, and the nucleophilicity or oxophilicity of the M-B fragments are an interesting avenue of study for the future.

4.2. Catalytic system based on Cu / NHC*

Since the introduction of a boronate group at the β-position in a carbonyl compound creates a stereogenic C-B bond, the enantioselective boration of α,β-unsaturated compounds easily provide enantioenriched organoboron compounds that can be further functionalised through retention of the configuration.[22] However, little research has been done on this topic. The first study was made by Yun et al.[7,23] on the β-boration of α,β-unsaturated esters and nitiriles by a nonracemic copper phosphine complex. Excellent yields and high enantiomeric excesses (determined on the hydroxyl compounds) were obtained using the chiral ligands (R)-(S)-Josiphos and (R)-(S)-NMe_2-PPh_2-Mandyphos (Scheme 4.14).

Both β-alkyl and β-aryl substituted unsaturated esters provided products with almost the same levels of enantioselectivity. However, *metha* and *ortho* substitution at the aryl ring slightly lowered the enantioselectivity of the

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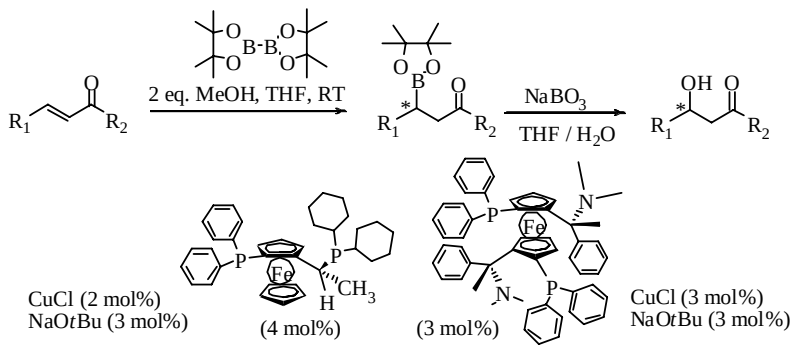
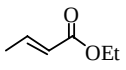
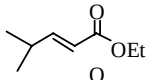
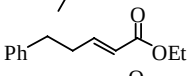
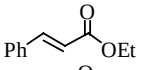
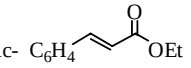
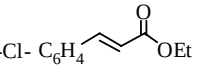
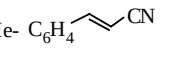
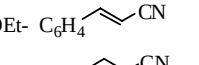
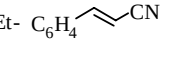
reaction. Nitrile substrates were generally more efficient than ester substrates with regard to both reactivity and enantioselectivity and they afforded the addition products with high enantioselectivities regardless of the substitution pattern at the aromatic ring. Yun et al. also observed that the nature of the ester moiety did not affect the reaction outcome: methyl and *tert*-butyl ester provided the same enantioselectivity.



Susbtrate	Yield (%)	e.e . (%)	Yield (%)	e.e . (%)
	94	90		
	92	91		
	97	89		
	94	90	94	87
3-OAc- 	95	87	89	84
4-Cl- 	90	91		
4-Me- 	94	90		
2-OEt- 	90	92		
3-OEt- 			94	91

Scheme 4.14. Enantioselective β-boration/oxidation described by Yun et al.[23]

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Recently, Oestreich[24] reported the catalytic asymmetric addition of $Me_2PhSiBpin$ across α,β-unsaturated acceptors to provide analogous chiral β-silyl carbonyl compounds.

In an attempt to contribute to the development of asymmetric induction in the β-boration of α,β-unsaturated carbonyl compounds, we turned our attention to the chiral copper catalytic system, matching the advantages that chiral NHC ligands provide on the catalyst (donor properties, ease of synthesis and robustness).[25]

The efficiency of using Cu/NHC complexes as catalyst precursors were previously reported in the catalytic diboration of alkenes and alkynes in Chapter 3, and the catalytic carboxylation of organoboronic esters.[26]

In collaboration with the group of Prof. P. J. Pérez (Huelva University), we investigated the potential of several complexes containing the (NHC)*Cu^+ core as the catalyst precursor for this reaction (Figure 4.1). The chiral NHC ligands display chirality either at the substituents on the nitrogen atom (L1 and L2) or in the backbone (L3-L5) of the NHC ring. The copper complexes used as catalyst were those of general formula (NHC)CuCl or [(NHC)Cu(NCMe)]BF_4, and were prepared in a similar way to complex **37-42** described in the literature.[27]

In the same experimental conditions as Yun et al.,[7,23] these catalyst precursors were used for the β-boration of the model substrate ethyl-*trans*-crotonate with B_2pin_2 in our preliminary studies. A 2% catalyst loading referred to substrate was used in all cases, in the presence of 3mol% of NaO*t*Bu and 2 equivalents of MeOH, relative to alkene. In order to determine the degree of enantioselection, the initially formed organoboron compounds were derivatized into the acylated products, through consecutive oxidation and acylation steps (Table 4.1).

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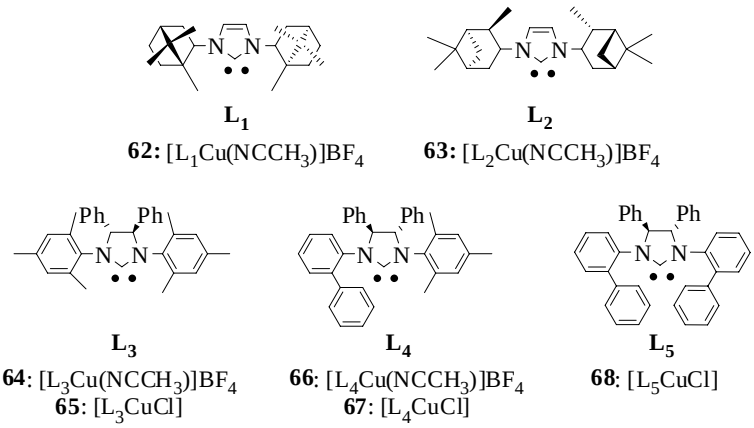

Figure 4.1. Chiral NHC ligands and complexes

The use of the chiral complexes **62** and **63** led to quantitative conversion, although enantiocontrol on the stereogenic β-carbon was low (Table 4.1, entries 1 and 2). However, the chiral complexes **64**-**68** provided moderate e.e. values (e.g., 58% e.e. with complex **66**). It seems that the nature of the anion does not affect either the conversion or the enantioselectivity (Table 4.1, entries 3-6). This could be the result of a common catalytic species of composition (NHC)*Cu^+ that can be reached from both starting materials. It seems obvious from these results that chirality in the backbone of the chiral NHC ligand plays an important role in inducing asymmetry in the β-boration reaction. Therefore, the simultaneous contribution of IMes and biphenyl in **L_4** gave optimal benefits for asymmetric induction. Moreover, the results obtained with **67** and **68** catalysts indicate that C_1 symmetry provides better results than the corresponding C_2 symmetry, which is interesting for any further catalyst development.

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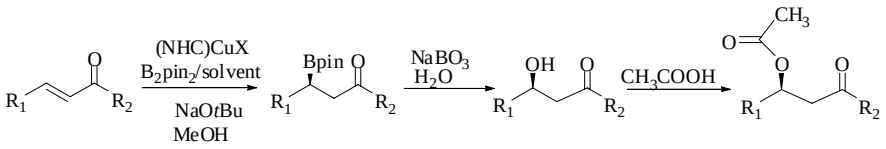
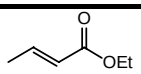
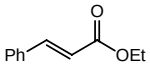
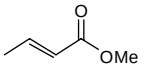
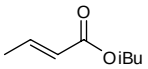


Table 4.1. Chiral (NHC)*Cu complex catalysed β-boration/oxidation/acylation of α,β-unsaturated esters[a]

Entry	Substrate	Catalyst	Base	Solvent	Conv. (%)[b]	e.e. (%)[c]
1		**62**	NaO*t*Bu	THF	93	10(R)
2	"	**63**	NaO*t*Bu	THF	99	16(S)
3	"	**64**	NaO*t*Bu	THF	99	25(S)
4	"	**65**	NaO*t*Bu	THF	96	31(S)
5	"	**66**	NaO*t*Bu	THF	99	58(R)
6	"	**67**	NaO*t*Bu	THF	99	55(R)
7	"	**68**	NaO*t*Bu	THF	99	52(R)
8	"	**67**	NaO*t*Bu	Toluene	99	59(R)
9	"	**67**	NaO*t*Bu	CH_3CN	88	52(R)
10	"	**67**	NaO*t*Bu	CH_2Cl_2	99	57(R)
11	"	**67**	NaOMe	THF	99	51(R)
12	"	**67**	NaOAc	THF	73	50(R)
13	"	**67**	NaH	THF	99	53(R)
14	"	**67**	---	THF	<10	63(R)
15	"	**66**	---	THF	25	62(R)
16		**64**	NaO*t*Bu	THF	92	23(S)[d]
17	"	**66**	NaO*t*Bu	THF	99	53(R)[d]
18	"	**67**	NaO*t*Bu	THF	99	61(R)[d]
19		**64**	NaO*t*Bu	THF	96	31(R)[d]
20	"	**66**	NaO*t*Bu	THF	96	48(R)[d]
21		**64**	NaO*t*Bu	THF	99	15(R)
22	"	**66**	NaO*t*Bu	THF	99	73(R)

[a] Standard conditions: Substrate / Cu complex = 0.5/0.01, 3mol% base; 1.1 eq of bis(pinacolato)diboron (B_2pin_2); 2 eq MeOH; Solvent: 2ml; T:25ºC; 6h. [b] Determined by ^1H NMR spectroscopy. [c] Determined on the acylated product by G.C.-MS equipped with chiral column β-cyclodex. [d] Determined on the β-alcohols by HPLC-MS equipped with chiral column Chiralcel OD-H.

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This improvement in the enantiocontrol of chiral (NHC)Cu^+ complexes prompted us to analyse the influence of the solvent and base on the β-boration of ethyl-*trans*-crotonate. As can be inferred from the data in Table 4.1, (entries 8-10), the use of THF or toluene has no effect on the reaction outcome.

Similarly, when the base is replaced from NaO*t*Bu to NaOMe, NaOAc or NaOH, small differences can be detected in the catalytic activity of complex **67** (Table 4.1, entries 11-13). However, the absence of the base in the β-boration of ethyl-*trans*-crotonate with the catalytic precursors **67** and **66** significantly decreases the conversion rate but slightly improves the enantioselectivity (Table 4.1, entries 14-15). Yun et al.[7] have postulated that the base is required to favour the formation of the LCu-boryl catalytic species from the catalyst precursor and the diboron reagent. As is demonstrated in chapter 3, we showed that dihapto-diborane complexes can be involved in a pre-equilibrium step before the catalytic species (NHC)Cu-Bpin is formed.

On the basis of the results obtained with the ethyl-*trans*-crotonate model, and with the aim of exploring the scope of this catalytic system, we carried out a series of experiments with a range of substrates under the optimised condition. The reactions of ethyl-*trans*-cinnamate with complexes **64** and **66** provided quantitative conversion into the desired product (Table 4.1, entries 16 and 17), but again the enantioselectivity was better when ligand $\mathbf{L_4}$ was involved in the catalytic system. In the presence of the neutral catalyst precursor **67** it increased to 61% e.e. (Table 4.1, entry 18). The catalytic performance of complexes **64** and **66** was similar in the β-boration of methyl-*trans*-crotonate ester (Table 4.1, entries 19-20). It is worth mentioning that the enantioselectivity induced by the metal center was different for the bulkiest *iso*-butyl-*trans*-crotonate ester. Thus, complex **64** afforded a 15% e.e. whereas complex **66** afforded 73%. These results contrast with the tendency observed by Yun et al.[7,23] that

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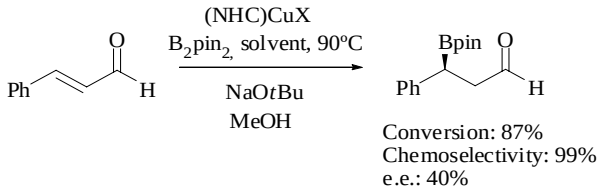
enantioselectivity was independent of the nature of the ester moiety when CuCl/(R)-(S)-Josiphos was used as the catalytic system.

The metal-catalysed β-boration of the most challenging α,β-unsaturated aldehydes has only been reported twice with the Pt[28] and Rh[5] catalyst because it suffers from a competitive 1,2-diboron addition reaction. Considering the benefits of copper-mediated B-addition reactions, we decided to carry out the (NHC)*Cu^{+}-catalysed β-boration of cinnamaldehyde as a model substrate. In this case the use of complex **65** afforded quantitative conversion and total chemoselectivity on the desired product with 40% e.e. (Scheme 4.15). For complexes **67** and **68** this value was no more than 10% e.e. Despite these moderate values, this is the first attempt to obtain enantioselectivity in the β-boration of α,β-unsaturated aldehydes.



Scheme 4.15

We also studied another variable that may affect the degree of enantioselection: the existence of α-substituents in the starting alkene (Figure 4.2).

Methyl tiglate **69** | Ethyl tiglate **70** | Isopropyl tiglate **71** | Isobuyl angelate **72**

Figure 4.2. α-methyl substituted esters

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We carried out the β-boration reaction with a series of α-methyl substituted esters, such as methyl tiglate (R_1= Me, $R_{1'}$= H, R_2= OMe, **69**), ethyl tiglate (R_1= Me, $R_{1'}$= H, R_2= OEt, **70**), isopropyl tiglate (R_1= Me, $R_{1'}$= H, R_2= OiPr, **71**) and isobutyl angelate (R_1= H, $R_{1'}$= Me, R_2= OiBu, **72**) (Table 4.2).

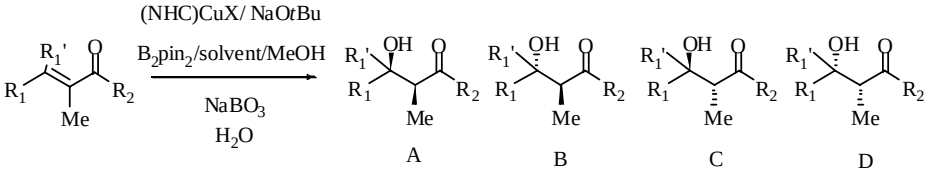

Table 4.2. Chiral (NHC)*Cu complex catalysed β-boration of α-methyl α,β-unsaturated esters[a]

Entry	Substrate	Catalyst	Conv. (%)[b]	syn / anti [b]	Syn e.e (%)[c]	Anti e.e (%)[c]
1	**69**	**67**	99	60/40	54[d]	5[d]
2	**69**	**68**	97	52/48	68[d]	25[d]
3	**70**	**67**	94	64/36	57	11
4	**70**	**68**	99	60/40	35	8
5	**71**	**67**	65	55/45	70	20
6	**71**	**68**	82	53/47	56	37
7	**72**	**67**	93	70/30	74	5
8	**72**	**68**	99	65/35	39	42

[a] Standard conditions: Substrate / Cu complex = 0.5/0.01; 3mol% of NaO*t*Bu; 1.1 eq of bis(pinacolato)diboron (B_2pin_2); 2 eq MeOH; Solvent: 2ml; T:25ºC; 6h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined on the acylated product by G.C.-MS equipped with chiral column β–cyclodex. [d] Determined on the β-alcohols by HPLC-MS equipped with chiral column Chiralcel OD-H.

These experiments were carried out with the complexes **67** and **68** as catalytic precursors. As shown in Table 4.2, we observed very high quantitative conversion into the β-boryl product in most cases (Table 4.2, entries 1-8) indicating that α-substitution does not diminish the borylation pathway.

The syn/anti product ratio slightly favoured the syn diastereoisomers, and e.e. values were markedly higher for the enantiomeric mixture of the syn than for the anti products: the bulkiest isobutyl angelate substrate can be borated at the β-position with the highest e.e. value (74%) on the syn diastereoisomers (Table 4.2, entry 7).

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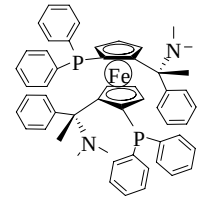
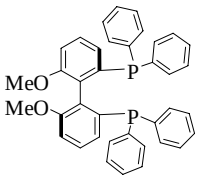
4.3. Catalytic system based on Ni / P-P*

Taking advantage of the benefits of nickel on the cross coupling reaction,[18,29] we also decided to establish a general methodology for the nickel-catalysed β-boration of α,β-unsaturated esters in an attempt to induce asymmetry on the organoboron product.

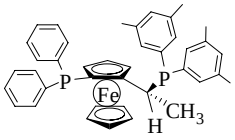
To this end, we first investigated the potential of $Ni(COD)_2$ modified with chiral bidentate ligands (Figure 4.3) in the β-boration of the model substrate ethyl-*trans*-crotonate with B_2pin_2 (**3**) as the boron source. Table 4.3 shows that when ligand (*R*)-(*S*)-Mandyphos (**73**), (*R*)-Ph-MeOBiphep (**74**) and (*R*)-(*S*)-Josiphos (**75**) modified the Ni(0) complex, the enantioselectivity was only moderate in the quantitative formation of the β-borylated ester (Table 4.3, entries 1-3), while in the presence of the chiral ligand (*R*)-(*R*)-Walphos (**76**) it was low (Table 4.3,entry 4). Enantioselectivity was also low with the P,N-ligand (*R*)-Quinap (**77**) despite successful asymmetric induction in the Rh-catalysed diboration of alkenes[22b,30] (Table 4.3, entry 5).



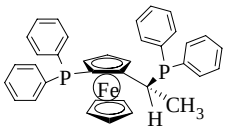
73: (*R*)-(*S*)-Mandyphos



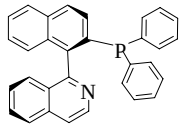
74: (*R*)-Ph-MeOBiphep



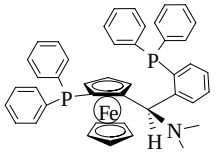
75: (*R*)-(*S*)-Josiphos



76: (*R*)-(*R*)-Walphos



77: (*R*)-Quinap



78: (*R*)-(*S*)-Taniaphos

Figure 4.3. Chiral diphosphines

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However, the use of ligand (*R*)-(*S*)-Taniaphos (**78**) provided very high enantioselection on the β-borylated ester with values up to 96% e.e., which was an improvement on those values observed by Yun et al. for the same substrate with the catalytic system CuCl/**75** (e.e. 90%).

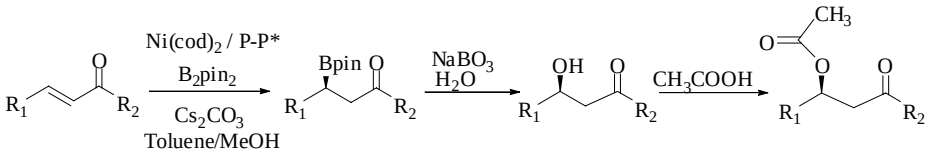
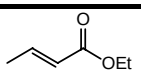
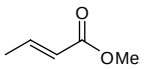
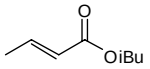
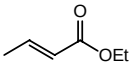
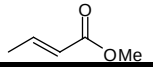


Table 4.3. Ni-catalyzed asymmetric 1,4-addition reaction of 3[a]

Entry	Substrate	Diphosphine	Conv. (%)[b]	e.e. (%)[c]
1		**73**	93	51
2	"	**74**	99	63
3	"	**75**	99	65
4	"	**76**	96	10
5	"	**77**	99	12
6	"	**78**	99	95
7	"	**78**[e]	99	90
8	"	**78**[f]	99	85
9		**78**	96	92[d]
10		**78**	99	98
11	"	**75**	99	90
12[g]	"	**75**	73	96
13[g]		**75**	92	81
14[g]		**75**	96	79[d]

[a] Standard conditions: Substrate / $Ni(COD)_2$ = 0.5/0.025; Diphosphine (0,025mmol); 1.5 eq Cs_2CO_3; 1.5 eq of bis(pinacolato)diboron (B_2pin_2); 1.5 eq H_2O; Solvent: Toluene(5ml)/MeOH(0.25ml); T:25ºC; 4h. [b] Determined by ^1H NMR spectroscopy. [c] Determined on the acylated product by G.C.-MS equipped with chiral column β-cyclodex. [d] Determined on the β-alcohols by HPLC-MS equipped with chiral column Chiralcel OD-H. [e] 1eq Cs_2CO_3. [f] 0.5eq Cs_2CO_3. [g] $NiCl_2$

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The presence of the base seemed to have a crucial influence on the catalytic activity of the catalyst, because when a lower amount of Cs_2CO_3 was used, the activity and enantioselectivity observed for the Ni(0)/Taniaphos catalytic system diminished (Table 4.3, entries 7-8). The nature of the base is also influential because when NaOH, NaOAc or NaO*t*Bu were used instead of Cs_2CO_3, only a small conversion into the corresponding product was observed. The effect of the base as an activator of diboron has been observed by Oshima et al.[31] and our group in the Pd- and Au- catalysed diboration reaction.[32]

In an attempt to explore the scope of the Ni(0)/Taniaphos catalytic system, we carried out a series of experiments with a range of α,β-unsaturated esters under the optimised reaction conditions.

Changing the ester moiety from OMe to O*i*Bu, we found that the bulkiest *iso*-butyl-*trans*-crotonate ester was the most effective substrate, as far as the enantioselection induced by the metal center was concerned. Values were up to 98% e.e. (Table 4.3, entries 9-10). These results contrast with the tendency observed by Yun et al,[7,23] for enantioselectivity to be independent of the nature of the ester moiety when CuCl /**75** was used as the catalytic system. The β-boration of *iso*-butyl-*trans*-crotonate with Ni(0)/**75** also provides a significant increase in enantioselectivity with e.e. values up to 90% (Table 4.3, entry 11). Interestingly, when the nickel source of the catalyst precursor was Ni(II) in $NiCl_2$/**75**, the activity and enantioselectivity were slightly better than $Ni(COD)_2$/**75** (Table 4.3, entries 12-14).

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4.4. Catalytic system based on Pd / P-P*

Encouraged by the results obtained using the $Ni(COD)_2$/P-P* catalytic systems and taking account the benefits that palladium complexes provide for the cross coupling reaction, we decided to check whether Pd(0) modified with the diphosphine ligand could perform the β-boration reaction under identical reaction conditions to Ni(0).

We were very pleased to observe that the catalyst precursor $Pd_2(dba)_3$ performed this reaction and became the first example of palladium-mediated β-boration of α,β-unsaturated carbonyl compounds. Table 4.4 shows how the β-boration of *iso*-butyl-*trans*-crotonate with $Pd_2(dba)_3$ modified with **73**, **77** remained unfinished after 4 hours of reaction. Enantioselection was low (Table 4.4, entries 1-2). However, when the chiral ligands involved in the modification of $Pd_2(dba)_3$ were **74** and **76**, the conversion of the reaction was higher and e.e. values rose to 56% and 75%, respectively (Table 4.4, entries 3-4). A more satisfactory enantioselection was provided by $Pd_2(dba)_3$/**78** (Table 4.4, entry 5) and $Pd_2(dba)_3$/**75** (Table 4.4, entry 6), which afforded enantioselectivity with e.e. values up to 91%, depending on the ester moiety of the substrate (Table 4.4, entries 6-8).

Surprisingly, when Pd(II) was tested as the catalyst precursor in $Pd(OAc)_2$/**75**, only the conversion was comparable to that obtained with Pd(0), while the enantioselectivity diminished significantly (Table 4.4, entries 9-11).

One of the key steps in this proposal is the transformation of the η^2-coordinated metal complex to the corresponding η^3-complex on reaction with B_2pin_2. However, as Kurosawa[16] and Morken[20] have previously observed, the Lewis acidity of boron could promote this pathway in palladium-mediated reactions.

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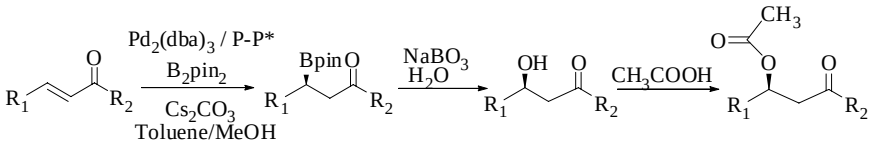
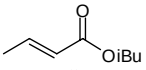
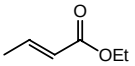
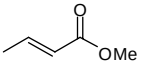
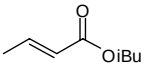
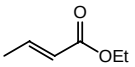
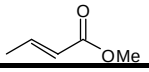


Table 4.4. Pd-catalyzed asymmetric 1,4-addition reaction of 3[a]

Entry	Substrate	Diphosphine	Conv. (%)[b]	e.e. (%)[c]
1		**73**	29	24
2	"	**77**	41	8
3	"	**74**	93	56
4	"	**76**	82	75
5	"	**78**	31	90
6	"	**75**	60	86
7		**75**	99	91
8		**75**	99	87[d]
9[e]		**75**	77	13
10[e]		**75**	99	3
11[e]		**75**	90	5[d]

[a] Standard conditions: Substrate / $Pd_2(dba)_3$ = 0.5/0.0125; Diphosphine (0,025mmol); 1.5 eq Cs_2CO_3; 1.5 eq of bis(pinacolato)diboron (B_2pin_2); 1.5 eq H_2O; Solvent: Toluene(5ml)/MeOH(0.25ml); T:25ºC; 4h. [b] Determined by ^1H NMR spectroscopy. [c] Determined on the acylated product by G.C.-MS equipped with chiral column β-cyclodex. [d] Determined on the β-alcohols by HPLC-MS equipped with chiral column Chiralcel OD-H. [e]Substrate/$Pd(OAc)_2$= 0.5/0.025

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4.5. Conclusions

We have found that complexes containing the (NHC)Cu core catalyse the selective β-boration of α,β-unsaturated esters and aldehydes under mild conditions. It has been shown that when chiral NHC ligands with chirality at both the substituents and the nitrogen atom (**L1** and **L2**) are used asymmetric induction was very low, even though these ligands led to quantitative conversion. The use of chiral NHC ligands with chirality in the backbone in the NHC ring (**L3**-**L5)** induced a certain degree of enantioselection in the final products, in a reaction for which only one precedent with asymmetric induction is known.

The α-substitution in the α,β-unsaturated esters did not diminish the borylation pathway.

The nature of the different NHC ligands and substrates used previously serve as the basis for developing more enantioselective catalysts for this transformation.

In the first study reported, moderate enantioselectivity was observed in the β-boration of α,β-unsaturated aldehydes (e.e. 40%).

By inducing asymmetry in the presence of chiral ligands, we have promoted not only the first Ni-mediated asymmetric boron addition reaction, but also the first described palladium β-boration of α,β-unsaturated esters. It opens up new perspectives in the tandem β-boration/cross coupling reaction with Ni and Pd complexes.

From a mechanistic point of view, we suggest that the catalytic cycle for Pd(0) could be similar to the cycle for Ni(0) proposed in the literature in which metal species react with substrate α,β-unsaturated esters and amides to generate the η^2-coordinated complex, followed by further reactivity with

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bis(pinacolato)diboron to favour the formation of η^3-coordinated boryl-nickel(II) complexes. An eventual reductive elimination provides the boryl enolate product, which is susceptible to protonolysis and affords the β-boryl ester product.

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Chapter 5

Catalytic tandem B-addition/cross coupling reactions

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Chapter 5

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5.1. Introduction

Some of the significant advantages of using organoboranes as intermediates for synthetic organic purposes[1] are their stability, relatively low toxicity and easy accessibility. In particular, the catalytic H-B and B-B addition across unsaturated carbon-carbon bonds can be a platform for introducing functionally with special emphasis on the selective control of the C-B formation and the retention of configuration in the functionalisation process from organoborane intermediates toward the targeted products.[2] Specifically, organoboronic acids and esters are very useful organometallic compounds to transmetalate with transition-metal complexes.[2,3]

The palladium-catalysed cross-coupling reaction has been widely used starting from the transmetallation pathway between organoborane derivates and the palladium-based catalytic system.

Suzuki and Miyaura[4] developed a double functionalization of a bis-boronate derivative in a tandem catalytic diboration C-C cross-coupling reaction. To this end, terminal and internal alkynes were first subjected to catalytic diboration with bis(pinacolato)diboron, B_2pin_2, in the presence of the catalytic system $Pt(PPh_3)_4$, providing the *cis*-bis(boryl)alkene product in excellent yield.[5] The potential use of these intermediates 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 5.1). The reaction provided the (Z)-1,2-diphenyl-1-alkene as the sole product whose stereochemistry was consistent with the *cis*-bis(boryl)alkene intermediate.

More recently, Miyaura et al.[6] have reported that the *cis*-bis(boryl)alkene derivative obtained from the catalytic diboration of terminal alkynes regioselectively cross-couples with aryl, 1-alkenyl, benzyl, and allyl halides in

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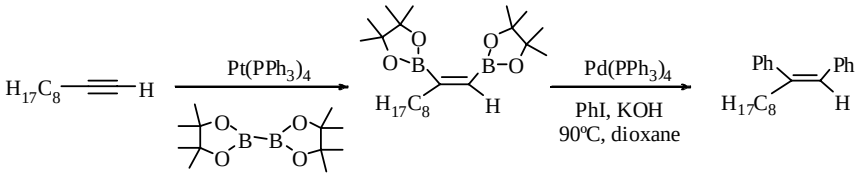
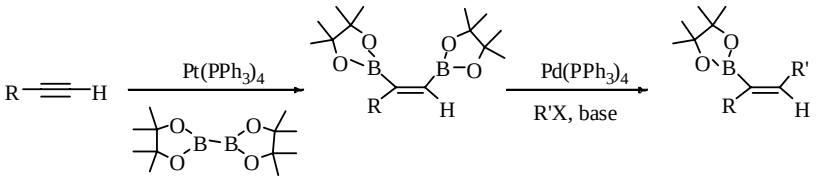
the presence of palladium catalyst and a base to give the corresponding product in which only a new C-C bond is formed in the terminal position (Scheme 5.2).



Scheme 5.1



Scheme 5.2

Another application related to C-C bond formation from bis-boronate esters has been developed by Armstrong et al.[7] to synthesise tetrasubstituted ethylenes in which all four substituents can be modified to provide an interesting route for synthesizing antiestrogenic triphenylethylene derivates.[8] These authors based their studies on the fact that a *cis*-bis(boryl)alkene derivate could be differentiated to introduce two additional substituents through the Suzuki-Miyaura cross coupling reaction. First the bis-boronate esters were monoalkylated with alkyl or aryl halides, and a second Suzuki reaction with a resin-bound aryl halide[9] led to the synthesis of substituent ethylenes involving three different components in a single-pot transformation, (Scheme 5.3). The study was also extended to symmetrical aryl-aryl and alkyl-alkyl boronates. This methodology efficiently provided sterically hindered tetraphenylethylenes in high yield.

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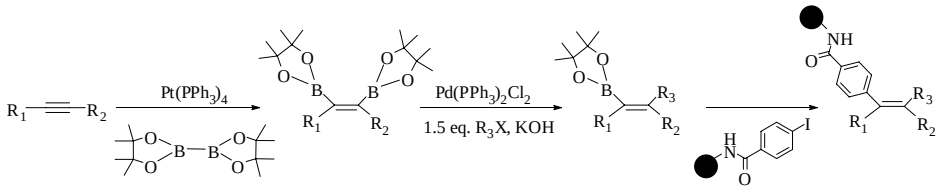
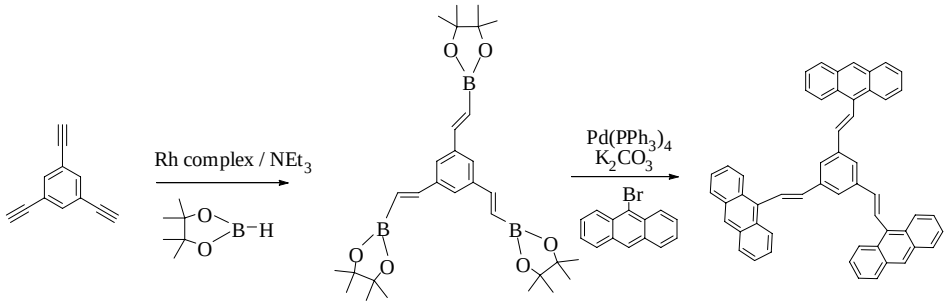


Scheme 5.3

The Rh(I)-catalysed hydroboration of a variety of aromatic diynes and triynes afforded bis(boryl)- and tris(boryl)vinyl products, which underwent Suzuki cross-coupling reactions with a variety of substrates containing chromophore units to give fluorescent dye-substituted products[10] (Scheme 5.4). Significantly, the use of NEt_3 was found to be essential to achieve good yields and *trans* selectivity for the catalytic hydroboration of some substrates.



Scheme 5.4

Interestingly, a very recent strategy for achieving chemoselectivity Zr(IV)-catalysed hydroboration of easily prepared allyl propargyl ethers can afford boron-substituted di(allyl)ethers as versatile intermediates for a consecutive chemoselective Ir(I)-catalysed isomerisation and in situ Claisen rearrangement to afford stereodefined B-boryl aldehyde products. Functionalization of the C-B linkage by oxidation or Suzuki cross-coupling provides a route to Claisen adducts that were previously inaccessible[11] (Scheme 5.5).

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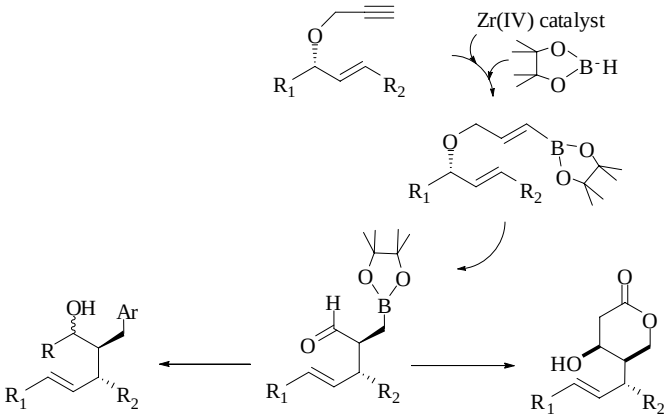
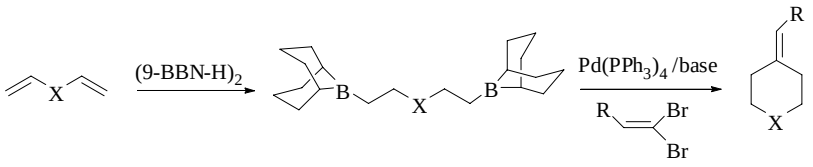


Scheme 5.5

When alkenes are used for hydroboration rather than alkynes, the corresponding alkylborane derivative is particularly useful for cross-coupling reactions. Specifically, the use of alkyldiboranes in cross-coupling with vinylidene dibromides offers a potentially versatile new synthetic pathway to isomerically pure six-membered ring carbo- and heterocycles which contain an exocyclic double-bond functionality[12] (Scheme 5.6).



Scheme 5.6

The usefulness of this methodology is demonstrated by several noteworthy applications of the tandem hydroboration of alkenes followed by the Suzuki-Miyaura coupling reaction in the synthesis of targeted molecules such as 1-tetralone derivatives,[13] 2-methoxy-5-Z-hexadecenoic[14] and a *cis*-clerodane diterpenic acid.[15]

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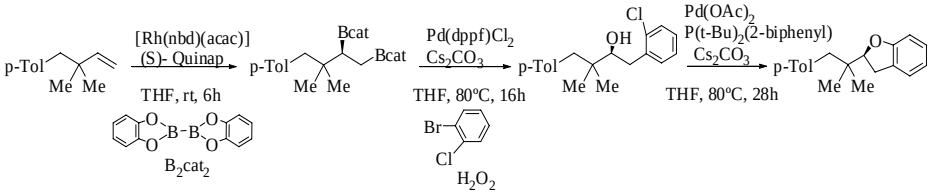
An interesting asymmetric version of the catalytic carbohydroxylation of alkenes by a tandem diboration/Suzuki-Miyaura cross-coupling/oxidation reaction has been developed.[16] Aliphatic alkenes can be efficiently diborated in a highly selective fashion and provide unsymmetrical 1,2-bis(boronates) which can be subjected to in situ cross-coupling with arylhalides (Scheme 5.7). The diboration reaction mixture can be diluted with THF/H_2O and Pd(dppf)Cl_2 (where dppf= 1,1'-Bis(diphenylphosphino)ferrocene) was added to catalyze the process in the presence of Cs_2CO_3. In this process, the more accessible C-B bond reacts faster, leaving the secondary C-B bond unreactive towards the C-C bond formation but available for alternative transformations such as oxidation. Finally, catalytic intramolecular etherification,[17] provides the benzofuran derivative, preserving chiral configuration up to 87% e.e.



Scheme 5.7

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 that can participate in a cross-Suzuki-Miyaura reaction (Scheme 5.8). However, only the primary boronate ester is transformed into the new C-C bond, while the remaining C-B bonds can be oxidised in the reaction work up to provide internal chiral diols in a concise single-pot fashion.[18] Interestingly, the second step in the hydroboration reaction of the organodiboron[19] proceeds in a stereoselective fashion. The origin of the diastereoselection has been rationalised with a

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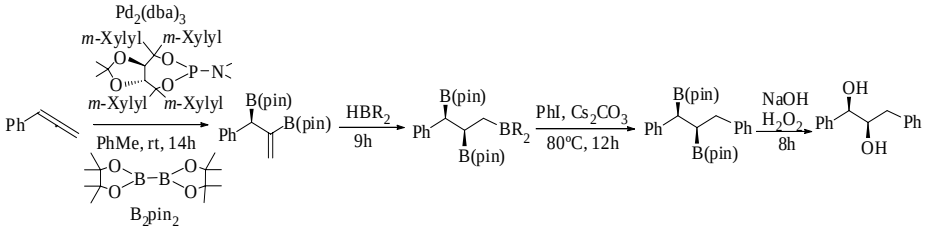
transition structure that involves aligning the electron-rich allylic C-B bond with the reacting π-system.



Scheme 5.8

5.2. Pt/NHC catalytic systems mediate tandem hydroboration-cross coupling reactions

The catalytic insertion of unsaturated moieties into a B-H bond through the hydroboration protocol is an effective strategy for selectively obtaining organoboron derivates,[2c] an important class of compounds used as synthetic intermediates[1c,e] especially for constructing carbon frameworks.[20] Although hydroboration can also be performed under non-catalytic conditions, the search for optimised selectivity on the target organoborane compounds requires metal-mediated catalysis to be used. The most efficient catalyst for hydroboration appears to be rhodium complexes,[21] especially for asymmetric B-H addition to alkenes.[3,22] However, iridium, palladium, ruthenium, niobium, titanium, zirconium and lanthanide-based catalysts are an interesting alternative.[2c] We were aware that hydroboration with platinum-based catalysts and catecholborane had not been reported even though they had been successfully used in catalytic B-B addition to alkenes and alkynes.[2g,i]

To the best of our knowledge, there are only two significant relative precedents: Pt(II)-catalysed hydroboration of terminal olefins with polyboranes[23] and Pt(0)-catalysed hydroboration of allenes with

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pinacolborane.[24] To verify whether Pt(0) could be a better alternative to the hydroboration/oxidation of vinylarenes, we first used the readily available $Pt(PPh_3)_4$ complex, which provided 18% of conversion from styrene with catecholborane, under standard reaction conditions after 3h at room temperature (Table 5.1, entry 1). This poor result, in comparison with the uncatalysed reaction (entry 0) was accompanied by a lack of regioselectivity, hence producing the Markovnikow and the anti-Markovnikow alcohol derivatives, together with phenylethane.

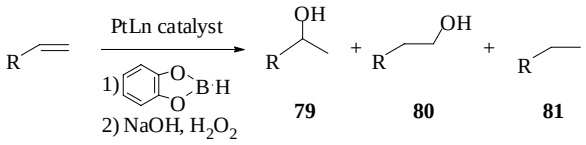

Table 5.1. Platinum-catalysed hydroboration/oxidation of styrene with catecholborane[a]

Entry	Catalytic system	Conv. (%)[b]	**79** (%)[b]	**80** (%)[b]	**81** (%)[b]
0	----	14	traces	99.9	---
1	$Pt(PPh_3)_4$	18	17	18	65
2	$Pt(COD)Cl_2$	100	49	51	---
3	$Pt(COD)Cl_2 + 1PPh_3$	92	15	85	---
4	$Pt(COD)Cl_2 + 2PPh_3$	0	---	---	---
5	$Pt(COD)Cl_2 + 4PPh_3$	0	---	---	---
6	$Pt(COD)Cl_2 + 1PCy_3$	71	25	59	15
7	$Pt(COD)Cl_2$+1$P(OR)_3$ [c]	80	19	28	53

[a] Standard conditions: Styrene / catecholborane / Pt complex = 0.5/0.55/0.025; Solvent: THF; T:25ºC; 3h. [b] Determined by ^{1}H NMR. [c] $P(OR)_3$= tris(2,4-di-tert-butylphenyl)phosphite.

This preliminary result may explain why phosphine-based Pt catalysts for the hydroboration of alkenes are so scarce. B-H addition to alkenes probably requires a phosphine dissociative pre-step to allow the formation of the hydridoboryl platinum complex, as has been suggested previously.[25] Phosphine-free platinum catalytic systems, such as $Pt(COD)Cl_2$, which have proved to be very effective in the catalytic diboration of terminal alkenes, alkynes and aldimines[26] show much higher conversion in the hydroboration of styrene, under

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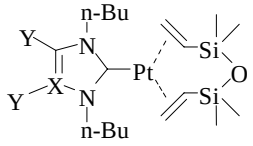
the same reaction conditions (Table 5.1, entry 2), although the system lacks selectivity. Addition of PPh_3 to this catalyst clearly decreases the activity. The extent of this decrease depends on the amount of phosphine added (Table 5.1, entries 2-5), in agreement with analogous catalytic B-B transformations.[27] Platinum complexes modified with electronically different phosphines and phosphites provided less than 25% of branched isomer (Table 5.1, entries 6,7), while diphosphines (dppm where dppm= diphenylphosphino methane and dppb where dppb= diphenylphosphino butane) resulted in complete loss of activity.

Taking all this into consideration and in collaboration with Prof. E. Peris and Dr. J. Mata from the Jaume I University (Spain), we explored the possibility of performing H-B addition to alkenes with N-heterocyclic carbene (NHC)Pt(0) complexes (Figure 5.1), because they are an effective alternative to phosphines in numerous catalytic exemples.[28,29,30] Our group has reported that compounds **33** and **34** are very efficient in the diboration of alkenes, alkynes and allylic sulfones (as shown in Chapter 3).[31]



34: X=N, Y=H **33:** X=C, Y=Cl
35: X=C, Y=H **82:** X=C, Y=Me

Figure 5.1. (NHC)Pt(0) complexes

When complexes **33** and **34** were initially tested in our model reaction with styrene as the substrate, the conversion was complete within 3 hours and the regioselectivity was 85-90%, surprisingly high for the branched alcohol (**79**) (Table 5.2, entries 1 and 2). No hydrogenated byproduct was detected.

It is worth mentioning that the catalytically active species was still active at the end of the reaction, because subsequent addition of a second and third

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amount of styrene and catecholborane led to the desired product without any measurable decrease in catalytic activity. Even more important is the observation that after several days at ambient temperature the NHC-Pt(0) complexes were still active in sharp contrast to many of the rhodium-phosphine catalyst precursors.

The use of catecholborane as the hydroborating reagent was beneficial because the addition of pinacolborane provided not only lower conversion but also low regioselectivity (Table 5.2, entry 2).

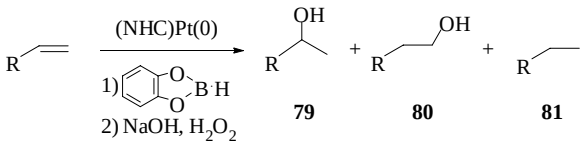

Table 5.2. NHC-Pt complex catalysed hydroboration/oxidation of styrene with catecholborane[a]

Entry	Catalyst	Conv. (%)[b]	**79** (%)[b]	**80** (%)[b]	**81** (%)[b]
0	**34**	100	85	15	---
1	**34**[c]	19	52	48	---
2	**33**	100	90	10	---
3	**35**	100	71.5	28.5	---
4	**82**	82	65	35	---

[a] Standard conditions: Styrene / catecholborane / Pt complex = 0.5/0.55/0.025; Solvent: THF; T:25ºC; 3h. [b] Determined by ^{1}H NMR. [c] Hydroborating reagent: pinacolborane.

Alternative NHC ligands with more basic properties in complex **35** and **82**, resulted in activities similar to those of **33** and **34** but lower selectivities.

Complex **33** (0.025 mmol) was dissolved in 1ml of THF-d_8 in a sealable NMR tube, and freshly distilled HBcat (**1**), (0.025eq.) was added via syringe. Despite the immediate change to a brownish colour, no specific signals were detected in the hydride region of the ^{1}H RMN spectra. Then 0.5 mmol of styrene and 0.5 mmol of **1** were added to monitor the formation of the product under these conditions. Figure 5.2 shows the styrene consumption within the first 3.5 h after the disappearance of the doublet at 5.7 ppm in the ^{1}H RMN.

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Similarly, Figure 5.3 shows the formation of the branched and linear product under these reaction conditions, attending to the increasing doublet at 1.5 ppm for the branched boronate ester, and the triplet at 1.6 ppm for the linear boronate ester.

In order to check whether **33** and **34** could also be applied to other substrates, we studied the hydroboration to other terminal and internal vinylarenes and vinylalkanes, as well as allylic systems such as allylsulfones (Figure 5.4).

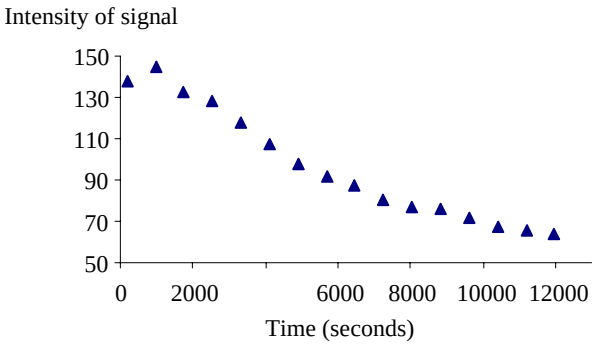

Figure 5.2. Monitoring the disappearance of styrene

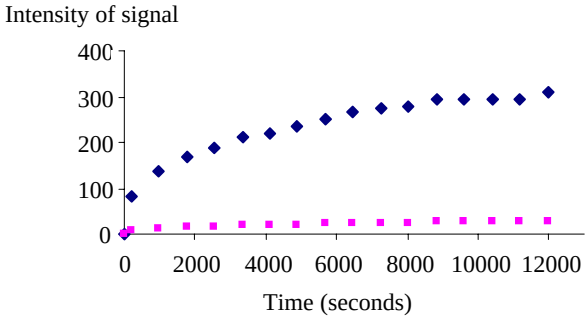

Figure 5.3. Monitoring the appearance of branched (◆) and linear (■) boronate esters

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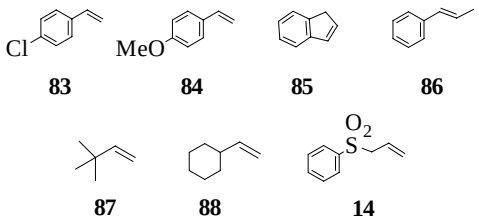
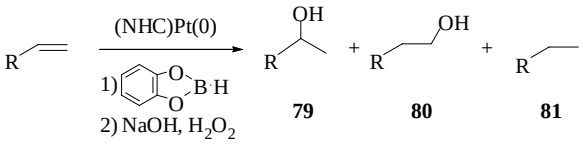


83 **84** **85** **86**

87 **88** **14**

Figure 5.4. Substrates used in table 5.3

As can be seen, the selectivity on the branched derivative increases with the electron-withdrawing properties of the aryl substituent (Table 5.3, entries 1, 2, 9 and 10). Internal vinylarenes also favour the formation of the branched isomer, up to values of about 97% for the 1-phenyl-1-propanol. However, the conversion is lower than with terminal substrates, because C=C is more hindered (Table 5.3, entries 3, 4 and 11, 12).



79 **80** **81**

Table 5.3. NHC-Pt complex catalysed hydroboration/oxidation of alkenes with 1[a]

Entry	Substrate	Catalyst	Conv. (%)[b]	**79** (%)[b]	**80** (%)[b]	**81** (%)[b]
1	**83**	**34**	100	90	10	---
2	**84**	**34**	100	74	26	---
3	**85**	**34**	60	87	13	---
4	**86**	**34**	77	92	8	---
5	**87**	**34**	100	5	95	---
6	**88**	**34**	100	15	85	---
7	**14**	**34**	41	69	21	10
8[c]	**14**	**34**	72	53	29	18
9	**83**	**33**	100	92	8	---
10	**84**	**33**	95	70	21	9
11	**85**	**33**	70	77	9	14
12	**86**	**33**	77	97	3	---
13[c]	**14**	**33**	73	64	21	15

[a] Standard conditions: Alkene / catecholborane / Pt complex = 0.5/0.55/0.025; Solvent: THF; T:25ºC; 3h. [b] Determined by ^{1}H NMR. [c] 3 eq. catecholborane.

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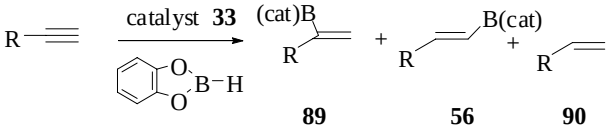
Complex **33** also provided small amounts of hydrogenated product in the hydroboration of indene (**85**) and trans-β-methylstyrene (**86**). Interestingly, the catalytic hydroboration of vinylalkanes (**87** and **88**) inverts the selectivity with respect to the other vinylarenes used (Table 5.3, entries 5 and 6).

Vinylcyclohexane (**88**) and tertbutylethene (**87**) mainly afforded the linear alcohol with complex **34**, probably because a η^3-metal-alkene intermediate cannot be formed in the catalytic cycle.[32] Finally, complex **33** and **34** are efficient catalysts for the hydroboration of phenyl allyl sulfones (**14**), although the regioselectivity is moderate because the hydrogenated product is also formed, (Table 5.3, entries 7,8 and 13).

The versatility of the platinum-catalysed hydroboration reaction is further substantiated by H-B addition to alkynes. In this case, complex **33** provided branched and linear alkenylboronic esters in moderate selectivities, within 3h at room temperature in THF (Table 5.4). Styrene was also formed under these reaction conditions.



89 **56** **90**

Table 5.4. NHC-Pt complex catalysed hydroboration of terminal arylalkynes with catecholborane[a]

Entry	Substrate	Conv. (%)[b]	**89** (%)[b]	**56** (%)[b]	**90** (%)[b]
1	Phenylacetylene	100	15	68	17
2	(*p*-Methoxyphenyl)acetylene	100	31	38	31
3	(*p*-Trifluoromethylphenyl)acetylene	100	18	62	20

[a] Standard conditions:Alkyne / catecholborane / Pt complex = 0.5/0.55/0.025; Solvent: THF; T:25ºC; 3h. [b] Determined by ^{1}H NMR.

In comparison, the uncatalysed hydroboration of alkynes required elevated temperatures[33] and the rhodium (I)-mediated hydroboration on

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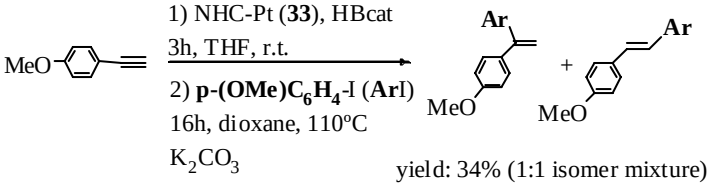
phenylethylene in the presence of variable amounts of PPh_3 resulted in a more complex mixture of byproducts.[34] However, the regioselectivity towards the alkenyl boronate isomer was optimal with alternative catalytic systems, such as $Cp_2Ti(CO)_2$, and Cp_2ZrHCl and nickel modified with diphosphines.[35]

One significant advantage of Pt-based catalysts over Rh-based catalysts in the hydroboration of olefins is their potential ability to perform the tandem H-B addition/cross coupling reaction under the same catalytic system. In a preliminary study, we tested the catalytic activity of complex **33** in the one-pot hydroboration of alkynes/Suzuki-Miyaura coupling reaction. Adding 4-iodoanisole to the (*p*-methoxyphenyl)acetylene hydroboration mixture in the presence of K_2CO_3 afforded the coupling product in 34% yield as a 1:1 mixture of isomers, after heating to 110ºC for 16h in dioxane (Scheme 5.9). The platinum catalyst affects both the hydroboration and the Suzuki-Miyaura coupling. It should be noted that there are few exemples in the literature of Pt catalysing this type of cross coupling reaction.[36]



Scheme 5.9

5.3. Pd/P catalytic systems mediate the tandem diboration-cross coupling reactions

The catalytic diboration of alkenes and alkynes afforded alkyl- and alkenyldiboronates, which are susceptible to being functionalised "in situ" by means of a cross-coupling reaction towards target molecules.[4, 5, 7, 16] However, in

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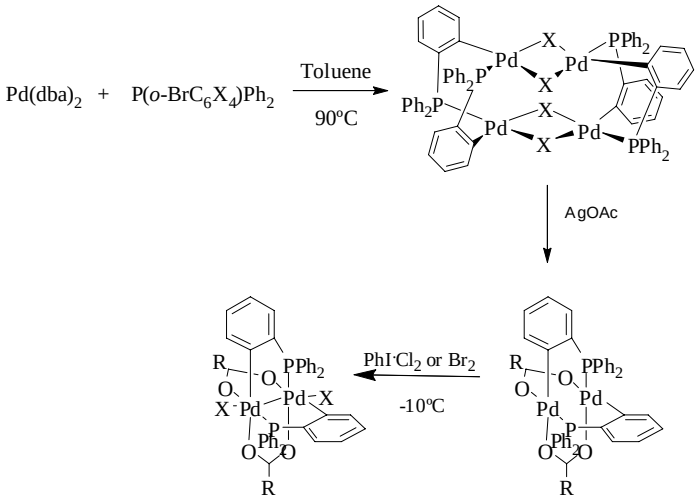
all these examples the catalytic system has to be switched from the Pt- or Rh-mediated diboration of alkenes and alkynes to Pd-mediated Suzuki-Miyaura C-C bond formation. In order to find a single catalytic system that can perform both sequences in a one-pot reaction and taking into account the precedents of the catalytic diboration in the presence of a base with Pd[37] complex (see Chapter 3), we focused on Pd-complexes.

In our collaboration with Prof. P. Lahuerta and Dr. M. A. Ubeda from Valencia University (Spain), we decided to explore different kinds of dinuclear and tetranuclear palladium complexes with bridging ortho-metalated phosphines as ligands (Scheme 5.10)

In the first screening, the previously described *cis*-$Pd_2(C_6H_4PPh_2)_2(O_2CR)_2$ (**91a-d**) with a Pd_2^{4+} core[38,39] and *cis*-$Pd_2(C_6H_4PPh_2)_2(O_2CR)_2X_2$ (**92a-d**) with a Pd_2^{6+} core[40] (Figure 5.5) were tested as catalytic precursors in the diboration of styrene as a model substrate with bis(catecholato)diboron.



Scheme 5.10. Synthesis of the dinuclear Pd_2^{4+}, Pd_2^{6+} and tetranuclear Pd_2^{4+} complexes

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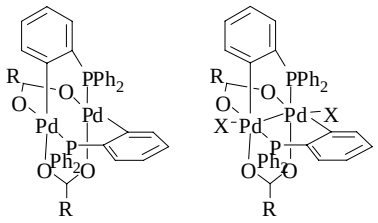

91a: R=CH_3
91b: R=CMe_3
91c: R=CF_3
91d: R=C_6F_5

92a: R=CH_3 X=Cl
92b: R=CMe_3 X= Cl
92c: R=CF_3 X=Cl
92d: R=CH_3 X=Br

Figure 5.5. Dinuclear palladium compounds

The catalytic precursor **91a** proved to be inactive until an excess of diboron was added to the reaction mixture (Table 5.5, entry 1). Chemoselectivity to the diborated product was enhanced by the presence of the base NaOAc, up to quantitative values when it is combined with an excess of B_2cat_2 (Table 5.5, entries 2-5). This is of particular interest because the catalytic diboration can compete with the catalytic dehydrogenative borylation,[2g,i,j,41] giving rise to alkenylboronates and hydroborated byproducts (Scheme 5.11).

Under these optimised reaction conditions, complexes **91b-d** also proved to be very active and selective in the 1-phenyl-1,2-ethanediol formation within 4h at room temperature (Table 5.5, entries 6-8). Surprisingly, complexes **92a-d**, which are based on Pd(III), were also very active and chemoselective for the diborated product (Table 5.5, entries 9-12).

To clarify the role of the carboxylate ligand present in the catalyst precursor, we made a comparative catalytic study with the solvated cationic complex $[Pd_2(C_6H_4PPh_2)_2(NCCH_3)_4](BF_4)_2$, **93**, (Figure 5.6), with acetonitrile molecules replacing the carboxylate goups.[38b]

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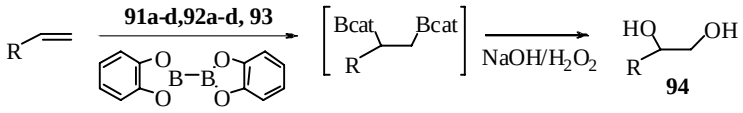
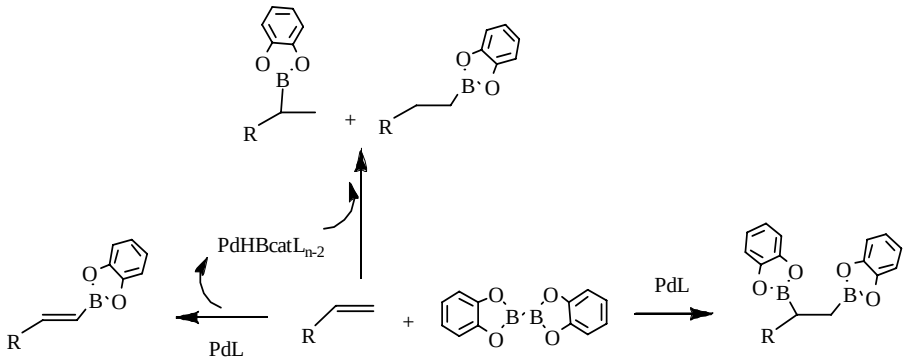


Table 5.5. Palladium (II) and (III) complexes mediate catalytic diboration/oxidation of styrene with bis(catecholato)diboron[a]

Entry	Catalytic system	NaOAc(eq)	B_2cat_2 (eq)	Conv (%)[b]	**94** (%)[b]
1	**91a**	---	3	54	32
2	**91a**	0.5	3	80	51
3	**91a**	1	1	38	60
4	**91a**	1	2	79	91
5	**91a**	1	3	81	99
6	**91b**	1	3	87	81
7	**91c**	1	3	99	99
8	**91d**	1	3	95	99
9	**92a**	1	3	86	99
10	**92b**	1	3	97	99
11	**92c**	1	3	98	99
12	**92d**	1	3	99	99
13	**93**	---	3	84	44
14	**93**	1	3	94	99

[a] Standard conditions: Substrate / Pd = 1/0.05; Solvent: THF; T = 25ºC; 4h. [b] Determined by ^1H NMR spectroscopy.



Scheme 5.11

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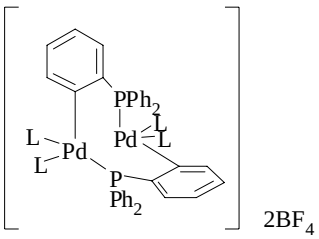

93 L= CH_3CN

Figure 5.6

Under reaction conditions similar to those in entry 1, moderate diol formation was observed, although the addition of 1eq. of NaOAc favoured the reaction quantitatively (Table 5.5, entries 13-14). The presence of the carboxylate anion in the catalyst precursor does not seem to be critical for the cleavage of the diboron, as the BF_4^- counterion also seems to contribute to this end, in view of entry 13 and the diboration reaction catalysed by (NHC)Cu complexes[42] (see Chapter 3).

In order to check whether **91a** and **92a** can also be applied to other substrates, we studied the diboration of other terminal and internal vinylarenes. Although both catalyst precursors performed with total chemoselectivity towards the diol product (Table 5.6), only complex **91a** gave quantitative conversion even in the diboration of internal vinylarenes such as indene (**85**) and *trans*-β-methylstyrene (**86**).

In order to gain further insight into the role of the catalyst, we monitored the metal catalyst under reaction conditions using NMR spectroscopy. Complex **92a** (0.01 mmol) was dissolved in a sealable NMR tube with 1ml of THF-d_8, and the colour immediately changed from red to yellow when B_2cat_2 (0.03mmol) and NaOAc were added. The ^{31}P NMR spectra showed a significant shift, from -13.9 ppm typical of the Pd(III) in **92a** to +26.8 ppm assigned to a new Pd(II) species, generated in situ. Analogously, the ^{11}B NMR spectra also

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showed how the original signal at 30.1 ppm due to B_2cat_2 decreased in favor of a new signal at 13.6ppm associated with the interaction of B_2cat_2-NaOAc (see Chapter 3).[37] The diboron seems to reduce Pd(III) to Pd(II), just as B_2X_4 has been reported to reduce Pd(II) to Pd(0).[43] The new palladium species formed in situ is assigned to tetranuclear palladium complex **95a** (Figure 5.7), in comparison with the NMR data reported previously in the literature as an isolated complex.[39]

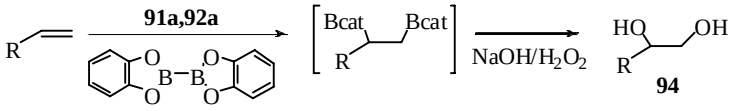

Table 5.6. Palladium (II) and (III) complexes mediate catalytic diboration/oxidation of vinylarenes with bis(catecholato)diboron[a]

Entry	Substrate	Catalytic system	Conv (%)[b]	**94** (%)[b]
1	*p*-Fluorostyrene	**91a**	79	99
2	*p*-Methylstyrene	**91a**	92	99
3	Indene	**91a**	40	99
4	*Trans*-β-methylstyrene	**91a**	17	99
5	*p*-Fluorostyrene	**92a**	99	99
6	*p*-Methylstyrene	**92a**	96	99
7	Indene	**92a**	99	99
8	*Trans*-β-methylstyrene	**92a**	94	99

[a] Standard conditions: Substrate / Pd = 1/0.05; B_2cat_2 = 3 eq.; NaOAc = 1 eq.; Solvent: THF; T = 25ºC; 4h. [b] Determined by ^{1}H NMR spectroscopy.

Bearing this in mind, we checked and compared the catalytic activities of the tetranuclear palladium complexes **95a-c** (Figure 5.7) with the activities observed for complexes **92a-b**. These complexes were prepared by Prof. P. Lahuerta's group.[39]

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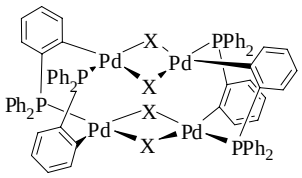

95a: X=Cl
95b: X=Br
95c: X=I

Figure 5.7. $[Pd(C_6H_4PPh_2)X]_4$ complexes without carboxylate ligands

Interestingly, catalyst precursors **95a-c** proved to be as active and chemoselective in the diboration/oxidation of styrene as complexes **92a-b**, (Table 5.7).

The nature of X (X=Cl, Br, I) does not change the reaction outcome. Further catalytic studies with complex **95b** provided quantitative conversions of the diol product for both terminal and internal vinylarenes. The fact that the catalytic behaviour was similar suggests that the catalytic species formed from **95a** and **92a** in the presence of B_2cat_2 differs from that of **91a** with B_2cat_2.

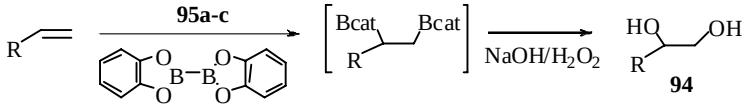

Table 5.7. Complex 95 mediates the catalytic diboration/oxidation of alkenes with bis(catecholato)diboron[a]

Entry	Substrate	Catalytic system	Conv (%)[b]	**94** (%)[b]
1	Styrene	**95a**	99	99
2	Styrene	**95b**	99	99
3	Styrene	**95c**	99	99
4	*p*-Methylstyrene	**95b**	99	99
5	*p*-Fluorostyrene	**95b**	99	99
6	*Trans*-β-methylstyrene	**95b**	95	99
7	Indene	**95b**	87	99
8	3,3-Dimethyl-1-butene	**95b**	99	99
9	Vinylcyclohexane	**95b**	99	99

[a] Standard conditions: Substrate / Pd = 1/0.05; B_2cat_2 = 3 eq.; NaOAc = 1 eq.; Solvent: THF; T = 25ºC; 4h. [b] Determined by ^1H NMR spectroscopy.

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To get a more complete picture of this hypothesis, styrene consumption and diborane ester formation were monitored at short intervals for 3 hours of the catalytic diboration with **91a**, **92a**, **95a** in the presence of B_2cat_2 and NaOAc (Figure 5.8). A typical catalytic experiment was carried out in an NMR tube. Styrene consumption and diborated product formation were followed by monitoring the doublets at 5.7ppm and 3.3ppm, respectively, in the ^1H NMR spectra.

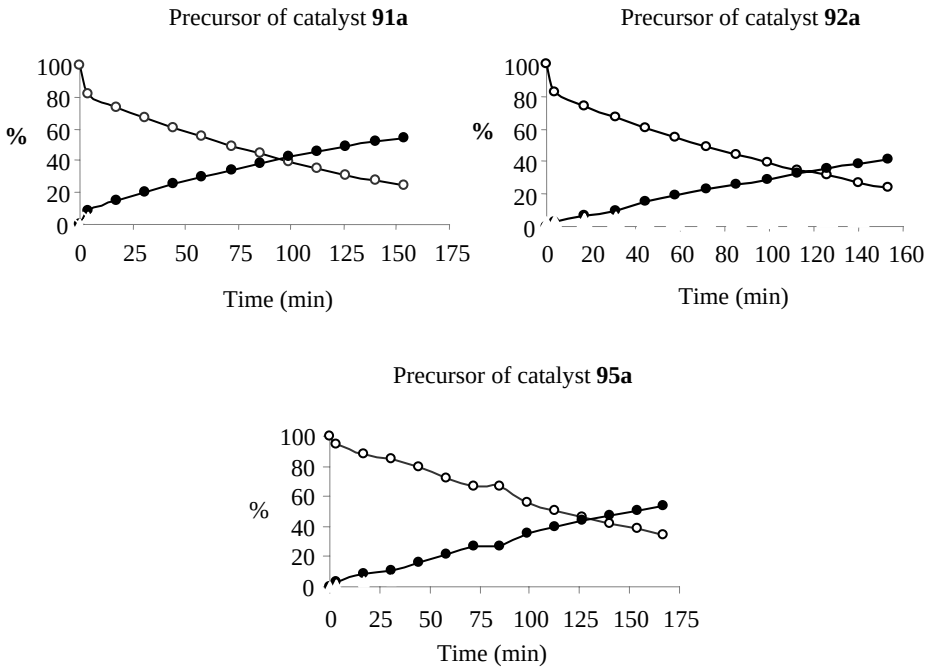

Figure 5.8. Evolution of catalytic diboration of styrene with catalyst precursor 91a, 92a and 95a. Styrene consumption ○, diborane formation ●

In order to gain further insights into the role of the catalyst, we monitored the metal catalyst under reaction conditions using NMR spectroscopy. When complex **91a** (0.01 mmol) was dissolved in a sealable NMR tube with 1ml of THF-d_8, the colour changed to brownish when B_2cat_2 (**4**, 0.03mmol) and

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NaOAc (0.01mmol) were added. The ^{31}P NMR spectra showed how the original signal corresponding to **91a**, at +21ppm, progressively disappeared. The ^{11}B NMR spectra also showed the disappearance of the signal corresponding to **4**, at 30.1 ppm, and the appearance of signals at 23 ppm (B_2cat_3), and at 13.6 ppm (B_2cat_2–NaOAc).[37] Interestingly, a black solid was recovered and characterised as "in situ" phosphine-stabilised palladium nanoparticles, the core size and size distribution of which were examined by transition electron microscopy (TEM).

The picture showed disperse nanoparticles 6.9±3.0nm in diameter (Figure 5.9). Thus, the reduction of Pd(II) to Pd(0) by B_2cat_2 in **91a** parallels a previous study that reported that PPh_3-stabilised gold nanoparticles can be obtained by reducing PPh_3AuCl with diboron B_2X_4[43a] and $BinapAu_2Cl_2$ with diboron B_2cat_2.[43b]

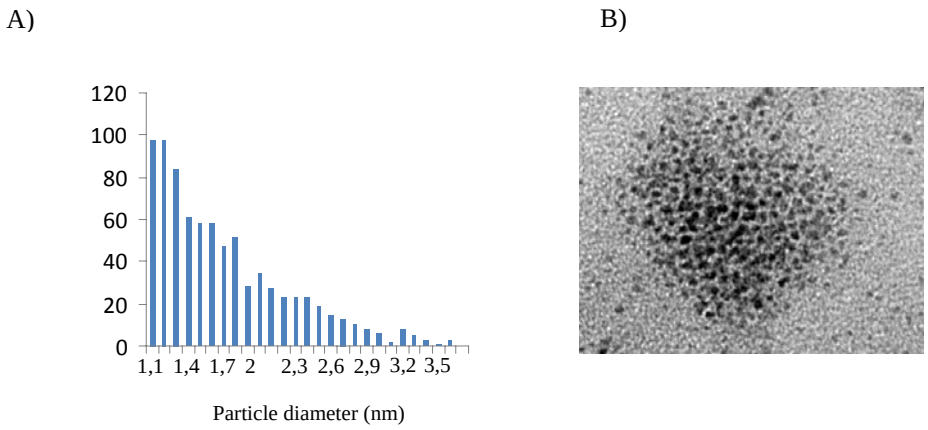

Figure 5.9. "In situ" Pd nanoparticles: A) core size distribution. B) TEM micrograph (x 500000)

In order to learn more about the nature of the active catalytic species in these systems, we performed three new styrene diboration experiments, with **91a**, **92a** and **95a** as catalyst precursors, and with an excess of Hg.[44] While

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complex **91a** became substantially inactive, catalyst precursors **92a** and **95a** gave quantitative conversion. Therefore, we decided to conduct new catalytic reactions with the enantiomerically pure complex **95b**, in an attempt to observe the induction of stereoselectivity.[38b] However, when 3,3-dimethyl-1-butene was diborated with **95b** and B_2cat_2 in the presence of the NaOAc, no enantioselectivity was observed even though total conversion and selectivity were achieved within 4 hours of reaction at room temperature. Considering that all catalyst precursors have backbone chirality this observation suggests that, in the diboration process, the metal-intermediates lose their chirality because of the cleavage of the complex structure.

Finally, we checked whether complexes **92** and **95** could perform the tandem single-diboration of alkenes/Suzuki-Miyaura cross coupling, by using only 5mol% of palladium throughout the tandem reaction. We were very pleased to observe that catalyst precursor **95b** performs this tandem reaction highly satisfactorily. Thus, once the diboration of 3,3-dimethyl-1-butene with B_2cat_2 has been properly completed (after 4 hours at room temperature in the presence of the **95** and the base NaOAc), the addition of aryl halides and aryl triflates provided total monoarylation of the primary alkylboronic ester. Further oxidative work up led to total conversion of the alkene into the carbohydroxylated adduct (Table 5.8, entry 1). Similar results were observed when complex **92a** was used instead (Table 5.8, entry 2). Aryl halides performed better than aryl triflates as reactives (Table 5.8, entries 3-5). The catalytic conditions for the cross-coupling reactions were optimised, and 10% H_2O was required to complete the monoarylation process. The absence of H_2O only provided 50% of desired product. The efficiency of base Cs_2CO_3 guaranteed the sequence of arylation, despite the excess of NaOAc present in the reaction. Like 3,3-dimethyl-1-butene, the substrate vinylcyclohexane performed the tandem reaction with identical success (Table 5.8, entry 6).

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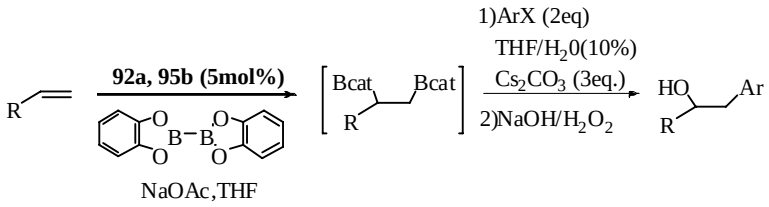
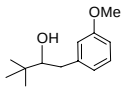
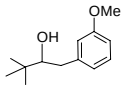
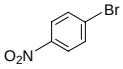
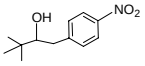
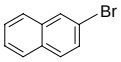
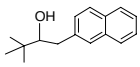
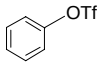
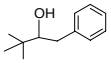
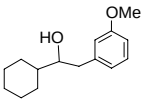


Table 5.8. Palladium complexes mediate catalytic diboration/monoarylation/oxidation of alkenes[a]

Entry	Cat.	Substrate	ArX	Product	Conv (%)[b]
1	**95b**				99
2	**92a**				90
3	**95b**				99
4	**95b**				99
5	**95b**				30
6	**95b**				99

[a] Standard conditions: Substrate/Pd = 1/0.05; B_2cat_2 = 3 eq.; NaOAc = 1 eq.; Solvent: THF; T=25ºC; 4h, then 3 eq. of Cs_2CO_3; 2eq ArX; THF/H_2O 10%; 75ºC; 15h. [b] Determined by G. C. and ^1H NMR spectroscopy.

Morken et al.[16] managed to prepare chiral nonsymmetric 1,2-diboron adducts by Rh-mediated diboration and further Pd-mediated cross-coupling favoured a new C-C bond formation from the less hindered C-B bond, while the remaining C-B bond was then oxidised. However, there are some differences between their work and ours: while they used [Rh(NBD)(acac)]/(S)-Quinap (5mol%) for the efficient asymmetric diboration sequence and [Pd(dppf)Cl_2] complexes (10mol%) for the cross-coupling sequence, we only required 5mol%

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of Pd complex for both sequences, but with 3eq. of diboron. The percentages of product formed also significantly improved from 60-77% with the Rh/Pd mixed catalytic system to 100% with our Pd system.

5.4. Conclusions

We have shown that NHC-Pt(0) complexes are an effective alternative for the catalytic regioselective hydroboration of alkenes, and that they can be applied in the one-pot tandem H-B addition / Suzuki-Miyaura coupling reaction, under the same catalytic system.

The structurally related di- and tetranuclear Pd_2^{4+} compounds and the novel Pd_2^{6+} compounds showed high selectivity in the catalytic diboration of alkenes under mild and basic conditions.

The presence of bis(catecholato)diboron (B_2cat_2) favoured the reduction of Pd(III) to Pd(II), while the catalytic precursor of Pd(II) was transformed into Pd(0)-nanoparticles.

Some of these compounds performed efficient catalytic tandem diboration-arylation of alkenes by using a single catalyst. This process is the first example of the multifaceted properties of a palladium complex participating in different catalytic cycles with identical success.

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Experimental section

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 stated otherwise. The solvents were distilled over dehydrating reagents (THF and toluene were distilled over Na using benzophenone as dryness indicator, CH_3CN was distilled over CaH_2) and were deoxygenated before use. Bis(pinacolato)diboron (**3**) was used as purchased from Lancaster. (S)-QUINAP and vinylcyclohexane were provided by Across. (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP and $Pd_2(dba)_3$ were used as purchased by Strem Chemicals. (*R*)-(*S*)-Mandyphos, (*R*)-Ph-MeOBiphep, (*R*)-(*S*)-Josiphos and (*R*)-(*R*)-Walphos were kindly supplied by Solvias. $RhCl_3 \cdot H_2O$ and $IrCl_3 \cdot xH_2O$ were used as purchased by Johnson Matthey. The rest of the reagents were provided by Sigma-Aldrich.

GC analyses of the solutions were performed on a Hewlett Packard 5890 Serier II apparatus with a flame ionisation detector equipped with a chiral column Supelco β-DEX 120 capillary column (30m, 0,25mm i. d., 0,25μm film thickness) or Chiraldex-GTA capillary column (30m, 0,25mm i. d., 0,12μm film thickness, for the substrates allyl phenyl sulfone and allyl phenyl ether) using H_2 as the carrier gas. The HPLC-TOF/MS analyses were performed in a chiral column Chiralcel OD-H (25cm, 0.4 cm i. d.).

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 resonances. ^{11}B NMR chemical shifts are reported in ppm (δ) relative to $BF_3 \cdot OEt_2$ as the external reference.

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2. Synthesis of the catalyst precursors

2.1 [RhCl(PPh$_3$)$_3$]

This complex was prepared according to the literature.[1] Under nitrogen atmosphere, 2.0g of $RhCl_3 \cdot H_2O$ (8.8 mmol) were introduced in a schlenk and dissolved in 70ml de ethanol. Next, a solution of 12.0g of triphenylphosphine in 350ml of hot ethanol was added. The solution obtained was stirred under reflux during 2 hours. The product was collected from the hot solution on a Büchner funner and washed with small portions of 50ml of anhydrous ether, to yield 6.2g of a deep red powder (88% yield). ^{1}H NMR (C_6D_6): 6.50-8.00 (m, 15H), ^{31}P NMR (C_6D_6): 46.34 (d, J_{Rh-P}= 160Hz), 48.31(d, J_{Rh-P}= 160Hz). Elemental analyses: C: 70.1 (70.0); H: 4.9 (5.0).

2.2. [Rh(μ-Cl)(COD)]$_2$

This complex was prepared according to the literature.[2] Under nitrogen atmosphere, 2.0g of $RhCl_3 \cdot H_2O$ (8.8 mmol) were introduced in a schlenk, and dissolved in ethanol. Next, 4ml of COD (*cis,cis*-1,5-cyclooctadiene) were 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 1,6g of a yellow powder (76% yield). ^{1}H NMR ($CDCl_3$): 4.30 (m, 8H), 1.71-2.63 (m, 16H).

2.3. [Rh(COD)$_2$]BF$_4$

This compound was prepared following a procedure previously reported.[3] Under nitrogen atmosphere, 0,71mmol of [Rh(μ-Cl)(COD)]$_2$ (350mg) were

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introduced in a schlenk and dissolved in the minimum quantity of dry and degassed dichloromethane. Next, 1ml of COD and 2,1mmol of $AgBF_4$ (415mg) were added. Quickly, the mixture obtained turned brown. The mixture was stirred under nitrogen and protected from the light. After 1 hour, a white precipitate corresponding to AgCl was formed. The mixture obtained was filtered through celite. The brown solution obtained was concentrated in a rotary evaporator until a brown precipitate was formed. The product was isolated by means of filtration, yielding 220mg of a brown powder (76% yield). ^{1}H NMR ($CDCl_3$): 5.10 (m, 8H), 2.45-2.64 (m, 16H).

2.4. $[Ir(\mu\text{-}Cl)(COD)]_2$

This compound was prepared following a procedure previously reported.[4] Under nitrogen atmosphere, 1.5g of $IrCl_3 \cdot xH_2O$ were introduced in a previously purged 250 ml three-necked flask and dissolved in 26ml of deoxygenated EtOH and 13.5ml of deoxygenated H_2O. Next, 5ml of COD were added. The dark green solution obtained was stirred under reflux and nitrogen during 8 hours. The mixture obtained was concentrated by nitrogen bubbling until the pale red precipitate was formed. Then, deoxygenated and cold MeOH was added to favour the precipitate formation. The product was isolated by means of filtration, yielding 1.2g of a red powder (63% yield). ^{1}H NMR ($CDCl_3$): 4.20 (m, 8H), 2.33 (m, 8H), 1.57 (m, 8H).

2.5. $[Ir(COD)_2]BF_4$

This compound was prepared following a procedure previously reported.[5] Under nitrogen atmosphere, 0,4mmol of $[It(\mu\text{-}Cl)(COD)]_2$ (254mg) were introduced in a schlenk and dissolved in dry and deoxygenated dichloromethane. Next, 0.9ml of COD and 0.8mmol of $AgBF_4$ (140mg) were

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added to the red-brown solution. The mixture was stirred under nitrogen and protected from the light. After 1 hour, a white precipitate corresponding to AgCl was formed. The mixture obtained was filtered through celite. The beige solution obtained was concentrated in a rotary evaporator until a beige precipitate was formed. The product was isolated by means of filtration, yielding 325mg of a beige powder (91% yield). ^{1}H NMR ($CDCl_3$): 5.22 (m, 8H), 2.54 (m, 16H).

2.6. Quinazolinaps ligands (*S*)-Diphenyl-[1-quinazolin-4-yl)(2-naphthyl)]phosphine ((*S*)-23), (*S*)-Diphenyl-[1-(2-methyl-quinazolin-4-yl)(2-naphthyl)]phosphine ((*S*)-24) and (*S*)-Diphenyl-[1-(2-isopropyl-quinazolin-4-yl)(2-naphthyl)]phosphine ((*S*)-25)

The synthesis of these ligands was carried out in the University College of Dublin under the supervision of Prof. P. Guiry following the procedure previously reported in the literature.[6]

2.7. (NHC)Pt(dvtms) compounds 33-35 and 82

These complexes were prepared by the group of Prof. Eduardo Peris.[7]

2.8. Complexes [(IPr)CuCl] (37), [(IPr)Cu($NCCH_3$)]BF_4 (38), [(IMes)CuCl] (39), [(IMes)Cu($NCCH_3$)]BF_4 (40), [(SIPr)CuCl] (41) and [(SIPr)Cu($NCCH_3$)]BF_4 (42)

These complexes were prepared by the group of Prof. Pedro J. Pérez.[8]

2.9. (NHC)Pd compounds 46-55

These complexes were prepared by the group of Prof. Eduardo Peris.[9]

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2.10. Chiral (NHC)IrCp* compound (57)[10], [Cp*Ir(μ-Cl)Cl_2]$_2$ compound (60)[11] and [(IMe)IrCp*Cl_2] compound (61)[12]

These complexes were prepared by the group of Prof. Eduardo Peris.

2.11. Chiral complexes [L_1Cu ($NCCH_3$)]BF_4 (62), [L_2Cu($NCCH_3$)]BF_4 (63), [L_3Cu($NCCH_3$)]BF_4 (64), [L_3CuCl]BF_4 (65), [L_4Cu($NCCH_3$)]BF_4 (66), [L_4CuCl]BF_4 (67), [L_5CuCl]BF_4 (68)[13a]

These chiral complexes were prepared by the group of Prof. Pedro J. Pérez.[13]

2.12. Complexes $Pd_2(C_6H_4PPh_2)_2(O_2C(CH_3))_2$ (91a)[14,15], $Pd_2(C_6H_4PPh_2)_2(O_2C(CMe_3))_2$ (91b)[14,15], $Pd_2(C_6H_4PPh_2)_2(O_2C(CF_3))_2$ (91c)[14,15], $Pd_2(C_6H_4PPh_2)_2(O_2C(C_6F_5))_2$ (91d)[14,15], $Pd_2(C_6H_4PPh_2)_2(O_2C(CH_3))_2Cl_2$ (92a)[16], $Pd_2(C_6H_4PPh_2)_2(O_2C(CMe_3))_2Cl_2$ (92b)[16], $Pd_2(C_6H_4PPh_2)_2(O_2C(CF_3))_2Cl_2$ (92c)[16], $Pd_2(C_6H_4PPh_2)_2(O_2C(CH_3))_2Br_2$ (92d)[16], [$Pd_2(C_6H_4PPh_2)_2(NCCH_3)_4$]($BF_4$) (93)[14b], [$Pd(C_6H_4PPh_2)Cl]_4$ (95a)[15], [$Pd(C_6H_4PPh_2)Br]_4$ (95b)[15], [$Pd(C_6H_4PPh_2)I]_4$ (95c) [15]

These complexes were prepared by the group of Prof. P. Lahuerta and Dr. M.A. Ubeda.

3. Synthesis of the *p*-substituted allyl aryl sulfones

This synthesis was performed following a previously efficient and inexpensive reported protocol.[17] Bismuth powder (1mmol) was added to a solution of allyl bromide (1.2mmol) in 10ml of dry THF, and the resulting mixture was stirred at room temperature for 30 minutes. Then, a mixture of *p*-

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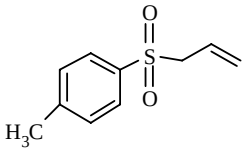
substituted aryl sulfonyl chlorine (1mmol) dissolved in 10ml of THF, was added dropwise. After 4 hours the reaction was quenched with a few drops of water and extracted with dichloromethane. The organic layer was separated, washed and dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel to get the corresponding *p*-substituted allyl aryl sulfone.

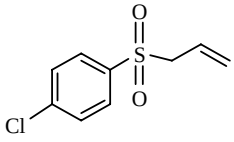
3.1. Selected NMR data[18]

_p_-Methylphenyl allyl sulfone (18)



Yield: 95%. ^{1}H NMR ($CDCl_3$) = 7.70 (d, J= 8.4Hz, 2H), 7.30 (d, J= 8.4Hz, 2H), 5.81 (m, 1H), 5.35 (d, J= 10.3Hz, 1H), 5.15 (d, J= 16.8Hz, 1H), 3.79 (d, J= 7.3Hz, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$) = 144.12, 134.91, 129.11, 127.72, 124.36, 123.89, 60.15, 20.95.

_p_-Chlorophenyl allyl sulfone (19)



Yield: 82%. ^{1}H NMR ($CDCl_3$) = 7,80 (d, J= 8.4Hz, 2H), 7.50 (d, J= 8.4Hz, 2H), 5.81 (m, 1H), 5.34 (d, J= 10.3Hz, 1H), 5.12 (d, J= 16.8Hz, 1H), 3.78 (d, J= 7.3Hz, 2H). ^{13}C NMR ($CDCl_3$) = 145.13, 132.68, 129.97, 128.01, 125.20, 124.82, 61.69.

4 General procedure for the homogeneous catalytic hydroboration/oxidation reaction of alkenes

Catalyst precursor (and ligand if necessary) were introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in 2ml of

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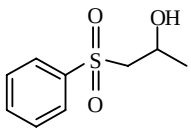
THF and the mixture was stirred for 5 minutes to reach complete dissolution (and formation of the catalytic complex *in situ*, when ligand was used). Next, substrate (alkene or alkyne) was added to the solution of catalyst. The solution was stirred for 5 minutes, and then the hydroborating reagent, freshly distilled catecholborane (**1**) or pinacolborane (**2**), was added. The mixture obtained was then stirred at room temperature to complete the addition of the B-H unit into the unsaturated bond. After the appropriate reaction time, the mixture was quenched with EtOH (2ml). Work up must be carried out carefully because of the risk explosion when peroxides are used with THF. Afterwards, NaOH (2M, 2ml) and H_2O_2 (2ml) were added successively to the hydroborated mixture and then it was stirred for 4 hours. After this time, the reaction mixture was extracted with Et_2O (3x30ml), the organic extracts were washed with NaOH (2M, 30ml), H_2O (30ml), brine (30ml) and lastly dried over $MgSO_4$ and followed by evaporation under reduced pressure to remove the solvent. The products were characterised by ^{1}H NMR spectroscopy to determinate the the degree of the conversion and the nature of the reaction products.

4.1. Selected NMR data for alcoholics derivatives [19,20,21]

1-Phenylsulfonyl-2-propanol (15)



^{1}H RMN δ($CDCl_3$)= 7.96-7.92 (m, 2H), 7.71-7.66 (m, 1H), 7.62-7.52 (m, 2H), 4.32 (m, 1H), 3.30 (dd, J = 2.4Hz, 9.2Hz, 1H), 3.22 (dd, J= 2.4Hz, 9.2Hz, 1H), 1.22 (d, J= 6.8Hz, 3H). Enantiomeric excess were determinated by GC; Chiraldex GTA, R_T= 46.3min (*R*), 45.2min (*S*).

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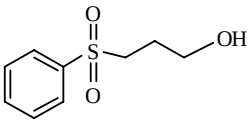
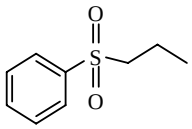
1-Phenylsulfonyl-3-propanol (16)



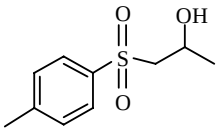
^{1}H RMN δ($CDCl_3$)= 7.96-7.92 (m, 2H), 7.71-7.66 (m, 1H), 7.62-7.52 (m, 2H), 3.71 (t, J = 5.6Hz, 2H), 3.21 (m, 2H), 1.95 (m, 2H)

1-Phenylsulfonylpropane (17)



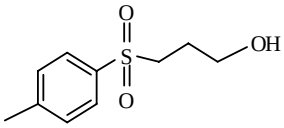
^{1}H RMN δ($CDCl_3$)= 7.96-7.92 (m, 2H), 7.71-7.66 (m, 1H), 7.62-7.52 (m, 2H), 3.06 (m, 2H), 1.71 (m, 2H), 1.95 (t, J = 7.6Hz, 3H)

1-*p*-Methylphenylsulfonyl-2-propanol



^{1}H RMN δ($CDCl_3$)= 7,70 (d, J= 8.4Hz, 2H), 7.30 (d, J = 8Hz, 2H), 4.32 (m, 1H), 3.22 (dd, J= 2.4Hz, 9.2Hz, 1H), 3.13 (dd, J= 2.4Hz, 9.2Hz, 1H), 2.35 (s, 3H), 1.25 (d, J= 6.8Hz, 3H). Enantiomeric excess were determinated by ^{1}H NMR in presence of $Eu(TFC)_3$, δ= 5.56ppm (*R*), 5.37ppm (*S*).

1-*p*-Methylphenylsulfonyl -3-propanol



^{1}H RMN δ($CDCl_3$)= 7,70 (d, J= 8.4Hz, 2H), 7.30 (d, J= 8Hz, 2H), 3.73 (t, J= 5.6Hz, 2H), 3.21 (m, 2H), 2.37 (s,3H), 1.95 (m, 2H)

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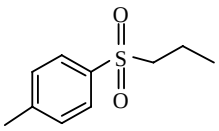
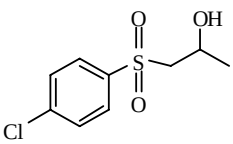
1-*p*-Methylphenylsulfonylpropane



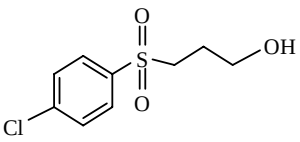
^{1}H RMN δ($CDCl_3$)= 7,70 (d, J = 8.4Hz, 2H), 7.30 (d, J= 8Hz, 2H), 3.05 (m, 2H), 2.37 (s, 3H), 1.71 (m, 2H), 1.92 (t, J = 7.6Hz, 3H)

1-*p*-Chlorophenylsulfonyl-2-propanol



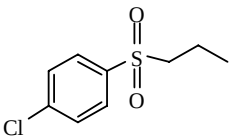
^{1}H RMN δ($CDCl_3$)= 7,80 (d, J= 8.4Hz, 2H), 7.50 (d, J = 8Hz, 2H), 4.32 (m, 1H), 3.22 (dd, J= 2.4Hz, 9.2Hz, 1H), 3.10 (dd, J= 2.4Hz, 9.2Hz, 1H), 1.25 (d, J= 6.8Hz, 3H). . Enantiomeric excess were determinated by ^{1}H NMR in presence of $Eu(TFC)_3$, δ= 5.57ppm (*R*), 5.38ppm (*S*).

1-*p*-Chlorophenylsulfonyl -3-propanol



^{1}H RMN δ($CDCl_3$)= 7,80 (d, J= 8.4Hz, 2H), 7.50 (d, J= 8Hz, 2H), 3.73 (t, J= 5.6Hz, 2H), 3.21 (m, 2H), 1.95 (m, 2H)

1-*p*-Chlorophenylsulfonylpropane



^{1}H RMN δ($CDCl_3$)= 7,80 (d, J = 8.4Hz, 2H), 7.50 (d, J= 8Hz, 2H), 3.06 (m, 2H), 1.71 (m, 2H), 1.95 (t, J = 7.6Hz, 3H)

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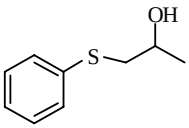
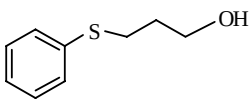
Experimental section

1-Phenylthio-2-propanol



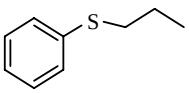
^{1}H RMN δ($CDCl_3$)= 7.34-7.31 (m, 2H), 7.29-7.25 (m, 2H), 7.18-7.14 (m, 1H), 3.85 (m, 1H), 3.05 (dd, J = 6.3Hz, 13.5Hz, 1H), 2.85 (dd, J= 8.1Hz, 13.5Hz, 1H), 1.15 (d, J= 6.2Hz, 3H). Enantiomeric excess was not detected.

1-Phenylthio-3-propanol



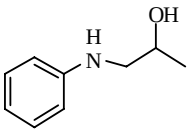
^{1}H RMN δ($CDCl_3$)= 7.34-7.31 (m, 2H), 7.29-7.25 (m, 2H), 7.18-7.14 (m, 1H), 3.78 (t, J = 6Hz, 2H), 3.05 (t, J= 7Hz, 2H), 1.91 (m, 2H)

1-Phenylsulfonylpropane



^{1}H RMN δ($CDCl_3$)= 7.34-7.31 (m, 2H), 7.29-7.25 (m, 2H), 7.18-7.14 (m, 1H), 2.90 (t, J= 7.3Hz, 2H), 1.67 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H)

1-Phenylamino-2-propanol



^{1}H RMN δ($CDCl_3$)= 7.20-7.10 (m, 2H), 6.78-6.60 (m, 3H), 4.00-3.39 (m, 1H), 3.18 (dd, J = 3.3Hz, 12.9Hz, 1H), 2.93 (dd, J= 8.5Hz, 12.9Hz, 1H), 1.22 (d, J= 6.3Hz, 3H). .

Enantiomeric excess were determinated by ^{1}H NMR in presence of $Eu(TFC)_3$, δ= 4.79ppm (*R*), 4.58ppm (*S*).

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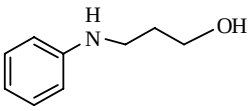
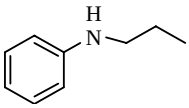
1-Phenylamino-3-propanol



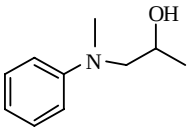
^{1}H RMN δ($CDCl_3$)= 7.20-7.10 (m, 2H), 6.78-6.60 (m, 3H), 3.76 (t, J = 6.1Hz, 2H), 3.26 (t, J= 6.1Hz, 2H), 1.86 (m, 2H)

1-Phenylaminopropane



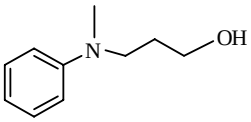
^{1}H RMN δ($CDCl_3$)= 7.20-7.10 (m, 2H), 6.78-6.60 (m, 3H), 3.11 (t, J= 7.2Hz, 2H), 1.72-1.63 (m, 2H), 1.03 (t, J = 7.6 Hz, 3H)

1-*N*-Methylphenylamino-2-propanol



^{1}H RMN δ($CDCl_3$)= 7.20-7.10 (m, 2H), 6.78-6.60 (m, 3H), 4.13 (m, 1H), 3.12 (dd, J = 3.5Hz, 12.8Hz, 1H), 3.02 (dd, J= 8.3Hz, 12.8Hz, 1H), 2.96 (s,3H), 1.28 (d, J= 6.2Hz, 3H). Enantiomeric excess were determinated by ^{1}H NMR in presence of Eu(TFC)$_3$, δ= 4.61ppm (*R*), 4.50ppm (*S*).

1-*N*-Methylphenylamino-3-propanol



^{1}H RMN δ($CDCl_3$)= 7.27-7.20 (m, 2H), 6.81-6.70 (m, 3H), 3.77 (t, J = 6.2Hz, 2H), 3.49 (t, J= 6.2Hz, 2H), 2.96 (s,3H), 1.86 (m, 2H)

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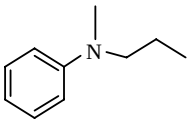
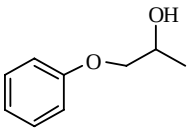
1-*N*-Methylphenylaminopropane



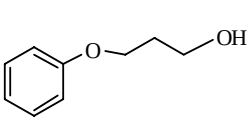
^{1}H RMN δ($CDCl_3$)= 7.27-7.20 (m, 2H), 6.81-6.70 (m, 3H), 3.21 (t, J= 7.4Hz, 2H), 2.96 (s,3H), 1.86 (m, 2H), 1.63 (m, 2H), 1.11 (t, J = 7.7 Hz, 3H)

1-Phenoxy-2-propanol



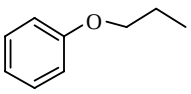
^{1}H RMN δ($CDCl_3$)= 7.30-7.22 (m, 2H), 6.97-6.87 (m, 3H), 4.19-4,15 (m, 1H), 3.92-3.74 (m,2H), 1.25 (d, J= 6.4Hz, 3H). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 18.6min (*S*), 17.8min (*R*).

1-Phenoxy-3-propanol



^{1}H RMN δ($CDCl_3$)= 7.30-7.22 (m, 2H), 6.97-6.87 (m, 3H), 4.11 (t, J= 6.0, 2H), 3.85 (t, J = 6.0Hz, 2H), 2.01 (m, 2H)

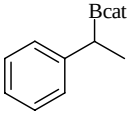
1-Phenoxypropane



^{1}H RMN δ($CDCl_3$7.30-7.22 (m, 2H), 6.97-6.87 (m, 3H), 3.93 (t, J= 6.6Hz, 2H), 1.81 (m, 2H), 1.04 (t, J = 7.4Hz, 3H)

4.2. Selected NMR data for alkylboronate esters[22]

2-(1-Phenylethyl)benzo[1,3,2]dioxaborole



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

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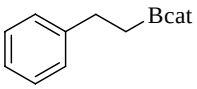
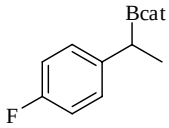
2-Phenethylbenzo[1,3,2]dioxaborole



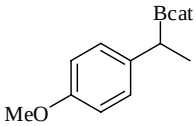
^{1}H NMR ($CDCl_3$): 7.20-7.00 (m, 9H), 2.99 (t, J= 8.2Hz, 2H), 1.67 (t, J= 8.2Hz, 2H)

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



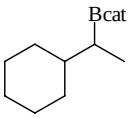
^{1}H NMR ($CDCl_3$): 7.42-7.10 (m, 8H), 3.02 (q, J= 7.6 Hz, 1H), 1.63 (d, J= 7.6 Hz, 3H)

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



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

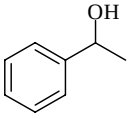
2,2'-(1-Cyclohexylethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.20 (m, 2H), 7.00 (m, 2H), 1.9-1.5 (m,4H), 1.5 (m,3H), 1.3-1 (m, 5H), 1-0.9 (m, 2H)

4.3. Selected NMR data for alcoholics derivatives[23]

1-Phenylethanol



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

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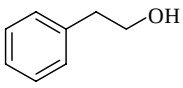
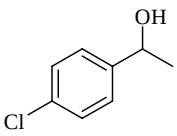
2-Phenylethanol



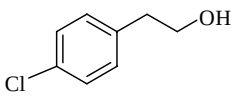
^{1}H NMR ($CDCl_3$): 7.37-7.22 (m, 5H), 3.85 (t, J= 6.6Hz, 2H), 2.88 (t, J= 6.6Hz, 2H)

1-(4-Chlorophenyl)ethanol



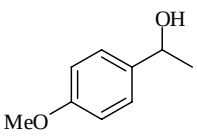
^{1}H NMR ($CDCl_3$): 7.40-7.10 (m, 4H), 4.85 (q, J= 6.6Hz, 1H), 1.47 (d, J= 6.6Hz, 3H)

2-(4-Chlorophenyl)ethanol



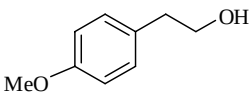
^{1}H NMR ($CDCl_3$): 7.40-7.10 (m, 45H), 3.95 (t, J= 6.6Hz, 2H), 2.86 (t, J= 6.6Hz, 2H)

1-(4-Methoxyphenyl)ethanol



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

2-(4-Methoxyphenyl)ethanol



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

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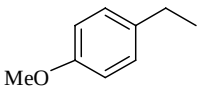
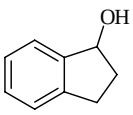
4-Methoxyphenylethane



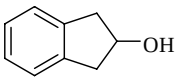
^{1}H NMR ($CDCl_3$): 7.10 (d, J= 8.7Hz, 2H), 6.82 (d, J= 8.7Hz, 2H), 3.78 (s,3H), 2.58 (q, J= 7.7Hz, 2H), 0.91 (t, J = 7.7Hz, 3H)

1-Indanol



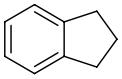
^{1}H NMR ($CDCl_3$): 7.43-7.40 (m,2H), 7.26-7.21 (m, 2H), 5.24 (t, J= 6Hz, 1H), 3.11-3.01 (m, 1H), 2.87-2.77 (m, 1H), 2.54-2.43 (m, 1H), 2.00-1.89 (m, 1H)

2-Indanol



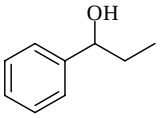
^{1}H NMR ($CDCl_3$): 7.21-7.14 (m, 4H), 4.42-4.38 (m,1H), 3.17 (dd, J= 6.2Hz, 15.8Hz, 2H), 2.85 (dd, J= 4.82Hz, 15.8Hz, 2H)

Indane



^{1}H NMR ($CDCl_3$): 7.52-7.48 (m, 2H), 7.43-7.39 (m, 2H), 3.01 (t, J= 7.5Hz, 4H), 2.20-2.13 (m, 2H)

1-Phenylpropanol



^{1}H NMR ($CDCl_3$): 7.50-7.20 (m, 5H), 4.55 (q, J= 6.7Hz, 1H), 3.02 (d, J= 11.6Hz, 1H), 1.90-1.50 (m, 2H), 0.88 (d, J= 6.7Hz, 3H)

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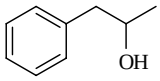
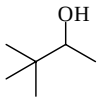
2-Phenylpropanol



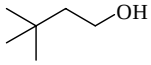
^{1}H NMR ($CDCl_3$): 7.38-7.19 (m, 5H), 4.05-3.95 (m, 1H), 2.80 (dd, J = 4.9Hz, 13.6Hz, 1H), 2.69 (dd, J = 7.9Hz, 13.6Hz, 1H), 1.25 (d, J = 6.1 Hz, 3H)

3,3-dimethyl-2-butanol



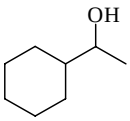
^{1}H NMR ($CDCl_3$): 3.49 (q, J= 6.3Hz, 1H), 1.13 (d, J= 6.3Hz, 3H), 0.91 (s, 9H)

3,3-dimethylbutanol



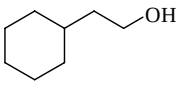
^{1}H NMR ($CDCl_3$): 3.57 (t, J= 7.8 Hz, 2H), 1.51 (t, J= 7.8 Hz, 2H), 0.92 (s, 9H)

1-Cyclohexylethanol



^{1}H NMR (CDCl3): 3.48 (quint, J= 6.2Hz, 1H), 1.80-1.56 (m, 4H), 1.09 (d, J= 6.4Hz, 3H), 1.25-0.84 (m, 7H)

2-Cyclohexylethanol



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

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5. Heterogenised catalytic hydroboration/oxidation reaction

5.1. Preparation of the heterogenised complex

The ionic rhodium complex [Rh(*R*,*R*)-BDPP(COD)$_2$]BF_4 (0.2mmol) was introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in 10ml of deoxygenated dichloromethane. Next, the solid support smectite clay MK-10 was added into the previously solution and the mixture was stirred for 24h under nitrogen at room temperature. The suspension formed was filtered off and the solid was washed with dichloromethane and dried under vacuum. The amount of metal complex immobilised on the clay was determined by gravimetric analysis and SEM analysis.

5.2. General procedure for the heterogenised catalytic hydroboration/oxidation reaction of allyl phenyl sulfones (14) and *p*-methylphenyl sulfone (18)

Supported catalyst (1mol% immobilised in 0.5g of solid) was introduced in a previously purged schlenk under nitrogen atmosphere and 2ml of THF were added. Next, substrate was added to the suspension previously formed. The solution was stirred for 5 minutes at room temperature and freshly distilled catecholborane (**1**) was then added. The mixture obtained was then stirred, using the chemical assembly shown in Figure 1. The solution was filtered off under vacuum and the filtrates were then quenched with EtOH (2ml). Work up must be carried out carefully because of the risk explosion when peroxides are used with THF. Afterwards, NaOH (2M, 2ml) and H_2O_2 (2ml) were added successively to the hydroborated mixture and then it was stirred for 4 hours. After this time, the reaction mixture was extracted with Et_2O (3x30ml), the organic extracts were washed with NaOH (2M, 30ml), H_2O (30ml), brine

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(30ml) and lastly dried over $MgSO_4$ and followed by evaporation under reduced pressure to remove the solvent. The products were characterised by NMR. The solid recovered in the filtration that contained the complex, was dried under vacuum for 10 minutes and put into the schlenk, previously purged, for another run.

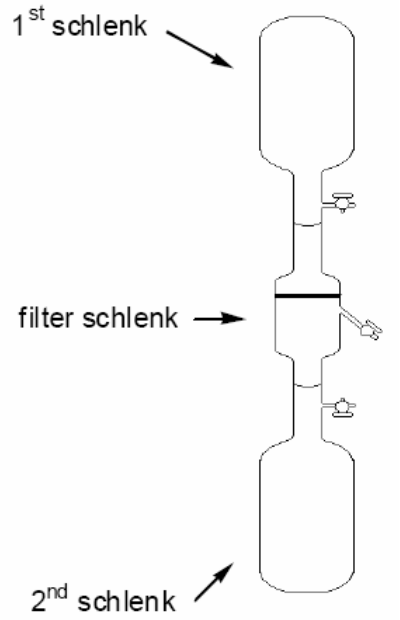

Figure 1

6. General procedure for the tandem catalytic alkyne hydroboration/suzuki cross-coupling reaction

Catalyst precursor (NHC)Pt(dvtms) (**33**) was introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in 2ml of THF and the mixture was stirred for 5 minutes to reach complete dissolution. The alkyne was added to the solution of catalyst. The solution was stirred for 5 minutes, and then the hydroborating reagent, freshly distilled catecholborane (**1**) was added.

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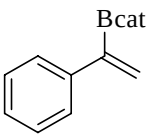
After the mixture was stirred during 3h at room temperature, the THF was removed in vacuo and dioxane (4ml) was added. The mixture was heating until 110ºC and K_2CO_3 (1eq.) and the aryl halide (1eq.) were added and the reaction mixture was stirred for 16h. After cooling to room temperature, the products obtained were analysed by ^{1}H NMR spectroscopy to determine the degree of conversion and the nature of the reaction products.

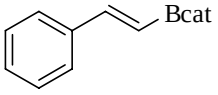
6.1 Selected MNR data[24,25]

2-(1-phenylvinyl)benzo[1,3,2]dioxaborole



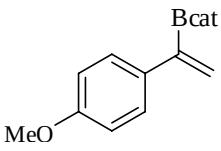
^{1}H NMR ($CDCl_3$): 7.63 (m, 2H), 7.44 (m, 3H), 7.32 (m, 2H), 7.15 (m, 2H), 6.41 (d, J= 2.7Hz, 1H), 6.28 (d, J= 2.4Hz, 1H)

(E)-2-styrylbenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.85 (d, J=18.3Hz, 1H), 7.63 (m, 2H), 7.40 (m, 3H), 7.32 (m, 2H), 7.11 (m, 2H), 6.57 (d, J=18.3Hz, 1H)

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



^{1}H NMR ($CDCl_3$): 7.31 (d, J= 8.2Hz, 2H), 7.4-7.3 (m, 4H), 6.9 (d, J= 8.2Hz, 2H), 6.43 (d, J= 2.5Hz, 1H), 6.29 (d, J= 2.3Hz, 1H), 3.82 (s, 3H)

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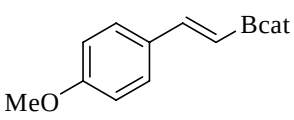
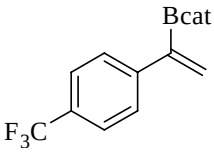
(E)-2-(4-methoxystyryl)benzo[1,3,2]dioxaborole



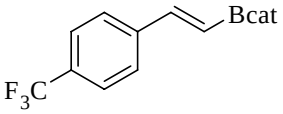
^{1}H NMR ($CDCl_3$): 7.87 (d, *J* = 18.5 Hz, 1H), 7.31 (d, J= 8.2Hz, 2H), 7.40-7.30 (m, 4H), 6.93 (d, *J* = 8.2Hz, 2H), 6.48 (d, *J* = 18.5 Hz, 1H), 3.81 (s, 3H)

2-(1-(4-(trifluoromethyl)phenyl)vinyl)benzo[1,3,2]dioxaborole



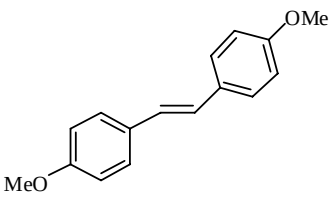
^{1}H NMR ($CDCl_3$): 7.00-7.50 (m, 8H), 6.36 (d, J= 2.7Hz, 1H), 6.13 (d, J= 2.4Hz, 1H)

(E)-2-(4-(trifluoromethyl)styryl)benzo[1,3,2]dioxaborole



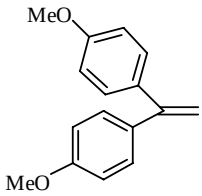
^{1}H NMR ($CDCl_3$): 7.70 (d, J= 17.9Hz, 1H), 7.01-7.45 (m, 8H), 6.39 (d, J=17.9Hz)

(*E*)-1,2-bis(4-methoxyphenyl)ethene



^{1}H NMR ($CDCl_3$): 7.43 (d, J=9Hz, 4H), 6.93 (s, 2H), 6.89 (d, J= 9Hz, 4H), 3.83 (s, 6H).

1,1-bis(4,4'-dimethoxyphenyl)ethene



^{1}H NMR ($CDCl_3$): 7.32 (d, J=8.5Hz, 4H), 6.89 (d, J=8.5Hz, 4H), 5.30 (s, 2H), 3.73(s, 6H).

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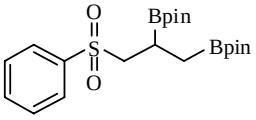
7. General procedure for the catalytic diboration reaction of alkenes

Catalyst precursor (and ligand when necessary) were introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in the corresponding solvent (THF, toluene or CH_3CN; 2 ml were used when the reaction was carried out at room temperature, and 4 ml when was carried out 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 was added. The mixture obtained was then stirred at the corresponding temperature to complete the addition of the diboron into the unsaturated bond. When the mild base NaOAc was used, it was added just before the diboron reagent. The products obtained were analysed by ^{1}H NMR spectroscopy to determinate the degree of conversion and nature of the reaction products.

7.1. Selected NMR data for alkyldiboronate esters[26]

2,2'-(3-(phenylsulfonyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (36a)



^{1}H NMR ($CDCl_3$): 7.96-7.92 (m, 2H), 7.71-7.66 (m, 1H), 7.62-7.52 (m, 2H), 3.43-3.32 (dd, J= 7.4Hz, 14.4Hz, 1H), 3.31-3.20 (dd, J= 7.2Hz, 14.4Hz, 1H), 1.61-1.49 (m, 1H), 1.28 (s,12H), 1.24 (s,12H) 1.12-1.02 (dd, J= 7.2Hz, 16Hz, 1H), 0.98-0.89 (dd, J= 6Hz, 16Hz, 1H)

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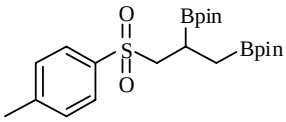
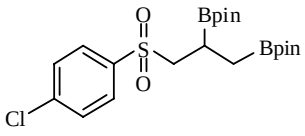
2,2'-(3-tosylpropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (36b)



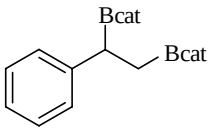
^{1}H NMR ($CDCl_3$): 7.84-7.75 (d, J= 8.7Hz, 2H), 7.35-7.31 (d, J= 8.1Hz, 2H), 3.43-3.32 (dd, J= 7.3Hz, 13.9Hz, 1H), 3.31-3.20 (dd, J= 6.6Hz, 13.9Hz, 1H), 2.35 (s, 3H), 1.61-1.49 (m, 1H), 1.28 (s,12H), 1.24 (s,12H) 1.12-1.02 (dd, J= 7.3Hz, 16.1Hz, 1H), 0.98-0.89 (dd, J= 5.8Hz, 16.1Hz, 1H)

2,2'-(3-(4-chlorophenylsulfonyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (36c)



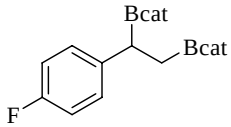
^{1}H NMR ($CDCl_3$): 7.89-7.80 (d, J= 8.1Hz, 2H), 7.57-7.48 (d, J= 8.8Hz, 2H), 3.43-3.32 (dd, J= 7.3Hz, 13.9Hz, 1H), 3.31-3.20 (dd, J= 6.6Hz,13.9Hz, 1H), 1.61-1.49 (m, 1H), 1.28 (s,12H), 1.24 (s,12H) 1.12-1.02 (dd, J= 7.3Hz, 16.1Hz, 1H), 0.98-0.89 (dd, J= 5.8Hz, 16.1Hz, 1H)

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



^{1}H NMR ($CDCl_3$): 7.45-7.00 (m, 13H), 3.36 (m, 1H), 2.19 (dd, J= 10Hz, 17Hz, 1H) 1.93 (dd, J= 6Hz, 17Hz, 1H)

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



^{1}H NMR ($CDCl_3$): 7.40-6.90 (m, 12H), 3.33 (m, 1H), 2.15 (dd, J= 9.8Hz, 17.1Hz, 1H), 1.90 (dd, J= 6Hz, 17.1Hz, 1H)

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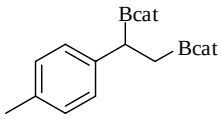
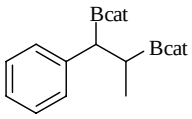
2,2'-(1-(4-methylphenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



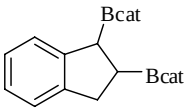
^{1}H NMR ($CDCl_3$): 7.35-7.00 (m, 10H), 7.19 (m, 2H), 3.76 (s, 3H), 3.28 (m, 1H), 2.09 (dd, J= 10.2Hz, 17Hz, 1H), 1.85 (dd, J= 6Hz, 17Hz, 1H)

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



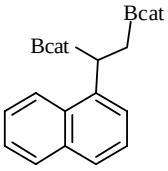
^{1}H NMR ($CDCl_3$): 7.50-7.00 (m, 13H), 3.02 (d, J= 11.6Hz, 1H), 2.34 (m, 1H), 1.13 (d, J= 7.6Hz, 3H)

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



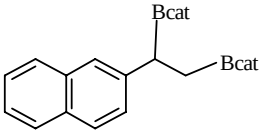
^{1}H NMR ($CDCl_3$): 7.50-7.00 (m, 12H), 3.67 (m, 1H), 3.47 (m, 1H), 3.35 (m, 1H), 2.77 (m, 1H)

2,2'-(1-(naphthalen-1-yl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.95–7.85 (m, 4H), 7.50–7.43 (m, 3H), 7.40-6.90 (m, 8H), 4.1 (m, 1H), 2.35 (dd, J= 10Hz, 16.8Hz, 1H), 2.02 (dd, J= 6Hz, 16.8Hz, 1H)

2,2'-(1-(naphthalen-2-yl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.85–7.80 (m, 4H), 7.50–7.43 (m, 3H), 7.40-6.90 (m, 8H), 3.53 (m, 1H), 2.28 (dd, J= 9.6Hz, 16.8Hz, 1H), 2.05 (dd, J= 6Hz, 16.8Hz, 1H)

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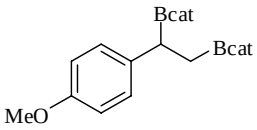
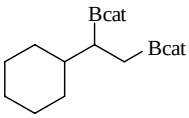
2,2'-(1-(4-methoxyphenyl)ethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.00-7.35 (m, 10H), 6.85 (m, 2H), 3.76 (s, 3H), 3.28 (m, 1H), 2.12 (dd, J= 10 Hz, 17 Hz, 1H), 1.88 (dd, J= 6Hz, 17 Hz, 1H)

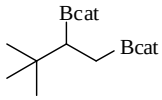
2,2'-(1-cyclohexylethane-1,2-diyl)dibenzo[1,3,2]dioxaborole



^{1}H NMR ($CDCl_3$): 7.45-7.00 (m, 8H), 1.00-1.95 (m, 14H)

.

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



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

7.2. General procedure for oxidative work up

Oxidation of the borylated products derivated from alkenes was done to quantify 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.

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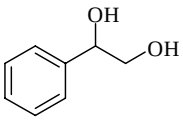
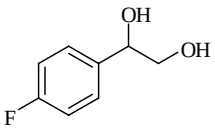
7.3. Selected NMR data for the alcoholic derivatives[27]

Phenylethane-1,2-diol



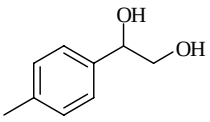
^{1}H NMR ($CDCl_3$): 7.41-7.26 (m, 5H), 4.81 (dd, J= 3.6Hz, 8Hz, 1H), 3.75 (dd, J= 3.6Hz, 10.8Hz, 1H), 3.65 (dd, J= 8.0Hz, 10.8Hz, 1H)

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



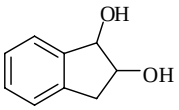
^{1}H NMR ($CDCl_3$): 7.34 (dd, J=5.5Hz, 8.1Hz, 2H), 7.06 (t, J=8.4 Hz, 2H), 4.82 (br, 1H), 3.76 (br, 1H), 3.64 (br, 1H)

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



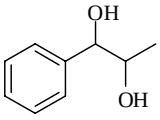
^{1}H NMR ($CDCl_3$): 7.28-7.17 (m, 4H), 4.80 (dd, J= 3.6Hz, 8.0Hz, 1H), 3.74 (m, 2H), 2.46 (br, 1H), 2.35 (s, 3H), 2.04 (br, 1H)

***cis*-Indan-1,2-diol**



^{1}H NMR ($CDCl_3$): 7.40 (m, 1H), 7.30-7.21 (m, 3H), 5.09 (dd, J= 5.6Hz, 4.4Hz, 1H), 4.51 (br s, 1H), 3.12 (dd, J= 5.6Hz, 16.4Hz, 1H), 2.95 (dd, J= 4.4Hz, 16.4Hz, 1H)

***cis*-Phenylpropan-1,2-diol**



^{1}H NMR ($CDCl_3$): 7.25-7.42 (m, 5H), 4.36 (d, J= 7.6Hz, 1H), 3.85 (qd, J = 6.4Hz, 7.2Hz, 1H), 1.05 (d, J = 6.4Hz, 3H)

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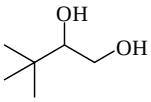
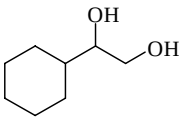
3,3-dimethylbutane-1,2-diol



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

Cyclohexylethane-1,2-diol



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

7.4. General procedure for diol derivatization

The diols are too polar to be resolved by means of gas cromatography in order to determine the enantiomeric excess. Therefore, the diols must be derivatized into the corresponding cetals (Figure 2). 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 derivatization, the enantioselectivity was comproved to be constant, comparing the results obtained with those reported in the literature.[27a]

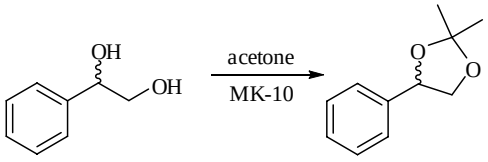


Figure 2

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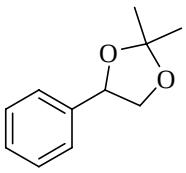
2,2-Dimethyl-4-phenyl-1,3-dioxolane[28]



^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 5.08 (dd, J= 8.1 Hz, 6 Hz, 1H), 1.50 (s, 3H), 4.32 (dd, J= 8.1 Hz, 6 Hz, 1H), 3.72 (t, J= 8.1 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR ($CDCl_3$): 139.39, 128.99, 128.51, 126.68, 110.17, 78.41, 72.15, 27.05, 26.43. Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 41.8min (*S*), 35.2min (*R*).

8. General procedure for tandem catalytic alkene diboration/suzuki cross-coupling/oxidation reaction

Catalyst precursor was introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in 2ml of THF and the mixture was stirred for 5 minutes to reach complete dissolution. Next, NaOAc (1eq) and diboron (**4**) were added. The solution was stirred for 5 minutes, and then the alkene was added. The mixture obtained was then stirred for 4h at room temperature. After heating to reflux, Cs_2CO_3 (3eq), substrate (2eq.) and water (degassed, 10%) were added and the reaction mixture was stirred for 15 h. After cooling to room temperature, NaOH (3M, 1mL) and H_2O_2 (1mL) were added carefully and stirring was continued for 2 h. The oxidation was quenched by adding a saturated aqueous solution of sodium thiosulfate (1mL) and NaOH (1M, 10mL). Then the reaction mixture was extracted with ethyl acetate (3x20mL) and the united organic phases were washed with brine (20mL), dried over magnesium sulfate and dried in vacuum. The products obtained were analysed by ^{1}H NMR spectroscopy to determine the degree of conversion and the nature of the reaction products.

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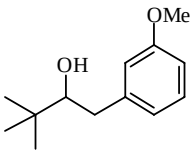
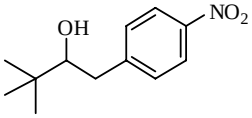
8.1. Selected NMR data[29]

1-(3-Methoxy-phenyl)-3,3-dimethyl-butan-2-ol



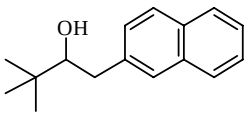
^{1}H NMR ($CDCl_3$): 7.25-7.18 (m, 1H), 6.83-6.75 (m, 3H), 3.79 (s, 3H), 3.42 (d, J = 10.4Hz, 1H), 2.87 (d, J = 13.6Hz, 1H), 2.43 (dd, J = 10.4Hz, 13.6Hz, 1H), 1.50 (br s, 1H), 0.99 (s, 9H)

3,3-Dimethyl-1-(4-nitrophenyl)-butan-2-ol



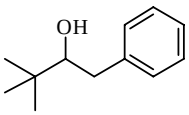
^{1}H NMR ($CDCl_3$): 8.15 (d, J= 8.7Hz, 2H), 7.40 (d, J = 8.7Hz, 2H), 3.44 (ddd, J = 2.0Hz, 4.5Hz, 10.6Hz, 1H), 2.95 (dd, J = 1.3Hz, 13.7Hz, 1H), 2.61 (dd, J = 10.6Hz, 13.7Hz, 1H), 1.40 (d, J = 4.5 Hz, 1H), 0.99 (s, 9H)

3,3-Dimethyl-1-napthalen-2-yl-l-butan-2-ol



^{1}H NMR ($CDCl_3$): 7.82-7.76 (m, 3H), 7.68 (s, 1H), 7.47-7.40 (m, 2H), 7.36 (dd, J = 1.7Hz, 9Hz, 1H), 3.53 (ddd, J = 2.0Hz, 3.4Hz, 10.8Hz, 1H), 3.07 (dd, J = 2.0Hz, 13.6Hz, 1H), 2.63 (dd, J = 10.8Hz, 13.6Hz, 1H), 1.46 (d, J= 3.4Hz, 1H), 1.03 (s, 9H)

3,3-Dimethyl-1-phenyl-butan-2-ol



^{1}H NMR ($CDCl_3$): 7.35-7.20 (m, 5H), 3.42 (dd, J =2.0Hz, 10.4Hz, 1H), 2.90 (dd, J = 2.0Hz, 13.6Hz, 1H), 2.46 (dd, J = 10.4Hz, 13.6Hz, 1H), 1.44 (br s, 1H), 0.99 (s, 9H)

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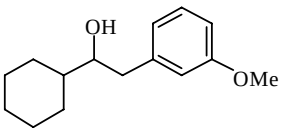
1-Cyclohexyl-2-(3-methoxyphenyl)ethanol



^{1}H NMR ($CDCl_3$): 7.23 (m, 1H), 6.78 (m, 3H), 3.80 (s, 3H), 3.58 (ddd, J= 3.6Hz, 6.0Hz, 9.6Hz, 1H), 2.85 (dd, J= 3.6Hz, 13.6Hz, 1H), 2.56 (dd, J= 9.5Hz, 13.6Hz, 1H), 2.04–1.67 (m, 5H), 1.52 (d, J= 6Hz, 1H), 1.44–1.41 (m, 1H), 1.29–1.07 (m, 5H). ^{13}C NMR ($CDCl_3$): 159.91, 141.08, 129.72, 122.87, 115.93, 111.94, 77.09, 55.34, 41.05, 29.57, 28.23, 26.79, 26.47.

9. General procedure for the catalytic β-boration of α,β-unsaturated esters and aldehydes

Catalyst precursor (and ligand when necessary) were introduced in a previously purged schlenk under nitrogen atmosphere and dissolved in the corresponding solvent (2ml of THF or toluene) at room temperature and the mixture was stirred for 5 minutes to reach complete dissolution (and formation of the complex *in situ*, when ligand was used). Next, base (3 mol% when Cu was used as catalytic precursor or 1.5eq. in the case of Ni or Pd as catalytic precursors) and diboron reagent were added. The solution was stirred for 5 minutes, and then substrate was added followed by the addition of MeOH (2eq when Cu was used as catalytic precursor) or MeOH/H_2O (125μl/1.5eq when Ni or Pd were used as catalytic precursor) were added. The mixture obtained was then stirred to complete the addition of the diboron into the unsaturated bond. The products obtained were analysed by ^{1}H NMR spectroscopy to determinate the degree of the conversion and the nature of the reaction products.

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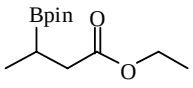
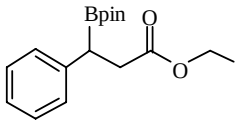
9.1. Selected NMR data for alkylboronate esters[30]

Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate



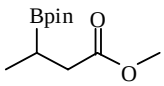
^{1}H NMR ($CDCl_3$): 4.11 (q, J= 7.1Hz, 2H), 2.39 (dd, J= 7.8Hz, 16.3Hz, 1H), 2.36 (dd, J= 8.6Hz, 16.6Hz), 1.45-1.30 (m, 1H), 1.23 (s, 15H), 0.99 (d, J= 7.8Hz, 3H)

Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate



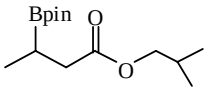
^{1}H NMR ($CDCl_3$): 7.27-7.15 (m, 5H), 4.12 (q, J= 7.14Hz, 2H), 2.85 (dd, J= 9.9Hz, 16.3Hz, 1H), 2.81-2.73(m, 1H), 2.65 (dd, J= 5.9Hz, 15.8Hz, 1H), 1.23-1.19 (m, 15H)

Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate



^{1}H NMR ($CDCl_3$): 3.58 (s, 3H), 2.38 (dd, J= 7.7Hz, 16.4Hz, 1H), 2.32 (dd, *J*= 8.7Hz, 16.3Hz, 1H), 1.42-1.22 (m, 1H), 1.17 (s, 12 H), 0.93 (d, J= 7.5Hz, 3H)

Isobutyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate



^{1}H NMR ($CDCl_3$): 3.87 (d, *J* = 6.6Hz, 2H), 2.35 (dd, J= 7.6Hz, 16.4Hz, 1H), 2.32 (dd, J= 6.9Hz, 16.3Hz, 1H), 1.97-1.72 (m, 1H), 1.42-1.24 (m, 1H), 1.12 (s, 12H), 0.93 (d, J=7.5 Hz, 3H), 0.85 (d, J= 6.7Hz, 6H)

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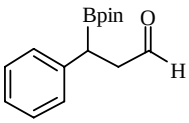
3-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanol



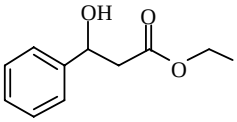
^{1}H NMR ($CDCl_3$): 9.6 (s, 1H), 7.27-7.15 (m, 5H), 2.78 (dd, J= 9.7Hz, 16.1Hz, 1H), 2.81-2.73 (m, 1H), 2.67 (dd, J= 5.7Hz, 15.9Hz, 1H), 1.21-1.11 (m, 12H)

9.2. General procedure for oxidative work up

Oxidation of the borylated products derivated from α,β-unsaturated esters were done to obtain the alcohol derivates which later will be transformed into the acylated products, and in the case of the of α-methyl substituted esters also to determine the percentages of product formation and the syn/anti product ratio. Water (2.5ml) and sodium perborate (5eq) were added successively to the borylated mixture and then it was stirred for 1 hour at room temperature. After this time, the reaction mixture was quenched with water and then was extracted into ethyl acetate (3x20 mL), washed with brine (15ml) and dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent.

9.3. Selected NMR data for the alcoholic derivatives[31]

Ethyl 3-hydroxy-3-phenylpropanoate



^{1}H NMR ($CDCl_3$): 7.44-7.26 (m, 5H), 5.16-5.10 (m, 1H), 4.18 (q, J= 7.2Hz, 2H), 3.29 (br, 1H), 2.75-2.71 (m, 2H), 1.26 (t, J= 7.2Hz, 3H). Enantiomeric excess were determinated by HPLC; Chiralcel OD-H, R_T= 16.9min (*R*), 14.8min (*S*)

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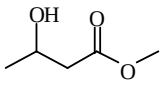
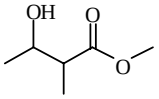
Methyl 3-hydroxybutanoate



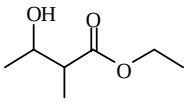
^{1}H NMR ($CDCl_3$): 4.21 (m, 1H), 3.72 (s, 3H), 2.8 (br, 1H), 2.51 (dd, J= 3.8Hz, 16.5Hz, 1H), 2.43 (dd, *J*= 7.4Hz, 16.5Hz, 1H), 1.24 (d, J= 6.3Hz, 3H). Enantiomeric excess were determinated by HPLC; Chiralcel OD-H, R_T= 15.6min (*R*), 11.9min (*S*)

3-Hydroxy-2-methylbutanoate



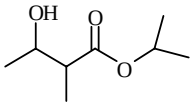
^{1}H NMR ($CDCl_3$): 4.28-4.01 (m, 1H), 3.7 (s, 3H), 2.67-2.4 (m, 1H), 1.22 (d, J= 6.4Hz, 3H), 1.21 (d, J= 6,4Hz, 3H, anti), 1.17 (d, J= 6.4Hz, 3H, syn). Enantiomeric excess were determinated by HPLC; Chiralcel OD-H, R_T= 45.1min and 39.5min (anti isomer), 34.3min and 29.9min (syn isomer)

3-Hydroxy-2-ethylbutanoate



^{1}H NMR ($CDCl_3$): 4.16 (q, J= 7.2Hz, 2H), 4.12-3.79 (m, 1H), 2.59-2.35 (m, 1H), 1.26 (t, J= 7.2Hz, 3H), 1.21 (d, J= 6,4Hz, 3H, anti), 1.19 (d, J= 7Hz, 3H), 1.17 (d, J= 6.4Hz, 3H, syn)

3-Hydroxy-2-isopropylbutanoate



^{1}H NMR ($CDCl_3$): 4.15-3.82 (m, 1H), 3.72 (m, 1H), 2.60-2.30 (m, 1H), 1.92-1.75 (d, J= 6.9Hz, 6H), 1.21 (d, J= 6,6Hz, 3H, anti), 1.19 (d, J= 7.2Hz, 3H), 1.17 (d, J= 6.6Hz, 3H, syn)

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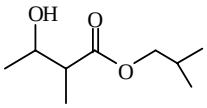
3-Hydroxy-2-isobutylbutanoate



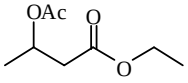
^{1}H NMR ($CDCl_3$): 4.21-3.77 (m, 1H), 3.89 (d, J= 6.6Hz, 2H), 2.58-2.38 (m, 1H), 2.04-1.84 (m, 1H), 1.21 (d, J= 6,6Hz, 3H, anti), 1.19 (d, J= 7.2Hz, 3H), 1.17 (d, J= 6.4Hz, 3H, syn), 0.96 (d, J= 6.8Hz, 6H).

9.4. General procedure for acylation work up

A solution of 3ml of acetic anhydride and 5ml of acetic acid in 25ml of chloroform were added to the β-alcohol product. The reaction was stirring overnight at 50ºC. After this time, the mixture was extracted into ethyl acetate (3x20ml) and dried over magnesium sulfate followed by evaporation under reduced pressure to remove the solvent. The products obtained were characterised by ^{1}H NMR and the enantiomeric excess was determined by gas chromatography.

9.5. Selected NMR data

Ethyl 3-acetoxybutanoate



^{1}H NMR ($CDCl_3$): 5.30-5.20 (m, 1H), 3.60 (q, J= 7.28Hz, 2H), 2.57 (dd, J= 7.4Hz, 15.4 Hz, 1H), 2.54 (dd, J= 8.0Hz, 15.4Hz, 1H), 2.01 (s, 3H), 1.29 (t, *J* = 7.2Hz, 3H), 1.22 (d, J= 7.4Hz, 3H). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 16.1min (*S*), 15.2min (*R*)

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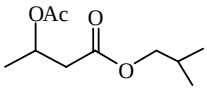
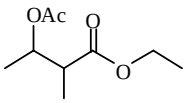
Isobutyl 3-acetoxybutanoate



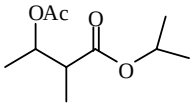
^{1}H NMR ($CDCl_3$): 5.31-5.19 (m,1H), 3.85 (d, J= 6.6Hz, 2H), 2.56 (dd, J= 7.5Hz, 15.5 Hz, 1H), 2.54 (dd, J= 5.6Hz, 15.5Hz, 1H), 1.99 (s, 3 H), 1.95-1.82 (m, 1H), 1.28 (d, J= 6.3Hz, 3H), 0.90 (d, J= 6.7Hz, 6H). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 47.3min (*S*), 43.6min (*R*)

3-Acetoxy-2-ethylbutanoate



^{1}H NMR ($CDCl_3$): 5.48-5.21 (m, 1H), 4.16 (q, J= 7.2Hz, 2H), 2.59-2.35 (m, 1H), 2.05 (s, 3H), 1.35 (t, J= 7.2Hz, 3H), 1.29 (d, J= 6,4Hz, 3H, anti), 1.27 (d, J= 7Hz, 3H), 1.23 (d, J= 6.4Hz, 3H, syn). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 64.9min and 60.9min (syn isomer), 59.6min and 57.7min (anti isomer)

3-Acetoxy-2-isopropylbutanoate



^{1}H NMR ($CDCl_3$): 5.45-5.23 (m, 1H), 4.15-3.82 (m, 1H), 2.6-2.3 (m, 1H), 2.11 (s, 3H), 1.96-1.78 (d, J= 6.5Hz, 6H), 1.31 (d, J= 6,2Hz, 3H, anti), 1.26 (d, J= 7.2Hz, 3H), 1.21 (d, J= 6.2Hz, 3H, syn). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 64.3min and 61.5min (syn isomer), 59.9min and 58.6min (anti isomer)

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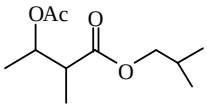
3-Acetoxy-2-isobutylbutanoate



^{1}H NMR ($CDCl_3$): 5.36-5.23 (m, 1H), 3.89 (d, J= 6.6Hz, 2H), 2.63-2.49 (m, 1H), 1.99 (s, 3H), 1.93-1.81 (m, 1H), 1.32 (d, J= 6,3Hz, 3H, anti), 1.23 (d, J= 7.3Hz, 3H), 1.19 (d, J= 6.3Hz, 3H, syn), 0.96 (d, J= 6.7Hz, 6H). Enantiomeric excess were determinated by GC; β-DEX 120, R_T= 166.2min and 158.7min (syn isomer), 155.2min and 148.9min (anti isomer)

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Resumen

Algunos de los campos de mayor extensión en síntesis orgánica son la formación de nuevos enlaces C-C y el diseño de procesos estereoselectivos que permiten acceder a compuestos enantiopuros. De hecho, el desarrollo de nuevas reacciones que permitan la formación de fragmentos orgánicos a través de la formación de enlaces C-C es uno de las principales retos en síntesis orgánica. El uso de compuestos organometálicos en este tipo de reacciones, ha permitido que se desarrollen una multitud de rutas sintéticas con el objetivo de conseguir este desafío. En éste contexto, los compuestos organoborados son considerados de gran interés en síntesis orgánica debido a que el enlace C-B puede ser funcionalizado de diferentes formas, siendo éstos compuestos los que comúnmente se utilizan como compuestos organometálicos en la reacción catalítica de formación de enlaces C-C. La adicción catalítica de H-B o B-B a enlaces C-C insaturados se considera uno de los procesos catalíticos con mayor control selectivo en la formación de dichos intermedios organoborados.

En el primer capítulo de la presente tesis se recoge la evolución a través de la bibliografía de las tres principales reacciones de adición catalítica de boro a alquenos, como son hidroboración, diboración y β-boración. Se presenta una breve recopilación de los diferentes sistemas catalíticos que se han utilizado para estas tres transformaciones, así como los mecanismos de reacción propuestos para cada una de ellas. También se describe la reacción de Suzuki-Miyaura cross-coupling, la cual es una de las reacciones más utilizada para la formación de enlaces C-C a través de compuestos organoborados.

En el segundo capítulo se describe por primera vez la hidroboración catalítica asimétrica tanto en versión homogénea como heterogeneizada de sistemas alílicos heterofuncionalizados. También se describe la primera diboración de fenil alil sulfonas con sistemas catalíticos de platino modificados

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con ligandos N-heterocíclicos. El primer apartado muestra la actividad, quimioselectividad y enantioselectividad que presentan los precursores catalíticos de rodio modificados con diferentes ligandos quirales bidentados P,P y P,N en la hidroboración homogénea de sistemas alílicos heterofuncionalizados. Un exceso del agente de hidroboración (HBcat) es necesario para conseguir conversión completa. La enantioselectividad mostrada por todos los sistemas catalíticos quirales fue moderada para todos los sistemas alílicos heterofuncionalizados, observándose que el ligando que ofrece una mayor enantiodiferenciación es el ligando BDPP (bis(difenilfosfino)pentano). La regioselectividad hacia el producto ramificado depende de las propiedades electrónicas del heteroátomo, siendo los sustratos con grupos sulfonas los que presentan mayor regioselectividad hacia el isómero ramificado. En el segundo apartado se muestran sistemas catalíticos heterogenizados preparados a partir de la inmovilización del complejo catalítico de rodio [Rh(*R*,*R*)BDPP(COD)]BF_4 por absorción en montmorillonita K-10 tratada térmicamente, los cuales permiten ser recuperados y reutilizados durante varios ensayos consecutivos sin pérdida de actividad y selectividad en la hidroboración catalítica de aril fenil sulfonas. El último apartado de este segundo capítulo describe la alta selectividad que muestran los complejos de platino modificados con ligandos carbenos N-heterocíclicos en la diboración catalizada de aril fenil sulfonas, siendo estos complejos de platino los únicos que han proporcionado ser activos en dicha transformación con este tipo de sustratos.

Los ligandos carbenos N-heterocíclicos (NHC) han emergido como una nueva prometedora familia de ligandos debido a que son considerados más básicos que las fosfinas. Esta característica confiere una gran estabilidad al complejo metálico una vez coordinado el ligando al metal, proporcionado mejoras significativas en catálisis homogénea. En éste contexto, el capitulo tercero describe la diboración catalítica de alquenos con diferentes sistemas

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catalíticos formados por Cu(I), Pd(II) e Ir(III), los cuales presentan como novedad el ser modificados con ligandos NHC. El primer apartado describe el alto grado de actividad y quimioselectividad en la diboración catalizada por complejos Cu/NHC del sustrato estireno con el agente de diboración bis(catecolato)diboro (B_2cat_2). Se observa que la selectividad es altamente sensible a la relación [estireno]/[diborano], siendo 1:1 la relación óptima. Los cálculos teóricos muestran la posibilidad de un mecanismo alternativo al convencional, en el cual, el primer paso del ciclo catalítico no sería la adición oxidante sino la formación de un aducto σ-borano. En los siguientes apartados se describe la utilización de diferentes complejos de Pd e Ir modificados con ligandos NHC en la diboración de alquenos, los cuales ofrecen una mayor selectividad y quimioselectividad de la reacción. La adición de una base (NaOAc) y un exceso de diborano son esenciales para la obtención de esos buenos resultados de selectividad y quimioselectividad. Los cálculos teóricos sugieren una ruptura heterolítica en lugar de la adición oxidante del diborano al metal. El uso de carbenos quirales de iridio no produjo inducción asimétrica, excepto cuando se adiciona $AgBF_4$ para formar “in situ” el sistema catalítico catiónico.

En las últimas décadas, la adición conjugada de nucleófilos borilos a alquenos activados ha abierto un nuevo frente en la química de organoboranos. Uno de los principales objetivos a conseguir en ésta reacción de borilación de compuestos α,β-insaturados es el uso de metales de bajo coste como son el Cu y Ni. El capítulo cuarto presenta un estudio sistemático de β-borilaciones de ésteres α,β-insaturados las cuales dan lugar a la formación de compuestos carbonilos β-borilados con elevado grado de inducción asimétrica a través de la adición 1,4 de diboranos a olefinas con deficiencia electrónica. En el primer apartado se describe la β-borilación de ésteres α,β-insaturados catalizada por sistemas catalíticos de Cu(I) modificados con carbenos NHC quirales bajo

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condiciones de reacción suaves. Aunque el grado de enantioselectividad es moderado para todos los ésteres y aldehídos α,β–insaturados probados, no ocurrió lo mismo con la quimioselectividad, la cual fue total hacia el producto β-borilado en todos los casos. La sustitución en la posición α de los ésteres α,β–insaturados no causa efecto ninguno en la quimioselectividad de la reacción. En los siguientes apartados se muestra la adición efectiva de una unidad de boro, de manera quimio- y enantioselectiva, en la posición β de los ésteres α,β–insaturados, que proporcionan los sistemas catalíticos basados en los metales Ni y Pd modificados con ligandos difosfina (P,P) quirales. La influencia de la naturaleza de la base afecta significativamente en la conversión de la reacción, obteniéndose los mejores resultados cuando se utiliza Cs_2CO_3 como base. Todos los ligandos P,P quirales utilizados presentan valores de quimioselectividad elevado independientemente de si se utiliza Ni o Pd. En el caso de sistemas catalíticos basados en Ni(0), es el ligando (*R*)-(*S*)-Taniaphos el que ofrece los mayores valores de enantioselectividad, en cambio, cuando es Pd(0) el que se utiliza, es el ligando (R)-(S)-Josiphos el que induce mayor nivel de enantioselectividad. Sistemas precursores basados en Ni(II) no muestran diferencia en términos de quimioselectividad si son comparados con sus análogos Ni(0), aunque en el caso de Ni(II), es el ligando (R)-(S)-Josiphos quien proporciona mayor enantioselectividad.

Dado el interés en la formación de enlaces C-C y la posibilidad de realizar reacciones catalíticas en cascada con el mismo sistema catalítico, hace que el capitulo quinto se centre en las reacciones tándem “in situ” tales como hidroboración-acoplamiento cruzado de alquinos y diboración-acoplamiento cruzado de alquenos sin la necesidad de cambiar el sistema catalítico y realizando ambas reacciones consecutivamente. El primer apartado describe la selectividad mostrada por complejos catalíticos de Pt(0) modificado con ligandos carbenos en la hidroboración de alquenos, los cuales son más activos y

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quimioselectivos hacia la formación del producto ramificado, que aquellos sistemas de Pt(0) y Pt(II) modificados con ligandos fosfinas. Cuando son utilizados en la hidroboración de alquinos, la quimioselectividad disminuye drásticamente obteniéndose la misma mezcla de isómeros alquenilmonoboratos (ramificado y lineal), sin embargo estos alquenilmonoboratos son capaces de ser funcionalizados "in situ", y de manera eficaz, a través de la reacción de formación de enlaces C-C acoplamiento cruzado del tipo Suzuki-Miyaura, obteniéndose como producto final de acoplamiento C-C una relación de isómeros 1:1 (ramificado/lineal) con un 34% de rendimiento. En el segundo apartado se describe la diboración catalítica de vinilarenos con sistemas catalíticos novedosos de Pd(II) y Pd(III) modificados con ligandos P,P en sus formas dinucleares y tetranucleares. Al igual que ocurría con los sistemas de Pd(II) e Ir (III), la presencia de la base (NaOAc) y un exceso del agente de diboración B_2cat_2 (3eq.) son necesarios para que estos sistemas catalíticos sean selectivos y presenten excelentes quimioselectividades hacia la formación de esteres 1,2-diboronatos. Estudios de resonancia magnética nuclear revelan que la presencia de B_2cat_2 favorece la reducción de Pd(III) a Pd (II), mientras que los precursores catalíticos de Pd(II) son transformados en nanopartículas de Pd(0). De todos los precursores catalíticos de Pd, la especie tetranuclear de Pd(II) es la que presenta la selectividad más elevada. Finalmente se muestra la reacción catalítica tándem diboración-arilación catalizada por un único sistema precursor de Pd(II), la cual se realiza "in situ" a través de la funcionalización del intermedio 1,2-diboronato, obteniéndose como único producto final de acoplamiento C-C hacia el producto monoarilado.

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Vanesa Lillo García
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Congress Contributions

1.- Lillo, V.; Fernández, E. *Asymmetric hydroboration of alkenyl sulfides and allyl sulfone*, **July 2005**, Florence (Italy), *12th International Symposium on Relations between Homogeneous and Heterogeneous Catalysis*. Poster contribution.

2.- Lillo, V.; Mata, J.; Ramírez, J.; Peris, E.; Fernández, E. *An unexpected metal promoted 1,2-diboration of C-C unsaturated bond with Pt(0)-N-heterocyclic carbene complexes*, **July 2006**, Zaragoza (Spain), *22nd International Conference on Organometallic Chemistry*. Poster Contribution.

3.- Ramírez, J.; Fructos, M. R.; Lillo, V.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Valuable but inexpensive Cu(I)-(NHC) catalytic system for B-addition to unsaturated C-C bonds*, **July 2006**, Zaragoza (Spain), *22nd International Conference on Organometallic Chemistry*. Poster Contribution.

4.- Fernández, E.; Lillo, V.; Bonet, A. *Catalytic tandem organic sequences through selective boron addition chemistry*, **July 2008**, Rennes (France), *13th International Conference on Organometallic Chemistry*. Oral contribution by E. Fernández.

5.- Bonet, A.; Lillo, V.; Prieto, A.; Ramírez, J.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Cu-NHC mediates selective catalytic approach to β-boryl compounds*, **July 2008**, Florence (Italy), *16th International Symposium on Homogeneous Catalysis*. Poster Contribution.

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